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REACTION OF DEHYDROACETIC ACID WITH AMMONIA

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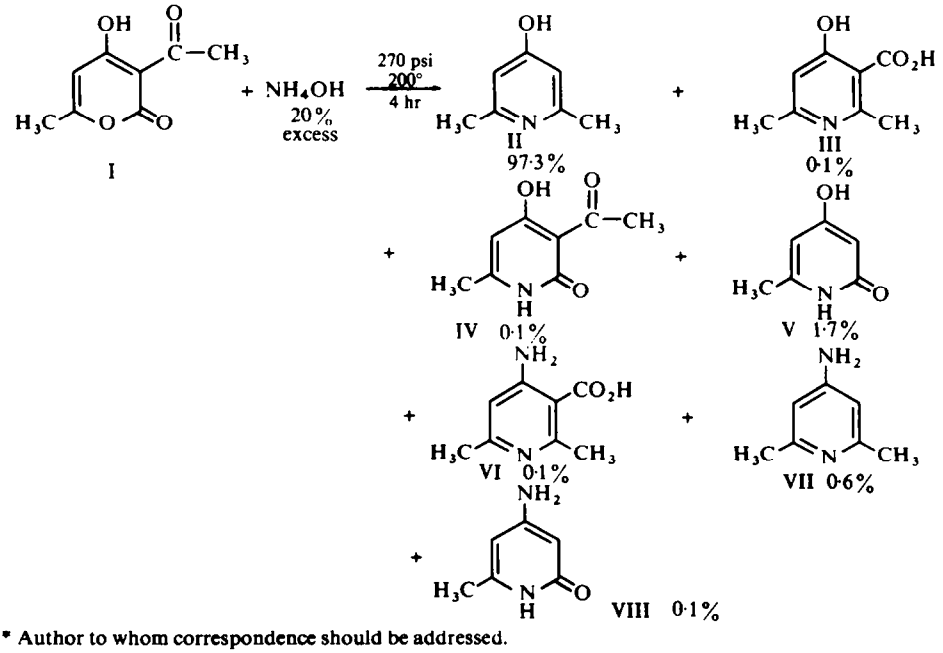
Abstract—Dehydroacetic acid reacts with aqueous NH_3 at 200° to give the major product 2,6-dimethyl-4-pyridinol and six minor by-products. Isolation and synthesis of the by-products, proof of the structures and the mechanistic interpretation of their formation are discussed.

THE conversion of dehydroacetic acid (I) into 2,6-dimethyl-4-pyridinol (II) by the action of aqueous ammonia was first reported by Haitinger in 1885.[1] Since then, several papers describing the mechanism of the reaction between dehydroacetic acid and alkylamines have been published.[2–6] The yields of II or the N-alkyl pyridinols which were reported range from 20–80%. Recently, to optimize the yield of II, we have identified six other by-products in the reaction of dehydroacetic acid with ammonia. Mechanistic interpretation and ways to minimize the formation of these by-products have been investigated. We have been able to achieve a 97% yield of II. The optimum condition is expressed in the following equation:



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Isolation and synthesis of by-products

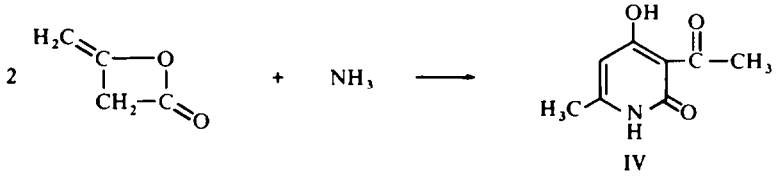
Isolation of the by-products was achieved by passing the aqueous reaction mixture through an ion exchange column. Separation of the individual impurities was accomplished by gradient elution with a mixture of acetic acid-methanol soln.[7] Evaporation of the elution fractions to dryness followed by further purification, if necessary, gave pure compounds. Their structures were not only confirmed by IR, NMR, MS and elemental analyses but also by comparison with synthesized compounds by m.ps, R_f values (TLC) and UV spectra. Compounds (IV), (VI) and (VIII) are new to the literature. Table I lists the R_f values of the dehydroacetic acid-NH_3 reaction products.

