Mass Spectral Fragmentation Patterns of Heterocycles. V [1]. Electron Impact Promoted Mass Spectral Fragmentation of Indolo[1,7-*ab*][1]benzazepine and Some of its Derivatives

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The fragmentation patterns of 1,2,6,7-tetrahydroindolo[1,7-*ab*][1]benzazepin-1-one (**1**), 6,7-dihydroindolo-[1,7-*ab*][1]benzazepine (**2**) and indolo[1,7-*ab*][1]benzazepine (**3**) on electron impact have been examined. Loss of carbon monoxide to form the base peak at m/e 207 and loss of CHO radical to give m/e 206 consititute the major fragmentation pathways for **1**. The moleclar ions (M^+) are abundant for each of the compounds; observed as the second most intense peak for **1** (85% relative intensity) and the base peaks for **2** and **3**. The spectrum of **2** is characterized by intense M-1 and M-2 ions and by the presence of a M-15 ion (m/e 204) of moderate intensity (11.4%). In all other respects the spectra of **2** and **3** are strikingly similar. The M-15 ion from **2**, assigned the heteroaromatic pyrroloacridinium structure, is also formed in the spectrum of **1**. A second heteroaromatic ion at m/e 191, common to the spectra of **1**, **2** and **3**, is believed to have the pyrrolocarbazolium structure. Metastable ion transitions and exact mass measurements support most of the proposed fragmentation pathways and structural assignments.

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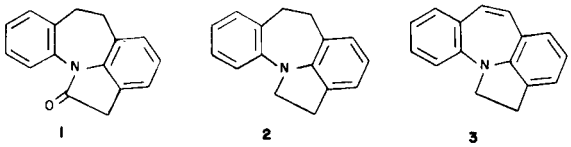
As part of a systematic study of the structure-activity relationships of tricyclic antidepressants and antipsychotics with restricted rotation in the side chain [2], we have been interested in utilizing a variety of tetracyclic ring systems as precursors. Along with our synthetic efforts we have instituted an investigation of the mass spectral and nuclear magnetic resonance properties of these tetracyclic compounds. In this conection we have previously reported on the mass spectral fragmentation patterns of pyrrolo-[3,2,1-*kl*]phenothiazine [1] and on the total assignment of the proton nuclear magnetic resonance spectrum of this compound and the indolo[1,7-*ab*][1]benzazepines **1**, **2** and **3** [3]. This report describes the fragmentation behavior of **1**, **2** and **3** on electron impact. Mass spectral fragmentation patterns of the parent dibenz[*b*,*f*]azepine and 10,11-dihydrodibenz[*b*,*f*]azepine ring systems and of some simple 5-substituted derivatives have been reported previously by others [4].



1 **2** **3**

The fragmentation of 1,2,6,7-tetrahydroindolo[1,7*ab*]-[1]benzazepin-1-one (**1**) is dominated by the expulsions of carbon monoxide and CHO radical to give the fragment ions I (m/e 207, base peak) and II (m/e 206, 61% relative intensity), respectively. Other fragments from the molecular ion of **1**, which include the M-1 ion III, IV (M-15, loss of methyl radical and V(M-42, loss of ketene) constitute only a small fraction of the total ion current. The primary fragmentation paths for **1** are outlined in Scheme 1. Observed metastable ion transitions along with calculated values (in parenthesis) are given over the arrows in each of the schemes. The presence of metastable ions support all of the primary fragmentation modes of **1** shown with the exception of the loss of ketene from the molecular ion. High resolution data for observed and calculated exact mass values for key ions are listed in Table 1.

Most of the ions resulting from secondary fragmentations of **1** appear to largely be derived from the abundant ions I and II (Scheme 2). The relatively high abundance of fragment ions m/e 204 (26.1%) and m/e 191 (18%) together with the occurrence of the corresponding doubly charged species of relatively high intensity at m/e 102 (21.8%) [5]) and m/e 95.5 (10.9%) suggest that these ions have the heteroaromatic structures VI and VII, respectively. Interestingly, VII is also prominent in the electron impact mass spectrum of pyrrolo[3,2,1-*kl*]phenothiazine [1]. Metastable ion studies indicate that VI is derived from II *via* loss of two hydrogen atoms, while VII comes from VIII

