Hydrogenation in the Pyridine Series. I. Catalytic Reduction of the Isomeric Acetylpyridines

MORRIS FREIFELDER

Organic Chemistry Department, Research Division, Abbott Laboratories, North Chicago, Illinois

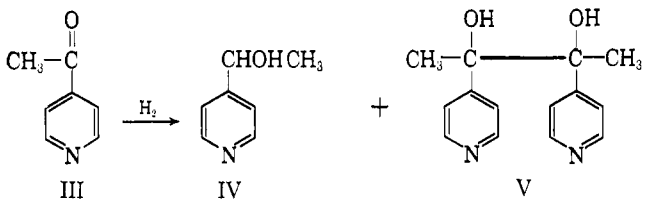
Received April 16, 1964

The catalytic reduction of the isomeric acetylpyridines with noble metal catalysts and with Raney nickel is studied. The formation of by-products during reduction is discussed. A mechanism of action for the formation of 3-acetyl-1,4,5,6-tetrahydropyridine from 3-acetylpyridine is presented and proof of structure of the compound is offered. N.m.r. data for most of the reduction products is also presented.

When the previously described method for the preparation of 3- and 4-(1-hydroxyethyl)pyridines[1] was followed, the ultraviolet spectra and gas phase chromatograms of these products showed that they were contaminated with the corresponding starting acetylpyridines and other products. A need for the pure carbinols led to an investigation of hydrogenation in this series with other noble metal catalysts and with Raney nickel, with some unexpected results.

2-(1-Hydroxyethyl)pyridine (II), previously prepared by chemical methods,[2a,b] was readily obtained from 2-acetylpyridine (I) with palladium on carbon. Reduction of I with nickel gave II, containing less than 5% of I. Hydrogenation of I in the presence of rhodium on carbon or platinum oxide gave a mixture of products which included 2-(1-hydroxyethyl)piperidine. The formation of this product from rhodium reduction was not surprising since it has been shown that this catalyst will convert pyridines to piperidines in the absence of acid.[3] These reductions are in line with the suggestion that a group adjacent to the ring nitrogen can prevent catalyst poisoning by physical shielding.[4]

When 4-acetylpyridine (III) was reduced in alcohol in the presence of platinum oxide, the desired carbinol (IV) was obtained, and also the pinacol, 2,3-di(4-pyridine)butane-2,3-diol (V). Hydrogenation with other catalysts gave varying large amounts of the same product, plus some III and IV. Indeed, in the reduction of III in alcohol with Raney nickel, and of a very concentrated aqueous solution of III in the presence of platinum oxide, V was formed in high yield. It was also the major product of reduction when palladium or rhodium on a carrier was used.



III IV V

In the reduction of 3-acetylpyridine (VI), mixtures always resulted when 1 equiv. of hydrogen was absorbed (see Table I). 3-(1-Hydroxyethyl)pyridine (VII) was obtained in pure form by sodium borohydride reduction.[5] Gas phase chromatographs of the solutions after catalytic reduction showed the presence of three major components: VI, VII, and an unknown VIII.[6]

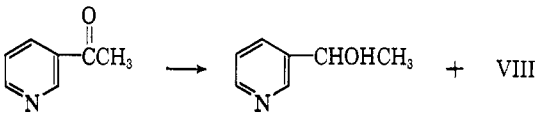
TABLE I

HYDROGENATION OF 3-ACETYLPYRIDINE[a]

Solvent[b]	Catalyst[c]	Ratio, %[d]	Results, %[e] VI	VII	VIII
B	D	5		*f*	
B	D[g]	2	5	75	21
B	D[h]	2	25	51[i]	24
C	D[g]	1	15	75	10
C	E	20		No uptake	
C	F	10	50	10	40
C	G	10	58	9	33

[a] Except where indicated, all reductions were stopped after 1 equiv. of hydrogen was absorbed. [b] B, water; C, ethyl alcohol. [c] D, platinum oxide; E, Raney nickel; F, 5% palladium on carbon; G, 5% rhodium on alumina. [d] Grams of catalyst per 100 g. of VI. [e] The values are approximate as determined by gas phase chromatography. The amounts of VI were corroborated by ultraviolet examination. [f] Vapor phase chromatography by Mr. P. F. Helgren of this laboratory showed at least five components. [g] Hydrogen uptake, 1.25 equiv. [h] Uptake, over 2 equiv. [i] The presence of 3-(1-hydroxyethyl)piperidine could not be ruled out. The products of this experiment were fractionated. The portion corresponding to VII was examined. Its near-infrared spectrum indicated the presence of NH as well as OH.

