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MASS SPECTROMETRY OF THE MORPHINE ALKALOIDS

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The morphine alkaloids undergo complex rearrangements. It was a reasonable a priori assumption that their behaviour under electron impact would be no less interesting.

The pentacyclic morphine system is of such complexity that several bonds must be cleaved before fragmentation is possible. All of the pentacyclic compounds studied indeed exhibited the molecular peak in highest abundance. The related tetracyclic derivatives in which the ether ring is absent, undergo fragmentation more readily.

It appears that on ionization, one electron is removed from the nitrogen atom. Subsequent one electron shifts can lead to intermediates capable of fragmentation. Such a pattern is clearly evident in one of the simplest spectra in this series, that of demexycodeine A, 1.

The most abundant ion in the mass spectrum of 1 is at m/e 178 (Scheme 1). This peak is shifted to m/e 179 in the O-deuterated compound, hence ring A is retained in this fragment. Changes in ring C do not affect the m/e of this peak although they affect its relative intensity. These

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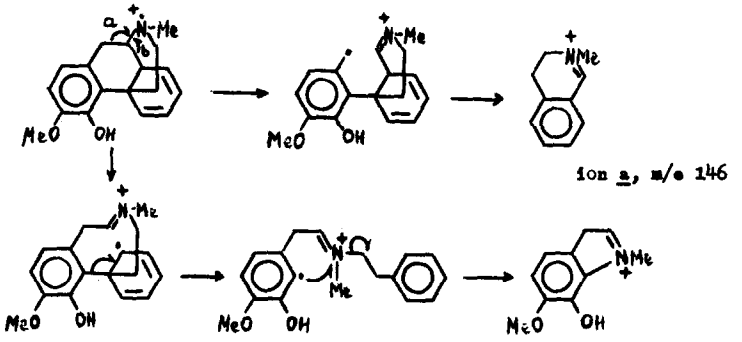
data are summarized in Table 1. Unsaturation in ring C increases the



SCHEME 1

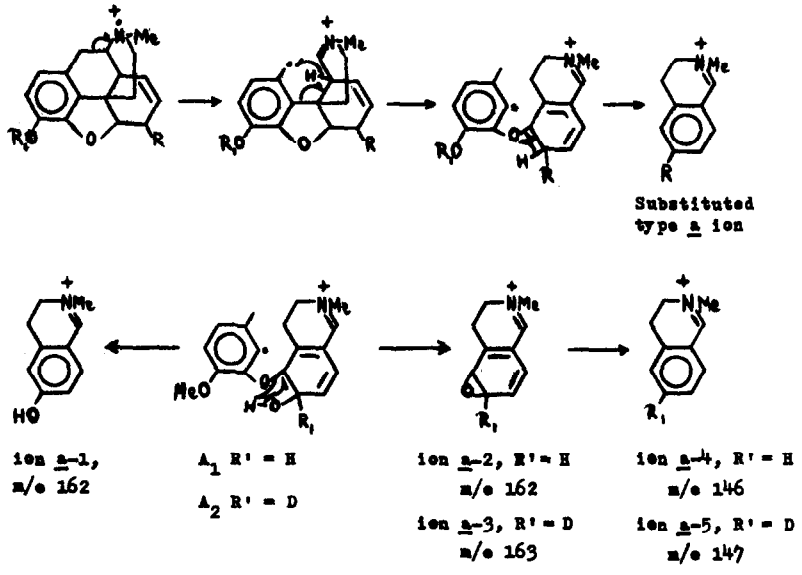
probability of formation of ion b through the driving force of aromatization. It should be noted that no significant m/e 178 peak (or its analogue) was found in any of the mass spectra of the pentacyclic compounds investigated.

