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Aberrant Biosynthesis of 5-Fluoroanabasine from 5-Fluoro[5,6-^{14}C,$^{13}C_2$]nicotinic Acid, Established by Means of Carbon-13 Nuclear Magnetic Resonance[1]

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5-Fluoro[5,6-^{14}C,$^{13}C_2$]nicotinic acid (prepared from [^{14}C,^{13}C]methyl iodide) was fed to *Nicotiana glauca* plants, resulting in the formation of racemic 5-fluoro[5,6-^{14}C,$^{13}C_2$]anabasine (16.2% absolute incorporation). The specific incorporation of this unnatural precursor was established by examination of the ^{13}C NMR spectrum of the isolated 5-fluoroanabasine, which exhibited satellites due to spin–spin coupling of the contiguous ^{13}C atoms. 5-Fluoroanabasine was prepared from ethyl 5-fluoronicotinate and *N*-(trimethylsilyl)-2-piperidone.

Aberrant biosynthesis is the term which we apply to abnormal synthetic reactions which occur in biological systems. These aberrant reactions can be divided into two classes. We refer to reactions in which a natural compound is formed from an unnatural precursor as Type I. The second class (Type II) involves the conversion of a unnatural precursor to an unnatural compound, presumably utilizing the same enzymes as those involved in the synthesis of a related natural product. An example of the Type I aberrant reaction is the formation of nicotine from δ-*N*-methylornithine (not a normal component of tobacco).[4] In this case a nonspecific enzyme apparently converts this unnatural amino acid to *N*-methylputrescine, which is on the normal biosynthetic route to nicotine. Aberrant reactions of Type II which have been demonstrated in higher plants include the formation of 3′-methylnicotine from 1,3-dimethyl-Δ^1-pyrrolinium chloride,[5] the formation of morphine analogues (e.g., bromomorphine) from codeine analogues in the opium poppy (*Papaver somniferum*),[6] and the formation of analogues of dolichotheline from analogues of its two natural precursors, histamine and isovaleric acid.[7] We have demonstrated the formation of 5-fluoronicotine from 5-fluoronicotinic acid in *Nicotiana tabacum*.[8]

In *Nicotiana glauca* the major alkaloid is anabasine (**4**), and the present article describes the formation of the unnatural 5-fluoroanabasine (**5**) from 5-fluoronicotinic acid. The 5-fluoronicotinic acid was labeled with both ^{14}C and ^{13}C at C-5 and C-6 using previously developed methods.[8,9] The ^{14}C was introduced to facilitate determination of any incorporation into alkaloids by simple radioactive assay. The ^{13}C was introduced at the contiguous carbons, so that the direct incorporation of the 5-fluoronicotinic acid into 5-fluoroanabasine could be demonstrated by examination of its ^{13}C NMR spectrum. The contiguous ^{13}C atoms engage in spin–spin coupling, giving rise to satellites in the ^{13}C NMR spectrum, arranged about the resonances due to singly labeled species. Use of this method of labeling with ^{13}C for biosynthetic experiments was first demonstrated by Seto and co-workers,[10] and many other examples are listed in ref 11.

The ^{13}C NMR spectrum of unenriched 5-fluoronicotinic acid (as its sodium salt in D_2O) is recorded in Table I. The introduction of a fluorine atom at C-5 of nicotinic acid produced the expected shifts for fluorine substitution in an aromatic ring.[12] One- to four-bond ^{19}F–^{13}C couplings were observed, and the values of the coupling constants are in accord with those previously reported for 2-fluoropyridine.[13] The ^{13}C NMR spectrum of the 5-fluoro[5,6-$^{13}C_2$]nicotinic acid is illustrated in Figure 1. The coupling constant between C-5 and C-6 was 72 Hz. Thus, the signal for C-5, already split 254 Hz because of one-bond coupling with fluorine, is now split into two triplets. The central peak in each triplet is due to the presence of 5-fluoro[5-^{13}C]nicotinic acid in the synthetic preparation. Similar satellites are also observed at C-6. The signal for C-4 (natural abundance) is split 70 Hz by a one-bond coupling with C-5, 19.5 Hz by a two-bond coupling with fluorine, and 3.5 Hz by a two-bond coupling with C-6. The ratio of the intensity of the satellite peaks to that of the central singlet peaks at C-5 and C-6 represents the ratio of doubly labeled species to singly labeled species. The observed ratios were in good agreement with the ratios of these species determined by mass spectrometry (see Experimental Section). The satellites are not symmetrically arranged about the central singlet peaks, the observed asymmetry (Table II) being due to an approach to an AB spin system, and is in agreement with theory.[14]

