Mass Spectrometry in Structural and Stereochemical Problems. CCXV.¹ Behavior of Phenyl-Substituted a.β-Unsaturated Ketones upon Electron Impact. Promotion of Hydrogen Rearrangement Processes²

R. J. LIEDTKE,^{3a} A. F. GERRARD,^{3b} J. DIEKMAN,³⁰ AND CARL DJERASSI*

Department of Chemistry, Stanford University, Stanford, California 94305

Received August 4, 1971

This study is concerned with the effect of phenyl substitution upon the mass spectral behavior of α,β -unsaturated ketones as an example of a substance with three potential charge-retaining sites (carbonyl, double bond, aromatic ring). Compounds of the type $C_{6}H_{5}(CH_{2})_{n}CH=CHCOCH_{3}$, n = 2-7 (I-VI), are examined. In general, the 70-eV spectra of these compounds are dominated by peaks at m/e 91 (tropylium ion) and m/e43 (α cleavage). At nominal 12 eV, however, lower activation energy rearrangement reactions are favored. 7-Phenylhept-3-en-2-one (II) exhibits intense peaks at m/e 84 and 130 (M - 58) in its mass spectrum which are notably absent in the spectrum of 3-octen-2-one (VII). The ion of mass 84 arises via a specific hydrogen transfer from the C₇ position while the origin of the M - 58 fragment is more complex and involves a double hydrogen atom rearrangement. The M - 58 peak in the spectrum of 6-phenylhex-3-en-2-one (I), on the other hand, is generated by transfer of a C_4 and C_6 hydrogen atom (Schemes I, IV, V). Alkyl radicals are expelled from the molecular ions of compounds II–VI. Elimination of a benzyl radical predominates for compounds in which n = 3-5, while other routes are favored in the higher homologs, n = 6-7. The loss of a water molecule is an important fragmentation pathway especially at low voltage for 9-phenylnon-3-en-2-one (IV) and 10-phenyldec-3-en-2-one (V). The "olefin McLafferty rearrangement" involves site specific hydrogen transfer when the hydrogen migrates from a benzylic position (e.g., 6-phenylhex-2-ene).

Part A

Recent years have seen much effort devoted to understanding the role various functional groups play in directing electron impact induced fragmentation processes.⁴ This has not only been essential for the facile application of mass spectrometry to problems of structure elucidation but has, moreover, enabled work to progress in this laboratory dedicated to the application of the principles of artificial intelligence to the interpretation of mass spectra.⁵ Naturally occurring molecules, however, often contain an array of functional groups. Thus, it is not only important to appreciate the fragmentation-directing capabilities of isolated functionalities in a molecule; it is of primary significance to determine the extent to which functional centers within a molecule interact with each other after ionization.⁶ In considering this problem with respect to a molecule containing functional groups A and B, two questions arise. (1) Are the individual fragmentation pathways associated with A and B retained in the spectrum of the bifunctional compound? (2) Do new decomposition routes not characteristic of either A or B individually appear? In answering, it is important to note the effect of varying the distance separating the A and B centers.

This paper is concerned with the mass spectrometric study of phenyl-substituted α,β -unsaturated ketones. In light of several recent investigations, this topic is

(5) (a) A. Buchs, A. M. Duffield, G. Schroll, C. Djerassi, A. B. Delfino, G. G. Buchanan, G. L. Sutherland, E. A. Feigenbaum, and J. Lederberg, J. Amer. Chem. Soc., 92, 6831 (1970); (b) A. Buchs, A. B. Delfino, A. M. Duffield, C. Djerassi, B. G. Buchanan, E. A. Feigenbaum, and J. Lederberg,

Helv. Chim. Acta, 53, 1394 (1970).
(6) See for example, (a) M. Sheehan, R. Spangler, and C. Djerassi, J. Org. Chem., in press; (b) J. R. Dias and C. Djerassi, unpublished work; (c) P. J. Wagner, Org. Mass Spectrom., 3, 1307 (1970); C. Fenselau, A. A. Baum, and D. O. Cowan, ibid., 4, 229 (1970).

particularly relevant. Although subject to little past attention, the mass spectral behavior of aliphatic unsaturated ketones has been the focus of a just completed, comprehensive study by Sheikh, et $al.^7$ In addition, the electron impact induced rearrangements of isomeric 1-phenylheptenes have seen recent intensive scrutiny,⁸ and the marked effect that a nonconjugated double bond can exert on the well-known fragmentation behavior of carbonyl compounds has just been evaluated.9

In the course of this work, then, compounds I-VI

were synthesized and their mass spectra were obtained at high and low ionizing energies.¹⁰ High-resolution mass measurements of fragment peaks were performed where necessary. Second-field free transitions were examined with computer assistance and first-field free transitions were observed using the defocusing method.¹¹ Compounds I-III attracted our main interest and a number of their deuterium labeled analogs were prepared, an effort that proved eminently useful.

Results and Discussion

The 70 and nominal 12 eV mass spectra of 7-phenylhept-3-en-2-one (II) and 8-phenyloct-3-en-2-one (III) are reproduced in Figures 1a,b and 2a,b, respectively. These suffice to demonstrate the typical fragmentation behavior exhibited by the compounds investigated. At 70 eV the principal peaks appear at m/e 91 (benzylic fission) and 43 (α cleavage adjacent to the vinylic bond). The spectrum of II exhibits a weak molecular ion even at low ionizing voltage, while that of III shows

(11) K. R. Jennings, J. Chem. Phys., 43, 4176 (1965).

⁽¹⁾ For the preceding paper, see P. D. Woodgate, K. K. Mayer, and C. Djerassi, J. Amer. Chem. Soc., in press. (2) Financial assistance by the National Institutes of Health (Grants

Nos. AM 12758 and AM 04257-11) is gratefully acknowledged.

^{(3) (}a) National Institutes of Health Predoctoral Fellow, 1968-1971; (b) Postdoctoral Research Fellow, 1968-1969; (c) Postdoctoral Research Fellow, summer, 1970. (4) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrom-

etry of Organic Compounds," Holden-Day, San Francisco, Calif., 1967.

⁽⁷⁾ Y. M. Sheikh, A. M. Duffield, and C. Djerassi, *ibid.*, **4**, 273 (1970).
(8) A. F. Gerrard and C. Djerassi, J. Amer. Chem. Soc., **91**, 6808 (1969).
(9) J. R. Dias, Y. M. Sheikh, and C. Djerassi, *ibid.*, submitted for publication.

⁽¹⁰⁾ The behavior of C₆H₆CH=CHCOCH₅ upon electron impact has been the subject of earlier work: J. Ronayne, D. H. Williams, and J. H. Bowie, ibid., 88, 4980 (1966).

a strong M^+ peak, a feature typical of the higher homologs IV-VI. Loss of water generates a significant M - 18 peak in the 12 eV spectrum (Figure 2b) of III and this process becomes increasingly more important in the spectra of 9-phenylnon-3-en-2-one (V) and 10phenyldec-3-en-2-one (VI). The dominant fragmentation process at low voltage for II-VI involves elimination of 58 mass units, formally the loss of a molecule of acetone from the molecular ion. Thus, the base peak in the 12 eV spectrum of 7-phenylhept-3-en-2-one (II) is found at m/e 130 while that of III appears at m/eThis rearrangement requires transfer of two hy-144. drogen atoms from the charge-retaining moiety to the ejected neutral fragment. Expulsion of a benzyl radical accounts for the abundant ion of mass 97 in Figure 1b and also the intense m/e 111 peak in Figure 2b. The molecular ion of 8-phenyloct-3-en-2-one (III) can also eject a 2-phenylethyl radical which generates a moderate peak at m/e 97 (Figure 2b). An intense peak in the 12 eV spectrum (Figure 1b) of 7-phenylhep-3-en-2-one (II) appears at m/e 84 and is the first subject to be dealt with in detail.

m/e 84 Peak.—The observation of an abundant ion of mass 84 (78%, $\Sigma_{40} = 26.6$)¹² in the spectrum of II (Figure 1b) is surprising since virtually no m/e 84 peak (2%, $\Sigma_{40} = 0.009$) is seen in the 12 eV spectrum (Figure 3) of 3-octen-2-one (VII). This observation is, in

$$\begin{array}{c} O \\ \parallel \\ \mathbb{R}CH_2CH_2CH \longrightarrow CHCCH_3 \\ \text{II, } \mathbb{R} = PhCH_2 \\ \text{VII, } \mathbb{R} = CH_3CH_2 \end{array}$$

itself, a striking reflection of the ability of a phenyl substituent to enhance a particular fragmentation pathway in concert with the α,β -unsaturated ketone function.

The mass 84 ion possesses the elemental composition C_5H_8O , thus requiring the transfer of one hydrogen atom for its formation. Its increased intensity at low ionizing energy suggests its generation directly from the molecular ion. Although no normal metastable peak can be seen, use of the defocusing method results in the observation of one parent, the molecular ion, for the mass 84 species. Examination of the mass spectra of the deuterium-labeled analogs IIa-f (Table I) clearly

TABLE I PEAK SHIFTS IN THE MASS SPECTRA OF ISOTOPICALLY LABELED ANALOGS OF 7-Phenylhept-3-en-2-one (II) for the m/e 84 Ion^a % of m/e 84 C₆H₃ which appears at 84 87 85 86 7,7-d2 IIa 4 96 $6, 6-d_2$ IIb 99 1 $5, 5-d_2$ He 1 99 $4-d_1$ IId $\mathbf{2}$ 98 1,1,1-d3 IIe 100 C_6D_5- IIf 95 $\mathbf{5}$

 $^{\alpha}$ All compounds have been corrected to 100% isotopic purity and the shifts calculated after correcting for natural $^{13}{\rm C}$ abundance.

demonstrates that bond fission occurs between carbon atoms 5 and 6 with carbon atoms 1-5 being en-

(12)~ The first number refers to the relative intensity, the second to the per cent total ionization.