TABLE I

Compound	m/e type b ion	Relative abundance ion b	m/e type a ion	Relative abundance type a ion
Desoxycodeine A, 1	178	100	146	55
Thebainone, 2	178	61	162	100
Sinomenine, 3	178	26	192	35
Dihydrothebainone, 4	178	15	164	100
Tetrahydropseudo-codeine, 5	178	5	166	100
Tetrahydrodesoxy-codeine, 6	178	3	150	100
3-Methoxy-N-methyl-morphinan, 21	162	—	150	38

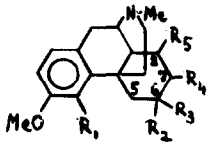
The other important peak in the mass spectrum of 1 is at m/e 146. This does not shift upon O-deuteration, hence this fragment does not contain ring A. However, the m/e values depend upon substituents in ring C (Table 1).

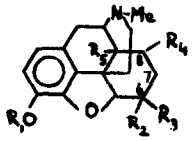
In contrast to ion b, type a ions are also found in the spectra of the pentacyclic compounds albeit in much lower abundance. This is due to the additional bond which must be cleaved in the latter before ions of type a may be formed (see Scheme 2). Type a ions do not form unless there are hydrogen atoms at C-14 and C-6. Thus, for example, there is no ion a peak in the spectra of 14-hydroxycodeinone 20, and thebaine 22, and only weak peaks appear in the region of type a ions resulting from methyldihydromorphinone 15, dihydromorphinone 16, dihydrocodeinone 17, codeinone 19, and 14-hydroxydihydrocodeinone 21.



SCHEME 2

Table 2 summarizes the data obtained for type a ions and demonstrates that compounds in which ring C is saturated also undergo fragmentations similar to that described in Scheme 2.





1 R_1,OH; $R_2R_4R_5$,H; $\Delta^{5,7}$;

2 R_1,OH; R_2R_3,=O; R_4R_5,H; Δ^{7};

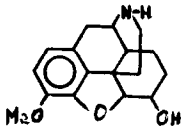
3 R_1,OH; R_2R_3,=O; R_4,OMe; R_5,H; Δ^{7};

4 R_1,OH; R_2R_3,=O; R_4R_5,H;

5 R_1R_5,OH; $R_2R_3R_4$,H;

6 R_1,OH; $R_2R_3R_4R_5$,H;

27 $R_1R_2R_3R_4R_5$,H;



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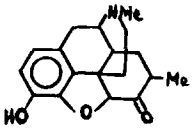

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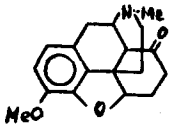

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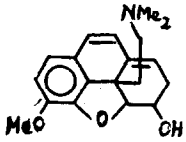

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7 $R_1R_3R_4R_5$,H; R_2,OH; Δ^{7};

8 R_1,Me; R_2,OH; $R_3R_4R_5$,H; Δ^{7};

9 R_1,Me; $R_3R_4R_5$,H; Δ^{6};

10 R_1,Me; R_2,OH; $R_3R_4R_5$,H;

11 as in 10; R_2 and R_3 interchanged;

12 R_1,Me; $R_2R_3R_4R_5$,H;

14 R_1,Me; $R_2R_3R_5$,H; R_4,OH;

16 $R_1R_4R_5$,H; R_2R_3,=O;

17 R_1,Me; R_2R_3,=O; R_4R_5,H;

19 R_1,Me; R_2R_3,=O; R_4R_5,H; Δ^{7}

20 R_1,Me; R_2R_3,=O; R_4,H; R_5,OH; Δ^{7}

21 R_1,Me; R_2R_3,=O; R_4,H; R_5,OH;

22 R_1,Me; R_2,OMe; R_4,H; $\Delta^{6,8}$;

23 R_1,Me; R_2,OH; R_3R_4,H; Δ^{8};

24 R_1,Me; $R_2R_3R_4$,H; Δ^{8};

25 R_1,Me; $R_2R_3R_4R_5$,H; Δ^{7};

26 R_1,Ac; R_2,OAc; $R_3R_4R_5$,H; Δ^{7};

TABLE 2

Compound	m/e of type a ion	Relative abundance (%)
Morphine, 7	162	24
Codeine, 8	162	24
Desoxycodeine C, 9	146	16
Dihydrocodeine, 10	164	31
Dihydroisocodeine, 11	164	12
Dihydrodesoxycodeine D, 12	148	13
Dihydronorcodeine, 13	150	25
Dihydropseudocodeine, 14	164	7
Desoxycodeine E, 25	146	62
Heroin (diacetylmorphine), 26	204	29

