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°.

Acknowledgments.—H. P. gratefully acknowledges a Fulbright travel grant. We thank Dr. M. Marzadro, Istituto Superiore di Sanita, Rome, for the microanalyses; Dr. J. M. Vandenbelt and colleagues, Parke, Davis and Co., for the ultraviolet spectra; and Dr. Harold Beachell and associates for the infrared spectra.

NEWARK, DEL.

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

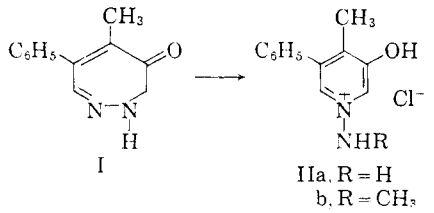
Heterocyclic Studies. VI. Some Observations on the Chemistry of 1-Amino-3-hydroxypyridinium Compounds[1]

BY JAMES A. MOORE AND JACOB BINKERT

RECEIVED FEBRUARY 19, 1959

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 $RCONH\overset{+}{N}\leqslant$ 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]



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.

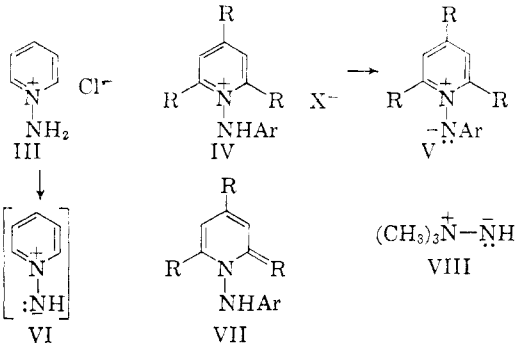
(5) *Cf.* ref. 6, paper IV.

(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.

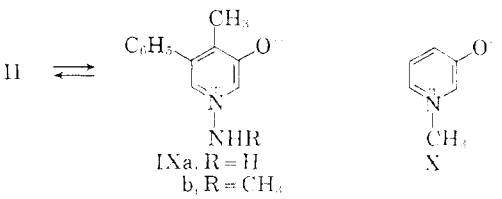
(7) W. Schneider, *Ann.*, **438**, 115 (1924); W. Schneider and W. Riedel, *Ber.*, **74**, 1252 (1941).

(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).



ether and could be conveniently recrystallized from hot water. In contrast to III, the conjugate base of II can exist as the zwitterion IX, and the properties of the compound fully confirm this structure. The pK_A value (4.9) of IIa is very close to that of 3-hydroxypyridine methochloride (X) (pK_A 5.0), and the ultraviolet spectra of the hydrochloride and base, with maxima at 290 and 320 mμ, respectively, strikingly resemble those of X in neutral and alkaline solution (λ_{max} 290 and 320). The base was unaffected by refluxing with alkali or treatment with diazomethane. The properties of the methylaminopyridinium betaine IXb obtained from II (R = CH_3) were very similar to those of IXa.



Hydrazinium betaines analogous to IX do not appear to have been previously described, but the fact that the positive chargei s neutralized internally should not greatly alter the chemical behavior of the $\overset{+}{\geqslant}NNH_2$ system, which has been likened[8] to the isosteric $\overset{+}{\geqslant}NCH_3$ grouping. The similarity in physical properties of IX and X bear out this comparison, but in contrast, we have found that the primary amino group in IXa, although devoid of basicity, displays a reactivity reminiscent of that of a primary amine. The condensation of the hydrochloride IIa with a ketone to give the Schiff base was mentioned in paper IV.[3]

The acylation of 1,1,1-trisubstituted hydrazinium compounds has received relatively little attention. Treatment of 1-aminopyridinium chloride (III),[6] and later 1,1,1-trimethylhydrazinium iodide,[10] with sulfonyl halides gave the sulfonamides XI, which were converted with alkali to the corresponding bases assigned the ylid structures XII,

