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Title STUDIES IN THE PINACOL-PINACOLONE REARRANGEMENT.

Abstract Approved: J.W. Ferguson
(Major Professor)

The synthesis of 3,3'-diphenylbenzopinacol was carried out both by means of the Grignard reaction between m-diphenyl magnesium iodide and benzil, and by reduction of m-phenyl benzophenone. The pinacol was rearranged and the products analyzed. The migration aptitude of m-biphenyl was determined to be 1.5.

Attempts to prepare 3,3'-diphenyl-4,4'-dimethylbenzopinacol were unsuccessful. 4,4'-Diethoxy-4,4'-dimethoxybenzopinacol was prepared by the grignard reaction, but it could not be crystallized; and rearrangement studies were not instigated. Alpha and beta desoxybenzoin pinacols were synthesized. These were very resistant to rearrangement, and ordinary methods gave none of pinacolone.

During the synthesis of some of the diphenyl intermediates, the Gomberg-Bachmann synthesis of diaryls was improved upon by substituting potassium carbonate for the strong base. The yield of m-nitroaniline was thus increased by six percent.

STUDIES IN THE PINACOL-PINACOLONE REARRANGEMENT

by

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A THESIS

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CONTENTS

page

2. sym-3,3'-Diphenyl-4,4'-dimethyl benzopinacol

3. sym-4,4'-Dimethoxy-4,4'-diethoxy benzopinacol

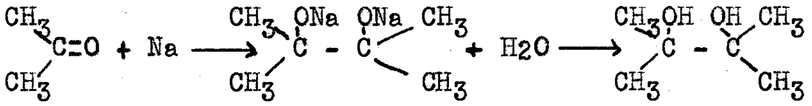
4. 1,2-Dibenzyl-1,2,-diphenyl benzopinacol

III. ANALYSIS OF RESULTS

STUDIES IN THE PINACOL-PINACOLONE REARRANGEMENT

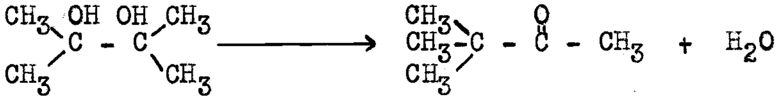
I. INTRODUCTION

Historical.- The pinacol-pinacolone rearrangement was discovered by Fittig(20) in 1860. In an attempt to reduce acetone by means of sodium, he found that a white, crystalline product which proved to be tetramethylethylene glycol(19) was produced by the simultaneous reduction and coupling of two molecules of the ketone:



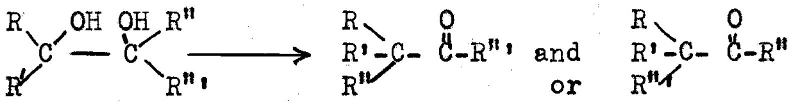
I.

The glycol thus formed proved very interesting since by heating with sulfuric acid a new compound was formed which was shown to be tertiary-butyl methyl ketone(13), and was called, by Fittig, Pinacolin. It was obvious that by the removal of a molecule of water, a ketone had been formed in which one methyl group had migrated from its normal position:



II.

Since its discovery, this rearrangement has been studied by many workers in almost all of its forms. In addition to the semipinacols which have one or more hydrogen atoms of the parent ethylene glycol still unsubstituted, there are four main types of completely substituted pinacols. Each of these has been studied, some more extensively than others, and it has been found that in all cases two rearrangement products are possible depending on the group which migrates(40):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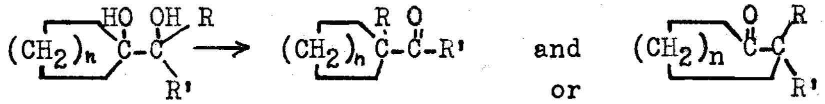
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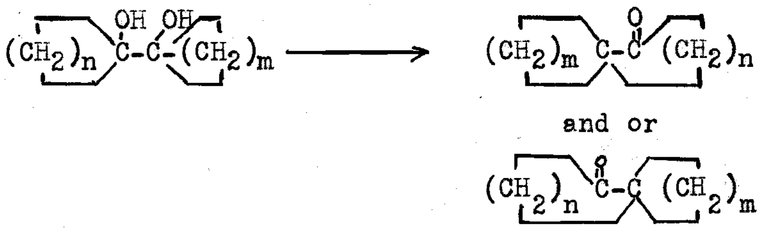
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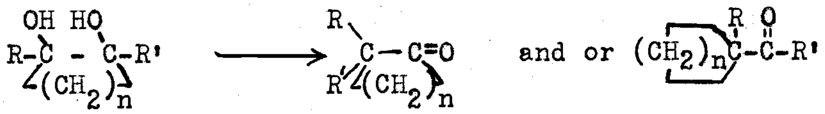
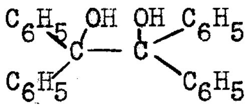
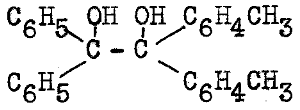

V.

The pinacol of type II has been worked with most. This type can be further divided depending on the degree of symmetry. Thus we have perfectly symmetrical pinacols in which all radicals are identical and of which benzopinacol is an example:

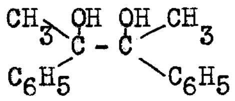

VI.

There are completely unsymmetrical types in which all radicals are different, partially unsymmetrical pinacols in which R and R' are alike but different from R" and R"'; i.e. unsymmetrical diphenylditolylethylene glycol:



VII.

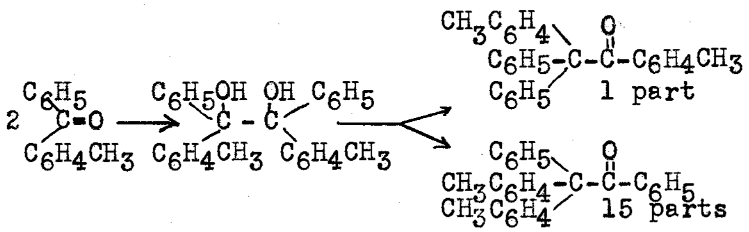
And finally there are the symmetrical pinacols in which R and R' are different but identical to R" and R"' as in acetophenonepinacol:



VIII.

It is this latter type in which we are primarily interested; for here it has been proven that the relative percent of rearranged products depends only on the radicals(5) and not on the symmetrical molecule to which it is attached.

Significance.- The interest in the pinacol rearrangement has its basis in purely theoretical grounds and the large volume of research on this problem has been carried out with the end in view of clarifying our knowledge of the structure and properties of the organic molecule and radical. This can best be shown by a consideration of a typical example. If phenyl-p-tolyl ketone is reduced under the proper conditions, the pinacol will result. This, on dehydration, will give a mixture of the pinacolones(7) in the ratio of about one to fifteen as illustrated below:



IX.

X.

On the basis of phenyl as one, a migratory aptitude(50) of fifteen is assigned to para-tolyl. This is merely another way of stating that para-tolyl migrates fifteen times as fast as phenyl. Since carbon atom number one is identical in all respects with carbon atom number two, any reason for the tolyl group migrating faster than the phenyl must be found in the characteristics of the respective radicals. Herein lies the basis for the study of the rearrangement of symmetrical pinacols. A large amount of research, mainly in the realm of aromatic chemistry, has been undertaken in order to collect data for study so that more definite conclusions may be drawn concerning the relative strength of certain carbon to carbon bonds, or as to the relative affinities of the various radicals.

A most careful study of the rearrangement of symmetrical pinacols has been made by Bachmann and co-workers(6,7), Montagne(37), Koopal(29), Tiffeneau(49,50,51), and others. By a study of the percent of migration that the various radicals undergo in the symmetrical pinacol rearrangement, the following series of numerical migratory aptitudes, calculated on the basis of phenyl as one, has been compiled. It would, perhaps, be advantageous, and a more representative picture would result, if the series could be calculated with the simplest radical as one; i.e. hydrogen. However, this is impossible at present due to lack of data.

TABLE I

Radical	Migratory Aptitude
Anisyl	500
Phenetyl	500
p-tolyl	15.7
p-biphenyl	11.5
p-isopropylphenyl	9.0
p-ethyl phenyl	5.0
m-tolyl	1.95
m-methoxy phenyl	1.6
Phenyl	1.0
p-iodophenyl	1.0
p-bromphenyl	0.7
p-chlorophenyl	0.66
o-methoxyphenyl	0.3
m-bromphenyl	0
o-bromphenyl	o
m-chlorophenyl	0
o-chlorophenyl	0
Methyl	0
Ethyl	0

Comparison has been made between this table and the table of electronegativities(28) of Kharasch which he has worked out from a study of the reaction

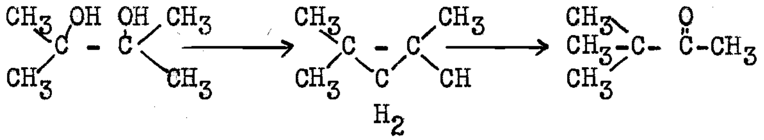
$$RHgR' + HCl = HR + RHgCl$$

and the relative ease with which the radicals in question are split from the mercurial compound. The order is found to be identical to that of the migration aptitudes as calculated in the pinacol rearrangement with the exception of the ortho compounds which show a high electronegativity but low migratory aptitude(6). This close correlation is significant; for it shows that the determining factor in both reactions is very nearly the same and must be something very fundamental in the molecular structure of the two types of molecules.

Since they are completely different species and their only similarity lies in the radicals envolved, it shows definitely that the course of migration is determined by some basic property of the respective radicals. Previous work has led to this same conclusion but no agreement has yet been reached as to just what this determining property of the radical is.

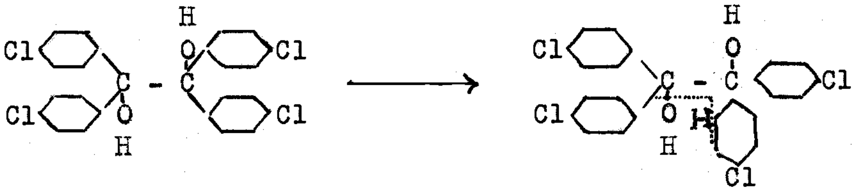
The situation at present is this; many workers have investigated some particular case of the pinacol-pinacolone rearrangement and have used their results, along with that of others, as a basis for their theory of the mechanism of the reaction. With the exception of two of the early theories, these have not lent themselves to any absolute proof.

