THE MASS SPECTRA OF N-ALKYL-α-CHLOROACETAMIDES

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A DISSERTATION

in

Chemistry

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I would like to express my appreciation to Dr. T.J. Adley for the assistance and guidance he has given me all through my graduate studies. I would also like to thank Professor J.G. Dick for his assistance in the preparation of sections of this work and to Dr. R.T.B. Rye for microanalyses and help with the interpretation of mass spectra.

I also wish to acknowledge the financial assistance of the National Research Council of Canada.

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ABSTRACT

The purpose of this research described in this thesis is to study the mass spectra of a number of N-alkyl-α-chloroacetamides. A total of nine acetamides were synthesized with methyl, ethyl or isopropyl alkyl groups and one, two or three chlorine atoms on the α-carbon atoms.

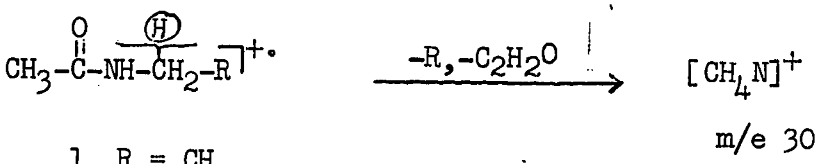
To aid in the assignment of empirical formulae and structures to specific ions in the mass spectra, a series of deuterated amides were synthesized and studied.

The majority of the ions which were observed in the mass spectra were of the type common to substituted acetamides. However, some unexpected and interesting rearrangement processes were also observed.

An attempt is made to assess the effects of varying chlorination and alkyl substitution on the relative abundances of certain ions common to all the spectra studied.

HISTORICAL REVIEW

In 1959, J.A. Gilpin[1] reported details of the mass spectra of a number of aliphatic primary, secondary and tertiary amides, including N-methyl, N-ethyl, N-n-butyl, and N-isobutyl acetamides among the compounds examined. In the mass spectra of the N-ethyl acetamide (1), N-n-butyl acetamide (2) and N-isobutyl acetamide (3), Gilpin observed that a significant path of fragmentation (1), leading in each case to the base peak of the spectrum, involved cleavage of the carbonyl-nitrogen bond and the carbon-carbon bond *beta* to the nitrogen atom with migration of one hydrogen atom to the nitrogen containing fragment.



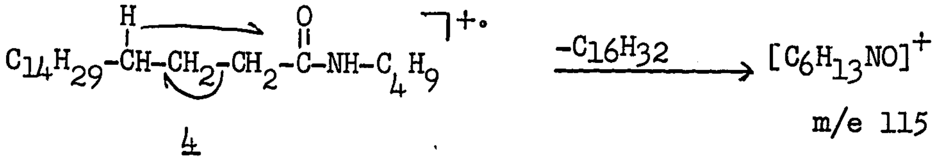
$$CH_3-\overset{O}{\overset{\|}{C}}-NH-\overset{\textcircled{H}}{C}H_2-R]^{+\cdot} \xrightarrow{-R,\,-C_2H_2O} \underset{m/e\ 30}{[CH_4N]^+} \qquad (1)$$

1 R = CH_3

2 R = C_3H_7

3 R = $CH(CH_3)_2$

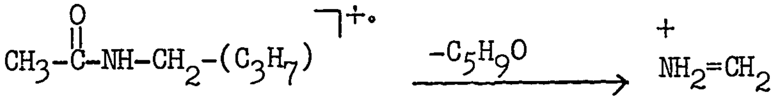
Gilpin also noted that, in amides with a hydrogen atom on a carbon atom *gamma* to the carbonyl group, a bond fission and rearrangement process was highly favored. This is illustrated below for the case of N-n-butyl octadecanamide (4).



$$C_{14}H_{29}-\overset{H}{\overset{|}{C}}H-CH_2-CH_2-\overset{O}{\overset{\|}{C}}-NH-C_4H_9]^{+\cdot} \xrightarrow{-C_{16}H_{32}} \underset{m/e\ 115}{[C_6H_{13}NO]^+} \qquad (2)$$

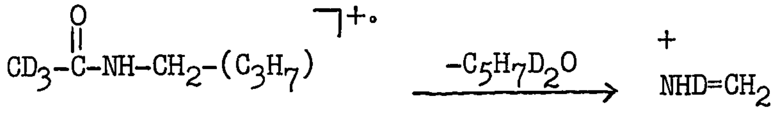
4

In 1963, Djerassi *et al.*,[2] established the mechanism by which process 1 occurs by studying the mass spectra of N-n-butyl acetamide (5) and N-n-butyl-α,α,α-d_3-acetamide (6). It was observed that 5 gave rise to an ion at m/e 30 in the mass spectrometer, which was observed at m/e 31 in the spectrum of <u>6</u>, thus establishing that the migrating hydrogen atom came from the carbon atom <u>alpha</u> to the carbonyl group.



$$\left[CH_3-\overset{\overset{O}{\|}}{C}-NH-CH_2-(C_3H_7)\right]^{+\cdot} \xrightarrow{-C_5H_9O} \overset{+}{N}H_2=CH_2 \qquad (3a)$$

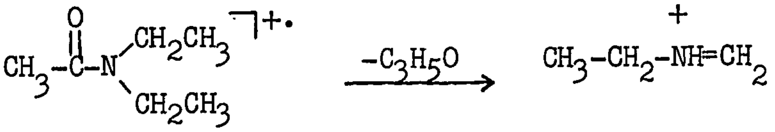
<u>5</u> m/e 30



$$\left[CD_3-\overset{\overset{O}{\|}}{C}-NH-CH_2-(C_3H_7)\right]^{+\cdot} \xrightarrow{-C_5H_7D_2O} \overset{+}{N}HD=CH_2 \qquad (3b)$$

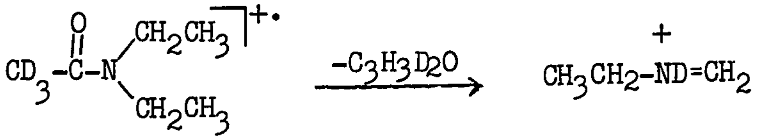
<u>6</u> m/e 31

Djerassi also studied the mass spectra of tertiary amides of the type N,N-diethylacetamide (<u>7</u>), N,N-diethyl-α,α,α-d_3-acetamide (<u>8</u>) and N,N-(2,2,2-d_3-)-diethylacetamide (<u>9</u>). The fragment in the mass spectrum of <u>7</u> arising <u>via</u> process (1) appeared at m/e 58. This peak was observed at m/e 59 in the spectrum of <u>8</u> and was equally distributed between m/e 58 and m/e 61 in the mass spectrum of <u>9</u>.



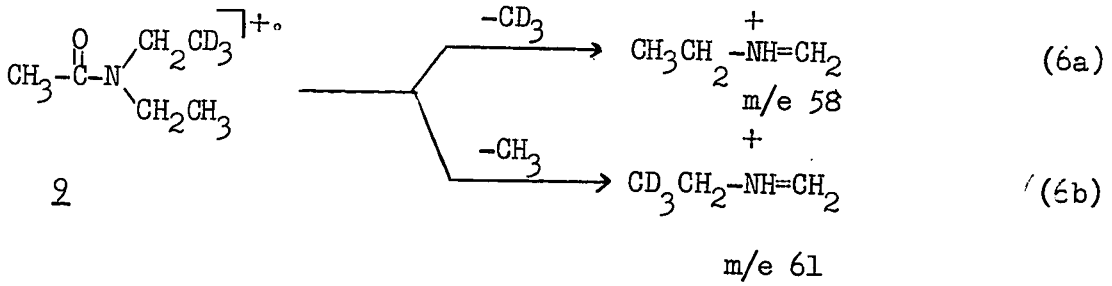
$$\left[CH_3-\overset{\overset{O}{\|}}{C}-N(CH_2CH_3)_2\right]^{+\cdot} \xrightarrow{-C_3H_5O} CH_3-CH_2-\overset{+}{N}H=CH_2 \qquad (4)$$

<u>7</u> m/e 58

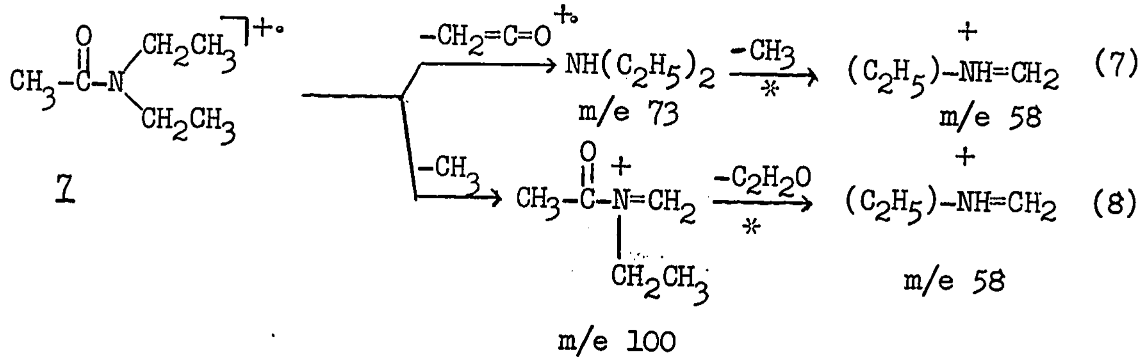


$$\left[CD_3-\overset{\overset{O}{\|}}{C}-N(CH_2CH_3)_2\right]^{+\cdot} \xrightarrow{-C_3H_3D_2O} CH_3CH_2-\overset{+}{N}D=CH_2 \qquad (5)$$

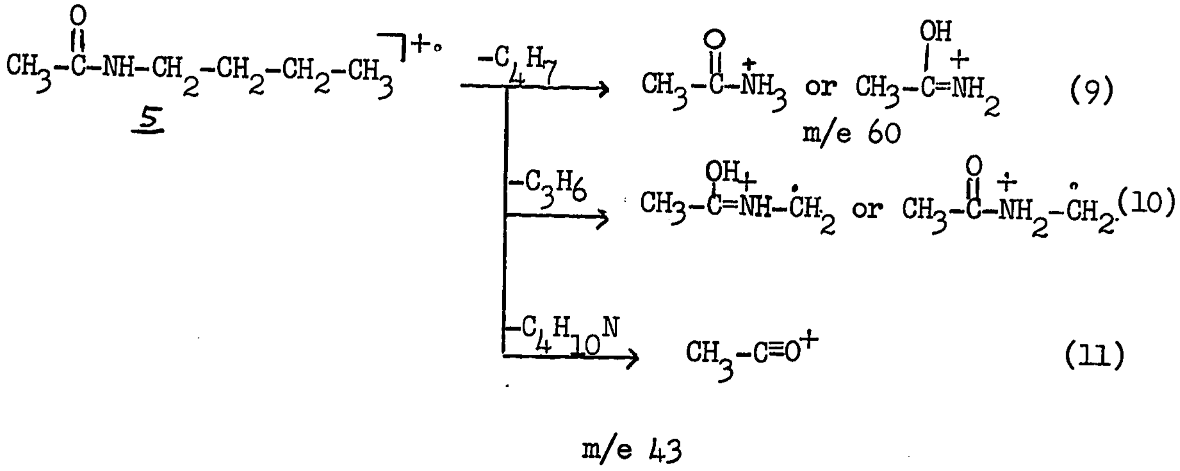
<u>8</u> m/e 59



It was also established, by examination of the appropriate metastable decompositions, that process 1 took place via two distinct mechanisms as shown below.



The significance of some other fragments of the N-n-butylamide shown below, will be discussed later in the text.

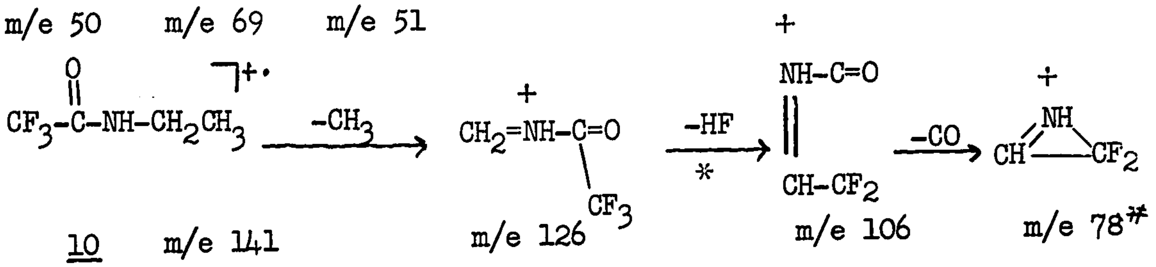


More recently, Saxby[3,4] studied the mass spectra of a number of N-alkyl-α,α,α-trifluoroacetamides, in particular the N-methyl, N-ethyl, N-n-propyl, N-n-butyl, N-sec-butyl, N-iso-butyl, N-t-butyl, N-n-pentyl and N-n-hexyl trifluoroacetamides. However, the only spectra analyzed in detail were those of N-ethyl-α,α,α-trifluoroacetamide (10) and N-t-buytl-α,α,α-trifluoroacetamide (11). In the spectrum of 10, Saxby observed equally intense peaks due to $^+CF_3$ (m/e 69) and the loss of $\cdot CF_3$ from the molecular ion yielding an ion at m/e 72. The intensity of the ion arising from the loss of $\cdot CF_3$ from the molecular ion was greatly reduced in the mass spectrum of the N-t-butyl derivative (11). Saxby[4] further noted that the intensity of the molecular ion was high in the mass spectra of the N-methyl and N-ethyl trifluoroacetamides but rapidly diminished to the vanishing point in the spectra of the higher alkyl substituted amides. The base peak in the mass spectrum of 10 appeared at m/e 126 and was due to the loss of a methyl group from the molecular ion. In the spectrum of the N-t-butyl derivative (11), this peak appeared at m/e 154 and was still very intense. Some other peaks observed and other fragmentation patterns proposed by Saxby for compounds 10 and 11 are shown below. Further comments will be made on these processes later in this work.

For compound 10;

$[CF_2]^{+\cdot}$ $[CF_3]^+$ $[CHF_2]^+$

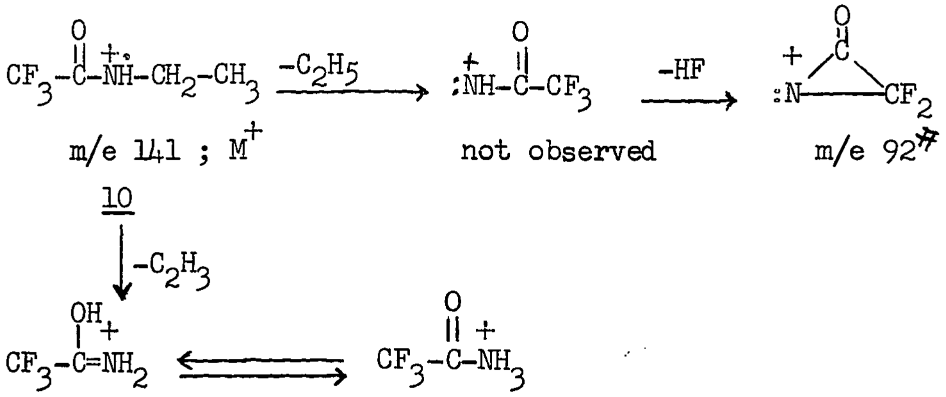
m/e 50 m/e 69 m/e 51



(12)

\# The molecular formula for this ion was determined by exact mass measurement.

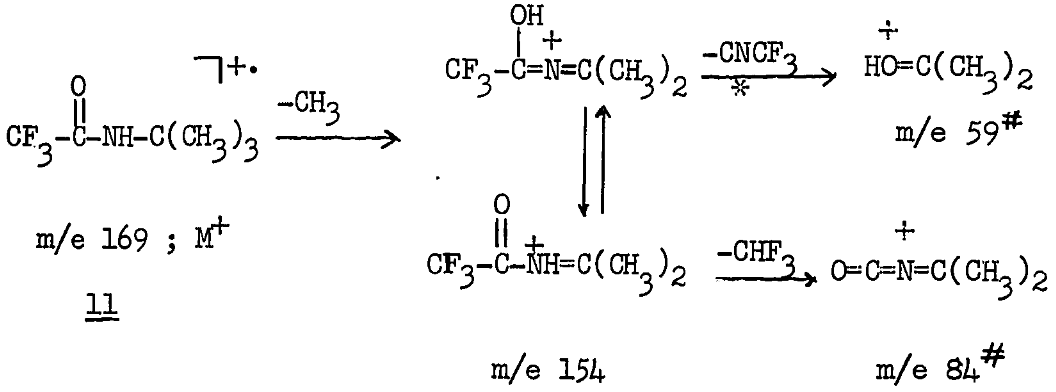
* Metastable transition observed for this process.



(13)

(14)

For compound 11;



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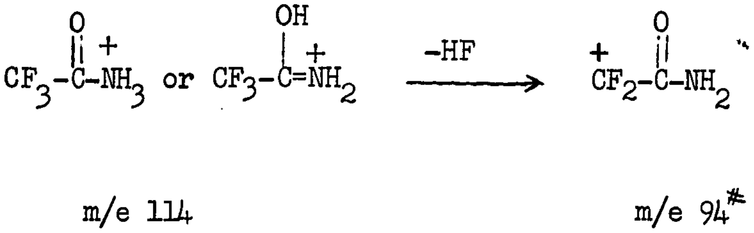
(16)

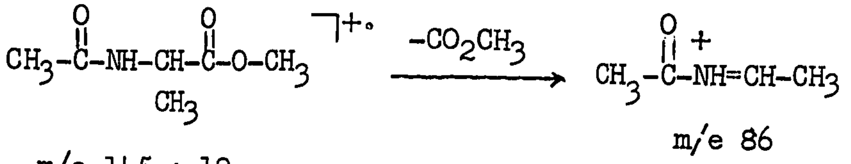


(17)

The molecular formula for these ions was determined by exact mass measurements.

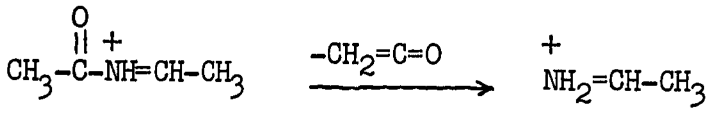
Appearing at approximately the same time as Saxby's work Zeman and Wirotama[5] published a paper concerning the mass spectra of a number of trifluoroacetamides which included many of the compounds which had been discussed by Saxby. Zeman and Wirotama observed essentially the same fragments as Saxby; however, by means of deuterium labelling studies, they found that the structure of the ion at m/e 78, which Saxby had reported in the spectrum of the N-ethyl derivative (<u>10</u>) was in fact $CH_2=\overset{+}{N}=CF_2$ and not $CH=\overset{+}{N}H-CF_2$.

In 1961, Anderson <u>et</u> <u>al</u>.,[6] studied the mass spectra of a number of methyl and ethyl esters of N-acetyl amino acids, some of which gave the same ion, after loss of the ester group, as did the alkyl acetamides after loss of an alkyl group or a hydrogen atom. Some fragmentation patterns observed by Anderson are shown below.



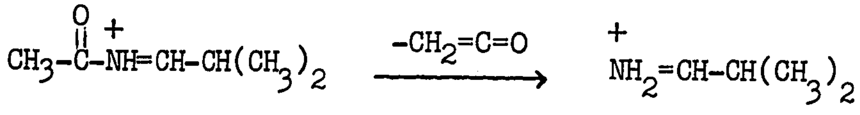
$$\left[CH_3-\overset{\overset{O}{\|}}{C}-NH-\underset{CH_3}{CH}-\overset{\overset{O}{\|}}{C}-O-CH_3\right]^{+\cdot} \xrightarrow{-CO_2CH_3} CH_3-\overset{\overset{O}{\|}}{C}-\overset{+}{N}H=CH-CH_3 \qquad (18)$$

m/e 145 ; <u>12</u> m/e 86



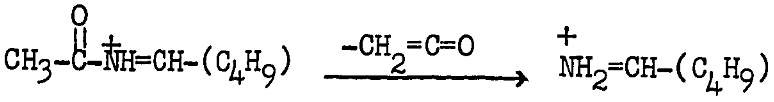
$$CH_3-\overset{\overset{O}{\|}}{C}-\overset{+}{N}H=CH-CH_3 \xrightarrow{-CH_2=C=O} \overset{+}{N}H_2=CH-CH_3 \qquad (19a)$$

m/e 86 m/e 44



$$CH_3-\overset{\overset{O}{\|}}{C}-\overset{+}{N}H=CH-CH(CH_3)_2 \xrightarrow{-CH_2=C=O} \overset{+}{N}H_2=CH-CH(CH_3)_2 \qquad (19b)$$

m/e 114 m/e 72

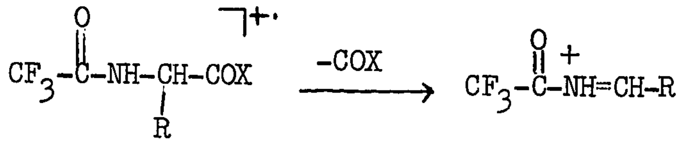


$$CH_3-\overset{\overset{O}{\|}}{C}-\overset{+}{N}H=CH-(C_4H_9) \xrightarrow{-CH_2=C=O} \overset{+}{N}H_2=CH-(C_4H_9) \qquad (19c)$$

m/e 128 m/e 86

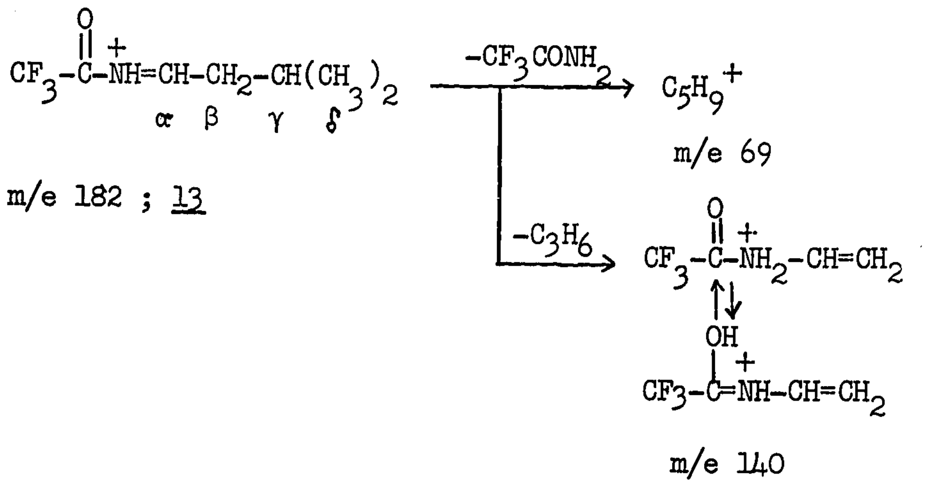
The rearrangements (19a-c) correspond to the migration of one hydrogen atom from the acyl group to the nitrogen containing fragment, analogous to the rearrangement observed by Gilpin[1] and Djerassi[2] in alkyl acetamides.

In 1969, Prox and Schmid[7] studied the mass spectra of a number of trifluoroacetamino-carbonium ions (13-15) produced in the mass spectra of trifluoroacetamino acids (20).



$$\left[CF_3-\overset{O}{\overset{\|}{C}}-NH-\underset{R}{\underset{|}{CH}}-COX\right]^{+\cdot} \xrightarrow{-COX} CF_3-\overset{O}{\overset{\|}{C}}-\overset{+}{N}H=CH-R \qquad (20)$$

They observed a number of rearrangements from these carbonium ions which are illustrated below.



$$CF_3-\overset{O}{\overset{\|}{C}}-\overset{+}{N}H=\underset{\alpha}{CH}-\underset{\beta}{CH_2}-\underset{\gamma}{CH}(\underset{\delta}{CH_3})_2 \xrightarrow{-CF_3CONH_2} C_5H_9^+ \qquad (21)$$

m/e 69

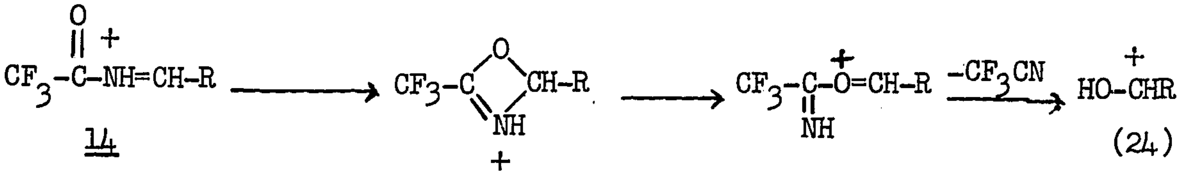
m/e 182 ; 13

$$\xrightarrow{-C_3H_6} CF_3-\overset{O}{\overset{\|}{C}}-\overset{+}{N}H_2-CH=CH_2 \qquad (22)$$

$$\updownarrow$$

$$CF_3-\overset{OH}{\overset{|}{C}}=\overset{+}{N}H-CH=CH_2 \qquad (23)$$

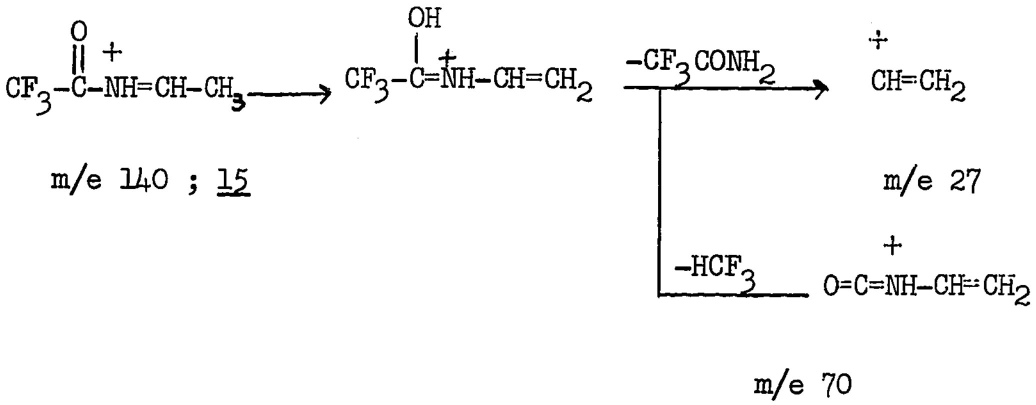
m/e 140



$$CF_3-\overset{O}{\overset{\|}{C}}-\overset{+}{N}H=CH-R \longrightarrow CF_3-C\overset{O}{\diamond}CH-R\,(\overset{+}{N}H) \longrightarrow CF_3-\underset{NH}{\underset{\|}{C}}-\overset{+}{O}=CH-R \xrightarrow{-CF_3CN} HO-\overset{+}{C}HR$$

14

(24)



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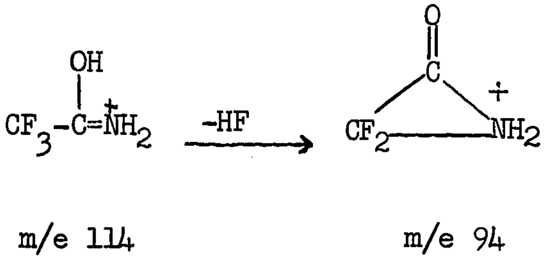
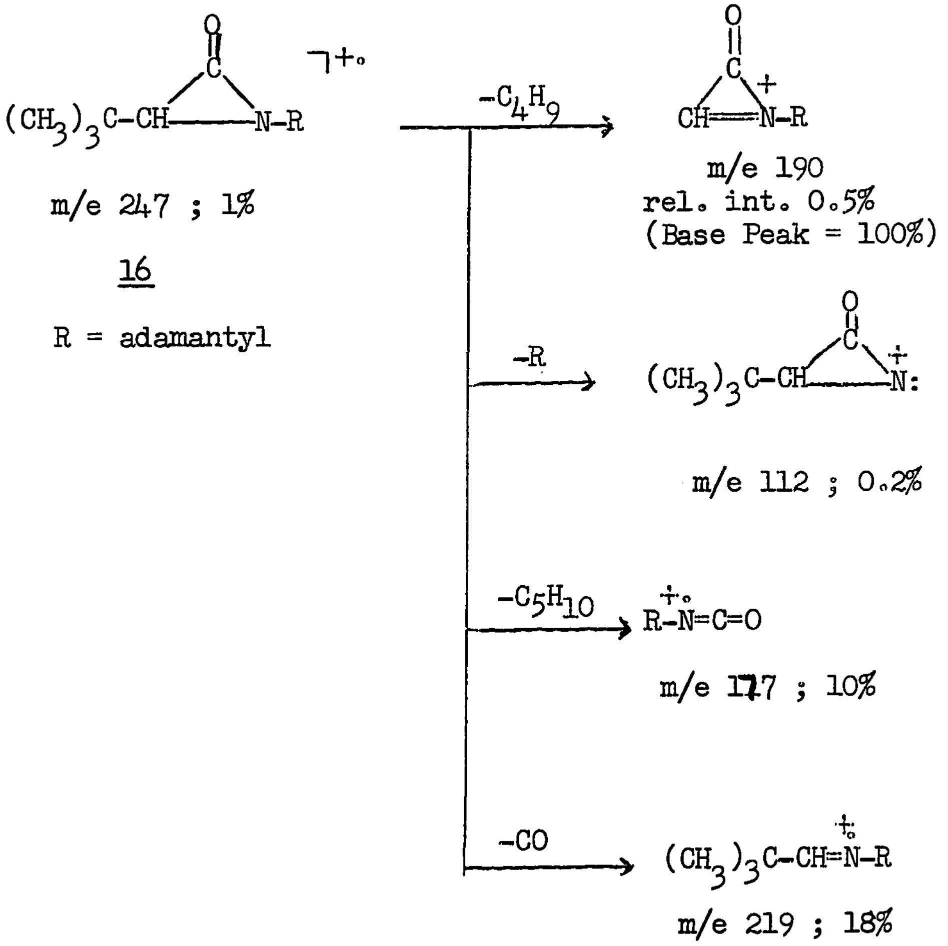


(27)

Prox and Schmid further ascertained, via studies of the mass spectra of appropriate deuterated compounds, that, in the rearrangement (21), 74% of the hydrogen atoms which were lost from the alkyl fragment came from the β-carbon atom of the N-alkyl side chain in 13 and 17% came from the γ-carbon atom. By similar methods, they determined that approximately 100% of the migrating hydrogen atoms in process (23) (13) came from the δ-carbon atom, in a mechanism similar to a McLafferty rearrangment.

An early paper by Lengyel and Uliss[8] reported the partial mass spectrum of the α-lactam (16).

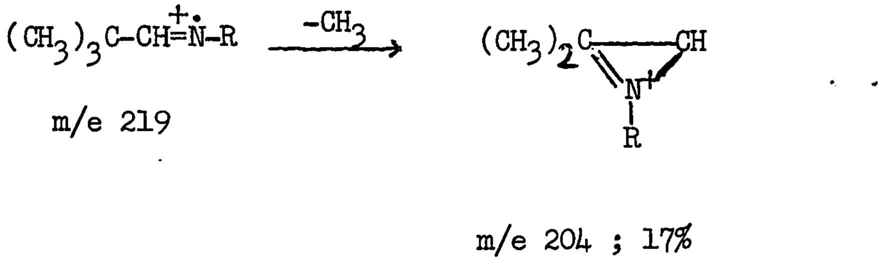


(28a)

(28b)

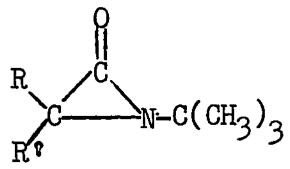
(28c)

(29)



(30)

Talaty and co-workers[9] have also observed similar fragments in the mass spectra of 16 and other α-lactams. Baumgarten *et al.*,[10], studied, in detail, the mass spectra of a number of α-lactams (17-22), the general fragmentation patterns of which are described below.



17 ; R = H, R' = ∅

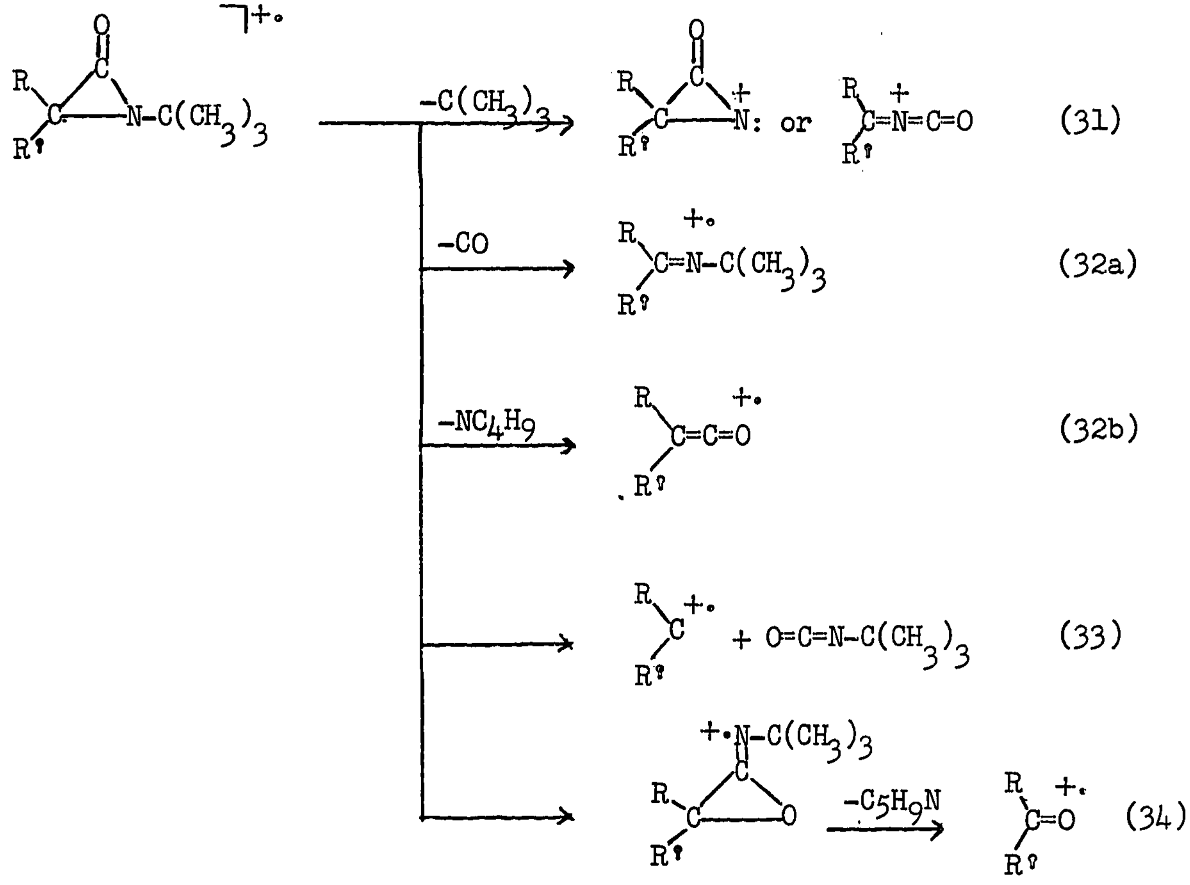
18 ; R = ∅, R' = ∅

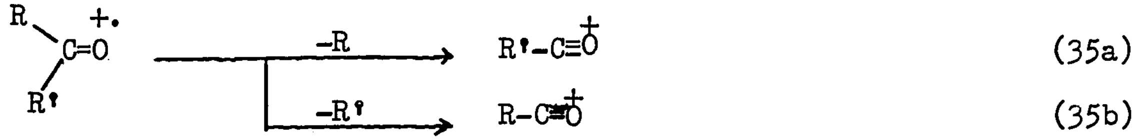
19 ; R = H, R' = $C(CH_3)_3$

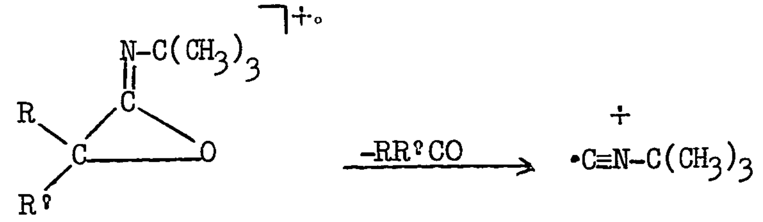
20 ; R = CH_3, R' = cyclohexyl

21 ; R = H , R' = p-Br-∅

22 ; R = CH_3, R' = CH_3







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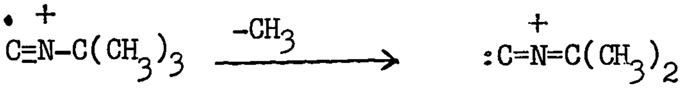
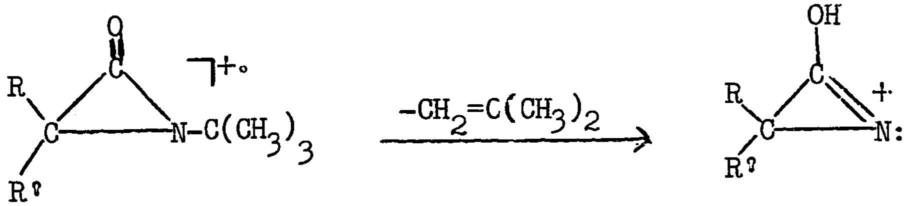


$$\overset{\bullet\;+}{C}{\equiv}N{-}C(CH_3)_3 \xrightarrow{-CH_3} :\overset{+}{C}{=}N{=}C(CH_3)_2$$

(37)



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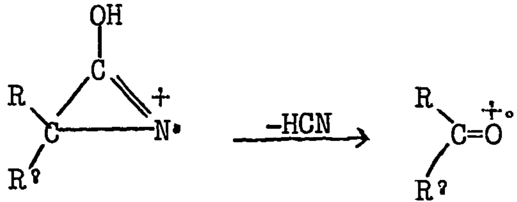

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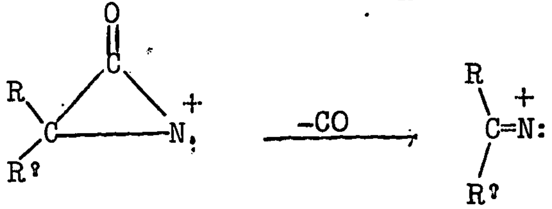

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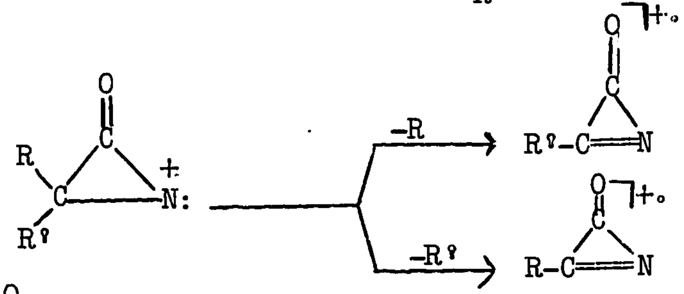

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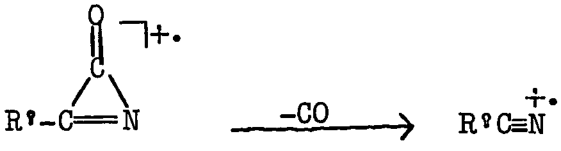

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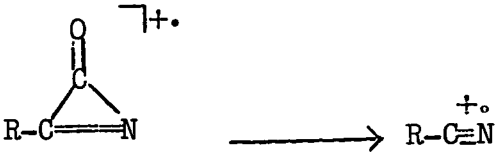

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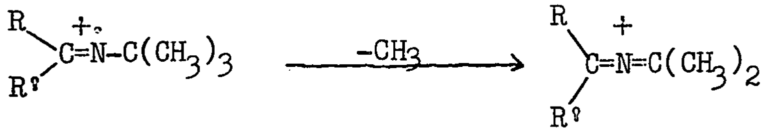

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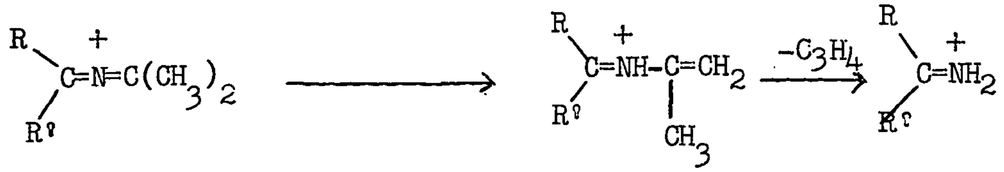
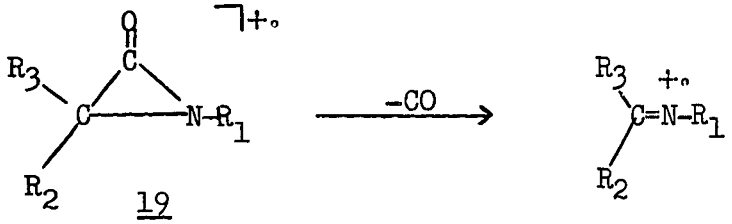


(46)

At approximately the same time as Baumgarten, Lengyel et al.[11] published a paper in which he also discussed the mass spectra of a number of α-lactams. Lengyel observed the same fragments as did Baumgarten, but by studying the mass spectra of some deuterated α-lactams, obtained more precise information than Baumgarten concerning two fragmentation patterns (47-49).



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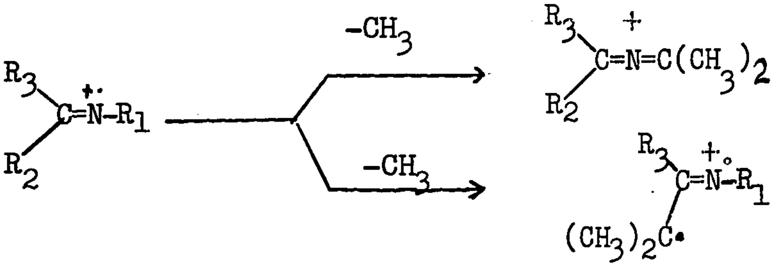
$R_1 = R_2 = C(CH_3)_3$

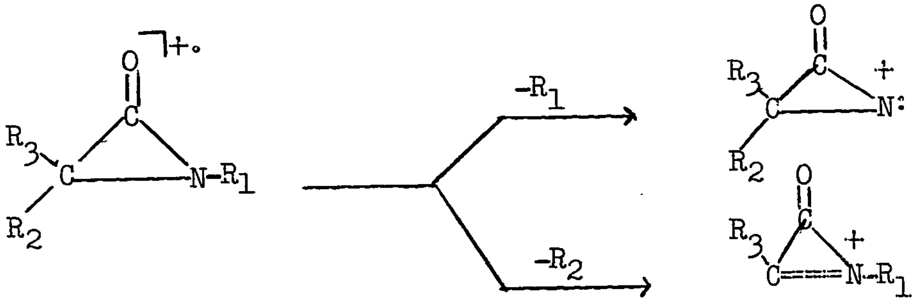
$R_3 = H$



(48)

(49)

Lengyel found that process (48) was favored by a ratio of 2:1 over process (49). He also found that process (50) was favored 10:1 over (51).



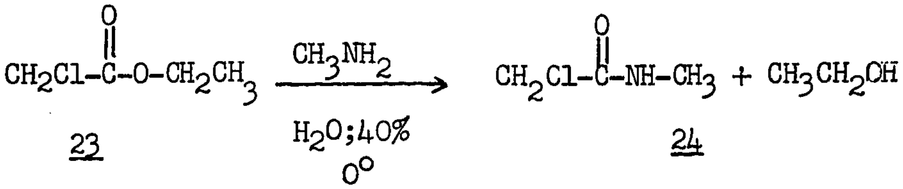
(50)

(51)

In later discussions the importance of these α-lactams and their role as intermediates in the fragmentation of α-halo acetamides will become apparent.

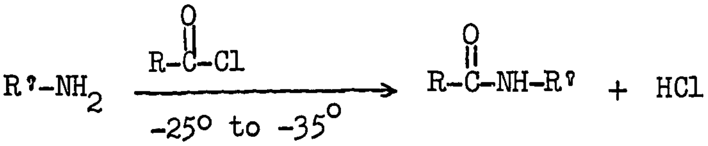
SYNTHESES

Nine N-alkyl-α-haloacetamides and the partially deuterated analogs which were synthesized for this project are shown in schemes (52) to (58). Also shown is the method of synthesis of 2,2,2,2',2',2',2",2",2"-d_9-t-butylamine (d_9-t-butylamine) in schemes (59) and (60).



$$CH_2Cl\text{-}\overset{O}{\overset{\|}{C}}\text{-}O\text{-}CH_2CH_3 \xrightarrow[H_2O;40\%,\ 0^\circ]{CH_3NH_2} CH_2Cl\text{-}\overset{O}{\overset{\|}{C}}\text{-}NH\text{-}CH_3 + CH_3CH_2OH \qquad (52)$$

23 24



$$R'\text{-}NH_2 \xrightarrow[-25^\circ \text{ to } -35^\circ]{R\text{-}\overset{O}{\overset{\|}{C}}\text{-}Cl} R\text{-}\overset{O}{\overset{\|}{C}}\text{-}NH\text{-}R' + HCl \qquad (53)$$

25 R = $-CHCl_2$, R' = $-CH_3$

26 R = $-CCl_3$, R' = $-CH_3$

27 R = $-CH_2Cl$, R' = $-CH_2CH_3$

28 R = $-CHCl_2$, R' = $-CH_2CH_3$

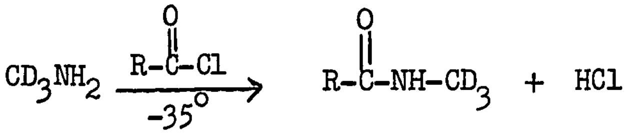
29 R= $-CCl_3$, R'= $-CH_2CH_3$

30 R= $-CH_2Cl$, R'= $-CH(CH_3)_2$

31 R= $-CHCl_2$, R'= $-CH(CH_3)_2$

32 R= $-CCl_3$, R'= $-CH(CH_3)_2$

$$\underset{}{CH_3NO_2} + D_2O \xrightarrow[\text{reflux}]{LiOD} \underset{33}{CD_3NO_2} \xrightarrow[2.\ H_2O]{1. LiAlD_4/Et_2O} \underset{34}{CD_3NH_2} \qquad (54a)$$

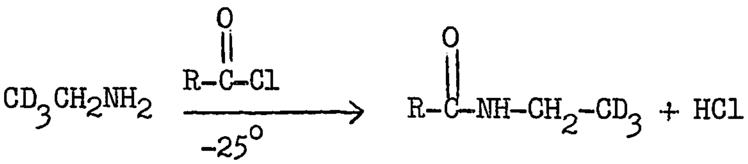


$$CD_3NH_2 \xrightarrow[-35^\circ]{R\text{-}\overset{O}{\overset{\|}{C}}\text{-}Cl} R\text{-}\overset{O}{\overset{\|}{C}}\text{-}NH\text{-}CD_3 + HCl \qquad (54b)$$

35 R = $-CHCl_2$

36 R = $-CCl_3$

$$CH_3CN + D_2O \xrightarrow{LiOD} \underset{\underline{37}}{CD_3CN} \xrightarrow[2.\ \ H_2O]{1.\ \ LiAlH_4/Et_2O} \underset{\underline{38}}{CD_3CH_2NH_2} \qquad (55a)$$



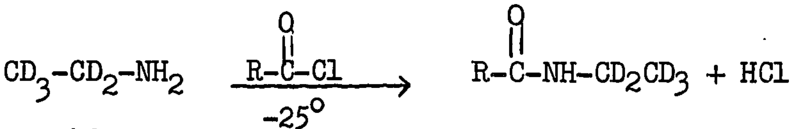
$$\underset{\underline{38}}{CD_3CH_2NH_2} \xrightarrow[-25^{\circ}]{R-\overset{\displaystyle O}{\overset{\|}{C}}-Cl} R-\overset{\displaystyle O}{\overset{\|}{C}}-NH-CH_2-CD_3 + HCl \qquad (55b)$$

$\underline{39}$ $R = -CH_2Cl$

$\underline{40}$ $R = -CHCl_2$

$\underline{41}$ $R = -CCl_3$

$$\underset{\underline{37}}{CD_3CN} \xrightarrow[2.\ \ H_2O]{1.\ \ LiAlD_4/Et_2O} \underset{\underline{42}}{CD_3-CD_2-NH_2} \qquad (56a)$$



$$\underset{\underline{42}}{CD_3-CD_2-NH_2} \xrightarrow[-25^{\circ}]{R-\overset{\displaystyle O}{\overset{\|}{C}}-Cl} R-\overset{\displaystyle O}{\overset{\|}{C}}-NH-CD_2CD_3 + HCl \qquad (56b)$$

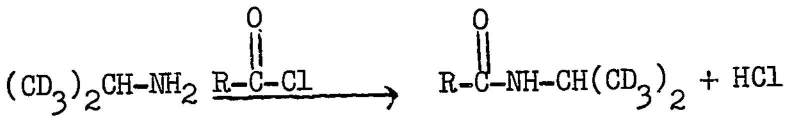
$\underline{43}$ $R = -CH_2Cl$

$\underline{44}$ $R = -CHCl_2$

$\underline{45}$ $R = -CCl_3$

$$(CH_3)_2C{=}O + \underset{\text{excess}}{D_2O} \xrightarrow{LiOD} \underset{\underline{46}}{(CD_3)_2C{=}O} \xrightarrow[D_2O]{NH_2OH} \underset{\underline{47}}{(CD_3)_2C{=}NOH} \qquad (57a)$$

$$\underset{\underline{47}}{(CD_3)_2C{=}NOH} \xrightarrow[2.\ \ H_2O]{1.\ \ LiAlH_4/Et_2O} \underset{\underline{48}}{(CD_3)_2CH-NH_2}$$



$$(CD_3)_2CH\text{-}NH_2 \xrightarrow{R\text{-}\overset{O}{\overset{\|}{C}}\text{-}Cl} R\text{-}\overset{O}{\overset{\|}{C}}\text{-}NH\text{-}CH(CD_3)_2 + HCl \qquad (57b)$$

48

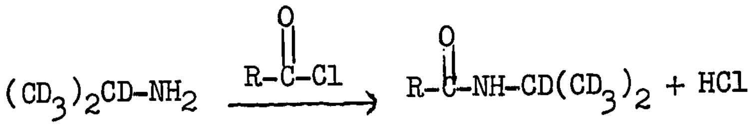
49 $R = -CH_2Cl$

50 $R = -CHCl_2$

51 $R = -CCl_3$

$$(CD_3)_2C{=}NOH \xrightarrow[2.\ H_2O]{1.\ LiAlD_4/Et_2O} (CD_3)_2CD\text{-}NH_2 \qquad (58a)$$

47 52



$$(CD_3)_2CD\text{-}NH_2 \xrightarrow{R\text{-}\overset{O}{\overset{\|}{C}}\text{-}Cl} R\text{-}\overset{O}{\overset{\|}{C}}\text{-}NH\text{-}CD(CD_3)_2 + HCl \qquad (58b)$$

52

53 $R = -CH_2Cl$

54 $R = -CHCl_2$

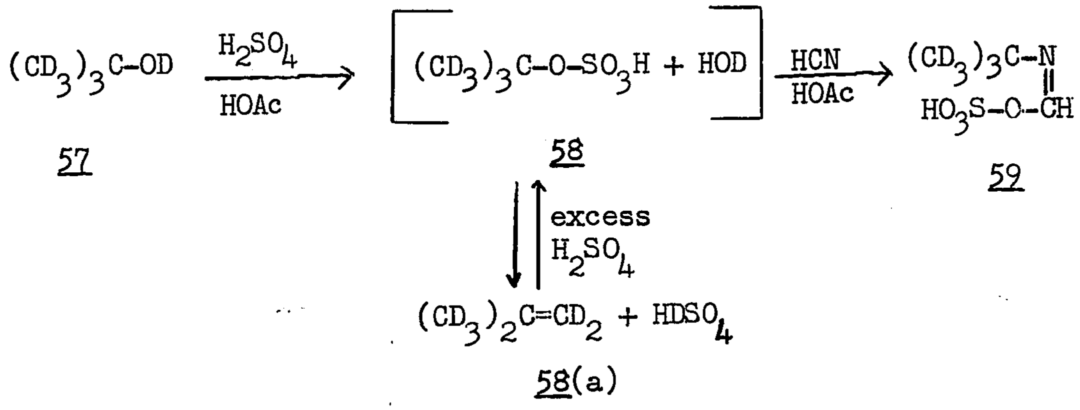
55 $R = -CCl_3$

$$(CH_3)_3C\text{-}Cl \leftrightarrows (CH_3)_2C{=}CH_2 + HCl \xrightarrow[D_2O]{10M\ DCl} (CD_3)_3C\text{-}Cl \qquad (59)$$

56

$$(CD_3)_3C\text{-}Cl \xrightarrow[D_2O]{LiOD} (CD_3)_3C\text{-}OD$$

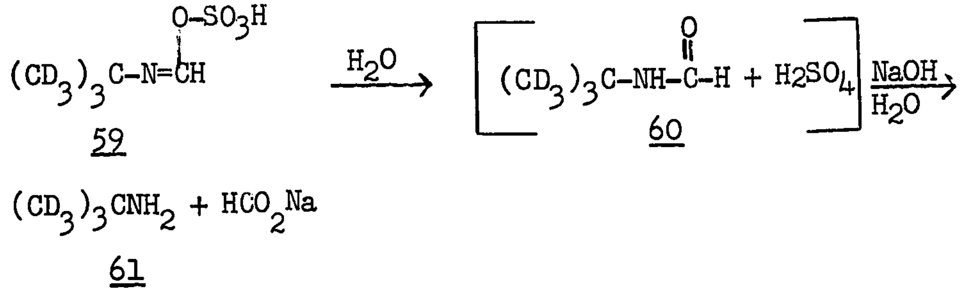
56 57



$$\underset{\underline{57}}{(CD_3)_3C\text{-}OD} \xrightarrow[HOAc]{H_2SO_4} \underset{\underline{58}}{\left[(CD_3)_3C\text{-}O\text{-}SO_3H + HOD\right]} \xrightarrow[HOAc]{HCN} \underset{\underline{59}}{\begin{matrix}(CD_3)_3C\text{-}N\\ \| \\ HO_3S\text{-}O\text{-}CH\end{matrix}} \quad (60a)$$

$$\underline{58} \underset{\text{excess } H_2SO_4}{\rightleftarrows} \underset{\underline{58}(a)}{(CD_3)_2C{=}CD_2 + HDSO_4}$$

(60a)



$$\underset{\underline{59}}{(CD_3)_3C\text{-}N{=}\overset{O\text{-}SO_3H}{\overset{|}{C}}H} \xrightarrow{H_2O} \underset{\underline{60}}{\left[(CD_3)_3C\text{-}NH\text{-}\overset{O}{\overset{\|}{C}}\text{-}H + H_2SO_4\right]} \xrightarrow[H_2O]{NaOH} \underset{\underline{61}}{(CD_3)_3CNH_2 + HCO_2Na}$$

(60b)

The deuterated amines (34, 38, 42, 48 and 52) formed according to schemes (54-58) were not isolated. These compounds were passed, with some diethyl ether, directly into the mixtures of the appropriate acid chlorides dissolved in 1,2-dichloroethane.

