acid (20 ml.) containing concentrated sulfuric acid (6 ml.) and distillation of the product from the reaction mixture into water afforded bromopropane-2,2-d_2 (9 g.) after isolation with ether. Mass spectrometry indicated the presence of 95% d_2 and 5% d_1 species.

The Grignard reagent, prepared from bromopropane-2,2-d_2 (4 g.) and magnesium turnings (0.7 g.) in ether (25 ml.), was poured onto crushed Dry Ice (30 g.). After evaporation of the excess Dry Ice 2 *N* hydrochloric acid (25 ml.) was added and *n*-butyric-3,3-d_2 acid (1.5 g.) isolated with ether. Reduction with lithium aluminum hydride afforded butanol-3,3-d_2 (0.95 g.) which was converted to bromobutane-3,3-d_2 (600 mg.) as described above.

Bromobutane-2,2-d_2. Reduction of propionic acid (3 g.) with lithium aluminum deuteride (1.3 g.) in anhydrous ether (50 ml.) afforded propanol-1,1-d_2 (2.5 g.) which yielded bromopropane-1,1-d_2 (3.0 g.) on bromination. The Grignard reagent, prepared from magnesium turnings (0.7 g.) in ether (25 ml.), was poured onto crushed Dry Ice (20 g.). The reaction was processed as described for the preparation of bromobutane-3,3-d_2 yielding *n*-butyric-2,2-d_2 acid (1.3 g.) which, after reduction with lithium aluminum hydride and bromination, gave bromobutane-2,2-d_2 (0.5 g.).

Bromobutane-1,1-d_2. Lithium aluminum deuteride reduction of *n*-butyric acid and bromination of the product afforded bromobutane-1,1-d_2.

Bromopentane-4,4-d_2. The Grignard reagent, prepared from bromopropane-2,2-d_2 (4.5 g.) and magnesium turnings (0.7 g.) in dry ether (20 ml.), was cooled to 0°, and ethylene oxide (6 g.) in dry ether (5 ml., cooled to −10°) was added. The reactants were stirred and slowly allowed to attain room temperature over a period of 6 hr., after which time they were heated under reflux for 30 min. Benzene (10 ml.) was added and solvent was removed by distillation until the temperature of the liquid remaining in the flask was 65°. After heating under reflux for a further 30 min. water (10 ml.) was added followed by 15% sulfuric acid (10 ml.). Isolation with ether and distillation afforded a clear liquid (3.5 g.) which was heated under reflux during 10 min. with 20% aqueous sodium hydroxide solution (10 ml.), and pentanol-4,4-d_2 (1.4 g.) isolated with ether. Bromination afforded bromopentane-4,4-d_2 (1.1 g.), shown by mass spectrometry to consist of 95% d_2 and 5% d_1 species.

Bromopentane-3,3-d_2. The Grignard reagent, prepared from bromopropane-1,1-d_2 (2 g.), was treated with ethylene oxide (3 g.) as described for the preparation of bromopentane-4,4-d_2, yielding after bromination bromopentane-3,3-d_2 (225 mg.).

N-Alkylation of Pyrrole. Pyrrole (200 mg.) was added to a suspension of sodium hydride (150 mg.) in tetrahydrofuran (2 ml., distilled from lithium aluminum hydride) under a nitrogen atmosphere. The reactants were stirred at room temperature for 30 min. when the labeled alkyl bromide (100 mg.) in dry tetrahydrofuran (1 ml.) was added and stirring under a nitrogen atmosphere continued overnight. Water (20 ml.) was added, the products were isolated with ether, and the desired N-alkylpyrrole was separated from unreacted pyrrole by vapor phase chromatography.[17]

Pyrrole-2,3,4,5-d_4. 30% Palladium on charcoal was stirred under deuterium gas in ethyl acetate during 1 hr. and collected by filtration. This catalyst (100 mg.), pyrrole (200 mg.), and deuterium oxide (3 ml.) were sealed in an evacuated tube (water pump) and heated at 100° for a period of 18 hr. The product was isolated with ether and distilled. Mass spectrometry indicated the presence of 80% d_4, 15% d_3, and 5% d_2 species. Repetition of this process raised the isotopic composition to 90% d_4, 7% d_3, and 3% d_2 species.

N-n-Butyl- and N-n-Pentylpyrrole-2',3',4',5'-d_4. These compounds were prepared from pyrrole-2,3,4,5-d_4 following the general procedure described for N-alkylation of pyrrole.

N-n-(Butyl-3,3-d_2)pyrrole-2',3',4',5'-d_4. Condensation of bromobutane-3,3-d_2 with pyrrole-2,3,4,5-d_4 using the general procedure described for N-alkylation of pyrrole yielded N-*n*-(butyl-3,3-d_2)pyrrole-2',3',4',5'-d_4 of 88% d_6, 7% d_5, and 5% d_4 species.

Mass Spectrometry in Structural and Stereochemical Problems. LXIV.[1] A Study of the Fragmentation Processes of Some Cyclic Amines[2]

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

Contribution from the Department of Chemistry, Stanford University, Stanford, California. *Received October 19, 1964*

Plausible mechanistic interpretations of the principal ions formed in the mass spectrometric fragmentation of pyrrolidine, N-methylpyrrolidine, piperidine, and N-methylpiperidine are presented. Deuterium labeling established the sources of hydrogen transfer in many of the rearrangement ions and which atoms were implicated in each of the ions studied. High-resolution mass spectrometry was used to determine the composition of many of the ions studied.

