1.1 Introduction

The synthetic methods for the preparation of pyridine compounds utilize 1,5-diketones or potential 1,5-diketones. Hantzsch reaction\textsuperscript{1,2,3} describes widely the application of this general method of pyridine synthesis.

The classical Hantzsch synthesis for pyridine system is conducted with two moles of $\beta$-keto ester and one mole of aldehyde in the presence of ammonia to give dihydropyridine (1). The product formed can be oxidized readily with nitric acid to give pyridine derivative (2) (Scheme I).
The mechanism of this reaction is explained as shown in Scheme IIa or IIb.\textsuperscript{4}

\[ \text{CH}_3\text{COCH}_2\text{CO}_2\text{C}_2\text{H}_5 + RCHO \rightarrow \text{CH}_3\text{COC}(=\text{CHR})\text{CO}_2\text{C}_2\text{H}_5 + \text{H}_2\text{O} \]

\text{SCHEME IIa}
\[ \text{CH}_3\text{COCH}_2\text{CO}_2\text{C}_2\text{H}_5 + \text{NH}_3 \rightarrow \text{CH}_3\text{(}=\text{NH})\text{CH}_2\text{CO}_2\text{C}_2\text{H}_5 \]

\[ \text{CH}_3\text{C(NH}_2\text{)=CHCO}_2\text{C}_2\text{H}_5 \]

\[ \text{6} \]

\[ \text{6} + 4 \rightarrow \text{H}_5\text{C}_2\text{O}_2\text{C}-\text{CHC}-\text{CO}_2\text{C}_2\text{H}_5 \]

\[ \text{7} \]

\[ \text{H}_3\text{C}-\text{C}-\text{NH}_2 \]

\[ \text{H}_3\text{C}-\text{C}-\text{OH} \]

\[ \text{NH}_2 \]

\[ \text{CH}_3 \]

\[ \text{7} \]

\[ \text{1} \]

\[ \text{2} \]

\[ \text{SCHEME IIb} \]
It is evident that the proposed Scheme (IIa and IIb) for the reaction mechanism are same in principle, but they differ in the sequence of the assumed steps. According to Scheme IIa, an alkylidene (or arylidene) bisacetoacetic ester (5) is formed first, probably by the addition of a molecule of acetoacetic ester (3) to the carbon-carbon double bond of (4) through Michael condensation. The condensation of acetoacetic ester (3) with aldehyde in the presence of a basic catalyst to yield (4) is an example of a typical Knoevenagel condensation.

Aminolysis of alkylidene (or arylidene) bisacetoacetic ester (5) by ammonia itself or by substituted ammonia results in ring closure to form dihydropyridine (1).

In an alternative pathway, the formation of a partially ammonolyzed alkylidene (or arylidene) bisacetoacetic ester (7) by the addition of β-aminocrotonic ester (6) to the double bond of an alkylidene (or arylidene) acetoacetic ester (4) is assumed (Scheme IIb). The β-aminocrotonic ester (6) is formed by the reaction of ammonia with acetoacetic ester (3). The resulting compound (7) on heating is converted to dihydropyridine (1).
Although, the Hantzsch synthesis has been successfully carried out by heating β-aminocrotonic ester (6) with alkylidene (or arylidene) bisacetoacetic ester,\(^5\),\(^6\) however, several investigators\(^7\) have reported failure to prepare dihydropyridines by aminolysis of alkylidene (or arylidene) bisacetoacetic ester (Scheme IIa). Rabe and Elze\(^8\),\(^9\) have shown that (5) undergoes to intramolecular aldol condensation to form (8) according to Scheme III. Loss of water from aldol (8) gives a cyclohexene derivative as reported by Knoevenagel.\(^10\)

![Scheme III](image-url)
Knoevenagel has also found that the 1,5-diketone (5) in presence of ammonia, is converted into a cyclohexanolimine derivative (9) as the primary reaction product (Scheme IV).

![Chemical structure](image)

**Scheme IV**

Neither alkylidene (or arylidene) bisacetoacetic ester nor ammonolysed alkylidene (or arylidene) bisacetoacetic ester has been isolated from the reaction mixture. In short, the initial condensation in the reaction can occur in several ways, but in all case, the ring closure is in the final step.

A variety of the pyridine derivatives can be obtained by the Hantzsch synthesis employing appropriate substituted aldehydes and β-ketonic esters or 1,3-diketones.
These reactions follow the same general pattern as the original Hantzsch synthesis and may conveniently be considered as its modifications.

When methylene bisacetylacetone (10) obtained by condensation of formaldehyde with acetylacetone is treated with ammonia, 3,5-diacetyl-1,4-dihydrolutidine (11) is formed\textsuperscript{12,13} (Scheme V). Starting with the methenyl bisacetylacetone, (-CH= instead of -CH\textsubscript{2} in formula (10)), pyridine compound is produced directly.\textsuperscript{14,15}
Haley and Maitland\textsuperscript{16} have synthesized 3,4-diacetyl
dihydrocollidine from acetaldehyde, acetylacetone and
ammonia in aqueous buffer (pH 5.5 to 9.3). Though, this
reaction shown in Scheme IIa and IIb are base catalyzed,
it takes place in acidic as well as in alkaline medium.\textsuperscript{16}

1.2 Application of Hantzsch Reaction

(i) Determination of formaldehyde

Nash\textsuperscript{17} has reported the formation of a yellow
colored product when formaldehyde is reacted with acetyl-
acetone in the presence of ammonium salt. The reaction
product has been identified as 3,5-diacetyl-1,4-
dihydrolutidine (11) (Scheme V). The color reaction
forms a basis of spectrophotometric estimation of
formaldehyde.\textsuperscript{18} The reaction product has maximum
absorbance at 412 nm.

The aqueous solution of 3,5-diacetyl-1,4-
dihydrolutidine gives green fluorescence under ultra-
violet light. This observation is utilized by Belman\textsuperscript{19}
to develop a fluorimetric method for the determination
of formaldehyde. The fluorescence excitation and
emission spectral maxima are at 410nm and 510nm,
respectively.
The dipolar structure (12) is suggested by Nash\(^{18}\) for 3,5-diacetyl-1,4-dihydrolutidine based on its insolubility in ether, its high melting point and the negligible effect of pH (4.0 to 10.0) on the absorption spectra. In dilute solution, the strong yellow color and fluorescence also support this structure. The structure (12) is stabilized by resonance with the equivalent structure (13).
The infrared data\textsuperscript{19} and other properties of 3,5-diacetyl-1,4-dihydrolutididine strongly suggest that the structure (12) predominates in dilute solution and that the dimer (14) or higher aggregates, mainly exists in concentrated solution and in solid form.
(ii) Detection of Ammonia

Belman\textsuperscript{19} has detected ammonia with modified reagent using fluorimetric procedure. When traces of ammonia are added to a mixture of sodium acetate pH 6, acetylacetone and formaldehyde, yellow color develops gradually due to the production of 3,5-diacetyl-1,4-dihydrolutidine having a excitation and emission maxima at 410\text{n}m and 510\text{n}m respectively.

However, the reaction has not been exploited fully for the spectrophotometric determination of ammonia.