<u>Theories of the Mechanism</u>.- The cyclopropane intermediate postulated by Erlenmeyer(16) in 1881 has been tested and found inadequate. According to this theory, the dehydration takes place by the removal of one hydroxyl and a hydrogen from the migrating group; thus producing an intermediate with a cyclopropane ring which then splits to the pinacolone.

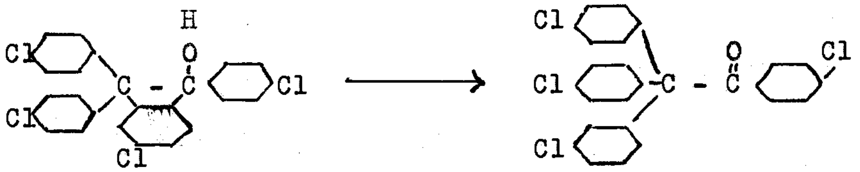


XI,

As has been shown by Montagne(37), this cannot be the case; for when the aromatic pinacol containing a substituent in the ring is rearranged, the resultant pinacolone retains the original aryl to carbon bond. In the case of tetra-p-chlorophenyl ethylene glycol, Montagne has shown that each of the chlorines is still para after rearrangement, and one is not meta as Erlenmeyer's theory demands. Thus the following formulation in untenable:

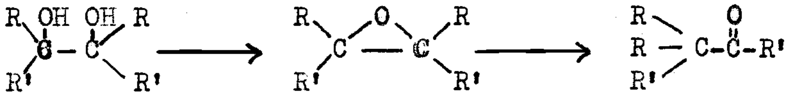


XII



XIII.

The second theory, which no longer has any support, is that of an intermediate ethylene oxide formation(12), according to which the removal of water results in the formation of an ethylene oxide intermediate which is unstable and decomposes into the pinacolone. In so doing, it is necessary for one of the radicals to shift in order to satisfy the valency requirements of the molecule. The point at which the oxygen bond is broken determines which radical will rearrange.

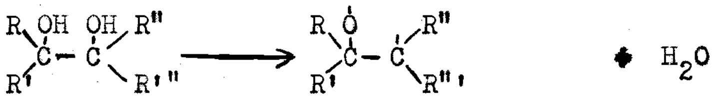


XIV

That this is not the case has been demonstrated by the synthesis of certain of the ethylene oxides(47) and their rearrangement which, although it does take place, requires much stronger conditions than for the pinacol(49) itself. In addition, Tiffeneau(50) has pointed out that, although the closely related iodohydrins are rearranged by silver nitrate, the ethylene oxides are not. The fact that ethylene oxides have been found as by-products in the rearrangement is additional contradictory evidence.

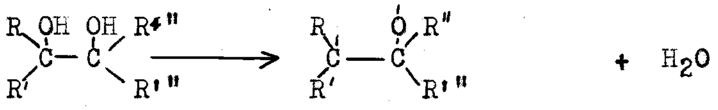
A theory which has been suggested by Meerburg(36) assumes no intermediate but a direct unimolecular reaction. Experiments on the rate of reaction of a typical pinacol has indicated a unimolecular reaction of a typical pinacol to support this. This, of course, does not preclude a slow formation of the intermediate at a measureable rate and the very rapid and immeasureable rearrangement of the intermediate to the pinacol.

Another mechanism which has been widely accepted is that of Tiffeneau(48,50) in which he has supposed that the manner in which water is removed from the two hydroxyl groups of the molecule determines which carbon atom will become the ketonic one in the pinacolone. The free valence radical thus formed will then undergo rearrangement into the pinacolone:



XV

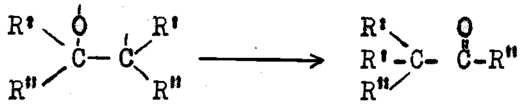
or:



XVI

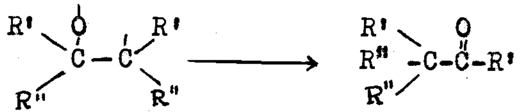
He has stated that the elimination of hydroxyl occurs preferentially from the carbon atom to which is attached the groups with the greatest capacity of electron release(51). This, of course, is immaterial in the case of symmetrical pinacols since R and R' are the same as R" and R'". This, then, is an added advantage in simplicity for using the symmetrical class as a medium for studying the rearrangement. However, according to the theory of Tiffeneau, the final product depends upon the relative facility with which the two groups will migrate from one carbon atom to the other in the intermediate.

Either



(R' migrates) XVII,

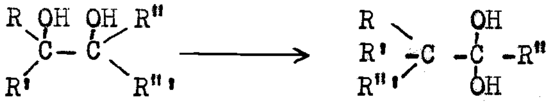
or



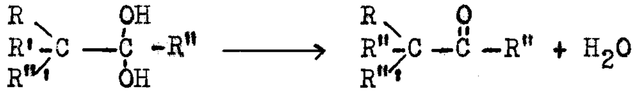
(R" migrates) XVIII,

may take place. It is his conclusion that the ease with which these radicals migrate within the molecule is evidently not related to any one single property of the radical and as yet it has not been established what these properties are.

A theory which has not found such wide acceptance, but which has in no way been disproven, suggests that it is the hydroxyl which migrates first, accompanied by rearrangement of the radical, while dehydration follows(31).



XIX,

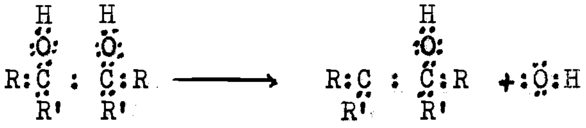


$$\mathrm{RR'R'''C{-}C(OH)_2{-}R'' \longrightarrow RR''R'''C{-}\overset{O}{\overset{\|}{C}}{-}R'' + H_2O}$$

XX.

Another theory which has been applied to the rearrangement is that presented by Nef(39) and envolves the concept of the anomalous valency of carbon.

Whitmore has made an attempt to explain a large number of molecular rearrangements on the same electronic basis. He has presented many papers(53) on the dehydration of alcohols in which he has successfully applied his theory. The formulation of the rearrangement in the case of a symmetrical pinacol would be as follows:

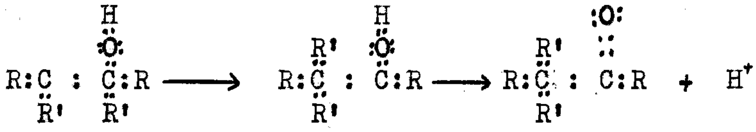


$$\mathrm{R{:}\underset{R'}{\overset{H:\ddot{O}:}{C}}\,{:}\,\underset{R'}{\overset{H:\ddot{O}:}{C}}{:}R \longrightarrow R{:}\underset{R'}{C}\,{:}\,\underset{R'}{\overset{H:\ddot{O}:}{C}}{:}R + {:}\ddot{O}{:}H}$$

XXI.

(1) H:Ö:Ä:B̈:Ö:H
pinacol molecule

(2) :A:B:Ö:H + :Ö:H
organic fragment



$$\mathrm{R{:}\underset{R'}{C}\,{:}\,\underset{R'}{\overset{H:\ddot{O}:}{C}}{:}R \longrightarrow R{:}\underset{R'}{\overset{R'}{C}}\,{:}\,\overset{H:\ddot{O}:}{C}{:}R \longrightarrow R{:}\underset{R'}{\overset{R'}{C}}\,{:}\,\overset{:O:}{C}{:}R + H^{+}}$$

XXII.

(2) :A:B̈:Ö:H
organic fragment

(3) :Ä:B̈:Ö:H
rearranged fragment

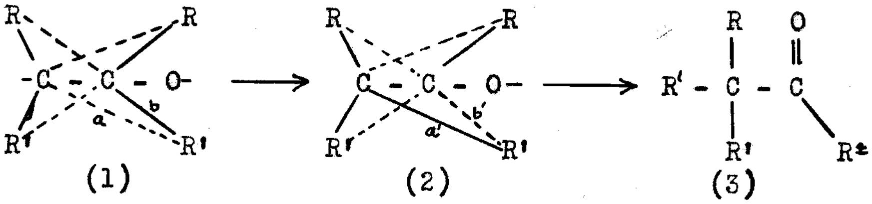
(4) :Ä:B̈::Ö: + H^+
pinacol molecule

The pinacol represented by (1) is stable and each atom has a complete octet. But once the negative hydroxyl group is removed, an unstable condition which has only a momentary existance as an organic fragment, results. The organic fragment, as shown (2), contains a carbon atom with an unstable sextet; for when the hydroxyl group is removed, it carries with it its pair of shared electrons and leaves the carbon atom deficient. There are now three possibilities open to the organic fragment; it may combine with another ion, such as chloride, and form a normal product; or, if the unsaturated carbon atom has a hydrogen attached to it, the fragment may lose a proton, forming an olefin, and thus accomplish the stabilization of the molecule; and finally, if the nature and / or environment of the fragment is such that carbon atom B has a greater attraction for electrons than A, (or the converse) then there will be an electron shift, leaving carbon atom A with an open sextet, as in X. As the electron pair shifts, it carries along with it the group to which it is attached. The new fragment now loses a proton from the hydroxyl and gives the stable ketone form. This third possibility is the one which takes place almost exclusively.

This theory has, in recent years, found the widest acceptance, although it has no concrete proof in fact, and has not been able to explain some cases in which a carbonium ion apparently is involved or where reaction is catalyzed by hydroxyl ion.

The partial or residual valency theory can be applied to all of the above intermediates to provide a more logical mechanism for the actual rearrangement to take place. For example in the intermediates of either Tiffeneau or Lachmann, the application would be as follows:

The dotted lines indicate the secondary valencies.



