Mass Spectrometry in Structural and Stereochemical Problems. CLXXIII.[1] The Electron Impact Induced Fragmentations and Rearrangements of Trimethylsilyl Esters of ω-Phenoxyalkanoic Acids[2]

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In connection with the computer-assisted interpretation of mass spectra, studies of the mass spectra of bifunctional compounds are needed in order to determine whether the electron impact induced fragmentations are characteristic of each functional group or whether they reflect some interaction of the two groups. In view of the wide applications of trimethylsilyl derivatives in combined vapor phase chromatography–mass spectrometry, the mass spectra of a series of trimethylsilyl ω-phenoxyalkanoates were investigated. These mass spectra exhibit four prominent decomposition modes (see Table I) which depend upon the interaction of the phenyl ether and silyl ester moieties. The mass spectra of some phenyl (II), benzyloxy (III), and alkoxy (IV) analogs, as well as some methyl ester analogs (V) illustrate the necessity of the presence of a heteroatom in *both* of the functional groups at the ends of the polymethylene chain in order to observe the appropriate interactions. Since these seem to be rather independent of chain length, it is suggested that charge transfer involving the heteroatoms is responsible for maintaining the heteroatoms in close proximity, thus resulting in coiling of the polymethylene chain. The cleavages characteristic of each separate functionality in these compounds (I–V) are also discussed.

Recently,[4] a program has been initiated in our laboratories on the application of artificial-intelligence computer techniques to the interpretation of mass spectra. Although the incipient stages of the program involved the establishment of rules for computer-assisted interpretation of the mass spectra of monofunctional compounds (*e.g.*, aliphatic ketones[4b]), the success to date has stimulated an anticipation of the problems involved in establishing rules for polyfunctional compounds. It is of particular importance to determine whether two functional groups in the same molecule will direct fragmentation patterns independent of one another, or whether their combination will cause unique sequences resulting from interaction of the two moieties. Obviously, the latter situation will necessitate significant variations in the "rules" for computer-assisted mass spectra interpretation. There already exist several documented instances where introduction of a second functional group into a monofunctional compound alters the independent fragmentation patterns, and there are a few striking examples of such interactions even when the functional groups are separated by long polymethylene chains.[5-10] A series of investigations into the mass spectral behavior of bifunctional compounds has been under way at Stanford[11-13] and the research described in this paper concerns still another group of such bifunctional compounds.

This study describes the electron impact induced fragmentation of a series of trimethylsilyl ω-phenoxyalkanoates (I) and some related species (II–V). Not

$C_6H_5O(CH_2)_nCO_2Si(CH_3)_3$
I (n = 1–6, 10)

$C_6H_5(CH_2)_nCO_2Si(CH_3)_3$
II (n = 2, 3)

$C_6H_5CH_2O(CH_2)_3CO_2Si(CH_3)_3$
III

$RO(CH_2)_nCO_2Si(CH_3)_3$
IV (n = 3, 4; R = CH_3)
(n = 3; R = C_2H_5)

$C_6H_5O(CH_2)_nCO_2CH_3$
V (n = 2, 3)

only are these results important for artificial intelligence studies, but there exist many other attractive reasons for investigating the mass spectra of this series. First, the ultimate intention of establishing a completely automated system capable of separating the components of a mixture by vapor phase chromatography, recording the mass spectrum of each component, and interpreting each spectrum with the aid of a computer necessitates establishing the "fragmentation rules" for derivatives particularly suited to vapor phase chromatographic separation. Trimethylsilyl derivatives have been the most popular choice as derivatives for facilitating vapor phase chromatographic separation of nonvolatile materials.[14] Second, a significant amount of research on the mass spectra of trimethylsilyl derivatives has been previously[9,15,16] accomplished at Stanford, and it is therefore attractive to investigate another type of trimethylsilyl derivative, trimethylsilyl esters. Third, these previous investigations[9,16] of

(1) For paper CLXXII, see M. K. Strong and C. Djerassi, *Org. Mass Spectrom.*, **2**, 631 (1969).

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(3) (a) National Science Foundation Predoctoral Fellow (1966–1967); National Institutes of Health Predoctoral Fellow (1967–1969). (b) National Institutes of Health International Postdoctoral Fellow (1965–1966) on leave from University College, Dublin.

(4) (a) J. Lederberg, G. L. Sutherland, B. G. Buchanan, E. A. Feigenbaum, A. V. Robertson, A. M. Duffield, and C. Djerassi, submitted for publication (b) A. M. Duffield, A. V. Robertson, C. Djerassi, G. L. Sutherland, E. A. Feigenbaum, and J. Lederberg, submitted for publication.

(5) A. Mandelbaum and K. Biemann, *J. Amer. Chem. Soc.*, **90**, 2975 (1968).

(6) W. J. Richter, D. H. Smith, and A. L. Burlingame, Abstracts, The Sixteenth Conference on Mass Spectrometry of the American Society for Testing Materials, Pittsburgh, Pa., 1968, p 186; W. J. Richter and A. L. Burlingame, *Chem. Comm.*, 1158 (1968).

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(8) (a) P. Capella and C. M. Zorzut, *Anal. Chem.*, **40**, 1458 (1968). (b) G. Eglinton, D. H. Hunneman, and A. McCormick, *Org. Mass Spectrom.*, **1**, 593 (1968).

(9) J. Diekman, J. B. Thomson, and C. Djerassi, *J. Org. Chem.*, **33**, 2271 (1968).

(10) J. A. McCloskey, R. N. Stillwell, and A. M. Lawson, *Anal. Chem.*, **40**, 233 (1968).

(11) R. Brandt and C. Djerassi, *Helv. Chim. Acta*, **51**, 1750 (1968).

(12) A. J. Weinheimer, R. J. Spangler, and C. Djerassi, to be submitted for publication.

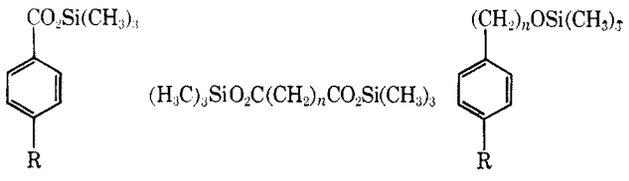
(13) R. T. Gray, M. Ikeda, and C. Djerassi, to be submitted for publication.

(14) A. E. Pierce, "Silylation of Organic Compounds," Pierce Chemical Company, Rockford, Ill., 1968, Chapter 2.

(15) J. Diekman and C. Djerassi, *J. Org. Chem.*, **32**, 1005 (1967).

(16) J. Diekman, J. B. Thomson, and C. Djerassi, *ibid.*, **32**, 3904 (1967).

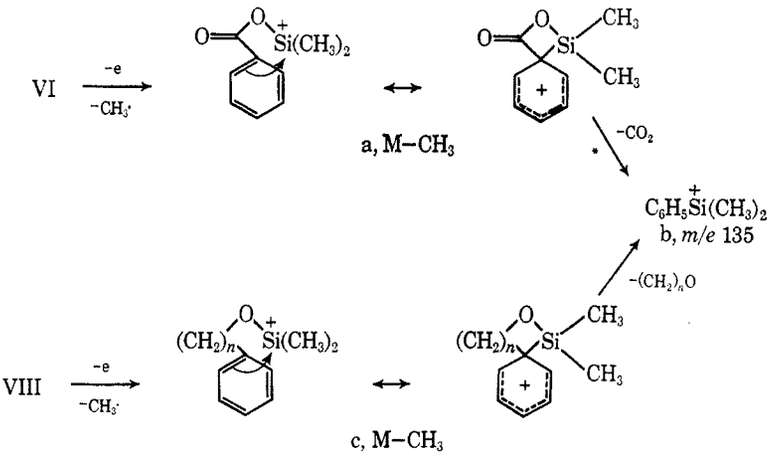
trimethylsilyl derivatives have provided a number of novel and interesting electron impact induced alkyl migrations,[17] and it was anticipated that trimethylsilyl esters would likewise exhibit new examples of these migrations. At present, there exist very few documented investigations of the mass-spectral behavior of trimethylsilyl esters.[18] Teeter[19] has reported the mass spectra of a number of substituted trimethylsilyl benzoates (VI) as well as the spectra of a number of tri-



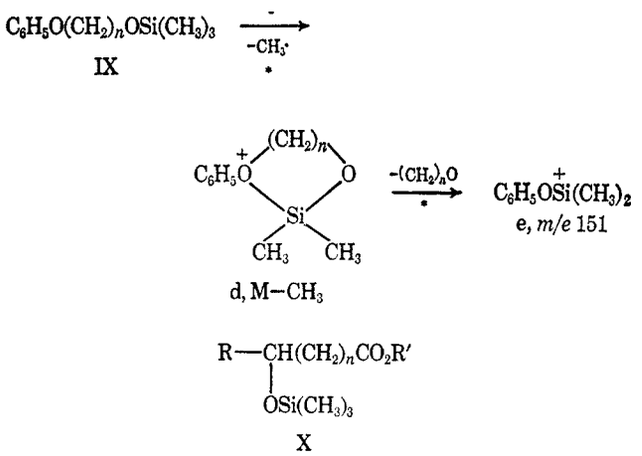
VI VII VIII

phenoxypolymethylene trimethylsilyl esters (IX). These three rearrangement processes (a → b, c → b, and d → e) stimulated a search for alkyl migrations in the fragmentation of terminally substituted phenoxypolymethylene trimethylsilyl esters (I). Parenthetically, it may be noted that there are a number of recent publications[6,8,21,22] which discuss the fragmentation patterns of the trimethylsilyl derivatives (ethers) of hydroxypolymethylene alkyl esters (X), but they have no important bearing on the present discussion.

The presently described investigation and elucidation of the electron impact induced fragmentations of some phenoxypolymethylene trimethylsilyl esters (I) and related compounds (II–V) employ deuterium labeling, high resolution mass measurements, and computer-assisted metastable peak evaluation[23] in order to assign fragmentation patterns.



methylsilyl derivatives of amino acids. More recently, McCloskey and collaborators[7] discussed the mass spectra of some bistrimethylsilyl polymethylene esters (VII). It is important to note that both of these publications[7,19] contain interesting examples of electron impact induced alkyl migrations involving the trimethylsilyl group. McCloskey[7] presented important evidence for the coiling of chains in molecules, thus allowing the interaction of otherwise remote sites (the terminal trimethylsilyl ester functions). Teeter[19] demonstrated that the intense *m/e* 135 peak in the mass spectrum of trimethylsilyl benzoate (VI, R = H) arose by elimination of carbon dioxide from the M − CH_3 species (a → b).[20] This process (a → b) is analogous to the rearrangement c → b,[16] with elimination of formaldehyde, of the M − CH_3 species in the electron impact induced behavior of benzyl trimethylsilyl ester (VIII, n = 1). It is also similar to the abundant rearrangement ion (e) generated[9] from the M − CH_3 fragments (d) in the fragmentation of terminally substituted



Discussion

As was pointed out in the introduction, the mass spectra (see for example, Figures 1–4) of a series of terminally substituted phenoxypolymethylene trimeth-

(17) For a complete review, see P. Brown and C. Djerassi, *Angew. Chem. Intern. Ed. Engl.*, **6**, 477 (1967).

(18) See ref 14, p 39.

(19) R. M. Teeter, Abstracts, Tenth Conference on Mass Spectrometry of the American Society for Testing Materials, New Orleans, La., 1962, p 51.

(20) The presence of a metastable ion for a given process is indicated in this paper by an asterisk (*) over the arrow in the fragmentation scheme.

(21) G. Eglinton, D. H. Hunneman, and K. Douraghi-Zadeh, *Tetrahedron*, **24**, 5929 (1968).

(22) G. Casparrini, M. G. Horning, and E. C. Horning, *Anal. Lett.*, **1**, 481 (1968).

(23) We wish to thank Mr. R. A. Stillman of this laboratory for writing this program.

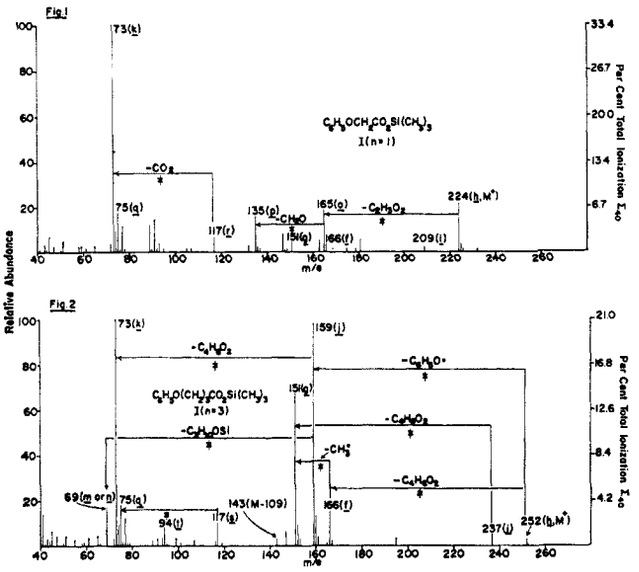


Figure 1.—Mass spectrum of trimethylsilyl phenoxyacetate (I, n = 1).

Figure 2.—Mass spectrum of trimethylsilyl 4-phenoxybutyrate (I, n = 3).

