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MASS SPECTROMETRY IN STRUCTURAL AND STEREOCHEMICAL PROBLEMS—CXXII

POSSIBLE OPERATION OF TAUTOMERISM BEFORE AND AFTER ELECTRON-IMPACT INDUCED FRAGMENTATION OF MOLECULAR IONS

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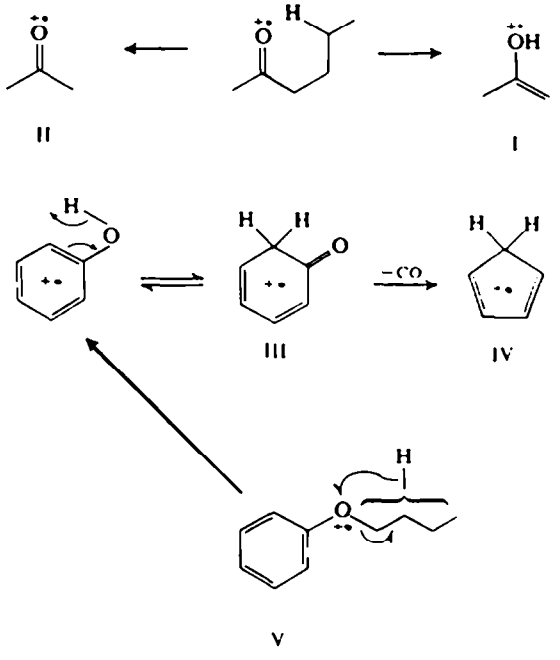
Abstract—A study of the double McLafferty transfer process in the mass spectra of two cyclic ketones and a substituted malonic ester, at both high and low electron energies, has shown that little tautomerism of the intermediate single McLafferty enolate ion occurs in these cases.

In addition, tautomerism of the molecular ion in a number of carbonyl derivatives appears not to be a prerequisite for γ-cleavage in the mass spectra of these compounds.

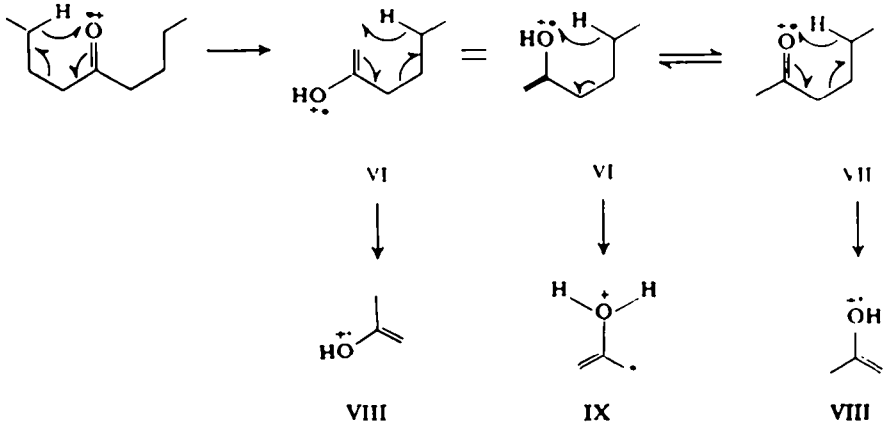
THERE is ample evidence[3] in favor of the formation of an enolic ion (I) rather than the keto form (II) from simple aliphatic ketones in the mass spectrometric γ-hydrogen transfer process commonly called the McLafferty rearrangement.[4] Further decomposition of this enol fragment I would therefore be expected to differ from that of the corresponding ketone II unless tautomerism occurs. In view of the difference in the ionization potentials of the enol and keto forms of carbonyl compounds,[3] ketonization would require an excess energy of the order of 1 eV (ca. 23 Kcals/mole). Unless an equivalent exothermic fragmentation process of the ketone ion, e.g. a second McLafferty transfer, can occur there seems little theoretical evidence to support tautomerism of such a stable enol species. Our findings discussed below are in full agreement with this hypothesis. On the other hand, loss of carbon monoxide from the molecular ion of phenol[5] has been rationalized as occurring through a cyclohexadienone intermediate (III), a proposal which would appear to be in contradiction to the above argument. However, as found in our laboratory, this process does not take place below 15 eV, which suggests that a large amount of excitation energy is necessary to tautomerize the phenol ion if in fact the reaction proceeds at all through the tautomer III. This suggestion is supported by the observation that the phenol fragment ion derived from electron impact induced cleavage of phenyl n-butyl ether (V)[6] shows a greatly reduced proportion of the *m/e* 66 species (IV) (5% of the mass 94 phenol ion compared with 30% in the mass spectrum[5] of phenol itself)