Scheme I

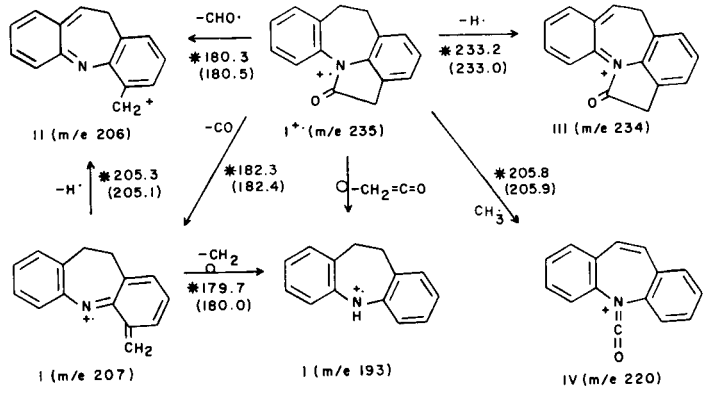


Table I

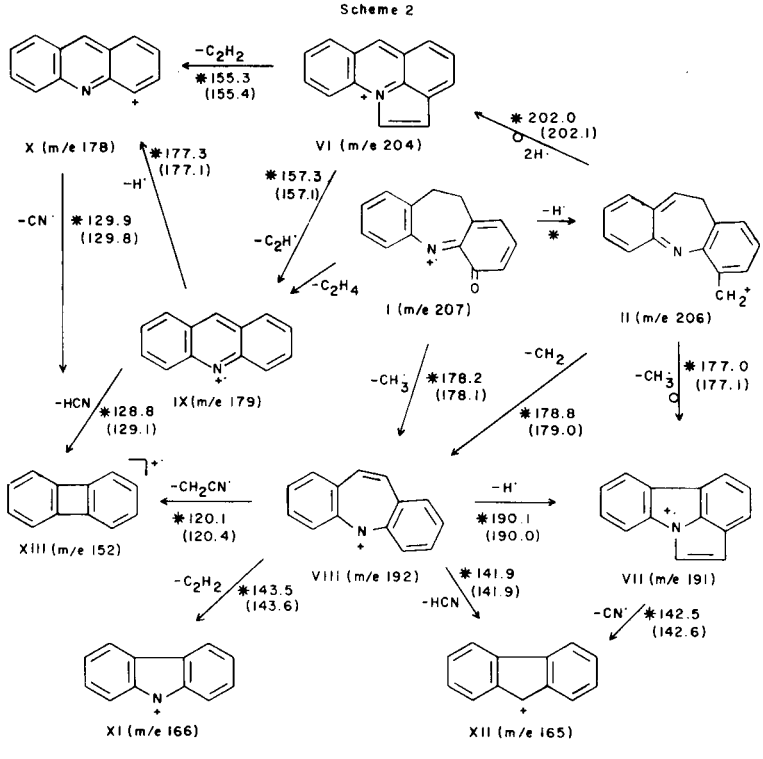
Exact Mass Measurements for 1,2,6,7-Tetrahedroindolo[1,7-*ab*][1]benzazepin-1-one (**1**)

Ion	Emperical Formula	Calcd.	Observed
1^+ (M^+)	$C_{16}H_{13}NO$	235.0977	235.1009
III (M-1)	$C_{16}H_{12}NO$	234.0918	234.0939
IV	$C_{15}H_{10}NO$	220.0763	220.0844
I	$C_{15}H_{13}N$	207.1039	207.1059
XV	$C_{14}H_9NO$	207.0684	207.0379
II	$C_{15}H_{12}N$	206.0972	206.0986
XIV	$C_{15}H_{11}N$	205.0928	205.0888
VI	$C_{15}H_{10}N$	204.0813	204.0825
V	$C_{14}H_7N$	193.0892	193.0865
VIII	$C_{14}H_{10}N$	192.0813	192.0810
VII	$C_{14}H_9N$	191.0735	191.0733
m/e 180	$C_{13}H_{10}N$	180.0814	180.0808
IX	$C_{13}H_9NO$	179.0735	179.0767
X	$C_{13}H_8N$	178.0656	179.0709
XI	$C_{12}H_8N$	166.0656	166.0663
XII	$C_{13}H_9$	165.0704	165.0694
XIII	$C_{12}H_8$	152.0624	152.0604