Authentic 5-fluoroanabasine was required for comparison with material which might be isolated from *N. glauca*, and it was prepared by the route illustrated in Scheme I.[15] Ethyl 5-fluoronicotinate (**1**) was condensed with *N*-(trimethylsilyl)-2-piperidone (**2**) in the presence of lithium diisopropylamide to afford, after removal of the trimethylsilyl group with water, 3-(5-fluoronicotinoyl)-2-piperidone (**3**). Hydrolysis of this lactam with 48% hydrobromic acid yielded 5-fluoroanabaseine (**6**), whose hydrochloride was reduced with sodium cyanoborohydride to yield 5-fluoroanabasine. The ^{13}C NMR spectrum of this material is illustrated in Figure 2. The fluorine substituent caused splitting of all of the pyridine

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Table I. Proton Noise-Decoupled ^{13}C NMR Spectra of 5-Fluoroanabasine and Related Compounds (δ_C in ppm from Me_4Si)

carbon no.	nicotinic acid (Na salt in D_2O)[9]	5-fluoronicotinic acid[a] (Na salt in D_2O) δ_C (ppm)	5-fluoronicotinic acid[a] (Na salt in D_2O) J_{CF} (Hz)	anabasine (in $CDCl_3$),[9] δ_C (ppm)	5-fluoroanabasine (5)[b] in $CDCl_3$, δ_C (ppm)	5-fluoroanabasine (5)[b] HCl^c in D_2O, δ_C (ppm)	5-fluoroanabasine (5)[b] J_{CF} (Hz)	5-fluoroanabaseine (6)[d] (in $CDCl_3$) δ_C (ppm)	5-fluoroanabaseine (6)[d] (in $CDCl_3$) J_{CF} (Hz)
2	150.3	146.4	3.9	148.9	144.7	141.6	3.8	145.6	3.9
3	133.5	135.3	3.0	140.9	143.3	133.8	2.5	139.3	3.1
4	138.6	125.1	19.5	134.3	121.1	123.3	19	121.9	19.2
5	124.8	160.4	254	123.6	160.1	158.1	257	162.2	261
6	151.5	139.9	25	148.8	137.0	136.0	27	141.0	23.9
7	173.8	172.4	none						
2′				59.9	59.1	55.8		165.0	
3′				34.9	35.2	27.4		27.5	
4′				24.3	25.2	19.7		19.7	
5′				25.7	25.7	20.4		22.0	
6′				47.7	47.6	44.2		50.9	

[a] Registry no., 2713-44-2. [b] Registry no., 68258-26-4. [c] Registry no., 68317-61-3. [d] Registry no., 68258-27-5.

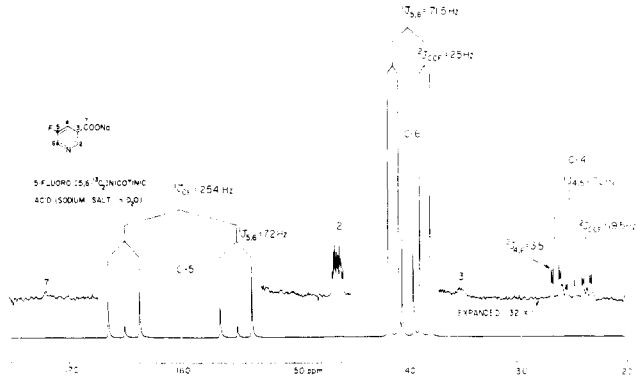
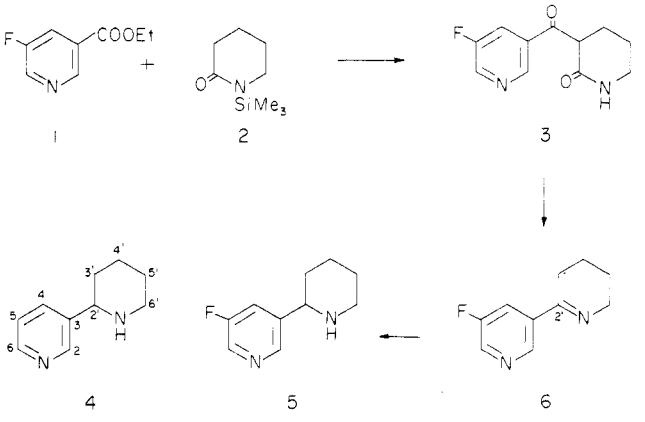


