CHAPTER - II

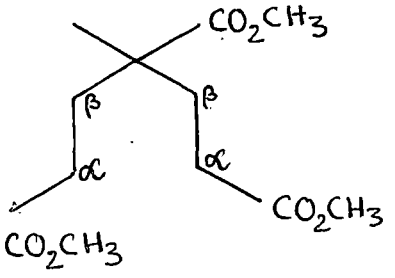
Discussion

Cyanoethylation of ethyl methyl ketone 7 (distilled, one mole) with freshly redistilled acrylonitrile 6 (two moles) in presence of strong base methanolic potassium hydroxide at low temperature 0° to 5° resulted 4-acetyl-4-methyl pimelonitrile 8. This was crystallised from benzene to yield colorless crystals m.p. $67^{\circ}C$. Yield of the 4-acetyl-4-methyl pimelonitrile 8 was found to be 89%. Infrared spectrum of this compound showed significant bands at 2230 (C≡N stretching), 1700 ($\rangle C=O$ stretching) cm^{-1} [Fig. 1]. The resulting pimelonitrile was hydrolysed by refluxing with aqueous potassium hydroxide solution and then upon acidification followed by water evaporation on steam bath and then extraction with boiling ethylene dichloride resulted the crude γ-methyl, γ-acetyl pimelic acid 9. This on crystallisation from ethylene dichloride afforded fine crystals, m.p. $125^{\circ}C$; yield was found to be 75%. Infrared spectrum showed bands at 1715 (due to $\rangle C = O$ stretching of -COOH group), 1690 (due to $\rangle C = O$ stretching of another -COOH group) cm^{-1}; thus accounting for two COOH groups, at 3020 - 2610 cm^{-1} (broad O-H stretching) [Fig. 2]. As calcium hypochloride (H.T.H. quality containing 80% available chlorine) used by Bruson *et al*[14]

was not available at hand, we oxidised the resulting diacid by sodium hypobromite. A different procedure[16] was adopted by us for the haloform reaction in view to oxidise $-COCH_3$ group of √-acetyl √-methyl pimelic acid to the corresponding triacid i.e. √-carboxy √-methyl pimelic acid 10. The well cooled alkaline solution of the diacid 9 was stirred mechanically with freshly prepared excess of sodium hypobromite at 0° - 10° when solid carbon tetrabromide along with sweet smelling bromoform separated. After removal of solid carbon tetrabromide and bromoform by steam distillation followed by addition of little sodium sulphite to destroy the excess of hypobromite it was then acidified with cold hydrochloric acid. The resulting aqueous solution was then evaporated on a steam bath under reduced pressure to dryness which was extracted with hot acetone using thimble in a Soxhlet apparatus. Upon evaporation of acetone from the acetone extract resulted a viscous liquid which gradually settled to a solid mass. This on crystallisation from nitromethane furnished crystals of m.p. 112°. The yield (88%) was found to be better than the triacid obtained by Bruson et al[14] using calcium hypochlorite as an oxidising agent. The resulting triacid i.e. √-methyl √-carboxy pimelic acid 10 was then esterified with diazomethane to give the corresponding

triester as follows:

To an ethereal solution of tri acid 10 excess of dry ethereal solution of diazomethane was added at 5 - 10° and kept overnight. After usual work up followed by distillation at reduced pressure, the triester √-methyl √-carbomethoxy dimethyl pimelate 11, b.p. 170-72° at 4.5 mm of Hg was obtained as colourless viscous liquid.



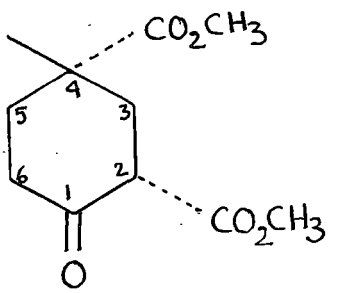
11

TLC of the compound showed it to be homogeneous. Analysis of carbon and hydrogen closely corresponded to that of required values. Infrared spectrum of the compound showed broad peak at 1720 cm^{-1} (due to >C = O stretching of three carbomethoxy groups) [Fig. 3].

^1H NMR (90 MHz) spectrum of triester 11 exhibited signals at 1.1 ppm for one methyl group (tert.), two multiplets centred at 2.22 and 1.88 ppm for the two α methylene protons and the other two β methylene protons respectively with respect to terminal carbomethoxy groups.

The three carbomethoxy methyl groups appeared at 3.65 ppm as singlet integrated for nine protons. [Fig. 4]

Dieckmann cyclisation[17] of the resulting tri-ester 11 with sodium dust resulted the β-keto ester 12 in 49% yield whereas Dieckmann cyclisation with the use of stronger base sodium hydride 12 resulted the β keto ester 12 in 90% yield. The low yield with sodium was traced to caking of the reaction product on the surface of the metal. The method of cyclisation was as follows: To a suspension sodium hydride in benzene under nitrogen atmosphere was added freshly distilled √-methyl √ carbomethoxy dimethyl pimelate. This was refluxed for five hours. After usual work up followed by double distillation, the colourless liquid having b.p. 132-35° at 2.5 mm of Hg was obtained; TLC showed two spots of close r_f values indicating a tautomeric mixture of both keto and enol forms. Moreover, it developed intense violet colour with alcoholic neutral ferric chloride solution.



12

Infrared spectrum of this β-keto ester 12 showed band at 2940 (due to intramolecular hydrogen bonding between the ester $\rangle C = O$ and the enolic hydroxyl group), 1735 (due to $\rangle C = O$ stretch of the carbomethoxy group) cm^{-1} . [Fig. 5]

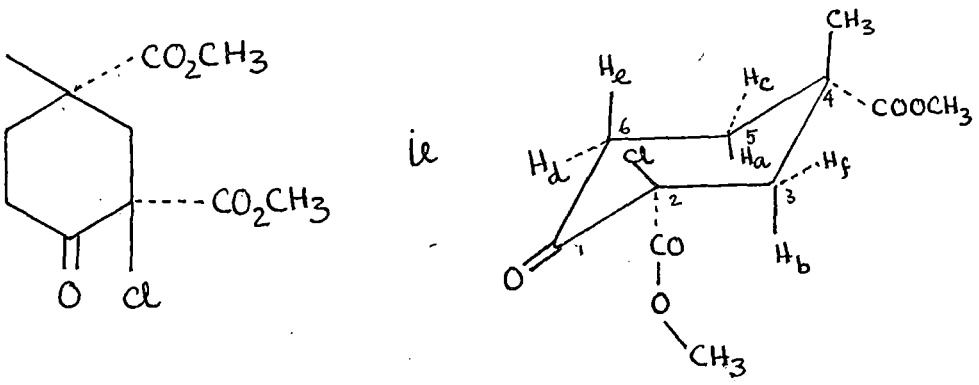
^1H NMR spectrum (90 MHz) of β -keto ester 12 exhibited signals at 1.2 ppm for one methyl group (tertiary), multiplets centred at 2.4 ppm for methylene proton adjacent to carbonyl group; multiplets centred at 3.22 ppm for one methine proton adjacent to carbonyl group and carbomethoxy bearing carbon atom and two sharp singlets one at 3.65 ppm for one carbomethoxy group attached to carbon bearing methyl group and the other at 3.72 ppm for one carbomethoxy group adjacent to carbonyl group, 2.75 ppm for methylene protons at C-3 and 2.09 ppm for methylene protons at C-5. [Fig. 6]

Introduction of halogen (Cl) to the more substituted carbon atom α to carbonyl group was carried out by treatment of the aforesaid β -keto ester 12 with sulfuryl chloride[18]. To the β -keto ester 12 in dry carbon tetra chloride, freshly distilled sulfuryl chloride in dry carbon tetrachloride was added slowly. This was stirred for six hours at room temperature. After usual work a gummy colourless solid was obtained. This was chromatographed over active silica gel column. Petrol:

benzene (9:1) eluate afforded a colourless solid. TLC showed it to be a homogeneous compound. This was crystallised thrice from methanol to afford needle shaped crystals of 2-chloro-4-methyl cyclohexanone 2:4 dimethyl dicarboxylate 13, m.p. 100°C. Infrared spectrum of the compound showed broad band at 1720 cm^{-1} (due to >C = O stretch of carbomethoxy group) [Fig. 7]. This gave positive Beilstein test for halogens. Elemental analysis showed the molecular formula as $C_{11}H_{15}O_5Cl$.

80 MHz ^1H NMR spectra of the chloro keto ester 13 [Fig. 8] showed a strong peak due to a tertiary methyl group at 1.25 (3H) ppm at 3.67 (3H, $COOCH_3$) ppm due to the carbomethoxyl group attached to the carbon atom bearing methyl group and at 3.72 (3H, $COOCH_3$) ppm due to carbomethoxyl group attached to carbon atom bearing chlorine. A more detailed analysis of six spin system was made, using Simulation techniques and plot expansions [Fig. 9 and Fig. 10] which represent different degrees of resolution ehancement, using increasing exponential weighing of the FID. Figure 10 indicated the axial (H_e) and equatorial (H_d) protons of carbon atom 6 at 3.04 and 2.59 ppm respectively. It also showed the axial (H_a) and equatorial (H_c) protons of carbon atom 5 at 1.67 and 2.4 ppm respectively. It further showed the axial

(H_b) and equatorial protons (H_f) of carbon atom 3 at 2.09 and 3.34 ppm respectively. From the coupling constants of the system ABCDEF[19], the coupling constants(J) of AB(0.00), AC(14.00), AD (4.50), AE(13.69), AF (0.00), BC(0.00), BD(0.00), BE(0.00), BF (14.30), CD (3.79), CE (5.69), CF (3.00), DE (15.00), DF (0.00) and EF (0.00) clearly deduces the conformation of the molecule 13 as indicated below.



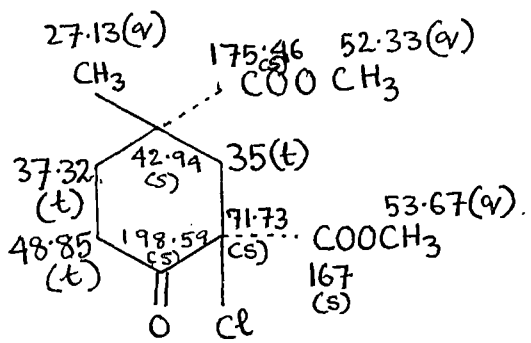
13

Figures 11 and 12 show the ^{13}C spectrum and the off-resonance spectrum of the chloro keto ester 13 . Figure 11 shows that there are eleven carbon atoms in

the molecule. The peak at 198.59 ppm is the carbonyl group. The peaks at 175.46 and 167 ppm are due to carbonyl of two carbomethoxy groups.

The peaks at 42.94 and 71.73 ppm are due to one tertiary carbons atom attached to methyl and carbomethoxy group and the other tertiary carbon atom attached to carbomethoxy and chlorine respectively.

The ^{13}C peaks of 2-chloro-4-methyl cyclohexanone 2:4 dimethyl dicarboxylate are assigned in the structure A given below.