TABLE 1. R_f VALUES OF 2,6-DIMETHYL-4-PYRIDINOL AND BY-PRODUCTS

	R_f Values	
	Solvent 1	Solvent 2
4-Amino-2,6-dimethylnicotinic acid	0·11	0·04
4-Hydroxy-6-methyl-2-pyridone	0·13	0·66
4-Hydroxy-2,6-dimethylnicotinic acid	0·21	0·32
2,6-Dimethyl-4-pyridinol	0·40	0·15
3-Acetyl-4-hydroxy-6-methyl-2-pyridone	0·51	0·64
4-Amino-6-methyl-2-pyridone	0·54	0·48
4-Amino-2,6-lutidine	0·60	0·06
Dehydroacetic acid	0·78	0·72
Dehydroacetic acid imine	0·80	0·62

Solvent 1 Acetone:methanol:30% NH_4OH = 80:15:2
Solvent 2 n-Butanol:acetic acid = 9:1

3-Acetyl-4-hydroxy-6-methyl-2-pyridone (IV) is synthesized by the reaction between anhydrous ammonia and diketene in dioxane.



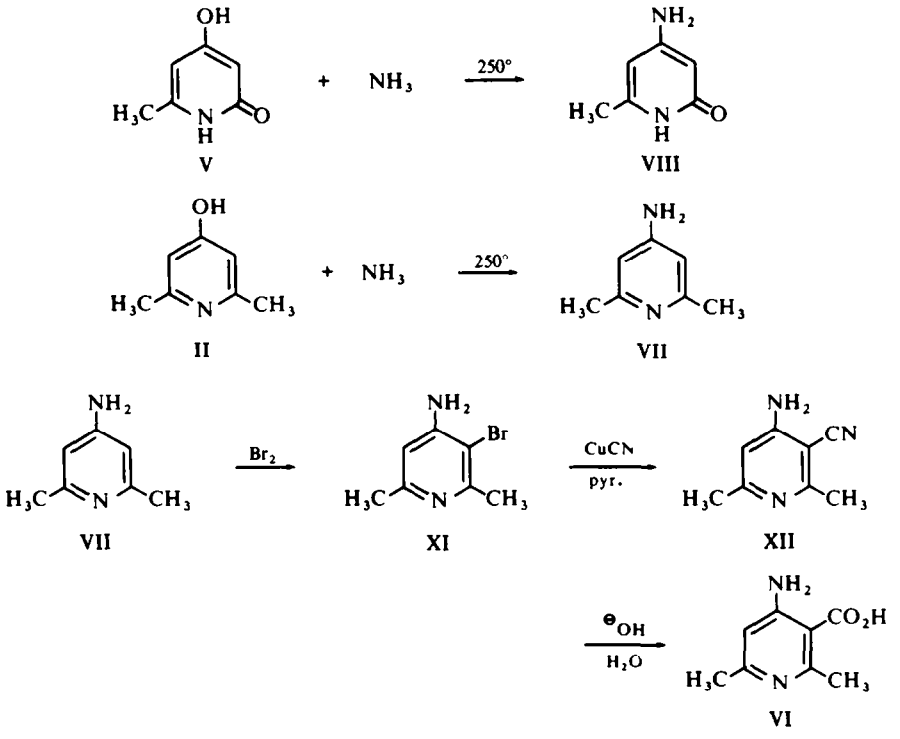
IV

4-Hydroxy-6-methyl-2-pyridone (V) is prepared by treating dehydroacetic acid with 90% H_2SO_4 to form 6-methyl-2H-pyran-2,4(3*H*)dione followed by aminolysis.[9]

4-Amino-6-methyl-2-pyridone (VIII) and 4-amino-2,6-lutidine (VII) are sythesized by the aminolysis of 4-hydroxy-6-methyl-2-pyridone (V) and 2,6-dimethyl-4-pyridinol (II) at 250°, respectively.

