1937

A new method for the preparation of alpha naphthyl-acetic acid.

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Thesis

A NEW METHOD FOR THE PREPARATION
OF
ALPHA NAPHTHYL-ACETIC ACID

by

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III. INTRODUCTION

The present day interest in the study of plant hormones has brought to the fore the problem of their synthetic production in organic chemical research. At present, most of the methods for the synthesis of such compounds, even when they are not complicated, are uneconomical. This research was undertaken in an effort to make alpha naphthyl-acetic acid by means of a relatively economical two-step process.

We were particularly interested in the substituted acetic acids which exhibit hormonal properties, (1) as for example, indole and naphthyl-acetic acid. The compound selected as a starting point in this research was alpha naphthyl-acetic acid.

Alpha naphthyl-acetic acid, C₁₀H₇CH₂COOH, was prepared by Bosseneck (2) from alpha naphthyl-formic acid. The acid chloride was first formed. This was treated with (potassium) cyanide. This nitrile on hydrolysis gave a keto acid which was reduced with hydriodic acid to the desired compound.

Mayer and Oppenheimer (3) synthesized the acid by brominating alpha methyl naphthalene. The cyanide was formed from the brominated hydrocarbon. Upon hydrolysis the substituted acetic acid was obtained.

(1) Hitchcock - Contrib. Boyce Thompson Inst. 7 349 (1935)
(2) Bosseneck - Ber. 16 641 (1883)
(3) Mayer and Oppenheimer - Ber. 49 2137 (1916)
A German patent (4) reports the preparation of alpha naphthyl-acetic acid by refluxing chloro-acetic acid and naphthalene for seventy-two hours at a temperature of one hundred and eighty-five degrees. This method has been tried in several laboratories without success. The reaction was also attempted with chloro-acetone and naphthalene. (see experimental part) It is quite probable that the patent-withholds some necessary catalytic agent which activates this reaction.

Gilman and Kirby (5) prepared the acid by treating alpha naphthylcarbinol with thionyl chloride. (6) The resulting alpha chloro-methylnaphthalene was then treated with magnesium to form the grignard reagent which was treated with carbon dioxide and hydrolized to yield alpha naphthyl-acetic acid. The reaction was also carried out with the bromo-methylnaphthalene.

The most recent method of synthesis of this acid is due to Keach. (7) In his method, alpha allylnaphthalene is oxidized with alkaline potassium permanganate. Naphthoic acid is formed as a by-product. The yield of crude acid is about 43% of the theoretical.

(4) I. G. Farbenind A.G. Ger. Pat. 562,391
(5) Gilman and Kirby - J. Am. Chem. Soc. 51 3476 (1929)
(6) Ziegler - Ber. 54 737 (1933)
(7) Keach - J. Am. Chem Soc. 55 2974 (1933)
III. THE PROPOSED METHOD OF SYNTHESIS

The method which we proposed for the synthesis of alpha naphthyl-acetic acid involved two generally applied reactions, the Friedel-Crafts reaction and the haloform reaction. The first step in the synthesis was to be the preparation of alpha naphthyl-acetone from chloro-acetone and naphthalene in the presence of anhydrous aluminum chloride.

\[
\text{AlCl}_3 + \text{C}_9\text{H}_8 + \text{ClCH}_2\text{COCH}_3 \rightarrow \text{C}_{10}\text{H}_7\text{CH}_2\text{COCH}_3 + \text{HCl}
\]

The alpha naphthyl-acetone thus prepared was to be treated with sodium hypochlorite. The hydrolysis of the reaction mixture should yield alpha naphthyl-acetic acid.

\[
\text{C}_{10}\text{H}_7\text{CH}_2\text{COCH}_3 + 3\text{Cl}_2 \rightarrow \text{C}_{10}\text{H}_7\text{CH}_2\text{COCl}_3 + 3\text{HCl}
\]

\[
\text{C}_{10}\text{H}_7\text{CH}_2\text{COCl}_3 + \text{NaOH} \rightarrow \text{C}_{10}\text{H}_7\text{CH}_2\text{COONa} + \text{CHCl}_3
\]
Alpha Naphthyl-acetone

