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

Synthesis of Isoquinoline Alkaloids. II. The Synthesis and Reactions of 4-Methyl-3-pyridinecarboxaldehyde and Other 4-Methyl-3-substituted Pyridines[1,2]

J. M. BOBBITT AND DANIEL A. SCOLA[3]

Received October 9, 1959

The synthesis of 4-methyl-3-pyridinecarboxaldehyde has been accomplished by an unequivocal route. The syntheses of several new 4-methyl-3-substituted pyridines have been carried out and the methods for the preparation of others have been improved.

In general, isoquinoline compounds are prepared from 2-arylethylamine derivatives or alkyl aldimine compounds (both containing a preformed benzene ring) by intramolecular cyclization.[4] This investigation is directed toward the synthesis of isoquinoline compounds from a preformed pyridine nucleus. Such a route would allow the introduction of complex substituents in the 6- and 7-positions at a late stage in the synthesis and would be particularly applicable to certain of the bisbenzylisoquinoline alkaloids. For this purpose, 4-methyl-3-pyridinecarboxaldehyde, X, presents two reactive functional groups, a γ-methyl group and a carbonyl, which could conceivably be converted into carbons five and eight of the isoquinoline molecule.

3-Cyano-4-methylpyridine, V, was chosen as a starting point for the synthesis of the desired aldehyde. The preparation of this nitrile was carried out by ring closure[5] followed by synthetic operations. This is in contrast to the reported synthesis[6,7] which involved substitution reactions on a pyridine nucleus. Thus, 3-cyano-2,6-dihydroxy-4-methylpyridine, III, which had been previously prepared in low yield by Guareschi[8] and Hope,[9] was obtained, as a salt, in yields of 85 to 95% by the condensation of ethyl acetoacetate and cyanoacetamide in the presence of a mole of piperidine or potassium hydroxide. In contrast to previous work,[9] the intermediate piperidinium or potassium salts, I and II, were isolated. This isolation might have been the reason for our near quantitative yields. The proposed structures of these salts are based upon their water solubility, elemental analysis, and the fact that I can be obtained by neutralization of 3-cyano-2,6-dihydroxy-4-methylpyridine with piperidine. The dihydroxypyridine, III, itself was obtained in essentially quantitative yield by the acidification of the salts. The conversion of 3-cyano-2,6-dihydroxy-4-methylpyridine to the corresponding 3-cyano-2,6-dichloro-4-methylpyridine, IV, in yields of 89 to 97% was effected by a fivefold excess of phosphorus oxychloride at elevated temperature. The dichloride did not form a hydrochloride or a picrate. Hydrogenolysis of 3-cyano-2,6-dichloro-4-methylpyridine proceeded satisfactorily in the presence of palladium (from palladium chloride) to give 3-cyano-4-methylpyridine, V, in yields of about 87%. The overall yield for the three steps was 66 to 80%.

Attempts to prepare 4-methyl-3-pyridinecarboxaldehyde, X, directly from the nitrile, V, failed. Controlled lithium aluminum hydride reduction,[10] sodium aluminum triethoxyhydride reduction,[11] Stephen's reduction,[12] and a modified Stephen's reduction[13] yielded only traces of the aldehyde, isolated as the 2,4-dinitrophenylhydrazone. Therefore, a somewhat more involved and indirect approach based upon ethyl 4-methyl-3-pyridinecarboxylate, VII, was followed.

4-Methyl-3-pyridinecarboxylic acid (homonicotinic acid, XI) had been prepared by the oxidation of 4-methylquinoline (lepidine)[14] and by the strong base[6] or strong acid[7] hydrolysis of 3-cyano-4-methylpyridine, V. In view of the difficulties in-

(1) Paper I: J. M. Bobbitt and T.-t. Chou, *J. Org. Chem.*, **24**, 1106 (1959).

(2) This investigation was supported in part by research grants CY-3437 and CY-3905 from the National Cancer Institute of the National Institutes of Health, Public Health Service.

(3) Abstracted from the thesis of Daniel A. Scola presented to the Graduate School, University of Connecticut, in partial fulfillment of the requirements for the degree of Doctor of Philosophy in March, 1959. Present address: Monsanto Chemical Co., Research and Engineering Div., Special Projects Department, Everett, Mass.

(4) W. J. Gensler, *Heterocyclic Compounds*, Vol. 4, R. C. Elderfield, ed., John Wiley and Sons, New York, 1952, p. 344.

(5) H. S. Mosher, *Heterocyclic Compounds*, Vol. 1, R. C. Elderfield, ed., John Wiley and Sons, New York, 1950, p. 448.

