Mass Spectrometry of *N*-Benzoyl-2-hydroxyalkylamines. Role of the Hydroxylic Hydrogen in the Fragmentation Pattern

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An interesting rearrangement has been observed in the mass spectra of a series of *N*-benzoyl-2-hydroxyalkylamines. The hydrogen atom of the hydroxyl group is transferred to the *N*-benzoyl portion of the molecular ion and the bond between positions 1 and 2 in the *N*-alkyl group is cleaved. A rearrangement ion, observed at *m/e* 135, is formed along with a neutral aldehyde or ketone. When the hydroxylic hydrogen is replaced by a trimethylsilyl substituent, the latter group is transferred with comparable efficiency. Differences in the relative importance of this rearrangement in the mass spectra of a series of related compounds with decreasing substitution at position 2, have been explained by differences in the stabilities of the neutral molecules formed along with *m/e* 135 and by the occurrence of a double hydrogen rearrangement which competes if hydrogen atoms are present in a relationship *gamma* and *delta* to the carbonyl group.

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Un réarrangement intéressant a été observé dans les spectres de masse d'une série de *N*-benzoyl hydroxy-2-alkylamines. Dans ce réarrangement, l'atome d'hydrogène du groupe hydroxyle est transposé à la partie *N*-benzoyle de l'ion moléculaire et le lien entre les positions 1 et 2 dans le groupe *N*-alkyle est scindé. Ceci donne lieu à la formation d'un ion, observé à *m/e* 135, ainsi qu'à un fragment neutre aldéhyde ou cétone. Lorsque l'hydrogène hydroxylique est remplacé par un groupe triméthylsilyle, ce dernier est aussi transposé avec une facilité comparable. Les différences observées dans l'importance relative de ce réarrangement dans les spectres de masse d'une série de composés reliés ont été expliquées par des différences dans les stabilités relatives des molécules neutres produites à côté de l'ion *m/e* 135 ainsi que par l'apparition d'un réarrangement à deux hydrogènes qui entre en compétition avec le processus décrit plus haut, lorsque la molécule possède des hydrogènes en position *gamma* et *delta* par rapport au carbonyle.

Introduction

Much attention has been focused on intramolecular hydrogen rearrangements observed upon electron impact. A recent review has covered those undergone by aliphatic hydrocarbons and aromatic compounds (1), whereas another has treated exclusively the so-called McLafferty rearrangement (2). The fact that the latter review contains 651 references attests to the importance of this reaction in mass spectrometry. Similarities between the McLafferty rearrangement, produced upon electron impact, and the Norrish Type II photochemical reaction also have been observed and discussed (3–6).

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The McLafferty rearrangement is defined as the transfer of a hydrogen in a relationship *gamma* to a double-bonded atom through a six-membered transition state, with *beta* bond cleavage (2). For example, an abundant ion is found in the mass spectrum of *N*-*p*-tolyl-3-phenyl-3-oxopropionamide, corresponding to the McLafferty rearrangement, Eq. 1 (4). At 15 eV, the molecular ion is the base peak in the

[1] $\left[Ph{-}\overset{O}{\overset{\|}{C}}{-}\overset{\alpha}{CH_2}{-}\overset{\beta}{CO}{-}\overset{\gamma}{\overset{|}{N}}{-}\overset{H}{}C_6H_4\text{-}p\text{-}CH_3 \right]^{+\cdot} \xrightarrow{15\ eV}$

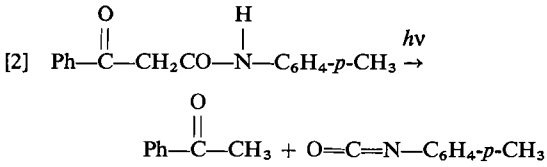
m/e 253 (100)

$$Ph{-}\overset{{}^{+}O{-}H}{\overset{\|}{C}}{-}CH_2\cdot + O{=}C{=}N{-}C_6H_4\text{-}p\text{-}CH_3$$

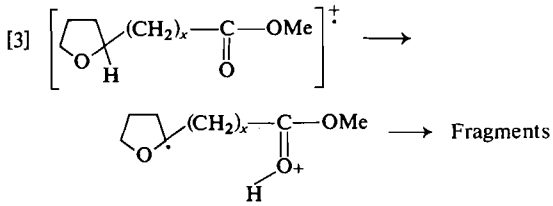
m/e 120 (50)

mass spectrum, and the relative intensity of the rearrangement ion at *m/e* 120 is 50%. Upon

photolysis, the same compound decomposes to acetophenone and *p*-tolylisocyanate, via the Norrish Type II reaction, Eq. 2.

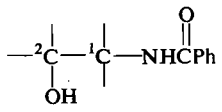


The McLafferty rearrangement has been observed in all classes of carbonyl compounds and also in noncarbonyl systems, such as unsaturated systems, sulfur-containing systems, nitrogen-containing systems, etc. If a hydrogen *gamma* to the double-bonded atom is not available or if the normal process is less favorable for structural or energetic reasons, an alternative or competing process may be preferred. For example, in the mass spectra of some esters containing the tetrahydrofuranyl system, a hydrogen remote from the carbonyl group is abstracted, Eq. 3 (7).



x = 2, 4, 7, and 13

In conjunction with a study of the photochemistry of *N*-substituted unsaturated amides, we have observed a rearrangement in the mass spectra of a series of *N*-benzoyl-2-hydroxyalkylamines of general structure **1**. During the course of the rearrangement, the hydrogen atom of the hydroxyl group is transferred to the *N*-benzoyl



1

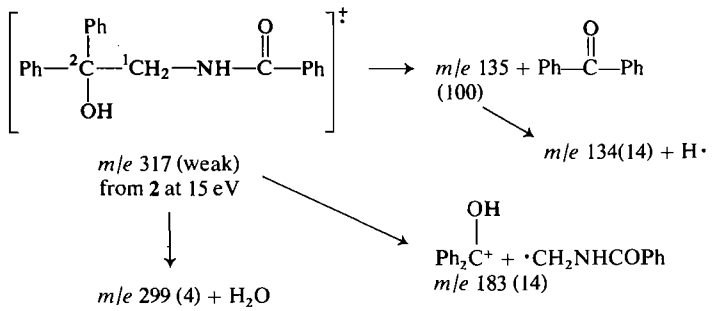
portion of the molecular ion and the single bond between carbons 1 and 2 cleaves.

