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The Mass Spectrum of Cocaine

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ABSTRACT: The current literature allows an analysis of the electron impact mass spectral fragmentations of cocaine (I). Using published high-resolution mass measurements as a reference, the mass spectra of several cocaine derivatives were examined—specifically those having individual functional group modifications at the nitrogen, alkyl ester group, aromatic ring and two-carbon bridge. Previously proposed major fragmentation pathways are supported by these data, and structures and mechanisms for lesser fragmentations are proposed. The relative intensities of the m/z 152 ions in the mass spectra of the cocaine diasteromers are rationalized based on these proposals.

KEYWORDS: forensic science, substance abuse, cocaine, chemistry, mass spectrometry

The electron impact mass spectrum of cocaine (I; $R^1 = R^2 = CH_3$, Ar = C_6H_5, Y = H) (Fig. 1) is familiar to most forensic drug chemists. Although mechanisms for the major mass spectral decompositions of this compound have been proposed (1–3), a systematic study of its fragmentations has never been carried out. At the same time, the literature is replete with mass spectra of cocaine derivatives, many of which are appropriate for gaining insight into the fragmentations of the parent molecule. However,

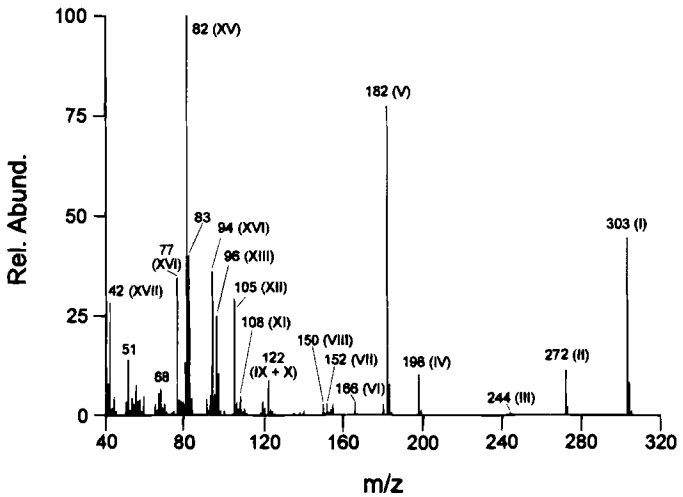

FIG. 1—*Electron impact mass spectrum of cocaine (I; $R^1 = R^2 = CH_3$, Ar = C_6H_5, Y = H). Roman numerals refer to ion structure designations in Table 1 and Figs. 2–8.*

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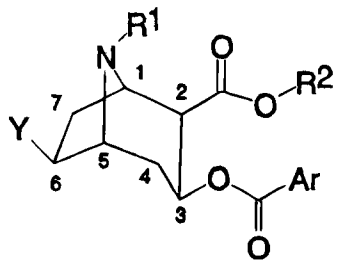

I

until the recent paper by Casale, Moore, and Cooper (4) describing the preparation of 6- and 7-chlorococaine, spectra for derivatives in which the two-carbon bridge of cocaine was functionalized were not available, seriously limiting knowledge of the fate of these carbons.

This study makes use of published mass spectral data, as well as one previously unpublished spectrum from this laboratory, for cocaine derivatives showing functional group modifications at the following locations: the nitrogen, the alkyl ester group, the aromatic ring, and the two-carbon bridge. Preference was given to deuterated derivatives, whose spectra should mirror those of parent compounds, and to compounds with functional groups that could act as "labels" without substantially altering the overall fragmentation of the tropane skeleton. In addition, an under-cited work by Shapiro et al. (5) provides exact mass measurements as well as empirical formula for most of the significant ions in the cocaine spectrum. These data support some previously proposed fragmentation mechanisms, and shed new light on others. These pathways are considered in light of all of the available data.

