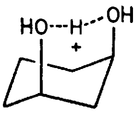
Ion-Molecule Reactions in the Gas Phase. Part 1. Stereospecific Nucleophilic Substitution of Tertiary Alcohols by Ammonia

By **J. Bastard, D. Do Khac Manh, M. Fetizon,** and **J. C. Tabet,*** Laboratoire de Synthèse Organique, Ecole Polytechnique, 91128 Palaiseau Cedex, France
D. Fraisse, Centre de Spectrometrie de Masse de Lyon B.P. 22, 69390 Vernaison, France

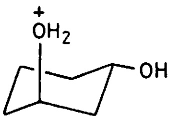
A study of the chemical ionisation of two pairs of diastereoisomeric unsaturated tertiary alcohols with isobutane as the protonating gas shows that hydrogen bonding between the protonated hydroxy-group and the double bond can stabilize the quasi-molecular ion, if the geometry is correct. Therefore, it is possible to differentiate between two isomers. With ammonia, the most interesting phenomenon is an S_N2-like reaction, in which the OH_2^+ group is replaced by NH_3^+, with Walden inversion.

WHEN alcohols are ionized by electron impact, molecular ions $M^{+\cdot}$ eliminate a molecule of water very rapidly, even at low energy (10—11 eV). The utilization of lower energy ionization methods, such as chemical ionization, leads to similar behaviour of the protonated molecular ion MH^+, even if it is produced during proton transfer with a reactive gas which has high proton affinity (p.a.) such as isobutane (p.a. *ca.* 807 kJ mol^{-1}).

Winkler and Stahl [1,2] demonstrated the possibility of distinguishing cyclic diastereoisomeric diols by protonation with NH_4^+. Thus, *cis*-cyclohexane-1,3-diol leads to a very intense MH^+ peak (ion *a*). This is not the case with the *trans*-diastereoisomer (ion *b*, 2.2% Σ_{80}).



a



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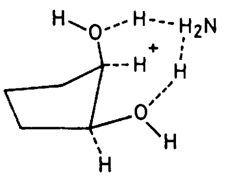


c

This result may be interpreted on the basis of differences in proton affinity. The possibility of forming a hydrogen bond in the protonated *cis*-isomer even leads to increased proton affinity in this isomer relative to the *trans*-diol.

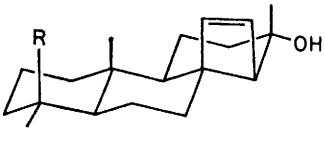
In addition, an ion $[M + NH_4]^+$ (ion *c*) appears next to the MH^+ peak; it is more abundant as reaction (1) is

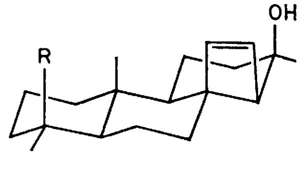
$$M + NH_4^+ \rightleftharpoons M \cdots \overset{+}{H} \cdots NH_3 \rightleftharpoons MH^+ + NH_3 \quad (1)$$

thermoneutral (or endothermic), all other variables being constant.

It may happen that only the chelate is present, and it is then not possible to distinguish between diastereoisomeric alcohols, as in the case of *cis*- and *trans*-cyclopentane-1,2-diol, where the intensity of the peak corresponding to the MH^+ ion is extremely low (<1%). Nevertheless, it has been demonstrated, in both positive and negative ionization, that it is possible unambiguously to differentiate among steroid polyols.[3]

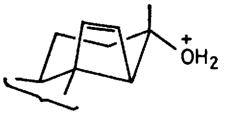
Hunt [4] correctly predicted the important role of NH_4^+ in the determination of the stereochemistry of organic compounds. The literature contains a large number of examples of the application of this technique. After consideration of the behaviour of NH_4^+ towards monocyclic diols, we attempted to distinguish between the pairs of diastereoisomeric alcohols (1) and (2) in a similar way.



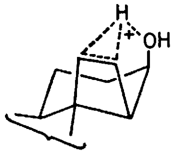


(1) R = CH_3 (2) R = $COOCH_3$

The spectra of these alcohols can be characterized by the presence of the MH^+ ion. In the case of the α-stereoisomer, the protonated molecular ion (ion *d*) should decompose more rapidly than that from the protonated β-alcohol. In the latter case, the MH^+ ion is stabilized by the presence of the hydrogen bond between the double bond and the protonated hydroxy-group (ion *e*).

