After 10 min. water was added and the solution was then concentrated until crystals began to separate. A total of 163 mg. of colorless needles, m.p. 109–117°, was obtained in several crops. Recrystallization from methanol gave short white needles of the iminohemiketal, m.p. 114–117°; λ_{max}^{EtOH} 245 mμ (20,000); $\lambda_{max}^{EtOH + HCl}$ 230 mμ (17,000); $\lambda_{max}^{EtOH + KOH}$ 247 mμ (19,000); λ^{KBr} 2.80, 2.90, 3.1, 6.224, 6.254(double, s), 6.352(m) μ (P.E. 13U).

Anal. Calcd. for $C_{19}H_{19}O_3N_3 \cdot CH_3OH$: C, 65.02; H, 6.28; N, 11.38. Calcd. for $C_{19}H_{19}O_3N_3 \cdot {}^1/_2CH_3OH$: C, 66.27; H, 5.99; N, 11.89. Found (Dried to constant wt. 50°): C, 65.80, 65.64; H, 6.47, 6.21; N, 11.31.

Eighteen mg. of the above-described material was dissolved in 0.3 ml. of acetic anhydride and the yellow solution was warmed to 80° for 5 min. After hydrolysis of the excess anhydride the solution was seeded with VIb and deposited 8 mg. of yellow prisms, m.p. 138–139°. Recrystallization from methanol gave VIb, m.p. and m.m.p. 147–148°; identical infrared spectra.

A small sample of the compound in methanol solution was treated with a 5% solution of potassium permanganate in acetone. As soon as a permanent purple color was present the mixture was diluted with water and extracted with ether. After washing with water the ether was dried and evaporated to give a yellow oil which crystallized on addition of a few drops of methanol; recrystallization from methanol gave yellow prisms of VIb, m.p. and mixed m.p. 145–147°.

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NEWARK, DEL.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF DELAWARE]

Heterocyclic Studies. V. Proof of Structure and Synthesis of 3-Hydroxy-4-methyl-5-phenylpyridine, A Degradation Product of 2,3-Dihydro-5-methyl-6-phenyl-4H-1,2-diazepin-4-one[1]

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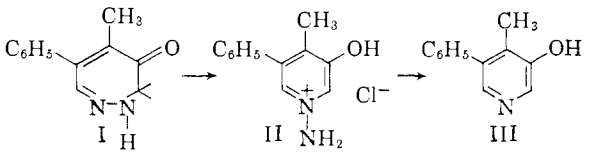
Evidence establishing the 3-hydroxypyridine structure III for a degradation product of the diazepine I is presented and a synthesis of III is described. The synthesis begins with 2-hydroxy-3-cyano-4-methyl-5-phenyl-6-aminopyridine and proceeds, with stepwise removal of the α-substituents, to 4-methyl-5-phenylnicotinic acid, which is then transformed by Hofmann degradation and diazotization to the hydroxypyridine.

As discussed in the foregoing article,[2] isomerization of the diazepinone I led to a product which was formulated as 1-amino-3-hydroxy-4-methyl-5-phenylpyridinium chloride (II) on the basis of its facile deamination to a compound which was in turn assigned the 3-hydroxy-4-methyl-5-phenylpyridine structure (III). Evidence supporting this latter structure, and definitive proof by synthesis, are presented in this paper.



The deamination product was characterized as a 3-hydroxypyridine by the red ferric chloride reaction, pK_A values (4.6, 9.5), characteristic ultraviolet spectra including changes in alcohol and aqueous solution with pH,[3] formation of an N-oxide (pK_A 6.9[4]) and formation of an acetate, and with diazomethane a methyl ether. A positive Gibbs reaction confirmed the presence of an unsubstituted 6-position[5] and in later work[6] the absence of substituents from both 2- and 6-positions was established by coupling with *p*-nitrobenzenediazonium chloride.

These results narrowed the structural possibilities to III and the 3-hydroxy-5-methyl-4-phenyl isomer. An attempt was made to demonstrate the presence of a 4-methyl substituent by condensation with benzaldehyde on both the base and the N-oxide, a reaction diagnostic of α- and γ-picoline derivatives, but a benzylidene derivative was not obtained, perhaps because of steric interference of the phenyl substituent and/or electron release by the hydroxyl group.[7] At this point, the necessity of a synthetic approach became apparent, but before embarking on the synthesis of III, it was hoped to simplify the task by elimination of the hydroxyl group, since synthesis of the resulting 4-methyl-3-phenylpyridine by the very satisfactory procedure[8] available for 3-phenylpyridine should be a relatively easy matter.

The conversion of 3-hydroxypyridine to pyridine by zinc dust distillation was reported in the earliest description of the compound,[9] and this reaction has subsequently been cited by many authors, apparently without further confirmation. We have been unable to carry out this transformation with III or with 3-hydroxypyridine under a variety of conditions with zinc, although the reduction of 2-pyri-

(1) Supported by a grant from the Geschickter Fund for Medical Research.

