trile in 0.01 M Na_2ETDA solvent at pH 7.8 (flow rate 2 mL/min) and the major component was found to be identical to isochelocardin according to retention volume (26 mL). The major component could not be isolated in pure enough form for full characterization.

Acknowledgment. We thank G. Nettleship for recording ^1H NMR spectra and LC analyses, Sandra L. Mueller and Ruth S. Stanaszek of Abbott Laboratories, North Chicago, for recording the mass spectra and ^{13}C NMR spectra, respectively, and the staff of the microanalytical department of Abbott Laboratories for the elemental analyses.

Registry No.—**1**, 29144-42-1; 1 HCl, 56433-46-6; **2**, 66290-79-7; **2** HCl, 66290-80-0; **3**, 66290-81-1; **4**, 65805-84-7; **9**, 66290-82-2; **10**, 66290-83-3; acethydrazone, 1068-57-1.

References and Notes

(1) For Part II, see D. T. W. Chu, S. N. Huckin, and E. Bernstein, *Can. J. Chem.*, **55**, 3341 (1977).
(2) T. J. Oliver, J. F. Prokop, R. R. Bower, and R. H. Otto, *Antimicrob. Agents Chemother*, 583 (1962).
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(4) L. A. Mitscher, J. V. Juvarkar, W. Rosenbrook, Jr., W. W. Andres, J. Schenck, and R. S. Egan, *J. Am. Chem. Soc.*, **92**, 6070 (1970); L. A. Mitscher, W. Rosenbrook, Jr., W. W. Andres, R. S. Egan, J. Schenck, and J. V. Juvarkar, *Antimicrob. Agents Chemother.*, 38 (1970).
(5) D. L. Garmaise, D. T. W. Chu, E. Bernstein, and M. Inaba, manuscript in preparation.
(6) D. T. W. Chu, D. L. Garmaise, and E. Bernstein, *Can. J. Chem.*, **53**, 1434 (1975).
(7) R. S. Egan, R. S. Stanaszek, E. Bernstein, D. T. W. Chu, and S. N. Huckin, manuscript in preparation.
(8) In this paper structures are given as tautomer (I) for simplicity but an equilibrium with the other tautomeric forms II and III is not excluded.
(9) It has been observed[4] that the ^1H NMR spectra of chelocardin and its derivatives (other than 4-*N*-acyl derivatives) are poorly resolved.

Synthesis and Mass Spectrometry of Some Structurally Related Nicotinoids

David F. Glenn*[1a] and William B. Edwards III*[1b]

Philip Morris, Inc., Research Center, P. O. Box 26583, Richmond, Virginia 23261

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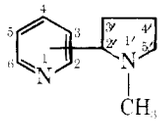
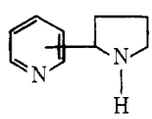
The synthesis and mass spectrometry of a group of structurally related nicotinoids (**1a–c–6a–c**) have been investigated. A detailed discussion is presented of their complex electron-induced fragmentation mechanisms, established with the aid of 27 site-labeled deuterium analogues, high-resolution measurements, and metastable ion studies.

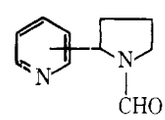
Substantial interest in the minor tobacco alkaloids, their mammalian metabolites, and the physiological effects of nicotine has been noted in the recent literature.[2–4] Further, the widespread occurrence of nicotine-like compounds in nature,[5,6] as well as the expanding interest in the trace components of tobacco and tobacco smoke,[7] have led us to undertake an investigation of the preparation and spectral properties of a group of structurally related nicotinoids (**1a–c–6a–c**). The



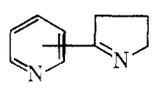
1a–c



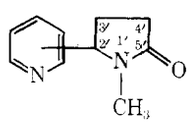
2a–c



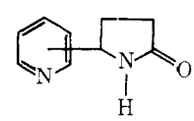
3a–c



4a–c



5a–c



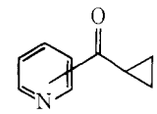
6a–c

a = 2-pyridyl; b = 3-pyridyl; c = 4-pyridyl

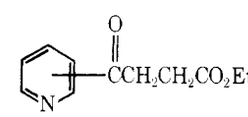
results of our synthetic and mass spectrometric studies are reported here.

Synthesis.[8] Despite the extensive studies[2–6,9–11] reported on the *Nicotiana* alkaloids (**1b–4b**), their metabolites (**5b** and **6b**), and a host of analogues, only a limited amount of diffuse work has been carried out on the isomeric nicotinoids (**1a,c–6a,c**).[12] It therefore seemed appropriate to investigate the applicability of newer methods of alkaloid synthesis to the preparation of this cohesive group of structurally related, isomeric nicotinoids.

The reaction of cyclopropyl 3-pyridyl ketone (**7b**) with formamide has been shown to give 3-nornicotine[13] (**2b**; via acid



7a–c



8a–c

a = 2-pyridyl; b = 3-pyridyl; c = 4-pyridyl

hydrolysis of *N'*-formyl-3-nornicotine (**3b**), generated in situ). This method was chosen as a route to the nornicotines (**2a** and **2c**) and the *N'*-formylnornicotines (**3a–c**). After having first established that **3b** could be isolated from the reaction of **7b** with formamide, the synthesis was used to prepare 2- and 4-nornicotine (**2a** and **2c**) and *N'*-formyl-2- and *N'*-formyl-4-nornicotine (**3a** and **3c**) from the appropriate cyclopropyl pyridyl ketone (**7a,c**).

The cotinines (**5a** and **5c**) were prepared by treatment of the pyridoylpropionates (**8a** and **8c**) with *N*-methylformamide using an altered version of Sugasawa's method.[14] The prerequisite α-keto esters were obtained from the reaction of ethyl acrylate with 2- and 4-pyridinecarboxaldehyde,[15] a method which was found preferable to the published procedure.[16]

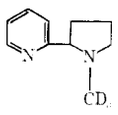
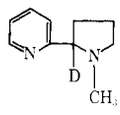
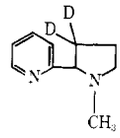
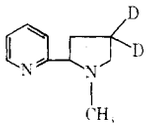
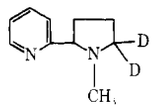
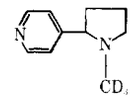
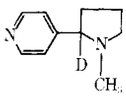
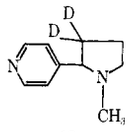
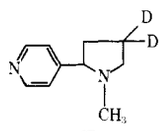
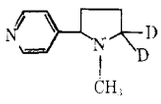
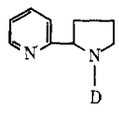
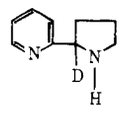
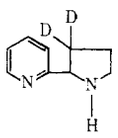
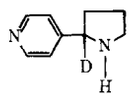
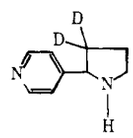
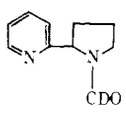
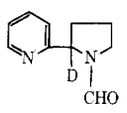
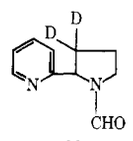
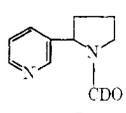
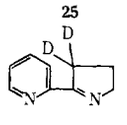
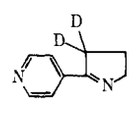
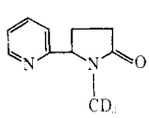
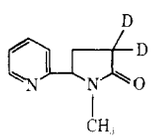
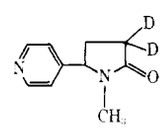
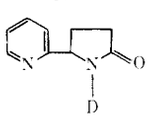
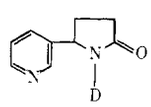
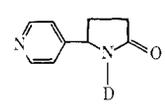
Attempts to apply the cotinine synthesis to the preparation of the norcotinines (**6a** and **6c**) by substituting formamide for *N*-methylformamide were unsuccessful. However, **6a** and **6c** could be obtained by reaction of the appropriate α-keto ester (**8a** or **8c**) with NH_4Cl and $NaBH_3CN$.

During the course of our study, Hu[18] reported an excellent improvement of Späth's original 3-myosmine (**4b**) synthesis.[19] This method,[18] with some modification, was used to prepare the myosmines (**4a–c**).

The synthesis of the deuterated nicotinoids (Table I), necessary for both this and NMR studies,[20] proved facile ex-

0022-3263/78/1943-2860$01.00/0

Table I. Deuterated Analogues

Compd[a]	Isotopic purity[b]	Compd[a]	Isotopic purity[b]	Compd[a]	Isotopic purity[b]
 9	97% d_3	 10	90% d_1	 11	87% d_2 12% d_1
 12	94% d_2 5% d_1	 13	95% d_2 5% d_1	 14	90% d_3
 15	86% d_1	 16	89% d_2 10% d_1	 17	85% d_2 12% d_1
 18	95% d_2 5% d_1	 19	97% d_1	 20	91% d_1
 21	88% d_2 9% d_1	 22	89% d_1	 23	88% d_2 10% d_1
 24	90% d_1	 25	93% d_1	 26	83% d_2 14% d_1
 27	84% d_1	 28	89% d_2 10% d_1	 29	88% d_2 11% d_1
 30	98% d_3	 31	97% d_2 2% d_1	 32	81% d_2 17% d_1
 33	92% d_1	 34	94% d_1	 35	95% d_1

[a] The structure and site of labeling were validated by comparison of their ^{1}H NMR and mass spectra with those of authentic nondeuterated compounds. The site of labeling was further confirmed by ^{2}H NMR spectroscopy (**9–18** and **20–32**). [b] Determined by mass spectral analysis (**9–35**) and confirmed by ^{1}H NMR spectroscopy (**9–18** and **20–32**).

cept in a few cases. The 2-cotinine-*4′,4′-d*$_2$ (**31**) was synthesized by deuterium exchange of the 4′ protons of **5a** by an established procedure.[21] This method (D_2O and K_2CO_3 at 101 °C for 12 days) could not be used to synthesize 4-cotinine-*4′,4′-d*$_2$ (**32** from **5c**) because it also caused exchange of the 2′ proton, giving 4-cotinine-*2′,4′,4′-d*$_3$ (45.6% d_3, 50.3% d_2, and 3.2% d_2).[22] If the K_2CO_3 was replaced by $KHCO_3$ and the reaction time shortened, **32** was obtained. The 2-cotinine-*methyl-d*$_3$ (**30**) was prepared from **8a** and CD_3NH_2·HCl via the method developed for the synthesis of the norcotinines. Reduction of the myosmines (**4a** and **4c**) with $NaBD_4$ yielded 2- and 4-nornicotine-*2′-d*$_1$ (**20** and **22**). Sodium borohydride reduction of 2- and 4-myosmine-*3′,3′-d*$_2$ (**28** and **29,** obtained from **4a** and **4c** by acid-catalyzed exchange of the 3′ protons) gave 2- and 4-nornicotine-*3′,3′-d*$_2$ (**21** and **23**). The 4-nicotine-*2′-d*$_1$ (**15**) was synthesized by iodomethylation of **22** because the methylation of **22** under Clark–Eschweiler conditions[13] resulted in loss (ca. 90%) of the deuteron. Formylation of **21** with HCO_2H and **2b** with DCO_2D afforded the *N′*-formyl derivatives **26** and **27.** This method could not be used to prepare *N′*-formyl-*d*$_1$-2-nornicotine (**24**) from **2a** or *N′*-formyl-2-nornicotine-*2′-d*$_1$ (**25**) from **20** due to the lability of the 2′

