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A STUDY OF RING-CHAIN TAUTOMERISM IN ORTHO-ACYLBENZOIC ACIDS BY CHEMICAL AND SPECTRAL METHODS

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A STUDY OF RING-CHAIN TAUTOMERISM IN o-ACYLBENZOIC ACIDS BY CHEMICAL AND SPECTRAL METHODS

BY

PETER JOHN DESIO

B. S., Boston College, 1960

A THESIS

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Date

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Peter J. Desio

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INTRODUCTION

Ketoacids in which there exists the possibility of ring-chain tautomerism have been studied by a variety of methods. With a combination of a chemical and a physical method structures were determined for twelve possible 2-benzoylbenzoic acids with or without methyl groups adjacent to the carboxyl group (1). By the use of Fischer-Speier esterifications it was found that only those acids with methyl groups next to the carboxyl group formed pseudo esters. It was also noted that the percent of acid in the ketoacid form as determined by ultraviolet analysis paralleled fairly closely the amount of normal methyl ester produced under the acid-catalyzed esterification conditions.

An opportunity for the application of a strictly chemical approach was afforded by employing the abnormal behavior toward organocadmium reagents of certain aldehydo-acids and ketoacids (2,3). This reaction might be a possible way of estimating ketoacid-pseudoacid equilibria.

Along with chemical means spectroscopic methods have been used to great advantage. The infrared (4), ultraviolet (5), and nuclear magnetic resonance (6) spectra have been shown to be increasingly valuable for structural studies as well as determining the equilibrium position of a pair of ring and chain tautomers.

Regarding the success achieved with chemical and spectroscopic methods it would be both interesting and profitable to explore ring-chain tautomerism in ketoacids where reactivity depends on structure.

The object of the present work was to investigate various substituted o-acylbenzoic acids by two chemical methods. The first would be the organocadmium reaction and the second the Fischer-Speier esterification to detect any correlation between the relative amounts of normal and pseudo methyl ester formed and the ketoacid-pseudoacid equilibrium. In addition, the infrared, ultraviolet, and nuclear magnetic resonance spectra were to be used as physical measurements of ring-chain tautomerism, with the hope of comparing these results with the conclusions from the chemical approaches.

It was also desired to explore further the effect of substituents, other than methyl, adjacent not only to the carboxyl group but also the ketone function, and in conclusion, to arrive at a general relationship concerning the effect of structure on the stability of the ring and chain tautomers.

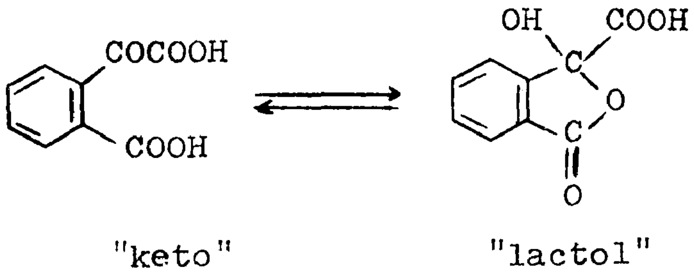
HISTORICAL BACKGROUND

One frequently encounters a material that seems to consist of a single pure substance, but which can more adequately be described by two or more structures which differ by the position of an atom. This phenomenon was referred to as tautomerism in 1886 by Laar (7), who wanted to describe the mobile equilibrium between two compounds containing weakly bonded hydrogen atoms. However, it was pointed out by Lippmann that Gerhardt in his book on organic chemistry discussed tautomerism in 1854 (8). "A phenomenon characterized by the establishment of an equilibrium resulting from the reversible interconversion of isomers" is the definition given to tautomerism by Thorpe and Ingold (9).

More of an insight into the nature of tautomerism is given by Wheland (10). He refers to a substance that demonstrates this phenomenon as a "tautomeric compound" and this compound may be represented by one or more structures known as tautomers. Why a tautomeric compound appears to be a single pure substance might be explained by a two-fold answer. First of all, a "tautomeric compound" is mostly a single pure substance due to the fact that usually only one of the tautomers exists to an appreciable extent in the equilibrium mixture. Secondly, if two or more tautomers are present in significant amounts, their interconversion is rather rapid. Therefore, it can be concluded that a separation of a mixture of tautomers would be difficult since each compound of the mixture can undergo reactions characteristic of any of its tautomers. This is understandable because a tautomer can readily be transformed into its counterpart.

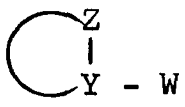
Wheland (10) divides tautomerism into two types, one being prototropy and the other, anionotropy. Prototropy refers to the difference in the position of a hydrogen atom in two or more tautomeric structures, while anionotropy refers to the difference in the position of an atom or group that can form a stable anion.

There also appears the possibility of a similar reversible isomeric change in which one of the tautomers is cyclic,and this was reviewed in 1934 by Baker in his book, "Tautomerism" (11). It is in this direction that the remaining discussion will be channeled. For example, Kirrman and Provost (12) discussed this isomeric change as applied to "keto-lactol" tautomerism exemplified in the following case.

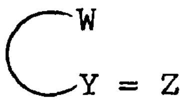


"keto" "lactol"

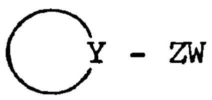
Jones (13) has recently treated the subject of ring-chain tautomerism from various aspects. In this survey the structural requirements for ring-chain tautomerism were stated generally in terms of the "chain" tautomer. There should be present at least two functional groups, one of which contains a multiple bond (Y=Z), and the other (W) should be capable of reacting at the multiple bond. The cyclic tautomer might possess one of the two structures (I or II) as shown below, and this depends on which way addition occurs.



I, "ring"



"chain"

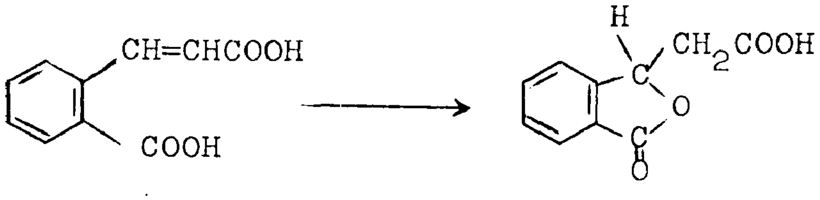


II, "ring"

Two types of ring-chain tautomers were encountered (13) in relation to the above direction of addition. When W (tending to be electron deficient) adds to Z (more electronegative atom), the term applied is "electrophilic tautomerism". When W (being electron rich) adds to Y, the term is referred to as "nucleophilic tautomerism".

As far as electrophilic tautomerism is concerned, most of the examples deal with a mobile hydrogen atom as the electrophile (W=H). This hydrogen atom besides being a carboxylic hydrogen is usually attached to such atoms as nitrogen, oxygen, and sulfur. As one might expect, this hydrogen is fairly acidic.

In 1877 Gabriel and Michael (14) found that they were able to convert o-carboxylcinnamic acid (chain) to 3-phthalidylacetic acid (ring).

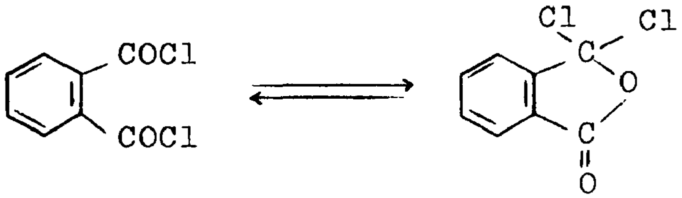


"chain" "ring"

However, conversions of this type do not always proceed in both directions, and to accomplish this would require forced conditions.

At first glance, nucleophilic tautomerism would seem to offer a wider variety of examples considering the possible nucleophiles (OCOR, OR, NH_2, OH, halogen), but not many are known.

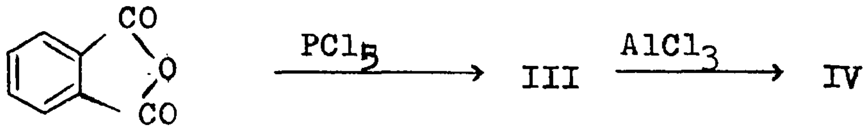
An example of this is o-phthaloyl chloride where YZ= -COCl. This is known in both the chain (III) and ring (IV) tautomeric forms (15,16).



III IV

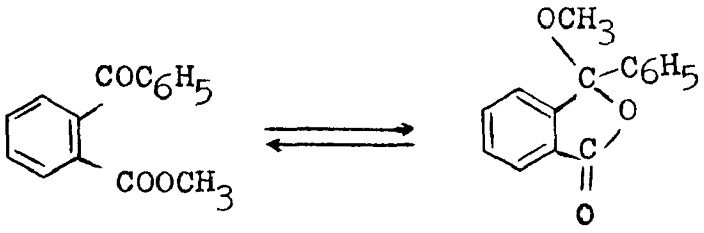
Even in its reactions, phthaloyl chloride reacts as if it has both structures (10). Thus, when treated with benzene and aluminum chloride, this compound gives not only anthraquinone but also 3,3-diphenylphthalide.

That the two tautomers actually exist has been proved by the isolation of each (17). The symmetrical form III is obtained by treatment of phthalic anhydride with phosphorus pentachloride. The unsymmetrical form IV can be prepared by heating its isomer with aluminum chloride,



but reverts partially to the symmetrical form when it is melted at 87-89°C.

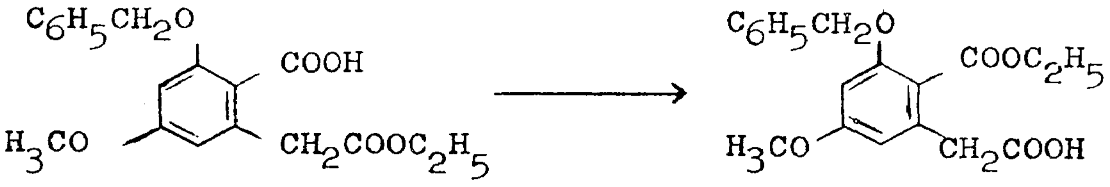
Egerer and Meyer (18) prepared both the normal (V) and pseudo (VI) methyl esters of o-benzoylbenzoic acid and isomerized them under a variety of conditions. A mixture of V and VI is obtained if a solution of the acid chloride of



V VI

o-benzoylbenzoic acid in methanol is allowed to stand for a number of hours at room temperature. The pseudo ester is also isomerized by moistening VI with thionyl chloride and heating with methanol, or by treating a solution of VI in methanol with sulfuric acid and heating.

Reversible functional exchange in acid esters is an excellent case of a rearrangement likely to occur involving ring-chain tautomerism. This has been observed by Allison and Newbold (19). The homophthalic acid VII was transformed to VIII in the presence of methanolic potassium hydroxide.

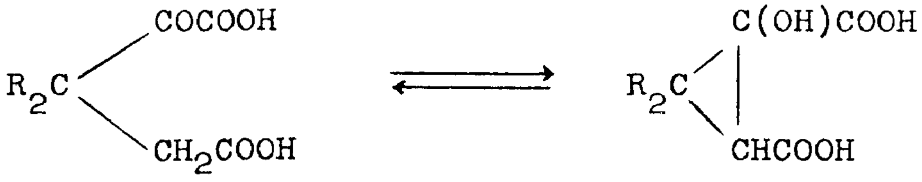


VII VIII

The acid chloride of o-benzoylbenzoic acid is cyclic (20), since on treatment with benzene and aluminum chloride 3,3-diphenylphthalide was produced. Also, the action of diphenylcadmium on the acid chloride yielded 3,3-diphenylphthalide (21). Acid chlorides of this type, i.e. formed from keto- or aldehydoacids which can produce five- or six-membered rings, are cyclic. In contrast, the salts of acids in which ring-chain tautomerism exists are always in the open-chain form (13).

As might be expected, the stability of the ring tautomer depends on the size of the ring as well as the spatial arrangement of the groups involved in forming the cyclic structure (-W and -YZ).

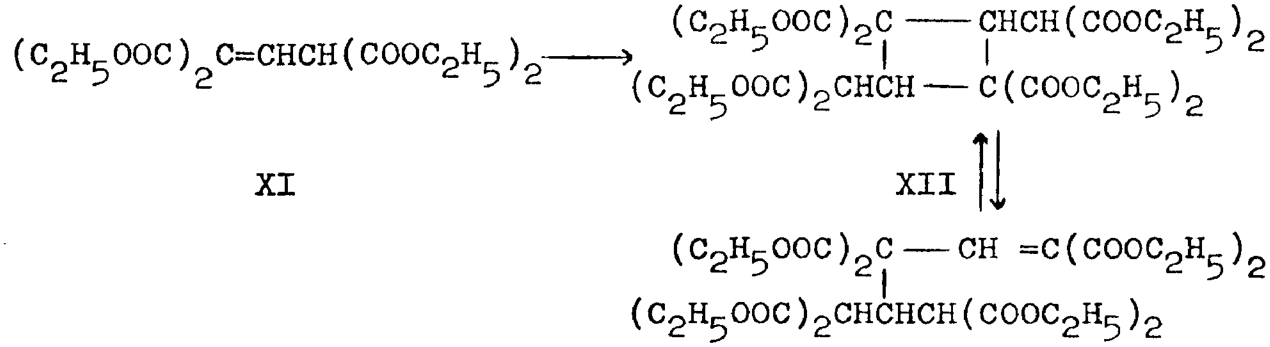
Various substituted β,β-dialkyl-α-ketoglutaric acids were studied and involve the formation of a three-membered ring (22). Where R is ethyl, the equilibrium mixture was estimated to consist of 38% of IX and 62% of X; where R is



IX X

n-propyl, the acid was estimated to consist of 29% of IX and 71% of X.

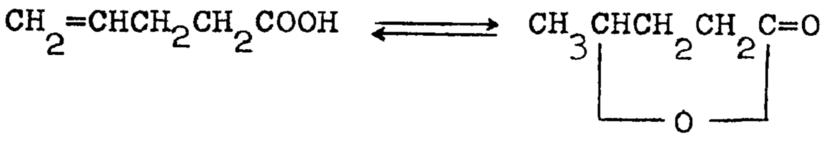
Evidence of a four-membered ring, which is seldom encountered, is given by the base-catalyzed dimerization of 1,1,3,3-tetracarbethoxypropene XI (23). The tautomeric mixture was estimated at 80% of XII and over 10% of XIII.



XI XII

XIII

In agreement with their high stability five- and six-membered rings are formed preferentially. 4-Pentenoic acid (XIV) isomerizes to the γ-lactone XV in cold 60% sulfuric acid (24).



$$CH_2{=}CHCH_2CH_2COOH \rightleftharpoons CH_3CHCH_2CH_2C{=}O$$

XIV XV

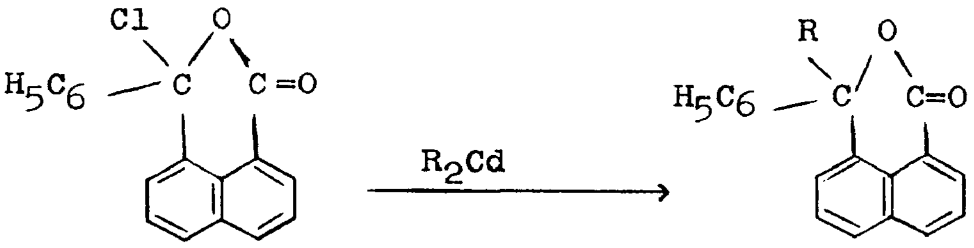
In Table 1 the extent of conversion to γ-lactone as a function of time is denoted.

Table 1

Isomerization of 4-Pentenoic Acid to the γ-Lactone (24)

Time	% Lactone
15 mins.	33
60 mins.	83
24 hrs.	99

A six-membered ring is observed in the case of 8-benzoyl-1-naphthoyl chloride (XVI) (25). Use of the organocadmium reagent gives further evidence of the cyclic structure XVII as seen in Table 2.



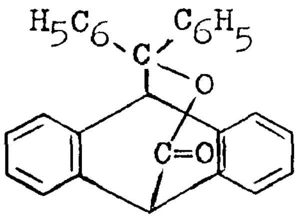
XVI XVII

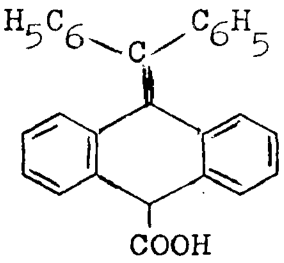
Table 2

Percent of XVII Formed by Organocadmium Reagent (25)

R	% XVII
C_2H_5	95
n-C_4H_9	99

The seven-membered lactone (ring) of anthracene is rearranged in acid to 9-diphenylmethylene-9,10-dihydroanthracene-10-carboxylic acid (chain) (26).

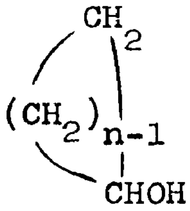

"ring"


"chain"

However, seven-membered rings and those higher are not common. This is borne out by a study made by Hurd and Saunders (27). These authors made quantitative estimates for a group of ω-hydroxyaldehydes and compared the ultraviolet absorption spectra of the compounds XVIII (or XIX)

$HO-(CH_2)_n-CHO$

XVIII



$$\begin{matrix} CH_2 \\ (CH_2)_{n-1} \\ CHOH \end{matrix}$$

XIX

$CH_3-O-(CH_2)_n-CHO$

XX

with those of the respective methyl ethers XX. The results are listed in Table 3. As might have been expected, the tendency of a hydroxyaldehyde to exhibit ring-chain tautomerism is greatest when the ring contains either five or six atoms.

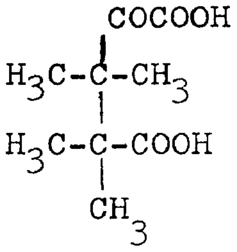
Table 3

Tautomerism of ω-Hydroxyaldehydes $HO-(CH_2)_n-CHO$ (27)

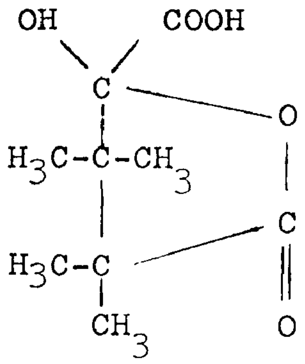
n	% Acyclic Form
3	11.4
4	6.1
5	85
7	80
8	91

It is generally observed (13) that the stability of the ring tautomer increases with increasing substitution and that also, ring formation is much more likely if the ring is unsaturated.

Determination of the structures of ring and chain tautomers can be accomplished by either chemical or physical means. Depending on the functional groups present the chemical approach can be very useful in obtaining evidence for or against a particular structure. For instance, the β,β,γ-γ,-tetramethyl ketoacid XXI behaves as a monobasic acid in base and therefore suggests that it exists as the ring tautomer XXII (28).

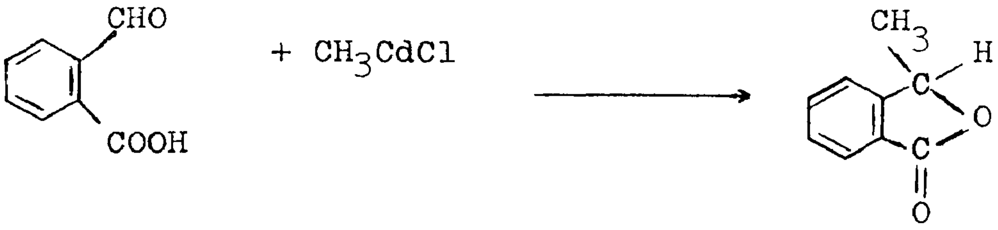


XXI

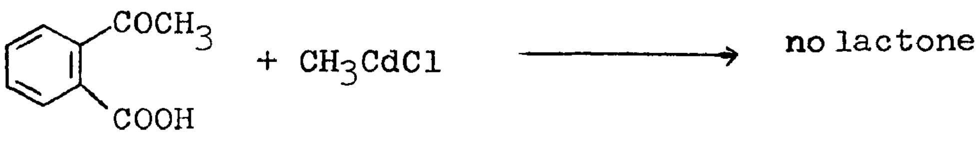


XXII

It was found that certain aldehydoacids and ketoacids behave abnormally toward the organocadmium reagent to form lactones (2,3). The action of methylcadmium reagent under the same conditions partially converts phthalaldehydic acid (XXIII) to 3-methylphthalide (31%), while o-acetylbenzoic acid (XXIV) does not form any lactone.



