on phthalidyl ring), 3.8 (multiplet, 1 methine H on glutaric anhydride ring), 2.2 ppm (multiplet, 4 methylene H's on glutaric anhydride ring). Anal. Calcd for $C_{13}H_{11}NO_5$ (the anhydride of **2**, where R = $CH_2CH_2CO_2H$): C, 59.77; H, 4.24; N, 5.36. Found: C, 59.68, 59.78; H, 4.58, 4.43; N, 5.34, 5.89.

After separation of the above product, the remaining base-soluble, BuOH-extracted, reaction mixture was chomatographed on a silica gel column with a mixture of C_6H_6 and EtOAc (70:30) in order to obtain a fraction that corresponded to 2-ketoglutaric acid (**4**, R = $CH_2CH_2CO_2H$), wt 1.54 g. This was treated with an equal weight of semicarbazide hydrochloride and 2.3 g of NaOAc in hot aqueous EtOH. Crystals of 2-ketoglutaric acid semicarbazone separated on cooling: wt 180 mg; mp 219.5–220.5 °C dec with gas evolution (lit. mp for 2-ketoglutaric acid semicarbazone is 220 °C); IR (Nujol) 3440 (NH stretching), 2500–2700 (bonded carboxyl OH), 1640–1700 (several bands for carboxyl carbonyl, imine, and urea moieties), 1440 and 1255 cm^{-1} (CO stretching). Another fraction of 2-ketoglutaric acid semicarbazone was obtained by treatment of the pH 2.0 BuOH-extracted aqueous solution with 1.0 g of semicarbazide hydrochloride and 1.5 g of NaOAc: wt 62.4 mg; mp 211.5–214.0 °C dec with gas evolution. The total yield of this product was 243 mg (16.6%).

***N*-(3-Phthalidyl)phthalimidine (3) from Phthalimidine and *o*-Formylbenzoic Acid.** A solution of 0.80 g (6 mmol) of phthalimidine,[3] 0.90 g (6 mmol) of *o*-formylbenzoic acid, 1.1 mL (1.15 g, 19.2 mmol) of HOAc, and 10 mL of toluene was heated to reflux for 6 h. A trap was used to collect the water of reaction. A white solid was separated by filtrating: wt approximately 2 g: mp 238.6–242.0 °C. This was suspended in MeOH for a few minutes and the insoluble fraction was collected and dried: wt of **3** was 0.79 g (49.7%); mp 241.5–242.5 °C; IR was identical to that of the product isolated from the transamination experiments.

Registry No.—**2** (R = $CH_2CH_2CO_2H$) anhydride, 65898-29-5; **3**, 65898-30-8; **4** (R = $CH_2CH_2CO_2H$), 328-50-7; **H** (R = $CH_2CH_2CO_2H$) semicarbazone, 2704-31-6; *o*-formylbenzoic acid, 119-67-5; L-alanine, 56-41-7; pyruvic acid phenylhydrazone, 5330-70-1; L-glutamic acid, 56-86-0; phthalimidine, 480-91-1.

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Iminium Salts from α-Amino Acid Decarbonylation. Application to the Synthesis of Berbines[1]

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Received November 21, 1977

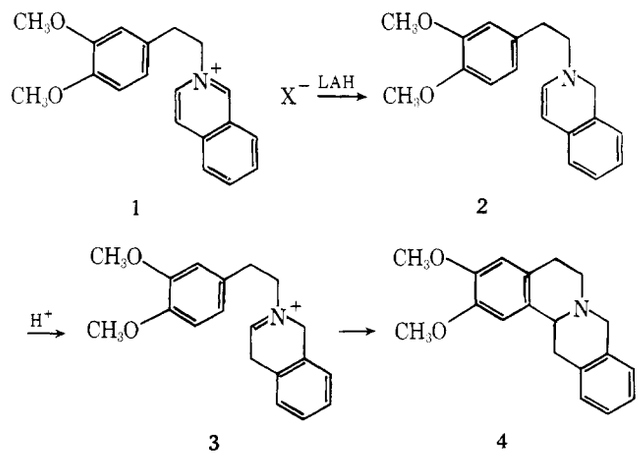
Berbines are synthesized from α-(tertiary amino) acids in high yields through decarbonylation to regiospecific iminium salts followed by an acid-catalyzed cyclization reaction. Syntheses of the α-(tertiary amino) acids from various phenylalanines which involve as the key step alkylation of a 1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid with a 2-phenylethyl bromide are described. The synthesis of isopropyl 1,2,3,4-tetrahydro-7,8-dimethoxy-3-isoquinolinecarboxylate (**15**), obligatory to the synthesis of 9,10-dimethoxyberbines by the above method, is described. It utilizes a metalation to align four contiguous substituents on the aromatic nucleus followed by a difficult selective reduction of an amide α to an ester.

A general, high-yield, regiospecific method for generating iminium salts should have broad applicability to the preparation of nitrogen-containing fused ring systems. One such system is the berbines, a class of naturally occurring and synthetic bases of the isoquinoline alkaloid group. Compounds of this type, such as 2,3-dimethoxyberbine (**4**),[2] have been synthesized via an iminium salt **3** derived from lithium aluminum hydride (LAH) reduction of an isoquinolinium salt **1**, followed by acid treatment of the dihydroisoquinoline **2** (Scheme I).

The overall yields of berbines reported for this process vary from low to moderate (18–66%).[2-4] Three factors may detract from the efficacy of generating the iminium salt by this reductive process. First, though reduction of the isoquinolinium salt with LAH produces the dihydroisoquinoline, this may be slowly reduced itself by LAH to the 1,2,3,4-tetrahydroisoquinoline.[5] Second, the resulting dihydroisoquinoline is subject to dimerization on acid treatment.[6,7] Third, dihydroisoquinolines are reported to disproportionate to a 1,2,3,4-tetrahydroisoquinoline and isoquinoline especially when a C-4 substituent is present.[8,9] In addition this classical process has significant limitations in potential substitution patterns.

We reported recently that iminium salts could be isolated from α-tertiaryamino acids by mild treatment (room temperature or warming in $POCl_3$) in high yields (>90%) and

Scheme I. Synthesis of Berbines via Partial Reduction of Isoquinolinium Salts



importantly regiospecifically by command of the position by the carboxyl substituent.[10] This decarbonylation of an α-tertiaryamino acid would avoid the pitfalls of the previous method. As a test of its effectiveness, we have applied our decarbonylative iminium salt procedure to the synthesis of a variety of berbines. Our process consists in every case of

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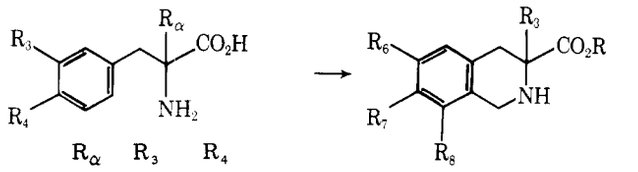
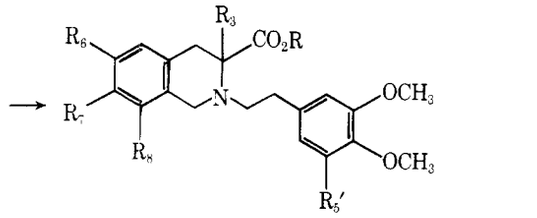
Scheme II. Phenylalanines, Tetrahydro-3-isoquinolinecarboxylates, and *N*-Phenylethylated-α-tertiaryamino Acids Required as Berbine Intermediates



	R_α	R_3	R_4
5	H	H	H
6	H	OMe	OMe
7	Me	OMe	OMe

	R	R_3	R_6	R_7	R_8
8	H	H	H	H	H
9	H	H	OMe	OMe	H
10	H	Me	OMe	OMe	H
11	Me	H	H	H	H
12	*i*-Pr	H	H	H	H
13	Et	H	OMe	OMe	H
14	*i*-Pr	Me	OMe	OMe	H
15	*i*-Pr	H	H	OMe	OMe

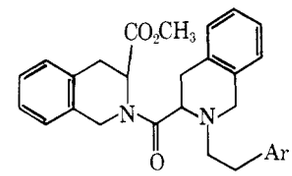


	R	R_3	R_6	R_7	R_8	R_5'
16	*i*-Pr	H	H	H	H	H
17	Et	H	OMe	OMe	H	H
18	*i*-Pr	Me	OMe	OMe	H	H
19	Et	H	OMe	OMe	H	OMe
20	*i*-Pr	H	H	OMe	OMe	H
21	H	H	H	H	H	H
22	H	H	OMe	OMe	H	H
23	H	Me	OMe	OMe	H	H
24	H	H	OMe	OMe	H	OMe
25	H	H	H	OMe	OMe	H

essentially four steps: (1) preparation of a substituted phenylalanine, (2) ring closure to the tetrahydroisoquinoline, (3) *N*-alkylation with a 2-phenylethyl bromide, and (4) decarbonylation followed by cyclization. Steps 1 and 2 are well documented in the literature; however, new procedures have been developed for the high-yield *N*-phenylethylation, for the synthesis of 8-substituted 1,2,3,4-tetrahydroisoquinolines, and primarily for the formation of iminium salts by decarbonylation and subsequent cyclization by electrophilic aromatic substitution.