XXIII,

These partial valencies are merely a representation of the fact that those atoms which lie close to each other, even though not bound by primary valency bonds, are not without mutual effect. The unstable intermediate (1) now makes adjustments for stabilization by conversion of the strongest residual valence (a) into a primary one (a') and simultaneously the complementary primary valency (b) is subordinated to the position of a secondary bond (b'). This picture of the rearrangement allows a more logical visualization of the process, not as a complete break and recombination of the radical, but as a continual process taking place within the molecule.

A summary of the theories reveals this; the better accepted theories postulate some very unstable and transitory intermediate which undergoes rearrangement and stabilization in accordance with the specific radicals envolved. Whitmore has clarified the previous theories by means of an electron interpretation of the previous structural representations; and his theory gives us a satisfactory mechanism whereby the rearrangement may take place, although the mechanism in itself will not allow us to predict, on theoretical grounds alone, the course of the reaction. An application of the principles of the partial valence theory, as indicated above, enables a more satisfactory interpretation of the rearrangement on the basis of a transition from one method of linkage to the new arrangement of binding by passing continuously through all the intermediate binding states. Finally, it should be pointed out that the present tendency is to interpret chemical reaction on the basis of energy content and electron structure of the molecule(19). In time, when our data becomes complete enough, we will, undoubtedly, be able, through a consideration of the atomic distances, vibrational frequencies, and energies of the various states of activation, be able to predict the speed constant for the reaction from the application of certain principles of quantum mechanics and thus determine theoretically the course of the reaction.

Bachmann(5) has been successful in such predictions in the realm of symmetrical pinacols by use of migratory aptitudes. It is still a problem in theoretical organic chemistry to explain the reason for the magnitude of the migration aptitude for specific radicals.

Nature of the work undertaken.- The purpose of the following investigation was to synthesize and study several symmetrical pinacols in order to clarify some doubtful cases, so that a more complete and accurate set of data might be available for study.

First, the preparation of two pinacols containing the m-biphenyl group was undertaken to ascertain the position of the radical in the series of relative migratory aptitudes and to check the unpublished work of Ruthruff(42), in which he obtained contradictory results. Secondly, the synthesis of 4,4'-diethoxy,4,4'dimethoxybenzopinacol was undertaken in order to check the work of Migita(34,35) who found that the pinacol migrated exclusively in one direction, results which are incompatible with the predictions of Gomberg and Bachmann. Thirdly, it was attempted to determine the migratory tendency of the benzyl radical in desoxybenzoin pinacol.

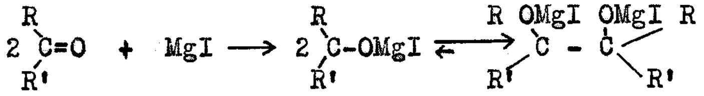
Methods of pinacol synthesis.- Most generally, the pinacols are prepared by the reduction of the appropriate ketone with use of various reducing agents. Fittig originally used metallic sodium upon the ketone. It is now established that this reduction takes place by the formation of an intermediate ketyl radical(44, 45) which immediately associates to form the pinacolate. This, on hydrolysis with acid, gives the pinacol(4). This is still a satisfactory reaction, in many cases, for the production of pinacols.

Photochemical reduction(29) is one of the simplest methods of converting an aromatic ketone to the pinacol. Here the ketone is placed in the sunlight in a solution of isopropyl alcohol and allowed to set until the pinacol crystallizes out. This has the disadvantage of the time required since, in a typical case, a month of exposure is needed before any appreciable reduction is apparent. In addition to this, the reaction works only in certain cases and in others hydrols are formed instead.

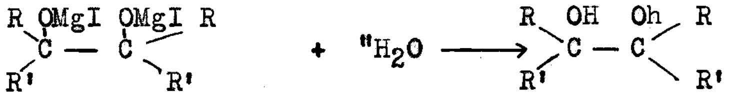
Of all the methods of reduction, the most useful is that using a mixture of magnesium and magnesium iodide discovered by Gomberg and Bachmann(22) in which the active reducing agent is the magnesious iodide produced according to the equation:

$$Mg + MgI_2 \rightleftarrows 2MgI \qquad XXIV.$$

The magnesious iodide readily reacts with the ketone and gives a metal ketyl which immediately associates to form the iodomagnesium pinacolate, which is readily hydrolysed to the pinacol.



$$2\,\overset{R}{\underset{R'}{>}}C{=}O + MgI \longrightarrow 2\,\overset{R}{\underset{R'}{>}}C{-}OMgI \rightleftarrows \overset{R}{\underset{R'}{>}}\overset{OMgI}{C} - \overset{OMgI}{C}\overset{R}{\underset{R'}{<}} \qquad XXV,$$

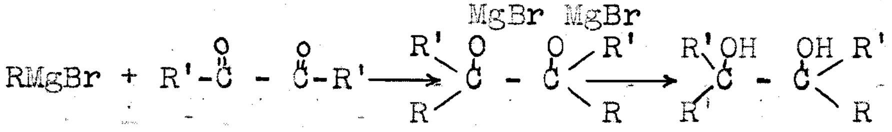


$$\overset{R}{\underset{R'}{>}}\overset{OMgI}{C} - \overset{OMgI}{C}\overset{R}{\underset{R'}{<}} + "H_2O \longrightarrow \overset{R}{\underset{R'}{>}}\overset{OH}{C} - \overset{Oh}{C}\overset{R}{\underset{R'}{<}} \qquad XXVI,$$

Since the reaction is of a nature which produces no side reactions, it is ideally suited for the production of the pinacols. Thus a yield of 99.6% is claimed for the production of benzophenone to the pinacol(22).

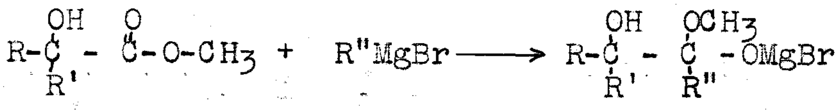
There are many other methods of reduction using the action of an active metal on an acid(15, 50, 54) or the action of sodium, aluminum, or magnesium amalgum in alcohol(33). These methods are not so valuable, though, for the reduction may easily take other courses such as the production of the alcohol or of the hydrol. The latter reaction predominates in basic solution. Another disadvantage is encountered in the fact that the acid treatment may rearrange some of the less stable pinacols into the pinacolone under the conditions of the reduction(34).

The only other methods of pinacol syntheses, in which ketone reduction is not involved, makes use of the action of a Grignard reagent on either a diketone(55),



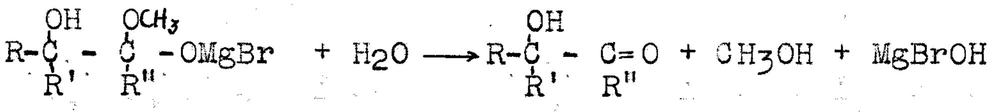
XXVII

or a benzillic acid ester or related compound(3).



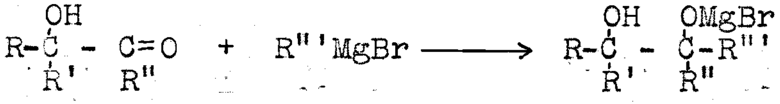
XXVIII

$$R-\underset{R'}{\overset{OH}{C}}-\overset{O}{\overset{\|}{C}}-O-CH_3 + R''MgBr \longrightarrow R-\underset{R'}{\overset{OH}{C}}-\underset{R''}{\overset{OCH_3}{C}}-OMgBr$$



XXIX

$$R-\underset{R'}{\overset{OH}{C}}-\underset{R''}{\overset{OCH_3}{C}}-OMgBr + H_2O \longrightarrow R-\underset{R'}{\overset{OH}{C}}-\underset{R''}{C=O} + CH_3OH + MgBrOH$$



XXX

$$R-\underset{R'}{\overset{OH}{C}}-\underset{R''}{C=O} + R'''MgBr \longrightarrow R-\underset{R'}{\overset{OH}{C}}-\underset{R''}{\overset{OMgBr}{C}}-R'''$$

XXXI

$$R-\underset{R'}{\overset{OH}{C}}-\underset{R''}{\overset{OMgBr}{C}}-R''' + H_2O \longrightarrow R-\underset{R'}{\overset{OH}{C}}-\underset{R''}{\overset{OH}{C}}-R''' + MgBrOH$$

Oxalic acid esters can likewise be converted to pinacols by the same reaction with four molecules of the Grignard reagent.

II. EXPERIMENTAL

1. sym-3,3'-Diphenylbenzopincol

A study of the possible methods of synthesis of 3,3'-diphenyl benzopinacol revealed that the process would be quite long and would involve at least one step which gives very poor yields unless some direct method was obtained. Such a method was suggested in the form of the oxidation of m-diphenyl benzene to m-phenyl benzoic acid. This could readily be changed to the desired ketone by a Friedel and Crafts reaction. The crude m-diphenyl benzene* proved to be quite impure, containing approximately seven percent of the ortho compound and twenty-three percent of the para compound as determined by differences in solubilities.

Oxidation of m-diphenyl benzene.- It was reported by Schmidt and Schultz(46) that m-phenyl benzoic acid was obtained, along with benzoic acid, upon the oxidation of m-diphenyl benzene with chromic oxide. Because of this statement, various oxidations were carried out on m-phenyl diphenyl.

Fifty grams of m-diphenyl benzene (crude) was mixed with a 35% solution of potassium dichromate in acetic acid and allowed to react at reflux for twenty hours. The mixture was cooled, filtered, neutralized, filtered, and salts concentrated. Forty-one grams of diphenyl benzene, 105 g. of dichromate, and 5 g. of chromium acetate were recovered. No base-soluble, acid-insoluble product, which

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* Furnished by Dow Chemical Corporation.

might be either benzoic or m-phenylbenzoic acid, was detected.

Oxidation was next attempted with potassium permanganate. A suspension of m-diphenylbenzene, (M.P. 77°) obtained by mixing 20 g. of the diphenyl benzene in 980 ml. of a five percent potassium permanganate solution, was refluxed for eight hours. Since at the end of this time there was no apparent reaction, the solution was made approximately 0.5N basic by the addition of 20 g. of sodium hydroxide and the refluxing was continued for an additional eight hours. The unreacted permanganate was removed by reacting with alcohol, cooling, and filtering entirely free of insoluble manganese dioxide. The clear filtrate was neutralized, but no insoluble matter was formed. A benzene extraction of the filtrate yielded 17.5 g. of the original 20 g. of hydrocarbon.

