THESIS

on

THE UTILIZATION OF ETHYL ORTHOFORMATE FOR THE
SYNTHESIS OF DERIVATIVES OF PROPIOPHENONE

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INTRODUCTION

In the course of devising an attack on the problem of synthesizing some derivatives of propiophenone, the plan selected necessitated the preparation of the diethyl acetal of propiophenone and its subsequent de-alcoholization. Thru a search of the literature it was disclosed that, although the diethyl acetal of acetophenone and of butyrophenone were described, no reference to the diethyl acetal nor to the monoethyl derivative of the desired ketone could be found. The preparation and determination of the physical constants of propiophenone diethyl acetal and of 1-phenyl-1-ethoxy-propene-1 is the substance of this thesis.
REVIEW OF PREVIOUS INVESTIGATIONS

Several methods for the esterification of aldehydes and ketones, forming acetalcs, are described in the literature. The term "Acetals" is derived from the name of the best known member of the series, CH$_3$CH(OC$_2$H$_5$)$_2$. Acetal, itself, may be prepared by the oxidation of ethyl alcohol with MnO$_2$ and H$_2$SO$_4$ (l), the acetaldehyde first formed uniting with alcohol with the separation of water.

Fischer's method (2), which cannot be applied to ketones, consists of treating the aldehyde with a dilute alcoholic solution of HCl (1%). He considers the formation of aldehyde acetals as analogous to the esterification of acids by the aid of HCl and an alcohol. This method gives very satisfactory yields with the aliphatic aldehydes and with aromatic aldehydes in which the aldehyde group is not directly attached to the phenyl nucleus (3). In the case of benzaldehyde the yield of acetal is small unless a strongly negative group is present on the phenyl nucleus. Thus good yields of 2,5-dichlor-benzo-dimethyl acetal were obtained by treating 2,5-dichlor-benzaldehyde with 1% HCl in dry methyl alcohol (2).
Although Claisen (4) first published an account of the treatment of aldehydes and ketones with ethyl orthoformate in 1896, it was not until 1907 that he described the necessary conditions and the catalyst used (5). The Claisen method calls for the treatment of the aldehyde or ketone (1 mol) with ethyl orthoformate (1.1 mols) in the presence of ethyl alcohol (3 mols) and the addition of the catalyst. The catalysts suggested (5) are HCl, H₂SO₄, NH₄Cl, FeCl₃, or KHSO₄. The mixture is then boiled for 10 minutes or allowed to stand for 24 hours at room temperature. In case an acid catalyst is employed it must be neutralized before fractionating the product.

Arbusow (6), found that pure ethyl orthoformate does not react with pure ketones, with or without ether, provided all traces of ethyl alcohol or water are absent, but that in the presence of ethyl alcohol, ketone acetals are formed. Carswell and Adkins (7) found that the reaction of ethyl orthoformate with ketones does not proceed in a xylene or toluene solution. They believe the true catalyst to be a compound of alcohol and hydrogen chloride.

Later, Claisen (8) was led to replace the orthoformates by the hydrochlorides of imidoformates. These were known to yield orthoformates with alcohol (9) at
ordinary temperatures and Claisen found them to react with ketones in alcoholic solution yielding acetals in accordance with the equation:

\[ R_2CO + 2EtOH + EtO.CH.NH.HCl = R_2C(OEt)_2 + H.CO0Et + NH_4Cl. \]

Helferich and Hansen (10) have developed a new method for preparing acetals based on the use of the esters of orthosilicic acid, which they claim to be superior to Claisen's method in that the esters of Si(OH)₄ are more easily prepared than those of HC(OH)₃ and also that acetals of unsaturated aldehydes and ketones can be prepared without addition of alcohol at the double bonds.

The removal of alcohol from an acetal results in the formation of an unsaturated compound as shown by the equation:

\[ CH_3.CR(OEt)_2 = EtOH + CH_2:CR(OEt). \]

