The Hofmann–Loeffler Hydrogen Abstraction Process in the Mass Spectrometry of 1-Alkoxy-9-methyl-9-azabicyclo[3.3.1]nonanes

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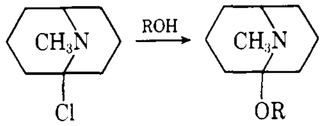
The electron impact induced fragmentation pathways of 15 bridgehead ethers in the 9-methyl-9-azabicyclo-[3.3.1]nonane system have been studied. The intensities of the base ions, as well as other fragment ions, are found to depend on the nature of the branching in the alkoxy group. The primary and secondary ethers display base peaks at *m/e* 112 which are formulated as arising by ejection of a lone pair electron from nitrogen, scission of the 1,2 bond, expulsion of cyclopropane, and loss of the alkyl portion of the alkoxy group. The latter two steps are supported by the observation of appropriate metastable peaks. The tertiary ethers have their base peaks at *m/e* 113 which are accounted for by invoking a hydrogen transfer from the alkoxy group to nitrogen, either by a McLafferty type rearrangement *subsequent* to α-cleavage or by a Hofmann–Loeffler type free radical abstraction *prior* to loss of the alkoxy group and α-cleavage. Evidence corroborating the latter process is presented. Other important primary ions occur at *m/e* values of 126, 138, 154, and 156; the mechanisms of their formations are described.

Based upon the definitive studies from the laboratories of Wawzonek[2a] and Corey[2b] the initial phases of the Hofmann–Loeffler reaction[3] are believed to involve homolysis of the nitrogen–halogen bond of an *N*-haloammonium ion to afford a nitrogen radical cation which abstracts a hydrogen intramolecularly from a δ carbon to generate a carbon radical. Since nitrogen cation radicals are produced in the electron impact induced ionization of amines, it might be expected that a Hofmann–Loeffler type hydrogen abstraction process should also take place in the mass spectrometer. In this report evidence implicating such an occurrence is presented.

Results and Discussion

The present mass spectrometric investigation was prompted by the observation that α-amino bridgehead ethers 1 and 14 exhibit different base peaks: ethyl ether 1 has its most abundant peak at *m/e* 112, whereas *tert*-amyl ether 14 displays its most intense peak at *m/e* 113. The constitutions of the *m/e* 112 and 113 ions were determined by high-resolution mass spectrometry to be $C_6H_{10}NO$ (found: 112.07714) and $C_6H_{11}NO$ (found: 113.08406). To probe the effect of the alkyl portion of the alkoxy group on the essence of the base peak, a number of α-amino bridgehead ethers were prepared by the alcoholysis of 1-chloro-9-methyl-9-azabicyclo[3.3.1]nonane[4] (eq 1). Table I presents the structures of the alkyl groups utilized in the present study along with pertinent relative intensity data.[5]



(1)

1, R = CH_2CH_3
14, R = $C(CH_3)_2CH_2CH_3$
17, R = C_6H_5

Upon inspection of the data in Table I it is seen that the most striking feature is the strong dependence of the relative abundances of a number of fragment ions, especially the base ions, upon the nature of the alkyl portion of the alkoxy group. For the *straight chain primary* ethers the base peaks are at *m/e* 112; the peaks at *m/e* 113 are actually quite small, since the isotopic P + 1 contributions from the *m/e* 112 ions are 7.1%. The *branched chain primary* ethers also show base peaks at *m/e* 112, but the intensities of the *m/e* 113 peaks are somewhat greater than those observed for the straight chain ethers. The *secondary* ethers display base peaks at *m/e* 112; however, the abundances of the *m/e* 113 peaks are substantial. Finally, the *tertiary* ethers have their base peaks at *m/e* 113, although the *m/e* 112 peaks are still rather intense. The mass spectra[6] of the butyl ethers are typical of the various classifications of ethers, and illustrate the trends of branching outlined above. Clearly, both the degree and position of branching are important in determining the relative intensities of the base peaks.

