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

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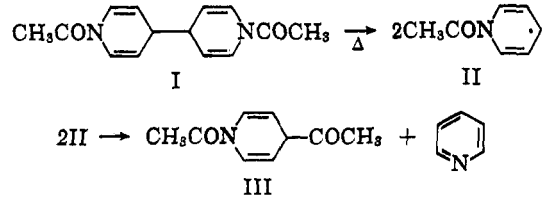
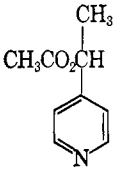
1,1′-Diacetyl-1,1′,4,4′-tetrahydro-4,4′-bipyridine (I) has been cleaved by pyrolysis at 250–275° to 1-(4-pyridyl)ethyl acetate (IV) in 42–48% yield. Evidence is presented establishing the structure of this product, which previously had been described by other workers as 1,4-diacetyl-1,4-dihydropyridine (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).

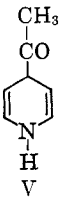


IV

In the original procedure of Wibaut and Arens the pyrolysis was conducted by heating 30-g. batches of I in a small flask at 200–230° at 15 mm. In our hands this method gave yields of pure product of 36–37%, but was unsuited to large-scale preparations. A more convenient procedure was developed for continuous introduction of reactant into a heated column packed with glass Raschig rings. Optimum conditions found (250–275° at 2 mm.) provided yields of pure IV of 42–48%.

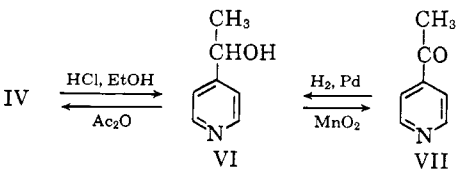
That structure III is incorrect (and structure IV correct) for the pyrolysis product was suggested by its spectrum. A strong carbonyl stretching band is found at 1765 cm.$^{-1}$ in the infrared region, a frequency too high to be that of a ketone or amide carbonyl, but characteristic of an ester. The n.m.r. spectrum (neat) revealed one doublet methyl (τ 8.53) and one singlet methyl group (τ 7.90), characteristic ring proton doublets of a 4-alkylpyridine (τ 1.32 and 2.63, four protons total), and a quartet at τ 4.05 representing the single tertiary hydrogen of the substituted ethyl group. Added structure proof was obtained in several ways while examining the chemical behavior of IV.

Wibaut and Arens[3] reported that treatment of III (*i.e.*, IV) with ethanolic hydrogen chloride led to a crystalline product, m.p. 60° (b.p. 254° at 760 mm., without decomposition), described as 4-acetyl-1,4-dihydropyridine (V). However, this material has now been shown to be 1-(4-pyridyl)ethanol (VI), expected

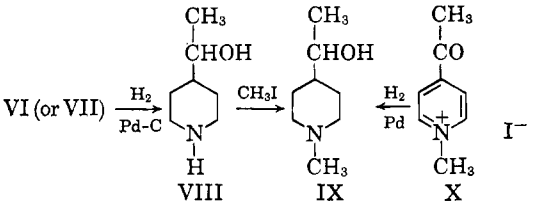


V

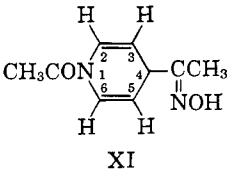
from ester IV. Alcohol VI was obtained in an alternate synthesis (50% yield) by hydrogenation of 4-acetylpyridine (VII) in absolute ethanol at 25° with palladium catalyst, 1 mole equiv. of hydrogen being quite rapidly absorbed, with hydrogen uptake proceeding extremely slowly thereafter.[7] The allylic nature of the hydroxyl group in VI was demonstrated by oxidation to ketone VII with manganese dioxide catalyst.[8] Alcohol VI had previously[3] been acetylated



with acetic anhydride to its precursor IV; it had also been dehydrogenated to ketone VII by heating with sulfur and oxidized to isonicotinic acid with permanganate. Its ultraviolet spectrum [λ_{max}^{EtOH} 256 mμ (ϵ 2230)] is almost identical with that of 4-ethylpyridine [λ_{max} 256 mμ (ϵ 2140)]. Hydrogenation of alcohol VI or ketone VII (palladium, palladium–charcoal, or rhodium–alumina catalysts) produced 1-(4-piperidyl)ethanol (VIII), m.p. 75°. This material was identified by conversion to its known[9] N-methyl derivative (IX). An authentic sample of IX was prepared by hydrogenation of N-methyl-4-acetylpyridinium iodide (X); both samples afforded the same picrate derivative.[9]



The degradation of I in refluxing methanolic hydroxylamine solution was reported by Emmert and Wolpert[6] to produce 1,4-diacetyl-1,4-dihydropyridine oxime (XI), m.p. 121–122°, in unstated yield. In



XI

our hands a 14% yield of XI was obtained, m.p. 121–125° to 124–129°; the melting point occurs with decomposition and depends on the rate of heating. 4-Acetylpyridine oxime was isolated as a product (8% yield) and was observed to form slowly when alcoholic solutions of XI were stored in air. In the absence of hydroxylamine, I was reported[6] to produce a 17% yield of 4-acetylpyridine in refluxing methanol. Since we found the substance described previously[4,6] as 1,4-diacetyl-1,4-dihydropyridine (III) to be a pyridine derivative (IV), it was felt that structure XI should be verified, because no proof supporting it had yet been presented.