(2) J. A. Moore and J. Binkert, THIS JOURNAL, **81**, 6029 (1959), paper IV.

(3) B. Witkop, *Experientia*, **10**, 419 (1954).

(4) E. Shaw, THIS JOURNAL, **71**, 67 (1949) reports pK_A 6.4 for 3-hydroxypyridine N-oxide.

(5) E. T. Stiller, J. C. Keresztesy and J. R. Stevens, *ibid.*, **61**, 1237 (1939).

(6) J. A. Moore and F. J. Marascia, *ibid.*, **81**, 6049 (1959); paper VII.

(7) D. Jerchel and H. E. Heck, *Ann.*, **613**, 171 (1958), have reported that formation of the benzylidene derivative of 3-hydroxy-2-methylpyridine is slower than in the case of α-picoline.

(8) H. Rapoport, M. Look and G. J. Kelly, THIS JOURNAL, **74**, 6293 (1952).

(9) O. Fischer and E. Renouf, *Ber.*, **17**, 764 (1884).

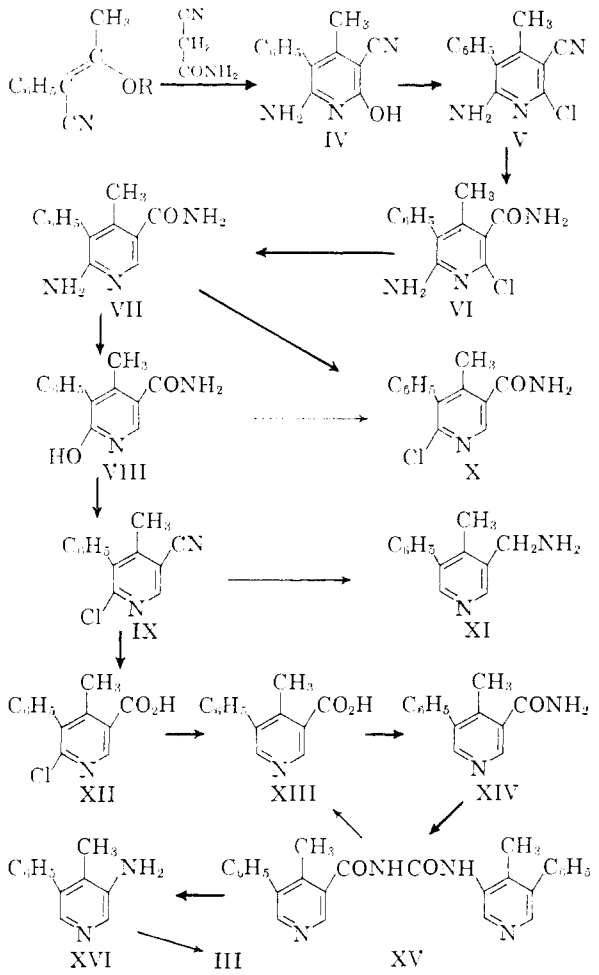


FIG. 1.—Bold arrows denote main synthetic path.

done proceeds quite smoothly. An alternative to zinc dust distillation for the removal of hydroxyl groups has been described by Kenner and Murray,[10] who reported the reduction of several phenols by treatment of the *p*-toluenesulfonate esters with Raney nickel. The tosylate of III, however, was recovered unchanged from several attempts at hydrogenolysis. The catalytic hydrogenation of III was also examined in the hope of obtaining the deoxygenated piperidine.[11] The product obtained by prolonged reduction using platinum oxide was apparently the 5-cyclohexylpyridine; a pure compound was not obtained, but the infrared spectrum of the amphoteric product showed complete disappearance of the prominent bands at 13.0 and 14.2 μ in the spectrum of III associated with a monosubstituted benzene ring. The failure of the pyridine nucleus to undergo reduction is attributed to the presence of substituents in the 3-, 4- and 5-positions, with unsubstituted 2- and 6-positions.[12]

Attention was then directed to the rather lengthy synthesis of III which is outlined in Fig. 1. The starting point of the scheme was 2-amino-5-cyano-6-hydroxy-4-methyl-3-phenylpyridine (IV),[13] first prepared by Chase and Walker.[14] Since this substance, as expected,[15] could not be diazotized to the dihydroxy compound, it was necessary to remove the α-substituents individually.

The chlorination of IV was very satisfactory, giving the 2-chloro compound V in 75% yield, as compared with a 22% yield in the case of the compound lacking the 4-methyl group.[14] In order to avoid reduction of the cyano group in the ensuing hydrogenolysis, V was first hydrolyzed in good yield to the amide VI and the chlorine atom then removed by catalytic hydrogenation. Although the direct conversion of the resulting amino amide VII to the required 6-chloro compound could be effected by diazotization with fuming hydrochloric acid,[16] it was more practical to proceed indirectly by diazotization to the hydroxy compound VIII and treatment with phosphorus oxychloride. This treatment furnished the chloronitrile IX in almost theoretical yield. Under milder chlorination conditions a very small amount of the amide X could be isolated. Hydrolysis of the chloronitrile IX under the identical conditions used in the hydrolysis of the 2-chloronitrile V gave the *acid* XII in 90% yield. Hydrogenolysis then furnished 4-methyl-5-phenylnicotinic acid (XIII).

