

THE PREPARATION OF 2-PHENYLCYCLOHEXANONE AND  
SUBSTITUTED 2-ARYLCYCLOHEXANONES

by

RICHARD GRANT HISKEY

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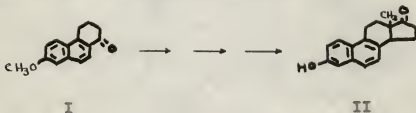
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## INTRODUCTION

In recent years both partial syntheses and total syntheses of natural products have become increasingly important. The total synthesis of these products is very desirable since total synthesis of a compound affords a method by which final, conclusive proof of its structure may be obtained. In addition, the total synthesis might prove economically feasible. For these reasons many workers have attempted to totally synthesize various natural products and their analogs.

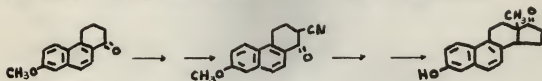
One of the outstanding examples of the synthesis of a relatively complex natural product was that of the female sex hormone, equilin (II), by Bachmann, Cole, and Wilds (1) in 1939-1940. The last portion of this synthesis utilized the cyclic ketone, 7-methoxy-1-keto-1,2,3,4 tetrahydro phenanthrene (I) as a key intermediate. A series of reactions involving the carbonyl group of the ketone (I) and the reactive methylene group, alpha to the carbonyl group, resulted in producing d,l-equilin (II), which was separated into its optical isomers, one of which was identical with the natural hormone.



This synthesis, although not commercially feasible, was the first total synthesis of a steroid and conclusively proved the

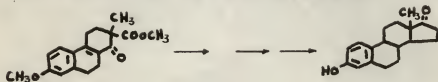
basic structure of the steroids.

Later, in 1945, Johnson and Gutsche (20) also reported a synthesis of equilin in employing the same starting material (I) but using different steps involving the intermediate 1-keto-2-cyano-7-methoxy-1,2,3,4 tetrahydrophenanthrene (III).



III

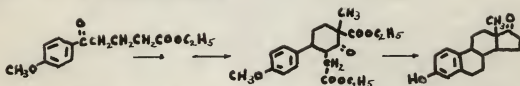
The synthesis of Estrone A (V), a stereo-isomer with less estrogenic activity than the natural hormone estrone (V) was first prepared by Bachmann, Kushner, and Stevenson (2). A cyclic ketone 7-methoxy-2-methyl-2-carbomethoxy-1-keto-1,2,3,4,9,10 hexahydrophenanthrene (IV) again was the key intermediate.



IV

V

Recently Johnson et al. (21) have succeeded in obtaining the correct isomer of estrone (VIII) via the Stobbe condensation with ethyl- $\gamma$ -anisoyl-butyrates (VI) followed by the Reformatsky reaction on the cyclic ketone (VII).

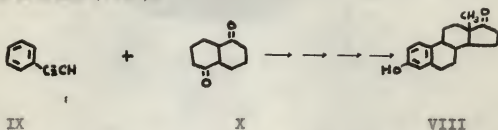


VI

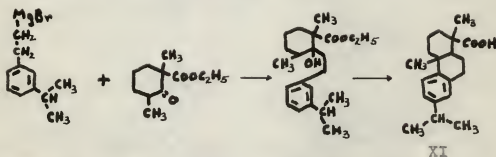
VII

VIII

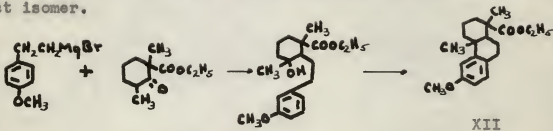
A second total synthesis by Johnson and co-workers (22) involving a different route has very recently been accomplished. By condensing phenyl acetylene (IX) with decalin-1,5-dione (X), followed by hydrogenation, cyclodehydration, benzylation, to permit introduction of the angular methyl group, opening of the six membered D ring followed by cyclization to a five membered ring yielded estrone (VIII).



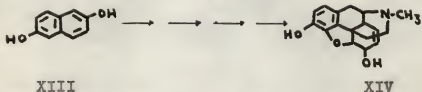
The resin acids have been the subject of several syntheses. Dehydroabietic acid (XI) has been prepared by Haworth and Barker (7) using the Bogart-Cook method.



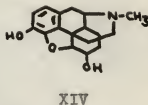
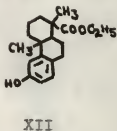
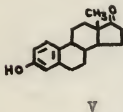
Podocarpic acid (XII), another acidic constituent in certain natural rosins, has been prepared by Haworth and Moore (18) and Bhattachanya (10). However, it has not been identified as the correct isomer.



The alkaloids are another group of compounds that has been studied extensively by synthetic means. The most recent accomplishment in this field is the total synthesis of morphine (XIV) by Gates and Tochudi (14). Starting with 2,6-dihydroxynaphthalene (XIII) and going through a long series of intermediates, they obtained the correct morphine structure (XIV).



It is apparent that the synthesis of these natural products is very important not only in purely academic work but also in pharmaceutical research. Examination of the formulae of such natural products as estrone (V), podocarpic acid (XII), and morphine (XIV) reveals the common cyclohexane nucleus (XV) in each.



The 2-arylcyclohexanones (XVI) appear as though they could serve as satisfactory starting materials for the synthesis of these natural products.



By a series of reactions involving the carbonyl group of various substituted 2-phenylcyclohexanones it may be possible to prepare these compounds or closely related analogs of them.

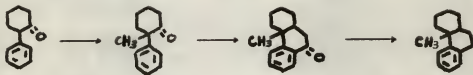
The first work to show a use of 2-phenylcyclohexanone (XVI), in synthesizing complex compounds, was that of Cook, Hewett, and Lawrence (11), who employed it as the starting material for the synthesis of 9-oxo-octahydrophenanthrene (XVII) via the Reformatsky reaction, followed by dehydration, hydrogenation, and cyclization.



XVI

XVII

Newman and Farbman (29) showed that hydrophenanthrene compounds, containing an angular methyl group in the 4a position, could be prepared from 2-phenylcyclohexanone. After the angular methyl group was introduced, the method of Cook, Hewett, and Lawrence was used to complete the formation of 4a-methyl-1,2,3,4a,9,10,10a octahydrophenanthrene (XVIII).



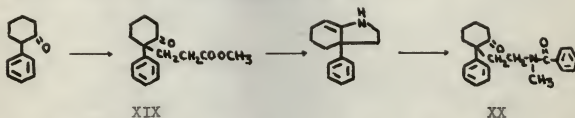
XVIII

More recently, great interest has been shown by various workers in using the 2-arylcyclohexanones as starting materials for the proposed synthesis of morphine (XIV); of estrone (V), and of the

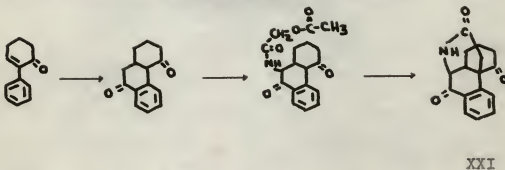


resin acids (XI), (XII).

Bachmann and Fornfeld (3), in preliminary work on a proposed synthesis of morphine, prepared methyl-1-oxo-2-phenylcyclohexane propionate (XIX) and via the Curtius degradation followed by a series of reactions obtained the N-Benzoyl derivative of N-methyl-2-oxo-1-phenylcyclohexethylamine (XX).



Ginsberg and Pappo (15) in recent work on morphine also employed 2-phenylcyclohexanone as the intermediate.



Using the Michael reaction and ring closure, the substituted diketone was obtained which followed by oximation, formation of the substituted amide and ring closure yielded a compound (XXI) similar to morphine (XIV).

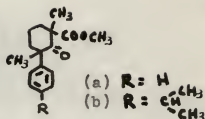
Bachmann and Wick (4) used certain 2-phenylcyclohexanones as intermediates for a proposed synthesis of certain resin acids. However, the carbonyl group of these ketones (XXII, XXIII) proved to be very unreactive, so that the approach apparently is not feasible. Horning (19) also found the carbonyl group (XXIII) to



be very unreactive.

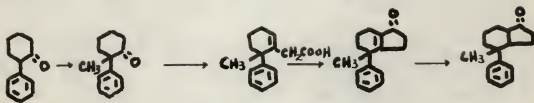


XXII



XXIII

Bachmann and Wick (4) have used 2-phenylcyclohexanone to prepare analogs of the sex hormones. Introduction of a methyl group in the same manner as Newman and Farbman (29) gave 2-methyl-2-phenylcyclohexanone (XXIV). The Reformatsky reaction followed by dehydration yielded 2-methyl-2-phenylcyclohexene acetic acid (XXV), which upon undergoing the Arndt-Eistert reaction, cyclization and hydrogenation produced 4-methyl-4-phenylhydrindanone (XXVI).

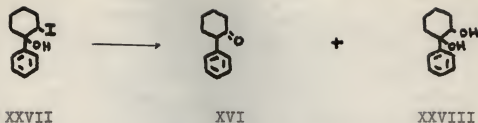


XXIV

XXV

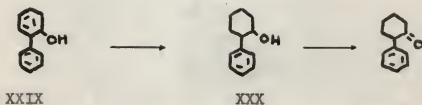
XXVI

Since the 2-arylcyclohexanones are of great potential interest in these proposed syntheses, their preparation is very important. The first preparation of 2-phenylcyclohexanone (XVI), by LeBradizec (25) in 1914, was accomplished by removing hydrogen iodide from 2-iodo-1-phenylcyclohexanone (XXVII) with silver nitrate.



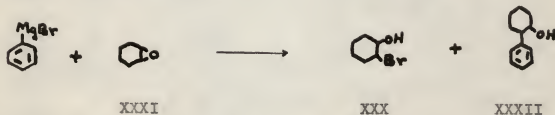
The diol (XXVIII) which also was formed; dehydrated with dilute sulfuric acid to give 2-phenylcyclohexanone (XVI).

VonBraun, Gruber, and Kerschbaum (42) prepared 2-phenylcyclohexanone in low yield by hydrogenating *o*-hydroxybiphenyl, (XXIX), then oxidizing the resulting 2-phenylcyclohexanol (XXX) with chromic anhydride.

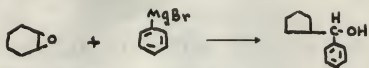


In 1940 Price and Karabinos (34) improved vonBraun's procedure of hydrogenation of biphenyl by using a lower temperature (140°) and a higher pressure (135 atmospheres).

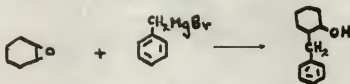
Bedos (9) attempted to prepare 2-phenylcyclohexanol, using the reaction between cyclohexene oxide (XXXI) and phenylmagnesium bromides. However, only a "trace" of the desired product, 2-phenylcyclohexanol (XXXII) was obtained, the majority being 2-bromocyclohexanol (XXX).