[1] Paper CXXI, see J. Gutzwiller and C. Djerassi, *Helv. Chim. Acta* **49**, 2108 (1966)
[2] N.I.H. International Postdoctoral Fellow on leave from University College, Dublin, Ireland.
[3] For a conclusive argument based on ionization potential measurements see S. Meyerson and J. D. McCollum, *Advances in Analytical Chemistry and Instrumentation*, (Edited by C. N. Reilley) Vol. 2, pp. 187–198 and Refs therein. Interscience, New York (1963).
[4] F. W. McLafferty, *Analyt. Chem.* **31**, 82 (1959).
[5] J. H. Beynon, G. R. Lester and A. E. Williams, *J. Phys. Chem.* **63**, 1861 (1959).
[6] J. K. MacLeod and C. Djerassi, *J. Am. Chem. Soc.* **88**, 1840 (1966).

probably as a result of the diminished internal energy of the phenol ion following the initial rearrangement process of the ether.



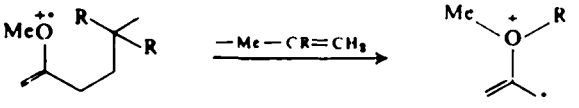
One of the more interesting aspects of this work has been an investigation of the nature of the intermediate electron impact induced "single McLafferty" species which subsequently fragments to the "double McLafferty"[7] ion. It has been tacitly



[7] H. Budzikiewicz, C. Fenselau and C. Djerassi, *Tetrahedron* **22**, 1391 (1966).

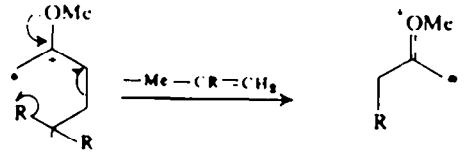
assumed[8] that rearrangement of the γ-hydrogen atom to the enolic double bond occurs (VI → VIII) but the other possibilities are either that rearrangement takes place to the enolic oxygen atom (VI → IX) or that tautomerism occurs with subsequent hydrogen transfer to the carbonyl group (VII → VIII).

In order to examine this question further, the methyl enol ether of 2-hexanone (X) and its γ-d_2 counterpart (XI) were prepared and investigated mass spectrometrically. Not only did the rearrangement (ion XII or XIIa, depending upon whether



X, R = H
XI, R = D

XII, R = H; *m/e* 72.
R = D; *m/e* 73.

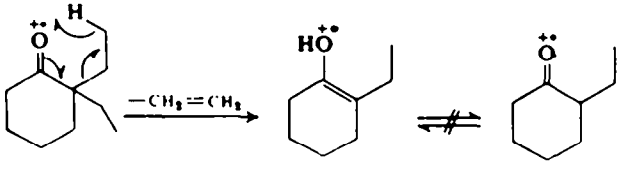


Xa, R = H
XIa, R = D

XIIa, R = H or D.

hydrogen rearrangement proceeds to oxygen or carbon) account for 39% of the total ionization of the compound, but the process also showed complete (>95%) γ-hydrogen transfer specificity. This result thus eliminates the possibility that tautomerism has to occur before the second McLafferty rearrangement can take place. Therefore it was thought advisable to investigate similar systems in which tautomerism would have to be a prerequisite to the second McLafferty rearrangement.