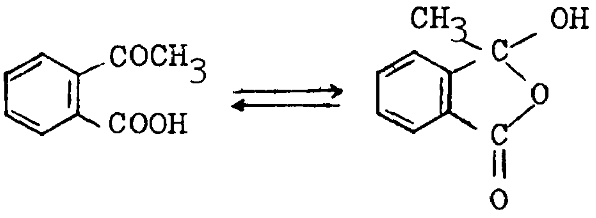
XXIII



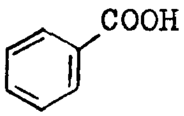
XXIV

It can be concluded that the lactone results only from the ring tautomer because acid or carbonyl functions usually do not undergo addition with organocadmium reagents. If this is true, it then follows that lactone formation would under the reaction conditions be a measure of ring tautomer present. This would hold provided that reaction with organocadmium reagents is faster than equilibration of the ring and chain tautomers.

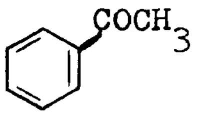
Physical methods present valuable means of estimating the equilibria of ring and chain tautomers. Some of these include optical activity, polarography, molar volume, and spectroscopy. The most promising physical method is that of spectroscopy in which absorption spectra are utilized very effectively. Of these, the ultraviolet (U.V.), infrared, and nuclear magnetic resonance (n.m.r.) spectra are the most worthwhile.



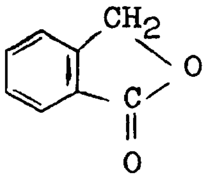
XXV XXVI



XXVII



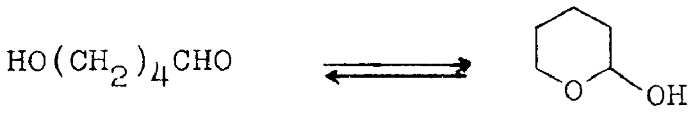
XXVIII



XXIX

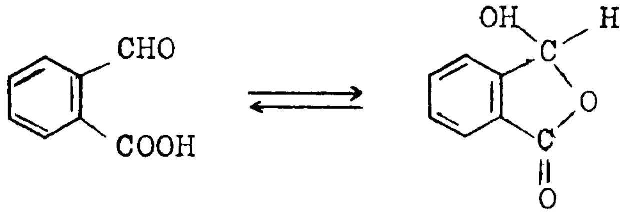
By the application of ultraviolet absorption spectra o-acetylbenzoic acid was assigned the ring structure XXVI (5). This acid showed maxima at 230, 275 (inflection), and 282 mμ. The main maximum is more characteristic of benzoic acid (XXVII) (λmax 230 mμ) than acetophenone (XXVIII) (λmax 240 mμ). However, the other maxima are not consistent with the simple structure XXV and the acid therefore probably exists in solution as the lactol XXVI. By comparison phthalide (XXIX) showed maxima at 227, 273, and 280 mμ.

It was concluded from its infrared spectrum that 5-hydroxypentanal (XXX) contains an appreciable amount of the ring tautomer, 2-hydroxytetrahydropyran (XXXI) (29). The spectrum has bands at 3500 cm.$^{-1}$ (-OH), 2850 and 2950 cm.$^{-1}$ (-CH$_2$), 1720 cm.$^{-1}$ (carbonyl of aldehyde), and 1000 - 1150 cm.$^{-1}$ (characteristic of cyclic tetrahydropyran).



XXX XXXI

The infrared spectrum of phthalaldehydic acid in the solid state indicates that it has the structure XXXIII and not the chain structure XXXII (4). There is found an "alcoholic" OH absorption at 3.01μ (~ 3320 cm.$^{-1}$) and a carbonyl absorption typical of a lactone at ~1750 cm.$^{-1}$.

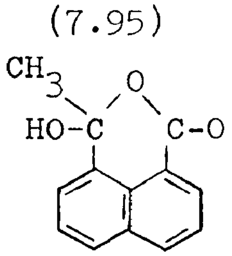


XXXII XXXIII

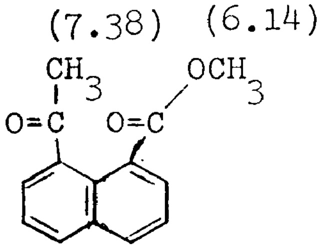
Application of n.m.r. spectroscopy to ketoacid-pseudoacid tautomerism has recently been reported (6). The n.m.r. spectrum of 8-acetyl-1-naphthoic acid was studied in deuterochloroform solution, while the spectra of the normal and pseudo methyl esters were examined in carbon tetrachloride solution.

To begin with, 8-acetyl-1-naphthoic acid (XXXIV) reportedly does not give carbonyl derivatives and its infrared spectrum further suggests that it exists as the pseudoacid. This was confirmed by a comparison of its n.m.r. spectrum with that of the normal (XXXV) and pseudo (XXXVI) methyl esters.

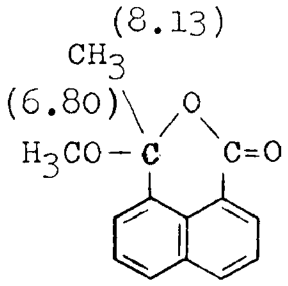
The chemical shifts (τ) of the different methyl protons are indicated below.



XXXIV



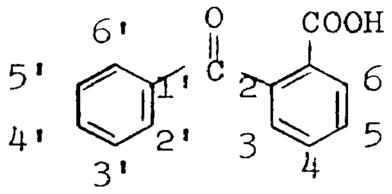
XXXV



XXXVI

The 8.13-τ signal in XXXVI corresponds closely to that of the methyl signal of XXXIV, thereby confirming the pseudoacid character of XXXIV.

A combination of physical and chemical methods was employed by Newman and Muth (1). They used ultraviolet absorption spectra run in methanol to determine the position of the ring-chain equilibrium in various methyl substituted 2-benzoylbenzoic acids (XXXVII). This was done via the Fischer-Speier esterification of these acids. The following points of interest were made in connection with the acid-catalyzed esterification of XXXVII with methanol:



XXXVII

(1) pseudo esters are formed only from acids which have a methyl group at 6

(2) if an acid has a methyl group at 6 and also one at 2', or at 2' and 6', no pseudo ester is formed

(3) in acids which have a methyl group at 6, the addition of a methyl group at 3 gives rise to surprising effects.

The normal esters were found to have a maximum near 250 mμ, whereas this peak is almost entirely lacking in the pseudo esters. By comparing the intensity of absorption at the appropriate wavelength near 250 mμ in the free acid to that of the normal and pseudo esters, an estimate was made of the position of the ketoacid-pseudoacid equilibrium as depicted in Table 4 below.

Table 4

Fischer-Speier Esterification of Substituted
2-Benzoylbenzoic Acids (1)

Acid	Yield, % Ester	Type of Ester, % Normal	Pseudo	Ketoacid, % by U.V. Analysis
XXXVII	91	All	--	100
6-Methyl	87	65	35	35
3,6-Dimethyl	90	--	85	14
2',4',6-Trimethyl	94	All	--	88
2',3,4',6-Tetramethyl	88	68	32	22
2',4',6,6'-Tetramethyl	4	All	--	--
2',3,4',6,6'-Pentamethyl	78	All	--	--

DESCRIPTION OF EXPERIMENTS

The infrared absorption spectra were determined with a Perkin-Elmer Model 21 infrared spectrophotomer with sodium chloride optics or a Perkin-Elmer Model 337 grating infrared spectrophotometer. The nuclear magnetic resonance spectra were determined with a Varian Model A-60 nuclear magnetic resonance spectrometer. Both types of spectra are described by medium, file number, and major bands. The ultraviolet absorption spectra, measured with a Perkin-Elmer Model 4000 recording spectrophotometer and a Beckman Model 2400 DU spectrophotometer, were determined in 95% ethanol.

Microanalyses were determined by Galbraith Laboratories, Knoxville, Tennessee. The boiling points and melting points are in degrees centigrade and are uncorrected. The melting points were taken in a Hershberg melting point apparatus.

Preparation of Ethyl Anthranilate Hydrochloride. (30)

In a 1-l., single-necked, round-bottomed flask was placed 300 g. (6.5 moles) of ethanol and this was then saturated with hydrogen chloride. To this solution was added 60.0 g. (0.44 mole) of anthranilic acid, and the flask was fitted with a reflux condenser with a calcium chloride tube. The contents of the flask were allowed to reflux for twenty-four hours. Upon cooling the flask in an ice bath a white solid separated and was collected. This amounted to 61.9 g.

(70.4%) of ethyl anthranilate hydrochloride, m.p. 152-162°, lit. (30) 170°.

Preparation of Ethyl o-Cyanobenzoate. (31) Ethyl anthranilate hydrochloride (20.2 g., 0.10 mole) was dissolved in a mixture of 20 ml. of water and 10 ml. of concentrated hydrochloric acid, and 100 g. of ice was added. The solution was diazotized with 8.0 g. (0.11 mole) of sodium nitrite in 20 ml. of water. In 45 ml. of water were dissolved 22.0 g. (0.34 mole) of potassium cyanide and 15.0 g. (0.16 mole) of cuprous cyanide, and 50 ml. of benzene was poured on the surface. The solution was chilled to 0-5°, and the neutralized solution of the diazonium salt was slowly added under rapid stirring. After the addition the solution was allowed to stand at room temperature for one hour. The benzene layer was then separated and the water solution extracted with ether. The combined ether-benzene solution was dried overnight over anhydrous magnesium sulfate. Upon evaporation of the solvent a brown crystalline mass was obtained. After recrystallization from dilute alcohol 4.5 g. (25.7%) of ethyl o-cyanobenzoate was obtained, m.p. 68-72°, lit. (32) 70°.

Preparation of o-Cyanobenzoic Acid. (31) Sodium (4.7 g., 0.2 g. atom) was dissolved in a mixture of 100 ml. of absolute alcohol and 4 ml. of water. The warm solution was rapidly mixed with a solution of 36.0 g. (0.2 mole) of ethyl o-cyanobenzoate in 125 ml. of warm absolute alcohol. The salt separated almost immediately. The mixture was allowed to stand at room temperature overnight. The salt was removed by filtration and washed with absolute alcohol, and amounted to 33.4 g. (97.2%). The sodium salt (21.7 g., 0.1 mole) was dissolved in water, and 5 ml. of concentrated hydrochloric acid was added, whereupon the acid separated as a thick mass and was removed by filtration. This was purified according to the procedure of Hoogewerff and Van Dorp (32). The crude acid was dissolved in an aqueous solution of barium carbonate and the solution filtered. The filtrate was acidified with concentrated hydrochloric acid. The o-cyanobenzoic acid (5.0 g., 34.0%) separated and was collected, m.p. 187-189°, lit. (32) 190°. The infrared spectrum (double mull) (spectrum #3037) contains a broad band at 2900 cm.$^{-1}$ with other bands at 2220 cm.$^{-1}$ (-CN) and 1685 cm.$^{-1}$ in the carbonyl region.

Action of Phenylmagnesium Bromide on o-Cyanobenzoic Acid. (2)

In a 500-ml., three-necked, round-bottomed flask fitted with a mechanical stirrer, a reflux condenser with a calcium chloride tube, and an addition funnel the Grignard reagent was prepared from 2.4 g. (0.10 g. atom) of magnesium, 15.7 g. (0.10 mole) of bromobenzene, and 250 ml. of dry ether as solvent. After all the bromobenzene was added, the reaction mixture was allowed to reflux for half an hour. The contents of the flask were allowed to reach room temperature and solid o-cyanobenzoic acid (5.0 g., 0.03 mole) was added with stirring. The reaction mixture was heated under gentle reflux for six hours, with stirring. The flask was cooled in an ice bath, and 10% sulfuric acid was added. The solution was filtered and the ether layer separated and combined with ether washings of the water layer. The combined ether layer was washed with 10% potassium carbonate. The potassium carbonate solution was acidified with 10% sulfuric acid with no separation of any acid. The ether solution was dried over anhydrous calcium chloride overnight. Evaporation of the ether produced a yellow oily substance. Upon recrystallization, first from ether, and then from ligroin (b.p. 90-120°) a yellow solid (3.2 g.) was obtained, m.p. 40-50°. The infrared spectra (spectrum #'s 3228, smear and 3245, double mull) contain bands at 3290, 3040, 2920, 2860, 1707, 1785, and 1765 cm.$^{-1}$. Further identification of the solid was not attempted.

Action of Phenylcadmium Reagent on *o*-Cyanobenzoic Acid. (33)

A 1-l., three-necked, round-bottomed flask was fitted with a reflux condenser with a calcium chloride tube, a mechanical stirrer, and an addition funnel. The Grignard reagent was prepared from 6.8 g. (0.28 g. atom) of magnesium, 43.9 g. (0.28 mole) of bromobenzene, and 350 ml. of dry ether as solvent. The cadmium reagent was prepared by the addition of 51.3 g. (0.28 mole) of anhydrous cadmium chloride over a period of fifteen minutes. When a Michler's ketone test (48) showed the absence of Grignard reagent after fifteen minutes, the ether was removed by distillation and replaced by 300 ml. of dry benzene. The reaction mixture was stirred and allowed to reflux for fifteen minutes. The flask was surrounded by an ice bath, and solid o-cyanobenzoic acid (10.0 g., 0.07 mole) was added with stirring over a period of twenty minutes. The contents of the flask were heated for six hours under reflux, with stirring. The flask was cooled in an ice bath, and dilute sulfuric acid (31.3 g., 0.32 mole, in 150 ml. of water) was added. The solution was filtered to yield 8.8 g. of a mixture of phthalic anhydride and phthalic acid, m.p. 120-210°. The infrared spectrum (double mull) (spectrum #3377) contains a broad band at 3000 cm.$^{-1}$ and bands at 1845, 1760, and 1680 cm.$^{-1}$ in the carbonyl region. These bands are present in the infrared spectra of authentic samples of phthalic acid (double mull) (spectrum #3519) with bands at 3000 cm.$^{-1}$ (broad) and 1680 cm.$^{-1}$, and phthalic anhydride (double mull) (spectrum #3533) with bands at 1845 and 1760 cm.$^{-1}$. The ether layer was separated from the water layer and combined with ether washings of the water layer. The combined ether layer was washed with a potassium carbonate solution (26.7 g., 0.20 mole, in 250 ml. of water). The potassium carbonate solution was acidified with 10% sulfuric acid. A white solid separated and was collected. This was found to be phthalic acid (1.0 g.), m.p. 105-210°. The infrared spectrum (double mull) (spectrum #3358) contains a broad band at 3000 cm.$^{-1}$ and a band at 1680 cm.$^{-1}$ in the carbonyl region. Evaporation of the benzene yielded a brown crystalline mass. Upon sublimation under reduced pressure 2.1 g. of biphenyl was obtained, m.p. 65-67°. The infrared spectrum (double mull) (spectrum #3308) was identical to that of an authentic sample. The above reaction was repeated with the following modifications: (1) the ether was removed by distillation and replaced by toluene, (2) the formation time of the cadmium reagent was twenty minutes, and (3) the reflux period was twenty-four hours. After the flask was cooled in an ice bath and dilute sulfuric acid added, a grey solid was removed by filtration and was found to be phthalic acid (9.3 g.), m.p. 105-210°. The infrared spectrum (double mull) (spectrum #1117) was similar to that of authentic sample. Also, phthalic acid (0.1 g.) was obtained upon acidification of the potassium carbonate solution with 10% sulfuric acid, m.p. 107-210°. From the toluene solution 1.9 g. of biphenyl was obtained, m.p. 55-65°. Therefore, in the two reactions just cited there was found no trace of any formation of o-benzoylbenzoic acid (cf. infrared spectrum #1118).

Preparation of o-Benzoylbenzoic Acid. (34)

Pure, anhydrous o-benzoylbenzoic acid was prepared by recrystallizing student preparation grade acid from benzene. The acid was made anhydrous by putting it in a round-bottomed flask, evacuating the flask with the suction pump, heating it in the open rings of the steam bath and covering the flask with a towel. The acid had a melting point of 127°, lit. (34) 126-127°. The infrared spectrum (chloroform) (spectrum #3549) contains a broad band at 3000 cm.$^{-1}$ in the OH region and two carbonyl bands at 1695 and 1665 cm.$^{-1}$.

Preparation of 3,4,5,6-Tetrachloro-2-benzoylbenzoic Acid (35). In a 1-l., three-necked, round-bottomed flask fitted with a mechanical stirrer and a reflux condenser with a calcium chloride tube was placed 97.2 g. (0.34 mole) of tetrachlorophthalic anhydride and 175 g. (2.25 moles) of dry benzene. The stirrer was started and 100 g. (0.75 mole) of powdered anhydrous aluminum chloride was added in small portions from an Erlenmeyer flask attached by means of Gooch tubing. The reaction mixture was allowed to reflux for half an hour. The flask was then surrounded with an ice bath, the stirrer was removed, and 150 ml. of water was slowly added from a dropping funnel inserted in the top of the reflux condenser. After the addition of water to the aluminum chloride complex 50 ml. of concentrated hydrochloric acid was added. The insoluble aluminum hydroxide was removed by filtration and the benzene layer was separated from the aqueous layer. The aqueous layer was then extracted twice with benzene and once with ether. The combined benzene-ether solution was evaporated under reduced pressure. The acid obtained was converted to the sodium salt and the salt was then acidified with 10% hydrochloric acid. By recrystallization from ethanol-water 82.0 g. (66.3% yield) of a white, powdery acid was obtained, m.p. 191-192°, lit. (36) 200°. The infrared spectrum (double mull) (spectrum #3679) contains sharp bands at 3280 $cm.^{-1}$ in the OH region and 1740 $cm.^{-1}$ in the carbonyl region.

Anal. Calcd. for $C_{14}H_6Cl_4O_3$: C, 46.19; H, 1.66; Cl, 38.95
Found : C, 46.08; H, 1.71; Cl, 39.03

Preparation of 3,4,5,6-Tetraiodo-2-benzoylbenzoic Acid. (35)

In a 500-ml., three-necked, round-bottomed flask fitted with a mechanical stirrer and a reflux condenser with a calcium chloride tube was placed 50.0 g. (0.08 mole) of tetraiodophthalic anhydride and 43.7 g. (0.56 mole) of dry benzene. The stirrer was started and 25.0 g. (0.18 mole) of powdered anhydrous aluminum chloride was added in small portions from an Erlenmeyer flask attached by means of Gooch tubing. The reaction mixture was allowed to reflux for half an hour. The flask was then surrounded with an ice bath, the stirrer was removed, and 50 ml. of water was slowly added from a dropping funnel inserted in the top of the reflux condenser. After the addition of water to the aluminum chloride complex 15 ml. of concentrated hydrochloric acid was added. The insoluble aluminum hydroxide was removed by filtration and the benzene layer was separated from the aqueous layer. The aqueous layer was extracted with benzene and the benzene evaporated under reduced pressure. After recrystallization of the residue from ethanol-water 40.8 g. (69.9% yield) of a yellow, powdery acid was obtained, m.p. 236-238°. lit. (37) 230-231°. The infrared spectrum (double mull) (spectrum #3732) contains a broad band at 3350 cm.$^{-1}$ in the OH region and a sharp band at 1735 cm.$^{-1}$ in the carbonyl region.

Anal. Calcd. for $C_{14}H_6I_4O_3$: C, 23.04; H, 0.83; I, 69.55
Found : C, 23.26; H, 0.97; I, 69.24

Preparation of 3-Nitrophthalic Anhydride. (38) To 211 g. (1 mole) of 3-nitrophthalic acid in a 500-ml. round-bottomed flask fitted with a reflux condenser was added 205 g. (190 ml., 2 moles) of acetic anhydride. The mixture was heated to gentle boiling until the acid was completely dissolved and then for about ten minutes longer. The hot mixture was poured into a porcelain evaporating dish and allowed to cool. The crystalline mass was ground thoroughly in a mortar and removed by suction filtration. The crystals were returned to the mortar and ground with 150 ml. of dry ether and again removed by suction filtration. They were again returned to the mortar, washed with dry ether, and collected. The crystals (156.8 g., 81.2%) were allowed to stand overnight to dry, m.p. 162-165°, lit. (38) 163-164°.