The route which was selected for the transformation of the acid to the desired 3-hydroxypyridine comprised Hofmann degradation of the amide and diazotization of the amine. The acid was esterified with diazomethane and the ester was treated with ammonia to furnish the amide. Although the Hofmann degradation of nicotinamide[17] is uncomplicated, and furnishes a very satisfactory yield of 3-aminopyridine, the reaction of XIV with excess alkaline hypobromite led to very dark products containing much intractable neutral material. The use of sodium methoxide in methanol for the degradation was also very unpromising.

When the amide was treated with slightly less than the theoretical amount of hypobromite and the alkaline solution then warmed, a very sparingly soluble neutral product was obtained in 36% yield. The analysis and physical properties of this substance indicated that it was N-(4-methyl-5-phenylnicotinyl)-N′-(4-methyl-5-phenylpyridyl)-urea (XV), although satisfactory molecular weight values could not be obtained. This type of product has frequently been encountered in the Hofmann degradation under these conditions.[18] Vigorous acid hydrolysis of XV confirmed this structure; the substituted nicotinic acid XIII and a basic substance were isolated in good yield, and ammonia was detected qualitatively.

The characterization of the basic component of the urea as the desired 3-amino-4-methyl-5-phenyl-

(10) G. W. Kenner and M. A. Murray, *J. Chem. Soc.*, S 178 (1949).

(11) C. Cavallito and T. H. Haskell, THIS JOURNAL, **66**, 1927 (1944).

(12) H. S. Mosher, in "Heterocyclic Compounds," Vol. I, R. C. Elderfield, ed., John Wiley and Sons, Inc., New York, N. Y., 1950, p. 633.

(13) In this discussion, the compounds with 2- or 6-hydroxy substituents are arbitrarily designated as hydroxypyridines rather than pyridones; this does not imply that the usual tautomeric equilibria do not exist.

(14) B. H. Chase and J. Walker, *J. Chem. Soc.*, 3548 (1953).

(15) A. I. Titov, *J. Gen. Chem. (U.S.S.R.)*, **8**, 1483 (1938); *C. A.*, **33**, 4248 (1939).

(16) W. Marckwald, *Ber.*, **27**, 1323 (1894).

(17) C. F. H. Allen and C. N. Wolf, *Org. Syntheses*, **30**, 3 (1950).

(18) E. S. Wallis and J. F. Lane, "Organic Reactions," Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1946, p. 269.

pyridine (XVI) was restricted by the very small quantities available. The properties (ultraviolet and infrared spectra, pK'_A value) corresponded to those expected; the base formed a monopicrate. Diazotization of this amine in the usual manner furnished the 3-hydroxy-4-methyl-5-phenylpyridine (III), which was identical in all respects with a sample obtained by deamination of II.

Experimental[19]

Properties and Derivatives of 3-Hydroxy-4-methyl-5-phenylpyridine (III).—A sample obtained by nitrous acid deamination of II,[2] m.p. 198° recrystallized from aqueous methanol, was used for spectra: $\lambda_{max}^{H_2O}$, *p*H 7, <220, 283 (ε 3150), 314 mμ (4700); $\lambda_{max}^{0.1\ N\ HCl}$ 225 (16,600), 287 mμ (8150); $\lambda_{max}^{0.1\ N\ NaOH}$ 225 (20,400), 304 mμ (6030); λ_{max}^{MeOH} 283 mμ (6600); $\lambda_{max}^{MeOH + HCl}$ 227 (17,600), 289 mμ (9050); $\lambda_{max}^{MeOH + NaOH}$ 228 (22,500), 306 mμ (6600); pK_A (50% MeOH) 4.6, 9.5; mol. wt. 185; λ^{KBr} 3.2–4.0(br), 6.35, 6.90, 7.05, 7.20, 7.56, 7.70, 8.74, 13.0, 14.2 μ. The compound gave a bright pink color with methanolic ferric chloride and an immediate deep blue-violet color with N,2,6-trichloro-*p*-quinoneimine (Gibbs test).

The acetate was prepared by warming a solution of III in acetic anhydride at 110° for one hour. After removal of the anhydride and treatment with water a colorless oil was obtained; the compound was freely soluble in ether; crystals were not obtained. The oily acetate was converted to the **picrate** in alcohol solution, recrystallization from ethanol gave yellow prisms, m.p. 147°.

Anal. Calcd. for $C_{20}H_{16}O_9N_4$ (456.36): C, 52.63; H, 3.53; N, 12.28. Found: C, 52.76; H, 3.51; N, 12.53.

