August 5, 1959

To the Graduate Council:

I am submitting herewith a dissertation written by Stanley Selman entitled "Rearrangements of the Benzilic Acid Type; Preparation and Use of Dialkali Metal Adducts of Aromatic Ketones." I recommend that it be accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy, with a major in Chemistry.

Jerome F. Eastham
Major Professor

We have read this dissertation
and recommend its acceptance:

D A Shirley

C A Brebbia

John W. Prados

Accepted for the Council:

Dale Krantling
Dean of the Graduate School

REARRANGEMENTS OF THE BENZILIC ACID TYPE; PREPARATION AND USE OF DIALKALI METAL ADDUCTS OF AROMATIC KETONES

A DISSERTATION

Submitted to
The Graduate Council
of
The University of Tennessee
in
Partial Fulfillment of the Requirements
for the Degree of
Doctor of Philosophy

---

by

Stanley Selman

August, 1959

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Thanks are also due to the Union Carbide Nuclear Corporation for the fellowship which helped support this work.

It is the author's pleasure to acknowledge his indebtedness to his wife whose patience, help, and understanding have been of inestimable value.

157749

To the Memory of My Beloved Mother

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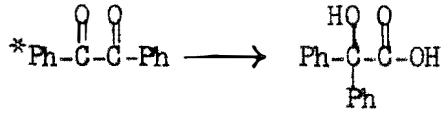
CHAPTER I

INTRODUCTION

A. The Benzilic Acid Rearrangement

The benzilic acid rearrangement is the base-catalyzed transformation of an α-diketone to the salt of an α-hydroxy acid. This rearrangement can be effected in aromatic, in semi-aromatic (o-quinones), in alicyclic, and in aliphatic, as well as in heterocyclic α-diketones. Examples of the rearrangement in the above type compounds are illustrated in equations 1-6.

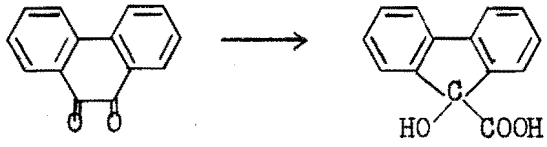
Aromatic diketones:[1]



(1)

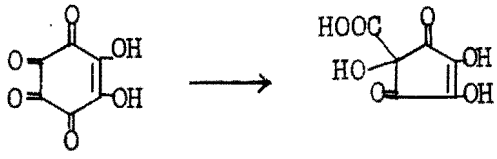
Benzil Benzilic Acid

Semi-aromatic diketones:[2,3]



(2)

Phenanthraquinone 9-Hydroxyfluorene-9-carboxylic acid



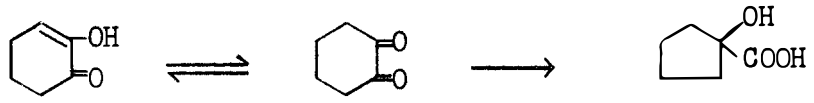
(3)

Rhodizonic Acid Croconic Acid

---

*"Ph" is used to represent the phenyl group, "An", the p-anisyl group, "Ar", other aryl groups and "R", alkyl groups throughout this dissertation. Another convention employed is that in Grignard reaction equations, the hydrolysis of the addition complex has been omitted for brevity.

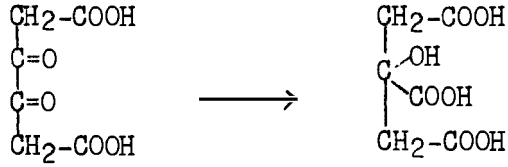
Alicyclic diketones:[4]



(4)

1,2-Cyclohexadione — 1-Hydroxycyclopentane-carboxylic Acid

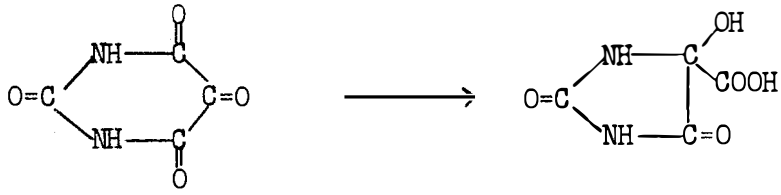
Aliphatic diketones:[5]



(5)

Ketipic Acid — Citric Acid

Heterocyclic diketones:[6]

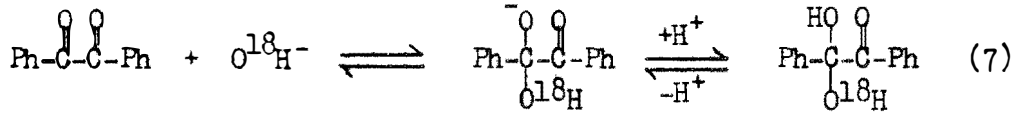


(6)

Alloxan — Alloxanic Acid

Westheimer[7] in his studies of the kinetics of this rearrangement, found the reaction to be strictly bimolecular between benzil and hydroxide ion, becoming pseudo-unimolecular in the presence of a large excess of alkali. The reaction is not one of general base catalysis (removal of a proton), as shown by the fact that phenoxide or o-chlorophenoxide ions do not catalyze the reaction, nor does it involve a free-radical mechanism since the rate is not affected by the addition of peroxides. Roberts and Urey[8] studied the rate of exchange between benzil and O^{18}-labeled water in neutral and in alkaline solution. That the exchange occurred slowly in neutral solution but was complete within four minutes in basic solution and was imperceptible in acid solution, suggested that

the rearrangement occurs after the preliminary reversible addition of hydroxide ion (equation 7).

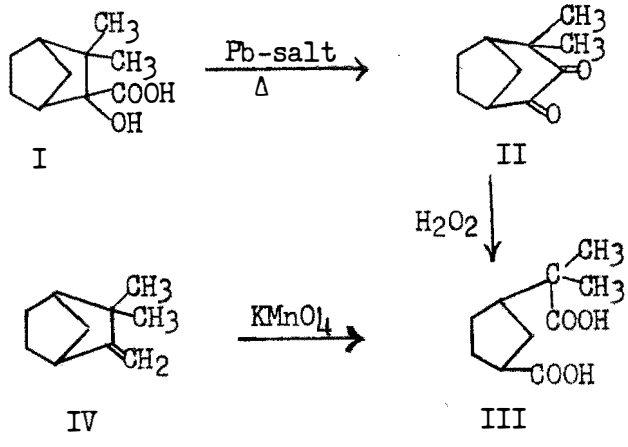


(7)

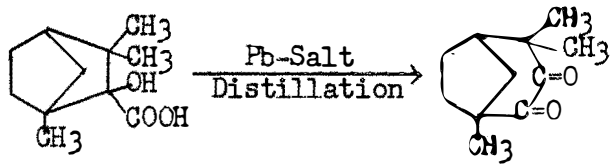
Doering and Urban[9] found that the rearrangement is not catalyzed specifically by hydroxide ion but that benzil would rearrange in the presence of properly selected alkoxide ions to yield the corresponding benzilic acid esters. That the rearrangement does not involve a proton transfer in the rate-determining step was shown by Hine and Haworth[10] who found that the rate of the rearrangement at 50° was about 85 per cent faster in 66.7 per cent dioxane-33.3 per cent deuterium oxide than in 66.7 per cent dioxane-33.3 per cent water.

The reversal of the benzilic acid rearrangement has been observed in a few isolated cases. For example, the lead salt of camphenylic acid (I) yields carbocamphenilonone (II) when heated. Since the oxidation of camphene (IV) with permanganate yields the same product, camphenic acid (III), as the peroxide oxidation of carbocamphenilonone (II), it appears as though the same reversal has also taken place in the oxidation of camphene (IV).[11]

CHART ONE



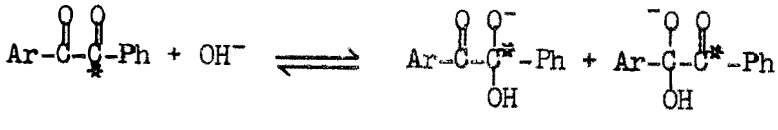
Another example of the reversal is the formation of carbofenchonone from the lead salt of α-fenchocarboxylic acid[12] (equation 8).



(8)

However, the dry distillation of the lead salt of benzilic acid and certain other α-hydroxy acids has yielded only decomposition products and no benzil or other α-diketones.[13]

That the rearrangement is generally irreversible has been shown by several investigators[14-17] in their studies of the relative migratory aptitudes of aryl groups in unsymmetrical benzils. In the most recent study[17] it was found that the rearrangement of 2-methylbenzil (V), labeled with carbon-14 in the carbonyl group adjacent to the unsubstituted phenyl ring, produces 2-methylbenzilic acid (VIII) with over 97 per cent of the labeling in the carboxyl group. This indicates that in the rearrangement the unsubstituted phenyl group migrates almost exclusively and that the rearrangement carried out under the usual conditions is irreversible. The first step of the rearrangement, i.e., the rapid and reversible addition of hydroxide ion, is shown in equation 9.

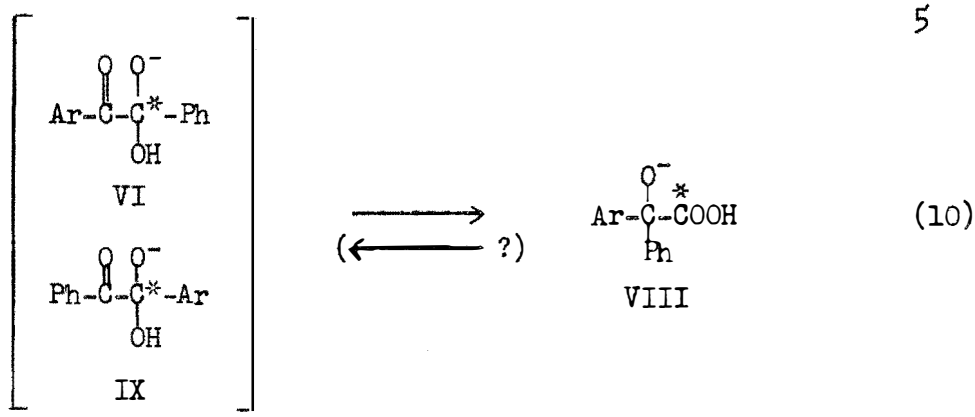


(9)

V VI VII

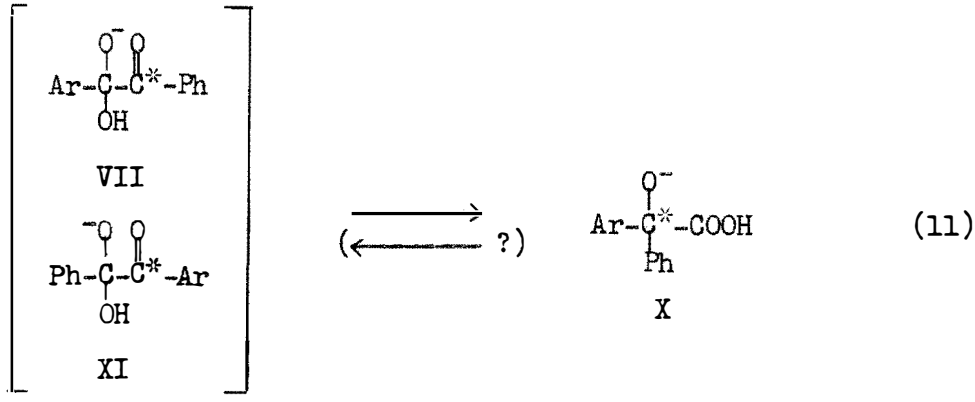
Ar = o-tolyl

Possible rate-determining rearrangements of VI and VII are shown in equations 10 and 11 respectively. Since either phenyl or o-tolyl could



(10)

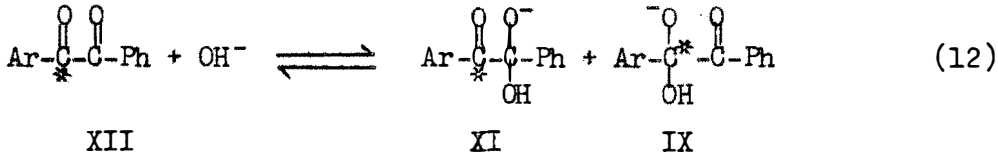
Ar = o-tolyl



(11)

Ar = o-tolyl

migrate in the proposed reverse reaction, two species VI and IX would emerge from VIII. In a similar manner VII and XI would come from X. The two species VI and VII are in equilibrium with the compound V as shown by equation 9. Similarly IX and XI would be in equilibrium with XII as shown by equation 12.



(12)

If the rate of the reverse benzilic acid rearrangement were significant, XII and V would eventually be present in approximately equal amounts and lead to approximately equal amounts of 2-methylbenzilic acid-1-C^{14}

and 2-methylbenzilic acid-2-C^{14}. In all of the rearrangements of labeled benzils studied, not one has yielded equal amounts of the two isomeric acids.

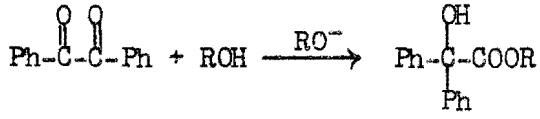
The mechanism suggested by Ingold,[18] in which there is rapid reversible addition of hydroxide ion to benzil followed by an irreversible migration of a phenyl group to the adjacent carbon atom to give an intermediate that is transformed to the benzilate anion by subsequent proton transfers (equation 13), is consistent with the present experimental data on the benzilic acid rearrangement.



(13)

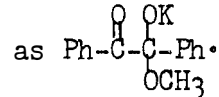
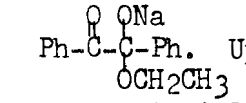
B. The Benzilic Ester Rearrangement

The benzilic ester rearrangement is the reaction of aromatic α-diketones with alkoxide ions and alcohols to yield the corresponding benzilic acid esters (equation 14).



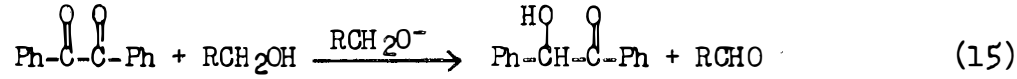
(14)

Prior to the findings of Doering and Urban[9] that benzil does rearrange in the presence of sodium methoxide or potassium t-butoxide to yield methyl benzilate and t-butyl benzilate, respectively, there were several unsuccessful attempts at effecting this type reaction. Scheuing[19] found that when a mixture of potassium methoxide, methanol and ether was added to an ethereal solution of benzil, crystals appeared after about thirty

minutes. These crystals analyzed for $C_{16}H_{17}O_4K$, which can be expressed as , and upon treatment with water gave benzil in about 80 per cent yield and benzilic acid in 14 per cent yield. No methyl benzilate was found. When the potassium methoxide-benzil adduct was dissolved in anhydrous benzene, heated for fifteen minutes, cooled and decomposed with dry carbon dioxide, the products were benzilic acid (6 per cent), benzoin (13 per cent) and benzil. The reaction of benzil with sodium ethoxide yielded crystals which analyzed for $C_{16}H_{15}O_3Na$, or . Upon treatment with water this adduct yielded benzil in 85 per cent yield and no ethyl benzilate. Lachman[20] also isolated the sodium ethoxide adduct of benzil and found that upon addition of water it decomposed quantitatively into benzil, sodium hydroxide and ethyl alcohol. When the adduct was formed in a mixture of ether with sufficient alcohol to prevent its precipitation, a number of products were formed after the solution stood three to five days at room temperature. These products were benzaldehyde, ethyl benzoate, a small amount of sodium benzoate, traces of benzilic acid, ethyl dibenzoin (1-hydroxy-3,4-diphenyl-4-benzoyltetrahydrofuran[21]) and no ethyl benzilate. More recently Swan[22] found that the reaction of potassium t-butoxide with benzil in ether gives benzilic acid and not t-butyl benzilate.

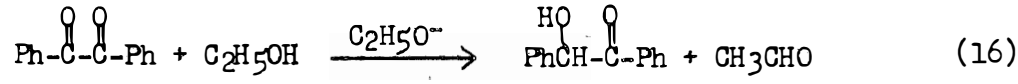
Doering and Urban[9] found that when benzil was treated with potassium t-butoxide in dry benzene, t-butyl alcohol or a mixture of the two solvents, t-butyl benzilate could be isolated in excellent yields (76-90 per cent). Up to 10 per cent of benzilic acid was also obtained. Similarly the reaction of benzil and sodium methoxide in methanol gave

methyl benzilate in 68 per cent yield along with benzilic acid (9.7 per cent), benzoin (9.6 per cent) and a small amount of benzaldehyde. The reaction of benzil with methoxide ion carried out in benzene solution yielded benzilic acid (30 per cent), methyl benzilate (18 per cent), benzoic acid (8 per cent) and benzoin (13 per cent). Doering and Urban attribute their success in effecting this reaction to the proper choice of alkoxide ion. They state that since the benzilic ester rearrangement will only be detectable when its rate is greater than roughly one-tenth the rate of the competing Meerwein-Ponndorf-Verley-Oppenauer equilibrium (equation 15), the choice of an unoxidizable (t-butoxide) or slowly oxidizable (methoxide) alkoxide ion should allow detection of the ester rearrangement. These authors also state that an additional



(15)

complication may arise if the conjugate aldehyde or ketone of the alkoxide ion undergoes aldol condensation with elimination of water. This water, which would be present largely as hydroxide ion when formed during an attempted benzilic ester rearrangement, could then effect the benzilic acid rearrangement. The formation of benzilic acid, benzoin, ethyl benzoate, benzaldehyde and ethyl dibenzoin from the reaction of benzil and sodium ethoxide in ethanol can then be rationalized by the following reactions. The reaction of benzil, ethanol and ethoxide ion produces acetaldehyde (equation 16).



(16)

The acetaldehyde undergoes aldol condensation with subsequent elimina-

ation of water (equation 17).

$$CH_3CHO \xrightarrow{CH_3CHO} CH_3\text{-}\overset{OH}{\underset{|}{C}}H\text{-}CH_2\text{-}CHO \longrightarrow CH_3\text{-}CH{=}CH\text{-}CHO + H_2O \qquad (17)$$

The water rapidly equilibrates with the ethoxide ion (equation 18).

$$H_2O + C_2H_5O^- \rightleftharpoons C_2H_5OH + OH^- \qquad (18)$$

The hydroxide ion formed leads to a benzilic acid rearrangement (equation 19).

$$Ph\text{-}\overset{O}{\overset{\|}{C}}\text{-}\overset{O}{\overset{\|}{C}}\text{-}Ph + OH^- \longrightarrow Ph\text{-}\overset{OH}{\underset{Ph}{\overset{|}{\underset{|}{C}}}}\text{-}COO^- \qquad (19)$$

The formation of benzaldehyde and ethyl benzoate can be accounted for by cleavage of the benzil perhaps by the mechanism[23] illustrated in equation 20 or by cleavage of benzoin. The ethyl dibenzoin has been shown to arise

$$Ph\text{-}\overset{O}{\overset{\|}{C}}\text{-}\overset{O}{\overset{\|}{C}}\text{-}Ph + C_2H_5O^- \rightleftharpoons Ph\text{-}\overset{O}{\overset{\|}{C}}\text{-}\overset{O^-}{\underset{OC_2H_5}{\overset{|}{\underset{|}{C}}}}\text{-}Ph \longrightarrow Ph\text{-}\overset{O}{\overset{\|}{C}}{}^{\ominus} + Ph\text{-}\overset{O}{\overset{\|}{C}}\text{-}OC_2H_5$$

$$\downarrow C_2H_5OH \qquad (20)$$

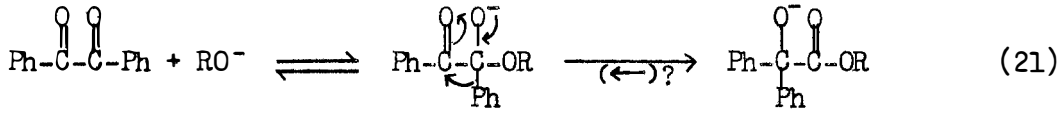
$$Ph\text{-}\overset{O}{\overset{\|}{C}}\text{-}H + C_2H_5O^-$$

from the condensation of benzaldehyde, acetaldehyde and benzoin,[21] and benzoic acid may arise from the saponification of ethyl benzoate.

If the above explanation is accepted, it is understandable why Lachman[20] did not obtain ethyl benzilate from the reaction of benzil and ethoxide ion in ethanol. However, the failure of Scheuing[19] to isolate methyl benzilate in his experiment and the inability of Swan[22] to isolate t-butyl benzilate in his experiment are not easily explained. The use of ether and benzene as a solvent for the reaction by these investigators is not a likely explanation since Doering and Urban found

that the rate of the ester rearrangement of benzil and t-butoxide ion was faster in benzene than in t-butyl alcohol.

Doering and Urban investigated the kinetics of the reaction of benzil with potassium t-butoxide in benzene solution and found that the reaction was second order overall, first order in benzil and first order in t-butoxide. They also found that the reaction is appreciably slower in t-butyl alcohol than in benzene. The mechanism which has been proposed to fit this data involves rapid and reversible addition of alkoxide to benzil followed by a rate-determining migration step (equation 21).



(21)

It appeared of interest to determine whether the reaction indicated in equation 21 by a question mark does occur to any appreciable extent under the conditions of the benzilic ester rearrangement.

After experiments were initiated towards answering this question, it was discovered that Sprecher[24] had already completed an investigation of this problem but had not published his results. In order to determine whether the benzilic ester rearrangement was reversible, Sprecher had synthesized (+)-methyl p-methylbenzilate and studied the effect of the action of alkoxide ion on its optical rotation. If the rearrangement step were reversible, the ester should racemize under these conditions. It was found that the optical rotation was, within experimental error, undiminished when the ester was refluxed for seven hours in t-butyl alcohol solution containing potassium t-butoxide, when it was refluxed

for five hours in a benzene solution containing potassium t-butoxide or when it was heated in a methanol solution containing potassium methoxide in a sealed tube at 175-180° for three hours. The conclusion was that not more than 10 per cent of the optically active material racemized in the above experiments.

Because of the large experimental error (10 per cent) inherent in the method of Sprecher and the fact that a benzilic acid ester could be chosen which should rearrange more readily than methyl p-methylbenzilate, it was decided to continue the investigation initiated in this laboratory.

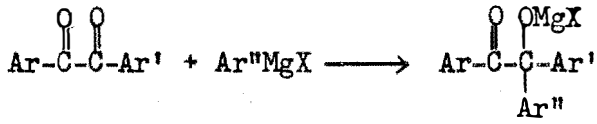
C. Tertiary Ketol Rearrangement

The tertiary ketol rearrangement (equation 22) occurs upon treat-



(22)

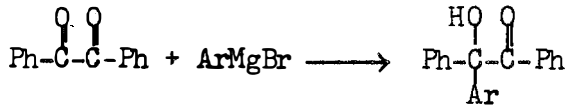
ment of an α-keto-tertiary alcohol with base. Presumably the rearranging species is the conjugate base of the alcohol. This type of species is produced when one equivalent of a Grignard reagent is added to benzil or a substituted benzil (equation 23).



(23)

Therefore it might be expected that rearranged products could be obtained from the addition of Grignard reagents to benzils.

In 1934, Roger and McGregor[25] added o-tolyl, m-tolyl and p-tolylmagnesium bromides inversely to benzil in an attempt to synthesize the corresponding α-tolylbenzoins (equation 24).



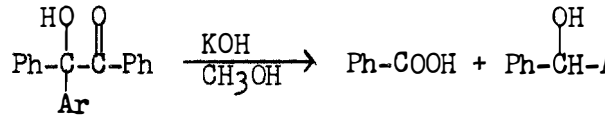
(24)

Ar = o-tolyl = XIII

Ar = m-tolyl = XIV

Ar = p-tolyl = XV

In the case of α-o-tolylbenzoin (XIII) and the α-m-tolylbenzoin (XIV), these workers obtained solid compounds, while in the case of the α-p-tolylbenzoin (XV) they obtained an oil. They cleaved the α-tolylbenzoins with alcoholic potassium hydroxide. The meta-isomer gave benzoic acid and phenyl-m-tolylcarbinol, the expected products (equation 25).



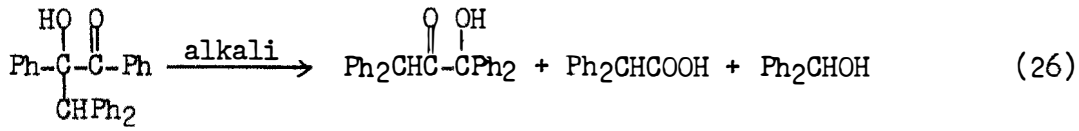
(25)

XIV

Ar = m -tolyl

However, the ortho-isomer gave o-toluic acid and benzhydrol, the products of a rearrangement. Roger and McGregor suggested that the rearrangement could have occurred during the Grignard reaction or during the alkaline cleavage.

In 1951 Curtin and Leskowitz[26] demonstrated that the treatment of α-benzhydrylbenzoin (XVI) with alkali gives α-hydroxydibenzhydryl ketone (XVII), diphenylacetic acid (XVIII) and benzhydrol (XIX). The reaction is illustrated in equation 26.



XVI XVII XVIII XIX

Since α-hydroxydibenzhydryl ketone (XVII) yields benzhydrol and diphenylacetic acid when treated with base, it was reasoned that the rearrangement and cleavage of α-benzhydrylbenzoin,(XVI) was occurring consecutively in the same medium.

Curtin and Leskowitz also suggested that this same phenomena occurred when α-o-tolylbenzoin supposedly obtained by Roger and McGregor from the reaction of benzil with o-tolylmagnesium bromide, was treated with alkali. In the opinion of these authors the α-o-tolylbenzoin (XIII) was first rearranged to α-phenyl-2-methylbenzoin (XX) and cleavage of this species gave o-toluic acid and benzhydrol (equation 27).

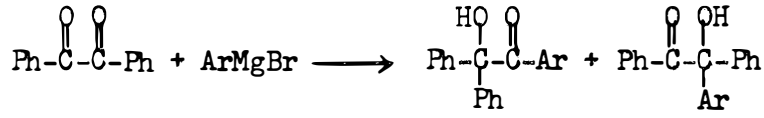


XIII XX

Ar = o-tolyl

In 1952 Sharp and Miller[27] investigated the alkaline cleavage of α-arylbenzoins and reported that the compounds obtained from the addition of tolylmagnesium bromides to benzil were produced without rearrangement and were α-tolylbenzoins. These compounds, when treated with alkali, partially or totally rearranged prior to cleavage, according to Sharp and Miller, thus explaining the presence of benzhydrol and toluic acid as cleavage products.