These schemes are straightforward and require little further elaboration. However, with two reactions, (54) and (60a,b), it was noted that some back exchange of hydrogen for deuterium was ocurring. In reaction (54), it was found that if lithium aluminum hydride was used for the reduction some exchange of the hydrogen atoms for the deuterium atoms took place. No improvment occured after working up the hydride reaction mixture with D_2O. When lithium aluminum deuteride was used for the reduction, exchange could still be detected since the final products 35 and 36 had a significantly higher percentage of deuterium incorporation than the starting nitromethane-d_3. Some exchange of hydrogen and deuterium atoms was also observed in the reaction forming the d_9-t-butylamine (61) from the deuterated alcohol (57). No experiments were conducted to ascertain at what stage of the reaction this exchange was taking place. However, it would seem that the most probable step at which back exchange could occur would be in the formation of 58(a) from the sulfate 58 in a step analogous to the formation of d_9-t-butylchloride *via* unsaturated olefin (scheme 59).

GENERAL

All formulae and structural assignments of fragments derived from amides 25 to 32 are based upon evidence from the mass spectra of the analogous deuterated amides, and in certain cases, upon high resolution measurements. The mass spectra of compounds 24 to 32 are shown in Figures 1, 3, 5, 7, 9, 11, 13, 15, and 17 respectively. The relative intensities of all peaks with $\%\Sigma_{36}$ greater than or equal to 0.8 are listed in Tables 7 to 15 of the Appendix. Some fragments of lower abundance, germaine to the discussion of the spectra of the other amides, are also included. The ion abundances (or intensities) in the discussion, are with respect to $\%\Sigma_{36}$ and are enclosed within brackets.

N-Methyl-α-chloroacetamide (24)

A. Fragmentation Peaks.

1. Primary fission processes.

Three peaks were observed which arose from the molecular ion (m/e 107). The first of these, at m/e 77 ($\%\Sigma_{36}$ 2.0), can be ascribed to the loss of the methylamino group from the molecular ion to give the fragment $[C_2H_2OCl]^{+}$. The base peak, at m/e 58, was probably formed by the loss of $\cdot CH_2Cl$ from the molecular ion (61), while the fragment at m/e 72 [4.2] was due to the loss of $\cdot Cl$ from the molecular ion (62). The structure of the ion at m/e 72 is discussed in Section B below.

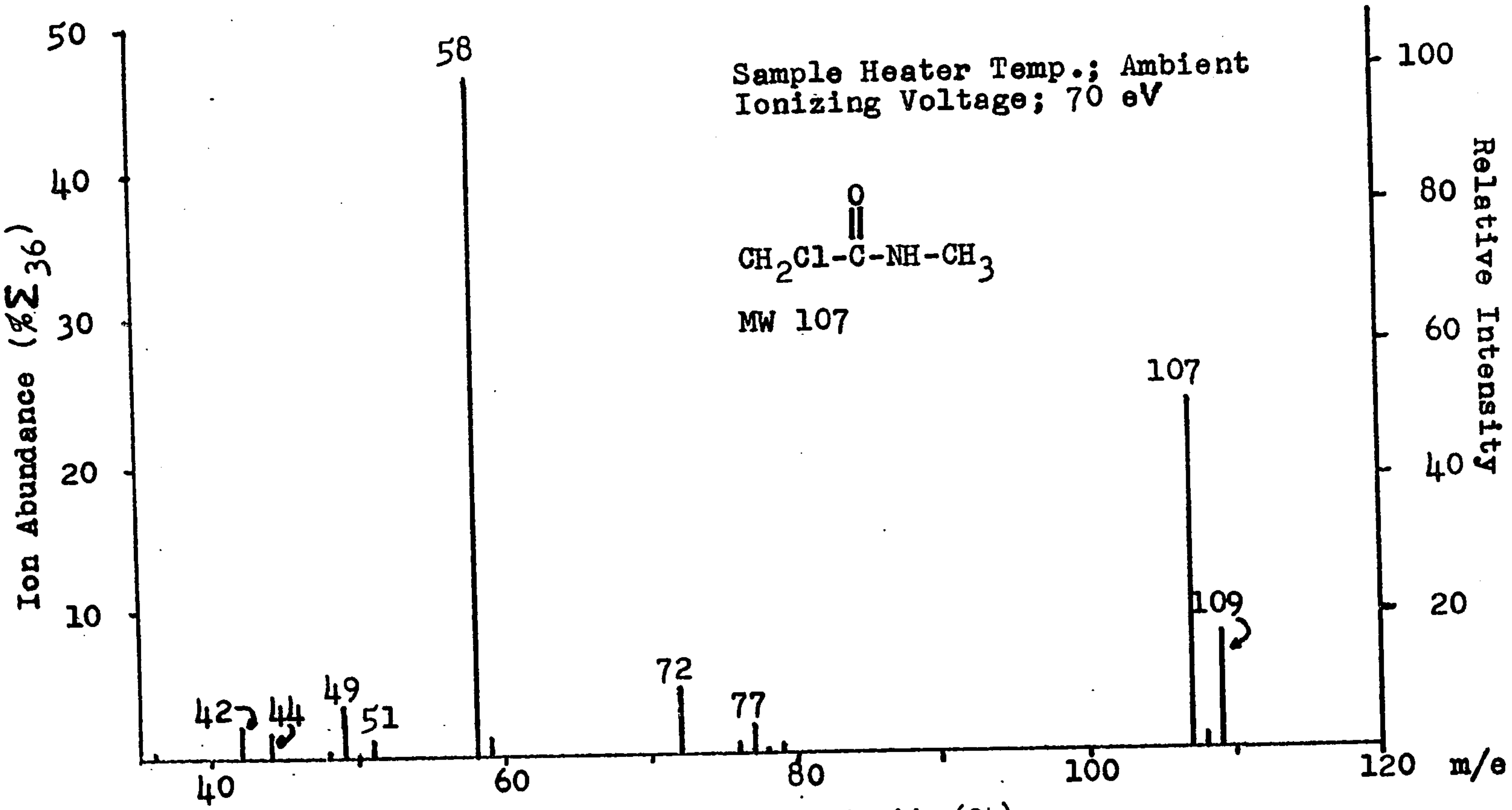
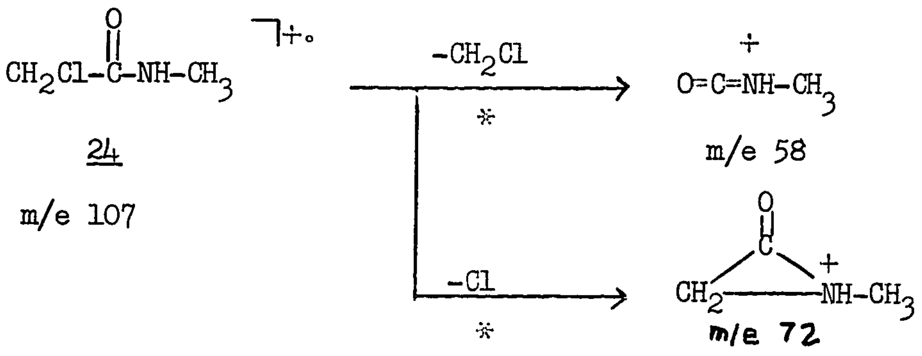


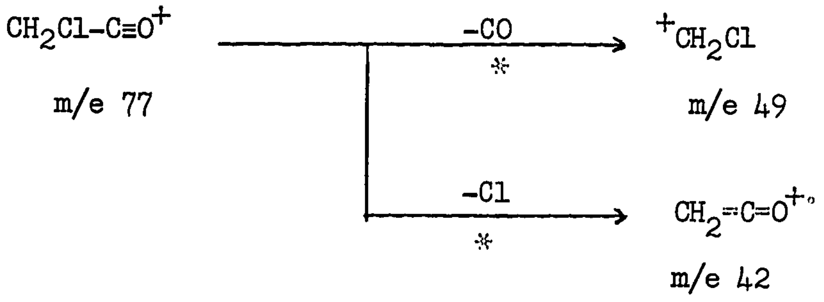
Fig. 1. Mass Spectrum of N-methyl-α-chloroacetamide (<u>24</u>).


(61)

(62)

2. Secondary fission processes.

The ion at m/e 77 could be demonstrated, by means of metastable decompositions, to be the precursor for two ions observed at m/e 49 and 42. These correspond to the loss of CO (m/e 49, process 63) from the ion at m/e 77 and the loss of Cl• (m/e 42, process 64) from the latter ion.


(63)

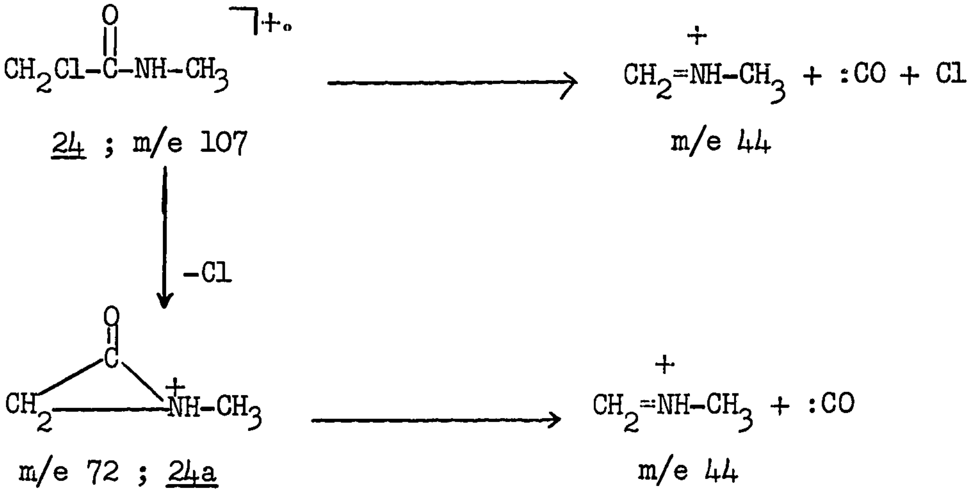
(64)

3. Ions whose sources were not established by metastable decompositions.

Only one significant fragment was observed whose source was not indicated by metastable decompositions, namely, $[C_2HOCl]^{+\cdot}$, (m/e 76)[1.3].

B. Rearrangement Ions.

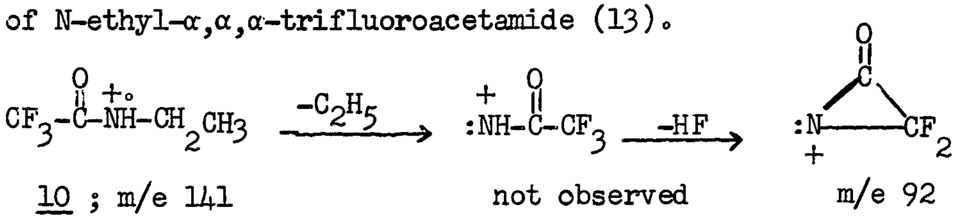
A fragment formed by a rearrangement process was observed at m/e 44, and was shown, by high resolution measurements, to be $[C_2H_6N]^+$ ($\%\Sigma_{36}$ 1.4). An ion of this formula may have arisen either from the molecular ion or from the fragment at m/e 72 as shown in schemes (65) and (66) respectively.



(65)

(66)

No appropriate metastable transitions were observed which would distinguish between the two possible precursor ions. However process (66) and Structure 24a are proposed for a number of reasons. Structure 24a resembles a protonated α-lactam. α-Lactams are known[8,9,10,11] to easily expel CO from their molecular ion, while such expulsion has not been reported for simple unhalogenated amides[1-7]. Saxby[3,4] has also proposed a similar structure in the fragmentation of N-ethyl-α,α,α-trifluoroacetamide (13).



(13)

A rearrangement peak was also observed at m/e 44 corresponding to the ion $[CH_2NO]^{+}$ [0.2]; this ion could be detected in the spectra of all the amides (24 to 32). However, only in the spectra of the N-ethyl amides (27, 28 and 29) was the peak for this fragment of sufficient abundance that, by examination of the spectra of the analogous deuterated compounds, the source of the migrating hydrogen atom could be determined.

The fragmentation processes which are believed to be taking place for 24 are summarized in Figure 2.

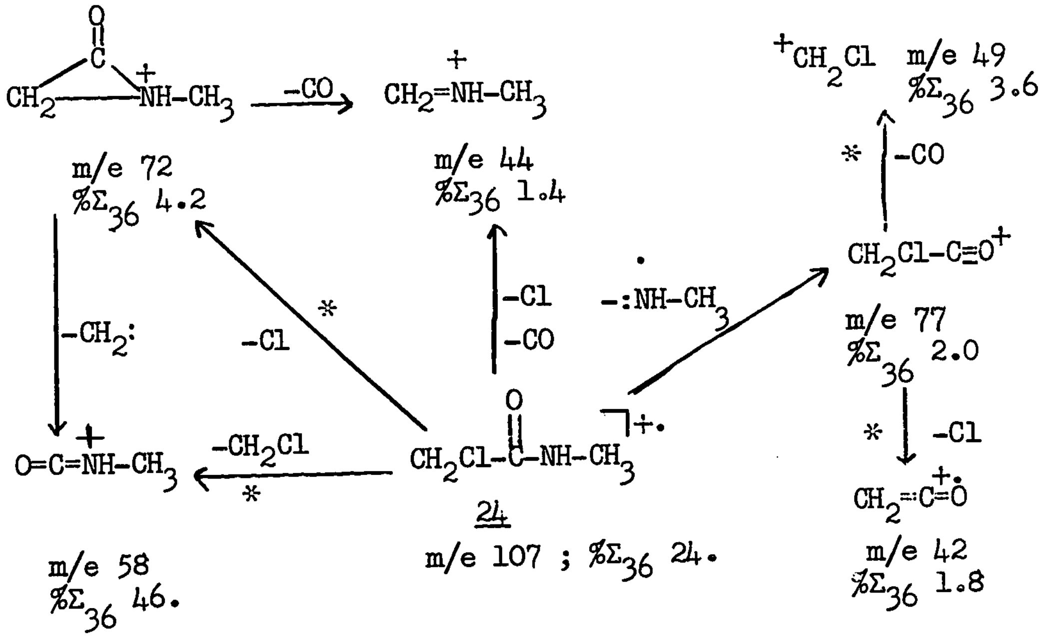


Fig. 2. Fragmentation processes for N-methyl-α-chloroacetamide (24).

N-Ethyl-α-chloroacetamide (27)

A. Fragmentation Peaks.

1. Primary Fission Processes.

Two ions were observed which were formed by fission of the

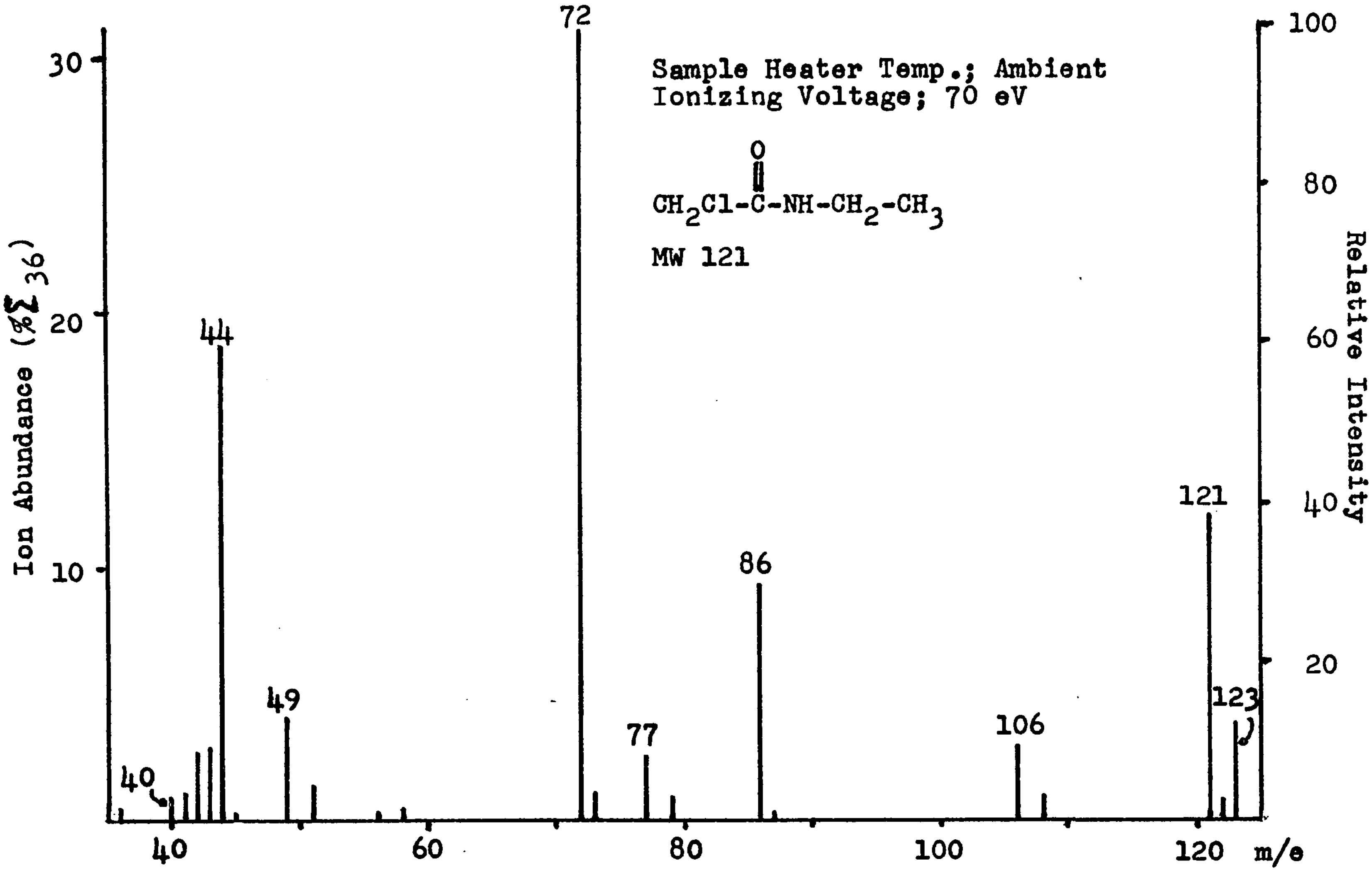
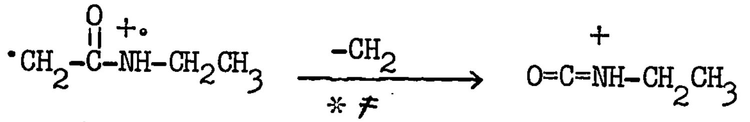


Fig. 3. Mass Spectrum of N-ethyl-α-chloroacetamide (27).

molecular ion, namely the ions at m/e 106 (M-CH_3)[3.0] and m/e 86 (M-Cl).[9.3]

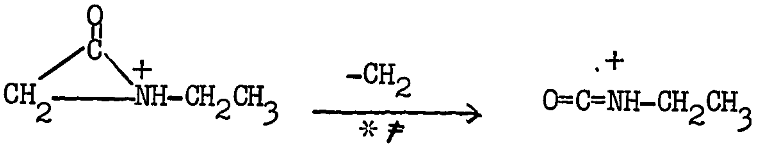
2. Secondary Fission Processes.

A number of secondary fission products were observed, in the spectrum of 27, the parent ions of which could be established by metastable decompositions. The base peak in the spectrum at m/e 72 arose *via* the loss of CH_2 from the fragment at m/e 86 (67a and 67b).



$$\cdot CH_2-\overset{\overset{O}{\|}}{C}{}^{+\cdot}-NH-CH_2CH_3 \xrightarrow[* \neq]{-CH_2} \overset{+}{O=C=NH-CH_2CH_3} \qquad (67a)$$

m/e 86 27b ; m/e 72

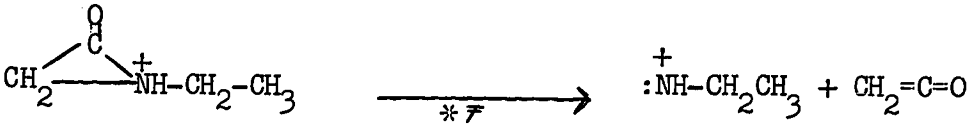


(67b)

27a ; m/e 86 27b ; m/e 72

Process (67b) has also been described for α-lactams[8-11] (see 28c). The somewhat unusual expulsion of $:CH_2$ from a lactam could be rationalized on the basis of the high stability of the resulting ion (27b).

The ion at m/e 86 also gave rise to an ion at m/e 44, $[C_2H_6N]^+$, $\%\Sigma_{36}$ 4.5, by the expulsion of ketene as shown in (68), a result in substantial agreement with the observations of Djerassi[2], Lengyel[8,11] and Baumgarten[10].

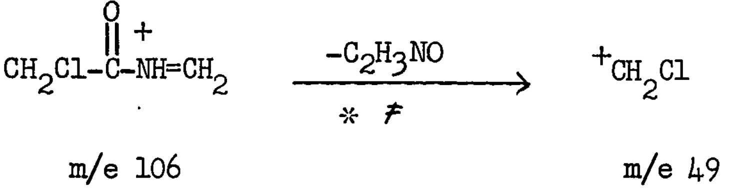


(68)

m/e 86 m/e 44

It was ascertained that only one half of the ion $[C_2H_6N]^+$ had the structure shown above. The other portion of this ion having a rearranged structure is discussed in Section B below.

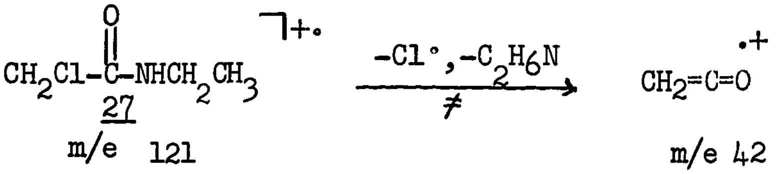
The ion at m/e 49 clearly could have arisen from a number of different precursors (69). It was however established, that the $M^{+}\text{-}CH_3$ ion (m/e 106) constituted a source for this fragment.



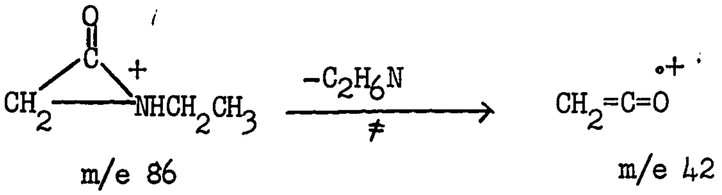
$$\underset{m/e\ 106}{CH_2Cl\text{-}\overset{\overset{O}{\|}}{C}\text{-}\overset{+}{N}H{=}CH_2} \xrightarrow[* \neq]{-C_2H_3NO} \underset{m/e\ 49}{{}^{+}CH_2Cl} \qquad (69)$$

Studies of metastable ion decompositions and results from the deuterium labelled compounds, demonstrated that the peak at m/e 42, $[C_2H_2O]^{+\bullet}$ [1.4] was formed by the loss of •Cl from the ion at m/e 77 and by cleavage of the molecular and $M^{+}\text{-}Cl$ ions (70a-c).

$$\underset{m/e\ 77}{CH_2Cl\text{-}C{\equiv}O^+} \xrightarrow[* \neq]{} \underset{m/e\ 42}{CH_2{=}C{=}\overset{+}{O}^{\bullet}} + {}^{\bullet}Cl \qquad (70a)$$



$$\underset{m/e\ 121}{\left[CH_2Cl\text{-}\overset{\overset{O}{\|}}{\underset{\underline{27}}{C}}\text{-}NHCH_2CH_3\right]^{+\bullet}} \xrightarrow[\neq]{-Cl^{\bullet},-C_2H_6N} \underset{m/e\ 42}{CH_2{=}C{=}O^{\bullet +}} \qquad (70b)$$



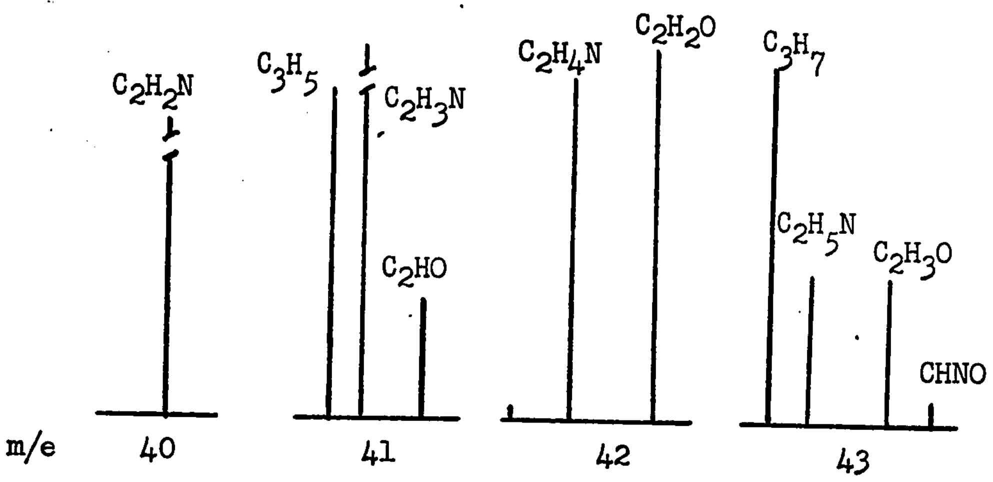
(70c)

These processes appeared to be common to this group of compounds. Thus, the dichloro-and trichloro-amides gave rise to the corresponding monochloro- and dichloro-ketene ions respectively. It would appear that neither increasing alkyl substitution nor increasing chlorination appreciably affects the probability of this ion being formed, since the intensities of the corresponding peaks were approximately the same in all nine spectra ($\%\Sigma_{36}$ 0.6-1.8). However, the precursor ion, M^+ -NMR, (R = Me, Et or i-Pr) virtually disappeared in the spectra of the dichloro- and trichloroacetamides. This is in agreement with the spectra of all the trifluoro derivatives[3,4,5,7] in which the ion $[CF_3\text{-}C{=}O]^+$ was consistently absent but the fragment $CF_2{=}C{=}O^{+\cdot}$ was always observed.

3. Ions whose sources were not established by metastable decompositions.

Six fragments were observed at m/e 77, 43, 42, 41 and 40 the precursors of which could not be established by metastable decompsotions. Chlorine isotope patterns and high resolution measurements clearly demonstrated the nature of these ions.

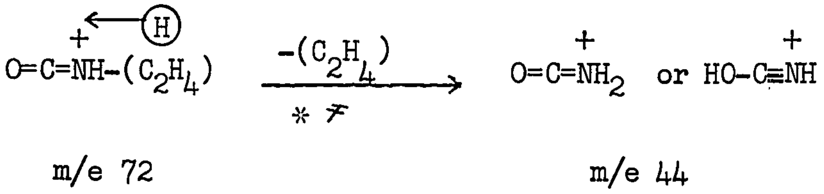
$CH_2Cl\text{-}C{\equiv}O^+$	$[C_2H_5N]^{+\cdot}$	$[C_2H_4N]^+$	$[C_2H_3N]^{+\cdot}$	$[C_2H_2N]^+$	$[C_3H_5]^+$
m/e 77	m/e 43	m/e 42	m/e 41	m/e 40	m/e 41
$\%\Sigma_{36}$ 2.5	$\%\Sigma_{36}$ 0.5	$\%\Sigma_{36}$ 1.3	$\%\Sigma_{36}$ 0.7	$\%\Sigma_{36}$ 0.9	$\%\Sigma_{36}$ 0.3



A portion of the high resolution spectrum of N-ethyl-α-chloro-acetamide (27).

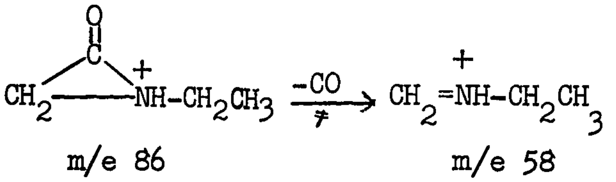
B. Rearrangement Ions.

Five rearrangement ions were observed in the spectrum of the monochloro-N-ethyl acetamide. One of these, at m/e 44 $\%\Sigma_{36}$ 14., appears to have been formed from the ion at m/e 72 by cleavage of the ethyl group and migration of a hydrogen atom. The source of the migrating atom has been established by deuterium labelling to be, in part, the C-1 and, in part, the C-2 atoms of the N-alkyl chain.

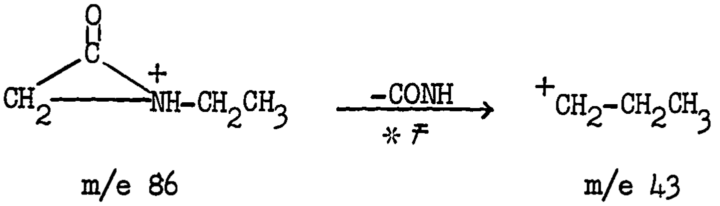


$$\overset{+}{O=C}=NH-(C_2H_4) \xrightarrow[* \neq]{-(C_2H_4)} O=\overset{+}{C}=NH_2 \text{ or } HO-\overset{+}{C}\equiv NH \qquad (71)$$

Two other fragments arising from rearrangement processes were both derived from the ion at m/e 86. One, at m/e 58 [0.4], was formed by the loss of CO from the fragment at m/e 86, and the other, at m/e 43 by the loss of CONH from this ion, as shown in (72) and (73) respectively.



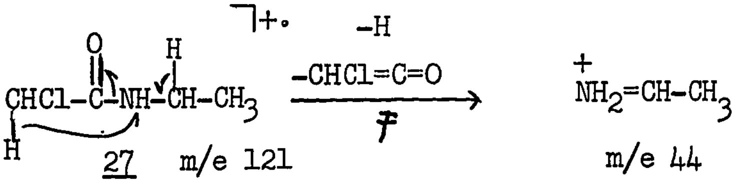
(72)



(73)

The latter process (73) is interesting and has not hitherto been reported in the spectra of any amides. The intensity of this ion (%Σ_{36} 1.4) was far from negligable, comparing favorably with the intensity of the peak due to the ketene ion, common to the spectra of all previously reported amides.

Examination of the deuterated amides showed that the peak due to $[C_2H_6N]^+$ consisted partially of a fragment which was formed by a rearrangement process found also to be significant in the N-isopropyl amides. (see also p.72) In the spectra of the N-isopropyl amides, the analogous process was found to occur by cleavage of the carbon-carbon bond beta to the nitrogen atom, accompanied by the migration of a hydrogen atom from the α-carbon atom to the nitrogen containing fragment as described by Gilpin[1] and Djerassi[2] (processes 1 and 3-8). However, in the spectrum of the monochloro-N-ethyl amide, it appears that this process took place by the cleavage of a carbon-hydrogen bond beta to the nitrogen atom rather than by fission of a carbon-carbon bond.



$$\left[\underset{\underset{H}{|}}{C}HCl{-}\overset{\overset{O}{\|}}{C}{-}NH{-}\overset{\overset{H}{|}}{C}H{-}CH_3\right]^{+\cdot} \xrightarrow[\mp]{-H \atop -CHCl{=}C{=}O} \overset{+}{N}H_2{=}CH{-}CH_3 \qquad (74)$$

27 m/e 121 m/e 44

Only one rearrangement fragment was observed whose source was not substantiated by a metastable transition. This ion appeared at m/e 43 and was due to the ion $[C_2H_3O]^+$, a formula suggesting either a protonated ketene ion, $CH_2{=}C{=}\overset{+}{O}H$, or an acetyl residue, $CH_3{-}C{\equiv}O^+$. In the formation of either of these possible structures, hydrogen atom migration must occur; however it was not possible to determine the source of the migrating hydrogen atom since the intensity of the ion [0.8] was too low for deuterium labelling to yield any significant information.

A general scheme, shown in Figure 4, summarizes the processes which are now believed to be taking place for the monochloro-N-ethyl amide.

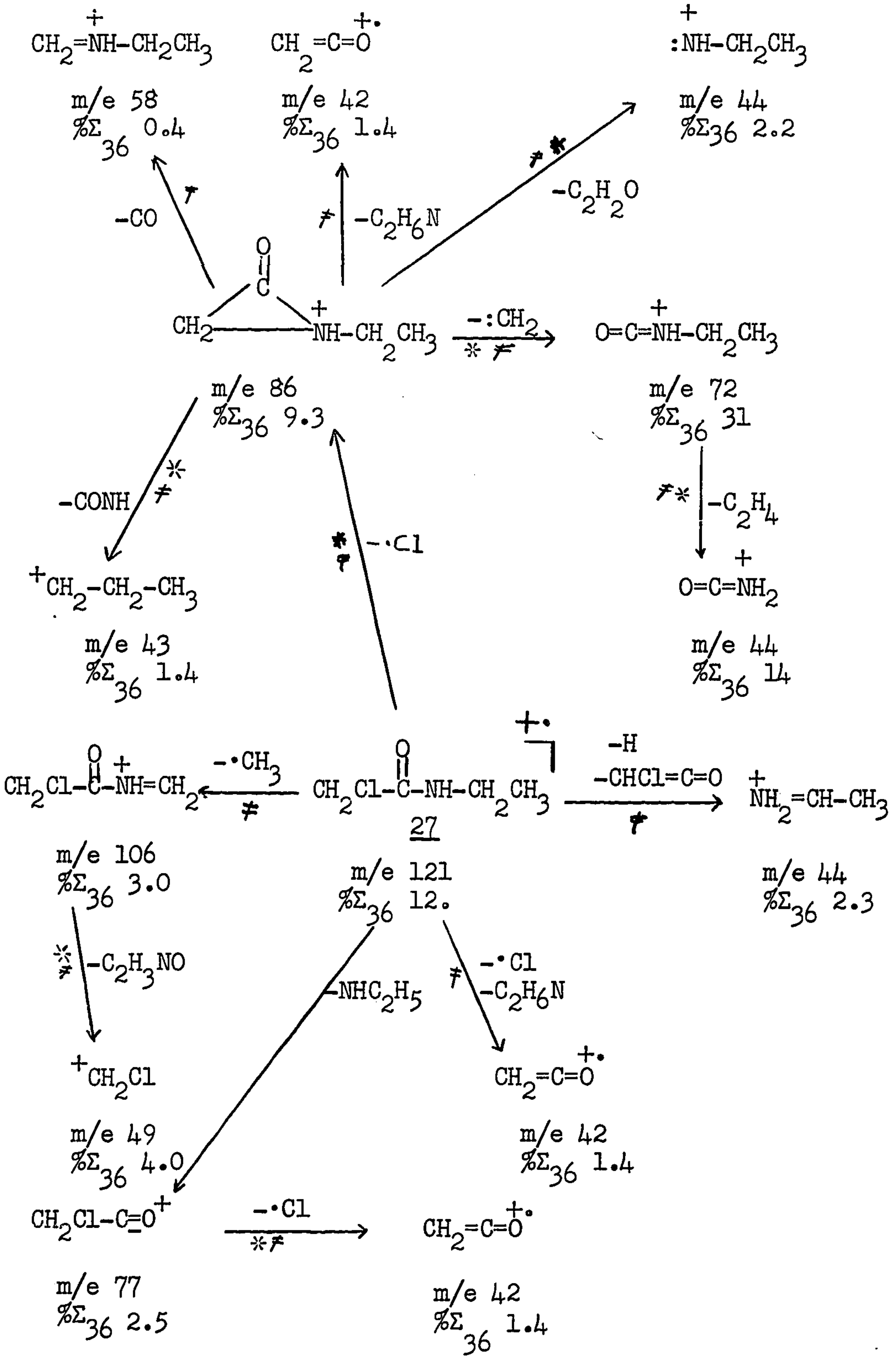


Fig. 4. Fragmentation processes for N-ethyl-α-chloroacetamide (27).

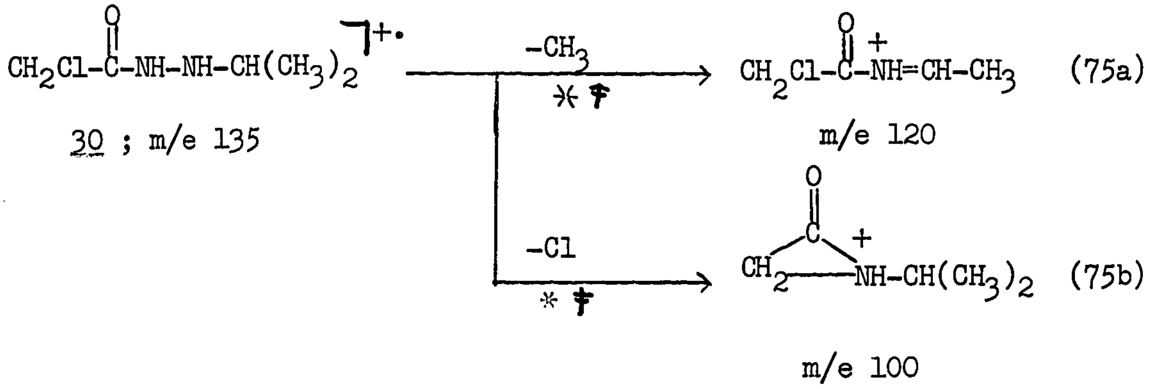
N-Isopropyl-α-chloroacetamide (30)

A. Fragmentation Peaks.

As would be expected the spectrum of the N-isopropyl amide was by far the most complex of the three monochloro amides.

1. Primary Fission Processes.

For the N-isopropyl amide, two peaks were observed which were formed by simple fission of the molecular ion. These are shown in (75a) and (75b) and in common with the other amides correspond to the loss of CH_3 and Cl respectively from the molecular ion, with intensities of 12 and 6.7 respectively.



$$\left[CH_2Cl-\overset{O}{\overset{\|}{C}}-NH-NH-CH(CH_3)_2\right]^{+\cdot} \xrightarrow[* \dagger]{-CH_3} CH_2Cl-\overset{O}{\overset{\|}{C}}-\overset{+}{N}H{=}CH-CH_3 \quad (75a)$$

2. Secondary fission processes.

Two ions whose sources were suggested by metastable decompositions appeared in the spectrum of 30. The first of these occured at m/e 86 [5.1] and was formed by the loss of $:CH_2$ from the fragment at m/e 100 (76a). This has been mentioned previously as being a type of fragmentation common to α-lactams[8-11] (process 67b). This ion may also have been formed by direct cleavage of the molecular ion (76b).

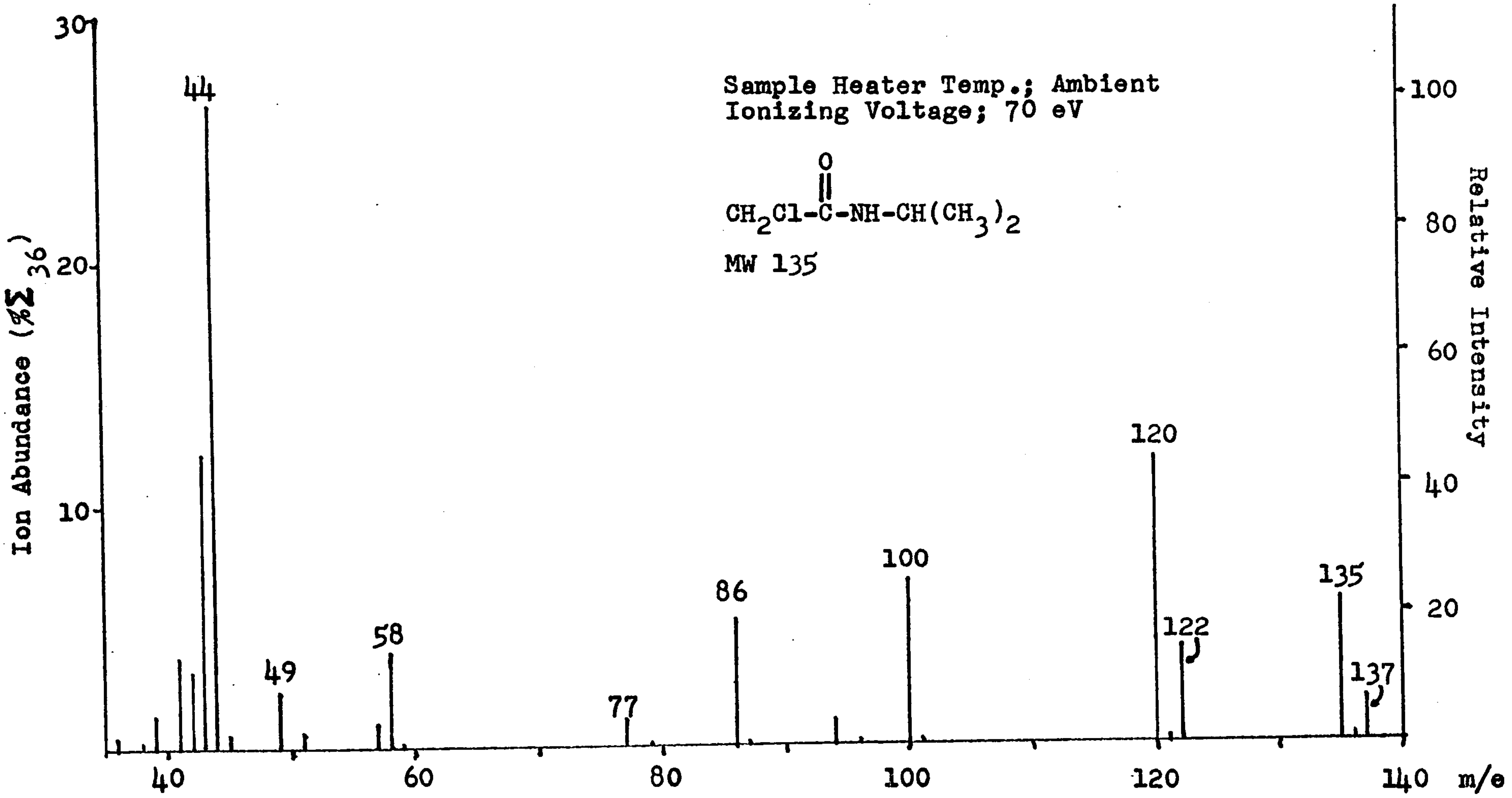
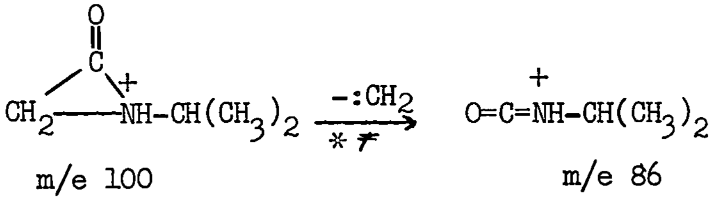
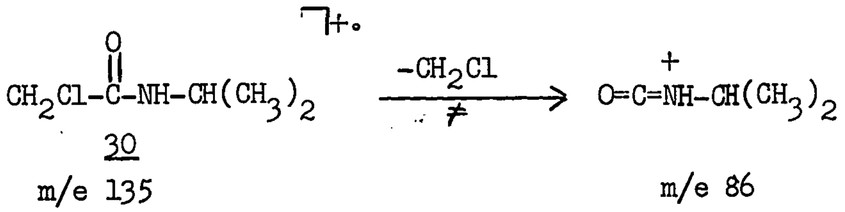


Fig. 5. Mass spectrum of N-isoporpyl-α-chloroacetamide (<u>30</u>).



$$\mathrm{O{=}C{=}\overset{+}{N}H\text{-}CH(CH_3)_2}$$

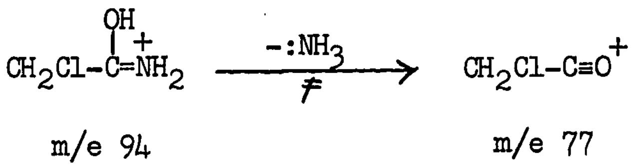
(76a)



$$\underset{\underset{\text{m/e 135}}{\underline{30}}}{\mathrm{CH_2Cl\text{-}\overset{\overset{O}{\|}}{C}\text{-}NH\text{-}CH(CH_3)_2}}\ \urcorner^{+\cdot} \xrightarrow[\neq]{-\mathrm{CH_2Cl}} \underset{\text{m/e 86}}{\mathrm{O{=}C{=}\overset{+}{N}H\text{-}CH(CH_3)_2}}$$

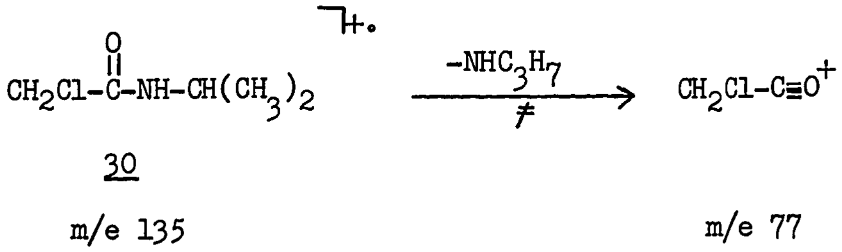
(76b)

The other fragment formed by a secondary fission process occured at m/e 77 and was formed by the loss of NH_3 from the double rearrangement ion at m/e 94 (77a) and by the loss of the isopropyl amino group from the molecular ion (77b).



$$\underset{\text{m/e 94}}{\mathrm{CH_2Cl\text{-}\overset{\overset{OH}{|}}{C}{=}\overset{+}{N}H_2}} \xrightarrow[\neq]{-:\mathrm{NH_3}} \underset{\text{m/e 77}}{\mathrm{CH_2Cl\text{-}C{\equiv}O^+}}$$

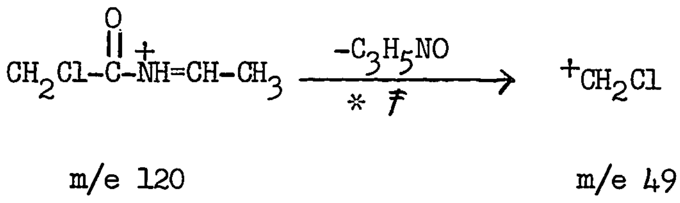
(77a)



$$\underset{\underset{\text{m/e 135}}{\underline{30}}}{\mathrm{CH_2Cl\text{-}\overset{\overset{O}{\|}}{C}\text{-}NH\text{-}CH(CH_3)_2}}\ \urcorner^{+\cdot} \xrightarrow[\neq]{-\mathrm{NHC_3H_7}} \underset{\text{m/e 77}}{\mathrm{CH_2Cl\text{-}C{\equiv}O^+}}$$

(77b)

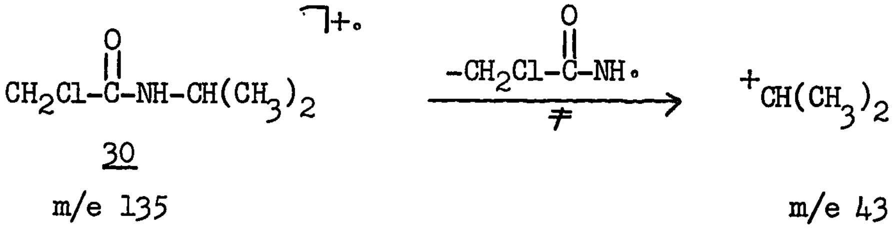
Isotope patterns demonstrated that the peak at m/e 49 corresponded to the ion $^+CH_2Cl$; however the precursor(s) to this ion are in some doubt. It was, however, established that the M^+-CH_3 fragment was one source for this ion (78).



$$\mathrm{CH_2Cl{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}\overset{+}{N}H{=}CH{-}CH_3} \xrightarrow[*\ \neq]{-\mathrm{C_3H_5NO}} {}^{+}\mathrm{CH_2Cl} \qquad (78)$$

m/e 120 m/e 49

Part of the multiplet, observed under high resolution conditions, at m/e 43 could be demonstrated to be the isopropyl ion. Metastable transitions established that this fragment was formed by cleavage of the molecular ion or the ion at m/e 86, and had a relative abundance of 10.



$$\left[\mathrm{CH_2Cl{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}NH{-}CH(CH_3)_2}\right]^{+\cdot} \xrightarrow[\neq]{-\mathrm{CH_2Cl{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}NH\cdot}} {}^{+}\mathrm{CH(CH_3)_2} \qquad (79a)$$

30

m/e 135 m/e 43

$$\mathrm{O{=}C{=}\overset{+}{N}H{-}CH(CH_3)_2} \xrightarrow[*\ \neq]{-\mathrm{HNCO}} {}^{+}\mathrm{CH(CH_3)_2} \qquad (79b)$$

m/e 86 m/e 43

A portion of the peak at m/e 42 was due to the fragment $[C_2H_2O]^{+}$ [0.8], which was derived from the ion at m/e 77 (80).

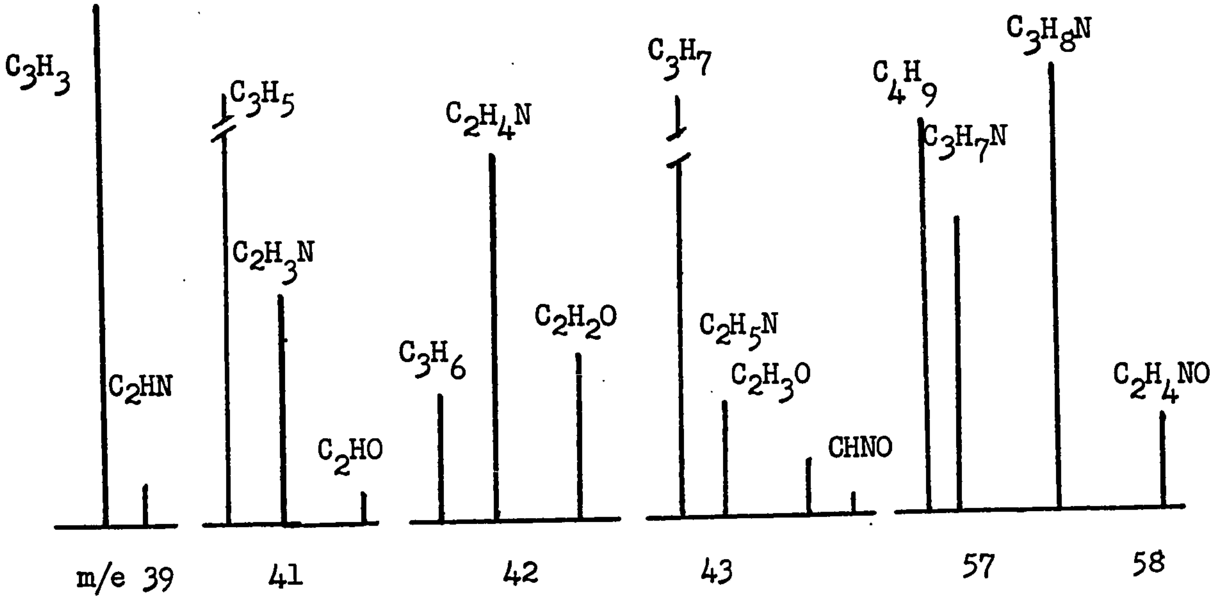
$$\mathrm{CH_2Cl{-}C{\equiv}O^{+}} \xrightarrow[*\ \neq]{-\cdot\mathrm{Cl}} \mathrm{CH_2{=}C{=}O^{+\cdot}} \qquad (80)$$

m/e 77 m/e 42

3. Ions whose sources were not established by metastable transitions.

The regions at m/e 58 to 57 and 43 to 39 were examined under high resolution conditions.