Figure 1a.—Mass spectrum (70 eV) of 7-phenylhept-3-en-2-one (II) (top). Figure 1b.—Mass spectrum (12 eV) of 7-phenylhept-3-en-2-one (II) (bottom). Figure 2a.—Mass spectrum (70 eV) of 8-phenyloct-3-en-2-one (III) (top). Figure 2b.—Mass spectrum (12 eV) fo 8-phenyloct-3-en-2-one (III) (bottom).

compassed by the charge-retaining moiety. Most importantly, *specific transfer* of a C₇ hydrogen to the m/e 84 fragment occurs. In the spectrum of 7,7-d₂-7-phenylhept-3-en-2-one (IIa) 96% of the m/e 84 peak is shifted to m/e 85.



Figure 3.—Mass spectrum (12 eV) of oct-3-en-2-one (VII). Figure 4.—Mass spectrum (12 eV) of 6-phenylhex-3-en-2-one (I). Figure 5.—Mass spectrum (12 eV) of hept-3-en-2-one (XVIII).

Although providing evidence regarding the generation of the m/e 84 peak, the deuterium labeling results do not allow an unequivocal distinction between two logical pathways which can generate ions of mass 84 with totally different structures. One mode of genesis (Scheme I, path A) involves site-specific transfer of the benzylic hydrogen atom to the C₈ position with elimination of the elements of styrene and the production of a β , γ -unsaturated ketone ion b. The alternate route (path B) invokes transfer of the benzylic hydrogen atom to the ketone oxygen atom through an unusual eight-membered transition state,^{13,14} with migration of the double bond to the C₄-C₅ position and the generation of a dienol ion c.

Further investigation reveals that the scope of this



rearrangement process is not limited to α,β -unsaturated methyl ketones (Table II). The spectra of the

TABLE II Abundances of Ions Resulting from the Process Depicted in Scheme I for Various α,β -Unsaturated Compounds

			70	eV		eV
Compd		Mass of ion formed	% rel abun- dance	% total ioniza- tion, Σ40	% rel abun- dance	% total ioniza- tion, Σ40
C ₆ H ₅	vm	86	14	2.5	28	5.9
C ₆ H ₅	IX	70	30	6.5	42	15.1
C _e H ₅ OMe	x	100	47	8.0	63	14.8
C _e H ₅ OEt	XI	114	45	6.9	73	20.4
C ₆ H ₆	XII	98	54	12.2	100	40
C ₆ H ₅	хш	112	43	13.3	100	25
	XIV	84	14	3.1	43	9.2
	xv	84	15	3.7	41	8.2

unsaturated acid VIII, the aldehyde IX, the methyl ester X, and ethyl ester XI all show loss of a styrene molecule to give intense peaks at m/e 86, 70, 100, and 114, respectively. Similarly, the process depicted in Scheme I generates the base peak of the 12-eV spectrum of both the ethyl and propyl ketones XII and XIII. All of the above-mentioned compounds have one important feature in common, a benzylicly activated hydrogen atom at C₇. An allylic or tertiary hydrogen atom can also be transferred as shown by the m/e 84 peaks in the spectra of XIV and XV, respec-

⁽¹³⁾ An eight-membered transition state plays the dominant role in the origin of the important M^+ - CH₈ ion in heptyl vinyl ether.

⁽¹⁴⁾ M. Katoh and C. Djerassi, Chem. Commun., 1385 (1969).

tively, although these peaks are of only moderate abundance. As noted before, the secondary hydrogen atom at C_7 in 3-octen-2-one (VII) does not migrate.

From the above data it is clear that phenyl substitution enables this hydrogen transfer process to compete successfully with other possible fragmentation routes by providing two driving forces. First, benzylic carbonhydrogen bond dissociation energy is about 10 kcal/ mol less than that of a secondary carbon-hydrogen bond.¹⁵ Second, the phenyl group serves to stabilize the neutral olefin fragment formed. Furthermore, it is evident that ring size is of particular importance in the rearrangement process. If the phenyl group is one further position removed from the unsaturated ketone center, as in 8-phenyloct-3-en-2-one (III), only a very weak peak at m/e 84 is observed ($\Sigma_{40} = 1.2$, Figure 2b). In the spectrum of $8,8-d_2$ -8-phenyloct-3en-2-one (IIIa), 60% of the small m/e 84 peak shifts to

$$RCH_{2}CH_{2}CH_{2}CH=CHCCH_{3}$$
$$III, R = C_{8}H_{5}CH_{2}$$
$$IIIa, R = C_{6}H_{5}CD_{2}$$

m/e 85 implying that some 40% C₇ hydrogen atom transfer is occurring. Transfer of a C₈ hydrogen atom through a seven- or nine-membered transition state results not in the expulsion of a neutral olefin but in a diradical species which in the absence of internal hydrogen migration occurs as a phenyl-substituted cyclopropane. Although this path can compete with unfavorable secondary hydrogen atom transfer from C₇, the transition state energy for the process is not sufficiently low to enable favorable competition with alternative fragmentation paths available to ionized III.

m/e 104 Peak.—The 70 eV spectrum (Figure 1a) of 7-phenylhept-3-en-2-one (II) exhibits a moderately intense peak at mass 104. The genesis of this ion could follow the process outlined in Scheme I, the charge in this case being retained by the olefin fragment with ejection of a neutral C_5H_8O moiety. Transfer of the C_7 benzylic hydrogen atom is involved as the m/e104 peak shifts (>90%) to mass 105 in the spectrum of the 7,7-d₂ labeled analog IIa. It has been observed that the mass spectrum of 7-phenylhept-3-ene (XVI)



exhibits a base peak at m/e 104 both at high and low ionizing voltages.⁸ The generation of this 104 ion could similarly involve specific transfer of a C₇ hydrogen to C₈, the charge remaining with the phenyl-substituted olefin fragment e, C₈H₈ (Scheme II). McLafferty type rearrangements of ionized disubstituted alkenes are known, however, to be preceded by extensive hydrogen randomization and double bond isomerization.¹⁶ Therefore, it is desirable to examine the nature of the process depicted in Scheme II in more detail, since the result could have a bearing on this present study.

6-Phenylhex-2-ene (XVII) and its $6,6-d_2$ analog

(16) (a) B. J. Millard and D. F. Shaw, J. Chem. Soc. B, 1529 (1966);
 (b) M. Kraft and G. Spiteller, Org. Mass Spectrom., 2, 865 (1969);
 (c) K. K. Mayer and C. Djerassi, *ibid.*, in press.



XVIIa were conveniently prepared and their mass spectra were scrutinized. The ion of mass 104 accounts for the base peak in the 12 eV spectrum of XVII, while in the spectrum of XVIIa the base peak is quantitatively shifted to m/e 105. Thus, the placement of a phenyl moiety at the γ position relative to the double bond results in a site-specific migration of the benzylic hydrogen atom and the process does occur as illustrated in Scheme II. It might be speculated, then, that the production of the mass 84 species by the ionized unsaturated ketone II is simply a special case of this "olefin McLafferty rearrangement." This argument would require some special charge-stabilizing capacity associated with the ionized β,γ -unsaturated species b, at least in relation to the alternative charge-carrying C₈H₈ fragment. Since authoritative information on this point is lacking, the opposite position could be taken. That is, path B of Scheme I must be operative, since only the dienol ion c could be expected to compete with the mass 104 species (e) in its ability to carry the positive charge. Clearly the method to settle the question would be to determine the actual structure of the mass 84 ion (b or c). Our previous experience with the ionmolecule reactions of other enol and keto ions¹⁷ suggested that ion cyclotron resonance (icr) studies would be an excellent way to approach this task. Unfortunately, however, differentiation between the enone b and the dienol c was not possible by icr. Results of this work are given in part B.

 M^+ - 58 Ion. -A striking feature of the 12 eV spectrum (Figure 4) of 6-phenylhex-3-en-2-one (I) is the base peak at m/e 116 (M⁺ - 58), formally corresponding to loss of an acetone molecule from the molecular ion. This takes on added significance when the spectrum in Figure 4 is compared with that (Figure 5) of hept-3-en-2-one (XVIII). The most abun-



dant ion observed in the latter's spectrum has a mass of 97 (M⁺ - 15) and is the result of the conventional α cleavage.⁷ Moreover, no peak at all is seen at M⁺ - 58 (m/e 54). Thus, replacement of a methyl group with a phenyl moiety (XVIII, R = CH₃, vs. I, R = C₆H₅) has resulted in a dramatic change in favored decomposition pathways.¹⁸ Operating the mass spec-

⁽¹⁸⁾ Loss of what formally is a molecule of acetone has been noted previously (ref 7) in the spectra of simple unsaturated methyl ketones but only for i, $R > C_4$, and in these cases the process is not the most favored fragmentation path.



