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MASS SPECTROMETRY OF MORPHINE ALKALOIDS. PART I.
FRAGMENTATION OF MORPHINAN AND RELATED COMPOUNDS

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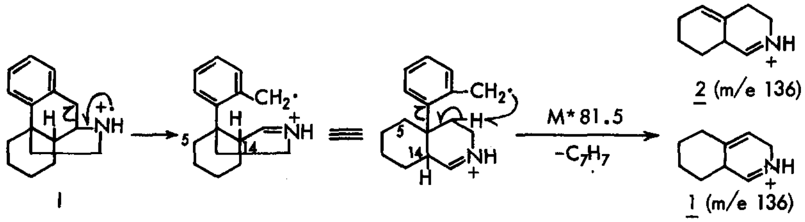
In recent years the importance of mass spectrometry as a useful tool for structure elucidation studies has been well established, particularly in the field of natural products. Although a large number of alkaloids have been examined in this connection (1), no report on the mass spectra of morphine group alkaloids had come to our attention until quite recently (2). The present paper describes mass spectra and general fragmentation patterns of morphinan and some related compounds (3). The interpretation of the spectrum is based on an assumption that upon electron impact one electron is removed either from the nitrogen atom or from the aromatic nucleus.

The spectrum of the simplest parent compound, morphinan (I), is shown in Fig. 1.

The appearance of a peak at m/e 136 is a characteristic feature of this spectrum, aside from a prominent molecular ion peak (M^+ : m/e 227) as well as an M-1 ion peak. The formation of this ion is probably associated with the loss of an aromatic moiety of the molecule and is depicted in the following manner (Type A fragmentation). The process is confirmed by the existence of an appropriate metastable ion peak at m/e 81.5.

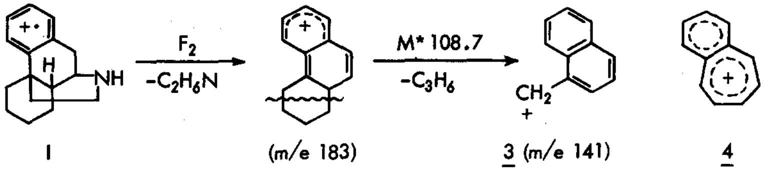
Type A Fragmentation :



The formation of an alternative ion 2 through an intramolecular abstraction of a hydrogen atom from C_5 by the benzyl radical is also conceivable. However, the abstraction from C_{14} to give a more stable, conjugated ion as reported by H. Audier, et al. (2) is stereochemically impossible. The type A fragmentation was observed in all compounds examined, and in most cases the resultant fragment ion has very high relative abundance in the spectrum, regardless of the substituents in ring C (See Table I).

A moderately intense peak at m/e 141 is attributed to a cation 3 (or its equivalent, 4) (Type B fragmentation). A prominent metastable ion peak at m/e 108.7 suggests that

Type B Fragmentation :



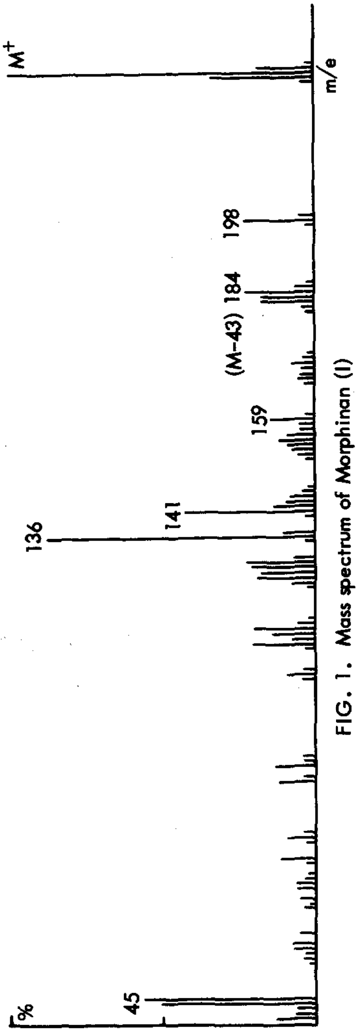


FIG. 1. Mass spectrum of Morphinan (I)

