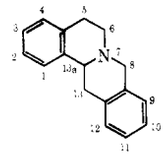
65495-41-2; **27,** 93-40-3; **28,** 951-82-6; **29,** 7417-21-2; **30,** 37785-48-1; **31,** 40173-90-8; **32,** 65495-26-3; **33,** 4216-86-8; **33** H_3PO_4 salt, 65495-27-4; **33** HCl, 10301-89-0; **33** HBF_4 salt, 65495-28-5; **34,** 65495-29-6; **35,** 22048-26-6; **35** HBF_4 salt, 65495-30-9; **36,** 10097-84-4; **36** HCl, 2506-20-9; **37,** 65495-21-8; **38,** 65495-31-0; **39,** 65516-34-9; **40,** 65495-22-9; **41,** 65495-23-0; **42,** 65495-24-1; **43,** 65495-25-2.

References and Notes

(1) The systematic name for the fundamental nucleus i of this ring system is 5,8,13,13a-tetrahydro-6*H*-dibenzo[*a,g*]quinolizine or alternatively 5,6,13,13a-tetrahydro-8*H*-dibenzo[*a,g*]quinolizine. Recently, the much less cumbersome name berbine is being used to represent this nucleus,



i

and we find it preferable to the somewhat confused nomenclature implicit in the two other widely used terms, tetrahydroberberine and tetrahydroprotoberberine. For those compounds where a common name derived from its natural product origins is available, it has been used.

(2) (a) J. W. Huffman and E. G. Miller, *J. Org. Chem.*, **25,** 90 (1960); (b) A. R. Battersby, D. J. LeCount, S. Garrett, and R. I. Thrift, *Tetrahedron*, **14,** 46 (1961).
(3) A. R. Battersby, R. Binks, and P. S. Uzzell, *Chem. Ind. (London)*, 1039 (1955).
(4) M. Sainsbury, D. W. Brown, S. F. Dyke, and G. Hardy, *Tetrahedron*, **25,** 1881 (1969).
(5) S. F. Dyke and M. Sainsbury, *Tetrahedron*, **21,** 1907 (1965).
(6) J. M. Bobbitt, J. M. Keily, K. L. Khanna, and R. Ebermann, *J. Org. Chem.*, **30,** 2247 (1965).
(7) P. Garside and A. C. Ritchie, *J. Chem. Soc.*, 2140 (1966).
(8) S. F. Dyke, M. Sainsbury, and B. J. Moon, *Tetrahedron*, **24,** 1467 (1968).
(9) S. F. Dyke, M. Sainsbury, D. W. Brown, M. N. Palfreyman, and D. W. Wiggens, *Tetrahedron*, **27,** 281 (1971).
(10) R. T. Dean, H. C. Padgett, and H. Rapoport, *J. Am. Chem. Soc.*, **98,** 7448 (1976).
(11) S. Archer, *J. Org. Chem.*, **16,** 430 (1951).
(12) V. Deulefeu and G. Mendivelzua, *Z. Physiol. Chem.*, **219,** 233 (1933).
(13) G. A. Stein, H. A. Bronner, and K. Pfister, *J. Am. Chem. Soc.*, **77,** 700 (1955).
(14) B. J. Wakefield, "The Chemistry of Organolithium Compounds", Pergamon Press, Elmsford, N.Y., 1974.
(15) D. A. Shirley, J. R. Johnson, and J. D. Hendrix, *J. Organomet. Chem.*, **11,** 209 (1968).
(16) F. M. Jones, M. F. Zinn, and C. R. Hauser, *J. Org. Chem.*, **28,** 663 (1963).
(17) W. H. Puterbaugh and C. R. Hauser, *J. Org. Chem.*, **29,** 853 (1964).
(18) R. E. Ludt, J. S. Griffiths, I. N. McGrath, and C. R. Hauser, *J. Org. Chem.*, **38,** 1668 (1973).
(19) P. Beak and R. A. Brown, *J. Org. Chem.*, **42,** 1823 (1977).
(20) H. Watanabe, R. L. Gay, and C. R. Hauser, *J. Org. Chem.*, **33,** 900 (1968).
(21) H. Watanabe, R. A. Schwartz, C. R. Hauser, J. Lewis, and D. W. Slocum, *Can. J. Chem.*, **47,** 1573 (1969).
(22) H. Gilman and T. S. Soddy, *J. Org. Chem.*, **22,** 1715 (1957).
(23) J. J. Fitt and H. W. Gschwend, *J. Org. Chem.*, **41,** 4029 (1976).
(24) H. Geschwend and A. Hamdan, *J. Org. Chem.*, **40,** 2008 (1975); A. I. Meyers and E. D. Mihelich, *ibid.* **40,** 3159 (1975).
(25) A. M. Roe, R. A. Burton, and D. R. Reavil, *Chem. Commun.*, 582 (1965).
(26) N. S. Narasimhan and B. H. Bhide, *Tetrahedron Lett.*, 4159 (1968).
(27) F. Sondheimer and A. Meisels, *Tetrahedron*, **9,** 139 (1960).
(28) R. F. Borch, *Tetrahedron Lett.*, 61 (1968).
(29) N. Umino, T. Iwakuma, and N. Itoh, *Tetrahedron Lett.*, 763 (1976).
(30) H. J. Monteiro, *Synthesis*, 137 (1974).
(31) M. E. Kuehne and P. J. Shannon, *J. Org. Chem.*, **42,** 2082 (1977).
(32) A. A. Pavlic and H. Adkins, *J. Am. Chem. Soc.*, **68,** 1471 (1946).
(33) H. Adkins and A. A. Pavlic, *J. Am. Chem. Soc.*, **69,** 3039 (1947).
(34) E. C. Kornfeld, *J. Org. Chem.*, **16,** 131 (1951).
(35) All reactions were performed under nitrogen with magnetic stirring unless otherwise indicated and all solvents were dried with $MgSO_4$ prior to evaporation in vacuo using a Berkeley rotary evaporator. Melting points are uncorrected and distillation was bulb-to bulb, Kugelrohr type. NMR spectra were determined in $CDCl_3$ solution, unless otherwise indicated, with a Varian T-60 instrument using internal Me_4Si; IR spectra were recorded neat for liquids and in a paraffin oil mull for solids on a Perkin-Elmer 337 spectraphotometer; CEC-103 and 110B mass spectometers were used for determining mass spectra. GC was done on 4 ft 2% OV-17 on 100/120 mesh Chromosorb W(AW) or 3% OV-17 on 100/120 mesh Aeorpak 30. TLC was done on SiO_2 (Eastman, Brinkman HR, or silica gel 60, E.M. Reagents, 63–200 μm), and column chromatography on silica gel 60, E.M. Reagents 63–200 μm. Elemental analyses were performed by the Analytical Laboratory, Department of Chemistry, University of California, Berkeley, Calif.
(36) N. Sugimoto, *Yakugaku Zasshi*, **64B,** 108 (1944).
(37) E. Champaigne and B. G. Heaton, *J. Org. Chem.*, **29,** 2372 (1964).
(38) J. M. Pepper and H. Hibbert, *J. Am. Chem. Soc.*, **70,** 67 (1948).
(39) S. Sugasawa, *Yakugaku Zasshi*, **57,** 296 (1937).
(40) E. A. Steck, L. T. Fletcher, and R. P. Brundage, *J. Org. Chem.*, **28,** 2233 (1963).
(41) E. Spath and E. Kruta, *Monatsh. Chem.*, **50,** 341 (1928).
(42) G. Hahn and W. Kley, *Chem. Ber.*, **70,** 685 (1937).
(43) E. L. Eliel, T. N. Ferdinand, and Sr. M. C. Herrmann, *J. Org. Chem.*, **19,** 1693 (1954).
(44) C. K. Bradsher and N. L. Dutta, *J. Org. Chem.*, **26,** 2231 (1961).