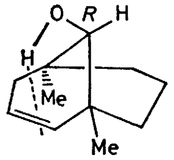


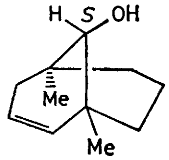
d



e

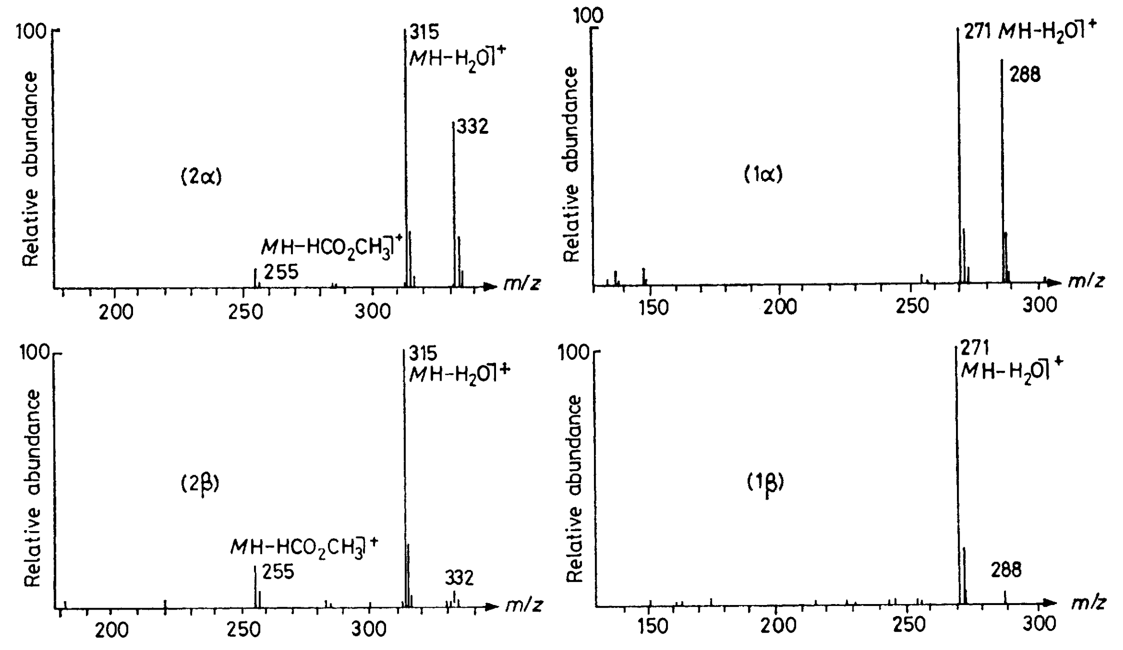
Joris [5] was able to demonstrate the existence of this type of hydrogen bond in an i.r. spectroscopic study of 1,5-dimethylbicyclo[3.3.1]non-2-en-9-ol stereoisomers. Only the β-alcohol generated an absorption band at 3 584 cm^{-1} characteristic of the intramolecular OH ··· π hydrogen bond.





OH free (cm^{-1})	3640	3640
OH (π.... H-bond)(cm^{-1})	3584	

Measurement of the chemical ionization spectra of (1) and (2) with isobutane confirmed our prediction (Table 1). The intensity of the MH^+ peak in the spectra of the



NH_4^+ Chemical ionization spectra of diastereoisomeric unsaturated alcohols (1) and (2) (no peak $>5\%$ below m/z 180)

TABLE 1

Chemical ionization spectrum[a] of the diastereoisomeric pairs (1) and (2) with isobutane

	(1α)	(1β)		(2α)	(2β)
MH^+ (m/z 289)	4.3	22.5	MH^+ (m/z 333)	8.2	28.9
$[MH - H_2O]^+$ (m/z 271)	88	70.1	$[MH - H_2O]^+$ (m/z 315)	81.2	67.2

[a] Peak intensities are normalized to 100% of total ionization and only the major ions MH^+ and $[MH - H_2O]^+$ are reported.

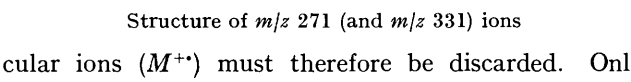
β-alcohols is about three times more intense than in the α-isomers. This result demonstrates the part played by a double bond in proximity to a protonated group and thus enables the stereochemistry of the alcohol studied to be elucidated.

