A Thesis Entitled

"SOME APPLICATIONS OF MASS SPECTROMETRY IN ORGANIC CHEMISTRY"

submitted by

David Ross Clarke

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Science of Technology,
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Abstract

The existing information concerning substituent effects in the mass spectra of aromatic compounds is reviewed.

The syntheses of representative compounds of the series 4-Y $C_6H_4(C_6H_5)CHCH_2R$ are described and their mass spectra discussed. Particular reference is made to the correlation between activation energies and Hammett substituent constants for the process 4-Y $C_6H_4(C_6H_5)CHCH_2Ph \longrightarrow$ 4-Y $C_6H_4(C_6H_5)CH^+ + PhCH_2^\bullet$

The preparation and mass spectra of several benzyloxycarbonyl derivatives of L-ornithine are discussed and a corresponding account of some derived piperid-2-ones is presented with a view to making a structural assignment to a new type of lipid known to contain L-ornithine.

The final section deals with the fragmentation of several acetals and fatty acid methyl esters, induced by photon- and electron-impact at room temperature and at 150°C. The significant observation was confirmed that the photon-impact spectra show enhancement of the relative abundance of the molecular ion.

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Contents

Introduction

Mass spectrometry, a study of the decomposition modes of ionic species in the vapour phase, may be used to obtain structural information when only submicrogram quantities of substances are available. Once a detailed knowledge of the fragmentation processes giving rise to the mass spectrum is mastered, a comparison of data from the spectrum of an unknown compound with that of model compounds may lead to the elucidation of the structure of the compound in question. This thesis presents an example of this type of work. In Part 2, a structural assignment is made for a new type of lipid found in Rhodopseudomonas spheroides. The model compounds are derived from L-ornithine and as a result, the electron-induced decomposition pathway of a number of piperid-2-ones and benzyloxycarbonyl derivatives are investigated.

Many delicate molecules may suffer thermal degradation on the walls and filament of a conventional electron-impact source. This may increase the complexity of the mass spectrum produced and hence interpretation of data may become difficult. Simplification of mass spectral decomposition pathways,

therefore, is of great interest to mass spectrometrists. In the light of this, the mass spectra of some acetals and fatty acid esters produced by high energy photons (10 - 20 eV) are investigated and a comparison is made with similar spectra produced by electron-impact to evaluate whether the former process offers any advantage over the latter.

An AEI MS9 double focussing mass spectrometer was used to record the mass spectra and unless noted otherwise all spectra are determined at 70 eV. In the mechanisms proposed in this thesis a single headed arrow ⌒↘ denotes a one-electron shift, whereas a double headed arrow ⌒↘ represents a two-electron shift. It must be pointed out that the use of arrows to indicate decomposition pathways does not accurately represent fragmentation modes since these cannot be a true interpretation of the electronic processes taking place.

In Part 1 and certain sections of Part 3 of this thesis, the intensities of ions in the mass spectra are designated as $\%\sum_{n}^{m}$ where

$$\%\sum_{n}^{m} = \frac{\text{Height of peak x 100}}{\text{Total heights of peaks between } m^{+} \text{ and m/e n}}$$

The alternate method which is used in the remainder of this thesis, represents the intensities of ions as a percentage of the intensity of the base peak.

A Review of Substituent Effects in the Mass Spectra of Aromatic Compounds

The purpose of this review is to describe for the field of mass spectrometry the application of some structure-reactivity relationships established for solution chemistry in the form of the well-known Hammett equation. This empirical formula relates structure to both equilibrium and rate constants, and is restricted to reactions of meta- and para-substituted benzene derivatives. In the form of equation (1), the rate constant **K** may be predicted from a knowledge of Ko, the rate constant for the similar reaction of the unsubstituted compound, σ a substituent constant which reflects the electron-donating or -withdrawing nature of the substituent, and ρ a reaction constant which is a measure of the sensitivity of the reaction to ring substitution.

$$\log (K/Ko) = \rho\sigma \qquad (1)$$

The ionization of benzoic acid has been arbitrarily chosen as the standard reaction for which ρ is fixed at unity and σ may be obtained by measuring the effect of a particular substituent on the ionization constant of benzoic acid in water at 25°C (equation 2). Substituents with

$$\sigma = \log \left(\frac{KX\ C_6H_4CO_2H}{K\ C_6H_5CO_2H} \right) \qquad (2)$$

positive σ values are stronger electron attractors than

hydrogen; substituents with negative σ values attract electrons more weakly than hydrogen. The slope of the best straight line drawn through the points of a plot of the logarithms of the measured constants versus the corresponding σ values, gives the ρ value for the reaction. Reactions with positive ρ values are accelerated by electron withdrawal from the benzene ring, whereas those with negative ρ values are retarded by electron withdrawal.

Since the expression log (K/Ko) is proportional to the differences in the free energies of reactions of substituted and unsubstituted compounds (if K refers to equilibrium constants) or the differences in energies of activation (if K refers to rate constants) the Hammett equation may be rewritten in terms of free-energy changes (equation 3). For a given

$$(G^{+}_{+} - Go^{+}_{+}) = - RT\rho\sigma \qquad (3)$$

reaction series at a given temperature, T, ρ and Go^{+}_{+} are constants, hence equation 3 is of the form $y = ax + b$, and the free-energy changes associated with the reactions are thus linearly related to the respective σ values.

The applicability of the linear relationship is usually quite poor for ortho-substituents since they exert not only an electron-attracting or electron-repelling effect, but also a steric effect. On the other hand, in meta- or para-substituted benzene derivatives, the substituents lie far enough away from the reaction centre to assume that steric interaction between the substituent and reaction centre is negligible and hence the linear relationship is usually obeyed.

In 1959, McLafferty[1] concluded that a correlation existed between the ion abundances in the mass spectra of substituted benzoyl compounds and Hammett sigma values. He suggested that for benzoyl compounds of the series Z C_6H_4COR, where R = CH_3, C_6H_5 and OH, the effect of the substituent Z on the rate of the reaction (equation 4) was shown by the substituent

$$Z\ C_6H_4\ COR^+ \longrightarrow COR^+ + Z\ C_6H_4\cdot \qquad (4)$$

constant σ. Furthermore, he indicated that to represent the abundance of the fragment ion with a single σ value, the reaction described in equation 4 must be the most predominant mode of decomposition affecting COR^+, unless such a reaction does not involve Z. A plot of log K/Ko,

where K = $COR^+/Z\ C_6H_4\ COR^+$ and Ko = $COR^+/C_6H_5\ COR^+$, against σ, gave for compounds of the series $Z\ C_6H_4\ COR$, linear correlations with almost identical ρ values.

In a later investigation,[2] it was found that substituent effects could be correlated with relative ion abundances providing the product ion did not contain the substituent. For ions in which the substituent was retained, it was suggested that the substituent would not only influence the decomposition pathway by which the ion was formed, but it would also influence the reactions by which the ion could fragment. The problem was resolved by eliminating further decompositions of such product ions by use of low-energy electrons. As a result, suitable Hammett correlations were obtained.

McLafferty and Bursey[3] in a study of substituent effects in unimolecular ion decompositions, invoked a kinetic argument as a basis for the applicability of free-energy relationships to ion abundances in mass spectrometry. They used the steady-state approximation applying it only to the concentration of ions in the source, where for the simple fragmentation $M^{\cdot +} \longrightarrow A^+$ in which $[A^+] / [M^{\cdot +}]$ was considered independent of other decomposition pathways, they arrived at an expression (equation 5) which could be fitted

into the Hammett equation (equation 6).

$$\frac{Z}{Zo} = \frac{\left[A^+\right] / \left[M^{\cdot+}\right]}{\left[Ao^+\right] / \left[Mo^{\cdot+}\right]} = \frac{K1}{Ko} \qquad (5)$$

$$\log \frac{Z}{Zo} = \sigma\rho \qquad (6)$$

Z is the ratio of the relative ion intensities of the fragment ion A^+ to the relative ion intensities of the molecular ion $M^{\cdot+}$ in substituted compounds, and Zo represents a similar ratio in unsubstituted compounds. The derived expression was based on the assumption that the recorded intensities of the ions under investigation were proportional to the concentration of ions in the source.

Howe and Williams,[4] however, questioned this hypothesis and with the use of an AEI MS 9 instrument and low voltage spectra (16 - 18 eV) (to minimize secondary decompositions) provided examples which cast doubt on the validity of the basic assumption made in developing the steady-state approach. They suggested for a unimolecular decomposition, where the molecular ion $M^{\cdot+}$ had only one decay pathway to the daughter ion A^+ and where A^+ did not further fragment, that

the relative abundance of $M^{+\cdot}$ reaching the collector was not only a function of the time spent in the ion chamber (t_1) but also a function of the time spent in travelling from the exit slit of the source to the collector (t_2), neglecting possible radiative transitions and loss of $M^{+\cdot}$ by instrumental parameters. Furthermore, the number of daughter ions (derived from the original molecular ions, $Mo^{+\cdot}$) reaching the collector were regarded to be independent of t_2 and only a function of the time spent in the source (t_1), By varying the accelerator potential V (for an ion of given mass $t_2 \propto 1/V^{\frac{1}{2}})^4$ changes in $[A^+] / [M^{+\cdot}]$ were observed for compounds which at low electron energies gave largely two ions in the mass spectrum. Such changes were attributed to the variation of t_2 since an alteration in V was considered to have a negligible effect on $[A^+]$ produced in the source.[5] These results were interpreted as strongly suggesting that the basic assumption did not hold, and questioned the validity of absolute ρ values calculated using the steady-state approach to evaluate substituent effects.[2,3]

Bursey and Rosenthal[6] failed to agree with the interpretation advanced by Howe and Williams.[4] They approximately reproduced the results using various ion accelerating potentials under low ionizing voltage (16 - 18 e V.) conditions on both an AEI MS 902 instrument and

a Hitachi RMU 6 E instrument. Although it had been reported[4] that $[A^+] / [M^{\cdot+}]$ varied by a factor of 5 for pyridine while the accelerating potential was decreased from 8 kV. to 2 kV., they found[6] that the ratio changed by a factor of less than two using the MS 902 instrument. Furthermore, the m/e 52 : m/e 79 ratio was decreased by a factor of two when the accelerating potential of the RMU 6 E was quadrupled. They suggested that the exact factor was a function of the ionizing potential used. Experimental data was provided which indicated that penetration of the source by the field of the accelerator would have a large effect on the relative ion intensities when the ionizing voltage was close to the appearance potential of A^+ .

By correcting for the penetration of the ion chamber by the accelerating potential field, new values for the magnitude of the variation of the relative ion intensities at different accelerating voltages were obtained. The results were interpreted as an indication that there was a small effect caused by the accelerating potential on the ion-intensity ratios. However, the authors[6] suggested that if log Z/Zo values were used in the steady-state approach this small effect could be neglected since it would be diminished to within the reproducibility of data at a given accelerator potential. Furthermore, they concluded that the assumption

that ion intensities were proportional to the concentration of ions in the source could still be used as a good approximation for calculations.

Re-evaluation of the results[5] reported in their original publication[4] supported the findings of Bursey and Rosenthal. In considering the possibility of penetration of the accelerating field into the source, they suggest that field penetration may alter the source residence time, t_1, resulting in significant changes in the abundance of $[A^+]$ produced in the ion chamber. Since a reduction of V allows a longer residence time for ions in the source, more $[M^{\cdot+}]$ ions should decompose to $[A^+]$ so that the $[A^+] / [M^{\cdot+}]$ ratio would increase. All the accumulated evidence appeared to show that source penetration played a major part in contributing to the increase of $[A^+] / [M^{\cdot+}]$ with a decrease in V. This factor substantially outweighed the variation in $[M^{\cdot+}]$ caused by t_2 and led to the conclusion that the results in reference 4 "had no absolute physical significance".

McLafferty[7] and others[8] enumerated a number of basic conditions in an attempt to clarify the manner in which a substituent affects ion abundances. By introducing a substituent into a molecule, the abundance of a given fragment relative to the molecular ion may be altered by any or all of the following effects.

1) Since the energy transferred by bombarding electrons to a molecule during the ionization process can vary over a wide range of values, the internal energies of the positive parent ions produced will have a distribution of values. Furthermore, the rate of decomposition of a molecular ion depends on its internal energy distribution and therefore the abundance of the product ion relative to the molecular ion is determined by the rates and abundances of the different energy forms of the precursor ions. The effect of substitution in a molecule is to alter the fraction of molecular ions having sufficient energy to decompose either by changing the internal energy distribution or by changing the activation energy for fragmentation.

The latter effect may be related to product ion stability. If the product ion retains the substituent, the effect of the substituent on the activation energy can offset its effect on the internal energy of the molecular ion.[7] For example, in the reaction

$$YPhCOPh^{+\cdot} \longrightarrow YPhCO^{+} + Ph\cdot \qquad (7)$$

a plot of log Z/Zo versus σ gave a negative ρ value (-0.4).[2] This was interpreted as strongly suggesting that the effect of a substituent on the even electron product ion

was more important than on the odd-electron molecular ion.[7] Alternatively, for the reaction

$$YC_6H_4COPh^{+\cdot} \longrightarrow PhCO^+ + YPh\cdot \qquad (8)$$

the positive ρ value (1.0) observed[2] indicates that the substituent should have a much smaller effect on product ion stability than was envisaged in the former case. However, the substituent effect in the latter case must have a greater effect on the electron density at the reaction site.[7]

2) In terms of the quasi-equilibrium theory,[9] the ion yield for $[A^+]$ for the reaction

$$M^{+\cdot} \longrightarrow A^+ + B\cdot \qquad (9)$$

must be considered in terms of the competition between other modes of decomposition open to the molecular ion. If the introduction of a substituent alters the rate of a competitive reaction more than the decomposition of interest, variations in the number of energetic ions available for fragmentation may result.

3) The effect of a substituent on secondary decompositions must be considered even if the product ion does not contain the substituent.[7,8] It has been shown[10] that product ions of identical structure not retaining the substituent may be formed by pathways with different internal energy distributions. Furthermore, if the substituent is retained by the product ion, competitive fragmentations will have to be considered unless further decompositions can be eliminated by lowering the electron energy.* Hence, the introduction of a substituent may lead to different rates of decomposition and different ion yields for the primary product ion.

Chin and Harrison[11] derived in terms of the quasi-equilibrium theory a quantitative expression (equation 10) which reflected the previously described enumerations. The derivation was based on the following assumptions:

$$\frac{[A^+]}{[M^{\cdot+}]} = \frac{f'}{f}\frac{[A_o^+]}{[M_o^{\cdot+}]} = \frac{K_1}{K_t}\left(\frac{1}{f} - 1\right) \qquad (10)$$

1) molecular ions are formed with a distribution of internal energy; 2) fragment ions are produced from molecular ions with sufficient energy to decompose by a series of competing and

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* lowering the electron energy will increase the number of molecular ions not having enough energy to decompose, which may have a significant effect on the abundance of $M^{\cdot+}$ reaching the collector.

consecutive unimolecular decomposition reactions; 3) these unimolecular decomposition reactions are fast in comparison to the ion source residence times, hence the instrumental parameters which affect the residence time will have little influence on the mass spectra. In equation (10) $[Ao^+]$ is the total number of fragment ions A^+ formed from the molecular ion $Mo^{+\cdot}$, where $[Mo^{+\cdot}]$ is the total number of molecular ions formed by the initial electron-impact process, $[M^{+\cdot}]$ represents the number of molecular ions incapable of undergoing fragmentation, and $[A^+]$ represents the total number of A^+ ions observed. The quantities f and f' are the fraction of molecular ions and fraction of A^+ ions, respectively, with insufficient energy to decompose. The rate constant for formation of A^+ is K_1 and K_t is the sum of all rate constants resulting in the decomposition of the molecular ion, hence K_1/K_t is the fraction of fragmenting ions which form A^+.

From equation (10) it can be seen that a substituent may affect the ratio of $[A^+] / [M^{+\cdot}]$ by changing f', f or K_1/K_t. If secondary decompositions from A^+ can be eliminated by lowering the electron energy, equation (10) may be simplified as the f' term will become unity. Moreover, further simplification of equation (10) arises, if competing fragmentation reactions of the molecular ion can

be eliminated, since the term K_t becomes equal to K_1 and the substituent will exert its influence entirely through changes in f. The authors[11] indicated that on the basis of these theoretical arguments the latter conclusion was in contrast[12] to that reached in the steady-state treatment where it was reported that at low energies the substituent effect was derived entirely from the variation of K_1.

Chin and Harrison[11] examined the fragmentation reactions of substituted acetophenones to obtain experimental evidence relevant to the theoretical arguments advanced. A plot of $\left[M^{+\cdot}\right] / \left[Mo^{+\cdot}\right]$ versus σ gave a moderately linear correlation and was indicative of the fact that f was dependent on the substituent since by definition $f = \left[M^{+\cdot}\right] / \left[Mo^{+\cdot}\right]$.

On the basis of preceding arguments, a new expression (equation 11) was introduced which led to the experimental evaluation of K_1/K_t. A plot of $\log \left[CH_3CO^+\right] / \left[Mo^{+\cdot}\right](1 - f)$

$$\frac{\left[A^+\right]}{\left[Mo^{+\cdot}\right]} = f' \frac{K_1}{K_t}(1 - f) \qquad (11)$$

against σ gave a linear correlation which indicated that

$\log \left[f'(K_1/K_t)\right]$ was a linear function of σ .* Hence, it was suggested that if f' was considered to be independent of the substituent, then $\log K_1/K_t$ varied linearly with σ . The authors[11] reported, however, that it was impossible to determine from experimental evidence whether this dependence could be attributed to a substituent effect on K_1 or some other fragmentation reaction. Furthermore, they suggested that for reasons postulated in the development of the theoretical hypothesis a decision on this matter was not possible from intensity measurements alone.

Chin and Harrison also showed that linear correlations were obtained when ionization potentials and appearance potentials of the $\left[YC_6H_4CO^+\right]$ ions were separately plotted against σ values. Such a correlation was a fully expected result.[13-19] In the process of ionization, an electron may be removed from the molecular orbital of the π system; the substituent may then affect the energy of the upper orbital in proportion to their degree of interaction with the phenyl ring (measured by σ).[13] Furthermore, it was suggested that a correlation of activation energies (difference between appearance potential and ionization potential) for the decomposition process under study, with Hammett substituent constants, could reveal information about both the reaction centre and the electronic state.[13]

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* Bursey and McLafferty[2] using the steady-state approach found a linear correlation for the same fragmentation reaction.

Recently, Johnstone and co-workers[20] questioned the relevance of equating the structure of molecular ions undergoing decomposition, to the structures of molecules before ionization to make deductions about reaction mechanisms, if there was a correlation between ion intensities and Hammett σ values. They analyzed the simple bond cleavage reaction (equation 12) in terms of its bond dissociation energy,

$$R - M^{+\cdot} \longrightarrow R - A\cdot + B^{+} \qquad (12)$$

ignoring kinetic shifts and possible electronically excited states. On the basis of their interpretation of the fragmentation process described above, they derived from the simplified rate equation 13,[21] an expression (equation 14) which included the molecular ionization potential terms

$$K = V \left[(E - E^{\circ})/E\right]^{N-1} \qquad (13)$$

$$\log (K_R/K_H) \cong \left[(N - 1)/E\right] \left[Im^R - Im^H\right] \qquad (14)$$

Im^R and Im^H of the substituted and unsubstituted benzenoid derivatives, respectively. In equation 14, K_R and K_H represent the rate constants for the decomposition reaction of the substituted and unsubstituted derivatives, respectively,

E is the excess internal energy and N represents the effective number of oscillators. Simplification of equation 14 gives

$$\log(K_R/K_H) = \log Z/Zo = K\sigma \qquad (15)$$

since $K_R/K_H = Z/Zo$,[3,20] and $Im^R - Im^H = K$ (K is a constant).[20] On the basis of this derived relationship, Johnstone and co-workers strongly suggest "that a correlation between log (Z/Zo) and Hammett σ values can be deduced from the quasi-equilibrium theory, but the correlation is due to the correlation of the molecular ionization potential with σ and not to the mechanism of bond cleavage".[20] Furthermore, the authors[20] reported that for complex fragmentations such as the loss of CHO from substituted phenols, which involved destruction of the aromatic ring, log Z/Zo correlated with σ. Moreover, they obtained a correlation for the decomposition of monosubstituted benzenes where Z was the ratio of the relative ion abundance of "the first major skeletal fragment ion irrespective of the actual fragmentation involved",[20] to the relative ion intensity of the molecular ion. The decompositions that produced the correlation were based on such diverse reactions as the loss of HCN from aniline, of NO_2 from nitrobenzene,

of Cl from chlorobenzene, of C_2H_2 from fluorobenzene, elimination of terminal C_2H_4 from ethyl benzoate and CO from phenol. Johnstone and co-workers[20] concluded that that the assumptions used in their mathematical treatment were similar to those used by Bursey[12] to derive the log Z/Zo relationship, however they stress that both treatments suffer from oversimplification.

Bursey and Buck[22] report that a correlation may exist between ion intensities of product ions and Hammett sigma constants based on a probability distribution of internal energies derived for aromatic molecules which decompose to give only a single product. They also suggest that the derived relationship may be extended to include molecular ions forming more than one product, since further fragmentation processes where energies can be related to substituent constants should allow the extraction of correlatable intensities from experimental data. Furthermore, Bursey and Kissinger[23] reiterate that there is no reason to exclude molecular ions which decompose to form more than one product since a distribution of energy similar to the form derived in the above mentioned publication is capable of explaining a multi-ion spectrum. However, they emphasize that for a three-ion system too many constants would be

present in the derived relationship to test its application critically. Hence, the theoretical deductions of Bursey and co-workers[22,23] may be of limited practical use.

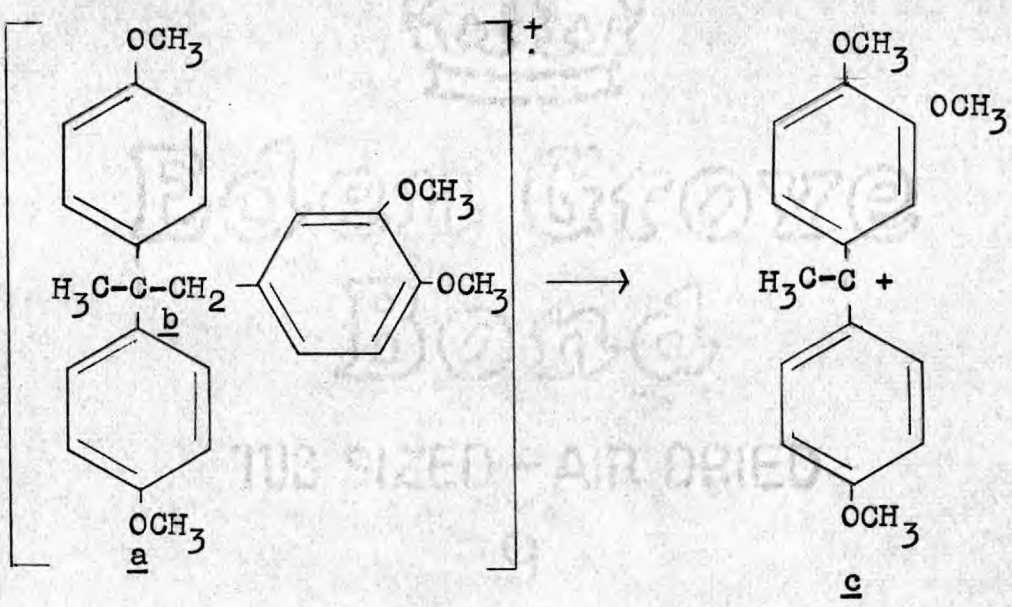
Of the correlations dealt with in this review, probably the only one with substantial interpretative value is that relating activation energies with Hammett substituent constants.

PART 1

Derivatives of 1,1,2-Triphenyl Ethane, 1,1-Diphenyl Propane and Related Compounds

1,1 Discussion of Experimental Work

Several substituted ethane derivatives of the series $4\text{-}YC_6H_4(C_6H_5)CHCH_2R$ have been prepared in order to investigate their electron-impact induced fragmentation. It has been observed in the mass spectrum of (a) that the intensity of the molecular ion was very weak.[24] This was attributed to the presence of an easily cleaved bond (b) and the resulting carbonium ion (c).



The decomposition pathway of compounds of the type $4\text{-}YC_6H_4(C_6H_5)CHCH_2R$, where R = C_6H_5, should give rise to

considerable differences in the relative abundance of the molecular ion. Electron donating substituents should enhance the formation of carbonium ions resulting in molecular ions of relatively low abundance, whereas electron withdrawing substituents should inhibit the facile cleavage, giving rise to more intense molecular ion peaks. Furthermore, the fragmentation pattern of this series of compounds should also demonstrate the competition between the formation of the tropylium ion (or benzyl ion) and an aryl substituted carbonium ion. The above argument assumes better stabilization of the positive charge by the aryl substituted carbonium ion.

It was decided to synthesize compounds with Y = NO_2 and NH_2, the extremes of electron withdrawing and electron donating substituents, respectively. Diazotization of the aromatic amine and replacement of the diazonium group with suitable substituents would readily afford the required class of compounds.

The Grignard reaction could not be applied in a direct synthesis of compounds when Y = NO_2 and NH_2, as most primary aromatic amines behave toward Grignard reagents as though they contain an active hydrogen and form so-called nitrogen Grignard reagents. Furthermore, the initial reaction of an aryl nitro compound with arylmagnesium halide consists of an addition followed by a reduction to a diarylhydroxylamine derivative.[25]

The same restrictions do not apply to the Wittig reaction and hence this approach to the desired products was investigated. In the Wittig reaction the initial nucleophilic attack by the ylid on the carbonyl function forms a betaine intermediate. This attack is accelerated by the presence of electron withdrawing groups (NO_2) in the component containing the carbonyl function.

The sequence of reactions employed in the synthesis of compounds of the type $4\text{-}YC_6H_5(C_6H_4)CHCH_2R$ is outlined in Scheme 1.

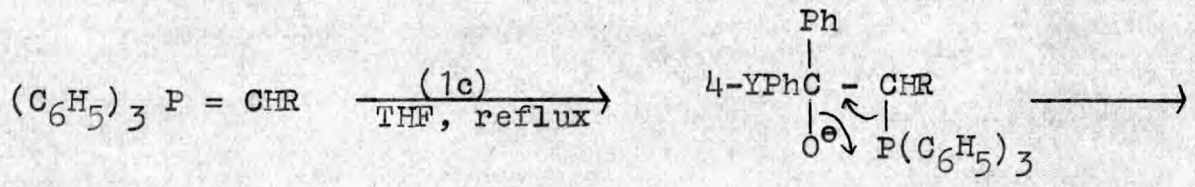
$$4\text{-}YPhCH_2Cl \xrightarrow[\text{reflux}]{C_6H_6,\ AlCl_3,\ CS_2} 4\text{-}YPhCH_2Ph \xrightarrow[\text{reflux}]{CrO_3,\ CH_3CO_2H} 4\text{-}YPhCOPh$$

(1a) $Y = NO_2$ (1b) $Y = NO_2$ (1c) $Y = NO_2$

$$(C_6H_5)_3P + RCH_2X \longrightarrow \left[(C_6H_5)_3PCH_2R\right]^{\oplus}X^{\ominus} \xrightarrow[(C_2H_5)_2O]{PhLi}$$

(2a) $X = Cl$, $R = C_6H_5$ (3a) $X = Cl$, $R = C_6H_5$

(2b) $X = Br$, $R = CH_3$ (3b) $X = Br$, $R = CH_3$

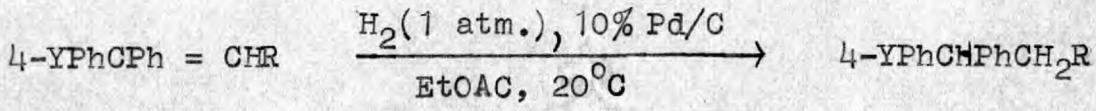


(4a) R = C_6H_5

(4b) R = CH_3

(5a) Y = NO_2, R = C_6H_5

(5b) Y = NO_2, R = CH_3

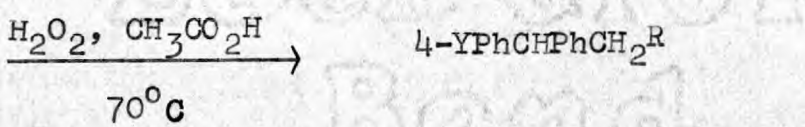


(6a) Y = NO_2, R = C_6H_5

(6b) Y = NO_2, R = CH_3

(7a) Y = NH_2, R = C_6H_5

(7b) Y = NH_2, R = CH_3



(7c) Y = NO_2, R = C_6H_5

(7d) Y = NO_2, R = CH_3

Scheme 1

Treatment of 4-nitrobenzyl chloride (1a) with benzene and aluminium chloride (Friedel-Crafts alkylation) in the presence of carbon disulphide after the method of Baeyer and Villeger[26] gave (1b). The authors suggested that one half the quantity of aluminium chloride used by Basler[27] would reduce side reactions at no expense to the yield. Attempts following this procedure afforded a mixture of (1a) and (1b) (50%). However, when an excess of aluminium chloride was used the yield was increased by 30% and the presence of (1a) was not detected. Since there was a difference in the chemical shift between the methylene protons of (1a) (δ 4.72) and (1b) (δ 4.02) the disappearance of the methylene protons of 4-nitrobenzylchloride (1a) was monitored by removing 5 ml. aliquots and examining the ^1H Nuclear Magnetic Resonance (n.m.r.) spectrum of the product after work-up. The reaction was generally complete after 90 minutes. If the reaction was allowed to proceed much longer, polymerisation occurred and the yield was decreased considerably.

4-Nitrodiphenylmethane (1b) could be oxidized with chromium trioxide in acetic acid to the corresponding ketone in 80% yield. An infrared spectrum (i.r.) of (1c) showed the presence of the diaryl ketone carbonyl stretching vibration at 1662 $cm.^{-1}$ and aromatic C-NO_2 asymmetric and symmetric stretching vibrations at 1536 and 1370 $cm.^{-1}$, respectively.

Although it was reported that benzentriphenylphosphonium chloride (3a) could be prepared in quantitative yield,[28] it was found that unless the procedure was modified the expected yield was not obtained. Triphenyl phosphine and benzyl chloride (2a) heated at 70°C on a Büchi evaporator afforded a thick slurry of crystals. The salt was removed by filtration and washed with ether to yield a white crystalline solid (3a), m.p. 317-318°C (lit. 317-318°C).

Reaction of triphenylphosphine dissolved in benzene and ethyl bromide (2b) in a Carius tube at 135°C for 20 hours gave (3b) in 82% yield.[29]

Treatment of benzyl triphenylphosphorane (4a) furnished by reacting phenyl lithium[30] and (3a) in ether, with (1c) dissolved in freshly distilled tetrahydrofuran afforded after refluxing for 12 hours cis and trans 1-(4'-nitrophenyl)-1,2-diphenyl ethylene (6a) in 82% yield.[31] An n.m.r. spectrum of (6a) clearly indicated the presence of an AA'BB' system centred at δ 7.45 corresponding to the aromatic moiety with the nitro substituent. A multiplet arising from nine benzenoid and one olefinic proton occurred in the range δ 6.58 - 7.50. The i.r. spectrum showed aromatic C = C skeletal in plane vibrations at 1600, 1500 and 1450 $cm.^{-1}$ and aromatic $C-NO_2$ asymmetric and symmetric stretching vibrations at 1535 and 1358 $cm.^{-1}$, respectively.

Addition of ethyl triphenylphosphorane, prepared by treating (3b) with phenyl lithium, to (1c) dissolved in freshly distilled tetrahydrofuran gave after refluxing for eight hours, cis and trans 1-(4'-nitrophenyl)-1-phenyl-propyl-2-ene (6b) in 63% yield. An n.m.r. spectrum of (6b) showed a complex multiplet from δ 7.10 - 8.40 (benzenoid protons), a multiplet from δ 6.15 - 6.62 (olefinic proton) and two doublets of equal intensity (cis and trans CH_3, J = 1.9 Hz) at δ 1.85 and δ 1.72.

Hydrogenation of (6a) and (6b) over 10% palladium on charcoal afforded (7a) and (7b) in nearly quantitative yields. An n.m.r. spectrum of (7a) showed a complex multiplet (benzenoid protons) from δ 6.40 - 7.32, in which an AA'BB' pattern centred at δ 6.75 was discernible. A triplet (CH, J = 7.5 Hz) centred at δ 4.16, and a doublet (CH_2, J = 7.5 Hz) centred at δ 3.32 superimposed on a singlet (NH_2) at δ 3.32 arising from the accidental degeneracy of the amino protons were observed. The resonance peak attributed to the amino protons disappeared when D_2O was added to the sample. The i.r. spectrum of (7a) indicated the presence of two N - H stretching vibration bands at 3480 and 3400 $cm.^{-1}$, an NH bending vibration at 1623 $cm.^{-1}$ and a C - N aromatic stretching vibration at 1280 $cm.^{-1}$. A mass spectrum (Figure 1, p.161) showed the presence of a molecular ion at m/e 273.

Treatment of (7a) with acetic anhydride in the presence of pyridine gave (±) 1-(4'-acetamidophenyl)-1,2,-diphenyl ethane (7e) in 95% yield. The n.m.r. spectrum of (7e) showed a complex multiplet (benzenoid protons overlapping with N - H) from δ 7.00 to 7.58, a triplet (CH, J = 7.5 Hz.) at δ 4.24, a doublet (CH_2, J = 7.5 Hz.) at δ 3.32 and a singlet (CH_3) at δ 2.10. An i.r. spectrum indicated the presence of an amide carbonyl stretching vibration at 1660 $cm.^{-1}$.

Compounds (7a) and (7b) could be oxidized with hydrogen peroxide[32] to (7c) and (7d) in yields of 70% and 63%, respectively. An n.m.r. spectrum of (7d) showed no resonance absorption arising from the amino protons of (7b). A multiplet corresponding to nine aromatic protons, in which an AA'BB' pattern was clearly discernible occurred in the range δ 6.95 - 8.18. A triplet (CH, J = 7.5 Hz.) at δ 3.81 , a pentuplet (CH_2, J = 7.5 Hz.) at δ 2.05 and a triplet (CH_3, J = 7.5 Hz.) at δ 0.91 were observed. An i.r. spectrum showed C - NO_2 aromatic asymmetric and symmetric stretching vibrations at 1526 and 1350 $cm.^{-1}$.

Diazotization of (7a) with hydrochloric acid and sodium nitrite, and addition of the diazonium salt to an aqueous solution of cuprous cyanide and sodium cyanide, afforded (±) 1-(4'-cyanophenyl)-1,2,-diphenyl ethane (7f) and 1,1,2-triphenyl ethane in 50% and 2% yield, respectively.

An i.r. spectrum of (7f) showed a CN stretching vibration band at 2235 $cm.^{-1}$.

Treatment of (7f) with aqueous sodium hydroxide gave a mixture of (±) 1-(4'-carbamoylphenyl)-1,2-diphenyl ethane (7g) and (±) 1-(4'-carboxyphenyl)-1,2-diphenyl ethane (7h) which were separated by preparative thin layer chromatography (t.l.c.) ($CHCl_3$). The i.r. spectra of (7g) and (7h) showed carbonyl stretching vibrations at 1675 and 1690 $cm.^{-1}$, respectively.

Addition of an aqueous solution of sodium fluoroborate to the diazonium salt of (7a) gave (±) 1-(4'-benzenediazonium fluoroborate)-1,2-diphenyl ethane, which in turn was heated under vacuum until decomposition occurred, resulting in the distillation of (±) 1-(4'-fluorophenyl)-1,2-diphenyl ethane (7i) (b.p. 136°C, 0.1 m.m.) Its i.r. spectrum showed C - F stretching vibrations at 1230 and 1102 $cm.^{-1}$.

Addition of the diazonium salt of (7a) to an acidic solution of freshly prepared cuprous chloride gave (±) 1-(4'-chlorophenyl)-1,2-diphenyl ethane (7j) in 58% yield. A mass spectrum of (7j) (Figure 2, p.162) showed the presence of a molecular ion at m/e 292.

Treatment of a suspension of cuprous bromide, prepared by dissolving copper sulphate pentahydrate and sodium bromide in water followed

by addition of sodium metabisulphite and sodium hydroxide, with (±) 1-(4'-benzenediazonium bromide)-1,2-diphenyl ethane afforded (±) 1-(4'-bromophenyl)-1,2-diphenyl ethane (7k) in 60% . The n.m.r. spectrum of (7k) indicated the presence of a complex multiplet (benzenoid protons) from δ 6.90 - 7.50, a triplet (CH, J = 7.5 Hz.) at δ 4.20 and a doublet (CH_2, J = 7.5 Hz.) at δ 3.33.

The iodide derivative (71) was prepared by addition of an aqueous solution of potassium iodide to a suspension of (±) 1-(4'-benzenediazonium chloride)-1,2-diphenyl ethane. A mass spectrum of (71) (Figure 3, p. 163) showed the presence of a molecular ion at m/e 384.

^{1}H Nuclear Magnetic Resonance Spectra Considerations

Chemical nonequivalence of geminal nuclei can always be expected if there is present somewhere in the molecule an asymmetric carbon atom. In general, the two criteria which can conveniently be applied to differentiate between such nuclei are the chemical shift difference between the mutual coupling constant and the coupling constants of these nuclei with a third nucleus. In order to exhibit the chemical shift difference between the nuclei two conditions must be met:

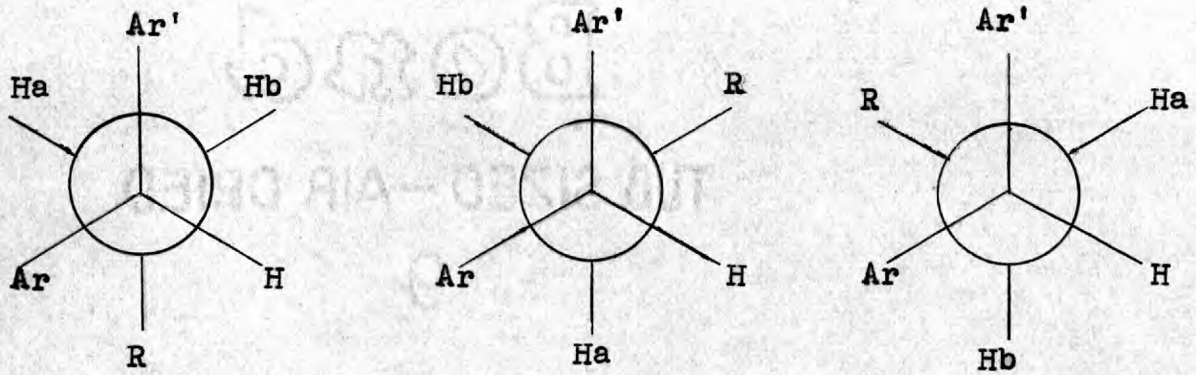
1) Atoms or groups which may exhibit nonequivalence cannot be related by any symmetry operation, taking into consideration internal motions that are rapid compared to the time scale of a ^{1}H nuclear magnetic resonance experiment.

2) There must exist a sufficient field gradient so that the nonequivalent atoms or groups of atoms exhibit chemical shifts resolvable on the instrument employed.[33] In other words, if the (average) environments are insufficiently dissimilar then chemical equivalence will be observed. The effect satisfying this condition appears to be transmitted mainly through space.[34]

The n.m.r. spectra of the substituted ethane derivatives were of interest since the methylene protons of this class of compounds were separated by one bond from a centre of molecular asymmetry and therefore expected to exhibit chemical nonequivalence.

An AB-type n.m.r. sub-spectrum should have been observed which would be further complicated by spin-spin coupling of the methylene groups with protons attached to adjacent carbon atoms.[35]

Consider a compound with three distinguishable rotational forms of the general formula $Ar'ArCHCH_2R$. Each



a b c

compound where R = C_6H_5 shows only a doublet for the CH_2 group due to spin-spin coupling with the methine proton. Furthermore, where R = CH_2CH_3, the methylene group appears

as a pentuplet due to spin-spin coupling with the methine and methyl protons. No case was observed in which any multiplicity was attributable to chemical nonequivalence.