A second and more drastic permanganate oxidation was undertaken, using a 10% solution with respect to permanganate and a 40% solution with respect to sodium hydroxide. This was refluxed for 70 hours with agitation. Separation, as above, revealed the same results with the exception that this time only forty-five percent of the original diphenylbenzene remained. Thus we see that the results from the oxidation of m-diphenyl benzene show that no benzoic or m-phenylbenzoic acids were produced; and seemingly the hydrocarbon is slowly oxidized completely to carbon dioxide and water under the conditions of the experiments.

The second manner of approach to the problem consisted in the preparation of m-iododiphenyl which was coupled with magnesium and reacted with benzil to give the sym-3',3-diphenylbenzopinacol according to the following set of equations:

$$NO_2C_6H_4NH_2HCl + HNO_2 \longrightarrow NO_2C_6H_4N_2Cl \qquad \text{I}$$

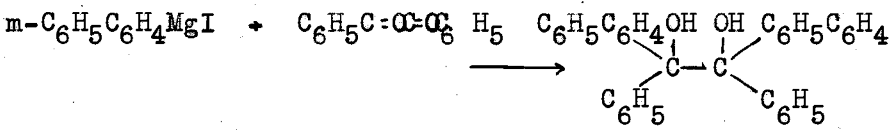
$$NO_2C_6H_4N_2Cl + C_6H_6 \longrightarrow m\text{-}C_6H_5C_6H_4NO_2 \qquad \text{II}$$

$$m\text{-}C_6H_5C_6H_4NO_2 + H_2 \longrightarrow m\text{-}C_6H_5C_6H_4NH_2 \qquad \text{III}$$

$$m\text{-}C_6H_5C_6H_4NH_2HCl + HNO_2 \longrightarrow m\text{-}C_6H_5C_6H_4N_2Cl \qquad \text{IV}$$

$$m\text{-}C_6H_5C_6H_4N_2Cl + KI \longrightarrow m\text{-}C_6H_5C_6H_4I \qquad \text{V}$$

$$m\text{-}C_6H_5C_6H_4I + Mg \longrightarrow m\text{-}C_6H_5C_6H_4MgI \qquad \text{VI}$$



$$m\text{-}C_6H_5C_6H_4MgI + C_6H_5C{=}O\,C{=}O\,C_6H_5 \longrightarrow (C_6H_5C_6H_4)(C_6H_5)C(OH){-}C(OH)(C_6H_4C_6H_5)(C_6H_5) \qquad \text{VII}$$

m-Nitrodiphenyl.- The reported method of preparation of m-nitrodiphenyl is by the Gomberg-Bachmann coupling of the hydrocarbon with diazotized m-nitroaniline in strong base(24). The course of the reaction has been postulated as follows:

$$2\ m\text{-}NO_2C_6H_4N_2Cl + NaOH \longrightarrow 2m\text{-}NO_2C_6H_4\ N_2ONa + NaCl \qquad \text{VIII}$$

$$2\ m\text{-}NO_2C_6H_4N_2ONa \longrightarrow 2\ m\text{-}NO_2C_6H_4N_2OH + 2\ NaOH \qquad \text{IX}$$

$$2\overset{m\text{-}no_2}{C}_6H_4N_2OH \longrightarrow m\text{-}NO_2C_6H_4N_2ON_2C_6H_4m\text{-}NO_2 \qquad \text{X}$$

$$m\text{-}NO_2C_6H_4N_2ON_2C_6H_4m\text{-}NO_2 + 2C_6H_6 \longrightarrow 2\ m\text{-}NO_2C_6H_4C_6H_5 + 2N_2 + 2H_2O \qquad \text{XI}$$

Reaction X represents the formation of the active tautomere.

One-half mole of Eastman's crude m-nitroaniline was diazotized in the usual manner at 5° using 0.5 mole of sodium nitrite and 1.25 moles of hydrochloric acid in a minimum volume of water. The resultant diazonium salt was produced in the form of a froth since it was not completely soluble in the amount of water present. Three hundred ml. of thiophene-free benzene was mixed with stirring and 170 ml. of 20% sodium hydroxide added dropwise over a period of $2\frac{1}{2}$ hours at a temperature of 5°C. The tarry mixture was slowly allowed to reach room temperature and the benzene layer, plus a benzene extract of the residue, was concentrated and steam distilled at 150°-170°C. Four liters of distillate were collected and these, on benzene extraction, gave 2 g. of m-nitrobiphenyl, which is two percent of the theoretical yield. The product formed light yellow crystals melting at 58.5° and boiling at 190-192° at 20mm. The melting point has been previously reported as 58.5°(23) and 61°(18).

This is obviously unsatisfactory. The low yield was traced to two causes other than the normally poor yields of the reaction; 20-30%. The low volatility of the m-nitrobiphenyl with steam, even at 150°, makes complete recovery long and probably incomplete, and the inefficient mixing of the reaction mixture lowered the yield considerably. It was found that the yields depend very decidedly upon the efficiency of the stirrer since it is a heterogeneous reaction, and if base is allowed to collect, decomposition results. The same experiment was repeated using an improved agitator and collecting the m-nitrobiphenyl, not by steam distillation but by the method of Scarborough(43) in which the benzene soluble layer is purified by washing with base and finally completely precipitating the tar by addition of ligroin. The ligroin soluble fraction was then concentrated and crystallized from alcohol. Yield, 14.5%. This is appreciably better but still below the yield of 18% as reported(24).

A third run in which magnesium sulfate was added previous to the addition of sodium hydroxide was carried out. The magnesium sulfate acts as a buffer(22) by the production of magnesium hydroxide which controls the hydroxyl ion concentration of the mixture. This, however, did not prove to be successful and gave only two percent of the maximum possible yield. This is undoubtedly due to the fact that the excess magnesium hydroxide produced acted as an emulsifying agent and resulted in a mixture which was too thick to stir thoroughly.

In a further attempt to better the yield, the inverted method(24), in which the diazotized m-nitroaniline was added to the well stirred benzene-sodium hydroxide solution, was tried. Although the control was more convenient, on purification only 9.2% of the product was obtained.

The next synthesis was undertaken by isolating the isonitroso-m-nitroaniline postulated as the reactive component in the coupling reaction(7,30). One-half mole of diazotized m-nitroaniline was poured, with continual cooling, into 700 g. of NaOH dissolved in 600 ml. of water. The precipitate was collected in a Büchner funnel and sucked dry over night. This crude isonitroso compound was then mixed with 300 ml. of pure benzene, and 80 ml. of acetyl chloride was then added over a two hour period. The solution was then made definitely acidic with acetic acid, the benzene layer separated and purified by addition of ligroin and washing with base. Final purification by vacuum distillation produced 12% of the product. This method gives no better results than the other and the decided disadvantage of isolating the isonitroso compound from concentrated base is definitely against its use.

A similar synthesis after the method of Grieve and Hey(26), in which one-half mole of m-nitroaniline was converted to m-nitroacetanilide by an equivalent quantity of acetic anhydride and reacted with nitrous fumes to give m-nitro iso-diazo acetanilide, failed to give the final product. Instead, a brick red, fine, crystalline compound, which melted at 176°C with the liberation of a gas, was formed.

Since it is evident that the Gomberg-Bachmann and Scarborough methods are best, it was attempted to improve upon these general procedures. It has been generally established that the reaction is inherently poor due to the heterogeneous nature of the reaction and due to the tendency for the product, as formed, to couple again and in this way build up higher molecular weight compounds(23). In addition to this, some of the diazotized substance is decomposed in the reaction to form phenols as is shown, both by the large amount of material which is washed out of the benzene layer by base, and by the brilliant, red colored phenol dye formed by removing some of the reaction medium, soon after the reaction with sodium hydroxide has started, and making alkaline.

That the addition of $MgSO_4$ to act as a buffer control is advantageous in some cases, has been shown by Gomberg and Bachmann(20) but that its tendency to emulsification more than offsets this advantage, has been definitely demonstrated in this case. It was thought, however, that by the use of some weaker base it would be possible to eliminate the undesirable effects and retain those of advantage. Thus the reaction was developed by use of sodium carbonate so that yields of 23% could be consistently obtained. *

One-half mole of Eastman's crude m-nitroaniline was made to a paste in 100 ml. of concentrated hydrochloric acid and 50 ml. of water. This was diazotized by adding to it 50 g. of sodium nitrite in 100 ml. of water at 5°. One hour reaction time was allowed to insure complete diazotization. The slight excess of nitrite was not detrimental. Three hundred ml. of thiophene-free benzene was added, and a saturated solution of 175 g. of sodium carbonate was dropped in at a slow rate. The temperature was maintained at 5°; and control was much simplified over the method in which sodium hydroxide is used. It required about one and one-half hours for the addition; vigorous stirring was continued for two more hours until the mixture had reached room temperature. The mixture was then acidified with acetic acid and heated to 50° on a steam bath. The benzene layer was separated and the remainder extracted twice with benzene. This was added to the original benzene layer which was purified by adding twice the volume of ligroin to precipitate the tar, washing three times with base, once with water, drying, and distilling off the solvent. The residue may be crystalized from ligroin, which gives a product melting at about 45°; or it may be purified by vacuum

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* It has subsequently been shown that anhydrous potassium carbonate is preferable to the sodium salt because of its greater solubility in water.

distillation at 190°-192° at 20 mm. and crystallization from ligroin, which gives a product with melting point of 58.5°; yield 23 g. (23%).

m-Aminobiphenyl.- Reduction of m-nitrobiphenyl was carried out by use of tin and hydrochloric acid. Two-tenths of a mole (20 g.) of the nitro compound was dissolved in 400 ml. of hot alcohol and maintained at a smooth rate of reaction by adding portions of hydrochloric acid. The reaction was refluxed for an additional half hour, and the mixture was then neutralized with an excess of sodium hydroxide. The alcohol was removed from the basic solution by distillation and the amine recovered from the residual solution by ether extraction. The extract was concentrated and vacuum distilled to obtain 18 g. of light yellow oil; b.p. 190-92° at 20 mm., which solidified on cooling and gave almost colorless crystals melting at 29°. Purification was also easily accomplished by converting it to the almost insoluble amine-sulfuric acid derivative which melts at 181°; reported for the amine by Fichter and Sultzburger(18) m.p. 30° and b.p. 254° at 135 mm.

m-Iododiphenyl.- One-tenth mole of the amine was converted to the diazonium chloride by mixing with 100 ml. of water, 15 ml. of concentrated sulfuric acid, and adding sodium nitrite to an end point with starch iodide at 5°. The diazo compound was quite insoluble, and the suspension was added cold(2°) to 20 g. of potassium iodide in 8 ml. of water over a period of one-half hour. A brilliant vermillion precipitate resulted. The diazo solution was stirred continuously as it was allowed to reach room temperature slowly. It was then warmed; and at 27° the decomposition took place rapidly liberating nitrogen and leaving a dark oily layer. This was extracted with benzene, washed with thiosulfate, dilute base, dried, concentrated, and distilled under reduced pressure. On redistillation, 16.2 g. (57%) of m-iododiphenyl, b.p. 195°-197° at 20 mm., was collected. Reported by Bowden(11) b.p. 188-89° at 16 mm.