Synthesis of the α-Tertiaryamino Acids. For a direct evaluation of our method, we considered the synthesis of 2,3-dimethoxyberbine for which the required α-tertiaryamino acid is 2-[2-(3,4-dimethoxyphenyl)ethyl]-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid (**21**). We envisioned this intermediate as being derived from phenylalanine (**5**), which when treated with formaldehyde and concentrated HCl gives 1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid (**8**) as the hydrochloride.[11] *N*-alkylation of the amino acid to produce the *N*-2-phenylethyl derivative completes the process which is summarized in Scheme II.

Alkylation of **8** was attempted reductively with phenylacetaldehyde but self-condensation products of the aldehyde necessitated chromatography to obtain a pure product. A cleaner route was sought through alkylation of the amino methyl ester **11**. Treatment of **11** with a 2-phenylethyl bromide derivative in DMF with potassium carbonate gave a low yield of the alkylated amino ester; however, **26** was a major side product. Its structure served to guide manipulation of factors necessary to avoid its formation. Increasing the steric hindrance at the carbonyl by using the isopropyl ester gave a marked improvement in the ratio of product to side product.



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Independent of the ester, adding benzene as a cosolvent favored product, indicating the transition state for acylation may be more polar than for alkylation. No reaction was observed in benzene alone, however. The bromide was found to give a better result than the *O*-tosylate, and the *O*-trichloro acetate was inert. Concentration of the reactants produced a surprising result. In experiments between 0.2 to 0.4 M in reactants in DMF/benzene, side product was suppressed enough so that even the ethyl ester could be used effectively. Thus it was found that optimum yields (75–88%) could be obtained by alkylating the ethyl or, better, isopropyl esters in DMF/benzene (1:1) at concentrations of 0.2 to 0.4 M using the 2-phenylethyl bromide.

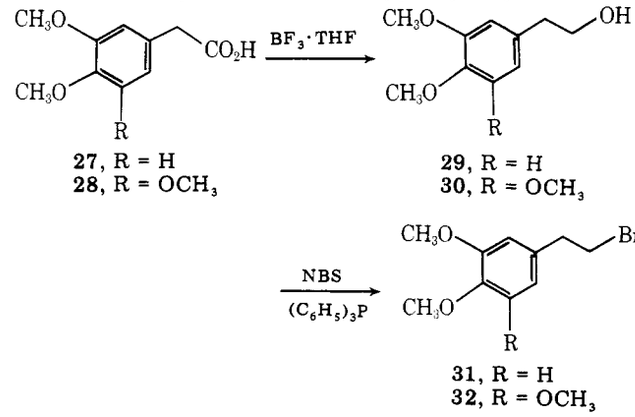
The 2-phenylethyl bromides were obtained from the readily available phenylacetic acids **27** and **28.** The acids were reduced with diborane/tetrahydrofuran to the alcohols **29** (98%) and **30** (94%), and the bromides **31** and **32** were prepared in 94% yield with the *N*-bromosuccinimide/triphenylphosphine reagent (Scheme III). The oxygenation pattern in the 2-phenylethyl bromides determined the substitution pattern in ring A of the berbines.

The isopropyl ester **12,** as well as other isopropyl esters, was prepared using 15% fuming sulfuric acid in *i*-PrOH; **12** was alkylated with 2-(3,4-dimethoxyphenyl)ethyl bromide (**31**) to give α-tertiary amino ester **16** which was hydrolyzed to *N*-phenylethylated isoquinoline carboxylic acid **21.** This process produced **21** in an overall yield of 63% from phenylalanine (**5**) and involves simple isolations.

We thought that this route to berbines could be demonstrated to be quite versatile and effective and accordingly set out to prepare five representative examples **4, 33, 34, 35,** and **36.** The versatility is derived from the ready availability of the required substituted phenylalanines. Thus **4** is derived from phenylalanine (**5**) itself as described, **33** (norcoralydine) requires 3,4-dimethoxyphenylalanine (**6**),[12] **34** requires α-methyl(3,4-dimethoxyphenyl)alanine (**7**),[13] and **35** is derived from **6** also using 2-(3,4,5-trimethoxyphenyl)ethyl bromide (**32**) to alkylate the nitrogen. The overall yields to the α-tertiaryamino acids **22** and **24** are 63 and 65%, respectively, as in the case of **21.** The yields from **14** are lower under the same conditions because hindrance of the α-methyl group retards the *N*-alkylation and subsequent ester hydrolysis; however, starting material is easily recovered.

9,10-Disubstituted Berbines. The Synthesis of Iso-

Scheme III. Preparation of Methoxyphenylethyl Bromides

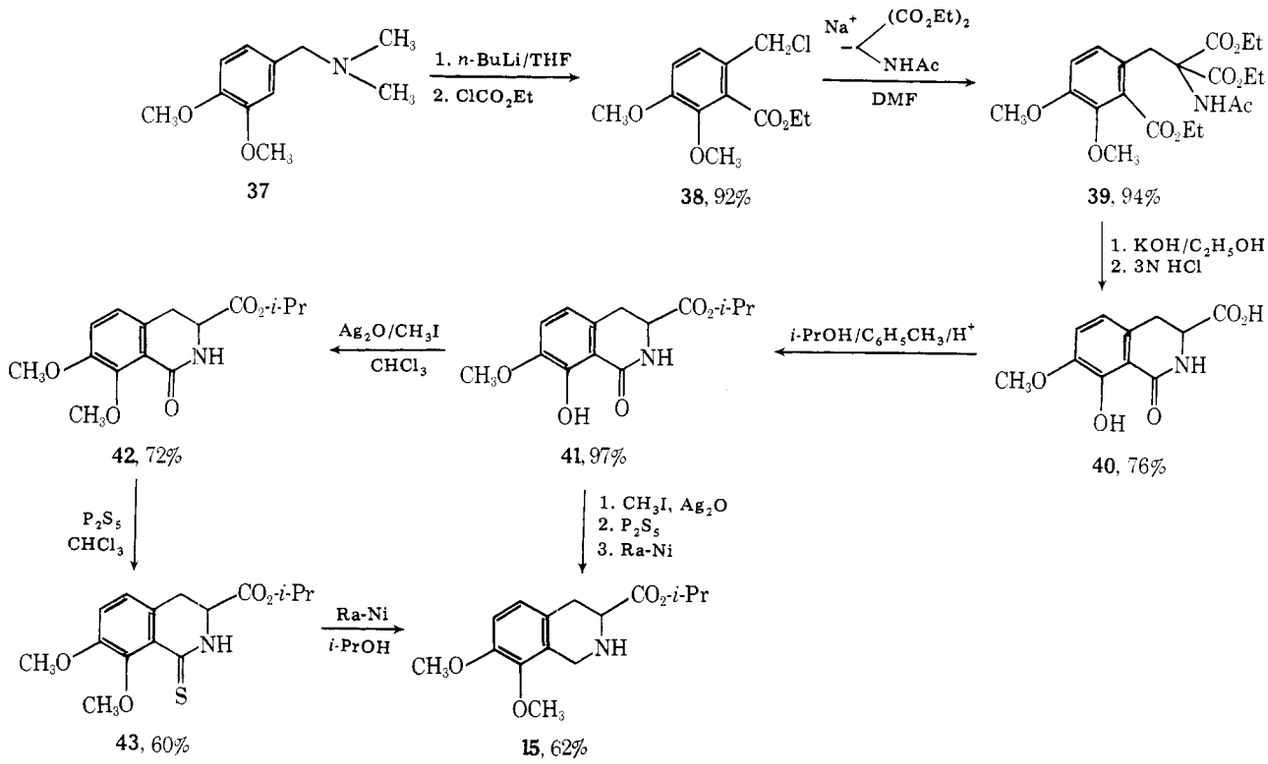


27, R = H
28, R = OCH_3

29, R = H
30, R = OCH_3

31, R = H
32, R = OCH_3

Scheme IV. Synthesis of 1,2,3,4-Tetrahydro-7,8-dimethoxy-3-isoquinolinecarboxylates



propyl 1,2,3,4-Tetrahydro-7,8-dimethoxy-3-isoquinolinecarboxylate (15). Tetrahydropalmatine (**36**) requires an unusual phenylalanine derivative since the natural tendency of the formaldehyde/H^+ type ring closure of (3,4-dimethoxyphenyl)alanine (**6**) is exclusively to the 6,7-substituted isoquinoline **9.** After investigating a number of routes to the 7,8-disubstituted 3-isoquinolinecarboxylate **15** a path was developed utilizing a metalation to align the four substituents on the aromatic ring. There is ample precedent for this procedure.[14] A number of substituents are now known which, when present on an aromatic ring, will direct the metal from an alkyllithium compound into the ortho position either preferentially or exclusively. The substituents giving the most impressive results, in terms of exclusive ortho metalation and high yield, include methyl ethers,[15] *N,N*-dimethylaminomethyls,[16] secondary and tertiary carboxamides,[17-19] secondary and tertiary sulfonamides,[20,21] fluorine,[22] secondary thioamides,[23] and oxazolines.[24] Trifluoromethyl[25] gives a fair yield of preferentially ortho metalation.

