

Similarly, the reaction of a mixture of the geometric isomers of 5-methyl-4-hepten-3-one (10 and 11) at 50° for 3.0 hr indicates 17.8% [100 (8.3 × 2)/91.6] rearrangement for that part of the reactants going through the reverse aldol reaction. However, in this case, the actual yield of butanone and 3-pentanone is low and the starting material is almost completely reacted. In this reaction, acetone cannot conceivably be produced *via* the proposed disproportionation mechanism; it is probably formed *via* an oxygen function migration in the olefinic ketone prior to dealdolization (see Discussion).

In the reaction of 18 with perchloric acid, the dihydrofuran fraction was also isolated and analyzed. It consisted of 95.8% unrearranged *cis* and *trans* dihydrofurans 16 and 17, and 3.5% of 31 plus 0.7% of 32, the *cis* and *trans* rearranged dihydrofurans. Dihydrofurans are relatively stable in perchloric acid, so this 4.2% rearrangement is probably a good measure of relative rates of rearrangement and dihydrofuran formation.

Rearranged dihydrofurans 12 and 13 were also detected in the reaction of 21 with perchloric acid.

It is interesting to note that 21 produces a significantly higher ratio of 2-pentanone to acetone than the 1:1 mixture expected from the reverse aldol reaction. Based on this fact and general observations about the reactivity of various ketones, it appears that lower molecular weight ketones disappear (polymerize) faster in perchloric acid than their higher molecular weight homologs. For this reason the relative yields in Table IV are highly dependent on reaction conditions.

Registry No.—Acetone, 67-64-1; butanone, 78-93-3; 3-pentanone, 96-22-0; 4-heptanone, 123-19-3; propiophenone, 93-55-0; MeCOCHMe₂, 563-80-4; Me₂CHCOEt, 565-69-5; Me₂CHCOCHMe₂, 565-80-0; perchloric acid, 7601-90-3; 12, 23537-60-2; 13, 23537-61-3; 16, 23537-62-4; 17, 23537-63-5; *cis*-24, 23537-64-6; *trans*-24, 23537-65-7; 31, 23537-66-8; 32, 23537-67-9; 35, 23537-68-0; *cis*-36, 23537-69-1; *trans*-36, 23537-70-4; 37, 23537-71-5.

Mass Spectrometry in Structural and Stereochemical Problems. CLXXXI.¹ Further Studies of Remote Group Interactions after Electron Impact in 4-Substituted Cyclohexanones²

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The mass spectral properties of a series of 4-substituted cyclohexanones have been investigated in an attempt to determine the scope and limitation of an electron impact induced oxygen rearrangement previously reported in the 4-hydroxy and 4-methoxy analogs. With the use of deuterium labeling, a similar rearrangement has been elucidated for 4-ethoxycyclohexanone, albeit to a smaller extent than in the methoxy analog. The mass spectral decomposition of 4-benzyloxycyclohexanone results in another important rearrangement process, giving styrene and a γ,δ -unsaturated acid as the final products, both of which retain part of the ionizing current. For several other analogs, including some containing a different oxygenated substituent, and others bearing a heteroatom (chlorine, sulfur) other than oxygen at the 4 position, no rearrangement processes are observed. Instead, the major fragmentation pathways are governed by the position of initial ionization, as determined by the relative ionization potentials of the different substituent groups.

The use of mass spectrometry in the structure elucidation of organic molecules is now widely accepted, and the characteristic fragmentation patterns associated with individual functional groups have been well documented.⁴ Although the techniques of high-resolution analysis, isotopic labeling, and metastable analysis have assisted the chemist greatly in the structure determination of fragment ions, erroneous conclusions are still possible if a fragmentation pathway involves a molecular rearrangement process.

Until recently most reported electron impact induced rearrangements have involved transfer of a hydrogen atom or a simple alkyl radical,^{4,5} usually producing a more stable fragment ion. Recent work, however, has uncovered rearrangements of larger groups.⁵ For example, during the course of a systematic study of bifunctionalized monocyclic systems in this laboratory, it was reported⁶ that abundant

fragment ions of masses 60 and 74, respectively, occurred in the mass spectra of 4-hydroxycyclohexanone (I) and 4-methoxycyclohexanone (II). From the elemental composition of these ions (C₂H₄O₂ and C₃H₆O₂, respectively) it followed that they were produced through a rearrangement process, bringing the two oxygen functions closer together in the daughter than they were in the parent ion. With the use of extensive deuterium labeling the rearrangement mechanism was deduced to be as in Scheme I.

In addition to the oxygen rearrangement summarized in Scheme I, other fragmentation pathways containing rearrangements of heteroatoms have been reported in the mass spectra of such compounds as methylglycosides,⁷ β -(alkylthio)propionic acids and esters,^{8a} dimethyl esters,^{8b} and 1,4-naphthoquinone dimers.^{8c} Also, we have recently found that a rearrangement, similar to that reported by Green and Djerassi, occurs in the corresponding α -decalone series,¹ except that in this system charge retention occurred on the more highly substituted hydrocarbon, rather than the oxygen-containing portion of the molecule.

(1) Part CLXXX: R. T. Gray, M. Ikeda, and C. Djerassi, *J. Org. Chem.*, **34**, 4091 (1969).

(2) Financial support from the National Institutes of Health (Grants GM-06840 and AM-04257) is gratefully acknowledged.

(3) (a) Postdoctoral Fellow, 1968-1969; (b) National Institutes of Health Postdoctoral Fellow, 1967-1968.

(4) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, Inc., San Francisco, Calif., 1967.

(5) P. Brown and C. Djerassi, *Angew. Chem.*, **79**, 481 (1967); *Angew. Chem. Intern. Ed. Engl.*, **6**, 477 (1967).

(6) M. M. Green, D. S. Weinberg, and C. Djerassi, *J. Amer. Chem. Soc.*, **88**, 3883 (1966); M. M. Green and C. Djerassi, *ibid.*, **89**, 5190 (1967).

(7) K. Heyns and D. Müller, *Tetrahedron*, **21**, 55 (1965); *Tetrahedron Lett.*, No. 4, 449 (1966); N. K. Kochetkov and O. S. Chizhov, *Tetrahedron*, **21**, 2029 (1965).

(8) (a) S.-O. Lawesson, L. Dalgaard, J. O. Madsen, J. H. Bowie, and D. B. Cobb, *Chem. Commun.*, 218 (1969); (b) I. Howe and D. H. Williams, *J. Chem. Soc.*, 202 (1968); (c) J. Dekker and D. P. Venter, *J. Amer. Chem. Soc.*, **90**, 1225 (1968).

