SYNTHESIS IN THE PYRIDINE SERIES

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

JAMES P. KUTNEY AND T. TABATA
Department of Chemistry, University of British Columbia, Vancouver, British Columbia
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ABSTRACT

A synthetic sequence leading to new and inaccessible 3,4,5-trialkylated pyridines has been developed. The nature of the synthesis allows the preparation of virtually any type of 3,4,5-trialkylated pyridine by simple, straightforward variations at the appropriate stage.

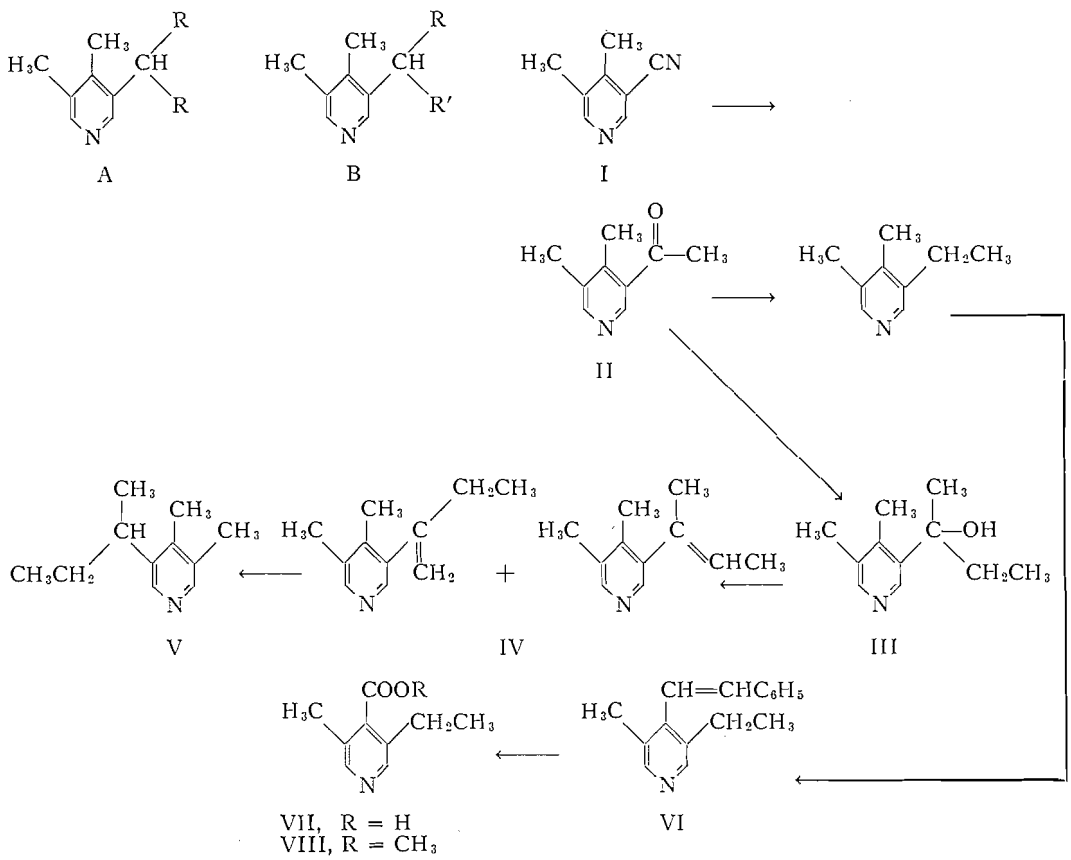
Recently, in connection with the structural elucidation of a new alkaloid, we became involved in the developing of a synthetic sequence to new 3,4,5-trialkylated pyridines. In Part I of this series (1) we described a general approach to this goal and, in particular, indicated that the substance 3,4-dimethyl-5-cyanopyridine (I) was a valuable intermediate for the synthesis of various new trialkylated pyridines of this type. We now wish to describe some of our results which support this view.