The infrared and ultraviolet spectra of the compound are in agreement with structure XI. In the double-bond stretching region two strong bands (1660 and 1630 cm.$^{-1}$) and a weak side band at 1700 cm.$^{-1}$ are found, very similar to those present in the spectrum of I.[4] These absorption bands have been tentatively assigned to amide carbonyl and olefinic C=C stretching.[4] A distinct oxime C=N stretching band is not evident in the spectrum, probably because it is too weak and is obscured by the very strong amide carbonyl band. In the ultraviolet spectrum a strong band appears at 252 mμ (ϵ_{max} 16,800, ethanol). The close model N-acetyl-9,10-dihydroacridine has maxima of nearly equal intensity at 252 and 258 mμ

(7) Acetophenone has been hydrogenated to phenyl methyl carbinol in 95% yield with palladium catalyst: F. Straus and H. Grindel, *Ann.*, **439**, 298 (1924).

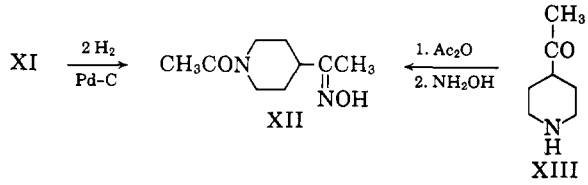
(8) M. Harfenist, A. Bavley, and W. A. Lazier, *J. Org. Chem.*, **19**, 1608 (1954).

(9) R. Lukes, O. Strouf, and M. Ferles, *Chem. Listy*, **51**, 923 (1957).

(ϵ_{max} 19,000)[10]; the ultraviolet maximum of I appears at 263 mμ (ϵ_{max} 24,000).[4]

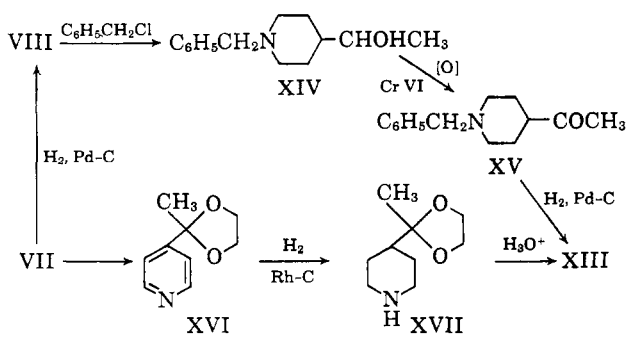
The n.m.r. spectrum of the dihydropyridine oxime (deuteriochloroform) is in agreement with structure XI. It reveals two methyl singlets (τ 7.75 and 8.12), one hydroxyl proton (τ 0.8), a complex multiplet centered at τ 6.15 (proton at C-4), and a broad band with much fine structure centered at τ 5.1 corresponding to the ring protons in the 3- and 5-positions. Finally, a pair of doublets at τ 2.75 and 3.33 represent the 2- and 6-position ring protons. The narrower 8-c.p.s. splitting of these two signals represents a *cis*-ethylenic coupling to adjacent ring protons in the 3- and 5-positions. The broad splitting (35 c.p.s.) of these twin peaks is almost identical with that found in I (33 c.p.s.), discussed in detail previously.[4] As in I, this anisotropic splitting is believed due to shielding by the carbonyl oxygen as a result of rotational restrictions about the amide C–N bond, and indicates much double bond character in this bond.

Structure XI was established by hydrogenation of the compound (palladium–charcoal, 1 atm.) to 1,4-diacetylpiperidine oxime (XII), 2 mole equiv. of hydrogen being rapidly absorbed before uptake of hydrogen ceased. An authentic sample of XII was prepared from 4-acetylpiperidine (XIII). The instability



of I and XI in air at room temperature (decomposition to brown oils) is compatible with their dihydropyridine structures. By contrast, the ester IV, b.p. 243°, and alcohol V, b.p. 254°, are quite stable, inconsistent with dihydropyridine structures III and V previously assigned.[3]

4-Acetylpiperidine (XIII) was synthesized by two new routes. Its synthesis by Claisen condensation from ethyl N-benzoylpiperidine-4-carboxylate and ethyl acetate (5–10% yield) has been reported,[11] although the substance was isolated only as derivatives. The ketone, isolated in pure form for the first time (m.p. 7–8°) was obtained in one synthesis by hydrogenolysis of the N-benzyl derivative XV (prepared by chromic acid oxidation of N-benzyl-1-(4-piperidyl)ethanol (XIV). The alcohol XIV was readily obtained from

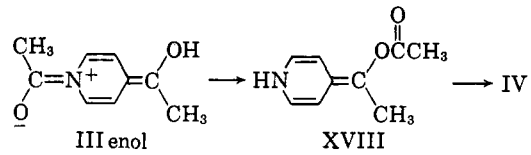


(10) E. R. Blout and R. S. Corley, *J. Am. Chem. Soc.*, **69**, 763 (1947); measurement was made in 95% ethanol. Numbers, taken from a curve, are approximate.

(11) V. Prelog, *Collection Czech. Chem. Commun.*, **10**, 380 (1938).

alcohol VIII and benzyl chloride. In the second synthesis 4-acetylpyridine ethylene ketal (XVI) was hydrogenated to the ethylene ketal XVII, which in turn was hydrolyzed to XIII; the isolation of ketal XVII prior to hydrolysis was not required.