Experimental

D_3-Cocaine and D_8-cocaethylene were purchased as analytical standards in solution from Sigma Chemical Company (St. Louis, MO) and Radian Corporation (Austin, TX) respectively. They were used without purification and subjected to GC/MS analysis using a Hewlett Packard 5890 Gas Chromatograph (30m HP-5MS capillary column; temperature program: hold 2 min at 100°C, ramp at 20°C/min for 5 min, ramp at 10°C/min for 10 min, ramp at 15°C/min for 1.3 min, then hold at 320°C for 3.7 min), and 5971 Mass Selective Detector.

Results and Discussion

Mass Correlations—The positions of 17 prominent ions in the cocaine mass spectrum were correlated with those of ions in the spectra of nine derivatives (Table 1). In Table 1, functional group assignments for each derivative are given next to the compound name, whereas Roman numerals corresponding to ion structures

TABLE 1—*Prominent ions in the mass spectra of substituted cocaines.*

Compound	FUNCTIONAL GROUP				ION STRUCTURE/EMPIRICAL FORMULA*																	
Name	R^1	R^2	Ar	Y_G	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV	XV	XVI	XVII	Ref
					$C_{17}H_{21}NO_4$	$C_{16}H_{18}NO_3$	—	$C_{10}H_{16}NO_3$	$C_{10}H_{16}NO_2$	$C_9H_{12}NO_2$	$C_8H_{10}NO_2$	$C_9H_{12}NO$	$C_8H_{12}N$	$C_7H_5O_2$	$C_7H_{10}N$	C_7H_5O	$C_6H_{10}N$	C_4H_8N	C_5H_8N	C_6H_5	—	
Cocaine	CH_3	CH_3	C_6H_5	H	303	272	244	198	182	166	152–55	150	122	122	108	105	96–7	94	82	77	42	†
D_3-Cocaine	CD_3	CH_3	C_6H_5	H	306	275	—	201	185	169	155–58	153	125	122	111	105	99–100	97	85	77	45	(1,6)
Norcocaine	H	CH_3	C_6H_5	H	289	—	—	184	168	?	138–41?	136?	?	?	94?	105	82–3	80	68	77	—	(7)
Benzoylecgonine	CH_3	H	C_6H_5	H	289	272	—	184	168	?	?	150?	?	122?	108	105	96–7	94	82	77	42	(2)
Cocaethylene	CH_3	CH_3CH_2	C_6H_5	H	317	272	244	212	196	166	166–69	150	122	122	108	105	96–7	94	82	77	42	(8)
D_8-Cocaethylene	CD_3	CD_3CD_2	C_6H_5	H	325	275	247	220	204	169	174–77	153	125	?	111	105	99–100	97	85	77	45	†
Arylhydroxycocaine	CH_3	CH_3	C_6H_4OH	H	319	288	260	198	182	166?	152–55	150	122	138	108	121	96–7	94	82	93	42	(9)
Hydroxymethoxycocaine	CH_3	CH_3	$C_6H_3(OH)(OMe)$	H	349	318	—	198	182	166?	152–55?	150?	122	168	108	151	96–7	94	82	123	42	(10)
Arylhydroxycocaethylene	CH_3	CH_3CH_2	C_6H_4OH	H	333	288	260	212	196	166?	166–69?	150	122?	138	?	121	96–7	94	82	93?	42	(8)
6-(or 7-)chlorococaine	CH_3	CH_3	C_6H_5	Cl	337‡	306‡	278‡	232‡	216‡	200‡	152†	184?	156‡	122	?	105	—	94	116‡, 82	77	42	(4)

*Ref 5.
†This laboratory.
‡Isotopic abundances consistent with the presence of chlorine.

proposed in Figs. 2 to 8 appear above the columns that list the mass correlations. Empirical formula for cocaine ions from Shapiro et al. are provided immediately below the ion structure designations.