We began with the *N,N*-dimethylaminomethyl substituent because it appeared the easiest to subsequently displace after quaternization, and by necessity the other substituent would be a methyl ether. Thus with ortho directing substituents in the 1, 3, and 4 position we expected attack exclusively at C-2. There is good precedent for this also in di- and trisubstituted systems.[25,26] Once committed to this strategy the final ring would be elaborated by selective transformations at the two carbon-containing substituents. The substituent introduced via the lithium could then be a carbon in one of three oxidation states. We reasoned that the alkoxycarbonyl group was a good first choice, being chemically more stable to subsequently envisioned reactions than either a formyl or hydroxymethyl group. Final ring closure would involve a very favorable amide formation.

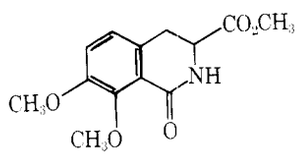
The process is shown in Scheme IV and began with metalation of (3,4-dimethoxyphenylmethyl)-*N,N*-dimethylamine (**37**). Addition of 150 mol % of ethyl chloroformate produced a 1:1 mixture of ethyl 6-(chloromethyl)-2,3-dimethoxybenzoate (**38**) and ethyl 6-(*N,N*-dimethylaminomethyl)-2,3-dimethoxybenzoate. The excess ethyl chloroformate had dealkylated the tertiary amine of the product to displace the benzyl group. This result was quite advantageous since nucleophilic displacement of a benzyl halide is more facile than that of a quaternary benzylamine. The reaction was repeated with 200 mol % of ethyl chloroformate to produce the desired benzyl chloride **38** in 92% yield, which was then treated with diethyl acetamidomalonate anion in DMF to give the substituted phenylalanine **39** in 94% yield.

Alkaline hydrolysis of one or more ester groups gave a more soluble product which was then heated with acid to effect complete amide and ester hydrolysis, decarboxylation, and ring closure to isoquinolone **40.** An *O*-methyl group was lost in the process and it was concluded that the phenolic group was at C-8 based on (1) precedent for the acid cleavage of the more hindered methyl ether;[27] (2) greater polarity on silica of the dimethoxy ester compared to the demethylated ester, suggesting hydrogen bonding of the 8-hydroxy with the 1-oxo substituent; (3) shift of the amide carbonyl from 1665 cm^{-1} in the dimethoxy case (**42**) to 1653 cm^{-1} in the hydroxy, methoxy compound **41,** strongly supporting the presence of a hydrogen bonded amine carbonyl.

Demethylation could be avoided by using only alkaline hydrolysis but yielded only 15% of the desired 1,2,3,4-tetrahydro-7,8-dimethoxy-1-oxo-3-isoquinolinecarboxylic acid (**48**). Under the alkaline conditions the *N*-acetyl was resistant to hydrolysis, possibly because of the sterically crowded environment at the adjacent tetrasubstituted carbon. However, the phenolic hydroxyl was easily and selectively methylated in the isopropyl ester with silver oxide and methyl iodide, yielding crystalline **42.** This methylation is a nearly quantitative reaction, and excess reagents or longer reaction times produced the imidate of **42** as a side product. At this point the remaining transformation for completion of the synthesis of **15** was the removal of the amide carbonyl at C-1.

The literature is surfeit with methods for the reduction of amides, a number purporting to be selective for this function

in the presence of an ester. However, with our amide **42** all methods reported to reduce the amide selectively, save one, produced either no reaction or an unsatisfactory mixture of products. The only method cleanly producing one basic product was conversion to the thioamide followed by Raney nickel desulfurization. Since these methods have broad potential applications, a brief description of our results follows. We attempted the reduction of **44** via the imidate–borohydride procedure.[28] Using trimethyloxonium tetrafluoroborate to prepare **45** followed by treatment with sodium borohydride in methanol, ethanol, or isopropyl alcohol gave only unreacted imidate **45.** Refluxing **45** in ethanol with sodium borohydride reduced the ester and not the imidate, and treatment with sodium cyanoborohydride at pH 4 gave no reaction. Amide **44** with phosphorus pentachloride/chloroform then sodium borohydride/ethanol gave no volatile products. Attempted catalytic hydrogenation of **45** in the presence of methanolic HCl and Pd/C gave no reaction. Treatment of **44** with phosphorus oxychloride followed by hydrogenation over Pd/C gave interestingly the isoquinoline **47** in low yield as the only basic product, whereas **44** with phosphorus oxychloride in the presence of hydrogen and Pd/C gave on isolation, with ethanol present, only imidate **46.** Treatment of the more hindered



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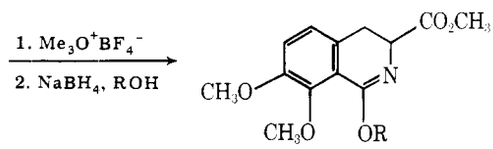
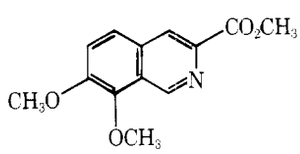


45, R = CH_3
46, R = C_2H_5



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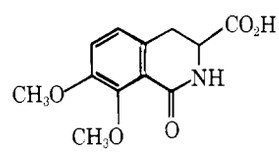

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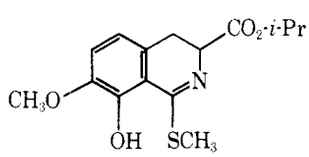

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ester **42** with (a) diborane gave a mixture of basic products, with (b) $POCl_3$, Pd/C, PtO_2, and hydrogen gave a mixture of three basic products in less than 30%, with (c) $NaBH_4$ and acetic acid[29] (1:1) in dioxane with heat gave a trace of material chromatographically similar to the desired product **15,** and (d) $NaBH_4$/acetic acid (1:1) in THF gave 20% of two basic products.

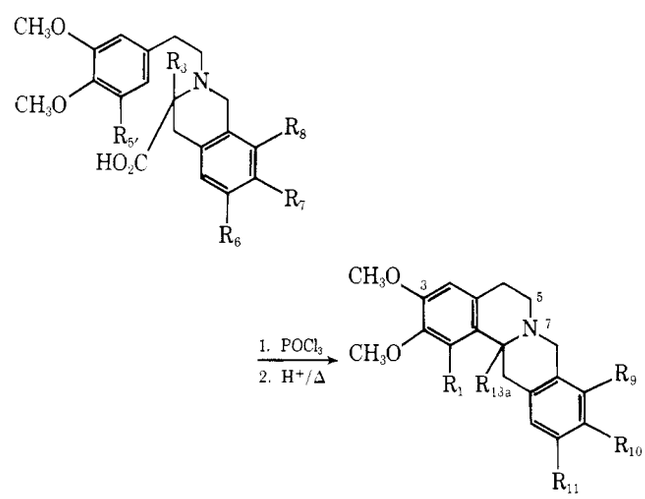
When acid **48** was treated with $NaBH_4$/acetic acid (1:1) in dioxane at reflux for 3 h, 83% of starting material was recovered, in *i*-PrOH at reflux for 3 h, 95% of starting material was recovered, and in Me_2SO at 100 °C for 5.25 h, 83% of starting material was recovered. Treatment of lactam acid **48** with trimethyloxonium tetrafluoroborate in methylene chloride followed by $NaBH_4$ in ethanol, conditions that have been reported to reduce pyroglutamic acid to glutamic acid,[30] gave a poor yield of a three-component mixture, whereas treating phenolic lactam acid **40** in the same manner gave no reaction and phenolic lactam ester **41** gave 38% of the imidate as the only basic product. Heating **48** in sodium cyanoborohydride and acetic acid gave no reaction. Finally, treating **48** with $NaBH_4/CF_3CO_2H$ (1:1) in Me_2SO at 100 °C gave a mixture of starting material and a reaction product which was not an amino acid.