Chemical ionization with NH_4^+ led to very different results. No spectrum of the various alcohols showed any MH^+ ion. These ions could not be observed at the temperature used in our study (190 °C).* It is thus impossible to demonstrate the existence of this type of hydrogen bond; therefore, these diastereoisomers could not be distinguished (Figure).

The experimental results indicate a substantial difference between the α- and β-compounds. Although in all cases loss of water results in the base peak, the spectra of diastereoisomers (1α) and (2α) are characterized by the presence of an intense peak at m/z 288 for (1α) [and at m/z 332 for (2α)], corresponding to the molecular ion of these alcohols.†

The increased intensity of the m/z 271 peaks for isomers (1α and β) [and m/z 315 for (2α and β)] may be interpreted as a consequence of the stabilization of the carbocation either as a non-classical ion (ion *f*) or as rearranged ions (ions *g* and *h*) after the elimination of a neutral molecule.

The interpretation of the presence of ions with even masses, m/z 288 for (1α) and 332 for (2α), as being molecular ions ($M^{+\cdot}$) must therefore be discarded. Only charge exchange reactions induced by $NH_3^{+\cdot}$ could produce such ions, and these could not have occurred under the conditions used in our experiments.



Structure of m/z 271 (and m/z 331) ions

Spectra were obtained with ND_3 (under the same conditions of temperature and pressure) in order to determine the origin of these ions. Would charge transfer be the occurring phenomenon which takes place, the peaks at m/z 288 should have been shifted by one dalton, since the hydrogen atom bound to the oxygen atom is mobile. The results indicated that this reaction was of minor importance. The peaks are, however, shifted by three daltons, leading to the conclusion that there were three mobile hydrogens present.

In addition, the high resolution measurement of these ions (resolution > 12 000) indicated that the hydroxy-function was exchanged for an NH_3^+ group. The results may be expressed in terms of a nucleophilic substitution which leads to a 'protonated amine' ion, $M_{s}H^+$, isobaric with the molecular ion $M^{+\cdot}$ of the alcohol.

A similar reaction was proposed by Lin and Smith[6] in their study of the behaviour of secondary (steroidal)

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* Isolated experiments were also carried out at lower temperatures. No MH^+ ion could be detected. There is a sharp increase of the intensity of the $[MH + NH_3]^+$ ion (from 3 to 20% of the base peak).

† These peaks are *ca.* 20 times less intense in the spectra of isomers with the β-configuration.

TABLE 2

Peak shifts[a] at *m/z* 271 (or 315) and *m/z* 288 (or 332) for the pairs (1α and β) [or (2α and β)]

m/z	270	271	272	273	274	288[b]	289	290	291	292	293
(1α)	1.1	64.0	26.5	6.5	1.9	0.6	0.6	1.8	76.1	18.3	2.6
(1β)	1.1	70.2	22.5	4.4	1.8	9.6	18.1	9.6	42.6	20.1	

m/z	314	315	316	317	318	319	332[c]	333	334	335	336	337
(2α)	3.5	44.5	33.5	11.1	7.4	5.5	2.8	7.1	3.9	59.2	17.9	3.6
(2β)	0.9	67.2	25.1	5.3	1.5	1.2	10.3	9.4	5.9	34.2	21.4	6.8

[a] These shifts are normalized to 100% total ionization by region. [b] For compound (1α) this peak corresponds to 48% of total ionisation, whereas for (1β) it is decreased to 2.5% only. [c] 37% for (2α) [and 2.1% for (2β)].

saturated or non-saturated alcohols with respect to NH_4^+. All the alcohols led to this type of substitution reaction, regardless of whether they were allylic or saturated alcohols (the presence of MH^+ was not observed in any case) (Table 3).

TABLE 3

NH_4^+ Chemical ionization spectrum[a] of aβ-stereochemical alcohol, saturated (or not) in the cholestane series

	3β-OH		Δ⁷-3β-OH	Δ⁵-3β-OH		Δ⁴-3β-OH
	100°	195°	100°	100°	195°	100°
$[MH + NH_3]^+$	73.5	3.5	45.7	33.3	3.5	7.2
$[MH]^+$	0	0	0	0	0	0
$[M_sH]^+$ [b]	26.5	67.1	48.1	33.3	27.6	20.3
$[MH - H_2O]^+$ [c]						
$[M_sH - H_2O]^+$		29.4	6.2	33.3	68.9	72.5

[a] Peaks are normalized to 100%. [b] This represents the ion $[MH + NH_3 - H_2O]^+$. [c] Lin and Smith gave no explanation of the reactions.