⁽¹⁵⁾ S. Meyerson and L. C. Leitch, J. Amer. Chem. Soc., 93, 2244 (1971), and references cited therein.

⁽¹⁷⁾ J. Diekman, J. K. MacLeod, C. Djerassi, and J. D. Baldeschwieler, J. Amer. Chem. Soc., 91, 2069 (1969).

trometer in the defocusing mode, two metastable transitions leading to the mass 116 species are observed (Scheme III) with direct formation from the molecular ion predominating [(1b)/(1a) = 2.3].

Several deuterium-labeled analogs of 6-phenylhex-3-en-2-one were synthesized and their mass spectra were recorded (Table III) in order to uncover the origin





of the two hydrogen atoms which must be transferred to the ejected neutral acetone molecule in the course of this process. Clearly a C₆ and the C₄ hydrogen atom are implicated. Migration of the C₄ hydrogen atom is remarkable, since fission through the C₃-C₄ olefinic bond must also occur, meaning that a total of three bonds to C₄ are broken. The possible interpretation outlined in Scheme IV is in accord with these labeling results.



Expulsion of $C_{2}H_{6}O$ by ionized 6-phenylhex-3-en-2one (I) is not atypical, as loss of 58 mass units constitutes common behavior of II–VI, especially at low ionizing energy where it accounts for the base peak in the 12 eV spectrum of each compound excepting 11phenylundec-3-en-2-one (VI), in which m/e 104 ion formation is slightly favored. With the several deuterium-labeled analogs of 7-phenylhept-3-en-2-one available, it is again possible to closely examine the M^{+} – 58 peak producing process (Table IV). As with 6phenylhex-2-en-2-one a major source of migrating hydrogen is the benzylic C₇ position and two progenitors are found for the M^{+} – 58 ions formed in the first field free region, the molecular ion (m/e 188) and the

 $M^+ - 43$ ion (*m/e* 145), the relative intensity being 1.6/1.¹⁹ The labeling results of II are more complex than those of I, since only 23% transfer of the C₄ vinylic hydrogen is observed and notably $52\%^{20}$ of the M^+ - 58 peak shifts to M^+ - 59 when the aromatic ring hydrogens are replaced with deuterium.

The labeling results are consistent with prior exchange of hydrogen between *certain* positions (note that IIb and IIf give clean distributions) before rearrangement and/or several differing specific paths. Nevertheless, since the aromatic and benzylic positions are the predominant sources of migrating hydrogen, a process such as that outlined in Scheme V $(j \rightarrow k)$



appears reasonable. The scheme has the advantage of accounting for $M^+ - 58$ ion generation irrespective of the distance between the phenyl and α,β -unsaturated ketone function. The only further stipulation is that the alkyl chain be allowed to coil in such a way as to bring the two groups into proximity, which certainly seems plausible.^{6,15} The only higher homolog for which a labeled derivative was available is 8-phenyloct-3-en-2-one (III). In the spectrum of $8,8-d_2$ -8phenyloct-3-en-2-one (IIIa) 41% of the $M^+ - 58$ peak is shifted to $M^+ - 59$ and 9% appears at $M^+ -$ 60. Thus, the benzylic position continues to be a major source of transferred hydrogen.

Like the process outlined in Scheme I, this double hydrogen rearrangement is not limited to ionized unsaturated methyl ketones. The α,β -unsaturated aldehydes IX and XIX exhibit intense M⁺ - 44 peaks in their 12 eV mass spectra while the ethyl and propyl unsaturated ketones of XII and XIII generate abundant M⁺ - 72 and M⁺ - 86 ions, respectively (Table V). Furthermore, allylic or tertiary hydrogen centers readily trigger this process (XIV, XV, XXII). On the other hand double hydrogen transfer is not such a favored fragmentation path for the unsaturated esters and acids examined.

⁽¹⁹⁾ In instances in which a value such as this is cited, the number given reflects the behavior of only those ions possessing an amount of excess energy such that they fragment in the first field free region. Thus, the behavior of only a small group of ions is observed. Those higher energy ions fragmenting in the source area which constitute the normal mass spectrum could give a quite different value.

⁽²⁰⁾ The 52% is a minimum value since correction for deuterium incorporation $(71\% d_5, 24\% d_4, 5\% d_5)$ was made assuming equal distribution of label about the ring positions; furthermore, it is not known whether hydrogen transfer originates from a specific ring position(s).

TABLE IV

Deuterium Incorporation into the Expelled Neutral Fragment during the Formation of the M - 58 Peak in the Spectrum of 7-Phenylhept-3-en-2-one (II)^a

C ₆ H ₅ 7 6 4		% M+ – 58	% M+ - 59	% M+ - 60	% M+ - 61	% M+ - 62	% M+ - 63
$7,7-d_2$	IIa	12	77	12			
$6, 6-d_2$	\mathbf{IIb}	97	3				
$5, 5-d_2$	IIc	89	11				
$4-d_1$	\mathbf{IId}	77	23				
C_6D_5	\mathbf{IIf}	48	52				
$1, 1, 1-d_3$	IIe				100		
1,1,1,3,5,5-d6	\mathbf{IIg}					10	90
		~					

^a Data obtained at 12 eV. See footnote α , Table I.

 Table V

 Abundances of Ionis Formed by Double Hhydrogen Transfer with Fission through the Olefinic Bond

 After Ionization of Various Phenyl-Substituted Unsaturated Carbonyl Compounds

			70	eV	12 eV		
Compd		Peak formed by process	% rel abundance	% total ionization, Σ_{40}	% rel abundance	% total ionization, Σ_{40}	
C _b H ₅	1	116 (M - 58)	20	11	100	41.1	
C ₆ H ₅	XIX	116 (M - 44)	17	10	100	40	
C _u H ₃ O OEt	XX	116 (M - 88)	1.3	0.9	10	3.6	
C _e H _a	XXI	116 (M - 60)	2.5	1.6	92	19.7	
C ₆ H ₅	п	130 (M - 58)	60	10.5	100	33.3	
C _e H ₅	IX	130 (M - 44)	46	10	100	36	
C ₆ H ₅	XI	130 (M – 88)	36	5.5	38	10.5	
C _b H ₅ OMe	х	130 (M - 74)	37	6.3	60	14	
C ₆ H ₃ OH	VIII	130 (M - 60)	28	7	100	16.2	
	XXII	66 (M - 58)	9	2.4	23	5.8	
	XIV	80 (M – 58)	34	7.5	100	21.4	
	xv	82 (M - 58)	22	5.5	100	20	
C ₆ H ₅	XII	130 (M - 72)	40	9.7	74	29.6	
C _e H ₅	XIII	130 (M - 86)	35	10.9	82	20.5	

m/e 91 Peak.—As mentioned earlier, the mass 91 ion is a dominant feature of the mass spectra of II–VI at high electron beam energies. Its intensity sharply diminishes at 12 eV (Figure 1a vs. Figure 1b), and this behavior is consistent with a high activation energy for this bond cleavage process. Data in Tables VI and VII, however, indicate that the situation is more complex. Table VI lists the shifts of the m/e 91 peak in

the spectra of analogs Ia, IIa, and IIIa in which the benzylic position has been specifically deuterated. While 96% of the m/e 91 peak in the spectrum of ℓ , ℓ^2 -6-phenyl-3-en-2-one (IVa) is shifted to m/e 93, only 78% shifts to mass 93 in the spectrum of γ , γ - d_2 -7phenylhept-3-en-2-one (IIa), 13% being found at m/e92 and 9% remaining at mass 91. Similarly intriguing, only 60% of the m/e 91 peak appears at mass 93 in the



ABELED ANALOGS OF 1-111"



^a Data collected at 70 eV; see footnote a, Table I.



C ₆ H ₆	% of peak at <i>m/e</i> 91 in the ——spectrum of II which appears at——						
$\tilde{\gamma}$ $\tilde{\gamma}$	×.	91	92	93	94	95	96
$C_6 D_5$	\mathbf{IIf}					8	92
$7,7-d_2$	IIa	9	13	78			
$6, 6-d_2$	IIb	87	13				
$5, 5-d_2$	IIc	78	22				
$4-d_1$	IId	97	3				
$1, 1, 1-d_3$	IIe	100	0				
$1, 1, 1, 3, 5, 5-d_6$	\mathbf{IIg}	78	22				

^a See footnote a, Table I; data taken at 70 eV and corrected for contribution of m/e 92 peak.

spectrum of $8,8-d_2$ -8-phenyloct-3-en-2-one, 18% actually remaining at m/e 91. It is evident that considerable hydrogen exchange is occurring in the last two cases. Shifts of the m/e 91 peak in the other available labeled analogs of 7-phenylhept-3-en-2-one (II) are shown in Table VII. The major contributors to the exchange process are the allylic hydrogens at C₅ and those at C₆.²¹

Generation of the m/e 91 peak in 6-phenylhex-3-en-2-one (I) is especially facile because the bond cleaved is both benzylic and allylic. This accounts for the relatively low degree of hydrogen exchange. In compounds II and III a slightly higher energy bond must be broken and additionally, more degrees of freedom are available in which to distribute excess excitation energy. Hydrogen exchange, thus, is more evident in the latter two cases. It is also conceivable that low activation rearrangement pathways involving hydrogen exchange could be directly contributing to mass 91 ion formation and concomitantly to the labeling results. The tropylium ion structure l is favored for the m/e



91 species²² and in these examples cleavage may be accompanied to some extent by simultaneous rearrangement to l.