(1) Paper LXIII: A. M. Duffield, R. Beugelmans, H. Budzikiewicz, D. A. Lightner, D. H. Williams, and C. Djerassi, *J. Am. Chem. Soc.*, **87**, 805 (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.

In continuation of our work on the mass spectrometric fragmentation of relatively simple organic molecules,[4] and as a background to a similar investigation of tobacco alkaloids, a study of pyrrolidine, piperidine, and their N-methylated analogs has been undertaken as typical representatives of five- and six-membered cyclic amines. Mechanistic interpretations of the ions formed on mass spectrometric fragmentation of pyrrolidine and piperidine have appeared,[5] and the present investigation was undertaken to test the validity of these suggestions.

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

Compound	Isotopic purity	m/e M+	M − 1	M − 3	M − 28	M − 29	M − 41
Pyrrolidine		71	70	68	43	42	30
Pyrrolidine-N-*d*	90% d_1 10% d_0	72	71 (q)	69 (q)	44 (q)	42 (q)	31 (q)
Pyrrolidine-2,2-d_2	98% d_2	73	72 (60%) 71 (40%)	69 (80%) 70 (20%)	45 (q)	44 (q)	30 (50%) 32 (50%)
Pyrrolidine-3,3-d_2	84% d_2 16% d_1	73	71 (q)	69 (55%) 70 (45%)	43 (q)	42 (q)	30 (50%) 31 (50%)

[a] Tables I–IV show the per cent shift of the compounds discussed when specifically labeled with deuterium. Sometimes the quantitative shift in a peak is difficult to observe due to the presence of adjacent peaks and in such cases any quantitative information which could be obtained is given. The symbol (q) signifies a quantitative transfer (>95%), while the transfers quoted are considered to be accurate to ±5% for peaks in excess of 20% relative abundance.

Deuterium labeling[6] of these cyclic amines was achieved by lithium aluminum deuteride reduction of the appropriate lactam (yielding 2,2-dideuterio compounds) or by lithium aluminum hydride reduction of the appropriate 3,3-dideuterated lactam.[4] Reduction of N-formylpyrrolidine[7] or N-formylpiperidine[7] with lithium aluminum deuteride yielded the corresponding N-(methyl-d_2) cyclic amine. The active hydrogen atom of pyrrolidine and piperidine was exchanged for deuterium in the mass spectrometer.[6]

Pyrrolidine (Figure 1). The mass spectrum of pyrrolidine[8] displays a molecular ion of some intensity (Figure 1) which can be represented[5] as arising from pyrrolidine by loss of a nonbonding electron from nitrogen.

I, *m/e* 71 a, *m/e* 70 b, *m/e* 68 b′, *m/e* 68

The M − 1 species in the spectrum of pyrrolidine was represented as a,[5] and this has now been confirmed by deuterium labeling (Table I). The spectrum of pyrrolidine-2,2-d_2 exhibited both M − 1 and M − 2 ions and an isotope effect[9] discriminating against deuterium (Table I) was observed.

An ion of low abundance at *m/e* 68 (M − 3) in the spectrum of pyrrolidine (Figure 1) was shifted to *m/e* 69 in the N-d_1 analog, to *m/e* 69 (80%) in pyrrolidine-2,2-d_2, and distributed between *m/e* 69 (55%) and 70 (45%) in the 3,3-d_2 analog. These displacements are consistent with the formation of this ion from a through loss of one hydrogen atom each from an α- and β-carbon atom and its representation as b, although some contribution from species b′ is indicated.

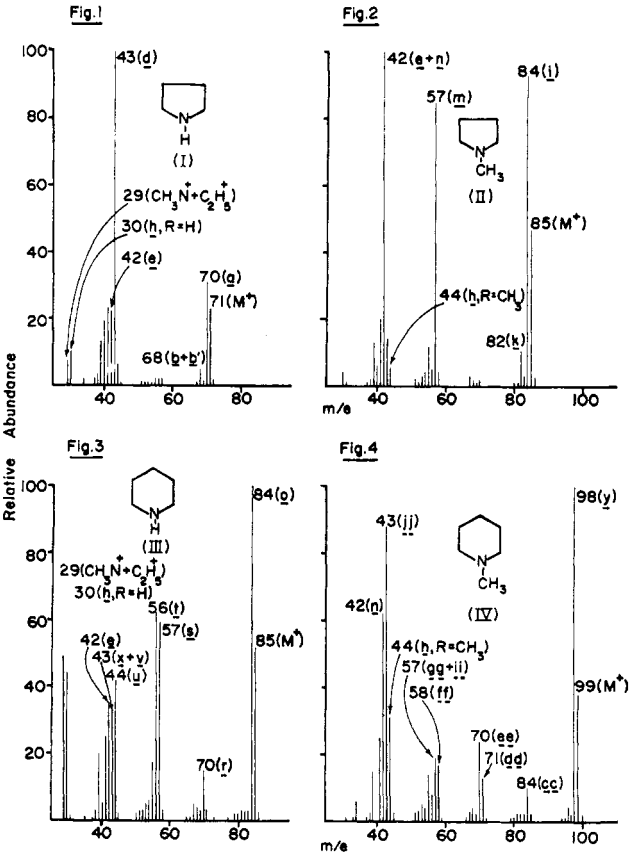
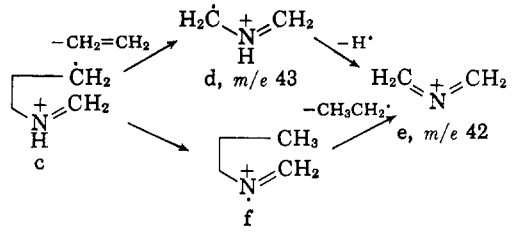