Ultraviolet spectra of these solutions confirmed the presence of VI and VII. Also seen in each spectrum was a very strong peak at 300 mμ.[7]



VI VII

Since the largest amount of the unknown was obtained from the palladium reduction of VI, it was the catalyst used for a preparative run. Uptake of hydrogen was allowed to continue until it stopped.[8] Fractionation gave VIII in good yield.

A single sharp peak at 452 c.p.s. in the n.m.r. spectrum suggested a vinyl proton. The ultraviolet spec-

(1) F. M. Strong and S. M. McElvain, *J. Am. Chem. Soc.*, **55**, 816 (1933).

(2) (a) O. H. Bullitt, Jr., and J. T. Maynard, *ibid.*, **76**, 1370 (1954); (b) D. O. Holland and J. H. C. Naylor, *J. Chem. Soc.*, 1659 (1955).

(3) M. Freifelder, R. M. Robinson, and G. R. Stone, *J. Org. Chem.*, **27**, 284 (1962).

(4) M. Freifelder, *Advan. Catalysis*, **14**, 203 (1962); G. N. Walker [*J. Org. Chem.*, **27**, 2966 (1962)] calls it *ortho-group assistance*.

(5) F. Hagglid and I. Wellings [*Acta Chem. Scand.*, **17**, 1735 (1963)] used potassium borohydride in methyl alcohol.

(6) Gas phase chromatography was carried out by Mrs. Taimi Anderson on a Barber-Colman Model 10 unit. Detector, thermal conductivity cell, 195°, column, 8 ft. × 1/4 in. glass U-tube, stationary phase 20% DC 550, support 40–50-mesh Chromosorb P, 180°; carrier gas, helium, 15 p.s.i.

(7) Ultraviclet and equivalent weight determinations were carried out by Mr. V. Papendick of this laboratory.

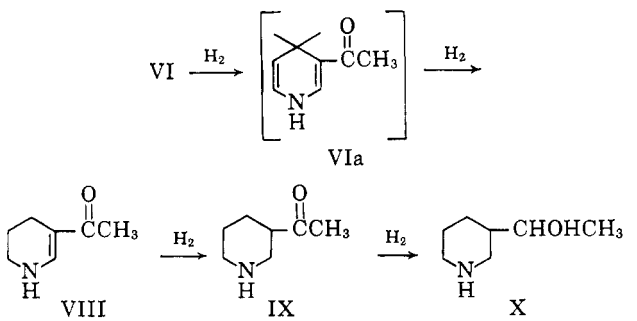
(8) In some later work, after the unknown was identified, it was found that it could not be reduced further with palladium catalyst in neutral or acid solution.

trum of the product showed a strong peak at 300 mμ as seen before. The infrared spectrum showed an NH band, a broad peak characteristic of β-amino-α,β-unsaturated carbonyl function, and absence of pyridine ring.[9] Near-infrared indicated the absence of OH and showed that the NH was amide-like, not basic.[9] Potentiometric titration in an aqueous system failed to show any titratable base. The vinylogous amide character was shown by its chemical unreactivity to ketonic agents. Attempted reduction with sodium borohydride was unsuccessful. In addition, it was not possible to acetylate the compound.

Equivalent weight determination suggested a weight of 125. Elemental analysis indicated a formula consistent with $C_7H_{10-11}NO$ (mol. wt. 124–125). Molecular weight determinations by two different methods gave values of 121 and 129.[10] A Kuhn–Roth C-methyl determination indicated a terminal methyl group.