Since conformer population differences are greatest at low temperature, an examination of the low temperature ($-50^{\circ}C$) spectra of (7a) and (7c) was carried out but revealed no change in the multiplicity of the methylene protons. These results can be interpreted in terms of energy difference between the three rotational isomers. Conformers (a) and (b) are of similar energy, whereas, if the energy difference between the two equivalent conformers and the third is greater than 800 calories per mole, then the temperature effect is very difficult to detect, and if it is greater than 1500 calories per mole, no temperature effect will be observed.

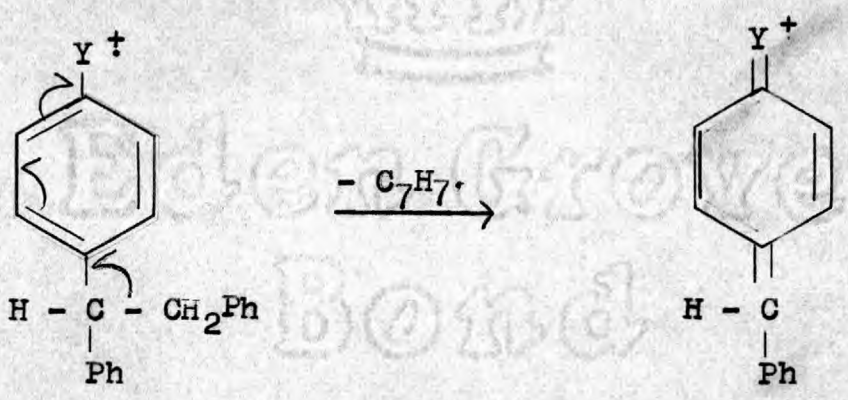
If we assume that the conformers are rapidly interconverting, then because of lack of symmetry the two protons of the methylene group are never stereochemically equivalent. If the electronic screening of Ha and Hb does not differ significantly for each of the rotational isomers, then chemical nonequivalence may not be observed. This could arise if the asymmetric field is too weak to exert any appreciable influence on Ha and Hb. However, this is not reconcilable with experimental results which show a chemical

shift difference of 9Hz. (100 MHz. spectra) for the methylene protons of (7a) and (7c). This leads to the conclusion that if there is "accidental" equivalence in one compound due to the balancing out of the symmetry effect with that due to conformer population differences, then changes at the <u>para</u> position may affect each of the methylene protons to the same extent and maintain chemical equivalence.[36]

The anisotropy of the field about the carbon atom bearing the nonequivalent groups may well be the most important factor determining the chemical shift difference between nonequivalent nuclei.[37] Hence the presence in a molecule of a centre of molecular asymmetry is not a sufficient condition for the actual observation of chemical nonequivalence. The fundamental requirement is that the asymmetric carbon bears substituents that differ significantly to bring the local field asymmetry above a threshold level. The threshold level for observation of magnetic nonequivalence will depend upon the field strength of the instrument.[36]

1,2 Discussion of Mass Spectra

The decomposition pathway of compounds of the series $4\text{-}YC_6H_4(C_6H_5)CHCH_2R$ (7) are characterized predominantly by homolytic bond fission facilitated by simultaneous formation of a well stabilized positive ion. The most abundant ion (a) in the mass spectra of these compounds arises from the loss of the C_7H_7 radical from the molecular ion.



I a

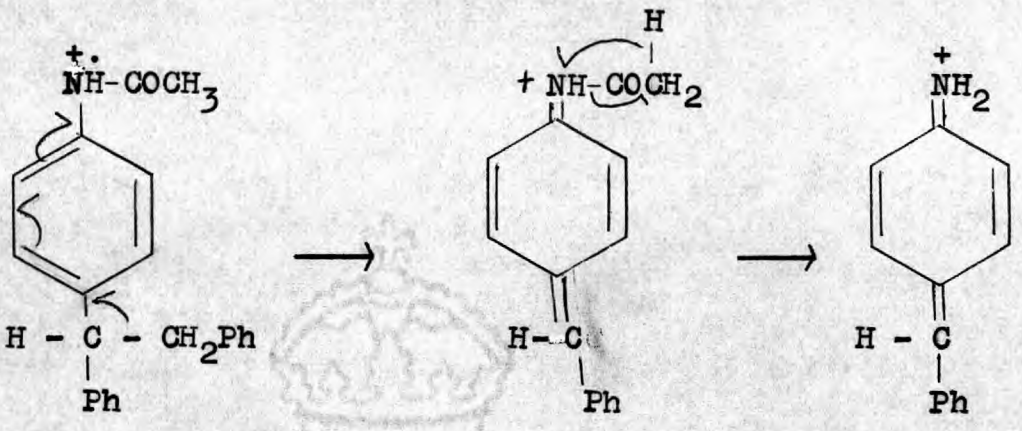
Other significant peaks are observed at m/e 166, 165 and 91 and are shown by mass measurement to be consistent with the formulae $C_{13}H_{10}$, $C_{13}H_9$ and C_7H_7, respectively.

Metastable defocussing techniques[38] indicate that the fragments at m/e 166 and 165 are formed directly from a, through loss of Y and HY, respectively. However, elucidation of the structure of these common ions proved unsuccessful.

Since completely identical breakdown patterns[39,40] imply a common structure and internal energy distributions, it was decided to compare the mass spectrum of fluorene with the significant portions of the spectra derived from compounds of the series (7). Inspection of the 70 eV spectra of the substituted ethane derivatives (7) reveal that the spectra below m/e 166 are very similar to the mass spectrum of fluorene. Weak ions (less than 1.1% of Σ_{91}) are observed at m/e 139 and m/e 115, however the abundance of the fragment at m/e 115 is nearly always greater than the intensity of the ion at m/e 139 for the ethane derivatives, whereas the intensity of the m/e 139 ion from fluorene is greater than the abundance of the m/e 115 fragment. Examination of their low electron energy sub-spectra does not provide any structural information as the intensity of the ions at m/e 139 and m/e 115 are too weak to be measured accurately. Furthermore, the absence of metastable ions for formation of the fragments at m/e 139 and m/e 115 ruled out the use of the metastable ratio method.[41] Hence, although the ions at m/e 166 and m/e 165 may have a fluorenyl type structure no conclusive evidence was obtained to substantiate this.

The formation of the ion (b) (m/e 224) affords the most abundant peak in the mass spectrum of (7e) (Figure 4, p.164), however the ion (c) (m/e 182) is very prominent (59.2% of the base peak). Metastable defocussing techniques

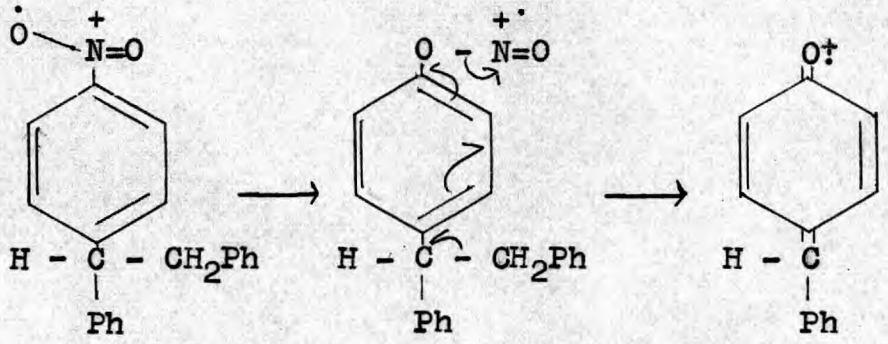
indicate that the ion arises through loss of the C_7H_7 radical from the molecular ion, followed by the elimination of ketene from (b) to afford (c).



b c

Although the ion (d) at m/e 182 is of low intensity its presence in the mass spectrum of (7c) (Figure 5, p. 165) provides an opportunity to distinguish between two plausible modes of decomposition. If mechanism 1 is operating the ion may arise as a result of concomitant loss of the C_7H_7 radical and NO radical from the rearranged molecular ion (e) to furnish (d) in a concerted process.

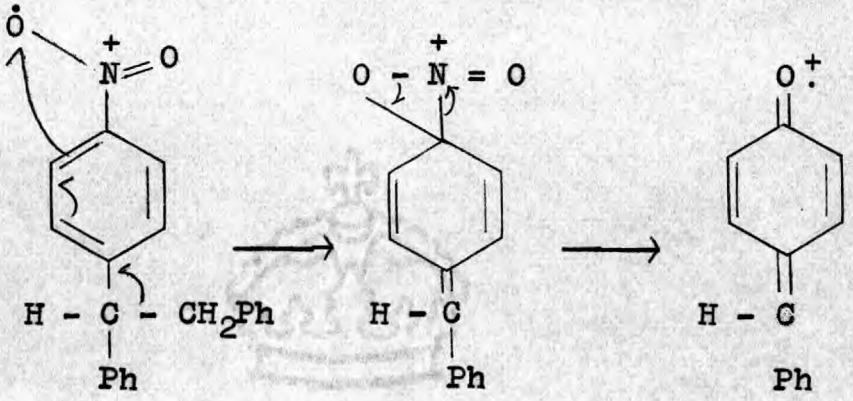
Mechanism 1



m/e 303 e d

Alternatively, mechanism 2 involves the loss of the C_7H_7 radical from the molecular ion (f) with simultaneous formation of a three-membered ring to give (g), which may decompose further eliminating the NO radical to afford (d).

Mechanism 2



f g d

Examination of the decomposition pathway of (7c) by metastable defocussing experiments shows that (d) is formed by a two step process; results which are consistent with the sequence f ⟶ g ⟶ d postulated in mechanism 2.

The mass spectra of compounds of the series (7) show considerable variations in the abundance of molecular ions depending on the nature of the <u>para</u>-substituent, consequently the reaction site must be influenced by the electron donating or electron withdrawing ability of the substituent. Table 1 shows the intensities of molecular ions and M-91 ions, expressed as percentages of the total ion current ($\%\Sigma_{91}$).

Table 1

Partial mass spectral data for compounds of the series $4\text{-}YC_6H_4(C_6H_5)CHCH_2R$

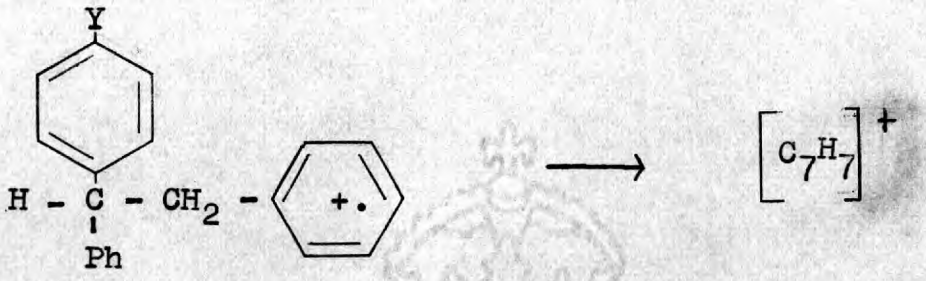
Compound	Substituent	Figure, page	Abundance of molecular ion peak $\%\Sigma_{91}$	Abundance of M-91 peak $\%\Sigma_{91}$	Ratio of intensities of M-91/m/e 91
(7a)	$4\text{-}NH_2$	1, 161	1.9	66.5	23.2
(7e)	$4\text{-}NHCOCH_3$	4, 164	0.6	47.8	11.4
(7i)	4-F	6, 166	0.8	64.8	26.5
(7j)	4-Cl	2, 162	1.2	55.7	25.4
(7k)	4-Br	7, 167	0.7	56.9	21.5
(7l)	4-I	3, 163	1.7	50.7	20.9
(7h)	$4\text{-}CO_2H$	8, 168	1.5	53.4	10.4
(7g)	$4\text{-}NH_2CO$	9, 169	5.0	53.7	13.0
(7f)	4-CN	10, 170	10.9	44.5	3.2
(7c)	$4\text{-}NO_2$	5, 165	5.2	35.1	2.0

From the table it is evident that although a correlation does not exist a trend is indicated, which reflects the fact that the electron donating substituents enhance the formation of (a). Therefore the molecular ion intensities are very weak (less than 2% of the total ion current). In contrast, when the substituent is electron withdrawing, higher activation energies (see Table 2) are required to produce the fragmentation resulting in formation of (a). Hence bond fission is not as facile and the molecular ions are more prominent.

Although the abundance of the molecular ion peak is less for compound (7c) than (7f) it was thought that the reverse would be observed. However, examination of the mass spectrum of (7c) indicates that the loss of NO_2 competes effectively with the loss of C_7H_7 from the molecular ion. The activation energy for the former process is only +0.35 eV (7.03 Kcal/mol) whereas the latter process requires 2.15 eV (49.57 Kcal/mol) for fragmentation to occur. Thus these measurements serve to rationalize the observed departure from the general trend.

From Table 1 it is also evident that a trend exists for the competition between formation of the carbonium ion (a) described by the sequence 7 $\longrightarrow$ a, and formation of the

C_7H_7 ion (h). When the substituent is either electron withdrawing or electron donating, the favoured fragmentation is 7 ⟶ a. However, the intensity ratio of ions (a) and



h

(h) reflects the competing abilities of the fragments involved to sustain a positive charge or radical status. The process 7 ⟶ a, may involve formation of a benzyl radical whereas in the other case (formation of h) a tropylium ion may be formed, but no experimental data was acquired to support one or other of these possibilities. As the electron donating character of the substituent decreases, the less favoured pathway becomes more prominent. For example, when the extremes of electron donating and electron withdrawing substituents are considered the ratio of intensities of a/h is 23.2 for (7a, Y = NH_2) and only 2.0 for (7c, Y = NO_2).

The difference between the appearance potentials (AP) of type (a) ions and ionization potentials,[13] are plotted against Hammett substituent[42] and Brown substituent*[43] constants with the results shown in Figures 11 and 12, respectively. The ionization and appearance potential data is summarized in Table 2. A reasonable linear correlation is obtained for both plots. The positive slope of the graph indicates that the formation of (a) is enhanced by electron donating substituents and retarded by those which are electron withdrawing. This is in agreement with electronic considerations and is consistent with the conclusions drawn earlier, when intensities measurements were used to rationalize the effect of different substituents on the reaction site for the sequence 7 ⟶ a. These measurements reflect the fact that a <u>para</u> electron donating substituent will furnish electron density to the reaction site and thereby reduce the activation energy for the transformation. Alternatively, they indicate that a <u>para</u> electron withdrawing substituent will increase the activation energy and hence bond fission will not be as facile.

---

* Brown substituent constants take into account resonance effects as evaluated through such studies as solvolysis of t-cumyl chlorides and ionization of trityl and benzhydryl alcohols.

Table 2

Table of Physical Characteristics

Relating to Figures 11 and 12

Compound	Hammett Function	Brown Function	IP'	AP	E	Point
(7a)	-0.66	-1.4	7.85	8.50	0.65	A
(7e)	-0.015	-0.6	8.05	9.10	1.05	B
(7i)	+0.06	-0.07	11.30	12.45	1.15	C
(7j)	$+0.22_7$	+0.11	9.95	11.40	1.35	D
(7k)	$+0.23_2$	+0.15	10.07	11.40	1.33	E
(7l)	+0.28	+0.15	10.15	11.50	1.35	F
(7h)	+0.27	+0.42	10.45	12.05	1.60	G
(7f)	+0.63	+0.66	10.57	12.39	1.82	H
(7c)	+0.78	+0.78	10.70	12.85	2.15	I

Graph of E = AP - IP versus σ for para Substituted Ethane Derivatives

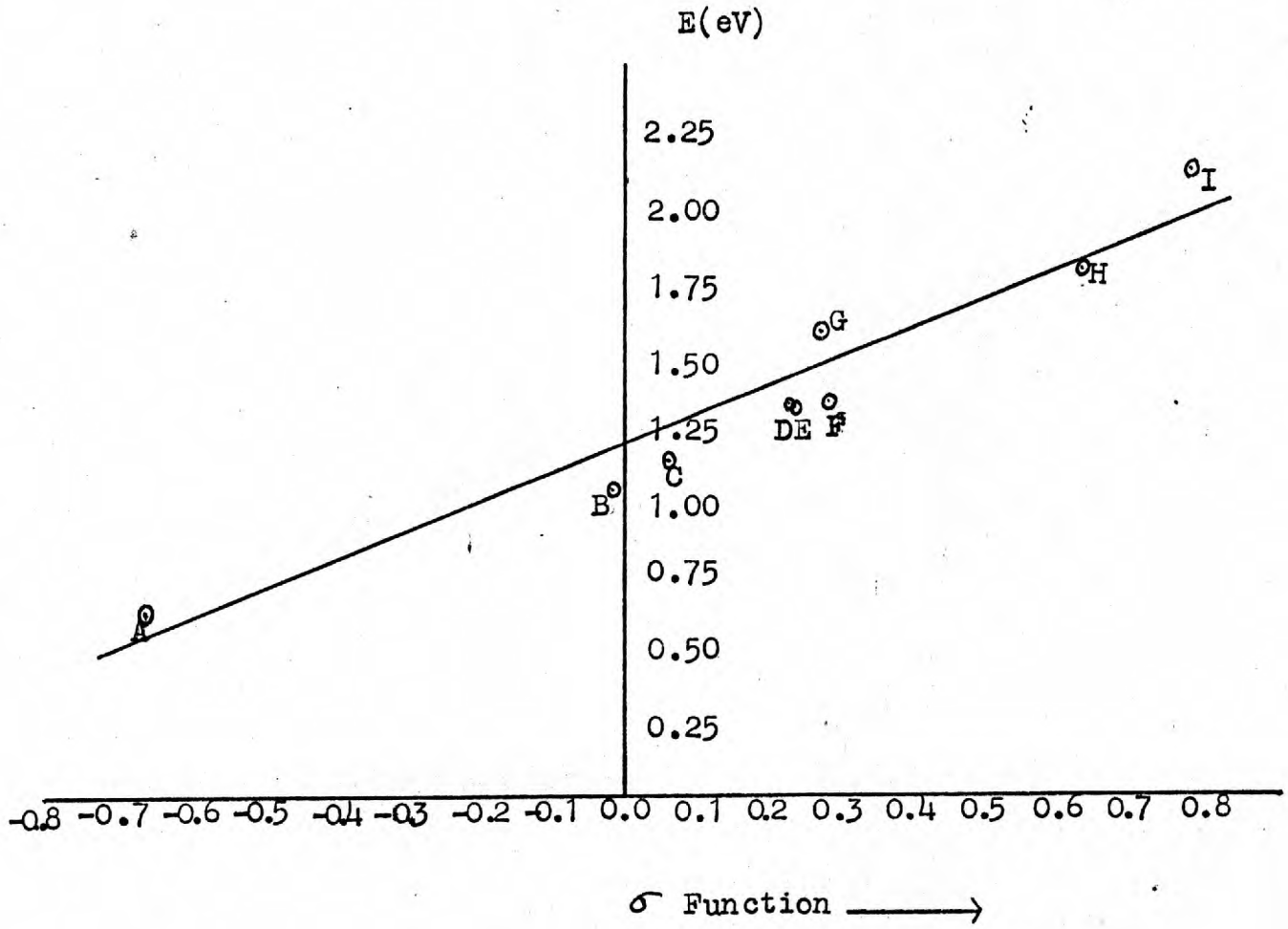


Figure 11

Graph of E = AP - IP versus σ^* for <u>para</u>-Substituted Ethane Derivatives

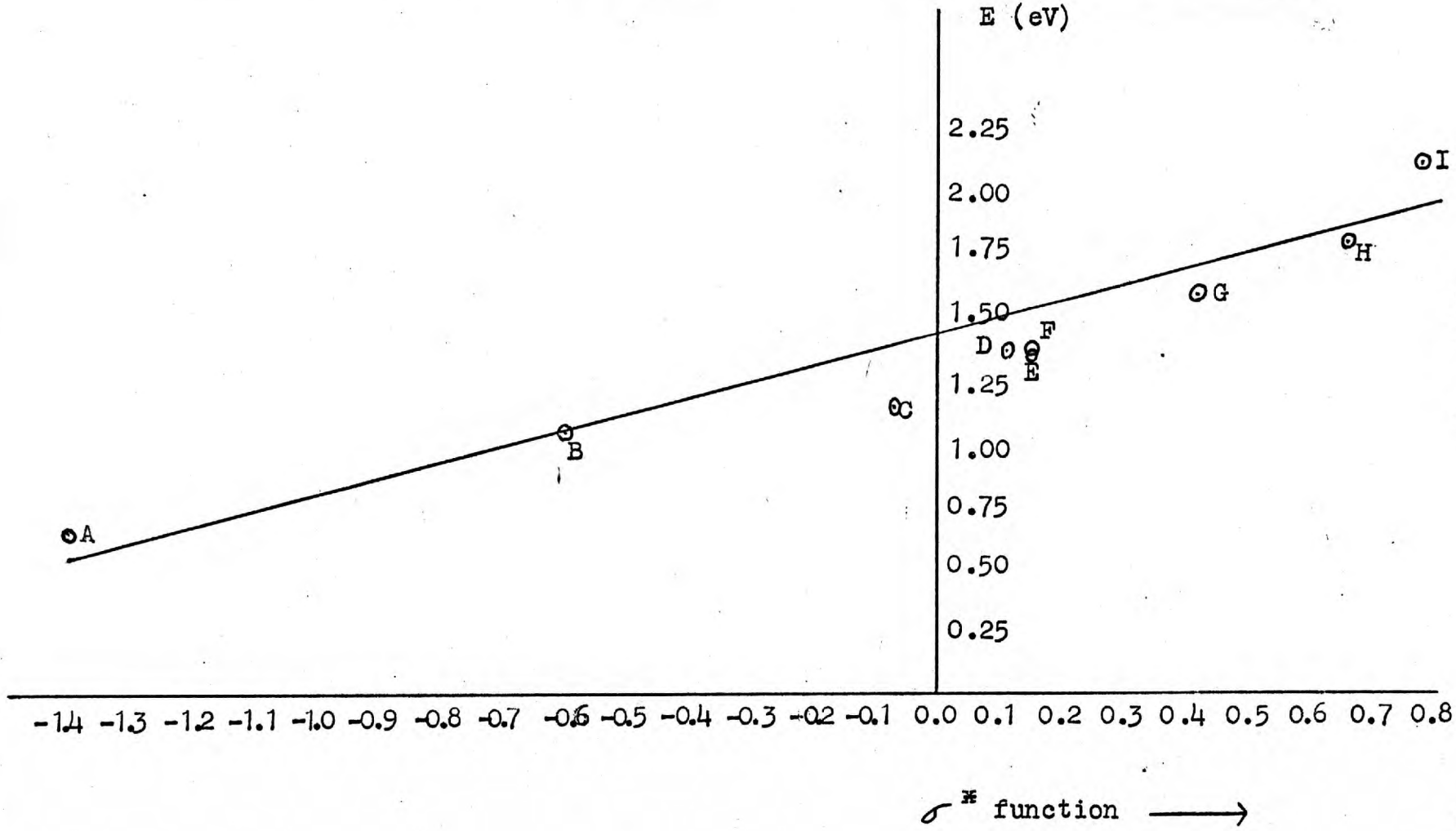


Figure 12

Part 2

Derivatives of L-Ornithine including Piperid-2-ones

2,1 Discussion of Experimental Work

A new type of lipid containing (+) L-ornithine was isolated from Rhodopseudomonas spheroides by Dr. A. Gorchein.[44] On the basis of physical measurements and chemical evidence he assigned a tentative structure of $H_2N(CH_2)_3CH(NHCOR_1)CO_2R_2$ (1) for the lipid, where R_1 was a fatty acid residue and R_2 a higher aliphatic alcohol.

Treatment of (1) with alcoholic alkali under mild conditions afforded (2). Under similar conditions DL-ornithine methyl ester hydrochloride was converted to 3-amino-piperid-2-one,[45] hence (2) probably has a lactam structure. Examination of the mass spectrum of (2) leads to the observation that R_1 contains either a keto group or an alcoholic group and one double bond. High resolution mass spectrometry gave the results shown in Table 3.

Table 3

Partial High Resolution Spectrum of Compound 2

Formula	Mass Found	Mass Calculated
$C_{25}H_{46}N_2O_3$	422.350	422.351
$C_8H_{13}N_2O_3$	185.094	185.093

/Contd. .....

Table 3 (Contd.)

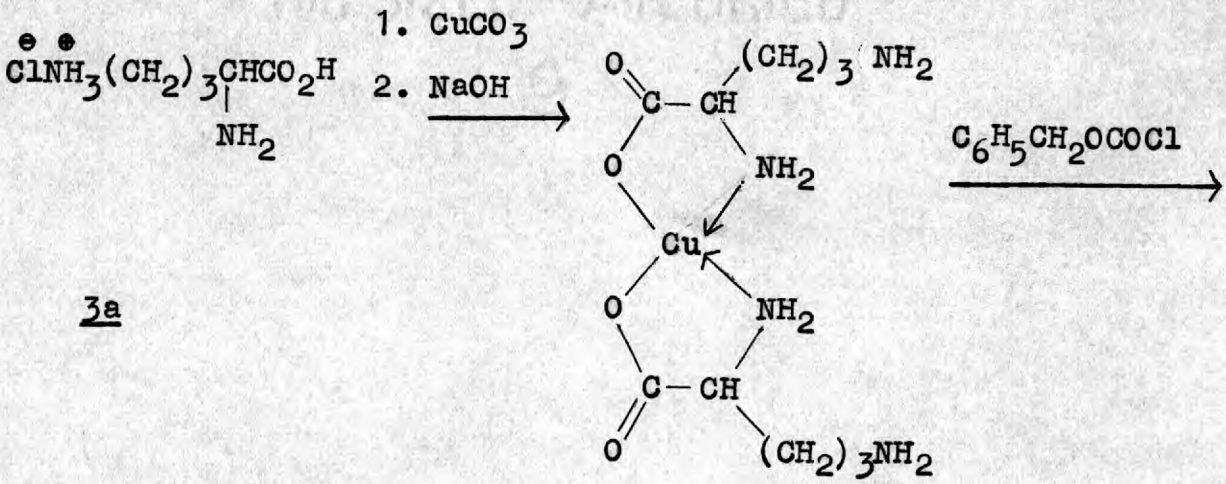
$C_7H_{12}N_2O_2$	156.089	156.090
$C_6H_9N_2O_2$	141.066	141.066
$C_5H_{11}N_2O$	115.084	115.087

The presence of a molecular ion was observed at m/e 464 and the base peak at m/e 115 was shown to arise by the loss of $C_3H_2O_2$ from the ion at m/e 185, as indicated by a metastable ion at m/e 71.5. The formation of the abundant ion at m/e 115 involves a double hydrogen rearrangement and is of importance in determining the position and nature of the functional group containing oxygen in (2).

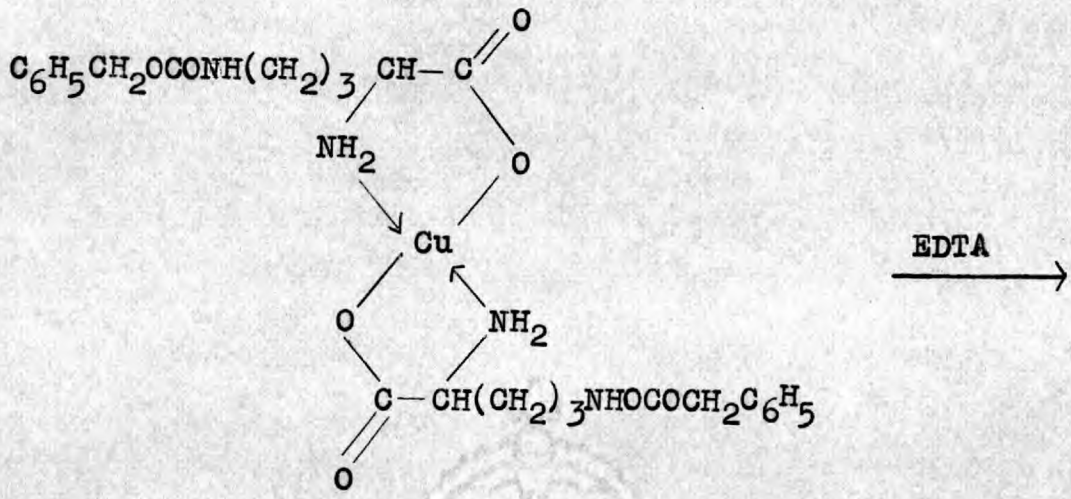
With a view to making a structural assignment for the lipid, several piperid-2-one derivatives have been prepared together with some deuterium labelled analogues to assist in the mass spectral interpretation of these compounds. One of the derivatives, (±) 3-acetamido-piperid-2-one, has previously been prepared,[46] however the procedure given in the literature was not adopted for the synthesis of the required class of compounds. Two different approaches were employed in an attempt to synthesize the desired compounds.

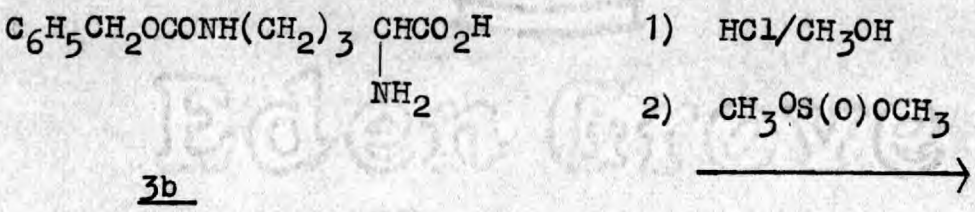
The first approach consisted of condensing 3-amino-piperid-2-one[45] with appropriately substituted carboxylic acid derivatives in the presence of N,N-dicyclohexyl-carbodiimide[47] in methylene chloride at 0°C. All attempts to isolate the required products failed. It was decided to concentrate on a different procedure.

Preferential δ -acylation of ornithine (3a) was accomplished by treatment of an aqueous solution of the amino acid cupric complex with carbobenzyloxy chloride,[48] followed by removal of copper as the ethylenediaminetetra-acetic acid (EDTA) complex.[49] The functional groups used in chelation by (+) L-ornithine in its Cu(II) complex have been deduced by Brubaker and Busch,[50] and are illustrated in Scheme 2.

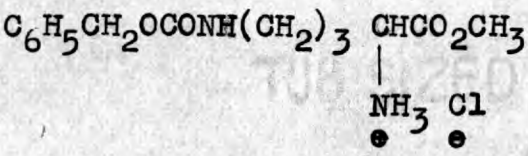


3a





3b



3c

Scheme 2

It has previously been reported[51] that (+) δ -N-carbobenzyloxy-L-ornithine methyl ester hydrochloride (3c) could be prepared in quantitative yield by three successive

treatments of (3b) with anhydrous methanol and anhydrous hydrogen chloride for 24 hours. Numerous attempts following this procedure gave a mixture of (3b) and the desired product (3c) in yields of the order of 50%. Esterification of the amino acid (3b) was found to proceed most smoothly with dimethyl sulphite after the method of Cruickshank and Sheehan[52] and readily furnished the methyl ester hydrochloride (3c) in 97% yield.

The sequence of reactions employed in the synthesis of 3-amido-piperid-2-one derivatives (6) is outlined in Scheme 3 (p.158).

Originally, it was planned to condense the appropriate carboxylic derivatives with (3c) in the presence of N,N-dicyclohexylcarbodiimide to produce compounds of series (4). This method, however, was discarded as treatment of (3c) with 3-ethylenedioxybutyric acid afforded (4a) which was difficult to isolate from by-products and purify, as the N,N-dicyclohexylurea formed in the process had similar solubility properties. In order to obtain the required class of compounds, it was decided to condense the carboxylic acid derivatives with (3c) in the presence of a water soluble carbodiimide which contained a tertiary amino group.[53,54] The tertiary amino group would be converted to the hydrochloride salt during the reaction and the urea formed in the process could easily be removed by simple extraction techniques.

The carboxylic acid derivatives were synthesized by several methods. Reaction of ethyl acetoacetate with ethylene glycol in benzene in the presence of a trace of p-toluenesulphonic acid, afforded ethyl-3-ethylenedioxybutyrate in 85.4% yield. Saponification of the ester with potassium hydroxide gave 3-ethylenedioxybutyric acid in only 37.4% yield. In view of some decomposition of the acid during distillation it was decided to change the method used to isolate the acid. The technique finally adopted utilized an amberlite resin IR-20(H). Filtration of the reaction mixture through the resin afforded the desired acid in 97% yield.

Difficulties arose in attempts to synthesize hydracrylic acid after the method of R.R. Read.[55] An i.r. spectrum of the product showed an acid carbonyl stretching vibration at 1718 $cm.^{-1}$. The ^{1}H n.m.r. spectrum indicated the presence of two complex multiplets from δ 2.46 - 2.78 and δ 3.50 - 4.08 probably arising from the methylene groups bonded to the acid carbonyl and hydroxyl group, respectively. In addition, however, a small broad peak from δ 4.17 - 4.51 was present. Moreover, the product was shown to be contaminated with diethyl ether and water used in the work-up procedure. After several days, an n.m.r. spectrum of the same sample showed that the broad peak had increased in

intensity and integration of the three signals gave the observed ratio of 3 : 2 : 1 for the proton resonance absorptions. On the basis of this evidence, it was thought that the product isolated was in fact a mixture of hydracrylic acid and 2'-carboxyethyl-2-hydroxypropionate. The latter compound could be formed by self-condensation of hydracrylic acid. This, however, was not confirmed by mass spectrometry, where no support for the structure postulated was obtained. Attempts to elucidate the structure of the compound formed in the reaction failed. Obviously a modification of the method used for synthesis of the acid was necessary.

Treatment of ethylene cyanohydrin with sodium hydroxide afforded sodium hydracrylate which was dissolved in aqueous methanol and filtered through amberlite resin IR-20(H) to yield hydracrylic acid. The mass spectrum of the acid showed no molecular ion, but a very characteristic peak was observed at m/e 72, due to loss of water.

Reduction of the keto group of ethyl acetoacetate with W-2 Raney nickel catalyst[56] gave ethyl 3-hydroxybutyrate in 92.9% yield. The ester was converted to 3-hydroxybutyric acid in 67% yield by methods previously described.

The remaining β -hydroxy acids were synthesized by the Reformatski reaction.[57] Condensation of homologous aldehydes with α -bromo ethyl acetate afforded β hydroxy

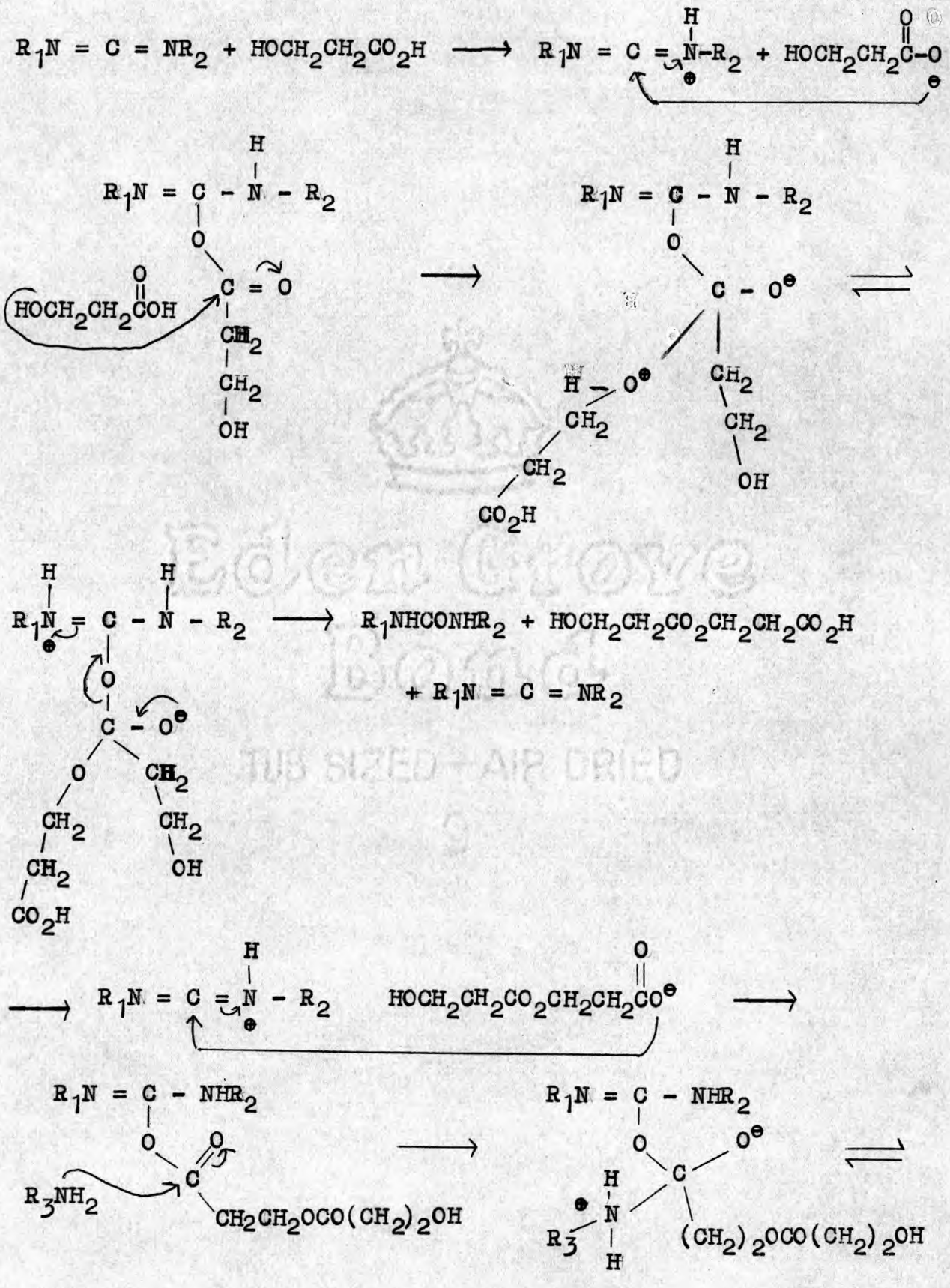
esters, which upon saponification readily furnished the desired acids. After the acids were synthesized, a direct synthesis of β -hydroxy acids by a modified Reformatski reaction was reported.[58]

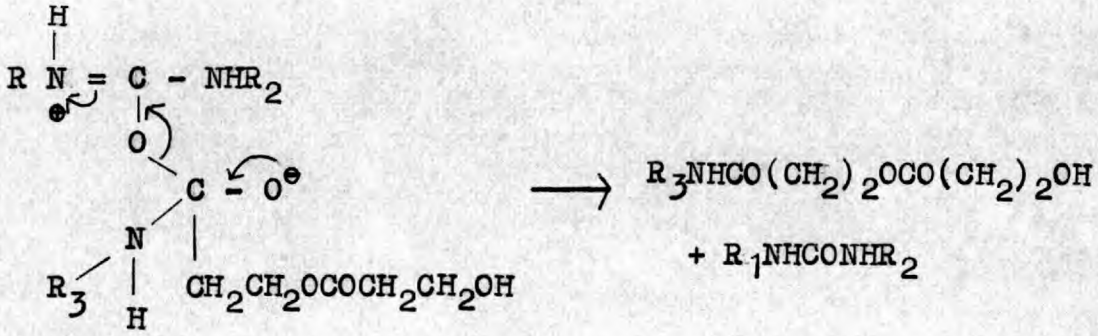
Treatment of $\left[{}^{2}H_{3}\right]$ acetaldehyde, which was prepared after the method of Baldwin and Pudussery[59] and generously donated by D.R. Buckle, with α -bromo ethyl acetate in the presence of zinc gave 4-$\left[{}^{2}H_{3}\right]$-3-hydroxybutyrate in 30% yield. Saponification of the ester gave 4-$\left[{}^{2}H_{3}\right]$-3-hydroxy butyric acid in high yield. The n.m.r. spectrum of this compound showed a one proton singlet at δ 6.95 (OH, acid) and no signal at δ 1.25, whereas a signal was observed at δ 1.25 for the methyl group (CH_3, doublet, J = 6.40 Hz.) of the undeuteriated acid. Its i.r. spectrum showed CD absorption at 2250 $cm.^{-1}$ and an acid carbonyl stretching vibration at 1720 $cm.^{-1}$.

Excluding (4b), compounds of type (4) were synthesized by the condensation of (3c) with the corresponding carboxylic acid in the presence of 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (7). No evidence of racemization was detected, hence optically active products were obtained.

Treatment of (4a) with refluxing acetone and p-toluenesulphonic acid gave the ketone (4b) in 97% yield.

