Additional Routes in the Metabolism of 3-Acetylpyridine*

HERBERT MCKENNIS, JR., LENNOX B. TURNBULL, AND EDWARD R. BOWMAN

From the Department of Pharmacology, Medical College of Virginia, Richmond 19, Virginia

(Received for publication, August 16, 1963)

The ability of 3-acetylpyridine to serve as an antagonist of niacin (see, for example, (2–4)) and on occasion to serve in a niacin-like capacity (see, for example, (4, 5)) has created a sustained interest in the various metabolic routes responsible for the observed nutritional effects. The demonstration (6–10) that 3-acetylpyridine is metabolized to nicotinic acid and N-phenylnicotinamide affords the basis for a biochemical explanation of the niacin-like effects. Similarly, the demonstration by Kaplan and Clotti (11) that 3-acetylpyridine forms a diphosphopyridine nucleotide analogue provides material upon which to construct rational hypotheses for a partial explanation of the anti-niacin effects, although the analogue does possess (12) some enzymatic activity. In recent years, during the investigation of the metabolism of 3-acetylpyridine-methyl-14C, Beher, Baker, and Madoff (8) presented evidence indicating the production of formate from oxidation of the labeled methyl group of 3-acetylpyridine. These authors suggested various routes which might be implicated in the oxidative metabolism of 3-acetylpyridine.

The current report provides data pointing to a wide variety of compounds that are excreted in the urine as a result of the metabolism of 3-acetylpyridine in the dog. Two of those compounds, new metabolites of 3-acetylpyridine, have been isolated and characterized as derivatives. The structure of one, N-methylated 1-(3-pyridyl)ethanol, has been confirmed by total synthesis.

**EXPERIMENTAL PROCEDURE**

**Paper Chromatographic Procedures—**All paper chromatograms, unless otherwise noted, were run by the descending method at ambient temperature, on Whatman No. 1 filter paper. Koenig-positive zones were disclosed as previously described (13). The reagent for disclosing Dragendorff-positive zones has been previously reported (14). The solvent systems were: A, acetic acid-n-butyl alcohol-water (22:100:50 by volume) (15); B, 0.5 N ammonia-ethanol (95%)-n-butyl alcohol (1:1:4 by volume) (16); C, 90% formic acid-sec-butyl alcohol-water (14:75:11 by volume) (17); D, heptane-methanol-water (4:3:1 by volume) (cf. (18)).

**3-Acetylpyridine—**The compound was obtained from Aldrich Chemical Company, Inc. The material was used directly or was redistilled before use. Only those samples showing upon paper chromatography a single Koenig-positive zone at \( R_f 0.83 \) (Solvent B) and \( R_f 0.77 \) (Solvent C) were employed.

1-(3-Pyridyl)ethanol—This compound, which has been previously described (19, 20), was conveniently obtained via a reduction of 3-acetylpyridine (50 g) in water (300 ml) with sodium borohydride (4.52 g). The sodium borohydride was added portionwise to the stirred solution over a period of 20 minutes. After an additional 15 minutes of stirring, 20 ml of acetone were added. The solution was then saturated with sodium chloride and extracted with two portions of chloroform (400 ml each). The viscous residue from evaporation of the chloroform distilled as a colorless liquid at 188–163° and 32 mm of Hg. The product (45 g) showed a single Koenig-positive zone at \( R_f 0.65 \) (Solvent A).

The carbinol (693 mg) readily yielded an N-phenylcarbamate upon treatment with phenyl isocyanate (670 mg). The resultant crystalline 1-(3-pyridyl)ethanol N-phenylcarbamate was recrystallized from acetone-hexane and then dried at 25° and 1 mm of Hg, m.p. 149–150°.

**C\(_7\)H\(_6\)N\(_2\)O\(_3\)**

Calculated: C 46.38, H 4.59, N 18.21

Found: C 46.43, H 4.59, N 18.21

The foregoing methiodide (24 mg) in 10 ml of water was placed on a small column of Dowex 21K (OH–). The effluent and water wash were brought to pH 7 by addition of an aqueous solution of 5-nitrobarbituric acid. The crystalline 5-nitrobarbiturate, obtained from evaporation of the water, was recrystallized several times from isopropyl alcohol and then dried at 25° and 1 mm of Hg, m.p. 171.5–172.5°.