From consideration of its chemical and physical data, it appeared that VIII was 3-acetyl-1,4,5,6-tetrahydropyridine. N.m.r. data offers substantiation. Integration shows that the C-4, -5, and -6 protons are equivalent (two each), the methyl protons equal three, and the vinyl proton and NH total two. Further substantiation was obtained when it was converted to the known 3-(1-hydroxyethyl)piperidine (X).[1]

The formation of VIII from VI probably takes place by 1,4-addition, giving the intermediate VIa. The isolated 5,6-double bond is then reduced preferentially over the 2,3-conjugated bond to yield VIII. Subsequently, VIII is converted to 3-acetylpiperidine (IX) and 3-(1-hydroxyethyl)piperidine (X). The isolation of



IX (in small yield) during the hydrogenation of VI in the presence of palladium gives added support to this proposal. In another reduction of VI with rhodium catalyst, which was allowed to continue until uptake of hydrogen stopped, X was the major product. In addition to VIII, IX was also isolated and identified.

It appears that reductions of 3-acetylpyridine with palladium and rhodium catalyst in neutral solution follow the pathway described above, and that normal reduction of it with these catalysts to 3-(1-hydroxyethyl)pyridine is in reality a side reaction. The larger amount of X obtained in the rhodium reduction (a combination of the described pathway and conversion of VII) indicates that the latter catalyst is less sensitive to nitrogen base poisoning than palladium.

(9) The spectra were run by Mr. A. Krammer and Mr. W. Washburn of this laboratory.

(10) The Rast method in camphor gave 250. It was shown that this method was unsatisfactory because of association. It also gave 228 and 240 for 3-acetylpiperidine (IX); theoretical value, 129.

The difference in reductions in this series is most striking. Only the 2-acetyl derivative more or less followed the expected reaction path with the catalysts used.

Experimental

N.m.r. spectra described in this work were determined on a Varian A-60 spectrometer at a frequency of 60 Mc./sec. and with internal standard, tetramethylsilane.

2-(1-Hydroxyethyl)pyridine (II).—A solution of 24.2 g. (0.2 mole) of 2-acetylpyridine in 50 ml. of 95% ethyl alcohol was hydrogenated in the presence of 2.4 g. of 5% palladium-on-carbon catalyst under 3-atm. pressure. When uptake of hydrogen was complete (2–3 hr.), the solution was filtered from the catalyst. When an ultraviolet determination showed that no starting material was present, the solution was concentrated under reduced pressure. The residues from two runs were distilled through a 6-in. column packed with glass helices. A fraction which boiled at 133° (58 mm.), $n^{25}D$ 1.5240, was collected in 79% yield [lit.[2a] b.p. 85–89° (5 mm.), $n^{25}D$ 1.5253].

Anal.[11] Calcd. for C_7H_9NO: C, 68.26; H, 7.37; N, 11.37. Found: C, 68.05; H, 7.70; N, 11.61.

N.m.r. ($CDCl_3$): C-3, -4, and -5 protons, numerous peaks, 416 to 466 c.p.s.; C-6 proton,[12] peaks at 503 and 508 c.p.s. with fine splitting (assigned to the C-6 proton also on the basis of integration of 1 proton to 3 at C-3, -4, and -5); side-chain methyl protons, doublet at 85 and 92 c.p.s.; C-1 side-chain proton, quartet at 282, 289, 296, 303 c.p.s. which contains in its midst the OH proton at 286 c.p.s. The latter is removed on addition of D_2O, leaving a sharply defined quartet at 282, 289, 296, 303 c.p.s. In carbon tetrachloride solution, all peaks moved slightly to the right. The quartet assigned to the proton on the α-carbon atom in the side chain stood out prominently at 277, 283, 290, 296, with the OH a sharp peak at 299 c.p.s.

Hydrogenation of I with a 20% ratio of Raney nickel catalyst to compound gave II contaminated with less than 5% of I. The use of platinum oxide or rhodium on a carrier gave mixtures which included 23–25% I, 60–70% of II, and varying amounts of 2-(1-hydroxyethyl)piperidine.

4-(1-Hydroxyethyl)pyridine (IV).—The described method[1] gave a product contaminated with 15–25% of III. The following procedure, however, gave pure material. Hydrogenation of 48.4 g. (0.4 mole) of 4-acetylpyridine (III) in 100 ml. of 95% ethyl alcohol in the presence of 0.4 g. of platinum oxide under 3-atm. pressure was complete in 2–3 hr. The solution was filtered from the catalyst. After the catalyst was washed with alcohol, the combined filtrates were concentrated under reduced pressure. The residue which contained some solid product was dissolved in ether and the solid was removed. After removal of solvent, the residue was combined with that of a second reduction was distilled under reduced pressure. The fraction collected at 150–152° (20 mm.)[13] weighed 61 g. (62%). It solidified on standing and melted at 57–59°. Examination of its ultraviolet spectrum showed that starting material was not present.