Thin layer chromatography of the crude reaction product from the condensation of (3c) with hydracrylic acid showed the presence of two compounds and these were separated by preparative t.l.c. The i.r. spectra of the compounds were identical. Carbonyl stretching vibrations were observed at 1736 (ester), 1690 (benzyloxycarbonyl) and 1640 $cm.^{-1}$ (amide). Mass spectrometry showed that the more polar compound was the expected product (4e) (54% yield), whereas the less polar compound had a molecular weight of 424 m.u. (10% yield) and was postulated to be (4f). The mechanism proposed for the formation of (4f) may be represented by Scheme 4.





R_1 = CH_2CH_3

R_2 = $(CH_2)_3N(CH_3)_2$

R_3 = $PhCH_2OCONH(CH_2)_3CH(CO_2CH_3)$

Scheme 4

Clarification of the decomposition pathway of benzyloxycarbonyl derivatives was assisted by the deuteriated compound (41). It has been reported that facile racemization occurs by heating acetylated amino acid derivatives to 160-165°.[60] On this basis, it was assumed that if the deuteriation was carried out in a deuterium donating solvent, then the hydrogen - deuterium exchange reaction should occur with the same rate as racemization. Three successive twenty-four hour treatments of (4d) with deuterio methyl alcohol[61] and deuterium oxide in a Carius tube at 180°C furnished (41) with a high degree of specificity and only a low degree of

incorporation (30%). The selectivity of deuteriation was ascertained from the n.m.r. spectrum of (41).

With the exception of (4m), hydrogenolysis of compounds of series (4) over 10% palladium on charcoal in the presence of hydrochloric acid (1 equiv.) furnished the corresponding hydrochloride salts of series (5), which could not be induced to crystallize. In the mass spectrometer compounds of type (5) did not show parent molecular ions, but their molecular weights were easily established from $[M - 36]^{+\cdot}$ fragments due to elimination of hydrogen chloride.

Although it has been previously reported[62] that aliphatic carbon halogen bonds are unaffected in acidic medium during hydrogenolysis it was found that catalytic hydrogenation of (4m) afforded (5c) in nearly quantitative yield.

Lactamization of the hydrochloride salts was accomplished by two different methods. Treatment of (5a) and (5b) with silver oxide[63] afforded the expected piperid-2-one derivatives in good yields. However, a less expensive route to the lactams involved filtration of compounds of series (5) through amberlite resin IR-45.

Elucidation of the fragmentation modes of (6f) was assisted by the deuteriated analogues (6j, 6l, 6m and 6n). Compound (6j) was synthesized according to the general procedure used for most of the piperid-2-one derivatives.

When ethyl acetoacetate was treated with boiling deuterium oxide, deuterium was incorporated in the C - 2 (72%) and C - 4 (18%) positions. Treatment of ethyl acetoacetate with deuterium oxide at room temperature gave incorporation of deuterium only in the C - 2 position. Since compound (6a) has an active methylene group it was conceivable that (6a) would behave in a similar manner. Three consecutive twenty-four hour treatments of (6a) with deuterium oxide and deuterio ethyl alcohol[64] readily furnished (6k). The n.m.r. spectrum of this compound did not show a signal at δ 3.42 for the active methylene group.

Reduction of (6k) with sodium borohydride in deuterio ethyl alcohol and deuterium oxide afforded (6l) in 65% yield. In the i.r. spectrum of the product, the carbonyl stretching absorption band at 1715 $cm.^{-1}$ (ketone) was not observed. The n.m.r. spectrum of (6l) showed a doublet at δ 1.23 (CH_3, J = 6.5 Hz.) and no signal for the methylene group at δ 2.31.

Compound (6m) was synthesized in 67% yield by reacting (6a) with $\left[{}^{2}H_4\right]$ sodium borohydride in ethyl alcohol. Its n.m.r. spectrum showed broad singlets at δ 1.23 (CH_3) and

2.31 (CH_2) and no signal for the methine proton between 3.84 - 4.50.

Exchange of active hydrogens is a well characterised phenomenon. As a consequence (6n) was readily prepared from (6f) on exchange with deuterium oxide.

The degree of incorporation (%) of deuterium in (6j, 6l, 6m and 6n) determined by mass spectrometry is shown in Table 4.

Table 4

Proportion of deuterium in labelled 3-(3-hydroxybutanamido)-piperid-2-one

Compound	Number of ^2H-atoms		
	3	2	1
6j	87.2	12.8	
6l		88.2	11.8
6m			100.0
6n	67.8	27.9	4.3

Optically active (+) 3-(3-hydroxynonanamido)-piperid-2-one (6i) (200 mg.) was pyrolyzed at a temperature of 500°C and a pressure of 1 mm. The receiver of the

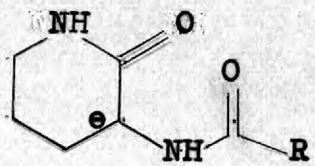
apparatus was cooled with liquid nitrogen to condense any volatile components generated. A cold trap containing aniline in methylene chloride was placed in series with the receiver and the vacuum system in an attempt to trap any ketene produced as the acetanilide derivative.

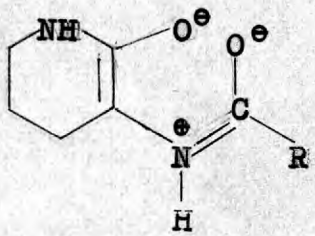
On completion of pyrolysis, removal of methylene chloride and aniline furnished a solid which had the same melting point as acetanilide (m.p. 113°C). Its i.r. spectrum showed an amide carbonyl stretching vibration and secondary amide bands at 1665, 1540 and 1505 $cm.^{-1}$, respectively.

Thin layer chromatography ($CHCl_3$ - CH_3OH, 9 : 1) of the crude reaction product showed the presence of five compounds, four solids which were separated by preparative t.l.c., and a liquid. The liquid which was the least polar product was identified as n-heptanal. The mass spectrum indicated a molecular weight of 114 m.u. and its i.r. spectrum showed an aldehyde carbonyl and CH stretching vibrations, respectively, at 1718, 2820 and 2720 cm^{-1}. Gas liquid chromatographic analysis indicated that the relative retention time of the liquid was analogous to authentic n-heptanal. Preparation of 2,4-dinitrophenylhydrazone derivatives from authentic n-heptanal and the liquid isolated in the pyrolysis reaction afforded two orange solids which had identical melting points (m.p. 106°C, lit., 108°C).

The four solids isolated by preparative t.l.c. were identified as optically active starting material (6i) (47.1 mg.), (+) 3-amino-piperid-2-one (3.2 mg.) (6s), (±)3-acetamido-piperid-2-one (46.4 mg.) and optically inactive (6o) (11.4 mg.)

With the exception of recovered optically active starting material and (6s) the piperid-2-one derivatives isolated were optically inactive. The tendency of amino acid derivatives to racemize has been attributed to the lability of the ∝ hydrogen and stabilization of the carbanion by enol like contributing species (Scheme 5).[65] The retarding effect of a free amino group on racemization[66] is consistent with the formation of optically active (6s), and since N-acylation not only abolishes this effect but accelerates racemization significantly, compounds (6b) and (6o) were recovered as racemates.



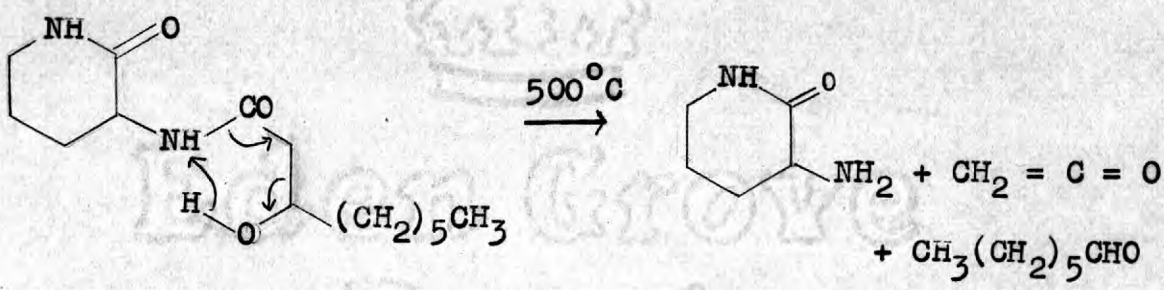


R = CH_3

R = CH = $CH(CH_2)_5CH_3$

Scheme 5

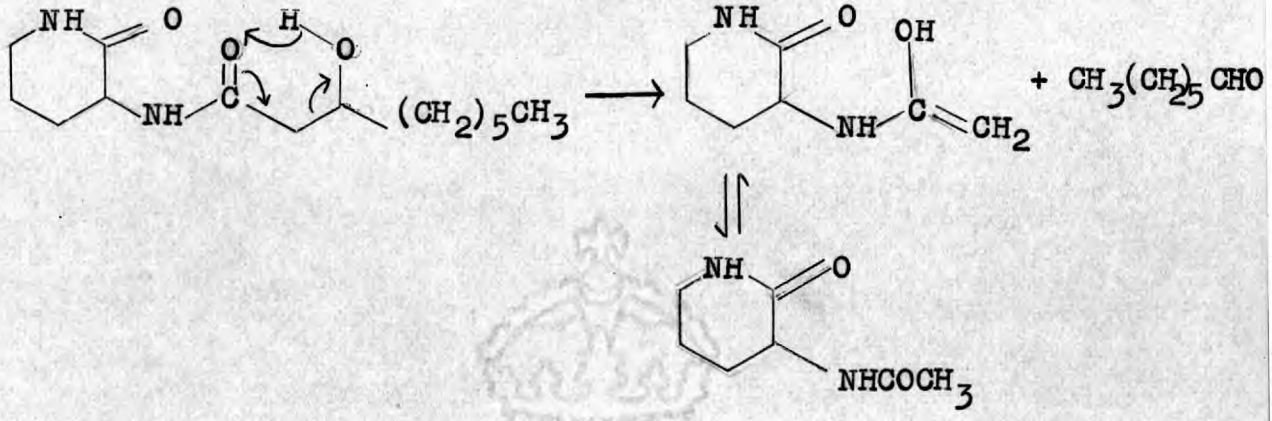
Identification of (+) 3-amino-piperid-2-one (6s) was accomplished by comparing its i.r. and mass spectral data with authentic material prepared after the method of Golankiewicz and Wiewiorowski.[45] The formation of (6s) probably arises from transfer of the alcoholic proton to the amide nitrogen with concomitant expulsion of ketene and n-heptanal (Scheme 6).



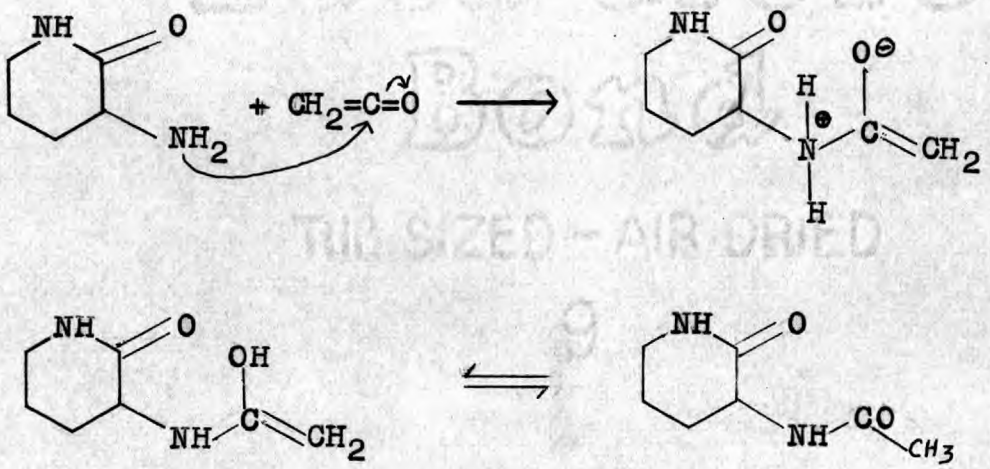
Scheme 6

The structure of (±) 3-acetamido-piperid-2-one (m.p. 185 - 187°C, lit., 185 - 187°C) was confirmed from its i.r. and mass spectrum, which were analogous to (+) 3-acetamido-piperid-2-one (6b) (m.p. 162°C) prepared by the carbodiimide method.[52] The formation of (±) 3-acetamido-piperid-2-one may arise by two different pathways. The alcoholic proton could be transferred to the amide carbonyl with expulsion of n-heptanal (Scheme 7), or (6s) could

combine with ketene (Scheme 8) formed during the pyrolysis reaction to yield the product.

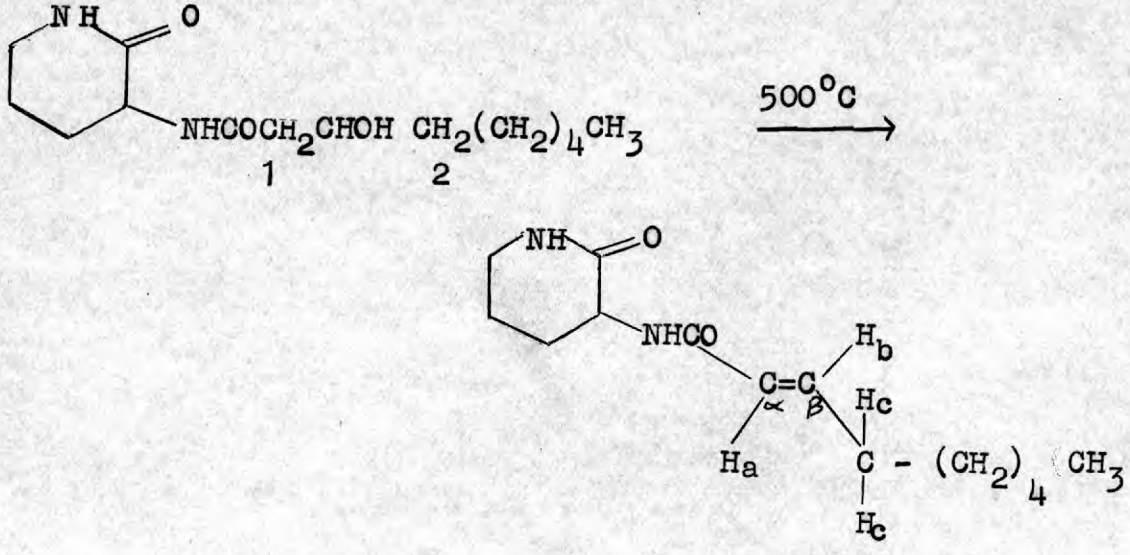


Scheme 7

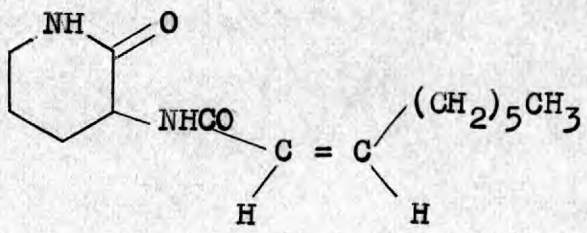


Scheme 8

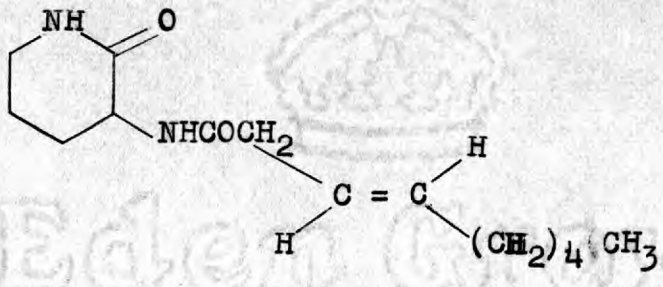
The dehydration product was more difficult to identify. Since hydrogen could be lost from carbons designated as 1 or 2 (Scheme 9), the possibility of obtaining four isomers could not be disregarded. The u.v. spectrum was indicative of the conjugated isomers (a) and (b): λ max. 218 m.μ., however this did not rule out the presence of the two non-conjugated isomers (c) and (d). The mass spectrum (Figure 13, p. 171) indicated that the solid had a molecular weight of 252 m.u. and was shown by mass measurement to have the formula $C_{14}H_{24}N_2O_2$. Unambiguous evidence that (c) and (d) were not obtained, was provided by thermal dehydration of deuterium labelled (6j) and (6l) in the heated inlet system of the mass spectrometer (200°C). The 1,2-elimination of H_2O and DOH from (6j) and (6l) furnished, respectively (6q) and (6r), (Figure 14, p. 172).



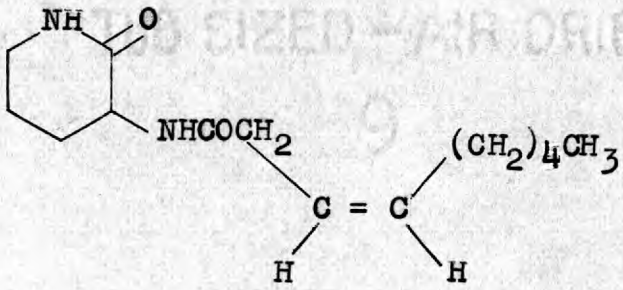
a



b



c



d

Scheme 9

Examination of the n.m.r. sub-spectrum of the solid (Figure 15, p.173) revealed that (a) was the only product formed. Its spectrum showed a double triplet (Hb) centred at δ 6.80 and a doublet (Ha) at δ 5.76 (Jab = 15.0 Hz.) The signal for the proton (Hb) was split into a doublet due to spin coupling with (Ha) and each component was further split into a triplet (Jbc = 6.5 Hz.) due to spin coupling with the (Hc) protons. The value of Jab establishes that compound (a) has the trans configuration.

Spin decoupling experiments were carried out on compound (a). Application of a strong secondary r - f magnetic field at the resonance frequency of the (Ha) proton (590 Hz.), to cause saturation of the spins of the (Ha) nucleus, resulted in (Ha) becoming effectively decoupled from (Hb). As the field was swept the absorption caused by the (Hb) nucleus collapsed into a triplet because the (Hb) proton was coupled only to the two (Hc) protons.

Molecular orbital Hückel calculations[67,68] showed that the electron density at C_β (0.7464) was lower than at C_α (1.0480), hence the proton bonded to C_β was deshielded and resonance absorption of (Hb) appeared at lower field than (Ha). A Dreiding model of (a) indicated that because of the relative mobility of the system it was impossible to make predictions based on non-bonded

interactions (e.g. electric field, diamagnetic anisotropy) with the lactam carbonyl.

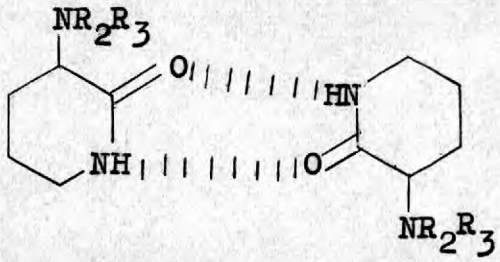
Infrared Spectra Considerations

The infrared spectra of compounds of series (6) are sensitive to the medium because of important hydrogen bonding effects. The intermolecular effects are negligible for solutions in methylene chloride or similarly polar solvents. In compounds (6d, 6f, 6g, 6h and 6i) intramolecular hydrogen bonding can occur between the hydrogen atom of the hydroxyl and carbonyl group of the open chain amide. Furthermore, the cyclic lactams under study exist in the *cis* configuration and the open chain amide groups have a *trans* arrangement.

Examination of the i.r. spectra of (6b) (Figure 16, p. 174) and (6c) in methylene chloride solution showed a non-associated NH band at 3420 $cm.^{-1}$, a carbonyl stretching vibration at 1662 $cm.^{-1}$ (*cis* and *trans* CONH), and an amide II band at 1510 $cm.^{-1}$. In the i.r. solution spectra of (6d, 6f, 6g, 6h and 6i) however, two unresolved carbonyl absorption bands were observed at 1673 (*cis* CONH) and 1658 $cm.^{-1}$ (*trans* CONH), a result which indicates that the carbonyl group of the trans amide is either inter or intramolecularly hydrogen bonded to the hydroxyl group. Evidence for the latter effect was shown when no shifts in the carbonyl absorption frequencies were observed for the solution spectra at various concentrations.

In view of the complexity of the solid state spectra (determined as nujol mulls) conclusions are drawn by considering only the region from 3350 - 3050 cm.$^{-1}$. In the i.r. spectrum of (6b) (Figure 17, p.175) absorption bands were observed at 3300 (*trans* CONH), 3220 (*cis* CONH) and 3095 cm.$^{-1}$. The higher frequency bands are due to the stretching mode of the NH bond which forms intermolecular hydrogen bonds. The assignment of the band at 3095 cm.$^{-1}$ has been the subject of considerable controversy.[69] Its original assignment as an overtone of the *trans* CONH amide II band was brought into doubt when the band was also observed for the *cis* CONH group which does not exhibit an amide II absorption. Miyazawa,[69] however, resolved this difficulty when he identified the in plane NH deformation band in *cis* amides as absorbing near 1450 cm.$^{-1}$. Hence, it became possible to assign the 3100 cm.$^{-1}$ band in the *cis* case as a combination of the NH bending (1450 cm.$^{-1}$) and carbonyl stretching (1650 cm.$^{-1}$) vibrations.

On the basis of this infrared data it is conceivable that compounds of type (6) form strong associate dimers in solid state spectra (Scheme 10),[70] which are destroyed in methylene chloride solution.



(6)

Scheme 10

2,2 Discussion of Mass Spectra

With a view to making a structural assignment for the lipid isolated from Rhodopseudomonas spheroides, the fragmentation patterns of several 3-amido - piperid-2-one derivatives were compared with the decomposition pathway of the lipid (Figure 18, p.176) and its hydrolysis product, compound (2) (Figure 19, p.177).[24] Certain similarities between the mass spectra of 3-(3-hydroxyamido)-piperid-2-one derivatives and (2) were quite evident. With the exception of (6d), the former series of compounds all showed significant fragments at m/e 185, 156, 141 and 115. High resolution mass measurements for these ions were consistent with the results obtained for (2). Furthermore, the peak at m/e 115 was shown to arise by a comparable mode of fragmentation as was observed for the formation of the ion in the mass spectrum of (2).

On the basis of this data and previously presented information, R_1 must contain a hydroxyl function β to the carbonyl group of the amide and probably one double bond. Moreover, it was concluded that R_1 was a C_{22} fatty acid residue which corresponded to the formula $C_{22}H_{43}O$.

The position of the double bond was not determined from the mass spectrum of (2) as it has been well-established

that if the double bond is further removed from the carbomethoxyl group of fatty acid esters than (Δ^6) the spectra of double bond isomers become indistinguishable.[71-73] It should be emphasized that the mass spectral decomposition of (6i) (Figure 20, p.178) is analogous to the fragmentation pattern of compound (2). Hence it was concluded that if an analogy could be made between the decomposition, induced by electron-impact of R_1 and fatty acid esters, the double bond in (2) was further removed from the carbonyl group of the amide than the (Δ^6) position.

Three approaches may be employed in an attempt to determine the position of the double bond. Deuteriation of the double bond in (2) and comparison of the spectrum with that of the undeuteriated saturated compound may be used to determine the position of the deuterium atoms and hence of the double bond.[74] The second and third procedures involve oxidation of the olefin to the epoxide, followed by ring opening of the derived epoxide by diethylamine[75] or sodium iodide[76] to furnish mixtures of N,N-dimethylamino alcohols and ketones, respectively. Examination of the resulting mixtures by mass spectrometry may be used to determine the position of the original double bond.

In view of the fact that only enough sample was supplied by Dr. Gorchein for mass spectral determinations, none of the approaches could be pursued.

Further complications arose when the mass spectrum of the lipid showed that it was a mixture of seven compounds. Hence the only conclusions that were drawn with respect to R_2 were based on the number of carbon atoms and double bonds present. High resolution mass spectrometry gave the results shown in Table 5.

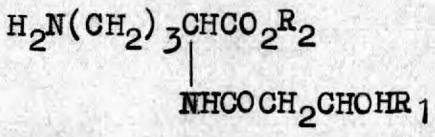
Table 5

Partial High Resolution Spectrum of the Purported Lipid (1)

Formula	Mass Found	Mass Calculated	R_2	Maximum possible number of double bonds
$C_{44}H_{80}N_2O_4$	700.617	700.612	$C_{16}H_{27}$	3
$C_{43}H_{80}N_2O_4$	688.611	688.612	$C_{15}H_{27}$	2
$C_{43}H_{78}N_2O_4$	686.596	686.596	$C_{15}H_{25}$	3
$C_{42}H_{78}N_2O_4$	674.593	674.596	$C_{14}H_{25}$	2
$C_{42}H_{76}N_2O_4$	672.579	672.580	$C_{14}H_{23}$	3
$C_{41}H_{76}N_2O_4$	660.574	660.580	$C_{13}H_{23}$	2
$C_{41}H_{74}N_2O_4$	658.567	658.565	$C_{13}H_{21}$	3

On the basis of these results, it would appear that two series of homologues are present. In the first series, which consists of four compounds, R_2 may possibly contain three double bonds with differences in the length of the carbon chain of 14 m.u. for each compound. Alternatively, series two is made up of three compounds in which R_2 may contain two double bonds and where similar differences, as in the former series, are observed for the length of the carbon chain.

From the evidence presented the following structural assignments for the lipids isolated by Dr. Gorchein seem plausible (Scheme 11). In view of the limited quantity of samples available, more satisfactory structural assignments for the natural products were impossible. A further point worth mentioning is that if enough sample had been supplied, the mass spectrum of each of the natural products may have been determined by the method which combines gas chromatography with mass spectrometry.



(1)

(1a) $R_1 = C_{20}H_{39}$ $R_2 = C_{16}H_{27}$

(1b) $R_1 = C_{20}H_{39}$ $R = C_{15}H_{27}$

/Contd. .....

(1c) $R_1 = C_{20}H_{39}$ $R_2 = C_{15}H_{25}$

(1d) $R_1 = C_{20}H_{39}$ $R_2 = C_{14}H_{25}$

(1e) $R_1 = C_{20}H_{39}$ $R_2 = C_{14}H_{23}$

(1f) $R_1 = C_{20}H_{39}$ $R_2 = C_{13}H_{23}$

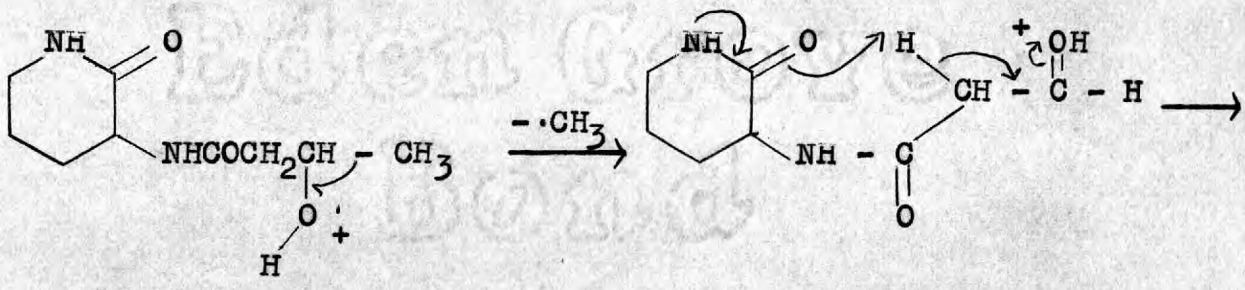
(1g) $R_1 = C_{20}H_{39}$ $R_2 = C_{13}H_{21}$

Scheme 11

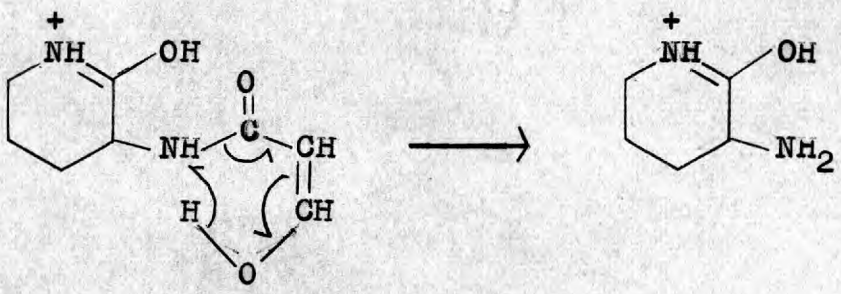
The mass spectra of (6f, 6g, 6h, and 6i) were examined and their general decomposition pathway investigated with the aid of deuterium labelling, mass measurement, metastable defocussing and metastable ion analysis. In view of the fact that the mass spectra of these compounds show certain similarities, the following discussion will be restricted to the fragmentation pattern exhibited by (6f) (Figure 21, p.179).

In the parent compound, loss of a methyl radical from the molecular ion gives a fragment at m/e 185 ($C_8H_{13}N_2O_3$). An abundant ion at m/e 115 ($C_5H_{11}N_2O$) has been shown by the presence of an accompanying metastable peak (m^* = 71.5) to owe its existence to a double hydrogen rearrangement followed by the one-step loss of $C_3H_2O_2$ from

the ion at m/e 185. Examination of the mass spectra of the deuteriated compounds (6j, 6l, 6m and 6n) (Figure 22, p.180) leaves little doubt that one of the hydrogen atoms bonded to the carbon adjacent to the carbonyl group of the amide migrates to the carbonyl group of the lactam. A Dreiding model of (6f) indicates that the hydrogen in question is suitably situated for the rearrangement to occur. Transfer of the alcoholic hydrogen to the amide nitrogen of the rearrangement ion with concomitant elimination of $C_3H_2O_2$ accounts for the ion at m/e 115.

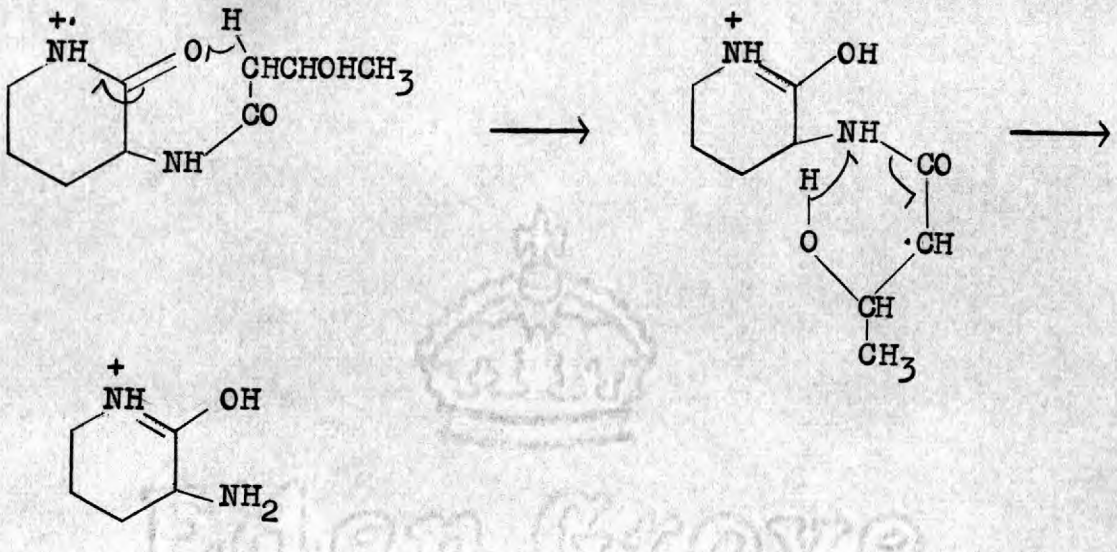


m/e 200 m/e 185



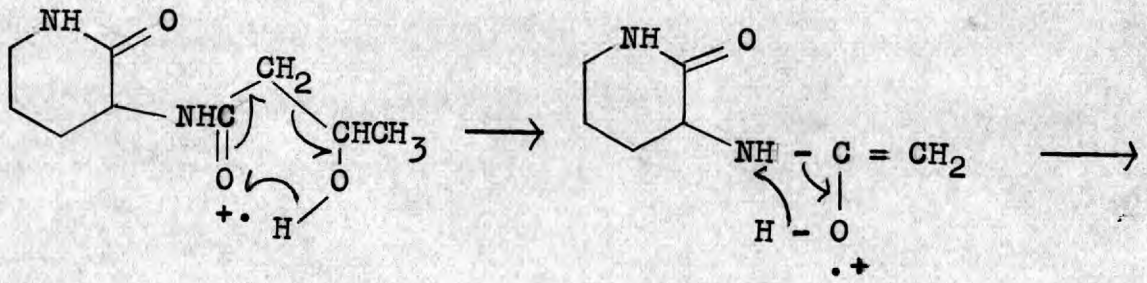
m/e 115

Metastable defocussing techniques indicate that the ion at m/e 115 is also formed directly from the molecular ion. A plausible mechanism for this fragmentation is shown below.

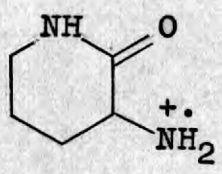


m/e 115

The fragment at 156 ($C_7H_{12}N_2O_2$) derived from the molecular ion arises as a result of a McLafferty rearrangement. Transfer of hydrogen from the hydroxyl group to the carbonyl group of the amide with subsequent elimination of acetaldehyde gives the ion at m/e 156, which in turn may lose ketene to afford (a) (m/e 114)($C_5H_{10}N_2O$) (m^{*} = 83.3).

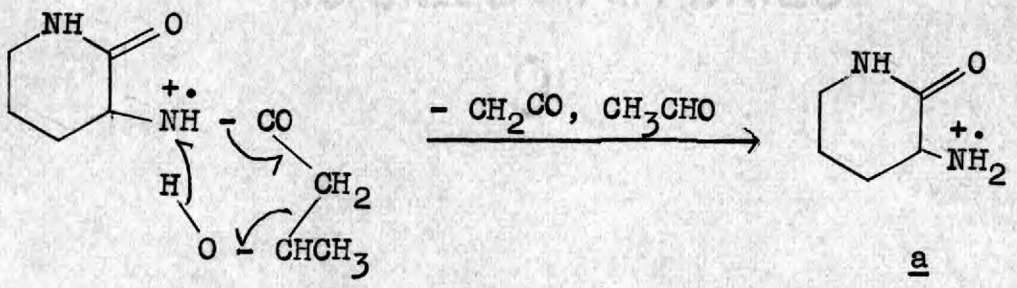


m/e 200 m/e 156



a

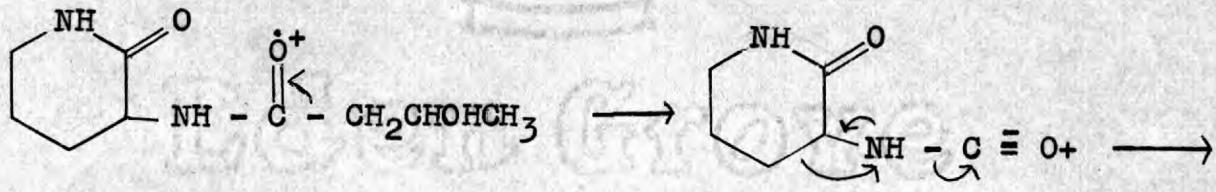
Alternatively, the ion (a) may be formed in a one-step process from the molecular ion by transfer of the hydroxyl hydrogen to the amide nitrogen with elision of ketene and acetaldehyde.



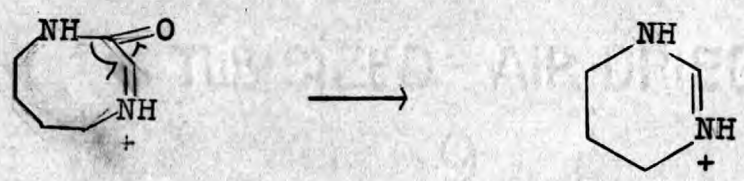
a

The ion at m/e 113 ($C_5H_9N_2O$) is formed from three different precursors (m/e 200, 156 and 141). Since it is

plausible that similar mechanisms are operating in each case only one mode of decomposition is described. Fragmentation triggered by ionization of the carbonyl group of the amide results in formation of the ion at m/e 141 ($C_6H_9N_2O_2$), which in turn may eliminate carbon monoxide in a Beckman type rearrangement to give the ring expanded ion at m/e 113 (m^{*} = 90.6). The latter then decomposes by the ejection of the carbonyl group of the lactam as carbon monoxide to furnish (b) (m/e 85, $C_4H_9N_2$).



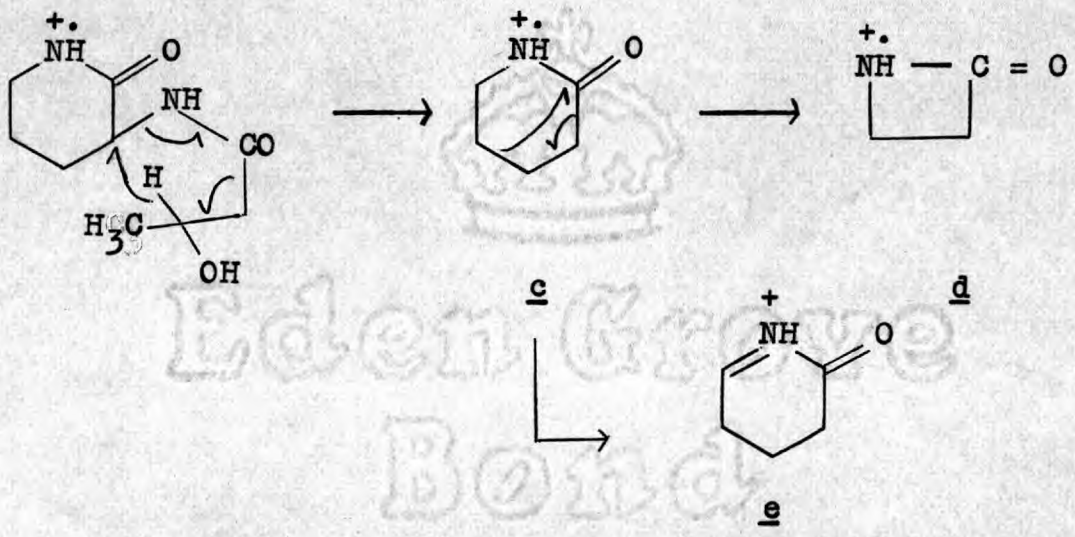
m/e 200 m/e 141



m/e 113 b

The fragment at m/e 99, derived from the molecular ion was shown by deuterium labelling to contain the C - 3

methine hydrogen of the open chain. Transfer of this hydrogen through a six-membered transition state to the C - 3 position of the lactam ring with concomitant expulsion of the neutral fragments NH = CO and $CH_3COH = CH_2$ affords (c). The ion (c) may decompose further by the loss of ethylene to give (d) at m/e 71 or expel a hydrogen from C - 6 to furnish

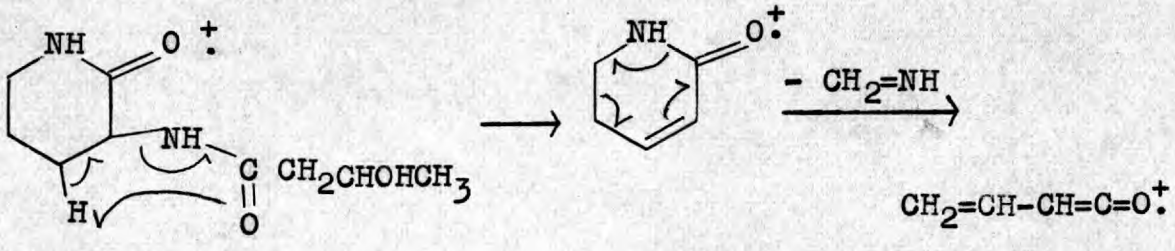


c d

e

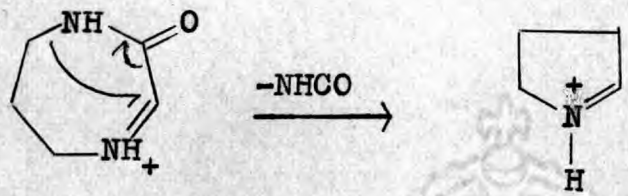
the ion (e) at m/e 98.[77]

Transfer of a hydrogen bonded to C - 4 of the lactam, to the carbonyl group of the amide with concomitant elimination of $NHCOHCH_2CHOHCH_3$ probably accounts for the ion (f) at m/e 97. Species (f) may fragment further by retro-Diels-Alder decomposition to give the ion radical at m/e 68.



f m/e 68

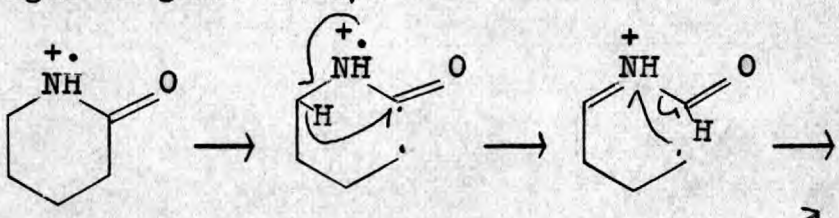
The abundant fragment at m/e 70 (86.2%) may be formed from two different precursors. The ejection of NHCO from the ion at m/e 113 as indicated by a metastable peak at 43.4 m.u. furnishes (g).



g

Alternatively, Djerassi and co-workers[77] have proposed mechanism 1 as a possible route to g. In principle, however, di- or tri-radical ions are high energy species and hence their formation is unlikely. A more plausible mode of decomposition is described by mechanism 2; α cleavage of (c) adjacent to nitrogen followed by transfer of a C - 6 hydrogen atom and loss of the formyl radical would also afford (g). Further loss of H_2 can occur to a limited extent to give the nitrogen fragment at m/e 68.[78]

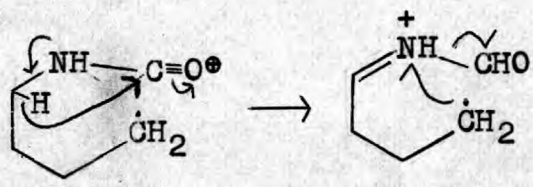
Mechanism 1.



c

g

Mechanism 2.

