SYNTHESES OF 2(3,4)- HYDROXY- (AND METHOXY)-2'(3',4')- CHLORO-STILBENES AND-BIBENZYLS

Thesis for the Degree of Ph. D.

MICHIGAN STATE COLLEGE

Robert Joseph Hathaway

1951

This is to certify that the

thesis entitled

''Syntheses of 2(3,4)-Hydroxy-(and Methoxy)-
2'(3',4')-chloro-stilbenes and-bibenzyls''

presented by

Robert J. Hathaway

has been accepted towards fulfillment
of the requirements for

Ph.D. degree in Chemistry

Gordon L Goerner
Major professor

Date May 16, 1951

O-169

[redacted]

SYNTHESES OF 2(3,4)-HYDROXY-(AND METHOXY)-2'(3',4')-CHLORO-STILBENES AND -BIBENZYLS

BY

ROBERT JOSEPH HATHAWAY

A THESIS

Submitted to the School of Graduate Studies of Michigan State College of Agriculture and Applied Science in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

Department of Chemistry

1951

ACKNOWLEDGEMENT

The author wishes to express his gratitude to his major professor, Doctor Gordon LaVerne Goerner, for constant guidance and assistance. Grateful acknowledgement is due his instructors for valuable teachings and suggestions, particularly Dean Ralph Chase Huston. The writer also deeply appreciates the financial support of the Graduate Council Fellowship provided by Michigan State College during his last year of graduate study.

SYNTHESES OF 2 (3,4)-HYDROXY-(AND METHOXY)-2' (3',4')-CHLORO-STILBENES AND -BIBENZYLS

BY

ROBERT JOSEPH HATHAWAY

AN ABSTRACT

Submitted to the School of Graduate Studies of Michigan State College of Agriculture and Applied Science in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

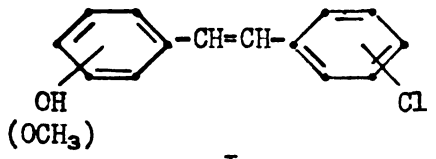
Department of Chemistry

Year 1951

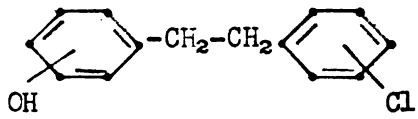
Approved Gordon L Goerner

ABSTRACT

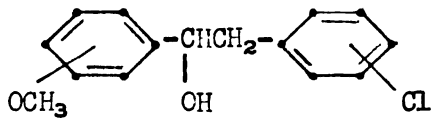
The syntheses of the isomeric hydroxy- and methoxychlorostilbenes (I) and the corresponding hydroxybibenzyls (II) have been investigated. Incidental to their preparation, the methoxyphenylchlorobenzyl carbinols (III) have also been prepared. Thirty-six compounds, excluding derivatives, have been synthesized and the majority submitted for pharmacological testing. Six of these compounds have been reported in the literature.



I.



II.



III.

The method of attack which appeared most suitable was to prepare substituted stilbenes of type I and reduce them catalytically to bibenzyls of type II, as there were several examples reported in the literature for the reduction of chlorostilbenes to chlorobibenzyls (1).

Among the methods of synthesis investigated for the preparation of the stilbenes were (a) the Meerwein reaction; (b) conversion of mixed benzoins into the stilbenes by simultaneous reduction-dehydration; and (c) the Grignard reaction. Of these methods, the latter proved to be the most satisfactory for general use.

The Meerwein reaction (2) appeared most promising inasmuch as 4-hydroxy-4'-chlorostilbene was reportedly obtained in 56% yield by Meerwein et. al. (2). However, the yields of this same compound in the present investigation were considerably lower and averaged 22%. The application of this reaction for the preparation of three other isomers proved unsatisfactory and its use was abandoned.

A second method was the attempted conversion of mixed benzoins (3) by simultaneous reduction-dehydration using zinc and hydrochloric acid, into the stilbenes (4). The yields in the latter step were so low that the method was abandoned.

The Grignard reaction (5) between the methoxybenzaldehydes and chlorobenzylmagnesium chlorides gave the corresponding methoxyphenylchlorobenzyl carbinols (III) in good yield. It was found possible to dehydrate these carbinols to the methoxystilbenes (I), but the conversion of the latter to the hydroxystilbenes proved difficult at first; normally used methods gave low yields of the desired product. However, after finding the excellent demethylation procedure of Buu-Hoi and Hoan (6) using pyridine hydrochloride at about 200°, not only was it possible to demethylate the methoxystilbenes in good yield, but also to demethylate and dehydrate the carbinols in one step to give the hydroxystilbenes.

Reduction of the stilbenes to the bibenzyls proceeded rather difficultly. Either W-2 Raney nickel (7) or copper chromium oxide gave in the neighborhood of 50% yields when used at 50-70° with hydrogen pressures of 1000-1500 p.s.i.

The p-chlorobenzoyl derivatives of the bibenzyls were prepared using p-chlorobenzoyl chloride. The interconversion between methoxy- and

hydroxystilbenes, and the ready dehydration of the carbinols to either of the above two types of compounds, made it unnecessary to prepare derivatives of these compounds.

All the compounds were analyzed for chloride as follows. The compounds were fused with sodium peroxide, the chloride precipitated with excess standard silver nitrate solution, and the excess silver titrated with standard thiocyanate solution.

REFERENCES

1. F. Bergmann, J. Weizman, and D. Schapiro, J. Org. Chem., 9, 408 (1944).

2. H. Meerwein, E. Buchner, and K. Van Enster, J. Prakt. Chem., 152, 258 (1939)

3. J. S. Buck and W. S. Ide, J. Am. Chem. Soc., 52, 4107 (1930).

4. J. Finkelstein and S. M. Linder, J. Am. Chem. Soc., 71, 1013 (1949).

5. S. S. Jenkins and E. M. Richardson, J. Am. Chem. Soc., 55, 3874 (1933).

6. Ng. Ph. Buu-Hoï and Ng. Hoán, J. Org. Chem., 14, 1032 (1949).

7. R. Mozingo, Org. Syntheses, 21, 15 (1941).

CONTENTS

INTRODUCTION AND HISTORICAL..... 1

FIGURES..... 5

1. General Formulas of Carbinols, Stilbenes, and Bibenzyls.... 5
2. Meerwein Reaction..... 5
3. Benzoin Condensation and Conversion to Stilbene..... 6
4. Grignard Preparation of Methoxychlorostilbene..... 6
5. Dehydration, Methylation, and Demethylation Reactions..... 7
6. Hydrogenation of Hydroxychlorostilbenes to Bibenzyls..... 7

DISCUSSION..... 8

I. General Discussion of Stilbenes and Bibenzyls..... 8

A. Structure and Properties..... 8
B. Chemotherapeutic Value..... 9
C. Absorption Spectra..... 9

II. Carbinols by the Grignard Reaction..... 10

A. Preparation..... 10
B. Crystallization..... 12
C. Dehydration..... 14

III. Methoxychlorostilbenes..... 18

A. General..... 18
B. Preparation..... 19

IV. Hydroxychlorostilbenes..... 22

A. General..... 22
B. Preparation..... 22

1. Demethylation-dehydration by Pyridine Hydrochloride 22
2. Demethylation of Methoxystilbenes..... 23
3. Meerwein Reaction..... 23
4. Demethoxymethylation..... 23

V. Hydroxychlorobibenzyls..... 25

A. General..... 25
B. Hydrogenation of Stilbenes..... 25
C. Derivatives..... 26

CONCLUSIONS 27

EXPERIMENTAL (General Information and Chemicals)..... 28

I. Intermediates 30

A. m-Chlorobenzyl Chloride..... 30
B. Purification of p-Hydroxybenzaldehyde..... 31
C. p-Hydroxycinnamic Acid..... 32
D. p-Methoxycinnamic Acid..... 33
E. m-Hydroxybenzaldehyde..... 34
F. m-Hydroxycinnamic Acid..... 35
G. m-Methoxybenzaldehyde..... 36
H. o-Methoxybenzaldehyde..... 36
I. Chloromethyl Ether..... 38
J. p-Methoxymethoxybenzaldehyde..... 38
K. 4-Methoxy-2'-chlorobenzoin..... 39

II. Carbinols by the Grignard Reaction..... 41

A. 4-Methoxyphenyl-2'-chlorobenzyl Carbinol..... 41
B. 4-Methoxyphenyl-3'-chlorobenzyl Carbinol..... 43
C. 4-Methoxyphenyl-4'-chlorobenzyl Carbinol..... 44
D. 3-Methoxyphenyl-2'-chlorobenzyl Carbinol..... 45
E. 3-Methoxyphenyl-3'-chlorobenzyl Carbinol..... 46
F. 3-Methoxyphenyl-4'-chlorobenzyl Carbinol..... 46
G. 2-Methoxyphenyl-2'-chlorobenzyl Carbinol..... 47
H. 2-Methoxyphenyl-3'-chlorobenzyl Carbinol..... 48
I. 2-Methoxyphenyl-4'-chlorobenzyl Carbinol..... 49
J. 4-Methoxymethoxyphenyl-2'-chlorobenzyl Carbinol..... 49

III. Methoxychlorostilbenes..... 51

A. 4-Methoxy-2'-chlorostilbene..... 51

1. Methylation of the Hydroxystilbene..... 51
2. Dehydration of the Carbinol..... 52
3. Reduction of the Benzoin..... 53

B. 4-Methoxy-3'-chlorostilbene..... 55
C. 4-Methoxy-4'-chlorostilbene..... 55

1. Meerwein Reaction..... 55
2. Methylation of the Hydroxystilbene..... 57

D. 3-Methoxy-2'-chlorostilbene..... 57
E. 3-Methoxy-3'-chlorostilbene..... 58
F. 3-Methoxy-4'-chlorostilbene..... 58
G. 2-Methoxy-2'-chlorostilbene..... 59
H. 2-Methoxy-3'-chlorostilbene..... 60
I. 2-Methoxy-4'-chlorostilbene..... 60

IV. Hydroxychlorostilbenes..... 61

A. 4-Hydroxy-2'-chlorostilbene..... 61

1. Demethylation-dehydration of the Carbinol..... 61
2. Cleavage of the methoxymethoxy ether..... 62
3. Meerwein Reaction..... 63
4. Demethylation of the Methoxystilbene..... 63

B. 4-Hydroxy-3'-chlorostilbene..... 64
C. 4-Hydroxy-4'-chlorostilbene..... 64
D. 3-Hydroxy-2'-chlorostilbene..... 65
E. 3-Hydroxy-3'-chlorostilbene..... 65
F. 3-Hydroxy-4'-chlorostilbene..... 66
G. 2-Hydroxy-2'-chlorostilbene..... 67
H. 2-Hydroxy-3'-chlorostilbene..... 67
I. 2-Hydroxy-4'-chlorostilbene..... 67

V. Hydroxychlorobibenzyls and Derivatives..... 68

A. 4-Hydroxy-2'-chlorobibenzyl..... 68

1. Hydrogenation of the Hydroxystilbene..... 68
2. Preparation of the p-Chlorobenzoate Derivative... 68

B. 4-Hydroxy-3'-chlorobibenzyl..... 69
C. 4-Hydroxy-4'-chlorobibenzyl..... 69
D. 3-Hydroxy-2'-chlorobibenzyl..... 70
E. 3-Hydroxy-3'-chlorobibenzyl..... 70
F. 3-Hydroxy-4'-chlorobibenzyl..... 70
G. 2-Hydroxy-2'-chlorobibenzyl..... 71
H. 2-Hydroxy-3'-chlorobibenzyl..... 71
I. 2-Hydroxy-4'-chlorobibenzyl..... 71

VI. Chloride Analysis..... 73

TABLES

I. Dehydration of Methoxyphenylchlorobenzyl Carbinols..... 17a
II. Methoxyphenylchlorobenzyl Carbinols..... 76
III. Methoxychlorostilbenes..... 77
IV. Hydroxychlorostilbenes..... 78
V. Hydroxychlorobibenzyls..... 79
VI. p-Chlorobenzoate Derivatives..... 80

REFERENCES..... 81

INTRODUCTION AND HISTORICAL

During the past several years at Michigan State College, a number of substituted diphenyl methanes have been prepared and submitted to pharmaceutical testing. The purpose of this investigation was to extend this series of compounds to the isomeric hydroxy-(and methoxy)-chloro'-stilbenes and -bibenzyls (See Figure 1) which have been synthesized and submitted to Eli Lilly and Company for testing against tuberculosis.

Several examples have been reported in the literature (8) for the reduction of chlorostilbenes to chlorobibenzyls, (Figure 6), consequently the method of attack which appeared most suitable in this work was to prepare the necessary series of substituted stilbenes and then reduce them to the corresponding bibenzyls. The availability of intermediate reagents was an important factor in the choice of methods of synthesis which were used in this laboratory.

At the outset, the Meerwein reaction (1), (2), (3), appeared most promising inasmuch as 4-hydroxy-4'-chlorostilbene was reportedly (1) obtained in 56% yield (Figure 2). However, for this same compound the yields in the present investigation were considerably lower and averaged 22%. Moreover, the application of this reaction for the preparation of most other isomers proved much less satisfactory.

A second method involved the conversion to stilbenes of mixed benzoins, prepared according to the procedure of Buck and Ide (4), by simultaneous reduction-dehydration (Figure 3), as has been done by Finkelstein and Linder (5) and Ballard and Dehn (10). The yields in the latter step were so low that the method was abandoned.

The Grignard reaction (Figure 4) between the methoxybenzaldehydes and chlorobenzylmagnesium chlorides, which has previously been used for the preparation of substituted stilbenes by Jenkins and Richardson (6), Hell and Hofmann (7), Bergmann and co-workers (8), and Orekhoff (20), was shown to give the corresponding methoxyphenylchlorobenzyl carbinols in good yield. It was found possible to dehydrate these carbinols to the methoxystilbenes (Figure 5), in a variety of ways, including distillation (7), heating with acetic acid and hydrochloric acid (6), and boiling with acetyl chloride and hydrogen chloride in acetic acid. Bergmann and co-workers (8) have dehydrated 2-chlorophenylbenzyl carbinol in 80% yield by treating the carbinol with acetic anhydride to form the acetate and then heating the acetate to 300°.

Conversion of the methoxystilbenes to the hydroxystilbenes was not practically achieved until the excellent demethylation procedure of Buu-Hoi and Hoan (9), utilizing pyridine hydrochloride (Figure 5), became available. Not only was it possible to obtain the hydroxystilbenes from the methoxystilbenes, but it was possible to demethylate and dehydrate the carbinols directly to the hydroxystilbenes in one step. Bergmann and Schapiro (2) failed to demethylate the methoxystilbenes by boiling with 48% hydrobromic acid. This was also found to be the case in this laboratory.

Reduction of the stilbenes to the bibenzyls (Figure 6) was accomplished through the use of Raney nickel at pressures varying from 75 to 100 atmospheres initial hydrogen pressure and temperatures ranging from 50 to 75°. Bergmann and co-workers (8) reduced m- and p-chlorostilbenes to the corresponding chlorobibenzyls with Raney nickel at 16° and 762 mm. mercury. Altogether thirty-six compounds were prepared, six of which are reported in the literature.

The carbinols were characterized both by dehydration to the corresponding methoxystilbenes, which are solids in most cases, and by demethylation-dehydration with pyridine hydrochloride to the hydroxystilbenes which were all crystalline compounds. Similarly, the methoxystilbenes were easily demethylated to the hydroxystilbenes for characterization. The hydroxystilbenes were methylated to the methoxystilbenes in six cases. The hydroxystilbenes were all hydrogenated to the hydroxybibenzyls, which were crystallizable except in three cases. In the single case where neither hydrogenation nor methylation gave a solid compound, the chlorobenzoate derivative of the hydroxystilbene was prepared. The nine hydroxybibenzyls were also characterized by preparation of the chlorobenzoates which were all easily crystallizable substances.

Substituted stilbenes have most generally been prepared in other laboratories by variations of the Perkin reaction; the carboxylic acid intermediates which were obtained were decarboxylated by various means to give the stilbenes. The overall yields appear in most cases to parallel the yields obtained with the Grignard method in the present work.

Benzaldehydes, substituted with methoxy, hydroxy, methyl, or nitro groups, have been condensed with nitrophenyl acetic acid in the presence of pyridine or piperidine at elevated temperatures by Kauffman (12) and Cullinane (13), yielding substituted nitrostilbenes in a single step.

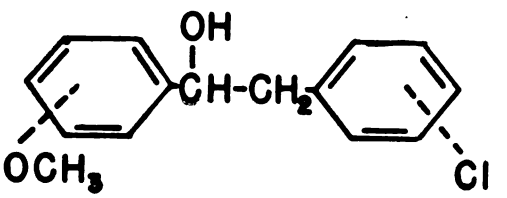
Instead of pyridine or piperidine, acetic anhydride has been used with the sodium salt of the substituted phenylacetic acid by Pschorr (21), Werner (22), Bergmann and Schapiro (2), Zincke and Geibel (23), Funk and Kostanecki (24), and Lewis et al. (25), all of whom first obtained the carboxylic acid intermediate which they decarboxylated by various means.