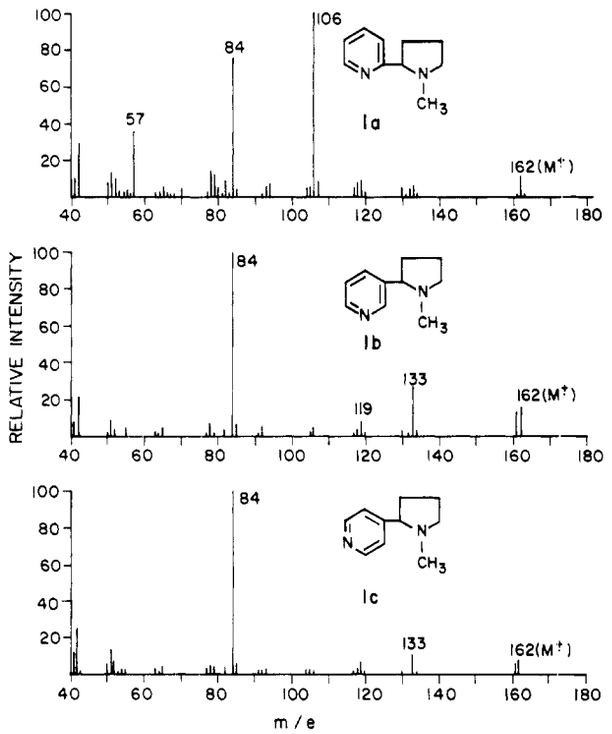


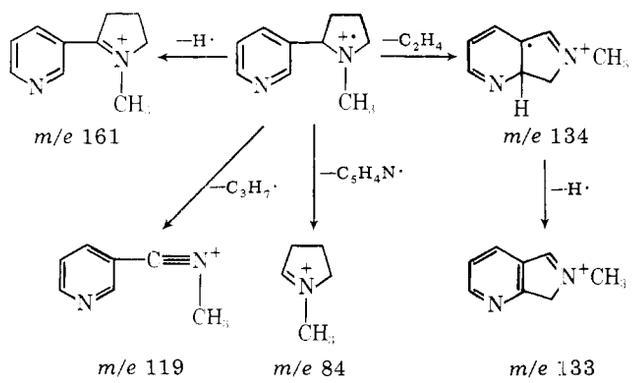
Figure 1. Mass spectra (70 eV) of 2-nicotine (**1a**), 3-nicotine (**1b**), and 4-nicotine (**1c**).

proton (deuteron). The milder reaction conditions of **2a** and DCO_2D or **20** and HCO_2H in the presence of dicyclohexylcarbodiimide proved effective, giving **24** and **25.** The 2-nornicotine-N'-d_1 (**19**) and the norcotinines-N'-d_1 (**33–35**) were prepared in the mass spectrometer from **2a** and **6a–c** by exchange with D_2O. The remaining deuterated analogues (**9–14** and **16–18**) were synthesized using the methods developed by Duffield et al.,[23] with minor modifications.

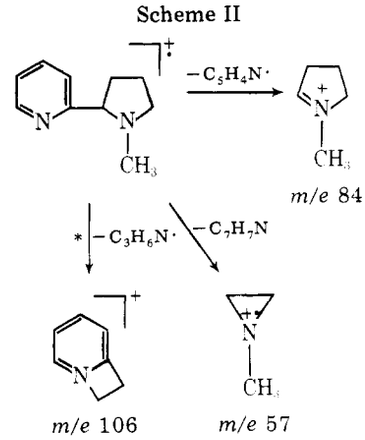
Mass Spectrometery. Recent studies have shown that during electron impact induced fragmentation the nitrogen atom in 2-substituted pyridines participates in unique fragmentation reactions.[24-28] The free-radical character of this nitrogen appears to be involved in bond-forming reactions,[29] which may occur in low yield, if at all, in 3- and 4-substituted pyridines. The mass spectrometry of the isomeric nicotinoids (**1a,c–6a,c**) has been neglected, although several investigators have conducted extensive studies on the tobacco alkaloids.[3a,23,30]

3-Nicotine (1b). The mass spectrum of 3-nicotine (Figure 1) has been discussed, and several mechanistic interpretations of the most abundant ions have appeared. The most complete investigation by Duffield et al.[23] and a direct analysis of daughter ions (DADI) study[30b] are combined to give the major

Scheme I



Scheme II



fragmentation pathways illustrated in Scheme I. The spectrum contains five major ions, three of which arise as a direct decomposition of the molecular ion (*m/e* 162).

The base peak in the spectrum occurs at *m/e* 84 (M − 78) due to the loss of the pyridyl moiety via α cleavage. The hydrogen atom lost to produce the M − 1 species comes 40% from the 2′ position, 15% from the 5′ position, and 10% from the 4′ position. The remaining 35% is postulated to come from the C-2, C-4, and/or C-3′ positions.[23] The peak at *m/e* 119 (M − 43) is the result of the loss of the 2′ proton with the 3′, 4′, and 5′ carbons and their attached hydrogens.

Formation of the *m/e* 133 (M − 29) ion has been shown by DADI to be a two-stage process. Ethylene, containing C-3′ and C-4′, is lost in the initial step from the molecular ion, and only after ring formation of *m/e* 134 is a proton lost from the 2 position of the pyridyl moiety.

2-Nicotine (1a). The dominant peak in the mass spectrum of 2-nicotine (Figure 1, Scheme II) occurs at *m/e* 106 (M − 56). The elemental composition of this ion was determined by high-resolution mass spectrometry to be $C_7H_8N^+\cdot$ (M − C_3H_6N), and metastable ion data indicate its formation from the molecular ion. The production of this ion requires the loss of the N′ CH_3 group and the 4′ and 5′ carbons and a hydrogen transfer from the leaving group to the charged moiety. The spectra of the deuterated analogues pinpoint the source of the transferred hydrogen to be 15% from the methyl, 24% from the 4′ position, and 61% from the 5′ position.

The reaction to form the *m/e* 106 ion demands participation of the pyridine nitrogen, and this ion is shown in Scheme II as a recyclization to the nitrogen. No metastable ions could be found to indicate its further fragmentation. The possibility has not been overlooked that this fragmentation could be initiated by a charge site different from that found in 3-nicotine.

A major peak in the spectrum is found at *m/e* 57 due to an ion having an elemental composition of $C_3H_7N^+\cdot$. This ion contains the 4′ and 5′ carbons and the N′ CH_3 group as well as their attached hydrogens. Other peaks found in the 2-nicotine spectrum are similar to those found in 3-nicotine. The abundant ion at *m/e* 84 is due to the loss of the pyridyl moiety via α cleavage.

4-Nicotine (1c). The mass spectrum of 4-nicotine (Figure 1) is, for the most part, identical with the spectrum of 3-nicotine. The only notable difference is that the α-cleavage reaction (M − 78) produces a higher percentage of the total ions formed than does this cleavage in the 3 isomer. Deuterium labeling, high-resolution results, and metastable data indicate the same mechanisms at work here as in the 3 isomer.

3-Nornicotine (2b). The mass spectrum of 3-nornicotine (Figure 2) contains a relatively abundant molecular ion and a more intense M − 1 species. The M − 1 peak has been shown by deuterium labeling to consist of a 55% loss of hydrogen from the 2′ position.[23] Lack of analogues deuterated in the 4′ or 5′

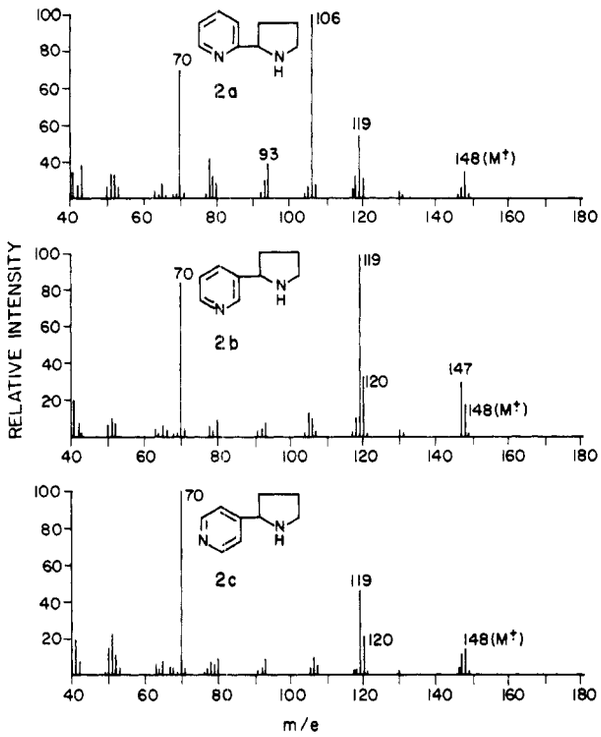


Figure 2. Mass spectra (70 eV) of 2-nornicotine (**2a**), 3-nornicotine (**2b**), and 4-nornicotine (**2c**).

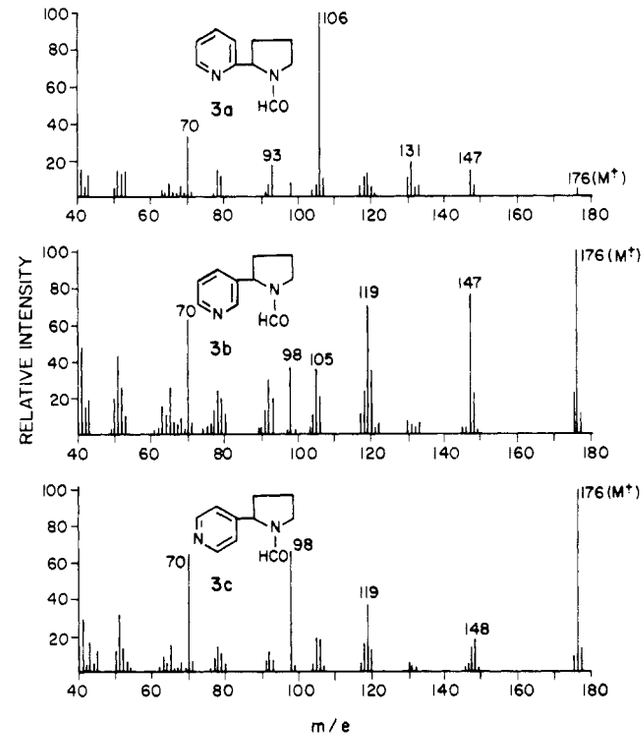


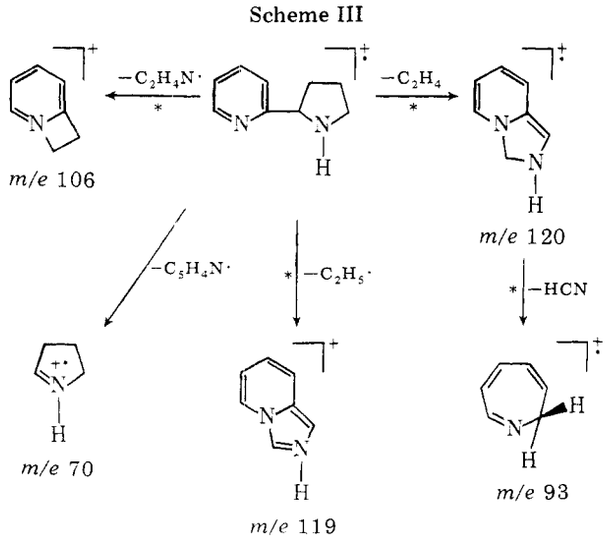
Figure 3. Mass spectra (70 eV) of *N'*-formyl-2-nornicotine (**3a**), *N'*-formyl-3-nornicotine (**3b**), and *N'*-formyl-4-nornicotine (**3c**).

positions precludes recognition of the other M − 1 species.