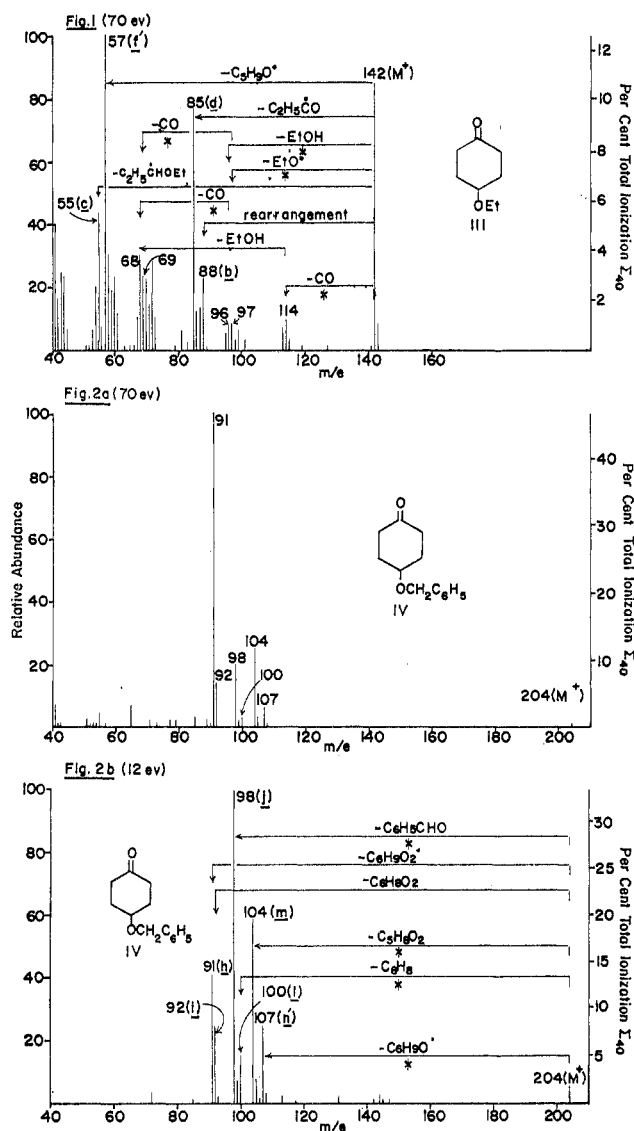
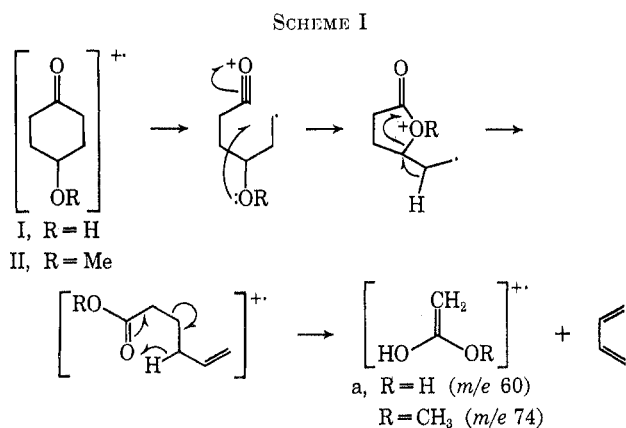


Figure 1.—Mass spectrum of 4-ethoxycyclohexanone (III).
Figure 2.—Mass spectrum of 4-benzyloxycyclohexanone (IV):
(a) at 70 eV; (b) at 12 eV.

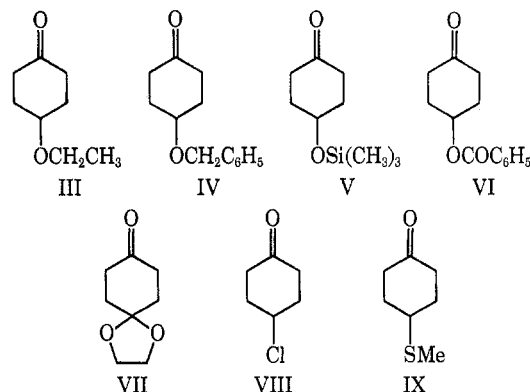
It is evident from Scheme I that the lone pair of electrons on the oxygen atom is attributed a leading role in the formation of fragment ion a. Hence, in an attempt to determine the scope and limitations of such a rearrangement process, we have undertaken a mass spectral investigation of a series of other 4-sub-



stituted cyclohexanones. Each of these compounds contains a heteroatom directly attached to the 4 position of the ring, giving the possibility for a transannular interaction such as found in the spectra of I and II. Principal emphasis has been placed on those fragmentations which appear to be triggered by the functional groups in each molecule and to examine what effect, if any, one group exerted on another. In those cases where such an interaction is evident, it has been useful to measure also the mass spectra of isotopically labeled analogs of the parent compounds in order to determine the specificity of bond cleavage and migration in such fragmentation pathways.

Results and Discussion

To determine the generality of electron impact induced transannular interaction between two remote⁹ functional groups, such as that found in the mass spectra of 4-hydroxy- and 4-methoxycyclohexanone (I and II), we have synthesized the following series of analogous compounds (III–IX).



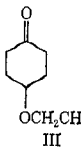
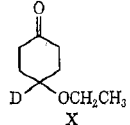
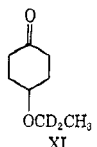
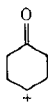
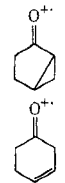
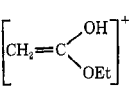





As a simple extension of our earlier work,⁶ 4-ethoxycyclohexanone (III) was prepared. It seemed reasonable to expect a functional-group interaction between the ethoxyl and carbonyl groups, especially since an important electron impact induced rearrangement process had been found in the mass spectrum of 4-ethoxy-1-decalone.¹ The spectrum (Figure 1)¹⁰ of III shows a peak of 23% relative abundance at m/e 88, which corresponds to the oxygen rearrangement peak at m/e 74 (a in Scheme I) from the methylated analog II. High-resolution measurements indeed show this fragment ion to have the elemental composition C₄H₅O₂,¹¹ indicating that a transannular interaction of the two functionalities must be occurring, albeit to a smaller extent than in compounds I and II. Conclusive evidence for such a rearrangement was obtained from the mass spectra of 4-*d*₁-4-ethoxycyclohexanone (X) and 1',1'-*d*₂-4-ethoxycyclohexanone (XI). As shown in Table I, this fragment ion is divided

(9) "Remote" is meant to designate numbers of bonds rather than spatial relationships.

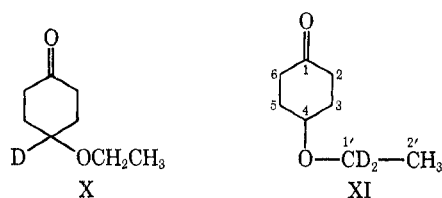
(10) All mass spectra were measured at both 12 and 70 eV. Unless otherwise stated, however, the spectra discussed in the text are those obtained at 70 eV.

(11) The composition of all relevant peaks were determined by high-resolution measurements.

TABLE I
m/e VALUES FOR VARIOUS FRAGMENT IONS OF 4-ETHOXYCYCLOHEXANONE (III) AND
 DEUTERATED DERIVATIVES (PER CENT RELATIVE ABUNDANCE)

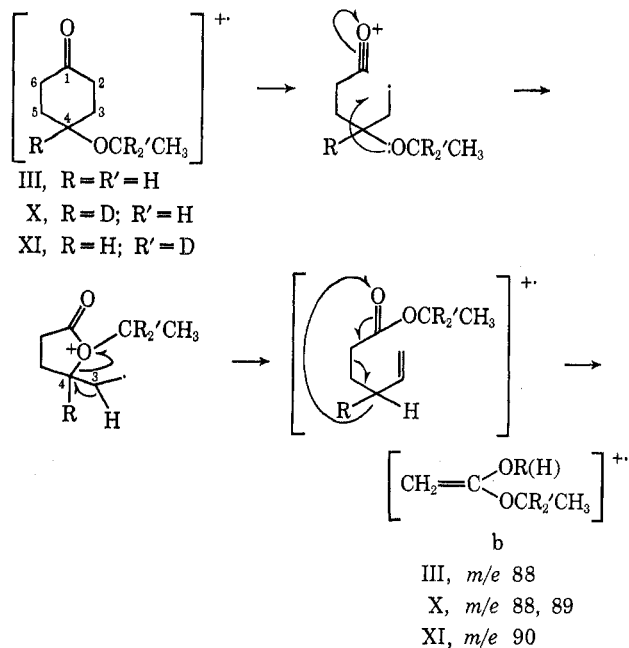
<i>M</i> ⁺	<i>M</i> - EtO ⁺	<i>M</i> - EtOH ⁺	C ₄ H ₅ O ₂ ⁺	C ₅ H ₉ O ⁺	C ₆ H ₉ ⁺	C ₆ H ₈ ⁺	C ₆ H ₇ O ⁺	C ₆ H ₆ ⁺ ^a	
 III	142 (85)	97 (8)	96 (8)	88 (23)	85 (76)	69 (22)	68 (30)	57 (100)	55 (22)
 X	143 (100)	98 (11)	97 (9)	88 (26) ^c 89 (9)	86 (92)	70 (54)	69 (33)	58 (98)	55 (26)
 XI	144 (100)	97 (9)	96 (10)	90 (20)	87 (76)	69 (21)	68 (31)	57 (92)	55 (21)
Proposed structure in parent	Molecular ion								

^a By high-resolution the fragment ion at *m/e* 55 consists of C₅H₉O and C₄H₇. Only the relative abundance of the oxygenated portion is given here. ^b 98% *d*₁, 2% *d*₀. ^c By high resolution, the *m/e* 88 peak contains some C₅H₁₀DO; see text. ^d 97% *d*₂, 3% *d*₁ by mass spectrometry.