Mass spectra of amides have been previously reported (8–10). If a γ-hydrogen atom is present in the acyl group of an amide, the McLafferty rearrangement predominates in its mass spectrum. McLafferty rearrangements can also occur between the carbonyl oxygen and a hydrogen in the *N*-alkyl group of the amide. Furthermore, the cleavage of the bond between positions 1 and 2 in the *N*-alkyl group is characteristic of the fragmentation of secondary amides.

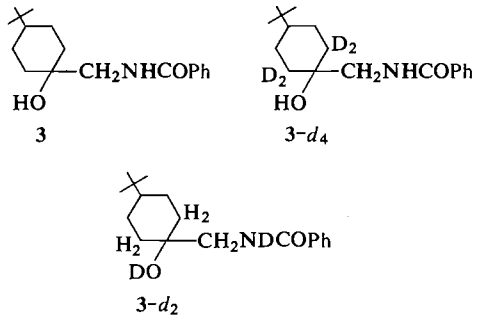
In this article, we will present the mass spectra of a series of compounds of general structure **1** in order to define the rearrangement. Then, we will show the effects of substitution in the 2-position of the *N*-alkyl group and compare the hydrogen-donating aptitudes of various groups. Mass-spectral data are presented in Schemes; however, structures given in the Schemes for ions are speculative. Relative intensities are also given in the Schemes, in parentheses.

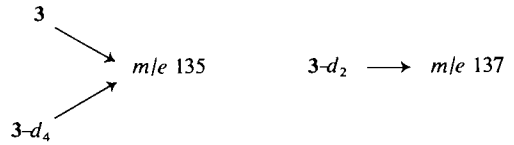
Results

In the 15 eV mass spectrum of *N*-benzoyl-2-hydroxy-2,2-diphenylethylamine (**2**), the molecular ion is weak and the base peak is found at *m/e* 135, Scheme 1. Minor peaks are present corresponding to fragmentations expected from alcohols: cleavage adjacent to the hydroxyl group (*m/e* 183) and elimination of H_2O (*m/e* 299). In the present case, we will focus our



SCHEME 1





attention on the formation of the ion found at *m/e* 135.

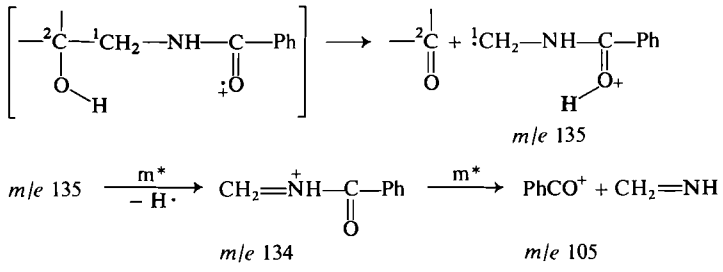
In the low-voltage mass spectrum of *N*-benzoyl-1-aminomethyl-4-*tert*-butylcyclohexanol (**3**), essentially the only peak present is the one at *m/e* 135. At 70 eV, there are weak peaks corresponding to the molecular ion and loss of $CH_3\cdot$, H_2O, and $CH_3\cdot + H_2O$, and intense peaks at *m/e* 135, 134 ($135 \xrightarrow{m^*} 134 + H\cdot$), 105 (PhCO), and 77 ($C_6H_5$).

Two deuterated analogs of **3**, **3**-d_4, and **3**-d_2, were also studied and provide some insight into the formation of this ion found at *m/e* 135. In the 15 eV mass spectrum of **3**-d_4, the rearrangement ion remains exclusively at *m/e* 135; however, in the 15 eV mass spectrum of **3**-d_2, the ion is found at *m/e* 137:

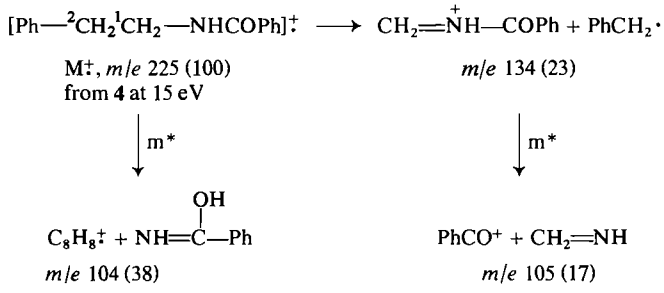
After correcting for the percentage of monodeuteration (there was ~16.5% d_1), the ratio of *m/e* 136 to *m/e* 137 was found to be 6:94 in the mass spectrum of **3**-d_2. Thus, there is no less than 94% transfer of deuterium from —OD and no more than 6% of transfer of hydrogen from C—H.

In terms of mass spectra taken at various voltages, deuterium labeling, exact-mass measurements, and metastable peaks, the rearrangement and subsequent fragmentations are consistent with the pathway presented in Scheme 2. The hydroxyl hydrogen is transferred to the *N*-benzoyl group and the bond between carbons 1 and 2 in the *N*-alkyl group cleaves, resulting in the elimination of a stable molecule containing a carbonyl group. We have placed the transferred hydrogen on the carbonyl group of the amide in Scheme 2, in analogy with the McLafferty rearrangement, although we have no information on the exact structures of the ions.

In order to have a point of reference, we have compared the mass spectra of **2** and **3** with the fragmentations observed in the 15 eV mass



SCHEME 2

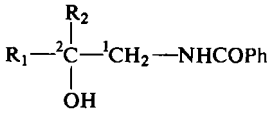


SCHEME 3[2]

[2]The structures and formulas are in agreement with the results of exact-mass measurements.

spectrum of *N*-benzoyl-2-phenylethylamine (**4**), Scheme 3. Compound **4** lacks a hydrogen in the *N*-alkyl group which could be involved in a transfer analogous to the one shown in Scheme 2. However, it does contain hydrogens *gamma* to the carbonyl, making the McLafferty rearrangement possible in the *N*-2-phenylethyl group. Two major fragmentation pathways are observed: (*1*) the cleavage of the benzylic bond, yielding the ion at *m/e* 134, and (*2*) a McLafferty rearrangement, with the charge remaining on the C_8H_8 portion. These are precisely the fragmentations expected from secondary amides (8–10).