Preparation of 3-Nitro-2-benzoylbenzoic and 6-Nitro-2-benzoylbenzoic Acids. (39,40). In a 1-l., three-necked, round-bottomed flask fitted with a mechanical stirrer, a reflux condenser with a calcium chloride tube, and an addition funnel the Grignard reagent was prepared from 6.3 g. (0.26 g. atom) of magnesium, 40.8 g. (0.26 mole) of bromobenzene, and 350 ml. of dry ether as solvent. The cadmium reagent was prepared by the addition of anhydrous cadmium chloride (47.7 g., 0.26 mole) over a period of ten minutes. When a Michler's ketone test showed the absence of Grignard reagent after fifteen minutes, solid 3-nitrophthalic anhydride (50.0 g., 0.26 mole) was added over a period of fifteen minutes with stirring. The contents of the flask were heated under gentle reflux for six and one-half hours without stirring because the reaction mixture solidified. The flask was cooled in an ice bath, and dilute sulfuric acid (31.4 g., 0.32 mole, in 150 ml. of water) was added. The solution was filtered and 23.6 g. of a mixture of 3-nitrophthalic anhydride and 3-nitrophthalic acid was obtained, m.p. 120-218°. The ether layer was separated from the water layer and combined with ether washings of the water layer. The combined ether layer was washed with a potassium carbonate solution (26.7 g., 0.20 mole, in 250 ml. of water). The potassium carbonate solution was acidified with a 10% solution of hydrochloric acid. A brown solid (20.5 g.) consisting of a mixture of the two keto-acids separated and was removed by filtration. Separation was accomplished by crystallization from chloroform in which 3-nitro-2-benzoylbenzoic acid was the less soluble. The chloroform soluble 6-nitro-2-benzoylbenzoic acid (11.3 g., 16.0%) was purified by being dissolved in a 10% potassium carbonate solution and the potassium carbonate solution slowly acidified with a 10% solution of hydrochloric acid over a period of two days, m.p. 156-160°, lit. (39,40), 159-160°. The infrared spectrum (double mull) (spectrum #4524) contains a small broad band at 2800 cm.$^{-1}$ and two bands at 1715 and 1675 cm.$^{-1}$ in the carbonyl region. The chloroform insoluble 3-nitro-2-benzoylbenzoic acid (9.1 g., 12.9%) was similarly purified, m.p. 231-235°, lit. (39) 237°. The infrared spectrum (double mull) (spectrum #4524) contains a small broad band at 2900 cm.$^{-1}$ and two bands at 1710 and 1690 cm.$^{-1}$ in the carbonyl region. The above reaction was repeated with the following modification. In the 1-l. flask were placed 6.3 g. (0.26 g. atom) of magnesium and 47.7 g. (0.26 mole) of anhydrous cadmium chloride suspended in 250 ml. of dry ether. To this mixture was added a solution of 40.8 g. (0.26 mole) of bromobenzene in 100 ml. of ether. When the reaction subsided, a Michler's ketone test was applied and was found to be negative. To this was added 50.0 g. (0.26 mole) of 3-nitrophthalic anhydride over a period of one hour. The contents of the flask were heated for six and one-half hours under gentle reflux, with stirring. At this point the procedure was exactly the same as before. A mixture of 3-nitrophthalic anhydride and 3-nitrophthalic acid (22.0 g.) was obtained as previously. Also, a mixture of keto-acids was obtained (17.0 g.): 11.7 g. (16.6%) of 6-nitro-2-benzoylbenzoic acid, m.p. 155-160° and 5.3 g. (7.5%) of 3-nitro-2-benzoylbenzoic acid, m.p. 230-235°.

Preparation of β-Benzoylpropionic Acid. (35) In a 1-l., three-necked, round-bottomed flask fitted with a mechanical stirrer, a reflux condenser connected to a gas absorption trap, and an addition funnel were placed 34.0 g. (0.34 mole) of succinic anhydride and 175.0 g. (2.25 moles) of dry benzene. The stirrer was started, and 100.0 g. (0.75 mole) of powdered anhydrous aluminum chloride was added all at once. Hydrogen chloride was evolved and the mixture became hot.

It was heated under reflux with continued stirring, for half an hour. The flask was then surrounded by cold water, and 150 ml. of water was slowly added from a dropping funnel inserted in the top of the condenser. After addition of water to the aluminum chloride complex 50 ml. of concentrated hydrochloric acid was added. The benzene layer was separated from the aqueous layer, washed again with water, and evaporated under reduced pressure. The residual yellow solid, m.p. 110-115°., was removed by filtration and washed with a cold mixture of 50 ml. of concentrated hydrochloric acid and 150 ml. of water, and then with 200 ml. of cold water. The crude acid was dissolved in a solution of 75.0 g. of anhydrous sodium carbonate in 500 ml. of water by boiling for fifteen minutes. The solution was filtered by suction and the small amount of aluminum hydroxide washed twice with 50 ml. portions of hot water. Four grams of charcoal was added to the hot filtrate; the solution was stirred for three to four minutes and then filtered with suction. The filtrate was transferred to a 2-l. beaker, cooled to 50-60°, and carefully acidified with 130 ml. of concentrated hydrochloric acid. After cooling to 0° in an ice-salt bath the acid was collected, washed well with water, and allowed to dry overnight at room temperature. The yield of acid amounted to 55.5 g. (91.6%), m.p. 113-114°.

<u>Preparation of γ-Phenylbutyric Acid. (41)</u> Amalgamated zinc was prepared by shaking for five minutes a mixture of 240.0 g. of mossy zinc, 24.0 g. of mercuric chloride, 400 ml. of

water, and 12 ml. of concentrated hydrochloric acid contained in 2-l. round-bottomed flask. The solution was decanted and the following reagents were added, in the order named, to the zinc: 150 ml. of water, 350 ml. of concentrated hydrochloric acid, 200 ml. of toluene, and 100.0 g. (0.56 mole) of β-benzoylpropionic acid. The flask was fitted with a vertical condenser connected to a gas absorption trap, and the reaction mixture was boiled vigorously for twenty-five hours. Three 100 ml. portions of concentrated hydrochloric acid were added at approximately six-hour intervals during the reflux period. After cooling to room temperature the layers were separated. The aqueous layer was diluted with 400 ml. of water and extracted with three 150-ml. portions of ether. The toluene layer and the ether extracts were combined and dried over anhydrous calcium chloride. After the solvents were removed by distillation under reduced pressure, γ-phenylbutyric acid was distilled at 178-181°. The yield of acid was 78.7 g. (85.5%).

Preparation of Ethyl γ-Phenylbutyrate. (42) A mixture of 65.0 g. (0.36 mole) of γ-phenylbutyric acid, 165.8 g. (3.6 moles) of absolute ethanol, and 6.8 g. of concentrated sulfuric acid was heated under reflux for three hours in a 500-ml., single-necked, round-bottomed flask fitted with a reflux condenser with a calcium chloride tube. The ester was isolated by distilling 150 ml. of the alcohol under reduced pressure, diluting the residue with 200 ml. of water, separating, and extracting the aqueous layer twice with 50 ml.

portions of ether. The combined ester and ether layers were dried over anhydrous magnesium sulfate, the ether removed, and the residue distilled under diminished pressure with the use of an aspirator; the portion boiling at 140-145° was collected. Ethyl γ-phenylbutyrate was obtained in a yield of 49.4 g. (71.4%).

Preparation of 3,4-Dihydro-1,2-naphthalic Anhydride. (42)

(A) Ester Condensation. Preparation of Powdered Sodium. (43)

In a 1-l. three-necked, round-bottomed flask fitted with a reflux condenser with a calcium chloride tube and a mechanical stirrer were placed 300 ml. of dry xylene and 6.1 g. (0.26 g. atom) of clean sodium cut in small pieces. The flask was surrounded by a wax bath and heated until the sodium was melted. At this point the stirrer was started and the sodium was broken up into very small particles. The wax bath was removed, but stirring was continued until the sodium had solidified in very fine particles. The xylene was poured off and 150 ml. of absolute ether was added.

The Condensation. A solution of 12.6 g. (0.26 mole) of absolute ethanol and 50 ml. of absolute ether was added to the above flask and the mixture allowed to stand overnight to complete the reaction. A solution of 57.0 g. (0.39 mole) of ethyl oxalate in 50 ml. of ether was added in portions to the suspension of sodium ethoxide. After the spontaneous reaction subsided, the pale yellow solution was allowed to stand for one-half hour, and 50.0 g. (0.26 mole) of ethyl γ-phenylbutyrate, diluted with 50 ml. of absolute ether, was added. The mixture was allowed to reflux gently with stirring for twenty-four hours. The deep red solution was cooled in an ice bath and neutralized by the addition, with shaking, of an ice-cold solution of 15 ml. of concentrated sulfuric acid in 200 ml. of water. The ether layer was separated, washed with water, and dried over anhydrous sodium sulfate. This was removed by distillation under aspirator pressure. The residue was a pale yellow oil consisting of a mixture of ethyl-α-ethoxalyl-γ-phenylbutyrate and unchanged ethyl oxalate.

(B) Cyclization. The above oil was poured slowly into 500 ml. of concentrated sulfuric acid, the temperature being kept at 20-25° by cooling in an ice bath. After standing for one and one-half hours at 20-25°, the deep red solution was poured on 3 l. of ice and water. The anhydride, precipitated as a pale yellow solid, was collected and washed thoroughly with water. The crude anhydride amounted to 36.1 g. (69.4%), m.p. 101-125°, lit. (43) 125-126°.

Preparation of 1,2-Naphthalic Anhydride. (44)

In a 50 ml. Claisen distilling flask were placed 20.0 g. of the crude 3,4-dihydro-1,2-naphthalic anhydride and 3.2 g. (0.10 g. atom) of sulfur. After the flask was immersed in a Wood's metal bath previously heated to 230-235° and shaken until the globule of sulfur had dissolved, the temperature was raised to 250° for thirty minutes. The residue was distilled under aspirator pressure with a bath temperature at 260-270°, and the distillate was crystallized from 150 ml.

of benzene to which 50 ml. of ligroin (b.p. 60-80°) had been added at the boiling point. The yield was 9.6 g. (47.0%) of light yellow needles melting at 164-167°, lit. (44) 166-167°.

Preparation of 1-Benzoyl-2-naphthoic and 2-Benzoyl-1-naphthoic Acids. A 500 ml., three-necked, round-bottomed flask was fitted with an addition funnel, a mechanical stirrer, and a reflux condenser with a calcium chloride tube. The Grignard reagent was prepared from 0.97 g. (0.04 g. atom) of magnesium, 6.28 g. (0.04 mole) of bromobenzene, and 250 ml. of dry ether as solvent. The cadmium reagent was prepared by the addition of 7.33 g. (0.04 mole) of anhydrous cadmium chloride over a period of five minutes. After ten minutes a Michler's ketone test showed the absence of Grignard reagent, and solid 1,2-naphthalic anhydride (8.00 g., 0.04 mole) was added over a period of ten minutes with stirring. The contents of the flask were heated for three hours under gentle reflux, with stirring. The flask was cooled in an ice bath, and dilute sulfuric acid (31.4 g., 0.32 mole, in 150 ml. of water) was added. The solution was filtered and the ether layer separated from the water layer and combined with ether washings of the water layer. The combined ether layer was washed with a potassium carbonate solution (26.7 g., 0.20 mole, in 250 ml. of water). The potassium carbonate solution was acidified with a 10% solution of hydrochloric acid. A light yellow solid (6.60 g.) consisting of a mixture of the two ketoacids separated and was collected. Separation was accomplished by crystallization from benzene in which 1-benzoyl-2-naphthoic acid was the less soluble. The benzene soluble 2-benzoyl-1-naphthoic acid (1.4 g., 12.8%) was purified by being dissolved in a 10% solution of potassium carbonate; then the potassium carbonate solution was acidified with a 10% solution of hydrochloric acid, m.p. 139-141°, lit. (45) 141.8-142.8°. The infrared spectrum (double mull) (spectrum #6305) contains a band at 3300 cm.$^{-1}$ in the OH region and a band at 1723 cm.$^{-1}$ in the carbonyl region. The benzene insoluble 1-benzoyl-2-naphthoic acid (1.5 g., 13.6%) was similarly purified, m.p. 223-225°, lit. (45) 223.5-224.5°. The infrared spectrum (double mull) (spectrum #6305) contains a band at 3300 cm.$^{-1}$ in the OH region and two bands at 1725 and 1675 cm.$^{-1}$ in the carbonyl region.

Preparation of *o*-Acetylbenzoic Acid. (2) A 500-ml., three-necked, round-bottomed flask was fitted with an addition funnel, a reflux condenser with a calcium chloride tube, and a mechanical stirrer. In the apparatus the Grignard reagent was prepared from 3.4 g. (0.14 g. atom) of magnesium, 19.8 g. (0.14 mole) of methyl iodide, and 250 ml. of dry ether as solvent. The cadmium reagent was prepared by the addition of 25.6 g. (0.14 mole) of anhydrous cadmium chloride during twelve minutes. When a Michler's ketone test showed the absence of Grignard reagent after three minutes, solid phthalic anhydride (20.0 g., 0.14 mole) was added over a period of ten minutes. The contents of the flask were heated for five hours under gentle reflux, with stirring. The flask was cooled in an ice bath, and a 10% solution of sulfuric acid was added. The solution was filtered and the ether layer separated and combined with ether washings of the water layer. The combined ether layer was washed with 10% potassium carbonate. The potassium carbonate solution was acidified with 10% hydrochloric acid with no separation of any solid. This acidic solution was extracted twice with ether and once with chloroform. The combined ether-chloroform solution was washed with 10% potassium carbonate, acidified with 10% hydrochloric acid, and the resulting solution refrigerated. A pink solid (10.9 g.) separated and was removed by filtration. The solid was redissolved in 10% potassium carbonate and some norite added. The solution was filtered, acidified with 10% hydrochloric acid, and refrigerated to yield 3.0 g. (12.9%) of <u>o</u>-acetylbenzoic acid, m.p. 114-117°, lit. (2) 114-115°. The n.m.r. spectrum (chloroform) (spectrum #259) contains an unsplit methyl peak at $\tau 8.02$ (-C$\underline{H}_3$). The infrared spectrum (double mull) (spectrum #629) contains a band at 3260 cm.$^{-1}$ in the OH region and a band at 1725 cm.$^{-1}$ in the carbonyl region. Evaporation of the original ether solution yielded 2.3 g. of light brown solid. Upon recrystallization from cyclohexane 1.5 g. (6.6%) of 3,3-dimethylphthalide was obtained, m.p. 67-69°, lit. (2) 69-70°. The n.m.r. spectrum (chloroform) (spectrum #316) contains an unsplit methyl peak at $\tau 8.35$ (-C$\underline{H}_3$).

Preparation of 3,4,5,6-Tetrachloro-2-acetylbenzoic Acid.

A 500-ml., three-necked, round-bottomed flask was fitted with an addition funnel, a reflux condenser with a calcium chloride tube, and a mechanical stirrer. In this apparatus the Grignard reagent was prepared from 3.4 g. (0.14 g. atom) of magnesium, 19.8 g. (0.14 mole) of methyl iodide, and 250 ml. of dry ether as solvent. The cadmium reagent was prepared by the addition of 25.6 g. (0.14 mole) of anhydrous cadmium chloride during ten minutes. When a Michler's ketone test showed the absence of Grignard reagent after five minutes, solid tetrachlorophthalic anhydride (40.0 g., 0.14 mole) was added over a period of twenty-five minutes. The contents of the flask were heated for five and one-half hours under gentle reflux, with stirring. The flask was cooled in an ice bath, and a 10% solution of sulfuric acid was added. The solution was filtered and the ether layer separated and combined with ether washings of the water layer. The combined ether layer was washed with 10% potassium carbonate. The potassium carbonate solution was acidified with 10% hydrochloric acid. A white solid separated and was collected. Upon recrystallization from dioxane-water 19.1 g. (49.9%) of 3,4,5,6-tetrachloro-2-acetylbenzoic acid was obtained, m.p. 184-186°. The n.m.r. spectrum (chloroform) (spectrum #266) contains a single methyl peak at τ 7.97 (-$\underline{\text{CH}}_3$). The infrared spectrum (double mull) (spectrum #574) contains bands at 3180 cm.$^{-1}$ in the OH region and 1755 cm.$^{-1}$ in the carbonyl region.

Anal. Calcd. for $C_9H_4Cl_4O_3$: C, 35.80; H, 1.34; Cl, 46.95
Found: C, 36.01; H, 1.43; Cl, 46.92

The combined ether solution was left to dry over anhydrous calcium chloride overnight and was then evaporated under reduced pressure to yield a white solid. After recrystallization from isopropyl alcohol 0.6 g. (1.4%) of 4,5,6,7-tetrachloro-3,3-dimethylphthalide was obtained, m.p. 163-165°. The infrared spectrum (double mull) (spectrum #575) contains a band at 1775 cm.$^{-1}$ which indicates the presence of a lactone carbonyl. The n.m.r. spectrum (chloroform) (spectrum #317) contains a single methyl peak at τ8.18 (-C$\underline{H}_3$).

Anal Calcd. for $C_{10}H_6Cl_4O_2$: C, 40.03; H, 1.51; Cl, 47.29
Found: C, 40.15; H, 1.87; Cl, 47.33

Preparation of 3-Nitro-2-acetylbenzoic Acid. (46) A 500-ml., three-necked, round-bottomed flask was fitted with a reflux condenser with a calcium chloride tube, an addition funnel, and a mechanical stirrer. The Grignard reagent was prepared from 4.8 g. (0.20 g. atom) of magnesium, 28.3 g. (0.20 mole) of methyl iodide, and 250 ml. of dry ether as solvent. The cadmium reagent was prepared by the addition of anhydrous cadmium chloride (36.7 g., 0.20 mole) during fifteen minutes. When a Michler's ketone test showed the absence of Grignard reagent after five minutes, solid 3-nitrophthalic anhydride (40.0 g., 0.20 mole) was added over a period of fifty minutes with stirring. The contents of the flask were heated for five and one-half hours under gentle reflux, with stirring. The flask was cooled in an ice bath, and dilute sulfuric acid (31.4 g., 0.32 mole, in 150 ml. of water) was added. The solution was filtered and 8.7 g. of a mixture of 3-nitrophthalic anhydride and 3-nitrophthalic acid was obtained, m.p. 119-217°. The ether layer was separated from the water layer and combined with ether washings of the water layer. The combined ether layer was washed with a potassium carbonate solution (26.7 g., 0.20 mole, in 250 ml. of water). The potassium carbonate solution was acidified with a 10% solution of hydrochloric acid. A solid (14.2 g.) separated and was removed by filtration. The solid was redissolved in the potassium carbonate solution and some norite added. The solution was filtered and acidified with 10% hydrochloric acid to yield 6.0 g. (14.3%) of 3-nitro-2-acetylbenzoic acid, m.p. 159-161°, lit. (46) 159-160°. The infrared spectrum (double mull) (spectrum #628) contains a broad band at 3100-2800 $cm.^{-1}$ in the OH region and two bands at 1710 and 1690 $cm.^{-1}$ in the carbonyl region. The n.m.r. spectrum (chloroform) (spectrum #298) contains an unsplit methyl peak at 7.67 ($-C\underline{H}_3$). Upon evaporation of the ether layer 0.1 g. of an oily film was obtained. The presence of a band at 1763 $cm.^{-1}$ in the infrared spectrum (smear) (spectrum #639) indicates a trace of 4-nitro-3,3-dimethylphthalide (39).

<u>Preparation of 3-Methylphthalic Anhydride. (47)</u> In a 1-l. Erlenmeyer flask was placed 65.7 g. (0.67 mole) of maleic anhydride in 360 ml. of dry benzene. To this 34.0 g.

(0.49 mole) of piperylene was added slowly with cooling (below 10°). After the contents of the flask were refrigerated for twenty days, the benzene was removed under reduced pressure and the remaining yellow liquid separated by distillation at 10 mm. into 29.8 g. of a forerun, b.p. 95-135°, consisting mostly of maleic anhydride. The liquid remaining in the distilling flask solidified to give 54.1 g. (66.4%) of 3-methyl-1,2,3,6-tetrahydrophthalic anhydride, m.p. 57-62°, lit. (47) 59-62°. To a solution of this anhydride (54.1 g., 0.32 mole) in 100 ml. of glacial acetic acid just below the boiling point in a 1-1,, single-necked, round-bottomed flask was added dropwise a solution of 124.0 g. of bromine in 110 ml. of acetic acid during one hour. The first third of the bromine solution was decolorized immediately and some hydrogen bromide was evolved. The flask was fitted with a reflux condenser and the contents of the flask allowed to reflux for sixteen hours. The solution was then concentrated under reduced pressure, and the residue heated at 210° in a wax bath for twelve hours. Much hydrogen bromide was evolved and the material became quite dark. On distillation at 0.15 mm., there was obtained a colorless liquid, b.p. 140° (wax bath temperature, 185°), which immediately crystallized. Crystallization from benzene-petroleum ether yielded 38.2 g. (73.7%) of 3-methylphthalic anhydride, m.p. 115-117°, lit. (47) 114.5-117°.

