SYNTHESIS IN THE PYRIDINE SERIES

Part I   The Synthesis of New 3,4,5-Trialkylated Pyridines

Part II The Synthesis of New 3,5-Dimethyl-4-Substituted
         Pyridines. Steric Effects as an Aid to Synthesis

by

TAKAO TABATA

B.Sc., The University of British Columbia, 1960

A THESIS SUBMITTED IN PARTIAL FULFILMENT OF

THE REQUIREMENTS FOR THE DEGREE OF

MASTER OF SCIENCE

in the Department

of

Chemistry

We accept this thesis as conforming to the

required standard

THE UNIVERSITY OF BRITISH COLUMBIA

September, 1962

In presenting this thesis in partial fulfilment of

the requirements for an advanced degree at the University of

British Columbia, I agree that the Library shall make it freely

available for reference and study. I further agree that permission

for extensive copying of this thesis for scholarly purposes may be

granted by the Head of my Department or by his representatives.

It is understood that copying or publication of this thesis for

financial gain shall not be allowed without my written permission.

Department of _Chemistry_

The University of British Columbia,
Vancouver 8, Canada.

Date _Aug 22, 1962_

ABSTRACT

PART I

A synthetic sequence leading to new and inaccessible 3,4,5-trialkylated pyridines has been developed. 3,4-Dimethyl-5-cyanopyridine was converted to 3,4-dimethyl-5-acetylpyridine on treatment with methylmagnesium iodide and the acetylpyridine was subsequently treated with ethylmagnesium iodide to yield 3,4-dimethyl-5(2-hydroxy-2-butyl)pyridine. Removal of the hydroxyl group was accomplished by means of red phosphorus and hydriodic acid and the resulting olefinic compounds were catalytically hydrogenated to 3,4-dimethyl-5-s-butylpyridine.

For further studies in this area, 3,4-dimethyl-5-acetylpyridine was reduced to 3,4-dimethyl-5-ethylpyridine by the Wolff-Kishner reaction and the latter was condensed with benzaldehyde to afford 3-methyl-4-styryl-5-ethylpyridine. This, on ozonolysis, was converted to 3-methyl-5-ethyl isonicotinic acid which was subsequently methylated with diazomethane to methyl 3-methyl-5-ethyl-4-pyridinecarboxylate.

The nature of the synthesis allows the preparation

of virtually any type of 3,4,5-trialkylated pyridine by straightforward variations at the appropriate stage.

PART II

In relation to Part I, the synthesis of 3,5-dimethyl-4-substituted pyridines was undertaken. 3,5-Lutidine was reacted with acetic anhydride and zinc to afford in good yield the unexpected 3,5-dimethyl-4-acetyl-pyridine. This was then conveniently converted to 3,5-dimethyl-5-ethylpyridine on reduction with acetic acid and zinc thereby confirming the structure of the acetylpyridine. The acetylpyridine was also reduced with lithium aluminum hydride to 3,5-dimethyl-4-(1-hydroxyethyl)pyridine which in turn was readily dehydrated with phosphorus pentoxide to 3,5-dimethyl-4-vinylpyridine. Both the hydroxypyridine and the vinylpyridine on treatment with hydrobromic acid yielded 3,5-dimethyl-4(2-bromoethyl)-pyridine hydrobromide. This was then converted to 3,5-dimethyl-4(2-cyanoethyl)pyridine.

The preparation of these compounds was possible due to the utilization of the steric effects enforced by the two neighbouring methyl groups at the 3 and 5 positions of the pyridine ring.

This sequence of reactions provides a valuable method by which 3,5-dimethyl-4-substituted pyridines can

be synthesized owing to the availability of the starting material and to the relatively high yielding reactions.

ACKNOWLEDGEMENTS

TABLE OF CONTENTS

List of Figures

PART I

THE SYNTHESIS OF NEW 3,4,5-TRIALKYLATED PYRIDINES

INTRODUCTION

In connection with the structural elucidation of a new alkaloid, skytanthine, (1,2) isolated from a Chilean plant, Skytanthus acutus Meyen, it became necessary to consider the identity of several 3,4,5-trialkylated pyridine derivatives. The particular compounds which were necessary for study were the two possible dimethylisopropylpyridines, namely, 3,4-dimethyl-5-isopropylpyridine and 3,5-dimethyl-4-isopropylpyridine. Investigation of the literature revealed however, that 3,4,5-trialkylated pyridines were not readily available and especially pyridines of this type possessing even the simplest branched chains were unknown. Hence investigation toward the synthesis of these trialkylated pyridines were undertaken.

Apart from the fact that 3,4,5-trialkylated pyridines were not readily synthesized except for the simple alkylated pyridines (3,4,5,6,7), perusal of the literature also revealed that these compounds were not commonly found in nature. In this connection, Tsuda, Mishima, and Maruyama (8) and Arnall (9) have reported the isolation of 3,4,5-trimethylpyridine from coal tar bases and this is the only compound of this type shown to exist in nature.

In order to facilitate the identification of
this collidine from amongst the many polymethylated
pyridine constituents in coal tar, Tsuda and his co-
workers (8) prepared 3,4,5-trimethylpyridine from γ-cyano-α,
β,γ-trimethylglutaconate as shown by the following sequence
of reactions (Figure 1). The method, however, was applied
with increasing difficulty to the synthesis of such higher
straight chain alkylated homologues as 3-ethyl-4,5-
dimethylpyridine and 3,5-diethyl-4-methylpyridine (6).
This method utilized by Bailey and Brunskill was merely a
modification of a previously established synthetic sequence
leading to the closely related substance, γ-cyano-α,β,γ-
trimethylglutaconate. This latter substance was converted
to 3,4,5-trimethyl-2,6-dihydroxypyridine as reported by
Rogerson and Thorpe (8,10). The original sequence of
reactions is represented by figure 2.

It was apparent therefore that replacement of the
methyl iodide by the appropriate alkyl iodide in one of
the above alkylation steps could conceivably lead to the
required modification. Hence Bailey and Brunskill (6)
prepared α,β,γ-trialkylglutaconates (I,R=CH$_3$,R'=C$_2$H$_5$;
R=R'=C$_2$H$_5$) by alkylating the crude potassium derivative of
the products formed by condensing ethyl cyanoacetate and
ethyl acetoacetate. An attempt to obtain the potassium
derivative of the α-ethyl-β-methyl ester (I,R=C$_2$H$_5$,R'=H)
by condensing ethyl α-acetobutyrate with ethyl cyanoacetate
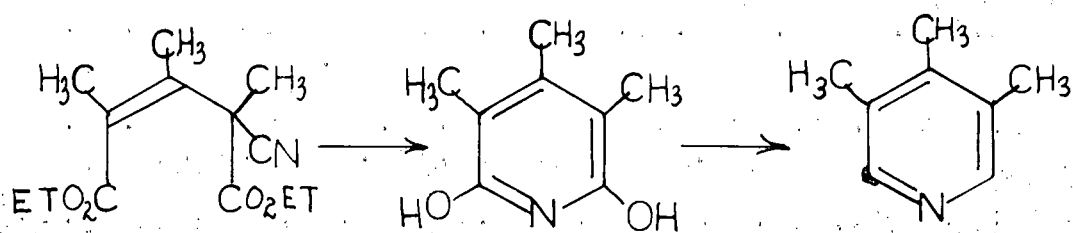
Figure 1. Preparation of 3,4,5-collidine from diethyl
γ-cyano-α,β,γ-trimethylglutaconate by Gouda et al

I, R = R' = CH₃

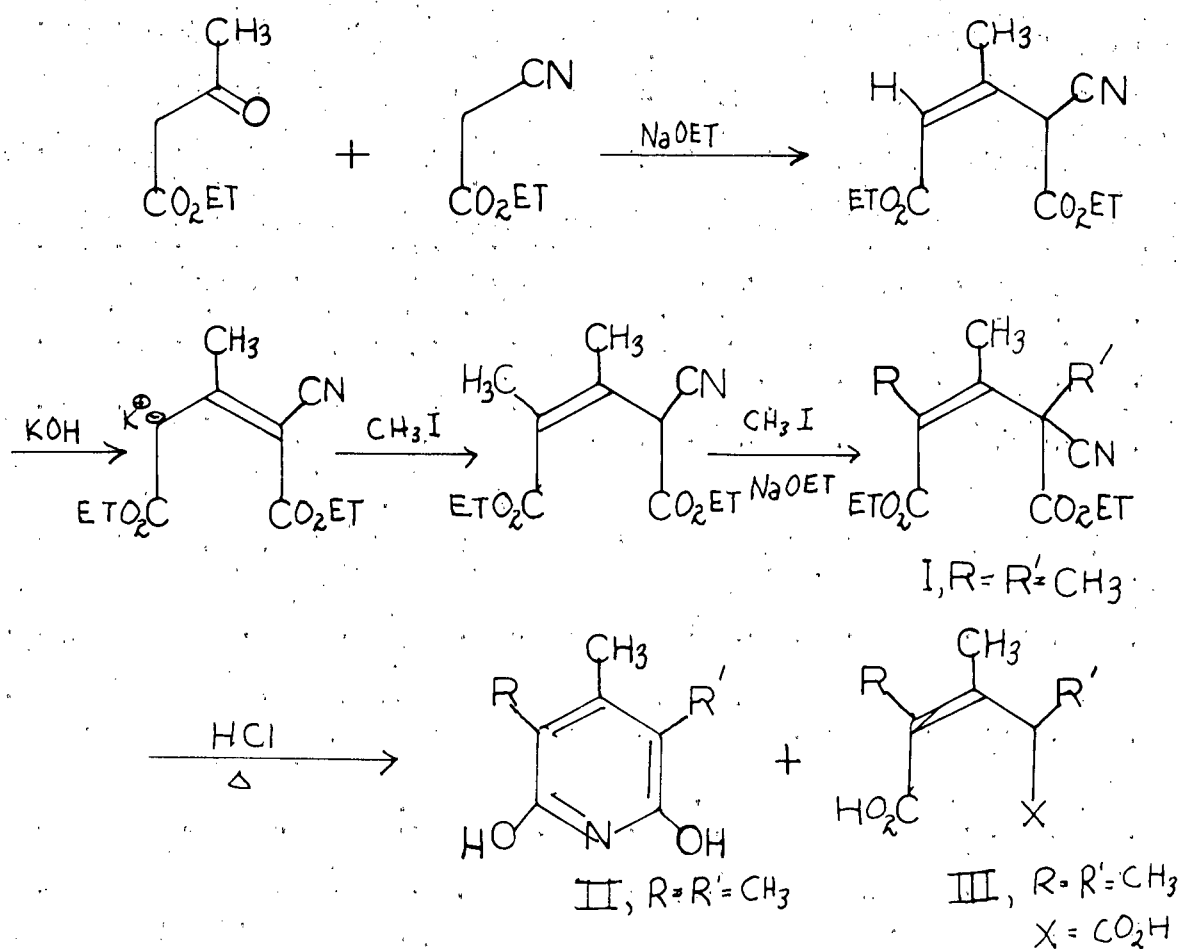II, R = R' = CH₃

III, R = R' = CH₃
X = CO₂H

Figure 2. Rogerson and Thorpe's original preparation of
glutaconates and the subsequent cyclization
products

was unsuccessful (6,10) although a similar preparation of the α,β-dimethyl analogue (I,R=CH$_3$,R'=H) had been previously described (6,11,12). Ethyl propionylacetate also failed to condense in the same manner with cyanoacetate so that this preparative approach was applicable only to the synthesis of 4-methylated homologues.

Furthermore, significant quantities of crotonic esters were isolated in the preparation of the trialky-cyanoglutaconic esters (III,X=CN) but only small quantities of the expected trialkylated esters were obtained (6,10,13). This was particularly true when the alkyl group represented by R was an ethyl group. The cyclization of the crotonates also furnished a very low yield of the key intermediate compound II. It was therefore obvious that this method could not be utilized to prepare any of the 3,4,5-trialkylated pyridines which were necessary for our work.

Another group of workers, Vaculik and Kuthan (7) have contributed to this field but once again the synthetic method for the preparation of 3,4,5-trialkylated pyridines has been restricted to the preparation of symmetrically substituted pyridines possessing only the straight chain alkyl groups (Figure 3).

The symmetrically substituted base (IV) was prepared by condensation of α,α'-dimethyl acetone

dicarboxylic acid ethyl ester with formaldehyde and benzylamine and converted to 1-benzyl-3,5-dimethyl-4-piperidone (V) via a keto ester cleavage. This compound, on treatment with the Grignard reagent gave the corresponding tertiary alcohol (VI) which on catalytic dehydrogenation yielded the 3,5-dimethyl-4-alkylpyridine (VII). It is noticeable here that this synthetic scheme, due to the nature of its starting material, can lead only to symmetrical and simple alkylation.