The methyl ether of III was prepared by treatment of a solution of 60 mg. of the hydroxypyridine in 0.5 ml. of methanol with excess ethereal diazomethane. After standing for 40 hr. the solution was evaporated to give a dark oil which was distilled at 0.1 mm. A total of 41 mg. of pale yellow oil was obtained in several fractions, most of the material distilling at a bath temperature of 120–150°. The fractions were treated separately with ethanolic picric acid, giving a total of 54 mg. of the **picrate** with m.p. ranges from 127–130° to 132–134°. The combined picrates were recrystallized from ethanol as yellow prisms, m.p. 129/137–138° (double m.p.).

Anal. Calcd. for $C_{19}H_{16}O_8N_4$(428.35): C, 53.27; H, 3.77; N, 13.08. Found: C, 53.47; H, 3.66; N, 13.06.

3-Hydroxy-4-methyl-5-phenylpyridine N-Oxide.—To a solution of 500 mg. of III in 2 ml. of chloroform was added a solution of perbenzoic acid in chloroform (60 mg./ml., 1.5 equiv.). The solution was stoppered and stored overnight; crystals began to separate after 20 min. The white prisms were then collected, 471 mg., m.p. 278–281° dec. Recrystallization from 120 ml. of boiling ethanol gave tiny white needles, m.p. 283–285° dec.; λ_{max}^{EtOH} 232 (ε 18,000), 266 (14,000), 308 mμ (3,400); $\lambda_{max}^{EtOH + HCl}$ 242 (20,400), 329 mμ (5,900); $\lambda_{max}^{0.1\ N\ HCl}$ 227 (22,800), 291 mμ (5,200); $\lambda_{max}^{0.1\ N\ NaOH}$ 236 (37,000), 320 mμ (5,800); pK'_A 6.9 (50% MeOH).

Anal. Calcd. for $C_{12}H_{11}O_2N$ (201.22): C, 71.62; H, 5.51; N, 6.96. Found: C, 71.73; H, 5.79; N, 6.70.

The compound was freely soluble in dilute acid and alkali; treatment with diazomethane furnished the **methyl ether** as transparent blades from ether, m.p. 176–178°.

3-Hydroxy-4-methyl-5-phenylpyridine *p*-Toluenesulfonate.—A solution of 555 mg. of III in 5 ml. of pyridine was treated with 1.1 g. of *p*-toluenesulfonyl chloride and allowed to stand at room temperature overnight. After diluting with water the solution was extracted with several portions of ether and the ether solution was washed thoroughly with water and evaporated. The pyridine was removed at 50° (0.1 mm.) and the residual pale yellow glass crystallized after standing at room temperature for seven weeks. The material was recrystallized from ether–pentane as large oblong prisms, m.p. 71–72°, 795 mg. The tosylate was converted to the **picrate** for analysis; lemon-yellow prisms from ethanol, m.p. 170–171°.

(19) Infrared spectra of all compounds were obtained in KBr disks. Only the most significant strong bands of the more important compounds are recorded.

Anal. Calcd. for $C_{25}H_{20}O_{10}N_4S$ (568.5): C, 52.81; H, 3.55; N, 9.86. Found: C, 52.62; H, 3.57; N, 9.68.

The crystalline tosylate was recovered after shaking with highly pyrophoric Raney nickel at 35 lb. hydrogen pressure for 15 hours and also after refluxing with a large amount of nickel in ethanol solution in a hydrogen stream.

3-Hydroxy-4-methyl-5-cyclohexylpyridine.—A solution of 290 mg. of crude III which had been prepared by catalytic hydrogenation of II[2] in 20 ml. of glacial acetic acid was treated with 0.5 ml. of concd. hydrochloric acid and shaken with 100 mg. of platinum oxide at 50 lb. pressure for 20 hr. After filtration of the catalyst the solution was concentrated and the semi-crystalline residue crystallized from ethanol–ether, giving 187 mg. of white prisms, m.p. 188–195°. This hydrochloride was then dissolved in aqueous alkali and the solution extracted with ether. The base obtained on neutralization had m.p. 172–173°. After recrystallization from methanol–ether the material had m.p. 198–201° (subl.); the mixed m.p. with III (m.p. 198–200°) was 173–175°. After several further recrystallizations from ethanol–ether the compound had m.p. 223–225°; λ_{max}^{MeOH} 277 mμ (4650); $\lambda_{max}^{MeOH + HCl}$ 284 mμ (6950); $\lambda_{max}^{MeOH + NaOH}$ 299 mμ (5360); pK_A 5.6, 10.0; mol. wt. 200; λ^{KBr} 3.36, 3.6–3.9(br), 6.36, 6.95, 7.67, 11.5, 11.9 μ.