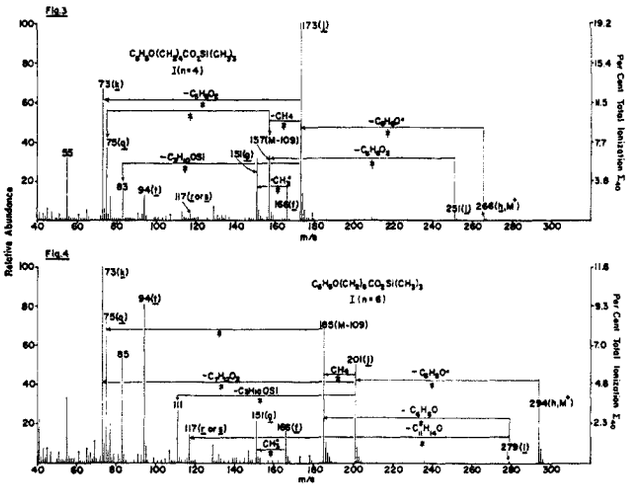


Figure 3.—Mass spectrum of trimethylsilyl 5-phenoxypentanoate (I, n = 4).

Figure 4.—Mass spectrum of trimethylsilyl 7-phenoxyheptanoate (I, n = 6).

ylsilyl esters (I, n = 1–6,10) were recorded in order to assess the influence of each functional group (the trimethylsilyl ester and the phenyl ether) upon each other in the electron impact induced fragmentation of the parent compound I. It was also pointed out that, because of the paucity of literature concerning the mass spectral behavior of trimethylsilyl esters, it is necessary to present a detailed discussion of their "characteristic" fragmentation patterns. The mass spectra of these phenoxypolymethylene trimethylsilyl esters (I) reveal some very interesting fragmentation schemes which result from interaction of the terminal functional groups, and these fragmentations are discussed prior to the "characteristic" trimethylsilyl ester fragmentations.

Fragmentation Patterns Resulting from Interaction of the Phenyl Ether and Trimethylsilyl Ester Moieties. The *m/e* 166 (f) and 151 (g) peaks.—The mass spectra (for examples, see Figures 1–4) of all of the phenoxypolymethylene trimethylsilyl esters (I) recorded in this study exhibit a peak at *m/e* 166 (see Table I), and high resolution mass measurements indicate that this peak corresponds to a fragment ion of composition $C_9H_{14}OSi$. A fragment ion having the same elemental composition was found previously[9] in the mass spectra of a series of phenoxypolymethylene trimethylsilyl ethers (IX) and was assumed to arise from the molecular ion by migration of the trimethylsilyl moiety to the phenoxy-oxygen atom with expulsion of the central portion of the molecule. An analogous fragmentation scheme (I → h → f) involving transfer of the trimethylsilyl group and expulsion of the central portion of the compound yields this same *m/e* 166 peak in the case of the trimethylsilyl esters (I). This fragmentation scheme is supported by large metastable peaks when n = 2 and n = 3. In accord with this proposed scheme is the observation that those compounds (see Table II) where deuterium atoms are incorporated into the *ortho* and *para* positions of the phenoxy ring (XI and XIV), the *m/e* 166 peak shifts to *m/e* 169. Those compounds which are labeled only in the methylene chain (see Table II) exhibit no shift of the *m/e* 166 peak in their mass spectra. It is clear, therefore, that no reciprocal hydrogen transfers are involved in this fragmentation.

At 70-eV ionizing energy, there appears to be no obvious dependence between the abundance of this *m/e* 166 peak (f) and the length of the methylene chain (see Table I). At low (12 eV) voltage, this peak increases substantially in per cent total ionization and also shows a preference for a 1,5 (n = 2) and 1,6 (n = 3) shift of the trimethylsilyl group. A similar situation had been encountered earlier[9] in the mass spectra of the phenoxytrimethylsilyl ethers (IX). Nevertheless, it is rather remarkable that the *m/e* 166 peak remains quite significant (37% relative abundance) even in the case of the trimethylsilyl ester of 11-phenoxyundecanoic acid (I, n = 10); this observation suggests that the molecular ion (h) of these molecules (I) is coiled in such a way as to permit the phenyl ether and trimethylsilyl ester moieties to remain close to one another. It is con-

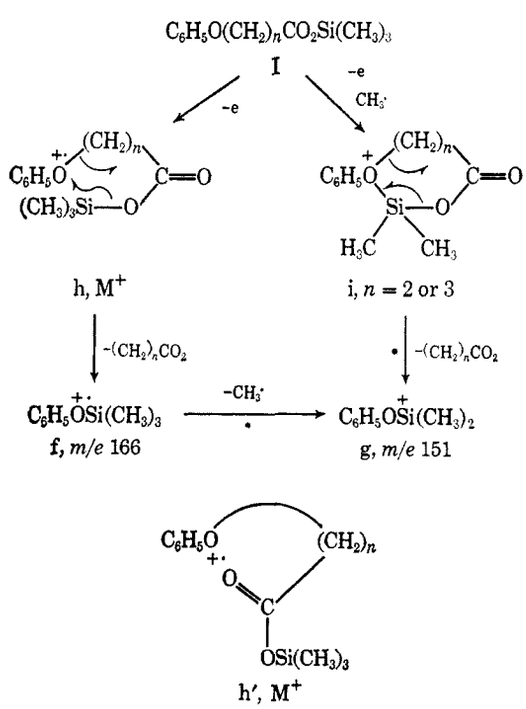


TABLE I

ABUNDANCE OF THE REARRANGEMENT PEAKS *m/e* 166 (f) AND 151 (g), M − 93 (j), AND M − 109 IN THE MASS SPECTRA OF THE PHENOXYPOLYMETHYLENE TRIMETHYLSILYL ESTERS (I), $C_6H_5O(CH_2)_nCO_2Si(CH_3)_3$

	m/e 166				*m/e* 151				M − 93 (j)					M − 109			
	70 eV		12 eV		70 eV		12 eV		70 eV		12 eV			70 eV		12 eV	
	Σ_{40},	RI,[a]	Σ_{40},	RI,[a]	Σ_{40},	RI,[a]	Σ_{40},	RI,[a]	Σ_{40},	RI,[a]	Σ_{40},	RI,[a]		Σ_{40},	RI,[a]	Σ_{40},	RI,[a]
n	%	%	%	%	%	%	%	%	*m/e*	%	%	%	%	*m/e*	%	%	%	%
1	0.7	2	0.3	1	1.3	4	0.0	0	131	0.0	0	0.0	0	115	0.0	0	0.0	0
2	4.1	27	11.7	39	15.1	100	4.8	16	145	5.7	38	12.6	42	129	3.8	25	4.5	15
3	3.1	15	14.4	27	14.1	67	7.0	13	159	20.6	98	53.5	100	143	0.6	3	0.0	0
4	1.2	6	6.5	10	6.1	32	0.6	1	173	19.2	100	64.9	100	157	6.3	33	2.6	4
5	1.3	10	3.2	7	3.3	25	0.0	0	187	13.3	100	45.5	100	171	9.7	73	9.6	21
6	1.9	16	4.8	22	2.4	21	0.4	2	201	5.8	50	18.8	87	185	7.9	68	10.8	50
10	4.2	37	6.2	15	2.5	22	0.0	0	257	6.3	55	11.1	27	241	8.0	70	1.2	3

[a] RI = Relative intensity of base peak.

TABLE II

SHIFTS OF THE REARRANGEMENT PEAKS IN THE MASS SPECTRA OF THE DEUTERIUM-LABELED PHENOXYPOLYMETHYLENE TRIMETHYLSILYL ESTERS (I)

	Fragment[a]					
Compd	f, *m/e*[b]	g, *m/e*[b]	j, *m/e*[b]	[M − (90 + 93)], *m/e*[b] (%)	M − C_7H_9O, *m/e*[b] (%) 70 eV	M − C_7H_9O, *m/e*[b] (%) 12 eV
2,4,6-d_3-$C_6H_2D_3OCH_2CO_2Si(CH_3)_3$ (XI)	166 → 169	151 → 154	...	...	...	...
$C_6H_5OCH_2CH_2CD_2CO_2Si(CH_3)_3$ (XII)	166 → 166	151 → 151	159 → 161	69 → 70 (*ca.* 74) 69 → 71 (*ca.* 26)	*c*	*c*
$C_6H_5OCH_2CD_2CH_2CO_2Si(CH_3)_3$ (XIII)	166 → 166	151 → 151	159 → 161	69 → 70 (*ca.* 25) 69 → 71 (*ca.* 75)	*c*	*c*
2,4,6-d_3-$C_6H_2D_3O(CH_2)_3CD_2CO_2Si(CH_3)_3$ (XIV)	166 → 169	151 → 154	173 → 175	83 → 84 (*ca.* 17) 83 → 85 (*ca.* 83)	157 → 159	157 → 159
$C_6H_5O(CH_2)_2CD_2CH_2CO_2Si(CH_3)_3$ (XV)	166 → 166	151 → 151	173 → 175	83 → 84 (*ca.* 25) 83 → 85 (*ca.* 75)	157 → 158 (36) 157 → 159 (64)	157 → 158 (41) 157 → 159 (59)
$C_6H_5OCH_2CD_2(CH_2)_2CO_2Si(CH_3)_3$ (XVI)	166 → 166	151 → 151	173 → 175	83 → 84 (*ca.* 40) 83 → 85 (*ca.* 60)	157 → 158 (24) 157 → 159 (76)	157 → 158 (20) 157 → 159 (80)

[a] In each case, the *m/e* value of the unlabeled fragment is shown being shifted to its *m/e* value for the indicated labeled analog. [b] Corrected for isotope abundance and calculated deuterium isotope composition. [c] Peak is too small to permit interpretation of the labeling data.

ceivable that a charge transfer between these functional groups could provide a means of holding these moieties in near proximity (h′).[24]

The increase in the contribution of the *m/e* 166 peak to the total ion current at 12 eV (see Table I) suggests that at higher electron voltages it fragments further to some other species; in fact, in all cases a large metastable ion is observed at *m/e* 137.4 (calcd $151^2/166$ = 137.4) corresponding to cleavage of a methyl group from f to yield the even-electron species g (*m/e* 151). The structure of this ion (g) is also supported by high resolution mass measurements ($C_8H_{11}OSi$) and deuterium-labeling experiments (see Table II).

A computer-assisted analysis[23] of all of the metastable peaks observed in the mass spectra of this series (I) points out that when $n = 2$ and $n = 3$ (but not in any of the other homologs) there exists a metastable ion corresponding to the genesis of the *m/e* 151 peak (g) from an M − CH_3 (i) precursor. An analogous fragmentation scheme was observed in the case of the trimethylsilyl ethers (IX), and it is suggested that the M − CH_3 ion (i) exists in a cyclic (6- or 7-membered ring) structure from which the *m/e* 151 ion g is generated by expulsion of the central part of the molecule.

M − 93 Rearrangement Peak.—The mass spectra of all of the ω-phenoxypolymethylene trimethylsilyl esters (I, see Figures 2–4) except the 2-phenoxyacetic acid derivative ($n = 1$, see Figure 1) exhibit an intense rearrangement peak (see Table I) resulting from the electron impact induced elimination of the terminal phenoxy group. There is abundant evidence substantiating the participation of the terminal ends of these molecules (I, $n = 2$–6, 10) in this important fragmentation process, which accounts for the base peak in the 70-eV spectra of trimethylsilyl 5-phenoxypentanoate ($n = 4$, see Figure 3) and 6-phenoxyhexanoate ($n = 5$). At 12 eV, this peak is outstanding in all of the spectra and accounts for more than 40% of the total ion current when $n = 3$, 4, and 5 (Table I). The substantiating evidence includes the following: first, the high resolution mass measurements in each case show the loss of a C_6H_5O radical; second, deuterium labeling (see Table II) verifies loss of the phenyl group in this process [the phenyl-labeled analog (XIV) exhibits cleavage of a $C_6H_2D_3O$ species (mass 96) whereas those analogs labeled in the methylene chain (XII, XIII, XV, and XVI) exhibit fission of an unlabeled C_6H_5O radical]; third, elimination of the phenoxy moiety without participation of the ester function would yield an energetically unfavorable primary radical (j″); fourth, in all instances ($n = 2$–6, 10) a very intense metastable peak supports the formation of this M-$C_6H_5O\cdot$ ion from the molecular ion; and finally, both high- (70 eV) and low- (12 eV) voltage spectra (see Table I) indicate some preference for a 3-, 4-, or 5-membered methylene chain in this fragmentation scheme, thus suggesting the possibility of at least a cyclic transition state and more likely a cyclic product ion. In such cases, a 5-, 6-, and 7-membered ring ($n = 3$, 4, and 5, respectively) might be more easily generated.

In the previously reported[9] mass spectra of some phenoxypolymethylene trimethylsilyl ethers (IX), there was reported a fragmentation involving bonding of the phenoxy radical to the charged siloxy-oxygen atom. This observation, coupled with the above experimental evidence, suggests a similar fragmentation scheme yielding an oxonium ion species j for the trimethylsilyl

(24) R. Brandt and C. Djerassi (see ref 11) have postulated a similar arrangement in their work on the mass spectra of some α-substituted tetrahydrofurans.