The present findings indicate that 1,4-diacetyl-1,4-dihydropyridine (III) is a cleavage product of I, since oxime XI would arise most readily from this substance. Formation of ester IV may be explained by successive transacetylations leading to XVIII and departing from the enol of III, a species possibly quite stable with respect to the keto form. The intermediate XVIII could then isomerize to IV. Other 4-substituted



pyridines derived from I under various conditions—4-acetylpyridine (refluxing methanol[6]) and 4-ethylpyridine (zinc and refluxing acetic anhydride–acetic acid[3])—may also arise from III enol.

Experimental[12]

Pyrolysis of 1,1′-Diacetyl-1,1′,4,4′-tetrahydro-4,4′-bipyridine (I) to 1-(4-Pyridyl)ethyl Acetate (IV).—The pyrolysis was conducted in an all-glass apparatus consisting of an asbestos-covered, vertically placed glass tube (45 × 160 mm.) packed with glass Raschig rings (10 × 10 mm.) to a volume of 45 × 120 mm., and wrapped with resistance wire for heating. Temperature was indicated by a thermometer introduced at the top of the tube, its bulb in the center of the column. The sample was introduced from a 500-ml. round-bottomed flask (attached to the top of the column by 24/40 standard taper joint) having a bent neck so that introduction of the sample could be controlled by rotation about the joint. The tube exit was connected directly to a large trap surrounded by a Dry Ice–acetone bath, the trap exit being connected to a vacuum pump.

A 156-g. (0.638 mole) sample of unrecrystallized 1,1′-diacetyl-1,1′,4,4′-tetrahydro-4,4′-bipyridine (I, m.p. 122–128°)[13] was introduced into the evacuated apparatus (250–275° at 1.6–2.0 mm.) during 3.5 hr. After cooling, the column was rinsed with methylene chloride. Some orange and yellow solid, insoluble in methylene chloride, was removed by filtration. The filtrate was distilled directly without further treatment[14] to yield fractions (1) b.p. 30–50° (58 mm.), 38 g., pyridine and acetic anhydride; (2) b.p. 40–104° (13 mm.), 24 g., mixture containing pyridine, 4-ethylpyridine, and other products[3]; (3) b.p. 110–125° (13 mm.), 55.7 g. (53%), principally 1-(4-pyridyl)ethyl acetate (IV); and (4) undistillable residue, 27 g. Redistillation of fraction 3 gave 46 g. (43.5%), b.p. 117–120° (15 mm.), n^{25}D 1.4951 [lit.[3] b.p. 109–110° (15 mm.), n^{18}D 1.4987]. Similar runs of various sizes at 250–280° (2–21 mm.) gave yields of crude IV of 51–59% and redistilled product of 42–48%.

Anal. Calcd. for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.25; H, 6.80; N, 8.59.

The picrate derivative was prepared, yielding prisms from water, m.p. 155–156°, lit.[3] m.p. 156.6–158.5°.

The n.m.r. spectrum of IV (neat) described in the discussion part may be compared with that of 4-ethylpyridine (neat) which

(12) Melting points determined on a Kofler hot stage are corrected. N.m.r. spectra were determined with a Varian A-60 spectrometer in deuteriochloroform solutions (*ca.* 20%) unless otherwise stated. Ultraviolet spectra were measured in 95% ethanol with a Cary Model 11 MS recording spectrophotometer.

(13) The crude, dried product, obtained directly by reductive acetylation of pyridine, was employed (*ca.* 95% assay).[4] Purified, recrystallized material was found not to provide improved yields.

(14) The washing of crude product with aqueous potassium hydroxide, employed by Wibaut and Arens[3] to assay acetic anhydride which is present in small amounts, was omitted, since this treatment did not improve yields.

shows aromatic protons as a pair of doublets centered at τ 1.50 and 3.02 and methyl and methylene protons at τ 8.92 and 7.55, respectively.

1-(4-Pyridyl)ethanol (VI). A. From 1-(4-Pyridyl)ethyl Acetate.—The procedure of Wibaut and Arens[3] employing ethanolic hydrogen chloride was followed. From 3.3 g. (0.02 mole) of 1-(4-pyridyl)ethyl acetate (IV) obtained by pyrolysis of I (b.p. 117–120° at 15 mm.) was obtained 2.4 g. (97%) of tan crystals, m.p. 50–53°. Recrystallization from carbon tetrachloride raised the melting point to 59–61°, lit.[3] m.p. 59.9–60.2°.