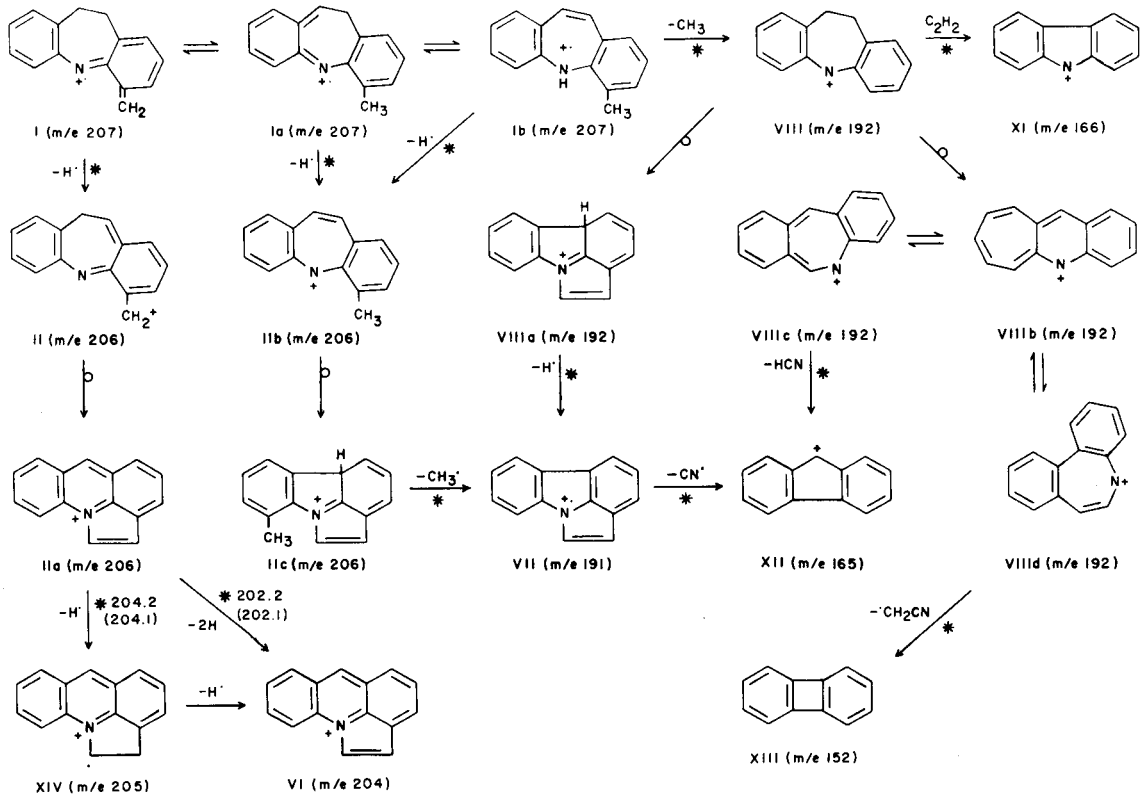
(loss of a hydrogen atom) and also from II (loss of a methyl radical). Metastable ion studies also indicate that the acridinium species IX (m/e 179) and X (m/e 178) are derived from VI *via* losses of acetylene radical and molecular acetylene, respectively. No metastable transition associated with the observed protonated acridinium species (m/e 180, 8.8%) could be detected. It is probable that ions I and/or II, or rearranged species derived therefrom, are sources of m/e 180 (loss of ethylene radical or ethylene, respectively). Each of these acridinium ions have been observed in the fragmentation of dibenz[*b*,*f*]azepines [4,6]. The genesis of the carbazolium ion XI ($C_{12}H_9N$, m/e 166) involves VIII, while the hydrocarbon ion XII ($C_{13}H_9$, m/e 165) is derived from both VII and VIII, or related rearrangement ions. The hydrocarbon ion XIII ($C_{12}H_8$, m/e 152) comes from IX and X (expulsion of hydrogen cyanide and cyanide radical, respectively) and from m/e 192 (loss of CH_2CN radical).

Mechanisms for many of the rearrangement processes implicit in the secondary fragmentations of I and II described in Scheme 2 are detailed in Scheme 3. Thus, it is suggested that I, by successive hydrogen atom transfers, rearranges to Ia and Ib. Loss of a methyl radical, accompanied by a hydrogen atom transfer is visualized to give VIII. Cleavage of the 10,11-carbon bond of II, followed by two ring closures gives IIa, the immediate precursor to ions VI and XIV. The pyrroloacridinium ions IIa, VI and XIV have been shown to be prominent in the fragmentation of 4-alkylacridines [7]. The formation of VII from II is thought to involve a methylpyrrolocarbazolium species such as IIc. Expulsion of a methyl group accompanied by a hydrogen atom transfer would be required. The formation of hydrocarbon ions XII and XIII from VIII is seen to require skeletal rearrangements to a species such as VIIIb which can further rearrange to VIIIc and VIIId. Loss of