Figure 1. Proton noise-decoupled ^{13}C NMR spectrum of 5-fluoronicotinic acid (68.6% [5,6-$^{13}C_2$], 14.2% [5-^{13}C], and 14.2% [6-^{13}C]).

Scheme I. Synthesis of 5-Fluoroanabasine



carbons. Chemical shifts were assigned by comparison with the spectra of anabasine[9] and 5-fluoronicotinic acid.

The 5-fluoro[5,6-^{14}C,$^{13}C_2$]nicotinic acid was fed to *N. glauca* plants growing in a greenhouse, and also out of doors. This duplicate feeding was carried out because we had previously found that the degree of incorporation of nicotinic acid into the alkaloids of *N. glutinosa* was dramatically different in plants cultivated outside from those growing in a greenhouse;[16] a much higher incorporation was obtained in plants growing in a greenhouse. However, in the present experiments the degree of incorporation of the labeled 5-fluoronicotinic acid into the alkaloids was uniformly high. The chromatographic properties (GLC and TLC) of 5-fluoroanabasine were quite different from anabasine and the other minor alkaloids (nicotine, nornicotine, and anatabine) of *N. glauca*. On TLC plates essentially all of the radioactivity was located at a position coincident with 5-fluoroanabasine. By combining the zones from several plates it was possible to separate labeled 5-fluoroanabasine (3.8 mg) from anabasine (463 mg). Its specific activity (^{14}C) was, as expected, identical with that of the administered 5-fluoronicotinic acid. Its ^{13}C NMR spectrum is illustrated in Figure 3. The enriched carbons C-5 and C-6 had the expected satellites, and their intensities relative to the central singlet peaks were in accord with the direct incorporation of the administered 5-fluoronicotinic acid. The predicted asymmetry of the satellites about the central peaks was also found (Table II).

It was initially surprising to discover that the labeled 5-fluoroanabasine isolated from the *N. glauca* was racemic. However, the anabasine found in *N. glauca* is also racemic, or has very low optical purity. Späth[17] reported that the $[\alpha]_D$ of optically pure anabasine, obtained by resolution, was −92°. In 1935 Smith[18] reported that anabasine isolated from *N. glauca* had $[\alpha]^{20}_D$ −9.1°. However, the methods used for purification of the anabasine were unsophisticated, and the alkaloid could well have been contaminated with small amounts of nicotine, nornicotine, and anatabine, all of which are present in *N. glauca* in a levorotatory form. Samples of anabasine which we have isolated from *N. glauca* over the last 20 years have been checked, and all of them had negligible or very low optical purity. The lack of optical activity in the anabasine from *N. glauca* does not appear to be a result of the method of isolation. When optically active anabasine[19] was subjected to all of the operations involved in the isolation of the alkaloid from *N. glauca*, it was recovered with essentially no change in its optical activity.

Racemic anabasine diperchlorate has a melting point of 155–156 °C.[21] Spenser and co-workers,[22] apparently unaware of the racemic nature of anabasine in *N. glauca*, carried out a dilution of radioactive anabasine, isolated from this species, with (−)-anabasine. The resultant diperchlorate (presumably mainly the (−) isomer) melted at 168–170 °C. We have confirmed that (−)-anabasine diperchlorate has this melting point.

The nicotine isolated from *N. glauca* was optically pure within experimental error. Nornicotine and anatabine were optically active but not optically pure. The production of a racemic natural product (in compounds which lack a facile mechanism for racemization) is uncommon. It may be that the bond formation between the pyridine and piperidine rings of anabasine is not controlled by an enzyme.