(6) S. M. McElvain and M. A. Goese, *J. Am. Chem. Soc.*, **65**, 2233 (1943).

(7) J. L. Webb and A. H. Corwin, *J. Am. Chem. Soc.*, **66**, 1456 (1944).

(8) I. Guareschi, *Estr. Mem. Reale Accad. Sci. Torino*, ii, 46; *J. Chem. Soc.*, **72**, Pt. I, 168 (1897).

(9) E. Hope, *J. Chem. Soc.*, **121**, 2216 (1922).

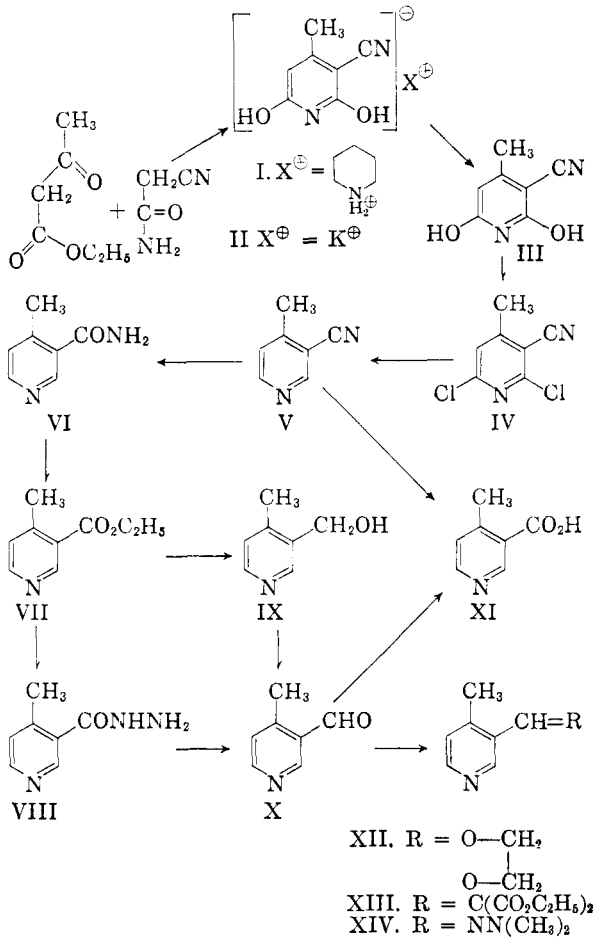
(10) L. Friedman, Abstracts, 116th Am. Chem. Soc. National Meeting, 5M (1949).

(11) G. Hesse and R. Schrodel, *Ann.*, **607**, 24 (1957).

(12) H. Stephen, *J. Chem. Soc.*, **127**, 1874 (1925).

(13) T. S. Gardner, F. A. Smith, E. Wenis, and J. Lee, *J. Org. Chem.*, **16**, 1121 (1951).

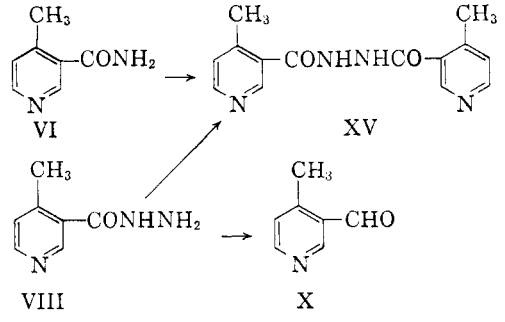
(14) S. Hoogewerff and W. A. van Dorp, *Ber.*, **13**, 1639 (1880).



volved in these reactions, it was of interest to study the direct conversion of the nitrile, V, to ethyl 4-methyl-3-pyridinecarboxylate. The conversion was accomplished successfully with sulfuric acid in absolute alcohol at elevated temperatures and pressures, although the ester, VII, was obtained in yields of only 48% and was contaminated by traces of nitrile. A better preparation of this ester involved the conversion of the nitrile to 4-methyl-3-pyridinecarboxamide, VI, by partial hydrolysis in the presence of Amberlite IRA-400 (over 90%)[15] followed by alcoholysis in absolute ethanol and anhydrous hydrogen chloride.[16] The ester was obtained in yields of 75 to 85% and its infrared spectrum showed the complete absence of any nitrile or amide impurity. The amide was characterized as a picrate and a hydrochloride and the physical constants of the ester agreed with those in the literature.[17]

The preparation of 4-methyl-3-pyridinecarboxhydrazide, VIII, was undertaken, as it was reported[18] that periodate oxidation of nicotinic acid hydrazide gave reasonable yields of nicotinaldehyde. The conversion of ethyl 4-methyl-3-pyridinecarboxylate, VII, to the hydrazide, VIII, proceeded smoothly in yields of about 90%, and oxidation of the hydrazide with sodium metaperiodate gave low but isolable yields (22 to 30%) of 4-methyl-3-pyridinecarboxaldehyde, X. Repeated attempts to increase this yield were not successful.