In order to examine the effect of substitution on the carbon atom bearing the hydroxyl group in **1**, we have studied a series of *N*-benzoyl-2-hydroxyalkylamines, **5–7**. Compound **5** is similar to compounds **2** and **3** in the sense



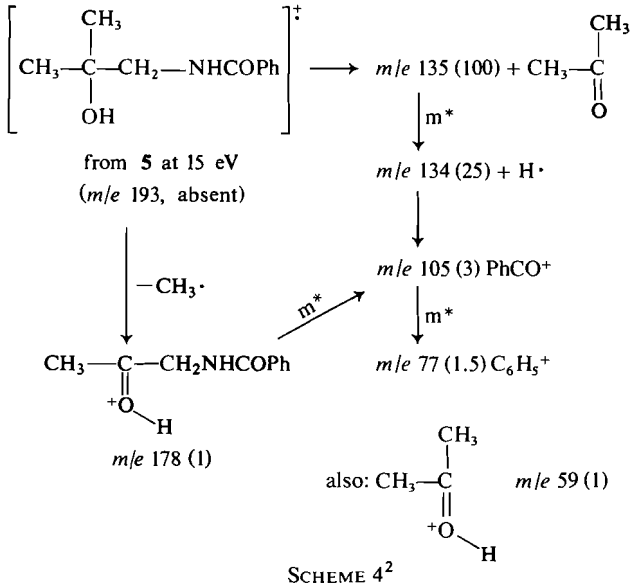
	R_1	R_2
5	CH_3	CH_3
6	CH_3	H
7	H	H

that it contains no hydrogen atoms *gamma* to the carbonyl group, thus the McLafferty rearrangement is blocked. However, compounds **6** and **7** do have hydrogen atoms *gamma* to the carbonyl group, as does **4**, as well as the hydrogen atom on the hydroxyl group, making possible a competition between the two rearrangements.

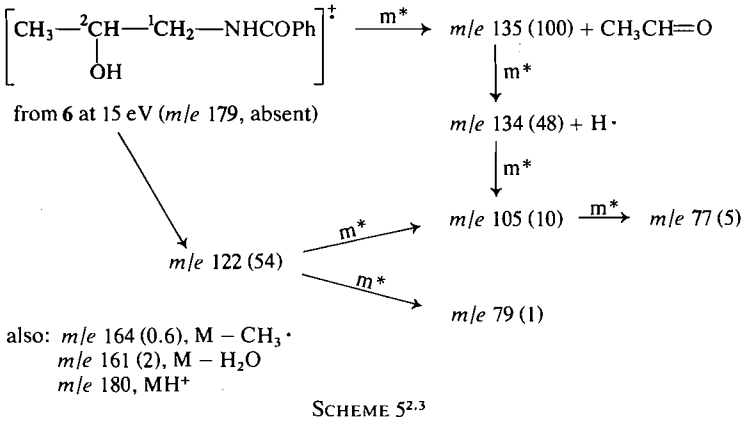
The 70 eV mass spectra of **5–7** are given in Table 1. Even though no molecular ions are observed in the spectra of **5** and **6**, peaks are found for MH^+ and $MH^+ - H_2O$ at high sample pressures, from a small amount of chemical ionization. Peaks are present for a fragmentation giving an ion corresponding to $M^{\cdot+} - CH_3\cdot$. All three compounds eliminate H_2O for which a metastable peak is present in the mass spectrum of **7**. From the consistent behavior of these compounds in different mass spectrometers at different ion-source temperatures, we feel confident that the elimination of H_2O from **5** and **6**, also, is induced by electron impact rather than by thermal excitation.

In the 15 eV mass spectrum of **5**, Scheme 4 (70 eV mass spectrum is given in Table 1), there is only one prominent fragmentation pathway, the elimination of acetone. This is essentially the same result observed in the mass spectra of compounds **2** and **3**. No peak is found for the molecular ion; however, peaks are present for MH^+, arising from a small amount of chemical ionization, and for the loss of a methyl group.

In the mass spectra of **6** (15 eV, Scheme 5; 70 eV, Table 1), there are indeed two competing hydrogen rearrangements. However, the McLafferty rearrangement, Eq. 4, is not observed.

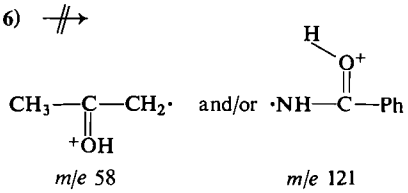


SCHEME 4[2]



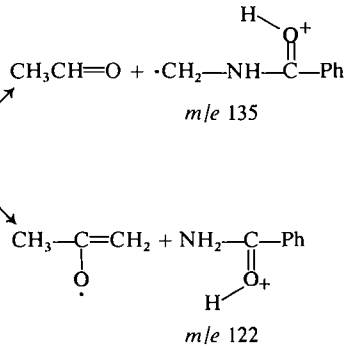
SCHEME 5[2,3]

[4] $M^{\ddagger}$(from **6**) ⇢



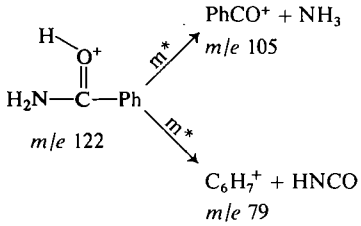
The rearrangements observed are those leading to the fragment at *m/e* 135, already observed in the spectra of **2**, **3**, and **5**, and a double hydrogen rearrangement leading to the ion found at *m/e* 122, Eq. 5. The double hydrogen transfer is a reaction typical of esters (11).

[5] $M^{\ddagger}$ (from **6**)



The presence of metastable peaks indicates that there are at least two further fragmentations of the ion found at *m/e* 122, Eq. 6. It is possible that the structure of the ion at *m/e* 122 is better represented by protonation on nitrogen, or by a mixture of protonated, tautomeric forms.[4] We have obtained the chemical ionization (isobutane) mass spectrum of benzamide. The MH^+ ion at *m/e* 122 is the base peak. The only important fragmentation is the elimination of NH_3

[6]



giving *m/e* 105, along with a metastable peak for the process.