Owing to decarboxylation during the reaction, a low yield of 4-amino-2,6-dimethylnicotinic acid (VI) is obtained through the aminolysis of 4-hydroxy-2,6-dimethylnicotininic acid (III). VI in respectable yield is finally attained by the following reaction sequence.

4-Hydroxy-2,6-dimethylnicotinic acid[5] (III) is isolated from the reaction mixture



which contains 16% II and 4% of III. The reaction mixture is obtained by treating dehydroacetic acid with aqueous ammonia at 160° for 1hr. The high solubility of II in water makes their separation feasible.

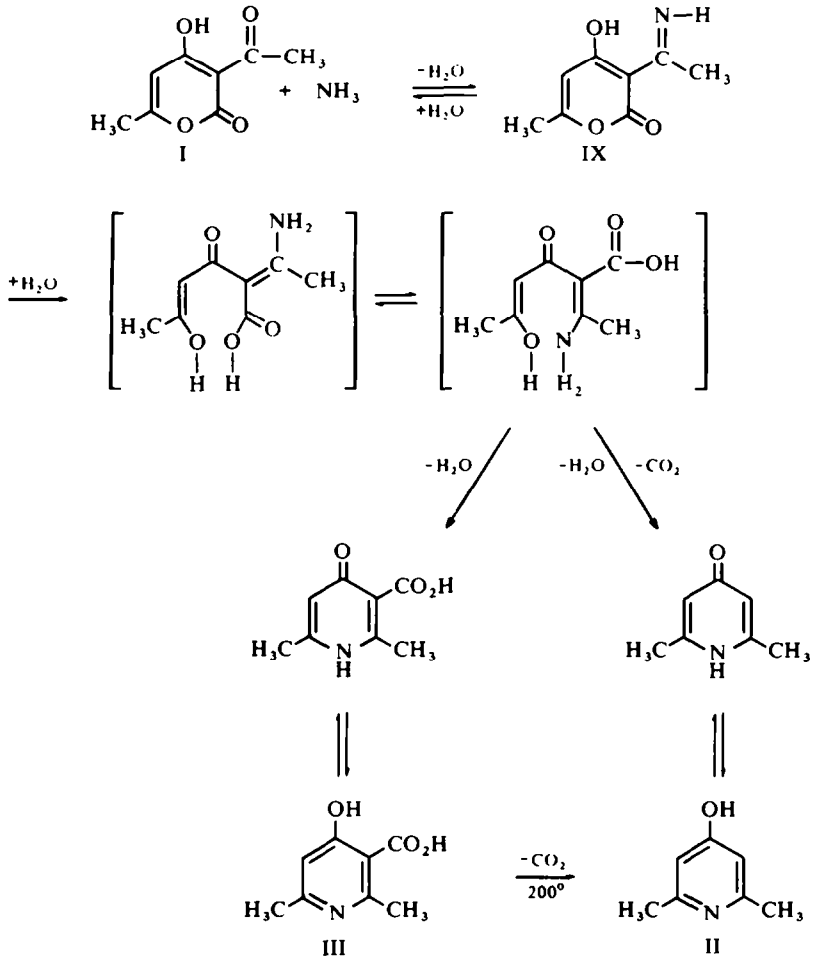
DISCUSSION

The mechanism for the formation of compounds II and III by the reaction of dehydroacetic acid and ammonia was well interpreted in the literature.[2–6] However, the mechanisms for the formation of compounds IV–VIII, which sometimes amount to 15%, were not explained. There are four possible sites in dehydroacetic acid which could be attacked by ammonia: the carbonyl of the acetyl side chain at the 3 position, the carbon atom terminating the conjugated carbon chain at the 6 position, the lactone carbonyl at the 2 position and the carbon atom at the 4 position.

If ammonia attacks at the carbonyl of the acetyl side chain at the 3 position of dehydroacetic acid (I), it will form an imine (IX).[8] Actually, dehydroacetic acid reacted with ammonia even at room temperature to yield a crystalline compound IX in more than 90% yield.[5] When IX is heated with water or aqueous NH_3 at 200°, compounds I–VIII are formed. Therefore, the formation of the Schiff base IX from the reaction of dehydroacetic acid with ammonia is in an equilibrium. The conversion of IX into 2,6-dimethyl-4-pyridinol (II) and 4-hydroxy-2,6-dimethylnicotinic acid (III) is depicted in Scheme I.

