THE PREPARATION OF SOME UNSYMMETRICAL ORTHO SUBSTITUTED o-DIBENZOYLBENZENES AND 1,3-DIPHENYLISOBENZOFURANS

By

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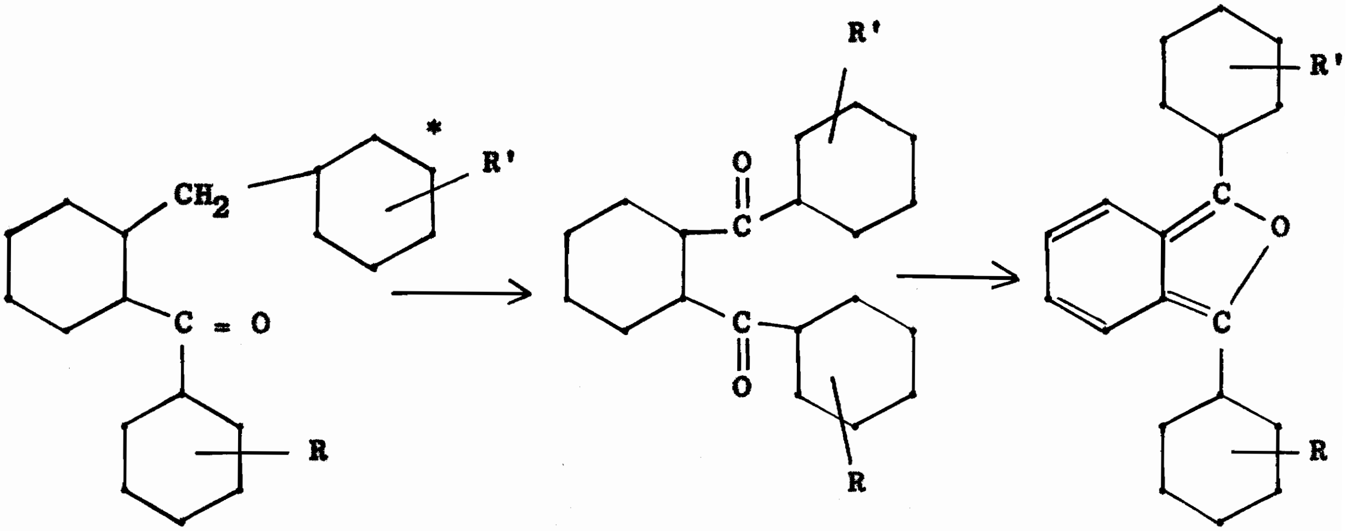
INTRODUCTION

INTRODUCTION

Ketones of type I may be oxidized to the corresponding diketones by the use of sodium dichromate and concentrated sulfuric acid in glacial acetic acid. These in turn may be converted to the 1,3-diphenylisobenzofurans by the use of zinc dust in glacial acetic acid.



I II III

The dichromate oxidation was first performed on this type of compound by R. A. Kasey, Jr. (1) in 1950. He noted

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*All rings are fully aromatic unless otherwise specified.

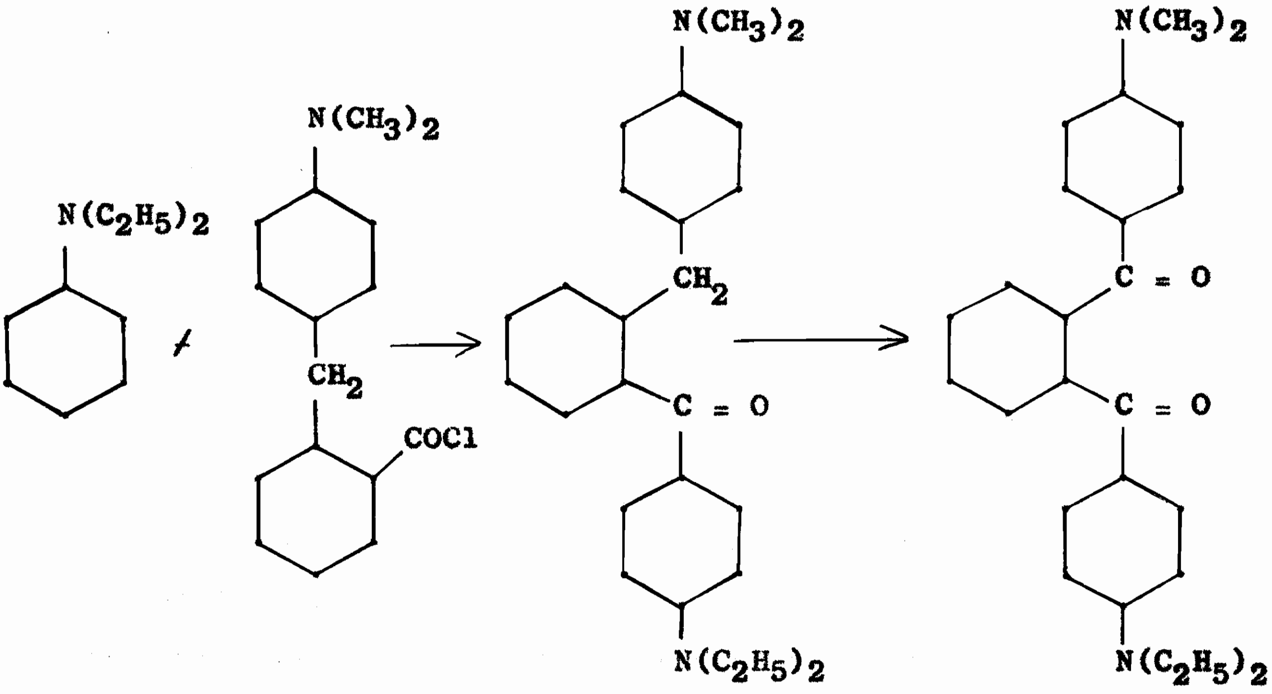
that this reaction afforded a method of synthesis of compounds of types I and II, which appeared to be superior to other methods. It would seem particularly useful where R and R' are not the same since these compounds are relatively difficult to prepare by other methods.

In order to show the applicability of this synthesis, Kasey prepared three 1,3-diphenylisobenzofurans by this method: one in which R=R'=H, one in which R=p-Cl and R'=H and one in which R=p-F and R'=H. Van Oot (26), using the same procedure, synthesized the o-diaroylbenzene in which R=H and R'=m-CF_3. It is the purpose of this investigation to further examine this series of reactions by preparing the 1,3-diphenylisobenzofurans in which R=o-CH_3 and R'=H and in which R=o-OCH_3 and R'=H. The o-CH_3 compound is of particular interest since the methyl group may be oxidized along with the methylene group.

HISTORICAL

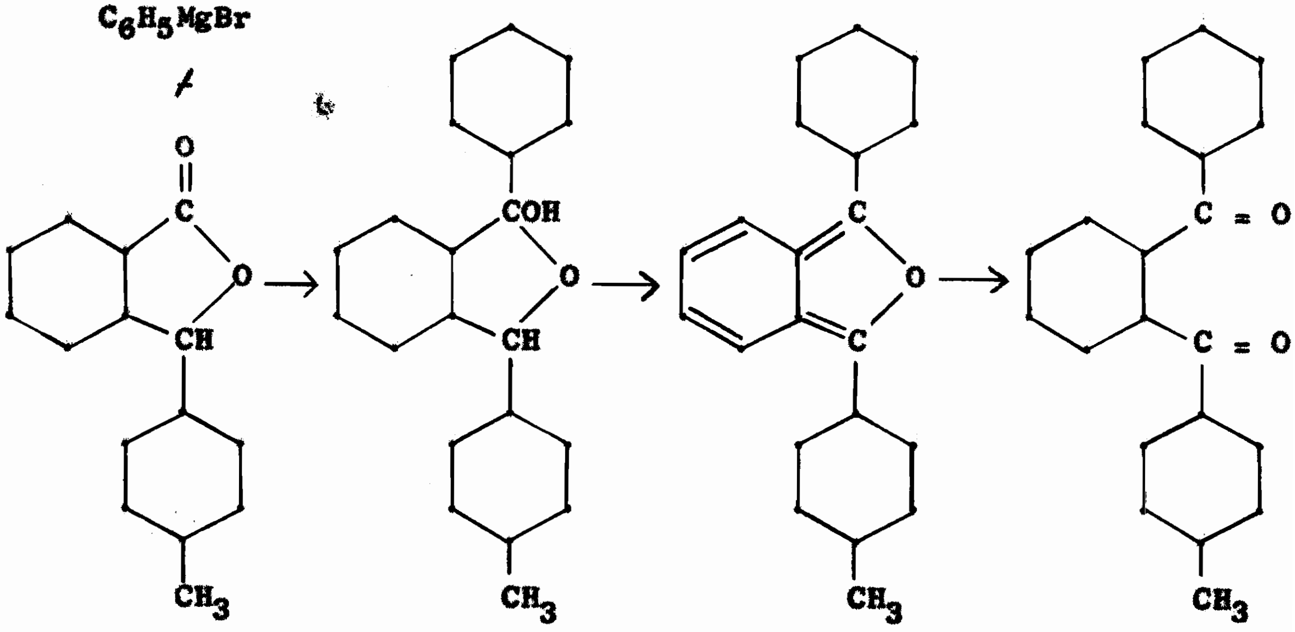
HISTORICAL

The first instance of the synthesis of an unsymmetrically substituted o-dibenzoylbenzene is found in the synthesis of 2-(4''-diethylaminobenzoyl)-4'-dimethylaminobenzophenone (VII) by Guyot and Pignet (4) in 1908. They prepared 2-(4''-dimethylaminobenzyl)-4'-diethylaminobenzophenone (VI) from diethylaniline (IV) and 2-(4'-dimethylaminobenzyl)-benzoyl chloride (V) in the presence of aluminum chloride in 60-70% yield. Oxidation of this product with chloranil gave the diketone. The corresponding isobenzofuran was not prepared.



IV V VI VII

The only other method by which unsymmetrically substituted compounds of this type have been prepared is that used by Guyot and Vallette (2) to prepare 1-tolyl-3-phenylisobenzofuran (X) and the corresponding diketone (XI). Phenylmagnesium bromide was allowed to react with p-tolylphthalide (VIII) to give 1-tolyl-3-phenyl-3-hydroxy-1,3-dihydroisobenzofuran (IX) which loses water readily to give 1-tolyl-3-phenylisobenzofuran (X). The diketone was prepared by oxidation of the 1,3-diphenylisobenzofuran with dichromate.