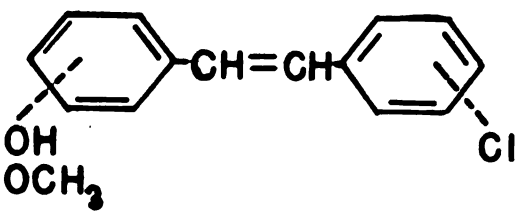
Substituted benzaldehydes were condensed with dinitrotoluene in a modification of the Perkin reaction by Cullinane (13), Pfeiffer (11, 14), Thiele (15) and Sachs and Hilpert (16), in yields as high as 90% (15). A much lower yield using a substituted mono-nitrotoluene was claimed by Chardonnens and Heinrich (17).

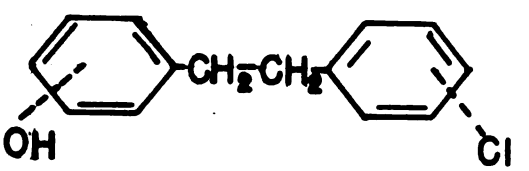
Anschutz (18) and von Auwers (19) found that aryl esters of cinnamic acids when heated underwent decomposition with loss of carbon dioxide to give stilbenes.

Substituted stilbene carboxylates were obtained by Fuson and Cooke (3) in yields of around 20% by means of the Reformatsky reaction.

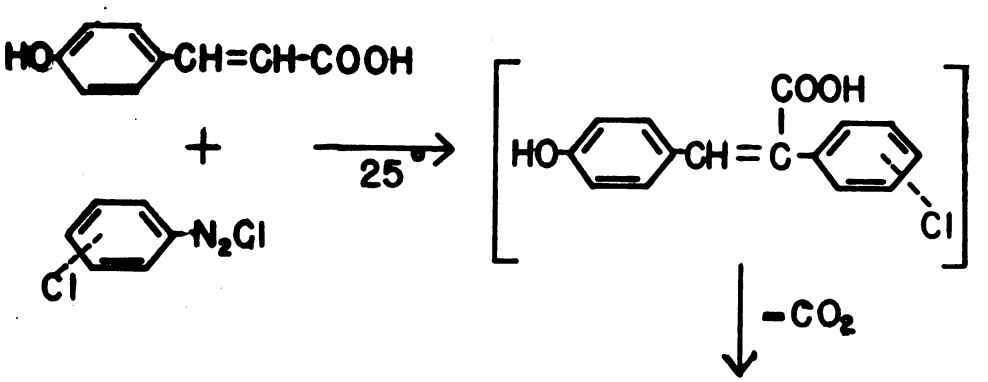
1.

I. 

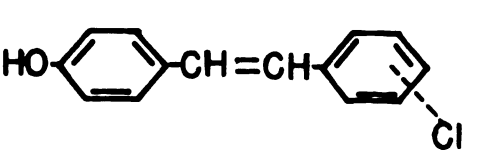
II. 

III. 

2.

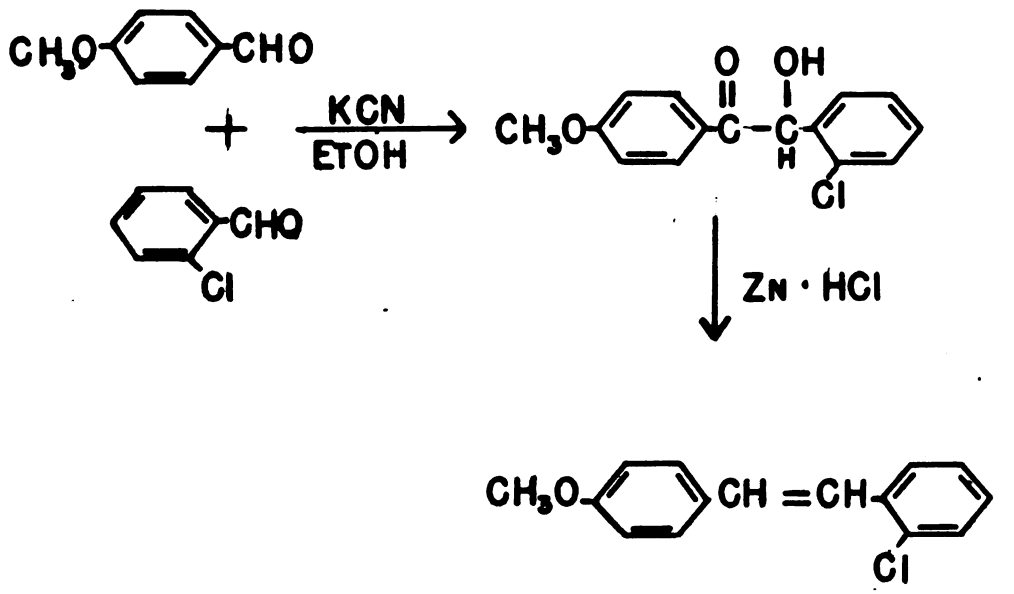


MEERWEIN

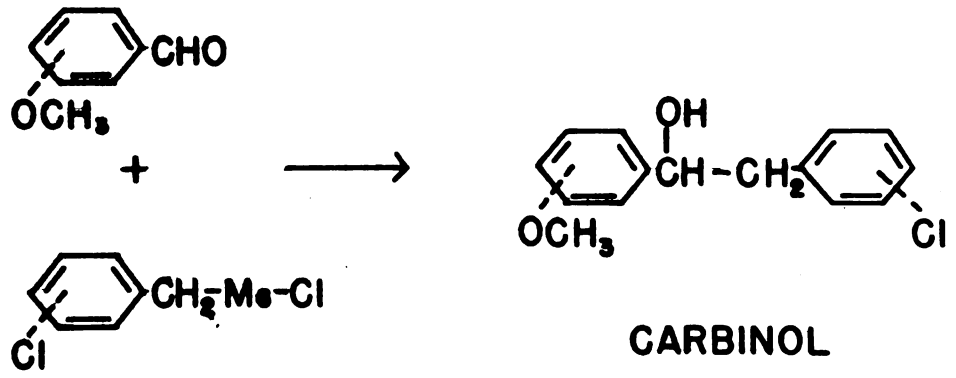


J. PR. CHEM. 152, 251 (1939)

3.

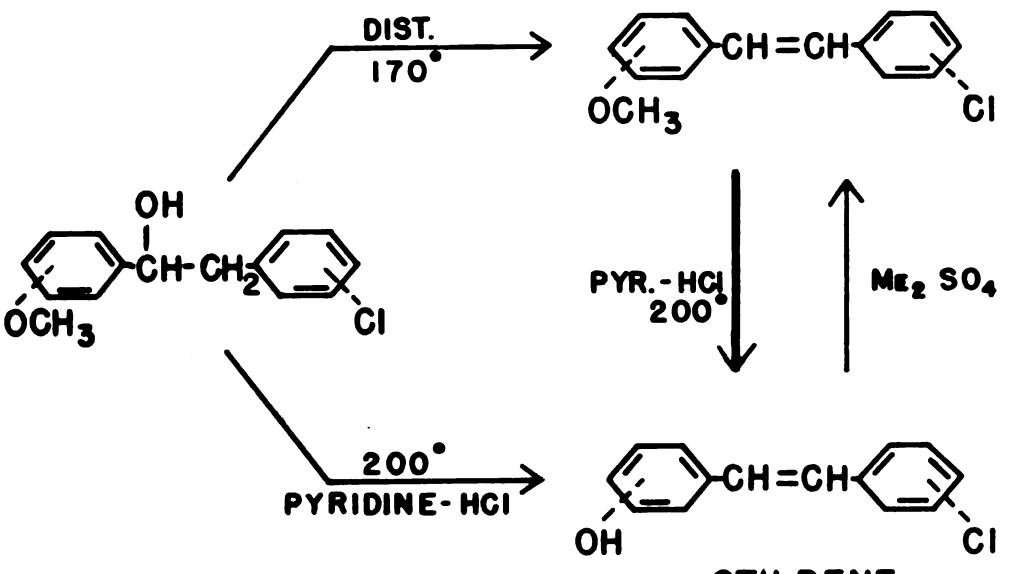

CH3O
CHO
+
KCN
ETOH
CHO
Cl
CH3O
O
OH
C
C
H
Cl
ZN · HCl
CH3O
CH =CH
Cl

4.


CHO
OCH3
+
CH2-Me-Cl
Cl
OH
CH-CH2
OCH3
Cl

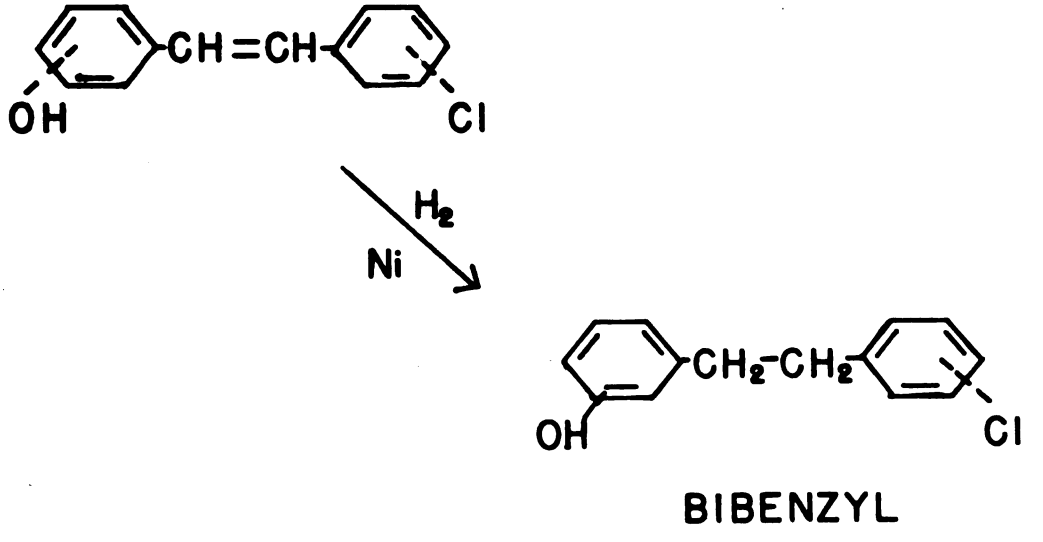
CARBINOL

5.



DEMETHYLATION — Buu-Hoï & Huán, J. Org. Chem., 1949

6.



DISCUSSION

I. GENERAL DISCUSSION OF STILBENES AND BIBENZYLS.

A. Structure and Properties.

An attempt to find generalizations about physical properties as related to structure of the stilbenes and bibenzyls reported here, was limited to a few generalizations which follow:

1. The hydroxystilbenes were always the highest melting isomers relative to the analogs which contained substituted groups in the same position.

2. The 4'-chloro isomers of a given series were always higher melting than the 2'-chloro with one exception — 2-hydroxy-2'-chlorostilbene melted higher than 2-hydroxy-4'-chlorostilbene by twelve degrees. Meta isomers generally melted lower than ortho or para.

3. The o-methoxycarbinols melted unusually high, possibly due to forces acting between the methoxy and hydroxy groups.

These properties in general are what one would predict.

When models were constructed using Fisher-Hirschfelder-Taylor models, which in theory closely approximate the size of the atoms as well as their spacing, the following observations were made.

1. In the carbinol series there can be free rotation of all members when the molecule is twisted into certain positions (without strain). When the hydroxy- and chloro- atoms are substituted in the respective ortho positions, the hydroxyl groups may come into contact with one another, or, each of the hydroxyls may come into contact with the chlorine atom, either independently or simultaneously, by proper rotation of parts of the molecule.

2. In the bibenzyls, the chlorine and hydroxy groups can come into contact when they are both in the ortho position; any part of the molecule may undergo free rotation.

3. In the cis stilbenes, there cannot be free rotation of the phenyl groups if the ortho positions are substituted. If the hydroxy and chloro atoms are both ortho, they may be either close together, or else at maximum distance opposite one another.

4. In the trans stilbenes, there can be free rotation of the phenyl groups. Substituted groups in this case probably do not approach closely enough for forces to interact.

B. Chemotherapeutic Value

A majority of the samples were submitted to Eli Lilly and Company for pharmacological testing against tuberculosis. Although in vitro tests with the hydroxystilbenes showed activity in dilutions of about one part per million, the in vivo tests showed little of the desired activity. The solubility of these compounds is quite low in aqueous medium, thereby limiting their activity. Kostanecki (46) has prepared the aryloxyacetic acid derivatives of some hydroxystilbenes. This type of derivative probably would be more satisfactory for pharmacological testing since its alkali salts would be soluble.

Certain dialkyl stilbenes and their reduced analogs have been prepared and tested for carcinogenic activity (47). Stilbenes have been tested for estrogenic activity, (48, 49), and as possible trypanocidal agents (50). Haskelberg and others (51, 52) have investigated certain substituted stilbenes as possible lipophilic chemotherapeuticals which could penetrate the waxy walls of certain bacteria.

C. Absorption Spectra

Hewitt, et al., (40) have shown that the stilbenes and hydroxystilbenes in alcohol, and the methoxystilbenes in sodium hydroxide, all absorb light similarly. The absorption spectra shift markedly, however, for the sodium salts of the hydroxystilbenes, from a maximum at 4000 to a maximum at about 3600 oscillation frequency units.

II. CARBINOLS BY THE GRIGNARD REACTION.

A. Preparation.

The complete series of nine different carbinols of the formula shown in Figure 4 was prepared by the addition of o, m or p-methoxybenzaldehyde to a suitable Grignard reagent prepared from o, m or p-chlorobenzyl chloride as outlined in Figure 4 and described in detail under Part II A, Experimental.

m-Methoxybenzaldehyde and m-chlorobenzyl chloride were synthesized (see Part I, Experimental), whereas the other four intermediates were purchased. The average yield of Grignard reagent for ten preparations was 92%. The yield in the Grignard preparation was essentially the same for the three isomeric chlorobenzyl chlorides.

The preparation of 4-methoxyphenyl-2'-chlorobenzyl carbinol is described in detail, whereas only pertinent information regarding the preparation of the other carbinols is given. Jenkins and Richardson (6) have prepared 4-methoxyphenyl-3'-chlorobenzyl carbinol by this method.

During the addition of the aldehyde to the Grignard reagent, a gentle reflux occurred until about three fourths to four fifths of the carbonyl compound had been added. At this point reflux generally ceased. This was taken to mean that the desired addition reaction was no longer taking place. Furthermore at this point the mixture had in most cases become thick and difficult to stir.

The addition of the aldehyde was carried out rapidly, usually during an hour or two, and the mixture was hydrolyzed immediately. This was done because of the following result obtained in the case of 4-methoxyphenyl-2'-chlorobenzyl carbinol. In one of the first preparations, when the mixture was refluxed for one or two hours following addition of the aldehyde and permitted to stand overnight, the yield of carbinol decreased and purification was very difficult. The impurity was finally isolated by reason of its slower rate of solution in diethyl ether. Recrystallization from ethanol or ligroin gave colorless prisms, m.p. 96.5° sharply. This compound showed no depression of melting point when mixed with another unidentified product obtained in small yield by reduction of 4-methoxy-2'-chlorobenzoin in hydrochloric acid with zinc. (See Part III A, Experimental). Since the only compound which might arise from both reactions is the corresponding desoxybenzoin (4-methoxyphenyl-2'-chlorobenzyl ketone), a single attempt to reduce the unknown compound to the corresponding carbinol was made. The catalyst used was Raney nickel (admittedly not the best catalyst for this type of reduction); only the unchanged starting material was isolated.

This presumed desoxybenzoin of m.p. 96.5° could reasonably be produced by an Oppenauer oxidation as shown by the equation:

$$CH_3O\text{-}C_6H_4\text{-}CHO + CH_3O\text{-}C_6H_4\text{-}\underset{\displaystyle OMgCl}{\underset{|}{C}}HCH_2C_6H_4Cl \rightleftharpoons CH_3O\text{-}C_6H_4\text{-}CH_2OMgCl + CH_3O\text{-}C_6H_4\text{-}COCH_2\text{-}C_6H_4Cl$$

Evidence in support of this mechanism was also offered by Meisenheimer (26) who isolated propiophenone as a product of the reaction between

excess benzaldehyde and ethyl Grignard reagent. The above equilibrium might be attained only slowly. Hence, by using no excess aldehyde and by hydrolyzing the reaction mixture before equilibrium could be attained, it appeared plausible that little or none of the by-product would be formed. This was indeed the case when the hydrolysis was carried out in the manner described on page 42.

At first the hydrolysis was carried out either by addition of mineral acid, or by addition of the theoretical amount of saturated ammonium chloride solution. The latter method was preferable and was adopted because it gave a lighter colored oil from which the crystalline carbinol could be isolated more easily.

The solid which precipitated during the hydrolysis of the carbinol complex by saturated ammonium chloride solution is probably mainly magnesium chloride hexahydrate, which, after decanting the ether solution and rinsing with ether, appears to retain up to 5% of the carbinol. This carbinol could be recovered by dissolving the residue in dilute mineral acid and extracting with ether.