In the mass spectrum of codeine (and morphine) there is a peak at m/e 146. In O-deuterated codeine this peak remains at m/e 146 whilst in 6-deuterocodeine it is shifted to m/e 147, hence ring C is retained in the ion responsible for this peak and corresponds to a type a ion from which oxygen has been abstracted.

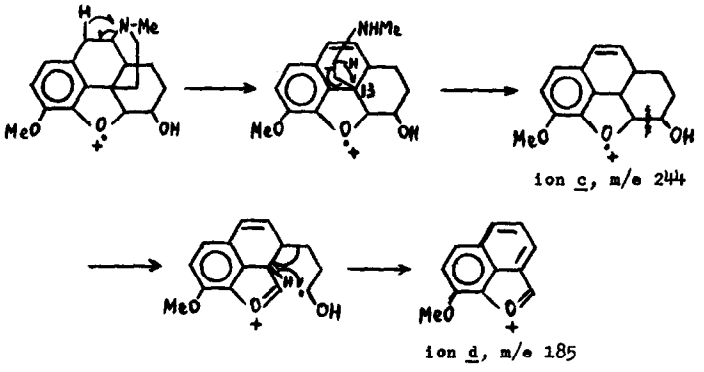
We suggest that ion a-4 m/e 146 (Scheme 2) arises from the intermediate A_1 through ion a-2. This mechanism explains the shift to m/e 147 mentioned for 6-deuterocodeine (sequence $A_2 \longrightarrow$ a-5). The peak at m/e 162 in codeine must represent both ions a-1 and a-2 arising from the same intermediate A_1 in the two concurrent mechanisms described in Scheme 2.

In 6-deuterocodeine the intermediate A_2 should lead to ion a-1, m/e 162, not differing in this respect from undeuterated codeine. However, the corresponding peak is in fact at m/e 162 and partially at m/e 163. Hence it appears that the two mechanisms in Scheme 2, the latter one through the epoxide

ions a-2 (for codeine) and a-3 (for 6-deuterocodeine), indeed operate concurrently. Further, in codeine-O-d there is only a partial shift of the peak to m/e 163 (about 75%). Sequence $A_1 \longrightarrow$ a-1 (OD instead of OH) requires 100% shift to m/e 163. The concurrent sequence A_1 (OD instead of OH) $\longrightarrow$ a-2, can explain this result.

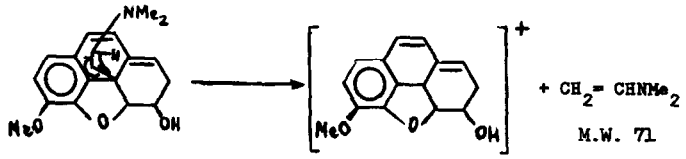
Let us now discuss other fragmentations which occur in alkaloids of the morphine type. Compounds which contain a methyl ether group, e.g. codeine 8, thebaine 22, etc., exhibit the fragmentation pattern typical for anisoles, M-15, M-43 and M-31 peaks representing the M-CH_3, M-CH_3-CO and M-OCH_3 cations, respectively (1). Compounds which contain a phenolic residue give the expected phenol pattern, M-28 and M-29 peaks representing loss of the elements of CO and CHO, respectively (2).

