Phospholane. This compound[27] was generously supplied by Professor A. B. Burg.

Silacyclopentane-1,1-d_2. 1,1-Dichlorosilacyclopentane[28] (150 mg.) in dry ether (25 ml.) was heated under reflux with lithium aluminum deuteride (80 mg.) during 4.5 hr. Excess reagent was destroyed with water and ether was removed through a fractionating column. Preparative vapor phase chromatography using polybutylene glycol[25] as the stationary phase at 54° and a helium pressure of 1.5 p.s.i. yielded silacyclopentane-1,1-d_2 (97% d_2 species) at a retention time of 9.5 min.

Germacyclopentane-1,1-d_2. 1,1-Diiodogermacyclopentane[29] (150 mg.) in dry ether (20 ml.) was reduced with lithium aluminum deuteride (50 mg.) under reflux for 2 hr. The reaction mixture was processed in the usual manner and germacyclopentane-1,1-d_2 (97% d_2 species) was isolated by preparative vapor phase chromatography using polybutylene glycol[25] as the stationary phase at 66° and helium pressure of 4 p.s.i. (retention time, 6.5 min.).

(27) A. B. Burg and P. J. Slota, Jr., *J. Am. Chem. Soc.*, **82**, 2148 (1960).

(28) R. A. Benkeser, R. F. Grossman, and G. M. Stanton, *ibid.*, **84**, 4723 (1962). We wish to thank Professor Benkeser for supplying us with samples of 1,1-dichlorosilacyclopentane and silacyclopentane.

(29) P. Mazerolles, *Bull. soc. chim. France*, 1907 (1962). We would like to thank Professor Mazerolles for gifts of germacyclopentane and 1,1-diiodogermacylopentane.

Mass Spectrometry in Structural and Stereochemical Problems. LXXII.[1] A Study of the Fragmentation Processes of Some Tobacco Alkaloids[2]

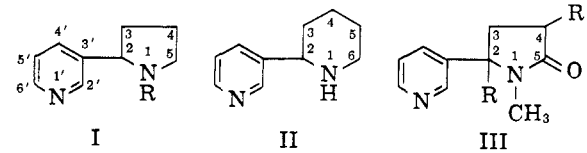
A. M. Duffield,[3] H. Budzikiewicz, and Carl Djerassi

Contribution from the Department of Chemistry, Stanford University, Stanford, California. *Received February 20, 1965*

Deuterium labeling studies have made possible mechanistic interpretations for the principal ions formed subsequent to electron impact in nicotine (I, R = CH_3), nornicotine (I, R = H), and anabasine (II). The product obtained from bromination of nicotine has been shown to possess the geminal dibromolactam structure IV (R = Br) rather than the previously assigned structure III (R = Br). The structure of anabasene has been shown to be VIII rather than VII.

A recent study of the mass spectrometric fragmentation of some five- and six-membered cyclic amines[4] was undertaken to determine modes of formation of the principal ions formed in this class of compounds subsequent to electron impact. With this information it was hoped to gain some insight into the probable fragmentation behavior of the principal tobacco alkaloids, nicotine (I, R = CH_3), nornicotine (I, R = H), and anabasine (II), which contain either a five- or a six-membered cyclic amine substituted at C-2 with a β-pyridyl moiety. The mass spectra of nicotine, nornicotine, and anabasine have been discussed[5] and recently new mechanistic interpretations of the more abundant ions have appeared.[6] The present investigation was commenced with a view of testing the validity of these suggestions.[6]

The structure of nicotine (I, R = CH_3) was suggested by Pinner[7] on the basis of results obtained from studies of the action of bromine on this alkaloid. He was able to obtain a crystalline compound analyzing for $C_{10}H_{10}Br_2NO$ to which structure III (R = Br) was assigned on the basis of its conversion to methylamine, oxalic acid, and methyl β-pyridyl ketone on alkaline hydrolytic fission.



I II III

The dibromolactam III (R = Br) should offer easy access for the introduction of deuterium into the nicotine molecule.[8] Thus debromination of III (R = Br) with zinc in acetic acid yielded continine (III, R = H) which on lithium aluminum deuteride reduction afforded nicotine-5,5-d_2. Exchange of the hydrogen atoms at C-4 in continine (III, R = H) with potassium carbonate–deuterium oxide[9] followed by lithium aluminum hydride reduction generated nicotine-4,4-d_2. Repetition of the debromination of III (R = Br) with zinc and deuterioacetic acid yielded a product

(1) Paper LXXI: A. M. Duffield, H. Budzikiewicz, and C. Djerassi, *J. Am. Chem. Soc.*, **87**, 2920 (1965).

(2) We are indebted to the National Institutes of Health of the U. S. Public Health Service for financial support (Grants No. GM-11309 and AM-04257).

(3) Postdoctoral Research Fellow 1963–1965.

(4) A. M. Duffield, H. Budzikiewicz, D. H. Williams, and C. Djerassi, *J. Am. Chem. Soc.*, **87**, 810 (1965).