B. From 4-Acetylpyridine.—A 24.2-g. (0.2 mole) sample of 4-acetylpyridine (Aldrich) in 100 ml. of absolute ethanol was hydrogenated for 1 hr. with 1.0 g. of palladium oxide catalyst at 24° in a Parr apparatus at 50 p.s.i. One mole equivalent of hydrogen was absorbed during 1 hr., after which time hydrogenation continued extremely slowly (0.025 mole equiv./hr). The catalyst was filtered and the solvent was evaporated to yield a mass of yellow crystals mixed with oil. Distillation gave fractions (1) 1.7 g., b.p. 90–103° (0.5 mm.); (2) 12.8 g. (50.5%) of colorless 1-(4-pyridyl)ethanol (VI), m.p. 51–55°; and (3) 7.8 g. of black residue. A recrystallized sample, m.p. 59–60°, when mixed with the sample obtained by procedure A above, showed no depression in the melting point. The infrared spectra of the two samples were identical (strong OH and NH stretching bands present). In another run employing 12.1 g. of 4-acetylpyridine, 1.2 g. of palladium oxide, and 100 ml. of absolute ethanol, 1 mole equiv. of hydrogen was absorbed within 30 min. Recrystallization of the oily product from carbon tetrachloride without prior distillation gave 7.4 g. (57%) of VI, m.p. 49–54°. The ultraviolet spectrum (95% ethanol) of the pure substance (m.p. 59–60°) showed the following maxima (ϵ_{max} in parentheses): 251 (1980), 256 (2230), and 262 mμ (1730). This spectrum is very similar to that of 4-ethylpyridine in the same solvent: maxima found at 251 (1850), 256 (2140), and 262 mμ (1650); lit.[15] for 4-ethylpyridine in 95% ethanol: maxima at 251 (1720), 256 (2020), and 262 mμ (1520).

Anal. Calcd. for C_7H_9NO: C, 68.27; H, 7.37; N, 11.37; mol. wt., 123.15. Found: C, 68.10; H, 7.20; N, 11.30; mol. wt., 128.

4-Acetylpyridine (VII).—A mixture of 1.0 g. of 1-(4-pyridyl)-ethanol (VI), 5 g. of active manganese dioxide catalyst,[8] and 50 ml. of cyclohexane was shaken continuously at 25° for 5 days. The mixture was filtered and the manganese dioxide was extracted with chloroform. The combined liquids were concentrated to remove solvents and the oily residue (0.90 g.) was diluted with a small amount of heptane and filtered. Concentration to remove all solvent gave 0.80 g. (81%) of 4-acetylpyridine, m.p. 12–14°. Redistillation with some losses gave 0.5 g., b.p. 210–213°, m.p. 14–16° (lit.[9] m.p. 15.5°), $n^{23}D$ 1.5248 (lit.[16] $n^{26}D$ 1.5254). The picrate derivative melted at 129–130° (long prisms from ethanol); lit. m.p. 128.5–129.5°,[3] 129.5–130°,[16] 129–130°.[17] When mixed with an authentic sample of 4-acetylpyridine picrate, m.p. 128–129°, the melting point was not depressed.

N-Methyl-4-acetylpyridinium Iodide (X).—To a solution 12.3 g. (0.101 mole) of 4-acetylpyridine (Aldrich) in 25 ml. of acetone was added 14.9 g. (0.105 mole) of methyl iodide. An orange precipitate formed immediately. After 5 hr. the mixture was filtered to yield 24.7 g. (92.5%) of the methiodide, m.p. 168–172°. Two recrystallizations from ethanol gave orange needles, m.p. 173–174°.

Anal. Calcd. for $C_8H_{10}INO$: C, 36.52; H, 3.83; I, 48.24; N, 5.32. Found: C, 36.48; H, 3.92; I, 48.23; N, 5.28.

1-(4-Piperidyl)ethanol (VIII). A. Hydrogenation of 4-Acetylpyridine.—To an ice-cold solution of 36.3 g. (0.3 mole) of 4-acetylpyridine in 150 ml. of absolute ethanol was added, in small portions, 15 g. of 10% palladium-charcoal catalyst (*Caution:* Ignition may result if the ethanol solution is not chilled before adding the catalyst, or the catalyst is added in one portion.) Hydrogenation of the mixture was conducted in a Parr apparatus (20–50 p.s.i., 25°) until hydrogen uptake ceased (70 hr., 3.5 mole equiv. of hydrogen absorbed). The catalyst was filtered and washed with ethanol and the filtrate was concentrated to remove the solvent. Crystallization of the residue from ether gave 29.0 g. (75%) of 1-(4-piperidyl)ethanol, m.p. 74–76°. In runs similar to that above employing 5% rhodium-on-alumina catalyst (5.8 g.) hydrogenation proceeded more rapidly and hydrogen uptake ceased after 18 hr., yielding 67–70%, b.p. 90–94° (1 mm.), m.p. 70–75°. Lower yields were obtained with use of platinum or palladium oxide catalysts, or higher temperatures.

B. Hydrogenation of 1-(4-Pyridyl)ethanol.—A mixture of 12.3 g. (0.1 mole) of 1-(4-pyridyl)ethanol in 100 ml. of 95% ethanol and 0.8 g. of palladium oxide catalyst was hydrogenated in the manner described under A above (72 hr.) to yield, by crystallization from ether, 6.7 g. (52%) of alcohol VIII, m.p. 72–74°, and 1.1 g., m.p. 50–73°. The n.m.r. spectrum shows one split methyl peak.

Anal. Calcd. for $C_7H_{15}NO$: C, 65.07; H, 11.70; N, 10.84; neut. equiv., 129.2. Found: C, 65.19; H, 11.37; N, 10.79; neut. equiv., 129.