Compounds II and III could also be formed by the attack of ammonia at the 6 position of dehydroacetic acid. However, the high yield of IX at room temperature makes this scheme less important.

SCHEME 1

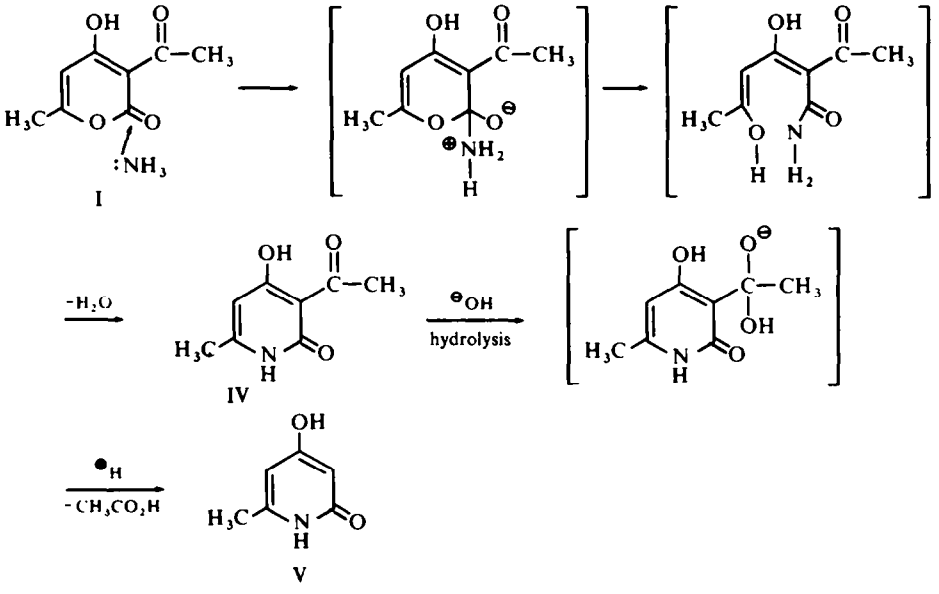


The attack of ammonia at the lactone carbonyl which is at the 2 position of dehydroacetic acid will give 3-acetyl-4-hydroxy-6-methyl-2-pyridone(IV). Compound IV in turn can be hydrolyzed by caustic alkali to give 4-hydroxy-6-methyl-2-pyridone (V).

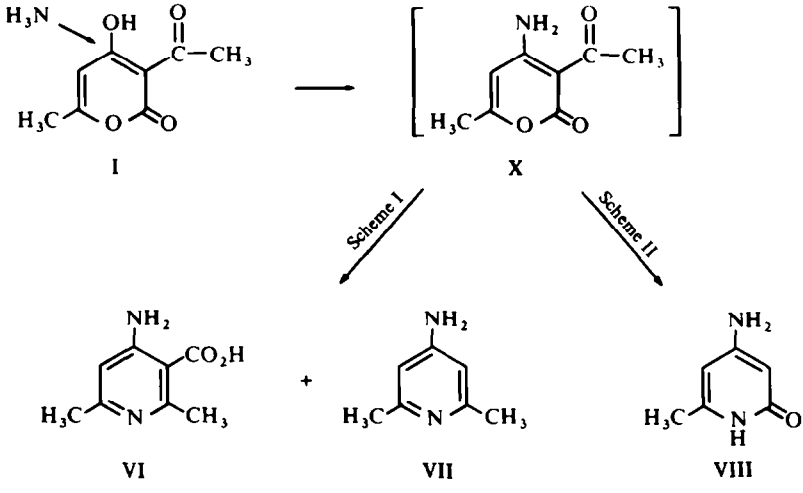
If ammonia attacks the carbon at the 4 position of dehydroacetic acid (I), a Michael type reaction will occur and give 3-acetyl-4-amino-6-methyl-2*H*-pyran-2-one (X). If compound X follows Scheme I, it will form 4-amino-2,6-lutidine (VII) and 4-amino-2,6-dimethylnicotinic acid (VI); if it follows Scheme II, it will yield 4-amino-6-methyl-2-pyridone (VIII).

