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I hereby recommend that the thesis prepared under my supervision by William A. Moonaw entitled The Synthesis and Resolution of Asymmetric Amines: Effect of Negative Substituents on Their Stability and Optical Rotations.

be accepted as fulfilling this part of the requirements for the degree of Doctor of Philosophy

Approved by:

Francis E. Ray
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THE SYNTHESIS AND RESOLUTION OF ASYMMETRIC AMINES:
EFFECT OF NEGATIVE SUBSTITUENTS ON THEIR
STABILITY AND OPTICAL ROTATION

A dissertation submitted to the

Graduate School
of the University of Cincinnati

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requirements for the degree of

DOCTOR OF PHILOSOPHY

1933

by

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EXPLANATION OF REACTION SCHEMES I & II

The reaction schemes on the following two pages illustrate diagrammatically each of the fundamental chemical reactions that were caused to take place during this investigation.

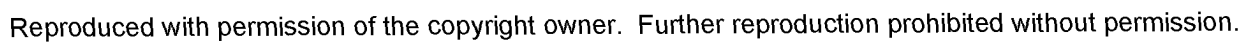
Reaction scheme I gives the fundamental reactions involved in the production of asymmetric amines by the Betti Condensation, the ortho, meta, and para-chloro deriv.

Reaction scheme II gives the reactions which were made to take place, with the principle products isolated, while developing a method for the preparation of the beta-methoxy derivative of Betti's amine.

In order to make the connecting link between Betti's amine, phenyl-beta-napthol-aminomethane, and the methoxy derivative complete, the reactions in scheme II marked (A) and (B) were included. These two reactions were carried out by Mr. Nzeer Ahmed.

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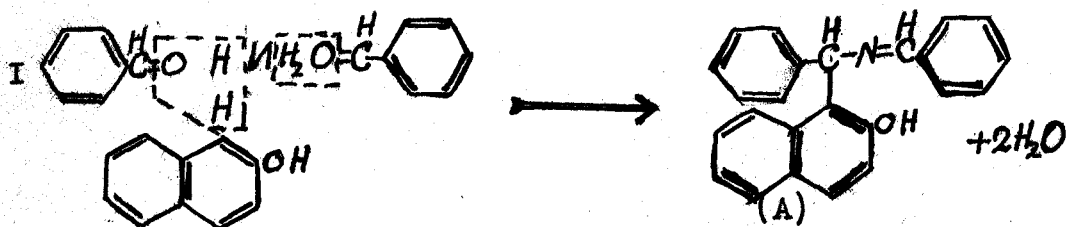
Reaction Scheme I



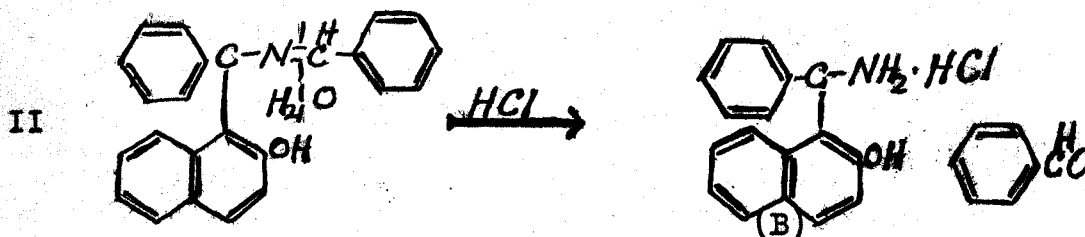
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DISCUSSION

The investigations described in this paper were carried out with the purpose of preparing optically active amines of the type $R'R''CHNH_2$, where R' and R'' are aryl groups. The first experimental work⁽¹⁾ of this kind was concerned with the syntheses of amines by the reaction discovered by Betti⁽²⁾ in 1900, which involved the condensation of benzaldehyde, ammonia, and beta-naphthol to give a Schiff's base (I A). On hydrolysis with dilute hydro-



chloric acid phenyl-beta-naphthol-amino-methane-hydrochloride and benzaldehyde were obtained (II B). The reac-



tion was extended by the use of primary amines, and quite recently Littman and Brode⁽³⁾ have further extended the application to secondary amines.

Betti⁽⁴⁾ in a study of the optical rotation has condensed his amine with substituted aldehydes and measured

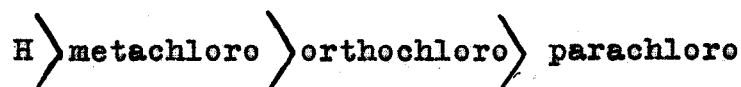
the rotation of the resulting Schiff's bases, but, in so far as we have been able to find, no one has investigated the use of substituted benzaldehydes in the original condensation with ammonia and beta-naphthol.

This part of our investigation in the production of asymmetric amines was undertaken partly to test the general applicability of the Betti Condensation by using substituted benzaldehydes. Positive results were obtained in the condensation of ortho-, meta-, and para-chloro-benzaldehydes with ammonia and beta-naphthol, while negative results were obtained by using the corresponding nitrobenzaldehydes.

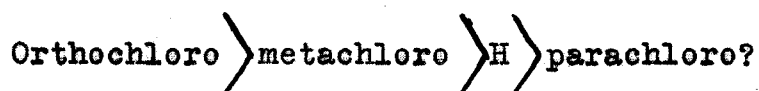
Betti's amine readily decomposes, especially in alkaline solution to give benzaldehyde, beta-naphthol, and ammonia. Each molecule of the benzaldehyde thus liberated combines with a molecule of the undecomposed amine to form the original Schiff's base. It was hoped that by the use of substituted benzaldehydes more stable amines would result. Just the opposite has, however, proven to be the case. The chloro-substituted amines were found to be considerably decomposed by alkaline solutions as well as a solution of tartaric or malic acid.

The reactions of the three monochlorobenzaldehydes followed closely that of benzaldehyde, but the resulting amines are less stable than the amine from the unsubstituted

ted aldehyde. The order of stability is:



The chloro substituted amines are also much more difficult to separate into their optical antipodes than is the unsubstituted amine. Tartartic acid, which affects a satisfactory resolution of the Betti amine, gives with the chloro compounds a very slightly soluble racemic salt which cannot easily be fractionally crystallized. The ortho and meta compounds were finally resolved with the aid of levo malic acid but the para resisted all efforts at resolution. The order of optical activity was:

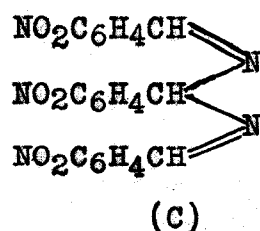


The parachloro compound could not be resolved. There are two probable explanations: the most usual of which is that the right conditions were not obtained; the other, which we favor, is that the instability of this amine precluded its resolution. While satisfactory resolution of the dextro form of the ortho and meta chloro compounds was possible, it was extremely difficult to obtain the more soluble levo antipodes in a state of purity. Even evaporation of an ether solution at room temperature caused some decomposition and racemization of the amines.

When the nitrobenzaldehydes were mixed with beta-

(4)

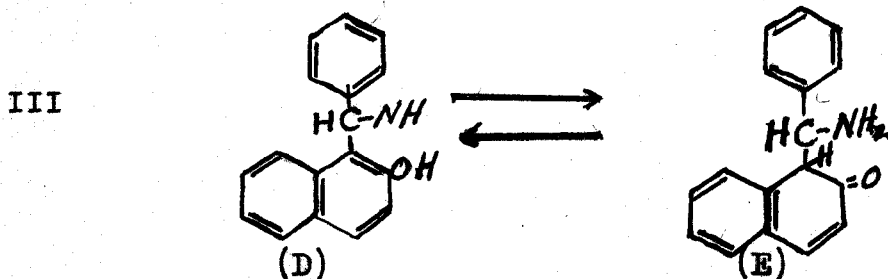
naphthol and ammonia in alcohol they reacted to the extent of 90 percent or more with the ammonia to give the corresponding nitrohydrobenzamides (C). In the case



of the meta-nitrobenzaldehyde, in addition to the hydrobenzamide, a small amount of a compound melting at 198° was recovered.

On the basis of this information the evidence is strongly in favor of the theory that, as the substituents increase in negativity, there is less tendency for the beta-naphthol to take part in the reaction. It may be said at this point that the Betti Condensation is a reaction with definite limits to its applicability. The ways in which it is limited with respect to the aldehydes used seems to be much the same as the limitations shown by the Benzoin Condensation.⁽⁵⁾ In both instances the limitations may be said to be due to the negative substituents in the ring of the benzaldehyde. A second disadvantage of the Betti Condensation, as a method for the preparation of asymmetric amines, is the instability of the compounds thus prepared. We have attributed the cause of the instability to the presence of the OH group in the naphthal-

ene ring; and this postulation has been substantiated by the stability of the methoxy derivative which has been synthesized. The hydroxy group allows for the tautomeric equilibrium as shown in equation (III). Most likely it is

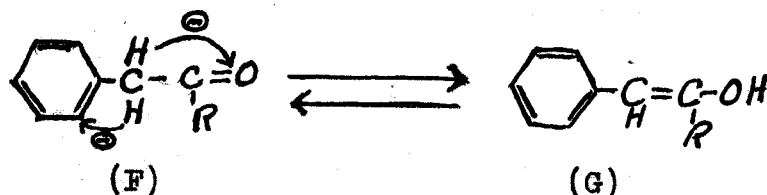


this tautomeric equilibrium that causes the instability of the union between the asymmetric carbon atom and the naphthalene ring, which is due to its influence on the character of the valence bonds possessed by the active methylene carbon atom of beta-naphthol. In compound (D) the methylene carbon atom is not only bound to the asymmetric carbon atom by its fourth valence bond, but this union is strengthened by a certain amount of residual⁽⁶⁾ affinity characteristic of unsaturated carbon atoms e.g. the double bond between the alpha and beta carbon atoms. This double bond is no longer present in compound (E), so that the bonds between the active methylene carbon atom and atoms outside of the ring are no longer reenforced by the residual affinity of unsaturated carbon atoms. In fact, it seems that the union has decreased below the strength of a normal carbon-carbon cleavage, since the

(6)

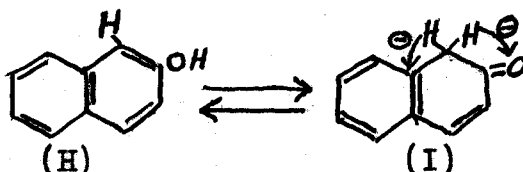
methylene carbon atom is now joined to a hydrogen atom as well as to an unsaturated carbon atom in the second ring of the naphthalene molecule, while for valence neutralization both the hydrogen and unsaturated carbon atoms require at least one-fourth and the unsaturated atom more than one-fourth of the valency shown by a normal carbon atom.

The more modern interpretation of this idea is expressed by use of an electronic shift. Consider any isomeric compounds (F) and (G) with an active methylene group.



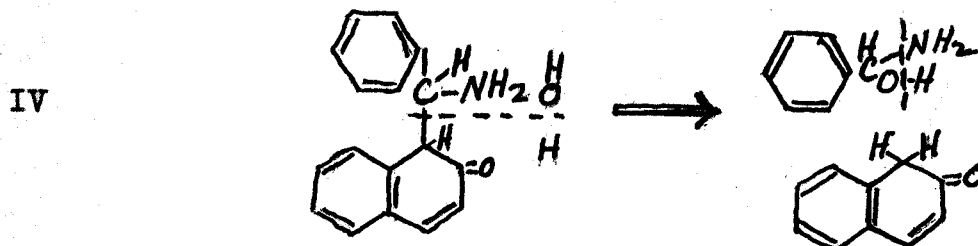
In (F) the active methylene carbon atom is joined to two unsaturated groups, and it is believed that these unsaturated groups attract electrons from the atoms joined to the methylene carbon atom. By the loss of electrons each atom attached to the active methylene is left with an excess positive charge; this permits it to separate as a positive ion. In compound (G) the methylene carbon atom is a member of a conjugated system, hence electrons are drawn to it. Here there is little tendency for the joined atoms to ionize, therefore, one expects very little decomposition of a compound with this structural arrangement. If we consider the tautomeric forms of beta-naphthol, (H) and (I), we find

that the configurations are very much the same as they are for any other compound with an active methylene group. Formula (H) represents the more stable configuration, and (I) the less stable one. Therefore, radicals joined to the



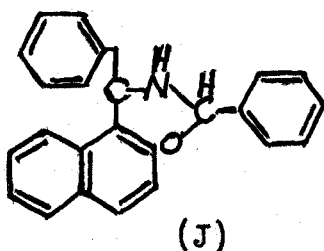
alpha carbon atom of beta-naphthol are very likely to exhibit a certain amount of ionic dissociation, whence occurs decomposition of the compound.