Action of Methylmagnesium Iodide on 3-Methylphthalic Anhydride. A 500-ml., three-necked, round-bottomed flask was fitted with a reflux condenser with a calcium chloride tube, a mechanical stirrer, and an addition funnel. The Grignard reagent was prepared from 3.6 g. (0.15 g. atom) of magnesium, 21.3 g. (0.15 mole) of methyl iodide, and 150 ml. of dry ether as solvent. A stream of nitrogen was used to force the Grignard reagent into a 250 ml. separatory funnel. This was then added to a solution of 25.0 g. (0.15 mole) of 3-methylphthalic anhydride in 150 ml. of dry ether over a period of three hours. The contents of the flask were heated for eight hours under gentle reflux, with stirring. The flask was cooled in an ice bath, and 20% sulfuric acid was added. The solution was filtered and the ether layer separated and combined with ether washings of the water layer. The combined ether layer was washed with 10% potassium carbonate. The potassium carbonate solution was acidified with 10% hydrochloric acid. An orange oil separated which failed to crystallize. The combined oil and aqueous mixture were extracted with ether. The ether was evaporated with the recovery of the orange oil. The oil was dissolved in benzene and a small amount of pentane added. The resulting solution was refrigerated and subsequently a white solid separated overnight. The infrared spectrum (double mull) (spectrum #693), containing broad bands at 3350 cm.$^{-1}$ and 1750 cm.$^{-1}$ is indicative of a lactol. Upon recrystallization from benzene-pentane a white solid (5.2 g., 1.9%) was obtained again, m.p.

122-124°. The n.m.r. spectrum (chloroform) (spectrum #343) contains two unsplit methyl peaks at τ7.44 (Ar-C$\underline{H}_3$) and τ8.17 (-C$\underline{H}_3$). The acid is assumed to be 6-methyl-2-acetylbenzoic acid. There also remained 6.9 g. of the orange oil after the filtrate obtained from the above recrystallization was concentrated.

Anal. Calcd. for $C_{10}H_{10}O_3$: C, 67.39; H, 5.66
Found: C, 67.47; H, 5.62

Preparation of 3,4,5,6-Tetrachloro-2-propionylbenzoic Acid. A 1-l., three-necked, round-bottomed flask was fitted with an addition funnel, a reflux condenser with a calcium chloride tube, and a mechanical stirrer. In this apparatus the Grignard reagent was prepared from 4.2 g. (0.17 g. atom) of magnesium, 18.9 g. (0.17 mole) of ethyl bromide, and 250 ml. of dry ether as solvent. The cadmium reagent was prepared by the addition of 31.9 g. (0.17 mole) of anhydrous cadmium chloride during ten minutes. When a Michler's ketone test showed the absence of Grignard reagent after ten minutes, solid tetrachlorophthalic anhydride (50.0 g., 0.17 mole) was added over a period of ten minutes with stirring. The contents of the flask were heated for three hours under gentle reflux, with stirring. The flask was cooled in an ice bath, and dilute sulfuric acid (31.4 g., 0.32 mole, in 150 ml. of water) was added. The solution was filtered and the ether layer separated and combined with ether washings of the water layer. The combined ether layer was washed with a dilute potassium carbonate solution (26.7 g., 0.20 mole, in 250 ml. of water). The potassium carbonate solution was acidified with a 10%

solution of hydrochloric acid. A white solid separated and was removed by filtration. Upon recrystallization from ethanol-water 28.5 g. (51.8%) of 3,4,5,6-tetrachloro-2-propionylbenzoic acid was obtained, m.p. 174-177°. The infrared spectrum (double mull) (spectrum #4549) contains a band at 3520 cm.$^{-1}$ in the OH region and a band at 1773 cm.$^{-1}$ in the carbonyl region with a shoulder at 1755 cm.$^{-1}$.

Anal. Calcd. for $C_{10}H_6Cl_4O_3$: C, 38.02; H, 1.92; Cl, 44.91
Found: C, 38.25; H, 2.01; Cl, 44.68

Action of Phenylcadmium Reagent on o-Benzoylbenzoic Acid.

The procedure employed was modeled after that which de Benneville (33) used for the preparation of o-acetylbenzoic acid. A 1-l., three-necked, round-bottomed flask was fitted with a mechanical stirrer, a reflux condenser with a calcium chloride tube, and an addition funnel. The Grignard reagent was prepared from 6.8 g. of magnesium (0.28 g. atom), 43.9 g. of bromobenzene (0.28 mole), and 300 ml. of dry ether as solvent. The cadmium reagent was prepared by the addition of 51.3 g. of anhydrous cadmium chloride (0.28 mole) during fifteen minutes. When a Michler's ketone test showed the absence of Grignard reagent after fifteen minutes, the mixture was stirred an additional ten minutes. Solid o-benzoylbenzoic acid (14.0 g., 0.06 mole) in 100 ml. of dry ether was added slowly over a period of fifteen minutes with stirring. The contents of the flask were heated for eight hours under gentle reflux, with stirring. The flask was cooled in an ice bath, and dilute sulfuric acid (31.3 g., 0.32 mole, in

150 ml. of water) was added. The solution was filtered and the ether layer separated and combined with ether washings of the water layer. The combined ether layer was carefully washed with a 10% potassium carbonate solution. The potassium carbonate solution was acidified with 10% sulfuric acid in order to precipitate any unchanged ketoacid. The _o_-benzoylbenzoic acid (13.7 g., 97.8% recovery) was crystallized from benzene and dried in a round-bottomed flask over a steam bath, m.p. 125-127°. A trace of a yellow oil was obtained upon evaporation of the ether layer and it was found to contain some biphenyl by a comparison to a spectrum of authentic sample. The presence in the infrared spectrum (chloroform) (spectrum #3680) of a broad band at 1750 cm.$^{-1}$ indicates a trace of 3,3-diphenylphthalide.

Preparation of 3,3-Diphenylphthalide. (49) A 1-l., three-necked, round-bottomed flask was fitted with a mechanical stirrer, a reflux condenser with a calcium chloride tube, and an addition funnel. The Grignard reagent was prepared in this apparatus from 13.0 g. of magnesium (0.53 g. atom), 85.0 g. of bromobenzene (0.55 mole), and 250 ml. of dry ether as solvent. The mixture was cooled in an ice bath, and powdered phthalic anhydride (37.0 g., 0.25 mole) was added with stirring over a period of thirty minutes. The mixture was allowed to warm to room temperature while being stirred for one-half hour; then 30 ml. of dry benzene was added and stirring continued for another hour.. The reaction mixture was decomposed with a solution of ammonium chloride (50.0 g., 0.95 mole, in 150 ml. of water). The yellow mixture was clarified by the addition of dilute hydrochloric acid. The ether layer was evaporated under reduced pressure to a reddish-brown oil and washed with a 10% potassium carbonate solution. The potassium carbonate solution was washed with ether and the washings combined with the oil. The ethereal solution was evaporated under reduced pressure and the crystals which formed were collected on a filter. After recrystallization from ethanol-water 6.4 g. (8.9%) of 3,3-diphenylphthalide was obtained, m.p. 113-114°, lit. (49) m.p. 114-115°. The infrared spectrum (halocarbon) (spectrum #3668) contains a lactone carbonyl band at 1663 cm.$^{-1}$.

Action of Ethylcadmium Reagent on *o*-Benzoylbenzoic Acid.

A 500-ml., three-necked, round-bottomed flask was fitted with a mechanical stirrer, a reflux condenser with a calcium chloride tube, and an addition funnel. The Grignard reagent was prepared from 6.4 g. (0.26 g. atom) of magnesium, 28.8 g. (0.26 mole) of ethyl bromide, and 200 ml. of dry ether as solvent. The cadmium reagent was prepared by the addition of 48.4 g. (0.26 mole) of anhydrous cadmium chloride during ten minutes. When a Michler's ketone test showed the absence of Grignard reagent after ten minutes, anhydrous *o*-benzoylbenzoic acid (10.0 g., 0.04 mole) in 50 ml. of dry ether was added slowly over a period of thirty minutes.

The contents of the flask were heated for eight hours under gentle reflux, with stirring. The flask was cooled in an ice bath, and dilute sulfuric acid (31.4 g., 0.32 mole, in 150 ml. of water) was added. The solution was filtered and the ether layer separated and combined with ether washings of the water layer. The combined ether layer was washed with a potassium carbonate solution (26.7 g., 0.20 mole, in 250 ml. in water). Upon acidification of the potassium carbonate solution with a 10% solution of hydrochloric acid a white solid separated and was collected. The o-benzoylbenzoic acid (7.1 g., 71% recovery) was crystallized from benzene and dried in a round-bottomed flask over a steam bath, m.p. 125-127°. A trace of a light yellow oil was obtained upon evaporation of the ether layer. The presence in the infrared spectrum (smear) (spectrum #3907) of a broad band at 1750 cm.$^{-1}$ indicates a trace of 3-ethyl-3-phenylphthalide (39). When the above reaction was repeated with a reflux time of ten hours, the amount of acid recovered was 8.2 g. (82%), m.p. 125-127°. The oil obtained from the ether layer also has a broad band at 1750 cm.$^{-1}$ in the infrared spectrum (smear) (spectrum #3907). The reaction was carried out a third time with the following slight change in the procedure. After o-benzoylbenzoic acid in ether solution was added to the reaction mixture, the contents of the flask were allowed to reach room temperature. When this was done, 160 ml. of dry benzene was added. At this point the procedure followed was the same as that of the previous runs. The yield of anhydrous acid was 5.1 g. (51%), m.p. 126-127°. A small amount of yellow oil (0.3 g.) was obtained from evaporation of the ether-benzene solution. The infrared spectrum (smear) (spectrum #3996) contains a medium band at 1750 cm.$^{-1}$.

Attempted Preparation of 3-Ethyl-3-phenylphthalide. (39)

In a 500-ml., three-necked, round-bottomed flask fitted with a mechanical stirrer, a reflux condenser with a calcium chloride tube and an addition funnel the Grignard reagent was prepared from 1.4 g. (0.057 g. atom) of magnesium, 6.2 g. (0.057 mole) of ethyl bromide, and 200 ml. of dry ether as solvent. After the Grignard reagent was formed, o-benzoylbenzoic acid (6.0 g., 0.026 mole) in 50 ml. of dry ether was added over a period of twenty minutes. The contents of the flask were heated for five and one-half hours under gentle reflux, with stirring. The flask was cooled in an ice bath, and a 10% solution of sulfuric acid was added. The solution was filtered and the ether layer separated and combined with ether washings of the water layer. The combined ether layer was washed with a 10% solution of potassium carbonate. The potassium carbonate solution was acidified with a 10% solution of hydrochloric acid. A light yellow oil (0.9 g.) was obtained and the infrared spectrum (smear) (spectrum #4765) contains a band at 1757 cm.$^{-1}$. After evaporation of the ether solution a yellow oil (0.8 g.) was also obtained. The infrared spectrum (smear) (spectrum #4764) contains a band at 1757 cm.$^{-1}$. The oils failed to crystallize, and these two similar spectra indicate the presence of 3-ethyl-3-phenylphthalide.

Action of Phenylcadmium Reagent on 3,4,5,6-Tetrachloro-2-benzoylbenzoic Acid. A 1-l., three-necked, round-bottomed flask was fitted with a mechanical stirrer, a reflux condenser with a calcium chloride tube, and an addition funnel. The Grignard reagent was prepared in this apparatus from 6.8 g. (0.28 g. atom) of magnesium, 43.9 g. (0.28 mole) of bromobenzene, and 300 ml. of dry ether as solvent. The cadmium reagent was prepared by the addition of 51.3 g. (0.28 mole) of anhydrous cadmium chloride during fifteen minutes. When a Michler's ketone test showed the absence of Grignard reagent after ten minutes, solid 3,4,5,6-tetrachloro-2-benzoylbenzoic acid (21.8 g., 0.06 mole) was added slowly over a period of thirty minutes. The contents of the flask were heated for eight hours under gentle reflux, with stirring. The flask was cooled in an ice bath, and dilute sulfuric acid (31.4 g., 0.32 mole , in 150 ml. of water) was added. The solution was filtered and the ether layer separated and combined with ether washings of the water layer. The combined ether layer was washed with a potassium carbonate solution (26.7 g., 0.20 mole, in 250 ml. of water). The potassium carbonate solution was acidified with a 10% solution of hydrochloric acid. A white solid separated and was removed by filtration. After recrystallization from ethanol-water unchanged 3,4,5,6-tetrachloro-2-benzoylbenzoic acid (15.9 g., 72.9% recovery) was obtained, m.p. 191-193°. A trace of yellow oil was obtained from evaporation of the ether solution and it was found to contain some biphenyl by comparison to an infrared spectrum of authentic sample. Also, the presence in the infrared spectrum (halocarbon) (spectrum #3716) of a band at 1740 cm.$^{-1}$ indicates the presence of a trace of 4,5,6,7-tetrachloro-3,3-diphenylphthalide (50). The above reaction was repeated with a reflux time of sixteen hours. The amount of acid recovered was 14.8 g. (76.8%), m.p. 191-193°. As before, a trace of a yellow oil was obtained from evaporation of the ether solution. The infrared spectrum (smear) (spectrum #3856) contains a band at 1735 cm.$^{-1}$.

Action of Phenylmagnesium Bromide on 3,4,5,6-Tetrachloro-2-benzoylbenzoic Acid. A 500-ml., three-necked, round-bottomed flask was fitted with a mechanical stirrer, a reflux condenser with a calcium chloride tube, and an addition funnel. The Grignard reagent was prepared from 3.9 g. (0.16 g. atom) of magnesium, 25.1 g. (0.16 mole) of bromobenzene, and 150 ml. of dry ether as solvent. The flask was cooled in an ice bath, and powdered 3,4,5,6-tetrachloro-2-benzoylbenzoic acid (14.6 g., 0.04 mole) was added with stirring over a period of thirty minutes. The reaction mixture was cooled in an ice bath and 100 ml. of dry benzene was added. The contents of the flask were then heated under gentle reflux for eight hours, with stirring. The flask was cooled in an ice bath, and a 10% solution of sulfuric acid was added. The solution was filtered and the ether layer separated and combined with ether washings of the water layer. The combined ether layer was washed with a 10% solution of potassium carbonate. A trace of dark red oil was obtained from evaporation of the ether-benzene solution. The infrared spectrum (smear) (spectrum #3885) contains a medium band at 1660 cm.$^{-1}$ and no evidence of a lactone carbonyl as would be expected had 4,5,6,7-tetrachloro-3,3-diphenylphthalide (50) been formed.

Attempted Preparation of 4,5,6,7-Tetrachloro-3,3-diphenylphthalide. A 1-l., three-necked, round-bottomed flask was fitted with a mechanical stirrer, a reflux condenser with a calcium chloride tube, and an addition funnel. In this apparatus the Grignard reagent was prepared from 13.0 g. (0.53 g. atom) of magnesium, 85.0 g. (0.55 mole) of bromobenzene, and 250 ml. of dry ether as solvent. The mixture was cooled in an ice bath, and powdered tetrachlorophthalic anhydride (71.5 g., 0.25 mole) was added with stirring over a period of thirty minutes. The contents of the flask were heated under gentle reflux for two hours, with stirring. The flask was cooled in an ice bath, and a 10% solution of hydrochloric acid was added. The solution was filtered and the ether layer separated and combined with ether washings of the water layer. The combined ether layer was washed with a 10% solution of potassium carbonate. The ethereal solution was evaporated under reduced pressure and a light yellow solid (14.5 g.) was obtained, m.p. 150-155°. The infrared spectrum (double mull) (spectrum #3777) contains two narrow bands at 1670 and 1655 cm.$^{-1}$ with no evidence of a lactone carbonyl. Further identification of the solid was not attempted.

Action of Ethylcadmium Reagent on 3,4,5,6-Tetrachloro-2-benzoylbenzoic Acid. In a 1-l., three-necked, round-bottomed flask fitted with a mechanical stirrer, a reflux condenser with a calcium chloride tube, and an addition funnel the Grignard reagent was prepared from 6.4 g. (0.26 g. atom) of magnesium, 28.8 g. (0.26 mole) of ethyl bromide, and 300 ml. of dry ether as solvent. The cadmium reagent was prepared by the addition of anhydrous cadmium chloride (48.4 g., 0.26 mole) during fifteen minutes. When a Michler's ketone test showed the absence of Grignard reagent after ten minutes, solid 3,4,5,6-tetrachloro-2-benzoylbenzoic acid (12.0 g., 0.03 mole) was added slowly over a period of twenty minutes. The contents of the flask were allowed to reach room temperature and then 150 ml. of dry benzene was added to the reaction mixture. Finally, the contents of the flask were heated for nine hours under gentle reflux, with stirring. The flask was cooled in an ice bath, and dilute sulfuric acid (31.4 g., 0.32 mole, in 150 ml. of water) was added. The solution was filtered and the ether layer separated and combined with ether washings of the water layer. The combined ether solution was washed with a potassium carbonate solution (26.7 g., 0.20 mole, in 250 ml. of water). The potassium carbonate solution was acidified with 10% hydrochloric acid. Unchanged 3,4,5,6-tetrachloro-

2-benzoylbenzoic acid was obtained (8.5 g., 70.8%) after recrystallization from ethanol-water, m.p. 191-193°. A yellow oil (0.2 g.) remained upon evaporation of the ether-benzene solution. The infrared spectrum (smear) (spectrum #3934) contains a band at 1775 cm.$^{-1}$ which would indicate some 3-ethyl-3-phenyl-4,5,6,7-tetrachlorophthalide present. The reaction was repeated with a reflux time of ten and one-half hours. As before, 8.5 g. of recovered acid was obtained. Again, a yellow oil (0.2 g.) was obtained after the ether-benzene solution was evaporated. The infrared spectrum (smear) (spectrum #4035) contains a band at 1775 cm.$^{-1}$ as was the case previously.

Action of Ethylcadmium Reagent on 3,4,5,6-Tetraiodo-2-benzoylbenzoic Acid. A 1-l., three-necked, round-bottomed flask was fitted with a reflux condenser with a calcium chloride tube, an addition funnel, and a mechanical stirrer. The Grignard reagent was prepared from 6.4 g. (0.26 g. atom) of magnesium, 28.8 g. (0.26 mole) of ethyl bromide, and 300 ml. of dry ether as solvent. The cadmium reagent was prepared by the addition of 48.4 g. (0.26 mole) of anhydrous cadmium chloride during ten minutes. When a Michler's ketone test showed the absence of Grignard reagent after fifteen minutes, solid 3,4,5,6-tetraiodo-2-benzoylbenzoic acid (18.9 g., 0.03 mole) was added over a period of fifteen minutes with stirring. The flask was cooled in an ice bath, and 150 ml. of dry benzene was added. The contents of the flask were then heated for eight hours under reflux, with stirring. The flask was again cooled in an ice bath, and dilute sulfuric acid (31.4 g., 0.32 mole, in 150 ml. of water) was added. The solution was filtered and the ether-benzene layer separated and combined with ether washings of the water layer. The combined ether-benzene layer was washed with a solution of potassium carbonate (26.7 g., 0.20 mole, in 250 ml. of water). The potassium carbonate solution was acidified with a 10% solution of hydrochloric acid, and the resulting yellow solid (2.6 g.) was collected, m.p. 99-109°. This unidentified acid was not the same as the starting acid and the infrared spectrum (double mull) (spectrum #3977) contains a broad band at 3530-3160 cm.$^{-1}$ in the OH region and a band at 1735 cm.$^{-1}$ in the carbonyl region. Upon evaporation of the ether-benzene solution a yellow oil (0.5 g.) was obtained. The presence in the infrared spectrum (smear) (spectrum #3977) of a band at 1750 cm.$^{-1}$ indicates some 4,5,6,7-tetraiodo-3-ethyl-3-phenylphthalide. When the above procedure was repeated and the reaction mixture allowed to reflux for ten and one-half hours, the same results were obtained.