When dehydroacetic acid (I) was treated with 20% excess ammonia at 200° for 1 hr., essentially all of it was converted to 2,6-dimethyl-4-pyridinol (II) and 4-hydroxy-2,6-dimethylnicotinic acid (III) with the formation of a small amount of compounds IV and V. Very little of the 4-amino compounds, VI, VII and VIII, were detected. Therefore, it was concluded that the reaction following Scheme III is very limited.

SCHEME 2



SCHEME 3

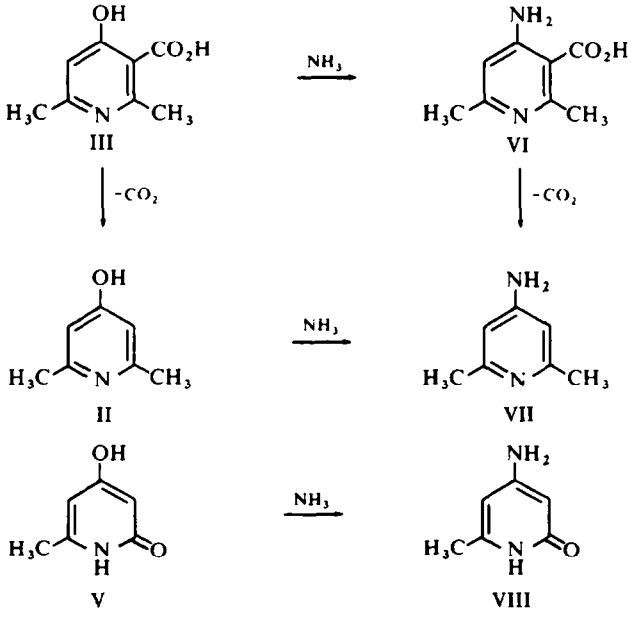


Compounds VI, VII and VIII were almost entirely formed during the decarboxylation of 4-hydroxy-2,6-dimethylnicotinic acid (III) to 2,6-dimethyl-4-pyridinol (II) at 200°. At 200°, compounds II, III and V reacted with the remaining ammonia in the solution to form 4-amino-2,6-lutidine (VII), 4-amino-2,6-dimethylnicotinic acid (VI) and 4-amino-6-methyl-2-pyridone (VIII), respectively. It was observed that at 200° for 3 hours with 50 % excess ammonia, 5 % of II or V was converted to VII or VIII and 8 % of III was converted to VII; at 250° for 6 hours, 50 % of II or V was converted to

TABLE 2. REACTION CONDITIONS ON YIELD OF II

Temp (°C)	Time (Hr)	% Excess Molar NH_3	% II	III	IV	V	VI	VII	VIII
160	4	20	83·3	14·5	0·2	1·9	0	0·1	0
170	4	20	89·5	8·2	0·1	2·0	0	0·2	0
180	4	20	93·0	4·6	0·1	2·0	0	0·3	0
190	4	20	96·8	0·7	0·1	1·9	0	0·5	0
200	4	20	97·3	0·1	0·1	1·7	0·1	0·6	0·1
210	4	20	97·5	0	0·1	1·3	0·1	0·8	0·2
200	4	0	89·2	0·8	0·7	8·7	0	0·6	0
200	4	10	93·9	0·4	0·3	4·8	0	0·6	0
200	4	30	97·1	0·1	0·1	1·5	0·1	0·9	0·2
200	4	40	96·8	0·1	0·1	1·4	0·1	1·2	0·3
200	1	20	92·2	5·1	0·2	2·3	0	0·2	0
200	2	20	96·4	0·9	0·1	2·1	0	0·4	0·1
200	3	20	96·9	0·3	0·1	2·1	0	0·5	0·1
200	4	20	97·3	0·1	0·1	1·7	0·1	0·6	0·1

VII or VIII. The structures of compounds VI, VII and VIII were confirmed by IR, NMR, UV and mass spectrometric analyses. Their formation is depicted as follows:



Therefore, for the complete decarboxylation of III, the reaction mixture should be maintained at 200° for 4 hr, and for the minimization of VI, VII and VIII, the ammonia should not be employed more than 20% molar excess.