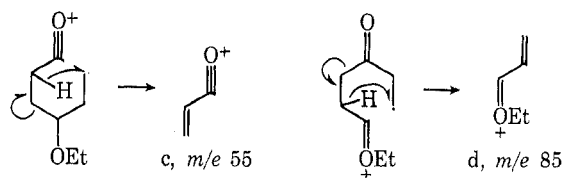
between *m/e* 88 and 89 for X, as expected from a mechanism as shown in Scheme II. That this splitting does not give an equal abundance of ions at *m/e* 88

SCHEME II



and 89 in X is due entirely to the fact that the peak at *m/e* 87 (100% C₅H₁₁O) in III has also shifted, at least in part, to *m/e* 88 (C₄H₉O₂, 58%; C₅H₁₀DO, 42%) in the spectrum of X. As expected from the proposed mechanism, retention of both deuterium atoms is quantitative (*m/e* 88 → 90) in the spectrum of XI.


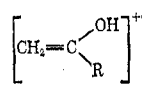


As shown in Table II most of the other major peaks in the mass spectrum of III are derived from fragmentation pathways associated with the independent functionalities. For example, cleavage α to both the carbonyl and the ethoxyl functions are important processes, leading to the expected fragment ions c and d, respectively.



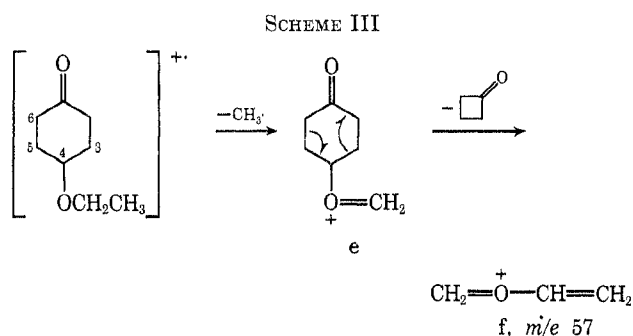
Of notable interest is the base peak of the spectrum at *m/e* 57 (100% C₃H₅O¹¹). To understand the mechanism of its formation it is important to know which oxygen atom is bearing the charge in the fragment ion. Although no metastable ions are observed for its formation, the relative shifts of this peak in the spectra of the isotopically labeled compounds give unambiguous information concerning its genesis. Deuteration at C-4 (X) results (Table I) in a shift to *m/e* 58, an observation which may be explained by two different mechanisms.

The first possibility, as shown in Scheme III, would involve loss of a methyl radical from the alkoxy group to give the stable oxonium ion e. Similar fragmentations

TABLE II
CHARACTERISTIC MASS SPECTRAL PEAKS IN THE SPECTRA OF 4-SUBSTITUTED
CYCLOHEXANONES (PER CENT RELATIVE ABUNDANCE)

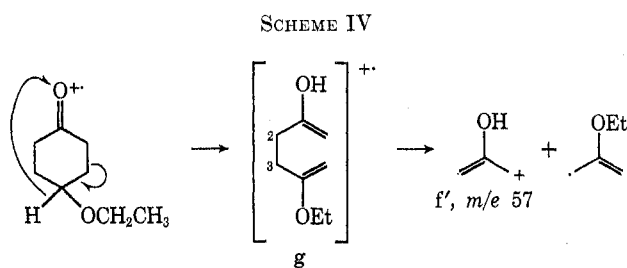
Peak	R = OH ^a	R = OMe ^a	R = OEt	R = OBz	R = OSi(CH ₃) ₃	R = OCOC ₂ H ₅	R = 	R = Cl	R = SMe
M ⁺	114 (100)	128 (82)	142 (85)	204 (1)	186 (18)	218 (<1)	156 (4)	132 (21) 134	144 (100)
M - R•	97 (2)	97 (8)	97 (8)	...	97 (1)	97 (6)	...	97 (12)	97 (19)
M - RH	96 (17)	96 (14)	96 (8)	...	96 (3)	96 (64)	...	96 (6)	96 (17)
M - (R• + CO)	69 (20)	69 (24)	69 (23)	69 (1)	...	69 (10)	69 (34)
M - (RH + CO)	68 (34)	68 (60)	68 (30)	68 (18)	...	68 (18)	68 (18)
M - CO	86 (4)	100 (6)	114 (9)	...	158 (2)	104 (2) 106	116 (8)
	60 (83)	74 (100)	88 (23)
	55 (84)	55 (38)	55 (22)	55 (4)	55 (9)	55 (5)	55 (14)	55 (100)	55 (32)
	57 (69)	71 (93)	85 (76)	...	129 (46)	...	99 (100)	75 (2) 77	87 (23)

^a From the mass spectra of these compounds described in ref 6. ^b See Table I, footnote a.



have been observed in straight-chain ethyl ethers,¹² and a minute $M - 15$ peak is observed in Figure 1. Scission of the 3-4 and 5-6 bonds, followed by loss of the elements of cyclobutanone, would then result in the stable ion f at *m/e* 57.

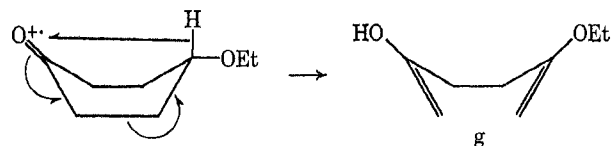
A second mechanism (Scheme IV) might involve ionization of the ketone function, followed by a six-centered McLafferty-type rearrangement of the hydrogen atom at C-4, to give species g. Cleavage of the 2-3 bond would then result in the stabilized allylic carbonium ion f'.



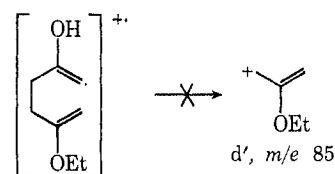
The validity of each mechanism may be tested by inspection of the mass spectrum (Table I) of 1',1'-d₂-4-ethoxycyclohexanone (XI). According to Scheme III, the peak at *m/e* 57 in Figure 1 should shift by two mass

(12) Reference 4, p 228.

units to *m/e* 59. In fact it remains exclusively at *m/e* 57, thus confirming Scheme IV as a plausible representation of this fragmentation pathway. For such an initial hydrogen transfer (Scheme IV) to take place, it appears from an inspection of molecular models for III that the molecule must be in a boat or twist conformation.



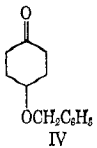
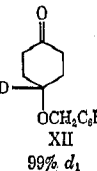
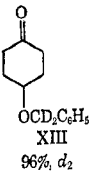
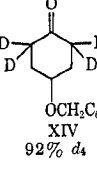
Also, it is apparent that the charge must remain with the carbonyl function throughout the fragmentation route. This conclusion is reached on the basis that if any charge distribution between the two oxygen atoms occurred during this sequence, a fragment ion at *m/e* 85 would result, with the charge localized on the ether oxygen. This fragment has the same mass value as that formed by simple cleavage α to the ether function,



as described above. However, if any part of the abundant fragment ion at *m/e* 85 were formed by this mechanism, deuteration at C-4 in III would not effect its position. In fact it shifts completely to *m/e* 86 in the spectrum of X (Table I), indicating its formation to be exclusively by way of the simple α -cleavage pathway.