Anal. Calcd. for C_7H_9NO: C, 68.27; H, 7.36; N, 11.37. Found: C, 68.18; H, 7.34; N, 11.42.

N.m.r. (D_2O): methyl protons, doublet at 91 and 98 c.p.s.; C-1 side-chain proton, quartet at 292, 300, 308, 316 c.p.s., the last peak somewhat less sharp because of the strong water peak at 312 c.p.s.; aromatic protons, C-3 and C-5, sharp doublet at 449 and 454 c.p.s., C-2 and C-6, sharp doublet at 513 and 519 c.p.s. (see ref. 12).

When the reduction solution was filtered from the catalyst, some solid was also found. The catalyst and adhering solid was suspended in 100 ml. of water and acetic acid was added until the solid dissolved. The solution was filtered from the catalyst and the filtrate then was made basic. The precipitate was filtered, then washed with water, and recrystallized from dilute alcohol. Infrared examination showed the presence of an OH function.

(11) Microanalyses were carried out by Mr. O. F. Kolsto and his group in this laboratory. Mr. V. Raenckel of the same group ran the molecular weight determinations of compound VIII, Rast method, freezing point in dimethyl sulfoxide, and the C-methyl analysis.

(12) L. M. Jackman (Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry, Pergamon Press, 1959, section 4.6) assigns the proton or protons adjacent to the heterocyclic atom furthest downfield.

(13) (a) G. R. Clemo and E. Hoggarth [*J. Chem. Soc.*, 41 (1941)] report 138–140° (30 mm.), m.p. 54°; (b) Z. J. Vejdelek and V. Trcka [*Collection Czech. Chem. Commun.*, **24**, 1860 (1959)] give 140–141° (20 mm.).

Its analysis (C, 68.87; H, 6.36; N, 11.37) fitted that of the pinacol, 2,3-di(4-pyridine)butane-2,3-diol ($C_{14}H_{16}N_2O_2$: C, 68.87; H, 6.60; N, 11.46). The product melted at 220° and sublimed at 247°. A search for the literature revealed that V was a known compound.[14]

The solid which was obtained from the residue prior to distillation was also found to be the pinacol (V); total yield, 15%.

N.m.r. (D_2O plus hydrochloric acid)[15]: C-methyl protons, single sharp peak, 119 c.p.s.; aromatic protons, two doublets at 518, 525 and 550, 557 c.p.s., assigned to C-3,3′, -5,5′ and C-2,2′, -6,6′, respectively.[12]

2,3-Di(4-pyridine)butane-2,3-diol (V).—When 0.2 mole of III was reduced in alcoholic solution in the presence of Raney nickel, only 0.1 mole of hydrogen was absorbed. A large amount of precipitate was present. The precipitate and catalyst were filtered and washed with alcohol The filtrate was concentrated to dryness. More precipitate was obtained. The total amount of precipitate was suspended in 300 ml. of water and treated with acetic acid until a solution was obtained. After removal of catalyst the filtrate was made alkaline, filtered, and washed with water. The pinacol was obtained in 90% yield. When the same hydrogenation was carried out in water containing 0.2 mole of acetic acid, the same amount of V was obtained.

Reduction of III in the presence of palladium on carbon or rhodium on alumina or carbon gave the pinacol in 60% yield in addition to III and IV. Hydrogenation in water (25 ml./0.2 mole of III) in the presence of platinum oxide gave 75–80% of V.

3-(1-Hydroxyethyl)pyridine (VII).—A solution of 5.0 g. (0.0413 mole) of 3-acetylpyridine in 100 ml. of 50% aqueous methyl alcohol was added gradually with stirring to a solution of 7.7 g. (0.2 mole) of sodium borohydride in 100 ml. of 50% aqueous methyl alcohol. The mixture was stirred for several hours and allowed to stand overnight. The solution was extracted with benzene and the extract was dried over anhydrous magnesium sulfate. After removal of drying agent, the solvent was distilled off under reduced pressure. The residue (5 g.), when free of solvent, was checked both by infrared and ultraviolet examinations and found to be the desired VII. Gas–liquid chromatography indicated only one component.