Other $C_{18}H_{16}O$ Double Bond Isomers.—It has been observed that the mass spectra of 1-phenylheptene isomers are qualitatively identical owing to the ease of double bond migration after ionization.⁸ Therefore, it is pertinent to compare the mass spectra of phenylsubstituted unsaturated ketone isomers of II in which the double bond is not in conjugation with the carbonyl function (e.g., XXIII–XV). The only abundant ion



generated by ionized 7-phenylhept-6-en-2-one (XXIII) at 70 eV has mass 130. Minor fragments of mass 43, 91, and 115 are observed. At 12 eV the ion of mass 130 accounts for 85% of the total ion current.²³ While in the case of 7-phenylhept-3-en-2-one (II) a double hydrogen transfer process is required for $M^+ - 58$ ion formation, in this instance a simple McLafferty rearrangement with preferred charge retention by the olefinic species m rather than the carbonyl-containing fragment no doubt accounts for the m/e 130 peak (Scheme VI).



The spectra of ionized 7-phenylhept-5-en-2-one (XXIV) at 70 and 12 eV are virtually identical with those of XXIII except for the much smaller molecular ion peak in the former. To elucidate the rearrangement pathway involved in the formation of the mass 130 species from ionized XXIV, the spectrum of its $7.7-d_2$ labeled analog XXIVa was examined. Direct transfer of a C₇ deuterium atom to the carbonyl oxygen through an eight-membered transition state, $n \rightarrow p$ (Scheme VII, path A) would require that the 130 peak shift solely to m/e 131 in the spectrum of XXIVa. In actual fact, however, 48% of the m/e 130 peak appears at m/e 131 and 52% at m/e 132. This striking result is best accommodated by double bond isomerization (1,3-hydrogen shift) to the C_6-C_7 position after ionization giving o and subsequent transfer of either hydrogen or deuterium from C5 via a six-membered transition state yielding respectively ion q $(m/e \ 132)$ and ion p $(m/e \ 131)$.

The β,γ -unsaturated ketone isomer 7-phenylhept-4en-2-one (XXV), on the other hand, exhibits a mass spectrum qualitatively similar to that of 7-phenylhept-3-en-2-one (II). The m/e 91 and 43 ions account for slightly higher portions of the ion current in the 70 eV spectrum of XXV compared with that of II, and at low

⁽²¹⁾ The data are internally consistent; *i.e.*, the sum of deuterium migration from positions C₄, C₅, and C₆ approximately equals that observed when C_7 and the aromatic ring positions are labeled.

⁽²²⁾ I. Howe and F. W. McLafferty, J. Amer. Chem. Soc., 93, 99 (1971). and references cited therein.

⁽²³⁾ Corrected for 1*C isotope contributions. The molecular ion accounts for the remaining 15%



ionizing voltage a notable difference is that the m/e97 ion $(M^+ - 91)$ rather than m/e 130 is base peak. These observations are reasonable, since α cleavage involves allylic rather than vinylic fission and the bond broken in the process of m/e 91 and m/e 97 generation is both benzylic and allylic in the case of XXV. Migration of the double bond into conjugation with the carbonyl group prior to fragmentation would account for the qualitative similarities of the spectra.

Part B

Expulsion of various phenyl-substituted alkyl radicals from the molecular ions of II-VI is a favored fragmentation behavior (Table VIII). Peaks formed as a result of these processes generally increase in relative intensity at low ionizing energy, indicating that low activation energy rearrangement pathways are likely being followed. Phenyl substitution is not a strict requirement for radical expulsion. The 12-eV spectrum of oct-3-en-2-one (Figure 3) contains a prominent m/e97 ion (M⁺ - C₂H₅) for which structure r, consistent with labeling results, has been postulated.⁷ Preferential formation of this six-membered ring structure is a satisfactory explanation for the predominance of m/e97 ion formation (M⁺ - R·) in the series of unsaturated ketones VII, XXVII, and XXVIII.



Examination of the data presented in Table VIII reyeals, however, that the relative stability of the departing radical has an important influence on the most favored ejection modes. Six-membered ring formation would be consistent with the generation of the intense m/e 97 peak (M⁺ - 91) in the spectrum (Figure 1b) of 7-phenylhept-2-en-3-one (II). However, in the spectrum of 8-phenyloct-3-en-2-one (III) and 9-pyenyl-3-en-2-one (IV) loss of the more stable benzyl radical effectively dominates the factor(s) (ring formation is a plausible one) favoring production of the m/e 97 species in the aliphatic ketone series. On the other hand, benzyl radical expulsion is not the dominant route followed by ionized 10-phenyldec-3-en-2-one (V) and 11phenyldodec-3-en-2-one (VI), thus confirming that the interplay of several factors must determine the extent to which the various possible radicals are ejected.

The shifts of the mass 97 peak in the spectra of the labeled analogs of II appear in Table IX. Significant exchange of the C_7 (benzylic), C_5 (allylic), and aromatic ring hydrogen atoms occurs before cleavage. A reciprocal hydrogen transfer process of the type illustrated in Scheme VIII (s \rightarrow t) offers a plausible ex-



planation for C₇-C₅ hydrogen exchange. As observed for the mass 91 ion, $M^+ - 91$ ion formation by III upon electron impact is accompanied by increased exchange of the benzylic hydrogens relative to II. In the 12 eV spectrum of the $8,8-d_2$ analog IIIa only 35% $M^+ - 93$ loss is observed while $48\% M^+ - 92$ and $17\% M^+ - 91$ expulsion is seen.

Further Discussion.—An abundant metastable ion at m/e 56.7 is found in the spectrum of II representing the ejection of a methyl radical from the mass 84 ion. Metastable defocusing confirms the mass 84 ion as a parent to the m/e 69 species. In the spectrum of $1,1,1-d_3$ -phenylhept-3-en-2-one (IIe), the m/e 84 peak shifts quantitatively to m/e 87 while 84% of the m/e 69

TABLE	VIII
-------	------

PHENYL-SUBSTITUTED ALKYL RADICAL EXPULSION PROCESSES IN THE MASS SPECTRA OF THE

Phenyl-Substituted Ketones II-VI

Compd	$PhCH_2$ (M - 91)	Radical expelle PhCH ₂ CH ₂ . (M - 105)	ed (relative abundar $Ph(CH_2)_2CH_2 \cdot (M - 119)$	nce, 12 eV) Ph(CH ₂) ₃ CH ₂ . (M - 133)	$\frac{Ph(CH_2)_4CH_2}{(M - 147)}$
$C_{\theta}H_{\delta}(CH_2)_{\theta}CH=CH(C=O)CH_{\theta}$ II	97ª (57)b				
$C_6H_5(CH_2)_4CH=CH(C=O)CH_3$ III	111 (87)	97(14)			
$C_6H_5(CH_2)_5(CH=CH(C=O)CH_3$ IV	125(79)	111(41)	97(52)		
$C_6H_5(CH_2)_6CH=CH(C=O)CH_3$ V	139 (18)	125(52)	111 (9)	97 (19)	
$C_6H_5(CH_2)_7CH \longrightarrow CH(C \longrightarrow O)CH_3$ VI	153(3)	139 (2)	125(20)	111 (6)	97(15)

^a Mass of ion formed. ^b Relative abundance.

TABLE IX							
Shift of m/e 97	PEAK IN THE MASS SPECTRA OF DEUTERIUM-LABELED ANALOGS ^a of II						

CH A A	0 	<u></u>			neek which enn	eers of		
		97	98	99	100	101	102	103
$C_6 D_5$	\mathbf{IIf}	70, ^b 79°	30, 21					
$7, 7-d_2$	IIa	84, 63	15, 36	1, 1				
$6, 6-d_2$	\mathbf{IIb}		2, 2	98, 98				
$5, 5-d_2$	IIc	1, 4	45, 42	54, 54				
$4-d_1$	\mathbf{IId}	0, 0	100, 100					
$1, 1, 1-d_3$	IIe			1, 1	99, 99			
1,1,1,3,5,5-d ₆	\mathbf{IIg}					1, 3	55, 55	44, 42
^a See footnote a, '	Table I.	^b 70 eV. ° 12 eV.					·	,

TABLE X Abundance of m/e 104, M⁺ - 104, and M - H₂O Ions in Spectra of II-VI (12 eV)

		m/e 104		M+ - 104		M + _ H ₂ O	
Compd		% rel abundance	% total ionization, Σ40	% rel abundance	% total ionization, Σ_{40}	% rel abundance	% total ionization, Σ40
$C_6H_5(CH_2)_3CH = CH(C=O)CH_3$	II	7	2.3	78	26.6	2	0.7
$C_6H_5(CH_2)_4CH=CH(C=O)CH_3$	III	40	6.0	8	1.2	14	2.1
$C_{6}H_{5}(CH_{2})_{5}CH = CH(C = O)CH_{3}$	IV	45	5.5	9	1.1	51	6.1
$C_6H_5(CH_2)_6CH=CH(C=O)CH_8$	V	43	4.9	2	0.2	56	6.4
$C_6H_5(CH_2)_7CH=CH(C=O)CH_3$	VI	60	12	2	0.4	15	3

peak remains at mass 69, demonstrating that predominant ejection of the C_1 carbon atom and attached hydrogens is taking place (Scheme IX, $R = CH_3$). Sig-



nificant m/e 69 peaks are likewise seen in the 70 eV spectra of 8-phenyloct-4-en-3-one (XII, R = C₂H₅) and 9-phenylnon-5-en-4-one (XIII, R = C₃H₇). The appropriate metastable peaks are observed for these latter two cases supporting the pathway outlined in Scheme IX.