Preparation of the pinacol.- Fourteen grams (0.05 moles) of m-iododiphenyl was added to 1.2 g. of magnesium turnings in 25 ml. of anhydrous ether, and no reaction took place even after addition of a crystal of iodine. The mixture was then refluxed for two hours after which time a positive test for the Grignard reagent(21) was obtained. However, no appreciable amount of the magnesium had been used up, and so 25 ml. of amyl ether was added and the refluxing was continued at the higher temperature for five hours, after which time most of the magnesium had reacted. Five grams of Benzil dissolved in benzene was then added and the mixture refluxed for one hours. At this time there was no test for the Grignard reagent, and so the mixture was made acidic with dilute hydrochloric acid to dissolve the magnesium hydroxide formed on hydrolysis. The benzene-ether layer was washed with carbonate solution, water, and dried over anhydrous sodium sulfate. The solvent was then removed by warming in a vacuum. The residue was first extracted with a 200 ml. portion of 50% chloroform-absolute alcohol solution. This was concentrated by warming in vacuum. It was evident that some unreacted benzil still remained; so it was removed by dissolving it out of the mixture in 90% ethyl alcohol and filtering. The remaining pinacol was crystallized from an alcohol-chloroform mixture and finally from hot absolute alcohol. This gave 0.082 grams of the pinacol; m.p. 166°.

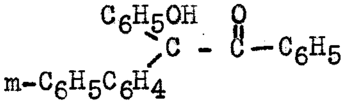
The pinacol gives with sodium ethoxide solutions a turquoise blue coloration and no color with concentrated sulfuric acid. Reported by Ruthruff; m.p. 167.5°.

Analysis.*		
	Calculated for $C_{38}H_{30}O_2$:	C, 87.99%
		H, 5.83%
	Found:	C, 87.97%
		H, 5.75%

As this is only a 0.3% yield, it cannot be used as a means of preparing a quantity large enough for rearrangement studies.

The alcohol insoluble portion consisted of a waxy inert compound which was probably formed by a Wurtz type reaction between the m-iodobiphenyl and the magnesium in the high boiling amyl ether. This product was crystallized in colorless flakes from hot benzene and gave a melting point of 83°. It was inert to concentrated sulfuric acid and was probably 3,3'-diphenyl biphenyl(11).

A third compound was also produced. This was suspected of being the compound between benzil and only one molecule of the grignard reagent:



V.

The losses in the purification were so great, however, that its identity could not be proven.

It is evident that this reaction could not be used to synthesize any quantity of the pinacol. The method of preparation which proved successful was the reduction of m-phenylbenzophenone, which was produced according to the following scheme:

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* The carbon, hydrogen determinations were carried out on a semi-micro scale (20mg.) using the apparatus of Natelson(38).

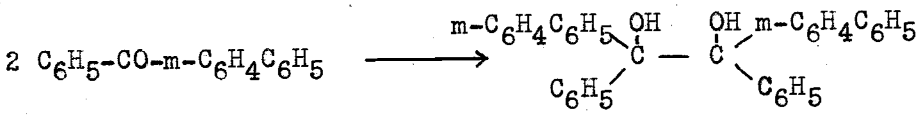
$C_6H_5COOH \longrightarrow C_6H_5COOEt \longrightarrow m\text{-}NO_2C_6H_4COOEt$ VI

$m\text{-}NO_2C_6H_4COOEt \longrightarrow m\text{-}NO_2C_6H_4COOH \longrightarrow m\text{-}NO_2C_6H_4COCl$ VII

$m\text{-}NO_2C_6H_4COCl \longrightarrow C_6H_5\text{-}CO\text{-}m\text{-}C_6H_4NO_2$ VIII

$C_6H_5\text{-}CO\text{-}m\text{-}C_6H_4NO_2 \longrightarrow C_6H_5\text{-}CO\text{-}m\text{-}C_6H_4NH_2$ IX

$C_6H_5\text{-}CO\text{-}m\text{-}C_6H_4NH_2 \longrightarrow C_6H_5\text{-}CO\text{-}m\text{-}C_6H_4C_6H_5$ X



$$2\ C_6H_5\text{-}CO\text{-}m\text{-}C_6H_4C_6H_5 \longrightarrow (m\text{-}C_6H_4C_6H_5)(C_6H_5)C(OH)\text{—}C(OH)(m\text{-}C_6H_4C_6H_5)(C_6H_5)$$

Ethyl benzoate.-- Eight moles of benzoic acid were converted to ethyl benzoate by means of an esterification apparatus in an 80% yield; b.p. 209°, 745 mm.

m-Nitro ethylbenzoate.-- The ester was nitrated with mixed acid by dissolving six moles in 1500 ml. of cold concentrated sulfuric, cooling to 5°, and adding, with continual cooling and stirring, 1000 ml. of 50% nitric and sulfuric acid mixture over a period of 3½ hours. The m-nitro compound was separated from the para by pouring onto 5 kilos. of crushed ice, filtering the product, and washing with 750 ml. of cold methyl alcohol. This gave a colorless product; m.p. 45°, b.p. 168-9° at 20mm. This, with the meta compound recovered from the washings, gave 973 g. (83.6%).

m-Nitro benzoic acid.-- The 5 moles of ester were hydrolyzed by refluxing with potassium hydroxide and separating as the acid by pouring the solution into hydrochloric acid. It was filtered, washed, and dried for 20 hours at 85°; after which time it had reached a constant weight and a yield of 98.5% was recorded; m.p. 142°C upon recrystallization from 1% hydrochloric acid.

m-Nitrobenzoyl chloride.- Four and eight-tenths moles of the acid were converted to the acid chloride by means of an equivalent amount of phosphorous pentachloride(14). The mixture was warmed on the steam bath until no more hydrogen chloride was evolved, and then the phosphorous oxychloride was removed by a distillation at ordinary pressure up to 150°C. The acid chloride was then distilled under vacuum. On redistillation 584.5 g. of almost colorless liquid, that crystallized in large colorless rombic crystals, was obtained; (66.8%) m.p. 31°, b.p. 140-2° at 12 mm.

m-Nitrobenzophenone.- One-third of this acid chloride was converted to m-nitro benzophenone by means of the Pierrier modification of the Friedel and Crafts reaction(41). One and one-tenth mole of the acid chloride was warmed on the steam bath with 1.15 moles of anhydrous powdered aluminum chloride until a homogeneous mixture was obtained. The aluminum chloride, acid chloride addition compound was cooled and 300 ml. of carbon disulfide and 200 ml. of pure benzene were added and gently refluxed on the steam bath until no more hydrogen chloride was evolved. It was then cooled and decomposed with 400 g. of crushed ice. The water layer was separated and the benzene-carbon disulfide was removed by distillation and the m-nitrobenzophenone purified by vacuum distillation at 218° 15mm. Two hundred and twenty-two grams of a light yellow liquid was obtained which solidified to a colorless solid; m.p. 92°C representing a yield of 89.2%. Reported by Greigs and Koenigs(25) b.p. 243° at 18 mm., m.p. 92°.

m-Aminobenzophenone.- The nitro compound was reduced to the amine by use of both tin and hydrochloric acid and stannous chloride. The latter method was much superior. One hundred and eighty-three grams (0.85 moles) of the nitro compound was dissolved in 2 liters of warm alcohol and added, at sufficient rate to maintain an even reaction, to a solution of 580 g. of stannous chloride in 625 ml. of concentrated hydrochloric acid. The reaction proceeded evenly and spontaneously until all of the nitro compound was added. This solution was refluxed for one-quarter hour and the alcohol then distilled off. The remaining solution of amine hydrochloride and stannic chloride was neutralized with 500 g. of sodium hydroxide in a 10% solution. The free amine separated from the warm solution as a surface oil where it solidified on cooling and was collected. It was purified by solution in 4 l. of dilute hydrochloric acid, neutralizing, and allowing to cool. The amine was filtered off and dried at 60° for four hours; yield 154 g. (86.6%). The product crystallizes from water in a thick gelatinous mass which retains water tenaciously and melts at 85°. Recrystallized from dilute alcohol it gave yellow needles, melting at 87°. It forms a stannous chloride addition complex, melting at 139°, and a slightly soluble amine hydrochloride; m.p. 168°. The free amine may be distilled in vacuum; b.p. 245-247° at 15 mm.

m-Pheylbenzophenone.- The Gomberg-Bachmann coupling was carried out using 0.925 mole of the amine which was diazotized in the usual manner. Since the amine hydrochloride was insoluble in water, the volume of water could not be kept as low as was desirable. One hundred and forty-two grams of the amine was converted, by 160 ml. of concentrated hydrochloric acid, to the hydrochloride; and 100 ml. of water was added to make a mixable slurry. This was cooled to 5°; and 50 g. of sodium nitrite dissolved in 100 ml. of water was added over a period of one-half hour and stirred for an additional hour to insure complete diazotization. The speed of stirring was then increased and 500 ml. of thiophene-free benzene added. To this heterogeneous mixture, 150 g. of sodium carbonate, dissolved in 425 ml. of water, was slowly added while the temperature was kept at 5°. After complete addition the mixture was allowed to attain room temperature slowly. It was then heated to 50°, acidified with acetic acid, and the benzene layer separated. This was purified by precipitating the tar with ligroin and washing the ligroin solution several times with base. After drying, concentrating, and vacuum distilling, 18.7 g. (10%) of m-phenylbenzophenone was obtained which boiled at 225-230°/15 mm. It crystalized in colorless crystals from ligroin; m.p. 76°. Reported by Ruthruff; 78°. A repetition of the synthesis using strong base and magnesium sulfate produced only a 6.7% yield. The ketone gave a bright yellow coloration with concentrated sulfuric acid.