In most cases, correlating the movement of ions from spectrum to spectrum was straightforward; indeed, spectra were chosen for analysis based to the relative ease with which correlations could be made. For example, the relative intensity pattern of m/z 82, 182, 198, 272, and 303 in Fig. 1 was discernibly reproduced by a combination of five relatively intense ions at appropriate masses in the spectra of nearly all of the derivatives [in cocaethylene these ions appeared at m/z 82 (100%), 196 (80%), 212 (12%), 272 (20%), and 317 (30%)]. With less intense ions, correlating peaks was somewhat more difficult. In those cases, the intensity of expected ions relative to surrounding ions was used as a primary criterion. A particularly difficult group was that located at m/z 150–155 in Fig. 1. In some spectra (D_3-cocaine, for example), the entire group was displaced three Daltons, with all of the relative intensities retained. In the cocaethylene spectrum, on the other hand, a single ion was observed at m/z 150 whereas the rest of the group seemed to disappear. After analysis of the D_8-cocaethylene spectrum, however, the presence of the rest of this group was discerned at m/z 166–9 in the cocaethylene spectrum. Where correlations were questionable or the movement of the ion could not be ascertained with relative certainty, a question mark appears in Table 1. In a few instances, ions were either too weak to be observed (as with ions correlating to m/z 244 in Fig. 1), or not expected (in the spectrum of norcocaine the ion corresponding to m/z 42 occurs below the low mass end of the scanned mass range). These situations are denoted with a dash in Table 1.

Guidelines for Proposed Fragmentation Mechanisms

Several guiding principles were applied to devising fragmentation mechanisms (11): 1. Because ejection of an electron from the nonbonding orbitals of a heteroatom requires substantially less energy than ejection of those from most bonding orbitals, it is assumed that compounds containing heteroatoms undergo initial ionization at the heteroatom. When several heteroatoms occur in the same molecule, initial ionization can occur with equal ease at each of them. 2. The most energetically favorable fragmentations for aliphatic compounds containing heteroatoms involve cleavage of bonds at carbon next to the heteroatom (commonly known as α-cleavage or β-scission), with the resultant positive charge stabilized by the heteroatom. Because of its lower electronegativity, nitrogen stabilizes this charge better than oxygen and thus directs a proportionately greater percentage of α-cleavage related fragmentation. 3. Neutral doubly- and triply-bonded molecules are often lost because of the energy gained in forming a new π-bond. 4. Hydrogen transfer to other sterically accessible radical sites within an ion occurs with relative ease, especially if the transfer leads to subsequent formation of a highly stable ion. 5. Mechanisms involving retention of charge in the same part of the molecule in which it was originally located are energetically more favorable than those in which the charge migrates to another site. 6. Whenever possible, proposed mechanisms utilize common intermediates and/or parallel modes of fragmentation.

M/z 303 (I)—The molecular ion in each spectrum is moderately intense and appropriately reflects the designated functional group modification(s).

M/z 272 (II)—The empirical formula for this ion shows loss of CH_3O · from the molecular ion, explained most obviously by α-cleavage of alkoxy radical from the carboalkoxy group after initial ionization at the carbonyl oxygen (Fig. 2) (1). In accordance with this interpretation the mass of this ion does not change with changes in R^2 (e.g., cocaethylene; $R^2 = C_2H_5$), but does respond to other changes in the molecule (Table 1).

M/z 244 (III)—This weak ion lies 28 Daltons below the mass of II in each spectrum in which it occurs. Because its mass is sensitive to modifications in R^1 and Ar but not to changes in R^2, this ion undoubtedly arises from loss of CO from II, assisted by displacement by one of the lone pairs of electrons on the carbonyl oxygen of the neighboring aroyl group (Fig. 2.). The driving force for this fragmentation is not only formation of the additional bond in CO, but also stabilization of the positive charge on both remaining oxygens.