Figure 1. Mass spectrum of pyrrolidine.
Figure 2. Mass spectrum of N-methylpyrrolidine.
Figure 3. Mass spectrum of piperidine.
Figure 4. Mass spectrum of N-methylpiperidine.

(4) A. M. Duffield, H. Budzikiewicz, and C. Djerassi, *J. Am. Chem. Soc.*, **86**, 5536 (1964), and ref. 4 therein.
(5) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Interpretation of Mass Spectra of Organic Compounds," Holden-Day Inc., San Francisco, Calif., 1964, pp. 98–102.
(6) For a review of the methods currently available 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. 1, Holden-Day Inc., San Francisco, Calif., 1964, Chapter 2.
(7) F. F. Blicke and C.-J. Lu, *J. Am. Chem. Soc.*, **74**, 3933 (1952).
(8) "Catalog of Mass Spectral Data," American Petroleum Institute Research Project 44, Carnegie Institute of Technology, Pittsburgh, Pa., spectrum no. 1533.
(9) (a) D. H. Williams, H. Budzikiewicz, and C. Djerassi, *J. Am. Chem. Soc.*, **86**, 284 (1964); (b) V. H. Dibeler and F. L. Hohler, *J. Res. Natl. Bur. Std.*, **45**, 441 (1950); (c) D. O. Schissler, S. O. Thompson, and J. Turkevich, *Discussions Faraday Soc.*, **10**, 46 (1951).

N-Methylpyrrolidine has a more prominent peak in its spectrum, corresponding to the loss of three mass units (Figure 2), which arises from a similar process as b (see below).

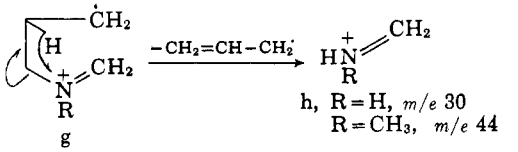
The alternative mode of α-cleavage of the molecular ion (I), namely, rupture of the 2,3-carbon–carbon bond and formation of c, followed by elimination of ethylene, was postulated[5] for the genesis of the fragment of mass 43 which was assigned structure d. This assignment has now been substantiated from the spectra of pyrrolidine-2,2-d_2 and -N-d_1 in which quantitative shifts to *m/e* 45 and 44 were observed. Further support for the process c → d was obtained from the spectrum of pyrrolidine-3,3-d_2 in which the ion at mass 43 was unaffected.



The ion of mass 42 (M − 29) in the spectrum of pyrrolidine could arise from loss of the hydrogen atom on nitrogen in d yielding e (*m/e* 42), and the occurrence of this process is supported by recognition of a metastable ion at *m/e* 41 ($42^2/43 = 41$). An alternative genesis for a portion of the peak of mass 42 can be envisaged as proceeding *via* transfer of the hydrogen atom on nitrogen in c to yield f, followed by expulsion of an ethyl radical. The deuterium labeling results (Table I) are consistent with structure e for the *m/e* 42 species.

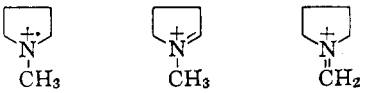
It is pertinent to note that earlier appearance potential measurements[10] had already established that the ions of mass 42 and 43 in the spectrum of pyrrolidine contain nitrogen and hence the isobaric ions $C_3H_6^+$ and $C_3H_7^+$ are eliminated from consideration.

A peak of low intensity at *m/e* 30 in the spectrum of pyrrolidine (Figure 1) shifted to the extent of 50% to *m/e* 32 in pyrrolidine-2,2-d_2 and to a similar degree to *m/e* 31 in pyrrolidine-3,3-d_2, while the N-d_1 analog registered a quantitative shift to *m/e* 31 (see Table I). High-resolution mass spectrometry (apparent resolution 1 in 15,000) established that this peak consisted entirely of the CH_4N^+ species. A mechanism consistent with the observed shifts in the spectra of the deuterated analogs is transfer of a β-hydrogen atom to nitrogen in g with concomitant carbon–nitrogen bond fission and formation of h (R = H, *m/e* 30) and the allyl radical.

