A STUDY OF THE RELATIONSHIP BETWEEN THE MOLECULAR STRUCTURE OF DDT AND ITS INSECTICIDAL ACTIVITY

Part I: A Survey of the Problem and the Preparation of Certain Intermediates in the Synthesis of DDT Analogs

by

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INTRODUCTION

Everyone knows of the destruction caused by insects. For this reason scientists in many fields have been making strong efforts along various paths of insect control. Much has been accomplished of a practical nature but though many have attacked the theoretical aspects of this subject it still lags far behind. One attack has been a study of the relationship between the molecular structure of certain organic insecticides and their insecticidal activity. In order to get more data on this problem we have proposed to synthesize a series of compounds related to DDT (I). The structures of these compounds are shown in formulas II, III, and IV.

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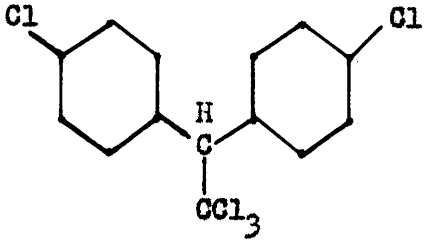
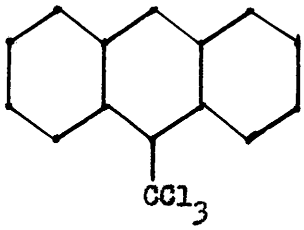


I



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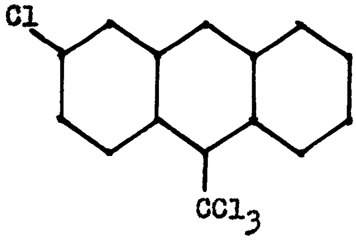

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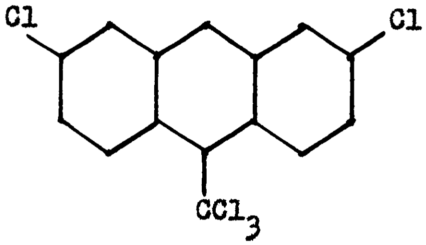

IV

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* All rings are fully aromatic unless otherwise specified.

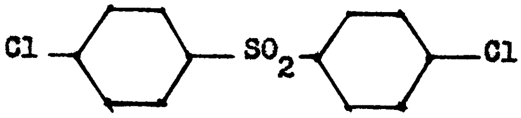
The object of this thesis is to: 1) make a survey of the work that has been done relating the structure of DDT to its insecticidal activity, 2) outline a synthesis for compounds II, III, and IV, and 3), determine in the laboratory whether the syntheses are feasible.

HISTORICAL AND LITERATURE REVIEW

History

The compound known as DDT (I) or 2,2-bis-(p-chlorophenyl)-1,1,1-trichloroethane was first synthesized and described by Zeidler (1) in 1874. Zeidler, as far as is known, made no effort to find practical applications for the compound.

About fifty years later research work on mothproofing chemicals was started in the laboratories of J. R. Geigy in Switzerland. In the following ten years a number of compounds were discovered which had considerable promise as moth preventatives. These were mainly diphenyl sulfones, and one of the most effective of these stomach poisons was bis-(p-chlorophenyl) sulfone (V).



V

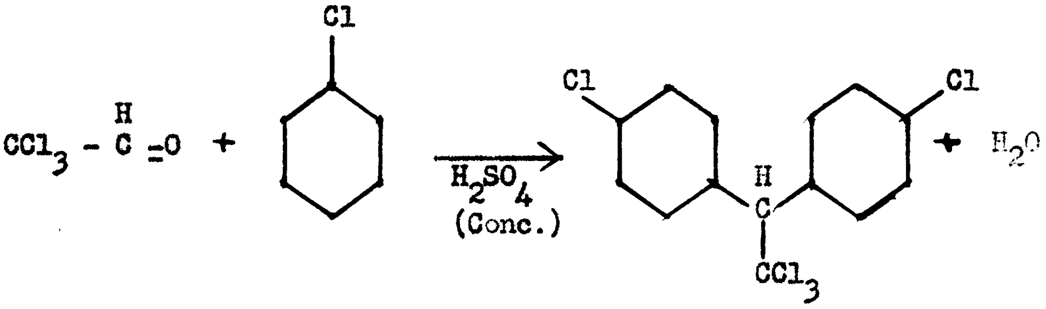
Substitution of various groups in the molecule ultimately led several Swiss workers, including Lauger, Martin, and Müller (2) to 2,2-bis-(p-chlorophenyl)-1,1,1-trichloroethane (I).

The insecticidal properties of the compound were discovered by Paul Müller in 1936-37 (3) and patented by him in 1940.

DDT had unprecedented development as a synthetic insecticide because it was found to have unusual properties of wide range of insecticidal action, simple structure promoting ready synthesis, stability to light and air resulting in enduring residual toxicity and low mammalian toxicity. The material ideally fulfilled a wartime demand for the control of insects of medical importance and soon found important agricultural uses. Approximately forty eight million pounds of it were produced in 1947.

Preparation of DDT

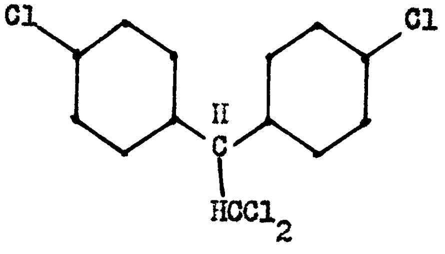
DDT was produced by Zeidler, and is still produced today, by the reaction of chloral (or its alcoholate or hydrate) with chlorobenzene in the presence of concentrated sulfuric acid (equation below).



The technical material has a rather variable composition and is composed of up to fourteen chemical compounds. The major constituents, other than the actual p,p'-isomer (DDT), all possess some slight degree of toxicity to insects (4).

Related Materials

Several compounds closely related to DDT have attained some importance as insecticides. A fairly extensive list, including references, can be found in Frear's book (5). DDD or 2,2-bis-(p-chlorophenyl)-1,1-dichloroethane (VI), methoxychlor or 2,2-bis-(p-methoxyphenyl)-1,1,1-trichloroethane (VII), DFDT or 2,2-bis-(p-fluorophenyl)-1,1,1-trichloroethane (VIII), and the dimethyl-analogue of DDT, 2,2-bis-(p-tolyl)-1,1,1-trichloroethane (IX) are among the more important of these.



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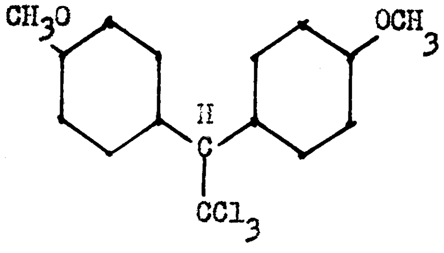

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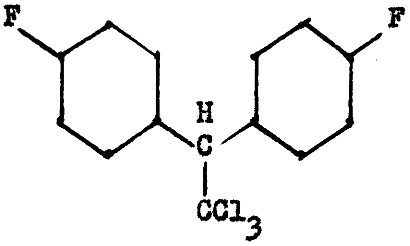
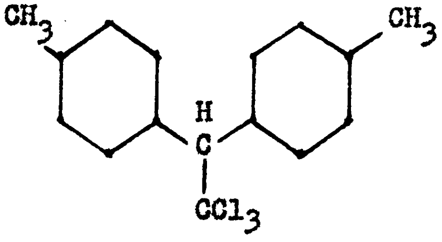


VIII



IX

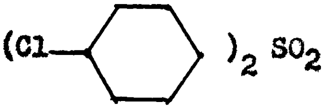
Toxicology of DDT Analogues

A very large number of analogues of DDT have been studied with regard to their toxicity to insects. Metcalf (4) gives several tables in his review.

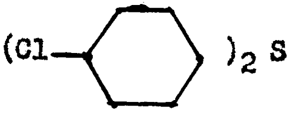
Martin and Wain (6) have studied the relative toxicities of a series of DDT analogues. They state that the nature of the nuclear (ring) substituent affects toxicity either because of the electronic effect of the group or because of solubility factors. When the substituent is either chlorine or methoxy, both inductive and electronic effects are operative but are opposite in influence on the alpha-carbon of ethane. The evidence appears to favor the solubility factor as being the controlling factor, Metcalf (4) claims, since compounds incorporating these two groups and the methyl substituted compound as well are highly toxic. The low activity shown by molecules with polar groups, such as hydroxyl- and nitro-ring substituents, indicates the importance of non-polar groups in this position (4). Martin and Wain point out that with asymmetrical analogues, solubility may likewise be the controlling factor as the surface activity of the molecule and its adsorption may be affected by symmetry. Busvine (7) notes that the molecules of the most toxic DDT-analogues are most similar to DDT in shape and weight, and he considers it possible that the entire molecule is involved in a steric association with a vital enzyme. Further theories of the influence of structure are presented below.

Theories of Mode of Toxic Action of DDT

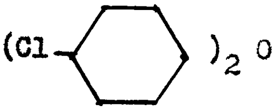
Two general theories of the mode of action of DDT and related materials have been suggested, both of which depend on the classical Overton-Meyer theory (8) which relates the lipoid solubility, i.e., the oil/water distribution coefficient of physiologically active materials and their activity. It was speculated by Lauger, Martin and Muller (2) that the effectiveness of DDT is due to combination in one molecule of a lipid solubilizing group, viz, the "trichloromethyl group" (XIV), and a toxic component the bis-(p-chlorophenyl)-methylene group (XIII). From data, gathered from a study of mothproofing agents, these investigators point out that many substances having two p-chlorophenyl groups attached to a central nucleus such as di-(p-chlorophenyl)-sulfone (X), di-(p-chlorophenyl)-sulfide (XI) and di-(p-chlorophenyl)-ether (XII), proved to be effective stomach poisons. The addition of a lipid



X

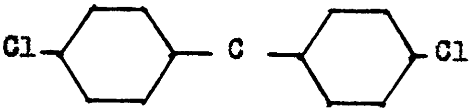


XI



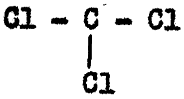
XII

solubilizing group, such as the trichloromethyl group, to the molecule resulted in the contact action of DDT. Therefore they theorize that the



XIII

group is the toxic portion of the molecule and that the

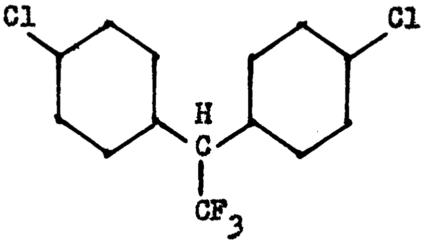


$$\begin{array}{ccccc} Cl & - & C & - & Cl \\ & & | & & \\ & & Cl & & \end{array}$$

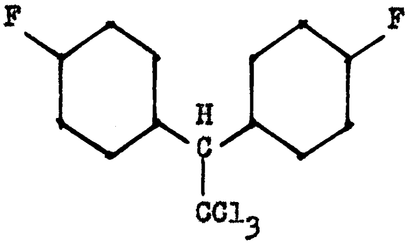
XIV

group is lipid-solubilizing group.

The work of Kirkwood and Phillips (9) gives some support to Lauger's theory. These investigators synthesized the compound 2,2-bis-(p-chlorophenyl)-1,1,1-trifluoroethane (XV) which was found to be only feebly insecticidal. This compound which contains a trifluoromethyl group was fed to rats and was not found to be stored in the perirenal fat, although the insecticidally active compound 2,2-bis-(p-fluorophenyl)-1,1,1-trichloroethane (XVI) fed in a similar manner accumulated to the extent of 3.2 mg./g. fat. In connection to this it was pointed out that the compound fluoroform, HCF_3, has no anesthetic properties (10).



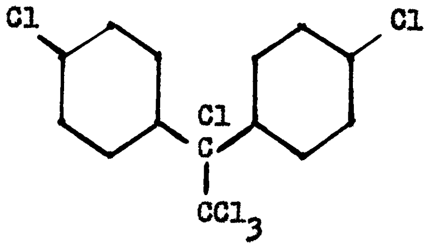
XV



XVI

It has however, been pointed out by Martin that various alkoxy analogues of DDT, such as the bis-(p-methoxy) (VII) and bis-(p-ethoxy), since they are toxic, make it evident that the toxicity of DDT is not uniquely explained by the presence of the dichlorodiphenyl system.

Metcalf (4) points out that 2,2-bis-(p-chlorophenyl)-2,1,1,1-tetrachloroethane (XVII) is almost completely inert insecticidally despite its close resemblance to DDT and its conformity with the theoretical requirements for toxicity according to Lauger's hypothesis.



XVII

The other theory on mode of action is attributed to Martin and Wain (11). Martin and Wain's theory is almost directly opposed to the theory of Lauger. Their theory suggests that the p-chlorophenyl groups are responsible for the lipid solubility of the compound and the trichloromethyl group for the toxic action, which is produced by the liberation of hydrogen chloride *in vivo* at vital centers. Martin (12) sums up his conclusions that DDT is insecticidal because it has (1) ability to penetrate and concentrate at the site of action, (2) adequate stability to reach site of action, and (3) ability to release hydrogen chloride when absorbed at the site of action.