(5) (a) W. F. Kuhn, C. J. Varsel, and W. A. Powell, paper presented at ASTM Committee E-14 Mass Spectrometry Conference, New Orleans, La., June 1962; (b) F. W. McLafferty, *Anal. Chem.*, **28**, 306 (1956).

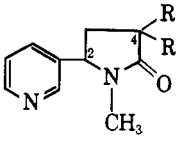
(6) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Interpretation of Mass Spectra of Organic Compounds," Holden-Day, Inc., San Francisco, Calif. 1964, pp. 104–110.

(7) A. Pinner, *Ber.*, **26**, 292 (1893).

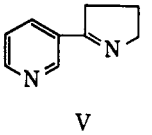
(8) For a review of the presently available methods for the introduction of deuterium into organic molecules, see H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Structure Elucidation of Natural Products by Mass Spectrometry," Vol. I, Holden-Day, Inc., San Francisco, Calif., 1964, Chapter 2.

(9) A. M. Duffield, H. Budzikiewicz, and C. Djerassi, *J. Am. Chem. Soc.*, **86**, 5536 (1964).

containing two deuterium atoms (mass spectrometry) which was assigned initially structure III (R = D). Back-exchange of this dideuterated lactam with potassium carbonate–water[9] followed by lithium aluminum hydride reduction yielded nicotine rather than the anticipated nicotine-2-d_1. Loss of the two initially introduced deuterium atoms can be envisaged if the dibromolactam had the geminal dibromo structure IV (R = Br). This conclusion was shown to be correct from the n.m.r. spectra of IV (R = Br) and its derived dideuterio analog IV (R = D). The spectra (determined in deuteriochloroform solution at 60 Mc.) showed a quartet (one proton) centered at 4.67 p.p.m. (relative to TMS) in the dibromo derivative which remained unaffected in the dideuterated lactam (quartet, 1 proton centered at 4.62 p.p.m.). Therefore, this resonance can be assigned to the proton at C-2 of the lactam ring in IV. If structure III (R = Br) were correct for the dibromolactam and the signal at 4.67 p.p.m. had corresponded to the proton at C-4, then a substantial upfield shift would have been anticipated on replacement of the C-4 bromine atom by deuterium. The n.m.r. evidence (considered in conjunction with the results from deuterium labeling) are consistent with structure IV (R = Br) for the product obtained on bromination of nicotine.



IV



V

Nicotine was labeled at C-2 with deuterium by catalytic deuteriation of myosmine (V)[10] which yielded nornicotine-2-d_1, N-methylation[11] of which afforded nicotine-2-d_1 containing 65% d_1 and 35% d_0 species (by mass spectrometry). The N-methyl group of nicotine (I, R = CH_3) was conveniently labeled with deuterium by N-methylation of nornicotine (I, R = H)[12a] using trideuteriomethyl iodide.

The exchangeable protons of nornicotine (I, R = H) and anabasine (II) were replaced with deuterium by equilibration with deuterium oxide in the inlet system of the mass spectrometer.[8,12b]

Anabasine (II) has been synthesized by condensation of ethyl nicotinate and N-benzoyl-2-piperidone with sodium ethoxide in benzene solution and heating the product, presumably VI, with concentrated hydrochloric acid to yield anabasene (formulated as VII) which on catalytic reduction afforded II.[13] As both myosmine (V) and anabasene can be synthesized by the same general reaction[13,14] it seemed much more likely that the correct structure for the latter compound should in fact be VIII. This was demonstrated by the n.m.r. spectrum of anabasene in which no signal corresponding to a proton attached to nitrogen could be observed. Resonances at 1.65 (four protons, two isolated methylene groups), 2.45 (two protons, a methylene group adjacent to nitrogen), and 3.75 p.p.m. (two protons, allylic methylene group) are clearly consistent with structure VIII for anabasene and are incompatible with representation of this compound as VII. Catalytic deuteration of anabasene (VIII) yielded anabasine-2-d_1 of 70% d_1 and 30% d_0 species, respectively (by mass spectrometry).

(10) Myosmine has been shown to have structure V rather than the Δ^2-pyrroline formulation by investigation of its infrared spectrum. See B. Witkop, *J. Am. Chem. Soc.*, **76**, 5597 (1954), and C. R. Eddy and A. Eisner, *Anal. Chem.*, **26**, 1428 (1954).

(11) W. Eschweiler, *Ber.*, **38**, 880 (1905).

(12) (a) L. C. Craig, *J. Am. Chem. Soc.*, **55**, 2854 (1933); (b) J. S. Shannon, *Australian J. Chem.*, **57**, 265 (1962).

(13) E. Späth and L. Mamoli, *Ber.*, **69**, 1082 (1936).

(14) E. Späth and L. Mamoli, *ibid.*, **69**, 757 (1936).