The attempted conversion of 4-methyl-3-pyridinecarboxamide to the hydrazide, VIII, by the transamidation reaction of Galat and Elion[19] was not successful but yielded interesting results. Thus, the fusion of 4-methyl-3-pyridinecarboxamide with hydrazine dihydrochloride gave, in 13% yield, 1,2-bis(4-methyl-3-pyridinoyl)hydrazine, XV. Confirmation of this result was established by an alternate synthesis of XV from 4-



methyl-3-pyridinecarboxhydrazide, VIII, by mercuric oxide oxidation.[20] It was observed that this oxidation yielded not only the diacylhydrazine, XV, but the desired aldehyde, X, which could be isolated in yields of 27 to 30% as its 2,4-dinitrophenylhydrazone. However, the reaction was considered inadequate as a preparative method for the aldehyde.

Finally, ethyl 4-methyl-3-pyridinecarboxylate was reduced in good yield (80%) to 3-hydroxymethyl-4-methylpyridine, IX, with lithium aluminum hydride.[21,22] This carbinol was converted to 4-methyl-3-pyridinecarboxaldehyde in 52 to 64% yield by oxidation with lead tetraacetate.[21] The aldehyde was characterized as a 2,4-dinitrophenylhydrazone, an oxime, a semicarbazone and a dimethylhydrazone, XIV.[23] The aldehyde is soluble in ether, chloroform, benzene, ethanol, and partially soluble in water, but is insoluble in hexane.

4-Methyl-3-pyridinecarboxaldehyde, X, is extremely easily oxidized by air to 4-methyl-3-pyridinecarboxylic acid, XI. This reaction con-

(15) A. Galat, *J. Am. Chem. Soc.*, **70**, 3945 (1948).
(16) F. Galinovsky and G. Kainz, *Monatsh.*, **77**, 137 (1947).
(17) P. Rabe and E. Jantzen, *Ber.*, **54**, 925 (1921).
(18) H. N. Wingfield, W. R. Harlan, and H. R. Hanmer, *J. Am. Chem. Soc.*, **74**, 5796 (1952).
(19) A. Galat and G. Elion, *J. Am. Chem. Soc.*, **65**, 1566 (1943).
(20) J. L. Yale, K. Losee, J. Martins, M. Holsing, M. Perry and J. Bernstein, *J. Am. Chem. Soc.*, **75**, 1933 (1953).
(21) V. M. Mićović and M. Lj. Mihailović, *Rec. trav. chim.*, **71**, 970 (1952).
(22) R. G. Jones and E. C. Kornfeld, *J. Am. Chem. Soc.*, **73**, 107 (1951).
(23) The dimethylhydrazone was prepared because it had been reported [R. H. Wiley, S. C. Slaymaker, and H. Kraus, *J. Org. Chem.*, **22**, 204 (1957)] that the dimethylhydrazone of nicotinaldehyde has some antitumor activity.

stitutes a structure proof, as the acid isolated is identical in all respects with an authentic sample prepared by the acid hydrolysis[7] of 3-cyano-4-methylpyridine. 2 - Methyl - 3 - pyridinecarboxaldehyde has been reported[24] to form a self condensation product on standing. Although 4-methyl-3-pyridinecarboxaldehyde is very easily oxidized, no dimerization product was observed.

The cyclic ethylene acetal, XII, and ethyl (4-methyl-3-pyridal)malonate, XIII, were prepared in order to explore the reactions of this new aldehyde and to test possible synthetic approaches to 6,7-disubstituted isoquinolines. The acetal, XII, was prepared (66%) by the procedure of Salmi[25] although it was necessary to modify the isolation method somewhat. The acetal was characterized as a picrate. Ethyl (4-methyl-3-pyridal)malonate, XIII, was prepared (69%) according to the method of Allen and Spangler[26] for the preparation of ethyl benzalmalonate. This ester, XIII, appears to hydrolyze and decarboxylate with great ease, as attempts to prepare its picrate yielded a compound whose analysis agrees closely with that of the picrate of β-(4-methyl-3-pyridyl)acrylic acid.