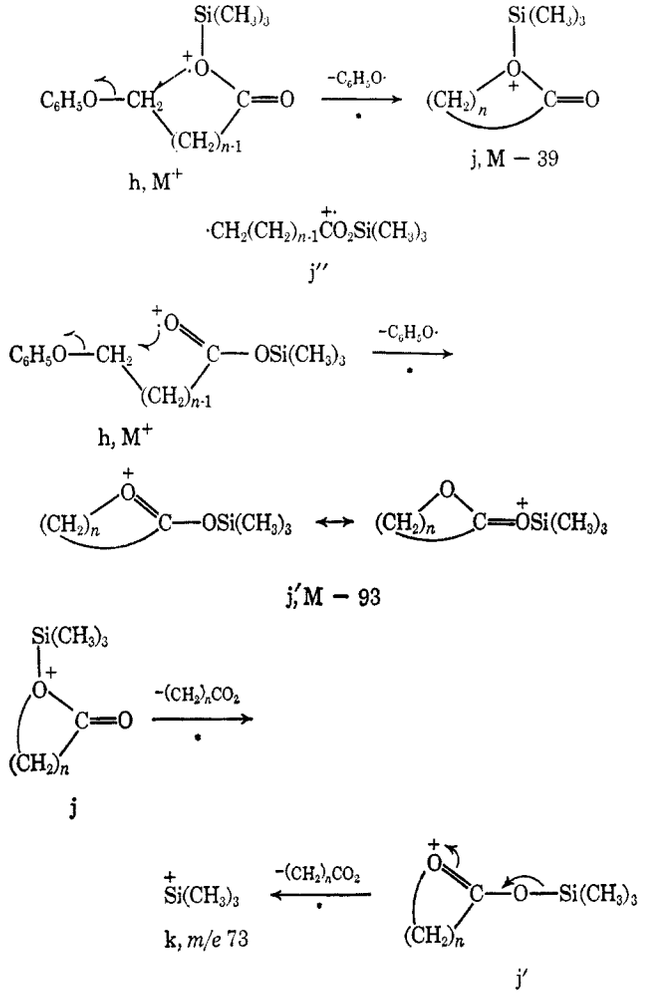
TABLE III

ABUNDANCE OF CERTAIN PEAKS "CHARACTERISTIC" OF PHENOXYPOLYMETHYLENE TRIMETHYLSILYL ESTERS (I), $C_6H_5O(CH_2)_nCO_2Si(CH_3)_3$

		M⁺ (i)				M − 15 (h)				*m/e* 75 (q)				*m/e* (73 (k)				*m/e* 94 (t)			
		70 eV		12 eV		70 eV		12 eV		70 eV		12 eV		70 eV		12 eV		70 eV		12 eV	
n	*m/e*	Σ_{40}, %	RI,[a] %	Σ_{40}, %	RI,[a] %	*m/e*	Σ_{40}, %	RI,[a] %	Σ_{40}, %	RI,[a] %	Σ_{40}, %	RI,[a] %	Σ_{40}, %	RI,[a] %	Σ_{40}, %	RI,[a] %	Σ_{40}, %	RI,[a] %	Σ_{40}, %	RI,[a] %	Σ_{40}, %	RI,[a] %
1	224	6.7	21	37.6	100	209	0.7	6	1.9	2	5.7	17	0.4	1	33.4	100	13.9	37	3.7	11	0.8	2
2	238	6.2	41	30.0	100	223	2.3	15	3.9	13	6.8	45	0.3	1	12.1	80	0.6	2	4.7	31	9.3	31
3	252	0.6	3	3.2	6	237	1.1	5	2.1	4	3.8	18	0.0	0	21.0	00	2.1	4	1.7	8	1.1	2
4	266	0.4	2	1.9	3	251	0.8	4	0.6	1	7.1	27	0.6	1	12.9	67	1.3	2	2.5	13	0.6	1
5	280	2.3	17	14.1	31	265	0.3	2	0.5	1	8.0	60	0.5	1	12.8	96	1.8	4	5.2	39	2.7	6
6	294	3.2	28	21.6	100	279	0.1	1	0.4	2	8.4	72	0.9	4	11.6	100	2.2	10	9.4	81	6.3	29
10	350	11.4	100	41.0	100	335	0.9	8	0.0	0	3.4	30	2.9	7	3.1	27	2.5	6	3.5	31	6.6	16

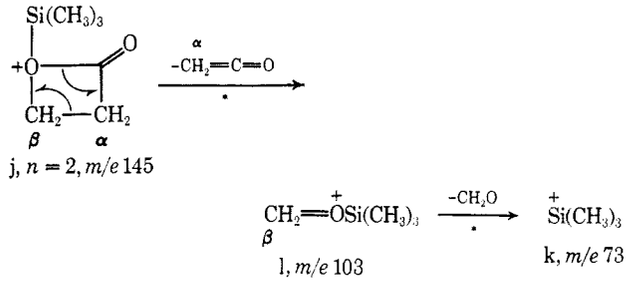
[a] RI = Relative intensity of base peak.

ester derivatives (I). Equally plausible, however, is displacement of the phenoxy radical by the carbonyl function to yield the product ion j′. In this case, j′ is seemingly energetically more favorable than j because of its resonance stabilization, and it is impossible to differentiate between these two species (j′ and j) by high-resolution mass measurements or deuterium-labeling experiments.



The significant increase in the contribution of the M − C_6H_5O ion (j or j′) to the total ion current at 12 eV (see Table I) suggests that this ion further decomposes (at 70 eV) to generate other fragment ions. In all cases, except n = 2 (the trimethylsilyl ester of 3-phenoxypropionic acid), there exists a large metastable peak corresponding to cleavage of a lactone moiety from j or j′ to yield the trimethylsilyl cation k (*m/e* 73). This peak (*m/e* 73), which is found in the mass spectra of practically all trimethylsilyl derivatives,[16,25] disappears when the spectra are recorded at low voltage.

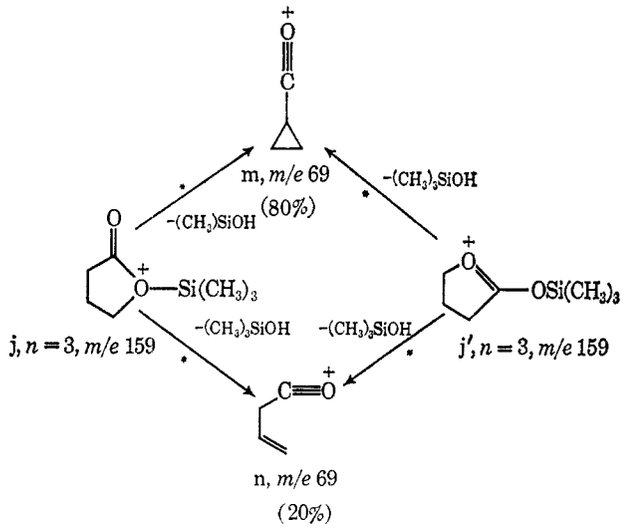
The decomposition of the M − C_6H_5O ion (j, *m/e* 145) in the mass spectrum of the trimethylsilyl ester of 3-phenoxypropionic acid (I, n = 2) appears to involve a fragmentation mode unique to this particular compound. A large metastable peak at *m/e* 73.2 (calcd $103^2/145 = 73.2$), as well as high-resolution mass measurements, suggest elimination of ketene from j to yield the ion l of mass 103 (Σ_{40} = 10.1, 67% relative abundance). This species (l) subsequently loses formaldehyde to yield the trimethylsilyl cation (k, *m/e* 73, Σ_{40} = 12.1) as is indicated by an intense metastable peak at *m/e* 51.8 (calcd $73^2/103 = 51.7$). Neither the *m/e* 103 peak nor any of its homologs (*m/e* 117, 131, etc.) are important in the mass spectra of the remaining trimethylsilyl ester derivatives (I, n = 3–6, 10). Since it is difficult to visualize a plausible path whereby this ion (l, *m/e* 103) could be generated from the isomeric ion j′ of mass 145, it is reasonable to assume that at least in the propionic acid case (I, n = 2), the ion of mass 145 should be represented by j rather than j′.



In every spectrum except that of the 2-phenoxyacetic acid (n = 1, Figure 1) and 3-phenoxypropionic acid (n = 2) derivatives, there is a peak of medium intensity (*m/e* 69 in Figure 2, *m/e* 83 in Figure 3, and *m/e* 111 in Figure 4) which, according to high-resolution mass measurements and metastable evidence, is generated by loss of trimethylsilanol [$(CH_3)_3SiOH$] from the M − C_6H_5O ion (j or j′). Labeling experiments (see Table II) indicate that the hydrogen-atom loss from the methylene chain in this process occurs in a random manner. Incorporation of deuterium atoms into the C-2 (XII) and C-3 (XIII) positions of the trimethylsilyl ester of 4-phenoxybutyric acid (I, n = 3) indicates that approximately 80% of the hydrogen lost in the expelled trimethylsilanol originates in the C-2 position and approximately 20% in the C-3 position. Although

(25) (a) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, Inc., San Francisco, Calif., 1967, Chapter 14-3; (b) see ref 14, p 35.

other formulations are possible, this process may be represented by elimination of trimethylsilanol from the M − C_6H_5O (j or j′, *m/e* 159) species to yield the cyclopropyl oxonium species m (*m/e* 69), and elimination of trimethylsilanol to yield the β,γ-unsaturated oxonium ion n (*m/e* 69), in a 4:1 ratio, respectively. In the case of the trimethylsilyl ester of 5-phenoxypentanoic acid (I, *n* = 4), labeling experiments (see Table II) indicate that the expelled hydrogen atom originates approximately 17% in the C-2 position, 25% in the C-3 position, and 40% in the C-4 position.[26] In the case of both labeled analogs (*n* = 3 and 4), it is impossible to determine whether these percentages differ at 12 eV, because these peaks are extremely weak under such conditions.

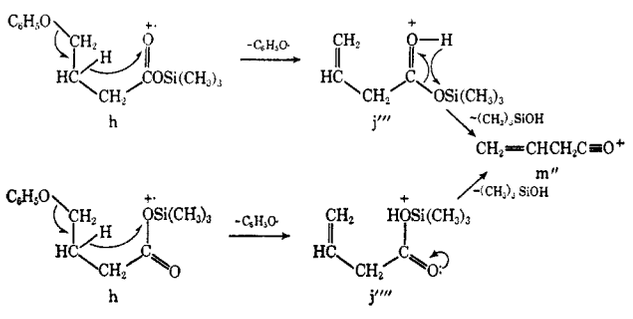


Other Rearrangement Species.—The mass spectra of all of the phenoxypolymethylene trimethylsilyl ester derivatives (I), except that of the 2-phenoxyacetic acid derivative (*n* = 1), exhibit a peak (see Table I) at M − C_7H_9O (M − 109), whose mode of genesis is very difficult to elucidate. Except for the case of trimethylsilyl 4-phenoxybutyrate (I, *n* = 3), where this peak is extremely small, there is metastable evidence for the production of this ion by two completely different fragmentation modes, both of which result in the same or isomeric M − C_7H_9O ions (as determined by high resolution mass measurements). One process involves elimination of methane from the M − C_6H_5O ion (j or j′), thus constituting a rearrangement process, and the other involves elimination of a C_6H_6O species, most likely phenol, from the M − CH_3 ion (i). The fact that this ion is practically nonexistent in the spectrum of the trimethylsilyl ester of 4-phenoxybutyric acid (see Table I) may be partially attributed to the preferential formation of other ions by the precursors of the M − 109 species. For instance, the M − CH_3 ion (i), which is a precursor of the M − 109 species, decomposes to g (*m/e* 151) in this case (*n* = 3) to a much greater extent than in most other cases.

The fact that two processes contribute to the same peak makes interpretation of the deuterium-labeling experiments practically impossible, especially when these experiments show (see Table II) that these two processes apparently contribute to varying extents at differing ionizing energies. About all that can be concluded is that the elimination of phenol from the M − CH_3 ion (i) most likely involves random abstraction of a hydrogen atom from the methylene chain. Similarly, loss of methane from the M − C_6H_5O ion (j or j′) probably involves ejection of a silyl-methyl group and random abstraction of a hydrogen atom as well.

All of the previously discussed electron impact induced rearrangement processes which involve participation of the terminal functional groups in the series of trimethylsilyl esters of phenoxypolymethylene acids (I) have been found to be very insignificant (see Table I) in the mass spectrum (Figure 1) of trimethylsilyl 2-phenoxyacetate (1, *n* = 1). Inspection of this spectrum (Figure 1) reveals a unique alkyl migration fragmentation scheme. The *m/e* 165 peak (Σ_{40} = 6.0), which shifts to *m/e* 168 in the spectrum of 2′,4′,6′-d_3-trimethylsilyl-2-phenoxyacetate (XI), represents a fragment ion whose elemental composition was determined by high-resolution mass measurements to be $C_9H_{13}OSi$. These results, as well as the metastable peak at *m/e* 121.6 (calcd 165²/224 = 121.5) suggest a fragmentation process involving concomitant loss of a silyl-methyl group and of carbon dioxide to yield the fragment ion o. This unusual scheme, which includes cleavage of two bonds bound to the same silicon atom, gives a product ion which can be stabilized by participation of the phenyl ring (o′). The increased contribution of this *m/e* 165 peak to the total ion current at 12 eV (Σ_{40} = 15.4, 41% relative abundance) and a metastable peak at *m/e* 110.5 (calcd 135²/165 = 110.5) provide evidence for the further decomposition of this species (o or o′), involving rearrangement of the dimethylsilyl moiety

(26) Another conceivable means of generating the M − 93 ion involves site-specific hydrogen transfer to the carbonyl-oxygen (j‴, for *n* = 3) or the silyl-oxygen atom (j⁗, for *n* = 3) with concomitant expulsion of the ω-phenoxy radical to yield the terminally unsaturated ions, j‴ or j⁗ (for *n* = 3) [see S. Meyerson, *Int. J. Mass Spectry. Ion Phys.*, **1**, 309 (1968)]. Although these schemes h → j‴ and h → j⁗ are possible, the deuterium-labeling experiments (see Table II) show that they certainly do not predominate. Loss of trimethylsilanol from j‴ (*n* = 3) would most likely involve fission of the C-3 hydrogen (j‴ or j⁗ → m″) which has been transferred to the carbonyl oxygen (j‴) or silyl oxygen (j⁗). However, only 20% of this hydrogen loss involves the C-3 hydrogen atom (see Table II). Similarly in the case of the 5-phenoxytrimethylsilyl derivative (*n* = 4), 40% of the hydrogen loss occurs from the C-4 position, thus showing that the hydrogen transfer is not site specific.