In a thorough reinvestigation of the alkaline cleavage of α-arylbenzoins, Eastham, Huffaker, Raaen and Collins[28] showed that the compound thought to be α-o-tolylbenzoin (XIII), obtained from the reaction of benzil and o-tolylmagnesium bromide, was in reality α-phenyl-2-methylbenzoin (XX). In addition to XX, the addition of o-tolylmagnesium bromide to benzil also yields some α-o-tolylbenzoin. It was shown that the additions of m-tolyl and p-tolylmagnesium bromides to benzil also yield the normal and the rearranged α-arylbenzoins (equation 28).

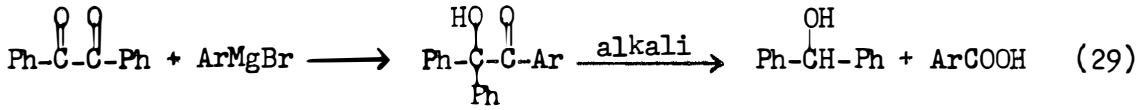


(28)

Ar = m-tolyl or p-tolyl

It was further shown that α-o-tolylbenzoin upon treatment with alkali is converted to α-phenyl-2-methylbenzoin which, in turn, is cleaved to benzhydrol and o-toluic acid (equation 27). Other α-arylbenzoins were shown to rearrange similarly in the presence of base.

Huffaker[29] showed that the additions of o-tolylmagnesium and mesitylmagnesium bromides to anisil also proceed with rearrangement. Later Doering and Urban[9] added mesitylmagnesium bromide to benzil and obtained a product (XXI) which yielded benzhydrol and mesitoic acid when treated with alkali (equation 29).

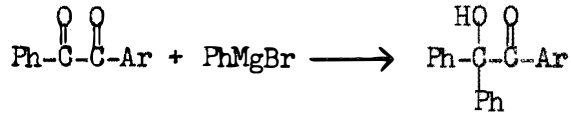


(29)

Ar = mesityl

XXI

The product (XXI) obtained by Doering and Urban was identical with that obtained from the reaction of mesityl phenyl diketone with phenylmagnesium bromide[30] (equation 30) and was assumed to be α-phenyl-2,4,6-trimethylbenzoin (XXI).

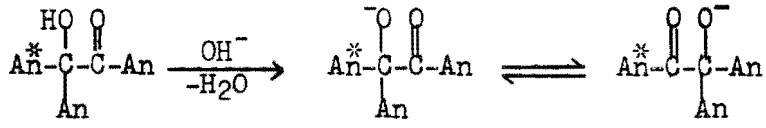


(30)

Ar = mesityl

XXI

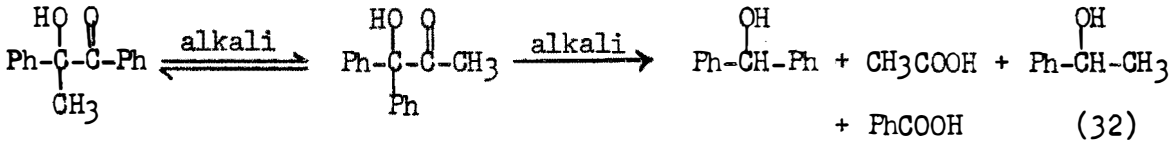
In addition to the tertiary ketol rearrangements observed when Grignard reagents are added to benzils, the rearrangements are known to occur when α-keto tertiary alcohols are subjected to alkaline conditions. Two rearrangements of this type have already been mentioned, i.e., the rearrangement of α-benzhydrylbenzoin (equation 26) and that of α-o-tolylbenzoin (equation 27). An interesting example of this type is the rearrangement of α-anisylanisoin labeled with C^{14} in one of the methoxy groups (equation 31). This reaction is analogous to the racemization



(31)

of an optically active isomer in that there is no free energy difference between the reactants and the products.

Sharp and Miller[27] reported several other rearrangements of this type, including that of α-methylbenzoin (XXII), which yielded benzhydrol in almost 50 per cent yield upon treatment with alkali (equation 32).

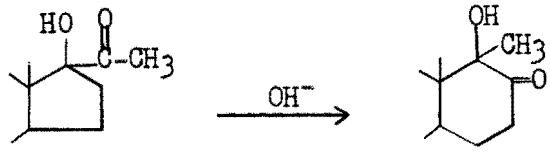


(32)

XXII

Doering and Urban[9] performed the same reaction using potassium butoxide as the base. There was obtained benzoic acid from the acid fraction and no benzhydrol from the neutral fraction, indicating that no rearrangement had taken place. Roger and McGregor[25] reported that only trace amounts of benzhydrol were obtained from the alkaline cleavage of α-methylbenzoin (XXII). The inability to quantitatively reproduce the extent of rearrangement in tertiary ketol rearrangements has also been noted by Eastham and coworkers[28] in the addition of phenyl or substituted phenyl Grignard reagents to benzil or to substituted benzils. All of the factors which control the extent of this rearrangement have yet to be elucidated.

A third type of tertiary ketol rearrangement is the acyloin rearrangement.[31] This rearrangement has been utilized almost exclusively in the steroid field and is illustrated in equation 33, where only the D-ring of a steroid is shown.



(33)

The mechanism proposed[27,28,32] for the tertiary ketol rearrangement is essentially the same as that proposed for the benzilic acid and ester rearrangements and is illustrated in equation 34.

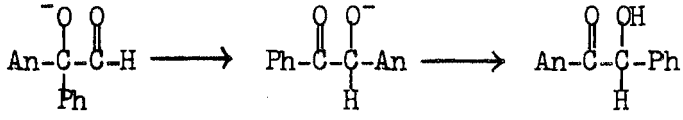


(34)

XXIII

When XXIII is formed from the addition of a Grignard reagent to a benzil or by the removal of a proton from an α-substituted benzoin (X=Z = Ar,

Y = Ar or R) then equation 34 represents the tertiary ketol rearrangement. If XXIII is formed from the reaction of benzil and hydroxide ion (Y=Z = Ar, X = OH), the equation represents the benzilic acid rearrangement. When Y=Z = Ar, X = OR then it is the benzilic ester rearrangement. The closely related rearrangement of phenylglyoxal to mandelic acid is illustrated by equation 34 when X = OH, Z = Ar, Y = H and the rearrangement of ethyl α,β-diketobutyrate to methyltartronic acid[33,34] is represented by X = OH, Y = $COOC_2H_5$, Z = CH_3 in the same equation. The rearrangement of the hydroxyaldehyde XXIII (Y = Ph, X = p-anisyl, Z = H) to 4-methoxybenzoin[35] is also readily represented by equation 34. In this last case, however, it is not clear whether phenyl or p-anisyl migrates since, under the conditions employed, if p-anisyl migrated the product (XXIV) would probably rearrange to 4-methoxybenzoin (equation 35) which is the product obtained from phenyl migration.

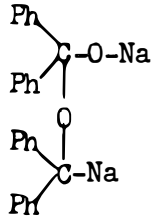


XXIII XXIV (35)

The few examples cited illustrate that the benzilic acid, the benzilic ester, the α-hydroxyketone and several other rearrangements, superficially distinct, are all mechanistically similar. Any entity possessing a carbonyl group, whether it be aldehyde, ketone, ester, acid, etc., attached to a carbon atom which possesses a hydroxyl group should be capable of exhibiting the type rearrangement illustrated in equation 34. In certain cases adverse energy or steric requirements, or competing reactions may hinder the rearrangement.

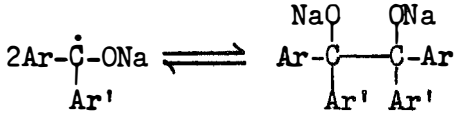
D. The Dialkali Salts of Benzophenones

In 1891 Beckmann and Paul[36] found that certain aromatic ketones react with metallic sodium in anhydrous ether and give deeply colored solutions; they considered that the compounds produced were dimolecular and had the formula XXV.



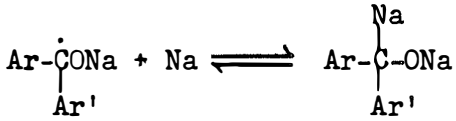
XXV

Twenty years later Schlenk and coworkers[37] proposed that these compounds were free radicals of the type Ar_2COMa formed by addition of an atom of sodium to a molecule of ketone. According to Schlenk, these ketyls, as they were named, are monomolecular and show little tendency to associate to the dimolecular form (equation 36).



(36)

Schlenk also found that disodium derivatives could be prepared by further action of metal on the ketyl in accordance with equation 37.



(37)

Whether the ketyls exist in the monomolecular or dimolecular form has been the subject of a controversy* and consequently there have been

*See W. E. Bachmann, J. Am. Chem. Soc., 55, 1179 (1933) for references to earlier papers and D. J. Morantz and E. Warhurst, Trans. Faraday Soc., 51, 1375 (1955) for references to more recent work.

numerous investigations into the reactions and physical properties of these highly colored free radicals. Several of the more important reactions of ketyls are briefly described in the following paragraph.

The ketyls react with oxygen (equation 38), as most free radicals

$$2\mathrm{Ar}\text{-}\overset{\bullet}{\underset{\mathrm{Ar'}}{\mathrm{C}}}\mathrm{ONa} + \mathrm{O_2} \longrightarrow 2\mathrm{Ar}\text{-}\underset{\mathrm{Ar'}}{\mathrm{C}}\mathrm{=O} + \mathrm{Na_2O_2} \qquad (38)$$

do, to produce sodium peroxide and starting ketone.[37] They are transformed into equimolecular amounts of starting ketone and corresponding carbinol when treated with water (equation 39).[37]

$$2\mathrm{Ar}\text{-}\overset{\bullet}{\underset{\mathrm{Ar'}}{\mathrm{C}}}\mathrm{ONa} + 2\mathrm{H_2O} \longrightarrow \mathrm{Ar}\text{-}\underset{\mathrm{Ar'}}{\mathrm{CHOH}} + \mathrm{Ar}\text{-}\underset{\mathrm{Ar'}}{\mathrm{C}}\mathrm{=O} + 2\mathrm{NaOH} \qquad (39)$$

Treatment of them with carbon dioxide followed by hydrolysis results in the formation of the corresponding benzilic acid along with starting ketone (equation 40).[37]

$$2\mathrm{Ar}\text{-}\overset{\bullet}{\underset{\mathrm{Ar'}}{\mathrm{C}}}\mathrm{ONa} \xrightarrow[2)\ \mathrm{H_2O}]{1)\ \mathrm{CO_2}} \mathrm{Ar}\text{-}\overset{\mathrm{OH}}{\underset{\mathrm{Ar'}}{\mathrm{C}}}\mathrm{-COOH} + \mathrm{Ar}\text{-}\underset{\mathrm{Ar'}}{\mathrm{C}}\mathrm{=O} + \mathrm{NaHCO_3} \qquad (40)$$

The ketyls react with alkyl halides in accordance with equation 41.[37]

$$2\mathrm{Ar}\text{-}\overset{\bullet}{\underset{\mathrm{Ar'}}{\mathrm{C}}}\mathrm{-ONa} \xrightarrow[2)\ \mathrm{H_2O}]{1)\ \mathrm{RX}} \mathrm{Ar}\text{-}\underset{\mathrm{Ar'}}{\mathrm{C}}\mathrm{=O} + \mathrm{Ar}\text{-}\overset{\mathrm{R}}{\underset{\mathrm{Ar'}}{\mathrm{C}}}\mathrm{-OH} + \mathrm{NaX} \qquad (41)$$

The literature is not quite as voluminous on reactions and properties of the dialkali salts of aromatic ketones. They were first prepared by Schlenk and coworkers[37] from benzophenone and sodium metal in ether. This procedure was carried out under a nitrogen atmosphere and took several days. Wooster,[38] following the suggestion of Kraus and White,[39] undertook an investigation of the reaction of sodium with benzophenone

in liquid ammonia. It was found that the reaction occurred readily and rapidly. Either a mono- or disodium derivative could be obtained by adding the correct proportion of sodium. It was also found that the dipotassium derivative could be prepared by the reaction of potassium amide with benzhydrol (equation 42).

$$Ph_2CHOH + 2KNH_2 \longrightarrow Ph_2\overset{K}{C}-OK + 2NH_3 \qquad (42)$$

Brook, Cohen and Wright[40] found that disodiobenzophenone could be prepared from the reaction of disodiostilbene and benzophenone (equation 43).

$$Ph-\overset{Na}{\underset{|}{C}}H-\overset{Na}{\underset{|}{C}}H-Ph + Ph_2C=O \longrightarrow Ph-\overset{H}{\underset{|}{C}}=\overset{H}{\underset{|}{C}}-Ph + Ph_2\overset{Na}{\underset{|}{C}}-ONa \qquad (43)$$

The dialkali salt of an aromatic ketone is an exceptional species in that it possesses a carbon-metal bond vicinal to an oxygen-metal bond. It might be expected to exhibit the properties of both an organometallic and an alkoxide group. It would, however, be expected that the metal atom directly attached to carbon would be more readily removed than that attached to oxygen. Therefore the dialkali salts of aromatic ketones should show all the usual organometallic reactions in addition to, if the possibility is present, the reactions of the alkali salt of an alcohol. That these expectations are not entirely correct is shown in the following discussion.

In the reaction of these dialkali salts with alkyl halides the organometallic property of the salt should manifest itself in an alkylation type reaction (equation 44).

$$Ar-M + R-X \longrightarrow Ar-R + MX \qquad (44)$$

M = alkali metal X = halogen

In addition, the salt of the alcohol would be expected to partake in a Williamson ether synthesis with the alkyl halide (equation 45).

$$R\text{-}C\text{-}OM + R'X \longrightarrow R\text{-}C\text{-}O\text{-}R' + MX \qquad (45)$$

Wooster[38] found that disodiobenzophenone can be alkylated in ammonia solution with ethyl bromide to form 1,1-diphenyl-1-propanol (XXVI). The yield was not reported and ethylamine was obtained as a side reaction product (equation 46).

$$Ph\text{-}\overset{\overset{Na}{|}}{\underset{\underset{Ph}{|}}{C}}\text{-}ONa \xrightarrow{C_2H_5Br} Ph\text{-}\overset{\overset{ONa}{|}}{\underset{\underset{Ph}{|}}{C}}\text{-}C_2H_5 \xrightarrow[NH_3]{C_2H_5Br} Ph\text{-}\overset{\overset{OH}{|}}{\underset{\underset{Ph}{|}}{C}}\text{-}C_2H_5 + C_2H_5NH_2 + NaBr \qquad (46)$$

XXVI

Prolonged action of ethyl bromide in large excess did not lead to the formation of 1,1-diphenylpropyl ethyl ether (XXVII). Schlenk and Bergmann[41] reported that the reaction of disodiobenzophenone with excess benzyl chloride (equation 47) in ether yields 1,1,2-triphenylethanol

$$Ph\text{-}\overset{\overset{OC_2H_5}{|}}{\underset{\underset{Ph}{|}}{C}}\text{-}C_2H_5$$

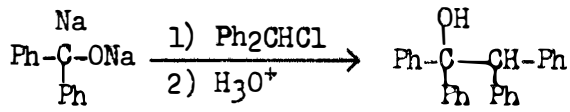
XXVII

$$Ph\text{-}\overset{\overset{Na}{|}}{\underset{\underset{Ph}{|}}{C}}\text{-}ONa \xrightarrow[2)\ H_3O^+]{1)\ PhCH_2Cl} Ph\text{-}\overset{\overset{OH}{|}}{\underset{\underset{Ph}{|}}{C}}\text{-}CH_2\text{-}Ph \qquad (47)$$

XXVIII

(XXVIII) as the sole product. Hamrick and Hauser[42] treated disodiobenzophenone in liquid ammonia solution with an equimolar amount of benzyl chloride and obtained XXVIII in 76 per cent yield. The latter investigators also treated disodiobenzophenone in liquid ammonia solution with an equimolar amount of benzhydryl chloride and obtained 1,1,2,2-tetra-

phenylethanol (XXIX) in 82 per cent yield (equation 48).



(48)

XXIX

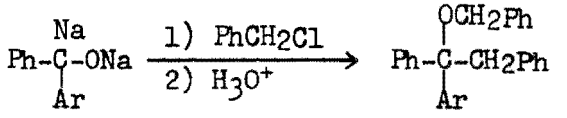
In none of the alkylations of disodiobenzophenone was any ether formation reported.

The apparent unreactivity of the oxygen-metal bond in disodiobenzophenone towards ether formation in the presence of alkyl halide could be attributed to the initial formation of the salt of a tertiary alcohol by the replacement of the sodium atom attached to carbon (equation 49).



(49)

It has been reported[43] that tertiary alkoxides do not perform well in a Williamson type ether synthesis. That this proposal might not be completely valid has been indicated by the reaction of disodio-4-phenylbenzophenone with excess benzyl chloride[41] (equation 50) to yield 1-biphenylyl-



(50)

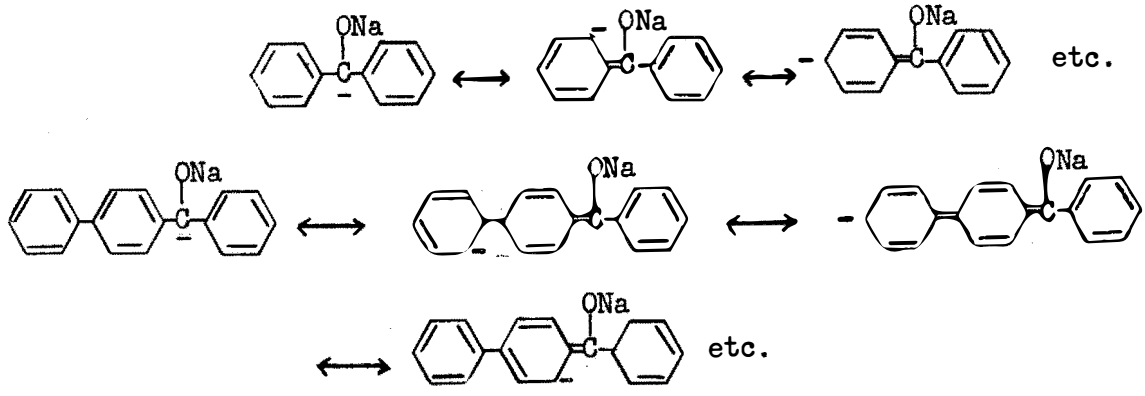
Ar = biphenylyl XXX

1,2-diphenylethyl benzyl ether (XXX), a product which indicates ether formation can occur on the tertiary alkoxide.

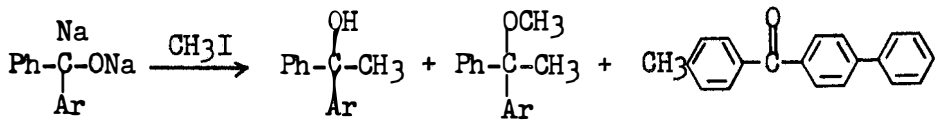
Another possible explanation of the alkoxide's unreactivity is that the proximity of the carbon-sodium bond to the oxygen-sodium bond might bring about a decrease in the latter's reactivity. The decrease

could be explained by a diminution in the ionic character of the oxygen-sodium bond caused inductively by the high electron density on the adjacent carbon atom. Of course the high electron density on the oxygen atom could also inductively produce a similar effect on the carbon bond. However, a small decrease in the reactivity of a highly reactive group would not be as noticeable as a similar decrease in an only moderately reactive group.

The fact that disodio-4-phenylbenzophenone forms an ether with benzyl chloride while disodiobenzophenone, under identical conditions, does not, could be explained by the greater ionic character, and therefore reactivity, of the oxygen-sodium bond in disodio-4-phenylbenzophenone. This bond, in comparison to the same bond in disodiobenzophenone, would be more ionic due to a lower electron density on its adjacent carbon atom. This lower electron density could be a result of a greater distribution of electrons in the 4-phenyl species than in the disodiobenzophenone. The distribution of electrons in both species is illustrated below.



Evidence that lends credence to the hypothesis that the charge is distributed into the aromatic rings is found in the reaction of disodio-4-phenylbenzophenone with methyl iodide (equation 51).[41]



(51)

XXXI XXXII XXXIII

Ar = biphenylyl

The products of this reaction are 1-phenyl-1-biphenylylethanol (XXXI), 1-phenyl-1-biphenylethyl methyl ether (XXXII) and a small amount of 4-phenyl-4'-methylbenzophenone (XXXIII). The formation of product such as XXXIII can be rationalized as a consequence of the delocalization of electrons into the rings from the carbonyl carbon atom.

Whatever explanation is correct, the dialkali salts of benzophenones do react like other organometallic compounds. In certain cases they act both as an organometallic and a tertiary alkoxide.

The addition of water, or ammonium chloride when the reaction is carried out in liquid ammonia, to disodiobenzophenone gives as a product benzhydrol[37,38] (equation 52).

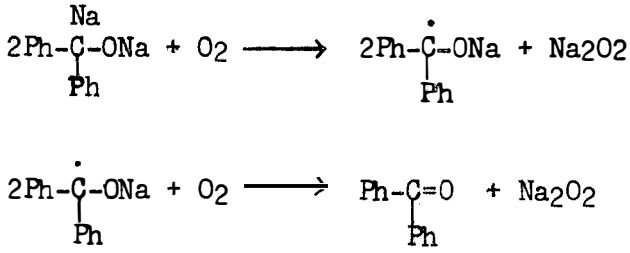


(52)

The water reacts with the organometallic bond in the usual manner and also hydrolyzes the alkoxide group.

The treatment of disodiobenzophenone with oxygen gives benzophenone and sodium peroxide. The reaction would be expected to involve primarily the carbon-sodium bond since oxygen does not generally affect

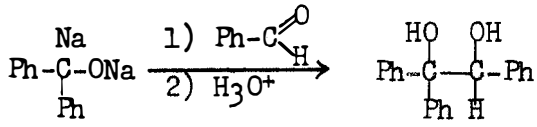
alkoxides. The reaction has been postulated[37] to proceed in accordance with equation 53.



(53)

The oxygen reacts with the carbon-metal bond thus forming the ketyl which reacts with oxygen to give benzophenone.

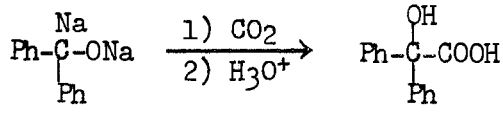
Disodiobenzophenone reacts in the usual organometallic fashion and adds to the carbonyl group of benzaldehyde to form 1,1,2-triphenylethylene glycol (XXXIV) in 91 per cent yield (equation 54).[42]



(54)

XXXIV

The reaction of carbon dioxide with disodiobenzophenone yields benzilic acid after hydrolysis (equation 55).[37]

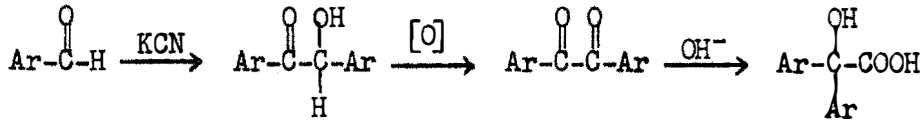


(55)

The reaction of carbon dioxide with an organometallic to produce the corresponding carboxylic acid is a well known reaction and has been utilized extensively in the elucidation of the structure of organometallic compounds. The disodium salts of several substituted benzophenones (4-phenyl and 4,4'-diphenyl)[37] have been prepared and subsequently carbonated for precisely this reason. Bachmann and Sternberger,[44]

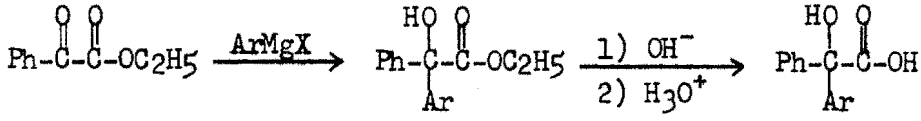
however, in one of the rare instances, utilized this reaction strictly for the purpose of synthesizing a benzilic acid.

The usual method for preparing benzilic acids that are similarly substituted in both phenyl rings is through the benzoin condensation of the corresponding aldehyde, followed by oxidation to the benzil and rearrangement of the latter by base (equation 56).



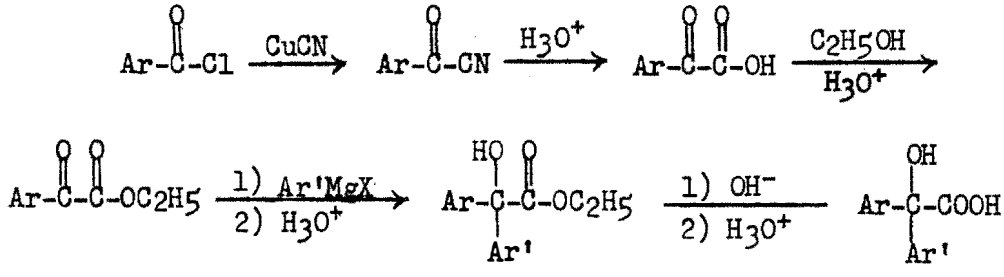
(56)

The preparation of benzilic acids substituted only in one phenyl ring is accomplished by the addition of the appropriate Grignard reagent to the commercially available ethyl phenylglyoxylate and saponification of the resulting ester (equation 57).



(57)

The general preparation of a benzilic acid substituted differently in each phenyl ring would probably entail the primary synthesis of the appropriate ethyl arylglyoxylate followed by Grignard addition and saponification:



Utilization of the reaction of the dialkali salts of aromatic ketones with carbon dioxide appears to be preferable to the above methods for the synthesis of benzilic acids.

The utility of these dialkali derivatives of aromatic ketones as intermediates in synthesis procedures has not been investigated extensively. After the present investigation was begun, Hamrick and Hauser[42] suggested their use in the synthesis of certain substituted glycols from appropriately substituted benzaldehydes. Since dialkali salts of aromatic ketones should undergo all reactions typical of organometallics, they should be capable of being transformed into many different types of compounds and could therefore become important intermediates in organic synthesis.