**C\(_7\)H\(_6\)N\(_2\)O\(_3\)**

Calculated: C 46.45, H 4.53, N 18.06

Found: C 46.38, H 4.59, N 18.21

Resolution of (\( +, + \))-1-(3-Pyridyl)ethanol—(\( +, + \))-1-(3-Pyridyl)ethanol (40.0 g) and 48.8 g of \( \beta \)-tartaric acid were dissolved in 400 ml of hot methanol. Upon cooling and scratching, a colorless crystalline precipitate (m.p. 138.5–141°) formed.
The acid tartrate was recrystallized six times from methanol to obtain a product (15.9 g), m.p. 146–147.5°, after recrystallization and drying at 25° and 1 mm of Hg, [α]D = +5.4° (5% in water). An additional crop (4.5 g) was obtained by processing the mother liquor.

\[
\text{C}_6\text{H}_8\text{NO}_3
\]

Calculated: C 48.35, H 5.53, N 5.13
Found: C 48.38, H 5.50, N 5.06

\(-\)\(1\)-(3-Pyridyl)ethanol Methiodide—\(\text{-}\)-The foregoing dextrorotatory tartrate (3.25 g) was dissolved in 25 ml of 5 N ammonium hydroxide. The solution was extracted with several portions of chloroform. The residue from evaporation of the chloroform was dissolved in 40 ml of methanol. After addition of 1.5 ml of methyl iodide, the mixture was heated under reflux overnight. The residue from evaporation of the solvent was recrystallized from isopropanol alcohol to obtain the product, m.p. 98.5–100.5°, 2.25 g. For analysis the compound was recrystallized from isopropanol alcohol and dried at 25° and 1 mm of Hg, m.p. 100–102°, [α]D = –23.6° (6% in methanol).

\[
\text{C}_7\text{H}_8\text{NO}_3
\]

Calculated: C 36.24, H 4.56, N 5.28
Found: C 35.59, H 4.79, N 5.44
C 36.66, H 4.50

A solution of 700 mg of the foregoing iodide in 10 ml of water was placed upon a column of Dowex 21 K (OH\(^–\)). The combined effluent and water wash were adjusted to pH 7 by addition of 5-nitrobarbituric acid. After evaporation of the water, the nitrobarbiturate was recrystallized several times from methanol. For analysis the product was dried at 25° and 1 mm of Hg, m.p. 158–159.5°, [α]D = –19.3° (5% in methanol).

\[
\text{C}_6\text{H}_7\text{NO}_4
\]

Calculated: C 36.58, H 3.73, N 10.21
Found: C 36.45, H 4.50, N 17.98

\(3\)-Acetyl-1-methylpyridinium Iodide—This compound was conveniently prepared by adding 5.82 g of methyl iodide to 5 g of 3-acetylpyridine in 10 ml of methanol. During 24 hours the mixture stood at room temperature in the dark and deposited yellow crystals (8.7 g, 86%), m.p. 159–163°. These were collected, recrystallized from acetone-methanol (98:3 by volume), and air-dried for analysis, m.p. 164–165°. 3-Acetyl-1-methylpyridinium iodide has been previously described with a melting point in substantial agreement (see, for example, (21, 22)) and also in a form melting at 154.5–155° (23). The iodide salt was conveniently converted to the acetate salt with the aid of Dowex 21K (acetate), \( R_f 0.46 \) (Solvent A).

\[
\text{C}_6\text{H}_7\text{NO}_3
\]