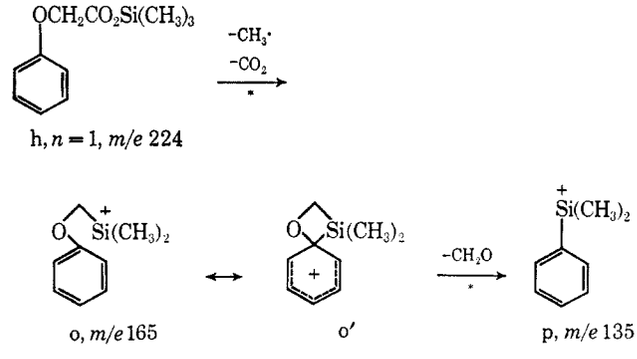


TABLE IV
SHIFTS OF THE "CHARACTERISTIC PEAKS" IN THE MASS SPECTRA OF THE DEUTERIUM-LABELED PHENOXYPOLYMETHYLENE TRIMETHYLSILYL ESTERS (I)

Compd	Fragment[a] q, m/e[b] (%)	r and s, m/e[b] (%)	t, m/e[b] (%)
2,4,6-d_3-$C_6H_2D_3OCH_2Si(CH_3)_3$ (XI)	75 → 75 (74)	117 → 117	94 → 97
	75 → 76 (26)		
$C_6H_5OCH_2CH_2CD_2CO_2Si(CH_3)_3$ (XII)	75 → 75 (46)	117 → 117 (<10)	94 → 94 (80)
	75 → 76 (54)	117 → 119 (>90)	94 → 95 (20)
$C_6H_5OCH_2CD_2CH_2CO_2Si(CH_3)_3$ (XIII)	75 → 75 (90)	117 → 117	94 → 94 (50)
	75 → 76 (10)		94 → 95 (50)
2,4,6-d_3-$C_6H_2D_3OCH_2CH_2CH_2CD_2CO_2Si(CH_3)_3$ (XIV)	75 → 75 (50)	c	94 → 97 (95)
	75 → 76 (50)		94 → 98 (5)
$C_6H_5OCH_2CH_2CD_2CH_2CO_2Si(CH_3)_3$ (XV)	75 → 75 (92)	c	94 → 94 (80)
	75 → 76 (8)		94 → 95 (20)
$C_6H_5OCH_2CD_2CH_2CH_2CO_2Si(CH_3)_3$ (XVI)	75 → 75 (95)	c	94 → 94 (67)
	75 → 76 (5)		94 → 95 (33)

[a] In each case, the m/e value of the unlabeled fragment is shown being shifted to its m/e value for the indicated labeled analog. [b] Corrected for isotope abundance and calculated deuterium isotope composition. [c] Peak is too small to permit interpretation of the labeling data.

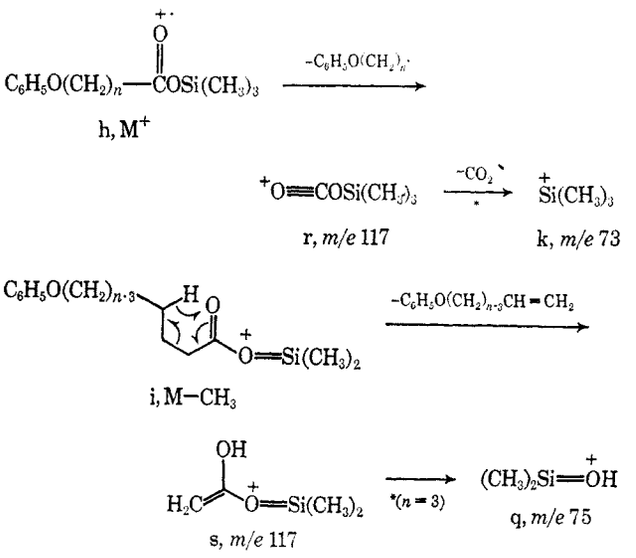
and loss of formaldehyde to yield the ion p (Σ_{40} = 3.4) of mass 135. High-resolution mass measurements ($C_8H_{11}Si$) and deuterium labeling (m/e 135 → 138 in the spectrum of XI) substantiate this fragmentation scheme. This over-all decomposition mode (i → o → p), or one analogous to it, is not found in any of the other phenoxypolymethylene trimethylsilyl ester derivatives (I, n = 2–6, 10).

Simple Fragmentations Characteristic of Trimethylsilyl ω-Phenoxypolymethylene Alkanoates (I).—In contrast to the detailed studies[16,27] concerning the characteristic electron impact induced fragmentations of trimethylsilyl ethers, there exists very little information[18,19] concerning the simple characteristic decomposition processes of trimethylsilyl esters. The present detailed analysis of the characteristic fragmentations of the series of phenoxypolymethylene trimethylsilyl esters (I), utilizing deuterium labeling, high-resolution mass measurements, and metastable analysis, sheds some light on this topic and a brief discussion of some of these observations will now be presented.

Teeter[19] stated that the M − 15 peak, resulting from loss of a silyl-methyl radical, is the most abundant peak in the mass spectra of the trimethylsilyl esters studied by him. In fact, in practically all the mass spectra of trimethylsilyl derivatives, the intensity of the molecular ion is very weak and the M − 15 peak is very intense. Table III contains the abundances of the molecular ions and the M − 15 peaks at both high and low voltages for the series of phenoxypolymethylene trimethylsilyl esters (I). It is surprising to note that this is one of the few instances where trimethylsilyl derivatives show weak M − 15 peaks and unusually intense molecular ions. At 12-eV ionizing energy, the molecular ion is the base peak when n = 1, 2, 6, and 10. The trimethylsilyl phenoxybutyric (n = 3) and pentanoic (n = 4) esters exhibit molecular ions and M − 15 peaks which are both weak. It is in these cases, however, that the M − C_6H_5O ion (j) contributes substantially more to the total ion current than in the other analogs.

Another intense characteristic ion at high voltage, which disappears at low voltage, is the dimethylsilanol ion q (m/e 75). There are metastable peaks indicating the formation of this species by multiple fragmentation pathways. When n = 4, 5, and 6, there is a large metastable peak corresponding to formation of q from the M − C_7H_9O ion (M − 109), and, when n = 3, it is generated from the McLafferty ion (s, see below, m/e 117), as is indicated by a metastable peak at m/e 48.2 (calcd ($75^2/117$ = 48.2). Undoubtedly, other ions also fragment to form this species. These multiple pathways make quantitative interpretation of the deuterium-labeling experiments (see Table IV) impossible. It can be said, however, that the transfered hydrogen atom originates predominantly (50%) from the α position of the methylene chain.

The trimethylsilyl cation k (m/e 73) which occupies greater than 10% of the total ion current (except when n = 10, see Table III) also arises from multiple fragmentation modes. As has been previously reported,[16] there is no evidence to support its formation by simple cleavage of the molecular ion. In all cases (I), there is a large metastable peak corresponding to the genesis of the trimethylsilyl cation from the M − C_6H_5O ion (j or j′ → k), and often (n = 1, 2, 10) there exists a metastable peak at m/e 45.4 (calcd $73^2/117$ = 45.5) corresponding to ejection of carbon dioxide from the α-cleavage ion of mass 117 (r → k). The formation of k (m/e 73) from

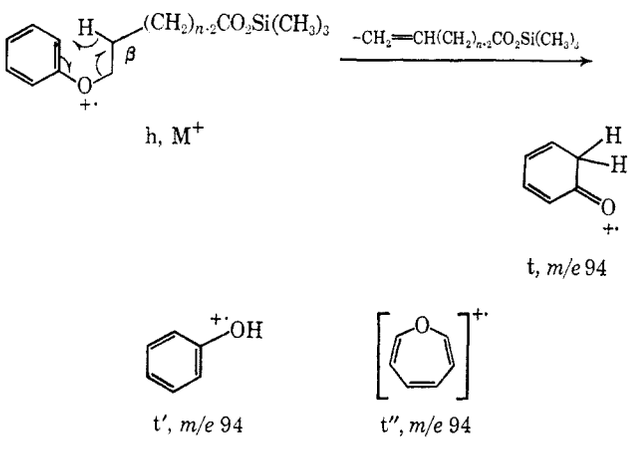


the m/e 103 precursor (l) in the spectrum of 3-phenoxypropionic trimethylsilyl ester (I, n = 2) has already been discussed.

(27) A. G. Sharkey, R. A. Friedel, and S. H. Langer, *Anal. Chem.*, **29**, 770 (1957); S. H. Langer, R. A. Friedel, I. Wender, and A. G. Sharkey, *ibid.*, **30**, 1353 (1958).

In all of the mass spectra of the phenoxypolymethylene trimethylsilyl esters (I), a relatively weak peak appears at m/e 117, which corresponds to a fragment ion of elemental composition $C_4H_9O_2Si$ (high resolution mass measurements). Cleavage of the molecular ion adjacent to the carbonyl group yields the siloxy-oxonium ion r (m/e 117) with the requisite elemental composition, and, in one instance (n = 5), a metastable peak was found to support this scheme. It appears plausible, however, that an alternative mode of fragmentation[7] can be invoked when the methylene chain contains three or more carbon atoms (n = 3–6, 10). Here, a McLafferty rearrangement of the even-electron M − CH_3 species (i) would yield an m/e 117 ion (s) having an elemental composition of $C_4H_9O_2Si$. In the spectrum of 7-phenoxyheptanoic trimethylsilyl ester (I, n = 6), there is a metastable peak at m/e 49.2 (calcd $117^2/279$ = 49.1) supporting this fragmentation. Even more important is the fact that greater than 90% of the m/e 117 peak in the mass spectrum of 2,2-d_2-4-phenoxybutyric trimethylsilyl ester (XII, see Table IV) shifts to m/e 119; thus, in this particular instance, ion s predominates over ion r by at least a 9:1 ratio.

The final "characteristic"peak to be discussed is the one at m/e 94, which is found in the mass spectra of many alkoxybenzene compounds[28] and has an elemental composition of C_6H_6O. This peak varies considerably in intensity (see Table III) in the phenoxypolymethylene trimethylsilyl ester series (I). Currently, there exists some controversy about the actual structure of this ion [ionized cyclohexadienone (t),[29,30] phenol (t'),[31] or oxepin (t'')].[32] The deuterium-labeling results (see Table IV)



support conclusions previously obtained[31] in this laboratory which negated the postulated[29] site-specific β-hydrogen atom transfer to yield the ketonic isomer (h → t). These results clearly indicate a random hydrogen transfer to the charge-retaining portion of the molecule with concomitant expulsion of an unsaturated ester moiety. The weak intensity of this peak at low voltages makes it impossible to determine if there are any variations in the labeling percentages at 12 eV.

Electron Impact Induced Interaction of Terminal Functional Groups in Some Compounds Related to the Phenoxypolymethylene Trimethylsilyl Esters (I).—The previous discussion has illustrated some important electron impact induced fragmentation schemes where the terminal phenyl ether and trimethylsilyl ester groups of some phenoxypolymethylene trimethylsilyl esters (I) have interacted with one another to produce abundant fragment ions. As was pointed out in the introduction, such behavior plays a very important role in the creation of "rules" for computer interpretation of the mass spectra of bifunctional compounds. Since the characteristic decomposition modes associated with individual phenyl ether and trimethylsilyl ester moieties do not occur entirely independently of each other when they are present in the same compound, it is necessary to develop new interpretation rules concerning the interaction of these species. The next step in "rule development" is to determine whether these interaction processes are specific for the interaction of the phenyl ether and trimethylsilyl ester groups or whether substitution of structurally similar functional groups for either or both of the phenyl ether or trimethylsilyl ester species will alter the nature of the interaction. For this reason, the mass spectra of the following substances have been recorded: some phenylpolymethylene trimethylsilyl esters (II); some benzyloxy- (III), methoxy- (IV, R = CH_3), and ethoxy- (IV, R = C_2H_5) polymethylene trimethylsilyl esters; and some phenoxypolymethylene methyl esters (V). Only brief comment will be made with regard to each mass spectrum and particular emphasis will be placed upon the interaction of the terminal functional groups.

Trimethylsilyl 3-Phenylpropionate (II, n = 2) and Trimethylsilyl 4-Phenylbutyrate (II, n = 3).—Substitution of a phenyl moiety for the phenoxy group of the previously discussed compounds I has a very significant effect upon the electron impact induced behavior of these compounds and stresses the influence of a heteroatom at each end of the molecule. Most important is the fact that neither of the two phenyl analogs investigated, trimethylsilyl 3-phenylpropionate (II, n = 2) and trimethylsilyl 4-phenylbutyrate (II, n = 3, see Figure 5), generate any significant ions due to an electron impact induced interaction of the terminal functional groups. It is particularly instructive that there is no rearrangement of the silyl function with expulsion of the central portion of the molecule either in the molecular ion (u) or in the M − CH_3 ion; an alkyl rearrangement of this type would yield species analogous to f (m/e 166) or g (m/e 151). Previous studies[16] of the mass spectral fragmentations of 3-phenylpropyl trimethylsilyl ether (VIII, n = 3, R = H) reported the existence of such a rearrangement (VIII → b), but to a rather small extent. The mass spectra of the phenyl analogs (II) also lack peaks corresponding to the M − 93 (j) and M − 109 ions found in the mass spectra of the phenoxy analogs.