B. Crystallization

Five of the nine carbinols were obtained, following hydrolysis of the Grignard, by crystallization directly from their ether solutions after first concentrating and cooling the concentrate to 0° for one to three days in the refrigerator. If the proper seed was available, crystallization was quite rapid. (See Part II B, Experimental). The synthesis and purification of two of the carbinols was done before the above method of isolation was worked out. These two carbinol isomers,

4-methoxyphenyl-2'chlorobenzyl carbinol and 2-methoxyphenyl-2'-chlorobenzyl carbinol, were more tediously crystallized from the crude oils by repeated extractions with ligroin as described under Part II A, Experimental.

3-Methoxyphenyl-3'-chlorobenzyl carbinol could not be induced to crystallize from alcohol, ligroin, ether, or toluene, either by cooling to temperatures as low as -80° and scratching the sides of the vessel, or by setting at room temperature or in the cold for as long as two months. Hell and Hofmann (7) reported that 4-methoxyphenylbenzyl carbinol, made by the Grignard method from anisaldehyde and benzyl chloride, would not crystallize in the summer but did in the winter. The fact that these two carbinols were prepared during the summer may have influenced their reluctance toward crystallization.

Four of the carbinols, 4-methoxyphenyl-2'-chlorobenzyl, 4-methoxyphenyl-4'-chlorobenzyl, 3-methoxyphenyl-2'-chlorobenzyl, and 2-methoxyphenyl-2'-chlorobenzyl carbinol, were purified by recrystallization from ligroin. 4-Methoxyphenyl-3'-chlorobenzyl and 2-methoxyphenyl-3'-chlorobenzyl carbinol were purified by recrystallization from ethyl ether. This is an uncommon solvent for recrystallization and rather difficult to work with because of its volatility, but it was found that recrystallization from ligroin in these two cases would not remove the impurities. When the carbinols were crystallized from ether and dried, a white powder resulted which gave crystals after a final recrystallization from ligroin. 2-Methoxyphenyl-4'-chlorobenzyl carbinol was most easily purified by recrystallization from absolute ethanol.

Yields of the recrystallized carbinol varied from 26% in the case of the 2-methoxy-2'-chloro- isomer to 82% in the case of the 4-methoxy-4'-chloro- isomer, being generally around 40 to 50%.

The melting points of the seven crystalline carbinols ranged from 64° to 122°, with six of them melting between 64° and 83°. The three carbinols containing the methoxy group in the ortho position had the highest melting points in relation to corresponding isomers of the meta- and para-methoxy series.

Jenkins and Richardson (6), who also prepared 4-methoxyphenyl-3'-chlorobenzyl carbinol by the Grignard method, reported a melting point of 43-44° (corr.). In this laboratory the compound was found to exist in two isomorphic forms, the less stable form, m.p. 37.5-38°, being transformed easily to the more stable form, m.p. 54.8-55.2°, by either grinding the dry material on a clay plate or by recrystallization from ligroin accompanied by scratching of the vessel. The higher melting form could not be converted to the lower melting form. When the two forms were mixed, melting began at 37°, but on slowly raising the temperature, resolidification took place with melting finally occurring at 55°. Dehydration gave the expected 4-methoxy-3'-chlorostilbene, m.p. 94-94.6°.

C. Dehydration. (Also summarized in Table I).

Dehydration of the carbinols to the methoxystilbenes was accomplished by two general methods: (1), physically by distillation in vacuo; (2), chemically by heating the carbinol with either a mixture of acetic acid and hydrochloric acid or an anhydrous mixture of acetic

acid, hydrogen chloride, and acetyl chloride, prepared by addition of excess acetyl chloride to concentrated hydrochloric acid. These are discussed below.

1. Distillation was limited mainly to the oil remaining after crystallization of the crude carbinol and evaporation of the solvent. These reddish viscous oils distilled in the neighborhood of 185°/1 mm. The dehydration, occurring to a greater or lesser extent at a pot temperature near 180°, was accompanied by much bubbling and by the collection of water in the dry ice trap. Usually the clear or slightly yellow colored distillate solidified on standing, but the solid showed a wide melting point range, indicating that it consisted of a mixture of the carbinol and its dehydration product, the methoxystilbene. Distillation of the oils from all three m-methoxy carbinols gave clear colored viscous liquids which could not be induced to crystallize. Pure carbinols were distilled in only three cases, as discussed below.

Hydrochloric acid was found to facilitate the dehydration. Concentrated hydrochloric acid was shaken with ether, the ether decanted and added to the carbinol in the distillation flask. By this method pure 4-methoxyphenyl-4'-chlorobenzyl carbinol was dehydrated in over 80% yield in contrast to the oily residues from its preparation, which failed to dehydrate appreciably when distilled without the presence of mineral acid.

Distillation in vacuo of pure 2-methoxyphenyl-3'-chlorobenzyl carbinol with mineral acid gave only 51% of the pure methoxystilbene, whereas distillation in a similar manner of pure 2-methoxyphenyl-4'-chlorobenzyl

carbinol gave even a lower yield (30%) of the dehydrated product. Thus, the ortho-methoxy series of carbinols appeared to undergo dehydration less easily than most of the other carbinols, even when mineral acid was used in the distillation. The fact that the carbinols of the o-methoxy series undergo dehydration more difficulty, and also have higher melting points than the carbinols of the meta- and para-methoxy series, indicates that chelation may occur between the hydroxy and methoxy groups when they are ortho to one another.

2. Chemical dehydration was less effective than distillation in the case of 2-methoxyphenyl-4'-chlorobenzyl carbinol, giving no dehydration when the pure carbinol was heated six hours at 52° with a mixture containing acetyl chloride, acetic acid, and hydrogen chloride, as compared to an optimum yield of 30% methoxy stilbene when the pure carbinol was vacuum distilled with a little mineral acid. The large temperature difference between the two methods may account for these results. On the other hand, 4-methoxyphenyl-2'-chlorobenzyl carbinol was dehydrated to the corresponding methoxy stilbene in 75% yield after six hours at 52° with the same dehydrating mixture used above.

Other chemical dehydrating methods which were used less successfully (on 4-methoxyphenyl-2'-chlorobenzyl carbinol) include that of Jenkins and Richardson (6) using concentrated hydrochloric acid in glacial acetic acid, giving a yield of 32% 4-methoxy-2'-chlorostilbene; acetic anhydride at 135° for 13 hours giving an oil which wouldn't crystallize; maleic anhydride at 200° for one hour giving a poor yield; benzoyl chloride at 195° for one hour giving a 25% yield of methoxy stilbene. (See Table I on the next page).

TABLE I

DEHYDRATION OF METHOXYPHENYLCHLORO-
BENZYL CARBINOLS

OCH_3	Cl	Dehydrated	Method [a]	Yield Pure Stilbene %	Page
4	2'	Oil	C	15	
		Crystals	C	32	52
		Crystals	D	75	52
		Crystals	E	b	53
		Crystals	F	low	16
		Crystals	G	25	16
		Residue	A	7	52
4	3'	Residue	A	30	55
4	4'	Residue	A	b	15,45
		Crystals	B	82	57
3	2'	Residue	A	b	57
3	3'	Oil	A	b	58
3	4'	Oil	A	33	58
2	2'	Residue	A	11	59
2	3'	Crystals	B	51	60
		Residue	A	b	15,48
2	4'	Crystals	D	0	16
		Crystals	B	30	60
		Residue	A	b	49

a. Methods: A, distillation; B, distillation with mineral acid; C, hydrochloric acid in acetic acid; D, acetyl chloride, acetic acid, and hydrogen chloride; E, acetic anhydride; F, maleic anhydride; G, benzoyl chloride.

b. No methoxystilbene could be isolated.

III. METHOXYCHLOROSTILBENES.

A. General.

The complete series of nine methoxychlorostilbenes was prepared by various methods as shown in Figures 3 and 5. Several of them were synthesized in at least two different ways, proving that the reactions used were all straightforward, and thus eliminated the necessity of proving the structure by degradation to known compounds.

The methoxystilbenes were solids, except in the case of 3-methoxy-2'-chlorostilbene, melting between 40 and 180°. As would be predicted from the symmetry of the compounds, the lower melting isomer is 3-methoxy-3'-chlorostilbene and the higher is 4-methoxy-4'-chlorostilbene. The latter compound melts almost 100° higher than any of the other isomers, which may be due not only to a more symmetrical structure but also to stabilization through resonance. The methoxystilbenes readily added bromine from a dilute solution of bromine in carbon tetrachloride, or glacial acetic acid. However, substitution also readily occurred and it was not always apparent when addition was complete. Furthermore, the derivatives so formed were often difficult to purify, indicating that some substitution probably occurred. However, the qualitative difference between the unsaturated stilbenes and the saturated carbinols and bibenzyls could readily be determined by means of this test.

The hydrogenation of the methoxystilbenes was not generally attempted, but in view of the relatively low melting points of most of the hy-

droxychlorobibenzyls (See Part V, Experimental), it is presumed that these would probably be mostly oils at room temperature. In a single case of hydrogenation of 4-methoxy-3'-chlorostilbene, using Raney nickel, an oil was isolated which could not be crystallized. The product was not characterized.

The methoxystilbenes were generally quite soluble in toluene, but crystallized nicely from absolute ethanol. Occasionally ligroin was used for recrystallization, although the compounds exhibited greater solubility in ligroin than in ethanol. Glacial acetic acid was found to be the best solvent for recrystallization of 4-methoxy-4'-chlorostilbene.

B. Preparation.

The most useful method for preparing the methoxystilbenes was the dehydration of the carbinols by distillation in the presence of a trace of mineral acid. It was also possible to dehydrate the carbinols by distillation without mineral acid, in lower yield, or by means of chemical dehydrating agents. This is discussed in the previous section on carbinols.

The Meerwein reaction, which was used to prepare 4-methoxy-4'-chlorostilbene, is discussed in the next section on hydroxystilbenes. This isomer was also made by means of the Meerwein reaction by Bergmann and Schapiro (2).

Methylation of the hydroxystilbenes was another convenient way of obtaining the methoxystilbenes, especially since the hydroxystilbenes could be obtained easily in good yield from the carbinols in one step by the use of pyridine hydrochloride at high temperature. This reaction is also discussed in the next section on hydroxystilbenes. Methylations

were carried out in dioxane since the potassium salts of the hydroxystilbenes were so insoluble in water. Small amounts of hydroxystilbene were generally used in the methylation reaction, so the yields are not too reliable, but in most cases they appeared to be almost quantitative.

An unusual method of preparation of these compounds was by a modified Clemmenson reduction of the corresponding benzoin according to the method of Ballard and Dehn (10), using zinc amalgam and hydrochloric acid. The yield of the desired product was quite low, but enough 4-methoxy-2'-chlorostilbene was obtained by this method of synthesis to check the melting point with that of the same compound prepared by both the Grignard method, and the Meerwein reaction followed by methylation. A product of this type of reduction which was generally isolated in slightly greater yield than the desired methoxystilbene, was an unidentified substance melting at about 96°, identical with a by-product from the Grignard reaction which produced 4-methoxyphenyl-2'-chlorobenzyl carbinol. The only compound which might logically arise in both instances is the desoxybenzoin. This is discussed in the section on carbinols.

Bergmann and Schapiro (2) obtained 4-methoxy-2'-chlorostilbene directly by means of the Meerwein reaction, and reported a melting point of 64°. This compound was prepared in this laboratory by three independent methods, one of which involved preparation of the hydroxystilbene by means of the Meerwein reaction, followed by methylation. This compound melted over a range of half a degree at 60°. The other two methods of synthesis used were through the benzoin and through the carbinol, the latter prepared by the Grignard reaction.

Bergmann and Schapiro also report in the same article that they failed to obtain demethylation of the methoxystilbene by boiling in 48% hydrobromic acid. The same result was obtained in this laboratory. However, by using a reagent prepared by adding 48% hydrobromic acid to acetyl chloride, and refluxing for a considerable length of time, a small yield of the demethylated 4-hydroxy-2'-chlorostilbene was isolated.

IV. HYDROXYCHLOROSTILBENES.

A. General.

The hydroxystilbenes are all solid compounds with well defined melting points. They are easily methylated to the methoxystilbenes, as described in Part III, Experimental, or they may be reduced to the bibenzyls as considered in Part V, Experimental. All the methoxystilbenes are solids suitable for characterization except 3-methoxy-2'-chlorostilbene. The p-chlorobenzoate of the corresponding stilbene was prepared as a derivative in this case. The double bond in the hydroxystilbenes, although it added bromine, did not hydrogenate so readily, indicating that it has less of the character of an ordinary aliphatic double bond.

B. Preparation. (See Figures 2 and 5).

1. Demethylation-dehydration by Pyridine Hydrochloride. The most useful method of synthesis was the one step demethylation-dehydration of the carbinol by pyridine hydrochloride at 200°, according to the procedure of Buu-Hoi and Hoan (9). (See Figure 5). The yields varied from 40 to 70%, being usually around 60%. The mechanism of this reaction may involve a complex which must be decomposed by water, since on two occasions, attempts were made to extract the products directly from the reaction mass after cooling, before adding water, but nothing could be extracted by either hot ligroin, or by ether. Following addition of water the organic material was easily extracted by ether.

2. Demethylation of the Methoxystilbene. The hydroxystilbenes were also prepared by demethylation of the methoxystilbenes using a mixture of 48 °/° hydrobromic acid and acetyl chloride. The yield was poor and did not compare with that obtained by using pyridine hydrochloride at 200° as a demethylating agent.

3. Demethoxymethylation of the Methoxymethoxystilbene. Another route to these compounds was demonstrated early in the work. This was the formation of 4-methoxymethoxyphenyl-2'-chlorobenzyl carbinol by means of the Grignard reaction, (See Part II K, Experimental), and then dehydrating and cleaving the ether group with acetic anhydride to produce the hydroxystilbene in approximately 15 °/° yield. (See Part IV, A, 2, Experimental). Finkelstein and Linder (5) prepared a methoxymethoxy substituted benzoin and were able to split the ether group using a mixture of acetic acid and sulfuric acid.

4. Meerwein Reaction. Four members of the hydroxystilbene series were also prepared by means of the Meerwein reaction (1). (See Figure 2). These were 3-hydroxy-4'-chlorostilbene, 4-hydroxy-2'-chlorostilbene, 4-hydroxy-3'-chlorostilbene, and 4-hydroxy-4'-chlorostilbene. The yields increased in the order listed, being about 4 °/° in the first case and 22 °/° in the latter case. 4-Hydroxy-4'-chlorostilbene was prepared in 56 °/° yield by Meerwein (1) by means of the Meerwein reaction. 4-Hydroxy-2'-chlorostilbene was also prepared by Meerwein (1) in much lower yield.

The mechanism of the reaction has been debated. Meerwein (1) postulated an ionic mechanism, the first step being the elimination of nitrogen from the aryl diazonium halide with the production of an aryl cation, which subsequently added in the alpha position to the carbonyl group of the cinnamic acid. The alpha carbon atom was considered to have an increment of negative charge. Following this addition, three things might happen. The

alpha carbon atom could lose a proton forming an aryl-substituted cinnamic acid. The beta carbon which was positively charged, could capture a chloride atom forming a saturated bond. The carboxyl group could split off with the evolution of carbon dioxide and the formation of a stilbene. All of these products have actually been isolated.

Bergmann and Schapiro (2), on the other hand, postulated a free radical mechanism. These workers have prepared the two corresponding isomers of the methoxystilbene series reacting p-methoxycinnamic acid with the diazonium chlorides of both o- and p-chloroaniline. Bergmann assumed that the aryl diazonium halide eliminated nitrogen with the formation of an aryl radical which then attached itself in the alpha position to the carbonyl group of the cinnamic acid. The odd electron, located in the vicinity of the beta carbon, was stabilized by resonance with the adjacent phenyl mucleus. The carboxyl group was then eliminated with regeneration of the double bond and formation of the stilbene. Bergman cited work by Koelsch (44, 45) as additional evidence for the radical mechanism. Koelsch found that aryl diazonium halides added not to the alpha but to the beta carbon atom of both acrylonitrile and crotonic acid. Bergmann claimed this reverse addition occured because the odd electron, after the aryl radical added to the vinyl group, was stabilized by the nitrile or carboxyl groups respectively since there was no adjacent phenyl group. If the mechanism were ionic as Meerwein claimed, there would be no apparent reason for this reversal of addition.

In this work, it was found that the temperature at which the aryl diazonium chloride decomposed was about 20° in the three cases where p-hydroxycinnamic acid was reacted with diazotized o-chloroaniline, m-chloroaniline, or p-chloroaniline. When m-hydroxy-cinnamic acid was used, however, the temperature at which the reaction started was about 50°.

V. HYDROXYCHLOROBIBENZYLS.

A. General.

The nine isomeric hydroxychlorobibenzyls were prepared by hydrogenation of the corresponding hydroxychlorostilbenes (Figure 6) at 50-70° using either W = 2 Raney nickel prepared by the Mozingo procedure (43), or copper chromium oxide catalyst under approximately 75 to 100 atmospheres hydrogen. These compounds were generally low melting solids and were quite difficult to purify, the yields of pure bibenzyl being in general 50% or below. Ligroin or petroleum ether was the most useful solvent for crystallization. Two of the bibenzyls were oils at room temperature. These were the 3-hydroxy-3'-chlorobibenzyl and 3-hydroxy-2'-chlorobibenzyl. The latter isomer was crystallized from ligroin at -30° and melted at 20-22°.