Calculated: C 46.45, H 4.55, N 18.06
Found: C 46.35, H 4.50, N 17.98

Examination of Urine for Metabolites of 3-Acetylpyridine—3-Acetylpyridine (50 mg per kg of body weight) in 0.9% sodium chloride was administered during 8 hours via a femoral vein to adult male mongrel dogs under pentobarbital anesthesia. Bladder urine was collected during infusion and the subsequent 10-hour period. The urine from eight dogs, representing a total dose of 0.08 g of 3-acetylpyridine, was combined and concentrated under diminished pressure at 40°. The dry residue was extracted with two portions (1 liter each) of boiling absolute ethanol. The residue from evaporation of the alcohol was dissolved in 0.25 ml of water. An aliquot (417 ml) was placed on 250 ml of wet Dowex 50W (H\(^+\)) resin. The column was washed thoroughly with distilled water and then was treated with 2 N ammonium hydroxide until the effluent no longer gave a positive Koenig reaction. The ammoniacal effluent was saved for subsequent investigation (Fraction I). After a water wash, the column was treated with 1 N hydrochloric acid until the effluent was free of ammonium ion. The solution was discarded. The column was then washed with 5 N hydrochloric acid and until the effluent showed no absorption at 265 μ. This 3 N hydrochloric acid fraction was concentrated to a brown gum (200 mg). An aqueous solution of the gum was placed upon a column (20 ml) of Dowex 21K (OH\(^–\)). The combined effluent and water wash were neutralized with acetic acid. A sample of the residue from evaporation of the solvent, when chromatographed on Grycksbo chromatographic paper, No. 3 (70 g per sq m), separated into two zones, \( R_f 0.56 \) and \( R_f 0.70 \) (Solvent A), which gave a positive reaction with Dragendorff's reagent. The residue was dissolved in 10 ml of Solvent A and placed upon a Chromax column, 58 x 360 cm, loaded with the Grycksbo No. 3 paper. By elution with Solvent A, two fractions were obtained. The fraction with \( R_f 0.70 \) (A) cochromatographed with authentic 3-(1-hydroxyethyl)-1-N-methylpyridinium acetate. In addition to quaternary ammonium compound, the fraction appeared to contain considerable quantities of material derived from the paper. The fraction containing material with \( R_f 0.56 \), corresponding in value to authentic N\(^-\)-methylnicotinamide acetate, was concentrated under diminished pressure to a dry residue (200 mg). A solution of the residue in 5 ml of water was placed upon a column (5 ml) of Dowex 50W (H\(^+\)). The effluent was discarded and the column was washed with water until a neutral effluent was obtained. The column was treated with 30 ml of 5 N hydrochloric acid. By evaporation of the acidic solution under diminished pressure, a residue of N\(^-\)-methylnicotinamide chloride was obtained. The chloride was dissolved in a small volume of water and placed upon a column (6 ml) of Dowex 21K (OH\(^–\)). An aqueous solution of picric acid (283 mg) was added to the combined effluent and water wash. The crude picrate of N\(^-\)-methylnicotinamide was obtained by evaporation of the solvent under diminished pressure. After seven recrystallizations from methanol, the product (20 mg) melted at 191.5–193° and did not depress the melting point of an authentic sample, m.p. 191.5–193° (24).

\[
\text{C}_7\text{H}_8\text{NO}_3
\]

Calculated: C 42.74, H 3.04, N 19.18
Found: C 42.87, H 3.09, N 19.21

Isolation of N\(^-\)-Methylated 1-(3-Pyridyl)ethanol—An adult male mongrel dog (10 kg) received orally 500 mg of 3-acetylpyridine in aqueous solution as a single dose on 8 consecutive days. An aliquot (1 liter) of the 8-day urine (2.5 liters) was concentrated as described above. The residue was placed upon Dowex 50W (H\(^+\)). After an elution with 2 N ammonium hydroxide to give a fraction which was not further investigated, the column was treated with 1 N hydrochloric acid and finally with 5 N hydrochloric acid. The residue from evaporation of the fraction...
obtained with 5 N hydrochloric acid was converted to the hydroxide form and finally the acetate form, a brown gum (921 mg), by the procedure described above. A solution of the residue in Solvent A was processed on the Chromax column to obtain fractions with RF values of 0.70 (A) and 0.56 (A). Those fractions showing material at RF 0.56, corresponding in value to N1-methylneotininamide, were discarded. The residue from the evaporation of the RF 0.70 fractions (213 mg) was dissolved in water and placed upon Dowex 50W (H+). After a water wash, the column was treated with 5 N hydrochloric acid. The residue from evaporation of this acidic solution was converted to the hydroxide form on Dowex 21K (OH-) by the procedure described above. After conversion to the chloride form by addition of hydrochloric acid, the fraction was dissolved in water (10 ml) and treated with a solution of ammonium reineckate (600 mg in 25 ml of water). The resultant crystalline reineckate of the quaternary ammonium compounds was then converted to the hydroxide with Dowex 21K (OH-) by the method previously described (25). The methanolic solution of the hydroxide form from the column was treated with 180 mg of 5-nitrobarbituric acid. A crystalline precipitate formed. This crude 3-(1-hydroxyethyl)-N methylpyridinium 5-nitrobarbiturate was recrystallized 5 times from methanol to obtain an analytical sample (80 mg), m.p. 169.5-170°C. The product at a concentration of 40 mg per ml in methanol showed no optical rotation with the 5461 A-line of mercury (10-dm tube).