2-Amino-5-cyano-6-hydroxy-4-methyl-3-phenylpyridine (IV).—A solution of 230 g. of 2-phenyl-2-isobutoxycrotononitrile prepared as described[14] but *not* distilled, 90 g. of cyanoacetamide and sodium ethoxide (from 25 g. of sodium) in 2.2 l. of ethanol was refluxed for three hours and then concentrated and evaporated to dryness *in vacuo*. The residue was then dissolved in 400 ml. of water and the red solution was extracted with ether. The light red aqueous solution was acidified and then neutralized with excess sodium bicarbonate. The precipitated pyridine was filtered and dried. The crude product (95 g., 40%) was recrystallized from methyl Cellosolve, m.p. 346°.

2-Amino-6-chloro-5-cyano-4-methyl-3-phenylpyridine (V).—In a Pyrex bomb tube were placed 7.3 g. of recrystallized IV and 30 ml. of freshly distilled phosphorus oxychloride. After heating for three hours at 150°, the tube contents were poured onto ice and the solution was made alkaline with ammonia. The crude product was filtered and then recrystallized from ethyl acetate to furnish 5.9 g. (75%) of pale tan crystals, m.p. 182–186°. The analytical sample was recrystallized three times from methanol, m.p. 186–188°.

Anal. Calcd. for $C_{13}H_{10}N_3Cl$ (243.70): N, 17.24; Cl, 14.56. Found: N, 17.29; Cl, 14.62.

2-Amino-5-carboxamido-6-chloro-4-methyl-3-phenylpyridine (VI).—A solution of 47.5 g. of the nitrile V in 475 ml. of 50% (w./w.) sulfuric acid was refluxed (150°) for three hours. The solution was then cooled, poured onto 2 kg. of ice and neutralized to *p*H 7 with sodium hydroxide solution. The crude amide was filtered, dried and recrystallized from methyl Cellosolve–water to give 42 g. (82%) of material, m.p. 273–278°. This compound was not obtained in analytical purity; carbon and nitrogen values were both high, and it is possible that a small amount of nitrile was present. This hydrolysis was also carried out with concd. hydrochloric acid in a sealed tube at 140°, but this procedure was in no way superior.

2-Amino-5-carboxamido-4-methyl-3-phenylpyridine (VII).—A solution of 15 g. of the chloroamide VI, 4.7 g. of anhydrous sodium acetate and 1 g. of 10% palladium-on-carbon catalyst was shaken with hydrogen at 50 lb. pressure. The reduction did not go rapidly to completion, and after two and four hours, 1 and 0.5 g. of fresh catalyst, respectively, were added. The theoretical amount of hydrogen was consumed after six hours, and the solution was filtered through Celite and concentrated *in vacuo*. The residue was dissolved in 80 ml. of 10% acetic acid and carefully neutralized with sodium hydroxide at 0°. The precipitated product was then filtered and dried, giving 12.5 g. (96%) of VII, m.p. 219–225°. The product was recrystallized from methanol for analysis, m.p. 226–228°.

Anal. Calcd. for $C_{13}H_{13}ON_3$ (227.26): C, 68.70; H, 5.77; N, 18.49. Found: C, 68.64; H, 5.56; N, 18.32.

3-Carboxamido-6-hydroxy-4-methyl-5-phenylpyridine (VIII).—A solution of 4.3 g. of methanol-recrystallized VII in 17.2 ml. of concd. sulfuric acid (dissolved with ice-bath cooling) was treated with 1.68 g. of finely powdered sodium

nitrite at 0°. The solution was stirred for 15 min. and became milky. It was then poured onto 500 g. of ice. The mixture was allowed to stand until the precipitation of the product was complete, and was then filtered. The colorless product, 3.9 g. (91%), was recrystallized from dimethylformamide, m.p. 350–352°. A sample was digested with ethanol for analysis.

Anal. Calcd. for $C_{13}H_{12}O_2N_2$ (228.24): C, 68.41; H, 5.30; N, 12.27. Found: C, 68.39; H, 5.30; N, 12.54.

2-Chloro-5-cyano-4-methyl-3-phenylpyridine (IX).—A solution of 10.2 g. of the hydroxyamide VIII in 50 ml. of freshly distilled phosphorus oxychloride was placed in a Pyrex bomb tube and heated at 150° for three hours. The tube contents were then cooled and poured onto 400 g. of ice, and the mixture was stirred at 0° for 6 hours. The mixture was then neutralized with ammonia and the solid was filtered and recrystallized from methanol, giving 9.9 g. of tan crystals, m.p. 118–121°. The compound was crystallized twice more from methanol for analysis, m.p. 120–122°. The infrared spectrum showed a sharp band at 4.48 μ.

Anal. Calcd. for $C_{13}H_9N_2Cl$ (228.68): Cl, 15.50. Found: Cl, 15.46.

3-Carboxamido-6-chloro-4-methyl-5-phenylpyridine (X).

A. **By Chlorination of VIII.**—When the chlorination of VIII described above was performed at 100°, and the reaction mixture processed as above, the main product was again the nitrile IX, but from the methanol mother liquors there was obtained, in about 5% yield, a second product. After repeated recrystallizations from methanol, this had m.p. 160–163°.