<u>Action of Ethylcadmium Reagent on 2-Benzoyl-1-naphthoic Acid.</u> A 250-ml., three-necked, round-bottomed flask was fitted with a mechanical stirrer, a reflux condenser with a calcium chloride tube, and an addition funnel. The Grignard reagent was prepared from 0.7 g. (0.028 g. atom) of magnesium, 3.1 g. (0.028 mole) of ethyl bromide, and 175 ml. of dry ether as solvent. The cadmium reagent was prepared by the

addition of 5.3 g. (0.028 mole) of anhydrous cadmium chloride during five minutes. When a Michler's ketone test showed the absence of Grignard reagent after five minutes, solid 2-benzoyl-1-naphthoic acid (1.0 g., 0.004 mole) was added over a period of five minutes. The contents of the flask were heated for eight hours under gentle reflux, with stirring. The flask was cooled in an ice bath, and a 10% solution of sulfuric acid was added. The solution was filtered and the ether layer separated and combined with ether washings of the water layer. The combined ether layer was washed with a 10% solution of potassium carbonate. The potassium carbonate solution was acidified with a 10% solution of hydrochloric acid. A white solid separated and was collected. Recovered 2-benzoyl-1-naphthoic acid (0.7 g., 70%) was obtained, m.p. 139-141°, lit. (45) 141.8-142.8°, and did not need further purification. Upon evaporation of the ether layer a yellow oil (0.1 g.) was obtained. The presence in the infrared spectrum (smear) (spectrum #4647) of a band at 1740 cm.$^{-1}$ indicates a trace of 2-(α-hydroxy-α-phenyl- _n_-propyl)-1-naphthoic acid lactone.

Action of Ethylcadmium Reagent on 3,4,5,6-Tetrachloro-2-propionylbenzoic Acid. A 1-l., three-necked, round-bottomed flask was fitted with a mechanical stirrer, a reflux condenser with a calcium chloride tube, and an addition funnel. The Grignard reagent was prepared from 6.2 g. (0.256 g. atom) of magnesium, 27.9 g. (0.256 mole) of ethyl bromide, and 350 ml. of dry ether as solvent. The cadmium reagent was prepared by the addition of 46.9 g. (0.256 mole) of anhydrous cadmium chloride over a period of twenty minutes. When a Michler's ketone test showed the absence of Grignard reagent after five minutes, solid 3,4,5,6-tetrachloro-2-propionylbenzoic acid (10.0 g., 0.032 mole) was added over a period of five minutes. The contents of the flask were heated for eight hours under gentle reflux, with stirring. The flask was cooled in an ice bath, and a 10% solution of sulfuric acid was added. The solution was filtered and the ether layer separated and combined with ether washings of the water layer. The combined ether layer was washed with a 10% solution of potassium carbonate. After acidification of the potassium carbonate solution with 10% hydrochloric acid a white solid separated and was removed by filtration. Upon recrystallization from ethanol-water 8.0 g. (80.0% recovery) of 3,4,5,6-tetrachloro-2-propionylbenzoic acid was obtained, m.p. 170-171°. The n.m.r. spectrum (chloroform) (spectrum #267) contains a quartet at τ 7.57 ($-C\underline{H}_2CH_3$) and a triplet at τ 9.03 ($-CH_2C\underline{H}_3$). From evaporation of the ether solution a light yellow oil (0.3 g.) was obtained. The presence in the infrared spectrum (smear) (spectrum #4820) of a band at 1740 cm.$^{-1}$ indicates the presence of 4,5,6,7-tetrachloro-3,3-diethylphthalide.

Action of Allylcadmium Reagent on 3,4,5,6-Tetrachloro-2-benzoylbenzoic Acid. *Modified Procedure* In a 500-ml., three-necked, round-bottomed flask fitted with an addition funnel, a reflux condenser with a calcium chloride tube, and a mechanical stirrer were placed 3.2 g. (0.132 g. atom) of magnesium, 24.2 g. (0.132 mole) of anhydrous cadmium chloride, and 200 ml. of dry ether as solvent. To this mixture was added a solution of 10.1 g. (0.132 mole) of allyl chloride in 50 ml. of dry ether. When the reaction subsided, a Michler's ketone test was applied and was found to be negative after three hours. To the reaction mixture was now added 6.0 g. (0.017 mole) of 3,4,5,6-tetrachloro-2-benzoylbenzoic acid over a period of twenty minutes. The contents of the flask were heated for eight hours under gentle reflux, with stirring. The flask was cooled in an ice bath, and 20% sulfuric acid was added. The solution was filtered and the ether layer separated and combined with ether washings of the water layer. From the above filtration a white solid, which had separated upon addition of the sulfuric acid, was collected and treated with acetone. The insoluble material was removed by filtration. Upon concentration of the acetone solution a white solid (3.1 g.) separated and was collected, m.p. 191-193°. The combined ether solution was washed with 10% potassium carbonate. The potassium carbonate solution was acidified with 10% hydrochloric acid. A white solid (0.3 g.) precipitated and was collected, m.p. 191-193°. The ether solution was left to dry over anhydrous calcium chloride overnight and then was evaporated under reduced pressure to yield a white solid. Upon recrystallization from ethanol 1.0 g. of the solid was obtained, m.p. 191-193°. The total amount of white solid was 4.4 g. (66.7%). This solid was found to absorb bromine after treatment with bromine in carbon tetrachloride. The infrared spectra (spectrum #329; double mull, #6047; chloroform, and #6048; double mull) contain a lactone carbonyl at 1763 cm.$^{-1}$ which indicates the solid to be 4,5,6,7-tetrachloro-3-allyl-3-phenylphthalide. The n.m.r. spectrum (chloroform) (spectrum #213) contains a multiplet (10 peaks) at τ4.46-5.10 ($CH_2-C\underline{H}=CH_2$), a multiplet (7 peaks) at τ6.09-6.70 ($-CH_2-CH=C\underline{H_2}$), and two doublets at τ8.46-8.64 and τ8.76-8.87 ($-C\underline{H_2}-CH=CH_2$).

Anal. Calcd. for $C_{17}H_{10}Cl_4O_2$: C, 52.61; H, 2.59; Cl, 36.53
Found: C, 52.57; H, 2.70; Cl, 36.61

Action of Allylcadmium Reagent on 4,5,6,7-Tetrachloro-3-allyl-3-phenylphthalide. A 250-ml., three-necked, round-bottomed flask was fitted with a mechanical stirrer, a reflux condenser with a calcium chloride tube, and an addition funnel. The Grignard reagent was prepared from 0.4 g. (0.016 g. atom) of magnesium, 1.2 g. (0.016 mole) of allyl chloride, and 125 ml. of dry ether as solvent. The cadmium reagent was prepared by the addition of 2.9 g. (0.016 mole) of anhydrous cadmium chloride during fifteen minutes. When a Michler's ketone test showed the absence of Grignard reagent after fifteen minutes, solid 4,5,6,7-tetrachloro-3-allyl-3-phenylphthalide (0.8 g., 0.002 mole) was added over a period of ten minutes. The contents of the flask were heated for eight hours under gentle reflux, with stirring. The flask was cooled in an ice bath, and 10% sulfuric acid was added. The solution was filtered and the ether layer separated and combined with ether washings of the water layer. The combined ether layer was washed with 10% potassium carbonate. Acidification of the potassium carbonate solution yielded no solid material. Upon evaporation of the ether layer a white solid (0.5 g., 62.5%) was obtained, m.p. 190-193°. This was found to be recovered starting material by comparison of its infrared spectrum (double mull) (spectrum #6165) with that of authentic sample, both containing a lactone carbonyl at 1765 cm.$^{-1}$.

Action of Acid on 4,5,6,7-Tetrachloro-3-allyl-3-phenylphthalide. A 100-ml., single-necked, round-bottomed flask was fitted with a reflux condenser with a calcium chloride tube. In this apparatus were placed 0.15 g. (0.0004 mole) of 4,5,6,7-tetrachloro-3-allyl-3-phenylphthalide, 40 ml. of dry benzene, and 10 ml. of concentrated hydrochloric acid. The contents of the flask were allowed to reflux for six hours. The flask was cooled in an ice bath, and the benzene layer separated and combined with a benzene washing of the water layer. The benzene solution was concentrated and the remaining solution cooled in an ice bath. A white solid (0.13 g.) separated and was removed by filtration. Upon recrystallization from isopropyl alcohol 0.06 g. (40%) of recovered 4,5,6,7-tetrachloro-3-allyl-

3-phenylphthalide was obtained, m.p. 189-193°. This was confirmed by a mixture melting point with an authentic sample, m.p. 189-193°. The infrared spectrum (double mull) (spectrum #6144) contains a lactone carbonyl at 1765 cm.$^{-1}$ and is identical to that of authentic sample.

Action of Base on 4,5,6,7-Tetrachloro-3-allyl-3-phenylphthalide. A 100-ml., single-necked round-bottomed flask was fitted with a reflux condenser with a calcium chloride tube. In this apparatus were placed 0.057 g. (0.00014 mole) of 4,5,6,7-tetrachloro-3-allyl-3-phenylphthalide, 40 ml. of dry benzene, and 2.5 g. of potassium hydroxide. The contents of the flask were allowed to reflux for six hours. The flask was cooled in an ice bath, and the benzene solution was washed with 10% potassium carbonate. The potassium carbonate solution was acidified with 10% hydrochloric acid with no separation of any material. Evaporation of the benzene yielded an unidentified brown oil (0.01 g.). The infrared spectrum (smear) (spectrum #6144) contains a band at 1737 cm.$^{-1}$ in the carbonyl region.

Action of Allylcadmium Reagent on 3,4,5,6-Tetrachloro-2-benzoylbenzoic Acid. A 500-ml., three-necked, round-bottomed flask was fitted with a mechanical stirrer, a reflux condenser with a calcium chloride tube, and an addition funnel. The Grignard reagent was prepared from 3.2 g. (0.132 g. atom) of magnesium, 10.1 g. (0.132 mole) of allyl chloride, and 250 ml. of dry ether as solvent. The cadmium reagent was prepared by the addition of 24.2 g. (0.132 mole) of anhydrous cadmium chloride during twenty minutes. When a Michler's ketone test showed the absence of Grignard reagent after ten minutes, solid 3,4,5,6-tetrachloro-2-benzoylbenzoic acid (6.0 g., 0.017 mole) was added over a period of fifteen minutes. The contents of the flask were heated for eight hours under gentle reflux, with stirring. The flask was cooled in an ice bath, and a 10% solution of sulfuric acid was added. The solution was filtered and the ether layer separated and combined with ether washings of the water layer. The combined ether layer was washed with 10% potassium carbonate and a white solid separated immediately. This solid (6.2 g.) was removed by filtration and recrystallized from water, m.p. 253-255°. The infrared spectrum (double mull) (spectrum #351) contains a broad band at 3350 cm.$^{-1}$ and a sharp band at 1775 cm.$^{-1}$. The potassium carbonate solution (filtrate) was acidified with 10% hydrochloric acid. A white solid (0.1 g.) separated and was collected, m.p. 165-200°. The infrared spectrum (double mull) (spectrum #352) contains sharp bands at 3380 cm.$^{-1}$ and 1775 cm.$^{-1}$. The combined ether layer was evaporated to yield a yellow oil (0.2 g.). The infrared spectrum (double mull) (spectrum #353) contains two bands at 1775 and 1740 cm.$^{-1}$ in the carbonyl region. Further identification of these substances was not attempted. The above reaction was repeated with 0.8 g. (0.034 g. atom) of magnesium, 2.6 g. (0.034 mole) of allyl chloride, and 250 ml. of dry ether as solvent. The cadmium reagent was prepared by the addition of 6.2 g. (0.034 mole) of anhydrous cadmium chloride during ten minutes. When a Michler's ketone test showed the absence of Grignard reagent after ten minutes, the acid (6.0 g., 0.017 mole) was added over a period of fifteen minutes. The contents of the flask were heated for eight hours under gentle reflux, with stirring. A white solid separated after the potassium carbonate solution was acidified with 10% hydrochloric acid. Upon recrystallization from ethanol-water 4.3 g. (71.7%) of recovered acid was obtained, m.p. 188-190°. The infrared spectrum (double mull) (spectrum #6088) was identical to that of authentic sample. From evaporation of the ether layer an unidentified yellow oil (0.3 g.) was obtained. The infrared spectrum (smear) (spectrum #6088) contains two bands at 1767 and 1735 cm.$^{-1}$.

Action of Allylcadmium Reagent on the Acid Chloride of 3,4,5,6-Tetrachloro-2-benzoylbenzoic Acid. Modified Procedure. In a 500-ml., three-necked, round-bottomed flask fitted with an addition funnel, a reflux condenser with a calcium chloride tube, and a mechanical stirrer were placed 3.2 g. (0.132 g. atom) of magnesium, 24.2 g. (0.132 mole) of anhydrous cadmium chloride, and 200 ml. of dry ether as solvent. To this mixture was added a solution of 10.1 g. (0.132 mole) of allyl chloride in 50 ml. of dry ether. When the reaction subsided after two hours, a Michler's ketone test was applied and found to be negative.

To the reaction mixture was now added 6.5 g. (0.017 mole) of the acid chloride of 3,4,5,6-tetrachloro-2-benzoylbenzoic acid (prepared by the action of 2.0 g. (0.017 mole) of thionyl chloride on 6.0 g. (0.017 mole) of 3,4,5,6-tetrachloro-2-benzoylbenzoic acid) over a period of ten minutes. The contents of the flask were heated for eight hours under gentle reflux, with stirring. The flask was cooled in an ice bath, and 20% sulfuric acid was added. The solution was filtered and the ether layer separated and combined with ether washings of the water layer. The combined ether solution was washed with 10% potassium carbonate. The potassium carbonate solution was acidified with 10% hydrochloric acid with no separation of any material. Evaporation of the ether solution yielded an orange solid. Upon four recrystallizations from isopropyl alcohol this unidentified orange solid was obtained in a yield of 4.2 g., m.p. 186-188°. The infrared spectrum (double mull) (spectrum #6167) contains a band at 1785 $cm.^{-1}$.

Fischer Esterification of o-Benzoylbenzoic Acid. (51)

A 250-ml., single-necked, round-bottomed flask was fitted with a reflux condenser and a calcium chloride tube. Anhydrous o-benzoylbenzoic acid (20.0 g., 0.088 mole) was dissolved in 125 ml. of pure, dry methanol, and the contents of the flask allowed to reflux for three hours. The reaction mixture was cooled, poured into water, and the ester isolated by ether extraction, washed with a saturated solution of sodium bicarbonate, and transferred to a small amount of dry methanol. Some of the ether was evaporated and the remaining ether-methanol solution was cooled in an ice bath. The crystals which separated were collected, washed with a small amount of ice cold methanol, and dried. Upon recrystallization from ligroin (b.p. 60-80°) the only product formed was the normal methyl ester of o-benzoylbenzoic acid (12.5 g., 59.1%), m.p. 54-56°, lit. (51) 51.0-51.8°. The n.m.r. spectrum (carbon tetrachloride) (spectrum #85) contains a single methyl peak at $\tau 6.53$ ($-OC\underline{H}_3$). The infrared spectrum (double mull) (spectrum #4646) contains two carbonyl bands at 1725 and 1673 cm.$^{-1}$.

Preparation of Normal Methyl Ester of o-Benzoylbenzoic Acid. (52,53) Solid anhydrous o-benzoylbenzoic acid (20.0 g., 0.088 mole) was dissolved in a solution of 9.3 g. of anhydrous sodium carbonate (0.088 mole) in 250 ml. of hot water. To this solution was added a hot aqueous solution of silver nitrate (14.9 g., 0.088 mole, in 100 ml. of water). The silver salt of the acid immediately separated and was removed by filtration. The salt was first washed with distilled water and then with ethanol, and finally dried in an oven at 70°. It was next placed in a 1-l., single-necked, round-bottomed flask fitted with a reflux condenser with a calcium chloride tube, and to the salt was added 500 ml. of dry benzene and 12.5 g. (0.088 mole) of methyl iodide. The contents of the flask were heated for three hours under reflux. The flask was cooled in an ice bath and the benzene solution filtered. The benzene solution was concentrated, and to the remainder was added a small amount of petroleum ether. This solution was cooled in an ice bath, resulting in the separation of a white solid which was removed by filtration. Upon recrystallization from ligroin (b.p. 60-80°) 6.9 g. (32.6%) of the normal methyl ester of o-benzoylbenzoic acid was obtained, m.p. 54-55°, lit. (51) 51.0-51.8°. In the n.m.r. spectrum (carbon tetrachloride) (spectrum #84) a single methyl peak was found at $\tau 6.53$ ($-OC\underline{H}_3$). The infrared spectrum (double mull) (spectrum #4641) contains two carbonyl bands at 1727 and 1673 $cm.^{-1}$.

Action of Ethylcadmium Reagent on the Normal Methyl Ester of o-Benzoylbenzoic Acid. In a 500-ml., three necked, round-bottomed flask fitted with a mechanical stirrer, a reflux condenser with a calcium chloride tube, and an addition funnel the Grignard reagent was prepared from 21.8 g. (0.200 mole) of ethyl bromide, 4.8 g. (0.200 g. atom) of magnesium, and 250 ml. of dry ether as solvent. The cadmium reagent was prepared by the addition of 36.7 g. (0.200 mole) of anhydrous cadmium chloride over a period of fifteen minutes. When a Michler's ketone test showed the absence of Grignard reagent after fifteen minutes, solid normal methyl o-benzoylbenzoate (6.0 g., 0.025 mole) was added over a period of ten minutes. The contents of the flask were heated for eight hours under gentle reflux, with stirring. The flask was cooled in an ice bath, and a 10% solution of sulfuric acid was added. The solution was filtered and the ether layer separated and combined with ether washings of the water layer. The combined ether layer was washed with a 10% solution of potassium carbonate. No o-benzoylbenzoic acid was found when the potassium carbonate solution was acidified with a 10% solution of hydrochloric acid. Upon evaporation of the ether 5.7 g. of a white solid was obtained. After two recrystallizations from ligroin 3.3 g. (55.0%) of the normal methyl ester of o-benzoylbenzoic acid was recovered, m.p. 51-54°, lit. (51) 51.0-51.8°. The infrared spectrum (double mull) (spectrum #4715) contains bands at 1725 cm.$^{-1}$ and 1670 cm.$^{-1}$. The n.m.r. spectrum (chloroform) (spectrum #400) contains a single peak at τ6.40 (-OC$\underline{H}_3$).

Preparation of Pseudo Methyl Ester of o-Benzoylbenzoic Acid. (51) In a 250-ml., three-necked, round-bottomed flask fitted with a reflux condenser with a trap for collection of hydrogen chloride and an addition funnel was placed 20.0 g. of anhydrous o-benzoylbenzoic acid (0.088 mole). The acid chloride was prepared by the slow addition of 10.5 g. (0.088 mole) of thionyl chloride (plus a slight excess) and the resulting solution was allowed to reflux for one hour. The excess of thionyl chloride was removed under reduced pressure. The flask was cooled in an ice bath, and a cold solution of equal parts of dry pyridine (7 ml.) and methanol (7 ml.) was added. The reaction mixture was allowed to stand for twelve hours, poured into water, and the ester taken up in ether. The ether layer was well washed with water, a saturated solution of sodium bicarbonate, and a saturated solution of sodium chloride. 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. A small amount of ester (0.3 g.) separated and was collected, m.p. 55-64°. This suggests a mixture of normal and pseudo methyl esters. However, after four months at room temperature the remaining oil deposited white crystals, which were removed by filtration. Upon recrystallization from ligroin (b.p. 60-80°) 2.7 g. (12.8%) of the pseudo methyl ester of o-benzoylbenzoic acid was obtained, m.p. 80-82°, lit. (51) 81.4-82.4°. The n.m.r. spectrum (carbon tetrachloride) (spectrum #86) contains a single methyl peak at τ6.74 (-OCH_3). The infrared spectrum (carbon tetrachloride) (spectrum #5035) contains a lactone carbonyl band at 1780 cm.$^{-1}$.

Attempted Preparation of Pseudo Methyl Ester of o-Benzoylbenzoic Acid. (54) In a 250-ml., three-necked, round-bottomed flask fitted with a reflux condenser with a trap for collection of hydrogen chloride and an addition funnel was placed 40.0 g. (0.176 mole) of o-benzoylbenzoic acid. The acid chloride was prepared by the slow addition of 20.9 g. (0.176 mole) of thionyl chloride (plus a slight excess), and the resulting solution was allowed to reflux for one hour. The excess of thionyl chloride was removed under reduced pressure. The acid chloride was then poured into 20 ml. of cold methanol, and to this mixture was added an excess of sodium carbonate solution (55.9 g., 0.528 mole, in 150 ml. of water). The reaction mixture was extracted with chloroform and the chloroform washed with water and a saturated solution of sodium bicarbonate. No recovered acid was obtained when the sodium bicarbonate solution was acidified with 10% hydrochloric acid. Upon evaporation of the chloroform solution a white solid was obtained, and found to be a mixture (24.9 g., 58.6%) of the normal and pseudo methyl esters of o-benzoylbenzoic acid, m.p. 53-62°. (54). The infrared spectrum (double mull) (spectrum #4658) contains three bands in the carbonyl region at 1770 cm.$^{-1}$, 1725 cm.$^{-1}$, and 1670 cm.$^{-1}$.