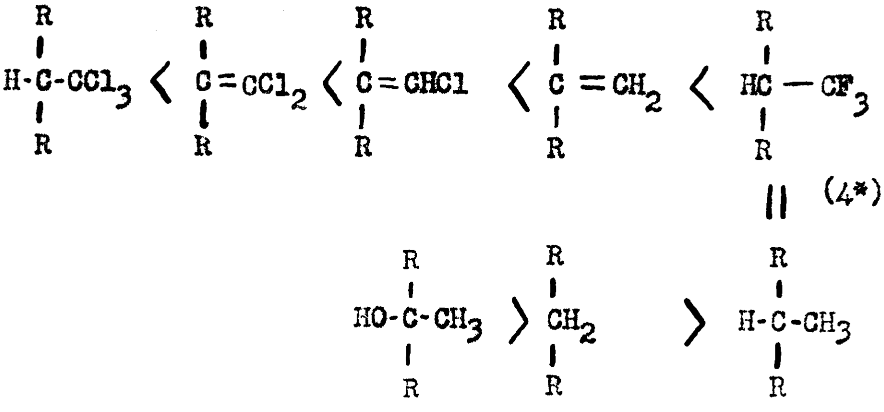
Some indirect evidence which favors the relation of the dehydrohalogenation reaction to toxicity lies in the fact that at 20°C the o,p'-isomer liberates hydrochloric acid only 1/67 as fast as does the p,p' isomer (13). The o,p'-isomer is by far the less toxic of the two isomers; it is reported by Cristol and Hallen (3) to be 1/10 as toxic to adult Anopheles mosquitoes. Shepard (14) notes that DDD (VI) is close to DDT (1) in toxicity to certain insects and undergoes dehydrohalogenation in the same manner. Shepard (14) further states that the compound corresponding to DDT but with all four available ethane linkages chlorinated (XVII) does not dehydrohalogenate, and it is almost completely inactive against insects.

There is considerable evidence against Martin and Wain's theory. Metcalf (4) in his review points out that as a consequence of the validity of such a theory one might expect a positive correlation between rate of dehydrochlorination and the degree of toxic action of DDT-analogues. These rates have been studied (13, 15) and it has been shown by Busvine (16), Muller (17), Domenjoz (18) and Cristol (13) that there is no correlation between the rate of dehydrochlorination and degree of toxicity to insects. This is especially noticeable in the case of 2,2-bis-(p-methoxyphenol)-1,1,1-trichloroethane (VII) which is comparable to DDT in insecticidal potency to many insects and yet has a dehydrochlorination rate constant of about 1/275 that of DDT. (Martin replies to this criticism that the factors of absorbability and permeability may also outweigh dehydrochlorination in determining the relative potency of the compound.

Furthermore, in vivo dehydrochlorination might be produced by enzyme action or other conditions completely dissimilar to exposure to alkali.) Shepard (14) brings forth the fact that when hydroxyl radicals replace the chlorine atoms of the trichloromethyl group so that dehydrohalogenation would not occur, the resulting compound is no less toxic than DDT.

In regard to both theories Busvine (7), and Domenjoz (18), after measuring the solubility of various DDT-analogues in fats, found no correlation between lipoid solubility and toxicity to mammals and insects. Browning and co-workers (19) have found no compound with low fat solubility to be highly toxic.

As a final comment upon these two theories the data obtained by Metcalf (20) are of interest. He found in his work with DDT-analogues as acaricides that DDT was completely inactive but progressive increases in toxicity were obtained by successive eliminations of aliphatic chlorine atoms, the order of effectiveness increasing from:



$$H\text{-}\underset{R}{\overset{R}{C}}\text{-}CCl_3 < \underset{R}{\overset{R}{C}}=CCl_2 < \underset{R}{\overset{R}{C}}=CHCl < \underset{R}{\overset{R}{C}}=CH_2 < \underset{R}{\overset{R}{HC}}-CF_3$$

(4*)

$$||$$

$$HO\text{-}\underset{R}{\overset{R}{C}}\text{-}CH_3 > \underset{R}{\overset{R}{CH_2}} > H\text{-}\underset{R}{\overset{R}{C}}\text{-}CH_3$$

(1*) (2*) (3*)

where R = p-chlorophenyl. The most effective ascaricides such as 1,1-bis-(p-chlorophenyl)-ethanol (1*), 4,4-dichlorodiphenylmethane (2*), 2,2-bis-(p-chlorophenyl)-ethane (3*) and 2,2-bis-(p-chlorophenyl)-1,1,1-trifluoroethane (4*) are much less effective insecticides than DDT and contain neither the lipid solubilizing groups (as defined by Lauger) nor are capable of eliminating hydrogen chloride.

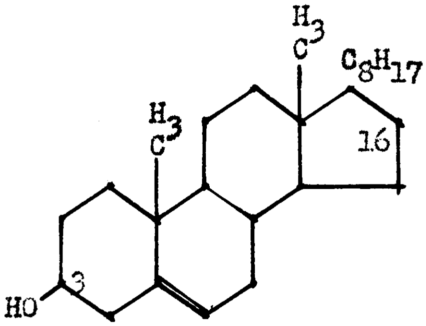
Gavaudan and Poussel (21) have explained the action of DDT as that of an indifferent narcotic acting on a lipoidic substrate. They determined the solubility of DDT in water as about 0.1 mg. per liter at 18°C. They calculated the thermodynamic activity for DDT using the expression C/Co where C is essentially the minimum lethal concentration of DDT to the organism and Co is the saturated concentration in water. Using values from the literature for the minimum lethal concentration in water for several species of insects they observed that the thermodynamic activity falls in the range 0.1 to 1.0. This value is in good agreement with the theory of indifferent narcotics of Meyer and Hommi (8), who have postulated that narcosis occurs when a chemically indifferent substance reaches a specific threshold concentration in the cell lipids, regardless of the concentration in the external environment (4). Using Busvine's (22) value for the solubility of DDT in olive oil, 10% or 0.28 moles per liter, as a measure of the lipid solubility of DDT and Meyers and Hemmi's average threshold value for various narcotics, 0.06 moles per liter, the authors obtained a ratio of $0.06/_{0.28}$ or 0.21 for the theoretical thermodynamic activity of DDT in the cellular phase. The close agreement of this value with the range of experimental values in the table shown in Metcalf's review, (4) is suggested as an indication that DDT acts as an indifferent narcotic.

Hurst (23) has suggested that DDT and analogous compounds act by indirect blocking of cytochrome oxidase and succinic dehydrogenase, which may be accomplished by uptake and storage of the insecticide in the phospholipids. The evidence for such theory is apparently derived from the behavior of chloroform in dispersing the lipids of the insect cuticle (4).

Hoffmann and Lendle's (24) experiments on possible inhibition of various enzyme systems, with DDT gave negative or inconclusive results. (Article not available to see which systems.)

Stereochemistry of the DDT Molecule

Lauger et al (25) state that the distance between the para chlorine atoms is 11.0 Angstroms and that the valence angle between the phenyl rings is 123°, as determined by X-ray diffraction analysis. Wilde (26), however, after presenting determinations of the dipole moments of a number of compounds related to DDT, calculated the valence angle lies between 110° and 120° for DDT and most other trichloroethanes studied. Lauger (25) believes that the dimensions of the DDT molecule from para-Cl to para'-Cl atom are similar to those of cholesterol (XVIII) (as measured from position 3 to position 16). Cholesterol is an important constituent of nerve tissue and is a fat-soluble vitamin for many insects (27). Lauger suggests that DDT may possess a particular affinity for cholesterol and other sterols present in nerve lipids.

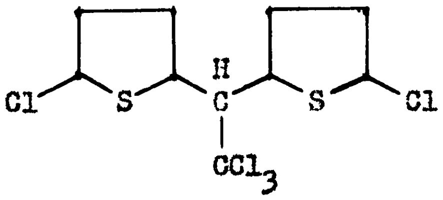


XVIII

Campbell and West (28) submitted a more general theory which according to Shepard (14) would appear to possess much merit. Their theory is as follows:

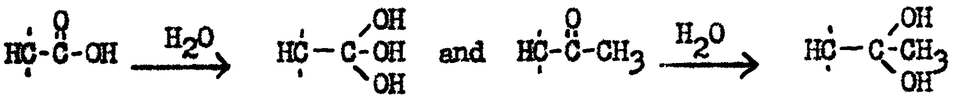
"The mode of action of DDT is clearly very complex, and with regard to the chemical mechanism responsible for toxicity we suggest that evolution of hydrogen chloride may be only a secondary effect accompanying the more fundamental alteration in the electromagnetic nature of the group from which it is evolved. The effect of the chlorine atoms, therefore, may be entirely steric and the fact that three alpha-chlorine atoms are necessary in order to confer optimum toxicity on the compound may be due to their giving the required steric orientation, and that this reaches a maximum when the remaining chlorine atoms are in the para-positions."

According to Metcalf (4), thiophene analogues of a number of biologically active compounds containing benzene rings have been reported to possess activities similar to those of the parent compound. In this connection, Metcalf and Gunther (29) prepared 2,2-bis-(2-chlorothienyl)-1,1,1-trichloroethane (XIX). This compound, according to the authors, was generally much less effective against several species of insects despite the similarity in size and shape of the benzene and thiophene rings, yet it dehydrochlorinated readily in dilute alkali. However, at high dosages the compound produced characteristic DDT-like tremors in insects so that it appears to resemble DDT in its mode of action (30).



XIX

Erlenmeyer et al (31) have studied the insecticidal properties of bis-(p-chlorophenyl)-acetic acid and 1,1-bis-(p-chlorophenyl)-acetone which they consider to be isosters of DDT by virtue of their ability to form hydrates as shown below. The hydrated



$$HC{-}\overset{O}{\overset{\|}{C}}{-}OH \xrightarrow{H_2O} HC{-}C{\begin{smallmatrix}OH\\OH\\OH\end{smallmatrix}} \quad \text{and} \quad HC{-}\overset{O}{\overset{\|}{C}}{-}CH_3 \xrightarrow{H_2O} HC{-}C{\begin{smallmatrix}OH\\CH_3\\OH\end{smallmatrix}}$$

products are isosteric with DDT because of the similar dimensions of the hydroxyl group (radius about 1.7 Angstroms), methyl group (radius 2.0 Angstroms), and chlorine atom (radius 1.8 Angstroms) (32). This degree of structural conformity has been shown by

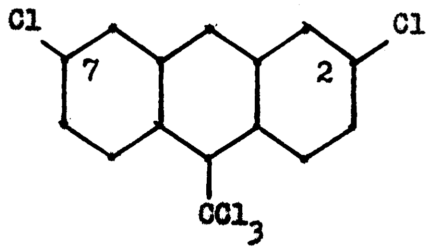
Pauling and Pressman (33) to be well within the limits required for isosteric activity in serological reactions. However, the authors found the DDT-isosters mentioned were insecticidally inactive on those insects tested. Thus the authors conclude that the similarity in inductive action on the remainder of the molecule which they ascribe to the trichloromethyl-, carboxy-, and acetyl-groups, is not a factor in the toxic action of DDT.

The main sources for the above review were (4), (5), and (14).

There was however another paper which appears to contain material of much interest in regard to this review, that is the paper by Hummer and Kenaga (56). These authors compared the structural and insecticidal relationships of Rotenone, Methoxychlor, and DDT and feel that the whole problem should be evaluated from the standpoint of the molecule as a whole, taking into consideration properties such as molecular weight, solubility, polar groups, hydrogen bond acceptors (or donors) and molecular shape and dimensions.

THEORETICAL AND DISCUSSION OF RESULTS

From what has been said under the topic "Stereochemistry of the DDT Molecule" and under the topic "Theories of Mode of Toxic Action," in the previous section, it would appear interesting to prepare a compound of the type shown in figure (IV). This compound, which is again pictured below, would appear to



have dimensions similar to the DDT molecule but would probably not be capable of dehydrochlorination.

Chart I gives the calculations which lead to the conclusion that the above molecule, 2,7-dichloro-10-trichloromethyl-anthracene, would have dimensions similar to DDT. These calculations are based on the following information:

1. Anthracene is known to be planar.
2. The hybrid bond distance between carbons in anthracene is 1.41 A (34).
3. The carbon-chlorine bond distance is 1.69 A (34) in chlorobenzene and would probably be about this distance in the above molecule.

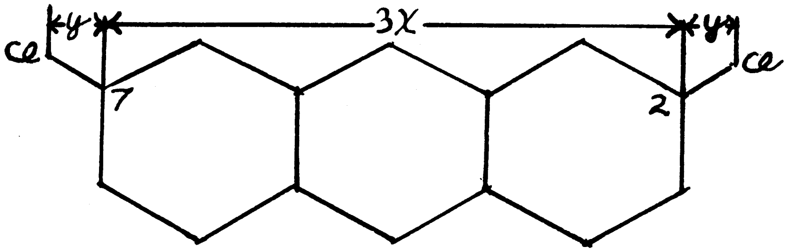
4. All the bond angles (between the carbons) are considered to be 120°.
5. The chlorine atom is considered to lie at a valence angle of 120°(see lower figure on Chart I).

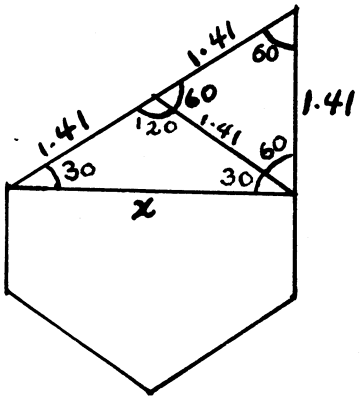
The distance between the two ring chlorine atoms, that is found by the calculations to be 10.24 Angstroms, is fairly close to the 11.0 Angstroms stated by Lauger (25) for the DDT molecule. The valence angle of 123° between the phenyl rings of DDT, as Lauger mentions, or between 110° and 120°, as Wilde (26) calculated, would be approximately the same as the 120° bond angle which would lie between the rings, bearing the chlorines, in the above anthracene molecule.

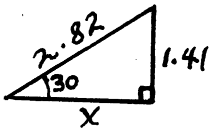
The other two anthracenes, 9-trichloromethylanthracene (11) and 3-chloro-9-trichloromethylanthracene (111), that were mentioned in the Introduction, might possibly be of some value in the insecticidal studies for as it can be seen from their structures they do possess certain components found in the above anthracene.

Should the case be that none of these compounds prove of insecticidal value in a theoretical or practical way, they might still be of great value in an indirect manner, for the reactions that would appear feasible for their production would be of interest in aromatic cyclodehydration mechanism studies (35).