Unlike the spectra of the phenoxy derivatives (I), the primary peaks in the mass spectra of the phenyl analogs (II, n = 2, 3, see Figure 5) result from the independent decomposition of the two functional groups, the trimethylsilyl ester and the alkyl phenyl moiety. The molecular ion is still unusually strong and the M − CH_3 peak is also quite intense. The trimethylsilyl cation k (m/e 73) and the dimethylsilanol ion q (m/e 75) are intense at 70 eV and practically disappear at 12 eV; metastable peaks indicate the formation of the latter

(28) See ref 25a, p 240–242.
(29) F. W. McLafferty, *Anal. Chem.*, **31**, 82 (1959).
(30) R. G. Gillis, G. J. Long, A. G. Moritz, and J. L. Occolowitz, *Org. Mass Spectrom.*, **1**, 527 (1968).
(31) J. K. MacLeod and C. Djerassi, *J. Amer. Chem. Soc.*, **88**, 1840 (1966).
(32) F. W. McLafferty, M. M. Bursey, and S. M. Kimball, *ibid.*, **88**, 5022 (1966).

species (q) from the M − CH_3 precursor. Both spectra exhibit abundant C_7H_7 tropylium ions at *m/e* 91.[33] It is interesting to note the absence of an *m/e* 92 peak. The mass spectra of alkyl benzene derivatives[33] with a propyl (or longer) side chain usually exhibit this *m/e* 92 peak (C_7H_8) which results from a McLafferty rearrangement[33] involving hydrogen transfer to the phenyl ring.

Both compounds (II, *n* = 2 and 3) exhibit an *m/e* 104 peak which is often found in the mass spectra of alkylbenzene derivatives.[33] In the case of trimethylsilyl 4-phenylbutyrate (*n* = 3, see Figure 5), a McLafferty rearrangement with charge retention on the phenyl group yields this species (u → v, Σ_{40} = 4.4); charge retention on the ester moiety affords the *m/e* 132 ion w (Σ_{40} = 2.9), which subsequently eliminates a methyl group, giving the *m/e* 117 ion (s, Σ_{40} = 19.3). The α-cleavage ion r (*m/e* 117) also undoubtedly contributes to this peak. Formation of the C_8H_8 ion of mass 104 (Σ_{40} = 21.9) in the mass spectrum of trimethylsilyl 3-phenylpropionate (II, *n* = 2) possibly involves transfer of a C-3 hydrogen atom to yield the conjugated product ion v. There is no *m/e* 132 peak (w) in this spectrum, presumably because the alkyl chain is not long enough to permit a McLafferty rearrangement. The base peak in the spectrum of trimethylsilyl 4-phenylbutyrate (II, *n* = 3) at 12 eV is at *m/e* 146, and a metastable peak at *m/e* 90.3 (calcd $146^2/236$ = 90.3) corresponds to elimination of trimethylsilanol from the molecular ion. The propionate derivative (II, *n* = 2) does not lose trimethylsilanol upon electron impact. Meyerson and Leitch[34] postulated that the elimination

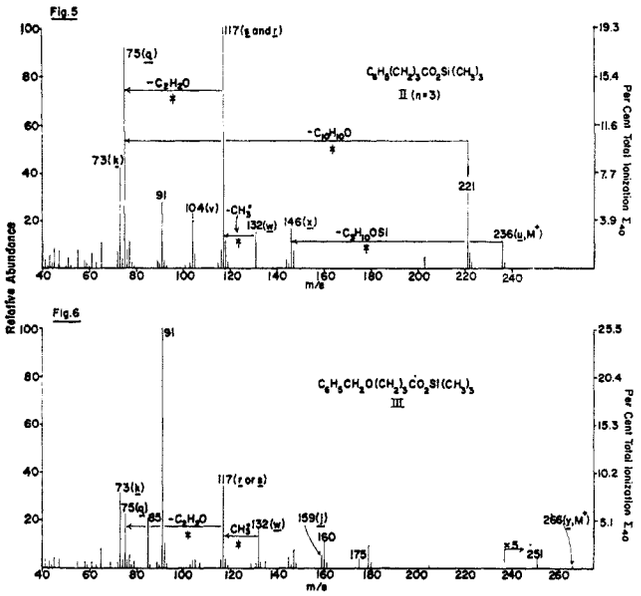
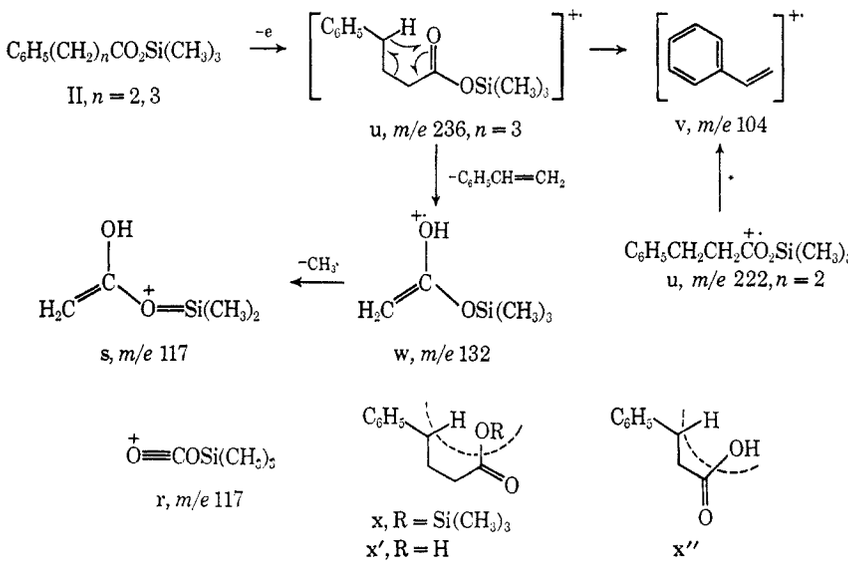


Figure 5.—Mass spectrum of trimethylsilyl 4-phenylbutyrate (II, *n* = 3).

Figure 6.—Mass spectrum of trimethylsilyl 4-benzyloxybutyrate (III, *n* = 3).

of Meyerson and Leitch.[34] As a supplementary piece of information which corroborates the above conclusion about the importance of ring size in the transition state, we now find that the loss of methanol from methyl 4-phenylbutyrate produces the base peak in the mass spectrum of this species at 12 eV (Σ_{40} = 32.5), whereas



of water from 4-phenylbutyric acid proceeds by a 1,4 elimination (x′) involving the hydroxyl group and the benzylically activated C-4 hydrogen atom. In the case of 3-phenylpropionic acid (x″) they found practically no elimination of water, which suggests that the size of the transition state rather than benzylic activation plays the key role in this reaction. The loss of trimethylsilanol (x) from trimethylsilyl 4-phenylbutyrate (II, *n* = 3) and not from its propionate analog (II, *n* = 2) can be explained by reasoning identical with that similar elimination of methanol from methyl 3-phenylpropionate is insignificant (Σ_{40} = 1.4).

Trimethylsilyl 4-Benzyloxybutyrate (III).—The mass spectra of 4-benzyloxybutyric acid and its methyl ester have been studied in other investigations[12] of the electron impact induced interactions of functional groups. The mass spectrum (Figure 6) of its trimethylsilyl ester (III) shows considerable interaction between the terminal benzyl ether and trimethylsilyl ester functions, as was found in the trimethylsilyl phenoxypolymethylene ester series (I).

(33) See ref 25a, Chapter 1-4, for leading references to the work of Meyerson and others.

(34) S. Meyerson and L. C. Leitch, *J. Amer. Chem. Soc.*, **88**, 56 (1966).

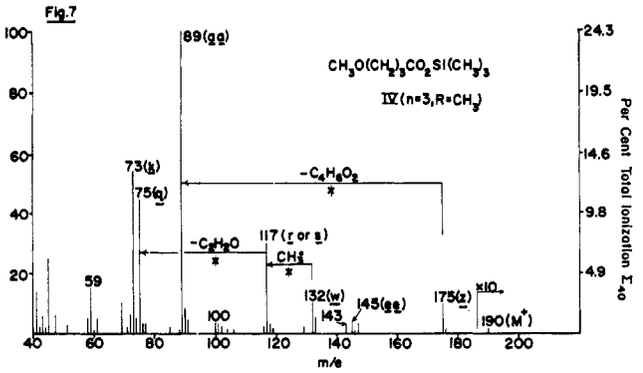
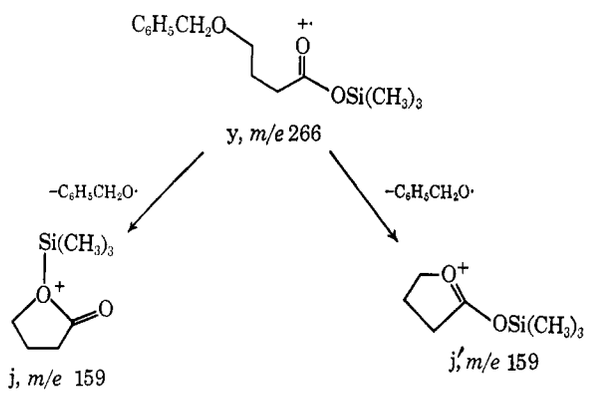


Figure 7.—Mass spectrum of trimethylsilyl 4-methoxybutyrate (IV, n = 3, R = CH_3).

Expulsion of a benzyloxy radical in a manner similar to the expulsion of a phenoxy radical in the parent series (I) probably accounts for the relatively small (Σ_{40} = 1.3) m/e 159 peak (y → j or j′) which becomes more intense at 12 eV (Σ_{40} = 3.2, 22% relative abundance). The fact that this process (y → j or j′) is much less prevalent here (Figure 6) than in the trimethylsilyl phenoxy case (Figure 2) can be partially explained by the observation that the benzyloxy group directs a greater number of fragmentation modes than does the phenoxy group, and thus less ion current is available for the y → j process (Figure 6) than for the h → j process (Figure 2). Unlike the mass spectrum of trimethylsilyl 4-phenoxybutyrate (I, n = 3, Figure 2), this spectrum (Figure 6) exhibits no metastable evidence for the decomposition of this ion (j) to yield the trimethylsilyl cation k (m/e 73), and also there is no loss of trimethylsilanol from this ion to yield the m/e 69 oxonium ion (m or n). Three other peaks, m/e 175 (Σ_{40} = 0.8), 160 (Σ_{40} = 2.8), and 85 (Σ_{40} = 5.4), which are particularly intense at 12 eV (Σ_{40} = 2.8, 14.7, and 4.3, respectively), are generated in fragmentation patterns involving the interaction of the benzyloxy and ester functions. They are exactly analogous to the M − $C_6H_5CH_2\cdot$, M − $C_6H_5CH{=}O$, and M − ($C_6H_5CH_2\cdot$ + CH_3OH) ions observed[12] in the spectrum of methyl 4-benzyloxybutyrate.



The remaining important peaks in Figure 6 are independently characteristic of the benzyl ether and trimethylsilyl ester functions, and include the McLafferty ion w at m/e 132 (Σ_{40} = 4.1 increasing to Σ_{40} = 14.1 at 12 eV), the McLafferty − $CH_3\cdot$ ion s or α-cleavage ion r at m/e 117 (Σ_{40} = 8.7), the tropylium ion at m/e 91

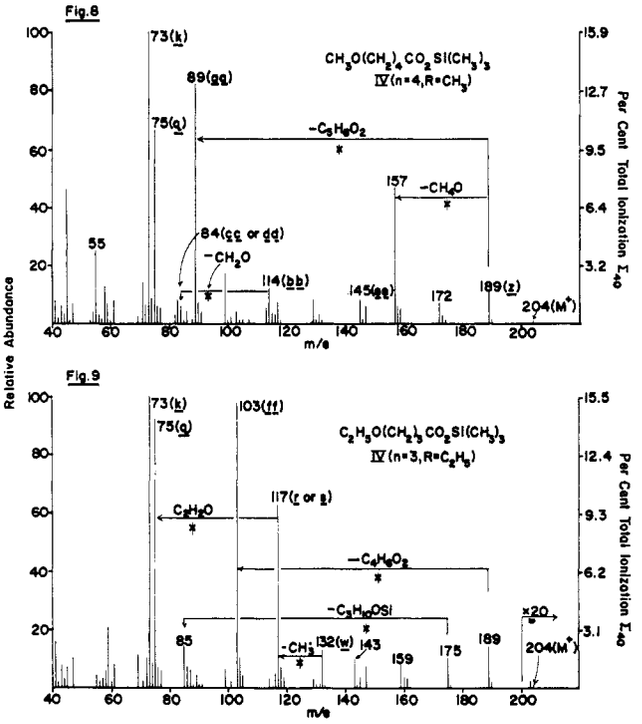


Figure 8.—Mass spectrum of trimethylsilyl 5-methoxypentanoate (IV, n = 4, R = CH_3).

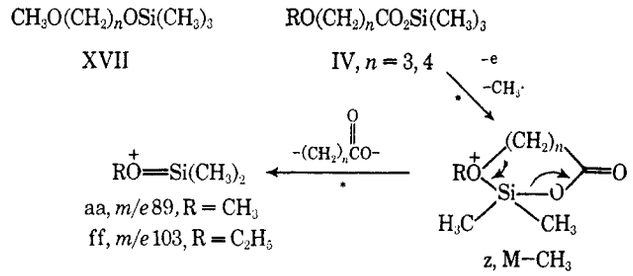
Figure 9.—Mass spectrum of trimethylsilyl 4-ethoxybutyrate (IV, n = 3, R = C_2H_5).

