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Stereochemical and structural assignment to benzomorphans by mass spectrometry

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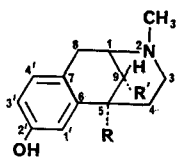
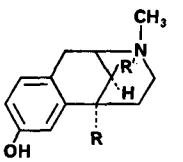
The fragmentation of some alkyl-substituted-6,7-benzomorphans upon electron impact (70eV) is characteristic. The relative intensities of some ions varies in a predictable manner depending on the configuration of the C-9 hydrogen atom. Configuration and structure of 5,9-disubstituted-6,7-benzomorphans can be assigned by mass spectrometry even when only one isomer of a structure capable of existing in diastereoisomeric forms is available.

Significant separation of analgesic activity from dependence liability has been achieved with benzomorphan derivatives (Jacobsen & May, 1964). One of these derivatives, pentazocine, is used clinically as a potent non-addicting analgesic.

Although there are three asymmetric carbons in 9-substituted-6,7-benzomorphans, only two diastereoisomeric forms are possible since the iminoethano-system must be *cis*-diaxially fused. These diastereoisomers differ in the configuration about carbon atom 9 and the substituents at this position are designated α and β. Differential aromatic screening results in a 0·5 ppm difference in the chemical shift of the α and β 9-methyl doublet in the proton magnetic resonance spectra of 2′-hydroxy-2,5,9-trimethyl-6,7-benzomorphan. This difference partially establishes that the C-5 and C-9 methyl substituents have a *cis* and *trans* configuration, with reference to the hydroaromatic ring, in the α- and β-isomers respectively (Fullerton, May & Becker, 1962). However, configurational assignment by pmr is only applicable to a few benzomorphans (Vaughan, 1972). A more general method of configuration assignment is based on the β-isomers quaternizing more slowly than the α-isomers with methyl iodide (Fullerton, & others, 1962).



α-9-substituted
-6,7-benzomorphans



β-9-substituted
-6,7 benzomorphans

Mass spectrometry has been successfully employed to differentiate between the diastereoisomeric pairs of diverse compounds (Beynon, Saunders & Williams, 1960; Lund, Budzikiewicz & others, 1963; Mandelbaum & Ginsburg, 1965). We have now investigated the mass fragmentation of some diastereoisomeric 6,7-benzomorphans with the intention of producing a method for establishing the configuration and structure of these benzomorphans, even when only one isomer of a diastereoisomeric pair is available.

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METHODS

Mass spectra were obtained using an A.E.I. M.S. 902 mass spectrometer running at a source temperature of 220° and a beam energy of 70 eV. Samples were introduced via the direct inlet system of the mass spectrometer. The elemental composition of the ions encountered in the fragmentation schemes outlined in the discussion were confirmed by accurate mass measurement at a resolving power of 20 000.

Table 1. *The configuration about carbon atom 9, the nature of the 2, 5 and 9 substituents and the relative intensity of the major fragment ions observed in the 2′-hydroxy-2,5,9-substituted-6,7-benzomorphans examined by mass spectrometry.*

Compound number	Configuration about C_9	Substituents N	C_5	C_9	'M⁺' m/e	r.i.	'M⁺−C_5' m/e	r.i.	'dihydropyridine ions' m/e	r.i.	'type b ions' m/e	r.i.	'methylethylamine ions' m/e	r.i.
1	α	Me	Me	Me	231	100	216	83	124	55	84	72	59	30
2	β	Me	Me	Me	231	60	216	100	124	85	84	25	59	5
3	α	H	Me	Me	217	44	202	35	110	37	70	100	45	83
4	α	CD_3	Me	Me	234	100	219	78	127	54	87	73	62	31
5	β	Me	Et	Et	259	27	230	100	152	14	98	14	59	1
6	α	Me	Pr	Pr	287	67	244	48	180	12	112	100	59	20
7	β	Me	Pr	Pr	287	27	244	100	180	12	112	12	59	2
8	α	Me	Me	Et	245	70	230	50	138	50	98	100	59	53
9	β	Me	Me	Et	245	50	230	100	138	90	98	35	59	11
10	α	Me	Pr	Me	259	60	216	50	152	18	84	100	59	26
11	β	Me	Et	Me	245	30	216	100	138	17	84	17	59	1
12	—	Me	Me	H	217	47	202	100	110	55	70	20	59	15