It was decided to prepare these three compounds; therefore a method of synthesis for them had to be developed. In Charts II, The distance between the chlorine atoms attached to carbons 2 and 7 is found as follows:







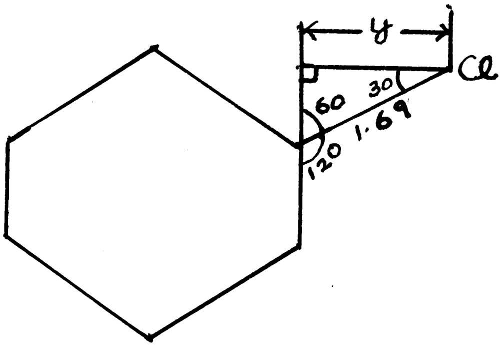
$\text{Cos } 30 = X/2.82$

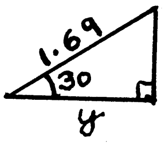
$.866 = X/2.82$

$X = 2.44 \text{ A}$

$3X = 7.32 \text{ A}$

(distance between carbons 2 & 7)





$\text{Cos } 30 = Y/1.69$

$.866 = Y/1.69$

$Y = 1.46 \text{ A}$

$2Y = 2.92$

$2Y + 3X = 2.92 + 7.32 = 10.24 \text{ A} = \text{Cl to Cl}$

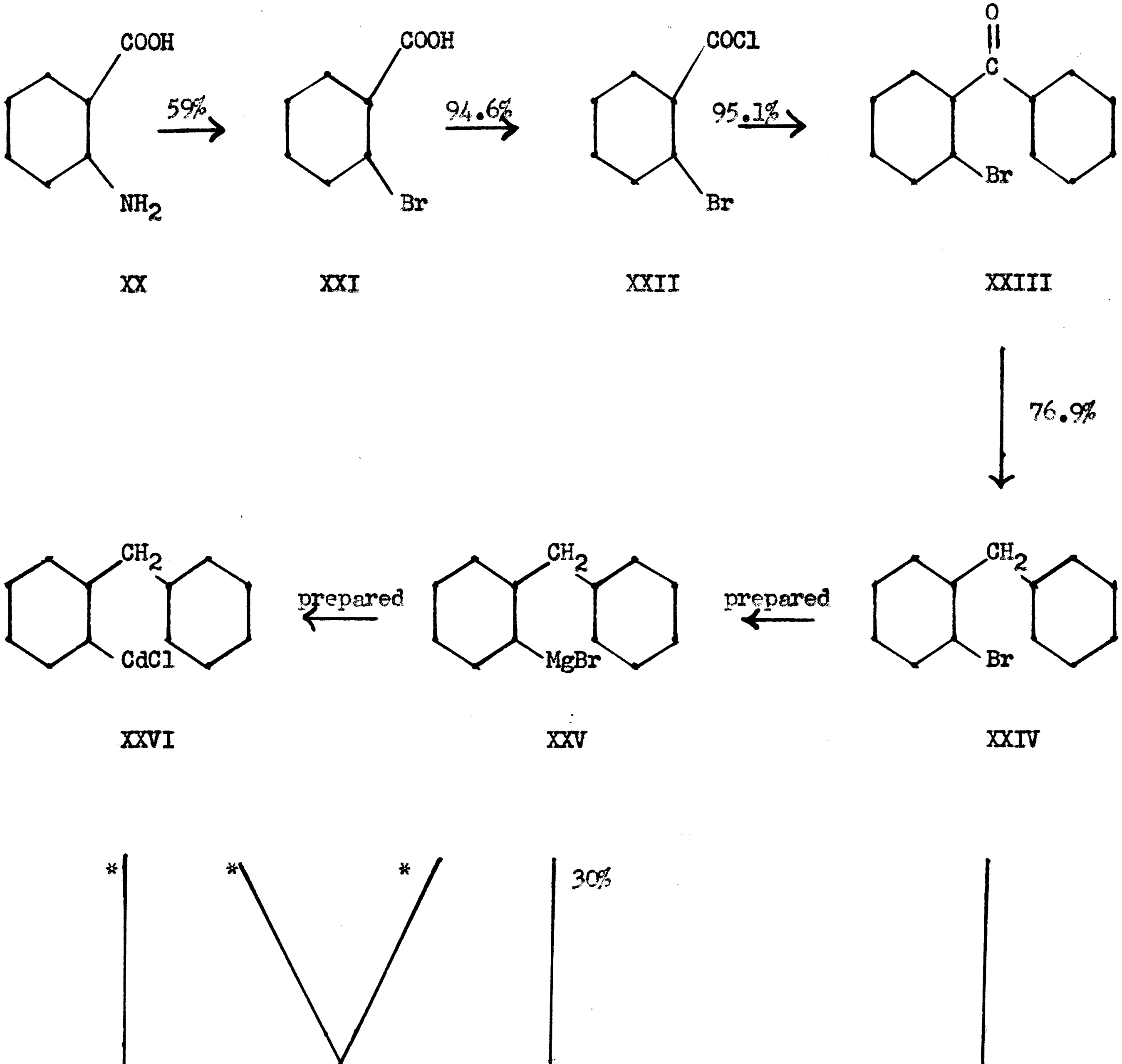
CHART I

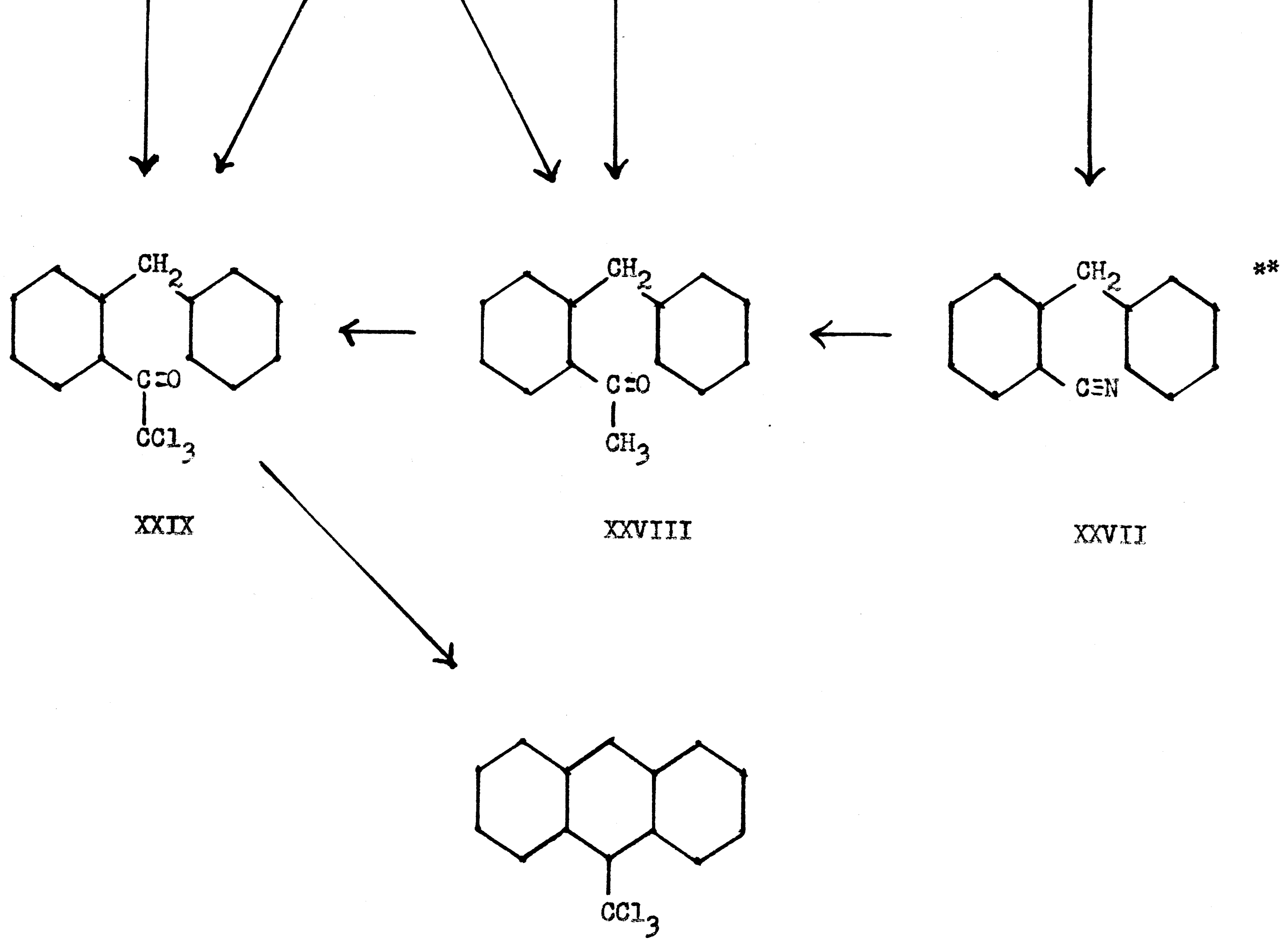
III, and IV are shown the paths that were decided upon. These were chosen because similar reactions had been run in the laboratories here at V.P.I., because they in general appeared to give good yields, and because they utilized ketones which would be of interest in the mechanism studies mentioned above.

The reactions shown in Chart II are, to compound (XXV), the same as those used by Vingiello (37) in his preparation of o-benzylphenones.

Anthranilic acid (XX) was converted to o-bromobenzoic acid (XXI) by means of the Sandmeyer reaction with a yield of 59%. This acid was converted to the acid chloride (XXII), using thionyl chloride, in 94.6% yield. Phosphorus pentachloride gave a yield of 92.6% when used for the same conversion. A Friedel-Crafts reaction between the acid chloride and benzene gave o-bromobenzophenone (XXIII) in 95.1% yield. By use of red phosphorus and hydriodic acid the above ketone was reduced to o-bromodiphenylmethane (XXIV) in 76.9% yield. The o-bromodiphenylmethane was then subjected to the following reactions:

1. Grignard reagent prepared from it (XXV) and a reverse Grignard reaction performed on acetyl chloride.
2. Grignard reagent prepared from it and this converted to the cadmium reagent (XXVI) (38) which in turn


COOH
NH2
59%
XX
COOH
Br
94.6%
XXI
COCl
Br
95.1%
XXII
O
C
Br
XXIII
76.9%
CH2
Br
XXIV
prepared
CH2
MgBr
XXV
prepared
CH2
CdCl
XXVI
*
*
*
30%