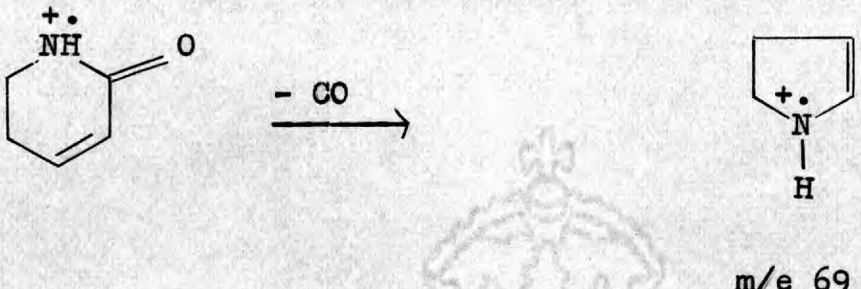


$\downarrow$ - H_2

$[C_4H_6N]^+$

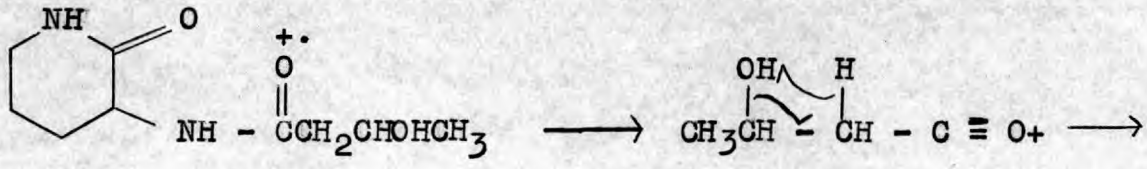
m/e 68

The most abundant peak (m/e 69) in the mass spectrum of (6f) consists of three isobaric species (C_5H_9, C_4H_7N and C_4H_5O in the ratio 9 : 3.9 : 1) (Table 6). The nitrogen fragment may arise by the ejection of carbon monoxide from (f).



m/e 69

The presence of a peak at m/e 72 in the d_3-analog (6g) and reversal of intensities for the m/e 69 (65.3%) and m/e 70 (88.1%) peaks in the d_2-analog (6m) seemed to be consistent with the fact that the formation of C_4H_5O resulted from a process involving decomposition of the open chain. An extensive examination of metastable transitions failed to show any metastable peaks leading to elucidation of the mechanism for formation of C_4H_5O. However, since dehydration of fragment ions does not proceed, necessarily, in the same specific fashion as observed for molecular ions,[79] fragmentation triggered by ionization of the carbonyl group may be responsible for the ion (h), which in turn may lose water to give (i) (m/e 69).



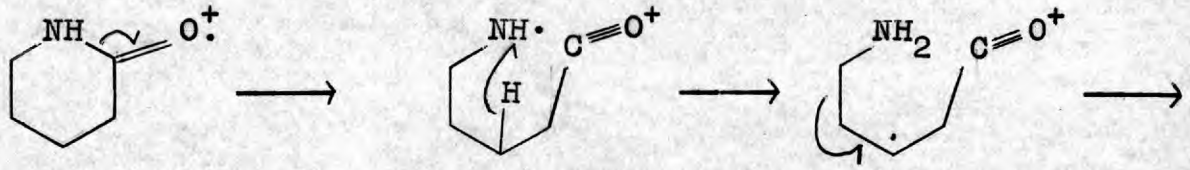
h

$CH_3CH = CH - C \equiv O^+$

i

However, this mechanism was shown to be untenable as the mass spectrum of the d_1-analog (6m) did not lead to peak shifts which were reconcilable with the sequence postulated. Moreover elucidation of the decomposition pathway becomes increasingly difficult for ions with low mass to charge ratios. Although metastable ions are present, they are observed in the first field free region between the source and electrostatic analyser, hence the assignment of a metastable peak to a particular transition is complicated by the fact that most peaks consist of contributions from two or three isobaric species as indicated in Table 6. Furthermore, peaks that shift upon deuterium labelling are not easy to rationalize as it is difficult to determine which isobaric fragment incorporated the deuterium atom to cause the shift in the m/e value. The ion C_4H_5O may be formed by the sequence proposed below where structure (j) arising from

(c) is consistent with the experimental facts observed for (6m).

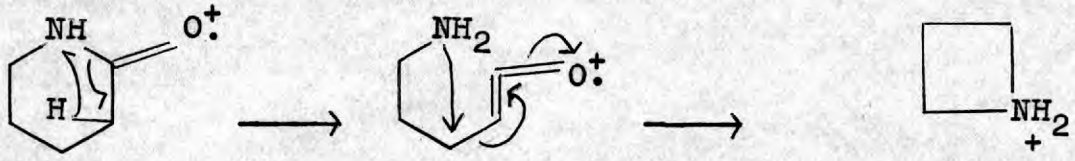


c

$CH_2 = CHCH_2\ C \equiv O^+$

j

The species corresponding to m/e 58 (C_3H_8N) was shown by metastable defocussing techniques to be derived from the fragment at m/e 99. Its formation was interpreted in terms of transfer of a C - 3 hydrogen to the amide nitrogen to afford (k) which may in turn eliminate the radical $CH \equiv C - O^{\bullet}$ to give (l)



c k l

Table 6

Partial High Resolution Spectrum of (6f)

Ion	Formula	Ratio of Isobaric Species*
m/e 69	C_5H_9	9.0
	C_4H_7N	3.9
	C_4H_5O	1.0
m/e 68	C_4H_6N	3.9
	C_4H_4O	1.0
m/e 57	C_4H_9	3.0
	C_3H_5O	1.0
m/e 55	C_4H_7	10.6
	C_3H_3O	3.0
	C_3H_5N	1.0
m/e 44	C_2H_4O	2.8
	C_2H_6N	1.0
m/e 43	C_2H_3O	2.8
	C_3H_7	1.6
	C_2H_5N	1.0

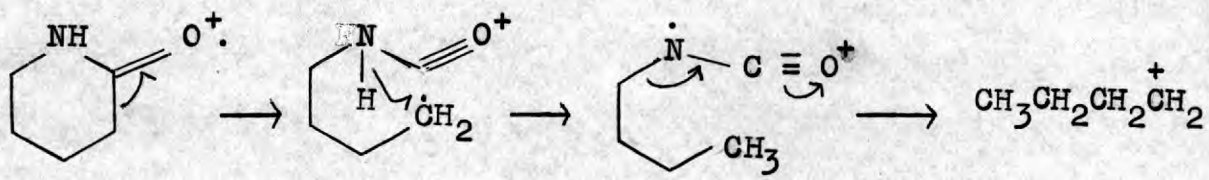
* The intensity of the weakest peak was set at 1.0.

/Contd. .....

Ion	Formula	Ratio of Isobaric Species*
m/e 42	C_2H_2O	2.1
	C_2H_4N	1.3
	C_3H_6	1.0
m/e 41	C_3H_5	6.6
	C_2H_3N	3.3
	C_2HO	1.0

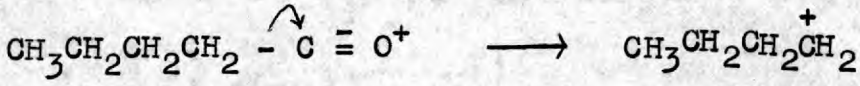
* The intensity of the weakest peak was set at 1.0.

The genesis of the hydrocarbon fragment at m/e 57 may be depicted in the sequence **c** ⟶ **m** ⟶ **n** ⟶ **o**, in which ∝ cleavage adjacent to nitrogen is followed by the transfer of the hydrogen atom on the nitrogen to the primary radical site with subsequent loss of a NCO radical. This view appeared to be substantiated by a partial shift from m/e 57 to m/e 58 in the mass spectrum of (6n), however the presence of adjacent ions makes a qualitative interpretation from deuterium labelling impossible.

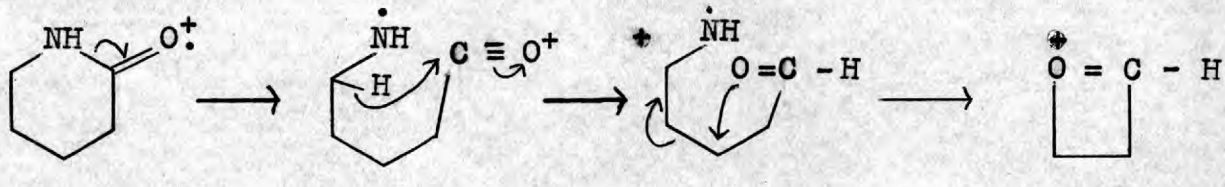


c m n o

Although the formation of the alkyl carbonium ion (o) seems improbable as the charge resides on a primary carbon atom, Djerassai and co-workers.[80] have proposed a similar structure for a $(C_4H_9)^+$ ion derived through loss of carbon monoxide from an ion at m/e 85 in the mass spectrum of di-n-butyl ketone.

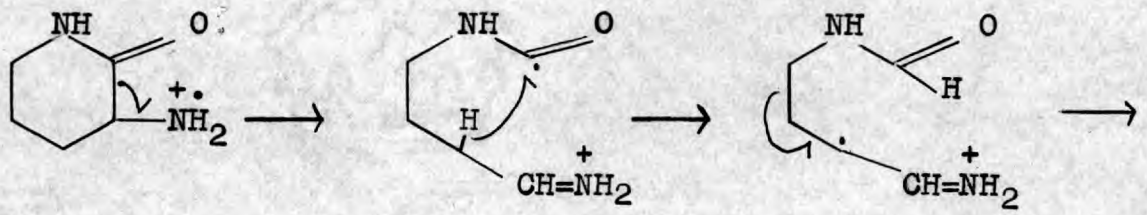


The species corresponding to C_3H_5O at m/e 57 may also be formed from (c). Its formation was interpreted in terms of cleavage of (c) to afford (p), followed by transfer of a C - 6 hydrogen to the carbonyl carbon atom to furnish (q), which in turn may lose the radical CH_2=CH-NH to give (r).

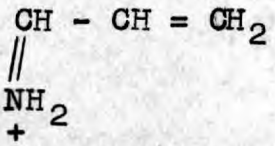


c p q r

The ion at m/e 56 (C_3H_6N) was at first assumed to arise from the ion at m/e 114. Cleavage of the 2,3 bond of the lactam, with subsequent hydrogen transfer from the allylic carbon atom to the radical site furnishes (s), which may lose a CH_2NHCHO radical to give (t).



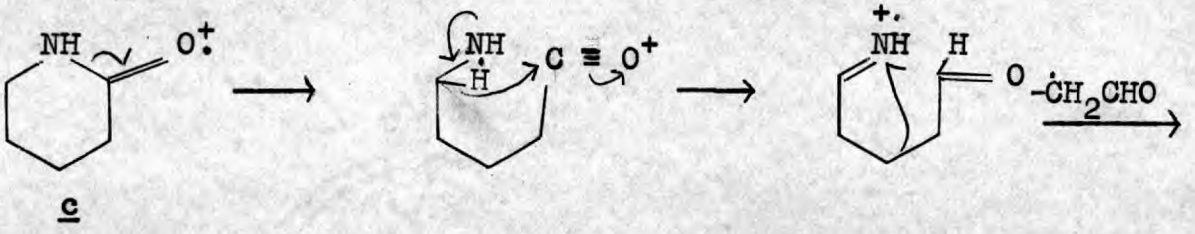
s



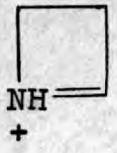
t

However, a thorough study of metastable transitions failed to substantiate this mode of decomposition. Furthermore, deuterium labelling led to peak shifts which were not reconcilable with the sequence proposed. If the nitrogen atom in the open chain was incorporated in the fragment at m/e 56 a peak shift of two mass units (m/e 56 ⟶ m/e 58) would have been observed in the mass spectrum of (6n). In view of the fact that only a shift of one mass unit was noted the ion must contain the nitrogen atom from the lactam.

Metastable defocussing techniques showed a metastable ion for the decomposition process m/e 99 ⟶ m/e 56, hence the following mechanism is proposed.

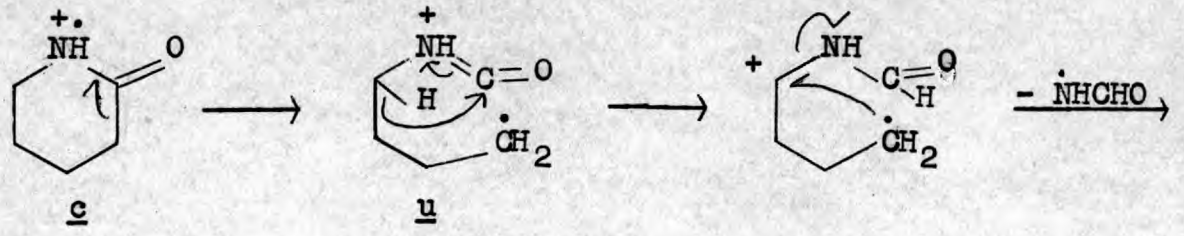


c

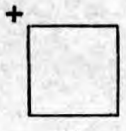


m/e 56

The C_4H_7 fragment at m/e 55 might arise by the following mechanism: ∝ cleavage of (c) adjacent to the nitrogen affords (u), which by hydrogen transfer from C - 6 and loss of the radical NHCHO leads to the ion (v).

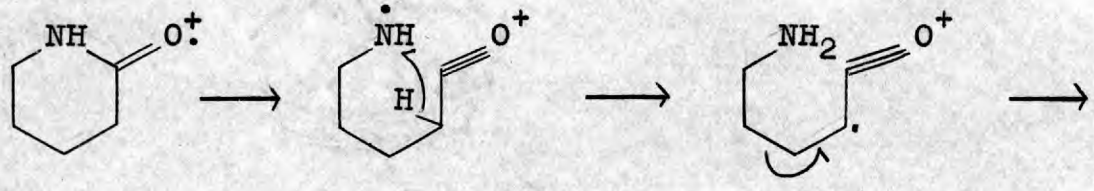


c u



v

The fragment ion at m/e 55 corresponding to the formula C_3H_3O may also be formed from (c).[77] Cleavage of (c) adjacent to the carbonyl group affords (p) which may transfer a C - 3 hydrogen atom to nitrogen to furnish (w). Subsequent homolysis of the 4 - 5 bond would give rise to the resonance stabilized ion (x).

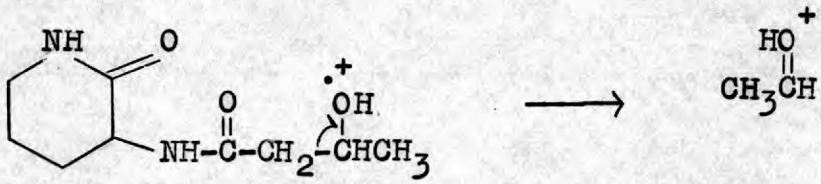


c p w

$CH_2{=}CH{-}C{\equiv}O^+$

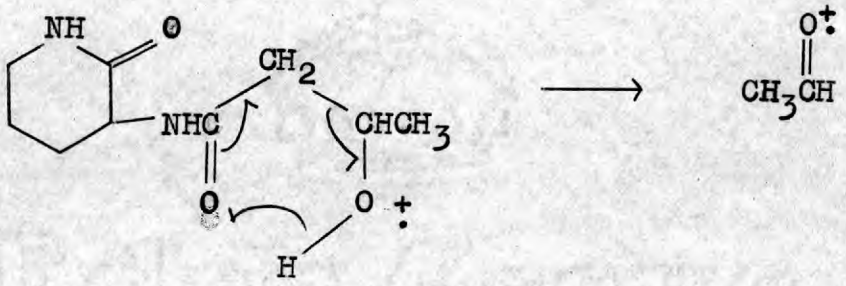
x

The standard fragmentation for alcohols gives rise to the ion at m/e 45 (C_2H_5O), which is probably formed directly from the molecular ion and can be envisaged as proceeding by the following sequence.



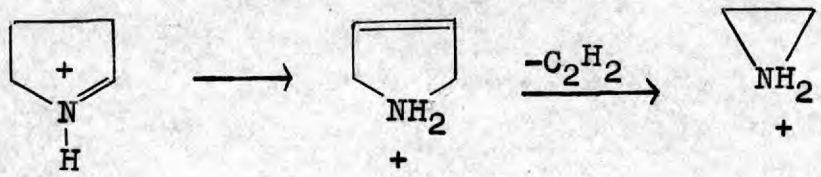
m/e 200 m/e 45

The peak at m/e 44 consists of contributions from two isobaric species (C_2H_4O and C_2H_6N). The former may arise by a process which is identical to the mechanism proposed for the formation of the ion at m/e 156, however in this case the charge remains with the fragment at m/e 44.



m/e 44

Saunders and Williams[81] have indicated that the nitrogen fragment formed from the ion (g) (m/e 70), most likely arises in a process similar to that shown below leading to the formation of a three membered ring.



g

m/e 44

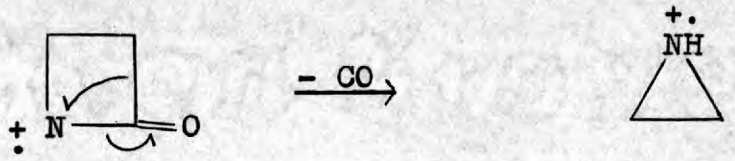
Examination of the mass spectra of the deuteriated compounds (6j, 6l, 6m and 6n) leaves little doubt that the C_2H_3O fragment at m/e 43 is formed from the ion at m/e 156. Deuteriation of the methyl group (6j) and the methine position (6m) results in no shift of the peak at m/e 43. On the other hand, deuteriation of the methylene (6l) and hydroxyl group (6n) produces shifts of two and one mass unit, respectively. A further point worth mentioning is

m/e 156 m/e 43

that the amine fragment will also cause a shift of one mass unit in the mass spectrum of (6n). However, a qualitative interpretation is difficult owing to the presence of strong adjacent ions.

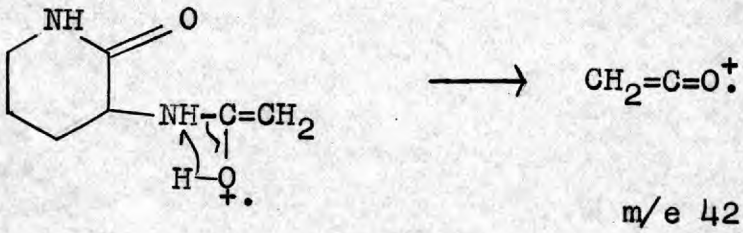
Saunders and Williams[81] postulated the formation of a nitrogen fragment at m/e 43 arising from the loss of the C_2H_3 radical from the ion at m/e 70 (g) on the basis of the presence of a metastable peak (m^* = 26.4). However, deuterium labelling[82,83] led to peak shifts which were not reconcilable with the sequence proposed. It was concluded that the

transition from m/e 70 ⟶ m/e 43 was connected with the hydrocarbon portion (C_3H_7) of m/e 43, which must be formed by the expulsion of the elements of hydrogen cyanide. Hence the metastable peak observed in the spectrum of (6f) for the transition from m/e 70 ⟶ m/e 43 must correspond to the formation of the $C_3H_7^+$ ion. The C_4H_5N ion may therefore be derived from the fragment at m/e 71 (d). Decomposition by loss of carbon monoxide would give the ion at m/e 43.[77]



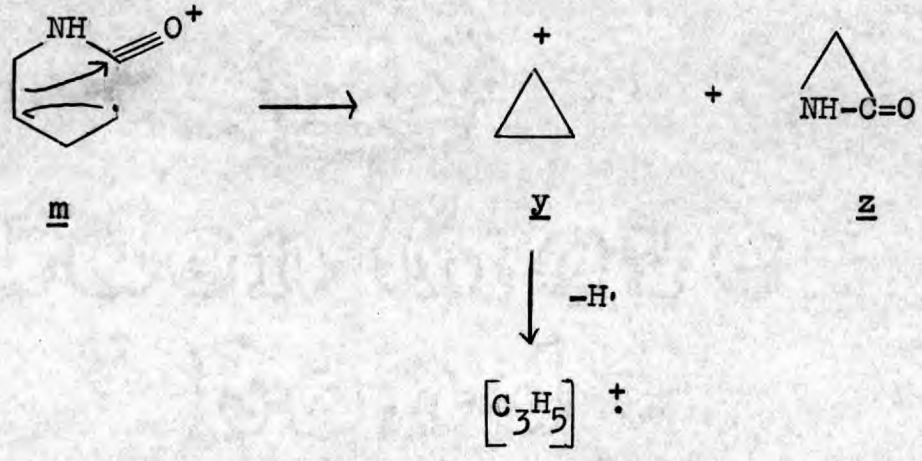
d m/e 43.

The C_2H_2O species at m/e 42 may correspond to ionized ketene. Its formation may be envisaged in terms of the first mechanism proposed as a route to the ion at m/e 114, however in this case the charge remains with the fragment at m/e 42.



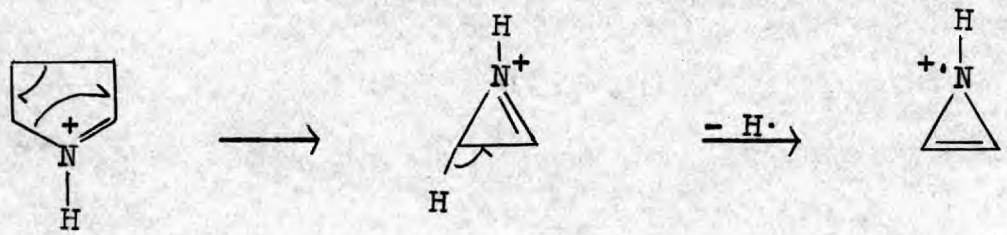
m/e 42

The C_3H_6 fragment (m/e 42) can be rationalized by representing the hydrocarbon species as the cyclopropane ion (y),[77] arising from (m) by cleavage of the C-2 - C-3 bond and ejection of the neutral fragment (z). Expulsion of hydrogen from (y) results in the formation of a C_3H_5 ion radical at m/e 41.[81]



m y z

Although no metastable ions were present to substantiate the process g ⟶ aa, it is plausible that the fragment C_2H_4N at m/e 42, may arise by ejection of ethylene from (g), which in turn may eliminate hydrogen to give (bb)



g aa bb

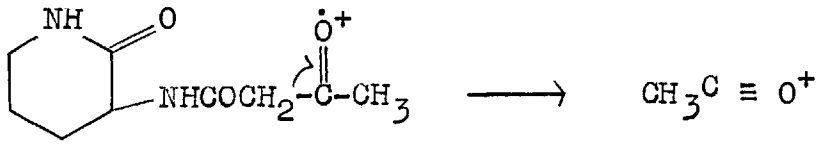
at m/e 41.[81]

Metastable defocussing techniques indicate that a transition occurs from m/e 68 ⟶ m/e 41. Hence it seems plausible that the C_2HO ion is formed from the former fragment.

$$CH_2 = CH - CH = C = O^{+\cdot} \xrightarrow{- CH_2{=}CH\cdot} \left[C_2HO\right]^+$$

m/e 41.

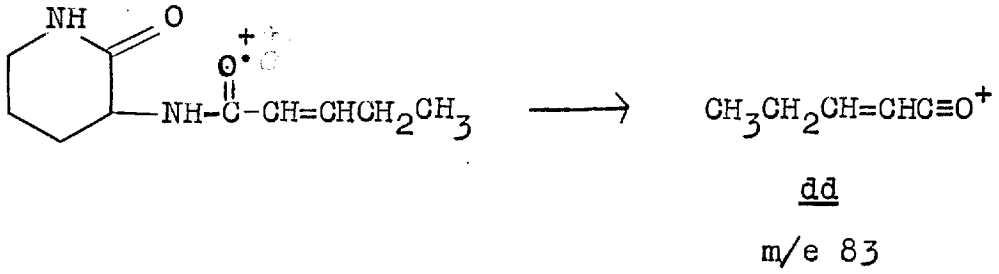
The mass spectrum of (6a) (Figure 23, p.182) did not show prominent fragments at m/e 156 and m/e 115. The most abundant ion corresponds to (cc) formed by the following process.



m/e 200 — cc — m/e 43

Examination of the mass spectra of the dehydration products (6o and 6p) derived from (6i) and (6g) (Figure 24, p.182), respectively, indicated that decompositions producing ions at m/e 156 and m/e 115 were not as significant as in the spectra of (6i) and (6g). In the case of the former compounds the relative abundances of the m/e 115 ions were

29% and 15% respectively, whereas in the latter series the base peak in both spectra occurred at m/e 115. The most abundant ion in the mass spectrum of (6p) (Figure 25, p.183) arises from the elimination of $C_5H_9N_2O$ from the molecular ion to afford (dd) at m/e 83.



dd

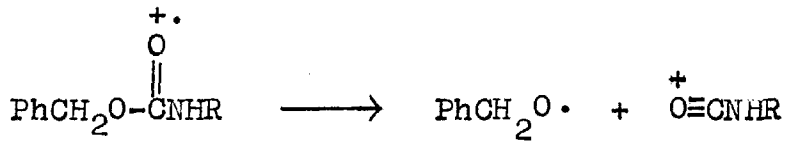
m/e 83

The mass spectra of a wide variety of benzoxycarbonyl derivatives have been reported,[84] but apparently none derived from ornithine. It has been observed that above 200°C the thermal loss of benzyl alcohol occurs from benzyloxycarbonyl derivatives.[85] Hence, the mass spectra of compounds (4b - 4j) were examined with source temperatures below 200°C.

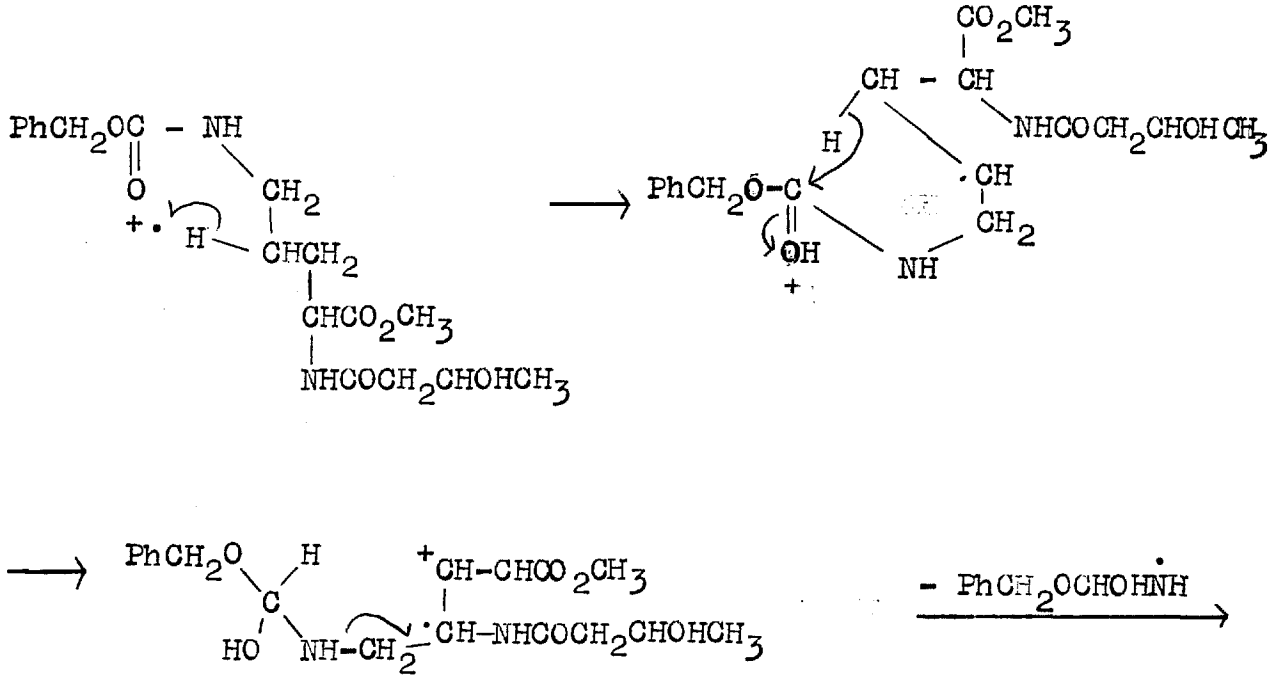
$$PhCH_2OCONHR \longrightarrow PhCH_2OH + R\text{-}N{=}C{=}O$$

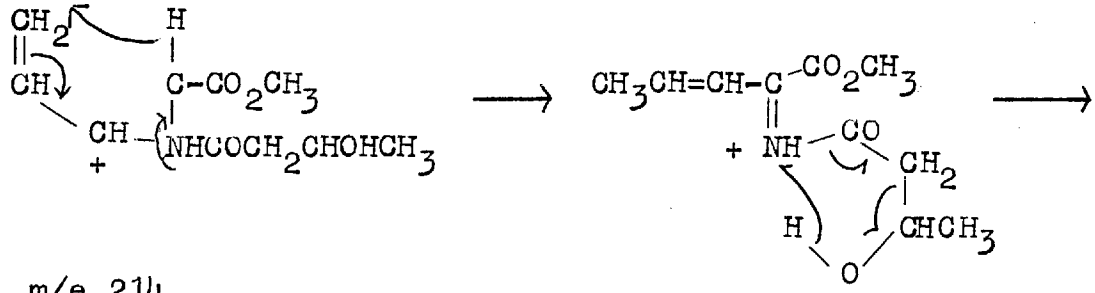
Because of the presence of a number of easily cleaved bonds in the molecules, the molecular ions were in general of low intensity. All compounds showed the loss of the

benzyloxy-radical from the molecular ion to give (m-107) ions.

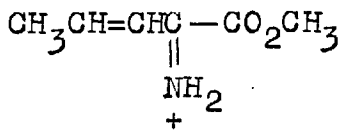


The formation of the tropylium ion (the base peak in every case) and an ion at m/e 128 dominated the spectra. Metastable defocussing techniques indicate that the ion at m/e 128 is formed by a two-step process from the molecular ion. The first-step involving a double hydrogen rearrangement results in the fragment ion at m/e 214 (4g), (Figure 26, p. 184) which, in turn, may eliminate ketene and acetaldehyde (m/e 128). Hence the following sequence is proposed.



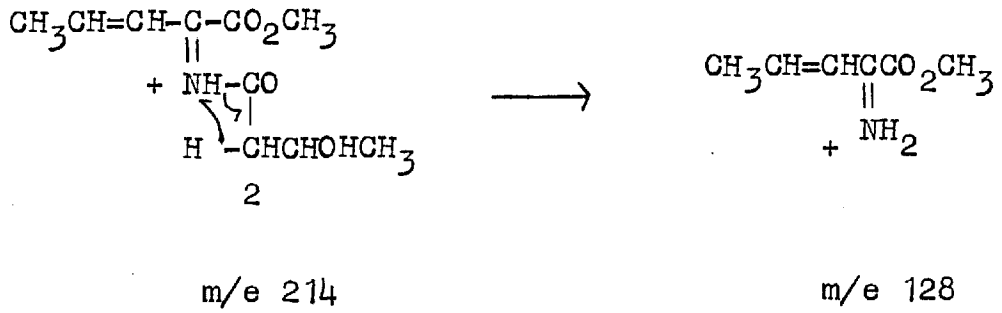


m/e 214



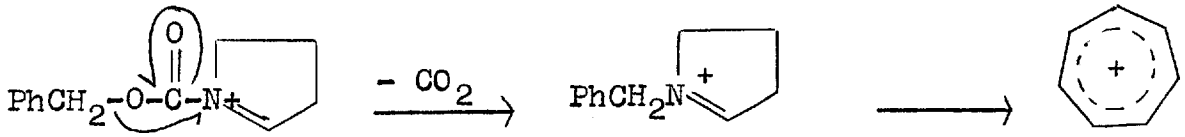
m/e 128

However, in the conventional McLafferty rearrangement, preference for a six-membered transition state is observed in ion radicals, but not necessarily in even electron species.[86] The dominant process for the decomposition (m/e 214 ⟶ m/e 128) probably involves the transfer of a hydrogen from C-2 (four-membered transition state) with concomitant expulsion of $CH_3CHOHCH{=}C{=}O$.



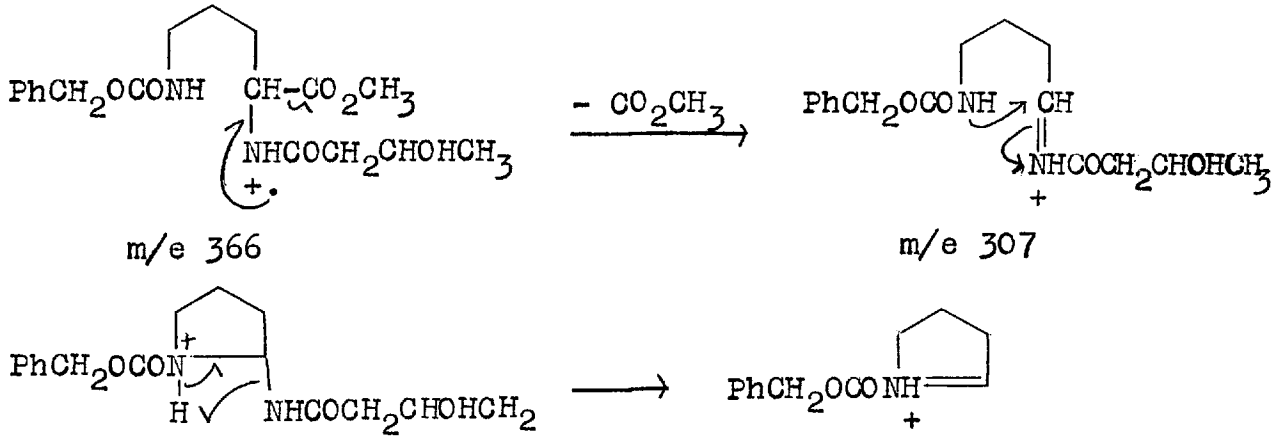
m/e 214 m/e 128

Although the ions at m/e 204 ($C_{12}H_{14}NO_2$) and 160 ($C_{11}H_{14}N$) were of low intensity (less than 20%) the expulsion of carbon dioxide from the ion at m/e 204 producing the fragment at m/e 160 proved to be interesting since it involved migration of the benzyl group[84]. The ion at m/e 160 then decomposes further to give the tropylium ion. These decompositions are well characterised by metastable ions and their positions are recorded in Table 7.



m/e 204 m/e 160 m/e91

Metastable defocussing techniques indicate that the ion at m/e 204 is formed by a two-step process from the molecular ion. Fission of the ester bond results in an ion of very low abundance which in turn may eliminate $NH_2COCH_2CHOHCH_3$ to produce the ion at m/e 204.



m/e 366 m/e 307

m/e 204

Table 7

Metastable transitions in the mass spectra of benzyloxycarbonyl derivatives

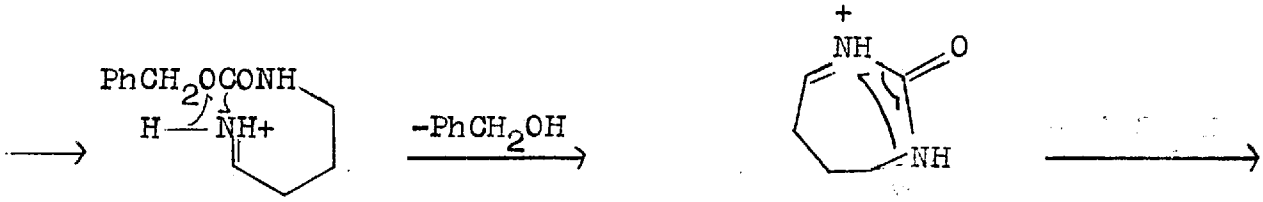
Compound	Transition		M. Calcd.	M. Observed	Fragment expelled
(4c)	322	215 + 107	143.56	143.5	$PhCH_2O$
	221	113 + 108	57.78	57.8	$PhCH_2OH$
	204	160 + 44	125.49	125.5	CO_2
	170	128 + 42	96.38	96.4	CH_2CO
	160	91 + 69	51.76	51.8	C_4H_7N
	113	70 + 43	43.46	43.4	NHCO
	91	65 + 26	46.43	46.4	CH≡CH
(4e)	352	245 + 107	170.53	170.6	$PhCH_2O$
	204	160 + 44	125.49	125.5	CO_2
	200	128 + 42 + 30	81.82	81.9	CH_2CO, CH_2O
	160	91 + 69	51.76	51.8	C_4H_7N
	113	70 + 43	43.46	43.4	NHCO
	91	65 + 26	46.43	46.4	CH≡CH
(4g)	366	259 + 107	183.28	183.2	$PhCH_2O$
	221	113 + 108	57.77	57.8	$PhCH_2OH$
	214	128 + 42 + 44	76.56	76.6	CH_2CO, CH_3CHO
	204	160 + 44	125.49	125.5	CO_2
	160	91 + 69	51.76	51.8	C_4H_7N
	113	70 + 43	43.46	43.4	NHCO
	91	65 + 26	46.43	46.4	CH≡CH

/contd. .....

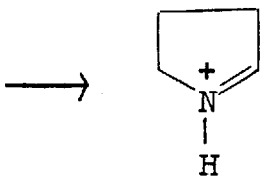
(4j)	394	287 + 107	209.06	209.0	$PhCH_2O$
	242	128 + 72 + 42	67.70	67.7	CH_2CO, $CH_3(CH_2)_2CHO$
	204	160 + 44	125.49	125.5	CO_2
	160	91 + 69	51.76	51.8	C_4H_7N
	113	70 + 43	43.46	43.4	NHCO
	91	65 + 26	46.43	46.4	CH≡CH

Finally, the ions at m/e 113 ($C_5H_9N_2O$) and m/e 70 (C_4H_8N) were also very prominent in the mass spectra of the benzyloxycarbonyl derivatives. Loss of the carbmethoxy group from the molecular ion (4c) gives (ee) (m/e 263) which in turn may lose ketene to afford (ff) (m/e 221). The ion (ff) then undergoes a rearrangement in which a hydrogen of the amino group is transferred to the oxygen atom of the benzyloxycarbonyl group resulting in the elision of benzyl alcohol with concomitant cyclization to form a seven-membered ring (gg) (m/e 113). The ejection of the neutral fragment NHCO from (gg) results in the ion (hh) m/e 70.

ee



ff gg



hh

In conclusion, many other fragmentations are evidently occurring but they are only of minor importance compared with the above mentioned decompositions.

Part 3

Derivatives of 1,3-Dioxane and Fatty Acid Esters

3,1 Discussion of Experimental Work

Many compounds suffer thermal degradation on the walls and filament of a conventional electron impact source, consequently the mass spectra obtained are sometimes complex and often not reproducible. There are also cases where electron bombardment of thermally stable compounds results in extremely facile fragmentation so that the molecular ion is not observed. Such difficulties make determination of molecular formulae by mass measurement difficult or impossible. Against this background the mass spectral decomposition pathways of a number of simple acetals and unsaturated fatty acid esters are investigated by electron-impact at different ionizing voltages and various source temperatures, and compared with mass spectral data produced by photon-impact (i.e. cold source).[87,88,89] In the latter case somewhat simpler spectra may be produced at lower energy, since highly excited states of the ion are not accessible.[87] Furthermore, photoionization mass spectra may show some enhancement of the relative intensities of characteristic peaks.