The ability to reduce an amide to an amine in the presence of an ester is synthetically very useful. The problem has been addressed again recently[31] and an additional selective method is reported; however all these methods were ineffective with our substrates. As mentioned previously, we reduced this amide most productively by the classical procedure of converting first to the thioamide and then treating with Raney nickel. The thioamide was formed with P_2S_5 in $CHCl_3$ or THF. Prolonged reaction times or other solvents (dioxane) resulted in the thioamide **43** being converted to its phenolic methyl thioimidate **49,** presumably by methyl transfer from the 8-methoxyl group. Crystalline thioamide **43** could be obtained in 60% after chromatography and the desulfurization was carried out with an active Raney nickel[32,33] in a manner described[34] in 62% yield. Starting with phenolic amide **41** and proceeding through **42** and **43** to **15** without any isolations, the yield for the three transformations is 45%. The overall sequence is simple and produces pure product without complex isolations; it is delineated in Scheme IV. The subsequent alkylation of 15 and hydrolysis to the α-tertiaryamino acid **25** was carried out in the same manner as described above.

Cyclization to the Berbines. With the α-tertiaryamino acids at hand, we were ready to complete the final step of our synthesis of berbines. This consisted in the regiospecific formation of iminium salts by decarbonylation followed by electrophilic cyclization. It is presented in Scheme V for the five variations we synthesized.

Decarbonylation of the α-tertiaryamino acids **21, 22, 23, 24,** and **25** was effected by brief heating in $POCl_3$. Subsequent addition of water followed by warming cyclized the iminium salts to the berbines: **4** (79%), **33** (82%), **34** (65%), **35** (85%), and **36** (90%). Except for **34,** where the 65% yield probably reflects a steric effect, the yields were 79–90% with the overall yields of **4, 33,** and **35** from **5** and **6** greater than 50%. Cyclization of the iminium salt from **24** involved electrophilic attack ortho

Scheme V



	R_1	R_9	R_{10}	R_{11}	R_{13a}
21 → **4**	H	H	H	H	H
22 → **33**	H	H	OCH_3	OCH_3	H
23 → **34**	H	H	OCH_3	OCH_3	CH_3
24 → **35**	OCH_3	H	OCH_3	OCH_3	H
25 → **36**	H	OCH_3	OCH_3	H	H

to a methoxyl group. However, the rate of ring closure relative to that of the iminium salt derived from **22**, which does not have this methoxyl, is 4.6 times faster, indicating the steric effect of the additional methoxyl group is less important on the rate than the added electronic effect.

The cyclization yields, where direct comparison can be made to identical products, are significantly higher when the iminium salt is generated via the decarbonylation method than through the dihydroisoquinoline method. Also, the general availability of α-amino acids, the immediate precursors to the iminium salts, gives this method considerable scope. The fact that the carboxyl group is sacrificed to obtain the iminium salt allows synthetic manipulation with the carboxyl protected as the relatively inert ester function until iminium salt is needed. Also, this method potentially may yield stereospecifically synthesized berbines. Although the asymmetry at the α carbon is lost when iminium salt is formed, the tetrahydroisoquinoline intermediate may bear other chirality which in turn may exert steric influence on the iminium salt cyclization.

Experimental Section[35]

1,2,3,4-Tetrahydro-3-isoquinolinecarboxylic acid hydrochloride (8) was prepared as described[11] in 88% yield, mp 286–290 °C dec (lit.[11] mp 308–309 °C).

1,2,3,4-Tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic Acid Hydrochloride (9). To (3,4-dimethoxyphenyl)alanine[6] (**6**, 10.41 g, 46.3 mmol) was added water (33 mL), concentrated HCl (42 mL) and 37% formaldehyde solution (42 mL, 558 mmol) and the mixture was heated at 97 °C for 20 min. The solvent was evaporated and the residue was dried in vacuo to give 12.52 g (45.7 mmol, 99%) of crude shown to be a single product by GC analysis [derivatization with *N,O*-bis(trimethylsilyl)acetamide]. A sample was recrystallized from ethanol mp 256–258 °C dec (lit.[36] mp 257 °C); however, all subsequent reactions were done using the crude product: IR 1750, 1618 cm^{-1}; NMR (CF_3CO_2H) δ 6.36 (2 H, s), 4.14–3.97 (1 H, c), 4.00–3.87 (6 H, m), 3.54–3.33 (2 H, c), 3.18–2.94 (2 H, c).

1,2,3,4-Tetrahydro-6,7-dimethoxy-3-methyl-3-isoquinolinecarboxylic Acid Hydrochloride (10). α-Methyl-(3,4-dimethoxyphenyl)alanine[13] (**7**, 12.00 g, 50.3 mmol), 37% formaldehyde solution (40 mL, 532 mmol) and 6 N HCl (95 mL) were heated at 100 °C for 35 min. The solvent was evaporated and the residue was dried in vacuo overnight to give 15.23 g; single spot by TLC and single peak by GC [derivatized by *N,O*-bis(trimethylsilyl)acetamide]. This material was used in the next step with no further purification. A sample was recrystallized from isopropyl alcohol: mp 231–233 °C dec; IR 3480, 3340, 2010, 1730, 1620, 1594 cm^{-1}; NMR (CF_3CO_2H) δ 6.93 (2 H, d), 4.87–4.51 (2 H, c), 4.04 (6 H, s), 3.57 (1 H, s), 3.45 (1 H, s), 1.99 (3 H, s). Anal. Calcd for $C_{13}H_{18}ClNO_4 \cdot H_2O$: C, 51.1; H, 6.6; N, 4.6. Found: C, 51.3; H, 6.3; N, 4.6.

Isopropyl 1,2,3,4-Tetrahydro-3-isoquinolinecarboxylate (12). To 1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid hydrochloride (**8**, 15.40 g, 71.6 mmol) in isopropyl alcohol (473 mL) was added 15% fuming sulfuric acid (40 mL, 161 mmol of SO_3) and the mixture was refluxed. After 90 min, benzene (600 mL) was added, and the solution was refluxed through 4A molecular sieves for 15 h. The solvent was evaporated and the residue was treated with 2 N NaOH (500 mL) and crushed ice and extracted with chloroform (200, 100, 50 mL). Drying, evaporating, and distilling to 125 °C (0.08 Torr) gave 14.02 g (64.0 mmol, 89%) of ester: IR 1737, 3350 cm^{-1}; NMR δ 6.94 (4, H, c), 5.02 (1 H, c), 3.94 (2 H, s), 3.65–3.35 (1 H, pr d), 2.95–2.71 (2 H, c), 2.13 (1 H, s), 1.22 (6 H, d).

Ethyl 1,2,3,4-Tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylate (13). To the crude amino acid **9** (7.12 g, 26.0 mmol) was added ethanol (125 mL), the mixture was heated to reflux, and thionyl chloride (4.0 mL, 55.7 mmol) was added dropwise. Reflux was continued for 5 h and the solvent was evaporated; to the residue was added water (150 mL) and 20% Na_2CO_3 solution (50 mL). The mixture was quickly extracted with CH_2Cl_2 (50, 35, 15 mL), the extracts were dried and evaporated, and the crystalline residue was distilled to 145 °C (0.3 Torr) to give 6.31 g (23.9 mmol, 92%) of the ethyl ester **13**: mp 81–84 °C; IR 3350, 1735, 1612 cm^{-1}; NMR δ 6.57 (2 H, d), 4.25 (2 H, q), 4.05 (2 H, d), 3.87 (6 H, s), 3.80–3.59 (1 H, c), 3.04–2.80 (2 H, c), 2.14 (1 H, s), 1.30 (3 H, t); MS *m/e* (rel intensity) 265 (12), 236 (9), 206 (5), 193 (13), 192 (100), 190 (30), 161 (27).

Isopropyl 1,2,3,4-Tetrahydro-6,7-dimethoxy-3-methyl-3-isoquinolinecarboxylate (14). Amino acid **10** (14.02 g, 46.4 mmol), isopropyl alcohol (675 mL), and *p*-toluenesulfonic acid (8.93 g, 47.0 mmol) were refluxed through 4A molecular sieves for 1 day, after which 15% fuming H_2SO_4 (4.5 mL, 16.0 mmol of SO_3) and toluene (50 mL) were added and refluxing continued until no starting acid remained (TLC, 20 days), replacing the sieves periodically. The solvent was evaporated, methylene chloride (100 mL) and saturated sodium carbonate solution (100 mL) were added to the residue, the organic layer was dried and evaporated, and the residue was distilled to 138 °C (0.08 Torr) to give 12.63 g (43.1 mmol, 93%) of the isopropyl ester **14**: mp 57–60 °C; IR 3315, 2845, 1720, 1610 cm^{-1}; NMR δ 6.56 (2 H, d), 5.0 (1 H, m), 4.03 (2 H, s, broad), 3.87 (6 H, d), 3.20 (1 H, d), 2.65 (1 H, d), 2.20 (1 H, s), 1.40 (3 H, s), 1.17 (6 H, t); MS *m/e* (rel intensity) 293 (3), 250 (4), 220 (2), 206 (100).