There are numerous possible modifications of the cyano group and we have already indicated (1) the conversion of this group to an ester function to provide an intermediate for the preparation of pyridines of the type A. In order to provide entry into another series of branched-chain pyridines (type B) we reacted 3,4-dimethyl-5-cyanopyridine with methylmagnesium iodide to obtain 3,4-dimethyl-5-acetylpyridine (II). The success of this reaction was readily evident from the infrared spectrum of the product, which indicated a virtual disappearance of the absorption due to the cyano function (4.48 μ) and the appearance of the characteristic carbonyl band (5.94 μ). This ketonic substance was subsequently treated with ethylmagnesium iodide, and the expected alcohol, III, was obtained as a light yellow viscous liquid. This substance resisted all attempts to crystallize —a rather surprising behavior since the analogous substance, 3,4-dimethyl-5-(2-hydroxy-2-propyl)-pyridine, reported previously (1), was a crystalline material. Nevertheless, characterization of the substance established, beyond doubt, that it possessed the expected structure. The infrared spectrum possessed a typical hydroxyl absorption and the nuclear magnetic resonance (n.m.r.) spectrum was particularly instructive. The presence of a triplet at high magnetic field (9.22 τ) indicated a methyl group flanked by a methylene carbon which in turn was indicated by a quartet centered at 8.16 τ. Another signal at 8.5 τ was assigned to a methyl group attached to an oxygen-bearing carbon and a weak signal at 4.6 τ was attributed to a proton on oxygen. This evidence established the presence of the 2-hydroxy-2-butyl group attached to the pyridine nucleus. The remaining signals—two sharp spikes at 7.85 and 7.58 τ characteristic of methyl protons attached to the pyridine ring (1), and a doublet at low field (2.08 τ) attributable to α protons on the pyridine ring (1, 2)—served to establish, beyond doubt, the structure III.

The removal of the hydroxyl function had been successfully accomplished in our previous work by means of red phosphorus and hydriodic acid and we attempted to utilize this reaction in this series. 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 III to the desired 3,4-dimethyl-5-*s*-butylpyridine (V) did not proceed to completion. Even

under more drastic conditions (48 hours' reflux), the reaction product always consisted of a mixture, the olefinic substance IV and the desired V. The greater resistance of the olefinic bond to reduction was further indicated by catalytic hydrogenation studies. When the hydrogenation of IV was performed under conditions previously used for 3,4-dimethyl-5-isopropenylpyridine (Adams catalyst, atmospheric pressure, and room temperature), incomplete reduction was observed, as evidenced by an olefinic signal in the n.m.r. spectrum. However, the desired pyridine, V, was obtained when the reduction was allowed to proceed at more stringent conditions (Adams catalyst, 32 p.s.i.). The ultraviolet spectrum of this product was characteristic of an alkylated pyridine and the n.m.r. spectrum provided strong support for this structure.

For the preparation of 3,4-dimethyl-5-ethylpyridine, which was necessary for further studies in this area, we considered the direct reduction of the acetyl function in II to an ethyl group. The most convenient method appeared to be the Wolff–Kishner reduction, a reaction frequently employed in the pyridine series (3). Indeed, reaction of 3,4-dimethyl-5-acetylpyridine under the Huang-Minlon modification of the Wolff–Kishner reduction (4) provided the expected 3,4-dimethyl-5-ethylpyridine. The n.m.r. spectrum was in complete agreement with the assigned structure. It indicated a triplet at high field (8.84 τ) and a quartet at lower field (7.42 τ), to provide strong evidence for the ethyl group. The intense signal at 7.86 τ, characteristic of methyl protons attached to the pyridine ring, and a weak signal at low field, typical of α protons, accounted for the remaining hydrogen atoms.



The successful synthesis of 3,4-dimethyl-5-ethylpyridine allowed us to consider the steric effects of the substituents attached to carbon atoms 3 and 5 on the reactivity of the methyl group at the 4 position. We became interested in this aspect of the problem, since some of our previous work has already indicated that this steric effect could be substantially important in certain reactions. For example, we had indicated previously (1) that 3,5-dimethyl-4-acetylpyridine possesses a very unreactive carbonyl group to organometallic reagents, a factor which must be attributed, at least in part, to the steric influence of the neighboring methyl groups. It appeared to us that some more information regarding this point could be deduced from the aldol-type condensation reactions of 3,4-dimethyl-5-ethylpyridine with such aldehydes as benzaldeyde. This reaction has been utilized in pyridine chemistry on numerous occasions and has proved to be of considerable synthetic value (5, p. 200). When 3,4-dimethyl-5-ethylpyridine was reacted with benzaldehyde under rather drastic conditions, the corresponding 3-methyl-5-ethyl-4-styrylpyridine, VI, was formed in moderate yield. The success of the reaction was easily recognized from consideration of the spectral data. The infrared spectrum, with a weak band at 6.12 μ, was consistent with the presence of a new olefinic bond and the n.m.r. spectrum was particularly informative. The characteristic signals for the ethyl group were still present and, in particular, the intense signal due to the C_3- and C_4-methyl groups in the starting material was considerably reduced and consistent with the presence of only *one* methyl group. The olefinic proton region exhibited a characteristic *AB* splitting pattern with a separation of 17 c.p.s., suggesting a trans orientation of the olefinic bond, and the appearance of the usual aromatic signals served to further confirm the 4-styrylpyridine structure. The ultraviolet spectrum was very interesting in that it was considerably different from the spectra reported previously for compounds of this type (6, 7). The main absorption band at 278 mμ represented a small bathochromic shift from the usual alkyl pyridine absorption (263–268 mμ) but this absorption is nevertheless significantly lower than that of such compounds as 4-styrylpyridine (307 mμ), and the intensity of the absorption of VI is lower. We believe that this rather anomalous spectrum is due to the fact that the neighboring 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 effect of the additional conjugation. From the above results it can be concluded that although the 4-methyl function is somewhat hindered it is still capable of entering into condensation reactions with carbonyl compounds. The yield in this reaction is, however, somewhat lower than reported in other series (8).