In the case of ethylic acetoacetate diethyl acetal, Claisen (11) found that distillation under atmospheric pressure was sufficient for the removal of the elements of alcohol. In general, however, this is not the case; some agent being necessary to act as an alcohol acceptor. Phosphoric anhydride may be used on some (11), but it cannot be used alone in the case of acetals of aldehydes and ketones, for these, especially the latter, are very easily decomposed by acids. Claisen (11) used a mixture of
phosphoric acid and quinoline for the treatment of ordinary acetal, the quinoline serving to neutralize the ethylphosphoric acid formed. In the case of acetals that more readily lose alcohol, the phosphoric anhydride may be replaced by an acid chloride. Thus if the expected product has a low boiling point, quinoline and benzoyl chloride should be used. If the unsaturated derivative has a high boiling point, as in the case of acetophenone acetal, the alcohol should be removed by the use of pyridine and acetyl chloride. Another method for the catalytic elimination of alcohol from acetals has been described (12). Briefly, it consists of passing the acetal over porous earth or nickel catalyst at 200° in a current of nitrogen.
PREPARATION OF REAGENTS

Absolute ethyl alcohol. U.S.P. ethyl alcohol was twice refluxed and distilled from lime and then treated with a small amount of metallic sodium and redistilled.

Ether. U.S.P. ether was allowed to stand over CaCl₂ over night, filtered, treated with metallic sodium, and distilled.

Chloroform. U.S.P. chloroform was dried over anhydrous CaCl₂ and distilled.

Propiophenone. The propiophenone employed was an Eastman product having a melting point of 16-18°. It was dried over fused K₂CO₃ for two days and distilled, boiling at 94° at 11 mm.

Ethyl Orthoformate. This reagent was prepared after the method given by Adkins and McElvain (13). Three liters of anhydrous ether was placed in a 5-liter round-bottom flask having a two-holed stopper carrying a reflux condenser and separatory funnel, both condenser and separatory funnel being protected by drying tubes. Then 250 Gm. of sodium cut into small strips was suspended in the ether and 500 cc. of absolute alcohol was slowly run in thru the dropping funnel. Considerable heat was evolved, the flask being cooled with ice water.
After all the sodium had reacted, 400 Gm. of dry chloroform was slowly added, cooling the flask as before. After standing over night, the reaction mixture was gently refluxed on a water-bath for an hour, cooled, and the sodium chloride filtered out at the pump. The precipitate of sodium chloride on the filter was washed with several portions of anhydrous ether, adding the washings to the filtrate. The ether was distilled off on the water-bath and the remainder fractionated. There was obtained 370 Gm. of ethyl orthoformate, having a boiling point of 143-146° after two fractionations.
EXPERIMENTAL

The Diethyl Acetal of Propiophenone

The method employed for preparing the diethyl acetal of propiophenone was that of Claisen (5), which calls for treating a mixture of the ketone (1 mol) and alcohol (3 mols), with ethyl orthoformate (1.1 mols) in the presence of a catalyst. The formation of the acetal is shown by the equation below:

$$C_6H_5 \cdot COEt + HC(OCH_2CH_3)_2 = C_6H_5 \cdot C(OCH_2CH_3)Et + HCOOEt.$$

Propiophenone 72 Gm., ethyl orthoformate 88 Gm., and ethyl alcohol 84 Gm., were weighed into an Erlenmeyer flask and thoroughly mixed. Hydrochloric acid (36%) was selected as the catalyst, exactly 0.3 cc. being added and the reaction mixture allowed to stand for 24 hours at room temperature. A slight rise in temperature of the mixture (8-10°) was noted in each case and after several hours the solution developed a beautiful cerise color which gradually faded to a yellow. At the end of 24 hours the product was neutralized with alcoholic KOH, the ethyl formate, alcohol, and excess ortho ester removed by distillation, and the acetal fractioned under reduced pressure. The yield was 109.4 Gm. of product.
boiling at 99-100° at 8 mm. pressure, constituting 97.9% of the theory. There was practically no higher boiling fraction. The yields from the several runs are given in the table below:

<table>
<thead>
<tr>
<th>Run</th>
<th>Per cent of the theory</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. 1</td>
<td>97.9</td>
</tr>
<tr>
<td>2</td>
<td>96.2</td>
</tr>
<tr>
<td>3</td>
<td>96.5</td>
</tr>
<tr>
<td>4</td>
<td>97.6</td>
</tr>
</tbody>
</table>

The product was a colorless, mobile liquid having a faint, but not unpleasant, aromatic odor. That the substance was pure propiophenone diethyl acetal was confirmed by determination of the molecular weight by cryoscopic methods, using benzene as the solvent. The molecular weight of the acetal as computed from the formula is 208.2, and the value found experimentally was 207.45.