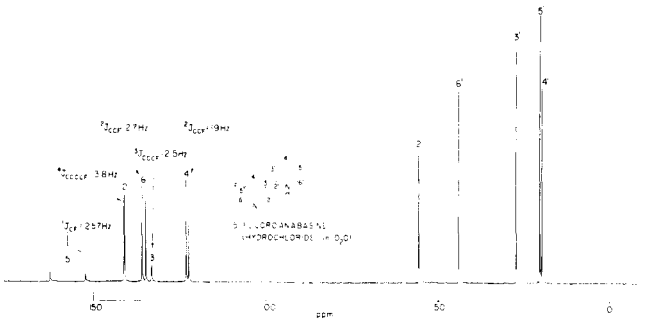


Figure 2. Proton noise-decoupled ^{13}C NMR spectrum of unenriched 5-fluoroanabasine.

Attempts to detect the formation of 5-fluoronicotine in the *N. glauca* were unsuccessful. Since *N. glauca* produces only a very small amount of nicotine (relative to anabasine), this failure could be due to the low levels of activity which might be expected in 5-fluoronicotine.

Experimental Section[23]

3-(5-Fluoronicotinoyl)-2-piperidone (3). *n*-Butyllithium (21 mL of a 2.6 M solution in hexane, 54.4 mmol) was added to a solution of diisopropylamine (5.5 g, 54.4 mmol) in dry ether (50 mL) at −78 °C in an N_2 atmosphere. *N*-(Trimethylsilyl)-2-piperidone[25] (9.3 g, 54.4 mol) was added and the mixture stirred for 15 min at −78 °C. Ethyl 5-fluoronicotinate[8] (4.6 g, 27.2 mmol) dissolved in ether (20 mL) was added, and the reaction mixture was allowed to warm up to room temperature. After 18 h, water (25 mL) was added and the ether layer discarded. The aqueous layer was adjusted to pH 7 with HCl and extracted with chloroform. Evaporation of the dried ($MgSO_4$) extract yielded a semicrystalline residue, which was crystallized from ethyl acetate, affording colorless needles of 3-(5-fluoronicotinoyl)-2-piperidone: 1.65 g, 27%; mp 165–166 °C; IR (KBr pellet) ν_{max} 3250 (NH), 1665 (ketone C=O), 1640 sh (amide C=O) cm^{-1}; MS *m/e* (rel intensity) 222 (M^+, 63), 124 (64), 98 (100), 96 (69). Anal. Calcd for $C_{11}H_{11}FN_2O_2$: C, 59.45; H, 4.99; F, 8.55; N, 12.60. Found: C, 59.47; H, 5.11; F, 8.40; N, 12.83.

5-Fluoroanabaseine (6). The piperidone **3** (0.8 g) was refluxed for 18 h in 48% HBr (20 mL) in an N_2 atmosphere. The solution was evaporated to dryness, and the residue was made basic with 10% NaOH and then extracted with chloroform. The residue obtained on evaporation of the dried ($MgSO_4$) extract was distilled (140 °C, 10^{-3} mm), affording 5-fluoroanabaseine as a colorless oil (0.42 g, 66%) which rapidly became yellow on exposure to air: IR (neat) ν_{max} 1640 cm^{-1} (C=N); UV (95% EtOH) λ_{max} (ϵ) 230 (8900), 275 (5200), with H^+ 229 (7100), 276 (5050) nm; MS *m/e* (rel intensity) 178 (M^+, 100), 163 (29), 149 (59), 122 (47), 96 (15). It formed a monopicrate, mp 163–164 °C. Anal. Calcd for $C_{16}H_{14}FN_5O_7$: C, 47.17; H, 3.46; N, 17.19. Found: C, 47.11; H, 3.69; N, 17.49.