(Σ_{40} = 25.5), the dimethylsilanol ion q at m/e 75 (Σ_{40} = 5.1), and the trimethylsilyl cation k at m/e 73 (Σ_{40} = 8.2).

Trimethylsilyl 4-Methoxybutyrate (IV, n = 3, R = CH_3) and Trimethylsilyl 5-Methoxypentanoate (IV, n = 4, R = CH_3).—It is apparent that, in the comparison of the mass spectra of some phenoxy- (Figures 1–4), phenyl- (Figure 5), and benzyloxy- (Figure 6) polymethylene trimethylsilyl esters, the presence of a heteroatom-containing functional group at each of the ends of the polymethylene chain appears to be a requisite for observing electron impact induced functional group interactions. The mass spectra of two trimethylsilyl methoxypolymethylene esters (IV, R = CH_3, n = 3, 4) were recorded (see Figures 7 and 8, respectively) in order to assess what the effect of replacing the aromatic ether with an aliphatic ether would have upon these functional group interactions.

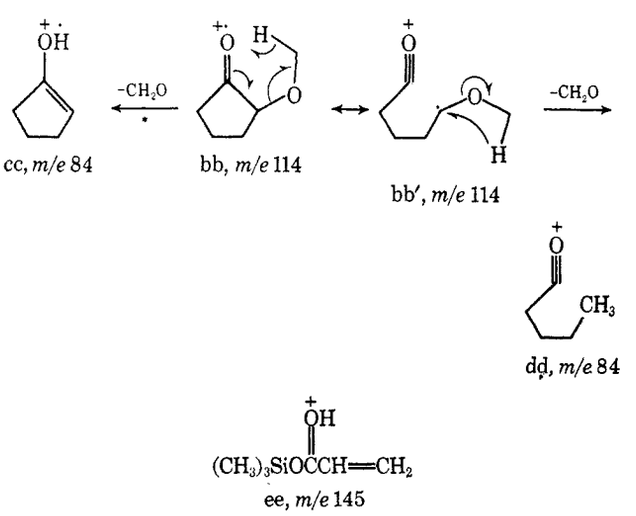
Observation of an intense peak at m/e 89 in both spectra (Figure 7 and 8) makes it immediately evident that the methoxy derivatives (IV, n = 3, 4), like the phenoxy and benzyloxy derivatives, exhibit fragmentation paths involving interaction of the methyl ether and trimethylsilyl ester functions. Consideration of the mode of genesis of the m/e 151 peak in the mass spectra of the phenoxypolymethylene trimethylsilyl esters (i → g, Figures 2–4), the previously reported[16] mass spectra of some methoxypolymethylene trimethylsilyl ethers (XVII), the high resolution mass measurements, the metastable evidence, and the intensity changes upon lowering the ionizing voltage make it obvious that the m/e 89 species (aa, C_3H_9OSi) results from rearrangement of the M − CH_3 peak (z) with expulsion of the central portion of the molecule. This species occupies 24.3 and 13.0% of the total ionization in Figures 7 and

8, respectively. The loss of a methoxyl radical from the molecular ion of these compounds (IV) in a manner



analogous to the formation of the M − C_6H_5O peak (j or j′) in Figures 2–4 is not significant. If there were a peak corresponding to the M − 109 (M − C_7H_9O) peak observed in the phenoxy series (I), it would have an elemental composition of M − C_2H_7O and fall at *m/e* 143 and 157 in Figures 7 and 8, respectively. Analogous to the previous series (I), a very small peak (Σ_{40} = 0.7) exists in the spectrum of the trimethylsilyl butyrate (*m/e* 143), and an intense peak, which is the base peak at 12 eV, is found at *m/e* 157 (Σ_{40} = 7.5) in Figure 8. As in the phenoxy series, a metastable peak corresponding to the loss of methanol from the M − CH_3 species (*m/e* 189) is observed at *m/e* 130.4 (calcd $157^2/189$ = 130.4) in this spectrum.

Although it is not an important fragmentation mode in the mass spectra of the trimethylsilyl phenoxypolymethylene esters (I), loss of trimethylsilanol from the molecular ion to give the *m/e* 100 (Σ_{40} = 0.7, Figure 7) and *m/e* 114 (Σ_{40} = 1.9, Figure 8) peaks could possibly involve interaction of the terminal ends of the methylene chain, especially in light of the metastable evidence found for the subsequent decomposition of the *m/e* 114 species (bb). Although no deuterium labeling has been performed, the *m/e* 114 species can be visualized to exist in the form of ionized 2-methoxycyclopentanone (bb); subsequent elimination of formaldehyde is suggested by the appropriate metastable peak and the fact that the *m/e* 114 peak increases substantially in intensity at 12 eV (Σ_{40} = 7.5 and 3.7, respectively). Loss of formaldehyde from the species



bb (*m/e* 114) could possibly involve a McLafferty rearrangement to yield the enolic species cc (*m/e* 84) in a manner analogous to the loss of ethylene from 2-ethylcyclopentanone.[35] It could also be visualized as occurring from the open-chain form of the *m/e* 114 ion bb′ to yield the oxonium ion species dd (*m/e* 84). Other formulations for this fragmentation are also conceivable, but are not reproduced for the sake of brevity.

The remaining important peaks are characteristic of the independent trimethylsilyl ester and methyl ether functions. The trimethylsilyl (k, *m/e* 73) and dimethylsilanol (q, *m/e* 75) ions are abundant in both cases. The *m/e* 145 ion, which is significant in the 12-eV spectrum (Σ_{40} = 4.5) of the methoxy butyrate derivative (IV, *n* = 3) has been shown by McCloskey[7] to have structure ee. Also significant in this spectrum (Figure 7) is the McLafferty peak w (*m/e* 132, Σ_{40} = 2.4) and its decomposition peak s (*m/e* 117, Σ_{40} = 7.3). Two peaks which are characteristic of the methyl ether and are very intense at low voltage (12 eV) are the *m/e* 172 (M − CH_3OH) peak in Figure 8 and the *m/e* 59 (C_3H_7O) peak[12] in Figure 7.

Trimethylsilyl 4-Ethoxybutyrate (IV, R = C_2H_5, *n* = 3).—The mass spectrum (Figure 9) of trimethylsilyl 4-ethoxybutyrate is very similar to that (Figure 7) of the methoxy analog (IV, *n* = 3, R = CH_3) in that it contains peaks corresponding to fragmentations involving terminal group participation as well as fragmentations independently characteristic of the ethyl ether and trimethylsilyl ester functions.

Peaks resulting from functional group interaction are the ones at *m/e* 103 (Σ_{40} = 15.2), 159 (Σ_{40} = 1.2), 143 (Σ_{40} = 1.5), 135 (Σ_{40} = 1.5), and 85 (Σ_{40} = 2.2). The abundant *m/e* 103 ion ff is generated from the M − CH_3 species (*m/e* 189) with expulsion of the central portion of the molecule in a manner analogous to the fragmentation paths z → aa and i → g in the trimethylsilyl methoxy- (IV, R = CH_3) and phenoxy- (I) polymethylene ester series, respectively. The weak *m/e* 159 (M − C_2H_5O) and 143 (M − C_3H_9O) peaks are probably generated in a manner similar to the electron impact induced formation of the M − C_6H_5O ion (j) and M − C_7H_9O ion in the phenoxy analogs (I). Elimination of an ethyl radical *via* participation of the silyl function[12] yields the *m/e* 175 ion, which occupies 8.1% of the total ion current at 12 eV, and a metastable peak at *m/e* 41.1 (calcd $85^2/175$ = 41.3) suggests elimination of trimethylsilanol from this species[12] to yield the *m/e* 85 ion. Those ions in Figure 9 characteristic of the trimethylsilyl moiety are the trimethylsilyl cation k (*m/e* 73), the dimethylsilanol ion q (*m/e* 75), the McLafferty ion w (*m/e* 132), and the McLafferty decomposition ion s or α-cleavage ion r (*m/e* 117). The *m/e* 73 peak remains the base peak at 12 eV implying that much of it may be due to the C_4H_9O ion found in 4-ethoxybutyric acid and its methyl ester;[12] the trimethylsilyl cation k, C_3H_9Si (*m/e* 73), normally disappears at 12 eV because it is never generated directly from the molecular ion as is the C_4H_9O ion.

Methyl 3-Phenoxypropionate (V, *n* = 2) and Methyl 4-Phenoxybutyrate (V, *n* = 3).—Substitution of a methyl ester function for the trimethylsilyl ester function of trimethylsilyl 3-phenoxypropionate (I, *n* = 2) and trimethylsilyl 4-phenoxybutyrate (I, *n* = 3) does not reduce the amount of the ion current attributed to fragmentation processes which result from interaction of the terminal functional groups. Although the mass

(35) J. Seibl and T. Gäumann, *Z. Anal. Chem.*, **197**, 33 (1963).

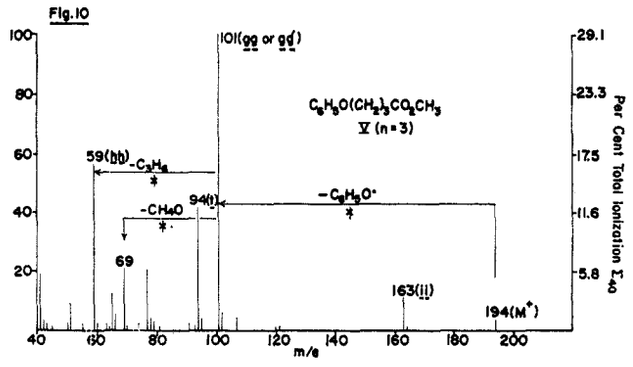
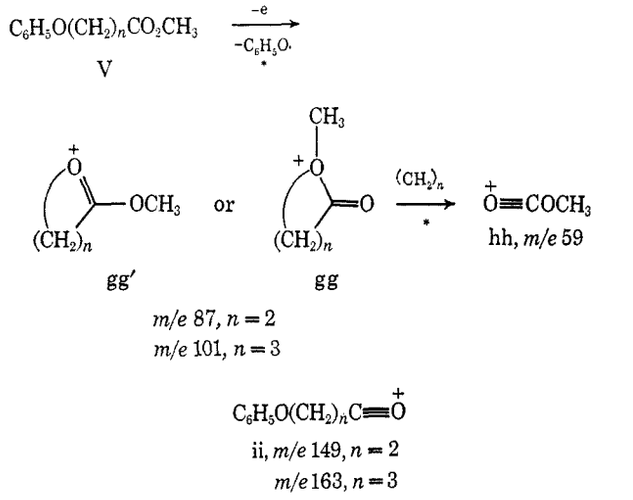


Figure 10.—Mass spectrum of methyl 4-phenoxybutyrate (V, $n = 3$).

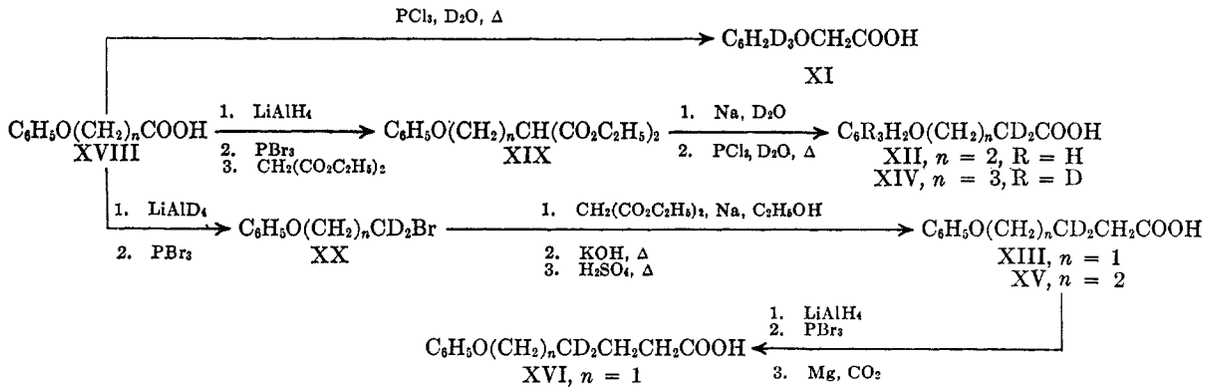
spectra of methyl 3-phenoxypropionate (V, $n = 2$) and methyl 4-phenoxybutyrate (V, $n = 3$, see Figure 10) show no evidence of fragmentations similar to the trimethylsilyl migration processes h → f and i → g, the M − 93 ion (gg or gg′) is considerably more intense ($\Sigma_{40} = 17.9$ and 29.1 for $n = 2$ and 3, respectively) than is the M − 93 ion in the mass spectra of the corresponding trimethylsilyl esters (see Table I). At 12 eV, this species (gg or gg′) amounts to 25.7 and 79.4% of the total ion current when $n = 2$ and $n = 3$, respectively. Analogous to the species j or j′ in the mass spectra of the trimethylsilyl analogs, this species gg or gg′ subsequently eliminates methanol (to produce the m/e 69 peak in Figure 10), as is evidenced by the appropriate metastable peaks. This species also decomposes to yield approximately 33% of the abundant m/e 59 ion (hh); the remaining portion of this m/e 59 species has the elemental composition C_3H_7O. The m/e 94 peak (t) has been previously discussed and is characteristic of alkoxy benzene derivatives. The only remaining important peak is the α-cleavage peak corresponding to ion ii (m/e 163 in Figure 10).