This investigation makes extensive use of the technique developed by Beynon and co-workers.[89] A stream of gas is passed through a photon lamp fitted to the entry ports of

the ionization chamber. The photons which are produced by applying a large d.c. potential across the gas at a pressure of 0.1 - 10 torr., pass through an open ended capillary directed into the source. Efficient differential pumping maintains a low pressure in the source. Ionization and dissociation of molecules by photons from hydrogen and helium give intense photoion beams and hence these gases are used to produce the mass spectra of the compounds under study.

A decrease in molecular ion intensities may be observed for compounds with long paraffin chains which are susceptible to high source temperatures.[90] On the other hand, acetals have not hitherto been shown to be heat sensitive but lack of molecular ions appears to be due to easy electron-impact induced fragmentation giving a resonance stabilized ion.[91,92]

Unsaturated fatty acid esters were investigated in an attempt to distinguish between the decomposition pathway of double bond positional isomers where the double bond is further removed from the carbomethoxyl group than the (Δ^5) position (see p.80). To this end, it was thought useful to examine an unsaturated long chain compound with the position of the double bond marked by deuterium labelling. However, attempts to prepare methyl 9,10-$\left[^2H_1\right]$ -oleate with

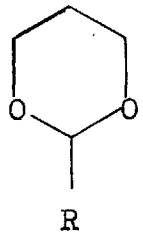
a high degree of deuterium incorporation and high degree of specificity proved unsuccessful. Treatment of methyl stearolate[93] with $[^2H_6]$ diborane generated externally[94] from $[^2H_4]$ lithium aluminium hydride and freshly distilled boron trifluoride etherate and subsequent deuterolysis with O- $[^2H_1]$ -acetic acid[95] did not yield methyl 9,10- $[^2H_1]$ - oleate. A second approach consisted of reacting methyl stearolate with $[^2H_6]$ diborane generated internally after the method of Brown and Zweifel.[96] However, starting material and a mixture of deuteriated methyl oleates ($^2H_2$ and $^2H_1$ incorporated) and undeuteriated methyl oleate were recovered.

The acetal derivatives were prepared by well-established routes.[97] Treatment of 1,3-propane diol with the corresponding aldehydes in diethyl ether saturated with anhydrous hydrogen chloride afforded the 1,3-dioxane derivatives and these were purified by preparative gas-liquid chromatography.

3,2 Discussion of Mass Spectra

Acetals

The mass spectra of the acetal compounds produced by photon-impact show some enhancement of the abundance of the molecular ion over the abundance from electron-impact.[98] The intensities of the molecular ions from compounds of series (1) where R represents an alkyl group are extremely weak (see also p. 120), however if R is a phenyl group, the abundance of the molecular ion is nearly as great as the prominent m-1 peak.



1

Table 8 shows the intensities of ions in the mass spectra of 2-phenyl-1,3-dioxane produced by photon and electron-impact at different temperatures expressed as percentages of the total ion current ($\%\Sigma_{77}$)

Table 8

Intensities ($\%\Sigma_{77}$) of ions in the mass spectra of 2-phenyl-1,3-dioxane

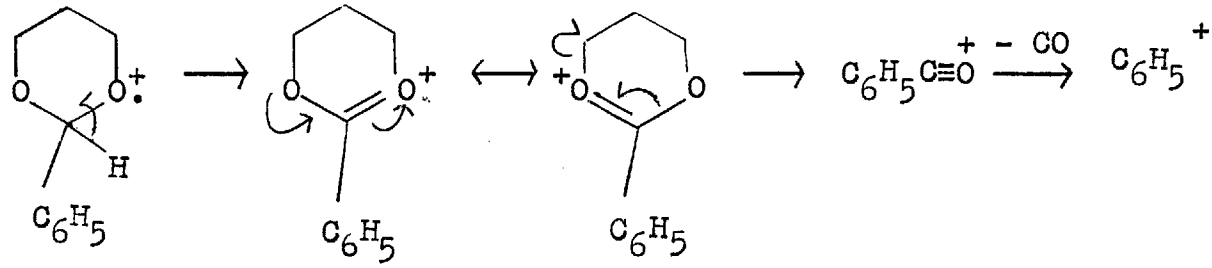
Ion	Electron-Impact			Photon-Impact, Hydrogen gas	
m/e	150°C, 70 eV	30°C, 70 eV	150°C, 10.2 eV	150°C	30°C
164	14.07	16.04	18.88	31.47	42.29
163	23.21	24.65	30.49	43.99	45.07
107	2.12	1.78	2.94	1.28	0.37
106	9.10	8.02	10.36	6.28	2.93
105	23.21	24.96	17.59	6.28	1.37
91	2.43	1.07	2.34		
87	7.43	7.13	7.04	8.38	7.32
79	2.43	3.03	1.76	0.63	
78	4.79	3.57	5.27	1.36	0.58
77	10.31	9.80	3.90	0.98	0.15

From the results in the table it is quite evident that there is a significant enhancement of the abundance of the molecular ion produced by the photoionization process

over the abundance from electron-impact. In the former process the molecular ion accounds for 31.47% (source 150°C, 70 eV) and 42.29% (source 30°C, 70 eV) of the total ion current, whereas in the latter process it accounts for less than 19% at different source temperatures.

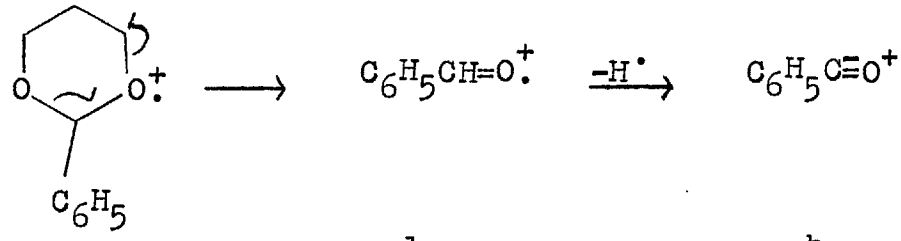
The peak at m/e 105 accounts for about 24% (source 150°C) and 25% (source 30°C) of the total ion current in the electron-impact 70 eV spectra. On the other hand, the photoionization spectra show that the peak has decreased in abundance and accounts for approximately 6.38% and 1.37% of the total ion current at source temperatures of 150°C and 30°C, respectively. The observed variations in intensity of the m/e 105 peak lacks interpretation since the peak accounts for 17.9% of the total ion current in the 10.2 eV (150°C) spectrum, and thus is much higher than anticipated from the probability factor versus activation energy effect.[8]

Loss of hydrogen from the molecular ion of 2-phenyl-1,3-dioxane (Figure 27, p. 185) results in the formation of the resonance stabilized oxonium ion (a),[91,92] which in turn may eliminate the neutral fragment C_3H_6O to afford the abundant ion at m/e 105 (b). The latter species may expel carbon monoxide to give (c).[100]



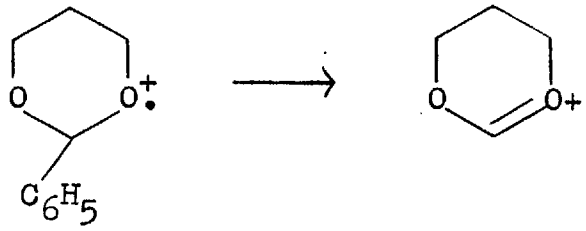
a b c

Alternatively, the ion (b) may arise as a result of the elimination of the neutral fragment C_3H_6O from the molecular ion to afford (d) (m/e 106), which may decompose further with the elision of hydrogen to give (b).[100]



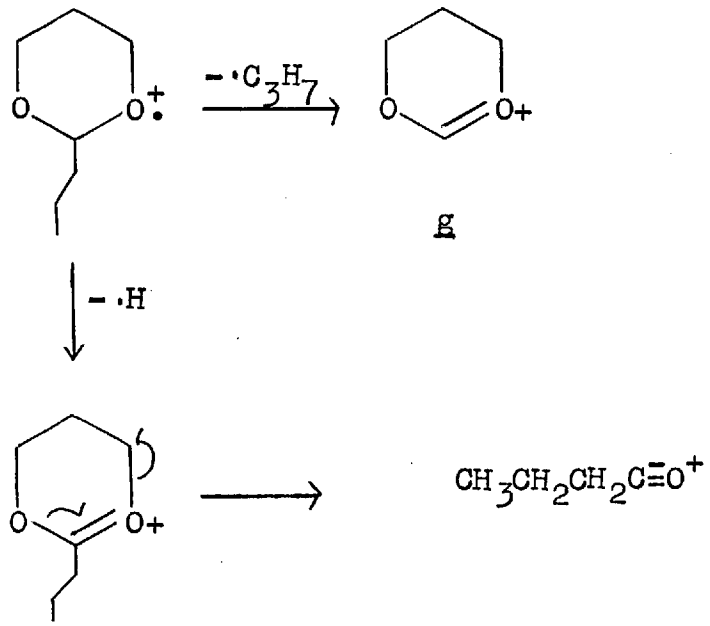
d b

The formation of the ion at m/e 87 is due to a very characteristic fragmentation attributed to acetals[91] and may be envisaged in terms of loss of the C-2 substituent (C_6H_5 radical) from the molecular ion to afford (e).



e

The fragmentation reactions which occur in the mass spectrum of 2-alkyl-1,3-dioxanes consistently show only two principal fragmentations; these correspond to the loss of the C-2 substituents.[91] The mass spectrum of 2-propyl-1,3-dioxane (Figure 28, p.186) exhibits significant m-1 (f, m-H) and m-43 (g, base peak, m-C_3H_7) fragments. Ion (f) may decompose further to yield (h) (m/e 71).



g

f

h

Long Chain Unsaturated Fatty Acid Esters

Photoionization mass spectra of methyl oleate (cis Δ^9), methyl elaidate (trans Δ^9), methyl petrosellinate (cis Δ^6), and methyl vaccinnate (cis Δ^{11}) showed slight enhancement of the relative abundance of the molecular ion over the abundance from electron-impact. The peaks below m-32 were suppressed in the former process; however, by lowering the electron beam energy similar spectra were obtained by the latter process. At room temperature and 150°C, the spectra of the double bond positional isomers produced by photon-impact and electron-impact were indistinguishable.[72-74] Hence, in the case of the unsaturated fatty acid esters investigated the process of photon-impact offers little advantage over electron-impact induced ionization and fragmentation.

Part 4

Experimental Section

General

Infrared spectra were recorded by Grub Parsons and/or Unicam SP 200 spectrometers with the sample in the form of a liquid film, nujol mull, or in solution using polystyrene as a reference marker. Ultraviolet spectra were obtained with a Unicam SP 800 instrument with a Holman filter standard.

The mass spectra were measured with an A.E.I. MS 9 double focussing instrument operated at 8 kV accelerating voltage, 70 eV ionizing energy and 100 μ A trap current. High resolution work was carried out at a resolving power of 10,000 (10% valley) using heptacosafluorotri-n-butylamine as an internal standard. Liquids and low m.p. solids were introduced through the heated inlet system. High and low m.p. solids were introduced directly into the source using the probe technique, at the minimum temperature that produced sufficient vapour pressure of sample (130 - 190°C).

The ^{1}H nuclear magnetic resonance spectra were recorded with Varian A-60 and HA-100 spectrometers operating at 60 and 100 MHz., respectively. The chemical shifts are in parts per million from tetramethylsilane as internal reference and are recorded on the δ scale.

The purity of all compounds was evaluated by t.l.c. on silica gel and alumina, or for volatile liquids by gas

chromatography using a Perkin-Elmer F11 fitted with 2 metre columns, packed with carbowax 1500 or apiezon L. Purification of liquids was achieved with a Pye series 105 preparative gas chromatograph using a 30 foot methyl silicone gum E30 column and a temperature programming sequence.

Melting points were determined with a Kofler Micro Heating Stage and are uncorrected.

The unsaturated fatty acid esters were obtained commercially.

4,1 Derivatives of 1,1,2-triphenyl ethane, 1,1-diphenyl propane and related compounds.

4-Nitrodiphenylmethane.[26]

4-Nitrobenzyl chloride (2.0 g., 0.012 m.), benzene (8 ml.) and dry carbon disulphide (10.0 g.) were stirred with gradual addition of aluminium chloride (2.0 g., 0.015 m.). After addition was complete, the mixture was gently heated until hydrogen chloride evolution ceased. After cooling, a further quantity of aluminium chloride (2.0 g., 0.015 m.) was added and when hydrogen chloride evolution subsided, the reaction mixture was slowly brought to reflux temperature. The reaction was monitored by removing 2 ml. aliquots and examining the n.m.r. spectrum of the product after work-up. The reaction was generally complete after two hours. The reaction mixture was cooled and poured into water. The oil which separated was extracted with diethyl ether and dried over anhydrous sodium sulphate. Concentration under reduced pressure afforded a liquid which was sufficiently pure to use in subsequent reactions. Yield 2.04 g. (80%); b.p. 185 - 195°C/11 mm.; δ ($CDCl_3$) 7.00 - 8.20 (9 proton multiplet, benzenoid, in which an AA'BB' pattern centred at 7.60 was clearly observed), 4.02 (singlet, CH_2).

4-Nitrobenzophenone

To a solution of 4-nitrodiphenyl methane (5 g., 0.023 m.) in acetic acid (40 ml.) was added chromium trioxide (6.9 g., 0.069 m.) dissolved in water (7 ml.). The mixture was brought to reflux and the disappearance of the methylene protons was monitored by removing 5 ml. aliquots and examining the n.m.r. spectrum of the product after work-up. The reaction was generally complete after 3 hrs. Upon cooling, a solid precipitated which was removed by filtration, washed with water, dried and recrystallized from ethanol. Yield 4.1 g. (80%); m.p. 138°C, (lit. m.p. 138°C); ν max (CH_2Cl_2) 1662 $cm.^{-1}$ (C = O, diaryl ketone); δ ($CDCl_3$) 7.59 - 8.61 (9 proton multiplet, benzenoid).

Benzenetriphenylphosphonium chloride.[28]

A mixture of triphenyl phosphine (39.3 g., 0.15 m.) and benzyl chloride (20 g., 0.16 m.) were heated on a Büchi evaporator for 1 hr. to afford a thick slurry of crystals. The salt was removed by filtration to give a white crystalline solid, m.p. 317 - 318°C, (lit. m.p. 317 - 318°C). Yield, quantitative.

Ethyltriphenylphosphonium bromide.[29]

Triphenylphosphine (19.5 g., 0.075 m.) dissolved in benzene (25 ml.) and ethyl bromide (11g., 0.10 m.), sealed in a Carius tube, were heated at 135°C for 20 hrs. The salt was removed by filtration and recrystallized from water. Yield 23 g. (82%); m.p. 209 - 210.5°C., (lit. m.p. 209 - 210.5°C).

Phenyl Lithium.[30]

This compound was prepared according to the method of L.A. Walter.[30]

1-(4'-Nitrophenyl)-1,2-diphenyl ethylene.[31]

An ethereal solution of phenyl lithium (35 ml., 0.030 m.) was added with vigorous stirring under dry nitrogen, to a suspension of benzenetriphenylphosphonium chloride (12.45 g., 0.032 m.) in anhydrous diethyl ether (50 ml.). After addition was complete the resulting orange-red solution was stirred for 30 minutes, at which time 4-nitrobenzene (6.81 g., 0.030 m.) dissolved in freshly distilled tetrahydrofuran (100 ml.) was added at once. The reaction mixture was heated gently to remove diethyl ether and tetrahydrofuran was added periodically to maintain an adequate quantity of solvent. After most of the diethyl ether was removed, the reaction mixture was

refluxed for 12 hours. Concentration under reduced pressure afforded a solid to which diethyl ether was added. Filtration of the mixture to remove triphenyl phosphine oxide and concentration of the filtrate under reduced pressure gave a yellow solid which was recrystallized from methanol. Yield 7.4 g. (82%); δ ($CDCl_3$) 6.58 - 7.50 (15 proton multiplet, benzenoid protons overlapping with one olefinic proton).

1-(4'-Nitrophenyl)-1-phenyl-propyl-1-ene.[31]

An ethereal solution of phenyl lithium (23 ml., 0.020 m.) was added with vigorous stirring under dry nitrogen to a suspension of ethyl triphenylphosphonium bromide (7.75 g., 0.021 m.) in anhydrous diethyl ether (100 ml.). After addition was complete the resulting orange solution was stirred for 1 hour, then added dropwise to a solution of 4-nitrobenzophenone (4.54 g., 0.020 m.) and tetrahydrofuran (150 ml). The reaction mixture was then treated in the same manner as described above to give a yellow oil. Chromatography of the yellow oil on silica gel (M.F.C.), eluting with benzene-petroleum ether (60 - 80°C) (4 : 1) gave a yellow glass which could not be induced to crystallize. Yield 3.0 g. (63%); δ ($CDCl_3$) 7.10 - 8.40 (9 proton multiplet, benzenoid protons), 6.15 - 6.62 (1 proton multiplet, olefinic proton) and 1.85 and 1.72 (a pair of doublets, 1 : 1 ratio, CH_3, J = 1.9 Hz.).

(±) 1-(4'-Aminophenyl)-1,2-diphenyl ethane

1-(4'-Nitrophenyl)-1,2-diphenyl ethylene (0.301 g., 0.001 m.) was dissolved in ethyl acetate (10 ml.) and hydrogenated at atmospheric pressure and room temperature in the presence of 10% palladium on charcoal (0.033 g.) until the uptake of hydrogen ceased. Concentration of the filtrate after removal of the catalyst by filtration, afforded an oil. Chromatography of the oil on neutral alumina (No. 3) eluting with benzene gave an oil which crystallized on standing. Yield 0.25 g. (97%); m.p. 34 - 35°C; ν max (CCl_4) 3480 (NH stretching), 1623 $cm.^{-1}$ (NH bending); δ ($CDCl_3$) 6.40 - 7.32 (14 proton multiplet, benzenoid, in which an AA'BB' pattern centred at 6.75 was observed), 4.16 (triplet, CH, J = 7.5 Hz.), 3.31 (4 protons, a singlet for NH_2 superimposed on a doublet, CH_2, J = 7.5 Hz.); (Found: C, 87.77; H, 6.93; N, 4.87. $C_{20}H_{19}N$ requires C, 87.87; H, 7.01; N, 5.12%).

(±) 1-(4'-Aminophenyl)-1-phenylpropane

Hydrogenation of 1-(4'-nitrophenyl)-1-phenyl-propyl-1-ene (0.200 g., 0.0008 m.) as above afforded the required compound as an oil. Yield 0.165 g. (97%); ν max ($CHCl_3$) 3480, 3400 (NH stretching), 1621 $cm.^{-1}$ (NH bending); δ ($CDCl_3$) 6.47 - 7.32 (9 proton multiplet, benzenoid, in which an AA'BB' pattern centred at 6.82 was clearly observed), 3.70 (triplet, CH, J = 8.0 Hz.), 3.41 (singlet, NH_2), 2.03 (pentuplet, CH_2,

J = 8.0 Hz.), 0.88 (triplet, CH_3, J = 8.0 Hz.); (Found: C, 85.15; H, 8.27; N, 6.43. $C_{15}H_{17}N$ requires C, 85.26; H, 8.11; N, 6.63%).

(±) 1-(4'-Nitrophenyl)-1,2-diphenyl ethane.[32]

(±) 1-(4'-Aminophenyl)-1,2-diphenyl ethane (2.0 g., 0.0073 m.) was added to a mixture of 25 ml. H_2O_2 (30%), concentrated H_2SO_4 (1.5 ml.), and acetic acid (50 ml.). The reaction mixture which immediately turned reddish-brown was slowly heated to 70°C at which point heating was discontinued. After approximately 30 minutes, heat was reapplied and the reaction mixture was then maintained between 70 - 80°C overnight. The reaction solution was then cooled, poured into ice-water and methylene chloride extracted. The extracts were washed with 10% aqueous sodium bicarbonate and water and dried over anhydrous calcium sulphate. Concentration of the filtrate under reduced pressure afforded an oil which crystallized on standing. Recrystallization from ethanol gave a white crystalline solid m.p. 57 - 58°C. Yield 1.52 g. (70%); ν max (CCl_4) 1535($C-NO_2$, asymmetric stretching), 1350 $cm.^{-1}$ ($C-NO_2$, symmetric stretching); δ ($CDCl_3$) 6.95 - 8.25 (14 proton multiplet, benzenoid, in which an AA'BB' pattern centred at 7.70 was observed), 4.35 (triplet, CH, J = 7.5 Hz.), 3.37 (doublet, CH_2, J = 7.5 Hz.); (Found: C, 79.11; H, 5.72; N, 4.54. $C_{20}H_{17}NO_2$ requires C, 79.18; H, 5.65; N, 4.62%).

(±) 1-(4'-Nitrophenyl)-1-phenylpropane

Oxidation of (±) 1-(4'-aminophenyl)-1-phenyl propane (0.50 g., 0.002 m.) as above afforded the required compound as an oil. Yield 0.35 (68%); δ ($CDCl_3$) 6.95 - 8.18 (9 proton multiplet, benzenoid, in which an AA'BB' pattern centred at 7.82 was clearly observed), 3.81 (triplet, CH, J = 8.0 Hz.), 2.05 (pentuplet, CH_2, J = 8.0 Hz.), 0.91 (triplet, CH_3, J = 8.0 Hz.); (Found: C, 74.45; H, 6.35; N, 5.59. $C_{15}H_{15}NO_2$ requires C, 74.66; H, 6.27; N, 5.81%).

(±) 1-(4'-Acetamidophenyl)-1,2-diphenyl ethane

(±) 1-(4'-Aminophenyl)-1,2-diphenyl ethane (1.0 g., 0.0035 m.) was acetylated at room temperature with acetic anhydride (2 g., 0.02 m.) in the presence of pyridine (5 ml.). After pouring the reaction mixture into water, the product was extracted with chloroform. The solution was washed successively with IN hydrochloric acid, water, IN sodium bicarbonate, and water and dried over anhydrous sodium sulphate. Concentration under reduced pressure afforded a solid which was recrystallized from ethyl acetate. Yield 1.05 g. (95%); m.p. 157 - 159°C; ν max ($CHCl_3$) 1660 cm^{-1} (C = O, amide); δ ($CDCl_3$) 7.00 - 7.58 (15 proton multiplet, benzenoid protons overlapping with N-H), 4.24 (triplet, CH, J = 8.0 Hz.), 3.32 (doublet, CH_2, J = 8.0 Hz.), 2.10 (singlet, CH_3); (Found:

C, 83.72; H, 6.79; N, 4.32. $C_{22}H_{21}NO$ requires C, 83.77; H, 6.71; N, 4.44%).

(±) 1-(4'-Cyanophenyl)-1,2-diphenyl ethane

To (±) 1-(4'-aminophenyl)-1,2-diphenyl ethane (4.00 g., 0.0148) was added 7N hydrochloric acid (24 ml.). The efficiently stirred mixture was cooled to 0°C and sodium nitrite (1.049 g., 0.0152 m.) dissolved in water (5 ml.) slowly added with the reaction mixture maintained between 0-5°C. The resulting diazonium salt was slowly added to a warm solution of freshly prepared cuprous cyanide (3.152 g., 0.016 m.), sodium cyanide (0.98 g.) and water (5 ml.) and the mixture was then rapidly stirred at 65°C for 15 min. After cooling, the product was extracted with methylene chloride and the extracts were washed successively with 2N hydrochloric acid, water, 5% aqueous sodium carbonate and water and dried over anhydrous calcium sulphate. Concentration under reduced pressure afforded a brown oil. Chromatography of the oil on silica gel (M.F.C.) yielded upon elution with benzene-petroleum ether (60 - 80°C) (4 : 1), two products. The less polar product 1,1,2-triphenyl ethane (yield 2%) was identified by its m.p. 58°C, (lit. m.p. 58°C); n.m.r. and m.s. The more polar product which was recrystallized from petroleum ether (60 - 80°C) was identified as (±) 1-(4'-cyanophenyl)-1,2-diphenyl ethane. Yield 4.19 g. (50%);

m.p. 58°C; ν max (CCl_4) 2235 cm.$^{-1}$ (CN stretching); (Found: C, 88.92, H, 6.08; N, 4.77. $C_{21}H_{17}N$ requires C, 89.01; H, 6.05; N, 4.94 %).

(±) 1-(4'-Carbamoylphenyl)-1,2-diphenyl ethane and (±) 1-(4'-Carboxyphenyl)-1,2-diphenyl ethane

A mixture of (±) 1-(4'-cyanophenyl)-1,2-diphenyl ethane (2.0 g., 0.007 m.) dissolved in ethanol (0.5 ml.) and 0.1 N aqueous sodium hydroxide (40 ml.) were refluxed overnight. The cooled reaction mixture was acidified with 1N hydrochloric acid and then extracted with methylene chloride. Concentration of the dried extracts ($CaSO_4$) gave a solid, shown by t.l.c. ($CHCl_3$ on silica) to contain two products and these were separated by preparative t.l.c. The less polar product was recrystallized from ethyl acetate and identified as (±) 1-(4'-carbamoylphenyl)-1,2-diphenyl ethane. Yield 0.86 g. (40%); m.p. 171.5 -172°C; ν max ($CHCl_3$) 3500, 3480 (NH), 1675 cm.$^{-1}$ (C = O, amide); (Found: C, 83.77; H, 6.36; N, 4.51. $C_{21}H_{19}NO$ requires C, 83.69; H, 6.35; N, 4.65%).

The more polar product was recrystallized from ethyl acetate and identified as (±) 1-(4'-carboxyphenyl)-1,2-diphenyl ethane. Yield 0.92 g. (43%); m.p. 169 - 170°C; ν max ($CHCl_3$) 1690 cm.$^{-1}$ (C = O, acid); (Found: C, 83.34; H, 6.16. $C_{21}H_{18}O_2$ requires C, 83.42; H, 6.00 %).

(±) 1-(4'-Fluorophenyl)-1,2-diphenyl ethane

To a stirred cooled suspension ($0^{o}C$) of the diazonium salt prepared in the same manner as for the cyano compound was added dropwise a solution of sodium fluoborate (1.023 g., 0.0093 m.) and water (2 ml.). After stirring the reaction mixture for 15 minutes, 1-(4'-benzenediazoniumfluoborate)-1,2-diphenyl ethane (99 - 100° dec.) was isolated by filtration, washed with ice-water, ethanol and diethyl ether and dried. Decomposition was accomplished by heating the salt (2.547 g., 0.0068 m.) under vacuum (0.1 mm.) and this resulted in the distillation of the required product (b.p. 136°C, 0.1 mm.). Yield 1.73 g. (83%); ν max (CCl_4) 1102 $cm.^{-1}$ (CF stretching); δ ($CDCl_3$) 6.75 - 7.40 (14 proton multiplet, benzenoid), 4.21 (triplet, CH, J = 8.0 Hz.), 3.30 (doublet, CH_2, J = 8.0 Hz.); (Found: C, 86.96; H, 6.16; F, 6.79. $C_{20}H_{17}F$ requires C, 86.92; H, 6.20; F, 6.88%).

(±) 1-(4'-Chlorophenyl) 1,2-diphenyl ethane

To a stirred cooled solution ($0^{o}C$) of freshly prepared cuprous chloride (0.5445 g., 0.0093 m.) and concentrated hydrochloric acid (2.7 ml.) was added (±) 1-(4'-benzenediazonium chloride)-1,2-diphenyl ethane prepared from (±) 1-(4'-aminophenyl)-1,2-diphenyl ethane (1.0 g., 0.0037 m.) by the

general method above. The reaction mixture was slowly brought to 60°C where it was maintained for 1 hour. After cooling the product was extracted with methylene chloride and the extracts were washed successively with 2N hydrochloric acid, water and 5% aqueous sodium carbonate and dried over anhydrous calcium sulphate. Concentration under reduced pressure afforded an oil. Chromatography of the oil on silica gel (M.F.C.) afforded upon elution with petroleum ether (60 - 80°C)-benzene (1.5 : 1) the required product which was recrystallized from petroleum ether (30 - 60°C). Yield 0.60 g. (55%); m.p. 48 - 49°C; δ ($CDCl_3$) 6.90 - 7.40 (14 proton multiplet, benzenoid), 4.22 (triplet, CH, J = 8.0 Hz.), 3.31 (doublet, CH_2, J = 8.0 Hz.); (Found: C, 81.94; H, 5.97; Cl, 11.92. $C_{20}H_{17}Cl$ requires C, 82.04; H, 5.85; Cl, 12.11%).

(±) 1-(4'-Bromophenyl)-1,2-diphenyl ethane

To a suspension of (±) 1-(4'-aminophenyl)-1,2-diphenyl ethane (0.326 g., 0.0012 m.) in water (5 ml.) was added 45% hydrogen bromide (2.6 ml.). The efficiently stirred mixture was cooled to 0°C and sodium nitrite (0.93 g., 0.0013 m.) dissolved in water (6 ml.) added with the reaction mixture maintained between 0 - 5°C. The resulting diazonium salt was slowly added to a warm suspension of freshly prepared cuprous bromide in water (6 ml.) and the reaction mixture was then

stirred rapidly at 60°C for 1 hour. After cooling, the product was extracted with methylene chloride and the extracts were washed successively with 2N hydrochloric acid, water, 5% aqueous sodium carbonate and water and dried over anhydrous calcium sulphate. Concentration under reduced pressure afforded a brown oil. Chromatography of the oil on silica gel (M.F.C.) eluting with petroleum ether (60 - 80°C)-benzene (1.5 : 1) afforded a solid which was recrystallized from petroleum ether (30 - 60°C). Yield 0.31 g. (77%); m.p. 66°C; (Found: C, 71.17; H, 5.22; Br, 23.82. $C_{20}H_{17}Br$ requires C, 71.23; H, 5.08; Br, 23.69%).

(±) 1-(4'-Iodophenyl)-1,2-diphenyl ethane

Potassium iodide (0.508 g., 0.004 m.) dissolved in water (1.10 ml.) was added to a cooled suspension (0°C) of (±) 1-(4'-benzenediazonium chloride)-1,2-diphenyl ethane prepared from (±) 1-(4'-aminophenyl)-1,2-diphenyl ethane (1g., 0.0037 m.) by the general method previously described. Stirring was continued for 1 hour at room temperature and then the reaction mixture was cautiously heated to 100°C over 1 hour. After cooling, the product was isolated by the procedure described above. Yield 1.17 g. (82%); m.p. 74°C; (Found: C, 62.47; H, 4.65; I, 33.16. $C_{20}H_{17}I$ requires C, 62.52; H, 4.46; I, 33.02%).

4,2 Derivatives of L-ornithine and related compounds

Ethyl 3-ethylenedioxybutyrate

A mixture of ethyl acetoacetate (2.00 g., 0.016 m.), ethylene glycol (1.00 g., 0.162 m.) and p-toluene sulphonic acid (0.001 g.) in benzene (25 ml.), were refluxed for 16 hours under a Dean-Stark water separator. After cooling and evaporation of the solvent under reduced pressure the residual liquid was distilled (b.p. 96 - 104°C/2 mm.), to give the title compound. Yield 2.36 g. (85.4%); ν max (liquid film) 1732 $cm.^{-1}$ (C = O, ester); δ ($CDCl_3$) 4.50 (quartet, CH_2, J = 7.2 Hz.), 3.99 (singlet, 4 protons, 2 x CH_2, overlapping with quartet), 2.65 (singlet, CH_2), 1.50 (singlet, CH_3), 1.25 (triplet, CH_3, J = 7.2 Hz.).

3-Ethylenedioxybutyric acid

Aqueous potassium hydroxide (9.5 ml., 0.0048 m.) was added dropwise to a solution of ethyl 3-ethylenedioxybutyrate (0.773 g., 0.0044 m.) and ethanol (3 ml.) which was then heated at 75°C for 3 hours. After cooling, the solvent was removed under reduced pressure to give a white solid which was dissolved in aqueous methanol (1 : 1) and filtered through amberlite resin IR-20 (H). The acidic filtrate was collected and concentrated in *vacuo* to give the title compound. Yield 0.62 g. (97%); ν max (liquid film) 1720 $cm.^{-1}$ (C = O, acid);

δ ($CDCl_3$) 11.17 (singlet, OH), 3.98 (singlet, 4 protons, 2 x CH_2), 2.70 (singlet, CH_2), 1.52 (singlet, CH_3).

Ethyl 3-hydroxybutyrate

This was prepared according to the method of Mozingo et al.[56] Yield 9.5 g. (92.9%); ν max (liquid film) 3495 (OH), 1725 $cm.^{-1}$ (C = O, ester); δ ($CDCl_3$) 4.18 (3 proton multiplet, quartet, J = 7.0 Hz., for CH_2 of ester group overlapping with signal for methine proton), 3.28 (broad singlet, OH), 2.43 (doublet, CH_2, J = 6.5 Hz.), 1.25 (6 proton multiplet, triplet for CH_3 of ester group overlapping with the signal for CH_3 adjacent to the carbon atom bearing the methine proton).

3-Hydroxybutyric acid

To a solution of ethyl 3-hydroxybutyrate (1.00 g., 0.008 m.) in ethanol (5 ml.) cooled to 0°C, potassium hydroxide (20 ml., 0.010 m.) was added dropwise with stirring. The mixture was stirred at 0°C for 4 hours and left at room temperature overnight. Evaporation to dryness gave a white solid which was dissolved in aqueous methanol (1 : 1) and filtered through amberlite resin IR-20 (H). The acidic filtrate was collected and concentrated in vacuo to afford the title compound. Yield 0.53 g. (67%); ν max (liquid film)

1709 cm.$^{-1}$ (C = O, acid); δ ($CDCl_3$) 5.85 (singlet, OH), 4.22 (hexaplet, CH, J = 6.40 Hz.), 3.71 (singlet, OH), 2.46 (doublet, CH_2, J = 6.40 Hz.), 1.25 (doublet, CH_3, J = 6.40 Hz.).

Ethyl 4- $[^2H_3]$ -3-hydroxybutyrate

To zinc dust (2.00 g., 0.031 m.) which had previously been washed with 1N hydrochloric acid, followed by water, ethanol, acetone and anhydrous diethyl ether and dried in vacuo at 100°C,[101] was added slowly 2.5 ml. of a mixture of freshly distilled ethyl bromo acetate (4.17 g., 0.025 m.) and $[^2H_3]$ acetaldehyde[59] (1.41 g., 0.030 m.) in dry benzene (8 ml.) and anhydrous diethyl ether (2 ml.) under dry nitrogen.[57] The suspension was gently heated until the reaction started and then the remainder of the mixture was introduced, with stirring, at a rate sufficiently rapid for refluxing to occur. After addition of the mixture, refluxing was continued for 30 minutes. The reaction solution was cooled and poured into a vigorously stirred ice-cooled solution of 2N sulphuric acid (30 ml.) before separating the organic layer and washing it with 1N sulphuric acid (2 x 5 ml.), 10% sodium carbonate (5 ml.), 1N sulphuric acid (5 ml.) and water (2 x 5 ml.). The acid extracts were washed with diethyl ether (2 x 5 ml.) and the combined organic fractions dried over anhydrous magnesium

sulphate. After removal of the solvent under reduced pressure, the residual liquid was distilled (b.p. 40°C/5 mm.), to give ethyl 4- $[^2H_3]$ -3-hydroxybutyrate. Yield 0.92 g. (30%); νmax (liquid film) 3500 (OH), 2250 (CD), 1730 cm.$^{-1}$ (C = O, ester); δ ($CDCl_3$) 3.82 - 4.35 (3 protons, CH_2, quartet, J = 7.3 Hz., superimposed on a complex multiplet, CH), 2.98 (singlet, OH), 2.43 (doublet, CH_2, J = 6.6 Hz.), 1.25 (triplet, CH_3 of ester group, J = 7.3 Hz.). No signal was observed at δ 1.25 for CH_3 adjacent to the carbon atom bearing the methine proton.

4- $[^2H_3]$ -3-hydroxybutyric acid

The above ester (0.411 g., 0.003 m.) was hydrolyzed according to the method given for the undeuteriated analogue. Yield 0.31 g. (97%); ν max (liquid film) 3450, 2650 (OH), 2250 (CD), 1720 cm.$^{-1}$ (C = O, acid); δ ($CDCl_3$) 6.95 (singlet, OH), 4.13 (multiplet, CH), 3.68 (singlet, OH), 2.40 (doublet, CH_2, J = 6.40 Hz.).

Ethyl 3-hydroxyvalerate

This was prepared by the Reformatski reaction on n-propionaldehyde (3.54 g., 0.061 m.) according to the method of Adickes and Andresen[57] as previously described. Yield 4.0 g (56%); b.p. 58 - 60°C/0.9 mm. (lit. b.p. 75 - 79°C/9 mm.);

ν max (liquid film) 3500 (OH), 1730 cm.$^{-1}$ (C = O, ester); δ ($CDCl_3$) 3.82 - 4.35 (3 protons, quartet, J = 7.3 Hz. for CH_2 of ester group overlapping with the multiplet for CH), 3.04 (singlet, OH), 2.43 (doublet, CH_2, J = 6.6 Hz.), 0.70 - 1.75 (8 protons, multiplet, 2 x CH_3, CH_2).

3-Hydroxyvaleric acid

Saponification of the above ester (2.50 g., 0.018 m.) by the method previously described afforded the title compound. Yield 2.06 g. (98%); ν max (liquid film) 3400, 2650 (OH), 1716 cm.$^{-1}$ (C = O, acid).

Ethyl 3-hydroxyhexanoate

Again prepared by the Reformatski reaction on n-butyraldehyde (4.40 g., 0.061 m.) according to the method of Adickes and Andresen.[57] Yield 3.42 g. (43.5%); b.p. 68 - 75°C/0.9 mm. (lit. b.p. 95 - 98°C/12 mm.); ν max (liquid film) 3490 (OH), 1724 cm.$^{-1}$ (C = O, ester).

3-Hydroxyhexanoic acid

Saponification of ethyl 3-hydroxyhexanoate (2.473 g., 0.154 m.) at 0°C with potassium hydroxide (40 ml., 0.020 m.) gave after work-up by the method described above, the hydroxy acid. Yield 2.2 g. (98%). The i.r. spectrum showed OH absorption at 3400 and 2650, and acid-carbonyl absorption at 1710 cm.$^{-1}$.

Ethyl 3-hydroxynonanoate

Again prepared by the Reformatski reaction[57] on n-heptanal (6.95 g., 0.061 m.). Yield 6.74 g. (55%); b.p. 100°C/0.9 mm. (lit. b.p. 145°C/3 mm.); ν max (liquid film) 3495 (OH), 1724 cm.$^{-1}$ (C = O, ester).

3-Hydroxynonanoic acid

Was prepared from the above ester (2.664 g., 0.0132 m.) according to the method previously described. Yield 2.29 g. (99%). m.p. 61°C (lit. m.p. 61°C); ν max (nujol mull) 3550, 2650 (OH), 1680 cm.$^{-1}$ (C = O, acid).

Hydracrylic acid.[55]

Ethylene cyanohydrin (12.50 g., 0.176 m.) was slowly added to a stirred solution of 8N aqueous sodium hydroxide (25 ml.) maintained below 20°C. After 16 hours, the solution was then slowly heated to 70°C, while a current of air was drawn through the reaction mixture. Evaporation to dryness gave a white solid which was dissolved in aqueous methanol (1 : 1) and filtered through amberlite resin IR-20 (H). The acidic filtrate was collected and concentrated in vacuo to yield a pale straw coloured viscous oil. Yield 8.55 g. (54%); ν max (liquid film) 1708 cm.$^{-1}$ (C = O, acid). Although mass spectrometry did not indicate the presence of a stable molecular ion, an m-18 ($-H_2O$) peak at m/e 72 was observed.

3,4-Dibromobutyric Acid.[102]

This was prepared by the method of Fichter and Sonneborn[102] from vinyl acetic acid (1 g., 0.011 m.). Yield 1.60 g. (60%); m.p. 47 - 48°C (lit., 48 - 50°C).

N,N-Dicyclohexycarbodiimide.

This was prepared by the method of Albertson.[47] Yield 13.5 g. (69%); m.p. 30°C, (lit. m.p. 34 - 35°C).