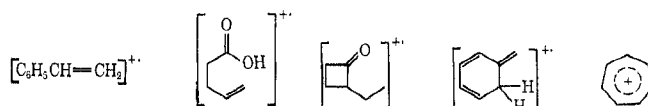
The data contained in Figure 1 and Table I thus demonstrate that 4-ethoxycyclohexanone (III) does exhibit some remote group interaction between the two functionalities, but its occurrence is considerably

TABLE III
 PRINCIPAL FRAGMENT IONS IN THE MASS SPECTRA OF 4-BENZYLOXYCYCLOHEXANONE
 AND ITS DEUTERATED DERIVATIVES AT 12 eV (PER CENT RELATIVE ABUNDANCE)^a

Compd	M ⁺	C ₇ H ₇ O	C ₈ H ₈	C ₈ H ₈ O ₂	C ₉ H ₁₀ O	C ₇ H ₈	C ₇ H ₇
 IV	204 (5)	107 (24)	104 (59)	100 (15)	98 (100)	92 (21)	91 (41)
 XII 99% d ₁	205 (7)	107 (29)	104 (60)	101 (15)	99 (100)	93 (13)	91 (38)
 XIII 96% d ₂	206 (14)	108 (16)	105 (76)	100 (44)	98 (11)	94 (56)	93 (48)
 XIV 92% d ₄	208 (36)	107 (33)	106 (40)	102 (100) ^e	101 (94)	92 (49) ^d	91 (8)
		108 (47)	104 (15) ^e	104 (15) ^e	102 (100) ^d		92 (49) ^d

Proposed structure in parent

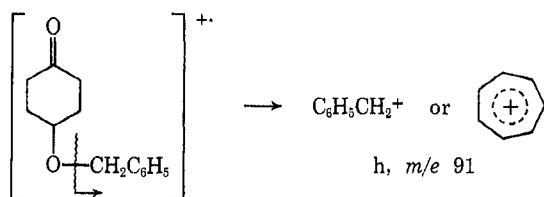
Molecular ion $C_6H_5CH=OH^+$



^a Although 12 eV is a "nominal" low voltage, attempts have been made to keep the ionizing voltage constant. ^b This spectrum was measured on the Atlas CH-4 spectrometer. ^c Includes contributions from C₈H₈D₂O₂ and C₈H₈D₄O. ^d Includes contributions from C₇H₈D and C₇H₈. ^e Includes contributions from C₈H₈D₄O₂ and C₈H₈.

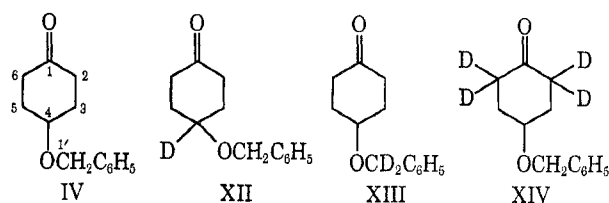
smaller than in the corresponding hydroxy (I) and methoxy (II) analogs. In order to explore further the scope and extent of this transannular migration, we have investigated the mass spectral properties of 4-benzyloxy-cyclohexanone (IV).

At high voltage the mass spectra of compounds containing benzyl groups are usually dominated by the highly stabilized benzyl or tropylium ion,¹³ and indeed 4-benzyloxy-cyclohexanone is no exception to this rule. At 70 eV (Figure 2a) the fragment ion at *m/e* 91 (h) carries nearly 50% of the total ionizing current.



The fragmentation pattern changes dramatically at low voltages (Figure 2b). The ion at *m/e* 91 decreases in intensity, and peaks at *m/e* 92 (C₇H₈), 98 (C₆H₁₀O), 100 (C₈H₈O₂), 104 (C₈H₈), and 107 (C₇H₇O) become significant in the spectrum. Of special significance are the fragment ions at *m/e* 100 and 104, since they must be formed through one or more skeletal rearrangement processes. In order to determine the specificity of

bond cleavage in the major fragmentation pathways, we have synthesized the labeled compounds XII, XIII, and XIV.

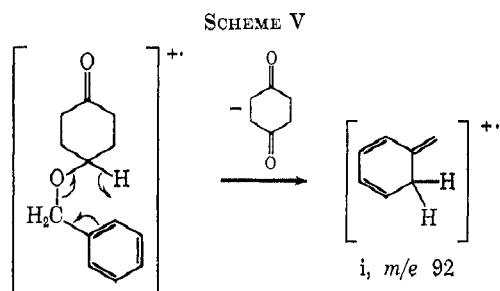


As shown in Table III, several of the peaks observed in the mass spectrum of IV are derived from fragmentations associated with the phenyl ring.¹⁴ In fact (Table II) very few of the navigable pathways usually taken by 4-substituted cyclohexanones after electron impact are followed by this compound. Even the ubiquitous fragment ion at *m/e* 55, originating from the usually facile cleavage α to the ketone function, is very small in this instance (4% relative abundance).

The fragment ion at *m/e* 92 (Figure 2a) is commonly observed in benzyl derivatives containing a γ proton¹⁵ and is derived from a six-centered hydrogen transfer of this proton to the benzene ring (Scheme V). That

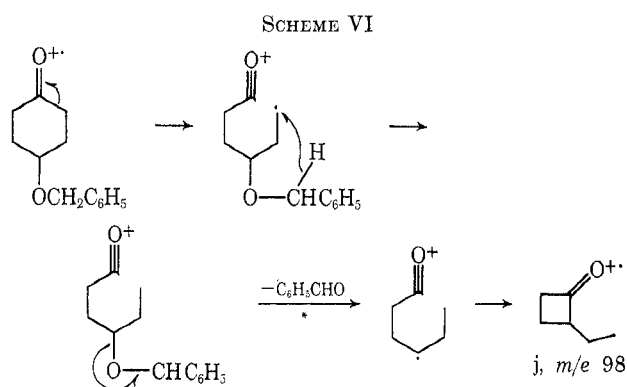
(14) This is not too surprising, since the ionization potential associated with the benzyl moiety (8.85 eV for benzyl methyl ether, is less than that for cyclohexanone (9.14 eV). For a compilation of ionization potentials see R. W. Kiser, "Introduction to Mass Spectrometry and Its Applications," Prentice-Hall, Inc., Englewood Cliffs, N. J., 1965.

(15) Reference 4, p 247.



this rearrangement is completely site-specific for IV is shown unambiguously by the fact that the peak is shifted quantitatively to m/e 93 in the mass spectrum of 4- d_1 -4-benzyloxycyclohexanone (XII, see Table III), and occurs exclusively at m/e 94 in the spectrum of the 1',1'- d_2 analog (XIII).

The base peak of the low-voltage spectrum (Figure 2b) occurs at m/e 98 and corresponds formally to the molecular ion of cyclohexanone. According to the labeling data (Table III), a hydrogen atom is transferred from the benzyl position to the ring, with concomitant loss of benzaldehyde. A possible mechanism for this fragmentation is shown in Scheme VI. Initial



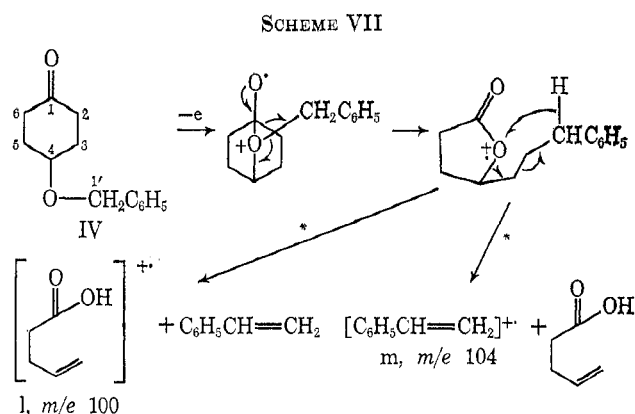
ionization of the ketone function, followed by a six-centered hydrogen transfer, would give a stabilized benzyl radical, which could decompose further, with generation of benzaldehyde, to yield ionized 2-ethylcyclobutanone (j) as the final product. The corresponding ion from 2,2,6,6- d_4 -4-benzyloxycyclohexanone (XIV) is split between m/e 101 and 102 (Table III), and that from XIII between m/e 98 and 99. One possible explanation for these facts is deuterium scrambling between the benzyl and the α positions in the molecular ion prior to the decomposition, analogous to that observed in 2,2,6,6- d_4 -4-methoxycyclohexanone^{6,16} and 3,3,5,5- d_4 -cyclohexanol.¹⁷ The consequences of this phenomenon will be discussed below in relation to the other major ions observed in the mass spectrum of this compound.

