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Short Communication

Electron Impact Mass Spectrometry of Deuteriated Atenolol

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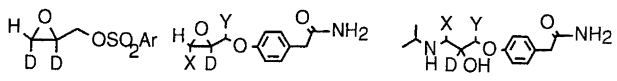
Atenolol, 1-(4-carbamoylmethylphenoxy)-3-isopropylamino-2-propanol, **1**, is a β-receptor blocking agent, that has found use in the treatment of hypertension, angina pectoris and arhythmias.[1] The drug is now being used as the racemic mixture. However, it has been shown that the *S*-form is more potent than the corresponding *R*-enantiomer.[2] Based on these discoveries and the increasing interest in chiral drugs, we have undertaken a study of the synthesis of β-adrenergic blocking agents of which atenolol, **1**, was of particular interest. Preparation of optically active atenolol has previously been reported in a number of patents.[3] The method we adopted was based on elaboration of chiral glycidol derivatives in analogy to work described by other groups for similar types of system.[4] Unfortunately, nucleophilic additions to chiral glycidol derivatives, e.g., the tosylate, is normally accompanied by the Payne rearrangement,[5] causing partial racemization of the products. For the general value of the synthetic scheme used by us, it was essential to eliminate this side reaction.

The extent of the Payne rearrangement can be determined by means of a number of techniques such as NMR spectroscopy, chiral HPLC or determination of the optical rotations. The accuracy of these methods vary and may also require enantiomerically pure reference materials. In general, mass spectrometric methods are more precise. Therefore we decided to study the degree of the Payne rearrangenemt for a series of racemic, deuterium-labelled glycidyl arylsulfonates, **2**-d_2, prepared from allyl alcohol-2,3-d_2.[6] Addition of 4-hydroxyphenylacetamide to **2**-d_2 yielded **3**-2,3-d_2 and, by the accompanying Payne rearrangement, **3**-1,2-d_2. Subsequent reaction with isopropylamine resulted in formation of atenolol-2,3-d_2, **1**-2,3-d_2 and the Payne product **1**-1,2-d_2.

Synthetic as well as NMR and MS evidence gave no indication of deuterium in the 1-position of allyl alcohol-2,3-d_2 or **2**-d_2. To establish possible deuterium scrambling during the mass spectrometry experiments, it was important to understand the fragmentation mechanisms. We here report the fragmentation of **1**-d_2 and **3**-d_2, which were the products formed by phenolate addition to **2**-d_2. The observed peaks in the mass spectra of compounds **1**, **1**-d_2, **3** and **3**-d_2 are shown in Table 1. The degree of Payne rearrangement can be determined by measuring the distribution of isotopes in fragments that contain only C-1 or C-3. It was necessary to establish the fragmentation pattern, to ensure that D-scrambling did not play any role in the formation of peaks important for the measurements. The fragmentation mechanisms could be deduced by comparison of the data for the compounds and their deuteriated analogues. The identities of important peaks were confirmed by exact mass measurements, Table 2.



2-d_2 **3**-1,2-d_2: X = H, Y = D **1**-1,2-d_2: X = H, Y = D

3-2,3-d_2: X = D, Y = H **1**-2,3-d_2: X = D, Y = H

Fig. 1.

Experimental

Mass spectra were measured with an AEI-MS-902 double-focusing mass spectrometer operating at an ionization voltage of 70 eV using the direct probe technique with a source temperature of 170°C. The relative intensities given are rounded figures and low values, usually less than 2%, have been omitted except for fragments of special interest in this study. Likewise, peaks below *m/z* 50 have been excluded. Exact mass measurements were performed by peak matching using perfluorokerosene as the standard to provide the reference masses.