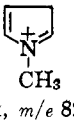


High-resolution mass spectrometry determined the composition of the peak at *m/e* 29 as CH_3N^+ (60%) and $C_2H_5^+$ (40%). As the abundance of *m/e* 29 is 80% that of *m/e* 30 (Figure 1), it is impossible for the increase of *m/e* 31 in pyrrolidine-3,3-d_2 to be entirely due to a dideuterated ethyl ion and hence the hydrogen transfer depicted in g → h (R = H) must occur. Such a transfer of a β-hydrogen atom to nitrogen with synchronous carbon–nitrogen bond fission has been established as an important process in the mass spectrometric fragmentation of some five- and six-membered lactams[4] and also has been postulated to account for the production of some rearrangement ions observed in the spectra of certain aliphatic amines.[11]

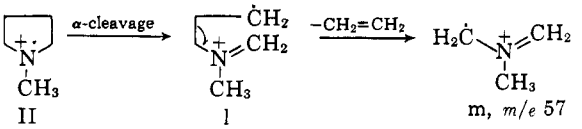
N-Methylpyrrolidine (Figure 2). Loss of a nonbonding electron from N-methylpyrrolidine would generate the molecular ion which we represent as II. Elimination of hydrogen from II might occur in two ways with the production of either i or j or a mixture of these two ions. Deuterium labeling (Table II) indicated no loss of deuterium from the N-methyl group so that the M − 1 species must be represented by i, and its preferred formation over j can be explained by the greater energy necessary for rupture of a primary carbon–hydrogen bond as compared to its secondary counterpart.



The mass spectrum of N-methylpyrrolidine is somewhat exceptional in exhibiting an M − 3 fragment of appreciable abundance (10% of the base peak, Figure 2). Deuterium labeling (Table II) established that 90% of this ion corresponded to a loss of two α- and one β-hydrogen atoms. It thus may be represented as k (*m/e* 82).



The genesis of the fragment of mass 57 (M − 28) in the spectrum of N-methylpyrrolidine is completely analogous to the formation of d (*m/e* 43) in pyrrolidine. High-resolution mass spectrometry[12] demonstrated that this peak was homogeneous, consisting only of the $C_3H_7N^+$ species. It may be considered as arising from II by α-cleavage to l, followed by elimination of ethylene to yield m (*m/e* 57). This proposal is in complete agreement with the results of deuterium labeling (Table II).



The spectrum (Figure 2) of N-methylpyrrolidine contains a peak of weak intensity at *m/e* 44 whose genesis may be ascribed to an identical process as that used to explain the ion h of mass 30 in the spectrum of pyrrolidine. A quantitative shift to *m/e* 46 was observed in N-methylpyrrolidine-N-d_2; in N-methylpyrrolidine-2,2-d_2 50% of the *m/e* 44 peak shifted to *m/e* 46 while the spectrum of the 3,3-d_2 analog displayed a 40%

(10) E. J. Gallegos and R. W. Kiser, *J. Phys. Chem.*, **66**, 136 (1962).

(11) R. S. Gohlke and F. W. McLafferty, *Anal. Chem.*, **34**, 1281 (1962).

(12) R. A. Saunders and A. E. Williams in "Mass Spectrometry of Organic Ions," F. W. McLafferty, Ed., Academic Press Inc., New York, N. Y., 1963, p. 371.

Table II. Principal Mass Spectral Peaks of N-Methylpyrrolidine and Deuterated Analogs

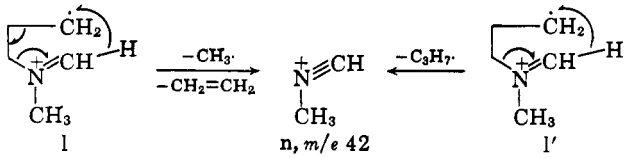
Compound	Isotopic purity	m/e M+	M − 1	M − 3	M − 28	M − 41	M − 43
N-Methylpyrrolidine		85	84	82	57	44	42
N-Methylpyrrolidine-N-d_2	98% d_2	87	86 (q)	84 (q)	59 (q)	46 (q)	44 (50%) 43 (8%) 42 (42%)
N-Methylpyrrolidine-2,2-d_2	98% d_2	87	86 (65%) 85 (35%)	84 (10%) 83 (90%)	59 (q)	46 (50%)	44 (46%) 43 (24%) 42 (30%)
N-Methylpyrrolidine-3,3-d_2	95% d_2 5% d_1	87	86 (q)	84 (50%) 83 (50%)	57 (q)	45 (40%) 44 (60%)	42 (q)

Table III. Principal Mass Spectral Peaks of Piperidine and Deuterated Analogs

Compound	Isotopic Purity	m/e M+	M − 1	M − 15	M − 28	M − 29	M − 41	M − 42	M − 43	M − 55
Piperidine		85	84	70	57	56	44	43	42	30
Piperidine-N-d	90% d_1 10% d_0	86	85 (q)	71 (80%)	58 (90%)	57 (90%)	45 (q)	43 (70%) 44 (30%)	42 (q)	31 (q)
Piperidine-2,2-d_2	98% d_2	87	86 (67%) 85 (33%)	72 (60%) 71 (40%)	59 (q)	58 (50%) 57 (50%)	46 (q)	45 (q)	44 (q)	30 (50%) 32 (50%)
Piperidine-3,3-d_2	92% d_2 8% d_1	87	86 (q)	72 (50%) 70 (50%)	59 (40%) 57 (60%)	57 (50%) 56 (50%)	44 (q)	43 (q)	42 (85%)	30 (62%) 31 (38%)

transfer to *m/e* 45. Transfer of a β-hydrogen atom to nitrogen in g (R = CH_3) with simultaneous carbon–nitrogen bond fission would yield h (R = CH_3, *m/e* 44).

