. . .

A STUDY OF THE HANTZSCH PYRIDINE SYNTHESIS

by

Allan T. Sabean

A thesis submitted to the Faculty of Graduate Studies and Research of McGill University, in partial fulfillment of the requirements for the Degree of Master of Science.

September, 1952.

ACKNOWLEDGMENT

and the second second

The present study was carried out under the direction of Dr. Alfred Taurins, and for his help and valuable advice, the writer desires to express his gratitude and appreciation.

- - - -

TABLE OF CONTENTS

| | GENER | AL INTRODUCTION | 1 |
|----|-------|---|----|
| I | HISTO | RICAL INTRODUCTION | 2 |
| | (a) | A short description of the Hantzsch pyridine synthesis | 2 |
| | (ъ) | Studies of previous aldehyde-ammonia condensations | 3 |
| | (c) | Mechanism of the Hantzsch pyridine synthesis | 5 |
| | (đ) | Knoevenagel's combinations | 6 |
| | (e) | Flow sheet | 8 |
| | (f) | The original collidine synthesis | 9 |
| | (g) | Studies using the Hantzsch method | 11 |
| | (h) | Results of these investigations | 13 |
| | (1) | Modifications of the Hantzsch pyridine synthesis | 14 |
| | (j) | Lithium aluminum hydride; Discovery and Use | 21 |
| | (k) | Reductions with lithium aluminum hydride. | 22 |
| | (1) | Examples of lithium aluminum hydride reductions | 23 |
| II | OUTLI | NE OF THE PROBLEM AND DISCUSSION | |
| | (a) | Outline of the problem | 25 |
| | (ъ) | Discussion of the Experimental Methods | 29 |
| | (c) | Yields | 35 |
| | (đ) | Conclusions | 36 |
| | | | |

III EXPERIMENTAL

• • •

٠

The Preparation of

| (a) | 2,4,6 trimethyl pyridine | 37 |
|-----|---|----|
| (Ъ) | 4-phenyl-2,6-dimethyl pyridine | 39 |
| (c) | 4-propyl-2,6-dimethyl pyridine | 40 |
| (d) | 4-anisic-2,6-dimethyl pyridine | 41 |
| (e) | 2,6-dimethyl-3,5-dichloromethyl pyridine. | 42 |
| | 2,6-dimethyl-3,5-diacetomethyl pyridine | 44 |
| | | |

 A second sec second sec

4

. . . .

IV SUMMARY

| | (a) | Summary of experimental results | 45 |
|---|------|---------------------------------|----|
| | (b) | General Summary | 46 |
| | (c) | Contribution to knowledge | 47 |
| v | BIBL | JOGRAPHY | 48 |

GENERAL INTRODUCTION

The objective of this thesis was to determine the value of Hantzsch pyridine synthesis in its application to the condensation of formaldehyde, acetaldehyde, n-butyraldehyde, and benzaldehyde with ethyl acetoacetate and ammonia to obtain the corresponding pyridine derivatives. Further, this method was extended to the reaction of anisic aldehyde with ethyl acetoacetate and ammonia to produce the 4-anisyl-2, 6-dimethyl-pyridine.

The other problem in this investigation was to study the use of 2,6-dimethyl-3,5-dicarbethoxy pyridine, an intermediate in the Hantzsch synthesis, as the starting material for further reactions. The carbethoxy groups of this compound were subjected to the reduction with lithium aluminum hydride to give hydroxy-methyl groups which could be transformed into chloromethyl groups by chlorination with thionyl chloride.

I. - HISTORICAL INTRODUCTION

(a) - <u>A short description of the Hantzsch</u> <u>pyridine synthesis</u>.

The original Hantzsch pyridine synthesis (1) of 1882 was the result of theoretical and experimental study of Dr. Arthur Hantzsch (2) (1857-1935), a German chemist whose additions to the field of organic chemistry were most extensive. The actual mechanism was suggested by C.Baeyer (3) and confirmed by Knoevenagel (4).

This synthesis consisted of the condensation of two molecular proportions of ethyl acetoacetate or similar compound with one of an aldehyde ammonia to form the dihydro pyridine ring which could be dehydrogenated with dinitrogen trioxide yielding eventually compounds of the general structure:



• •

(R' = H or alkyls, aryls)
(R = alkyls or aryls)

Ι

-2-

(b) - <u>Studies of previous aldehyde-ammonia</u> condensations.

Among the earliest pyridine syntheses by condensation involving ammonia with aldehydes were those of Baeyer and Bottinger independently. Bottinger (5), by heating aldehyde ammonia, obtained aldehyde collidine.



also by heating acrolein ammonia obtained -picoline.



Baeyer (6) concluded that comparatively large amounts of picoline present in bone oil must have been caused by a reaction of acrolein, from the pyrolysis of the glycerine in fats with ammonia from nitrogeneous material. Hence, by passing acrolein vapors into ammonia and evaporating the solution to dryness, then by heating the residue in quantities of 200-300 grams in a copper vessel, he obtained an aequous distillate from which an oil was recovered which boiled around 132° and formed crystals of a platinate salt (C₆H₈NCl₃)₂PT, which was identified as being similar to that obtained previously from picoline isolated from bone oil.

Wurtz (7) also prepared aldehyde collidine from aldol ammonia while Kramer (8) obtained some from ethylidine dichloride and alcoholic ammonia.

This work was further extended to propionaldehyde ammonia and iso-valeraldehyde ammonia by Ljubavin (9) who called the products parvoline and valeritine, respectively.

Dürkopf (10) and Chichibabin (11), with co-workers, gave the pyridine derivatives obtained by the aldehyde-ammonia process much study and indicated that the condensations can take several courses depending on the aldehyde and conditions.

(c) Mechanism of the synthesis.

The following mechanism was advanced by Hantzsch:



IV

That is, the Keto form of the ethyl acetoacetate enolizes and the 1:5 - diketone (alkalidene bisacetoacetic ester) undergoes ring closure by the addition of ammonia with the elimination of two moles of water.

If R is CH3, the product would be dihydrocollidine dicarboxylic-ester.

(d) - Knoevenagel's combinations

Knoevenagel (4) showed that these three components may be combined in several different ways before condensation as long as the intermediate formation of β -amino crotonic ester is not precluded, along with alkylidene (or arylidene) aceto ester. For example:



Hence, he found the different methods of condensation were:
1. Two moles of acetoacetic ester plus one mole of an aliphatic or an aromatic aldehyde with one mole of ammonia.
2. Two moles of acetoacetic ester reacting with one mole of aldehydic ammonia.

3. - Two moles of *p* -amino crotonic ester and one mole of an aldehyde.