The literature offers very little information about alpha naphthyl-acetone. A survey of the journals gave only one reference to its preparation and properties. It was prepared (8) from alpha pseudo allyl naphthalene by the action of mercuric oxide and iodine. The mechanism of the reaction involved the migration of the naphthyl radical.

\[
\text{HgO} + \text{I}_2 \rightarrow \text{C}_9\text{H}_7\text{CH} = \text{CHCH}_3 \rightarrow \text{C}_9\text{H}_7\text{CH}_2\text{COCH}_3
\]

Discussion of the Reaction

A study was made of a comprehensive article on the Friedel-Crafts reactions (9) before the experimental work was undertaken. This study made it quite clear that the type of reaction (alkylation) involved in this synthesis is the most unreliable of any of the Friedel-Crafts reactions. It did not, however, offer any evidence which would lead to the belief that the reaction would not take place.

Consideration of the reactivity of the chlorine atom in the chloro-acetone would lead to the belief in the possibility of the reaction. The type compound RCOCH\(_2\)X is more reactive: i.e., the halogen is more reactive than in a compound of the type RX.

(8) Tiffeneau and Daudel - Compt. rend. 147 679 (1908)
(9) Φ.H. Galloway - Chem. Rev. 17 327 (1935)
Furthermore, the reaction

\[
\text{CH}_3X + \text{C}_6\text{H}_5\xrightarrow{\text{AlCl}_3} \text{C}_6\text{H}_7\text{CH}_3 + \text{HX}
\]

is known to take place. This would certainly be evidence in favor of the postulated reaction.

Regardless of the evidence in favor of the reaction, there is a considerable possibility of secondary reactions taking place. The formation of the isomeric dinaphthyls by the action of aluminum chloride is well known. The further reaction of the 1,1 dinaphthyl formed to give perylene is highly probable, although most workers report that this reaction does not take place until temperatures of the order of two hundred are reached. Schmidt (10) says that the reaction takes place to a certain extent even at one hundred degrees.

Calloway (11) reports certain reactions of ketones in the Friedel-Crafts synthesis, which although they are not common, might very likely form here. They are:

(10) Text Book of Organic Chemistry - J. Schmidt (Rule)

Just what the effect of the chlorine atom substituted in one of the methyl groups might be cannot be stated definitely. The chlorine atom does not affect the other ketonic properties, e.g., formation of addition products, the iodoform reaction, etc. It would not then be expected to affect markedly the reaction of the carbonyl group in this instance.

Finally the acidic nature of the aluminum chloride might well bring about a condensation of the chloro-acetone. We do not attempt to formulate an opinion as to what the nature of these condensation products might be.
Experimental
Run #1

Seventeen gms. of naphthalene (0.13 mol) and 10.7 cc. of chloro-acetone (0.13 mol) were dissolved in 100 cc. of carbon disulphide in a 500 cc. round bottom flask. This flask was fitted with a three neck addition tube. One neck was equipped with a mercury seal stirrer. A second was attached to a reflux condenser having a gas absorption bottle attached to take care of the hydrochloric acid gas generated in the reaction. The third neck was stoppered with a cork and served to introduce the aluminium chloride to the reaction mixture.

The reaction mixture was immersed in an ice bath. Seventeen gm. of aluminum chloride (0.13 mol) was introduced over a period of half an hour. After all the aluminum chloride had been added, the reaction mixture was allowed to come to room temperature and allowed to stand for a period of two hours.

During the period of reaction, no appreciable heat was generated, neither was there very much hydrochloric acid evolved. The water coming from the gas trap would barely affect litmus. However, there formed in the flask a black solid insoluble in the carbon disulphide.

At the end of the reaction period, the carbon disulphide was decanted from the insoluble black solid. Upon evaporation of the solvent, the naphthalene was recovered. This excluded the possibility of any reaction having taken place between the
chloro-acetone and the naphthalene.

When the black residue in the flask was treated with water it decomposed exothermally and gave rise to a brown oily layer. The oil was separated from the water and then distilled. It boiled at 121°C. The distillate was colorless and from its odor and lachrymatory properties was identified as chloro-acetone. The brown color before distillation was probably due to some decomposition products.