EXPERIMENTAL[27]

3-Cyano-2,6-dihydroxy-4-methylpyridine, III; *piperidine method.*[28] A mixture of 210 g. (2.5 moles) of cyanoacetamide, 316 ml. (325 g., 2.5 moles) of ethyl acetoacetate, 250 ml. (213 g., 2.5 moles) of freshly distilled piperidine, and 800 ml. of methanol was refluxed until crystals began to separate from the reaction mixture and then for 1 hr. more (total time, about 24 hr.). The mixture was allowed to cool and the crystalline salt was separated by filtration and washed thoroughly with methanol to yield 348 g. of the white piperidinium salt of 3-cyano-2,6-dihydroxy-4-methylpyridine, m.p. 229–235° (dec.). The salt gave a deep blue coloration with 5% alcoholic ferric chloride and turned pink in moist air.

Anal. Calcd. for $C_{12}H_{17}N_3O_2$: C, 61.25; H, 7.28; N, 17.86. Found: C, 61.28; H, 7.37; N, 17.81.

A compound identical with the above salt in all respects was formed by heating equimolar amounts of piperidine and 3-cyano-2,6-dihydroxy-4-methylpyridine in ethanol.

The salt was dissolved in warm water, filtered, and allowed to cool. Additional water was added, if needed, to dissolve any precipitate and the solution was cautiously acidified with concentrated hydrochloric acid and allowed to cool. The product was separated by filtration, washed with methanol, water, and methanol again, and dried at 60° to yield 257 g., m.p. 295–300° (dec.), lit.,[8,9] chars at 300–304°, m.p. 316–319° (dec.). An additional 97.5 g. (total, 354.5 g., 94.5%) was obtained by acidification of the filtrate from the piperidinium salt. A sample recrystallized from ethanol-water melted at 315–320° (dec.). The compound gave a blue-green coloration with aqueous potassium nitrite, a violet color with 5% ferric chloride solution and turned green on standing in moist air.

3-Cyano-2,6-dihydroxy-4-methylpyridine; potassium hydroxide method. A mixture of 336 g. (4 moles) of cyanoacetamide, 507 ml. (520 g., 4 moles) of ethyl acetoacetate, and 850 ml. of methanol was warmed to attain solution and 275 g. (4.18 moles) of potassium hydroxide dissolved in 200 ml. of methanol was added (during 2 hr.) with stirring. During the addition, a white precipitate formed and enough methanol was added to prevent caking. The mixture was heated at reflux temperature and stirred for 8 hr., and the product was removed from the cooled reaction mixture by filtration and washed with methanol. The 3-cyano-2,6-dihydroxy-4-methylpyridine monopotassium salt thus formed was dissolved in warm water, filtered, cooled, acidified with concentrated hydrochloric acid, and isolated as described above. The yield of the pyridinediol, III, varied from 404 to 544 g. (68 to 90%).

3-Cyano-2,6-dichloro-4-methylpyridine, IV.[28] 3-Cyano-2,6-dihydroxy-4-methylpyridine (50 g., 0.33 mole) and phosphorus oxychloride (120 ml., 201 g., 1.3 moles) were placed in a glass-lined stainless steel autoclave and maintained at 180° for 4–6 hr. After cooling, the contents were transferred cautiously and with stirring onto cracked ice. The crystalline product was removed by filtration, washed thoroughly with water and dried at 60°. The yield of crude yellow product varied from 55 to 60 g. (88 to 96%), m.p. 109–110°. The analytical sample, m.p. 110–110.5°, was recrystallized twice from ethanol.

Anal. Calcd. for $C_7H_4N_2Cl_2$: C, 44.92; H, 2.14; N, 14.97; Cl, 37.90. Found: C, 45.19; H, 2.20; N, 14.95; Cl, 37.86.

3-Cyano-4-methylpyridine, V.[28] Crude 3-cyano-2,6-dichloro-4-methylpyridine, (40 g., 0.214 mole), anhydrous sodium acetate (35 g., 0.43 mole), 200 ml. of methanol and 0.5 g. of palladium chloride[29] were shaken with hydrogen (50 p.s.i.) until no more hydrogen was taken up. The catalyst and residue were removed by filtration and washed several times with methanol. The filtrates from ten of these reductions were combined and the methanol was distilled through a 3-ft. Vigreux column. The residue was dissolved in 500 ml. of water, neutralized with solid sodium bicarbonate and extracted with ether. The ether solution was dried over anhydrous sodium sulfate, the solvent was removed, and the oily residue was distilled to yield 219 g. (87%) of 3-cyano-4-methylpyridine, b.p. 79–82°/3 mm., m.p. 45–46°, lit., b.p. 64°/1–2 mm.,[7] m.p. 43–44°.[6] The *picrate* melted at 185–186.5°, lit.[7] 184.5–185.5°, and the *hydrochloride* sublimed at 188–190° and decomposed at 211°, lit.,[7] sublimes 208–209°.