1-Ethyl-3-(3-dimethylaminopropyl)-carbodiimide.[53,54]

This compound was prepared in 40% yield according to the procedure of Sheehan et al.[53] The liquid obtained had a b.p. 53 - 54°C/0.60 mm. in agreement with the literature value.

O- $[^2H_1]$ -Methyl alcohol.[61]

Deuterium oxide (3.26 g., 0.163 m.), dimethyl oxalate (23.6 g., 0.200 m.) and anhydrous sodium carbonate (21.2g, 0.200 m.) were heated under reflux overnight. After cooling, the deuteriomethanol was distilled (b.p. 65°C) from the resulting slurry. Yield 11.0 g. (90%); δ (neat) 2.87 (singlet, CH_3).

O- $[^2H_1]$ -Ethyl alcohol.[64]

This was prepared from diethyl oxalate (29.2 g., 0.200 m.) according to the method described above. Yield 11.1 g. (73%).

S-N-benzyloxycarbonyl-L-ornithine.[48,49]

To L-ornithine monohydrochloride (2.23 g., 0.0133 m.) dissolved in boiling water (25 ml.) was added basic copper carbonate (2.50 g.). After cooling, the unreacted copper carbonate was removed by filtration. The filtrate was then cooled to 0°C, magnesium oxide (2.30 g.) added with stirring and the resulting mixture treated with benzyl chloroformate (2.30 ml.) portionwise over a 30 minute period. After precipitation of the copper complex was complete, the blue solid was collected and washed successively with water, ethanol, and diethyl ether. The copper complex (4.50 g.) was dissolved in 2N hydrochloric acid (75 ml.) and ethylenediaminetetracetic acid (0.1N., 150 ml.) added. Upon cooling, a solid precipitated which was removed by filtration, washed with water and recrystallized from water-ethanol (1 : 1) to give the title compound. Yield 3.12 g. (90%); m.p. 255 - 256°C (lit. m.p. 253 - 255°C); ν max (nujol mull) 1684 $cm.^{-1}$ (C = O, acid and benzyloxycarbonyl).

Methyl δ -N-benzyloxycarbonyl-L-ornithine ester hydrochloride

δ -N-Benzyloxycarbonyl-L-ornithine (1.00 g., 0.0036 m.) was suspended in anhydrous methanol (5 ml.) and the cooled solution (5°C) saturated with anhydrous hydrogen chloride. Dimethyl sulphite[52] (2.20 g., 0.20 m.) was added and the reaction mixture heated to 60°C for 30 minutes. Evaporation of the solvent under reduced pressure afforded a solid which recrystallized from acetone to give the title compound. Yield 1.10 g. (97%); m.p. 134 - 135°C (lit. m.p. 132 - 134°C); ν max (nujol mull) 3340 (NH), 1738 (C = O, ester), 1682 cm.$^{-1}$ (C = O, benzyloxycarbonyl); δ ($CDCl_3$) 8.71 - 9.04 (broad singlet, NH_3), 7.25 (singlet, 5 benzenoid protons), 5.55 - 5.90 (broad multiplet, NH), 5.10 (singlet, CH_2), 3.90 - 4.25 (multiplet, CH), 3.67 (singlet, CH_3), 3.00 - 3.30 (multiplet, 2 protons, NCH_2), 1.50 - 2.20 (broad multiplet, CH_2CH_2).

Methyl α - [N-(3-hydroxybut-4- [$^2H_3$] -yroyl)] - δ -(N-benzyloxycarbonyl)-L-ornithine ester hydrochloride

4- [$^2H_3$] -3-Hydroxybutyric acid (0.350 g., 0.0033 m.) was added to a previously cooled homogeneous solution (0°C) of the above ester (1.043 g., 0.0033 m.), 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (0.527 g., 0.0034 m.) and

methylene chloride (25 ml.). After 4 hours at 0°C the solution was washed successively with water, 1N hydrochloric acid, water, 1N potassium bicarbonate, and water. The dried solution (Na_2SO_4) was evaporated under reduced pressure to give the title compound. Yield 1.00 g. (83%); m.p. 73 - 74°C; ν max (nujol mull) 3350 (NH), 2250 (CD), 1742 (C = O, ester), 1684 (C = O, benzyloxycarbonyl), 1642 $cm.^{-1}$ (C = O, amide); δ ($CDCl_3$) 7.28 (singlet, benzenoid protons), 6.60 (broad peak, NH), 4.89 - 5.12 (3 protons, CH_2, singlet, superimposed on a broad peak, NH), 4.30 - 4.67 (multiplet, CH), 4.12 (broad singlet, OH), 3.64 (singlet, CH_3), 3.00 - 3.30 (multiplet, NCH_2), 2.20 - 2.35 (multiplet, CH_2), 1.32 - 1.92 (broad multiplet, CH_2CH_2).

Eight other substituted L-ornithine derivatives were prepared by the same method and are listed in Table 9.

Table 9.

Table of substituted L-ornithine derivatives

Compound*	Yield	m.p. °C
(4a)	89%	-
(4c)	86%	128 - 129.5
(4d)	80%	88 - 89
(4g)	53%	70 - 72
(4h)	80%	67 - 68
(4i)	76%	68 - 69
(4j)	80%	77 - 78
(4m)	76%	109 - 111

* Compound numbers correspond to those listed for Scheme 3, p.158.

Methyl α - [N-(3-oxobutyroyl)] - δ -(N-benzyloxycarbonyl)-L-ornithine ester

A mixture of (4a) (Scheme 3, p.158) (1.50 g., 0.003 m.), acetone (20 ml.) and p-toluene sulphonic acid (0.001 g.) were refluxed until t.l.c. ($CHCl_3$-methanol on silica gel, 9 : 1) showed the disappearance of (4a). The reaction was generally

complete after 15 hours. Concentration under reduced pressure afforded an oil which was dissolved in methylene chloride and washed with 1N potassium bicarbonate, then water and dried over anhydrous sodium sulphate. Removal of the solvent under vacuo gave the title compound. Yield 1.30 g. (97%); δ ($CDCl_3$) 7.26 (singlet, benzenoid protons), 5.02 (singlet, CH_2), 4.33 - 4.73 (multiplet, CH), 3.70 (singlet, CH_3), 3.40 (singlet, CH_2), 2.95 - 3.40 (multiplet, NCH_2), 2.23 (singlet, CH_3), 1.36 - 1.90 (broad multiplet, CH_2CH_2)

Methyl α - [N-(3-hydroxypropionoyl)] - δ -(N-benzyloxycarbonyl)-L-ornithine ester

Hydracrylic acid (0.569 g., 0.0063 m.) was added to a previously cooled homogeneous solution (0°C) of methyl δ-N-benzyloxycarbonyl-L-ornithine ester hydrochloride (2.00 g., 0.0063 m.), 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (1.008 g., 0.0065 m.) and methylene chloride (60 ml.). After 4 hours at 0°C, the solution was washed successively with water, 1N hydrochloric acid, water, 1N potassium bicarbonate and water. The dried solution (Na_2SO_4) was evaporated under reduced pressure to afford a solid which was shown by t.l.c. ($CHCl_3$-methanol on silica gel, 9 : 1) to contain two products and these were separated by preparative t.l.c. The less polar

product which was recrystallized from ethyl acetate - methanol (2 : 1) was identified as (4f) (Scheme 3, p.158). Yield 0.027 g. (10%); m.p. 98 - 99°C. Mass spectrometry showed the presence of a molecular ion at m/e 424.

The more polar product was recrystallized from ethyl acetate and identified as the title compound. Yield 1.20 g. (54%); m.p. 68 - 69°C; ν max (nujol mull) 3350 (NH), 1736 (C = O, ester), 1690 (C = O, benzyloxycarbonyl) 1640 $cm.^{-1}$ (C = O, amide).

Methyl α - [N-(3-oxobutyroyl)] -L-ornithine ester hydrochloride

Methyl α - [N-(3-oxobutyroyl)] - δ -(N-benzyloxycarbonyl)-L-ornithine ester (1.30 g., 0.0036 m.) was dissolved in a mixture of aqueous methanol (methanol-water, 40 ml, 8 : 1) and 1N hydrochloric acid (3.6 ml.) and hydrogenated at atmospheric pressure and room temperature in the presence of 10% palladium on charcoal (0.6 g.). The reaction was generally complete after 1 hour. The residue obtained after removal of catalyst and solvent was partitioned between ethyl acetate and water (1 : 1), and the aqueous fraction concentrated (reduced pressure) and dried overnight over potassium hydroxide pellets under vacuo to afford the title compound as a glass.

Yield 0.86 g. (90%); ν max ($CHCl_3$) 1724 (C = O, ester), 1650 $cm.^{-1}$ (C = O, amide); δ (DMSO) 7.80 - 8.20 (broad multiplet, NH_3), 4.10 - 4.40 (multiplet, CH), 3.58 (singlet, CH_3), 3.32 (singlet, CH_2), 2.60 - 2.90 (broad multiplet, NCH_2), 2.10 (singlet, CH_3) 1.40 - 1.82 (broad multiplet, CH_2CH_2).

Nine other benzyloxycarbonyl-L-ornithine derivatives were hydrogenated by this general procedure and their yields are listed in Table 10.

Table 10

Hydrogenolysis products of some benzyloxycarbonyl-L-ornithine derivatives

Compound*	Yield
(5b)	89%
(5c)	88%
(5d)	90%
(5e)	90%
(5f)	92%
(5g)	98%
(5h)	97%
(5i)	91%
(5j)	89%

*Compound numbers correspond to those listed for Scheme 3, p. 158

Hydrogenolysis of methyl ∝ - [N-(3,4-dibromobutyroyl)] - δ-(N-benzyloxycarvonyl)-L-ornithine ester

The title compound (0.384 g., 0.0073 m.) was dissolved in a mixture of aqueous methanol (methanol-water, 10 ml., 8 : 1) and 1N hydrochloric acid (0.7 ml.) and hydrogenated at atmospheric pressure and room temperature in the presence of 10% palladium on charcoal (0.20 g.). The residue obtained after removal of catalyst and solvent, was partitioned between ethyl acetate and water (1 : 1) and the aqueous layer concentrated (reduced pressure) and dried overnight over potassium hydroxide pellets under vacuo to afford methyl ∝ -(N-butyroyl)-L-ornithine ester hydrochloride. Yield quantitative. Mass spectrometry did not show a parent molecular ion but an m-36 peak at m/e 216 was observed.

(+) 3-Acetamido-piperid-2-one

To methyl ∝ -(N-acetyl)-L-ornithine ester hydrochloride (0.880 g., 0.0022 equiv.) dissolved in aqueous methanol (10 ml., 1 : 1) was added silver oxide (0.245 g., 0.0022 equiv.) with stirring. After 16 hours the precipitate was removed by filtration and washed with methanol. The filtrate was saturated with hydrogen sulphide and then filtered through a thin layer of norit. Concentration of the filtrate under

reduced pressure afforded the required compound which recrystallized from ethyl acetate. Yield 0.33 g. (97%); m.p. 159 - 160°C; ν max (nujol mull) 3300 (NH), 1672 (C = O, lactam), 1656 cm.$^{-1}$ (C = O, amide); (Found: C, 53.60; H, 7.57; N, 17.77. $C_7H_{12}N_2O_2$ requires C, 53.83; H, 7.74; N, 17.94%).

(+) 3-(3-Oxobutanamido)-piperid-2-one

This was prepared from methyl α - [N-(3-oxobutyroyl)] - L-ornithine ester hydrochloride (0.483 g., 0.0018 m.) as above in 96% yield, m.p. 83 - 84°C; (Found: C, 54.55; H, 7.15; N, 14.11. $C_9H_{14}N_2O_3$ requires C, 54.53; H, 7.12; N, 14.13%).

3-(3-Hydroxypropanamido)-piperid-2-one

Methyl α - [N-(3-hydroxypropionoyl)] -L-ornithine ester hydrochloride (0.285 g., 0.0011 m.) was dissolved in aqueous methanol (10 ml., 1 : 1) and filtered through amberlite resin IR-45 (25 g., 60 - 80 mesh). Concentration of the filtrate under vacuo afforded the required product which recrystallized from methylene chloride. Yield 0.196 g. (96%); m.p. 131.5 - 132°C; ν max (CH_2Cl_2) 1673 (C = O, lactam), 1658 cm.$^{-1}$ (C = O, amide); (Found: C, 51.56; H, 7.62; N, 15.10. $C_8H_{14}N_2O_3$ requires C, 51.56; H, 7.58; N, 15.04%).

The substituted piperid-2-one derivatives shown in Table 11 were prepared by the same method.

Table 11

Substituted piperid-2-one derivatives

Compound*	Recrystallized from	Yield	m.p. °C
(6c)	diethyl ether	98%	92 - 93
(6e)	ethyl acetate-methanol, 1 : 1	96%	200 - 201
(6f)	ethyl acetate	98%	126 - 128
(6g)	ethyl acetate	95%	109 - 110
(6h)	ethyl acetate	90%	101 - 102
(6i)	ethyl acetate	95%	116 - 117
(6j)	ethyl acetate	94%	127 - 128

* Compound numbers correspond to those listed for Scheme 3, p.158.

Analyses

6c (Found: C, 58.54; H, 8.68; N, 15.02. $C_9H_{16}N_2O_2$ requires C, 58.67; H, 8.75; N, 15.20%).

6f (Found: C, 53.99; H, 8.15; N, 14.18. $C_9H_{16}N_2O_3$ requires C, 53.98; H, 8.06; N, 13.99%).

6g (Found: C, 55.94; H, 8.22; N, 13.16. $C_{10}H_{18}N_2O_3$ requires C, 56.05; H, 8.47; N, 13.08%).

6h (Found: C, 57.83; H, 8.72; N, 12.30. $C_{11}H_{20}N_2O_3$ requires C, 57.87; H, 8.83; N, 12.27%).

6i (Found: C, 62.04; H, 9.59; N, 10.37. $C_{14}H_{26}N_2O_3$ requires C, 62.19; H, 9.69; N, 10.36%).

(+) 3-(3-Oxobut-2-$\left[^2H_2\right]$-anamido-N-$\left[^2H_1\right]$)-1-$\left[^2H_1\right]$-piperid-2-one

To 3-(3-oxobutanamido)-piperid-2-one (0.100 g., 0.0005 m.) dissolved in O-$\left[^2H_1\right]$-ethyl alcohol (0.50 ml.) was added deuterium oxide (0.10 ml.). After stirring for 24 hours, the reaction mixture was concentrated under reduced pressure to give a white solid. This method repeated three times afforded the title compound. Yield 0.1002 g. (99%); m.p. 84 - 85°C. Its n.m.r. spectrum did not show a singlet (CH_2) superimposed on a multiplet (NCH_2) at 3.42.

(+) 3-(3-Hydroxybut-2-$\left[^2H_2\right]$-anamido)-piperid-2-one

To sodium borohydride (0.009 g.) dissolved in O-$\left[^2H_1\right]$-ethyl alcohol-deuterium oxide (0.3 ml., 1 : 2) was added (+) 3-(3-oxobut-2$\left[^2H_2\right]$-anamido-N-$\left[^2H_1\right]$-)-1-$\left[^2H_1\right]$-piperid-2-one (0.1002 g., 0.0005 m.) dissolved in O-$\left[^2H_1\right]$-ethyl alcohol (1 ml.). After stirring for 30 minutes, the reaction mixture was concentrated in *vacuo* and

the product isolated by preparative t.l.c. ($CHCl_3$-methanol on silica gel, 9 : 1) as a colourless gum. Yield 0.065 g. (65%). Its i.r. spectrum did not indicate the presence of a ketone stretching vibration at 1715 $cm.^{-1}$ and the n.m.r. spectrum showed a doublet at δ 1.23 (CH_3) and no signal for the CH_2 group at δ 2.31. Mass spectrometry indicated the presence of a molecular ion at m/e 202.

(+) 3-(3-Hydroxybut-3-[$^2H_1$]-anamido)-piperid-2-one

Reduction of (+) 3-(3-oxobutanamido)-piperid-2-one (0.100 g., 0.0005 m.) with [$^2H_4$] sodium borohydride (0.009 g.) in aqueous ethanol (ethanol - water, 0.3 ml., 1 : 2) according to the procedure above afforded the title compound. Yield 0.0067 g. (67%). Its i.r. spectrum did not indicate the presence of a ketone stretching frequency at 1715 $cm.^{-1}$. The n.m.r. spectrum of the product showed broad singlets at δ1.23 (CH_3) and δ 2.31 (CH_2) and no signal for the CH group between δ 3.84 - 4.50; mass spectrometry indicated the presence of a molecular ion at m/e 201.

(+) 3-(3-Hydroxybutanamido-O-[$^2H_1$]-N-[$^2H_1$]-)-1-[$^2H_1$]-piperid-2-one

A mixture of (+) 3-(3-hydroxybutanamido)-piperid-2-one (0.100 g., 0.0005 m.), O-[$^2H_1$]-ethyl alcohol (0.1 ml.) and deuterium oxide (0.2 ml.) was stirred for 24 hours and

then the reaction solution was concentrated under reduced pressure. This procedure was repeated twice more and the title compound isolated. Yield quantitative.

3-Amino-piperid-2-one

This compound was prepared according to the method of Golankiewicz and Wiewiorowski.[45] Yield 2.79 g. (50%); b.p. 185 - 190°C/1 mm. (lit. b.p. 185 - 190°C/1 mm.).

Pyrolysis of (+) 3-(3-hydroxynonanamido)-piperid-2-one

The above compound (0.200 g.) was pyrolyzed by slowly distilling through a silica tube 9 inches long and maintained at 500°C under a pressure of 1 mm. The receiver of the apparatus was cooled with liquid nitrogen to condense any volatile components generated. The isolation and identification of the products formed are described in the main text of this thesis (p. 68).

Part 5

Synthetic Scheme and Spectral Data

$X(CH_2)_3CHYCO_2R$

3

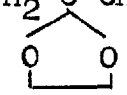
3a X = NH_3Cl, Y = NH_2, R = H

3b X = $NHOCOCH_2C_6H_5$, Y = NH_2, R = H

3c X = $NHOCOCH_2C_6H_5$, Y = NH_3Cl, R = CH_3

$C_6H_5CH_2OCO(CH_2)_3CR_1CO_2CH_3$ (NHCOR$_2$)

4

4a R_1 = H, R_2 = 

4b R_1 = H, R_2 = CH_2COCH_3

4c R_1 = H, R_2 = CH_3

4d R_1 = H, R_2 = $CH_2CH_2CH_3$

4e R_1 = H, R_2 = CH_2CH_2OH

4f R_1 = H, R_2 = $CH_2CH_2OCOCH_2CH_2OH$

4g R_1 = H, R_2 = $CH_2CHOHCH_3$

4h R_1 = H, R_2 = $CH_2CHOHCH_2CH_3$

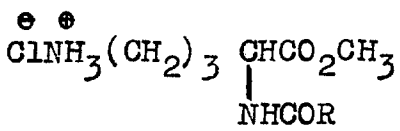
4i R_1 = H, R_2 = $CH_2CHOH(CH_2)_2CH_3$

4j R_1 = H, R_2 = $CH_2CHOH(CH_2)_5CH_3$

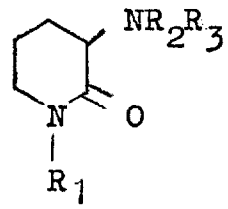
4k R = H, R_2 = $CH_2CHOHCD_3$

4l R = D, R_2 = $CH_2CH_2CH_3$

4m R_1 = H, R_2 = $CH_2CHBrCH_2Br$



5



6

5a R = CH_2COCH_3

5b R = CH_3

5c R = $(CH_2)_2CH_3$

5d R = CH_2CH_2OH

5e R = $CH_2CH_2OCOCH_2CH_2OH$

5f R = $CH_2CHOHCH_3$

5g R = $CH_2CHOHCH_2CH_3$

5h R = $CH_2CHOH(CH_2)_2CH_3$

5i R = $CH_2CHOH(CH_2)_5CH_3$

5j R = $CH_2CHOHCD_3$

6a R_1 = H, R_2 = H, R_3 = $COCH_2COCH_3$

6b R_1 = H, R_2 = H, R_3 = $COCH_3$

6c R_1 = H, R_2 = H, R_3 = $CO(CH_2)_2CH_3$

6d R_1 = H, R_2 = H, R_3 = $COCH_2CH_2OH$

6e R_1 = H, R_2 = H, R_3 = $COCH_2CH_2OCOCH_2CH_2OH$

6f R_1 = H, R_2 = H, R_3 = $COCH_2CHOH\ CH_3$

6g R_1 = H, R_2 = H, R_3 = $COCH_2CHOHCH_2CH_3$

6h R_1 = H, R_2 = H, R_3 = $COCH_2CHOH(CH_2)_2CH_3$

6i R_1 = H, R_2 = H, R_3 = $COCH_2CHOH(CH_2)_5CH_3$

6j R_1 = H, R_2 = H, R_3 = $COCH_2CHOHCD_3$

6k $R_1 = D, R_2 = D, R_3 = COCD_2COCH_3$

6l $R_1 = H, R_2 = H, R_3 = COCD_2CHOHCH_3$

6m $R_1 = H, R_2 = H, R_3 = COCH_2CDOHCH_3$

6n $R_1 = D, R_2 = D, R_3 = COCH_2CHODCH_3$

6o $R_1 = H, R_2 = H, R_3 = COCH{=}CH(CH_2)_5CH_3$

6p $R_1 = H, R_2 = H, R_3 = COCH{=}CHCH_2CH_3$

6q $R_1 = H, R_2 = H, R_3 = COCH{=}CHCD_3$

6r $R_1 = H, R_2 = H, R_3 = COCD{=}CHCH_3$

6s $R_1 = H, R_2 = H, R_3 = H$

Scheme 3

The sequence of reactions employed in the syntheses of substituted piperid-2-ones (p.59)*