B. Hydrogenation of Stilbenes.

Hydrogenation was at first attempted at 25° and one atmosphere pressure, but although partial reduction occurred sometimes, not enough of the bibenzyls was formed to be separable in pure form. It was found that in order for reduction to proceed reasonably well, the ethanol solution of the stilbene had to be refluxed at least once and preferably twice over Raney nickel. Large amounts of catalyst, from one half to equal the weight of stilbene, had to be used. This would be a distinct disadvantage in reduction of large quantities of material.

Copper chromium oxide appeared to be as useful as nickel, and was generally used in smaller amounts. This catalyst was not tried in all cases however. Refluxing over nickel catalyst was necessary for reduction using the copper chromium oxide also. Since the prime purpose in mind was the preparation of the compounds, no other catalysts were prepared and tested. Bergmann and co-workers (8) successfully reduced chloro substituted stilbenes to the bibenzyls with Raney nickel at 25° and one atmosphere. Their compounds, however, did not contain a hydroxy group, which may cause the difference in ease of reduction.

C. Derivatives.

The p-chlorobenzoate esters were easily prepared by the method described in Part V A, Experimental. They were all crystalline solids with well defined melting points. The melting points of the derivatives in general appeared always to be about thirty degrees higher than the melting points of the bibenzyls.

CONCLUSIONS

In this work it has been shown that stilbenes may be conveniently synthesized through an intermediate carbinol, prepared by means of the Grignard reagent, which is dehydrated and demethylated in a single step by means of pyridine hydrochloride. The overall yield compares favorably with other methods, particularly the Perkin method of synthesizing stilbenes which has been used extensively.

It has been concluded that the Meerwein reaction cannot be satisfactorily extended to the general preparation of other than 4-hydroxy-4'-chlorostilbene because of low yields.

Finally, it has been demonstrated that the hydroxy- and methoxystilbenes, and the hydroxybibenzyls have little or no activity in vivo against tuberculosis. (These results were made available through the courtesy of Dr. R. G. Jones of Eli Lilly and Company.)

EXPERIMENTAL

General Information:

All compounds which were prepared, including intermediates, are described. Representative reactions are given in detail, usually in connection with the first compound for which they were used. Melting points are given along with the compounds as well as in the Tabular Summary. All melting points of compounds not already reported in the literature were taken in capillary tubes, using Anschutz thermometers, but are not corrected. It was found that melting points taken on a block were in general not more than one degree higher than the capillary melting points. All temperatures are given as degrees Centigrade.

The source of chemicals used is listed below.

Analyses of the compounds are listed in Tables II-VI.

Chemicals:

m-Chlorotoluene, Eastman, N_D^{20} 1.5220, b.p. 50°/13 mm.

Sulfuryl Chloride, Eastman, pract., redistilled, b.p. 67°.

Carbon Tetrachloride, redistilled, b.p. 74.5°, N_D^{20} 1.461.

p-Hydroxybenzaldehyde, Eastman (tech.), recrystallized, m.p. 116°.

o-Chlorobenzaldehyde, redistilled, b.p. 96°/16 mm., N_D^{20} 1.5670.

Anisaldehyde, Eastman.

m-Nitrobenzaldehyde, Eastman, m.p. 57-58°.

Malonic Acid, Dow.

Pyridine, redistilled over barium oxide, b.p. 113-114.5°.

Dimethyl Sulfate, redistilled, b.p. 76°/15 mm., N_D^{20} 1.3872.

Salicylaldehyde, Dow, N_D^{20} 1.5726.

o-Chlorobenzyl Chloride, Eastman.

Magnesium, fine grade turnings for Grignards.

p-Chlorobenzyl Chloride, Eastman, recrystallized from absolute ethanol, m.p. 27-28.5°.

o-Chloroaniline, Monsanto, N_D^{29} 1.586.

m-Chloroaniline, Monsanto, N_D^{29} 1.591.

p-Chloroaniline, Monsanto, m.p. 70-72.

p-Chlorobenzoyl Chloride, Heyden.

Norite, A.

I. INTERMEDIATES.

A. m-Chlorobenzyl Chloride

Reactants:

m-chlorotoluene	748 g.	(5.9 moles)
sulfuryl chloride	405 g.	(3.0 moles)
benzoyl peroxide	8 g.	
carbon tetrachloride	314 ml.	

The procedure of Kharasch and Brown (27) was used for this preparation. In a 3 l. three-necked flask fitted with two condensers and a thermometer, and heated by a mantle, were placed the m-chlorotoluene (Eastman N_D^{20} 1.5520), sulfuryl chloride (redistilled), and carbon tetrachloride (redistilled). To this was added 2.0 g. benzoyl peroxide and the solution heated first to 73° where a slight reaction occurred, and then slowly to 85° where the evolution of sulfur dioxide and hydrogen chloride became moderately vigorous. These gases were led into the hood drain thru rubber tubing and washed down with water.

After two hours at 85°, the temperature was slowly raised during one hour to 90°. Benzoyl peroxide (2.0 g.) was again added and the temperature raised to 100° during three hours, whereupon another 2.0 g. of catalyst was added. After each addition of the benzoyl peroxide, the evolution of gases temporarily increased. After six more hours (total twelve hours), the temperature was 110°. The reaction mixture was not refluxing, however. Two grams benzoyl peroxide was added and the orange solution allowed to stand overnight at room temperature.

The reaction mixture was distilled through a 12 inch Fenske-type column packed with glass helices. The carbon tetrachloride (250 ml.) distilled at 74° at atmospheric pressure. After the dark colored liquid residue had cooled, the pressure was reduced by a water aspirator and the distillation continued. The excess m-chlorotoluene (414 g.), b.p. 50° (13 mm.), N_D^{20} 1.5520, was recovered at the rate of about 90 ml. per hour. An intermediate fraction of 10 ml. was collected between 50 and 98°. There was obtained 400 g., (2.5 moles) m-chlorobenzyl chloride, b.p. 98° (14 mm.); N_D^{20} 1.5563-1.5576; yield 83.5% based on sulfuryl chloride. Two other runs of comparable size, carried out in the same manner, gave yields of 80 and 84.5%.

Kharasch and Brown (27) report that gases escaping during the reaction carry off some of the reactants. If these gases are condensed in a dry ice trap and returned to the reaction mixture, these same authors reported the yield to be almost quantitative. The reaction mixture should reflux in order to displace oxygen which strongly inhibits the chlorination.

m-Chlorobenzyl chloride has been prepared by other workers (28, 29) from m-chlorobenzyl alcohol in 78% yield by the action of thionyl chloride.

B. Purification of p-Hydroxybenzaldehyde.

Technical p-hydroxybenzaldehyde (Eastman), which was at least 20 years old and deep red in color, was recrystallized from seven times its weight of water using Norite at the boiling point, filtering, and cooling in the refrigerator. The material thus obtained was pink in color but had a good melting point of 116° which checks with Lange's Handbook. An additional quantity of material could be obtained by concentrating the

filtrate and treating with charcoal as before. No better than a 50% yield of pure aldehyde could be obtained from the crude.

Other purifications were tried and found less desirable such as extracting the aldehyde away from its colored impurities with hot ligroin or hot toluene, or proceeding thru the bisulfite addition compound.

C. p-Hydroxycinnamic Acid.

Reactants:

p-hydroxybenzaldehyde	260 g.	(2.13 moles)
malonic acid (Dow)	312 g.	(3.0 moles)
pyridine (redistilled)	330 ml.	
aniline	8 ml.	

p-Hydroxycinnamic acid was prepared by a modification of the procedure of Overberger and co-workers (30). The two solid reactants were first mixed in a 1-l. flask and shaken well until homogenized. The pyridine and aniline were then added and the mixture stirred mechanically while heating with a glas-col mantle at 50° for six hours. At the end of this time, after the foaming due to the evolution of carbon dioxide had almost ceased, the temperature was raised to 70° for another three hours.

Two liters of hot water (65°) containing slightly more than the theoretical amount of sodium bicarbonate was stirred by hand while the orange-red reaction mixture was poured into it with considerable foaming. To this clear solution was added about 350 ml. 37% hydrochloric acid at 65° and the acid solution allowed to cool overnight. Filtration of the precipitated cinnamic acid, washing with water once, and drying in air at 70° gave 195 g. (75% yield) of p-hydroxycinnamic acid, m.p. 212° dec. The reported melting point is 210-213° dec. (37).

When the period of heating was two to three hours, the yield was between 32% and 56%. Unreacted p-hydroxybenzaldehyde sometimes contaminated the cinnamic acid, evidently having been carried thru the alkaline extraction process.

D. p-Methoxycinnamic Acid.

Reactants:

anisaldehyde	68 g.	(0.5 mole)
malonic acid	52 g.	(0.5 mole)
pyridine	10 ml.	
diethyl amine	7 ml.	

The procedure of Wilson and Wilson (31) was used for this preparation. The reactants were mixed and heated at 100-105° for nineteen hours using a glas-col mantle. Enough ethanol was then added to the hot mixture to dissolve it. After cooling slowly to 0° the light yellow crystals were filtered, washed once with a little cold ethanol, and dried, giving 53 g., m.p. 173° (anisotropic to 185°). The reported value (32) is 170°.

Another 10 g. was obtained from the alcohol filtrate after concentrating on the steam bath, adding 500 ml. 5% sodium carbonate solution, extracting any unreacted aldehyde with ether, and finally precipitating the cinnamic acid with concentrated hydrochloric acid and filtering. The total yield was 63 g. (71%).

Wilson (31) reported a 90% yield (before recrystallization) using pyridine and heating seventeen hours. After finishing the preparation by the described method, the procedure of Robinson and Shinoda (33) was discovered which claims a quantitative yield. Borsche and Walter (34) reported 80-90% yield using pyridine and piperidine.

E. m-Hydroxybenzaldehyde.

Four separate runs were carried out according to the procedure described in Organic Syntheses (35). The following observations and recommendations may be helpful.

m-Nitrobenzaldehyde (Eastman m.p. 57-58°) and crystalline stannous chloride dihydrate were used. A round bottom flask was employed instead of an open beaker.

When a reduction of triple the size described in Organic Syntheses was carried out, the temperature began to rise rapidly at about 25-30° and the ice bath was applied at 50-60° in order to prevent the reaction from boiling over as the temperature continued to climb to 95-100°.

Filtration of the amino-tin complex was slow and proceeded as well with a Buchner funnel and filter paper as with the recommended sintered glass funnel. On large runs, two or three filtering flasks were assembled to speed operations.

The diazonium complex, in contrast to the amino-complex mentioned above, filtered well. After filtration this was added as rapidly as possible with vigorous stirring to water heated with live steam to just below the boiling point. Material from a 200 g. run was added in 1/2 hour. If the temperature was just at the boiling point, there was more foaming, and the time of addition of the diazonium complex to the water was necessarily much longer.

Following decomposition, the water solution was treated while hot with Norite, filtered, cooled and the tan crystals filtered and dried. Extraction of the aqueous filtrate with ether gave an additional 10% m-hydroxybenzaldehyde. Final yields were 69, 68, 73, and 66%, average, 69%.

The crude aldehyde melting at 101-102° was purified by dissolving 200 g. in 1500 ml. hot toluene and treating with charcoal. m-Hydroxybenzaldehyde was thus obtained as almost pure white crystals, m.p. 103.5°, in a yield of about 80% from the crude. The reported m.p. (35) is 101-102°.

A small amount of impure m-hydroxybenzaldehyde was sublimed under vacuum at about 100° into beautiful white needles, m.p. 103.5°.

F. m-Hydroxycinnamic Acid.

Reactants:

m-hydroxybenzaldehyde	46 g.	(0.38 mole)
malonic acid (Dow)	42 g.	(0.38 mole)
pyridine	9 ml.	

m-Hydroxycinnamic acid was prepared by the procedure of Vorsatz (36). The two solid reactants were first mixed by shaking together in a 500 ml. flask. Pyridine was introduced and the mixture placed on a steam bath for one hour. Stirring was ineffective since the reaction mixture solidified around the interior of the entire flask.

After one hour the contents of the flask were scraped into a hot solution of 40 g. sodium bicarbonate in 350 ml. water. There was attained a clear, slightly yellow solution which was cooled and extracted with ether prior to acidification with hydrochloric acid. (The ether extract gave a small amount of unreacted aldehyde after evaporation).

The white precipitate from acidification was filtered, washed with water, and dried in air at 45° to give 58 g. (92%) crude m-hydroxycinnamic acid, m.p. 186-191°. Recrystallization from about 1200 ml. water and filtration at 0° gave 51 g. white crystals; m.p. 193.5-195.5°. The reported value (37) is 191°. The yield was 81%.

G. m-Methoxybenzaldehyde.

Reactants:

m-hydroxybenzaldehyde	146 g.	(1.2 moles)
dimethyl sulfate	171 ml.	(1.8 moles)

This compound was prepared by the procedure of Icke and co-workers (38). The hydroxybenzaldehyde was dissolved in 600 ml. 2 N. sodium hydroxide solution at 40° and stirred mechanically while 114 ml. (1.2 moles) dimethyl sulfate was added over three hours. The heat of reaction maintained the temperature at 40-45°. After three hours the mixture was still alkaline.

Dimethyl sulfate (57 ml.) was added at 45-50°. During this addition, the mixture became acidic and was again made basic by adding 200 ml. 2 N. sodium hydroxide.

After stirring at 25° overnight, the alkaline mixture was extracted with ether, the extract washed and dried over sodium sulfate for several hours, the solvent stripped off and the m-methoxybenzaldehyde distilled through a short column packed with helices. The yield was 150 g. (92%); b.p. 72°/1 mm.; N_D^{20} 1.5533; (Heilbron (39) reports N_D^{20} 1.5530).

A second run of one mole gave a yield of 88%.

H. o-Methoxybenzaldehyde.

Reactants:

salicylaldehyde	488 g.	(4.0 moles)
dimethyl sulfate	570 ml.	(6.0 moles)

The methylation of the salicylaldehyde was carried out in a 5 l. flask in a manner similar to that of the meta isomer in the previous experiment. (See G). Some difficulty with an emulsion was encountered during the extraction of the product with ether.

Isolation of the m-methoxybenzaldehyde was accomplished in one preparation by fractional distillation thru a 12 inch column packed with glass helices. The first fraction consisted of 53 g. salicylaldehyde, b.p. 73°/10 mm. A small amount of material boiling at 73-112°/10 mm. was discarded.

The main fraction consisted of 389 g. o-methoxybenzaldehyde, b.p. 112°/10 mm., N_D^{20} 1.5683 (reported N_D^{20} 1.560 (39). This is a yield of 72%.

An additional 45 g. unreacted salicylaldehyde was recovered from the reaction liquors by acidifying with concentrated hydrochloric acid, extracting with ether, washing, drying over potassium carbonate, and distilling. Thus, considering the recovery of starting material, the yield becomes 90%.

The product may also be isolated by crystallization from petroleum ether as was done in a later preparation. Following methylation, the reaction mixture was extracted with ether, the ether solution washed with water, dried over potassium carbonate, and the ether evaporated on the steam bath. The ether was replaced first with ligroin and boiled to remove the last traces of ether, then with about eight parts of petroleum ether. The solution was treated with charcoal and cooled to 0°, decanted from some residual oil, and seeded with some of the methoxysalicylaldehyde. Beautiful spear like crystals, m.p. 35.5-36°, were obtained after filtration. The reported melting point is 36.3° (39). The residual oil after the decantation eventually solidified. It was re-treated with petroleum ether as before to produce an additional quantity of material. The yield of o-methoxybenzaldehyde was 75%.

I. Chloromethyl Ether.

Reactants:

methyl alcohol	112 g.	(3.5 moles)
formalin (40%)	270 g.	(3.5 moles)
hydrogen chloride		

The procedure of Clark, Cox and Mack (41) was used for the preparation of chloromethyl ether. Hydrogen chloride gas (cylinder) was passed into the solution of methanol and formalin until saturation was reached in about ten hours. The top organic layer was separated and aerated for three hours with dry air. It is suspected that some material was lost by evaporation during this process.

After drying with calcium chloride the liquid was distilled thru a 12 inch column packed with glass helices. The chloromethyl ether boiling at 57-59° weighed 90 g. This is a 36% yield. Clark reported a 43% yield. The chloromethyl ether was stored away from moisture.

J. p-Methoxymethoxybenzaldehyde.

Reactants:

p-hydroxybenzaldehyde	61.0 g.	(0.5 mole)
chloromethyl ether	40.0 g.	(0.5 mole)
sodium	11.5 g.	(0.5 mole)
methanol	200.0 ml.	

The procedure of Finkelstein and Linder (5) was used in this preparation. Sodium methylate was formed by adding the sodium to the methanol in a one liter flask. To this solution was added with stirring the p-hydroxybenzaldehyde. The methanol was distilled, the final portion being removed by adding 500 ml. toluene and distilling until the temperature of the distillate reached 110°. The sodium salt of the hydroxybenzaldehyde precipitated as a white solid.