E. Statement of the Problem

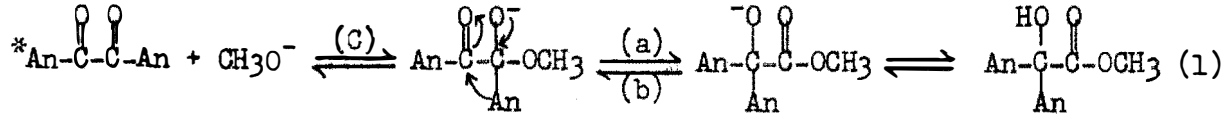
The initial purpose of this work was to determine whether the rate-determining step of the benzilic ester rearrangement was, in reality, an equilibrium process with a measurable reverse rate. In order to attain this goal it was necessary to synthesize methyl anisilate-1-C^{14}. The utilization of a dialkali salt of an aromatic ketone as an intermediate in this synthesis appeared promising. For this reason a secondary investigation was initiated to determine the factors which affect the formation of these dialkali salts and the feasibility of their use as intermediates in the synthesis of certain types of compounds which are arduous to attain by other methods.

In addition certain base-catalyzed rearrangements similar to the benzilic acid rearrangement were briefly investigated.

CHAPTER II

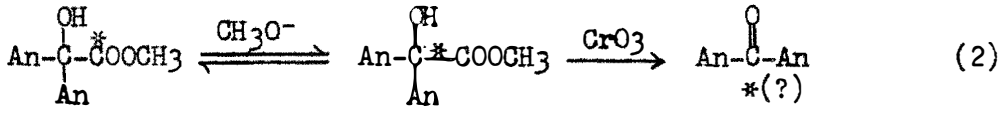
PRESENTATION AND DISCUSSION OF RESULTS

By analogy to the results obtained by Doering and Urban[9] on the reaction of benzil and methoxide ion, the reaction of anisil and methoxide ion would give methyl anisilate as a product and would be expected to proceed according to the mechanism illustrated in equation 1.



II I (1)

It appeared of interest to determine whether reaction "b" in equation 1 does occur under the conditions of the benzilic ester rearrangement. It was proposed that the treatment of methyl anisilate-1-C^{14} with methoxide ion in methanol, reisolation of the ester (I), degradation of it to 4,4'-dimethoxybenzophenone (III) and determination whether this ketone possessed any radioactivity (equation 2) would ascertain whether reaction "b" in equation 1 did occur.



III (2)

A compound was needed which contained a group which would migrate readily to an electrophilic carbon atom in a 1,2-shift, i.e., the group should have a large intrinsic migratory aptitude. Bachmann[45] has shown that the p-anisyl group possesses an extremely large intrinsic migratory

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*The Roman numerals begin anew in this chapter.

aptitude. Another desirable feature was that the intermediate α-diketone should possess a large amount of resonance energy. This was desired in order that there be an optimum in the free energy difference between the ester and the diketone. Methyl anisilate-1-C^{14} conformed to both of the above criteria and was therefore synthesized and utilized to determine whether reaction "b" in equation 1 does occur.

The reaction of sodium methoxide with methyl esters can yield the sodium salt of the carboxylic acid and dimethyl ether.[46] This reaction of methyl anisilate-1-C^{14} with methoxide ion is shown in equation 3.



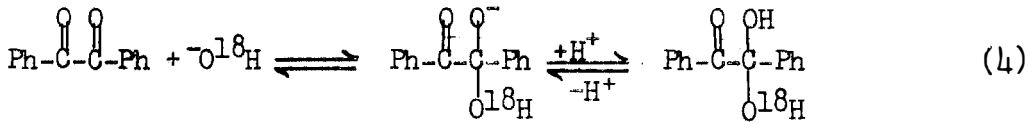
(3)

I XIII

The reaction probably consists of a direct nucleophilic displacement on the methyl carbon atom of the ester and would therefore involve no migration of p-anisyl groups. If the displacement reaction (equation 3) were rapid the ester (I) might not be long lived enough to rearrange (reaction "b" in equation 1). However, a qualitative estimate of the velocity of the displacement reaction (equation 3) could be obtained by refluxing a solution of methyl anisilate, sodium methoxide and methanol in the same relative proportions and for the same time as would be used in the radioactive experiment and determining the quantity of ester that could be reisolated.

If reaction "b" in equation 1 does occur then radioactivity would appear in the degradation product (4,4'-dimethoxybenzophenone) only if

the reaction of methoxide ion with anisil (reaction "C" equation 1) is rapid and reversible. This rapid reversibility was assumed to be true on the basis of the findings of Roberts and Urey[8] and Bender and Glasson.[47] Roberts and Urey found that benzil rapidly exchanged oxygen-18 with H_2O^{18} in the presence of hydroxide ion (equation 4).



(4)

This fact proved that the first step in the benzilic acid rearrangement is a rapid and reversible addition of hydroxide ion to a carbonyl group in benzil. There is evidence that the reversible attack of methoxide ion on a carbonyl is even more rapid than that of hydroxide ion. Bender and Glasson have shown that in aqueous alcohol solutions the basic alcoholysis of esters (a reversible reaction) occurs faster than hydrolysis in many cases; i.e., the rate of attack of methoxide ion on an ester carbonyl is greater than that of hydroxide ion.

Therefore, if the displacement reaction (equation 3) is relatively slow and the above assumption is correct, then the proposed scheme (reaction 2) will unequivocally ascertain whether reaction "b" in equation 1 occurs under the specified conditions.

Another possible method of ascertaining whether reaction "b" in equation 1 does occur would be the treatment of methyl anisilate or methyl benzilate with sodium ethoxide in ethanol followed by the identification of all reaction products. The reaction of benzil with sodium ethoxide in ethanol has been shown[9,20] to yield as products benzoic acid, ethyl benzoate, benzaldehyde, benzoin and benzilic acid. The

benzilic acid was probably formed via the displacement reaction of ethoxide ion on ethyl benzilate or the reaction of hydroxide ion on benzil (see page 9).

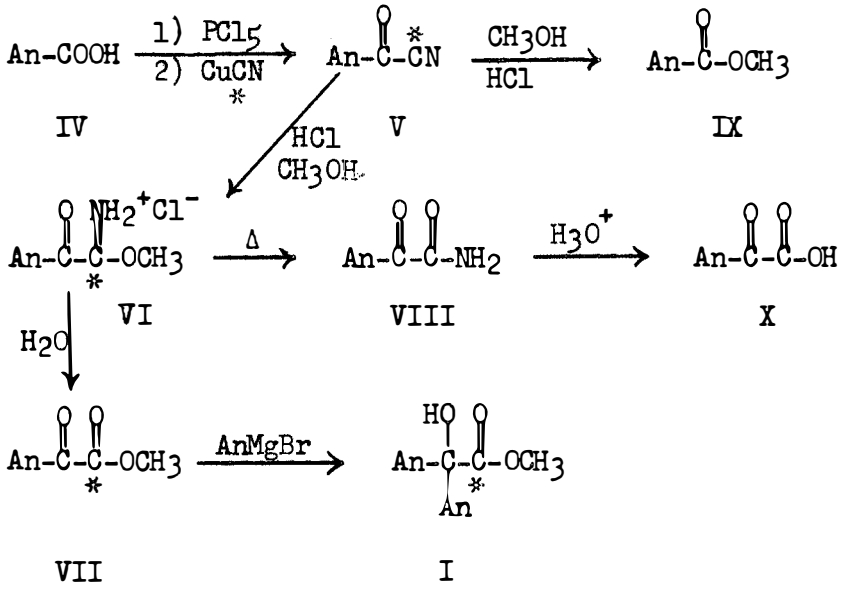
If reaction "b" in equation 1 does occur, then treatment of methyl anisilate with ethoxide ion will cause the ester (I) to be in equilibrium with a finite amount of anisil. The anisil should react with ethoxide ion analogously to benzil's reaction with ethoxide ion and yield anisic acid, ethyl anisate, anisaldehyde, anisoin and anisilic acid. The position of equilibrium should continuously change as the anisil is removed until virtually no methyl anisilate remains. Anisic acid, ethyl anisate, anisaldehyde and anisoin can only arise from anisil and not from methyl anisilate under these conditions. Therefore, the presence of any of the above compounds when methyl anisilate is treated with ethoxide ion in ethanol would prove the occurrence of reaction "b" in equation 1.

A. Synthesis of Methyl Anisilate-1-C^{14}

The method of synthesis which was utilized in the preparation of methyl anisilate-1-C^{14} (I) is outlined in Chart One. Anisoyl chloride was prepared by the reaction of anisic acid (IV) with phosphorus pentachloride and treated with cuprous cyanide-C^{14} to give anisoyl cyanide-1-C^{14} (V) in 62 per cent yield. Treatment of anisoyl cyanide-1-C^{14} with anhydrous methanol and hydrochloric acid in ether by the method of Pinner[48] gave 4-methoxyphenylglyoxylimino methyl ether hydrochloride (VI), which was immediately hydrolyzed to methyl 4-methoxy-

phenylglyoxylate-1-C^{14} (VII). The overall yield from anisoyl cyanide-1-C^{14} (V) to methyl 4-methoxyphenylglyoxylate-1-C^{14} (VII) was 48 per cent. The addition of p-methoxyphenylmagnesium bromide to VII gave methyl anisilate-1-C^{14} (I) in 22 per cent yield.

CHART ONE



The critical step in the synthesis shown in Chart One was the preparation of 4-methoxyphenylglyoxylimino methyl ether hydrochloride (VI). Although VI was not purified nor carefully characterized, it was isolated in a crystalline form whose solubility characteristics and chemical reactions establish its structure. Compound VI is apparently the first iminoether hydrochloride to be obtained from an aroyl cyanide. The principal difficulty encountered in preparing compounds like VI is the formation of decarbonylation products (IX) and decomposition products VIII. Whether the decarbonylation products come about from the decarbonylation of the incipient arylglyoxylic acid ester or from the direct reaction of the nitrile with the alcohol (equation 5)

$$Ar\text{-}\overset{O}{\overset{\|}{C}}\text{-}CN + HOCH_3 \longrightarrow Ar\text{-}\overset{O}{\overset{\|}{C}}\text{-}OCH_3 + HCN \qquad (5)$$

was not ascertained in this study. Migrdichian[49] reported that benzoyl cyanide does not form an iminoether but reacts with alcohols in the presence of hydrochloric acid to form benzoic acid esters. This was found to be the case when anisoyl cyanide (V) was treated with a large excess of anhydrous methanol in the presence of hydrochloric acid. The product obtained was methyl anisate (IX) in 88 per cent yield. The obtaining of the iminoether (VI) was facilitated by the use of anhydrous ether as a solvent, a stoichiometric amount of methanol, low temperatures and strictly anhydrous conditions throughout the reaction. When the ethereal solution of hydrochloric acid, nitrile and alcohol was allowed to remain for prolonged periods, even at 10°, without inducing crystallization, or when the temperature of the solution was allowed to rise considerably, the product was 4-methoxyphenylglyoxylamide (VIII). The amide VIII was identified by its physical properties and hydrolysis to 4-methoxyphenylglyoxylic acid (X). The formation of amides by decomposition of iminoethers is a known reaction[49] and is shown by equation 6.

$$An\text{-}\overset{O}{\overset{\|}{C}}\text{-}\overset{NH_2^+Cl^-}{\overset{|}{\overset{\|}{C}}}\text{-}OCH_3 \longrightarrow An\text{-}\overset{O}{\overset{\|}{C}}\text{-}\overset{O}{\overset{\|}{C}}\text{-}NH_2 + CH_3Cl \qquad (6)$$

VI VIII

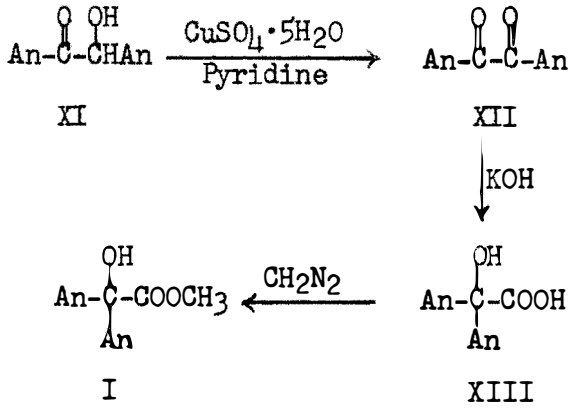
Therefore, in addition to the conditions mentioned above for obtaining aroyl iminoethers, care should also be taken to insure rapid crystallization of the hydrochloride (VI) from solution and it should be hydrolyzed shortly thereafter to obtain the ester (VII).

An attempt was made to prepare methyl p-methoxyphenylglyoxylate (VII) directly from anisoyl cyanide (V) without isolating the iminoether (VI). Anisoyl cyanide was treated with methanol, sulfuric acid and water according to the method of Spiegel.[50] The product was methyl anisate in 70 per cent yield. Hydrolysis of anisoyl cyanide with concentrated hydrochloric acid proved unsatisfactory for the preparation of 4-methoxyphenylglyoxylic acid (X) due to the formation of anisic acid along with the desired product.

B. Proof of Position of Labeling in Methyl Anisilate-1-C^{14} and Irreversibility of the Benzilic Ester Rearrangement

Unlabeled methyl anisilate was prepared from anisoin (XI) as outlined in Chart Two.

CHART TWO

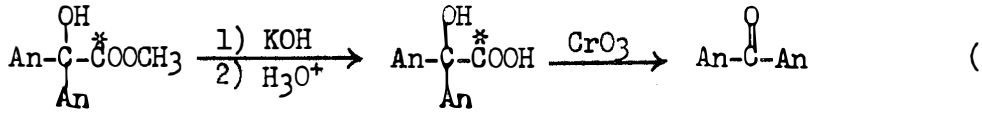


Anisoin (XI) was oxidized to anisil (XII) in 97 per cent yield with cupric sulfate in pyridine by the method of Clarke and Dreger.[51] Rearrangement of the anisil to anisilic acid (XIII) was accomplished using potassium hydroxide in n-butanol[52] or potassium hydroxide in a

mixture of absolute ethanol and anhydrous ether.[44] The yield in either case was 48 per cent. Methyl anisilate was obtained in 94 per cent yield by the esterification of the acid with diazomethane.

Experiments with the unlabeled methyl anisilate (I) indicated that this ester would have to be saponified before it could be successfully degraded. Direct chromic acid oxidation of I yielded no crystalline product. However, when chromic acid oxidation was carried out on anisilic acid (XIII), the expected product, 4,4'-dimethoxybenzophenone (III), was obtained.

It was shown that no rearrangement had occurred during the synthesis of methyl anisilate-1-C^{14} (I) and that none would occur during its saponification or oxidation by treating a sample of methyl anisilate-1-C^{14} with aqueous alcoholic potassium hydroxide, isolating anisilic acid-1-C^{14} (XIII) and oxidizing it to unlabeled 4,4'-dimethoxybenzophenone (III). The conditions used in this experiment were identical with those to be used after treatment of the methyl anisilate-1-C^{14} (I) with methoxide ion. The yield of anisilic acid-1-C^{14} (XIII) was 75 per cent from methyl anisilate-1-C^{14} (I, 4.62 mc./mole) and the yield of 4,4'-dimethoxybenzophenone (III, <0.016 mc./mole)* was 44 per cent from anisilic acid-1-C^{14}. The above series of reactions are shown in equation 7.



(7)

4.62 mc./mole XIII <0.016 mc./mole

*Since measured activities were not corrected for background activity, values less than 0.02 mc./mole are insignificant.

A qualitative estimate of the velocity of the displacement reaction (equation 3) was obtained by refluxing a solution of methyl anisilate, sodium methoxide and anhydrous methanol for two days. The relative proportions of ester and base were the same as those used in the radioactive run. There was obtained an 80 per cent recovery of methyl anisilate indicating that the displacement reaction (equation 3) is slow and would allow rearrangement of the methyl anisilate-1-C^{14} (I) if the rate of reaction "b" in equation 1 were appreciable.

Methyl anisilate-1-C^{14} (I, 4.62 mc./mole) was treated with sodium methoxide in anhydrous methanol at 97 ± 2° for two days. An aqueous solution of potassium hydroxide was added to saponify the ester (I) remaining in solution. The anisilic acid-1-C^{14} (XIII) obtained was oxidized to 4,4'-dimethoxybenzophenone (III) whose activity was less than 0.017 mc./mole. No rearrangement was therefore detected.

Rearrangement of the ester (I) was then attempted under more vigorous conditions. Methyl anisilate-1-C^{14} (I, 4.62 mc./mole) was treated with sodium methoxide in anhydrous methanol at 200 ± 6° for two days. The crude anisilic acid-1-C^{14} (XIII), which constituted the majority of the reaction product, was isolated and oxidized to 4,4'-dimethoxybenzophenone (III) whose activity was less than 0.035 mc./mole. Still no rearrangement was detected within experimental error.

This study has shown that the rate of reaction "b" in equation 1 must be negligible, if existent at all, at 97 ± 2°. The results at 200 ± 6° are not unequivocal since at this temperature the rate of the displacement reaction (equation 3) which gave rise to the acid analyzed

could be much greater than that of the rearrangement. That is, the lack of activity in the 4,4'-dimethoxybenzophenone (III) resulting from the oxidation of the acid fraction may have been because the acid (XIII) was formed via the displacement reaction before any ester (I) could rearrange. The neutral fraction remaining after treatment of methyl anisilate-1-C^{14} with methoxide ion was very small and was not analyzed.

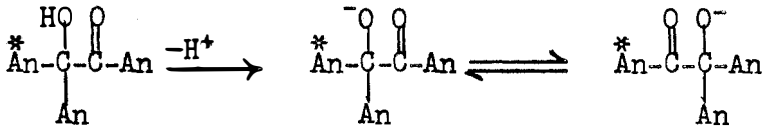
C. Additional Evidence Indicating Irreversibility of the Benzilic Ester Rearrangement

In addition to the evidence obtained from the above experiments, additional evidence that reaction "b" in equation 1 does not occur was obtained by the treatment of methyl benzilate and methyl anisilate with ethoxide ion. A solution of methyl anisilate (I) and sodium ethoxide in anhydrous ethanol was refluxed for forty-eight hours. The reaction mixture was worked up and the products were identified. None of the possible reduction or cleavage products (anisoin, ethyl anisate, anisaldehyde, etc.) of anisil were found to be present. The amounts of the products identified corresponded to an 82 per cent recovery of starting ester (I). A similar experiment was performed on methyl benzilate and the results were the same.

It may therefore be concluded that the benzilic ester, as well as the benzilic acid, rearrangement carried out under the usual conditions is virtually irreversible.

Apparently the resonance energy in the carboalkoxy group causes the difference in energy between the ester and the transition state to be much greater than the energy difference between the benzil and the transition state. The difference in energies is even greater in the benzilic acid rearrangement where the product contains the highly resonance stabilized carboxylate anion. Therefore these two rearrangements are irreversible under the usual operating conditions because the activation energy of the reverse reaction in either rearrangement is considerably greater than the energy present in the system.

In contrast to the benzilic acid and ester rearrangement, the rearrangement of α-anisylanisoin[28] (equation 8) possesses no free energy

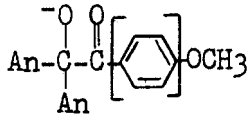


(8)

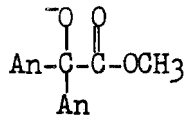
XIV

difference between the reactants and the products. That is, the difference in energy between the reactant and the transition state is the same as the difference in energy between the transition state and the product. Therefore if sufficient energy is present to cause the reactant to attain the transition state and proceed on to the product, sufficient energy is also present to cause the product to proceed through the transition state back to starting material. The reaction is therefore reversible.

The only structural difference between α-anisylanisoin (XIV) and methyl anisilate (I) is the presence of a benzene ring between the carbonyl and the methoxy group as shown below.

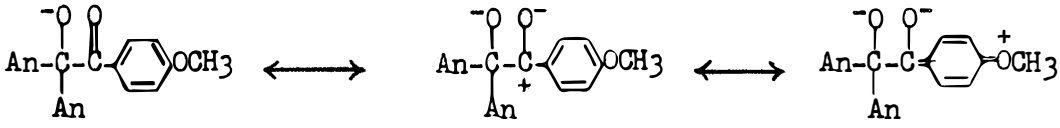


XIV

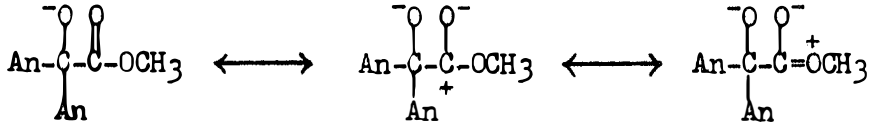


I

The most important pertinent contributing resonance forms of these two structures (XIV and I) are listed below.



XIV XIVa XIVb

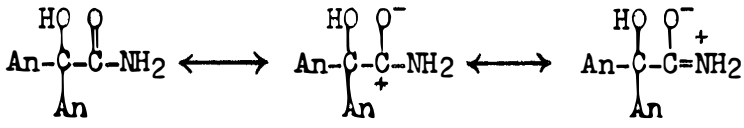


I Ia Ib

The structures XIVb and Ib involve a transfer of a pair of electrons from the p orbital of oxygen to a π orbital involving the carbonyl carbon atom. These two structures therefore give rise to an increase in electron density in the vicinity of the carbonyl carbon atom in the actual molecule. Since steric encumbrances are probably not a factor, the high activation energy for the rearrangement of methyl anisilate is probably due to the lack of electrophilic character of the carbon atom of the carbonyl group caused by the large contribution of structure Ib to the actual structure of the molecule. Structure Ib probably makes a far more important contribution to the actual structure of methyl anisilate than structure XIVb makes to the actual structure of α-anisyl-anisoin since structure XIVb contains a ring with a quinoid structure while XIV and XIVa contain only benzenoid rings. Therefore the carbonyl

carbon atom in α-anisylanisoin is probably more electrophilic than the corresponding carbon atom in methyl anisilate and the activation energy for the rearrangement of the anisoin would be less.

The above line of reasoning can be extended and utilized to predict whether or not certain other rearrangements might occur. For example, a compound such as anisilamide (XV) when subjected to basic conditions (that would not hydrolyze it to anisilic acid) would not be expected to rearrange. The contribution of structure XVb to the actual



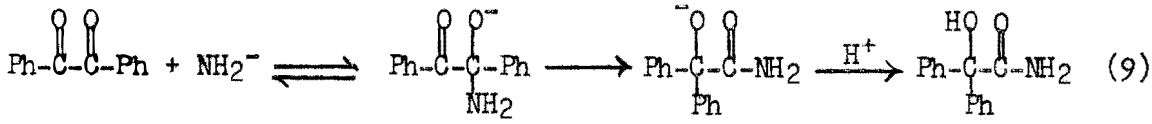
XV XVa XVb

structure of anisilamide is probably greater than the contribution of structure Ib to the actual structure of methyl anisilate due to the fact that nitrogen will more readily give up a pair of electrons and accept a positive charge than oxygen will. Thus the carbon atom of the carbonyl group in anisilamide (XV) is less electrophilic than the corresponding carbon atom in methyl anisilate. Since methyl anisilate does not rearrange, it would not be expected that anisilamide (XV) would.

D. Related Rearrangements

1. Reaction of Benzils With Amide Ion

In the reaction of benzil with sodamide, it would be expected that benzilamide would be the product if the reaction proceeds analogously to the benzilic acid and ester rearrangements (equation 9).

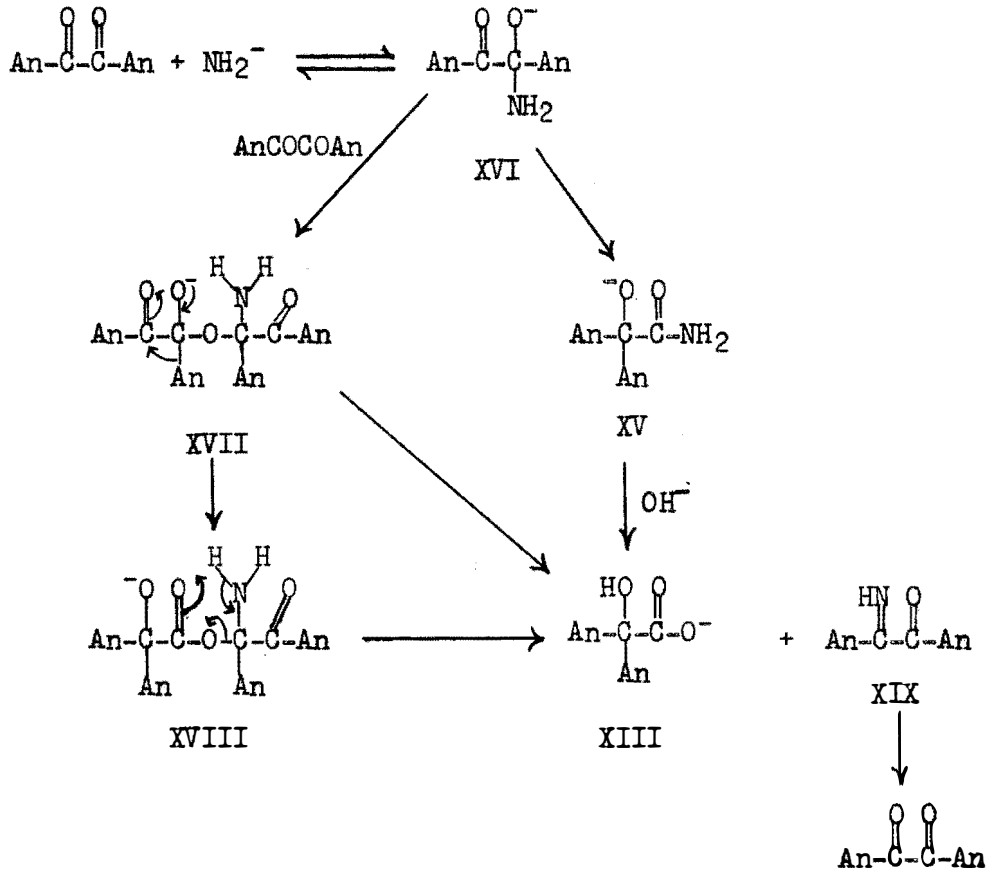


Kasiwagi[53] treated benzil with sodamide in toluene and, upon addition of water to the resultant mixture, obtained benzilic acid, not benzilamide as the product. The yield of benzilic acid and the identity of the products prior to the addition of water were not reported. In order to ascertain the magnitude of the yield of a benzilic acid in a benzil-amide ion reaction and also to learn whether or not anisil would react analogously to benzil, the reaction of anisil and sodamide was carried out.