Phenyl substitution stimulates the loss of H_2O from the molecular ions of compounds III-VI at low ionizing voltage (Table X). In the spectrum of 11-phenylundec-3-en-2-one (VI) the M^+ – 18 ion has a 54% relative abundance, the base peak being the molecular ion. Similarly, the mass 104 ion, although of minor importance in the 12 eV spectrum of II (Figure 1b), exhibits a higher degree of prominence in the low voltage spectra of III-VI and the mass 104 ion, in fact, is the most abundant fragment generated by VI upon ionization. Large-membered transition states could be involved on the transfer of the single hydrogen atom that is necessarily part of this latter process. On the other hand, double bond migration to the γ,δ position relative to the benzylic carbon atom followed by hydrogen transfer through a favorable six-membered ring is also possible. In the spectrum of $8, 8-d_2-8$ phenyloct-3-en-2-one (IIIa) 63% of the m/e 104 peak moves to mass 105, 17% to 106, with 20% remaining at m/e 104. Thus, the progenitors of the mass 104 species possess sufficient lifetimes for extensive hydrogen exchange to take place, and concomitant double bond migration in these ions would not be surprising. Mass 104 ion generation by various 1-phenylheptene isomers was found to be far from straightforward, and several rearrangement pathways involving extensive 1, 2 and 1, 3 hydrogen shifts were invoked to explain the labeling data.⁸

Ion Cyclotron Resonance Studies.—In order to differentiate between paths A and B (Scheme I), facile and unambiguous generation of the isomeric enone b and dienol c $C_{\delta}H_{6}O$ ions by electron impact followed by a comparison of the ion—molecule reactions of each by ion cyclotron resonance techniques would be necessary. The enone ion b is generated by ionization of pent-4-en-2-one (XXIX) and the ion cyclotron resonance spectrum of XXIX does display a strong molecular ion at mass $84.^{24}$ The two α -cleavage ions, m/e43 (aa) and 69 (bb), result from collision induced²⁵ or unimolecular decompositions of ionized pent-4-en-2one. Ion-molecule reactions produce the protonated molecular ion (u, m/e 85) and the loosely bound protonated dimer (v, m/e 169).^{17,22} Surprisingly, none of



the condensation reactions found in the ion cyclotron resonance spectra^{17,26} of saturated alkanones are ob-

(24) It is reported (E. Stenhagen, S. Abrahamsson and F. W. McLafferty, "Atlas of Mass Spectral Data," Vol. 1, Interscience Publishers, New York, N. Y., 1969, p 124) that this molecular ion of pent-4-en-2-one is very weak at 70 eV, but we observed that this peak carries 24% of the total ion current at 12 eV.

(25) F. Kaplan, J. Amer. Chem. Soc., 90, 4483 (1968).

(26) F. Kaplan, unpublished work; F. Kaplan, J. L. Beauchamp, J. Diekman, and C. Djerassi, unpublished observations.



Figure 6.—Ion cyclotron resonance spectrum of pent-4-en-2-one (XXIX), $\omega_1/2\pi = 123.0$ kcps, 6×10^{-6} Torr, 14 eV

served, thereby eliminating the possibility of utilizing condensation reactions to differentiate between the isomeric mass 84 ions. Such reactions are important in distinguishing between the enol and keto ions of acetone. Emphasis thus focussed on proton transfer reactions for purposes of distinguishing the enone b and dienol c isomers. Pulsed double resonance spectra of the protonated molecular ion u (m/e 85) reveal that only the m/e 43 acylium ion as transfers a proton to neutral pent-4-en-2-one. That proton transfer from the enone b (m/e 84) ion to neutral ketone does not occur was determined by pulsed double resonance experiments on the protonated molecular ion of 3-heptanone (equimolar mixture with pent-4-en-2-one).

Fragmentation of the molecular ion of 2-vinyl-1methylcyclobutan-1-ol (XXX) should yield the desired dienol ion c of mass 84. Although the 12 eV mass spectrum (Figure 6) of this compound indicates that the preferred ring fission involves loss of butadiene (XXX \rightarrow w, Scheme X), the m/e 84 peak (XXX \rightarrow c)



is of significant enough intensity $(47\%, \Sigma_{40} = 9.8)$ to be useful in ion cyclotron resonance experiments. With the intention of studying proton transfer from the dienol ion c to a neutral ketone acceptor, the ion cyclotron resonance spectrum of a mixture of $2,2,4,4-d_4$ -3heptanone²⁷ (XXXI) and 2-vinyl-1-methylcyclobutan-1-ol (XXX) was recorded. As anticipated, the only peaks observed, except for those attributed to the normal unimolecular decomposition of compounds XXX

(27) A deuterated analog (XXXI) of 3-heptanone was utilized so as to move the protonated molecular ion of 3-heptanone into a region of the spectrum entirely free of other peaks. The protonated molecular ion thus has a mass of 119 and the deuterated molecular ion a mass of 120.

and XXXI, are those associated with the protonated $(x, m/e \ 119)$ and deuterated $(y, m/e \ 120)$ molecular ions of $2,2,4,4-d_4$ -3-heptanone (XXXI). It was sur-

$\mathrm{CH}_3\mathrm{CD}_2\mathrm{COCD}_2\mathrm{CH}_2\mathrm{CH}_2\mathrm{CH}_3$	$\operatorname{OR}_{\parallel}^{\parallel}$ CH ₃ CD ₂ CCD ₂ CH ₂ CH ₂ CH ₂ CH ₃
XXXI	x, R = H, m/e 119 y, R = D, m/e 120

prising to observe that the dienol species (c) of mass 84 does not transfer a proton to the neutral ketone (XX-XI). The ion of mass 43 is the only significant proton transfer agent, as its signal pictured in the double resonance spectrum (Figure 7) is only 20% of its actual intensity. As observed in previous studies,¹⁷ the mass 58 acetone enol ion donates a proton; and to a very minor extent the enolic species of mass 76^{28} and the α cleavage ion of mass 59 also donate a proton to the 3heptanone analog (XXXI). Other work in these laboratories²⁹ has shown that triethylamine is far superior to aliphatic ketones in abstracting protons from charged species, but ion cyclotron resonance experiments involving a mixture of triethylamine and 2vinyl-1-methylcyclobutan-1-ol (XXX) indicated again that no proton transfer from the dienol ion c to triethylamine occurs.

Since no characteristic reactions were observed for the C_5H_8O ions of either the dienol (c) or enone (b) structure, no statement is possible concerning the structure of the mass 84 ion generated from 7-phenyl-3hepten-2-one (II). The inertness of the C_5H_8O ions toward ion-molecule reactions under experimental conditions¹⁷ in which the acetone enol and keto species do indeed react deserves further comment. Proton transfer reactions from the dienol c may be endothermic and thus not detectable. Although the C_3H_6O enol ion readily transfers a proton to neutral species, subtle changes in ion structure can totally alter the reactivity of the ion. The additional conjugated double bond in

(28) This enolic species is generated from 2.2.4.4-d4-3-heptanone via the McLafferty rearrangement.



(29) M. Sheehan and C. Djerassi, unpublished observations.

Observe m/e 119



Figure 7.—The pulsed double resonance spectrum of the M + 1 $(m/e \ 119)$ ion of 2,2,4,4-d₄-3-heptanone (XXXI) in an equimolar mixture of 2-vinyl-1-methylcyclobutan-1-ol (XXX), and 2,2,4,4-d₄-3-heptanone. The species of mass 119 is observed with $\omega_1/2\pi$ = 151.0 kcps, while frequency ω_2 is swept through the mass range 40-115. The recorder has been increased in attenuation to the point where the intensity of the m/e 43 signal is only 20% of its true value. This was done in order to observe any possible minor contributions from the m/e 84 species. The spectrum was recorded at 5 \times 10⁻⁶ Torr, 0.08 irradiating voltage, and 13 eV ionizing energy.

dienol c may allow delocalization of the positive charge throughout the ion so as to make transfer of a proton an unfavorable process. It is also a possibility that the dienol ion c rearranges to some other structure, perhaps b, which does not participate in proton transfer reactions. That the m/e 84 enone ion b does not take part in the condensation reactions found to be typical of smaller aliphatic keto ions is also surprising, since both the radical eliminated and the product ion formed would appear to be quite stable species (Scheme XI).



The presence of a double bond in the β , γ position of the side chain of b apparently makes the occurrence of these reactions less favorable.