Isopropyl 1,2,3,4-Tetrahydro-7,8-dimethoxy-3-isoquinolinecarboxylate (15). A. From 41. To **41** (1.37 g, 4.90 mmol) was added $CHCl_3$ (20 mL), Ag_2O (1.35 g, 5.80 mmol), and CH_3I (0.82 mL, 13.6 mmol) and the mixture was shaken at room temperature for 39 h. The catalyst was removed and the solvent was evaporated to leave a residue of 1.44 g (4.90 mmol) to which was added $CHCl_3$ (58 mL) and P_2S_5 (1.44 g, 32.4 mmol of S) and this mixture was heated at reflux for 40 min. After addition of saturated Na_2CO_3 solution (200 mL) and water (50 mL) the $CHCl_3$ layer was separated and the aqueous phase was extracted further with $CHCl_3$ (2 × 20 mL) and then ether (20 mL). The combined organic extracts were washed with saturated NaCl solution (70 mL), dried, and evaporated. Isopropyl alcohol (100 mL) and Raney nickel (8.35 g, W-4) were added to the residue of 1.60 g and the mixture was heated at reflux for 20 min, the catalyst was removed and washed with boiling isopropyl alcohol (4 × 25 mL), the solvent was evaporated, and the residue was distilled to 130 °C (0.03 Torr) to give 614 mg (2.20 mmol, 45%) of isopropyl ester **15**: NMR δ 6.72 (2 H, s), 5.03 (1 H, m), 4.27 (1 H, d, J_{ab} = 16 Hz), 3.87 (1 H, d, J_{ab} = 16 Hz), 3.80 (6 H, d), 3.70–3.44 (1 H, c), 3.00–2.75 (2 H, c), 2.30 (1 H, s), 1.29 (6 H, d); IR 3340, 1739 cm^{-1}. $C_{15}H_{21}NO_4$ requires 279.1470; found 279.1459.

B. From 42. To **42** (2.84 g, 9.70 mmol) was added $CHCl_3$ (100 mL) and P_2S_5 (2.84 g, 64.1 mmol of sulfur), the mixture was heated at reflux for 40 min and then poured into saturated Na_2CO_3 solution (300 mL), and the aqueous phase was extracted with $CHCl_3$ (2 × 25 mL) and then with ether (50 mL). The combined organic extracts were dried and evaporated to give 2.80 g of residue which was dissolved in isopropyl alcohol (150 mL); Raney nickel (7.7 g, W-4) was added and the solution refluxed for 15 min. More Raney nickel (7.7 g, W-4) was added and refluxing was continued for 17 min. The catalyst was removed and washed with boiling isopropyl alcohol (2 × 25 mL), the solvent was evaporated, and the residue was distilled to 130 °C (0.01 Torr) to give 1.22 g (4.36 mmol, 45%) of isopropyl ester **15**.

C. From 43. To **43** (110 mg, 0.356 mmol) was added isopropyl alcohol (5 mL) then Raney nickel (1.1 g, W-4) and the mixture was refluxed for 20 min. The catalyst was removed and washed successfully with isopropyl alcohol (5 mL), $CHCl_3$ (5 mL), and acetone (5 mL), and the filtrates were combined and evaporated to give the isopropyl ester **15** (64 mg, 0.22 mmol, 62%).

Isopropyl 2-[2-(3,4-Dimethoxyphenyl)ethyl]-1,2,3,4-tetrahydro-3-isoquinolinecarboxylate (16). Amino ester **12** (8.054 g, 38.9 mmol) in benzene/DMF (100 ml, 1/1), potassium carbonate (13.8 g, 100 mmol), and 2-(3,4-dimethoxyphenyl)ethyl bromide (11.9 g, 48.6 mmol) were heated at reflux for 21.5 h, the mixture was cooled, and water (250 mL) and ether (150 mL) were added. After separation, the aqueous layer was re-extracted with ether (50 mL), the combined organic phase was washed with water (200 mL) and 0.1 N HCl (70 mL), and the product was then extracted quantitatively from the organic phase with 1 N HCl (3 × 100 mL). These extracts were basified (K_2CO_3) and extracted into ether (150, 50 mL), dried, and evaporated and the residue was distilled at 180 °C (0.06 Torr) to give 12.5 g (32.7 mmol, 84%) of amino ester **16**: IR 1725 cm^{-1}; NMR (CCl_4) δ 7.02 (4 H, s), 6.68 (3 H, s), 4.91 (1, H, c), 3.97 (2 H, c), 3.72 (6 H, s), 3.66 (1 H, s), 3.17–2.67 (6 H, c), 1.12 (3 H, d), 1.06 (3 H, d).

Ethyl 2-[2-(3,4-Dimethoxyphenyl)ethyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylate (17). This was prepared from amino ester **13** in the same manner as described for **16** and distilled to 215 °C (0.08 Torr) to give **17** in 88% yield: mp 100–102 °C; IR 1730, 1615, 1591 cm^{-1}; NMR δ 6.73 (3 H, s), 6.55 (2 H, d), 5.05 (1 H, m), 4.10–3.87 (2 H, c), 3.85 (12 H, s), 3.80–3.51 (1 H, m), 3.10–2.74 (4 H, c), 1.33–1.05 (6 H, c); MS *m/e* (rel intensity) 443 (0.4), 356 (12), 292 (24), 165 (19).

Isopropyl 2-[2-(3,4-Dimethoxyphenyl)ethyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-3-methyl-3-isoquinolinecarboxylate (18). The amino ester **14** (5.86 g, 20 mmol) was alkylated with the ethyl bromide **31** as described for the preparation of **16** but heating for 91.5

h. Distillation to 150 °C (0.04 Torr) gave 2.6 g of recovered **14**; continued distillation to 190 °C (0.09 Torr) gave 4.67 g (10.2 mmol, 76%) of alkylated ester **18**: IR 2850, 1723, 1614, 1590 cm^{-1}; NMR δ 6.72 (3 H, s), 6.50 (2 H, s), 4.94 (1 H, m), 3.92 (2 H, s, broad), 3.80 (12 H, s), 3.05–2.50 (6 H, c), 1.30 (3 H, s), 1.14 (3 H, d), 1.09 (3 H, d); MS *m/e* (rel intensity) 455 (2), 370 (39), 306 (94), 165 (100).

Ethyl 2-[2-(3,4,5-trimethoxyphenyl)ethyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylate (19) was prepared in the manner described for **16** starting with amino ester **13** and the phenylethyl bromide **32**. Distillation at 140–200 °C (0.08 Torr) gave **19** in 80% yield: mp 92–94 °C; IR 2840, 1728, 1610, 1588 cm^{-1}; NMR δ 6.63–6.57 (4 H, c), 4.30–4.07 (3 H, c), 3.84 (15 H, s), 3.78–3.28 (2 H, c), 3.11–2.81 (6 H, c), 1.17 (3 H, t); MS *m/e* (rel intensity) 459 (3), 386 (15), 279 (17), 280 (100), 250 (17).

Isopropyl 2-[2-(3,4-dimethoxyphenyl)ethyl]-1,2,3,4-tetrahydro-7,8-dimethoxy-3-isoquinolinecarboxylate (20) was prepared from amino ester **15** in the manner described for the preparation of **16** and distilled collecting the fraction between 150 and 185 °C (0.05 Torr) to give 1.91 g (4.30 mmol, 75.9%) of **20**: NMR δ 6.72 (5 H, s), 4.94 (1 H, m), 3.99 (2 H, s), 3.81 (12 H, d), 3.71–3.51 (1 H, c), 3.07–2.84 (6 H, c), 1.15 (6 H, d); IR 1728, 1610, 1590 cm^{-1}; MS *m/e* (rel intensity) 443 (2), 292 (100).

2-[2-(3,4-Dimethoxyphenyl)ethyl]-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic Acid (21). Amino ester **16** (12.16 g, 31.8 mmol), 95% ethanol (50 mL), and KOH (3.8 g, 60 mmol) were refluxed for 2 h (hydrolysis complete by GC) after which the solvent was evaporated. To the residue was added water (70 mL), the solution was filtered, and 1 N HCl was added until pH 9. After standing overnight, the solution was acidified with 1 N HCl to pH 4, giving 10.41 g (30.6 mmol, 96%) of acid **21**: mp 131–135 °C dec; mp 157 °C dec after recrystallization from methanol. Anal. Calcd for $C_{20}H_{23}NO_4$: C, 70.4; H, 6.8; N, 4.1. Found: C, 70.1; H, 6.8; N, 4.2.