A peak common to all of the non-ketonic N-methylated morphine alkaloids investigated appears at M-57. This is due to the loss of the ethanamine bridge and in fact in dihydronorcodeine 13 which is not N-methylated, the corresponding peak appears at M-43. Scheme 3, although general, exemplifies the specific case of dihydrocodeine 10 which has also been proven by high resolution mass spectrometry (HRMS).



SCHEME 3

The mechanism of formation of the M-57 fragments (ions of type c) involves a hydrogen transfer from C-16 which is α- to nitrogen, to C-13. A similar cleavage clearly involving a similar hydrogen transfer was observed in the mass spectrum of β-methylmorphimethine 28, where the expected type c ion corresponds to M-71 (since two methyl groups are attached to nitrogen). In fact this ion, c-1 at m/e 242 is the most abundant in the spectrum of 28.



M.W. 313 ion c-1, m/e 242

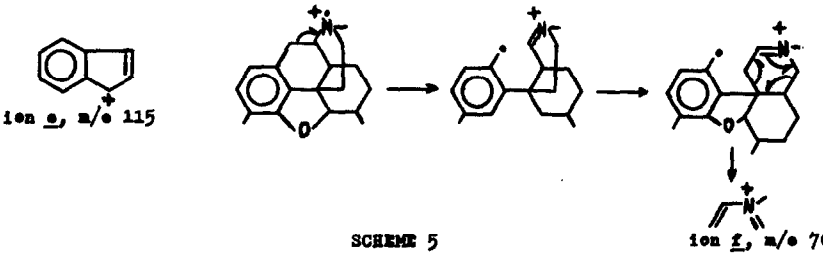
SCHEME 4

Many of the pentacyclic 3-methoxy compounds exhibit a marked peak at m/e 185 (ion d). In several non-methoxylated pentacyclic compounds there is an analogous peak at m/e 171. In 14-hydroxydihydrocodeinone 21, the corresponding peak is at m/e 201. Ring A as well as C-14 are therefore retained in type d ions responsible for these peaks. Since the tetracyclic compounds do not show such peaks it is clear that the ether ring is necessary for the formation of type d ions. The loss of both the ethanamine bridge and carbons 6,7 and 8 is involved in this type of fragmentation, as shown in Scheme 3.

Two peaks appear in all mass spectra of the compounds examined, at m/e 115 and m/e 70.

The peak at m/e 115 was shown by HRMS to correspond to an ion of empirical formula C_9H_7. A plausible structure is e (Scheme 5). The peak at m/e 70 was shown in the same way to correspond to C_4H_8N, for which structure f is proposed. It is possibly formed by the mechanism shown

in Scheme 5. It should be noted that dihydronorcodeine 13, which cannot give rise to ion f does not exhibit a peak at m/e 70.

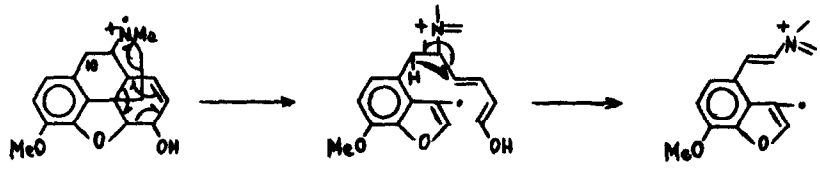


ion e, m/e 115

ion f, m/e 70

SCHEME 5

The mass spectrum of morphine 7, exhibits in addition to the molecular peak, seven conspicuous peaks at m/e values of 258 (M-CO), 215, 162, 124, 115, 94 and 70. The peak at m/e 215 appears at m/e 216 in morphine deuterated at both oxygens and at m/e 229 in codeine 8 or in codeine-O-d. The ion responsible must therefore contain ring A (see Scheme 6, as represented for codeine).