RESULTS AND DISCUSSION

The configuration, structure and the relative intensity of the major fragment ions of the compounds investigated are given in Table 1. An example of the mass spectra of a diastereoisomeric pair of benzomorphans is given in Fig. 1.*

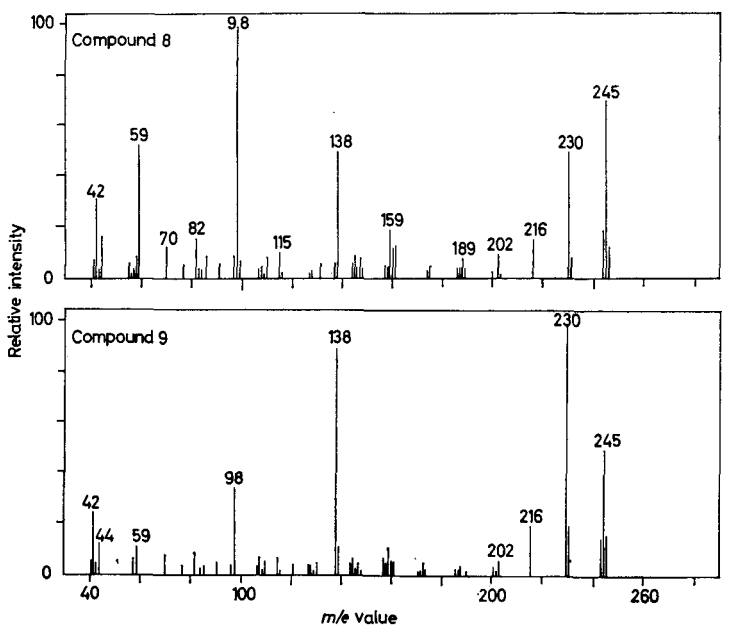


FIG. 1. The mass spectra of α- and β-2′-hydroxy-2,5-dimethyl-9-ethyl-6,7-benzomorphan (Compounds 8 & 9).

* Detailed spectra are obtainable on request from the authors.

All the benzomorphans examined (Table 1) produce, upon electron impact, intense molecular ions (M^+) and also ions that are characterized by the elimination of the C-5 alkyl substituent (M^+-C5 ions). The evidence for the elimination of the C-5 alkyl group from the molecular ion is as follows:—

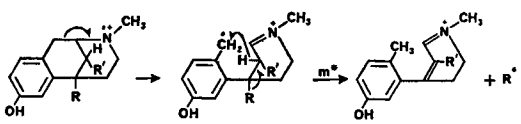
(a) Those compounds with a C-5 ethyl substituent (5,11) have intense M^+-29 ions (i.e. M^+ minus ethyl) in their mass spectrum; similarly, compounds with a C-5 propyl substituent (6,7,10) have intense M^+-43 ions (i.e. M^+ minus propyl) in their mass spectra. The rest of the compounds (Table 1) containing a C-5 methyl substituent have intense M^+-15 (i.e. M^+ minus methyl) ions in their spectra.

(b) When the C-5 and C-9 substituents differ (8,9,10,11,12), ions characteristic of the elimination of the C-5 alkyl substituent rather than the elimination of the C-9 substituent are present in the spectra. For example, 8 and 9 have M^+-15 (M^+ minus methyl) ions rather than M^+-29 (M^+ minus ethyl) ions in their respective spectra whereas 11 has M^+-29, rather than M^+-15 ions in its spectrum.

(c) The loss of the 2-methyl substituent (N–Me) to produce M^+-15 ions, in the spectra of these compounds (Table 1) is not indicated since 3, which has no N–Me substituent, has intense M^+-15 ions in its spectrum; also the spectrum of 4, a compound with an N–CD_3 substituent, does not exhibit M^+-18 ions.

The intensities of M^+-C5 ions are not greater than those of M^+ ions in α-benzomorphans and in general are much less but, in contrast, the M^+-C5 ions are considerably more intense in the β-isomers. Consequently, the relative intensity of these two ions can be used to establish configuration in these diastereoisomers.