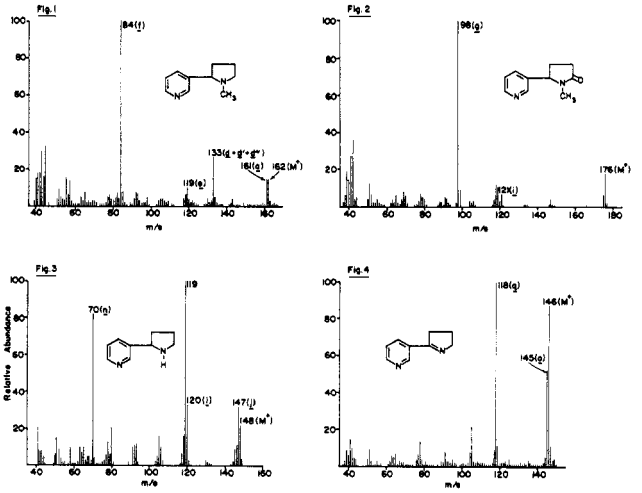
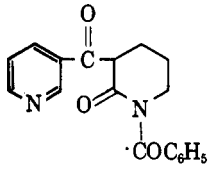
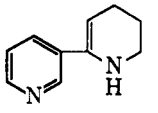


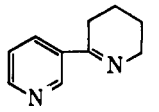
Figure 1. Mass spectrum of nicotine (I, R = CH_3).
Figure 2. Mass spectrum of continine (IV, R = H).
Figure 3. Mass spectrum of nornicotine (I, R = H).
Figure 4. Mass spectrum of myosmine (V).



VI



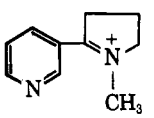
VII



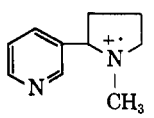
VIII

Mass Spectrometry

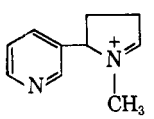
Nicotine. The mass spectrum of nicotine[5] (Figure 1) exhibits a relatively strong molecular ion which in view of appearance potential measurements[5a] can be attributed structure Ia.[5a,6] Loss of a hydrogen atom generates an M − 1 species which was suggested might correspond to the α-cleavage products a, a′, or a″, although the conjugated immonium ion a was preferred.[6] Deuterium labeling (Table I) demonstrated that the ion a constitutes only 40% of the ion yield at *m/e* 161 in the spectrum of nicotine (Figure 1), while the species a′ contributes 15% and a smaller amount (10%) is generated from loss of a hydrogen atom from C-4 of the N-methylpyrrolidine ring. The suggestion[5a] that the ion a″ corresponds to the



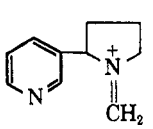
a, *m/e* 161



Ia

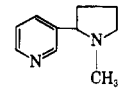
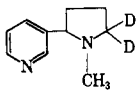
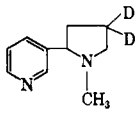
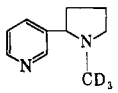
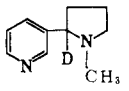


a′, *m/e* 161



a″

Table I.[a] Principal Mass Spectral Peaks of Nicotine and Deuterated Analogs

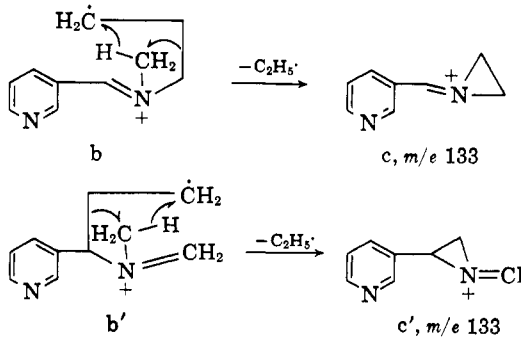
Compd.	Isotopic purity	M+	M − 1	M − 29	M − 43	M − 78
	...	162	161	133	119	84
	97% d_2	164	163 (85%) 162 (15%)	134 (20%) 135 (80%)	119 (85%) 121 (15%)	86 (q)
	92% d_2 8% d_1	164	163 (90%) 162 (10%	133(q)	119 (80%) 120 (20%)	86 (q)
	92% d_3	165	164 (q)	136 (q)	119 (30%) 122 (70%)	87 (q)
	65% d_1 35% d_0[b]	163	162 (60%) 161 (40%)	133 (20%) 134 (80%)	119 (80%)	85 (q)

[a] Tables I–III show the per cent shift of the compounds discussed in the text when specifically labeled with deuterium. The symbol q refers to a quantitative transfer (>95%) and the transfer values quoted are considered accurate to ±5% for peaks in excess of 20% relative abundance. [b] All peak shifts in the adjacent columns are corrected for the presence of this d_0 contaminant.

M − 1 species is incorrect as no loss of deuterium was observed (Table I) from nicotine-N-d_3. This is in agreement with the observation that no loss of hydrogen occurred from the N-methyl group in the genesis of the M − 1 species in the mass spectrum of N-methylpyrrolidine.[4]

Deuterium labeling of nicotine at the positions designated in Table I accounts for 65% of the M − 1 species, and if no isotope effect[15] is operative the remainder of this ion yield might be expected to arise from loss of a hydrogen atom from C-3, C-2′, or C-4′ of nicotine (I, R = CH_3), in preference to other positions.