The ***p*-toluenesulfonamide** derivative was prepared from equivalent amounts of alcohol and *p*-toluenesulfonyl chloride in pyridine solvent by heating on the steam bath for 15 min.; crystals from carbon tetrachloride, m.p. 73–74°. The derivative was insoluble in hot aqueous 10% sodium hydroxide or hot 1 *N* hydrochloric acid solution. The infrared spectrum showed a strong OH stretching band at 3500 cm.$^{-1}$ and strong sulfonamide bands at 1330 and 1160 cm.$^{-1}$. The n.m.r. spectrum showed one split methyl peak.

Anal. Calcd. for $C_{14}H_{21}NO_3S$: C, 59.33; H, 7.47; N, 4.94; S, 11.32. Found: C, 59.89; H, 7.18; N, 4.82; S, 11.14.

A **benzenesulfonamide** derivative was also prepared in a similar manner; crystals from carbon tetrachloride, m.p. 36–38°. Infrared showed bands at 3500 (OH) and 1330 and 1150 cm.$^{-1}$ (SO_2).

Anal. Calcd. for $C_{13}H_{19}NO_3S$: N, 5.20. Found: N, 5.37.

The **picrate** was prepared and crystallized from water, m.p. 132–134°.

Anal. Calcd. for $C_{13}H_{18}N_4O_8$: N, 15.64. Found: N, 15.81.

N-Methyl-1-(4-piperidyl)ethanol (IX).—A mixture of 22.7 g. of N-methyl-4-acetylpyridinium iodide (X), 22 g. of triethyl amine, 180 ml. of absolute ethanol, and 4.0 g. of palladium oxide catalyst was hydrogenated in a Parr apparatus (40–50 p.s.i., 25°) until hydrogen uptake ceased (57 hr., 2.7 mole equiv. of hydrogen absorbed). The catalyst was filtered and the filtrate was concentrated to dryness under vacuum (temperature below 35°). The residue was made alkaline with concentrated aqueous potassium carbonate solution and the mixture was extracted three times with methylene chloride. After drying and concentrating the combined methylene chloride extracts, the oily residue was distilled to yield 4.0 g. of N-methyl-1-(4-piperidyl)ethanol (IX), b.p. 104–111 °(3 mm.), $n^{24}D$ 1.4728 (lit.[9] b.p. 111° at 15 mm., $n^{20}D$ 1.4736), and 4 g. of undistillable residue.

Anal. Calcd. for $C_8H_{17}NO$: C, 68.04; H, 10.71; N, 9.91. Found: C, 67.69; H, 10.81; N, 9.94.

A **picrate** derivative was prepared, m.p. 175–176°, lit.[9] m.p. 177.5°.

N-methyl-1-(4-piperidyl)ethanol was also prepared from 1-(4-piperidyl)ethanol (VIII). A mixture of 1.0 g. of the alcohol VIII, 1.0 g. of methyl iodide, 0.41 g. of sodium carbonate, and 10 ml. of ethanol was heated under reflux for 24 hr. to yield an oil having the same infrared spectrum as the distilled sample prepared above. The picrate derivative melted at 177–178° and, when mixed with the sample obtained above, the melting point was not depressed.

N-Benzyl-1-(4-piperidyl)ethanol (XIV).—A mixture of 24.5 g. (0.19 mole) of 1-(4-piperidyl)ethanol (VIII), 24.1 g. (0.19 mole) of benzyl chloride, 10.1 g. of powdered anhydrous sodium carbonate, and 200 ml. of absolute ethanol was stirred in a nitrogen atmosphere. After an initial spontaneous temperature increase to 37°, stirring was continued at 25° for 3 days and finally at reflux temperature for 5 hr. The mixture was concentrated to a small volume under vacuum, and the residue after cooling was diluted with water and extracted with ether. The extracts were dried with magnesium sulfate and distilled to yield 35.0 g. (84%) of N-benzyl derivative XIV, b.p. 138–142° (0.4 mm.), $n^{25}D$ 1.5366, and 2.5 g. of residue.

Anal. Calcd. for $C_{14}H_{21}NO$: C, 76.66; H, 9.65; N, 6.39. Found: C, 76.74; H, 9.73; N, 6.37.

A mixture of the alcohol XIV and N-benzyl-4-acetylpiperidine (XV), inseparable by distillation, was prepared by hydrogenation of N-benzyl-4-acetylpyridinium chloride, m.p. 164–166° (platinum or palladium catalyst, ethanol, 50 p.s.i.) in *ca.* 30% over-all yield from 4-acetylpyridine. This mixture could be

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(16) C. Chu and P. C. Teague, *J. Org. Chem.*, **23**, 1578 (1958).

(17) A. Pinner, *Ber.*, **34**, 4251 (1901).

used for the preparation of pure ketone XV by chromic acid oxidation.

N-Benzyl-4-acetylpiperidine (XV).—To 109.7 g. (0.5 mole) of pure N-benzyl-1-(4-piperidylethanol (XIV) was added, with cooling (temperature below 25°), 400 ml. of acetic acid and 530 ml. of 0.67 *M* chromic acid solution (100 g. of sodium dichromate dihydrate and 65 ml. of concentrated sulfuric acid diluted to 1 l. with water). The solution, after standing at 25° for 5 days, was chilled and made alkaline (pH 12) with 25% sodium hydroxide solution. The mixture containing chromium hydroxide was extracted with ether twice. Celite filter aid was added to the aqueous part and the mixture was filtered and washed with ether. The filter cake was stirred with ether and filtered. The combined ether extracts were dried with magnesium sulfate and distilled to yield 98.7 g. (91%) of N-benzyl-4-acetylpiperidine (XV), b.p. 130° (0.5 mm.), $n^{25}D$ 1.5270, m.p. 20–22°. A redistilled sample had b.p. 124° (0.4 mm.), $n^{25}D$ 1.5276, m.p. 22–23°.