In each nominal mass region a large number of peaks were observed whose origins could not be established with certainty by metastable decompositions.



A portion of the high resolution spectrum of N-isopropyl-α-chloroacetamide (<u>30</u>).

The major portion, $\%\Sigma_{36}3.4$, of the doublet at m/e 58 could be ascribed to $[C_3H_8N]^+$. From the spectra of the analogous deuterated amides, it appeared that most of the ions had a structure which corresponded to fragmentation without rearrangement, i.e. simple fission of the aminoalkyl portion of the amide to give a fragment of the type $^+NH\text{-}CH(CH_3)_2$. This appears to have been accompanied by a small amount of ^2H scrambling.

The remainder of the fragments of undetermined origin most probably arose from successive loss of hydrogen atoms from the isopropyl ion to give fragments at m/e 42, 41 and 39.

$[C_3H_6]^{+\cdot}$ $[C_3H_5]^{+}$ $[C_3H_3]^{+}$

m/e 42 m/e 41 m/e 39

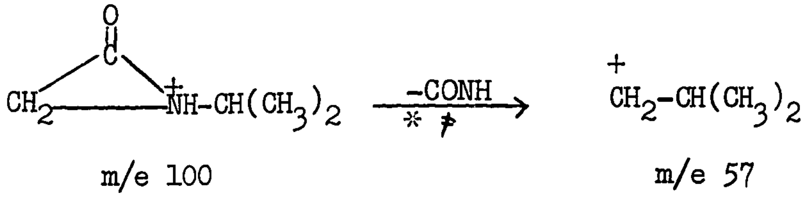
The ion at m/e 44, $[C_2H_6N]^{+}$, the source of which is discussed in Section B, underwent similar processes to yield ions at m/e 43, 42 and 41.

$[C_2H_5N]^{+\cdot}$ $[C_2H_4N]^{+}$ $[C_2H_3N]^{+\cdot}$

m/e 43 m/e 42 m/e 41

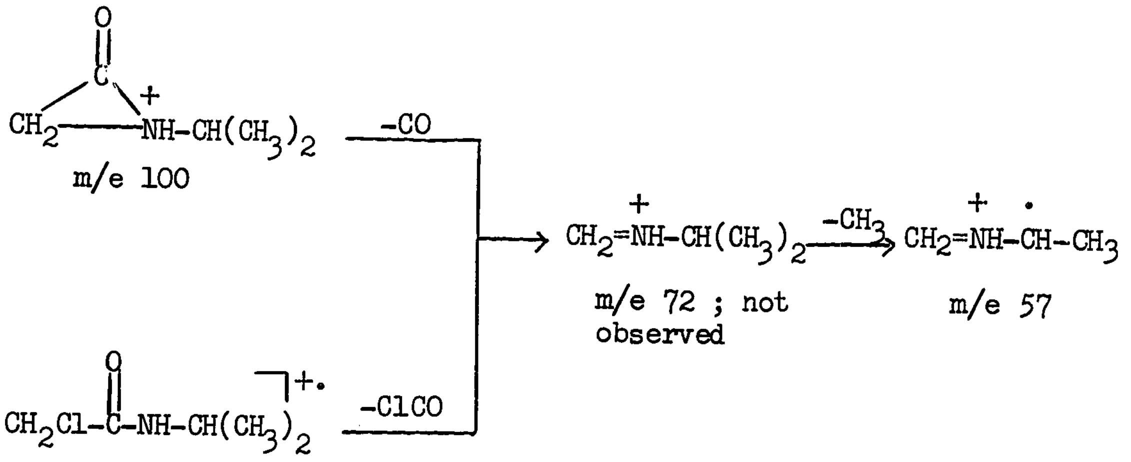
B. Rearrangement Ions.

High resolution measurements disclosed that approximately half of the peak at nominal m/e 57 could be ascribed to the fragment $[C_4H_9]^{+}$ [0.6] which appeared to be formed directly from the ion at m/e 100 (81).



(81)

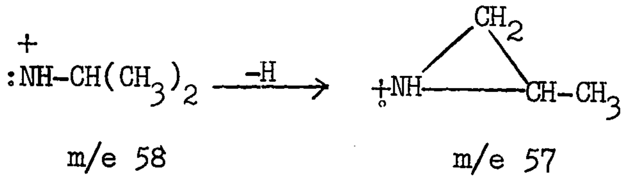
This process is analogous to the fragmentation and rearrangement (process 73) observed for the monochloro-N-ethyl acetamide. A second ion occured at the same nominal mass and was shown to be $[C_3H_7N]^{+}$. It is believed that the peak at m/e 57, corresponding to $[C_3H_7N]^{+}$ [0.5], could be derived from two different precursors: the accuracy of this assessment could be demonstrated by studies of labelled compounds. Thus, the major portion of the peak at m/e 57 in the light compound was observed at m/e 60 in the spectrum of the d_6-amide and at m/e 61 in the spectrum of the d_7-amide. These results showed that the major portion of the ion retained only one methyl group of the isopropyl group. It could thus be deduced that this fragment was primarily due to an ion which was formed by the loss of a methyl group from an unobserved rearrangement ion occurring at m/e 72 (82).



30 ; m/e 135

(82)

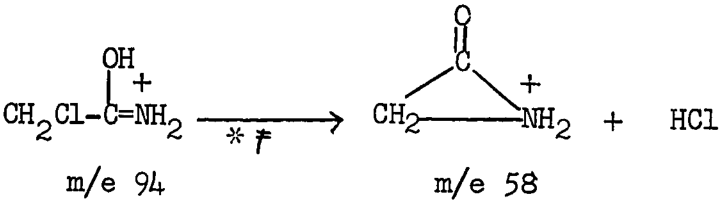
This is analogous to processes (29), (30), (32) and (35) which were described for the α-lactams. From the above data it may be inferred that the ion at m/e 72 was decomposing to the ion at m/e 57 so rapidly that only the daughter ion was observed. A small portion of the fragment $[C_3H_7N]^{+}$ was due to the loss of one hydrogen atom from the CH_3 portion of the ion at m/e 58.



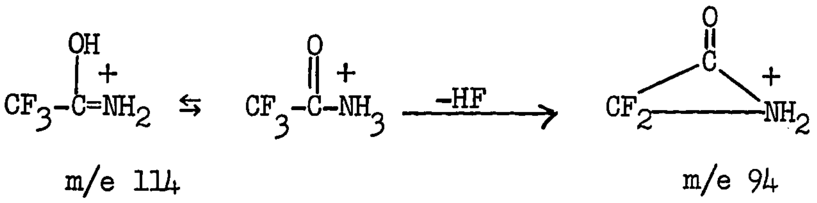
(83)

In agreement with the assignment of the structures shown, a portion of this fragment was observed five mass units higher in the spectrum of the d_6-amide and six mass units higher in the spectrum of the d_7-amide.

An ion which was observed in all the N-isopropyl amides, as well as the α-lactams, appeared at m/e 58 [0.6] in the spectrum of the monochloro-N-isopropyl acetamide. Examination of metastable transitions suggested that this ion was formed by the loss of HCl from the fragment at m/e 94 as shown in (84). A similar process has also been observed by Saxby[3,4] and Prox and Schmid[7] in the spectra of the trifluoro derivatives (process 17).



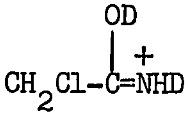
(84)



(17)

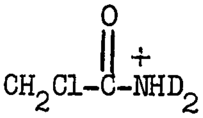
The spectra of the analogous deuterated compounds established that the hydrogen atom, lost as HCl was bonded to the oxygen atom.

The ion observed at m/e 94 in the spectrum of 30, was observed at m/e 96 in the spectra of the analogous d_6- and d_7-amides thus showing that both of the hydrogen atoms involved in the migration were derived from the methyl groups of the iso-propyl side chain. The spectrum of the d_7 amide also showed no peak whatsoever at m/e 60, but an ion at m/e 59 was present in both cases. The above data established that the ion at m/e 58, in the spectrum of 30, if derived from the fragment at m/e 94, must have been formed by the loss of a deuterium atom and a chlorine atom. This specific loss of deuterium, establishes the hitherto ambiguous structure of the double rearrangement ion at m/e 94 to be analogous to 30b. The tautomeric fragment of structure 30c is incompatable with these results, since 30c would be expected to lose a hydrogen or deuterium atom.



$CH_2Cl-\overset{+}{C}(OD)=NHD$

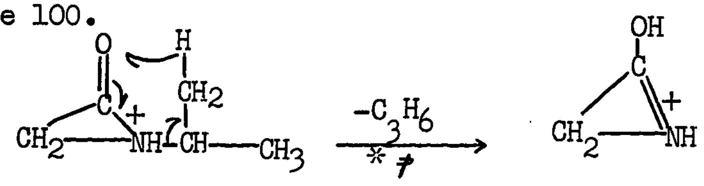
30b



$CH_2Cl-\overset{+}{C}(=O)-NHD_2$

30c

Observed appropriate metastable decompositions indicated that the ion at m/e 58 may also have been formed from the fragment at m/e 100.

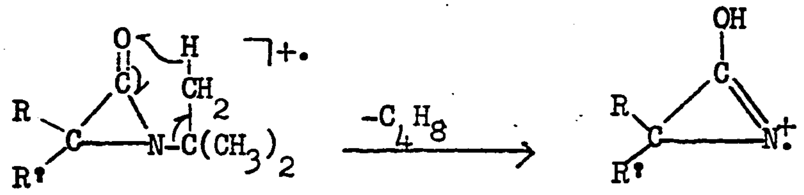


(85)

m/e 100

m/e 58

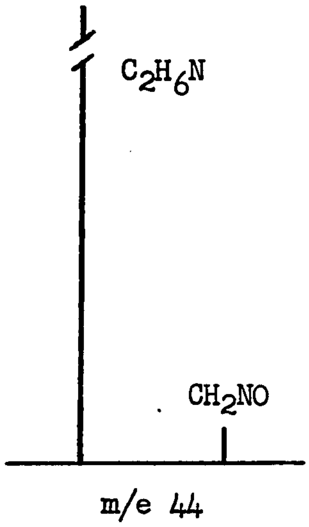
Baumgarten[10] has also reported a similar fragmentation mechanism in the spectra of the α-lactams as illustrated by process (38).



(38)

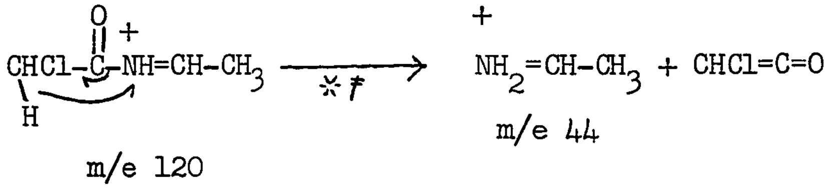
Clearly, both processes (84) and (85) would give rise to ions at m/e 59 in the spectra of the analogous deuterated amides.

The base peak of the spectrum appeared at m/e 44 and was ascribed to the ion $[C_2H_6N]^+$ on the basis of high resolution measurements.



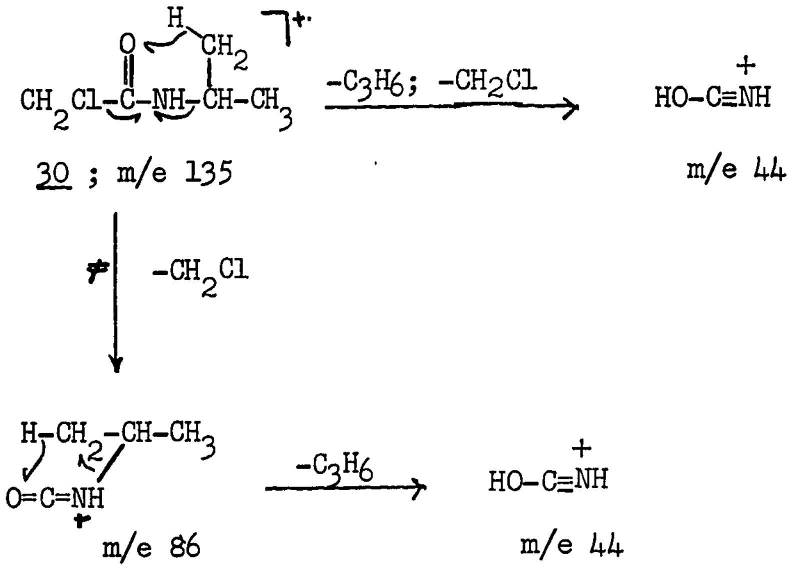
A portion of the high resolution spectrum of N-isopropyl-α-chloroacetamide (<u>30</u>).

This ion is exactly analogous to a fragment observed by Gilpin[1] and Djerassi[2] in the spectra of alkyl acetamides (see processes 1 and 3-8). The ion was formed by cleavage of the carbonyl-nitrogen bond, and the carbon-carbon bond beta to the nitrogen atom with the migration of one hydrogen atom from the α-carbon atom to the nitrogen containing fragment.



(86)

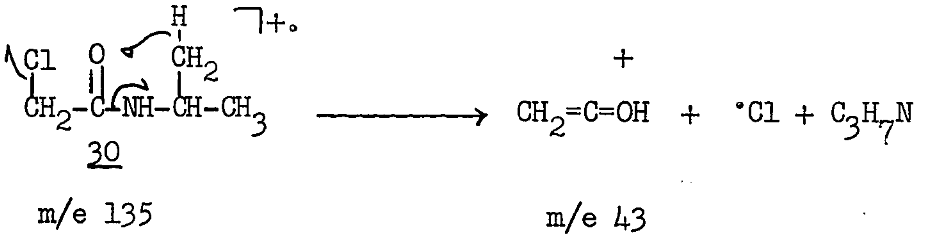
This rearrangement process also led to the formation of the base peak in the spectra of the amides studied by Gilpin and Pelah. High resolution measurements revealed that the peak at m/e 44 also consisted partly [1.1] of the ion $[CH_2NO]^+$. The presence of this ion is consistent with a McLafferty-like rearrangement subsequent, or prior to, fission of the chloromethylene side chain (87a, 87b).



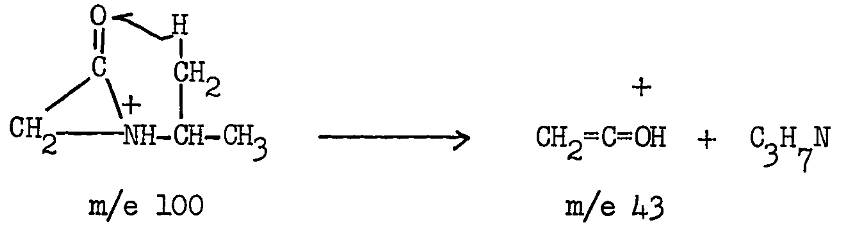
(87a)

(87b)

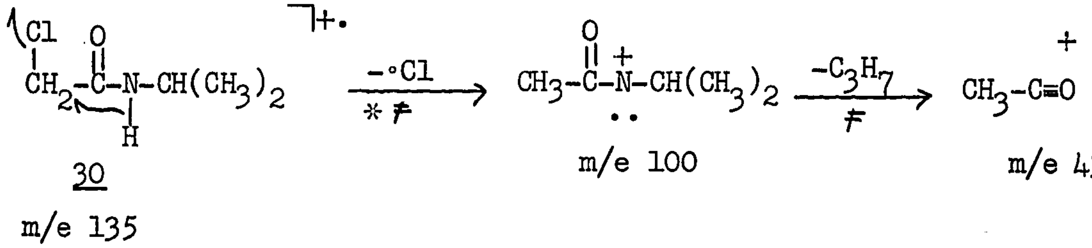
It was also demonstrated by high resolution measurements that the fragment $[C_2H_3O]^+$ made a small contribution [0.5] to the peak at m/e 43. Of the many possible structures, which may be written for this rearrangement fragment, two of the more probable structures and their modes of formation are illustrated below (88 a,b and c).



(88a)



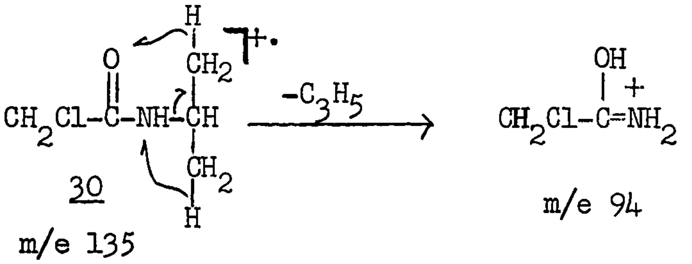
(88b)



(88c)

The task of distinguishing between the above three schemes proved to be difficult. It was not possible to determine exactly the origin of the migrating hydrogen atom. Conceivably, processes (88a) and (88b) are similar to the McLafferty rearrangement described by process (87). Scheme (88c) must also be considered, since, in the spectra of the di- and trichloroacetamides, the rearrangement ions $^+CH_2Cl$ and $^+CHCl_2$ were respectively observed. It is interesting to note that Saxby[3,4] also reported the presence of the rearrangement ion $^+CHF_2$ in the spectra of the α,α,α-trifluoroacetamides.

A double rearrangement process which has been reported by Djerassi[2] (process 9) and Saxby[3,4] (process 14) was also observed in the spectrum of 30. This ion, $[C_2H_5NOCl]^{+\cdot}$, $\%\Sigma_{36}$ 1.1, at m/e 94, was formed as illustrated by process (89), where both migrating hydrogen atoms are derived from the methyl groups of the isopropyl side chain. The structure of this ion has been discussed previously (p.41). Prox and Schmid[7] also observed the ion $[C_2H_3NOF_3]^+$ in the mass spectra of the compounds which they studied.

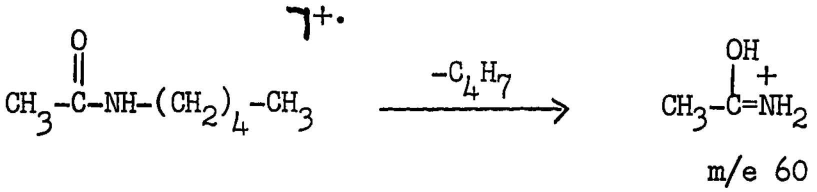


$$\left[CH_2Cl-\overset{\overset{O}{\|}}{C}-NH-\underset{\underset{H}{|}}{\underset{CH_2}{|}}{\overset{\overset{H}{|}}{\overset{CH_2}{|}}{CH}}\right]^{+\cdot} \xrightarrow{-C_3H_5} CH_2Cl-\overset{\overset{OH}{|}}{C}\overset{+}{=}NH_2 \qquad (89)$$

30

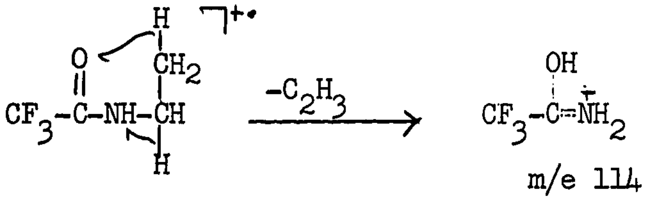
m/e 135

m/e 94



$$\left[CH_3-\overset{\overset{O}{\|}}{C}-NH-(CH_2)_4-CH_3\right]^{+\cdot} \xrightarrow{-C_4H_7} CH_3-\overset{\overset{OH}{|}}{C}\overset{+}{=}NH_2 \qquad (9)$$

m/e 60



$$\left[CF_3-\overset{\overset{O}{\|}}{C}-NH-\underset{\underset{H}{|}}{\overset{\overset{H}{|}}{\overset{CH_2}{|}}{CH}}\right]^{+\cdot} \xrightarrow{-C_2H_3} CF_3-\overset{\overset{OH}{|}}{C}=\overset{+}{N}H_2 \qquad (14)$$

m/e 114

The fragmentation processes which are now believed to be taking place for 30 are summarized in Figure 6.

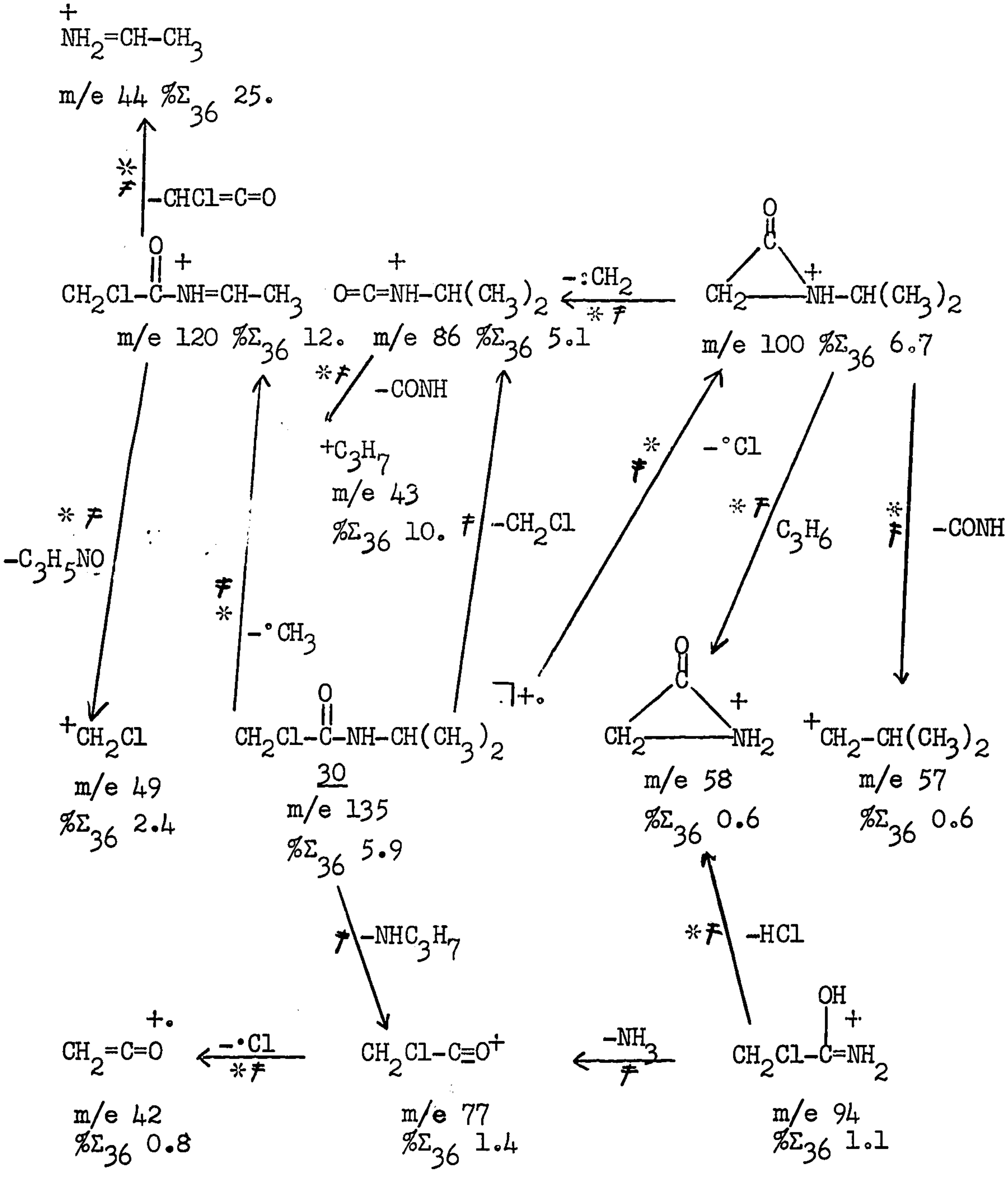


Fig. 6. Fragmentation processes for N-isopropyl-α-chloroacetamide (30).

N-Methyl-α,α-dichloroacetamide (25)

A. Fragmentation Peaks.

1. Primary Fission Processes.

Two fragments in the spectrum of 25 formed by fission of the molecular ion (m/e 141) were analogous to those found for the monochloro-N-methyl amide. Thus, loss of Cl° from the molecular ion yielded a fragment at m/e 106 [0.4] and loss of $^{\cdot}CHCl_2$ produced the base peak at m/e 58. However, the fragment formed by the loss of the methylamino group from the molecular ion to form an ion of the type $CHCl_2\text{-}C{\equiv}O^+$, was not observed in the spectrum of the dichloro amide, probably due to the rapid decomposition of the latter ion.

2. Secondary Fission Processes.

No ions produced by secondary fission processes were observed whose sources could be established by metastable decompositions.

3. Ions whose sources were not established by metastable decompositions.

Four ions were formed in the mass spectrum of 25, the parent ions of which were not indicated by metastable transitions. However, by comparison with the spectrum of N-methyl-α-chloroacetamide (24), it may be postulated that two of these ions were formed from a fragment which decomposed rapidly within the source and therefore was not observed. These two fragments appeared at m/e 76 [1.4] and m/e 83 [2.7] and were established by deuterium labelling studies to be $CHCl{=}C{=}O^{+\circ}$ and $^{+}CHCl_2$ respectively.

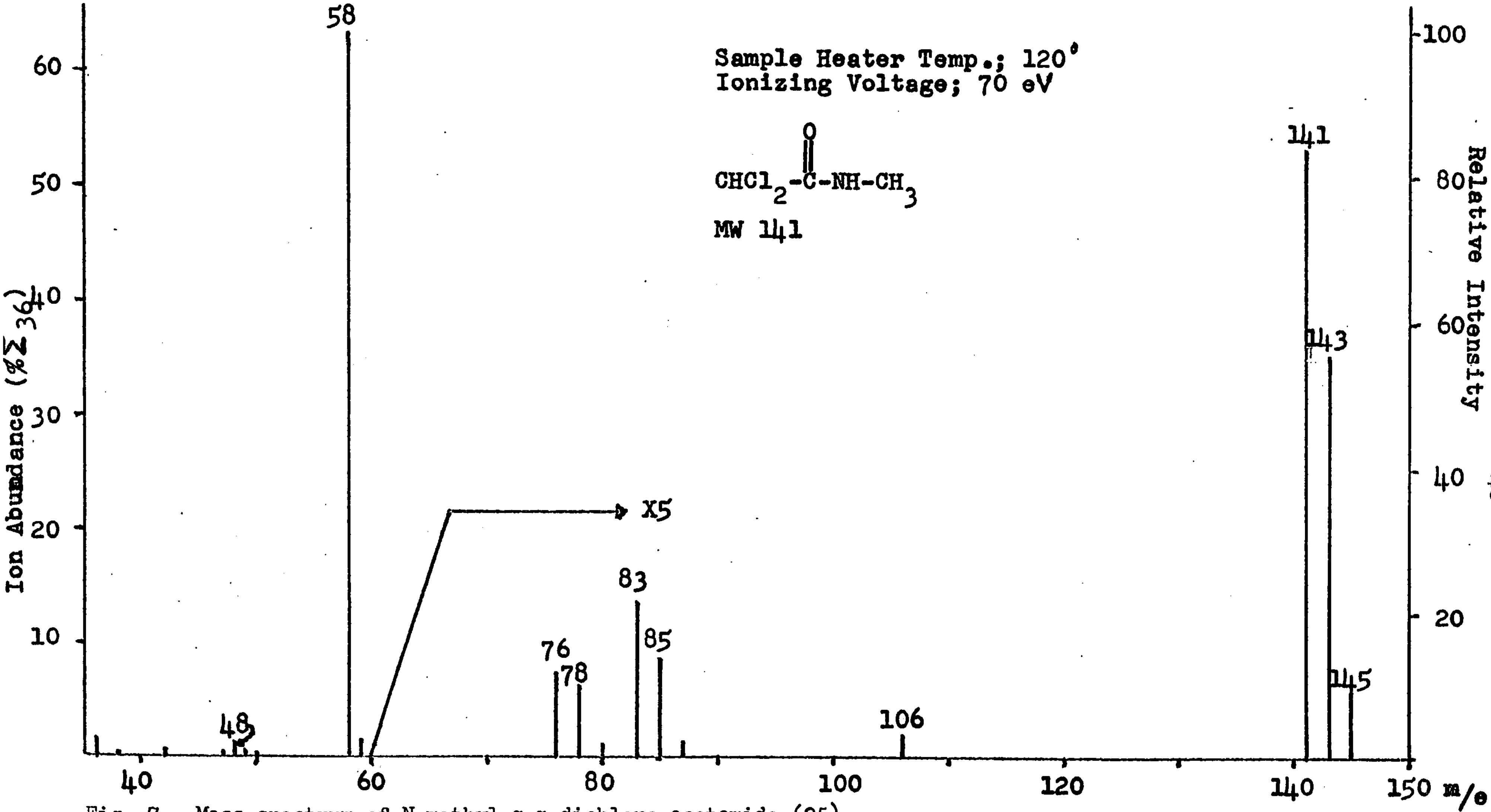
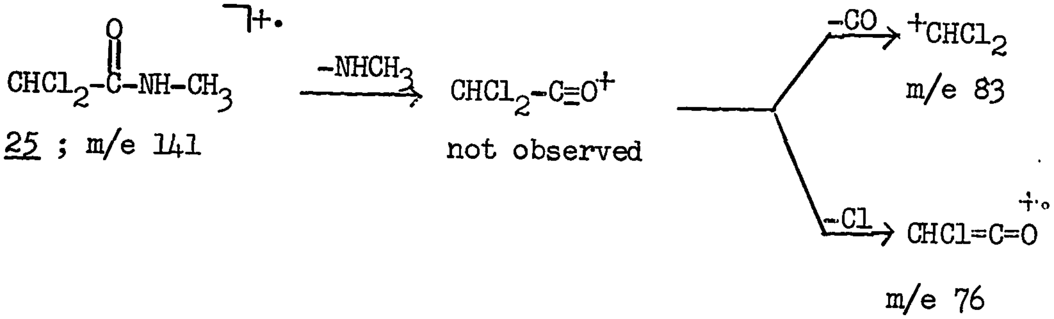


Fig. 7. Mass spectrum of N-methyl-α,α-dichloro-acetamide (25).

Processes (90a) and (90b) analogous to (61) and (62) for the monochloro derivative, depict how the ions at m/e 76 and 83 were formed.



$$\mathrm{CHCl_2{-}\overset{O}{\overset{\|}{C}}{-}NH{-}CH_3}\,]^{+\cdot} \xrightarrow{-\mathrm{NHCH_3}} \mathrm{CHCl_2{-}C{\equiv}O^+} \xrightarrow{-\mathrm{CO}} {}^{+}\mathrm{CHCl_2} \qquad (90a)$$

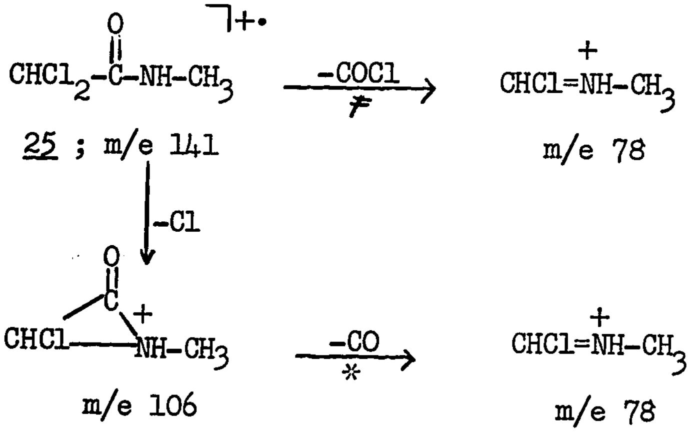
$$\mathrm{CHCl_2{-}C{\equiv}O^+} \xrightarrow{-\mathrm{Cl}} \mathrm{CHCl{=}C{=}\overset{+\cdot}{O}} \qquad (90b)$$

25 ; m/e 141 → not observed → m/e 83 (90a); m/e 76 (90b)

The other two fragments, whose precursors were not determined, appeared at m/e 48 [1.5] and 47 [0.6] and corresponded to $^{+\cdot}$CHCl and :$^{+}$CCl respectively.

B. Rearrangement Ions.

A fragment formed by a rearrangement process, exactly analogous to a process observed in the spectrum of the monochloromethyl amide, appeared at m/e 78, $\%\Sigma_{36}$ 1.0. Metastable decompositions suggested that this ion, $[\mathrm{C_2H_5NCl}]^+$, was formed by the two modes of fragmentation which are shown in (91a) and (91b).



$$\mathrm{CHCl_2{-}\overset{O}{\overset{\|}{C}}{-}NH{-}CH_3}\,]^{+\cdot} \xrightarrow[\not *]{-\mathrm{COCl}} \mathrm{CHCl{=}\overset{+}{N}H{-}CH_3} \qquad (91a)$$

25 ; m/e 141 → m/e 78

$$\xrightarrow{-\mathrm{CO}}_{*} \mathrm{CHCl{=}\overset{+}{N}H{-}CH_3} \qquad (91b)$$

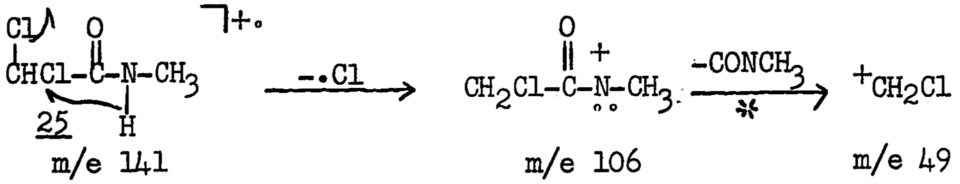
m/e 106 → m/e 78

These processes, (91a) and (91b), are similar to (65) and (66) for the monochloromethyl amide (24). As was mentioned previously (page23), process (66) is common to the electron impact spectra of α-lactams [8-11].

Metastable transitions indicated that the fragment at m/e 78 further decomposed, by losing HCl, to an ion at m/e 42 [0.8]. Deuterium labelling established that some of the hydrogen atoms lost as HCl had been bonded to the nitrogen atom and some had been bonded to the carbon atom of the methyl group. Thus the fragment at m/e 42 was observed partitioned between m/e 44 and m/e 45 in the spectrum of the analogous d_3-amide.

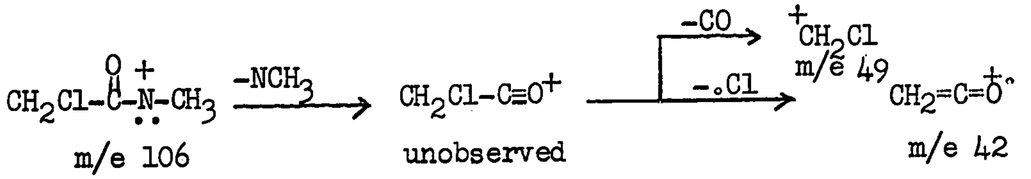
$$\underset{m/e\ 78}{\mathrm{CHCl{=}\overset{+}{N}H\text{-}CH_3}} \xrightarrow[*\neq]{-\mathrm{HCl}} \underset{m/e\ 42}{[\mathrm{C_2H_2N}]^+} \qquad (92)$$

Two further rearrangement ions appearing at m/e 49 [0.5] and m/e 42 [0.1], supported process (88c) which was postulated for N-isopropyl-α-chloroacetamide (30). The ions CH_2Cl^+ (m/e 49) and $[C_2H_2O]^{+\cdot}$ (m/e 42), were probably formed as shown in (93) and (94) respectively.



$$\underset{m/e\ 141}{\left[\mathrm{\overset{Cl}{\overset{|}{C}}HCl\text{-}\overset{O}{\overset{\|}{C}}\text{-}\underset{\underset{H}{|}}{N}\text{-}CH_3}\right]^{+\cdot}} \xrightarrow{-\cdot\mathrm{Cl}} \underset{m/e\ 106}{\mathrm{CH_2Cl\text{-}\overset{O}{\overset{\|}{C}}\text{-}\overset{+}{\underset{\circ\circ}{N}}\text{-}CH_3}} \xrightarrow[*]{-\mathrm{CONCH_3}} \underset{m/e\ 49}{{}^+\mathrm{CH_2Cl}} \qquad (93)$$

25



$$\underset{m/e\ 106}{\mathrm{CH_2Cl\text{-}\overset{O}{\overset{\|}{C}}\text{-}\overset{+}{\underset{\bullet\bullet}{N}}\text{-}CH_3}} \xrightarrow{-\mathrm{NCH_3}} \underset{\text{unobserved}}{\mathrm{CH_2Cl\text{-}C{\equiv}O^+}} \begin{cases} \xrightarrow{-\mathrm{CO}} \underset{m/e\ 49}{{}^+\mathrm{CH_2Cl}} \\ \xrightarrow{-\cdot\mathrm{Cl}} \underset{m/e\ 42}{\mathrm{CH_2{=}C{=}\overset{+}{O}{}^{\cdot}}} \end{cases} \qquad (94)$$

A general scheme, shown in Figure 8, summarizes the processes taking place.

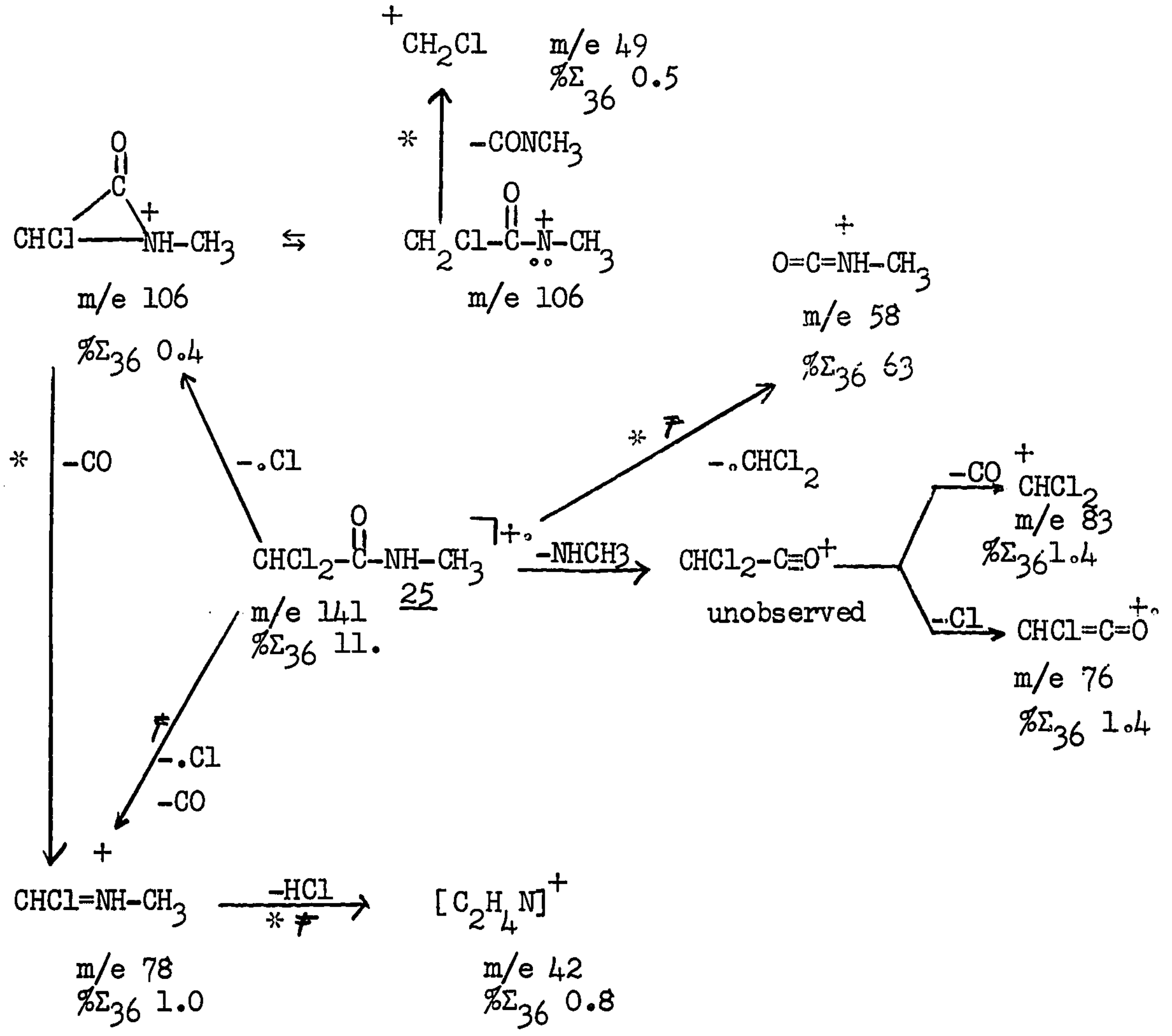


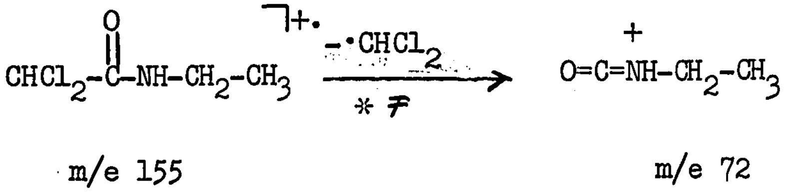
Fig. 8 Fragmentation processes for N-methyl-α,α-dichloroacetamide (25).

N-Ethyl-α,α-dichloroacetamide (28)

A. Fragmentation Peaks.

1. Primary Fission Processes.

As in the case of the monochloro-N-ethyl amide (27), two peaks were formed by simple fission of the molecular ion (m/e 155). These appeared at m/e 140 [1.8] and 120 [0.7] and were due to the loss of $\cdot CH_3$ and $\cdot Cl$ respectively. However, in the spectrum of 28, it was readily ascertained from metastable transitions, that the base peak of the spectrum at m/e 72 arose by the loss of $\cdot CHCl_2$ from the molecular ion.



$$\mathrm{CHCl_2\text{-}\overset{\overset{O}{\|}}{C}\text{-}NH\text{-}CH_2\text{-}CH_3}\,\rceil^{+\cdot} \xrightarrow[\ast\ \neq]{-\cdot CHCl_2} \overset{+}{\mathrm{O{=}C{=}NH\text{-}CH_2\text{-}CH_3}} \qquad (95)$$

m/e 155 m/e 72

This is in contrast to the fragmentation pattern observed for the N-ethyl-monochloro amide, in which the base peak, again at m/e 72, was formed in a stepwise manner by cleavage of $:CH_2$ from the fragment corresponding to the loss of $\cdot Cl$ from the molecular ion (processes 67a and 67b).

This difference in the mode of formation of the base peak may be rationalized on the basis of the low abundance [0.7] of the $(M^+\text{-}Cl)$ fragment in the dichloro amide compared to the high intensity [9.3] of the $(M^+\text{-}Cl)$ ion in the monochloro amide. Consideration must also be given to the possibility that the fragment at m/e 72 was formed by both pathways and that the metastable decompositions were observed for only one of the two processes.

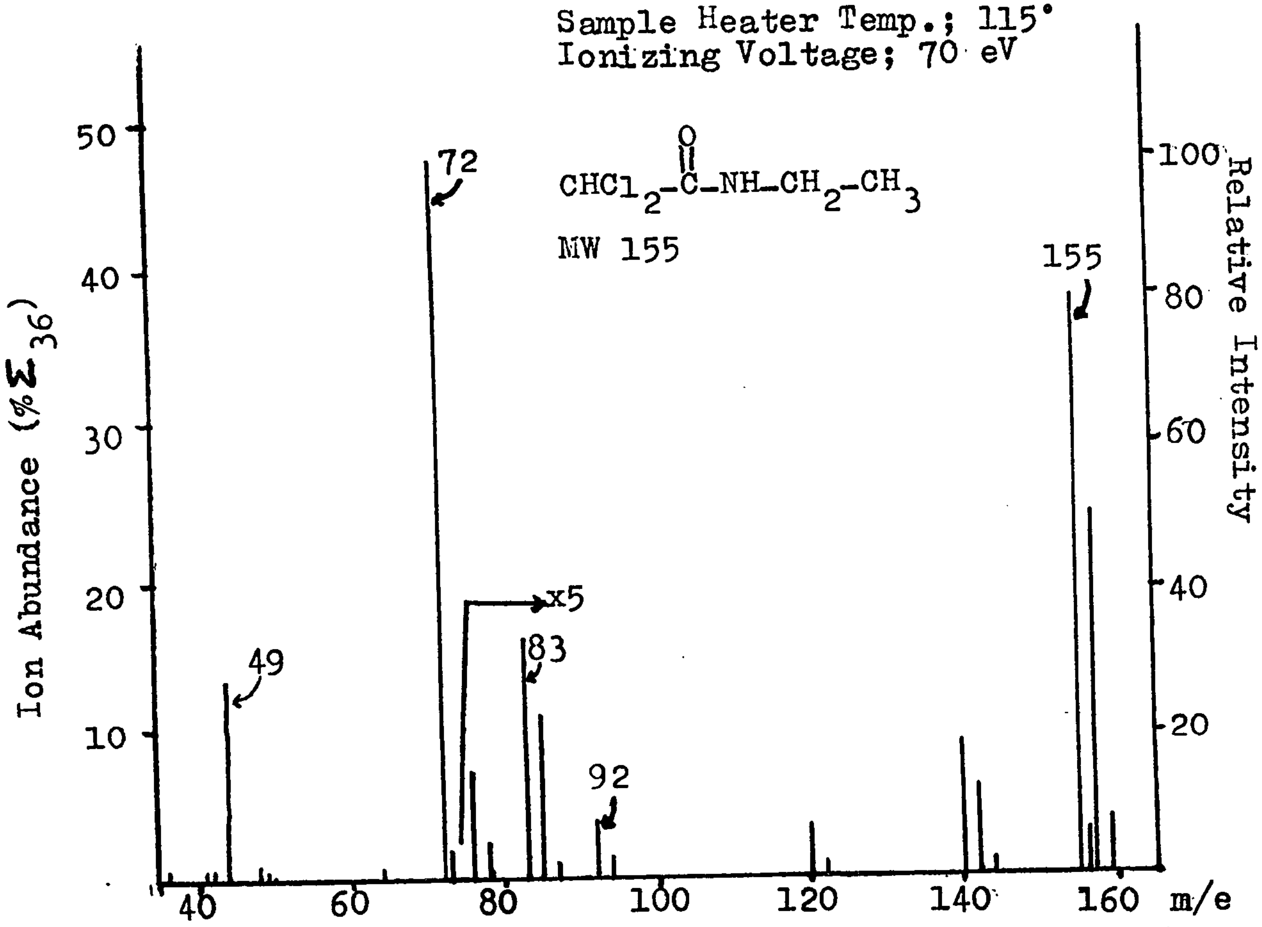
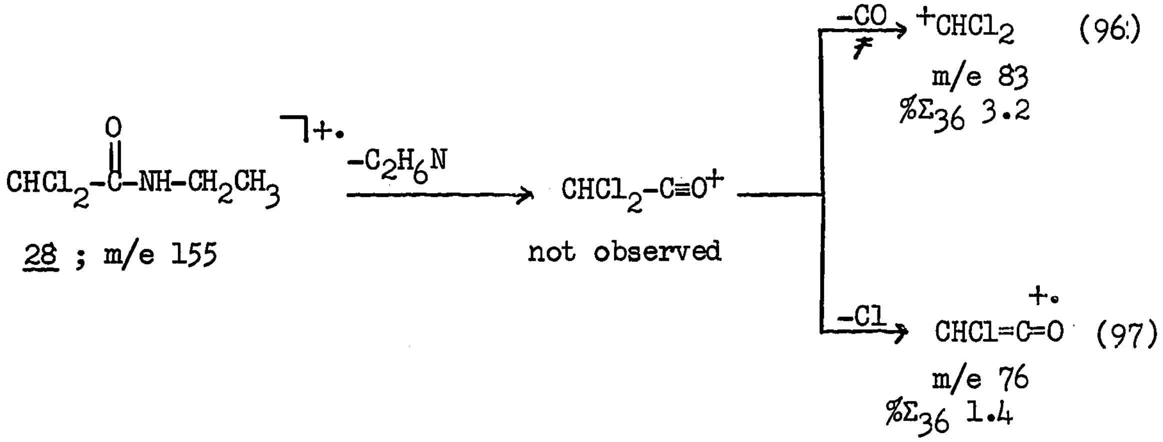


Fig. 9. Mass spectrum of N-ethyl-α,α-dichloro-acetamide. (28).

2. Secondary Fission Processes

In exact analogy to processes (90a) and (90b) which were discussed for the dichloro-N-methyl amide (25), and (61) and (62) for the monochloro-N-methyl amide (24), two peaks were obtained in the spectrum of 28, at m/e 83 and 76, whose precursors were not observed (96, 97). However, in contrast to the spectrum of the dichloro-N-methyl amide, one of the appropriate metastable decompositions was present in the spectra of the dichloro-N-ethyl amide.



$$\mathrm{CHCl_2\text{-}\overset{\overset{O}{\|}}{C}\text{-}NH\text{-}CH_2CH_3}\rceil^{+\cdot} \xrightarrow{-\mathrm{C_2H_6N}} \mathrm{CHCl_2\text{-}C{\equiv}O^+}$$

28 ; m/e 155

not observed

$$\mathrm{CHCl_2\text{-}C{\equiv}O^+} \xrightarrow[\not\ ]{-\mathrm{CO}} \mathrm{{}^+CHCl_2} \qquad (96)$$

m/e 83

$\%\Sigma_{36}$ 3.2

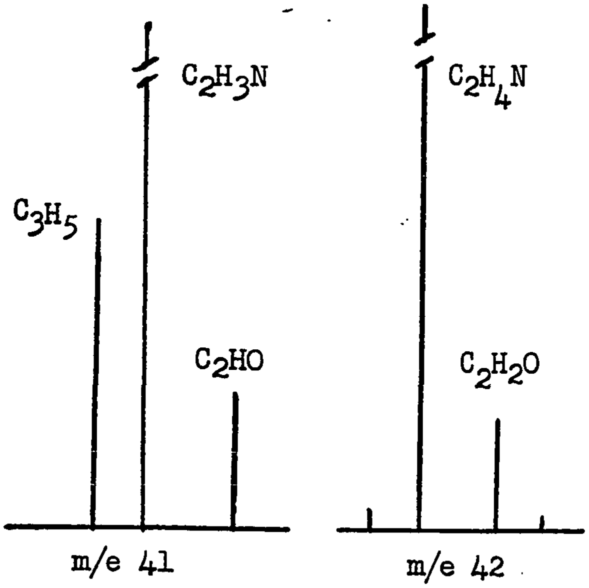
$$\mathrm{CHCl_2\text{-}C{\equiv}O^+} \xrightarrow{-\mathrm{Cl}} \mathrm{CHCl{=}C{=}O}^{+\cdot} \qquad (97)$$

m/e 76

$\%\Sigma_{36}$ 1.4

3. Ions whose sources were not established by metastable decompositions.

A fragment, whose precursor was not indicated by metastable transitions, appeared at m/e 48 and was shown to be $^{+\cdot}\mathrm{CHCl}$. The region from m/e 41-42 was examined under high resolution conditions and a number of fragments were found whose sources could not be determined with any certainty.

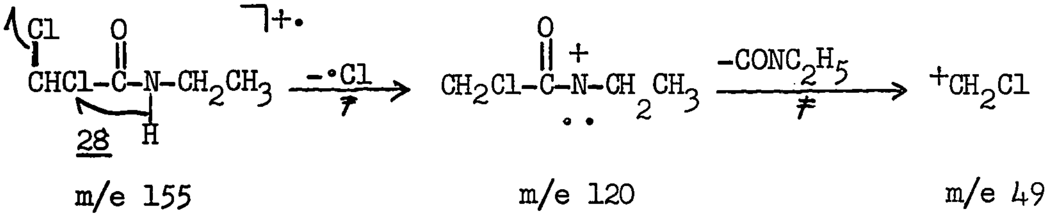


A portion of the high resolution spectrum of N-ethyl-α,α-dichloroacetamide (<u>28</u>).

The major portion ($\%\Sigma_{36}$ 0.7) of the peak at m/e 42 was determined to be $[C_2H_4N]^+$ and was most probably formed by the loss of hydrogen atoms from the fragment at m/e 44, $[C_2H_6N]^+$; the latter ion is discussed in Section B below. Similarly, the most abundant fragment of nominal m/e 41 was due to $[C_2H_3N]^{+\cdot}$ and was probably formed in a similar manner to the $[C_2H_4N]^+$ ion. It was also established that the ion $[C_2HO]^+$ made a small ($\%\Sigma_{36}$ 0.1) contribution to the peak at nominal m/e 41. This fragment was most probably produced by the loss of a hydrogen atom from the rearrangement ion, $[C_2H_2O]^{+\cdot}$, at m/e 42 (to be discussed in the following section.)