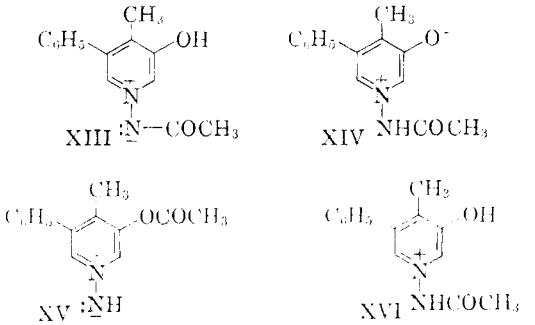
$$[R_3\overset{+}{N}-NH_2]X^- \longrightarrow [R_3\overset{+}{N}-NH-SO_2Ar]X^- \longrightarrow \underset{XI}{} \qquad R_3\overset{+}{N}-\overset{-}{N}-SO_2Ar \quad XII$$

the sulfonyl group conferring stabilization of the negative charge on nitrogen as in the aryl ylids V.

(10) S. Wawzonek and E. Meyer, THIS JOURNAL, **76**, 2918 (1954).

Compound III was also converted to an acetyl derivative which was isolated as the hydrochloride[6]; the corresponding base was not mentioned.

In the present work, IXa was found to react exothermally with acetic anhydride to give in excellent yield an ether-insoluble acetyl derivative which could be recrystallized from hot water. The compound was amphoteric (pK_A 4.2, 6.3) and the ultraviolet spectra in acid and alkaline solution closely resembled those of II and IX, respectively. A propionyl derivative was also prepared which had properties very similar to those of the acetylation product (pK_A 4.1, 6.2). The acetate was unaffected by fairly vigorous alkaline treatment but was hydrolyzed to II with hydrochloric acid. Two structures, XIII and XIV, come into consideration for the acetylation product. A third possibility, the 3-acetoxyylid XV, can be dismissed immediately[11]; it would be expected to exhibit the lability of the ylid VI; moreover, this structure is incompatible with the stability to alkali and the dependence of the ultraviolet spectrum on *p*H. Structures XIII and XIV are both plausible, *a priori*, the question being simply a matter of the relative acid strengths of the –OH and –NH– groups in the conjugate acid XVI.



The correctness of the ylid structure XIII was demonstrated by the reaction of the acetate with diazomethane, which led to a basic methylation product (pK_A 4.3), characterized as the crystalline picrate. Acid hydrolysis of this product gave a hydrochloride which on deamination with nitrous acid[2] furnished 3-methoxy-4-methyl-5-phenylpyridine (XIX), identical with a sample prepared by methylation of the hydroxypyridine XXII.[12] This sequence of reactions establishes structures XVIIa and XVIII for the methylation product and hydrochloride, respectively. The N-oxide XXI, which as discussed below is quite analogous to the ylid XIII and is known to have a 3-hydroxyl group of comparable acidity,[13] was found[12] to be similarly methylated by diazomethane.[14] Had the acetate of IXa been the zwitterion XIV, methylation followed by hydrolysis would have been expected to furnish the methylaminopyridinium betaine IXb which was

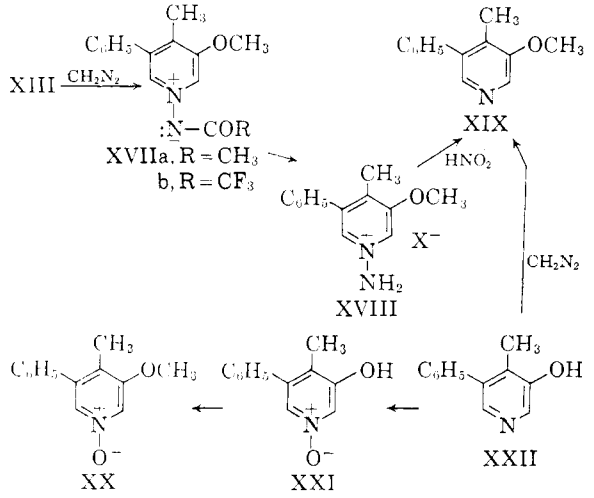
(11) This structure, as the hydrochloride, was erroneously attributed to the compound in ref. 3 on the basis of a rather cryptic preliminary communication (J. A. Moore, *ibid.*, **77**, 3417 (1955)).