Lin and Smith, in their interpretation of these results, suggested two different mechanisms which could produce the nucleophilic substitution (without demonstrating the occurrence of either of them): a two-step mechanism (S_N1-like), with carbocation formation as a first step [reaction (2)] or a concerted one-step mechanism

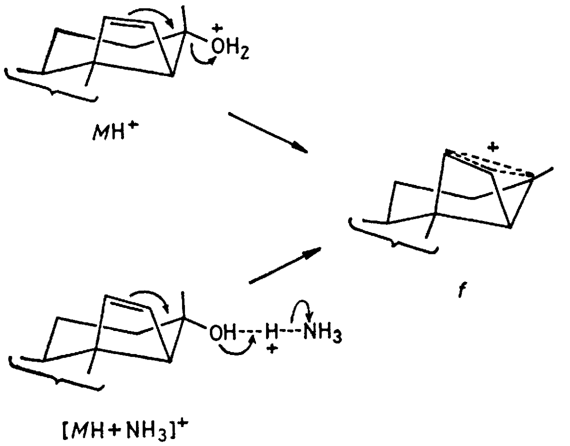
$$[MH]^+ \xrightarrow{-H_2O} [MH - H_2O]^+ \xrightarrow{+NH_3} [MH - H_2O + NH_3]^+ \qquad (2)$$

[reaction (3)]. The formation of a carbocation must lead

$$[MH]^+ \xrightarrow{-H_2O\ +NH_3} [MH + NH_3 - H_2O]^+ \qquad (3)$$

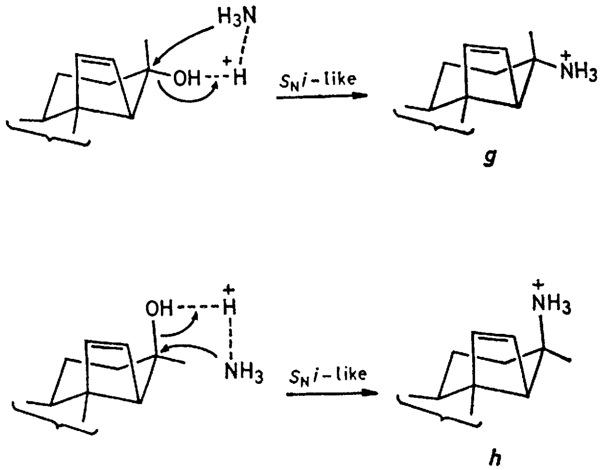
to nearly identical reactivity with ammonia, whether the initial alcohol has α- or β-stereochemistry, and thus to identical spectra. The experimental results demonstrate a definite influence by the configurations of the starting compounds which rules out reaction (2).

This difference could, however, be due to the rate of carbocation formation, which should be larger in the case of the axial alcohol through anchimeric assistance (Scheme 1). The following remarks can be made. 1. Reaction (3) theoretically should be a more rapid decomposition of protonated (or adduct) molecular ions with higher internal energy. This is certainly not correct since the MH^+ ion has a non-negligible intensity with isobutane* (Table 1). 2. The determination of the precursor carbocations (*m/z* 271 or 315) by the 'linked scan B^2/E method'[7] indicates that it is produced primarily by $[M_sH]^+$ (*m/z* 288 or 332).† The $[M_sH]^+$ ion decomposes to eliminate primarily an ammonia molecule, as shown by the unimolecular decomposition spectrum of this ion by the 'linked scan B/E' mode.



SCHEME 1

Thus, the *m/z* 271 and 315 ions arise from the $[M_sH]^+$ ions only by the elimination of ammonia, and the inintensity of the $[M_sH]^+$ ions is directly related to the stability of these ions (for identical final states) and not to the more or less rapid production of carbocations from $[MH + NH_3]^+$ or $[MH]^+$ (which never appear at low temperature).



