

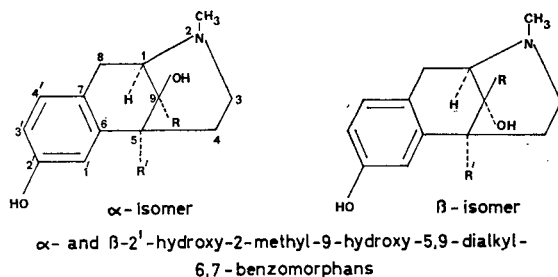
Assignment of configuration to 2'-hydroxy-2-methyl-9-hydroxy-5,9-dialkyl-6,7-benzomorphans using mass spectrometry

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The configuration and structure of α - and β -2'-hydroxy-2-methyl-9-hydroxy-5,9-dialkyl-6,7-benzomorphans have been determined by mass spectrometry.

The benzomorphan analogues of the potent analgesic 14-hydroxy-morphine are α - and β -9-hydroxy-5,9-dialkyl-2'-hydroxy-6,7-benzomorphans. Some of these derivatives are equipotent, as analgesics, with morphine (Saito & May, 1961).



Since the iminoethano system must be *cis*-diaxially fused in 9-hydroxy-5,9-dialkyl-6,7-benzomorphans, only two diastereoisomeric forms, differing in the configuration about carbon atom 9, are possible. These diastereoisomers are designated α and β . The α -isomers exhibit broad maxima (*ca* 3450 cm^{-1}) typical of OH—N bonding, in their infrared spectra. In contrast, the β -isomers exhibit weak maxima characteristic of a free OH and strong absorption bands (*ca* 3622 cm^{-1}) characteristic of OH— π bonding (May & Kugita, 1961). These differences partially establish that the C-5 alkyl and C-9 hydroxyl substituents have a *cis*- and *trans*-configuration with reference to the hydroaromatic ring, in the β - and α -isomers of 9-hydroxy-5,9-dialkyl-6,7-benzomorphans respectively.

Mass spectrometry has been used to assign the configuration to α - and β -5,9-dialkyl-6,7-benzomorphans even when only one isomer of a diastereoisomeric pair was available (Vaughan & Beckett, 1973). This method of establishing the configuration depends on a stereochemically controlled rearrangement of the C-9 hydrogen atom during fragmentation of the molecular ions to give ions that are characterized by the loss of the C-5 alkyl substituent.

We have now investigated the fragmentation of some α - and β -9-hydroxy-5,9-dialkyl-6,7-benzomorphans, which do not contain a C₉ hydrogen atom, in order to further substantiate the fragmentation mechanisms proposed by Vaughan & Beckett (1973) and to establish a method for assigning a structure and configuration to these C-9-disubstituted benzomorphans.

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METHODS

Mass spectra of the 9-hydroxy-5,9-dialkyl-6,7-benzomorphans (Table 1) 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. Deuteriation was carried out by introducing deuterium oxide into the heated inlet system of the mass spectrometer concurrently with the samples. The elemental composition of the ions encountered in the fragmentation schemes outlined in the discussion was confirmed by accurate mass measurements at a resolving power of 20 000.

RESULTS AND DISCUSSION

The configuration, structure and 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 9-hydroxy-5,9-dialkyl-6,7-benzomorphans is given in Fig. 1.

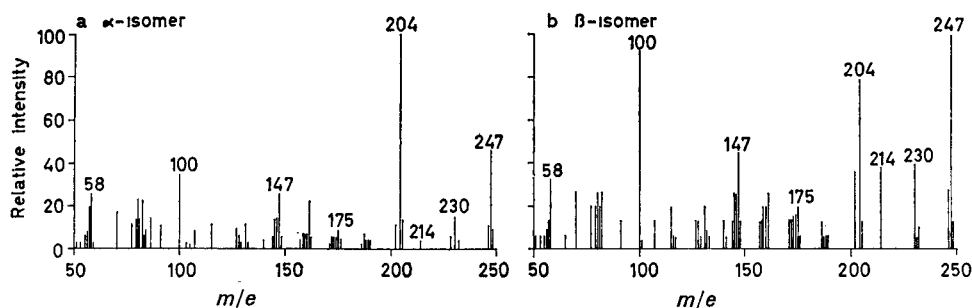


FIG. 1. The mass spectra of α - and β -2'-hydroxy-9-hydroxy-2,5,9-trimethyl-6,7-benzomorphan hydrobromides.

The 9-hydroxybenzomorphans examined by mass spectrometry (Table 1) produced intense molecular ions (M^+ ions) upon electron impact. However, in contrast to 5,9-dialkyl-6,7-benzomorphans no intense ions characterized by the elimination of the C-5 alkyl substituent from the molecular ions ($M^+ - C5$ ions i.e. $M^+ - 15$ in 1 and 2 or $M^+ - 29$ in 3 and 4) are formed. Thus, in the absence of a C-9 hydrogen atom, fragmentation of M^+ ions to $M^+ - C5$ ions is unfavourable and the highly stereospecific elimination of the C-5 alkyl substituent in 5, 9-dialkyl-6,7-benzomorphans (Vaughan & Beckett, 1973) must involve the stereospecific rearrangement of the C-9 hydrogen atom during fragmentation.