(12) J. A. Moore and H. H. Püschner, *ibid.*, **81**, 6041 (1959), paper V.

(13) E. Shaw, *ibid.*, **71**, 67 (1949).

(14) In contrast to the behavior of these 3-hydroxy betaines, the hydroxyl group in the hydrochloride IIa was not methylated with diazomethane; treatment of IIa with diazomethane liberated the base IXa.

available by rearrangement of the 1-methyl derivative of the diazepine I.[2] The 3-methoxy hydrochloride XVIII, which as expected showed no measurable pK_A value, furnished a dark oil on basification, paralleling the behavior of III[6]; this material was not further investigated.

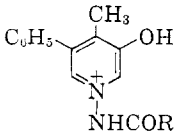


These findings reveal that the pK_A values of 4.2 and 6.3 of the acetate are associated with the –NH– and –OH groups, respectively, in the conjugate acid XVI. This conclusion was confirmed by the pK_A values of the trifluoroacetyl and benzoyl derivatives, prepared by treatment of IX with the anhydride and acid chloride, respectively. The trifluoroacetyl derivative was readily hydrolyzed to IX with alkali; methylation furnished the crystalline betaine XVIIb, which on hydrolysis gave XVIII. The benzoyl derivative was first obtained by another route from I, and the preparation and characterization will be described in a later paper.

The trifluoroacetyl amide showed a single pK_A of 6.0, and the methylation product XVIIb had no measurable pK_A value, indicating that the pK_A of the $\geqslant\overset{+}{N}NHCOCF_3$ group was below 2.5. The pK_A values of the benzoyl derivative were 3.3 and 6.4 (in 50% methanol). It is thus apparent (Table I) that the acidity of the $\geqslant\overset{+}{N}NHCOR$ grouping parallels that of the corresponding carboxylic acids RCO_2H very closely; the acylhydrazinium ion is the stronger acid by about 0.7 pK_A unit in the acetyl, propionyl and benzoyl cases. Whereas the pK_A of the –NH– group in these compounds depends, as expected, on the acyl group, the second pK_A, associated with the 3-hydroxyl function, falls in the fairly narrow range of 6.0–6.4, quite near that of the N-oxide XXI, which has a pK_A of 6.9.[12] These data appear to permit the generalization that in 3-hydroxypyridinium compounds with a full positive charge on nitrogen, such as the conjugate acids of IX or X, a pK_A of about 5 will be observed, while 3-hydroxy derivatives in which a negatively charged group such as $-O^-$ or $-NR^-$ is attached to the positive nitrogen will be weaker acids by about 1–1.5 pK_A units.

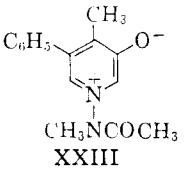
TABLE I

pK_A VALUES OF 1-ACYLAMINO-3-HYDROXYPYRIDINIUM DERIVATIVES



R	pK_A –OH	pK_A –NH	pK_A RCO_2H
CH_3	6.3	4.2	4.8
C_2H_5	6.2	4.1	4.9
CF_3	6.0[a]	<2.4	
C_6H_5	6.4[a]	3.3	4.2

[a] In 50% methanol.