C₁₆H₁₁N₃O₆
Calculated: C 46.45, H 4.55, N 18.06
Found: C 46.38, H 4.58, N 17.95

Isolation of a Diol Arising from Metabolism of 3-Acetylpyridine—The ammoniacal urinary fraction (Fraction I) from the intravenous administration of 3-acetylpyridine to eight dogs (above) was concentrated under diminished pressure to a volume of 50 ml. The solution was adjusted to pH 9 by addition of ammonia and then continuously extracted overnight with chloroform. The chloroform solution was concentrated under diminished pressure to an oily residue. An aqueous solution of the residue was placed upon a column (300 ml) of Dowex 50W (H+). After a water wash, the column was treated with 2 N ammonium hydroxide until no more Koenig-positive material appeared in the effluent. The ammoniacal solution was placed upon Dowex 21K (OH-). The effluent and water wash were combined and evaporated to a clear gum (213 mg), which upon paper chromatography on Whatman No. 1 paper showed Koenig-positive zones at RF 0.49 (heavy), 0.70 (light), and 0.76 (trace). The product was dried at 50°C and 1 mm of Hg over KOH. 

C₁₆H₁₁N₃O₆.H₂O
Calculated: C 40.00, H 4.27, N 16.97
Found: C 40.43, H 4.37

The foregoing monohydrate (by analysis) of (3-pyridyl)-1,2-ethanediol 5-nitrobarbiturate was dried at 60°C and 1 mm of Hg for 3 hours; m.p. 196-197°C, [α]₄₂₄ +17.2º (3% in water).

C₁₆H₁₆N₄O₄
Calculated: C 42.31, H 3.87, N 17.95
Found: C 42.24, H 3.89, N 17.99

The mother liquors from the diol 5-nitrobarbiturate were dissolved in alcohol-water and placed upon a column (4 ml) of Dowex 50W (H+). After a water wash to insure removal of 5-nitrobarbituric acid, the column was treated with 2 N ammonium hydroxide until the effluent gave no Koenig reaction. The solvent was removed under diminished pressure and the residue was treated overnight with 2 ml of acetic anhydride-pyridine (1:1 by volume). Methanol (3 ml) was added dropwise to the mixture. The mixture was concentrated on the steam bath under a stream of nitrogen to an oily residue (61 mg), which gave a single Koenig-positive zone at RF 0.78 (Solvent A) and RF 0.11 (Solvent D). The residue was treated with picric acid (100 mg). The crystalline picrate was recrystallized three times from 95% ethanol to obtain a product (59 mg), m.p. 86-87°C. For analysis, the product was dried at 50°C and 1 mm of Hg over KOH, [α]₄₂₄ +28.2º (2.5% in methanol).

C₁₆H₁₆N₄O₄.H₂O
Calculated: C 45.14, H 3.57, N 12.39
Found: C 45.23, H 3.68, N 12.30