A peak at *m/e* 133 (M − 29) in the mass spectrum of nicotine (Figure 1) was postulated[6] to have its genesis from either of the α-cleavage products b or b′ *via* hydrogen transfer from the N-methyl group with the production of c or c′, together with an ethyl radical. Preference was expressed[6] for c as such an ion would be formed from the conjugated species b.

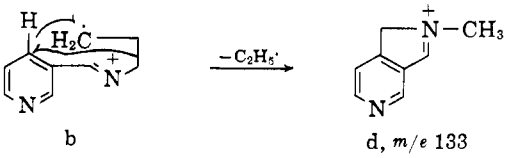


However, deuterium labeling (Table I) unequivocally demonstrated that these two attractive mechanisms, b → c and b′ → c′, were untenable since no loss of deuterium was found in the spectrum of nicotine-N-d_3.

(15) D. H. Williams, H. Budzikiewicz, and C. Djerassi, *J. Am. Chem. Soc.*, **86**, 284 (1964); V. H. Dibeler and F. L. Mohler, *J. Res. Natl. Bur. Std.*, **45** 441 (1950).

This observation also eliminated the suggestion[5a] that the peak at *m/e* 133 in the spectrum of nicotine arose from expulsion of the nitrogen atom with its attached methyl group.

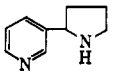
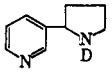
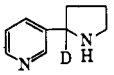
The results obtained from the spectra of the deuterated analogs (Table I) show that C-4 is quantitatively expelled. The second carbon atom of the ejected ethyl radical must be C-3 (otherwise two bonds to one atom would be ruptured, a process not commonly observed). The source of the transferred hydrogen of the eliminated ethyl radical has not been completely determined from deuterium labeling (except for a 20% transfer each from C-2 and C-5; see Table I), and any suggestions must therefore be speculative. The two most likely positions from which additional hydrogen transfer could occur would appear to be C-2′ or C-4′. Mechanistically this could be written as proceeding from the α-cleavage product b (drawn as C-4′ hydrogen transfer) with the formation of d, *m/e* 133. Attempts to substitute preferentially some of the aromatic hydrogens by deuterium proved abortive so that the proposed path (b → d) could not be established rigorously.



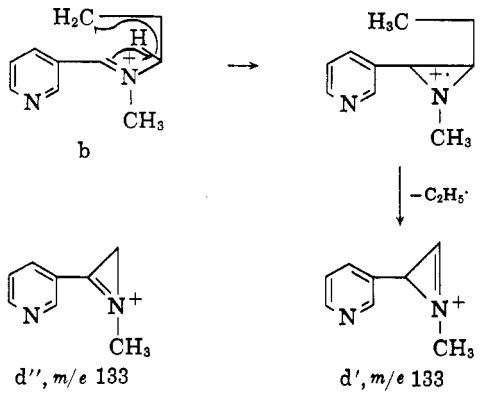
A mechanism consistent with the observed 20% transfer of hydrogen from C-5 (Table I) in the formation of the ion of mass 133 in the spectrum (Figure 1) of nicotine is depicted by the sequence b → d′ (*m/e* 133). A similar process utilizing b and hydrogen transfer from C-2 would generate d″ (*m/e* 133) and account for the production of an additional 20% (Table I) of the ion yield at *m/e* 133.

An ion of low abundance of mass 119 (M − 43) in the spectrum of nicotine (Figure 1) does not incorporate

Table II.[a] Principal Mass Spectral Peaks of Nornicotine and Deuterated Analogs

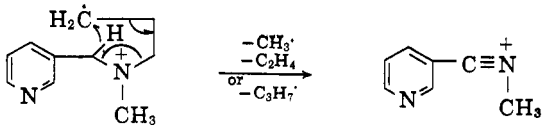
Compd.	Isotopic purity	M+	M − 1	M − 28	M − 29	M − 78
	...	148	147	120	119	70
	90% d_1 10% d_0	149	148 (q)	121 (q)	119 (20%) 120 (80%)	71 (90%)
	65% d_1 35% d_0[a]	149	148 (45%) 147 (55%)	121 (q)	119 (10%) 120 (90%)	71 (90%)

[a] See footnotes to Table I.



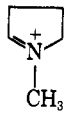
b d'', *m/e* 133 d', *m/e* 133

either C-4 or C-5 with their attached hydrogen atoms, while the N-methyl group is largely (70%) retained (Table I). The hydrogen atom transferred to the eliminated portion of the molecule originates from C-2 (Table I) and the mechanism b → e (*m/e* 119), consistent with the results from deuterium labeling, may correspond to 70% of the ion yield at *m/e* 119.



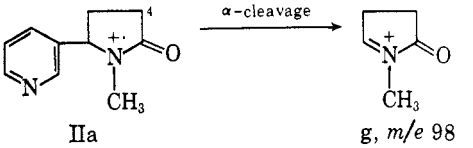
b e, *m/e* 119

The dominant peak in the spectrum of nicotine (Figure 1) occurs at *m/e* 84 (M − 78), and the genesis of this ion corresponds to loss[5a,5b,6] of the pyridyl moiety and formation of f (*m/e* 84) as substantiated by deuterium labeling (Table I). It is interesting to note that f arises by fission of a vinylic carbon bond (a process not usually favored in mass spectrometric fragmentations), and the driving force is presumably the greater stability of the α-cleavage product f.