The very intense peak at *m/e* 42 (M − 43) in N-methylpyrrolidine consists entirely of the $C_2H_4N^+$ species, and it was suggested[12] that it may have structure e. Loss of a methyl radical from m (*m/e* 57) would afford e, and a metastable ion at *m/e* 31 ($42^2/57$ = 30.9) furnishes support for such a reaction. However, in the spectrum of methylpyrrolidine-N-d_2 50% of the *m/e* 42 peak shifted to *m/e* 44 and it was apparent that a second mechanism retaining the N-methyl group was being utilized in the formation of this ion. In the spectrum of the 2,2-d_2 analog the fragment of mass 42 appeared in part at *m/e* 43 (24%) and 44 (46%), the remainder being unaffected. A mechanism involving the concerted loss of a methyl radical and ethylene from l affording the triply unsaturated ion n is consistent with the observed shifts in the spectra of the deuterated analogs (Table II). A stepwise process (l′) with loss of a propyl radical (rather than methyl and ethylene) is, of course, equally feasible. It is interesting to note



l n, *m/e* 42 l′

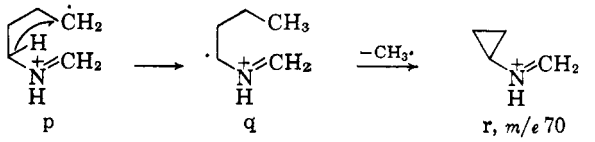
that a mechanism similar to l → n was found to be responsible for the major portion (60%) of the *m/e* 42 peak in the mass spectrum of N-methyl-2-pyrrolidone.[4]

Piperidine (Figure 3). The most intense peak in the spectrum of piperidine[13] occurs at *m/e* 84 (M − 1) and deuterium labeling shows it to be associated with the loss of an α-hydrogen atom (Table III). This process can be rationalized as α-cleavage of the molecular ion (III) with the formation of o. A very substantial isotope effect,[9] similar to that operating in the pyrrolidine series (Tables I and II), discriminating against deuterium, was observed in the formation of this fragment in piperidine-2,2-d_2 (Table III). No loss of deuterium was observed in the spectrum of piperidine-N-d_1 and hence elimination of the hydrogen atom on nitrogen does not contribute toward the M − 1 species.

III, *m/e* 85 o, *m/e* 84

The spectrum (Figure 3) of piperidine displays a fragment of moderate abundance at mass 70 (M − 15) which appeared to the extent of 50% at *m/e* 72 in piperidine-3,3-d_2, thus establishing that one β-carbon with its two hydrogen atoms was not incorporated into the charge-bearing species. Deuterium labeling (Table III) demonstrated that the third hydrogen atom of the expelled methyl group originated from one of the α-carbon atoms since, in the spectrum of the 2,2-d_2 analog, *m/e* 70 was displaced to *m/e* 72 (60%) and 71 (40%). These results are in agreement with the previously postulated[5] mechanism p → q → r (*m/e* 70).

The peak at *m/e* 57 (M − 28) in the spectrum of piperidine is homogeneous,[14] having the composition $C_3H_7N^+$. Deuterium labeling (Table III) indicated that the hydrogen atom on nitrogen as well as both α-

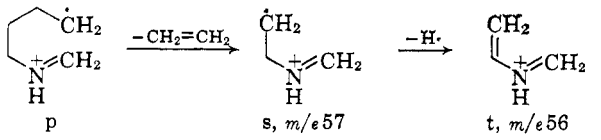


p q r, *m/e* 70

and one β-carbon together with their attached hydrogen atoms were retained in the charged species. Loss of ethylene from p would generate s (*m/e* 57), a mechanism[5] in complete agreement with the observed shifts in the deuterated analogs.

(13) Ref. 8, spectrum no. 618.

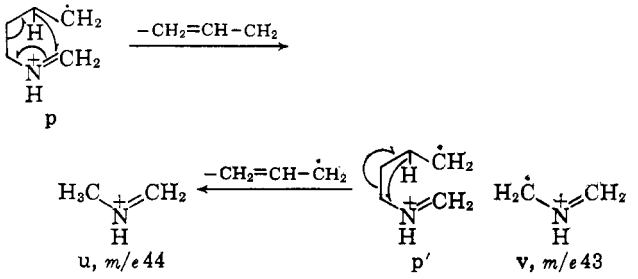
(14) We are indebted to Dr. D. F. Shaw of the University of Liverpool for some high-resolution mass spectral measurements of piperidine which were determined on an A.E.I. MS-9 mass spectrometer.



p s, *m/e* 57 t, *m/e* 56

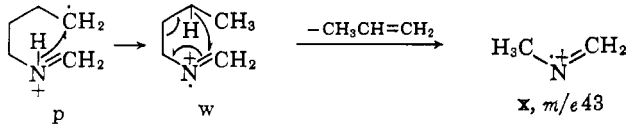
The ion of mass 56 (M − 29) consists entirely of the $C_3H_6N^+$ species,[14] and deuterium labeling (Table III) is consistent with the loss of hydrogen from s and formation of t (*m/e* 56); the occurrence of this process was supported by recognition of a metastable ion at *m/e* 55.1 ($56^2/57 = 55.0$). An alternative path[5] to the latter ion involving loss of an ethyl radical from q cannot be excluded, although no metastable ion justifying this transition could be discerned.