It might be said that for these reasons just described the hydrolysis of Betti's amine occurs spontaneously (IV). It has been found that, as the benzaldehyde is formed



by the decomposition of the amine, the original Schiff's base (I A) is regenerated, that this base is very stable in neutral and alkaline solutions, and that it fails to give tests showing the presence of the phenolic group; hence it has been proposed that the correct formula for this compound is as shown in (J). One can see by observing this formula that its structure prevents the tautomerism (IV),

(8)



and enhances the stability of the compound.

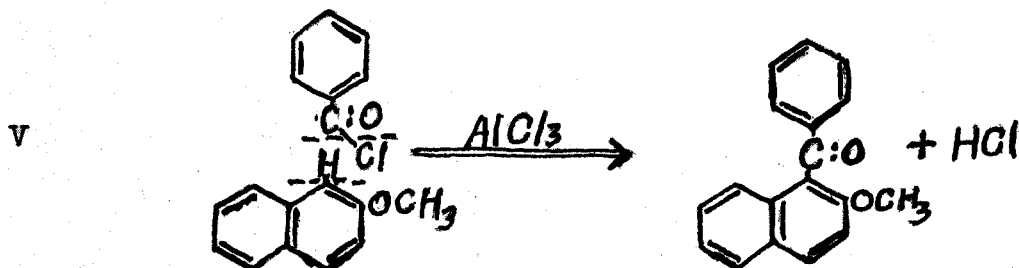
The object, therefore, of the second part of this investigation has been to prevent the tautomerism of Betti's amine by blocking the OH group, and then to study the properties of the resulting compound. It was believed that after blocking the OH group the amine would be more stable, and more useful as a resolving agent, than any of the unblocked naphtholic amines⁽¹⁾ already prepared. It is possible to accomplish this purpose by the methylation of the OH group, whereby we obtain the methoxy derivative of the amine.

The methylation can be performed before or after the beta-naphthol has been combined with the aldehyde and ammonia. If the original beta-naphthol is methylated then the Betti Condensation cannot be applied, because the active methylene group present in beta-naphthol is no longer present in the beta-methoxynaphthalene.

Methylation after the preparation of the naphtholic amine requires that the amine nitrogen be blocked in a suitable manner to prevent chemical action of the methylating agent on this part of the molecule. So far, the

free methylated amine has not been regenerated by hydrolyzing off any blocking agent found suitable to use.

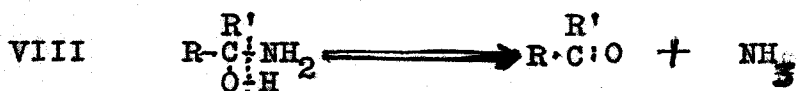
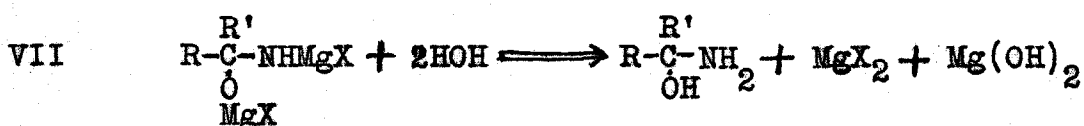
In order to prepare some of the free methylated amine, it was then thought most feasible to prepare first alpha-(beta-methoxynaphthalene)phenyl-ketone, and from this the oxime, and then reduce the oxime to the desired amine. This ketone was prepared by the Friedel-Craft reaction. Beta-methoxynaphthalene was condensed with benzoyl chloride (V). By using this method one can prepare readily large



quantities of the ketone. Somewhat to our surprise the ketone prepared could not be converted into the oxime or phenylhydrazone. Since anhydrous aluminum chloride often causes intra-molecular rearrangements to take place, we doubted the structure of this compound. In order to obtain the ketone and establish its structure, it was thought wise to choose certain reactions of the Grignard reagent. I will give a summary of the previous work, done by other investigators, on the synthesis of carbonyl compounds by means of the Grignard reagent.

GRIGNARD REAGENT FOR THE SYNTHESIS OF
CARBONYL COMPOUNDS

Beis⁽⁷⁾ was the first to introduce the reaction of the Grignard reagent with acid amides as a general method for the preparation of ketones. He explained the mechanism of the reaction as given in equation (VI,VII,VIII).



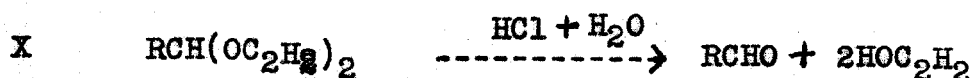
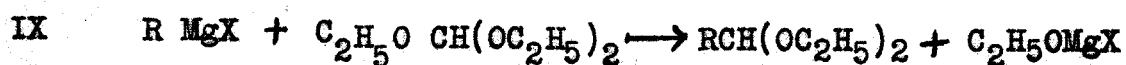
The halogen derivatives selected were usually the bromides and iodides; while all of the acid amides, except formamide, were found to yield the ketone in accordance with the reaction scheme just given.

Although Beis obtained fairly good results when he employed only a small excess of the Grignard reagent, e.g. a small amount over two moles of reagent for one mole of acid amide, the yields he obtained were always low.

Jenkins⁽⁸⁾ in a recent investigation of this method for the synthesis of ketones, found that in order to obtain maximum yields, it was best first, to use three to four equivalents of the magnesium halide to one equivalent of the acid amide,

and in the second place, to prolong the heating of the reacting mixture. He was able, by these modifications, to increase the yield of the ketones from as low as twenty percent for Beis to as high as eighty percent. Jenkins considered the reaction of benzylmagnesium halides with benzamides to be a general method for the production of desoxybenzoins, and also a reliable means for the determination of their structures. No rearranged products, as described by Johnson⁽⁹⁾ and others⁽¹⁰⁾, have been obtained by the action of benzylmagnesium halides on acid amides.

Bedraux⁽¹¹⁾ gave a general method for the syntheses of aldehydes by the condensation of organomagnesium halides with ethyl ortho formate. Yields for a number of the halogen derivatives of phenylmagnesium bromide varied from fifty-five to seventy-five percent. The scheme for the reaction is given here (IX, X):

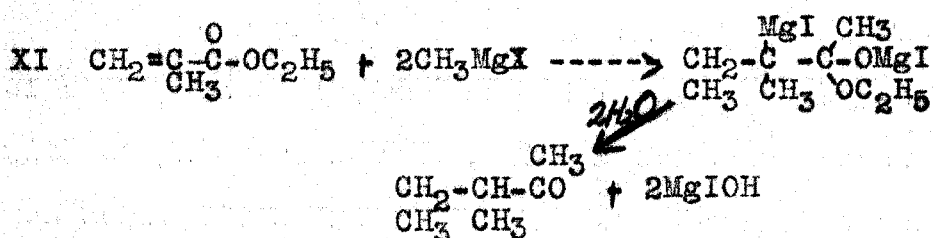


Gattermann and Maffezzoli⁽¹²⁾ have reported on the synthesis of aldehydes from organomagnesium compounds and ethyl formate. Fifty percent yields of the carbonyl compounds were obtained when the reaction was made to take place at -50° . (It is very interesting to note the use of

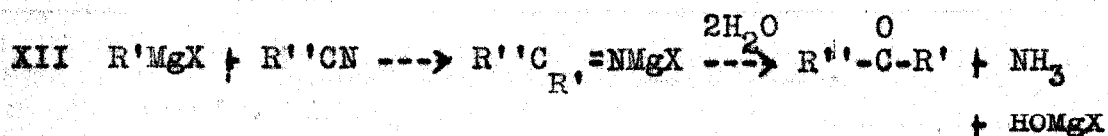
(12)

solid carbon dioxide for cooling purposes in the organic laboratory as early as 1903). Solid carbon dioxide-ether mixtures were used to cool both reactants before they were mixed, and then the RMgX compound in ether was rapidly added to the ester. It was observed that as the temperature was increased the yield of the ketone diminished.

Blaise⁽¹³⁾ and Courtot isolated certain ketones by hydrolysis of the addition compound formed between esters of unsaturated acids and Grignard reagents. Usually the saturated ketone was obtained. (XI).

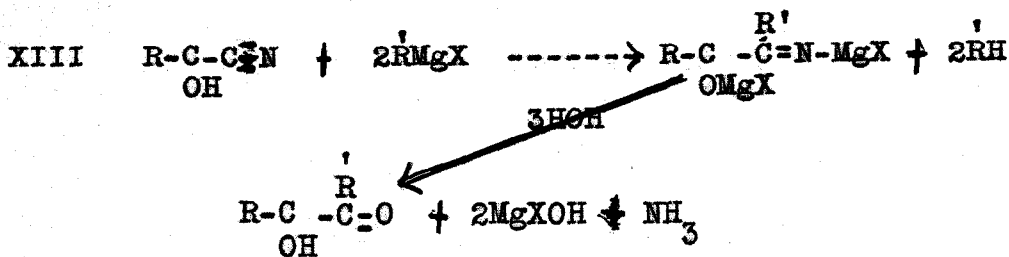


Blaise⁽¹⁴⁾ was able to present a general method for the synthesis of ketones from Grignard reagents and alkyl nitriles. Yields of the ketones varying from seven-teen to eighty per cent of the theoretical amounts, depend-
ing on the nitrile derivative employed, were obtained. (XII).

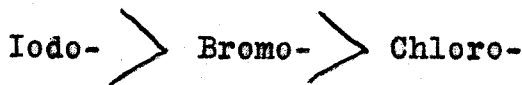


Somewhat later Gautier⁽¹⁵⁾ applied this same reaction to cyanhydrines and alkoxy nitriles, and in each case synthesized the corresponding ketone. (XIII).

(13)

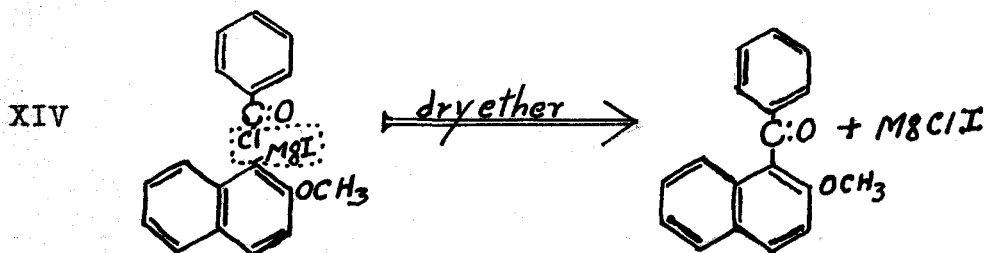


Gilman⁽¹⁶⁾ and collaborators investigated the possibilities for the production of ketones by the interaction of Grignard reagents and acid halides. It was found too that organozinc derivatives could be used with a decided advantage over organo-magnesium compounds for the production of ketones. The zinc compounds did not form the tertiary alcohols so readily. Limitations⁽¹⁷⁾ on the synthesis of ketones from Grignard reagents and acid halides are very peculiar. Sometimes a tertiary group to the -MgX increases the production of the ketone. It is believed that ketones in general can be prepared by this method. The best procedure⁽¹⁸⁾ found seems to be the addition of the Grignard reagent to the acid halide with moderate cooling. Formation of ketones by this method is to be commended because the reaction takes place almost instantaneously. It has been found that the yield decreases progressively as follows with the change of the halogen derivatives:



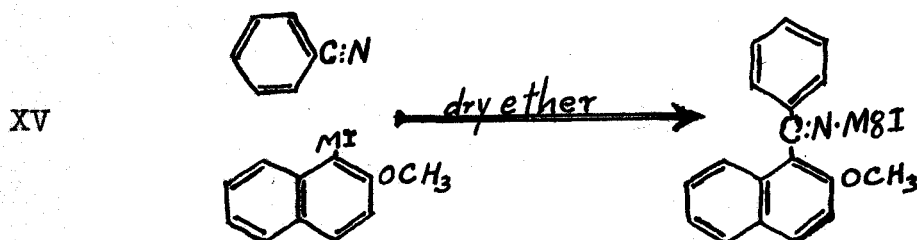
(19)
It has been reported that a good yield of
alpha-naphthyl phenyl ketone can be obtained from a

reaction of alpha-naphthyl-magnesium-bromide with benzoyl chloride. From chemical analogy I concluded that one should be able to prepare alpha(beta-methoxy naphthyl)phenyl-ketone from alpha(beta-methoxy naphthyl)magnesium-iodide and benzoyl chloride (XIV). However, one trial pro-

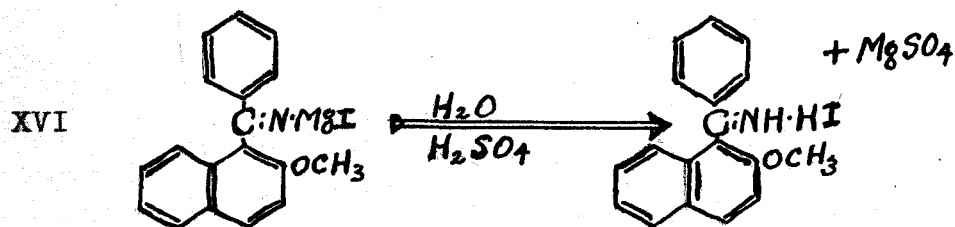


cedure failed to produce any of the ketone.