Synthesis of Labeled Compounds.—In general, the deuterium-labeled α,β -unsaturated ketones employed in this study were prepared by the reaction of the appropriate deuterium-labeled aldehyde with the ylide derived from 2-oxopropyltriphenylphosphonium chloride. The aldehydes were synthesized as outlined in Scheme XII (A, B,⁸⁰ C,³⁰ D). Deuterium was first



introduced into a suitable phenyl-substituted alcohol by lithium aluminum deuteride reduction of the corresponding acid, followed by alkyl chain homologation of the corresponding labeled alkyl halide. Reaction of α -deuterium labeled aldehydes such as XXXIV with the ylide was complicated by exchange of the deuterium atoms with the active hydrogen of the ylide under a variety of experimental conditions.³¹ However, stirring equimolar amounts of Li₂CO₃, the phosphonium salt, and aldehyde XXXIV in 70% THF-H₂O overnight at room temperature effectively avoided this problem.

 $7,7-d_2$ -7-Phenylhept-5-en-2-one (XXIVa) and $1,1,1-d_3$ -phenylhept-3-en-2-one (IIf) were made as illustrated in Scheme XII (E and F, respectively).

(30) (a) A. I. Meyers, A. Nabeya, H. Adickes, and I. R. Politzer, J. Amer. Chem. Soc., 91, 763 (1969); (b) A. I. Meyers, E. M. Smith, and A. F. Jurjevich, *ibid.*, 93, 2314 (1971), and references cited therein to experimental procedures.

⁽³¹⁾ T. B. Malloy, Jr., R. M. Hedges, and F. Fisher, J. Org. Chem., 35, 4256 (1970).

Experimental Section

Mass spectra were obtained by Mr. R. G. Ross using an AEI MS-9 double-focusing mass spectrometer (heated inlet 150°, ion source temperature 180°) and by Mr. R. Conover on an Atlas CH-4 instrument using an E-4B ion source and direct insertion probe (samples absorbed on charcoal). Spectra of compounds run on both of these instruments were essentially identical. The direct inlet procedure had the advantage of minimizing metalcatalyzed dehydrogenation observed to a slight extent when several of the samples were passed through the heated inlet system of the MS-9. Metastable transitions in the first field-free region were observed with the aid of the defocusing procedure.¹¹ The Varian V-5900 spectrometer fitted with a dual inlet system was used in the ion cyclotron resonance studies. The spectrometer, the method, and applications of single and double resonance have been described.^{82,33} Compounds were submitted for mass spectral measurement only after purification by vapor phase chromatography (6 ft \times 0.25 in., 3% OV 25 on Gas-Chrom Q; 6 ft \times 0.25 in, 5% Carbowax 20M on Chromosorb W, both columns glass).

Infrared characterization was carried out using a Perkin-Elmer Model 700 spectrophotometer. Nmr spectra were ob-tained with either a Varian Model T-60 spectrometer or a Varian HA-100 spectrometer (measured by Mr. M. Bramwell) and are recorded in δ values with carbon tetrachloride as solvent and tetramethylsilane as an internal reference standard. The spectral characteristics not explicitly stated of all compounds used in this study were found to be in agreement with the material's assigned structure. The elementary composition of all new compounds was determined by mass spectral molecular weight determination.

 α,β -Unsaturated Ketones C₆H₅(CH₂)_nCH=CHCOCH₃ (n = 2-7) (I-VI).-Compounds I-VI were prepared from the appropriate aldehyde precursor by similar procedures illustrated for II (n = 3). 4-Phenylbutanal was prepared in 80% yield by oxidation of 4-phenylbutanol³⁴ on a 10-mmol scale using chromium trioxide-pyridine complex made in situ.³⁵ The aldehyde (1.0 g, 6.75 mmol), 2-oxopropyltriphenylphosphonium chloride (2.4 g, 6.75 mmol), and 800 mg of sodium carbonate were stirred with 23 $\,$ ml of tetrahydrofuran and 7 ml of water at reflux for 15 hr. Ether was added, the layers were separated, and the organic material was washed with brine and dried over magnesium sulfate. Evaporation of the solvent was followed by the addition of hexane and gravity filtration to remove the crystalline triphenylphosphine oxide. The hexane was evaporated and the product was distilled (bulb to bulb, 1 Torr) to give 1.1 g (87%)of 7-phenylhept-3-en-2-one (II). Analysis by vpc showed the presence of two isomers (ratio \sim 90:10) and the major peak was collected: ir $\lambda_{\text{max}}^{\text{aest}}$ 1618, 1670, and 1690 cm⁻¹; nmr δ 1.83 (m, 2 H, CH₂CH₂CH₂), 2.12 (s, 3 H, COCH₃), 2.22 (m, 2 H, CH₂-CH₂CH₂), 2.64 (t, 2 H, C₆H₆CH₂CH₂), 5.96 (d, 1 H, J = 16 Hz, CH=CH(CO), 6.65 (d of t, 1 H, CH₂CH=CH), 7.12 (m, 5 H, C_6H_5). The 16-Hz coupling constant allows assignment of

trans double bond geometry. The other aldehydes used in preparation of III-VI were obtained as follows. 3-Phenylpropanal is commercially available. 5-Phenylpentanal was obtained in moderate yield from 1-bromo-3-phenylpropane using the procedure of Meyers, et al.³⁰ The precursor of IV (n = 5), 6-phenylhexanal, is available by conversion of 4-phenylbutanol to its bromide (hydrobromic acidsulfuric acid) and then two carbon chain homologation employing the standard diethyl malonate procedure.³⁶ Reduction of the resulting 6-phenylhexanoic acid to its alcohol and subsequent oxidation³⁵ gave 6-phenylhexanal.

The synthesis of 7-phenylheptanal was accomplished by first converting 6-phenylhexanol to its bromide. Then, under argon, 643 mg of magnesium (26.4 mmol, 10% excess) was placed in a dry 250-ml flask equipped with magnetic stirrer, reflux condenser,

(34) Prepared by reduction of 4-phenylbutanoic acid, the synthesis of which is described by E. L. Martin, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, p 499.
(35) R. Ratcliffe and R. Rodehorst, J. Org. Chem., 35, 4000 (1970).

and serum cap. 1-Bromo-6-phenylhexane (500 mg) in 3 ml of dry ether was added. After reaction initiation the remainder of the bromide (5.04 g, 24 mmol total) was added with 75 ml of After heating under reflux for 45 min the mixture was ether. cooled (ice bath) and diethyl phenyl orthoformate³⁷ (4.24 g, 21.6 mmol) in 10 ml of ether was added. The mixture was refluxed for 1 hr, cooled to room temperature, and poured into 30% ammonium chloride. The organic layer was washed with 5% sodium hydroxide (three times), water, and brine. Distillation gave 3.8 g of the diethyl acetal of 7-phenylheptanal (63% from the bromide).³⁸ Conversion to the aldehyde was done by stirring the acetal (25°) with 25 ml of 5% hydrochloric acid overnight (argon). Distillation (bulb to bulb, 1 Torr) gave 7-phenylheptanal (2.4 g, 90%).

8-Phenyloctanal was prepared by oxidation²⁵ of 8-phenyloctan-1-ol, which was made from 1-bromo-4-phenylbutane by successive diethyl malonate homologations and reduction of the resulting 8-phenyloctanoic acid.

O-Methyloxime Derivatives .- Due to the low-intensity molecular ion peak observed for compounds IIa-f it was necessary to find a suitable derivative having an abundant molecular ion and negligible $M^+ - 1$ and $M^+ - 2$ peaks for isotopic analysis. The O-methyloxime fulfilled these requirements and in addition was easily prepared. Equimolar amounts of the unsaturated ketone, N-methoxyamine hydrochloride, and pyridine were heated for 10 min on a steam bath and allowed to stand overnight. Ether was added and the organic material was washed with water and dried (magnesium sulfate). A sample of the unsaturated O-methyloxime was then purified by vpc and submitted for mass spectral analysis at 12 eV.

 γ , γ - d_2 -7-Phenylhept-3-en-2-one (IIa).—Reduction of methyl benzoate (11 g, 80 mmol) with lithium aluminum deuteride (2.5 g, 60 mmol) in dry ether and work-up by adding first 2 ml of deuterium oxide followed by 10% sulfuric acid gave after distillation $\alpha, \alpha - d_2$ -benzyl alcohol (7.7 g, 90%). Conversion to the chloride was accomplished by dissolving pyridine (5.5 g, 70 mmol) and the alcohol (7.7 g, 70 mmol) in 50 ml of chloroform. Thionyl chloride (8.82 g, 73.5 mmol) in 25 ml of chloroform was then added dropwise over 30 min (spontaneous reflux). The mixture was stirred at 25° for 3 hr, washed with water, 5% sulfuric acid, 10% sodium bicarbonate, and brine, and dried over magnesium sulfate. Distillation gave $\alpha, \alpha-d_2$ -benzyl chloride (7.4 g, 83%). The chloride (7.4 g) was converted to the Grignard reagent which was coupled with allyl bromide³⁹ to give 4,4-d2-4-phenylbut-1-ene (5.63 g, 74%). Conversion to $4,4-d_2$ -phenylbutan-1-ol using diborane and hydrogen peroxide was done in the usual way. Oxidation³⁵ of the alcohol gave $4,4-d_2-4$ -phenylbutanal (XXXII) $(2\% d_1, 98\% d_2)$, which gave IIa as described above for II. A sample of IIa was converted to its O-methyloxime derivative, $M^+ 219 (98\% d_2), 218 (2\% d_1).$

(IIb).--Reduction 6,6-d₂-7-Phenylhept-3-en-2-one (lithium aluminum deuteride) of methyl phenylacetate gave 1,1-d2-2phenylethanol, which after conversion to its bromide⁴⁰ gave according to the procedure of Meyers, et al.,³⁰ $3,3-d_2-4$ -phenylbutanal $(2\% d_1, 98\% d_2)$ which was converted to IIb as above; O-methyloxime derivative, M⁺ 219 (98% d_2), 218 (2% d_1).