M/z 198 (IV)—Both the empirical formula and mass correlations for IV indicate loss of the aroyl (ArCO) group from the molecular ion. The moderate intensity of this ion makes direct cleavage of the aroyl radical after initial ionization at the C(3) oxygen seem unlikely (11). Because the entire $ArCO_2$ · group is lost when V is formed by α-cleavage after initial ionization at *nitrogen* (see below), a low-energy mechanism using a common intermediate might account for the formation of IV as well (Fig. 2). Several structures are possible for IV including an epoxide and the ketone shown. There is still insufficient information to distinguish between the possibilities.

M/z 182 (V)—The empirical formula, supported by the mass correlation data, shows that this ion results from loss of $ArCO_2$ · from the molecular ion. The intensity of V demands an energetically favorable mechanism of formation. In accordance with previous proposals, initial ionization at nitrogen, α-cleavage with formation of a radical site at C(4) and subsequent loss of the stable benzoate radical with concurrent generation of an additional π-bond accounts nicely for the formation of this ion (Fig. 2) (1–3).

M/z 166 (VI)—No mechanism has previously been proposed for the formation of this small ion. Because it involves loss of the aromatic ring and *two* additional carbons (the empirical formula shows the loss of C_8H_9O), it seems unlikely that this loss occurs in one step. Surprisingly, the mass correlation data reveals that this ion appears at the same mass regardless of the nature of R^2 or Ar, indicating that both of these groups are lost in the formation of VI.

Several structures, as well as several pathways for its formation, are possible for this ion. Loss of ArCO · from II with formation of a cyclic lactone involving the C(2) carbonyl and the C(3) oxygen is tempting to postulate, but the intensity of VI appears to be insensitive to stereochemical inversion at either C(2) or C(3) (12). A second mechanism involves loss of R^2OH from IV in a manner analogous to that shown in Fig. 3 for the formation of VIII from V. However, subsequent loss of CO from VI is inconsequential in cocaine (m/z 138 < 1%), in contrast to the intensities of IX in most spectra and of m/z 120 in the spectra of the chlorococaines. An alternative path (Fig. 3) is derived from a plausible mechanism for the (not insignificant) loss of methyl from the molecular ion of methylecgonidine. Subsequent loss of CO_2 from this structure would provide an additional route to IX.

M/z 152–55 (VII)—The weak peaks between m/z 152 and 155 are empirically related to each other through the successive loss of hydrogen, but not to m/z 150 (5). The empirical formula and the mass correlation data show that, although the aromatic ring is gone, R^2 is still attached. The response of this group of ions to deuterium labeling at the N-methyl indicates that the nitrogen, and probably the two-carbon bridge, are still intact. Ideally, the spectra of the chlorococaines should clarify the presence or absence of

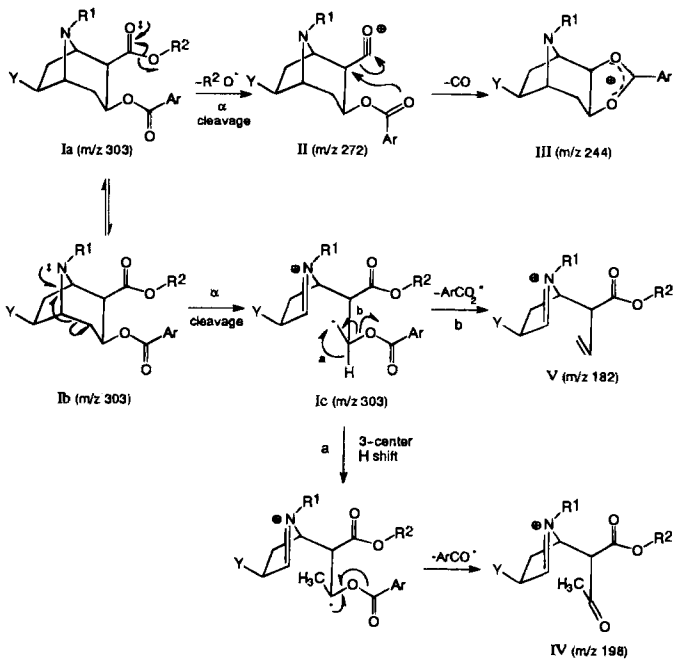

FIG. 2—*Mechanisms for formation of II, III, IV, and V by α-cleavage after initial ionization at nitrogen or the carbonyl oxygen at C(2).*