Anal. Calcd. for C_7H_9NO: C, 68.27; H, 7.36. Found: C, 68.40; H, 7.52.

The product was then distilled at 150° (20 mm.), $n^{25}D$ 1.5266; lit.[13b] 151–152° (22 mm.), $n^{20}D$ 1.5265; λ_{max}^{film} 3.14 broad (OH), 6.28, 6.34, 14.08 μ broad (pyridine).

N.m.r. (carbon tetrachloride): CH_3, doublet at 79, 86 c.p.s.; side-chain CH, quartet at 278, 285, 292, 299 c.p.s.; OH, single sharp peak at 366 c.p.s.; C-2 and C-6 protons, doublet of equal height at 500.5, 503 c.p.s., and a pair of doublets at 491, 492.5 and 495, 497.5 c.p.s. (integration, 2)[16]; C-4 proton, doublet at 457, 465 c.p.s., further split into two symmetrical triplets by long-range effect of the C-2 and C-6 protons; C-5 proton, four peaks of increasing height at 423, 427, 431, 435 c.p.s.[17]

3-Acetyl-1,4,5,6-tetrahydropyridine (VIII).—A solution of 45.0 g. (0.372 mole) of 3-acetylpyridine (VI) in 250 ml. of absolute ethyl alcohol was hydrogenated in the presence of 5.0 g. of 5% palladium on carbon under 3-atm. pressure until no further uptake was noted. An additional 0.2 mole of VI was similarly reduced. The solutions, after removal of the catalyst, were concentrated under reduced pressure and the residue was distilled over a 6-in. column packed with glass beads. Two constant-boiling fractions were set aside for further identification. The major component, VIII, was collected at 175° (10 mm.): $n^{25}D$ 1.6022, 70% yield, λ_{max}^{EtOH} 301 mμ (ϵ 21,150), $\lambda_{max}^{CCl_4}$ 1.48 μ (NH, amide) and no OH absorption, λ_{max}^{film} 3.07 (NH) and 6.25–6.65 μ (α,β-unsaturated β-amino C=O).

Anal. Calcd. for $C_7H_{11}NO$: C, 67.17; H, 8.85; N, 11.19; C-methyl, 12.01. Found: C, 67.43; H, 8.54; N, 11.22; C-methyl, 10.44.

The equivalent weight of the compound, determined by titration with perchloric acid in dioxane using acetonitrile as solvent, was found to be 125. Attempts to obtain a pK_a value of an aqueous solution or an extrapolated value of an acetonitrile–water solution showed that no titratable base was present. Molecular weight, determined by freezing point in dimethyl sulfoxide, was shown to be 121.[11] Another method gave a value of 129.[18]

N.m.r. (carbon tetrachloride): C-5 protons, multiple peaks of which three at 101, 106, 111 c.p.s. stand out (integration, 2); CH_3, single sharp peak, 122 c.p.s. (integration, 3); C-4 protons (assigned on the basis of adjacency to the double bond), triplet at 131, 137, 143 c.p.s. (integration, 2); C-6 protons, unsharp triplet, 188, 194, 200 c.p.s. (integration, 2); NH, a broad arc, 412–442 c.p.s.; C-2 vinyl proton, doublet 446, 452 c.p.s. The splitting is apparently caused by NH. Treatment with D_2O caused removal of NH and conversion of the doublet to a sharp singlet, 458 c.p.s. The group NH and CH integrated to 2, after D_2O; integration equaled 1.[19]

Hydrochloride Salt.—Compound VIII was converted to a hydrochloride salt in quantitative yield. It was recrystallized by treating an absolute alcoholic solution with anhydrous ether to the beginning of cloudiness, whereupon crystallization took place on standing; the salt had m.p. 169–170.5°.

Anal. Calcd. for $C_7H_{12}ClNO$: C, 52.01; H, 7.48; N, 8.67. Found: C, 52.16; H, 7.20; N, 8.70.