4-Methyl-3-pyridinecarboxamide, VI. Amberlite IRA-400-OH (70 g.), 60 g. (0.51 mole) of 3-cyano-4-methylpyridine, and 350 ml. of water were stirred at reflux temperature for 3 hr. The warm mixture was filtered and the filtrate was evaporated on a steam bath to yield 62 g. (89%) of 4-

(24) A. Dornow and H. Bormann, *Chem. Ber.*, **82**, 216 (1949).

(25) E. J. Salmi, *Ber.*, **71**, 1803 (1938).

(26) C. F. H. Allen and F. W. Spangler, *Org. Syntheses*, **Coll. Vol. III**, 377 (1955).

(27) All melting points were taken on a Kofler Micro Hot Stage Apparatus and are corrected. The analyses were performed by Geller Laboratories of Bardonia, N. Y., and Drs. Weiler and Strauss of Oxford, England. We would like to thank the Rohm and Haas Co. of Philadelphia, the Kay-Fries Co. of West Haverstraw, N. J., and the General Aniline and Film Co. of Easton, Pa., for gifts of Amberlite IRA-400, cyanoacetamide, and diglyme (dimethyldiethyleneglycol) respectively.

(28) This is a modification of a procedure used [T. R. Govindachari, K. Nagarajan, and S. Rajappa, *J. Chem. Soc.*, 551 (1957)] for the synthesis, in poor yield, of 3-cyano-2,6-dihydroxy-4-ethylpyridine and ultimately 3-cyano-4-ethylpyridine.

(29) Commercial palladium chloride gave erratic results. Best results were obtained with freshly prepared palladium chloride. See F. P. Treadwell and W. T. Hall, *Analytical Chemistry*, 9th ed., John Wiley and Sons, New York, 1955, p. 525.

methyl-3-pyridinecarboxamide, m.p. 165–167°.[30] The analytical sample, m.p. 167–167.5°, was recrystallized twice from ethanol.

Anal. Calcd. for $C_7H_8N_2O$: C, 61.75; H, 5.92; N, 20.58. Found: C, 61.42; H, 5.91; N, 20.77.

A *hydrochloride* was prepared in ethanol with anhydrous hydrogen chloride. After three recrystallizations from absolute ethanol, it exhibits m.p. 239–241° (dec).

Anal. Calcd. for $C_7H_9N_2Cl$: C, 48.64; H, 5.24; N, 16.24; Cl, 20.54. Found: C, 48.53; H, 5.44, N, 16.01; Cl, 20.49.

A *picrate*, m.p. 217–217.5° was prepared in ethanol and recrystallized three times from the same solvent.

Anal. Calcd. for $C_{13}H_{11}N_5O_8$: C, 42.74; H, 3.04; N, 19.17. Found: C, 43.18; H, 3.31; N, 19.23.

Ethyl 4-methyl-3-pyridinecarboxylate, VII, *from 3-cyano-4-methylpyridine.* Concentrated sulfuric acid (33 ml.) was added, with stirring, to 25 g. (0.21 mole) of the nitrile, V, in 90 ml. of absolute ethanol and the mixture was maintained at 130° for 14–16 hr. in a glass-lined autoclave. After cooling, the reaction mixture was poured onto 200 g. of cracked ice and the alcohol was removed under vacuum. The resulting aqueous solution was neutralized with sodium bicarbonate and ex racted with several portions of ether. The ether solution was dried over anhydrous sodium sulfate, the ether was distilled, and the residue was distilled to yield 16.7 g. (48%) of ester, b.p. 60–62°/0.3–0.5 mm. The infrared spectrum showed that a small amount of nitrile was present.

Ethyl 4-methyl-3-pyridinecarboxylate, VII, *from 4-methyl-3-pyridinecarboxamide*, VI. 4-Methyl-3-pyridinecarboxamide (65 g., 0.48 mole) in 3500 ml. of refluxing absolute ethanol[16] was stirred and anhydrous hydrogen chloride was passed in for 5 hr. The solution was heated under reflux with occasional introduction of more hydrogen chloride until solid ammonium chloride precipitated (about 30 hr.). Three liters of alcohol was distilled and the residue was evaporated to dryness under vacuum. The solid residue was dissolved in 300 ml. of water, cautiously neutralized with solid sodium bicarbonate, and extracted with several portions of ether. The combined ether extracts were dried over sodium sulfate, the ether was removed, and the residue was distilled to yield 66.7 g. (85%) of ethyl 4-methyl-3-pyridinecarboxylate, b.p. 96–98°/6 mm., lit.[17] 118°/12 mm., n_D^{20} 1.5059, d_{25}^{25} 1.087. The *picrate* melted at 138.5–140°, lit.[17] 137°.