The fragment of mass 44 (M − 41) is homogeneous,[14] corresponding to $C_2H_6N^+$, and is completely shifted to *m/e* 45 and 46, respectively, in the spectra of the N-d_1 and 2,2-d_2 analogs, while in piperidine-3,3-d_2 no change in mass was observed (see Table III). The only remaining position from which hydrogen could be transferred is C-4 and mechanisms consistent with these facts can be depicted in terms of six- (p → u) or four- (p′ → u) membered intermediates, the expelled neutral fragment being the allyl radical.



p u, *m/e* 44 p′ v, *m/e* 43

High-resolution mass spectrometry established the composition of the peak at *m/e* 43 (M − 42) as $C_2H_5N^+$ (96%) and $C_3H_7^+$ (4%). Loss[5] of cyclopropane from p would yield the ion radical v (*m/e* 43). However, no more than 30% of *m/e* 43 can be represented as v since only this amount shifted to *m/e* 44 in the piperidine-N-d_1 spectrum. The remainder of this ion must arise from loss of the hydrogen atom on nitrogen with transfer of a second hydrogen atom to the charged species. This transfer does not originate from either C-2 or C-3 (Table III), and hence must occur from C-4. A mechanism consistent with these results is shown in p → x (*m/e* 43), the eliminated neutral species being propene.

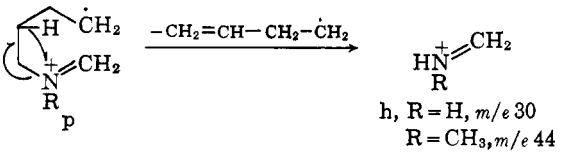


p w x, *m/e* 43

The ion x would also result if the hydrogen transfer in w occurred *via* a four-membered intermediate to the α-methylene group with concomitant α,β-carbon bond rupture.

The ion of mass 42 (M − 43) in the spectrum of piperidine is also homogeneous[14] and corresponds to $C_2H_4N^+$. *A priori*, this fragment could be formed by three mechanisms involving loss of hydrogen from either *m/e* 43 species (v or x), or by elimination of a propyl radical[5] from w. No loss of deuterium was found to occur from C-2 in the formation of the ion of mass 42 (Table III), and hence the possibility of loss of hydrogen from species x can be discarded. The labeling results show that transfer of the hydrogen attached to nitrogen is involved, which, of course, does not differentiate between the remaining two possible geneses of *m/e* 42 but is in agreement with its representation as e.

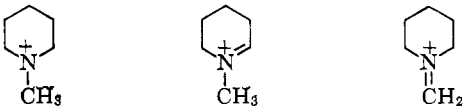
Piperidine (Figure III) has a more intense peak at *m/e* 30 than pyrrolidine (Figure 1), and high-resolution mass spectrometry established its composition as CH_4N^+. Deuterium labeling (Table III) showed that a quantitative transfer to *m/e* 31 occurred in piperidine-N-d_1 while the 2,2-d_2 analog exhibited a 50% shift to *m/e* 32. In piperidine-3,3-d_2 a 38% transfer to *m/e* 31 was observed, and this is consistent with the genesis of this ion in terms of p → h (R = H, *m/e* 30).



p h, R = H, *m/e* 30; R = CH_3, *m/e* 44

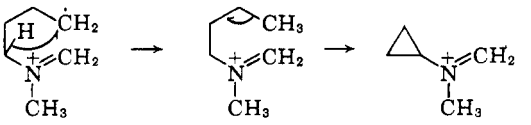
The composition of the peak at *m/e* 29 in piperidine (Figure 3) was shown by high-resolution mass spectrometry to consist of CH_3N^+ (70%) and $C_2H_5^+$ (30%). As this peak is only slightly more intense than that at *m/e* 30, it is impossible that the transfer of *m/e* 30 to 31 observed in the 3,3-d_2 analog could be due completely to a dideuterated ethyl radical, and the mechanism p → h must be valid for at least a portion of the ion yield at *m/e* 30.

N-Methylpiperidine (*Figure 4*). Loss of a nonbonding electron from nitrogen in N-methylpiperidine would generate the molecular ion IV. The M − 1 species has its genesis from loss of an α-hydrogen atom (Table IV) and is represented by y (*m/e* 98). Just as in N-methylpyrrolidine (Table II), no loss of deuterium was observed in the spectrum of methylpiperidine-N-d_2, thus showing that the ion z does not contribute to the M − 1 species.



IV y, *m/e* 98 z

Deuterium labeling (Table IV) substantiated the genesis of the fragment of low abundance at *m/e* 84 (M − 15), arising from aa → bb → cc, a mechanism analogous to that used in explaining the genesis of the ion r (*m/e* 70) in piperidine.