SCHEME 2

If the two-step mechanism is untenable, a concerted mechanism leading to $[M_sH]^+$ ions must be considered: either an S_Ni-like mechanism with retention of configuration (Scheme 2), or an S_N2-like substitution with Walden inversion.

Since the intensity of the peak corresponding to any ion is related to its stability, the $[M_sH]_\beta^+$ ion which is

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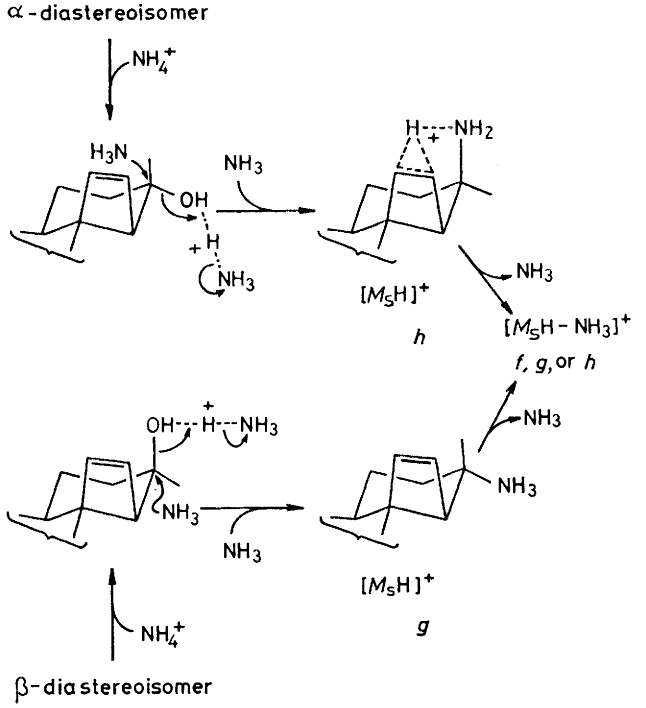
* Isobutane has a lower proton affinity than ammonia.

† $[MH + NH_3]^+$ is also a precursor, but present in small quantities (sensitivity limit). Furthermore, it is not demonstrated in the case of the β-isomer, because of the low abundance of $[M_sH]^+$ (*m/z* 288 or 332).

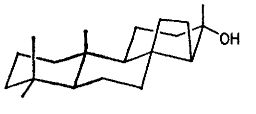
stabilized by hydrogen bonding, should give rise to a more intense signal, in contrast to the experimental data. Thus an S_Ni-like mechanism is also ruled out. Therefore, the only remaining possibility is an S_N2-like substitution which involves a Walden inversion (Scheme 3). The substitution may take place close to the exit of the source, where the pressure of ammonia is still relatively high, which is consistent with the B^2/E scanning results.



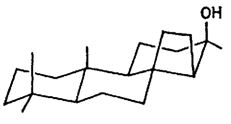
Scheme 3

Configurational inversion in the gas phase is generally difficult to prove. It seems that our compounds provide data which support the detailed description of the substitution mechanism. In fact, the spectra of the α-alcohols (1α) and (2α) show that the rate of substitution is much higher than for the β-isomers (1β) and (2β).

If our S_N2-like mechanism is correct, α-alcohols should lead to β-amino-protonated intermediates, stabilized by hydrogen bonding, whereas β-alcohols would give α-amino-isomers in which such intramolecular stabilization is impossible. On the other hand, the double bond, as expected, plays a major part: The spectra of the saturated alcohols (3α and β), under the same conditions, are quite similar (Table 4). The intensity of the $[MH + NH_3]^+$ ion is no longer negligible, and the rate of substitution is very low. Since there is no double bond to stabilize the $[M_sH]^+$ ions,* their decomposition, with loss of ammonia, is extremely rapid.



(3α)



(3β)

Conclusions.—This observed stereospecific nucleophilic substitution in the gas phase, which proceeds very probably through an S_N2-like mechanism, provides a further example of related reactions studied in i.c.r.[8] Our results are the first examples of S_N2 substitution on a tertiary carbon atom. In addition, these observations show that the results of c.i. mass spectrometry [9,10] give rise to ideas which may be used in the field of preparative organic chemistry.