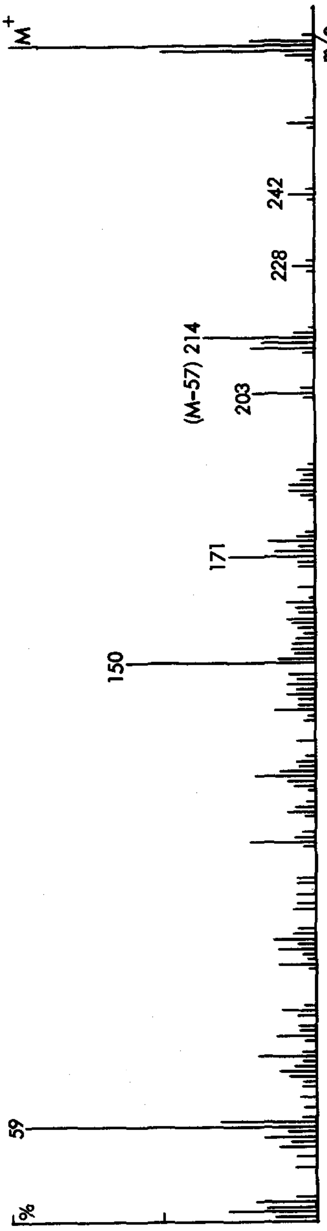


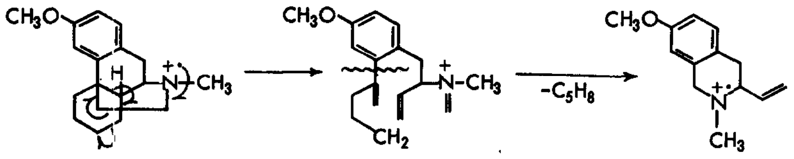
FIG. 2. Mass spectrum of 3-Methoxy-N-methylmorphinan (III)

this ion arises from an ion of m/e 183, which, in turn, is formed by the type F_2 fragmentation discussed later.

3-Methoxy-N-methylmorphinan (III) exhibited a similar spectrum (Fig. 2). In this case, type A and type B fragmentations afford, respectively, ions of m/e 150 and 171.

To account for an M-68 fragment in I (m/e 159) and in III (m/e 203) the following mechanistic pathway is postulated (Type C fragmentation).

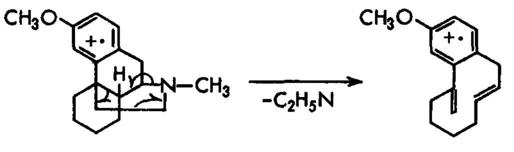
Type C Fragmentation :



III 5 (m/e 203)

While the primary cleavage of ring C seems to be of minor importance in general, the retro-Diels-Alder fragmentation of ring D in a manner indicated below gives rise to an M-43 ion (m/e 228) from III (Type D fragmentation). A similar breakdown of the ring D in another fashion followed by homolytic expulsion of a benzylic hydrogen atom yields an M-29 ion (m/e 242) (Type E_1 fragmentation). Formulation of the M-29 ion through a removal of an electron from the nitrogen atom is also feasible (Type E_2 fragmentation). These D and E fragmentations gave ions of identical mass number (m/e 198)

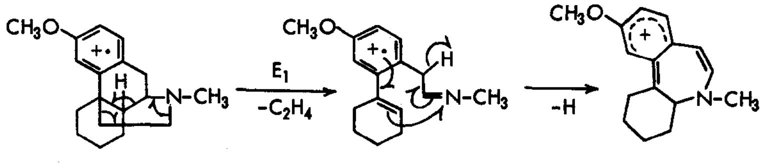
Type D Fragmentation :



III 6 (m/e 228)

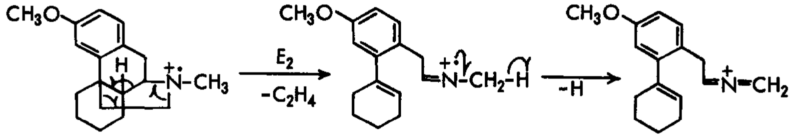
for compound I, and this is responsible for an increase of the relative abundance of the peak (See Fig. 1).

Type E Fragmentation :



III

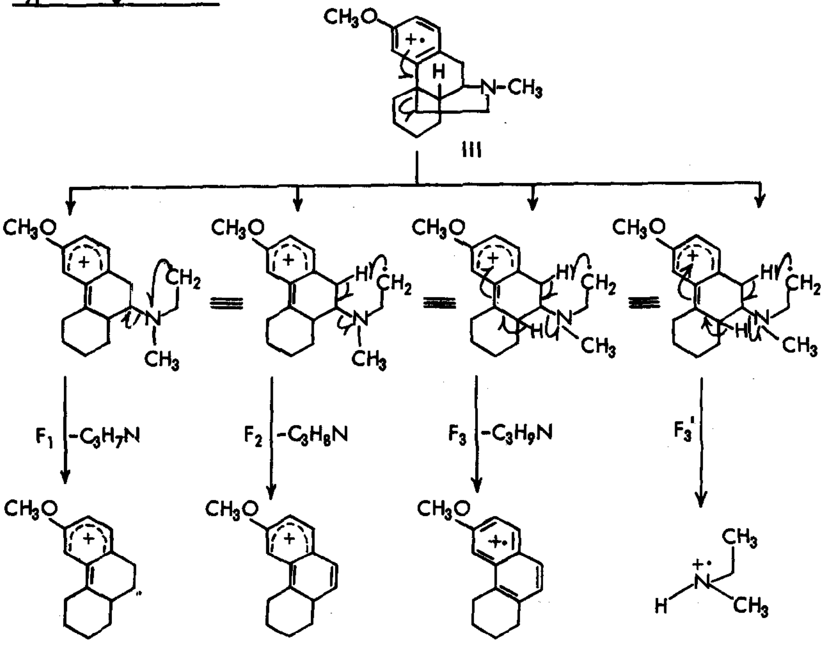
·7 (m/e 242)