Summary.—It was the purpose of this work to investigate the interactions of the functional groups in the electron impact induced fragmentations of some trimethylsilyl ω-phenoxyalkanoates (I) and related compounds (II–V). In general, the mass spectra of the parent trimethylsilyl esters (I) exhibit four fragmentation schemes which yield peaks (m/e 166, m/e 151, M − 93, and M − 109) resulting from functional group participation (see Table I). Having determined the extent of analogous fragmentations in the related species II–V, it is evident that, because of one important exception, no *general* rules can be formulated which will account for the existence of these interaction processes in *all* of the cases studied (I–V). This exception relates to the observation that *none* of these processes is evident in the mass spectra of the ω-phenylalkanoates (II). Thus, for functional group interaction of the type discussed in this work, it is necessary to have a heteroatom-containing species (alkyl ether and alkyl ester) at *both* ends of the molecule. This observation firmly supports the conclusion of Brandt and Djerassi[11] that many rearrangement processes involving participation of functional groups at the ends of long polymethylene chains may depend upon the molecular ion existing in a coiled manner (see structure h′), which permits these groups to be in sufficiently close proximity so as to allow charge exchange between the heteroatoms. Each analog containing *both* an ether and an ester group at the ends of the polymethylene chain (III–V) did not produce *all* of the four interaction peaks found in the mass spectra of the trimethylsilyl ω-phenoxyalkanoates (I, see Table I). Instead, the extent of participation of their functionalities in these processes is affected by the nature of the ether or ester moiety itself. For instance, benzyl ethers exhibit a much greater degree of independent fragmentation (see Discussion) than do phenyl ethers, thus limiting the amount of ion current available for interaction processes (compared to the phenoxy analogs). Another example is the stability of the eliminated radical in the fragmentation analogous to the M − 93 (C_6H_5O) elimination in I, which certainly plays a role in determining the extent of this decomposition mode in the analogs (III–V). There are other peculiarities of each particular functional group which govern the amount of ion current occupied by the discussed interaction processes, but what is most important is that these processes do not occur at all unless the functional groups contain an oxygen heteroatom.

Synthesis of Labeled Compounds.—It is only necessary to describe the syntheses of the parent carboxylic acids, as all trimethylsilyl derivatives are prepared with the commonly employed hexamethyldisilazane reagent.[9,16,36] 2′,4′,6′-d_3-Phenoxyacetic acid (XI) is prepared by an unusually facile exchange procedure which involves heating a mixture of deuterium oxide, phenoxyacetic acid (XVIII, $n = 1$), and phosphorus trichloride under reflux for 20 hr. Utilizing a similar procedure, 2-(2′-phenoxyethyl) diethyl malonate (XIX, $n = 2$), prepared from diethyl malonate and 2-phenoxyethyl bromide, is hydrolyzed with sodium deuterioxide and subsequently decarboxylated and exchanged with phosphorus trichloride and deuterium oxide to yield 2,2-d_2-4-phenoxybutyric acid (XII). The nuclear magnetic resonance and mass spectra reveal approximately 39% d_3 species and 15% d_4 species. From the m/e 166 peak (f) and the m/e 159 peak (j) of the mass spectrum (see Discussion), it is determined that the phenyl ring is about 53% d_0, 32% d_1, 9% d_2, and 5% d_3, and that the α position is approximately 90% d_2. Reduction of phenoxyacetic acid (XVIII, $n = 1$) with lithium aluminum deuteride yields 1,1-d_2-2-phenoxyethanol, which is converted into its bromide

(36) S. H. Langer, S. Connell, and I. Wender, *J. Org. Chem.*, **23**, 50 (1958); see ref 14, Chapters 1–7.



(XX, $n = 1$) with phosphorus tribromide. A diethyl malonate condensation followed by hydrolysis and decarboxylation affords 3,3-d_2-4-phenoxybutyric acid (XIII). Hydrolysis and exchange of 2-(3′-phenoxypropyl) diethyl malonate (XIX, $n = 3$), prepared from 3-phenoxypropionic acid (XVIII, $n = 2$), with deuterium oxide and phosphorus trichloride yields 2′,4′,6′-2,2-d_5-5-phenoxypentanoic acid (XIV) in high isotopic purity. A lithium aluminum deuteride reduction of 3-phenoxypropionic acid (XVIII, $n = 2$) followed by a phosphorus tribromide bromination gives 1,1-d_2-4-phenoxybutyl bromide (XX, $n = 3$). A diethyl malonate alkylation followed by hydrolysis and decarboxylation produces 3,3-d_2-5-phenoxypentanoic acid (XV). Reduction of 3,3-d_2-4-phenoxybutyric acid (XIII) with lithium aluminum hydride, bromination of the product with phosphorus tribromide, and carbonation of the corresponding Grignard reagent yields 4,4-d_2-5-phenoxypentanoic acid (XVI).

Experimental Section[37]

Trimethylsilyl Esters.[9,16,36]—A mixture of 1.0 mmol of the disilazone[38] was heated under reflux with 1 drop of trimethylchlorosilane[38] until evolution of ammonia ceased (1–4 hr). The trimethylsilyl esters were isolated by preparative gas-liquid partition chromatography of the reaction mixture; Table V indicates the column and conditions utilized for each derivative. Retention times varied from 5 to 10 min. In all cases the yields of the colorless liquids were quantitative.

5-Phenoxypentanoic Acid.—To a well-stirred suspension of 1.7 g of lithium aluminum hydride in 30 ml of anhydrous ether at 0° was added dropwise 5.4 g of 4-phenoxybutyric acid[40] in 20 ml of anhydrous ether. After complete addition, the mixture was heated under reflux for 6 hr, cooled to 10°, and the excess lithium aluminum hydride decomposed by the dropwise addition of a saturated sodium sulfate solution. The mixture was filtered, dried over anhydrous magnesium sulfate, and refiltered, and the ether stripped on a rotary evaporator, yielding 4.9 g of 4-phenoxybutanol. The infrared spectrum exhibited characteristic absorptions at λ_{max} 3.1, 8.1, 9.5, 13.2, and 14.4 μ.[42] Utilizing the conditions of Wood,[43] 4-phenoxybutanol was treated with 1.0 ml of phosphorus tribromide to yield, after distillation at 134–135° (10 mm),[44] 4.4 g of 4-phenoxy-1-bromobutane (λ_{max} 8.1, 9.6, 13.2, and 14.4 μ). Utilizing the procedure and apparatus described in previous work,[16] 1.0 g of 4-phenoxy-1-bromobutane was converted into its Grignard regent with 200 mg of magnesium. Subsequent carbonation with anhydrous carbon dioxide[16] gave, after recrystallization from ether–hexane (1:1), 630 mg of 5-phenoxypentanoic acid: mp 62–63° (lit.[45] mp 65–66°); λ_{max}^{Nujol} 3.4 (broad), 5.8, 8.0, 9.6, 13.2, and 14.4 μ.

7-Phenoxyheptanoic Acid.—To a stirred solution of 268 mg of 7-phenoxyheptanol[9] in 10 ml of pure acetone at room temperature was added dropwise 0.80 ml of Jones reagent.[46] The mixture was stirred for 20 min and enough isopropanol was added to consume the excess Jones reagent. The solution was added to water, acidified, and extracted twice with 50-ml portions of ether. The combined ethereal layers were washed with water, dried over anhydrous magnesium sulfate, and filtered; solvent was stripped on a rotatory evaporator. The crude product, mp 52–53° (lit.[47] mp 55°) exhibited characteristic infrared absorptions at λ_{max}^{Nujol} 3.0 (broad), 5.8, 8.0, 9.6, 13.3, and 14.4 μ. It was converted directly into its trimethylsilyl ester without recrystallization.

11-Phenoxyundecanoic Acid.—In 40 ml of water was placed 13.8 g of 11-bromoundecanoic acid,[38] 10.0 g of phenol, and 7.0 g of sodium hydroxide, and the solution was heated under reflux for 3 hr. After cooling, the solution was acidified with dilute hydrochloric acid and extracted twice with ether; the combined ethereal layers were extracted with a sodium bicarbonate solution. The sodium bicarbonate layer was acidified with dilute hydrochloric acid and extracted twice with ether; the combined ether-

TABLE V

CHROMATOGRAPHY CONDITIONS FOR TRIMETHYLSILYL ESTERS[a]

Compd	Column (ft)	Column temp, °C
$C_6H_5OCH_2CO_2Si(CH_3)_3$ (I, $n = 1$)	5% SE-30	150
$C_6H_5O(CH_2)_2CO_2Si(CH_3)_3$ (I, $n = 2$)	10% SE-30	190
$C_6H_5O(CH_2)_3CO_2Si(CH_3)_3$ (I, $n = 3$)	1% SE-30	200
$C_6H_5O(CH_2)_4CO_2Si(CH_3)_3$ (I, $n = 4$)	1% SE-30	200
$C_6H_5O(CH_2)_5CO_2Si(CH_3)_3$ (I, $n = 5$)	5% SE-30	205
$C_6H_5O(CH_2)_6CO_2Si(CH_3)_3$ (I, $n = 6$)	1% SE-30	185
$C_6H_5O(CH_2)_{10}CO_2Si(CH_3)_3$ (I, $n = 10$)	1% SE-30	225
$C_6H_5(CH_2)_2CO_2Si(CH_3)_3$ (II, $n = 2$)	3% SE-30 (5)	180
$C_6H_5(CH_2)_3CO_2Si(CH_3)_3$ (II, $n = 3$)	3% SE-30 (5)	200
$C_6H_5CH_2O(CH_2)_3CO_2Si(CH_3)_3$ (III)	3% SE-30 (5)	210
$CH_3O(CH_2)_3CO_2Si(CH_3)_3$ (IV, $n = 3$, R = CH_3)	3% SE-30 (5)	130
$CH_3O(CH_2)_4CO_2Si(CH_3)_3$ (IV, $n = 4$, R = CH_3)	3% SE-30 (5)	150
$C_2H_5O(CH_2)_3CO_2Si(CH_3)_3$ (IV, $n = 3$, R = C_2H_5)	3% SE-30 (5)	140

[a] The dimensions of all columns were 10 ft × 0.25 in., and they were packed with indicated liquid phase on Chromosorb W. A He flow rate of 90 ml/min was employed.

(37) Melting points (uncorrected) were determined on the Kofler block and infrared absorption spectra were measured with a Perkin-Elmer Model 700 infrared spectrophotometer. Most low-resolution mass spectra and all high-resolution mass measurements were carried out by Mr. R. G. Ross using an A. E. I. MS-9 instrument equipped with a 200° heated inlet system. Mass spectra of a few synthetic intermediates were obtained on a Finnigan 1015 Quadrupole mass spectrometer. Nmr spectra werer ecorded by Dr. R. T. Gray with a Varian A-60 spectrometer, employing deuteriochloroform as solvent and tetramethylsilane as internal reference.

(38) Hexamethyldisilazane and chlorotrimethylsilane were purchased from Pierce Chemical Co., Rockford, Ill.

(39) Phenoxyacetic acid, 3-phenylpropionic acid, 4-phenylbutyric acid, and 11-bromoundecanoic acid were purchased from Eastman Organic Chemicals, Rochester, N. Y.

(40) 2-Phenoxyethyl bromide and 3-phenoxypropionic acid were purchased from Aldrich Chemicals, Milwaukee, Wis.

(41) 4-Phenoxybutyric acid, 3-phenoxypropyl bromide, and 6-phenoxyhexanoic acid were purchased from K and K Laboratories, Plainview, N. Y.

(42) E. L. Eliel, B. E. Nowak, R. A. Daignault, and V. G. Badding, *J. Org. Chem.*, **30**, 2441 (1965).

(43) H. B. Wood and E. C. Horning, *J. Amer. Chem. Soc.*, **75**, 5511 (1953).

(44) R. F. Brown and G. H. Schmid, *J. Org. Chem.*, **27**, 1288 (1962).

(45) A. N. Nesmeyanov and L. I. Zakharkin, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 224 (1955).

(46) C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

(47) E. Dobrowolska and Z. Eckstein, *Przemysl Chem.*, **42**, 556 (1963).

eal layers were dried over anhydrous magnesium sulfate. After filtration and evaporation of the solvent, the yellow oil obtained was recrystallized twice from ether–hexane (1:1), yielding 2.0 g of yellow crystals; analytic thin layer chromatography (tlc) on silica gel GF_{254} (Merck A. G. Darmstadt) indicated a mixture of two compounds. Preparative tlc of 100 mg of the crude product on silica gel HF_{254} (Merck A. G. Darmstadt) having a thickness of 1.0 mm and utilizing a 1:1 benzene–ethyl acetate development yielded 67 mg of 11-phenoxyundecanoic acid (λ_{max} 3.3, 5.8, 8.0, 9.8, 13.3, and 14.5 μ) which still appeared to be slightly impure. This crude product was isolated in pure form as its trimethylsilyl ester.

Methyl 3-Phenoxypropionate (V, n = 2).—Diazomethane, prepared from N-nitrosomethylurea,[48] was added dropwise to 1.7 g of 3-phenoxypropionic acid[39] in 20 ml of ether until nitrogen evolution ceased and a yellow color persisted. The solution was dried over anhydrous magnesium sulfate, filtered, and the ether removed on a rotary evaporator. Analytic tlc (benzene–ethyl acetate, 85:15) indicated only one product. Preparative glpc on a 10 ft × 0.25 in. 3% SE-30 column at 190° yielded 1.5 g of the desired product, whose infrared spectrum exhibited characteristic absorptions at λ_{max} 5.7, 8.0, 8.4, 9.6, 13.2, and 14.4 μ.