The synthesis of 3,4-dimethyl-5-isopropylpyridine reported by Kutney and Selby (2) represents the first successful preparation of a branched chain 3,4,5-trialkylated pyridine. Before the successful method which did provide the difficultly accessible pyridine is discussed it is of some interest to elaborate on the previous work leading to their success since it does indicate some of the difficulties encountered in the synthesis of alkylated pyridines of this type.

The first consideration to synthesize the unsymmetrical dimethylisopropylpyridine was an endeavour to prepare the appropriate diethyl isopropyl glutaconate (Figure 2). This method was unsuccessful in that the introduction of the third alkyl group resulted in the isolation of undesirable low boiling esters. Similar difficulties in preparing the higher trialkylcyanoglutaconates have been encountered by other workers (6).
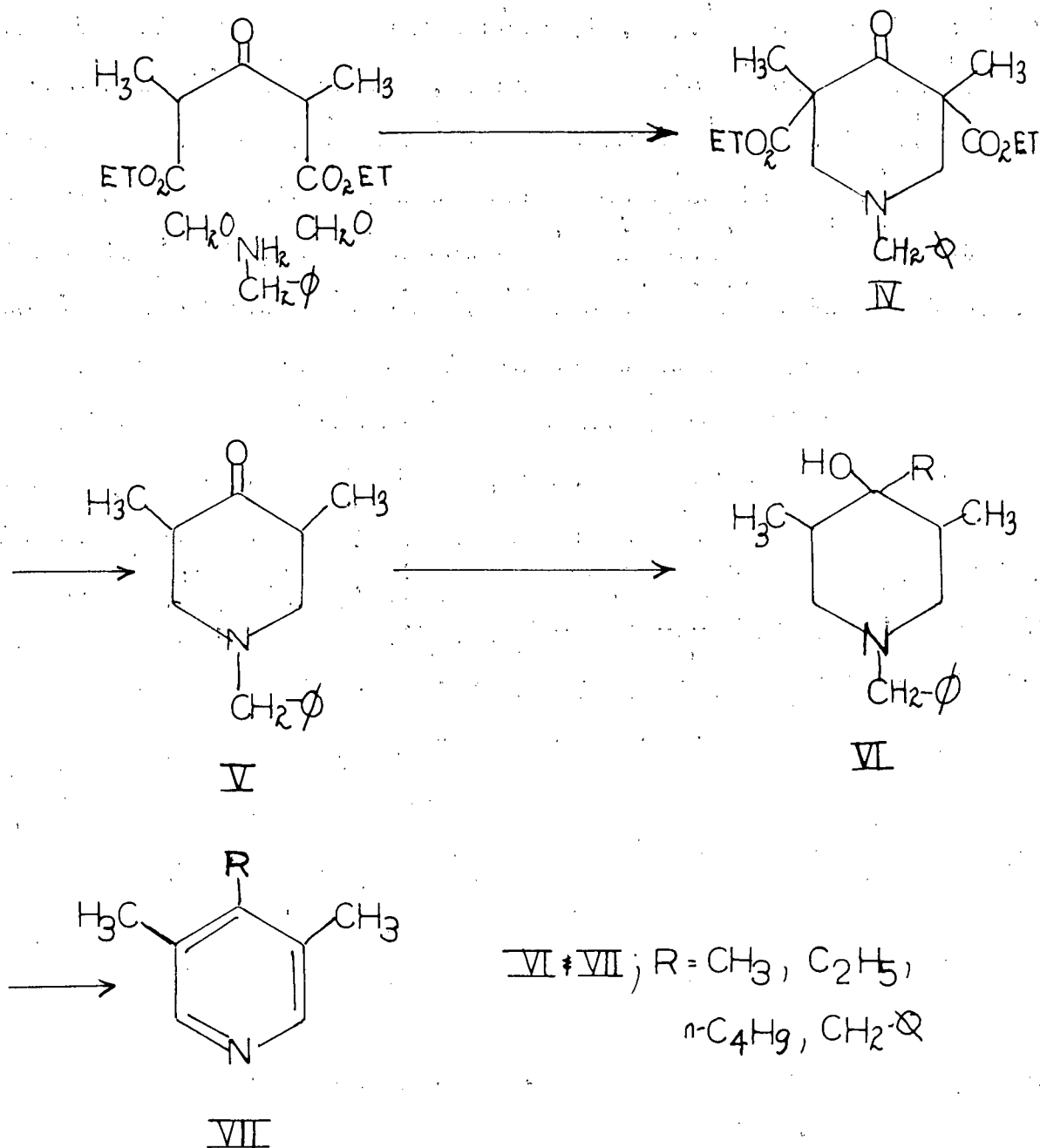
Figure 3. Preparation of 3,5-dimethyl-4-alkylpyridines by Vaculik and Kuthan

Consideration of another synthetic path however led to the desirable 3,4-dimethyl-5-isopropylpyridine. This synthetic sequence in fact provided a general approach to new and otherwise difficultly accessible 3,4,5-trialkylated pyridines (Figure 4).

The initial starting point of the synthesis was the preparation of 5-cyano-2,6-dihydroxy-3,4-dimethyl-pyridine (VIII), a compound which had been previously reported by Guareschi (14). The Guareschi-type cyclization had also been employed in several other cases by Ruzicka (15), Hope (12) and Bobbit (16). A simple modification of the previous sequences permitted the preparation of the desirable dihydroxy compound (VIII). The preparation of 5-cyano-3,4-dimethylpyridine (IX) provided a versatile intermediate which was easily converted to the pyridine carboxylate (X). Reaction of (X) with methylmagnesium iodide allowed the preparation of the tertiary alcohol (XI) which in turn was transformed to 3,4-dimethyl-5-isopropyl-pyridine (XII).

With this achievement, 5-cyano-3,4-dimethyl-pyridine became a valuable intermediate for the synthesis of various types of new and otherwise difficultly accessible 3,4,5-trialkylated derivatives. Since numerous modifications of the cyano function were apparent, the compound lent itself to a rather general approach to pyridines of
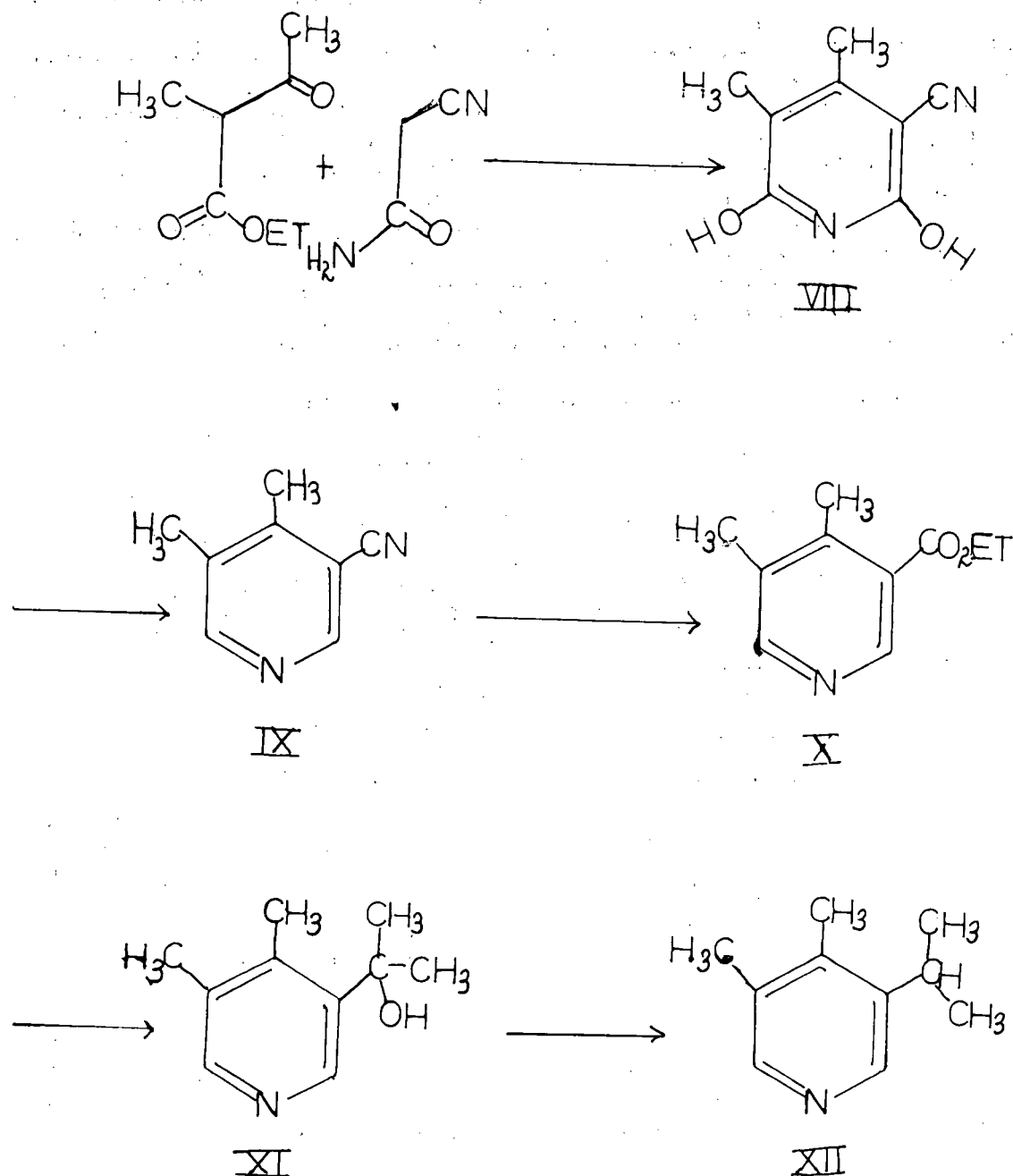
8

Figure 4. Synthesis of 3,4-dimethyl-5-isopropylpyridine from 5-cyano-3,4-dimethylpyridine by Kutney and Selby

the type mentioned above (Figures 1,2,3,4). Some results
supporting this view are described in this part of the
thesis.

DISCUSSION

There are numerous possible modifications of the
cyano group and it was already indicated that conversion
of this group to an ester function provides an intermediate
for the preparation of pyridines of type A (Figure 5). In
order to provide an entry into another series of branched
chain pyridines (type B), 3,4-dimethyl-5-cyanopyridine XIII
was reacted with methylmagnesium iodide to afford 3,4-
dimethyl-5-acetylpyridine (XIV). The success of this
reaction was clearly shown by the infrared spectrum of the
product, which indicated the disappearance of the cyano
function (4.43μ) and the appearance of a strong carbonyl
absorption at 5.94μ. This acetylpyridine was then treated
with ethylmagnesium iodide to yield the expected alcohol
(XV) as a light viscous liquid. This substance however
resisted all attempts to crystallize - a rather unusual
behaviour since an analogous substance, 3,4-dimethyl-5-
(2-hydroxy-2-propyl)-pyridine, previously prepared by us,
was crystalline. The infrared spectrum of this compound
showed the usual intense and broad hydroxyl band at
2.95μ-3.30μ and the N.M.R. spectrum here was very infor-
mative. The presence of a triplet at high field (9.22τ)
indicated a methyl group flanked by a methylene carbon which

in turn was split into a quartet at 8.16τ. Another
absorption at 8.50τ was assigned to the tertiary methyl
group attached to an oxygen bearing carbon and a singlet
at 4.60τ was attributed to the hydroxyl proton. The
remaining signals at 7.85τ and 7.58τ were characteristic
of methyl groups attached to the pyridine nucleus (2) and
a doublet at low applied magnetic field (2.08τ) was
assigned to the two α protons of the pyridine ring. These
signals clearly indicate that an unsymmetrical substitution
of the ring at 3,4, and 5 positions was present, thus con-
clusively establishing the structure of the alcohol (XV).