4. - One mole of *s*-amino crotonic ester with one mole of an alkylidine or arylidine acetoacetic ester.

5. - One mole of acetoacetic ester with one mole of an alkylidine or arylidine reacting with one mole of ammonia.

The tendency for an aldehyde to react with ammonia (or a primary alkyl or aryl amine) to form an imine is well known, taking place in the following way:



This reaction usually occurs readily, hence Knoevenagel's second method of condensation was the one most often used.

It was also established that various aldehydes, Keto esters, β -diketones and the like may be used in the synthesis; nitules, amides, amines with appropriately spaced carbongl groups and hydrogen atoms can also be used. The condensation product was a derivative of dihydropyridine at this point and was only converted into a true pyridine derivative by dehydrogenation. (e) - Flow Sheet

1

The Hantzsch Pyridine Synthesis can be indicated in the following manner:



-9-

(f) - The original collidine synthesis.

The following procedure was undertaken by Hantzsch in the preparation of collidine by this method. $(R = CH_3)$.

1. - Paraldehyde was heated with a few drops of sulphuric acid and distilled. The acetaldehyde formed was collected in ether.

2. - Ammonia gas, dried over calcium oxide, was passed through this liquid which was kept cold by salt and ice. Acetaldehyde ammonia crystals were formed.

3. - These were washed with ether and dried over sulphuric acid in a dessicator.

4. - Ethyl acetoacetate and aldehyde ammonia were mixed in molar proportions 2:1, heated gently to 100-110° in an open beaker.

5. - After cooling, this volume was measured and twice this volume of 2N hydrochloric acid was added slowly with vigorous stirring. The solid dihydrocollidine ethyl dicarboxylate was formed.

6. - The liquid was removed by decanting, the dihydrocollidine ethyl dicarboxylate washed with distilled water, dried in vacuo and twice recrystallized from ethanol, m.p. 131.
7. - The dihydrocollidine ethyl dicarboxylate was weighed.
Twice this weight of ethanol was added to it. Dinitrogen trioxide gas was passed through this solution for one hour. 8. - The ethyl collidine dicarboxylate was formed and poured into a separatory funnel, ice added, neutralized with sodium carbonate, ether added, followed by three washings with distilled water to complete the extraction. Potassium carbonate was added to the ether solution to take up the small amount of water remaining.

9. - The ether was distilled off, the ethyl collidine dicarboxylate remaining being obtained in pure form after two vacuum distillations; B.p 175-178°/12 mm.

10. - Ethyl collidine dicarboxylate was refluxed from four to six hours with a freshly prepared sodium ethoxide solution. Potassium collidine dicarboxylate, which was sparingly soluble in the alcohol crystallized.

11. - After washing with ethanol and drying, these crystals were well mixed, by mortar, with twice their weight of soda lime, dry distilled in a gas furnace and the distillate, collidine, was collected in ether.

12. - The ether was removed by distillation after which the remainder was also distilled (twice) to obtain an 8.1% yield of pure collidine: B.p. 172-3°.

-10-

(g) - Syntheses using the Hantzsch Method

Much work followed, using the Pyridine Synthesis by Hantzsch and employing the various Knoevenagel combinations. Condensations such as the following were studied:

| ester or diketone | with aldehyde | with amine | reference |
|----------------------------------|--|-------------------|------------------------|
| 2 moles of ethyl acetoacetate | н.сно | NH_{3} | 21,22,23,24 |
| TT TT | H.CHO | CH3,NH2 | 15,16 |
| 17 11 | CH3.CH0 | NH3 | 1,4,13,14, 15,16,25 |
| 11 11 | CH3.CHO | CH3.NH2 | 16,26 |
| TT TT | C ₂ H ₅ .CHO | NH3 | 19 |
| TT TT | CH(CH ₃) ₂ .CHO | NH_{3} | 19 |
| 11 11 | CH(CH3)2CH2.CH0 | NH3 | 19 |
| 11 17 | C6H5.CHO | NH3 | 4,18 |
| 11. 11 | C6H5.CHO | CH3.NH2 | 26 |
| 17 17 | m.NO2.C6H4.CHO | NH3 | 20 |
| 11 11 | p.(CH3)2NC6H4.CHO | NH3 | 27 |
| ** ** | C6H5.CH.CH.CHO | NH3 | 18 |
| ** ** | furfurol | NH3 | 25 |
| ** ** | acrolein | NH3 | 19 Fails |

| ester or diketone | with aldehyde | with amine | reference |
|--|------------------------------------|------------------------------|-----------|
| 2 moles of benzoylacetate ester | СН3.СНО | NH3 | 4 |
| TT 1T TT | CH3.CHO | CH3.NH2 | 4 |
| 2 moles of benzoyl acetone | C6H5.CHO | NH3 | 26 |
| 2 moles of acetyl acetone | CH3.CH0 | NH3 | 24 |
| 17 17 | CH3.CH0 | CH3.NH2 | 24 |
| 11 11 | C ₆ H ₅ .CHO | NH3 | 29 |
| l mole of acetoacetic ester with | | | |
| acetaldehyde | CH3.CHO | NH3 | 17 |
| desoxybenzoin | С ₆ Н ₅ .СНО | $\mathrm{NH}_{\mathfrak{Z}}$ | 22 |
| acetylacetone | CH3.CHO | CH3.NH2 | 26 |
| 17 17 | C6H5.CHO | NH2 | 4 |
| 11 H | C6H5.CH0 | CH3.NH2 | 26 Fails |
| benzoylacetone | C6H5.CHO | $\rm NH_3$ | 26 |

ŗ

A comparatively recent work by Phillips (28) has shown much success using complex aldehydes in conjunction with methyl, ethyl and n-butyl esters, and many quaternary salts were prepared.

A typical reaction was the use of cinchoninaldehyde with acetoacetic ester and ammonia. The general structure of the resulting dihydro pyridine compound being:



VIII

(RX = CH3, C2H5, C6H5CH Cl, C6H5CH2OSO2C2H5.H2O, B CH2COOC2H5). Yields from 60 to 100% were reported. Using m-substituted benzaldehyde with various esters equally satisfactory results were obtained. m-nitrobenzaldehyde (29), p-dimethyl amino (29), p-diethyl aminobenzaldehyde (29) with a variety of alkyl acetoacetates were previously reported in good yield adding further evidence to the practability of The Hantzsch pyridine synthesis.

(h) - <u>Results of these investigations</u>.

In general, the yields obtained were satisfactory, 60% being average. The results obtained substantiated a past claim of the synthesis, - that many aldehydes, alkyl acetoacetates with ammonia would condense successfully regardless of the complex chemical nature of the reactants involved. (1) - Modifications of the Hantzsch pyridine synthesis

1. <u>Michaels' Modification</u> (17): where one of the molecules of ethyl acetoacetate was replaced by an additional molecule of aldehyde.