The salt is soluble in water but apparently dissociates to the base, which is also water soluble, and hydrochloric acid. The pH of the solution is below 1.5 (indicator paper).

The n.m.r. spectrum of the salt in D_2O showed all peaks moving sharply to the left; C-5 protons, numerous peaks with fine splitting, 126–153 c.p.s.; CH_3, sharp, 167 c.p.s.; C-4 protons, triplet, 168, 174, 180 c.p.s. partly obscured at 168; C-6 protons, triplet, 232, 238, 244 c.p.s.; vinyl proton, single sharp peak, 518 c.p.s.

3-Acetylpiperidine (IX).—In the preparation of VIII, a constant-boiling fraction, 100° (12 mm.), $n^{25}D$ 1.4788, was obtained in 7.2% yield. It appeared to be 3-acetylpiperidine from its spectra: $\lambda_{max}^{CCl_4}$ 1.54 μ (NH) and no OH absorption, λ_{max}^{film} 3.04 (NH) and 5.8 μ (C=O) with no pyridine absorption. The material was redistilled at 127° (62 mm.), $n^{25}D$ 1.4701.[20a] It was analyzed almost immediately. This procedure was necessary for good analytical results since the base absorbed carbon dioxide rapidly.

Anal. Calcd. for $C_7H_{13}NO$: C, 66.10; H, 10.30; N, 11.02. Found: C, 66.14; H, 10.31; N, 10.99.

A hydrochloride salt was prepared. It was somewhat hygroscopic which may account for its m.p. 96–100°.[20b]

Anal. Calcd. for $C_7H_{14}ClNO$: C, 51.49; H, 8.62; N, 8.56. Found: C, 51.61; H, 8.98; N, 8.76.

N.m.r. (carbon tetrachloride): C-3, -4, and -5 protons, series of peaks at 70–106 c.p.s. merging with a group of peaks with fine splitting at 106–121 c.p.s. (separate integration is difficult but the total integrates nicely to 5): CH_3, strong sharp peak at 125 c.p.s. (integration, 3); C-2 and C-6 protons, series of peaks, considerably split, from 130–210 c.p.s., containing a strong peak at 164 c.p.s. due to NH (integration, 5). Treatment with D_2O removed the peak at 164, sharpened the series of peaks, and changed the integration to 4. The group was still too complex to separate into C-2 and C-6 protons.

(14) M. J. Allen and H. Cohen [*J. Electrochem. Soc.*, **106**, 451 (1959)] obtained the pinacol by electrolytic reduction of III. They report a melting point of 219–220°.

(15) Poor solubility of V in organic solvents made it necessary to use water and acid. No peak appears for OH, only a very strong peak, off scale, at 305 c.p.s. for water and HCl.

(16) It is likely that the C-2 proton is the one farthest downfield because it may also be affected by the OH in the side chain.

(17) Assignments of C-4 and C-5 protons are based on Jackman.[12] Irradiation and double resonance studies on a 100-Mc./sec. unit should help to clarify the assignment of the protons attached to the ring. When the work is completed, the results will be reported in another journal.

(18) The determination was run on the Mechrolab vapor pressure osmometer, Model 301A, by Dr. H. H. Stein and Mrs. J. M. Ambrose of this laboratory. Water served as solvent; dextrose was used to construct the calibration curve. Three weight levels of sample, 0.079–0.295 g./10 ml., were employed. It was shown that, as the concentration was increased, the value rose, indicating association as noted in ref. 10.

(19) In some instances it was difficult to get a sharp separation between the CH_3 signal and the C-4 protons. In such cases, integration of the two was 5. At other times, integration for the C-5 protons was high because of imputities of 3-(1-hydroxyethyl)piperidine. In order to get a good n.m.r. spectrum for VIII, it was often necessary to distil the product through a tall column packed with helices to remove impurities which codistilled with it.

(20) (a) N. F. Leonard, J. W. Curry, and J. J. Sagura [*J. Am. Chem. Soc.*, **75**, 6249 (1953)] identify the product as a picrate. They decomposed a portion and obtained these constants: b.p. 63° (4.5 mm.), $n^{20}D$ 1.4875. (b) L. F. Kuick and H. Adkins [*J. Am. Chem. Soc.*, **57**, 143 (1935)] reported that they obtained this product. They gave molecular weight based on neutralization equivalent (131 against 127 calculated) and a hydrochloride salt (m.p. 114°) which was analyzed for chlorine only.