EXPERIMENTAL

M.ps were determined on a Thomas-Hoover capillary melting point apparatus and were corrected. Elemental analyses were done by the staff of L. Swim, The Dow Chemical Company. IR spectra were recorded on a Perkin–Elmer 237 spectrophotometer, the UV spectra on a Cary 15, recording spectrophotometer, and the NMR spectra on a Varian Associates A-60 spectrometer. Mass spectra were obtained by Dr. J. Tou, the Dow Chemical Company, on an Atlas CH4B.

Ion exchange separations were monitored by a Gilford, Model 222, power supply connected to a Beckman Model DU monochromator. Columns and fittings were obtained from Chromatronix, Inc. Solvents were propelled through the system with a Milton Roy minipump.

Reaction of dehydroacetic acid with ammonia. Into a 1 l. Parr Series 4500 reactor was placed dehydroacetic acid (84 g; 0·50 mol) 28% NH_4OH (36·5 g; 0·60 mol) and water (238 g). The mixture was heated with stirring at 200° for 4 hr. The pressure of the mixture was maintained at 260–270 psi by venting CO_2 periodically from the reactor. The reactor was then allowed to cool to the room temp and the resulting slurry collected.

A representative 5 g sample of the reactor slurry was diluted to volume with water in a 10 ml volumetric flask. Five μl of sample soln was injected into a 2·8 × 500 mm Bio Rad AG1-X2 (Bio. Rad Laboratories, Richmond, Calif), acetate form, 200–400 mesh anion exchange column. Separation of the impurities was achieved with a gradient elution of 1% v/v AcOH-MeOH into 40 ml MeOH. Column eluate was monitored in a 1-cm optical cell at 270 nm. Concentrations of the impurities were determined by comparing peak areas in the resulting chromatogram with those of a standard separated under identical conditions.

Isolation of by-products

4-Amino-2,6-dimethylnicotinic acid (VI) *and 3-acetyl-4-hydroxy-6-methyl-2-pyridone* (IV). These two impurities were isolated by ion exchange chromatography. A sample of the reaction product (dry basis, 0·1 g) was introduced to a 13 × 250 mm column of Bio-Rad AGl-X2. Following a MeOH wash to remove the 2,6-dimethyl-4-pyridinol, the column was subjected to a gradient elution with 0·05% v/v AcOH–MeOH soln. Compounds IV and VI had retention volumes of 110 and 150 ml, respectively. Both compounds gave NMR, IR, and MS identical to their synthesized counterparts.

4-Hydroxy-2,6-dimethylnicotinic acid (III). This impurity was found to have similar ion exchange retention volume and R_f value when compared with the synthesized compound. UV spectra in acidic and basic MeOH soln were also identical.

4-Hydroxy-6-methyl-2-pyridone (V). A sample (0·1 g) of the reaction product (dry basis) was introduced on a 13 × 150 mm Dowex 2-X8, acetate form, ion exchange column. The material was isolated by gradient elution with 0·1% v/v AcOH–MeOH soln. Compound V had a retention volume of 360 ml. Following evaporation of the impurity fraction to dryness, the residue was recrystallized from MeOH. Comparison by NMR, IR, and MS proved it to be identical with the synthesized material.

4-Amino-2,6-lutidine (VII). Isolation of this impurity was achieved by dry-column chromatography on a 4 × 60 cm bed of silicic acid. A sample of reaction product (dry weight 0·1 g) was applied in a minimum volume of MeOH. Elution was carried out with this same solvent. After extrusion of the absorbent, the top 10 cm was slurried with 5% HCl-MeOH soln. Following filtration, the soln was evaporated to dryness. The residue was taken up with 1N NaOH and extracted 3 times with equal volume of ether. IR and NMR proved it to be identical to the synthesized materials.