The black solid which gave rise to the impure layer of chloro-acetone on treatment with water was probably an addition product of the ketone with aluminum chloride.

Run #2

From the results of the first run, it was thought that an increase in temperature might activate the addition product of the ketone to react with naphthalene. Consequently the procedure of the first run was repeated. In this experiment, the aluminum chloride was added while the reaction mixture was at room temperature. When all of the aluminum chloride had been added, the flask was heated to 45°C and the reaction allowed to continue at this temperature for two hours.

The visible signs of reaction were the same as in the first trial with the exception that the amount of black solid which formed seemed greater. The reaction mixture was treated in exactly the same manner as run #1. The results were the same. The recovery of the naphthalene was complete and distillation of the
oil layer formed on decomposition of the black solid was easily identified as chloro-acetone.

Run #3

The reaction was attempted by carrying it out for a period of four hours at a temperature of 46°C. Considerable experimental difficulty is encountered in the addition of the aluminum chloride at this temperature due to the refluxing of the solvent which wets the neck of the addition tube and causes the aluminum chloride to stick and in time clog the system. This difficulty may be surmounted to a certain extent by keeping the addition tube open with a piece of wire. This is not, however, too satisfactory.

This run was unsuccessful; the results being exactly the same as those described under the two preceding runs.

Run #4

In order to carry out the reaction at a still higher temperature, the solvent was changed. 100 cc. of symmetrical tetra chloro-ethane was substituted for the carbon disulphide in the procedure. The aluminum chloride was added while the reaction mixture in the flask was at room temperature. After addition of the aluminum chloride was complete, the flask was heated on a steam bath for four hours. At the end of the reaction time, the reaction mixture was decomposed with hydrochloric acid and then steam distilled. The steam distillation removed the solvent and
and left two layers in the flask, an upper aqueous layer and a lower dark brown oily layer. The oil layer solidified on standing overnight.

The aqueous layer was found to contain only aluminum chloride. The dark solid was extracted with alcohol. On evaporation of the alcohol, an impure residue of naphthalene was obtained. The small amount of residue, remaining from the alcohol extraction, was accidentally lost before it could be further identified.

Run #5

There is a possibility that the addition of aluminum chloride mol for mol of chloro-acetone might tie up the aluminum chloride as the ketone addition product and having tied up all the aluminum chloride, there would not be any activating agent to bring about the desired reaction between the ketone addition product and the naphthalene.

To test this theory, it was decided to make all further runs with an excess of aluminum chloride. Instead of 1 mol of aluminum chloride per mol of chloro-acetone, the ratio was changed to 2:1. This would make the amount of aluminum chloride to be used, still following the original procedure, 34 gms. (0.26 mol.)

In this run the solvent was again changed. Chloro-acetone was used (100 cc.) in place of the symmetrical tetra chloro-ethane. The aluminum chloride was added (at room temperature) and the reaction mixture, after the final addition of aluminum
chloride, was heated on a steam bath for four hours.

The reaction mixture became very viscous and doughy and at the end of the reaction time, the stirrer could hardly rotate. Upon cooling, the mass became very hard. It was impossible to decompose it with hydrochloric acid and it was insoluble in all solvents. It could be softened with and benzene to such an extent that it could be removed from the reaction flask.

This tar was treated with concentrated sulphuric acid. The acid was discolored. It did however extract some naphthalene from the black mass. On neutralizing the acid with ammonium hydroxide, a precipitate of aluminum hydroxide came down. It was impossible to obtain any definite compounds from this run with the exception of a small amount of naphthalene.

Run #6

This run was carried out identically with run #4 with the exception of the amount of aluminum chloride added, (2 mols of AlCl₃ to 1 of ClCH₂COCH₃). There was very little sign of reaction until about three quarters of the aluminum chloride had been added. Then the reaction mixture darkened somewhat and a slight evolution of hydrochloric acid began. (This is positive evidence in support of the theory advanced under the discussion of the fourth run concerning the amount of aluminum chloride necessary to activate the reaction)

When the reaction is heated on a steam bath, the evolution of hydrochloric acid gas is copious and water from the gas trap
is quite acid to litmus. It is to be noted that this is the first time in any run that there was any good indication that a reaction was taking place. The fact that considerable hydrochloric acid gas was given off indicated that coupling was taking place either in the main reaction or as a side reaction.