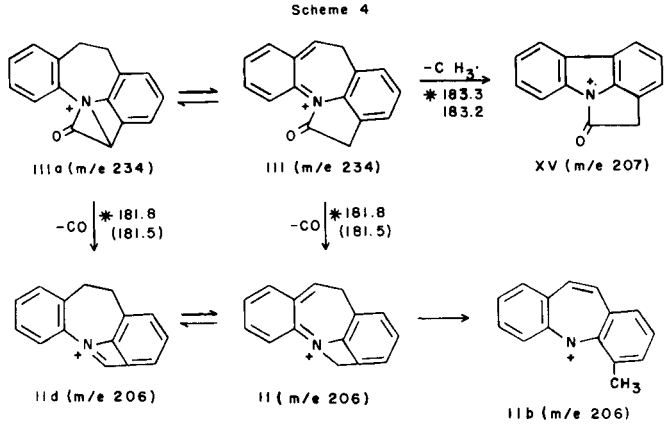
Scheme 2



Scheme 3



Scheme 4

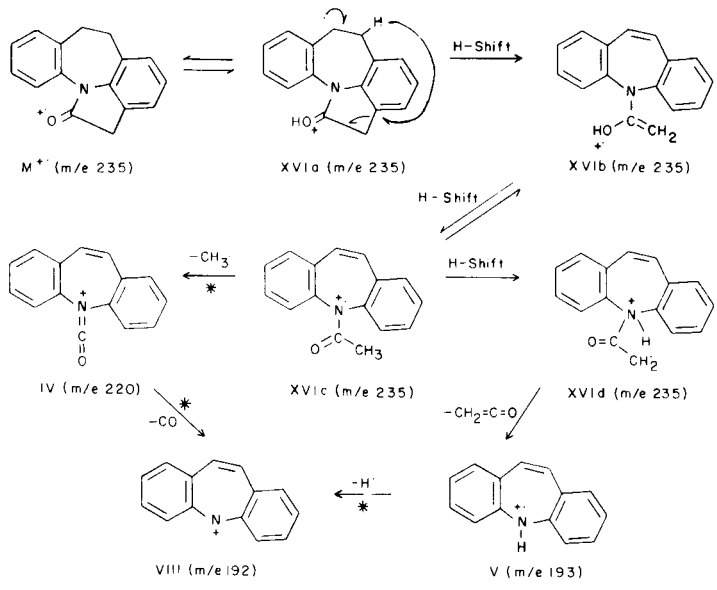


hydrogen cyanide from VIIIc gives XII, while expulsion of CH_2CN radical from VIIId gives XIII. A mechanism similar to the former has been previously proposed for the loss of H_2CN radical from the m/e 193 species formed in the mass spectrum of 5*H*-dibenz[*b*,*f*]azepine-5-carboxamide [6].

The abundance of the M-1 ion III derived from **1** is seen to be very low (relative intensity 6%). Metastable ion studies led to the detection of only two fragmentation processes involving the M-1 ion (Scheme 4). By far the most important of these is the loss of carbon monoxide from M-1 to give m/e 206, which can be assigned the interconvertible structures IId and/or IIe. A precedent for the formation of IId, derived from the structural variant of M-1, IIIa, is provided by the observed expulsion of carbon monoxide from oxindoles on electron impact [8]. Ions IId, IIe and IIb are interconvertible by hydrogen atom transfers. Metastable ion studies indicated a transition consistent with the formation of an ion m/e 207 isobaric with the base peak I. High resolution measurements showed that this ion, present in less than 0.2% relative intensity, has the empirical formula $C_{13}H_9NO$. Its structure is given as XV.

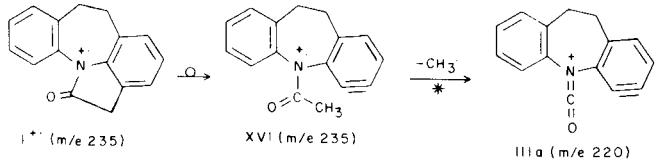
Ring opening reactions of the molecular ion of **1** associated with the loss of methyl radical (M-15) or ketene constitute minor, but nonetheless interesting, processes. Formation of the M-15 ion (m/e 220, 0.7%) is accompanied by the appropriate metastable ion transition. The more plausible mechanism for the formation of m/e 220, tentatively assigned the structure IV, is shown in Scheme 5. This mechanism requires a series of hydrogen shifts, which can be followed through the rearranged molecular ion species XVIa, XVIb and XVIc. Loss of a methyl radical from XVIc should give IV. However, no m/e 220 ion is observed in the electron impact mass spectrum of 5-acetyldibenz-[*b*,*f*]azepine [4,8]. The formation of ion V in the spectrum of **1** is also nicely explained in theory by the intermediacy

Scheme 5



of XVIc [4]. However, no metastable ion associated with the loss of ketene from the molecular ion could be detected. An alternative mechanism for the formation of m/e 220 and a proposed structure is given in Scheme 6. This mechanism requires the formation of the benzyne variant of the molecular ion depicted as XVIe, and loss of a methyl radical to form the benzyne M-15 ion IIIa. Since benzynes are high energy intermediates, Scheme 6 is less attractive than Scheme 5.

Scheme 6



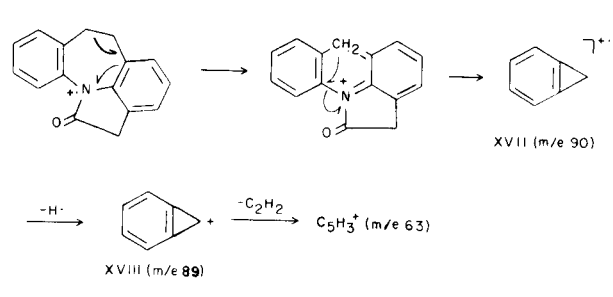
The detection of low mass fragment hydrocarbon ions at m/e 90 and m/e 89 of moderate intensity suggest the possibility of a retro-Diels Alder-like process involving the M ion of **1** (Scheme 7). These ions are assigned the benzocyclopropane structures XVII and XVIII. It should be noted, however, that the counter ion m/e 145 (C_9H_7NO) could not be detected, nor were metastable ions corresponding to the formation of XVII or XVIII from M or M-1 observed.