Synthesis of 4-Methylnicotine and an Examination of Its Possible Biosynthesis from 4-Methylnicotinic Acid in *Nicotiana tabacum*[1]

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Condensation of ethyl 4-methylnicotinate with *N*-methyl-2-pyrrolidone in the presence of sodium hydride yielded the nicotinoyl derivative **6,** which on hydrolysis and reduction afforded 4-methylnicotine (**8**). This nicotine analogue was also obtained from 4-methylpyridine-3-carboxaldehyde by preparing the acyl carbanion equivalent **2,** which was added to acrylonitrile. Hydrolysis of the Michael addition product yielded the ketonitrile **3,** which was hydrogenated to give 4-methylnornicotine, which afforded **8** on methylation. A biomimetic synthesis of **8** involved reaction between 3-methylglutaraldehyde, ammonia, and *N*-methyl-Δ^1-pyrrolinium acetate in the presence of air. Optically active 4-methylnicotine was obtained as previously described by reaction of (−)-(2′*S*)-nicotine with methyllithium. The administration of 4-methyl[4-^{14}C]nicotinic acid (prepared from ethyl [3-^{14}C]acetoacetate) to *Nicotiana tabacum* plants did not result in the formation of radioactive 4-methylnicotine. 4-Methylnicotine showed no nicotine-like activity in pharmacological tests.

Nicotinic acid is the established precursor of the pyridine ring of the tobacco alkaloid nicotine.[4,5] We have previously shown[6] that 5-fluoronicotinic acid was utilized by *Nicotiana tabacum* to yield 5-fluoronicotine by what we term an "aberrant biosynthesis". The present article describes our attempts to produce 4-methylnicotine (**8**) by administering 4-methylnicotinic acid to the tobacco plant.