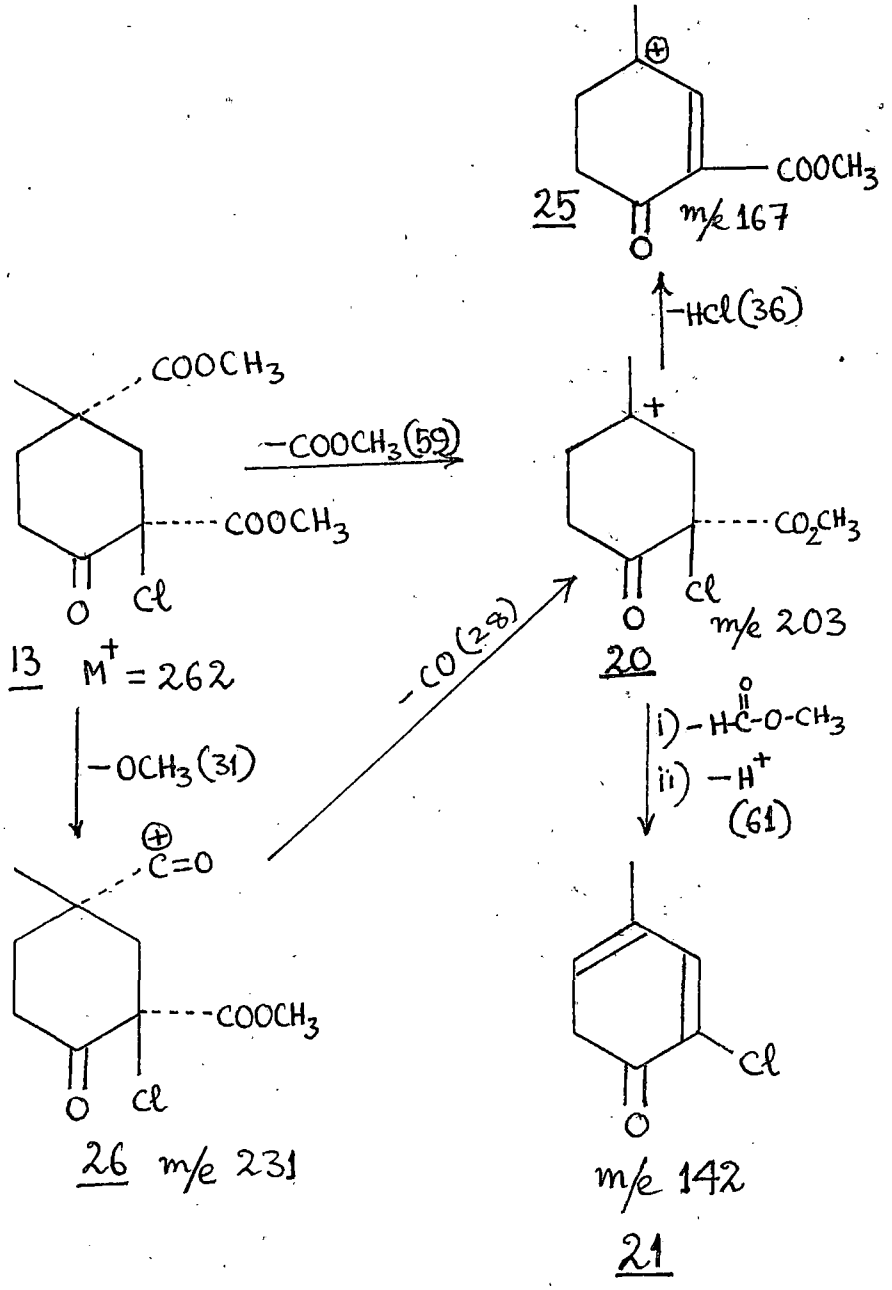


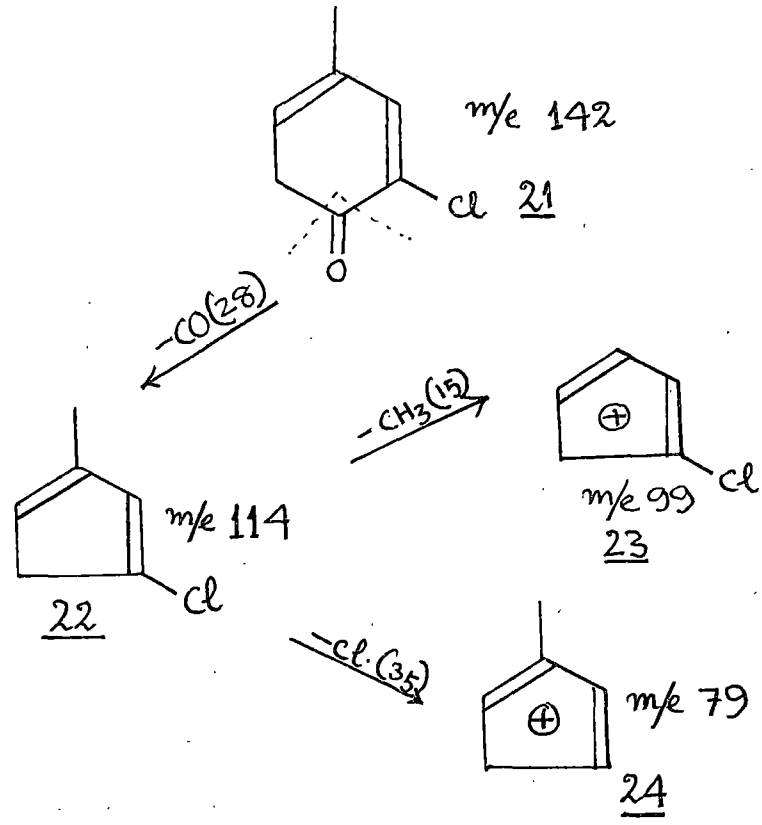
s = singlet
t = triplet
q = quartet

The molecular ion of 2-chloro-4-methyl-cyclohexanone 2:4 dimethyl dicarboxylate 13 has been found to be (M^+ = 262) by chemical ionisation method (Fig. 13). Ion peak at m/e 231 due to fragment 26 is due to the loss of $-OCH_3$ i.e. 31 mass unit from the molecular ion. Fragment 26 loϕses CO to furnish the fragment 20. Ion peak at m/e 203 due to fragment 20 is attributable to the loss of a carbomethoxy group (59) from the molecular ion. Ion peak at m/e 142 arises due to fragment 21. Further loss of CO (28) results fragment 22 which is responsible for the ion peak at m/e 114. Loss of methyl mass unit (15) gives the fragment 23 responsible for the ion peak at m/e 99. Loss of Cl·(35) from m/e 114 affords the fragment 24 responsible for the ion peak at m/e 79. Loss of HCl (36) from the ion peak at m/e 203 resulted the fragment 25 which is responsible for the base peak at m/e 167. The mass fragmentation pattern of 2-chloro-4-methyl cyclohexanone 2:4 dimethyl dicarboxylate 13 has been depicted in Chart-I.

Chart - I

Mass fragmentation of 2-chloro-4-methyl-cyclohexanone 2:4 dimethyl dicarboxylate 13





Attempted dehydrochlorination of 2-chloro-4-methyl cyclohexanone 2:4 dimethyl dicarboxylate 13 by collidine[20].

The α chloro keto ester 13 (3.5 g) was taken in a 250 ml three necked flask fitted with a sealed mechanical stirrer and two condensers fitted with two large size balloons and the air was replaced by nitrogen. To the flask was added 50 ml collidine. This was stirred without heating for 30 minutes when no observable change took place and the reaction mixture was then heated on oil bath. As soon as the temperature of the reaction mixture

reached 145 - 150°, there was sudden exothermic reaction with evolution of a gas as indicated by the rapid expansion of the balloons with simultaneous separation of solid mass from the reaction mixture. The gas collected in the balloons was passed through lime water which turned milky indicating the gas to be carbon dioxide. The heating was discontinued and the mixture was cooled and 50 ml of boiling benzene was added through condenser in order to maintain fluidity. The collidine salt separated was collected by filtration. Then 50 ml of benzene was added to the filtrate. The dark brown solution was washed gradually with two 100 ml portions of 10% HCl saturated with sodium chloride then with one 100 ml portion of sodium bicarbonate solution (saturated) and finally with one 100 ml portion of saturated salt solution which was ultimately dried over anhydrous sodium sulphate. Benzene was removed by distillation through a 15 cm Vigreux column and the UV absorption of the residual liquid was found to be λ_{max}^{MeOH} 232 and 247 nm. This was then distilled through a fractionating column packed with steel saddles when a liquid having b.p. 142-158° at 5.5 mm of Hg was obtained. This showed UV absorption characteristic for $\alpha\beta$ unsaturated carbonyl compound at 231 nm and 247 nm. TLC showed three spots with one spot prominent.

The IR spectrum (Fig. 14) showed broad peak at 1720-1730 cm^{-1} due to carbomethoxy and carbonyl group.

The appearance of OH band at 3410 - 3430 cm^{-1} could not be accounted as this may be due to moisture.

The liquid gave positive Beilstein test for halogens and the elemental analysis of the compound showed the percentage of chlorine to be 16.5. Though the formation of salt of collidine chloride raised our hope for the expected product, the evolution of carbon dioxide gas and the following observations were baffling for further progress for the synthesis of C_{11}- acid.

The jolt was first felt when we found the absence of any peaks around m/e 226 of the desired dehydrohalogenated product in the mass spectrum of the liquid which was further endorsed by the ^{1}H and ^{13}C NMR of the product as discussed in the following para:

80 MHz ^{1}H NMR spectrum of the liquid in $CDCl_3$ was taken (Fig. 15). There is a strong peak due to tertiary methyl group at 1.22 ppm and a carbomethoxy peak at 3.7 ppm. A pair of doublets at 4.6 ppm (J = 13 Hz) is due to CH bonded to chlorine ortho to the carbonyl group and the triplets centred at 1.75 ppm which has the same spacing (J = 13 Hz) as the larger spacing in the pair of doublets suggesting that these protons are coupled together with 13 Hz coupling constant. Since coupling this large requires a 180° dihedral angle it is concluded that the two adjacent protons are axially oriented.

The lines centred at 2.8 ppm are due to C-3 equatorial hydrogen which has coupling constant 12 Hz (geminal with C-3 axial protons) and 6 Hz (vicinal with C-2 axial proton).

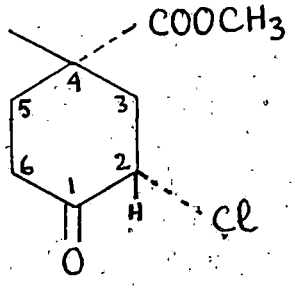
The complexity of methoxyl region and methyl region suggests that the liquid is a mixture of compounds, with one predominant species present to 50 to 60 percent. The ^{13}C spectrum (Fig. 16) confirms this view. A large number of peaks are found in the region 20-60 ppm, and several peaks in the 120-150 ppm region. A very small peak is found at 176 ppm and one at 202 ppm; these are carbonyl carbons and would be expected to be small under the conditions of the epxeriment (60° tip angle and 1.0 second repetition rate). The methoxyl region (50-55 ppm) is about as complex as the corresponding region (3.55 - 375 ppm) in the ^{1}H spectrum, and the methyl region shows 5 peaks.

Nevertheless, the six strongest peaks in the spectrum almost certainly arise from a predominant molecular species. An off-resonance spectrum (Fig. 17) was run and showed that the line at 26.4 (q) ppm is a methyl carbon, the lines at 36 (t) and 38(t) ppm are methylene carbons, the line at 44.8 ppm increases in relative intensity and is a singlet, the line at 47 (t) ppm is a methylene carbon, the line at 52.4 (q) ppm is a methoxyl (carbomethoxy) and the line at 61 (d) ppm is a methine carbon bearing chlorine. The small lines between 130 and 150 ppm are all doublets, hence they are protonated doubly

bonded carbons. These may be due to the possible side products C and D since they are so small relative to the protonated carbons at the high field end of the spectrum, they must belong to the minor components of the mixture. Hence it was concluded that there are no double bonds in the predominant component of the mixture, but there is a tertiary methyl, a carbomethoxy, a ketone carbonyl, a quaternary carbon, a CH adjacent to chlorine and three CH_2 groups.

An off-resonance noise modulated decoupled spectrum (Fig. 18) was also run. All carbons coupled to protons are smeared into broad lines, while non protonated carbons are sharp. The lines at 45, 176 and 202 ppm are thus confirmed as belonging to the predominant species.

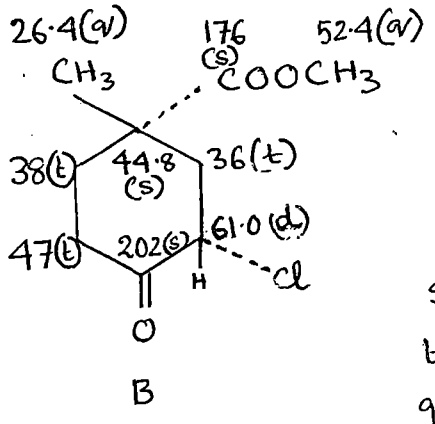
The NMR data obtained are hence consistent with the following structure B for the predominant species.



B

The chlorine has been located next to carbonyl in order to account for the peak at 4.6 ppm. The axial proton has an axial and equatorial neighbour. The axial neighbour is the triplet at 1.75 ppm and the equatorial neighbour is the pair of multiplets at 2.8 ppm.

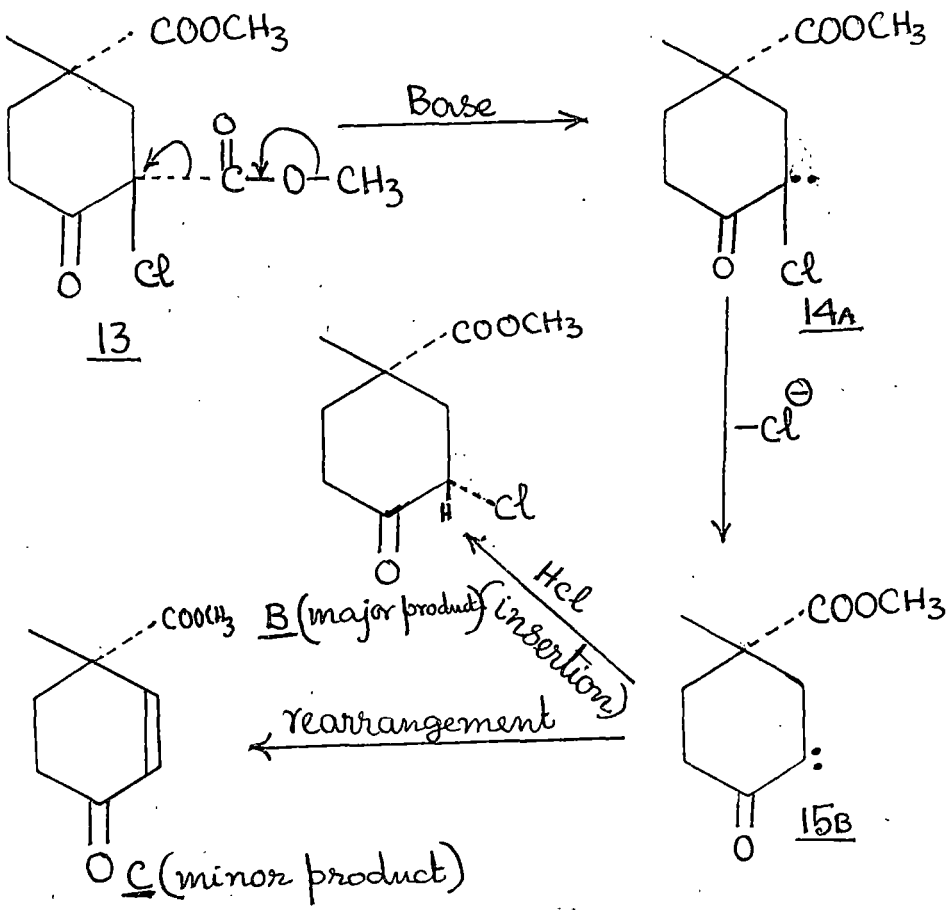
The ^{13}C peaks of the main compound B are assigned in the structure given below:



B

S = Singlet
t = triplet
q = quartet
d = doublet

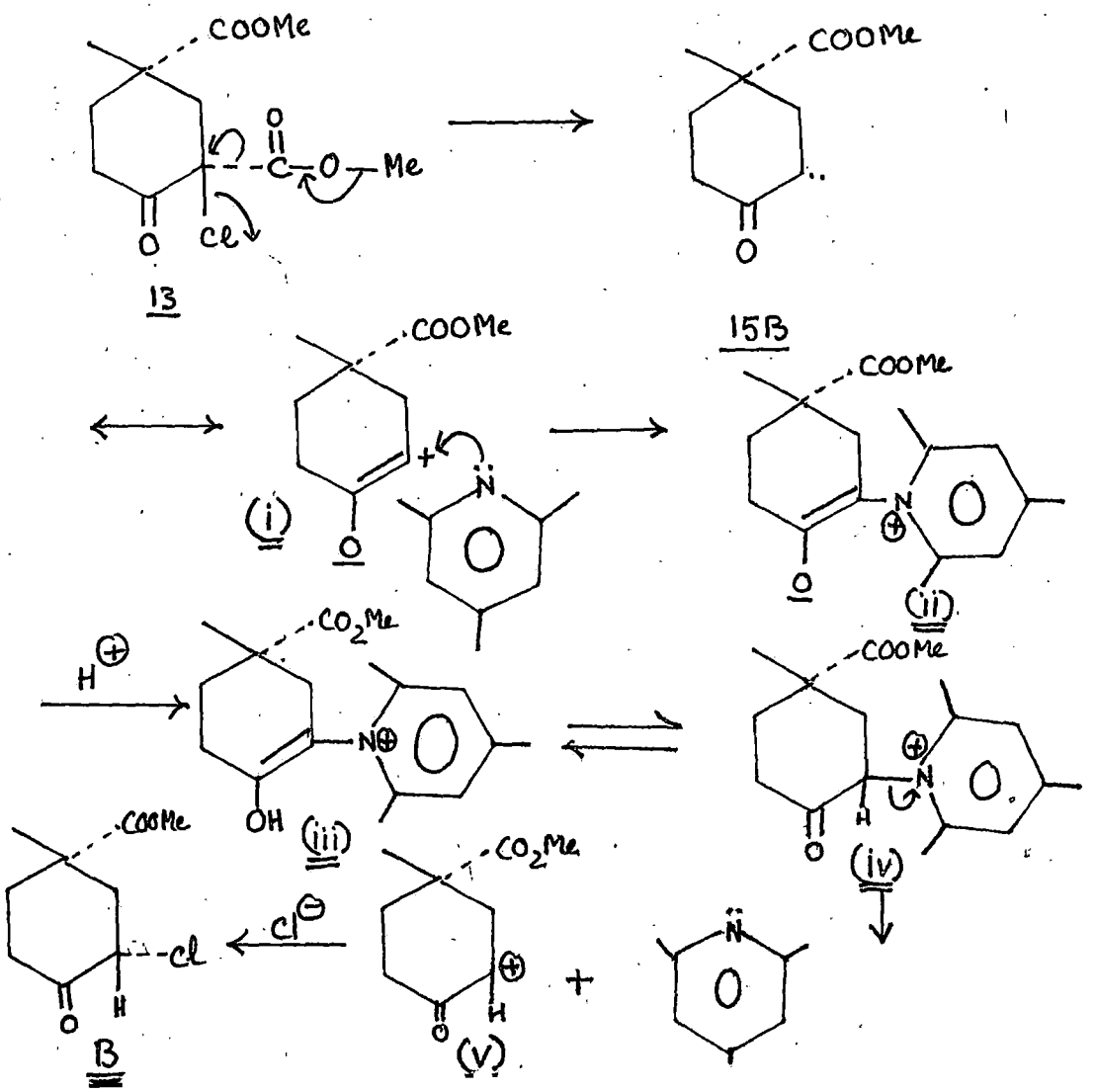
The formation of methyl 2-chloro-4-methyl-cyclohexanone-4-carboxylate B along with the other side products C & D could be explained only through the carbene intermediate as depicted below.

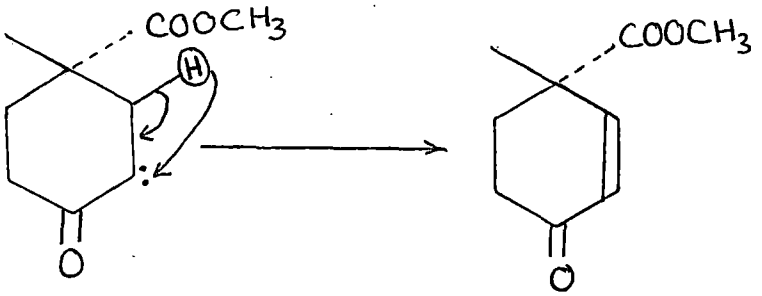


Here instead of dehydrohalogenation the sterically crowded α chloro keto ester 13 gets releived of its sterical interaction by decarboxylation giving the anion 14A which then loses the chloride ion to furnish the carbene intermediate 15B This carbene may be stabilised[21] by the lone pair of electrons on nitrogen of collidine which would give the α chloroketone B on acidification with dil HCl or by rearrangement of H atom β with respect to carbonyl group would form $\alpha\beta$ unsaturated ketone[22] C.

Addendum 3

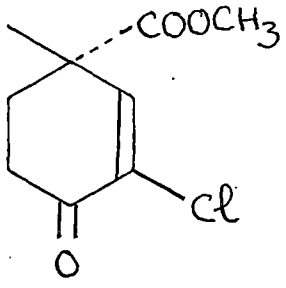
A more plausible mechanism for the formation of α-chloro ketone B may be via the formation of dipolar ion (i) which in presence of collidine will behave as an electrophile to give the corresponding dipolar ion (ii). This salt may be stable enough to react with dil HCl to form the enol (iii) which may tautomerise to the keto form (iv). Intermediate (iv) may eventually lose collidine to form the carbonium ion (v) which will react with the chloride ion to form B.





15B C

The exothermic reaction with evolution of carbon dioxide (tested by lime water) and formation of collidine N-methyl chloride supported the above mechanism. The appearance of UV absorption at 231 nm may be due to unsaturated ketone C and the one at 247 nm may be due to methyl 2-chloro-4-methyl 2,3 cyclohexanone-4-carboxylate D



D (minor amount)

This may give rise to the cluster of protonated double bonded doublets in the region 130-150 ppm in the ^{13}C NMR. Further appearance of minor peaks in the mass spectrum at 202 and 144 confirms the existence of these minor products.

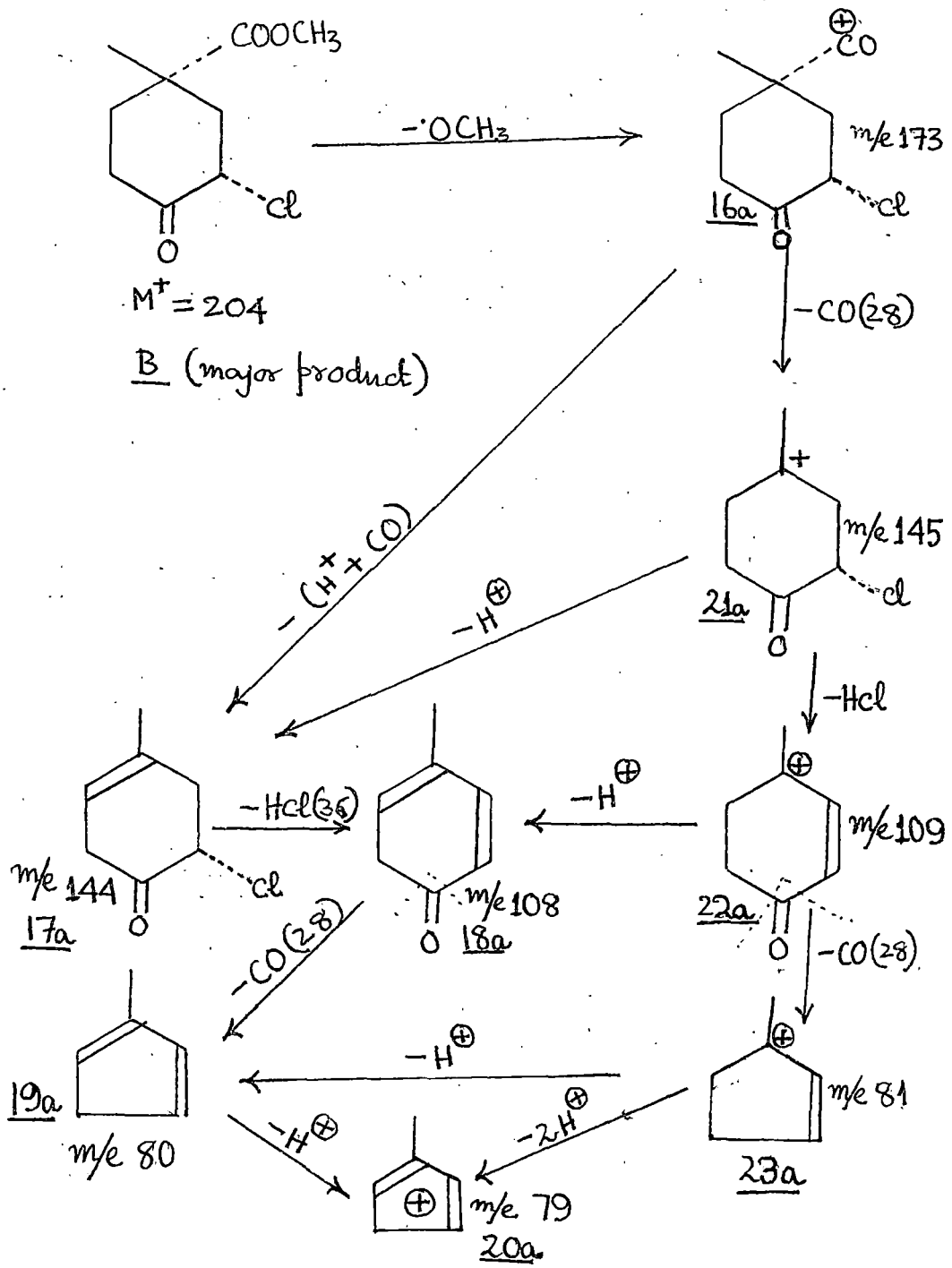
The mass spectrum of the liquid product showed mass peak at 204 (M^+) as the main peak and at 202 (Fig. 19) as the minor peak. The fragmentation pattern has been explained for both the products as in Chart I and Chart II.

The molecular ion of the main product B has been found to be (M^+= 204). Loss of $-OCH_3$ i.e. 31 mass units from the molecular ion yields the fragment 16a responsible for the ion peak at m/e 173; loss of CO i.e. 28 mass units from fragment 16a gives rise to fragment 21a attributable for the ion peak at m/e 145. Loss of HCl i.e. 36 mass units resulted the fragment 22a for which ion peak at m/e 109 is observed. Further loss of CO i.e. 28 mass units from the latter results the ion peak at m/e 81 for the fragment 23a and loss of (H^++CO) i.e. 29 mass unit from fragment 16a results the ion peak at m/e 144 for the fragment 17a. Elimination of HCl i.e. 36 mass units from 17a furnished 18a for which ion peak at m/e 108 is indicated and that of carbon monoxide i.e. 28 mass units from 18a gave fragment 19a for which ion peak at m/e 80 is observed. This on elimination of one proton furnished

fragment 20a responsible for ion peak at m/e 79 which also resulted by the loss of two protons from fragment 23a. Elimination of a Proton from 22a gave 18a responsible also for ion peak at m/e 108.

Chart -I

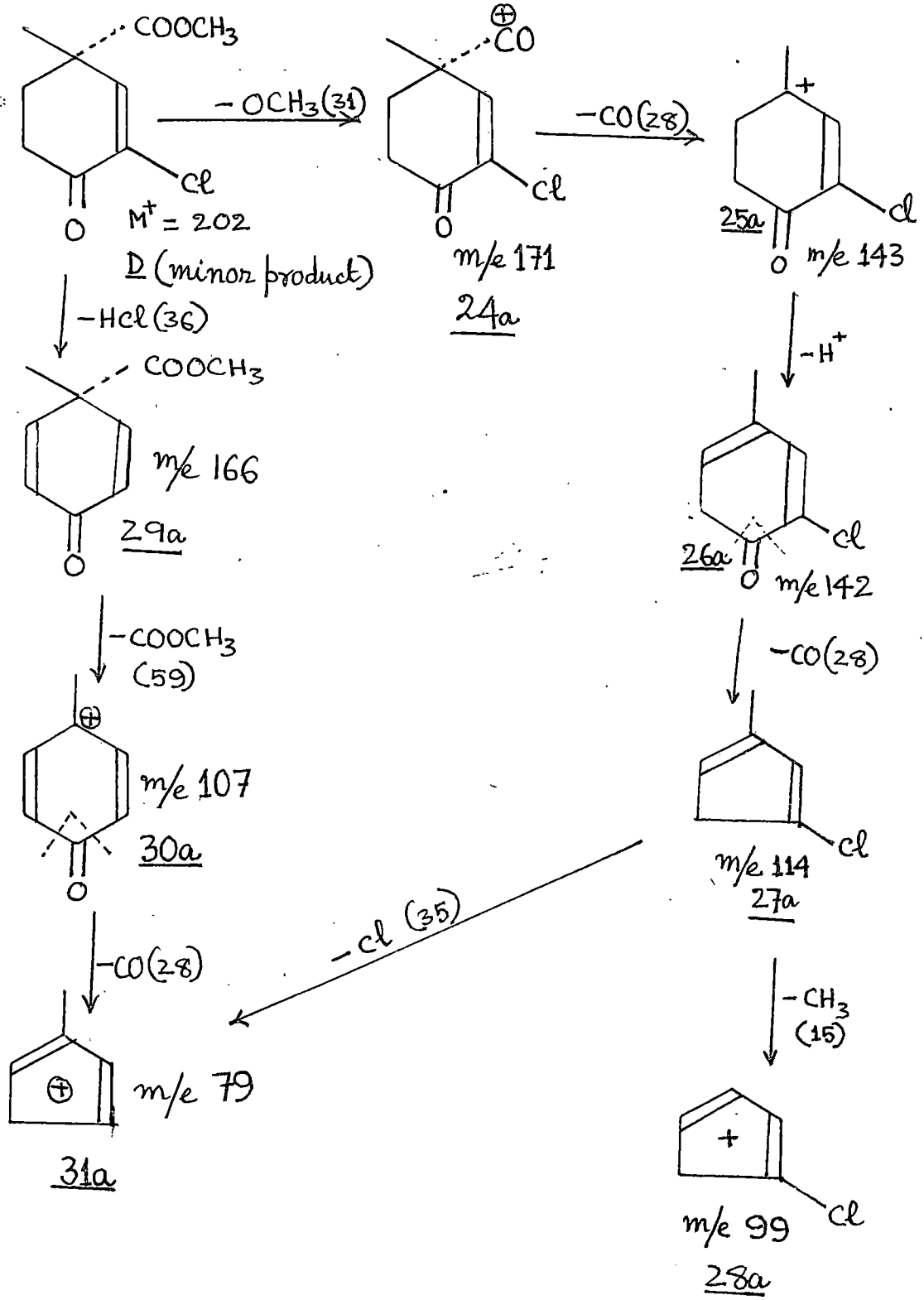
Mass fragmentation of methyl 2-chloro-4-methyl cyclohexanone 4-carboxylate (major product) B (Fig. 19)



The molecular ion for the minor product D has been found to be M^+ = 202. The loss of $-OCH_3$ i.e. 31 mass units results ion peak at m/e 171 responsible for fragment 24a and that of CO i.e. 28 mass units from 24a resulted ion peak at m/e 143 responsible for fragment 25a which eliminated a proton to form fragment 26a responsible for ion peak at m/e 142. Loss of CO i.e. 28 mass units resulted fragment 27a for which ion peak at m/e 114 is obtained which subsequently loøses methyl group to give rise the fragment 28a for which ion peak at m/e 99 is obtained. Loss of HCl i.e. 36 mass units from the molecular ion furnished the fragment 29a responsible for ion peak at m/e 166 which on further loss of carbomethoxy i.e. 59 mass units resulted fragment 30a ion peak at m/e 107 is obtained. This loøses CO i.e. 28 mass units further to yield fragment 31a giving rise to the ion peak at m/e 79. This also results by the loss of chlorine i.e. 35 mass units from fragment 27a.