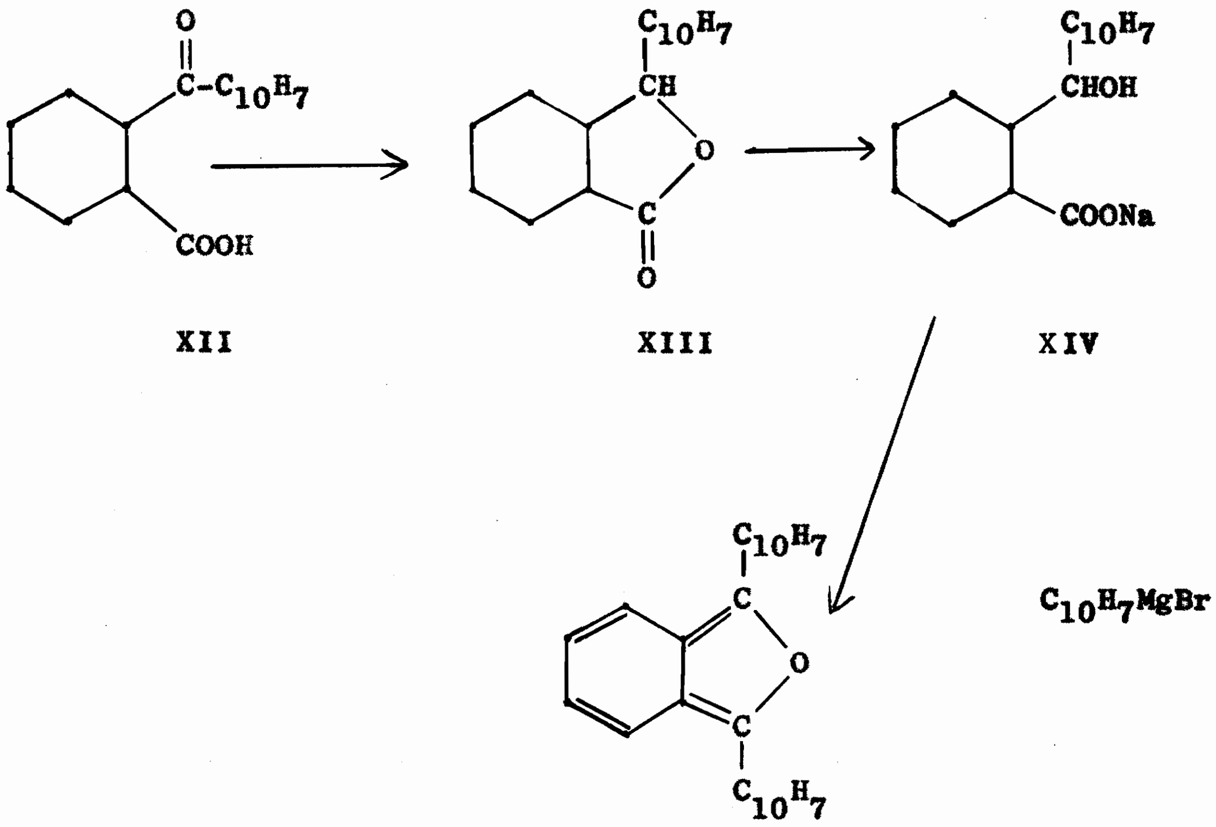


VIII IX X XI

They also prepared 2-(α-naphthoyl)-benzophenone by the action of α-naphthylmagnesium bromide on phenylphthalide and oxidizing the oil product obtained. The corresponding isobenzofuran was not isolated. The yields involved here were reported to be excellent. Blicke and Patelski (3) used the same method to prepare 2-(2''-methoxybenzoyl)-4'-methoxybenzophenone from 2-anisylmagnesium iodide and 4'-methoxyphenylphthalide with subsequent oxidation of the crude isobenzofuran, which was not isolated in crystalline form.

There are many methods of preparation for symmetrical derivatives of *o*-dibenzoylbenzene and 1,3-diphenylisobenzofuran, but most of them are limited in scope or give low yields. Some of the more general types will be listed here, particularly those which may be applied to the synthesis of unsymmetrically substituted compounds.

Seer and Dischendorfer (5) prepared 1,3-di-*α*-naphthylisobenzofuran (XV) from *α*-naphthylmagnesium bromide and the sodium salt of 2-carboxy-*α*-naphthylcarbinol (XIV) in a 46% yield. The carbinol (XIV) was obtained by reducing 2-naphthoylbenzoic acid (XII) with zinc dust in acetic acid and treating the product, *α*-naphthylphthalide (XIII), with sodium hydroxide.



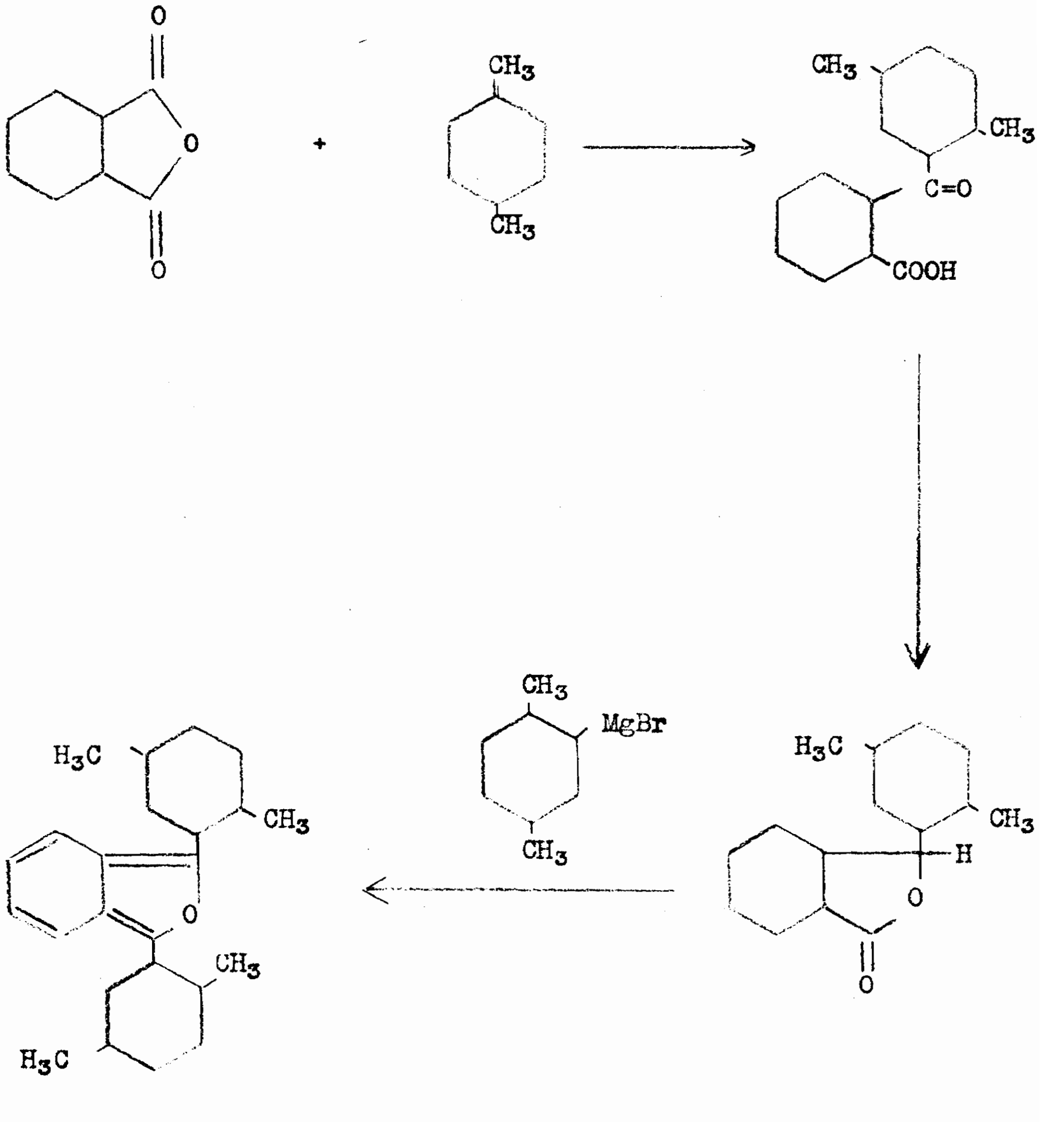
XII XIII XIV

XV

Clar, John, and Hawran (6) reported the synthesis of what appeared to be 1,3-bis(2',5'-dimethylphenyl)-isobenzofuran (XVII) from 2,5-dimethylphenylmagnesium bromide and 2',5'-dimethylphenylphthalide (XVI). They were unable to isolate the final product in pure form. This series of reactions is shown on Chart I.

Blicke and Patelski (7) found that some diarylphthalins (XVIII) give 1,3-diarylisobenzofurans (XX) on treatment

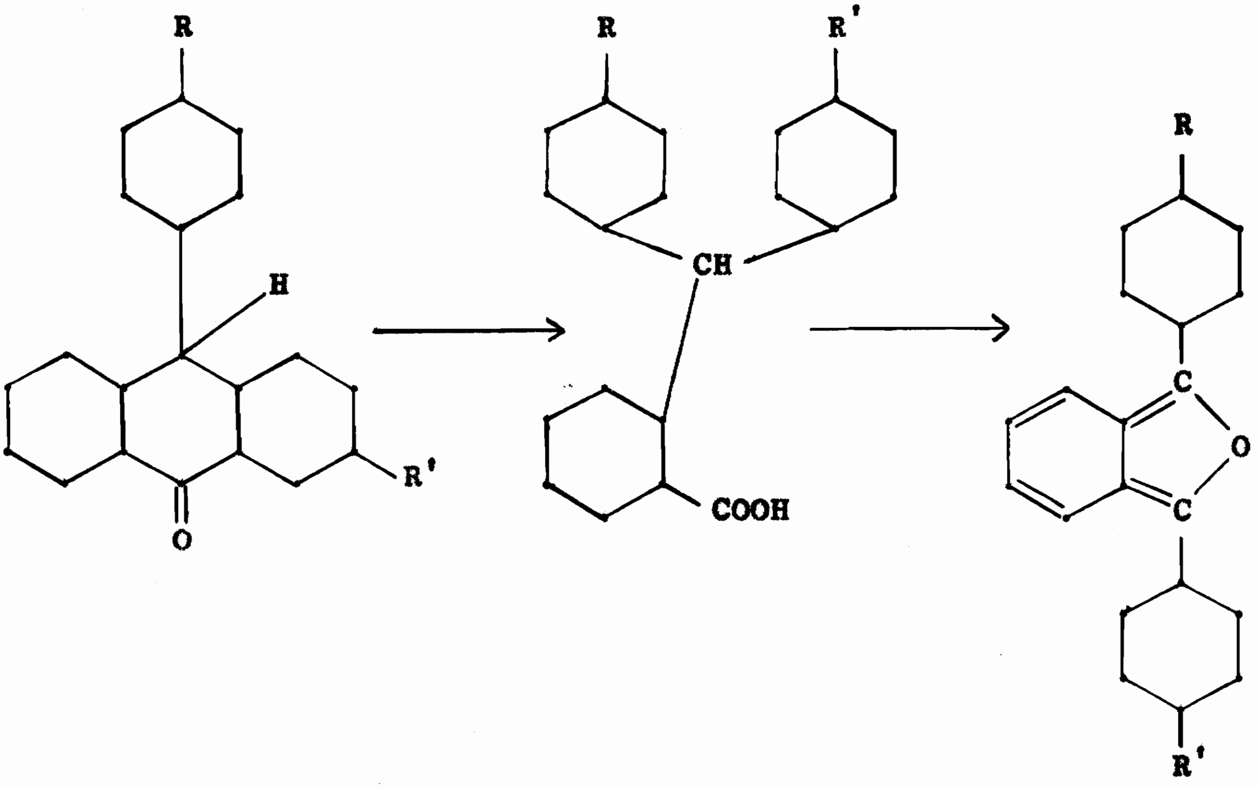
CHART I



XVII

XVI

with sulfuric acid. However, they sometimes give anthrones (XIX) or mixtures of the two. For example: 4',4''-dichlorodiphenylphthalin is converted to an anthrone (8), 4',4''-dimethoxydiphenylphthalin gives a 1,3-diphenylisobenzofuran (9) and 4'-methoxydiphenylphthalin gives a mixture (10).

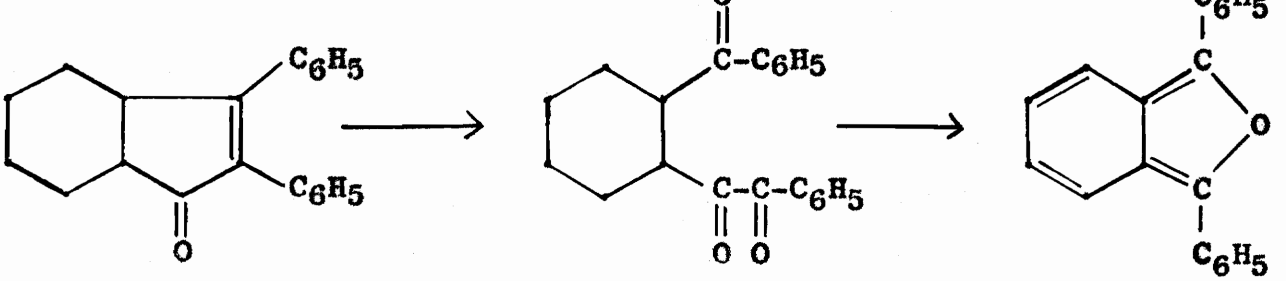


XIX XVIII XX

R=Cl, OCH$_3$, etc.
R'=Cl, OCH$_3$, H, etc.

