data of Fava[22] on exchange in acetonitrile of tri(*p*-nitrophenyl)methyl chloride, $(O_2NC_6H_4)_3CCl$, with up to 0.10 *M* TEACl give no evidence that the apparent second-order component might be competition of chloride exchange with the collapse of a short-lived intermediate. Since the rate constant for such chloride exchange would presumably be of the order of 10^{10} l./mole sec, any ion pairs in this medium collapse in considerably less than 1 nsec.

Competition of this type in a partially protic solvent was recently claimed by Sneen and Larsen.[23] They studied the reaction of 2-octyl mesylate with sodium azide in aqueous dioxane. If k_{-1} is the first-order rate constant for collapse of an ion pair, and if k_N is the second-order rate constant for substitution of mesylate by azide in the ion pair, they find k_{-1}/k_N = 0.27 mole/l. in 75 vol. % water at 36.2°. It is not certain that the reaction of azide ion with the 2-octyl mesylate ion pair is diffusion controlled, but if it is then k_{-1} is about 3×10^9 sec^{-1}. In 25 vol. % water, 2-octyl brosylate and azide ion react with clean second-order kinetics indicating that $k_{-1} \gg k_N[N_3^-]$. The results suggest that ion-pair lifetimes decrease as solvents become more aprotic and that competitive techniques may be unsuitable for estimating lifetimes in such solvents, but more information is needed before mechanistic conclusions can be drawn with any confidence.

(22) A. Fava, private communication.
(23) R. A. Sneen and J. W. Larsen, *J. Am. Chem. Soc.*, 88, 2593 1966).

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Mass Spectrometry in Structural and Stereochemical Problems. CXLIX.[1] The Question of Ring Expansion in the Fragmentation of ^{13}C-Labeled Nitrogen Heterocycles[2]

Michael Marx[3] and Carl Djerassi

Contribution from the Department of Chemistry, Stanford University, Stanford, California. *Received August 21, 1967*

Abstract: The mass spectra of 1-^{13}C-methylisoquinoline, 1-methyl-^{13}C-isoquinoline, 2-^{13}C-methylindole, 2-methyl-^{13}C-indole, N-methyl-^{13}C-pyrrole, and N-methyl-^{13}C-indole were examined. In each case a large degree of skeletal rearrangement involving migration of the exocyclic methyl group was found to accompany the fragmentation leading to an [M − (H + HCN)] ion. The data are consistent with the intermediacy of azatropylium, quinolinium, pyridinium, or other ring-expanded ions along this fragmentation pathway. In the case of the C-methylated compounds, a marked preference for carbon–carbon *vs.* carbon–nitrogen migration was observed.

One of the more intriguing problems in mass spectrometry concerns the determination of the actual structures of fragment ions produced by electron impact. In the fragmentation of alkyl aromatic compounds, the question of ring expansion to tropylium ions has been of particular interest. Following the classic studies[4] of Meyerson and coworkers demonstrating that the fragment of mass 91 in the spectrum of toluene is best represented as a tropylium ion, similar ring-expansion processes have been proposed, generally on an intuitive basis, for the fragmentations of various alkylated heteroaromatic systems:[5] *e.g.*, furans[6] and benzofurans[7] → pyrylium ions, pyrroles[8] and indoles[9] →