Chart-II

Mass fragmentation of Methyl-2-chloro-4-methyl 2,3 cyclohexenone 4-carboxylate D (minor product) D. (Fig.19)


COOCH3
-OCH3 (31)
Cl
O
M+ = 202
D (minor product)
-HCl (36)
COOCH3
m/e 166
29a
-COOCH3 (59)
m/e 107
30a
-CO (28)
m/e 79
31a
⊕CO
m/e 171
24a
-CO (28)
25a
m/e 143
-H+
26a
m/e 142
-CO (28)
m/e 114
27a
-Cl (35)
-CH3 (15)
m/e 99
28a

Since not even a minor amount of our desired product was formed as evident from the above facts the explanation for the failure of this step may be explained by assuming that the collidine being large molecule with the nitrogen being flanked by two methyl groups on ortho positions is unable to abstract a proton from the C-3 carbon atom of the α chloro keto ester 13 due to sterical crowding both at C-2 and C-4 positions by chlorine and carbomethoxy group at C-2 position and methyl and carbomethoxy group at C-4 position. The stereochemistry and conformation of which has already been established by us.

Further progress has been suspended for the time being as the chloro keto ester 13 is exhausted which is being synthesised by us.

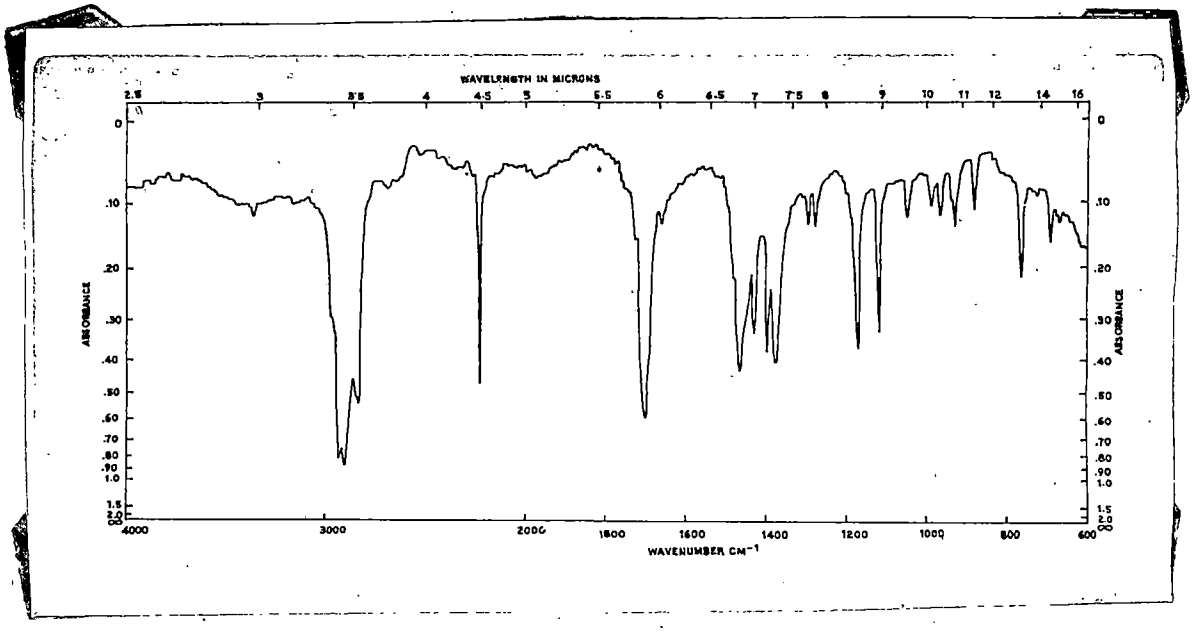


Fig. 1 IR spectrum of 4-acetyl-4-methyl-Pimelonitrile

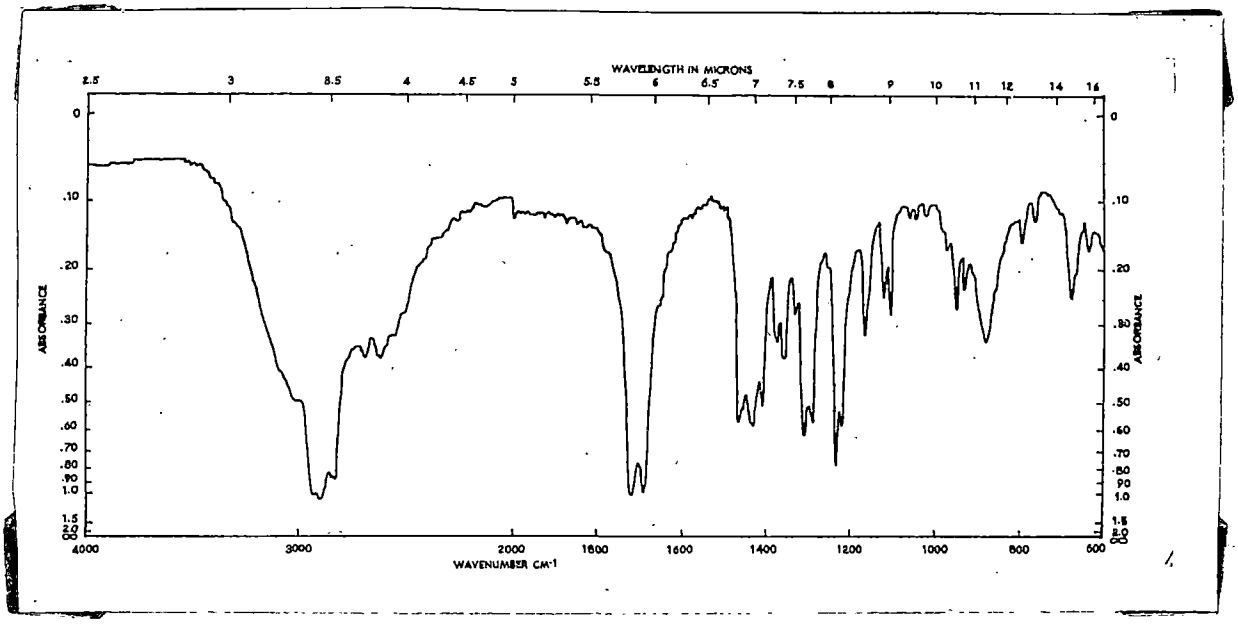


Fig. 2 IR spectrum of ν -methyl- ν -acetyl Pimelic acid

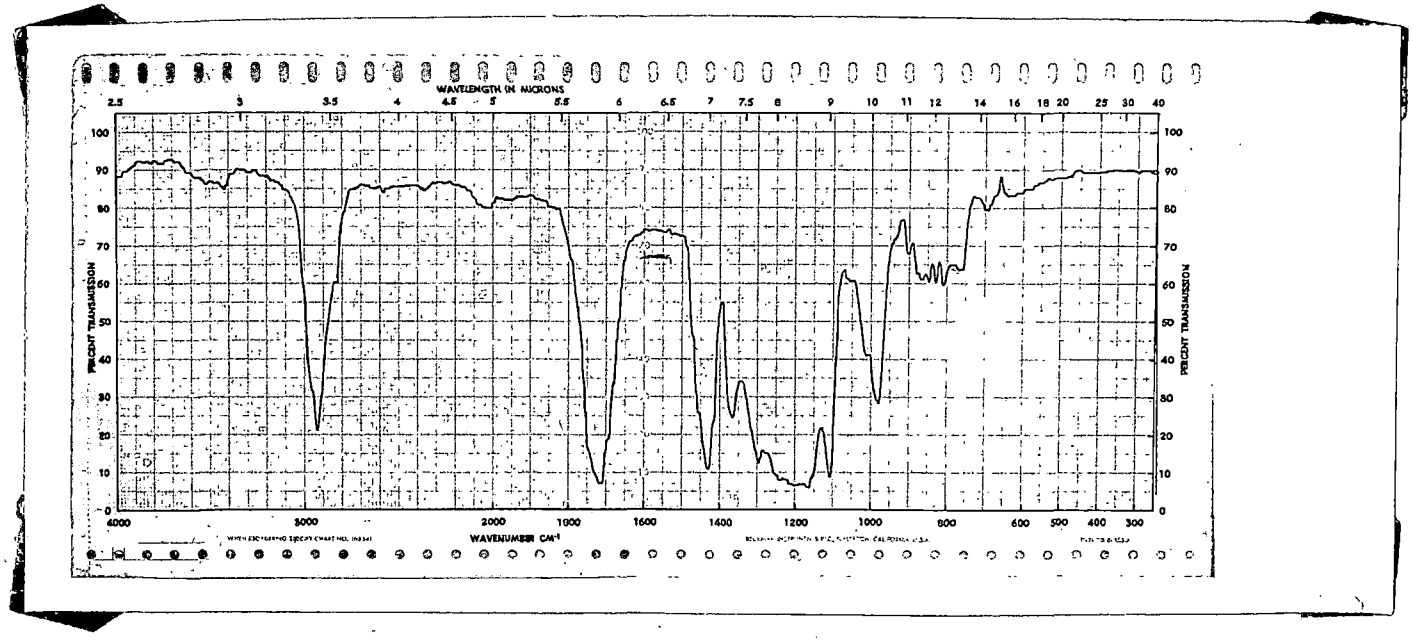


Fig. 3 IR spectrum of ν-methyl - ν-carbomethoxy dimethyl pimelate

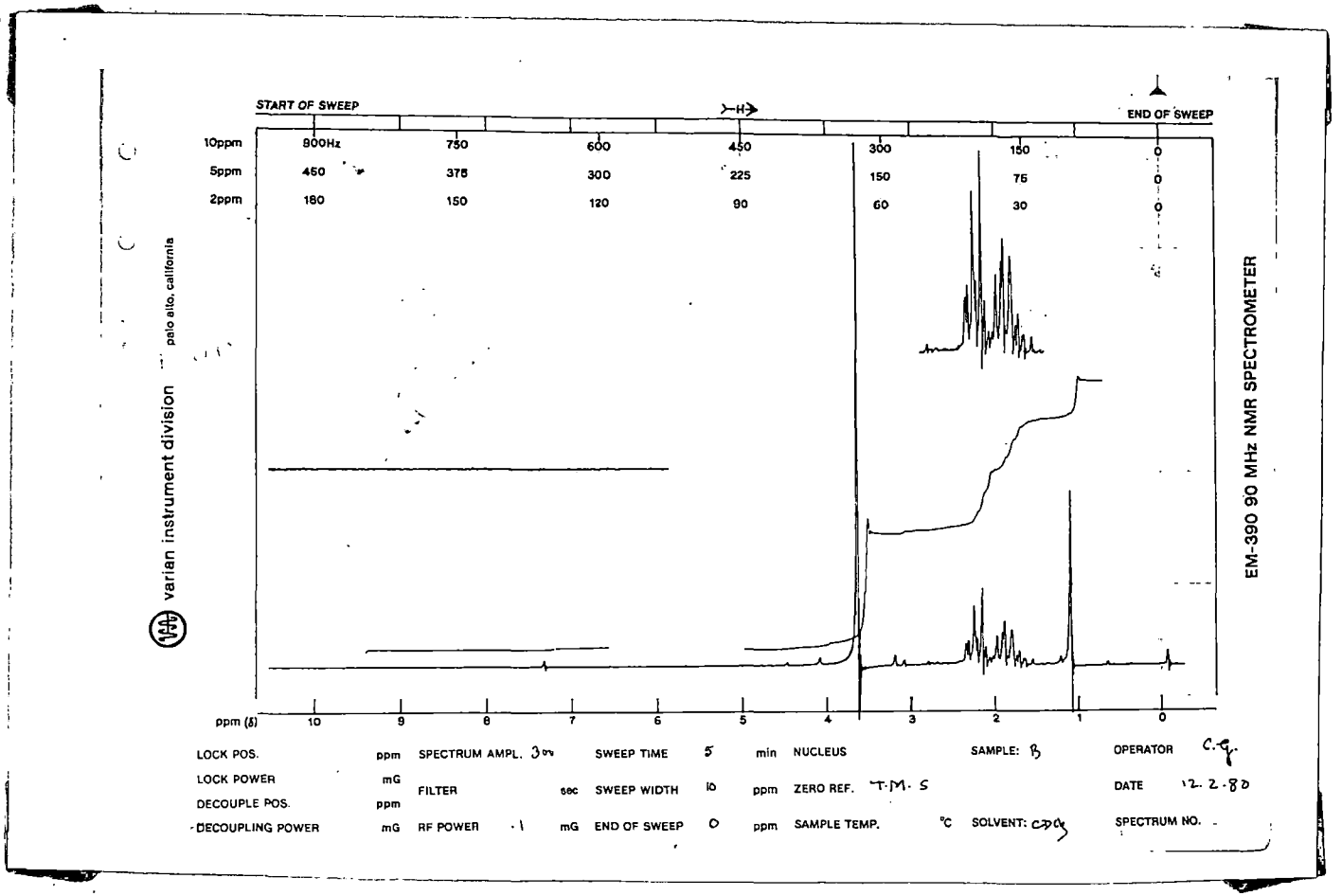


Fig. 4 ^{1}H NMR spectrum of γ-methyl - γ-carbomethoxy dimethyl pimelate

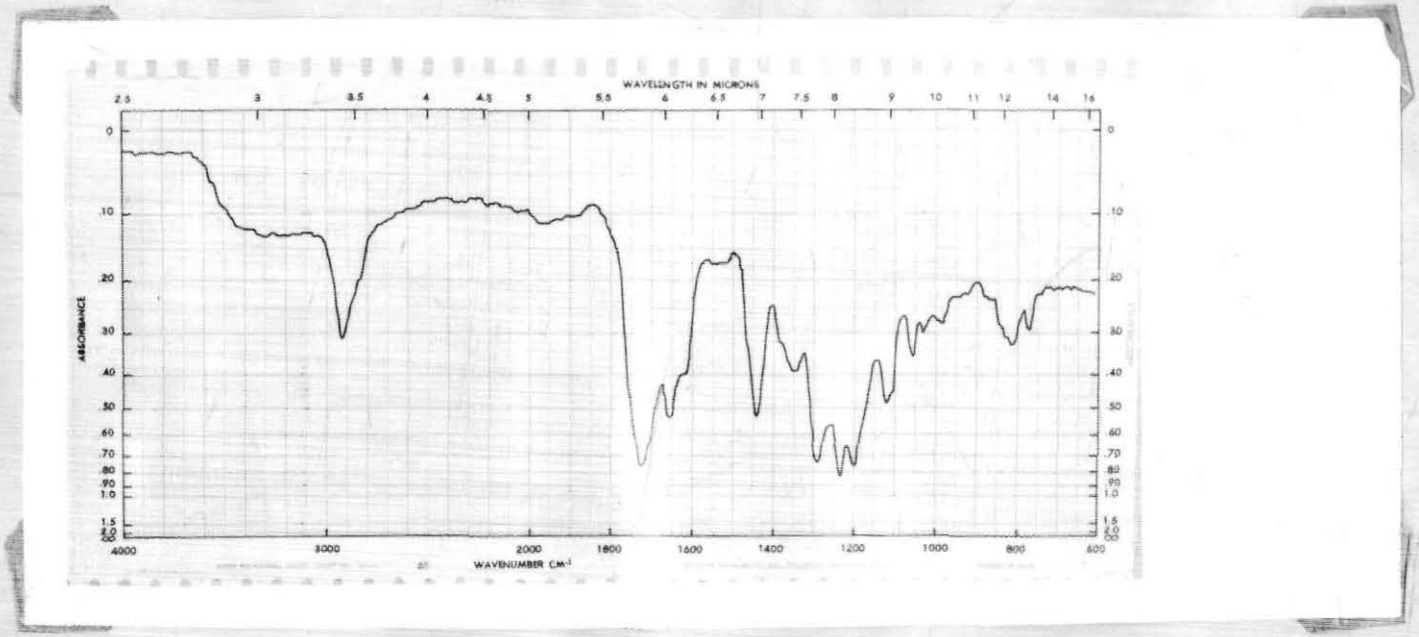


Fig. 5 IR spectrum of 4-methyl-cyclohexanone 2:4 dimethyl dicarboxylate (β-keto ester)

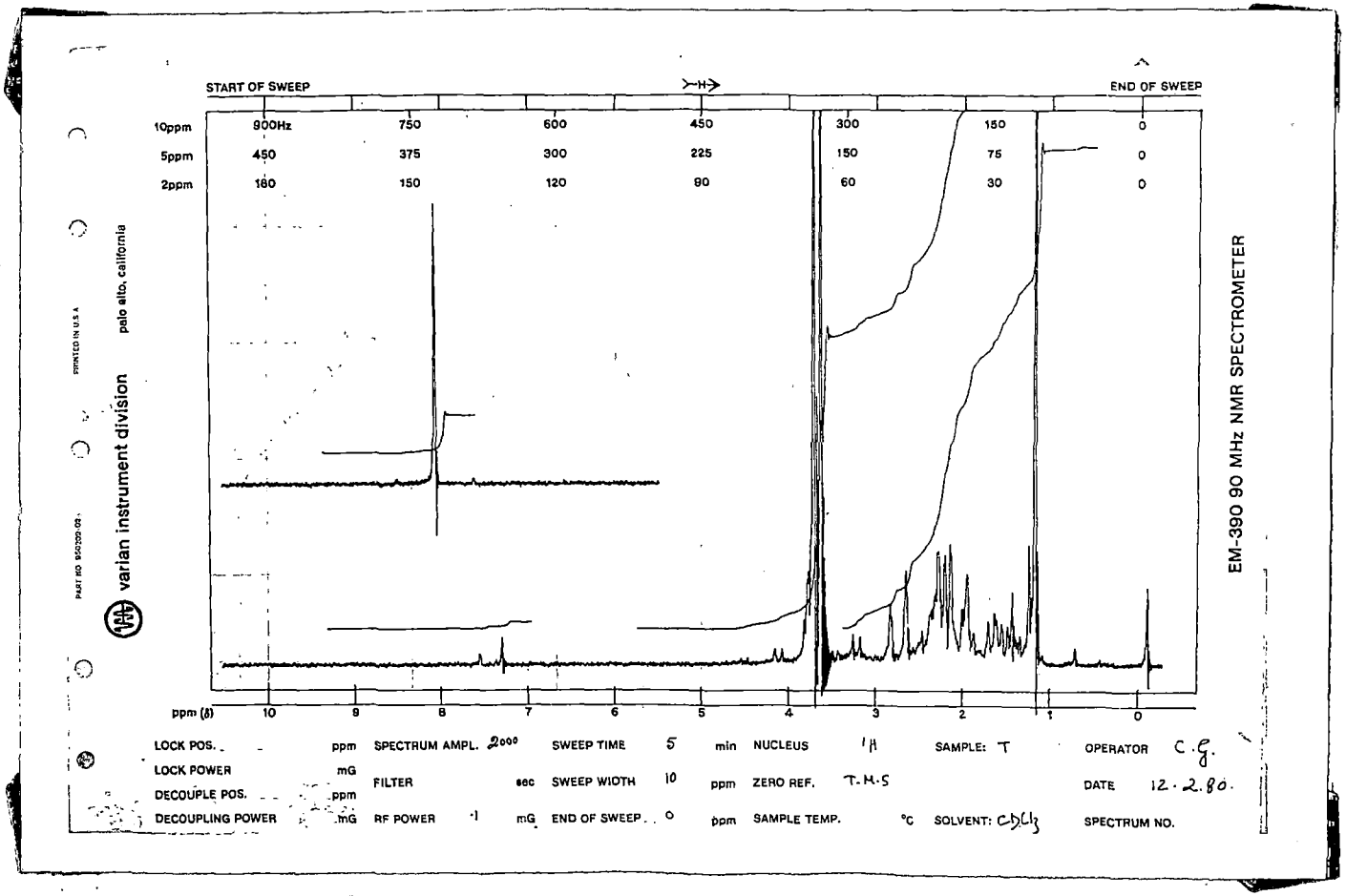


Fig. 6 ^{1}H NMR spectrum of 4-methyl-cyclohexanone 2:4 dimethyl dicarboxylate (β -keto ester)

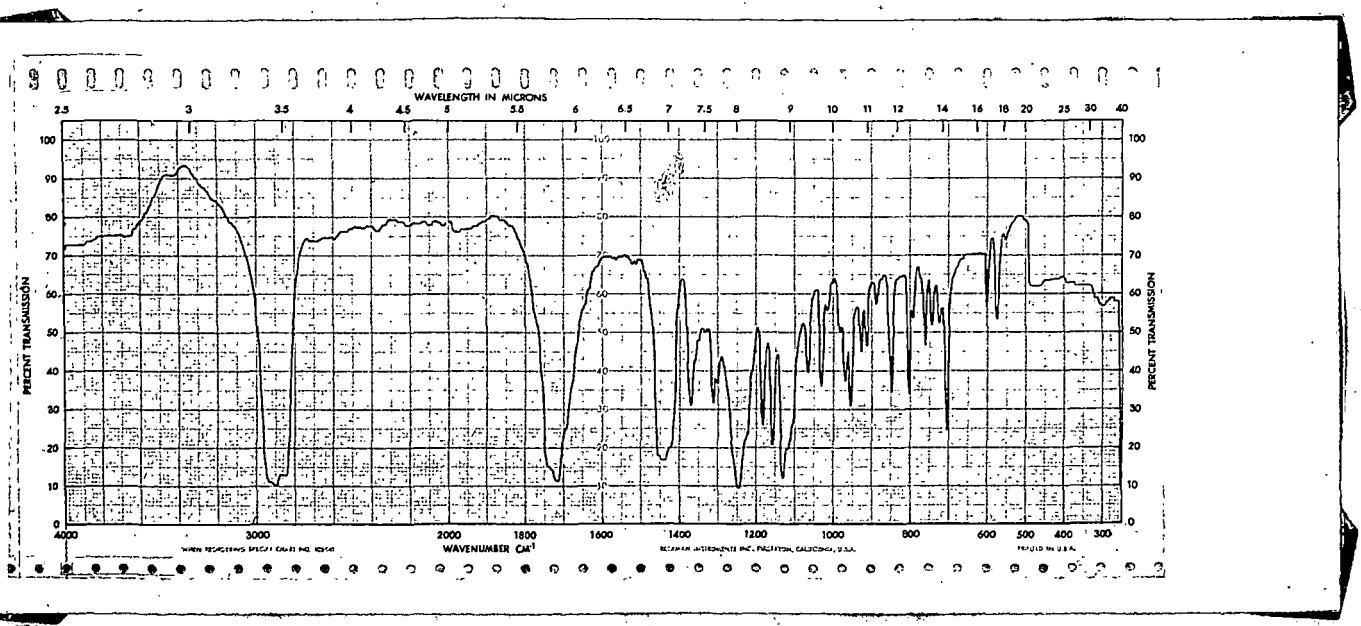


Fig. 7 IR spectrum of 2-chloro-4-methyl cyclohexanone 2:4 dimethyl dicarboxylate (α-chloro keto ester)

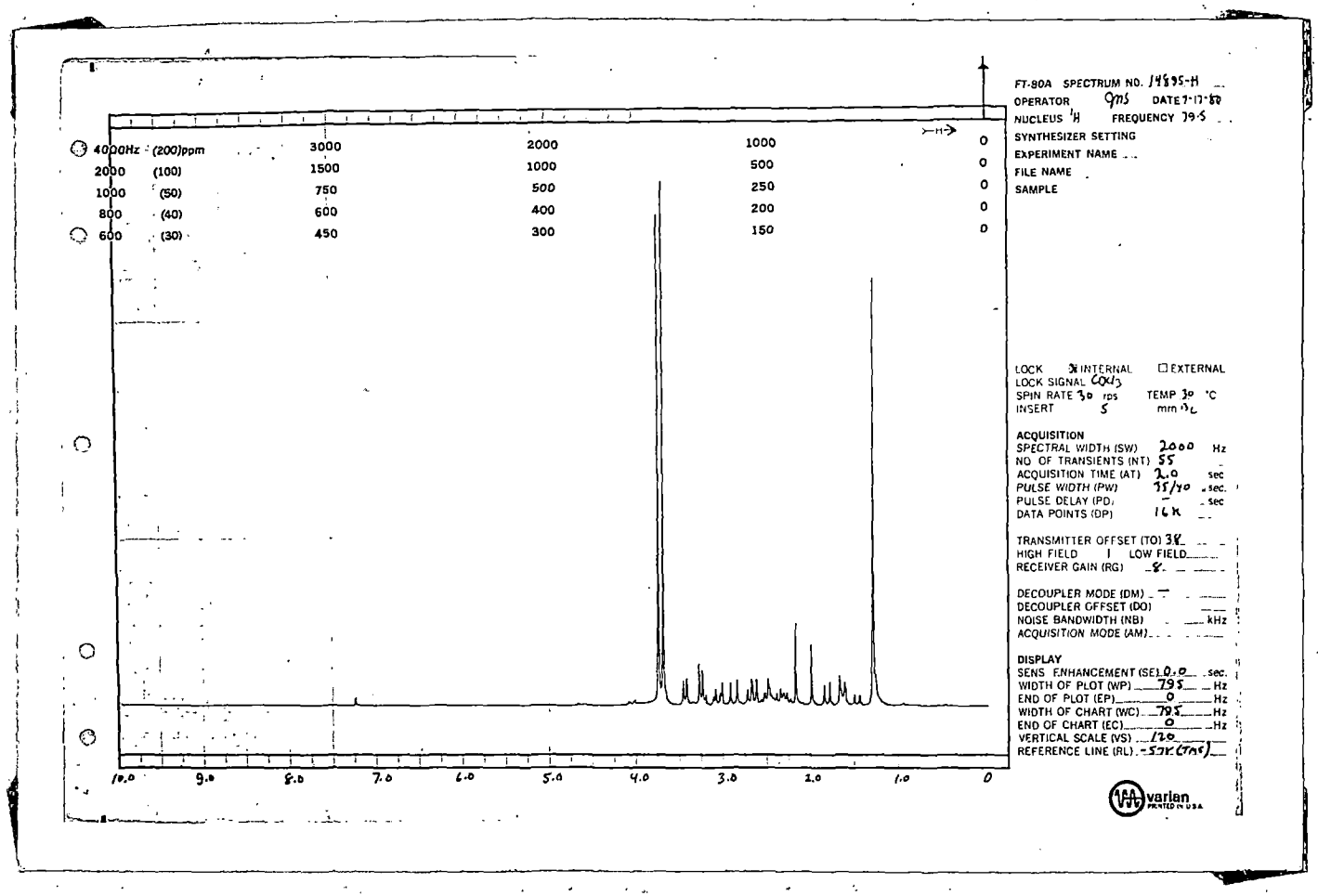


Fig. 8 ^{1}H NMR spectrum of 2-chloro-4 methyl cyclohexanone 2:4 dimethyl dicarboxylate (α-chloro keto ester)