The removal of a hydroxyl function of this type
has been successfully accomplished by previous workers by
means of red phosphorus and hydriodic acid and this reaction
has been frequently employed in the pyridine series (2,18,
19). Consequently the utilization of this method was
attempted in this series. However, in contrast to the
successful conversion of 3,4-dimethyl-5-(2-hydroxy-2-propyl)-
pyridine to 3,4-dimethyl-5-isopropylpyridine by conducting
the reaction at the reflux temperature for 24 hours, the
corresponding conversion of XV to the desired 3,4-dimethyl-
5-s-butylpyridine (XVII) did not proceed to completion.
Even under more stringent conditions (48 hrs. reflux) the
product of the reaction still contained a mixture of the
desirable compound, XVII, and the olefinic substances XVI.
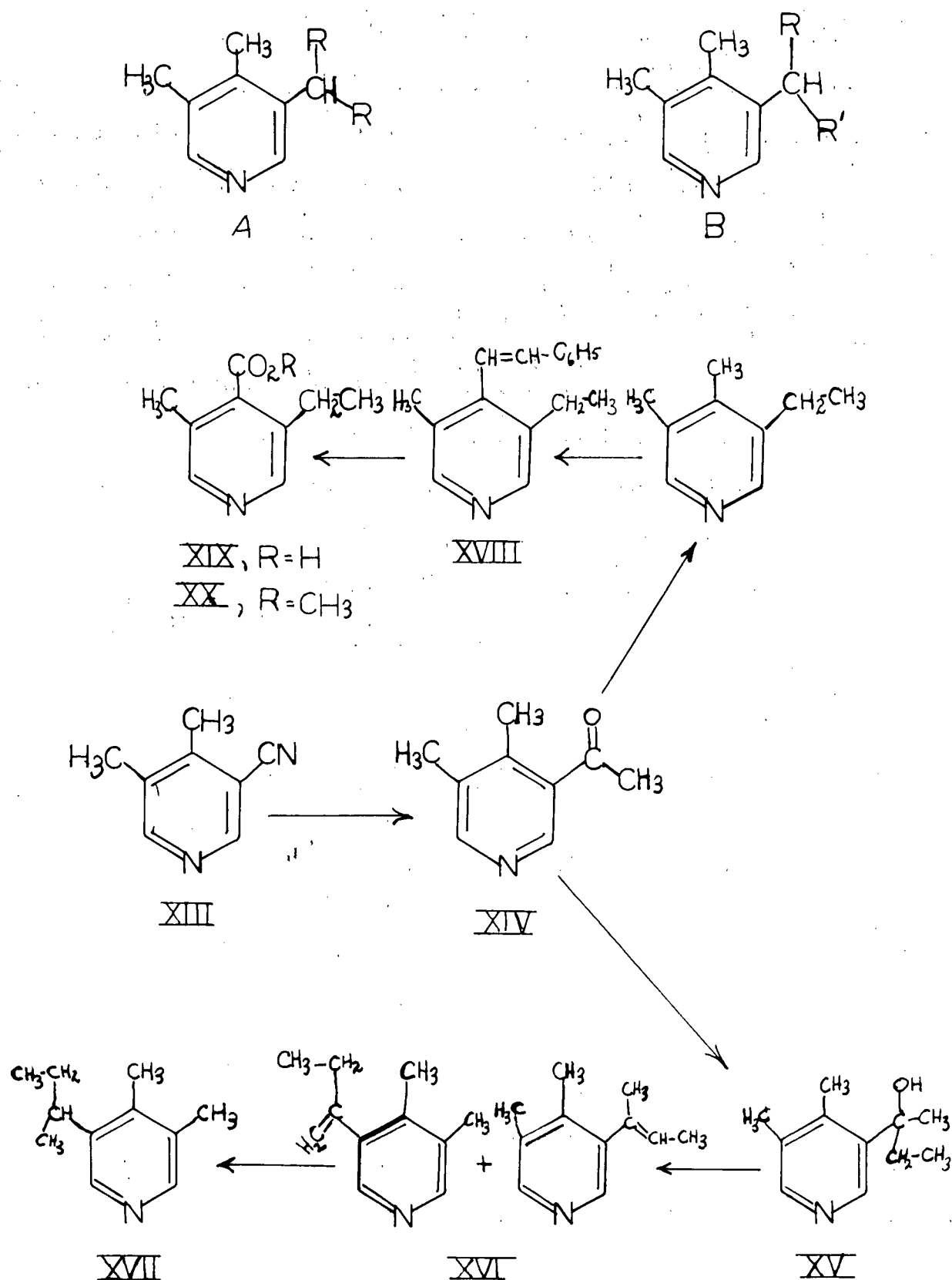
Figure 5. Synthesis of new 3,4,5-trialkylated pyridines from 5-cyano-3,4-dimethylpyridine

The greater resistance of the olefinic bonds to reduction was further exemplified by hydrogenation studies. When hydrogenation of XVI was performed under similar conditions used to reduce the corresponding 3,4-dimethyl-5-isopropenylpyridine, (Adams catalyst, atmospheric pressure, room temperature) incomplete reduction was still observed, as indicated by the olefinic signals in the N.M.R. spectrum. Nevertheless, the desired compound, XVII, was obtained under more drastic reaction conditions (Adams catalyst, 32 psi). The ultraviolet spectrum was characteristic of an alkylated pyridine and the N.M.R. spectrum provided strong support for the structure. The successful completion of this sequence now allows the preparation of virtually any type of trialkylated pyridine possessing branched alkyl chains at the 3 position.

It has been recently reported that steric effects of substituents attached to carbon atoms 3 and 5 on the pyridine ring appeared to play an important role in influencing the course of reaction of functional groups at the 4-position of the pyridine ring. For example, Kutney and Selby (2) have found that 3,5-dimethyl-4-acetylpyridine possessed a very unreactive carbonyl function that resisted reaction under various conditions to organometallic reagents. This factor, must be attributed, at least in part, to the steric influence of the two neighbouring

methyl groups. In hope of obtaining more information as to

the steric effects of the substituents at the 3 and 5-

positions on the reactivity of alkyl groups at the 4-

position, an aldol-type condensation reaction of 3,4-

dimethyl-5-ethylpyridine with benzaldehyde was considered.

This type of reaction has been well utilized in pyridine

chemistry on numerous occasions and has proven to be of

considerable synthetic value (22, p. 200).

For the preparation of 3,4-dimethyl-5-ethylpyri-

dine, a direct reduction of the acetyl function to the

ethyl group was then considered. The most convenient method

for this conversion appeared to be the Wolff-Kishner

reaction since this procedure has been frequently employed

in the pyridine series (20). When 3,4-dimethyl-5-acetyl-

pyridine was reduced under the Huang-Minlon modification of

the Wolff-Kishner reaction (20), the expected 3,4-dimethyl-

5-ethylpyridine was obtained. The N.M.R. spectrum was in

complete agreement with the assignment of the structure in

that it indicated a triplet at high field (8.84τ) and a

quartet at (7.42τ) providing strong support for an ethyl

group. The remaining signal at 7.86τ was readily attributed

to the methyl protons of carbons attached to the pyridine

ring and the weak signal at low field (1.96τ) was typical

of α-protons on the pyridine nucleus.

Now, when the ethylpyridine was reacted with

benzaldehyde, under rather drastic conditions, the
corresponding 3-methyl-4-styryl-5-ethylpyridine XVIII was
obtained in a reasonable yield. The success of this
reaction was clearly evident from spectroscopic consider-
ations. The infrared spectrum indicated that a new olefinic
bond had been formed (6.12μ) and the N.M.R. spectrum cer-
tainly supported this evidence. The olefinic proton region
exhibited a characteristic AB splitting pattern with a
separation of 17cps, suggesting a trans orientation of the
olefinic bond. The characteristic signals for the ethyl
group were still present, and more importantly, the intense
signal due to the methyl groups attached to the 3- and 4-
positions of the pyridine ring in the starting material was
significantly reduced and consistent with the presence of
only one methyl group. The presence of the aromatic
signals due to the styryl moiety and the α protons served
to further confirm the 4-styrylpyridine structure. The
ultraviolet spectrum, on the other hand, was considerably
different from the spectra reported previously for com-
pounds of this type (23,24). The main absorption at 278mμ
represented a relatively small bathochromic shift from the
usual alkylpyridine absorption (263-268mμ) but this absor-
ption is considerably lower than that of 4-styrylpyridine
(307mμ) and the intensity is significantly less. This
anomolous spectrum can be due to the fact that the alkyl
substituents at the 3 and 5 positions cause the styryl

moiety to lie out of the plane of the pyridine ring thereby reducing the extended conjugation. The fact that the yield was somewhat lower in this case than that already reported in the other series (25), gives some support to the view that the 4-methyl group is somewhat hindered although it is still capable of entering into condensation reactions with carbonyl compounds.

The isolation of 3-methyl-4-styryl-5-ethylpyridine from the condensation reaction proved to be very useful in providing a synthetic intermediate for the synthesis of pyridine derivatives having different functions at the 4-position. Hence several methods to transform the linkage to a carboxyl function were considered. This type of reaction has been extensively employed in pyridine chemistry for the synthesis of pyridine aldehydes and carboxylic acids (5,p.207). Because methods such as nitric acid oxidation (26) and permanganate oxidation (27) were not too attractive, the reaction of choice involved ozonolysis. When 3-methyl-4-styryl-5-ethylpyridine was subjected to this reaction the expected 3-methyl-5-ethyl isonicotinic acid (XIX) was obtained as a high melting crystalline compound. Recently the ozonolysis of vinyl-pyridines has been shown to give pyridine carboxylic acids under analogous conditions (28).

The isolation of this pyridine carboxylic acid in

turn furnished a substance with a versatile functional group at the 4-position of the pyridine ring. Hence attempts were made to esterify the carboxylic acid. After the usual types of acid-catalysed esterification procedure (29,30) failed, an equally attractive method was tried. The pyridine carboxylic acid on treatment with an ethereal solution of diazomethane afforded the expected methyl ester (XX). Apart from the expected ultra violet and the infrared spectrum, the consideration of the N.M.R. spectrum proved to establish beyond any doubt, the structure of this ester. The characteristic ethyl and methyl groups attached to the pyridine nucleus were clearly evident and the appearance of a sharp signal at 6.17τ due to the methyl group of the ester function was observed.

CONCLUSION

In conclusion, these studies discussed in this part have provided intermediates which can be utilized to prepare any type of 3,4,5-trialkylated pyridines. Firstly, it is obvious that any Grignard reaction on 3,4-dimethyl-5-cyanopyridine, followed by the appropriate steps, provides numerous variation to the type of groups attached to C_5. Secondly, the appropriate ester analagous to XX provides entry into various possibilities at C_4, and finally the nature of the alkyl group at C_3 can be varied. It is pertinent to note that in the original Guareschi cyclization, which provides the starting material for this work, the nature of the alkyl group at C_3 is determined by the nature of the acetoacetic ester molecule used in the cyclization. Consequently appropriate variations in the synthetic sequence will yield numerous new and otherwise difficultly accessible 3,4,5-trialkylated pyridines.

EXPERIMENTAL

All melting points were determined on a Fischer-Johns apparatus and are uncorrected. The ultraviolet spectra were recorded in 95% ethanol on a Cary 14 recording spectrophotometer. Infrared spectra were recorded on a Perkin-Elmer model 21 spectrophotometer. The N.M.R. spectra were taken at 60 Mc on a Varian A60 instrument. In all cases integration of areas under the signals was carried out and the number of protons corresponding to each signal is indicated in parentheses. Values are given in the Tiers τ scale with tetramethylsilane used as the external standard, set at 10.0 τ units. The solvent used was carbon tetrachloride. The analyses were performed by Dr. A. Bernhardt and his associates, Mulheim (Ruhr), Germany, and by Mrs. A. Aldridge, University of British Columbia.

3,4-Dimethyl-5-acetylpyridine (XIV)

A solution of 3,4-dimethyl-5-cyanopyridine (XIII 22.2g) in anhydrous ether (350 ml) was added slowly to a stirred solution of methylmagnesium iodide, prepared in the usual manner (48.5 g Mg, 385 g methyl iodide) in dry ether (630 ml). After the addition was complete, the

reaction mixture was refluxed for 4 hours and then allowed
to stand overnight at room temperature. The excess
Grignard and the complex were destroyed by the addition
of dilute ammonia until there was no further reaction. The
resulting mixture was saturated with sodium chloride and
extracted exhaustively with ether. The ether extract was
dried over anhydrous magnesium sulphate and the solvent
evaporated to yield a liquid product. Distillation of this
material at a bath temperature of 120-130° at 2.5 mm pro-
vided a clear liquid product (10.9 g). This material was
suitable for subsequent reactions although it contained
traces of the starting cyano compound, which was very
difficult to remove by distillation.

Chromatography of a small portion (3.8 g) of this
liquid on alumina (250 g) provided a good separation.
Elution with petroleum ether - ethyl ether (4:1) yielded a
mixture of the acetylpyridine and the cyanopyridine in the
initial fractions, and then the pure 3,4-dimethyl-5-
acetylpyridine (1.2 g) was obtained in the later fractions.
Elution with pure ether removed the remaining material.

An analytical sample of the acetylpyridine
distilled at 144° at 22 mm; n_D^{20} 1.4166; infrared: 5.94 μ;
ultraviolet: λ_{max} 231 mμ (logε=3.73), λ_{max} 271 mμ
(logε=3.40), λ_{min} 254 mμ (logε=3.24). Found: C, 72.43;
H, 7.38; O, 10.74; N, 9.39. Calc. for $C_9H_{11}ON$: C, 72.45;

H, 7.43; O, 10.72; N, 9.39.