Similar to 3-nicotine, the 3-nornicotine spectrum contains an intense peak due to the loss of the pyridyl moiety producing the *m/e* 70 ion via α cleavage. The loss of 28 mass units from the molecular ion produces a peak at *m/e* 120 ($C_7H_8N_2^{+\cdot}$). The available deuterated analogues indicate the formation of this ion by the loss of ethylene containing the 3′ and 4′ carbons and their hydrogens.[23] The base peak of 3-nornicotine occurs at *m/e* 119 (M − C_2H_5) due to the loss of the 3′ and 4′ CH_2 groups and an additional hydrogen. This can occur either as a transfer of hydrogen to the leaving group or, by analogy to 3-nicotine, as the loss of hydrogen from the pyridine ring after cyclization of the *m/e* 120 ion.

2-Nornicotine (2a). The most abundant peak in the spectrum of 2-nornicotine (Figure 2, Scheme III) occurs at *m/e* 106. This ion has the same elemental composition as the *m/e* 106 ion found in 2-nicotine; in this case, however, it is due to the loss of C_2H_4N. Deuterium labeling indicates its formation

Scheme III



by the loss of the pyrrolidine nitrogen with the 4′ and 5′ carbons, hydrogen transfer to the charged species, and recyclization. The available deuterium analogues show 38% of the hydrogen transferred to be from the N′ position, and one can postulate the remainder to come from both the 4′ and 5′ positions, as was seen with 2-nicotine.

The mass spectrum contains a prominent α-cleavage product at *m/e* 70 and a relatively abundant *m/e* 119. A metastable ion indicates the formation of *m/e* 119 from the molecular ion, and deuterium analogues show its formation from *m/e* 120 via the loss of a 5′ hydrogen.

4-Nornicotine (2c). The mass spectrum of 4-nornicotine (Figure 2), as with 4-nicotine, shows that the further the substituent group from the pyridyl nitrogen, the more facile the α-cleavage. Here the α-cleavage product at *m/e* 70 has become the most abundant ion. No differences were found in the elemental compositions of the major ions from those of 3-nornicotine.

***N'*-Formyl-3-nornicotine (3b).** The electron impact induced fragmentation of *N'*-formyl-3-nornicotine includes many competing reactions (Scheme IV) which produce a complex spectrum (Figure 3). The most abundant ion is the molecular ion at *m/e* 176, from which only two major fragment ions are formed.

The first major ion is found at *m/e* 147 due mainly to the loss of CHO via simple cleavage. Ten percent of the ion abundance at *m/e* 147 is due to the loss of $C_2H_5\cdot$, presumably by the same mechanisms found in 3-nicotine involving the 3′ and 4′ carbons. The second major molecular ion fragmentation is due to the anticipated α cleavage, forming *m/e* 98. Loss of CO from *m/e* 98 leads to an *m/e* 70 fragment ion.

Large metastable ions indicate that both the expulsion of ethylene to form *m/e* 119 and the loss of $C_2H_3\cdot$ to give *m/e* 120 occur from the *m/e* 147 ion. While no deuterium analogues were available, the probability appears high that the 3′ and 4′ carbons are involved in these losses, considering the evidence found for the 2 isomer.

***N'*-Formyl-2-nornicotine (3a).** The mass spectrometric fragmentation of *N'*-formyl-2-nornicotine follows the same

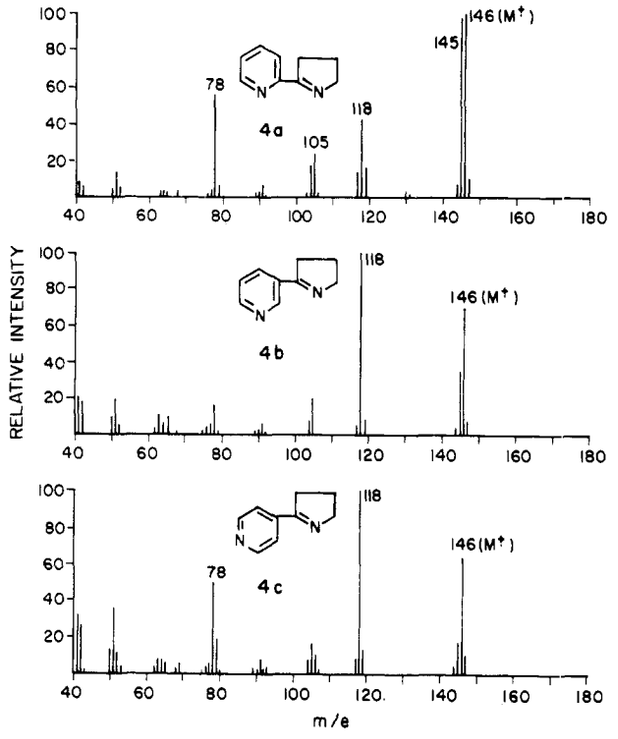
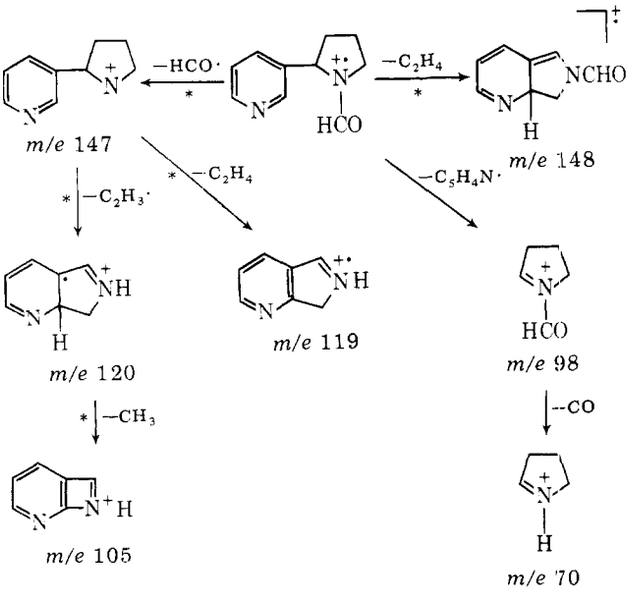


Figure 4. Mass spectra (70 eV) of 2-myosmine (**4a**), 3-myosmine (**4b**), and 4-myosmine (**4c**).

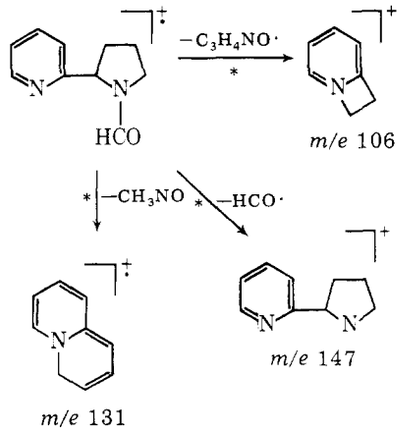
mechanism that has characterized the other 2 isomers of these nicotinoids. The most abundant ion in the spectrum (Figure 3) is found at *m/e* 106 due to the loss of $C_3H_4NO\cdot$ (Scheme V). Deuterium labeling shows that 25% of the hydrogen transferred in this reaction is from the formyl proton. The remaining 75% is postulated to come from both the 4′ and 5′ positions. A relatively abundant *m/e* 131 peak is present due to the loss of CH_3NO from *m/e* 176. This fragmentation requires the transfer of two hydrogens to the leaving group or a two-stage process. Approximately 50% of the hydrogens lost comes from the 3′ position. The remaining hydrogens may be lost from the 4′ position or, if cyclization occurs, the pyridine ring.

***N′*-Formyl-4-nornicotine (3c).** The mass spectrum of *N′*-formyl-4-nornicotine (Figure 3) closely resembles that of

Scheme IV



Scheme V



the 3 isomer insofar as the major peaks are concerned. As in other 4 isomers, the spectrum presents a marked increase in the α-cleavage product at the expense of the other ions, although the *m/e* 176 remains the most abundant ion.

3-Myosmine (4b). The mass spectrum of 3-myosmine (Figure 4) contains only three abundant peaks; the molecular ion, the M − 1 species, and the base peak at *m/e* 118. The loss of ethylene from M^+ to produce the most abundant ion at *m/e* 118 is due to the expulsion of C-3′ and C-4′ with their attached hydrogens.[23] It is noteworthy that α cleavage, which would result in the formation of an *m/e* 68 ion, is not a favored process since it would involve cleavage of a vinylic linkage.

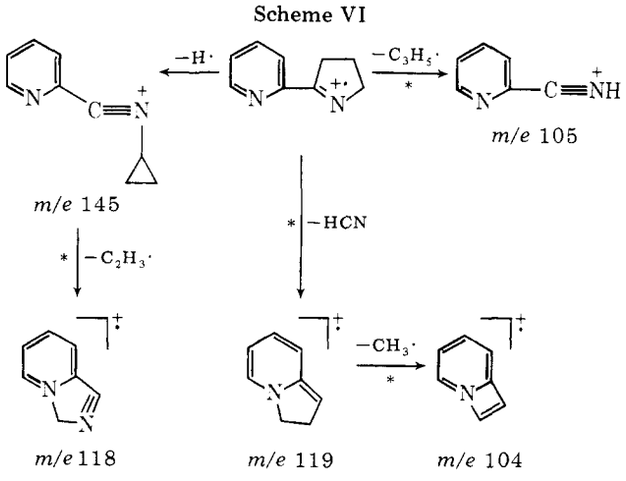
2-Myosmine (4a). The fragmentation of 2-myosmine produces a slightly more complex spectrum (Figure 4) than was found with the 3 and 4 isomers. The most abundant ion is now the molecular ion at *m/e* 146 (Scheme VI). A very stable M − 1 ion is formed involving the loss of a proton from the 4′ and/or 5′ position.

A large metastable ion suggests the formation of *m/e* 118 via the loss of $C_2H_3\cdot$ from *m/e* 145 (M − 1). Deuterium labeling shows that the 3′ position is always involved in this loss, and therefore by structural considerations the 4′ position is also. The peak at *m/e* 117 was found to be M − CH_3N rather than the loss of hydrogen from *m/e* 118. It was noted that approximately 30% of the hydrogen lost here involves the 3′ position.

The ion at *m/e* 119 is due to the loss of HCN from the molecular ion. The loss of $CH_3\cdot$, indicated by a metastable ion to be from *m/e* 119, results in the formation of *m/e* 104. The peak at *m/e* 105 is due to the loss of the 3′, 4′, and 5′ carbons from the molecular ion, and the major peak at *m/e* 78 was determined to be the pyridyl moiety.