4-Methyl-3-pyridinecarboxhydrazide, VIII. Ethyl 4-methyl-3-pyridinecarboxylate (38.5 g., 0.23 mole) and 100 ml. of 48% hydrazine hydrate containing 5 ml. of absolute ethanol were heated under reflux for 20 hr., cooled, and the precipitated product was removed by filtration, washed with cold water and dried *in vacuo* to yield 32 g. (91%) of product, m.p. 173–175°. The analytical sample, m.p. 176.5–177.3° was recrystallized twice from methanol.

Anal. Calcd. for $C_7H_9N_3O$: C, 55.61; H, 6.00; N, 27.80. Found: C, 55.41; H, 5.98; N, 27.97.

1,2-Bis(4-methyl-3-pyridinoyl)hydrazine, XV, *from* VI. Analogous to the transamidation method of Galat and Elion,[19] a mixture of 5 g. (0.037 mole) of 4-methyl-3-pyridinecarboxamide and 7.7 g. (0.073 mole) of hydrazine dihydrochloride was ground and heated to the melting point until bubbling and foaming subsided. Absolute ethanol (25 ml.) was added to the cooled mixture which was then filtered to remove ammonium chloride. The filtrate was neutralized with aqueous sodium bicarbonate and evaporated to dryness on a steam bath. The residue was extracted with boiling absolute ethanol and the extract was filtered, concentrated, and cooled to yield, after recrystallization from ethanol-water, 1.3 g. (13%) of white crystalline product, m.p. 249–249.5°.

(30) This compound has been reported[7] to melt at 146.5–147°, but no nitrogen analysis was given. For this reason, a complete analyses and the preparation of two derivatives are reported. The compound was also prepared from the nitrile by the action of hydrogen peroxide by the method of Noller, *Org. Syntheses*, **Coll. Vol. II**, 586 (1943).

Anal. Calcd. for $C_{14}H_{14}N_4O_2$: C, 62.21; H, 5.22; N, 20.73. Found: C, 62.13; H, 5.23; N, 20.87.

1,2-Bis(4-methyl-3-pyridinoyl)hydrazine was also prepared in 15% yield by oxidation with mercuric oxide of 4-methyl-3-pyridinecarboxhydrazide according to a described procedure.[20]

Oxidation of 4-methyl-3-pyridinecarboxhydrazide, VIII, *with mercuric oxide. 4-Methyl-3-pyridinecarboxaldehyde 2,4-dinitrophenylhydrazone.* To a stirred mixture of 2.8 g. (0.013 mole) of yellow mercuric oxide, 20 ml. of ethanol, and 1.0 g. of sodium bicarbonate, was added 1.0 g. (0.0066 mole) of 4-methyl-3-pyridinecarboxhydrazide in 50 ml. of ethanol (during 10 min.). The mixture turned dark brown and was heated at reflux for 0.5 hr. The cooled mixture was filtered and the precipitated mercurous oxide was washed with absolute ethanol. One half of the alcoholic filtrate was treated with 250 ml. of a saturated solution of 2,4-dinitrophenylhydrazine in 2*N* hydrochloric acid. The 2,4-dinitrophenylhydrazone which precipitated amounted to 0.28 g. (28%) m.p. 250–255°. After two recrystallizations from absolute ethanol and a vacuum sublimation, the analytical sample melted at 255.5–256°.

Anal. Calcd. for $C_{13}H_{11}N_5O_4$: C, 51.83; H, 3.68; N, 23.25. Found: C, 52.11; H, 4.05; N, 23.11.

3-(Hydroxymethyl)-4-methylpyridine, IX. Lithium aluminum hydride (23 g., 0.61 mole) was triturated with ether,[22] suspended in 1000 ml. of dry ether and heated, with stirring under reflux for 3 hr. in an atmosphere of nitrogen. A solution of 76 g. (0.46 mole) of ethyl 4-methyl-3-pyridinecarboxylate in 500 ml. of dry ether was added dropwise within 1.5 hr. The reaction mixture was cooled to 0° and decomposed by the cautious addition of 125 ml. of water. The ether layer was decanted and dried over anhydrous potassium carbonate. The remaining solid was extracted with three portions of boiling methanol. The methanol was removed under vacuum from the combined methanol extracts, the residue extracted with chloroform, and the resulting extract dried over potassium carbonate. The respective solvents were removed from the chloroform and ether layers and the combined residues were fractionated through a Wheeler Column (GV 130) to yield 45 g. (80%) of 3-(hydroxymethyl)-4-methylpyridine as a colorless liquid, b.p. 125–127°/1.5–2 mm., which solidified, m.p. 44–46°.