A reference specimen of 4-methylnicotine was required for comparison with any material which might be isolated from tobacco. 4-Methylnicotine has been previously described by

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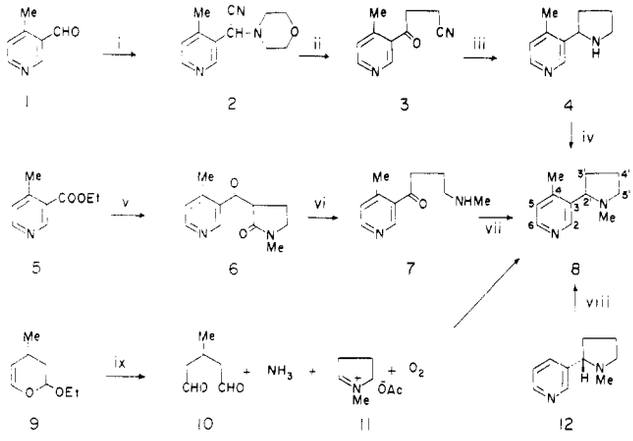
Scheme I. Syntheses of 4-Methylnicotine[a]

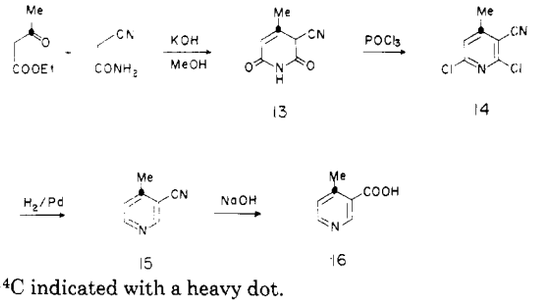


[a] i, Morpholine, $HClO_4$, KCN; ii, KO-*t*-Bu, CH_2=CHCN, HOAc; iii, H_2/Ni, $NaBH_4$; iv, HCHO, HCOOH; v, *N*-methyl-2-pyrrolidone, NaH; vi, 48% HBr; vii, $NaBH_4$; viii, MeLi; ix, HCl.

Haglid,[7] who obtained it in small yield, along with 6-methylnicotine, by the reaction of nicotine with methyllithium. We have repeated this reaction obtaining essentially the same results, except that our 4-methylnicotine derived from (−)-(2′*S*)-nicotine (the natural isomer) had a higher specific rotation ($[\alpha]^{23}_D$ −170°) than that reported by Haglid ($[\alpha]^{22}_D$ −103.5°). (*RS*)-4-Methylnicotine was prepared by three methods which are illustrated in Scheme I. The first is analogous to that used by Späth[8] for the synthesis of nicotine. In contrast to the experience of Haglid,[9] we were able to condense ethyl 4-methylnicotinate (**5**)[10] with *N*-methyl-2-pyrrolidone, in the presence of sodium hydride, to yield the nicotinoyl derivative **6**. The second synthesis started with 4-methylpyridine-3-carboxaldehyde (**1**)[10] using the procedure recently developed for the synthesis of myosmine and nornicotine[11]. The third method is analogous to the biomimetic synthesis of nicotine from glutaraldehyde, ammonia, and *N*-methyl-Δ^1-pyrrolinium acetate (**11**)[12] in the presence of air.[13] 3-Methylglutaraldehyde (**10**) was obtained by acid hydrolysis of the commercially available 2-ethoxy-4-methyl-2,3-dihydropyran (**9**). Reaction with ammonia and **11** in the presence of air gave a small yield of 4-methylnicotine and 4-methylpyridine.

4-Methyl[4-^{14}C]nicotinic acid (**16**) was made from ethyl [3-^{14}C]acetoacetate by the route illustrated in Scheme II, which is essentially that developed by Bobbit,[10] modified for synthesis on a small scale. The ^{14}C-labeled 4-methylnicotinic acid was fed to *N. tabacum* plants by the wick method, along with an equivalent amount of [2-^{3}H]nicotinic acid. The latter was fed at the same time so that the efficiency of "aberrant biosynthesis" could be compared with the normal biosynthesis of nicotine. A similar experimental procedure was used by Kirby[14] in a study of the biosynthesis of morphine and its analogues in *Papaver somniferum*. The crude alkaloids from tobacco contained both ^{14}C and tritium. A portion of the crude

Scheme II. Synthesis of 4-Methyl[4-^{14}C]nicotinic Acid[a]



[a] ^{14}C indicated with a heavy dot.

alkaloids was diluted with nonradioactive (*RS*)-4-methylnicotine. Nicotine and 4-methylnicotine were then separated by GLC. The resultant nicotine was labeled, as expected, with tritium (0.72% absolute incorporation); however, the recovered 4-methylnicotine was completely devoid of ^{14}C. Thus the enzymes responsible for nicotine biosynthesis from nicotinic acid are apparently incapable of utilizing an analogue which contains a methyl group in the 4 position. This result contrasts with the observations of Rueppel and Rapoport,[15] who found that methyl groups could be introduced into the *N*-methyl-Δ^1-pyrrolinium salt (even at C-2, the point of attachment to C-3 of nicotinic acid) to afford analogues of nicotine with extra methyl groups in the pyrrolidine ring. The utilization of other methyl derivatives of nicotinic acid, where the methyl groups are further removed from the site of condensation with **11**, is being examined.