The mixture was cooled and chloromethyl ether added dropwise over 1/2 hour at 0-5°. After refluxing one hour with stirring, water was added to dissolve the sodium chloride, and the layers were separated. Acidification of the aqueous layer gave 7 g. unreacted aldehyde. Extraction of the toluene layer with 5% sodium hydroxide followed by acidification of the extract gave an additional 18 g. p-hydroxybenzaldehyde. It is suspected that the alkali wash may have hydrolyzed some of the methoxymethoxy ether, so it may be advisable to eliminate this step.

The toluene layer was washed twice with water and dried over sodium sulfate. The toluene was removed under vacuum and the p-methoxymethoxybenzaldehyde distilled thru a 12 inch column packed with glass helices and enclosed in a heated jacket. There was obtained 30 g. of product, b.p. 121°/4 mm., N_D^{20} 1.5460. No fore-run and very little residue was obtained. The yield was (60%) based on a recovery of 25 g. of the starting material.

K. 4-Methoxy-2'-chlorobenzoin.

Reactants:

o-chlorobenzaldehyde	14.0 g.	(0.1 mole)
anisaldehyde	13.6 g.	(0.1 mole)
potassium cyanide	9.0 g.	(0.15 mole)

4-Methoxy-2'-chlorobenzoin has been prepared by Buck and Ide (4) and their procedure was followed in this work. The potassium cyanide (95%) was dissolved in 71 ml. hot water in a 250 ml. flask on the steam bath and stirred while adding the anisaldehyde and o-chlorobenzaldehyde together in 80 ml. 95% ethanol. The mixture was refluxed 2 1/2 hours.

During reflux a yellow-red color clouded the solution. After reflux but before cooling, the mixture was decanted from some dark red gummy

material, cooled in the refrigerator and seeded with crystals of the benzoin.

After several hours the crystals were filtered by suction from the heavy red liquid, washed with a very small amount of cold ethanol and recrystallized from ligroin twice. The solubility is relatively low in ligroin and perhaps ethanol would work better.

Large, colorless, cubic prisms, m.p. 88-89°, were obtained in an average yield of 25% in five runs, the largest run being 1/2 mole. On standing in air the crystals of the benzoin became coated with a yellow color, probably due to their oxydation to the benzil. Steam distillation of the crude reaction mixture before isolation of the product proved to be of no value. The use of pure potassium cyanide rather than the 95% grade which we used is reported to give better yields (4).

II. CARBINOLS. (By the Grignard reaction). (Figure 4).

A. 4-Methoxyphenyl-2'-chlorobenzyl Carbinol.

Reactants:

o-chlorobenzyl chloride	80.0 g.	(0.50 mole)
magnesium	12.2 g.	(0.50 mole)
p-methoxybenzaldehyde	63.3 g.	(0.46 mole)

A 2 l. three-necked flask, fitted with condenser and calcium chloride drying tube, Hershberg dropping funnel, direct drive stirrer, and heating mantle, and containing the magnesium, was dried overnight in the hot room. To the magnesium in the flask was added 5 g. o-chlorobenzyl chloride in 75 ml. dry ether and the mixture allowed to stand three to five minutes until reaction commenced. If difficulty arose in starting, the mixture was "spiked" by the Grignard from a smaller reaction started in a test tube. The stirrer was started and 75 ml. dry ether added through the condenser. The rest of the halide was dissolved in 100 ml. dry ether and added dropwise over a period of two hours. Reflux occurred during this addition. After stirring an additional fifteen minutes, the volume of the black solution was measured in a graduate. Three aliquot portions of 2 ml. each were analyzed for Grignard reagent by the method of Gilman (42), by adding 25 ml. water, 25 ml. 0.1 N. sulfuric acid, digesting 1/2 hour on the steam bath, cooling, adding 5 drops methyl red indicator, and titrating to the first noticeable color change (orange) with 0.1 N. sodium hydroxide. The average yield of Grignard reagent for ten preparations was 92% including reactions using m-chloro and p-chlorobenzyl chlorides.

The p-methoxybenzaldehyde was dissolved in 100 ml. dry ether and was added to the Grignard reagent during 1/2 hour at reflux. Near the end of the addition a greenish-gray syrupy material separated from solution and the mixture became very difficult to stir -- hence, the use of a direct drive stirrer was advantageous.

Hydrolysis was accomplished by the dropwise addition of 80 ml. (0.46 mole) saturated ammonium chloride solution with cooling and stirring. Saturated ammonium chloride solution contains 53.5 g. (1.0 mole) ammonium chloride in 136 ml. water at 25°, making 175 ml. of approximately 28% solution. The ether layer was decanted. The solid residue contained about 5% product which was recovered by dissolving the residue with dilute sulfuric acid and extracting with ether. The combined ether extracts were washed, dried over anhydrous potassium carbonate, and most of the ether evaporated on the steam bath.

The remaining ether was removed by adding ligroin (60°) and again evaporating. Finally, the volume was brought to about one liter and the hot solution cooled to 0°. After decanting from a yellow oil, the yellow solution was seeded with seed which had been obtained by cooling a small amount of the solution to -20° in a test tube and scratching the walls. In an hour or so the carbinol had all precipitated as a bulky white solid, which after filtration and drying, gave 22 g. product melting at 64-65°. The yellow residue from decantation was re-extracted with the ligroin filtrate at the boiling point, cooled to 0°, decanted from a small amount of oil, and seeded as before. Five repetitions of the ligroin extraction gave yields of 17, 12, 9, 5, and 2 g. respectively, with the latter material being slightly colored and melting at 62-64°. The

total yield of carbinol after drying in air at 40° was 67 g. (51%). The product was recrystallized from ligroin in one operation without separation of any of the yellow oil.

In other similar preparations, 4-methoxyphenyl-2'-chlorobenzyl carbinol was obtained in yields of 50 and 57.5%.

A somewhat easier method of isolation (See II B, Experimental) used for most of the other isomeric carbinols, was not attempted with this particular one.

Vacuum distillation of the residue as described under Part II B, Experimental and discussed under Part II C, Discussion, gave 7% methoxystilbene, based on anisaldehyde. (See also Part III A, Experimental).

B. 4-Methoxyphenyl-3'-chlorobenzyl Carbinol.

Reactants:

m-chlorobenzyl chloride	80.0 g.	(0.5 mole)
magnesium	12.1 g.	(0.5 mole)
p-anisaldehyde	62.0 g.	(0.46 mole)

This alcohol was prepared from the above reactants by the procedure used for the preparation of the 2'-chloro isomer (See II A, Experimental); it has been prepared by Jenkins and Richardson (6), also by means of the Grignard reaction.

The isolation of the carbinol in this case was somewhat different than that described for the 2'-chloro isomer. The ether from the dried ether extract was evaporated, not quite completely, and the resulting solution kept at 0° for two days in the refrigerator until crystallization occurred. Filtration gave 70 g. white carbinol, m. p. 35-37°. This was recrystallized from ligroin (60°) to give a pure product, m. p. 37.5-38°. However, scratching the walls of the recrystallization vessel,

or grinding the dry material on a clay plate produced an isomorphic, stable form, m. p. 54.8-55.2°, which could not be changed back to the lower melting form. Recrystallization of the crude material from ether and drying in air at 50° gave 52 g. (44%) of the pure higher melting form.

A second preparation of about two moles size gave first the lower melting form and then after recrystallization from ether, the higher melting form in a yield of 41% based on p-anisaldehyde.

Vacuum distillation of the residues from both runs gave the corresponding methoxystilbene by dehydration in 30% yield based on anisaldehyde. The distillation was carried out in an all glass apparatus with a six inch Vigreux column. The distillation pot was heated by means of a glas-col mantle; the column and side arm could be freely brushed with a flame in case any of the distillate solidified before reaching the receiver. The distillate came over at 185-190°/1 mm. as was the case for most of the other members of this series. Before the distillate began to distill over, the material in the distillation pot underwent dehydration as visibly evidenced by bubbling in the pot and the collection of water in the dry-ice trap. This occurred at a pot temperature of about 180°.

C. 4-Methoxypheryl-4'-chlorobenzyl Carbinol.

Reactants:

p-chlorobenzyl chloride	118.0 g.	(0.74 mole)
magnesium	12.2 g.	(0.74 mole)
p-methoxybenzaldehyde	88.5 g.	(0.65 mole)

The preparation was carried out in a manner similar to that described in II A. Titration of the Grignard reagent showed a 94% yield,

so the amount of aldehyde added was regulated accordingly to 0.65 moles.

After hydrolysis of the complex with ammonium chloride and extraction of the carbinol with ether, the ether solution was dried over potassium carbonate and evaporated to about 250 ml. On standing several hours in the refrigerator at 0°, the carbinol crystallized in an almost solid white mass. This was broken up with a flat stirring rod, filtered with weak vacuum, and washed with a little cold ether.

After air-drying at 50°, the white material weighed 130 g. This was dissolved in about 750 ml. hot ligroin (95°) and treated with Norite. Small white needles, m. p. 83.0-83.6°, were obtained in a yield of 120 g. after drying in air. An additional 20 g. pure carbinol was recovered by distillation of the residue at 185-190°/1 mm. and recrystallization of the distillate from ligroin. The total yield was 140 g. (82%).

D. 3-Methoxyphenyl-2'-chlorobenzyl Carbinol.

Reactants:

o-chlorobenzyl chloride	80.0 g.	(0.50 mole)
magnesium	12.2 g.	(0.50 mole)
m-methoxybenzaldehyde	61.0 g.	(0.45 mole)

This preparation was carried out in a manner similar to those described previously. The carbinol was isolated from the ether solution directly as described in Part II B, Experimental, and recrystallized from 400 ml. ligroin (60°) to give 38 g. pure white carbinol, m. p. 66-66.6°.

An additional 20 g. of impure carbinol, m. p. 60-64°, was obtained from the ether solution as follows: The ether was evaporated and the residue dissolved in the ligroin from the first recrystallization. After cooling to 0° and decanting the ligroin from the yellow oil which sepa-

rated, the solution was seeded and the second crop of crystals permitted to separate. This second crop gave 12 g. of pure carbinol upon recrystallization. The total yield of pure carbinol was 50 g. (43%).

A second preparation gave a yield of 36%.

Distillation of the residues at 180-190°/1 mm. gave an oil which couldn't be crystallized. About a month later this oil was treated with pyridine hydrochloride (See Part IV D, Experimental) but no hydroxystilbene was isolated.

E. 3-Methoxyphenyl-3'-chlorobenzyl Carbinol.

Reactants:

m-chlorobenzyl chloride	128.0 g.	(0.80 mole)
magnesium	19.4 g.	(0.80 mole)
m-methoxybenzaldehyde	90.0 g.	(0.66 mole)

The procedure in Part II A, Experimental, was followed for this isomer. No solid carbinol could be isolated by either the method of crystallization given in Part II A or II B, Experimental, so the oil was distilled under vacuum. There was little pre-run or residue. The clear viscous distillate, b. p. 185-190°/1 mm., weighing 160 g., could not be induced to crystallize, but on treatment with pyridine hydrochloride (See Part IV E, Experimental) the corresponding hydroxystilbene was obtained as a solid. The yield was 40%, assuming that the oil before distillation was an equal mixture of the carbinol and its dehydration product, the methoxystilbene.

F. 3-Methoxyphenyl-4'-chlorobenzyl Carbinol.

Reactants:

m-chlorobenzyl chloride	80.0 g.	(0.50 mole)
magnesium	12.2 g.	(0.50 mole)
p-methoxybenzaldehyde	57.0 g.	(0.42 mole)

The procedure described in Part II A, Experimental, was followed. Titration of the Grignard reagent showed only an 84% yield in this particular run, so a correspondingly smaller amount of aldehyde was added.

The crude carbinol could not be crystallized so it was distilled at 185-190°/1.5 mm., yielding 46 g. of a yellow colored distillate which solidified upon cooling. This material had a rather wide melting range beginning at 45°. It was purified by recrystallizing twice from ligroin (60°) and gave 33 g. (32%) of the corresponding methoxystilbene. (See Part II F, Experimental).

G. 2-Methoxyphenyl-2'-chlorobenzyl Carbinol.

Reactants:

o-chlorobenzyl chloride	256.0 g.	(1.60 mole)
magnesium	39.0 g.	(1.60 mole)
o-anisaldehyde	170.0 g.	(1.25 mole)

The preparation was carried out according to the procedure described in Part II A, Experimental, and the carbinol was isolated from ligroin following evaporation of the ether in the manner described also in Part II A, Experimental. Recrystallization from ligroin gave 85 g. (26%) carbinol, m. p. 71.2-71.4°.

Distillation of the residue gave 20 g. of pre-run, boiling at 100°/4.5 mm., and a fraction of heavy reddish-colored oil boiling at 185-190°/4 mm. From the latter there was obtained 27 g. (9%) of the corresponding methoxystilbene, m. p. 62-62.5°, following recrystallization from absolute ethanol and then from petroleum ether. (See Part III G, Experimental).

H. 2-Methoxyphenyl-3'-chlorobenzyl Carbinol.

Reactants:

m-chlorobenzyl chloride	272.0 g.	(1.7 mole)
mganesium	41.3 g.	(1.7 mole)
o-methoxybenzaldehyde	190.0 g.	(1.4 mole)

The procedure outlined in Part II A, Experimental, was followed, except correspondingly larger amounts of reagents were necessary, and a three liter flask was used.

The carbinol crystallized from the concentrated ether solution as outlined in Part II B, Experimental, after standing at 0° for two and a half days. After filtering and washing with a little cold ether, 200 g. yellowish carbinol, m. p. 57-62°, was obtained. Recrystallization from ligroin did not purify the compound, but two recrystallizations from dry ether, using 200 ml. each time and cooling to 0°, gave 133 g. pure carbinol, m.p. 71-72.2°.

The solvents from the crystallization were evaporated and the residue distilled under vacuum. A small amount of pre-run boiling at 50-100°/11 mm. was discarded. Most of the remaining residue distilled at 170-190°/1 mm. as a slightly yellow oil which solidified on standing several hours. Two successive recrystallizations of the distillate from 400 ml. ligroin (60°) gave an additional 48 g. white carbinol of the same melting point as the main portion. The total yield was 180 g. or 49%.

A second preparation of 0.5 mole size gave a yield of 48%.

The distillation of the combined carbinol residues from both runs produced an oil which could not be crystallized. (See Part III H, Experimental).

I. 2-Methoxyphenyl-4'-chlorobenzyl Carbinol.

Reactants:

p-chlorobenzyl chloride	160.0 g.	(1.0 mole)
magnesium	24.3 g.	(1.0 mole)
o-anisaldehyde	109.9 g.	(0.8 mole)

The preparation of the Grignard reagent in 92% yield and the aldehyde addition were carried out according to the procedure outlined in Part II A, Experimental. The carbinol was isolated from the dried ether extract by cooling to 0° for several hours as described in Part II B, Experimental. Recrystallization from absolute ethanol gave 70 g. of carbinol, m. p. 120-122°. Recrystallization from ligroin gave a less pure product of m. p. 116-121° whereas recrystallization from toluene raised the m. p, to 122-123°.

The ether liquors were evaporated and the residue dissolved in the alcohol liquors. After cooling several hours, a second crop of crystals was obtained. This gave 9 g. pure carbinol after recrystallization from absolute ethanol. The total yield at this point was 79 g. (43%).

Vacuum distillation of the residue (See Part II B, Experimental) produced a reddish oil, b. p. 185-190°/1 mm., which after recrystallization from ethanol gave white crystals having a wide melting range. Recrystallization from toluene produced a small amount (7 g.) of the carbinol of m. p. 122-123°. The total yield of carbinol was 46%.

In two other preparation the yields were 32% and 23%.

J. 4-Methoxymethoxyphenyl-2'-chlorobenzyl Carbinol.

Reactants:

o-chlorobenzyl chloride	24.0 g.	(0.15 mole)
magnesium	3.6 g.	(0.15 mole)
p-methoxymethoxybenzaldehyde	25.0 g.	(0.15 mole)

This preparation was carried out in the manner described in Part A of this section. About 40 g. of an oil was obtained after evaporation of the ether. This oil did not solidify in two days at -80°. It could not be crystallized from ligroin, benzene, ethanol, nor dilute methanol. Five grams of the yellow, viscous methoxymethoxy carbinol were heated at 110° for 1/2 hour with stirring in 100 ml. of a solution of 20% concentrated hydrochloric acid in glacial acetic acid. The solution turned dark after 15 minutes. At the end of the reaction period the mixture was poured into water. A dark green resin was precipitated which had no definite melting point but appeared to soften around 130°. It was soluble in ethanol and dissolved in 5% potassium hydroxide. Nothing could be obtained upon attempted recrystallization.

A portion of the methoxymethoxy carbinol was converted to the corresponding hydroxystilbene in 15% yield by refluxing with acetic anhydride, followed by hydrolysis of the resulting acetate with alkali. (See Part V A, Experimental).