Anal. Calcd. for C_7H_9NO: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.20; H, 7.38; N, 11.54.

When this reduction was carried out at 0°,[21] a gummy mass formed during ester addition and the reaction mixture was difficult to stir.

The *hydrochloride* was prepared by passing dry hydrogen chloride into an ethereal solution of the carbinol and was crystallized three times from ethanol, m.p. 191–192°.

Anal. Calcd. for $C_7H_{10}ClNO$: C, 52.67; H, 6.27; N, 8.77; Cl, 22.21; Found: C, 52.96; H, 6.24; N, 8.59; Cl, 21.91.

The *picrate*, m.p. 160.5–162° was prepared in ethanol and recrystallized twice from the same solvent.

Anal. Calcd. for $C_{13}H_{12}N_4O_8$: C, 44.32; H, 3.43; N, 15.91. Found: C, 44.38; H, 3.36; N, 15.72.

4-Methyl-3-pyridinecarboxaldehyde, X, *from 4-methyl-3-pyridinecarboxhydrazide.* In a manner similar to the procedure of Wingfield, Harlan, and Harmer,[18] approximately 60 ml. of concentrated ammonium hydroxide was added in small portions to a cooled (0°) solution of 16.2 g. (0.076 mole) of sodium metaperiodate in 250 ml. of water. To the cooled, resultant slurry was added 10 g. of 4-methyl-3-pyridinecarboxhydrazide (0.066 mole) in 105 ml. of 8% ammonium hydroxide; the mixture was stirred, with cooling, for an additional 10 min. and allowed to stand at 25° for 20 min. in an atmosphere of nitrogen. A solution of 17.5 g. (0.069 mole) of barium acetate in 150 ml. of water was added, the slurry was filtered, and the filtrate was made nearly neutral with acetic acid. The solution was made basic with solid sodium bicarbonate and extracted with chloroform. The chloroform extracts were dried over an-

hydrous sodium sulfate. The chloroform was removed under vacuum and the residue was distilled through a six-inch, semimicro Vigreux column to yield 1.8 g. (22%) of 4-methyl-3-pyridinecarboxaldehyde, b.p. 62–64°/3 mm. The analytical sample, b.p. 109–110°/11 mm., was distilled through a Wheeler Column.

Anal. Calcd. for C_7H_7NO: C, 69.40; H, 5.83; N, 11.56. Found: C, 69.20; H, 6.24; N, 11.79.

4-Methyl-3-pyridinecarboxaldehyde, X, *from 3-(hydroxymethyl)-4-methylpyridine*. According to the general method of Mićović and Mihailović,[21] lead tetraacetate (107 g., 0.24 mole), and 450 ml. of sodium-dried benzene were heated to reflux in a dry nitrogen filled atmosphere. The heat was removed, and 29.5 g. (0.24 mole) of 3-(hydroxymethyl)-4-methylpyridine in 100 ml. of dry benzene was added dropwise during 10 min. After considerable foaming, the reaction subsided and was heated under reflux for 1.5 hr. After cooling, the tan lead acetate was removed by filtration and was washed with benzene. The benzene filtrate and washings were combined and neutralized by shaking with 10% potassium carbonate. The aqueous layer was washed with chloroform until no further aldehyde was obtained (2,4-dinitrophenylhydrazine solution). The combined benzene and chloroform solutions were dried over sodium carbonate, concentrated under vacuum, and the residue was distilled to yield 18.5 g. (64%) of 4-methyl-3-pyridinecarboxaldehyde, b.p. 62–64°/3 mm.

The *oxime*, m.p. 177.5–180.5° was prepared in water by conventional methods and recrystallized three times from ethanol.

Anal. Calcd. for $C_7H_8N_2O$: C, 61.75; H, 5.92; N, 20.58. Found: C, 61.61; H, 6.26; N, 20.34.

The *semicarbazone* was prepared by conventional methods and recrystallized three times from absolute ethanol, m.p. 195.5–198.5°.

Anal. Calcd. for $C_8H_{10}N_4O$: C, 53.92; H, 5.66; N, 31.45. Found: C, 53.87; H, 5.93; N, 31.14.