(yield 25-30%)

Dehydrogenation of the mono-carboxylic ester by dinitrogen trioxide very readily gave 2,4-dimethylnicotine ester.

1

2. Knoevenagel (4) similarly condensed benzal acetoacetic ester with desoxybenzoin and ammonia.



-15-

3. This reaction was further extended by Knoevenagel and Ruschhaupt (4) to *P*-diketones and their ammonia derivatives. Thus, benzalacetoacetone condensed with acetylacetoamine to give 4-phenyl-3,5-diacetyl dihydrolutidine.



It was also found that β -amino crotonic ester and benzalbenzoylacetone gave the corresponding dihydro pyridine in 40-50% yield.

$$\begin{array}{cccc} C_2H_5OOC-C-H & C_6H_5-C-H \\ & \\ CH_3-C & \neq CH_3CO-C & \longrightarrow IV (R - C_6H_5) \\ & \\ & \\ NH_2 & C_6H_5C = 0 \end{array}$$

Here, as in other condensations of benzalbenzoylacetone, the $C_{6}H_{5}CO$, rather than the CH3CO, is the reactive (the enolizable) group, and hence the $C_{6}H_{5}$, not the CH3, appears in the \propto -position in the product.

4. The Guareschi (and Thorpe) Modification (30) :

This synthesis, involving no aldehyde, has been investigated for the normal and branched chain alkyl derivatives with acetoacetamide or cyanoacetamide or ester. A typical example is the condensation of cyanoacetic ester and ethyl \propto -acetoacetate (R = C₂H₅) with ammonia to give an 85% yield of 2,6-dihydroxy-3-cyano-5-ethyl-4-methyl pyridine.



Х

5. The Knoevenagel Modification (31) :

Knoevenagel found that if the synthesis is carried out without ammonia in a stepwise manner, the formation of a six membered ring takes place. This, which is catalytically induced by bases such as dimethylamine or piperidine, consists of ring closure of the intermediate product. That is, it is like the Hantzsch pyridine synthesis carried out stepwise. The carbon segments are first joined under the influence of the catalyst and the nitrogen atom is then put in place by heating the dioxime rather than by condensing with ammonia.



-18-

6. The von Meyer Modification (32) :

An unsaturated aminonitrile, β phenyl- β -amino-acryls nitrile, was condensed with acetoacetic ester in the presence of hydrochlorie acid, the product being a derivative of γ -hydroxy pyridine.





XII

7. When the aldehyde was replaced by a ketone, such as acetone, the product was a dihydro compound that was easily oxidized by chromic acid in acetic acid solution to a pyridine derivative. (33)



XIII

XIV

Other modifications have been noted in the literature but the above suffice to show the adaptability of the original synthesis.

(j) - Lithium Aluminum Hydride, Discovery and Use.

LiAlH₄ was first prepared by Finholt, Bond and Schlesinger (34) by treating lithium hydride with an ether solution of aluminum chloride.

This white microcrystalline compound was shown by preliminary experiments to be capable of reducing carbonyl, carbalkoxy, acyl chloride, highly conjugated esters, amino and hydroxy esters, etc., but without action on the double bond of simple olefines. Consequently, the principal interest in it was its usefulness as a powerful reducing agent of organic compounds.

It was found to be unique in that - 1) it was easily prepared on a large (or small) scale from commercially available litnium hydride; 2) it was indefinitely stable at room temperature, provided it was kept in air tight containers; 3) it was ether soluble, 25-30 grams per 100 ml. of dietnyl ether at 25 over a long period of time; 4) as compared with other reducing agents, excepting hydrogen, it had a favorable ratio of reducing capacity to mass, the reduction products being obtained in yields that were almost quantitative in a purity seldom obtained by other methods; 5) it had a tendency to avoid side reactions, polimerizations, condensations or cleavage; 6) "hindered" compounds not generally amenable to other processes were usually reduced with it; 7) the reductions occurred at room temperature; 8) no unusual equipment was needed, the experimental procedures being substantially identical to those commonly employed in Grignard synthesis.

-21-

(k) - <u>Reductions with LiAlH</u>.

Various aldehydes, ketones, esters, acid chlorides anhydrides, etc., have been reduced to the corresponding alcoholic products with excellent results, (35).

n-heptaldehyde, crotonaldehyde, benzaldehyde, butanone-2, cyclopentanone, methyl oleate, ethyl benzoate, benzoyl chloride, palymityl chloride, sorbyl chloride, are examples where yields greater than 70% were found. Some, such as palymityl chloride and methyl laurate gave 99% and 94% yields. Esters of imidazole (36), pyrazole (36), pyrsole (37), furan (37), indole (37), and other heterocyclic carboxylic acids were easily reduced.

A variety of pyridine carboxylic acid esters have also been reduced with LiAlH₄ with good to excellent yields of the corresponding hydroxy methyl compounds being obtained.

For example: 3-hydroxy methyl pyridine (38) from ethyl nicotinate gave 80% yield, diethyl-2,6-dimethyl-3,4-pyridine dicarboxylate, when reduced to 2,6-dimethyl-3,4-dihydroxymethyl pyridine (39) yielded 50%.

Later, work was done on compounds which might give vitamin B₆ directly. Hence, ethers of 2-methyl-3-hydroxy-4, 5-pyridine dicarboxylic acid (39), and 2-methyl-3-amino-4, 5-pyridine dicarboxylic acid (39) were prepared which yielded excellent hydroxymethyl compounds, both in purity and quantity, when reduced by LiAlH₄.

-22-

(1) - Examples of lithium aluminum hydride reductions:

Some react

The reduction with LiAlH₄ can be shown by the following examples: (34), (35), (40).