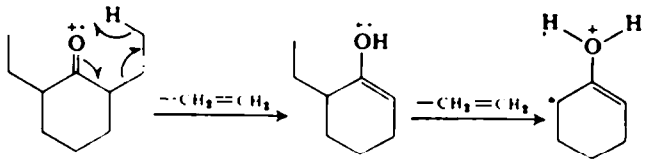
The spectra (Figs 1 and 2) of 2,2-diethyl (XIII) and 2,6-diethyl cyclohexanone (XIV) both show a considerable peak (Table 1), especially strong at low electron voltages (Figs 1b and 2b), for the single McLafferty rearrangement species (XV and XVI) at *m/e* 126. However, only the 2,6-disubstituted compound (XIV) exhibits any appreciable amount of an *m/e* 98 peak for the expected double McLafferty ion (XVII)[9]. Obviously the enolic structure of the ion XV precludes any further γ-transfers with β-cleavage unless ketonization occurs, which it apparently does not.



XIII XV, *m/e* 126

[8] H. Budzikiewicz, C. Djerassi and D. H. Williams, *Interpretation of Mass Spectra of Organic Compounds* p. 7. Holden-Day, San Francisco (1964).

[9] While there is a possibility that m/e 98 could also arise from XVI via a retro-Diels. Alder fragmentation with ethylene loss from the ring, the absence of this peak in the spectrum of XIII (Fig. 1a and b) would seem to preclude its presence in the cleavage of XIV.



XIV XVI, *m/e* 126. XVII, *m/e* 98

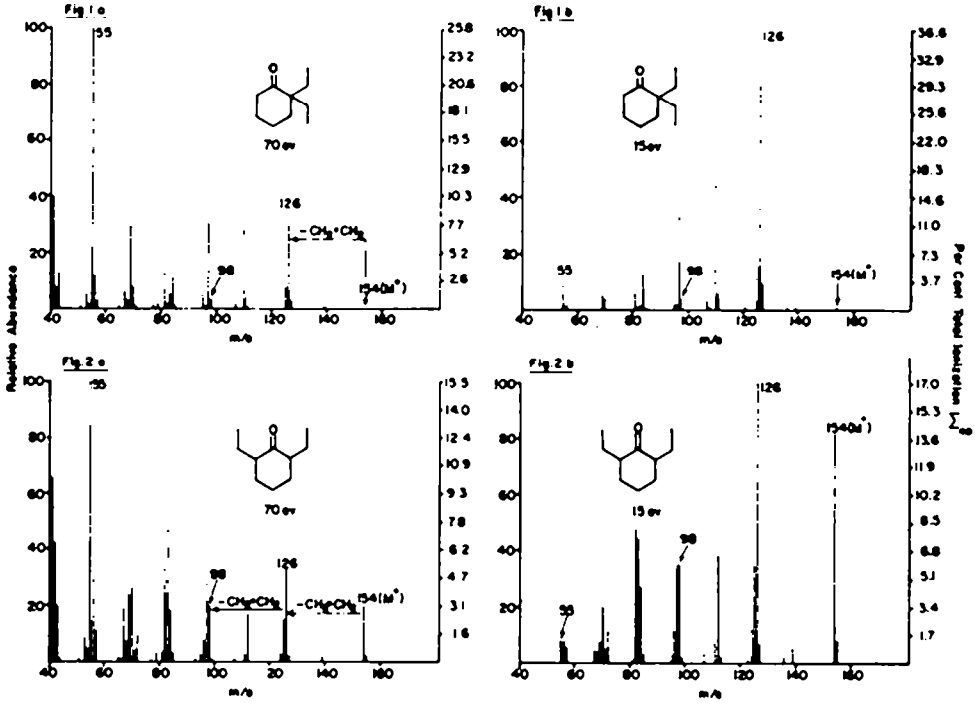
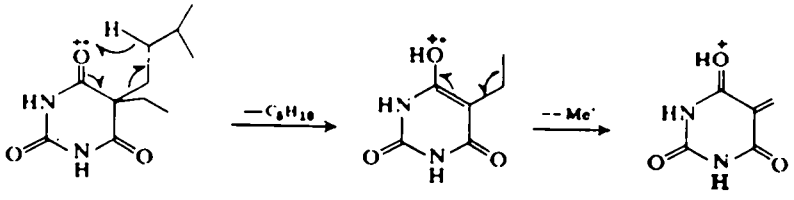