When the evolution of gas ceased, the contents of the reaction flask were decomposed with hydrochloric acid and then steam distilled to remove the solvent. The contents of the flask were then extracted with benzene. The benzene extraction was shaken with a saturated sodium bisulphite solution in the hope that the alpha naphthyl-acetone would form an insoluble bisulphite addition product. After standing for twenty-four hours there was no sign of an addition product.

The reaction mixture was further extracted with ether and alcohol-ether mixture. The extractions were distilled. The products obtained were symmetrical tetra chloro-ethane and some chloro-acetone, (3 cc.). The ketone was identified by the iodoform test and by its boiling point.

All of the extractions showed a blue fluorescence. However, it was impossible to isolate the compound to which this was due. The fluorescence was probably due to 22′ dinaphthyl which formed as a side reaction. It is also possible that some perylene, which also fluoresces, might have been present.

The flask after extraction contained a brown solid and some tar. The brown solid was transferred to a filter by suspension in alcohol. The tar remained stuck to the sides of the flask.
This brown solid did not give a definite melting point but blackened and turned to a tar at about 195°C. The brown solid was heated in an evaporating dish which had a funnel suspended over it. This was done to sublime any perylene which was present. This treatment resulted in charring of the solid and a small amount of tarry material was distilled into the funnel. The perylene would have sublimed in yellow flakes.

The residual tar in the flask was probably produced by some polymerization of the chloro-acetone by the action of the aluminum chloride. At least this conclusion seems the most logical and best supported from the evidence of other runs. The results of the fifth run are offered especially in support of this idea. The great amount of tarry material obtained in this run (#5) could only have come from the chloro-acetone inasmuch as the amount of naphthalene used could not have produced such an amount of tar.

This run was by far the most successful from the standpoint of the activation of the reaction and with the hope of making some positive identification of the reaction products, it was repeated. The material in the reaction flask after steam distillation consisted of an amount of black tar, an aqueous layer, and a dark red oil layer above the water layer. Two hundred cc. of ether were added and a separation was then affected between the ether solution of the oil and the aqueous layer. To one half of the ethereal solution, acetone was added. This threw out a red oil which was then separated from the ether-acetone mixture.
This oil was shaken with saturated sodium bisulphite solution and was allowed to stand over the bisulphite for a week. At the end of this time, no addition product had formed.

The remaining ether solution was shaken with saturated sodium bisulphite solution to extract any ketone present as the bisulphite addition product. This, however, was not successful. The ethereal solution was separated from the aqueous bisulphite layer. The ether was removed by evaporation and the oil which remained was baked on a steam bath for two days. At the end of this time, the oil had changed to a dark red-brown solid.

It was thought that the solid might consist of mixtures of the dinaphthyls and probably some perylene. A search of the literature revealed that the 1,1'-dinaphthyl could be crystallized from acetic acid. (12) The solid was then extracted with hot acetic acid. It was impossible to obtain crystals from the solution obtained, even when cooled in an ice bath. It was only when all the acetic acid was removed that a solid was obtained and it was a dark brown tarry substance. An attempt was made to crystallize the tar from benzene without success.

The residue remaining after the acetic acid extraction was treated with hot petroleum ether as this would dissolve any of the dinaphthyls which remained. It was impossible to crystallize anything from this solution either. On evaporation of the petroleum ether, a small amount of a thick red oil was obtained.

(12) C. S. Schoepfle - J. Am. Chem. Soc. 55 1569 (1923)
If this was a mixture or a pure sample of any of the dinaphthyls they should form characteristic compounds with picric acid. This oil did not.

After these two extractions, there remained a brown solid. An attempt was made to take the melting point of this substance. It did not melt but turned to a black tar at about 65°C.

Run #7

This run was made in the same manner as the preceding run (#6) with one exception. The quantity of solvent (s. tetra chloro-ethylene) was reduced to 25 cc. This increased the concentration of reactants and it was hoped that it would increase the possibility of reaction. Less reaction took place than in the case where 100 cc. was used. The reaction mixture did not decompose very readily with acid and when it finally decomposed, it yielded a hard carbonaceous solid which was discarded.