XXIII

The acetylation product of the 1-methylaminopyridinium betaine IXb, which must have the O-betaine structure XXIII (analogous to XIV), presented a sharp contrast to the acetate XIII. The latter compound in neutral or alkaline solution is, of course, considerably stabilized by the resonance $\geqslant\overset{+}{N}\overset{-}{N}\overset{O}{\overset{\|}{C}}CH_3 \longleftrightarrow \geqslant\overset{+}{N}N{=}\overset{O^-}{\overset{|}{C}}{-}CH_3$, which accounts for the strongly acidic character of the $\geqslant\overset{+}{N}NH\text{-}COCH_3$ grouping. In contrast, the N-methyl-N-acetyl compound XXIII, which is a monoacidic base with pK_A about 6.0, was extraordinarily susceptible to hydrolysis. The compound was quite soluble in cold water, and was converted to the free base IXb in cold carbonate solution. Attempted methylation of XXIII with diazomethane in methanol solution also gave IXb. Another point of interest in the chemical properties of IXb was the finding that the compound furnished the theoretical amount of methyl iodide under the usual Zeisel methoxyl conditions. The facile cleavage of an N-methylamino group under these conditions has also been observed with 1-acyl-2-methyl- and 1-acyl-1-methylhydrazines.[15]

Experimental

1-Amino-3-hydroxy-4-methyl-5-phenylpyridinium Betaine (IXa).—A solution of 1 g. of the hydrochloride IIa[2] in 15 ml. of warm water was treated with 3 ml. of 10% sodium hydroxide solution. The base IXa crystallized immediately in felted laths which were washed with water and dried; 784 mg., m.p. 192–195° dec., change in form at 130–140°. A sample was recrystallized from ethanol–ether as glistening needles, m.p. 170/200–201° dec. After drying at 100° *in vacuo* for 3 hr., a sample lost about 5% weight and analyzed for a hemi-hydrate.

Anal. Calcd. for $C_{12}H_{12}ON_2 \cdot 1/2H_2O$: C, 68.87; H, 6.26; N, 13.40. Found: C, 68.82, 68.63; H, 6.31, 6 43; N, 13.19, 13.03.

After drying an additional four hours at 110°, anhydrous material was obtained; this had m.p. 191–195° dec.

Anal. Calcd. for $C_{12}H_{12}ON_2$: C, 71.97; H, 6.04; N, 13.99. Found: C, 71.73, 72.03; H, 6.01, 6.11; N, 14.27, 14.17; wt. loss, 1.97.

(15) M. Busch, *Ber.*, **35**, 1565 (1902).

The material for physical properties contained about 4% solvent water: pK_A[16] 4.9, mol. wt. 207; $\lambda_{max}^{H_2O}$ 228 (ϵ 23,200), 320 mμ (5700); $\lambda_{max}^{0.1\ N\ HCl}$ 225 (21,800), 292 mμ (6700).

The base was quite soluble in hot water, and was readily purified by recrystallization from water. It was unaffected by warming in 10% potassium hydroxide solution. The compound gave a yellow color with Ehrlich reagent (*p*-dimenthylaminobenzaldehyde in hydrochloric acid); it did not reduce Tollens reagent. A solution of the base in methanol was unaffected by diazomethane; no nitrogen was evolved, and the starting material crystallized, m.p. 192–195° dec., on concentrating the solution and diluting with ether.

1-Methylamino-3-hydroxy-4-methyl-5-phenylpyridine (IXb).—The hydrochloride IIb[2] was crystallized from methanol–ether for analysis; shiny platelets, m.p. 205–207°, pK_A 5.0 (50% methanol); λ_{max}^{EtOH} 232 (20,600), 296 mμ (6700); $\lambda_{max}^{EtOH\ +\ KOH}$ 244 (18,600), 334 mμ (7100) (this is the spectrum of the base).

Anal. Calcd. for $C_{13}H_{14}ON_2 \cdot HCl$ (250.72): C, 62.27; H, 6.03; N, 11.18; (N)-CH_3, 5.98. Found: C, 62.80; H, 6.05; N, 11.39; "OCH_3," 12.38; calcd. as (N)-CH_3, 5.98.