As indicated earlier, peaks at m/e 100 ($C_5H_8O_2$) and 104 (C_8H_8), whose masses and elemental compositions together equal those of the molecular ion, must necessarily be formed through a rearrangement process. From a consideration of the corresponding peaks (Table III) in the spectra of the labeled compounds,

(16) Green⁶ has postulated that a similar process was in effect before decomposition of the molecular ion of 2,2,6,6- d_4 -4-methoxycyclohexanone.

(17) H. Budzikiewicz, Z. Pelah, and C. Djerassi, *Monatsh. Chem.*, **95**, 158 (1964).

it is apparent that these two fragments arise in the same process, with charge retention on each fragment. Indeed, the most satisfactory mechanism (Scheme VII) accounting for the available data leads to struc-

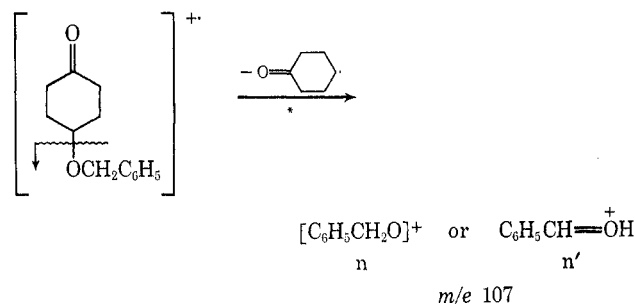


tures for these two fragments which are both capable of supporting the ionizing charge.

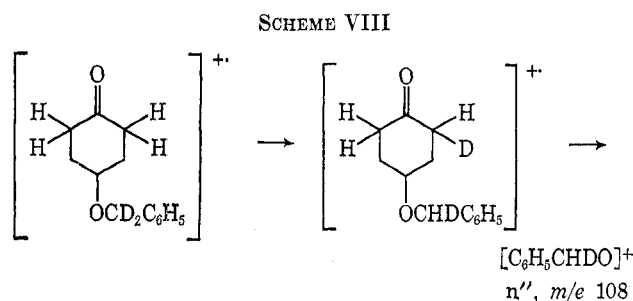
Since the peak (m/e 104 in Figure 2) corresponding to ionized styrene remains unlabeled in the spectrum of the 4- d_1 analog (XII), the possibility of a 1,2-benzyl or a 1,3-phenyl migration may be eliminated from any mechanistic considerations. The corresponding peak in the 1',1'- d_2 -4-benzyloxycyclohexanone (XIII) spectrum is split unevenly (3:2) between m/e 105 and 106, confirming a benzyl migration and suggesting that, to a large extent, one deuterium is lost from the benzyl position along the fragmentation route. The residue at m/e 106 may be accounted for by invoking deuterium scrambling prior to fragmentation. Similarly, the corresponding peak in XIV occurs predominantly at m/e 106 (Table III), suggesting the participation of C-2 (C-6) in the rearrangement pathway. A possible mechanism for these observations is shown in Scheme VII.

A transannular interaction between the two functional groups, similar to that observed in the 4-hydroxy- (I) and 4-alkoxy- (II, III) cyclohexanones, is postulated as the initial step, followed by cleavage of the 1-2 bond and rearrangement of the benzyl group to C-2. Hydrogen transfer in a six-centered transition state then gives two species, an unsaturated acid (l) and styrene (m), both capable of supporting the ionizing charge. Except for the small fragment ion at m/e 104 in the spectrum of the 2,2,6,6- d_4 analog (XIV), which may be formed by another, more subtle pathway, this mechanism accommodates all the available data from the labeled compounds.

The last significant peak in the low-voltage spectrum (Figure 2b) of IV occurs at m/e 107 (C_7H_7O), and is



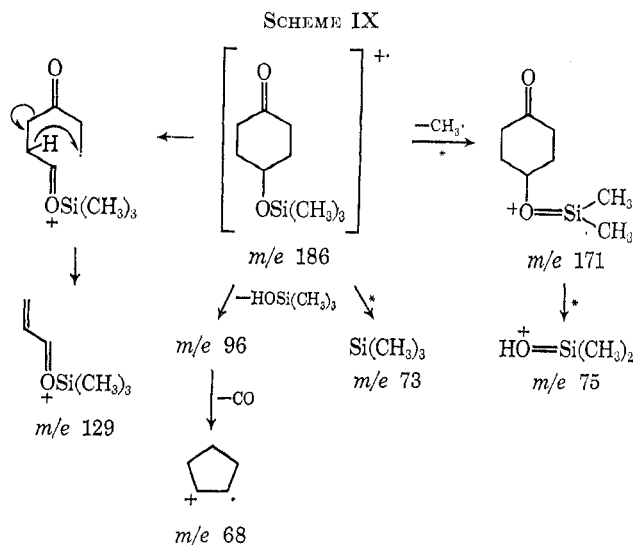
probably derived by simple cleavage of the benzyloxy group from the ring, with charge retention on the aromatic moiety. Although the formal structure of this fragment would be n , a more plausible representation may be n' . The labeling data supports such a mechanism (Table III), but even for this simple cleavage, it is apparent that some scrambling occurs prior to fragmentation, since peaks at m/e 109 and 108, in about a 2:1 ratio, are observed in the spectrum of the 1',1'- d_2 analog (XIII). Scheme VIII outlines how such a process could give rise to m/e 108 from XIII.¹⁶



In order to define further the scope of these remote group interactions, it was decided to examine next the effect on the mass spectra of changing the type of group attached to the oxygen at the 4 position of a cyclohexanone ring, as well as of replacing the oxygen by other heteroatoms bearing a lone pair of electrons.

To investigate the first point we have measured the mass spectra of cyclohexanone-4-trimethylsilyl ether (V),¹⁸ 4-benzoyloxycyclohexanone (VI),¹⁹ and 1,4-cyclohexanedione monoethylene ketal (VII). In none of the spectra was there evidence of an electron impact induced rearrangement process. In fact, the major fragmentation patterns are those expected from the individual groups in the corresponding monofunctionalized molecules (Table II).

The spectrum of V (Figure 3) is relatively uncomplicated, and possible routes to the major fragment ions are shown in Scheme IX. The absence of any obvious rearrangement processes is very striking, in view of the



(18) This compound was made in these laboratories by Dr. J. Diekman.
(19) Synthesized by Dr. M. M. Green.

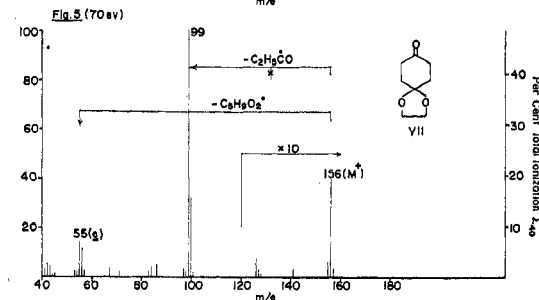
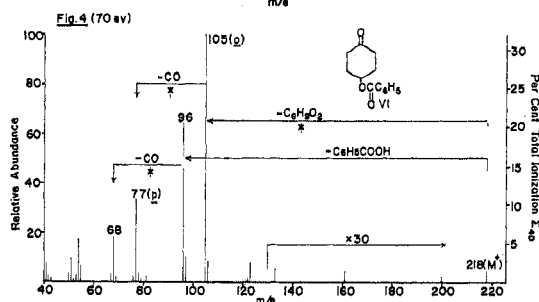
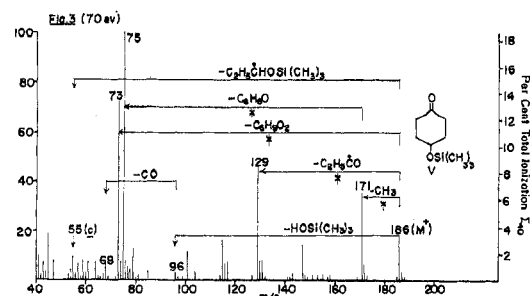


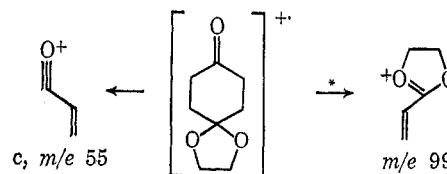
Figure 3.—Mass spectrum of cyclohexanone-4-trimethylsilyl ether (V).