4-Myosmine (4c). The mass spectrum of 4-myosmine

Scheme VI



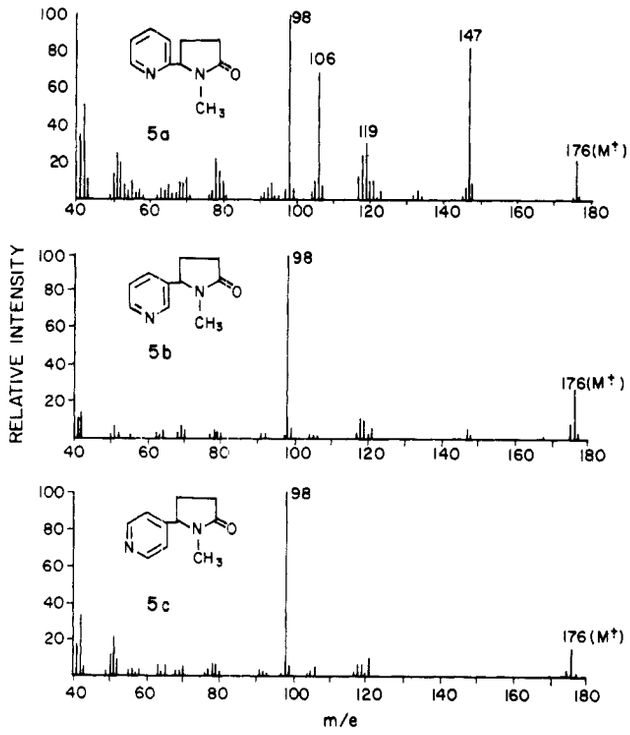


Figure 5. Mass spectra (70 eV) of 2-cotinine (**5a**), (*S*)-(−)-3-cotinine (**5b**), and 4-cotinine (**5c**).

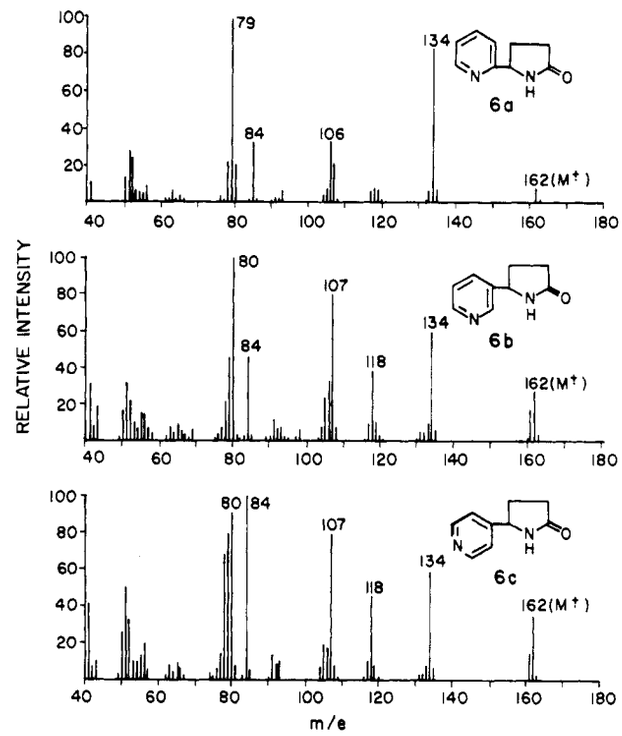


Figure 6. Mass spectra (70 eV) of 2-norcotinine (**6a**), (*S*)-(−)-3-norcotinine (**6b**), and 4-norcotinine (**6c**).

(Figure 4) contains the same major peaks found in the 3 isomer as well as the increased intensity of *m/e* 78 found in the 2 isomer. Clearly, the major structural influence in these three isomers is the vinylic linkage and not the position of pyridine substitution.

(*S*)-(−)-3-Cotinine (5b). The mass spectrum of (*S*)-(−)-3-cotinine (Figure 5) is dominated by the ion at *m/e* 98, and few other ions exceed 10% relative abundance. The *m/e* 98 ion corresponds to the loss of the pyridyl moiety via α cleavage. The spectrum contains a relatively abundant molecular ion at *m/e* 176, and the only other peaks of interest are found at *m/e* 118 and 119. The *m/e* 118 ion is due to the loss of $C_2H_4NO\cdot$ and *m/e* 119 to the loss of C_2H_3NO, both from the molecular ion.

2-Cotinine (5a). The mass spectrum of 2-cotinine (Figure 5) follows the pattern set by the other 2 isomers and demonstrates the influence of the pyridine nitrogen on its fragmentation mechanisms (Scheme VII). The expected peak at *m/e* 106 has the same elemental composition as found in the 2 isomers of nicotine, nornicotine, and *N'*-formylnornicotine. In this case, the peak at *m/e* 106 is not the most abundant ion.

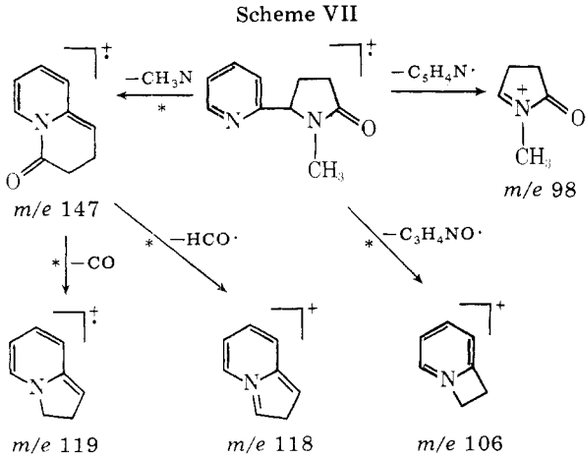
In 2-cotinine, the hydrogen transferred from the leaving group cannot come from the 5′ position. In fact, deuterium labeling shows that 100% of the hydrogen transferred comes from the methyl groups.

The α-cleavage product at *m/e* 98 remains the most abundant ion. A prominent ion at *m/e* 147 is due to the loss of the N′ CH_3 group. Further fragmentation of this ion results in the formation of the *m/e* 119 ion via the loss of CO and the *m/e* 118 ion from the loss of HCO·.

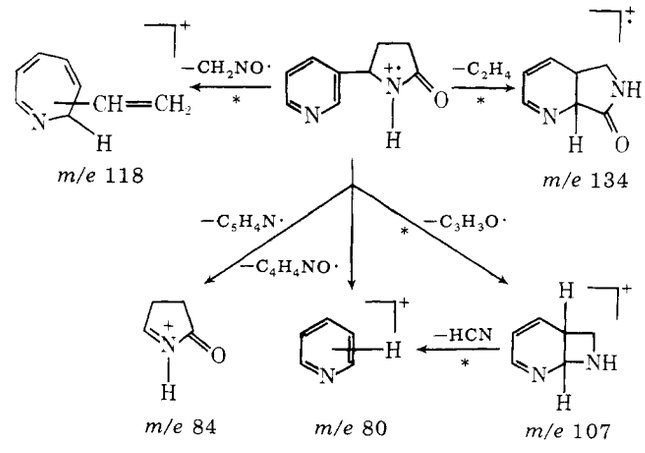
4-Cotinine (5c). The mass spectrum of 4-cotinine (Figure 5) contains the same peaks found in the 3 isomer. There is, as expected, an increase in the total number of ions formed by α cleavage.

(*S*)-(−)-3-Norcotinine (6b). The mass spectrum of (*S*)-(−)-3-norcotinine (Figure 6) is an anomaly among the 3-substituted pyridines presented here. While appearing to have every reason to undergo α cleavage to produce the base peak, the most abundant ion is found instead at *m/e* 80 (Scheme VIII). High-resolution data reveal this ion to be $C_5H_6N^+$, a protonated pyridine species. Deuterium exchange of the pyrrolidinone *N'*-hydrogen shows that 100% of this hydro n

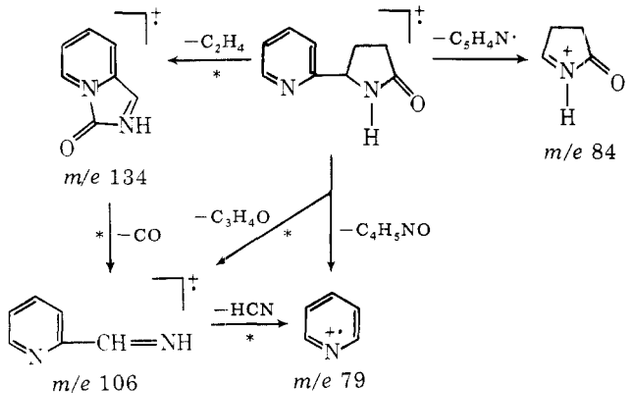
Scheme VII



Scheme VIII



Scheme IX



is transferred in the formation of the *m/e* 80 ion. The second hydrogen could not be identified due to the lack of deuterated analogues. The extreme ease with which the N′ proton is transferred to the pyridyl moiety relative to the other 3 isomers accounts for the low intensity of the α-cleavage product.

The α-cleavage product appears at *m/e* 84 and has an elemental composition of $C_4H_6NO^+$. Other fragment ions of interest include *m/e* 134, 118, and 107. The peak at *m/e* 134 is due to the loss of C_2H_4, presumably from the molecular ion and involving the loss of the 3′ and 4′ carbons. The ion at *m/e* 118 (M − CH_2NO·) involves the transfer of a hydrogen from the 3′ position to the leaving group. The peak at *m/e* 107 (M − C_3H_3O·) requires the transfer of a hydrogen from the leaving group. This proton can come from the 3′ and/or 4′ position.

2-Norcotinine (6a). The mass spectrum of 2-norcotinine (Figure 6) displays little indication of the expected pyridine nitrogen influence on the fragmentation mechanisms (Scheme IX). The expected formation of a $C_7H_8N^+$ ion (M − C_2H_3NO) does not occur. The peak at *m/e* 106 results from the loss of ethylene involving the expulsion of the 3′ and 4′ carbons followed by the loss of CO. This process appears favored over the loss of C_2H_3NO due to the stability of the neutral fragments generated. The major differences in this isomer relative to (*S*)-(−)-3-norcotinine are found in the marked decrease in intensity of *m/e* 118, 107, and 80 ions and the promotion of *m/e* 79 to become the base peak. This pyridine ion (*m/e* 79, $C_5H_5N^+$·) involves the transfer of a hydrogen, 70% of which was found to come from the N′ position.

4-Norcotinine (6c). The mass spectrum of 4-norcotinine (Figure 6) contains the same major ions as were found in the 3 isomer. High-resolution data show them to have the same elemental compositions as found in 3-norcotinine. As with other 4 isomers, the α-cleavage product is more pronounced. In this case, *m/e* 84 has become the most abundant ion.

Summary

The electron impact induced fragmentation of these 2-substituted pyridines shows a marked influence of the pyridine nitrogen. Where structural limitations do not prohibit it, as in 2-myosmine and 2-norcotinine, this influence manifests itself in the production of an intense *m/e* 106 ion ($C_7H_8N^+$). The spectra of the 3 and 4 isomers are dominated by the α-cleavage product (M − 78), except in the case of the 3- and 4-myosmines and 3-norcotinine. The myosmines are prohibited from following the expected pathways by their vinylic linkage, 2-norcotinine by the stability of the neutral fragments formed, and (*S*)-(−)-3-norcotinine by the ease of hydrogen transfer from the pyrrolidinone.