ion g, m/e 229

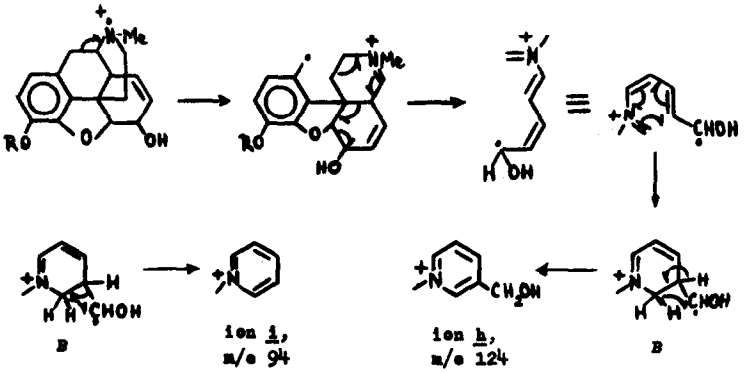
SCHEME 6

Codeinone 19, 14-hydroxycodeinone 20, and desoxycodeine E 25, all give an ion g at m/e 229. However, 14-hydroxydihydrocodeinone 21, shows a strong peak at m/e 230 and both dihydrocodeinone 17 and dihydropseudocodeinone 18 show peaks at m/e 228 albeit they lack a Δ^7 double bond. A retro Diels-Alder reaction as postulated in Scheme 6 is unlikely to occur when ring C is saturated. Further evidence for the mechanism in Scheme 6 must be sought, for example, by deuteration at C-10 and by proving the nature of the peaks at m/e 228 and 230 by HRMS. It must nevertheless be noted that for codeine the respective ion g expected by the above mechanism should have the empirical

formula $C_{14}H_{15}O_2N$ and this formula has been demonstrated through the use of HRMS.

The peak at m/e 162 for morphine and codeine corresponds by HRMS to an ion of empirical formula $C_{10}H_{12}ON$. This is an ion of type a which has been discussed above (Scheme 2; Table 2).

The peak at m/e 124 in the mass spectra of morphine and codeine corresponds by HRMS to an ion $C_7H_{10}NO$ (ion h). It is at m/e 125 in morphine O-d or in codeine O-d as well as in 6-deuterecodeine, and at m/e 108 in desoxycodeine E 25. Hence ion h must contain C-6 and it contains the hydroxyl group. This may be interpreted as shown in Scheme 7.

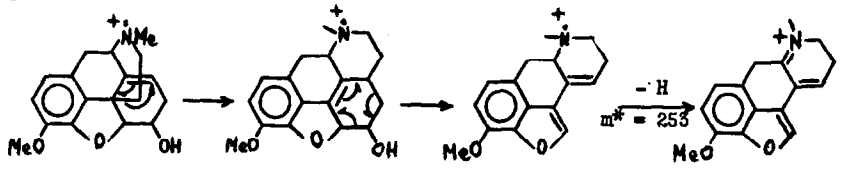


SCHEME 7

Ion h arises from the intermediate B shown in Scheme 7. B may, however, lead also to ion i at m/e 94 and this explains the appearance of the corresponding peak. The peaks at m/e 115 and 70 have already been discussed (Scheme 5).

The mass spectrum of neopine 23 contains in addition to the molecular peak only two intense peaks at m/e 254 and 255 (ions i and i-1); m/e 254 = 82% of base peak and m/e 255 = 25% of base peak. The ion i-1 arises from ion i as demonstrated by the existence of a metastable peak at m/e 253. A similar behaviour is exhibited by thebaine 22, although the peaks are less intense.

At a low voltage (10 eV) the peak corresponding to j is as intense as that of j-1. These two peaks are found in the mass spectra of neopine-O-d and desoxyneopine 24. Ion j therefore cannot contain C-6. HRMS proves that in the case of neopine the eliminated fragment leading to ion j has the empirical formula C_2H_4O. The mechanism shown in Scheme 8 permits interpretation of the results.



ion j, m/e 255 ion j-1

SCHEME 8

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