Methyl 4-Phenoxybutyrate (V, n = 3).—Addition of diazomethane to 1.8 g of 4-phenoxybutyric acid[40] in a manner identical with the preparation of methyl 3-phenoxypropionate (V, n = 2) yielded 1.7 g of methyl 4-phenoxybutyrate (λ_{max} 5.7, 8.0, 8.5, 9.5, 13.2, and 14.4 μ).

2′,4′,6′-d_3-Phenoxyacetic Acid (XI).—In a nitrogen atmosphere was placed 1.98 g of phenoxyacetic acid[38] in 9 ml of deuterium oxide (99.8% d_2). The mixture was cooled to 10° and 3.8 ml of phosphorus trichloride was added dropwise with stirring. The solution was gradually warmed to room temperature and then heated under reflux for 20 hr. After cooling, the mixture was added to mildly acidic deuterium oxide and extracted twice with ether; the combined ethereal extracts were dried over anhydrous magnesium sulfate. After filtering and evaporating the solvent, the solid product was recrystallized from ether–hexane (1:1), yielding 1.8 g of white needles, mp 98–99°. The mass spectrum indicated the following isotopic composition: 4.2% d_2, 68.4% d_3, and 27.4% d_4. The nmr spectrum exhibited singlets at δ 10.52, 7.32, and 4.70, which integrated for 0.3, 2.0, and 1.4 protons, respectively; the infrared absorption at $\lambda_{max}^{CHCl_3}$ 3.4 μ was considerably weaker than in the spectrum of unlabeled phenoxyacetic acid. The mass spectrum of the trimethylsilyl ester derivative indicated the following isotopic composition: 7.2% d_2, 79.2% d_3, and 13.7% d_4.

2,2-d_2-4-Phenoxybutyric Acid (XII).—In a nitrogen atmosphere, 230 mg of finely divided sodium was dissolved in 5 ml of absolute ethanol, and to the stirred solution was added 1.76 ml of diethyl malonate followed by 2.0 g of 2-phenoxyethyl bromide.[39] The mixture was heated under reflux for 4 hr, cooled, and the ethanol removed by distillation, leaving a blue solid, which was added to water. The aqueous solution was extracted three times with ether and the combined ethereal layers were dried over anhydrous magnesium sulfate. Filtration and evaporation of the ether gave 2.7 g of a colorless oil (λ_{max} 5.7, 8.0, 9.6, 13.2, and 14.4 μ).

Deuterium labeling was accomplished *via* a procedure similar to one previously employed by Duffield, *et al.*[49] In a nitrogen atmosphere and at 0°, 1.4 g of finely divided sodium was cautiously dissolved in 7.2 ml of deuterium oxide (99.8% d_2). To the stirred solution was added dropwise the alkylated diethylmalonate, and the mixture was heated under reflux for 3 hr. Ethanol was removed by distillation until the temperature of the solution reached 100°. After cooling to 0°, 3.04 ml of phosphorus trichloride was slowly added, and the mixture was warmed to room temperature and then heated under reflux for 20 hr. The solution was cooled, poured into acidic deuterium oxide, and extracted twice with ether; the combined ethereal extracts were dried over anhydrous magnesium sulfate. After filtration and removal of the ether by evaporation, 1.3 g of labeled 4-phenoxybutyric acid was obtained: mp 59–61° (lit.[50] mp 64–65°). The mass spectrum indicated the following isotopic composition: 40.7% d_2, 39.0% d_3, 14.7% d_4, and 5.6% d_5. The nmr spectrum exhibited a singlet at δ 11.9, a multiplet at δ 7.1, a triplet at δ 4.0, and a triplet at δ 2.1, which integrated for 0.6, 4.1, 2.0, and 2.0 protons, respectively. The mass spectrum of the trimethylsilyl ester derivative indicated the following isotopic composition: 55.0% d_2, 29.0% d_3, 10.1% d_4, and 5.0% d_5. From the mass spectrum of this derivative it was determined [from m/e 159 (j), see Discussion] that the C-2 position contained 89.0% d_2 and 11.0% d_1, and from the m/e 166 peak (f) (see Discussion) that the phenyl ring had the following isotopic composition: 53.2% d_0, 32.1% d_1, 8.7% d_2, and 6.0% d_3.

3,3-d_2-4-Phenoxybutyric Acid (XIII).—In a procedure identical with that utilized in the preparation of 5-phenoxypentanoic acid, 4.6 g of phenoxyacetic acid[38] was reduced with 1.3 g of lithium aluminum deuteride[51] (whereas lithium aluminum hydride was used in the previous case) to yield 4.1 g of 1,1-d_2-2-phenoxyethanol (λ_{max} 3.0, 8.0, 9.5, 13.2, and 14.4 μ). Bromination of this compound with 1.0 ml of phosphorus tribromide, again according to the previously described procedure, yielded 3.7 g of 1,1-d_2-2-phenoxyethyl bromide: λ_{max} 8.1, 9.5, 13.2, and 14.4 μ.

In a nitrogen atmosphere, 415 mg of finely divided sodium metal was dissolved in 9.0 ml of absolute ethanol, and to this solution was added dropwise 3.2 ml of diethyl malonate followed by 3.7 g of 1,1-d_2-2-phenoxyethyl bromide. The mixture was then heated under reflux for 4 hr. The ethanol was distilled from the reaction mixture and 4.5 g of potassium hydroxide in 5.4 ml of water was slowly added; the solution was again heated under reflux for 4 hr. After the addition of 3 ml of water, the remaining ethanol was distilled from the reaction mixture until the temperature reached 100°. The solution was cooled to 5°, 8.1 ml of concentrated sulfuric acid in 13.1 ml of water was added, and the mixture was again heated under reflux for 15 hr. After cooling, threefold extraction with dichloromethane, and drying with anhydrous magnesium sulfate, the dichloromethane was evaporated, yielding a yellow solid. Recrystallization, first from ether–hexane (1:1) and then from hexane, gave 2.0 g of 3,3-d_2-4-phenoxybutyric acid, mp 63–64° (lit.[50] mp 64–65°), whose mass spectrum indicated the following isotopic composition: 99.0% d_2 and 1.0% d_1.

2′,4′,6′,2,2-d_5-5-Phenoxypentanoic Acid (XIV).—In a manner identical with the preparation of 2,2-d_2-4-phenoxybutyric acid (XII), 2.15 g of 3-phenoxypropyl bromide[40] yielded impure diethyl 2-(3-phenoxypropyl)malonate (XXIV, n = 2), which was distilled at 160–162° (0.7 mm) to give 1.8 g of pure material (λ_{max} 5.8, 8.0, 9.7, 13.2, and 14.4 μ). Deuteration with 4.5 ml of deuterium oxide, 900 mg of finely divided sodium, and 1.9 ml of phosphorus trichloride yielded 890 mg of labeled 5-phenoxypentanoic acid after one recrystallization from ether–hexane (1:1), mp 62–64° (lit.[45] mp 65–66°). The mass spectrum indicated the following isotopic composition: 76.3% d_5, 20.6% d_4, and 3.1% d_3. The nmr spectrum exhibited a singlet at δ 11.75 (1 H), a singlet at δ 7.17 (2 H), a triplet at δ 3.92 (2 H), and a multiplet at δ 1.81 (4 H). The mass spectrum of the trimethylsilyl ester derivative indicated that the isotopic composition at C-2 (from m/e 173, see Discussion) was 87.0% d_2 and 13.0% d_1, and at the phenyl ring, 86.1% d_3 and 13.9% d_2 (from m/e 151, see Discussion).

3,3-d_2-5-Phenoxypentanoic Acid (XV).—Utilizing a procedure identical with that employed in the synthesis of 3,3-d_2-4-phenoxybutyric acid (XII), 4.15 g of 3-phenoxypropionic acid[39] was reduced with 1.26 g of lithium aluminum deuteride,[51] yielding 3.8 g of 1,1-d_2-3-phenoxypropanol (λ_{max} 3.0, 8.1, 9.6, 13.3, and 14.4 μ). Bromination with 0.8 ml of phosphorus tribromide gave 4.02 g of 1,1-d_2-3-phenoxypropyl bromide (λ_{max} 8.0, 9.5, 13.1, and 14.2 μ). Alkylation with 3.17 ml of diethylmalonate, followed by hydrolysis and decarboxylation as previously described, yielded, after recrystallization from ether–hexane (1:1) followed by recrystallization from hexane, 2.40 g of 3,3-d_2-5-phenoxypentanoic acid, mp 64.3–64.8° (lit.[45] mp 65–66°), whose mass spectrum indicated the following isotopic composition: 96.2% d_2 and 3.8% d_1.

Registry No.—I, n = 1, 21273-08-5; I, n = 2, 21273-09-6; I, n = 3, 21273-10-9; I, n = 4, 21273-11-0; I, n = 5, 21273-12-1; I, n = 6, 21273-13-2; I, n = 10, 21273-14-3; II, n = 2, 21273-15-4; II, n = 3, 21273-16-5; III, n = 3, 21273-17-6; IV, n = 3, R = Me,

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Pyrimido[5,4-e]-as-triazines. IV. The Preparation and Some Reactions of Pyrimido[5,4-e]-as-triazine-5(6H)-thiones[1]

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Reaction of 5-(benzylthio)- and 5-chloro-1,2-dihydropyrimido[5,4-e]-as-triazine (**8** and **4**), respectively, with NaSH gave 1,2-dihydropyrimido[5,4-e]-as-triazine-5(6H)-thione (**3**). Treatment of **4** with thiourea also gave **3** and a 2-thiospeudourea addition product that was rearranged in HCl to give 9-amino-9H-purine-8(7H)-one-6(1H)-thione (**11**). Oxidation of **3** and some 5-alkylthio derivatives with diethyl azodicarboxylate gave the corresponding heteroaromatic compounds. Replacement of the 5-alkylthio group with various nucleophiles occurred readily to give 5-substituted pyrimido[5,4-e]-as-triazines. Also, the rearrangement of 7-hydrazinothiazolo[5,4-d]pyrimidine to **3** is demonstrated.

In the previous papers of this series, the preparation and some reactions of 5-substituted pyrimido[5,4-e]-as-triazines were reported.[2] The present paper is concerned with the preparation of pyrimido[5,4-e]-as-triazine-5(6H)-thione and some of its 5-alkylthio derivatives. The latter were desired as potential substrates for nucleophilic displacement reactions to give various 5-substituted compounds. In addition, rearrangements involving the 7-hydrazinothiazolo[5,4-d]pyrimidine–pyrimido[5,4-e]-as-triazine-5(6H)-thione ring systems are discussed.

The preparation of **3** by the reaction of **1** with hydrazine to give **2**,[3] and cyclization of the latter with the $(EtO)_3CH$–concentrated HCl reagent[2c] was unsuccessful (see Scheme I). This reaction gave only the HCl salt of **2**. To increase the solubility and reactivity of **2**, the thione group was blocked by alkylation. Although **2** has been reported to undergo rapid oxidation in an alkaline medium,[3] treatment of a NaOH solution of **2** with $C_6H_5CH_2Cl$ gave a good yield of 4-(benzylthio)-pyrimidine **5**. Cyclization of **5** with the $(EtO)_3CH$–concentrated HCl reagent gave the HCl of 5-(benzylthio)-1,2-dihydropyrimido[5,4-e]-as-triazine (**8**), and a smaller amount of the 9-[(ethoxymethylene)amino]-purine **6**. Acid hydrolysis of the latter gave the known 9-aminopurine **7**.[4] The free base of **8** was obtained by neutralization of a solution of the HCl with $NaHCO_3$.

The interaction of **8** with hydrated NaSH in EtOH replaced the benzylthio group to give a 59% yield of **3**.[5] Similarly, the reaction of **4**[2c] with NaSH gave an 85% yield of **3**. The preparation of **3** was also attempted by reaction of **4** with thiourea. This reaction gave a 13% yield of **3**, apparently formed from the 2-thiopseudourea **9**. Also, a second product was obtained in 52% yield that analyzed correctly for the hydrochloride of **9**, but treatment of this material with aqueous NaOH gave none of **3**. This result suggested that **9** had undergone an intramolecular addition reaction to give the hydrochloride of the isomeric tricyclic compound **10** (see Scheme II). Support for structure **10** was provided by its rearrangement in HCl to give **11**, identified by elemental anaylses and comparison of its ultraviolet spectrum with that of purine-8(7H)-one-6(1H)-thione.[6] A similar tricyclic compound, obtained from the reaction of 6-chloropurine with thiourea, also undergoes this type of rearrangement,[7] which, in the present case, involves cleavage of both the thiazole and as-triazine rings, and hydrolysis of the guanidino moiety of **10** to give, presumably, the intermediate pyrimidine **12** which then undergoes cyclization and deformylation to give **11**.

Reaction of **3** with 4 N HCl at room temperature cleaved the as-triazine ring to give the pyrimidine **2**. In contrast, the product resulting from treatment of **3** with CF_3CO_2H was identified by elemental analyses and spectral data as the thiazolo[5,4-d] pyrimidine **13** (see Scheme III). The nmr spectrum of **3** in CF_3CO_2D showed the appearance of two new CH peaks in about 20 min and the disappearance of the two CH peaks of **3** in about 1 hr. Presumably, this rearrangement involves the trifluoroacetylation and ring opening of **3** to give **15**, which then undergoes recyclization to give **13**. The nmr data suggested that the recyclization step might have occurred during the reaction work-up. The assignment of the position of the CF_3CO group in **13** is based on analogy with the products obtained from the acylation and ring opening of the triazine ring of other 1,2-dihydropyrimido[5,4-e-]-as-triazines with carboxylic acids.[2a,c] To study the reverse rearrangement (**14** → **16** → **3**), the preparation of the known 7-hydra-

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