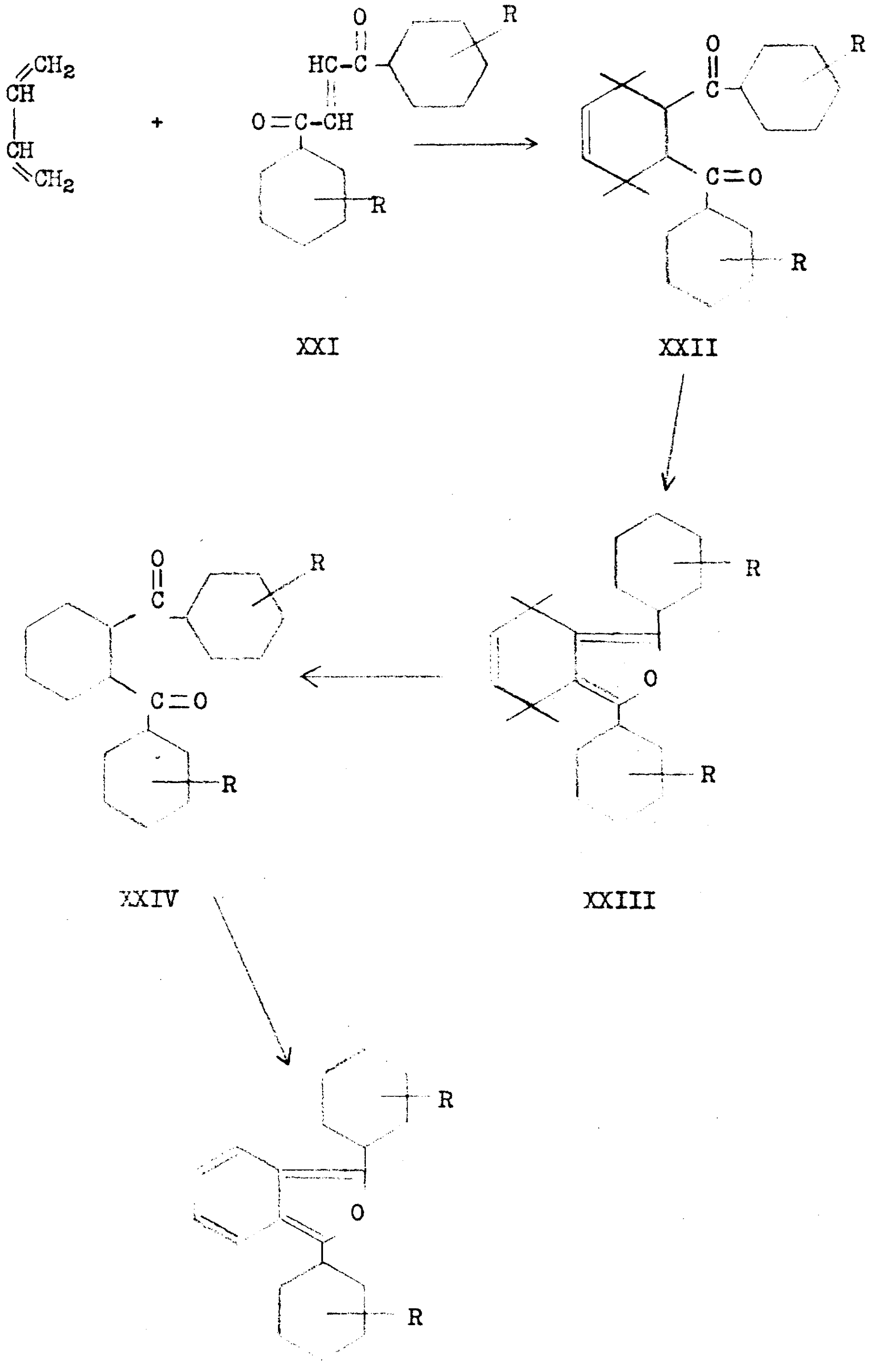
Adams and Gold (11) prepared symmetrically substituted o-dibenzoylbenzenes and 1,3-diphenylisobenzofurans in very good yields by means of the Diels-Alder reaction between butadienes and substituted trans-dibenzoylethylenes. This series is illustrated on Chart II. The initial product, 4,5-diaroylcyclohexene (XXII), is treated with phosphoric acid in acetic anhydride to give the 1,3-diaroyl-4,7-dihydroisobenzofuran (XXIII). This compound was oxidized to the o-diaroylbenzene (XXIV) by the use of bromine and sodium acetate. The diketone was then converted to the 1,3-diarylisobenzofuran (XXV) with zinc dust and ethanolic sodium hydroxide.

Allen and Van Allan (12) prepared 1,3-diphenylisobenzofuran (XXVIII) from 2,3-diphenylindone (XXVI). This was first oxidized to 2-benzoylbenzil (XXVII) in a quantitative yield with potassium permanganate. The 2-benzoylbenzil (XXVII) was converted to 1,3-diphenylisobenzofuran (XXVIII) by the use of ethanolic potassium hydroxide. The yield was 85% of theoretical.



XXVI XXVII XXVIII

CHART II



XXI

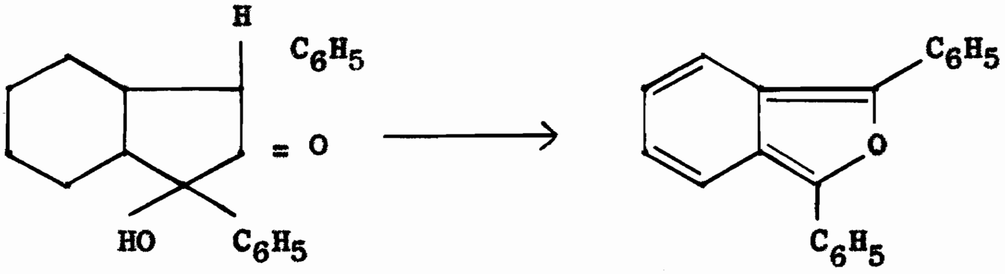
XXII

XXIII

XXIV

XXV

Ecary (13) prepared 1,3-diphenylisobenzofuran (XXVIII) from 1,3-diphenyl-1-hydroxy-2-indanone (XXIX) by the action of air or oxygen bubbled through alcoholic potassium hydroxide followed by treatment with formic acid. The yield was 80% of theoretical.



XXIX XXVIII

THEORETICAL AND DISCUSSION OF RESULTS

THEORETICAL AND DISCUSSION OF RESULTS

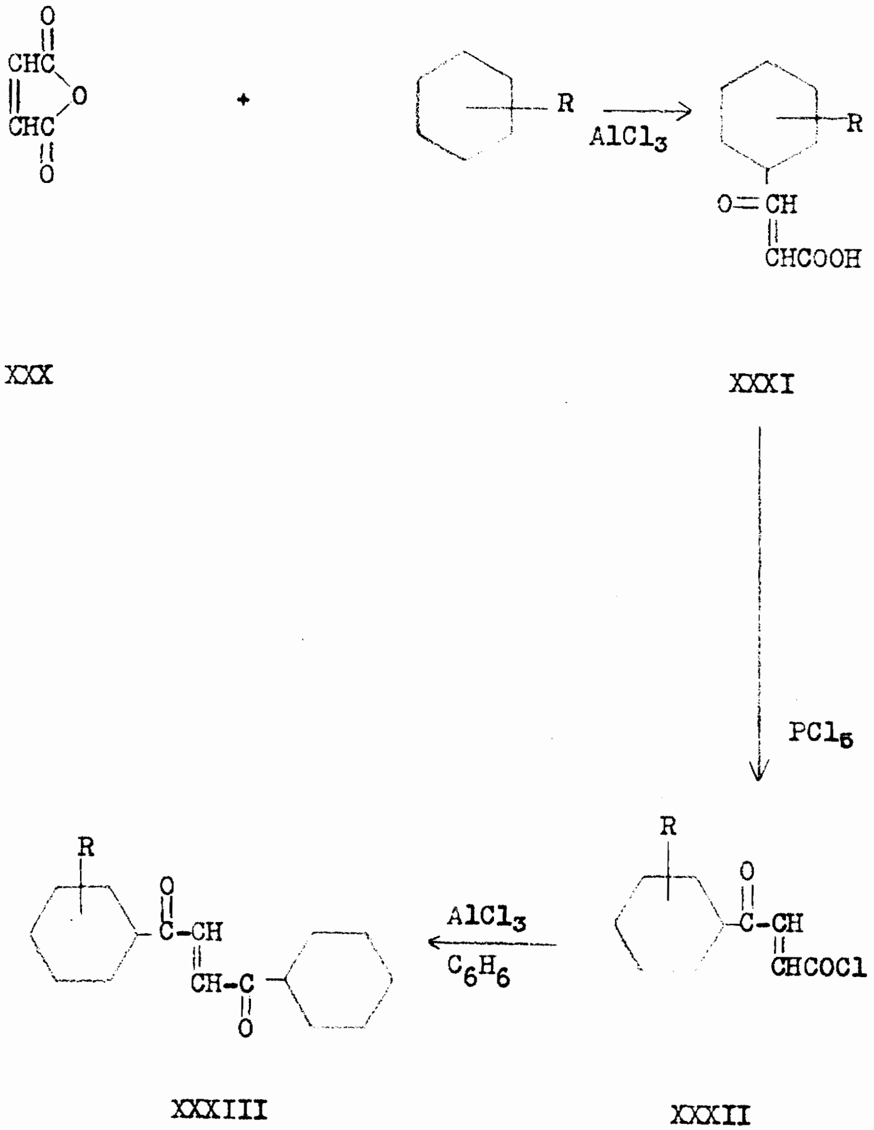
In connection with an investigation of the methods used by Kasey (1) to prepare substituted 1,3-diphenylisobenzofurans (III) and *o*-dibenzoylbenzenes (II), it would seem appropriate to compare them with methods already used. The most useful and most general of the other methods would appear to be that used by Guyot and Vallette (2) since the yields are reported as excellent and the number of steps in the synthesis is few. The method is limited by the availability of the substituted phthalides. These are usually prepared by the action of a benzene derivative with phthalic anhydride in the presence of aluminum chloride. (Chart I). Thus it is seen that the substituents on one ring are limited by the possible orientations involved in the Friedel-Crafts reaction and the other only by those involved in the Grignard reaction. The procedure used by Guyot and Pignet (4) to obtain the *o*-dibenzoylbenzene (II) was actually of the same type as that used by Kasey (1) although the oxidizing agent used was different. The low yield reported in the work of Seer and Dischendorfer (5) seems to indicate that the formation of the sodium salt of the *o*-benzoylbenzoic acid from the substituted phthalide affords no advantage over adding the Grignard reagent directly to the phthalide.

The treatment of diarylphthalins with sulfuric acid to obtain 1,3-diarylisobenzofurans is extremely limited due to the formation of anthrones with some substituents.