The mass spectra of **2** and **3**, in contrast to **1**, are relatively simple. Major fragmentation pathways are shown in Schemes 8, 9 and 10. High resolution data are provided in Table 2. For both **2** and **3**, the molecular ions are the base peaks in their spectra. The primary fragmentation pathways for **2** involve the loss of hydrogen atoms to give m/e 217 (the molecular ion of **3**, relative intensity 24.2%), the expulsion of a methyl radical to give VI (m/e 204, 11.4%), and losses of ethylene radical and ethylene to give VIIIa (m/e 191, 4.4%) and VII (m/e 192, 1.8%), respectively. Each of these processes is accompanied by the appropriate metastable ion. In most other respects, the spectrum of **2** resembled that of **3**.

The aromatic stability of **3**, an 18π electron heteroaromatic compound [9], is exemplified by the abundance of its molecular ion (base peak), its M-1 ion XIX (23.2%) and its double charged molecular ion (m/e 108.5, 18.8%). A further indication of the stability of this system is provided by the observation that the doubly charged M-2 ion from **2** (m/e 108.5) is more abundant (21.7%) than its doubly charged molecular ion (m/e 109.5).

Because of the relatively efficient conversion of $\mathbf{2}^{+\cdot}$ to $\mathbf{3}^{+\cdot}$ on electron impact, much of the fragmentation of **2** must resemble the primary fragmentation pathways for **3**. These interrelationships are shown in Scheme 9.

Scheme 7



The more interesting fragmentations are associated with the loss of nitrogen (plus one to three hydrogen atoms) from **2** and/or **3** to give the hydrocarbon ions XX (m/e 190, $C_{15}H_{10}$) and XXI (m/e 189, $C_{15}H_9$). Metastable ion

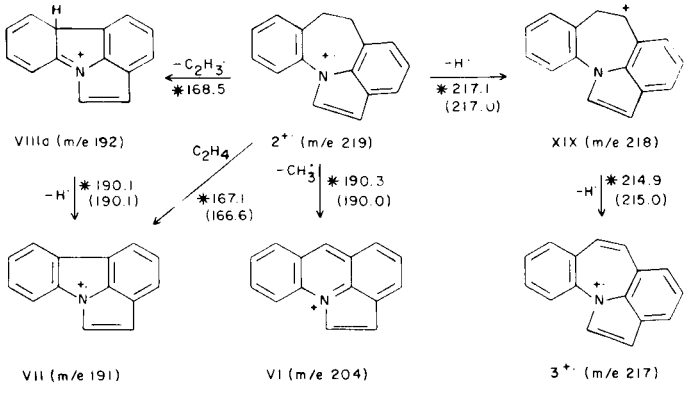
Table 2

Exact Mass Measurements for 6,7-Dihydroindolo[1,7-*ab*][1]-benzazepine (**2**) and Indolo[1,7-*ab*][1]benzazepine (**3**)

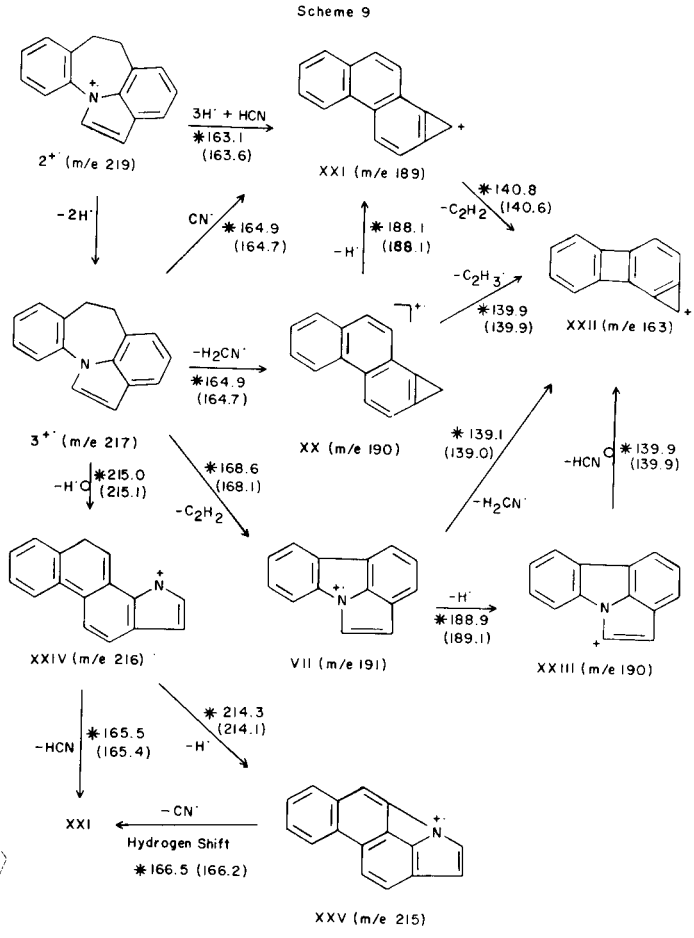
Ion	Emperical Formula	Calcd.	Observed
2$^{+\cdot}$	$C_{16}H_{13}N$	219.1048	219.1034
XIX	$C_{16}H_{12}N$	218.0970	218.0963
3$^{+\cdot}$	$C_{16}H_{11}N$	217.0891	217.0886 [a]
			217.0893 [b]
XXIV	$C_{16}H_{10}N$	216.0817	216.0813 [a]
			216.0814 [b]
XXV	$C_{16}H_{9}N$	215.0735	215.0739 [a]
			215.0740 [b]
VII	$C_{15}H_{10}N$	204.0813	204.0807
VIII	$C_{14}H_{9}N$	191.0735	191.0736 [a]
			191.0741 [b]
XX	$C_{15}H_{10}$	190.0783	190.0752 [a]
			190.0734 [b]
XXIII	$C_{14}H_{8}N$	190.0657	190.0656 [a]
			190.0640 [b]
XXI	$C_{15}H_{9}$	189.0704	189.0702 [a]
			189.0698 [b]
XXII	$C_{13}H_{7}$	163.0548	163.0546 [b]