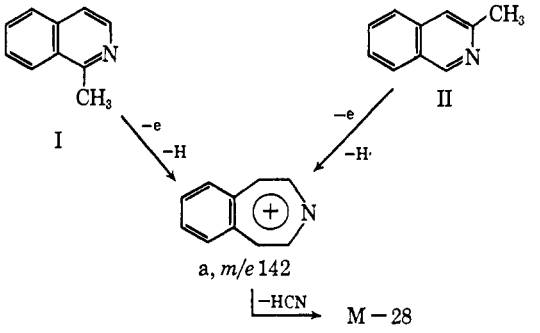
(1) For paper CXLVIII see P. Brown and C. Djerassi, *Tetrahedron*, in press.
(2) Financial assistance from the National Institutes of Health (Grant No. GM-11309) is gratefully acknowledged.
(3) Postdoctoral Fellow, 1966–1967.
(4) S. Meyerson and P. N. Rylander, *J. Chem. Phys.*, 27, 901 (1957); P. N. Rylander, S. Meyerson, and H. M. Grubb, *J. Amer. Chem. Soc.*, 79, 842 (1957); for a comprehensive review, see H. M. Grubb and S. Meyerson in "Mass Spectrometry of Organic Ions," F. W. McLafferty, Ed., Academic Press Inc., New York, N. Y., 1963, pp 488–507.
(5) For summaries and discussion, see (a) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, Inc., San Francisco, Calif., 1967, Chapters 20, 22, 23, and 24; (b) G. Spiteller in "Advances in Heterocyclic Chemistry," Vol. VII, A. R. Katritzky and A. J. Boulton, Ed., Academic Press Inc., New York, N. Y., 1966, pp 301–376.
(6) J. Collin, *Bull. Soc. Chim. Belges*, 69, 575 (1960).
(7) B. Willhalm, A. F. Thomas, and F. Gautschi, *Tetrahedron*, 20, 1185 (1964).
(8) (a) H. Budzikiewicz, C. Djerassi, A. H. Jackson, G. W. Kenner, D. J. Newman, and J. M. Wilson, *J. Chem. Soc.*, 1949 (1964); (b) A. M. Duffield, R. Beugelmans, H. Budzikiewicz, D. A. Lightner, D. H. Williams, and C. Djerassi, *J. Amer. Chem. Soc.*, 87, 805 (1965).
(9) J. H. Beynon, "Mass Spectrometry and Its Application to Organic Chemistry," Elsevier Publishing Co., Amsterdam, 1960, p 397. See also C. La Lau, *Anal. Chim. Acta*, 22, 239 (1960).

pyridinium and quinolinium ions, thiophenes[10] and benzothiophenes[11] → thiopyrylium ions, quinolines[12] and isoquinolines[12] → azatropylium ions.

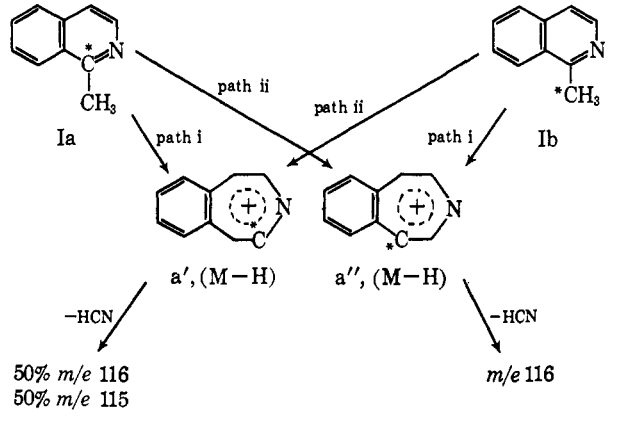
We report here the results of mass spectral studies on several ^{13}C-labeled N-heteroaromatic compounds which we prepared in order to examine the plausibility of the ring-expansion hypothesis.

1-Methylisoquinoline (I)

The mass spectra[12] of 1- and 3-methylisoquinolines (I and II) are characterized by peaks representing the successive loss of H and HCN from the molecular ion. Since the observed ratio of (M − H):[M − (H + HCN)] peaks is the same for either compound, a common M − 1 species, the benzazatropylium ion a, has been proposed.[12] In order to further investigate this assumption, we obtained the mass spectra of 1-methylisoquinolines labeled at C-1 (Ia) and at the methyl group (Ib), respectively, with ^{13}C. The ^{13}C sources were sodium 1-^{13}C acetate (53% isotopic purity) and sodium 2-^{13}C acetate (52% isotopic purity). The synthetic procedure for the isoquinolines involved N-acetylation of β-phenylethylamine, followed by polyphosphoric acid catalyzed Bischler–Napieralski cyclization[13] and catalytic dehydrogenation.