5-Fluoroanabasine (5). 5-Fluoroanabaseine (0.4 g) was dissolved in methanol (10 mL) containing HCl (0.1 g) and stirred at room temperature with sodium cyanoborohydride (0.4 g) for 18 h. The solution was then made strongly acidic with HCl and evaporated to dryness. The residue was made basic with NaOH and extracted with methylene chloride. The residue obtained on evaporation of the dried ($MgSO_4$) extract was distilled (140 °C, 10^{-3} mm), affording colorless crystals of (*RS*)-5-fluoroanabasine (0.37 g), mp 65–66 °C. Gas chromatography (in a Varian Aerograph 90AP instrument), on an 8 ft × 1/8 in. column containing 10% 20M Carbowax, 70–80 mesh, with a He flow rate of 60 mL/min at 180 °C, of this compound and related tobacco alkaloids afforded the following retention times (min): 5-fluoronicotine (2.6), nicotine (3.6), 5-fluoroanabasine (6.1), anabasine (8.1), and nornicotine (9.6). TLC on silica gel PF 254 (Merck) developing with a mixture of chloroform, methanol, and concentrated NH_3 (100:10:1) afforded the following R_f values (color with *p*-aminobenzoic acid and CNBr): nicotine, 0.82 (brown); 5-fluoroanabasine, 0.72 (purple); anatabine, 0.56 (pink); anabasine, 0.50 (brown); and nornicotine, 0.21 (pink). IR (neat) ν_{max} 3310 (NH), 1600, 1580 (pyridine C=N) cm^{-1}; UV (95% EtOH) λ_{max} (ϵ) 266 (4160), 274 sh (3470) nm; unlike nicotine and anabasine, there was little change in the spectra on addition of HCl; ^1H NMR ($CDCl_3$) δ 8.40 (t, 1 H, 2-Py H), 8.32 (d, 1 H, 6-Py H), 7.45 (dt, 1 H, 4-Py H), 3.68 (d, 1 H, 2′), 3.11 (dd, 2 H, 6′), 1.87 (s, 1 H, NH), 1.76–1.30 (complex multiplet, 6 H, 3′, 4′, 5′); MS *m/e* (rel intensity) 180 (M^+, 34), 151 (44), 137 (31), 123 (48), 84 (100). Anal. Calcd for $C_{10}H_{13}FN_2$: C, 66.64; H, 7.27; F, 10.54; N, 15.55. Found: C, 66.39; H, 7.59; F, 10.26; N, 15.66. It afforded a dipicrate, mp 180–181 °C (from EtOH). Anal. Calcd for $C_{22}H_{19}FN_8O_{14}$: C, 41.39; H, 3.00; F, 2.98; N, 17.55. Found: C, 41.60; H, 3.08; F, 2.88; N, 17.51.

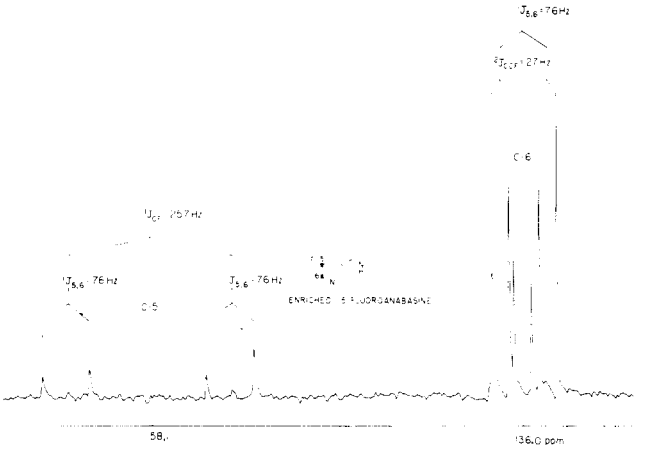


Figure 3. Proton noise-decoupled ^{13}C NMR spectrum of enriched (at C-5 and C-6) 5-fluoroanabasine.

Table II. Coupling Constants and Related Data for the Enriched 5-Fluoronicotinic Acid and 5-Fluoroanabasine

	5-fluoro[5,6-$^{13}C_2$]nicotinic acid (Na salt in D_2O)[e]	5-fluoro[5,6-$^{13}C_2$]anabasine (HCl in D_2O)[f]
V_{AB},[a] Hz	517	557
J_{AB}, Hz	71.7[b]	76.1[b]
distance between central peaks and satellites,[c] Hz	C-5: +37.9, −33.7 C-6: +32.5, −38.8	+40.5, −35.5 +35.0, −41.2
theoretical distance between inner satellite and central peak,[d] Hz	33.3	35.5

[a] Difference in the chemical shifts between the coupled carbons. [b] Average value. [c] Positive downfield, negative upfield. [d] Calculated with the formula: inner satellite distance = $1/2(V_{AB} + J_{AB} - \sqrt{V_{AB}^2 + J_{AB}^2})$. [e] Registry no., 68258-28-6. [f] Registry no., 68258-29-7.