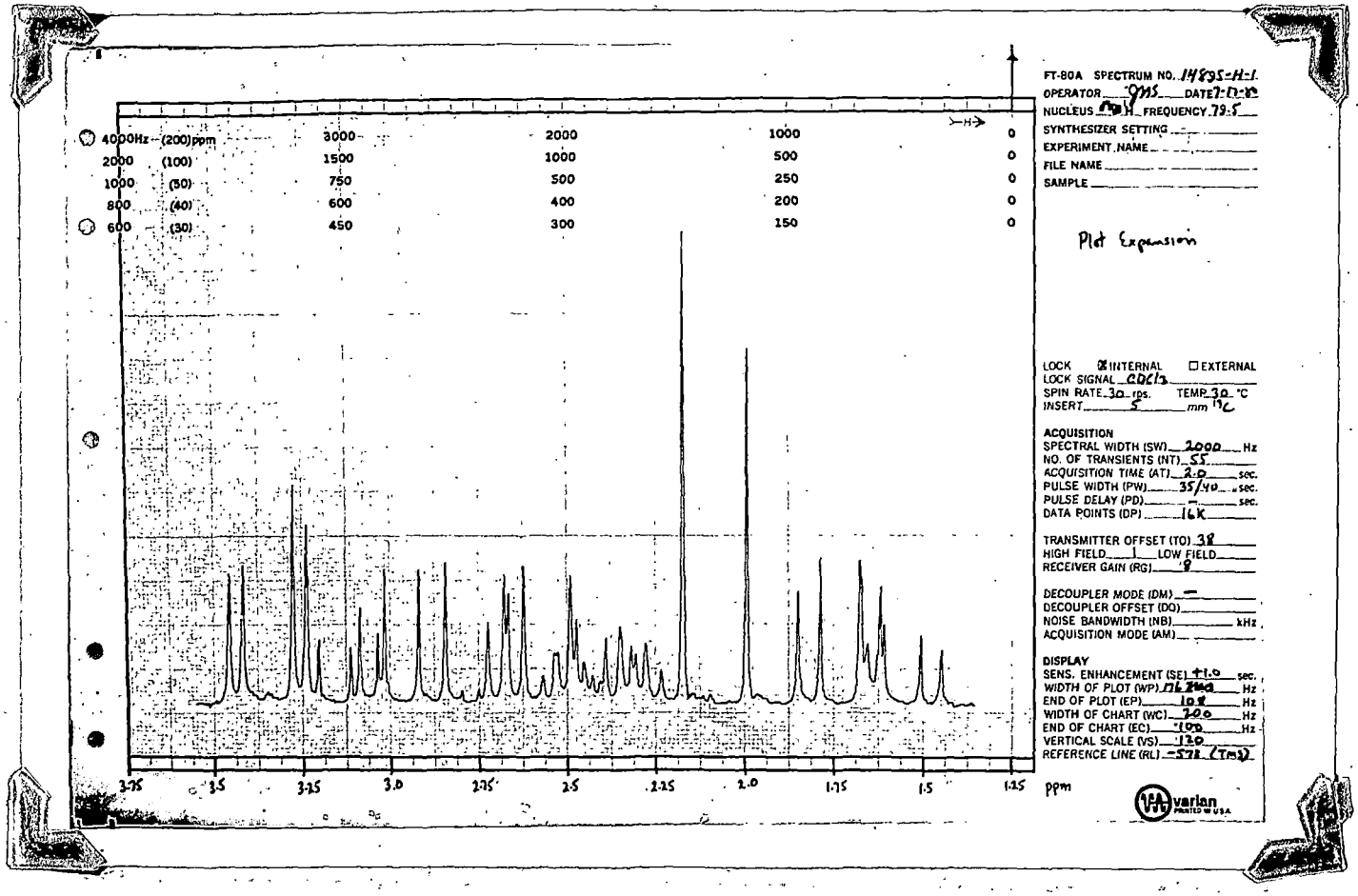


Fig. 9 Plot expanion of ^{1}H NMR spectrum of 2-chloro-4-methyl cyclohexanone 2:4 dimethyl dicarboxylate (α-chloro keto ester)

/ Different degrees of resolution enhancement, using increasing exponential weighing of the FID /

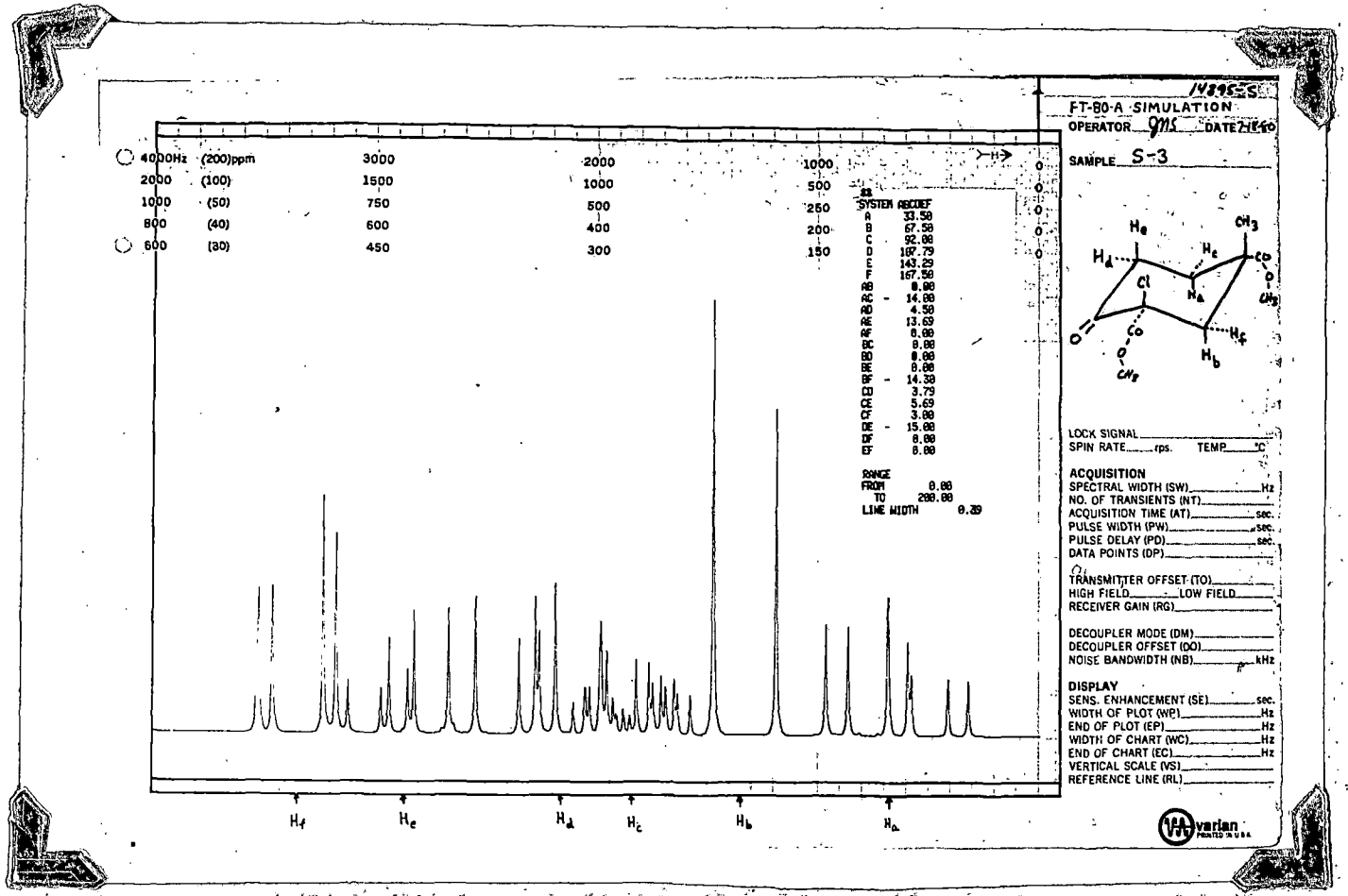


Fig. 10 ^{1}H NMR spectrum of 2-chloro-4-methyl cyclohexanone 2:4 dimethyl dicarboxylate (α-chloro keto ester)

[deducing conformation from coupling constants]

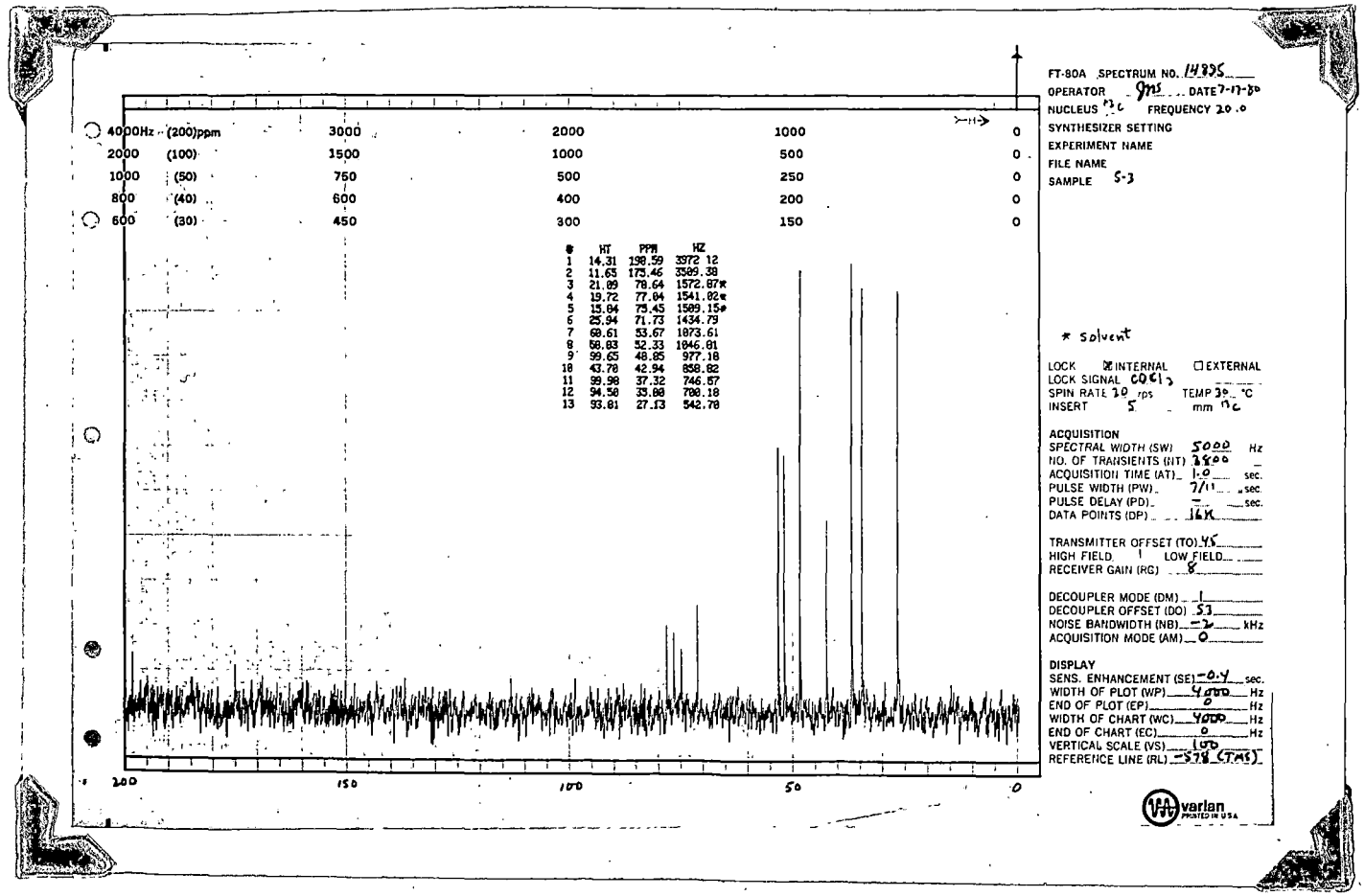


Fig. 11 ^{13}C NMR spectrum of 2-chloro-4-methyl cyclohexanone 2:4 dimethyl dicarboxylate (α-chloro keto ester)

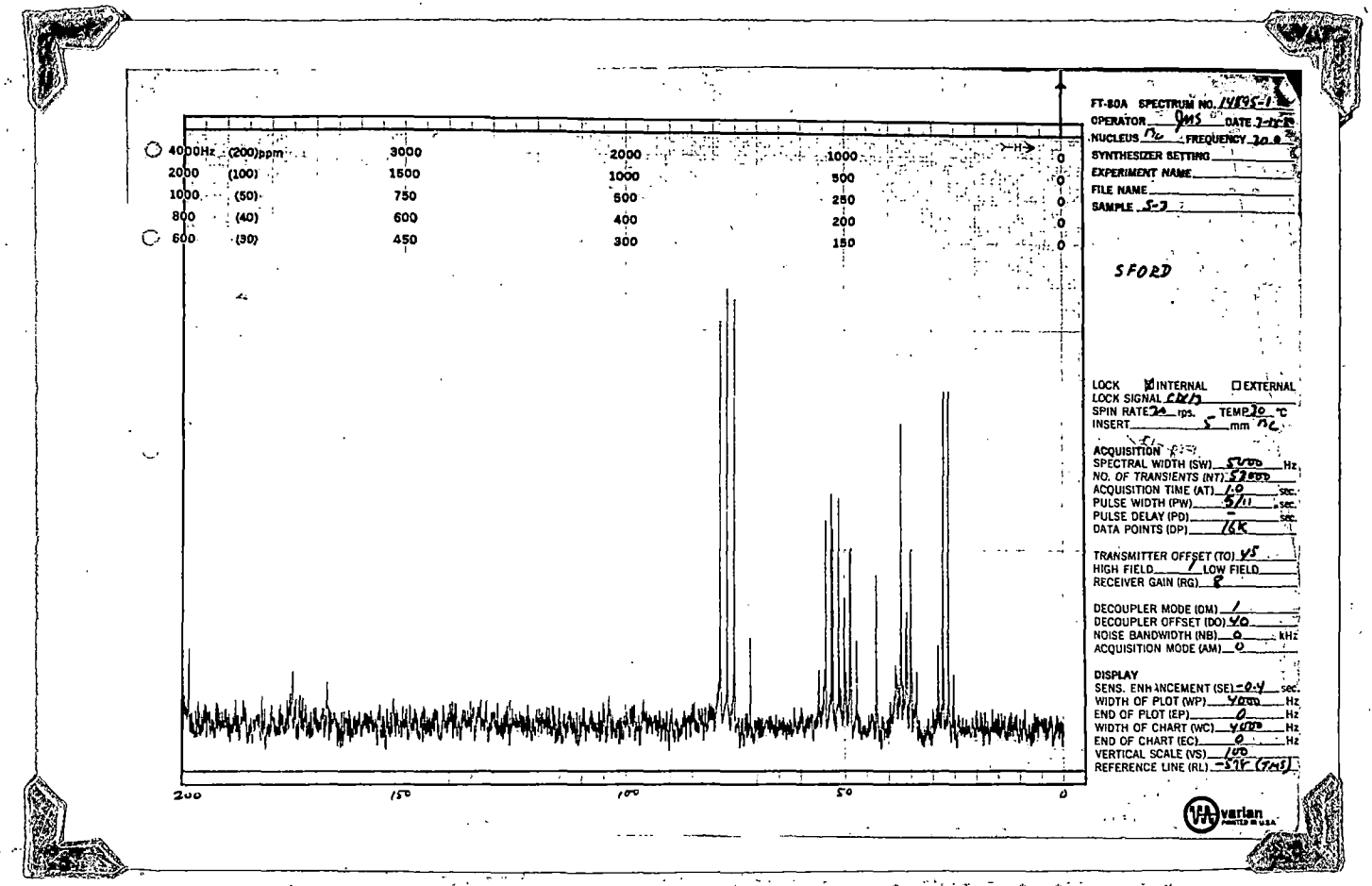


Fig. 12 ^{13}C NMR off-resonance spectrum of 2-chloro-4-methyl cyclohexanone 2:4 dimethyl dicarboxylate (α-chloro keto ester)