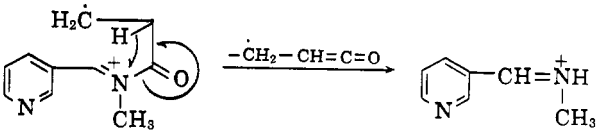
f, *m/e* 84

Continine. The mass spectrum (Figure 2) of continine (IV, R = H) is dominated by the peak at *m/e* 98 and few of the other ions exceed 10% relative abundance. This peak (*m/e* 98) corresponds to loss of the pyridyl moiety, and the ion may thus be represented as the α-cleavage product g of the molecular ion IIa. Only one deuterated analog was available (continine-4,4-d_2) and in the spectrum of this compound the peak at *m/e* 98 was shifted quantitatively to *m/e* 100.



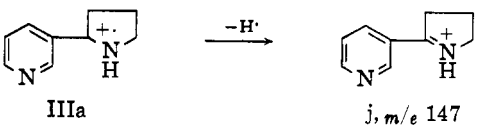
IIa g, *m/e* 98

A peak of low yield at *m/e* 121 in the spectrum of continine (Figure 2) is displaced to *m/e* 122 in the 4,4-d_2 analog. This ion's genesis can be interpreted in terms of hydrogen transfer from C-4 to nitrogen in the α-cleavage product h of the molecular ion IIa, followed by expulsion of a resonance-stabilized substituted ketene fragment and generation of i (*m/e* 121). A completely analogous sequence of events affords the base peak in the spectrum of N-methyl-2-pyrrolidone.[9]



h i, *m/e* 121

Nornicotine. The mass spectrum[5a] (Figure 3) of nornicotine (I, R = H) contains a relatively abundant molecular ion; appearance potential measurements[5a] suggest its representation as IIIa.[6] A more intense M − 1 species was suggested[6] to be the conjugated α-cleavage product j (*m/e* 147), and deuterium labeling (Table II) is consistent with designation of 55% of the ion yield in this manner. Lack of deuterated analogs precludes recognition of other M − 1 species.

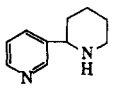
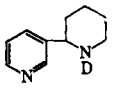
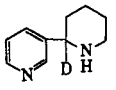


IIIa j, *m/e* 147

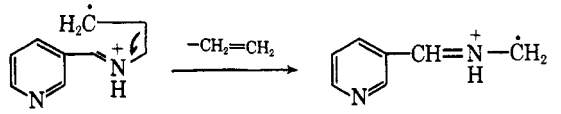
Loss of 28 mass units from nornicotine generates an ion of mass 120. It has been suggested[6] that this species might correspond to l being formed from the α-cleavage product k of the molecular ion IIIa by elimination of C-3 and C-4 as ethylene. The deuterated analogs available support this assignment, as is evidenced by the quantitative displacement of *m/e* 120 to *m/e* 121 in the N-d_1 and 2-d_1 derivatives (Table II).

The base peak in the spectrum of nornicotine (Figure 3) occurs at *m/e* 119 (M − 29), and the genesis of this

Table III.[a] Principal Mass Spectral Peaks of Anabasine and Deuterated Analogs

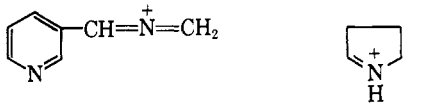
Compd.	Isotopic purity	M+	M − 1	M − 29	M − 42	M − 43	M − 56	M − 57	M − 78
	...	162	161	133	120	119	106	105	84
	90% d_1 10% d_0	163	162	134 (90%)	120 (50%) 121 (50%)	119 (60%) 120 (40%)	107 (90%)	106 (90%)	85 (q)
	70% d_1 30% d_0[a]	163	161 (40%) 162 (60%)	133 (10%) 134 (90%)	120 (20%) 121 (80%)	119 (20%) 120 (80%)	107 (90%)	105 (65%) 106 (35%)	85 (q)

[a] See footnotes to Table I.



k l, *m/e* 120

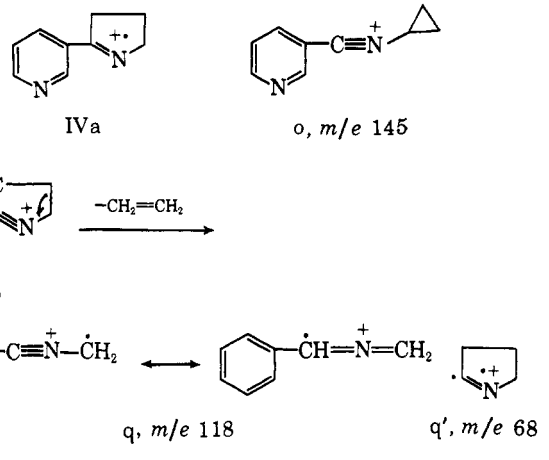
ion was postulated[6] in terms of hydrogen transfer from nitrogen in k, to satisfy the primary radical site, followed by elimination of an ethyl radical and generation of the even-electron species m (*m/e* 119). Deuterium labeling (Table II) is consistent with a minor portion (20%) of the ion yield having its origin in this manner. The major source of the transferred hydrogen has not been determined but, by analogy to nicotine, the C-2′ and C-4′ positions of the pyridine ring might be anticipated to contribute (see b → d).