Experimental Section[16]

4-Methylnicotine. (a) From Ethyl 4-Methylnicotinate by the Späth Method. Ethyl 4-methylnicotinate[10] (6.0 g, 36 mmol) and *N*-methyl-2-pyrrolidone (7.2 g, 72 mmol) were added slowly in a N_2 atmosphere to a magnetically stirred suspension of sodium hydride (3.5 g, 146 mmol) in benzene (25 mL), and the mixture was refluxed for 18 h. The cooled mixture was added to ice, neutralized with acetic acid, and extracted with benzene (4 × 50 mL). The combined organic extracts were washed with 10% $NaHCO_3$. Distillation (140 °C, 10^{-3} mm) of the residue obtained on evaporation of the dried ($MgSO_4$) benzene extract afforded a colorless solid (2.76 g) (**6**). This compound was refluxed with 48% HBr (10 mL) in a N_2 atmosphere for 18 h. The residue obtained on evaporation of this reaction mixture was dissolved in methanol (50 mL), the solution neutralized with KOH, and sodium borohydride (3 g) added. After standing 18 h the solution was acidified with HCl and evaporated to dryness. The residue was made basic with NaOH, extracted with chloroform, dried ($MgSO_4$), and evaporated to yield a brown oil. Distillation (110 °C, 10^{-3} mm) afforded (*RS*)-4-methylnicotine (1.66 g) as a colorless oil: IR (neat) 1600 cm^{-1} (C=N); ^{13}C NMR[18] ($CDCl_3$) ppm from Me_4Si, 151.1 (C-2), 150.0 (6), 147.4 (4), 139.3 (3), 127.1 (5), 67.1 (2′), 57.9 (5′), 41.2 (NMe), 34.1 (3′), 23.1 (4′), 19.0 (4-Me); mass spectrum, *m/e* 176 (M^+), 161 (M − Me), 147, 133; TLC on silica gel G (Merck), developing with a mixture of chloroform, methanol, and concentrated NH_3 (100:10:1), indicated that 4-methylnicotine had an R_f of 0.85 (nicotine 0.83). It was revealed as a purple spot (nicotine, orange-brown) on spraying with *p*-aminobenzoic acid and then exposing to CNBr. It afforded a dipicrate, mp 212–213 °C, yellow needles from ethanol.

Anal. Calcd for $C_{23}H_{22}N_8O_{14}$: C, 43.54; H, 3.50; N, 17.66. Found: C, 43.97; H, 3.29; N, 17.21.

It yielded a diperchlorate, colorless plates from ethanol–ethyl acetate, mp 276–277 °C dec.

Anal. Calcd for $C_{11}H_{16}N_2 \cdot 2HClO_4$: C, 35.03; H, 4.81; N, 7.43. Found: C, 35.03; H, 4.57; N, 7.55.

(b) From 4-Methylpyridine-3-carboxaldehyde. α-(4-Methyl-3-pyridyl)-α-morpholinoacetonitrile (2). 4-Methylpyridine-3-carboxaldehyde[10] (1.61 g) and morpholine perchlorate (2.8 g) were dissolved in morpholine (10 mL) and the solution was heated at 80 °C for 1 h under N_2. Potassium cyanide (1 g) dissolved in a minimum of water was added and the mixture heated at 100 °C for 2 h. The cooled mixture was added to 10% K_2CO_3 and extracted with chloroform. The dried ($MgSO_4$) extract was evaporated, and the residue sublimed (110 °C, 10^{-4} mm), affording **2**, which was crystallized from benzene–hexane to yield colorless plates (1.5 g), mp 127–128 °C.

Anal. Calcd for $C_{12}H_{15}N_3O$: C, 66.34; H, 6.96; N, 19.34. Found: C, 65.97; H, 6.97; N, 18.83.

3-Cyano-1-(4-methyl-3-pyridyl)propan-1-one (3). The nitrile (**2**) (0.94 g) was dissolved in *tert*-butyl alcohol (50 mL) containing 30% KOH in methanol (0.2 mL). Acrylonitrile (0.37 mL) in *tert*-butyl alcohol (15 mL) was added to the mixture which was then stirred at room temperature for 45 min. After dilution with an equal volume of water the mixture was extracted with chloroform, which was then back-washed with water and dried over $MgSO_4$. Evaporation yielded a viscous oil, having an absorption in the IR at 2250 cm^{-1} (C≡N) and a mass spectrum *m/e* 270 (M^+ for $C_{15}H_{18}N_4O$) and 244 (M − HCN). This crude γ-cyano-γ-morpholino-γ-(4-methyl-3-pyridyl)butyronitrile (0.75 g) was dissolved in a mixture of acetic acid (10 mL), water (5 mL), and tetrahydrofuran (1.5 mL) and heated at 53 °C for 24 h. The reaction mixture was added to K_2CO_3 and water and extracted

with chloroform. The solid residue obtained on evaporation of the dried ($MgSO_4$) pale purple extract was sublimed (70 °C, 10^{-4} mm) to afford **3**, which yielded colorless needles from ether (0.75 g): mp 83–84 °C; mass spectrum, *m/e* 174 (M^+), 144 ($M - CH_2CH_2CN$).