Fig. 1. Mass Spectrum of 2,2-diethylcyclohexanone at 70 eV, (a); and at 15 eV, (b).
Fig. 2. Mass Spectrum of 2,6-diethylcyclohexanone at 70 eV, (a); and at 15 eV, (b).

A similar result has been reported by Grützmacher and Arnold[10] in the mass spectra of substituted barbituric acids. The ion XIX formed from a McLafferty rearrangement of the dialkylated barbituric acid XVIII does not tautomerize and further rearrange, but instead loses a methyl radical to afford an even electron species, which was depicted[10] in terms of structure XX.



XVIII XIX XX

[10] F. Grützmacher and W. Arnold, *Tetrahedron Letters* No 13, 1365 (1966).

An even more striking example of this allylic cleavage of the enol ion is shown in the low electron voltage (12 ev) spectrum (Fig. 3b) of dimethyl di-n-propylmalonate (XXI). Virtually the only two peaks in the spectrum are those associated with the

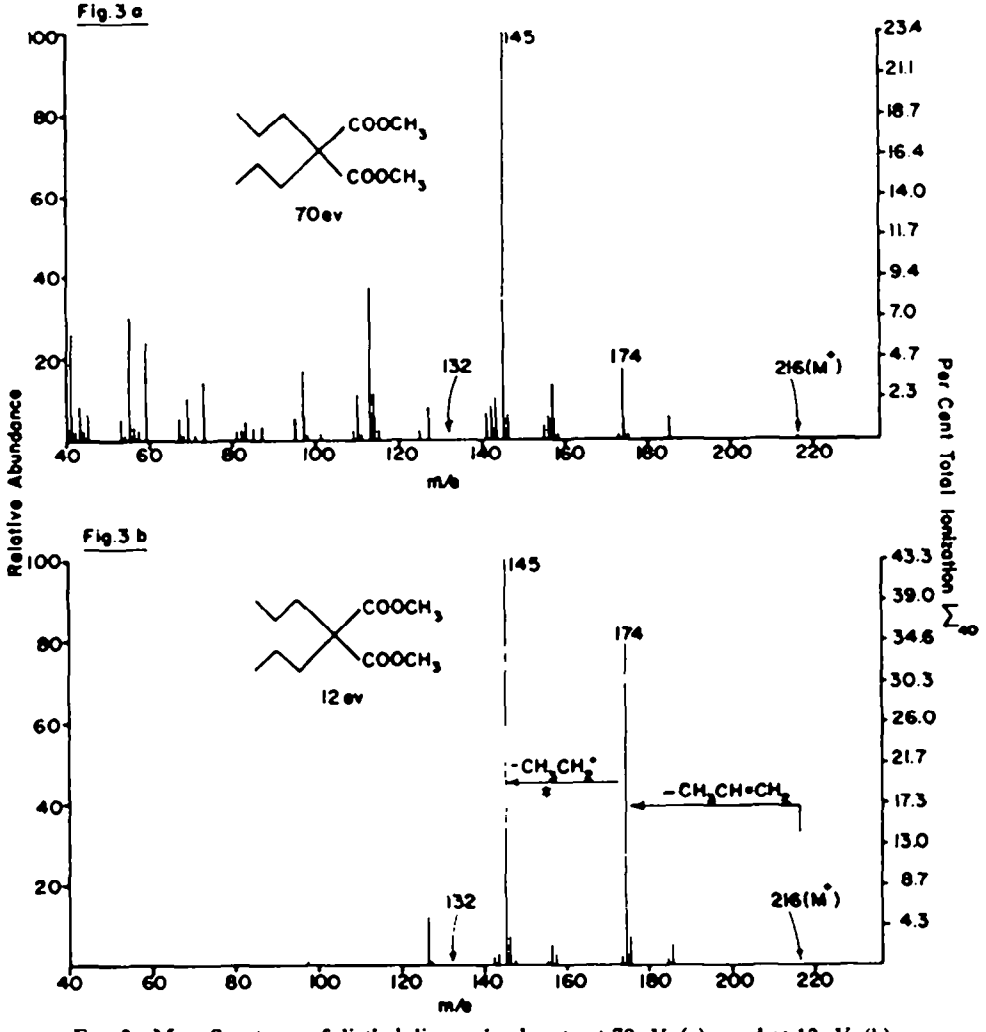
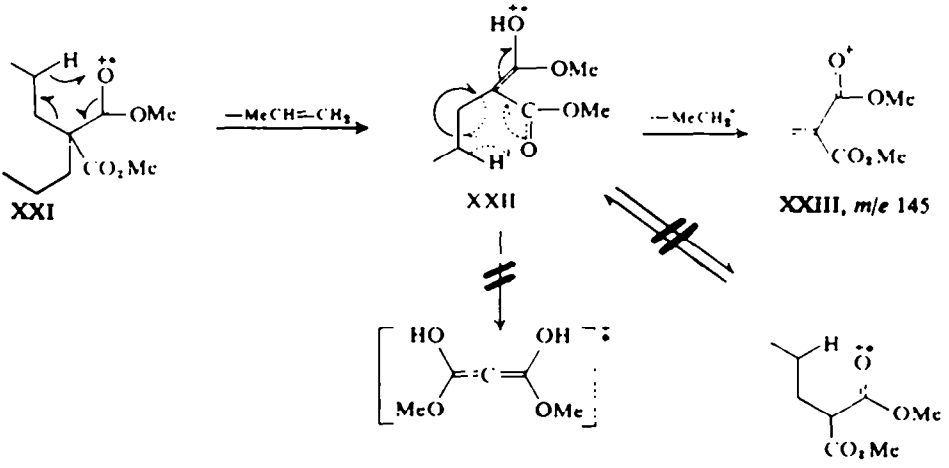