[a] From the spectrum of **2**. [b] From the spectrum of **3**.

Scheme 8



Scheme 9

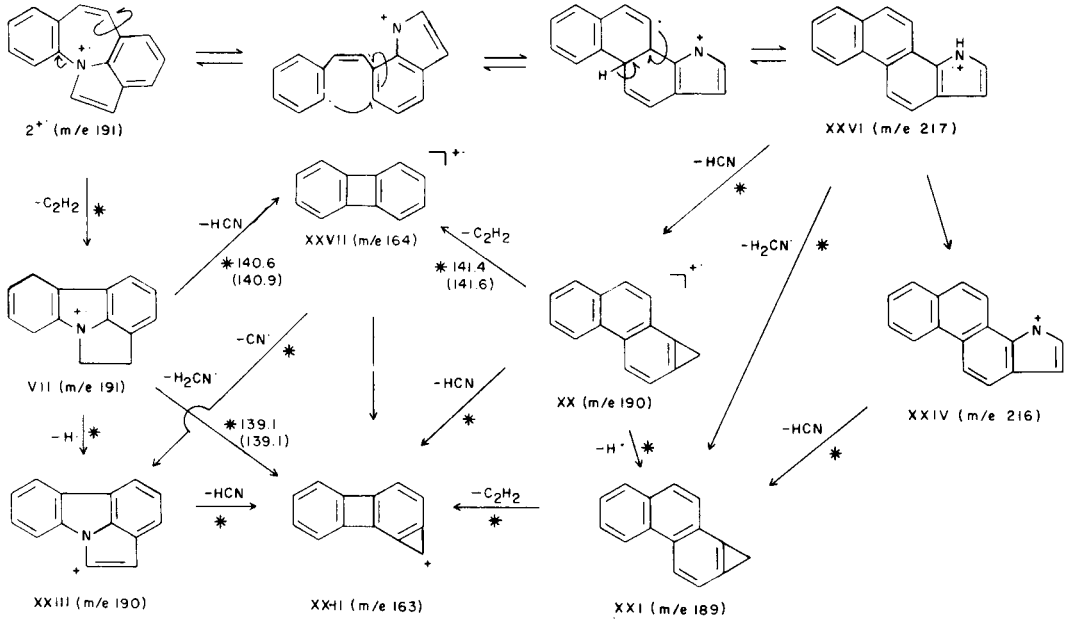


studies are consistent with the expulsions of HCN from **3**$^{+}$ to give XX, of H_2CN radical (or HCN plus a hydrogen atom) from **3**$^{+}$ to give XXI, and of HCN plus three hydrogen atoms from **2**$^{+}$ to give XXI. Ions XX and XXI are also seen in the electron impact spectrum of pyrrolo-[3,2,1-*kl*]phenothiazine [1].