In another experiment, a male mongrel dog (25 kg) received 1 g of 3-acetylpyridine orally per day for 2 days. The combined urine from the 2-day period and 2 subsequent days was concentrated to dryness under diminished pressure. The residue was extracted with two portions of boiling absolute ethanol (1 liter and 500 ml). After filtrations, the combined alcoholic solutions were diluted to 3 liters with water. The resultant solution was placed upon a column (1 liter) of Dowex 50W (H+). The effluent and water wash, which contained Koenig-positive material, RF 0.73 (Solvent A), were saved for possible further investigation. The resin column was treated with 2 N ammonium hydroxide until no more Koenig-positive material was obtained. An
exhaustive continuous extraction of the ammoniacal solution with chloroform removed 278 mg of oil. The oil in aqueous solution was reprocessed upon Dowex 50W (H+). The ammoniacal eluate from this column was placed upon Dowex 21K (OH-). The combined effluent and water wash were concentrated. The residue was dissolved in a minimal amount of chloroform and placed upon a column of Florisil (approximately 0 g). An elution with acetic-benzene (1.9 by volume, and incrementally increased to 100% acetone) served to remove two Koenig-positive fractions: \( R_f 0.68 \) (A), which cochromatographed with an authentic sample of 1-(3-pyridyl)ethanol, and \( R_f 0.46 \) (A). The second fraction (\( R_f 0.46 \)) was concentrated to an almost colorless oil (53 mg). The light-yellow crystalline 5-nitrobarbiturate of the diol formed upon addition of 5-nitrobarbituric acid (87 mg) and a small volume of 75% ethanol. The product was recrystallized 3 times from 75% ethanol to obtain the analytical sample (50 mg), which was dried for 3 hours at 80° and 1 mm of Hg. The diol 5-nitrobarbiturate melted at 193.5-195°. The melting point was not depressed upon admixture with the diol 5-nitrobarbiturate obtained from the urine after intravenous administration of 3-acetylpyridine as described above.

\[
C_{11}H_{17}N_3O_7
\]

Calculated: C 42.31, H 3.87, N 17.95

Found: C 42.35, H 4.00, N 17.95

Chemical Oxidation of (3-Pyridyl)-1,2-ethanediol to Nicotinic Acid—(3-Pyridyl)-1,2-ethanediol (50 mg) in 0.5 ml of water was oxidized at 70-80° by dropwise addition of 2% aqueous potassium permanganate, which was added until a faint pink color was no longer discharged. The solution was filtered to remove manganese dioxide and then placed upon a column (2 ml) of Dowex 21K (OH-). After a water wash, the column was treated with 2 N acetic acid. The acidic eluate was concentrated to a white crystalline solid (27 mg), which chromatographed on paper to give a single Koenig-positive zone, \( R_f 0.68 \) (Solvent A), corresponding in \( R_f \) value to authentic nicotinic acid. The product, after recrystallization from water, melted at 235.5-236.5°. Upon admixture with an authentic sample of nicotinic acid, m.p. 235.5-236.5°, the melting point was underpressed.

RESULTS AND DISCUSSION

From a series of investigations, Beher et al. (6-10) have presented a variety of data on the metabolism of 3-acetylpyridine in vitro and in vivo. These studies and others led to the suggestion (10) that 3-acetylpyridine during the course of its metabolism might displace nicotinamide and thus enter into nucleotide formation. Experimental confirmation of this possibility has been achieved (11), and other possible metabolic routes have been experimentally considered (6-10).

By analogy with the metabolism of methyl phenyl ketone (20), it was considered (6) that \( \beta \)-pyridylmethylcarbinol, 1-(3-pyridyl)ethanol, could be one of the major metabolites of 3-acetylpyridine. Although no 1-(3-pyridyl)ethanol was found in

\footnote{After an exhaustive extraction with chloroform, the ammoniacal solution contains Koenig-positive material which is readily hydrolyzed at 100° in 5 N HCl to form material that is extractable from alkaline solution with chloroform. This new material, which corresponds in \( R_f \) value to 1-(3-pyridyl)ethanol, is possibly derived from hydrolysis of a glucuronide.

the urine of the dog after administration of 3-acetylpyridine, it was noted (6) that urinary excretion of glucuronide, nicotinic acid, and N\(^1\)-methylbeotinamide was enhanced by administration of 1-(3-pyridyl)ethanol, to a degree comparable to that achieved with 3-acetylpyridine.

In our study also, indirect evidence for the possible intermediatory role of 1-(3-pyridyl)ethanol was obtained. A chloroform extract of dog urine after the administration of 3-acetylpyridine showed two Koenig-positive zones upon paper chromatography. The \( R_f \) value of one of these corresponded to that of authentic 1-(3-pyridyl)ethanol. The aqueous phase which remained from the extraction was heated with acid under conditions generally adequate for hydrolysis of glucuronides. The re-emergence of chloroform-extractable material with \( R_f \) value corresponding to that of 1-(3-pyridyl)ethanol was again noted.