Figure 4.—Mass spectrum of 4-benzoyloxycyclohexanone (VI).
Figure 5.—Mass spectrum of 1,4-cyclohexanedione monoethylene ketal (VII).

copious number of such fragmentations found in the mass spectra of other trimethylsilyl derivatives.²⁰

Although the ionization potentials of the two functional groups are similar,²¹ the major navigable pathways in the fragmentation (Figure 4) of 4-benzoyloxycyclohexanone (VI) are directed by the ester grouping and are in fact quite characteristic of simple benzoic acid esters²² (see m/e 105 and 77). The other major peaks at m/e 96 and 68 are derived from loss of benzoic acid, followed by elimination of carbon monoxide, as shown in Scheme X.

In a similar way the mass spectrum (Figure 5) of cyclohexanedione monoethylene ketal (VII) is dominated by fragmentations triggered by initial ionization of the ketal moiety ($\Sigma_{40} = 49\%$ for m/e 99). In fact,



(20) For examples, see (a) J. Diekman, J. B. Thomson, and C. Djerassi, *J. Org. Chem.*, **32**, 3904 (1967); **33**, 2271 (1968); (b) P. Capella and C. M. Zorzut, *Anal. Chem.*, **40**, 1458 (1968); (c) G. H. Draffan, R. N. Stillwell, and J. A. McCloskey, *Org. Mass Spectrom.*, **1**, 669 (1968).

(21) The ionization potential of methyl benzoate (10.0 eV) is higher than that of cyclohexanone (9.14 eV) (see ref 14). However, the relative stability of the product ions and radicals probably determine the navigability of each fragmentation pathway for this compound.

(22) Reference 4, p 197.

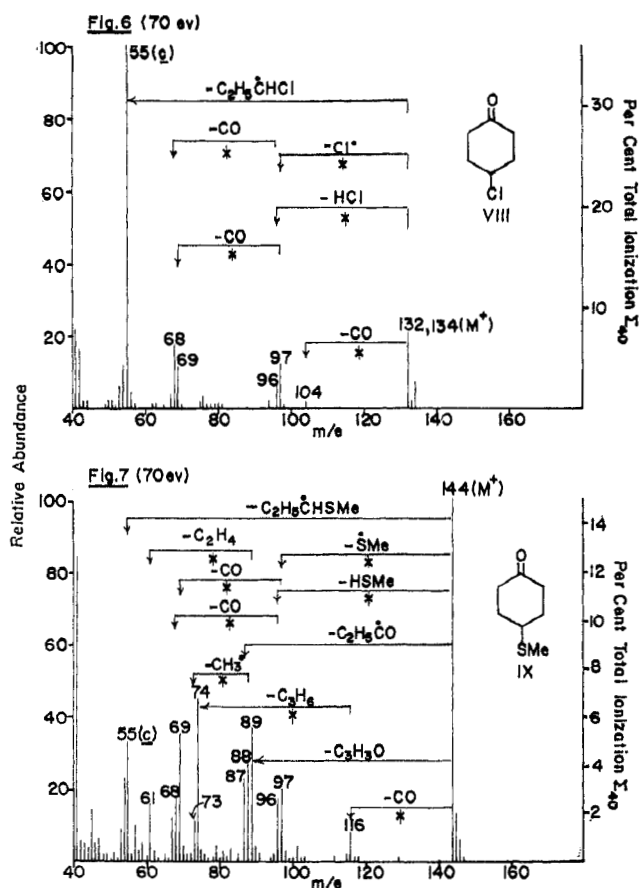
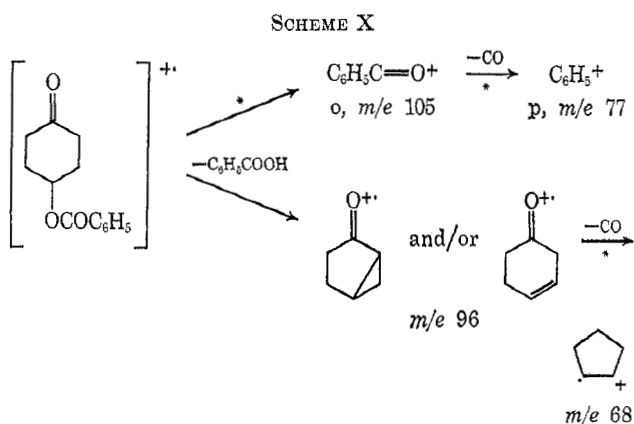


Figure 6.—Mass spectrum of 4-chlorocyclohexanone (VIII).
Figure 7.—Mass spectrum of 4-thiomethylcyclohexanone (IX).



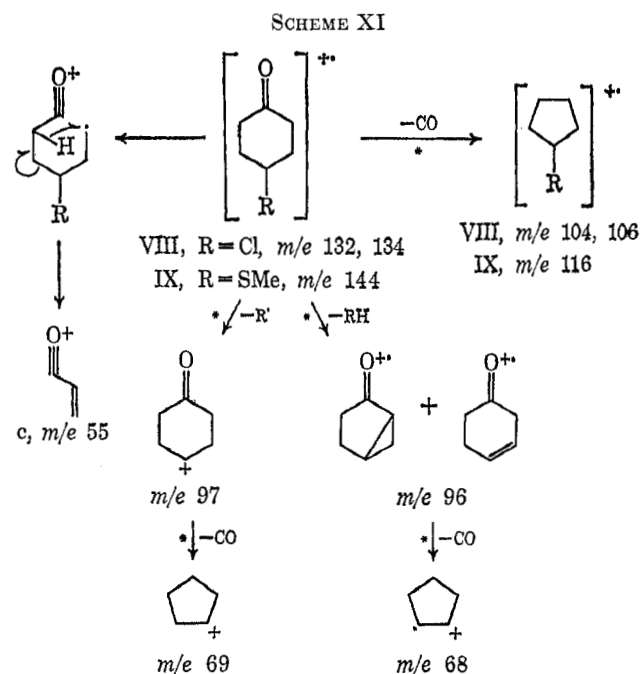
the corresponding ion from initial ionization of the ketone function (*c*, *m/e* 55) is responsible for only 6.9% of the same current at 70 eV. These results are in full agreement with earlier observations that ionization of the ketal function dominates the mass spectra of most compounds in which it is present.²³

We have also examined the mass spectra of 4-chlorocyclohexanone (VIII) and 4-thiomethylcyclohexanone (IX), to see if any transannular interaction occurs between a ketone group and a heteroatom other than oxygen. Apparently there are no such rearrangements among the electron impact induced fragmentations observed for these compounds. Instead, the modes of bond cleavage and charge retention are very similar for both compounds (Scheme XI), indicating that ioniza-

(23) Reference 4, p 265.

tion around the ketone function can be visualized as the trigger for most of the decompositions.

As can be seen in Table II and Figure 6, important bond cleavages for VIII involve expulsion of a chlorine radical and hydrogen chloride, followed by elimination of carbon monoxide in each case to yield ions at *m/e* 69 and 68, respectively. As may be expected from a comparison of the ionization potentials of cyclohexanone (9.14 eV) and of ethyl chloride (*ca.* 11.0 eV),²⁴ the base peak of this compound, as for cyclohexanone itself,²⁵ occurs at *m/e* 55 and carries 36.1% of the total ionizing current.