Experimental Section

Melting points and boiling points are uncorrected. The ^1H NMR spectra were determined on either a Varian A60A or XL-100 spectrometer equipped with a Digilab FT accessory, with Me_4Si as an internal standard. The ^2H NMR spectra were run on the latter instrument using $CDCl_3$ as an internal standard. The structures of the isomeric nicotinoids (**1a,c–6a,c**) were confirmed by ^1H NMR spectroscopy, which will be reported elsewhere[20] with the ^1H and ^2H NMR analyses of the deuterated analogues. The IR spectra were run on either a Perkin-Elmer 621 or a Digilab FTS-14 spectrophotometer. The GLC and preparative GLC (PGLC) analyses were carried out using a Bendix 2300 instrument with 5 ft × 0.25 in stainless steel columns packed with 5% SE-30 on Chromosorb G-HP (80–100 mesh) with He carrier gas at 60 mL/min flow rate. The TLC and PTLC analyses were run on silica gel GF plates using $CHCl_3$/EtOH/NH_4OH (85:14:1) as the developing solvent. For PTLC purifications, after elution[31] and evaporation in air (ca. 1 h)[32] of solvent from the plates, the silica gel containing the desired compound was collected and washed with excess CH_2Cl_2 to eliminate trace impurities, care being taken to remove the majority of the CH_2Cl_2 without pulling much air through the gel. The silica gel was slurried with 10% HCl (ca. 10 mL per plate used) and the acid filtered off. The acid wash was repeated twice. The combined filtrates at <10 °C were basified with excess 50% NaOH (pH 11) and extracted with Et_2O. The Et_2O was dried[31] (NaOH) for 2–3 h and removed to give the desired compound, from which trace solvent was removed in 3–6 h under vacuum (0.1 mm). Low-resolution mass spectra were obtained on a CEC 21-104 mass spectrometer at 70 eV, 10 μA, 2000-V ion-accelerating voltage, and a source temperature of 250 °C. Accurate mass measurements were made on a CEC 21-110B with a resolution of 12 000. The metastable ion measurements were made by an accelerating voltage scan method similar to the one used by Schulze and Burlingame.[33]

2-(2-Pyrrolidinyl)pyridine (2-Nornicotine; 2a). To 4.35 g (0.03 mol) of cyclopropyl 2-pyridyl ketone[34] (**7a**) was added 4.0 g (0.089 mol) of $HCONH_2$, 1.2 g (0.0059 mol) of $MgSO_4 \cdot 6H_2O$, and 15 mL of 2-ethoxyethyl ether. The stirring mixture was heated at reflux under N_2 for 21 h, cooled (5 °C), and acidified (pH 2) with 25 mL of concentrated HCl. The solution was extracted with $CHCl_3$. The $CHCl_3$ layers were washed with 10% HCl (20 mL). The combined acid layers, after removal of traces of $CHCl_3$ under reduced pressure, were heated at reflux under N_2 for 16 h, cooled (5 °C), and basified with 50 mL of 50% NaOH (pH 11). The mixture was extracted with Et_2O. The Et_2O was dried (NaOH) and removed to give 1.49 g of an oil. The aqueous layer and insoluble solids were continuously extracted for 24 h with Et_2O. The Et_2O was dried (NaOH) and removed to give an additional 0.11 g of oil. The oil was distilled to give 1.31 g (30%) of crude **2a:** bp 60–65 °C (1.0 mm); GLC purity >70%. The distilled **2a** was dissolved in 100 mL of EtOH and treated with 6.1 g (0.027 mol) of picric acid. The mixture was stirred overnight. The picrate salt was collected, washed with EtOH, and air-dried. Two recrystallizations from H_2O gave 3.40 g of analytically pure dipicrate salt, mp 167–168 °C (lit.[35] mp 166 °C).

The dipicrate salt (3.0 g) was added to 50 mL of 10% NaOH, and the stirring mixture was heated at reflux under N_2 for 1.5 h. The solution was cooled (5 °C), treated with 20 mL of 50% NaOH (pH 11), and extracted with Et_2O (4 × 40 mL). The Et_2O was dried (NaOH) and removed to leave an oil which was distilled to give 0.65 g (88%) of analytically pure **2a:** bp 54 °C (0.24 mm) [lit.[35] bp 120 °C (12 mm)]; IR (neat) 3310 (NH), 2990, 2890, 1597, 1573, 1478, 1440, 780, 750 cm^{-1}.

4-(2-Pyrrolidinyl)pyridine (4-nornicotine; 2c) was prepared in 54% crude yield from cyclopropyl 4-pyridyl ketone[34] (**7c**) by the procedure used for the synthesis of crude **2a:**[32] bp 68–71 °C (0.02 mm); NMR purity, >90%. TLC showed a major component (**2c**), a minor component (**4c**), and two unidentified trace components. The product (**2c**) air-oxidized to **4c** on standing, and this coupled with the fact that it codistilled with **4c,** had the same GLC retention time as **4c** (12 columns), was partially oxidized to **4c** during PGLC, and corecrystallized as a dipicrate salt with the picrate salt of **4c** precluded the preparation of an analytically pure sample. However, **4c** of sufficient purity for spectral analysis was obtained by PTLC: IR (neat) 3300 (NH), 2970, 2880, 1602, 1413, 992, 815 cm^{-1}.

4-[1-(*N*-Phenylthiocarbonylimino)-2-pyrrolidinyl]pyridine. To 0.24 g (0.016 mmol) of freshly prepared **2c** (purity >90%) in 5 mL of dry benzene was added 265 μL (0.032 mol) of phenyl isothiocyanate, and the solution was allowed to stand overnight under N_2. The precipitated crystals were collected and air-dried to yield 0.33 g (74%) of the phenyl isothiocyanate derivative, mp 180–183 °C. Recrystallization from EtOH and drying in vacuo over P_2O_5 gave analytically pure material: mp 185.5–186.5 °C; IR (KBr) 3240 (NH), 2970, 1597, 1545, 1445, 1386, 1290, 750, 690 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.08 (m, 4, 3′- and 4′-CH_2), 3.87 (m, 2, 5′-CH_2), 5.66 (m, 1, 2′-CH_2), 7.24 (m, 7, phenyl H and 3- and 5-pyridyl H), 8.53 (m, 2, 2- and 6-pyridyl H), 9.04

(s, 1, NH).

2-(1-Methyl-2-pyrrolidinyl)pyridine (2-Nicotine; 1a). To a stirred solution of 1.39 g (27 mmol) of 88% HCO_2H and 1.08 g (13 mmol) of 36.9% H_2CO at 5 °C was added slowly 0.77 g (5.2 mmol) of **2a** in 1 mL of H_2O. The solution was heated at reflux under N_2 for 16 h, cooled (5 °C), and basified with 50% NaOH (pH 11). The mixture was extracted with Et_2O (4 × 10 mL). The Et_2O was dried (NaOH) and removed [20 °C (15 mm)] to leave 0.76 g (90%) of **1a** as an oil which on distillation afforded 0.69 g (82%) of analytically pure **1a:** bp 87–88 °C (4.2 mm) [lit.[35] bp 122 °C (24 mm)]; IR (neat) 2970, 2945, 2782, 1592, 1572, 1473, 1437, 1048, 781, 751 cm^{-1}.

4-(1-Methyl-2-pyrrolidinyl)pyridine (4-Nicotine; 1c). To a stirred solution of 4.17 g (0.08 mol) of 88% HCO_2H and 3.24 g (0.04 mol) of 36.9% H_2CO in 4 mL of H_2O at 5 °C under N_2 was added dropwise 2.36 g (0.016 mol) of freshly prepared **2c** (purity >90%) in 1 mL of H_2O. The solution was allowed to warm to room temperature over 20 min and was cautiously warmed with a water bath to ca. 50 °C, where gas evolution became quite vigorous. Heating was discontinued until after the vigorous reaction subsided and was then resumed at reflux for 5 h. The reaction mixture was cooled (5 °C), basified with 50% NaOH (pH 11), and extracted with Et_2O (4 × 15 mL). The Et_2O was dried (NaOH) and removed [20 °C (15 mm)] to afford 2.01 g of **1c** as an oil. Distillation gave 1.36 g (52%; >95% pure by GLC) of **1c:** bp 43–45 °C (0.006 mm) [lit.[14] bp 94–95 °C (67 mm)]. Analytically pure **1c** was obtained by PGLC: IR (neat) 2975, 2950, 2785, 1600, 1461, 1414, 1316, 1048, 993, and 820 cm^{-1}.

2-(1-Formyl-2-pyrrolidinyl)pyridine (*N'*-Formyl-2-nornicotine; 3a). To 4.35 g (0.03 mol) of cyclopropyl 2-pyridyl ketone[34] (**7a**) was added 4.0 g (0.089 mol) of $HCONH_2$, 1.2 g (0.0059 mol) of $MgCl_2{\cdot}6H_2O$, and 15 mL of 2-ethoxyethyl ether. The stirring mixture was heated at reflux under N_2 for 21 h. After cooling, the insoluble solids were broken up and the reaction was stirred with 50 mL of H_2O to give an aqueous/oil mixture which was extracted with CH_2Cl_2. The CH_2Cl_2 was dried (Na_2SO_4) and removed to leave an oil, which was distilled [66–74 °C (7 mm)] to remove the 2-ethoxyethyl ether and volatile impurities. Distillation of the residue afforded 1.79 g (34.4%) of **3a:** bp 99–101 °C (0.01 mm); GLC purity >89%. Analytically pure **3a** was obtained by PGLC: IR ($CHCl_3$) 1663 (C=O), 1595, 1437, 1419, 1382, 750 cm^{-1}.

Anal. Calcd for $C_{10}H_{12}N_2O$: C, 68.16; H, 6.86; N, 15.90. Found: C, 68.32; H, 7.06; N, 16.18.

3-(1-Formyl-2-pyrrolidinyl)pyridine (*N'*-formyl-3-nornicotine; 3b) was prepared in 54.6% yield from cyclopropyl 3-pyridyl ketone[34] (**7b**) by the procedure used for the synthesis of **3a:** bp 129–131 °C (0.03 mm) [lit.[36] bp 206 °C (10 mm)]; GLC purity >98%. An analytically pure sample of **3b** whose IR and NMR spectra were consistent with those reported[37] was prepared by PGLC.

4-(1-Formyl-2-pyrrolidinyl)pyridine (*N'*-formyl-4-nornicotine; 3c) was prepared in 52% yield from cyclopropyl 4-pyridyl ketone[34] (**7c**) by the procedure used for the synthesis of **3a:** bp 120–126 °C (0.25 mm); GLC purity >90%. The oil partially solidified on standing. Trituration of the solid with Et_2O gave a crystalline product (35%): mp 71–76 °C; GLC purity >98%. Analytically pure **3c** was prepared by sublimation [45–85 °C (0.02 mm)] followed by drying in vacuo over P_2O_5: mp 74–76 °C; IR ($CHCl_3$) 1668 (C=O), 1601, 1417, 1380 cm^{-1}.