For conversion to the **free base IXb**, a solution of 225 mg. of the hydrochloride IIb in 1 ml. of water was treated with 10% potassium hydroxide solution until the *p*H was 10. The clear solution suddenly crystallized to a mass of felted white needles; 165 mg. (85%), m.p. 146–148°. Recrystallization from methanol–ether did not raise the m.p., although in other instances, crystals with m.p. 150–152 were obtained. The compound was readily soluble in hot water, which was a very satisfactory recrystallization solvent.

The base was reconverted to the hydrochloride with methanolic hydrogen chloride; white prisms from methanol–ether, m.p. and m.m.p. 203–205°. **The picrate** was prepared in ethanol, yellow prisms, m.p. 142–144°.

1-Acetylamino-3-hydroxy-4-methyl-5-phenylpyridinium N-Betaine (XIII).—One hundred mg. of the betaine IXa was dissolved in 0.5 cc. of acetic anhydride; the solution became warm. After warming at 50° for 30 seconds, water was added and the solution was boiled briefly to hydrolyze the excess anhydride. The hot solution was concentrated almost to dryness in a current of air; more water was added and large colorless prisms separated. The crystals were filtered, dried, and recrystallized from methanol–ether, furnishing 106 mg. of small, glistening prisms, m.p. 216–217°; pK_A' 4.1, 6.3; $\lambda_{max}^{0.1\ N\ HCl}$ 230 (ϵ 17,500), 296 mμ (8250); $\lambda_{max}^{0.1\ N\ NaOH}$ 232 μ (25,000), 321 mμ (7,350); the isosbestic point was 306 mμ (determined from spectra at *p*H 4, 6, 7 and 11).

Anal. Calcd. for $C_{14}H_{14}O_2N_2$ (242.27): C, 69.40; H, 5.82; N, 11.56. Found: C, 69.18; H, 5.77; N, 11.68.

This compound could also be isolated from the acetylation mixture by adding potassium hydroxide solution to a *p*H of 6–7; the acetate then separated as an oil which rapidly crystallized. The acetate was appreciably soluble in water, and was freely soluble in aqueous acid or carbonate solution; it was virtually insoluble in ether. In an attempted alkaline hydrolysis of the compound, a 15-mg. sample was dissolved in 0.5 cc. of 0.5 *N* potassium hydroxide and the solution was heated for 1.5 hr. at 90°. No crystals separated on cooling; on neutralization with one drop of 10% hydrochloric acid, 10 mg. of unreacted acetate, m.p. and mixed m.p. 216–217°, was obtained. This recovered material was then subjected to acid hydrolysis by dissolving in 0.2 cc. of 10% hydrochloric acid and warming for one hour. On cooling, characteristic crystals of the base hydrochloride separated, these were filtered and washed with one drop of water, m.p. and mixed m.p. with IIa 193–195°.

The acetyl derivative was recovered unchanged from attempted Pt-catalyzed hydrogenolysis under conditions which brought about reduction of IIa to XXII.

1-Propionamido-3-hydroxy-4-methyl-5-phenylpyridinium N-Betaine.—A solution of 50 mg. of IXa in 0.11 ml. of propionic anhydride was heated for 1 min. on the steam-bath. Water was then added, the solution was boiled briefly and evaporated to an oil. The oil crystallized slowly after addition of ether. The material was recrystallized from methanol–ether, double m.p. 151–153/175–177°, and finally from acetone–ether, white prisms, m.p. 177–178°; pK_A' 4.05, 6.2; the ultraviolet and infrared spectra were practically identical with those of the acetate.

Anal. Calcd. for $C_{15}H_{16}O_2N_2$ (256.30): C, 70.29; H, 6.30; N, 10.93. Found: C, 70.33; H, 6.38; N, 11.13.