<u>Analysis</u>.- Calculated for $C_{19}H_{14}O$: C, 88.34%

H, 5.59%

Found: C, 88.25%

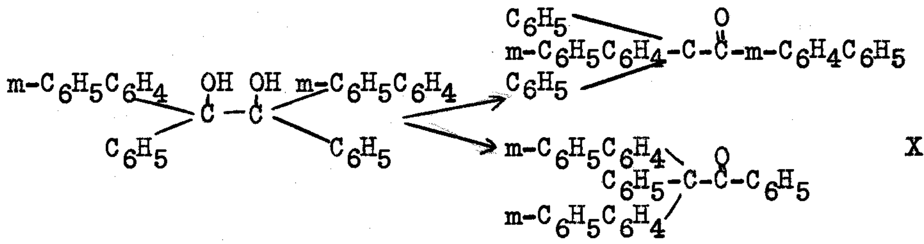
H, 5.65%

Preparation of the pinacol.- Thirty ml. of anhydrous ether, 20 ml. of benzene, and 1.8 g. of magnesium powder were placed in a 200 ml. round-bottomed flask and 1.9 g. of iodine was added in small lots. After complete addition, the mixture was refluxed for three quarters of an hour until the solution became clear. Ten grams (0.039 moles) of the ketone was added in 20 ml. of benzene and the mixture, which gave only a slight precipitate of the addition product, was warmed and then shaken for two hours. The solution turned a wine color after the first fifteen minutes but this finally disappeared. The ether-benzene solution was decanted, hydrolyzed, extracted with ether, and the extract was washed, dried, and the solvent removed by warming in a vacuum. The residue was freed from unreacted ketone by warming with two portions of petroleum ether (40-60°) and then crystallized from an alcohol-chloroform mixture; m.p. 167.5°, yield 25%. When this product was mixed with that prepared by the Grignard, the melting point of the mixture was 166°.

Analysis.- Calculated for $C_{38}H_{30}O_2$: C, 87.99%
H, 5.83%

Found: C, 87.90%
H, 5.68%

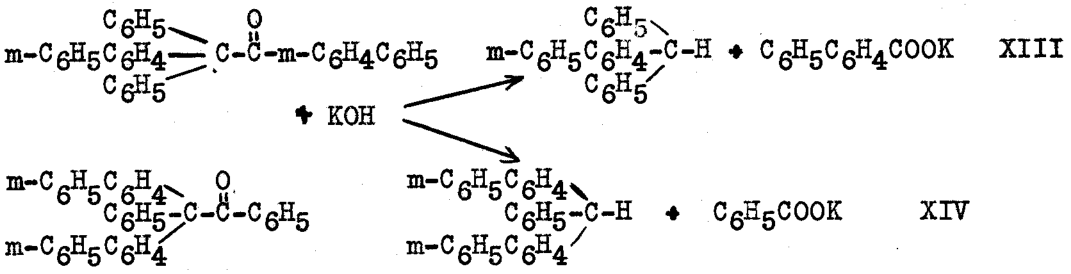
Rearrangement of the Pinacol:-



XII

Two hundred and fifty-eight milligrams (0.0005 moles) was rearranged by refluxing for thirty minutes with fifty ml. of glacial acetic acid and 0.1 grams of iodine (20). The acetic acid was removed by warming in a vacuum and the mixture of pinacolones produced was not isolated.

Analysis of the Pinacolones.-



$$\text{m-}C_6H_5C_6H_4(C_6H_5)_2C\text{-}CO\text{-m-}C_6H_4C_6H_5 + KOH \rightarrow \text{m-}C_6H_5C_6H_4(C_6H_5)_2C\text{-}H + C_6H_5C_6H_4COOK \quad \text{XIII}$$

$$(\text{m-}C_6H_5C_6H_4)_2(C_6H_5)C\text{-}CO\text{-}C_6H_5 + KOH \rightarrow (\text{m-}C_6H_5C_6H_4)_2(C_6H_5)C\text{-}H + C_6H_5COOK \quad \text{XIV}$$

The mixture of pinacolones was cleaved by refluxing for 36 hours with 20 ml. of 25% KOH in methyl alcohol and benzene. The solvent was evaporated off under vacuum. The remaining solution was diluted and the methanes extracted from the solution by three successive washings with benzene, 20, 15, and 10 ml. respectively. The solution was then warmed to insure the complete removal of benzene and filtered free of all methanes. It was then acidified and again extracted with benzene, this time to remove all of the acids formed. Another sample was rearranged and analyzed in a like manner. The results are recorded in the following table:

Table II

Sample no.	Weight mg.	Rear. time. min.	Cleavage time hrs.	Yield of methanes g.	Yield of methanes %	Yield of acids g.	Yield of acids %*
I	0.2500	30	36	0.1854	107	0.0648	83.9
II	1.2500	46	50	0.8960	103	0.3441	89.4

* Per cent yields calculated on the assumption that there is equal migration of radicals.

Analysis of the acid mixtures.- The analysis of the mixture of acids was carried out on the basis of their different solubilities in water. Twenty to forty mg. samples were introduced into 10 mm. tubes which were drawn out to a capillary at one end. The sample was washed three successive times with 0.5, 0.25, and 0.1 ml. of water at 80° by stirring the acid mixture thoroughly while in a water bath of the proper temperature, then transferring to a centrifuge while the tubes were still surrounded by water at 80°, and, finally, removing the water with a capillary pipette. The water soluble portion was evaporated and both residues were dried in a vacuum desiccator before weighing.

This procedure was first carried out on synthetic mixtures in order to determine the efficiency of the separation. The results are recorded below.

Table III

Sample	Known composition of acid mixture		Weight of recovered acids in mg.		Solubility of the m-phenyl benzoic acid mg.
	Benzoic mg.	m-phenyl benzoic mg.	Dissolved	Residue	
I	30.4	12.5	33.2	9.8	2.7
II	15.6	9.8	18.2	7.0	2.8
III	7.5	7.0	10.5	4.3	2.7

The acid used in the above tests was prepared by a Sandmeyer reaction on m-amino diphenyl and from m-nitrobenzoic acid by reduction and coupling according to the Gomberg-Bachmann reaction.

m-Aminobenzoic acid.- In the latter synthesis an attempt was first made to prepare the amine by a stannous chloride reduction of the nitro compound by the same general procedure as used in the reduction of m-nitrobenzophenone and m-nitrodiphenyl. But due to the amphoteric nature of both the amino acid and the stannic ion present, separation was difficult and the m-nitrobenzoic acid was lost in the process. It was successfully prepared by catalytic hydrogenation with platinum catalyst (21) at 30-45 pounds pressure with the hydrogenation apparatus of Adams (2). Two-tenths of a mole was completely reduced after one hour. The catalyst was filtered off and the amine purified by evaporating off the alcohol solvent and crystallizing from a minimum of hot alcohol; yield 88.5%, M.P. 175°. It forms a slightly soluble amine hydrochloride which melts above 255°.

m-Phenylbenzoic acid.- Thirty-five grams of the amine was diazotized in the usual manner. The diazonium chloride was then vigorously stirred with 300 ml. of thiophene-free benzene, and 50 g. of anhydrous potassium carbonate, dissolved in 50 ml. of water, was added. Since potassium carbonate is much more soluble than the sodium salt, it is a decided improvement over the latter. It is important that the volume of solution be kept at a minimum during the reaction. As well as the greater solubility, it has the added advantage of smoother control. Thus the temperature remained at 2° throughout the reaction without the need of any special care. The solution was stirred for an additional 2 1/2 hours during which time the mixture was slowly allowed to reach room temperature. The solution was then acidified and a large mass of tarry substance was precipitated. The mixture was steam distilled. Although apparently nothing came over with the steam, a subsequent ether extraction separated a very small amount of the acid. This was introduced into a capillary tube and purified by treating with norite and crystallizing from alcohol; M.P. 152°. On recrystallization it melted at the reported value of 161°; neutralization equivalent 198.[illegible] ± 10; yield 15.7 mg. The tarry mixture proved to be very interesting, for, even though it gave the appearance of being a carbonized decomposition product, it proved to be a strong acid. It dissolves instantly in dilute carbonate solution, but is insoluble in water or acid. In base it gives a deep red solution but a dark brown solution in most organic solvents. It was carried through the following steps in an attempt at purification but remained unchanged throughout. It was dissolved in base, warmed with decolorizing charcoal, filtered, and precipitated by neutralization. The precipitate was completely dissolved in 95% alcohol made slightly acidic and again treated with charcoal adsorbant. The solution was filtered and the acid again precipitated, this time by dilution with water. On filtration and drying it appeared in its original form. It is of a non-phenolic nature.

m-Phenylbenzoic acid was also prepared from m-aminobiphenyl; .560 grams of the amine was diazotized in a 50 ml. beaker with 10 ml. of water, .5 ml. of hydrochloric acid, and .175 g. of sodium nitrite. This solution was then slowly added to a solution of cuprous cyanide (.35 g.) in potassium cyanide with constant stirring. The solution was warmed and the nitrile extracted and hydrolyzed with 70% sulfuric acid for 45 minutes. The acid solution was diluted, filtered, and purified in a capillary as previously indicated; yield 7.8 mg.