A picrate, m.p. 162-163°, was prepared in ethanol and recrystallized several times from ethanol. Found: C, 47.82; H, 3.81; O, 33.52; N, 14.90. Calc. for $C_{15}H_{14}O_8N_4$: C, 47.62; H, 3.73; O, 33.84; N, 14.81.

3,4-Dimethyl-5-(2-hydroxy-2-butyl)-pyridine (XV)

A solution of 3,4-dimethyl-5-acetylpyridine (0.81 g) in anhydrous ether (14 ml) was added slowly to a stirred solution of ethylmagnesium iodide (1.8 ml ethyl iodide, 0.52 g Mg turnings) in ether (20 ml). After the addition was complete, the reaction mixture was refluxed for 12 hours and then allowed to stand overnight at room temperature. The mixture was cautiously treated with dilute ammonia and the resulting basic mixture was saturated with solium chloride. The reaction mixture was then extracted several times with ether and the ethereal layer dried over anhydrous magnesium sulphate. Removal of the solvent yielded a viscous liquid (1.07 g). This material was taken up in a small amount of chloroform and placed on a column of alumina (100 g). Elution with petroleum ether – ethyl ether (9:1) yielded traces of the starting material. Further elution with ethyl ether and chloroform provided the desired alcohol (XV, 0.54 g). A small portion of this material was distilled to yield the analytical sample of the alcohol, as a light yellow viscous liquid

(b.p. 144° at .01 mm); infrared: 2.95-3.2 μ, very broad; ultraviolet: λ_{max} 263 mμ (log ϵ = 3.36), λ_{max} 271 mμ (log ϵ = 3.30), λ_{min} 236 mμ (log ϵ = 2.83); N.M.R. signals: triplet centered at 9.22 τ (methyl of ethyl group, area = 3H), 8.5 τ (CH_3-C-OH, area = 3H), quartet centered at 8.16 τ (methylene of CH_3CH_2-C-OH), 7.85; 7.58 τ (methyls attached to ring, area = 6H), 4.6 τ (OH, area $\cong$ 1H), doublet centered at 2.08 τ (α H, area = 2H). Found: C, 73.37; H, 9.40; O, 9.11; N, 8.27. Calc. for $C_{11}H_{17}ON$: C, 73.70; H, 9.56; O, 8.93; N, 7.81.

The picrate, prepared in the usual manner, was recrystallized several times from ethanol to yield an analytical sample which melted at 136-137.5°. Found: C, 50.32; H, 4.40; O, 31.22; N, 13.73. Calc. for $C_{17}H_{20}O_8N_4$: C, 50.00; H, 4.84; O, 31.34; N, 13.72.

Subsequent preparations of this alcohol were carried out very conveniently from the acetylpyridine without careful purification of the intermediates. That is, the crude product from the reaction of 3,4-dimethyl-5-cyanopyridine and methylmagnesium iodide was treated directly with ethylmagnesium iodide and this product chromatographed as above. An overall yield of 27% of the pure alcohol was obtained.

3,4-Dimethyl-5-s-butylpyridine (XVII)

A mixture of 5-(2-hydroxy-2-butyl)-3,4-

dimethylpyridine (0.85 g), concentrated hydriodic acid
(9.3 ml, 47%), and red phosphorus (1.1 g) was refluxed for
24 hours. After the mixture had been cooled, the phos-
phorus was removed by filtration and the filtrate con-
centrated by distillation in vacuo. The dark residual oil
was taken up in water (6 ml) and decolorized by the addition
of sodium bisulphite. The mixture was made alkaline by the
addition of potassium hydroxide pellets and the alkaline
mixture was then extracted thoroughly with ether. After
the ethereal extract had been dried over anhydrous sodium
sulphate, the solvent was removed and the residual liquid
was distilled using a bath temperature of 60-100° at 0.07 mm.
The yield of the colorless liquid product was 478 mg. This
product was a mixture of the desired material and some
olefin resulting from incomplete reduction (N.M.R. signal
at 4.5 τ). This olefinic material was present in small
quantities even if the reflux period was increased to 48
hours. Consequently, it was found most convenient to carry
out the reduction under catalytic hydrogenation conditions.
A portion of the distilled liquid product (102 mg) was
dissolved in glacial acetic acid (14 ml) and catalytically
hydrogenated over Adam's catalyst (100 mg) at room temper-
ature with a hydrogen pressure of 32 p.s.i. After 5 hours,
the catalyst was filtered and the solvent removed on a
steam bath in vacuo. The residue was treated with water
(3 ml), and made alkaline by the addition of sodium
bicarbonate and the resulting mixture was extracted

exhaustively with ether. After the ethereal extract had been dried over anhydrous magnesium sulphate, the solvent was removed and the residual liquid distilled at 60-70° (bath temp.) at 0.05 mm to provide 73 mg of a pure liquid. A small portion was redistilled for an analytical sample (b.p. 135° at 22 mm); n_D^{20} 1.5078; ultraviolet: λ_{max} 264 mμ (log ϵ = 3.41), λ_{max} 272 mμ (log ϵ = 3.33), λ_{min} 231 mμ (log ϵ = 2.39); N.M.R. signals: triplet centered at 9.18 τ (methyl of ethyl group, area = 3H), doublet centered at 8.80 τ (CH_3-C-H, area = 3H), multiplet centered at 8.38 τ (methylene of ethyl group, area = 2H), 7.83 τ (intense, methyls attached to ring, area = 6H), multiplet centered at 7.2 τ (H-C-CH_3, area = 1H), doublet centered at 1.98 τ (αH, area = 2H). Found: C, 80.95; H, 10.52; N, 8.40. Calc. for $C_{11}H_{17}N$: C, 80.92; H, 10.50; N, 8.58.

A picrate was readily prepared in the usual manner, and this upon several recrystallizations from alcohol provided a pure sample, m.p. 131-132°. Found: C, 52.07; H, 5.03; N, 14.43; Calc. for $C_{17}H_{20}N_4O_7$: C, 52.04; N, 5.14; N, 14.28.

3,4-Dimethyl-5-ethylpyridine

The reaction product (11.1 g) resulting from the reaction of 3,4-dimethyl-5-cyanopyridine (20 g) with a fourfold excess of methylmagnesium iodide was treated with hydrazine (6.5 ml), potassium hydroxide pellets (90 g),

and diethylene glycol (13 ml) and heated in an oil bath at
150-170° for 2 hours. The bath temperature was then
raised to 200° and the reaction mixture was kept at this
temperature for a further 2 hours. The cooled reaction
mixture was treated cautiously with a small portion of
water and the resulting mixture was distilled. The fraction
which came over at 109-116° was treated with more water
(250 ml) and this aqueous mixture was thoroughly extracted
with ether. After the ether extract had been dried over
anhydrous magnesium sulphate, the solvent was removed and
the residual liquid was distilled from potassium hydroxide
pellets. A fraction (7.6 g) distilling over at 50-70°
(bath temp.) at 0.14 mm was completely free from any
carbonyl or cyanide impurities and proved to be the desired
material. A small portion of this liquid was redistilled
(b.p. 115-116° at 22 mm) and provided an analytical sample.
n_D^{20} 1.5151; ultraviolet: λ_{max} 263 mμ (logϵ = 3.39),
λ_{max} 266 mμ (log ϵ = 3.38), λ_{max} 271 mu (logϵ = 3.31),
λ_{min} 238 mμ (logϵ = 2.91); N.M.R. signals: triplet centered
at 8.84 τ (methyl of ethyl group, area = 3H), 7.86 τ
(intense, area = 6H, methyls attached to ring), quartet
centered at 7.42 τ (methylene of ethyl group, area = 2H),
1.98 τ (αH, area = 2H). Literature values (6): $_D^{20}$ 1.5136;
b.p. 217° at 744 mm. Found: C, 79.82; H, 9.69; N, 10.25.
Calc. for $C_9H_{13}N$: C, 79.95; H, 9.69; N, 10.36.

A picrate of the substance was prepared in ethyl

alcohol and after several recrystallizations from this solvent an analytical sample, m.p. 130-131°, was obtained. Literature (6): m.p. 133°. Found: C, 49.54; H, 4.34; O, 30.88; N, 15.23. Calc. for $C_{15}H_{16}N_4O_7$: C, 49.45; H, 4.43; O, 30.74; N, 15.38.

3-Methyl-4-styryl-5-ethylpyridine (XVIII)

A mixture of 3,4-dimethyl-5-ethylpyridine (2.82 g), benzaldehyde (6.3 ml), potassium acetate (1.95 g), acetic anhydride (5.9 ml), and a small crystal of iodine was refluxed for 40 hours. The resultant dark brown reaction mixture was cooled and treated with aqueous hydrochloric acid until acidic, and the excess benzaldehyde was removed by steam distillation. The residue from the steam distillation was extracted with ether to remove acidic or neutral materials and the resulting aqueous layer was then made basic by the addition of sodium hydroxide pellets. This basic layer was extracted several times with ether, the ether extract dried over anhydrous magnesium sulphate, and the solvent removed. The residual liquid product was fractionally distilled and a fraction distilling up to 140° (bath temp.) at 0.4 mm, which contained a considerable amount of starting material, was separated. The subsequent fraction (2.59 g) came over as a yellow slightly viscous liquid at a bath temperature up to 240° at 0.45 mm. A small portion was distilled again to provide an analytical sample (b.p. 153° at 0.02 mm). Infrared: 6.12 μ;

n_D^{20} 1.6144; ultraviolet: λ_{max} 276 mμ (broad, logϵ= 4.20), λ_{min} 239 mμ (log ϵ= 3.73); N.M.R. signals: triplet centered at 8.84τ (methyl of ethyl group, area = 3H), 7.78τ (methyl attached to ring at C$_3$, area = 3H), quartet centered at 7.37γ (methylene of ethyl group, area = 2H), four signals centered at 3.2τ (olefinic H, area = 2H), multiplet centered at 2.72γ (aromatic H, area $\cong$ 5H), 1.82 τ (αH, area = 2H). Found: C, 85.42; H, 7.52; N, 6.44. Calc. for $C_{16}H_{17}N$: C, 86.05; H, 7.67; N, 6.27.

A picrate of this substance was prepared in ethyl alcohol and after several recrystallizations from this solvent, an analytical sample, m.p. 182-183°, was obtained. Found: C, 58.23; H, 4.50; O, 24.50; N, 12.52. Calc. for $C_{22}H_{20}N_4O_7$: C, 58.40; H, 4.46; O, 24.76; N, 12.39.

3-Methyl-5-ethyl isonicotinic Acid (XIX)

A solution of 3-methyl-4-styryl-5-ethylpyridine (2.32 g, 0.01 mole) in glacial acetic acid (70 ml) was treated with ozone (0.015 mole) at room temperature. The reaction mixture was treated with 3% aqueous hydrogen peroxide (10 ml) and the mixture was refluxed for 10 minutes. The solvent was removed in vacuo and the residue washed with ether to remove the benzoic acid. To the ether-insoluble residue water (4 ml) was added, and the mixture was warmed in a steam bath until all the material had dissolved. As the solution gradually cooled, small, needle-like crystals separated (304 mg). Recrystallization

of this substance from absolute ethanol provided the pure
acid, m.p. 268-269°, infrared: 5.88 μ.

An additional 1.51 g of material was recovered
from the mother liquors. Although this latter crop was
not as crystalline as the initial crop, it was shown to be
the desired acid since on esterification with diazomethane,
in a subsequent experiment, it provided the identical
methyl ester. Found: C, 65.29; H, 7.00; O, 19.69. Calc.
for $C_9H_{11}O_2N$: C, 65.44; H, 6.71; O, 19.37.

Methyl 3-Methyl-5-ethyl-4-pyridinecarboxylate (XX)

To a stirred solution of 3-methyl-5-ethyl isoni-
nicotinic acid (1.5 g) in absolute ethyl alcohol (300 ml)
an ethereal solution of diazomethane (containing 2 g
CH_2N_2) was added. The reaction mixture was cooled in ice
and stirred at ice-bath temperature for 3 hours. The
reaction mixture was then treated with 2 N hydrochloric
acid (35 ml) and extracted with ether to remove any neutral
contaminants. The aqueous layer was made basic by the
addition of sodium bicarbonate and then extracted con-
tinuously with ether for 20 hours. The ether extract was
dried over anhydrous magnesium sulphate and the solvent
removed to yield a liquid product. Distillation of this
material at 70-100° (bath temp.) at 0.2 mm yielded 0.50 g
of a clear liquid. A small portion of this substance was

distilled again to provide an analytical sample (b.p. 135° at 22 mm); n_D^{20} 1.5025; infrared: 5.78 µ; ultraviolet: λ_{max} 274 mµ (logϵ = 3.48), λ_{min} 238 mµ (logϵ = 2.85); N.M.R. signals: triplet centered at 8.9γ (methyl of ethyl group, area = 3H), 7.85 γ (methyl attached to ring, area = 3H), quartet centered at 7.5γ (methylene of ethyl group, area = 2H), 6.21γ (-COOCH$_3$, area = 3H), 1.83γ (αH, area = 2H). Found: C, 67.16; H, 7.26; N, 7.90. Calc. for $C_{10}H_{13}O_2N$: C, 67.12; H, 7.31; N, 7.82.