m, *m/e* 119 n, *m/e* 70

The mass spectrum (Figure 3) of nornicotine has an intense peak at *m/e* 70 (M − 78) which has been assigned[6] to the species n, and this representation is supported by displacements to the extent of 90% to *m/e* 71 in the spectra of nornicotine-N-d_1 and nornicotine-2-d_1, respectively.

Myosmine. The mass spectrum (Figure 4) of myosmine (V) contains only three abundant ions corresponding to the molecular ion (represented as IVa), an M − 1 species (possibly o, *m/e* 145), and the base peak at *m/e* 118 (M − 28). The obvious loss of ethylene from IVa would involve expulsion of C-3 and C-4 and might arise *via* the sequence p → q (*m/e* 118). It is pertinent to note that α-cleavage of IVa with the elimination of the pyridyl ring and formation of q′ (*m/e* 68) (Figure 4) is not a favored process. This is understandable since it must involve fission between two vinylic linkages.

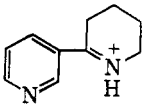


IVa o, *m/e* 145

p

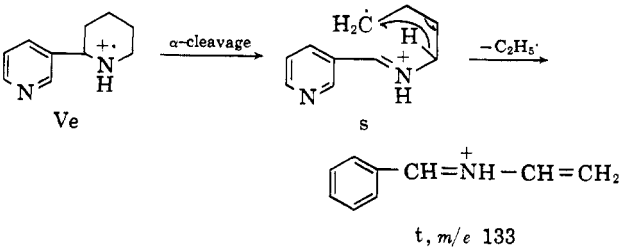
q, *m/e* 118 q′, *m/e* 68

Anabasine. The presence of a piperidine ring in anabasine results in a more complex spectrum than was observed for nicotine (Figure 1). The M − 1 ion in the mass spectrum of anabasine[5a] (Figure 5) was suggested[6] to be represented by the species r (*m/e* 161), and deuterium labeling (Table III) is in harmony with 40% of the ion yield being designated in this manner. The remaining M − 1 species cannot be identified in the absence of other deuterated analogs.



r, *m/e* 161

The mass spectrum of anabasine (Figure 5) contains a peak at *m/e* 133 (M − 29) which (as suggested[6]) might arise from the α-cleavage product s of the molecular ion Va *via* hydrogen transfer from C-6 to the primary radical site in s followed by elimination of an ethyl radical and formation of t (*m/e* 133). Deuterium labeling (Table III) is in agreement with the postulated genesis for this ion but the source of the transferred hydrogen was not determined, and the possibility remains that this could be supplied from either C-2′ or C-4′ of the pyridine ring analogous to the situation existing in nicotine (b → d) and nornicotine (I, R = H).

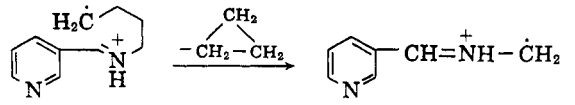


Ve s

t, *m/e* 133

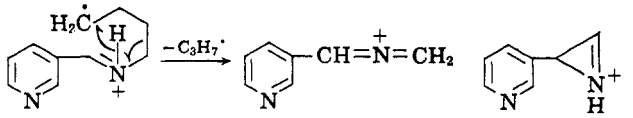
The production of the ion of mass 120 (M − 42) in the spectrum of anabasine (Figure 5) might occur by expulsion[5a] of cyclopropane from s with the formation of l (*m/e* 120). Deuterium labeling (Table III), how-

ever, is consistent with only 50% of the ion yield arising in this manner and a second process, requiring loss of the hydrogen atom on nitrogen, is required to satisfy the 50% displacement of *m/e* 120 to *m/e* 121 observed in the spectrum of anabasine-N-d_1.



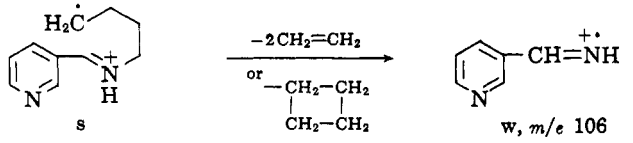
s I, *m/e* 120

Loss of 43 mass units from the molecular ion (Va) of anabasine generates an ion of mass 119 in the spectrum (Figure 5) of this compound; this has been explained[6] as being formed by hydrogen transfer from nitrogen to the primary radical site in s with the elimination of a propyl radical and formation of u (*m/e* 119). Such a mechanism accounts for 60% of the ion yield at *m/e* 119 because in the spectrum of anabasine-N-d_1 40% was displaced to *m/e* 120 (Table III). The remaining 40% may correspond to v which would be formed by a process completely analogous to that depicted in b → d′. Deuterium labeling at C-6 will be required to establish this proposal, but in spite of extensive experimentation we were unable to synthesize this labeled analog.