2-[2-(3,4-Dimethoxyphenyl)ethyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic acid (22) was prepared in 82% yield by hydrolysis of the corresponding ester **17** as described above. A sample was recrystallized from methanol: mp 179–182 °C dec; IR 3520, 1659, 1612 cm^{-1}; NMR (CF_3CO_2H) δ 8.22–7.58 (1 H, br), 6.92 (1 H, br), 4.92–4.36 (3 H, c), 3.95 (12 H, s), 3.86–3.00 (6 H, c). Anal. Calcd for $C_{22}H_{27}NO_6 \cdot {}^1/_4 H_2O$: C, 65.1; H, 6.8; N, 3.5. Found: C, 65.1; H, 6.8; N, 3.6.

2-[2-(3,4-Dimethoxyphenyl)ethyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-3-methyl-3-isoquinolinecarboxylic Acid (23). To amino ester **18** (4.38 g, 9.6 mmol) was added 95% ethanol (50 mL) and KOH (600 mg, 10.8 mmol) and the mixture was refluxed for 72 h. More water (10 mL) and KOH (300 mg, 5.4 mmol) were added and reflux continued for 3 days. The solvent was evaporated, water (50 mL) and ether (50 mL) were added to the residue, and the ether layer was dried and evaporated to give 1.58 g, 3.46 mmol, of recovered starting material. The aqueous layer was adjusted to pH 6.0 with 6 N HCl, and after reducing the volume to 15 mL, it was extracted with chloroform (3 × 15 mL). Drying and evaporating the chloroform gave 2.47 g (5.90 mmol, 97% based on recovered **18**) of acid **23**: mp 189–192 °C dec; IR ($CDCl_3$) 2840, 2580, 2240, 1620, 1513 cm^{-1}; NMR δ 10.28 (1 H, s, br), 6.65 (5 H, s), 4.57 (2 H, s, br), 3.87 (6 H, s), 3.80 (3 H, s), 3.72 (3, H, s), 3.46–2.95 (6 H, c), 1.59 (3 H, s). Anal. Calcd for $C_{23}H_{29}NO_6$: C, 66.5; H, 7.0; N, 3.4. Found: C, 66.2; H, 7.0; N, 3.4.

1,2,3,4-Tetrahydro-6,7-dimethoxy-[2-(3,4,5-trimethoxyphenyl)ethyl]-3-isoquinolinecarboxylic acid (24) was prepared by hydrolysis of ester **19** in the manner described above to give crystalline amino acid **24** in 88% yield: mp 110–112 °C, resolidified at 142 °C, melts again 188–191 °C dec; IR 3430, 1654, 1626, 1587 cm^{-1}; NMR (CF_3CO_2H) δ 7.02–6.72 (4 H, c), 5.05–4.40 (3 H, c), 4.02 (15 H, s), 3.81–3.08 (6 H, c). Anal. Calcd for $C_{23}H_{29}NO_7$: C, 64.0; H, 6.8; N, 3.3. Found: C, 63.8; H, 6.8; N, 3.3.

2-[2-(3,4-Dimethoxyphenyl)ethyl]-1,2,3,4-tetrahydro-7,8-dimethoxy-3-isoquinolinecarboxylic acid (25) was prepared by hydrolysis of **20** and was isolated as described in the preparation of **21**. Crystals which formed slowly over a 16-h period were collected, washed with water (5 mL), and dried to give 1.38 g (3.45 mmol, 84%) of acid **25**: mp 162–164 °C dec; NMR δ 6.77–6.56 (6 H, m), 4.40–4.17 (2 H, d), 3.87–3.57 (1 H, c), 3.76 (12 H, s), 3.24–2.80 (6 H, c); IR 3570, 3450, 1655 cm^{-1}. Anal. Calcd for $C_{22}H_{27}O_6N$: C, 65.8; H, 6.8; N, 3.5. Found: C, 65.6; H, 6.7; N, 3.4.

2-(3,4-Dimethoxyphenyl)ethanol (29). To (3,4-dimethoxyphenyl)acetic acid in THF (30 mL) at 0 °C was added BH_3·THF (99 mL, 1 M in THF, 99 mmol) over 15 min. The mixture was stirred at room temperature for 2 days and then quenched by slowly adding THF/water (1/1, 30 mL) and potassium carbonate (excess, until H_2O layer saturated). The layers were separated, the aqueous layer was extracted with ether (3 × 50 mL), the combined organic extracts were dried and evaporated, and the residue was distilled at 110 °C (0.2 Torr) to give 13.38 g (73.5 mmol, 98%) of alcohol **29**: mp 44–45 °C (lit.[37] mp 44.5–45.0 °C).

2-(3,4,5-Trimethoxyphenyl)ethanol (30). To (3,4,5-trimethoxyphenyl)acetic acid (38.9 g, 0.172 mol) in THF (100 mL) was added BH_3·THF (200 mL, 1 M in THF, 200 mmol) while cooling in an ice bath, over 20 min. The mixture was allowed to stir overnight and excess hydride was destroyed by slowly adding H_2O/THF (100 mL, 1/1) then potassium hydroxide (ca. 25 g, 0.4 mol). Solvent was evaporated, the residue was extracted with ether (3 × 100 mL), and the ether was dried and evaporated. Distillation of the residue at 170 °C (0.25 Torr) gave 34.2 g (0.162 mol, 94%) of alcohol **30**: mp 39–40 °C (previously reported[38] as an oil); IR 3450 cm^{-1}; NMR δ 6.5 (2 H, s), 3.8 (9 H, s), 3.8 (2 H, t), 2.8 (2 H, t), 2.4 (1 H, s). Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.2; H, 7.6. Found: C, 62.1; H, 7.6.

2-(3,4-Dimethoxyphenyl)ethyl Bromide (31). To 2-(3,4-dimethoxyphenyl)ethanol (13.12 g, 72 mmol) dissolved in benzene (70 mL) was added triphenylphosphine (26.3 g, 80 mmol). The mixture was cooled in an ice bath and NBS (13.3 g, 75.0 mmol) was added portionwise such that the internal temperature did not rise above 10 °C. After the addition the ice bath was removed, the mixture was allowed to stir for 1 h, 10% $Na_2S_2O_3$ solution (70 mL) was added, and the two phases were separated. The organic layer was extracted with 1 N NaOH (70 mL) and then water (70 mL), extracting each aqueous layer with ether (20 mL), and the combined organic layers were dried and evaporated. To the residual oil was added ether (125 mL) to precipitate triphenylphosphine oxide, the solution was filtered, and the filtrate was evaporated and distilled to 110 °C (0.1 Torr) to give 16.62 g (67.9 mmol, 94%) of bromide **31**, mp 51–52 °C, on crystallization from ethanol (lit.[39] mp 47–50 °C).

2-(3,4,5-Trimethoxyphenyl)ethyl Bromide (32). To 2-(3,4,5-trimethoxyphenyl)ethanol (**30**) (33.9 g, 160 mmol) in benzene (170 mL) was added triphenylphosphine (42.2 g, 160 mmol), the mixture was cooled to 0 °C, and NBS (28.8 g, 160 mmol) was added portionwise keeping the temperature below 10 °C. The mixture was then allowed to reach room temperature and stirred for 16 h after which it was filtered and washed with 5% $Na_2S_2O_3$ (150 mL), then 0.5 N NaOH (2 × 150 mL), and finally saturated NaCl (150 mL). The benzene was evaporated, ether (250 mL) was added, the precipitated triphenylphosphine oxide was removed after cooling, and the filtrate was passed through an alumina filter. The filtrate was evaporated and the residue distilled to 120 °C (0.2 Torr) (lit.[40] bp 92–96 °C (1 μm)) to give 41.3 g (150 mmol, 94%) of bromide **32**: mp 30–31 °C; MS *m/e* (rel intensity) 276 (61), 274 (61), 261 (24), 259 (25), 195 (31), 181 (100), 179 (28); IR 1587, 1507, 1457, 1418 cm^{-1}; NMR δ 6.4 (2 H, s), 3.9 (9 H, s), 3.7–3.4 (2 H, c), 3.3–2.9 (2 H, c). Anal. Calcd for $C_{11}H_{15}O_3Br$: C, 48.0; H, 5.5. Found: C, 48.2; H, 5.5.