1. Acids:

4

4 RCOOH \neq 3 LiAlH₄ \longrightarrow 2 LiAlO₂ \neq 4 H₂

 \neq (RCH₂0)₄ LiAl \longrightarrow RCH₂0H

2. Esters:

2 RCOOR' \neq LiAlH₄ $\longrightarrow \frac{1}{2}$ (RCH₂O)₄LiAl $\neq \frac{1}{2}$ (R'O)₄LiAl \longrightarrow 2 RCH₂OH \neq 2 R'OH

3. Aldehydes:

4 RCHO \neq LialH4 \longrightarrow (RCH₂O)₄Lial \longrightarrow 4 RCH₂OH

4. Ketones:

 $4 R_2 CO \neq LialH_4 \longrightarrow (R_2 CHO)Lial \longrightarrow 4 R_2 CHOH$

5. Anhydrides:

 $(RCO)_{20} \neq \text{LiAlH}_{4} \longrightarrow \frac{1}{2} \text{LiAlO}_{2} \neq \frac{1}{2} (RCH_{2}O)_{4} \text{LiAl}$ $\longrightarrow 2 \text{ RCH}_{2}OH$

6. Acid chlorides:

2 RCOC1 \neq LiAlH₄ $\longrightarrow \frac{1}{2}$ LiCl $-\frac{1}{2}$ AlCl₃ $\neq \frac{1}{2}$ (RCH₂O)₄LiAl \longrightarrow 2 RCH₂OH

- 7. Amides:
 - $2 \operatorname{RCONR}_2 \neq \operatorname{LiAlH}_4 \longrightarrow 2 \operatorname{RCH}_2\operatorname{NR}_2 \neq \operatorname{LiAlO}_2$

4 RCONR'₂ \neq 2 LiAlH₄ \longrightarrow LiAl(OCH₂R)₄ \neq LiAl(NR'₂)₄

 \rightarrow 4 RCH₂OH \neq 4 R'₂NH

- 4 RCONHR' \neq 3 LialH₄ \longrightarrow Lial(OCH₂R)₄ \neq 2 Lial(R'N)₂
- \neq 4 H₂ \longrightarrow 4 RCH₂OH \neq 4 R'NH₂

-5

8. Nitriles:

2 RCN \neq LiAlH₄ \longrightarrow (RCH₂N)₂LiAl \longrightarrow 2 RCH₂NH 9. Aldimines:

4 RCH=NR \neq LiAlH4 \longrightarrow (RCH₂NR₄)LiAl \longrightarrow 4 RCH₂NHR 10. Heterocyclic carboxylic esters:



11. Aromatic nitro compounds:

RNO₂ \neq LiAlH₄ $\longrightarrow \frac{1}{2}R - N = N - R - 2 H₂ <math>\neq$ LiAlO₂ 12. Aliphatic nitro compounds:

 $2 \text{ RNO}_2 \neq 3 \text{ LiAlH}_4 \longrightarrow 6 \text{ H}_2 \neq 2 \text{ LiAlO}_2 \neq (\text{RN})_2 \text{LiAl}$ $\longrightarrow 2 \text{ RNH}_2$

13. Quinolines were reduced to hydroquinones in excellent yields. The equation for the reaction has not yet been established.

14. Alkyl halides:

4 RX \neq LiAlH4 \longrightarrow 4 RH \neq LiAlX4

II. - OUTLINE OF THE PROBLEM AND DISCUSSION

(a) - Outline of the problem

The objective of this work was:

1. - To investigate the Hantzsch pyridine synthesis.

2. - To synthesize new compounds.

According to the Hantzsch pyridine synthesis, the condensation of ethyl acetoacetate and ammonia with an aldehyde yielded a dihydro pyridine compound.

The 2,6-dimethyl-3,5-dicarbethoxy dihydro pyridine could be dehydrogenated with dinitrogen trioxide:

IV \neq N203 \longrightarrow V

The 2,6-dimethyl-3,5-dicarbethoxy pyridine formed could be transferred into a potassium salt of pyridine dicarboxylic by the action of potassium ethoxide:

$\nabla \neq 2 \text{KOC}_{2\text{H}_5} \longrightarrow \forall I$

The 2,6-dimethyl-3,5-potassium dicarboxy pyridine converted to the final product, 4-alkyl-2,6-dimethyl pyridine, by heating:

 $VI \longrightarrow VII$

Accordingly, acetaldehyde was condensed with ethyl acetoacetate and ammonia, giving 2,4,6,-trimethyl pyridine. n-butyraldehyde was used with ethyl acetoacetate to yield 4-propyl-2,6-dimethyl pyridine and benzaldehyde with ammonia and ethyl acetoacetate gave 4-phenyl-2,6-dimethyl pyridine. The results obtained were in agreement with literature.

Anisic aldehyde was used as the aldehydic reactant in conjunction with ethyl acetoacetate and ammonia. It was believed the reaction took place in the following way:

 $(R = C_6H_5OCH_3(p))$

 $\begin{array}{cccc} C_{2}H_{5}OOC-CH_{2} & \neq & NH_{3} \\ CH_{3}-C = 0 & OHC-C_{6}H_{5}OCH_{3}(p) \longrightarrow IV \end{array}$

The dehydrogenation of the 4-anisyl-2,6-dimethyl-3-5dicarbethoxy dihydro pyridine with dinitrogen trioxide should have proceeded as shown:

 $IV \longrightarrow V$

The 4-anisyl-2,6-dimethyl-3,5-dicarbethoxy pyridine should be converted to the potassium salt of pyridine dicarboxylic acid by the action of potassium ethoxide:

 $V \neq 2KOC_{2H_5} \longrightarrow VI$

Heating should yield the final product 4-anisyl-2,6dimethyl pyridine:

VI ----> VII This reaction proceeded readily, giving a good yield of the

final product and a pictrate salt from it.

Formaldehyde was condensed with ethyl acetoacetate and ammonia to obtained the known compound: 2,6-dimethyl-3,5dicarbethoxy dihydro pyridine. On dehydrogenation with dinitrogen trioxide, 2,6-dimethyl-3-5-dicarbethoxy pyridine was obtained. Where the reduction of an ester with LiAlH₄ procedes according to the equation:

2RCOOR' \neq LiAlH₄ \longrightarrow $\frac{1}{2}$ (RCH₂O)₄LiAl \neq $\frac{1}{2}$ (R'O)₄LiAl \longrightarrow 2 RCH₂OH \neq 2R'OH

it was believed that the reduction of the 2,6-dimethy1-3, 5-dicarbethoxy pyridine proceeded in the same manner.



On treating the 2,6-dimethyl-3,5-dihydroxymethyl pyridine with acetic anhydride 2,6-dimethyl-3,5-diacetomethyl pyridine should form.



On treating the 2,6-dimethyl-3,5-dihydroxymethyl with thionylchloride, 2,6-dimethyl-3,5-dichloromethyl pyridine should be prepared.



.

(b) - Discussion of the Experimental Methods.

The dihydropyridine compound was the product formed by condensing the aldehyde with ammonia and ethyl acetoacetate.

Using anisic aldehyde, even after repeated attempts, only an oil was obtained which subsequently proved to be satisfactory for the following reactions. With benzaldehyde, the dihydro pyridine compound was obtained in solid form after standing for two days; using n-butyraldehyde, three days were required, but with formaldehyde and acetaldehyde, the solid formed with ease. In some of the attempts, the distillation of a small volume of the liquid, later shown to be ethyl acetoacetate, aided considerably in the formation of the dihydro pyridine compound.