Anal. Calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.70; H, 5.71; N, 15.85.

4-Methylnornicotine (4). The keto nitrile (**3**) (184 mg) dissolved in a mixture of ethanol (20 mL) and concentrated NH_3 (2 mL) was hydrogenated at 2 atm pressure in the presence of Raney nickel (½ teaspoon) for 18 h. TLC of the reaction mixture indicated the presence of mostly 4-methylnornicotine with some 4-methylmyosmine (4-methyl-1′,2′-dehydronornicotine). Sodium borohydride was added to the filtered mixture, and the solution refluxed for 1 h. The cooled solution was acidified with HCl and evaporated to dryness. The residue was made basic with NaOH and extracted with methylene chloride, dried ($MgSO_4$), evaporated, and distilled (140 °C, 10^{-2} mm) to afford 4-methylnornicotine as a colorless oil (140 mg), mass spectrum, *m/e* 162 (M^+), 147 ($M - Me$). It afforded a dipicrate, yellow needles from 95% ethanol, mp 230–231 °C.

Anal. Calcd for $C_{22}H_{20}N_8O_{14}$: C, 42.59; H, 3.25; N, 18.06. Found: C, 42.16; H, 3.11; N, 18.47.

4-Methylnicotine (8). 4-Methylnornicotine (100 mg), 90% formic acid (1 mL), and 40% formaldehyde (3 mL) were refluxed for 18 h. One drop of concentrated HCl was then added, and the refluxing continued for an additional hour. The residue obtained on evaporation was made basic with NaOH, extracted with chloroform, dried ($MgSO_4$), evaporated, and distilled to yield 4-methylnicotine (95 mg), identical (IR, TLC, mixed mp of dipicrate) with material obtained by method a.

(c) From 3-Methylglutaraldehyde and *N*-Methyl-Δ¹-pyrrolinium Acetate. *N*-Methyl-2-pyrrolidone (1.0 g) was added to a suspension of sodium aluminum hydride (170 mg) in ether (50 mL) and the mixture refluxed for 2 h. The cooled solution was added to ice and acetic acid (2 mL) and then lyophilized. The resultant residue was dissolved in water (50 mL) and filtered, and 3-methylglutaraldehyde[20] (1.14 g) and concentrated NH_3 (10 mL) were added. The solution (pH 10.5) was stirred in an open beaker at room temperature for 3 days. The mixture was then extracted with chloroform. This solution was then extracted with 2 N HCl (3 × 50 mL). The aqueous extract was made basic with NaOH and extracted with ether. The residue obtained on evaporation of the dried ($MgSO_4$) extract was distilled (140 °C, 10^{-3} mm), yielding a pale yellow oil which was subjected to preparative TLC in silica gel PF-254 (Merck), developing with a mixture of chloroform, benzene, ethanol, and concentrated NH_3 (125:75:20:1). The zone at R_f 0.4 corresponded to 4-methylnicotine. This was extracted with methanol and evaporated, and the residue distilled, affording 4-methylnicotine (75 mg) identical with material obtained by the previous methods. 4-Methylpyridine (R_f 0.6) was also obtained from the preparative TLC plates and was characterized as its picrate, mp 166–167 °C.

(d) From Nicotine and Methyllithium.[10] Methyl iodide (1.25 mL) was added to a suspension of lithium ribbon (0.28 g) in ether (30 mL), and the mixture stirred under N_2 until all the lithium had dissolved. (−)-(2′*S*)-Nicotine (1.62 g, 20 mmol) in toluene (50 mL) was added. Ether was distilled out of the reaction mixture and the residual solution was heated under reflux for 7 h with stirring. The dark brown reaction mixture was cooled and added to ice and 2 N HCl. The aqueous solution was extracted with ether which was discarded. The aqueous solution was made basic with NaOH, extracted with chloroform, dried ($MgSO_4$), evaporated, and distilled (140 °C, 10^{-3} mm). The pale yellow distillate (250 mg) was subjected to GLC (Varian Aerograph 90 AP) on an 8 ft × ⅜ in. column of 10% 20M Carbowax, 70/80 mesh, with an He flow rate of 60 mL/min at 180 °C. Under these conditions the retention times of nicotine, 6-methylnicotine, and 4-methylnicotine were 4.4, 4.8, and 6.5 min, respectively. 4-Methylnicotine was obtained as a colorless oil (52 mg, 3% yield from nicotine) having an IR spectrum identical with that of a previously prepared racemic material. Its specific rotation was $[\alpha]^{23}_D$ −170°, $[\alpha]^{23}_{365}$ −593° (*c* 1.8 in $CHCl_3$). Its picrate was obtained as fine yellow needles from 95% ethanol, mp 195–197 °C (lit.[7] 193–195 °C).