B. Rearrangement Ions.

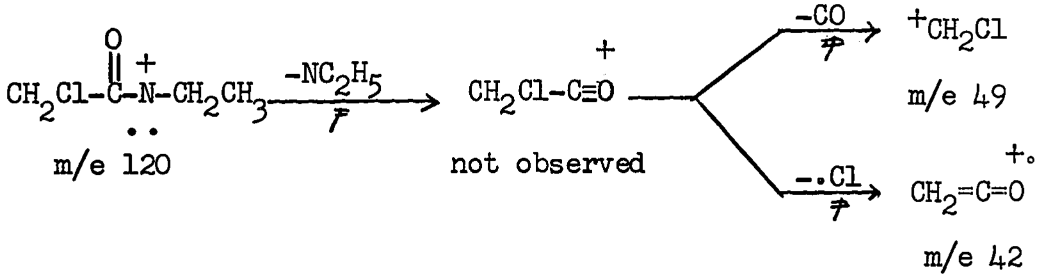
In direct analogy with the spectrum of N-methyl-α,α-dichloroacetamide (<u>25</u>), two schemes,(98) and (99), were observed which again lent support to process (88c) postulated for the N-isopropyl-α-chloroacetamide (30).



$$\left[\overset{Cl}{CHCl}-\overset{O}{\overset{\|}{C}}-\underset{H}{N}-CH_2CH_3\right]^{+\cdot} \xrightarrow[\not{f}]{-\cdot Cl} CH_2Cl-\overset{O}{\overset{\|}{C}}-\underset{\cdot\cdot}{\overset{+}{N}}-CH_2CH_3 \xrightarrow[\not{f}]{-CONC_2H_5} {}^{+}CH_2Cl \qquad (98)$$

28

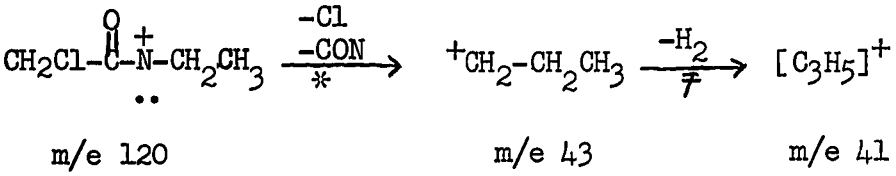
m/e 155 m/e 120 m/e 49



$$CH_2Cl-\overset{O}{\overset{\|}{C}}-\underset{\cdot\cdot}{\overset{+}{N}}-CH_2CH_3 \xrightarrow[\not{f}]{-NC_2H_5} CH_2Cl-C\overset{+}{\equiv}O \begin{cases} \xrightarrow[\not{f}]{-CO} {}^{+}CH_2Cl \\ \xrightarrow[\not{f}]{-\cdot Cl} CH_2{=}C{=}O^{+\cdot} \end{cases} \qquad (99)$$

m/e 120 not observed m/e 49 m/e 42

A third rearrangement ion occurring at m/e 41, was established to be $[C_3H_5]^+[\%\Sigma_{36}\ 0.5]$ providing further evidence for process (88c). A possible mode of formation of this ion is shown below.

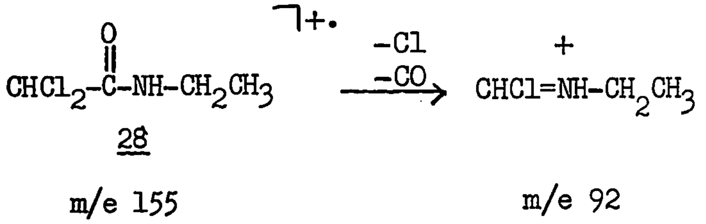


$$CH_2Cl-\overset{O}{\overset{\|}{C}}-\underset{\cdot\cdot}{\overset{+}{N}}-CH_2CH_3 \xrightarrow[*]{\substack{-Cl \\ -CON}} {}^{+}CH_2-CH_2CH_3 \xrightarrow[\not{f}]{-H_2} [C_3H_5]^+ \qquad (100)$$

m/e 120 m/e 43 m/e 41

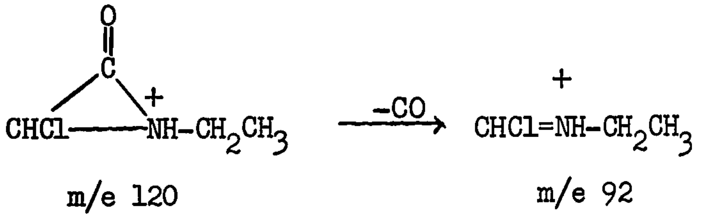
Processes (93), (94), (99), and (100) show the formation and fate of ions containing a single chlorine atom from a <u>dichloro-</u> precursor. It may be remarked that the subsequent fragmentation of these ions containing only one chlorine atom was essentially the same as the analogous ions derived from a <u>monochloro-</u> precursor.

A rearrangement ion $[C_3H_2NCl]^+$ (m/e 92) $\%\Sigma_{36}$ 0.8, analogous to ions found in the monochloromethyl-and ethyl-amides, was observed in the spectrum of the dichloroethyl amide (28). No metastable transitions were found which would indicate the source(s) of this fragment. Thus it can only be stated that this ion may be been formed by rearrangement and cleavage of the molecular ion (101) or the M-Cl ion (102).



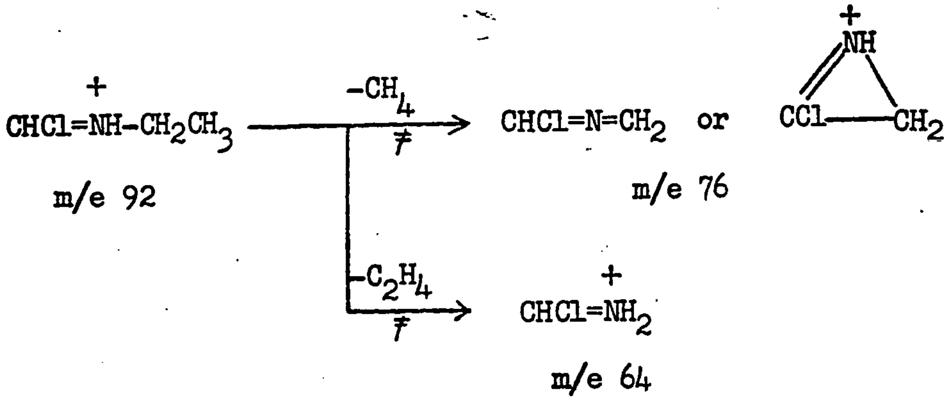
$$\left[CHCl_2-\overset{\overset{O}{\|}}{C}-NH-CH_2CH_3\right]^{+\cdot} \xrightarrow[-CO]{-Cl} \overset{+}{CHCl=NH}-CH_2CH_3$$

(101)



(102)

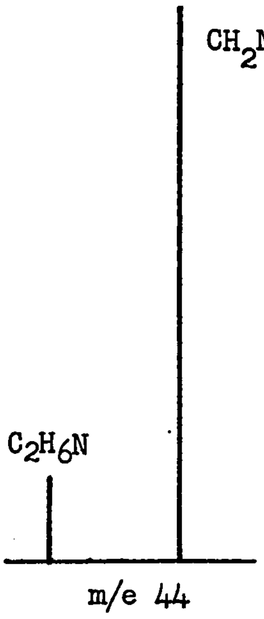
The ion at m/e 92 fragmented (103) to the ion at m/e 76 [0.1] by the loss of CH_4 and also rearranged (104) to the ion at m/e 64, (%Σ_{36} 0.9) by the loss of C_2H_4, a process accompanied by the migration of one hydrogen atom. The peak at m/e 64 was observed at m/e 64 and 65 in the spectrum of the analogous d_3-amide and at m/e 65 in the spectrum of the d_5-amide, thus establishing that the migrating atom came in part from the C-1 and C-2 atoms of the N-ethyl chain.



(103)

(104)

The region at nominal m/e 44 was examined under high resolution conditions and was found to consist of a doublet comprising the ions $[C_2H_6N]^+$ and $[CH_2NO]^+$ in the ratio of 1:8 respectively.



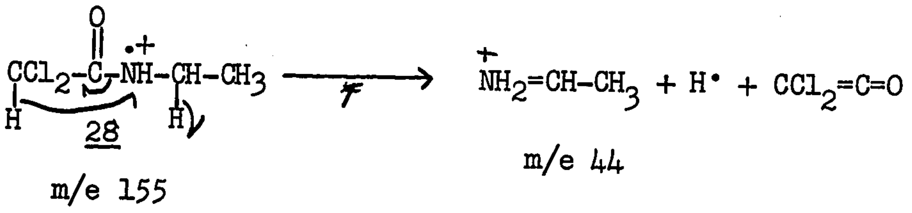
A portion of the high resolution spectrum of N-ethyl-α,α-dichloroacetamide (<u>28</u>).

The peak at nominal m/e 44 due to $[CH_2NO]^+$ was observed at m/e 44 and 45 in the spectrum of the analogous d_3-amide and at m/e 45 in the spectrum of the d_5-amide, confirming that the migrating hydrogen atom came, in part, from the C-1 atom and, in part, from the C-2 atom of the ethyl group. Metastable transitions also showed that the precursor for this rearrangement fragment, as in the case of the monochloro derivative, was the ion at m/e 72.

$$\overset{+}{O{=}C{=}NH{-}CH_2CH_3} \xrightarrow[*]{-C_2H_4} \overset{+}{O{=}C{=}NH_2} \text{ or } \overset{+}{HO{-}C{\equiv}NH}$$

$$\underset{m/e\ 72}{} \qquad\qquad \underset{m/e\ 44}{} \qquad\qquad (105)$$

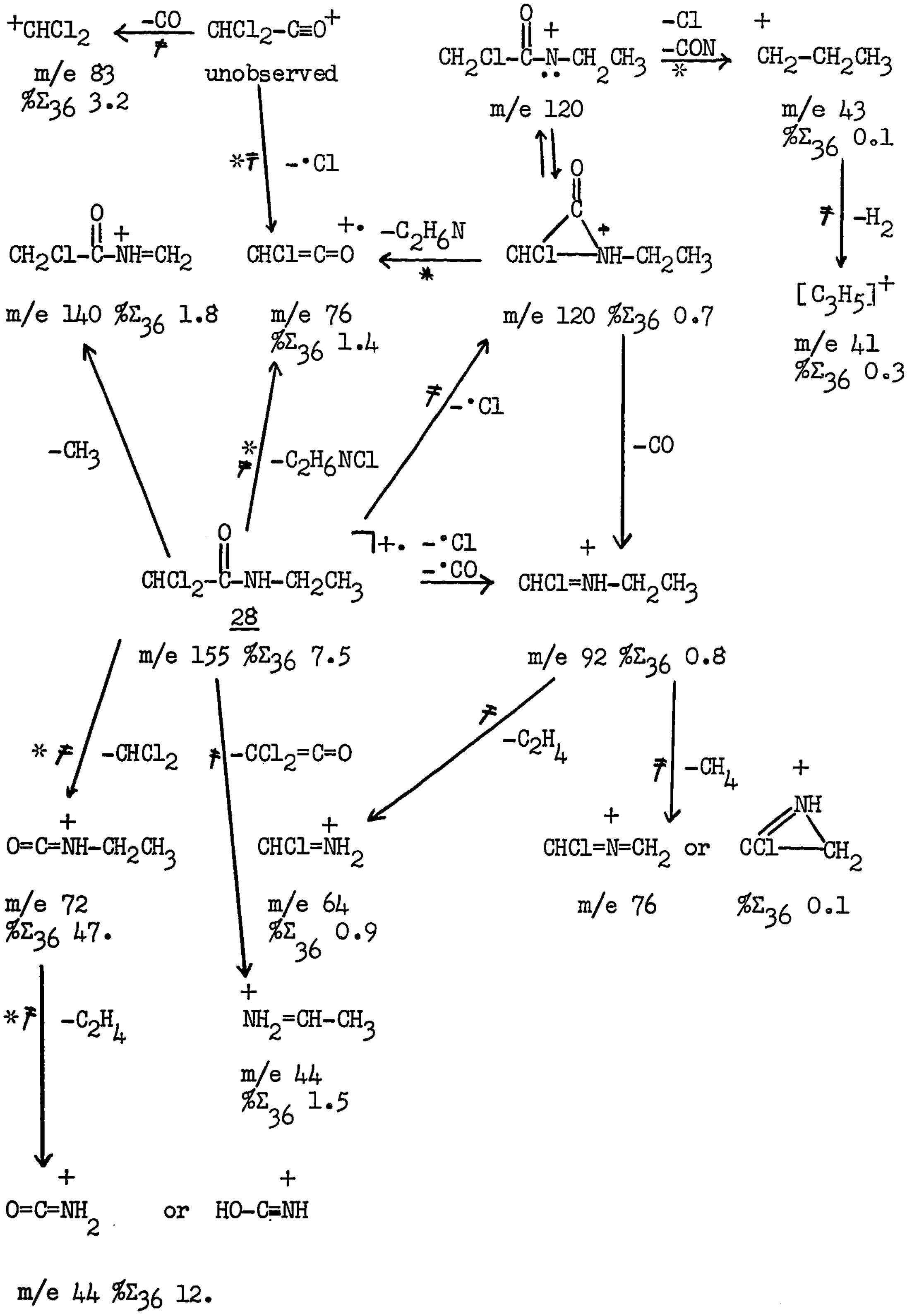
Examination of the deuterated amides showed that the other member of the doublet, $[C_2H_6N]^+$, could be ascribed to a fragment formed by a rearrangement process also found in the N-isopropyl amides and the monochloro-N-ethyl amide (See also processes 86 and 74).



$$\underset{m/e\ 155}{CCl_2H{-}\overset{O}{\overset{\|}{C}}{-}\overset{\cdot+}{N}H{-}CH_2{-}CH_3} \xrightarrow{*} \underset{m/e\ 44}{\overset{+}{N}H_2{=}CH{-}CH_3} + H^{\cdot} + CCl_2{=}C{=}O \qquad (106)$$

The peak due to $[C_2H_6N]^+$ was observed at m/e 47 in the spectrum of the d_3-amide and at m/e 48 in the d_5-amide, confirming process (106). A very small portion of the $[C_2H_6N]^+$ peak was observed at m/e 49 in the spectrum of the d_5-amide, which indicated that a minor contributor to this peak was the ethylamino fragment $:\overset{+}{N}H{-}CH_2{-}CH_3$.

The fragmentation processes taking place in the spectrum of the dichloroethyl amide (<u>28</u>) are summarized in Figure 10.


+CHCl2
-CO
m/e 83
%Σ36 3.2
CHCl2-C≡O+
unobserved
-•Cl
CH2Cl-C(=O)-N-CH2CH3 +
m/e 120
-Cl
-CON
CH2-CH2CH3 +
m/e 43
%Σ36 0.1
-H2
[C3H5]+
m/e 41
%Σ36 0.3
CH2Cl-C(=O)-NH=CH2 +
m/e 140 %Σ36 1.8
CHCl=C=O +•
m/e 76
%Σ36 1.4
-C2H6N
CHCl—NH-CH2CH3
m/e 120 %Σ36 0.7
-CH3
-C2H6NCl
-•Cl
-CO
CHCl2-C(=O)-NH-CH2CH3 +•
28
m/e 155 %Σ36 7.5
-•Cl
-•CO
CHCl=NH-CH2CH3 +
m/e 92 %Σ36 0.8
-CHCl2
-CCl2=C=O
-C2H4
-CH4
O=C=NH-CH2CH3 +
m/e 72
%Σ36 47.
CHCl=NH2 +
m/e 64
%Σ36 0.9
CHCl=N=CH2 + or
m/e 76
CCl—CH2 NH +
%Σ36 0.1
-C2H4
NH2=CH-CH3 +
m/e 44
%Σ36 1.5
O=C=NH2 + or HO-C≡NH +
m/e 44 %Σ36 12.

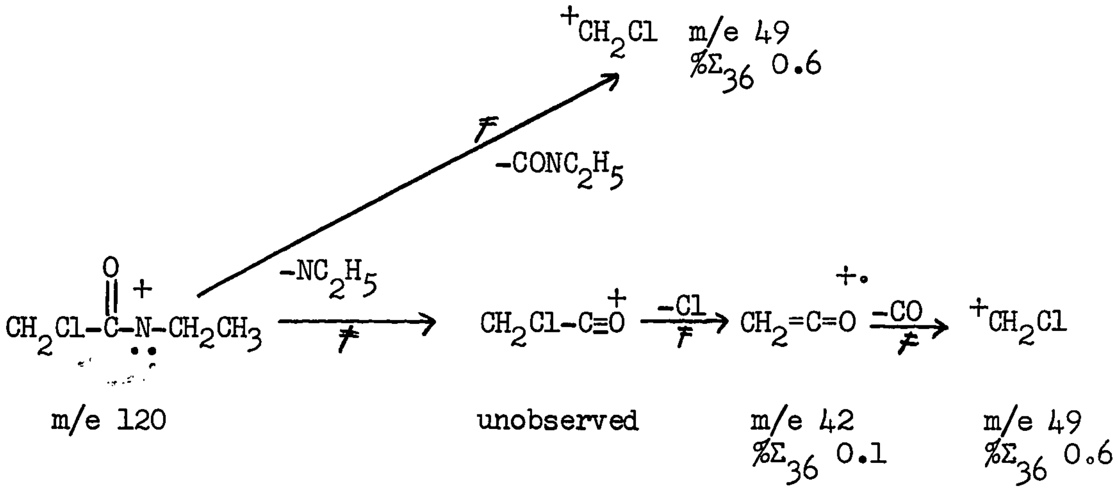


Fig. 10 Fragmentation patterns for N-ethyl-α,α-dichloroacetamide (<u>28</u>).

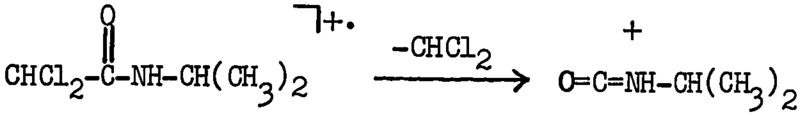
N-Isopropyl-α,α-dichloroacetamide (31)

As was observed earlier in the case of the monochloro-N-isopropyl amide (30), the spectrum of the N-isopropyl species (31) was the most complex of the three alkylated dichloro-amides.

A. Fragmentation Peaks.

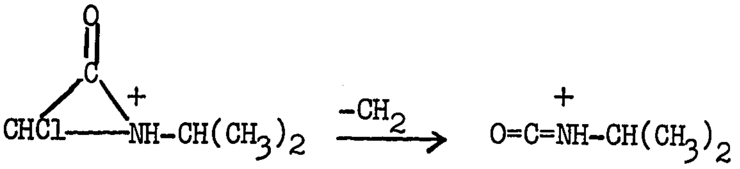
1. Primary Fission Processes.

Again two peaks were observed, at m/e 154 [7.0] and 134 [0.7], which were formed by the loss of $\cdot CH_3$ and $\cdot Cl$ respectively from the molecular ion (m/e 169). The base peak which may have been formed either by fission of the molecular ion (107) or the M-Cl ion (108) appeared at m/e 86.



$$\left.\mathrm{CHCl_2{-}\overset{\overset{O}{\|}}{C}{-}NH{-}CH(CH_3)_2}\right\rceil^{+\cdot} \xrightarrow{-CHCl_2} \overset{+}{\mathrm{O{=}C{=}NH{-}CH(CH_3)_2}} \qquad (107)$$

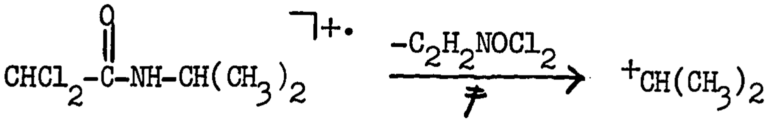
31 ; m/e 169 m/e 86



(108)

m/e 134 m/e 86

The alkyl fragment, $[C_3H_7]^+$ $\%\Sigma_{36}$ 20, appeared to have a number of precursor ions as shown in (109) - (111).



$$\left.\mathrm{CHCl_2{-}\overset{\overset{O}{\|}}{C}{-}NH{-}CH(CH_3)_2}\right\rceil^{+\cdot} \xrightarrow[\neq]{-C_2H_2NOCl_2} {}^{+}\mathrm{CH(CH_3)_2} \qquad (109)$$

31 m/e 169 m/e 43

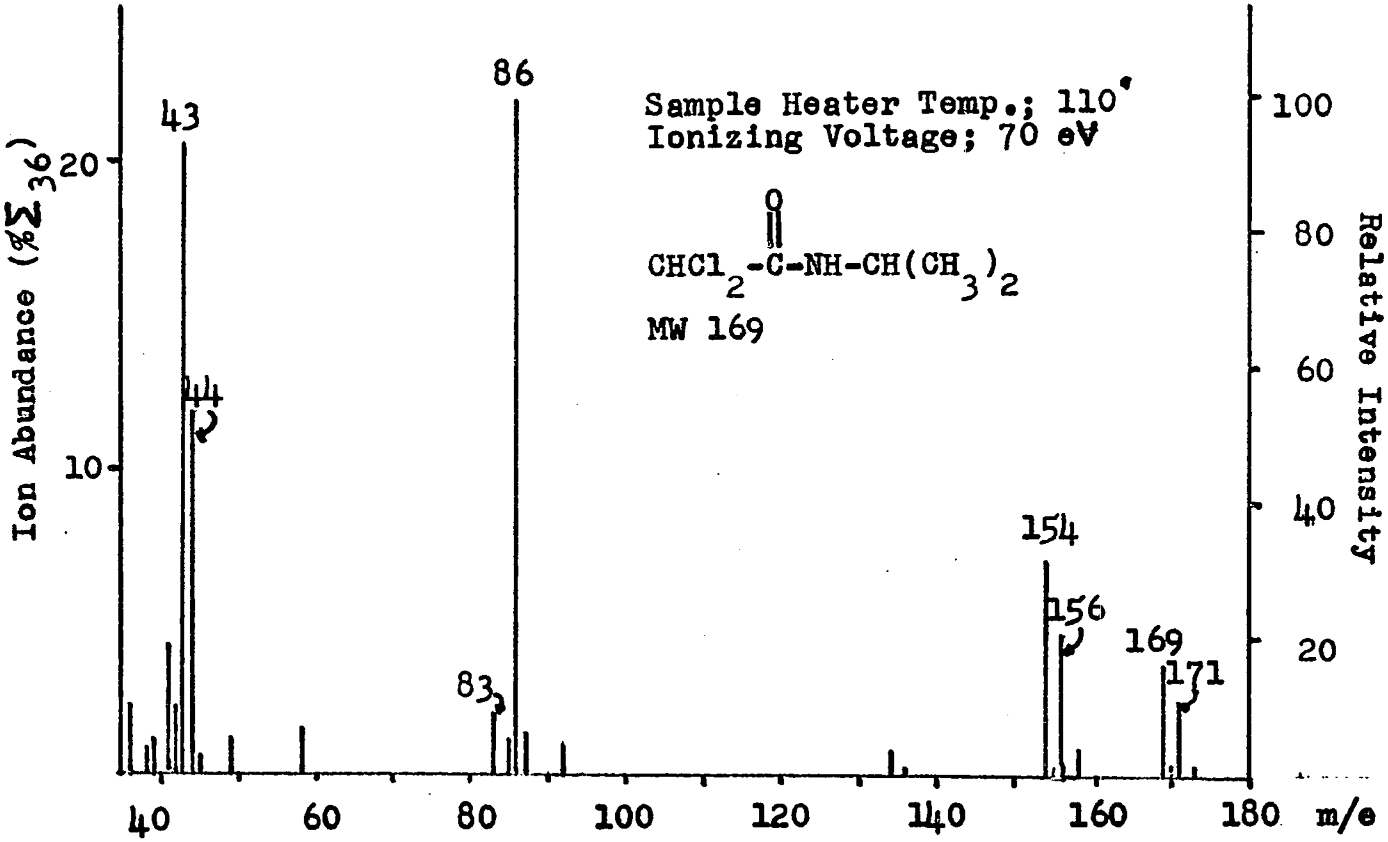
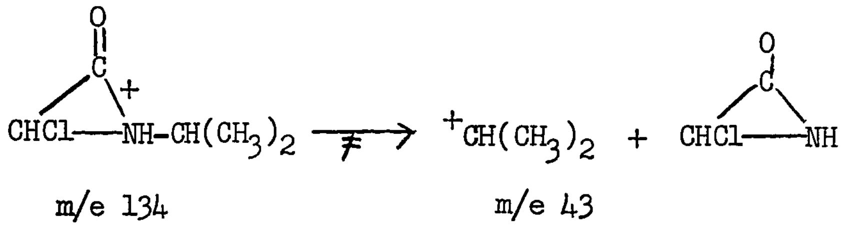


Fig. 11. Mass spectrum of N-isopropyl-α,α-dichloroacetamide (31).



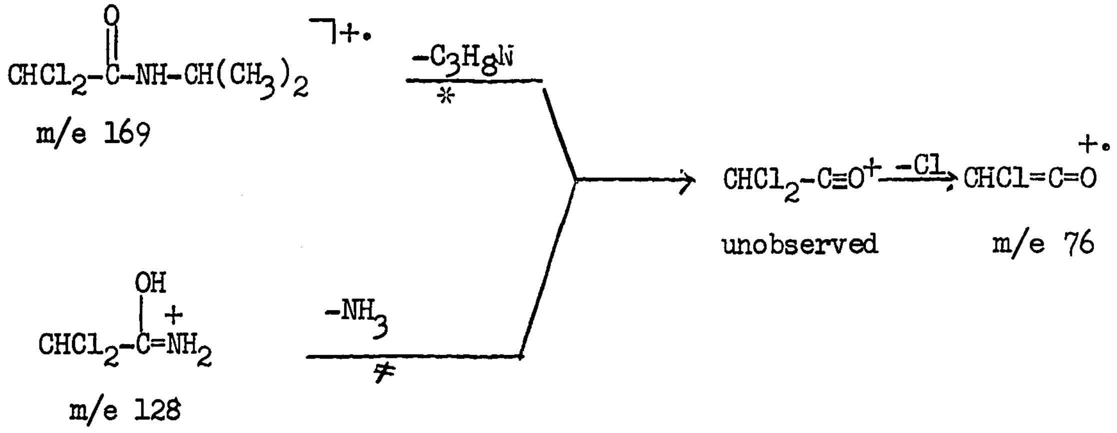
(110)

$$\overset{+}{O{=}C{=}NH\text{-}CH(CH_3)_2} \xrightarrow[* \neq]{-CONH} {}^{+}CH(CH_3)_2 \qquad (111)$$

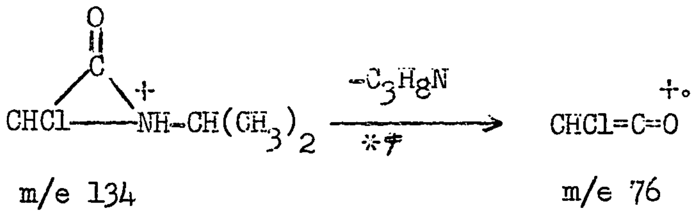
m/e 86 m/e 43

2. Secondary Fission Processes.

Two secondary ions, whose sources were established by metastable transitions, were observed at m/e 76 and 58. The peak at m/e 76 [0.6] due to the fragment $[C_2HOCl]^{+\cdot}$ may have arisen either by the loss of ·Cl from an unobserved ion $[C_2HOCl_2]^+$ (112), or by the loss of the isopropylamino group from the M-Cl moiety (113).



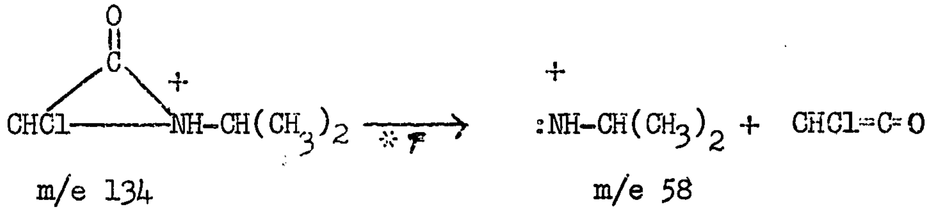
(112)



(113)

Process (113) has previously[10,11] been reported for α-lactams (see process 32b).

The ion at m/e 58, ascertained by deuterium labelling to be $[C_3H_8N]^{+\cdot}$ $\%\Sigma_{36}$ 1.4, arose from two sources as shown in (114) and (115).

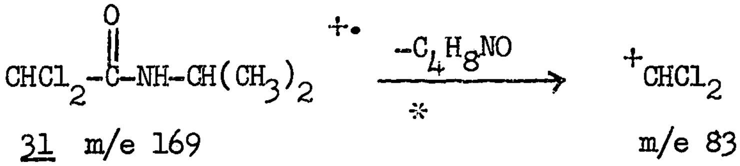


(114)

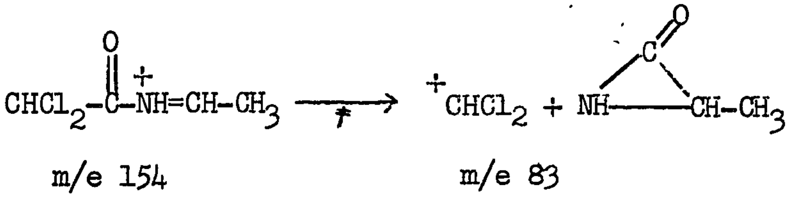
$$\overset{+}{O{=}C{=}NH\text{-}CH(CH_3)_2} \xrightarrow[\ast\ \dagger]{-CO} \overset{+}{:NH\text{-}CH(CH_3)_2} \qquad (115)$$

m/e 86 m/e 58

A third fragment, at m/e 83, appears to have been formed by fission of the molecular ion (115), the M-CH$_3$ ion (117) and an unobserved ion, $[C_2HOCl_2]^{+}$, (118).



$$\underset{\underline{31}\ \ m/e\ 169}{CHCl_2\text{-}\overset{O}{\overset{\|}{C}}\text{-}NH\text{-}CH(CH_3)_2^{+\cdot}} \xrightarrow[\ast]{-C_4H_8NO} \underset{m/e\ 83}{{}^{+}CHCl_2} \qquad (116)$$



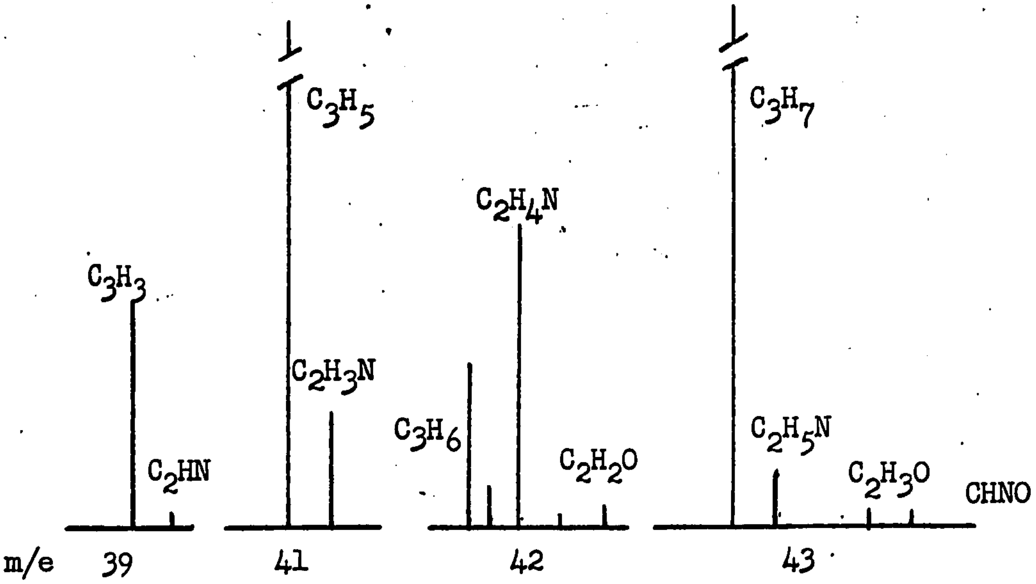
(117)

$$CHCl_2\text{-}C{\equiv}O^+ \xrightarrow[*]{-CO} {}^+CHCl_2 \qquad (118)$$

(not observed) m/e 83

3. Ions whose sources were not established by metastable decompositions.

The region from m/e 39 to m/e 43 was examined under high resolution conditions, and a number of fragments whose precursor ions could not be determined, were found.



A portion of the high resolution spectrum of N-isopropyl-α,α-dichloroacetamide (31).

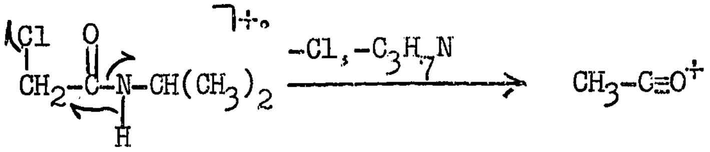
The hydrocarbon ions at m.e 42, $[C_2H_6]^{+\bullet}$, 41, $[C_3H_5]^+$ and 39, $[C_3H_3]^+$, most probably arose by the successive loss of hydrogen atoms from the isopropyl ion.

Similarly, two ions at m/e 44 formed by rearrangement processes, discussed in Section B below also gave rise to ions at m/e 43, 42 and 41.

$[CHNO]^{+\cdot}$	$[C_2H_5N]^{+\cdot}$	$[C_2H_4N]^{+}$	$[C_2H_3N]^{+\cdot}$
m/e 43	m/e 43	m/e 42	m/e 41

B. Rearrangement Ions.

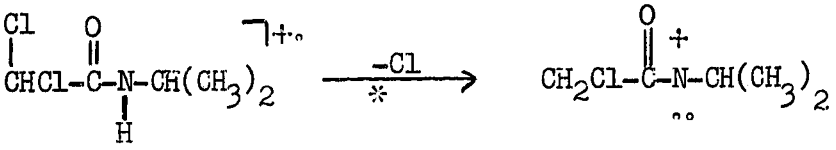
A number of ions appearing at m/e 49, 43 and 42 were observed which again tended to confirm the rearrangement previously described for the monochloro-N-isopropylamide (process 88c).



$$\left[\overset{Cl}{CH_2}-\overset{O}{\overset{\|}{C}}-\underset{H}{N}-CH(CH_3)_2\right]^{+\cdot} \xrightarrow{-Cl,\,-C_3H_7N} CH_3-C\equiv O^{+} \qquad (88c)$$

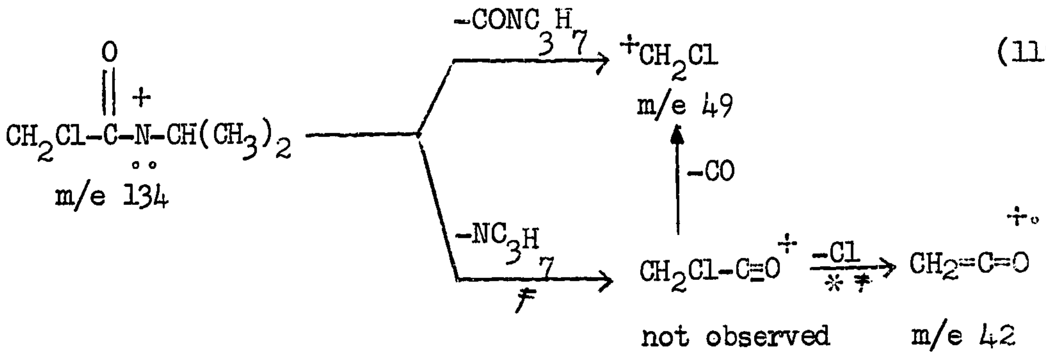
30 m/e 135 m/e 43

The fragments $^{+}CH_2Cl$ (m/e 49) [1.1] and $[C_2H_2O]^{+\cdot}$ (m/e 42), $\%\Sigma_{36}$ 0.1, were in all probability formed as denoted by schemes (119) and (120), analogous respectively to (98) and (99) for the dichloro-N-ethyl amide (28).



$$\left[\overset{Cl}{CHCl}-\overset{O}{\overset{\|}{C}}-\underset{H}{N}-CH(CH_3)_2\right]^{+\cdot} \xrightarrow[*]{-Cl} CH_2Cl-\overset{O}{\overset{\|}{C}}-\overset{+}{\underset{\cdot\cdot}{N}}-CH(CH_3)_2$$

31 ; m/e 169 m/e 134

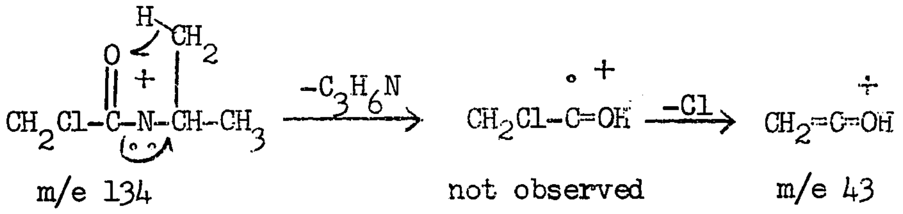


$$CH_2Cl-\overset{O}{\overset{\|}{C}}-\overset{+}{\underset{\cdot\cdot}{N}}-CH(CH_3)_2 \xrightarrow{-CONC_3H_7} {}^{+}CH_2Cl \qquad (119)$$

$$CH_2Cl-\overset{O}{\overset{\|}{C}}-\overset{+}{\underset{\cdot\cdot}{N}}-CH(CH_3)_2 \xrightarrow[\neq]{-NC_3H_7} CH_2Cl-C\equiv O^{+} \xrightarrow[*\,\neq]{-Cl} CH_2=C=O^{+\cdot} \qquad (120)$$

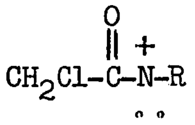
$$CH_2Cl-C\equiv O^{+} \xrightarrow{-CO} {}^{+}CH_2Cl$$

The fragment at m/e 43, $[C_2H_3O]^{\dot{+}}$ $\%\Sigma_{36}$ 0.1, could only have been formed by a process similar to (119) and (120), as shown in (121).



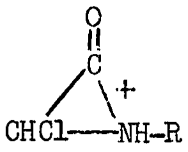
(121)

Thus, from the evidence obtained from the dichloro-amides according to processes (93), (94), (98), (99) and (119-121), it would appear that a small proportion of the M-Cl ion in the spectra of these amides had a structure of the type 62, as well as the protonated α-lactam structure 63 and the straight chain structure 64.

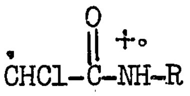


$CH_2Cl-\overset{\overset{O}{\|}}{C}-\ddot{N}^{+}-R$

62



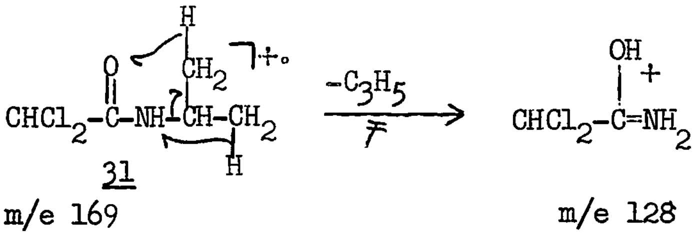
63



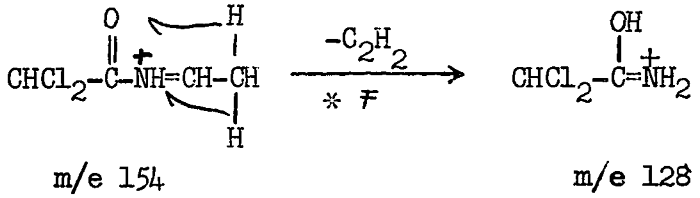
$\dot{C}HCl-\overset{\overset{O}{\|}}{C}-NH-R^{+\circ}$

64

A mode of fragmentation which is analogous to (84) and (89) described for the monochloro-N-isopropyl amide (30), was also observed in the spectrum of 31. The double rearrangement ion, at m/e 128 [0.3], was found to have a structure analogous to that observed for the monochloro derivative. This peak appeared at m/e 130 in both the d_6- and d_7-amides, establishing that both the migrating hydrogen atoms were originally bonded to the methyl groups of the isopropyl side chain. Metastable transitions indicated that this ion was formed from both the molecular ion and the M-CH_3 fragment. (122, 123).

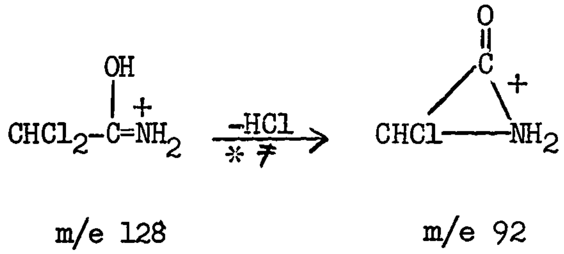


(122)

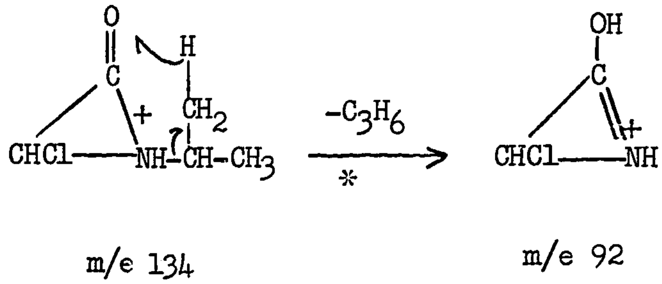


(123)

The fragment at m/e 128 lost HCl (124) to yield the ion $[C_2H_3NOCl]^+$ (m/e 92 $\%\Sigma_{36}$ 1.0). However deuterium labelling failed to determine the exact structure of the latter fragment, since the region of interest was obscured by the base peak in the spectra of the deuterated amides. The fragment at m/e 92 also appeared to have been formed by fission and rearrangement of the M-Cl ion (125).



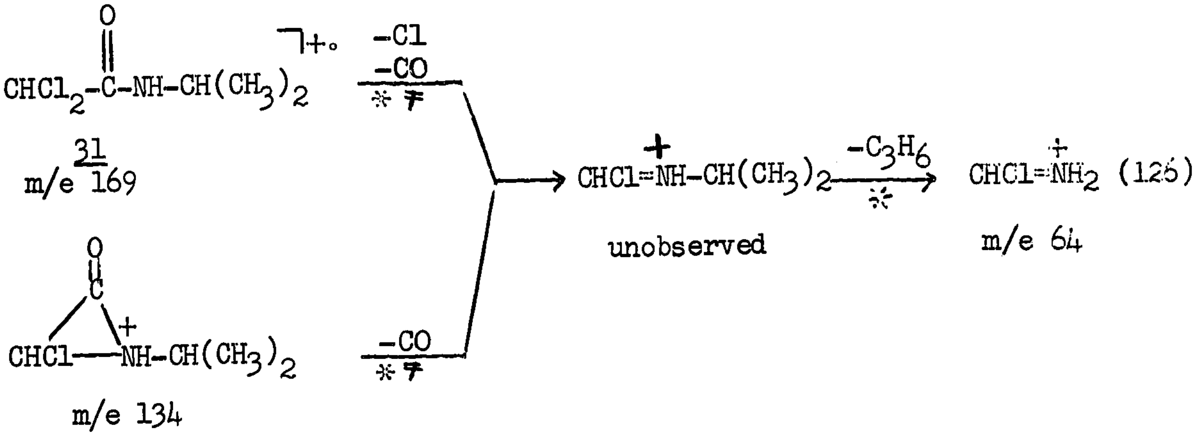
(124)



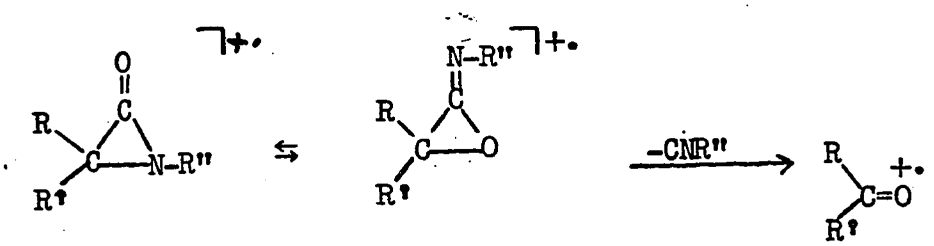
(125)

Both processes (124) and (125) would give rise to peaks at the same nominal mass in the spectra of the light and deuterated amides.

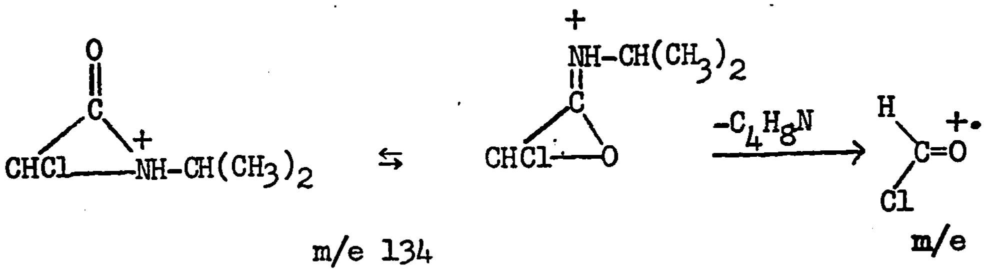
The peak at m/e 64 consisted of two fragments, $[CH_3NCl]^{+\cdot}$ [0.4] and $[CHOCl]^{+\cdot}$ [0.2], the latter establishing the presence of the protonated α-lactam structure 63. The peak at m/e 64 was partitioned between m/e 64 and m/e 65 in the spectra of both the d_6- and d_7- amides, from which it could be concluded that the ion $[CH_3NCl]^+$ was formed by a process similar to (104), with the migrating hydrogen once again being derived from the methyl groups of the isopropyl side chain.



The fragment $[CHOCl]^{+\cdot}$ (m/e 64) was most probably formed by a rearrangement and fission process (127) similar to that described[10,11] for α-lactams (see (34)).

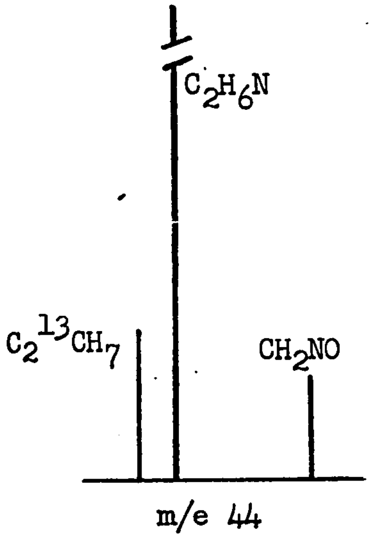


(34)



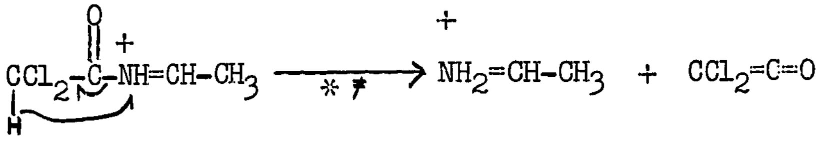
(127)

In an exact analogy to process (86), described for the monochloroisopropyl amide (<u>30</u>) and reported by Gilpin[1] and Djerassi[2] as a major mode of fragmentation in amides, a rearrangement ion was observed at m/e 44. The region of nominal m/e 44 was examined under high resolution conditions, and it was ascertained that the major (85%) contributor to this peak $\%\Sigma_{36}$ 9.9, was the fragment $[C_2H_6N]^+$.



A portion of the high resolution spectrum of N-isopropyl-α,α-dichloroacetamide (<u>31</u>).

This ion was formed by fission and rearrangement of the $M-CH_3$ fragment as depicted below.



$$\underset{\underset{H}{|}}{CCl_2}-\overset{\overset{O}{\|}}{C}-\overset{+}{N}H{=}CH-CH_3 \xrightarrow[\ast\ \neq]{} \overset{+}{N}H_2{=}CH-CH_3 + CCl_2{=}C{=}O \qquad (128)$$

m/e 154 m/e 44

The ion $[CH_2NO]^{+}$ also made a small contribution [0.8] to the peak at nominal m/e 44. This peak was of too small intensity for any significant information to be gained from deuterium labelling studies. As mentioned in the discussion of the mono-chloro isopropyl amide (30), this ion may have a number of possible precursor fragments, and most probably has the structure (65) shown below.

$$H-O-C{\equiv}\overset{+}{N}H$$

65

m/e 44

Figure 12 summarizes the processes which have been described for N-isopropyl-α,α-dichloroacetamide (31).

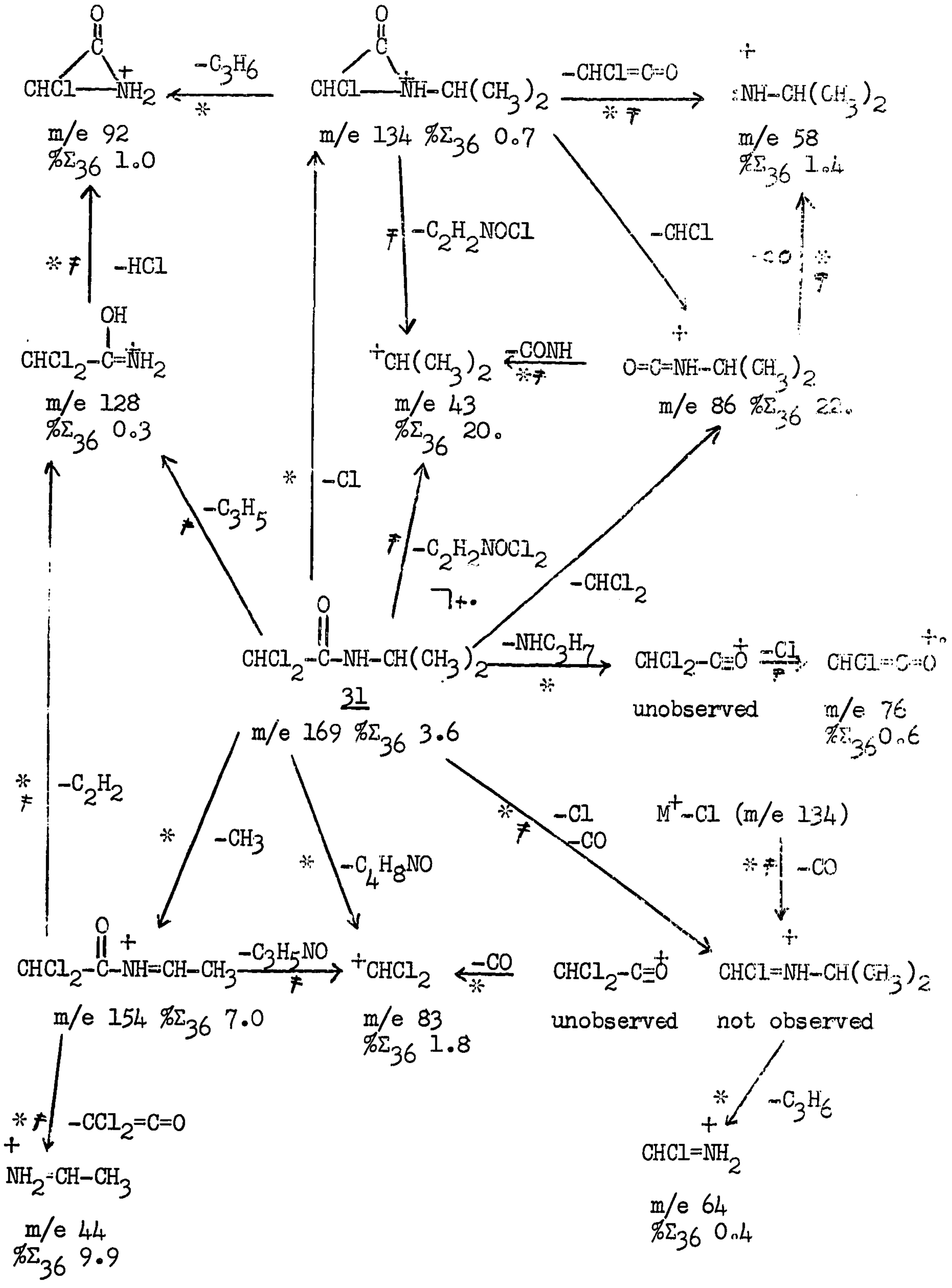


Fig. 12. Fragmentation patterns for N-isopropyl-α,α-dichloroacetamide (31).