After treatment of anisil with sodamide in toluene, no attempt was made to identify products prior to treatment of the reaction mixture with water. The products obtained were unreacted anisil (80 per cent recovery) and anisilic acid in 19 per cent yield based on reacted anisil. The anisilic acid (XIII) was probably formed by one of the mechanisms outlined in Chart Three. Amide ion could react with a carbonyl group in the anisil molecule to yield the adduct XVI which could rearrange to anisilamide (XV). Upon addition of water to the reaction mixture, the basic solution obtained might effect the hydrolysis of the amide (XV) to anisilic acid (XIII). It is also possible that the intermediate adduct XVI instead of rearranging might react with a carbonyl group of an anisil molecule. This would produce XVII which could rearrange in the usual benzilic acid manner to yield XVIII which could readily rearrange through a quasi six-membered ring to give anisilic acid (XIII) in addition to XIX, the monoketimine of anisil. It is also possible that XVII might rearrange directly to

yield XIII and XIX. The ketimine XIX in aqueous base would probably be transformed into anisil.

CHART THREE

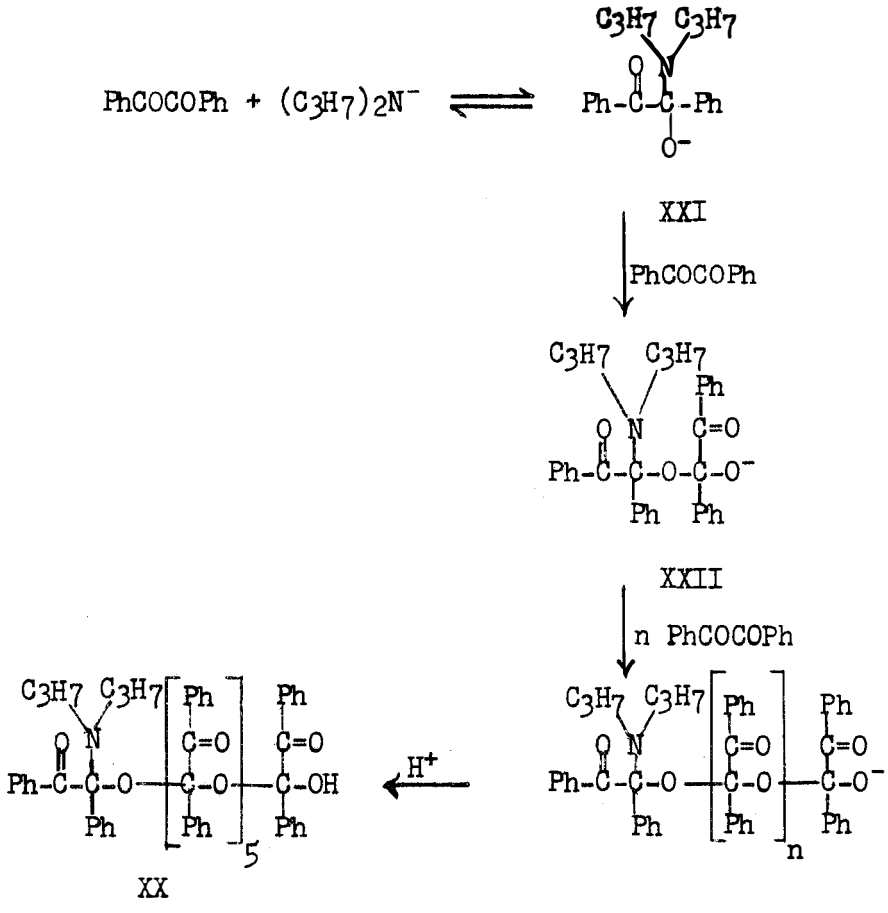


In the transformation of anisil to anisilic acid catalyzed by amide ion in a non-hydroxylic solvent, the acquisition of an oxygen atom must be accounted for. The first mechanism proposed above, i.e., the acid (XIII) arises from hydrolysis of the amide XV, attributes the oxygen atom as coming from a water molecule. However, the hydrolysis of an amide under the mild conditions employed is improbable. The other alternative suggested, which appears more probable, is the acquisition of an oxygen atom from another anisil molecule. This is the crux of

the second proposed mechanism.

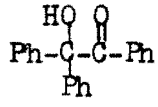
The system consisting of sodamide and toluene is a heterogeneous one and it is therefore difficult to estimate the concentration of amide ion in solution. The alkali dialkylamides are ether soluble and the corresponding N,N'-dialkylamides of benzilic acids, if formed, would probably be less susceptible to alkaline hydrolysis. In addition, the absence of any hydrogens on nitrogen would prohibit the cleave rearrangement of intermediate XVIII to the ketimine (XIX) and acid (XIII) as outlined in Chart Three. For these reasons a solution of lithium dipropylamide was prepared and allowed to react with benzil. A new, neutral, crystalline compound, but no benzilic acid, was obtained from the reaction.

CHART FOUR



XX

The new compound, $C_{104}H_{85}O_{14}N$, is assigned the structure XX. Evidence for this structure is found in the infrared and ultraviolet spectra of the product and in its carbon, hydrogen and nitrogen analyses. The infrared spectrum possesses the strong bands at 705 cm.$^{-1}$ and 755 cm.$^{-1}$ characteristic of mono-substituted aromatic rings[54] and also bands at 1680 cm.$^{-1}$ and 3400 cm.$^{-1}$ characteristic of carbonyl conjugated with an aromatic ring and free hydroxyl,[54] respectively. Perhaps the most conclusive piece of evidence is the strong doublet present in the 1065-1100 cm.$^{-1}$ region which is characteristic of the C-O-C-O-C ether linkage.[55,56] The ultraviolet spectrum of XX exhibits a maxima at 247 mμ, ϵ 10.2 x 10^4, while the ultraviolet spectrum of α-phenylbenzoin[28] (XXIII) exhibits a maxima at 247.5 mμ, ϵ 1.49 x 10^4. The value



XXIII

of the molecular extinction coefficient of XX is 6.9 times larger than that of XXIII; this relationship would be expected since XX contains seven carbonyl groups of the type found in α-phenylbenzoin (XXIII).

Compound XX was probably formed by the mechanism outlined in Chart Four. The reaction of dipropylamide ion with benzil yields the adduct XXI which can react with another benzil molecule to form XXII. This addition of alkoxide ion to benzil to form a new alkoxide ion which can also react with benzil continues until n = 5. Hydrolysis of the reaction mixture produces the product (XX).

The obtaining of a product such as XX from a reaction of benzil with a disubstituted amide ion lends support to the mechanism proposed in Chart Three, i.e., that XVI does not rearrange but adds to another anisil molecule to give XVII which rearranges to form the acid XIII, for the formation of anisilic acid from anisil and amide ion. An important question which has yet to be answered is why adducts such as XXI do not rearrange but react with the diketone present in the solution to form a heptamer.

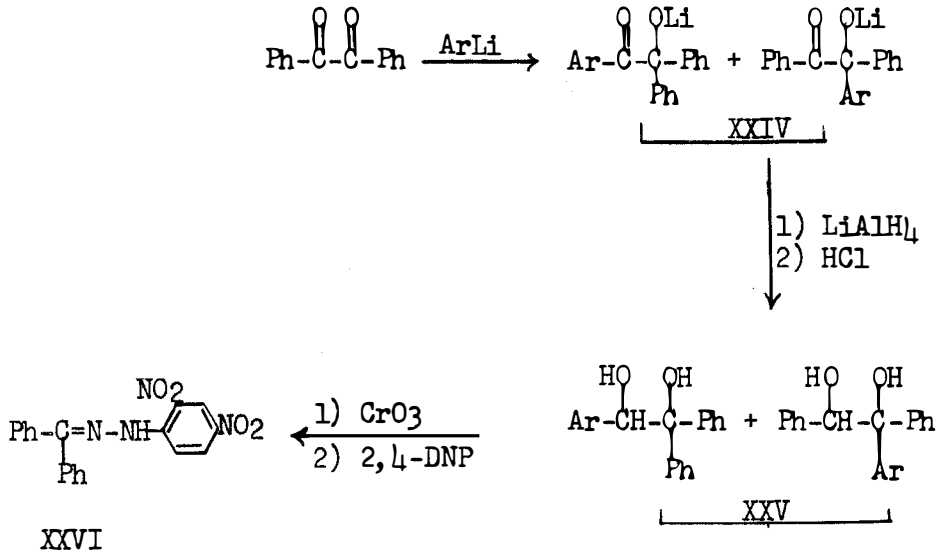
2. The Reaction of Benzil With Grignard Reagents and Organolithium Reagents

Rearranged products have been obtained from the reaction of Grignard reagents with benzil (see page 14). It has never been ascertained whether this rearrangement occurs during the addition of the Grignard reagent or in the subsequent hydrolysis and work-up procedure which frequently entails a relatively high temperature vacuum distillation. Whether or not organolithium compounds when added to benzil will also produce rearranged products has never been demonstrated.

In order to establish whether organolithium compounds will produce rearranged products and to establish in which step any rearrangement occurs, m-tolyllithium was prepared from m-bromotoluene and lithium and added to benzil. The mixture of addition products (XXIV) in ether was directly reduced with lithium aluminum hydride and the resultant mixture of glycols (XXV) was isolated and vigorously oxidized with chromic acid. Benzophenone in the form of its 2,4-dinitrophenylhydrazone (XXVI) was obtained as the product of the oxidation in 4 per cent yield.

This series of reactions is outlined in Chart Five.

CHART FIVE

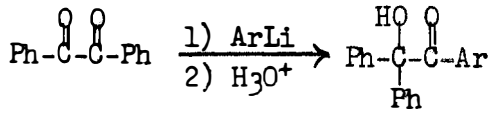


Ar = m-tolyl

2,4-DNP = 2,4-dinitrophenylhydrazine

In order to eliminate the possibility of the formation of benzophenone from the decarboxylation of m-benzoylbenzoic acid, the chromic acid oxidation procedure employed was that of Wertheim[58] who used it to prepare p-benzoylbenzoic acid from 4-methylbenzophenone. That benzophenone was a product of the reactions shown in Chart Five demonstrated that rearrangement does take place in the reaction of benzil and m-tolyllithium and that a hydrolytic work-up is not necessary for the rearrangement.

Another example of rearrangement was found in the reaction of o-tolyllithium with benzil. In this case the rearranged product, α-phenyl-2-methylbenzoin, was isolated in 13 per cent yield (equation 10).



(10)

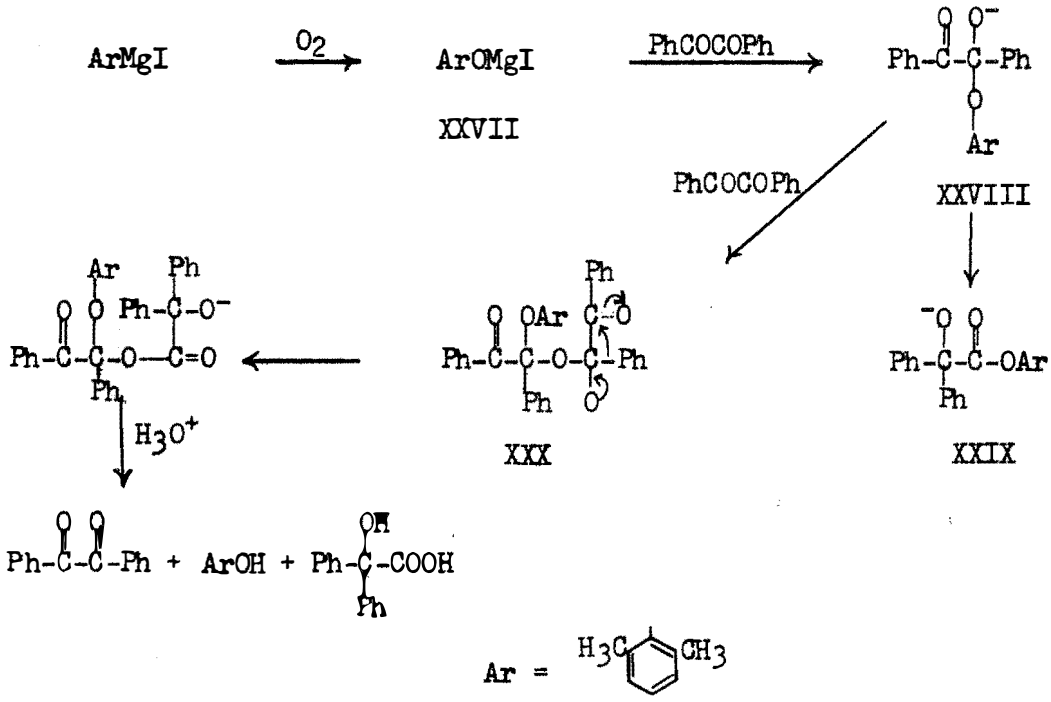
Ar = o-tolyl

In an attempt to find another example of rearrangement, benzil was treated with 2,6-dimethylphenylmagnesium iodide. In order to be certain that one mole of Grignard reagent was added to one mole of benzil, a titration of an aliquot of the Grignard solution was performed. Also, after the Grignard reagent and benzil were mixed, but before hydrolysis, the reaction mixture was poured onto Dry Ice to determine whether any unreacted Grignard reagent remained. An acid was obtained but its melting point was above that of the expected acid, 2,6-dimethylbenzoic acid. In a subsequent run the acid was identified as benzilic acid. In a series of reactions of benzil with 2,6-dimethylphenylmagnesium iodide under different conditions, it was found that carbonation of the reaction mixture was not necessary for the formation of benzilic acid. However, the presence of air or oxygen was necessary; in fact, the yield of benzilic acid was increased from 0 per cent to 10 per cent by changing the atmosphere in which the reaction was carried out from nitrogen to oxygen.

If the addition of the Grignard reagent was slow due to steric encumbrances, then in the presence of oxygen the Grignard reagent could be oxidized to the corresponding 2,6-dimethylphenoxide ion (XXVII). This ion could attack a benzil molecule to produce the adduct (XXVIII) which could rearrange to a stable ester (XXIX) or react with another benzil molecule to yield XXX. Rearrangement and hydrolysis of XXX

would yield benzilic acid, benzil and 2,6-dimethylphenol. This series of reactions is outlined in Chart Six.

CHART SIX

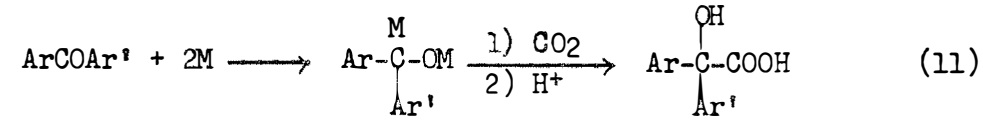


The mechanism is similar to the one proposed for the amide catalyzed transformation of benzil to benzilic acid and the same objection may be raised, i.e., why does XXVIII react with another benzil molecule instead of rearranging to the stable ester? At the present time this question cannot be answered.

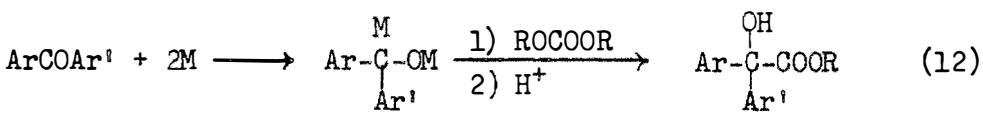
E. Preparation of the Dialkali Salts of Benzophenones and Their Reaction With Carbon Dioxide, Ethyl Chloroformate and Alkyl Carbonates

The ultimate goal of this study was to develop a useful synthetic procedure for the preparation of substituted benzilic acids and their

esters. The esters of benzilic acid, specifically the dialkylaminoalkyl esters have been shown to possess significant physiological activity.[59-62] The synthetic route proposed for the preparation of the benzilic acids is illustrated in equation 11 and the route to the esters is shown in equation 12.



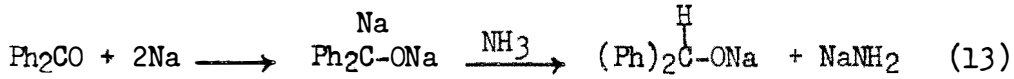
(11)



(12)

M = sodium, lithium, potassium or stilbene-dilithio or disodio adduct

Wooster[38] has shown that benzophenone quantitatively forms disodiobenzophenone when treated with two moles of sodium in liquid ammonia. The reaction of carbon dioxide with ammonia prevents the use of this solvent for the synthesis of benzilic acids by the method expressed in equation 11. There was the possibility that the formation of disodiobenzophenone could be carried out in ammonia and this solvent then replaced by ether prior to carbonation. However, carrying out the reaction in that manner gave benzhydrol in 85 per cent yield and not any benzilic acid. Hamrick and Hauser[42] subsequently reported that the same reaction gave a 50 per cent yield of benzilic acid and some benzhydrol. The reduction of the disodiobenzophenone probably occurs during the change of solvents just prior to the complete expulsion of the ammonia in accordance with the reaction illustrated in equation 13.



(13)

Scott, Walker and Hansley[63] found that the reaction of sodium with hydrocarbons was greatly facilitated by employing 1,2-dimethoxyethane as the solvent in place of diethyl ether. Brook, Cohen and Wright[40] found that this solvent was an excellent one for the formation of stilbene-disodium and dilithium adducts. For these reasons 1,2-dimethoxyethane was employed as the solvent in a series of reactions of benzophenone with alkali metals and with stilbene-dialkali metal adducts. That the formation of disodiobenzophenone in 1,2-dimethoxyethane was advantageous to its formation in ether or benzene was pointed out by the results of this series of reactions.

Mixtures of alkali metal (in small pieces) and benzophenone in 1,2-dimethoxyethane were allowed to react and then treated with carbon dioxide. The yield of benzilic acid was approximately the same (45-50 per cent) whether the mixture of benzophenone, sodium and 1,2-dimethoxyethane was refluxed for two hours or stirred for five hours or three days prior to carbonation. The method of carbonation, i.e., passing in gaseous carbon dioxide or pouring the reaction mixture onto Dry Ice, had no effect on the yield of acid. The presence of sodium in excess of the theoretically required amount also had no effect. When the sodium employed was sufficiently finely divided to yield a suspension, the yield of benzilic acid was increased to 62 per cent. The usual time required for the formation of a disodio-salt of an aromatic ketone in ether is five to six days.[41,44] The more rapid formation of disodiobenzophenone in 1,2-dimethoxyethane is probably due to this solvent's greater solvating ability.

One drawback in the use of 1,2-dimethoxyethane was the agglomeration of small pieces of sodium into one lump during the reaction. Lithium did not agglomerate as readily as sodium, but carbonation of the dilithiobenzophenone gave benzilic acid in only 26 per cent yield, indicating that lithium was not as satisfactory as sodium in the synthesis. Since the particle size of the sodium has been shown to be an important factor, the agglomeration of the sodium in 1,2-dimethoxyethane was probably what kept the yields of benzilic acid under 70 per cent. The great saving in time when employing this solvent as compared to benzene or ether overshadows this one drawback.

When dilithiobenzophenone was prepared by the treatment of benzophenone with stilbene-dilithium adduct in 1,2-dimethoxyethane, the yield of benzilic acid upon carbonation was 57 per cent.

It is concluded that in preparing benzilic acid in accordance with equation 11 the best yields are obtained when "M" is either sodium in the form of a suspension or stilbene-dilithium adduct.

The aromatic ketones whose reactions with alkali metals were studied, references to their methods of preparation and the yields obtained are listed in Table I.

The utility of the procedure illustrated in equation 11 was demonstrated by the synthesis of 4-methylbenzilic acid (41 per cent yield), 3,4'-dimethylbenzilic acid (55 per cent yield) and 2-phenylbenzilic acid (21 per cent yield). The synthesis of 3,4'-dimethylbenzilic acid, or any benzilic acid with substituents in different positions in each ring would be a tedious procedure by other methods (see page 26). Previously

TABLE I

SOURCES OF KETONES

Ketone	Reference to Preparation	Yield
4-Methoxybenzophenone	64, 65	25%
4,4'-Dimethoxybenzophenone	65	70%
3,4'-Dimethylbenzophenone	66	38%
2-Methylbenzophenone	67	52%
2-Phenylbenzophenone	68	72%
Benzophenone	Commercially Available	
4-Methylbenzophenone	Commercially Available	
4,4'-Dimethylbenzophenone	Commercially Available	

2-phenylbenzilic acid had been synthesized from 2-phenylphenylmagnesium iodide and ethyl phenylglyoxylate.[69] Recently however difficulty had been encountered in the synthesis of this acid by the above method and by two other methods.[70] That 2-phenylbenzilic acid was obtained as the product in this study was shown by its melting point and its oxidation to the starting material, 2-phenylbenzophenone. It can therefore be concluded that when Ar and Ar' in equation 11 are alkyl substituted or phenyl substituted benzene rings with the substituents in the 2,3 or 4 positions, the corresponding benzilic acids can readily be synthesized by the method illustrated in equation 11.

Carbonation of the purple solution produced from stilbene-disodium and 4-methoxybenzophenone in 1,2-dimethoxyethane produced a 5.5 per cent yield of 4-methoxybenzilic acid. When 4-methoxybenzophenone was treated with sodium directly, carbonation of the resultant purple solution yielded no acid. Several attempts were made to prepare anisilic acid from 4,4'-dimethoxybenzophenone in accordance with equation 11 but none were successful. When 4,4'-dimethoxybenzophenone in 1,2-dimethoxyethane was treated with potassium, the characteristic purple color appeared but no anisilic acid was obtained upon carbonation of this colored solution. Similar results were obtained when sodium, sodium suspension and stilbene-disodium were used in place of potassium.

The results with the methoxybenzophenones is not easy to rationalize. The inability of the methoxy substituted benzophenones to form dialkali salts can be rationalized as a consequence of the electron repelling resonance effect of the methoxy group which would impede the formation

of the carbanion. However, even if only a monoalkali salt (ketyl) were formed, some acid could be expected (page 19). In the reaction of the methoxy substituted benzophenones with alkali metal, the color formation indicated the presence of ketyl. The low yield of acid after carbonation showed that either this color was a consequence of a very small concentration of highly colored ketyl or that the ketyl reacted slowly with carbon dioxide allowing other reactions to occur. The rather low solubility of the methoxy substituted benzophenones, especially 4,4'-dimethoxybenzophenone, in ether and 1,2-dimethoxyethane may also have been an important factor causing these low yields of acid. No matter what the cause though, it has been shown that the preparation of benzilic acids substituted by methoxy groups in the 4-positions cannot be accomplished in good yield by the method illustrated in equation 11.

The preparation of benzilic acid esters directly from aromatic ketones may be accomplished by treating the dialkali salt of the ketone with an alkyl haloformate or with an alkyl carbonate. The alkyl haloformates such as ethyl chloroformate cannot be used in ammonia while the alkyl carbonates can.

The reaction of disodiobenzophenone with ethyl chloroformate in 1,2-dimethoxyethane followed by saponification of the residue yielded benzilic acid in 14 per cent. This reaction is illustrated in equation 14.

$$Ph_2CO + 2Na \longrightarrow Ph_2\overset{Na}{C}-ONa \xrightarrow[2)\ H_3O^+]{1)\ ClCOC_2H_5} Ph_2\overset{OH}{C}-COOC_2H_5 \xrightarrow{OH^-} Ph_2\overset{OH}{C}-COOH \quad (14)$$

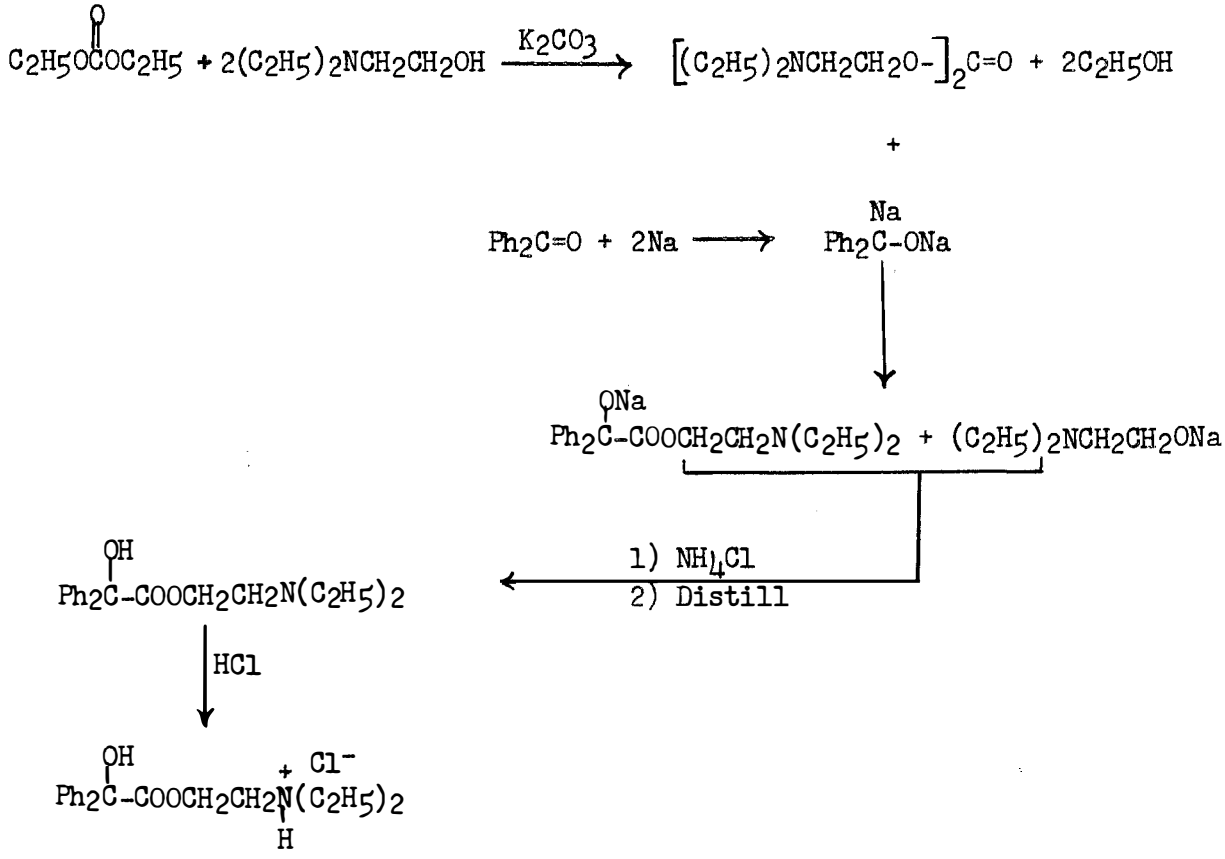
When the purple solution obtained from 4,4'-dimethoxybenzophenone and stilbene-disodium in 1,2-dimethoxyethane was treated with ethyl chloroformate decolorization occurred. The only products that could be isolated from the reaction mixture were stilbene and 4,4'-dimethoxybenzophenone. The use of ethyl chloroformate for the preparation of benzilic acid esters, therefore, does not appear to be a satisfactory method.