The second constant-boiling fraction obtained from the preparation of VIII was collected at 144–150° (12 mm.), $n^{25}D$ 1.5176. It appeared to be essentially 3-(1-hydroxyethyl)pyridine (VII), contaminated with a small amount of VI (infrared shows the presence of a small amount of carbonyl compound).

Anal. Calcd. for C_7H_9NO: C, 68.26; H, 7.37; N, 11.37; O, 13.00. Found: C, 68.03; H, 7.40; N, 11.63; O, 12.95.

Reduction of 3-Acetylpyridine with Rhodium Catalyst.—A solution of 24.2 g. (0.2 mole) of VI in 150 ml. of absolute ethyl alcohol was hydrogenated under 3-atm. pressure in the presence of 4.8 g. of 5% rhodium on alumina. After uptake of hydrogen stopped (total uptake about 4 equiv. in 15–18 hr.), the solution was filtered and concentrated under reduced pressure. Distillation of the residue from three runs gave a few grams of forerun which, from near-infrared [$\lambda_{max}^{CCl_4}$ 1.54 μ (NH) and no OH absorption] and infrared [λ_{max}^{film} 3.05 (NH), 6.27, 6.34, 6.77, 13.1 μ (pyridine)] appeared to be a mixture of 3-ethylpiperidine and 3-ethylpyridine. The main fraction, b.p. 140–143° (38 mm.), $n^{25}D$ 1.4871 [lit.[1] b.p. 105–120° (3 mm.)], was 3-(1-hydroxyethyl)piperidine (X), 37.15 g. (48% yield). It solidified on standing, m.p. 65–70°, $\lambda_{max}^{CCl_4}$ 1.42 (OH) and 1.54 μ (NH), with no pyridine absorption in the infrared spectrum.

Anal. Calcd. for $C_7H_{15}NO$: C, 65.07; H, 11.70; N, 10.84. Found: C, 64.83; H, 11.63; N, 10.74.

The final fraction, b.p. 210–211° (32–35 mm.), $n^{25}D$ 1.6005, weighed 20.9 g. (*ca.* 28% yield). Its ultraviolet, infrared, near-infrared, and n.m.r. spectra indicated it was 3-acetyl-1,4,5,6-tetrahydropyridine (VIII).

3-(1-Hydroxyethyl)piperidine (X). Reduction of VIII.—A solution of 25.0 g. (0.2 mole) of VIII in 200 ml. of absolute methyl alcohol containing 0.2 mole of hydrogen chloride was hydrogenated in the presence of 1.0 g. of platinum oxide until uptake of hydrogen stopped. After removal of the catalyst, the solution was concentrated to dryness. Except for a very small amount of material, about 0.3 g., m.p. 84–87° after recrystallization from acetone, the residue would not solidify. This material, on analysis, appeared to be a hydrochloride salt of X.[21] Infrared examination did not show anything inconsistent with the structure.

Anal. Calcd. for $C_7H_{16}ClNO$: C, 50.74; H, 9.73; N, 8.45. Found: C, 50.99; H, 9.49; N, 8.68.

The remainder of the residue was dissolved in about 50 ml. of water. The solution was made strongly basic with 40–50% aqueous sodium hydroxide solution and, when cool, thoroughly extracted with ether. The ether solution was dried over anhydrous magnesium sulfate and, after removal of drying agent, was concentrated. The residue was fractionated. Most of it was collected at 125–130° (15 mm.), but it did not solidify.[22] Its infrared spectrum resembled that of the solid X obtained during the rhodium reduction of 3-acetylpyridine. It may consist of a different ratio of enantiomorphs.

When the reduction of VIII under similar conditions was interrupted after 1 equiv. of hydrogenation, a mixture of products resulted. However, selective reduction of the double bond of VIII to form 3-acetylpiperidine was accomplished when a Parr hydrogenator, contaminated by previous work with a sulfur containing compound, was used.