5,5-d2-7-Phenylhept-3-en-2-one (IIc).-Reduction of methyl 3-phenylpropionate with lithium aluminum deuteride was followed by conversion of the resulting alcohol to its bromide. Treatment of the corresponding Grignard reagent with diethyl phenyl orthoformate gave the diethyl acetal of $2,2-d_2-4$ -phenylbutanal. Hydrolysis (5% deuteriochloric acid-deuteriophosphoric acid from deuterium oxide and phosphorus pentachloride) gave $2, 2-d_2-4$ -phenylbutanal (5% $d_1, 95\% d_2$). Reaction of the aldehyde with the ylide derived from 2-oxopropyltriphenylphosphonium chloride (equimolar amount) in 70% tetrahydrofuran-water at 25° overnight gave IIc: O-methyloxime deriv-ative, M⁺ 220 ($\langle 2\% \rangle d_3 \rangle$, 219 (93% $d_2 \rangle$, 218 ($\langle 5\% \rangle d_1 \rangle$; nmr δ 2.22 (CH₂CH₂CH=) absent, integration of olefinic protons at δ 5.96 and 6.65 gave a ratio of one to one.

4-d1-7-Phenylhept-3-en-2-one (IId).-Treatment of methyl 4phenylbutanoate with lithium aluminum deuteride gave 1,1-d2-

⁽³²⁾ J. L. Beauchamp, Ph.D. Thesis, Harvard University, Cambridge, Mass., 1967.

⁽³³⁾ J. D. Baldeschwieler, Science, 159, 263 (1968).

^{(36) (}a) R. Adams and R. M. Kamm, "Organic Syntheses," Collect. Vol. I, Wiley, New York, N. Y., 1932, p 250; (b) E. Vliet, C. S. Marvel, and C. M. Hseuh, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, p 416.

⁽³⁷⁾ Available from the Aldrich Chemical Co.

⁽³⁸⁾ The procedure is essentially that of H. Stetter and E. Reske, Chem. Ber., 103, 643 (1970).

⁽³⁹⁾ A. Turk and H. Chanan, "Organic Syntheses," Collect. Vol. III,

<sup>Wiley, New York, N. Y., 1955, p 121.
(40) G. A. Wiley, R. L. Hershkowitz, B. M. Rein, and B. C. Chang, J. Amer. Chem. Soc., 86, 964 (1964).</sup>

4-phenylbutan-1-ol, which was oxidized⁸⁵ to 1- d_1 -4-phenylbutanal $(1\% d_0, 99\% d_1)$ and converted to IId, O-methyloxime derivative, M⁺ 218 (99% d_2), 217 (1% d_1).

1,1,1-d₃-7-Phenylhept-3-en-2-one (IIe).—4-Phenylbutanal (11.4 g, 77 mmol) was converted to ethyl 6-phenylhex-2-enoate (XI) (10.5 g, 48 mmol) using the ylide derived from triethyl phosphonoacetate and sodium hydride.41 Reduction of XI (10 g) with aluminum hydride (lithium aluminum hydride and 100% sulfuric acid)42 yielded 6-phenylhex-2-en-1-ol (6.5 g, 37 This material was oxidized³⁵ to 6-phenylhex-2-en-1-al mmol). (IX) (4.4 g, 25.5 mmol) which was then added (1.74 g, 10 mmol) to an equimolar amount of d_3 -methylmagnesium iodide in the normal manner to give 1,1,1-d3-7-phenylhept-3-en-2-ol (1.15 g, 6 mmol). Oxidation³⁵ of this led to IIe. Ice cold aqueous solutions were employed in the work-up procedure. A sample (10 mg) of IIe was obtained by preparative gas chromatography and converted to its O-methyloxime derivative, M⁺ 220, $(91\%, d_3), 219 (9\% d_2).$

7- $(d_{5}$ -Phenyl)hept-3-en-2-one (IIf).— d_{6} -Benzene was converted to 4- $(d_{5}$ -phenyl)butanoic acid via Friedel-Crafts reaction with succinic anhydride⁴³ and subsequent reduction of the keto acid.⁴⁴ Lithium aluminum hydride reduction gave 4- $(d_{5}$ -phenyl)butan-1-ol and oxidation⁸⁵ produced 4- $(d_{6}$ -phenyl)butanal $(5\% d_{5}, 23\% d_{4}, 72\% d_{5})$. Conversion to IIf followed as usual; O-methyloxime derivative, M⁺ 222 (71% d_{5}), 221 (24% d_{4}), 220 (5% d_{3}).

(6.76 ds). $6,6-d_2$ -6-Phenylhex-3-en-2-one (Ia) $(2\% d_1, 98\% d_2), 5,5-d_2$ -6phenylhex-3-en-2-one (Ib) $(19\% d_1, 75\% d_2, 5\% d_3)$, and 4-d₁-6phenylhex-3-en-2-one (Ic) $(1\% d_0, 99\% d_1)$ were prepared in ways analogous to the syntheses of IIa, IIc, and IId. $8,8-d_2$ -8phenyloct-3-en-2-one (IIIa) was made by treatment of the Grignard reagent derived from $4,4-d_2$ -1-bromo-4-phenylbutane (see above) with diethyl phenyl orthoformate and hydrolysis by the resulting acetal to give $\delta, 5-d_2$ -5-phenylpentanal ($2\% d_1, 98\% d_2$), also available via Scheme XIIA, which was combined with the ylide derived from 2-oxopropyltriphenylphosphonium chloride, O-methyloxime derivative of IIIa, M⁺ 233 (98\% d_2), 232 ($2\% d_1$).

Treatment of 6-phenylhex-2-en-1-al (IX) with ethylmagnesium bromide and propylmagnesium bromide, respectively, followed by oxidation³⁵ of the resulting unsaturated alcohols gave 8-phenyloct-4-en-3-one (XII) and 9-phenylnon-5-en-4-one (XIII). Hydrolysis of ethyl 6-phenylhex-2-enoate (XI) and ethyl-5phenylpent-2-enoate (XX) (5% sodium hydroxide) gave 6-phenylhex-2-enoic acid (VIII) and 5-phenylpent-2-enoic acid (XXI). Ethyl-5-phenylpent-2-enoate (XX) was prepared using the Wadsworth-Emmons procedure, while 5-phenylpent-2-en-1-al (XIX) was obtained under the conditions of Meyers, *et al.*³¹ Methyl 6-phenylhex-2-enoate (X) was made by the reaction of carbomethoxymethylenetriphenylphosphorane with 4-phenylbutanal in refluxing tetrahydrofuran. Vapor phase oxidation over cupric oxide⁷ of hex-5-en-1-ol and 4-methylpentan-1-ol gave hex-5-en-1-al and 4-methylpentanal. Reaction of these aldehydes with the ylide derived from 2-oxopropyltriphenylphosphonium chloride gave nona-3,8-dien-2-one (XIV) and 7methyloct-3-en-2-one (XV), respectively. Likewise, octa-3,7diene-2-one (XXII) was synthesized starting with pent-4-en-1-ol.

6-Phenylhex-2-ene (XVII) and $\theta_1\theta_2d_2$ -6-phenylhex-2-ene (XVIIa) were prepared by the reaction of the appropriate aldehyde (see above) with the ylide generated from ethyltriphenylphosphonium bromide by butyllithium in diethyl ether, XVIIa M⁺ 162 (98% d_2), 161 (2% d_1).

1,1,1,3,5,5- d_6 -7-Phenylhept-3-en-2-one (IIf) was prepared in low yield by the aldol condensation (5% NaOD, D₂O) of d_6 acetone with 2,2- d_2 -4-phenylbutanal,⁴⁵ isotopic purity 9% d_5 , 91% d_6 .

7-Phenylhept-6-en-2-one (XXIII)—Reaction of cyclopropylphenylcarbinol (7.4 g) with a fourfold excess of 48% hydrobromic acid for 10 min at 0° gave after distillation 7.8 g of 1-bromo-4-phenylbut-3-ene. Addition of this bromide to the anion derived by reaction of sodium hydride and methyl acetoacetate in tetrahydrofuran, stirring at room temperature over-

(45) See ref 7 and references cited therein.

night, and heating the crude alkylation product with ethanolic barium hydroxide⁴⁶ gave in low yield 7-phenylhept-6-en-2-one (XXIII): ir $\nu_{max}^{CCl_4}$ 1710, 1600, 960 cm⁻¹ (s); nmr δ 1.78 (m, 2 H, CH₂CH₂CH₂), 2.06 (s, 3 H, COCH₃), 2.18 (t, 2 H, CH₂-CH₂CO), 2.40 (t, 2 H, CHCH₂CH₂), 6.06 (d of t, 1 H, CH=CHCH₂), 6.34 (d, 1 H, J = 16 Hz, C_6H₃CH=CH), 7.20 (m, 5 H, C_6H₅). The coupling constant (J = 16 Hz) and ir band at 960 cm⁻¹ indicate trans double bond geometry.