The reaction of disodiobenzophenone with dimethyl carbonate in liquid ammonia yielded methyl benzilate in 70 per cent yield. This reaction is illustrated in equation 15.

$$Ph_2CO + 2Na \longrightarrow Ph_2\overset{Na}{C}-ONa \xrightarrow[2)\ NH_4Cl]{1)\ CH_3OCOOCH_3} Ph_2\overset{OH}{C}-COOCH_3 + CH_3OH \quad (15)$$

2-Diethylaminoethyl carbonate was prepared by the method of Dornfeld[71] in 34 per cent yield and added to disodiobenzophenone in liquid ammonia. The 2-diethylaminoethyl benzilate was isolated as its hydrochloride in 77 per cent yield from benzophenone. This series of reactions is illustrated in Chart Seven. The reaction of disodiobenzophenone with diethyl carbonate in liquid ammonia followed by saponification of the product yielded benzilic acid in good yield from benzophenone.

CHART SEVEN*



The results of the three reactions mentioned above showed that esters of benzilic acid could be prepared in good yield from disodiobenzophenone in accordance with equation 12 and that the nature of the alkyl groups in the carbonate determines only the type of ester obtained and not the yield in which it can be obtained. The results also indi-

*The experimental simplicity of reactions involving dialkali salts of benzophenones is not aptly revealed by the equations. The experimental procedure entails addition of the alkali metal to liquid ammonia followed by addition of the ketone and the carbonate ester. Ammonium chloride is added after one hour of reflux and the ammonia and volatile products are evaporated. The residue is dissolved in ether and anhydrous hydrochloric acid is added. It is experimentally a one step process for conversion of benzophenone to diethylaminoethyl benzilate hydrochloride.

cated that the preparation of benzilic acid esters in ammonia followed by saponification to the corresponding benzilic acid was advantageous, both in experimental manipulations required and in yields obtained, to the direct route of obtaining the acids illustrated in equation 11. The utility of ammonia as a solvent for preparing acids was further demonstrated with the reaction of 4-methylbenzophenone, sodium and diethyl carbonate in liquid ammonia, which after saponification of the crude ester obtained, yielded 4-methylbenzilic acid in 70 per cent yield. This method for the preparation of benzilic acids is illustrated in equation 16.

$$ArCOAr' + 2M \longrightarrow Ar\text{-}\overset{\displaystyle M}{\underset{\displaystyle Ar'}{C}}\text{-}OM \xrightarrow[2)\ H^+]{1)\ ROCOOR} Ar\text{-}\overset{\displaystyle OH}{\underset{\displaystyle Ar'}{C}}\text{-}COOR \xrightarrow{OH^-} Ar\text{-}\overset{\displaystyle OH}{\underset{\displaystyle Ar'}{C}}\text{-}COOH \qquad (16)$$

It was found that the nature of the alkali metal employed had a profound effect upon the yield of the benzilic acid obtained in accordance with equation 16. When sodium was employed in the transformation of 4-methylbenzophenone into 4-methylbenzilic acid, the yield was 70 per cent. The use of potassium in place of sodium decreased the yield to 49 per cent and when lithium was used there was obtained a 60 per cent yield of 4-methylbenzhydrol and not any 4-methylbenzilic acid. Of the three alkali metals used the least effective one, lithium, possesses the largest oxidation potential while the most effective one, sodium, possesses the smallest oxidation potential. In almost every reaction of a dialkali salt of benzophenone or a substituted benzophenone in liquid ammonia some reduction product, i.e., benzhydrol or substituted benzhydrol, was found as a reaction product in the reactions where all

products were identified. The yield of this reduction product was found to increase as the time between the addition of the ketone and the addition of the alkyl carbonate to the alkali metal-ammonia solution was increased. Thus, when a solution of 4-methylbenzophenone and lithium in ammonia was refluxed for two hours prior to the addition of the alkyl carbonate, an 80 per cent yield of 4-methylbenzhydrol was obtained, but when the alkyl carbonate was added immediately, only a 60 per cent yield of 4-methylbenzhydrol was obtained. This observation indicates that the alkyl carbonate was not involved in the reduction process. The use of lithium as the alkali metal in the formation of the dialkali salts of aromatic ketones results in the formation of more reduction product than the use of either sodium or potassium. The amount of reduction is also determined by the length of time the ketone alkali metal and ammonia are refluxed prior to addition of the ester.

The inhibiting effect of strongly electron releasing groups on the formation of dialkali salts of benzophenones again became apparent when 4,4'-dimethoxybenzophenone was treated with sodium and dimethyl carbonate in liquid ammonia. The products isolated after saponification of the crude residue were 4,4'-dimethoxybenzhydrol and 4,4'-dimethoxybenzophenone in 44 and 10 per cent yields, respectively and not any anisilic acid. When this reaction was performed with lithium, the solution of lithium and 4,4'-dimethoxybenzophenone in ammonia was refluxed for two hours prior to the addition of the dimethyl carbonate; there was obtained a 68 per cent yield of 4,4'-dimethoxybenzhydrol.

The reaction of 4,4'-dimethylbenzophenone, sodium and dimethyl carbonate in liquid ammonia yielded upon saponification of the crude

product, 4,4'-dimethylbenzilic acid in 15 per cent yield and 4,4'-dimethylbenzhydrol.

In summary, it has been shown that good yields of benzilic acid esters can be obtained from aromatic ketones, alkali metals and alkyl carbonates in liquid ammonia. The best yields were obtained when the aromatic ketone was not substituted with strongly electron releasing groups, when sodium was employed as the alkali metal, and when the time between the addition of the aromatic ketone and the alkyl carbonate to the alkali metal-ammonia solution was a minimum. It was also shown that the nature of the alkyl group in the carbonate ester did not effect the yields obtainable by this method. Since aromatic ketones containing a variety of substituents can readily be synthesized by known methods and since benzilic acid esters are potentially valuable substances due to their physiological properties, the synthesis of these esters directly from aromatic ketones may prove to be a useful type of reaction.

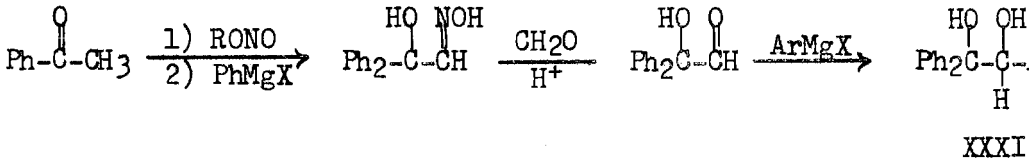
F. Reaction of the Dialkali Salts of Benzophenones With Aromatic Aldehydes

Recently Eastham and Feeney[72] reported the synthesis of several 1,1-diphenyl-2-arylethylene glycols (XXXI). These glycols were prepared by the addition of excess phenyl Grignard reagent to methyl esters of substituted mandelic acids (equation 17) or through addition of aryl

$$ArCCH_3 \xrightarrow[2)\ OH^-]{1)\ SeO_2} ArCH(OH)-COOH \xrightarrow{CH_2N_2} ArCH(OH)-COOCH_3 \xrightarrow{PhMgX} Ar-CH(OH)-C(OH)-Ph_2 \quad (17)$$

XXXI

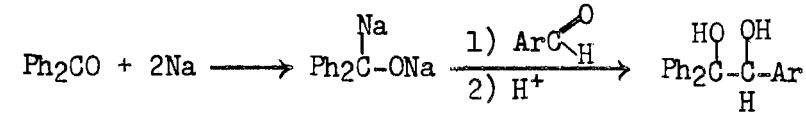
Grignard reagents to benzilaldehyde (equation 18).



(18)

XXXI

The reaction of a dialkali salt of an aromatic ketone with an aromatic aldehyde, illustrated in equation 19, appeared to be another method which

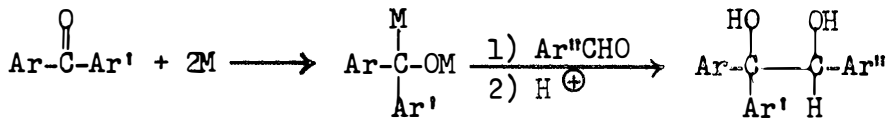


(19)

would be useful for the preparation of certain substituted glycols from appropriately substituted ketones and aldehydes. For this reason an investigation was initiated in order to ascertain whether or not the proposed method would produce these glycols in satisfactory yields.

In accordance with equation 19, the reaction of disodiobenzophenone and benzaldehyde in 1,2-dimethoxyethane yielded triphenylethylene glycol in 24 per cent yield. 1,1-Diphenyl-2-anisylethylene glycol was prepared in 22 per cent yield from the reaction of disodiobenzophenone with anisaldehyde in 1,2-dimethoxyethane. While this investigation was in progress, Hamrick and Hauser[42] reported a 91 per cent yield of triphenylethylene glycol from the reaction of disodiobenzophenone with benzaldehyde in liquid ammonia. Since anisaldehyde, which is a relatively unreactive aromatic aldehyde, reacts with disodiobenzophenone to yield 1,1-diphenyl-2-anisylethylene glycol in an acceptable yield, it was assumed that this method, whether carried out in liquid ammonia or 1,2-dimethoxyethane, was a general one for the synthesis of 1,1-diphenyl-2-arylethylene glycols and therefore was not further investigated.

In a more general synthesis, illustrated in equation 20, an un-



(20)

symmetrical aromatic ketone could be employed, but then the resulting glycol would contain two centers of asymmetry. This, of course, means that there would be a total of four possible isomers. These isomers would be in the form of two enantiomorphic pairs which would be diastereoisomeric to each other. Therefore two products (diastereoisomeric pairs of optical isomers) possessing different physical and chemical properties would be obtained from the reaction. When there is no steric obstruction in the starting ketone or aldehyde molecule which could render the formation of one of the enantiomorphic pairs more favorable than the other, approximately equal amounts of these two compounds should be obtained.

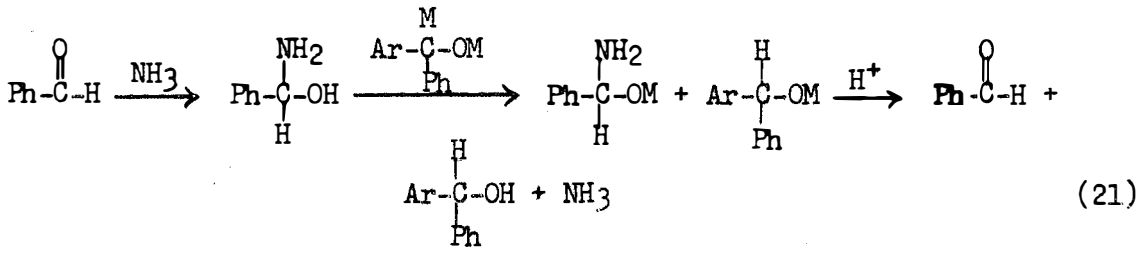
The reaction of 4-methylbenzophenone, sodium and anisaldehyde in liquid ammonia yielded a product which melted over a 10° range after two recrystallizations but analyzed correctly for 1-phenyl-1-p-tolyl-2-p-anisylethylene glycol. The product was apparently the expected mixture of diastereoisomers.

When there is some factor present in a reaction that leads to the formation of one pair of optical isomers in preference to another, the reaction is said to be stereospecific.[73] It seemed worthwhile to determine if a bulky group in the 2-position of the dialkali salt would cause a stereospecific reaction in the synthesis of glycols by equation 20.

The reaction of 2-phenylbenzophenone, lithium and benzaldehyde in 1,2-dimethoxyethane gave 1-(2-biphenylyl)-1,2-diphenylethylene glycol in 18 per cent yield from benzophenone. That this was the product was shown by the correct carbon and hydrogen analysis and by oxidation of the product to 2-phenylbenzophenone and benzoic acid. The glycol was sharp melting and was therefore assumed to be one enantiomorphic pair. The same reaction carried out in liquid ammonia using sodium as the alkali metal yielded as a product what appeared to be a mixture of diastereoisomers. The melting point of the product kept increasing upon recrystallization, but after several recrystallizations the product remaining still did not melt sharply. Continued recrystallization might have ultimately resulted in the isolation of one enantiomorphic pair but the yield would have been of a magnitude which would not justify labeling the reaction stereospecific. Similar results were obtained in the reaction of 2-phenylbenzophenone, lithium suspension and benzaldehyde in diethyl ether.

The reaction of 2-methylbenzophenone, sodium and benzaldehyde in liquid ammonia yielded 2-methylbenzhydrol in 69 per cent yield. The conditions under which this reaction was carried out were those chosen as least likely to cause reduction, i.e., the use of sodium as the alkali metal and immediate addition of the benzaldehyde solution after completion of the addition of the 2-methylbenzophenone solution to the alkali metal in ammonia. It appeared as though the steric obstruction (which would be necessary for stereospecificity) was slowing down the addition reaction of the dialkali salt to the aromatic aldehyde sufficiently to

allow the aldehyde to react with the ammonia and furnish active hydrogen for the reduction of the dialkali salt. A possible mode of the formation of 2-methylbenzhydrol is illustrated in equation 21.



(21)

Ar = o-tolyl

When anisaldehyde, a less reactive aldehyde than benzaldehyde, was used in the same reaction no 2-methylbenzhydrol was obtained. The product, 1-phenyl-1-o-tolyl-2-p-anisylethylene glycol, appeared from its 5° melting point range to be a mixture of diastereoisomers. In this case the competing reaction of the aldehyde with the ammonia to form active hydrogen was probably slow enough, due to the relative unreactivity of the anisaldehyde, that it did not interfere with the normal addition reaction which forms the glycol.

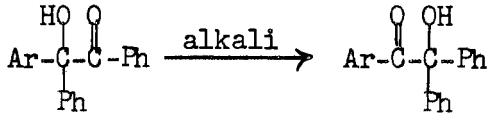
The reaction of 2-methylbenzophenone, lithium and anisaldehyde in 1,2-dimethoxyethane yielded an oil which would not crystallize from a variety of solvents.

In summary, it has been shown that the reaction of dialkali salts of monosubstituted benzophenones with aromatic aldehydes yields mainly mixtures of diastereoisomers or reduction products. In one case a stereospecific reaction was obtained by this method, but in general the method appears unsatisfactory for the stereospecific synthesis of these

glycols. The reaction of the dialkali salts of benzophenone with aromatic aldehydes yields the corresponding glycols in good yields and appears to be a satisfactory method for their preparation.

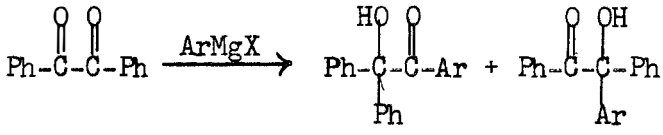
G. Reaction of the Dialkali Salts of Benzophenones With Aromatic Nitriles

The unequivocal synthesis of α-arylbenzoins (XXXII) has been difficult to accomplish since these compounds undergo molecular rearrangement when treated with alkali[27] (equation 22) and since the obvious synthesis of this type compound, inverse addition of a Grignard reagent to benzil, also may proceed with rearrangement[28] (equation 23).



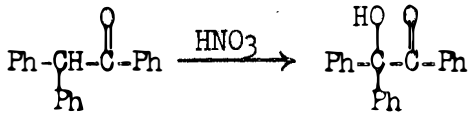
(22)

XXXII

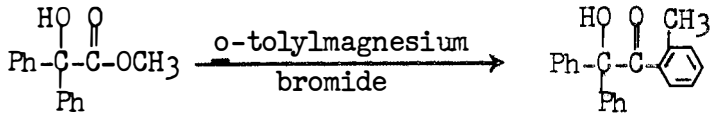


(23)

Previous methods of synthesis, other than that of equation 23, have yielded only two crystalline α-arylbenzoins. Blitz[74] obtained α-phenylbenzoin by oxidation of α-phenyldesoxybenzoin with nitric acid (equation 24) and Bachmann[75] obtained 2-methyl-α-phenylbenzoin by the addition of o-tolylmagnesium bromide to methyl benzilate (equation 25). Neither of these methods of synthesis seems general.

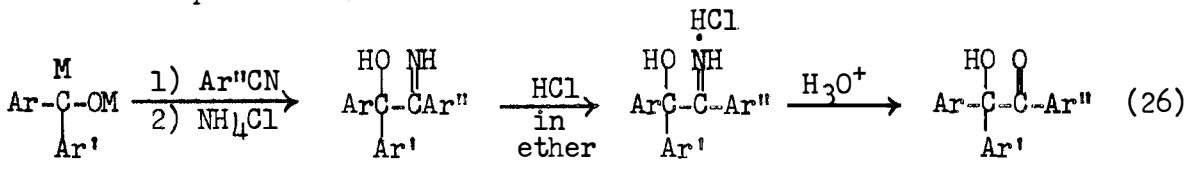


(24)



(25)

It was thought that a general, unequivocal synthesis of α-arylbenzoins could be accomplished by the reaction of the dialkali salt of an aromatic ketone with an aromatic nitrile in liquid ammonia as illustrated in equation 26.



XXXIII XXXII (26)

Since high purity of the α-arylbenzoins seems to be required for their crystallization,[72] the above method appeared promising because all side products and starting materials could be separated from the product when the ketimine hydrochloride (XXXIII) was precipitated and filtered from the reaction. The hydrolysis of this ketimine hydrochloride (XXXIII) would then yield the corresponding α-arylbenzoin.

That the method of synthesis of α-arylbenzoins illustrated in equation 26 could be accomplished was shown by the preparation of α-phenylbenzoin from disodiobenzophenone and benzonitrile. The identity of the product was ascertained by a mixed melting point determination with α-phenylbenzoin prepared from benzil and phenylmagnesium bromide. The reaction of disodiobenzophenone with p-tolunitrile yielded a ketimine hydrochloride when the ethereal reaction mixture was treated with anhydrous hydrochloric acid. The elemental analysis of this hydrochloride differed slightly from the calculated values for α-phenyl-4-methylbenzoin ketimine hydrochloride, but when the hydrochloride was hydrolyzed, the

analysis of the product checked with the calculated values for α-phenyl-4-methylbenzoin.

The inability of 4,4'-dimethoxybenzophenone to form a dialkali salt was again apparent in the attempted preparation of α-anisyl-4-methoxybenzoin from 4,4'-dimethoxybenzophenone, sodium and benzonitrile. No ketimine hydrochloride was obtained from the reaction.

The reaction of disodiobenzophenone with p-anisonitrile and subsequent treatment of the ethereal residue with anhydrous hydrochloric acid yielded a ketimine hydrochloride. The elemental analysis of this hydrochloride differed slightly from the calculated analysis of α-phenyl-4-methoxybenzoin ketimine hydrochloride. Hydrolysis of the hydrochloride yielded a glass-like substance which could not be crystallized from a variety of solvents. The analysis of this glass differed slightly from the calculated analysis of α-phenyl-4-methoxybenzoin. The formation of a precipitate when hydrochloric acid was added to the ethereal solution of the reaction residue, and the proximity of the calculated and found elemental analyses, indicate that the α-phenyl-4-methoxybenzoin ketimine was formed but, probably some impurity was precipitated along with the hydrochloride. The inability to crystallize the hydrolysis product, and its analysis also indicates a small amount of impurity present.

In summary it has been shown that α-arylbenzoins can be synthesized from the dialkali salts of benzophenones and aromatic nitriles. The same limitations previously mentioned for the formation of these dialkali salts are also applicable in the synthesis of α-arylbenzoins.

CHAPTER III

EXPERIMENTAL*

A. Synthesis of Methyl Anisilate-1-C^{14}

1. Anisoyl Chloride

a. Method 1. Anisic acid (228 g., 1.50 mole) and phosphorus pentachloride (324 g., 1.56 mole) were placed in a one-necked, 1-l. flask equipped with a reflux condenser which was attached through a drying tube to a hydrochloric acid trap. The flask was heated carefully on a steam bath until reaction commenced. The reaction became vigorous and the flask was taken from the steam bath and placed in an ice bath in order to moderate the reaction. After the vigorous reaction subsided the flask was returned to the steam bath for one hour. The phosphorus oxychloride was removed by distillation at atmospheric pressure, and the product vacuum distilled. The yield of anisoyl chloride was 220 g. (87 per cent), b.p. 172-174° (50 mm.).

b. Method 2. Anisic acid (228 g., 1.50 mole) and thionyl chloride (268 g., 2.25 mole) were placed in a one-necked, 1-l. flask equipped with a reflux condenser and drying tube. The resulting solution was re-

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*Elemental analyses were performed by Weiler and Strauss Microanalytical Laboratory, Oxford, England. The melting points and boiling points are uncorrected, unless otherwise stated. The melting points were determined on a Kofler micro hot stage melting point apparatus. All ultraviolet spectra were taken on a Beckman Model DU spectrophotometer using 95 per cent ethanol as solvent. All infrared spectra were determined using a Perkin-Elmer Model 21 Infrared Spectrophotometer employing the potassium bromide disc technique. Carbon-14 analyses were performed by the dry combustion and ionization chamber techniques.[93]

fluxed for one hour. The excess thionyl chloride was removed by distillation at atmospheric pressure, and the product vacuum distilled, b.p. 168-170° (50 mm.). The yield was 205 g. (82 per cent).

2. Anisoyl Cyanide-1-C^{14}

Anisoyl chloride (9.50 g., 0.056 mole) and cuprous cyanide-C^{14} (5.0 g., 0.056 mole, previously dried in vacuo over phosphorus pentoxide for two days) were placed in a 50-ml., one-necked flask equipped with a reflux condenser and drying tube. The flask was placed in a Wood's metal bath which had been previously heated to 110°. The temperature of the bath was raised to 120-130° and maintained between these limits for three and one-half hours. During this heating period the flask was removed from the bath and vigorously shaken at thirty minute intervals. The crude product was vacuum distilled (0.7 mm.) from the reaction mixture and the distillation continued until the flask contained no more liquid. The solid distillate was dissolved in hot benzene. After some of the benzene was distilled, a few milliliters of ligroin were added and the solution was cooled. The crystals which appeared were collected and recrystallized from benzene-ligroin. The yield of anisoyl cyanide-1-C^{14} was 5.70 g. (62 per cent) of colorless needles, m.p. 57-59° (lit. values[76,77] 60° and 63-64°).

3. Alcoholysis of Anisoyl Cyanide-1-C^{14}

a. Method 1. A solution of anisoyl cyanide-1-C^{14} (3.00 g., 0.0187 mole, dried in vacuo over phosphorus pentoxide for one day) and anhydrous methanol (0.60 g., 0.0187 mole, freshly distilled from magnesium methoxide)

in 40 ml. of anhydrous ether was cooled to 0°. The solution was kept at this temperature by means of an ice bath while anhydrous hydrochloric acid (previously passed through concentrated sulfuric acid) was passed through it for forty-five minutes. The solution was then seeded (with seeds obtained from a previous run on unlabeled material) and placed in the refrigerator for three hours. The crystals of p-methoxyphenylglyoxyl-imino methyl ether hydrochloride were removed by filtration, washed twice with anhydrous ether, and added to 50 ml. of water. The aqueous mixture was stirred for five minutes and filtered. The precipitate was washed with water and recrystallized from dilute ethanol. The yield of methyl p-methoxyphenylglyoxylate-1-C^{14} was 1.74 g. (48 per cent), m.p. 50-51°, (lit. value[78] 54°), 8.80 mc./mole.

A solution of anisoyl cyanide (9.0 g., 0.056 mole) and anhydrous methanol (2.24 g., 0.070 mole) in 60 ml. of anhydrous ether was cooled to 0°. The solution was kept at this temperature by means of an ice bath while anhydrous hydrochloric acid was passed through it for sixty minutes. The solution was then placed in the refrigerator for three days and the crystals which appeared were filtered, m.p. 147-150°, and added to 60 ml. of 2 N hydrochloric acid. After thirty minutes at room temperature the mixture was heated to boiling, cooled and filtered. The precipitate was dissolved in ether and the ethereal solution was extracted with 5 per cent sodium carbonate. Acidification of the basic aqueous extract yielded 4-methoxyphenylglyoxylic acid, m.p. 91-93° (lit. value[79] 93°) and evaporation of the ethereal solution yielded 4-methoxyphenylglyoxyl-amide, m.p. 148-149° (lit. value[77] 151-152°).

b. Method 2. A solution of anisoyl cyanide (10.0 g., 0.062 mole) in 100 ml. of anhydrous methanol (distilled from magnesium methoxide) was cooled to 0°. The solution was kept at this temperature by means of an ice bath while anhydrous hydrochloric acid (previously passed through concentrated sulfuric acid) was passed through it for ten minutes. The solution was placed in a refrigerator for eight days, diluted with 300 ml. of water and extracted three times with ether. The combined extracts were washed with 5 per cent sodium bicarbonate (acidification of which yielded no acid) and with water. The ethereal solution was dried with anhydrous magnesium sulfate and evaporated. The solid residue was recrystallized from aqueous methanol. The yield of methyl anisate was 9.0 g. (88 per cent), m.p. 46-48°. This compound was identified as methyl anisate by mixed m.p. and comparison of infrared spectra with an authentic sample prepared by the reaction of anisic acid with methanol.

c. Method 3. A mixture of anisoyl cyanide (2.00 g., 0.012 mole), 15 ml. of methanol, sulfuric acid (2.36 g., 0.024 mole) and seven drops of water was refluxed for seven hours. The solution was poured onto 100 g. of ice and extracted three times with ether. The combined ethereal extract was washed with 5 per cent sodium bicarbonate (acidification of which yielded no acid) and with water, dried with anhydrous magnesium sulfate, and evaporated. The solid residue was recrystallized from aqueous methanol. The yield of methyl anisate was 1.40 g. (70 per cent). This compound was identified as methyl anisate by its infrared spectra which was identical with the spectra of an authentic sample of methyl anisate.