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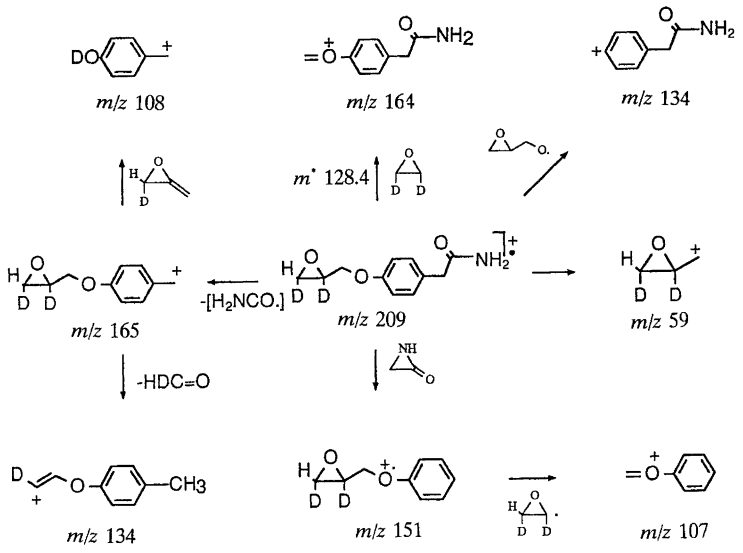
Table 1. Mass spectra of compounds **1**, **1**-d_2, **3** and **3**-d_2.

m/z	**1**	**1**-d_2	**3**	**3**-d_2
268		0.3		
266	0.2			
253		2		
251	2			
224		2		
223	1	7		
222	6	1		
210				21
209				38
208			7	9
207			48	
166				38
165			1	68
164			13	18
163			100	
134			4	8
133			4	2
108		1	10	38
107	3	7	81	100
79			3	4
78			5	10
77			9	11
74		22		
73	5	100		
72	100	18		
59		2		22
58	2	4		
57	3	3	36	

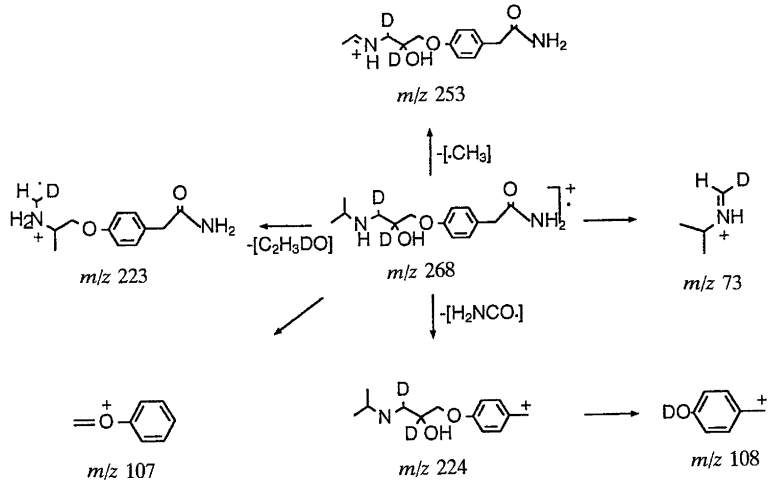
Table 2. Exact masses determined for compounds **1**, **1**-d_2, **3** and **3**-d_2

Compound	Fragment *m/z*	Composition	Exact mass Calcd.	Found
1	251	$C_{13}H_{19}N_2O_3$	251.1396	251.1397
	222	$C_{12}H_{18}N_2O_2$	222.1368	222.1373
	107	C_7H_7O	107.0497	107.0500
	72	$C_4H_{10}N$	72.0813	72.0814
1-d_2	253	$C_{13}H_{17}D_2N_2O_3$	253.1521	253.1524
	223	$C_{12}H_{17}DN_2O_2$	223.1431	223.1428
	108	C_7H_6DO	108.0560	108.0559
	107	C_7H_7O	107.0497	107.0500
	73	C_4H_9DN	73.0976	73.0875
3	207	$C_{11}H_{13}NO_3$	207.0895	207.0893
	164	$C_9H_{10}NO_2$	164.0712	164.0710
	163	$C_{10}H_{11}O_2$	163.0759	163.0757
	134	C_8H_8NO	134.0606	134.0610
	133	C_9H_9O	133.0653	133.0655
	107	C_7H_7O	107.0497	107.0500
	57	C_3H_5O	57.0340	57.0341
3-d_2	209	$C_{11}H_{11}D_2NO_3$	209.1021	209.1023
	165	$C_{10}H_9D_2O_2$	165.0885	165.0883
	164	$C_9H_{10}NO_2$	164.0712	164.0710
	134	C_9H_8DO	134.0716	134.0716
	134	C_8H_8NO	134.0606	134.0610
	108	C_7H_6DO	108.0560	108.0556
	107	C_7H_7O	107.0497	107.0500
	59	$C_3H_3D_2O$	59.0466	59.0466