4-Methyl[4-^{14}C]nicotinic Acid (16). Potassium hydroxide (0.275 g) dissolved in methanol (5 mL) was added to a solution of 2-cyanoacetamide (0.336 g, 4 mmol) and ethyl [3-^{14}C]acetoacetate (0.52 g, 4 mmol, nominal activity 0.25 mCi, Amersham-Searle) in methanol (5 mL). After refluxing for 5 h, the mixture was cooled and the white potassium salt which separated was removed by filtration. This salt was dissolved in water, and the solution neutralized with HCl when **13** separated (0.37 g, 62%). This compound was heated in a sealed glass tube with $POCl_3$ (1 mL) for 5 h at 180 °C. The contents of the tube were added to ice when 2,6-dichloro-3-cyano-4-methylpyridine (**14**) (0.421 g, 91%) separated. This dichloro compound was dissolved in methanol (10 mL) containing sodium acetate (0.4 g) and palladium chloride (50 mg) and hydrogenated for 18 h at 3 atm pressure. The filtered mixture was evaporated, aqueous $NaHCO_3$ added to the residue, and the mixture extracted several times with ether. The dried ($MgSO_4$) extract was evaporated, affording 3-cyano-4-methylpyridine (**15**) (150 mg, 57%). This compound was heated with NaOH (0.2 g) in ethylene glycol (3 mL) at 175 °C in an N_2 atmosphere for 18 h. The cooled reaction mixture was diluted with water, adjusted to pH 4 with HCl, and extracted continuously with ether. The residue obtained on evaporation of the ether extract was sublimed (200 °C, 10^{-4} mm), affording 4-methyl[4-^{14}C]nicotinic acid (65 mg, 37%), mp 219–220 °C (lit.[10] 215–216 °C). Specific activity was 1.31×10^8 dpm/mmol (theoretical activity based on the nominal activity of the starting material: 1.37×10^8 dpm/mmol).

Feeding of 4-Methyl[4-^{14}C]nicotinic Acid and [2-^{3}H]Nicotinic Acid to *Nicotiana tabacum*, and Isolation of the Alkaloids. An aqueous solution (10 mL) of 4-methyl[4-^{14}C]nicotinic acid (15 mg, 0.11 mmol, 1.43×10^7 dpm) and [2-^{3}H]nicotinic acid[4] (13.3 mg, 0.11 mmol, 5.73×10^7 dpm), $^3H/^{14}C = 4.0$, was administered to four 3-month-old (12 in. high) *N. tabacum* plants growing in soil in a greenhouse, by the wick method. After 5 days the plants (fresh weight 550 g) were harvested and maserated with chloroform (2 L) and concentrated NH_3 (200 mL). Filtration yielded two layers. The aqueous layer had an activity (^3H) of 3.42×10^7 dpm and $^3H/^{14}C = 3.6$. The chloroform layer was evaporated in the presence of 2 N HCl. The filtered aqueous solution was made basic with NaOH and extracted with chloroform. Distillation (140 °C, 10^{-3} mm) of this dried ($MgSO_4$) extract afforded a pale yellow oil (146 mg) having an activity (^3H) of 1.87×10^6 dpm (3.3% of the amount of [^{3}H]nicotinic acid fed), $^3H/^{14}C = 5.0$. Some of this oil (50 mg) was mixed with (*RS*)-4-methylnicotine (50 mg) and the mixture subjected to GLC as previously described. The recovered nicotine, assayed as its dipicrate, had a specific activity (^3H) of 4.6×10^5 dpm/mmol and was devoid of ^{14}C. The recovered 4-methylnicotine, characterized and assayed as its dipicrate, was completely inactive (both ^3H and ^{14}C).

Pharmacology of (*RS*)-4-Methylnicotine. (The procedure was carried out by Herbert McKennis, Professor of Pharmacology, Medical College of Virginia, Richmond, Va.) The (*RS*)-4-methylnicotine diperchlorate (5×10^{-4} M) showed no nicotine-like activity when tested on isolated rabbit aortic strips. One easily sees a contractile response to nicotine at 1×10^{-4} M. The 4-methylnicotine (5×10^{-4} M) showed no antagonism to the stimulating effect of norepinephrine (5×10^{-8} M). These results are consistent with those of Haglid,[7] who reported very low pharmacological activity for 4-methylnicotine.

Registry No.—**1,** 51227-28-2; **2,** 65504-55-4; **3,** 65504-56-5; **4,** 65504-58-7; **4** picrate, 65504-59-8; **5,** 55314-29-9; **6,** 65504-63-4; **7,** 65504-64-5; **8,** 65556-02-7; **8** dipicrate, 65556-03-8; **8** diperchlorate, 65556-04-9; **10,** 6280-15-5; **11,** 65504-65-6; **12,** 54-11-5; **13,** 65504-60-1; **14,** 65504-61-2; **15,** 65504-66-7; **16,** 65504-62-3; 4-methylpyridine, 108-89-4; 4-methylpyridine picrate, 4810-81-5; 2-cyanoacetamide, 107-91-5; ethyl [3-^{14}C]acetoacetate, 39169-78-3; [2-^{3}H]nicotinic acid, 65878-88-8; γ-cyano-γ-morpholino-γ-(4-methyl-3-pyridyl)butyronitrile, 65504-57-6.