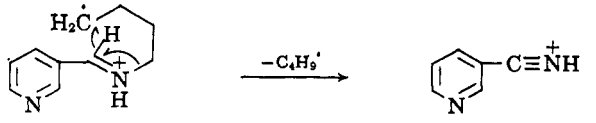
s u, *m/e* 119 v, *m/e* 119

Elimination of cyclobutane (or two molecules of ethylene) from s was postulated[5a,6] for the genesis of the ion of mass 106 (M − 56) in the spectrum (Figure 5) of anabasine, and the resulting species was assigned[6] structure w. The spectra of the deuterated analogs are in agreement with this representation (Table III).



s w, *m/e* 106

The ion of mass 105 (M − 57) in the spectrum of anabasine could arise from transfer of hydrogen from C-2 in s to satisfy the primary radical site, followed by expulsion of a butyl radical and generation of x (*m/e* 105). Deuterium labeling (Table III) is consistent with formation of 65% of the ion yield by this mechanism as only this amount remained at *m/e* 105 in the spectrum of anabasine-2-d_1. The even-electron species x (*m/e* 105) might also be produced by hydrogen expulsion from w (*m/e* 106), but no metastable ion corresponding to this transition could be discerned.



s x, *m/e* 105

The base peak in the spectrum (Figure 5) of anabasine occurs at *m/e* 84 (M − 78) and corresponds to loss of the pyridine ring through α-cleavage of the molecular

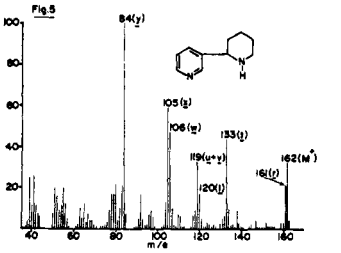
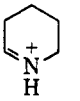


Figure 5. Mass spectrum of anabasine (II).

ion (Va) to yield y (*m/e* 84). This proposal[5a,6] is consistent with the spectra of the deuterated analogs (*m/e* 84 quantitatively displaced to *m/e* 85 in anabasine-N-d_1 and -2-d_1) and is analogous to the formation of the base peaks in nicotine (f) and continine (g).



y, *m/e* 84

Summary

Deuterium labeling has shown the mass spectrometric fragmentations of nicotine, nornicotine, and anabasine to be more complex than was originally thought, as often more than one process is responsible for the formation of a particular ion. Nevertheless many of the processes do follow the general guidelines laid down in the earlier study[4] of the mass spectra of five- and six-membered cyclic amines.

The M − 1 species in nicotine, nornicotine, and anabasine is formed largely by loss of the hydrogen atom at C-2 affording the conjugated immonium species a, j, and r, respectively.

Loss of 29 mass units in nicotine is accomplished (80%) through expulsion of C-3 and C-4 of the N-methylpyrrolidine ring, the principal source of the transferred hydrogen being the pyridine nucleus. Sterically, the most likely sources are C-2′ and C-4′ of the pyridine ring yielding d (*m/e* 133) if the latter source is correct. Loss of 29 mass units from nornicotine yields the base peak and the hydrogen eliminated in this rearrangement ion also appears to originate from the aromatic ring.

The most pronounced cleavage in nicotine and anabasine (as well as continine) results from α-cleavage and expulsion of a pyridyl radical.

Experimental[16]

4,4-Dibromocontinine (IV, R = Br). To nicotine (5 g.) in glacial acetic acid–water (4:1, 15 ml.) bromine (18 g.) in the same solvent (18 ml.) was added dropwise during 1 hr. After standing at room temperature overnight, water (20 ml.) was added followed by sodium sulfite until the solution was colorless. The reaction mixture was made alkaline with potassium

(16) Mass spectra were obtained with a Consolidated Electrodynamics Corp. Model No. 21-103C mass spectrometer using an all-glass inlet system heated to 200°. The ionizing energy was maintained at 70 e.v. and the ionizing current at 50 μa. Preparative vapor phase chromatography was conducted on a Wilkens Aerograph instrument using 20% polybutylene glycol[17] as the stationary phase at a temperature of 195° and helium pressure of 8 p.s.i. Under these conditions nicotine had a retention time of 8 min., nornicotine 12 min., and anabasine 15 min.

(17) L. D. Quin, *J. Org. Chem.*, **24**, 911 (1959).

carbonate, and the solid was filtered and washed with a little water and recrystallized from aqueous ethanol, yielding 4,4-dibromocontinine (1 g.) as needles, m.p. 124° (lit.[7] m.p. 125°), $\nu_{max}^{CHCl_3}$ 1715 cm.$^{-1}$ (five-membered lactam).