Run #8

On the strength of the information of the German patent mentioned previously, we refluxed a mixture of chloro-acetone and naphthalene at a temperature of 185°C for 72 hours. Seventeen gm. of naphthalene and 10.7 cc. of chloro-acetone were placed in a 250 cc. round bottom flask. This was attached to a reflux condenser and then heated on an oil bath for 72 hours at approximately 185°C. At the end of this time, no apparent reaction had taken place. The mixture had darkened only a little.
tle. The naphthalene and chloro-acetone were easily recovered by distillation of the chloro-acetone.

Run #9

This run was made to verify the idea offered in the discussion of run #6 concerning the polymerization of the chloro-acetone. This experiment was conducted in the same manner as run #6 but the naphthalene is omitted. As the reaction proceeds, the mixture darkens and a small amount of sensible heat is evolved. When the mixture is first heated on the steam bath, hydrochloric acid is evolved, but this ceases after a little while. The reaction was allowed to continue at the temperature of the steam bath for six hours. At the end of this time, the contents of this flask had become very dark. The reaction product was decomposed as usual and steam distilled. The non-aqueous layer was colored orange. This layer was separated from the water and distilled. A residue of 2 cc. of a dark brown oil was left behind. It was very similar to oils obtained in other runs. The above distillate was fractionally distilled to recover any chloro-acetone which might have steam distilled with it. Three cc. of chloro-acetone was recovered. The contents of the reaction flask were now extracted with 100 cc. of ether and filtered. This filtration yielded 0.9 gm. of a black carbonaceous solid. The ether extract which was almost black in color was evaporated and yielded 3.3 gm. of a black tar. From the results of this run it is quite evident that much of the tarry material obtained in
previous runs resulted from some obscure polymerization of the chloro-acetone.
V. Phenyl Acetone

Phenyl acetone has been prepared in a number of different ways. Grignard and Chambret (13) prepared it by distillation of benzyl, methyl, allyl carbinol \((\text{C}_6\text{H}_5-\text{CH}_2)(\text{CH}_3)(\text{CH}_2\text{CH} = \text{CH}_2)\text{COH}\). According to a German patent (14) it has been made by passing aliphatic or side chain cyclo aliphatic or aromatic di hydric alcohols over catalysts containing one or more of the heavy metals of groups one and eight of the periodic table. The catalyst preferably contains copper. (specific compounds not given) Ivanoff and Nicoloff (15) have prepared the ketone by refluxing complex compounds of the type \(\text{C}_6\text{H}_5-\text{CH(MgX)}\text{COONa}\) with acid chlorides. Yields of 50-75% of benzylated ketones are reported. Richards (16) reports that some phenyl acetone is obtained when dry potassium hydroxide is allowed to act on an ether solution of alpha phenyl chloro-acetone. Tiffeneau (17) prepared the ketone by a molecular rearrangement and oxidation of an unsaturated hydrocarbon in the presence of mercuric oxide.

\[
\begin{align*}
\text{R-CH}=\text{CH}_2 & \rightarrow \text{RCH}_2\text{COCH}_3 \\
\text{CH}_3 & 
\end{align*}
\]

(13) V. Grignard & F. Chambret - Compt. Rend. 182 299 (1926) C.A. 20 1602 (1926)
(17) M. Tiffeneau - Compt. Rend. 154 1506
The most commonly used method of preparation is reported by Ludlam (18) in which he heats the calcium salts of phenyl acetic acid and acetic acid.

Although phenyl acetone has been prepared by a number of methods, the literature does not report any synthesis from benzene and chloro-acetone. We became interested in this reaction when naphthalene and chloro-acetone failed to give any positive results. It was thought that if benzene reacted in the desired direction some hopes might still be held in the case of naphthalene.

The proposed reaction in this case was:

$$C_6H_6 + ClCH_2COCH_2 \xrightarrow{AlCl_3} C_6H_5CH_3COCH_3 + HCl$$
Experimental
Run #1

A solution of 100 cc. of benzene and 10.7 cc. of chloroacetone (0.13 mol) were placed in a 500 cc. round bottom flask. The flask was fitted with a three neck addition tube. One neck was equipped with a mercury seal stirrer, a second with a condenser fixed to reflux, the condenser had a gas absorption bottle attached to take care of the hydrochloric acid gas generated in the reaction, the third neck was stoppered with a cork and served to introduce the aluminum chloride.