FIG. 3. Mass Spectrum of diethyl dipropylmalonate at 70 eV, (a); and at 12 eV, (b).

initial loss of propylene (XXI → XXII) via a McLafferty rearrangement with subsequent allylic fission of an ethyl radical (XXIII, *m/e* 145). This latter species also is the base peak in the 70 ev spectrum of the ester and the absence of an *m/e* 132 peak for the double McLafferty transfer ion in either the high (Fig. 3a) or low energy spectra (Fig. 3b) indicates that no tautomerism of the intermediate enol ion XXII occurs. Furthermore there is no evidence of rearrangement to the other ester carbonyl group which would give rise to the less stable allene species XXIV (*m/e* 132). Williams *et al.*[11] have published a similar finding for the mass spectra of diethyl

[11] J. H. Bowie, D. H. Williams, S.-O. Lawesson and G. Schroll, *J. Org. Chem.* 31, 1792 (1966).

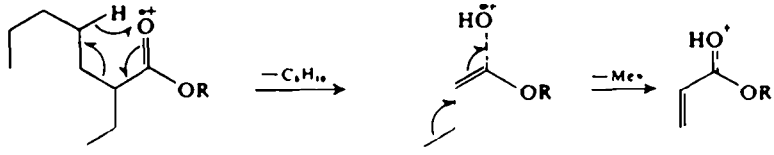
dialkylmalonates but these are complicated by additional rearrangements of the ethyl ester functions.