Anal. Calcd for $C_{10}H_{12}N_2O$: C, 68.16; H, 6.86; N, 15.90. Found: C, 68.49; H, 6.96; N, 16.08.

2-(3,4-Dihydro-2*H*-pyrrol-5-yl)pyridine (2-Myosmine, Apoferrorosamine; 4a). To a stirred solution of 22.0 g (0.2 mol) of diisopropylamine in 200 mL of anhydrous Et_2O at −65 °C under N_2 was added 43.7 g (0.15 mol) of a 2.2 M solution of *n*-butyllithium in hexane. The solution was stirred for 15 min, followed by the addition of 25.0 g (0.16 mol) of *N*-trimethylsilyl-2-pyrrolidone,[18] keeping the reaction below −60 °C. After stirring for 15 min, 15.1 g (0.1 mol) of ethyl picolinate was added with the mixture maintained below −60 °C. The reaction mixture was stirred at −65 °C for 15 min, allowed to warm to room temperature, and stirred overnight while a yellow solid precipitated. The mixture was cooled (5 °C) and acidified with 400 mL of 10% HCl (pH 2). The Et_2O layer was separated from the solid/aqueous acid mixture and washed with 50 mL of 10% HCl. The solid/aqueous acid layer and washings were combined and concentrated to 150 mL. The acid solution was heated at reflux for 18 h under N_2, cooled (5 °C), and basified with 50% NaOH (pH 10). The mixture was extracted with Et_2O (4 × 100 mL). The Et_2O was dried (Na_2SO_4) and removed to give 12.04 g of **4a** as a slightly gummy solid. Recrystallization from petroleum ether (30–60 °C) gave 10.1 g (67%) of **4a,** mp 48–50.5 °C. Pure **4a** was prepared by sublimation, 33–45 °C (0.02 mm), followed by drying in vacuo over P_2O_5, mp 52–53 °C (lit.[38] mp 46–49 °C). The IR and NMR spectra agreed with those reported.[38]

4-(3,4-Dihydro-2*H*-pyrrol-5-yl)pyridine (4-myosmine; 4c) was prepared from ethyl isonicotinate using the method described for the synthesis of **4a** with the following changes in the isolation and purification. The solid/aqueous layer and washing which resulted from the acidification of the reaction mixture were combined and heated at reflux under N_2 for 18 h. The solution was cooled (5 °C) and basified with 50% NaOH (pH 10). A solid separated, and the entire mixture was continuously extracted[39] with Et_2O for 24 h. The Et_2O was removed and the residue dissolved in CH_2Cl_2. The CH_2Cl_2 was dried (Na_2SO_4) and removed to give **4c** (81.5%, mp 86–89.5 °C). Recrystallization from petroleum ether (90–120 °C) or sublimation [40–54 °C (0.01 mm)] and drying in vacuo over P_2O_5 afforded pure **4c,** mp 89–90 °C (lit.[12b] mp 91 °C). The IR spectrum was consistent with that reported.[12b] As was found for **4b,**[12a] pure **4c** is hygroscopic.

3-(3,4-Dihydro-2*H*-pyrrol-5-yl)pyridine (3-myosmine; 4b) was prepared in 82% yield from ethyl nicotinate by the method used for the synthesis of **4c,** mp 37–43 °C. The sample was sublimed [25–39 °C (0.01 mm)] and dried in vacuo over P_2O_5 to give pure **5b,** mp 40–44 °C (lit.[19] mp 44–45 °C). The IR and NMR spectra were identical with those reported for the natural base.[40]

Ethyl 3-(2-Pyridoyl)propionate (8a). To a stirred mixture of 9.8 g (0.2 mol) of NaCN in 200 mL of dry DMF at 15 °C was added 42.8 g (0.48 mol) of freshly distilled 2-pyridinecarboxaldehyde over 30 min. A deep red solution resulted to which, after it had warmed to room temperature, was added 38.8 g (0.4 mol) of freshly distilled ethyl acrylate over 1 h while keeping the reaction temperature from rising above 40 °C. The mixture was allowed to cool and stir for 2 h. It was poured into 1000 mL of H_2O and extracted with $CHCl_3$ (3 × 300 mL). The $CHCl_3$ was dried (Na_2SO_4) and removed to give an oil. Distillation [33–47 °C (7 mm)] removed the residual DMF and volatile impurities. The remaining oil precipitated a solid which was collected and discarded. The filtrate oil was distilled to afford 9.1 g (11%) of **8a:** bp 122–133 °C (0.09 mm); GLC purity >92%. Redistillation gave pure **8a:** bp 97–98 °C (0.07 mm) [lit.[17] bp 135–140 °C (0.2 mm)]; IR (neat) 2990, 1740 (ester C=O), 1705 (C=O), 1412, 1223, 1175, 1030, 810 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (t, 3, J = 7 Hz, CH_3), 2.8 (m, 2, $-CH_2-$), 3.63 (m, 2, $-COCH_2-$), 4.23 (d, 2, J = 7 Hz, $-CO_2CH_2-$), 7.87 (m, 3, 3-, 4-, and 5-pyridyl H), 8.82 (m, 1, 6-pyridyl H).

Ethyl 3-(4-pyridoyl)propionate (8c) was prepared by reaction of 4-pyridinecarboxaldehyde with ethyl acrylate in the presence of NaCN as described for the synthesis of **8a.** Distillation [15–60 °C (10 mm)] of the crude reaction oil removed the residual DMF and volatile impurities. The remaining oil was distilled to yield analytically pure **8c** (33%): bp 123–125 °C (0.05 mm) [lit.[14,41] bp 145–147 °C (4 mm)]; IR (neat) 2995, 2940, 1743 (ester C=O), 1710 (C=O), 1592, 1443, 1218, 1165, 998, 778, 762 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (t, 3, J = 7 Hz, CH_3), 2.8 (m, 2, $-CH_2CO_2-$), 3.38 (m, 2, $-COCH_2-$), 4.20 (d, 2, J = 7 Hz, $-CO_2CH_2-$), 7.86 (m, 2, 3- and 5-pyridyl H), 8.93 (m, 2, 2- and 6-pyridyl H).

Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.75; H, 6.32; N, 6.76. Found: C, 63.55; H, 6.14; N, 6.87.

1-Methyl-5-(2-pyridyl)-2-pyrrolidinone Monohydrate (2-Cotinine Monohydrate; 5a). To a solution of 6.21 g (0.03 mol) of **8a** and 17.7 g (0.3 mol) of $HCONHCH_3$ under anhydrous conditions (drybox) was added 0.29 g (0.003 mol) of anhydrous $MgCl_2$. The stirring mixture was heated at reflux under N_2 for 30 h. The mixture was cooled (5 °C), acidified (pH 2) with 10% HCl, and extracted with $CHCl_3$. The aqueous layer was cooled (5 °C), basified (pH 9) with 10% NaOH, stirred overnight, and then continuously extracted with Et_2O for 20 h. The Et_2O was removed. The residual oil was taken up in CH_2Cl_2 and dried (Na_2SO_4). Removal of the CH_2Cl_2 left an oil which was distilled to give 0.63 g (12%) of **5a:** bp 112–114 °C (0.03 mm); GLC purity >95%. PGLC afforded analytically pure **5a** as a monohydrate: IR (neat) 3470 (OH), 2960, 1787 (C=O), 1596, 1478, 1440, 1400, 1285, 1120, 996, 790, 755 cm^{-1}.

Anal. Calcd for $C_{10}H_{14}N_2O_2$: C, 61.83; H, 7.26; N, 14.42. Found: C, 61.68; H, 7.32; N, 14.61.

1-Methyl-5-(4-pyridyl)-2-pyrrolidinone monohydrate (4-cotinine monohydrate; 5c)[42] was prepared in 23% yield from **8c** by the procedure used for the synthesis of **5a.** The crude product was obtained as an oil which almost completely solidified on standing: bp 117–119 °C (0.02 mm); GLC purity >90%. PGLC gave analytically pure **5c** as a monohydrate: IR (neat) 3460 (OH), 3030, 2960, 1785 (C=O), 1601, 1417, 1400, 1310, 1118, 994, 817 cm^{-1}.

Anal. Calcd for $C_{10}H_{14}N_2O_2$: C, 61.83; H, 7.26; N, 14.42. Found: C, 61.78; H, 7.27; N, 14.33.

5-(2-Pyridyl)-2-pyrrolidinone (2-Norcotinine; 6a). To a mixture of 2.42 g (0.012 mol) of **8a** and 5.4 g (0.07 mol) of NH_4OAc in 80 mL of anhydrous MeOH was added 1.1 g (0.018 mol) of $NaBH_3CN$. The mixture was stirred under N_2 for 10 days. The reaction was cooled

(5 °C) and acidified with 10% HCl (pH 2). The MeOH was removed and the residue basified at 5 °C with 40 mL of 15% NaOH (pH 10). The mixture was stirred overnight at room temperature and then continuously extracted with Et_2O for 16 h. The Et_2O was dried (Na_2SO_4) and removed to give 278 mg (15%) of **6a** as a gummy solid, mp 83–92 °C. Recrystallization from cyclohexane/benzene (3:1) followed by drying in vacuo afforded an analytical sample: mp 96–97 °C; IR (KBr) 3240 (NH), 3110, 2985, 1690 and 1670 (lactone C=O), 1595, 1432, 1345, 1280, 1086, 992, 780, 757 cm^{-1}.

Anal. Calcd for $C_9H_{10}N_2O$: C, 66.65; H, 6.22; N, 17.27. Found: C, 66.56; H, 6.44; N, 17.09.

5-(4-Pyridyl)-2-pyrrolidinone (4-norcotinine; 6c) was prepared in 11% yield from **8c** by the method used for the synthesis of **6a**, mp 124–132 °C. Recrystallization from cyclohexane/benzene (2:1) and drying in vacuo gave analytically pure **6c**: mp 134–135.5 °C; IR (KBr) 3180 (NH), 3095, 2925, 1787 (C=O), 1603, 1156, 1068, 615, 600 cm^{-1}.

Anal. Calcd for $C_9H_{10}N_2O$: C, 66.65; H, 6.22; N, 17.27. Found: C, 66.69; H, 6.30; N, 17.17.

Deuterated Derivatives. All reaction apparatus were dried at 150–200 °C with a heat gun. All syntheses were run under N_2. The deuterated reagents used were as follows: D_2O (Bio-Rad Laboratories), 99.84 atom % enrichment; CH_3OD (Wilmad Glass Co., Inc.), 99 atom % enrichment; CF_3CO_2D (Wilmad Glass Co., Inc.), 99 atom % enrichment; CH_3CH_2OD (Diaprep, Inc.), 99 atom % enrichment; CD_3I (Diaprep, Inc.), 99+ atom % enrichment; $NaBD_4$ (Merck Sharp & Dohme Canada, Limited, Isotope Division), 98 atom % enrichment; DCO_2D (EM Laboratories, Inc.), >99 atom % enrichment; CD_3NH_2·HCl (EM Laboratories, Inc.), >99 atom % enrichment; and $LiAlD_4$ (Merck Sharp & Dohme Canada, Limited, Isotope Division), 99 atom % enrichment. The percent deuteration for all derivatives is given in Table I.