Literature has called for the neutralization of excess ammonia of this reaction by using twice the solution volume of 2 N hydrochloric acid. This was found to give smaller yields than by other methods.

For example, the volume of acid which just neutralized the reaction when formaldehyde was used gave the largest yield; if more was added, a heavy red oil was obtained. Similar results were noted with the other aldehydes. Greater yields were in evidence when this acid was added to a cooled solution. That is, the volume, concentration and temperature of the neutralizing acid are definite factors in the yields obtained.

Various Knoevenagel combinations of the original starting materials were tried; the ones recorded in the experimental part proving the most satisfactory.

-29-

Purification of crude dihydro pyridine esters was accomplished by washing with cold distilled water, followed by crystallization from hot ethanol (twice). The first ethanol wash was usually discarded but subsequent washes retained and later distilled to recover this comparatively large amount (600-800 ml.)

This purification of the dihydro pyridine compounds in crystal form occurred easily and gave good yields in all cases. Dehydrogenation with dinitrogen trioxide gas proceeded readily. In all cases, gentle heating of the ethanol solutions of the dihydro compound during the reaction nelped considerably. Noticeable color changes, usually from a dark to a lighter color, together with a failure of the dihydro pyridine compound to crystallize out of solution indicated the completeness of the reaction.

In general, the reaction occurred in the following way:

$$\frac{IV}{(in \text{ ethanol})} \xrightarrow{N_2O_3} V \neq 2H$$

$$N_2O_3 \neq 2H \longrightarrow H_2O \neq 2NO$$

Extraction with ether was undertaken. Powdered sodium carbonate was used as a neutralizer. Here, caution must be used. It was imperative that ice be added before proceeding with neutralization, as the reaction was exothermic. That is, ice, water, sodium carbonate and ether must be added in this order.

-30-

The ether solution of the dimethyl dicarbethoxy pyridine was washed three times with distilled water and dried for two hours with anhydrous potassium carbonate. Removal of the ether by suction followed by distillation at reduced pressure for all (except the product of the formaldehyde reaction which required two crystallizations to give a solid product) yielded the purified form of the dimethyl dicarbethoxy pyridine. Potassium salts of pyridine dicarboxylic acid were prepared by separately refluxing these substances with potassium ethoxide. It was important at this stage to use absolute alcohol, as all the salts so obtained were highly soluble in water.

4-anisyl-2,6-dimethyl-3,5-dicarbethoxy pyridine reacted extraordinarily readily with potassium ethoxide, while 4-propyl -2,6-dimethyl-3,5-dicarbethoxy pyridine reacting with potassium ethoxide, left much to be desired.

4-methyl-2-6-dimethyl-3,5-dicarbethoxy pyridine, 2,6-dimethyl-3,5-dicarbethoxy pyridine, and 4-phenyl-2,6-dimethyl-3, 5-dicarbethoxy pyridine reacted separately with the potassium ethoxide to give sufficient yields to be considered satisfactory. In general, this reaction could be indicated in the following way:

 $\nabla \neq 2HOC_{2H5} \longrightarrow \nabla I \neq 2(C_{2H5})_{2}O$

-31-

The crystals of the potassium salt of pyridine dicarboxylic acid obtained were washed with absolute alcohol and dried in a desiccator over sulphuric acid. After weighing and mixing with slaked lime in the proportions of 1:2 (by weight) the mixture of 2,6-dimethyl-3,5-potassium dicarboxylate and slaked lime was placed in a long (85 cm) heavy glass tube, in such a way that it was evenly distributed.

This tube was inserted in an inclined gas furnace. A long glass lead off tube was placed over the open mouth of the tube leading to the collecting flask. All vapors and distillate were collected in ether.

The reaction took much time, varying from 1.5 hours, in the case of collidine, to 7 hours for 4-anisic-2,6-dimethyl pyridine. In general, this reaction could be shown in the following way:

VI \longrightarrow VII \neq K₂CO₃ \neq CaCO₃

It was found, after many trials, that the yield was only fair but can be increased slightly by increasing the time of heating. Evaporation of ether and distillation at reduced pressure yielded the final product.

In the reduction of the 3,5-dicarbethoxy-2,6-dimethyl pyridine with lithium aluminum hydride, great care must be taken, due to the sensitivity to moisture of the latter compound, which is highly reactive with water occurring extremely rapidly and completely.

LiAlH₄ \neq 2H₂0 \longrightarrow LiAlO₂ \neq 4H₂

-32-

Consequently, to prepare an ethereal solution of lithium aluminum hydride, attention must be paid to the preparation of absolute ether.

Anhydrous (commercial) ether, after preliminary drying for 8 hours over calcium chloride, was treated with a very small quantity of lithium aluminum hydride to remove peroxides and other impurities. After decanting, the ether was distilled. Using ground glass apparatus, nitrogen gas was passed through a three necked flask and an electrical mercury sealed stirrer set in motion to keep the ether in the flask moving.

Calculations were made as to the amount of lithium aluminum hydride necessary for the reaction. This quantity was accordingly weighed out under nitrogen atmosphere, using goggles and rubber gloves to ensure safe handling. After which it was inserted slowly through the third neck of the flask. A condensor and thermometer were inserted to complete the apparatus.

Gentle heating for 24 hours with continued stirring followed, for the lithium aluminum hydride dissolved very slowly. The 3,5-etnyl dicarboxy-2,6-dimethyl pyridine was easily soluble in absolute ether. This solution (100 ml.) was added dropwise to the solution of lithium aluminum hydride.

This was extremely important for, although the reaction takes place immediately, sufficient heat was involved to cause the ether vapors to be ejected through the condensor and drying tube of calcium chloride attached to it. Accordingly, the slower the addition, the more the ether was retained.

-33-

After an hour of standing, 20 ml. of water was added in a similar manner for the same reason. After four trials, it was concluded that if the nitrogen flow be kept to a bubble every two seconds, sufficient gas would be present to ensure safety, yet not be sufficient to cause excess ether to be ejected despite the condensor.

This flow can be noted by watching the gas flow through the sulphuric acid washing flask. Once completed, the contents of the flask were filtered, the residue returned to the flask and 100 ml. methanol added. The mixture was heated to boiling, then filtered. This was repeated. All filtrates were combined and the residue discarded.

Distillation, under reduced pressure of the ether, methanol and some water, was completed in the usual manner. The residue liquid was carefully distilled under reduced pressure after it had been dried for one hour with annydrous potassium carbonate.

The general reaction occurred in the following way:

 $V \neq \text{Lialh}_4 \longrightarrow XV \neq 2C_2H_5OH$

After recrystallization of the 3,5-dihydroxymethyl pyridine with hot methanol, an acetate derivative was prepared by the straight addition of acetic anhydride to a small sample, using pyridine as an acid neutralizer.