The *dimethylhydrazone*, XIV, was prepared from 1,1-dimethylhydrazine by the method of Wiley, Slaymaker, and Kraus,[23] b.p. 90–99°/0.5 mm. The distillate which solidified on standing was recrystallized from pentane (by cooling to 0°) or acetone (by cooling to −50°), m.p. 49.5–51°.

Anal. Calcd. for $C_9H_{13}N_3$: C, 66.22; H, 8.03; N, 25.75. Found: C, 66.15; H, 8.06; N, 25.50.

4-Methyl-3-pyridinecarboxylic acid, XI, *from 4-methyl-3-pyridinecarboxaldehyde*, X. A portion of aldehyde, X, (about 0.5 g.) was allowed to stand uncovered in air for 2 hr., and the solid which formed was washed with acetone and recrystallized from absolute ethanol to yield 4-methyl-3-pyridinecarboxylic acid, m.p. 213.5–215.5° (dec.), lit.,[7] 215–216°. A mixture melting point of this material and a sample prepared by the method of Webb and Corwin[7] was undepressed.

2-(4-Methyl-3-pyridyl)-1,3-dioxolane, XII, (*ethylene acetal of the aldehyde*). A modification of the method of Salmi[25] was used. A mixture of 5 ml. (5.5 g., 0.09 mole) of ethylene glycol, 4 g. (0.033 mole) of 4-methyl-3-pyridinecarboxaldehyde, 30 ml. of dry benzene and a few crystals of *p*-toluenesulfonic acid was refluxed in an atmosphere of nitrogen until a maximum amount of water had collected in an appropriately arranged Dean-Stark water separation apparatus. After cooling, 50 ml. of benzene was added and the solution was washed with 10% sodium carbonate solution. The aqueous solution was in turn washed with chloroform and the combined chloroform and benzene solutions were dried over sodium carbonate and the solvents were evaporated. The residue was heated with 60 ml. of 5% sodium hydroxide solution containing 30 ml. of 3% hydrogen peroxide (ethanol added to maintain solution) to 70–80° for 15 min. (to remove unreacted aldehyde). Another portion of peroxide (20 ml.) was added and the solution was heated for 10 min. more. The alcohol and excess peroxide were removed under vacuum and the liquid residue was extracted with chloroform. The chloroform extract was dried over potassium carbonate and evaporated under vacuum to a residue which on fractionation (Wheeler Column) yielded 3.6 g. of acetal (66%), b.p. 111–113°/2 mm., n_D^{20} 1.5280, d_{25}^{25} 1.154.

Anal. Calcd. for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.15; H, 6.63; N, 8.48.

The *picrate*, m.p. 181.5–184° was prepared in ethanol and recrystallized three times from the same solvent.

Anal. Calcd. for $C_{15}H_{14}N_4O_9$: C, 45.69; H, 3.58; N, 14.21. Found: C, 45.82; H, 3.90; N, 14.14.

Ethyl (4-methyl-3-pyridal) malonate, XIII. According to the general method of Allen and Spangler[26] a mixture of 5 ml. of freshly distilled ethyl malonate (8.78 g., 0.055 mole), 50 ml. of dry benzene, 4 g. of 4-methyl-3-pyridinecarboxaldehyde (0.033 mole), and a few drops of piperidine was refluxed in an atmosphere of nitrogen until a maximum of water had collected in an appropriately arranged Dean-Stark tube. After the solution had cooled, ether was added and the mixture was extracted with 3*N* hydrochloric acid. The acid extract was washed with ether, made basic with solid sodium carbonate, and again extracted with ether. The ether extract was dried over potassium carbonate and fractionated to yield 6.0 g. (69%) of ethyl (4-methyl-3-pyridal)malonate, b.p. 139–143°/0.5 mm., n_D^{20} 1.5241.

Anal. Calcd. for $C_{14}H_{17}NO_4$: C, 63.86; H, 6.51; N, 5.32. Found: C, 63.83; H, 6.32; N, 5.53.

The *picrate* was prepared in ethanol, m.p. 107–110.5°. Two recrystallizations for ethanol yielded a new substance, m.p. 136–138.5°, which appeared to be β-(4-methyl-3-pyridyl)acrylic acid picrate.

Anal. Calcd. for $C_{20}H_{20}N_4O_{11}$ (expected picrate): C, 48.78; H, 4.09; N, 11.37. Calcd. for $C_{15}H_{12}N_4O_9$ [β-(4-methyl-3-pyridyl)acrylic acid picrate]: C, 45.92; H, 3.08; N, 14.28. Found: C, 45.89; H, 3.72; N, 14.34.

STORRS, CONN.