4. Attempted Hydrolysis of Anisoyl Cyanide

a. Method 1. A mixture of anisoyl cyanide (10.00 g., 0.062 mole) and 200 ml. of concentrated hydrochloric acid was stirred for one day. To this mixture was added 50 ml. of 1,2-dimethoxyethane and the stirring was continued for five more days. The mixture was diluted with 300 ml. of water and extracted three times with ether. The combined ethereal extract was washed with 50-ml. portions of 5 per cent sodium bicarbonate until no precipitate appeared upon acidification of the sodium bicarbonate solution. The combined, acidified sodium bicarbonate solution was extracted three times with ether. The extracts were combined, dried with anhydrous magnesium sulfate, and evaporated. The solid residue was dissolved in hot aqueous ethanol and the solution cooled. The crystals were collected and recrystallized from benzene. The yield of anisic acid was 1.0 g. (11 per cent), m.p. 182-183°, undepressed by an authentic sample. The aqueous alcoholic filtrate was boiled, with repeated additions of benzene, until the solution was homogeneous. The solution was cooled and the crystals which separated were collected and recrystallized twice from benzene-hexane. The yield was 4.0 g. of product, m.p. 88-91°, which was probably p-methoxyphenylglyoxylic acid (lit. value[79] 93°) but which was not positively identified.

b. Method 2. To 200 ml. of concentrated hydrochloric acid was added anisoyl cyanide (9.0 g., 0.049 mole) and the mixture stirred for two weeks. The mixture was extracted five times with 100-ml. portions of ether. The combined ethereal extract was washed with 50-ml. portions of 10 per cent sodium carbonate until no precipitate appeared upon acidifica-

tion of the sodium carbonate solution. The combined acidified sodium carbonate solution was cooled and filtered yielding approximately 7.0 g. of solid material, m.p. 40°. This material was recrystallized twice from benzene-hexane to yield 4.0 g. of product, m.p. 88-90°, which was probably p-methoxyphenylglyoxylic acid (lit. value[79] 93°) but which was not positively identified.

5. Methyl Anisilate-1-C^{14}

The Grignard reagent prepared from p-bromoanisole (4.00 g., 0.021 mole) and magnesium (0.52 g., 0.021 mole) in 25 ml. of anhydrous ether was added to a solution of methyl p-methoxyphenylglyoxylate-1-C^{14} (3.20 g., 0.017 mole) in 100 ml. of anhydrous ether. A heavy yellow precipitate appeared during addition; stirring was continued for fifteen minutes after addition was complete. Dilute hydrochloric acid was added to the reaction mixture. The ether layer was separated, dried with anhydrous magnesium sulfate and evaporated. The residue was a yellow oil which solidified when stirred with benzene-ligroin. The solid was recrystallized from benzene-ligroin to yield 0.7 g. of methyl anisilate, m.p. 109-110°. Removal of the solvent from the supernatant liquid and recrystallization of the residual solid yielded another 0.4 g., m.p. 108-109°. To the supernatant liquid from the last recrystallization was added 1.1 g. of unlabeled methyl anisilate; the mixture was heated and a recrystallization carried out in the usual manner. The yield was 0.85 g., m.p. 106-108°, activity 2.56 mc./mole. It was calculated from this activity that another 0.45 g. of reaction product had been isolated; the total yield was thus 1.55 g. (22 per cent). The three batches of labeled methyl

anisilate were combined and added to 0.5 g. of unlabeled methyl anisilate, and the entire amount recrystallized from benzene ligroin. The yield was 1.9 g., 4.62 mc./mole, m.p. 110.0-111.5° (lit. value[44] 110.0-110.5°).

B. Proof of Position of Labeling in Methyl Anisilate-1-C^{14}, and Irreversibility of the Benzilic Ester Rearrangement

1. Anisil

A mixture of anisoin (50 g., 0.184 mole), cupric sulfate pentahydrate (110 g., 0.44 mole), pyridine (180 g., 2.26 mole) and 90 ml. of water was placed in a round-bottomed flask equipped with a reflux condenser. The mixture was refluxed for two and one-half hours and poured onto 200 g. of ice. The solid material was removed from the mixture by filtration, washed several times with cold dilute hydrochloric acid, washed with water, and recrystallized from ethanol. The yield of anisil was 48 g. (97 per cent), m.p. 132-133°.

2. Anisilic Acid

a. Method 1. To a boiling solution of potassium hydroxide (4.9 g., 0.087 mole) in 30 ml. of n-butanol was added anisil (10.0 g., 0.037 mole) and the mixture was refluxed for ten minutes. The mixture was extracted three times with 30-ml. portions of water, some ether being added to facilitate separation of the layers. The combined aqueous extract was washed once with ether, acidified with hydrochloric acid, cooled, and filtered. The solid material was recrystallized from aqueous ethanol to yield 5.0 g. (48 per cent) of anisilic acid, m.p. 162-164°. The litera-

ture values for the m.p. of anisilic acid vary from 159-160°[44] to 175° (d).[80]

b. Method 2. To a solution of potassium hydroxide (12.0 g., 0.215 mole) in 75 ml. of absolute alcohol contained in a 250-ml. bottle was added anisil (20 g., 0.074 mole) and enough anhydrous ether to fill the bottle. The bottle was stoppered and shaken for two weeks. The mixture was filtered and the solid material dissolved in water. The aqueous solution was acidified, cooled, and filtered. The crystals were recrystallized twice from ethanol to yield 10 g. (48 per cent) of anisilic acid, m.p. 173° (d).

3. Methyl Anisilate

To an ethereal solution of anisilic acid (5.00 g., 0.017 mole) was added an excess of diazomethane dissolved in ether. The resulting solution was kept at room temperature for twenty-four hours. Half of the ether was distilled and the remaining ethereal solution was washed with 5 per cent sodium carbonate and evaporated. Recrystallization of the residue from benzene-ligroin yielded 4.8 g. (94 per cent) of methyl anisilate, m.p. 110-111°.

4. Treatment of Methyl Anisilate With Sodium Methoxide

To 10 ml. of anhydrous methanol (distilled from magnesium methoxide) in a 50-ml., round-bottomed flask was added 0.138 g. of sodium metal. After the metal had dissolved, methyl anisilate (1.0 g., 3.3 mmole, dried in vacuo for one day) was added to the reaction mixture and the solution was refluxed for two days. All the preceding operations were carried out

in an atmosphere of nitrogen. The solution was poured into 100 ml. of water and extracted with two 100-ml. portions of ether. The combined ethereal extract was dried with anhydrous magnesium sulfate and the ether evaporated to leave 0.8 g. (80 per cent) of methyl anisilate, m.p. 109-110°.

5. Attempted Oxidation of Methyl Anisilate

To a solution of methyl anisilate (0.80 g., 2.65 mmole) in 11 ml. of warm glacial acetic acid was added a solution of chromium trioxide (0.80 g., 7.95 mmole) in 7 ml. of glacial acetic acid containing a few drops of water. The resulting solution was heated on a steam bath for thirty minutes and poured into 30 ml. of water. The aqueous mixture was extracted twice with ether. The combined ethereal extract was washed with water, washed with 5 per cent sodium carbonate until the washings were basic, washed again with water, dried with anhydrous magnesium sulfate and evaporated to leave an oil which failed to crystallize from a variety of solvents.

6. Oxidation of Anisilic Acid

To a solution of anisilic acid (80 mg., 0.28 mmole) in 5 ml. of warm glacial acetic acid was added a solution of chromium trioxide (28 mg., 0.28 mmole) in 3 ml. of glacial acetic acid containing a few drops of water. The resulting solution was heated on a steam bath for thirty minutes and poured into 25 ml. of water. The aqueous mixture was extracted with three 25-ml. portions of ether. The combined ethereal extract was washed with water, washed with 5 per cent sodium carbonate

until the washings were basic, washed again with water, dried with anhydrous magnesium sulfate, and evaporated until 2 ml. remained. The solution was cooled and the ether decanted from the crystals which appeared. The crystals were washed with ether and dried in vacuo. The yield was 47 mg. (68 per cent) of 4,4'-dimethoxybenzophenone, m.p. 140-142°, with or without admixture of authentic 4,4'-dimethoxybenzophenone.

7. Saponification of Methyl Anisilate-1-C^{14}

Two and one-half ml. of freshly boiled water was added to a solution of 0.6 mmole of sodium methoxide in 10 ml. of methanol. One and one-quarter ml. of this solution was added to methyl anisilate-1-C^{14} (100 mg., 0.33 mmole, 4.62 mc./mole) contained in a small vial. The vial was sealed and placed in a steam bath for fifty minutes. The contents of the vial were poured into 10 ml. of water and the aqueous solution was washed with ether, acidified with hydrochloric acid, cooled and extracted with two 25-ml. portions of ether. The combined ethereal extract was dried with anhydrous magnesium sulfate and the ether removed by heating. There remained 71.5 mg. (75 per cent) of crude anisilic acid-1-C^{14}.

8. Oxidation of Anisilic Acid-1-C^{14}

To a solution of the crude anisilic acid (71.5 mg.) in 3 ml. of warm glacial acetic acid was added a solution of chromium trioxide (25 mg., 0.25 mmole) in 2 ml. of glacial acetic acid containing two drops of water. The resulting solution was heated on a steam bath for thirty minutes and poured into 15 ml. of water. The aqueous mixture was extracted with three 20-ml. portions of ether. The combined ethereal extract was

washed with water, washed with 5 per cent sodium carbonate until the washings were basic, washed again with water, dried with anhydrous magnesium sulfate and evaporated until 4 ml. remained. The solution was cooled and the ether decanted from the crystals which appeared. The crystals were washed with ether and dried in vacuo. The yield was 26.5 mg. (44 per cent from the crude acid) of 4,4'-dimethoxybenzophenone, m.p. 142-144° (lit. value[83] 144-145°), <0.016 mc./mole.

9. Reaction of Methyl Anisilate-1-C^{14} and Sodium Methoxide at 100°

To 10 ml. of anhydrous methanol (distilled from magnesium methoxide) contained in a nitrogen filled 50-ml., round bottomed flask was added 70 mg. of sodium metal. One ml. of the resultant solution was added to methyl anisilate-1-C^{14} (100 mg., 0.33 mmole, 4.62 mc./mole) contained in a small, carefully dried tube. The tube was sealed and placed in a 95-99° oven for two days. The tube was opened and 0.25 ml. of 1.25 N potassium hydroxide added. The tube was sealed again and placed in a steam bath for fifty minutes. The contents of the tube were poured into 15 ml. of water and the aqueous solution was washed twice with ether, acidified with hydrochloric acid, cooled and extracted with three 15-ml. portions of ether. The combined ethereal extract was dried with anhydrous magnesium sulfate and evaporated. There remained 65 mg. (68 per cent) of crude anisilic acid-1-C^{14}. The crude acid was oxidized with 23 mg. of chromic acid by the procedure described in the preceding experiment. The yield was 20 mg. (36 per cent from the crude acid) of 4,4'-dimethoxybenzophenone, m.p. 140-141.5°, <0.017 mc./mole.

10. Reaction of Methyl Anisilate-1-C^{14} and Sodium Methoxide at 200°

To 10 ml. of anhydrous methanol (distilled from magnesium methoxide) contained in a nitrogen filled 50-ml., round-bottomed flask was added 70 mg. of sodium metal. Two ml. of the resultant solution was added to methyl anisilate-1-C^{14} (200 mg., 0.66 mmole, 4.62 mc./mole) contained in a carefully dried Carius tube. The tube was sealed and placed in an oven at 200 ± 6° for two days. The tube was opened and its contents poured into 15 ml. of water. The aqueous mixture was extracted three times with ether, filtered, acidified with hydrochloric acid, and extracted three more times with ether. The combined ethereal extract from the acid solution was dried with anhydrous magnesium sulfate and evaporated to leave 163 mg. of brownish, semi-solid, very impure anisilic acid-1-C^{14}. The combined ethereal extract from the basic solution was dried with anhydrous sodium sulfate and the ether removed by heating. There remained 50 mg. of brownish semi-solid, which was not further examined. The crude acid (163 mg.) was oxidized with 60 mg. of chromic acid by the procedure described above. In this case the 4,4'-dimethoxybenzophenone was recrystallized three times from ether. The yield was 14 mg. of 4,4'-dimethoxybenzophenone, m.p. 142-144°, < 0.035 mc./mole.

C. Additional Evidence Indicating Irreversibility of the Benzilic Ester Rearrangement

1. Methyl Benzilate

To an ethereal solution of benzilic acid (16.3 g., 0.072 mole) was added an excess of a solution of diazomethane in ether. After a few hours

the ether was evaporated and the product recrystallized twice from ethanol and once from methanol. The yield was 13.0 g. (75 per cent) of methyl benzilate, m.p. 71° (lit. value[84] 73°).

2. Reaction of Methyl Benzilate and Sodium Ethoxide

To 100 ml. of anhydrous ethanol (distilled from magnesium ethoxide) contained in a 200-ml., one-necked, nitrogen filled flask was added sodium metal (0.97 g., 0.042 mole) and, after the sodium had reacted, methyl benzilate (5.0 g., 0.0206 mole). The flask was closed and stored at room temperature for two weeks. Fifty milliliters of alcohol were vacuum distilled (1 mm.) from the reaction mixture and the remaining solution was poured into 200 ml. of water. The aqueous mixture was extracted twice with ether, work-up of which is described in the next paragraph, acidified with hydrochloric acid and filtered. Vacuum sublimation was attempted on a portion of the filtered solid, but no benzoic acid sublimed. The solid was recrystallized from aqueous ethanol. The yield was 0.5 g. of benzilic acid, m.p. 150°, with or without admixture of an authentic sample.

The combined ethereal extract was dried with anhydrous magnesium sulfate and evaporated. To the residue was added a solution of 2.0 g. of potassium hydroxide in 50 ml. of 80 per cent ethanol and the resulting solution was refluxed for two hours. The solution was diluted with 150 ml. of water, extracted twice with ether, acidified and filtered. There was obtained 2.5 g. of crude benzilic acid, m.p. 147-148°. The combined ethereal extract was dried with anhydrous magnesium sulfate and evaporated to leave a small amount of brown oil which failed to crystallize from a

variety of solvents.

3. Reaction of Methyl Anisilate and Sodium Ethoxide

To 75 ml. of anhydrous ethanol (distilled from magnesium ethoxide) contained in a 200-ml., one-necked, nitrogen filled flask was added sodium metal (0.51 g., 0.022 mole) and, after the sodium had reacted, methyl anisilate (3.2 g., 0.011 mole). The solution was refluxed for two days and 25 ml. of ethanol were distilled from the reaction mixture. The remaining solution was poured into 300 ml. of water, extracted twice with ether, acidified with hydrochloric acid and filtered. There was obtained 1.6 g. (52 per cent) of anisilic acid, m.p. 172-173° (d). The combined ethereal extract was dried with anhydrous magnesium sulfate and evaporated to leave 1.1 g. of solid, m.p. 91-92°. To this solid was added a solution of 0.5 g. of potassium hydroxide in 50 ml. of 80 per cent ethanol and the resulting solution was refluxed for two hours. The solution was diluted with 150 ml. of water and the crystals which appeared were collected and recrystallized from ether. The yield was 100 mg. (3.9 per cent) of 4,4'-dimethoxybenzophenone, m.p. 144-145°, with or without admixture of an authentic sample. The filtrate was acidified with hydrochloric acid and the crystals were collected and dried. There was obtained 0.8 g. (26 per cent) of anisilic acid, m.p. 172-173° (d).

D. Related Rearrangements

1. Amide Ion Catalysis

a. Reaction of anisil and sodium amide. Two hundred and fifty ml. of toluene, anisil (10.0 g., 0.037 mole) and sodium amide (2.90 g.,

0.074 mole) were placed in a 500-ml., one-necked flask equipped with a reflux condenser. The mixture was refluxed for twenty hours and water was added cautiously until two homogeneous layers were present. The two layers were separated and the aqueous layer was acidified and filtered. The solid obtained was recrystallized from ethanol and from benzene. There was obtained 0.4 g. (19 per cent based on reacted anisil) of anisilic acid, m.p. 163-164°, with or without admixture of an authentic sample. The toluene was evaporated from the non-aqueous layer to leave 8.0 g. of anisil, m.p. 132-133°.

b. Reaction of benzil and lithium dipropylamide. A mixture of lithium (0.76 g., 0.11 mole, cut into 25 small pieces) and 15 ml. of anhydrous ether was placed in a 200-ml., three-necked, nitrogen filled flask equipped with a stirrer, reflux condenser and dropping funnel. Bromobenzene (7.85 g., 0.050 mole) was added to the mixture in two portions; forty drops were added to initiate reaction and the remainder was dissolved in 15 ml. of anhydrous ether and added dropwise over a thirty minute period. The solution was refluxed and stirred for one hour and diluted with 70 ml. of anhydrous ether. To this solution was added dropwise a solution of dipropylamine (5.06 g., 0.050 mole) in 10 ml. of anhydrous ether and the resulting solution was refluxed for thirty minutes. Benzil (5.5 g., 0.26 mole) was slowly added to the reaction mixture causing a vigorous reaction to occur. The resulting mixture was refluxed for thirty minutes and poured into 100 ml. of water. The two layers were separated and the aqueous layer was acidified with hydrochloric acid and cooled. No precipitate appeared upon acidification or cooling. The

ethereal layer was evaporated and 40 ml. of hot benzene were added to the residue. The solution was cooled and the crystals (m.p. 125-128°) which appeared were collected and recrystallized from benzene. The yield of product was 3.0 g., m.p. 129-130.5°. The ultraviolet spectra of this compound had a maxima at 247 mμ, ϵ 1.02 x 10^5. The infrared spectra showed bands at 3400 cm.$^{-1}$, 1680 cm.$^{-1}$, 1065-1100 cm.$^{-1}$ (doublet), 755 cm.$^{-1}$ and 705 cm.$^{-1}$.

Anal. Calcd. for $C_{104}H_{85}O_{14}N$: C, 79.40; H, 5.46; N, 0.89.
Found: C, 79.31; H, 5.98; N, 0.81.

2. Grignard Reagent Catalysis

A 10 ml. aliquot of the Grignard reagent prepared from 2,6-dimethyliodobenzene (11.6 g., 0.05 mole) and magnesium (1.22 g., 0.05 mole) in sufficient ether to make the total volume 100 ml. was added to 150 ml. of distilled water. To this mixture was added 40.0 ml. of 0.294 N sulfuric acid and the resulting solution heated to 70° and titrated to the phenolphthalein end point with 0.216 N sodium hydroxide. A volume of 31.3 ml. of base was required. The calculated yield of Grignard reagent was therefore 49.9 per cent.

a. Reaction of benzil and 2,6-dimethylphenylmagnesium iodide. The Grignard reagent prepared from 2,6-dimethyliodobenzene (31 g., 0.13 mole) and magnesium (2.80 g., 0.12 mole) in 100 ml. of anhydrous ether was added to a solution of benzil (21.0 g., 0.10 mole) in 300 ml. of anhydrous ether. The solution turned deep red and was hydrolyzed immediately with cold saturated ammonium chloride solution. The ethereal layer was isolated, dried with anhydrous magnesium sulfate and evaporated. To

the residual oil (25 g.) was added 10 ml. of 95 per cent ethanol, whereupon 6 g. of benzil crystallized from the solution and was removed by filtration. The alcohol was evaporated from the filtrate and the residual oil was vacuum distilled (0.8 mm.). A few milliliters of 2,6-dimethyliodobenzene distilled at 80° and some benzil at 150-200°. At this point the distillation was terminated and the residue cooled. To this residue was added a few milliliters of alcohol and the crystals which appeared were collected and dried. The yield of product was 0.25 g., m.p. 262-264°.

Anal. Calcd. for $C_{22}H_{20}O_2$: C, 83.51; H, 6.37.

Found: C, 85.37; H, 5.75.

The product was not further characterized.

The Grignard reagent prepared from 2,6-dimethyliodobenzene (23.2 g., 0.10 mole) and magnesium (2.43 g., 0.10 mole) in 100 ml. of anhydrous ether was added to a solution of benzil (10.5 g., 0.050 mole) in anhydrous ether and the resulting mixture was refluxed in an air atmosphere for three hours. Small pieces of Dry Ice were added to the reaction mixture and it was hydrolyzed with saturated ammonium chloride solution. The ether layer was isolated and extracted with 10 per cent sodium hydroxide solution. The basic extract was acidified and the crystals which appeared were collected and dried. The m.p. of this solid was above 120°; the reported value for 2,6-dimethylbenzoic acid is m.p. 116°.[82]

Repetition of the above reaction in a nitrogen atmosphere with a three day reflux period and extracting the ethereal solution with 5 per

cent sodium bicarbonate instead of 10 per cent sodium hydroxide yielded 0.2 g. of product, m.p. 116°. This product was probably 2,6-dimethylbenzoic acid, but it was not characterized.

The reaction was repeated (3 day reflux period) in the absence of a nitrogen atomsphere. Whether the ethereal solution was extracted with 10 per cent sodium hydroxide or 5 per cent sodium bicarbonate, whether Dry Ice was added or not, the product was 0.5 g. of benzilic acid, m.p. 151° with or without admixture of an authentic sample.

The reaction carried out in a nitrogen atmosphere with an 18 hour reflux period and no Dry Ice addition yielded no benzilic acid.

The Grignard reagent prepared from 2,6-dimethyliodobenzene (23.2 g., 0.10 mole) and magnesium (2.43 g., 0.10 mole) in 100 ml. of anhydrous ether was added to a solution of benzil (10.5 g., 0.050 mole) in anhydrous ether. The mixture was refluxed for fifteen minutes and cooled. Dry oxygen was passed through the mixture for twenty minutes. The mixture was kept at room temperature for twelve hours and hydrolyzed with saturated ammonium chloride solution. The ether layer was isolated and extracted with 5 per cent sodium bicarbonate. The basic extract was acidified with hydrochloric acid and the solid which appeared was collected and dried. The yield of benzilic acid was 0.90 g. (8.6 per cent).

3. Tertiary Ketol Rearrangement

a. Reaction of benzil and o-tolyllithium. A solution of o-tolyllithium prepared from o-bromotoluene (8.6 g., 0.05 mole) and lithium (0.60 g., 0.086 mole) in 53 ml. of anhydrous ether was added dropwise to a stirred solution of benzil (10.5 g., 0.05 mole) in anhydrous ether.

The reaction was carried out in a nitrogen atmosphere. The reaction mixture was hydrolyzed with dilute hydrochloric acid. The ethereal layer was isolated, dried and evaporated to an oil. The oil was vacuum distilled and the fraction with b.p. 200-225° (1.0 mm.) was collected. The distillate solidified when stirred with hexane and was recrystallized four times from hexane and once from absolute ethanol. The yield of α-phenyl-2-methylbenzoin was 1.8 g. (12.4 per cent), m.p. 116-117° with or without admixture of an authentic sample.

b. Reaction of benzil and m-tolyllithium. A solution of m-tolyllithium prepared from m-bromotoluene (8.60 g., 0.050 mole) and lithium (0.60 g., 0.086 mole) in 50 ml. of anhydrous ether was added dropwise to a stirred solution of benzil (8.40 g., 0.040 mole) in 300 ml. of anhydrous ether. The resulting solution was deep red colored and to it was added dropwise a solution of 3.80 g. of lithium aluminum hydride in 100 ml. of anhydrous ether. The reaction was carried out in a nitrogen atmosphere. The reaction mixture was carefully hydrolyzed with dilute hydrochloric acid. The ethereal layer was isolated and dried with anhydrous magnesium sulfate. Evaporation of the ether gave 15 g. of solid material. Four grams of this solid were dissolved in 25 ml. of glacial acetic acid and to this stirred solution was added dropwise a solution of 10 g. of chromium trioxide in a mixture of 25 ml. of glacial acetic acid, 5 ml. of concentrated sulfuric acid and 15 ml. of water. The resu ting solution was refluxed for ninety minutes and diluted with 200 ml. of water. The mixture was extracted four times with 40-ml. portions of ether and the combined ethereal extract was washed with 10 per

cent sodium hydroxide until the washings were basic. The ether was dried with anhydrous magnesium sulfate and evaporated. The residue (0.4 g.) was dissolved in 20 ml. of 95 per cent ethanol and to this solution was added a solution of 0.2 g. of 2,4-dinitrophenylhydrazine in a mixture of 2 ml. of concentrated sulfuric acid, 3 ml. of water and 10 ml. of 95 per cent ethanol. The crystals which appeared were collected and recrystallized twice from ethanol. The yield of the 2,4-dinitrophenylhydrazone of benzophenone was 0.15 g. (4 per cent), m.p. 234-236° with or without admixture of an authentic sample.