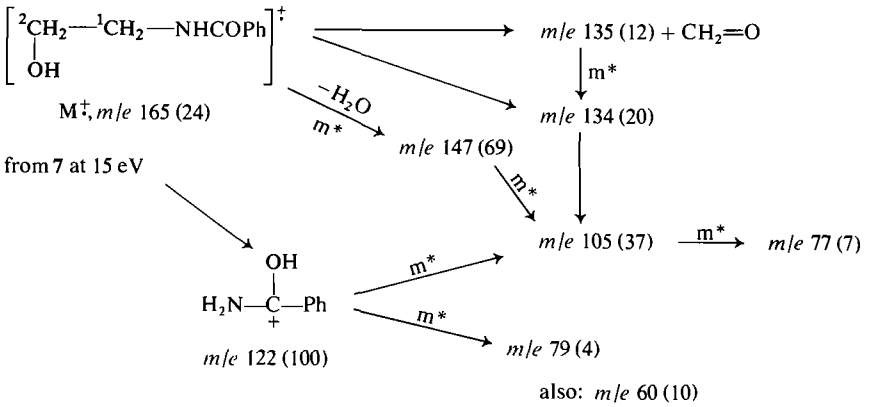
In the mass spectrum of **7** (15 eV, Scheme 6; 70 eV, Table 1), the situation has shifted largely in favor of the double hydrogen transfer: the base peak is the ion at *m/e* 122. The molecular ion is relatively abundant, as is the loss of H_2O. Thus, as substitution decreases on the 2-carbon atom (in **1**), the relative importance of cleavage of the bond between positions 1 and 2 decreases and the intensity of the molecular ion increases. Also, the double hydrogen transfer becomes more abundant with increasing hydrogen atom availability on the 2-carbon.

In contrast to what is observed in the spectra of previous compounds, *m/e* 134 is more intense than *m/e* 135, in the spectrum of **7**. This can be rationalized by a competing formation of *m/e* 134 by cleavage of the 1,2-bond, as was observed in the mass spectrum of **4**, Scheme 3, and as is observed in the mass spectra of secondary amides in general (8–10).

It now becomes important to look more closely at the competition between hydrogen

[3]Also see Eqs. 5 and 6.

[4]The u.v. spectra of benzamide in concentrated sulfuric acid show a tautomeric change from the *N*-protonated form in 60% sulfuric acid to the *O*-protonated form in 100% sulfuric acid (12).



SCHEME 6[2,5]

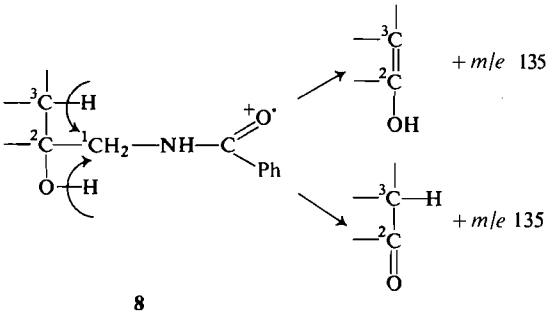
TABLE 1. The 70 eV mass spectra of compounds **5**–**7**[a]

m/e	**5**	**6**	**7**
178	3		
175	0.5		
165			4
164		1	
148			2
147			13
136	8	5	
135	86	53	4
134	100	59	10
123		2	1
122		22	18
117	2	2	1
116	4	1	
106	9	9	7
105	90	100	100
79		3	
78	6	4	7
77	55	44	76
59	16		
51	20	13	34
45		4	
43	12		

[a]Relative intensities from *m/e* 200–40 are given in percentage of the most intense peak. Ions less abundant than 1% are not included except for M^+, $(M - CH_3)^+$, and $(M - H_2O)^+$.

transfers from OH and from CH, giving ketonic *vs.* enolic neutral products (see structure **8**). We have already shown (*vide supra*) that the ion at *m/e* 135 in the mass spectrum of **3** shifts overwhelmingly to *m/e* 137 in the mass spectrum of **3**-d_2. This preference is all the more impressive in light of the statistical factor of 4 in favor of C—H transfer over O—D transfer, and the

[5]The abundance of *m/e* 135 has been corrected for the isotopic contribution of *m/e* 134.



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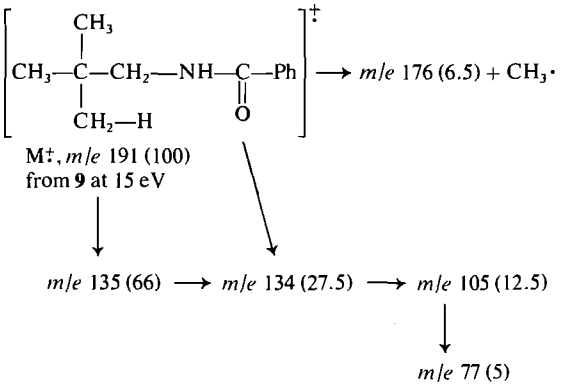
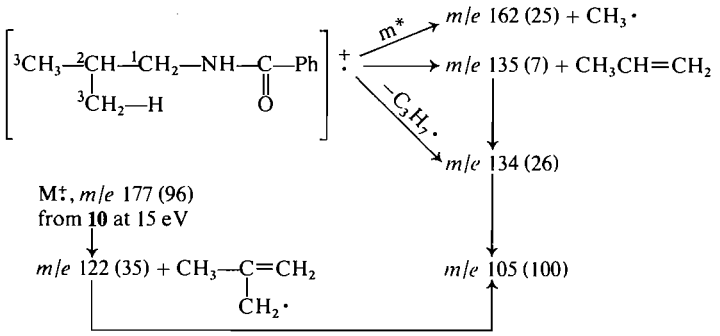
isotope effect which would run in favor of transfer of H over D.