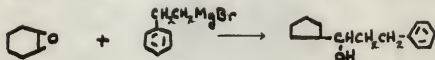
Cook, Hewett, and Lawrence (11) upon further investigation showed the Grignard reagent caused ring contractions and cyclopentyl carbinols were obtained.



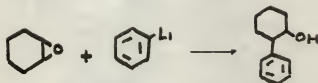
The Grignard reagent from benzyl bromide did not cause this contraction.



However, the next higher homologue led to ring contraction.



By substituting phenyl lithium (XXXIII) for the Grignard reagent, Cook, Hewett, and Lawrence (11) showed 2-phenylcyclohexanol (XXXII) could be obtained in good yield.

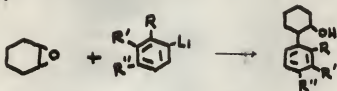


XXXIII

Oxidation of the 2-phenylcyclohexanol gave the desired 2-phenylcyclohexanone (XVI).

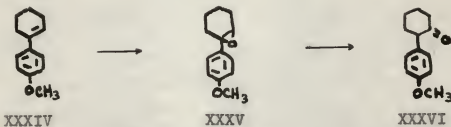


In 1948 McKusick (27) prepared a number of substituted 2-arylcylohexanols, in an effort to find better insect repellents, using the same general method of Cook, Hewett, and Lawrence (11).

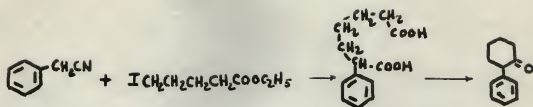


However, no attempt was made to form the substituted ketones.

Mueller and May (28) prepared 2-(p-anisyl)-cyclohexanone (XXXVI) by treatment of 1-(p-anisyl)-cyclohex-1-ene (XXXIV) with perbenzoic acid. The intermediate 2-(p-anisyl)-epoxy-cyclohexane (XXXV) rearranged on distillation and the ketone (XXXVI) resulted in a low yield.



Bachmann, Fujimato, and Wick (5) prepared 2-phenylcyclohexanone by a series of reactions involving the condensation between benzyl cyanide (XXXVII) and ethyl- $\gamma$ -iodo valerate (XXXVIII) which, followed by hydrolysis, yielded  $\alpha$ -phenyl pimilic acid (XXXIX). Dieckmann cyclization and decarboxylation yielded 2-phenylcyclohexanone.

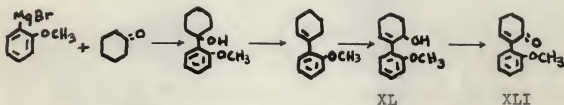


XXXVII

XXXVIII

XXXIX

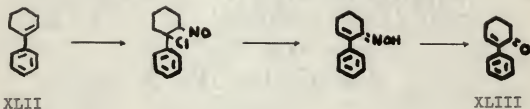
Ginsberg and Pappo (15) have produced 2-(*o*-anisyl)-cyclohex-2-ene-one (XLI) by reacting *o*-anisyl magnesium bromide and cyclohexanone. Dehydration followed by addition of tertbutyl hypochlorite and consequent loss of butyl alcohol gave the unsaturated alcohol 2-(*o*-anisyl)-cyclohex-2-ene-ol (XL). Openhauer oxidation of the alcohol yielded the unsaturated ketone 2-(*o*-anisyl)-cyclohex-2-ene-one (XLI).



XL

XLI

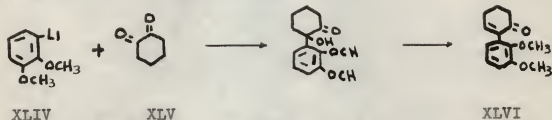
C. F. Koelsch (24) and Ginsberg and Pappo (15) have prepared the unsaturated ketone, 2-phenylcyclohex-2-enone (XLIII), by another method. By nitrosoating 1-phenylcyclohexene (XLII) with nitrosyl chloride and treatment with base, the oxime was prepared. Upon acid hydrolysis the oxime was converted into the unsaturated ketone (XLIII).



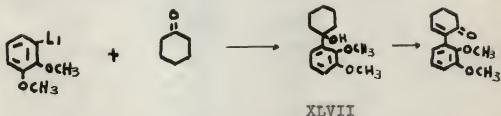
XLII

XLIII

Barnes and Reinhold (7) have recently introduced a method of preparing substituted 2-phenylcyclohexanones. The procedure involves the reaction between 2,3-dimethoxyphenyl lithium (XLIV) and 1,2-cyclohexanedione (XLV). A mono-keto addition compound was produced, which on reacting with 2,4-dinitrophenyl hydrazine followed by cleavage in acid solution, produced 1-(2',3'-dimethoxy)-phenyl-1-cyclohexene-6-one (XLVI).



An alternate synthesis (XLVI) was realized by the same workers, through the reactions of 2,3-dimethoxyphenyl lithium (XLIV) with cyclohexanone to obtain 1-(2',3'-dimethoxy)-phenyl-cyclohexanol (XLVII). Dehydration followed by oxidation with selenium dioxide gave the desired ketone, 1-(2',3'-dimethoxy)-1-phenyl-cyclohexene-6-one (XLVI).



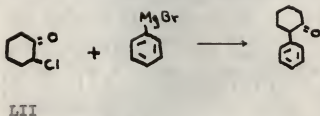
Another preparation of 2-arylcyclohexanones has recently been accomplished. By means of the Diels-Alder synthesis  $\gamma$ -nitrostyrene (XLVIII) or substituted analogs were condensed with butadiene (XLIX) at 200° C. to form substituted 3-nitro-4-phenylcyclohexenes (L). Employing the Nef reaction, the sodium salt



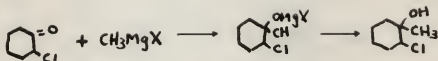
of the nitro groups was prepared and slowly acidified to yield 2-phenyl-cyclohex-4-ene-one (LI).



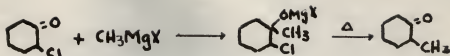
The most convenient and rapid synthesis of 2-phenyl cyclohexanone (XVI) was introduced by Newman and Farbman (29) in 1944. The preparation involves the reaction between 2-chlorocyclohexanone (LII) and phenyl magnesium bromide.



The method is based on the work of Tiffineau et al. (38, 39, 40, 41) and Bartlett and Rosenwald (8) who, by isolating the intermediate chlorohydrins (LIII), have shown that, at least in the alkyl series, the Grignard Reagents adds to the carbonyl group first.

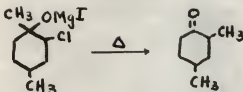


Upon heating, however, the intermediate Grignard complex loses magnesium halide and rearranges to the ketone (LIV).

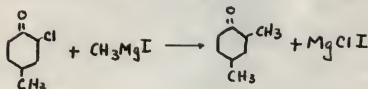


LIV

Tiffeneau (40) provided evidence that it was the methyl group which migrated and not the oxygen atom.

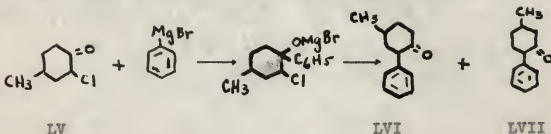


In accord with Godchot and Bedos (32)

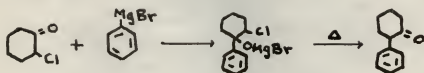


Thus in the alkyl series, the alkyl Grignard reagents result in products in which the entering group is attached to the carbon atom which originally held the halogen.

In the phenyl series, however, investigation by Newman and Booth (30) shows that only partial rearrangement occurs. When 2-chloro-4-methyl cyclohexanone (XL) was reacted with phenyl magnesium bromide, a mixture of 2-phenyl-4-methyl-cyclohexanone (LVI) and 2-phenyl-5-methyl-cyclohexanone (LVII) was obtained.



From this work then it appears most likely that in the formation of 2-phenylcyclohexanone, the same two-step reaction occurs in which the second step is the loss of magnesium halide and a rearrangement, in which either the phenyl group or the chlorine atom rearranges.



LVIII

Hydrolysis of the Grignard complex (LVIII) before heating and thus avoiding rearrangement, should give the chlorhydrin, 2-chloro-1-phenylcyclohexanol (LIX).



LIX

From the structural formula of the chlorhydrin (LIX), it is apparent that there are two asymmetric carbon atoms and thus four possible isomers which are present in two racemic mixtures. In one racemic mixture, referred to as *cis*-2-chloro-1-phenyl cyclohexane (LX), the chlorine and hydroxyl group are on the same side of the cyclohexane ring. In the other racemic mixture, referred to as *trans*-2-chloro-1-phenyl cyclohexanol (LXI), the chlorine and hydroxyl group are on opposite sides of the cyclohexane ring.



LX



LXI

It appeared of interest therefore, to attempt to isolate these intermediate chlorohydrins (LX, LXI) and to determine the amount of rearrangement contributed by each isomer.

#### PURPOSE OF THE INVESTIGATION

The purpose of the investigation was as follows:

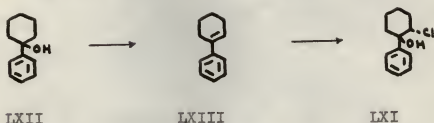
- I. The study of the addition of Grignard reagents to 2-chlorocyclohexanone by:
  - A. Isolation and identification of the intermediate chlorohydrins and,
  - B. Comparison of the rearrangement of the cis and of the trans chlorohydrins.
- II. The preparation of a number of new 2-arylcyclohexanones.

#### RESULTS OF THE INVESTIGATION

##### Isolation and Identification of the Intermediate Chlorohydrins

In 1943 Tiffeneau et al. (41) apparently prepared the cis and trans isomers of 2-chloro-1-phenylcyclohexanol (LIX) in an attempt to determine the migration tendencies of the phenyl radical. The trans isomer was prepared by the method of Deteouf (12) in treating 1-phenylcyclohexene (LXIII) with hypochlorous

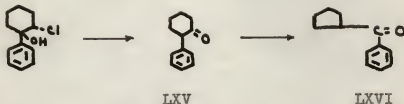
acid. However, the resulting trans-2-chloro-1-phenylcyclohexanol (LXI) was "unable to be distilled in vacuum without decomposition." Their compounds were impure and no derivatives were reported.



To prove this isomer was the trans isomer Tiffeneau treated the crude trans product (LXI) with cold potassium hydroxide and obtained 1-epoxy-2-phenylcyclohexane (LXIV).



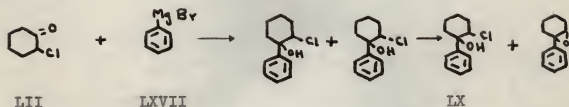
Levy and Sfiras (26) also prepared the impure trans chlorohydrin (LXI) by a similar method. Treatment of the trans-2-chloro-1-phenylcyclohexanol with zinc chloride, in acid medium, (12) converted the chlorohydrin into 2-phenylcyclohexanone (LXV) and a "small quantity" of cyclopentylphenylketone (LXVI).