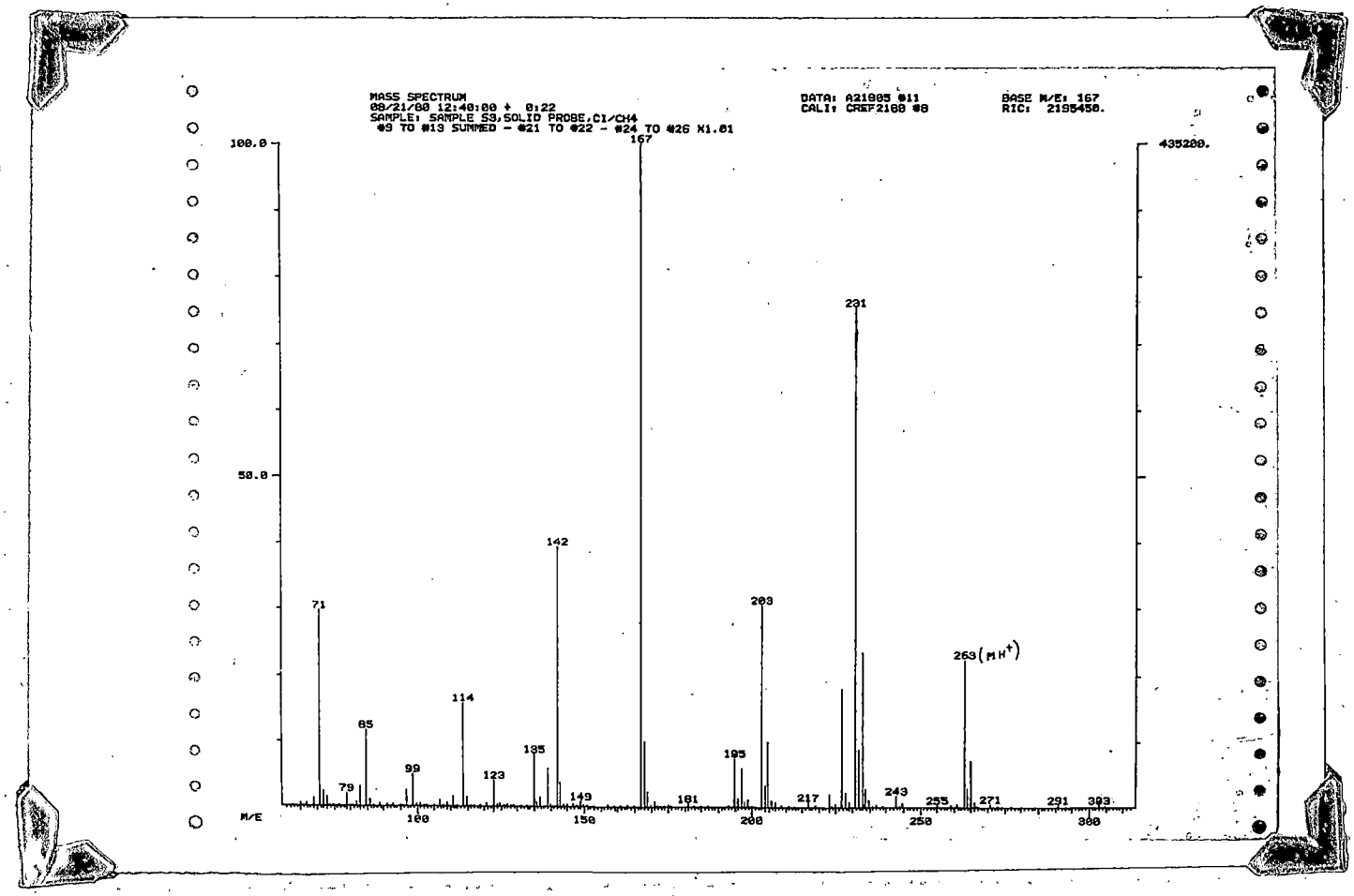


Fig. 13 Mass spectrum of 2-chloro-4-methyl cyclohexanone 2:4 dimethyl dicarboxylate (α -chloro keto ester)

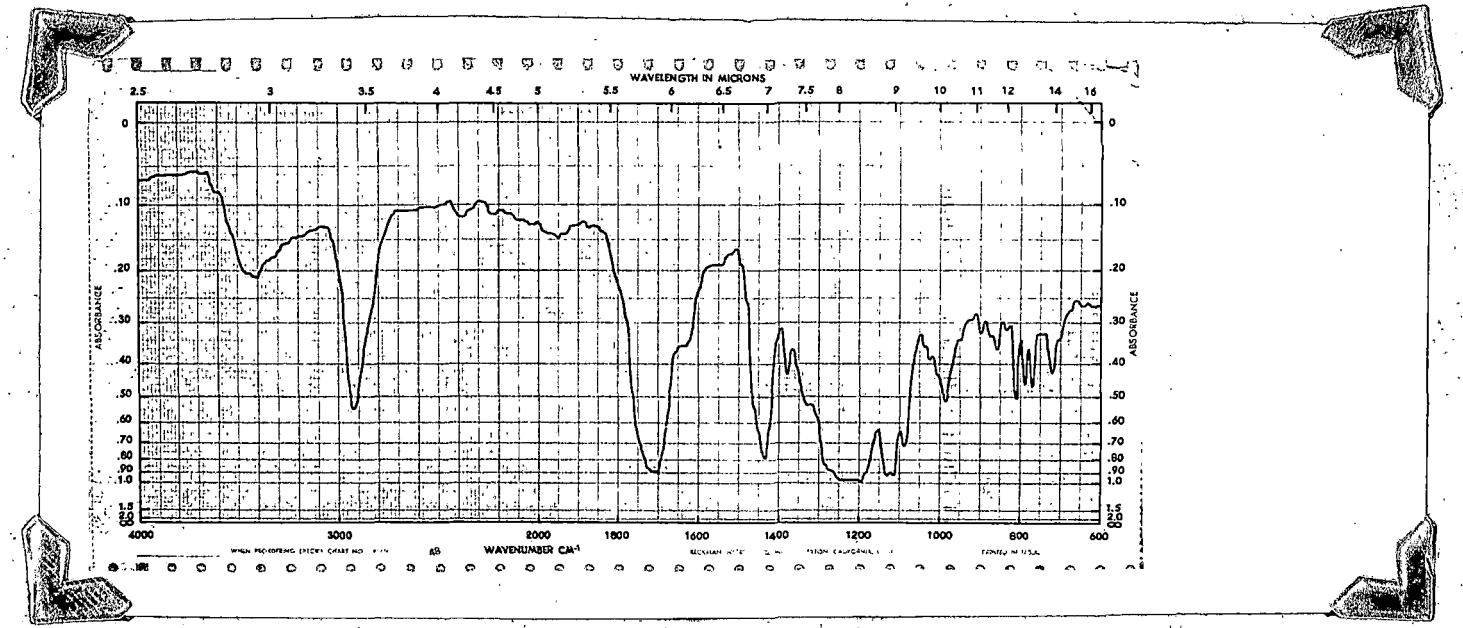


Fig. 14 IR spectra of the products obtained after collidine treatment with 2-chloro-4-methyl-cyclohexanone 2:4 dimethyl dicarboxylate (α-chloro keto ester)

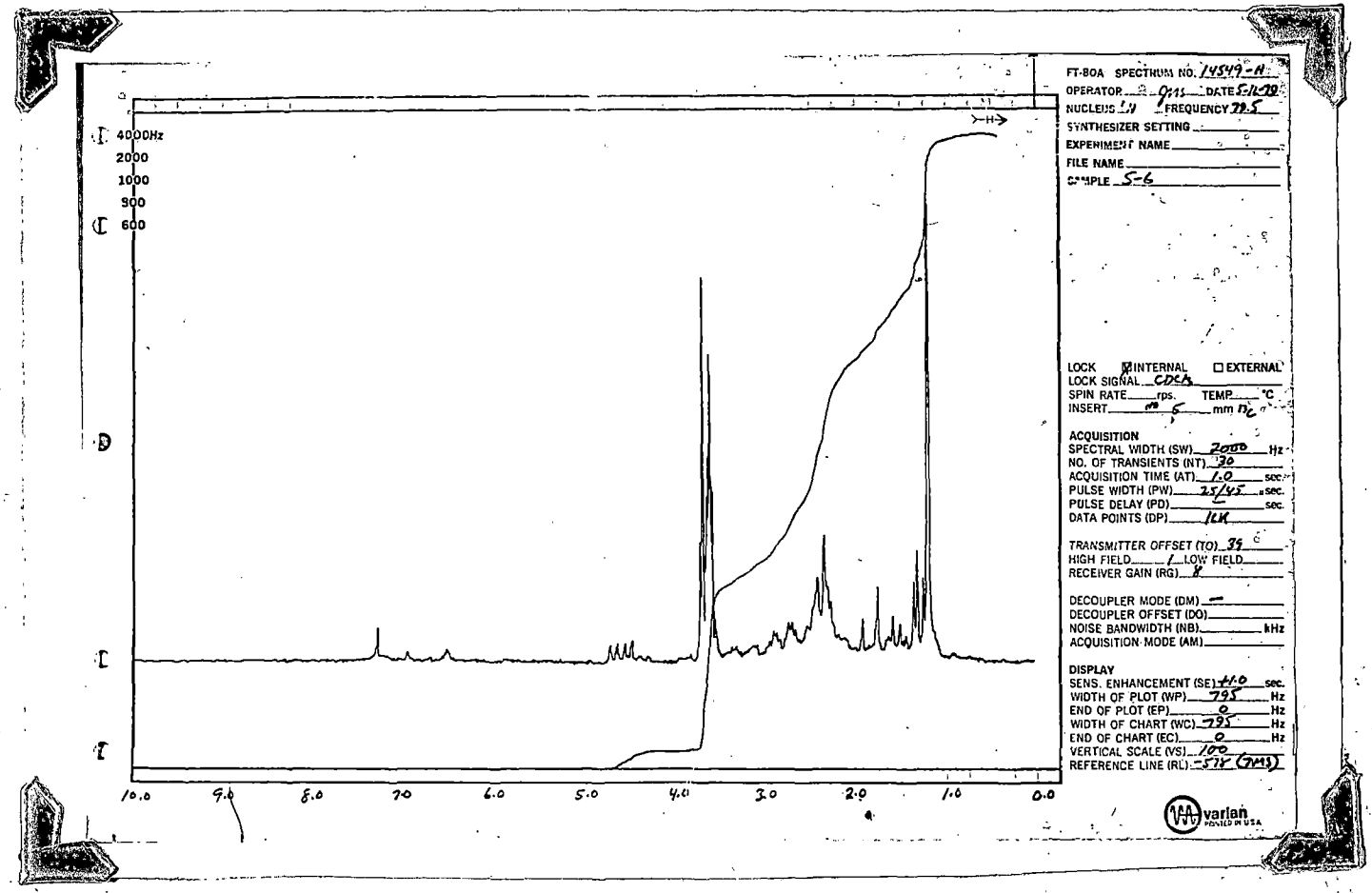


Fig. 15 ^{1}H NMR spectra of the products obtained after collidine treatment with 2-chloro-4-methyl cyclohexanone 2:4 dimethyl dicarboxylate (α-chloro keto ester)