5-Fluoro[5,6-^{14}C,$^{13}C_2$]nicotinic Acid. This was prepared by the method previously described[8] for the synthesis of 5-fluoro[5,6-^{14}C]-nicotinic acid from 3-nitro[2,3-^{14}C]quinoline. 3-Nitro-[2,3-^{14}C,$^{13}C_2$]quinoline was prepared from a mixture of [^{14}C]methyl iodide (Amersham-Searle) and [^{13}C]methyl iodide (90% ^{13}C)[26] as previously described.[9] Mass spectrometry on the product indicated the following composition: 68.6% $^{13}C_2$, 28.4% $^{13}C_1$, and 3.0% $^{13}C_0$. Thus, the ratio of $^{13}C_2/^{13}C_1$ on each enriched carbon is 4.8. Its ^{13}C NMR spectrum is illustrated in Figure 1. The ratio of the intensities of the satellite peaks to the central peaks was determined by expanding the spectra and then cutting out and weighing the peaks. The following values were obtained: C-5, 4.8; and C-6, 4.6.

Administration of 5-Fluoro[5,6-^{14}C,$^{13}C_2$]nicotinic Acid to *Nicotiana glauca* and Isolation of the Alkaloids. 5-Fluoro[5,6-^{14}C,$^{13}C_2$]nicotinic acid (18.2 mg, 5.32×10^7 dpm, 4.18×10^8 dpm/mmol) dissolved in water, containing a drop of ammonia, was fed to 11 3-month old *N. glauca* plants growing in a greenhouse by the wick method. After 14 days, the plants were harvested (fresh wt, 1600 g) and extracted as previously described.[16] The aqueous ammoniacal layer had an activity of 2.1×10^7 dpm (39.5% of the activity fed). The crude alkaloids (617 mg), having an activity of 1.11×10^7 dpm (20.9% absolute incorporation), were separated both by GLC and TLC using the conditions described under the synthesis of 5-fluoroanabasine. Essentially all (95%) of the activity on a TLC plate was at a position coincident with authentic 5-fluoroanabasine. Many preparative TLC plates were run, and the zones corresponding to 5-fluoroanabasine were combined, extracted with methanol, and rechromatographed, affording pure 5-fluoroanabasine (3.8 mg, amount determined by UV spectroscopy) having an activity of 4.16×10^8 dpm/mmol. Some of this material (1.3 mg) was dissolved in D_2O (0.4 mL) containing HCl

for determination of its ^{13}C NMR spectrum, $[\alpha]^{25}_D$ 0.0 ± 1° (c 0.1, 95% EtOH). Other alkaloids were isolated: anabasine (463 mg), 1.61 × 10^4 dpm/mmol, $[\alpha]^{25}_D$ −0.3 ± 0.4° (c 4.3, $CHCl_3$); nicotine (1.5 mg), 1.3 × 10^3 dpm/mmol, $[\alpha]^{25}_D$ −102 ± 2° (75% MeOH);[27] nornicotine (8.5 mg), 1.8 × 10^4 dpm/mmol, $[\alpha]^{25}_D$ −51°[28] (c 0.4, $CHCl_3$); and anatabine (2.8 mg), 5.3 × 10^3 dpm/mmol, $[\alpha]^{25}_D$ −43° (95% EtOH).

That part of the TLC plate where 5-fluoronicotine would be expected to occur was extracted with methanol and diluted with inactive 5-fluoronicotine, which was then reisolated and crystallized as its perchlorate and dipicrate. The amount of activity in these derivatives was not significant.

N. glauca plants growing out of doors (July) were also fed 5-fluoro[5,6-^{14}C,$^{13}C_2$]nicotinic acid (18.2 mg, 5.32 × 10^7 dpm/mmol). The plants were harvested after 14 days. The distribution of activity in the various fractions from the plant was essentially the same as that found in plants cultivated in a greenhouse: crude alkaloids, 9.75 × 10^6 dpm; aqueous ammoniacal layer, 1.71 × 10^7 dpm.