Chart I

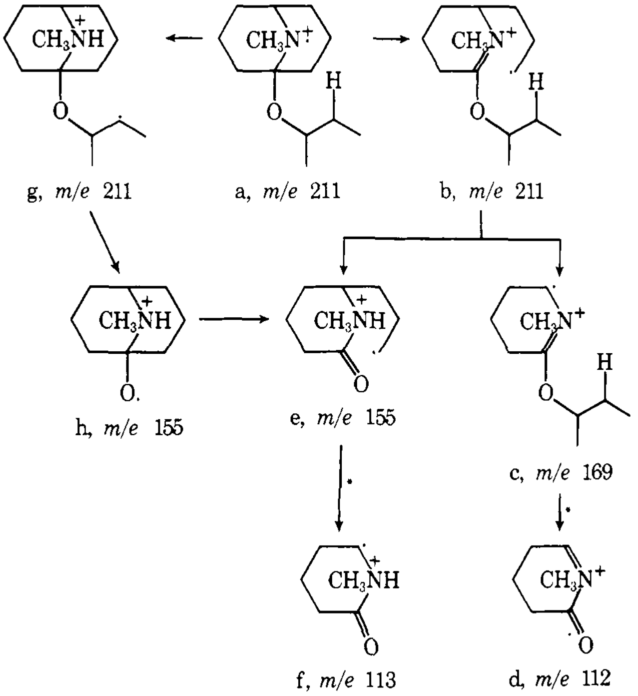


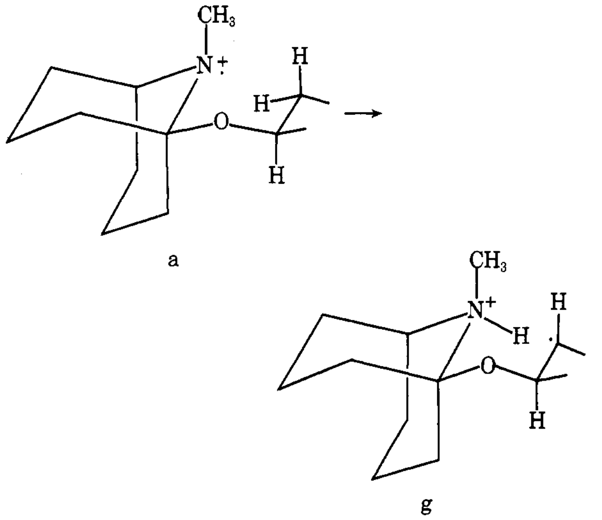
Chart I contains the proposed fragmentation pathways leading to the production of the base peaks; 2-butyl ether **10** is employed as the model substrate. Based on ionization potentials[7] and other studies[8,9] it can be assumed that upon electron bombardment, an electron is preferentially ejected from the lone pair of electrons on nitrogen rather than from a lone pair on oxygen; the fragmentation sequences are triggered by radical cation a. A primary decomposition process is the usual homolytic cleavage of a carbon–carbon bond adjacent to nitrogen to provide the immonium ion b. Such a bond rupture is typical of amines[10] and is well documented by the mass spectra of derivatives of the alkaloids tropane[11] and granatanine.[12] Scission of the 1,2 bond is expected to be preferable to 4,5-bond cleavage, since in the former instance the ether oxygen atom can also stabilize the intermediate cationic species. Radical ion b is transformed into radical

Table I. Relative Intensity Data for α-Amino Bridgehead Ethers

Compd	Alkyl group	M^+	M − 29	M − 42	m/e 110	m/e 112	m/e 113	m/e 126	m/e 138	m/e 154	m/e 155	m/e 156
1	CH_3CH_2	33	52	15	8	100	7	19	5	52	6	1
2	$CH_3CH_2CH_2$	16	11	8	6	100	8	17	4	23	8	1
3	$CH_3(CH_2)_2CH_2$	11	11	4	4	100	9	17	4	20	3	3
4	$CH_3(CH_2)_3CH_2$	10	8	4	6	100	9	16	4	20	3	4
5	$(CH_3)_2CHCH_2$	8	5	4	9	100	15	27	7	20	4	20
6	$C_2H_5(CH_3)CHCH_2$	12	8	4	7	100	22	34	10	26	6	49
7	$(CH_3)_2CHCH_2CH_2$	14	9	4	8	100	15	23	8	26	6	37
8	$(CH_3)_3CCH_2$	40	9	21	20	100	63	70	28	45	20	18
9	$(CH_3)_2CH$	21	4	9	15	100	33	44	7	31	9	1
10	$CH_3CH_2(CH_3)CH$	13	2	2	16	100	49	53	15	26	8	20
11	n-$C_3H_7(CH_3)CH$	22	3	2	14	100	59	55	18	34	12	45
12	$(CH_3CH_2)_2CH$	18	2	2	26	100	78	69	36	32	15	50
13	$(CH_3)_3C$	14	1	1	17	76	100	69	14	5	42	5
14	$CH_3CH_2(CH_3)_2C$	4	1	1	27	46	100	71	33	4	45	7

cation c ($M^+ - 42$) by the expulsion of cyclopropane; a metastable peak corresponding to the b → c transition was observed for some of the substrates.[13] Subsequent loss of the alkyl portion of the alkoxy group of c results in the formation of the *m/e* 112 ion (d). The c → d step is also supported by appropriate metastable peaks for several of the compounds.