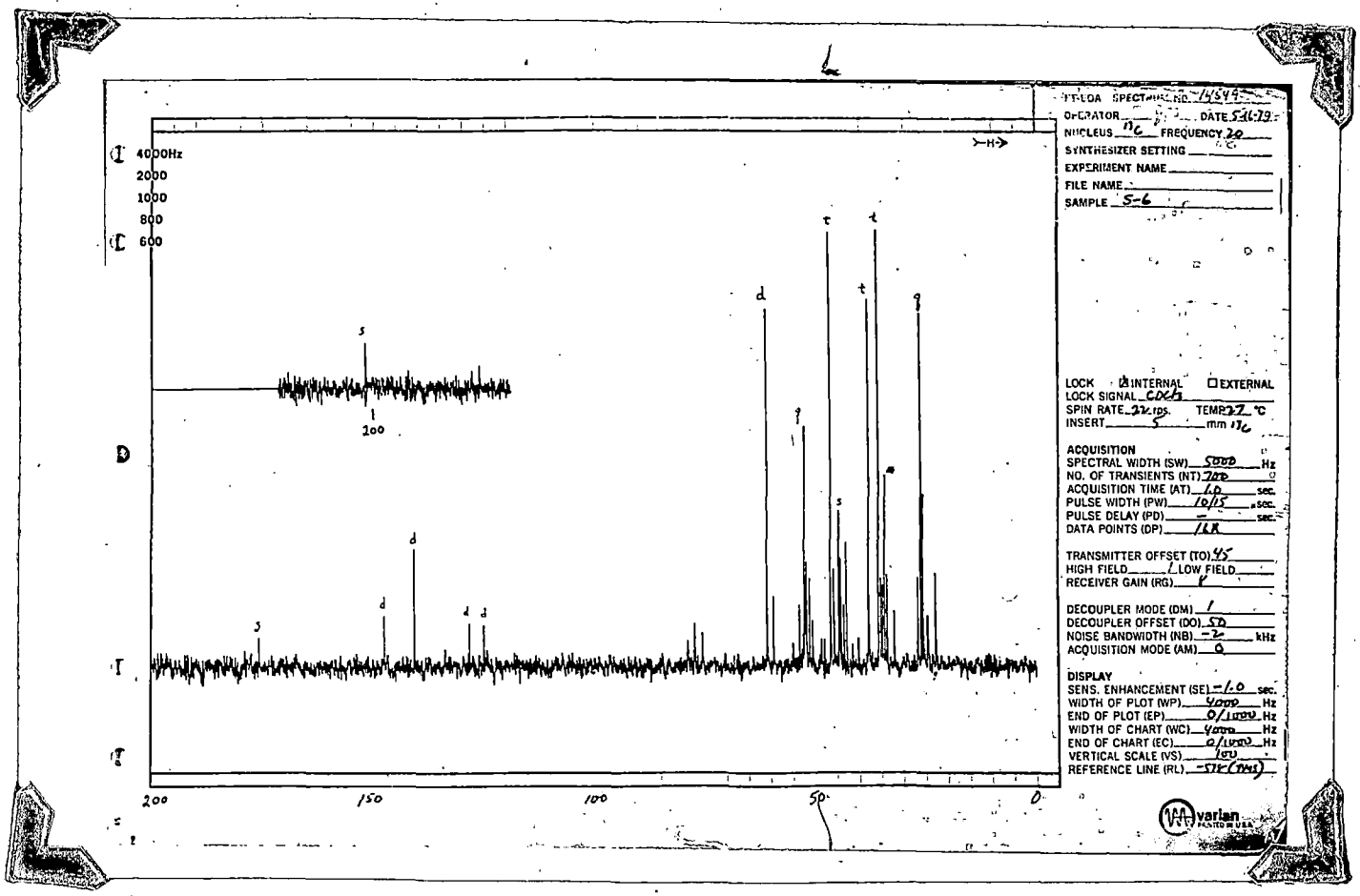


Fig. 16 ^{13}C NMR spectra of the products obtained after collidine treatment with 2-chloro 4-methyl cyclohexanone 2:4 dimethyl dicarboxylate (α-chloro keto ester)

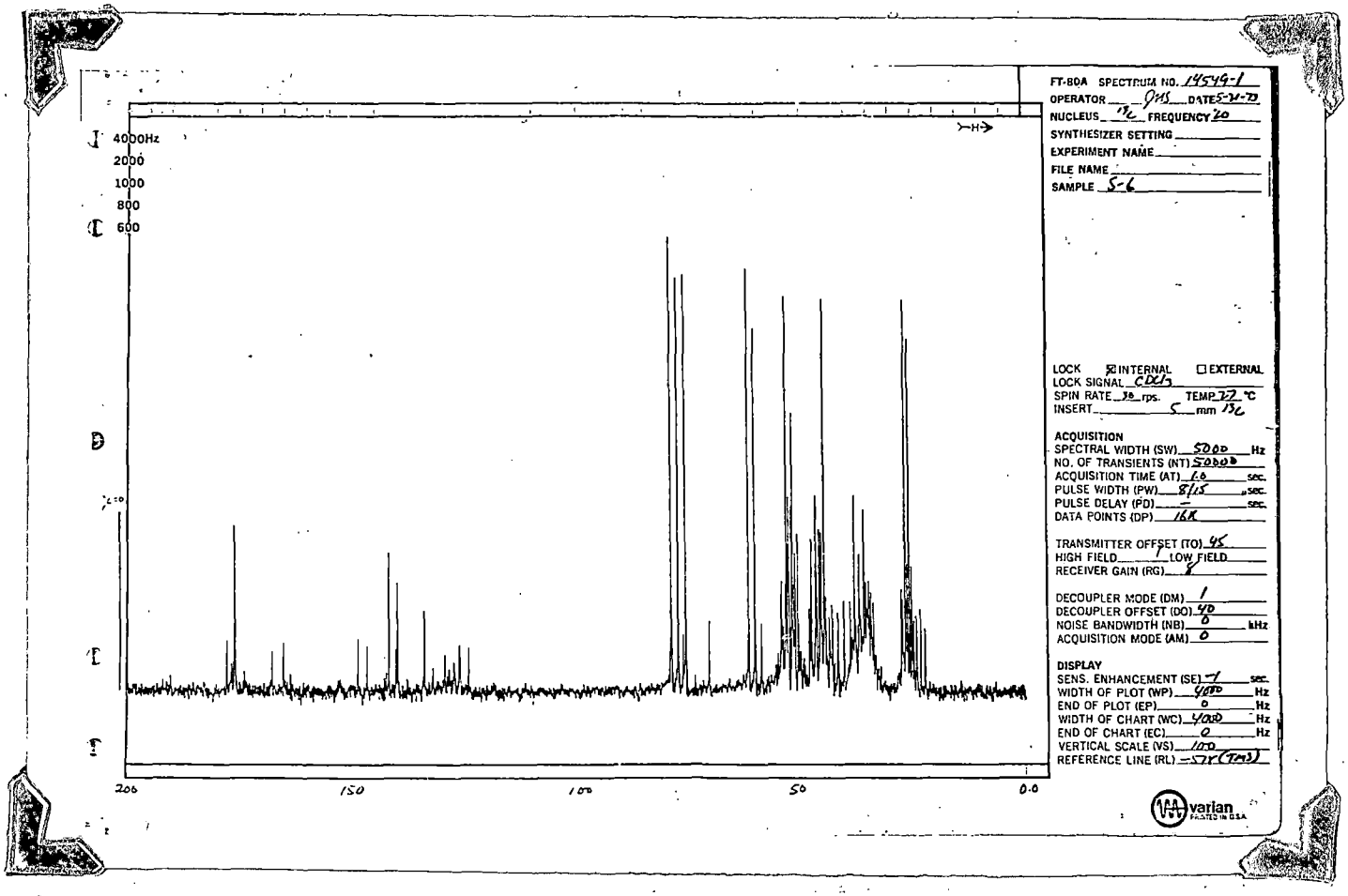


Fig. 17 ^{13}C NMR off-resonance spectrum of the products obtained after collidine treatment with 2-chloro-4-methyl cyclohexanone 2:4 dimethyl dicarboxylate (α-chloro keto ester)

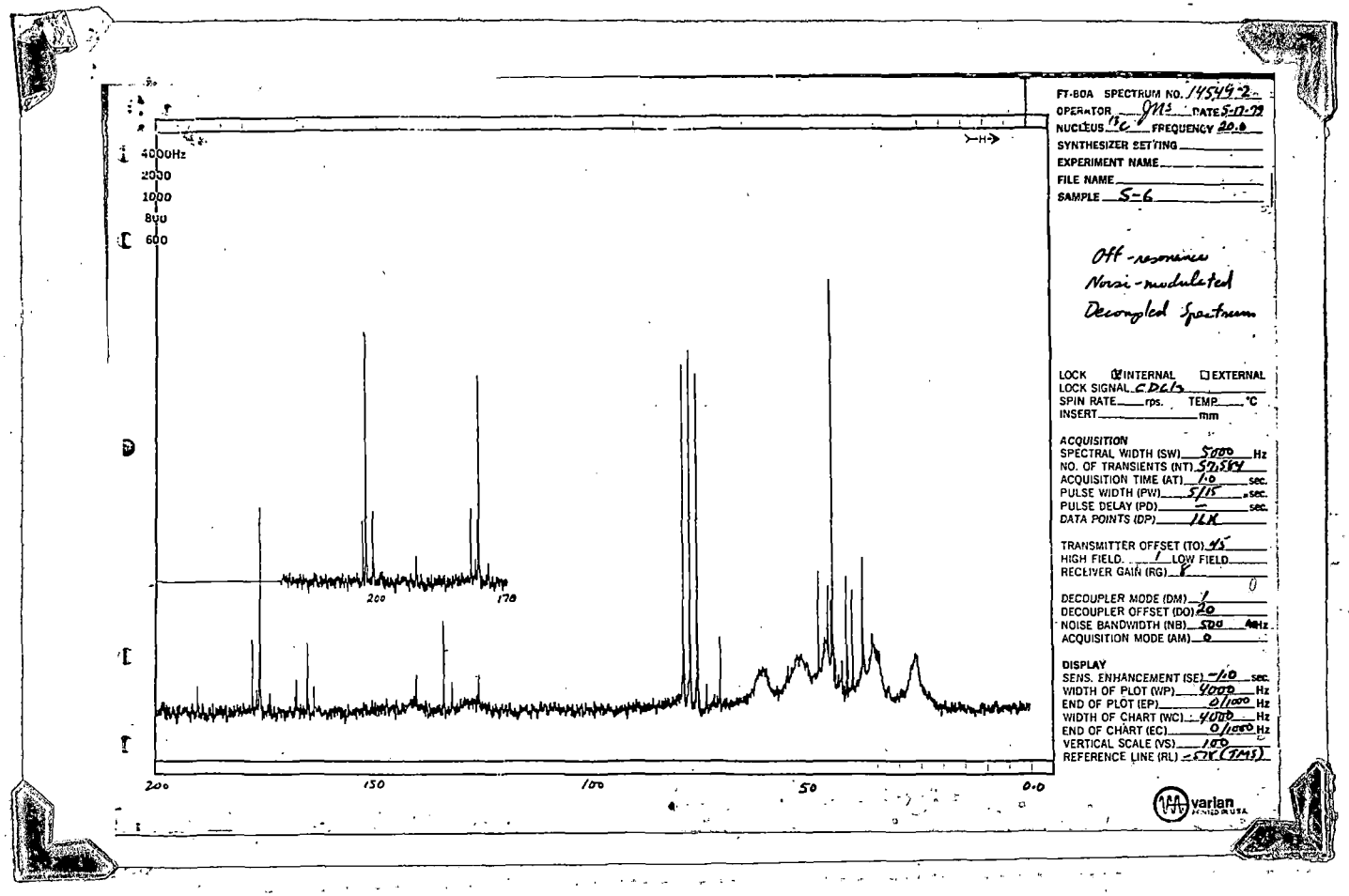


Fig. 18 ^{13}C NMR off-resonance noise modulated decoupled spectrum of the products obtained after collidine treatment with 2-chloro-4-methyl cyclohexanone 2:4 dimethyl dicarboxylate (α-chloro keto ester)

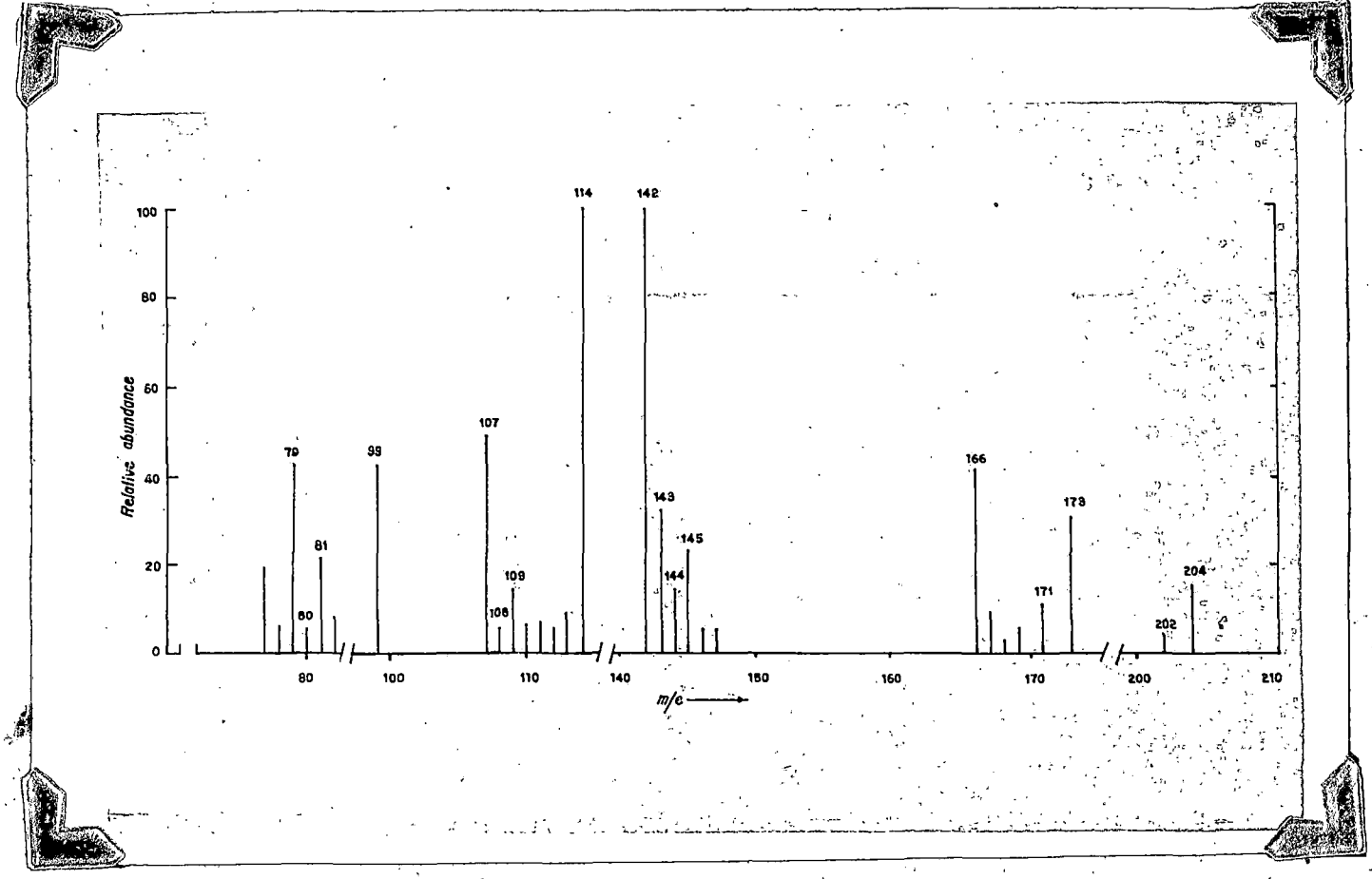


Fig. 19 Mass spectra of the products obtained after collidine treatment with 2-chloro-4-methyl cyclohexanone 2:4 dimethyl dicarboxylate (-chloro keto ester)