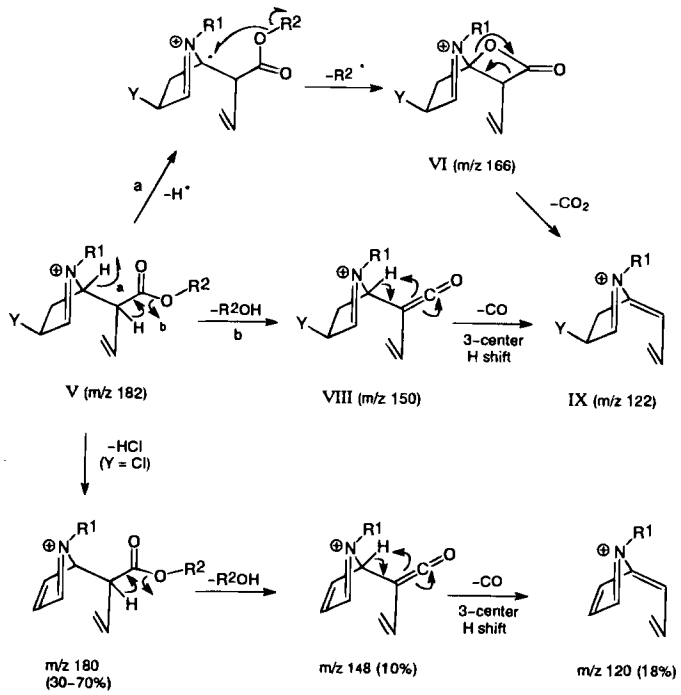

FIG. 3—*Mechanisms for formation of VI, VIII, and IX from V.*

the two-carbon bridge, but the very weak ion (<1%) at m/z 189 in only one of the spectra fails to resolve this issue, apparently because of the propensity for this and several other ions in the spectra to lose HCl. Facile formation of ions correlated to m/z 155 from the previously proposed intermediate Ic is shown in Fig. 4.

We expect formation of m/z 152 from m/z 155 to be driven by development of a fairly extensive π-system. Indeed an N-methylpyridinium structure (VIIa), similar to that proposed by Zhang and Foltz (13) to account for the base peak in the spectrum of methylecgonidine, is consistent with the available data. An alternative structure, the azafulvene VIIb (Fig. 4), cannot be ruled out, even though the enhanced stability of the pyridinium structure is attainable without substantial inputs of enthalpy or entropy.

The proposed fragmentations of m/z 155 offer a plausible point for energy partitioning that could account for differences in the relative intensities of these ions observed in the spectra of the cocaine diastereomers. Of the four diastereomers defined by the N-methyl-2-carbomethoxy-3-benzoyloxytropane structure, only one (cocaine) displays an m/z 152 ion which is similar in intensity to those of the surrounding ions (2,5,12,14). For example, although m/z 152 is less than 1.5 times more intense than m/z 155 in the spectrum of cocaine, it is at least 5 times more intense than m/z 155 in the spectrum of pseudococaine, which has inverted stereochemistry at C(2). In the spectra of allo- and allopseudococaine, the ratios are intermediate in value.