It is seen that ion a can be formed from I by either phenyl migration (path i) or nitrogen migration (path ii). The labeling consequences of these possibilities, and of the subsequent HCN loss, are depicted below (labeled positions starred).



(10) V. Hanus and V. Čermák, *Collection Czech Chem. Commun.*, **24**, 1602 (1959). See also N. G. Foster and R. W. Higgins, ASTM Committee E-14 Annual Conference on Mass Spectrometry, Dallas, 1966, and earlier references cited therein.

(11) Q. N. Porter, *Australian J. Chem.*, **20**, 103 (1967).

(12) S. D. Sample, D. A. Lightner, O. Buchardt, and C. Djerassi, *J. Org. Chem.*, **32**, 997 (1967).

(13) J. Thesing and F. H. Funk, *Ber.*, **91**, 1546 (1958).

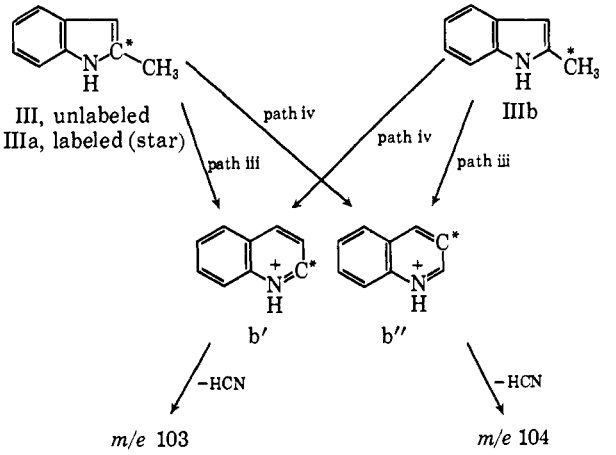
Table I. Constitution of [M − (H + HCN)] Peak

Compd	Label retained, % (*m/e*)	Label lost, % (*m/e*)
Ia	74 (116)	26 (115)
Ib	86 (116)	14 (115)
IIIa	42 (104)	58 (103)
IIIb	72 (104)	28 (103)
IVa	65 (54)	35 (53)
Va	52 (104)	48 (103)

The observed results are listed in Table I. A value of ≤52%[14] for the contribution of ion a′ (and path i) to the fragmentation of Ia can then be calculated. Similarly a contribution of ≤28%[14] for a′ (and path ii) is derived for the fragmentation of Ib. It is clear then that, should an azatropylium ion be an intermediate in the fragmentation of I, it may be responsible for as much as 80% of the [M − (H + HCN)] peak. Furthermore, the data demonstrate unequivocally that migration of the methyl carbon, regardless of mechanism, is a very significant process accompanying the formation of the [M − (H + HCN)] fragment. In Ia, 26% of the label is lost as HCN, implying ≥26% methyl carbon migration to another carbon terminus, while the loss of 14% of the labeled methyl group in Ib implies ≥14% migration to nitrogen. A lower limit of 40% is therefore established for the methyl migration processes. Also, phenyl migration (path i) is seen to be a preferred process to nitrogen migration (path ii) by a ratio of nearly 2:1 in the formation of the azatropylium ion a from I.

2-Methylindole (III)

The base peak in the mass spectrum[9] of III is an M − 1 species, which then suffers loss of HCN, and for which the quinolinium ion structure has been postulated.[9] We examined the spectra of 2-methylindoles labeled at C-2 (IIIa) and at the methyl group (IIIb), respectively, with ^{13}C. These compounds were prepared by N-acetylation of *o*-toluidine followed by base-catalyzed cyclization.[15] Again two possibilities exist for the formation of the quinolinium ions b′ and b″,



(14) Since a′ is symmetrical with respect to nitrogen, the loss of HCN will result in a 50% loss of labeled carbon. Its maximum contribution to the fragmentation process is therefore equal to twice the observed label loss.

(15) E. C. Horning, Ed., "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p 597.