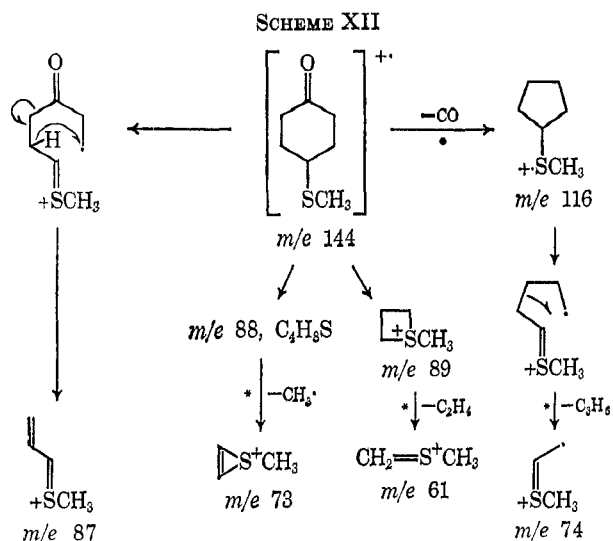
In addition to those fragmentations shown in Scheme XI, the mass spectrum (Figure 7) of 4-thiomethylcyclohexanone (IX) contains evidence for fragment ions in which charge retention is on the sulfur atom. This is not too surprising, since, on the basis of a comparison of the ionization potentials of the two functionalities,²⁶ initial ionization of IX may actually occur on the thiomethyl group. High-resolution measurements and metastable ion data form the basis for the suggested decomposition paths summarized in Scheme XII.

Worthy of special note are the fragment ions at *m/e* 74 and 87 in Figure 7, because their genesis is apparently quite similar to that of the corresponding ions in the alkoxy series. However, since no fragment ions resulting from rearrangement processes are observed, it can be seen that the ability of a heteroatom to use its lone pair of electrons to initiate a fragmentation pathway is not a prerequisite for transannular interaction with another functional group. In fact, a more plausible basis for prediction of the major fragmentation pathways of 4-substituted cyclohexanones is a comparison of the relative ionization

(24) R. I. Reed, "Ion Production by Electron Impact," Academic Press, New York, N. Y., 1962, p 9.

(25) D. H. Williams, H. Budzikiewicz, Z. Pelah, and C. Djerassi, *Monatsh. Chem.*, **95**, 166 (1964).

(26) The ionization potential of methyl isopropyl sulfide (8.7 eV, see ref 14) is in fact lower than that of cyclohexanone (9.14 eV).



potentials of the two functionalities, which in turn govern the position of initial ionization after electron impact.

Synthesis of Labeled Compounds.—For this investigation it was necessary to synthesize one compound with deuterium at the activated 2 and 6 positions, and others labeled at the “nonactivated” 1' and 4 positions of the cyclohexanone ring.

Using a previously described procedure,^{1,6} the former compound (XIV) was prepared by repeated equilibration of the parent ketone with sodium in a mixture of deuteriomethanol and deuterium oxide. A suitable precursor to 4-substituted cyclohexanones with a deuterium at C-1' (XI and XIII) and C-4 (X and XII) proved to be 1,4-cyclohexanedione monoethylene ketal (VII), which in turn was prepared from 1,4-cyclohexanediol (see Experimental Section). The overall reaction pathway is shown in Scheme XIII.

Experimental Section

Low-resolution mass spectra were measured by Mr. R. G. Ross using an A.E.I. MS-9 double-focussing spectrometer, and by Mr. R. Conover using an Atlas CH-4 spectrometer. High-resolution measurements with the MS-9 spectrometer were obtained by Mr. R. G. Ross. All compounds for mass spectral analysis were purified and checked for purity by vpc. The column used in each purification was 5% SE-30 on Chromosorb W (5 ft \times 0.25 in.). The oven temperature varied between 110 and 140°.

Infrared spectral data were recorded with a Perkin-Elmer Model 700 spectrophotometer, and elemental analyses were done by Mr. S. Meier and Mr. J. Consul of the Stanford microanalytical laboratory.

4-Benzoyloxycyclohexanone (VI)¹⁹ and 4-hydroxycyclohexanone (I) were prepared according to the method of Jones and Sondheimer.²⁷ Compound VI was thus obtained as a white, crystalline solid, mp 59–61° (lit.²⁷ mp 63°).

Anal. Calcd for C₁₂H₁₄O₂: mol wt, 218. Found: mol wt, 218 (mass spectrum).

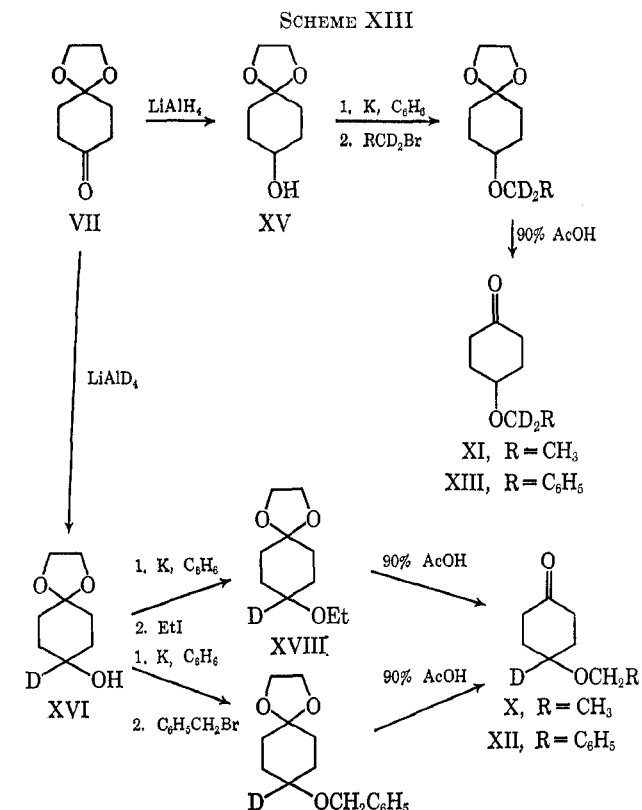
4-Hydroxycyclohexanone Ethylene Ketal (XV) and 1,4-Cyclohexanedione Monoethylene Ketal (VII).—Using a previously described procedure,²⁸ from 16 g (0.14 mol) of I and 9.3 g of ethylene glycol was obtained 8 g (36%) of XV as a colorless oil.

Following the procedure of Prins,²⁹ oxidation of 3.5 g (0.022 mol) of XV with chromium trioxide in pyridine gave a good yield of VII as colorless prisms, mp 65–67° (lit.²⁹ mp 72–73°).

(27) E. R. H. Jones and F. Sondheimer, *J. Chem. Soc.*, 615 (1949).

(28) H. Plieninger and H. J. Grasshoff, *Chem. Ber.*, **90**, 1973 (1957).

(29) D. A. Prins, *Helv. Chim. Acta*, **40**, 1621 (1957).



Anal. Calcd for C₈H₁₂O₂: mol wt, 156. Found: mol wt, 156 (mass spectrum).

4-Ethoxycyclohexanone (III).—A mixture of 190 mg (0.0012 mol) of XV and 150 mg (0.0038 g-atom) of potassium metal in 10 ml of dry benzene was heated at reflux under nitrogen for 18 hr. To this solution was added 5 ml of ethyl iodide all at once, and the mixture was heated for a further 6 hr. After cooling, methanol was added, followed by water and ether. The organic layer was separated, washed with water, dried (MgSO₄), and evaporated, giving 4-ethoxycyclohexanone ethylene ketal (200 mg, 100%) as a pale yellow oil.

A solution of this total product in 5 ml of 90% acetic acid was heated at 60° for 17 hr when water (5 ml) and ether (20 ml) were added. The organic layer was then separated, washed successively with saturated Na₂CO₃ solution (three times) and water, dried (MgSO₄), and evaporated, giving 140 mg (60%) of III as a pale yellow oil: ir (film) 1720 (C=O) and 1120 cm⁻¹ (COC); mass spectrum *m/e* 142 M⁺.

Anal. Calcd for C₈H₁₄O₂: C, 67.57; H, 9.92. Found: C, 67.44; H, 9.91.

4-d₁-4-Ethoxycyclohexanone (X).—To a stirred suspension of 100 mg (0.0024 mol) of lithium aluminum deuteride (Roth Chemicals) in 5 ml of dry ether was added a solution of 100 mg (0.64 mmol) of VII in 5 ml of ether. The mixture was heated at reflux for 2 hr, when excess deuteride was destroyed with saturated Na₂SO₄ solution. After filtration and evaporation there was obtained 100 mg (98%) of 4-d₁-4-hydroxycyclohexanone ethylene ketal (XVI) as a colorless oil.