Action of Ethylcadmium Reagent on Mixture of Normal and Pseudo Methyl Esters of o-Benzoylbenzoic Acid. A 500-ml., three-necked, round-bottomed flask was fitted with a mechanical stirrer, a reflux condenser with a calcium chloride tube, and an addition funnel. The Grignard reagent was prepared from 1.8 g. (0.075 g. atom) magnesium, 8.2 g. (0.075 mole) of ethyl bromide, and 250 ml. of dry ether as solvent. The cadmium reagent was prepared by the addition of 13.7 g. (0.075 mole) of anhydrous cadmium chloride during fifteen minutes. When a Michler's ketone test showed the absence of Grignard reagent after five mintues, a mixture (sample used was that described above) of the normal and pseudo methyl esters of o-benzoylbenzoic acid (3.1 g., 0.013 mole) was added over a period of ten minutes. The contents of the flask were heated for six hours under gentle reflux, with stirring. The flask was cooled in an ice bath, and a 10% solution of sulfuric acid was added. The solution was filtered and the ether layer separated and combined with ether washings of the water layer. The combined ether layer was washed with a 10% solution of potassium carbonate. The potassium carbonate solution was acidified with a 10% solution of hydrochloric acid. An unidentified brown oil (3.2 g.) was obtained and the infrared spectrum (smear) (spectrum #4765) contains a broad band at 1755 cm.$^{-1}$ and one at 1700 cm.$^{-1}$. Upon evaporation of the ether a yellow oil (1.0 g.) was obtained. The infrared spectrum (smear) (spectrum #4728) contains bands at 1767 cm.$^{-1}$, 1720 cm.$^{-1}$, and 1667 cm.$^{-1}$ and would seem to suggest recovery of the mixture of normal and pseudo methyl esters of _o_-benzoylbenzoic acid.

Fischer Esterification of 3,4,5,6-Tetrachloro-2-benzoylbenzoic Acid. This esterification and those to follow are modeled after that of _o_-benzoylbenzoic acid. A 250-ml., single-necked, round-bottomed flask was fitted with a reflux condenser and a calcium chloride tube. Solid 3,4,5,6-tetrachloro-2-benzoylbenzoic acid (15.0 g., 0.04 mole) was dissolved in 125 ml. of pure, dry methanol, the resulting solution saturated with hydrogen chloride, and the contents of the flask allowed to reflux for three hours. The reaction mixture was cooled, poured into water, and the ester isolated by ether extraction. The ether layer was washed with a saturated solution of sodium bicarbonate and transferred to a small amount of dry methanol. Some of the ether was evaporated and the remaining ether-methanol solution was cooled in an ice bath. The crystals which separated were collected, washed with a small amount of ice cold methanol, and dried. There was obtained 13.2 g. (87.4%) of a white solid, m.p. 81-147° (36,54). The presence in the infrared spectrum (chloroform) (spectrum #4766) of bands at 1780, 1735, and 1675 $cm.^{-1}$ indicates a mixture of the normal and pseudo methyl esters of 3,4,5,6-tetrachloro-2-benzoylbenzoic acid. This was confirmed by the n.m.r. spectrum (deuterochloroform) (spectrum #124) which contains singlet methyl peaks at $\tau 6.36$ (normal ester, $-OC\underline{H}_3$) and $\tau 6.64$ (pseudo ester, $-OC\underline{H}_3$). By integration of the two methyl peaks the mixture was found to consist of 82.6% of the normal ester and 17.4% of the pseudo ester. After acidification of the sodium bicarbonate solution with 10% hydrochloric acid a white solid separated and was collected. Upon recrystallization from ethanol-water 1.0 g. (6.7% recovery) of 3,4,5,6-tetrachloro-2-benzoylbenzoic acid was obtained, m.p. 188-191°. The above reaction was repeated in a 100-ml., single-necked, round-bottomed flask with 50 ml. of dry methanol and 2.0 g. (0.005 mole) of 3,4,5,6-tetrachloro-2-benzoylbenzoic acid. This time the methanol was previously saturated with hydrogen chloride and to this solution was added the acid. The reaction mixture was allowed to reflux for fifteen minutes. From the ether layer was obtained 1.0 g. (52.6%) of the mixture of esters.

The infrared spectrum (double mull) (spectrum #1014) contains the same three bands as before. The n.m.r. spectrum (chloroform) (spectrum #378) contains singlet methyl peaks at τ 6.37 (normal ester) and τ 6.65 (pseudo ester). Upon integration of the two methyl peaks the mixture was found to consist of 75.6% of the normal ester and 24.4% of the pseudo ester. From acidification of the sodium bicarbonate solution with 10% hydrochloric acid 3,4,5,6-tetrachloro-2-benzoylbenzoic acid was obtained. This was recrystallized from ethanol-water to give 0.9 g. (45% recovery) of the acid, m.p. 191-193°.

Preparation of Normal Methyl Ester of 3,4,5,6-Tetrachloro-2-benzoylbenzoic Acid. Solid 3,4,5,6-tetrachloro-2-benzoylbenzoic acid (20.0 g., 0.055 mole) was dissolved in a solution of 2.9 g. of anhydrous sodium carbonate (0.028 mole) in 250 ml. of hot water. To this solution was added a hot aqueous solution of silver nitrate (9.3 g., 0.055 mole, in 100 ml. of water). The silver salt of the acid immediately separated and was removed by filtration. The salt was first washed with distilled water and then with ethanol, and finally dried in an oven at 70°. It was next placed in a 500-ml., single-necked, round-bottomed flask fitted with a reflux condenser with a calcium chloride tube, and to the salt was added 250 ml. of dry benzene and 7.8 g. (0.055 mole) of methyl iodide. The contents of the flask were heated for two hours under reflux. The flask was cooled in an ice bath and the benzene solution filtered. The benzene solution was concentrated under reduced pressure. The remaining solution was cooled in an ice bath, resulting in the separation of a white solid which was removed by filtration. Upon recrystallization from methanol 8.3 g. (39.9%) of the normal methyl ester of 3,4,5,6-tetrachloro-2-benzoylbenzoic acid was obtained, m.p. 90-92°, lit. (36) 92°. The infrared spectrum (double mull) (spectrum #4999) contains bands at 1740, 1720, and 1680 cm.$^{-1}$. The n.m.r. spectrum (deuterochloroform) (spectrum #123) contains a single methyl peak at τ 6.36 (OC$\underline{H}_3$).

Attempted Preparation of 4,5,6,7-Tetrachloro-3-methoxy-3-phenylphthalide. In a 250-ml., three-necked, round-bottomed flask fitted with a reflux condenser with a trap for collection of hydrogen chloride and an addition funnel was placed 10.0 g. (0.028 mole) of 3,4,5,6-tetrachloro-2-benzoylbenzoic acid. The acid chloride was prepared by the slow addition of 3.3 g. (0.028 mole) of thionyl chloride (plus a slight excess); and the resulting solution was allowed to reflux for one hour. The excess of thionyl chloride was removed under reduced pressure. The flask was cooled in an ice bath, and a cold solution of equal parts of dry pyridine (34 ml.) and methanol (34 ml.) was added. The reaction mixture was stirred by means of a magnetic stirrer for a period of two days and then poured into water. A white solid separated and was collected. This solid was found to be the normal methyl ester of 3,4,5,6-tetrachloro-2-benzoylbenzoic acid (8.8 g., 83.8%), m.p. 87-93°, lit.

(36) 92° and this was confirmed by a mixture melting point with that of authentic sample, m.p. 87-93°. The infrared spectrum (double mull) (spectrum #197) contains bands at 1730 and 1675 cm.$^{-1}$ with a slight shoulder at 1755 cm.$^{-1}$. The filtrate from which the ester was collected was washed with ether. The ether layer was washed with water, a saturated solution of sodium bircarbonate, and a saturated solution of sodium chloride. Evaporation of the ether layer did not yield any product. Also, acidification of the sodium bicarbonate solution with 10% hydrochloric acid did not yield any acid.

<u>Fischer Esterification of 6-Nitro-2-benzoylbenzoic Acid.</u> The reaction was carried out in a 100-ml., single-necked, round-bottomed flask with 50 ml. of dry methanol and 2.3 g. (0.008 mole) of 6-nitro-2-benzoylbenzoic acid. After saturation of the above solution with hydrogen chloride the contents of the flask were allowed to reflux for three hours. From the ether layer a yellow solid was obtained. After recrystallization from methanol 2.1 g. (91.3%) of the normal methyl ester of 6-nitro-2-benzoylbenzoic acid was obtained, m.p. 92-94°. The infrared spectrum (double mull) (spectrum #6279) contains two carbonyl bands at 1735 and 1660 cm.$^{-1}$. The n.m.r. spectrum (chloroform) (spectrum #332) contains a singlet methyl peak at τ 6.27 (-OC$\underline{H}_3$).

Anal. Calcd. for $C_{15}H_{11}NO_5$: C, 63.16; H, 3.88; N, 4.91
: C, 63.36; H, 4.01; N, 4.94

No acid was recovered when the sodium bicarbonate solution was acidified with 10% hydrochloric acid.

Fischer Esterification of 3-Nitro-2-benzoylbenzoic Acid.

The reaction was carried out in a 250-ml., single-necked, round-bottomed flask with 125 ml. of dry methanol and 5.0 g. (0.02 mole) of 3-nitro-2-benzoylbenzoic acid. After saturation of the above solution with hydrogen chloride the contents of the flask were allowed to reflux for three hours. From the ether layer was obtained a yellow solid. Upon recrystallization from methanol 3.4 g. (59.6%) of the normal methyl ester of 3-nitro-2-benzoylbenzoic acid was obtained, m.p. 122-124° C, lit. (39) 122° C. The infrared spectrum (double mull) (spectrum #6269) contains two carbonyl bands at 1723 and 1671 $cm.^{-1}$. In the n.m.r. spectrum (chloroform) (spectrum #327) a single methyl peak is found at τ 6.32 ($-OC\underline{H}_3$).

Anal. Calcd. for $C_{15}H_{11}NO_5$: C, 63.16; H, 3.88; N, 4.91

Found: C, 63.09; H, 3.88; N, 4.97

From acidification of the sodium bicarbonate solution with 10% hydrochloric acid a yellow solid was obtained. This was recovered 3-nitro-2-benzolybenzoic acid (1.0 g., 20%), m.p. 219-223°, lit. (39) 225-226°.

Fischer Esterification of 2-Benzoyl-1-naphthoic Acid.

The esterification was carried out in a 50-ml., single-necked, round-bottomed flask with 25 ml. of dry methanol and 0.7 g. (0.002 mole) of 2-benzoyl-1-naphthoic acid. After saturation of the above solution with hydrogen chloride the contents of the flask were allowed to reflux for three hours. From the ether layer a while solid was obtained. Upon recrystallization from methanol 0.5 g. (83.3%) of the pseudo methyl ester was obtained, m.p. 154-156°, lit. (45) 153-154°. The infrared spectrum (double mull) (spectrum #1012) contains a band at 1763 cm.$^{-1}$ in the carbonyl region. The n.m.r. spectrum (chloroform) (spectrum #379) contains a singlet methyl peak at τ 6.67 (-OC$\underline{H}_3$). No acid was recovered when the sodium bicarbonate solution was acidified with 10% hydrochloric acid.

Fischer Esterification of 1-Benzoyl-2-naphthoic Acid. The esterification was carried out with a 100-ml., single-necked, round-bottomed flask, 50 ml. of dry methanol, and 1.5 g. (0.005 mole) of 1-benzoyl-2-naphthoic acid. After saturation of the above solution with hydrogen chloride the contents of the flask were allowed to reflux for three hours. From the ether layer was obtained a light yellow oil (1.4 g.) and this was found to consist of a mixture of normal and pseudo methyl esters of 1-benzoyl-2-naphthoic acid. The infrared spectrum (smear) (spectrum #761) contains three carbonyl bands at 1750, 1720, and 1663 cm.$^{-1}$. The n.m.r. spectrum (chloroform) (spectrum #326) contains unsplit methyl peaks at τ 6.28 (-OC$\underline{H}_3$, normal ester) and τ 6.66 (-OC$\underline{H}_3$, pseudo ester). Upon integration of the two methyl peaks the mixture was found to consist of 58.4% of the pseudo ester and 41.6% of the normal ester. Crystallization of the oil from methanol yielded a white solid. After recrystallization from methanol 0.5 g. (35.7%) of the pseudo ester was obtained, m.p. 155-157°. The infrared spectrum (double mull) (spectrum #1013) contains a lactone carbonyl band at 1750 cm.$^{-1}$. The n.m.r. spectrum (chloroform) (spectrum #342) contain an unsplit methyl peak at τ 6.67.

Anal. Calcd. for $C_{19}H_{14}O_3$: C, 78.61; H, 4.86
Found: C, 78.38; H, 4.82

The filtrate from above was evaporated to yield a white solid. Upon several recrystallizations from methanol 0.3 g. (21.4%) of the normal ester was obtained, m.p. 114-116°. The infrared spectrum (double mull) (spectrum #1060) contains two carbonyl bands at 1715 and 1663 cm.$^{-1}$. The n.m.r. spectrum (chloroform) (spectrum #447) contains a singlet methyl peak at τ 6.27.

Anal. Calcd. for $C_{19}H_{14}O_3$: C, 78.61; H, 4.86
Found: C, 78.42; H, 4.83

Preparation of Normal Methyl Ester of 1-Benzoyl-2-naphthoic Acid. Solid 1-benzoyl-2-naphthoic acid (1.0g., 0.004 mole) was dissolved in a solution of 0.2 g. (0.002 mole) of anhydrous sodium carbonate in 25 ml. of hot water. To this solution was added a hot aqueous solution of silver nitrate (0.7 g., 0.004 mole, in 50 ml. of water). The silver salt of the acid immediately separated and was removed by filtration. The salt (1.4 g., 93.3%) was first washed successively with water and ethanol, and finally dried in an oven at 70° for one and one-half hours. It was next placed in a 50-ml., single-necked, round-bottomed flask fitted with a reflux condenser with a calcium chloride tube, and to the salt was added 25 ml. of dry benzene and 0.6 g. (0.004 mole) of methyl iodide. The contents of the flask were heated for two and one-half hours under reflux. The flask was cooled in an ice bath and the benzene solution filtered. The benzene solution was concentrated under reduced pressure. The remaining solution was cooled in an ice bath, resulting in the formation of an oil. To this was added some pentane and a white solid separated which was removed by filtration. Upon several recrystallizations from methanol 0.6 g. (54.5%) of the normal methyl ester of 1-benzoyl-2-naphthoic acid was obtained, m.p. 111-114°. The infrared spectrum (double mull) (spectrum #1152) contains two carbonyl bands at 1720 and 1660 cm.$^{-1}$. That this ester was the same as the normal ester produced in the Fischer esterification was confirmed by a mixture melting point determination, m.p. 111-115°. The n.m.r. spectrum (chloroform) (spectrum #445) contains an unsplit methyl peak at τ 6.27.

Fischer Esterification of o-Acetylbenzoic Acid. The reaction was carried out in a 250-ml., single-necked, round-bottomed flask with 100 ml. of dry methanol and 3.6 g. (0.02 mole) of o-acetylbenzoic acid. After saturation of the above solution with hydrogen chloride the contents of the flask were allowed to reflux for three hours. From the ether layer was obtained a yellow liquid. After distillation under reduced pressure from a Babcock tube (55)

2.3 g. (65.7%) of a mixture of esters was obtained. The infrared spectrum (smear) (spectrum #702) contains three bands at 1775, 1725, and 1705 cm.$^{-1}$ in the carbonyl region. The n.m.r. spectrum (chloroform) (spectrum #314) contains four single methyl peaks at τ 6.10 (-OC$\underline{H}_3$) and τ 7.47 (-C$\underline{H}_3$) for the normal ester and τ 6.94 (-OC$\underline{H}_3$) and τ 8.17 (-C$\underline{H}_3$) for the pseudo ester. Upon integration of these methyl peaks the mixture was found to consist of 75% of the pseudo ester and 25% of the normal ester (56).

Anal. Calcd. for $C_{10}H_{10}O_3$: C, 67.39; H, 5.66
Found: C, 67.18; H, 5.61
C, 67.16; H, 5.60

No acid was obtained when the sodium bicarbonate solution was acidified with 10% hydrochloric acid. The above reaction was repeated in a 50-ml., single-necked, round-bottomed flask with 25 ml. of dry methanol and 1.0 g. (0.006 mole) of o-acetylbenzoic acid. This time the methanol was previously saturated with hydrogen chloride and to this solution was added the acid. The reaction mixture was allowed to reflux for fifteen minutes. From the ether layer was obtained a yellow liquid. After distillation under reduced pressure from a Babcock tube 0.9 g. (81.8%) of a mixture of esters was obtained. The infrared spectrum (smear) (spectrum #1015) contains the same three bands as before. The n.m.r. spectrum (chloroform) (spectrum #377) contains the same four methyl peaks. Upon integration of these peaks the mixture was found to consist of 60% of the pseudo ester and 40% of the normal ester. Again, no acid was obtained from the acidification of the sodium bicarbonate solution.

Fischer Esterification of 3,4,5,6-Tetrachloro-2-acetylbenzoic Acid. The esterification was carried out with a 250-ml., single-necked, round-bottomed flask, 125 ml. of dry methanol, and 6.0 g. (0.02 mole) of 3,4,5,6-tetrachloro-2-acetylbenzoic acid. After saturation of the above solution with hydrogen chloride the contents of the flask were allowed to reflux for three hours. From the ether layer was obtained a white solid. After recrystallization from methanol 3.2 g. (53.3%) of the pseudo methyl ester of 3,4,5,6-tetrachloro-2-acetylbenzoic acid was obtained exclusively, m.p. 191-192°. The infrared spectrum (double mull) (spectrum #631) contains a band at 1775 cm.$^{-1}$ in the carbonyl region. In the n.m.r. spectrum (chloroform) (spectrum #299) two singlet methyl peaks are found at τ6.82 ($-OC\underline{H}_3$) and τ8.05 ($-C\underline{H}_3$).

Anal. Calcd. for $C_{10}H_6Cl_4O_3$: C, 38.02; H, 1.92; Cl, 44.88
Found: C, 38.07; H, 1.97; Cl, 44.69

No acid was recovered when the sodium bicarbonate solution was acidified with 10% hydrochloric acid. The above reaction was repeated using a 100-ml., single-necked, round-bottomed flask, 50 ml. of dry methanol, and 2.0 g. (0.007 mole) of 3,4,5,6-tetrachloro-2-acetylbenzoic acid. The methanol was previously saturated with hydrogen chloride and to this was added the acid. The contents of the flask were allowed to reflux for fifteen minutes. From the ether layer was obtained a white solid as was the case upon acidification of the sodium bicarbonate solution. These two solids were found to be identical upon comparison of their infrared spectra (double mulls) (spectrum #'s 965 and 966), both with a band at 1775 cm.$^{-1}$ in the carbonyl region. The two solids were combined and recrystallized from methanol to give 1.6 g. (72.7%) of the pseudo methyl ester, m.p. 190-191°. That this ester was identical to that obtained after a three hour reflux period was confirmed by a mixture melting point. In addition, the n.m.r. spectrum (chloroform) (spectrum #360) with single methyl peaks τ6.83 ($-OC\underline{H}_3$) and τ8.05 ($-CH_3$) was the same as spectrum #299.

Treatment of Pseudo Methyl Ester of 3,4,5,6-Tetrachloro-2-acetylbenzoic Acid Under Fischer Esterification Conditions.

A 50-ml., single-necked, round-bottomed flask was fitted with a reflux condenser and a calcium chloride tube. Solid 4,5,6,7-tetrachloro-3-methoxy-3-methylphthalide (1.0 g., 0.003 mole) was dissolved in 25 ml. of pure, dry methanol, the resulting solution saturated with hydrogen chloride, and the contents of the flask allowed to reflux for three hours. The reaction mixture was cooled, poured into water, and the ester isolated by ether extraction, washed with a saturated solution of sodium bicarbonate, and transferred to a small amount of dry methanol. Some of the ether was evaporated and the remaining ether-methanol solution was cooled in an ice bath. The crystals which separated were collected, washed with a small amount of ice cold methanol, and dried.