1-Acetylamino-3-methoxy-4-methyl-5-phenylpyridinium N-Betaine (XVIIa).—A solution of 50 mg. of XIII in 2 ml. of methanol and 5 ml. of ether was treated with ethereal diazomethane. Nitrogen was briskly evolved; after standing for 2 min. with excess diazomethane, the solution was evaporated *in vacuo* to a light pink oil which could not be crystallized. This oil, which was freely soluble in water, was treated in methanol solution with 50 mg. of picric acid and a light yellow **picrate** crystallized immediately. The derivative, 40 mg., was recrystallized from ethanol as small, bright yellow prisms, m.p. 149–151°; it was finally recrystallized from methanol, m.p. 152–153°, pK_A' 4.3 (in 50% methanol).

Anal. Calcd. for $C_{21}H_{19}N_5O_9$ (485.40): C, 51.96; H, 3.95; N, 14.43. Found: C, 51.90; H, 4.02; N, 14.60, 14.88.

1-Amino-3-methoxy-4-methyl-5-phenylpyridinium Chloride (XVIII).—A methanol–ether solution of 500 mg. of XIII was treated with excess diazomethane and after 30 sec. standing the solution was evaporated *in vacuo*. The resulting pink oil was dissolved in 2 cc. of 10% hydrochloric acid and the solution was heated for 25 min. on the steam-bath and then was reduced to a thick sirup *in vacuo*. This material was taken up in a few cc. of ethanol, and the amber solution was filtered. Dilution with ether and scratching gave heavy, cream-colored prisms of the hydrochloride XVIII; 415 mg., m.p. 186–187°. After recrystallizing from ethanol–ether and finally ethanol–petroleum ether, the material was obtained as tiny glistening white prisms, m.p. 193–195°; mixed m.p. with hydrochloride IIa (m.p. 192–195°) 168–170°; no pK_A' from *p*H 2–12; $\lambda_{max}^{H_2O}$ 227 (22,000), 291 mμ (6400); the spectra in 0.1 *N* HCl, *p*H 7 and 0.1 *N* NaHO were the same.

Anal. Calcd. for $C_{13}H_{15}ON_2Cl$ (250.72): C, 62.27; H, 6.03; N, 11.18. Found: C, 62.29; H, 6.16; N, 10.91.

This hydrochloride was very soluble in water and less so in absolute ethanol. When a sample of the salt in water was made alkaline, a dark brown oil separated.

A sample (30 mg.) of this hydrochloride was converted to the **picrate**, in methanol solution, with 30 mg. of picric acid. The picrate separated as golden plates, m.p. 170–173°. Recrystallization from ethanol gave dark gold leaves, m.p. 175–176°.

Anal. Calcd. for $C_{19}H_{17}N_5O_8$ (443.37): C, 51.47; H, 3.87; N, 15.80. Found: C, 51.16; H, 3.66; N, 15.74.

3-Methoxy-4-methyl-5-phenylpyridine (XIX).—To a solution of 108 mg. of the 1-amino-3-methoxyhydrochloride XVIII in 4 ml. of ethanol was added 190 mg. of sodium nitrite in 0.5 ml. of water and then 1 ml. of 10% hydrochloric acid. The solution was allowed to stand for 0.5 hr. and the alcohol was evaporated. The aqueous solution was made basic with potassium hydroxide and an oil separated which crystallized on chilling the mixture but remelted at room temperature. The mixture was extracted with ether and the ether solution was washed with water, dried and evaporated. The resulting yellow oil could not be crystallized, even at −20°, the solid obtained from aqueous suspension evidently being a hydrate. The oil was then redissolved in ether and the solution was treated with dry hydrogen chloride. Colorless prisms of the hydrochloride separated immediately. The material was filtered and recrystallized from absolute ethanol–ether as white needles; 55 mg., m.p. 157–159° (subl.). Final recrystallization from ethanol–petroleum ether gave shining needles, m.p. 152–155° (sub.), pK_A' 5.0; $\lambda_{max}^{H_2O\ or\ 0.1\ N\ NaOH}$ 280 mμ (6600); $\lambda_{max}^{HCl-MeOH}$ 228 (17,500), 287 mμ (8700). Repeated analyses on this compound gave inexplicably low carbon values; hydrogen and nitrogen were in good agreement.