> XV / (CH3CO)20 ----- XVI pyridine

-34-

The vacuum distillation of the liquid portion must be done by oil vacuum pump, with which a pressure of lmm (Hg) was obtained. Recrystallization from hot benzene was found to give the most satisfactory purity and yield, other solvents being tried and rejected.

Chlorination by thionyl chloride of the dihydroxymethyl compound yielded the final product according to:

 $XV \neq SOCl_2 \longrightarrow XVII \neq 2H_2SO_3$

(c) Yields

Yields obtained were found to be satisfactory for all reactions with the exception of the 4-propyl-2,6-dimethyl pyridine which, despite repeated attempts, gave only 7.7% as a maximum.

The collidine yield, although small, 6.7%, was in close agreement with the literature.

4-anisyl-2,6-dimethyl pyridine was obtained in 60% yield; 4-phenyl-2,6-dimethyl pyridine in 43% yield, and 2,6-dimethyl-3,5-dichloromethyl pyridine in 59% yield. (d) - <u>Conclusions</u>.

1. The Hantzsch pyridine synthesis was found to be a successful method for obtaining dicarboxylic esters of pyridine, which can be used as starting material for further reactions.

2. Yields obtained were sufficiently great in all cases to extend this procedure for other similar substances.

3. The lithium aluminum hydride reduction of dicarboxylic esters to dihydroxymethyl derivatives was very satisfactory, providing attention be paid to technique and amounts involved.

4. The Hantzsch pyridine synthesis was easily modified, provided the dihydro compounds formed were dehydrogenated to true pyridine compounds.

III. - EXPERIMENTAL

(a) - The preparation of 2,4,6 trimethyl pyridine, by the condensation of acetaldehyde ammonia with ethyl acetoacetate.

50 ml. of acetaldehyde was prepared by distilling 60 ml. of paraldehyde with 3 ml. of 1 N sulphuric acid in a 250 ml. round bottomed flask. Acetaldehyde was collected in 100 ml. of cold ether, placed in a 250 ml. flask and kept cold by an ice and salt bath. Ammonia gas was passed through the solution of acetaldehyde for 25 minutes.

This gas was obtained by heating 200 ml. of ammonium hydroxide in a 250 ml. round bottomed flask and dried by passing through a calcium oxide tube. The resulting aldehyde ammonia crystals and liquid were allowed to stand 3 hours in the refrigerator in a stoppered flask.

The crystals were washed 3 times with 50 ml. of ether and dried in a desiccator over sulphuric acid. 10 grams of this product were placed in a weighed 250 ml. beaker, containing 33 grams of ethyl acetoacetate. This mixture was heated to $100-110^{\circ}$ to obtain a solution.

After cooling to room temperature, 60 ml. of 2 N hydrochloric acid was added with vigorous stirring. A solid precipitated, which was thoroughly washed with distilled water. The product was dried on a porous plate.

Crystallization from 200 ml. of hot ethanol twice gave a 70% yield of dihydrocollidine-3,5-diethylcarboxylate, melting

point 131°. 15 grams was dissolved in 40 ml. of warm ethanol, placed in a 125 ml. flask and dinitrogen trioxide gas was passed through for one hour. A safety trap, consisting of an empty flask, was used. The dinitrogen trioxide was prepared by heating 50 grams of arsenous oxide with 75 ml. of concentrated nitric acid and 30 ml. of water in a 500 ml. round bottomed flask, using no rubber connections.

The collidine-3,5-diethyl carboxylate, was extracted in a one liter separatory funnel, using 200 ml. of ether, 4 grams of sodium carbonate to neutralize the acid, and 100 grams of ice. The ether solution was washed four times with distilled water, then dried with 1.3 grams of potassium carbonate for 2 hours.

After the ether was removed by vacuum, the remaining liquid, collidine-3,5-diethyl carboxylate, was distilled at reduced pressure in a 100 ml. Claisen flask. The resulting liquid was redistilled. 11.8 grams were obtained at 76-78^o (27mm).

120 ml. of absolute ethyl alcohol was prepared by refluxing 10 grams of calcium oxide with 150 ml. of ethanol for 6 hours and distilling. Refluxing with 30 grams of pure dry potassium hydroxide for 3 hours followed. 11.8 grams of the ethyl collidine dicarboxylate was next refluxed with 100 ml. of 30% potassium ethoxide solution in a 250 ml. round bottom flask for 5 hours.

Potassium collidine dicarboxylate (crystals) was obtained. This product was washed with ethanol and dried. The yield was 5.2 grams. This quantity was mixed with 10.4 grams of soda lime in a mortar, placed in an 85 cm. long heavy glass tube and heated in a gas furnace for 1.5 hours. The distillate, which was collected in ether, was dried with 1 gram of anhydrous potassium hydroxide for 1 hour.

The ether was removed at reduced pressure. The remaining liquid was distilled from a small flask. 2.2 grams of collidine was obtained, boiling point 174°. This was in agreement with that observed by Hantzsch.

(b) - The preparation of 4-phenyl-2,6-dimethyl pyridine, by the condensation of benzaldehyde-ammonia with ethyl acetoacetate.

In this condensation, the same procedure was followed and the same apparatus used. 10 grams of penzaldenyde ammonia were prepared which were reacted with 25 grams of ethyl acetoacetate. The resulting solid was twice **rystallized** from 200 ml. of hot ethanol to yield 16 grams of 4-phenyl-2,6-dimethyl-3,5-ethyl dicarboxy dihydro pyridine, melting point 141°.

This compound was dissolved in hot ethanol, dehydrogenated by dinitrogen trioxide and the resulting product 2,6-dimethyl-3, 5-diethylcarboxy pyridine extracted in a one liter separatory funnel, using 200 ml. of ether, 5 grams of sodium carbonate, 100 ml. of distilled water and 100 grams of ice.

The ether solution was washed four times with distilled water, then dried with 1.8 grams of potassium carbonate for 2 hours. After the removal of ether by vacuum, the remaining liquid was distilled at reduced pressure to obtain a yield of 11.7 grams of 2,6-dimethyl-3,5-diethylcarboxy pyridine, boiling point 157-160° at 30mm.

10 grams of this substance was refluxed with 100 ml. of 30% potassium ethoxide for 4 hours. After washing in 40 ml. of absolute ethyl alcohol and dried in a desiccator over sulphuric acid, a yield of 5.9 grams of 4-phenyl-2,6-dimethyl-3, 5-potassium dicarboxy pyridine was obtained.