Anal. Calcd. for $C_{13}H_{11}N_2OCl$ (246.70): N, 11.35; Cl, 14.37. Found: N, 11.62; Cl, 14.50.

B. **By Diazotization of VII.**—The diazotization of 390 mg. of the aminoamide VII with 2 ml. of concd. sulfuric acid and 154 mg. of sodium nitrite was carried out as described above for the preparation of VIII. The sulfuric acid solution was then added dropwise to 50 ml. of concd. hydrochloric acid which had been saturated at −20° with hydrogen chloride. The solution was then concentrated at reduced pressure, and the solid residue was treated with 10% aqueous ammonia and filtered. The crystalline solid was recrystallized from methanol to give 120 mg. of X; m.p. and mixed m.p. with above preparation (method A) 160–162°.

The ammoniacal filtrate was then neutralized with dilute acetic acid, and the precipitate was filtered and recrystallized from dimethylformamide, furnishing 205 mg. of VIII, m.p. 350–352°.

3-Aminomethyl-4-methyl-5-phenylpyridine (XI.)—To test the remote possibility that the chlorine atom of the chloronitrile IX could be selectively reduced, 1.5 g. of IX was reduced in 40 ml. of acetic acid with 1 g. of 10% palladium-carbon catalyst, in the presence of 0.6 g. of sodium acetate. The solution was then filtered through Celite and evaporated *in vacuo* to give an oil which did not crystallize. The oil was distilled in a Kugelrohr, b.p. 120–130° (0.5 mm.). A total of 1.1 g. of colorless oil was obtained; a sample was treated with excess picric acid in ethanol solution to furnish the **dipicrate**, m.p. 218–221°.

Anal. Calcd. for $C_{25}H_{20}O_{14}N_8$ (656.47): C, 45.73; H, 3.07; N, 17.07. Found: C, 46.18; H, 3.24; N, 16.49.

2-Chloro-4-methyl-3-phenylnicotinic Acid (XII).—A solution of 2.55 g. of the chloronitrile IX in 30 ml. of 50% sulfuric acid was refluxed for three hours and then poured onto ice and made alkaline with 10% potassium hydroxide. The pale red solution was then clarified by filtration and made just acid to congo red with acetic acid. The precipitated acid was filtered and dried, giving 2.49 g. (90%) of product, m.p. 213–219°. The compound was recrystallized twice from methanol–water, m.p. 222–223°.

Anal. Calcd. for $C_{13}H_{10}O_2NCl$ (247.68): N, 5.65; Cl, 14.32. Found: N, 5.68; Cl, 14.23.

4-Methyl-5-phenylnicotinic Acid (XIII).—A solution of 1.0 g. of the chloroacid XII and 0.3 g. of sodium acetate in 40 ml. of glacial acetic acid was shaken at 50 lb. hydrogen pressure with 0.5 g. of 10% palladium–carbon catalyst for two hours. An additional 0.3 g. of catalyst was then added and the shaking continued for two more hours. The solution was filtered and the acetic acid removed *in vacuo*. The residue was then dissolved in a small volume of dilute ammonia and the filtered solution adjusted to congo red *p*H with acetic acid. The acid XIII crystallized on standing and scratching, to give 650 mg. of white prisms, m.p. 215–220°. The acid was twice recrystallized from water, for analysis, m.p. 219–221°; pK'_A 2.5, 4.8 (50% methanol). The ultraviolet spectrum in ethanol showed only steadily declining adsorption between 220 and 310 mμ, with a shoulder at 270 mμ on addition of base.[20]

Anal. Calcd. for $C_{13}H_{11}O_2N$ (213.23): C, 73.22; H, 5.20; N, 6.57. Found: C, 73.14; H, 5.11; N, 6.40.

4-Methyl-5-phenylnicotinamide (XIV).—A solution of 2.7 g. of the acid XIII in methanol was treated with a slight excess of diazomethane. After several minutes standing at 0°, the excess diazomethane was destroyed with acetic acid and the solution was evaporated. The resulting sirup was distilled in a Kugelrohr at 160–165° (2.5 mm.) to give 2.29 g. of colorless ester.

A solution of 970 mg. of the ester in 25 ml. of methanol was saturated with ammonia at 0°, and the solution was then heated in a sealed tube at 100° for 16 hours. The methanol was then removed, and crystallization of the amide was induced by the addition of a few drops of ethyl acetate. The amide crystallized in white cubes; 560 mg., m.p. 153–157°. The analytical sample was prepared by further recrystallization from ethyl acetate; m.p. 158–160°; ultraviolet, see ref. 20.

Anal. Calcd. for $C_{13}H_{12}ON_2$ (212.24); C, 73.56; H, 5.70; N, 13.20. Found: C, 73.73; H, 5.61; N, 13.06.