2-(1-Methyl-*d*$_3$-2-pyrrolidinyl)pyridine (2-Nicotine-*methyl-d*$_3$; 9). To a stirred mixture of 202 mg (1.36 mmol) of **2a** and 219 mg (1.59 mmol) of K_2CO_3 in 5 mL of pesticide grade CH_3CN was added 218 mg (1.50 mmol) of CD_3I. After stirring for 18 h, the solvent and unreacted CD_3I were removed [20 °C (15 mm)]. The residue was dissolved in 5 mL of H_2O, basified (pH 11) at 5 °C with 2 mL of 50% NaOH, and extracted with Et_2O (4 × 3 mL). The Et_2O was dried (NaOH) and removed [20 °C (15 mm)] to give 154 mg (67%) of **9**. GLC showed ca. 75% **9** and ca. 25% **2a**. PGLC gave spectroscopically pure **9**.

2-(1-Methyl-2-pyrrolidinyl-*2-d*$_1$)pyridine (2-Nicotine-*2'-d*$_1$; 10). To a cooled (5 °C), stirred solution of 175 mg (3.4 mmol) of 88% HCO_2H and 141 mg (1.7 mmol) of 36.9% H_2CO in 2 mL of H_2O was added 100 mg (0.67 mmol) of **20** in 1 mL of H_2O. The reaction was heated at reflux for 16 h, basified (pH 11) at 5 °C with 2 mL of 50% NaOH, and extracted with Et_2O (4 × 5 mL). The Et_2O was dried (NaOH) and removed [20 °C (15 mm)] to afford 57 mg (52%) of **10**. GLC showed ca. 97% **10** and ca. 3% **20**. PGLC gave spectroscopically pure **10**.

2-(1-Methyl-2-pyrrolidinyl-*3,3-d*$_2$)pyridine (2-nicotine-*3',3'-d*$_2$; 11) was prepared from **21** in 81% yield by the procedure used to synthesize **10**. GLC showed ca. 97% **11** and ca. 3% **21**. PGLC gave spectroscopically pure **11**.

2-(1-Methyl-2-pyrrolidinyl-*4,4-d*$_2$)pyridine (2-Nicotine-*4',4'-d*$_2$; 12). To a cooled (5 °C), stirred slurry of 173 mg (4.6 mmol) of $LiAlH_4$ in 25 mL of anhydrous Et_2O was added slowly 104 mg (0.58 mmol) of **31**. The stirred mixture was heated at reflux for 16 h, cooled (5 °C), treated slowly with 0.75 mL of H_2O, and stirred for 1 h. The insoluble salts were removed and washed with Et_2O. The Et_2O was dried (NaOH) and removed [20 °C (15 mm)] to yield 73 mg (77%) of **12**. GLC purity >90%. PGLC gave spectroscopically pure **12**.

2-(1-Methyl-2-pyrrolidinyl-*5,5-d*$_2$)pyridine (2-nicotine-*5',5'-d*$_2$; 13) was prepared in 95% yield by reaction of **5a** with $LiAlD_4$ by the method used to obtain **12**. GLC purity was >90%. PGLC gave spectroscopically pure **13**.

4-(1-Methyl-*d*$_3$-2-pyrrolidinyl)pyridine (4-nicotine-*methyl-d*$_3$; 14) was obtained from PTLC pure **2c** in 36% yield by the method used to prepare **9**. GLC showed ca. 70% **14**, ca. 18% **2c**, and two unidentified compounds. PGLC gave spectroscopically pure **14**.

4-(1-Methyl-2-pyrrolidinyl-*2-d*$_1$)pyridine (4-Nicotine-*2'-d*$_1$; 15). Treatment of 462 mg of crude **22**, which was synthesized from 500 mg (3.4 mmol) of **4c** as described subsequently, with 440 mg (3.1 mmol) of CH_3I as shown for the preparation of **9** gave 166 mg of a solid/oil mixture. TLC showed no **22**, and GLC showed ca. 86% **15** and ca. 14% **4c**. PGLC gave spectroscopically pure **15**.

4-(1-Methyl-2-pyrrolidinyl-*3,3-d*$_2$)pyridine (4-Nicotine-*3',3'-d*$_2$; 16). To a cooled (0 °C), stirred solution of 841 mg (16.1 mmol) of 88% HCO_2H and 665 mg (8.2 mmol) of 36.9% H_2CO in 5 mL of H_2O was added dropwise over 5 min 490 mg (3.3 mmol) of **23** in 4 mL of H_2O. The reaction mixture was allowed to warm to room temperature over 20 min, was heated at 50–55 °C with a water bath for 30 min, and then was heated at reflux for 5 h. The solution was cooled (5 °C), basified (pH 11) with 50% NaOH, and extracted with Et_2O (4 × 15 mL). The Et_2O was dried (NaOH) and removed [20 °C (15 mm)] to give 0.486 g (88%) of **16**. GLC purity was >95%. PGLC gave spectroscopically pure **16**.

4-(1-Methyl-2-pyrrolidinyl-*4,4-d*$_2$)pyridine (4-nicotine-*4',4'-d*$_2$; 17) was synthesized in 96% yield from **32** by the method used for the preparation of **12**. GLC purity was >95%. PGLC gave spectroscopically pure **17**.

4-(1-Methyl-2-pyrrolidinyl-*5,5-d*$_2$)pyridine (4-nicotine-*5',5'-d*$_2$; 18) was prepared in 92% yield from **5c** by the method reported for the synthesis of **13**. GLC purity was >85%. PGLC gave spectroscopically pure **18**.

2-(2-Pyrrolidinyl-*1-d*$_1$)pyridine (2-Nornicotine-*1'-d*$_1$; 19). After D_2O equilibration of the mass spectrometer, a D_2O slurry of **2a** was introduced into the inlet system to give **19**.

2-(2-Pyrrolidinyl-*2-d*$_1$)pyridine (2-Nornicotine-*2'-d*$_1$; 20). To a stirred solution of 1.0 g (6.8 mmol) of **4a** in 40 mL of EtOH was added 421 mg (10.0 mmol) of $NaBD_4$. The mixture was stirred at room temperature for 24 h and was then slowly acidified (pH 2) with 10% HCl at 5 °C. After stirring for 30 min, the EtOH was removed. The residue was basified (pH 11) at 5 °C with 5 mL of 50% NaOH and extracted with Et_2O (4 × 20 mL). The Et_2O was dried (NaOH) and removed to give 734 mg of **20**, which TLC showed contained a minor amount of **4a**. The **4a** was removed by PTLC, giving 395 mg (39%) of **20**. PGLC gave spectroscopically pure **20**.

2-(2-Pyrrolidinyl-*3,3-d*$_2$)pyridine (2-nornicotine-*3', 3'-d*$_2$; 21) was prepared from **28** by reduction with $NaBH_4$ in EtOD using the method given for the synthesis of **20**. The crude **21** was shown by TLC to contain a trace of **4a**/**28**, which was removed by PTLC to give 170 mg (29%) of **21**. PGLC gave spectroscopically pure **21**.

4-(2-Pyrrolidinyl-*2-d*$_1$)pyridine (4-nornicotine-*2'-d*$_1$; 22) was synthesized from **4c** by the method used for the preparation of **20**. TLC indicated that the crude **22** contained a minor amount of **4c**. PTLC gave spectroscopically pure **22** (38%).

4-(2-Pyrrolidinyl-*3,3-d*$_2$)pyridine (4-nornicotine-*3', 3'-d*$_2$; 23) was obtained from **29** by the method used for the preparation of **21**. TLC showed that the product contained no **29**, and after removing trace solvent under vacuum (0.1 mm) spectroscopically pure **23** (79%) was obtained.

2-(1-Formyl-*d*$_1$-2-pyrrolidinyl)pyridine (*N'*-Formyl-*d*$_1$-2-nornicotine; 24). To a stirred solution of 102 mg (0.69 mmol) of **2a** and 34 mg (0.71 mmol) of DCO_2D in 4 mL of CH_2Cl_2 was added 153 mg (0.74 mmol) of dicyclohexylcarbodiimide in 3 mL of CH_2Cl_2. After stirring for 30 min, TLC indicated that all of the **2a** had been consumed. The reaction mixture was treated with 2 mL of D_2O and stirred for 2 h. The insoluble solid was removed. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (4 × 2 mL). The CH_2Cl_2 was dried (Na_2SO_4) and removed to leave 136 mg of **24**, which was contaminated with dicyclohexylurea. PGLC gave spectroscopically pure **24**.

2-(1-Formyl-2-pyrrolidinyl-*2-d*$_1$)pyridine (*N'*-formyl-2-nornicotine-*2'-d*$_1$; 25) was synthesized by the reaction of **20** with HCO_2H using the method given for the preparation of **24**. The crude **25** was contaminated with a small amount of dicyclohexylurea. PGLC gave spectroscopically pure **25**.

2-(1-Formyl-2-pyrrolidinyl-*3,3-d*$_2$)pyridine (*N'*-Formyl-2-nornicotine-*3',3'-d*$_2$; 26). To 299 mg (6.5 mmol) of HCO_2H (>97%) in a 1-mL Pierce Reacti-Vial at 5 °C was added 194 mg (0.99 mmol) of **21**.[43] The closed vial was heated on a steam bath for 16 h and cooled. The reaction solution was dissolved in 2 mL of H_2O, basified with saturated K_2CO_3 (pH 9), and extracted with Et_2O (4 × 2 mL). The Et_2O was dried (Na_2SO_4) and removed to leave 147 mg (83%) of **26**. GLC purity was >95%. PGLC gave spectroscopically pure **26**.

3-(1-Formyl-*d*$_1$-2-pyrrolidinyl)pyridine (*N'*-formyl-*d*$_1$-3-nornicotine; 27) was prepared in 45% yield by the reaction of **2b** with DCO_2D using the method described for the synthesis of **26**. GLC purity was >95%. PGLC gave spectroscopically pure **27**.

2-(3,4-Dihydro-2*H*-pyrrol-5-yl-*4,4-d*$_2$)pyridine (2-Myosmine-*3',3'-d*$_2$; 28).[44] A stirred solution of 1.0 g (0.0068 mol) of **4a** in 22.6 g (0.685 mol) of MeOD was treated with 50 μL of CF_3CO_2D and heated for 16 h at 40 °C. The reaction was cooled (20 °C), and 50 mg of Na_2CO_3 was added. The mixture was stirred for 2 h, followed by removal of the MeOD to leave an oil. The oil was taken up in CH_2Cl_2 and the insoluble material removed. Removal of the CH_2Cl_2 left 0.85 g of a solid (mp 46–51 °C) which was sublimed [35–60 °C (0.035 mm)] and dried in vacuo over P_2O_5 to give 0.626 g (62%) of spectroscopically

pure **28**, mp 51–52 °C.

4-(3,4-Dihydro-2*H*-pyrrol-5-yl-*4,4-d*$_2$)pyridine (4-myosmine-*3',3'-d*$_2$; 29) was synthesized from **4c** by the method used for the preparation of **28**. The dried product (mp 88–89 °C; 92%) was of sufficient purity for subsequent reaction. Spectroscopically pure **29** was obtained by sublimation [45–54 °C (0.04 mm)] and drying in vacuo over P_2O_5, mp 89–90 °C.