References and Notes

(1) Part 3 in the series "Aberrant Syntheses in Higher Plants". For Part 2 see ref 2. This investigation was supported by Research Grant GM-13246 from the National Institutes of Health, U.S. Public Health Service, and also by Grant 929 from the Council for Tobacco Research—U.S.A., Inc. Presented in part at the 31st Tobacco Chemists Research Conference, Oct 5–7, 1977, Greensboro, N.C.
(2) E. Leete and M. R. Chedekel, *Phytochemistry*, **11**, 2751 (1972).
(3) Contribution No. 151 from this laboratory.
(4) R. F. Dawson, D. R. Christman, A. D'Adamo, M. L. Solt, and A. P. Wolf, *J. Am. Chem. Soc.*, **82**, 2628 (1960).
(5) R. F. Dawson, D. R. Christman, M. L. Solt, and A. P. Wolf, *Arch. Biochem. Biophys.*, **91**, 144 (1960).
(6) E. Leete, G. B. Bodem, and M. F. Manuel, *Phytochemistry*, **10**, 2687 (1971).
(7) F. Haglid, *Acta Chem. Scand.*, **21**, 329 (1967).
(8) E. Späth and H. Bretschneider, *Chem. Ber.*, **61**, 327 (1928).
(9) F. Haglid, *Acta Pharm. Suec.*, **4**, 117 (1967); see footnote 1.
(10) J. M. Bobbit and D. A. Scola, *J. Org. Chem.*, **25**, 560 (1960).
(11) E. Leete, M. R. Chedekel, and G. B. Bodem, *J. Org. Chem.*, **37**, 4465 (1972).
(12) E. Leete, *J. Am. Chem. Soc.*, **89**, 7081 (1967).
(13) E. Leete, *J. Chem. Soc., Chem. Commun.*, 1091 (1972).
(14) G. W. Kirby, S. R. Massey, and P. Steinreich, *J. Chem. Soc., Perkin Trans. 1*, 1642 (1972).
(15) M. L. Rueppel and H. Rapoport, *J. Am. Chem. Soc.*, **93**, 7021 (1971).
(16) Melting points are corrected. Elemental analyses were performed by Clark

Microanalytical Laboratories, Urbana, Ill. Mass spectra were determined by Dr. Roger Upham and his assistants at the University of Minnesota on an AEI-MS-30 instrument. Optical rotations were determined on a Perkin-Elmer 241 instrument. Radioactivity measurements were carried out on a Nuclear Chicago liquid scintillation Mark II counter, using as solvent dioxane–ethanol with the usual scintillators.[17]

(17) A. R. Friedman and E. Leete, *J. Am. Chem. Soc.*, **85**, 2141 (1963).
(18) The Fourier transform ^{13}C NMR spectra were determined by Dr. Robert M. Riddle at the University of Minnesota on a Varian XL-100 spectrometer (25.2 MHz). Assignments were made by comparison with the ^{13}C NMR spectrum of nicotine[19] and by continuous wave off-resonance decoupling.
(19) E. Leete, *Bioorg. Chem.*, **6**, 273 (1977).
(20) Obtained by the acid hydrolysis of 2-ethoxy-4-methyl-2,3-dihydropyran (Aldrich Chemical Co.) and distilled (bp 80 °C, 100 mm) immediately before use. Its IR (neat) had absorptions at 2740 (CH stretch of CHO) and 1730 cm^{-1} (C=O): K. Adler, H. Betzing, R. Kuth, and H. A. Dortmann, *Justus Liebigs Ann. Chem.*, **620**, 73 (1959).

Synthesis of a "Bridged Nicotine": 1,2,3,5,6,10b-Hexahydropyrido[2,3-*g*]indolizine[1]

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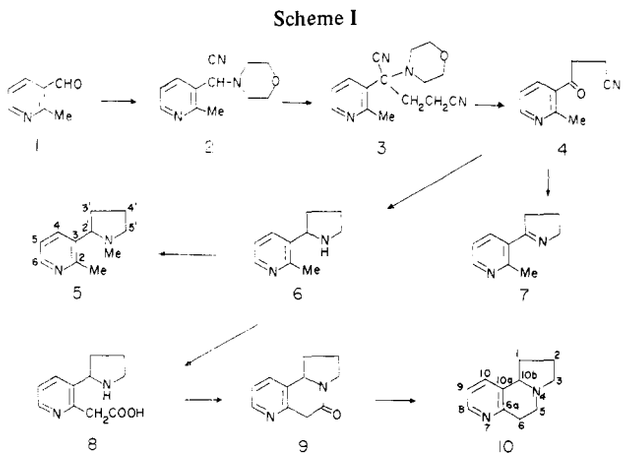
The bridged nicotine **10**, a pyridoindolizidine, has been prepared by reduction of the tricyclic lactam **9**, which was obtained by cyclization of the amino acid **8**. This compound was produced by carboxylation of the dilithium derivative of 2-methylnornicotine, which was synthesized by recently developed methods.