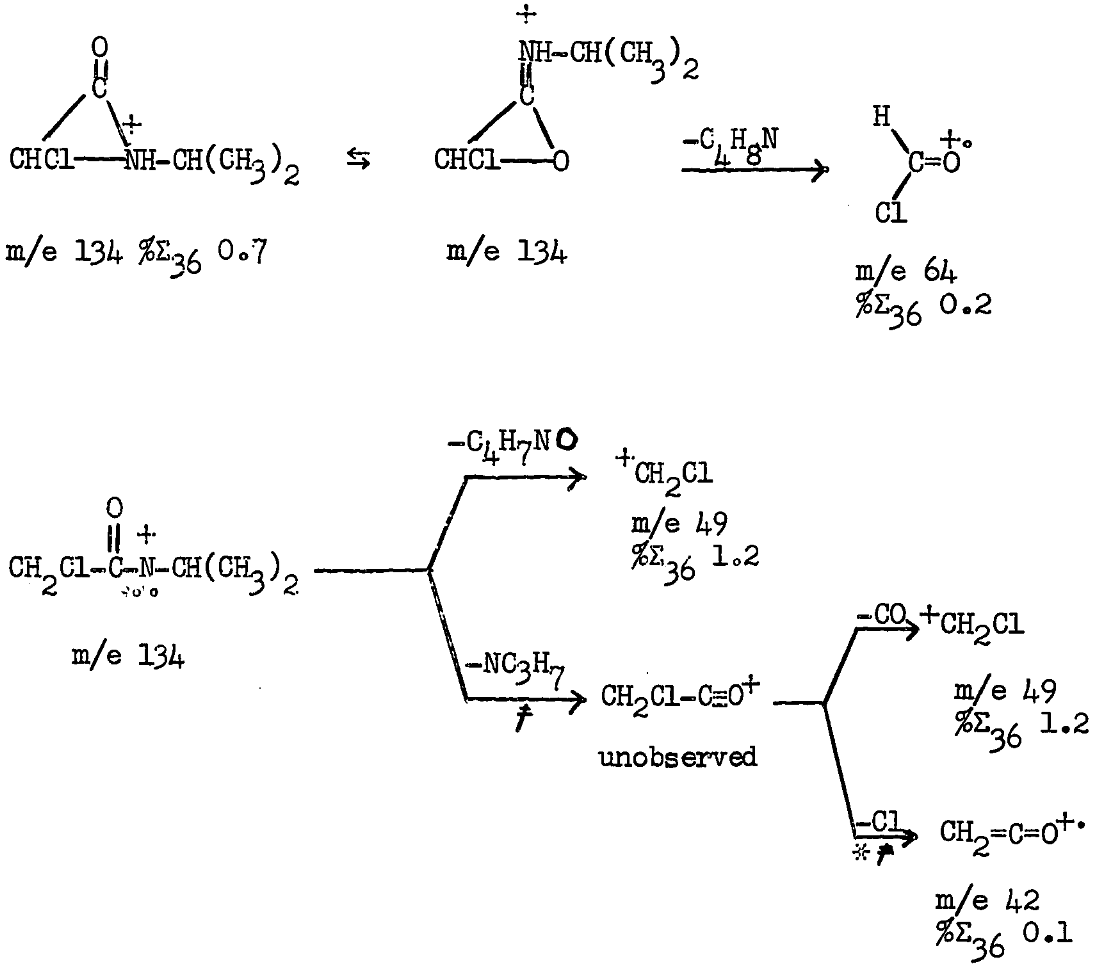


Fig. 12 Continued.

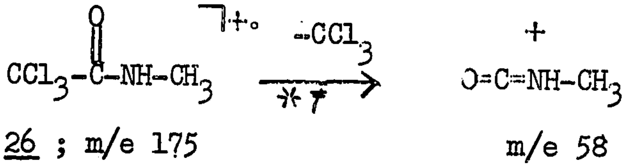
<u>N-Methyl-α,α,α-trichloroacetamide</u> (<u>26</u>)

The ions and fragmentation paths observed for <u>26</u> were exactly analogous to those observed in the spectra of the mono- and dichloromethyl amides, although considerable differences in ion abundances were noted.

A. Fragmentation Peaks.

1. Primary Fission Processes.

The M-Cl peak appeared at m/e 140 [1.6] and the base peak of the spectrum, $[C_2H_4NO]^{+}$, at m/e 58 was formed by the loss of $\cdot CCl_3$ from the molecular ion (m/e 175).



$$\left[CCl_3-\overset{O}{\overset{\|}{C}}-NH-CH_3\right]^{+\cdot} \xrightarrow[*]{-CCl_3} \overset{+}{O=C=NH-CH_3} \qquad (129)$$

<u>26</u> ; m/e 175 m/e 58

2. Secondary Fission Processes.

As in the case of the dichloro-N-methyl amide (<u>25</u>), no ions in this category were observed, whose parent ions could be determined by metastable decompositions.

3. Ions whose sources were not established by metastable transitions.

Four fragments were observed whose precursor ions could not be determined by means of metastable decompositions. Processes (130) and (131) show the probable modes of formation of the ions $^{+}CCl_3$ (m/e 117) [2.0] and $CCl_2=C=\overset{+\cdot}{O}$ (M/e 110) [0.9] in analogy to (90a) and (90b) proposed in the discussion of the dichloromethyl amide.

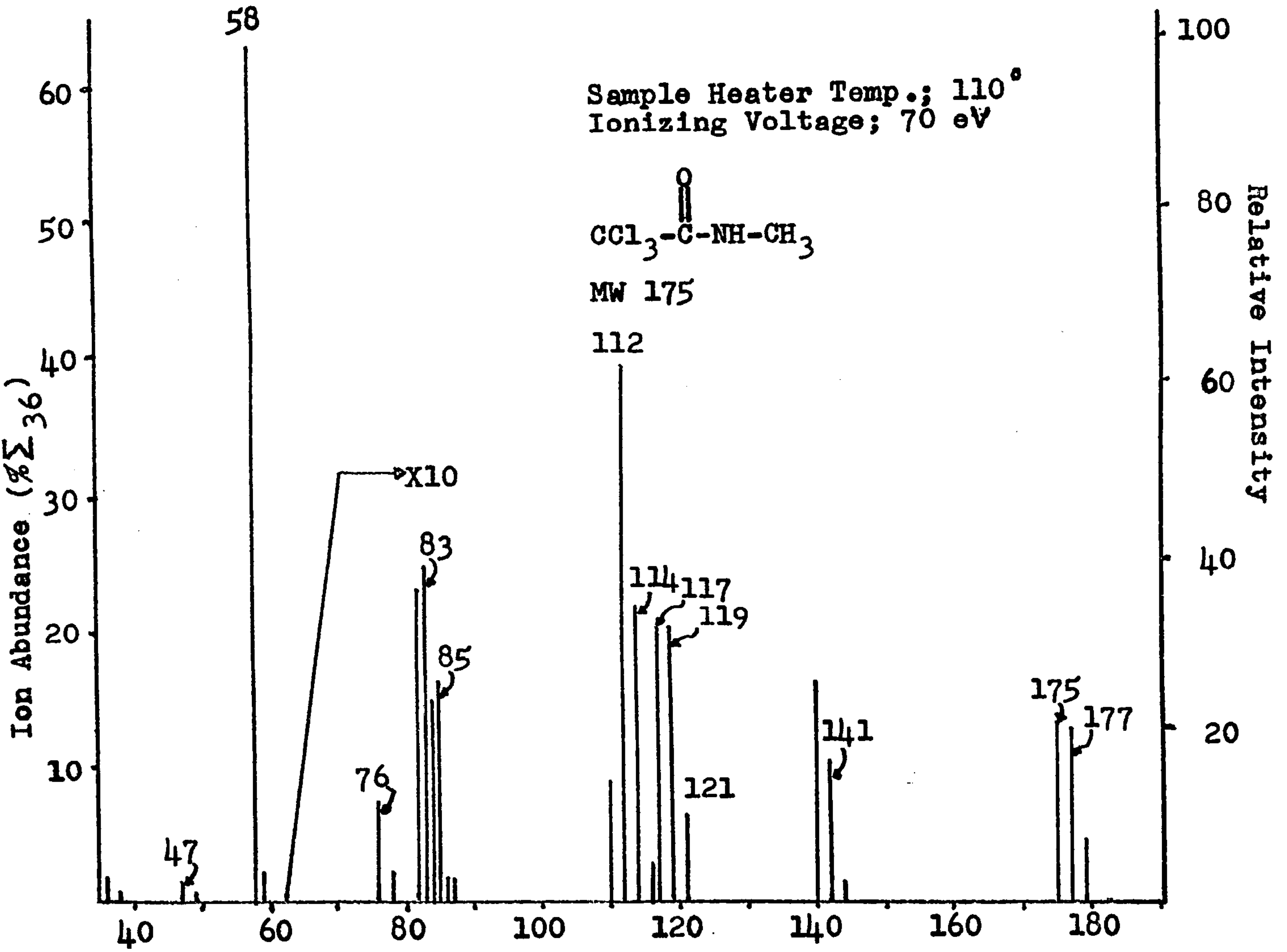
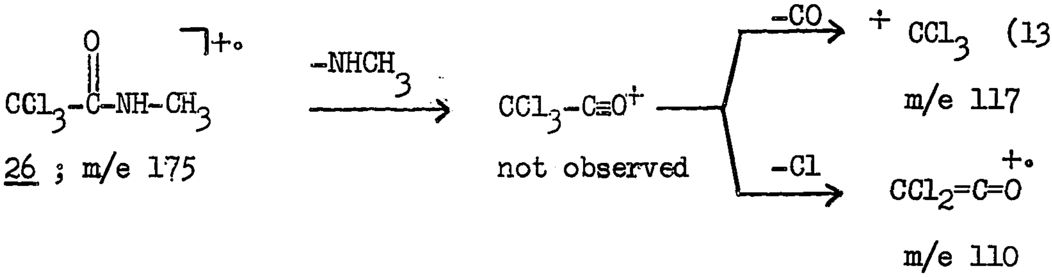


Fig. 13. Mass spectrum of N-methyl-α,α,α-trichloroacetamide (26).



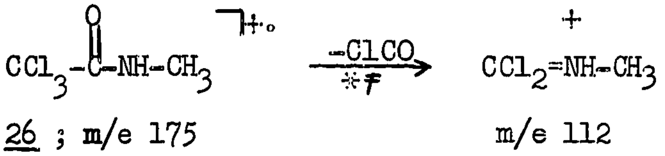
(130)

(131)

The fragments $\overset{+\cdot}{C}Cl_2$ (m/e 82) and $:\overset{+}{C}Cl$ (m/e 47) may have arisen from a number of precursor ions and no metastable decompositions were observed which would distinguish between these sources.

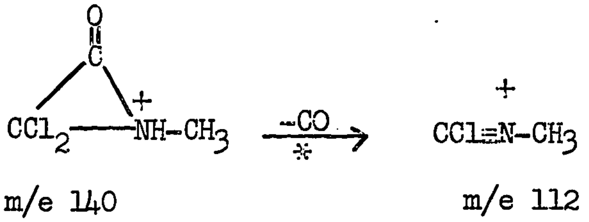
B. Rearrangement Ions.

In exact analogy to the spectra of the mono-and dichloromethyl amides the fragment $[C_2H_4NCl_2]^{+\cdot}$ %Σ_{36} 3.4, (m/e 112) appeared to have been formed by concerted fission and rearrangement of the molecular ion (132) and by the loss of :CO from the M-Cl ion (133).



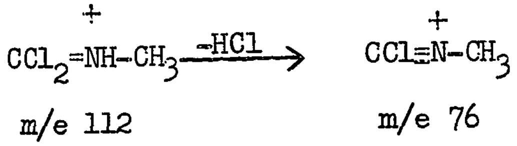
$$CCl_3-\overset{O}{\overset{\|}{C}}-NH-CH_3\ ^{\rceil+\cdot} \xrightarrow[*\dagger]{-ClCO} \overset{+}{C}Cl_2=NH-CH_3 \qquad (132)$$

26 ; m/e 175 m/e 112



(133)

Although no appropriate metastable decompositions were observed, the fragment at m/e 76, $[C_2H_3NCl]^+$ [0.7] was most probably formed by the loss of HCl from the ion at m/e 112 as depicted by (134).

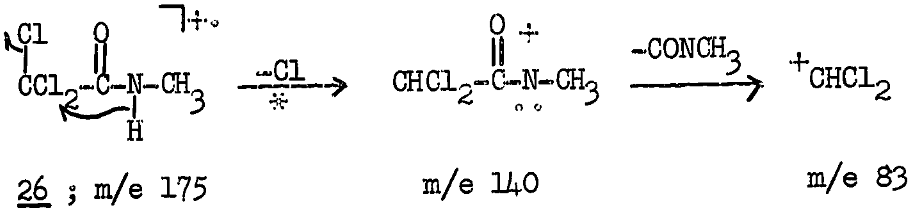


$$\overset{+}{\text{CCl}_2\text{=NH-CH}_3} \xrightarrow{-\text{HCl}} \overset{+}{\text{CCl}\equiv\text{N-CH}_3} \qquad (134)$$

m/e 112 m/e 76

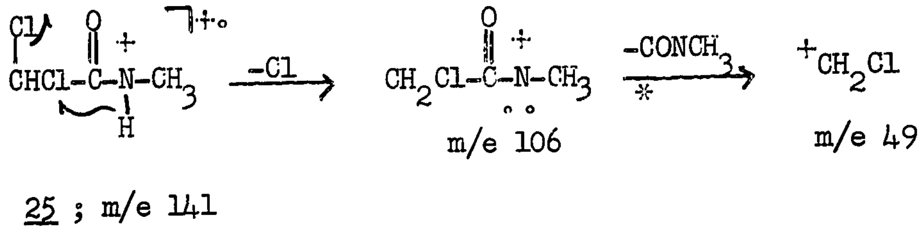
The fragment $\overset{+}{\text{CCl}\equiv\text{N-CH}_3}$ appeared at m/e 79 in the spectrum of the d_3-trichloro-amide thus establishing that the methyl group was still intact and the hydrogen atom lost as HCl was bonded to the nitrogen atom.

No definite evidence was found which could establish the precursor ion of the rearrangement fragment $^+\text{CHCl}_2$, $\%\Sigma_{36}$ 2.5 at m/e 83; however, by analogy to process (93) one may write (135).



(135)

26 ; m/e 175 m/e 140 m/e 83



(93)

25 ; m/e 141 m/e 106 m/e 49

A summary of the modes of fragmentation which are believed to be taking place for the trichloro-N-methyl amide 26 is presented in Figure 14.

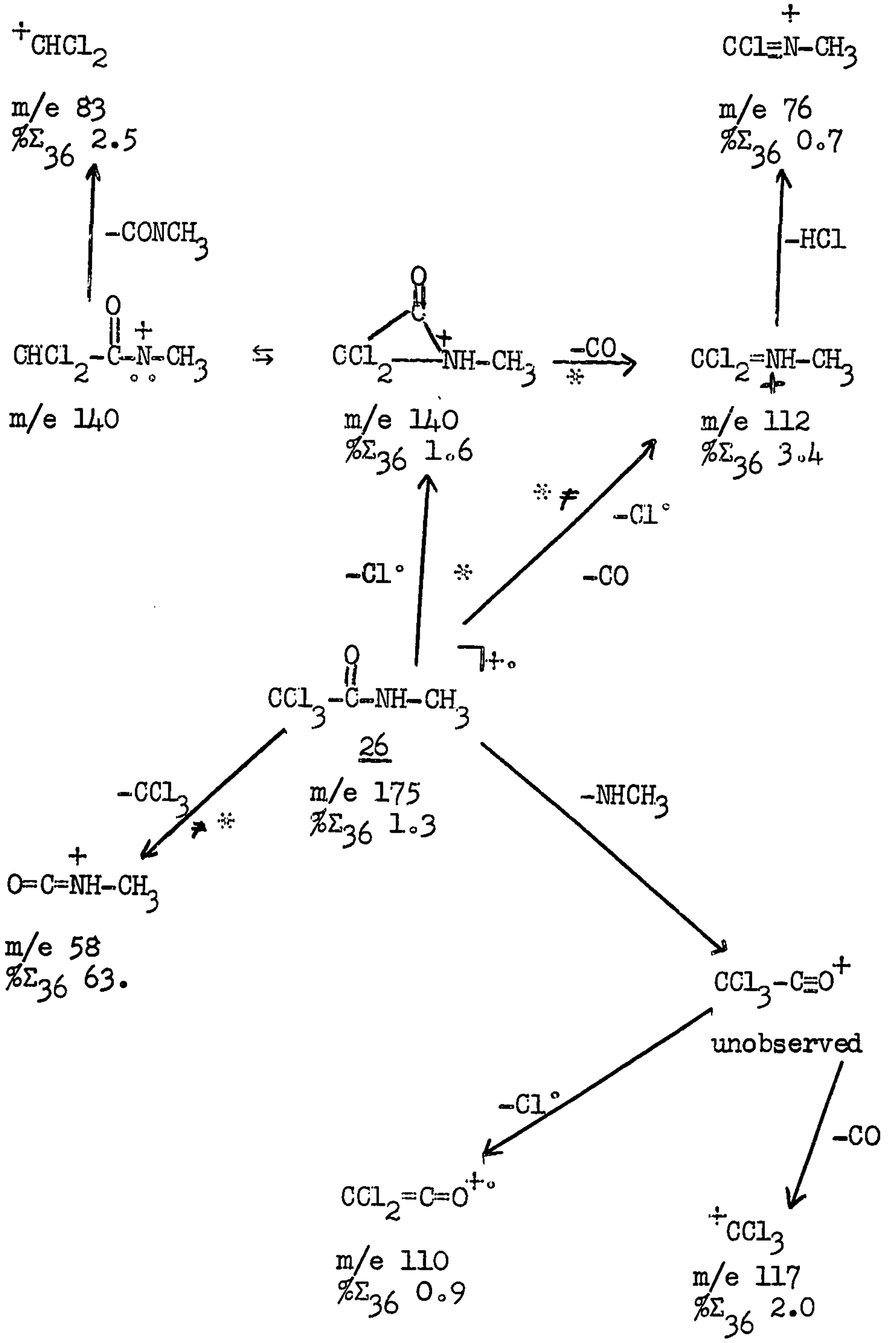


Fig. 14. Fragmentation patterns for N-Methyl-α,α,α-trichloroacetamide (26).

N-Ethyl-α,α,α-trichloroacetamide (29)

Of the fragments observed for the N-ethyl derivative (29) the majority have their counterpart in the spectra of the mono- and dichloro-N-ethyl amides. However, many of the ions resulting from the metastable decompositions which were observed in the spectra of the mono- and dichloro ethyl amides were absent in the spectrum of the trichloro-N-ethyl amide.

A. Fragmentation Peaks.

1. Primary Fission Processes.

As in the case of the other N-ethyl amides, the M^{+}-Cl (m/e 154) [1.3] and the M^{+}-CH_3(m/e 174) [$\%\Sigma_{36}$ 1.4] fragments were formed by fission of the molecular ion (m/e 189). However, no other metastable decompositions compatible with ions produced by simple cleavage of the molecular ion were present.

2. Secondary Fission Processes.

Of the large number of possible precursor ions for the fragment $:CCl^{+}$ (m/e 47), the only source confirmed by metastable transitions was the ion at m/e 82 (136).

$$\underset{m/e\ 82}{{}^{+\circ}\mathrm{CCl_2}} \xrightarrow[\ast f]{-\mathrm{Cl}} \underset{m/e\ 47}{:\overset{+}{\mathrm{C}}\mathrm{Cl}} \qquad (136)$$

The region of nominal m/e 44 was examined under high resolution conditions and it was ascertained, by deuterium labelling studies, that only a small proportion $\%\Sigma_{36}$ 0.3, of this peak was due to the ethylamino ion $CH_3CH_2\overset{+}{N}H$. It appears that this fragment was formed by the loss of CO from the ion at m/e 72 as shown in (137). The origin of the ion making the major contribution to the peak at m/e 44 will be discussed in Section B.

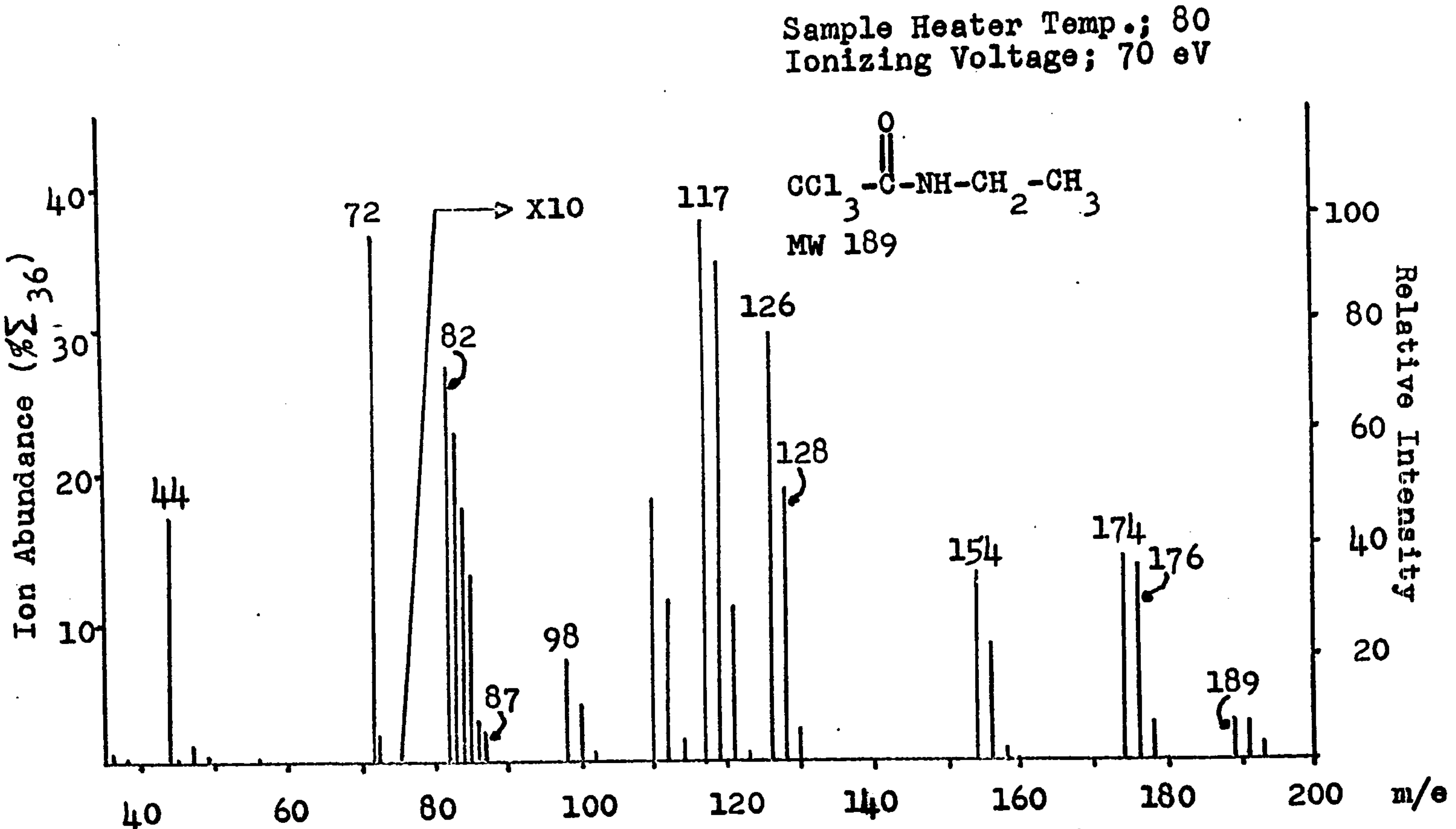
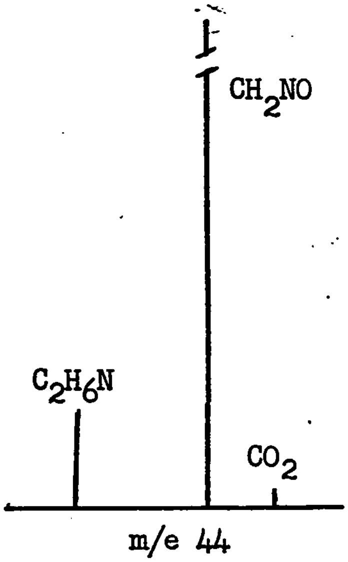
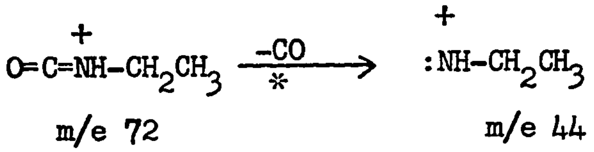


Fig. 15. Mass spectrum of N-ethyl-α,α,α-trichloroacetamide (29).



A portion of the high resolution spectrum of N-ethyl-α,α-trichloroacetamide (29).

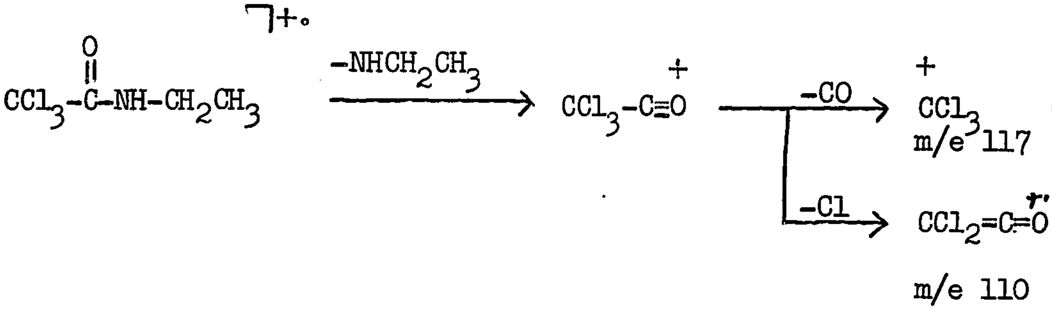


$$\underset{m/e\ 72}{O{=}C{=}\overset{+}{N}H{-}CH_2CH_3} \xrightarrow[*]{-CO} \underset{m/e\ 44}{:\overset{+}{N}H{-}CH_2CH_3} \qquad (137)$$

3. Ions whose sources were not established by metastable transitions.

The fragment $^{+\cdot}CCl_2$ at m/e 82 may have been produced by the fission of a number of ions, but no appropriate metastable decompositions were observed, and its precise origin must therefore remain in doubt.

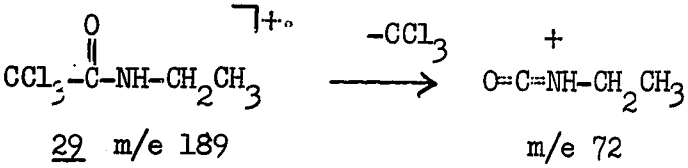
Although the two ions, at m/e 117 [$\%\Sigma_{36}$ 3.8] and 110 [$\%\Sigma_{36}$ 1.6] have arisen from a number of sources their most probable mode of formation is outlined in processes (138) and (139) which are analogous to (70), (96) and (97).



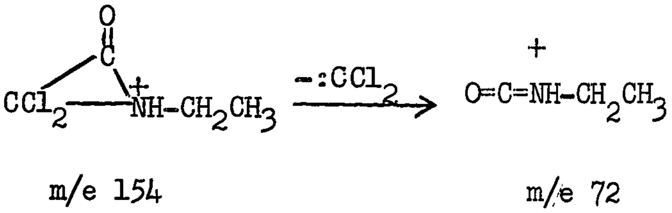
$$\left[CCl_3-\overset{O}{\overset{\|}{C}}-NH-CH_2CH_3\right]^{+\cdot} \xrightarrow{-NHCH_2CH_3} CCl_3-\overset{+}{C}\equiv O \xrightarrow{-CO} \underset{m/e\ 117}{\overset{+}{CCl_3}}$$ (138)

$$CCl_3-\overset{+}{C}\equiv O \xrightarrow{-Cl} \underset{m/e\ 110}{CCl_2=C=\overset{+\cdot}{O}}$$ (139)

As in the spectra of the mono- and dichloro-N-ethyl amides it was readily established that the base peak in the spectrum of 29 was $[C_3H_6NO]^+$ (m/e 72). No metastable transitions were observed which would suggest the precursor of this ion. Two plausible processes, fission of the molecular ion (140) and the $M^{+\cdot}$-Cl ion (141) are shown below.



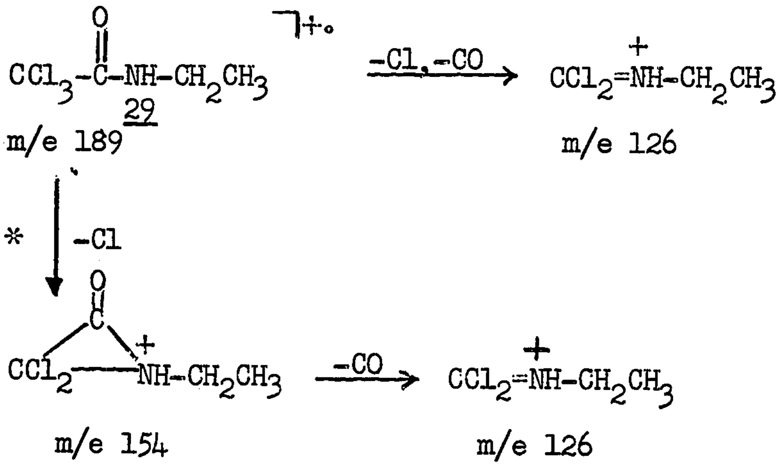
$$\underset{\underline{29}\ m/e\ 189}{\left[CCl_3-\overset{O}{\overset{\|}{C}}-NH-CH_2CH_3\right]^{+\cdot}} \xrightarrow{-CCl_3} \underset{m/e\ 72}{\overset{+}{O=C=NH-CH_2CH_3}}$$ (140)



(141)

B. Rearrangment Ions.

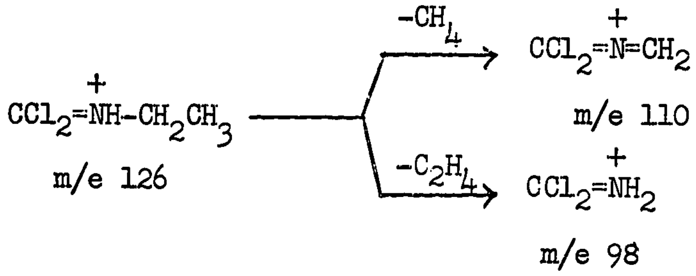
A rearrangement fragment, at m/e 126 [$\%\Sigma_{36}$ 3.0], may have been formed by fission and rearrangement of the molecular ion (142) or by loss of :CO from the $M^{+\cdot}$-Cl ion (143). No conclusive evidence which would enable one to distinguish between these possibilities was forthcoming.



(142)

(143)

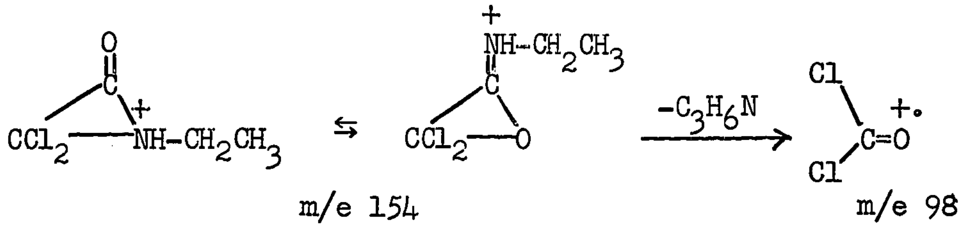
Two ions, at m/e 110 and 98, were most probably produced by fission of the fragment at m/e 126 in a process analogous to (103) and (104), but again no metastable transitions were observed which would confirm either or both of these pathyways as being correct.



(144)

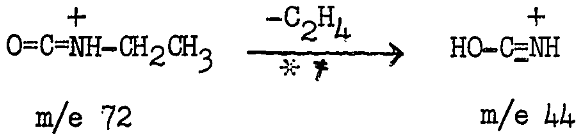
(145)

The ion $[C_2H_2NCl_2]^{+}$ [0.2] (m/e 110) was observed at m/e 112 in the spectrum of the d_5-amide thus establishing that the hydrogen atom lost with the methyl group had been bonded to the nitrogen atom (144). The fragment $[CH_2NCl_2]^{+}$ [$\%\Sigma_{36}$ 0.8] appeared partially at m/e 99 in the spectrum of the d_3-amide and totally at m/e 99 in the spectrum of the d_5-amide. This indicated that some of the migrating hydrogen atoms were bonded to the methyl group and some to the methylene group of the ethyl side chain. It was also noticed that a portion (approximately one third) of the peak at m/e 98 in the spectrum of (<u>29</u>) appeared at m/e 98 in the spectra of both the d_3- and d_5-amides. It would therefore seem that a rearrangement process, hitherto reported only for α-lactams[10,11] (see 34), was taking place. (See also process (127)).



(146)

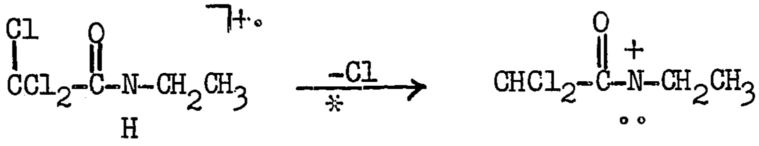
The major part [%Σ_{36} 17.] of the doublet at m/e 44 was $[CH_2NO]^+$, and it was determined by deuterium labelling, that the migrating hydrogen atoms originated from both carbon atoms of the N-ethyl side chain. As in the cases of the mono- and dichloro-N-ethyl amides, the precursor of this rearrangement ion was the fragment at m/e 72.



$$\underset{m/e\ 72}{O{=}C{=}\overset{+}{N}H{-}CH_2CH_3} \xrightarrow[*\ \not{}]{-C_2H_4} \underset{m/e\ 44}{HO{-}\overset{+}{C}{\equiv}NH}$$

(147)

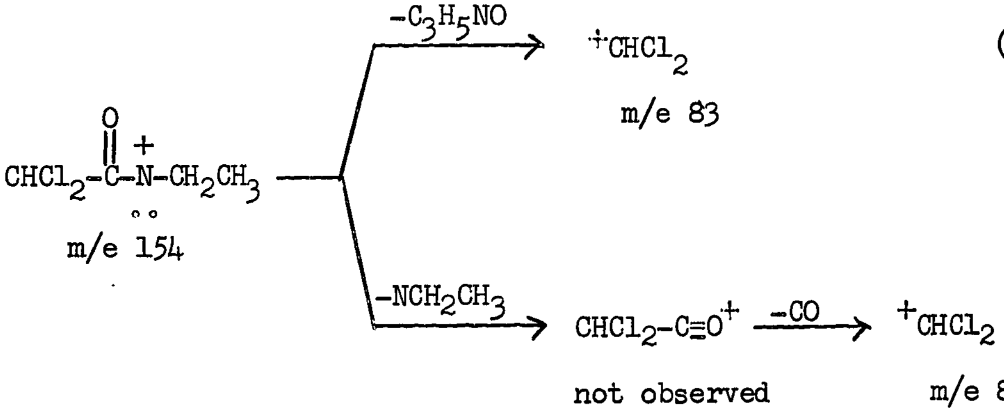
The fragment ${}^{+}\mathrm{CHCl_2}$ (m/e 83) [$\%\Sigma_{36}$ 2.3] was possibly formed as shown in (148) and (149) in analogy to the modes of decomposition which were observed earlier in the spectrum of the dichloro-N-ethyl amide.



$$\left[\mathrm{CCl_2(Cl)\text{-}C(=O)\text{-}N(H)\text{-}CH_2CH_3}\right]^{+\cdot} \xrightarrow[*]{-\mathrm{Cl}} \mathrm{CHCl_2\text{-}C(=O)\text{-}\overset{+}{N}\text{-}CH_2CH_3}$$

29; m/e 189

m/e 154



$$\mathrm{CHCl_2\text{-}C(=O)\text{-}\overset{+}{N}\text{-}CH_2CH_3} \xrightarrow{-\mathrm{C_3H_5NO}} {}^{+}\mathrm{CHCl_2} \qquad (148)$$

$$\mathrm{CHCl_2\text{-}C(=O)\text{-}\overset{+}{N}\text{-}CH_2CH_3} \xrightarrow{-\mathrm{NCH_2CH_3}} \mathrm{CHCl_2\text{-}C{\equiv}O^{+}} \xrightarrow{-\mathrm{CO}} {}^{+}\mathrm{CHCl_2} \qquad (149)$$

m/e 154

m/e 83

not observed

m/e 83

Figure 16 summarizes the processes which were observed for N-ethyl-α,α,α-trichloroacetamide (29).

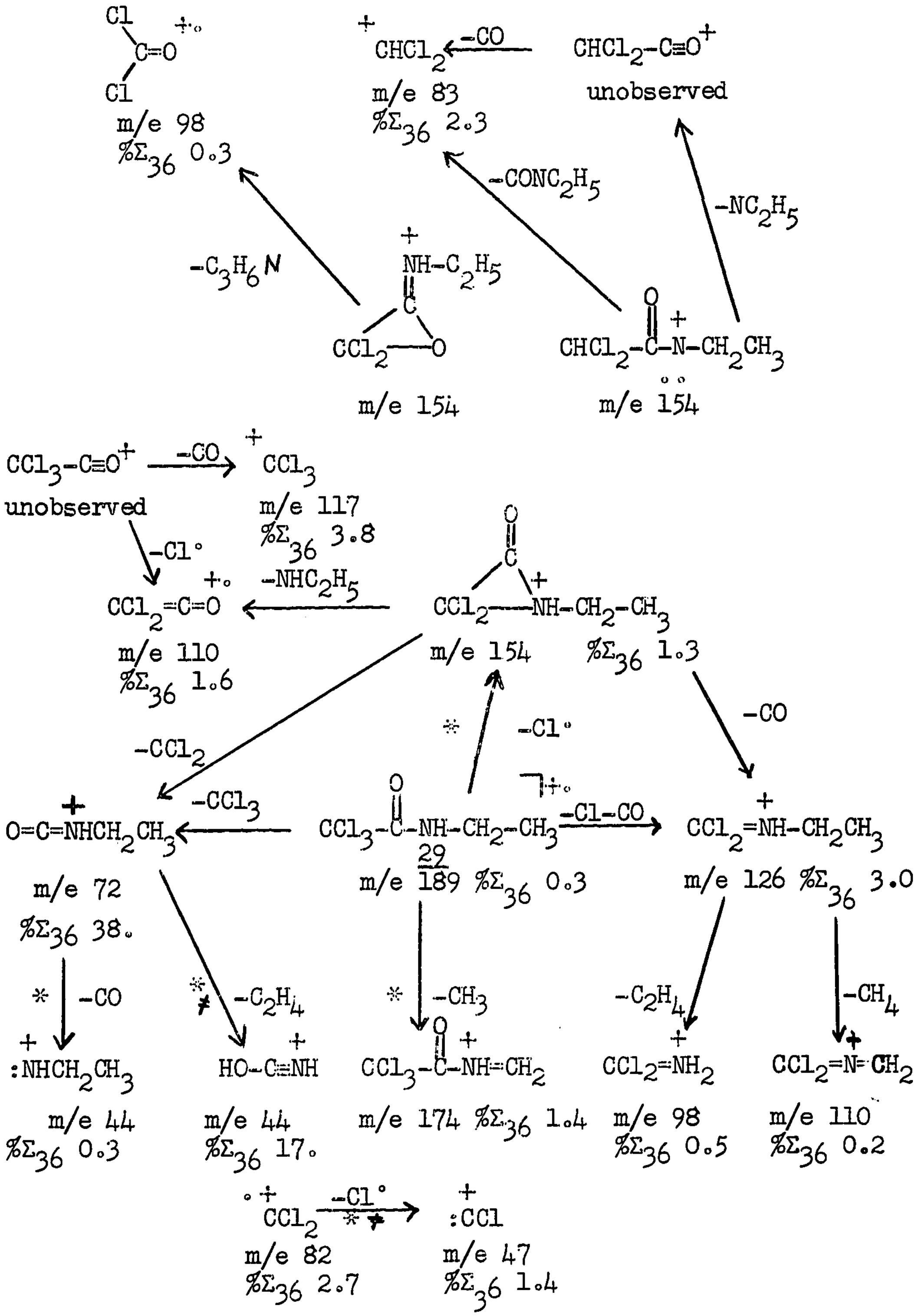


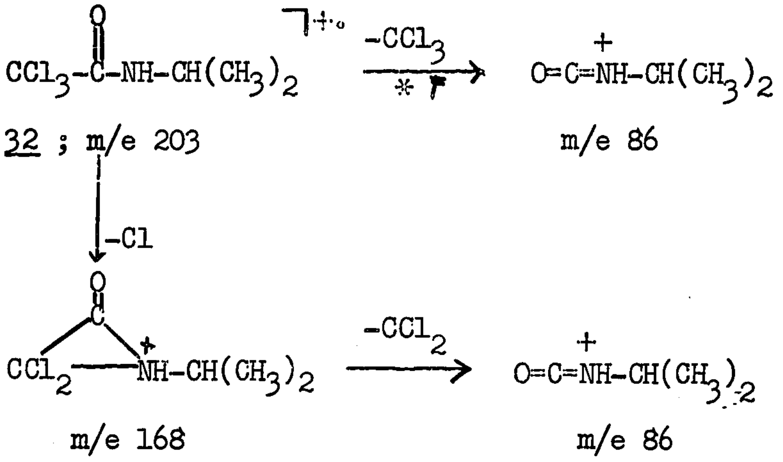
Fig. 16. Fragmentation processes for N-ethyl-α,α,α-trichloroacetamide (29).

N-Isopropyl-α,α,α-trichloroacetamide (32)

A. Fragmentation Peaks.

1. Primary Fission Processes.

An examination of metastable transitions indicated that at least three ions were formed by fission of the molecular ion (m/e 203). As in the cases of the mono- and dichloro-N-isopropyl amides, peaks were observed which corresponded to the loss of Cl• (m/e 168) $[\%\Sigma_{36}\ 0.9]$ and the loss of a methyl group (m/e 188) [5.5] from the molecular ion. The base peak of the spectrum, $[C_4H_8NO]^+$, appeared at m/e 86 and, in analogy to the other isopropyl amides, may have been formed by cleavage of either the molecular ion or the M-Cl ion. However, it was confirmed, by metastable transitions, that the molecular ion constitued a definite precursor for the fragment at m/e 86.



$$CCl_3-\overset{\overset{O}{\|}}{C}-NH-CH(CH_3)_2^{\,+\cdot} \xrightarrow[*]{-CCl_3} \overset{+}{O=C=NH}-CH(CH_3)_2 \qquad (150)$$

(151)

2. Secondary Fission Processes

Four fragments appeared in the spectrum of 32 which may have arisen from a number of precursor ions, as was demonstrated in the analysis of the spectra of the mono- and dichloro-N-iso-

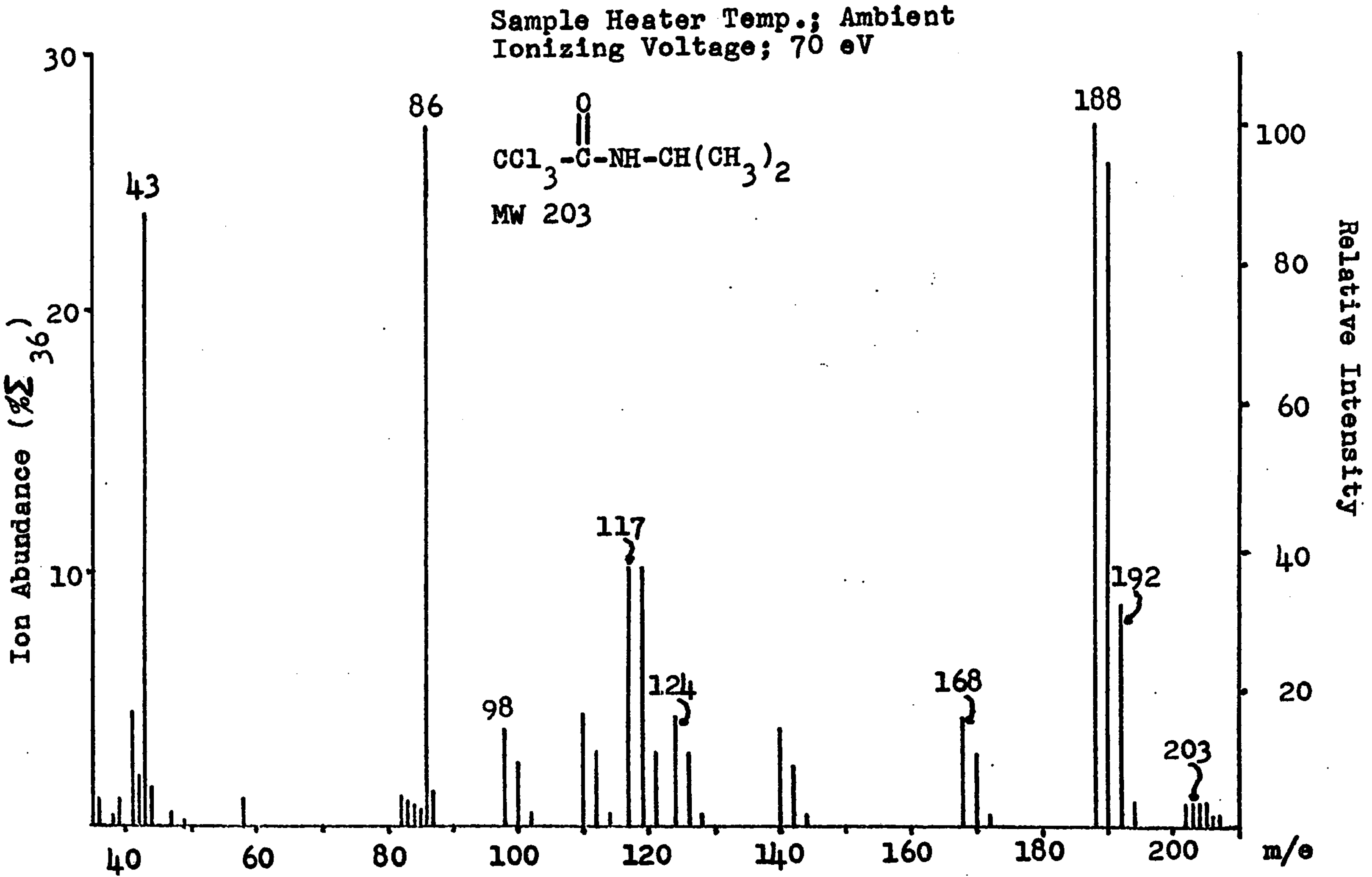
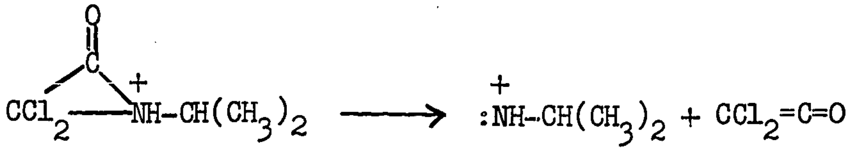


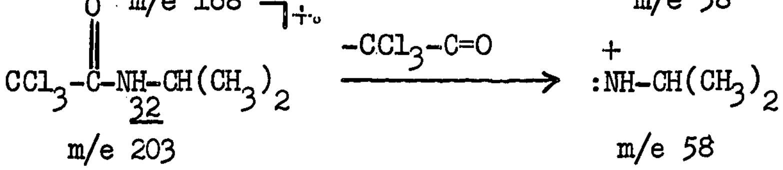
Fig. 17. Mass spectrum of N-isopropyl-α,α,α-trichloroacetamide (32).

propyl amides. However, in each case, at least one of the possible modes of formation was confirmed by observed metastable decompositions. The ion $[C_3H_8N]^+$ (m/e 58) [$\%\Sigma_{36}$ 1.1] which corresponded to the isopropyl amino group, and the isopropyl ion, $[C_3H_7]^+$ (m/e 43) [$\%\Sigma_{36}$ 24.] were both produced by cleavage of the fragment at m/e 86 (152a, 153a). However, it must be emphasized that both of these ions may have been formed by modes of decomposition for which metastable transitions were not observed.

$$\underset{\text{m/e } 86}{O{=}C{=}\overset{+}{N}H\text{-}CH(CH_3)_2} \xrightarrow[*]{-CO} \underset{\text{m/e } 58}{:\overset{+\cdot}{N}H\text{-}CH(CH_3)_2} \qquad (152a)$$



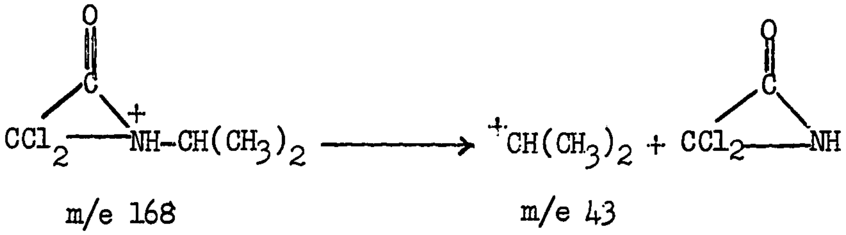
(152b)



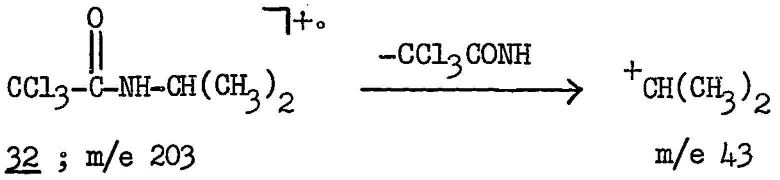
$$\underset{\text{m/e } 203}{CCl_3\text{-}\overset{O}{\overset{\|}{C}}\text{-}NH\text{-}CH(CH_3)_2} \xrightarrow{-CCl_3\text{-}C=O} \underset{\text{m/e } 58}{:\overset{+}{N}H\text{-}CH(CH_3)_2}$$

(152c)

$$\underset{\text{m/e } 86}{O{=}C{=}\overset{+}{N}H\text{-}CH(CH_3)_2} \xrightarrow[*\neq]{} \underset{\text{m/e } 43}{{}^{+}CH(CH_3)_2} + O{=}C{=}NH \qquad (153a)$$



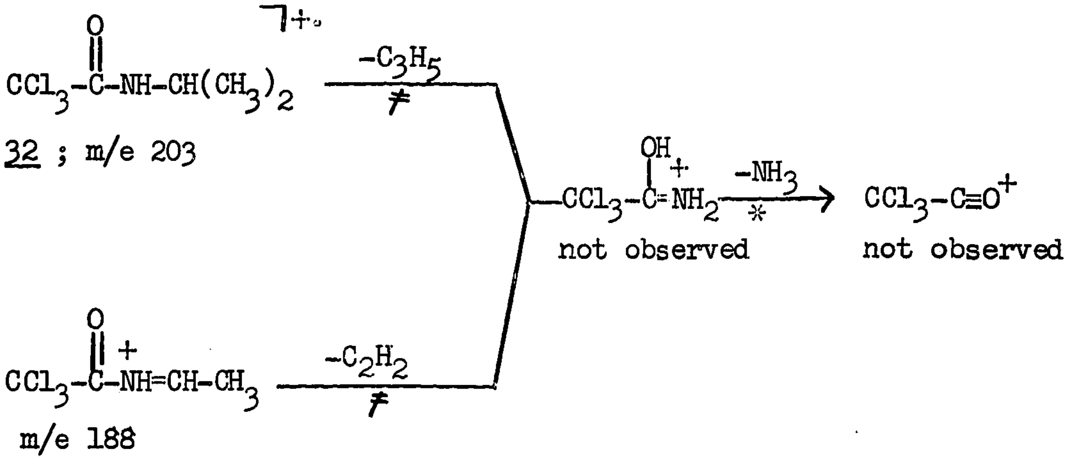
(153b)



$$\underset{\underline{32}\ ;\ m/e\ 203}{\left.\mathrm{CCl_3{-}\overset{\overset{O}{\|}}{C}{-}NH{-}CH(CH_3)_2}\right\rceil^{+\cdot}} \xrightarrow{-\mathrm{CCl_3CONH}} \underset{m/e\ 43}{{}^{+}\mathrm{CH(CH_3)_2}} \qquad (153c)$$

Pathways (152b) and (153c) were found to be operative for both the mono- and dichloro-N-isopropyl amides, and (152c) and (153b) were observed in the spectra of the mono- and dichloro amides respectively.

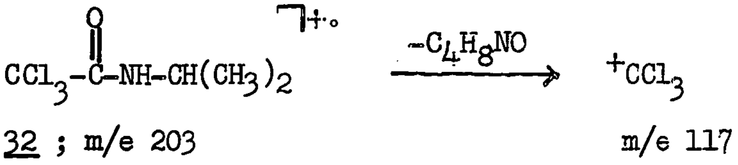
Similarly, the moieties at m/e 117, ${}^{+}\mathrm{CCl_3}$, [2.1] and m/e 110, $\mathrm{CCl_2{=}C{=}O}^{+\cdot}$, [0.9] may have been formed by a number of fragmentation pathways, some of which are depicted below.