The method used by Adams and Gold (11) (Chart II) was applied to symmetrically substituted compounds and seems almost completely restricted to this type. This is due to the fact that the _trans_-dibenzoylethylenes are usually prepared by the Friedel-Crafts reaction using benzene derivatives with fumaryl chloride (14a). However, unsymmetrical dibenzoylethylene derivatives may be prepared. Lutz (14b) obtained _trans_-1-benzoyl-2-(2,4,6-trimethylbenzoyl)ethylene (XXXIII, R=2,4,6 trimethyl) from _trans_-mesitoylacrylic acid chloride (XXXII, R=2,4,6 trimethyl) and benzene with aluminum chloride in a 32% yield. The aryl substituted benzoylacrylic acids (XXXI) are readily prepared from maleic anhydride (XXX) by the Friedel-Crafts reaction (15). It has been shown that these acids have the _trans_ configuration (16). The above reactions are outlined in Chart III. This method seems to be limited then by Friedel-Crafts orientation and substituents in both rings and by one step in the synthesis, XXXII to XXXIII, which often gives low yields.

The synthesis of 1,3-diphenylisobenzofurans and _o_-dibenzoylbenzenes by the procedure used by Allen and

CHART III

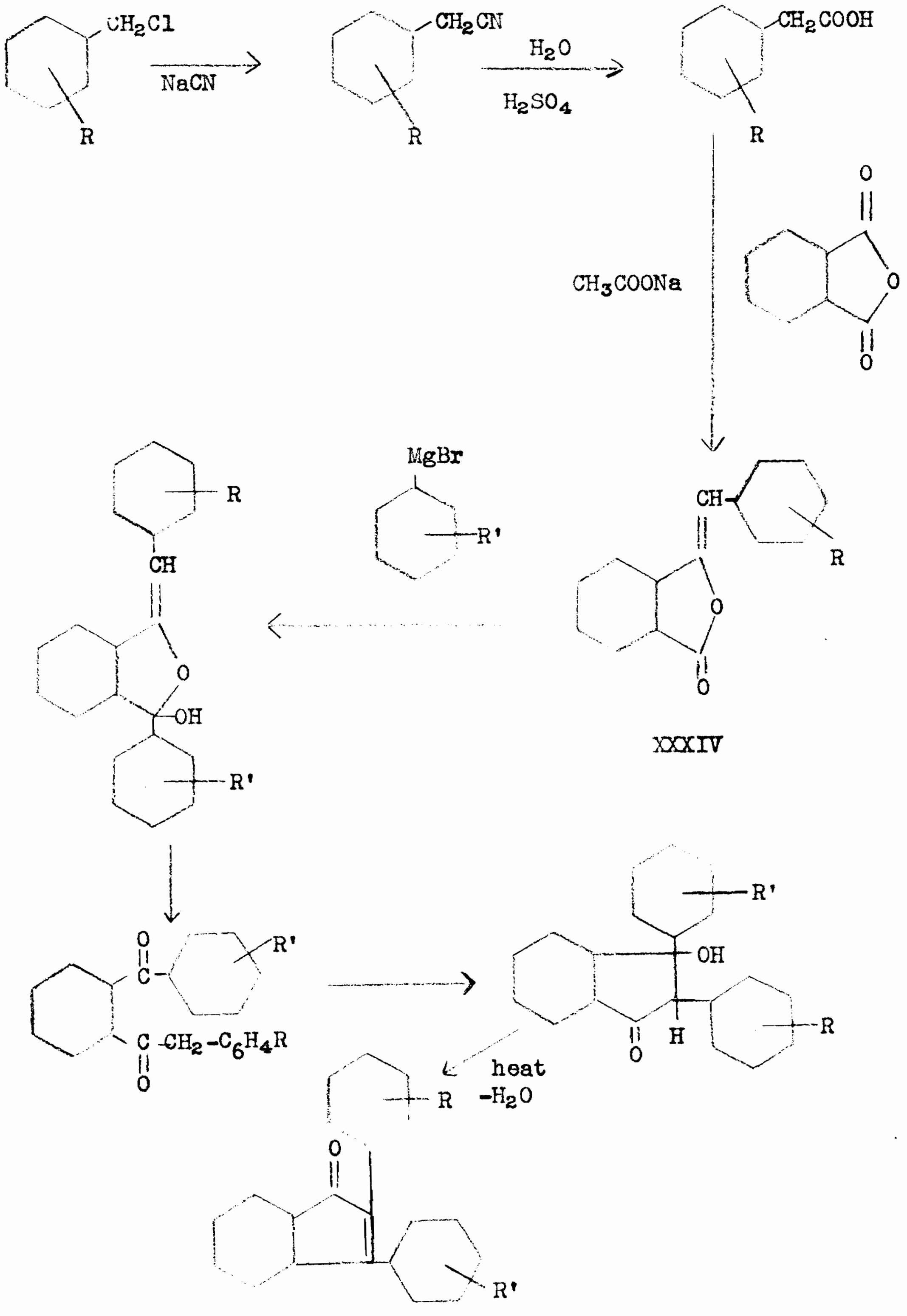


Van Allan (12) to obtain the unsubstituted compounds is inconvenient due to the length of synthesis necessary to obtain the 2,3-diphenylindone (17,18,19). Chart IV illustrates this. The 2,3-diphenylindone (XXXV) is obtained from the benzalphthalide (XXXIV) without isolating the intermediate substances.

The method used by Ecary (13) is also of little value as a general method of synthesis since his condensation of benzophenone with ethyl monochloroacetate gave only a 30% yield. This scheme is shown on Chart V.

The procedure used by Kasey (1) depends upon the availability of compounds of type I. It is possible to obtain a very large variety of substituents in all three rings. Compounds in which R=p-CH_3,p-Br, p-Cl and p-F and R'=H have been prepared by Vingiello (20). Similar compounds in which R=m-Br and m-CF_3 have been prepared by Hannabass (21). Those in which R=m-Cl,m-CH_3 and o-OCH_3 and R'=H have been synthesized by Caplan and Dressler (22), by Shields and Wallerstein (23) and by Culpeper and Hale (24) respectively. Bondurant (25) synthesized a group of the ortho compounds in which R=o-OCH_3,o-CH_3, o-Cl, o-F and R'=H. Van Oot (26) prepared compounds of this type in which R=p-CF_3 and m-F and R'=H and also those in which R=H and R'=o-CH_3, m-CH_3, p-CH_3, m-CF_3 and p-F. Guyot and Pignet (4) obtained those in which R=p-$N(C_2H_5)_2$ and

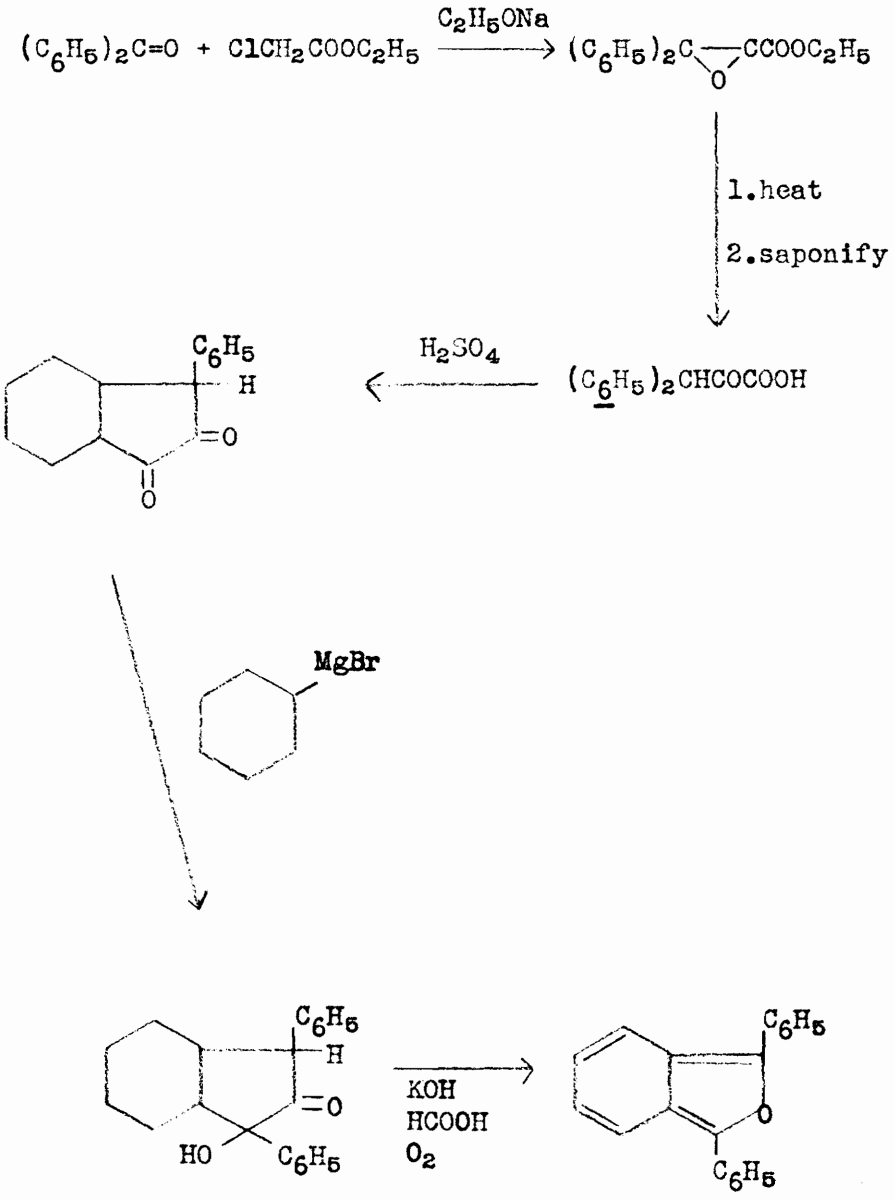
CHART IV



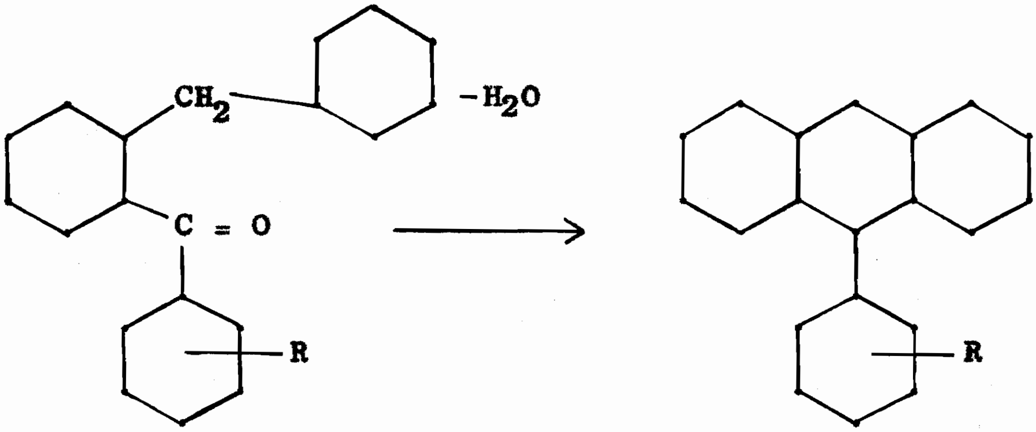
XXXIV

XXXV

CHART V


(C6H5)2C=O + ClCH2COOC2H5
C2H5ONa
(C6H5)2C—CCOOC2H5
O
1.heat
2.saponify
(C6H5)2CHCOCOOH
H2SO4
C6H5
H
=O
O
MgBr
C6H5
H
=O
HO
C6H5
KOH
HCOOH
O2
C6H5
O
C6H5

R'=p-$N(CH_3)_2$ and R=R'=p-$N(CH_3)_2$. All the above compounds except those prepared by Guyot and Pignet (4) used the methods of Bradsher (27) and Vingiello (20). These are outlined on Chart VI and Chart VII respectively. They were prepared in connection with studies of the following cyclization mechanism:



Following Chart VI, o-chlorobenzaldehyde (XXXVI) is allowed to react with an arylmagnesium halide to form the hydrol (XXXVII). This is reduced with red phosphorus and iodine in acetic acid to the diphenylmethane (XXXIX). The diphenylmethane derivative (XXXIX) may also be obtained by means of the Friedel-Crafts reaction with o-chlorobenzyl chloride (XL). The diphenylmethane derivative (XXXIX) is

CHART VI

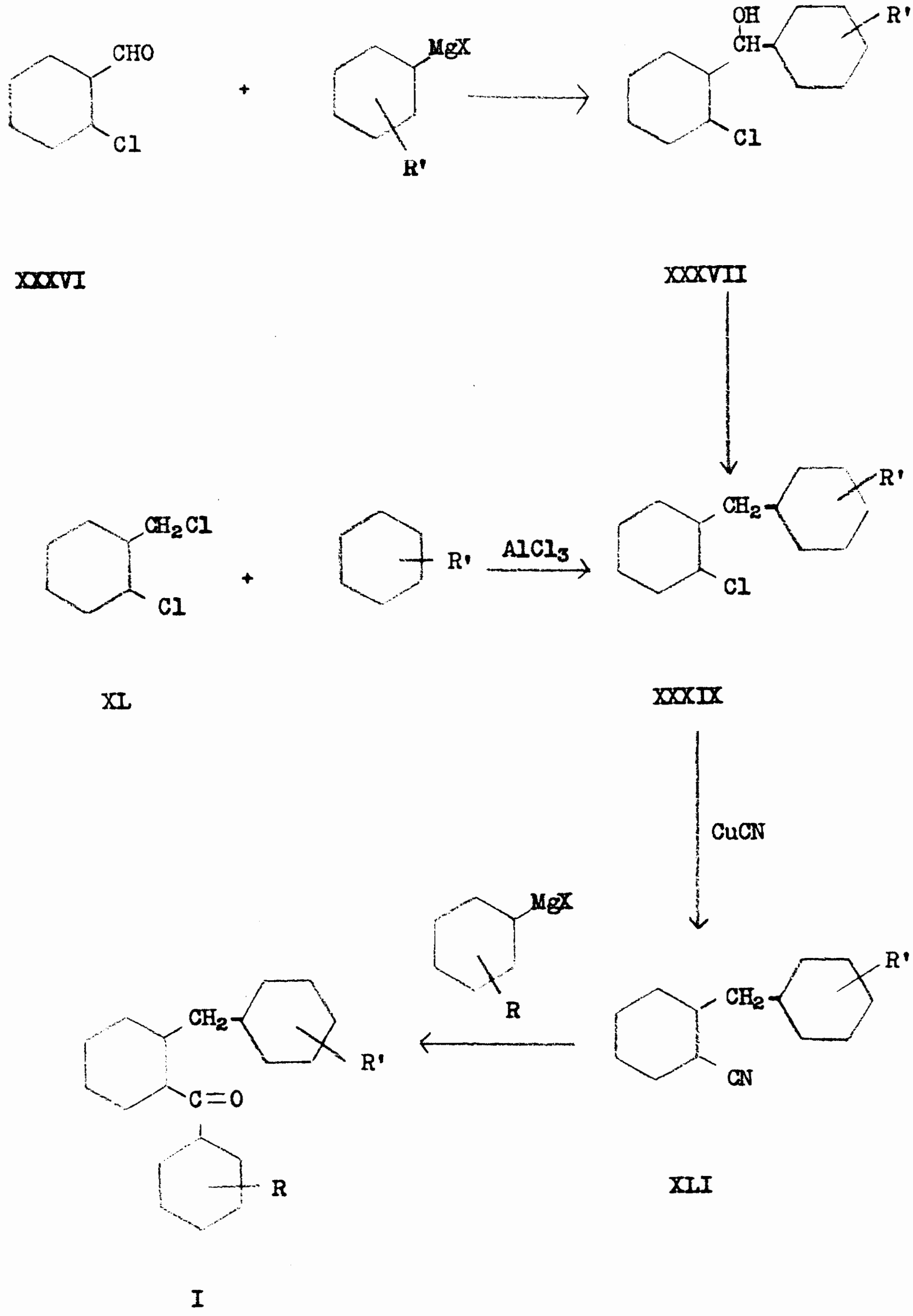
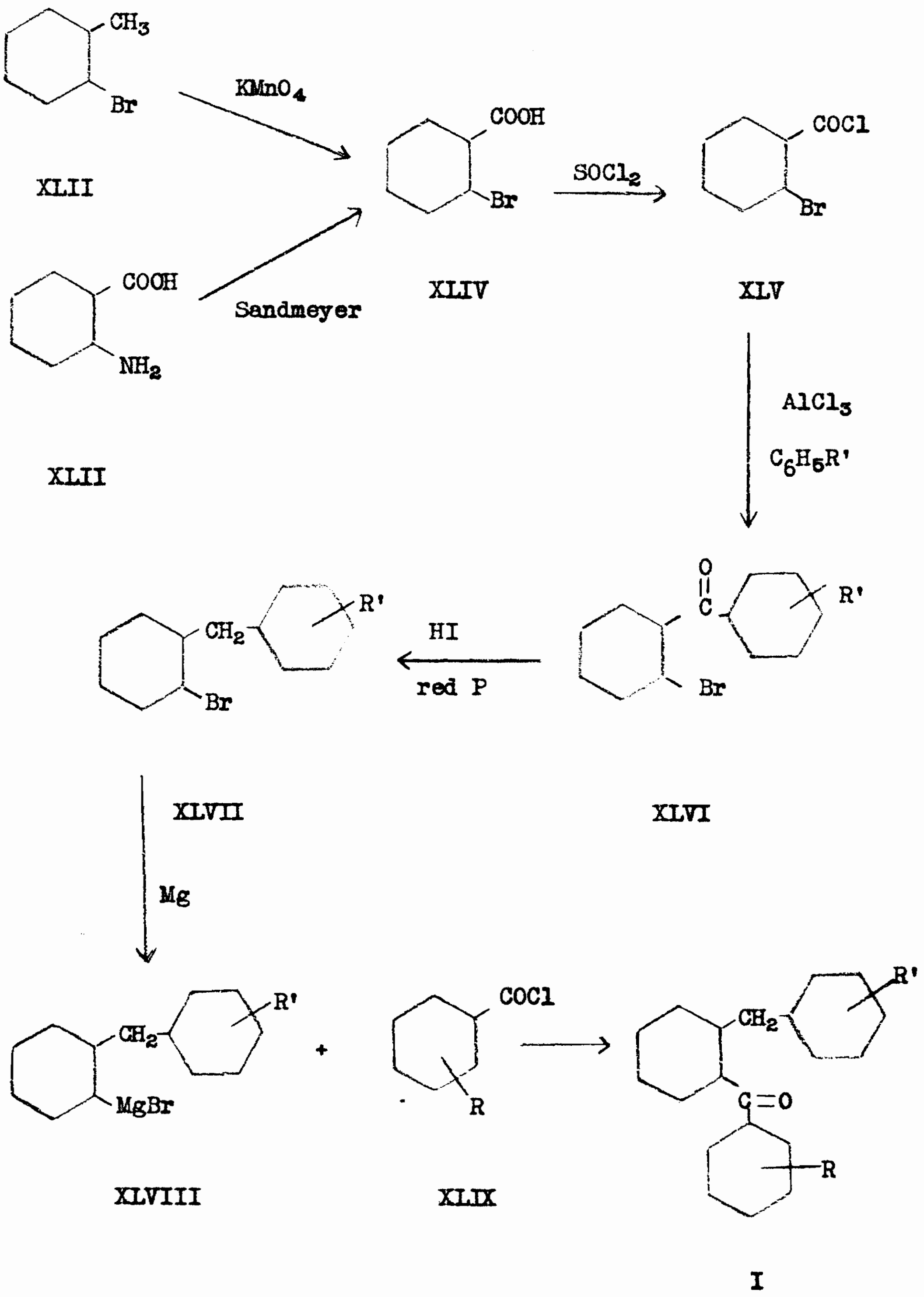

CHO
Cl
+
MgX
R'
OH
CH
R'
Cl
XXXVI
XXXVII
CH$_2$Cl
Cl
+
R'
AlCl$_3$
CH$_2$
R'
Cl
XL
XXXIX
CuCN
MgX
R
CH$_2$
R'
CN
CH$_2$
R'
C=O
R
XLI
I

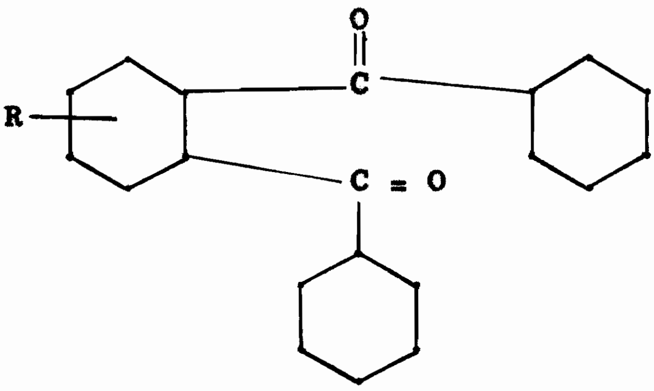
CHART VII



CH3
Br
XLII
KMnO4
COOH
NH2
XLII
Sandmeyer
COOH
Br
XLIV
SOCl2
COCl
Br
XLV
AlCl3
C6H5R'
O
C
R'
Br
XLVI
HI
red P
CH2
R'
Br
XLVII
Mg
CH2
R'
MgBr
XLVIII
+
COCl
R
XLIX
CH2
R'
C=O
R
I

treated with cuprous cyanide in pyridine to give the corresponding nitrile (XLI). This, upon reaction with an arylmagnesium halide and subsequent hydrolysis gives the desired type of compound (I).

Following Chart VII, o-bromotoluene (XLII) with potassium permanganate or anthranilic acid (XLIII) through the Sandmeyer reaction gives o-bromobenzoic acid (XLIV). This forms the acid chloride (XLV), on treatment with thionyl chloride, which reacts in the Friedel-Crafts reaction to give the o-bromobenzophenone derivative (XLVI). Reduction of this compound gives the o-bromodiphenylmethane derivative (XLVII). This forms a Grignard with magnesium which reacts with a benzoic acid chloride (XLIX) to give the desired type of compound (I). Of course this method would also be useful in the synthesis of compounds of type LXI in which the central ring is substituted.