XXI XXII XXIII, *m/e* 145

XXIV, *m/e* 132

One might expect that the presence of the second alkoxycarbonyl group in the malonates has an additional stabilizing influence on the enolate structure XXII. It is therefore reassuring to note that in the spectra of 2-ethyl-heptanoic acid[12] and its methyl ester (XXV) the major fragmentations are the loss of pentene (XXV → XXVI) followed by scission of a methyl radical. Only a small amount (<5%) of a possible double McLafferty rearrangement ion is discernible.



XXV, R = H or Me XXVI, R = H or Me

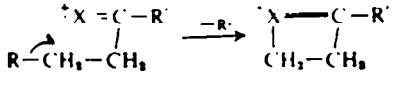
In conclusion, there is little evidence at present for the operation of tautomerism of an intermediate enol fragment ion in simple mass spectrometric cleavage processes. We feel that such processes are best studied at low electron voltages when the possibility of formation of ions possessing high internal energy is greatly reduced. For example the *m/e* 55 peak, which is the base peak at 70 ev in both cyclohexanones (Figs 1a and 2a) and is usually depicted[13] as XXVII, shows a sharp decrease in intensity at 15 ev (Figs 1b and 2b) and is absent at 12 ev. This result is associated with the high appearance potential of the ion, the formation of which must involve a less favorable energetic pathway to that of the *m/e* 126 ion.

We can now turn to another aspect of tautomerism that should be considered in mass spectrometry. Recent work in these laboratories has shown that γ-cleavage is a

[12] F. M. Trent, F. D. Miller and G. H. Brown, *Appl. Spectrosc.* **15**, 64 (1961).
[13] Ref. 8, p. 18.

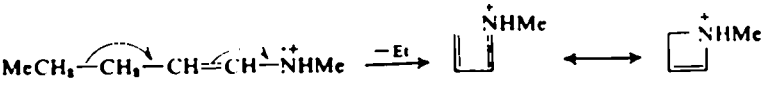
XXVII

significant fragmentation mode of aldehyde and ketone alkylimines,[14] oximes[15] and semicarbazones[16] of type A. Two explanations have been offered[14] for this fragmentation: (i) a straightforward γ-cleavage with formation of an even-electron ion for which representation XXVIII may be particularly plausible, or (ii) allylic cleavage of the tautomeric form of the molecular ion, e.g. formation of species XXX from the tautomer XXIX of valeraldehyde methylimine (XXXI). It is known[17]



XXVIII

A



XXIX XXX

that tautomerism (such as enolization of ketones) can occur in the mass spectrometer prior to ionization.

In order to ascertain the importance of tautomerism in this γ-cleavage, we have examined the mass spectra of the methylimine (XXXIII), oxime (XXXIV) and semicarbazone (XXXV) of the non-enolizable 2,2-dimethylvaleraldehyde. The results are summarized in Table 2. It is apparent that straightforward γ-cleavage does occur but that a substantial amount of fragmentation may proceed through the tautomer of the molecular ion. It should be born in mind, however, that some or all of the reduction in the ion yield of the γ-cleavage species in the non-enolizable, 2,2-dimethyl derivatives may be due to increased competition from other fragmentation modes caused by the change in structure. Thus the α-cleavage fragment, $CH{\equiv}\overset{+}{N}NHCONH_2$, from the semicarbazones carries 7% of the total ion current ($\%\Sigma_{40}^{M}$) in the case of XXXV and only 1·8% in the case of the valeraldehyde derivative (XXXII).[16] In this connection, it may be noted that the same yield of the α-cleavage ion, $CH{\equiv}\overset{+}{N}CH_3$, is obtained from both methylimines (XXXI and XXXIII) (39·2 and 40·5% Σ_{40}^{M}, respectively), so that in this instance the reduced intensity of the γ-cleavage species in XXXIII as compared to XXXI may well be indicative of the intervention of a tautomeric molecular ion XXIX in the latter.