XXIX

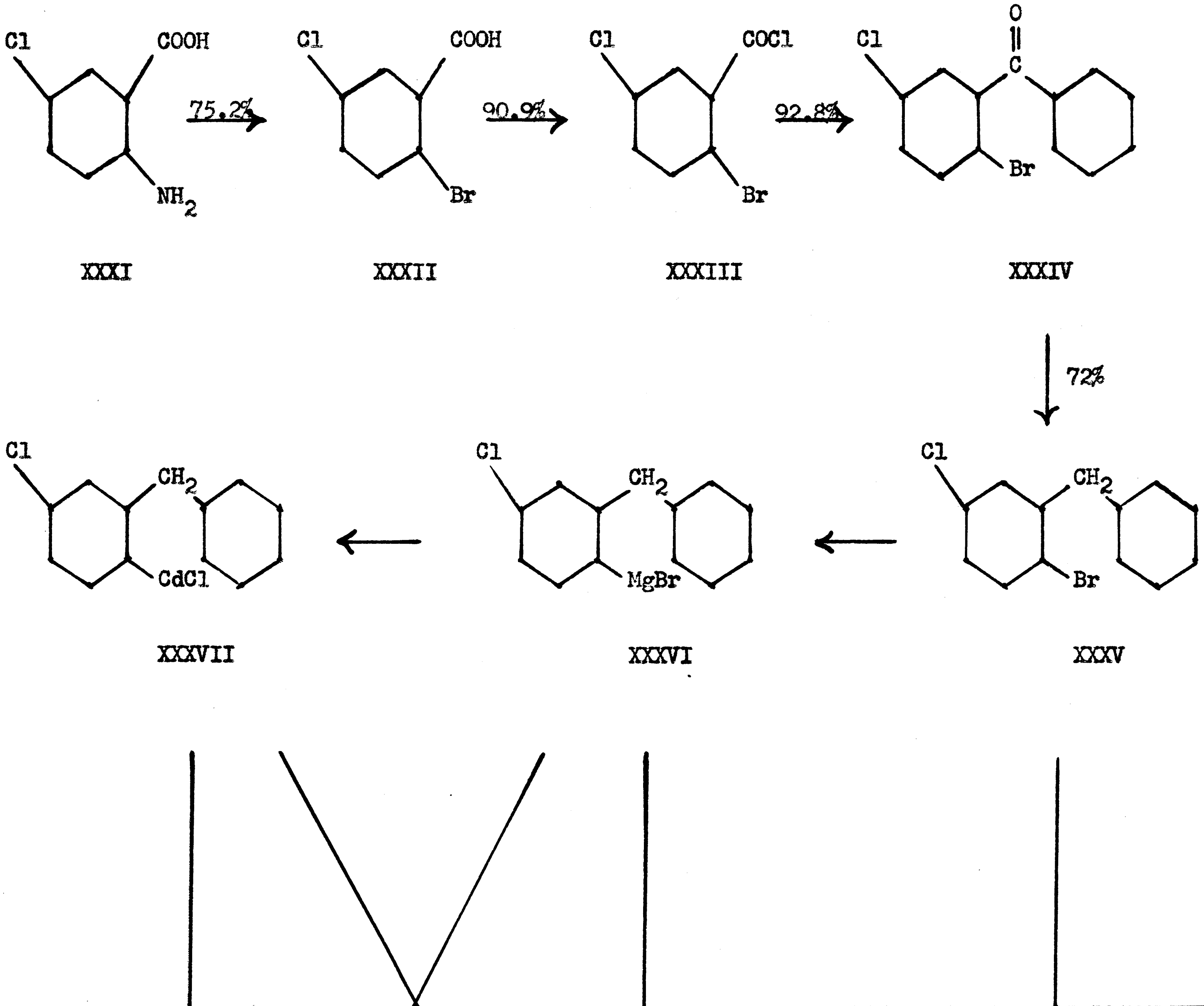
XXVIII

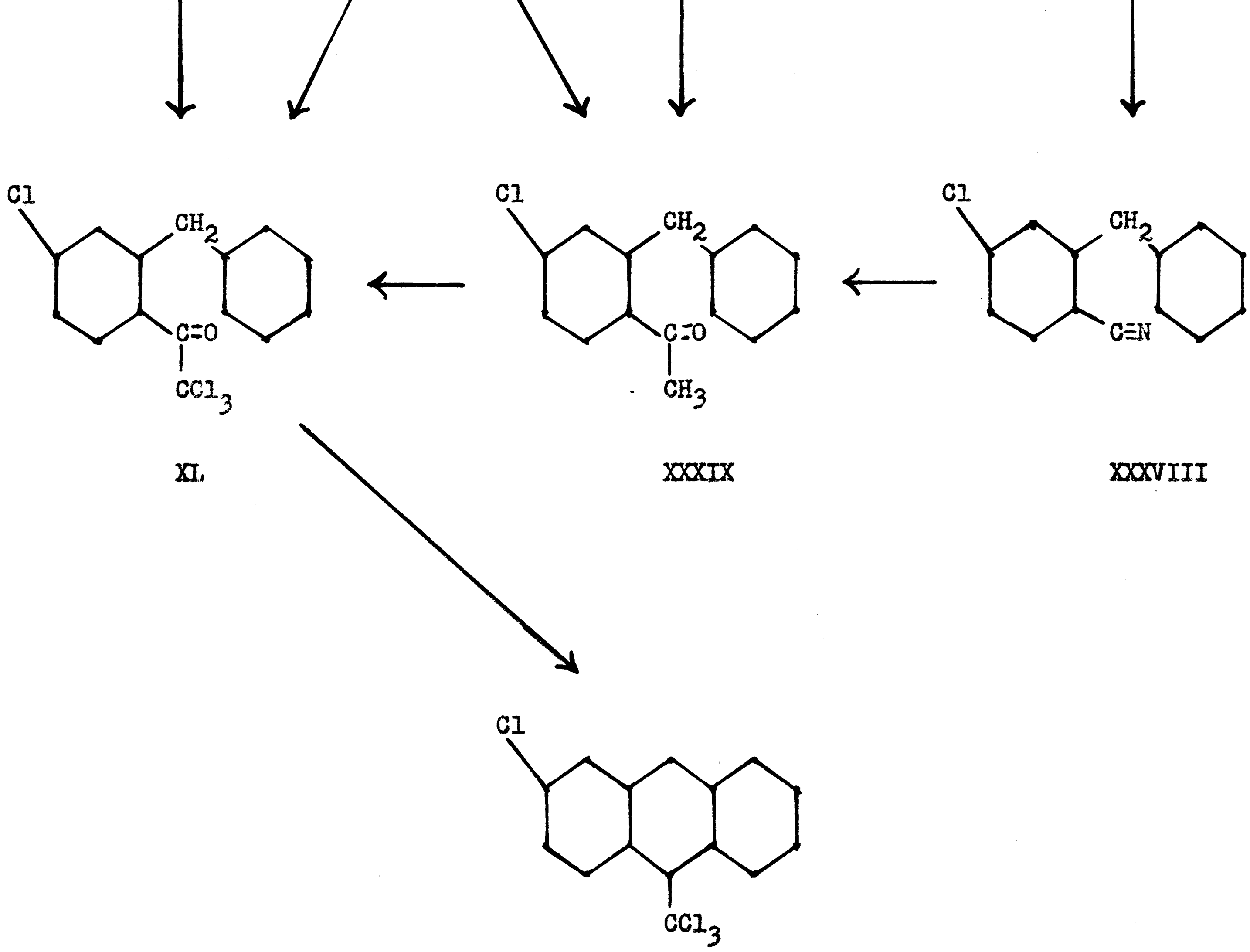
XXVII

XXX or 11

CHART II

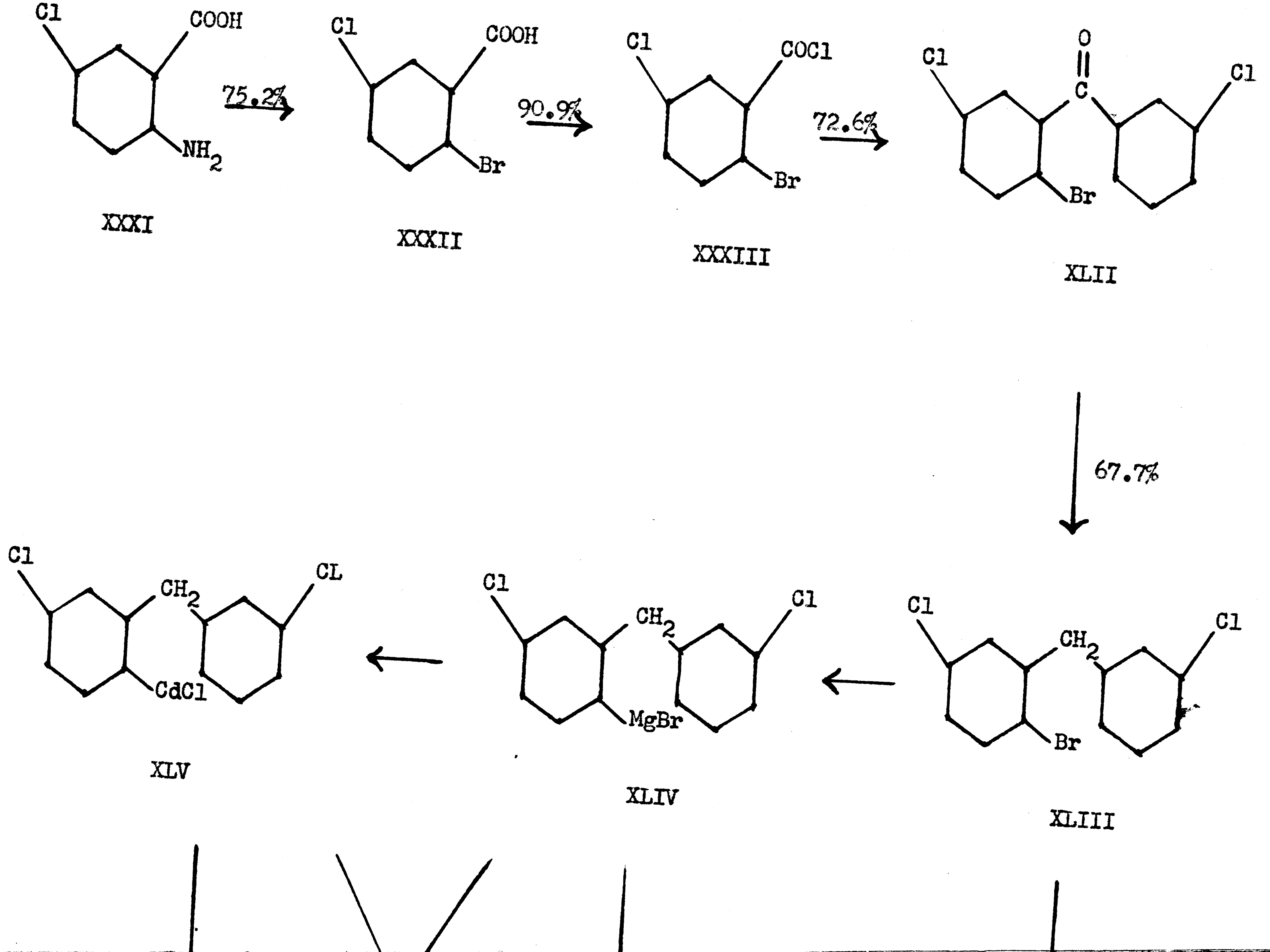
** Prepared by a simple (two step) reaction path.
* Attempts were unsuccessful.


Cl
COOH
NH$_2$
75.2%
XXXI
Cl
COOH
Br
90.9%
XXXII
Cl
COCl
Br
92.8%
XXXIII
O
C
Cl
Br
XXXIV
72%
Cl
CH$_2$
Br
XXXV
Cl
CH$_2$
MgBr
XXXVI
Cl
CH$_2$
CdCl
XXXVII



XLI or 111

CHART III


Cl
COOH
NH$_2$
XXXI
75.2%
Cl
COOH
Br
XXXII
90.9%
Cl
COCl
Br
XXXIII
72.6%
Cl
O
C
Cl
Br
XLII
67.7%
Cl
CH$_2$
Cl
Br
XLIII
Cl
CH$_2$
Cl
MgBr
XLIV
Cl
CH$_2$
CL
CdCl
XLV

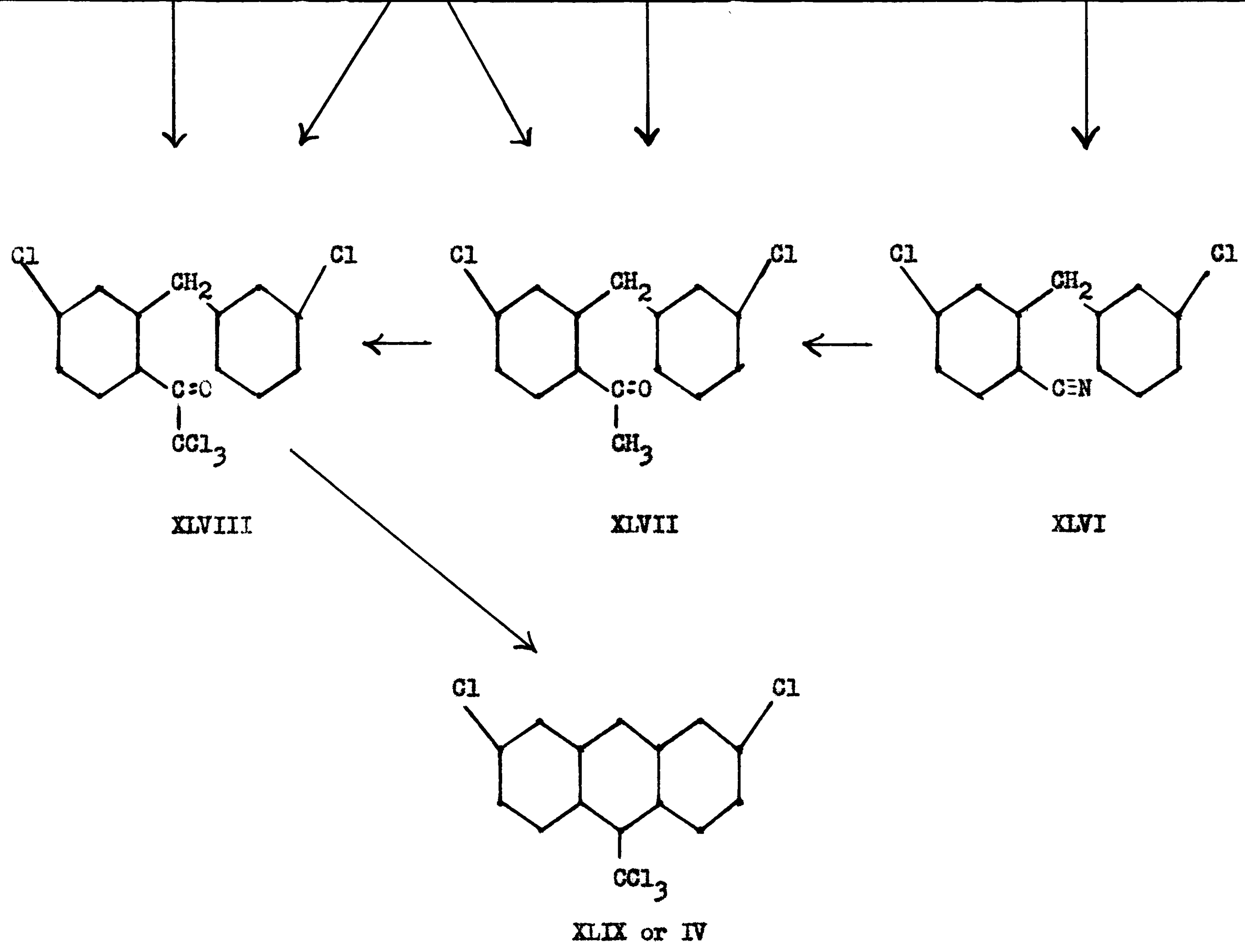

Cl
CH2
C≡N
Cl
XLVI
Cl
CH2
C=O
CH3
Cl
XLVII
Cl
CH2
C=O
CCl3
Cl
XLVIII
Cl
Cl
CCl3
XLIX or IV

CHART IV

was allowed to react with acetyl chloride.

3. Grignard reagent prepared from it and this brought into reaction with acetic anhydride according to the procedure of Newman and Booth (39).
4. Grignard reagent prepared from it and this permitted to react reversibly with 2-chlorobenzoyl chloride.
5. Grignard reagent prepared from it and this converted to the cadmium reagent which in turn was allowed to react with 2-chlorobenzoyl chloride.
6. Grignard reagent prepared from it and this reversibly added to trichloroacetyl chloride.
7. Grignard reagent prepared from it and this converted to the cadmium reagent which in turn was brought into reaction with trichloroacetyl chloride.
8. Grignard reagent prepared from it and this was permitted to react with trichloroacetonitrile; this was followed by hydrolysis.
9. Grignard reagent prepared from it and this was converted to the cadmium reagent which in turn was allowed to react with trichloroacetonitrile; hydrolysis followed this.

In the case of (1) above there were three separate reactions run, one at room temperature, another at -10°, and a third at -70°.