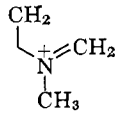


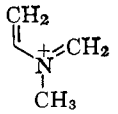
aa bb cc, *m/e* 84

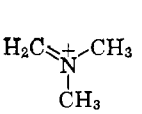
The ions at *m/e* 71 (M − 28) and 70 (M − 29) in N-methylpiperidine have been shown by deuterium labeling (Table IV) to be represented by dd and ee, respectively, their mode of origin being analogous to that of s (*m/e* 57) and t (*m/e* 56) in piperidine.

Table IV. Principal Mass Spectral Peaks of N-Methylpiperidine and Deuterated Analogs

Compound	Isotopic purity	m/e M+	M − 1	M − 15	M − 28	M − 29	M − 41	M − 42	M − 55	M − 56	M − 57
N-Methylpiperidine		99	98	84	71	70	58	57	44	43	42
N-(Methyl-d_2)piperidine	98% d_2	101	100 (q)	86 (90%)	73 (q)	72 (q)	60 (q)	58 (40%) 59 (60%)	46 (80%)	45 (q)	44 (q)
N-Methylpiperidine-2,2-d_2	98% d_2	101	99 (40%) 100 (60%)	86 (50%) 85 (50%)	73 (q)	71 (45%) 72 (55%)	60 (q)	59 (q)	46 (40%) 44 (60%)	43 (40%) 45 (60%)	42 (50%) 43 (40%)
N-Methylpiperidine-3,3-d_2	95% d_2 5% d_1	101	100 (q)	86 (50%) 84 (50%)	71 (40%) 73 (60%)	70 (45%) 72 (55)	58 (q)	57 (q)	44 (65%) 45 (35%)	43 (q)	42 (q)

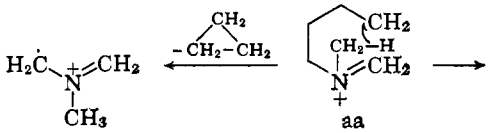

dd, *m/e* 71

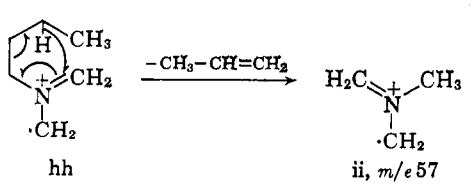

ee, *m/e* 70


ff, *m/e* 58

The fragment of mass 58 (M − 41) in the spectrum (Figure 4) of N-methylpiperidine is shifted to *m/e* 60 in both the N-methyl-d_2 and N-methyl-2,2-d_2 analogs and is unchanged in the 3,3-dideuterio compound. The hydrogen transferred in the formation of this ion must originate from C-4, and a mechanism completely analogous to p (or p′) → u would rationalize the production of this species (ff, *m/e* 58).

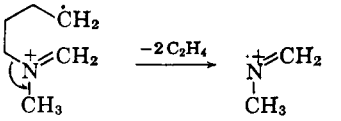
Deuterium labeling established that the ion of mass 57 (M − 42) originated *via* two mechanisms. This became apparent on examination of the spectrum of methylpiperidine-N-d_2 in which *m/e* 57 shifted to 58 (40%) and 59 (60%). Assuming no isotope effect,[9a-c] 40% of the abundance of the fragment of mass 57 must arise from a process retaining the N-methyl group (aa → gg, Table IV) while 60% has its genesis from hydrogen transfer from the N-methyl group with a second hydrogen transfer to the charged fragment. (If an isotope effect of 1.5 is assumed to operate as was found for the removal of an α-deuterium atom in the compounds studied (Tables I–IV), then these results are adjusted to 30 and 70%, respectively.) This second transfer does not originate from the α- or β-carbon atoms of N-methylpiperidine (Table IV) and must occur from C-4. The mechanism aa → ii is compatible with the shifts in the spectra of the labeled compounds and accounts for 60% of the abundance of the ion at *m/e* 57. Transfer of hydrogen from C-4 in hh through a four-membered intermediate with the production of the same ion ii (*m/e* 57) cannot be excluded.


gg, *m/e* 57 aa

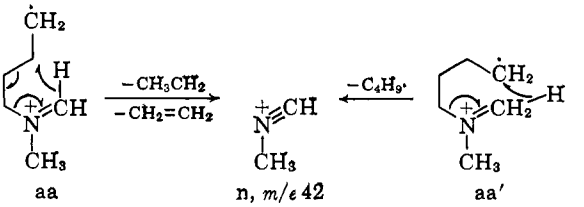

hh ii, *m/e* 57

The ion of mass 44 (M − 55) in the spectrum of N-methylpiperidine was transferred to the extent of 80 and 40%, respectively, to *m/e* 46 in the spectra of the methyl-N-d_2 and 2,2-d_2 compounds, while in N-methylpiperidine-3,3-d_2 35% of the peak appeared at *m/e* 45. The displacements in the deuterated analogs are thus similar to those observed for the *m/e* 44 peak in the N-methylpyrrolidine spectrum (Figure 2) and the *m/e* 30 peak in pyrrolidine (Figure 1) and piperidine (Figure 3). A mechanism consistent with the observed shifts in the deuterated N-methylpiperidines is given by p (R = CH_3) → h (R = CH_3, *m/e* 44).