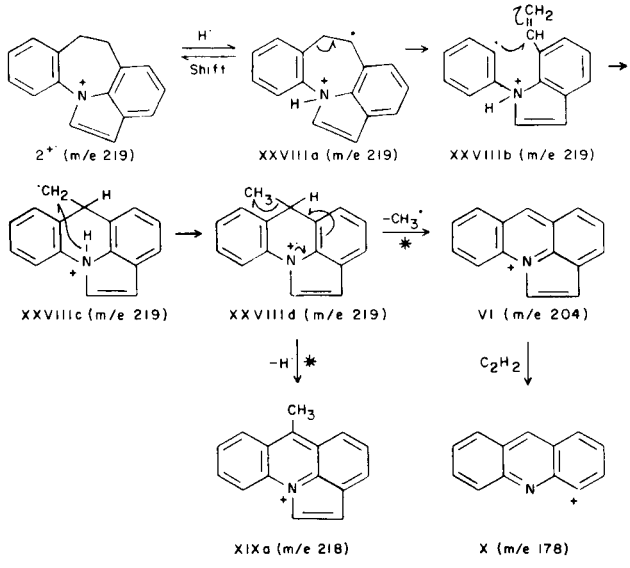
Loss of acetylene from **3**$^{+}$ to give the familiar ion VII (m/e 191, 4.4%) [1] also occurs. Metastable studies indicate that VII gives rise to the hydrocarbon ion XXII (m/e 163 $C_{13}H_7$) *via* two paths; one requiring the direct loss of H_2CN radical, the other involving expulsion of a hydrogen atom giving XXIII (m/e 190) followed by loss of hydrogen cyanide to form XXII. it should be noted that m/e 190 is a doublet consisting of ions XX and XXIII in approximately equal abundance. The formation of the M-1 and M-2 ions from **2** is believed to initially involve skeletal rearrangement (see Scheme 10) to the naphtho[*b*]indole ion XXVI which then suffers successive losses of hydrogen atoms to give XXIV (M-1, m/e 216) and XXV (M-2, m/e 215) (Scheme 9). Metastable studies indicate that ions XXVI, XXIV and XXV expel H_2CN radical, HCN and/or CN radical to give ions XXI and XXII (see Schemes 9 and 10). A similar skeletal rearrangement to a benzo[*b*]indole species has been invoked by us [1] to explain the loss of these nitrogen species from pyrrolocarbazole and its M-1 ion. Metastable ion studies and exact mass measurements show that these same processes occur in the fragmentation of **2** and **3** (see Schemes 9 and 10).

The formation of the M-15 ion from **2** reqiures a skeletal rearrangement accompanied by hydrogen atom shifts. A plausible mechanism is outlined in Scheme 11. The process is presumed to be initiated by the genesis of a radical cation XXVIIIa from **2**$^{+}$ resulting from the shift of a 6-hydrogen atom to nitrogen. This variant of the molecular ion is then believed to undergo ring opening to XXVIIIb, which then closes to the 6-membered ring radical cation XXVIIIc. A simple hydrogen atom shift gives XXVIIId. Expulsion of a methyl radical from XXVIIId gives the M-15 ion VI directly. The high relative intensity (72.5%)

Scheme 10



Scheme 11



of the M-1 derived from **2** suggests that a significant fraction of the m/e 218 peak may be due to the formation of the stable pyrroloacridinium ion XIXa formed from XXVId.

In summary, the mass spectral fragmentation pathways of indolo[1,7-*ab*][1]benzazepine and its 6,7-dihydroderivatives are characterized by a variety of skeletal rearrangements and accompanying hydrogen atom shifts. Formation of the pyrrolocarbazolium species VII appears to be diagnostic for all indolo[1,7-*ab*][1]benzazepines, while only the 6,7-dihydroderivatives form the pyrroloacridinium ion V. Metastable ion studies and high resolution measurements lend considerable support to the proposed fragmentation pathways.

EXPERIMENTAL

The mass spectra were recorded on a Varian MAT 311A double focusing mass spectrometer at 70 eV. The samples were introduced by a direct inlet probe and were heated at a rate of about 450° in 200 seconds. The metastable ion spectra were obtained by focusing on the parent ion and scanning the electrostatic sector and magnetic fields in the first filed free region of the spectrum at a rate such that the ratio E/B remained constant at a constant accelerating voltage. The high resolution spectra were recorded at a resolution of 7000 and processed with a Varian SS-200 data system. The temperature was raised manually to obtain the optimum spectrum. Compound purity was checked by tlc and gc (Varian model 3700) with fid.

1,2,6,7-Tetrahydroindolo[1,7-*ab*][1]benzazepin-1-one (**1**).

This compound was prepared according to the literature procedure [10] and had mp 197-198° (lit [9] mp 196-198°); ms: m/e 237 (M+2, 1.6), 263 (M+1, 15.7), 235 (M$^+$, 85), 234 (M−1, 6.0), 220 (0.7), 218 (0.8), 208 (15.7), 207 (100), 206 (60.6), 205 (11.4), 204 (26.1), 203 (3.8), 195 (1.1), 194 (1.6), 193 (3.8), 192 (16.5), 191 (18.0), 190 (5.4), 189 (2.1), 197 (6.0), 183 (3.2), 181 (3.2), 180 (8.8), 179 (7.4), 178 (10.3), 177 (4.0), 176 (3.7), 167 (3.4), 166 (2.8), 165 (4.5), 164 (2.9), 163 (2.2), 153 (2.2), 152 (7.0), 151 (4.6), 150 (2.5), 140 (2.5), 139 (2.5), 130 (4.2), 128 (6.4), 117.5 (1.9), 116 (1.9), 115 (4.3), 104 (2.4), 103.5 (9.7), 103 (8.3), 102.5 (20.5), 102 (21.8), 101.5 (5.3), 101 (5.4), 96 (3.5), 95.5 (10.9), 91 (5.3), 90.5 (5.7), 90 (10.5), 89.5 (7.2), 89 (23.0), 88.5 (2.6), 88.0 (.95), 87 (3.5), 8.25 (2.3), 82 (2.5), 78 (4.2), 77 (15.5), 76 (12.3), 75.5 (2.7), 75 (8.3), 74 (3.8), 65 (8.0), 63 (15.6), 57 (3.3), 51 (14.8), 50 (6.9).