7-Phenylhept-5-en-2-one (XXIV) and $7,7-d_2$ -7-phenylhept-5-en-2-one (XXIVa).—Reaction of phenyl acetaldehyde with the ylide generated by the action of butyllithium on the ethylene ketal of 4-oxopentyltriphenylphosphonium bromide⁴⁷ in dry ether gave the ethylene ketal of XXIV. Treatment of this ketal with 5% perchloric acid-tetrahydrofuran for 15 min (25°) gave 7-phenylhept-5-en-2-one (XXIV): ir λ_{max}^{CCl4} 1710, 1600, 960 cm⁻¹ (w); nmr δ 2.06 (s, 3 H, COCH₃), 240 (m, 4 H, HC-CH₂CH₂CO), 3.37 (d, 2 H, J = 6 Hz, $C_{\theta}H_{\delta}CH_{2}CH$), 5.5 (m, 2 H, CH=CH), 7.14 (m, 5 H, $C_{\theta}H_{\delta}$). Spectral data indicated a mixture of cis and trans isomers. The labeled analog was similarly prepared from $\alpha, \alpha - d_2$ -phenylacetaldehyde and the ylide, M⁺ 189 (4.5% d_1), 190 (89% d_2), 191 (6.5% d_3).

7-Phenylhept-4-en-2-one (XXV) was prepared by the photolysis of 7-phenylhept-3-en-2-one under the conditions of Yang:⁴⁸ ir $\lambda_{\max}^{CCl_4}$ 1710 cm⁻¹; nmr δ 1.98 and 2.00 [s, 3 H (sum), COCH₃], 2.37 (m, 2 H, CH₂CH₂CH), 2.66 (m, 2 H, PhCH₂CH₂), 2.98 (m, 2 H, CH₂CH₂CH), 5.56 (m, 2 H, CH=CH), 7.12 H, C₆H₅). The absorptions quoted indicate the presenced of cis and trans β , β -unsaturated isomer present (13%).

Pent-4-en-2-one (XXIX).—Oxidation of 860 mg of pent-4-en-2-ol in 70 ml of acetone at 15° with 2.5 ml of Jones reagent according to the conditions of Djerassi, *et al.*,⁴⁹ yielded 820 mg of crude pent-4-en-2-one. Vapor phase chromatography gave the pure ketone, ir $\lambda_{\text{max}}^{\text{mod}}$ 1715 and 1649 cm⁻¹.

2-Vinyl-1-methylcyclobutan-1-ol (XXX).—Reaction of the sodium enolate of ethyl acetoacetate with 4-bromobut-1-ene in dry tetrahydrofuran according to the conditions of Ronald⁵⁰ yielded 3-carboethoxyhept-6-en-2-one: bp 115-118° (20 Torr); ir λ_{max}^{neat} 1740, 1720, 1650, 915 cm⁻¹. Hydrolysis with sodium hydroxide and decarboxylation in dimethylformamide also according to the conditions of Ronald⁵⁰ gave hept-6-en-2-one, which was isolated by distillation: bp 97-98° (110 Torr) [lit.⁵¹ bp 41-43° (10 Torr)]; ir λ_{max}^{neat} 1709, 1640, 920 cm⁻¹. Photolysis of a 10% solution of hept-6-en-2-one in pentane according to the conditions of Yang⁵² gave a mixture of products from which pure 2-vinyl-1-methylcyclobutan-1-ol was isolated by preparative vpc. The infrared and nmr spectra were identical with those reported by Yang.⁵²

 $2,2,4,4-d_4$ -3-Heptanone (XXXI).—A mixture of 1.5 g of 3-heptanone, 30 ml of deuterium oxide, and 30 ml of glyme was heated under reflux for 48 hr. Sodium chloride was added and the labeled 3-heptanone (XXXI) was extracted with ether. After evaporation of the ether, $2,2,4,4-d_4$ -3-heptanone was isolated by preparative vpc, M⁺ 116 (3% d_2), 117 (6% d_3), 118 (91% d_4).

Registry	No. —I,	33046-41-2	; Ia,	33046-42-3;	Ib,
33046-43-4;	Ic, 3	3191-92-3;	II,	33191-93-4;	IIa,
33191-94-5;	IIb, 3	3046-44-5;	IIc,	33191-95-6;	IId,
33046-64-9;	IIe, 3	3046-65-0;	IIf,	33046-66-1;	IIg,
33046-67-2;	III, 3	3046-68-3;	IIIa,	33046-69-4;	IV,
33046-70-7;	V, 33	3046-71-8;	VI,	33046-72-9;	VII,

(46) S. F. Brady, M. A. Ilton, and W. S. Johnson, J. Amer. Chem. Soc., 90, 2882 (1968).

(47) We express thanks to the Zoecon Corp., Palo Alto, Calif., for a generous sample of this material.
(48) N. C. Yang and M. J. Jorgenson, *Tetrahedro Lett.*, 1203 (1964).

(48) N. C. Yang and M. J. Jorgenson, Tetrahedro Lett., 1203 (1964).
(49) C. Djerassi, R. R. Engle, and A. Bowers, J. Org. Chem., 21, 1547 (1956).

(50) R. Ronald, Ph.D. Thesis, Stanford University, Stanford, Calif., 1970.

(51) "Dictionary of Organic Compounds," Vol. 3, Oxford University Press, New York, N. Y., 1965.

(52) N. C. Yang, S. P. Elliot, and B. Kim, J. Amer. Chem. Soc., **91**, 7551 (1969); N. C. Yang, A. Morduchowitz and D. H. Yang, *ibid.*, **85**, 1017 (1963). We thank Professor Yang for supplying us with detailed experimental conditions regarding both the photolysis and isolation of XXX.

⁽⁴¹⁾ W. S. Wadsworth, Jr., and W. D. Emmons, J. Amer. Chem. Soc., 83, 1733 (1961).

⁽⁴²⁾ W. M. Yoon and H. C. Brown, ibid., 90, 2927 (1968).

⁽⁴³⁾ L. F. Somerville and C. F. Allen, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, p 81.

⁽⁴⁴⁾ Huang-Minlon, J. Amer. Chem. Soc., 68, 2487 (1946).

6048-08-4; XXI, 24271-22-5; XXII, 3643-55-8; XXIII, 33046-88-7; XXIV, 33046-89-8; XXIVa, 33046-90-1; XXV, 33046-91-2; XXIX, 13891-87-7; XXX, 33046-93-4.

The Synthesis of the A,B and D,E Rings of Medicagenic Acid¹

JAMES D. METZGER, MICHAEL W. BAKER, AND ROBERT J. MORRIS*

Department of Chemistry and the Division of Biochemistry, University of Nevada System, Reno, Nevada 89507

Received July 6, 1971

The synthesis of two decalin derivatives to be used in an AB + DE type synthesis of dimethyl diacetoxymedicagenate (3) has been accomplished. The A, B segment has a final structure of 1β , 6, 10β -trimethyl- 1α -carbomethoxy-2 β , 3β -diacetoxy-trans-5-decalone (1). The D,E portion has a final structure of 10-carbethoxy-2,7,7trimethyl-cis-decal-1-one (2). These compounds represent versatile intermediates which will be used in seeking a total synthesis of the sapogenin molecule through annelation of the two fragments.

Interest in medicagenic acid has developed from several studies including its isolation, purification, physiological activity, and biological role in alfalfa forage.^{2,3} As reported in earlier communications,^{4,5} medicagenic acid was found to be the aglycone in both alfalfa root and blossom saponins, and a pure root saponin was synthesized from the purified natural acid and β -D-glucose.⁶

Our approach to the synthesis focused on an AB + DE sequence in order to avoid the extremely difficult task of building the molecule by attaching each of the five rings with their variety of substituents in successive order. The first half of the study, reported here, required the creation of two stereospecific decalin precursors possessing suitable reaction sites for coupling. A second investigation will be devoted to an examination of different annelation procedures in order to successfully join these two compounds (Scheme I).



⁽¹⁾ Partial support for this work provided by the University of Nevada, Reno, Agricultural Experiment Station, Journal Series 188 is gratefully acknowledged.

- (6) R. J. Morris and D. L. Tankersley, ibid., 28, 240 (1963).

To allow for flexibility in the synthesis, bicyclic systems were chosen which offer both a high degree of versatility and yet essentially duplicate large portions of the natural molecule. The adaptability of these compounds for the coupling reaction is determined by the variety of reactions which can occur at the ketone groups.

The two compounds will be treated separately, beginning with the synthesis of the A,B ring system (Scheme II). The problems anticipated were es-



sentially threefold: (1) effecting a trans ring juncture; (2) the formation of the correct stereochemistry for the groups at carbon 1; and (3) the introduction of the 2β . 3β -diacetoxy group.

A solution to the first two of these problems was conveniently offered by one series of reactions. Stork

⁽²⁾ E. D. Walter, G. R. Van Atta, C. R. Thompson, and W. D. Maclay, J. Amer. Chem. Soc., 76, 2271 (1954).
 (3) C. Djerassi, D. B. Thomas, A. L. Livingston, and C. R. Thompson,

ibid., 79, 5292 (1957). (4) R. J. Morris, W. B. Dye, and P. S. Gisler, J. Org. Chem., 26, 1241

^{(1961).} (5) R. J. Morris and E. W. Hussey, *ibid.*, **30**, 166 (1965).