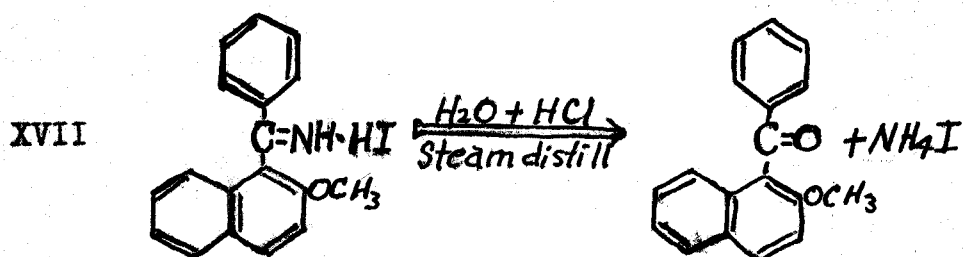
A second method for the synthesis of alpha(beta-methoxy naphthyl)phenyl-ketone was developed. Alpha(beta-methoxy naphthyl)magnesium-iodide was condensed with benzonitrile (XV), and this addition compound was hydrolyzed



with dilute sulfuric acid producing the ketimine hydroiodide (XVI). By steam distilling the ketimine salt in a



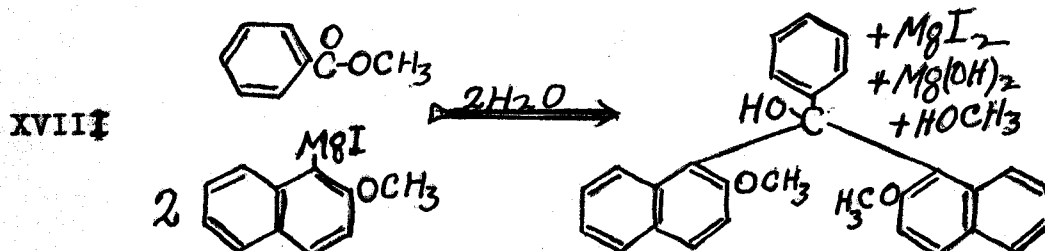
dilute hydrochloric acid solution the ketone was produced (XVII).



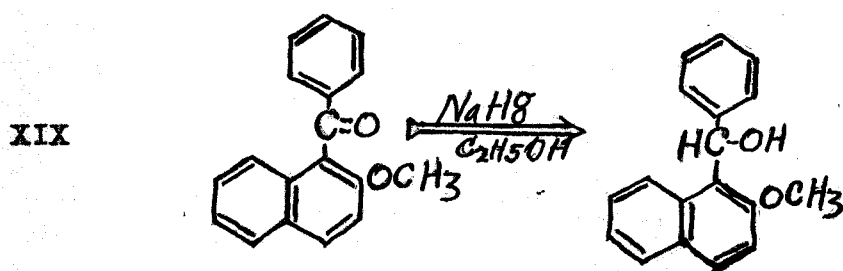
The procedure for this synthesis was as follows: One mole of the nitrile was slowly added to an amount of organo-magnesium compound varying from one to one and one-half mole equivalents. The Grignard was decomposed with dilute acid (sulfuric) giving a salt-like product containing nitrogen. This proved to be the ketimine hydroiodide(XVI). In this specific investigation it was found necessary to prolong the steam distillation of the alpha(beta-methoxy-naphthyl)-phenyl-ketimine-salt in acid solution to convert it into the ketone. After steam distilling a hydrochloric acid solution of the salt for two hours only about twenty percent of it had been converted into the ketone. This fact emphasized its abnormal stability toward hydrolyzing conditions. The ketone formed by hydrolysis of this ketimine was proven to be the same compound as that prepared by the Friedel-Craft synthesis. Their mixed and unmixed melting points were identical.

The third synthesis of alpha (beta-methoxy-naphthyl)-phenyl-ketone was carried out in a manner analogous to that used by Gattermann and Maffezzoli⁽¹²⁾. Methylbenzoate was dissolved in dry ether and then added rather rapidly to a dry ether solution of alpha (beta-methoxy-

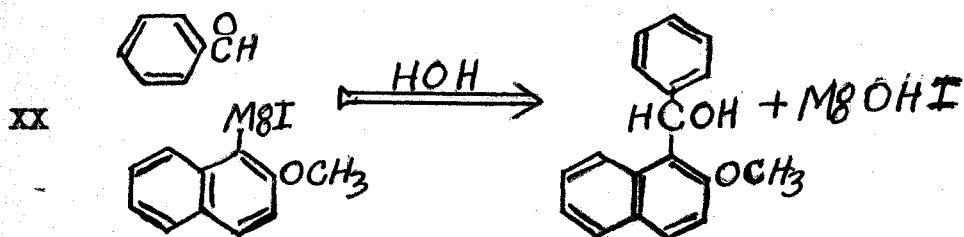
haphthyl)-magnesium-iodide at about 30° . On hydrolysis with dilute sulfuric acid a forty percent yield of the ketone (XVII), and a fifteen percent yield of the tertiary alcohol (XVIII) were obtained.



The identity of the ketone prepared by the three methods just described was checked by the mixed melting point method. In each case the mixture melted at the same temperature as the unmixed substances (124° to 125°). Although this ketone could not be converted into the oxime and phenylhydrazone it produced the corresponding alcohol when reduced with sodium amalgam⁽²⁰⁾ (XXX). This alcohol



was also prepared from benzaldehyde and alpha (beta-methoxy-naphthyl)-magnesium-iodide (XX), and by mixed

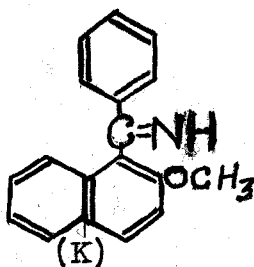


melting points found to be identical with the alcohol

formed by the reduction of alpha (beta-methoxy naphthyl)-phenyl ketone (XIX). The melting point is 98°. Bauer⁽⁴⁰⁾ reported on the synthesis of this alcohol from the same compounds and by the same method that I used, but he found its melting point to be 237°. However, he did not give a report of the carbon and hydrogen analysis or the molecular weight measurement of this high melting compound. Since I have prepared alpha(beta-methoxy-naphthyl)-phenyl-carbinol by two different methods, and found its melting point to be 98° in both instances as well as its carbon-hydrogen analysis and molecular weight to correspond to the formula $C_{18}H_{14}O_2$, I feel sure that Bauer either reported the wrong melting point or else the wrong compound. Further evidence, in favor of my last statement, can be gained by comparing the melting points of the following di-aryl carbinol compounds, which have about the same molecular weight and structural configuration as does "alpha (beta-methoxy-naphthyl)-phenyl-carbinol":

Compound	Melting point
<u>Di-phenyl-carbinol</u> -----	67.5° - 68°
<u>Alpha(naphthyl)-phenyl-carbinol</u> -----	86.5°
<u>"Alpha (beta-methoxy-naphthyl)-phenyl-carbinol"</u> -----	98°
<u>Di(alpha-naphthyl)-carbinol</u> -----	146°-147°

The difficulty encountered in the attempted preparation of the oxime from alpha(beta-methoxy-naphthyl)-phenyl-ketone led us to seek another intermediate for the preparation of the amine. The ketimine (K) seemed to offer the greatest possibilities, so a study of its properties was undertaken.

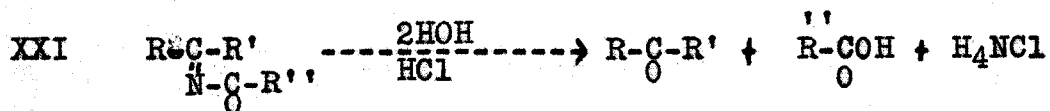


KETIMINES

The term 'imine' was introduced by Moureu and Mignonac⁽²¹⁾ to designate the characteristic bivalent group, '=NH', most commonly found substituted for the oxygen of the carbonyl in ketones and aldehydes. Our present interest is in the ketimines, whose properties are much the same as those of the other members of this class of compounds. They are usually oils or low melting solids possessing a disagreeable odor, colorless, and highly refractory. Ketimines are basic and give crystalline salts with hydrochloric, acetic, and benzoic acids. Their hydrochlorides are usually soluble in water and these hydrolyze readily to produce ketones. The acetyl derivatives are also

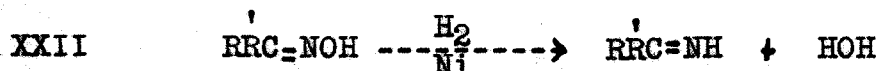
(22)

generally decomposed in the presence of hydrochloric acid according to the reaction(XXI).

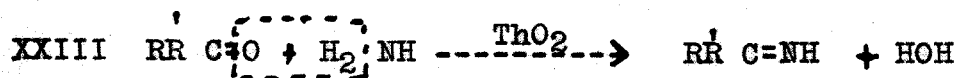


Blaise⁽²³⁾ is accredited with a general method for the synthesis of ketimines from Grignard-nitrile addition compounds. This has been found to be the best method for obtaining the free ketimine, especially of the more stable aryl derivatives.

Catalytic reduction of an oxime to the ketimine was accomplished by Mignonac⁽²⁴⁾ using finely divided nickel for a catalyst (XXII). He was also able to arrive at

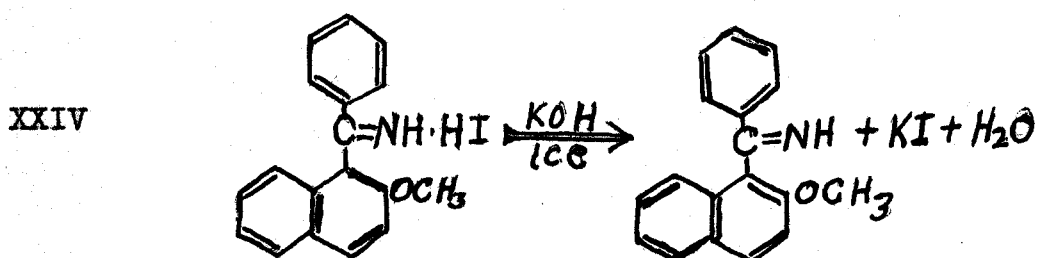


another important method for the synthesis of aliphatic ketimines⁽²⁵⁾. This synthetic method was suggested to Mignonac by the work of Sabatier and Mailhe⁽²⁶⁾. It involved the use of thorium oxide as a dehydrating agent for the condensation of ketones and ammonia (XXIII).