In the case of (2), two reactions were run, one at room temperature and the other at about 80° (temperature of boiling benzene). There was none of the desired ketone, o-benzylacetophenone (XXVIII), isolated from any of these reactions. This ketone, which was first prepared by Bradsher (36), was obtained from (3), above, by running the Grignard in reverse at -70°. This procedure gave a slightly impure material, in 30% yield, which upon two recrystallizations from petroleum ether had the proper melting point. The ketone when made by Bradsher's method (methyl-magnesium-iodide brought into reaction with o-benzylbenzonitrile and this followed by hydrolysis) had a boiling point of 160-161 (3 mm.), but when made by reaction (3) it had the boiling point 146-150.5 (3 mm.). It would appear from the boiling point obtained from (3) that some of the earlier reactions may have actually yielded some of the ketone, for in some of these reactions a fairly large amount of material had a boiling point lower than that stated by Bradsher and near that found in (3). In connection with this it should however be pointed out that repeated attempts at crystallization of the material derived from the earlier reaction, from several solvents, including petroleum ether which Bradsher used for his recrystallizations, did not yield the ketone.

It is believed that the yield of ketones by (3), may be greatly increased by permitting the reaction to run for a much longer period of time, for much material which was believed to be diphenylmethane (the hydrolysis product of the Grignard reagent) was obtained. There was extremely little material left in the still pot after the distillation which resulted in the ketone and the only materials which were obtained in any appreciable yield were the ketone and the diphenylmethane.

The ketone from (3) showed no change in melting point when a mixed melting point was run with a sample obtained by Bradsher's method. The ketone also gave a positive iodoform test.

Cases (4) and (5), above, are shown in Chart V. Bondurant (40), using a different method, made several attempts at the preparation of the ketone, 2-chloro-2'-benzylbenzophenone (L), which was obtained from (4) in 33.3% yield and from (5) in 43% yield. He did not obtain the compound. This ketone is important in aromatic cyclodehydration studies.

Attempts at cyclization of this ketone were not successful.

In the case of (6), above, as in cases (7), (8), and (9), no reactions were found in the literature that were similar in nature. The reverse Grignard reaction on trichloroacetyl chloride (6) did not give any of the desired ketone, trichloromethyl-2-benzylphenyl ketone (XXIX), in isolatable quantity. Reaction (7), above, was run twice, the first time the reactants were heated under reflux for three and one-half hours and the second time for almost

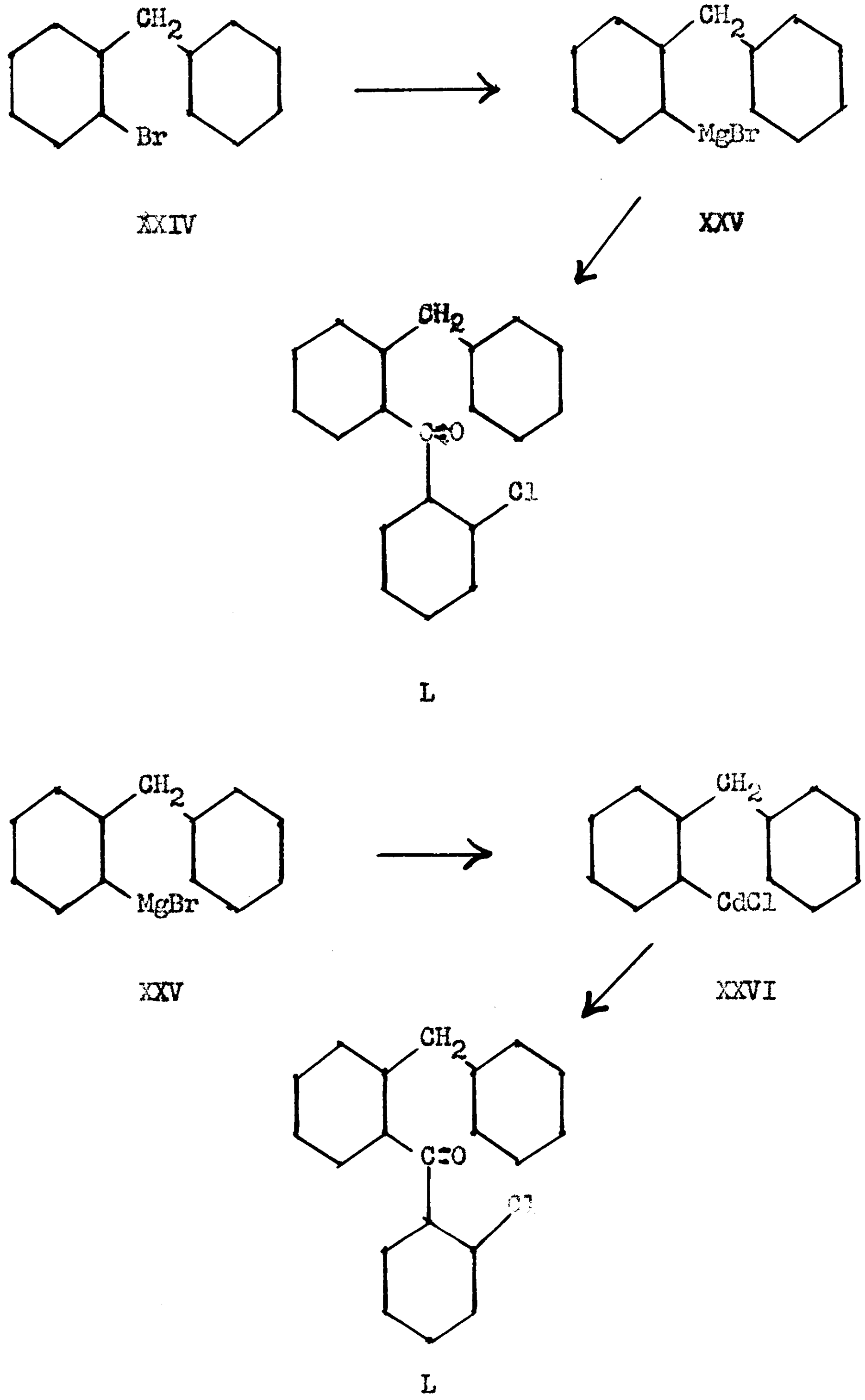
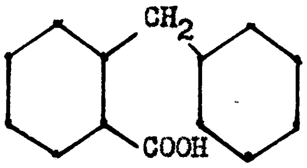

CH2
Br
CH2
MgBr
XXIV
XXV
CH2
C=O
Cl
L
CH2
MgBr
CH2
CdCl
XXV
XXVI
CH2
C=O
Cl
L

CHART V

nineteen hours. In the first of these reactions some material was obtained, in very poor yield, which had the boiling point 145° (3 mm.). This material gave a positive halogen test but attempts at preparation of the oxime were not successful. In the second reaction no attempt was made at distillation, for great difficulty was found in the previous distillation as well as strong decomposition. In this instance the material was chromatographed and those portions which gave a positive halogen test were treated with strong sodium hydroxide solution, in a manner to be described shortly, in an attempt to convert any of the ketone (XXIX) that might have been present to o-benzylbenzoic acid (LI). This acid is a solid with a known melting point (41). None of the above acid was obtained from these attempts, however there was a slight indication that a small, non-isolatable, quantity may have been present (explained shortly).



LI

In an effort to try to prove whether the Cason type of reaction (cadmium reagent brought into reaction with an acid chloride) (38) could or could not be used for the preparation of trichloromethyl-ketones of the type desired, a reaction was carried out using diphenylcadmium and trichloroacetyl chloride. This reaction gave only about a 5% yield of the expected ketone, 1,1,1-trichloroacetophenone, which is a known compound with a definite boiling point (42).

Reaction (8), above, was run only once. This reaction resulted in much charcoal-like material which was only slightly soluble in acetone and which could neither be distilled nor chromatographed. Reaction (9) was run three times, the first time in ether, the second in benzene with heating under reflux for a period of about three hours, and the third in benzene with heating under reflux for fourteen hours. All three reactions gave small amounts of yellowish oil plus a few crystals along with a considerable quantity of what is believed to have been diphenylmethane. Some charcoal-like material was also obtained from these reactions. The oils and crystals were subjected to treatment as follows:

They were tested for halogen and those fractions which were found to contain halogen were treated at room temperature (in one or two cases even heated a little) with five normal sodium hydroxide for somewhat more than a half hour*. The material which did not dissolve (often almost all) in the strong base was extracted with ether. The basic solution was then neutralized with hydrochloric acid. The neutral solution was then cooled with an ice-salt bath and was observed to see whether any of the acid (LI) was obtained. The acid should have come out of solution for it is only slightly soluble in cold water (41). A slight indication that some of the ketone (XXIX) may have been present and that it may have been converted to the acid is supported by the fact that the basic solution upon neutralization showed a definite cloudiness. In an effort to isolate some of the acid from the neutral solution, the solution was extracted with ether and this was followed by the evaporating of the ether; in a few cases a very small amount of oil was obtained but never a crystal.

From what has been said about reactions (6), (7), (8) and (9), it would seem fairly safe to say that the ketone (XXIX) cannot be prepared by this method, at least not in large enough quantity to make the synthesis worth-while. It should

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*Based on the work of J. G. Aston, J. D. Newkirk, J. Dorsky and D. Jenkins (43). These workers found that treating 1,1,1-trichloroacetophenone with 5.2 normal sodium hydroxide solution at zero degrees for half an hour resulted in the conversion of 59% of the ketone to the acid salt. The unreacted ketone was extracted with ether and the salt was converted to benzoic acid by neutralizing the sodium hydroxide solution with acid.

never-the-less be noted that there might be a possibility of obtaining the compound by a reaction similar to (3), for under the conditions of (3) many of the possible side reactions might be cut down.

As a concluding statement on the preparation of the desired trichloromethyl ketones (XXIX), (XL) and (XLVIII), Bigelow* of Duke University states that he is of the opinion that the haloform reaction (44) would probably be the best method for their synthesis. This reaction was not looked into as part of the preparative work of this thesis.

Since none of the ketones, (XXIX), (XL) and (XLVIII), were obtained none of the anthracenes, (XXX), (XLI) and (XLIX), could be obtained.

The starting materials for the preparation of the ketones shown on Charts III and IV were all obtained in fairly good yield. Both charts show the same reactions through compound (XXXIII) and deviate from there on. The 2-amino-5-chlorobenzoic acid (XXXI) was obtained from the Eastman Kodak Company. This acid was converted to 2-bromo-5-chlorobenzoic acid (XXXII) by means of the Sandmeyer reaction with a yield of 75.24% (Though it was stated in the literature (45) that the bromo compound was made

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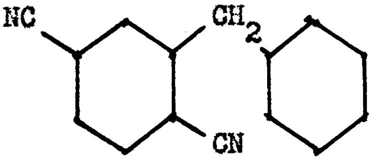
* In recent private communication to Dr. Vingiello — thesis director.

from the amino compound by means of the Sandmeyer reaction, neither the conditions nor the amounts of material to use were stated; therefore this information had to be obtained experimentally). The acid (XXXII) was converted to the acid chloride (XXXIII) by use of phosphorus pentachloride (46) in better than 90% yield.

For the preparation of the ketones, 2-bromo-5-chlorobenzophenone (XXXIV) (Chart III) and 2-bromo-5-chloro-3'-chlorobenzophenone (XLII) (Chart IV), as well as the diphenylmethanes, 2-bromo-5-chlorodiphenylmethane (XXXV) (Chart III) and 2-bromo-5-chloro-3'chlorodiphenylmethane (XLIII) (Chart IV), the syntheses had to be worked out for none of these had been previously reported in the literature. Compound (XXXIV) was prepared in better than 92% yield, compound (XLII) in better than 72% yield, compound (XXXV) in 72% yield and compound (XLIII) in better than 67% yield.

The nitriles shown on Charts III and IV also had not previously been prepared. The preparation of these compounds, (XXXVIII) (Chart III) and (XLVI) (Chart IV), would appear similar, therefore the experimental work was limited to the synthesis of (XXXVIII). Several experiments were carried out, one at 235-245°, another at 190-200°, the third at 220-225°, and the last at about 115-116° (temperature of boiling pyridine). The reactions at 235-245, 190-200 and 115-116°, were run with equal molar quantities of cuprous cyanide and bromide (XXXV) whereas the reaction at 220-225° was run with better than a two molar excess of copper cyanide over bromide. The first reaction, 235-245°, gave a very low yield of crystalline material and much coal-like material; the reaction at 190-200° gave a mixture of crystalline materials and only a small amount of coal-like material; the reaction run at 200-225° gave a good yield of what is believed to be the dinitrile (LII) shown below; the reaction at 115-116° gave a mixture of crystalline materials in much poorer yield than the reaction run at 190-200°. The material believed to be the dinitrile gave a positive nitrogen test and a negative halogen test; an analytical sample was taken of this material.



LII

No attempts were made at the preparation of the Grignard reagents, (XXXVI) and (XLIV), from compounds (XXXV) and (XLIII) but it is not believed that much difficulty will arise when these attempts are made.

EXPERIMENTAL

Preparation of o-Bromodiphenylmethane XXIV (37a) (47).

o-Bromobenzoic acid XXI (37a). A mixture of 62.4 g. of cupric sulfate pentahydrate, 51.4 g. of sodium bromide, 296 ml. of 48% hydrobromic acid and 35 g. of fine copper turnings was heated under reflux for three hours. This hot solution was then filtered through glass wool into a boiling solution of 100 g. of anthranilic acid (XX), 230 ml. of 48% hydrobromic acid and 1800 ml. of water. The solution was stirred continuously during this addition. The temperature was lowered to about 95° and a solution of 100 g. of sodium nitrite in 500 ml. of water was added dropwise with stirring. After addition of the sodium nitrite solution, the reaction mixture was cooled to room temperature while being stirred. The solid was filtered off and recrystallized from hot water using a little charcoal. The crystalline material was finally dried in a vacuum desiccator, m.p. 146-148° (Lit. (48), 149°); yield 88.6 g. (59.1%).

o-Bromobenzoyl chloride XXII (37a). A mixture of 41 g. of o-bromobenzoic acid (XXI) and 32 ml. of stock thionyl chloride was heated under reflux for three hours. The excess thionyl chloride was distilled off at atmospheric pressure and the residue was fractionated under reduced pressure. The fraction boiling at 133-

135° (23 mm.) (Lit. (37a), 132-134 (22 mm.)) weighed 42.4 g. (94.6%).