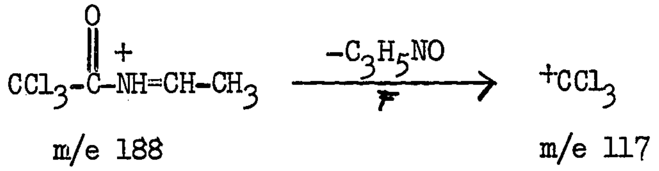
$$\underset{\underline{32}\ ;\ m/e\ 203}{\left.\mathrm{CCl_3{-}\overset{\overset{O}{\|}}{C}{-}NH{-}CH(CH_3)_2}\right\rceil^{+\cdot}} \xrightarrow[\neq]{-\mathrm{C_3H_5}} \underset{\text{not observed}}{\mathrm{CCl_3{-}\overset{\overset{OH}{|}}{C}{\overset{+}{=}}NH_2}} \xrightarrow[*]{-\mathrm{NH_3}} \underset{\text{not observed}}{\mathrm{CCl_3{-}C{\equiv}O^{+}}}$$

$$\underset{m/e\ 188}{\mathrm{CCl_3{-}\overset{\overset{O}{\|}}{C}{-}\overset{+}{N}H{=}CH{-}CH_3}} \xrightarrow[\neq]{-\mathrm{C_2H_2}} \mathrm{CCl_3{-}\overset{\overset{OH}{|}}{C}{\overset{+}{=}}NH_2}$$

$$\underset{\text{not observed}}{\mathrm{CCl_3{-}C{\equiv}O^{+}}} \xrightarrow{-\mathrm{CO}} \underset{m/e\ 117}{{}^{+}\mathrm{CCl_3}} \qquad (154a)$$



$$\underset{\underline{32}\ ;\ m/e\ 203}{\left.\mathrm{CCl_3{-}\overset{\overset{O}{\|}}{C}{-}NH{-}CH(CH_3)_2}\right\rceil^{+\cdot}} \xrightarrow{-\mathrm{C_4H_8NO}} \underset{m/e\ 117}{{}^{+}\mathrm{CCl_3}} \qquad (154b)$$



$$CCl_3-\overset{\overset{\displaystyle O}{\|}}{C}\overset{+}{-}NH=CH-CH_3 \xrightarrow[\ast]{-C_3H_5NO} {}^{+}CCl_3 \qquad (154c)$$

m/e 188 m/e 117

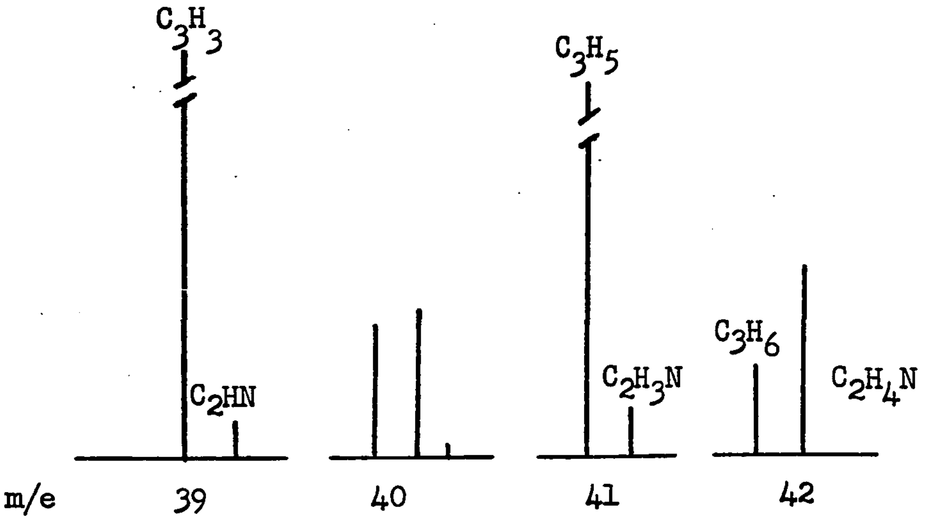
$$CCl_3-C{\equiv}O^{+} \xrightarrow[\ast]{-Cl} CCl_2=C=O^{+\circ} \qquad (155)$$

not observed m/e 110

Metastable transitions were observed in the spectrum of the dichloro-N-isopropyl amide for processes which are analogous to (154a) and (154b), although no evidence for the occurance of these pathways in the case of the trichloro derivative was forthcoming.

3. Ions whose sources were not confirmed by metastable decompositions.

The fragments ${}^{+}CCl_2$ (m/e 82) and $:\overset{+}{C}Cl$ (m/e 47) may have arisen from a number of precursors but once again no appropriate metastable transitions were observed which would distinguish between the various possibilities. The regions of nominal m/e 39 to 42 were examined under high resolution conditions and a number of fragments, whose precursor ions could not be established with certainty, were observed.



A portion of the high resolution spectrum of N-isopropyl-α,α,α-trichloroacetamide (32).

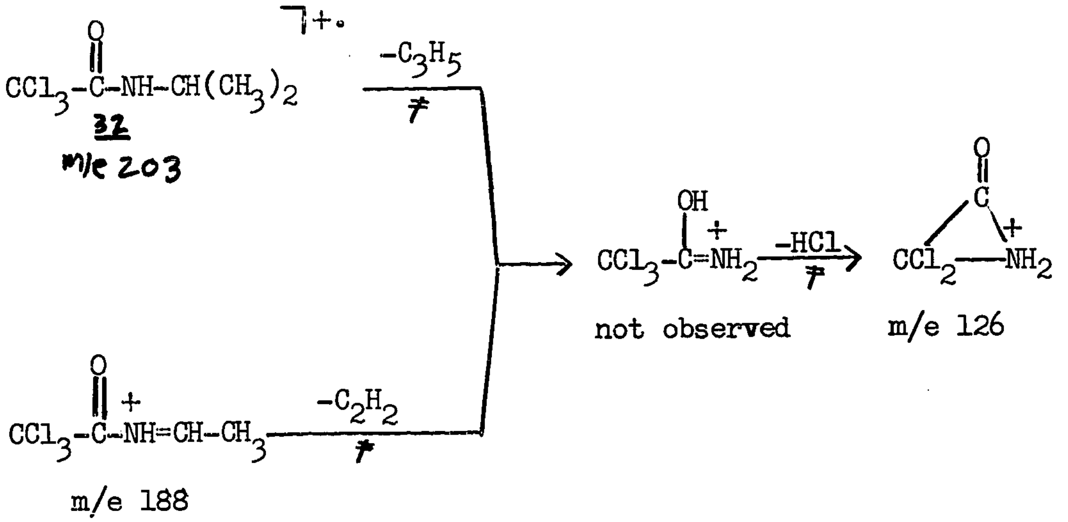
It may be conjectured that the isopropyl ion may have given rise to the fragments at m/e 42, $[C_3H_6]^{+\cdot}$, 41 $[C_3H_5]^+$ and 39 $[C_3H_3]^+$ by the successive loss of hydrogen atoms.

In a similar manner, the ion at m/e 58 may have lost a methyl group and hydrogen atoms to produce fragments at m/e 42 and 41.

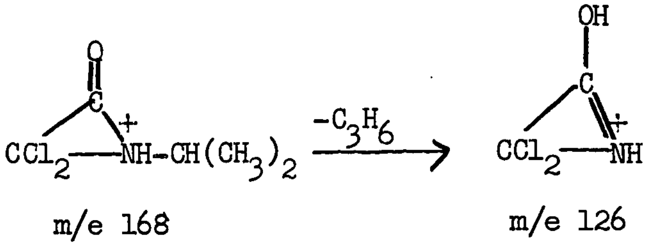
$[C_2H_4N]^+$	$[C_2H_3N]^{+\cdot}$
m/e 42	m/e 41

B. Rearrangement Ions.

A rearrangement fragment was observed at m/e 126 and was established by high resolution measurements and deuterium labelling to be the ion $[C_2H_2NOCl_2]^+$, [$\%\Sigma_{36}$ 0.1]. There is evidence that this fragment was formed both by the loss of HCl from an unobserved double rearrangement ion at m/e 162 and by rearrangement and fission of the M-Cl fragment as shown below (156,157).

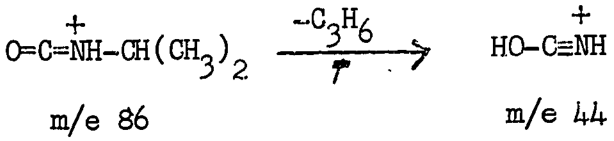


(156)



(157)

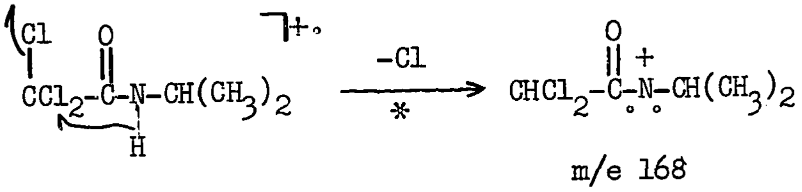
The rearrangement ion $[CH_2NO]^+$ (m/e 44) [0.8] was produced by the loss of C_3H_6 from the fragment at m/e 86. As in the spectra of the mono- and dichloro-N-isopropyl amides, the intensity of this ion was too weak for any significant information to be derived from deuterium labelling studies.



$$O{=}C{=}\overset{+}{N}H{-}CH(CH_3)_2 \xrightarrow[\neq]{-C_3H_6} HO{-}C{\equiv}\overset{+}{N}H$$

(158)

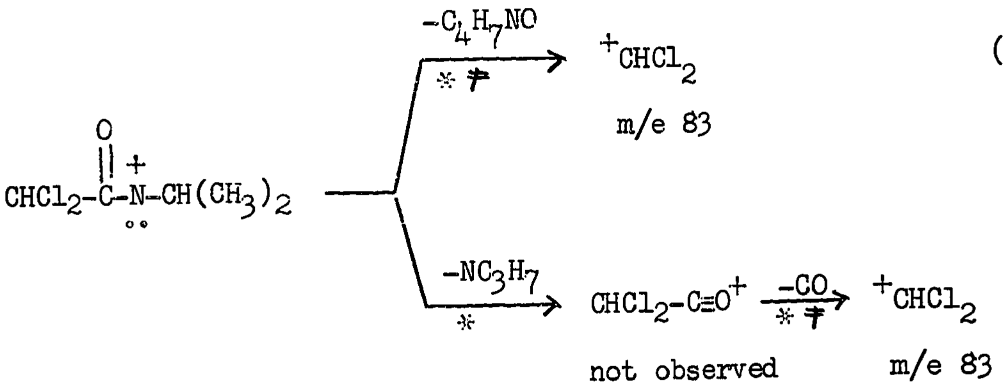
The ion $^+CHCl_2$ (m/e 83) [$\%\Sigma_{36}$ 1.0], which was found in the spectra of all the trichloro amides appeared to have been formed as shown in (159a) and (159b).



$$\left[\overset{\overset{\displaystyle Cl}{|}}{\mathrm{CCl_2}}\text{-}\overset{\overset{\displaystyle O}{\|}}{\mathrm{C}}\text{-}\underset{\underset{\displaystyle H}{|}}{\mathrm{N}}\text{-}\mathrm{CH(CH_3)_2}\right]^{+\cdot} \xrightarrow[*]{-\mathrm{Cl}} \mathrm{CHCl_2}\text{-}\overset{\overset{\displaystyle O}{\|}}{\mathrm{C}}\text{-}\overset{+}{\mathrm{N}}\text{-}\mathrm{CH(CH_3)_2}$$

m/e 168

32 ; m/e 203



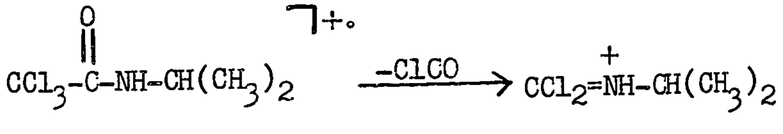
$$\mathrm{CHCl_2}\text{-}\overset{\overset{\displaystyle O}{\|}}{\mathrm{C}}\text{-}\overset{+}{\mathrm{N}}\text{-}\mathrm{CH(CH_3)_2} \xrightarrow[*\ \dagger]{-\mathrm{C_4H_7NO}} {}^{+}\mathrm{CHCl_2} \qquad (159a)$$

m/e 83

$$\mathrm{CHCl_2}\text{-}\overset{\overset{\displaystyle O}{\|}}{\mathrm{C}}\text{-}\overset{+}{\mathrm{N}}\text{-}\mathrm{CH(CH_3)_2} \xrightarrow[*]{-\mathrm{NC_3H_7}} \mathrm{CHCl_2\text{-}C{\equiv}O^{+}} \xrightarrow[*\ \dagger]{-\mathrm{CO}} {}^{+}\mathrm{CHCl_2} \qquad (159b)$$

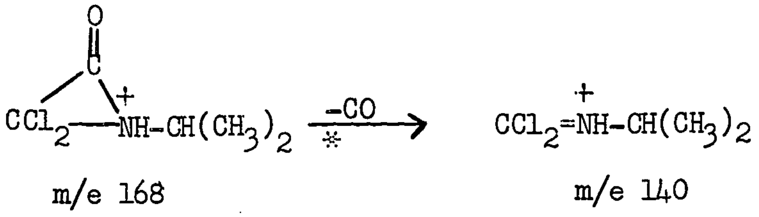
not observed m/e 83

A further rearrangement fragment, $[C_4H_8NCl_2]^{+}$ [0.8] which could have been formed by the loss of CO from the lactam-type M-Cl ion or by concerted fission and rearrangement of the molecular ion, appeared at m/e 140. Only evidence for the latter process was obtained.



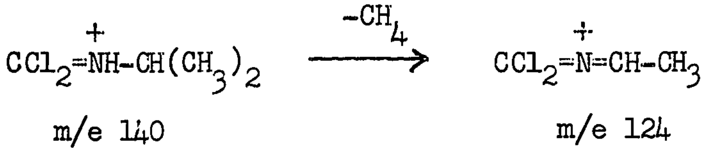
$$\left[\mathrm{CCl_3}\text{-}\overset{\overset{\displaystyle O}{\|}}{\mathrm{C}}\text{-}\mathrm{NH}\text{-}\mathrm{CH(CH_3)_2}\right]^{+\cdot} \xrightarrow{-\mathrm{ClCO}} \mathrm{CCl_2{=}\overset{+}{N}H\text{-}CH(CH_3)_2} \qquad (160a)$$

32 ; ,/e 203 m/e 140

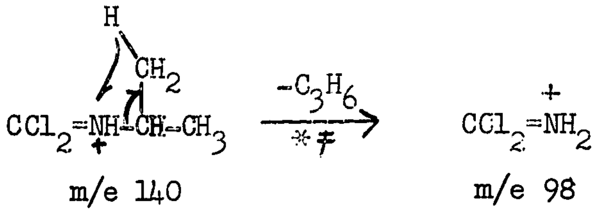


(160b)

This ion (m/e 140) subsequently lost CH_4 or C_3H_6 to give fragments at m/e 124 and 98 respectively. The ion at m/e 98 [0.8] appeared at m/e 99 in the spectra of the d_6- and d_7- amides again establishing that the migrating hydrogen atom was bonded to a methyl group of the isopropyl side chain. Furthermore, the peak at m/e 124 [0.9] was observed at m/e 127 in the spectrum of the d_6- amide and at m/e 128 in the spectrum of the d_7- amide, indicating that one of the hydrogen atoms, lost as CH_4, had been bonded to the nitrogen atom.

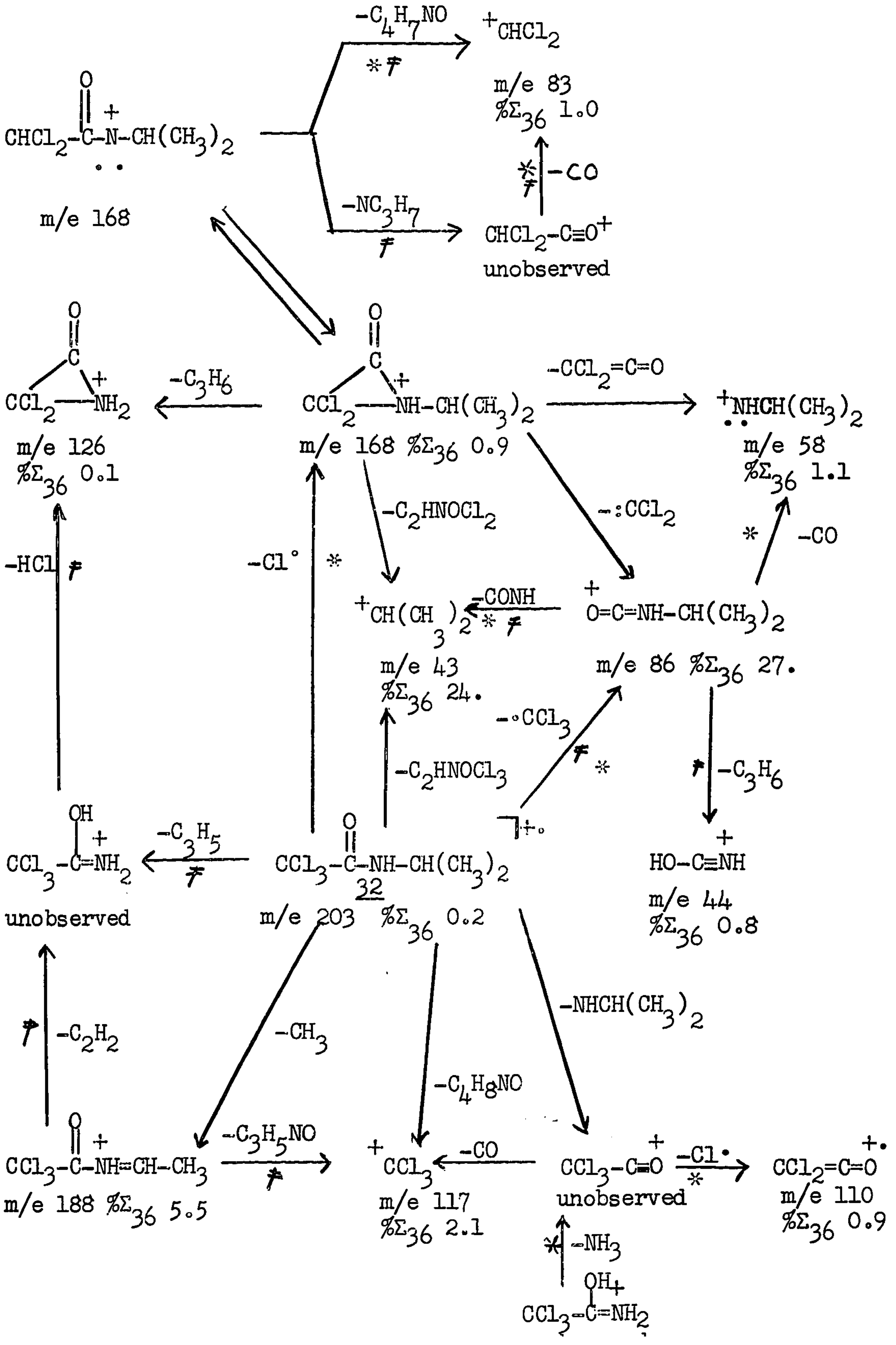


$$\underset{\text{m/e }140}{CCl_2{=}\overset{+}{N}H{-}CH(CH_3)_2} \xrightarrow{-CH_4} \underset{\text{m/e }124}{CCl_2{=}\overset{+\cdot}{N}{=}CH{-}CH_3} \qquad (161)$$



(162)

Figure 18 summarizes the processes taking place for <u>32</u>.


-C4H7NO
+CHCl2
*≠
m/e 83
%Σ36 1.0
*≠ -CO
CHCl2-C-N-CH(CH3)2
m/e 168
-NC3H7
≠
CHCl2-C≡O+
unobserved
CCl2—NH2
m/e 126
%Σ36 0.1
-C3H6
CCl2—NH-CH(CH3)2
m/e 168 %Σ36 0.9
-CCl2=C=O
+NHCH(CH3)2
m/e 58
%Σ36 1.1
* -CO
-HCl ≠
-Cl° *
-C2HNOCl2
-:CCl2
+CH(CH3)2
-CONH
* ≠
O=C=NH-CH(CH3)2
m/e 43
%Σ36 24.
m/e 86 %Σ36 27.
-◦CCl3
≠ *
-C2HNOCl3
≠ -C3H6
CCl3-C=NH2
unobserved
-C3H5
≠
CCl3-C-NH-CH(CH3)2
32
m/e 203 %Σ36 0.2
HO-C≡NH
m/e 44
%Σ36 0.8
-NHCH(CH3)2
≠ -C2H2
-CH3
-C4H8NO
CCl3-C-NH=CH-CH3
m/e 188 %Σ36 5.5
-C3H5NO
≠
+CCl3
m/e 117
%Σ36 2.1
-CO
CCl3-C≡O
unobserved
-Cl•
*
CCl2=C=O
m/e 110
%Σ36 0.9
* -NH3
CCl3-C=NH2

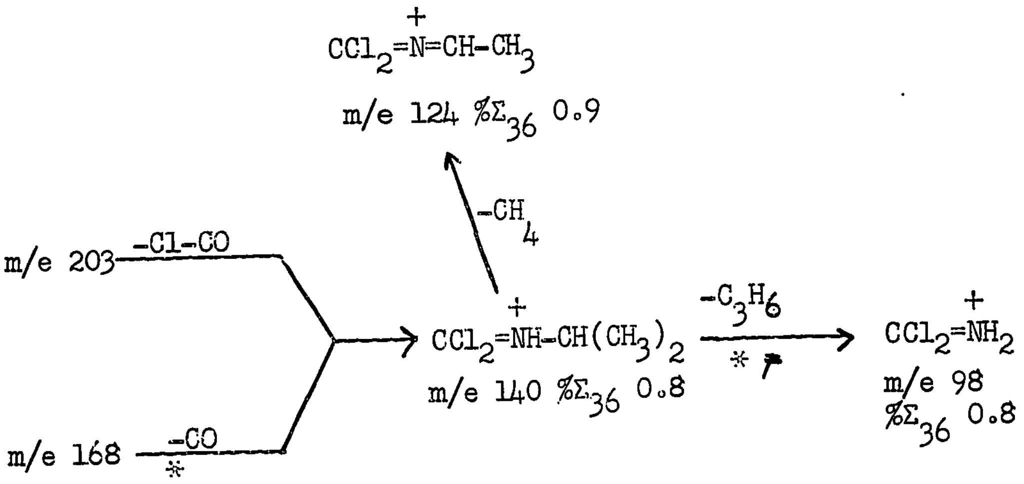


Fig. 18. Fragmentation patterns for N-isopropyl-α,α,α-trichloroacetamide (32).

COMPARISONS

The effects of increased alkyl substitution and chloroination upon the relative abundance of the ions observed for compounds 24 to 32 are discussed in this section. The only measurements used for this purpose are the changes in the peak intensities ($\%\Sigma_{36}$). As would be expected, small variations in relative peak heights were observed in spectra obtained on different days for a given compound. Such differences may be ascribed to differing source pressures, lens and repeller settings, target current as well as the immediate history and cleanliness of the source.

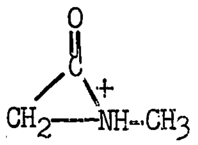
Furthermore, as alkyl substitution was increased, a number of rearrangement and fragmentation pathyways were observed which were not open to the lower alkylated homologues, or which would be expected to increase in probability as more migrating atoms became available. Particular effects of this nature are not discussed in the sections dealing with the effects of alkyl substitution but will be considered when the effects of increased chlorination are discussed. Although changing alkyl and chlorine substitution is suspected to change the principal precursors for many ions with homologous structures, these effects were unconfirmed since metastable transitions could not be assigned with certainity.

The use of metastable ion defocusing techniques[28] whereby short lived species decomposing in the first field free region of the mass spectrometer can be detected, would do much to remove the ambiguity of the origin of these ions. The defocusing technique which provides pure metastable spectra has the additional important advantage of uniquely determining the precursor and daughter ion for the transition which is usually but not necessarily a one step process.[29] By allowing the observation of a second metastable transition of a metastable ion, consecutive decompositions in the mass spectrometer can be demonstrated.[30]

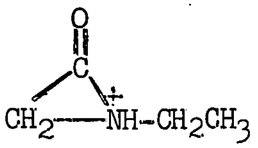
In an examination of alkyl substituent effects the importance of small changes in ion abundances is difficult to assess. Small decreases in intensity, due to the increased number of possible fragmentation modes brought about by the increasing size of alkyl groups, may frequently occur. Similarly, the effect of chlorine substitution is often ambiguous, since the univalent chlorine atoms are replacing hydrogen atoms and thus the <u>number</u> of fragmentation modes open to an ion may not significantly increase, although large or small variations in individual ion abundances can be expected.

1. Effects of alkyl substitution upon simple cleavage of the monochloro-amides.

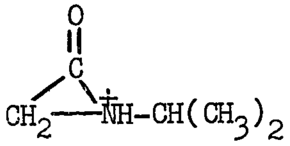
Five fragmentation pathways, in the monochloro-series of compounds (<u>24</u>, <u>27</u> and <u>30</u>), appeared to be significantly affected by increasing alkyl substitution. The molecular ion steadily decreased in intensity, from $\%\Sigma_{36}$ 24 to 12 to 5.9, as the alkyl chain was increased from methyl to ethyl to isopropyl. Similarly, the intensity of the ion corresponding to the loss of $:CH_2$ from the $[M^{+}-Cl]$ ion yielding the ion $O{=}C{=}\overset{+}{N}H{-}R$ (R=Me, Et and i-Pr) which decreased in the order $\%\Sigma_{36}$ 46, $\%\Sigma_{36}$ 9.3, $\%\Sigma_{36}$ 5.1 respectively. From observation of metastable transitions in the spectra of the three amides, it would appear that the ion $O=C=\overset{+}{N}H-R$ was formed by cleavage of the $[M^{+}-Cl]$ ion and the molecular ion. Although the ion $O=C=\overset{+}{N}H-R$ and the molecular ion decreased in abundance with heavier alkyl groups, the intensity of the $M^{+}-Cl$ ion fluctuated only slightly between the three compounds, as illustrated below:



m/e 72
$\%\Sigma_{36}$ 4.2



m/e 86
$\%\Sigma_{36}$ 9.3



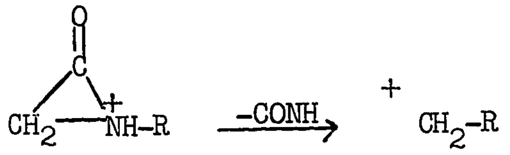
m/e 100
$\%\Sigma_{36}$ 6.7

Another ion which also exhibited a decrease in intensity with higher alkylation, was the $CHCl=C=\overset{+\circ}{O}$ fragment (m/e 76). In the spectrum of the monochloro-N-methyl amide, this ion had an abundance of $\%\Sigma_{36}$ 1.3 while in the ethyl and isopropyl amides, the abundance was less than 0.4.

2. The effects of alkyl substitution upon the relative abundance of certain rearrangement ions of the monochloro-amides.

The intensity of the rearrangement ion $CH_2=\overset{+}{N}H-R$ (R=Me, Et and i-Pr) (formed by the loss of Cl and CO from the molecular ion or the loss of CO from the $[M^{+}-Cl]$ ion), was observed to decrease from 1.4 to the vanishing point as alkyl substitution was increased. The additional methyl groups of the isopropyl amide probably facilitated fragmentation to other stabilized species such as $CH_2=\overset{+}{N}=CH-CH_3$.

One process was observed in the spectra of the ethyl and isopropyl amides which yielded an ion of the type shown below:



(163)

R=Me, Et and i-Pr

This sequence led to an ion in the spectrum of the ethyl amide, which had an intensity of 1.4 and, in the spectrum of the isopropyl amide, to an ion with an abundance of 0.6.

The fragment $[CH_2NO]^{+}$ (m/e 44) was observed in all three spectra but the intensities followed an unusual pattern. As the alkyl chain was expanded, the intensity of this ion rose from 0.2 to 14 and subsequently fell to 1.1 for the N-isopropyl compound. This irregular effect was most probably due to the existence of more than one mode of formation for this ion, although, due to the absencence of appropriate metastable transitions formed in the second field free region, this assumption could not be confirmed.

3. The effects of alkyl substitution upon simple cleavage of the dichloro-amides.

Although the actual $\%\Sigma_{36}$ values differed, the general trends which were observed for the dichloro amides (25, 28 and 31) were identical to those described for the monochloro-amides. Thus the intensities of the molecular ion and the $[M^{+}-CHCl_2]$ ion decreased steadily as the alkyl substitution was increased, while the abundance of the $[M^{+}-Cl]$ fragment remained essentially the same.

The only exception noted was that the ion corresponding to the loss of $:NH_2R$ (R=Me, Et and i-Pr) was not observed in dichloro-series.

4. The effects of alkyl substitution upon rearrangement of the dichloro-amides.

As in the case of the monochloro-amides, the intensity of the $[M^{+}-ClCO]$ ion decreased from 1.0 to the vanishing point as the alkyl group was changed from a methyl to an ethyl to an isopropyl group. No peak was observed which corresponded to the loss of Cl and CONH from the molecular ion. However, the intensity of the rearrangement fragment $^{+}CH_2Cl$ (m/e 49) was observed to increase as the alkyl substitution was increased. This is to be expected since the formation of this ion appeared to depend upon the loss of either $O{=}C{=}N{-}R$ or, $:\overset{\circ}{N}{-}R$ (R=Me, Et and i-Pr) from the $[M^{+}-Cl]$ ion (see processes 93, 94, 98, 99, 119 and 120). Higher alkylation would presumably tend to stabilize these groups, thus rendering the processes more favorable. The ion $[CH_2NO]^{+}$ (m/e 44) was again observed in all three spectra and the intensities followed the same pattern as in the spectra of the monochloro-amides, increasing from 0.2 for the N-methyl amide to 12 for the N-ethyl amide and falling to 0.8 for the N-isopropyl amide.

5. The effects of alkyl substitution upon simple cleavage modes of the trichloro-amides.

The trends which were observed in the spectra of the trichloro amides (26, 29 and 32) were the same as those described for the dichloro amides. The actual $\%\Sigma_{36}$ values are listed below in Table 1.

TABLE 1

Fragments produced by simple cleavage of the trichloro amides.

ion	Abundance ($\%\Sigma_{36}$)		
	R=Me(26)	R=Et(29)	R=i-Pr(32)
$\overset{+\cdot}{\mathrm{R}}\mathrm{NHCOCCl_3}$	1.3	0.3	0.2
$\mathrm{O{=}C{=}\overset{+}{N}H{-}R}$	63.	38.	27.
$\mathrm{M^{+\cdot}{-}Cl}$	1.6	1.3	0.9
$:\overset{+}{\mathrm{N}}\mathrm{H{-}R}$	*	0.3	1.1

* The region in which this peak appeared was not scanned in the spectrum of compound 26.

6. The effects of alkyl substitution upon the rearrangement of the trichloro-amides.

Here again the intensity variations of rearrangement ions from the trichloro-amides were essentailly the same as those for the dichloro-amides. The only exception was that the abundance of the rearrangement ion $^{+}\mathrm{CHCl_2}$ (m/e 83) decreased slightly as the alkyl substitution was increased, whereas the dichloro-derived ion, $^{+}\mathrm{CH_2Cl}$, increased slightly in intensity. The $\%\Sigma_{36}$ values are listed below in Table 2.

TABLE 2

Fragments produced by rearrangements of the trichloro amides.

ion	Abundance ($\%\Sigma_{36}$)		
	R=Me(26)	R=Et (29)	R=i-Pr(32)
$\overset{+}{R}NHCOCCl_3$-COCl	3.4	3.0	0.8
$^{+}CHCl_2$	2.5	2.3	1.0
$[CH_2NO]^{+\cdot}$	0.2	17.	0.8

7. The effects of chlorination upon simple cleavage modes of the N-methyl amides.

Five ions were observed to decrease in intensity as the number of chlorine atoms on the carbon atom alpha to the carbonyl group, was increased. The molecular ion, $M^{+\cdot}$-Cl ion, $R'-C\equiv O^{+}$ ion, $(R'-Cl)=C=\overset{+}{\ddot{O}}^{\circ}$ ion and $R'^{+\cdot}$ ion ($R'=CH_2Cl$, $CHCl_2$ and CCl_3) all decreased in abundance as shown in Table 3.

TABLE 3

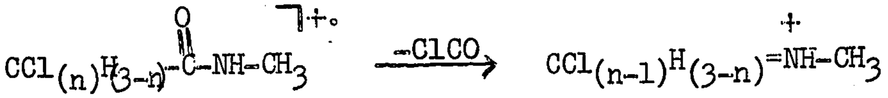
Fragments produced by simple cleavage of the methyl amides.

ion	Abundance ($\%\Sigma_{36}$)		
	R'=CH_2Cl(<u>24</u>)	R'=$CHCl_2$(<u>25</u>)	R'=CCl_3(<u>26</u>)
$\overset{+\cdot}{\mathrm{CH_3\text{-}NH\text{-}CO\text{-}R'}}$	24.	11.	1.3
$\overset{+\cdot}{\mathrm{CH_3\text{-}NH\text{-}CO\text{-}(R'\text{-}Cl)}}$	4.2	0.4	1.6
$R'\text{-}C{\equiv}O^{+}$	2.0	0.0	0.0
$(R'\text{-}Cl){=}C{=}\overset{+\cdot}{O}$	1.8	1.4	0.9
R'^{+}	3.6	2.7	2.0

This trend may have been due, in part, to the inductive effect of the chlorine atoms tending to polarize and thus weaken the adjacent bonds. Large ions containing the chlorine atoms would then fragment more readily to lower mass ions and the relative intensitiy of the precursors decreases. The polarization of the carbon-chlorine bonding electrons toward the chlorine atom increases the probability of positive charge retention upon the unhalogenated fragment. In accordance with these effects one may readily rationalize the increasing intensity of the ion $O{=}C{=}\overset{+}{N}H\text{-}CH_3$ from 46 in the monochloro-derivative to 63 in the di- and trichloro-amides.

8. The effects of chlorination upon rearrangements of the N-methyl amides.

Two rearrangement ions were observed to increase in abundance as chlorine substitution was increased. The ion, which corresponds to the loss of Cl and CO from the molecular ion, may have been formed by either or both of the mechanisms shown below.



$$\left.CCl_{(n)}H_{(3-n)}-\overset{\overset{O}{\|}}{C}-NH-CH_3\right]^{+\cdot} \xrightarrow{-ClCO} CCl_{(n-1)}H_{(3-n)}=\overset{+}{N}H-CH_3$$

(164a)

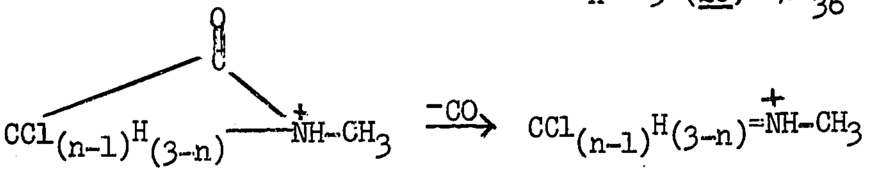
M^{+}

A

n = 1 (24) $\%\Sigma_{36} = 1.4$

n = 2 (25) $\%\Sigma_{36} = 1.0$

n = 3 (26) $\%\Sigma_{36} = 3.4$



$$CCl_{(n-1)}H_{(3-n)}-\overset{+}{N}H-CH_3 \xrightarrow{-CO} CCl_{(n-1)}H_{(3-n)}=\overset{+}{N}H-CH_3$$

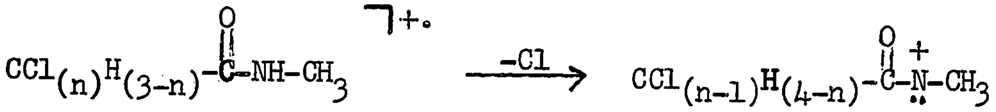
(164b)

$M^{+}-Cl$

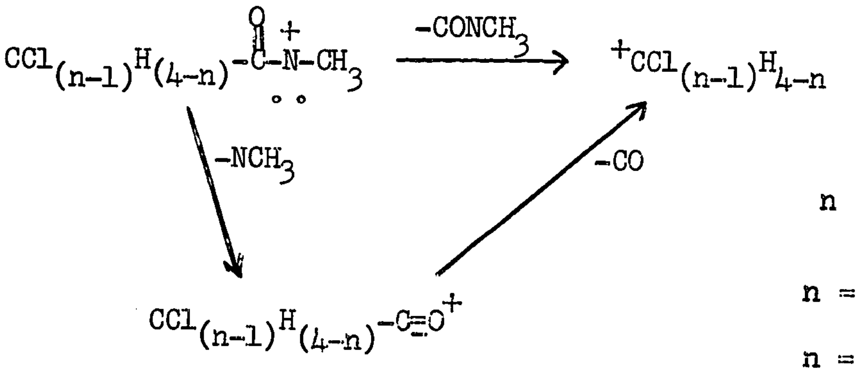
B

Regardless of the precise nature of the precursor (A or B) it would be expected that the intensity of these rearrangement ions would increase with increasing chlorination. This may be rationalized as in previous cases, by the destabilizing effect of the chlorine atoms upon the immediate precursors.

The ion arising from the loss of Cl and $CONCH_3$ from the molecular ion with the migration of one hydrogen atom from the nitrogen atom to the alpha carbon atom is believed to have been formed as illustrated below.



$$CCl_{(n)}H_{(3-n)}-\overset{O}{\overset{\|}{C}}-NH-CH_3\Big]^{+\cdot} \xrightarrow{-Cl} CCl_{(n-1)}H_{(4-n)}-\overset{O}{\overset{\|}{C}}-\overset{+}{\underset{\cdot\cdot}{N}}-CH_3$$ (165)



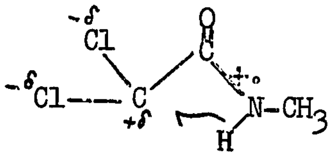
(166a)

n = 1 (24) region not scanned

n = 2 (25) $\%\Sigma_{36}$ 0.5

n = 3 (26) $\%\Sigma_{36}$ 2.5

From purely electronic considerations the initial migration of the hydrogen atom from the nitrogen atom (165) would be expected to be enhanced by the presence of additional chlorine atoms (166b) and thus, the rearrangement ion would increase in intensity while the precursor [$M^{+\cdot}$-Cl] fragement would exhibit a concomitant decrease in abundance.



(166b)

9. The effects of chlorination upon simple cleavage of the N-ethyl amides.

The abundance of the $M^{+\cdot}$, [$M^{+\cdot}$-Cl], $R'-C\equiv O^+$($R'=CH_2Cl$, $CHCl_2$ and CCl_3) and $O=C=\overset{+}{N}H-CH_2CH_3$ ions in the spectra of the N-ethyl derivatives (27, 28 and 29) exhibited the same behavior as the corresponding ions in the N-methyl amides. The abundances are tabulated below.

TABLE 4

Fragments formed by simple cleavage of the ethyl amides.

Ion	Abundance ($\%\Sigma_{36}$)		
	$R'=CH_2Cl$ (27)	$R'=CHCl_2$ (28)	$R'=CCl_3$ (29)
$R'CONHEt$ ($M^{+\cdot}$)	12.	7.5	0.3
$M^{+}-Cl$	9.3	0.7	1.3
$R'-C\equiv O^{+}$	2.5	0.0	0.0
$O=C=\overset{+}{N}H-(C_2H_5)$	31.	47.	38.

In contrast to the methyl amides, the $(R'-Cl)=C=\overset{+}{O}$. and R'^{+} ions ($R'=CH_2Cl$, $CHCl_2$, CCl_3) did not appreciably vary in abundance as chlorination was increased in the ethyl series. This is most proabably because the inductive effect tending to weaken the bonds, and the opposing resonance effect (chlorine atoms stabilizing an adjacent charge) are cancelling out.

The $[M^{+}-CH_3]$ ion also decreased in abundance (from 3.0 to 1.8 to 1.4), most probably due to the inductive effect of the chlorine atoms.

10. The effects of chlorination upon rearrangement of N-ethyl amides.

The intensities of the $[M^{+}-ClCO]$ and $[R'-Cl+H]^{+}$ ($R'=CH_2Cl$, $CHCl_2$, CCl_3) ions followed the same trends in the spectra of the N-ethyl amides as did the analogous fragments in the spectra of the methyl derivatives. The ion corresponding to the loss of Cl and CONH from the molecular ion had an abundance of 1.4 in the spectrum of the N-ethyl-α-chloroacetamide (27) and was not observed in the spectra of the di- (28) and trichloro (29) amides. (This is most probably due to the fact that, in the case of the monochloro derivative, this ion contained no chlorine atoms.) The presence of one and two chlorine atoms in the fragment under consideration in the di- and trichloro-amides respectively diminished the degree of charge retention on the rearrangement ion reducing its abundance. The ion $[CH_2NO]^{+\cdot}$ increased in intensity slightly as chlorination was increased, in part because its immediate precursor, $O=C=\overset{+}{N}H-CH_2CH_3$, also increased in abundance as the number of chlorine atoms rose.

11. The effects of chlorination upon simple cleavage of the N-isopropyl amides.

The abundances of the M^{+}, $\overset{+}{M}-Cl$, $M^{+}-CH_3$, $R'-C\equiv O^{+}$, $(R'-Cl)=C=O^{+\cdot}$, R'^{+} ($R'=CH_2Cl, CHCl_2$ and CCl_3), $O=C=NH-(C_3H_7)$ and alkylamino ions in the spectra of the N-isopropyl amides (30, 31 and 32) followed the same pattern as the corresponding fragments in the spectra of the N-ethyl amides. These trends may be rationalized in the same manner as was done for the N-ethyl amides. The isopropyl fragment,

$[C_3H_7]^{+\cdot}$, was also observed to increase in intensity as the chlorination was increased. This was to be expected since a precursor for this ion, the fragment $O=C=\overset{+}{N}H-(C_3H_7)$ also became more abundant as the number of chlorine atoms was increased. The trends are summarized below.

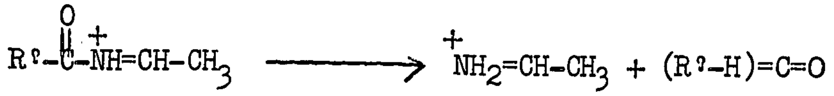
TABLE 5

Fragments formed by simple cleavage of the isopropyl amides.

<u>Ion</u>	Abundance ($\%\Sigma_{36}$)		
	$R'=CH_2Cl$(<u>30</u>)	$R'=CHCl_2$(<u>31</u>)	$R'=CCl_3$(<u>32</u>)
$R'CONHiPr$ ($M^{+\cdot}$)	5.9	3.6	0.2
$M^{+}-Cl$	6.7	0.7	0.9
$M^{+}-CH_3$	12.	7.0	5.5
$R'-C\equiv O^{+}$	1.4	0.0	0.0
$(R'-Cl)=C=\overset{+\cdot}{O}$	0.8	0.6	0.9
R'^{+}	2.4	1.8	2.1
$O=C=\overset{+}{N}H-(C_3H_7)$	5.1	22.	27.
$\overset{+}{N}H-(C_3H_7)$	3.4	1.4	1.1
$[C_3H_7]^{+\cdot}$	10.	20.	24.

12. The effects of chlorination upon rearrangement of the N-isopropyl amides.

The $[M^{+}-ClCO]$ ion increased and the $[M^{+}-ClCONH]$ ion decreased in abundance as the number of halogen atoms was increased, in exact analogy to the trends observed in the spectra of the N-ethyl series. However, in contrast to the N-ethyl series the ion $[R'-Cl+H]^{+}$ ($R'=CH_2Cl$, $CHCl_2$ and CCl_3) showed virtually no change in intensity between the di- and trichloro-derivaties. Thus, it would appear that the opposing inductive and resonance effects of the chlorine atoms cancelled each other. The rearrangement ion formed by the process described by both Gilpin[1] and Djerassi[2] (see process 167) decreased in abundance as the number of halogen atoms was increased.



$$R'-\overset{O}{\overset{\|}{C}}-\overset{+}{N}H=CH-CH_3 \longrightarrow \overset{+}{N}H_2=CH-CH_3 + (R'-H)=C=O \qquad (167)$$

m/e 44

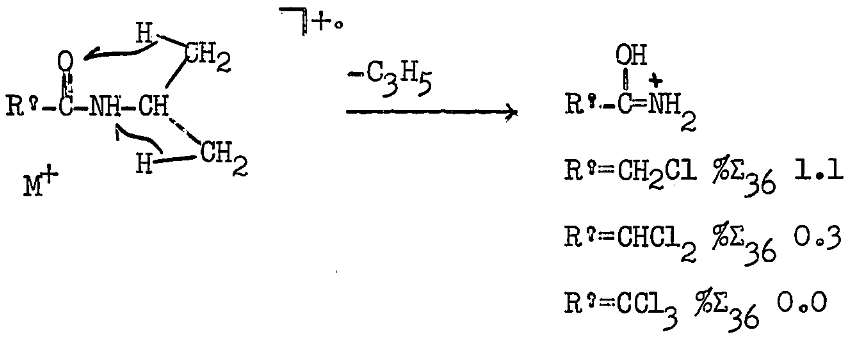
$R'=CH_2Cl$ $\%\Sigma_{36}$ 25

$R'=CHCl_2$ $\%\Sigma_{36}$ 9.9

$R'=CCl_3$ can not occur

This effect is simply due to the decreased number of hydrogen atoms available for migration.

The double rearrangement ion $R'-C(OH)=\overset{+}{N}H_2$ $[R'=CH_2Cl, CHCl_2, CCl_3.]$ appears to have been formed by two distinct mechanisms, both involving the migration of two hydrogen atoms from the methyl groups of the isopropyl side chain.

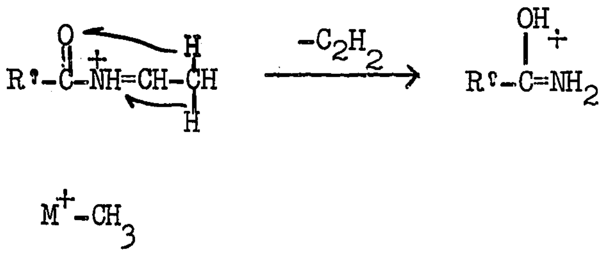


R'=CH_2Cl %Σ_{36} 1.1

R'=$CHCl_2$ %Σ_{36} 0.3

R'=CCl_3 %Σ_{36} 0.0

(168a)



(168b)

Probably, three effects contributed to the decrease in the abundance of this double rearrangement ion as chlorination increased. (a) Both of the precursor fragments (M^+ and M^+-CH_3) decreased in stability as the degree of chlorination was increased and fragmented to ions other than the double rearrangement fragment in question. (b) The inductive effect of the chlorine atoms would tend to enhance further fragmentation of the rearrangement ion. (c) Finally, increased chlorination would retard the retention of the charge on the chlorine containing rearragement fragment contributing to a decrease in the observed abundance. Table 6 summarizes the results for the rearrangements of the N-isopropyl amides.

TABLE 6

Fragments formed by rearrangement of the isopropyl amides.

<u>Ion</u>	Abundance ($\%\Sigma_{36}$)		
	$R'=CH_2Cl$(<u>30</u>)	$R'=CHCl_2$(<u>31</u>)	$R'=CCl_3$(<u>32</u>)
$M^{+}-ClCO$	0.0	0.0	0.8
$M^{+}-ClCONH$	0.6	0.0	0.0
$[R'-Cl+H]^{+}$	#	1.2	1.0
$R'-C(OH)=\overset{+}{N}H_2$	1.1	0.3	0.0
$NH_2=CH-CH_3$	25.	9.9	----

The region in which this ion would have appeared was not scanned in the spectrum of <u>30</u>.

EXPERIMENTAL

Melting points were determined on a Mettler FPI Melting and Boiling Point Apparatus and are uncorrected. Elemental analyses were carried out on compounds 24, 30, 25, 28, 31, 26, 29, and 32 using an F and M Model 185 CHN analyser.

Infrared spectra were carried out on a Beckman IR-8 spectrophotometer.

The ^{1}H nuclear magnetic resonance (n.m.r.) spectra were recorded on a Varian A-60A spectrometer operating at 60 MHz. and a probe temperature of approximately 37°.

The identity of all the amides described in this thesis was verified by n.m.r. and i.r. spectroscopy.

Mass spectra were determined on a Hitachi RMU-7E double focussing mass spectrometer using an ionizing voltage of 70 e.v. The spectrometer has a maximum resolving power of approximately 1 part in 20,000 with 15% valley.

N-Methyl-α-chloroacetamide (24)

This compound was prepared by the method of Bergmann and Kaluszyner[12]. The white crystals obtained were vacuum sublimed three times. M.P. 46.6°, (Lit. m.p. 43-45°[13]).

N-Ethyl-α-chloroacetamide (27)

This compound was prepared by the general procedure described by Speziale and Hamm[14], with the following modifications.

(a) The ethylamine was generated by reacting ethylamine hydrochloride with sodium hydroxide solution. The evolved ethylamine was passed over anhydrous calcium chloride into a cooled (-20°) solution of α-chloroacetylchloride in dry 1,2-dichloroethane until the reaction ceased.

(b) No sodium hydroxide solution was used in the reaction mixture.

The clear liquid obtained was distilled three times under vacuum. B.P. 67.5-66.0° at 1-2 mm. (Lit. b.p. 96.5° at 13 mm[15]).

N-Isopropyl-α-chloroacetamide (30)

This compound was prepared by the general procedure described by Speziale and Hamm[14], with the following modifications.

(a) No sodium hydroxide solution was used in the reaction mixture.

(b) The white crystals obtained were vacuum sublimed three times to give the amide (30), m.p. 57.4°. (Lit. m.p. 62-62.5°[14] and 60-62°[13]).

N-Methyl-α,α-dichloroacetamide (25)

This compound was prepared by the general procedure described by Speziale and Hamm[14], with the following modifications.

(a) The methylamine was generated by reacting methylamine hydrochloride with sodium hydroxide solution. The evolved methylamine was passed over anhydrous calcium chloride into a cooled (-20°) solution of α,α-dichloroacetylchloride in dry 1,2-dichloroethane until the reaction ceased.

(b) No sodium hydroxide solution was used in the reaction mixture.

(c) The white crystals obtained were vacuum sublimed three times to give the dihaloamide, m.p. 77.6°. (Lit. m.p 79°[16,17]).

N-Ethyl-α,α-dichloroacetamide (28)

This compound was prepared in the same manner N-ethyl-α-chloroacetamide (27). The white crystals obtained were vacuum sublimed three times to give the amide (28), m.p. 58.1°. (Lit m.p. 59°[16,18]).

N-Isopropyl-α,α-dichloroacetamide (31)

This compound was prepared and purified in the same manner as the N-isopropyl-α-chloroacetamide (30). M.P. 128.0°. (Lit. m.p. 127°[16]).

N-Methyl-α,α,α-trichloroacetamide (26)

This compound was prepared and purified in the same manner as the N-methyl-α,α-dichloroacetamide (25). M.p. 102.9°. (Lit. m.p. 104-106°[19]).

N-Ethyl-α,α,α-trichloroacetamide (29)

This compound was prepared and purified in the same manner as the N-ethyl-α,α-dichloroacetamide (28). M.p. 69.7°. (Lit. m.p. 73-74°[20]).

N-Isopropyl-α,α,α-trichloroacetamide (32)

This compound was prepared in the same manner as the N-isopropyl-α-chloroacetamide (30). M.p. 84.2°. (Lit. m.p. 86°[20] and 82.5-84°[19]).

Acetone-d_6 (46)

The procedure of Paulsen and Cooke[21] was used to prepare the acetone-d_6. The product was distilled twice. b.p. 59.5°

(azeotrope with D_2O). The deuterium incorporation (estimated by n.m.r.) was 99 ± 1%.

N-2,2,2,2',2',2'-d_6-Acetoxime (47)

The procedure described by Vogel[22] was used to prepare the 2,2,2,2',2',2',-d_6-acetoxime (47) (acetoxime-d_6), acetone-d_6, D_2O and LiOD replacing acetone, H_2O and NaOH. M.p. 59.7°. The deuterium incorporation was 95 ± 1%.