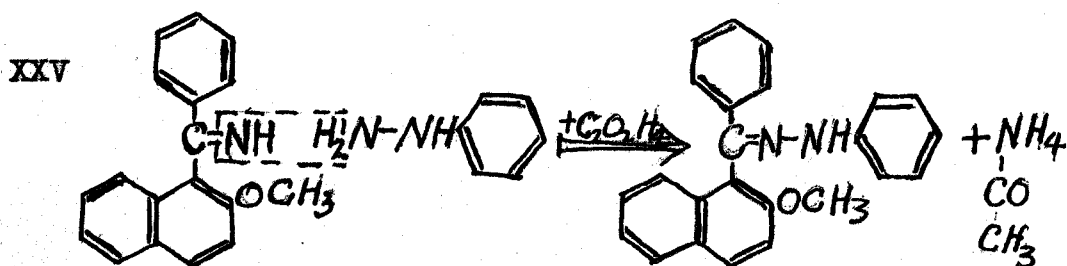


In the present investigation alpha & beta-

methoxy naphthyl)-phenyl-ketimine was synthesized from the Grignard-nitrile addition compound (XV). The addition compound was hydrolyzed with dilute sulfuric acid and crushed ice to produce the ketimine hydroiodide (XVI). By neutralizing this salt with an ice mixture of dilute alkali the free ketimine was obtained as white crystals (XXIV).



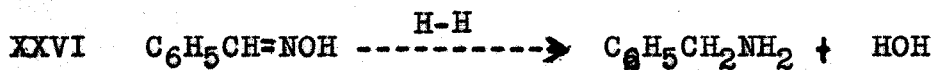
This ketimine was found to be extremely stable as compared with most aliphatic ketimines described in the literature. The free base showed no signs of hydrolysis in the presence of water at room temperature. The abnormal stability of this imino nitrogen, which holds the same position as the oxygen of the corresponding ketone, gives us a reason for not being very much surprised at the inert behavior of the carbonyl oxygen in the ketone, alpha (beta-methoxy naphthyl)-phenyl-ketone. Moreover, when this ketimine was treated with phenylhydrazine the corresponding hydrazone was formed (XXV), which I said before could not be prepared from the ketone. As yet, however, the oxime has not been synthesized from



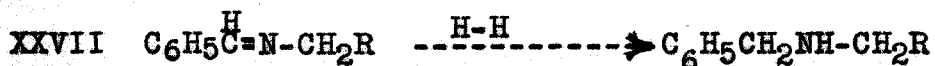
the ketone or the ketimine.

AMINES BY THE REDUCTION OF CERTAIN NITROGEN COMPOUNDS

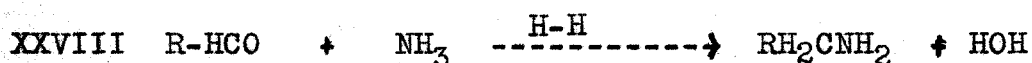
Amino compounds can be synthesized from almost any unsaturated nitrogen-carbon compounds by reducing them. Catalytic hydrogenation of oximes was first realized by Mailhe⁽²⁷⁾, who applied the Sabatier and Senderes' ⁽²⁸⁾ method of reduction. The same general procedure was also followed by Mignonac⁽²⁹⁾. Paal and Gerum⁽³⁰⁾ were able to reduce benzaldoxime to the amine with hydrogen and colloidal palladium as a catalyst (XXVI).



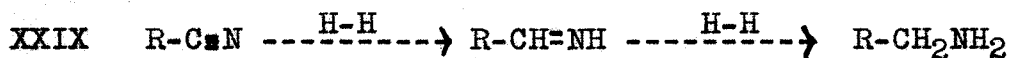
Mailhe⁽³¹⁾ accomplished the reduction of Schiff bases to the amines (XXVII).



Skita and Keil⁽³²⁾, and also Mignonac⁽³³⁾, were able to prepare amines by the hydrogenation of mixtures of ammonia and aldehydes (XXVIII); while Guyot and Karl Fournier⁽³⁴⁾ used mixtures of ammonia and alcohols, and Karl Löffler⁽³⁵⁾ used ketone and ammonia reducing with sodium.



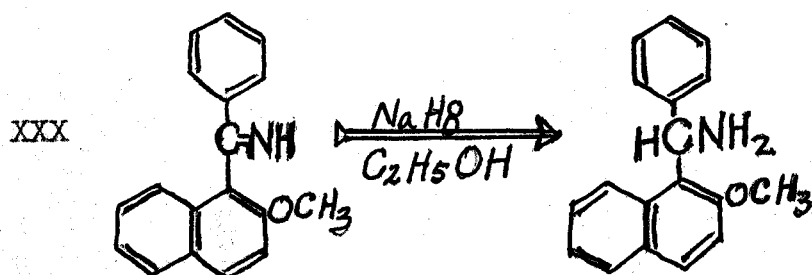
Carothers and Jones⁽³⁶⁾ studied the synthesis of amines in general by the reduction of nitriles. A similar experimental study was made by Mignonac⁽³⁷⁾, who found the reduction to take place in steps (XXIX). Hydrogen-



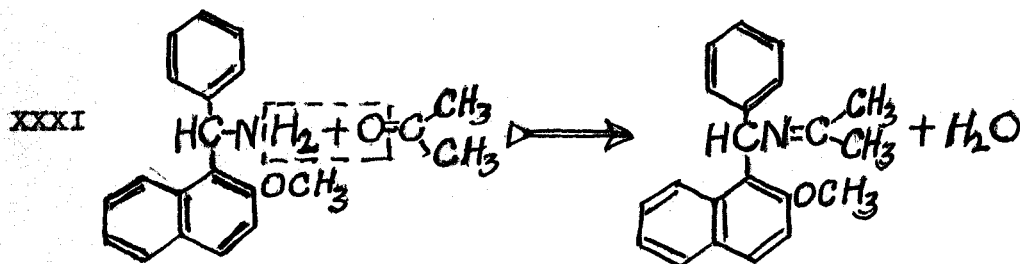
ation of hydrobenzamides is also noted by Mignonac as well as by O. Fischer⁽³⁸⁾.

The reduction of aliphatic phenyl-hydrazones and oximes with activated aluminum was carried out by Matzrevich⁽³⁹⁾, and the resulting compounds were found to be identical with those obtained when using sodium amalgam.

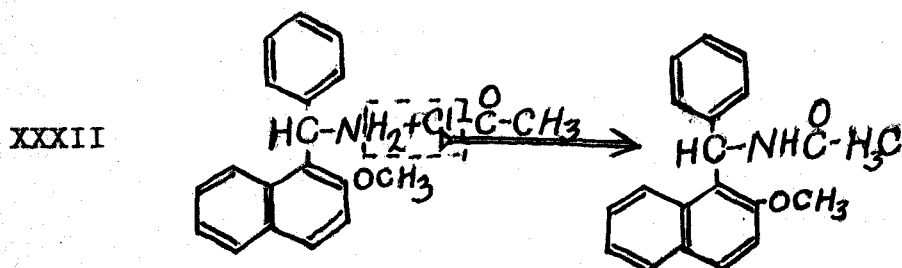
We therefore undertook the reduction of alpha-(beta-methoxy-naphthyl)phenyl-ketimine which was readily accomplished with 2% sodium amalgam⁽²⁰⁾. Alpha(beta-methoxy-naphthyl)phenyl-aminomethane melting at 101° to 102° was obtained in excellent yields (XXX).



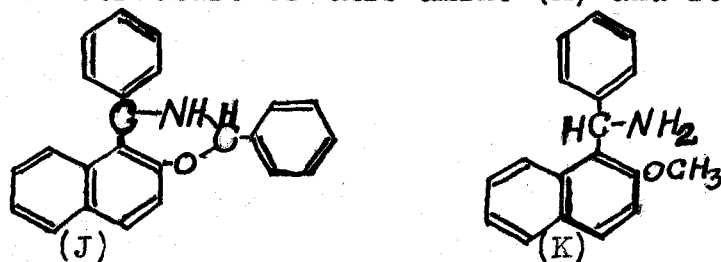
This amine has the properties which correspond very closely to those we predicted for it before its preparation. It is relatively stable in the presence of acids or bases, and shows no signs of decomposing into the compounds from which it was synthesized as did the compound with the free beta-hydroxy group, prepared by Betti⁽²⁾ (I,II,III). It can readily be resolved into its dextro- and levo- antipodes with levo-malic acid. Alpha (beta-methoxy naphthyl)-phenyl-amino-methane has a specific rotation over three times that of Betti's amine. The stronger basic character of this amine is shown firstly, by its reaction with mineral acids to produce salts with high melting points; and secondly, by its condensation with both benzaldehyde and acetone to produce the corresponding Schiff bases (XXXI).



(Betti's amine forms salts with mineral acids and condenses with benzaldehyde but not with acetone). With acetyl chloride the amine was easily acetylated (XXXII) and identified, by mixed melting points, to be the same compound as was obtained by methylating the nitrogen acetylated Betti's amine.[#]



I wish to call attention at this time to the similarity in structure of this amine (K) and formula (J),



which was proposed for Betti's condensation product; which it will be recalled is quite stable and is formed from Betti's amine (IV page 7) by partial decomposition and rearrangement (I page 1). It can readily be seen that formulas (J) & (K) are similar in that no hydrogen is attached to the oxygen atom. The alpha carbon atom in each

[#] I wish to thank Mr. Nzeer Ahmed for supplying this derivative of Betti's amine.

case being joined to one carbon atom of the naphthalene ring by a single bond and to another in the same ring by a double bond with no possibility of tautomerism. The tautomerism as shown by Betti's amine (III) is prevented in (K) because the beta-hydroxy hydrogen atom has been replaced by the 'CH₃' group. We see, therefore, that the theory on which the properties for alpha(beta-methoxy-naphthyl)-phenyl-aminomethane were predicted was correct, since these properties have been tested and verified by experiment.

EXPERIMENTAL PARTSYNTHESES BY THE BETTI CONDENSATIONMeta-chlorophenyl-beta-naphtholaminomethane. --

m-Chlorobenzaldehyde for this reaction was prepared from m-nitrobenzaldehyde by the Sandmeyer reaction⁽⁴¹⁾. The aldehyde was purified by fractional distillation and the fraction used which boiled between 208° and 215°. Eleven grams (one mol equiv.) of beta-naphthol were dissolved in 25cc. of 95% alcohol in a 100cc. Erlenmeyer flask to which 20grams (two mol equiv.) of m-chlorobenzaldehyde was added. The flask was cooled by immersing in an ice-water bath, and the mixture was then saturated with ammonia gas, requiring about five minutes. After shaking the flask it was tightly corked and allowed to warm to room temperature. The flask was repeatedly shaken during the first hour by which time a brownish oil had begun to separate. After standing 24 hours the contents had changed to an almost solid viscous substance which, when treated with a few drops of ether and stirred, changed to fine yellowish crystals. The crystals were filtered from the mother liquor and washed six times with small portions of alcohol. The washing almost completely removed the yellowish color and left 23grams (82% theoretical) of pure white crystals melting at 109°. No change was

observed in the melting point after the product was recrystallized from acetone.

Analysis Calculated for $C_{24}H_{17}Cl_2ON$;
C, 70.94; H, 4.19; Cl, 17.47; N, 3.45.
Found: C, 70.53; H, 4.25; Cl, 17.30; N, 3.34.

The aminehydrochloride was prepared by steam distilling 15 grams of the condensation product suspended in 20cc. of 6N hydrochloric acid for an hour, or until free aldehyde ceases to pass over to a noticeable extent. Three grams of the free aldehyde were recovered from the aqueous distillate, and 11.5 grams (96% theoretical) of the m-chlorophenyl-beta-naphtholaminomethane hydrochloride was obtained from the acid solution in the flask. Decomposition temperature 220° to 230°.

Analysis Calculated for $C_{17}H_{15}ONCl_2$; Cl, 22.17.
Found: Cl, 22.40.

To prepare the free racemic amine 10 grams of the aminehydrochloride was treated in an ice mixture with a 25% solution of potassium hydroxide until the solution was strongly alkaline to litmus (2 to 5 cc.). From 3 to 5cc. of ether was added and stirred for just a short time until the amine formed a flocculent precipitate due to the absorption of ether by the amine. The precipitate was immediately filtered from the alkaline solution and washed free from alkali with water. This procedure yielded

7 grams (77% theoretical) of m-chloro-beta-naphthol-aminomethane melting at 124° to 125°.

