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# THE ACTION OF GRIGNARD REAGENTS ON OXIMES. III. THE MECHANISM OF THE ACTION OF ARYLMAGNESIUM HALIDES ON MIXED KETOXIMES. A NEW SYNTHESIS OF ETHYLENEIMINES

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Ethyleneimines, unlike their analogs, the ethylene oxides, have not been studied extensively. This is due, in part at least, to the fact that there is no general method for the synthesis of ethyleneimines, and but few compounds of this class are known. Ethyleneimine itself, and a few of its derivatives can be prepared from the sulfate of the corresponding amino alcohol (1, 2).

 $CH_2OHCH_2NH_2 \longrightarrow CH_2OHCH_2NH_2 \cdot H_2SO_4 \longrightarrow$ 



This method is not applicable to aryl-substituted amino alcohols, for with these dehydration by sulfuric acid leads to vinyl amines and other compounds (3). 2-Phenyl- and 2,3-diphenyl-ethyleneimine have been prepared from the amino alcohols *via* the corresponding chloroamines (4, 5).

$$C_{6}H_{5}CHOHCH_{2}NH_{2} \longrightarrow C_{6}H_{5}CHClCH_{2}NH_{2} \longrightarrow C_{6}H_{5}CH - CH_{2}$$

This method fails with tertiary amino alcohols, because it is extremely difficult to prepare the necessary chloroamines (6, 7).

Previous work in this Laboratory (8, 9) has shown that arylmagnesium halides react with mixed aryl-alkyl ketoximes to give beta-amino alcohols by rearrangement, rather than the expected hydroxylamines. This rearrangement is a fairly general one, and amino alcohols have been obtained from a wide variety of aryl Grignard reagents and substituted acetophenone oximes:

$$\begin{array}{ccc} \operatorname{ArMgBr} + \operatorname{Ar'C--CH_2R} & \longrightarrow & \operatorname{Ar'} \\ & & & & \\ &$$

In every case the structure of the amino alcohol was established by comparison with an authentic sample. The reaction has shown itself to be a useful one for the synthesis of aryl-substituted beta-amino alcohols, and in many cases the preparation of the amino alcohol is simpler by this method than by older ones.

Although in the earlier work no attempt was made to determine the mechanism

of this rearrangement, it seemed probable than an ethyleneimine was formed as intermediate, and that this subsequently cleaved to the amino alcohol.



Hoch (10) reported that he obtained an ethyleneimine from the action of phenylmagnesium bromide on propiophenone oxime, but he did not give any experimental details or proof of structure of his product. Since the reaction might lead to a general method of preparation of ethyleneimines, and since it was of interest to determine the mechanism of the reaction between Grignard reagents and ketoximes, a detailed study was made of the action of phenylmagnesium bromide on propiophenone and butyrophenone oximes.

When propiophenone oxime was treated with phenylmagnesium bromide, it was found that the conditions of the experiment markedly affected not only the vields but also the nature of the product isolated. When the reaction was carried out as previously described (8), namely, using a concentrated Grignard reagent and hydrolyzing the reaction complex with acid and ice, the amino alcohol, 1,1-diphenyl-2-aminopropanol, m.p. 103-104°, was obtained in 30-40% yield. If no acid was used in the hydrolysis, or if the complex was hydrolyzed with acid at 0°, immediately made basic with ammonium hydroxide, and extracted, a product melting at 72-73° was obtained. This same material was isolated, in better yield and in a purer state, when the Grignard reaction was carried out in toluene solution at 135-145° and the complex hydrolyzed without the use of acid, or the acid solution kept very cold and worked up at once. If the acid hydrolysis mixture was allowed to stand for any length of time, or to get warm, both the substance melting at 72–73° and the amino alcohol were obtained. When the Grignard reaction was carried out in diethyl ether, and the mixture hydrolyzed without the use of acid, a large amount of propiophenone oxime was recovered, and some of the compound melting at 72-73° was isolated.

Analysis of the compound melting at  $72-73^{\circ}$  gave values agreeing with those calculated for a substance of the formula  $C_{15}H_{15}N$ . It seemed likely, therefore, that the substance was the ethyleneimine of structure I. This was then definitely shown to be the case by chemical evidence which ruled out the other possibilities, IIa, IIb, and III, and by synthesis.