The above compound (XXII) was also synthesized in the following manner:

> A mixture of 85 g. of acid (XXI) and 92 g. of phosphorus pentachloride was heated for half an hour using an oil bath which was kept between 130-140°. Care was taken to leave ample space for the gas which was evolved almost all at once (only large pieces of calcium chloride were used in the drying tube that was attached to the reflux condenser) and the escaping gas was led out through a funnel which was inverted over a solution of sodium hydroxide. After the half hour of refluxing, the lower boiling material was taken off at slightly reduced pressure and the residue was distilled at 25 mm. pressure. That fraction which boiled between 137-138.7° weighed 86 g. (92.6%).

<u>o-Bromobenzophenone</u> <u>XXIII</u> <u>(37a)</u>. This ketone had been previously prepared by Bergmann (47). The procedure used has been changed to some extent (51). A mixture of 62 g. of aluminum chloride and 300 ml. of anhydrous benzene was cooled in an ice bath and stirred. A few drops of o-bromobenzoyl chloride (XXII) were added immediately to prevent the benzene from freezing. To this cold solution, 83 g. of the above acid chloride (XXII) in 100 ml. of dry benzene was added dropwise. The mixture was

stirred overnight and allowed to warm slowly to room temperature. The reaction mixture was then heated under reflux for three hours, then cooled in an ice-salt bath and decomposed with ice and 200 ml. of concentrated hydrochloric acid. The benzene layer was separated and the acid layer was extracted three times with fresh benzene. The combined benzene layers was then washed with water which was followed by a washing with sodium carbonate solution which in turn was followed by another wash with water. The benzene solution was concentrated and then fractionated under reduced pressure. The fraction boiling at 179-182 (7 mm.) (Lit. (47), 151-153 (0.05 mm.); (49), 180-183 (7 mm.)) weighed 93.8 g. (95%).

o-Bromodiphenylmethane (XXIV) (37b). This compound was prepared previously by Bergmann (47). Vingiello (37b) found that hydriodic acid, red phosphorus reduction gave a higher yield than the Clemmenson reduction, used by Bergmann, provided not more than about 50 g. of ketone was reduced at one time. The following procedure is a slight modification of Vingiello's which works for larger amounts of ketone. A mixture of 93.8 g. of the above ketone (XXIII), 93.8 g. of red phosphorus and 93.8 ml. of about 57% hydriodic acid (that portion of 48% hydriodic acid which did not boil below 123° (715 mm.) or, in other words, approximately constant boiling hydriodic acid) was stirred and heated under reflux for twenty-four hours. At the end of the twenty-four hours an additional 47 ml. of 48% hydriodic acid was added and the reaction mixture was stirred with strong refluxing for another twenty-four hours. The reaction mixture was then cooled to about 15° and made basic to litmus with 10% sodium hydroxide. The excess red phosphorus was filtered off, using suction, and washed with ether. The filtrate was extracted twice with ether and then all the ethereal layers were combined, washed twice with water and dried over anhydrous calcium sulfate. The ethereal solution was finally concentrated and the residue was distilled at 23 mm. pressure. That fraction which boiled at 180-182° (Lit. (47), 175 (22 mm.)) weighed 68.3 g. (76.9%).

Attempted Synthesis of o-Benzylacetophenone (XXVIII) from o-Bromodiphenylmethane (XXIV).*

EXPERIMENT #1

A Grignard reagent was prepared from 0.82 g. of magnesium, 8.3 g. of o-bromodiphenylmethane and a crystal of iodine in about 40-50 ml. of anhydrous ether. It took about two hours for this reaction to go to completion. The Grignard reagent was siphoned with nitrogen pressure into a separatory funnel and added dropwise, with stirring, (over a period of about an hour) to 3.2 g. of

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* In the order under which the reactions were discussed in the Theoretical and Discussion of Results.

acetyl chloride in 50 ml. of anhydrous ether. In the beginning of this addition an ice-bath was used but when it was noticed there was no strong exothermic reaction taking place this was removed. Just before all the Grignard reagent had been added a precipitate settled out of the reaction mixture and tended to block the stirrer. The reaction was stirred one hour after the addition of the Grignard reagent and was then decomposed with hydrochloric acid. The acid layer was separated and extracted several times with ether. The ether layers were combined and washed with water, then with 10% sodium carbonate solution and finally with water. The ethereal solution was dried over Drierite and the ether distilled off; the residue was then distilled at 5 mm. pressure. There were 3.3 g. of material which boiled below 167°, one gram which boiled between 167-170°, and most of the rest remained in the still pot. The literature (36) states the boiling point as 167° (5 mm.) and that the material solidifies and has the melting point 49-50. Attempts at solidifying and crystallization of the lower boiling fraction as well as the fraction which had approximately the right boiling range were not successful.

EXPERIMENT #2

A Grignard reagent was prepared from 20 g. of o-bromodiphenylmethane, 2.0 g. of magnesium and a crystal of iodine in 150 ml. of anhydrous ether. It took 17.5 hours for this reaction to go to completion. The Grignard reagent was siphoned with nitrogen pressure into a separatory funnel from which it was added dropwise, with stirring, to 5.73 g. of acetyl chloride in 130 ml. of anhydrous ether (took about an hour for this addition). The acetyl chloride solution was kept at about -10° during the addition of the Grignard and for two hours after. Just before all the Grignard reagent had been added the stirrer was stopped by the precipitate which had formed. After the stirrer was started again the reaction was stirred for two hours with the ice-salt bath present and then for three hours with the bath absent. The reaction mixture was then decomposed with 20% ammonium chloride solution. The ether layer was separated and the acid layer was extracted several times with ether. The ether layers were combined and washed with water, then with 10% sodium carbonate solution and then with water again. Following the drying of the ethereal solution over anhydrous calcium sulfate the solution was concentrated. The residue was then distilled under reduced pressure. The material had the boiling range 105-185° (5 mm.) and there was quite a large amount of material left in the still pot. Fractions were cut from this wide boiling material as follows: 105-158° (7.6 g.), 158-167° and 167-185° (the total weight of the fraction 158-185 was 3.5 g.). Several attempts were made at crystallization of each fraction but none was successful. It was later found by very careful fractionation that most of the lower boiling fraction was diphenylmethane.

EXPERIMENT #3

A Grignard reagent was prepared from 23.9 g. of o-bromodiphenylmethane, 2.4 g. of magnesium and a crystal of iodine in 115 ml. of dry ether. The reaction was complete at the end of three hours. The reagent was siphoned into a dry separatory funnel by use of nitrogen pressure. From the separatory funnel the reagent was added dropwise, with stirring, (over a period of about an hour) to a solution of 8.0 g. of acetyl chloride in 200 ml. of dry ether. The acetyl chloride solution was cooled with a dry-ice-acetone bath during this addition. The contents of the reaction flask were then stirred for about two hours with the dry ice bath present and then for two additional hours with it present but with all the dry ice gone. The reaction mixture was then decomposed with hydrochloric acid and dealt with in the same manner as in the two previous experiments. Upon distillation, 8.8 g. of material which boiled at 103-165° (5 mm.) was collected along with 6.5 g. of material which boiled at 165-175° (5 mm.); some material remained in the still pot. The higher boiling material was redistilled and that portion which boiled at very near the range stated in the literature (see experiment #1) was collected and attempts at crystallization were made but were not successful. Later, when the lower boiling fraction was redistilled, it was found to be mainly diphenylmethane.

EXPERIMENT #4

A Grignard reagent was prepared from 1.2 g. of magnesium, 12.35 g. of o-bromodiphenylmethane and a crystal of iodine in about 90 ml. of dry ether. This reagent took eighteen hours to prepare. The reagent was cooled with an ice-salt bath and 8.8 g. of anhydrous cadmium chloride (The hydrated cadmium chloride had been dehydrated by heating with a free flame in a large evaporating dish, had been kept overnight in a drying oven maintained at 103°, ground to a fine powder in a mortar and stored over anhydrous calcium chloride in a desiccator.) was added in one batch. The Grignard-cadmium chloride mixture was stirred and heated under reflux for twenty minutes at the end of which time the Gilman test (50) was negative. The ether was distilled off until the residue was nearly dry and 25 ml. of dry benzene was added and most of this was distilled off. Then 50 ml. of benzene was added and the solution was kept at room temperature. To this cadmium reagent was added 3.94 g. of acetyl chloride in about 40 ml. of dry benzene (over a period of about three minutes). The reaction mixture was then stirred for several hours and finally decomposed by addition of ice and ice-cold hydrochloric acid. The benzene layer was separated and the acid layer was extracted with fresh benzene. The combined benzene layers were washed with 10% sodium hydroxide and then with water and finally dried with Drierite. After distilling off the benzene the residue was fractionated. From this distillation the following fractions were collected: 4.65 g. of material with boiling range 105-153.5° (3 mm.), 1.65 g. of material with boiling range 153.5-156 (3 mm.) and 1.1 g. in the range 156-165 (3 mm.). None of these fractions gave the desired ketone even though several attempts at crystallization were made.

EXPERIMENT #5

A Grignard reagent was prepared from 20 g. (0.08 mole) of o-bromodiphenylmethane, 2 g. (0.08 mole) of magnesium and a crystal of iodine in 100 ml. of dry ether. This reagent took fourteen hours for its preparation. The reagent was cooled down with an ice salt bath and 14.3 g. of anhydrous cadmium chloride was added in one batch. The Grignard cadmium chloride mixture was stirred and heated under reflux for about twenty minutes at the end of which time the Gilman test (50) was negative. The ether was distilled off until the residue was nearly dry and 25 ml. of dry benzene was added and most of this was distilled off. Then 80 ml. of dry benzene was added and the solution brought to a boil. Ten grams of acetyl chloride in about 50 ml. of anhydrous benzene was added to the boiling cadmium reagent over a period of about three minutes. Following this the solution was stirred and heated under reflux for about three hours and then finally decomposed and "worked up" in the same manner as reaction four. Nine g. of material had boiling range 105-155° (5.0 mm.), 1.8 g. 155-162° (5.0 mm.), and 1.7 g. 162-170 (5.0 mm.). Attempts at crystallization were not successful.

The Preparation of o-Benzylacetophenone (XXVIII) from o-Bromodiphenylmethane (XXIV).

A Grignard reagent was prepared from 18.087 g. of o-bromodiphenylmethane and 1.899 g. of magnesium in 80 ml. of dry ether. The reaction did not start immediately therefore a few drops of methyl iodide were added and the reaction started and went to completion in a short time (about an hour). The Grignard reagent was siphoned, using nitrogen pressure, into a long stemmed dropping funnel. On the long stem was attached a funnel in such a manner that the stem of the dropping funnel was cooled when dry ice and acetone were introduced into the funnel. The Grignard reagent, which was cooled by passing it through the cold stem of the dropping funnel, was added dropwise, with stirring, to a solution of 14.56 g. of acetic anhydride in 80 ml. of dry ether. The acetic anhydride solution was cooled with a dry ice and acetone bath throughout the addition of the Grignard reagent (took about 45 minutes) and for 2.5 hours after the reagent had all been added (the stirring was continued throughout the reaction). After this cooling period was over the dry-ice bath was removed and the reaction mixture was decomposed with 100 ml. of 20% ammonium chloride solution. The acid layer was separated and extracted several times with fresh ether. The combined ether layers were washed with water, then with 10% sodium hydroxide solution and finally with water again. After drying the ethereal solution over Drierite it was concentrated and the residue distilled at reduced pressure. There were two fractions obtained from this distillation, the first had the boiling point 122-125° (7-8 mm.) and the second 146-150.5° (3 mm.). The first fraction was diphenylmethane as was found from its boiling point and melting point; there was 6.65 g. of diphenylmethane in this fraction which would account for 54.7% of the starting material. The second fraction amounted to 4.65 g. (30.4%) of material which solidified and which after two recrystallizations from petroleum ether had the melting point 49-50°. (Lit. (36), b.p. 167° (5 mm.), m.p. 49-50°). This compound gave a positive iodoform test when run by the method of Fuson and Tullock (52).

Syntheses of 2-Benzyl-2'-chlorobenzophenone (L) from o-Bromodiphenylmethane (XXIV).

A Grignard reagent was prepared from 2.4 g. (0.1 mole) of magnesium, a crystal of iodine, and 24.8 g. (0.1 mole) of o-bromodiphenylmethane in 150 ml. of anhydrous ether. The reaction mixture was stirred and heated under reflux for nineteen hours. The Grignard reagent was siphoned with nitrogen pressure into a separatory funnel and added dropwise, with stirring to 17 g. (0.1 mole) of o-chlorobenzoyl chloride in 400 ml. of anhydrous benzene. The reaction mixture was then heated under reflux for three hours. Following this the mixture was decomposed with ice and ice-cold hydrochloric acid. The benzene layer was separated and the acid layer was extracted with fresh benzene. The combined benzene layers were washed with water, then with 10% sodium hydroxide, and finally with water. The benzene solution was dried over anhydrous calcium chloride and concentrated. The residue was fractionated twice under reduced pressure. The fraction boiling at 220-223° (2mm.) 206-208° (0.5 mm.) weighed 9.1 g. (33.3%). Attempts to crystallize from 95% ethanol were not successful. An analytical sample was taken at 207° (0.5 mm.).