Analysis: A sample was prepared by recrystallizing it once from ether, melting point 125°.

Calculated for $C_{17}H_{14}ONCl$;

C, 71.94; H, 4.94; Cl, 12.51; N, 4.94.

Found: C, 72.12; H, 4.85; Cl, 12.68; N, 5.23.

Ortho-chlorophenyl-beta-naphtholaminomethane. -- The o-chlorobenzaldehyde for this experiment was Eastman's "practical grade" which was purified by distillation. The fraction boiling between 205° and 215° was used. Fifty-three grams of beta-naphthol (one mol equiv.) and 100 grams of o-chlorobenzaldehyde (two mol equiv.) were dissolved in 75cc. of 95% alcohol. The mixture was then treated with ammonia gas as described for the m-chloro derivative. White crystals began to separate after three hours, and after 10 hours 108 grams of condensation product was obtained. The mother liquor was set aside and after 5 days yielded 16 grams additional, making a total of 124 grams (81.5% theoretical). Melting point 165-167°. After recrystallizing the material once from chloroform and once from benzene it melted rather sharply at 173°, (uncorrected). Analysis was made of the substance melting at 173°.

Analysis Calculated for $C_{24}H_{17}Cl_2ON$:

C, 70.94; H, 4.19; Cl, 17.47.

Found: C, 70.87; H, 4.42; Cl, 17.69.

Ortho-chlorophenyl-beta-naphtholaminomethane Hydrochloride was prepared by steam distilling 30 grams of the original condensation product with hydrochloric acid as described for the m-chloro derivative; 21 grams (88% theoretical) of the amine hydrochloride was obtained, decomposition point 185° to 190°; and 6 grams (94% theoretical) of the free aldehyde was recovered. Analysis was made from a sample recrystallized twice from hydrochloric acid solution and then dried in a desiccator over sulfuric acid.

Analysis Calculated for $C_{17}H_{15}ONCl_2$:

C, 63.77; H, 4.69; Cl, 22.17.

Found: C, 63.93; H, 4.79; Cl, 21.79.

The free amine was prepared as described for the m-chloro derivative. Five and one-half grams (62% theoretical) of a cream colored amine was obtained, melting point 129° to 136°. After recrystallizing twice from ether and once from acetone it was almost pure white and melted at 133° to 134°. Analysis was made of a sample dried in a desiccator over sulfuric acid.

Analysis Calculated for $C_{17}H_{14}ONCl$:

C, 71.97; H, 4.94; Cl, 12.51.

Found: C, 72.24; H, 5.22; Cl, 12.76.

~~Para~~-chlorophenyl-beta-naphtholaminomethane. --

The p-chlorobenzaldehyde used in this experiment was prepared from crude p-toluidine, first replacing the amino group by chlorine by means of the Sandmeyer reaction, and then oxidizing the methyl group to the aldehyde by Etard's reagent. The aldehyde was purified by fractional distillation and the fraction boiling between 210° and 215° was used. Eleven grams (two mols) of the p-chlorobenzaldehyde and 6 grams (one mol) of beta-naphthol were dissolved in 20cc. of 95% alcohol. The solution was then saturated with ammonia gas. After 24 hours 12 grams of a crystalline condensation product was filtered from this solution and washed free from coloring matter with alcohol. Analysis was made of a sample dried over sulfuric acid and melting at 150° .

Analysis Calculated for $C_{24}H_{17}ONCl_2$:

C, 70.94; H, 4.19; Cl, 17.47.

Found: C, 71.64; H, 4.27; Cl, 17.33.

Six grams of the condensation product were subjected to steam distillation in a suspension of hydrochloric acid. Four and three-tenths grams (91%

theoretical) of the whitish flaky aminehydrochloride was obtained, decomposition temperature 190° to 195° .

Analysis Calculated for $C_{17}H_{18}ONCl_2$: Cl, 22.17.

Found: Cl, 22.40.

The free p-chloro-amine was prepared from the hydrochloride as previously described. The ether extract yielded 2.5 grams (80% theoretical) of the white crystalline amine, melting at 120° .

Analysis Calculated for $C_{17}H_{14}ONCl$: Cl, 12.51.

Found: Cl, 12.94.

RESOLUTION OF THE RACEMIC AMINES

The m-chlorophenyl-beta-naphthylaminomethane was resolved into its optically active antipodes by treating 5.3 grams (one mol equivalent) of the amine in 130 cc. of 95% alcohol with 2.5 grams (One mol equiv.) of levo-malic acid. The mixture was stirred for 10 minutes with a mechanical stirrer after which the small amount of undissolved material was filtered off. A current of air was directed across the top of the solution to hasten the evaporation of the alcohol. When the volume of the solution had been reduced to about 50 cc. the sides of the beaker were scratched with a stirring rod to aid in starting crystallization of the least

soluble salt. When once started to form, crystals of the salt continued to separate until the solution had been concentrated to a volume of approximately 35 cc. At this point the major part of the least soluble salt had crystallized. Two and seven-tenths grams of the salt was obtained. The liquid was further evaporated by an air current and agitated until crystals of the more soluble salt began to separate. When a volume of about 10 cc. was reached the solution was again filtered and yielded 2.8 grams of the more soluble salt. The filtrate was then evaporated almost to dryness and again filtered. The precipitate in each case was washed with a little ether.

The salt obtained in the first fraction was hydrolyzed in an ice mixture with 25% solution of potassium hydroxide. Coagulation of the amine was affected by a cc. of ether and about 2 grams of the dextro- amine was filtered and washed free of alkali with distilled water. Melting point not sharp at 126° .

In a 1 dm. tube 0.0667 grams of the dry amine in 10 cc. of diethyl ether gave $\alpha_D = +0.53^{\circ}$, $[\alpha]_D = +79.5^{\circ}$

The levo- amine was obtained by hydrolyzing the second fraction with 25% potassium hydroxide in an ice mixture. The amine was coagulated with ether and filtered to yield 2.1 grams of the levo- amine with a melting point of 122° . This material gave a rotation of -0.37°

with 0.0667 gram of the amine dissolved in 10 cc. of ether at room temperature, using a 1 dm. tube. $[\alpha]_D = -55.5^\circ$.

The last crystalline salt fraction from above yielded the levo- amine on hydrolysis with the same specific rotation as that obtained from the salt of the second fraction. An attempt was made to increase the specific rotation of the levo- amine above -55.5° , first by recrystallizing the salt before hydrolysis, and finally by use of Ingersoll's method⁽⁴²⁾, but a more complete resolution was never effected.

Resolution of the o-chlorophenyl-beta-naphthol-aminomethane was carried out by dissolving 0.5 gram of levo-malic acid in 10 cc. of alcohol and adding to the acid solution a suspension of 1.05 grams of the racemic amine in 40 cc. of alcohol. The solution was stirred mechanically for 10 minutes, after which any undissolved matter was filtered from the solution. The filtrate was concentrated to about 10 cc. to give the least soluble batch of crystals. They were filtered and washed with ether, yielding 0.35 gram, while the filtrate was further evaporated to yield 0.67 gram of a more soluble salt.

Hydrolysis of the 0.35 gram of salt obtained in the first fraction was accomplished by suspending it in an ice mixture, adding 25% potassium hydroxide solution

until the solution was strongly alkaline to litmus and the amine was extracted with ether. After drying the ether extract over anhydrous sodium sulphate the optical rotation of the solution taken in a 1 dm. tube was -0.65° , and 10 cc. of the solution contained 0.0722 grams of the amine, $[\alpha]_D = +89.8^{\circ}$.

Hydrolysis and extraction of the 0.67 grams of salt from the second fraction was accomplished as described previously. With 0.1207 gram in 10 cc. of ether in a 1dm. tube gave $\alpha_D = -1.01^{\circ}$ $[\alpha]_D = -83.7^{\circ}$.

Attempts to recrystallize the levo-acid-1-base only resulted in a less active amine.

THE SYNTHESIS OF ALPHA(BETA-METHOXY NAPHTHYL)-PHENYL-AMINO-
METHANE AND CERTAIN INTERMEDIATE COMPOUNDS AND DERIVATIVES

Alpha(beta-methoxy naphthyl)-phenyl-ketone. -- Ten grams (one mol equivalent) of beta-methoxy-naphthalene was dissolved in 100 cc. of dry carbon disulfide contained in a three neck 500 cc. round bottom flask. The flask was fitted with an upright water cooled condenser, a mechanical stirrer, and a dropping funnel. Ten grams of anhydrous aluminum chloride was then added to the mixture in the flask. About 9.8 grams (one mol equivalent) of benzoyl

chloride was placed in the dropping funnel. The stirrer was started and then the benzoyl chloride was added dropwise to the reaction mixture. After fifteen minutes all of the benzoyl chloride had been added and the reaction was well under way, as was indicated by the evolution of HCl gas from a lead tube connected to the top of the condenser. The reaction mixture was refluxed for an hour by placing a hot water bath under the flask. At the end of this time the heat was removed so that the contents of the flask might cool. After cooling, the material in the flask was poured into a beaker containing crushed ice and hydrochloric acid. The carbon disulfide was then separated from the water by means of a separatory funnel and washed several times with pure water. Next the organic solution was steam distilled to remove the carbon disulfide and unreacted benzoyl chloride from the less volatile ketone. A solid residue remained which was filtered from the water and recrystallized from alcohol to a constant melting point (125°corr.).

The molecular weight was determined by the RAST method. With 0.0169 gram of compound in 0.1380 gram camphor the melting point depression of camphor was 17° .

Calculated for $\text{C}_{18}\text{H}_{14}\text{O}_2$; ~~FORMULA~~ M, 262.

Found: - - - - - M, 270.

Analysis for carbon and hydrogen was made by combustion of a sample dried for 2 hours in the oven at 110° and then

placed in a desiccator over phosphorus pentoxide.

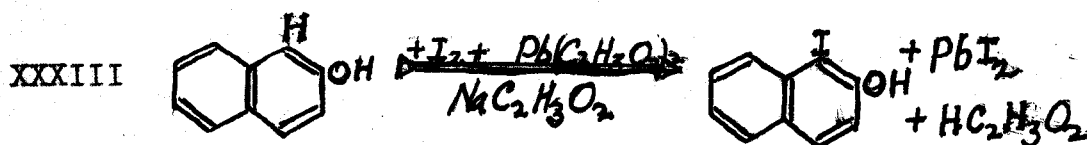
Analysis:

weight of sample grams	weight carbon dioxide grams	weight water grams	percent of elements found		percent of elements calculated for $C_{18}H_{14}O_2$	
			H	C	H	C
0.1481	0.4485	0.0712	5.38	82.59	5.34	82.44

(43)

Alpha-iodo-beta-naphthol. -- Forty grams of commercial beta-naphthol (one mol equiv.) was placed in a 1-liter beaker, with 45 grams of lead acetate and 40 grams of sodium acetate. The mixture was dissolved in 400 cc. of glacial acetic acid by heating. When all of the solid material had dissolved the solution was cooled to about 25° by placing the beaker in a vessel of cold water. (It was found best to keep the beaker surrounded with cold water during the addition of the hot iodine solution.) A mechanical stirrer was arranged to agitate the solution mixture in the beaker. The stirrer was started and a hot solution, prepared by dissolving 70.4 grams (one mol equivalent of I_2) of iodine in 500 cc. of glacial acetic acid by heating, was slowly added. The iodine was absorbed rapidly by the naphthol, and yellow lead iodide precipitated out. The solution was stirred continuously while adding the iodine and for about 15 minutes longer after it had all been added. (reaction XXXIII).