All the compounds examined in the present study give intense $M^+ - 43$ ions; ($M^+ - C9CO$ ions) these ions are produced by the elimination of the C-9 alkyl substituent as a methyl carbonyl radical ($\cdot CO-Me$)* from the molecular ion. The $M^+ - C9CO$ ions constitute the base peak in the spectra of α -isomers and are much more intense than the molecular ions. In contrast, in the β -isomers the base peaks are the molecular ions (Table 1). Consequently, the relative intensities of the M^+ and $M^+ - C9CO$ ions can be used to establish the configuration about carbon atom C-9 in these diastereoisomeric benzomorphans.

*No 9-hydroxy-5,9-alkyl-6,7-benzomorphans with a C-9 substituent other than methyl are available.

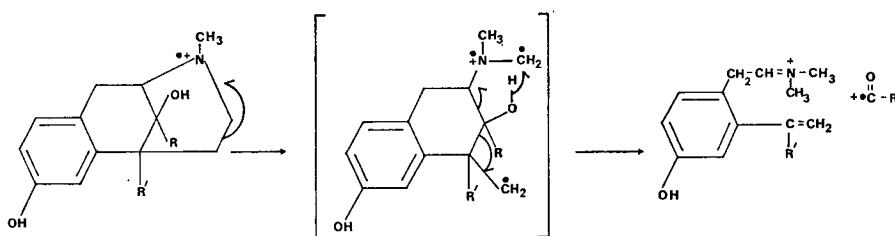
Table 1. The configuration, structure and the relative intensities of the major fragment ions of the 2'-hydroxy-9-hydroxy-5,9-dialkyl-6,7-benzomorphans examined by mass spectrometry.

Compound number	Configuration about C9	Substituents			M ⁺ ions		M ⁺ -C9CO ions		Type b ions	
		N	C5	C9	m/e	r.i.	m/e	r.i.	m/e	r.i.
1	α	Me	Me	Me, OH	247	46	204	100	100	34
2	β	Me	Me	Me, OH	247	100	204	79	100	93
3	α	Me	Et	Me, OH	261	40	218	100	100	37
4	β	Me	Et	Me, OH	261	100	218	50	100	60

Table 2. The intensities of the major fragment ions expressed as a percentage of the ion group after deuterium incorporation into the 2'-hydroxy-9-hydroxy-5,9-dialkyl-6,7-benzomorphans.

Compound number	M ⁺ ions %	M ⁺ +2D ions %	M ⁺ -C9CO ions %	M ⁺ +2D -C9CO ions %	'type b' ions %	'type b+D' ions %
1	30	23	36	25	53	47
2	29.3	24.4	33	20	48	52
3	34	21	37.5	21	55	45
4	27	22.5	32	18.7	51	49

A fragmentation mechanism that accounts for the differences in the ratio of M⁺-C9CO ions to M⁺ ions in α- and β-9-hydroxy-5,9-dialkyl-6,7-benzomorphans upon electron impact is given in Scheme 1.

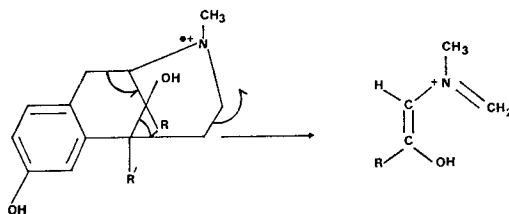


Intermediate 1a

SCHEME 1

In the intermediate 1a ion (Scheme 1) the hydrogen atom of the C-9 hydroxy substituent is closer to the radical on C-3 in those ions derived from the α-isomers (the closest distance of approach is 1.4 and 1.8 Å in the α- and β-1a intermediate ions respectively). Consequently, hydrogen abstraction from the hydroxyl substituent is more facile in intermediate 1a ions derived from the α-isomers and results in the greater intensity of M⁺-C9CO ions relative to that of the M⁺ ions in these isomers. The single step fragmentation of the M⁺ ions to M⁺-C9CO ions was confirmed by the presence of appropriate metastable transition ions.

The involvement of the C-9 hydroxy hydrogen atom in the proposed stereospecific hydrogen rearrangement was confirmed by deuterium exchange. In the α-isomers 90% of the hydrogen rearrangement involves the C-9 hydroxy hydrogen,



'Type b ions'

SCHEME 2

whereas, in the β -isomers some hydrogen rearrangement (27%) not involving this hydrogen atom occurs (see Table 2).*

The 9-hydroxy-5,9-dialkyl-6,7-benzomorphan produced upon electron impact, 'type b ions' (m/e 100) which may be produced by a retro-Diels Alder rearrangement of the molecular ion or by a non-stereospecific fragmentation of the molecular ion (Scheme 2). The structures of 'type b ions' were supported by accurate mass measurements and by deuteration.

In contrast to the 'type b ions' obtained from 5,9-dialkyl-6,7-benzomorphan (Vaughan & Beckett, 1973) the intensities of the 'type b ions' obtained from 9-hydroxy-5,9-dialkyl-6,7-benzomorphan cannot be used to assign the configuration about C-9.

In conclusion, despite the absence of a C-9 hydrogen atom, mass spectrometry can be used to establish the structure of and assign a configuration to 9-hydroxy-5,9-dialkyl-6,7-benzomorphan.

Acknowledgement

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* The percentage of C-9 hydroxy hydrogen rearrangement was calculated as follows. After deuterium exchange each peak in the molecular ion group (M^+ group) and the $M^+ - C_9CO$ ion group was expressed as a percentage of the group intensity (see Table 2). The difference in the ratio of M^+ to $M^+ + 2D$ from the ratio of $M^+ + 2D - C_9CO$ and expressed as a percentage of the former gives the percentage of hydrogen rearrangement not involving C-9 hydrogen atom.