R=alkyl

or aryl groups

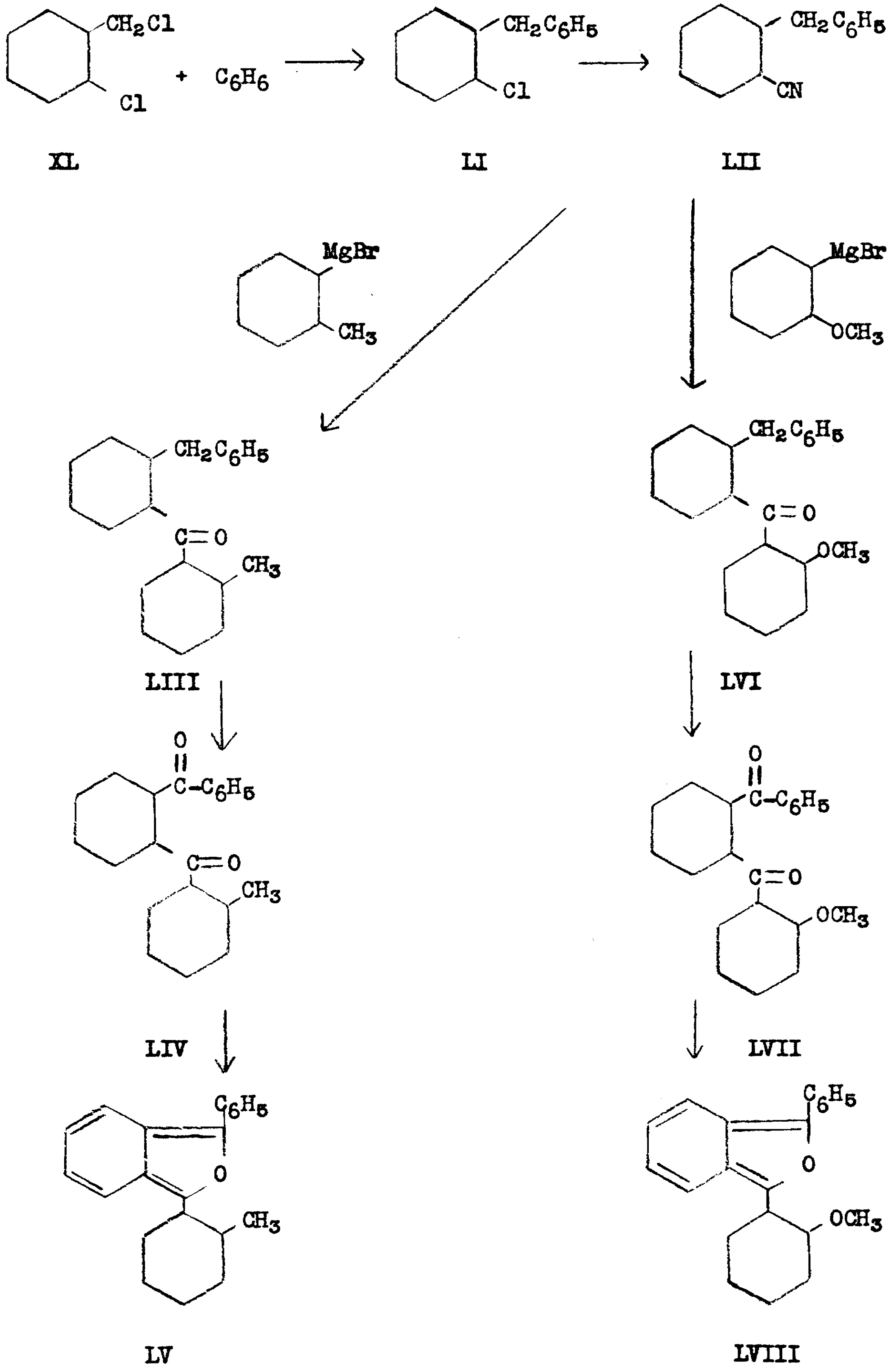
LXI

The procedure outlined in Chart VI was used to obtain the mono-ketones. The addition of *o*-chlorobenzyl chloride to benzene in the presence of aluminum chloride gave *o*-chlorodiphenylmethane (LI) in a 69.3% yield. This modification of the method used by Bradsher (27) and by Vingiello (2) was first successfully used by Barrett (28). A von Braun reaction on the diphenylmethane derivative gave *o*-cyanodiphenylmethane (LII) in a 60% yield.

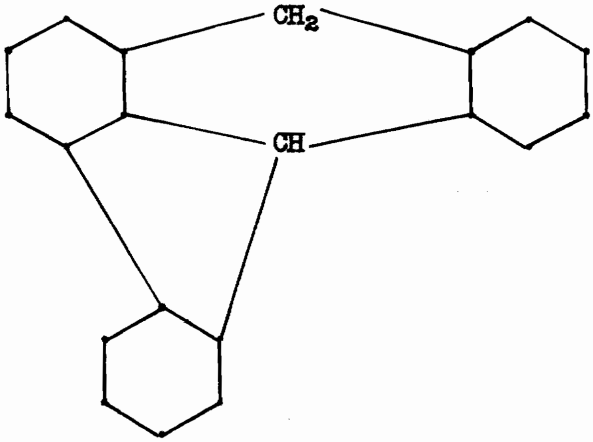
Treatment of this compound with the Grignard reagent prepared from *o*-bromotoluene and subsequent hydrolysis of the resulting ketimine gave a 57.4% yield of 2'-methyl-2-benzylbenzophenone (LIII). 2'-Methoxy-2-benzylbenzophenone (LVI) was prepared in a similar manner from *o*-bromoanisole and the nitrile in a 69.6% yield. These particular reactions are outlined in Chart VIII.

The preparation of 2'-chloro-2-benzylbenzophenone (II; R=*o*-Cl and R'=H) was attempted by the same method. No product could be isolated. This compound has been successfully synthesized by Buese (29) by the action of the Grignard reagent or cadmium reagent of *o*-bromodiphenylmethane (XLVIII, R'=H) on *o*-chlorobenzoyl chloride (XLIX, R=Cl). The yield obtained was 33% with the Grignard reagent and 43% with the cadmium reagent. In one experiment a small amount of hydrocarbon which gave an analysis corresponding to the formula $C_{20}H_{14}$ was

CHART VIII


CH2Cl
Cl
+
C6H6
XL
CH2C6H5
Cl
LI
CH2C6H5
CN
LII
MgBr
CH3
MgBr
OCH3
CH2C6H5
C=O
CH3
LIII
CH2C6H5
C=O
OCH3
LVI
O
C-C6H5
C=O
CH3
LIV
O
C-C6H5
C=O
OCH3
LVII
C6H5
O
CH3
LV
C6H5
O
OCH3
LVIII

isolated. It melted at 197°C.* This is apparently some cyclization product such as one of the mono-phenylanthracenes or a compound of type L. The melting point of 9-phenylanthracene is 153°C. (30).



L

The first step in the series of reactions illustrated in Chart IX was taken by the synthesis of 2-chloro-2',4'-dimethylbenzohydrol (LI') in a 38% yield. This was done by the addition of the Grignard of 4-iodo-1,3-dimethylbenzene to o-chlorobenzaldehyde. The nitrile (LXI') could be used to produce a rather large number of variously substituted o-dibenzoylbenzenes and 1,3-diphenylisobenzofurans following the procedure outlined in Chart VI.

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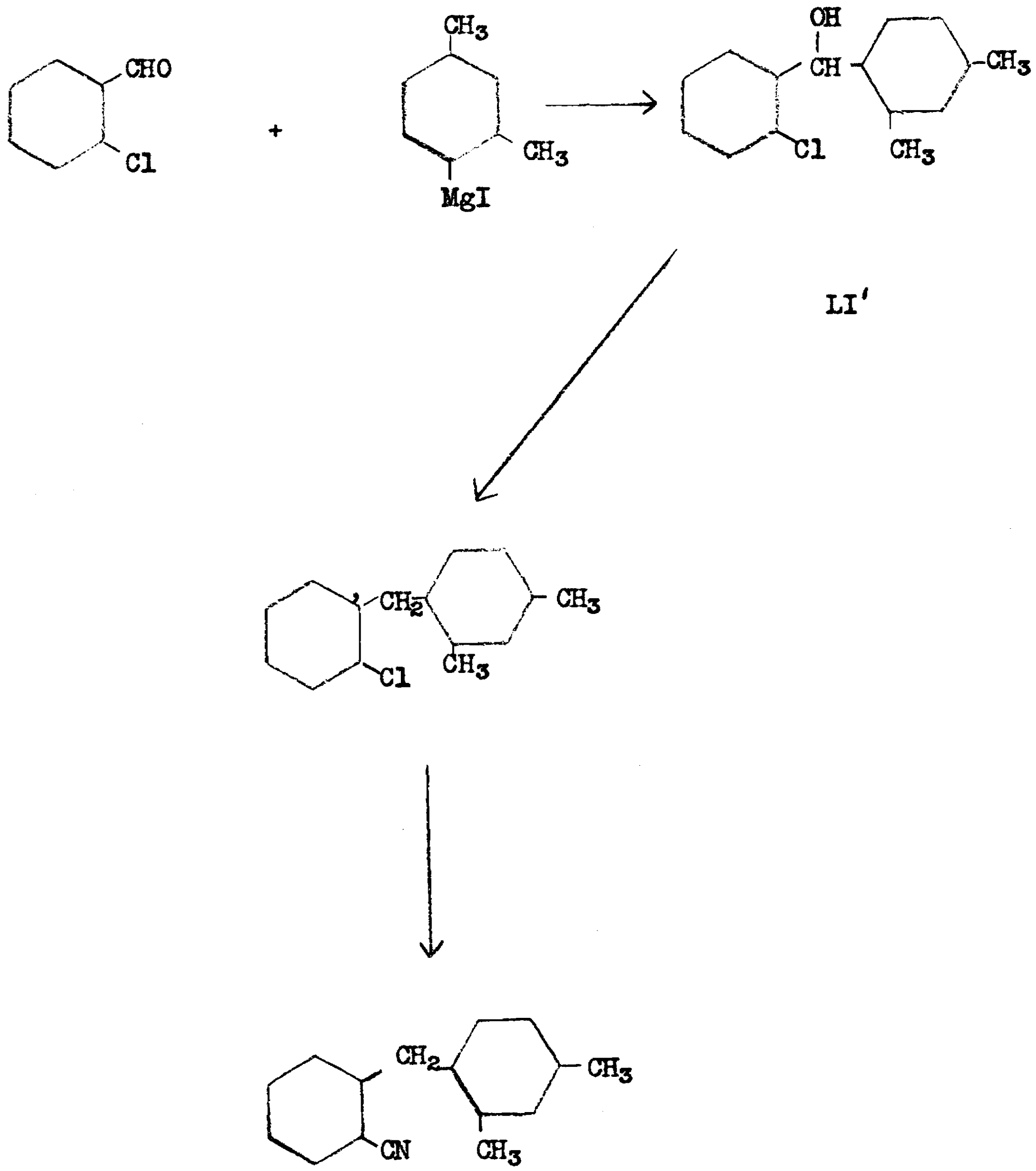
*All melting points are corrected.

CHART IX



LI'

LXI'

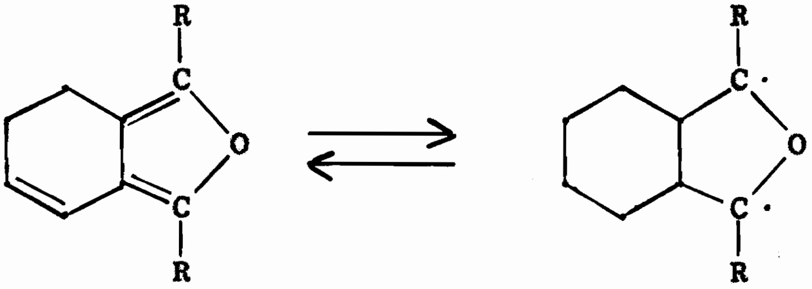
The oxidation of 2'-methyl-2-benzylbenzophenone (LIII) by the procedure used by Kasey (1) gave 2'-methyl-2-benzoylbenzophenone (LIV) on a 63.5% yield. The same procedure with the corresponding methoxy compound gave a 45.1% yield of the diketone, (LVII). In both cases the product obtained was a black oil or solid which appeared to indicate that conditions were too strong. In an effort to improve conditions the sulfuric acid added was diluted with glacial acetic acid and, instead of an excess of acid and dichromate, equivalent amounts of the two were used corresponding to the following equation:

$$3\ \overset{|}{\underset{|}{C}}H_2 + 2\ Na_2Cr_2O_7 + 8\ H_2SO_4 \longrightarrow 3\ \overset{|}{\underset{|}{C}}{=}O + 2\ Na_2SO_4$$

$$+ 2\ Cr_2(SO_4)_3 + 11\ H_2O$$

For the methyl compound the yield was lowered to 20.2% although the crude product was almost white. With the methoxy compound weaker conditions gave an apparent increase in yield (66%) but the product was less pure even though it was not as dark in color. This is shown by the melting points of the two crude products. Under strong conditions the melting point was 94°C. Using weaker conditions the crude product of white crystals melted at 71-76°C. Pure 2'-methoxy-2-benzoylbenzophenone (LVII) melts at 129.5-130.5°C. These low melting products appear to be mixtures of the mono- and diketones. It is difficult to separate this mixture since both substances have quite similar solubilities in most solvents used for crystallization. Ethanol did not give sufficient separation to be useful but methanol or ligroin were found to give better separation. Many recrystallizations were necessary to obtain a product relatively free of the monoketone. This problem did not exist with the methyl compound since the monoketone, 2'-methyl-2-benzylbenzophenone (LIII) is an oil. Also, this difficulty does not exist if the oxidation proceeds in high yield. It would seem profitable to further investigate this oxidation reaction by using other oxidizing agents to try to obtain higher yields.