The ester formed a picrate readily and this derivative, after recrystallizing from alcohol, melted at 151-153°. Found: C, 47.21; H, 4.09; O, 35.15; N, 13.43. Calc. for $C_{16}H_{16}O_9N_4$: C, 47.16; H, 3.95; O, 35.27; N, 13.72.

It should be pointed out that we found it very convenient to convert the entire reaction product into the picrate, purify the picrate by several crystallizations from alcohol, and finally regenerate the ester by decomposition of the picrate with lithium hydroxide (31). The recovery in this reaction is good and this provided an excellent method for purifying small quantities.

BIBLIOGRAPHY

References to Part I

1. a) C. Djerassi, J. P. Kutney, M. Shamma, J. N.
    Shoolery, L. F. Johnson. Chem. and Ind. 210
    (1961). b) C. Djerassi, J. P. Kutney and
    N. Shamma. Tetrahedron. $\underline{18}$, 183 (1962).

2. J. P. Kutney and R. C. Selby. J. Org. Chem.
    $\underline{26}$, 2733 (1961).

3. E. Dürkof and H. Göttsch. Ber. $\underline{23}$, 685 (1890).

4. E. Klingsberg. "Heterocyclic Compounds, Pyridine
    and Its Derivatives." Part 1, Interscience
    Publishers Inc., New York, 1961, p. 474, 476.

5. A. E. Tschitschibabin and M. P. Oparina. J. parkt.
    Chem. 1926, $\underline{107}$, 154.

6. A. S. Bailey and J. S. A. Brunskill. J. Chem. Soc.
    1959, 2554.

7. P. Vaculik and J. Kuthan. Collection Czechoslov.
    Chem. Communs. $\underline{24}$, 174 (1959).

8. K. Tsuda, H. Mishima and M. Maruyama. Pharm. Bull.
    (Japan) 1953, $\underline{1}$, 283.

9. P. Arnall. J. Chem. Soc. 1958, 1702.

10. H. Rogerson and T. F. Thorpe. J. Chem. Soc. $\underline{87}$,
    1685 (1905).

11. G. A. R. Kon and K. R. Nanji. J. Chem. Soc. 1931,
    560.

12. E. Hope, J. Chem. Soc. 1922, $\underline{121}$, 2216.

13. E. Hope and W. Sheldon. J. Chem. Soc. 1922, 2233.

14. I. Guareschi. a) Estr. Mem. Reale Accad. Sci.
    Torino, ii 46. b) J. Chem. Soc. 1897, $\underline{72}$, Pt. 1,
    168.

15. L. Ruzicka and V. Fornasir. Helv. Chem. Acta
    2, 338 (1919).

16. J. M. Bobbitt and D. A. Scola. J. Org. Chem. 25,
    560 (1960).

17. W. G. Schneider, H. J. Bernstein, and J. A. Pople.
    Can. J. Chem. 35, 1487 (1957).

18. T. Nakashima, J. Pharm. Soc. (Japan). 75, 1010 (1955)
    Chem. Abstr. 50, 4944e (1956).

19. R. Lukes and M. Pergal. Chem. Listy. 52, 68 (1958).

20. C. T. Kyte, G. H. Jeffery, and A. I. Vogel.
    J. Chem. Soc. 1960, 4454.

21. Huang-Minlon. J. Am. Chem. Soc. 68, 2487 (1946).

22. E. Klingsberg. "Heterocyclic Compounds, Pyridine and
    Its Derivatives." Part 2. Interscience Publishers
    Inc., New York, 1961.

23. E. R. Blout and V. W. Eager. J. Am. Chem. Soc.
    67, 1315 (1945).

24. J. L. R. Williams, S. K. Webster, and J. A. Van Allan.
    J. Org. Chem. 26, 4893 (1961).

25. A. P. Phillips. J. Am. Chem. Soc. 76, 3986 (1954).

26. F. Melescher. Ber. 88, 1208 (1955). S. M. McElvain ed.
    Organic Syntheses Col. Vol. I, Wiley, 2nd Ed.,
    1958, p. 385.

27. F. Kogel, G. M. Van Der Want, and C. A. Salmenk.
    Rec. trav. Chim. 67, 29 (1948).

28. R. H. Callighan and M. H. Wilt. J. Org. Chem. 26,
    4912 (1961).

29. H. O. Burrus and G. Powell. J. Am. Chem. Soc. 67, 1468
    (1945).

30. M. A. Newman. J. Am. Chem. Soc. 63, 2431 (1941).

31. A. Burger. J. Am. Chem. Soc. 67, 1615 (1945).

PART II

THE SYNTHESIS OF NEW 3,5-DIMETHYL-4-
SUBSTITUTED PYRIDINES

STERIC EFFECTS AS AN AID TO SYNTHESIS

INTRODUCTION

As indicated in Part I, Kutney et al (1,2)
investigated the synthesis of 3,4,5-trialkylated pyridines
because these compounds were virtually unknown and were
not readily available from natural sources or synthetic
routes. On accomplishing the synthesis of 3,4-dimethyl-
5-isopropylpyridine (1) and 3,4-dimethyl-5-s-butylpyridine
(2), a general synthetic approach to virtually any type of
trialkylated pyridine of this type was soon realized.

In relation to these studies, Kutney and Selby
(1) also became involved in the synthesis of the sym-
metrical 3,5-dimethyl-4-isopropylpyridine. To approach
this problem they considered the preparation of 3,5-
dimethyl-4-ethylpyridine by a possible extension of the
Wibaut-Arens alkylation method (3-11).

This alkylation reaction has been utilized
extensively in the preparation of various γ-alkylated
pyridines. The method was first described by Dohrn and
Horster (6) and developed by Wibaut and Arens (3,7) and by
Emmert and Wolpert (8). The reaction consists of the
treatment of a pyridine with the corresponding acid
anhydride followed by a rearrangement to a 1,4-diacyl-1,

4-dihydropyridine (II-Figure 1) and reduction of this
compound to a 4-alkylpyridine (III).

A possible mechanism which has been proposed by
Mosher (10) involves a resonance-stabilized ionic inter-
mediate IV (Figure 2). On the other hand, Bachman and
Schisla (11) have postulated that the reaction involves a
free radical mechanism after the formation of the ionic
intermediate IV suggested by Mosher (10) (Figure 3). The
mechanism of the dissociation of I has been studied by
Frank et al (4,9) and they support the view that the key
intermediate taking part in the reaction is N,N'-dia-
cyltetrahydro-4-4'-dipyridyl, I.

Although this reaction works well with unsub-
stituted pyridines, it was found in our laboratory that
treatment of 3,5-lutidine with acetic anhydride and zinc
according to the specified conditions (3-11) did not however,
lead to the expected product, 3,5-dimethyl-4-ethyl-
pyridine (1) but to 3,5-dimethyl-4-acetylpyridine. This
acetylpyridine was converted to the 4-ethylpyridine only
under much more drastic reaction conditions. Apparently
the steric hindrance by the two neighbouring methyl groups
had been sufficient to allow isolation of the 3,5-dimethyl-
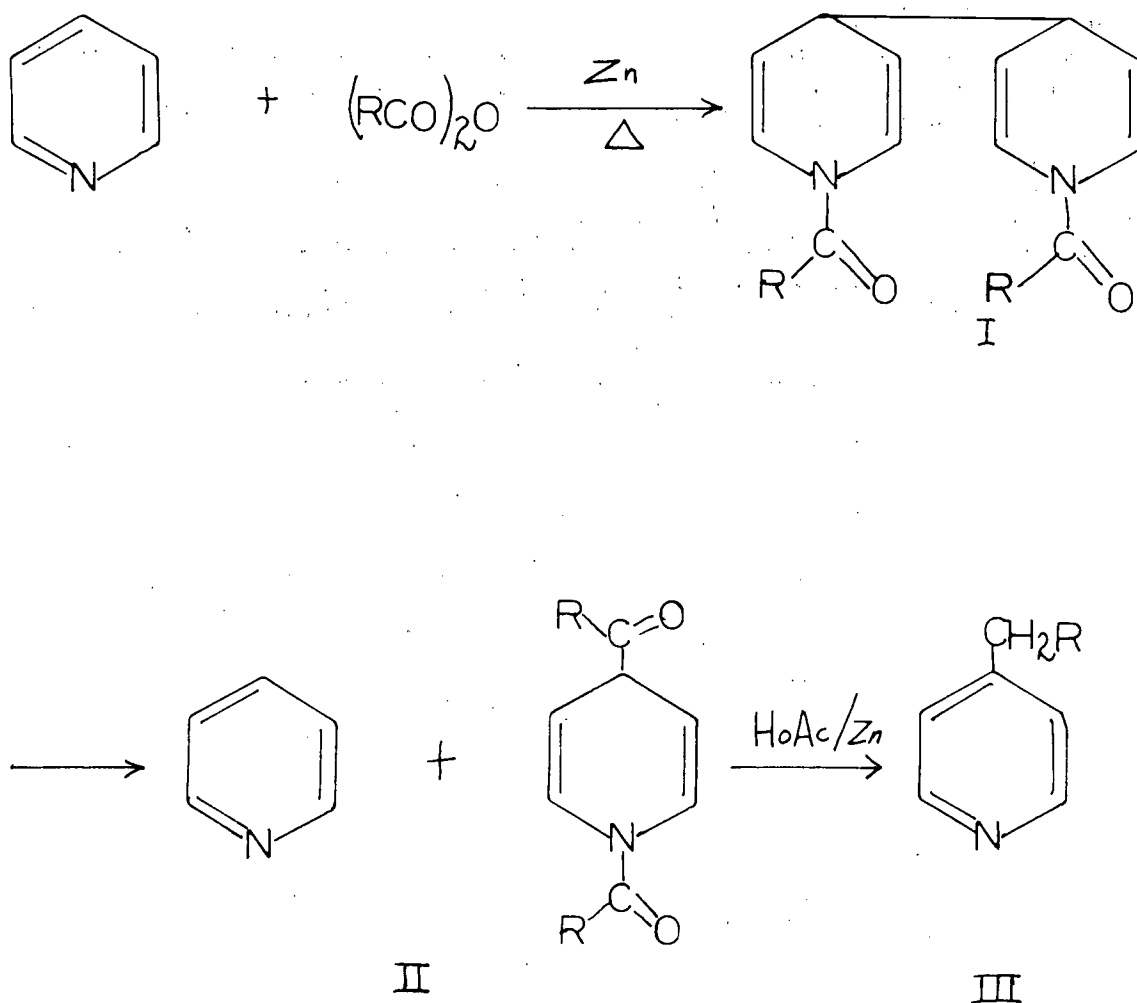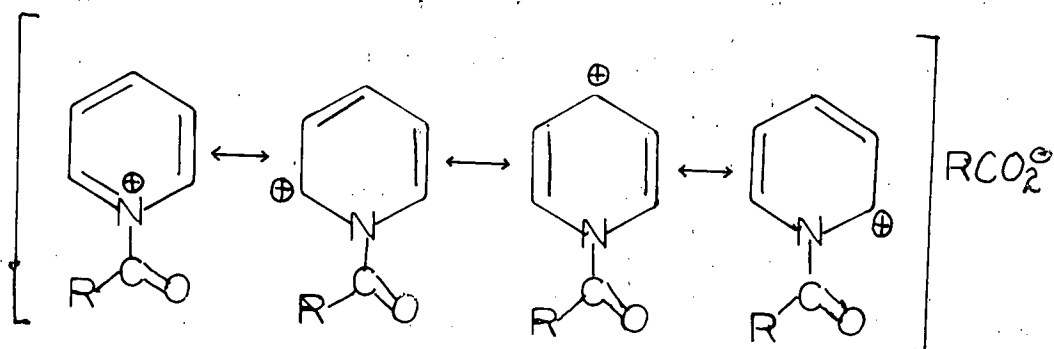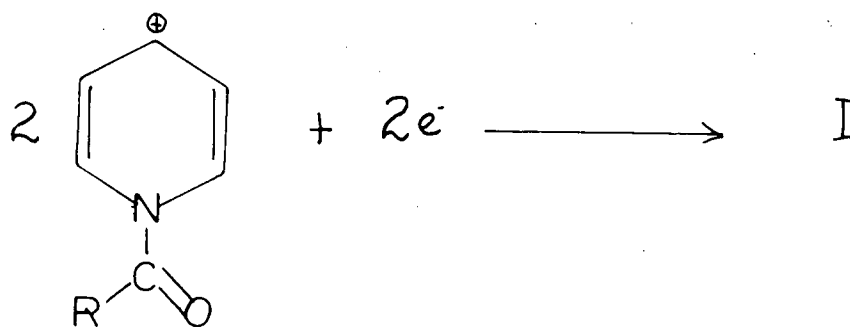4-acetylpyridine.