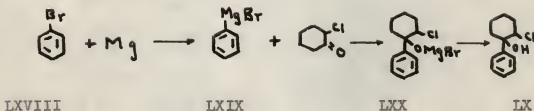
The yield of ketone, however, was not reported.

Tiffeneau (41) prepared cis-2-chloro-1-phenylcyclohexanol

(LX) using the reaction between 2-chlorocyclohexanone (LII) and phenyl magnesium bromide (LXVII) in the cold. To obtain the pure isomer the Grignard mixture was treated with potassium hydroxide, thus removing any remaining trans isomer as the epoxide (LXIV). Distillation of the product gave *cis*-2-chloro-1-phenylcyclohexanol (LX). Tiffeneau reports this isomer as a liquid. No yield was given of this isomer.



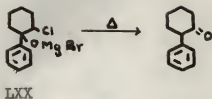
Using the same general procedure as Tiffeneau et al. (41), the *cis*-2-chloro-1-phenylcyclohexanol (LX) was prepared by the reaction between bromobenzene (LXVIII) and magnesium metal to form the Grignard reagent (LXIX). To this mixture 2-chlorocyclohexanone was slowly added. Best results were obtained when the addition was made at 0° and the mixture allowed to slowly warm to room temperature after the addition.



Hydrolysis of the Grignard complex (LXX) resulted in the crude rather yellow *cis*-2-chloro-1-phenylcyclohexanol (LX). Heating the Grignard complex after the addition of the 2-chlorocyclohexanone, would have resulted in the rearrangement of the



chlorohydrin to 2-phenylcyclohexanone. At this point, of course, this was undesirable.

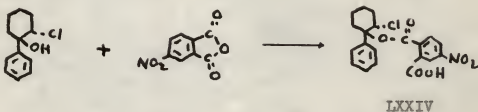
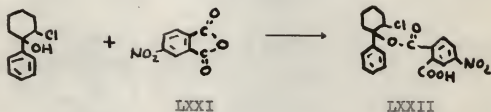


Distillation of the hydrolyzed product under high vacuum yielded a colorless product which quickly solidified on cooling to yield 41 per cent of the theoretical. In contrast to the liquid which Tiffeneau (41) obtained these white, irregular, low-melting (41°) crystals represent the *cis* isomer in a much purer form. Lower fractions of the distillation gave mainly 2-chloro-cyclohexanone while fractions above 110°/0.1 mm immediately turned red, indicating possible decomposition. This trace of red color was difficult to remove from the solid and several recrystallizations were required to obtain white crystals. Later a much better method was found in the use of chromatography with an alumina column and petroleum ether (60-75°). Slightly yellow to clear crystals were obtained in 52 per cent yield by passing the red distillation fractions through the column m.p. 41°.

To determine whether the chlorine atom was still present, the following qualitative tests were performed on the white solid:

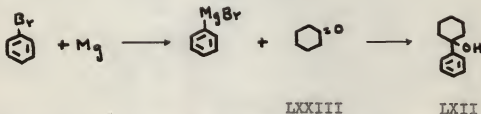
5 per cent  $\text{AgNO}_3(\text{alc})$  + (on warming)  
 Beilstein Test +

Examination of the structure of 2-chloro-1-phenylcyclohexanol (LIX) reveals it as a substituted, tertiary alcohol. For this reason and from the rather protected position of the hydroxyl group, it might be expected that the hydroxyl group would be rather unreactive. This proved to be the case for the 3,5 dinitrobenzoate and the phenylurethan, usual alcohol derivatives, could not be prepared. Following the procedure of Dickinson et al. (13) however, the preparation of a 3-nitrophthalic anhydride derivative was attempted by refluxing the cis and trans chlorohydrins with 3-nitrophthalic anhydride (LXXI) in toluene. A white crystalline solid was obtained from each reaction and was presumed to be the 3-nitrophthalate of the cis and of the trans 2-chloro-1-phenylcyclohexanols (LXXII) (LXXIV). The supposed cis derivative melted at 155-155.5° while the trans derivative melted at 160-161°. A mixed melting point gave a melting range of 145-158°. However, the titration of the free carboxyl group in both derivatives gave only a neutral equivalent of 241 compared to the expected value of 403.



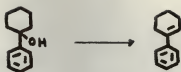
Analysis of the supposed trans-3-nitrophthalate checked closely with the structure of the original 3-nitrophthalic anhydride. Since the melting points of both the trans derivative and the 3-nitrophthalic anhydride are 160° and a mixed melting point of the two was not depressed, it appears that the supposed trans derivative was only 3-nitrophthalic anhydride. Further work will be done on the supposed cis-3-nitrophthalate, but at this time it must be assumed that the 3-nitrophthalates of both isomers were not formed since no analytical proof can be offered.

The trans-2-chloro-1-phenylcyclohexanol (LXI) was also prepared in a manner similar to that of Tiffeneau (41). By allowing bromobenzene to react with magnesium and then slowly adding cyclohexanone (LXXIII) the tertiary alcohol, 1-phenylcyclohexanol (LXII) was obtained in 57 per cent yield.



The 1-phenylcyclohexanol was dehydrated by heating with potassium acid sulfate at 160-180° for one hour. The resulting unsaturated product, 1-phenylcyclohexene (LXIII) appeared as a colorless liquid obtained in 85 per cent yield. The following qualitative tests were run on the 1-phenylcyclohexene:

5 per cent  $\text{KMnO}_4$  + immediately  
 $\text{Br}_2$  in  $\text{CCl}_4$  + immediately



LXIII

Following the procedure of Organic Synthesis (33) hypochlorous acid was prepared by bubbling chlorine gas into a cold aqueous alkaline solution. The hypochlorous acid was then reacted with 1-phenylcyclohexene by stirring the mixture vigorously for 24-48 hours. The best results appeared to be obtained when a 0.3 mole excess of hypochlorous acid was used and the mixture stirred 48 hours at 15-25°. The crude product, trans-2-chloro-1-phenylcyclohexanol (LXI), appeared as a slightly yellow liquid, solid at approximately -10° C, in 80-85 per cent yield. The all-over yield of product from 1-phenylcyclohexanol was 65-72 per cent.



LXI

To determine whether addition had taken place, the following qualitative tests were performed on the trans-2-chloro-1-phenylcyclohexanol:

Br <sub>2</sub> in CCl <sub>4</sub>	-
5 per cent KMnO <sub>4</sub>	-
Beilstein Test	+
5 per cent AgNO <sub>3</sub> (alc)	+ on warming

Thus it appears that the addition of the hypochlorous acid to the double bond was successful and since it has been shown (46) that hypochlorous acids generally add in the trans position on a double bond the trans-2-chloro-1-phenylcyclohexanol (LXI) would be expected to be formed.

On distillation under high vacuum (0.1 mm) a colorless liquid was obtained. Since it was reported by Tiffeneau (20) that the trans-isomer was "unable to be distilled in vacuum without decomposition" qualitative tests were run on the colorless distillate.

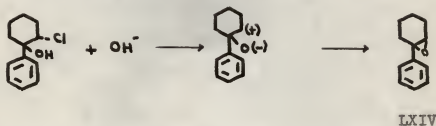
Br <sub>2</sub> in CCl <sub>4</sub>	+	purple color developed slowly
5 per cent KMnO <sub>4</sub>	-	
5 per cent AgNO <sub>3</sub> (alc)	+	on warming
Beilstein	+	

Apparently the distilled product is not decomposed under high vacuum and is undoubtedly the trans-2-chloro-1-phenylcyclohexanol.

Examination of the infra-red graph of the trans-chlorohydrin shows some remaining double bond from 1-phenylcyclohexene. This impurity was not removed by three careful fractionations of the trans isomer. However, the double bond was not revealed by the qualitative tests on the isomer and thus is probably present in a rather small amount.

To further verify the structure and isomerism of the two intermediate chlorohydrins, both isomers of 2-chloro-1-phenylcyclohexanol were vigorously stirred, at room temperature, for

one hour, with 4.3 M sodium hydroxide. A Walden Inversion should occur involving a backside attack on the trans isomer by the hydroxyl ion and consequent elimination of hydrogen chloride to form 1-epoxy-2-phenylcyclohexane (LXIV). This proved to be the case as an apparent reaction resulted and a colorless liquid was obtained on distillation under high vacuum. The refractive index compares with that reported by Levy and Sfiras (34).



To determine if any chlorohydrin remained, the following qualitative tests were run on the supposed epoxide:

5 per cent $\text{KMnO}_4$	+	green color
$\text{Br}_2$ in $\text{CCl}_4$	-	
5 per cent $\text{AgNO}_3$ (alc)	-	
Beilstein Test	-	

Since no such backside attack by the hydroxyl ion to form the epoxide, can occur in the cis isomer, no such product should be expected. Again this proved to be the case and 96 per cent of the original cis-2-chloro-1-phenylcyclohexanol was recovered unchanged as shown by a mixed melting point taken with some of the pure cis-chlorohydrins.

In an effort to further establish the differences in structure and isomerism of the two 2-chloro-1-phenylcyclohexanols, an infra-red spectra of each isomer was taken. Inspection of the



two graphs indicate several noteworthy differences in the spectras.

The peak due to the chlorine present in each isomer, apparently appears in the 700 to 800  $\text{cm}^{-1}$  range. This is indicated by the presence of the strong absorption band. The phenyl group is shown by the 1600  $\text{cm}^{-1}$  peak. The peak occurring at 1645  $\text{cm}^{-1}$  in the trans chlorohydrin is not a double bond from a benzene nucleus and thus is probably contributed by unreacted 1-phenylcyclohexene-1. This could not be removed by several careful fractionations of the trans isomer. The most distinguishing difference lies in the strength of hydroxyl group peak. In the trans chlorohydrin it may be observed that the peak appearing at 3480  $\text{cm}^{-1}$ , is noticeably weaker than that of the peak in the same position in the cis chlorohydrin. It seems logical to assume that this strong absorption for the hydroxyl group of the cis chlorohydrin is due to the fact that both the hydroxyl group and the chlorine atom are on the same side of the molecule, thus strengthening the absorption peak. In the trans chlorohydrin, however, the groups are away from each other and no such reinforcement can occur and thus the peak associated with the hydroxyl group appears weaker.

The graphs do not prove conclusively the presence of the two isomers, but the differences in the spectrum of chlorohydrin seems to coincide with the evidence already present. From this data then it seems reasonable to conclude that the compounds prepared were the cis and trans isomers of the intermediate 2-chloro-1-phenylcyclohexanone.