Many analogues of nicotine have been prepared, and their pharmacology has been studied in an effort to obtain structure–activity relationships.[3] Haglid has reviewed[4] this work and stated that it would be of great interest to examine the pharmacology of bridged nicotines, such as the pyridoindolizidine **10**, in which the configuration of the pyrrolidine ring would be fixed relative to the pyridine ring. This article describes the synthesis of compound **10** and also 2-methylnicotine (**5**) by the route illustrated in Scheme I.[5]

2-Methylpyridine-3-aldehyde (**1**) was converted to 2-methylnornicotine (**6**) by the procedure recently developed for the synthesis of myosmine and nornicotine.[7] Reaction of **1** with morpholine and sodium cyanide in the presence of perchloric acid yielded **2**. The anion generated by reaction of **2** with potassium *tert*-butoxide was added to acrylonitrile to yield the Michael addition product **3**. Acid hydrolysis of this compound afforded the keto nitrile **4**.[8] Hydrogenation of this compound in the presence of Raney nickel yielded a mixture of 2-methylmyosmine (**7**) and 2-methylnornicotine (**6**). The yield of the latter increased with the duration of the hydrogenation. Reaction of 2-methylnornicotine with 2 equiv[9] of butyllithium, followed by treatment with carbon dioxide, afforded the carboxylic acid **8**, which was cyclized to the lactam **9**. This reaction was achieved with the aid of 1-ethyl-3(3-dimethylaminopropyl)carbodiimide.[10] However, a better yield of the lactam was obtained by prolonged chloroform extraction of a solution of the amino acid **8** in dilute aqueous hydrochloric acid. Reduction of the lactam with borane in tetrahydrofuran produced the desired bridged nicotine **10** in excellent yield. Reduction of the lactam with lithium aluminum hydride gave only a 30% yield.

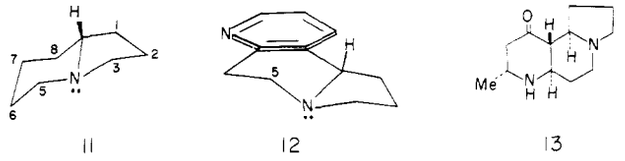
Scheme I



The indolizidine ring system can exist in two configurations, a conversion of the cis to the trans fused ring junction occurring by inversion of the lone electron pair. It is generally agreed that the trans configuration (**11**) is thermodynamically more stable.[11] The infrared spectrum of **10** has Bohlmann bands[12] at 2730, 2675, and 2630 cm^{-1} characteristic of an axial C–H group trans to the lone electron pair on nitrogen. We thus assign the trans configuration to the indolizidine ring system in the bridged nicotine **10**. The (*S*) enantiomer of **10** is illustrated in formula **12**. In nicotine an analogous configuration has been found,[13] i.e., the *N*-methyl group (equivalent to C-5 in the bridged nicotine) is trans to the pyridine ring.

No Bohlmann bands were found in the IR spectrum of the lactam **9**. It is, therefore, suggested that this compound has a *cis*-indolizidine ring junction. Indeed, inspection of a Dreiding model of the lactam indicates a preference for the cis isomer.

The heterocyclic system found in compounds **9** and **10** exists in elaeokanidine A (**13**), one of the alkaloids of *Elaeocarpus*



11 12 13

kaniensis.[14] The pharmacology of 2-methylnicotine and the bridged nicotine **10** is being examined and will be reported elsewhere.

Experimental Section[15]

α-(2-Methyl-3-pyridyl)-α-morpholinoacetonitrile (2). 2-Methylpyridine-3-aldehyde[16] (3.31 g, 27 mmol) was added to a solution of morpholine perchlorate (5.64 g, 30 mmol) in morpholine (35 mL), and the mixture was heated at 76 °C for 1 h under N_2. Sodium cyanide (1.32 g, 27 mmol) in water (2 mL) was added and the mixture was heated at 100 °C for 45 min. The cooled solution was poured into 10% sodium carbonate (100 mL) and extracted with chloroform. The residue obtained on evaporation of the dried (K_2CO_3) extract was triturated with ether to yield **2** (4.82 g, 82%). Crystallization from ether afforded colorless prisms: mp 112.5–113.5 °C; IR (Nujol) ν_{max} 1590, 1580, 1105 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.58 (t, 4 H, NCH_2), 2.65 (s, 3 H, $PyCH_3$), 3.69 (t, 4 H, OCH_2), 4.90 (s, 1 H, α-H), 7.17 (dd, 1 H, 5-PyH), 7.80 (dd, 1 H, 4-PyH), 8.54 (dd, 1 H, 6-PyH); *m/e* 217 (M^+). Anal.

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