The remaining oil was distilled under vacuum. At a pot temperature a little above 100° water appeared to be split out of the compound. A small amount of white distillate came over at 80-100° and solidified almost immediately. Two recrystallizations from toluene gave crystals melting at 116° with some previous softening. A dilute solution of bromine in carbon tetrachloride showed that the unidentified compound was saturated. The residue in the distillation flask had rather suddenly become quite thick at the end of the distillation, as if polymerization had taken place.

III. METHOXYCHLOROSTILBENES.

A. 4-Methoxy-2'-chlorostilbene.

1. By Methylation of the Hydroxystilbene (Figure 5).

Reactants:

4-hydroxy-2'-chlorostilbene	3 g.
dimethyl sulfate	4 ml.
potassium hydroxide	4 g.
dioxane (commercial grade)	60 ml.

To the stilbene dissolved in dioxane was added, with mechanical stirring, 2 g. potassium hydroxide dissolved in 3 ml. water. The yellow potassium salt of the hydroxystilbene began to appear immediately, and tended to stick to the sides of the flask. After 1/2 hour, dimethyl sulfate (2 ml.) was added. The temperature rose to 30° and did not begin to fall for 15 minutes. After one hour the yellow potassium salt had disappeared, leaving a clear solution which tested basic. Methyl sulfate (2 ml.) and potassium hydroxide (2 g.) in 2 ml. water were added and the mixture stirred at room temperature for about 4 1/2 hours.

The reaction mixture was decanted into water leaving some residue at the bottom of the flask. The product precipitated and was filtered off. Recrystallization from ethanol or glacial acetic acid gave an almost quantitative yield of 4-methoxy-2'-chlorostilbene as white plates, m.p. 59.8-60.4°.

Bergmann and Schapiro (2) have prepared this compound in 14% yield by the Meerwein reaction (1).

2. By Dehydration of the Carbinol (Figure 5).

(a). Dehydration of carbinols by distillation is discussed under Part II C, Discussion, and a representative procedure is described under Part II B, Experimental. Distillation of the oil which was left after crystallization of the 4-methoxyphenyl-2'-chlorobenzyl carbinol gave a 7% yield of the methoxystilbene based on the anisaldehyde used in the Grignard reaction. This product was identical with the 4-methoxy-2'-chlorostilbene obtained by the several other methods herein described, as shown by mixed melting points.

(b). Chemical dehydration as discussed under Part II, Discussion, was accomplished by refluxing 2 g. of the carbinol at 52° for six hours with a mixture made by cautiously adding 40 ml. acetyl chloride to 6 ml. 37% hydrochloric acid with cooling. Ice and water (200 ml.) were added with stirring. The product separated as a solid and was filtered and pressed as dry as possible on the filter. The damp solid was then recrystallized from absolute ethanol to give 1.4 g. (75%) of 4-methoxy-2'-chlorostilbene.

The method of Jenkins and Richardson (6) was also repeated. 4-Methoxyphenyl-2'-chlorobenzyl carbinol (26 g.) was heated at 100° one hour with 400 ml. of 20% by weight concentrated hydrochloric acid in glacial acetic acid. Ice and water were added with stirring to make one liter and the white solid which precipitated was filtered. After solution in hot absolute ethanol and cooling, the solution was decanted from a red oil which settled on the bottom of the flask and was seeded with some crystals of the methoxystilbene at 0°. When crystallization was complete, the mixture was filtered, giving 8 g. (32%) of the methoxystilbene, m.p. 57-59°.

Recrystallization from absolute ethanol gave 6 g. pure product, m.p. 59.8-60.4°. Reworking the filtrates and oil gave another 4 g. of slightly less pure material. The total yield was 40%.

When the residues were retreated with acetic acid and hydrochloric acid at 100° as before, another 3 g. was obtained.

Dehydration was also attempted with acetic anhydride (40 ml.) using 2 g. of the carbinol and refluxing at 135° for 13 hours. After hydrolysis with ice and water, the products were extracted with ether. The ether solution was washed with water, dried over potassium carbonate, and evaporated on the steam bath while replacing the ether with ligroin (60°). Cooling the ligroin solution for several hours gave an oil which did not crystallize.

3. By Reduction-dehydration of the Benzoin (Figure 3).

Reactants:

4-methoxy-2'-chlorobenzoin	5.0 g.
zinc (powdered)	10.0 g.
mercuric chloride	2.5 g.

An amalgam was prepared according to the procedure of Ballard and Dehn (10), by adding the powdered zinc with stirring to a solution of the mercuric chloride in 35 ml. water. The temperature rose to 32° then subsided. After two or three hours stirring, the amalgam was washed three times with water by decantation.

The benzoin, prepared in Part I, K, Experimental, was dissolved in 35 ml. ethanol and added to the amalgam. Concentrated hydrochloric acid (20 ml.) was added dropwise over a period of 1 1/2 hours. During this time, the amalgam became coated, reducing its efficiency, but after the addition of 25 ml. benzene the coating disappeared. Hydrochloric acid

(20 ml.) was added rapidly and the mixture stirred three hours. At the end of this time 15 ml. hydrochloric acid and 15 ml. benzene were added and stirring continued for six hours. The temperature throughout was about 25°. The amalgam eventually rolled up into large balls and was then useless for further reaction.

The aqueous layer was separated and discarded after extracting once with ether. The organic portion was washed once with water, then 5% sodium carbonate solution, and dried over potassium carbonate. The solvent was removed under vacuum and the residual oil taken up in hot ligroin. The ligroin was decanted from some undissolved oil and on cooling, precipitated crystals of an unidentified substance in small yield. One recrystallization from acetic acid gave crystals, m.p. 220°. The material showed no unsaturation when treated with dilute bromine in carbon tetrachloride.

The same treatment of the oil using petroleum ether gave a small amount of the desired methoxystilbene, m.p. 59-60°, as shown by a mixed melting point with this compound prepared by other methods.

When dioxane instead of ethanol was used as a solvent for the benzoin, only the high melting unidentified compound was isolated in small yield.

When methanol was used as a solvent and the time of reaction was four hours, another unidentified product was isolated in small yield as the sole product of reaction. Recrystallization from 95% ethanol gave white needles, m.p. 96-96.5°. This compound was found, by mixed melting point, to be identical to that obtained as a by-product during the preparation of 4-methoxyphenyl-2'-chlorobenzyl carbinol by the Grignard reaction.

(See Part II, A, Discussion). This may be the desoxybenzoin. It showed no unsaturation when treated with a dilute solution of bromine in carbon tetrachloride.

B. 4-Methoxy-3'-chlorostilbene (Distillation of the Carbinol).

The residual oil from the isolation and purification of the carbinol, prepared in a yield of 42% by the Grignard method in two runs totaling 2.5 moles, as described in Part II B, Experimental, was vacuum distilled at about 180°/1 mm. to give a clear distillate which solidified in the receiver. Two recrystallizations from absolute ethanol gave 176 g. of the methoxystilbene as white plates, m.p. 94.0-94.6°. This represents a yield of 30% based on anisaldehyde. The procedure and equipment used is described under Part II B, Experimental. This compound has also been prepared by Jenkins and Richardson (6) by dehydration of the carbinol using concentrated hydrochloric acid and glacial acetic acid at 100°.

C. 4-Methoxy-4'-chlorostilbene.

1. By the Meerwein Reaction (Figure 2).

Reactants:

p-chloroaniline	32.0 g.	(0.25 mole)
sodium nitrite	17.0 g.	(0.25 mole)
p-methoxycinnamic acid	44.5 g.	(0.25 mole)
acetone	400.0 ml.	
chloroacetic acid	35.0 g.	(0.37 mole)
sodium bicarbonate	31.0 g.	(0.37 mole)
cupric chloride dihydrate	10.0 g.	

A diazonium salt solution was prepared by dissolving the p-chloroaniline in a solution containing 200 ml. 37% hydrochloric acid and 370 ml. water with mechanical stirring, cooling to 2° (whereupon the white

hydrochloride separated from solution) and then adding the sodium nitrite dissolved in 25 ml. water slowly over about five hours at 2° to 4°.

The above solution was added all at once at about 10° to a solution of the methoxycinnamic acid in 400 ml. acetone, buffered with the chloroacetic acid and sodium bicarbonate in 100 ml. water, in a 1-l. flask. The cupric chloride dihydrate in 10 ml. water was then added to catalyze the reaction, and the temperature was slowly raised to 20° where the first signs of reaction became apparent, namely the evolution of gas bubbles and a spontaneous temperature increase. The reaction was more vigorous at 27°, where the temperature was held for 1/2 hour with some cooling necessary. The reaction mixture was stirred three hours at room temperature following which the acetone was removed under vacuum. The dark gummy mass which remained after the removal of the acetone was taken up in ether and the ether solution extracted with 5% sodium carbonate solution. Upon acidification of the extract, 17 g. unreacted p-methoxycinnamic acid was isolated. The ether solution after the carbonate extraction was washed with water and dried over sodium sulfate. Some difficulty with emulsion was encountered during extraction and washing of the ether solution.

The ether was evaporated on the steam bath and replaced with toluene, which was heated to boiling on a hot plate. The hot toluene was decanted from some tarry residue and evaporated under vacuum. The residue was recrystallized from 200 ml. absolute ethanol. After filtration and drying in air, the crystalline 4-methoxy-4'-chlorostilbene weighed 10 g. and melted at 180.5-181.0°. Re-working of the residues gave an additional 3 g. product of lower purity. The total yield was 15 g. or 25%. The yield based on recovery of p-methoxycinnamic acid was 40%.

4-Methoxy-2'-chlorostilbene has been prepared by Meerwein and co-workers (1) by the above method in 60% yield.

2. By Methylation of the Hydroxystilbene.

4-Hydroxy-4'-chlorostilbene, prepared by the Meerwein reaction (see Part IV C, Experimental), was methylated by the procedure described in Part III A, 1, Experimental, in almost quantitative yield, giving a product identical to that obtained by methods 1 and 3.

3. Dehydration of the Carbinol.

Pure 4-methoxyphenyl-4'-chlorobenzyl carbinol (52 g.) was distilled with a little mineral acid in an all glass apparatus described in Part II B, Experimental. (See also Part II C, Discussion). The distillate came over colorless at 185-200°/1 mm. and solifified in the receiver almost immediately. Recrystallization from glacial acetic acid gave shiny plates. A mixed melting point showed the compound to be identical with that obtained in 1 and 2. The yield was 82%.

D. 3-Methoxy-2'-chlorostilbene.

Methylation of the hydroxystilbene with dimethyl sulfate according to the procedure described in Part III A, 1, Experimental, gave an oil which could not be crystallized from absolute ethanol or petroleum ether even after distillation of the oil at 158°/2 mm. The oil had a slight yellow coloration. An index of refraction could not be found at 20° but on heating the refractometer a very faint line was found, N_D^{40} 1.6403. (This was checked by another observer).

E. 3-Methoxy-3'-chlorostilbene.

Reactants:

3-hydroxy-3'-chlorostilbene	20 g.
dimethyl sulfate	50 ml.
potassium hydroxide	40 g.

The methylation was carried out in 50 ml. dioxane as described in Part III A, 1, Experimental. The reaction mixture was diluted with water following methylation, but no precipitate formed so the mixture was extracted with ether. The ether solution was washed once with water, dried over potassium carbonate and the ether evaporated on the steam bath, being replaced with 200 ml. absolute ethanol. The hot ethanol solution was cooled to 0° overnight, whereupon crystals separated. Filtration gave 16 g. of product, m.p. 40-42°. Recrystallization from petroleum ether gave 10 g., m.p. 41.8-42.2°. A further recrystallization produced no change in melting point. Re-working the liquors gave an additional 3 g. of slightly less pure material. The total yield was 14.5 g. or 70%.

F. 3-Methoxy-4'-chlorostilbene.

1. By distillation.

The oil obtained as a product of the Grignard reaction between m-methoxybenzaldehyde and p-chlorobenzylmagnesium chloride (See Part II F, Experimental) was distilled at 175°/0.5 mm. to give 46 g. yellowish oil which solidified in the receiver after standing several hours at room temperature. Two recrystallizations from ligroin gave 33 g. of 3-methoxy-4'-chlorostilbene, m.p. 71.0-71.6°. This is a yield of 33% based on m-methoxybenzaldehyde. (See also Part II, C, Discussion).

The dark colored residue which remained in the distillation flask was treated with hot ligroin, the ligroin decanted and cooled to give a small number of crystals, m.p. 133-133.5°. This was not the hydroxystilbene which melts at about 135°, as shown by a mixed melting point with that material. A dilute bromine in carbon tetrachloride solution showed the unidentified substance to be saturated. It could possibly be 3-methoxyphenyl-4'-chlorobenzyl carbinol which had not been isolated in crystalline form, although with such a high melting point, it should not have been so resistanct to crystallization when first prepared.

2. By methylation.

One gram 3-hydroxy-4'-chlorostilbene (See Part IV F, Experimental) was methylated in the manner described in Part III A, Experimental, to give an almost quantitative yield of the methoxystilbene after recrystallization from absolute ethanol. The melting point and mixed melting point was identical to that obtained for the 3-methoxy-4'-chlorostilbene prepared above in 1.

G. 2-Methoxy-2'-chlorostilbene.

The red oily residue, following isolation of the carbinol in 30% yield (See Part II G, Experimental), was distilled (See Part II B, Experimental, and Part II C, Discussion) at 185°/3 mm. to give a viscous yellowish oil which crystallized from petroleum ether when the solution cooled to the temperature of dry ice. Recrystallization gave beautiful prisms, m.p. 62.0-62.5°. The yield was about 11% based on o-methoxybenzaldehyde used in the Grignard reaction.

H. 2-Methoxy-3'-chlorostilbene.

1. Methylation of 1 g. 2-hydroxy-3'-chlorostilbene (See Part IV, H, Experimental) with dimethyl sulfate in the manner described in Part III A, Experimental, gave an almost quantitative yield of methoxystilbene after recrystallization from absolute ethanol, m.p. 36.3-36.4°.

2. Pure 2-methoxyphenyl-3'-chlorobenzyl carbinol (See Part II H, Experimental) was distilled under vacuum in the presence of mineral acid. (See Part II B, Experimental, and also Part II, C, Discussion). The distillate from 40 g. carbinol, b.p. 185-190°/1 mm. weighed 29 g. and crystallized upon cooling to 0° in absolute ethanol to give 19 g. white needles, m.p. 36.2-36.4°. The yield was 51%.

I. 2-Methoxy-4'-chlorostilbene.

Pure 2-methoxyphenyl-4'-chlorobenzyl carbinol (See Part II, I, Experimental) was distilled under vacuum in the presence of mineral acid. (See Part II B, Experimental, and also Part II, C, Discussion). The fraction coming over at 170-180°/1 mm. solidified in the receiver almost immediately. Two recrystallizations from absolute ethanol gave 8 g. methoxystilbene, m.p. 82.4-83.1°. The fraction coming over at 180-200/1 mm. was recrystallized from ligroin to give mainly undehydrated carbinol. The residues from distillation and crystallization were again combined and distilled with a little mineral acid present. This time 14 g. of pure methoxystilbene was isolated, bringing the total yield to 22 g. or about 50%.

IV. HYDROXYCHLOROSTILBENES.

A. 4-Hydroxy-2'-chlorostilbene.

1. By Demethylation-dehydration of the Carbinol (Figure 5).

Reactants:

4-methoxyphenyl-2'-chlorobenzyl carbinol	60 g.
pyridine	180 ml.
hydrochloric acid (concentrated)	180 ml.

The pyridine hydrochloride reagent was made by adding the pyridine (redistilled) to the hydrochloric acid all at once, whereupon the temperature rose almost to the boiling point of pyridine. The temperature was raised to 200° with the flask open to the air, allowing any excess of reagents to boil out, leaving only pyridine hydrochloride. Buu-Hoi and Hoan (9) made this reagent by introducing anhydrous hydrogen chloride into anhydrous pyridine in a suitable solvent. This latter method was more troublesome and gave no better yields in this work. Ordinary technical grade pyridine gave a 5% lower yield in a single run.

The carbinol, dissolved in about 20 ml. pyridine was added all at once to the pyridine hydrochloride reagent, and the solution was stirred mechanically at 200° for one and a half hours. The light red solution was then cooled to about 120°. Below this temperature, the mixture began to solidify. Ice was added and then cold water was rapidly added to make a volume of about 600 ml. Ether was added and stirring continued for several minutes. The ether layer was separated, washed twice with water, and dried over potassium carbonate. The light red ether solution

was then concentrated in an air stream on the steam bath and the ether replaced with ligroin (90°). The hot ligroin was decanted from the red tar on the bottom of the flask. It was necessary that the ether was completely removed or some of the tar carried over into the toluene and contaminated the product. The ligroin solution was cooled and the crystals filtered to give 43 g. of crude hydroxystilbene (slightly pink colored), m. p. 113-114°. Two recrystallizations of the crude product from toluene, using 130 ml. and 80 ml. respectively, gave crystals of m. p. 113.8-114.1°. Norite was used in some cases to remove some of the color. The yield was 67%. Two other runs gave yields of 48% and 83%.

When the carbinol was heated with pyridine hydrochloride longer than 1 1/2 hours at 200°, the yield was somewhat lower and more tar was formed. A heating period of less than 1 1/2 hours, however, also gave a somewhat lower yield.