Assuming that cleavage in m/z 155 by either path a or b in Fig. 4 proceeds rapidly enough to restrict rotation around the C(1)-C(2) bond before the π-bond is formed, the orientation of the carbomethoxy group relative to the N-methyl group in the resulting intermediate should be determined by the initial orientations of these groups in the parent molecules. Newman projections along the C(1)-C(2) bond (Fig. 5) indicate that, in the fragmentation of cocaine, the carbomethoxy and N-methyl groups are *syn* (60°) with respect to one another and therefore should develop the *cis*

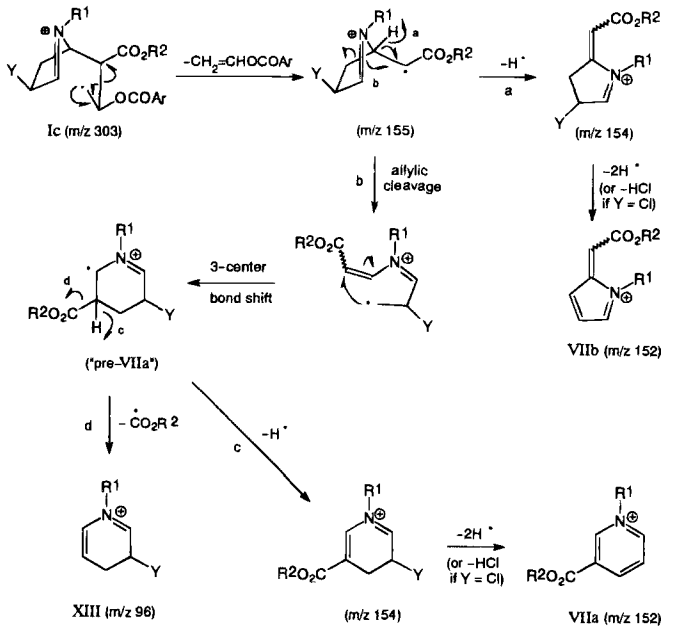

FIG. 4—*Formation of VII and XIII from Ic. Fragmentation of m/z 155 generates different steric environments for each of the cocaine diastereomers, which may account for the different relative intensities of m/z 152 in their spectra.*

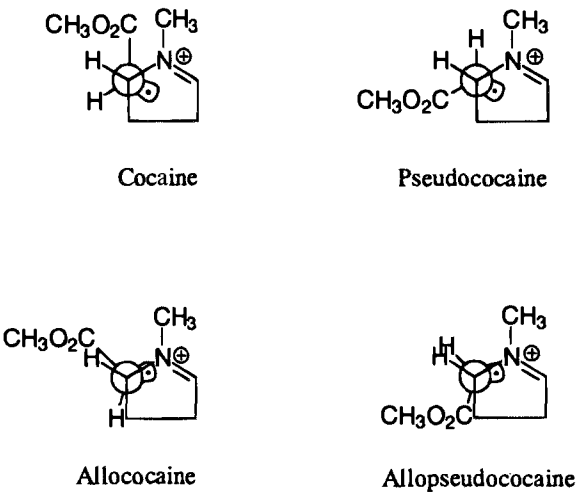

FIG. 5—*Newman projections along the C(1)-C(2) bond axis of the m/z 155 radical ions formed in the fragmentation of the four cocaine diasteromers.*

configuration about the double bond. In pseudococaine, on the other hand, they are *anti* (150°) and should develop the more stable *trans* configuration. In allo- and allopseudococaine the cyclohexane ring undoubtedly assumes a "twist-boat" conformation due to the bulk of the *endo*-benzoyloxy group, and the carbomethoxy and N-methyl groups become more neutrally situated (approximately 120° apart), allowing formation of the more favored *trans* configuration with minimal additional energy input. Thus, of the four diastereomers, only cocaine is deterred from forming intermediates that lose hydrogen; conversely, pseudococaine is the only diastereomer that is sterically encouraged to do so.