The compound, m.p.  $72-73^{\circ}$ , readily forms a stable, non-hygroscopic hydrochloride, from which the free base can be regenerated by treatment with aqueous alkali. It reduces an aqueous or acetone solution of potassium permanganate in the cold very slowly. When it is warmed for a short while with 2 N sulfuric acid or 6 N hydrochloric acid, it is converted quantitatively into 1, 1-diphenyl-2-



aminopropanol; on longer warming, a mixture of diphenylacetone, ammonia, and the amino alcohol is obtained. The amino alcohol itself undergoes decomposition on treatment with acid, to diphenylacetone and ammonia (11).

$$(C_{6}H_{5})_{2}C \xrightarrow{} CHCH_{3} \xrightarrow{H_{2}O} (C_{6}H_{5})_{2}C \xrightarrow{} CHCH_{3} \xrightarrow{H_{2}O} H^{+} \xrightarrow{} (C_{6}H_{5})_{2}C \xrightarrow{} CHCH_{3} \xrightarrow{H_{2}O} H^{+} \xrightarrow{} (C_{6}H_{5})_{2}CHCOCH_{3} + NH_{3}$$

These data conclusively eliminate structures IIa, IIb, and III from consideration. Benzophenone ethylimide, III, melts at  $62^{\circ}$  (12), and is very easily hydrolyzed by aqueous acid, cold, to benzophenone and ethylamine; furthermore, it does not form a stable hydrochloride. A vinyl amine, such as IIa, would be hydrolyzed by dilute acid to ammonia and diphenylacetone, and would not give the amino alcohol under these conditions. An unsaturated amine such as IIb should be readily oxidized by potassium permanganate, whereas ethyleneimines are known to be stable to this reagent (13).

It seems certain, therefore, that the primary product from the reaction of phenylmagnesium bromide on propiophenone oxime is 2,2-diphenyl-3-methyl-ethleneimine (I), and that the amino alcohol obtained previously resulted from acid cleavage of the ring. An attempt was made to synthesize the ethyleneimine from the amino alcohol by the following series of reactions, which are similar to those which have been used successfully for the synthesis of 2,3-diphenyl-ethyleneimine (5):

$$\begin{array}{cccc} (C_6H_5)_2C & --CHCH_3 \rightarrow (C_6H_5)_2C - CHCH_3 \rightarrow (C_6H_5)_2C - CHCH_3 \\ & & | & | & | \\ & & | & | & | \\ & & OH & NH_2 & Cl & NH_3Cl & NH \end{array}$$

Although the hydroxyl group in the amino alcohol is tertiary, and hence should be easily replaceable by halogen, we were unable to find conditions which would give a good yield of the chloro amine. Others (6, 7) have had similar difficulties with related amino alcohols. A small amount of a product was obtained, however, when the amino alcohol was treated with thionyl chloride. Treatment of this material with alcoholic potassium hydroxide yielded an amine, m.p. 72–73°, which did not depress the melting point of the ethyleneimine obtained from propiophenone oxime.

2,2-Diphenyl-3-ethylethyleneimine was made by the action of phenylmagnesium bromide on butyrophenone oxime in toluene solution. Like its lower homolog, this compound forms a stable hydrochloride from which the free base can be regenerated. It does not readily reduce an acetone solution of potassium permanganate, and is hydrolyzed by dilute acids to 1,1-diphenyl-2-aminobutanol.

The hydrochlorides of the two ethyleneimines have the formula:



as shown by analysis for ionizable and total chlorine. In this respect these ethyleneimines differ from some of the previously known compounds of this class, for 2,3-diphenylethyleneimine (5) and 2-phenylethyleneimine (4) react with anhydrous hydrogen chloride to give ring-opening, with the formation of the corresponding chloro amine hydrochlorides.

Both the ethyleneimines reported react with isocyanates and isothiocyanates to give characteristic derivatives, but all attempts to prepare benzoyl derivatives were fruitless.

#### EXPERIMENTAL

Reaction of phenylmagnesium bromide with propiophenone oxime. (A). In concentrated solution. This reaction was carried out substantially as described earlier (8), using one mole of phenylmagnesium bromide and 25 g. of propiophenone oxime. The reaction mixture was hydrolyzed with ice and ammonium chloride; the aqueous layer was extracted several times with ether, and the ether extracts, dried over potassium carbonate, were treated with an ether solution of hydrogen chloride. The white solid so obtained weighed 12 g., and melted at  $141-142^{\circ}$ . When it was dissolved in cold water and treated with dilute sodium hydroxide, a free base was obtained which melted at  $72-73^{\circ}$  after recrystallization from aqueous alcohol.

The reaction was repeated, except that the Girgnard complex was hydrolyzed with ice acidified with 150 ml. of concentrated hydrochloric acid. The acid solution was immediately extracted with ether to remove non-basic impurities, and the aqueous layer was at once made basic with ammonium hydroxide and again extracted with ether. From this ether extract was isolated 15 g. of a hydrochloride, m.p. 140–142°, whose free base melted at 72–73°. Other runs were made, following the same procedure, except that the reaction mixture was hydrolyzed with ice and hydrochloric acid, the mixture extracted with ether, and the acid solution allowed to stand for several hours before it was made basic and again extracted. In this case 10–12 g. of 1,1-diphenyl-2-aminopropanol, m.p. 103–104°, was obtained.