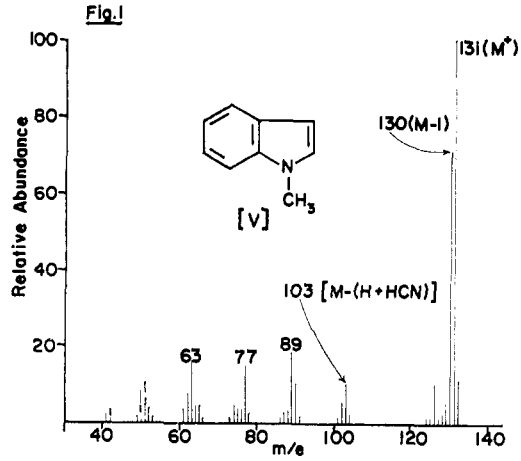


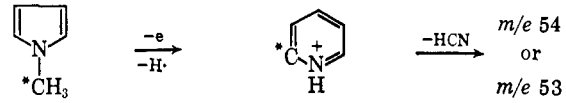
Figure 1. Mass spectrum of N-methylindole (V).

involving either carbon migration (path *iii*) or nitrogen migration (path iv).

The results (see Table I) allow the following conclusions. Since ion b'' should lose no label, its contribution (and that of path iv) to the fragmentation of IIIa is calculated from Table I to be $\leq 42\%$, while the data for IIIb indicate a contribution of $\leq 72\%$ from ion b' (and path iii). These findings are therefore consistent with the hypothesis that all of the [M − (H + HCN)] fragment arises from the quinolinium ions b' and b'', although of course not demanding such a conclusion. If all the loss of C-2 and the methyl carbon proceeds *via* the quinolinium ions, the contributions of ions b' and b'' lie in the ranges of 58–72 and 28–42%, respectively. As in the methylisoquinolines (see above) a marked preference for C- *vs.* N-migration is apparent, and once again the formation of the [M − (H + HCN)] fragment is demonstrated to be accompanied by a high percentage ($\geq 58\%$ to carbon + $\geq 28\%$ to nitrogen = $\geq 86\%$ total) of methyl carbon migration. Of additional interest is the finding that 14% of the [M − (H + HCN)] peak cannot be accounted for by either labeled carbon, and possibly involves rupture of the phenyl ring.

N-Methylpyrrole (IV) and N-Methylindole (V)

The spectrum[16] of IV displays a prominent M − 1 ion (*m/e* 80) which then undergoes the familiar HCN expulsion. The mass 80 fragment is also observed in the spectra of other N-alkylpyrroles and has been postulated[8b] to have the pyridinium ion structure c. We examined the spectrum of methyl-^{13}C-labeled IV (IVa), prepared by alkylation of the sodium salt of pyrrole with methyl-^{13}C iodide, and found that 65% of the [M − (H + HCN)] peak (*m/e* 53) in the spectrum of IV moved to *m/e* 54 (label retention) in IVa (Table I).

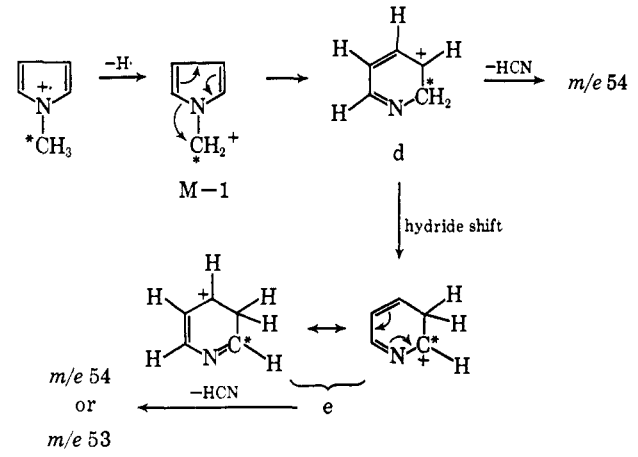


IV, unlabeled
IVa, labeled (star)

