

CHAPTER - III

EXPERIMENTAL

Melting and boiling points are uncorrected. All the chemicals were used after distillation in case of liquids. Petrol used throughout had b.p. 60-80°. UV absorption was measured in Beckmann DU-2 Spectrophotometer in methanol solution. IR spectra were recorded in Beckmann IR-20 Spectrophotometer. ^{13}C NMR were recorded on Varian FT-80A Spectrophotometer using chloroform -D solution containing tetramethyl silane as reference. ^1H NMR spectra were recorded on Varian (90 MHz) as well as FT-80A Spectrophotometer using chloroform -D-solution containing tetramethyl silane as reference. The mass spectra were recorded by chemical ionisation method (methane ionisation) as well as by conventional method. Silica gel for column chromatography was of 60-120 mesh (B.D.H). TLC was carried out in Silica gel plate and spots were developed in iodine chamber.

Preparation of 4-acetyl-4-methyl-pimelonitrile-8 by cyanoethylation.

A solution consisting of 160 g freshly redistilled acrylonitrile and 100g distilled tertiary butyl alcohol

was added dropwise during the course of 3 hours to a rapidly stirred ice cold solution of 144g of ethyl methyl ketone, 200g tertiary butyl alcohol and 10g methanolic potassium hydroxide (30% solution). Care being taken that the reaction temperature did not exceed 5°. During the addition a crystalline solid separated. After all the acrylonitrile had been added, the mixture was stirred for 2 hours longer at 5-10°, then filtered by suction while still cold.

After air drying for 24 hours, the product was obtained as an almost white crystalline material.

Yield 239 g (89%)

Upon recrystallisation from benzene, it formed colourless crystals m.p. 67°C

IR: $\left. \begin{array}{l} \text{nujol} \\ \text{max} \end{array} \right\} 2230 \text{ (C} \equiv \text{N stretching), } 1700 \text{ cm}^{-1}$
(C = O stretching) [Fig. 1]

Hydrolysis of 4-acetyl-4-methyl pimelonitrile 8:

Preparation of γ -methyl γ -acetyl pimelic acid 9.

A mixture of crystallised 50g of 4-acetyl-4-methyl pimelonitrile, 400g of distilled water and 39.2g of potassium hydroxide was gradually heated to boiling under reflux (exothermic reaction). Boiling was continued for 3 hours. The product was then evaporated to expel the

ammonia and acidified with hydrochloric acid. The mixture was then evaporated to dryness in a steam bath and the powdered residue was extracted with boiling ethylene dichloride. Upon chilling the extract, 38g of colourless crystals was obtained. After recrystallisation from ethylene dichloride the product had m.p. 125°C .

IR: ν_{max} ^{nujol} 1715 (C = O stretch of -COOH group),
1690 (C = O stretch of -COOH group),
3020-2610 cm^{-1} (broad O-H stretch)

[Fig. 2]

Oxidation of γ methyl γ acetyl pimelic acid 9 by haloform reaction: Preparation of γ carboxy γ methyl pimelic acid 10.

To a 2-litre three necked flask equipped with a dropping funnel, a mechanical stirrer and a thermometer, a solution of 125g of sodium hydroxide in 1050 ml of water was placed in the flask and cooled in a freezing mixture to 0° . 60 ml of bromine was added from the dropping funnel slowly so that the temperature of the stirred solution did not rise above 10° . Now 71g of γ acetyl γ methyl pimelic acid in 200g of 20% sodium hydroxide solution, was added at such a rate that the temperature

was kept below 10° . When addition was complete, the solution became colourless. During addition carbon tetrabromide separated out along with bromoform. The freezing mixture was removed and stirring was continued for 1.5 hours at room temperature. Carbon tetrabromide was removed by filtration as far as possible and the filtrate was steam distilled for 4 hours to remove bromoform and traces of carbon tetrabromide.

The contents of the flask were cooled and acidified with hydrochloric acid. The solution acquired a very pale yellow colour; a little sodium sulphite was added till it became colourless. The clear solution was then evaporated on a steam bath under reduced pressure. The solid residue was extracted with hot acetone in a Soxhlet apparatus for 24 hours. Upon evaporation of acetone, the viscous syrup set into solid mass. This was crystallised from nitromethane to give crystals of γ carboxyl - γ methyl pimelic acid m.p. $111-12^{\circ}$ on drying over phosphorous pentoxide.