A picrate prepared from this amide had m.p. 215–217°. The ethyl acetate mother liquors from crystallization of the amide were combined, evaporated, and redistilled to give 250 mg. of recovered methyl ester.

N-(4-Methyl-5-phenylnicotinyl)-N′-(4-methyl-5-phenylpyridyl)-urea (XV).—A suspension of 370 mg. of the finely powdered amide XIV in 1.5 ml. of distilled water was treated with 2.0 ml. of a solution of sodium hypobromite prepared from 0.86 g. of bromine, 2.14 g. of sodium hydroxide and 20 ml. of water. The addition was made at 0°, and the mixture was stirred in the ice-bath for 15 min. and then filtered to remove a small amount of unchanged amide. The solution was then layered with 5 ml. of ethyl acetate and warmed to 70° with vigorous stirring for five minutes. The ethyl acetate layer was then separated and, on cooling, the deep red solution deposited 130 mg. of pale pink prisms. Two recrystallizations from ethyl Cellosolve furnished the analytical sample as prisms, m.p. 248–250°. The infrared spectrum contained a double band at 5.85 and 5.95 μ; ultraviolet spectrum see ref. 20.

Anal. Calcd. for $C_{26}H_{22}N_4O_2$ (422.27): C, 73.91; H, 5.25; N, 13.26. Found: C, 73.56; H, 5.42; N, 12.91.

3-Amino-4-methyl-5-phenylpyridine (XVI).—A solution of 58 mg. of the urea XV in 2 ml. of concd. hydrochloric acid was heated in a sealed tube at 200° for six hours. The light yellow solution was then evaporated to dryness at 50° and the solid residue was dissolved in 2 ml. of distilled water and filtered to remove a trace of amorphous material. The solution was then made basic with three drops of 10% sodium hydroxide solution (a gas, which reacted basic to test paper and smelled of ammonia, was evolved). The solution was then extracted with five 5-ml. portions of ether. The ether solution was washed with dilute alkali and water, dried with sodium sulfate and evaporated to give 29.4 mg. of yellow oil which crystallized on brief standing. This material was recrystallized twice from ether to give 12 mg. of cream colored needles, m.p. 134.5–136°. A sample of this material was sublimed for analysis, m.p. 136–136.5°; ultraviolet: λ_{max}^{EtOH} 226 (ϵ 18,800), 305 mμ (ϵ 3,980); $\lambda_{max}^{EtOH + HCl}$ 218 (ϵ 18,900), 248 (ϵ 14,300), 324 mμ (ϵ 5,500); pK'_A 5.6 (50% methanol); KBr 2.95, 3.05(sh), 3.15, 6.15, 6.42 μ.[23]

(20) This same type of ultraviolet spectrum, without discrete maxima and with steadily declining absorption between 220 and 300 mμ, was also shown by compounds XIV and XV. It appears that the characteristic maxima for 3-phenylpyridine (λ_{max} 245 mμ, ϵ 14,000)[21] and of nicotinic acid (λ_{max} 262 mμ, ϵ 4000)[22] become fused in the spectra of these 5-phenylnicotinic acid derivatives.

(21) P. Krumholz, THIS JOURNAL, **73**, 3487 (1951).

(22) E. B. Hughes, H. H. Jellinek and B. A. Ambrose, *J. Phys. Coll. Chem.*, **53**, 414 (1949).

(23) These data may be compared with those for 3-aminopyridine: λ_{max}^{EtOH} 240 (ϵ 10,000), 300 mμ (2000); $\lambda_{max}^{0.1\ N\ HCl}$ 250 (7000), 215 mμ (3400)[24]; pK'_A 5.98 (H_2O).[25]

(24) E. A. Steck and G. W. Ewing, THIS JOURNAL, **70**, 3397 (1948).

(25) A. Albert, R. Goldacre and J. Phillips, *J. Chem. Soc.*, 2240 (1948).

Anal. Calcd. for $C_{12}H_{12}N_2$ (184.23): C, 78.23; H, 6.57; N, 15.21. Found: C, 78.54; H, 6.55; N, 14.96.

The picrate was prepared by treating 3.4 mg. of the amine in 0.5 ml. of ethanol with an ether solution of 10.2 mg. of picric acid (2.5 equiv.). The picrate separated in orange-yellow needles which were recrystallized from methanol–ether for analysis; m.p. 193°. The analysis indicates that under these conditions, the monopicrate is formed.

Anal. Calcd. for $C_{18}H_{15}O_7N_5$ (413.34): C, 52.30; H, 3.66; N, 16.94. Found: C, 52.29; H, 3.66; N, 16.82.

The aqueous alkaline solution from the above hydrolysis was brought to *p*H 5 by the addition of acetic acid, and the solution deposited 21.4 mg. of solid on standing. This precipitate was filtered, dried and recrystallized from methanol–ether to give white needles, m.p. 216–218°, no depression on mixing with acid XIII.