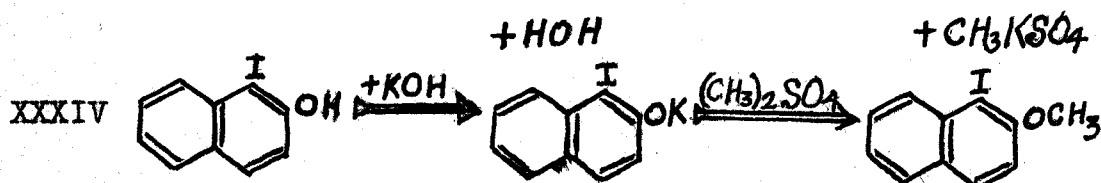
After stopping the stirrer the lead iodide was removed



by filtering with suction. (The lead iodide was kept for recovery of the iodine.) The acetic acid solution was poured into a 4l-beaker and diluted slowly while stirring with about three times its volume of water. After coagulation of the precipitate it was filtered from the solution by suction and washed with pure water, pressed, and sucked dry. (The filtrate and wash solution was rejected). A yield of 72 grams (about 95% theoretical) of a whitish pulpy-like material, melting point 94° , was obtained. The material was further purified by dissolving it in glacial acetic acid and precipitated by diluting with water. Melting point 94.5° .

Alpha-iodo-beta-methoxy-naphthalene. -- Fifty grams of crude alpha-iodo-beta-naphthol was treated in a 1-liter beaker with 400 cc. of water. The mixture was stirred with a mechanical stirrer until thoroughly mixed and the flaky needles had become well moistened by the water. A potassium hydroxide solution, prepared by dissolving 25 grams of KOH in about 250 cc. of water, was then slowly added to the suspension. The mixture was well stirred and by the time that all of the alkaline solution had been added the naphthol had completely dissolved. Any undissolved material was

filtered from the solution. The filtrate was returned to the beaker and the stirring was continued while 35 grams (about 45% excess) of methyl sulfate were added drop-wise from a dropping funnel. The time required for this addition was from 1.5 to 2 hours. A fine white crystalline product separated out as the methyl sulphate was added (XXXIV). The mixture was stirred for 1/2 hour after



the last of the methyl sulphate had been added, and then the methylated product was removed from the solution by filtering with suction. After washing the product with pure water to remove the mother liquor it was sucked dry. (The filtrate was usually rejected, but in case it was dark colored showing that a considerable amount of the naphthol remained^d unmethylated, then it was treated as described before with more methyl sulphate.) Forty grams (about 80% theoretical) of a whitish crystalline product was obtained. Melting point 87° to 88°.

Purification of the methylated product was easily carried out by recrystallizing it from hot alcohol using bone-black to remove the coloring matter. Two recrystallizations from alcohol gave cream-colored crystalline plates melting at 88°.

A second procedure followed for the methylation of alpha-iodo-beta-naphthol, which always gave good results, was as follows:- Thirty grams of alpha-iodo-beta-naphthol was placed in a 500 cc. beaker and mixed with 200 cc. of water. The water-soaked substance was then added slowly to a beaker containing 300 cc. of cold 10% potassium hydroxide solution. The naphthol was quickly dissolved to give a dark colored solution, which was then filtered to remove any undissolved material. The filtrate was poured into a one liter flat bottom flask and treated (by adding all at once) with 25 cc. (an excess) of dimethyl sulfate. In order to mix the contents thoroughly the flask was corked tightly and shaken. After about five minutes a considerable amount of the methylated iodo-compound had separated as fine white crystals. The mixture was allowed to stand for about 40 minutes and then filtered. Twenty-seven grams (86% theoretical) of an almost white product was obtained when the solution was filtered. It was recrystallized as described before and gave white shiny plates melting at 88° . Analysis was made of samples taken from a portion of the substance which had been dried in a desiccator over P_2O_5 for several days.

Analysis for carbon and hydrogen by combustion.

Calculated for $C_{11}H_9OI$: C, 46.49; H, 3.17.

Found: C, 46.77, 46.92; H, 3.18, 3.17.

Alpha (beta-methoxy-naphthyl)-magnesium-iodide. --

Ten grams (one mol equivalent) of pure alpha-iodo-beta-methoxy-naphthalene was dissolved in a small excess (about 150 cc.) of sodium dried ether contained in a dropping funnel. In a dry 500 cc. round bottom flask was placed 0.85 gram (one mol equiv.) of pure finely ground magnesium and 0.1 gram of magnesium-iodide catalyst⁽⁴⁵⁾. The flask was a three neck one attached to a reflux condenser, mechanical stirrer, and the dropping funnel containing the ether solution. After starting the stirrer a few cc. of the ether solution were added and the flask was warmed to start the reaction. (Often the reaction starts spontaneously). Addition of the ether solution was continued drop-wise as soon as the reaction was started. After all of the iodide solution had been added the solution mixture in the flask was refluxed for three hours. (The heat was supplied by placing a hot water bath under the flask). This procedure was found to give slightly higher yields of the organo-magnesium compound than when no stirrer was used. This is especially true with amounts greater than 10 grams of the iodo compound.

The procedure followed in most instances during this investigation for the preparation of small amounts of the Grignard reagent at a time was as follows: Ten grams of alpha-iodo-beta-methoxy-naphthalene was dissolved in 150

cc. of sodium dried ether contained in a dropping funnel connected to the top of an upright water cooled condenser. At least 1.5 equivalents (as compared to the equivalents of the iodo compound) of pure magnesium turnings were treated in a dry test tube with a few crystals of iodine and about 10 cc. dry benzene and 5 cc. of dry ether. After the iodine had combined with the magnesium, which was aided by warming, the ether-benzene solvent was distilled from the magnesium residue. As soon as the solvent had evaporated the residue was baked carefully until all signs of moistness had disappeared. The test tube containing the magnesium catalyst was either corked until ready to use or transferred immediately to a dry 500 cc. round bottom single neck flask; and the flask was connected to the reflux condenser described before. The ether solution was then added to the magnesium reagent and the same procedure followed at the end as described for the stirring apparatus.

Quantitative estimation of the extent to which the Grignard reagent was formed was determined by acid-base titration⁽⁴⁶⁾. The quantitative estimations were made for the purpose of determining the conditions which tended to produce the organo-magnesium compound as the major product. Actual measurements were discontinued when the conditions were arrived at which produced the

organo-magnesium compound to an extent greater than 50%, but in some of the experiments carried out this reaction took place to an extent greater than 80%.

Data from a few of the quantitative estimations is given as follows:

Trial	Weight of iodo comp'd gram	Time for reaction	Mixture refluxed	Percent of RMgX formed	Kind of magnesium reagent
1. --	0.50 ---	4 hours	- no ---	14.5	- Mg turnings
2. --	0.50 ---	4 "	- no ---	30.8	- Mg powder
3. --	0.50 ---	4 "	- no ---	55.3	- Mg powder & CuMg alloy
4. --	0.50 ---	0.5 "	- yes --	15.5	- Mg powder
5. --	0.50 ---	1.5 "	+ yes --	68.8	- Mg turnings and iodine

Alpha (beta-methoxy naphthyl)-phenyl-carbinol from alpha(beta-methoxy naphthyl)magnesium-iodide and benzaldehyde. -- Ten grams of alpha-iodo-beta-methoxy-naphthalene was converted into the Grignard reagent. The Grignard reagent solution was filtered from the excess magnesium into a dry 500 cc. flask ready to be attached to a reflux condenser carrying a calcium chloride tube and a dropping funnel. Three and two-tenths grams of benzaldehyde, purified by redistilling in an atmosphere of carbon dioxide, in 10 cc. of dry ether were added dropwise to the boiling ether solution of Grignard reagent.

The organo-magnesium addition compound began to form immediately. Its presence was indicated by a cloudy formation after each drop of the aldehyde solution was added. The addition compound first settled as an oil, but after refluxing the solution for 1.5 hours it changed to a yellowish white crystalline material. Refluxing was stopped after 2 hours, and the solution was allowed to cool. After cooling, the ether was decanted from the crystalline material. The crystals were washed with 15.cc. of pure dry ether to remove any unreacted organic compounds. The organo-magnesium addition compound was decomposed by adding crushed ice and dilute sulfuric acid. A white crystalline product separated, and it was filtered from the acid solution, washed with water, and sucked dry. The yield was 6.7 grams (70% theoretical) of a compound melting at 93°. Further purification of the crude product was carried out by recrystallizing it from a small amount of alcohol. Melting point 97° to 98°corr.

Molecular weight determination and analyses for carbon and hydrogen were made from a sample of the substance dried in a desiccator over P_2O_5 for 3 days. The molecular weight was determined by the Rast method: With 0.0157 gram of the substance in 0.2064 gram of camphor the melting point of the camphor was lowered 11.5 degrees.

Calculated for $C_{18}H_{16}O_2$:	M,	264
Found:-----	M,	265

Analysis by combustion for carbon and hydrogen:

Weight sample gram	Weight of carbon dioxide gram	Weight of water gram	percent of elements found		percent of elements calc. for $C_{18}H_{16}O_2$	
			C	H	C	H
0.2178	0.6510	0.1110	81.52	5.70	81.79	6.10
0.2030	0.66067	0.1097	81.51	6.05	-----	-----
0.2230	0.6687	0.1225	81.78	6.15	-----	-----

Alpha(beta-methoxy naphthyl)phenyl-carbinol from
alpha(beta-methoxy naphthyl)phenyl-ketone. Sixty grams of
 2% sodium amalgam⁽²⁰⁾ was prepared and placed in a dry 150 cc.
 Erlenmeyer flask. Twenty cc. of sodium dried benzene and
 15 cc. of ether were poured into the flask as a solvent.
 Five cc. of absolute alcohol was added. Three grams of
 alpha(beta-methoxy naphthyl)phenyl-ketone, prepared by the
 Friedel-Craft synthesis, were added (in small portions at
 a time) to the mixture in the flask, while the flask was
 well shaken between each addition of the ketone. After
 making the first addition the clear solution in the flask
 turned to a pinkish color due to the formation of a sodium
 ketyl. After all of the ketone had been added the reaction
 mixture was allowed to stand, with the flask tightly
 corked, for thirty minutes. At the end of this time the
 solution was only slightly bluish-pink in color indicat-
 ing that most all of the ketone had been reduced. The
 solution was poured (by decanting from the mercury which

is now a liquid) into a separatory funnel containing 25 cc. of water, and well mixed with the water to decompose all of the sodium ketyl as well as dissolve the alkali present. After separation of the first water layer the benzene-ether solution was washed three times with small portions of pure water. The organic layer was then dried with calcium chloride and filtered into a dry evaporating dish. The solvent was quickly evaporated to dryness by passing a current of dry air over the dish. Two and one-half grams (83% theoretical) of the alcohol was obtained, melting at 90° . After recrystallizing the product from alcohol it melted at 95° to 96° . Further recrystallization gave a substance melting at 98° . Mixed melting point of this alcohol with the alcohol prepared from the Grignard reagent and benzaldehyde showed that the two compounds were the same.

Alpha(beta-methoxy naphthyl)phenyl-ketimine-hydro-iodide. -- Twenty grams (one mol equivalent) of alpha-iodo-beta-methoxy-naphthalene was converted into the Grignard reagent in a well stirred solution. The excess magnesium was filtered from the Grignard solution, and the solution was collected in a dry three neck flask, The flask was later connected up with a condenser, stirrer, and dropping funnel. Six grams (0.87 mol equivalent) of

benzonitrile dissolved in 25 cc. of ether was poured into the dropping funnel. The stirrer was started and the benzonitrile solution was added to the Grignard reagent solution drop-wise. Grignard-nitrile addition compound began to form at once, and its presence was indicated by a cloudy suspension of the slightly ether-soluble material. At first the addition compound settled to the bottom of the flask as an oil, but after prolonged refluxing it changed to a yellowish crystalline solid. After refluxing on a water bath for four hours the solution was allowed to cool. The apparatus was disassembled and the ether was decanted from the solid material in the flask. Crushed ice was then added to the flask and well mixed with the contents. After the ice mixture had stood for a few minutes dilute sulfuric acid was added to neutralize the basic magnesium salt, as well as to speed up the hydrolysis. At first the product of hydrolysis separated as a yellow oil, but soon changed to a light yellow crystalline substance melting at 179° to 180° . (a) When recrystallized from hot water the substance melted at 180°corr. (b) When treated with concentrated nitric acid it dissolved and on warming liberated free iodine. It dissolved in other mineral acids with warming to produce a yellow solution. (c) Silver iodide was precipitated when an alcohol-water solution

of this compound was treated with a silver nitrate solution. (d) Neutralizing an ice cold solution of this salt with dilute alkali converted it into a white basic substance containing nitrogen and no iodine. (e) The yellow compound was very soluble in alcohol, benzene, acetone, and chloroform; fairly soluble in hot water and warm mineral acids; sparingly soluble in cold water and ether.