In order to provide a route to pyridine

Figure 1. Preparation of γ-alkylpyridines by the Wibaut-
Arens alkylation method

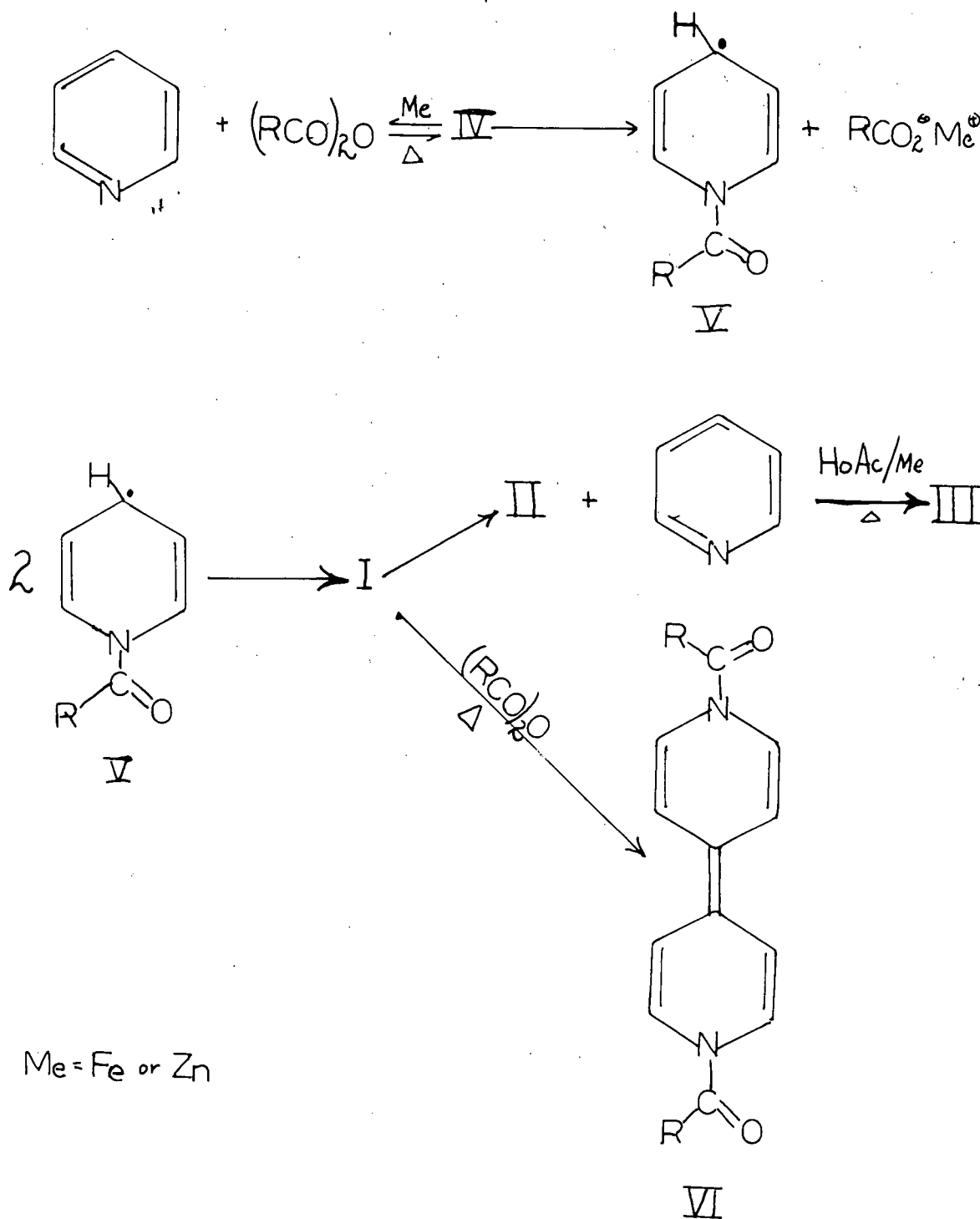Figure 2. Ionic mechanism of the Wibaut-Arens alkylation reaction proposed by Mosher

Figure 3. Free radical mechanism of the Wibaut-Arens alkylation reaction proposed by Bachman and Schisla

derivatives possessing branched alkyl chains at the γ-position, Kutney et al (1) attempted to react the acetyl-pyridine with various organometallic reagents, although it was anticipated that the steric factor might prevent a successful reaction. Reaction of this pyridine with methylmagnesium iodide and bromide under various reaction conditions met with failure. It should be pointed out that in an attempt to obtain a reaction, these experiments were performed under drastic conditions using high boiling solvents such as diglyme and dibutylcarbitol. In the latter case a trace of an alcoholic component was obtained but the extremely poor yield discouraged any further characterization. Similar unsuccessful attempts were also made with methyllithium. It thus became evident that the steric hindrance of the carbonyl function was so effective as to make this group completely unreactive toward organo-metallic reagents.

Furthermore, the Wittig reagent derived from methyltriphenylphosphonium bromide (12,13) also failed to react with 3,5-dimethyl-4-acetylpyridine.

A simple modification of Vaculik's method (14) (see Part I, Figure 3), in which an attempt to react 1-benzyl-3,5-dimethyl-4-piperidone with isopropylmagnesium bromide under a variety of reaction conditions, was also unsuccessful. This supports the view that the methyl

groups at the 3 and 5 positions of the pyridine ring have
a considerable blocking effect.

It therefore became apparent to us that the
steric influence of the methyl groups at the β-positions
could be utilized to advantage in synthesizing new 3,4,5-
trialkylated pyridines since the 4-acetylpyridine deri-
vative is a very versatile synthetic intermediate. Hence
studies in this direction were undertaken and the results
are presented in this part of the thesis.

DISCUSSION

As has been already mentioned, the Wibaut-Arens alkylation method has been used quite extensively for the introduction of alkyl substituents into the γ-position of the pyridine ring but it was found in our laboratory that the application of this method to 3,5-lutidine yielded the unexpected compound, 3,5-dimethyl-4-acetylpyridine, VII, rather than the corresponding 3,5-dimethyl-4-ethylpyridine. This preparation of the acetylpyridine has now been repeated according to the Wibaut-Arens procedure and the structure of the 3,5-dimethyl-4-acetylpyridine has been confirmed. The acetylpyridine possessed a strong carbonyl absorption in the infrared spectrum (5.84 μ) and the ultraviolet spectrum was characteristic of a trialkylated pyridine of this type (2). Furthermore, the N.M.R. spectrum showed a sharp signal at 7.16 τ which established the presence of an acetyl group. In addition, a strong signal at high field (7.83 τ), typical of methyl groups attached at the β-positions of the pyridine ring, and a weak signal at low field (1.82 τ), attributable to the α protons on the nucleus (1,2), served to confirm the structure.

The reduction of this acetylpyridine to the known compound, 3,5-dimethyl-4-ethylpyridine (15,16) on treatment with acetic acid and zinc, provided complete chemical evidence for the assigned structure.

Because it had been reported that the carbonyl function of this acetylpyridine resisted any reaction with organometallic reagents, an attempt to reduce the acetyl group to the corresponding alcohol was then made. It was felt that the latter compound could lend itself to a variety of interesting reactions. When 3,5-dimethyl-4-acetylpyridine was treated with lithium aluminum hydride the expected alcohol, VIII, was obtained as a crystalline substance. The success of the reaction was clearly evident from spectroscopic considerations. Apart from the typical strong hydroxyl band in the infrared spectrum at 3.09μ, and the characteristic ultraviolet spectrum of a pyridine (1,2), the N.M.R. spectrum was very instructive. The presence of the hydroxyethyl group was shown by a doublet at high field centered at 8.62γ, as would be expected for a methyl group, and a quartet centered at 4.88γ due to the tertiary proton attached to the oxygen-bearing carbon. The remaining signals at 7.75γ and 2.28γ were assigned to the β-methyl groups and the α protons on the pyridine ring respectively.

Having obtained the desired alcohol, VIII,

conversion to other analogues in this series was then pro-
posed. The first reaction attempted was the preparation
of the bromoethylpyridine, XII, by treatment with hydro-
bromic acid in the normal manner (17,18). Because these
methods were unsuccessful, a more drastic procedure was
then applied and a crystalline substance was obtained.
After consideration of both the spectroscopic and the
analytical data, the product of the reaction appeared not
to be the expected compound, XII, but an isomeric substance.
The infrared spectrum had indicated that the hydroxyl
function had been removed and the analytical figures
further supported this inference. On these grounds alone
it could be argued that a simple displacement of the
hydroxyl function had taken place and that the structure
was the expected compound, XII. However, this argument was
quickly dismissed after close inspection of the N.M.R.
spectrum. A feature which was obviously absent was a
doublet at high applied magnetic field which would be
expected for the methyl group if the correct structure was
XII. Moreover, the tertiary proton of the bromoethyl group
should exhibit a quartet. The highest signal observed in
the spectrum in this case was a singlet at 7.32Υ and its
position as well as its intensity indicated beyond doubt,
that this signal was due to the β-methyl groups attached
to the pyridine nucleus (1,2). The remaining signals were
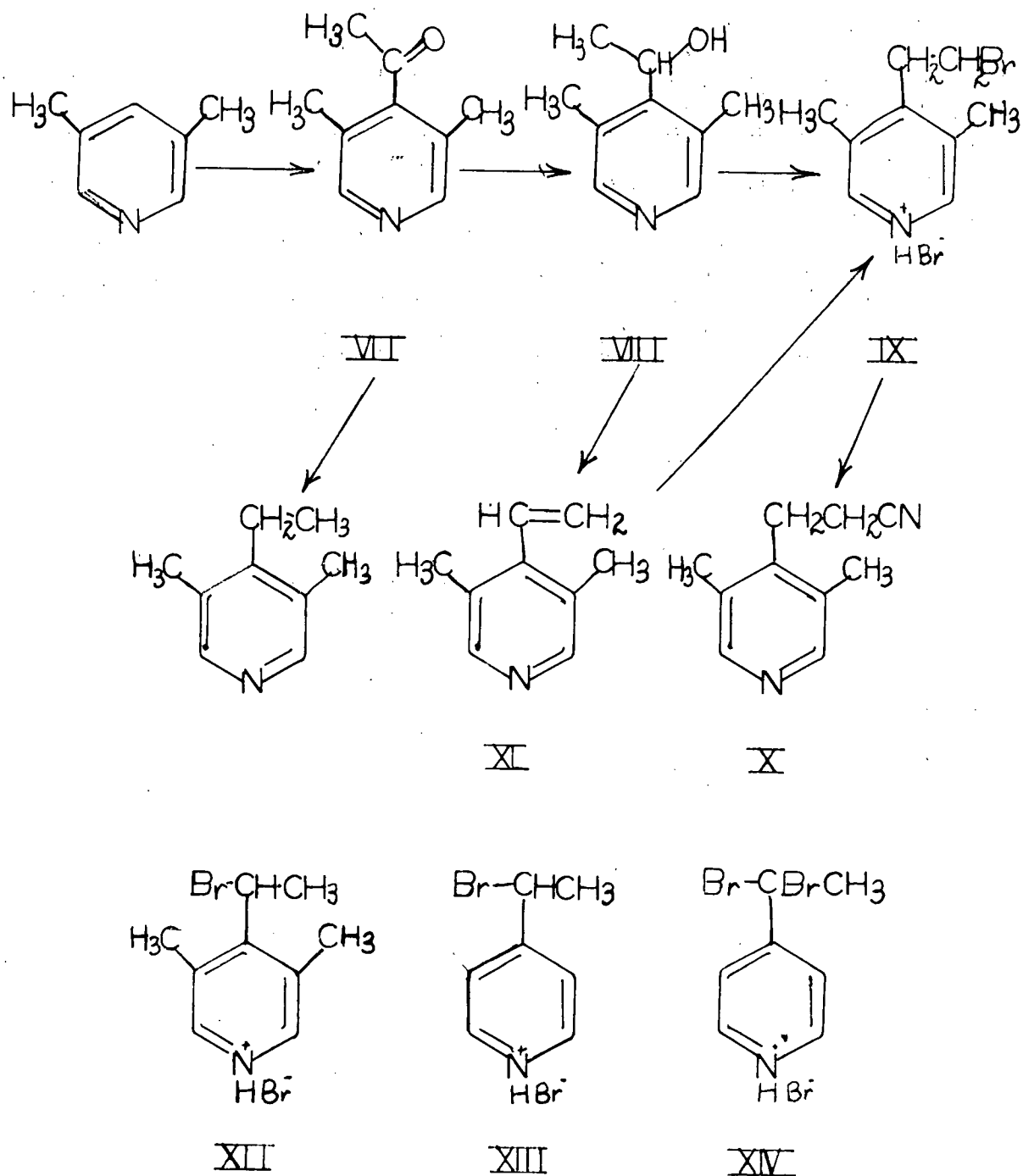at lower fields and therefore, it was clear that the

Figure 4. Synthesis of new 3,5-dimethyl-4-substituted pyridines with steric effects as an aid to synthesis

substance obtained in this reaction was not XII. Taking
into consideration the nature of the entire N.M.R. spectrum
and the integrated areas, it was deduced that the alter-
native structure, IX, was the correct one. A more detailed
description of the N.M.R. results is given in the experi-
mental section.