Fragmentation of **3**-d_2. In Scheme 1 is shown the proposed fragmentations of **3**-d_2. The molecular ion *m/z* 209 appeared to fragment by several routes. Thus, fissions of the ether bonds resulted in formation of fragments *m/z* 59 and 134 respectively. α-Cleavage of the M^+ ether moiety yielded fragment *m/z* 164 as well as *m/z* 107 after an initial fission of the amide side-chain. The *m/z* 209 to 164 transformation was confirmed by the presence of *m** 128.4. The *m/z* 165 was a prominent peak for **1**-d_2, caused by loss of H_2NCO from the M^+ ion. A metastable peak was observed at 129.9 corresponding to this transformation (209 to 165). The *m/z* 165 peak appeared to undergo further fissions to *m/z* 108 and 134. All fragments but *m/z* 164 and 107 were shown to contain C-1 as well as the C-3 positions, and were therefore of no use for distinguishing between the purely nucleophilic displacement and the Payne product. Fragments *m/z* 164 and 107 contained only the C-1 position. The rearranged product



Scheme 1.



Scheme 2.

would contain a D-atom at the C-1 position, resulting in an *m/z* 165 peak. However, *m/z* 165 was also produced by an alternative mechanism. The same was the case for the 107 and 108 peaks. These results indicate that the addition product **3**-d_2 is unable to serve as a probe for monitoring the degree of the Payne rearrangement. We therefore decided to study the properties of the end product, atenolol, **1** and **1**-d_2.

Fragmentation of **1**-d_2. Compound **1**-d_2 exhibited fewer fragments. Simple α-fissions of the amine function produced the *m/z* 253 ion. A combination of cleavage of the acetamide side chain and α-fission of the ether gave *m/z* 107. The formation of the 223 fraction was not straightforward, but proceeded via a series of rearrangements and fragmentations. The proposed structure is shown in Scheme 2. None of the peaks described so far satisfies our objective. However, the molecular ion also undergoes a simple, clean α-cleavage of the amino function. Fission of the 2,3-bond yielded the *m/z* 73 peak with no D-scrambling. This peak was also the base peak. The Payne product, on the other hand produces an *m/z* 72 peak. Thus, the relative intensities of the *m/z* 72 and 73 peaks respectively, reflect the degree of Payne rearrangement during the nucleophilic addition process. We also note that C–D bonds were not cleaved during the course of the *m/z* 73 (and 72) formation, and we therefore need not take into account possible primary kinetic isotope effects.

In conclusion, this investigation showed that the degree of Payne rearrangement cannot be determined by mass spectrometric analysis of the epoxide, **3**-d_2. Fragmentation of atenolol-d_2, **1**-d_2, however, produced *m/z* 73 exclusively owing to the direct nucleophilic displacement of the leaving group in the glycidyl derivative, while *m/z* 72 reflected exclusively the formation of the Payne product.

References

1. Frishman, W. *New Engl. J. Med.* **306** (1982) 1456
2. Morris, T. M. and Kaumann, A. J. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **327** (1984) 176
3. *Jap. Pat.* 02225970; *Jap. Pat.* 0229569; *Eur. Pat.* 256586: *Eur. Pat.* 0135162; *US Pat.* 3686320
4. Klunder, J. M., Onami, T. and Sharpless, K. B. *J. Org. Chem.* **54** (1989) 1295
5. Payne, G. B. *J. Org. Chem.* **27** (1962) 3819
6. Carlsen, P. H. J. and Aase, K. *Unpublished results*

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