N-2,2,2,2',2',2'-d_6-Isopropyl-α-chloroacetamide (49)

Acetoxime-d_6 (47) (2.37 g, 0.03 mole) in 30 ml of anhydrous diethyl ether was added slowly, over a 15 minute period, to a refluxing solution of lithium aluminum hydride (LAH) (1.9 g, 0.05 mole) in 30 ml of anhydrous diethyl ether (Fig. 19). The reaction mixture was refluxed for five hours and then cooled in an ice bath. Water (15ml) was added slowly, followed by sodium hydroxide solution (10 ml, 10% aq.) and sodium potassium tartrate solution (20 ml, 20% aq.). Potassium hydroxide (90 g) was added and the reaction mixture was heated. The 2-amino-1,1,1,3,3,3-d_6-propane (d_6-isopropylamine) and ether were passed into dry 1,2-dichloroethane (50 ml) maintained at -20°. Heating was continued until no further d_6-isopropylamine was evolved. A solution of 3.39 g (0.03 mole) of α-chloroacetyl chloride in 30 ml of dry 1,2-dichloroethane was added dropwise to the cooled and stirred dichloroethane solution. After 30 minutes, 30 ml of water were added and the mixture was allowed to warm to room temperature. The aqueous layer was separated and extracted with two 30 ml portions of 1,2-dichloroethane which were combined with the reaction mixture. After washing with 5% hydrochloric acid

5% sodium bicarbonate solution (2 x 75 ml) and water (2 x 75 ml), the dichlorethane was dried over anhydrous magnesium sulfate. The solvent was then removed under reduced pressure leaving a pale yellow solid which was recrystallized from ligroin (b.p. 66-75°) yielding white crystals. Vacuum sublimation gave 0.93 g (22% based on d_6-acetoxime) of the amide (49), m.p. 58.7°. The deuterium incorporation was estimated at 98 ± 2%.

N-2,2,2,2',2',2'-d_6-Isopropyl-α,α-dichloroacetamide (50)

Acetoxime-d_6(47) (2.37 g, 0.03 mole) in 30 ml of anhydrous diethyl ether was added slowly, over a 15 minute period, to a refluxing solution of LAH (3.0 g, 0.08 mole) in 40 ml of anhydrous diethyl ether (Fig. 19). The reaction mixture was refluxed for five and one half hours and then cooled in an ice bath. Water (15 ml) was added slowly and the reaction mixture was heated. The d_6-isopropylamine and ether were passed into dry 1,2-dichloroethane (50 ml) maintained at -20°. Heating was continued until no further d_6-isopropylamine was evolved. A solution of α,α-dichloroacetyl chloride (5.89 g, 0.04 mole) in 20 ml of dry 1,2-dichloroethane was added dropwise to the cooled and stirred dichloroethane solution. After 30 minutes, a solution of triethylamine (3 g, 0.03 mole) in dry 1,2-dichloroethane (20 ml) was added slowly. Water (15 ml) was then added and the mixture was permitted to warm to room temperature. The aqueous layer was separated and extracted with one 10 ml portion of 1,2-dichloroethane which was combined with the reaction mixture. After washing with 5% hydrochloric acid (2 x 50 ml), 5% sodium bicarbonate solution

(2 x 50 ml) and water (2 x 50 ml), the dichloroethane solution was dried over anhydrous magnesium sulfate. The solvent was then removed under pressure leaving a white solid which was recrystallized from a 2:3 mixture of benzene and ligroin (b.p. 100-115°). Vacuum sublimation gave 1.32 g (25% based on d_6-acetoxime) of the amide (50), m.p. 128.1°. The deuterium incorporation was estimated at 98 ± 1%.

N-2,2,2,2',2',2'-d_6-Isopropyl-α,α,α-trichloroacetamide (51)

This compound was prepared in the same manner as (50), α,α,α-trichloroacetylchloride (5.45 g, 0.03 mole) replacing the α,α,-dichloroacetylchloride. Vaccum sublimation gave 1.7 g (27% based on d_6-acetoxime) of the amide (51), m.p. 82.8°. The deuterium incorporation was 99 ± 1%.

N-1,2,2,2,2',2',2'-d_7-Isopropyl-α-chloroacetamide (53)

Acetoxime-d_6 (4.74 g, 0.06 mole) in 50 ml of anhydrous diethyl ether was added slowly to a refluxing solution of lithium aluminum deteride (LAD) (4.2 g, 0.1 mole) in 70 ml of anhydrous diethyl ether (Fig. 19). The reaction mixture was refluxed for three hours and then cooled in an ice bath. Water (7.2 ml) was added slowly and the reaction mixture was heated. The deuterated isopropylamine and ether were passed into a solution of triethylamine (6.06 g, 0.06 mole) in 70 ml of dry 1,2-dichloroethane maintained at -25°. Heating was continued until no further amine was evolved. The solution of amine was divided into two approximately equal portions. One portion was set aside for the preparation of the amide (54). To the other cooled (-25°) and stirred portion, was added slowly, a solution of α-chloroacetyl chloride (3.39 g, 0.03 mole) in 30 ml of dry 1,2-dichloroethane. After 30 minutes, the mixture was allowed to warm to room temperature, and water (15 ml) was added. The aqueous layer was separated and extracted with two 20 ml portions of 1,2-dichloroethane which were combined with the reaction mixture. The dichloroethane solution was washed with 5% hydrochloric acid (2 x 35 ml), 5% sodium bicarbonate solution (2 x 35 ml) and water (2 x 35 ml) and dried over anhydrous magnesium sulfate. The solvent was then removed under reduced pressure leaving a yellow solid which was added to a mixture of tetrahydrofuran (30 ml) water (30 ml) and 10 drops of 10% sodium hydroxide solution. The mixture was stirred for 30 minutes and the tetrahydrofuran was then removed under reduced pressure. The aqueous mixture was extracted with 1,2-dichloroethane. After drying (magnesium sulfate), the solvent was removed under reduced pressure leaving a solid which was added to a second mixture of tetrahydrofuran (30 ml), water (30 ml) and 10 drops of 10% sodium hydroxide solution. After stirring the solution for 30 minutes, the tetrahydrofuran was removed under pressure. The aqueous mixture was extracted with 1,2-dichloroethane; after drying (magnesium sulfate), the solvent was removed under pressure leaving a yellow residue which was recrystallized from a 1:3 mixture of benzene and ligroin (b.p. 35-60°) yielding white crystals. Vacuum sublimation gave 0.85 g of the amide (53), m.p. 59.4°. The deuterium incorporation was 96 ± 1% in the C-2 and C-2' positions and 100 ± 1% in the C-1 position.

N-1,2,2,2,2',2',2'-d_7-Isopropyl-α,α-dichloroacetamide (54)

To the cooled (-25°) solution of isopropylamine and triethylamine in dry 1,2-dichloroethane obtained in the previous preparation, a solution of α,α-dichloroacetyl chloride (4.41 g, 0.03 mole) in 30 ml of dry 1,2-dichloroethane was slowly added. The rest of the preparation and the purification of the amide (54) were the same as that for the amide (53). Vacuum sublimation gave 2.94 g of (54), m.p. 127.6°. The total yield for the preparation of the amides (53) and (54) was 37% based on acetoxime-d_6. The deuterium incorporation was 97 ± 1% in the C-2 and C-2' positions and 100 ± 1% in the C-1 position.

N-1,2,2,2,2',2',2'-d_7-Isopropyl-α,α,α-trichloroacetamide (55)

Acetoxime-d_6 (1.18 g, 0.015 mole) in 25 ml of anhydrous diethyl ether was added slowly to a refluxing solution of LAD (1.05 g, 0.025 mole) in 30 ml of anhydrous diethyl ether (Fig. 19). The reaction mixture was refluxed for three and one half hours and then cooled in an ice bath. Water (5.4 ml) was added slowly and the reaction mixture was heated. The deuterated isopropylamine and ether were passed into a solution of triethylamine (1.15 g, 0.015 mole) in 50 ml of dry 1,2-dichloroethane maintained at -20°. Heating was continued until no further isopropylamine was evolved. A solution of α,α,α-trichloroacetyl chloride (5.44 g, 0.03 mole) in 25 ml of dry 1,2-dichloroethane was added slowly dropwise to the cooled (-25°) and stirred dichloroethane solution. After 30 minutes, 20 ml of water were added and the mixture was allowed to warm to room temperature. The aqueous layer was separated and extracted with one portion of 1,2-dichloroethane (20 ml) which was combined with the reaction mixture. After washing with5% hydrochloric acid (2 x 50 ml), 5% sodium bicarbonate solution (2 x 50 ml) and water (2 x 50 ml), the dichloroethane solution was dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure leaving a pale yellow solid which was recrystallized from a 1:3 mixture of benzene and ligroin (b.p. 100-115°) yielding 0.60 g of crude product (19% based on acetoxime-d_6). This product was added to a mixture of tetrahydrofuran (20 ml) water (20 ml) and 3 drops of 10% sodium hydroxide solution and the mixture was stirred for 90 minutes. After extraction with 1,2-dichloroethane (5 x 30 ml) and drying over anhydrous magnesium sulfate, the solvent was removed under reduced pressure leaving a pale yellow solid which was recrystallized from ligroin (b.p. 66-75°) giving 0.53 g of white crystals. These crystals were vacuum sublimed once and then added to a mixture of tetrahydrofuran (20 ml), water (20 ml) and 6 drops of 10% sodium hydroxide solution. The mixture was stirred for one hour and the tetrahydrofuran was then removed under reduced pressure. The aqueous mixture was extracted with portions of 1,2-dichloroethane (4 x 20 ml) which were combined and dried over anhydrous magnesium sulfate. The solvent was again removed leaving a pale yellow solid which was recrystallized from ligroin (b.p. 66-75°) yielding white crystals. Vacuum sublimation gave the amide (55), m.p. 85.0°. The deuterium incorporation was estimated as 98 ± 1% in the C-2 and C-2' positions and 100 ± 1% in the C-1 position.

Acetonitrile-d_3 (37)

A mixture of acetonitrile (10 g, 0.24 mole), D_2O (30 ml) and 1 ml of a saturated solution of LiOD in D_2O was stirred for 30 minutes. The acetonitrile was distilled from the mixture and added to another portion of D_2O and LiOD. A total of six such exchanges were carried out. The acetonitrile-d_3 was distilled and then dried over anhydrous magnesium sulfate. B.p. 77-78°. The deuterium incorporation was estimated as 98 ± 1%.

N-2,2,2-d_3-Ethyl-α-chloroacetamide (39)

Acetonitrile-d_3 (4.05 g, 0.092 mole) in 50 ml of anhydrous diethyl ether was added dropwise to a refluxing solution of LAH (2.62 g, 0.069 mole) in 40 ml of anhydrous diethyl ether (Fig. 19). The reaction mixture was refluxed for three hours and then cooled in an ice bath. Water (5.0 ml, 0.28 mole) was added slowly and the reaction mixture was heated. The 2,2,2-d_3-ethylamine (d_3-ethylamine) and ether were distilled into a cooled (-25°) solution of triethylamine (9.29 g, 0.092 mole) in 70 ml of dry 1,2-dichloroethane. Heating was continued until no further d_3-ethylamine was evolved. The dichloroethane solution was divided into two portions with volume ratios of approximately 2:1. The smaller portion was set aside for the preparation of the amide (40).

A solution of α-chloroacetyl chloride (7.00 g, 0.062 mole) in 25 ml of dry 1,2-dichloroethane was added slowly to the stirred and cooled (-25°) larger volume of the dichloroethane solution. After 30 minutes, the mixture was allowed to warm to room temperature and water (15 ml) was added slowly. The aqueous layer was separated and extracted twice with 20 ml portions of 1,2-dichloroethane which were combined with the reaction mixture. After washing with5% hydrochloric acid (2 x 15 ml), 5% sodium bicarbonate solution (2 x 15 ml) and water (2 x 15 ml), the dichloroethane solution was dried over annydrous magnesium sulfate. The solvent was then removed under reduced pressure leaving a yellow liquid which was vacuum distilled three times, yielding the amide (39) as a clear liquid, b.p. 68° at 1.8-2.0 mm. The deuterium incorporation was 95 ± 1%.

N-2,2,2-d_3-α,α-dichloroacetamide (40)

A solution of α,α-dichloroacetyl chloride (4.57 g, 0.031 mole) in dry 1,2-dichloroethane (25 ml) was added slowly to the cooled (-25°) and stirred solution of d_3-ethylamine and triethylamine in dry 1,2-dichloroethane obtained as described in the previous preparation. The preparation followed that for the amide (39). Removal of the solvent under reduced pressure gave a yellow solid which was recrystallized from a 1:1 mixture of benzene and ligroin (b.p. 66-75°), yielding white crystals. Vacuum sublimation gave 2.7 g of the amide (40), m.p. 59.0°. The deuterium incorporation was 93 ± 1%.

N-2,2,2-d_3-Ethyl-α,α,α-trichloroacetamide (41)

Acetonitrile-d_3 (2.05 g, 0.05 mole) in 30 ml of anhydrous diethyl ether was added dropwise, over a 15 minute period, to a refluxing solution of LAH (4.2 g, 0.11 mole) in 40 ml of anhydrous diethyl ether (Fig. 19). The reaction mixture was refluxed for four hours and then cooled in an ice bath. Water (8 ml) was added slowly and the mixture was heated. The d_3-ethylamine and ether were passed into a solution of α,α,α-trichloroacetyl chloride (9.1 g, 0.05 mole) in 30 ml of dry 1,2-dichloroethane maintained at -25°. Heating was continued until no further d_3-ethylamine was evolved. After 15 minutes, water (15 ml) was added slowly and the reaction mixture was allowed to warm to room temperature. The aqueous layer was separated and extracted with 1,2-dichloroethane (2 x 20 ml) which was combined with the reaction mixture. After washing with 5% hydrochloric acid (2 x 40 ml), 5% sodium bicarbonate solution (2 x 40 ml) and water (2 x 40 ml), the dichloroethane solution was dried over anhydrous magnesium sulfate. The solvent was then removed under pressure leaving a white solid which was recrystallized from a 1:3 mixture of benzene and ligroin (b.p. 100-115°). Vacuum sublimation gave 2.77 g, (29% based on acetonitrile-d_3) of the amide (41), m.p. 73.0°. The deuterium incorporation was 93 ± 3%.

N-1,1,2,2,2-d_5-Ethyl-α-chloroacetamide (43)

Acetonitrile-d_3 (2.06 g, 0.05 mole) in 40 ml of anhydrous diethyl ether was added dropwise to a refluxing solution of LAD (2.10 g, 0.05 mole) in 60 ml of anhydrous diethyl ether (Fig. 19). The reaction mixture was refluxed for three hours and then cooled in an ice bath. Water (10.8 ml) was added slowly and the mixture was heated. The 1,1,2,2,2-d_5-ethylamine (d_5-ethylamine) and ether were passed into a solution of triethylamine (5.0 g) in 60 ml) of dry 1,2-dichloroethane maintained at -25°. Heating was continued until no further d_5-ethylamine was evolved. The dichloroethane solution was divided into two portions with volume ratios of approximately 2:1. The smaller portion was set aside for the preparation of the amide (<u>44</u>).

A solution of α-chloroacetyl chloride (3.84 g, 0.034 mole) in 25 ml of dry 1,2-dichloroethane was added slowly to the stirred and cooled (-25°) larger volume of the solution of amine in dichloroethane. After 30 minutes, the mixture was allowed to warm to room temperature, and water (15 ml) was added slowly. The aqueous layer was separated and extracted twice with 15 ml portions of 1,2-dichloroethane which were combined with the reaction mixture. After washing with5% hydrochloric acid (2 x 15 ml), 5% sodium bicarbonate solution (2 x 15 ml) and water (2 x 15 ml), the dichloroethane solution was dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure leaving a yellow liquid which was vacuum distilled three times yielding 0.5 g of the amide (<u>43</u>), b.p. 67° at 1.7 mm. The deuterium incorporation was assessed at 98 ± 1% in the C-2 position and 99 ± 1% in the C-1 position.

<u>N-1,1,2,2,2-d_5-Ethyl-α,α-dichloroacetamide</u> (<u>44</u>)

A solution of α,α-dichloroacetyl chloride (2.51 g, 0.017 mole) in 25 ml of dry 1,2-dichloroethane was added slowly to the cooled (-25°) and stirred solution of d_5-ethylamine and triethylamine in dry 1,2-dichloroethane obtained as described in the previous preparation. The preparation followed that for the amide (<u>43</u>). Removal of the solvent under reduced pressure gave a pale yellow solid which was recrystallized from a 1:1 mixture of benzene and ligroin (b.p. 66-75°) yielding white crystals. Vacuum sublimation gave 1.2 g of the amide (44), m.p. 58.8°. The deuterium incorporation was 96 ± 1 % at C-2 and 99 ± 1 % in the C-1 position. The total yield for the preparations of the amides (43) and (44) was 23% based on acetonitrile-d_3.

N-1,1,2,2,2-d_5-Ethyl-α,α,α-trichloroacetamide (45)

Acetonitrile-d_3 (1.03 g, 0.025 mole) in 25 ml of anhydrous diethyl ether was added dropwise, over a period of 10 minutes, to a refluxing solution of LAD (1.05 g, 0.025 mole) in 40 ml of anhydrous diethyl ether. The reaction mixture was refluxed for three hours and then cooled in an ice bath. Water (5.4 ml) was added slowly and the mixture was heated. The d_5-ethylamine and ether were passed into a solution of triethylamine (2.5 g) in 50 ml of dry 1,2-dichloroethane maintained at -25°. Heating was continued until no further d_5-ethylamine was evolved. A solution of α,α,α-trichloroacetyl chloride (10.88 g, 0.06 mole) in 30 ml of dry 1,2-dichloroethane was added dropwise to the cooled (-25°) and stirred dichloroethane solution. After 30 minutes, water (20 ml) was added slowly and the reaction mixture was allowed to warm to room temperature. The aqueous layer was separated and extracted with 20 ml of 1,2-dichloroethane which were combined with the reaction mixture. After washing with 5% hydrochloric acid (2 x 50 ml), 5% sodium bicarbonate (2 x 50 ml) and water (2 x 50 ml), the dichloroethane solution was dried over anhydrous magnesium sulfate. The solvent was then removed under reduced pressure leaving a pale yellow solid which was recrystallized from a 1:3 mixture of benzene and ligroin (b.p. 110-115°) yielding white crystals. Vacuum sublimation gave 1.8 g (37% based on acetonitrile-d_3) of the amide (45), m.p. 67.2°. The deuterium incorporation was 93 ± 2% in the C-2 position and 100 ± 1% in the C-1 position.

Nitromethane-d_3 (33)

A mixture of nitromethane (41.5 g, 0.68 mole), D_2O (100 ml) and 0.4 ml of a saturated solution of LiOD in D_2O was refluxed for one hour. The mixture was cooled and extracted with dichloromethane (4 x 25 ml) which was dried over anhydrous magnesium sulfate. After removal of the dichloromethane, the remaining nitromethane was added to another portion of D_2O and LiOD. A total of five such exchanges were carried out. The nitromethane-d_3 was distilled and dried over molecular sieves. B.p. 97-98°. The deuterium incorporation was estimated as 98 ± 1%.

N-1,1,1,-d_3-Methyl-α,α-dichloroacetamide (35)

Nitromethane-d_3 (4.09 g, 0.064 mole) in 50 ml of anhydrous diethyl ether was added dropwise to a solution of LAD (4.03 g, 0.096 mole) in 70 ml of anhydrous diethyl ether at room temperature. The reaction mixture was refluxed for three hours and then cooled in an ice bath. Water (7 ml) was added slowly and the reaction mixture was heated. The 1,1,1-d_3-methylamine (d$_3$-methylamine) and ether were passed into a solution of triethylamine (6.46 g, 0.064 mole) in 70 ml of dry 1,2-dichloroethane maintained at -35°. The heating was continued until no further d_3-methylamine was evolved. The dichloroethane solution was divided into two approximately equal portions. To one cooled (-35°) portion α,α-dichloroacetyl chloride (4.72 g, 0.032 mole) in 25 ml of dry 1,2-dichloroethane was added. After 30 minutes, the solution was permitted to warm to room temperature and water (15 ml) was added slowly. The aqueous layer was separated and extracted with 1,2-dichloroethane (2 x 20 ml) which was combined with the reaction mixture. After washing with 5% hydrochloric acid (2 x 20 ml), 5% sodium bicarbonate solution (2 x 20 ml) and water (2 x 20 ml), the dichloroethane solution was dried over anhydrous magnesium sulfate. The solvent was then removed under reduced pressure leaving a pale yellow solid which was recrystallized from a 1:3 mixture of benzene and ligroin (b.p. 66-75°) yielding white crystals. Vacuum sublimation gave 1.76 g (38% based on nitromethane-d_3) of the amide (35), m.p. 76.3°. The deuterium incorporation was assessed at 98 ± 2%.

N-1,1,1-d_3-Methyl-α,α,α-trichloroacetamide (36)

Nitromethane-d_3 (1.28 g, 0.02 mole) in 50 ml of anhydrous diethyl ether was added dropwise to a solution of LAD (1.68 g, 0.04 mole) in 50 ml of anhydrous diethyl ether at room temperature. The reaction mixture was refluxed for three hours and then cooled in an ice bath. Deuterium oxide (D_2O) (5 ml) was added slowly and the reaction mixture was heated. The d_5-methylamine and ether were passed into a solution of triethylamine (2.02 g, 0.02 mole) in 80 ml of dry 1,2-dichloroethane maintained at -31°. Heating was continued until no further d_5-methylamine was evolved. A solution of

α,α,α-trichloroacetyl chloride (3.64 g, 0.02 mole) in 30 ml of dry 1,2-dichloroethane was added slowly to the cooled (-31°) and stirred dichloroethane solution. After 30 minutes, the reaction mixture was allowed to warm to room temperature and water (15 ml) was added slowly. The aqueous layer was separated and extracted with two 20 ml portions of 1,2-dichloroethane which were combined with the reaction mixture. After washing with 5% hydrochloric acid (2 x 35 ml), 5% sodium bicarbonate solution (2 x 35 ml) and water (2 x 35 ml), the dichloroethane solution was dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure leaving a pale yellow solid which was added to a mixture of tetrahydrofuran (30 ml), water (30 ml) and 10 drops of 10% sodium hydroxide solution. The mixture was stirred for 30 minutes and the tetrahydrofuran was removed under reduced pressure. The aqueous mixture was extracted with dichloroethane (5 x 20 ml). The dried ($MgSO_4$) dichloroethane solution was concentrated under reduced pressure leaving a pale yellow solid. After two more exchanges in the tetrahydrofurn-water-sodium hydroxide system a crude product was obtained which could be recrystallized from a 1:3 mixture of benzene and ligroin (b.p. 66-75°) yielding white crystals. Vacuum sublimation gave 0.89 g (25% based on nitromethane-d_3) of the amide (36), m.p. 104.0°. The deuterium incorporation was 98 ± 1%.

Deuterium Chloride

A solution of deuterium chloride in D_2O (400 ml, 9.8 N) was prepared by the general method of Baudler[23].

d_9-tert-Butyl Chloride (56)

This compound was prepared by the method of Stephens and Leitch[24] with the following modifications.

(a) Sealed tubes were used for each exchange.

(b) 55 ml of 9.8 N DCl in D_2O was used for each 62 g (0.66 mole) of tert-butyl chloride.

(c) Each exchange was carried out over 9 to 10 hours at 57-58°.

(d) A total of 6 exchanges were made. The final product was distilled twice. B.p. 49-51°. The deuterium incorporation was 95 ± 1%.

d_{10}-tert-Butyl Alcohol (57)

A mixture of d_9-tert-butyl chloride (5.05 g, 0.05 mole), D_2O (50 ml) and 9.8 ml of a saturated solution of LiOD in D_2O was stirred for 48 hours. The d_{10}-tert-butyl alcohol was distilled twice. B.p. 81-85°. The deuterium incorporation was 95 ± 1%.

2,2,2,2',2',2'',2''-d_9-tert-Butylamine (61)

The procedure of Ritter and Kalish[25] was used for this preparation with d_{10}-tert-butyl alcohol replacing tert-butyl alcohol. The N-2,2,2,2',2',2',2'',2'',2''-d_9-tert-butyl formamide reaction mixture was hydrolyzed directly to give the 2,2,2,2',2',2',2'',2'',2''-d_9-tert-butylamine (61) which was distilled once and dried over molecular sieves, to give 5.0 g of 31, b.p. 43-44°. The deuterium incorporation was 79 ± 7%.

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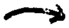
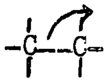
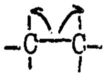
APPENDIX A

Abbreviations suggested by the Journal of Organic Mass Spectroscopy[26] have been incorporated in this work.

Abbreviations

IP	ionization potential (voltage)
m/e	mass to charge ratio
Rel. int.	relative intensity
eV	electron volts
Mol. wt. or MW	molecular weight

Symbols

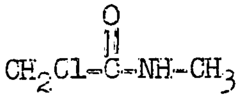
$M^{+\cdot}$	molecular ion
$(X)^{+}$	e.g. $(M-CH_3$, even electron ion
$(X)^{+\cdot}$	e.g. $(M-CO)^{+\cdot}$, odd electron ion
$\overset{*}{m}$	metastable peak
$\xrightarrow{*}$	for this process, a metastable peak has been observed.
	a metastable decomposition has been observed for this process in the mass spectra of the analogous deuterated amide(s).
	'fish hook', one electron shift
	'full arrow', two electron shift
	heterolysis
	homolysis
$-\underset{\mid}{\overset{+\cdot}{N}}-$	radical ion formed by the removal of one electron from a nitrogen atom
$-\underset{\mid}{\overset{+}{N}}=$	even electron ion with the positive charge on the nitrogen atom
$(R)^{+}$, $(R)^{+\cdot}$	locus of charge localization not defined

$\urcorner^{\div}$, $\urcorner^{\div}$	same meaning; employed to avoid large brackets around structural formulae
$15\%\Sigma_{36}$	15% of total ionization encompassing the mass range from m/e 36 to the molecular ion.
15% rel. int.	15% of the most intense peak
X10	in bar graphs; the indicated peak or group of peaks has been enlarged by a factor of 10

APPENDIX B

TABLE 7

N-Methyl-α-chloroacetamide (24)

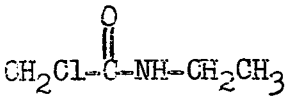


$CH_2Cl-C(=O)-NH-CH_3$

m/e	$\%\Sigma_{36}$	rel. int. (base pk. = 100)	Formula
109	8.0	17.	$C_3H_6NO^{37}Cl$
108	0.9	2.0	$C_2{}^{13}CH_6NOCl$
107	24.	52.	C_3H_6NOCl
79	0.6	1.3	$C_2H_2O^{37}Cl$
78	0.2	0.4	$C_2HO^{37}Cl$
77	2.0	4.3	C_2H_2OCl
76	0.6	1.3	C_2HOCl
72	4.2	9.1	C_3H_6NO
59	1.2	2.6	$C^{13}CH_4NO$
58	46.	100.	C_2H_4NO
51	1.2	2.6	$CH_2{}^{37}Cl$
50	0.2	0.4	$CH^{37}Cl$
49	3.6	7.8	CH_2Cl
44	1.4	3.1	C_2H_6N
	0.2	0.4	CH_2NO
42	0.4	0.9	C_2H_4N
	1.8	3.9	C_2H_2O
38	0.1	0.3	$H^{37}Cl$
36	0.4	0.8	HCl

TABLE 8

N-Ethyl-α-chloroacetamide (27)

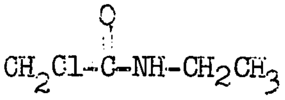


$$CH_2Cl-\overset{\displaystyle O}{\overset{\|}{C}}-NH-CH_2CH_3$$

m/e	$\%\Sigma_{36}$	rel. int. (base pk. = 100)	Formula
123	3.8	12.	$C_4H_8NO^{37}Cl$
122	0.8	2.5	$C_3{}^{13}CH_8NOCl$
121	12.	37.	C_4H_8NOCl
108	0.9	3.0	$C_3H_5NO^{37}Cl$
106	3.0	9.6	C_3H_5NOCl
87	0.4	1.2	$C_3{}^{13}CH_8NO$
86	9.3	30.	C_4H_8NO
79	0.8	2.7	$C_2H_2O^{37}Cl$
77	2.5	8.2	C_2H_2OCl
73	1.1	3.4	$C_2{}^{13}CH_6NO$
72	31.	100.	C_3H_6NO
58	0.4	1.3	C_3H_8N
51	1.3	4.1	$CH_2{}^{37}Cl$
49	4.0	13.	CH_2Cl
45	0.3	1.1	$C^{13}CH_6N$ $^{13}CH_2NO$
44	4.5	14.	C_2H_6N
	14.	46.	CH_2NO
43	1.4	4.5	C_3H_7
	0.5	1.7	C_2H_5N

TABLE 8

N-Ethyl-α-chloroacetamide (27) (Cont'd)

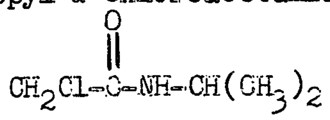


$CH_2Cl-\overset{O}{\overset{\|}{C}}-NH-CH_2CH_3$

m/e	$\%\Sigma_{36}$	rel. int. (base pk. = 100)	Formula
	0.8	2.4	C_2H_3O
	0.1	0.4	$CHNO$
42	0.1	0.2	C_3H_6
	1.3	4.1	C_2H_4N
	1.4	4.4	C_2H_2O
41	0.3	0.9	C_3H_5
	0.7	2.3	C_2H_3N
	0.1	0.3	C_2HO
40	0.9	2.8	C_2H_2N
38	0.1	0.3	$H^{37}Cl$
36	0.3	0.9	HCl

TABLE 9

N-Isopropyl-α-chloroacetamide (30)

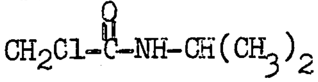


$CH_2Cl-C(=O)-NH-CH(CH_3)_2$

m/e	$\%\Sigma_{36}$	rel. int. (base pk. = 100)	Formula
137	1.8	6.9	$C_5H_{10}NO^{37}Cl$
136	0.5	1.9	$C_4{}^{13}CH_{10}NOCl$
135	5.9	22.	$C_5H_{10}NOCl$
122	3.9	15.	$C_4H_7NO^{37}Cl$
121	0.6	2.2	$C_3{}^{13}CH_7NOCl$
120	12.	44.	C_4H_7NOCl
101	0.4	1.5	$C_4{}^{13}CH_{10}NO$
100	6.7	26.	$C_5H_{10}NO$
96	0.4	1.5	$C_2H_5NO^{37}Cl$
94	1.1	4.0	C_2H_5NOCl
87	0.3	1.0	$C_3{}^{13}CH_8NO$
86	5.1	19.	C_4H_8NO
79	0.4	1.5	$C_2H_2O^{37}Cl$
77	1.4	5.5	C_2H_2OCl
59	0.2	0.7	$C_2{}^{13}CH_8N$
58	3.4	13.	C_3H_8N
	0.6	2.3	C_2H_4NO
57	0.6	2.4	C_4H_9
	0.5	1.9	C_3H_7N
51	0.7	2.7	$CH_2{}^{37}Cl$

TABLE 9

N-Isopropyl-α-chloroacetamide (<u>30</u>) (Cont'd)

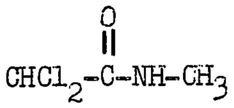


$CH_2Cl-\overset{O}{\overset{\|}{C}}-NH-CH(CH_3)_2$

m/e	$\%\Sigma_{36}$	rel. int. (base pk. = 100)	Formula
49	2.4	8.9	CH_2Cl
45	0.7	2.5	$C^{13}CH_6N$
44	25.	96.	C_2H_6N
	1.1	4.0	CH_2NO
43	10.	38.	C_3H_7
	1.4	5.5	C_2H_5N
	0.5	1.8	C_2H_3O
	0.1	0.5	CHNO
42	0.6	2.4	C_3H_6
	1.7	6.5	C_2H_4N
	0.8	3.1	C_2H_2O
41	2.4	9.1	C_3H_5
	1.3	5.0	C_2H_3N
39	1.2	4.5	C_3H_3
38	0.3	1.0	$H^{37}Cl$
36	0.6	2.1	HCl

TABLE 10

N-Methyl-α,α-dichloroacetamide (25)

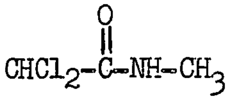


$$CHCl_2-\overset{\overset{\displaystyle O}{\|}}{C}-NH-CH_3$$

m/e	$\%\Sigma_{36}$	rel. int. (base pk. = 100)	Formula
145	1.2	1.8	$C_3H_5NO^{37}Cl_2$
143	7.0	11.	$C_3H_5NOCl^{37}Cl$
141	11.	17.	$C_3H_5NOCl_2$
106	0.4	0.7	C_3H_5NOCl
87	0.3	0.5	$CH^{37}Cl_2$
85	1.7	2.8	$CHCl^{37}Cl$
83	2.7	4.4	$CHCl_2$
80	0.3	0.5	$C_2H_5N^{37}Cl$
78	1.0	1.6	C_2H_5NCl
	0.3	0.4	$C_2HO^{37}Cl$
76	1.4	2.2	C_2HOCl
59	1.7	2.8	$C^{13}CH_4NO$
58	63.	100.	C_2H_4NO
51	0.2	0.3	$CH_2{}^{37}Cl$
50	0.5	0.8	$CH^{37}Cl$
49	0.2	0.3	$C^{37}Cl$
	0.5	0.8	CH_2Cl
48	1.5	2.4	$CHCl$
47	0.6	0.9	CCl

TABLE 10

N-Methyl-α,α-dichloroacetamide (25) (Cont'd)

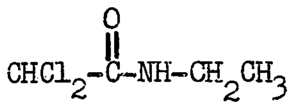


$CHCl_2-\overset{\overset{O}{\|}}{C}-NH-CH_3$

m/e	%Σ_{36}	rel. int. (base pk. = 100)	Formula
42	0.8	1.2	C_2H_4N
	0.1	0.2	C_2H_2O
38	0.6	0.9	$H^{37}Cl$
36	1.7	2.8	HCl

TABLE 11

N-Ethyl-α,α-dichloroacetamide (28)

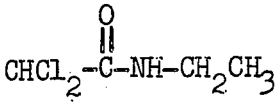


$$CHCl_2-\overset{\overset{O}{\|}}{C}-NH-CH_2CH_3$$

m/e	$\%\Sigma_{36}$	rel. int. (base pk. = 100)	Formula
159	0.8	1.7	$C_4H_7NO^{37}Cl_2$
157	4.8	10.	$C_4H_7NOCl^{37}Cl$
156	0.6	1.2	$C_3{}^{13}CH_7NOCl_2$
155	7.5	16.	$C_4H_7NOCl_2$
144	0.2	0.4	$C_3H_4NO^{37}Cl_2$
142	1.2	2.5	$C_3H_4NOCl^{37}Cl$
140	1.8	3.7	$C_3H_4NOCl_2$
122	0.2	0.5	$C_4H_7NO^{37}Cl$
120	0.7	1.4	C_4H_7NOCl
94	0.3	0.6	$C_3H_7N^{37}Cl$
92	0.8	1.7	C_3H_7NCl
87	0.2	0.5	$CH^{37}Cl_2$
85	2.2	4.6	$CHCl^{37}Cl$
83	3.2	6.8	$CHCl_2$
78	0.5	1.0	$C_2HO^{37}Cl$
76	0.1	0.3	C_2H_3NCl
	1.4	3.0	C_2HOCl
73	1.9	3.9	$C_2{}^{13}CH_6NO$
72	47.	100.	C_3H_6NO
66	0.2	0.4	$CH_3N^{37}Cl$

TABLE 11

N-Ethyl-α,α-dichloroacetamide (28) (Cont'd)

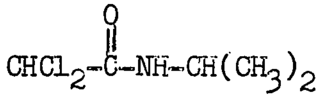


$CHCl_2-\overset{\overset{O}{\|}}{C}-NH-CH_2CH_3$

m/e	%Σ36	rel. int. (base pk. = 100)	Formula	
64	0.9	1.9	CH_3NCl	
50	0.4	0.8	$CH^{37}Cl$	
48	1.2	2.5	$CHCl$	
45	0.2	0.5	$C^{13}CH_6N$	$^{13}CH_2NO$
44	1.5	3.1	C_2H_6N	
	12.	25.	CH_2NO	
42	0.7	1.5	C_2H_4N	
	0.1	0.3	C_2H_2O	
41	0.3	0.6	C_3H_5	
	0.4	0.9	C_2H_3N	
	0.1	0.3	C_2HO	
38	0.3	0.6	$H^{37}Cl$	
36	0.9	2.0	HCl	

TABLE 12

N-Isopropyl-α,α-dichloroacetamide (<u>31</u>)

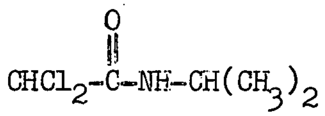


$CHCl_2-\overset{\overset{O}{\|}}{C}-NH-CH(CH_3)_2$

m/e	$\%\Sigma_{36}$	rel. int. (base pk. = 100)	Formula
173	0.4	1.7	$C_5H_9NO^{37}Cl_2$
171	2 3	10.	$C_5H_9NOCl^{37}Cl$
170	0.3	1.5	$C_4{}^{13}CH_9NOCl_2$
169	3.6	16.	$C_5H_9NOCl_2$
158	0.7	3.4	$C_4H_6NO^{37}Cl_2$
156	4.6	21.	$C_4H_6NOCl^{37}Cl$
155	0.3	1.4	$C_3{}^{13}CH_6NOCl_2$
154	7.0	32.	$C_4H_6NOCl_2$
136	0.2	1.1	$C_5H_9NO^{37}Cl$
134	0.7	3.4	C_5H_9NOCl
128	0.3	1.3	$C_2H_4NOCl_2$
92	1.0	4.4	C_2H_3NOCl
87	1.2	5.5	$CH^{37}Cl_2$
			$C_3{}^{13}CH_8NO$
86	22.	100.	C_4H_8NO
85	1.2	5.2	$CHCl^{37}Cl$
83	1.8	8.2	$CHCl_2$
76	0.6	2.9	C_2HOCl
64	0.4	1.7	CH_3NCl
	0.2	1.1	$CHOCl$
58	1.4	6.4	C_3H_8N

TABLE 12

N-Isopropyl-α,α-dichloroacetamide (<u>31</u>) (Cont'd)

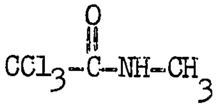


$CHCl_2-\overset{\overset{O}{\|}}{C}-NH-CH(CH_3)_2$

m/e	$\%\Sigma_{36}$	rel. int. (base pk. = 100)	Formula
49	1.1	5.2	CH_2Cl
45	0.6	2.5	$C^{13}CH_6N$
44	1.1	4.8	$C_2{}^{13}CH_7$
	9.9	45.	C_2H_6N
	0.8	3.7	CH_2NO
43	20.	91.	C_3H_7
	0.4	1.9	C_2H_5N
	0.1	0.5	C_2H_3O
	0.1	0.5	$CHNO$
42	0.7	3.0	C_3H_6
	0.1	0.4	$C_2{}^{13}CH_5$
	1.3	5.7	C_2H_4N
	0.1	0.2	C_2H_2O
41	3.7	17.	C_3H_5
	0.4	1.7	C_2H_3N
39	1.0	4.5	C_3H_3
38	0.7	3.4	$H^{37}Cl$
36	2.2	9.9	HCl

TABLE 13

N-Methyl-α,α,α-trichloroacetamide (26)

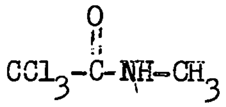


$CCl_3-C(=O)-NH-CH_3$

m/e	$\%\Sigma_{36}$	rel. int. (base pk. = 100)	Formula
179	0.4	0.7	$C_3H_4NOCl^{37}Cl_2$
177	1.3	2.0	$C_3H_4NOCl_2{}^{37}Cl$
175	1.3	2.1	$C_3H_4NOCl_3$
144	0.2	0.3	$C_3H_4NO^{37}Cl_2$
142	1.0	1.6	$C_3H_4NOCl_2$
140	1.6	2.6	$C_3H_4NOCl_2$
121	0.6	1.0	$CCl^{37}Cl_2$
119	2.0	3.2	$CCl_2{}^{37}Cl$
117	2.0	3.2	CCl_3
116	0.3	0.5	$C_2H_4N^{37}Cl_2$
114	0.1	0.2	$C_2O^{37}Cl_2$
	2.1	3.3	$C_2H_4NCl^{37}Cl$
112	0.6	0.9	$C_2OCl^{37}Cl$
	3.4	5.3	$C_2H_4NCl_2$
110	0.9	1.4	C_2OCl_2
87	0.2	0.3	$CH^{37}Cl_2$
86	0.2	0.3	$C^{37}Cl_2$
85	1.6	2.6	$CHCl^{37}Cl$
84	1.5	2.3	$CCl^{37}Cl$
83	2.5	3.9	$CHCl_2$
82	2.3	3.7	CCl_2
78	0.2	0.4	$C_2H_3N^{37}Cl$

TABLE 13

N-Methyl-α,α,α-trichloroacetamide (<u>26</u>) (Cont'd)

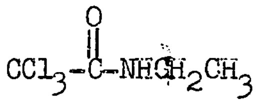


$CCl_3-\overset{\overset{O}{\|}}{C}-NH-CH_3$

m/e	%Σ_{36}	rel. int. (base pk. = 100)	Formula
76	0.7	1.2	C_2H_3NCl
59	2.0	3.2	$C^{13}CH_4NO$
58	63.	100.	C_2H_4NO
49	0.7	1.1	$C^{37}Cl$
47	1.6	2.6	CCl
38	0.6	0.9	$H^{37}Cl$
36	1.8	2.8	HCl

TABLE 14

N-Ethyl-α,α,α-trichloroacetamide (<u>29</u>)

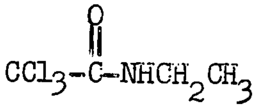


$CCl_3-\overset{\overset{O}{\|}}{C}-NHCH_2CH_3$

m/e	$\%\Sigma_{36}$	rel. int. (base pk. = 100)	Formula
193	0.1	0.4	$C_4H_6NOCl^{37}Cl_2$
191	0.3	0.8	$C_4H_6NOCl_2{}^{37}Cl$
189	0.3	0.8	$C_4H_6NOCl_3$
178	0.3	0.8	$C_3H_3NOCl^{37}Cl_2$
176	1.4	3.7	$C_3H_3NOCl_2{}^{37}Cl$
174	1.4	3.8	$C_3H_3NOCl_3$
158	0.1	0.3	$C_4H_6NO^{37}Cl_2$
156	0.9	2.3	$C_4H_6NOCl^{37}Cl$
154	1.3	3.6	$C_4H_6NOCl_2$
130	0.2	0.6	$C_3H_6N^{37}Cl_2$
128	1.9	5.0	$C_3H_6NCl^{37}Cl$
126	3.0	7.9	$C_3H_6NCl_2$
121	1.1	2.9	$CCl^{37}Cl_2$
119	3.5	9.2	$CCl_2{}^{37}Cl$
117	3.8	10.	CCl_3
114	0.2	0.4	$C_2O^{37}Cl_2$
112	0.1	0.4	$C_2H_2NCl^{37}Cl$
	1.0	2.7	$C_2OCl^{37}Cl$
110	0.2	0.6	$C_2H_2NCl_2$
	1.6	4.2	C_2OCl_2
102	0.1	0.2	$CH_2N^{37}Cl_2$

TABLE 14

N-Ethyl-α,α,α-trichloroacetamide (29) (Cont'd)

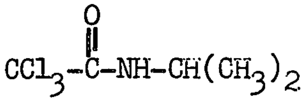


$CCl_3-\overset{\overset{O}{\|}}{C}-NHCH_2CH_3$

m/e	$\%\Sigma_{36}$	rel. int. (base pk. = 100)	Formula
100	0.4	1.1	$CH_2NCl^{37}Cl$
98	0.8	2.0	CH_2NCl_2
87	0.2	0.6	$CH^{37}Cl_2$
86	0.3	0.8	$C^{37}Cl_2$
85	1.3	3.6	$CHCl^{37}Cl$
84	1.8	4.7	$CCl^{37}Cl$
83	2.3	6.0	$CHCl_2$
82	2.7	7.2	CCl_2
73	1.9	5.0	$C_2{}^{13}CH_6NO$
72	38.	100.	C_3H_6NO
49	0.5	1.3	$C^{37}Cl$
47	1.4	3.7	CCl
45	0.3	0.8	$^{13}CH_2NO$
44	0.3	0.9	C_2H_6N
	17.	45.	CH_2NO
38	0.3	0.7	$H^{37}Cl$
36	0.8	2.1	HCl

TABLE 15

N-Isopropyl-α,α,α-trichloroacetamide (32)

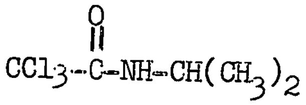


$CCl_3-C(=O)-NH-CH(CH_3)_2$

m/e	$\%\Sigma_{36}$	rel. int. (base pk. = 100)	Formula
207	0.1	0.4	$C_5H_8NOCl^{37}Cl_2$
205	0.2	0.7	$C_5H_8NOCl_2{}^{37}Cl$
203	0.2	0.7	$C_5H_8NOCl_3$
194	0.2	0.7	$C_4H_5NO^{37}Cl_3$
192	1.8	6.5	$C_4H_5NOCl^{37}Cl_2$
190	5.2	19.	$C_4H_5NOCl_2{}^{37}Cl$
188	5.5	20.	$C_4H_5NOCl_3$
172	0.1	0.4	$C_5H_8NO^{37}Cl_2$
170	0.6	2.2	$C_5H_8NOCl^{37}Cl$
168	0.9	3.2	$C_5H_8NOCl_2$
144	0.1	0.4	$C_4H_8N^{37}Cl_2$
142	0.5	1.8	$C_4H_8NCl^{37}Cl$
140	0.8	2.9	$C_4H_8NCl_2$
128	0.1	0.4	$C_3H_4N^{37}Cl_2$
126	0.5	1.7	$C_3H_4NCl^{37}Cl$
	0.1	0.4	$C_2H_2NOCl_2$
124	0.9	3.2	$C_3H_4NCl_2$
121	0.6	2.2	$CCl^{37}Cl_2$
119	2.1	7.6	$CCl_2{}^{37}Cl$
117	2.1	7.6	CCl_3
114	0.1	0.4	$C_2O^{37}Cl_2$

TABLE 15

N-Isopropyl-α,α,α-trichloroacetamide (32) (Cont'd)

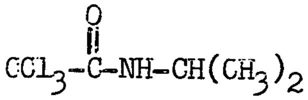


$CCl_3-C(=O)-NH-CH(CH_3)_2$

m/e	%Σ_{36}	rel. int. (base pk. = 100)	Formula
112	0.6	2.2	$C_2OCl^{37}Cl$
110	0.9	3.2	C_2OCl_2
102	0.1	0.4	$CH_2N^{37}Cl_2$
100	0.5	1.8	$CH_2NCl^{37}Cl$
98	0.8	2.9	CH_2NCl_2
87	1.4	5.0	$C_3{}^{13}CH_8NO$ $CH^{37}Cl_2$
86	27.	100.	C_4H_8NO $C^{37}Cl_2$
85	0.6	2.2	$CHCl^{37}Cl$
84	0.8	2.9	$CCl^{37}Cl$
83	1.0	3.6	$CHCl_2$
82	1.2	4.3	CCl_2
58	1.1	4.0	C_3H_8N
49	0.2	0.7	$C^{37}Cl$
47	0.6	2.2	CCl
44	0.7	2.6	$C_2{}^{13}CH_7$
	0.8	2.8	CH_2NO
43	24.	88.	C_3H_7

TABLE 15

N-Isopropyl-α,α,α-trichloroacetamide (<u>32</u>) (Cont'd)



$CCl_3-\overset{\overset{O}{\|}}{C}-NH-CH(CH_3)_2$

m/e	$\%\Sigma_{36}$	rel. int. (base pk. = 100)	Formula
42	0.6	2.2	C_3H_6
	0.1	0.5	$C_2{}^{13}CH_5$
	1.2	4.5	C_2H_4N
41	4.2	15.	C_3H_5
	0.5	1.9	C_2H_3N
39	1.1	4.2	C_3H_3
	0.1	0.2	C_2HN
38	0.4	1.4	$H^{37}Cl$
36	1.1	4.0	HCl

APPENDIX C

CALCULATION OF PERCENT DEUTERATION

Three separate methods were used to ascertain the percent of deuteration by use of the n.m.r. spectra of the acetamides and the reagents used to synthesize them. One procedure involved the use of an "internal standard". In this case the percent deuteration was determined by comparing the n.m.r. integration of an undeuterated position in the compound to that of the deuterated position.

First let z equal the ratio of the n.m.r. integral of the position to be deuterated to that of the "standard" position in the spectrum of the undeuterated compound. Then let x and y equal the n.m.r. integrations of the deuterated and "standard" positions respectively in the spectrum of the deuterated compound. If w is the number of hydrogen atoms assigned to the standard position, the percent of hydrogen (%H) in the deuterated position of the heavy compound is given by:

$$\%H = \left(\frac{\frac{x}{y/w}}{z}\right) \cdot 100 \tag{169}$$

or

$$\%H = \frac{100xw}{yz} \tag{170}$$

Thus the percent of deuterium (%D) present in the position under consideration will be given by:

$$\%D = 100 - \%H \tag{171}$$

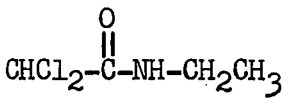
or, by substituting equation (170) into (171):

$$\%D = 100 - \frac{100xw}{yz} \qquad (172)$$

The maximum possible error in the calculation of %D (Δ%D) will be the same as that in the calculation of %H (Δ%H) and will be given by:

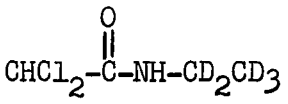
$$\Delta\%D = \Delta\%H = \%H\left(\pm\frac{\Delta x}{x} \pm \frac{\Delta y}{y} \pm \frac{\Delta z}{z}\right) \qquad (173)$$

where Δx, Δy and Δz are the uncertainties in x, y, and z respectively. This procedure was used to calculate the %D for compounds 39, 40, 43, 44 and 47. The calculation for 44 is shown below as an example.



$CHCl_2-\overset{O}{\overset{\|}{C}}-NH-CH_2CH_3$

28



$CHCl_2-\overset{O}{\overset{\|}{C}}-NH-CD_2CD_3$

44

For the light compound (28) the following values were obtained for z for the C-1 (z_1) and C-2 (z_2) positions. The alpha carbon position was used as the "standard".

z_1	z_2
2.031	3.000
2.000	2.935

$\overline{z_1} = 2.015$ $\qquad$ $\overline{z_2} = 2.967$

$S_{z_1} = \Delta_{z_1} = \pm 0.04^6$ $\qquad$ $S_{z_2} = \Delta_{z_2} = \pm 0.02^2$

For the deuterated compound (44), the following values were obtained for y and the n.m.r. integrations of the deuterated C-1 position (x_1) and the deuterated C-2 position (x_2).

$y = 19.0$ $x_1 = 0.5$ $x_2 = 2.0$

$\Delta y = \pm 0.5$ (estimated) $\Delta x_1 = \pm 0.5$ (estimated) $\Delta x_2 = \pm 0.5$ (estimated)

Thus with $w = 1.000\ldots.$, the percent deuteration in the C-1 position ($\%D_1$) is given by equation (172):

$$\%D_1 = 100 - \frac{100(0.5)(1.00)}{(19.0(2.015)}$$

$$= 100 - (1.306\ldots..)$$

From the equation (173):

$$\Delta\%D_1 = 1.306 \left(\pm \frac{0.5}{0.5} \pm \frac{0.5}{19.0} \pm \frac{0.02^2}{2.015}\right) = \pm 1\%$$

$$\%D_1 = (100-1)\% = 99\%$$

Thus, for the C-1 position, the percent deuteration was 99 ± 1%. In a similar manner, the percent deuteration for the C-2 position was calculated to be 96 ± 1%.

The second procedure involved the use of an "external standard" for the compounds used in the synthesis of the deuterated amides.