Anal. Calcd. for $C_{13}H_{14}ONCl$ (235.71): C, 66.24; H, 5.99; N, 5.94. Found: C, 65.04, 65.07, 64.17; H, 6.19, 5.96, 6.20; N, 5.98.

A sample (10 mg.) of the hydrochloride was treated in ethanol solution with 10 mg. of picric acid; **the picrate** separated in matted yellow needles, m.p. 135–136°. Recrystallization from ethanol gave yellow needle clusters, m.p. 136–137°, no depression on mixture with the picrate obtained[12] by methylation of XXII; the infrared spectra of these two picrates were superimposable.

(16) The pK_A values are apparent dissociation constants determined by the method of T. V. Parke and W. W. Davis, *Anal. Chem.*, **26**, 642 (1954).

1-Trifluoroacetylamino-3-hydroxy-4-methyl-5-phenylpyridinium N-Betaine.—A suspension of 100 mg. of IXa in 2 ml. of benzene was treated, at 5–12°, with 0.3 ml. of trifluoroacetic anhydride. The base immediately dissolved, and after 20 sec. the solution was evaporated to a colorless oil. The oil crystallized on treatment with water followed by a drop of methanol. The colorless plates of the trifluoroacetate were filtered, washed with water and dried; m.p. 178–179°, 107 mg. Recrystallization from methanol–water gave glistening prisms, m.p. 179–180°, pK_A' 6.0 (50% methanol); $\lambda_{max}^{H_2O \text{ or } 0.1\ N\ NaOH}$ 229 (ϵ 23,400), 322 mμ (7,300); $\lambda_{max}^{0.1\ N\ HCl}$ 228 (20,000), 292 mμ (7,100).

Anal. Calcd. for $C_{14}H_{11}N_2O_3F_3$ (296.25): C, 56.76; H, 3.74; N, 9.46. Found: C, 56.88; H, 3.95; N, 9.52.

This compound was virtually insoluble in water or acid, but was freely soluble in carbonate solution; it was significantly more soluble in organic solvents such as benzene or ether than was the acetate.

A sample (20 mg.) of this derivative was hydrolyzed by warming in 0.5 cc. of 10% potassium hydroxide solution for 20 min. The solution, which contained a trace of oil, was cooled and treated with one ml. of water and a few drops of methanol; white needles separated. This material was filtered and dried; wt. 11 mg., m.p. and m.m.p. with the original base IXa, 195–196° dec.

1-Trifluoroacetylamino-3-methoxy-4-methyl-5-phenylpyridinium N-Betaine (XVIIb).—A solution of 340 mg. of the trifluoroacetylbetaine in 6 ml. of methanol was treated with excess ethereal diazomethane. When the vigorous gas evolution had ceased, the solution was evaporated *in vacuo*. The oil was dissolved in ether and the solution crystallized upon the addition of petroleum ether. The product was recrystallized twice from methanol–water, furnishing 150 mg. of XVIIb, white prisms, m.p. 134–135°, no pK_A' between pH 2 and 12; λ_{max}^{EtOH} 233 (ϵ 15,000), 295 mμ (9,600); the spectra in acidic and alkaline solutions were unchanged.

Anal. Calcd. for $C_{15}H_{13}N_2O_2F_3$ (310.27); C, 58.06; H, 4.22; N, 9.03. Found: C, 58.10; H, 4.17; N, 9.71, 9.85.

A 60-mg. sample of this product was heated for 20 min. on the steam-bath in 1 ml. of 5% methanolic potassium hydroxide solution. Evaporation of the solution gave a dark brown water-insoluble oil which was dissolved in methanol and treated with a methanol solution of 50 mg. of picric acid. Dark gold plates of the picrate separated immediately; recrystallization from ethanol gave 50 mg. of derivative, m.p. 171–172°, no depression with picrate (m.p. 174–175°) prepared by hydrolysis of XVIIa.