In order to confirm that the assignment of the
structure, IX, was correct and eliminate any doubt as to
the actual chemical shifts that a methyl group of the type
shown in XII should exhibit, an unambiguous synthesis of a
compound having analogous structural features to XII was
then devised. The most direct approach to this problem
was reaction of 4-ethylpyridine with N-bromosuccinimide
(NBS), a reagent which has been recently utilized to intro-
duce a bromine atom into a 2-methylpyridine derivative (19).
When 4-ethylpyridine was treated with NBS, the expected
4-(1-bromoethyl)-pyridine, XIII, was obtained as a crystal-
line material. The analytical and the spectroscopic data
were in complete agreement with the expected structure.
The N.M.R. spectrum of XIII was of particular importance
here since it served to confirm the assignment of the
signals in the N.M.R. spectrum of IX. The presence of the
1-bromoethyl group in XIII was established by a doublet at
7.89τ as would be expected for the methyl group attached
to the halogen-bearing carbon atom, and a quartet at 4.66τ

for the tertiary hydrogen atom. It should be mentioned here that 4(1,1-dibromoethyl)-pyridine, XIV, was also obtained by reacting the corresponding ethylpyridine with NBS under more drastic reaction conditions. Details of this reaction are given in the experimental portion.

The isolation of IX is of some theoretical interest since it is apparent that a simple substitution of the hydroxyl group by the halogen atom has not taken place. The reaction path appears to be similar to that previously encountered in the hydriodic acid--red phosphorus reaction in which the reductive removal of the hydroxyl function gave the intermediate olefinic substances (1,2). Undoubtedly, in these instances, the olefinic compounds arose from an acid catalyzed elimination reaction. The subsequent addition of the hydrobromic acid to the olefinic bonds, in our case, provides the product actually isolated. The mode of electrophilic addition to the double bond of alkenylpyridines has not been studied in great detail and, in particular, little is known about the addition of hydrogen halide to these types of compounds (20, p. 364). Although products resulting from the addition of hydrogen halide to vinyl pyridines have been reported (21,22), there is no conclusive evidence as to the correct structure of these substances. It has been suggested (20, p. 364) that the halogen atom would enter

at the carbon atom adjacent to the pyridine nucleus. Our present studies do not bear out this statement although it must be recognized that steric factors may play a dominant role in directing the addition in our compound. Further studies are obviously necessary before any definite conclusions can be reached. In this connection, the introduction of bromine at the methylenic carbon of 3,5-dimethyl-4-ethylpyridine with NBS, under conditions identical to those used in the unsubstituted 4-ethylpyridine, has met with failure. This result lends some support to the importance of the steric factor.

We believe that the formation of the hydrobromide, IX, from the alcohol, VIII, involves the formation of the intermediate olefinic substance, 3,5-dimethyl-4-vinyl-pyridine. In order to provide some support for this proposal, we undertook to prepare the vinylpyridine by an unambiguous synthetic route and then react this compound under the identical reaction conditions to those used for the treatment of the hydroxyethylpyridine, VIII, with hydrobromic acid. Indeed, when the reaction was run in this manner, we obtained, in excellent yield, the same crystalline hydrobromide, IX. Therefore this sequence of reaction shows that the vinylpyridine could be an intermediate in the conversion, VIII —— IX.

The structure of the vinylpyridine obtained by

dehydration of VIII was readily established from spectroscopic data. The infrared spectrum indicated the formation of a new double bond (6.11μ) and the ultraviolet spectrum of the product showed a significant bathochromic shift due to an extended conjugation. Furthermore, appearance of multiplets in the N.M.R. spectrum at 4.27τ and 3.62τ provided strong support for the presence of a vinyl group.

Finally, we considered the possibility of converting the bromide, IX, into a pyridine derivative which was somewhat more stable and where one could actually obtain the N.M.R. spectrum of the parent base. It should be noted at this point that halopyridines are known to be unstable as their free bases and can only be isolated as salts.

An attractive analogue appeared to be the corresponding nitrile since in addition to being comparatively stable, it would provide a versatile synthetic intermediate for a variety of 4-substituted pyridines. When the hydrobromide IX was reacted in an aqueous alcoholic solution of potassium cyanide (23), an excellent yield of 3,5-dimethyl-4-(2-cyanoethyl)-pyridine was obtained. The isolation of this compound and consideration of the N.M.R. spectrum enabled us to confirm the previous assignment of the structure, IX. The cyanoethylpyridine possessed similar structural features to the corresponding hydrobromide, IX.

The N.M.R. spectrum indicated an intense signal at 7.61τ due to the methyl groups attached to the pyridine nucleus. Moreover, the four protons of the cyanoethyl group were clearly evident as two sets of multiplets centered at 6.94τ and 7.34τ, and finally a signal at low field (1.67τ) accounted for the two α protons on the ring. The relative areas under the signals served to establish the structure, X. Since numerous modification of the cyano function are possible, this material may be utilized to prepare new types of 4-substituted pyridine analogues.

CONCLUSION

It is therefore apparent that the steric hindrance created by substituents attached to the β-positions of the pyridine nucleus can be used to considerable advantage in the synthesis of new and otherwise inaccessible 3,4,5-trisubstituted pyridines.

EXPERIMENTAL

All melting points were determined on a Fischer-Johns apparatus and are uncorrected. The ultraviolet spectra were recorded in 95% ethyl alcohol on a Cary 14 recording spectrophotometer. Infrared spectra were recorded on a Perkin-Elmer model 21 spectrophotometer. The N.M.R. spectra were done at 60 Mc on a Varian A60 instrument. The values are given in the Tiers γ scale with the signal of tetramethylsilane, which was used as the internal standard, set at 10.0γ units. Integration of areas under the signals was carried out in all cases and the number of protons is indicated in parentheses. The solvents used were carbon tetrachloride or deuterio-chloroform. The analyses were performed by Dr. A. Bernhardt and his associates, Mulheim (Ruhr), Germany, and by Mrs. A. Aldridge, University of British Columbia.

3,5-Dimethyl-4-acetylpyridine (VII)

The zinc which was used in this experiment was activated as follows. Zinc dust (208 g) was stirred in 10% aqueous hydrochloric acid (75 ml) for 2-3 minutes. It was then filtered, washed with distilled water (150 ml), acetone (100 ml), anhydrous ether (50 ml) and dried

in vacuo. It was then ready for use.

A 1-liter 3-necked flask was fitted with a mechanical stirrer and acetic anhydride (250 ml) and 3,5-lutidine (136 g, dried over calcium oxide and freshly distilled in vacuo) were then added to the flask. This stirred mixture was then treated with small portions of zinc until a total of 100 g had been added. The addition required about one-half hour during which time the temperature of the reaction rose to 70° and the mixture developed a light green color. Glacial acetic acid (100 ml) and activated zinc (40 g) were added and the reaction mixture was refluxed for 15 minutes. After allowing to stand overnight at room temperature, the mixture was cooled in ice and treated cautiously with 40% aqueous sodium hydroxide (700 ml). The resulting brown oil which formed as a layer at the top was extracted with ether. The ethereal extract was dried over anhydrous magnesium sulfate, and the solvent evaporated to leave a brown viscous liquid (172 g). This liquid was fractionally distilled to yield an initial fraction (57.2 g, distilling up to 189°) of unreacted 3,5-lutidine. The second fraction (24.9 g) distilling in the range of 190-220° contained some 3,5-lutidine and some of the desired acetylpyridine whereas the last fraction (61.8 g) collected at 220-295° was the desired 3,5-dimethyl-4-acetylpyridine. A second distillation of the

last fraction at 167-169°/100 mm provided the pure product
(55.8 g). An analytical sample could also be conveniently
obtained on purification by vapour phase chromatography on
the Megachrome, operating at 240° with a column of Apiezon
J and using helium as the carrier gas. The retention time
was 10.2 minutes.

The product after this purification still
distilled at 167-169°/100 mm or 252-254°; n_D^{25} 1.5152;
infrared: 5.90 μ; ultraviolet: λ_{max} 270 mμ ($\log \epsilon = 3.42$),
λ_{min} 234 mμ ($\log \epsilon = 2.54$); N.M.R. signals (CCl_4): intense
signal at 7.83 τ (methyls attached to ring, area = 6H),
signal at 7.62 τ (CH_3-C-, area = 3H), 1.82 τ (αH, area =
2H). Found: C, 72.10; H, 7.48; O, 10.71; N, 9.32. Calc.
for $C_9H_{11}NO$: C, 72.45; H, 7.43; O, 10.72; N, 9.37.

A picrate was prepared and after several recry-
stallizations from alcohol melted at 181-183°. Found:
C, 47.81; H, 3.76; O, 33.37; N, 14.71. Calc. for
$C_{15}H_{14}O_8N_4$: C, 47.62; H, 3.73; O, 33.84; N, 14.81.

It is pertinent to note that it was found
imperative to carry out the initial fractional distillation
of the crude reaction product at atmospheric pressure. In
this way, the high temperature ensures that the inter-
mediates are decomposed to the desired product. If the
distillation is carried out at lower temperatures under

reduced pressure, the intermediates are actually distilled over and it becomes necessary to heat these to a higher temperature to convert them to VII.

3,5-Dimethyl-4-(1-hydroxyethyl) pyridine (VIII)

A 50 ml three necked flask was fitted with a dropping funnel, a reflux condenser and a magnetic stirrer, and charged with a solution of lithium aluminum hydride (0.819 g) in anhydrous ethyl ether (12 ml). To this was added cautiously from the dropping funnel, a solution of 3,5-dimethyl-4-acetylpyridine (3.22 g) in anhydrous ether (11 ml), over a period of 20 minutes. After the addition was complete, the reaction mixture was stirred at room temperature for one half hour and then water (20 ml) was added slowly to destroy the excess hydride. The reaction mixture was filtered, the solid which remained on the filter paper was washed thoroughly with methanol, and the methanol washings were combined with the ethereal filtrate. The filtrate was then concentrated and the soluble organic materials were extracted with chloroform. After drying the chloroform extract over anhydrous magnesium sulfate and removing the solvent, the residual product was distilled. The initial fraction (220 mg) distilling up to a temperature of 130° (bath temperature) at 0.5 mm proved to be unreacted acetyl pyridine. The second fraction (2.3 g) which came over at 145-210° (bath temp.) at 0.1 mm was the desired

alcohol, VIII. An analytical sample was prepared by several recrystallizations from a chloroform-petroleum ether mixture, and melted at 85-86°; infrared: 3.09 μ; ultraviolet: λ_{max} 267 mμ (logϵ= 3.40), shoulder at 274 mμ (logϵ= 3.35), λ_{min} 231 mμ (logϵ= 2.69); N.M.R. signals (CCl$_4$): doublet centered at 8.62 γ (CH$_3$-COOH, area = 3H), intense signal at 7.75γ (methyls attached to ring, area = 6H), quartet centered at 4.88 γ (tertiary proton of CH$_3$-C-OH, area = 1H), signal at 2.28 γ (αH, area = 2H). Found: C, 71.57; H, 8.70; O, 10.76; N, 9.07. Calc. for C$_9$H$_{13}$ON: C, 71.49; H, 8.67; O, 10.58; N, 9.26.

A picrate, m.p. 148-148.5°, was prepared in ethanol and recrystallized from the same solvent. Found: C, 47.88; H, 4.29; N, 14.48. Calc. for C$_{15}$H$_{16}$O$_8$N$_4$: C, 47.37; H, 4.24; N, 14.73.