Reduction of 2'-methyl- and 2'-methoxy-2-benzoylbenzophenone with zinc dust in glacial acetic acid yielded the corresponding 1-(2'-methyl-phenyl)-3-phenyl isobenzofuran (LV) and 1-(2'-methoxyphenyl)-3-phenylisobenzofuran (LVIII). The methyl compound could not be obtained in crystalline form. These 1,3-diarylisobenzofurans are very reactive compounds. This was noticeable particularly in losses incurred when recrystallization was attempted. The two most common reactions that have been observed in connection with these substances are oxidation to the o-diaroylbenzenes by oxygen and oxidizing agents in the absence of light and dimerization in the presence of sunlight. Adams and Gold (11) have postulated the transitory formation of free radicals of type (LIX) and presented some spectroscopic data to support this hypothesis. The reaction with oxygen and dimerization are also



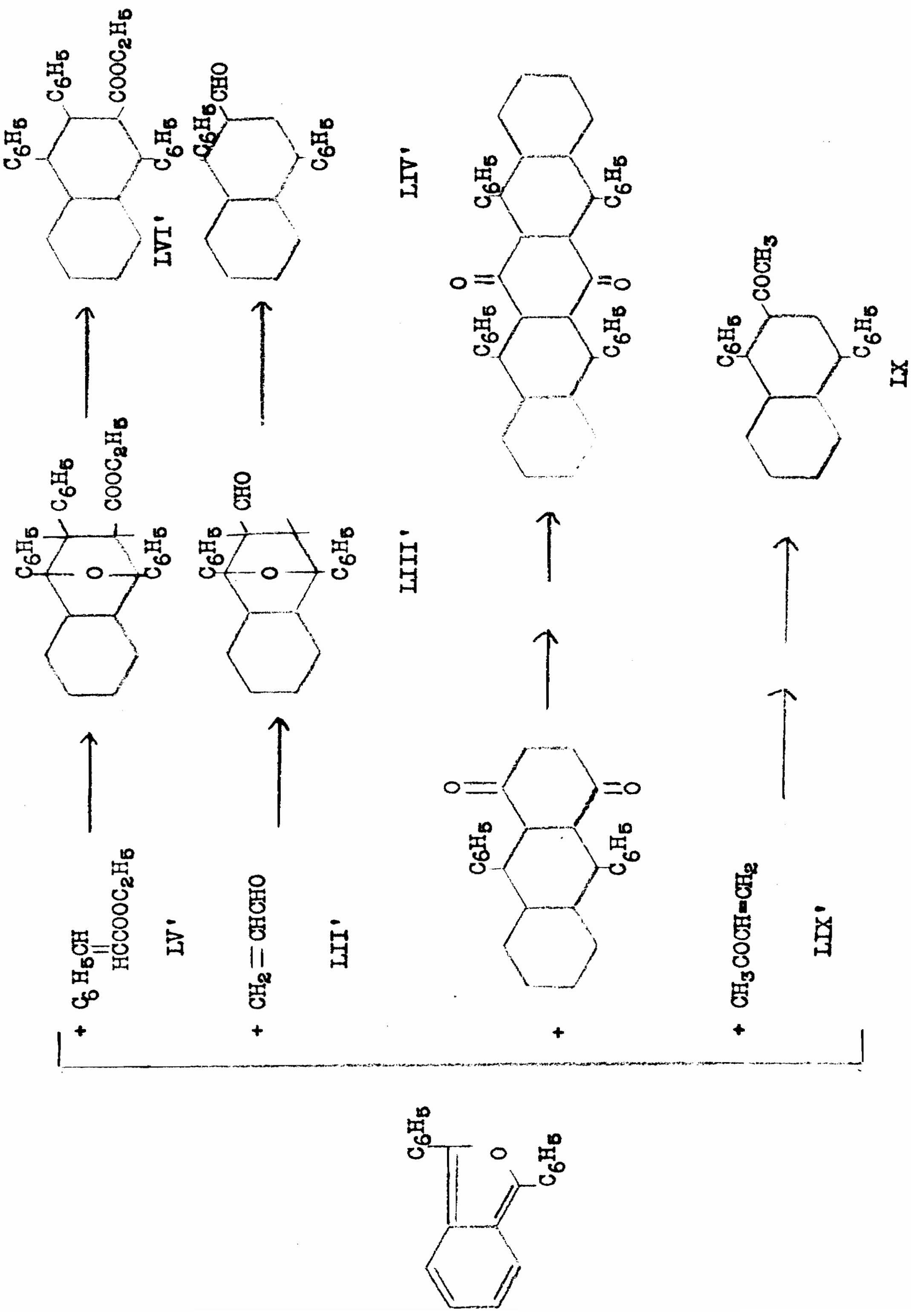
R-aryl group

LIX

typical of free radical intermediates.

The diarylisobenzofurans are useful in synthesis due to the active diene system present which is susceptible to the Diels-Alder reaction with α,β-unsaturated carbonyl compounds. They are particularly useful in the preparation of substituted naphthalenes. Some of these are illustrated in Chart X. The combination of 1,3-diphenylisobenzofuran with acrolein (LII') yields 1,4-diphenyl-2-formyl-1,4-oxido-1,2,3,4-tetrahydronaphthalene (LIII'.) Dehydration of this adduct with absolute ethanol saturated with hydrogen chloride gives 1,4-diphenyl-2-formylnaphthalene (LIV') (31). Similar procedures with ethyl cinnamate (LV), 9,10-diphenyl-1,4-anthraquinone (LVII')

CHART X


$C_6H_5CH=HCCOOC_2H_5$
LV'
$CH_2=CHCHO$
LII'
$CH_3COCH=CH_2$
LIX'
LIII'
LVI'
LIV'
LX
C_6H_5
$COOC_2H_5$
CHO
$COCH_3$
O

and methyl vinyl ketone (LIX') give 1,2,4-triphenyl-3-carbethoxynaphthalene (LVI'), sym. mesotetraphenylpentacenequinone (LVIII') and 1,4-diphenyl-2-acetylnaphthalene (LX) (31) (32) (33).

EXPERIMENTAL

EXPERIMENTAL

Preparation of o-Benzylbenzonitrile (LII) (27)(28)

o-Chlorodiphenylmethane (LI) (28). A mixture of 150 g. of anhydrous benzene and 4 g. of anhydrous aluminum chloride were placed in a three-neck flask which was equipped with a dropping funnel and tubing ending in an inverted funnel over water to absorb hydrogen chloride gas which is given off in the reaction. A solution of 50 g. of o-chlorobenzylchloride in 150 g. of benzene was added drop by drop with cooling. The temperature was kept below 15°C. The reaction mixture was allowed to come to room temperature. When the reaction was complete the benzene solution was washed once with 2 N hydrochloric acid, once with 10% sodium hydroxide, twice with distilled water and dried over anhydrous calcium sulfate (Drierite). The solution was concentrated and distilled under reduced pressure. The fraction boiling at 120-126°C at 1 mm. weighed 43.6 g. (69.3%).

o-Benzylbenzonitrile (LII) (27). A mixture of 92.4 g. of o-chlorodiphenylmethane (LI), 50 g. of anhydrous pyridine, 50 g. of cuprous cyanide and a small crystal of cupric sulfate were added to a 500 ml. round bottom flask. The mixture was stirred and heated under reflux at about 250°C in a metal bath for 22 hours. At the end of this time, the pyridine was allowed to boil off and the resulting mixture was heated under reflux for 29 hours at 250°C by use of a metal bath. The mixture was cooled to room temperature and distilled at 6 mm. pressure using a von Braun distilling apparatus. The crude distillate was poured into dilute ammonium hydroxide. This solution was extracted four times with ether. The combined ethereal extracts were washed with cold 2 N hydrochloric acid, then with water, and dried over anhydrous calcium sulfate (Drierite). The dried extracts were concentrated and fractionated at 0.5 mm. The fraction boiling at 134-140°C weighed 74.8 g. This was redistilled at 4.8 mm. The fraction boiling at 160-162°C weighed 52.7 g. (60%).

Compounds Prepared From o-Benzylbenzonitrile (LII) (28) (27)

2'-Methyl-2-benzylbenzophenone (LIII) (25). A Grignard reagent was prepared from 7.5 g. of magnesium and 53 g. of *o*-bromotoluene in 300 ml. of anhydrous ether in a 500 ml. three-neck flask equipped with dropping funnel, mechanical stirrer and reflux condenser. The reaction was initiated by running in about 15 ml. of the ethereal *o*-bromotoluene and heating the mixture of magnesium and solution for about one minute with a large incandescent bulb. The remainder of the o-bromotoluene solution was added slowly with cooling. When all the solution had been added the mixture was refluxed for 1-1/2 hours. After distilling off 150 ml. of the ether, 20 g. of o-benzylbenzonitrile (LII) in 150 ml. of benzene was added slowly. No evidence of reaction was observed. The mixture was refluxed for 22 hours, cooled to room temperature and the complex decomposed with the slow addition of 35 ml. of ice-cold 20% ammonium chloride. The benzene layer was decanted and the residue extracted twice with 50 ml. portions of benzene. The combined benzene layer and extracts were refluxed for 50 hours with 400 ml. of 2 N hydrochloric acid. When the mixture had cooled to room temperature the benzene layer was separated and the acid layer was extracted twice with 25 ml. portions of benzene. The solution containing the benzene layer and extracts was dried over anhydrous calcium sulfate (Drierite), concentrated and distilled at reduced pressure. The fraction boiling at 219-222°C at 4.6 mm. weighed 17.4 g. (57.4%).

Preparation of 2'-Methyl-2-benzoylbenzophenone (LIV) (1).

EXPERIMENT #1

A solution of 3 g. of 2'-methyl-2-benzylbenzophenone (LIII) in 30 ml. of glacial acetic acid was placed in a

200 ml. 3-neck flask equipped with a reflux condenser, a dropping funnel and mechanical stirrer. To this was added 3.8 g. of sodium dichromate crystals. The solution was warmed and stirred until the dichromate dissolved. When the mixture had cooled to room temperature 8 ml. of concentrated sulfuric acid was added dropwise with stirring. The mixture was then refluxed for half an hour and poured into 85 g. of crushed ice. A black, sticky viscous oil separated. Crystallization was attempted from 95% ethanol, methanol, heptane, and ligroin. Crystals were obtained from ligroin (b.p. 90-120°) with difficulty. The acid solution was extracted with hot ligroin. The crystals obtained weighed 2.0 g. (63.5%) and melted at 72.5-73.5°C. After recrystallizations from ligroin and two recrystallizations from 95% ethanol the pure compound melted at 76-77°C. An analytical sample was taken from this material.*

For $C_{21}H_{16}O_2$:

Calculated: C = 83.98%
H = 5.37%
O = 10.65%

Found: C = 84.10%
H - 5.54%

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*All analyses were made by Micro-Tech. Laboratories, Skokie, Illinois.