The isolation of 3-methyl-5-ethyl-4-styrylpyridine from the condensation reaction was useful in providing a synthetic intermediate for the synthesis of pyridine derivatives possessing different functions at the 4-position. We therefore considered several methods to convert the olefinic linkage to a carboxyl function. This type of reaction has been used in pyridine chemistry for the synthesis of pyridine carboxylic acids or aldehydes (5, p. 207). The reaction of choice involved ozonolysis, and we subjected 3-methyl-5-ethyl-4-styrylpyridine to this reaction. The product of this reaction was the expected carboxylic acid, VII, obtained as a high-melting, crystalline substance. Recently the ozonolysis of vinylpyridines has been shown to yield, under similar conditions, the corresponding pyridinecarboxylic acids (9). This material was readily converted to the methyl ester VIII by treatment with an ethereal solution of diazomethane. The structure of the ester was established, beyond doubt, by the n.m.r. spectrum of this substance. Apart from the characteristic signals for the presence of the ethyl and methyl groups attached directly to the pyridine nucleus, a sharp signal at 6.21 τ confirmed the presence of the ester methyl.

In conclusion, we would like to point out that these studies have provided intermediates which can be used to prepare virtually any type of 3,4,5-trialkylated pyridine. Firstly, it is obvious that any Grignard reaction on 3,4-dimethyl-5-cyanopyridine, followed by the appropriate steps, provides numerous variations to the type of group attached at C_5. Secondly, the appropriate ester analogous to VIII provides entry into various possibilities at C_4 and finally the nature of the alkyl group at C_3 can be likewise varied. It is pertinent to note that in the original Guareschi cyclization, which provides the starting material for the above 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-trialkyl 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 (II)

A solution of 3,4-dimethyl-5-cyanopyridine (I, 22.2 g) 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 provided 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 (log ϵ 3.73), λ_{max} 271 mμ (log ϵ 3.40), λ_{min} 254 mμ (log ϵ 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 (III)

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 sodium 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 (III, 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 = 1H), doublet centered at 2.08 τ (—αH, 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-acetylpyridine 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 (V)

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 phosphorus was removed by filtration and the filtrate concentrated 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 temperature 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; H, 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 (log ϵ 3.39), λ_{max} 266 mμ (log ϵ 3.38), λ_{max} 271 mμ (log ϵ 3.31), λ_{min} 238 mμ (log ϵ 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 (10): n_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 (10): 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 (VI)

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, log ϵ 4.20), λ_{min} 239 mμ (log ϵ 3.73); n.m.r. signals: triplet centered at 8.84 τ (methyl of ethyl group, area = 3H), 7.78 τ (methyl attached to ring at C_3, area = 3H), quartet centered at 7.37 τ (methylene of ethyl group, area = 2H), four signals centered at 3.2 τ (olefinic H, area = 2H), multiplet centered at 2.72 τ (aromatic H, area = 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 (VII)

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 (VIII)

To a stirred solution of 3-methyl-5-ethyl isonicotinic 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 continuously 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 (log ϵ 3.48), λ_{min} 238 mμ (log ϵ 2.85); n.m.r. signals: triplet centered at 8.9 τ (methyl of ethyl group, area = 3H), 7.85 τ (methyl attached to ring, area = 3H), quartet centered at 7.5 τ (methylene of ethyl group, area = 2H), 6.21 τ (—$COOCH_3$, area = 3H), 1.83 τ (αH, area = 2H). Found: C, 67.16; H, 7.26; N, 7.90. Calc. for $C_{10}H_{13}O_2N$: C, 67.02; 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, 47.06; 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 (11). The recovery in this reaction is good and this provided an excellent method for purifying small quantities.

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