6,7-Dihydrindolo[1.7-*ab*][1]benzazepine (**2**).

This compound is reported in the literature [11,12]. We also have prepared it by an alternative method [12]. It had mp 100-101° (lit [10] mp 100-102° and [11] mp 99-101°); ms: m/e (%) 221 (M+2, 1.4), 220 (M−1, 16.8), 219 (M$^+$, 100), 218 (M−1, 72.5), 217 (24.2), 216 (9.7), 215 (4.6), 205

(1.8), 204 (11.4), 195 (5.4), 193 (3.7), 192 (1.8), 191 (4.4), 190 (3.2), 189 (6.1) 180 (1.9), 178 (1.1), 165 (1.4), 164 (1.3), 163 (1.7), 109.5 (M^{2+}, 4.7), 109 (5.1), 108.5 ($[M-2]^{2+}$, 21.7), 107.5 (5.4), 103 (2), 102 (7.7), 101 (2), 96.5 (2.3), 96 (2.7), 95.5 (15.1), 91 (1.4), 90 (1.3), 89 (5.3), 88 (3.0), 82.5 (2.4), 82 (2.7), 81.5 (2.9), 81 (3), 77 (3.8), 76 (2.7), 75 (5.2), 73 (2.9), 73 (3.0), 65 (1.7), 63 (7.8), 62 (3), 51 (8).

Indolo[1,7-*ab*][1]benzazepine (**3**).

This compound was prepared by us [9,13] and had mp 113-114°; ms: m/e (%) 219 (M + 2, 1.7), 218 (M + 1, 16.5), 217 (M^+, 100), 216 (23.2), 215 (8.8), 214 (5.3), 191 (3.3), 190 (8.5), 189 (30.5), 188 (3.8), 187 (3.9), 164 (1.3), 163 (2.6), 109 (3.6), 108.5 (M^{2+}, 18.8), 108 (3.6), 107.5 (14.5), 106.5 (1.7), 95.5 (14.5), 95 (4.9), 94.5 (17.4), 94 (7.3), 93.5 (7.6), 82 (3.6), 81 (5.7), 77 (1.0), 75 (2), 63 (3.6).

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REFERENCES

[1] Part IV. L. C. Vishwakarma, A. Hallberg, T. Dahlgren and A. R. Martin, *J. Heterocyclic Chem.*, in press.

[2] A. R. Martin, V. M. Paradkar, G. W. Peng, R. C. Speth, H. I. Hamamura and A. S. Horn, *J. Med. Chem.*, **23**, 865 (1980); A. R. Martin, S. H. Kim, H. I. Yamamura and A. S. Horn, *ibid.*, **23**, 938 (1980).

[3] A. Hallberg, T. Dahlgren, A. Martin and K. Christiansen, *J. Heterocyclic Chem.*, **20**, 37 (1983).

[4] D. Janovic, *Adv. Mass Spectrom.*, **6**, 61 (1974).

[5] It is possible, of course, that a protion of the m/e peak is due to a singly charged species of lower mass.

[6] K. M. Baker and A. Frigerio, *J. Chem. Soc., Perkin Trans. II*, 648 (1973).

[7] R. M. Acheson, R. T. Alpin and R. G. Botlon, *Org. Mass Spectrom.*, **12**, 518 (1977).

[8] T. Hino, N. Nakagawa, K. Tsuneoka, S. Misawa and S. Akaboshi, *Chem. Pharm. Bull.*, **17**, 1651 (1969).

[9] A. Hallberg and A. R. Martin, *J. Heterocyclic Chem.*, **18**, 1255 (1981).

[10] R. J. Abraham, R. Robinson, L. J. Kricka and A. Ledwith, *J. Chem. Soc., Perkin Trans. II*, 1646 (1974).

[11] C. J. Cattanach, A. Cohen and B. Heath-Brown, *J. Chem. Soc., Perkin Trans. I*, 1041 (1973).

[12] L. Toscano, G. Grisanti, G. Fioriello and E. Seghetti, *J. Med. Chem.*, **19**, 208 (1976).

[13] A. Hallberg, D. Deardorff and A. R. Martin, *Heterocycles*, **19**, 75 (1982).