1-(N-Methylacetylamino)-3-hydroxy-4-methyl-5-phenylpyridinium Betaine (XXIII).—A 60-mg. sample of IXb was dissolved in 0.3 ml. of acetic anhydride; the solution became warm and developed an orange color. After standing for 30 sec. at 60°, 0.5 ml. of water was added and the solution was evaporated to a sirup. This compound was exceedingly difficult to crystallize. Treatment with chloroform and ether gave an amorphous solid which slowly crystallized from a mixture of methanol, acetone and ether to give 38 mg. of of slightly colored prisms, m.p. 194–198°. After treatment with carbon, recrystallization from the same solvent mixture gave short white prisms, m.p. 198–200°.

For analysis the compound was converted to the picrate which was twice recrystallized from ethanol, m.p. 179–180°, pK_A 6.0.

Anal. Calcd. for $C_{21}H_{19}O_9N_5$ (485.4): C, 51.96; H, 3.94; N, 14.43. Found: C, 51.87; H, 4.00; N, 14.36.

A solution of 16 mg. of the acetylation product in 0.1 ml. of methanol was allowed to stand for 2.5 hours with excess ethereal diazomethane. Evaporation of the solution gave a crystalline residue, m.p. and m.m.p. with IXb, 150–152°.

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Heterocyclic Studies. VII. The Preparation and Reactions of 2-Amino-5-hydroxypyridines; the Formation of an Azaquinone[1]

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2-Amino-5-hydroxypyridine has been prepared by the diazotization of 5-amino-2-benzamidopyridine and by reduction of 5-hydroxy-2-*p*-nitrobenzeneazopyridine; the diazo coupling of 3-hydroxypyridines has been shown to be a generally useful method for the preparation of 2-amino-5-hydroxypyridines. Treatment of 2-amino-5-hydroxypyridine and 2-amino-5-hydroxy-4-methyl-3-phenylpyridine with excess nitrous acid furnished nitrosodihydroxypyridines. Hydrolysis of 2-nitroso-3,6-dihydroxy-4-methyl-3-phenylpyridine led to an azaquinone. Several reactions of the latter compound are described.

In connection with other work in this series, samples of 2- and 6-amino-3-hydroxy-4-methyl-5-phenylpyridine and information on some reactions of 2-amino-5-hydroxypyridines were required. Although several generally applicable synthetic paths for the preparation of 2-amino-3-hydroxypyridines are available, no satisfactory synthetic methods leading to the 2-amino-5-hydroxypyridine system have been described. The studies reported in this paper were undertaken to develop preparative methods for 2-amino-5-hydroxypyridines and to obtain precise information on the properties and reactions of this type of substituted pyridine. Parallel investigations were carried out with the 4-methyl-5-phenyl- and the 4,5-unsubstituted pyridine series, the latter serving as model compounds.

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2-Amino-5-hydroxypyridine has had a checkered past, and appears never to have been adequately characterized. The compound was reported by Koenigs, Gerdes and Sirot[3] to arise by reduction of the nitration product of 3-hydroxypyridine, but it was subsequently established by Schickh, *et al.*,[4] and by Plazek[5] that the product from this sequence of reactions is the 2-amino-3-hydroxy isomer. Renewed interest in 2-amino-5-hydroxypyridine stemmed from a study of the metabolic product of sulfapyridine in the rabbit and dog.[6–8] Hydrolysis of this metabolite furnished an aminohydroxypyridine,[6,8] characterized as the picrate and hydrochlo-

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(7) J. V. Scudi, *ibid.*, **55**, 197 (1944).

(8) H. G. Bray, F. C. Neale and W. V. Thorpe, *Biochem. J.*, **40**, 406 (1946).