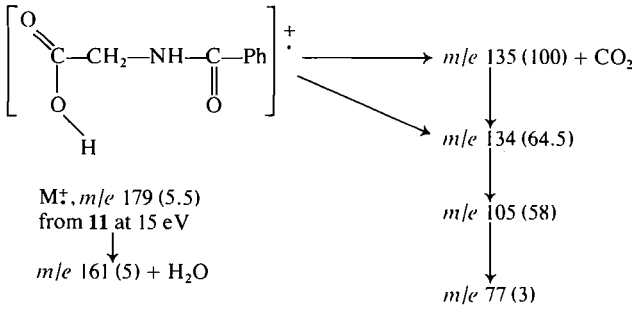
We were also interested in observing the course which fragmentation would take if there were no 2-hydroxyl group and if the McLafferty and double hydrogen rearrangements were rendered impossible. To that effect, the *N*-benzoyl derivative (**9**) of 2,2-dimethylpropylamine was prepared, and its mass spectrum (Scheme 7) was compared with that of 2-



SCHEME 7[2,5]



SCHEME 8[2,5]

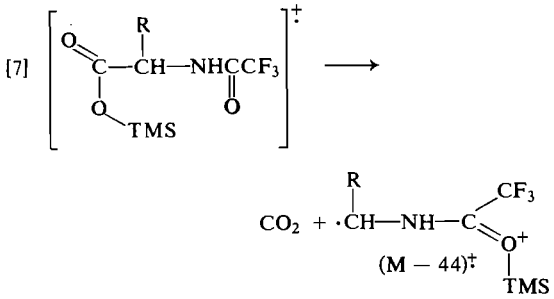


SCHEME 9[2]

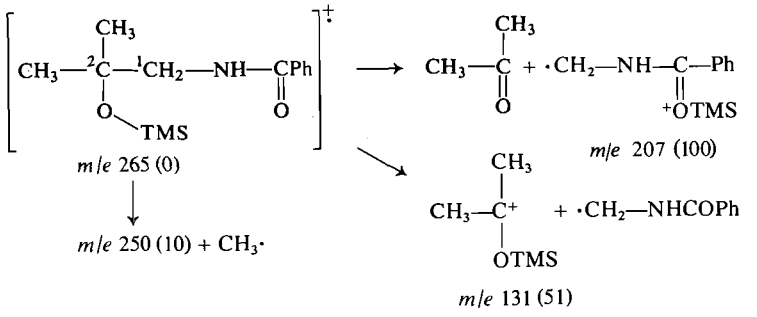
hydroxy-2-methylpropylamine (**5**, Scheme 4). The fragmentations are essentially the same. However, the molecular ion from **5** is absent, whereas the molecular ion from **9** is the base peak; the rearrangement ion found at *m/e* 135 is the base peak in the mass spectrum of **5**. The presence of the rearrangement ion at *m/e* 135 in the mass spectrum of **9** shows that hydrogen is transferred from carbon if the other rearrangements are blocked by lack of appropriate hydrogens to transfer. However, transfer of hydrogen from a methyl group on the 2-position is obviously much less favorable than transfer of hydrogen from a hydroxyl group on the 2-position.

Likewise, **6** was compared with its counterpart having a methyl group in place of hydroxyl. In the 15 eV mass spectrum (Scheme 8) of the *N*-benzoyl derivative of isobutylamine (**10**), the double hydrogen rearrangement, giving *m/e* 122, is more prominent than the formation of *m/e* 135. Once again, hydrogen transfer from OH is shown to be more favorable than transfer from CH_3.

In order to test the generality of the observed rearrangement of hydroxylic hydrogen atoms, we have taken the mass spectrum of the *N*-benzoyl derivative of glycine (**11**; 15 eV spectrum, Scheme 9). Now there is only one abundant fragmentation path, the formation of *m/e* 135. In the mass spectrum of the ethyl ester of **11**, on the other hand, the formation of ion 135 is blocked. The base peak corresponds to the molecular ion, and there are two fragmentation pathways: (*1*) loss of EtOH, and (*2*) loss of EtO· followed by CO, or of EtOCO·, giving *m/e* 134.



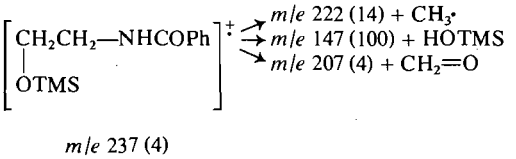
[8]



The result obtained from the ethyl ester shows that, even though the hydrogen transfer is highly favored, transfer of an alkyl group does not occur. However, trimethylsilyl (TMS) groups have been found to be transferred in the mass spectra of *N*-trifluoroacetyl α-amino acid trimethylsilyl esters, Eq. 7 (13). For this reason, we prepared the TMS esters of compounds **5** and **7**. The base peak in the mass spectrum of the *O*-TMS derivative of **5** is found at *m/e* 207, Eq. 8. The only other abundant ion present in the 15 eV spectrum of this derivative is found at *m/e* 131, due to cleavage of the bond between positions 1 and 2.

In contrast, the 15 eV mass spectrum of the *O*-TMS derivative of **7** is dominated by the elimination of HOTMS, Eq. 9, and the intensity of *m/e* 207 is only 4%. These are fragmentations characteristic of the mass spectra of *O*-TMS derivatives of alcohols (14).

[9]

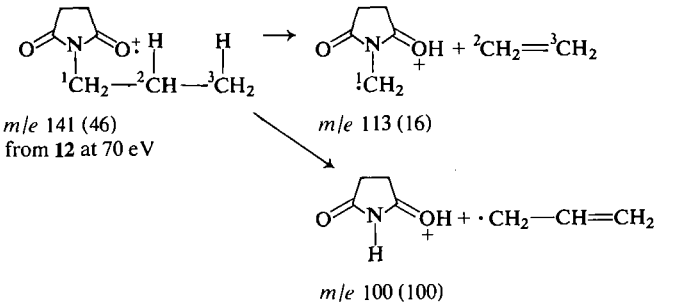


m/e 237 (4)

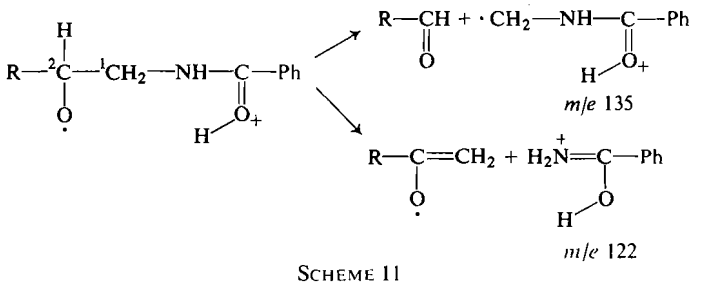
Discussion

It is interesting to compare our results with those obtained from *N*-*n*-propylsuccinimide (**12**) (15). Even though the McLafferty rearrangement is not important in the mass spectrum of **12**, a competition between single hydrogen transfer and double hydrogen transfer occurs, Scheme 10. The authors were not willing to decide upon a most-favored structure for the ion at *m/e* 113; however, deuterium labeling showed that the two hydrogens on the 1-carbon were retained and that 90% of the hydrogen transferred originated from the 3-carbon atom of the alkyl chain. The base peak occurs at *m/e* 100; in this case the source of the transferred hydrogens was principally the 2- and 3-carbon atoms of the *N*-alkyl chain.