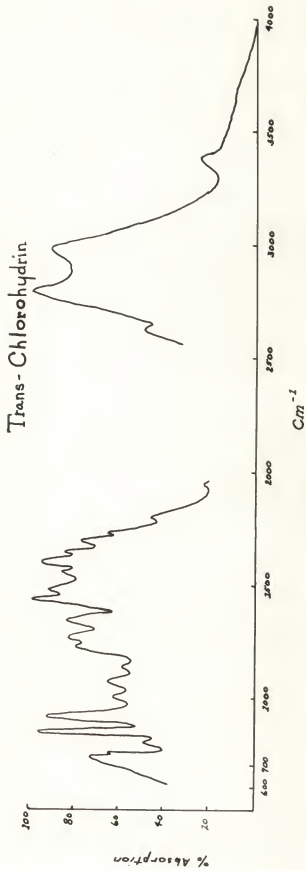


Figure 1. Infrared graph of the trans-chlorohydrin.

Cis-Chlorohydrin

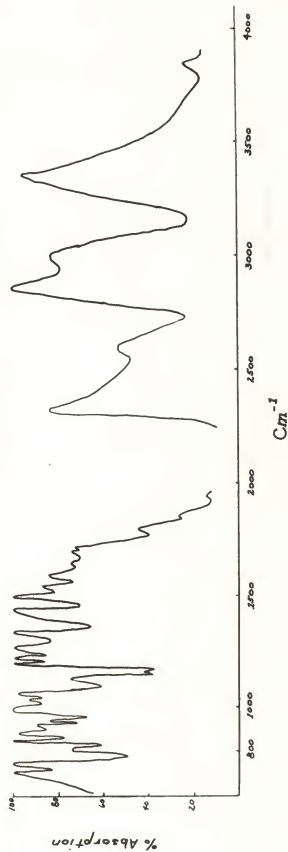
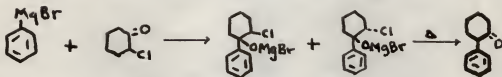


Figure 2. Infrared graph of the cis-chlorohydrin.

Comparison of the Rearrangement of the Cis- and Trans- Chlorohydrins

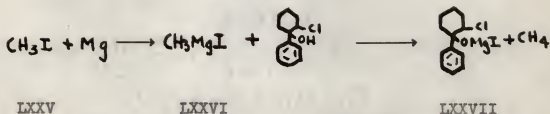
In the reaction between phenyl magnesium bromide and 2-chloro cyclohexanone, 2-phenylcyclohexanone is prepared by heating the mixture after the addition of 2-chlorocyclohexanone.



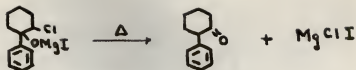
The isomeric chlorohydrins as their bromomagnesium salts, are, then, intermediates in the final rearrangement to the ketone.

To determine the amount of rearrangement contributed by each isomer, both forms were treated with methyl magnesium iodide (LXXVI), prepared from methyl iodide (LXXV) and magnesium, and heated to bring about the rearrangement.

As the cis-2-chloro-1-phenylcyclohexanol was slowly added to the Grignard reagent (LXXVI); methane was evolved, indicating reaction had occurred.



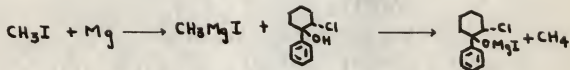
The Grignard complex (LXXVII) was then refluxed in dry benzene solution for 14 hours to effect the loss of magnesium halide and the rearrangement to 2-phenylcyclohexanone.



LXXVII

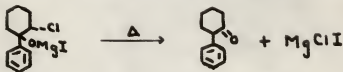
From this rearrangement of the *cis* chlorohydrin 44 per cent of pure solid 2-phenylcyclohexanone was obtained. Treatment of the mother liquor with 2,4-dinitro-phenylhydrazine solution yielded an additional 6.5 per cent of 2-phenylcyclohexanone, calculated on the basis of the yield of 2,4-dinitrophenylhydrazone formed. Thus from the *cis*-2-chloro-1-phenylcyclohexanone, the total amount of rearrangement to 2-phenylcyclohexanone was 50.5 per cent.

Treatment of the *trans* chlorohydrin, under the same conditions, with methylmagnesium iodide again produced the Grignard complex (LXXVIII).



LXXVIII

The Grignard complex (LXXVIII) was likewise refluxed 14 hours in benzene to complete the rearrangement to 2-phenylcyclohexanone.

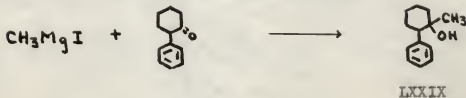


LXXVIII

The trans isomer, however, produced no pure solid ketone but rather an impure mixture of unreacted trans-chlorohydrin and 2-phenylcyclohexanone. Because of this it was necessary to calculate the yield of ketone on the basis of the yield of 2,4-dinitrophenylhydrazone. Treatment of the main fraction (b.p. 151-154° at 21 mm) of product, collected in distillation, with 2,4-dinitrophenylhydrazine solution yielded 33 per cent of the 2,4-dinitrophenylhydrazone of 2-phenylcyclohexanone. Apparently then this fraction was only one-third ketone. The lower boiling fraction (145-151°) on treatment with 2,4-dinitrophenylhydrazine gave an additional 10.4 per cent of 2-phenylcyclohexanone, again calculated on the basis of yield of 2,4-dinitrophenylhydrazone derivation.

The total amount of rearrangement in the trans-2-chloro-1-phenylcyclohexanol was 43.4 per cent. This was contaminated material, however, while the cis chlorohydrin rearranged to give 44 per cent of pure ketone and only 6.5 per cent of impure product.

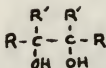
The yields of 2-phenylcyclohexanone might have been increased somewhat by the use of equimolar amounts of chlorohydrin and methyl magnesium iodide. In the amounts used, a 0.0045 mole excess of methyl magnesium iodide was present and of course, any excess Grignard reagent would destroy the 2-phenylcyclohexanone by the formation of the tertiary alcohol (LXXIX).



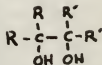


## Preparation of Some New 2-Arylcyclohexanones

The pinacol-pinacolone rearrangement has been the subject of much investigation and workers have been able to prepare various symmetrical (LXXX) and unsymmetrical (LXXXI) pinacols.

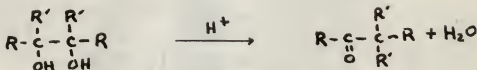


LXXX



LXXXI

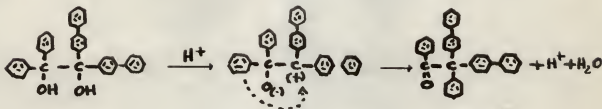
The pinacol-pinacolone rearrangement is a classic example of a carbonium ion rearrangement in which polysubstituted ethylene glycols are converted into substituted ketones by the action of acidic reagents. The reaction involves the separation of the hydroxyl, together with a shift of one of the groups to the backside of the carbon atom from which the separation occurred. The product of this rearrangement is called a pinacolone (LXXXIII).



LXXXIII

The tendency of various groups to migrate has received considerable attention. In 1934 Bachmann and Ferguson (6) prepared numerous pinacols and from the ability of the substituted groups to separate the hydroxyl group from the carbon atom, found that this tendency or migratory aptitude could be expressed as a remarkably accurate numerical value. For example, the rearrange-

ment of 1,1-diphenyl-2,2-di-p-biphenylethylene glycol (LXXXIV) gives a mixture of 46 per cent  $\alpha$ -phenyl- $\alpha, \alpha$ -di-p-biphenylacetophenone (LXXXV) resulting from the migration of the phenyl group and 54 per cent  $\alpha, \alpha$ -diphenyl-d-(p-biphenyl)-p-biphenyl ketone (LXXXVI) resulting from the migration of the biphenyl group. Since this is an unsymmetrical pinacol type, the migratory aptitudes will be 46:54 or 1.0:1.18. Others may be calculated in this manner (44).



LXXXIV

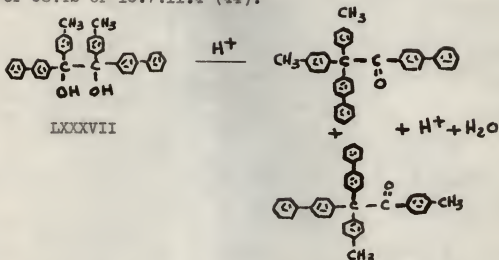
LXXXV



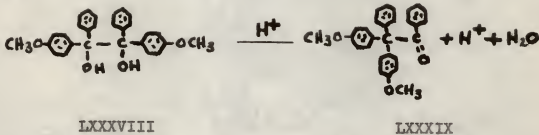
LXXXVI

As might be expected, the migratory aptitudes of the symmetrical pinacols are very dissimilar to those of the unsymmetrical type. The former has a much larger range than the latter. This difference arises from the fact that while the unsymmetrical pinacols merely ionize the hydroxyl group, the symmetrical pinacols give a measure of the group's tendency to migrate since only a single cation is possible no matter which

hydroxyl group is removed. Thus the rearrangement of 1,2-d-p-biphenyl ethylene glycol (LXXXVII) yields two ketones in the ratio of 58:42 or 15.7:11.4 (44).

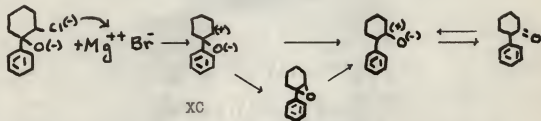


Bachmann and Ferguson (6) determined the migratory aptitudes of many pinacols, obtaining unusual although consistent results. In the rearrangement of 1,2-di-p-anisyl-1,2-di-phenyl ethylene glycol (LXXXVIII) to the ketone  $\alpha$ -phenyl- $\alpha$ ,  $\alpha$ -p-anisyl acetophenone (LXXXIX), the migratory aptitude of the p-anisyl group is 500. However, the resulting migratory aptitudes of the m-anisyl and o-anisyl groups are only 1.6 and 0.5 respectively.

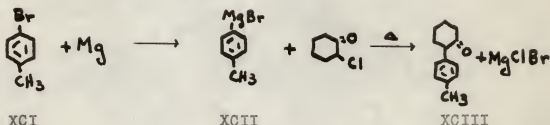


The lack of rearrangement of many of the ortho substituents is quite probably due to steric effects.

It thus appeared of interest to investigate the migratory aptitudes of certain substituted aryl groups as applied to the  $\alpha$ -chloro-ketone rearrangement of the 2-arylcyclohexanones. Certainly the rearrangement is not of the pinacol-pinacolone type but since only one carbonium ion (XC) can be formed, as in pinacols of the symmetrical type, similar results could be expected in the ease of formation of certain new 2-arylcyclohexanones.

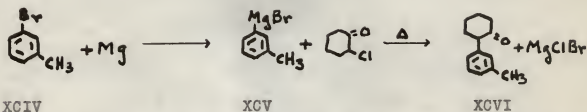


The tolyl series offered an opportunity to study the ease of rearrangement of the ortho, meta and para isomers. The preparation of 2-(p-tolyl)-cyclohexanone (XVIII) was accomplished via the reaction between p-bromotoluene (XCI) magnesium turnings and 2-chlorocyclohexanone. The latter was added slowly to the Grignard reagent (XCII) at room temperature and the mixture refluxed for 14 hours.