5,8,13,13a-Tetrahydro-2,3-dimethoxy-6*H*-dibenzo[*a,g*]quinolizine; 2,3-Dimethoxyberbine (4). To amino acid **21** (341 mg, 1.0 mmol) was added phosphorus oxychloride (1.0 mL, 10.95 mmol) and the mixture was heated for 2.5 min in a 100 °C bath, with vigorous stirring, then cooled quickly in an ice bath. Through the condensor was added concentrated HCl (10 mL) with vigorous stirring, and the mixture was heated at 50–53 °C for 22 h. The contents of the flask were emptied into a separatory funnel, basified with excess K_2CO_3, and extracted with chloroform (2 × 50 mL). The aqueous layer was dried and evaporated and the dark red residue was dissolved in acetone (5 mL). To this was added concentrated HCl (1.0 mmol) and a white solid precipitated, which was collected, washed with acetone, and dried to give 263 mg (0.793 mmol, 79%) of berbine **4** hydrochloride, mp 236–239 °C dec and mp 238–241 °C after recrystallization from ethanol/ether (lit.[2a] mp 236–238 °C dec).

5,8,13,13a-Tetrahydro-2,3,10,11-tetramethoxy-6*H*-dibenzo[*a,g*]-quinolizine; Norcoralydine (33). A. Isolation as the Hydrochloride. To amino acid **22** (203 mg, 0.505 mmol) was added $POCl_3$ (1.0 mL), the mixture was immersed in a 70 °C bath and stirred vigorously for 9.0 min and then cooled in an ice bath and water (11 mL) added all at once with vigorous stirring. The mixture was then heated at 100 °C for 1 h, the volume was reduced to 2 mL, the mixture was cooled, and the crystals were collected by filtration, washed with ether (2 × 3 mL), and dried to yield 169 mg, mp 132–138 °C, which was a mixture of H_3PO_4 (48%) and HCl (52%) salts. The crystalline solid was sustended in water (50 mL), 6 N HCl (1.0 mL) was added, the mixture was extracted with chloroform (2 × 17 mL), NaCl solution (150 mL) was added, and again the mixture was extracted with chloroform (17 mL). The chloroform extracts were filtered, the filtrate was evaporated, and the residue was dried to give 154 mg (0.394 mmol, 78%) of pure hydrochloride: mp 220–222 °C (lit.[41] mp 220–221 °C); IR 3450, 2530, 1615 cm^{-1}; NMR (CF_3CO_2H) δ 6.97–6.70 (4 H, c), 4.65 (3 H, c, br), 3.98 (12 H, s), 3.81–2.91 (6 H, c).

A portion of the hydrochloride was added to water, basified with 20% Na_2CO_3, and extracted into chloroform. The residue on evaporation was recrystallized from ethanol/water (1:1): mp 146–147 °C (lit.[42] mp 146 °C, α form); NMR ($CDCl_3$) δ 7.26 (1 H, s), 6.76–6.53 (3 H, c), 3.90 (12 H, m), 3.80–2.35 (9 H, c); MS *m/e* (rel intensity) 355 (1).

B. Isolation as the Hydrofluoroborate. After reaction as described above, the water was evaporated and to the residue was added water (30 mL) and 48% hydrofluoroboric acid (0.6 mL), followed by ethanol (5 mL) addition at the boiling point to dissolve all solid. The solution was cooled and the resulting crystals, 185 mg, 0.42 mmol, 82%, melted at 235–238 °C dec after recrystallized from acetone. Anal. Calcd for $C_{21}H_{26}BF_4NO_4$: C, 56.9; H, 5.9; N, 3.2. Found: C, 56.9; H, 5.8; N, 3.2.

5,8,13,13a-Tetrahydro-2,3,10,11-tetramethoxy-13a-methyl-6*H*-dibenzo[*a*,*g*]quinolizine; 2,3,10,11-Tetramethoxyberbine (34). The amino acid **23** (215 mg, 0.51 mmol) and phosphorus oxychloride (1.0 mL, 10.95 mmol) were heated at 73 °C for 5 min then cooled in an ice bath and water was (11 mL) added. The solution was heated at 100 °C for 4 h, cooled, poured into 2 N NaOH (30 mL), and the precipitate collected after 16 h to give 122 mg (0.33 mmol, 65%) of **34**, mp 101–104 °C after recrystallized from acetone/water: IR 1614, 1591 cm^{-1}; NMR (CF_3CO_2H) δ 6.92–6.65 (4 H, c), 4.89 (2 H, s, br), 4.36 (2 H, t), 4.07 (2 H, s, br), 3.99 (6 H, s), 3.92 (3 H, s), 3.70 (3 H, s), 3.18 (2 H, t), 2.40 (3 H, s); MS *m/e* (rel intensity) 371 (4), 370 (27), 269 (100), 354 (13), 231 (22), 218 (96), 203 (23). Anal. Calcd for $C_{22}H_{27}NO_4$: C, 71.5; H, 7.4; N, 3.8. Found: C, 71.3; H, 7.3; N, 3.7.

5,8,13,13a-Tetrahydro-1,2,3,10,11-pentamethoxy-6*H*-dibenzo[*a*,*g*]quinolizine; 1,2,3,10,11-Pentamethoxyberbine (35). A. Isolation as Hydrofluoroborate Salt. To amino acid **24** as the half hydrate (230 mg, 0.522 mmol) was added phosphorus oxychloride (1.0 mL, 11 mmol) and the mixture was heated with vigorous stirring at 70 °C for 7.0 min and then cooled thoroughly in an ice bath before adding water (11 mL). The mixture was then heated at 100 °C for 45 min, diluted to 30 mL with water, and 48% HBF_4 (0.6 mL) was added. A light yellow precipitate formed which was removed and dried to give 46 mg (0.1 mmol) and a second crop of 150 mg (0.32 mmol, total 0.42 mmol, 79%) was obtained by reducing the volume of the mother liquor to 10 mL and cooling: mp 229–232 °C; IR 3180, 1612, 1600, 1588 cm^{-1}; NMR (CF_3CO_2H) δ 6.97 (1 H, s), 6.90 (1 H, s), 6.80 (1 H, s), 5.34–4.95 (1 H, c), 4.77–4.40 (2 H, c), 4.20 (3 H, s), 4.12 (3 H, s), 4.02 (9 H, s), 3.84–3.02 (6 H, c). Anal. Calcd for $C_{22}H_{28}BF_4NO_5$: C, 55.8; H, 6.0; N, 3.0. Found: C, 55.7; H, 6.0; N, 3.0.

B. Isolation as the Free Base. After reaction as above, the mixture was cooled, poured into 1 N NaOH (60 mL) and ice (40 mL), and the precipitate collected by filtration, washed thoroughly with water, and dried. Two additional crops were obtained from the mother liquor; total, 164 mg, 0.43 mmol, 84.5% of **35**: mp 151–152 °C (lit.[43] mp 154–155 °C); IR 3620, 2805, 2760, 1612, 1580 cm^{-1}; NMR δ 6.63 (2 H, d), 6.48 (1 H, s), 3.91 (15 H, m), 3.84–2.40 (9 H, c); MS *m/e* (rel intensity) 385 (6), 220 (18), 164 (100).

5,8,13,13a-Tetrahydro-2,3,9,10-tetramethoxy-6*H*-dibenzo-[*a*,*g*]quinolizine; Tetrahydropalmatine (36). A. Isolation as the Free Base. Amino acid **25** (203 mg, 0.51 mmol) and $POCl_3$ (1.0 mL, 11 mmol) were heated at 70 °C for 10 min and cooled in an ice bath, water (11 mL) was added, and the solution was heated at reflux for 1 h and then poured into 2 N NaOH (30 mL) and ice (30 mL) to give a total of 161 mg (0.45 mmol, 90%) of **36**: mp 145–146 °C from ethanol/H_2O (lit.[44] mp 147 °C); NMR δ 6.90 (2 H, slightly broadened singlet with a small peak downfield at 7.00, J_{ab} = 8 Hz), 6.77 (1 H, s), 6.65 (1 H, s), 3.95 (12 H, c), 3.74–2.52 (9 H, c); MS *m/e* (rel intensity) 356 (19), 355 (81), 354 (46), 353 (18), 324 (16).

B. Isolation as the Hydrochloride. The reaction was performed as described above, omitting the final NaOH and H_2O treatment. Cooling at room temperature for 16 h gave 154 mg (0.39 mmol, 78%) of **36** HCl: mp 227–228 °C dec (lit.[44] mp 215–216 °C) and 206–208 °C after recrystallization from CH_3OH/H_2O; NMR (CF_3CO_2H) δ 7.07 (2 H, s), 6.87 (1 H, s), 6.78 (1 H, s), 5.20–4.35 (3 H, s), 4.00 (12 H, c), 3.87–2.90 (6 H, c); IR 3570, 3450, 3380, 2600, 1612 cm^{-1}. Anal. Calcd for $C_{21}H_{26}ClNO_4$: C, 64.4; H, 6.7; N, 3.6. Found: C, 64.1; H, 6.9; N, 3.5.