Continine (5-Oxonicotine) (IV, R = H). 4,4-Dibromocontinine (280 mg.) in glacial acetic acid (10 ml.) was stirred for 18 hr. at room temperature with zinc dust (1 g.). Water (10 ml.) was added and the reaction mixture was rendered alkaline (potassium carbonate) and extracted with chloroform, yielding a clear oil (134 mg.) which was distilled at 130–140° (0.8 mm.) (air-bath temperature).

Nicotine-5,5-d_2. Continine (28 mg.) in anhydrous ether (15 ml.) was reduced with lithium aluminum deuteride (45 mg.). Excess reagent was destroyed with water, the inorganic suspension was removed by filtration, and the residual product (24 mg.) was distilled, b.p. 60–65° (0.8 mm.) (air-bath temperature). Mass spectrometry indicated the presence of 97% d_2 species.

Continine-4,4-d_2. Continine (55 mg.) was heated under reflux for 12 days with deuterium oxide (2 ml.) containing anhydrous potassium carbonate (60 mg.).[9] The reaction mixture was cooled and lyophilized, and the dry residue was leached with chloroform. Removal of the solvent afforded continine-4,4-d_2 (40 mg.), shown by mass spectrometry to contain 92% d_2 and 8% d_1 species.

Nicotine-4,4-d_2. Lithium aluminum hydride reduction of continine-4,4-d_2 (35 mg.) in dry ether (10 ml.) and processing as described for the preparation of nicotine-5,5-d_2 yielded nicotine-4,4-d_2 of 92% d_2 and 8% d_1 composition (mass spectrometry).

Nicotine-N-d_3. Nornicotine (65 mg.) in methanol (0.1 ml.) was treated with trideuteriomethyl iodide (0.025 ml. 92% d_3 species) in methanol (0.025 ml.)[12] and the reaction mixture was allowed to stand at room temperature for 4 days. Ether (1.5 ml.) was added, the reaction mixture was shaken well, and the ether layer was removed. Repetition of this process with ether (1.5 ml.), combination of the ether extracts, and removal of the solvent afforded an oil (25 mg.). Nicotine-N-d_3 was isolated by preparative vapor phase chromatography[16] and was shown by mass spectrometry to contain 92% d_3 species.

Nornicotine-2-d_1. Catalytic deuteration of myosmine[14] (95 mg.) over 10% palladium on carbon (50 mg.) in anhydrous ethyl acetate (15 ml.) during 7 hr. and preparative vapor phase chromatography[16] of the product yielded nornicotine-2-d_1 of 65% d_1 and 35% d_0 composition.

Nicotine-2-d_1. Nornicotine-2-d_1 (70 mg.) was heated under reflux during 5 hr. with 80% formic acid (0.1 ml.) containing 30% formaldehyde (0.2 ml.). The crude reaction mixture was basified (sodium hydroxide), extracted with ether, and nicotine-2-d_1 was isolated by preparative vapor phase chromatography.[16] Mass spectrometry showed the product to consist of 65% d_1 and 35% d_0 species.

Nornicotine-N-d_1 and Anabasine-N-d_1. These compounds were prepared by shaking the amine (20 mg.) with deuterium oxide (0.1 ml.) and then determining the mass spectrum.[8,12b] The following deuterium incorporations were obtained: nornicotine-N-d_1, 90% d_1 and 10% d_0; anabasine-N-d_1, 90% d_1 and 10% d_0.

Anabasine-2-d_1. Anabasene dipicrate was prepared according to Späth[13] and had m.p. 170–172° (lit.[13] m.p. 173–174°). Anabasene was recovered from its dipicrate as previously described[13] and distilled, b.p. (0.8 mm.) (air-bath temperature). The product (120 mg.) was immediately dissolved in anhydrous ethyl acetate (20 ml.) and stirred for 20 hr. with 5% palladium on carbon in an atmosphere of deuterium. Anabasine-2-d_1 was isolated by preparative vapor phase chromatography[16] and shown by mass spectrometry to contain 70% d_1 and 30% d_0 species.

Strain Effects. II. Diimide Reductions of Olefins

Edgar W. Garbisch, Jr.,[1a] Steven M. Schildcrout,[1b] Dennis B. Patterson,[1b] and Carol M. Sprecher[1a]

Contribution from the Departments of Chemistry, University of Minnesota, Minneapolis, Minnesota, and University of Chicago, Chicago, Illinois.
Received January 15, 1965

Relative rates of diimide reductions of nearly 40 cyclic, exocyclic, and acyclic alkenes have been determined at 80°. The relative reactivities which are found to vary over a range of 38,000 have been qualitatively calculated. The agreement found between the calculated and observed values (generally within a factor of 2) suggests that the major factors that contribute to the observed reactivity differences are torsional strain, bond angle bending strain, and α-alkyl substituent effects. Some possibly significant conclusions regarding structure vs. reactivity and stereoselectivity of diimide reductions of alkenes are discussed in the light of the available data.

The influence of structure on the reactivities of alkenes toward various types of addition reactions has been investigated in some detail within the past 20

(1) (a) University of Minnesota; (b) American Chemical Society Petroleum Research Fund Scholar, University of Chicago.