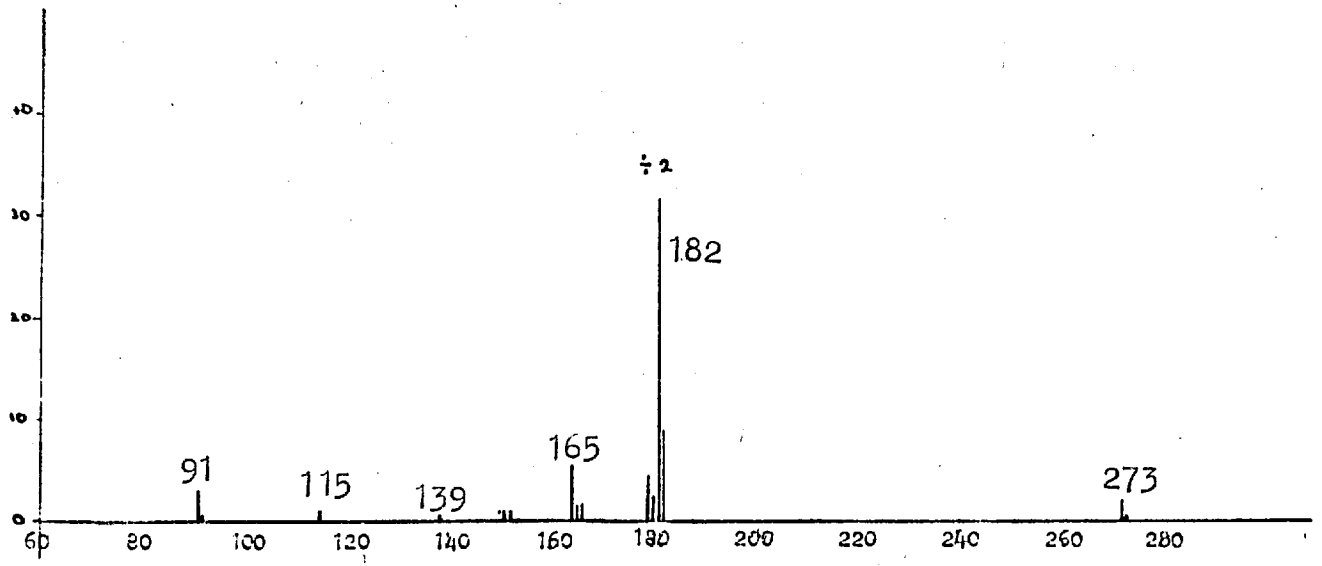


Figure 1

Mass Spectrum of (±) 1-(4'-aminophenyl)-1,2-diphenyl ethane

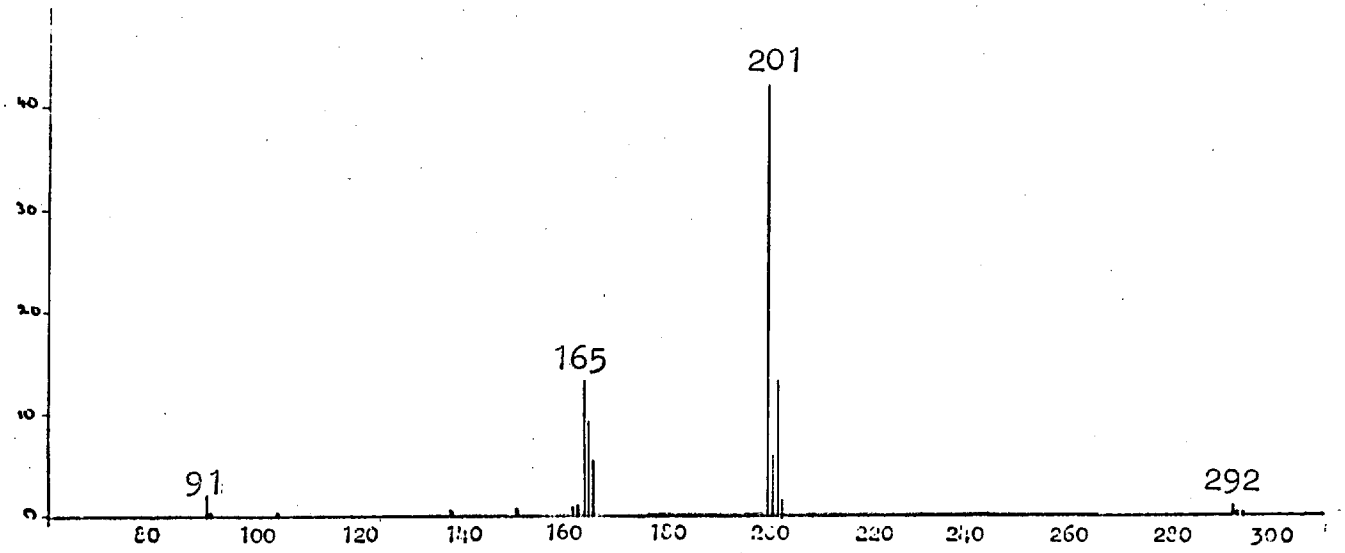


Figure 2

Mass spectrum of (±) 1-(4'-chlorophenyl)-1,2-diphenyl ethane

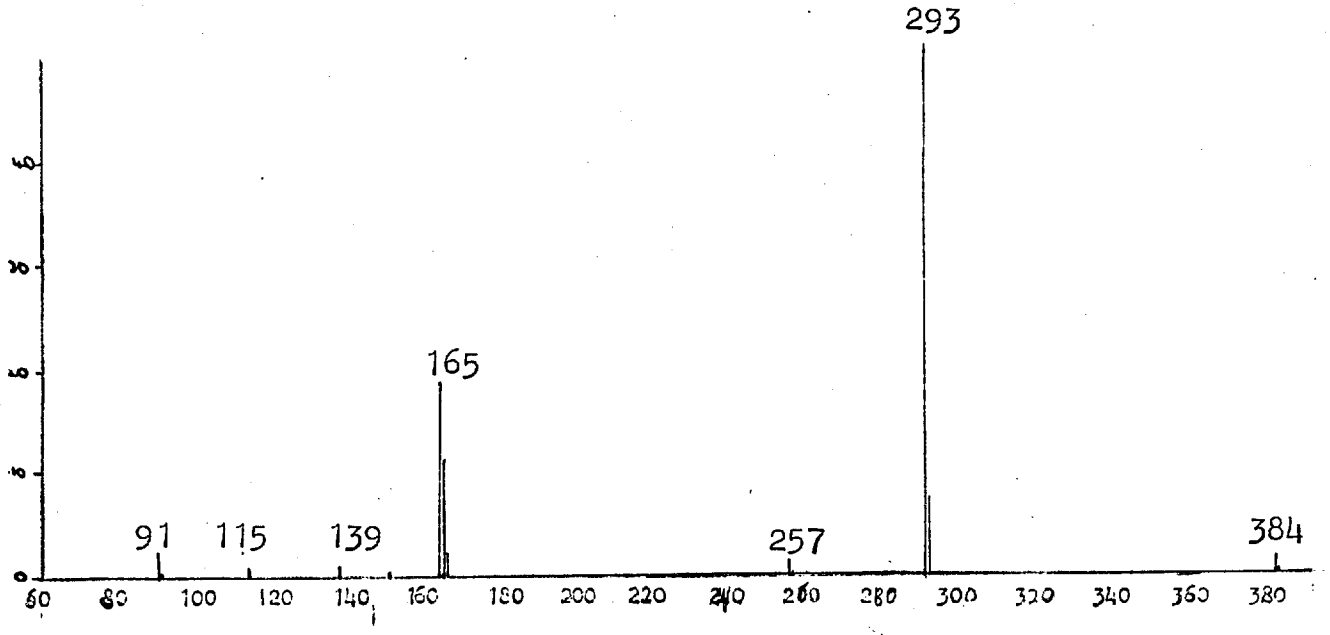


Figure 3

Mass spectrum of (±) 1-(4'-iodophenyl)-1,2-diphenyl ethane

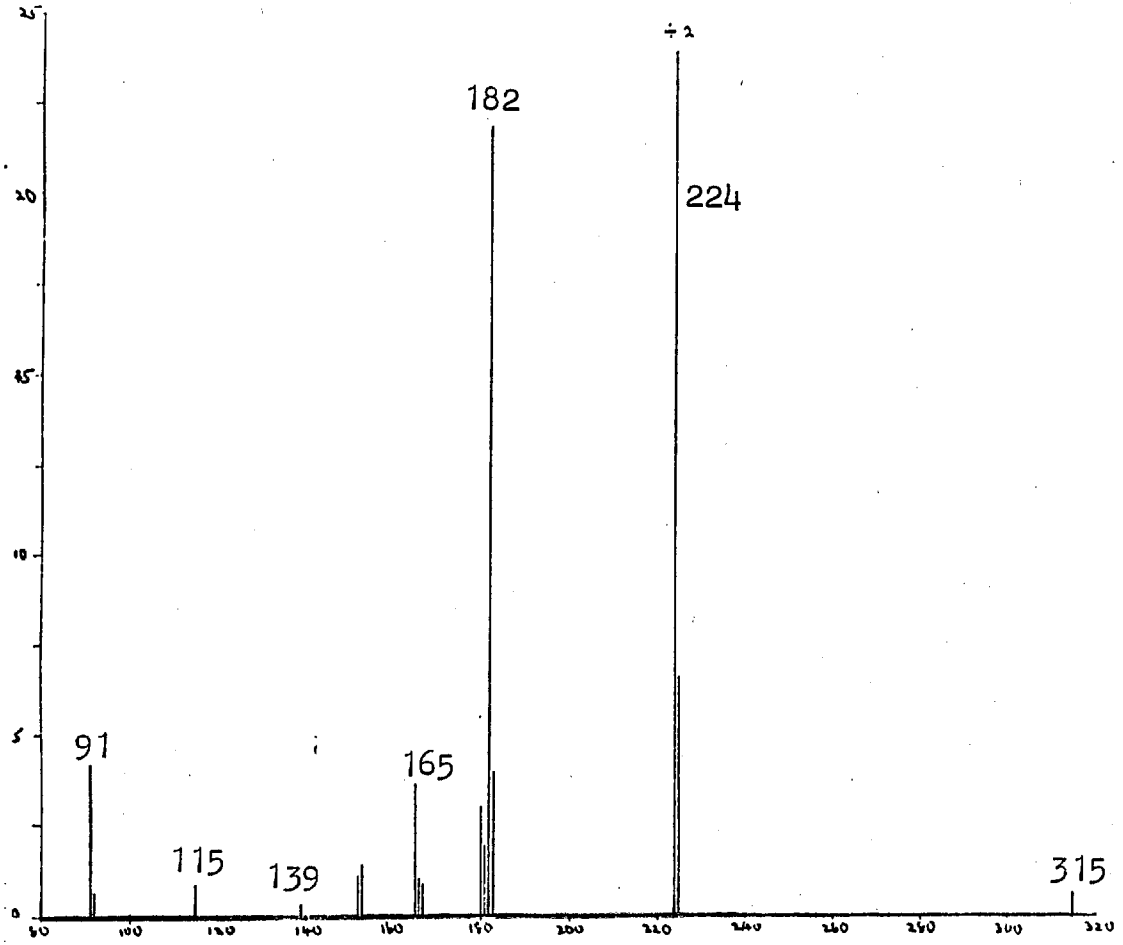


Figure 4

Mass spectrum of (±) 1-(4'-acetamidophenyl)-1,2-diphenyl ethane

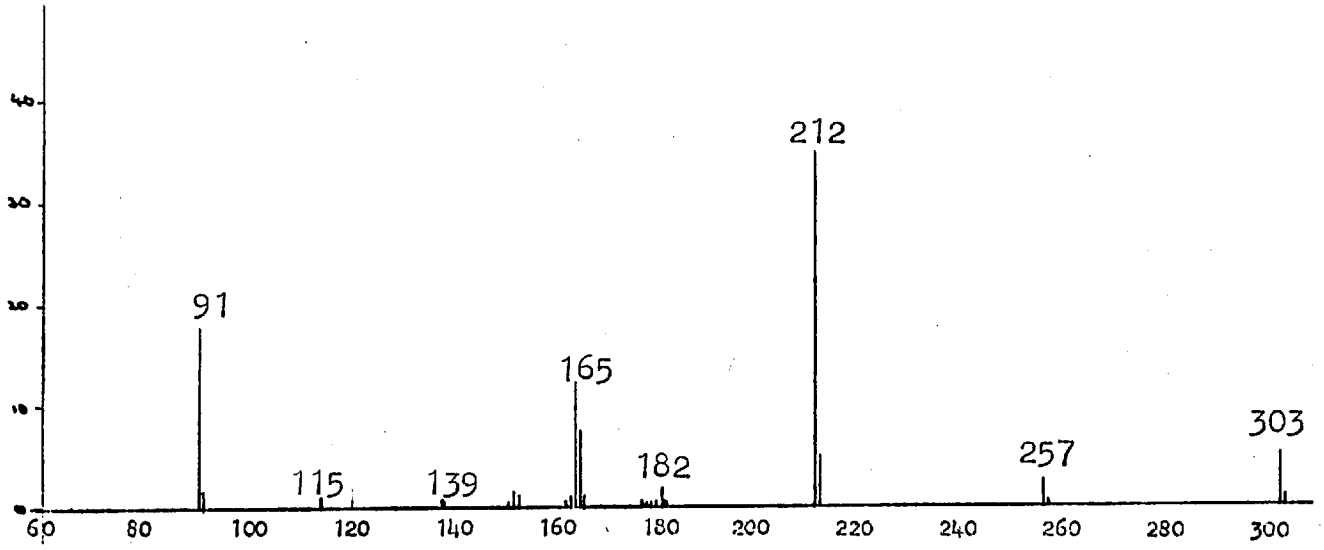


Figure 5

Mass spectrum of (±) 1-(4'-nitrophenyl)-1,2-diphenyl ethane

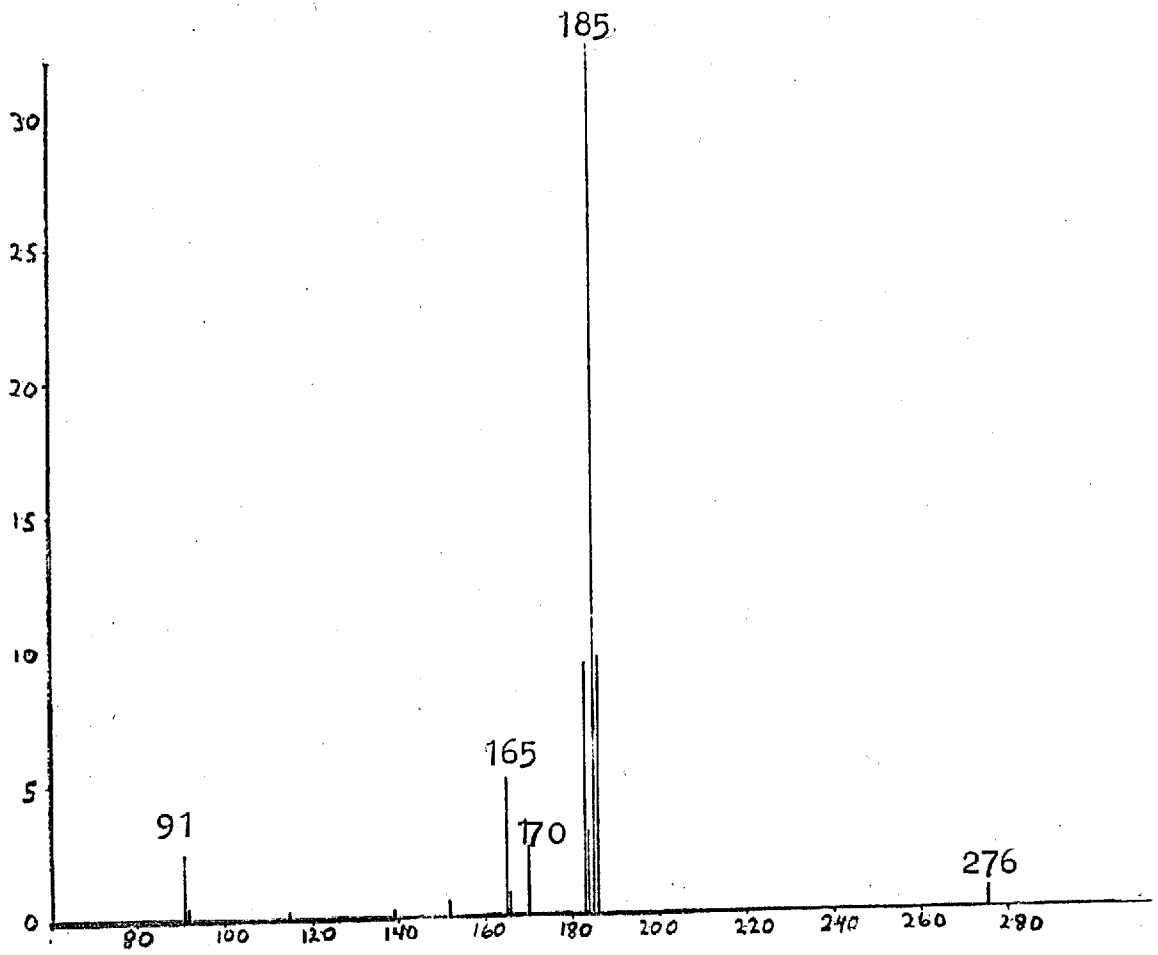


Figure 6

Mass spectrum of (±) 1-(4'-fluorophenyl)-1,2-diphenyl ethane

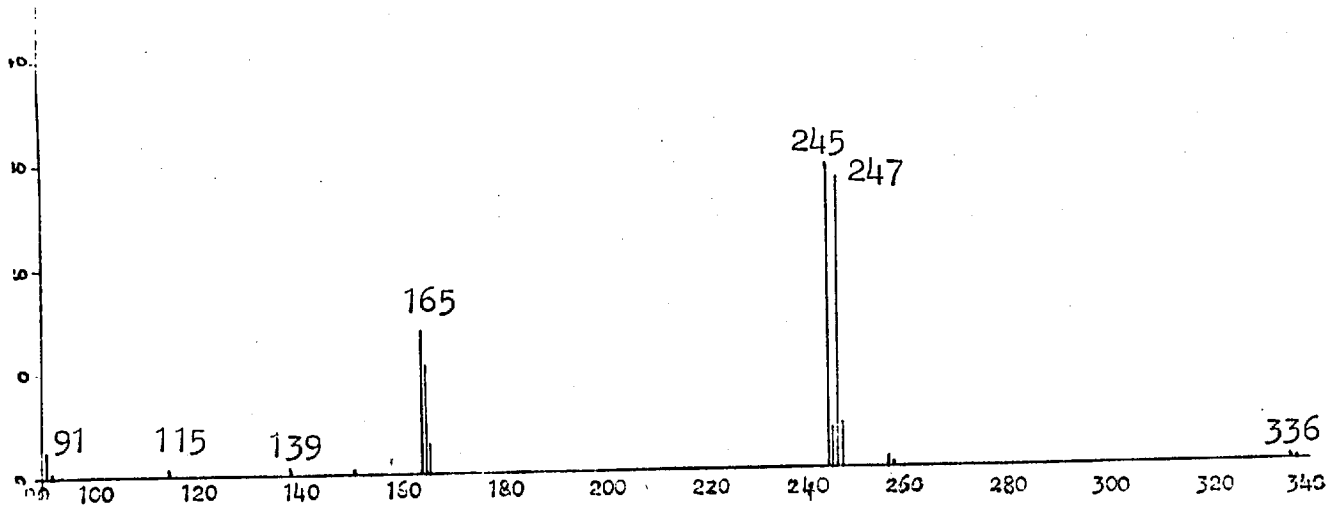


Figure 7

Mass spectrum of (±) 1-(4'bromophenyl)-1,2-diphenyl ethane

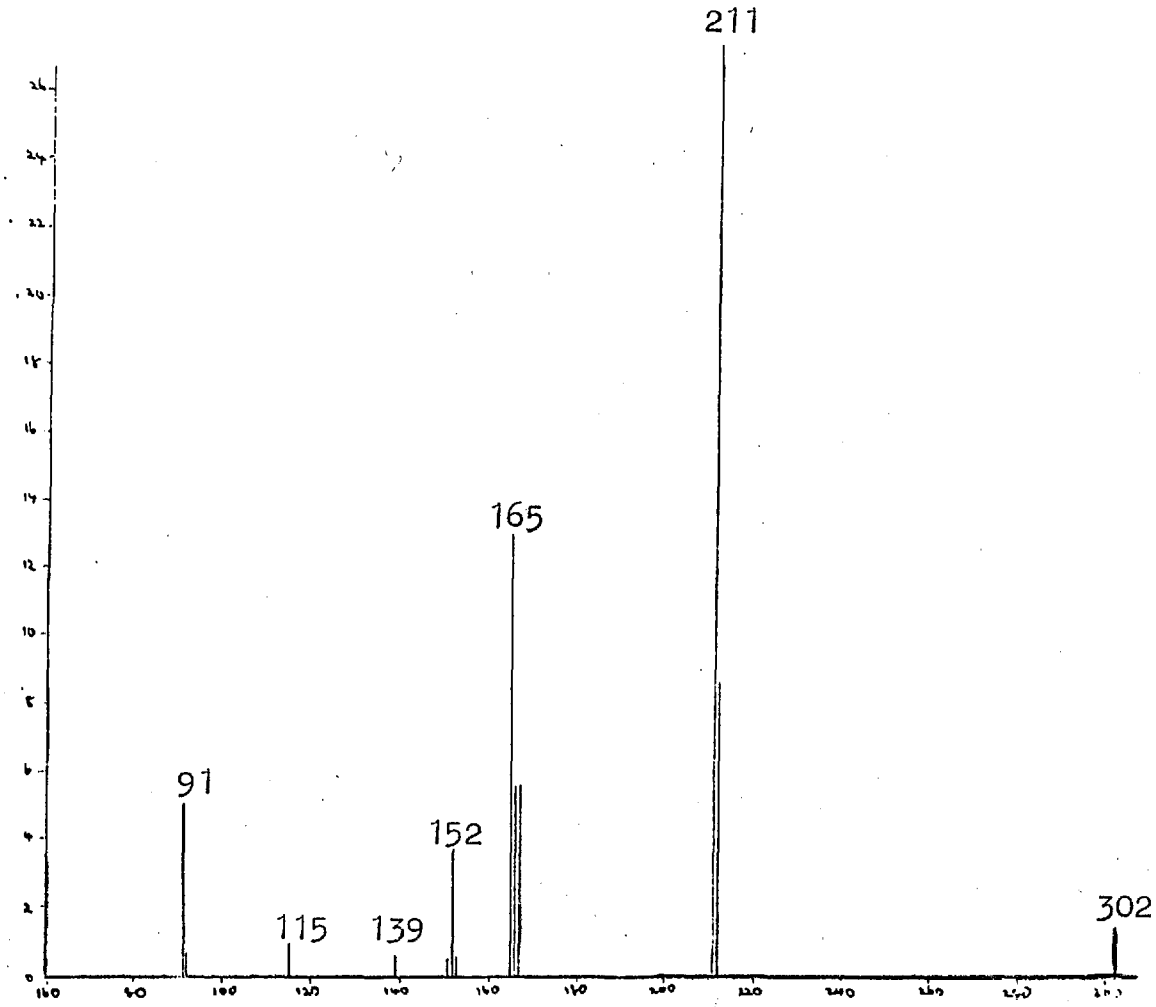


Figure 8

Mass spectrum of (±) 1-(4'-carboxyphenyl)-1,2-diphenyl ethane

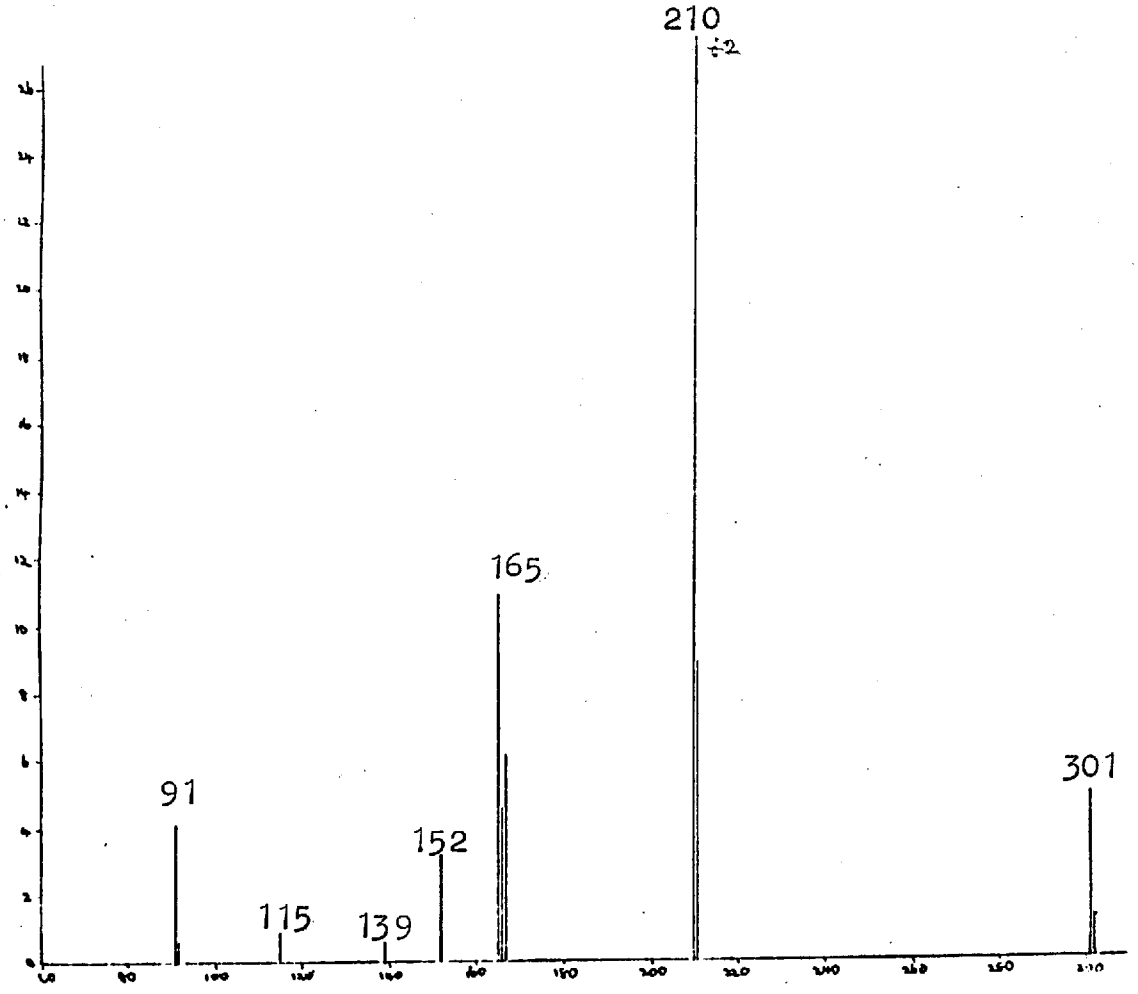


Figure 9

Mass spectrum of 1-(4'-carbamoylphenyl)-1,2-diphenyl ethane

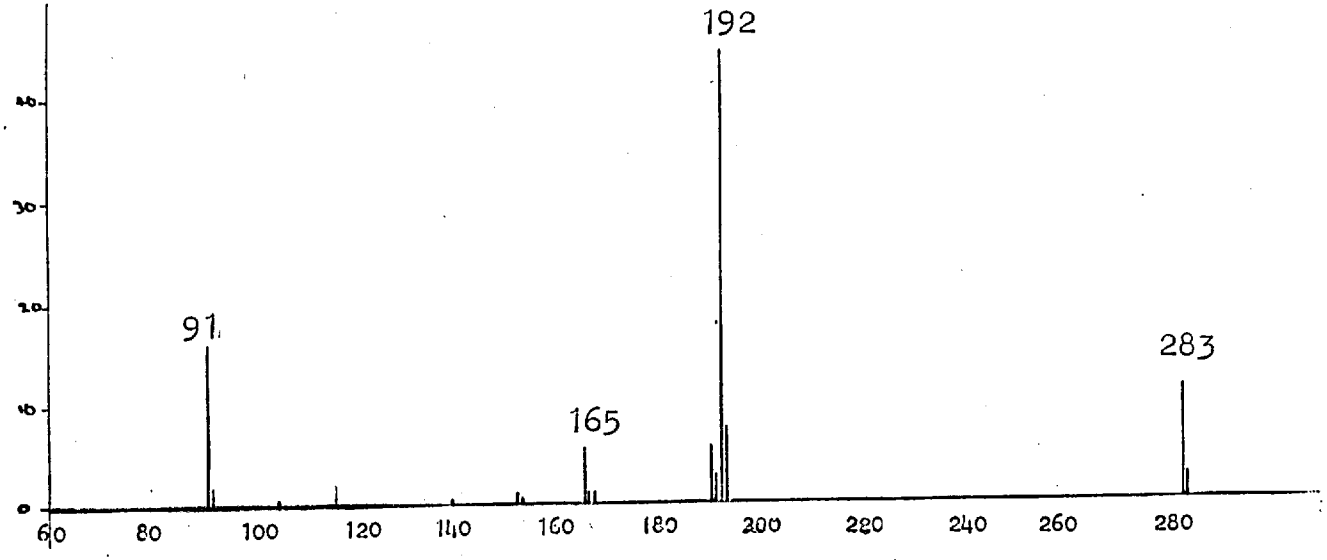


Figure 10

Mass spectrum of 1-(4'-cyanophenyl)-1,2-diphenyl ethane

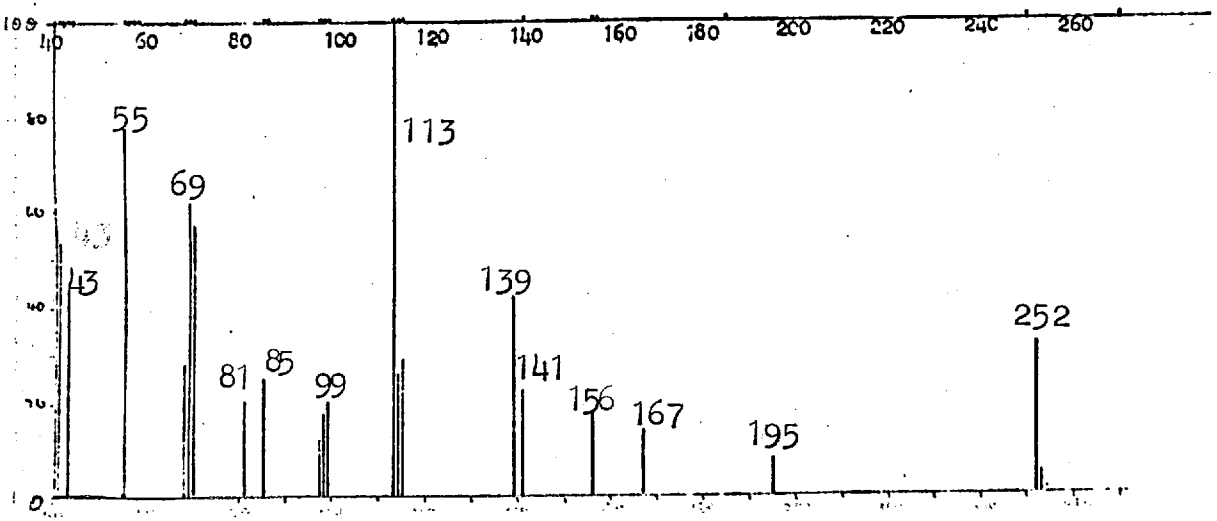


Figure 13

Mass spectrum of 3-(non-2-enamido)-piperid-2-one

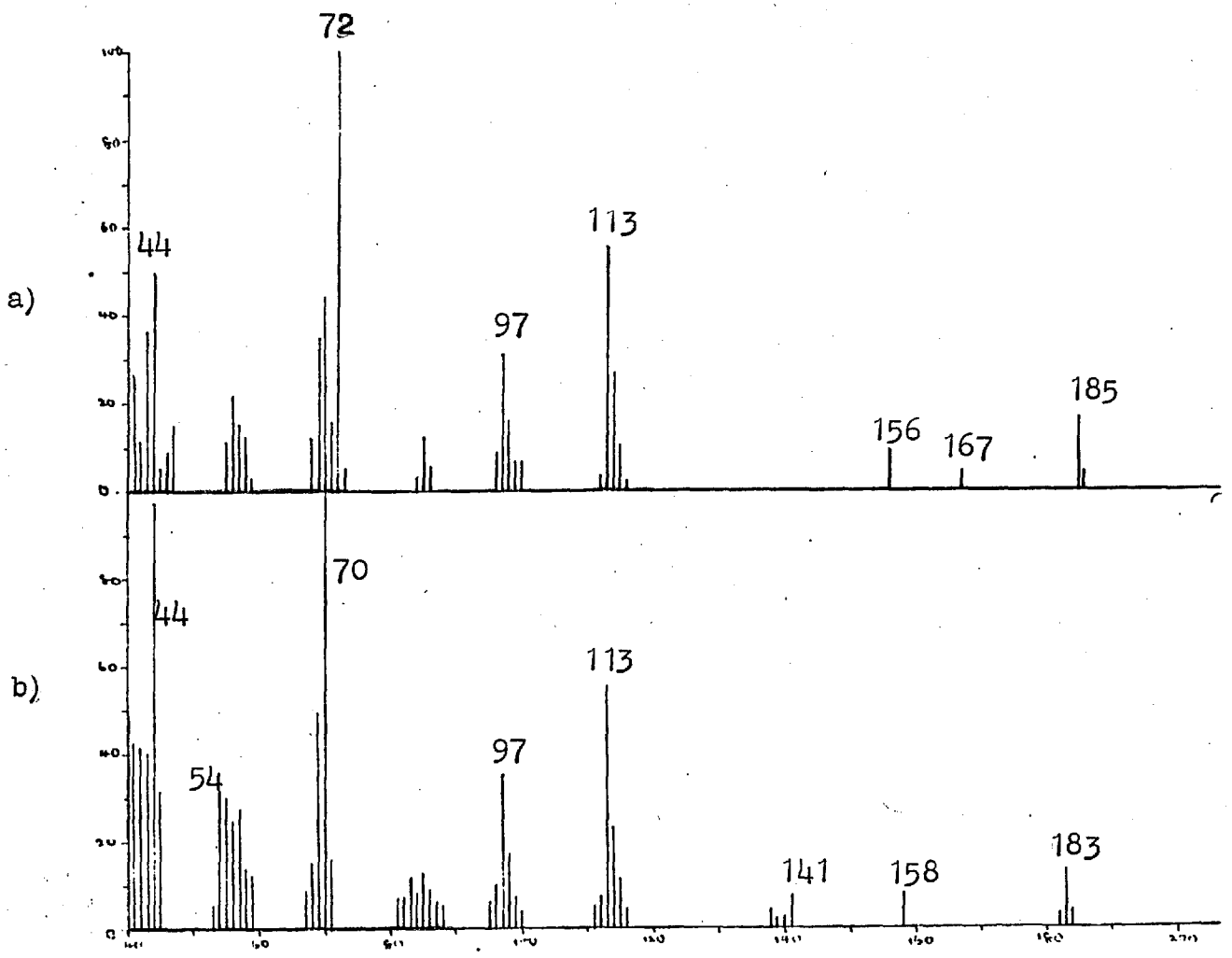


Figure 14

Mass Spectrum of a) (+)3-(4-$\left[^{2}H_{3}\right]$-but-2-enamido)-piperid-2-one,

b) (+)3-(2-$\left[^{2}H_{1}\right]$-but-2-enamido)-piperid-2-one

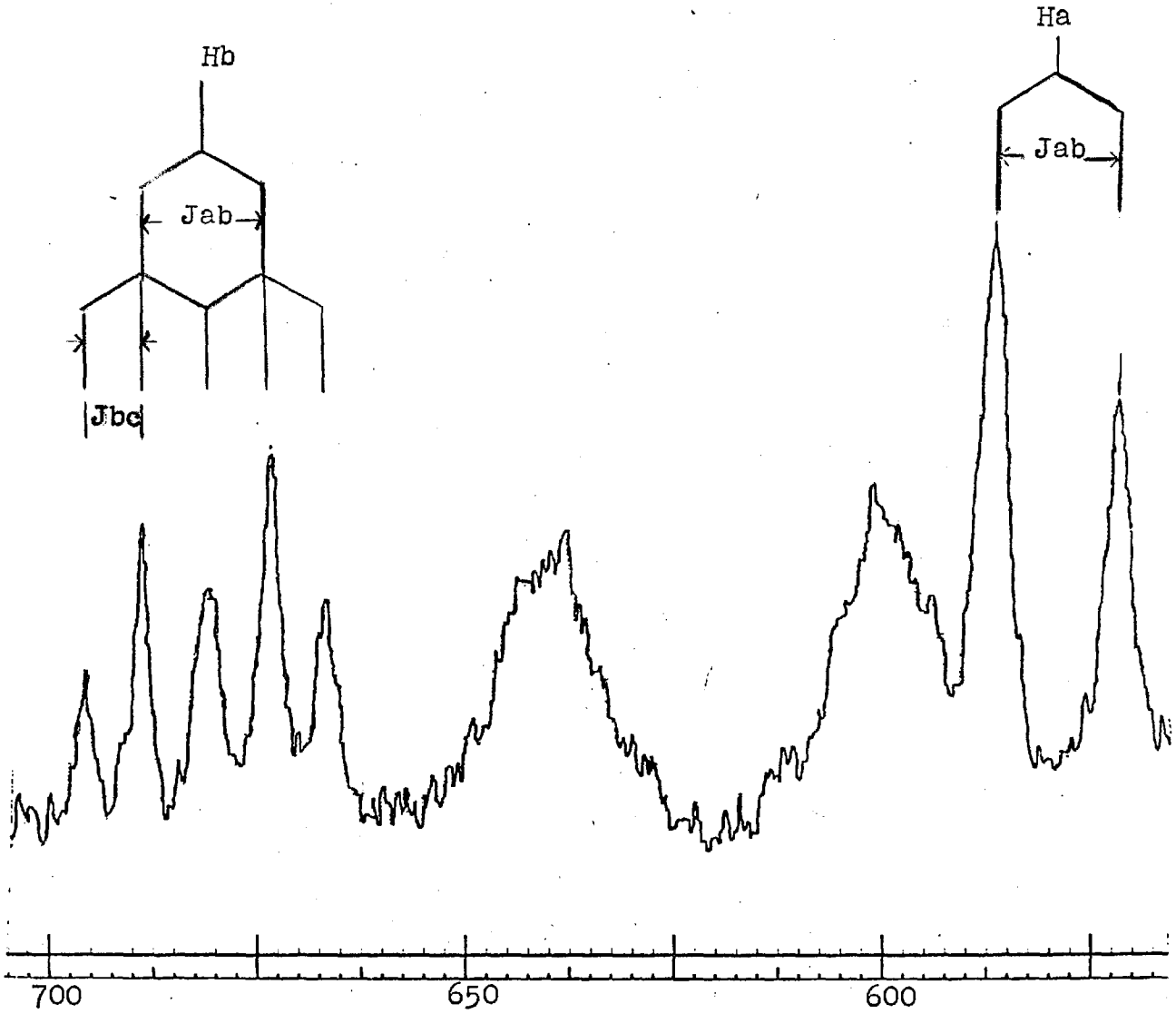


Figure 15

^{1}H nuclear magnetic resonance sub-spectrum of (±)3-(non-2-enamido)-piperid-2-one, 100 MHz., 250 sweep width, 500 sweep offset,

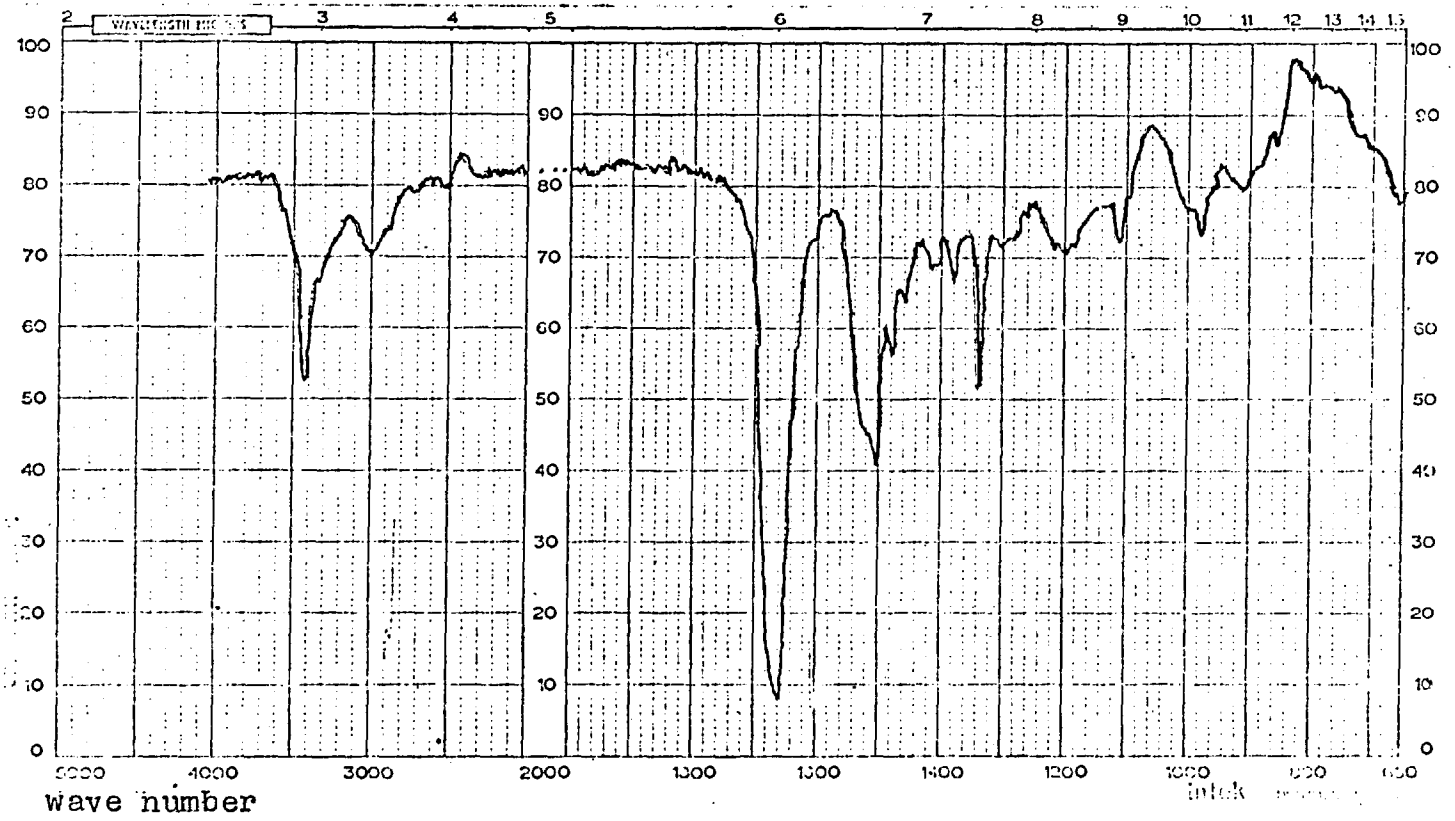


Figure 16

Infrared spectrum (CH_2Cl_2); (±) 3-acetamido-piperid-2-one

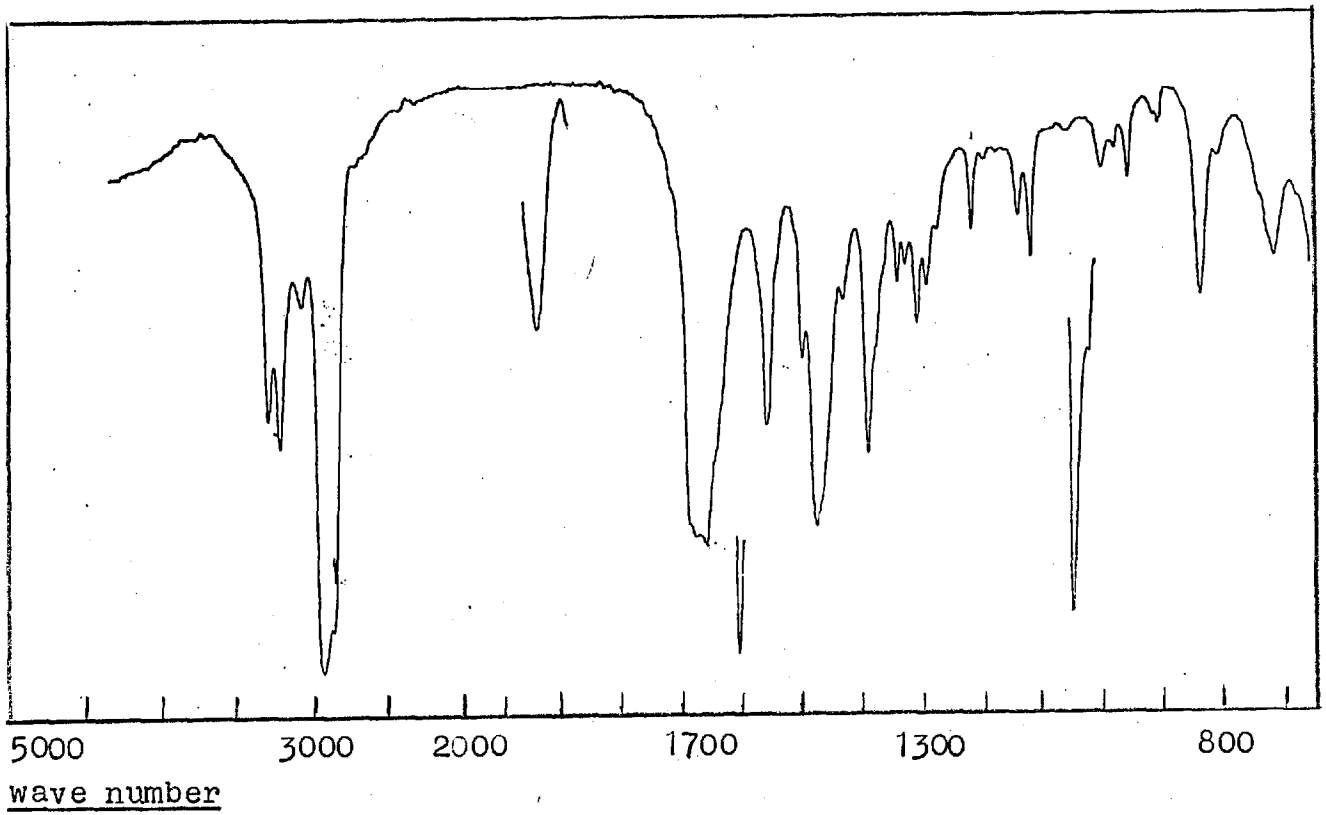


Figure 17

Infrared spectrum (nujol mull); (±) 3-acetamido-piperid-2-one

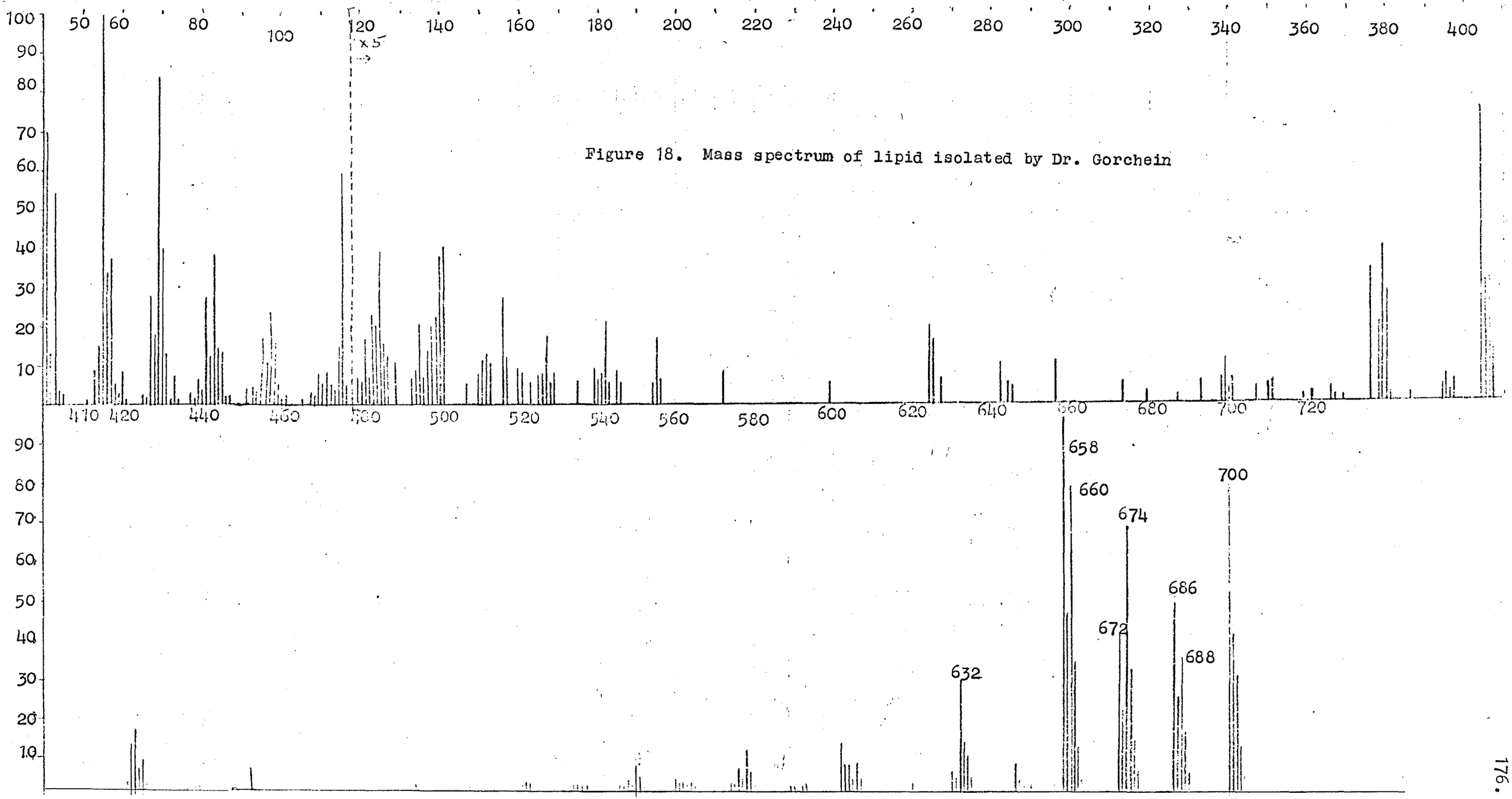
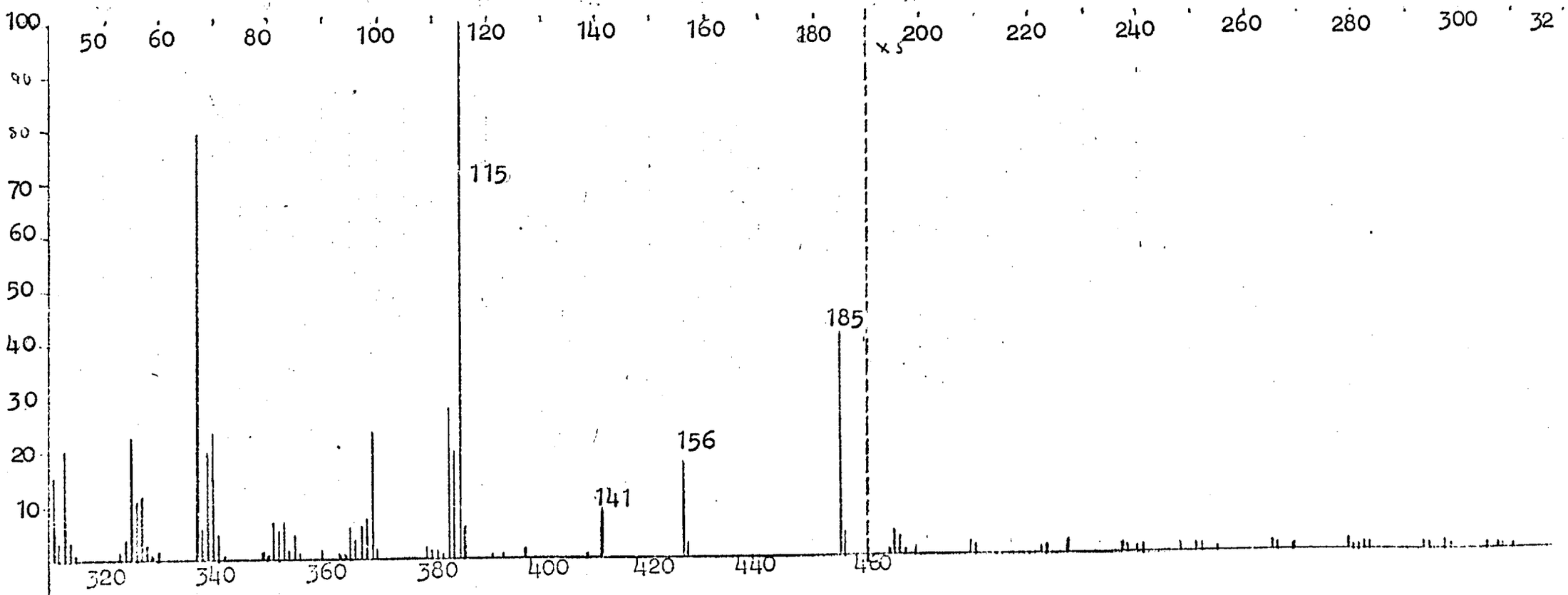