In the case of the compounds of general structure **1**, the one hydrogen transfer is, for all practical purposes, the only fragmentation if there are no hydrogens on the 2-carbon atom of the *N*-alkyl chain. Hydrogen from a hydroxyl group on C-2 is much more readily transferred than hydrogen from a methyl group on C-2. If hydrogen is present on the 2-position, two transfers compete, just as they do in the mass spectrum of **12** (compare Schemes 10 and 11).



SCHEME 10



SCHEME 11

In fact, we can use the deuterium-labeling studies (Scheme 10) reported earlier (15) to support our suggestion in Scheme 11 that the peak at *m/e* 122 forms via transfer of hydrogens from the 2-carbon atom and from the hydroxyl group. We have shown the rearrangements in two steps rather than concerted. This is in agreement with evidence, recently reviewed (2), that indicates that the McLafferty rearrangement proceeds via a stepwise pathway: initial hydrogen transfer followed by carbon–carbon bond cleavage.

It is interesting to note that the base peak in the mass spectrum of *N*-*n*-propyl-2-pyrrolidone is *m/e* 98, resulting from α-cleavage of the alkyl chain (15). The abundance of the ion due to double hydrogen rearrangement (*m/e* 86) is only 7% and that due to single hydrogen rearrangement (*m/e* 99, similar to formation of *m/e* 113 in Scheme 10) is 6.5%. The authors speculated that the difference in the modes of fragmentation of the molecular ions of the *N*-alkylsuccinimides and the *N*-alkyl-2-pyrrolidones studied might be attributed to the larger number of atoms involved in resonance forms of the molecular ions in the former compounds. In regard to our compounds, the ions formed from these two rearrangements are always *m/e* 122 and *m/e* 135, so we must attribute differences in fragmentation to differences in the *N*-alkyl groups and the neutral species formed.

It has been generally observed that a large proportion of skeletal rearrangements induced by electron impact are accompanied by expulsion of neutral entities which have favorably negative heats of formation (16). This is also true of the neutral molecules ejected from the *N*-benzoyl-2-hydroxyalkylamines (**5–7**) and from the *N*-benzoyl derivative (**11**) of glycine upon formation of *m/e* 135, as shown in Table 2. The percentage of the total ion current carried by *m/e* 135 is included in Table 2 for comparison.

TABLE 2. Heats of formation (17) of neutral molecules accompanying the formation of *m/e* 135

From compound	Neutral molecule	(g kcal/mol at 25 °C) ΔH_f	*m/e* 135[a]
5	$(CH_3)_2C{=}O$	−51.8	76
6	$CH_3CH{=}O$	−39.8	45
7	$CH_2{=}O$	−27.7	4
9	$(CH_3)_2C{=}CH_2$	−3.3	30
10	$CH_3CH{=}CH_2$	+4.9	2.5
11	CO_2	−94.1	42

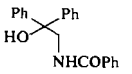
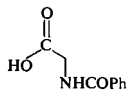
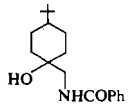
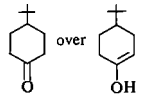
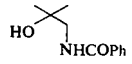
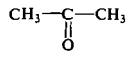
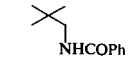
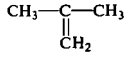
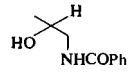
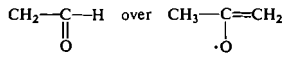
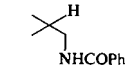
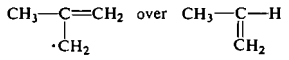
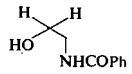
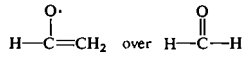
[a]Percent of total ion current.

It can be seen from Table 2 that the importance of *m/e* 135 decreases in the series **5–7** and **9–10**. This can be rationalized by two factors: (*1*) the stabilities of the neutral molecules formed decrease,[6] and (*2*) as the substitution decreases on position 2, competing rearrangements occur. The differences in the stabilities of the neutral molecules formed can also be involved to explain the greater importance of *m/e* 135 in the mass spectra of **5** compared to **9** and of **6** compared to **10**.

The relative intensities of the molecular ions and of the rearrangement ions *m/e* 135 and 122 are compared in Table 3. Two main observations can be made from these data. First, the presence

[6]The assumption implied here is that the compounds compared are sufficiently similar to allow the following approximations: since compound A: AP (*m/e* 135) = ΔH_f (*m/e* 135) + ΔH_f (neutral fragment) − ΔH_f (compound A) + E_A, and compound B: AP (*m/e* 135) = ΔH_f (*m/e* 135) + ΔH_f (neutral fragment) − ΔH_f (compound B) + E_B. Then, ΔAP (*m/e* 135) = $\Delta\Delta H_f$ (neutral fragments) − $\Delta\Delta H_f$ (compounds), where (*1*) $\Delta\Delta H_f$ (neutral fragments) > $\Delta\Delta H_f$ (compounds), (*2*) $E_A \cong E_B$, and (*3*) the ion at *m/e* 135 is the same from compounds A and B.

TABLE 3. Relative intensities of M^+, *m/e* 135, and *m/e* 122

Compound	M^+	*m/e* 135	*m/e* 122	Preferred fragment expelled
	**2**	~0	100	—	
	**11**	5.5	100	—	CO_2
	**3**	0	100	—	
	**5**	0	100	—	
	**9**	100	66	—	
	**6**	0	100	54	
	**10**	~100	7	35	
	**7**	24	12	100	

of a hydroxyl group at position 2 of the *N*-alkyl group renders the molecular ions very labile. It can be seen from Eqs. 8 and 9 that this is also true of the presence of an *O*-TMS group. This is related to the fact that the transfer of hydrogen from a hydroxyl group on C-2 is preferred over the transfer of hydrogen from a methyl group at C-2, as was shown in the spectra of **3** and its deuterated analogs. This conclusion is supported by the fact that the molecular ions are the base peaks in the spectra of **9** and **10** which contain no hydroxyl groups. This behavior is in agreement with the weaker bond strength of the O—H bond with respect to the C—H bond and also in agreement with the greater stability of keto forms over corresponding enol forms (18).