Registry No.—**1**, 22620-29-7; **2**, 3553-93-3; **3**, 68258-30-0; **5** dipicrate, 68258-31-1; **6**, monopicrate, 68258-32-2; 5-fluoro[5-^{13}C,6-^{14}C]nicotinic acid, 68258-33-3; 5-fluoro[5-^{14}C,6-^{13}C]nicotinic acid, 68317-60-2; 5-fluoro[5,6-$^{14}C_2$]nicotinic acid, 35286-42-1; (±)-5-fluoro[5-^{13}C,6-^{14}C]anabasine, 68258-34-4; (±)-5-fluoro[5-^{14}C,6-^{13}C]-anabasine, 68258-35-5; (±)-5-fluoro[5,6-$^{14}C_2$]anabasine, 68258-36-6.

References and Notes

(1) Part 4 in the series, "Aberrant Syntheses in Higher Plants". For Part 3, 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—USA, Inc. Presented in part at the 31st Tobacco Chemists Research Conference, Oct 5–7, 1977, Greensboro, N.C.
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(19) Anabasine purchased from the Aldrich Chemical Co. had $[\alpha]^{25}_D$ −51°. This company no longer sells anabasine, and they are unable to determine the source of the material they previously provided. It is possible that it was obtained from the USSR, where it is extracted from *Anabasis aphylla* and used as an insecticide. Anabasine from this source has $[\alpha]_D$ −52 to −83°.[20]
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(23) Melting points were determined in capillary tubes and are corrected. Elemental analyses were performed by Clark, Means and Perkins Microanalytical Laboratories, Urbana, Ill. ^{13}C NMR spectra were determined by Dr. Robert M. Riddle at the University of Minnesota on a Varian XL-100-15 spectrometer operating at 25.2 MHz, equipped with a VFT Fourier transform accessory. ^1H NMR spectra were determined on a Varian HFT-80 spectrometer. 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 in a Nuclear Chicago Mark II liquid scintillation counter, using as solvents dioxane–water or dioxane–ethanol with the usual scintillators.[24]
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(26) The author wishes to thank the Stable Isotope Resource (SIR) at the Los Alamos Scientific Laboratory (supported by NIH Grant RR-00962) for supplying the [^{13}C]methyl iodide.
(27) The following specific rotations (determined at 25 °C) were obtained for optically pure nicotine (c 4) in the indicated solvents: −169 (neat), −167 ($CHCl_3$), −127 (MeOH), −104 (75% MeOH and 25% H_2O, by volume), and −94° (50% MeOH).
(28) This represents a 56% optical purity.

Synthesis of 9-Deoxy-11-oxoprostaglandins. Selective Reduction of an 11,15-Dione[1]

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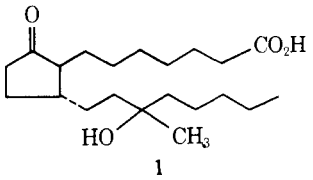
Prostaglandins containing an oxygen function at C-9 but not at C-11 have been reported to show a separation of biological activity. This prompted the synthesis of a 9-deoxy-11-oxoprostaglandin for evaluation. In this synthesis, which began with 4,7-dioxo-7-(*p*-methoxyphenyl)heptanoic acid (**5**), the 20 carbon atoms were assembled to afford a mixture of acyclic compounds, **17** and **18**. The five-membered ring of the prostaglandin system was obtained by coupling C-8 to C-12. The resultant 11,15-dioxoprostanoid **19** possesses an asymmetric center at C-4. Reduction by the Meerwein–Ponndorf–Verley procedure proceeded regioselectively but not stereoselectively at C-15.

The prostaglandins are extremely potent substances, and they display an extensive range of biological activities. Although they are flexible molecules, some have preferred conformations in solution as well as in the solid state.[2-6] The prostaglandins are usually unstable oils or low-melting solids. Hopes have been entertained that through structural modification stability can be imparted to them and a separation of biological activity can be achieved.

Beginning in the late 1960's Bagli et al.[7-9] reported the synthesis of several 9-oxygenated 15-hydroxyprostanoic acids (e.g., 1) without an oxygen function at C-11. A significant



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dissociation of activity was achieved with these compounds. Since the primary natural prostaglandins are oxygenated at both C-11 and -9, conceivably a similarly interesting separation of activity could be found in prostaglandins bearing an

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