For this method, approximately 5% solutions of the undeuterated compounds in CCl_4 were used as standards. The molar concentrations (C) of these solutions are given by:

$$C = \frac{dV_1}{V_2(MW)} \tag{174}$$

where d is the density of the pure compound, V_1 is the volume of the compound used, V_2 is the total volume of the solution and MW is the molecular weight of the compound. The samples of the deuterated compounds were run neat so that $V_1 = V_2$ and the concentrations (C') are given by:

$$C' = \frac{d'}{(MW)'} \tag{175}$$

However, (MW)', the molecular weight of the deuterated compound, will depend upon the percent of deuteration and therefore must be written

$$(MW)' = (0.01 \text{ x } \%D)(AW_D)(N) + (1-0.01x\%D)](AW_H)(N)+(MW)'' \tag{176}$$

where AW_D and AW_H are the atomic weights of deuterium and hydrogen respectively, N is the number of hydrogen atoms in the position to be deuterated in the light compound, and (MW)'' is the molecular weight of the light compound not including the hydrogen atoms to be replaced by deuterium atoms. Since $AW_D = 2.014$(1002) and $AW_H = 1.0078$(246), equation (176) may be written as

$$(MW)' = 0.01\%D(2.014)(N) + (1-0.01\%D)(1.008)(N) + (MW)'' \tag{177}$$

or

$$(MW)' = (0.02014)(\%D)(N) + 1.008N - (0.01008)(\%D)(N) + (MW)'' \tag{178}$$

Substitution of equation (178) into (175) gives:

$$C' = d' / [(0.02014)(\%D)(N) + 1.008N - (0.01008)(\%D)(N) + (MW)'' \qquad (179)$$

If x is the n.m.r. integration for the position to be deuterated in the spectrum of the light compound and z is the integration for the same position in the spectrum of the deuterated compound, the percent of hydrogen (%H) in the deuterated compound will be given by:

$$\%H = \frac{z/C'}{x/100C} \qquad (180)$$

or

$$\%H = \frac{100Cz}{xC'} \qquad (181)$$

The percent of deuteration (%D) will be given by:

$$\%D = 100 - \frac{100Cz}{xC'} \qquad (182)$$

Substitution of equation (179) into (182) gives:

$$\%D = 100 - \frac{100Cz}{xd'/[(0.02014)(\%D)(N) + 1.008N - (0.01008)(\%D)(N) + (MW)'']} \qquad (183)$$

and upon rearranging and solving for %D,

$$\%D = \frac{100\left[1 - \frac{Cz(1.008)N}{xd'} - \frac{Cz(MW)''}{xd'}\right]}{1 + \frac{Cz(2.014)N}{xd'} - \frac{Cz(1.008)N}{xd'}} \qquad (184)$$

The error in the calculation of %D (Δ%D) will be the same as that in the calculation of %H (Δ%H) and will be given by:

$$\Delta\%D = \Delta\%H = \%H\left[\pm\frac{\Delta x}{x} \pm \frac{\Delta C}{C} \pm \frac{\Delta z}{z} \pm \frac{\Delta C'}{C'}\right] \qquad (185)$$

where Δx, ΔC, and Δz and $\Delta C'$ are the uncertainties in x, C, z and C' respectively. However,

$$\Delta C' = C'\left[\pm\frac{\Delta d'}{d'} \pm \frac{\Delta(MW)'}{(MW)'}\right] \qquad (186)$$

and since ΔAW_H and ΔAW_D are insignificant in terms of the present calculation and $\Delta\%D = \Delta\%H$, $\Delta(MW)'$ may be calculated as shown below (from equation (178)).

$$\Delta(MW)' = \pm(0.03022)(N)(\Delta\%H) \pm \Delta(MW)'' \qquad (187)$$

Subsitution of (187) into (186) gives:

$$\Delta C' = C' \quad \pm\frac{\Delta d'}{d'} \pm \frac{0.03022)(N)(\Delta\%H) \pm \Delta(MW)''}{(MW)'} \qquad (188)$$

Substitution of equation (188) into (185) and solving for Δ%H gives:

$$\Delta\%D = \Delta\%H = \%H\,\frac{\frac{\Delta x}{x} \pm \frac{\Delta C}{C} \pm \frac{\Delta z}{z} \pm \frac{\Delta D'}{D'} \pm \frac{\Delta(MW)''}{(MW)'}}{1 \pm \frac{0.03022(\%H)(N)}{(MW)'}} \qquad (189)$$

This procedure was used to calculate the percent deuteration for compounds 33, 37, 46, 56, 57, 61. The calculation for the percent of deuteration of 56 is shown below as an example

$(CH_3)_3C{-}Cl$ $\qquad\qquad$ $(CD_3)_3C{-}Cl$

56

The values for d, Δd, V_1, ΔV_1, V_2, ΔV_2, MW and ΔMW are listed below for the undeuterated compound.

$d = 851.1$ mg/ml $\qquad \Delta d = \pm\ 0.1$ mg/ml

$V_1 = 5.000$ml $\qquad \Delta V_1 = \pm\ 0.001$ ml

$V_2 = 100.00$ ml $\qquad \Delta V_2 = \pm\ 0.08$ ml

$MW = 92.569$ $\qquad \Delta MW = \pm\ 0.014$

Thus, the concentration (C) for the light compound is

$$C = \frac{(851.1)(5.000)}{(100.00(92.569)} = 0.45971 \text{ moles/liter}$$

The error in C (ΔC) will be given by

$$\Delta C = C\left[\pm\frac{\Delta d}{d} \pm \frac{\Delta V_1}{V_1} \pm \frac{\Delta V_2}{V_2} \pm \frac{\Delta(MW)}{MW}\right] \qquad (190)$$

$$\Delta C = 0.45971\left[\pm\frac{0.1}{851.1} \pm \frac{0.001}{5.000} \pm \frac{0.08}{100.00} \pm \frac{0.014}{92.569}\right]$$

$= 0.0006$ moles liter^{-1}.

Therefore we have $C = 0.4597 \pm 0.0006$ moles liter^{-1}.

The values for the integration (x) of the light compound are listed below

$x = 5.0,\ 4.5,\ 4.5,\ 5.0$ and 4.5

$\bar{x} = 4.7 \quad S_x = \Delta x = \pm\ 0.2^7$

For the deuterated compound (56), the values of d', $\Delta d'$, (MW)", Δ(MW)", N, z and Δz are listed below. (It is assumed that the density of the deuterated compound will be approximately equal to that of the light compound. To compensate for this, the error for the density is estimated as being much larger.

$d' = 851.1$ mg/ml $\qquad \Delta d' = \pm\ 100$ mg/ml

$(MW)'' = 83.497 \qquad \Delta(MW)'' = \pm\ 0.005$

$N = 9$

z	$\bar{z}$	$S_z = \Delta z$
4.0	4.0	0
4.0		
4.0		
4.0		
4.0		

Thus, the percent deuteration will be given by equation (184):

$$\%D = \frac{100\left[1-\left(\frac{(0.45971)(4.0)(1.008)(9)}{(4.7)(851.1)} - \frac{(0.45971)(4.0)(83.497)}{(4.7)(851.1)}\right)\right]}{1+\frac{(0.45971)(4.0)(2.014)(9)}{(4.7)(851.1)} - \frac{(0.45971)(4.0)(1.008)(9)}{(4.7)(851.1)}}$$

$\%D = 95.35\ldots\ldots\%$

$\%H = 4.65\ldots\ldots\%$

From equation (178)

$$(MW)' = (0.02014)(95.35)(9) + 1.008(9) - (0.01008)(95.35)(9)+83.497$$

$$(MW)' = 101.202$$

From equation (189) the error ($\Delta\%D$) is given by:

$$\Delta\%D = \Delta\%H = 4.65\ \frac{\pm\frac{0.2}{4.7} \pm \frac{0.0005}{0.45971} \pm \frac{100}{851} \pm \frac{0.005}{101.202}}{1 \pm \frac{(0.03022)(9)(4.65)}{101.202}}$$

$\Delta\%D = \pm\ 1\%$

Thus for <u>56</u>, the percent deuteration was 95 ± 1%.

The third procedure made use of an "external standard" to calculate the percent deuteration of the deuterated amides. This method was analogous to the external standard method used for the reagents. However, the concentration (C) of the standard solution is given by:

$$C = \frac{W}{V(MW)} \tag{191}$$

where W is the weight of sample used (in mg), V is the volume of the solution (in ml) and MW is the molecular weight of the compound. The error (ΔC) in C is given by:

$$\Delta C = C\left[\pm \frac{\Delta W}{W} \pm \frac{\Delta V}{V} \pm \frac{\Delta(MW)}{MW}\right] \tag{192}$$

where ΔW, ΔV and $\Delta(MW)$ are the errors in W, V and MW respectively.

The concentration (C') for the deuterated compound is given by:

$$C' = \frac{W'}{V'(MW)'} \tag{193}$$

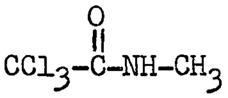
where W' is the weight of deuterated compound used, V' is the volume of the solution and $(MW)'$ is the molecular weight of the deuterated compound and is calculated by the use of equation (178).

The final equations for %D and Δ%D are,

$$\%D = \frac{100\left[1 - \frac{CzV'(1.008)N}{xW'} - \frac{CzV'(MW)'}{xW'}\right]}{1 + \frac{CzV'(2.014)N}{xW'} - \frac{CzV'(1.008)N}{xW'}} \tag{194}$$

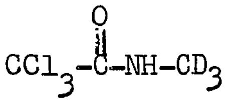
$$\Delta\%D = \Delta\%H = \%H \pm \frac{\frac{\Delta x}{x} \pm \frac{\Delta C}{C} \pm \frac{\Delta z}{z} \pm \frac{\Delta W'}{W'} \pm \frac{\Delta V'}{V'} \pm \frac{\Delta(MW)''}{(MW)'}}{1 \pm \frac{0.03022(N)(\%H)}{(MW)'}} \tag{195}$$

This procedure was used to calculate the percent deuteration for compounds 35, 36, 41, 45, 49, 50, 51, 53, 54 and 55. The calculations for 36 are shown below as an example.



$CCl_3-C(=O)-NH-CH_3$

26



$CCl_3-C(=O)-NH-CD_3$

36

The values of W, ΔW, V, ΔV, MW, ΔMW, x and Δx are listed below for the light compound (26).

$W = 69.5$ mg $\qquad \Delta W = \pm\ 0.1$ mg

$V = 0.50$ ml $\qquad \Delta V = \pm\ 0.05$ ml

$MW = 176.430 \qquad \Delta MW = \pm\ 0.012$

x	$\bar{x}$
80.0	$79.^{2}$
78.0	
79.5	

$S_x = \Delta x = \pm\ 1.^{0}$

From equation (191):

$$C = \frac{69.5}{(0.50)(176.430)}$$

$C = 0.78785......$moles liter $^{-1}$.

and from equation (192):

$$\Delta C = (0.78785...)\left[\pm\frac{0.1}{69.5} \pm \frac{0.05}{0.5} \pm \frac{0.012}{176.430}\right]$$

$\Delta C = \pm 0.08$

$C = 0.79 \pm 0.08$ moles liter^{-1}

The values of W', ΔW', V', ΔV', (MW)", Δ(MW)", N, z and Δz for the deuterated compound (36) are listed below.

$W' = 59.0$ mlg $\Delta W' = 0.1$ mg

$V' = 0.5$ ml $\Delta V' = 0.05$ ml

$(MW)'' = 173.406$ $\Delta(MW)'' = 0.009$

$N = 3$

$S_z = \Delta z = 0.0$

$\underline{z}$	$\bar{z}$
1.0	1.0
1.0	
1.0	

From equation (194):

$$\%D = \frac{100\left[1 - \frac{(0.78785)(1.0)(0.5)(1.008)(3)}{(79.2)(59.0)} - \frac{(0.78785)(1.0)(0.5)(173.406)}{(79.2)(59.0)}\right]}{1 - \frac{(0.78785)(1.0)(0.5)(2.014)(3)}{(79.2)(59.0} - \frac{(0.78785)(1.0)(0.5)(1.008)(3)}{(79.2(59.0)}}$$

$\%D = 98.49\ldots\ldots$

$\%H = 1.51\ldots\ldots$

Equation (178) gives $(MW)'$:

$$(MW)' = (0.02014)(98.49)(3) + (1.008)(3) - (0.01008)(98.49)(3) + 173.406$$

$(MW)' = 179.402$

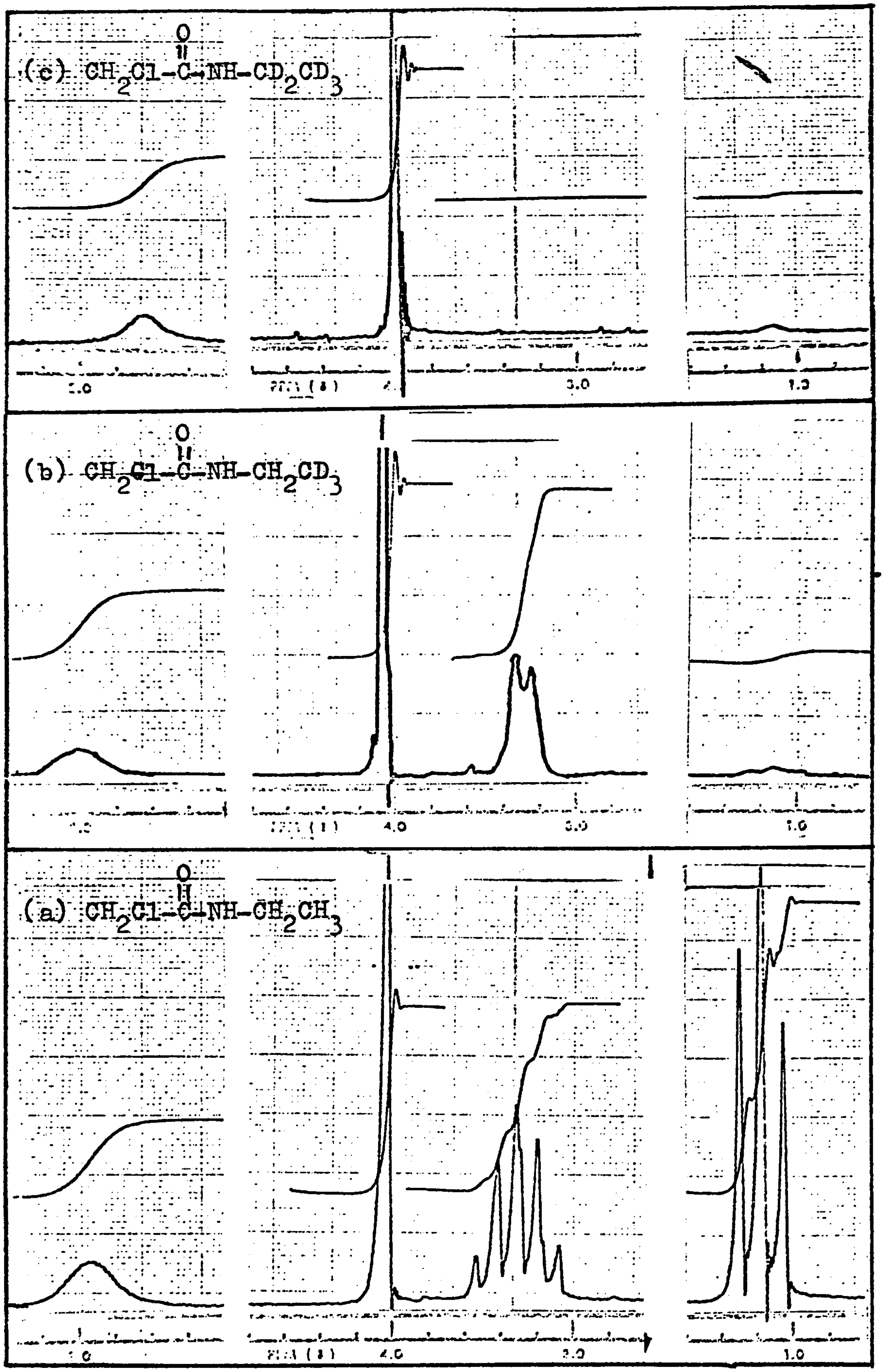
Similarly $\Delta\%D$ and $\Delta\%H$ can be obtained from equation (195):

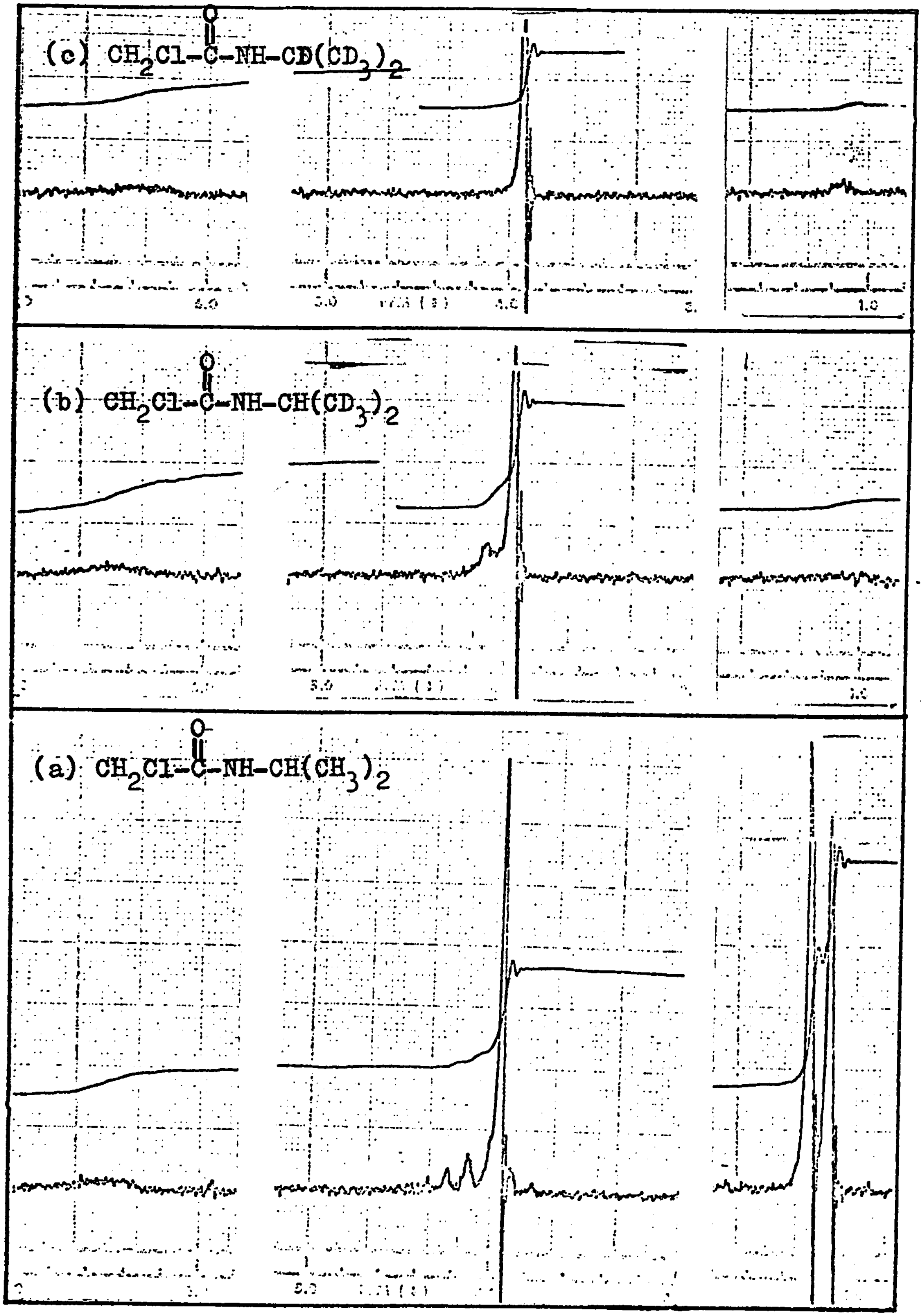
$\Delta\%H = \Delta\%D = \pm 1\%.$

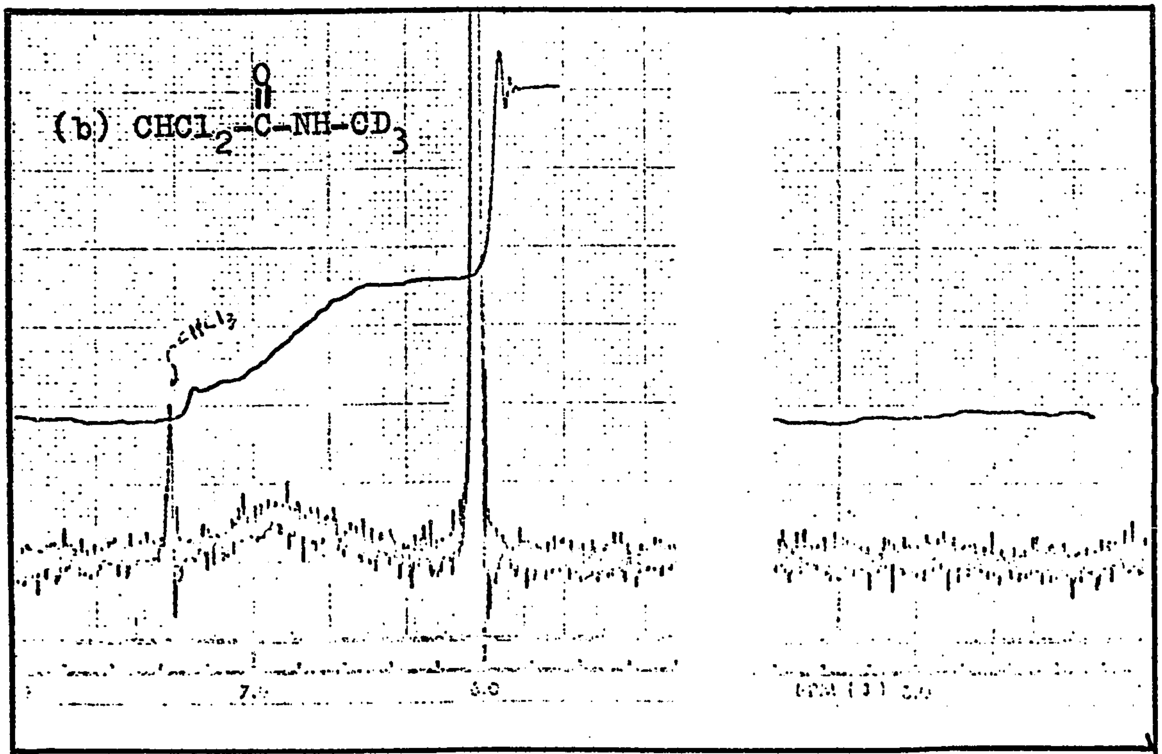
And the percent deuteration for <u>36</u> is 98 ± 1%.

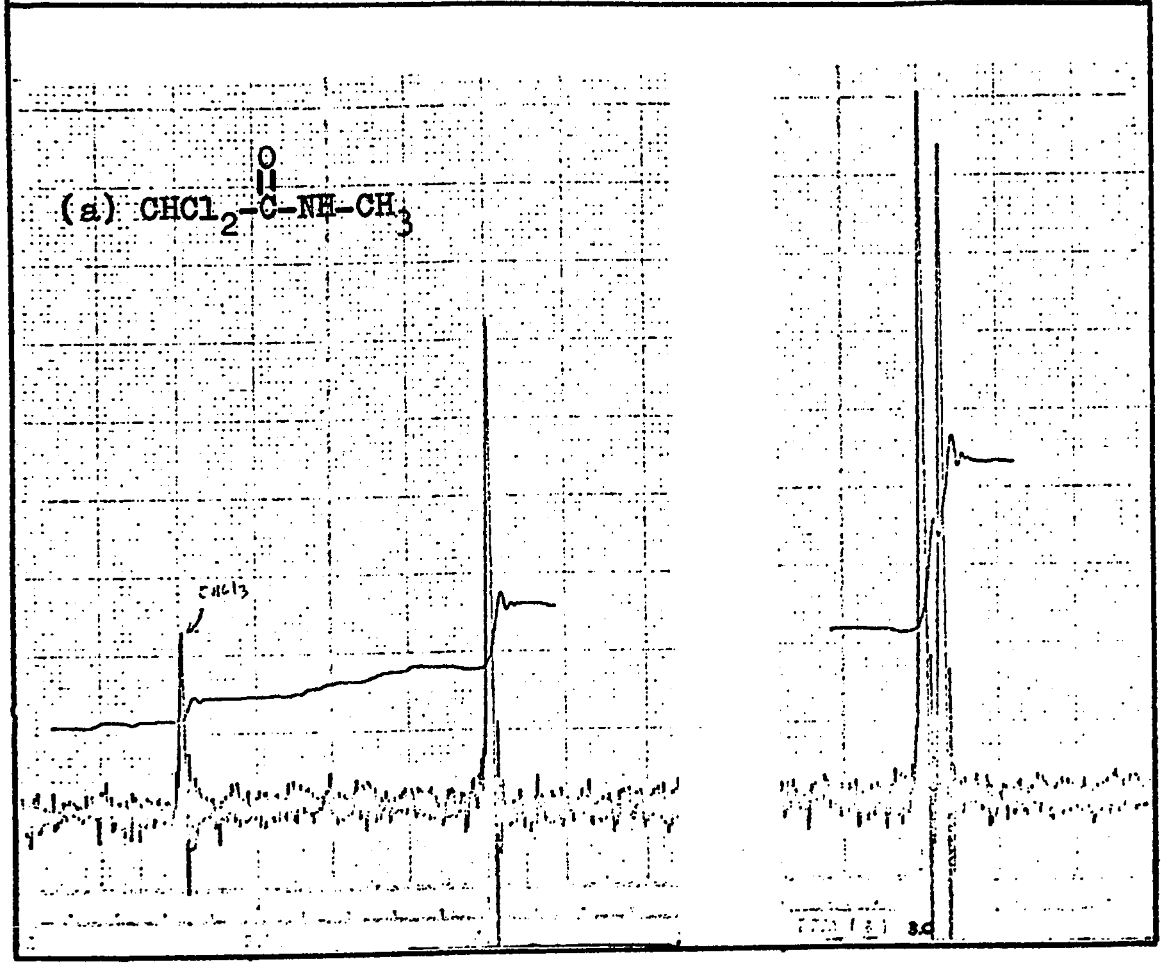
APPENDIX D

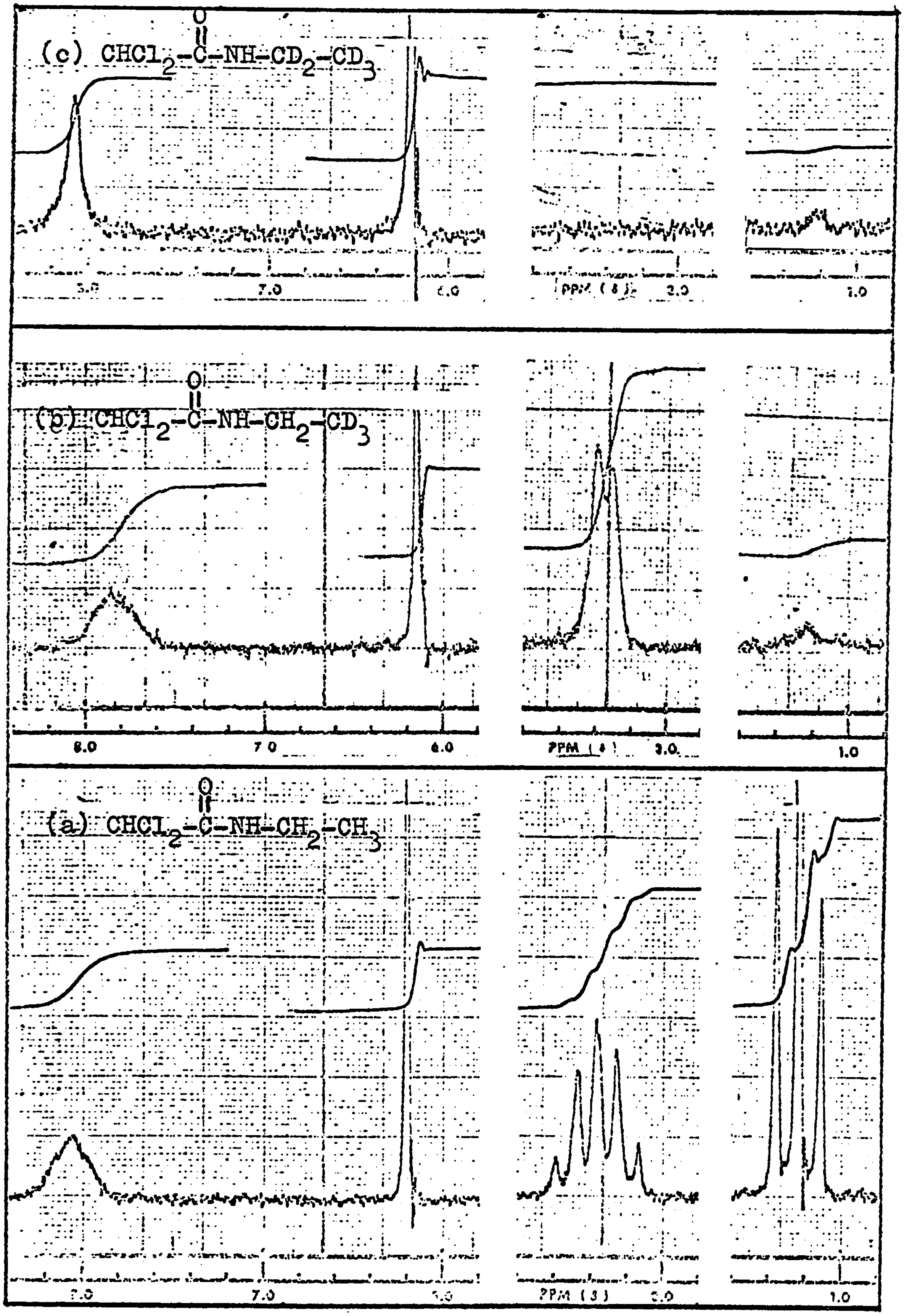
NMR SPECTRA

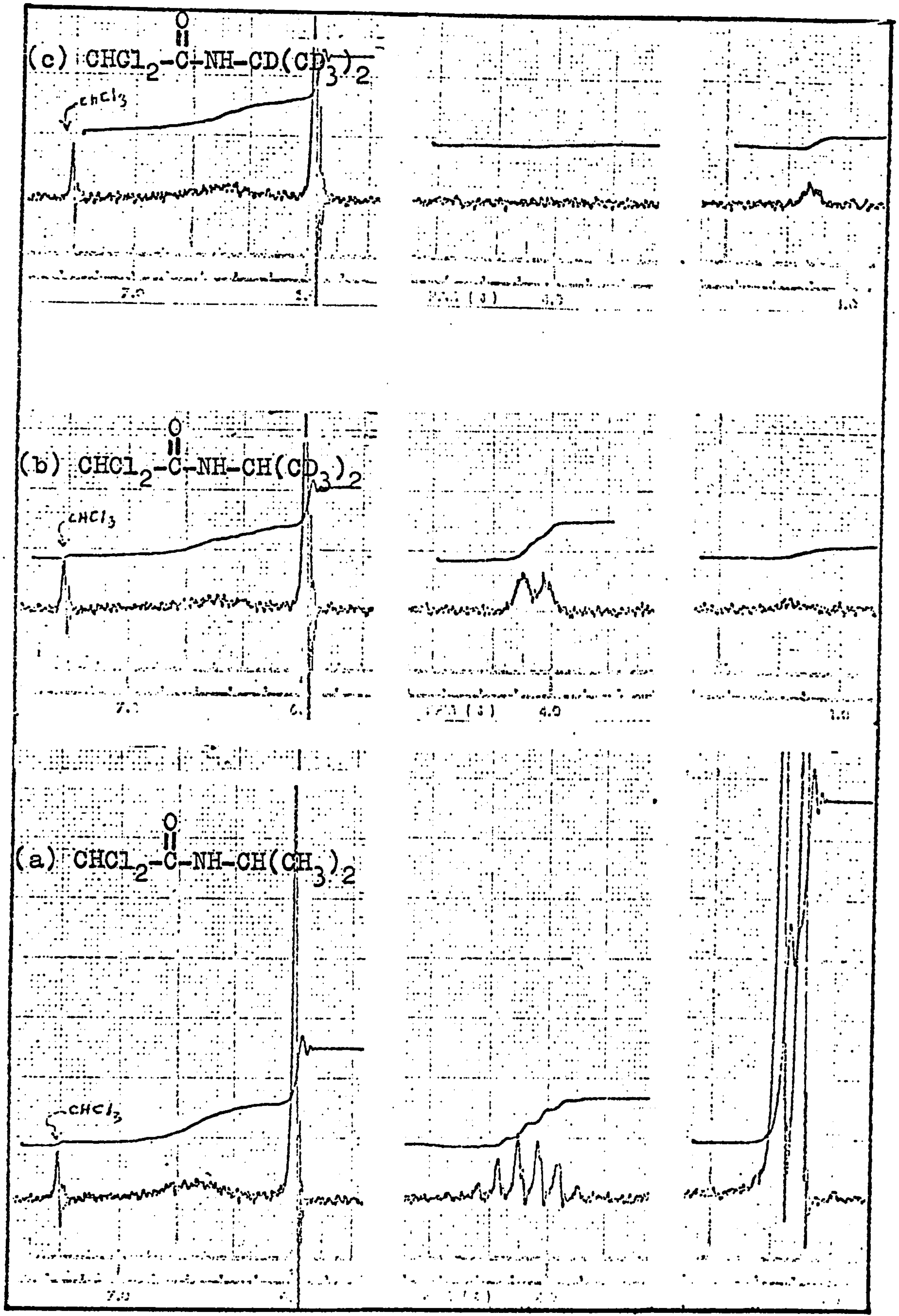

(c) CH2Cl-C(=O)-NH-CD2CD3
7.0
PPM (δ)
4.0
3.0
1.0
(b) CH2Cl-C(=O)-NH-CH2CD3
7.0
PPM (δ)
4.0
3.0
1.0
(a) CH2Cl-C(=O)-NH-CH2CH3
7.0
PPM (δ)
4.0
3.0
1.0

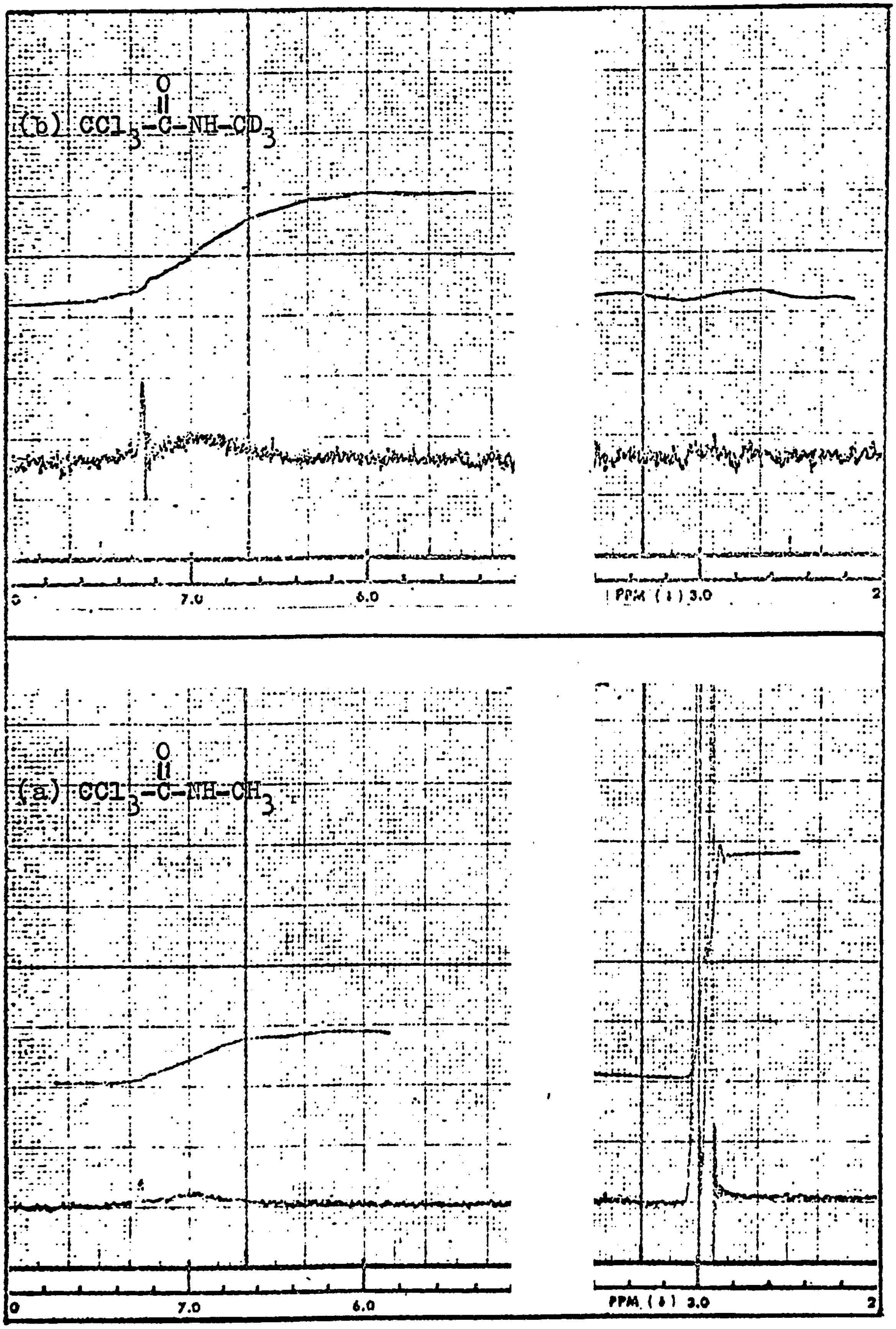

(c) CH2Cl-C(=O)-NH-CD(CD3)2
5.0
3.0
4.0
1.0
(b) CH2Cl-C(=O)-NH-CH(CD3)2
5.0
1.0
(a) CH2Cl-C(=O)-NH-CH(CH3)2
5.0

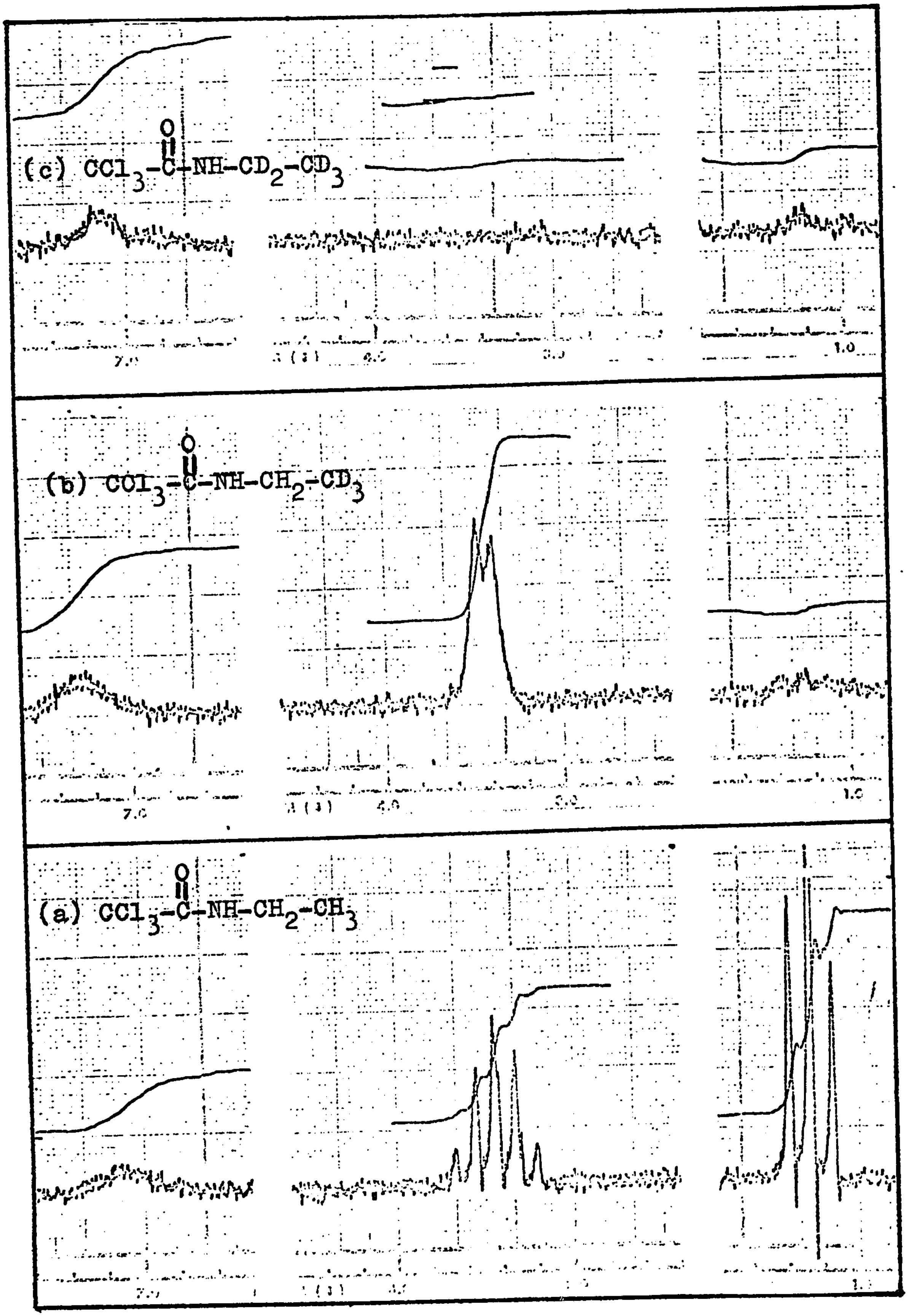

(b) $CHCl_2-\overset{O}{\overset{\|}{C}}-NH-CD_3$
CHCl3

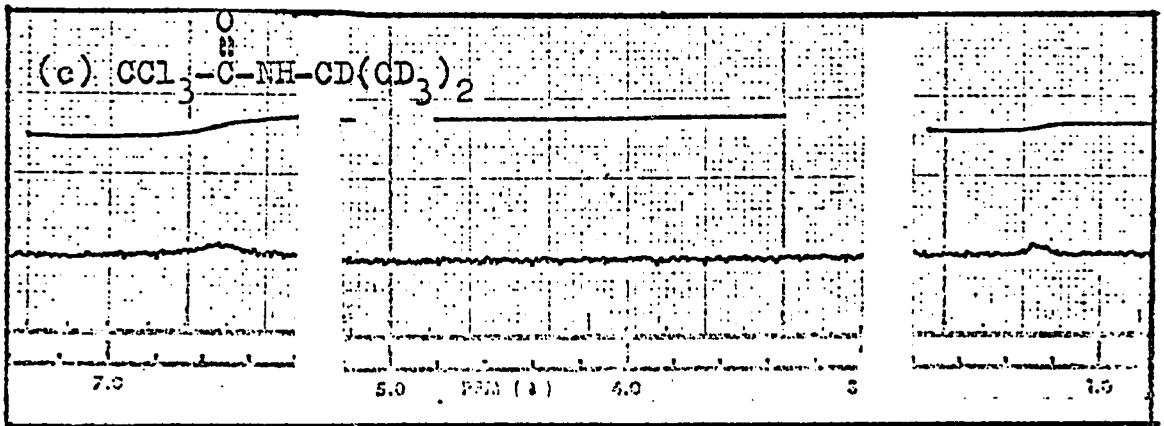

(a) $CHCl_2-\overset{O}{\overset{\|}{C}}-NH-CH_3$
CHCl3
3.0

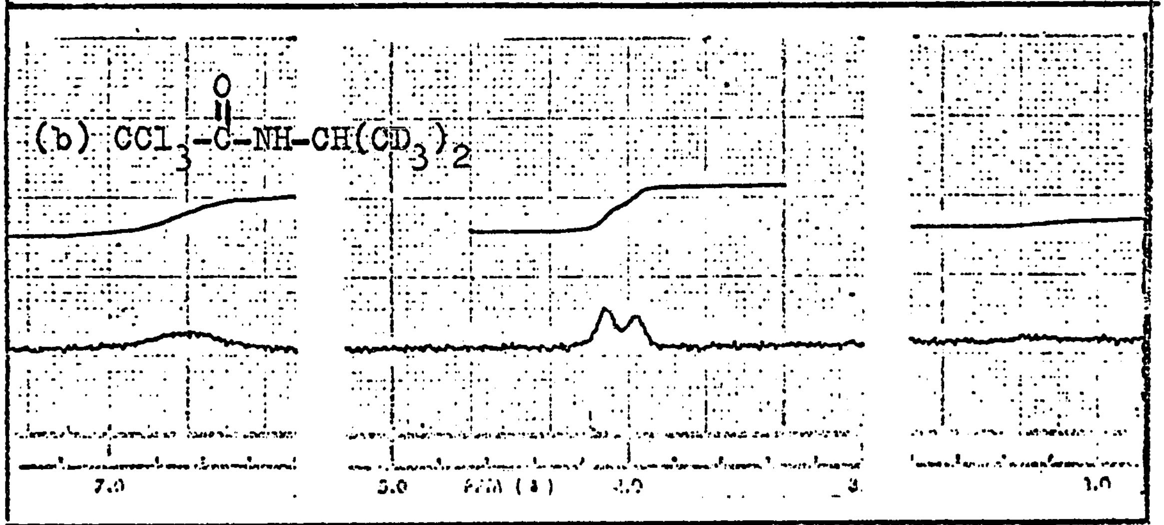

(c) CHCl2-C(=O)-NH-CD2-CD3
8.0
7.0
6.0
PPM (δ)
3.0
1.0
(b) CHCl2-C(=O)-NH-CH2-CD3
8.0
7.0
6.0
PPM (δ)
3.0
1.0
(a) CHCl2-C(=O)-NH-CH2-CH3
8.0
7.0
6.0
PPM (δ)
3.0
1.0

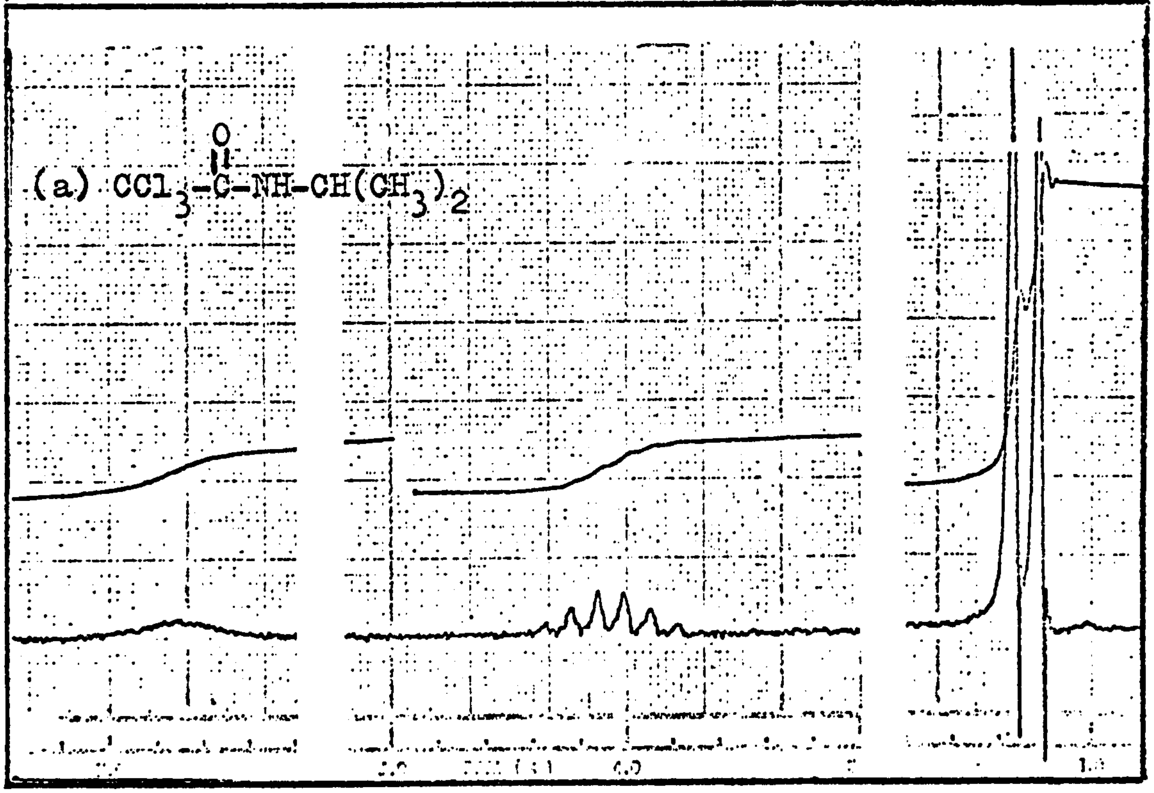

(c) CHCl2-C(=O)-NH-CD(CD3)2
CHCl3
7.0
PPM (δ)
4.0
1.0
(b) CHCl2-C(=O)-NH-CH(CD3)2
CHCl3
7.0
PPM (δ)
4.0
1.0
(a) CHCl2-C(=O)-NH-CH(CH3)2
CHCl3
7.0
PPM (δ)


(b) CCl3-C(=O)-NH-CD3
0
7.0
6.0
PPM (δ) 3.0
2
(a) CCl3-C(=O)-NH-CH3
0
7.0
6.0
PPM (δ) 3.0
2


(c) CCl$_3$-C(=O)-NH-CD$_2$-CD$_3$
7.0
4.0
3.0
1.0
(b) CCl$_3$-C(=O)-NH-CH$_2$-CD$_3$
7.0
4.0
3.0
1.0
(a) CCl$_3$-C(=O)-NH-CH$_2$-CH$_3$
7.0
4.0
3.0
1.0


(c) $CCl_3-\overset{O}{\overset{\|}{C}}-NH-CD(CD_3)_2$
7.0
5.0
PPM (δ)
4.0
3
1.0


(b) $CCl_3-\overset{O}{\overset{\|}{C}}-NH-CH(CD_3)_2$
7.0
5.0
PPM (δ)
4.0
3
1.0


(a) $CCl_3-\overset{O}{\overset{\|}{C}}-NH-CH(CH_3)_2$
7.0
5.0
PPM (δ)
4.0
3
1.0

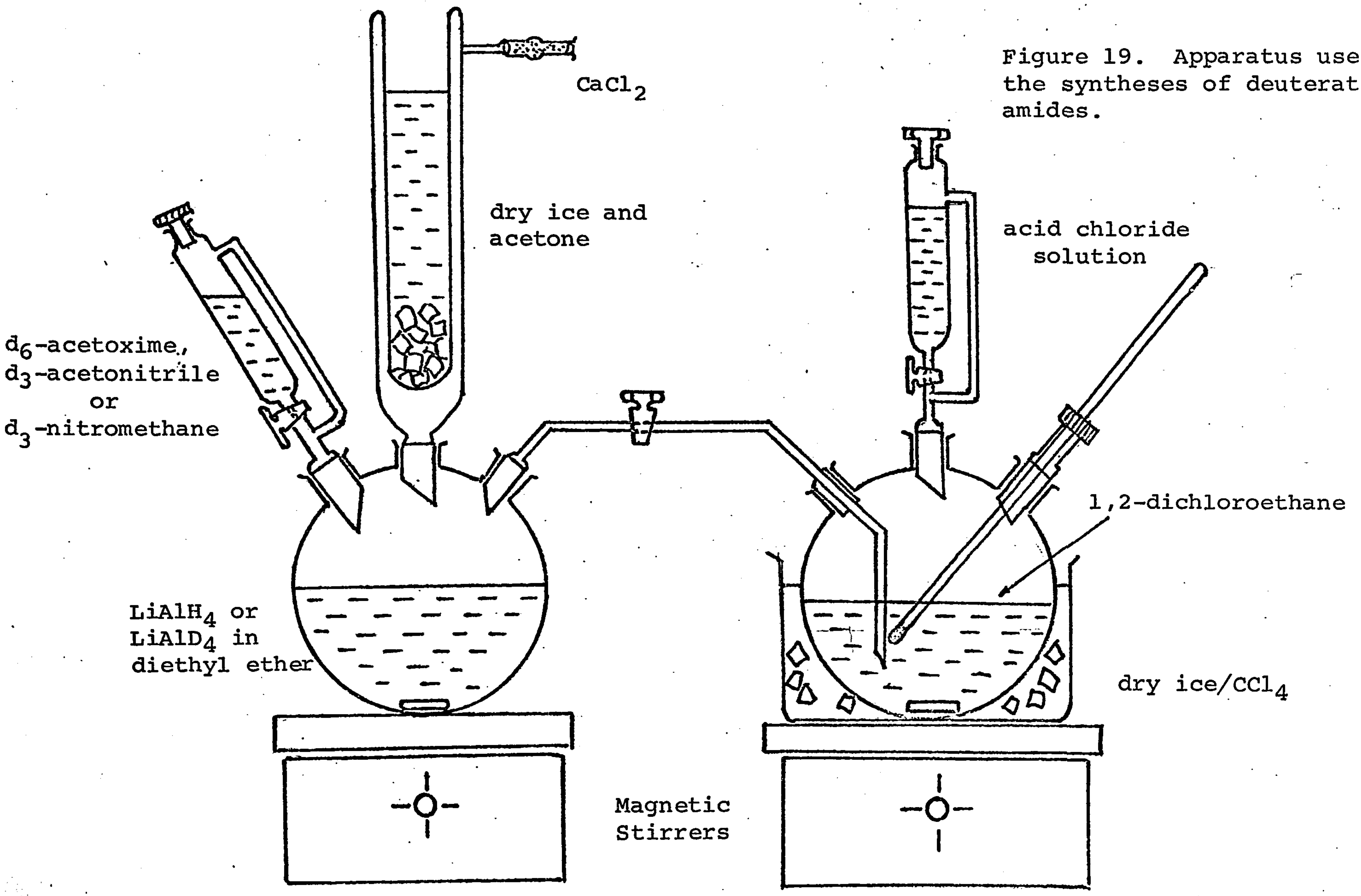


Figure 19. Apparatus used in the syntheses of deuterated amides.