4-Amino-6-methyl-2-pyridone (VIII). This impurity was not isolated from pyridinol reactor samples. However, an impurity was observed by TLC that gave an R_f value identical to the synthesized product. Also both the unknown impurity and the synthesized product failed to exchange on to AGl-X2, acetate form, ion exchange resin.

Syntheses of by-products

Dehydroacetic acid imine (IX). Into a 3-neck round bottomed flask were placed dehydroacetic acid (336 g, 2·0 mol) and water(2000 g). Conc NH_4OH (28%, 2·2 mol) was added to the above slurry with stirring. A very slight exotherm occurred and a soln obtained. The contents were filtered to remove a small amount of insoluble matter, and the soln allowed to set 3 days at room temp, resulting in precipitation of IX. The solid was washed with water and dried under vacuum at 55–60° to give 282 g (91%) of white crystalline solid, m.p. 210–210·5° (lit.[8] 210°).

4-Amino-2,6-lutidine (VII). Into a 500 ml stainless steel rocker bomb was placed 2,6-dimethyl-4-pyridinal, (24·6 g, 0·2 mol) 28% NH_4OH (36·2 g, 0·6 mol) and water (100 g). The contents were heated with rocking to 200° and held there for 2 hr. The bomb was cooled, vented, and opened. A sample was analyzed as follows:

A sample of the reaction product (1 g) was placed into a 125 ml separatory funnel and 0·5N NaOH (50 ml) was added. The aqueous soln was extracted with three 25 ml portions $CHCl_3$. The combined chloroform layer was reextracted with exactly 50 ml 1N HCl. The absorbance of this soln was measured at 261 nm in a 1-cm optical cell with water as the reference solvent. The concentration was calculated by comparison with a standard measured under identical conditions. It indicated the presence of 1·7% 4-amino-2,6-lutidine.

The same experiment was carried out at 250° for 6 hr and the final slurry dried in an oven at 100°. The solids from the drying were recrystallized 3 times from acetone to give 4-amino-2,6-lutidine (11·5 g, 47·9%), m.p. 189–191° (lit.[10] 189–190°).

3-Acetyl-4-hydroxy-6-methyl-2-pyridone (IV). Anhydrous NH_3 (1·7 g, 0·1 mol) was bubbled into a soln of diketene (16·8 g, 0·2 mol) in anhyd dioxane (100 ml) at 0–5°. The resulting soln was heated at reflux for 24 hr. The mixture was cooled to 10° and filtered. The tan solid was recrystallized twice from EtOH to yield IV (6·8 g, 40·7%), m.p. 269–271°. NMR (d_6 DMSO) δ 2·54 (s., $COC\underline{H}_3$); δ 2·17 (broad, $C\underline{H}_3$); δ 2·54 (5H, J = 0·7 c/s aromatic $\underline{H}$); δ 10·8 (broad, N$\underline{H}$ and O$\underline{H}$). (Found: M^+, 167; C, 57·64; H, 5·39; N, 8·23. $C_8H_9NO_3$ requires: M, 167; C, 57·48; H, 5·43; N, 8·38).

4-Hydroxy-6-methyl-2-pyridone (V). This compound was prepared from dehydroacetic acid according to the procedure of Collie.[11] Light tan solids were obtained after recrystallization, m.p. 326–327° (lit.[11, 12] 330°).

4-Amino-6-methyl-2-pyridone (VIII). Into a 500 ml rocker bomb was placed V (75 g, 0·591 mol), 28% NH_4OH (44 g, 0·721 mol) and water (125 g). The contents were heated with rocking to 250° for 6 hr. The bomb was cooled, vented and opened. The resulting solid was collected and washed with ice-cold water. The solid was dissolved in 700 ml of EtOH heated at reflux with activated carbon, and filtered hot. The filtrate was concentrated until solidification occurred. The contents were cooled and 32 g (43·7%) of white crystals, m.p. 277–278°, were obtained. NMR (d_6DMSO) δ 2·1 (broad, $C\underline{H}_3$); δ 5·0 (3H, d, J = 2·6 c/s); δ 5·5 (5H, m); δ 5·9 (broad, N$\underline{H}_2$); δ 11·0 (broad N$\underline{H}$). UV $\lambda_{max}\mu$ (log ε): 281 (3·79). (Found: M^+, 124; C, 58·14; H, 6·56; N, 22·4. $C_6H_8N_2O$ requires: M, 124; C, 58·06; H, 6·45; N, 22·58).