1-Methyl-*d*$_3$-5-(2-pyridyl)-2-pyrrolidinone (2-Cotinine-*methyl-d*$_3$; 30). A mixture of 826 mg (4.0 mmol) of **8a** and 975 mg (13.8 mmol) of CD_3NH_2·HCl in 50 mL of MeOH was treated with 375 mg (6.0 mmol) of $NaBH_3CN$ and stirred for 4 days at room temperature. The reaction mixture was acidified (pH 2) with 2.5 mL of 10% HCl and stirred for 2 h. After removal of the MeOH, the mixture was basified (pH 10) at 5 °C with 10 mL of 10% NaOH, stirred for 16 h at room temperature, and then continuously extracted with Et_2O for 16 h. The Et_2O was dried (Na_2SO_4) and removed to give 124 mg (17%) of **30**. GLC purity was >95%. PGLC gave spectroscopically pure **30**.

1-Methyl-5-(2-pyridyl)-2-pyrrolidinone-*3,3-d*$_2$ (2-Cotinine-*4',4'-d*$_2$; 31). A stirred mixture of 502 mg (2.9 mmol) of **5a** and 500 mg (3.6 mmol) of K_2CO_3 in 10 mL (0.56 mol) of D_2O was heated at reflux for 12 days. The resulting solution was cooled and extracted with CH_2Cl_2 (4 × 10 mL). The CH_2Cl_2 was dried (Na_2SO_4) and removed to leave 448 mg (87%) of **31**. GLC purity was >95%. PGLC gave spectroscopically pure **31**.

1-Methyl-5-(4-pyridyl)-2-pyrrolidinone-*3,3-d*$_2$ (4-Cotinine-*4',4'-d*$_2$; 32). A stirred mixture of 251 mg (1.4 mmol) of **5c** and 200 mg (2.0 mmol) of $KHCO_3$ in 7 mL (0.39 mol) of D_2O was heated at reflux for 7 days. The solution was cooled and extracted with CH_2Cl_2 (4 × 5 mL). The CH_2Cl_2 was dried (Na_2SO_4) and removed to yield 239 mg (96%) of **32**. GLC purity was >95%. PGLC gave spectroscopically pure **32**.

5-(2-Pyridyl)-2-pyrrolidinone-*1-d*$_1$ (2-norcotinine-*1'-d*$_1$; 33) was prepared from **6a** by the method used to synthesize **19**.

(*S*)-(−)-5-(3-Pyridyl)-2-pyrrolidinone-*1-d*$_1$ [(*S*)-(−)-3-norcotinine-*1'-d*$_1$; 34] was synthesized from **6b** by the method used to obtain **19**.

5-(4-Pyridyl)-2-pyrrolidinone-*1-d*$_1$ (4-norcotinine-*1'-d*$_1$; 35) was obtained from **6c** by the method used to obtain **19**.

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Registry No.—**1a**, 23950-04-1; **1b**, 54-11-5; **1c**, 66269-72-5; **2a**, 66269-73-6; **2a** dipicrate, 66269-74-7; **2b**, 494-97-3; **2c**, 66269-75-8; **3a**, 66269-76-9; **3b**, 38840-03-8; **3c**, 66269-77-0; **4a**, 4593-27-5; **4b**, 532-12-7; **4c**, 66269-78-1; **5a**, 66269-79-2; **5b**, 486-56-6; **5c**, 66269-80-5; **6a**, 66269-81-6; **6b**, 5980-06-3; **6c**, 66269-82-7; **7a**, 57276-28-5; **7b**, 24966-13-0; **7c**, 39512-48-6; **8a**, 66269-83-8; **8c**, 66269-84-9; **9**, 66269-85-0; **10**, 66269-86-1; **11**, 66269-87-2; **12**, 66269-88-3; **13**, 66269-89-4; **14**, 66269-90-7; **15**, 66269-91-8; **16**, 66269-92-9; **17**, 66269-93-0; **18**, 62453-04-7; **19**, 66269-94-1; **20**, 66269-95-2; **21**, 66269-96-3; **22**, 66269-97-4; **23**, 66269-98-5; **24**, 66269-99-6; **25**, 66270-00-6; **26**, 66270-01-7; **27**, 66270-02-8; **28**, 66270-03-9; **29**, 66269-65-6; **30**, 66269-66-7; **31**, 66269-67-8; **32**, 66269-68-9; **33**, 66269-69-0; **34**, 66269-70-3; **35**, 66269-71-4; $HCONH_2$, 75-12-7; $HCONHCH_3$, 123-39-7; phenyl isothiocyanate, 103-72-0; 4-[1-(*N*-phenylthiocarbonylimino)-2-pyrrolidinyl]pyridine, 66322-96-1; *N*-trimethylsilyl-2-pyrrolidone, 14468-90-7; ethyl picolinate, 2524-52-9; ethyl isonicotinate, 1570-45-2; ethyl nicotinate, 614-18-6; 2-pyridinecarboxaldehyde, 1121-60-4; ethyl acrylate, 140-88-5; 4-pyridinecarboxaldehyde, 872-85-5.

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(44) One of us acknowledges Dr. J. I. Seeman for discussions on this reaction.

C-5 Substituted Pyrimidine Nucleosides. 1. Synthesis of C-5 Allyl, Propyl, and Propenyl Uracil and Cytosine Nucleosides via Organopalladium Intermediates

Jerry L. Ruth and Donald E. Bergstrom*

Department of Chemistry, University of California, Davis, Davis, California 95616

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Reaction of 5-chloromercuriuracil nucleosides (**1a,b**) with allyl chloride in the presence of Li_2PdCl_4 gives 5-allyluridine (**2a**) and 5-allyl-2′-deoxyuridine (**2b**), respectively, in good yields with minimal purification. $RhCl_3$ and $Rh(Ph_3P)_3Cl$ do not catalyze this alkylation. Hydrogenation of these 5-allyluracil nucleosides (**2a,b**) to 5-propyluridine (**3a**) and 5-propyl-2′-deoxyuridine (**3b**) occurs readily with no reduction of the pyrimidine ring. Isomerization of **2b** to 5-(1-propenyl)-2′-deoxyuridine (**4**) is achieved in the presence of $Rh(Ph_3P)_3Cl$. A similar reaction sequence with 5-chloromercuricytosine nucleosides (**5a,b**) gives good yields of 5-allyl- and 5-propylcytidines (**6a** and **7a**, respectively) and 5-allyl-, 5-propyl-, and 5-(1-propenyl)-2′-deoxycytidines (**6b**, **7b**, and **8**, respectively), none of which have been reported in the literature previously. Characterization of products includes melting point, ^1H NMR, UV, TLC, elemental analysis, and IR. The probable mechanism and potential biological activities are discussed briefly.

In addition to thymidine, many naturally occurring C-5 substituted pyrimidine nucleosides are found in the RNA and DNA of living organisms,[1-4] although the specific function of the C-5 modification is unknown for most of these. As chemotherapeutic agents many C-5 substituted pyrimidine nucleosides have been shown to exhibit activity against Herpes simplex[5] and vaccinia viruses;[6] one of these, 5-iodo-2′-deoxyuridine, is used clinically[7] against Herpes keratitis infections. Several C-5 substituted pyrimidine nucleosides have been shown to act with varying specificity as inhibitors of certain enzymes, such as the inhibition of nucleoside phosphorylase by 5-trifluoromethyl-2′-deoxyuridine[8] or the mild inhibition of deoxythymidine kinase from human acute myelocytic blast cells by 5-propyl-2′-deoxyuridine.[9] One modified nucleoside, 5-fluoro-2′-deoxyuridine, is an inhibitor of thymidylate synthetase after in vivo 5′-monophosphorylation. Others may act as competitive substrates for enzymes, and many, such as 5-ethyl-2′-deoxyuridine in *E. coli*,[10] may be directly incorporated into DNA.

Many C-5 alkylated uracil nucleosides, such as 5-allyl-2′-deoxyuridine[11] (**2b**) and 5-propyl-2′-deoxyuridine[12] (**3b**), have been synthesized and assayed for biological activity. Studies with 5-allyl-2′-deoxyuridine (**2b**) have shown the following: **2b** inhibits the growth of Herpes simplex virus (HSV) I and II, without being cytotoxic;[5,9] **2b** as its 5′-monophosphate exhibits only weak inhibition of deoxythymidylate synthetase;[13] and it was reported that **2b** also inhibits nucleoside phosphorylase[14] in HeLa cells as efficiently as 5-trifluoromethyl-2′-deoxyuridine.[8] (Recently it has been shown that **2b** is a competitive substrate for horse liver thymidine phosphorylase[15] rather than an inhibitor.) Biological assays of 5-propyl-2′-deoxyuridine (**3b**) have shown that **3b** weakly inhibits both mitochondrial and cytoplasmic deoxythymidine kinases of acute myelocytic blast cells.[9,16] It (**3b**) also inhibits growth of HSV I transformed HeLa cells which are deficient in deoxythymidine kinase, without being cytotoxic.[5] When *E. coli* is grown in the presence of **3b**, the *E. coli* show much more resistance to damage by UV light,[17] presumably due to less UV-induced dimerization after incorporation of **3b** into the DNA.

Like the corresponding halogenated 2′-deoxyuridines, the C-5 halogenated 2′-deoxycytidines show pronounced biological activity.[9,18] With the exception of 5-ethylcytidine and 5-ethyl-2′-deoxycytidine,[21] alkylated cytosine nucleosides with two or more carbons at C-5 have not been available for study, but in analogy to the alkylated uracil nucleosides the C-5 alkylated cytosine nucleosides may exhibit significant biological activity.

In light of their known and potential biological effects, much recent effort[11,12,19-28] has been directed towards the synthesis of C-5 substituted pyrimidine nucleosides. We have been particularly interested in obtaining nucleosides with carbon chains attached at C-5. Synthetic approaches to date have usually involved synthesis of a C-5 substituted pyrimidine and condensation of this with a suitably protected and activated sugar followed by deprotection and separation of the α and β anomers.[11,12,20-24] In order to overcome some of the drawbacks inherent in this procedure, we sought a general synthetic route beginning with the unprotected parent nucleosides. Recent results in this laboratory have established that pyrimidine nucleosides can be substituted at the C-5 position via organopalladium intermediates.[27,28] The 5-chloromercuripyrimidine nucleosides **1a, 1b, 5a,** and **5b,** which are readily available from uridine, 2′-deoxyuridine, cytidine, and 2′-deoxycytidine,[25,26] respectively, can react with olefins in the presence of Pd(II) to give the corresponding C-5 alkylated nucleosides directly. Although this general coupling reaction is similar to the results seen with phenylmercuric chloride and allyl chloride in the presence of Pd(II),[29] some interesting differences are observed. The present paper describes the following: (1) the reaction of allyl chloride with the 5-chloromercuripyrimidine nucleosides **1a, 1b, 5a,** and **5b** and Li_2PdCl_4 to form 5-allyluridine[27] (**2a**), 5-allyl-2′-deoxyuridine (**2b**), 5-allylcytidine (**6a**), and 5-allyl-2′-deoxycytidine (**6b**), respectively; (2) the subsequent reduction of these 5-allylpyrimidine nucleosides to 5-propyluridine (**3a**), 5-propyl-2′-

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