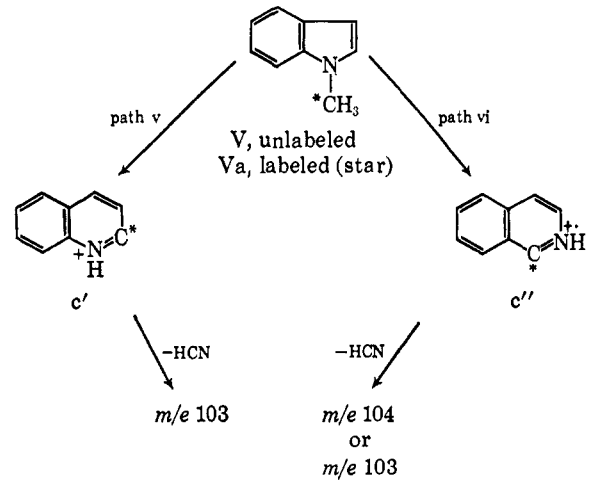
c, unlabeled (*m/e* 80)
c', labeled (*m/e* 81)

(16) Catalog of Mass Spectral Data, American Petroleum Institute Research Project 44, Carnegie Institute of Technology, Pittsburgh, Pa., Spectra No. 632 and 1719.

This result is clearly inconsistent with the intermediacy of the symmetrical ion c', which would require equal parts of label loss and retention. At least 30% of the [M − (H + HCN)] peak must therefore arise by another pathway (or pathways). One such possibility, which satisfies the necessary criteria of proceeding through an unsymmetrical intermediate and of providing for methyl migration from nitrogen, involves ring expansion of the initially formed M − 1 species to the unsymmetrical ion d, which can lose HCN directly with *retention* of label or undergo a hydride shift to form e, from which either labeled or unlabeled HCN may be lost.



The spectrum (Figure 1) of N-methylindole (V) is analogous to that of N-methylpyrrole (IV) and displays the customary M − 1 and [M − (H + HCN)] peaks. As with the C-methylindoles,[9] it is tempting to represent the M − 1 ion as a ring-expanded species. We found, in the spectrum of methyl-^{13}C-labeled V (Va), prepared by alkylation of the sodium salt of indole with methyl-^{13}C iodide, that 52% of the label was retained in the [M − (H + HCN)] fragment (Table I). Of the two possible quinolinium ions, c' is ruled out as a major contributor by the labeling results, since loss of HCN would remove all but a small percentage of label (see preceding discussion of 2-methylindoles in which 14% of HCN elimination involved a phenyl carbon atom). The intermediacy of ion c'' would appear to be consistent



with these data. It should be noted, however, that c'' is unsymmetrical with respect to nitrogen, and the losses of unlabeled and labeled HCN from c'' would

not, *a priori*, be anticipated to proceed with equal facility. Also the results obtained in the simpler N-methylpyrrole system (see above) suggest that a somewhat more complex fragmentation pathway is operative. Once again the importance of methyl carbon migration (52%) in the course of the [M − (H + HCN)] fragmentation is demonstrated.

In summary, our results show unequivocally that formation of the [M − (H + HCN)] fragment in the decomposition of 1-methylisoquinoline (I), 2-methylindole (III), N-methylpyrrole (IV), and N-methylindole (V) is accompanied by a very significant degree of skeletal rearrangement involving migration of the exocyclic methyl group. While the intermediacy of azatropylium, quinolinium, or pyridinium ions is not thereby established, the experimental data can be interpreted most readily by postulating that such ions, or other ring-expanded species, contribute significantly to the (M − 1) fragment. The apparent preference for migration of the exocyclic methyl group to carbon rather than to nitrogen in those compounds (I and III) where a choice exists is also noteworthy. No deuterium labeling has been performed to settle the question of the source of the lost hydrogen in the genesis of the various M − 1 species; as indicated elsewhere[17] both the methyl and the ring hydrogen atoms may be implicated.