(B). In toluene solution. The Grignard reagent prepared from 24 g. of magnesium turnings, 160 g. of bromobenzene, and 315 ml. of dry ether was concentrated until the color change occurred (8). The hot mixture was diluted with 120 ml. of dry toluene, and a solution of 25 g. of propiophenone oxime in 100 ml. of dry toluene was added over a period of 15 minutes, while the temperature of the oil-bath was kept at 135–145°. Stirring and heating were continued for an additional 20-30 minutes. The reaction mixture was allowed to cool to room temperature, and was then hydrolyzed with ice and ammonium chloride. From this reaction was isolated 18.5 g. of a hydrochloride, m.p. 146°, whose free base melted at 72–73°. Less tar was formed in this reaction than when no toluene was used. The free base could be isolated directly, instead of *via* the hydrochloride, by evaporating the ether and toluene and distilling the residue under reduced pressure. In a typical experiment 15 g. of material, b.p.  $130-132^{\circ}/1$  mm., m.p.  $72^{\circ}$ , was obtained.

When the Grignard complex was hydrolyzed with ice and acid, and worked up immediately, 11-15 g. of free base, m.p.  $72-73^{\circ}$  was obtained. If the acid hydrolysis mixture was allowed to stand for a few hours, the main product was the amino alcohol, of which 6-10 g. was obtained.

(C). In dilute ether solution. In this run the Grignard reagent was not concentrated. The oxime was added over a period of 15 minutes, at room temperature, with no visible reaction; the mixture was then refluxed for two hours. Hydrolysis was accomplished with ice and ammonium chloride. By repeated freezing of the oil obtained on evaporation of the ether extracts, various crops of unreacted oxime were recovered, amounting altogether to 10.2 g. From the residual oil a small amount of a hydrochloride was isolated, from which the free base, m.p. 72–73° was obtained.

2,2-Diphenyl-3-methylethyleneimine is best purified by distillation at 1 mm. or less, followed by recrystallization from aqueous alcohol. When so purified it is obtained as white or very light cream colored prisms, m.p. 74.5-75°. When pure, it reduces potassium permanganate in acetone only very slowly.

Anal. Calc'd for C<sub>15</sub>H<sub>15</sub>N: C, 86.15; H, 7.18; N, 6.70; Mol. wt. 209.

Found: C, 85.98; H, 7.09; N, 6.70; Mol. wt. (cryoscopic), 217.

Treatment of the amine in dry ether with an ether solution of hydrogen chloride yields a white, stable, non-hygroscopic hydrochloride which melts at 139–140° after recrystallization from an alcohol-ether mixture.

Anal. Calc'd for C<sub>15</sub>H<sub>16</sub>ClN: N, 5.70; Cl, 14.45.

Found: N, 5.75; Cl, 14.40.

The amine forms a picrate which was obtained as yellow crystals, m.p. 199-200°. It also forms a phenylthiourea, m.p. 126.5-127° after recrystallization from alcohol. On treatment with 3-nitrophthalic anhydride (14) the amine forms a derivative melting at 190-192°.

Anal. Neutralization equivalent calculated for  $(C_{22}H_{17}N_2O_3)CO_2H$ , 402. Found, 405. Hydrolysis of 2,2-diphenyl-3-methylethyleneimine. (A). With dilute sulfuric acid. One gram of the ring hydrochloride was refluxed for one hour with 50 ml. of 2 N sulfurie acid. The reaction mixture was cooled, extracted with ether, and the aqueous layer made basic with ammonium hydroxide and then extracted with benzene. Evaporation of the ether extract yielded nothing. Evaporation of the benzene extract yielded 0.7 g. of 1,1-diphenyl-2aminopropanol, m.p. 103-104° (8). A mixture of this material with an authentic sample showed no depression of the melting point. The hydrolysis product formed a hydrochloride, m.p. 246°, which did not depress the melting point of 1,1-diphenyl-2-aminopropanol hydrochloride (246-247°).

(B). With dilute hydrochloric acid. When the amine was dissolved in 5% hydrochloric acid and the solution at once made basic and extracted with ether, the original substance was recovered quantitatively. If the hydrochloric acid solution was allowed to stand overnight at room temperature, or was refluxed for 20 minutes, the amino alcohol was obtained.

One gram of the amine was dissolved in 35-40 ml. of 6 N hydrochloric acid and the solution was refluxed for 30 minutes. A purple oil which floated on top of the aqueous layer was taken up in ether. From this ether layer a solid was isolated which melted at  $44-45^{\circ}$ . This compound formed a semicarbazone, m.p.  $166.5-167^{\circ}$ , and a 2,4-dinitrophenylhydrazone, m.p.  $142.5-143^{\circ}$ . No depression of the melting point occurred when these substances were mixed with unsymmetrical diphenylacetone (m.p.  $46^{\circ}$ ), its semicarbazone (m.p.  $168^{\circ}$ ), and its 2,4-dinitrophenylhydrazone (m.p.  $143-144^{\circ}$ ), respectively.