3,5-Dimethyl-4-(2-bromoethyl) pyridine hydrobromide (IX)

A mixture of 3,5-dimethyl-4-(1-hydroxyethyl)-pyridine (196 mg) and concentrated hydrobromic acid (171 ml, 48%) was heated at 160° in a sealed tube for 24 hours. After cooling, the contents of the tube was evaporated to dryness in vacuo. The residual material was taken up in ethyl alcohol and recrystallized from a mixture of alcohol-chloroform to yield a first crop of crystals (235 mg). An additional 66 mg (total 301 mg) was obtained when the mother liquor was diluted with petroleum. Several

recrystallizations of this product from ethanol-petroleum
ether provided an analytical sample, m.p. 208-209°;
infrared: absence of hydroxyl absorption; ultraviolet:
λ_{max} 266 mμ (logϵ= 3.76), λ_{min} 245 mμ (logϵ= 3.62);
N.M.R. signals (CDCl$_3$): intense signal at 7.32τ (methyls
attached to ring, area = 6H), multiplet centered at 6.40τ
(CH$_2$CH$_2$Br, area = 4H), 1.32τ (αH, area = 2H). Found:
C, 36.43; H, 4.31; N, 4.62; Br, 54.22. Calc. for
C$_9$H$_{13}$NBr$_2$: C, 36.64; H, 4.41; N, 4.74; Br, 54.44.

3,5-Dimethyl-4-(2-cyanoethyl) pyridine (X)

The pyridine hydrobromide, IX (206 mg) was added
to a solution of potassium cyanide (610 mg) in water
(4.6 ml) and methanol (11 ml) and the mixture was refluxed
for 2 hours. On cooling, water (10 ml) was added and the
reaction mixture was then made alkaline by the addition of
sodium bicarbonate. This reaction mixture was extracted
exhaustively with ethyl acetate. The ethyl acetate extract
was dried over anhydrous magnesium sulfate and the solvent
was removed to yield a viscous liquid. This liquid was
distilled at 100-150° (bath temperature) at 0.1 mm to
yield 1o6 mg of a viscous liquid which solidified partially
on short standing. Crystallization from a mixture of
benzene-petroleum ether-acetone provided a crystalline
material m.p. 74-75°. Infrared: 4.46 μ; ultraviolet:
λ_{max} 2.66 mμ (log ϵ=3.31), λ_{min} 230 mμ (log ϵ= 2.78);

N.M.R. signals ($CDCl_3$): intense signal at 7.61τ (methyls attached to ring, area = 6H), two sets of multiplets centered at 7.34 τ and 6.94 τ ($-CH_2CH_2-CN$, area = 4H), 1.67τ (αH, area = 2H).

A picrate of this material was readily prepared and upon several recrystallizations from alcohol an analytical sample was obtained, m.p. 177-178.5°. Found: C, 49.01; H, 4.08; N, 17.78. Calc. for $C_{16}H_{15}N_5O_7$: C, 49.36; H, 3.88; N, 17.99.

3,5-Dimethyl-4-vinylpyridine (XI)

A solution of 3,5-dimethyl-4-(1-hydroxyethyl)-pyridine (991 mg) in anhydrous xylene (30 ml) was treated with phosphorus pentoxide (7.73 g) and the mixture was refluxed for 3 hours. After cooling, the reaction mixture was treated cautiously with water (20 ml) to destroy the excess phosphorus pentoxide and the resulting solution was separated into the respective organic and aqueous portions. The acidic aqueous layer was neutralized, then made alkaline by the addition of potassium hydroxide pellets and this mixture was extracted with ether. The ethereal extract was dried over anhydrous magnesium sulfate and the solvent evaporated to yield a mobile liquid. Distillation of this liquid provided the desired vinylpyridine (475 mg, b.p. 146-147° at 90 mm.); n_D^{27} 1.5333; infrared: 6.11 μ; ultraviolet: λ_{max} 273 mμ (log ϵ = 3.39), λ_{min} 261 mμ

(log ϵ = 3.32), λ_{max} 234 mμ (logϵ = 3.77), λ_{min} 223 mμ
(logϵ = 3.71); N.M.R. signals (CCl$_4$): intense signal at
8.02 (methyls attached to ring, area $\geqq$ 6H), multiplet
centered at 4.72 τ (-C=CH$_2$, area = 2H), quartet centered
at 3.62 τ (-C=C, area = 1H), 2.10 τ (H, area = 2H).
Found: C, 80.86; H, 8.34; N, 10.31. Calc. for C$_9$H$_{11}$N:
C, 81.16; H, 8.33; N, 10.52.

A picrate of this material was prepared in the
usual manner and recrystallized from ethanol several times
to yield an analytical sample which melted at 155-156°.
Found: C, 49.75; H, 3.90; O, 30.45; N, 15.41. Calc. for
C$_{15}$H$_{14}$N$_4$O$_7$: C, 49.73; H, 3.84; O, 30.52; N, 15.20.

3,5-Dimethyl-4-(2-bromoethyl)-pyridine hydrobromide (IX) from 3,4-Dimethyl-4-vinylpyridine

A mixture of 3,5-dimethyl-4-vinylpyridine
(188 mg) and concentrated hydrobromic acid (16 ml, 48%)
was heated for 24 hours in a sealed tube at 160°. On
working up the reaction mixture in exactly the same manner
as given above for the alcohol, a crystalline hydrobromide
(348 mg) was obtained. This was shown to be (IX) by mixed
melting point, infrared, ultraviolet and NMR comparison.

3,5-Dimethyl-4-ethylpyridine

A stirred solution of 3,5-dimethyl-4-acetyl-
pyridine (19 g) in glacial acid (200 ml) was cautiously

treated with activated zinc (10 g) and the whole mixture
was then refluxed for one hour. An additional 18 g of
activated zinc was added and refluxing was continued for
a further 15 hours, by which time the reaction mixture had
become intensely yellow in color. After cooling, the
mixture was made alkaline by the addition of 40% aqueous
sodium hydroxide (400 ml) and the resulting mixture was
steam distilled until the distillate was clear. The
distillate was then extracted exhaustively with ether and
the ethereal extract dried over anhydrous magnesium sulfate.
Evaporation of the solvent left a brown residual liquid
(17.7 g) which upon distillation (b.p. 218-219°) yielded
12.7 g of 3,5-dimethyl-4-ethyl-pyridine. Infrared:
complete disappearance of carbonyl band; ultraviolet:
λ_{max} 263 mμ (log ϵ = 3.45), λ_{max} 273 mμ (log ϵ = 3.38),
λ_{min} 231 mμ (log ϵ = 7.87); N.M.R. signals (CCl_4):
triplet centered at 8.94 τ (methyl of ethyl group,
area = 3H), intense signal 7.80 τ (methyls attached to
ring, area = 6H), quartet centered at 7.42 τ (methylene of
ethyl group, area = 2H), 1.96 τ (αH, area = 2H). A
picrate of this compound was readily prepared and the
analytical sample melted at 156.5-157°. Found: C, 49.49;
H, 4.17; N, 15.36. Calc. for $C_{15}H_{16}N_{14}O_7$: C, 49.45;
H, 4.43; N, 15.38.

The literature values (15, 16) are b.p. 216-217°,

219-220° for the base and m.p. 155-156° for the picrate.

4-(1-Bromoethyl)-pyridine hydrobromide (XIII)

A solution of 4-ethylpyridine (6.41 g) in anhydrous carbon tetrachloride (200 ml) was treated with N-bromosuccinimide (10.7 g) and benzoyl peroxide (0.91 g) and the whole mixture was refluxed for three hours. The slightly brown reaction mixture was filtered to remove the solid suspension and the filtrate was washed successively with 4% aqueous sodium hydroxide (100 ml), water (100 ml), 2% aqueous hydrobromic acid (100 ml) and finally dried over anhydrous magnesium sulfate. This dried carbon tetrachloride extract was then saturated with hydrogen bromide and finally the solvent was removed to furnish a residual gum (7.4 g). The latter was taken up in ethanol and then crystallized from a solvent mixture of ethanol-ethyl ether to afford 3.25 g of a crystalline hydrobromide, m.p. 151-151.5°; ultraviolet: λ_{max} 260 mμ (logϵ = 3.50), λ_{min} 235 mμ (logϵ = 3.30); N.M.R. signals (CDCl$_3$): doublet centered at 7.89Υ (CH$_3$-C-Br, area = 3H), quartet centered at 4.66Υ (tertiary hydrogen of CH$_3$-C-H, area = 1H), doublet centered at 1.85Υ (βH, area = 2H), doublet centered at 0.83Υ (αH, area = 2H); Found: C, 31.56; H, 3.39; N, 5.40; Br, 59.87. Calc. for C$_7$H$_9$NBr$_2$: C, 31.47; H, 3.40; N, 5.25; Br, 59.88.

4(1,1-dibromoethyl) pyridine hydrobromide (XIV)

A mixture of 4-ethylpyridine (6.5 g), N-bromo-
succinimide (15.0 g) and benzoyl peroxide (1.0 g) in carbon
tetrachloride (200 ml) was refluxed for 6 hours. After
cooling, the reaction mixture was filtered and the filtrate
was washed successively with 4% sodium hydroxide (100 ml),
water (100 ml), 2% hydrobromic acid (100 ml), and finally
dried over anhydrous magnesium selfate. The carbon tetra-
chloride solution was then saturated with hydrogen bromide
gas whereupon a light brown gum precipitated out. Upon
evaporation of the solvent, the resulting residual gum was
taken up in 95% ethanol and left under refrigeration. The
first crop (9.32 g) of crystalline substance was obtained
and melted at 129-135°. Repeated crystallization (4 times)
from ethanol-petroleum ether afforded an analytically pure
sample (308 mg) which decomposed at 158-160°. Ultraviolet:
λ_{max} 264 mμ (log ϵ = 3.43), λ_{min} 249 mμ (log $\epsilon \doteq$ 3.37);
N.M.R. signals (CDCl$_3$): Intense singlet at 6.95 τ
(CH$_3$-C- , area = 3H), doublet centered at 1.56 τ (βH,
area = 2H), doublet centered at 0.75 τ (α H, area = 2H).
Found: C, 24.36; H, 2.54; N, 4.04; Br, 69.40. Calc. for
C$_7$H$_8$NBr$_3$: C, 24.29; H, 2.33; N, 4.05; Br, 69.33.

It was subsequently shown that the product obtained

under these conditions gave a mixture of mono and dibromo-ethyl pyridines which were separable by fractional crystallization.

BIBLIOGRAPHY

References to Part II

1. J. P. Kutney and R. C. Selby. J. Org. Chem. $\underline{26}$, 2733 (1961).

2. J. P. Kutney and T. Tabata. Can. J. Chem. $\underline{40}$, 1140 (1962).

3. J. F. Arens and J. P. Wibaut. Rec. trav. chim. $\underline{61}$, 59 (1942).

4. R. L. Frank and P. V. Smith. Org. Synthesis. $\underline{27}$, 38 (1947).

5. S. Wawzonek, M. F. Nelson and P. J. Thelen. J. Am. Chem. Soc. $\underline{74}$, 2894 (1952).

6. M. Dohrn and H. Horster. German Patent 390, 333, 1924.

7. J. P. Wibaut and J. F. Arens. Rec. trav. chim. $\underline{60}$, 119 (1941).

8. B. Emmert and A. Wolpert. Ber., $\underline{74}$, 1015 (1941).

9. R. L. Frank, F. Pellitier, and F. W. Starks. J. Am. Chem. Soc. $\underline{70}$, 1767 (1948).

10. H. S. Mosher. "The Chemistry of the Pyridines" in Elderfield, ed. Heterocyclic Compounds, Wiley, New York, 1950, Vol. I, p. 482.

11. G. B. Bachman and R. M. Schisla. J. Org. Chem. $\underline{22}$, 1302 (1957).

12. G. Wittig and V. Schollkopf. Ber., $\underline{87}$, 1318 (1954).

13. F. Sondheimer and R. Mechoulam. J. Am. Chem. Soc. $\underline{80}$, 3087 (1958).

14. P. Vaculik and J. Kuthan. Collection Czecholslov Chem. Communs. $\underline{24}$, 174 (1959).

15. I. Heilbron and H. M. Bunbury. "Dictionary of Organic Compounds," Vol. I, London, Eyre & Spottiswoode, 1946, p. 913.

16. Beilstein. Handbuch der Organischen Chemie. 20, 254 (1935); ibid II, 166 (1953).

17. S. A. Harris and K. Folkers. J. Am. Chem. Soc. 61, 1245 (1939).

18. F. Sorm and L. Sedivy. Collection Czechoslov Chem. Communication. 13, 289 (1948) C.A. 43, 2996 (1949).

19. J. Hurst and N. G. Wibberley. J. Chem. Soc. 1962 (119).

20. E. Klingsberg. "Heterocyclic compounds, Pyridines and its Derivatives," Part 2, Interscience Publishers Inc., New York, 1961.

21. G. H. Lenart. Ann. 410, 95 (1915).

22. H. Bach. Ber. 34, 2223 (1901).

23. H. S. Mosher and J. E. Tessieri. J. Am. Chem. Soc. 73, 4925 (1951).