The second main observation drawn from Table 3 is that the formation of *m/e* 122, the ion formed by double hydrogen rearrangement competes increasingly successfully with formation of *m/e* 135 as substitution decreases at position 2 and in the absence of a hydroxyl group at position 2. From the comparison of the spectra of **6** and **10**, it can be seen that the hydroxylic hydrogen still plays a predominant role in giving fragmentation patterns which should reflect to a certain extent the relative stabilities of the neutral fragments formed. However, a more rigorous analysis cannot be

made at this stage due to the large number of variables at play.

Experimental

Mass spectra were obtained from AEI MS902 and Hitachi Perkin-Elmer RMU6D mass spectrometers, via the direct-probe introduction system. The low-voltage data reported are values read directly from the dials. In each case, spectra were taken at various dial readings, and small variations of the voltage did not change the results qualitatively. Exact-mass data were obtained from the MS 902, in conjunction with a PDP-8 computer.

The i.r. spectra were recorded in $CHCl_3$ solution, unless otherwise stated, on a Beckman model IR-8 double beam spectrometer. The n.m.r. spectra were recorded in $CDCl_3$ solution, unless otherwise specified, using a Varian A-60 spectrometer; peak positions are recorded in δ units and the internal standard used was TMS. Melting points were taken on a Büchi apparatus and are uncorrected.

N-Benzoyl-1-aminomethyl-4-tert-butylcyclohexanol-cis (3)

Product **3** is prepared under Schotten–Baumann conditions (19) by adding over a period of 3 h a solution of 3.44 g (24 mmol) of benzoyl chloride in 200 ml of benzene to a dispersion of 4.51 g (24 mmol) of 1-aminomethyl-4-*tert*-butylcyclohexanol (20), 3.26 g (24 mmol) of potassium carbonate, 50 ml of ether, and 50 ml of water. The mixture is left standing overnight and after the usual work-up and crystallization from chloroform–hexane yields 5.65 g (80%) of the pure *N*-benzoyl derivative (**3**); m.p. 192–193 °C; i.r. (Nujol) 3330, 1640, and 1545 cm^{-1}; n.m.r. (CF_3COOH) 0.95 (9H, s), 1.70 (10H, m), 4.00 (2H, d, J = 6 Hz), 7.80 (5H, m), and 9.10 p.p.m. (1H, t, J = 6 Hz).

N-Benzoyl-1-aminomethyl-4-tert-butyl-2,2,6,6-tetradeuterocyclohexanol-cis (3-d_4)

The tetradeuterated analog of **3** is prepared in the same manner as described above with the exception that 4-*tert*-butyl-2,2,6,6-tetradeuterocyclohexanone instead of the undeuterated ketone is used as starting material. The deuteration is carried out according to the procedure of Cope and Gale (21), *i.e.* by heating to reflux a mixture of 4-*tert*-butylcyclohexanone and heavy water. Yield 88%; mass spectrum *m/e* 158, 157, and 156 in respective ratios of 93%, 6%, and 1% which indicates 98% deuteration; i.r. (Nujol) 3350, 1640, and 1545 cm^{-1}; n.m.r. 0.95 (9H, s), 1.42 (5H, m), 2.45 (1H, m), 3.43 (1H, d, J = 6 Hz), 3.60 (1H, d, J = 6 Hz), 6.80 (1H, m), and 7.70 p.p.m. (5H, m).

N-Deutero-O-deutero-N-benzoyl-1-aminomethyl-4-tert-butylcyclohexanol-cis (3-d_2)

The dideutero analog **3**-d_2 is prepared by stirring 0.110 g (0.4 mmol) of the *N*-benzoyl derivative **3** in 1 ml of methanol O—D (purity 99%). After exchange is complete, aliquots of the solution are introduced into the mass spectrometer by means of a direct probe. Methanol O—D was introduced simultaneously via a reservoir inlet system.

N-Benzoyl-β-phenethylamine (4)

The title compound is prepared by treating 6.05 g (50 mmol) of β-phenethylamine with benzoyl chloride under Schotten–Baumann conditions (*vide supra*). Yield 10.46 g (93%); m.p. (chloroform–hexane) 116–117 °C; i.r. 3470, 1655, and 1515 cm^{-1}; n.m.r. 2.85 (2H, t, J = 7.2 Hz), 3.63 (2H, m), 6.64 (1H, broad), and 7.41 p.p.m. (10H, complex system).

N-Benzoyl-2-hydroxyisobutylamine (5)

2-Hydroxyisobutylamine

The title compound is prepared according to the procedure of Nace and Smith (22) by adding 13.60 g (150 mmol) of acetone cyanohydrin (23), dissolved in 200 ml of anhydrous ether, to a stirred suspension of 6.1 g (160 mmol) of lithium aluminum hydride in 300 ml of anhydrous ether. The mixture is heated to reflux for 3 h and the intermediate salts hydrolyzed with 7 ml of water and 7 ml of 5% aqueous potassium carbonate. The mixture is decanted and the residue triturated and digested with 200 ml of ether. The mixture is cooled and decanted after which both ethereal fractions are joined, dried, and evaporated to yield 4.81 g (34%) of the amino alcohol which is purified by distillation; b.p. 49 °C/2.5 Torr (lit. (24) 81 °C/20 Torr).

N-Benzoyl-2-hydroxyisobutylamine (5)

The title compound is prepared by treating 7.53 g (60 mmol) of 2-hydroxyisobutylamine hydrochloride with benzoyl chloride under Schotten–Baumann conditions (*vide supra*). Yield 11.03 g (95%); m.p. (chloroform–hexane) 104–105 °C; i.r. 3500–3300, 1650, and 1525 cm^{-1}; n.m.r. 1.25 (6H, s), 3.43 (2H, d, J = 6 Hz), 4.18 (1H, s), and 7.72 p.p.m. (6H, m).

N-Benzoyl-2-hydroxy-n-propylamine (6)

The title compound is prepared by treating 7.50 g (100 mmol) of 2-hydroxy-*n*-propylamine with benzoyl chloride under Schotten–Baumann conditions (*vide supra*). Yield 17.23 g (96%); m.p. (chloroform–hexane) 93–94 °C; i.r. 3500–3300, 1645, and 1525 cm^{-1}; n.m.r. 1.15 (3H, d, J = 6 Hz), 3.30 (2H, m), 3.80 (1H, m), 3.90 (1H, s), and 7.50 p.p.m. (6H, m).