The aluminum chloride was added in small portions over a period of one half hour. There was no sensible heat of reaction and the water from the gas trap was only slightly acid to litmus. When the addition of aluminum chloride was complete the reaction mixture was heated on a steam bath and the reaction was allowed to continue for four hours. At the end of this period, the reaction mixture had changed to a dark rather viscous liquid. The reaction mixture was decomposed with hydrochloric acid and water. (exothermic reaction) After decomposition the mixture was steam distilled. This removed the benzene. There remained in the flask a lot of water and above this was a small amount of brown oil which when separated from the water proved to have a very pleasant odor. There was not sufficient oil to work with.
Run #2

At about the time that this run was contemplated, the use of an excess of aluminum chloride (2 mols to 1 of chloro-acetone) was giving better results in the activation of the reaction between naphthalene and chloro-acetone. It was then decided that such a change in the procedure with benzene might be advantageous in preparing a quantity of the oil mentioned in run #1. This was done with 34 gm of aluminum chloride (0.26 mol) being used instead of the original 17 gm. (0.13 mol).

The reaction in this run was quite vigorous. Considerable heat was produced and considerable hydrogen chloride evolved. It is to be noted again in this reaction the formation of heat and the evolution of gas did not begin until about three quarters of the aluminum chloride had been added. When hydrogen chloride was no longer given off, the reaction mixture was decomposed and steam distilled as usual.

The amount of oil layer which formed in this run was considerably greater than in the previous run. It was very viscous and red-brown in color. To facilitate its separation from the aqueous layer, 100 cc. of ether was added which dissolved it and gave a more mobile solution which was separated from the water with a separatory funnel.

The ethereal solution was distilled. After the ether was removed, 1.9 cc. of a pale golden oil boiling at 214°-218° was collected. This was a good indication that the substance was phenyl-acetone. (B. Pt.-216°) The ketonic nature of the oil was
established by formation of the sodium bisulphite addition product.

This amount of oil represents a yield of 9.8% of the theoretical.

Run #3

In order to identify the ketone positively, it was necessary to prepare more of it. Consequently run #2 was repeated. The method of purification of the ketone was varied from that used in the second run. The ethereal solution was shaken with a saturated solution of sodium bisulphite. After standing for twenty-four hours, none of the addition product had formed. Although most of the authorities say that the bisulphite addition product can be formed from ether solution, it was necessary in this case, to evaporate off the ether and shake the impure ketone directly with the bisulphite solution. On standing twenty-four hours, the addition product had formed. It was a quite impure dark brown solid. Washing it with ether many times removed the brown color and left a white solid. The ketone was regenerated by heating with sodium carbonate solution and separating the ketone from the aqueous layer by means of a separatory funnel. The ketone was further purified by distillation. In its final form, it was a very pale golden color, almost colorless. It was positively identified by its index of refraction and the melting point of its semi carbazone.
The yield was 2.4 gm. This was 12.1% of the theoretical.

Run #4

This run was carried out in the attempt to increase the yield of ketone. The procedure was modified in that the chloroacetone was allowed to drop slowly into the benzene and aluminum chloride while in previous runs the aluminum chloride was added to the mixture of chloroacetone and benzene. The procedure with this exception was not changed from that of previous runs. It might be well to emphasize at this point that the solvent obtained by steam distillation must be redistilled as it will contain almost half of the yield of ketone. In this run 4.2 gm. of phenyl acetone was obtained. This represents a yield of 21.2% of the theoretical.
IV. SUMMARY

The synthesis of alpha naphthyl-acetic acid has been attempted by first preparing alpha naphthyl-acetone from chloroacetone and naphthalene in the presence of anhydrous aluminum chloride. It has been impossible to prepare any of this ketone.

Phenyl-acetone has been prepared from chloro-acetone and benzene in the presence of anhydrous aluminum chloride. The yields are small.
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