Ethyl 6-Chloromethyl-2,3-dimethoxybenzoate (38). To [(3,4-dimethoxyphenyl)methyl]-*N,N*-dimethylamine (**37**)[43] (39 g) in THF (500 mL) cooled in an ice bath was added *n*-butyllithium (121 mL of 1.82 M in hexane, 220 mmol), the mixture was stirred at 0 °C for 1 h and then cooled to −78 °C, $ClCO_2Et$ (45.6 g, 420 mmol) was added all at once, and the mixture was then stirred at room temperature for 12 h. The solvent was evaporated and to the residue was added CH_2Cl_2 (150 mL) then water (100 mL). The aqueous layer was extracted again with CH_2Cl_2 (50 mL) and the combined organic extracts were dried and evaporated and the residue was distilled to 130 °C (0.04 Torr) to give 47.3 g (183 mmol, 92%) of **38**: NMR δ 7.08 (2 H, d, J_{ab} = 8 Hz), 6.85 (2 H, d, J_{ab} = 8 Hz), 4.60 (2 H, s), 4.43 (2 H, q), 3.87 (6 H, d), 1.40 (3 H, t); IR 1728, 1601, 1584 cm^{-1}; MS *m/e* (rel intensity) 260 (11), 259 (5), 258 (32), 212 (100).

Diethyl 1-Acetamido-2-(2-ethoxycarbonyl-3,4-dimethoxyphenyl)-1,1-ethanedicarboxylate (39). To NaH (2.16 g of a 50% dispersion in oil, 45 mmol) washed with hexane (3 × 10 mL) was added DMF (60 mL) followed by diethyl acetamidomalonate (9.76 g, 45 mmol) in portions with stirring. After being stirred for 2.5 h at room temperature the mixture was filtered into ethyl 6-chloromethyl-2,3-dimethoxybenzoate (**38**) (8.38 g, 32.4 mmol) and stirred at room temperature for 14 h, after which the dimethylformamide was evaporated and water (200 mL) was added. Extraction with benzene (100, 50, 50 mL), drying, and evaporating left a residue which was distilled, collecting the fraction between 155–190 °C (0.03 Torr) to give 13.4 g (30.5 mmol, 94%) of **39**: NMR δ 6.93–6.47 (3 H, c), 4.55–4.05 (6 H, c), 3.85 (6 H, s), 3.60 (2 H, s), 2.01 (3 H, s), 1.50–1.10 (9 H, c); IR 3420, 1738, 1672 cm^{-1}; MS *m/e* (rel intensity) 440 (3), 439 (12), 394 (3), 380 (27).

1,2,3,4-Tetrahydro-8-hydroxy-7-methoxy-1-oxo-3-isoquinolinecarboxylic Acid (40). To malonate **39** (2.49 g, 5.7 mmol) in ethanol/H_2O (36.4 mL/3.6 mL) was added KOH (1.3 g, 23 mmol) and the mixture was refluxed for 1.25 h, the solvent was evaporated, and 3 N HCl (140 mL) was added. This mixture was refluxed for 18 h, decolorizing carbon was added, and the solution was filtered hot and allowed to stand for two days to give 1.026 g (4.3 mmol, 76%) of **40**: mp 250–251 °C; NMR (Me_2SO-d_6) δ 8.53–8.40 (1 H, d, br), 6.98 (1 H, d, J_{ab} = 8 Hz), 6.58 (1 H, d, J_{ab} = 8 Hg), 4.37–4.10 (1 H, c), 3.77 (3 H, s), 3.25–3.02 (2 H, c); IR 3250, 1725, 1624 cm^{-1}. Anal. Calcd for $C_{11}H_{11}NO_5$: C, 55.7; H, 4.7; N, 5.9. Found: C, 55.6; H, 4.7; N, 5.9.

Isopropyl 1,2,3,4-Tetrahydro-8-hydroxy-7-methoxy-1-oxo-3-isoquinolinecarboxylate (41). Acid **40** (3.55 g, 15 mmol), isopropyl alcohol (75 mL), and 100% H_2SO_4 (10 drops) were refluxed for 2 h, then toluene was added and the solution was refluxed through 4A molecular sieves for 48 h, replacing the molecular sieves twice. The solvent was evaporated, the residue was dissolved in $CHCl_3$ (100 mL) and washed with 50% saturated $NaHCO_3$ (100 mL), the aqueous phase was backwashed with $CHCl_3$ (20 mL) and the combined organic layers were dried and evaporated to give 4.05 g (14.5 mmol, 97%) of **41**: mp 123–124 °C; NMR δ 12.38 (1 H, s), 6.86 (1 H, d, J_{ab} = 8 Hz), 6.53 (1 H, d, J_{ab} = 8 Hz), 6.50 (1 H, br), 5.07 (1 H, m), 4.47–4.14 (1 H, c), 3.90 (3 H, s), 3.23–3.01 (2 H, c), 1.29 (6 H, d); IR 3280, 1740, 1653 cm^{-1}; MS *m/e* (rel intensity) 280 (1), 279 (24), 192 (67).

Isopropyl 1,2,3,4-Tetrahydro-7,8-dimethoxy-1-oxo-3-isoquinolinecarboxylate (42). Phenolic acid **41** (8.97 g, 32.2 mmol), $CHCl_3$ (200 mL), CH_3I (14.5 g, 102 mmol), and Ag_2O (8.60 g, 37.2 mmol) were shaken at room temperature of 10 h. More CH_3I (7.25 g, 51 mmol) and Ag_2O (4.30 g, 18.6 mmol) were added and shaking was continued at room temperature an additional 17 h. The silver salts were removed, the solvent was evaporated, and the residue was recrystallized (*n*-propylacetate) to give **42** in two crops of 5.42 g (18.5 mmol, 58%), mp 116–117 °C. An additional 1.33 g (4.55 mmol, total yield 72%) was recovered from the mother liquor by column chromatography (silica, 60 g, Et_2O): NMR δ 6.88 (2 H, s), 6.37 (1 H, br), 5.02 (1 H, m), 4.35–3.99 (1 H, c), 3.93 (3 H, s), 3.85 (3 H, s), 3.16–2.91 (2 H, c), 1.22 (6 H, d); IR 3320, 1740, 1665 cm^{-1}; MS *m/e* (rel intensity) 294 (2), 293 (20), 250 (13), 206 (100). Anal. Calcd for $C_{15}H_{19}NO_5$: C, 61.4; H, 6.5; N, 4.8. Found: C, 61.6, H, 6.5; N, 4.7.

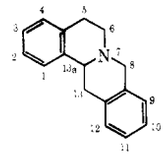
Isopropyl 1,2,3,4-Tetrahydro-7,8-dimethoxy-1-thio-3-isoquinolinecarboxylate (43). To **42** (200 mg, 0.68 mmol) was added THF (6 mL) then P_2S_5 (200 mg, 4.52 mmol sulfur) and the mixture was refluxed for 30 min after which the solvent was evaporated. To the residue was added $CHCl_3$ (20 mL) and 5% Na_2CO_3 solution (20 mL). The aqueous portion was extracted again with $CHCl_3$ (3 × 10 mL). The combined organic extracts were washed with saturated NaCl solution (60 mL), dried, and evaporated, and the residue was chromatographed (silica, 15 g, Et_2O) to give 127 mg (0.412 mmol, 60%) of thiolactam **43**, mp 88–90 °C after recrystallization from ethyl acetate/hexane: NMR δ 8.50 (1 H, br), 6.90 (2 H, s), 5.02 (1 H, m), 4.44–3.97 (1 H, c), 3.95 (3 H, s), 3.87 (3, H, s), 3.30–2.86 (2 H, c), 1.30 (6 H, d); IR 3360, 1737, 1500, 1435, 1247 cm^{-1}; MS *m/e* (rel intensity) 311 (7), 310 (20), 309 (99). Anal. Calcd for $C_{15}H_{27}NO_4S$: C, 58.3; H, 6.2; N, 4.5. Found: C, 58.3; H, 6.2; N, 4.5.

Registry No.—**4** HCl, 3972-88-1; **6**, 55-59-4; **7**, 10128-06-0; **8** HCl, 41994-51-8; **9** HCl, 30740-95-5; **10** HCl, 65495-42-3; **12**, 61212-42-8; **13**, 50290-79-4; **14**, 65495-32-1; **15**, 65495-33-2; **16**, 61212-43-9; **17**, 65495-34-3; **18**, 65495-35-4; **19**, 65495-36-5; **20**, 65495-37-6; **21**, 61212-44-0; **22**, 65495-38-7; **23**, 65495-39-8; **24**, 65495-40-1; **25**,

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,



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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.

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

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Received October 31, 1977

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

0022-3263/78/1943-2122$01.00/0