The analysis of the compound melting at 180° gave the percent composition of iodine, carbon, and hydrogen corresponding to $\alpha(\beta\text{-methoxy naphthyl})\text{phenylketimine-hydroiodide}$; The substance was dried in an oven at 110° for 2 hours and then placed in a desiccator over P_2O_5 for several days before the analysis was made.

Iodine was liberated in a Parr-bomb with sodium peroxide. The free iodine was reduced in a weakly acid solution with sulfur dioxide, and the iodine was then precipitated with silver nitrate as silver iodide.

Trial	Weight of sample gram	Weight of AgI gram	Percent of iodine found	Percent of iodine calcu. for $\text{C}_{18}\text{H}_{16}\text{ONI}$
1.	0.3172	0.1846	31.46	32.62
2.	0.2358	0.1440	33.04	-----

by

Analysis of compound for carbon and hydrogen combustion:

Weight of sample gram	Weight of carbon dioxide gram	Weight of water grams	Percent of elements found		Percent of elements calc. for $C_{18}H_{16}ONI$	
			C	H	C	H
0.2016	0.4115	0.0758	55.67	4.21	55.53	4.14

Alpha(beta-methoxy naphthyl)phenyl-ketone from alpha-(beta-methoxy naphthyl)phenyl-ketimine-hydroiodide. -- Ten grams of alpha(beta-methoxy naphthyl)phenyl-ketimine-hydroiodide was placed in a 150 cc. distilling flask to which 10 cc. of dilute hydrochloric acid was added. The mixture was then steam distilled for two hours. At first most of the ketimine salt dissolved to produce a yellow solution. At the end of two hours there was a certain amount of a solid hydrolytic product which had separated to the bottom of the flask. The hot solution was decanted from the flask leaving about two grams (25% theoretical) of a light yellow colored product melting at 123° . (The decanted solution yielded most of the solid unchanged salt on cooling). After two recrystallizations from hot alcohol the hydrolytic product gave an almost pure white substance melting at 125° (corr). This compound was found to be the same ketone as that prepared by the Friedel-Craft synthesis (page 34). The melting point of a mixture of the two was the same as the unmixed substances (125°).

Alpha(beta-methoxy naphthyl)phenyl-ketone from alpha (beta-methoxy naphthyl)magnesium-iodide and methyl benzoate. -- Ten grams of alpha-iodo-beta-methoxy-naphthalene was converted into the Grignard reagent. The ether-Grignard solution was filtered from the excess magnesium and collected in a dry dropping funnel. Five grams of methyl-benzoate (a small excess over one mol per mol of iodo compound) was dissolved in about three times its volume of dry ether contained in a dry 500 cc. round bottom single neck flask. The flask was then connected to an upright water cooled condenser carrying the dropping funnel containing the Grignard reagent at the top. With all reagents at about room temperature (25° to 30°) the Grignard reagent was added drop-wise to the methyl-benzoate solution. As soon as the Grignard reagent was introduced the flask was placed on a water bath and refluxed for 1.5 hours. Refluxing was stopped and the solution mixture was allowed to cool, after which the ether was decanted from the solid addition compound, which had settled to the bottom of the flask. Crushed ice was added to the flask and well mixed with the solid material. Dilute sulfuric acid was later added to the ice mixture to neutralize the basic magnesium salt as well as to speed up the hydrolysis. As soon as hydrolysis was affected the organic material was filtered from the aqueous solution.

Five grams of a material melting at 100° was obtained. An attempt was made to recrystallize this material from alcohol. Part of it dissolved in hot alcohol while part remained undissolved. The portion remaining undissolved melted at 185° ; and on recovering the dissolved portion it was found to melt at 118° .

After recrystallizing the material melting at 185° twice, from an acetone-nitrobenzene solution, a substance melting at 202° to 203° was obtained. Several recrystallizations of the substance melting at 118° , from an alcohol solution, gave a substance melting at 125° corr.

Di-alpha(beta-methoxy naphthyl)-phenyl-carbinol.--

Analysis and molecular weight determination of the compound melting at 202° to 203° corr. showed it to be the tertiary alcohol, equation (XVIII) page 16, which was formed in about 15% yields. The analytical measurements were made from a sample of this alcohol which had been dried in the oven at 110° for 2 hours and then placed in a desiccator over P_2O_5 until ready to use.

Molecular weight measurement by the Rast method: With 0.0153 gram of compound in 0.1380 gram of camphor the melting point of camphor was lowered 10.4 degrees.

Calculated for $C_{29}H_{24}O_3$: M, 420.

Found: ----- M, 426.

Analysis for carbon and hydrogen by combustion;

Weight of sample gram	Weight of carbon dioxide gram	Weight of water gram	Percent of elements found calculated for $C_{29}H_{24}O_3$			
			C	H	C	H
0.1154	0.3475	0.0600	82.12	5.82	82.82	5.76

By the mixed melting point method the compound melting at 125° was shown to be the same ketone as was prepared by the Friedel-Craft synthesis, alpha(beta-methoxy naphthyl)phenyl-ketone.

Alpha(beta-methoxy naphthyl)phenyl-ketimine. -- A ten gram sample of alpha(beta-methoxy naphthyl)phenyl-ketimine-hydroiodide was dissolved in 50 cc. of alcohol. To this solution was added crushed ice. As soon as the solution was thoroughly cooled, enough dilute potassium hydroxide solution was added to make the solution alkaline to litmus. (It was necessary to cool the mixture with ice; otherwise a small amount of the ketimine was converted into the ketone in a warm medium). More crushed ice was then added to keep the solution cool for about an hour, and at the same time to dilute the alcohol so that it would give up the ketimine. The mixture was allowed to stand over night so that the fine precipitate which first formed might change to a coarse granular one. (A little sodium

bisulfite was added to the solution to reduce any free iodine that might separate and contaminate the product). After standing the solution was filtered from the precipitate and gave almost a quantitative yield of the ketimine, melting at 98° to 99° . This ketimine was found to be very soluble in alcohol, ether, and benzene, but only sparingly soluble in water and petroleum ether. When it was heated in the dry condition with sodium or calcium oxide it decomposed liberating ammonia. (This fact was illustrated by placing a mixture of the compound and reagent in the bottom of a small test tube, placing a moist piece of red litmus near the mouth of the tube, and heating the bottom of the tube: the litmus turned blue).

Analysis was made from a sample which had been recrystallized from alcohol and dried over P_2O_5 for 3 days, melting at 99° .

Analysis for carbon and hydrogen by combustion:

Weight of sample gram	Weight of carbon dioxide gram	Weight of Water gram	Percent of elements found		Percent of elements calcu. for $C_{18}H_{15}ON$	
			C	H	C	H
0.1535	0.4700	0.0796	83.51	5.80	82.78	5.75
0.1267	0.3878	0.0695	83.48	6.14	-----	-----

Analysis for nitrogen was made by the Dumas method: With a sample of 0.2229 grams 10.6 cc. of N_2 gas at 19° and 744mm were obtained; Found: N, 5.39%; Calcu. for $C_{18}H_{15}ON$: N, 5.36.

The phenyl hydrazone of alpha(beta-methoxy naphthyl) phenyl-ketone. -- It was pointed out before that alpha (beta-methoxy naphthyl)phenyl-ketone could not be converted into the oxime or phenyl hydrazone, (page 9). However, the hydrazone was prepared from the corresponding ketimine as follows: -- (See reaction XXV page 21)-- Seven-tenths gram of alpha(beta-methoxy naphthyl)phenyl-ketimine was dissolved in 10 cc. of 95% alcohol and 1 cc. of glacial acetic acid contained in a test tube. One-half gram of phenyl-hydrazone was then added. The mixture was then heated to boiling 3 times after 5-minute intervals. A few cc. of water was added to dilute the alcohol after the mixture had stood for about 3 hours. After standing for a day about 1 gram (80% theoretical) of an almost white crystalline substance was obtained. It was filtered and well washed with alcohol, in which it is only slightly soluble, then dried in an oven at 110°, Melting at 183.3corr. Analysis was made of a sample melting at 183.5:

Carbon and hydrogen by combustion;

Weight of sample gram	Weight of carbon dioxide gram	Weight of water gram	Percent of elements found		Percent of elements calc. for $C_{24}H_{20}ON_2$	
			C	H	C	H
0.1475	0.4415	0.0755	81.63	5.73	81.82	5.72
0.1913	0.5710	0.0940	81.41	5.50	-----	-----

Analysis for nitrogen by the Dumas method: With a sample of 0.1608 gr. a volume of 12.0 cc. dry nitrogen at 24° and

741mm. was obtained: Calculated for $C_{24}H_{20}ON_2$; N, 7.95%

Found: N, 8.35%

Alpha(beta-methoxy naphthyl)phenyl-aminomethane. --

One hundred and twenty grams of 2% sodium amalgam was prepared⁽²⁰⁾ and placed in a dry 200 cc. Erlenmeyer flask. A dry solvent mixture composed of sodium dried benzene and ether, 40 and 20 cc. respectively, was added to the flask. Then 15 cc. of absolute alcohol was added, and finally 8.5 grams of alpha(beta-methoxy naphthyl)phenyl-ketimine, melting at 98° to 99°, were added in small portions at a time until the total amount had been added. The flask was well shaken after each addition to mix the contents; and sufficient time was allowed between each addition to permit the flask and contents to cool, so that the mixture would remain near the room temperature during the entire reaction. (The heat liberated during this reaction was easily detected by the warming up of the flask). About 15 minutes had elapsed before all of the ketimine had been added, and then the flask was corked tightly and allowed to stand for 25 minutes. The flask was well shaken 5 times during this period of the reaction.

After standing 25 minutes the ether-benzene solution was decanted from the mercury into a separatory funnel containing 25 cc. of water, and the mercury was rinsed with

5 cc. of benzene, which was added to the original solution. After separating the first water layer the organic layer was washed 4 times with pure water to remove all inorganic matter. The organic solution was dried over anhydrous sodium sulphate, which was removed by filtering. The dry benzene solution of the amine was collected in a dry evaporating dish, and the solvent was quickly evaporated by passing a current of dry air across the top of the dish. After evaporating the solution almost to dryness a considerable amount of the amine had crystallized on the side of the dish. A few cc. of petroleum ether was added to dissolve the coloring matter and the whitish crystalline amine was filtered from this solution with suction, washed with a few small portions of pure petroleum ether, and sucked dry. Six grams (70% theoretical) of the amine melting at 100° to 101° was recovered. After recrystallizing from alcohol twice the amine was almost pure white, melting at 102° (corr.).

This amine was found to be very soluble in cold benzene, and hot alcohol; fairly soluble in cold alcohol, ether, and chloroform; and when dissolved in acetone it reacted with it to produce a Schiff base (XXI page 23).

Analysis was made from a sample melting at 102° which had been dried over P_2O_5 for several days. The carbon and hydrogen content was determined by combustion:

Weight of sample gram	Weight of carbon dioxide gram	Weight of water gram	Percent of elements found		Percent of elements calcu. for $C_{18}H_{17}ON$	
			C	H	C	H
0.1174	0.3349	0.0654	81.99	6.57	82.13	6.46
0.1255	0.3784	0.0738	82.30	6.58	-----	-----

Determination of nitrogen by the Dumas method:

Weight of sample gram	Volume, cc. of dry nitrogen	Temp. degree C	Pressure mm. Hg	Percent nitrogen found	Percent N calcu. $C_{18}H_{17}ON$
0.1517	7.8	23	742	5.73	5.32
0.2200	10.9	24	744	5.57	----
0.2319	11.5	22	750	5.66	----

Acetone condensed with alpha(beta-methoxy naphthyl)-phenyl-aminomethane. -- (See reaction XXI page 23)-- One-half gram of the amine was dissolved in 5 cc. of 95% alcohol contained in a test tube. Two cc. of acetone was added and the mixture was heated to the boiling point. After heating the solution it was allowed to cool to room temperature. Semi-transparent crystals began to separate from the solution after about 30 minutes. About 0.47 gram (82% theory) of the crystalline condensation product was filtered from the solution after it had stood for 1.5 hours. The crystals were washed with alcohol, sucked dry at the pump, and then dried in the oven at 100° for 2 hours, and placed in a desiccator over P_2O_5 until ready to use.