EXPERIMENT #2

A solution of 4 g. of 2'-methyl-2-benzylbenzophenone (LIII) in 50 ml. of glacial acetic acid was placed in a 200 ml. 3-neck flask equipped as in the above experiment. To this solution was added 2.8 g. of sodium dichromate crystals. After warming to effect solution of the dichromate, 2 ml. of concentrated sulfuric acid in 10 ml. of glacial acetic acid was added dropwise with stirring and cooling. The mixture was heated under reflux for 10 minutes and poured into 95 g. of ice. The oil which separated was light brown in color. The oil was separated from the acid mixture by extracting with benzene. The benzene solution was washed with 50 ml. portions of water, sodium carbonate and again water. The solution was dried and concentrated. The residual oil was crystallized from ligroin (b.p. 66-75°C). The crystals weighed 0.85 g. (20.2%) and melted at 72-73°C.

1-(2'-Methylphenyl)-3-phenylisobenzofuran (LV) (1). A solution of 1 g. of 2'-methyl-2-benzoylbenzophenone (LIV) in 53 ml. of glacial acetic acid was placed in a 200 ml. 3-neck flask equipped with mechanical stirrer and condenser. To this solution was added 2 g. of zinc dust. The mixture was heated for 5 minutes during which time the solution turned bright yellow. The excess zinc dust was filtered off and the acidic solution cooled to

$0^{o}C$. The material that separated upon addition of water to the cold solution was an oil. Crystallization was attempted from ligroin, methanol, acetone-water mixture, and ethanol. The product could not be obtained in pure form.

2'-Methoxy-2-benzylbenzophenone (LVI) (20). A Grignard reagent was prepared from 7.6 g. of magnesium and 61.4 g. of o-bromoanisole in 250 ml. of anhydrous ether in a 500 ml. three-neck flask with a mechanical stirrer, mercury seal, dropping funnel, and reflux condenser. The reaction was begun by the use of a crystal of iodine. The o-bromoanisole was added slowly with cooling. After the addition was complete the reaction mixture was refluxed for 45 minutes. About 200 ml. of ether were distilled off and 20 g. of o-benzylbenzonitrile (LII) in 150 ml. of anhydrous benzene were added. Following this addition slowly through the dropping funnel the mixture was refluxed for 21 hours. The Grignard complex was decomposed with 30 ml. of 20% ammonium chloride. The benzene layer and two 50 ml. benzene extracts were combined and refluxed with 300 ml. of 2 N hydrochloric acid. The reflux period was 60 hours. The benzene layer was separated, washed with distilled water and dried over anhydrous calcium sulfate (Drierite). The solution was then concentrated and distilled at reduced pressure. The material boiling at 245-250°C at 6.9 mm. weighed 21.8 g. This was 69.6% of the theoretical yield. Crystallization of this material from 95% ethanol gave white crystals melting at 66-67°C.

Preparation of 2'-Methoxy-2-benzoylbenzophenone (LVII) (1).

EXPERIMENT #1

A solution of 8 g. of 2'-methoxy-2-benzylbenzophenone (LVI) in 50 ml. of glacial acetic acid was placed in a 200 ml. 3-neck flask with stirrer, condenser and dropping funnel. To this was added 8.9 g. of sodium dichromate crystals. The solution was warmed until these dissolved. Then 13 ml. of concentrated sulfuric acid were added drop by drop with cooling. The reaction mixture was then heated under reflux for 5 minutes and poured into 80 g. of crushed ice. The product precipitated as a black solid. Recrystallization from 95% ethanol using charcoal gave 3.7 g. of crystals melting at 94°C. This represents a 45.1% yield. Repeated crystallizations give a pure product melting at 129.5-130.5°C. An analytical sample was taken from this material. For $C_{21}H_{16}O_3$:

Calculated: C=79.73%; H=5.10%; O=15.17%

Found: C=79.57%; H=5.12%

EXPERIMENT #2

A solution of 4 g. of 2'-methoxy-2-benzylbenzophenone (LVI) in 50 ml. of glacial acetic acid was placed in a 200 ml. 3-neck flask equipped with stirrer and dropping funnel. To this was added 2.6 g. of sodium dichromate crystals. The mixture was stirred and warmed until solution was effected. Then 2 ml. of concentrated sulfuric acid in 10 ml. of glacial acetic acid was added dropwise with cooling. The mixture was heated under reflux for 10 minutes and poured onto 100 g. of crushed ice. The crude substance separated as light brown crystals. Crystallization from ethanol using charcoal gave 2.3 g. of white crystals (m.p. 71-76°C). Concentration of the supernatant liquid gave 0.4 g. more. The total of 2.7 g. of product represents a yield of 66% of theoretical.

1-(2'-Methoxyphenyl)-3-phenylisobenzofuran (LVIII) (1). A mixture of 0.6 g. of 2'-methoxy-2-benzoylbenzophenone (LVII) (m.p. 100-114°C) and 50 ml. of glacial acetic acid was warmed to obtain solution of the diketone. To this was added 1.4 g. of zinc dust. The mixture was heated under reflux for 15 minutes. During this time the solution turned a bright yellow color. The excess zinc was filtered from the hot solution which was then cooled to 0°C. The whole solution solidified at this temperature. At room temperature the solid mass melted. The addition of water precipitated an amorphous yellow substance which was crystallized from 95% ethanol and cooled. A yellow solid separated which melted at 104-108°C, and weighed 0.2 g. (35%). The pure material melts at 114-114.5°C.

Analysis of $C_{21}H_{16}O_2$: Calculated: C, 83.98%; H, 5.37%
O, 10.65%.

Found: C, ; H

Attempted Preparation of 2'-Chloro-2-benzylbenzophenone (II); R=o-Cl and R'=H (27).

EXPERIMENT #1

A Grignard reagent was prepared from 5.6 g. of magnesium and 55.0 g. of o-chloroiodobenzene in 160 ml. of anhydrous ether in a 500 ml. 3-neck flask equipped with mercury seal, stirrer, condenser and dropping funnel. The reaction started readily with a little heat from an electric light bulb. After all the o-chloroiodobenzene had been added the mixture was heated under reflux for 30 minutes. After about 90 ml. of ether had been distilled off, 15 g. of o-benzylbenzonitrile in 100 ml. of anhydrous benzene was added slowly, although no evidence of reaction was observed. The mixture was refluxed for 25 hours. The complex was decomposed with 21 ml. of ice-cold 20% ammonium chloride. The benzene layer and three benzene extracts were combined and refluxed for 49 hours with

400 ml. of 2 N hydrochloric acid. The benzene layer was dried over anhydrous calcium sulfate (Drierite) and separated into three parts; one 98 ml., one 100 ml. and one 40 ml. portion.

The 100 ml. portion was concentrated and distilled at 2.4 mm. pressure. The highest boiling fraction came over at 140-160°C and weighed 2.7 g. The residue from the distillation was extracted and crystallization attempted from 95% ethanol. No pure product could be obtained.

The 40 ml. portion was concentrated and crystallization was attempted. An oil separated from the solvent in each case. The 98 ml. portion was chromatographed on "Alumina Adsorption" (Fisher Sci. A-541/2). A viscous red oil was obtained which gave no satisfactory results on analysis. Oxidation of some of this oil with sodium dichromate failed to produce enough solid material for identification as the diketone. Oxidation of 2.4 g. of this oil gave about 0.05 g. of white crystalline solid melting at 134-143°C.

EXPERIMENT #2

A Grignard reagent was prepared from 5.6 g. of magnesium and 56 g. of o-chloroiodobenzene in 150 ml. of anhydrous ether. After all the o-chloroiodobenzene had been added the mixture was refluxed for 1 hour.

After removal of most of the ether, 14.8 g. of o-benzylbenzonitrile was added in 100 ml. of anhydrous benzene. This mixture was refluxed for 24 hours. The complex was decomposed with 4.5 N sulfuric acid and refluxed with 400 ml. of this acid for 53 hours. The benzene layer was washed, dried over calcium chloride, concentrated and distilled under reduced pressure. The highest boiling fraction boiled at 195-250°C at 5 mm. and weighed 7.5 g. An attempt was made to purify this by redistilling at 11 mm. Three fractions were obtained:

I - 195-209°C; 3 g.
II - 209-225°C; 1.1 g.
III - 225-265°C; 2.2 g.

Crystals formed in Fractions II and III. Recrystallization of these from ligroin (b.p. 66-75°C) gave 0.2 g. of white needles melting at 187°C. Further crystallization gave crystals melting at 197°C. This substance is a hydrocarbon.

Analysis: Calculated for $C_{20}H_{14}$: C, 94.45%; H, 5.55%

Found: C, 94.41%; H, 5.68%

The Preparation of 2'-Chloro-2,4-dimethylbenzohydrol (LII) (27).

A Grignard reagent was prepared from 67.8gof 4-iodo-1,3-dimethylbenzene in 200 ml. of anhydrous ether and 7.1 g.

of magnesium in a 500 ml. 3-neck flask with stirrer, condenser, and dropping funnel. The reaction started in about 2 minutes by simply stirring a small amount of the ethereal solution in the presence of the magnesium. The main portion of the solution was then added slowly with cooling. The solution was refluxed for 2 hours. Not all of the magnesium went into solution. A solution of 30.3 g. of o-chlorobenzaldehyde in 50 ml. of anhydrous ether was added slowly with cooling. The resulting mixture was heated under reflux for 1 hour. The Grignard complex was decomposed with ice-cold 20% ammonium chloride. The ethereal solution and washings of the solid residue were dried over anhydrous calcium sulfate (Drierite) and concentrated. The product crystallized on standing. The yield of white crystals from 95% ethanol was 20.0 g. melting at 119-125°C (38%). An analytical sample was prepared with a melting point of 125-125.5°C.

Analysis for $C_{15}H_{15}OCl$: Calculated: C, 73.02%; H, 6.13%; Cl, 14.37%; O, 6.48%;

C, 73.05%; H, 5.12%; Cl, 15.33%.

SUMMARY

SUMMARY

A review of the more important methods of synthesis of 1,3-diarylisobenzofurans (III) and o-diaroylbenzenes (II) was made. These were compared with the possibilities involved in the type of synthesis in which substituted o-benzylbenzophenones (I) are oxidized to o-diaroylbenzenes (II) and subsequently reduced to 1,3-diarylisobenzofurans (III). It is seen that this latter method affords a greater variety of substituents for these types of compounds than the other methods. The possible orientations of substituents are also greater.

Two o-benzylbenzophenones (I), 2'-methyl-2-benzylbenzophenone (LIII) and 2'-methoxy-2-benzylbenzophenone (LVI), were prepared by the action of the appropriate Grignard reagent on o-benzylbenzonitrile (LII) and subsequent hydrolysis of the intermediate ketimine. These were oxidized to the corresponding o-dibenzoylbenzenes (II), 2'-methyl-2-benzoylbenzophenone (LIV) and 2'-methoxy-2-benzoylbenzophenone (LVII), by the use of sodium dichromate and sulfuric acid. Reduction of these with zinc dust in acetic acid gave the corresponding 1,3-diarylisobenzofurans (III), 1-(2'-methylphenyl)-3-phenylisobenzofuran (LV) and 1-(2'-methoxyphenyl)-3-phenyl isobenzofuran (LVIII).

Attempts were made to prepare 2'-chloro-2-benzylbenzophenone (I; R=o-Cl and R'=R) by the same method as that in the above mentioned paragraph. None of the ketone could be obtained. A small amount of a hydrocarbon was obtained in one case which analyzed as $C_{20}H_{14}$.

The action of the Grignard reagent of 4-iodo-1,3-dimethylbenzene on o-chlorobenzaldehyde gave 2-chloro-2',4'-dimethylbenzohydrol (LI).

New compounds synthesized are 2'-methyl-2-benzoylbenzophenone (LIV), 2'-methoxy-2-benzoylbenzophenone (LVII), 1-(2'-methylphenyl)-3-phenylisobenzofuran (LV), 1-(2'-methoxyphenyl)-3-phenylisobenzofuran (LVIII), and 2-chloro-2',4'-dimethylbenzohydrol (LI).

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