The aqueous acid layer from the hydrolysis was evaporated to dryness under reduced pressure, and the resulting white solid was extracted with absolute alcohol. The alcoholinsoluble portion was shown to be ammonium chloride by the fact that it did not melt, was not hygroscopic, and on treatment with 10% sodium hydroxide solution it yielded a volatile, non-inflammable base. The alcohol-soluble portion melted at 244° and when mixed with the amino alcohol hydrochloride there was no depression of the melting point.

Synthesis of 2,2-diphenyl-3-methylethyleneimine from 1,1-diphenyl-2-aminopropanol.

A suspension of 10 g. of the amino alcohol hydrochloride in 200 ml. of dry chloroform was treated with 20 ml. of redistilled thionyl chloride, and the mixture was refluxed for five hours. Filtration of the mixture yielded 5.7 g. of recovered amino alcohol hydrochloride. The filtrate was concentrated under reduced pressure to a volume of about 50 ml. The addition of ligroin caused the precipitation of 0.4 g. of a dark yellow solid, which melted at 139°. A mixture of this with the ethyleneimine hydrochloride melted at 130°. The solid was dissolved in 30 ml. of 95% alcohol and a solution of 1 g. of potassium hydroxide in 10 ml. of alcohol was added. The solution was allowed to stand at room temperature for several hours, and was then poured into a large volume of cold water and extracted with ether. Evaporation of the dried ether solution yielded an oil which would not crystallize. The oil was treated with hydrogen chloride in ether solution to give a white solid, m.p. 139-140° which did not depress the melting point of the ethyleneimine hydrochloride (142°). On treatment of an aqueous solution of this hydrochloride with 10% potassium hydroxide a white solid formed, which melted at 73° after recrystallization from aqueous alcohol, and did not depress the melting point of the ethyleneimine (m.p. 73°).

Reaction of phenylmagnesium bromide with butyrophenone oxime. The Grignard reagent from 24 g. of magnesium, 160 g. of bromobenzene and 325 ml. of dry ether was concentrated until the color change occurred, and then 125 ml. of dry toluene was added. A solution of 28 g. (0.19 mole) of dry butyrophenone oxime in 100 ml. of dry toluene was added dropwise with stirring while the oil-bath was maintained at 150°. Stirring and heating were continued for thirty minutes, and the reaction mixture was then allowed to cool. It was hydrolyzed by pouring onto ice and ammonium chloride, and the mixture was extracted with ether. The combined ether-toluene solutions were dried over anhydrous potassium carbonate. The product could be isolated by direct distillation under reduced pressure (b.p.  $124^{\circ}/0.5$  mm.), or by forming the hydrochloride. In the latter case 15–18 g. of a white hydrochloride was obtained, m.p.  $144.5-145^{\circ}$  after recrystallization from chloroform-ligroin and alcohol-ether mixtures.

Anal. Calc'd for C<sub>16</sub>H<sub>18</sub>ClN: N, 5.4; Cl, 13.68.

Found: N, 5.3; Cl, 13.86.

The free base was obtained as white crystals, m.p. 44.5-45° after recrystallization from aqueous alcohol.

Anal. Calc'd for C<sub>16</sub>H<sub>17</sub>N: C, 86.10; H, 7.62; N, 6.28.

Found: C, 85.90; H, 7.79; N, 6.35.

The free base reduced an acetone solution of potassium permanganate very slowly. It formed an alpha-naphthylurea, m.p. 184-185° after recrystallization from carbon tetrachloride; the phenylthiourea was an oil.

When the compound was warmed with 3 N sulfuric acid for an hour, and the solution made basic, a white solid was obtained which melted at 77-78° after recrystallization from dilute alcohol. Comparison of this material with the 1,1-diphenyl-2-aminobutanol (9) showed them to be identical.

### SUMMARY

1. The primary product of the action of phenylmagnesium bromide on propiophenone oxime has been found to be 2,2-diphenyl-3-ethylethyleneimine. The structure of this compound has been established by analysis, by hydrolysis to 1,1-diphenyl-2-amino-1-propanol, and by synthesis from this amino alcohol.

2. If the Grignard reaction product is allowed to stand for a short while with aqueous acid the amino alcohol, previously isolated from this reaction, is obtained.

3. Phenylmagnesium bromide reacts with butyrophenone oxime at  $150^{\circ}$  to form 2,2-diphenyl-3-ethylethyleneimine.

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