Anal. Calcd. for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.31; H, 8.87; N, 6.42.

The **semicarbazone** derivative recrystallized from dilute ethanol as large flat prisms, m.p. 180–182°.

Anal. Calcd. for $C_{15}H_{22}N_4O$: C, 65.66; H, 8.08; N, 20.42. Found: C, 66.13; H, 8.13; N, 20.18.

2-(4-Pyridyl)-2-methyl-1,3-dioxolane (XVI).—4-Acetylpyridine (49.2 g., 0.406 mole) was dissolved in 500 ml. of absolute ether contained in a 1-l. three-necked flask, and the solution was chilled in an ice bath. Dry hydrogen chloride was passed into the cold solution until precipitation of the hydrochloride was complete; the mixture was then concentrated to dryness under vacuum. Benzene (400 ml.) and ethylene glycol (26.7 g. of 97% assay, 0.416 mole) were added to the residue and the flask was fitted with a Dean–Stark tube, reflux condenser and nitrogen inlet. The flask was surrounded by an oil bath maintained at 110° and the mixture was heated under reflux with stirring for 24 hr. in a nitrogen atmosphere; 8.6 ml. of water was collected. The resulting mixture containing crystals of XVI hydrochloride was cooled to 10° and treated, with stirring, with a solution of 20 g. of sodium hydroxide in 60 ml. of water. The benzene layer was separated and the aqueous part was extracted once with ether, and the combined organic solutions were dried with magnesium sulfate. Concentration under vacuum to remove solvent gave a mass of slightly oily crystals, crystallized from heptane to yield 45.9 g. of ketal XVI, m.p. 46–48°; concentration of the filtrate to *ca.* 50 ml. gave a second crop, 9.2 g., m.p. 35–45° [total yield of crystallized product, 55.1 g. (82%)]. A recrystallized sample melted at 47–48°. The infrared spectrum showed no OH or C=O bands.

Anal. Calcd. for $C_9H_{11}NO_2$: C, 65.47; H, 6.67. Found: C, 65.62; H, 7.04.

2-(4-Piperidyl)-2-methyl-1,3-dioxolane (XVII).—A mixture of 8.25 g. (0.05 mole) of 2-(4-pyridyl)-2-methyl-1,3-dioxalane, 50 ml. of water, and 3.0 g. of 5% rhodium–alumina catalyst was hydrogenated in a Parr apparatus (40–55 p.s.i., 25°) until hydrogen uptake ceased (28 hr., 3.0 mole equiv. of hydrogen absorbed). The catalyst was filtered and potassium carbonate was added to the filtrate until an oil separated; the mixture was then extracted with ether. After drying, the ether extracts on distillation gave 5.0 g. (58%) of ketal XVII, b.p. 105–107° (7 mm.), $n^{24}D$ 1.4792, m.p. 8–11°. The material readily absorbs carbon dioxide from the air to form a solid carbonate. In a parallel experiment employing 5% rhodium-on-charcoal catalyst a slower uptake of hydrogen occurred affording a 77% yield of XVIII.

Anal. Calcd. for $C_9H_{17}NO_2$: C, 63.13; H, 10.00; N, 8.18; neut. equiv., 171.2. Found: C, 62.89; H, 9.86; N, 8.00; neut. equiv., 171.

4-Acetylpiperidine (XIII). A. Hydrogenolysis of N-Benzyl-4-acetylpiperidine.—A mixture of 26.0 g. (0.12 mole) of N-benzyl-4-acetylpiperidine (XV), 200 ml. of absolute ethanol, and 4.0 g. of 10% palladium–charcoal catalyst was hydrogenated in a Parr apparatus (40–50 p.s.i., 25°) until hydrogen uptake ceased (4 hr., 1.0 mole equiv. of hydrogen absorbed). The solution was filtered and the catalyst was washed several times with ethanol and the residue was distilled through a 1-ft. Vigreux column at atmospheric pressure to remove solvent. The residue was distilled under vacuum through a short column to yield 12.8 g. (84%) of 4-acetylpiperidine, b.p. 104–109° (16 mm.), $n^{25}D$ 1.4738, m.p. 2–4°, and 1.74 g. of residue. A redistilled sample had b.p. 79–80° (3.2 mm.), $n^{25}D$ 1.4735, m.p. 8°. The material readily absorbs carbon dioxide from the air to form a solid carbonate. Infrared showed a NH stretching band at 3400 cm.$^{-1}$ and carbonyl band at 1700 cm.$^{-1}$ (neat).