<u>Anal</u>. Calc'd. for $C_{20}H_{15}OCl$: C,78.30; H,4.93

Found: C, 78.69; H, 4.92

The above compound (L) was also synthesized in the following manner:*

A Grignard reagent was prepared from 1.2 g. of magnesium, 12.35 g. of o-bromodiphenylmethane, and a crystal of iodine in 100 ml. of dry ether. This reagent was cooled with an ice-salt bath and 8.8 g. of anhydrous cadmium chloride (The hydrated cadmium chloride had been dehydrated by heating with a free flame in a large evaporating dish, had been kept overnight in a drying oven maintained at 103°, ground to a fine powder in a mortar and stored over anhydrous calcium chloride in a desiccator.) was added in one batch.

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* This preparation is in accordance with the procedure of Cason (38).

The Grignard-cadmium chloride mixture was stirred and heated under reflux for fifteen minutes at the end of which time the Gilman test (50) was negative. The ether was distilled off until the residue was nearly dry, and 25 ml. of dry benzene was added and most of this was distilled off. Then 100 ml. of benzene was added and the solution heated to boiling. 8.75 g. of o-chlorobenzoyl-chloride in about 50 ml. of benzene was added as fast as the refluxing from the exothermic reaction would allow. The refluxing was maintained for 15-20 minutes by application of external heat. The solution was then decomposed by addition of ice-cold hydrochloric acid. The benzene layer was separated and the acid layer was extracted with fresh benzene. The combined benzene layers were washed with 10% sodium hydroxide and then with water, and finally dried with Drierite. After distilling off the benzene the residue was fractionated. That portion which boiled at 206-207° (0.5 mm.) weighed 6.6 g. (43%).

Attempt to Cyclize 2-Benzyl-2'-chlorobenzophenone.

A solution of 0.432 g. of the above ketone (L) in 20 ml. of acetic acid and 5 ml. of 48% hydrobromic acid was heated under reflux for twenty-two hours. The reaction mixture was cooled slowly to room temperature and then to about 1°. The acid mixture did not yield any crystals. Following this 25 ml. of water were added and the solution was carefully neutralized with sodium carbonate and the organic material was extracted with ether. The ether extract was washed with water and finally dried over calcium chloride. The ether was driven off leaving a black oil. Attempts to crystallize this residue from ethanol were not successful.

Bondurant (40) made several other attempts at the cyclization of the above ketone but all were unsuccessful.

Attempted Preparation of Trichloromethyl-2-benzylphenyl ketone (XXVIII).

EXPERIMENT #1

A Grignard reagent was prepared from 2.5 g. of magnesium, 25 g. of o-bromodiphenylmethane and a crystal of iodine in 150 ml. of anhydrous ether. At first the magnesium did not appear to react therefore a few drops of methyl iodide were introduced and the reaction went to completion within an hour. The Grignard reagent was siphoned with nitrogen pressure into a separatory funnel and then added dropwise, with stirring, to 18.2 g. of trichloroacetyl chloride in 400 ml. of anhydrous benzene (an ice bath was used to cool the trichloroacetyl chloride solution, in the beginning, but when it was noticed there was no strong exothermic reaction taking place the bath was removed). The mixture was heated under reflux for two hours with the ether being distilled off at the same time; the solution was then heated under full reflux for an additional two hours. Following the above, the material was decomposed with ice and ice-cold hydrochloric acid. The acid layer was separated and extracted with fresh benzene. The benzene layers were combined and washed four times with water and then dried over Drierite. After distilling off the benzene the residue was fractionated under reduced pressure and the following fractions were collected: 95-100° (0.1 mm.), 100-116.5° (0.1 mm.) and 117-140° (0.1 mm.). Another distillation of the above fractions, which amounted to 1.2 g. for the first fraction, 4.9 g. for the second and 7.9 g. for the last, did not give any material with a sharp boiling point.

A mixture of 1.5 g. of the high boiling material was boiled with 50 ml. of four percent sodium hydroxide solution and was then cooled and extracted with ether. The sodium hydroxide layer was then neutralized with hydrochloric acid and extracted with ether. The ethereal extract was concentrated and revealed only a very small amount of oil but no crystalline material. It is therefore believed that there was very little, if any, of the desired ketone prepared by this experiment.

EXPERIMENT #2

A Grignard reagent was prepared from 1.2 g. of magnesium, 12.38 g. of o-bromodiphenylmethane and a crystal of iodine in 60 ml. of dry ether; this reagent took seven hours for its preparation. The reagent was cooled with an ice-salt bath and 8.8 g. of anhydrous cadmium chloride was introduced in one batch. The mixture was stirred and heated under reflux until the Gilman test (50) was negative (about 20 minutes). The ether was distilled off until the residue was nearly dry, and then 25 ml. of dry benzene was added and most of this was distilled off. Then 40 ml. of dry benzene was added and the solution heated to boiling. A solution of 9.09 g. of trichloroacetyl chloride in 50 ml. of anhydrous benzene was added to this boiling cadmium reagent, over a period of about two minutes, and the mixture was heated under reflux for 3.5 hours. The material in the reaction flask was then decomposed with cold 20% ammonium chloride solution and the acid layer was separated and extracted with fresh benzene. The benzene layers were combined and washed six times with water and finally dried over anhydrous calcium sulfate. After distilling off the benzene an attempt was made at fractionation of the residue. From this fractionation only one gram of material was obtained (besides some lower boiling material which proved to be diphenylmethane) and it was noticed that strong decomposition took place. This material had the boiling point 145°(3 mm.). A test for halogen on this material, by the sodium fusion method, was positive but an attempt at the preparation of the oxime was not successful.

EXPERIMENT #3

A Grignard reagent was prepared using the same amounts of material as in the reaction above and in a like manner, to the above experiment, this was converted to the cadmium reagent. In this experiment 70 ml. of benzene was added after all the ether had been removed and instead of adding 9.09 g. of acid chloride, 14.4 g. was added. The cadmium reagent-acid chloride mixture was heated under reflux for 18.75 hours and then decomposed with 20% ammonium chloride solution and "worked up" the same as in the previous reaction. There was no attempt to distill the material in this reaction, instead chromatography was resorted to. The chromatography column was wet packed with A-54½ Adsorption Alumina, 80-200 mm., and Celite Analytical Filter Aid and had the dimensions one inch in diameter by nine inches in length (very similar to the column shown in figure I of the thesis of H.H. Hannabass (49). Hexane proved to be the solvent which gave the best separation and was used in this work. A total of fourteen separate fractions were collected, the first twelve were with hexane as solvent, the next with ethyl alcohol and the last with acetone. After all the solvent was driven off these fractions, they were observed to see whether any crystalline material had formed; crystalline material was not present. Following this some of the earlier fractions were combined and were found to be mainly diphenylmethane upon distillation. The rest of the fractions were tested for halogen (those fractions with smaller amounts of material were combined with the next higher or lower fraction so as to have more material with which to work) by the sodium fusion method and those fractions which gave a positive test were treated as follows:*

> About 15 ml. of about five normal sodium hydroxide solution was added to each fraction and the materials were shaken vigorously (this was at room temperature) every few minutes until about 40 minutes had passed. Following this each fraction was extracted with ether. The sodium hydroxide solutions were neutralized with hydrochloric acid (one portion showed a fairly strong cloudiness at this point but no solid settled out) and cooled in an ice-salt bath. The neutral solution was then carefully extracted with ether. When the ether solutions were concentrated there was no crystalline material to be observed but only a very small amount of oil.

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* For conditions for conversion of 1,1,1-trichloroacetophenone to benzoic acid see reference (43).

EXPERIMENT #4*

A Grignard reagent was prepared from 28.3 g. of o-bromodiphenylmethane, 2.78 g. of magnesium and a crystal of iodine in 120 ml. of dry ether; this reagent took two hours to prepare. The ether was replaced by benzene and the reagent cooled with an ice-salt bath. To this cold Grignard reagent was added dropwise, with stirring, 16.55 g. of trichloroacetonitrile in 50 ml. of dry benzene (later more benzene was added). The first drop of nitrile turned black and before many more drops were added a black gummy precipitate was formed. The stirrer was able to keep going just long enough to allow all the nitrile to be added. The ice-bath was present throughout the addition of the nitrile but was eliminated when the stirrer stopped. The material was allowed to heat to room temperature and yet it was impossible to stir it. The reaction mixture was then subjected to decomposition with ammonium chloride, but this was not successful, therefore dilute hydrochloric acid was used and this was only slightly successful. The solid material was removed and the liquid that was left was "worked up" in the usual manner. The

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* In experiments #4 - #7 trichloroacetonitrile is used. This material was obtained by following the procedure of Bisschopinck (53) (distilling with a free flame, at atmospheric pressure, equal molar quantities of phosphorus pentaoxide and trichloroacetamide) in 61% yield. The procedure of Steinkopf (54) was used to eliminate any hydrogen chloride that might have been present (shaking of the material with calcined potassium carbonate).

solid material was insoluble in boiling hydrochloric acid as well as in alcohol, benzene and acetone. From the liquid portion only a small amount of material, which is believed to be diphenylmethane, was obtained.

EXPERIMENT #5

A Grignard reagent was prepared from 19.2 g. of o-bromodiphenylmethane, 1.9 g. of magnesium and a crystal of iodine in 120 ml. of dry ether; the reagent took eight hours to prepare. The Grignard reagent was cooled with an ice-salt bath and 7.4 g. of cadmium chloride was added in one batch. The Gilman test was negative at the end of 15 minutes of refluxing. To this cadmium reagent was added 100 ml. of ether and the reagent was cooled again in an ice-salt bath. A mixture of 10.0 g. of trichloroacetonitrile in 100 ml. of ether was then added, slowly at first and later rather rapidly, for no strong exothermic reaction took place. The reactants were then heated under reflux for three hours and finally decomposed, after first cooling, with dilute hydrochloric acid. The acid layer was separated and extracted with fresh ether. The ether layers were combined, washed three times with water, and finally dried over Drierite. After distilling off the ether the residue was chromatographed in the same manner as in experiment #3. From this experiment a large amount of diphenylmethane was obtained (the equivalent of more than half of the starting material) along with less than 0.175 g. of crystalline material and 2.7 g. of some gummy material. Also obtained was some black material very similar in nature to the material obtained in experiment #4. The crystalline material gave a weak halogen test but was insoluble in strong sodium hydroxide solution (did not dissolve even after standing in the base for several days). The 2.7 g. of somewhat gummy material and the material that was obtained by washing the column with acetone were subjected to the sodium hydroxide treatment described in experiment #3 and no acid (LI) was obtained.

EXPERIMENT #6

A Grignard reagent was prepared from 16.7 g. of o-bromodiphenylmethane, 1.66 g. of magnesium and a crystal of iodine in 70 ml. of dry ether. This reagent was cooled with an ice-bath and 6.65 g. of anhydrous cadmium chloride was added in one batch. The Grignard-cadmium chloride mixture was heated under reflux for about twenty minutes and the Gilman test was applied and proved negative. The ether was distilled off until the material in the flask was almost dry and then 20 ml. of dry benzene was added and most of this was distilled off. Following this 70 ml. of dry benzene was added and the material was cooled with an ice-salt bath. To this cold reagent was added 8.3 g. of trichloroacetonitrile in 40 ml. of benzene and the mixture was then heated under reflux for 3.5 hours. After this reflux period the material was decomposed with very dilute hydrochloric acid (the acid-complex mix was heated for a short while to insure the decomposition). The acid layer was separated and extracted several times with benzene. The benzene layers were combined and washed three times with water. The benzene was next distilled off and the residue chromatographed through a column similar to that explained in experiment #3; petroleum ether was used as solvent, for hexane was not available at the time. Much material, which did not give a positive test for halogen, was obtained (8.8 g.) along with 0.37 g. of crystalline material and about 0.5 g. of yellow oil. The oil and crystalline material as well as the column wash (the material that was washed from the column with alcohol and acetone) were subjected to the strong base treatment explained in experiment #3, but did not yield any of the acid. Some black material similar to that explained in experiment #4 was also obtained.

EXPERIMENT #7

A Grignard reagent was prepared from 15.7 g. of o-bromodiphenylmethane and 1.55 g. of magnesium in 100 ml. of dry ether. A few drops of methyliodide were added and the reaction started and went to completion quickly. This Grignard reagent was converted to the cadmium reagent and the ether was distilled off and replaced by 110 ml. of dry benzene. This benzene mixture was kept at room temperature and 11.9 g. trichloroacetonitrile in 20 ml. of dry benzene was introduced all at once. The reaction mixture was stirred and heated under reflux for fourteen hours (it had a very dark brown color at the end of this time). The complex, after first cooling, was decomposed with cold, one-normal, sulfuric acid. After separating the acid layer and extracting it with benzene, the benzene layers were combined and washed several times with water. The benzene was distilled off and the residue was fractionated at reduced pressure. Several fractions were collected, the first was diphenylmethane, the second was a reddish material which had the boiling range 127-145 (1.0 mm.) and the last was solid material which was obtained (in small yield) by heating the still column. None of these fractions gave any o-benzylbenzoic acid (LI) when treated with strong base (in the same manner as is explained in experiment #3; the solid material when it was treated with the base was heated a little, but it did not dissolve). Some black material was also obtained in this experiment that had properties similar to those explained for the material obtained in experiment #4.

Preparation of 2-Bromo-5-chlorodiphenylmethane (XXXV).

2-Bromo-5-chlorobenzoic acid XXXII (45). A mixture of 90 g. of cupric sulfate pentahydrate, 75 g. of sodium bromide, 50 g. of fine copper turnings and 400 ml. of 48% hydrobromic acid was heated under strong reflux for three hours. This hot solution was filtered through glass wool into a boiling solution of 150 g. of 2-amino-5-chlorobenzoic acid (XXXI), 600 ml. of 48% hydrobromic acid and 5000 ml. of water (the solution was stirred continuously during this addition and was kept boiling until the addition of the sodium nitrite solution). A solution of 150 g. of sodium nitrite in 700 ml. of water was added dropwise, with stirring, to the hot acid solution and heat was applied spasmodically to keep the temperature of the solution high. After addition of the sodium nitrite solution, the reaction mixture was cooled to room temperature while being stirred. Following this the mixture was cooled in an ice-salt bath and then the acid filtered off. The solid was recrystallized from water using a little charcoal. The crystals were finally dried in a vacuum desiccator, m. p. 148-149° (Lit. 45), 148-149°; 153°); yield 155 g. (75.24%).