Comparative migratory aptitudes of the phenyl and m-biphenyl radicals.- It is evident from the analysis on known mixtures of benzoic and m-phenylbenzoic acids that, for the amount of water used (0.850 g.) and the temperature (80°), the benzoic acid is completely soluble and the m-phenylbenzoic acid dissolves to the extent of 2.7 mg. (0.32%). A correction of 2.7 mg. must, therefore, be added to the residue and subtracted from the soluble fraction to obtain the correct values for the respective acids. The following table gives the results from the analysis of the acid mixtures produced by rearrangement and cleavage of the 3,3'-diphenylbenzopinacol.

Table IV

sample no.	sample weight mg.	water soluble fraction mg.	residue mg.	total recovered acids mg.
I. a	18.7	6.7	11.8	18.5
b	30.0	12.4 12.2	16.8	29.2
II. a	32.4	12.2	20.2	32.4
b	21.6	7.4	14.4	21.8
c	27.3	10.8	16.7	27.5

By applying the correction factor we can convert these figures into grams of acids and calculate the percent migration.

Table V

sample no.	sample weight mg.	amounts of acids found				% migration of m-biphenyl
		m-phenyl benzoic mg.	moles	benzoic mg.	moles	
I. a	18.7	14.5	7.32×10^{-5}	4.0	3.28×10^{-5}	69.1
b	30.0	19.7	9.85 "	9.7	7.95 "	55.3
II. a	32.4	22.9	11.55 "	9.5	7.79 "	59.7
b	21.6	17.1	8.64 "	4.7	3.85 "	69.2
c	27.3	19.4	9.80 "	8.1	6.63 "	59.6
					Ave.	62.6

The results show that the average per cent migration of m-biphenyl with respect to phenyl is 60%. The average per cent migration of phenyl is then 40%. Since the migration aptitude is the relative rearrangement with respect to phenyl as one, the relative tendency of m-biphenyl to migrate would be

$$\frac{\text{m-biphenyl}}{\text{phenyl}} = \frac{62.2}{37.4} = 11.67$$

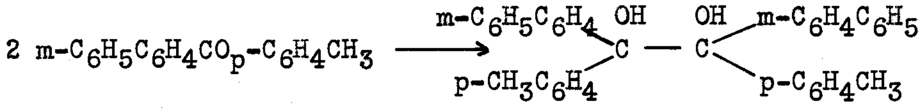
2. sym-3,3'-Diphenyl-4,4'-dimethyl-benzopinacol

Attempted preparation of the pinacol was carried out according to the following scheme:

$$\text{m-}NO_2C_6H_4COCl + C_6H_5CH_3 \longrightarrow \text{m-}NO_2C_6H_4CO\,\text{p-}C_6H_4CH_3 + HCl \qquad \text{XIV}$$

$$\text{m-}NO_2C_6H_4CO\,\text{p-}C_6H_4CH_3 + H_2 \longrightarrow \text{m-}H_2N\,C_6H_4CO\,\text{p-}C_6H_4CH_3 \qquad \text{XV}$$

$$\text{m-}H_2N\,C_6H_4CO\,\text{p-}C_6H_4CH_3 + C_6H_6 \longrightarrow \text{m-}C_6H_5C_6H_4CO\,\text{p-}C_6H_4CH_3 \qquad \text{XVI}$$



$$2\ \text{m-}C_6H_5C_6H_4CO\,\text{p-}C_6H_4CH_3 \longrightarrow (\text{m-}C_6H_5C_6H_4)(\text{p-}CH_3C_6H_4)C(OH)-C(OH)(\text{m-}C_6H_4C_6H_5)(\text{p-}C_6H_4CH_3) \qquad \text{XVII}$$

<u></u>**3-Nitro-4'-methylbenzophenone.-** One hundred and eighty-six grams of pure m-nitrobenzoyl chloride, prepared as previously described, was warmed with 136 g. of powdered, anhydrous aluminum chloride until a homogeneous mixture resulted. This was then cooled and three hundred ml. of carbon disulfide added. To this solution was then added, by way of a dropping funnel, 250 ml. of toluene. The reaction was continued until all of the hydrogen chloride had been evolved,

then cooled and hydrolyzed with ice and hydrochloric acid. The carbon disulfide layer was separated and the remainder extracted with benzene to remove all of the ketone. It was purified by washing a few times with base, concentrating, and crystallizing the residue from benzene-ligroin and alcohol-chloroform mixtures; yield 115 g. (48%), m.p.113°; reported (32) 111°.

<u>3-Amino 4'-methylbenzophenone</u>.- Ninety-nine grams (0.5 moles) of the m-nitro compound was reduced by adding it, in alcohol solution, to 335 g. of stannous chloride dissolved in 300 cc. of concentrated hydrochloric acid. The reaction was controlled by the rate of addition of the nitro compound and was complete in 1.25 hours. The amine was separated by distilling off the alcohol, adding an excess of strong base, diluting, and allowing the solution to cool. It was filtered free from the sodium stannate solution and purified by solution in a dilute hydrochloric acid, filtration, and neutralization. The amine was filtered off when cold. Weight on drying, 79 g. (82%); m.p. 111.5°. It forms an amine hydrochloride; m.p. 199°. The amine melts 0.5° higher and the hydrochloride 1.0° higher than that reported (32).

<u>3-Phenyl-4'-methylbenzophenone</u>.- The amine was diazotized and coupled with benzene in the presence of sodium carbonate by converting 77 g. (.33 mole.) of the amine to the hydrochloride with 75 ml. of concentrated hydrochloric acid in 250 ml. of water. This was cooled down to 5°, and 22 g. of sodium nitrite in 50 ml. of water was added dropwise over an half hour period. Stirring was continued for

an additional half hour to insure complete diazotization. Three hundred ml. of pure benzene was then added and 105 g. of potassium carbonate was added in 100 ml. of solution over a period of two hours. The stirring was continued while the mixture was allowed to reach room temperature. It was heated on a steam bath to 50°, cooled, and the benzene layer separated and purified by addition of ligroin and washing three times with dilute base. The solvent was removed and the residue vacuum distilled. The fraction coming over at 185-225°, 18 mm. pressure was collected and redistilled. Two fractions were obtained: 185-190° 18 mm., 2.4 g. and 215-220°, 18 mm., 2.5 g. Neither substance would crystallize and so each was steam distilled. The lower boiling fraction was completely volatile and came over as a light yellow oil. On analysis it gave: C = 82.5%,

H = 7.1%.

Calculated for the expected ketone, $C_{20}H_{16}O$: C = 88.3%,

H = 5.89%.

The second fraction was only slightly volatile with steam even at 200°, and, like the first, did not show any properties of the desired ketone.

Obviously the expected ketone was not produced by the reaction. Work is being continued in order that this ketone and corresponding pinacol may be synthesized.

3. 4,4'-Diethoxy,4,4'-dimethoxybenzopinacol.

This pinacol was prepared by Grignard reaction from p-bromphenetol and anisil by the following procedures.

p-Bromphenetol.- p-Bromphenol was converted to the sodium salt and ethylated by use of diethyl sulfate. Yield 97.5% of product boiling at 230° at 758 mm.

4,4'-Dimethoxybenzoin.- Three hundred grams of anisaldehyde, 800 ml. of 65% ethyl alcohol, and 60 g. of potassium cyanide were refluxed for 2 hours. One half of the alcohol was distilled off and the remaining mixture refrigerated over night. The oil which separated was washed with two portions of acid carbonate solution, dried, and vacuum distilled. One hundred and eighty grams, boiling point 135-40°, 19 mm. distilled over first. This proved to be unreacted anisaldehyde. At 205° and 18 mm. 104 g. of anisoin came over; yield on the basis of the anisaldehyde used 86.6%. On crystallization from alcohol it melted at 109° as reported.

4,4'-Dimethoxy benzil.- Three hundred ml. of pyridine, 200 g. of copper sulfate penta-hydrate, and 150 ml. of water were refluxed until completely dissolved, and then 100 g. of anisoin added. Refluxing was continued for 2 1/2 hours, the mixture was allowed to cool in the refrigerator over night, and the crystals of anisil were filtered off. Purification was accomplished by warming with 30 ml. of concentrated hydrochloric acid and 100 ml. of water, cooling, filtering, and washing the product with water until the color of copper sulfate was gone; yield 82%, m.p. 130°. On recrystallization from carbon tetrachloride it melted at 133° as reported.

Preparation of the pinacol.- The p-bromphenetol (0.125 moles.) was Grignarded and to the ether solution was added anisil (0.10 moles.) in benzene. The reaction took place spontaneously. After the addition was complete, the solution was warmed for 15 minutes and a test for Grignard reagent made and found negative. The intermediate was hydrolyzed by adding a solution of ammonium chloride and shaking. The ether-benzene layer was separated and the solvent removed under vacuum. The syrupy pinacol which remained was washed with three separate portions of petroleum ether to remove any unreacted anisil or bromphenetol. The pinacol would not crystallize from any solvents that were tried even when cooled to -15°. The crude pinacol was partially rearranged by storage over phosphorous pentoxide for several months; since attempts at crystallization after this time separated small amounts of the pinacolone, which gave a bright yellow coloration with concentrated sulfuric but failed to show any color with sodium ethoxide.

Since the pinacol could not be crystallized, no attempts were made to rearrange and analyze it.

4. 1,2-Dibenzyl-1,2-diphenylethylene glycol

Beta desoxybenzoinpinacol.- According to the method of Ballard and Dehn, (9) one hundred and seventy grams of benzoin, 80 g. of potassium iodide, and 17 g. of red phosphorus were heated together on a steam bath while 44 ml. of concentrated hydrochloric acid was slowly added. Heating was continued for twenty hours after which time the mixture was extracted with benzene, dried, and the product crystallized from alcohol. In this manner 85 g. of the desoxybenzoin; m.p. 59.5°, and 41 g. of beta desoxybenzoin pinacol; m.p. 171-2° were obtained. The yield of the ketone was 54% and of the Pinacol 27%.

Alpha desoxybenzoin pinacol.- Thirty grams of the desoxybenzoin was dissolved in 500 ml. of isopropyl alcohol along with 0.5 ml. of acetic acid and allowed to set in the sun from October through May. At the end of this time the pinacol was filtered off and recrystallized from alcohol-chloroform mixture; m.p. 208°, yield 50%.