[14] M. Fischer and C. Djerassi, *Chem. Ber.* **99**, 1541 (1966).
[15] D. Goldsmith, D. Becher, S. Sample and C. Djerassi, *Tetrahedron* **22**, Supp. 7, 145 (1966).
[16] D. Becher, S. Sample and C. Djerassi, *Chem. Ber.* **99**, 2284 (1966).
[17] H. Budzikiewicz and C. Djerassi, *Chem. & Ind.* 1697 (1965); C. Djerassi, R. H. Shapiro and M. Vandewalle, *J. Am. Chem. Soc.* **87**, 4892 (1965) and Refs. therein.

$CH_3CH_2CH_2CR_2CH{:}X$

XXXI: R = H, X = NMe
XXXII: R = H, X = $NNHCONH_2$
XXXIII: R = Me, X = NMe
XXXIV: R = Me, X = NOH
XXXV R = Me, X = $NNHCONH_2$

The one definite conclusion that can be drawn from these results is that while tautomerism may play some part in γ-cleavage *it is not a necessary prerequisite for this type of fragmentation.* In the future, this observation will have to be taken into consideration in proposing fragmentation paths for carbonyl compounds and their derivatives.

Table 1. Relative abundance* of γ-hydrogen rearrangement peaks in the mass spectra of 2,2- and 2,6-diethyl cyclohexanones

		70 ev		15 ev	
	m/e	XIII	XIV	XIII	XIV
Molecular ion	154	—	20·0	1·0	82·0
Single McLafferty	126	35·0	32·0	98·5	97·0
Double McLafferty	98	1·5	18·0	1·5	33·0

* Above values are quoted as percent relative abundance corrected for natural C^{13}.

Table 2. Ion yield ($\%\Sigma^{M}_{40}$) of γ-cleavage species ($M-C_3H_6$) from $CH_3CH_2CH_2CR_2CH{:}X$

	X = NCH_3	X = NOH	X = $NNHCONH_2$
R = H	7·8	5·9	1·1 (6·8)*
R = CH_3	2·1	1·2	0·9 (1·6)*

* The γ-cleavage fragment from semicarbazones decomposes further[16] with loss of HNCO. The figure in parentheses is the total ion yield of the γ-cleavage fragment and its decomposition product.

EXPERIMENTAL

The mass spectra of compounds X, XI, XIII, XIV and XXI were recorded on an Atlas CH-4 instrument at ionizing voltages of 70, 15 and 12 ev with a trap current of 10 μamps using a TO-4 ion source with gas cartridge operating at 190°. High resolution measurements were carried out on all relevant peaks by Mr. R. Ross using at A.E.I. MS-9 mass spectrometer. Low resolution mass spectra of XXIII and XXXIV were measured on the latter instrument using the heated (140°) inlet system while compound XXXV was introduced into the ion source (temp 200°) via the direct insertion probe.

2,2-Diethylcyclohexanone (XIII) was prepared[18] by alkylation of 2-ethylcyclohexanone with EtI, while its 2,6-isomer was obtained from the pyrolysis of the Ba-salt of 2,6-diethyl pimelic acid.[19] Dimethyl di-n-propylmalonate[20] was synthesized in the usual way by alkylation of dimethyl malonate.