E. Preparation of the Dialkali Salts of Benzophenones and Their Reaction With Carbon Dioxide

1. Preparation of Benzilic Acid

a. Method 1. To a mixture of sodium (1.20 g., 0.052 mole, cut into small pieces) and 100 ml. of anhydrous 1,2-dimethoxyethane (distilled from a mixture of sodium and benzophenone, and stored under nitrogen) contained in a 200-ml., nitrogen filled flask equipped with a reflux condenser and a magnetic stirrer, was added benzophenone (5.47 g., 0.30 mole) and the resulting mixture was refluxed for two hours under nitrogen. The color of the mixture changed from blue to purple. Carbon dioxide was passed through the reaction mixture and decolorization occurred within three minutes. The solvent was evaporated and the residue diluted with 100 ml. of water. The resulting mixture was washed with ether, acidified with hydrochloric acid and the crystals which appeared were collected and dried. The yield was 3.0 g. (45 per cent)

of crude benzilic acid, m.p. 146°.

b. Method 2. To a mixture of sodium (0.46 g., 0.02 mole, cut into small pieces) and 40 ml. of anhydrous 1,2-dimethoxyethane contained in a 100-ml., nitrogen filled flask equipped with a magnetic stirrer was added benzophenone (1.82 g., 0.010 mole) and the resulting mixture was stirred for five hours under nitrogen, added to an excess of carbon dioxide (Dry Ice crushed into very small pieces) and allowed to come to room temperature. The solvent was evaporated and the residue diluted with 20 ml. of water containing two potassium hydroxide pellets. The mixture was extracted with ether, acidified with hydrochloric acid and extracted again with ether. The ethereal extract of the basic aqueous solution was dried with anhydrous magnesium sulfate and evaporated to leave 0.7 g. (38 per cent) of crude benzhydrol, m.p. 60-63° with or without admixture of an authentic sample. The ethereal extract of the acidic aqueous solution was dried and evaporated to leave 1.1 g. (48 per cent) of crude benzilic acid.

c. Method 3. To a mixture of sodium (1.84 g., 0.080 mole, cut into small pieces) and 50 ml. of anhydrous 1,2-dimethoxyethane contained in a 100-ml., nitrogen filled flask equipped with a magnetic stirrer was added benzophenone (3.64 g., 0.02 mole) and the resulting mixture was stirred for three days under nitrogen and added to an excess of Dry Ice. There remained in the flask 1.2 g. of sodium metal in one large lump. The work-up procedure was the same as that described in the preceding experiment. The yield of crude benzilic acid was 2.28 g. (50 per cent).

d. Method 4. A mixture of sodium (1.84 g., 0.080 mole) and 50 ml. of anhydrous toluene contained in a 100-ml., nitrogen filled flask equipped with a reflux condenser and a magnetic stirrer was heated to reflux. The mixture was vigorously stirred and allowed to cool to room temperature. The toluene was decanted from the sodium which was in the form of a semi-powder. The sodium was washed twice with anhydrous ether and to it was added 50 ml. of anhydrous 1,2-dimethoxyethane and benzophenone (3.64 g., 0.020 mole). The resulting mixture was stirred for twelve hours under nitrogen and added to an excess of Dry Ice. There remained in the flask 1.1 g. of sodium metal. Work-up of the acid fraction in the usual manner yielded 2.74 g. (60 per cent) of crude benzilic acid.

e. Method 5. To a mixture of sodium (5.0 g., 0.22 mole, made into a suspension by the procedure described above) in 100 ml. of anhydrous ether contained in a 200-ml., nitrogen filled flask equipped with a magnetic stirrer was added benzophenone (3.64 g., 0.02 mole). The mixture was stirred for one day under nitrogen and one-half of the ether was evaporated and replaced by anhydrous 1,2-dimethoxyethane. The mixture was stirred for another day and added to excess carbon dioxide (Dry Ice). Work-up of the acid fraction in the usual manner yielded 2.83 g. (62 per cent) of crude benzilic acid.

f. Method 6. To a stirred solution of sodium metal (0.90 g., 0.039 mole) in 100 ml. of freshly distilled anhydrous liquid ammonia contained in a 500-ml., three-necked flask equipped with a reflux condenser, magnetic stirrer and a dropping funnel was added dropwise a solu-

tion of benzophenone (3.64 g., 0.02 mole) in 50 ml. of anhydrous ether. The ammonia was evaporated from the purple solution and 50 ml. of ether was added. The light blue ethereal solution was boiled for a few minutes and cooled. Carbon dioxide gas was passed into the flask and a heavy white precipitate appeared. During all of the above operations, moisture and air were carefully excluded from the reaction flask. A few pieces of Dry Ice were placed in the flask to insure complete carbonation and the mixture was hydrolyzed with water. The basic aqueous layer was acidified with hydrochloric acid and cooled overnight. A negligible amount of solid material precipitated from the solution. The ether layer was dried with anhydrous magnesium sulfate and evaporated to leave 3.1 g. (84 per cent) of benzhydrol, m.p. 58-60° with or without admixture of an authentic sample.

g. Method 7. To a mixture of lithium (0.30 g., 0.043 mole, cut into small pieces) and 50 ml. of anhydrous 1,2-dimethoxyethane contained in a 100-ml., nitrogen filled flask equipped with a magnetic stirrer was added benzophenone (1.82 g., 0.01 mole) and the resulting mixture stirred for forty-eight hours under nitrogen. The nitrogen atmosphere was replaced by a carbon dioxide atmosphere and some lumps of Dry Ice were added to the reaction mixture. Work-up of the acid fraction in the usual manner yielded 0.6 g. (26 per cent) of crude benzilic acid.

h. Method 8. To a mixture of lithium (0.5 g., 0.072 mole, cut into small pieces) and 50 ml. of anhydrous 1,2-dimethoxyethane contained in a 100-ml., nitrogen filled flask equipped with a magnetic stirrer was added stilbene (1.80 g., 0.010 mole) and the resulting mixture was stirred

for twenty-four hours under nitrogen. To this mixture was added a solution of benzophenone (1.82 g., 0.010 mole) in 10 ml. of anhydrous 1,2-dimethoxyethane and the resulting purple mixture was stirred for two hours. The nitrogen atmosphere was replaced by a carbon dioxide atmosphere. Decolorization of the mixture occurred in a few minutes and 25 ml. of water were added. The mixture was acidified with hydrochloric acid and extracted twice with ether. The combined ethereal extract was extracted with 10 per cent sodium carbonate until no more solid appeared upon acidification of the basic extract. The acidified basic extracts were combined and filtered. The yield of crude benzilic acid was 1.3 g. (57 per cent).

2. Preparation of Methoxy Substituted Benzilic Acids

a. 4,4'-Dimethoxybenzophenone. A mixture of anisole (16.2 g., 0.150 mole), anisic acid (30.4 g., 0.20 mole) and 185 g. of polyphosphoric acid contained in a 125-ml. Erlenmeyer flask was heated to 70° and maintained within the temperature range 70-80° for two hours. During the heating period the mixture, which was stirred frequently with a stout glass stirring rod, changed color from yellow to orange red. The reaction mixture was poured onto 750 g. of ice and the resultant mass was thoroughly stirred. The mixture was filtered and the crystals were washed with 200 ml. of 10 per cent sodium hydroxide and with water. Recrystallization from absolute alcohol gave 25.4 g. (70 per cent) of 4,4'-dimethoxybenzophenone, m.p. 144-145°, (lit. value[83] 144-145°).

b. 4-Methoxybenzophenone. A mixture of anisole (21.6 g., 0.20 mole), benzoic acid (18.5 g., 0.15 mole) and 185 g. of polyphosphoric acid contained in a 125-ml. Erlenmeyer flask was heated to 75° and maintained within the temperature range 70-80° for two hours. During the heating period the mixture was stirred frequently with a stout glass stirring rod. The mixture was poured onto 650 g. of ice and the resultant mass was thoroughly stirred and extracted with ether. The ethereal extract was washed with 10 per cent sodium hydroxide and dried with anhydrous magnesium sulfate. Evaporation of the ether followed by two recrystallizations of the residue from methanol gave 6.0 g. (25 per cent) of 4-methoxybenzophenone, m.p. 61° (lit. value[84] 61-62°).

c. Attempted preparation of 4,4'-dimethoxybenzilic acid. To a mixture of potassium (0.94 g., 0.024 mole, cut into small pieces) and 50 ml. of anhydrous 1,2-dimethoxyethane contained in a 100-ml., nitrogen filled flask equipped with a magnetic stirrer was added 4,4'-dimethoxybenzophenone (3.00 g., 0.012 mole) and the resulting mixture was stirred under nitrogen for six hours. The solution turned deep blue and then purple and was poured onto excess Dry Ice. Work-up of the acid fraction in the usual manner yielded no 4,4'-dimethoxybenzilic acid.

The above reaction was repeated using a sodium suspension in 1,2-dimethoxyethane and again the purple color appeared but no 4,4'-dimethoxybenzilic acid could be isolated from the reaction mixture.

To a mixture of sodium (0.65 g., 0.028 mole, cut into small pieces) and 50 ml. of anhydrous 1,2-dimethoxyethane contained in a 100-ml, nitrogen filled flask equipped with a magnetic stirrer was added stilbene (2.52

g., 0.014 mole) and the resultant mixture was stirred for six hours under nitrogen. The brownish-black mixture was added to a solution of 4,4'-dimethoxybenzophenone (3.42 g., 0.014 mole) in anhydrous 1,2-dimethoxyethane and the resulting purple mixture was immediately poured onto excess Dry Ice. The purple color only slowly disappeared when in contact with the Dry Ice. Work-up of the acid fraction in the usual manner yielded no 4,4'-dimethoxybenzilic acid.

d. 4-Methoxybenzilic acid. To a mixture of sodium (0.65 g., 0.028 mole, cut into small pieces) and 50 ml. of anhydrous 1,2-dimethoxyethane contained in a 100-ml., nitrogen filled flask equipped with a magnetic stirrer was added stilbene (2.52 g., 0.014 mole) and the resulting mixture was stirred for six hours under nitrogen. The brownish-black mixture was added to a solution of 4-methoxybenzophenone (3.0 g., 0.014 mole) in anhydrous 1,2-dimethoxyethane and the resulting purple mixture was immediately poured onto excess Dry Ice. The solvent was evaporated and the residue diluted with 100 ml. of water. The resulting mixture was washed with ether, acidified and filtered. The yield was 0.2 g. (5.5 per cent) of crude 4-methoxybenzilic acid, m.p. 145-146° (lit. value[85] 148-149°).

To a mixture of sodium (0.65 g., 0.028 mole, cut into small pieces) and 50 ml. of anhydrous 1,2-dimethoxyethane contained in a 100-ml., nitrogen filled flask equipped with a magnetic stirrer was added 4-methoxybenzophenone (3.00 g., 0.014 mole) and the mixture was stirred for six hours under nitrogen. The purple mixture was poured onto excess Dry Ice and allowed to come to room temperature. The solvent was evaporated and

the residue diluted with water. The resulting aqueous mixture was washed with ether and acidified with hydrochloric acid. No 4-methoxybenzilic acid was obtained.

3. Preparation of Methyl Substituted Benzilic Acids

a. 4-Methylbenzilic acid. To a mixture of sodium (0.71 g., 0.031 mole, cut into small pieces) and 50 ml. of anhydrous 1,2-dimethoxyethane contained in a 100-ml., nitrogen filled flask equipped with a magnetic stirrer and a reflux condenser was added 4-methylbenzophenone (3.00 g., 0.0153 mole) and the mixture was stirred and refluxed for four hours under nitrogen. The resulting purple mixture was cooled and poured onto excess Dry Ice and allowed to come to room temperature. The solvent was evaporated and the residue was diluted with water. The aqueous mixture was washed with ether and acidified with hydrochloric acid and cooled. The crystals were collected and recrystallized from benzene-hexane. The yield was 1.5 g. (41 per cent) of 4-methylbenzilic acid, m.p. 129-130° (lit. value[52] 132°) with or without admixture of an authentic sample.

To a mixture of sodium (0.71 g., 0.031 mole, cut into small pieces) and 50 ml. of anhydrous 1,2-dimethoxyethane contained in a 100-ml., nitrogen filled flask equipped with a magnetic stirrer and a reflux condenser was added stilbene (2.76 g., 0.0153 mole) and the mixture was stirred and refluxed for three hours under nitrogen. The brownish-black mixture was added to a solution of 4-methylbenzophenone (3.00 g., 0.0153 mole) in anhydrous 1,2-dimethoxyethane. The resulting purple mixture was poured onto excess Dry Ice and allowed to come to room temperature. The solvent was evaporated and the residue was diluted with water. The aqueous mixture

was washed with ether, acidified with hydrochloric acid and cooled. The crystals were collected and recrystallized from water. The yield was 1.0 g. (27 per cent) of 4-methylbenzilic acid, m.p. 132-133°.

b. 3,4'-Dimethylbenzophenone. A mixture of m-toluic acid (12.0 g., 0.088 mole), toluene (9.2 g., 0.10 mole) and 125 g. of polyphosphoric acid was placed in a 200-ml., three-necked flask equipped with a reflux condenser and a mechanical stirrer. The flask was placed in a Wood's metal bath which had been previously heated to 110°. The temperature of the bath was raised to 160-165° and maintained between these limits for three hours. During this heating period the contents of the flask were vigorously stirred. The mixture was allowed to come to room temperature, poured onto 250 g. of ice and extracted twice with ether. The combined ethereal extract was extracted with 5 per cent sodium hydroxide until no solid appeared upon acidification of the basic extract. There was obtained 3.5 g. of solid from the basic extracts. This material was probably m-toluic acid but was not further characterized. The ether was dried with anhydrous magnesium sulfate and evaporated. The solid obtained was recrystallized from ethanol yielding 5.0 g. (38 per cent based on reacted m-toluic acid) of 3,4'-dimethylbenzophenone, m.p. 72-73° (lit. value[86] 82°).

c. 3,4'-Dimethylbenzilic acid. To a mixture of sodium (0.46 g., 0.022 mole, cut into small pieces) and 25 ml. of anhydrous 1,2-dimethoxyethane contained in a 50-ml., nitrogen filled flask equipped with a magnetic stirrer and a reflux condenser was added 3,4'-dimethylbenzophenone (2.0 g., 0.0095 mole) and the resulting mixture was refluxed for ten

minutes and stirred for five hours under nitrogen. The resulting purple mixture was poured onto excess Dry Ice and allowed to come to room temperature. The solvent was evaporated and the residue was diluted with 50 ml. of water. The aqueous mixture was washed with ether, acidified with hydrochloric acid and cooled. The crystals were collected and dried. The yield of crude 3,4'-dimethylbenzilic acid was 1.4 g. (55 per cent) which after three recrystallizations from benzene-hexane melted at 132.0-132.5°.

Anal. Calcd. for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29.

Found: C, 75.0; H, 6.38.

d. o-Toluoyl chloride. A mixture of o-toluic acid (68 g., 0.50 mole) and thionyl chloride (89.2 g., 0.75 mole) was placed in a one-necked flask equipped with a reflux condenser and drying tube. The resulting solution was refluxed for one hour. The excess thionyl chloride was removed by distillation at atmospheric pressure, and the product vacuum distilled, b.p. 68-70° (1.5 mm.). The yield was 55 g. (72 per cent).

e. 2-Methylbenzophenone. A mixture of o-toluoyl chloride (30.0 g., 0.194 mole), anhydrous aluminum chloride (28.0 g., 0.21 mole) and 100 ml. of anhydrous benzene was shaken vigorously, refluxed for three hours and poured onto a mixture of 200 g. of crushed ice and 100 ml. of concentrated hydrochloric acid. The benzene layer was separated, filtered, washed with 50 ml. of 5 per cent sodium hydroxide, washed with water and evaporated. The 2-methylbenzophenone was vacuum distilled, b.p. 114-115° (0.5 mm.) (lit. value[87] b.p. 295°/722 mm.). The yield was 19.8 g. (52 per cent).

f. Attempted preparation of 2-methylbenzilic acid. A mixture of lithium (0.28 g., 0.040 mole, cut into small pieces), 2-methylbenzophenone (3.0 g., 0.015 mole) and 25 ml. of anhydrous 1,2-dimethoxyethane contained in a 50-ml., nitrogen filled flask equipped with a magnetic stirrer was stirred for fifty-three hours. The color of the mixture changed from blue to purple to red. The mixture was poured onto excess Dry Ice, allowed to come to room temperature, diluted with 100 ml. of water, cooled and filtered. The solid material was recrystallized from ligroin to give 1.1 g. (36 per cent) of crude 2-methylbenzhydrol which melted 88-90° after being recrystallized from benzene-ligroin. The melting point was undepressed by admixture of an authentic sample of 2-methylbenzhydrol prepared from o-tolylmagnesium bromide and benzaldehyde. The basic aqueous filtrate was acidifed, cooled and extracted with ether. The ethereal extract was dried with anhydrous magnesium sulfate and evaporated, leaving a negligible amount of oil.

4. Preparation of 2-Phenylbenzilic Acid

a. 2-Phenylbenzophenone. To a stirred solution of Grignard reagent prepared from 2-bromobiphenyl (46.6 g., 0.20 mole) and magnesium (4.86 g., 0.20 mole) in 100 ml. of ether contained in a 500-ml., nitrogen filled, three-necked flask equipped with a reflux condenser, dropping funnel and mechanical stirrer was added dropwise a solution of freshly distilled benzaldehyde (21.2 g., 0.20 mole) in 40 ml. of anhydrous benzene. To the semi-solid reaction mixture was added 100 ml. of anhydrous benzene which dissolved the dense precipitate, and 40 ml. of benzaldehyde. Ninety ml. of ether were distilled from the reaction mixture and the resulting solution was

refluxed for twenty hours and hydrolyzed with saturated aqueous ammonium chloride. The solvent was evaporated from the ether-benzene layer and the residue was vacuum distilled. The fraction, b.p. 140-190° (1 mm.), was collected and, upon standing for twelve hours, it crystallized. The solid was recrystallized from methanol to give 24.0 g. (47 per cent) of 2-phenylbenzophenone, m.p. 86.5-88.0° (lit. value[68] 86-87°).

b. 2-Phenylbenzilic acid. To a mixture of lithium (0.14 g., 0.020 mole, cut into small pieces) and 25 ml. of 1,2-dimethoxyethane contained in a 50-ml., nitrogen filled flask equipped with a magnetic stirrer was added stilbene (1.39 g., 0.0077 mole). The resulting mixture was stirred for seven hours under nitrogen and added to a solution of 2-phenylbenzophenone (2.00 g., 0.0077 mole) in 15 ml. of anhydrous 1,2-dimethoxyethane. The resulting blue mixture was poured onto excess Dry Ice and allowed to come to room temperature. The solvent was evaporated and the residue diluted with 75 ml. of water. The aqueous mixture was washed with ether, acidified with hydrochloric acid and cooled. The crystals were collected, washed with water and dried. The yield was 0.50 g. (21 per cent) of 2-phenylbenzilic acid, m.p. 188-190°(d) (lit. value[69] 189-191 (d)).

c. Oxidation of 2-phenylbenzilic acid. To a solution of 2-phenylbenzilic acid (100 mg., 0.33 mmole) in 3 ml. of warm glacial acetic acid was added a solution of chromium trioxide (33 mg., 0.33 mmole) in 2 ml. of glacial acetic acid containing two drops of water. The resulting solution was heated on a steam bath for thirty minutes and diluted with 15 ml. of water. The aqueous mixture was extracted with three 20-ml. portions of ether. The combined ethereal extract was washed with water,

washed with 5 per cent sodium carbonate until the washings were basic, washed again with water, dried with anhydrous magnesium sulfate and evaporated to an oil. The oil crystallized when stirred and was recrystallized from methanol to give 35 mg. (41 per cent) of 2-phenylbenzophenone, m.p. 86.5-88.0° with or without admixture of an authentic sample.

F. Preparation of the Dialkali Salts of Benzophenones and Their Reaction With Esters

1. Reactions With Ethyl Chloroformate

a. Benzophenone and sodium. To a mixture of sodium (0.76 g., 0.033 mole, cut into small pieces) and 90 ml. of anhydrous 1,2-dimethoxyethane contained in a 200-ml., nitrogen filled flask equipped with a magnetic stirrer and reflux condenser was added 3.00 g. of benzophenone (0.016 mole). The resulting blue mixture was stirred and refluxed for four hours under nitrogen, cooled and added to a solution of ethyl chloroformate (2.00 g., 0.018 mole) in 50 ml. of 1,2-dimethoxyethane. The solvent was evaporated and to the residue was added 200 ml. of 5 per cent sodium hydroxide. This mixture was refluxed for two hours, cooled, washed with ether and acidified with hydrochloric acid. The crystals were collected, dried and recrystallized from water. The yield was 0.50 g. (14 per cent) of benzilic acid, m.p. 148-149° with or without admixture of an authentic sample.

b. 4,4'-Dimethoxybenzophenone, sodium and stilbene. To a mixture of sodium (0.55 g., 0.024 mole, cut into small pieces) and 50 ml. of an-

hydrous 1,2-dimethoxyethane contained in a 100-ml., nitrogen filled flask equipped with a magnetic stirrer was added stilbene (2.17 g., 0.012 mole) and the resulting mixture was stirred for six hours under nitrogen. The brownish-black mixture was added to a solution of 4,4'-dimethoxybenzophenone (3.00 g., 0.012 mole) in anhydrous 1,2-dimethoxyethane and the resulting purple mixture was immediately added to a solution of ethyl chloroformate in anhydrous 1,2-dimethoxyethane. The solvent was evaporated from the resulting solution and the residue was dissolved in benzene. The benzene solution was applied to a chromatographic column packed with Florisil (60/100 mesh) and the column was eluted successively with a graded series of eluents: benzene, ether, acetone and ethyl acetate. There were twenty-three fractions collected but upon evaporation of the solvents, only fractions two and three yielded appreciable residues. These were recrystallized from benzene-hexane and proved to be stilbene and 4,4'-dimethoxybenzophenone respectively.

2. Reactions With Alkyl Carbonates

a. Benzophenone, sodium and dimethyl carbonate. To a stirred solution of sodium (2.3 g., 0.10 mole) in 200 ml. of freshly distilled anhydrous liquid ammonia contained in a 500-ml., three-necked flask equipped with an ammonia inlet tube, magnetic stirrer and a Dry Ice condenser which was attached to a modified mercury filled manostat[88] was added dropwise a solution of benzophenone (9.1 g., 0.050 mole) in 50 ml. of anhydrous ether.* Immediately upon completion of the addition of the benzo-

*All subsequent preparations of dialkali salts of aromatic ketones in liquid ammonia were performed in the apparatus as described above.

phenone solution there was added to the purple reaction mixture a solution of dimethyl carbonate (4.51 g., 0.050 mole) in 50 ml. of anhydrous ether. After the resulting blue solution was refluxed for one hour, solid ammonium chloride (5.35 g., 0.10 mole) was cautiously added to it. The ammonia was evaporated and anhydrous ether was added to the residue. The ethereal mixture was filtered and the ether was evaporated from the filtrate leaving 11 g. of solid yellowish residue. This residue was recrystallized from hexane to give 8.40 g. (70 per cent) of methyl benzilate, m.p. 69.5-71.0° with or without admixture of an authentic sample prepared from benzilic acid and diazomethane.

b. Benzophenone, sodium and diethyl carbonate. To a stirred solution of sodium (4.6 g., 0.20 mole) in 250 ml. of liquid ammonia there was added dropwise a solution of benzophenone (18.2 g., 0.10 mole) in 50 ml. of anhydrous ether. To the purple solution was added dropwise 11.8 g. of diethyl carbonate (0.10 mole) and the resulting blue solution was refluxed for one hour, during which time a stopper blew out and some of the solution was lost. Solid ammonium chloride (10.7 g., 0.20 mole) was cautiously added to the reaction mixture. The ammonia was evaporated and anhydrous ether was added to the residue. The ethereal mixture was filtered and the ether was evaporated from the filtrate leaving a light yellow oil. The oil was vacuum distilled and the fraction, b.p. 160-165° (1 mm.), was collected. The yield was 16.5 g. of liquid which failed to crystallize from a variety of solvents. A mixture of 5.0 g. of this liquid, 2.5 g. of sodium hydroxide, 25 ml. of water and 25 ml. of ethanol was refluxed for ninety minutes, cooled, diluted with 50 ml. of water,

extracted with ether, acidified and cooled. The crystals which appeared were collected and dried to yield 3.9 g. (57 per cent from benzophenone) of benzilic acid, m.p. 147.5-149.5° with or without admixture of an authentic sample. The ethereal extract was dried with anhydrous magnesium sulfate and evaporated to an oil. This oil crystallized when heated with benzene-hexane and was recrystallized from hexane to give 0.10 g. of benzhydrol, m.p. 63.5-64.5° with or without admixture of an authentic sample.

c. 4,4'-Dimethoxybenzophenone, sodium and dimethyl carbonate. To a stirred solution of sodium (0.95 g., 0.041 mole) in 250 ml. of liquid ammonia there was added dropwise a solution of 4,4'-dimethoxybenzophenone (5.00 g., 0.0206 mole) in 60 ml. of anhydrous 1,2-dimethoxyethane. Dimethyl carbonate (1.86 g., 0.0206 mole) was added to the reaction mixture and the resulting solution was refluxed for ninety minutes and treated with solid ammonium chloride (2.20 g., 0.041 mole). The ammonia was evaporated and anhydrous ether was added to the residue. The ethereal mixture was filtered and the solvent was evaporated from the filtrate leaving an oil which solidified upon stirring. Fractional crystallization of this solid from benzene-hexane yielded four fractions, all of which melted 60-70°. The four fractions were combined (4.4 g.) and dissolved in 50 ml. of 50 per cent aqueous ethanol containing 2.5 g. of potassium hydroxide. The resulting solution was refluxed for ninety minutes, cooled, diluted with 50 ml. of water, extracted three times with ether, acidified and cooled. No precipitate appeared upon acidification and cooling of the basic solution. The combined ethereal ex-

tract was evaporated until no more ether remained in solution. The resulting alcoholic solution was diluted with water and cooled. The crystals which appeared were collected, recrystallized from benzene-hexane and dried. The yield was 0.5 g. (10 per cent) of 4,4'-dimethoxybenzophenone, m.p. 145-146° with or without admixture of an authentic sample. The aqueous alcoholic filtrate was evaporated until only a few milliliters remained. This residue was diluted with water and extracted with benzene-ether. The extract was evaporated to an oil which solidified when stirred. The solid was recrystallized from hexane to yield 2.2 g. (44 per cent) of 4,4'-dimethoxybenzhydrol, m.p. 70-71° (lit. value[89] 72°).

d. 4,4'-Dimethoxybenzophenone, lithium and diethyl carbonate. To a stirred solution of lithium (0.29 g., 0.041 mole) in 250 ml. of liquid ammonia, there was added dropwise a solution of 4,4'-dimethoxybenzophenone (2.50 g., 0.0103 mole) in anhydrous 1,2-dimethoxyethane and the resulting purple solution was refluxed for two hours. A solution of diethyl carbonate (1.22 g., 0.0103 mole) in 50 ml. of anhydrous ether was prepared. After about one-half of the diethyl carbonate solution had been added to the ammonia solution, the latter became colorless and the addition was discontinued. Solid ammonium chloride (2.20 g., 0.041 mole) was added to the reaction mixture and the ammonia was evaporated and anhydrous ether was added to the residue. The ethereal mixture was filtered and the solvent was evaporated from the filtrate leaving 2.5 g. of crude solid which was recrystallized twice from benzene-hexane. The yield was 1.7 g. (68 per cent) of 4,4'-dimethoxybenzhydrol, m.p. 69.5-70.5° undepressed by the

compound obtained from the preceding reaction.