Also, a white solid was obtained upon acidification of the sodium bicarbonate solution with 10% hydrochloric acid. The two solids were found to be identical upon comparison of their infrared spectra (double mulls) (spectrum #'s 969 and 970), which both contained a band at 1775 cm.$^{-1}$ in the carbonyl region. The two solids were combined and recrystallized from methanol to give 0.8 g. (80% recovery) of the pseudo methyl ester of 3,4,5,6-tetrachloro-2-acetylbenzoic acid, m.p. 190-191°. That this ester was identical to that obtained from the Fischer esterification of 3,4,5,6-tetrachloro-2-acetylbenzoic acid with a reflux period of three hours was confirmed by a mixture melting point, m.p. 190-191°. Also the n.m.r. spectrum (chloroform) (spectrum #359) with two single methyl peaks at τ 6.82 ($-OC\underline{H}_3$) and τ 8.05 ($-C\underline{H}_3$) was the same as that of the starting ester.

Action of Methylcadmium Reagent on 4,5,6,7-Tetrachloro-3-methoxy-3-methylphthalide. A 250 ml., three-necked, round-bottomed flask was fitted with a mechanical stirrer, a reflux condenser with a calcium chloride tube, and an addition funnel. The Grignard reagent was prepared from 1.2 g. (0.048 g. atom) of magnesium, 6.8 g. (0.048 mole) of methyl iodide, and 125 ml. of dry ether as solvent. The cadmium reagent was prepared by the addition of 8.8 g. (0.048 mole) of anhydrous cadmium chloride during ten minutes. When a Michler's ketone test showed the absence of Grignard reagent after seven minutes, solid 4,5,6,7-tetrachloro-3-methoxy-3-methylphthalide (2.0 g., 0.006 mole) was added over a period of five minutes. The contents of the flask were heated for eight hours under gentle reflux, with stirring. The flask was cooled in an ice bath, and 10% sulfuric acid was added. The solution was filtered and the ether layer separated and combined with ether washings of the water layer. The combined ether layer was washed with 10% potassium carbonate. The potassium carbonate solution was acidified with 10% hydrochloric acid. A white solid separated and was collected. Upon recrystallization from methanol 1.2 g. (66.7%) of recovered 4,5,6,7-tetrachloro-3-methoxy-3-methylphthalide was obtained, m.p. 189-191°. This was confirmed by a mixture melting point with an authentic sample, m.p. 189-191°. The infrared spectrum (double mull) (spectrum #1036) contains a lactone carbonyl band at 1775 cm.$^{-1}$. The n.m.r. spectrum (chloroform) (spectrum #403) contains two unsplit methyl peaks at τ6.83 ($-OC\underline{H}_3$) and τ8.05 ($\equiv C\underline{H}_3$). From evaporation of the ether solution a brown oil (0.4 g.) was obtained and was found to be some more recovered 4,5,6,7-tetrachloro-3-methoxy-3-methylphthalide. The infrared spectrum (double mull) (spectrum #1035) also contains a lactone carbonyl band at 1775 cm.$^{-1}$. The n.m.r. spectrum (chloroform) (spectrum #446) contains the same two unsplit methyl peaks as above.

Fischer Esterification of 3-Nitro-2-acetylbenzoic Acid. The esterification was carried out in a 250-ml., single-necked, round-bottomed flask with 125 ml. of dry methanol and 4.0 g. (0.02 mole) of 3-nitro-2-acetylbenzoic acid.

After saturation of the above solution with hydrogen chloride the contents of the flask were allowed to reflux for three hours. From the ether layer was obtained a light yellow solid. After recrystallization from methanol 3.0 g. (73.2%) of a mixture of esters was obtained, m.p. 81-134°. The infrared spectrum (double mull) (spectrum #685) contains bands at 1775 cm.$^{-1}$ (shoulder) and at 1725 and 1710 cm.$^{-1}$ in the carbonyl region. The n.m.r. spectrum (chloroform) (spectrum #315) contains four singlet methyl peaks at τ 6.05 (-OC$\underline{H}_3$) and τ 7.30 (-C$\underline{H}_3$) for the normal ester and at τ 6.77 (-OC$\underline{H}_3$) and τ 7.95 (-C$\underline{H}_3$) for the pseudo ester. Upon integration of these methyl peaks the mixture was found to consist of 86.6% of the normal ester (39) and 13.4% of the pseudo ester.

Anal. Calcd. for $C_{10}H_9NO_5$: C, 53.80; H, 4.06; N, 6.28
Found: C, 53.91; H, 4.20; N, 6.08

No acid was obtained when the sodium bicarbonate solution was acidified with 10% hydrochloric acid.

Fischer Esterification of Postulated 6-Methyl-2-acetylbenzoic Acid. The reaction was carried out in a 50-ml., single-necked, round-bottomed flask with 25 ml. of dry methanol and 0.7 g. (0.004 mole) of the postulated 6-methyl-2-acetylbenzoic acid. After saturation of the solution with hydrogen chloride the contents of the flask were allowed to reflux three hours. From the ether layer was obtained a white solid. Upon crystallization from methanol 0.6 g. (78.9%) of a presumed pseudo methyl ester was obtained, m.p. 170-180°. This is supported by the presence of a lactone carbonyl at 1775 cm.$^{-1}$ in the infrared spectrum (double mull) (spectrum #1034). The n.m.r. spectrum contains three unsplit methyl peaks at τ 6.95 (-OC$\underline{H}_3$), τ 7.30 (Ar-C$\underline{H}_3$), and τ 8.21 (-C$\underline{H}_3$).

Anal. Calcd. for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29
Found: C, 68.54; H, 6.09

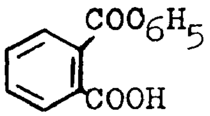
No acid was recovered by acidification of the sodium bicarbonate solution with 10% hydrochloric acid.

RESULTS AND DISCUSSION

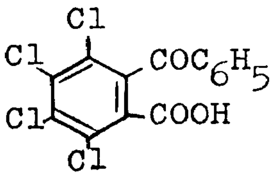
The substituted ketoacids investigated are shown below in Chart 1, and the possible ring-chain tautomerism in these acids is represented by the structures in Chart 2.

Chart 1

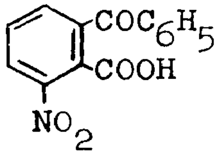
Substituted Ketoacids Investigated



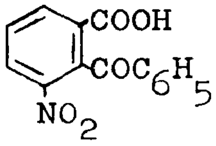
XXXVIII



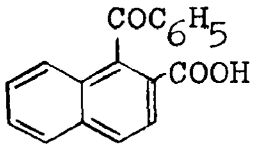
XXXIX



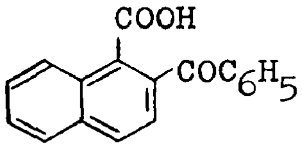
XL



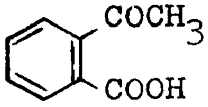
XLI



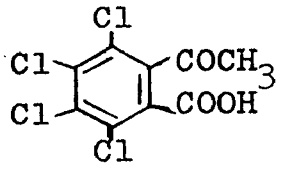
XLII



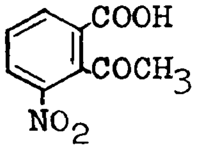
XLIII



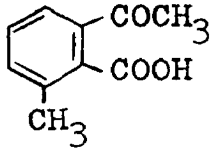
XLIV



XLV



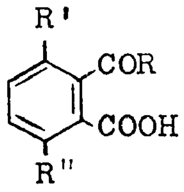
XLVI



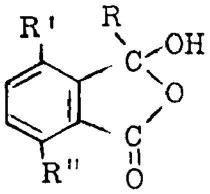
XLVII

Chart 2

Ring-chain Tautomerism Possible in the Substituted Ketoacids

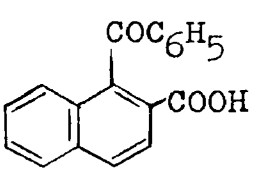


XLVIII

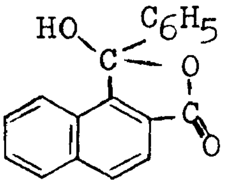


where R=CH_3, or C_6H_5

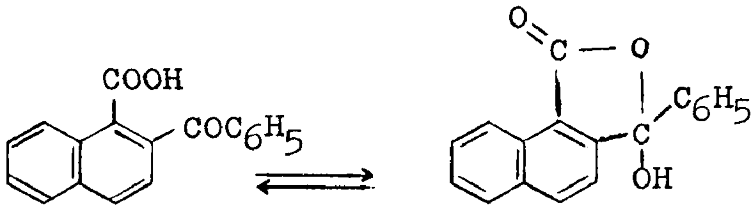
XLIX



XLII



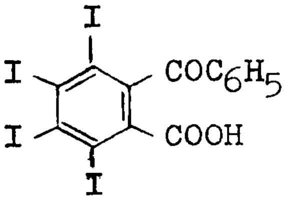
L



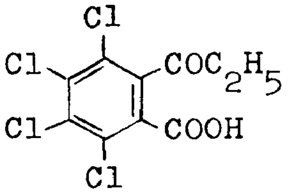
XLIII

LI

As was mentioned earlier, the organocadmium reaction appeared to present a means of estimating ketoacid—pseudoacid equilibria (2,3). The reaction with phenylcadmium and ethylcadmium reagent was therefore attempted on acids XXXVIII, XXXIX, XLIII, and two additional ones depicted below. The procedures for the organocadmium reactions were modeled after those of Jones (2,3) and de Benneville (33). The results are summarized in Tables 5 and 6.



LII

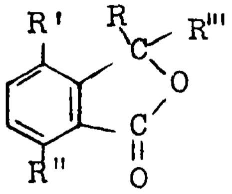


LIII

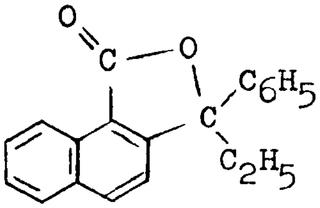
The following observations are made in regard to the data in Tables 5 and 6:

(1) Recovered acid is obtained in every instance except in the case of acid LII (see note 9 in Table 6).

(2) In each reaction the neutral product indicates the presence of a lactone of the general structure LIV with or without substituents R' and R" or the lactone LV (cf. acid LII in Table 6). This is based mainly on the lactone carbonyl absorption bands in the infrared spectra.



LIV



LV

Table 5.

Reaction with C_6H_5CdCl[1,2]

Acid	M (Acid)[3]	M (C_6H_5CdCl)[4]	% of Recovered Acid	Amt. of Neutral Prod.[5,6,7]	t_r[8]
XXXVIII	0.06	0.28	97.8	trace (1750 $cm.^{-1}$)	8
XXXIX	0.06	0.28	72.9	trace (1740 $cm.^{-1}$)	8
XXXIX	0.06	0.28	67.8	trace (1735 $cm.^{-1}$)	8

Notes:

1 : cadmium reagent prepared by the addition of anhydrous cadmium chloride to the phenyl Grignard reagent in 1:1 molar ratio
2 : formation time of the cadmium reagent was between 25-30 minutes
3 : molar amount of acid used
4 : molar amount of cadmium reagent used
5 : all neutral products were yellow oils
6 : bands of infrared carbonyl absorption, determined as films, are indicated
7 : found to contain some biphenyl
8 : reaction time in hours of cadmium reagent with the acid

Table 6.

Reaction with $C_2H_5CdCl^{1,2}$

Acid	M (Acid)^3	M (C_2H_5CdCl)^4	% of Recovered Acid	Amt. of Neutral Prod.^{5,6}	t_r^{7}
XXXVIII	0.04	0.26	71.0	trace (1750)	8
XXXVIII	0.04	0.26	82.0	trace (1750)	10
XXXVIII^8	0.04	0.26	51.0	0.3 g. (1750)	10
XXXIX^8	0.03	0.26	70.8	0.2 g. (1775)	9, 10.5
XLIII	0.004	0.028	70.0	0.1 g. (1740)	8
LII^8	0.03	0.26	00.0^9	0.1 g. (1750)	8, 10.5
LIII	0.032	0.256	80.0	0.3 g. (1740)	8

Notes:

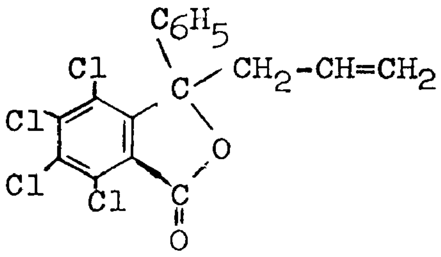
1 : cadmium reagent prepared by the addition of anhydrous cadmium chloride to the ethyl Grignard reagent in 1:1 molar ratio
2 : formation time of cadmium reagent was between 10-25 minutes
3 : molar amount of acid used
4 : molar amount of cadmium reagent used
5 : all neutral products were yellow oils
6 : bands of infrared carbonyl absorption in cm.$^{-1}$ are stated in parentheses and were determined as smears
7 : reaction time in hours of cadmium reagent with the acid
8 : after the formation of the cadmium reagent, the ether was replaced by benzene according to the procedure of Cason (57).
9 : no recovered acid was obtained but an acid not identical to the starting acid was formed

(3) The very small amounts of neutral product (lactone) do not provide a sufficient measure of the keto-acid-pseudoacid equilibrium. This stems from the assumption that the cadmium reagent would react only with the ring tautomer of the acid to form the lactone.

(4) The long reaction time, the excess of cadmium reagent, and a change in solvent (acids XXXVIII, XXXIX, and LII) do not appear to affect results significantly.

Only in one instance was there evidence of lactone formation. This occurred in the reaction of acid XXXIX with allylcadmium chloride. This involved a modified procedure for preparing the cadmium compound, in which a solution of allyl chloride in ether was added to a mixture of magnesium and cadmium chloride in ether. Once the reaction subsided, the acid was added.

The lactone is indicated to be LVI because of the presence of a lactone carbonyl band at 1753 cm.$^{-1}$ (determined as double mull) in the infrared spectrum, the decolorization of a solution of bromine in carbon tetrachloride, and the consistency of the microanalysis with the derived formula from LVI. It should also be mentioned here that

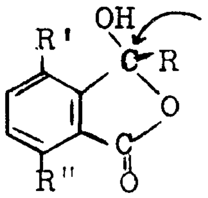


LVI

treatment of LVI with acid or allylcadmium chloride had no effect, and recovered LVI was obtained. However, upon treatment with base an unidentified oil was produced and the infrared spectrum contained a band at 1737 cm.$^{-1}$. In addition, the n.m.r. spectrum of LVI is not consistent with a substance containing a propenyl group, which would have resulted had isomerization of the double bond taken place.

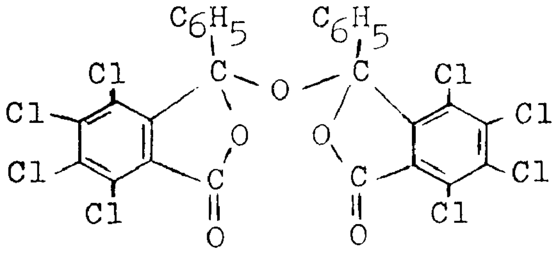
When the above reaction was repeated employing the conventional method, i.e., addition of cadmium chloride to the previously prepared Grignard reagent, a white solid was obtained that was not identical to LVI. Further investigation of the solid and the difference in the reactions is needed.

The results obtained by the use of the organocadmium reagent might imply that equilibration of the ring and chain tautomers is faster than reaction with the cadmium reagent under the conditions of the experiment, along with the possibility of steric hindrance at the reaction site (indicated by the arrow head in the structure below).



A steric effect could explain lactone formation in the reaction of acid XXXIX with allylcadmium chloride by the modified procedure. The allyl group might not be as sensitive to a steric effect as would the phenyl, or less so, the ethyl group (58).

The reaction of the acid chloride of XXXIX with the allylcadmium reagent did not yield the lactone LVI, but an unidentified solid which contains no aliphatic protons in the n.m.r. spectrum. Formation of an ether C is possible and could have occurred during the course of the reaction or in the work up. Formation of this type of an ether has been observed. Formation of the lactone was expected since the reaction of the acid chloride of o-benzoylbenzoic acid with diphenylcadmium produces 3,3-diphenylphthalide (21).



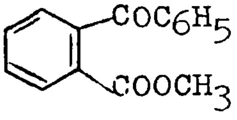
C

The Fischer-Speier esterification, or simply the Fischer esterification, has been widely used and the mechanism has been treated and discussed (59,60). In the present investigation the Fischer esterification was applied to acids XXXVIII-XLVII (see Chart 1). The esters thus formed are depicted in Chart 3.

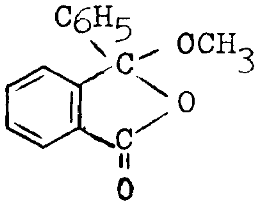
Nuclear magnetic resonance spectroscopy was applied

Chart 3

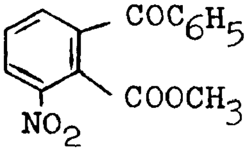
Prepared Esters of Acids XXXVIII-XLVII



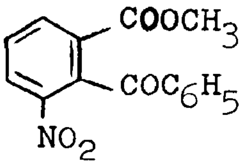
LVII



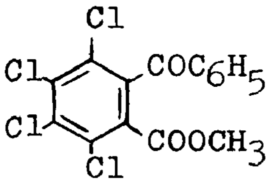
LVIII



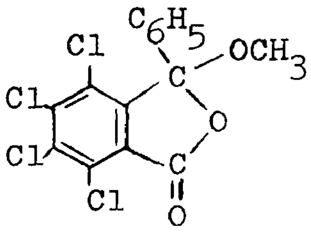
LIX



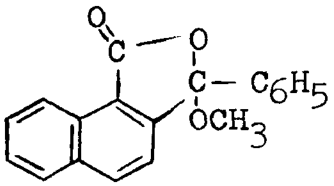
LX



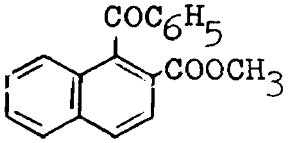
LXI



LXII



LXIII



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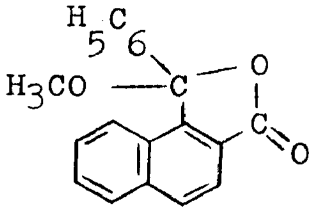
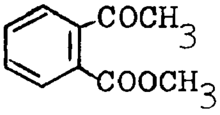
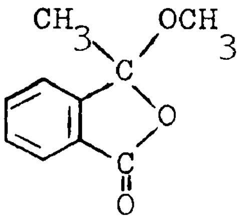


LXV

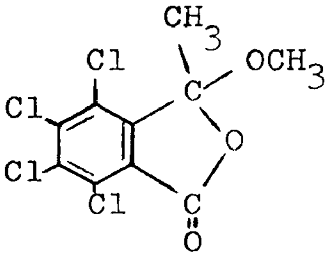
Chart 3 - continued



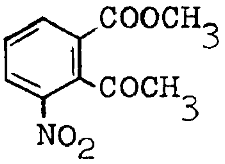
LXVI



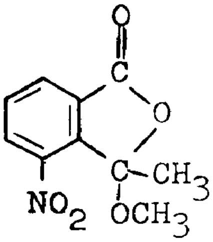
LXVII



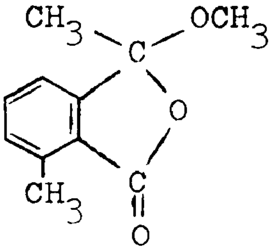
LXVIII



LXIX



LXX



LXXI

(proposed structure)

by Lansbury to distinguish between normal and pseudo esters (6). The τ values of the methyl signals for methyl ketones and methyl benzoates are given as 7.90 and 6.35, respectively, whereas the τ value for methyl esters is 6.71 (61). Quantitative analysis of mixtures of normal and pseudo esters was accomplished readily by integration of the methyl peaks. Application of the Fischer esterification to acids XXXVIII-XLVII and analysis by use of n.m.r. spectra are described in Tables 7 and 8. In addition, all the infrared carbonyl frequencies of the esters studies are recorded in Table 9.