2-*Methoxy*-1-*hexene* (X)[21] A mixture of paraldehyde (50 g) and MeOH (50 g) was cooled (−10° to −20°) and treated with dry HCl (50 g). The reaction mixture separated into 2 layers, the upper layer being dried ($CaCl_2$) but not further purified to prevent loss by decomposition. The 1-methoxy-1-chloroethane was cooled in an ice-bath and the theoretical amount of Br_2 added in small portions with stirring, allowing the reaction mixture to decolorize after each addition. The addition is complete

[18] P. Nedenskow, W. Taub and D. Ginsburg, *Acta Chem. Scand.* **12**, 1405 (1958).
[19] B. Rickborn, *J. Am. Chem. Soc.* **84**, 2414 (1962) and Refs. therein.
[20] A. I. Vogel, *J. Chem. Soc.* **340** (1934).
[21] C. G. Schmidt and C. E. Boord, *J. Am. Chem. Soc.* **54**, 751 (1932) and previous Refs.

when the color persists. Excess HCl liberated was blown out by passing a stream of dry N_2 gas through the soln. The resulting 1-methoxy-1,2-dibromoethane distilled over at 36–7°/10 mm.

The Grignard reagent formed from n-BuBr (10·5 ml) and Mg (2·5 g) in ether soln, was cooled in an ice-bath and the dibromoether (21·8 g) in dry ether was added slowly with strong stirring, allowing the reaction mixture to slowly warm up to room temp. Stirring was continued for 30 min after addition was complete, then the complex was decomposed by the addition of a sat Na_2SO_4aq. After filtration, the ether soln was dried (Na_2SO_4), the solvent removed under vacuum, and the residue distilled, giving 2-methoxyhexylbromide b.p. 69–70°/27 mm.

The above bromoether (5 g) was mixed with an equal amount of powdered KOH and the mixture refluxed gently for 1 hr. The product was then distilled at atm press (b.p. 109°) and further purified by VPC on an Apiezon L column, giving pure X. (Found: C, 73·33; H, 12·30. Calc. for $C_7H_{14}O$: C, 73·7; H, 12·3%.) Its NMR spectrum measured in pyridine soln showed a sharp two proton singlet at 4·05 ppm (terminal methylene) and a three proton signal at 4·55 ppm (OMe group). The splitting pattern of the rest of the protons at higher field was in full agreement with that expected for structure X.

2-*Methoxy*-1-*hexene*-5-d_2 was prepared in an identical manner from the dibromoether (2·2 g) and n-BuBr-γ-d_2 (1 ml).

2,2-*Dimethylvaleraldehyde* was prepared by Jones oxidation[22] of 2,2-dimethylamyl alcohol. The product, purified by gas chromatography on a 6 ft column containing 20% polybutylene glycol on firebrick at 110° with a He flow rate of 200 ml/min, boiled at 134°; retention time 3·1 mins (Lit.[23] b.p. 126–127°).

The N-*methylimine* (XXXIII) was prepared by the method of Fischer and Djerassi[14] and purified by gas chromatography on a 6 ft column containing 10% GE SF-96 on Chromosorb W at 110° with a He flow rate of 200 ml/min; retention time 5·7 mins; ν_{max}^{Film} 1679 cm^{-1} (C=N). The *oxime* (XXXIV) was obtained by refluxing a soln of the aldehyde in EtOH with hydroxylamine hydrochloride in pyridine for 20 hr, followed by gas chromatography on the GE SF-96 column as for the imine (above); retention time 7·5 mins; ν_{max}^{Film} 1645 (C=N) and 940 cm^{-1} (N-O). (Found: C, 64·91; H, 11·90; N, 10·69. $C_7H_{15}NO$ requires: C, 65·07; H, 11·70; N, 10·84%.)

The semicarbazone (XXXV) was prepared in the conventional manner as colorless flakes, m.p. 140–140·5° (capillary), from aqueous EtOH. (Found: C, 55·90; H, 9·91. $C_8H_{17}N_3O$ requires: C, 56·11; H, 10·01%.)

Acknowledgments—Financial assistance by the National Institutes of Health (grants No. AM-04257 and CA-07195) is gratefully acknowledged. The purchase of the Atlas CH-4 Mass Spectrometer was made possible by NASA grant NsG 81-60.

[22] K. Bowden, I. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, *J. Chem. Soc.* 39 (1946).
[23] K. C. Brannock, *J. Am. Chem. Soc.* **81**, 3379 (1959).