There are two similar mechanisms by which the radical ion at *m/e* 113 can be generated. In one pathway a hydrogen from the alkoxy side chain is transferred to nitrogen with concomitant expulsion of the alkyl portion to produce e (*m/e* 155) from b. Such a migration–elimination process is closely related mechanistically to the McLafferty rearrangement.[14] Expulsion of cyclopropane from e (substantiated by metastable peaks in numerous instances) gives the *m/e* 113 ion (f). The alternate sequence leading to the production of the *m/e* 113 peak consists of hydrogen abstraction from the alkoxy side chain by the initially generated nitrogen radical cation a to provide the isomeric ammonium radical g. Subsequent loss of an alkene affords the ammonium alkoxy radical (*m/e* 155) which undergoes scission of the 1,2 bond to give the isomeric species e which goes on to f (*m/e* 113) as indicated above. The a → g process is ideally suited conformationally (eq 2) to compete effectively with the usual α-cleavage mechanism and is completely analogous to the hydrogen abstraction portion of the condensed phase Hofmann–Loeffler reaction.



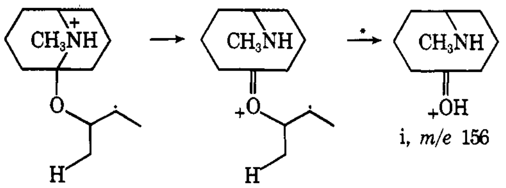
a

g

(2)

One line of evidence which is supportive of the Hofmann–Loeffler type process is the general increase in the relative intensities of the *m/e* 156 ion as one proceeds from primary to secondary (but not tertiary) ethers; the intensities of the *m/e* 156 ions tend to parallel those of the *m/e* 113 ions. Since the 1-oxy-9-methyl-9-azabicyclo[3.3.1]nonane framework has a molecular weight of 154, two hydrogens must be added to the nucleus to obtain a species of *m/e* 156. With the McLafferty rearrangement (b → e) a hydrogen can be transferred to nitrogen only with the simultaneous elimination of the side chain. Thus, the McLafferty rearrangement generates an ion of *m/e* 155, but provides no viable means of adding the second hydrogen. The Hofmann–Loeffler process, on the other hand, does not require the expulsion of the side chain. The radical cation g can transfer a hydrogen to oxygen with concomitant ejection of the side chain as a stable allylic radical to form the *m/e* 156 ion i (Chart II). This latter process is substantiated by the detection of appropriate metastable peaks on several occasions.[15] The only apparent exceptions to the trend relating the intensities of the *m/e* 113 and 156 ions are isopropyl ether **9** and tertiary ethers **13** and **14** which show relatively small magnitudes for the *m/e* 156 ions even though the *m/e* 113 ions are of substantial abundance. However, such results would be predicted for these substrates. Hydrogen abstraction by nitrogen (a → g) generates a primary carbon radical in these cases. To circumvent the intermediacy of a primary radical, the elimination of the side chain occurs in concert with the Hofmann–Loeffler hydrogen migration to nitrogen, and essentially precludes the production of the *m/e* 156 ion (h).

Chart II



g, *m/e* 211 g′, *m/e* 211 i, *m/e* 156

Further evidence militating against the McLafferty rearrangement comes from the mass spectrum of neopentyl ether **8**. It has been determined that the McLafferty rearrangement proceeds mainly through a six-membered transition state[14] which is not possible with **8**. The Hofmann–Loeffler free radical abstraction mechanism has been found not to be confined to this restriction.[4] For neopentyl ether **8** a seven-membered transition state serves to transfer a hydrogen to nitrogen, while migration of a second hydrogen to oxygen is accompanied by the elimination of a cyclopropylcarbinyl radical to produce h.