When the reduction of VIII in neutral alcoholic solution was carried out in the presence of a 40% ratio of 5% rhodium on alumina, X was obtained in almost quantitative yield, b.p. 136–138° (29–30 mm.), m.p. 67–70°.

When VIII was hydrogenated in neutral solution in the presence of platinum oxide or palladium on carbon, there was no observable uptake. The latter catalyst was also ineffective in acid solution.

Acknowledgment.—The author is indebted to Mr. R. Kriese for the n.m.r. spectra and to Mr. Y. H. Ng for technical assistance, and is especially grateful to Dr. R. W. Mattoon for interpreting the n.m.r. spectra. The author, in particular, wishes to thank Dr. J. Tadanier of this laboratory for the lively discussions in connection with the structure of compound VIII.

(21) In ref. 1, the authors were able to get a salt, m.p. 154–156°, from one of the enantiomorphs but not the other. This product may be a salt of the mixture or of the lower melting product.

(22) Seeding with a known sample induced solidification after severa weeks. Melting point was below 60°, not sharp.

Thermal Cleavage of 1,1′-Diacetyl-1,1′,4,4′-tetrahydro-4,4′-bipyridine

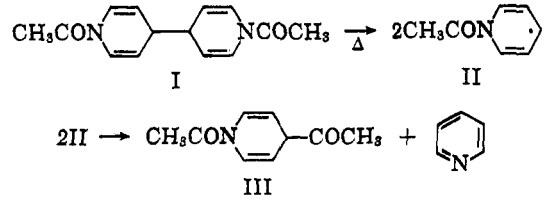
ARNOLD T. NIELSEN, DONALD W. MOORE, JUDITH HEITZ MAZUR, AND KRISTIN HIGHBERG BERRY

Chemistry Division, U. S. Naval Ordnance Test Station, China Lake, California

Received April 21, 1964

1,1′-Diacetyl-1,1′,4,4′-tetrahydro-4,4′-bipyridine (I) has been cleaved by pyrolysis at 250–275° to 1-(4-pyridyl)ethyl acetate (IV) in 42–48% yield. Evidence is presented establishing the structure of this product, which previously had been described by other workers as 1,4-diacetyl-1,4-dihydropyridine (III). Dihydropyridine III may be trapped as its oxime (XI), however, by cleavage of I in refluxing methanolic hydroxylamine solution, and evidence in support of this structure is presented, including hydrogenation of XI to 1,4-diacetylpiperidine oxime (XII). An independent synthesis of XII from 4-acetylpiperidine is described. A compound previously known as 4-acetyl-1,4-dihydropyridine has been shown to be 1-(4-pyridyl)ethanol.

1,1′-Diacetyl-1,1′,4,4′-tetrahydrobipyridine (I) is obtained by bimolecular reduction and acetylation of pyridine with zinc dust and acetic anhydride.[1–4] An improved procedure for preparing I and conclusive proof of its structure have been presented.[4] An interesting property of I is its thermal cleavage to 1-acetylpyridinyl (II), followed by reported formation at 200–230° of a liquid product described as 1,4-diacetyl-1,4-dihydropyridine (III), b.p. 242–243° at 760 mm.[3,5,6]



Careful examination of the properties of this product has revealed in the present work that its correct structure is 1-(4-pyridyl)ethyl acetate (IV). On the other hand, the oxime of III is said to result by heating I with methanolic hydroxylamine.[6] The first evidence clearly establishing this dihydropyridine oxime structure is described.

(1) O. Dimroth and R. Heene, *Ber.*, **54**, 2934 (1921).
(2) O. Dimroth and F. Frister, *ibid.*, **55**, 1223 (1922).
(3) J. P. Wibaut and J. F. Arens, *Rec. trav. chim.*, **60**, 119 (1941).
(4) A. T. Nielsen, D. W. Moore, G. Muha, and K. H. Berry, *J. Org. Chem.*, **29**, 2175 (1964).
(5) R. A. Barnes in "Pyridine and its Derivatives," part 1, E. Klingsberg, Ed., Interscience Publishers, Inc., New York, N. Y., 1960, pp. 55, 56.
(6) B. Emmert and A. Wolpert, *Ber.*, **74**, 1015 (1941).