B. Hydrolysis of 2-(4-Piperidyl)-2-methyl-1,3-dioxolane.—An 8.0 g. (0.0485 mole) sample of 2-(4-pyridyl)-2-methyl-1,3-dioxolane (XVI) was hydrogenated as described above (rhodium–alumina catalyst). After filtering the catalyst, the aqueous filtrate containing 2-(4-piperidyl)-2-methyl-1,3-dioxolane (XVII, not isolated) was treated with 8 ml. of concentrated hydrochloric acid and the solution was heated under reflux for 5 hr. The solution was concentrated to a small volume, cooled, and made alkaline with saturated potassium carbonate solution. The mixture was extracted with methylene chloride and the extracts were dried with potassium carbonate and distilled to yield 2.3 g. (37% yield from ketal XVI) of 4-acetylpiperidine, b.p. 84–85° (7 mm.), $n^{25}D$ 1.4730, m.p. 5–7°, and 1.7 g. of residue. The infrared spectrum of the product was identical with that of the sample obtained in procedure A above.

Anal. Calcd. for $C_7H_{13}NO$: C, 66.10; H, 10.30; N, 11.01. Found: C, 65.58; H, 10.21; N, 11.09.

Direct chromic acid oxidation of 1-(4-piperidyl)ethanol (VIII) by the procedure employed above with N-benzyl-1-(4-piperidyl)-ethanol (XIV) to yield ketone XV gave low yields of 4-acetylpiperidine. Attempts to directly reduce 4-acetylpyridine to 4-acetylpiperidine were unsuccessful.

The **picrate** derivative crystallized from water as long prisms, m.p. 165–167°, lit.[11] m.p. 163.5°.

Anal. Calcd. for $C_{13}H_{16}N_4O_8$: C, 43.82; H, 4.53; N, 15.73. Found: C, 44.18; H, 4.68; N, 15.60.

1,4-Diacetyl-1,4-dihydropyridine Oxime (XI).—The procedure of Emmert and Wolbert[6] was followed in one run, employing a nitrogen rather than carbon dioxide atmosphere, to yield 8.7 g. (56%) of crude colorless product, m.p. 90–125°, from 20.0 g. of purified 1,1′-diacetyl-1,1′,4,4′-tetrahydrobypyridine. Two recrystallizations from methanol gave 4.0 g., m.p. 115–119°, and a third recrystallization gave 2.1 g. (14%), m.p. 121–125°. The crude product (7.5 g.) obtained from another run of the same size, identical except that a carbon dioxide atmosphere was employed, was crystallized from ethanol to yield 2.1 g. (14%) of product, m.p. 124–129° (the melting point occurs with decomposition and depends on the rate of heating). Much difficulty was experienced in reproducing the preparation. Often brown oils were obtained as the only product. Use of a carbon dioxide rather than nitrogen atmosphere appears to be preferable for avoiding oil formation. It is important to maintain an inert atmosphere throughout the preparation since the product is unstable in air at room temperature, particularly when impure, and within a few hours is transformed into a brown oil. Recrystallized samples, however, have been stored in a refrigerator for several months without decomposition. Strong infrared bands were at 3350 cm.$^{-1}$ (OH), 1660 and 1630 cm.$^{-1}$ with side band at 1700 cm.$^{-1}$; ultraviolet, λ_{max} 252 mμ (ϵ_{max} 16,800, 95% ethanol).

Anal. Calcd. for $C_9H_{12}N_2O_2$: C, 59.98; H,6.71; N, 15.55 mol. wt., 180.2. Found: C, 59.74; H, 6.89; N, 15.40; mol. wt., 188.

The aqueous alcoholic filtrate remaining from the second run (described above), after removing the initially formed crude product, slowly deposited crystals of **4-acetylpyridine oxime** on standing in air (0.86 g., 7.9%, m.p. 153–155°, after 2 months); other runs produced similar precipitates. When mixed with an authentic sample of the oxime, m.p. 157–158°, the melting point was not depressed; lit.[6] m.p. 157.5–158°. Alcoholic filtrates obtained from crystallization of the product, XI, also slowly deposited crystals of 4-acetylpyridine oxime on standing in air in a stoppered flask.

1,4-Diacetylpiperidine Oxime (XII). A. By Hydrogenation of 1,4-Diacetyl-1,4-dihydropyridine Oxime (XI).—A mixture of 0.15 g. of oxime XI, 0.1 g. of 10% palladium–charcoal catalyst, and 15 ml. of ethanol was hydrogenated at 702 mm., 26°, until hydrogen uptake practically ceased (20 min., 2.1 mole equiv. of hydrogen absorbed). The mixture was filtered and the filtrate was concentrated to yield 0.13 g. (87%) of reduced oxime XII, m.p. 156–157°; recrystallization from acetone gave 0.08 g., m.p. 165–170°, and further recrystallization gave m.p. 169–170°. The infrared spectrum showed an OH stretching band at 3250 cm.$^{-1}$ and amide carbonyl band at 1650 cm.$^{-1}$.

B. From 4-Acetylpiperidine.—A mixture of 1.0 g. of 4-acetylpiperidine, 2.5 ml. of acetic anhydride, and 10 ml. of 20% sodium hydroxide solution was shaken for several minutes at 25°.

Potassium carbonate was added until the solution became turbid and 2.5 g. of hydroxylamine hydrochloride was then added. The mixture was heated on the steam bath for 20 min., cooled, and filtered to yield 1.20 g. (84%) of oxime XII, m.p. 169–171°. When mixed with the sample obtained from XI above, the melting point was not depressed. The infrared spectra of the two samples were identical.

Anal. Calcd. for $C_9H_{16}N_2O_2$: C, 58.71; H, 8.75; N, 15.21; mol. wt., 184.2. Found: C, 58.69; H, 8.71; N, 15.22; mol. wt., 186.