Attempted rearrangement of the pinacol.- Two and one half grams of the beta desoxybenzoin pinacol was refluxed for 1.3 hours in 50 g. of glacial acetic acid and 0.1 g. of iodine. Upon cooling the pinacol crystallized out unchanged. This was diluted, filtered and 2.4 g. recovered. It melted at 171° and gave a mixed melting point with the original of 171°. Boiling with dilute sulfuric, and acetic acid-acetyl chloride mixtures likewise produced no rearrangement on either the alpha or beta pinacol.

III ANALYSIS OF RESULTS

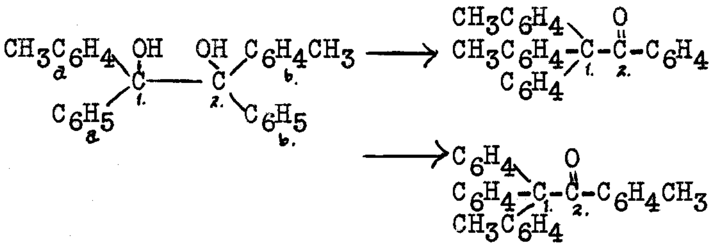
The migratory aptitude of m-biphenyl.- We can now place the m-biphenyl group in its proper position in the series of relative migration aptitudes. As shown by the fact that 62.6 60% of the biphenyl migration product is produced against 37.4 40% of the phenyl, biphenyl must have 1.5 times the tendency to rearrange as does phenyl.

Prediction of migration tendency.- Now if it is true that the course of the rearrangement depends only on the radicals involved (6,8), then we should be able to predict the per cent migration of m-biphenyl to p-tolyl, or any other radical, if we know the per cent migration of phenyl to biphenyl and of phenyl to tolyl. The validity of this type of prediction has been established (6,8). It has been determined that the p-tolyl radical migrates 15.7 times as fast as phenyl (7) and it has likewise been shown above that m-biphenyl migrates 1.5 times faster than phenyl. On this basis, p-tolyl should migrate 15.7/1.5 or 10.5 times faster than tolyl. m-biphenyl It is with the end in view of checking the validity of this prediction that further work is being undertaken to prepare the sym-3,3'diphenyl-4,4'-dimethylbenzopinacol.

The effect of position on the migration aptitude.- The fact that m-biphenyl has a lower migratory aptitude than para biphenyl is in accord with the previous data which shows that the closer the substituent is to the connecting bond of the molecule, the greater will be its hindrance to migration.

Significance of Migratory tendencies.- The migratory aptitude is a measure of the relative speed or ease of rearrangement of one radical with respect to another. But what causes one radical to migrate more readily than another? As has been shown, it is some property or properties characteristic of the radical itself and not due to the molecule. Just what these determining characteristics are we do not know; we know only that the migratory aptitudes, as determined by the rearrangement of symmetrical pinacols, are a measure of this property. Since we have here a means of measuring one of the very basic properties of radicals in the organic molecule, it is important that as complete a list as possible be developed so that our study of the properties of radicals in chemical change may be facilitated.

This rearrangement can tell us more than it has, not only with respect to the radicals involved in the rearrangement, but also in regard to the structure of the pinacol molecule as a whole. A theoretical consideration of a typical case may make this clearer. Let us consider the symmetrical pinacol 4,4'-dimethylbenzopinacol which, when rearranged, yields two products according to the two simultaneous reactions in the ratio of about one to fifteen and seven-tenths (8)

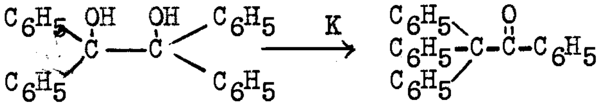


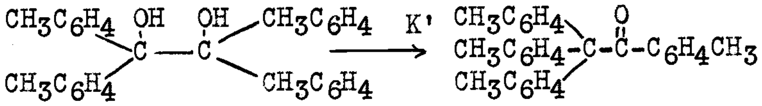
I 15.7 Parts

II 1 Part

It is well established that the product that predominates in a chemical change is the one that is produced by the fastest reaction. The fact that 15.7 times as much of the p-tolyl rearrangement product is obtained must mean that this reaction proceeds 15.7 times as rapidly. The explanation for the one reaction proceeding faster than the other has been attributed to the property of the radical which determines its strength of attachment to the molecule. This has been designated as electronegativity (28) or combining affinity(50). These explanations have their basis in the fact that each of the theories for the mechanism of the reaction postulates an intermediate in which, if rearrangement is to take place, one of two conditions must exist. Either the bond between carbon atom number 2. and tolyl group b. must be 15.7 times as strong as that between carbon atom number 2. and phenyl group b., or, which would result in the same thing but which is theoretically quite different, carbon atom number 1. and p-tolyl group b. are attracted by a force which is 15.7 times as strong as that force attracting phenyl group b. to carbon atom number 1. This merely means, when analyzed on the basis of the kinetics of the reaction, that reaction I. has an energy of activation which is enough lower than that of reaction II to allow it, according to laws of the distributions of energies, to take place 15.7 times as fast.

Whether we look at the reaction on the basis of kinetics and energies of activation or interpret it simply on the basis of the strength of carbon to radical bonds, it is apparent that the property of the radical measured by its migratory aptitude, should not be changed by the symmetrical molecule to which it is attached. A perfectly symmetrical pinacol in which all of the substituents are p-tolyl groups should be constructed just 1/15.7 times as firmly and should rearrange just 15.7 times faster than the corresponding pinacol which is made up of four phenyl groups. In other words K and K', the rate constants of the two reactions, should be in the ratio of one to fifteen and seven-tenths for the two following reactions:


III.


IV.

Thus, if the rate of rearrangement in symmetrical pinacols depends only on the radicals involved, the rate of rearrangement of phenyl and p-tolyl in equations I and II should bear a direct relationship to the migratory aptitudes of the respective groups; and the energy of activation derived from a kinetical study of the rearrangements III and IV should likewise apply to cases I and II.

Although we have no quantitative measurements by which to test this, qualitatively this proves to be true; for the perfectly symmetrical p-tolyl pinacol rearranges under the action of acetic acid and iodine when the solution is only warm (15), whereas benzopinacol must be heated for a short time with the same reagent to bring about rearrangement.

But we cannot draw conclusions as to any absolute correlation between ease of rearrangement of perfectly symmetrical pinacols and the relative migratory tendencies from just two cases. A careful quantitive study on the basis of the kinetics of reaction of several representative cases should be undertaken to establish the existence of such a relationship. We should, however, be able to obtain a good idea if the above relationship exists by a study of the literature; since the rearrangement of some of these perfectly symmetrical pinacols have been reported and the conditions for rearrangement given. Since the speed of rearrangement has never been a primary consideration in the many pinacol investigations*, exact data is not available. A survey of some cases with reagents used and the condition under which the rearrangement is carried out should give a qualitative basis for determining the correlation between migratory aptitudes and relative speeds of rearrangements of perfectly symmetrical pinacols.

The literature reveals the following set of pinacols which have been prepared. The table lists the pinacol, the migration aptitude of the radicals in order, and the conditions for rearrangement with the approximate order of ease of rearrangement given for each.

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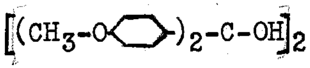
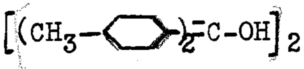
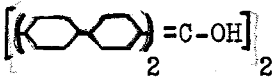
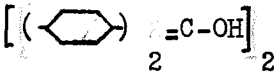
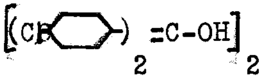
* Meerburg (36) has studied the rate of rearrangement of the perfectly symmetrical p-chloropinacol, but only with the object of determining the order of reaction.

Table VI.

No.	Radical	Migration aptitude	Pinacol	Rearranging agent and conditions	Order of ease of rearrangement
1.	Anisyl (35)	500		Spontaneously on reduction of ketone.	1.
2.	Tolyl (22,15)	15.7		By the addition of a crystal of iodine to a warm acetic acid solution.	2.
3.	p-Biphenyl (22)	11.5		Acetyl chloride acetic acid mixture gently boiled for six hours.	4.
4.	Phenyl (22,27)	1.		A crystal of iodine in acetic acid for a few minutes.	3.
5.	p-Chlorophenyl (36)	0.66		Setting for days in acetyl chloride at 30°.	5.
6.	Methyl (20)	.0	$[(CH_3)_2{=}C\text{-}OH]_2$	Heating for two hours with phosphorous pentachloride. But oxolic acid will also accomplish the rearrangement.	7.?
7.	Ethyl (55)	.0?	$[(C_2H_5)_2\text{-}C\text{-}OH]_2$	Boiling for two hours with dilute sulfuric acid.	6.
8.	n-Propyl (55)	.0?	$[(C_3H_7)_2\text{-}C\text{-}OH]_2$	Action of 20% sulfuric acid at 150°.	8.

A survey of the table shows a very definite correlation, but in one case at least, i.e. the phenyl and p-biphenyl radicals, the results are contradictory. But with each rearrangement performed by a different investigator under dissimilar conditions, this is understandable.

In summary it may be said that in a qualitative way we do find a direct correlation between speed of rearrangement of perfectly symmetrical pinacols and migratory aptitudes from the data given. This must, of necessity, be incomplete and only approximate due to lack of quantitative data and diverse conditions. In order that a valid and just evaluation could be made, research with respect to the kinetics of reaction of the rearrangement of typical ones of the perfectly symmetrical pinacols should be undertaken, and calculations should be made of energies of reaction, as well as of the speed constants. Since the cases in which the correlation does not hold apparently challenge the validity of certain assumptions as to the significance of migratory aptitudes, it is important that such an investigation should be made.

IV SUMMARY

1. The migratory aptitude for the meta-biphenyl group has been established.

2. Attempts at determining the per cent migration of phenetyl against anisyl were unsuccessful.

3. The unaccountable stability of desoxybenzoin pinacol to rearrangement has been noted.

4. A method of testing the validity of certain accepted theories concerning the significance of the migration aptitudes has been presented.

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