M/z 150 (VIII) *and m/z 122* (IX)—Surprisingly, VIII is structurally unrelated to VII and lacks both the R^2 and Ar groups and three of the four oxygens. At the same time, however, IX shows loss of an additional CO, so it is tempting to devise a mechanism leading to formation of IX from V using VIII as an intermediate. Such a pathway is illustrated in Fig. 3, in which R^2OH is eliminated in either a step-wise or concerted manner to form the substituted ketene VIII (11), which in turn is unstable to the loss of CO to form the highly unsaturated IX (15). This proposal stands in contrast to that of Ethier and Neville, who postulate formation of IX from V by losses of CO_2R^2 and H radicals (3). Support for the sequence in Fig. 3 is seen in the spectra of the chlorococaines (4), in which V (m/z 216) loses HCl to form m/z 180. This ion already possesses a high degree of unsaturation and readily relinquishes both R^2OH and CO to produce prominent ions at m/z 148 and 120 respectively.

M/z 122 (X)—High resolution mass spectrometry (5) easily discerns two unrelated ions at m/z 122 in the cocaine spectrum, an observation born out by the mass correlation data. The second of these ions (X), whose intensity varies greatly depending on the nature of the Ar group, arises from the aromatic acid. A possible mechanism for formation of this ion from Ie is shown in Fig. 6. The hydrogen on C(4) was chosen for rearrangement simply for steric reasons; the one on C(2) is *trans* to the benzoate oxygen and would require molecular distortion for transfer to occur.

M/z 108 (XI)—Despite the data available for this ion, which has lost both R^2 and Ar as well as one undetermined carbon from

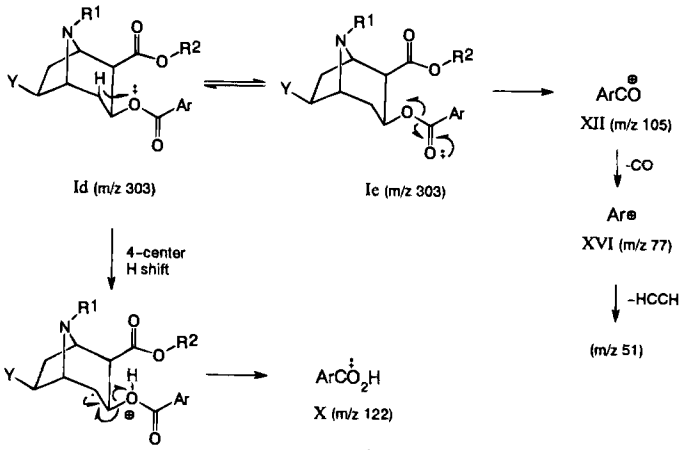

FIG. 6—*Formation of X, XII, and XVI after initial ionization at the oxygens of the aroyl group.*

the three-carbon bridge, several structures are possible. Formation of all of them via already proposed intermediates requires substantial molecular rearrangement. No attempt is made here to define this ion further.

M/z 105 (XII) *and m/z 77* (XVI)—Not surprisingly, XII corresponds to the aroyl ion (1,5) formed by initial ionization at the aroyl oxygen (Ie) and subsequent α-cleavage (Fig. 6). Benzoyl ions readily lose CO to produce the corresponding phenyl ions (XVI) (15), which in turn lose acetylene to form ions corresponding to m/z 51 in the cocaine spectrum.

M/z 94–97 (XIII *and* XIV) *and m/z 42* (XVII)—Ions XIII and XIV are separated in Table 1 mainly because of the apparent disappearance of the ions corresponding to XIII in the spectra of the chlorococaines (4). It seems likely, however, that not only are these ions interrelated in much the same way as the ions at m/z 152–55 (from which they differ in mass by 58 Daltons), but also that their formation is connected in some way to the formation of at least the ions corresponding to m/z 152–54.

As with the ions leading to VII (Fig. 4), structures for XIII and XIV cannot be determined with certainty. Both the N-methylpyridinium ions XIIIa and XIVa and the N-methylazafulvenyl ions XIIIb and XIVb are reasonable alternatives; mechanisms leading to their formation (Fig. 7) are completely analogous to those described previously for VII and to that outlined by Ethier and Neville from 2-carbomethoxytropinone (3). As with the immediate precursors to VII, the disappearance of XIII from the spectra of the chlorococaines reflects the greater propensity of the precursor ions to lose HCl than hydrogen.