The Synthesis of 2,4,6-Trisubstituted Pyrido[2,3-*d*]pyrimidines from 2-Amino-3,5-Dicyanopyridine[1]

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Reductive dehalogenation of 2-amino-3,5-dicyano-6-chloropyridine gave 2-amino-3,5-dicyanopyridine in good yield. This pyridine has been converted to 2-amino-5-cyano-3-pyridinecarboxamide, 2-amino-3,5-pyridinedicarboxamide, and 2-amino-3-carbethoxy-5-pyridinecarboxylic acid which were excellent precursors to 2,4,6-trisubstituted pyrido[2,3-*d*]pyrimidines. 2,4-Dihydroxy-6-cyanopyrido[2,3-*d*]pyrimidine, 2-amino-4-hydroxy-6-carbethoxypyrido[2,3-*d*]pyrimidine, and several related pyridopyrimidines have been prepared by these routes. Catalytic hydrogenation of 2-amino-5-cyano-3-pyridinecarboxamide gave 2-amino-5-aminomethyl-3-pyridinecarboxamide. The formation of several 2,4,6,7-tetrasubstituted pyrido[2,3-*d*]pyrimidines from 2,3,5,6-tetrasubstituted pyridine precursors is reported.

The availability of 2,3,5,6-tetra functionally substituted pyridines *via* 1,3-dinitrile cyclizations[3] has led us to the consideration of these substrates as intermediates for the synthesis of fused heterocyclic systems. This article reports the synthesis of several pyrido[2,3-*d*]pyrimidines *via* routes having advantages over those previously reported.

Although pyrido[2,3-*d*]pyrimidines are well known,[4–6] 6 functionally substituted pyrido[2,3-*d*]pyrimidines are comparatively rare. Oakes and Rydon have prepared 2,4-dihydroxy-6-methylpyrido[2,3-*d*]pyrimidine and the corresponding 2,4-dichloro compound, but were unable to convert the 6-methyl group to one of greater synthetic utility.[4] Recently, Bernetti, Mancini, and Price have synthesized a series of 2-amino-4-hydroxy-6 functionally substituted pyrido[2,3-*d*]pyrimidines from 2,4-diamino-6-hydroxypyrimidine.[5]

2-Amino-3,5-dicyano-6-alkylthiopyridines[7] and 2-amino-3,5-dicyano-6-chloropyridine (**2**)[8] were considered as potential precursors to 2-amino-3,5-dicyanopyridine (**1**),[8] a useful intermediate for the preparation of 6-substituted pyrido[2,3-*d*]pyrimidines (Scheme I). Conventional reductive desulfurization techniques involving Raney nickel had no effect on the alkylthiopyridines and attempted hydrolytic desulfurization of 2-amino-3,5-dicyano-6-ethylthiopyridine (**3**)[7] gave 2-hydroxy-5-cyano-6-ethylthio-3-pyridinecarboxamide (**4**).

Reductive dehalogenation of **2**, however, gave **1** in good yield. The choice of acid scavenger employed in this reaction was found to be important, since compound **2** reacted readily with pyridine to form N-(2-amino-3,5-dicyano-6-pyridyl)pyridinium chloride (**5**).

The behavior of **1** in aqueous base differed appreciably from that of similar pyridines. Under conditions where 6-substituted 2-amino-3,5-dicyanopyridines are hydrolyzed to the corresponding 5-cyano-3-pyridinecarboxamides (refluxing 0.1 *N* potassium hydroxide),[7] **1** gave the corresponding diamide **6**. Further, conditions under which 6-substituted 2-amino-3,5-dicyanopyridines were converted to the corresponding dicarboxylic acids (10 *N* potassium hydroxide) led to extensive tar formation with **1**. 2-Amino-3,5-pyridinedicarboxylic acid (**7**) was prepared under milder hydrolytic conditions (2.5 *N* sodium hydroxide).

Recent work,[9,10] dealing with strong solvation of nitrile groups in dimethyl sulfoxide suggested that selective hydrolysis of the 3-cyano group of **1** could be achieved. In **1**, preferred solvation of the 5-cyano group (more sterically free) can occur in dimethyl sulfoxide, leaving the 3-cyano group relatively less "protected" and more susceptible to hydrolysis. The reaction was observed to follow the predicted course in dimethyl sulfoxide–aqueous sodium hydroxide mixtures at room temperature, although yields of 2-amino-5-cyano-3-pyridinecarboxamide (**8**) were dependent upon base concentration. That the dimethyl sulfoxide plays a role is indicated by failure to observe monoamide formation in aqueous ethanol. The structure of **8** was established by condensation with diethyl carbonate to give 2,4-dihydroxy-6-cyanopyrido[2,3-*d*]pyrimidine (**9**).

Dicarboxylic acid (**7**) was readily converted to the diethyl ester **10**. Smaller amounts of the corresponding 3-monoester **11** and the 5-monoester **12** were also formed. The structures of the monoesters were determined by condensation with guanidine. Monoester **11** gave 2-amino-4-hydroxy-6-pyrido[2,3-*d*]pyrimidine carboxylic acid (**13**),[5] whereas monoester **12** gave a lower melting colorless solid which was clearly different. Mild saponification of diester **10** gave monoester **12** in excel-

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