2. By Demethoxymethylation-dehydration of the Methoxymethoxy Carbinol.

4-Methoxymethoxyphenyl-2'-chlorobenzyl carbinol, 5 g., prepared in Part II J, Experimental, was stirred for two hours at 120-135° with 30 ml. acetic anhydride. The solution became very dark red during 1/2 hour of heating, but then became lighter in color. After three hours it was again relatively light colored. The mixture was poured into ice and water and extracted with ether. The ether extract was washed and heated with 15% potassium hydroxide solution at 100° for 4 hours. This mixture was poured into water and extracted with ether. The alkaline aqueous portion was acidified, giving an oil which was extracted with ether. The ether solution was washed with water and dried over sodium sulfate. The

ether was evaporated on the steam bath and the residue taken up in ligroin. Upon cooling the ligroin solution, white crystals were obtained. After recrystallizing twice from toluene, in which the substance was quite soluble at room temperature, and cooling to the temperature of dry ice, a 15% yield of the desired hydroxystilbene was obtained, m. p. 112-113°. This melting point is a little low, but a mixed melting point with material prepared by means of the Meerwein reaction showed no depression.

3. By the Meerwein Reaction (Figure 2).

The procedure described in Part III C, Experimental, was followed, except that half the quantities of materials was used, and o-chloroaniline was substituted for p-chloroaniline.

After addition of the catalyst and warming, reaction commenced at 19-21° but was not very vigorous. The temperature climbed slowly to 37° and then began to fall. The mixture was stirred two hours longer at room temperature and then worked up as before. Only 1 1/4 g. product could be isolated in pure form (after recrystallization from toluene). The melting point and mixed melting point were identical with that obtained for this compound by method 1. The yield was 4.5%. Bergmann and Schapiro (2) obtained a yield of 14% using p-methoxycinnamic acid and o-chloroaniline.

4. By Demethylation of the Methoxystilbene (Figure 5).

4-Methoxy-2'-chlorostilbene (1 1/2 g.) was stirred at reflux for six hours with a reagent prepared by adding 10 ml. 48% hydrobromic acid cautiously to 50 ml. acetic anhydride. After refluxing, the solution was poured with stirring into about 600 ml. water. The mixture was extracted

with ether and the ether washed and dried. The ether was removed by evaporation on the steam bath and was replaced with methanol. About 10 g. potassium hydroxide in 10 ml. warm water was added and the solution refluxed for four hours. The solution was acidified with concentrated hydrochloric acid, and extracted with ligroin while warm. Upon cooling the ligroin solution, crystals of hydroxystilbene were obtained in low yield (0.2 g.).

Bergmann and Schapiro (2) prepared the methoxystilbene by means of the Meerwein reaction. Their attempt to demethylate this compound by boiling in 48% hydrobromic acid was unsuccessful.

B. 4-Hydroxy-3'-chlorostilbene.

This compound was prepared by dehydration-demethylation with pyridine hydrochloride in the manner described in Part IV A, 1, Experimental. Recrystallization of the crude material from toluene gave white needles, m. p. 129.9-130.1°. Four runs averaging about 50 g. each gave yields of 34%, 50%, 50%, and 55%, respectively.

C. 4-Hydroxy-4'-chlorostilbene.

This compound was prepared by the Meerwein reaction as described in Part III C, 1, Experimental. In a 0.25 mole run, 41 g. of p-hydroxycinnamic acid was used instead of p-methoxycinnamic acid. The other reactants were used in the same quantities. Reaction commenced at about 20°. The mixture was stirred 3 hours at room temperature. The crude compound was obtained from toluene, after decantation from tar, but upon attempted recrystallization it was found to have become less soluble in toluene. Recrystallization from glacial acetic acid gave 14 g., (22%),

m. p. 183.5-184.0°. About 22 g. of the unreacted cinnamic acid was recovered. The yield is about 40% based on this recovery.

Meerwein (1) also prepared this compound in 56% yield by the same method.

D. 3-Hydroxy-2'-chlorostilbene.

The procedure for demethylation-dehydration of the corresponding carbinol by means of pyridine hydrochloride at 200° as described in Part IV A, 1, Experimental, was used for the preparation of this isomer. Recrystallization of the crude material once from toluene followed by a single recrystallization from ligroin gave needles, m. p. 83.8-84.2°, in a yield of 58%.

Since neither methylation nor hydrogenation produced well defined crystalline compounds, the p-chlorobenzoate derivative was prepared in the manner described in Part V A, Experimental. Two recrystallizations from absolute ethanol gave the pure p-chlorobenzoate, m. p. 104.6-105.0°.

E. 3-Hydroxy-3'-chlorostilbene.

The procedure for demethylation-dehydration of the carbinol by means of pyridine hydrochloride at 200°, as described in Part IV A, 1, Experimental, was used for the preparation of this isomer. The starting material was not pure since the carbinol did not crystallize after its preparation by the Grignard reaction; the oil was distilled, however, and used as a viscous, light colored liquid, which contained both carbinol and methoxystilbene. (See Part II E, Experimental).

The crude hydroxychlorostilbene was somewhat less soluble in hot ligroin than the other hydroxychlorostilbenes, hence, several extractions

of the tar with ligroin were necessary. After recrystallization from toluene and then from ligroin, material of melting point 68.5-69.2° was obtained in an average yield of 31% for four runs, based on the weight of oil used.

F. 3-Hydroxy-4'-chlorostilbene.

1. By Dehydration-demethylation of the Carbinol.

The starting material was a clear viscous oil, containing both the carbinol and the methoxystilbene, obtained by distillation of the crude yellow oil from the Grignard reaction. (See Part II F, Experimental). The pure carbinol could not be crystallized, either from the crude yellow oil before distillation, or from the distillate. After treatment of the above material with pyridine hydrochloride, the crude hydroxystilbene was extracted with hot ligroin and worked up as described in Part IV A, 1, Experimental. Recrystallization from toluene after Norite treatment gave a product of m. p. 134.7-134.9°. The yields in this and another reaction, respectively, were 70% and 60% based on the weight of the oil used.

2. By Demethylation of the Methoxystilbene.

Some of the oil containing both carbinol and methoxystilbene which was used as a starting material in the preceding experiment, was subsequently crystallized from ethanol to give pure 3-methoxy-4'-chlorostilbene. (See Part II F, Experimental). This pure compound was then demethylated with pyridine hydrochloride as in method 1, above, to give a 77% yield of the corresponding hydroxystilbene.

3. By the Meerwein Reaction.

The method described in Part III G, 1, Experimental, was used to prepare this isomer in 1.0% yield. The melting point and mixed melting point checked with that obtained above by a different method.

G. 2-Hydroxy-2'-chlorostilbene.

The procedure for demethylation-dehydration of the carbinol by means of pyridine hydrochloride at 200°, as described in Part IV A, 1, Experimental, was used for the preparation of this compound. The crude material from the ligroin extraction was orange in color and there seemed to be more tar than usual. Two recrystallizations from small amounts of toluene, without Norite treatment, gave white prisms, m. p. 132.0-132.6°. The yields of pure material in three runs were 47%, 32%, and 37%.

H. 2-Hydroxy-3'-chlorostilbene.

The carbinol was treated with pyridine hydrochloride at 200° as described in Part IV A, 1, Experimental. Two recrystallizations of the crude material from toluene gave white crystals, m.p. 80.8-81.1°. The yields of pure material in three runs were 36%, 38%, and 45%.

I. 2-Hydroxy-4'-chlorostilbene.

The carbinol was treated with pyridine hydrochloride at 200° as described in Part IV A, 1, Experimental. Two recrystallizations of the crude material from toluene gave a pure white product, m. p. 122.5-123.0°. This is almost exactly the melting point of the carbinol, but a mixed melting point with that material showed a large depression. The yields of hydroxystilbene in three reactions were 50%, 48%, and 54%.

V. HYDROXYCHLOROBIBENZYLS.

A. 4-Hydroxy-2'-chlorobibenzyl.

1. Hydrogenation of the Hydroxystilbene (Figure 6).

Raney nickel catalyst (W-2) was prepared according to the procedure of Mozingo (43). For the preparation of this bibenzyl, 19 g. 4-hydroxy-2'-chlorostilbene was dissolved in 50 ml. absolute ethanol and refluxed twice over 5 g. portions of Raney nickel; the clear solution after filtration was rocked at 50° for five hours under 1000 pounds initial hydrogen pressure, using 10 g. Raney nickel catalyst, in a 500 ml. hydrogenation bomb. The solution was filtered and the ethanol evaporated, being replaced with petroleum ether. The solvent was cooled to 0° and decanted from an oil which settled to the bottom of the flask. On standing overnight at 0°, the bibenzyl crystallized and was filtered and dried. Several extractions of the oil which settled out gave additional material. The bibenzyl was recrystallized from petroleum ether, giving 10 g. (53%), m. p. 60.0-61.0°.

Hydrogenation of the stilbene was also successful when copper chromium oxide catalyst was substituted for Raney nickel.

Attempts to reduce this compound without first refluxing over Raney nickel at least once and preferably twice were unsuccessful.

2. Preparation of the p-Chlorobenzoate Derivative.

4-Hydroxy-2'-chlorobibenzyl (3 g.) was dissolved in 10 ml. dry, redistilled pyridine, and 2 ml. p-chlorobenzoyl chloride added. Heat was

generated and in a moment the mixture became a semi-solid mass. The mixture was heated for a few minutes on the steam bath, diluted with water, and extracted with ether. The ether was washed with water, dilute (2 N.) sulfuric acid solution, water, and finally with 5% sodium bicarbonate solution. After drying over potassium carbonate, the ether was evaporated on the steam bath and the residue taken up in absolute ethanol. Crystals precipitated from the ethanol solution when it was cooled to 25°. These were filtered and recrystallized a second time from ethanol to give about 1.5 g. of the p-chlorobenzoate, m.p. 109.4-109.8°.

B. 4-Hydroxy-3'-chlorobibenzyl.

Several attempts were made to obtain a pure bibenzyl by reduction of the corresponding stilbene according to the method described in Part A of this section. The bibenzyl was isolated in low yield, m. p. 36-38°, and gave a chloride analysis which was approximately one per-cent low. (See Table V). The p-chlorobenzoate derivative which was prepared by the method described in Part A of this section, however, was easily purified and gave the correct analysis. After two recrystallizations from absolute ethanol, the melting point was 90.5-91.1°.

C. 4-Hydroxy-4'-chlorobibenzyl.

Hydrogenation of 22 g. 4-hydroxy-4'-chlorostilbene by the method described in Part A of this section, using 10 g. Raney nickel at 70° for 3 1/2 hours under 1000 pounds initial hydrogen pressure, gave 14 g. crude bibenzyl from ligroin, m. p. 114-116°. Recrystallization from ligroin (90°) gave 11.5 g. (51%) of product, m. p. 115.8-116.1°. Several hydro-

genations were carried out, each giving approximately the same results.

The p-chlorobenzoate derivative was prepared as described in Part A of this section. Two recrystallizations from absolute ethanol gave a nicely crystalline material, m. p. 133.8-134.4°.

D. 3-Hydroxy-2'-chlorobibenzyl.

The corresponding stilbene was hydrogenated by the method described in Part A of this section. The bibenzyl was an oil at room temperature. It was crystallized from ligroin at -30°, and the melting point taken on a previously cooled block. M. p. 20-22°. The bibenzyl was distilled at 160°/2 mm. N_D^{50} 1.5812. No refractive index could be found at 20°.

The p-chlorobenzoate, prepared in the manner described above and recrystallized twice from absolute ethanol, melted at 60.2-60.8°.

E. 3-Hydroxy-3'-chlorobibenzyl.

The corresponding stilbene (20 g.) was hydrogenated by the method described in Part A of this section. Four grams of product, m. p. 30-32°, was obtained as crystals from ligroin after standing two days at -30°. The remaining material was distilled at 165°/1 mm. to give an oil. It was impossible to find a refractive index for this material at temperatures up to 50°.

The p-chlorobenzoate, prepared in the manner described above and recrystallized twice from absolute ethanol, melted at 59.8-60.5°.

F. 3-Hydroxy-4'-chlorobibenzyl.

The corresponding stilbene was hydrogenated by the method described in Part A of this section. The crude material, recrystallized twice from

petroleum ether gave a product of 44.8-45.3°. Further recrystallization from either petroleum ether or absolute ethanol did not raise the melting point. The yield was 38%. Hydrogenation with copper-chromium oxide catalyst under the same conditions gave the bibenzyl in about 70% yield.

The p-chlorobenzoate derivative, prepared in the manner previously described and recrystallized twice from absolute ethanol, melted at 75.2-76.0°.

G. 2-Hydroxy-2'-chlorobibenzyl.

The corresponding stilbene (11 g.) was hydrogenated by the method described in Part A of this section. The temperature of reduction was 70° in this case. After two recrystallizations from ligroin, the yield was 36%. M. p. 71.2-71.5°.

The p-chlorobenzoate, prepared and recrystallized as described above, melted at 99.3-99.9°.

H. 2-Hydroxy-3'-chlorobibenzyl.

The corresponding stilbene (18 g.) was hydrogenated by the method described in Part A of this section. The temperature of reduction was 70° and the time of heating was five hours. The yield of product of m. p. 54.0-54.6°, crystallization from ligroin, was 9 g. or 50%.

The p-chlorobenzoate, prepared and recrystallized as described in Part A of this section, melted at 67.1-67.9°.

I. 2-Hydroxy-4'-chlorobibenzyl.

The corresponding stilbene (11 g.) was hydrogenated by the method described in Part A of this section. The bibenzyl was obtained in 55%

yield after one recrystallization from ligroin using Norite A and melted at 95.4-96.0°. In a second run the hydrogenation was carried out at 70° for twelve hours, giving the bibenzyl in 63% yield.

The p-chlorobenzoate, m. p. 55.8-56.2°, was prepared and recrystallized twice from absolute ethanol. In the first crystallization it was necessary to cool the alcohol solution to -30° before crystallization occurred.

VI. CHLORIDE ANALYSIS.

The chloride analyses were carried out by fusing the organic compound in a Parr bomb with sodium peroxide, and determining the chloride volumetrically by a modification of the Volhard method (53) as described below. The directions followed for the fusion were those given in a monograph published by the Parr Instrument company of Moline, Illinois (53).

To approximately 0.2 g. organic sample was added 15 g. sodium peroxide, 3 g. potassium nitrate, and 1 g. sucrose, the bomb sealed and the mixture shaken well to mix. Potassium nitrate is not necessary according to Beamish (53). In the few cases where a liquid sample was used, the fusion mixture was stirred well before sealing the bomb. The fusion bomb was placed in a special metal cylinder which exposed only the bottom portion of the bomb and protected the rubber gasket from overheating; the fusion mixture was ignited by heating a minute or two with a Meeker burner. A hissing sound was evidence that fusion had taken place; the bomb was heated another 10 or 15 seconds and quenched by immersion in cold water. The bomb was dried, opened carefully, and laid sideways in a beaker of hot distilled water, the water just covering the bomb. The fusion mixture dissolved rapidly. The bomb was removed with tongs and washed with distilled water. Concentrated nitric acid was added to

the solution in the beaker, cautiously, as the peroxide decomposed with considerable foaming; the solution was boiled for about five minutes. While waiting for the solution to cool, more samples were weighed out.

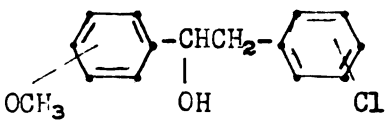
To the acid solution, containing the chloride to be determined, was added excess standard silver nitrate solution, approximately 0.1 N., which had been prepared by drying silver nitrate in an oven at about 105°, weighing a given amount carefully, and diluting to a know volume. Nitrobenzene, 5 ml., was added to coat the silver chloride precipitate and prevent its further reaction during titration. Ferric alum indicator, 5 ml. was added and the excess silver nitrate titrated to the first appearance of a pink color with approximately 0.1 N. potassium thiocyanate solution, which had previously been standardized against the silver nitrate solution. A blank determination was carried out in duplicate, showing that there was no measurable chloride contamination from outside.

Eight samples were carried through the fusion and titration as a unit. This required about 3 1/2 hours for the complete determination, but during this time it was also possible to weigh out the next batch of samples, and to make most of the calculations using logarithms. It was found possible to do eight samples in as little as 2 1/2 hours by working rapidly and efficiently.

Results of the chloride analyses appear in Tables II-VI. In general they tend to be a little low. This may be normal for these types of compounds since Lemp and Broderson (56), as well as Cook and Cook (57), reported that consistantly low results were normal for chlorinated biphenyls.