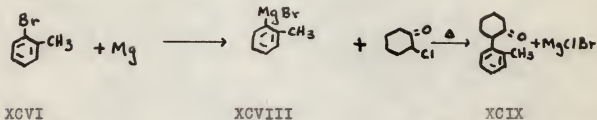
The solid 2-(p-tolyl)-cyclohexanone (XCIII) was obtained in very low yield (9.1 per cent).

The meta isomer, 2-(m-tolyl)-cyclohexanone (XCVI) was prepared in a similar manner using m-bromo toluene (XCIV) and magnesium to form the Grignard reagent (XCV). The 2-chlorocyclohexanone was added to the mixture at room temperature and the resulting solution was refluxed for 18 hours.



However, the 2-(m-tolyl)-cyclohexanone (XCVI) was not obtained as a solid but rather as a red liquid, doubtlessly impure. The impure product was obtained in a 30.7 per cent yield. This, of course, cannot be considered as the true amount of product.

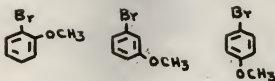
The 2-(o-tolyl)-cyclohexanone (XCIX) was again prepared via the Grignard reaction. The Grignard reagent (XCVIII) prepared from o-bromotoluene (XCVII) and magnesium turnings was reacted with 2-chlorocyclohexanone, slowly added at room temperature, and the solution refluxed 14 hours.



The 2-(o-tolyl)-cyclohexanone (XCIX) appeared as a solid in 16.5 per cent yield.

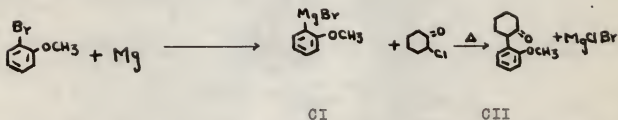
Another group of interesting compounds with which to prepare

substituted 2-arylcyclohexanones via the Grignard reaction are the ortho, meta, and para bromoanisoles (C).



C

The preparation of 2-(o-anisyl)-cyclohexanone (CII) was attempted from o-bromoanisole and magnesium turnings to form the Grignard reagent, anisyl magnesium bromide (CI). To the refluxing ethereal solution of the Grignard reagent was added 2-chlorocyclohexanone. The ether was replaced with benzene and the mixture refluxed 14 hours.



CI

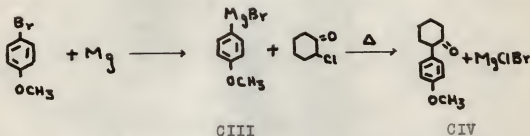
CII

However, no solid product was obtained but rather a light yellow liquid in 34.3 per cent yield. Although a yellow color appeared when the liquid was treated with 2,4-dinitrophenylhydrazone, no derivative was able to be obtained. Likewise no oxime could be made from this material. Apparently the steric factors will not allow the rearrangement to take place at these conditions.

The 2-(p-anisyl)-cyclohexanone (CIV) was prepared in much the same manner. The Grignard reagent (CIII) was produced from p-bromoanisole and magnesium. To this refluxing solution of the



Grignard reagent, 2-chlorocyclohexanone was slowly added at room temperature. The ether was replaced by benzene and the solution refluxed for 14 hours. The 2-(p-anisyl)-cyclohexanone (XIV) appeared as a white solid in 10.9 per cent yield.



Again the yield of product was very low. Earlier work by Bachmann, Fujimoto, and Wick (5) has shown that the 2-(p-anisyl)-cyclohexanone can be prepared in 50-60 per cent yields by adding the 2-chlorocyclohexanone to the ice cold Grignard reagent prepared from p-bromoanisole and magnesium in ether and allowing the solution to warm to room temperature and stand<sup>d</sup> for 8 to 12 hours. No doubt the other compounds prepared could have been produced in much better yields by similar conditions. However, this will be attempted at a later date.

To prove the structure of the 2-(p-anisyl)-cyclohexanone (CIV) the same workers (5) used a variety of reactions. Clemmensen reduction with amalgamated zinc and hydrochloric acid gave p-anisylcyclohexane (CV). This compound had been previously reported by Price (34) who prepared it by a Friedel-Crafts reaction between cyclohexene (CVI) and anisole (CVII). Reduction of 2-(p-anisyl)-cyclohexanone with aluminum isopropoxide gave 2-(p-anisyl)-cyclohexanol (CVIII).



CV



CVI



CVII



CVIII



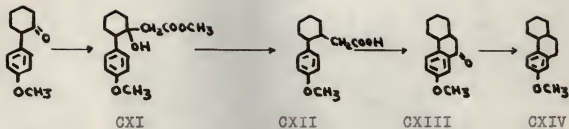
CIX



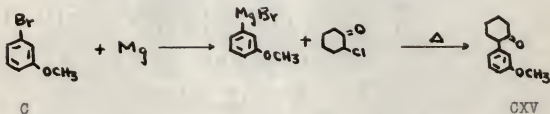
CX

Dehydration and dehydrogenation of the alcohol (CVIII) with palladium on charcoal at 300° gave p-methoxybiphenyl (CIX) identified by melting point and mixed melting point with an authentic sample.

The above reactions prove the presence of two six-membered rings and the presence of a methoxy group in the para position. They do not prove the position of the carbonyl group, however. To show this, 2-methoxyphenanthrene (CX) was prepared, starting with 2-(p-anisyl)-cyclohexanone. The Reformatsky reaction on 2-(p-anisyl)-cyclohexanone with zinc and methyl bromoacetates gave methyl-1-hydroxy-2-(p-anisyl)-cyclohexaneacetate (CXI). Dehydration of the hydroxy-ester and treatment with alcoholic potassium hydroxide gave 2-(p-anisyl)-1-cyclohexaneacetic acid (CXII). Cyclization of the substituted acetic acid (CXII) yielded 7-methoxy-9-oxo-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (CXIII). Clemmensen reduction of the ketone (CXIII) gave 7-methoxy-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (CXIV) which on treatment with palladium charcoal at 280-310° led to the production of 2-methoxyphenanthrene (CX) identified by its melting point and by its picrate.



Bachmann, Fujimoto, and Wick (5) also prepared the 2-(*m*-anisyl)-cyclohexanone (CXV). The Grignard reagent was prepared from *m*-bromoanisole (C) and magnesium turnings. To the Grignard reagent, 2-chlorocyclohexanone was added slowly at room temperature, toluene substituted for the ether, and the solution refluxed for 24 hours.

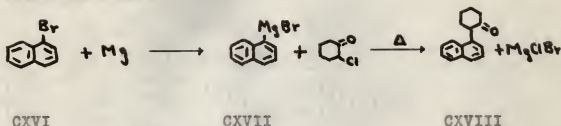


The ketone (CXV) was obtained as a colorless liquid that was not pure, in 34.3 per cent yield.

If the migratory aptitudes and the ease of formation of the 2-arylcyclohexanones are compared, it is evident that the *para*-anisyl (500) rearranges much more readily than the *meta*-anisyl (1.6) and the *ortho*-anisyl (0.3). These "migratory aptitudes" appear, then, to be in at least general agreement with the ease of formation of the *ortho*, *meta*, and *para*-anisyl cyclohexanones.

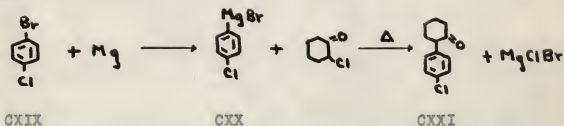
The 2-( $\alpha$ -naphthyl)-cyclohexanone (CXVIII) was prepared in much the same manner as the other compounds. The Grignard reagent was produced by reacting  $\alpha$ -bromo naphthalene (CXVI) with

magnesium turnings in an ether solution. To this Grignard reagent (CXVII), 2-chlorocyclohexanone was slowly added at room temperature. The ether was replaced by benzene and the solution was refluxed 14 hours.



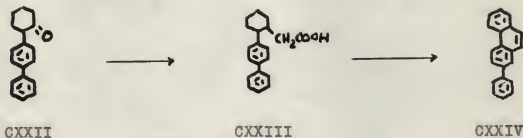
The 2-( $\alpha$ -naphthyl)-cyclohexanone (CXVIII) was obtained as a solid in 13 per cent yield. Orchin (31) obtained an impure product by this method and isolated the ketone (CXVIII) as the semicarbazone. Later, however, Orchin and Reggel (32) obtained the ketone in a 14.8 per cent yield by stirring the Grignard reagent and 2-chlorocyclohexanone 17 hours at room temperature. From these results it might be concluded that, at least for an  $\alpha$ -chloro-ketone rearrangement, the migratory aptitudes of the  $\alpha$ -naphthyl group lie near that of the ortho (XCIX) and para (CXXIII) tolyl groups.

By adding 2-chlorocyclohexanone to the Grignard reagent, (CXX) formed by reacting p-bromochlorobenzene (CXIX) and magnesium turnings at room temperature and refluxing the ethereal solution 15 hours, 2-(p-chlorophenyl)-cyclohexanone (CXXI) was prepared.



The ketone (CXXI) appeared as a solid in 9.9 per cent yield. This yield compares with several of the preceding 2-aryl-cyclohexanones prepared and thus quite possibly the chloro-phenyl group has a similar migratory aptitude. As with the preceding compounds, the yield could probably have been increased using milder conditions.

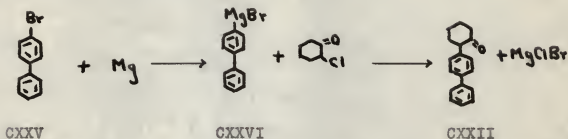
The rearrangement of the biphenyl group appeared interesting for several reasons. The migratory aptitude of the biphenyl group is rather large (11.5), and seemingly it should rearrange easily. Also a compound of the 2-(p-biphenyl)-cyclohexanone (CXXII) type would serve as an excellent starting material for several syntheses. By reacting 2-(p-biphenyl)-cyclohexanone (CXXII) with methyl bromoacetate and zinc in a Reformatsky reaction followed by dehydration, hydrogenation, and saponification, 2-(p-biphenyl)-cyclohexaneacetic acid (CXXIII) could be prepared. The acid (CXXIII) could then be converted to the acid chloride, and cyclization with aluminum chloride and dehydrogenation would give 2-phenylphenanthrene (CXXIV).



The above series of reactions would appear to offer an excellent proof of structure.

An attempt was made, therefore, to prepare the 2-(p-biphenyl)-

cyclohexanone. The Grignard reagent (CXXVI) was made by reacting p-bromobiphenyl (CXXV) with magnesium turnings in ether for 22 hours. To this solution 2-chlorocyclohexanone was added and the addition was apparently satisfactory as heat was evolved as in a typical Grignard reagent.