A paper chromatographic examination of the strongly basic (quaternary ammonium) fraction of the urine showed two Dragendorff-positive zones attributable to metabolites of 3-acetylpyridine. Material at one of these zones had the same \( R_f \) value as N\(^1\)-methylnicotinamide. Chemical confirmation of the presence of this compound, which has been previously shown to be a metabolite of 3-acetylpyridine (10) as well as nicotinic acid, was achieved through isolation of a picric acid salt which was identified by analysis and comparison with an authentic sample. The other Dragendorff-positive zone corresponded in \( R_f \) value to a synthetic sample of N-methylated 1-(3-pyridyl)-ethanol, 3-(1-hydroxyethyl)-N-methylpyridinium ion, and was present after either intravenous or oral administration of 3-acetylpyridine.

After preliminary purification of the urine of a dog that had received a total of 4.00 g of 3-acetylpyridine over an 8-day period, the fraction with \( R_f \) value corresponding to the N-methylated 1-(3-pyridyl)ethanol was converted to a crystalline Reinecke salt. The Reinecke salt, in turn, was converted to a crystalline 5-nitrobarbiturate. The salt, m.p. 169.5-170°, did not depress the melting point of an authentic sample, m.p. 169.5-170°, and gave the correct elementary analysis. A solution of the salt of the metabolite in methanol showed no optical rotation when examined with the 5461 A-line of mercury. For comparative purposes, (+, -)-1-(3-pyridyl)ethanol was resolved via a tartaric acid salt. The dextrorotatory tartrate was then converted to a base which, upon treatment with methyl iodide, readily formed a levorotatory methiodide. The methiodide was converted to a 5-nitrobarbiturate, m.p. 158-159.5°, which showed a readily observable rotation in contrast to the salt of the metabolite.

Stability studies were conducted on the optically active synthetic N-methylated 1-(3-pyridyl)ethanol (3-(1-hydroxyethyl)-N-methylpyridinium ion). The compound showed good stability during contact with Dowex 50W (H+) and Dowex 21K (OH-) under conditions comparable to those employed in the isolation procedures. No significant loss of optical activity was observed under these conditions or as a result of acidic conditions comparable to those employed in the isolation procedures. Perforce it is reasonable to look in vivo to enzymatic processes as the basic source of the racemic product that was obtained from urine. A detailed, systematic study of conditions necessary for racemization of N-methylated 1-(3-pyridyl)ethanol in vivo and in vitro is highly desirable.
affords the first direct experimental evidence for the participation of the 1-(3-pyridyl)ethanol moiety in the metabolism of 3-acetylpyridine. Since the immediate precursor of the N methylated 1-(3-pyridyl)ethanol could be another quaternary ammonium compound, such as the nucleotides which have been previously discussed, N-methylated 3-acetylpyridine, or 1-(3-pyridyl)ethanol itself, a considerable body of new data is required to establish the sequence of metabolic events in the metabolism of 3-acetylpyridine.

Additional evidence which may suggest the participation of 1-(3-pyridyl)ethanol in the metabolism of 3-acetylpyridine was obtained during an examination of the weakly basic Koenig-positive fraction that was obtained from urine after administration of 3-acetylpyridine to dogs. One component of this fraction which was isolated as an oil showed a single Koenig-positive zone upon paper chromatography and was converted to a crystalline nitrobarbituric acid salt. The salt, which was initially obtained in a form that gave an elementary analysis corresponding approximately to the monohydrate, 

\[ \text{C}_6\text{H}_5\text{N}_2\text{O}_3 \cdot \text{H}_2\text{O} \]

was converted upon further drying to an anhydrous salt, 

\[ \text{C}_6\text{H}_5\text{N}_2\text{O}_2 \]

by analysis. The mother liquors from recrystallization of the nitrobarbiturate were reprocessed to obtain an additional quantity of the base. Reaction with acetic anhydride served to convert the base to a diacetyl derivative, which was obtained as an oil. The oil readily afforded a crystalline picrate, 

\[ \text{C}_6\text{H}_5\text{N}_2\text{O}_2 \]

by analysis. The analytical data was consistent with that expected for the monoplate of an O,O'-diacetyl derivative of 3-pyridylethylene glycol. Solutions of salts of both the base, 

\[ \text{C}_6\text{H}_5\text{N}_2\text{O}_2 \]

and its diacetyl derivative showed optical activity when examined in the polarimeter; in contrast, the salt of metabolic N-methylated 1-(3-pyridyl)ethanol showed none.