2-Bromo-5-chlorobenzoyl chloride XXXIII (46). A mixture of 20.3 g. of 2-bromo-5-chlorobenzoic acid and 18.5 g. of phosphorus pentachloride was heated under reflux, using an oil bath which was kept between 130° and 140°, for a half hour. The lower boiling material was distilled off under slightly reduced pressure and the residue was then fractionated. That fraction which boiled at 146.5-149.5°(22.3 mm.) (Lit. (46), 146-147°(23 mm.) m.p. 34-35°) weighed 19.9 g. (90.9%) and had m.p. 34-35°.

2-Bromo-5-chlorobenzophenone XXXIV. This compound has not been reported in the literature, therefore the same procedure was used for its preparation as was used for the preparation of o-bromobenzophenone (XXIII). A mixture of 25.3 g. of aluminum chloride and 180 ml. of benzene was cooled in an ice bath and stirred. A few drops of a solution of 38.5 g. of 2-bromo-5-chlorobenzoyl chloride (XXXIII) in about $\overset{70}{10}$ ml. of benzene was added immediately to prevent the benzene from freezing and then the remainder was added dropwise. The mixture was stirred overnight and allowed to warm to room temperature. The reaction mixture was heated under reflux for three hours, then cooled in an ice bath and decomposed with ice and about 120 ml. of concentrated hydrochloric acid. The acid layer was separated and extracted with fresh benzene. The benzene layers were combined, washed with water, then with sodium carbonate solution, and again with water. The benzene solution was concentrated and then fractionated under reduced pressure. The fraction boiling at 172-173°(1 mm.) later solidified and had the melting point 100.5-102°; this fraction weighed 42.3 g. (92.8%). The material was recrystallized from ethanol.

Anal. Calcd. for $C_{13}H_8OClBr$: C, 52.82; H, 2.73

Found: C, 52.66; H, 2.80.

2-Bromo-5-chloro-diphenylmethane *XXXV*. This compound has not been reported in the literature therefore the same method was tried as was used to prepare o-bromodiphenylmethane (XXIV); the procedure gave only a very poor yield therefore it was modified as follows: A mixture of 33 g. of 2-bromo-5-chlorobenzophenone (XXXIV), 33 g. of red phosphorus and 33 ml. of that fraction of 48% hydriodic acid which boiled above 122° (715 mm.), was stirred and heated under strong reflux for 44 hours. The reaction flask was cooled to room temperature and about 50 ml. of distilled water was added. The red phosphorus was filtered off using suction, and was washed with ether. The acidic solution was then neutralized with 10% sodium hydroxide and then extracted with ether. The ethereal solutions were combined, washed with water several times and dried over anhydrous calcium sulfate. After distilling off the ether the residue was fractionated. That fraction which boiled at 168-170° (3.5 mm.) weighed 22.6 g. (72%). (At one mm. pressure the boiling point is 158-158.5°).

Anal. Calcd. for $C_{13}H_{10}ClBr$: C, 55.446; H, 3.58

Found: C, 55.30; H, 3.71.

Preparation of 2-Bromo-5-chloro-3'-chlorodiphenylmethane (XLIII).

2-Bromo-5-chloro-3'-chlorobenzophenone XLII. This compound has not been reported in the literature. The method that was used for its preparation is similar to that used by Van Oot (55) for the preparation of one of his halogen substituted benzophenones. A Grignard reagent was prepared from 60.32 g. of m-chlorobromobenzene, 7.65 g. of magnesium and a crystal of iodine in about 200 ml. of ether. The reaction was complete in about an hour but was let run an additional hour at which time the solution was cooled with an ice bath. Cadmium chloride, 28.9 g., which had previously been treated as described below was added in one batch (the hydrated cadmium chloride had been dehydrated by heating with a free flame in a large evaporating dish, had been kept overnight in a drying oven maintained at about 103°, ground to a fine powder in a mortar and stored over calcium chloride in a desiccator). Within 20 minutes the solution had darkened and the Gilman test (50) proved negative at the end of this time. The ether was distilled off to almost dryness and then 50 ml. of anhydrous benzene was added and most of this was distilled off. Then 150 ml. of dry benzene was added and the solution was heated to boiling. To this boiling solution was added 65.5 g. of 2-bromo-5-chlorobenzoyl chloride (XXXIII) just as quickly as the refluxing would allow (2-3 min.). Following this external heat was applied for 40 minutes at the end of which time the solution was decomposed by pouring it on ice mixed with dilute sulfuric acid. The benzene layer was separated and the acid layer was extracted twice with fresh benzene. The acid layer was then made just basic with sodium hydroxide solution and was extracted with ether. The benzene extractions were combined and washed with water, dilute sodium hydroxide solution and finally with water again. The ether extraction was washed with water and combined with the benzene solution. The combined solution was dried over Drierite and then concentrated. The residue was fractionated and that fraction which boiled between 203-206.5° (3 mm.) or 178-183°(0.5-1.0 mm.) weighed 57.4 g. (72.6%). This material solidified and was recrystallized from ethanol, m. p. 75-75.5°.

? O Anal. Calcd. for $C_{13}H_9Cl_2Br$: C, 47.31; H, 2.14

Found: C, 47.30; H, 2.27

2-Bromo-5-chloro-3'-chlorodiphenylmethane XLIII. A mixture of 70 g. of the above ketone, 70 g. of red phosphorus and 75 ml. of that fraction of 48% hydriodic acid which boiled above 122° (715 mm.), was stirred and heated under strong reflux for 40 hours. The reaction mixture was cooled with an ice bath, about 60 ml. of distilled water was added and the red phosphorus was filtered off using suction; the red phosphorus was then washed with ether. The acid mixture was made just basic with cold 15% sodium carbonate solution and extracted with ether. The ether solutions were combined and washed with 10% sodium hydroxide solution which was followed by several washings with water. The ethereal solution was dried over Drierite and the ether was distilled off. The residue was fractionated at reduced pressure. That fraction which boiled at 180.5 - 182.5° (2.0 mm.) weighed 45.25 g. (67.7%). An analytical sample was taken at 166° (0.5 mm.).

Anal. Calcd. for $C_{13}H_9Cl_2Br$: C, 49.40; H, 2.87

Found: C, 49.62; H, 2.91

Attempted Preparation of 2-Benzyl-4-chlorobenzonitrile (XXXVIII)

EXPERIMENT #1

A mixture of 22.6 g. (0.08 mole) of 2-bromo-5-chlorodiphenylmethane, 7.2 g. (0.08 mole) of cuprous cyanide and a small crystal of anhydrous cupric sulfate was placed in a 100 ml. flask with 18 ml. of anhydrous pyridine. The mixture was stirred and heated for 24 hours at a bath temperature of 235-245°; the pyridine was permitted to evaporate off gradually during this period through an air condenser which was attached to the reaction flask. Following this the material was subjected to a crude distillation by use of a von Braun distilling apparatus; this was run at 2.0 mm. pressure. The material, which was a solid at this time, was dissolved in ether and then washed with dilute ammonium hydroxide. After extracting the ammonium hydroxide layer with fresh ether, the ether solutions were combined, washed with two normal hydrochloric acid, then with water and finally dried over Drierite. The ether was distilled off and the residue was fractionated. From this fractionation 6.1 g. of material was obtained which had the boiling range 95-148° (1.0 mm.). The distilling flask, after the von Braun distillation, contained 20.1 g. of coal-like material. The experiment was discontinued because the material that was obtained was a mixture (the liquid solidified and had a wide melting point range) and because it appeared more feasible to try another reaction at a lower temperature.

EXPERIMENT #2

This experiment was run in approximately the same manner as the reaction above; the only differences were that in this case slightly larger amounts of material were used (but the molar ratio was not changed), the bath was kept at 195-205° instead of 235-245°, and a benzene-ether solvent (one to one volume ratio) was used for the extractions instead of ether. Upon distillation the following fractions were collected: 143-149°, 149-153°, 153-157°, 157-164°, 164-170° and 170-173° (all were at about 1.0 mm. pressure). The first fraction gave a few crystals after standing a week, the second gave some crystals after standing a few hours and the third crystallized out immediately upon cooling. All these crystals had the melting point 65-67° and the total yield was 6.15 g. Upon recrystallization of fraction three, which amounted to 3.65 g., from petroleum ether some crystals appeared which had melting point 72-75°; the mother liquor gave some crystals with melting point 67-69°. Fraction four also crystallized out immediately upon cooling and this fraction, which weighed 6.9 g., gave material with melting point 72-74° upon recrystallization from ethanol; after two more recrystallizations from ethanol the melting point rose to 75-77°. Upon recrystallization of a portion of fraction four from petroleum ether, crystals formed which had melting point 77-78.5° and that portion which refused to dissolve in the petroleum ether had melting point 82.5-85°. The mother liquor from these recrystallizations gave crystals with melting point 70-71°. Fraction five consisted of crystalline material as did fraction six. These fractions had wide melting point ranges (80-95°). It is definite, from what is said above as well as what is said in the following experiment, that this procedure gives a mixture of materials and therefore is probably of little synthetic value.

EXPERIMENT #3

A mixture of 10 g. of 2-bromo-5-chlorodiphenylmethane (0.035 mole), 3.18 g. (0.035) of cuprous cyanide and a very small pinch of anhydrous cupric sulfate were placed in a 100 ml. flask along with 30 ml. of anhydrous pyridine. This mixture was heated under full reflux for 48 hours. At the end of this period the mixture was cooled and filtered. The pyridine solution was then washed with dilute ammonium hydroxide (one part concentrated to five parts water). The combined ammonium hydroxide-pyridine solution was extracted with a benzene-ether (one to one volume ratio) solvent. The benzene-ether solution was washed with water, then with two normal hydrochloric acid, and finally with water again. After drying the solution over Drierite the solvent was distilled off and the residue crystallized. This crystalline material was recrystallized from ethanol with the use of a small amount of charcoal, and had the melting point 73-75°; upon repeated recrystallizations the melting point kept on rising, the last melting point was 83-85°.

Preparation of 1,4-Dicyanodiphenylmethane (LII).

A mixture of 10 g. (0.035 mole) of 2-bromo-5-chlorodiphenylmethane, 7 g. (2 X .035 + .64 g.) of cuprous cyanide, a very small pinch of anhydrous cupric sulfate and 10 ml. of anhydrous pyridine were placed in a 50 ml. round bottom flask which was equipped with an air condenser. The pyridine was allowed to evaporate slowly by gradually raising the temperature of the bath in which the reaction flask was placed. The bath was maintained at 220-225° for 48 hours after the pyridine was removed. At the end of the two day period the reaction flask was cooled and the air condenser was replaced by a von Braun distilling head. The reaction mixture was crudely distilled at 2.0 mm. pressure and the distilled material subjected to extraction with a benzene-ether solvent. The benzene-ether solution was washed with dilute ammonium hydroxide, then with water, then with 2.0 normal hydrochloric acid and finally with water again. After drying the solution over Drierite the solvent was distilled off and the residue crystallized. This crystalline material weighed 3.3 g. (42.6%) after one recrystallization from ethanol and had the melting point 119-120.5° (this melting point did not change upon repeated recrystallization).

Anal. Calcd.: C, 82.54; H, 4.62
Found: C, 82.51 ; H, 4.70
82.77; 4.48

SUMMARY

A literature review has been made concerning the structural relationship of DDT to its insecticidal activity.

Three reaction paths (Charts II, III and IV) have been shown for the preparation of the following three compounds which are of interest because they are structurally related to DDT: 9-trichloromethylanthracene, 3-chloro-9-trichloromethylanthracene and 2,7-dichloro-10-trichloromethylanthracene. The reactions shown in these outlines were carried through to the preparation of the following compounds:

Path 1 (Chart II) o-benzylacetophenone (XXVIII) and to the attempted, but unsuccessful, preparation of trichloromethyl-2-benzylphenyl ketone (XXIX).

Path 2 (Chart III) 2-bromo-5-chlorodiphenylmethane (XXXV) and to the attempted preparation of 2-benzyl-4-chlorobenzonitrile (XXXVIII) (explained further below).

Path 3 (Chart IV) 2-bromo-5-chloro-3'-chlorodiphenylmethane (XLIII).

The preparation of o-benzylacetophenone was accomplished by using the appropriate Grignard reagent and following the procedure of Newman and Booth. This method, which had not been used previously for the preparation of this compound, opens another line of attack for the preparation of the trichloromethyl ketones

from which the anthracenes might be prepared. Two other methods were studied for the preparation of this compound, they were the reaction of (1) the appropriate Grignard reagent and (2) the appropriate cadmium reagent with acetyl chloride, but both proved to be valueless.

A series of experiments have been shown whereby the conversion of 2-bromo-5-chlorodiphenylmethane to 2-cyano-5-chlorodiphenylmethane has been attempted. The study of this conversion was not completed but it does appear that it would probably be of little synthetic value because of the mixture of compounds obtained.

The synthesis of 2-benzyl-2'-chlorobenzophenone, which is of interest in the study of aromatic cyclodehydration and which has not previously been reported in the literature, has been accomplished by two different methods.

Two new benzophenones, 2-bromo-5-chlorobenzophenone and 2-bromo-5-chloro-3'-chlorobenzophenone, and two new diphenylmethanes, 2-bromo-5-chlorodiphenylmethane and 2-bromo-5-chloro-3'-chlorodiphenylmethane, as well as a new dicyano compound, 1,4-dicyanodiphenylmethane, have been synthesized and some of their physical properties reported.

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