Analysis for carbon and hydrogen by combustion:

A sample of 0.1451 gram gave 0.4445 gram of carbon dioxide and 0.0930 gram of water; Found: C, 83.55; H, 7.17.

Calculated for $C_{21}H_{21}ON$: C, 83.13; H, 6.98.

Analysis for nitrogen by the Dumas method; A 0.2110 gram sample gave 9.4 cc. of dry nitrogen gas at 25° and 741 mm.

pressure; Found: ----- N, 4.97.

Calculated for $C_{21}H_{21}ON$: ----- N, 4.62.

Benzaldehyde condensed with alpha(beta-methoxy-naphthyl)phenyl-aminomethane.--- Seven-tenths gram of the amine was dissolved in 8 cc. of hot alcohol contained in a small test tube. The solution was then cooled to room temperature and 0.5 cc. of benzaldehyde was added. This mixture was allowed to stand. After 30 minutes an oily-like product had begun to separate. When the mixture had stood for two hours a small portion of the oily material was removed with a spatula, dried in the air, then treated with a drop of alcohol, and finally scratched with a stirring rod, with the result that the oil was changed to a crystalline material. These crystals were thoroughly mixed with the contents of the test tube; and the entire oily material was slowly converted into a whitish crystalline product. The mixture was allowed to stand for an hour longer before the crystals were filtered from the solvent.

After filtering the crystals they were washed with alcohol and sucked dry at the pump. A yield of 0.73 gram (79% theoretical) of the ^{white} condensation product was recovered, melting point 98° (corr.).

A small amount of this condensation product melting at 98° was refluxed for four hours in a 10% aqueous potassium hydroxide solution. After this treatment a white crystalline material remained which melted at 65° to 70° . It is quite evident that some kind of decomposition took place during the treatment just described, but as yet the decomposition products have not been identified.

Analysis was made from a sample of the condensation product which had been dried in an oven at 80° for 3 hrs. and then over P_2O_5 for several days. The carbon and hydrogen content was determined by combustion: A sample of 0.1197 gram gave 0.3760 gram of CO_2 and 0.0674 gram of water. Found: ----- C, 85.67; H, 6.30%.

Calculated for $C_{25}H_{21}ON$: C, 85.43; H, 6.03%.

Analysis for nitrogen was carried out by the Dumas method: A 0.3746 gram sample gave 13.4 cc. of dry nitrogen gas at $23.5^{\circ}C$. and 741 mm. Hg pressure; Found: N, 4.01%.

Calculated for $C_{25}H_{21}ON$: --- N, 3.99%.

"Acetylated" alpha(beta-methoxy naphthyl)phenyl-amino-methane. -- One gram of alpha(beta-methoxy naphthyl)phenyl-aminomethane was dissolved in a dry mixture of 10 cc. benzene and 3 cc. ether. An excess (0.5 cc.) of acetyl-chloride in dry ether was added to the amine solution at room temperature. After the mixture had stood for 10 minutes a small amount of pyridine was added to destroy the excess acetyl-chloride. The reaction which took place on the addition of the pyridine liberated a great deal of heat which evaporated most of the solvent. An excess of water was then added to dissolve the pyridine addition compound. Enough benzene was added to dissolve the acetyl-derivative, and this organic solution was washed in a separatory funnel with three 10 cc. portions of pure water. After the final washing the organic solution was dried with anhydrous sodium sulphate. As soon as it was dry the solution was filtered into a dry 50 cc. beaker and evaporated almost to dryness. One-half gram (43% theoretical) of the crude substance was obtained. Melting point 185° to 186° . After recrystallizing the crude substance once from alcohol (in which it was very soluble) a white crystalline compound was obtained. Melting point 186.5° to 187° (corr.).

By mixed melting points the compound just described was shown to be identical with the compound prepared by methylating the nitrogen-acetyl derivative of phenyl-beta-

naphthol-aminomethane. Analysis was made of samples taken from a portion of the product which had been dried in an oven at 110° for 2 hours. Nitrogen was determined by the Dumas method:

Weight of sample gram	Volume dry nitrogen gas cc.	Temp. gas was measured deg. C.	Pressure in mm. Hg	Percent nitrogen found	Percent nitrogen calculated $C_{20}H_{19}O_2N$
0.2862	12.2	23	732	4.72	4.59
0.3174	13.6	24	736	4.77	----

Alpha(beta-methoxy-naphthyl)phenyl-aminomethane-hydrochloride. -- A small sample (about 1 gram) of the amine was dissolved in the minimum amount of warm alcohol contained in a test tube. This solution was treated with sufficient dilute hydrochloric acid to make it acid to litmus; then the solution was heated almost to the boiling point and set aside to cool. A flocculent white precipitate of the amine hydrochloride separated out as the solution cooled. The solution was filtered and the precipitate was washed with a little alcohol to remove the coloring matter. (Too much alcohol will dissolve it). An almost pure white product was obtained, melting with decomposition at 237° to 240° . This substance was dried in a desiccator over P_2O_5 4 days and analyzed for chlorine.

A sample of 0.2045 gr. gave 0.1036 gr. of AgCl:

"	"	"	0.2035	"	0.0984	"	"	"
FOUND:						Cl, 12.53%.		
						" 11.96		
Calculated for $C_{18}H_{18}ONCl$:						Cl, 11.84%.		

RESOLUTION OF ALPHA(BETA-METHOXY NAPHTHYL)PHENYL AMINO-
METHANE

One mol equivalent (2.53 grams) of the amine melting at 101° to 102° was dissolved in 60 cc. of 95% alcohol at 40° . To this solution was added a solution prepared by dissolving one mol equivalent (1.27 grams) of levo-malic acid in 10 cc. of 95% alcohol. The solutions were well mixed and then filtered, to remove any undissolved matter, into a 100 cc. beaker. The solution was set aside to cool. From time to time the side of the beaker was scratched to aid the beginning of crystal formation. In about 10 minutes crystals of the least soluble isomer of the salt had begun to separate. After standing for four hours all signs of crystal formation had ceased. The mixture in the beaker was thoroughly stirred and the crystals were allowed to settle again. Next the solution was filtered and the precipitate washed with a little pure alcohol. A yield of

1.81 grams of a salt melting at 186° was obtained.

The filtrate was returned to the beaker and evaporated by passing a current of dry air across the beaker. When a volume of about 20 cc. was reached the solution was again filtered and it yielded 0.07 gram of a salt melting at 160° to 165° . Further evaporation of the solution to about 5 cc. resulted in the precipitation of 0.93 gram of the more soluble salt melting at 164° . On evaporating the remainder of the solution to dryness a fourth fraction of the salt was obtained. (0.47 grams melting at 160°).

A sample from each of the crystalline salt fractions was dissolved in methyl alcohol, and the solutions were tested in the polarimeter for the purpose of measuring their optical rotation. In each case, however, the salt solution was inactive.

The first salt fraction above was hydrolyzed by treating it in a 50 cc. beaker with crushed ice and then enough dilute potassium hydroxide solution to make the entire solution alkaline to litmus. Five cc. of ether was then added and the mixture stirred. Enough ether was then added to dissolve all of the amine liberated. The ether layer was separated from the water layer and washed well with pure water, then it was dried over anhydrous sodium sulfate, and finally filtered into a dry 50 cc. beaker. On evaporation of the ether a viscous-like mass remained. This mass

was the dextro- isomer of the amine, which as yet has not been converted into a crystalline form.

The optical rotation of the dextro- amine was made of a solution prepared by dissolving 0.104 gram of the viscous material, described above, in 10 cc. of benzene. A rotation of $+2.06^\circ$ was obtained. $[\alpha]_D^{25} = +198^\circ$.

The third fraction was hydrolyzed in a manner similar to that described for the hydrolysis of the first fraction. This salt also gave an amine which remained in a viscous state, but in this instance the levo- isomer. The optical rotation of this isomer was measured in a solution prepared by dissolving 0.143 gram of the viscous amine in 10 cc. of benzene. A rotation of -3.15° was obtained. $[\alpha]_D^{25} = -220^\circ$.

A second procedure for the resolution of the racemic amine was carried out in much the same manner as described above, but the ether amine solution was more thoroughly washed with pure water than in the first experiment. With 0.1229 gr. of the levo-amine in 10 cc. of ether solution a rotation of -2.49° was obtained. $[\alpha]_D^{25} = -202^\circ$. With 0.155 gr. of the dextro-amine in 10 cc. of ether solution a rotation of $+3.05^\circ$ was obtained. $[\alpha]_D^{25} = +197^\circ$.

The measurement was made at 25° in a tube 10cm. long.

SUMMARY

1. The Betti Condensation of aromatic aldehydes, ammonia, and beta-naphthol has been applied to the mono-chlorobenzaldehydes.
2. Of the three resulting amines the ortho- and meta-compounds have been resolved into their active forms.
3. The nitrobenzaldehydes give chiefly the corresponding hydrobenzamides.
4. Due to the instability of the chlorophenyl-beta-naphthol-amines and the difficulty encountered in their resolution, these bases are less useful as resolving agents than the unsubstituted amine.
5. The instability of the beta-naphthol amines has been shown to be due to the presence of the beta-hydroxy group in as much as the replacement of the ionizable hydrogen of this group by a methyl group produced a stable compound.
6. Alpha(beta-methoxy-naphthyl)phenyl-ketone was prepared by means of the Friedel-Craft reaction, and also by the Grignard reaction, but it could not be converted into the oxime or phenyl-hydrazone. This is an example of Victor Meyer's Law of Esterification: "Acids which contain a carboxyl group placed between two radicals in the ortho position to this group, do not yield esters when a solution of the acid in alcohol is saturated with hydrogen chloride"⁽⁴⁴⁾. In this case, however, one of the ortho substituents is the residue of the naphthalene molecule.

7. The desired amine was prepared by condensing alpha-(beta-methoxy-naphthyl)magnesium-iodide with benzonitrile, isolating the ketimine, and reducing it to the amine.
8. The following compounds, with their empirical formulae and melting points, were synthesized during this study:
- (a) Three condensation products by Betti's Condensation using o-, m-, and p- chlorobenzaldehydes, $C_{24}H_{17}ONCl_2$, melting at, o, 173° ; m, 109° ; p, 150° ; which gave the amine-hydrochlorides decomp. at, o, 185° ; m, 220° ; p, 190° ; $C_{17}H_{15}ONCl_2$; and these gave the free amines, $C_{17}H_{14}ONCl$, melting at, o, 125° ; m, 133° ; p, 120° ; (b) Alpha(beta-methoxy-naphthyl)phenyl-ketone, $C_{18}H_{14}O_2$, m.pt. 125° ; (c) Alpha(beta-methoxy-naphthyl)phenyl-ketimine-hydroiodide, $C_{18}H_{16}ONI$, m.pt. 180° ; (d) Alpha(beta-methoxy-naphthyl)-phenyl-ketimine, $C_{18}H_{15}ON$, m.pt. 99° ; (e) Alpha(beta-methoxy-naphthyl)phenyl-aminomethane, $C_{18}H_{17}ON$, m.pt. 102° ; (f) Alpha(beta-methoxy-naphthyl)phenyl-carbinol, $C_{18}H_{16}O_2$, m.pt. 98° ; (g) Alpha(beta-methoxy-naphthyl)phenyl-ketophenyl-hydrazone, $C_{24}H_{20}ON_2$, m.pt. 183° ; (h) Derivatives of the amine, alpha(beta-methoxy-naphthyl)phenyl-aminomethane:
- (1) The amine-hydrochloride, $C_{18}H_{18}ONCl$, m.pt. with decomp. 237° to 240° ; (2) The acetyl-amine, $C_{20}H_{19}O_2N$, m.pt. 186.5° ; (3) Acetone-condensation-product, $C_{21}H_{21}ON$, m.pt. 162° ; (4) Benzaldehyde-condensation-product, $C_{25}H_{21}ON$, m.pt. 98° ;

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