An approximation can be made in connection with the amount of normal and pseudo ester formed and the ring-chain equilibrium of the respective acids. The results suggest that acids XXXVIII, XXXIX, XL, XLI, and XLVI exist mainly in the chain form, while acids XLIII, XLIV, XLV, and XLVII appear to exist mainly as the ring tautomer. However, from the results obtained acid XLII does not appear to exist predominantly in either the chain or ring form, but in nearly equal amounts of both.

One also notices that the amount of pseudo ester increases from the o-benzoylbenzoic acid series (XXXVIII to XLI) to the o-acetylbenzoic acid series (XLIV to XLVII). It is generally known that methyl ketones are more reactive than phenyl ketones, and as a result, more of an attack by an ortho substituent on the methyl ketone function is favored. In addition to this a steric factor would also be important

Table 7

Fischer Esterification of Acids XXXVIII-XLVII

Acid[1]	%, Ester	Type of Ester, %[2,3,4] Normal	Type of Ester, %[2,3,4] Pseudo	t^5 reac.
XXXVIII	59.1	All (LVII)	--	3 hrs.
XXXIX	87.4	82.6 (LXI)	17.4 (LXII)	3 hrs.
XXXIX	52.6	75.6 (LXI)	24.4 (LXII)	15 mins.
XL	91.3	All (LIX)	--	3 hrs.
XLI[6]	59.6	All (LX)	--	3 hrs.
XLII	100.0[7]	41.6 (LXIV)	58.4 (LXV)	3 hrs.
XLIII	83.3	--	All (LXIII)	3 hrs.
XLIV	65.7	25.0 (LXVI)	75.0 (LXVII)	3 hrs.
XLIV	81.8	40.0 (LXVI)	60.0 (LXVII)	15 mins.
XLV	53.3	--	All (LXVIII)	3 hrs.
XLV	72.7	--	All (LXVIII)	15 mins.
XLVI	73.2	86.6 (LXIX)	13.4 (LXX)	3 hrs.
XLVII	78.9	--	All[8] (LXXI)	3 hrs.

Notes:

1 : esterification was carried out with anhydrous hydrogen chloride and dry methanol

2 : percentages of normal pseudo ester were determined by integration of methyl peaks in n.m.r. spectra (chloroform) with tetramethylsilane as internal standard

3 : esters are denoted by Roman numerals in parentheses

Table 7 - continued

4 : medium is carbon tetrachloride for first entry and deuterochloroform for the second entry
5 : reaction time for esterification
6 : recovered acid was obtained
7 : obtained as an oil and is not a true measure of ester

Table 8

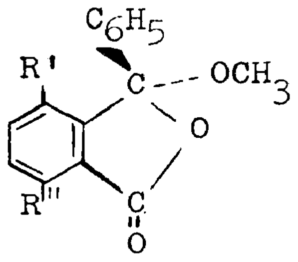
Chemical Shifts (τ) for Normal and Pseudo Methyl Esters

Ester	Normal Ester[1] -OC$\underline{H}_3$	Normal Ester[1] -C$\underline{H}_3$	Pseudo Ester[1] -OC$\underline{H}_3$	Pseudo Ester[1] -C$\underline{H}_3$
LVII	6.53	--	--	--
LVIII	--	--	6.74	--
LXI	6.36	--	--	--
LXII	--	--	6.64	--
LIX	6.27	--	--	--
LX	6.32	--	--	--
LXIV	6.27	--	--	--
LXV	--	--	6.67	--
LXIII	--	--	6.67	--
LXVI	6.10	7.47	--	--
LXVII	--	--	6.94	8.17
LXVIII	--	--	6.82	8.05
LXIX	6.05	7.30	--	--
LXX	--	--	6.77	7.95
LXXI	--	--	6.95	8.21

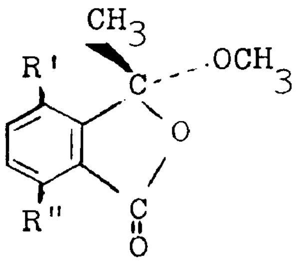
Notes:

1 : All n.m.r. spectra were determined in chloroform except for the first (carbon tetrachloride) and second (deuterochloroform) entries with tetramethylsilane as an internal standard.

here. Certainly the methyl group is smaller than the phenyl and this fact alone would seem to enhance pseudo ester formation as exemplified by A vs. B. There is less crowding with the methyl group in relation to R' in the cyclic tautomer than is the case with that of phenyl group.



A

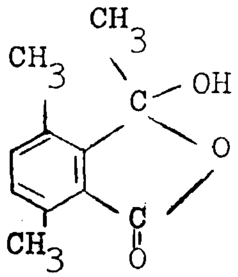


B

Considering acids XLII and LIII separately, it appears that formation of only pseudo ester from acid XLIII is a result of a hindering effect of two substituents ortho to the carboxyl group: the peri hydrogen atom of the fused aromatic ring and the benzoyl group. On the other hand, the carboxyl group in acid XLII is not as sterically hindered. This would tend to enhance formation of normal ester as was observed.

The question arises: Is a reaction time of three hours sufficient for attaining equilibration between the normal and pseudo esters in the Fischer esterification? This was answered by the esterification of acids XXXIX, XLIV, and XLV with reaction times of fifteen minutes and three hours. The data in Table 7 indicates that equilibrium is almost reached in fifteen minutes as compared to after three hours. In this regard Newman (62) found that the Fischer esterification of o-benzoylbenzoic acid after fifteen minutes yielded ester of composition 70.5% normal-29.5% pseudo. When the pseudo methyl ester was treated under the same reaction conditions, the ester obtained was 94% normal. It was also found that at equilibrium the esters are 98% normal-2% pseudo. In the present investigation no pseudo ester was found at equilibrium (three hours), just normal ester (see acid XXXVIII in Table 7). Newman does not state the period of time it took to obtain his equilibrium values, and also does not employ anhydrous conditions.

It was further pointed out by the same author that o-benzoylbenzoic acid, which seems to be present mainly in the keto form (1), yields the pseudo ester preferentially under kinetic control, whereas 3,6-dimethyl-2-benzoylbenzoic acid, which seems to be present mainly in the ring form LXXII (1), yields mainly normal ester under kinetic control. The assumptions involved were tested in the esterification of acid XLV in the present work. After fifteen minutes or three hours only pseudo ester was formed. The pseudo ester



LXII

was subjected to the same esterification conditions for an additional three hours, and only recovered pseudo ester was obtained.

It was found by Tirouflet (39) that in the Fischer esterification of acid XLVI after thirty minutes only normal ester was formed. This result, along with the observations made previously, suggests that a three hour reaction time is enough for a reliable equilibrium value.

The action of ethylcadmium reagent on ester LVII and of methylcadmium reagent on ester LXVIII were attempted. In each case only the recovered ester was obtained. The purpose of this experiment was to observe that no reaction should have occurred with the normal ester, a prediction which was verified, but also that reaction should have taken place with the pseudo ester, and this was not observed. The reaction performed with the pseudo ester LXVIII stemmed from the assumption that the cadmium reagent would react only with the cyclic form and not with the chain form (2,3).

The chemical shifts of the methyl protons in the normal and pseudo esters are recorded in Table 8. The values are in good agreement with those of Lansbury (6) and those tabulated by Jackman (61). Also, in agreement with Lansbury, the chemical shifts of the methyl protons in the normal esters are at lower field (lower τ values) than the pseudo esters.

The esters are readily distinguishable by their infrared absorption spectra as evidenced in Table 9.

Table 9

Infrared Spectra of Esters

			Carbonyl Frequencies (cm.$^{-1}$)		
Entry	Ester[1]	Aryl	Methyl	Lactone	Ester
1	LVII	1673	--	--	1725
2	LVIII	--	--	1780	--
3	LXI	1680	--	--	1720
4	LXII	--	--	1780	--
5	LIX	1660	--	--	1735
6	LX	1671	--	--	1723
7	LXIII	--	--	1763	--
8	LXIV	1663	--	--	1715
9	LXV	--	--	1750	--
10	LXVI	--	1705	--	1725
11	LXVII	--	--	1775	--
12	LXVIII	--	--	1775	--
13	LXIX	--	1710	--	1725
14	LXX	--	--	1775	--
15	LXXI	--	--	1775	--

Notes:

1 : the following entries were determined as follows: 2 in carbon tetrachloride, 3 and 4 in chloroform, 10 and 11 as smears, the rest as double mulls.

The higher carbonyl absorption frequencies in the pseudo esters are in agreement for those in a phthalide ring (63), while the ester (64), aryl, and methyl carbonyl frequencies fall within the reported ranges (63).

The remainder of this section will deal with the application of spectral methods in an attempt to establish the equilibrium position of the ring and chain tautomers in acids XXXVIII through XLVII. Table 10 contains a summary of infrared spectral study made on the above acids.

Table 10

Infrared Spectra of Acids

Acid[1]	OH Region (cm.$^{-1}$)	Carbonyl Region (cm.$^{-1}$)
XXXVIII	3000	1695, 1665
XXXIX	3280	1740
XL	2800	1715, 1675
XLI	2900	1710, 1690
XLII	3300	1725, 1675
XLIII	3300	1723
XLIV	3260	1725
XLV	3180	1755
XLVI	2950	1710, 1690
XLVII	3350	1750

Notes:

1 : infrared spectra were determined as double mulls except for the first (chloroform) and last (smear) entries

The results indicate ring structures for acids XLIII, XLIV, XLV, XLVII, and XXXIX. These have an OH absorption which is not as high as an alcoholic OH (65). In addition, the high carboxyl carbonyl frequencies and the apparent lack of ketone absorption is further support for a lactol structure. This fact is supported by the example of phthalaldehydic acid which exists as the lactol rather than as the free acid, based on the five-membered ring lactol carbonyl absorption at 1738 cm.$^{-1}$ and the "alcoholic" OH absorption at $\sim$3320 cm.$^{-1}$ (4).

Acids XXXVIII, XL, XLI, and XLVI appeared to be present predominantly in the keto form as dimers. The OH absorption in dimers occurs in the range 3000-2500 cm.$^{-1}$ (66) and this agrees with the above cases. In conjunction with this there are present two carbonyl frequencies corresponding to the carboxyl group and the aryl ketone function (63).

Acid XLII has an OH absorption at 3300 cm.$^{-1}$ and two carbonyl frequencies at 1725 and 1675 cm.$^{-1}$. It is difficult to characterize this acid because there is evidence for both the lactol and keto structures.

It was of interest to see how closely the ultraviolet spectra of the acids in question follow the infrared spectral data and, in particular, to study the spectra of these acids in relation to those of their respective normal and pseudo esters. In this manner additional information would be provided for or against the ring and chain forms.

The data in Table 11 support the lactol structure for acids XLIII, XLIV, XLV, and XLVII, whereas acids

Table 11

Ultraviolet Spectra of Acids and Esters[1,2]

Acid			Esters					
			Normal			Pseudo		
#	λmax	(log ϵ)	#	λmax	(log ϵ)	#	λmax	(log ϵ)
XXXVIII	244	(3.69)	LVII	244	(4.15)	LVIII	280 244	(3.18) (4.15)
XXXIX	244	(4.01)	LXI[3]	247	(3.19)	--	--	--
XL	248	(4.28)	LIX	247	(4.03)	--	--	--
XLI	246	(3.96)	LX	246	(4.07)	--	--	--
XLII	291 228	(3.72) (4.56)[4]	LXIV	240 227	(4.50) (4.41)	LXV	312 225	(3.80) (4.59)
XLIII	292 234	(3.78) (4.51)	--	--	--	LXIII	306 241	(3.80) (4.50)
XLIV	279 272 229	(3.00) (3.00) (3.98)	--	--	--	LXVII[5]	278 272 230	(2.95) (2.88) (4.18)
XLV	305 295 222	(2.95) (2.92) (4.44)	--	--	--	LXVIII	305 295 224	(3.16) (3.06) (4.59)
XLVI	247 216	(3.72) (4.28)	LXIX[6]	247 217	(3.72) (3.84)	--	--	--
XLVII	284 235	(2.68) (3.71	--	--	--	LXXI	284 234	(3.06) (3.57)

Table 11 - continued

Notes:

1 : ultraviolet spectra were determined in 95% ethanol except acid XLIV (methanol)

2 : concentrations of solutions were $5x10^{-5}$M/L except LXVII ($6x10^{-5}$M/L) and acid XLI (10^{-4}M/L) and λmax are recorded in mμ.

3 : ester was found to be 82.6% normal ester by n.m.r. analysis

4 : midpoint of a broad peak

5 : ester was found to be 75% pseudo ester by n.m.r. analysis

6: ester was found to be 86.6% normal ester by n.m.r. analysis

XXXVIII, XXXIX, XL, XLI, and XLVI seem to be present mainly in the keto form. The prediction for acid XXXVIII agrees with the observation made by Newman (1) and the results for XLIV are in good accord with Wheeler (5). In certain instances (esters LXI and LXII, LXVI, and LXVII, and LXIX and LXX) the ultraviolet spectrum was determined on a mixture of the normal and pseudo methyl esters. It is assumed that the values obtained from the mixture are due to the predominant ester. On this basis the structures of the acids related to these esters were accordingly predicted.

Once again it is difficult to speculate on the structure of acid XLII. This acid (λmax 228,291 mμ) compared to its normal (λmax 227, 240 mμ) and pseudo (λmax 224, 312 mμ) esters appears to behave more nearly like its pseudo ester, although the evidence is not clear cut.

For the examination of the structures of acids XLIV, XLV, XLVI, and XLVII it was found that n.m.r. spectroscopy was indeed a valuable tool. As reported in Table 12 acids XLIV, XLV, and XLVII have a τ value approximately at 8.00, which is in good agreement with Lansbury for ring tautomers (6).

By a comparison of the chemical shifts of the methyl protons in the acids to those of the pseudo esters, the ring structure is confirmed for acids XLIV, XLV, and XLVII. The τ-7.67 value of the methyl protons in acid XLVI is almost intermediate between the τ values of the normal (7.30) and pseudo (7.95) methyl esters. The presence of a sharp peak indicates only one structure, or else there should have been another peak present. If τ-value for the acid was a time average, the peak would be broad.

Table 12

Chemical Shifts (τ) of Methyl Protons in the o-Acetylbenzoic Acids and Pseudo Methyl Esters

Acid[1]	Methyl Protons	Pseudo Ester[1]	Methyl Protons (-CH_3)
XLIV	8.02	LXVII	8.17
XLV	7.97	LXVIII	8.05
XLVI	7.67	LXX	7.95
XLVII	8.17	LXXI	8.21

Notes:

1 : all n.m.r. spectra were determined in chloroform solution with tetramethylsilane as internal standard

It is easier to assign structures to acids XLIV, XLV, and XLVII which can be compared to model compounds for the lactol structures in the form of pseudo esters. A structure cannot be predicted on the same basis for XLVI, since there are at the present time too few model compounds with which to draw analogies. For the chain structure, the effect on the chemical shift of the methyl group exerted by the o-carboxyl function must be considered, and this information is not known.

Consideration of the effect of hydrogen bonding must also be included in both the ring and chain structures. Hydrogen bonding has the effect of lowering the OH chemical shift in phenols (67). This might also be the case for the OH peak in the ring structures for acids XLV and XLVI, but one cannot assume that the methyl peak would likewise be lowered. A trend in this direction is observed in the τ-values for the pseudo methyl esters LXVII, LXVIII, and LXX (8.17, 8.05, and 7.95 respectively), and provides an argument for the assumption that the methyl peak will be at successively lower fields in the lactol acids XLIV, XLV, and XLVI (as is observed). In addition, another factor is the overall substituent effect on the chemical shift, and is exemplified for substituted toluenes (68). It is observed that chloro and nitro groups cause a shift to lower fields, whereas the methyl group exerts the opposite effect. This general effect might be operating in the case of either the ring or chain structure and account for the trend in the chemical shifts.

The results obtained from the Fischer esterification and the three spectral methods confirm that acids XLIII, XLIV, XLV, and XLVII exist mainly as the ring tautomer. Moreover, acid XLII appears to contain contributions from both the ring and chain forms, but evidence is not conclusive for a more accurate prediction. There is, however, more of a conflict in the results in the case of two acids. Both the Fischer esterification and the ultraviolet spectrum indicate that acid XXXIX exists predominantly in the keto form, while the infrared spectrum suggests the ring. Also the Fischer esterification and both the infrared and ultraviolet spectra suggest the keto form for acid XLVI, whereas the n.m.r. spectrum at the present time does not provide conclusive evidence for either.

As far as the three spectral methods are concerned, a word here about their roles is in order. Firstly, the infrared spectra are not specific enough as to which structure is present and were used only for qualitative purposes in this study. Secondly, since no quantitative correlations were made with the ultraviolet spectra, it is difficult to predict structures as accurately as desired. Hence, it is only possible to suggest one structure or another. Thirdly, n.m.r. spectroscopy appears to be the most conclusive method for this type of problem. It can readily distinguish between the two possibilities, and is the only spectral method providing a direct quantitative measure of the relative amounts of each.

Excluding acids XLII and XLIII, substituents situated next to the ketone function (acids XLI and XLVI) do not appear to have any major effect on the ring-chain tautomeric equilibrium. On the other hand, with a substituent situated next to the carboxyl group (acids XXXIX, XLV, and XLVII), evidence for the ring tautomer increases. A bulky group situated next to the carboxyl group would favor ring formation and this in turn, would greatly reduce the effect of steric hindrance. Acid XL, an exception, is present mainly in the keto form. An explanation for this might be intramolecular hydrogen bonding between the oxygen atom of the nitro group and the hydrogen atom of the adjacent carboxyl group. This would necessarily involve formation of a seven-membered ring, which of course, is less stable than the six-membered ring.

The amount of ring tautomer increases in passing from the benzoyl acid series (acids XXXVIII, XXXIX, and XLI) to the acetyl series (acids XLIV, XLV, XLVI, and XLVII). This result is attributed to a steric factor and ring formation is enhanced in the acetyl acids because the smaller methyl group is in a more favorable environment in relation to the groups in its immediate vicinity. Or in other words, the carbonyl carbon atom of the ketone function involved in ring formation might attain a tetrahedral configuration less readily with the bulkier phenyl group.

Where groups are situated adjacent to both the carboxyl and ketone functions, the acid exists as the ring tautomer in the acid XLV (acetyl series). In acid XXXIX the evidence is not straightforward, but the results imply that the ring form is not present to such a great extent as it is in acid XLV. Another reason why acid XLV exists more in the ring form may be explained by a "buttressing effect" (69) of the two chlorine atoms at positions four and five. This effect would favor more ring character in acid XLV than in acid XXXIX, since the methyl group would fare better than the phenyl group in the presence of an ortho substituent.

It should be mentioned here that the acid referred to as XLVII was assumed to have the structure as indicated on the basis of the following arguments. Firstly, in the reaction of 3-methylphthalic anhydride with methylmagnesium iodide, addition at the unhindered carbonyl group is favored both sterically and electronically. Secondly, the acid would be expected to be acyclic if the methyl group were in the 3-position rather than the 6-position.

As far as the two naphthoic acids XLII and XLIII are concerned, they differ in that the carbonyl group in XLIII is more hindered than the one in XLII. Hence, more ring character should be observed in XLIII, as the results indicated. Also, there are no conflicts in this regard as there are in the case of XLII.

SUMMARY

The method of estimating the equilibrium position of ring and chain tautomers by use of the organocadmium reaction appears ineffective.

Approximation of the ring-chain equilibrium position of acids XXXVIII through XLVII by the Fischer esterification and n.m.r. analysis indicates ring character for XLIII, XLIV, XLV, and XLVII, whereas acid XLII appears to have contributions from both the ring and the chain forms.

Infrared, ultraviolet, and n.m.r. spectra favor ring structure in acids XLIII, XLIV, XLV, and XLVII. The same conclusion is drawn here for the structure of acid XLII as above. No decision can be made concerning the structure of acids XXXIX and XLVI because of conflicting results.

The amount of ring form is present to a greater extent with substituents adjacent to the carboxyl group, with the exception of acid XL. The bulkiness of the group situated next to the carboxyl function favors formation of the more stable ring structure, in which interference between the two groups is greatly reduced.

The amount of ring form increases in passing from the o-benzoylbenzoic acids to the o-acetylbenzoic acids. The presence of more ring character in the o-acetylbenzoic acids indicates that the carbonyl carbon atom involved in ring formation is better able to attain a tetrahedral configuration when it is attached to a methyl group rather than a phenyl group.

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