TABLE II

METHOXYPHENYLCHLOROBENZYL CARBINOLS

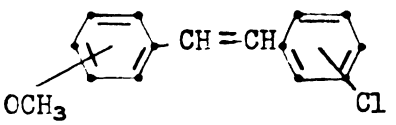


OCH_3	Cl	M.P., °C.	Average Yield, %	% Cl [a]	Page
4	2'	64.0-65.0	51	13.32	41
4	3'	37.5-38.0 54.8-55.2 [b]	44	c	43
4	4'	83.0-83.6	82	13.23	44
3	2'	66.0-66.6	43	13.49	45
3	3'	Oil [e]		d	46
3	4'	Oil [e]		d	46
2	2'	71.2-71.4	26	13.25	47
2	3'	71.6-72.2	48	13.25	48
2	4'	122-123	46	12.73	49

a. Calculated for $C_{15}H_{15}ClO_2$: Cl, 13.49%.
b. This compound exists in two isomorphic forms, the higher melting one being the most stable.
c. Previously prepared by Jenkins and Richardson (6).
d. These oils were not purified sufficiently for analysis.
e. Oil obtained by distillation of crude reaction product at 185-190°/1 mm. gave no crystalline carbinol.

TABLE III

METHOXYCHLOROSTILBENES [a]

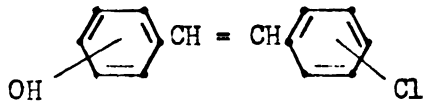


OCH_3	Cl	M.P., °C. [b]	Method [c]	Average Yield, %	% Cl [d]	Page
4	2'	60	D	75	e	52
			S	f		51
			R	low		53
4	3'	94	D"	30	g	55
4	4'	181	M	25	h	55
			D'	82		57
			S	f		57
3	2'	158/2 mm. [i]	S	f	14.32	57
3	3'	42	S	70	14.38	58
3	4'	71	S	f	14.29	59
			D"	33		58
2	2'	62	D"	11	14.35	59
2	3'	36	S	f	14.38	60
			D'	51		60
2	4'	83	D'	30	14.45	60

a. See Table I for complete data on dehydration of carbinols.
b. Melting point ranges are listed in the Experimental section.
c. Methods: D, dehydration of carbinol with AcCl, HCl, and HOAc; D', dehydration of pure carbinol by distillation with mineral acid; D", dehydration of carbinol residues by distillation (without acid); S, methylation of the Hydroxystilbene; M, Meerwein reaction; R, reduction and dehydration of the benzoin.
d. Calculated for $C_{15}H_{13}ClO$: Cl, 14.49%.
e. Prep'd by Bergmann (2) in 14% yield by the Meerwein reaction.
f. Yield almost quantitative.
g. Prep'd by Jenkins and Richardson (6) by a similar method.
h. Prep'd by Bergmann (2) in 65% yield by the Meerwein reaction.
i. Boiling point. This oil could not be crystallized.

TABLE IV

HYDROXYCHLOROSTILBENES

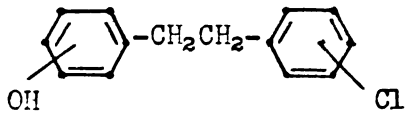


OH	Cl	M.P., °C [a]	Method [b]	Average Yield, %	% Cl [c]	Page
4	2'	114	P	67	15.30	61
			M	4.5 [d]		63
			A	5		63
			C	15		62
4	3'	130	P	50	15.18	64
4	4'	184	M	22	[e]	64
3	2'	84	P	58	15.28	65
3	3'	69	P [f]	31	15.18	65
3	4'	134	P [f]	60	15.32	66
			P [g]	77		66
			M	1		67
2	2'	132	P	39	15.14	67
2	3'	81	P	40	15.29	67
2	4'	122	P	51	15.27	67

a. Melting point ranges are listed in the Experimental section.
b. Methods: P, demethylation-dehydration of the carbinol with pyridine hydrochloride; M, Meerwein reaction; A, demethylation with acetic anhydride; C, Cleavage of the methoxymethoxy ether.
c. Calculated for $C_{14}H_{11}ClO$: Cl, 15.37%.
d. Meerwein (1) obt'd this comp'd in 8% yield by this method.
e. Meerwein (1) obt'd this comp'd in 56% yield by this method.
f. Starting material was an oil containing both carbinol and methoxystilbene.
g. Demethylation of methoxystilbene pyridine hydrochloride.

TABLE V

HYDROXYCHLOROBIBENZYLS [a]



Hydroxy	Chloro	M.P., °C.	Average Yield, %	% Cl [b]	Page
4	2'	60.0-61.0	53	15.25	68
4	3'	36.0-38.0	low [c]	14.00	69
4	4'	115.8-116.1	51	15.09	69
3	2'	20.0-22.0 [d]	low	15.23	70
3	3'	30.0-32.0 [e]	low	15.01	70
3	4'	44.8-45.3	38 [f]	15.14	70
2	2'	71.2-71.5	36	15.20	71
2	3'	54.0-54.6	50	15.12	71
2	4'	95.4-96.0	63	15.02	71

a. Prepared from hydroxystilbenes by hydrogenation using W-2 Raney nickel catalyst.
b. Calculated for $C_{14}H_{13}ClO$: Cl, 15.23%.
c. This compound could not be purified.
d. Boiling point, 160°/2 mm.; N_D^{20} 1.5812.
e. Boiling point, 165°/1 mm.; no refractive index could be found.
f. Copper chromium oxide catalyst gave 70% yield.

TABLE VI

p-CHLOROBENZOATE DERIVATIVES

p-Chlorobenzoate of-	M.P., °C.	%Cl[a]	Page
4-Hydroxy-2'-chlorobibenzyl	109.4-109.8	18.99	68
4-Hydroxy-3'-chlorobibenzyl	90.5-91.1	18.88	69
4-Hydroxy-4'-chlorobibenzyl	133.8-134.4	19.03	69
3-Hydroxy-2'-chlorobibenzyl	60.2-60.8	18.98	70
3-Hydroxy-3'-chlorobibenzyl	59.8-60.5	18.96	70
3-Hydroxy-4'-chlorobibenzyl	75.2-76.0	19.10	71
2-Hydroxy-2'-chlorobibenzyl	99.3-99.9	19.08	71
2-Hydroxy-3'-chlorobibenzyl	67.1-67.9	18.92	71
2-Hydroxy-4'-chlorobibenzyl	55.8-56.2	19.01	72
3-Hydroxy-2'-chlorostilbene	104.6-105.0	19.12[b]	65

a. Calculated for $C_{21}H_{16}ClO_2$: Cl, 19.11%.
b. Calculated for $C_{21}H_{14}ClO_2$: Cl, 19.20%.

REFERENCES

1. H. Meerwein, E. Buchner, and K. van Emster, J. Prakt. Chem., 152, 258 (1939).

2. F. Bergmann and D. Schapiro, J. Org. Chem., 12, 57 (1947).

3. R. C. Fuson and H. G. Cooke, Jr., J. Am. Chem. Soc., 62, 1180 (1940).

4. J. S. Buck and W. S. Ide, J. Am. Chem. Soc., 52, 4107 (1930).

5. J. Finkelstein and S. M. Linder, J. Am. Chem. Soc., 71, 1013 (1949).

6. S. S. Jenkins and E. M. Richardson, J. Am. Chem. Soc., 55, 3874 (1933).

7. C. Hell, Ber., 37, 454 (1904).

8. F. Bergmann, J. Weizman, and D. Schapiro, J. Org. Chem. 9, 408 (1944).

9. Ng. Ph. Buu-Hoi and Ng. Hoan, J. Org. Chem., 14, 1032 (1949).

10. D. A. Ballard and W. M. Dehn, J. Am. Chem. Soc., 54, 3970 (1932).

11. P. Pfeiffer, Ber., 48, 1777 (1915).

12. H. Kauffmann, Ber., 54, 795 (1921).

13. N. M. Cullinane, J. Chem. Soc., 123, 2053 (1923).

14. P. Pfeiffer, Ann., 411, 72 (1916).

15. J. Thiele and R. Escales, Ber., 34, 2842 (1901).

16. F. Sachs and S. Hilpert, Ber., 39, 899 (1906).

17. L. Chardonnens and P. Heinrich, Helv. Chim. Acta, 23, 292 (1940).

18. R. Anschutz, Ber., 60, 1320 (1927); C. A., 21, 2893 (1927).

19. K. v. Auwers and A. Fruhling, Ann., 422, 192 (1921).

20. A. Orekhoff and M. Tiffeneau, Bull. Soc. Chim. France, (4) 37, 1410 (1925).

21. R. Pschorr, Ber., 33, 176 (1900).

22. G. Werner, Ber., 28, 1999 (1895).

23. Th. Zincke and W. Geibel, Ann., 349, 110 (1906).

24. C. Funk and St. v. Kostanecki, Ber., 38, 939 (1905).

25. T. R. Lewis, et al., J. Am. Chem. Soc., 71, 3749 (1949).

26. J. Meisenheimer, Ann., 446, 76 (1926).

27. M. S. Kharasch and H. C. Brown, J. Am. Chem. Soc., 61, 2142 (1939).

28. M. M. Sprung, J. Am. Chem. Soc., 52, 1643 (1930).

29. G. M. Bennett and B. Jones, J. Chem. Soc., 1815 (1935).

30. C. G. Overberger, E. J. Luhrs, and P. K. Chien, J. Am. Chem. Soc., 72, 1201 (1950).

31. C. L. Wilson and K. B. Wilson, Trans. Electrochem. Soc., 84, 159 (1943).

32. M. Heilbron, "Dictionary of Organic Compounds", Vol. II, Oxford University Press, New York, N. Y., 1943, p. 600.

33. R. Robinson and J. Shinoda, J. Chem. Soc., 127, 1977 (1925).

34. W. Borsche and C. Walter, Ber., 60, 2112 (1927).

35. R. B. Woodward, Org. Syntheses, 25, 55 (1945).

36. F. Vorsatz, J. Prakt. Chem., 145, 265 (1936).

37. Reference 32, Vol. I, p. 574.

38. R. N. Icke, et al., Org. Syntheses, 29, 64 (1949).

39. Reference 32, Vol. II, p. 599.

40. J. T. Hewitt, W. Lewcock, and F. G. Pope, J. Chem. Soc., 101, 604 (1912).

41. F. E. Clark, S. F. Cox, and E. Mack, J. Am. Chem. Soc., 39, 712 (1917).

42. H. Gilman, et al., J. Am. Chem. Soc., 45, 150 (1923).

43. R. Mozingo, Org. Syntheses, 21, 15 (1941).

44. C. F. Koelsch, J. Am. Chem. Soc., 65, 57 (1943).

45. C. F. Koelsch and V. Boekelheide, J. Am. Chem. Soc., 66, 412 (1944).

46. St. v. Kostanecki and J. Tambor, Ber., 42, 826 (1909).

47. Ng. Ph. Buu-Hoï, K. W. Hiong, A. Lacassagne, and J. Lecocq, Compt. rend., 219, 589 (1944); C. A., 40, 1489 (1946).

48. E. C. Dodds, et al., Nature, 141, 247 (1938).

49. E. C. Dodds, et al, Nature, 142, 34 (1938).

50. E. M. Lourie and W. Yorke, Ann. Trop. Med. Parasitol, 33, 289 (1939); C. A., 34, 5943 (1940).

51. E. Bergmann and L. Haskelberg, J. Chem. Soc., 1, (1939).

52. S. Adler, L. Haskelberg, and F. Bergmann, J. Chem. Soc., 576 (1940).

53. I. M. Kolthoff and E. B. Sandell, "Textbook of Inorganic Quantitative Analysis", The MacMillan Company, New York, New York, 1936, p. 455.

54. Parr Instrument Company, "Peroxide Sulfur Bombs", Moline, Illinois, Direction booklet no. 116.

55. F. E. Beamish, Ind. Eng. Chem., Anal. ed., 6, 352 (1934).

56. J. F. Lemp and H. J. Broderson, J. Am. Chem. Soc., 39, 2069 (1917).

57. W. A. Cook and K. H. Cook, Ind. Eng. Chem., Anal. ed., 5, 186 (1933).

Robert Joseph Hathaway

candidate for the degree of

Doctor of Philosophy

Final examination, May 14, 1951, 2:00 P.M., Chemistry conference room.

Dissertation: Syntheses of 2(3,4)-Hydroxy-(and Methoxy)-2'(3',4')-Chloro-Stilbenes and -Bibenzyls.

Outline of Studies

Major subject: Organic Chemistry
Minor subjects: Physical and Biochemistry

Biographical Items

Born, December 2, 1921, Glendive, Montana

Undergraduate Studies, Northwestern University, 1940-41; University of Illinois, 1941-43.

Graduate Studies, Northwestern University, 1945. Michigan State College, 1946-1950.

Experience: Chemist, Abbott Laboratories, North Chicago, Illinois, 1943-46, Graduate Assistant, Michigan State College, 1947-49, Chemist, Sumner Chemical Co., Elkhart, Indiana, 1950-present.

Member of the Society of the Sigma Xi and of the American Chemical Society.

SYNTHESES OF 2 (3,4)-HYDROXY-(AND METHOXY)-2' (3',4')-CHLORO-STILBENES AND -BIBENZYLS

BY

ROBERT JOSEPH HATHAWAY

AN ABSTRACT

Submitted to the School of Graduate Studies of Michigan State College of Agriculture and Applied Science in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

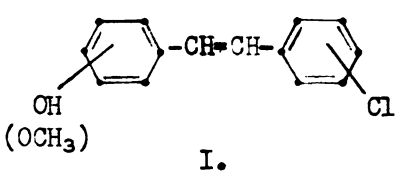
Department of Chemistry

Year 1951

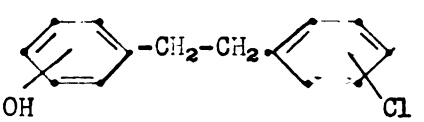
Approved Gordon L. Gaerner

ABSTRACT

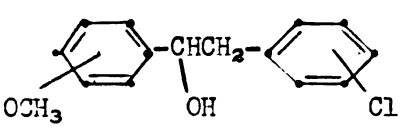
The syntheses of the isomeric hydroxy- and methoxychlorostilbenes (I) and the corresponding hydroxybibenzyls (II) have been investigated. Incidental to their preparation, the methoxyphenylchlorobenzyl carbinols (III) have also been prepared. Thirty-six compounds, excluding derivatives, have been synthesized and the majority submitted for pharmacological testing. Six of these compounds have been reported in the literature.



I.



II.



III.

The method of attack which appeared most suitable was to prepare substituted stilbenes of type I and reduce them catalytically to bibenzyls of type II, as there were several examples reported in the literature for the reduction of chlorostilbenes to chlorobibenzyls (1).

Among the methods of synthesis investigated for the preparation of the stilbenes were (a) the Meerwein reaction; (b) conversion of mixed benzoins into the stilbenes by simultaneous reduction-dehydration; and (c) the Grignard reaction. Of these methods, the latter proved to be the most satisfactory for general use.

The Meerwein reaction (2) appeared most promising inasmuch as 4-hydroxy-4'-chlorostilbene was reportedly obtained in 56% yield by Meerwein et. al. (2). However, the yields of this same compound in the present investigation were considerably lower and averaged 22%. The application of this reaction for the preparation of three other isomers proved unsatisfactory and its use was abandoned.

A second method was the attempted conversion of mixed benzoins (3) by simultaneous reduction-dehydration using zinc and hydrochloric acid, into the stilbenes (4). The yields in the latter step were so low that the method was abandoned.

The Grignard reaction (5) between the methoxybenzaldehydes and chlorobenzylmagnesium chlorides gave the corresponding methoxyphenylchlorobenzyl carbinols (III) in good yield. It was found possible to dehydrate these carbinols to the methoxystilbenes (I), but the conversion of the latter to the hydroxystilbenes proved difficult at first; normally used methods gave low yields of the desired product. However, after finding the excellent demethylation procedure of Buu-Hoi and Hoan (6) using pyridine hydrochloride at about 200°, not only was it possible to demethylate the methoxystilbenes in good yield, but also to demethylate and dehydrate the carbinols in one step to give the hydroxystilbenes.

Reduction of the stilbenes to the bibenzyls proceeded rather difficultly. Either W-2 Raney nickel (7) or copper chromium oxide gave in the neighborhood of 50% yields when used at 50-70° with hydrogen pressures of 1000-1500 p.s.i.

The p-chlorobenzoyl derivatives of the bibenzyls were prepared using p-chlorobenzoyl chloride. The interconversion between methoxy- and

hydroxystilbenes, and the ready dehydration of the carbinols to either of the above two types of compounds, made it unnecessary to prepare derivatives of these compounds.

All the compounds were analyzed for chloride as follows. The compounds were fused with sodium peroxide, the chloride precipitated with excess standard silver nitrate solution, and the excess silver titrated with standard thiocyanate solution.

REFERENCES

1. F. Bergmann, J. Weizman, and D. Schapiro, J. Org. Chem., 9, 408 (1944).

2. H. Meerwein, E. Buchner, and K. Van Enster, J. Prakt. Chem., 152, 258 (1939).

3. J. S. Buck and W. S. Ide, J. Am. Chem. Soc., 52, 4107 (1930).

4. J. Finkelstein and S. M. Linder, J. Am. Chem. Soc., 71, 1013 (1949).

5. S. S. Jenkins and E. M. Richardson, J. Am. Chem. Soc., 55, 3874 (1933).

6. Ng. Ph. Buu-Hoi and Ng. Hoan, J. Org. Chem., 14, 1032 (1949).

7. R. Mozingo, Org. Syntheses, 21, 15 (1941).