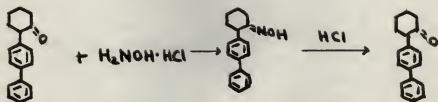


The ethereal solution was refluxed 24 hours and allowed to stand at room temperature 24 hours. However, the only workable product obtained was reclaimed p-bromobiphenyl (CXXV) (52 per cent) and a large amount of high boiling residue. The addition of 2-chlorocyclohexanone to the Grignard reagent, prepared from p-bromobiphenyl and magnesium, was next done in an ice bath. Again the formation of a yellow complex upon addition of the 2-chlorocyclohexanone appeared to indicate the Grignard reagent had been produced. However, on distillation, only unreacted starting material, p-bromobiphenyl (36 per cent) and high boiling resinous residue were obtained. A qualitative test for the carbonyl group on the residue, with 2,4-dinitrophenylhydrazine, was positive.

This would indicate the 2-(p-biphenyl)-cyclohexanone had decomposed on distillation but was present in the high boiling residue. A third reaction, in which the 2-chlorocyclohexanone was added to the Grignard reagent (CXXVI) in the cold and the



etheral solution allowed to warm to room temperature and stand for 48 hours, was attempted. The crude product was not distilled but rather converted to the oxime (CXXVII) and hydrolyzed back to the ketone.



CXXVII

The product from this treatment was, however, only a resinous mass and further treatment was impossible. These reactions suggest that very mild conditions are necessary to effect the isolation of 2-(p-biphenyl)-cyclohexanone and quite probably the methods used have been too drastic. Further work will be done on this compound.

#### EXPERIMENTAL

##### Isolation and Identification of the Intermediate Chlorhydrins

2-Chlorocyclohexanone (LII). In a three-neck flask filled with a gas inlet and outlet tubes and a mechanical stirrer, was placed 294 g of cyclohexanone and 900 ml of water. The flask was cooled in an ice bath and 215 g of chlorine was rapidly bubbled in with vigorous stirring for two hours. The heavier 2-chloro-cyclohexanone was separated and combined with two ether extracts of the aqueous phase and dried over anhydrous  $\text{MgSO}_4$ . The ether

was removed on a steam bath and the residue distilled at 18 mm, the portion boiling between 50-110° being collected. Fractionation through a 6-bulb Snyder column gave 246 g (51 per cent) of 2-chlorocyclohexanone. B.P. 90-93° at 18 mm (Reported by Newman and Farbman (29) 90-91° 14-15 mm).

Cis-2-Chloro-1-Phenyl Cyclohexanol (IX). A mixture of 100 g of freshly distilled bromobenzene and 16 g of magnesium turnings in 300 ml of dry ether was allowed to react. Upon warming the solution refluxed spontaneously for one hour, requiring some cooling. The solution was refluxed for one and one-half hours. After cooling the flask in an ice-salt bath, 85.5 g 2-chlorocyclohexanone (b.p. 86-87°/14 mm) in 300 ml of dry ether was added slowly, with stirring, over a period of two hours. The ice bath was then allowed to warm to 0°, about one hour, and then 900 ml of cold, saturated ammonium chloride solution was added slowly with stirring, to dissolve the yellow complex, which was very difficult to hydrolyze. Some ether was then added to the aqueous solution. The water phase was washed several times with ether, and the washings combined with the organic layer which was washed twice with water and dried over anhydrous Mg SO<sub>4</sub>. The ether was removed by vacuum and the yellow residue distilled. Distillation at 0.5 mm gave 43 g of red liquid b.p. 102-110°. When cooled, the fractions solidified. After three recrystallizations from petroleum ether (60-75°), 30.2 g (41 per cent) of white crystals were obtained m.p. 32-41°. Lower boiling fractions yielded mainly unreacted 2-chlorocyclohexanone. Tiffeneau

et al. (39) reported this compound as a liquid which would not crystallize, b.p. 160-165° at 16 mm.

Using the same procedure but different conditions, the following results were obtained from other preparations of 2-chloro-1-phenylcyclohexanol:

	:Bath temperature :	Reaction time :	Complex :	% yield
B	Dry ice - Acetone kept cold after addition	Addition in 2 hours then stand 1 hour after addition	Difficult to hydrolyze	37.5 m.p. 40-41°
C	-6°, kept cold after addition	Addition in 2 hours, then stand 1 hour after addition	Hydrolysis easy	31 m.p. 39-41°

1-Phenylcyclohexanol (LXII). A mixture of 250 g of bromo benzene and 25 g of magnesium turnings in 300 ml of dry ether was warmed. An immediate reaction resulted, and after spontaneous refluxing ceased (about one hour) 160 g of cyclohexanone in 200 ml of dry ether was added dropwise in one hour with stirring. After hydrolysis with 300 ml of cold saturated ammonium chloride solution, the ether and water layers were separated and the aqueous phase washed three times with fresh ether. The washings were combined with the ether layer, washed twice with water, and dried. After removal of the solvent, the product was obtained as 269 g of a viscous orange oil. Distillation at 0.1 mm gave a clear liquid, b.p. 90-110° which crystallized on cooling to yield 150 g (57.3 per cent) of a white solid, m.p. 59-61°. One re-

crystallization from petroleum ether raised the m.p. to 60-61°. Sabatur and Mailhe (36, 37) report m.p. 62-63.5°, b.p. 156.5-158.5°/28 mm, 153°/20 mm.

1-Phenylcyclohexene (LXIII). To 24.3 g of 1-phenylcyclohexanol was added 36 g of anhydrous potassium hydrogen sulfate. The mixture was heated in an oil bath at 160-170° for one hour, the organic material dissolved in ether, and the potassium hydrogen sulfate filtered off. After removal of the solvent under vacuum the product appeared as a light yellow liquid. Distillation yielded 20 g (83 per cent) of a clear liquid, b.p. 130-135° at 18 mm. Sabatur and Mailhe (36, 37) report b.p. 133°/20 mm.

The 1-phenylcyclohexene gave the following qualitative tests:

Br <sub>2</sub> in CCl <sub>4</sub>	+	very rapid
5% KMnO <sub>4</sub>	+	immediately

Trans-2-Chloro-1-Phenylcyclohexanol (LXI). Following the procedure of Organix Xyntheses (33), hypochlorous acid was prepared by passing chlorine into a cold solution of 19 g of sodium hydroxide in 50 ml of water and 80 g of cracked ice. After the mercuric oxide had dissolved, the addition of chlorine was stopped and 160 ml of cold 1.5 N nitric acid was added slowly with air bubbled in to provide stirring.

About 20 g of the hypochlorous acid solution, weighed on the rough balance, was added to 20.7 g of 1-phenylcyclohexene. The resulting solution was stirred vigorously for 15 hours at 15-25°. Another 20 g of the acid solution was added and the stirring

continued for five hours at 15-20°. The organic layer was separated, the water layer was washed several times with ether, and the washings combined with the organic layer, which was then washed twice with water and dried over anhydrous magnesium sulfate. Removal of the ether under vacuum left a light yellow liquid which gave the following qualitative tests:

5% $\text{KMnO}_4$	-	
5% $\text{Br}_2$ in $\text{CCl}_4$	-	
Alc $\text{AgNO}_3$	+	on warming
Bellstein test for halogen	+	green color

Distillation of the crude chlorohydrin at 0.1 mm gave 17.5 g (68 per cent) of a colorless liquid, b.p. 75-75.5° and a very small amount of yellow residue. The colorless fraction gave the following qualitative tests:

5% $\text{KMnO}_4$	-	
5% $\text{Br}_2$ in $\text{CCl}_4$	+	purple color
$\text{AgNO}_3$ (alc)	+	on warming
Bellstein test for halogen	+	green color

Tiffeneau et al. (41) report the trans-2-chloro-1-phenyl cyclohexanol was "not able to be distilled in vacuum without decomposition." Conditions under which the distillation was attempted and physical constants of the crude chlorohydrin were not reported. The refractive index of the trans-2-chloro-1-phenylcyclohexanone was 1.5659 at 22.5°.



1-Phenylcyclohexene Oxide (LXIV). According to the procedure of Organic Synthesis (33), 5 g of crude trans-2-chloro-1-phenylcyclohexanol was treated with 1 g of sodium hydroxide in 6 g of water. The mixture was stirred vigorously, at room temperature, for one hour. Ether was added and the two resulting layers were separated. The aqueous phase was washed twice with fresh ether and the washings combined with the yellow organic layer which was then washed twice with water and dried over anhydrous sodium sulfate. Removal of the ether under vacuum gave 3.6 g (72 per cent) of a light yellow liquid; distillation at 0.5 mm gave 2.6 g of a colorless liquid, b.p. 70-72°. A small amount of solid residue was obtained. Levy and Sficas (26) and Tiffeneau et al. (29) report b.p. 136/15 mm;  $d_4^{20}$  1.8075;  $n_D^{17}$  1.5434. The refractive index taken on the sample was 1.4899 at 22.5°.

Qualitative tests on the colorless fraction gave the following results:

5% $KMnO_4$	+	green color
5% $Br_2$ in $CCl_4$	-	
$AgNO_3$ (alc)	-	
Beilstein test for halogen	-	

Using the same procedure, 5 g of cis-2-chloro-1-phenylcyclohexanol was treated with 1.0 g of sodium hydroxide in 6 g of water. After vigorous stirring for one hour at room temperature, 5 g of unreacted chlorohydrin was recovered, m.p. 37-39°. A mixed melting point with pure cis-2-chloro-1-phenylcyclohexanol



gave a m.p. of 39-40°.

Rearrangement of the Cis and Trans Chlorohydrins  
to 2-Phenylcyclohexanone

From Cis-2-chloro-1-phenylcyclohexanol. To 3.8 g (0.0268 mole) of methyl iodide and 0.65 g of magnesium turnings was added 25 ml of dry ether. The mixture was refluxed for one hour, and a white solid formed. To the Grignard reagent, 4.7 g (0.0223 mole) of cis-2-chloro-1-phenylcyclohexanol in 100 ml of dry ether, was added dropwise, with stirring, at the rate which permitted gentle refluxing (about one hour). The ether was then removed by distillation and replaced with 150 ml of dry benzene. The benzene solution was refluxed 14 hours and then poured into 600 ml of cold saturated ammonium chloride solution. The two layers were separated and the water phase washed several times with ether. The ether washings were combined with the organic layer which was washed twice with water and dried. Removal of the solvent in vacuum left a yellow residue which was distilled at 17 mm. The fraction boiling at 149-156° yielded 1.8 g (44 per cent) of a white solid, m.p. 52-53°. Recrystallization from petroleum ether (60-75°) raised the melting point to 54.5-55°. Reported by Cook et al. (11), m.p. 50-55°; Price and Karabinos (34), m.p. 52.5-54.5; Newman and Farbman (29), m.p. 53-55°; Bachmann, Fujimoto, and Wick (5), m.p. 59.5-60°.

Treatment of 0.3 g of the mother liquor with 0.3 g of 2,4-dinitrophenylhydrazine, in 20 ml of ethanol, followed by heating the mixture to boiling and acidifying with 1 ml of hydrochloric

acid, yielded 0.07 g (6.5 per cent) of orange crystals, m.p. 132-134°. Reported by Bachmann, Fujimoto, and Wick (5), m.p. 138-139°.