On the basis of the analytical data, chemical reactions, and the strong positive Koenig reaction, a provisional assignment of structure for the new metabolite of 3-acetylpyridine, 

\[ \text{C}_6\text{H}_5\text{N}_2\text{O}_2 \]

appeared to be warranted. In view of the fact, however, that the Koenig reaction has not been fully studied on a variety of C-substituted hydroxypyridines or pyridones, the compound was subjected to an oxidative degradation. This afforded nicotinic acid. It may be concluded then that both hydroxyl groups of the base are positioned on the side chain at position 3 of the pyridine ring, and that (3-pyridyl)-1,2-ethanediol is the most reasonable structure for the metabolite. For confirmation of this structure, a synthesis of the compound is required. Although 1-(3-pyridyl)ethanol may be considered a logical natural precursor of (3-pyridyl)-1,2-ethanediol, a number of other possibilities must also be considered. Beher et al. (8), discussing the possible routes by which the methyl carbon atom of 3-acetylpyridine is converted to formate in the rat, considered the possibility of 3-acetylpyridine being converted to a keto alcohol, 3-pyridyl hydroxymethyl ketone. This compound, or associated intermediates, upon reduction would yield (3-pyridyl)-1,2-ethanediol.

There are currently no direct data available on the metabolism of (3-pyridyl)-1,2-ethanediol or 3-pyridyl hydroxymethyl ketone. It is fortunate, however, that there exists a large body of literature on the metabolism of analogous phenyl compounds. Much of this literature has been reviewed by Williams (27). El Masri, Smith, and Williams (28) studied the metabolism of phenacyl alcohol, the phenyl analogue of 3-pyridyl hydroxymethyl ketone, in the rabbit. The authors found no evidence that phenacyl alcohol was converted to either phenyl-1,2-ethanediol or mandelic acid, both of which have been reported as metabolites of acetophenone (27, 29). These data, previous experiments and discussions (8) on the metabolism of 3-acetylpyridine, and a summary of related data by Williams (27) permit

![Fig. 1. Abridged tentative scheme for the metabolism of 3-acetylpyridine](http://www.jbc.org/)

the consideration of a tentative scheme for the metabolism of 3-acetylpyridine as shown in Fig. 1. Characterization and study of the yet unidentified intermediates will facilitate acceptance, rejection, or modification of the indicated routes.

SUMMARY

The metabolism of 3-acetylpyridine was investigated in the mongrel dog after oral and intravenous administration of the compound. A paper chromatographic examination of the processed urine from the animals suggested the presence of a variety of metabolites, including 1-(3-pyridyl)ethanol, which had been previously indirectly implicated by other workers. The quaternary ammonium fraction from the urine was chromatographed on paper to provide separation of N1-methyl-nicotinamide, a previously recorded metabolite of 3-acetylpyridine, and N-methylated 1-(3-pyridyl)ethanol. The latter was characterized as a 5-nitrobarbiturate acid salt in comparison to an optically active 5-nitrobarbituric acid salt obtained from urine. A paper chromatographic examination of the urine was chromatographed on paper to provide separation of N1-methyl-nicotinamide, a previously recorded metabolite of 3-acetylpyridine, and N-methylated 1-(3-pyridyl)ethanol. The latter was characterized as a 5-nitrobarbiturate acid salt in comparison to an optically active 5-nitrobarbituric acid salt obtained from urine.

REFERENCES

Additional Routes in the Metabolism of 3-Acetylpyridine
Herbert McKennis, Jr., Lennox B. Turnbull and Edward R. Bowman


Access the most updated version of this article at http://www.jbc.org/content/239/4/1215.citation

Alerts:
- When this article is cited
- When a correction for this article is posted

Click here to choose from all of JBC's e-mail alerts

This article cites 0 references, 0 of which can be accessed free at http://www.jbc.org/content/239/4/1215.citation.full.html#ref-list-1