Experimental Section[18]

1-^{13}C-Methylisoquinoline (Ia). An ice-cooled slurry of anhydrous sodium 1-^{13}C-acetate[19] (0.240 g, 0.0029 mol) in dry benzene (6 ml) containing a few drops of pyridine was protected with reflux condenser and drying tube while oxalyl chloride (0.25 ml, 0.0029 mol) was added. After the initial brisk gas evolution had subsided, the slurry was stirred for 2 hr at room temperature and for another hour at 45°. The mixture was again cooled in an ice bath while 2-phenylethylamine (0.8 ml, ~0.06 mol) was added, then allowed to stir for 4 hr at room temperature. The mixture was diluted with water and extracted with chloroform, and the extracts were washed successively with 1 *N* hydrochloric acid, water, and saturated salt solution, dried over magnesium sulfate, and evaporated. The resulting residue was purified by preparative thin layer chromatography on silica gel G[20] and furnished crystalline N-(1-^{13}C-acetyl)-2-phenylethylamine (0.255 g, mp 46–47°). Polyphosphoric acid cyclization of this substance (0.160 g) as described by Thesing and Funk[13] furnished, after short-path distillation, 0.091 g of the corresponding dihydroisoquinoline. Dehydrogenation was effected by heating this material at reflux for 3 hr with 0.06 g of 10% palladium on charcoal in 3 ml of *p*-cymene. The resulting crude 1-^{13}C-methylisoquinoline (Ia, 0.07 g) was purified by gas chromatography (DC-200 on Teflon support, 190°).

1-Methyl-^{13}C-isoquinoline (Ib). The preparation of Ib was carried out exactly as above, except that sodium- 2-^{13}C-acetate[19] was employed as the starting material.

2-^{13}C-Methylindole (IIIa). The N-1-^{13}C-acetyl derivative of *o*-toluidine (0.222 g), mp 104–106°, was prepared in the same manner as described above for the corresponding 2-phenylethylamine derivative, starting from 0.245 g of sodium 1-^{13}C-acetate. This material on fusion with sodium amide at 250–265°[15] furnished crude crystalline IIIa (0.209 g) which was purified by gas chromatography (DC-200 on Teflon support, 175°).

2-Methyl-^{13}C-indole (IIIb). In analogous manner to the preceding experiment, but starting from sodium 2-^{13}C-acetate, IIIb was prepared.

N-Methyl-^{13}C-pyrrole (IVa). A solution of freshly distilled pyrrole (1 ml, 0.015 mol) in a mixture of dry benzene (1 ml) and dry N,N-dimethylformamide (0.5 ml) was treated with sodium hydride (0.088 g, 0.0037 mol) at room temperature. After the initial vigorous reaction had subsided the mixture was heated for 1 hr at 80°. Methyl-^{13}C iodide[19] (0.50 g, 0.0035 mol) was then transferred, employing a vacuum line, to the cooled flask containing the pyrrole salt. The mixture was heated periodically to 50° during 3 hr, then allowed to stand 16 hr at room temperature. Dilution with water and ether, followed by washing, drying, and careful distillation of the ether extracts at atmospheric pressure, furnished a concentrate from which the desired IVa, identical in retention time with unlabeled N-methylpyrrole, was obtained by gas chromatography (20% DEGS, 70°).

N-Methyl-^{13}C-indole (Va). Employing the procedure of Potts and Saxton[21] the sodium salt of indole was alkylated in liquid ammonia with methyl-^{13}C iodide[19] to furnish the N-methyl derivative, which was purified by gas chromatography (20% DEGS, 180°).

(17) See ref 5a, p 574.

(18) Mass spectra were recorded by Mr. N. S. Garcia, employing a CEC 21-103 instrument equipped with an all-glass heated inlet system at 200°, ion source temperature 250°, and ionizing energy 70 eV. All samples for the mass spectral studies were purified by preparative gas chromatography on an Aerograph instrument equipped with the column indicated in the experimental section.

(19) The labeled sodium acetates and methyl iodide, each having an isotope purity of *ca.* 50%, were obtained from Merck Sharp and Dohme, Ltd., Montreal.

(20) Merck A.G., Darmstadt.

(21) K. T. Potts and J. E. Saxton, *J. Chem. Soc.*, 2641 (1954).