3-Hydroxy-4-methyl-5-phenylpyridine (III).—A solution of 8.5 mg. of the amine XVI in 0.3 ml. of 25% sulfuric acid was cooled to 0° and diluted with 0.2 ml. of water. A solution of 4.8 mg. of sodium nitrite was then added dropwise. After five minutes, the solution was poured into 0.2 ml. of boiling 50% sulfuric acid. The solution was then cooled, neutralized with solid sodium bicarbonate and extracted with four 5-ml. portions of benzene. The combined extracts were concentrated and the residue was sublimed at 130–140° (0.5 mm.). A total of 5.6 mg. of white prisms, m.p. 194–197°, was obtained. This material was resublimed for analysis, m.p. 196–198°.

Anal. Calcd. for $C_{12}H_{11}ON$ (185.22): C, 77.81; H, 5.99. Found: C, 78.12; H, 5.96.

The infrared spectrum of this compound was superposable with that of the 3-hydroxy-4-methyl-5-phenylpyridine obtained from II, with 31 prominent bands matching exactly. The mixed m.p. of the two samples was 197–199°.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF DELAWARE]

Heterocyclic Studies. VI. Some Observations on the Chemistry of 1-Amino-3-hydroxypyridinium Compounds[1]

BY JAMES A. MOORE AND JACOB BINKERT

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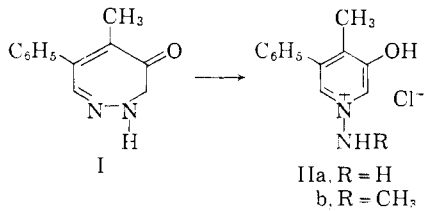
1-Amino-3-hydroxy-4-methyl-5-phenylpyridinium betaine (IXa) is a stable compound which is readily converted to an N-acetylbetaine with the $R_3\overset{+}{N}\overset{-}{N}COCH_3$ structure. The corresponding propionyl, trifluoroacetyl and benzoyl derivatives were also prepared, and it was found that the acids $RCONHN\overset{+}{<}$ are stronger than the corresponding carboxylic acids RCO_2H by about 0.7 pK_a unit.

In the course of the characterization of the 1-amino - 3 - hydroxy - 4 - methyl - 5 - phenylpyridinium chlorides (II), obtained from the diazepinone I,[2] certain points of interest emerged which were unrelated to the chemistry of I and are discussed separately in this paper. The ready availability of II has provided an opportunity to extend certain areas of the somewhat limited body of information on the chemistry of quaternary hydrazine derivatives.[3]



I

IIa, R = H
b, R = CH_3

The previously known 1-aminopyridinium salts[4] are restricted to the parent substance III, obtained[6] by decomposition of an arylsulfonylazide in pyridine solution followed by hydrolysis of the intermediate sulfonamide, and the series of N-anilinopyridinium halides (IV) prepared by Schneider[7] by the reaction of pyrylium salts and arylhydrazines. The unsubstituted compound III and the N-aryl derivatives differ markedly in their behavior with alkali. The N-aryl compounds IV gave rise to deeply colored anhydro bases; the latter have been studied by Dimroth[8] and clearly have the betaine or ylid structures V, although in compounds in which one R group is alkyl, alkylidenedihydropyridine structures such as VII play a role in certain reactions. Compound III, on the other hand, furnished decomposition products including pyridine, presumably arising from the ylid VI, analogous to pyridine N-oxide. The lability of the N-unsubstituted 1-iminopyridinium system may be due in part to rapid intermolecular amination; the corresponding trimethylhydrazinium ylid VIII is reported to be a stable solid,[9] although some reservations have been expressed[8] concerning this structure.

The conversion of the hydrochloride II (R = H) to the free base was effected with either alkali or carbonate; the compound crystallized in colorless needles which were almost completely insoluble in

(1) Supported by a grant from the Geschickter Fund for Medical Research.

(2) J. A. Moore and J. Binkert, THIS JOURNAL, **81**, 6029 (1959), paper IV.

(3) A recent review has been presented by H. H. Sisler, G. M. Omietanski and B. Rudner, *Chem. Revs.*, **57**, 1021 (1957).

(4) 1-Aminopyridones[6] are not considered here.

(5) *Cf.* ref. 6, paper IV.

(6) J. N. Ashley, G. L. Buchanan and A. P. T. Easson, *J. Chem. Soc.*, 60 (1947); A. Meuwsen and R. Gösl, *Angew. Chem.*, **69**, 754 (1957), have reported the preparation of a compound assigned this structure by reaction of hydroxylamine-O-sulfonic acid with pyridine; no details were given.

(7) W. Schneider, *Ann.*, **438**, 115 (1924); W. Schneider and W. Riedel, *Ber.*, **74**, 1252 (1941).

(8) K. Dimroth, G. Arnoldy, S. v. Eicken and G. Schiffler, *Ann.*, **604**, 221 (1957).

(9) G. Wittig and M. Rieber, *ibid.*, **562**, 177 (1949).