From Trans-2-chloro-1-phenylcyclohexanol. To 3.8 g (0.0268 mole) of methyl iodide and 0.7 g of magnesium turnings, 25 ml of dry ether was added. The mixture was refluxed for one hour. To this Grignard reagent, 5.0 g (0.0237 mole) of trans-2-chloro-1-phenylcyclohexanol, in 100 ml of dry ether, was added dropwise with stirring at a rate which permitted gentle refluxing. No white solid appeared during the addition. The ether was removed by distillation and 150 ml of dry benzene added. The benzene solution was refluxed 14 hours and poured into 600 ml of cold saturated ammonium chloride solution. The two layers were separated and the aqueous phase was washed several times with ether. The ether washings were combined with the organic layer, washed twice with water, and dried over anhydrous magnesium sulfate. The solvent was removed by vacuum and the residue distilled at 21 mm. From the fraction boiling at 151-154°, 1.4 g of a clear liquid was obtained. A lower boiling fraction was collected at 145-151°, weighing 2.4 g.

Treatment of 0.3 g of the 151-154° fraction with 0.3 g of 2,4-dinitrophenylhydrazine in 20 ml of 95 per cent ethanol, followed by heating to boiling and acidification with 1 ml of HCl, gave 0.15 g (33 per cent) of orange fluffy crystals, m.p. 126-127°. Recrystallization from methanol raised the m.p. to 132-135°.

To 0.3 g of the lower boiling fraction (145-151°) was added 0.3 g of 2,4-dinitrophenylhydrazine in 20 ml of 95 per cent ethanol. The mixture was heated to boiling and acidified with 1 ml of concentrated hydrochloric acid. Cooling yielded 0.25 g (55 per cent) of orange fluffy crystals, m.p. 124-126°. Recrystallization from methanol raised the m.p. to 131-133°.

The total amount of 2-phenylcyclohexanone, calculated on the basis of the yield of 2,4-dinitrophenylhydrazone derivative, amounts of 1.78 (43.4 per cent). The remaining liquid in both fractions may be unreacted trans-2-chloro-1-phenylcyclohexanol.

#### Preparation of Some New 2-Arylcyclohexanones

2-(p-tolyl)-cyclohexanone (XCIII). A mixture of 10 g of p-bromotoluene and 1.6 g of magnesium turnings in 100 ml of dry ether was refluxed four hours. To this yellow solution, 7.8 g of 2-chlorocyclohexanone was added dropwise with stirring, at a rate which permitted gentle refluxing, about one hour. The ether was removed by distillation and 200 ml of dry benzene was added. The mixture was then refluxed 14 hours and the dark red product was poured into 600 ml of cold saturated ammonium chloride solution. The resulting layers were separated and the aqueous phase washed several times with ether. The washings were added to the organic layer which was then washed twice with water and dried. The solvent was removed by vacuum and the residue distilled at 1.5 mm yield, 1.3 g of a liquid was collected at 133-138°. Cooling and three recrystallizations from petroleum gave a white crystalline solid, m.p. 51-52°.

Calcd C, 82.99; H, 8.52  
 Anal C, 81.01; H, 8.14

The 2,4-dinitrophenylhydrazone was prepared by treating 0.3 g of the ketone with 6 ml of 0.25 M 2,4-dinitrophenylhydrazine solution in phosphoric acid (23). Recrystallization from methanol yielded 0.35 g of orange crystals, m.p. 148-149°.

Calcd N, 15.20  
 Anal N, 14.54

The Oxime was prepared by refluxing 0.3 g of the ketone and 0.3 g of hydroxylamine hydrochloride in 5 ml of absolute alcohol and 5 ml of pyridine for two hours. The solvent was then blown off in a stream of air, water was added and the white crystals filtered. Recrystallization from methanol gave 0.32 g of white solid, m.p. 166.5-168.5°.

Calcd N, 6.90  
 Anal N, 7.01

2-(m-tolyl)-cyclohexanone (XCVI). A mixture of 10 g of m-bromotoluene and 1.65 g of magnesium turnings in 100 ml of dry ether was refluxed for 7 hours. To this solution 7.75 g of 2-chlorocyclohexanone, in 180 ml of dry ether, was added dropwise with stirring, in one hour. The ether was removed and 200 ml of dry benzene was added. The benzene solution was refluxed 18 hours and then allowed to stand at room temperature for four days. The mixture was poured into 600 ml of cold saturated ammonium hydroxide solution. The two resulting layers were separated and the water layer was washed several times with ether. The washings were combined with the organic layer, washed twice with water and dried. The solvent was removed by vacuum and the residue distill-

ed at 1.5-2 mm. A red liquid, 3.6 g (30.7 per cent) was obtained at 200-210° which would not solidify on cooling and was not analytically pure.

The 2,4-dinitrophenylhydrazone was attempted by treating 1 g of the red liquid with 10 ml of 0.25 M 2,4-dinitrophenylhydrazine, in phosphoric acid and ethanol, and warming. An immediate orange color was obtained but no solid product could be obtained on filtration.

The Oxime was prepared by refluxing 1 g of the red liquid with 1 g of hydroxylaminehydrochloride in 5 ml of pyridine and 5 ml of absolute alcohol for two hours. Removal of the solvents in a stream of air, followed by addition of water and filtration, gave 0.51 g of a white solid, m.p. 115-118°.

Calcd N,	6.90
Anal N,	6.60

2-(o-tolyl)-cyclohexanone (XCIX). A mixture of 10 g of magnesium turnings, in 100 ml of dry ether, was refluxed 8 hours. To this mixture, 7.7 g of 2-chlorocyclohexanone in 180 ml of dry ether was added slowly with stirring in one hour. The ether was removed by distillation and 200 ml of dry benzene was added. The mixture was refluxed 14 hours and then poured into 600 ml of cold saturated ammonium chloride solution. The organic and aqueous layers were separated and the aqueous layer washed several times with ether. The washings were combined with the organic layer, washed twice with water, and dried. The solvent was removed under vacuum and the residue distilled at 2.5 mm. The material boiling at 210-220° was collected, and immediately solidified on



cooling. Through recrystallizations from petroleum, ether (60-75°) gave 1.8 g (16.5 per cent) of a white crystalline solid, m.p. 55-56.5°.

Calcd C, 82.99; H, 8.52  
Anal C, 82.33; H, 8.68

The 2,4-dinitrophenylhydrazone was prepared, using 0.3 g of the ketone, dissolved in 5 ml of 95 per cent ethanol, and 7 ml of 0.25 M 2,4-dinitrophenylhydrazine solution in phosphoric acid and ethanol. Immediate precipitation occurred, filtration gave 0.4 g of orange fluffy crystals, m.p. 108-110°. Recrystallization from methanol raised the m.p. to 110-112°.

Calcd N, 15.20  
Anal N, 14.84

The Oxime was prepared by refluxing 0.4 g of the ketone and 0.4 g of hydroxylaminehydrochloride in 5 ml of absolute alcohol and 5 ml of pyridine for two hours. Removal of solvents in a stream of air followed by addition of water and filtration gave 0.4 g of a white crystalline solid, m.p. 173-178°. Recrystallization from methanol raised the m.p. to 185-187°.

Calcd N, 6.90  
Anal N, 6.86

2-(o-anisyl)-cyclohexanone (CII). A mixture of 10 g of magnesium turnings, in 100 ml of dry ether, was refluxed for four hours. To this mixture, 7.2 g of 2-chlorocyclohexanone, in 180 ml of dry ether, was added dropwise, with stirring, in one hour. The ether was removed by distillation and replaced with 200 ml of dry benzene. The resulting yellow mixture was refluxed 14 hours. The reaction mixture was then poured into 600 ml of cold, satur-



ated ammonium chloride solution and the two layers separated. The aqueous phase was washed several times with ether. The washings were combined with the organic layer which was then washed twice with water and dried. The solvent was removed by vacuum and the residue distilled at 0.07 mm. On distillation, 3.2 g of a clear liquid, gradually turning yellow, was obtained, b.p. 113-117°. The product would not solidify on cooling and was not analytically pure.

The 2,4-dinitrophenylhydrazine derivative was attempted by treating 1 g of the liquid with 10 ml of 0.25 M 2,4-dinitrophenylhydrazine solution in phosphoric acid and ethanol. Although an orange color was immediately produced, no solid product could be obtained.

The Oxime was attempted by refluxing 0.5 g of the liquid and 0.4 g of hydroxylaminehydrochloride in 5 ml of absolute alcohol and 5 ml of pyridine for two hours. The solvent was removed in a stream of air and water was added, but only a brown resinous mass, which could not be filtered, was obtained.

2-(p-anisyl)-cyclohexanone (CIV). A mixture of 10 g of p-bromoisole and 1.5 g of magnesium turnings, in 75 ml of ether, was refluxed for 7 hours. To this Grignard reagent, 7.1 g of 2-chlorocyclohexanone in 100 ml of ether was added dropwise, with stirring, in one-half hour. The ether was removed by distillation and 220 ml of dry benzene was added. The mixture was refluxed 14 hours and poured into 600 ml of cold saturated ammonium chloride solution. The two resulting layers were

separated and the water layer was washed several times with ether. The ether washings were combined with the organic layer, washed twice with water, and dried. The solvent was removed by vacuum and the residue was distilled at 0.2 mm. Distillation yielded a clear liquid, boiling at 162-171°, which solidified on cooling. Two recrystallizations from petroleum ether, 60-75°, gave 1.2 g (10.9 per cent) of a white crystalline solid, m.p. 78-82°. Recrystallization from 60-75° petroleum ether raised the m.p. to 84-85.5°. (Reported (5), m.p. 89-89.2°).

The 2,4-dinitrophenylhydrazone was prepared by adding 10 ml of 0.25 M 2,4-dinitrophenylhydrazine, in phosphoric acid and ethanol, to 0.3 g of the ketone in 5 ml of 95 per cent ethanol. Cooling yielded 0.35 g of orange crystals, m.p. 130-134°. Recrystallization from methanol raised the m.p. to 140-141°. (Reported (5), m.p. 144-145°).

The Oxime was prepared by refluxing 0.3 g of the ketone and 0.3 g of hydroxylaminehydrochloride in 5 ml of absolute alcohol and 5 ml of pyridine for two hours. The solvent was removed in a stream of air, water was added, and the mixture filtered. A slightly brown solid was obtained, m.p. 161-162°. Recrystallization from methanol gave white crystals, m.p. 165-166°. (Reported (5), m.p. 166-167°).