Reaction of 4-hydroxy-2,6-dimethylnicotinic acid with ammonia. Into a 500 ml rocker bomb was placed 4-hydroxy-2,6-dimethylnicotinic acid (33·4 g, 0·2 mol), 28% NH_4OH (36·2 g, 0·6 mol) and water (100 ml). The contents were heated with rocking to 200° for 3 hr. The bomb was cooled, vented, and opened. A sample was analyzed according to the procedure described in the determination of VII. Conversion of 4-hydroxy-2,6-dimethylnicotinic acid 8% into 4-amino-2,6-lutidine was observed. The same reaction was carried out at 170° for 6 hr. The resulting solids were analyzed accordingly, indicating that 0·6% of 4-amino-2,6-lutidine and 1·3% of 4-amino-2,6-dimethylnicotinic acid were present.

4-Amino-3-bromo-2,6-lutidine (XI). This compound was prepared from 4-amino-2,6- lutidine according to the procedure of Marchwald.[13] White solids were obtained after recrystallization, m.p. 88–89° (lit.[13] 88–89°).

4-Amino-3-cyano-2,6-lutidine (XII). 4-Amino-3-bromo-2,6- lutidine (30 g, 0·149 mol) was mixed with CuCN (40 g) and pyridine (150 ml). The mixture was heated to boiling and the b.p. was raised to 160° by evaporating off some pyridine. The mixture was then refluxed at 160° overnight. The remaining pyridine was removed by vacuum distillation and the residue refluxed with 500 ml 15% HCl aq for 2 hr. The dark brown soln thus obtained was treated with Norite and neutralized with Na_2CO_3. The brown solids which precipitated from the soln were collected and digested with 1 liter acetone. The acetone soln was filtered and the filtrate evaporated to dryness to give a yellowish green solid, m.p. 204–205°, yield 18 g (82%). (Found: M^+, 147; C, 65·28; H, 6·01; N, 28·71. $C_8H_9N_3$ requires: M, 147; C, 65·31; H, 6·12; N, 28·57%).

4-Amino-2,6-dimethylnicotinic acid (VI). 4-Amino-3-cyano-2,6-lutidine (5 g, 0·34 mol) was dissolved in 25% NaOH aq (75 ml). The resulting soln was refluxed with stirring for 4 hr. The alkaline soln was diluted with water to 150 ml and then adjusted with H_2SO_4 to pH 8·0. Pale green solids which precipitated from the soln were removed by filtration. The filtrate was then evaporated to dryness on a rotary evaporator. The residue and the pale green solids were extracted with 500 ml of MeOH. The MeOH extract was concentrated to 10 ml to give a white crystalline solid, m.p. 260–261° (decarboxylation), yield, 3·1 g (62%). NMR (CF_3COOD) δ 2·25 (broad, $6C\underline{H}_3$): δ 2·98 (s, $2C\underline{H}_3$): δ 6·82 (q, 5$\underline{H}$): ν_{max} 1670 cm^{-1} (C=O). (Found: M^+, 166; C, 57·90; H, 6·15; N, 16·73. $C_8H_{10}N_2O_2$ requires: M, 166; C, 57·83; H, 6·02; N, 16·87).

2,6-Dimethyl-4-hydroxynicotinic acid (III). Dehydroacetic acid was treated with 20% mole excess NH_4OH at 160° for 1 hr. The mixture which contains ~16% II and ~4% III was allowed to cool to room temp precipitating II. II was removed by filtration and washed with ice-cold water. The combined filtrate and water wash was acidified with conc HCl, resulting in the precipitation of III. III was collected,

washed with water, and sucked to near dryness. The product was refluxed in 8–9 parts by weight of water with stirring for 1 hr. After cooling, filtering, and drying, a white crystalline solid, m.p. 258–259° (lit.[14, 15] 258°) was obtained.

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