The salt, on mixing with 15 grams of slaked lime, was heated in a gas furnace and the distillate collected in ether. After the removal of the latter, the remaining liquid was distilled at reduced pressure to yield 4.3 grams of 4-phenyl-2, 6-dimethyl-3 pyridine, boiling point 142° at 30mm. A picrate salt formed had a melting point 226°, in close agreement with the literature.

(c) - The preparation of 4-propyl-2,6-dimethyl pyridine by the condensation of butyraldehyde-ammonia with ethyl acetoacetate.

In this condensation, the same procedure was followed and the same apparatus used. 15 grams of butyraldehyde ammonia reacted with 45 grams of ethyl acetoacetate very slowly, taking two days to obtain the crystals of the crude dihydro ester. After two crystallizations from hot ethanol, a yield of 14.2 grams was obtained.

The dihydro ester melted at 120°. Dehydrogenation, by dinitrogen trioxide, extraction with ether, washing with distilled water, drying with potassium carbonate and distillation under reduced pressure, gave 9.3 grams of the 4-propy1-2, 6-dimethyl-3,5-dicarbethoxy pyridine, which had a very consistant boiling point of 203⁰ at 26mm.

After refluxing with 100 ml. of 25% solution of potassium ethoxide for 6 hours, 4-propyl-2,6-dimethyl-3,5-potassium dicarboxy pyridine crystals appeared which, after washing in 40 ml. of absolute ethyl alcohol and in 40 ml. of ether and dried in a desiccator, gave only 2.3 grams as a yield.

Dry distillation in a gas furnace with 5 grams of slaked lime for 6 hours yielded a liquid of heavy odor which, when distilled, had a very definite boiling point of 196°. The yield was 1.1 grams. A pictrate formed easily which had a melting point of 136°. This result was in agreement with that found by Jaeckle (41).

(d) - The preparation of 4-anisyl-2,6-dimethyl pyridine by the condensation of anisic aldehyde-ammonia with ethyl acetoacetate.

In this condensation, the same procedure was followed and the same apparatus used as in (a). 20 grams of anisic aldehydeammonia was prepared which reacted with 50 grams of ethyl acetoacetate to yield a light yellow liquid, 4-anisyl-2,6-dimethyl-3, 5-dicarbethoxy dihydro pyridine.

On dehydrogenation with dinitrogen trioxide, extraction with ether, washing with water, drying with potassium carbonate and distilling twice under reduced pressure, 28 grams of 4-anisic-2,6-dimethyl-3,5-dicarbethoxy, were obtained. The boiling point was 127-128°. On refluxing with 120 ml. of 30% potassium ethoxide for 3 hours, 17 grams of 4-anisyl-2,6-dimethyl-3,5-potassium dicarboxy pyridine was readily prepared in crystal form. After washing in 40 ml. of absolute ethyl alcohol and 40 ml. of ether and dried in a desiccator, the potassium dicarboxy pyridine was dry distilled in a gas furnace with 35 grams of soda lime for 7 hours.

The yield was 11 ml. of a distillate from which, on distilling under reduced pressure at 184[°] and 25mm gave 6 grams of 4-anisy1-2,6-dimethyl pyridine. A pictrate salt formed readily, melting point 149-151[°].

Anal. Calcd. for C14H15NO: N, 6.64%. Found: N, 6.69%.

(e) - The preparation of 2,6-dimethyl-3, 5-dichloromethyl pyridine.

Dry ammonia gas was passed through 50 grams of ethyl acetoacetate for 1.5 hours. The β -amino crotonic ester which readily formed was allowed to stand for 12 hours under refrigeration. After which time it was washed with ether twice and dried in a desiccator to obtain 43 grams as a yield.

25 ml. of formaldehyde solution (40%) was added to this amount in a 500 ml. beaker, kept cold by ice and salt. 8 ml. of 2 N hydrochloric acid was added with vigorous stirring. After recrystallization twice from 600 ml. of hot ethanol, 30 grams of 2,6-dimethyl-3,5-ethyl dicarboxy dihydro pyridine was obtained, melting point 144-145°.

15 grams were dissolved in 45 ml. of hot ethanol, through which was passed dinitrogen trioxide gas for 1.5 hours. Extrac-

-42-

tion with ether, washing with distilled water, drying with potassium carbonate, and distillation under reduced pressure to remove ether, gave a solid. The substance obtained was twice recrystallized from 150 ml. of ether to yield 12.1 grams of 2,6-dimethyl-3,5-dicarbethoxy pyridine, m.p. 72°.

5 ml. of a 10% solution of sodium ethoxide was prepared in a 50 ml. flask. .25 gram of these crystals was added and allowed to boil for one-half hour. After washing with ether and drying, the melting point of 329° was found by means of a melting block. This was in close agreement with the literature (43).

6 grams of lithium aluminum hydride were dissolved over a twelve hour period in 200 ml. of absolute ether in nitrogen atmosphere with constant heat. A one liter three neck flask, equipped with stirrer, nitrogen gas inlet and dropping funnel (combined) and reflex condensor, 400 ml. of absolute ether had been carefully prepared previously by drying commercial anhydrous ether with calcium chloride, decanting, treating with a very small quantity of lithium aluminum hydride (.5 gram per liter) and distilling.

10 grams of 2,6-dimethyl-3,5-dicarbethoxy pyridine, were readily dissolved in 100 ml. of absolute ether. This was added drop by drop over a one hour period to the reaction flask which was kept cold by dry ice. Constant stirring was employed using a mercury sealed stirrer.

After an interval of one-half hour, 20 ml. of distilled water was added in a similar manner over a one hour period.

-43-

Nitrogen gas was bubbling through at all times. The mixture was filtered, the filtrate retained, the residue returned to the flask, 100 ml. of methanol added, heated to boiling and filtered. The process was repeated.

The combined filtrates or extracts, after the removal of ether, methanol and much of the water by distillation at reduced pressure, were dried with anhydrous potassium carbonate. The remaining liquid was distilled at reduced pressure at $78^{\circ}/25$ mm to yield 4 ml. of a liquid which, after treating with hot methanol, yielded very fine crystals. These were twice recrystallized from hot methanol and charcoal.

A yield of 3.5 grams of 2,6-dimethyl-3,5-dihydroxymethyl pyridine was obtained, m.p. 135°. 4 ml. of thionyl chloride was distilled and added slowly to the 35 grams of the 2,6-dimethyl-3,5-dihydroxymethyl pyridine. 2,6-dimethyl-3,5-dichloromethyl pyridine, m.p. 163°, was obtained after the removal of liquid by oil vacuum pump and recrystallization from 10 ml. of ethanol.

Anal. Calcd. for C₉H₁₁NCl₂: N, 6.68%. Found: N, 6.83%.