e. 4,4'-Dimethylbenzophenone, sodium and dimethyl carbonate. To a stirred solution of sodium (2.18 g., 0.095 mole) in 200 ml. of liquid ammonia there was added dropwise a solution of 4,4'-dimethylbenzophenone (10.0 g., 0.048 mole) in 50 ml. of anhydrous ether and the resulting purple solution was refluxed for fifteen minutes. To this was added dropwise a solution of dimethyl carbonate (4.30 g., 0.048 mole) in 50 ml. of anhydrous ether and, after the resulting blue solution was refluxed for one hour, solid ammonium chloride (5.1 g., 0.095 mole) was added to it. The ammonia was evaporated and anhydrous ether was added to the residue. The ethereal mixture was filtered and the ether was evaporated from the filtrate leaving an oil which solidified upon stirring. The solid was recrystallized twice from hexane to give 5.0 g. of product, m.p. 65-69°. Two grams of this product were dissolved in a mixture of 1.25 g. of potassium hydroxide, 13 ml. of water and 12 ml. of ethanol. The resulting solution was refluxed for two hours, cooled, diluted with 50 ml. of water, extracted with ether, acidified with hydrochloric acid and cooled to yield no acid fraction. The ethereal extract was dried and evaporated to give pure 4,4'-dimethylbenzhydrol, m.p. 70.5-71° (lit. value[89] 72°). The supernatant liquid from the first hexane recrystallization was evaporated to leave an oil which was dissolved in a mixture of 200 g. of potassium hydroxide, 25 ml. of water and 25 ml. of ethanol. The resulting solution was refluxed for two hours, cooled, diluted with 50 ml. of water, extracted with ether, acidified with hydrochloric acid and cooled. The crystals which appeared were filtered and recrystallized

from benzene-hexane to give 1.8 g. (15 per cent, based on starting ketone) of 4,4'-dimethylbenzilic acid, m.p. 132-133° (lit. value[90] 131-132°). The ethereal extract was dried with anhydrous magnesium sulfate and evaporated to give 1.0 g. of 4,4'-dimethylbenzhydrol, m.p. 68-70° (lit. value[91] 69°).

f. 4-Methylbenzophenone, sodium and diethyl carbonate. To a stirred solution of sodium (1.17 g., 0.051 mole) in 200 ml. of liquid ammonia there was added dropwise a solution of 4-methylbenzophenone (5.00 g., 0.0255 mole) in 50 ml. of anhydrous ether. Immediately upon completion of the addition of the 4-methylbenzophenone solution there was added dropwise to the reaction mixture a solution of diethyl carbonate (3.01 g., 0.0255 mole) in 50 ml. of anhydrous ether. The resulting blue solution was refluxed for one hour and treated with solid ammonium chloride (2.73 g., 0.051 mole). The ammonia was evaporated and anhydrous ether was added to the residue. The ethereal mixture was filtered and the ether was evaporated from the filtrate. To the residue was added a mixture of 2.5 g. of potassium hydroxide, 25 ml. of water and 25 ml. of ethanol. The resulting solution was refluxed for ninety minutes, cooled, diluted with 50 ml. of water, washed with ether, acidified with hydrochloric acid and cooled. The crystals which appeared were collected and dried. The yield was 4.3 g. (70 per cent) of crude 4-methylbenzilic acid which melted 133-134° after one recrystallization from benzene-hexane. The melting point was undepressed by admixture of an authentic sample of 4-methylbenzilic acid.

g. 4-Methylbenzophenone, potassium and diethyl carbonate. The preceding reaction was repeated using potassium metal (1.99 g., 0.051 mole) instead of sodium. The yield was 3.0 g. (49 per cent) of crude 4-methylbenzilic acid which melted 133-134° after one recrystallization from benzene-hexane. The melting point was undepressed by admixture of an authentic sample of 4-methylbenzilic acid.

h. 4-Methylbenzophenone, lithium and diethyl carbonate. To a stirred solution of lithium (0.35 g., 0.051 mole) in 200 ml. of anhydrous liquid ammonia there was added dropwise a solution of 4-methylbenzophenone (5.00 g., 0.0255 mole) in 50 ml. of anhydrous ether. Immediately upon completion of the addition of the 4-methylbenzophenone solution, there was added to the reaction mixture a solution of diethyl carbonate (3.01 g., 0.0255 mole) in 50 ml. of anhydrous ether. The resulting pale blue solution was treated with solid ammonium chloride (2.73 g., 0.051 mole). The ammonia was evaporated and anhydrous ether was added to the residue. The ethereal mixture was filtered and the ether was evaporated from the filtrate. To the residue was added a mixture of 2.5 g. of potassium hydroxide, 25 ml. of water and 25 ml. of ethanol. The resulting solution was refluxed for ninety minutes, cooled, diluted with 50 ml. of water, extracted with ether, acidified with hydrochloric acid and cooled. There was no acid obtained upon acidification and cooling of the basic solution. The ethereal extract was dried with anhydrous magnesium sulfate and evaporated to an oil which solidified when stirred. The solid was recrystallized from hexane to give 3.0 g. (60 per cent) of 4-methylbenzhydrol, m.p. 49-51° (lit. value[92] 52-53°). The supernatant

liquid from the recrystallization was evaporated to an oil. This oil failed to crystallize from a variety of solvents.

The above reaction was repeated with the exception that the ammoniacal solution of lithium and 4-methylbenzophenone was refluxed for two hours prior to the addition of the diethyl carbonate solution. During this reflux period, the color of the solution turned from purple to blue and a white precipitate appeared. Only a fraction of the theoretical amount of diethyl carbonate was required to decolorize the blue solution. After solid ammonium chloride was added to the reaction mixture, the ammonia was evaporated and anhydrous ether was added to the residue. The ethereal mixture was filtered and the ether was evaporated from the filtrate to leave an oil which solidified upon stirring. The solid was recrystallized from hexane to give 4.0 g. (80 per cent) of 4-methylbenzhydrol, m.p. 51.0-52.5°.

i. Preparation of 2-diethylaminoethyl carbonate. A mixture of diethyl carbonate (37.8 g., 0.32 mole), 2-diethylaminoethanol (75 g., 0.64 mole) and 30 mg. of anhydrous potassium carbonate was placed in a 200-ml. flask equipped with a condenser arranged for distillation. The flask was maintained for two hours at 100° and for two hours at 115° but during these heating periods no ethyl alcohol distilled. A one-foot Vigereaux column was placed between the flask and the condenser and an additional 30 mg. of potassium carbonate were added to the reaction mixture. The flask was heated to 155° by means of a Wood's metal bath and maintained between 155-160° for three hours. During these three hours, approximately 20 ml. of ethyl alcohol distilled; the temperature at the top of the

column did not exceed 80°. The reaction mixture was cooled, filtered and fractionated *in vacuo*. The yield of 2-diethylaminoethyl carbonate, b.p. 95-99° (0.1 mm.) (lit. value[71] 112-116° (0.25 mm.)), was 28 g. (34 per cent).

j. *Benzophenone, sodium and 2-diethylaminoethyl carbonate.* To a stirred solution of sodium (0.88 g., 0.038 mole) in 200 ml. of liquid ammonia there was added dropwise a solution of benzophenone (3.50 g., 0.019 mole) in 50 ml. of anhydrous ether. Immediately upon completion of the addition of the benzophenone solution there was added to the reaction mixture a solution of 2-diethylaminoethyl carbonate (5.0 g., 0.019 mole) in 50 ml. of anhydrous ether. The resulting blue solution was refluxed for one hour and treated with solid ammonium chloride (2.06 g., 0.038 mole). The ammonia was evaporated and anhydrous ether added to the residue. The ethereal mixture was filtered and the ether, unreacted ester and alcohol evaporated from the filtrate leaving an oil which would not crystallize from a variety of solvents. One-half of the oil was dissolved in anhydrous ether and cooled to 0°. The solution was kept at 0° by means of an ice bath while anhydrous hydrochloric acid was bubbled through it. A dense white precipitate appeared and was collected and washed several times with anhydrous ether. The yield was 2.70 g. (77 per cent from benzophenone) of 2-diethylaminoethyl benzilate hydrochloride, m.p. 173-175° with or without admixture of an authentic sample.

G. Reaction of the Dialkali Salts of Benzophenone With Aromatic Aldehydes

1. Reactions With Benzaldehyde

a. Benzophenone and sodium. A mixture of sodium (0.46 g., 0.020 mole, cut into small pieces), benzophenone (1.82 g., 0.010 mole) and 40 ml. of anhydrous 1,2-dimethoxyethane contained in a 100-ml., nitrogen filled flask equipped with a magnetic stirrer was stirred for five hours and the resulting purple solution was added dropwise to a stirred solution of benzaldehyde (1.06 g., 0.010 mole) in 10 ml. of anhydrous 1,2-dimethoxyethane. The resulting colorless solution was stirred for two hours under nitrogen and evaporated by a stream of dry air. The residue was diluted with 50 ml. of water, extracted three times with ether, acidified, cooled and filtered. The crystals were recrystallized from water to give 0.5 g. of benzoic acid. The combined ethereal extract was dried and evaporated to give 0.7 g. (24 per cent) of crude 1,1,2-triphenylethylene glycol, m.p. 165-166° after one recrystallization from dilute ethanol. The melting point was undepressed by admixture of an authentic sample of 1,1,2-triphenylethylene glycol.

b. 2-Phenylbenzophenone and lithium. A mixture of lithium (0.28 g., 0.040 mole, cut into small pieces), 2-phenylbenzophenone (4.00 g., 0.0155 mole) and 50 ml. of anhydrous 1,2-dimethoxyethane contained in a 100-ml., nitrogen filled flask equipped with a magnetic stirrer was stirred for twenty-nine hours. To this mixture was added dropwise a solution of benzaldehyde (1.64 g., 0.0155 mole) in 10 ml. of anhydrous 1,2-dimethoxyethane. The resulting mixture was refluxed for six hours

under nitrogen, cooled, and poured onto excess Dry Ice and allowed to come to room temperature. The solvent was evaporated and the residue was diluted with 100 ml. of water and extracted twice with ether. The combined ethereal extract was dried with anhydrous magnesium sulfate and evaporated. The residue was dissolved in hot benzene and the solution was cooled and filtered. There was obtained 1.2 g. of solid material, m.p. 158-162°. One-tenth of a gram of this material was oxidized with chromium trioxide and the remainder was recrystallized from methanol to give 1.0 g. (18 per cent from benzophenone) of 1-(2-biphenylyl)-1,2-diphenylethylene glycol, m.p. 175-177°.

Anal. Calcd. for $C_{26}H_{22}O_2$: C, 85.21; H, 6.05.

Found: C, 85.32; H, 5.71.

To a solution of 1-(2-biphenyl)-1,2-diphenylethylene glycol (100 mg., 0.27 mmole) in 3 ml. of warm glacial acetic acid was added a solution of chromium trioxide (64 mg., 0.64 mmole) in 2 ml. of glacial acetic acid containing two drops of water. The resulting solution was heated on a steam bath for one hour and diluted with 15 ml. of water. The aqueous mixture was extracted with two 20-ml. portions of ether. The combined ethereal extract was washed with water, extracted several times with aqueous potassium hydroxide, washed again with water, dried with anhydrous magnesium sulfate and evaporated. The solid residue was recrystallized from methanol to give 30 mg. (43 per cent) of 2-phenylbenzophenone, m.p. 86-87° with or without admixture of an authentic sample. The combined basic aqueous extract was acidified with hydrochloric acid, cooled and extracted twice with ether. The combined

ethereal extract was dried with anhydrous magnesium sulfate and evaporated. The residue was vacuum sublimed (100° (1 mm.)) to give 20 mg. (60 per cent) of benzoic acid, m.p. 118-120° with or without admixture of an authentic sample.

c. 2-Phenylbenzophenone and lithium suspension. A mixture of lithium suspension (1.0 g., 0.044 mole), 2-phenylbenzophenone (3.00 g., 0.012 mole) and 50 ml. of anhydrous ether contained in a 100-ml., nitrogen filled flask equipped with a magnetic stirrer was stirred for one hour. To this mixture was added dropwise a solution of benzaldehyde (1.22 g., 0.012 mole) in 10 ml. of anhydrous ether which decolorized the solution. Ethanol was added to decompose the lithium and the resulting mixture was diluted with water and extracted with ether. The combined ethereal extract was dried and evaporated to an oil. The oil was crystallized from benzene-hexane to give 0.4 g. of material, m.p. 145-160°. Recrystallization from benzene-hexane yielded a product, m.p. 140-150°, which was probably a mixture of the diastereoisomers of 1-(2-biphenylyl)-1,2-diphenylethylene glycol.

d. 2-Phenylbenzophenone and sodium. To a stirred solution of sodium (0.89 g., 0.0388 mole) in 200 ml. of liquid ammonia was added dropwise a solution of 2-phenylbenzophenone (5.00 g., 0.0194 mole) in 50 ml. of anhydrous ether. Immediately upon completion of the addition of the 2-phenylbenzophenone solution, there was added to the purple reaction mixture a solution of benzaldehyde (2.05 g., 0.0194 mole) in 50 ml. of anhydrous ether. The resulting green solution was refluxed for one hour and treated with solid ammonium chloride (2.08 g., 0.0388 mole).

The ammonia was evaporated and anhydrous ether was added to the residue. The ethereal mixture was filtered and the ether was evaporated from the filtrate. There was obtained 7.0 g. of yellow oil which was dissolved in hot benzene-hexane and the resulting solution was cooled and filtered to give 1.7 g. of solid, m.p. 97-100°. After two more recrystallizations from benzene-hexane, the product melted at 121-124°. This product was probably a mixture of the diastereoisomers of 1-(2-biphenylyl)-1,2-diphenylethylene glycol and was not further characterized.

e. 2-Methylbenzophenone and sodium. To a stirred solution of sodium (1.17 g., 0.051 mole) in 200 ml. of liquid ammonia was added dropwise a solution of 2-methylbenzophenone (5.00 g., 0.0255 mole) in 50 ml. of anhydrous ether. Immediately upon completion of the addition of the 2-methylbenzophenone solution, there was added to the purple reaction mixture a solution of benzaldehyde (2.70 g., 0.0255 mole) in 50 ml. of anhydrous ether. The resulting light yellow solution was hydrolyzed with solid ammonium chloride (2.73 g., 0.051 mole). The ammonia was evaporated and anhydrous ether was added to the residue. The ethereal mixture was filtered and the ether was evaporated from the filtrate. To the residue was added a few milliliters of ligroin and the crystals were collected and recrystallized from benzene-ligroin. The yield was 3.5 g. (69 per cent) of 2-methylbenzhydrol, m.p. 91.5-93.0° with or without admixture of an authentic sample.

2. Reactions With Anisaldehyde

a. Benzophenone and sodium. A mixture of sodium (5.00 g., 0.22 mole, cut into small pieces) and 50 ml. of anhydrous toluene contained

in a 100-ml., nitrogen filled flask equipped with a reflux condenser and a magnetic stirrer was heated to reflux. The mixture was vigorously stirred and allowed to cool to room temperature. The toluene was decanted from the sodium which was in the form of a semi-powder. The sodium was washed twice with anhydrous ether and to it was added 50 ml. of anhydrous ether and benzophenone (3.64 g., 0.020 mole). The resulting mixture was stirred for one day under nitrogen and one-half of the ether was evaporated and replaced by anhydrous 1,2-dimethoxyethane. The mixture was stirred for another day and one-half of it was added to a stirred solution of anisaldehyde (1.45 g., 0.0105 mole) in 10 ml. of 1,2-dimethoxyethane. The solvent was evaporated from the resulting mixture by a stream of dry air and the residue was diluted with 50 ml. of water. The aqueous mixture was extracted twice with benzene-ether, acidified with hydrochloric acid, cooled and filtered to give 0.7 g. of crude anisic acid, m.p. 177° with or without admixture of an authentic sample. The combined benzene-ether extract was filtered and evaporated to give 0.70 g. (22 per cent) of crude 1,1-diphenyl-2-anisylethylene glycol, m.p. 203.5-204.0° after one recrystallization from benzene. The melting point was undepressed by admixture of an authentic sample of 1,1-diphenyl-2-anisylethylene glycol.

b. 2-Methylbenzophenone and sodium. To a stirred solution of sodium (1.17 g., 0.0510 mole) in 200 ml. of liquid ammonia there was added dropwise a solution of 2-methylbenzophenone (5.00 g., 0.0255 mole) in 50 ml. of anhydrous ether. Immediately upon completion of the addition of the 2-methylbenzophenone solution, there was added to the purple reaction

mixture a solution of anisaldehyde (3.47 g., 0.0255 mole) in 50 ml. of anhydrous ether. The resulting blue solution was refluxed for one hour and hydrolyzed with solid ammonium chloride (2.73 g., 0.0510 mole). The ammonia was evaporated and anhydrous ether added to the residue. The ethereal mixture was filtered and the ether was evaporated from the filtrate. The residue was dissolved in hot benzene-hexane and the resulting solution was cooled and filtered. There was obtained 2.0 g. of solid, m.p. 164-180°. Another recrystallization from benzene gave 1.5 g. of product, m.p. 183-188° which was a mixture of diastereoisomers of 1-phenyl-1-o-tolyl-2-p-anisylethylene glycol.

Anal. Calcd. for $C_{22}H_{22}O_3$: C, 79.01; H, 6.63.

Found: C, 79.26; H, 6.42.

c. 2-Methylbenzophenone and lithium. A mixture of lithium (0.28 g., 0.040 mole, cut into small pieces), 2-methylbenzophenone (3.00 g., 0.0153 mole) and 25 ml. of anhydrous 1,2-dimethoxyethane contained in a 50-ml., nitrogen filled flask equipped with a magnetic stirrer and reflux condenser was stirred for forty-four hours. The color of the mixture changed from blue to purple to red. Anisaldehyde (2.08 g., 0.0153 mole) was added and the resulting mixture was refluxed for two hours and poured onto excess Dry Ice. The solution was allowed to come to room temperature, diluted with water, extracted with ether, acidified with hydrochloric acid, cooled and filtered to yield a small amount of anisic acid. The ethereal extract was dried with anhydrous magnesium sulfate and evaporated to an oil which failed to crystallize from a variety of solvents.

d. 4-Methylbenzophenone and sodium. To a stirred mixture of 4-methylbenzophenone (7.84 g., 0.040 mole), 50 ml. of anhydrous ether and 250 ml. of liquid ammonia, there was added sodium metal (1.84 g., 0.080 mole, cut into small pieces) and the resulting purple solution was refluxed for thirty minutes. To the reaction mixture was added a solution of anisaldehyde (5.44 g., 0.040 mole) in 50 ml. of anhydrous ether and the resulting light blue solution was refluxed for one hour and treated with solid ammonium chloride (4.28 g., 0.080 mole). The ammonia was evaporated and anhydrous ether was added to the residue. The ethereal mixture was filtered and the ether was evaporated from the filtrate until only 30 ml. remained. The solution was cooled and filtered yielding 3.0 g. of material, m.p. 148-158°. This material was recrystallized from benzene. The product, m.p. 155-165°, was a mixture of diastereoisomers of 1-phenyl-1-p-tolyl-2-p-anisylethylene glycol.

Anal. Calcd. for $C_{22}H_{22}O_3$: C, 79.01; H, 6.63.

Found: C, 78.74; H, 6.55.

H. Reaction of the Dialkali Salts of Benzophenone With Aromatic Nitriles

1. Preparation of α-Phenylbenzoin

To a stirred mixture of benzophenone (3.64 g., 0.020 mole), sodium metal (0.90 g., 0.039 mole) and 100 ml. of liquid ammonia, there was added dropwise benzonitrile (2.15 g., 0.021 mole). The resulting solution was refluxed for seven hours and treated with solid ammonium chloride (2.14 g., 0.040 mole). The ammonia was evaporated and anhydrous ether was

added to the residue. The ethereal solution was filtered and the filtrate was cooled to 0° and kept at this temperature by means of an ice bath while anhydrous hydrochloric acid was passed through it. A dense white precipitate appeared (1.8 g.) and was removed by filtration and washed with ether. One gram of the hydrochloride was added to 6 N hydrochloric acid and the mixture was boiled for a few minutes, filtered and left standing for twelve hours. The crystals which appeared were collected and dried. The yield was 0.2 g. of α-phenylbenzoin, m.p. 87-88° with or without admixture of an authentic sample.

2. Preparation of α-Phenyl-4-methylbenzoin

To a stirred mixture of benzophenone (3.64 g., 0.020 mole), sodium metal (0.90 g., 0.039 mole) and 250 ml. of liquid ammonia, there was added p-tolunitrile (2.34 g., 0.020 mole). The resulting solution was refluxed for six and one-half hours and treated with ammonium chloride (2.14 g., 0.040 mole). The ammonia was evaporated and some anhydrous ether added to the residue. The ethereal mixture was boiled for a few minutes and filtered. The filtrate was cooled to 0° and kept at this temperature while anhydrous hydrochloric acid was passed through it. A dense white precipitate appeared (4 g.) and was removed by filtration and washed with ether. One gram of this precipitate was dissolved in hot absolute ethanol and reprecipitated by the addition of anhydrous ether to give α-phenyl-4-methylbenzoin ketimine hydrochloride, m.p. 170-174°.

Anal. Calcd. for $C_{21}H_{20}ClNO$: C, 74.66; H, 5.97; Cl, 10.50; N, 4.15.
Found: C, 72.61; H, 6.16; Cl, 11.4; N, 4.87.

To 1.0 g. of the crude hydrochloride was added 35 ml. of 20 per cent hydrochloric acid and the resulting mixture was refluxed for thirty minutes, cooled and extracted twice with ether. The combined ethereal extract was dried with anhydrous magnesium sulfate and evaporated to an oil. The oil was dissolved in benzene-hexane and stored for two weeks at room temperature. The crystals which appeared were collected and dried. Two attempts were made to recrystallize the material but it would not crystallize from a solution. The oil obtained when the solvent was evaporated in these attempted recrystallizations would crystallize when seeded. These crystals were collected, washed with hexane and dried. The product was α-phenyl-4-methylbenzoin, m.p. 57.0-59.5°.

Anal. Calcd. for $C_{21}H_{18}O_2$: C, 83.42; H, 6.00.

Found: C, 83.60; H, 6.18.

3. Attempted Preparation of α-Anisyl-4-methoxybenzoin

To a stirred mixture of 4,4'-dimethoxybenzophenone (2.42 g., 0.010 mole), sodium metal (0.45 g., 0.019 mole) and 100 ml. of liquid ammonia, there was added dropwise a solution of benzonitrile (1.03 g., 0.010 mole) in 50 ml. of anhydrous ether. The resulting blue solution was refluxed for seven hours and a portion of the ammonia was evaporated whereupon the blue color disappeared. Solid ammonium chloride (1.07 g., 0.020 mole) was added and the remaining ammonia was evaporated. Anhydrous ether was added to the residue and the mixture was boiled for a few minutes and filtered. The filtrate was cooled to 0° and kept at this temperature by means of an ice bath while anhydrous hydrochloric acid was passed through it. No precipitate appeared.

4. Attempted Preparation of α-Phenyl-4-methoxybenzoin

To a stirred solution of sodium (2.3 g., 0.10 mole) in 200 ml. of liquid ammonia, there was added dropwise a solution of benzophenone (9.10 g., 0.050 mole) in 50 ml. of anhydrous ether. Immediately upon completion of the addition of the benzophenone solution, there was added dropwise to the reaction mixture a solution of p-anisonitrile (6.65 g., 0.050 mole) in 50 ml. of anhydrous ether. The resulting blue solution was refluxed for six hours and hydrolyzed with solid ammonium chloride (10.7 g., 0.20 mole). The ammonia was evaporated and anhydrous ether added to the residue. The ethereal mixture was boiled for a few minutes and filtered. The filtrate was cooled to 0° and kept at this temperature by means of an ice bath while anhydrous hydrochloric acid was passed through it. A dense white precipitate appeared (10 g.) and was removed by filtration and washed with ether. A portion of this hydrochloride was recrystallized from ethanol-ether-chloroform and melted at 205-210° (d).

Anal. Calcd. for $C_{21}H_{20}ClNO_2$: C, 71.28; H, 5.70; Cl, 10.02; N, 3.96.
Found: C, 75.75; H, 5.81; Cl, 9.51; N, 3.62.

To 5.0 g. of the crude hydrochloride was added 50 ml. of 18 per cent hydrochloric acid and the resulting mixture was refluxed for six hours. Upon cooling the oil which was present at the bottom of the flask solidified and the aqueous acid was decanted from it. The solid mass was ground in a mortar and pestle, washed with water and dried. The yield was 4.1 g. of product, m.p. 58-63°, which could not be crystallized from a variety of solvents.

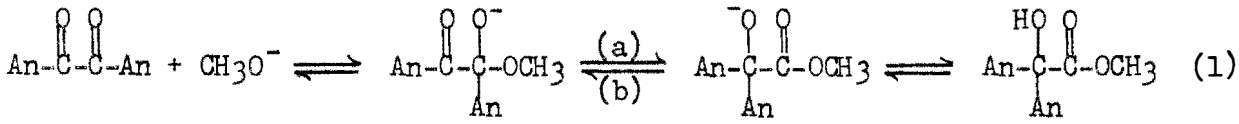
Anal. Calcd. for $C_{21}H_{18}O_3$: C, 79.22; H, 5.70

Found: C, 74.02; H, 4.99.

CHAPTER IV

SUMMARY

The reversibility of the benzilic ester rearrangement has been studied with methyl anisilate-1-C^{14} (I). The results show that the rate of reaction "b" in equation 1 must be negligible, if existent at all, at



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97°. At a higher temperature, 200°, the results were similar but not unequivocal due to the possibility that certain competing reactions obtain. During the course of this study an imino ether hydrochloride was prepared from an aroyl cyanide; this is apparently the first time this type of transformation has been accomplished.

Several other base catalyzed rearrangements mechanistically similar to the benzilic acid rearrangement have been studied. The reaction of anisil with amide ion has been shown to yield anisilic acid as a product while the reaction of dipropylamide ion with benzil yields a neutral product identified as a benzil heptamer. The reaction of benzil with 2,6-dimethylphenylmagnesium iodide in the presence of air yields benzilic acid. Possible mechanisms for the formation of these products have been postulated.

The tertiary ketol rearrangement which sometimes occurs upon addition of Grignard reagents to benzil or substituted benzils has been shown to also take place upon the addition of aromatic organolithium reagents

to benzil. It has been demonstrated that this rearrangement occurs in the reaction of the organometallic and benzil and that hydrolytic work-up is not necessary for the rearrangement.

The factors affecting the formation of the dialkali salts of aromatic ketones have been qualitatively studied. It was found that liquid ammonia was superior as a solvent to 1,2-dimethoxyethane which was better than ether. Sodium appeared to be the most satisfactory alkali metal followed by potassium and then lithium. Aromatic ketones containing strongly electron releasing substituents do not readily form dialkali salts.

The reactivity of the dialkali salts of aromatic ketones, which renders them interesting and potentially useful synthesis intermediates, has been demonstrated by their conversion to several different types of organic compounds which would be difficult and/or tedious to obtain by other methods. The dialkali salts of aromatic ketones react with carbon dioxide to give benzilic acids, aromatic nitriles to yield α-arylbenzoins, aromatic aldehydes to give 1,1,2-triarylethyleneglycols and alkyl carbonates to yield benzilic acid esters.

Some of the factors which contribute favorably and unfavorably to the yields obtained in these conversions have been elucidated.

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