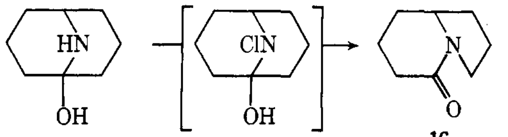
The fact that the relative intensities of the *m/e* 113 ions increase as the number of hydrogens suitable for transference to nitrogen via a six-membered transition state increases (from one or two for the primary ethers to five or six for the secondary ethers to eight or nine for the tertiary ethers) is also in complete accord with the involvement of the Hofmann–Loeffler type hydrogen abstraction process. For the secondary and tertiary ethers the hydrogens capable of participating in a six-membered transition state are mostly primary, but just as in the Hofmann–Loeffler reaction the proximity of the hydrogen to nitrogen is usually more important than its substituent nature. A similar situation exists for the mechanistically related Barton reaction[16] which has also been found to occur in the mass spectrometer.[17] The branched chain primary ethers have their *m/e* 113 ions more intense than the straight chain primary ethers probably owing to the availability of tertiary hydrogens in the former substrates.[3]

In summary, based upon the observations and arguments made above, the Hofmann–Loeffler type hydrogen abstraction process is a perfectly viable mode of fragmentation in the mass spectrometer, and at least for some of the substrates studied here can compete effectively with the usual α-cleavage mechanism.

Besides the *m/e* 112 and 113 ions and their progenitors, the peaks at *m/e* 154, 138, 126, and 110 are of significant intensity. Chart III presents the proposed fragmentations leading to the ions at *m/e* 138 and 110. Loss of alkoxyl from molecular ion a produces immonium ion j (*m/e* 138)[18] which undergoes a retrograde Diels–Alder reaction to give k (*m/e* 110).

The *m/e* 126 ion is accounted for as shown in Chart IV. Intramolecular abstraction of the bridgehead hydrogen within b produces l which loses ethyl radical to afford m $(M^+ - 29)$ which goes on to the *m/e* 126 ion n by way of a McLafferty type rearrangement. The last step of the proposed sequence is supported by the detection of metastable peaks on many occasions.

The *m/e* 154 ion formation is rationalized by the (perhaps concerted) loss of the alkyl side chain and migration of the 2 carbon atom to the nitrogen radical a to provide the quaternary amide cation o (Chart V).[19] In support of the Wagner–Meerwein type fragmentation advocated in Chart V is the finding that treatment of amino alcohol **15** with calcium hypochlorite gave a nearly quantitative yield of lactam **16** (eq 3).[20]



15 **16** (3)

Chart III

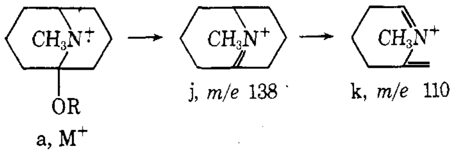


Chart IV

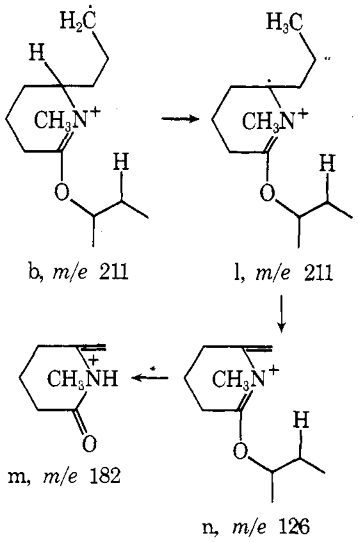
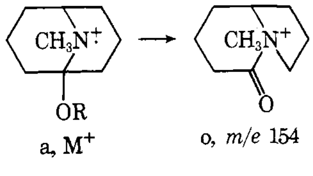
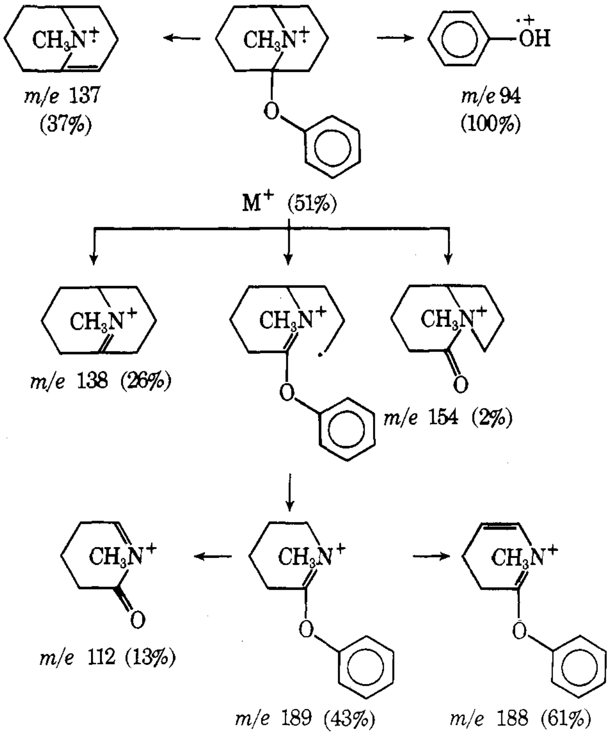