2-( $\alpha$ -naphthyl)-cyclohexanone (CXVIII). A mixture of 10 g of  $\alpha$ -bromo-naphthalene and 1.8 g of magnesium turnings, in 100 ml of ether, was added dropwise, with stirring, in one-half hour. The ether was removed by distillation and 220 ml of dry benzene

was added. The solution was refluxed 14 hours and then poured into 600 ml of cold saturated ammonium chloride solution. The two layers were separated and the water layer washed several times with ether. The ether washings were combined with the organic layer, washed twice with water, and dried. The solvent was removed under vacuum and the residue was distilled. Distillation at 0.5 mm yielded a fraction boiling at 162-165° which would not solidify on cooling. Petroleum ether (95-100°) was added to the liquid and upon cooling, 1.4 g (13 per cent) of a white crystalline solid was obtained, m.p. 78-79°. Recrystallization from petroleum ether (95-100°) raised the m.p. 81-82°. (Reported (32), m.p. 80-85°).

The 2,4-dinitrophenylhydrazone was prepared by adding 6 ml of 0.25 M 2,4-dinitrophenylhydrazene, in phosphoric acid and ethanol, and warming. On cooling, 0.4 g of yellow crystals were immediately formed. Recrystallization from methanol gave 0.37 g of product, m.p. 135-137°.

The Oxime was prepared by refluxing 0.4 g of the ketone with 0.4 g of hydroxylaminehydrochloride in 5 ml of pyridine and 5 ml of absolute alcohol for two hours. The solvent was removed in a stream of air, water was added, and the mixture was filtered. A white crystalline solid, 0.38 g, was obtained, m.p. 183-190°. Recrystallization from methanol raised the m.p. 200-202.5°.

Calcd N, 5.85  
Anal N, 6.02

The semicarbazone was prepared by refluxing 0.5 g of the ketone with 0.5 g of semicarbazide hydrochloride, 2 ml of pyridine, and 5 ml of absolute alcohol for two hours. The solvents were removed by a stream of air, water was added, and the mixture was filtered. A white crystalline solid, 0.4 g, was obtained, m.p. 206-210°. (Reported (32), m.p. 211-216°.)

2-(p-chlorophenyl)-cyclohexanone (CX XI). A mixture of 10 g of p-bromochlorobenzene and 1.4 g of magnesium turnings in 100 ml of dry ether was refluxed for 10 hours. To this mixture, 6.95 g of 2-chlorocyclohexanone, in 100 ml of dry ether, was added dropwise with stirring in one-half hour. The ether solution was refluxed 15 hours and poured into 600 ml of cold saturated ammonium chloride solution. The two layers were separated and the aqueous phase was washed several times with ether. The ether washings were combined with the organic layer, washed twice with water, and dried. The solvents were removed by vacuum and the residue distilled. Distillation at 0.2-0.1 mm gave a liquid boiling at 108-118°. On cooling, the fraction solidified and two recrystallizations from petroleum ether, 60-75°, gave 1.1 g (9.9 per cent) of a white crystalline solid, m.p. 54-56°.

Calcd	Cl, 16.95
Anal	Cl, 16.77

The Oxime was prepared by refluxing 0.3 g of the ketone with 0.3 g of hydroxylaminehydrochloride in 5 ml of absolute alcohol and 5 ml of pyridine for two hours. Removal of the solvent in a stream of air followed by addition of water and filtra-

tion gave 0.32 g of a white crystalline solid, crude m.p. 124-136°. Recrystallization from methanol raised the m.p. to 171.5-173°.

Calcd N, 6.27  
Anal N, 6.46

The 2,4-dinitrophenylhydrazone was attempted by adding 6 ml of 0.25 M 2,4-dinitrophenylhydrazine, in phosphoric acid and ethanol, to 0.3 g of the ketone. An immediate yellow color appeared but no solid derivative could be obtained on filtration.

2-(p-biphenyl)-cyclohexanone (CXXII). A. A mixture of 10 g of p-bromobiphenyl and 1.2 g of magnesium turnings in 150 ml of dry ether was refluxed for 22 hours. At the end of this period, some unreacted magnesium remained. To this mixture, 5.8 g of 2-chlorocyclohexanone in 100 ml of dry ether was added dropwise, with stirring, at a rate which permitted gentle refluxing (about one-half hour). The ether solution was refluxed 24 hours and then allowed to stand at room temperature for 24 hours. The dark yellow solution was then poured into 600 ml of cold saturated ammonium chloride solution. The two layers were separated and the aqueous phase was washed several times with fresh ether. The ether washings were combined with the organic layer, washed twice with water, and dried. The solvents were removed under vacuum and the residue distilled. Distillation at 0.2 mm yielded a fraction boiling at 98-110° which quickly solidified. A large amount of yellow-brown residue remained.

The 98-110° fraction was recrystallized three times from petroleum ether (60-75°), and 5.2 g of slightly pink crystals



were obtained, m.p. 88-90°. Beilstein test for halogen was positive. A mixed melting point with p-bromobiphenyl gave a m.p. of 85-89°. This is apparently unreacted p-bromo-biphenyl. The residue was dissolved in petroleum ether (95-100°) but only a resinous mass could be obtained.

B. A second attempt was made to prepare 2-(p-biphenyl)-cyclohexanone using slightly different conditions. A mixture of 10 g of p-bromobiphenyl in 150 ml of dry ether and 1.2 g of magnesium turnings (0.2 g excess) were refluxed for 46 hours. To this mixture, 5.8 g of 2-chlorocyclohexanone was added dropwise to the reaction mixture, which was kept at 0° in a salt-ice bath, with stirring, in one hour. A yellow-brown solid formed, indicating a reaction had taken place. The flask was allowed to warm to room temperature and stand for 24 hours. No apparent change in the solution was observed. The solution was cooled and poured into 600 ml of cold saturated ammonium chloride solution. The two layers were separated and the aqueous phase was washed several times with fresh ether. The ether washings were combined with the organic layer, washed twice with water, and dried. The solvent was removed under vacuum and the residue distilled. Distillation at 0.1 mm yielded a fraction boiling at 85-105° which quickly solidified. The yellow-brown residue was dissolved in hot petroleum ether (95-100°). Upon cooling, a yellow solid, which changed to a resinous mass on filtering, was obtained. About 1 g of the residue was treated with 10 ml of 0.25 M 2,4-dinitrophenylhydrazine in phosphoric acid and ethanol and an



immediate red-orange precipitate was obtained. The red-orange solid could not be filtered, however, and was not collected.

The 85-110° fraction was recrystallized twice from petroleum ether (60-75°) and 3.6 g of a white solid was obtained, m.p. 89-90°. Beilstein test for halogen was positive.

C. Using the same amounts of reactants, the Grignard reagent was prepared from p-bromobiphenyl and magnesium turnings. To this mixture, cooled to 0° in a salt-ice bath, 5.8 g of 2-chlorocyclohexanone was added dropwise with stirring in one-half hour. A yellow solid formed on the addition, and the mixture was allowed to warm to room temperature and stand for 48 hours. The mixture was poured into 600 ml of cold saturated ammonium chloride solution. The two layers were separated and the aqueous phase was washed several times with fresh ether. The washings were combined with the organic layer, washed twice with water, and dried.

The solvent was removed under vacuum but the residue was not distilled. About 2.0 g of the yellow residue was dissolved in hot petroleum ether (95-100°) and allowed to stand in the cold for 12 days. However, no workable product could be obtained and on evaporation of the solvent, only a resinous mass remained.

To 3.0 g of the residue, 3.0 g of hydroxylaminehydrochloride, 15 ml of pyridine and 15 ml of absolute alcohol were added. The solution was refluxed two hours. The solvents were removed in a stream of air and the product was washed twice with 50 ml of concentrated hydrochloric acid. The residue was then heated

on a steam bath with 100 ml of concentrated hydrochloric acid and 100 ml of water for three hours. The cool solution was washed three times with benzene and the organic and water layers were separated. The benzene washings were dried and the solvent removed under vacuum. The residue appeared as a brown resinous material unable to be filtered.

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THE PREPARATION OF 2-PHENYL-  
CYCLOHEXANONE AND SUBSTITUTED  
2-ARYLCYCLOHEXANONES

by

RICHARD G. HISKEY

A. B., Kansas State Teachers College, Emporia, 1951

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A THESIS

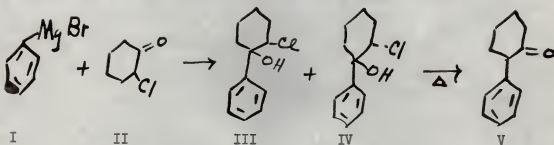
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The 2-Arylcyclohexanones appear to be excellent starting materials for the syntheses of various natural products and their analogs. For this reason their role in the synthetic aspect of organic chemistry may become increasingly important. The most common 2-Arylcyclohexanone, 2-phenylcyclohexanone (V), is prepared by the action of the Grignard Reagent, phenyl magnesium bromide (I), on 2-chlorocyclohexanone (II). If the reaction mixture is kept cold, two intermediate chlorohydrins may be isolated, *cis* and *trans*-2-chloro-1-phenylcyclohexanol (III)(IV). Upon heating, a rearrangement occurs and the desired ketone, 2-phenylcyclohexanone (V) is obtained.



It appeared of interest, therefore, to attempt to isolate the intermediate chlorohydrins and determine the amount of rearrangement contributed by each isomer in the formation of the ketone (V). Also, since migratory aptitudes in at least one similar type of rearrangement, the pinacol reaction, are known, the possibility of comparing the migration tendencies of different aryl groups in the two rearrangements appeared interesting. This should lead of course to some interesting substituted 2-arylcyclohexanones.

The two stereoisomers, *cis* and *trans*-2-chloro 1-phenylcyclohexanol, were both prepared independently and isolated in the purified form. Each isomer was then allowed to rearrange to the ketone and the per cent rearrangement of each was determined. The *cis* and *trans* isomers were isolated in much purer

form than previous workers had accomplished. Both isomers were found to contribute to the rearrangement but the *cis*-2-chloro-1-phenylcyclohexanol yielded pure solid 2-phenylcyclohexanone while the *trans* isomer gave only an impure liquid on rearrangement indicating perhaps different modes of rearrangement by the two isomers.

By using various substituted Grignard reagents several substituted 2-arylcyclohexanones were prepared and from the yields of these compounds a general insight in the migratory aptitudes of these various groups was attained. It was found that the migration of these substituted aryl groups in this chloroketone rearrangement were in general agreement with the migratory aptitudes of the same substituents in the pinacol reaction. The 2-*ortho*, 2-*meta* and 2-*para*-tolylcyclohexanones were prepared and the migration of the tolyl groups was found to be similar in both rearrangements. The 2-(*o*-methoxy)-phenylcyclohexanone could not be prepared in the pure form; however, the 2-(*p*-methoxy)-phenylcyclohexanone was prepared. These results indicate steric factors may play a role in this rearrangement. The 2-(*p*-biphenyl)-cyclohexanone could not be prepared although several different sets of conditions were used. These results are inconsistent with the pinacol migratory aptitudes and also with the other data obtained.

Thus, from this investigation the intermediate chlorohydrins in the preparation of 2-phenylcyclohexanone have been isolated and studied and also a number of new substituted 2-arylcyclohexanones have been prepared.