Yield = 60g (86% approx)

Esterification of γ carboxy γ methyl pimelic acid 10 with diazomethane : Preparation of γ methyl γ carbomethoxy dimethyl pimelate 11.

To an ethereal solution of 45g of γ carboxy γ methyl pimelic acid was added a well cooled solution of excess diazomethane in ether (prepared from 75g of nitrosomethyl urea). The reaction mixture was kept cooled overnight. Next day excess of diazomethane was destroyed by adding acetic acid. The ethereal solution was washed with water till neutral, then with 5% sodium bicarbonate solution and then water till neutral and finally dried over anhydrous sodium sulphate. Evaporation of ether yielded the crude triester. This was distilled when γ methyl γ carbomethoxy dimethyl pimelate b.p. $170-172^{\circ}$ at 4.5 mm of Hg distilled over.

Yield 38g (84%)

Found C = 55.25%; H = 7.63%

$C_{12}H_{20}O_6$ required C = 55.37%; H = 7.74%

IR: ν_{\max} 1720 cm^{-1} ($\text{C}=\text{O}$ stretch of carbomethoxy group)

[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 two β methylene protons respectively with respect to terminal methoxy groups and 3.65 ppm for the three carbomethoxy groups.

[Fig. 4]

Dieckmann condensation of γ methyl γ carbomethoxy dimethyl pimelate 11: Preparation of 4-methyl cyclohexanone 2:4 dimethyl dicarboxylate 12.

A small portion (3g) of γ methyl γ carbomethoxy dimethyl pimelate (30g) was added to refluxing A.R. dried benzene (300 ml) suspension of sodium hydride (12g) in an atmosphere of nitrogen. After the reaction started ($\frac{1}{2}$ hour) the rest of the triester was slowly added and the refluxing continued for 4 hours. The cooled reaction mixture was decomposed with cold dilute hydrochloric acid under nitrogen atmosphere. The organic layer was separated and washed successively with water, ice cold sodium bicarbonate and water. The solvent was removed and the residue distilled to give the β keto ester 12 b.p. 132-35° at 2.5 mm of Hg. yield 25g. It produced intense violet colour with neutral ferric chloride solution.

Found	C, 57.62%; H, 7.1%
$C_{11}H_{16}O_5$ required	C, 57.89%; H, 7.07%

IR: ν_{\max} 2940 (intramolecular hydrogen bonding between the ester $C=O$ and the enolic hydroxyl group), 1735 cm^{-1} ($C=O$ stretch of carbomethoxy group).

[Fig. 5]

$^1\text{H NMR}$ (90 MHz): 1.2 [s, 3H, CH_3 (tertiary)], 2.4 (multiplet, CH_2 proton adjacent to $C=O$ group), 3.22 (multiplet CH adjacent to carbonyl group and $-\text{CO}_2\text{Me}$ group bearing carbon atom), 3.65 ($-\text{CO}_2\text{Me}$ gr. attached to carbon bearing methyl group), 3.72 ($-\text{CO}_2\text{Me}$ gr. adjacent to carbonyl gr), 2.75 (for $-\text{CH}_2$ protons at C-3) and 2.09 ppm (for $-\text{CH}_2$ protons at C-5).

[Fig. 6]

Preparation of 2-chloro-4-methyl cyclohexanone 2:4 dimethyl dicarboxylate 13.

In a 250 ml three necked flask 10.4 g of 4-methyl cyclohexanone 2:4 dimethyl dicarboxylate (β -keto ester) dissolved in 35 ml dry carbon tetrachloride was taken. Then a solution of freshly distilled sulfuryl chloride (13g) in 30 ml dry carbon tetrachloride was added dropwise for 1 hour and the temperature kept at 20°. One neck of the flask was fitted with stopper and the other was fitted with fused calcium chloride guard tube. The mixture was magnetically stirred at room temperature for 6 hours. After short induction of sulfuryl chloride, evolution of sulphur dioxide occurred.

The reaction mixture was washed with water and cautiously with 5% sodium bicarbonate and then with saturated brine and finally dried over anhydrous sodium sulphate to afford the crude chloro keto ester 13 (solid) yield 10g.