The origin of the ion of mass 43 (M − 56) in the spectrum of N-methylpiperidine may be represented by aa → jj with the elimination of two molecules of ethylene (or one molecule of cyclobutane) and this is in harmony with the spectra (Table IV) of the deuterated analogs studied.


aa jj, *m/e* 43

Finally, deuterium labeling established that the fragment of mass 42 (M − 57) does not arise from jj (*m/e* 43) by loss of hydrogen from the methyl group since a quantitative shift to *m/e* 44 was noted in N-methylpiperidine-N-d_2. This observation also eliminated the possibility that loss of the N-methyl group from gg (*m/e* 57) contributed toward its formation. A mechanism involving loss of an ethyl radical and ethylene by a synchronous mechanism (aa) or of a butyl radical (aa′) and representation of the ion of mass 42 as n is consistent with the spectra of the deuterated analogs studied.


aa n, *m/e* 42 aa′

Summary

The formation of all of the principal ions in the mass spectrometric fragmentation of the cyclic amines studied can be explained by initial bond fission due to the usual α-cleavage[5] of the respective molecular ions with and without hydrogen rearrangement.

(i) Loss of a methyl group is not a favored process in either pyrrolidine or its N-methylated analog and occurs only to a small extent in piperidine and N-methylpiperidine, the mode of expulsion being similar in these two compounds.

(ii) The base peak in pyrrolidine has its genesis from loss of C-3 and C-4 as ethylene, and this process

accounts for an abundant ion in N-methylpyrrolidine. Expulsion of ethylene in the six-membered cyclic amines is less favored, being greater in piperidine than the N-methyl compound.

(iii) Ejection of an ethyl radical is very much less favored in pyrrolidine and its N-methylated derivatives as compared to loss of ethylene. Conversely, in the six-membered cyclic amines loss of an ethyl radical is as preferred (piperidine) or more so (N-methylpiperidine) than loss of ethylene.

(iv) α-Cleavage of the respective molecular ions between carbon atoms 2 and 3 and β-hydrogen transfer to nitrogen with concomitant carbon–nitrogen bond fission yield ions of mass 30 in pyrrolidine and piperidine and mass 44 in their N-methylated derivatives.

(v) Loss of 42 mass units in both six-membered cyclic amines is accomplished in part by loss of cyclopropane (*e.g.*, p → v) and partly by double hydrogen rearrangement and loss of propene (*e.g.*, p → x).

(vi) The spectra of both N-methylpyrrolidine and N-methylpiperidine contain a peak at *m/e* 42. In the former compound its genesis is evenly divided between loss of the N-methyl group from m (*m/e* 57) and by loss of a methyl radical and ethylene from the molecular ion. Expulsion of an ethyl radical and ethylene or of a butyl radical from the molecular ion of N-methylpiperidine accounts for at least 90% of the ion at mass 42.

(vii) Several of the hydrogen transfer reactions appear to proceed through four-membered intermediates (*e.g.*, g → h, p → h).

Experimental[15]

N-Deuterated Amines. The amine (30 mg.) was shaken with deuterium oxide (0.1 ml.) and the mass spectrum determined.[6,16] The following deuterium incorporations were obtained: pyrrolidine-N-d_1 90% d_1, 10% d_0; piperidine-N-d_1 90% d_1, 10% d_0.

2,2-d_2-Cyclic Amines. The required lactam (150 mg.) was reduced with lithium aluminum deuteride (40 mg.) in refluxing anhydrous ether (15 ml.) over a period of 2 hr. The reaction mixture was decomposed with a saturated sodium sulfate solution and the inorganic suspension was filtered. The amines were isolated from the filtrate as their hydrochloride (piperidine) or picrate (pyrrolidine, N-methylpyrrolidine, and N-methylpiperidine). The free amines were generated by decomposition of the respective salt in 20% aqueous sodium hydroxide solution (0.5 ml.). Sodium hydroxide (1 g.) was added and the amine codistilled with water. Mass spectrometry established the isotopic purity of the amines prepared by this method as 98% d_2 species.

3,3-d_2-Cyclic Amines. Lithium aluminum hydride reduction of the required 3,3-d_2-lactam[4] (150 mg.) and processing as above generated 3,3-d_2-cyclic amines. The following isotopic purities were obtained: pyrrolidine-3,3-d_2 84% d_2, 16% d_1; piperidine-3,3-d_2 92% d_2, 8% d_1; N-methylpyrrolidine-3,3-d_2 95% d_2, 5% d_1; N-methylpiperidine-3,3-d_2 95% d_2, 5% d_1.

N-Methylpyrrolidine-N-d_2 and N-Methylpiperidine-N-d_2. N-Formylpyrrolidine[7] or N-formylpiperidine[7] (80 mg.) was reduced with lithium aluminum deuteride (40 mg.) in refluxing anhydrous ether (15 ml.) over a period of 12 hr. The reaction was processed as for the preparation of 2,2-d_2-cyclic amines yielding N-methylpyrrolidine-N-d_2 or N-methylpiperidine-N-d_2, each of 98% isotopic purity.

(15) All 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. High-resolution mass spectra unless otherwise indicated were determined using an A.E.I. MS-9 mass spectrometer with an apparent resolution of 1 in 15,000.

(16) See J. S. Shannon, *Australian J. Chem.*, **15**, 265 (1962).