Chart V



Finally, the mass spectrum of phenyl ether **17**[6,21] clearly demonstrates the importance of the side chain on the fragmentation pathways of the α-amino bridgehead ethers (Chart VI). Most of the primary fragmentation processes (Charts I, II, IV, V) observed for the *alkyl* ethers are substantially retarded. Since phenyl radical is a much poorer leaving group than an alkyl radical, production of the *m/e* 112 ion is reduced from 100% relative intensity for the alkyl ethers to 13% for aromatic ether **17**. The phenyl group also precludes the migration of a hydrogen to nitrogen, since only aryl hydrogens are available, and thus the terminal ions f (*m/e* 113), h (*m/e* 156), and m (*m/e* 126) as well as intermediate ion e (*m/e* 155) are not observed in the mass spectrum of **17**.

Chart VI



Experimental Section

Mass spectra were obtained with an A. E. I. MS-9 mass spectrometer at 70 eV; source temperatures were about 160 °C.

1-Alkoxy-9-methyl-9-azabicyclo[3.3.1]nonanes (1–14). Approximately 300 mg of 1-chloro-9-methyl-9-azabicyclo[3.3.1]nonane[4] was dissolved in 30 ml of the appropriate alcohol. To these solutions were added 100 mg of NaOH and 500 mg of $AgNO_3$, and the resulting mixtures stirred in the dark at room temperature for 2 h, after which the reactions were processed by filtration, addition of CH_2Cl_2 and H_2O to the filtrates, separation of the phases, washing of the organic layers with H_2O and saturated aqueous NaCl solution, drying over Na_2SO_4, and concentration with a rotary evaporator. Crude yields of products were in the 50–85% range. Pure samples of **1–14** (all of which are oils) for spectra[22] and elemental analyses[23] were obtained by preparative GC with a Varian Aerograph Model 90-P gas chromatograph utilizing a 6 ft × 0.25 in. stainless steel column containing 5% SE-30 on Chromosorb G; the column temperatures employed for sample collection were about 190 °C (which established that the substrates are thermally stable for the conditions used on the mass spectrometer).

1-Phenoxy-9-methyl-9-azabicyclo[3.3.1]nonane (17). To a solution of 1-chloro-9-methyl-9-azabicyclo[3.3.1]nonane in 5 ml of benzene were added 1.0 g of phenol and 0.200 g of $AgNO_3$. After stirring in the dark at room temperature for a couple of hours the reaction mixture was worked up by adding H_2O and CH_2Cl_2, separating layers, washing the organic phase with 5% aqueous NaOH solution, H_2O, and saturated aqueous NaCl solution, drying over K_2CO_3, and concentrating under vacuum. Pure **17** was obtained from preparative GC as an oil: NMR ($CDCl_3$) δ 6.7–7.5 (m, 5 H), 3.13 (br m, 1 H), 2.52 (s, 3 H), 0.9–2.5 (12 H).

Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.05. Found: C, 77.85; H, 9.20; N, 6.06.

1-Azabicyclo[4.3.0]nonan-2-one (16). Utilizing the procedure of Gassman and Cryberg[24] a solution prepared from 693 mg (4.91 mmol) of **15**[4] and a minimum volume of H_2O was basicified with 5% aqueous NaOH solution, treated with 2 g of $Ca(OCl)_2$ and 10 ml of H_2O, and stirred at room temperature for 0.5 h, after which the reaction mixture was worked up by extraction with CH_2Cl_2, washing the combined extracts with water and saturated aqueous NaCl solution, drying over Na_2SO_4, and concentrating under vacuum to give 647 mg (93%) of an oil which was shown by GC analysis to consist of only one component and whose ir and NMR spectra were identical with those reported previously for **16**.[25]

Acknowledgments. The author is grateful to Mrs. Margaret Johnson for excellent mass spectral service and to Professor John R. Wiseman for providing partial support.