Following a procedure similar to that described above for the preparation of III, deketalization of this total product gave 85 mg (92% from VII) of X as a pale yellow oil. Mass spectral analysis showed that the compound consisted of the d₁ (98%) and d₀ (2%) species.

Anal. Calcd for C₈H₁₃DO₂: mol wt, 143. Found: mol wt, 143 (mass spectrum).

1',1'-d₂-4-Ethoxycyclohexanone (XI).—Using the same procedure as that described above for III, from 115 mg (0.74 mmol) of XV, 110 mg (0.0028 g-atom) of potassium metal, and 2 ml of 1,1-d₂-ethyl bromide,³⁰ there was obtained 75 mg (81% from XV)

(30) This compound was prepared in 54% overall yield by reduction of acetic acid with lithium aluminum deuteride in diglyme [L. Friedman and A. T. Jurewicz, *J. Org. Chem.*, **33**, 1254 (1968)], followed by treatment of the resulting alcohol with bromine and triphenylphosphine in DMF [G. A. Wiley, R. L. Hershkowitz, B. M. Rein, and B. C. Chung, *J. Amer. Chem. Soc.*, **86**, 964 (1964)].

of XI as a pale yellow oil. A pure sample was obtained by vpc and consisted of 97% d_2 and 3% d_1 species by mass spectrometry.

Anal. Calcd for $C_8H_{12}D_2O_2$: mol wt, 144. Found: mol wt, 144 (mass spectrum).

4-Benzoyloxycyclohexanone (IV)²⁸ and Its 2,2,6,6- d_4 Analog (XIV).—Using a similar preparative procedure to that described above for the synthesis of III, from 200 mg (0.0013 mol) of XV, 150 mg (0.0038 g-atom) of potassium metal, and 350 mg (0.0021 mol) of benzyl bromide there was obtained an oily residue. After the total product had been heated in 10 ml of 90% acetic acid at 60° for 18 hr, a conventional work-up gave 250 mg of a mixture of three major components. Separation was accomplished by vpc, giving IV as a colorless oil: ir (film) 1720 (C=O) and 1110 cm^{-1} (COC); mass spectrum m/e 204 (M^+).

Anal. Calcd for $C_{13}H_{18}O_2$: C, 76.44; H, 7.90. Found: C, 76.51; H, 8.00.

Using a procedure described earlier,^{1,6} four repeated equilibrations of a portion of IV with 2 ml of a standard solution of sodium metal (75 mg) in deuteriomethanol (4.5 ml) and deuterium oxide (1.5 ml) gave a good return of XIV. Mass spectral analysis indicated a mixture of the d_4 (92%) and d_3 (8%) species.

Anal. Calcd for $C_{13}H_{12}D_4O_2$: mol wt, 208. Found: mol wt, 208 (mass spectrum).

4- d_1 -4-Benzoyloxycyclohexanone (XII).—Using a procedure similar to that described for X, from 100 mg (0.64 mmol) of 4- d_1 -4-hydroxycyclohexanone ethylene ketal (XVI), 80 mg (0.0020 g-atom) of potassium metal, and 190 mg (0.0012 mol) of benzyl bromide there was obtained a yellow oil (150 mg). Deketalization in 90% acetic acid, followed by final purification with vpc, gave XII as a colorless oil, consisting of >99% of the d_1 species by mass spectrometry.

Anal. Calcd for $C_{13}H_{15}DO_2$: mol wt, 205. Found: mol wt, 205 (mass spectrum).

1,1'- d_2 -4-Benzoyloxycyclohexanone (XIII).—A similar preparative procedure to that described for IV was utilized, except that 1,1- d_2 -benzyl bromide³¹ was used as the alkylating agent. Final purification by vpc gave XIII (96% d_2 , 4% d_1) as a colorless oil.

Anal. Calcd for $C_{13}H_{14}D_2O_2$: mol wt, 206. Found: mol wt, 206 (mass spectrum).

Cyclohexanone-4-trimethylsilyl Ether (V).¹⁸—Using a previously described procedure,^{20a} from 230 mg (0.0020 mol) of I and 0.25 ml of hexamethyldisilazane there was obtained a good yield of V. Final purification with vpc gave V as a colorless oil.

Anal. Calcd for $C_9H_{18}O_2Si$: mol wt, 186. Found: mol wt, 186 (mass spectrum).

4-Chlorocyclohexanone (VIII).—Utilizing a modification of a previously described procedure,³² hydrogen chloride gas was

passed for 2 hr through 50.76 g (0.52 mol) of 7-oxabicyclo[2.2.1]-heptane maintained at 120°. Vacuum distillation of the product gave a colorless oil which crystallized on cooling. Recrystallization from cyclohexane gave 53.1 g (73%) of 4-chlorocyclohexanol as colorless prisms, mp 84–86° (lit.³² mp 82–83°).

Oxidation of 2.69 g (0.023 mol) of this product with chromium trioxide in acetone,³³ followed by a conventional work-up procedure, gave 1.89 g (70%) of VIII as a colorless oil, bp 106–107° (16 mm), ir (film) 1715 cm^{-1} (C=O).

Anal. Calcd for C_6H_9ClO : mol wt, 132, 134. Found: mol wt, 132, 134 (mass spectrum).

4-Thiomethylcyclohexanone (IX).—Using a previously described procedure,³⁴ from 11.81 g (0.102 mol) of quinitol and 16.26 g (0.085 mol) of *p*-toluenesulfonyl chloride there was obtained 20.25 g (74%) of 4-tosyloxycyclohexanol as a white solid.

Oxidation of 9.7 g (0.036 mol) of this product with chromium trioxide in an acetone–acetic acid mixture³⁴ gave a good yield of 4-tosyloxycyclohexanone as a white, crystalline solid, mp 97–98°. Ketalization of 1.88 g (0.007 mol) of this compound with ethylene glycol in benzene, as described earlier for the preparation of XV,²⁸ gave 2.02 g (94%) of 4-tosyloxycyclohexanone ethylene ketal as a colorless oil which crystallized on standing. Recrystallization from an ether–pentane mixture gave colorless prisms, mp 69–71°.

Into a mixture of 0.5 g (0.022 g-atom) of sodium metal in 25 ml of DMF was bubbled methyl mercaptan gas until reaction was complete. After passing nitrogen through the system for 10 min, a solution of 1.59 g (0.0051 mol) of 4-tosyloxycyclohexanone ethylene ketal in 5 ml of DMF was slowly added. The mixture was stored in the dark for 116 hr, when a conventional work-up was performed. There was thus obtained 0.60 g (67%) of 4-thiomethylcyclohexanone ethylene ketal as a pale yellow oil.

Deketalization with 90% acetic acid as described above gave 0.35 g (77%) of IX as a pale yellow oil, ir (film) 1720 cm^{-1} (C=O) mass spectrum m/e 144 (M^+).

Anal. Calcd for $C_7H_{12}OS$: C, 58.32; H, 8.33. Found: C, 58.64; H, 8.48.

Registry No.—III, 23510-92-1; IV, 2987-06-6; V, 23510-94-3; VI, 23510-95-4; VII, 4746-97-8; VIII, 21299-26-3; IX, 23510-98-7; X, 23510-99-8; XI, 23511-00-4; XII, 23511-01-5; XIII, 23511-02-6; XIV, 23511-03-7; 4-tosyloxycyclohexanone, 23511-04-8; 4-tosyloxycyclohexanone ethylene ketal, 23511-05-9.

(32) E. A. Fehnel, S. Goodyear, and J. Berkowitz, *ibid.*, **73**, 4978 (1951).

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

(34) N. A. Nelson and G. A. Mortimer, *ibid.*, **22**, 1146 (1957).

(31) Prepared in 84% overall yield by reduction of ethyl benzoate with lithium aluminum deuteride, followed by treatment of the resulting labeled alcohol with 48% hydrobromic acid, as described by A. F. Gerrard and C. Djerassi *J. Amer. Chem. Soc.*, **91**, 6808 (1969).