Any mechanism proposed for the fragmentation of benzomorphans upon electron impact must account for the differences in the ratio of M^+ to M^+-C5 ions in diastereoisomeric pairs; such a mechanism is given in Scheme I.



M^+ ion intermediate Ia ion $M^+ - C5$ ion

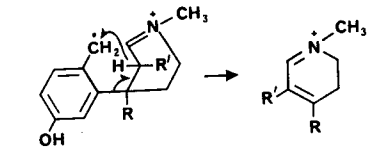
SCHEME I

The configuration of the C-5 and C-9 alkyl substituents are *trans* and *cis* in intermediate Ia derived from α- and β-benzomorphans respectively (Scheme I), and the C-9 hydrogen is closer to the radical on C-8 in Ia derived from β-isomers (the closest distance of approach is 1·8Å and 1·5Å in α- and β- Ia intermediate ions respectively). Consequently, hydrogen abstraction from C-9 is more facile in the β-isomer and results in a greater intensity of the M^+-C5 ions relative to that of the M^+ ions. The one step decomposition of M^+ ions to M^+-C5 ions is confirmed by the presence of appropriate "metastable ions" when the C-5 alkyl substituent is either ethyl or propyl.

Another method, based on mass spectrometry, for assigning the configuration about C-9 in isomeric benzomorphans has been suggested by Mandelbaum & Ginsburg (1965). This method is based on the intensities of "dihydropyridine ions" (see Scheme II) being less intense, and more intense, than the molecular ions in α- and β-benzomorphans respectively. Our results indicate that this method of configurational assignment is only valid when the C-5 alkyl substituent is a methyl group (1,2,3,4,8,9,12). With larger alkyl substituents (5,6,7,10,11), there is a preferential

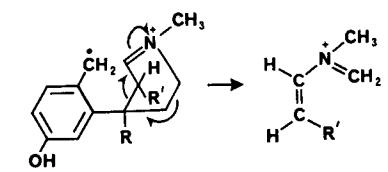
elimination of the C-5 alkyl substituent to produce M^+-C5 ions and as a result the intensity of the "dihydropyridine ions" is similar in both diastereoisomers.

A further method of establishing the configuration of 5,9-disubstituted benzomorphan is by comparing the relative intensity of "type b ions" and the molecular ion (see Scheme III). In all the β-isomers examined, the relative intensity of "type b ions" never exceeded 40% of the base peak (M^+-C5 ions) whereas in the corresponding α-isomers, they are more intense and constitute the base peak in the spectra of some



M^+ (intermediate Ia) ion "dihydropyridine ion"

SCHEME II



M (intermediate Ia) ion "type b ion"

SCHEME III

compounds (3,8 and 10). "Type b ions"* may be produced from the intermediate ion 1a via a *retro* Diels–Alder rearrangement (Scheme III). The low intensity of "type b ions" in β-benzomorphans may result from the preferential fragmentation to M^+-C5 ion of intermediate 1a derived from β-benzomorphans.

N-Methyl morphinans and benzomorphans produce "methylethylamine ions" upon electron impact (Nakata, Tatematsu & others, 1965) and it has been suggested that the relative intensity of these ions (m/e 59) can be used to distinguish between diastereoisomeric benzomorphans (Mandelbaum & Ginsburg, 1965). However, in the present study, the relative intensity of "methylethylamine ions" (m/e 59) derived from pairs of diastereoisomeric benzomorphans was found to be unpredictable and thus they could not be used to assign the configuration of any diastereoisomeric benzomorphan without specific reference to the spectrum of the corresponding diastereoisomer.

The above demonstrates that the configuration of 5,9-dialkyl-substituted-*N*-methyl-6,7-benzomorphans can be established by mass spectrometry. The most useful method is to compare the relative intensities of the M^+ ions with those of the M^+-C5 ions or to those of "type b ions". Also the results show that the nature of the C5 and C9 alkyl substituents of benzomorphans can be readily deduced from their fragmentation patterns.

* Accurate mass determinations demonstrated that these ions had the predicted elemental composition in all the compounds examined.

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