8 (m/4 242)

A group of peaks, M-57, M-58, and M-59 ions, is characteristic for all N-methyl derivatives. Since it appeared around M-43 ion in I, the origin of the peaks would presumably be due to a loss of the nitrogen-containing bridge with or without an additional hydrogen atom (or atoms) (Type F fragmentation). The previously reported mechanism of a similar process in the pentacyclic morphine system (2) is not applicable in this case, for it does not explain the formation of the three related ions. We now suggest the following mechanisms involving a common intermediate ion. Since one of the driving forces of the F_3 fragmentation is the electron withdrawal by a positively charged benzene nucleus with generation of a stable aromatic ring system, either a one- or two-electron shift is possible and thus either fragment is capable of carrying the positive charge. This is not expected in F_1 or F_2 fragmentation. In fact, all N-methyl compounds showed a strong peak at m/e 59, while compound I exhibited a corresponding peak at m/e 45.

Type F Fragmentation :

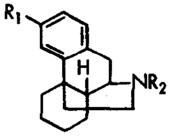
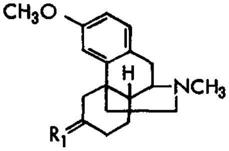
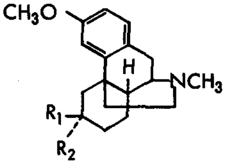
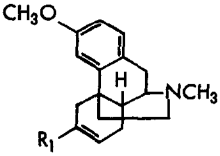
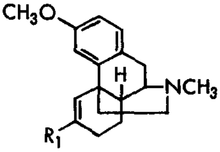


9 M-57 (m/e 214) 10 M-58 (m/e 213) 11 M-59 (m/e 212) 12 (m/e 59)

The important fragment ions of several morphinan derivatives are summarized in Table I. Special types of fragmentation of individual compounds will be discussed in a forthcoming publication.

Finally, it should be pointed out that some of the fragmentations illustrated above and those of the pentacyclic morphine system (2) are quite different. Our own interpretation of the mass spectra of morphine alkaloids will be reported elsewhere.

TABLE I. Important Fragment Ions (m/e)

Compound	No.	Substituent			Fragmentation Type				
		R_1	R_2	M^+	A	B	C	D	E
	I	H	H	227	136	141	159	198	198
	II	H	CH_3	241	150	141	173	198	212
	III	CH_3O	CH_3	271	150	171	203	228	242
	IV	O	-	285	164	171	203	242	256
	V	CH_2	-	283	162	171	203	240	-
	VI	CH_3	H	285	164	171	203	-	-
	VII	H	CH_3	285	164	171	203	-	-
	VIII	CH_3	OH	301	180	171	203	-	-
	IX	OH	H	287	166	171	203	-	-
	X	H	OH	287	166	171	203	-	-
	XI	H	-	269	148	-	203	226	-
	XII	CH_3	-	283	162	-	203	240	-
	XIII	H	-	269	148	-	-	226	240
	XIV	CH_3	-	283	162	-	-	240	254

REFERENCES

1. See, for example, H. Budzikiewicz, C. Djerassi and D. H. Williams, Structure Elucidation of Natural Products by Mass Spectrometry, Vol. I, "Alkaloids", Holden-Day, Inc., San Francisco (1964).

2. After the present work had been completed, the mass spectra of several morphine alkaloids was reported: H. Audier, M. Fetizon, D. Ginsburg, A. Mandelbaum and Th. Rüll, Tetrahedron Letters, 1965, 13.

3. The mass spectra were taken with a Hitachi Mass Spectrometer Model RMU-6C, using an all-glass inlet system. The ionizing energy was kept at 70 e.V. and the ionizing current at 80 μA. Two authors (H. N. and Y. H.) are grateful to the Grant from the Toyo-Rayon Co., Ltd. for purchase of the mass spectrometer.