Chromatography of the crude chloro keto ester (4g)

A column of 100g silica gel was developed with petrol. 4g of the compound being dissolved in minimum volume of benzene was poured over the column and eluted with the following solvents:

Table - 1

Eluent	Fractions 75 ml	Residue on evaporation	Melting point °C
Petrol	1-10	Oil	
Petrol	11-17	Solid	90-95°

Further elution was not carried out because the solid m.p. 90-95°, gave positive Beilstein test for halogens. This was crystallised from methanol thrice to afford colourless needle shaped crystals m.p. 100°C. TLC showed it to be homogeneous.

	C%	H%	Cl %
Found	49.89	5.74	11.45
Required for $C_{11}H_{15}O_6Cl$	50.2	5.7	11.65

IR: $\left. \begin{array}{l} \text{nujol} \\ \text{max} \end{array} \right\} 1720 \text{ cm}^{-1}$ (C = O stretch of carbomethoxy group).

[Fig. 7]

^1H NMR: 1.25 (s, 3H, tert. CH_3), 3.67 (s, 3H, COOCH_3), 3.72 (s, 3H, COOCH_3) [Fig. 8],
3.04 (q, 1H, C-6- H_e), 2.59 (m, 1H, C-6- H_d),
1.67 (q, 1H, C-5- H_a), 2.4 (m, 1H, C-5- H_c)
2.09 (d, 1H, C-3- H_b), 3.34 (q, 1H, C-3- H_f) PPM

$\frac{1}{2}$ [Figs. 9, 10]

^{13}C NMR: 198.59 (s, C = O), 175.46, 167 (s, 2 COOMe), 27.13 (q, tert. CH_3), 52.33 and 53.67 (q, 2 COOCH_3), 71.73 (s, C-Cl), 35 (t, C-3) 42.94 (s, C-4), 37.32 (t, C-5), 48.85 (t, C-6).

[Figs. 11, 12]

Mass $^+$ MH (263), m/e 231, 203, 167, 142, 114, 99, 85, 79, 71.

[Fig. 13]

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

The α chloro keto ester 13 (3.5g) 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. The reaction mixture was then heated on an oil bath. As soon as the temperature of the reaction mixture reached 145-150^o, 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 reaction 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 and purified by repeated boiling on benzene and 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, then with one 100 ml portion saturated salt solution which was ultimately dried over anhydrous sodium sulphate. Benzene was removed by distillation through a 15 cm Vigreux column and 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. TLC showed three spots with one spot prominent. It gave positive Beilstein test for halogens.

UV: $\lambda_{\text{max}}^{\text{MeOH}}$ 231 and 247 nm

IR: ν_{max} 1720-1730 (due to carbomethoxy and carbonyl group) cm^{-1}

[Fig. 19]

Analysis of collidine N-Methyl chloride

	%C	%H	%N	%Cl
Found :	63.8	7.99	8.4	19.8
C ₉ H ₁₄ NCl requires	63.15	8.18	8.18	20.46

Analysis of liquid mixture

	%C	%H	%Cl	
Found :	54.02	7.01	16.5	

¹H NMR(80 MHz): 1.22 (3H, CH₃), 3.7 (3H, -COOCH₃)
4.6 (pair of doublets CH bonded to chlorine ortho to carbonyl group)
1.75 (triplets C-6-CH₂ J = 13 Hz)
2.8 (triplet C-C-CH₂ J = 12Hz with C-3, axial H, J = 6Hz with C-2, axial H) ppm.

[Fig. 15]

^{13}C NMR (80 MHz)

202 (s, $\text{C}=\text{O}$), 176 (s, COOCH_3), 61 (d , $\text{C}-\text{Cl}$),

52.4 (q, COOCH_3), 47 (t, $\text{C}-\text{CH}_2$),

44.8 (s, $\text{C}-4$), 38 (t, $\text{C}-5$, CH_2), 26.4 (q, CH_3) ppm

[Figs. 16 and 17]

Mass

M^+ = 204, m/e 173, 145, 144, 109, 108, 81, 80, 79

M^+ = 202, m/e 171, 166, 143, 142, 114, 107, 99, 79.

[Fig. 19]