Curiously, the intensities of m/z 94 relative to m/z 96 and 97 in the spectra of the cocaine diastereomers varies with two apparently unrelated factors. First, in the spectra of cocaine and allopseudococaine, in which the substituents on C(2) and C(3) are *cis* to one another, m/z 94 is larger than m/z 96 (12). For pseudo- and allococaine, in which these substituents are *trans*, m/z 96 is larger. Second, the relative size of m/z 94 in these spectra is inversely related to the intensity of m/z 152! The relative intensities of m/z 152 and 96 might be explained by a partitioning of energy between paths c and d in Fig. 4 for reasons that are not obvious. However, it is even less clear what factors determine the relative difficulty of hydrogen loss from m/z 96. An additional path to m/z 94, bypassing m/z 96, might account for these differences.

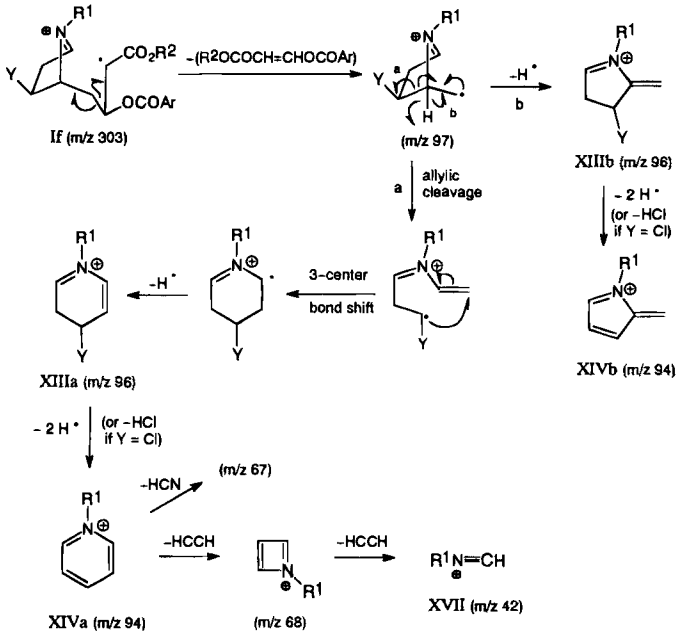

FIG. 7—*Formation of XIII and XIV by an alternative α-cleavage of I after initial ionization at nitrogen. The fragmentations of XIVa are typical of aromatic nitrogen compounds.*

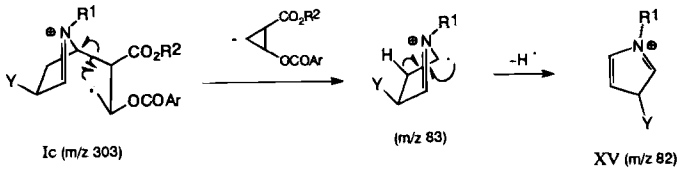

FIG. 8—*Formation of XV from Ic by α-cleavage and subsequent allylic cleavage (after Ref 3).*

The unsaturated ions XIVa and XIVb are expected to fragment further with losses of acetylene and HCN (Fig. 7) (15). Ions corresponding to m/z 68 further can lose acetylene to produce XVII.

M/z 82-3 (XV)—These intense ions arise from loss of the entire 3-carbon bridge (Fig. 8) (2,3). Without additional studies, it cannot be determined whether this occurs in one or several steps. Either way, its formation is consistent with the tendency of aliphatic amines to shed large portions of the molecule while retaining the positive charge on the nitrogen.

Opportunities for Further Study

Much remains unclear about several important (and in some cases, discriminating) fragmentations of cocaine. Additional insight would be gained by examination of these fragmentations by tandem mass spectrometry (ms/ms), patterned after the work of McLafferty, Cooper et al. on (16) fentanyl derivatives related to "China White."

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