A derivative was prepared from 2,6-dimethyl-3,5-didroxymethyl pyridine, 0.25 gram of which reacted with 0.75 gram of acetic anhydride and 0.25 gram of pyridine as an acid neutralizer to yield a solid suspended in a liquid.

The liquid part was removed by means of an oil vacuum pump. Two recrystallizations from hot benzene yield .25 gram of 2,6-dimethyl-3,5-diacetomethyl pyridine, m.p. 69⁰.

Anal. Calca. for C13H17NO4: N, 5.58%. Found: N, 5.71%.

-44-

IV. SUMMARY

(a) - Summary of experimental results.

- 1. 2,4,6 trimethyl pyridine; 4-propyl-2,6-dimethyl pyridine; 4-phenyl-2,6-dimethyl pyridine were prepared in fair yield using the Hantzsch pyridine synthesis.
- These were confirmed by comparing results obtained with literature data.
- 3. The synthesis of the following new compounds has been accomplished:
 - (a) 4-anisyl-2,6-dimethyl pyridine, thus extending the Hantzsch pyridine synthesis.
 - (b) 2,6-dimethyl-3,5-dichloromethyl pyridine by using

 a lithium hydride reduction followed by a chloride
 chlorination of 2,6-dimethyl-3,5-dicarbethoxy pyri dine.
 - (c) 2,6-dimethyl-3,5-diacetomethyl pyridine, a compound formed by the acetylation of 2,6-dimethyl-3,5-dihydroxymethyl pyridine, using acetic anhydride.

(b) - General summary.

1. - The Hantzsch pyridine synthesis was found to be one of the most successful condensation methods for the preparation of pyridine compounds with the general structure:



- 2. Lithium aluminum hydride was found to be most effective in the reduction of carbethoxy groups, giving hydroxymethyl compounds with ease from the carboxy esters used.
 3. - An account of the relative success of the procedures for synthesizing:
 - (a) 2,4,6 trimethyl pyridine.
 - (b) 4-phenyl-2,6-dimethyl pyridine.
 - (c) 4-propyl-2,6-dimethyl pyridine.
 - (d) 4-anisyl-2,6-dimethyl pyridine.
 - (e) 2,6-dimethyl-3,5-dichloromethyl pyridine.
 - (f) 2,6-dimethyl-3,5-diacetomethyl pyridine.

has been given.

(c) - Contribution to knowledge.

The synthesis of the following new organic compounds has been accomplished:

- 1. 4-anisyl-2,6-dimethyl pyridine.
- 2. 2,6-dimethyl-3,5-dihydroxymethyl pyridine.
- 3. 2,6-dimethyl-3,5-dichloromethyl pyridine.
- 4. 2,6-dimethyl-3,5-diacetomethyl pyridine.

-48-

.

.

BIBLIOGRAPHY

| 1. | Hantzsch, | Annalen, <u>215</u> , 1 (1882). |
|-----|-----------------------|--|
| 2. | Moore, | A History of Chemistry, 320 (1939). |
| 3. | Baeyer, C., | Berichte, <u>24</u> , 1662 (1891). |
| 4. | Knoevenagel, | Berichte, <u>31</u> , 738 (1898). |
| 5. | Bottinger, | Berichte, <u>10</u> , 362 (1877). |
| 6. | Baeyer, A., | Berichte, <u>2</u> , 398 (1869). |
| 7. | Wurtz, | Berichte, <u>8</u> , 1196 (1875). |
| 8. | Kramer, | Berichte, <u>3</u> , 257 (1870). |
| 9. | Ljubavin, | J. Russ, <u>5</u> , 339 (1886). |
| 10. | Dürkopf, | Berichte, <u>20</u> , 444,1660 (1887). |
| 11. | Chichibabin and Opari | na, J.Pract.Chem. (2), <u>107</u> , 138-145 (1924). |
| 12. | Gatterman, | Lab. Methods of Org. Chem. MacMillan Co., London, 352 (1932). |
| 13. | Hantzsch, | Berichte, <u>16</u> , 1946 (1883). |
| 14. | Michael, | Annalen, <u>225</u> , 121 (1884). |
| 15. | Kuekert, | Berichte, <u>18</u> , 620 (1885). |
| 16. | Hantzsch, | Berichte, <u>18</u> , 1774,2579 (1885). |
| 17. | Michael, | Berichte, <u>18</u> , 2020 (1885). |
| 18. | Epstein, | Annalen, <u>231</u> , 3 (1885). |
| 19. | Engelmann, | Annalen, <u>231</u> , 38,47,56 (1885). |
| 20. | D. R. P. | 42295, (1887). |
| 21. | Greiss and Harrow, | Berichte, <u>21</u> , 2740 (1888). |
| 22. | Knoevenagel, | Annalen, <u>281</u> , 74,77,95 (1899). |

•

.

| 23. | Schiff and Prosio, | Gazz, <u>25</u> , II, 65 (1895). |
|-------------|------------------------|---|
| 24. | Knoevenagel, | Berichte, <u>35</u> , 1791 (1902). |
| 25. | Ruhemann, | J. C. S. <u>83</u> , 377 (1903). |
| 26. | Knoevenagel, | Berichte, <u>36</u> , 2180-2190 (1903). |
| 27. | Henkel and Cremer, | J. C. S. <u>117</u> , 137 (1920). |
| 28. | Phillips and Randall, | U.S. patent, 2,359,329 (1949). |
| 29. | Heilbron, | J. C. S. <u>413</u> , (1943). |
| 30. | Guareschi, | Zentr, II, 280 (1899). |
| 31. | Knoevenagel, | Annalen, <u>288</u> , 348 (1895). |
| 32. | Meyer, | J.Pract.Chem. (2) 78, 497 (1908). |
| 33. | Meyer, | J.Pract.Chem. <u>92</u> , 174 (1915). |
| 34. | Finkolt, Bond, Schlesi | nger, A. C. J. S. <u>69</u> , 1199 (1947). |
| 35. | Nystrom and Brown, | A. C. J. S. <u>69</u> , 1197 (1947). |
| 36. | Jones, | A. C. J. S. <u>71</u> , 3994 (1949). |
| 37. | Brown and Cornfield, | Unpublished papers. |
| 38. | Panizoh, | Helv. Chim. Acta, <u>24E</u> , 24 (1941). |
| 39. | Ibita and Emoto, | Sci. Papers Inst. Phys. Chem. Research Tokio <u>38</u> , 347 (1940). |
| 40 . | Nystrom and Brown, | J. A. C. S. <u>70</u> , 3738 (1948). |
| 41. | Jaeckle, | Annalen, <u>246</u> , 32 (1888). |
| 42. | Mohr, Schneider, | J.Pract.Chem. <u>69</u> , 245 (1904). |