Figure 18. Mass spectrum of lipid isolated by Dr. Gorchein



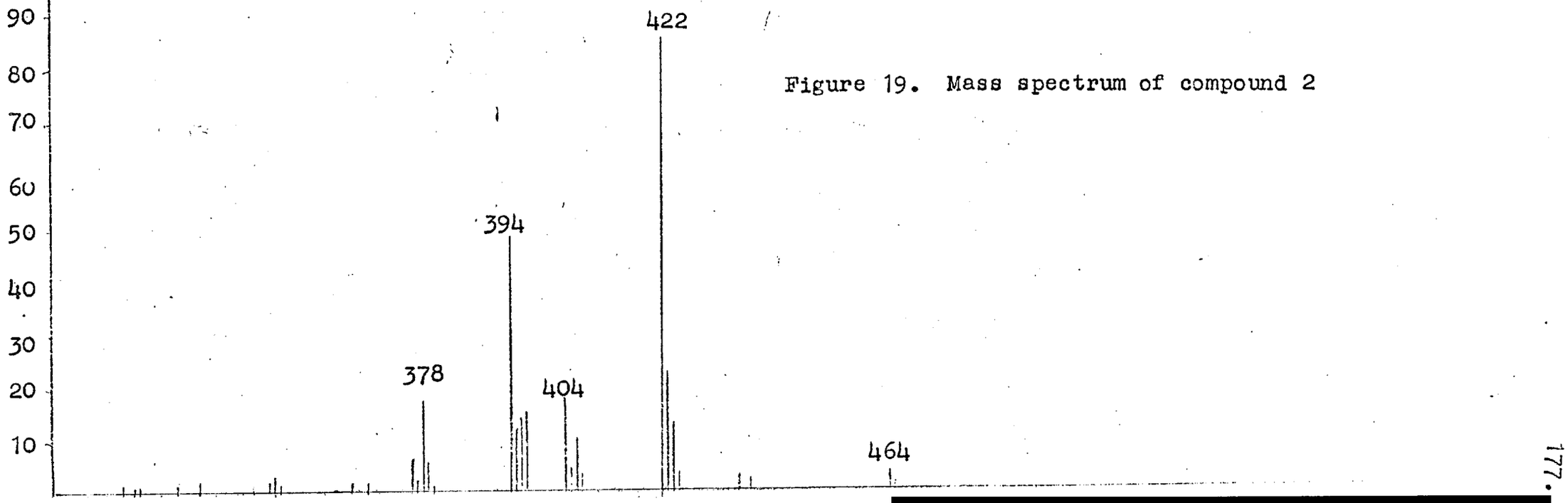


Figure 19. Mass spectrum of compound 2

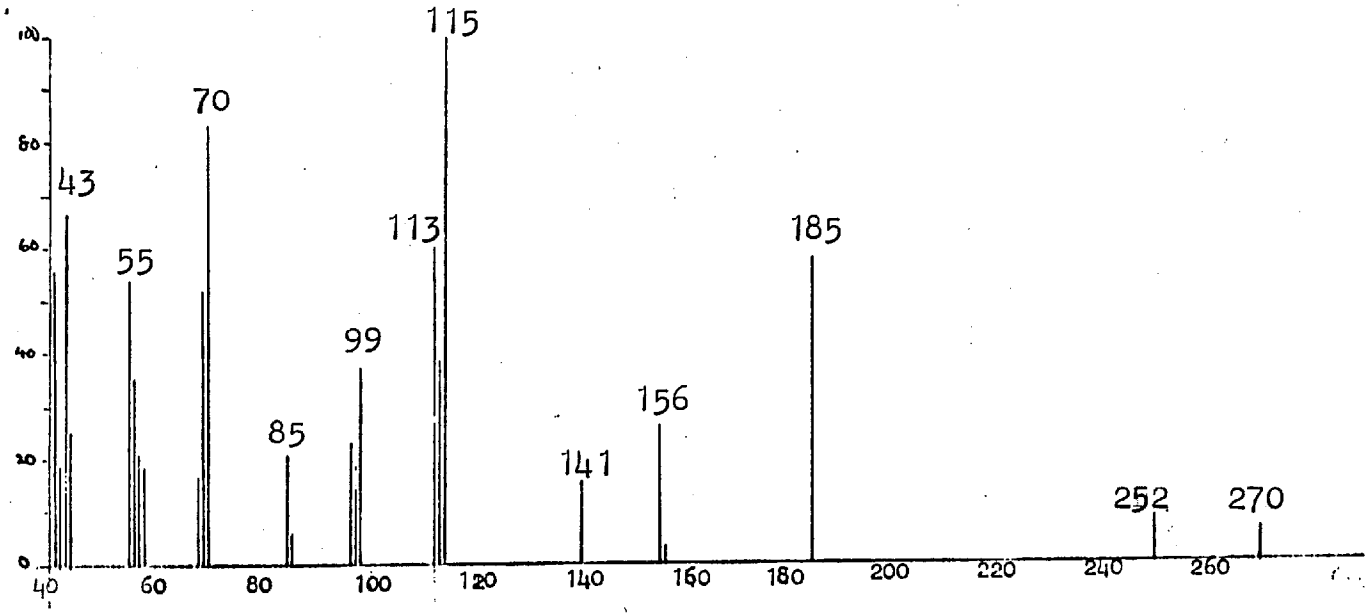


Figure 20

Mass spectrum of (+) 3-(3-hydroxynonanamido)-piperid-2-one

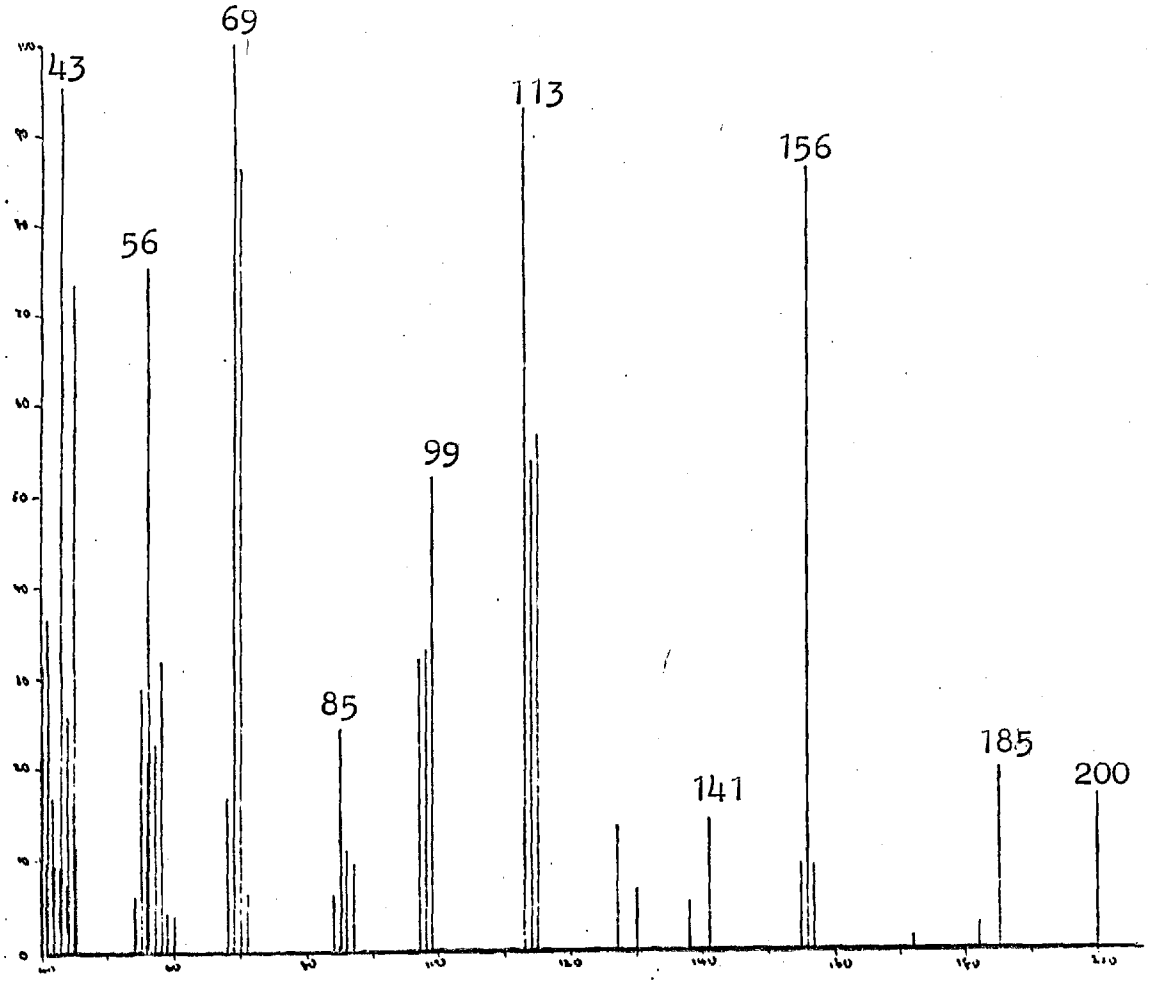


Figure 21

Mass spectrum of (+) 3-(3-hydroxybutanamido)-piperid-2-one

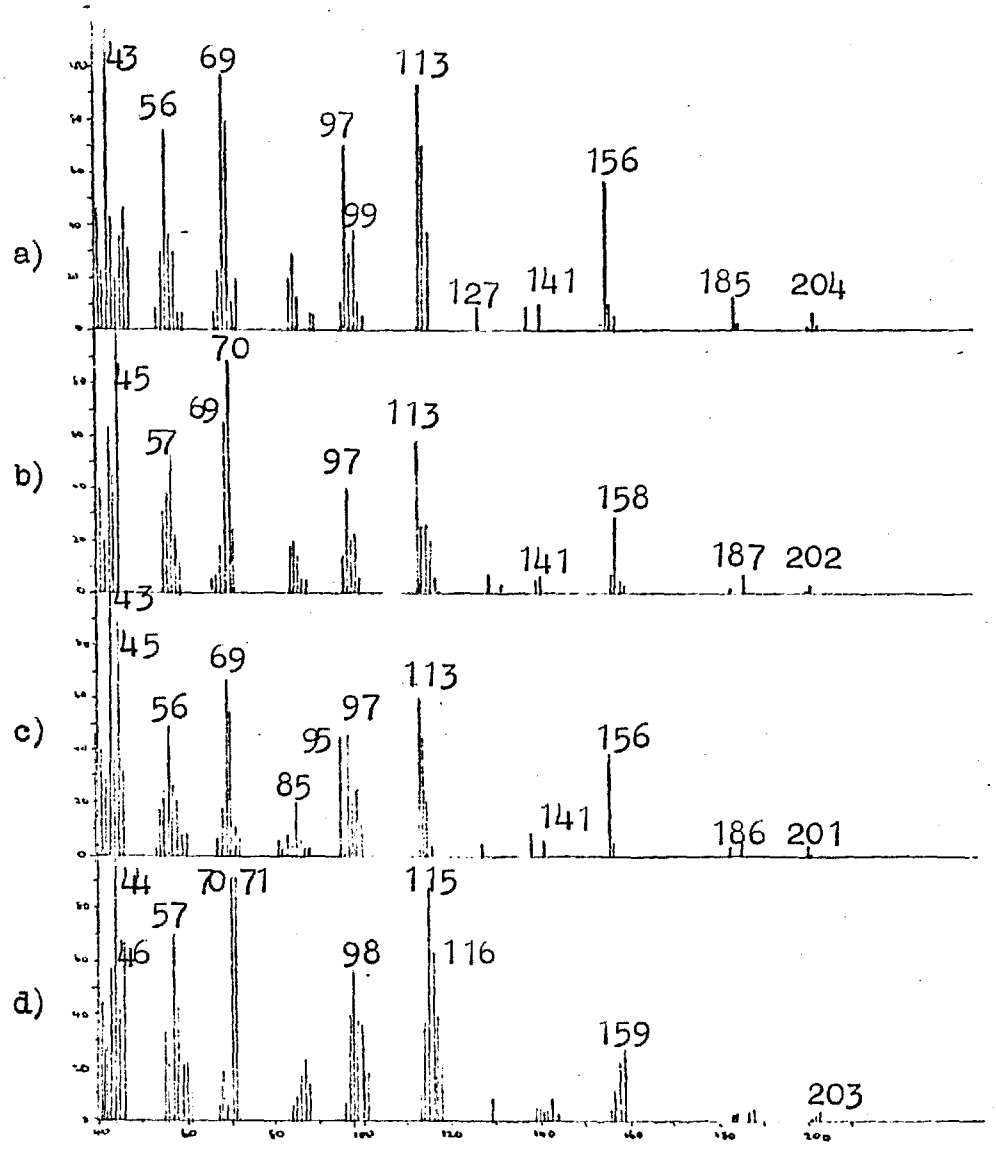


Figure 22

Mass spectrum of a) (+)3-(4-$[^2H_3]$-3-hydroxybutanamido)-piperid-2-one; b) (+)3-(2-$[^2H_2]$-3-hydroxybutanamido)-piperid-2-one; c) (+)3-(3-$[^2H_1]$-3-hydroxybutanamido)-piperid-2-one; d) (+)3-(3-hydroxybutanamido-O-$[^2H_1]$-N-$[^2H_1]$)-1-$[^2H_1]$-piperid-2-one

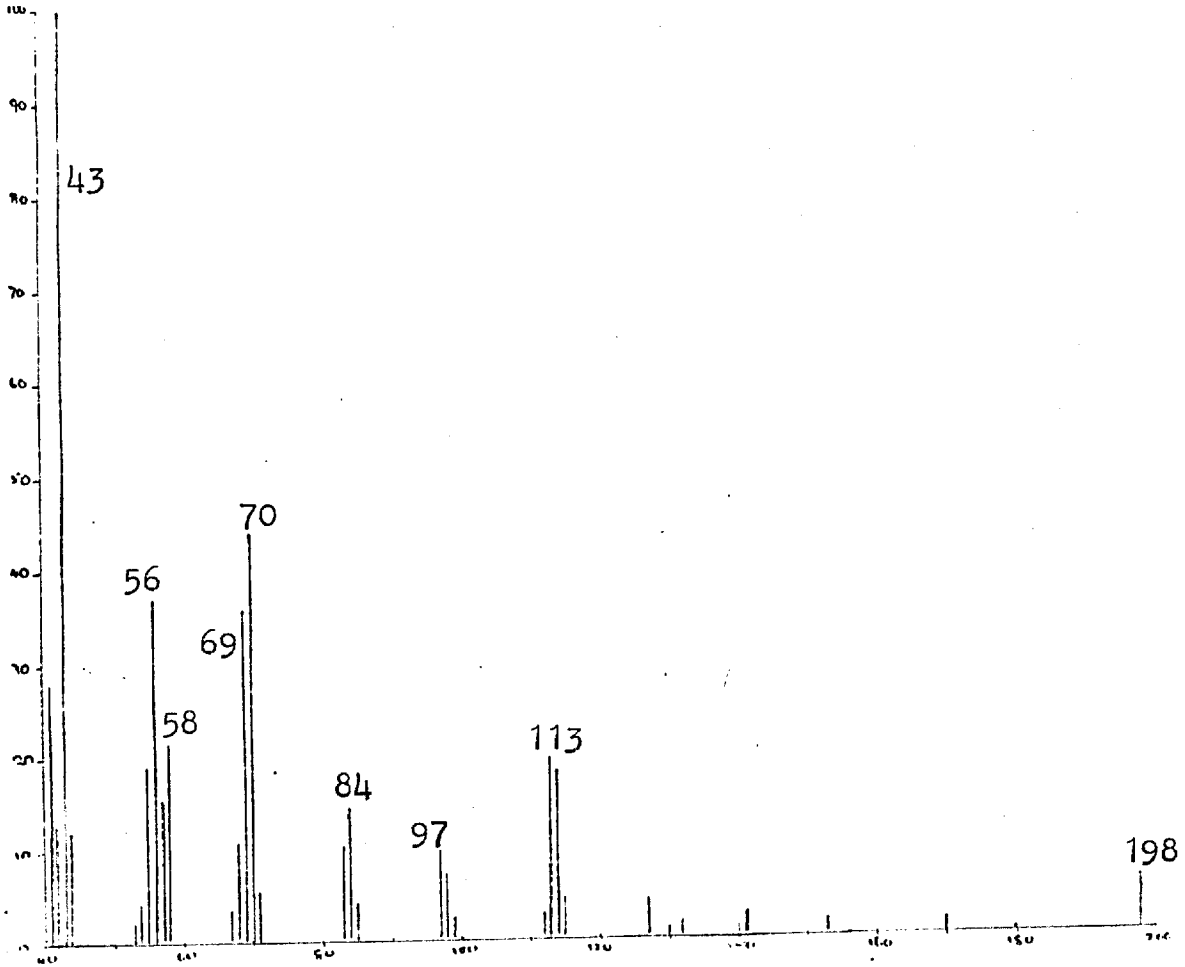


Figure 23

Mass spectrum of (+) 3-(3-oxobutanamido)-piperid-2-one

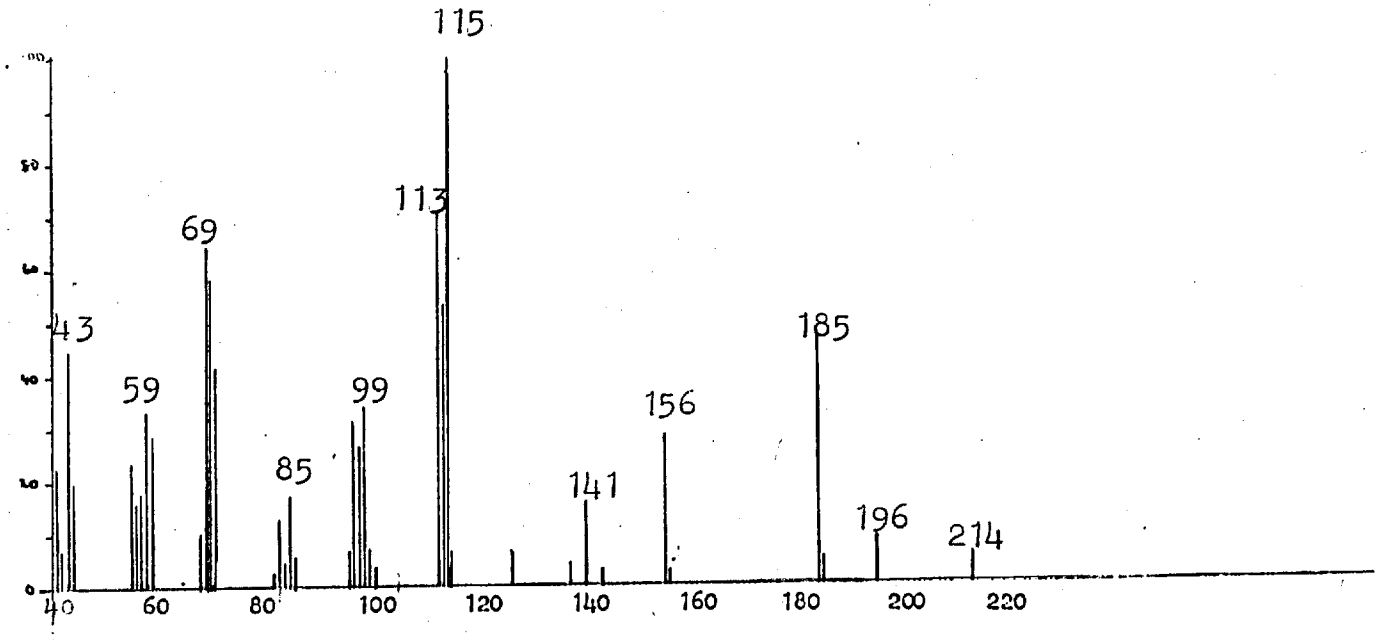


Figure 24

Mass spectrum of (+) 3-(pentanamido)-piperid-2-one

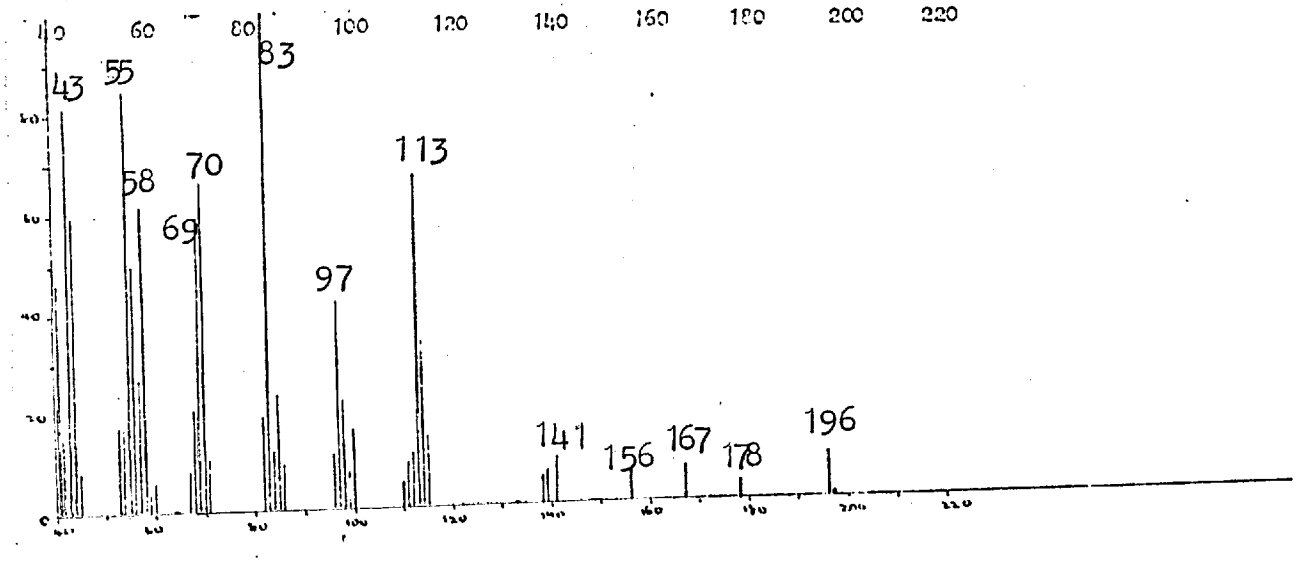


Figure 25

Mass spectrum of 3-(pent-2-enamido)-piperid-2-one

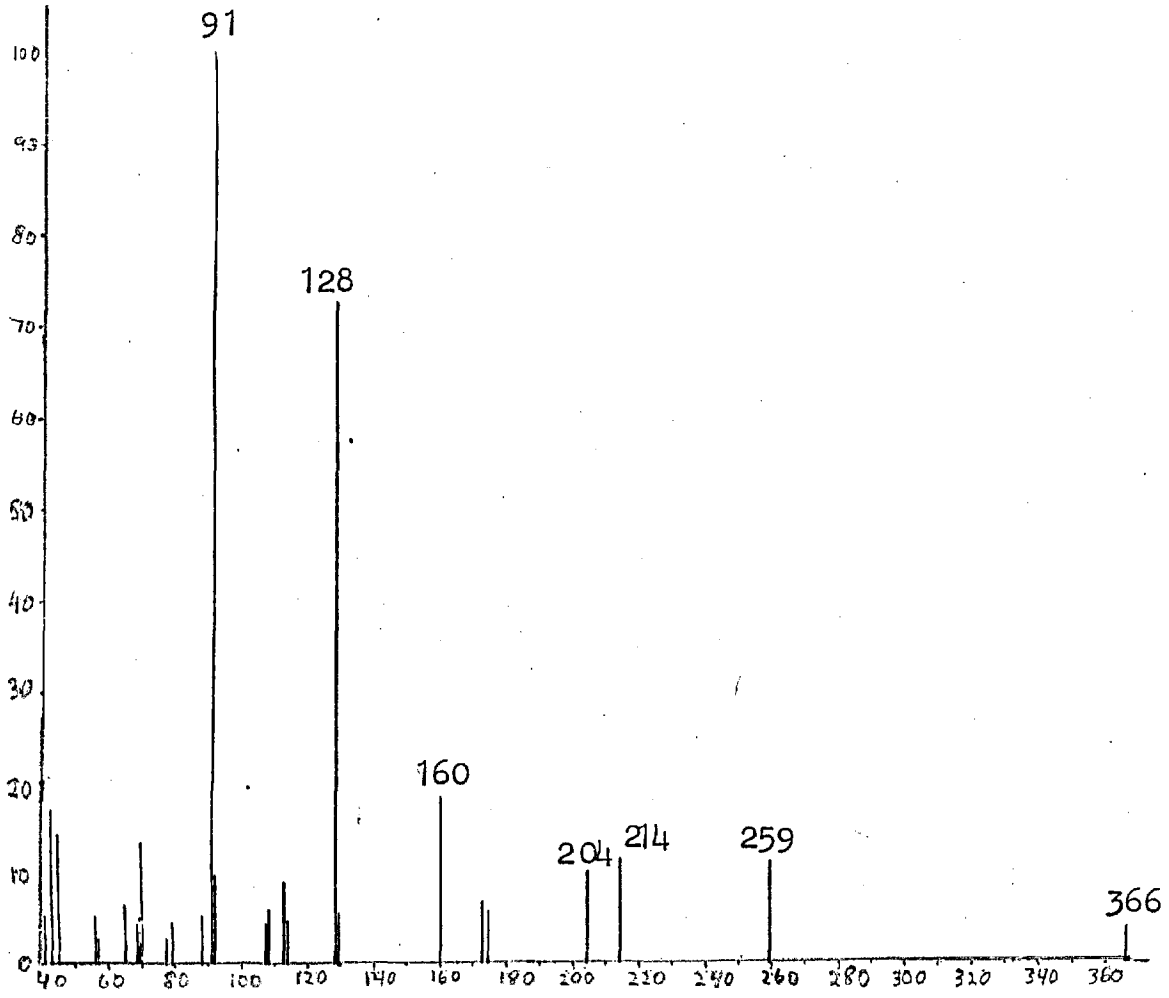


Figure 26

Mass spectrum of (+) methyl α-(N-3-hydroxybutyroyl)-δ-(N-benzyloxycarbonyl)-L-ornithine ester

Figure 27

Mass spectrum of 2-phenyl-1,3-dioxane a) electron-impact, 70 eV, 150°C; b) electron-impact, 70 eV, 30°C; c) photon-impact, hydrogen gas, 150°C; d) photon-impact, hydrogen gas, 30°C.,

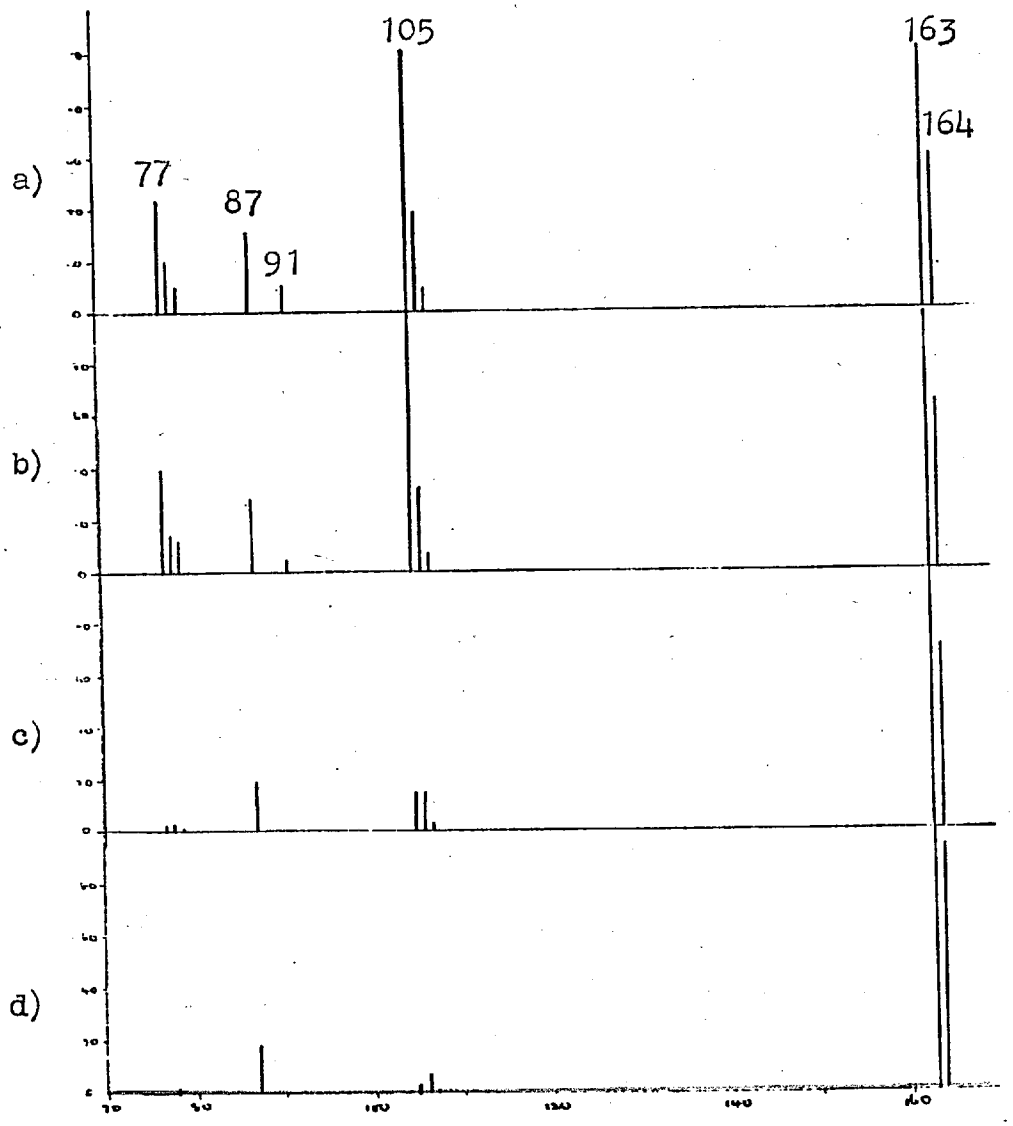
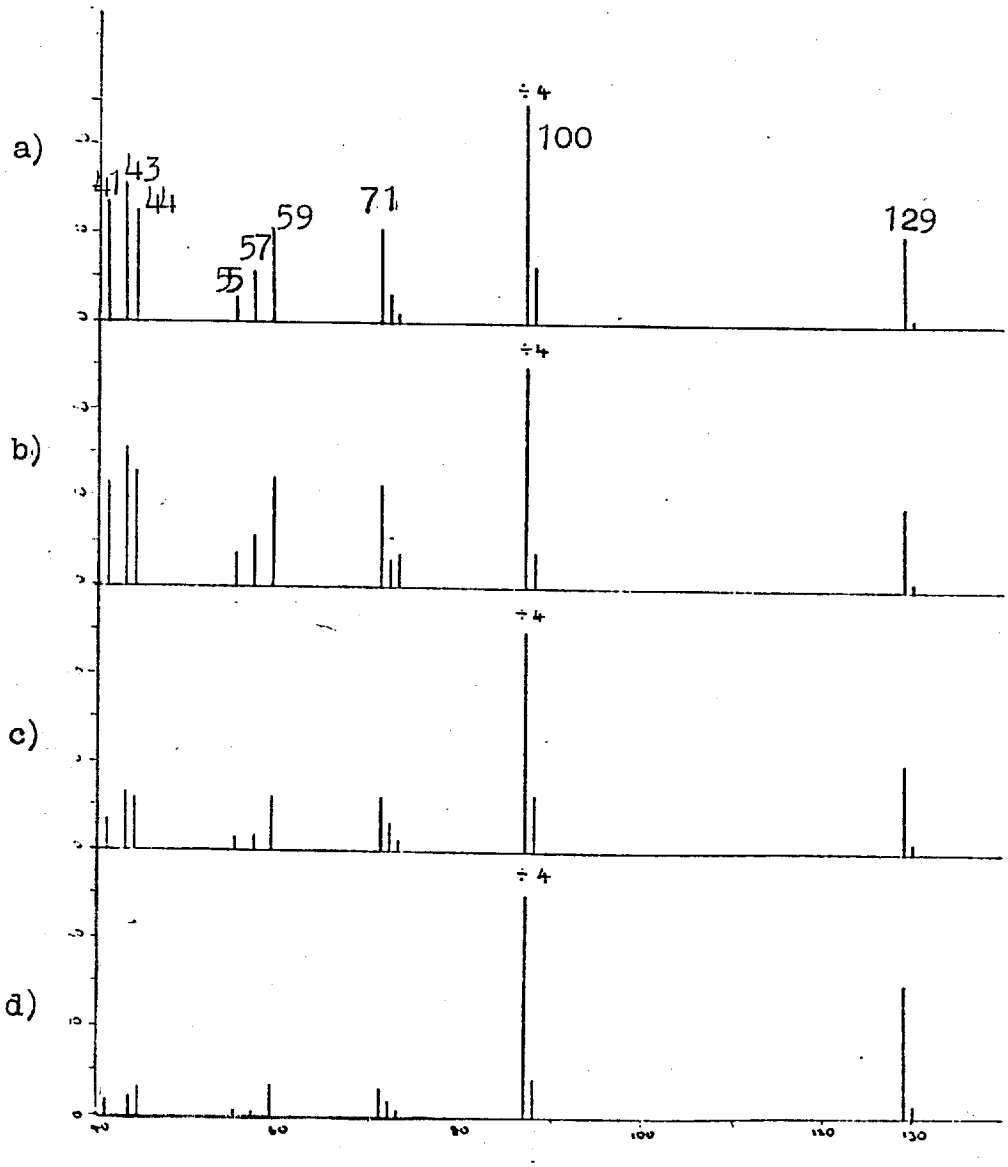


Figure 28

Mass spectrum of 2-propyl-1,3-dioxane a) electron-impact, 70 eV, 150°C; b) electron-impact, 70 eV, 30°C; c) photon-impact, hydrogen gas, 150°C; d) photon-impact, hydrogen gas, 30°C.



References

1. F.W. McLafferty, Anal. Chem., 1959, 31, 477.
2. M.M. Bursey and F.W. McLafferty, J. Amer. Chem. Soc., 1967, 89, 1.
3. M.M. Bursey and F.W. McLafferty, ibid, 1966, 88, 529.
4. I. Howe and D.H. Williams, Chem. Comm., 1968, 220; I. Howe and D.H. Williams, J. Chem. Soc. (B)., 1968, 1213.
5. I. Howe and D.H. Williams, Org. Mass Spectrom., 1969, 2, 1141.
6. M.M. Bursey and D. Rosenthal, Chem. Comm., 1968, 1010.
7. F.W. McLafferty, ibid., 1968, 956.
8. I. Howe, D.H. Williams and R.G. Cooks, Org. Mass Spectrom., 1969, 2, 137.
9. H.M. Rosenstock and M. Krauss, 'Mass Spectrometry of Organic Ions', F.W. McLafferty, Academic Press, New York, 1963, p.1.
10. M.L. Gross and F.W. McLafferty, Chem. Comm., 1968, 254.
11. M.S. Chin and A.G. Harrison, Org. Mass Spectrom., 1969, 2, 1073.
12. M.M. Bursey, ibid, 1968, 1, 31.
13. R.A.W. Johnstone and D.W. Payling, Chem. Comm., 1968, 601.

14. J. Jacobus and K. Mislow, J. Amer. Chem. Soc., 1967, 89, 5228.

15. A. Buchs, G.P. Rossetti and B.P. Susz, Helv. Chim. Acta., 1964, 47, 1563.

16. A. Foffani, S. Pignataro, B. Cantone and F. Grasso, Z. Physik. Chem. (Frankfurt), 1964, 42, 221.

17. S. Pignataro, A. Foffani, G. Inorta and G. Distefano, ibid., 1966, 49, 291.

18. A.G. Harrison, A. Ivko and D. Van Raalte, Can. J. Chem., 1966, 44, 1625.

19. B.G. Keyes and A.G. Harrison, J. Amer. Chem. Soc., 1968, 90, 5671.

20. T.W. Bentley, R.A.W. Johnstone and D.W. Payling, ibid., 1969, 91, 3978.

21. H.M. Rosenstock, M.B. Wallenstein, A.L. Wahrhaftig, and H. Eyring, Proc. Natl. Acad. Sci. U.S., 1952, 38, 667.

22. M.M. Bursey and R.P. Buck, Org. Mass Spectrom., 1970, 3, 387.

23. M.M. Bursey and P.T. Kissinger, ibid., 1970, 3, 395.

24. E.S. Waight, Personal Communication.

25. M.S. Kharasch and O. Reinmuth, 'Grignard Reactions of Nonmetallic Substances.' Prentice-Hall Inc., New York, 1954, p. 1199.

26. A. Baeyer and V. Villiger, Chem. Ber., 1904, 37, 605.

27. A. Basler, ibid., 1883, 16, 2716.

28. K. Friedrich and H.G. Henning, ibid., 1959, 92, 2756.

29. H.O. House and G. Rasmusson, J. Org. Chem., 1961, 26, 4278.

30. L.A. Walter, Organic Synthesis Coll. Vol. 3, p. 757.

31. G. Wittig and V. Scholkopf, Chem. Ber., 1954, 87, 1318.

32. R.R. Holmes and R.P. Bayer, J. Amer. Chem. Soc., 1960, 82, 3454.

33. V.J. Morlino and R.B. Martin, ibid., 1967, 89, 3107.

34. M. van Gorkom and G.E. Hall, Quart. Rev., 1968, 22, 14.

35. G.M. Whitesides, F. Kaplan, K. Nagarajan , and J.D. Roberts, Proc. Natl. Acad. Sci. U.S., 1962, 48, 1112 and references therein.

36. L. Phillips, Personal Communication.

37. E.I. Snyder, J. Amer. Chem. Soc., 1963, 85, 2624.

38. M. Barber and R.M. Elliot, ASTM Committee E-14th, Annual Conference on Mass Spectrometry, Montreal June 1964; J.H. Futrell, K.R. Ryan and L.W. Sieck, J. Chem. Phys., 1965, 43, 1832; K.R. Jennings, ibid., p.4176; K.R. Jennings, 'Some Newer Physical Methods in Structural Chemistry', R. Bonnett and J.G. Davis, United Trade Press, London, 1967, p.105; T.W. Shannon, T.E. Mead, G.G. Warner and F.W. McLafferty, Anal.Chem., 1967, 39, 1748.

39. J.A. Sphon and J.N. Daminco, Org. Mass Spectrom., 1970, 3, 51, and references cited therein.

40. P. Brown, ibid., 1969, 2, 1085, and references cited therein.

41. R.G. Cooks, I. Howe and D.H. Williams, ibid., p. 137.

42. H.H. Jaffe, Chemical Reviews, 1953, 53, 191.

43. H.C. Brown and Y. Okamoto, J. Amer. Chem. Soc., 1958, 80, 4979.

44. A. Gorchein, Biochim. Biophys. Acta., 1968., 152, 358.

45. K. Golankiewicz and M. Wiewiorowski, Acta. Biochimica Polanica, 1963, 10, 443.

46. E.A. Bell, J. Chem. Soc., 1958, 2423.

47. N.F. Albertson, Org. Reactions, 1962, 12, 205.

48. R.C. Barass and D.T. Elmore, J. Chem. Soc., 1957, 3134, and references cited therein.

49. R. Ledger and C. Stewart, Aust. J. Chem., 1965, 18, 933.

50. G.R. Brubaker and D.H. Busch, Inorg. Chem., 1966, 5, 2110.

51. R.L.M. Synge, Biochem. J., 1948, 42, 99.

52. P.A. Cruickshank and J.C. Sheehan, Anal. Chem., 1964, 36, 1191.

53. J.C. Sheehan, P.A. Cruickshank and G.L. Boshart, J. Org. Chem., 1961, 26, 2525.

54. J.C. Sheehan and P.A. Cruickshank, Organic Synthesis, 1968, 48, 83.

55. R.R. Read, ibid., Coll. Vol. 1, 1941, p. 321.

56. R. Mozingo, D.F. Wolf, S.A. Harris and K. Folkers, J. Amer. Chem. Soc., 1944, 66, 1859.

57. F. Adickes and G. Andresen, Annalen, 1944, 555, 41.

58. A.E. Opara and G. Read, Chem. Comm., 1969, 679.

59. J.E. Baldwin and R.G. Pudussery, ibid., 1968, 408.

60. Y. Kameda, K. Matsui and Y. Hotta, CA., 55, 407i.

61. J. Beermans and J.C. Jungers, Bull. Soc. Chim. Belges., 1947, 56, 72.

62. M.G. Reenecke, J. Org. Chem., 1964, 29, 299.

63. B. Fischer and G. Zemplén, Ber., 1909, 42, 4886.

64. C. Parkanyi and F. Sorm, Coll. Czech. Chem. Comm., 1963, 28, 2491.

65. B. Liberek and Z. Grzonka, Tetrahedron Letters, 1964, 159.

66. H. Matsuo and Y. Kawazoe, Chem. Pharm. Bull. Japan., 1967, 15, 391.

67. A. Stretiwieser Jr., 'Molecular Orbital Theory for Organic Chemists', J. Wiley and Sons Inc., New York, 1961, p. 97.

68. K.B. Wiberg, 'Computer Programming for Chemists', W.A. Benjamin Inc., New York, 1965, p. 215.

69. T. Miyazawa, J. Mol. Spect., 1960, 4, 155.

70. K. Golankiewicz, M. Dejor and M. Wiewiorowski, Acta. Biochimica Polanica, 1966, 13, 1.

71. S. Abrahamsson, S. Ställberg-Stenhagen, and E. Stenhagen, 'Progress in the Chemistry of Fats and other Lipids' R.T. Holman, Pergamon Press, Oxford, 1963, Vol. 7, part 1.

72. B. Hallgren, R. Ryhage, and E. Stenhagen, Acta. Chem. Scand., 1959, 13, 845.

73. R. Ryhage, S. Ställberg-Stenhagen, and E. Stenhagen, Arkiv. Kemi, 1959, 18, 179.

74. N. Ding-Nguyen, R. Ryhage and S. Ställberg-Stenhagen, ibid., 1960, 15, 433.

75. H. Audier, S. Bory, M. Fétizon, P. Longevialle, and R. Toubiana, Bull. Soc. Chim. France., 1964, 3034.

76. G.W. Kenner and E. Stenhagen, Acta. Chem. Scand., 1964, 18, 1551.

77. A.M. Duffield, H. Budziekiewicz and C. Djerassi, J. Amer. Chem. Soc., 1964, 86, 5536.

78. J.H. Beynon, R.A. Saunders and A.E. Williams, 'The Mass Spectra of Organic Molecules', Elsevier Amsterdam, 1968, p. 280.

79. H. Budziekiewicz, C. Djerassi and D.H. Williams, 'Mass Spectrometry of Organic Compounds' Holden Day, San Francisco, 1967, p. 99.

80. ibid., p. 162.

81. R.A. Saunders and A.E. Williams, 'Advances in Mass Spectrometry', V.L. Mead; The Institute of Petroleum, London, 1966, 3, 681.

82. A.M. Duffield, H. Budziekiewicz, D.H. Williams and C. Djerassi, J. Amer. Chem. Soc., 1965, 87, 810.

83. A.M. Duffield, H. Budziekiewicz and C. Djerassi, ibid., 1965, 87, 2920.

84. R.T. Aplin, J.J.Jones and B. Liberek, J. Chem. Soc., (C), 1968, 1011.

85. N.V. Sidgwick, 'The Organic Chemistry of Nitrogen', 3rd edn., I.T. Miller and H.D. Springall, Oxford University Press, 1966, p. 43.

86. H. Budziekiewicz, C. Djerassi and D.H. Williams, 'Mass Spectrometry of Organic Compounds', Holden Day, San Francisco, 1967, p. 348.

87. C.E. Brion, Anal. Chem., 1965, 37, 1706.

88. C.E. Brion, ibid 1966, 38, 1941.

89. J.H. Beynon, A.E. Fontaine, D.W. Turner and A.E. Williams, J. Sci. Instrum., 1967, 44, 283.

90. G. Spiteller and M. Spiteller-Friedmann, Monatsch, 1962, 93, 1395.

91. J.T.B. Marshall and D.H. Williams, Tetrahedron, 1967, 23, 321.

92. H. Budziekiewicz, C. Djerassi and D.H. Williams, 'Mass Spectrometry of Organic Compounds' Holden Day, San Francisco, 1967, p. 263.

93. N.A. Khan, F.E. Deatherage and J.B. Brown, Organic Synthesis Coll. Vol. 4, p. 851.

94. A.C. Cope, G.A. Berchtold, P.E. Peterson and S.H. Sharman, J. Amer. Chem. Soc., 1960, 82, 6370.

95. E.G. Corey and R.A. Sneen, ibid., 1956, 78, 6269.

96. H.C. Brown and G. Zweifel, ibid., 1959, 81, 1512.

97. G. Schneider, O. Kovacs and M. Chinorai, Acta. Phys. Chem., 1964, 10, 95.

98. J.H. Beynon and A.E. Fontaine, Inst. Rev., 1967, 14, 501.

99. D.H. Williams and R.G. Cooks, Chem. Comm., 1968, 663.

100. H. Budziekiewicz, C. Djerassi and D.H. Williams, 'Mass Spectrometry of Organic Compounds' Holden Day, San Francisco, 1967, p. 163.

101. R.L. Shriner, Org. Reactions, 1942, 1, 1.

102. F. Fichter and F. Sonneborn, Chem. Ber., 1902, 35, 942.