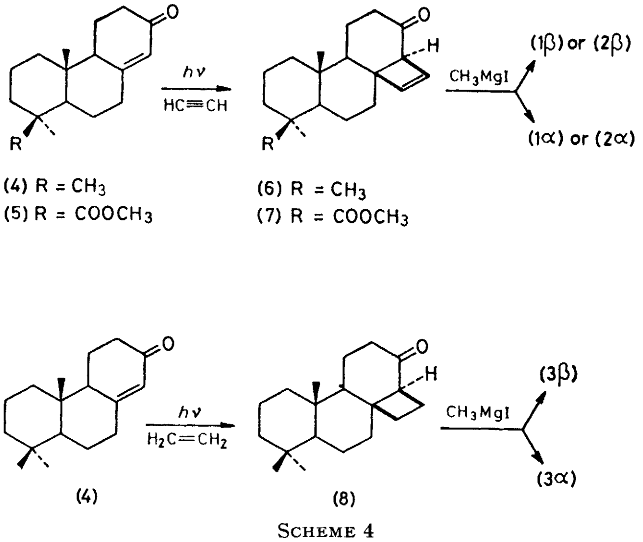
Table 4

	(3α)	(3β)
$[MH + NH_3]^+$	5	12
$[MH]^+$	0	0
$[M_sH]^+$	3	5
$[M_sH - NH_3]^+$	92	83

EXPERIMENTAL

Spectra were obtained with a spectrometer equipped with a mixed C.I.—E.I. VG Micromass 7070 source at a 4 kV acceleration voltage and a 500 μA emission current (ion repeller zero). The plasma of protonating gas at 0.8 Torr pressure (measured in the source) is composed of 3—5% $NH_3^{+\bullet}$, 90% NH_4^+, and 5—7% $N_2H_7^+$. The compounds were introduced through a direct introduction probe (source temperature 180 °C). Spectra were repeated 3—5 times, in order to obtain reliable data (error ±2%) after computer processing (PDP 8). The metastable transitions produced in the first free field region are detected with the linked scan B/E and B^2/E methods.[7] Deuteriated ammonia gas (99% > ND_3) was furnished by C.E.A., Saclay.

The cycloaddition of acetylene with the unsaturated ketone (4) or (5) leads to the ketone (6) or (7).[11] Methylmagnesium iodide in ether reacts with ketone (6) or (7) to yield a mixture of two tertiary alcohols in the proportion 6:4, separated by t.l.c. The major alcohol is (1α) or (2α), the minor alcohol (1β) or (2β) (Scheme 4).[12]



Scheme 4

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* The linked scan B/E spectra of $[M_sH]^+$ ions show that they decompose into $[M_sH - NH_3]^+$ ions.

Condensation of ethylene with the unsaturated ketone (4) or (5) yields the ketone (8).[12] Methylmagnesium iodide in ether reacts with (8) to yield two alcohols (3α and β) in the proportion 5.5 : 4.5, separated by t.l.c.

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REFERENCES

[1] F. J. Winkler and D. Stahl, *J. Am. Chem. Soc.*, 1979, **101**, 3685.

[2] F. J. Winkler, D. Stahl, and T. Gaumann, 26th Conference on Mass Spectrometry and Allied Topics, St Louis, 1978, p. 611.

[3] F. J. Winkler, D. Stahl, and G. Guenat, Euchem Conference: Ion Beam Chemistry, Utrecht, 1980.

[4] D. F. Hunt and S. K. Sethi, in ' High Performance Mass Spectrometry,' M. L. Gross, Am. Chem. Soc., Washington, 1977.

[5] L. Joris and P. v. R. Schleyer, *J. Am. Chem. Soc.*, 1968, **90**, 4599.

[6] Y. Y. Lin and L. L. Smith, *Biomed. Mass Spectrom.*, 1978, **5**, 604.

[7] R. K. Boyd and J. H. Beynon, *Org. Mass Spectrom.*, 1977, **12**, 183.

[8] J. H. Bowie, *Acc. Chem. Res.*, 1980, **13**, 76.

[9] J. C. Tabet and D. Fraisse, *Org. Mass Spectrom.*, 1981, **16**, 46.

[10] G. L. Glisch and R. G. Cooks, *J. Am. Chem. Soc.*, 1978, **100**, 6720.

[11] D. Do Khac Manh, M. Fetizon, and S. Lazare, *J. Chem. Res.*, 1978, (*S*), 22; (*M*) 167.

[12] D. Do Khac Manh, M. Fetizon, and J. P. Flament, *Tetrahedron*, 1975, **31**, 1897.