Registry No. — **1**, 58408-47-2; **2**, 58408-48-3; **3**, 58408-49-4; **4**, 58408-50-7; **5**, 58408-51-8; **6**, 58408-52-9; **7**, 58408-53-0; **8**, 58408-54-1; **9**, 58408-55-2; **10**, 58408-56-3; **11**, 58408-57-4; **12**, 58408-58-5; **13**, 58408-59-6; **14**, 58408-60-9; **17**, 58408-61-0; 1-chloro-9-methyl-9-azabicyclo[3.3.1]nonane, 51209-45-1; phenol, 108-95-2; ethanol, 64-17-5; 1-propanol, 71-23-8; 1-butanol, 71-36-3; 2-methyl-1-propanol, 78-83-1; 2-methyl-1-butanol, 137-32-6; 3-methyl-1-butanol, 123-51-3; 2,2-dimethyl-1-propanol, 75-84-3; 2-propanol, 67-63-0; 2-butanol, 78-92-2; 2-pentanol, 6032-29-7; 3-pentanol, 584-02-1; 2-methyl-2-propanol, 75-65-0; 2-methyl-2-butanol, 75-85-4.

Supplementary Material Available. Bar graphs of the spectra of the butyl ethers (**3**, **5**, **10**, and **13**) and phenyl ether **17** and tables of metastable peaks and ^1H NMR spectral data for compounds **1–14** (8 pages). Ordering information is given on any current masthead page.

References and Notes

(1) Inquiries concerning this manuscript should be directed to the author at the Department of Chemistry, University of California, Berkeley, Calif. 94720.

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(6) See paragraph at end of paper regarding supplementary material.

(7) J. Collin, *Bull. Soc. R. Sci. Liege*, **25**, 441 (1956).

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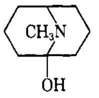
(13) A table of metastable peaks found in the mass spectra of α-amino bridgehead ethers **1–14** appears in the microfilm edition; see paragraph at end of paper regarding supplementary material.

(14) K. Biemann, J. Seibl, and F. Gapp, *J. Am. Chem. Soc.*, **83**, 3795 (1961); D. G. I. Kingston, J. T. Bursey, and M. M. Bursey, *Chem. Rev.*, **74**, 215 (1974).

(15) The hydrogen transfer to oxygen is represented as taking place with oxonium tautomer g′ since (1) it is well established as an intermediate in the fragmentation process in the mass spectra of ethers [C. Djerassi and C. Fenslau, *J. Am. Chem. Soc.*, **87**, 5757 (1965)] and (2) although tautomeric form A is greatly preferred over B,[5] tautomer B plays an important (frequently dominant) role in the chemical reactions of the equilibrium mixture [H. O. Krabbenhoft, Ph.D. Thesis, University of Michigan, Ann Arbor, Mich., 1974]. Furthermore, the g ⇄ g′ tautomerism is entirely intramolecular and does not require any shift of hydrogen; in this regard the situation resembles that of resonance.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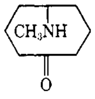
B

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(19) Other examples of Wagner–Meerwein shifts occurring in the mass spectrometer include F. Komitsky, Jr., J. E. Gurst, and C. Djerassi, *J. Am. Chem. Soc.*, **87**, 1398 (1965), and D. C. DeJongh and S. R. Shrader, *ibid.*, **88**, 3881 (1966).

(20) For related examples see P. G. Gassman, *Acc. Chem. Res.*, **3**, 26 (1970), and H. H. Wasserman and E. Glazer, *J. Org. Chem.*, **40**, 1505 (1975).

(21) The base peak actually occurs at *m/e* 43; the *m/e* 94 peak is 10% as intense as the *m/e* 43 peak. The peaks at *m/e* 136, 122, 109, 108, 82, 81, 79, 68, and 67 are due to daughter ions of the *m/e* 137 ion [H. O. Krabbenhoft, Ph.D. Thesis, University of Michigan, Ann Arbor, Mich., 1974].

(22) A table of NMR spectral data for α-amino bridgehead ethers **1–14** appears in the microfilm edition; see paragraph at end of paper regarding supplementary material.

(23) Satisfactory combustion analyses (±0.23% for C, H, N) were obtained for each compound.

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