The diethyl acetal of propiophenone, when quickly distilled, was found to boil at 226-228° (corrected) with only a small amount of decomposition into the monooethyl derivative. The table on the following page gives the boiling points under varying pressures:
<table>
<thead>
<tr>
<th>Pressure</th>
<th>Boiling Point</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 mm</td>
<td>93-96°</td>
</tr>
<tr>
<td>8 mm</td>
<td>99-100°</td>
</tr>
<tr>
<td>10 mm</td>
<td>100-101°</td>
</tr>
<tr>
<td>14 mm</td>
<td>108-110°</td>
</tr>
<tr>
<td>23 mm</td>
<td>119°</td>
</tr>
<tr>
<td>760 mm</td>
<td>226-228°</td>
</tr>
</tbody>
</table>

The refractive index of the acetal was determined by means of the Abbe refractometer and found to be $d_{25}$ 1.4767. The specific gravity at $\frac{25}{40}$° was 0.94476.
1-phenyl-1-ethoxy-propene-1

When the diethyl acetal of propiophenone was boiled for some time under atmospheric pressure it was partially decomposed into the monoethyl derivative and ethyl alcohol. Although boiling is sufficient to remove alcohol from some acetals such is not usually the case. Some agent is necessary to act as an alcohol acceptor. As the product was expected to have a high boiling point, acetyl chloride was used to remove the elements of alcohol from the acetal. Since hydrochloric acid is formed in the reaction, some low-boiling substance must be used for its neutralization or else a complete hydrolysis of the acetal would result. Pyridine, having a comparatively low boiling point and being thus easily removed by fractional distillation, was selected.

To a mixture of 25 Gm. of the diethyl acetal of propiophenone with 10 Gm. of pyridine, 10 Gm. of acetyl chloride was slowly added with stirring, the mixture being chilled with ice and salt. The odor of pyridine disappeared, the contents of the flask becoming a pasty white mass. After standing for 15-20 minutes a slight excess of pyridine was added and the reaction was allowed to stand over night. At the end of this time ether was added and the flask contents filtered, washing the precipitate
of pyridine hydrochloride, flask and filter with several small portions of ether. The ether was removed by heating on a water-bath and the remainder distilled over a free flame. The distillate coming over at 72° had a strong odor of ethyl acetate. The next fraction distilling chiefly at 136°, had a strong odor of pyridine. The remaining liquid in the flask was distilled under reduced pressure, practically the entire amount passing over at 105° at 19 mm. The yield was 16.225 Gm., or 83.6% of the theory. The yield on a second run was 92.8% of the theory.

The product was a colorless, oily-like liquid having a rather aromatic odor. When boiled for some time at atmospheric pressure a pale yellow color developed. It was found to be immiscible with water and in the presence of acids was readily hydrolyzed to the original ketone. That it was unsaturated was indicated by the fact that it instantly decolorized a solution of bromine in carbon tetrachloride. A determination of the molecular weight by the freezing point method in benzene, gave a value of 161. The molecular weight of 1-phenyl-1-ethoxy-propene-1 is 162.

The boiling point of this monoethyl derivative was found to be 220-221° (corrected). On the following page are given the boiling points under varying pressures:
The product had a refractive index of $d_{25}$ 1.5207 to 1.5210 and a specific gravity of 0.95441 at $\frac{25^\circ}{4^\circ}$.

A comparison of the constants of the two compounds prepared is shown in the table below:

<table>
<thead>
<tr>
<th>Compound</th>
<th>Ref. Index</th>
<th>Sp. Gr.</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_6H_5.C(0Et)_2CH_2CH_3$</td>
<td>1.4767</td>
<td>0.94476</td>
</tr>
<tr>
<td>$C_6H_5.C(0Et):CH.CH_3$</td>
<td>1.5207-1.5210</td>
<td>0.95441</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Compound</th>
<th>B.P.</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_6H_5.C(0Et)_2CH_2CH_3$</td>
<td>226-228°</td>
</tr>
<tr>
<td>$C_6H_5.C(0Et):CH.CH_3$</td>
<td>220-221°</td>
</tr>
</tbody>
</table>
SUMMARY

1. The diethyl acetal of propiophenone has been prepared, in excellent yield, by treatment of the ketone with ethyl orthoformate.

2. By dealcoholization of the above compound, the monoethyl derivative, 1-phenyl-1-ethoxy-propene-1, was obtained in good yield.

3. The physical constants of propiophenone diethyl acetal and of 1-phenyl-1-ethoxy-propene-1 have been determined.

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