N-Benzoyl-2-hydroxyethylamine (7)

The title compound is prepared by treating 4.88 g (80 mmol) of ethanolamine with benzoyl chloride under Schotten–Baumann conditions (*vide supra*). Yield 11.52 g (87%); m.p. (chloroform–hexane) 64–65 °C; i.r. (Nujol) 3500–3300, 1630, and 1550 cm^{-1}; n.m.r. 3.57 (4H, m), 4.77 (1H, s), and 7.48 p.p.m. (6H, m).

N-Benzoylneopentylamine (9)

Pivalaldoxime

The title compound is prepared (25) by adding 60 ml of an aqueous solution of sodium carbonate (10.6 g, 100 mmol) to a stirred suspension of 12.92 g (150 mmol) of pivalaldehyde in a solution of 14.02 g (200 mmol) of hydroxylamine hydrochloride in 25 ml of cold water. The mixture is stirred for one additional hour and extracted three times with 15 ml of chloroform. The organic layer is then washed with a saturated solution of sodium chloride, dried, and evaporated *in vacuo*. The residue is recrystallized from hexane to yield 10.45 g (69%) of pivalaldoxime, m.p. 38–39 °C (lit. (26) 41 °C).

Neopentylamine Hydrochloride

Pivalaldoxime is reduced according to the procedure of Cristol and Stermitz (27) by adding a solution of 10.10 g (100 mmol) of the oxime in 200 ml of anhydrous ether to a stirred suspension of 7.6 g (200 mmol) of lithium aluminium hydride in 100 ml of anhydrous ether, at such a rate as to cause a slight reflux. The mixture is then heated to reflux for 18 h and the intermediate hydrolyzed, first with humid ether, then with 5–10 ml of water. The ethereal layer is decanted and the white residual mass digested with 200 ml of chloroform for 1 h. The chloroformic phase is decanted, combined with the ethereal fraction, dried, and evaporated *in vacuo*. The residue is dissolved in 100 ml of anhydrous ether and treated with gaseous hydrogen chloride to yield 6.34 g (52%) of neopentylamine hydrochloride; m.p. (absolute ethanol – ether) 266–267 °C (lit. (28*a*) 274 °C; lit. (28*b*) 275 °C; lit. (28*c*): 273 °C).

N-Benzoylneopentylamine (9)

The title compound is prepared by treating 6.20 g (44 mmol) of neopentylamine hydrochloride under Schotten–Baumann conditions (*vide supra*). Yield 8.03 g (84%); m.p. (chloroform–hexane) 112–113 °C; i.r. 3480, 1660, and 1520 cm^{-1}; n.m.r. 0.98 (9H, s), 3.24 (2H, d, $J = 6.8$ Hz), 6.27 (1H, broad), and 7.59 p.p.m. (5H, complex system).

N-Benzoylisobutylamine (10)

The title compound is prepared by treating 7.3 g (100 mmol) of isobutylamine with benzoyl chloride under Schotten–Baumann conditions (*vide supra*). Yield 16.65 g (94%); m.p. (chloroform–hexane) 57–58 °C; i.r. 3480, 3380, 1660, and 1520 cm^{-1}; n.m.r. 0.93 (6H, d, $J = 6.6$ Hz), 1.85 (1H, n, $J = 6.6$ Hz), 3.17 (2H, t, $J = 6.6$ Hz), and 7.50 p.p.m. (6H, complex system).

Ethyl-N-benzoylglycinate

The title compound is obtained by treating 27.92 g (200 mmol) of ethylglycinate hydrochloride with benzoyl chloride under Schotten–Baumann conditions (*vide supra*). Yield 33.48 g (80%); m.p. (chloroform–hexane) 59–60 °C; i.r. 3450, 3370, 1740, 1660, and 1520 cm^{-1}; n.m.r. 1.23 (3H, t, $J = 6.8$ Hz), 4.05 (2H, d, $J = 5.3$ Hz), 4.09 (2H, quad., $J = 6.8$ Hz), and 7.53 p.p.m. (6H, complex system).

N-Benzoylglycine (11)

A solution of 8.90 g (43 mmol) of ethyl-*N*-benzoylglycinate in 50 ml of methanol is treated with 50 ml of a 10% aqueous solution of potassium hydroxide and the mixture heated to reflux for 6 h. The methanol is evaporated *in vacuo* and the remaining aqueous solution is washed with chloroform, acidified with dilute hydrochloric acid, and cooled in the refrigerator to complete crystallization, filtered *in vacuo*, and dried. Yield 6.36 g (83%); m.p. (chloroform–hexane) 186–187 °C (lit. (29) 186–187 °C); i.r. (Nujol) 3355, 3500–2500, 1740, 1600, and 1550 cm^{-1}; n.m.r. 4.05 (2H, d, $J = 5.7$ Hz), 6.70 (5H, complex system), 8.87 (1H, t, $J = 5.7$ Hz), and 11.68 p.p.m. (1H, broad).

N-Benzoyl-2-hydroxy-2,2-diphenylethylamine (2)

A solution of 20.70 g (100 mmol) of ethyl-*N*-benzoylglycinate in 50 ml of ether is added dropwise to a solution of phenylmagnesium bromide in ether at such a rate as to cause a slight reflux. The Grignard reagent is prepared by adding slowly, at room temperature, a solution of 31.4 g (200 mmol) of phenyl bromide in 400 ml of ether to 5.28 g (220 mmol) of magnesium turnings covered with a little ether. The reaction mixture is stirred at room temperature for an additional 15 min. The resulting magnesium salt is hydrolyzed with an ice-cold saturated solution of ammonium chloride in water until two layers are formed. The layers are decanted and the aqueous solution extracted with chloroform. The ethereal and chloroformic fractions are joined and the resulting mixture dried and evaporated *in vacuo*. Yield 25.42 g (82%); m.p. (absolute ethanol) 181–182 °C; i.r. (Nujol) 3435, 3360, 1630, and 1530 cm^{-1}; n.m.r. (DMSO-d_6) 4.12 (2H, d, $J = 5.3$ Hz), 6.25 (1H, s), 7.43 (15H, complex system), and 8.00 p.p.m. (1H, t, $J = 5.3$ Hz).

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