CHAPTER - II

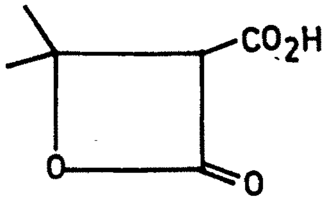
ALKYLATION STUDIES WITH MELDRUM'S ACID.

CHAPTER - II

INTRODUCTION :

Discovery and application of new reagents has been one of the most fascinating aspects of synthetic organic Chemistry. Recently **Meldrum's** acid (1.2) has attracted much attention as a versatile synthon[1] in organic synthesis. Our attention was focussed on Meldrum's acid by its high acidity (pk 4.83), ease with which it undergoes a variety of reactions and the possibility that it could serve as an attractive alternative to malonic esters in organic syntheses.[2-5]

The preparation of "Meldrum's acid" was reported by Meldrum in 1908 by the condensation of malonic acid with acetone in acetic anhydride containing a small amount of sulphuric acid.[6] The white crystalline product obtained ($C_6H_8O_4$) was acidic and lost carbon dixide on heating. Meldrum suggested that the compound should have structure (1.1). In 1948 Davidson and Bernhard suggested that the condensation must involve the two carboxyl groups of malonic acid and the structure assigned by Meldrum was incorrect.[7] They assigned the correct structure to Meldrum's acid as 2,2-dimethyl-1, 3-dioxan-4, 6dione (1.2), whose properties, therefore, can be compared to those of other cylic 1, 3-diones such as dimedone (1.3) and barbituric acid (1.4).



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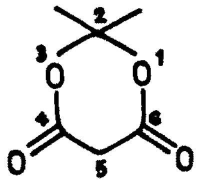

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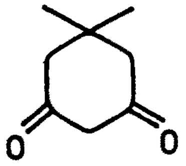

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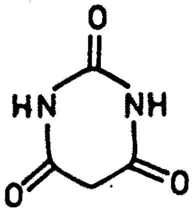

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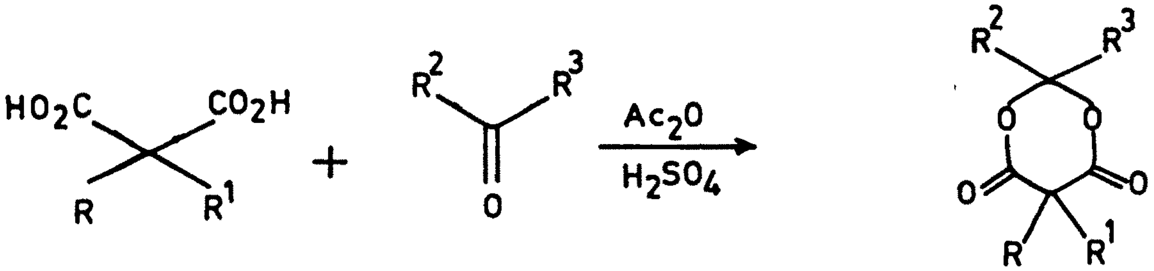

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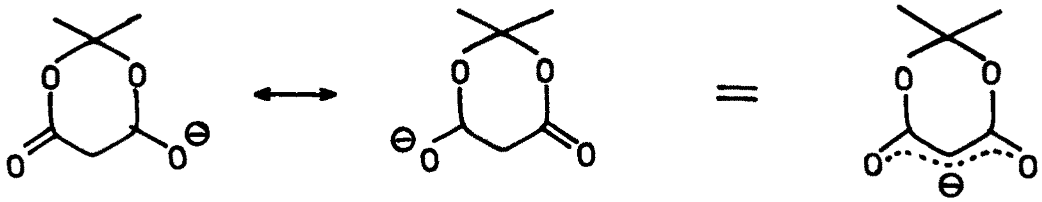

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CHART-1

PREPARATION :

Meldrum's acid is prepared in about 50% yield by the reaction of malonic acid and acetone with either acetic anhydride[6] or isopropenyl acetate[7], in each case, in the presence of a catalytic amount of sulphuric acid (1.5 → 1.6). An alternative and unusual preparation of Meldrum's acid is from the action of carbon suboxide on acetone in the presence of oxalic acid.[8] The role of the latter may be to supply the elements of water needed for the stoicheiometry[9].

The derivatives of Meldrum's acid have been prepared by condensation of aliphatic[10] or aromatic ketones,[11] or aryl aldehydes[12] with unsubstituted, monosubstituted,[10,13] or disubstituted[7,14] malonic acids. The reaction is inapplicable for all alkyl aldehydes.

The mechanism of the reaction has not been investigated although it has been recognised that the first step involves acid catalysed formation of a mixed anhydride of malonic and acetic acids.[13,15]

Reactions with nucleophiles

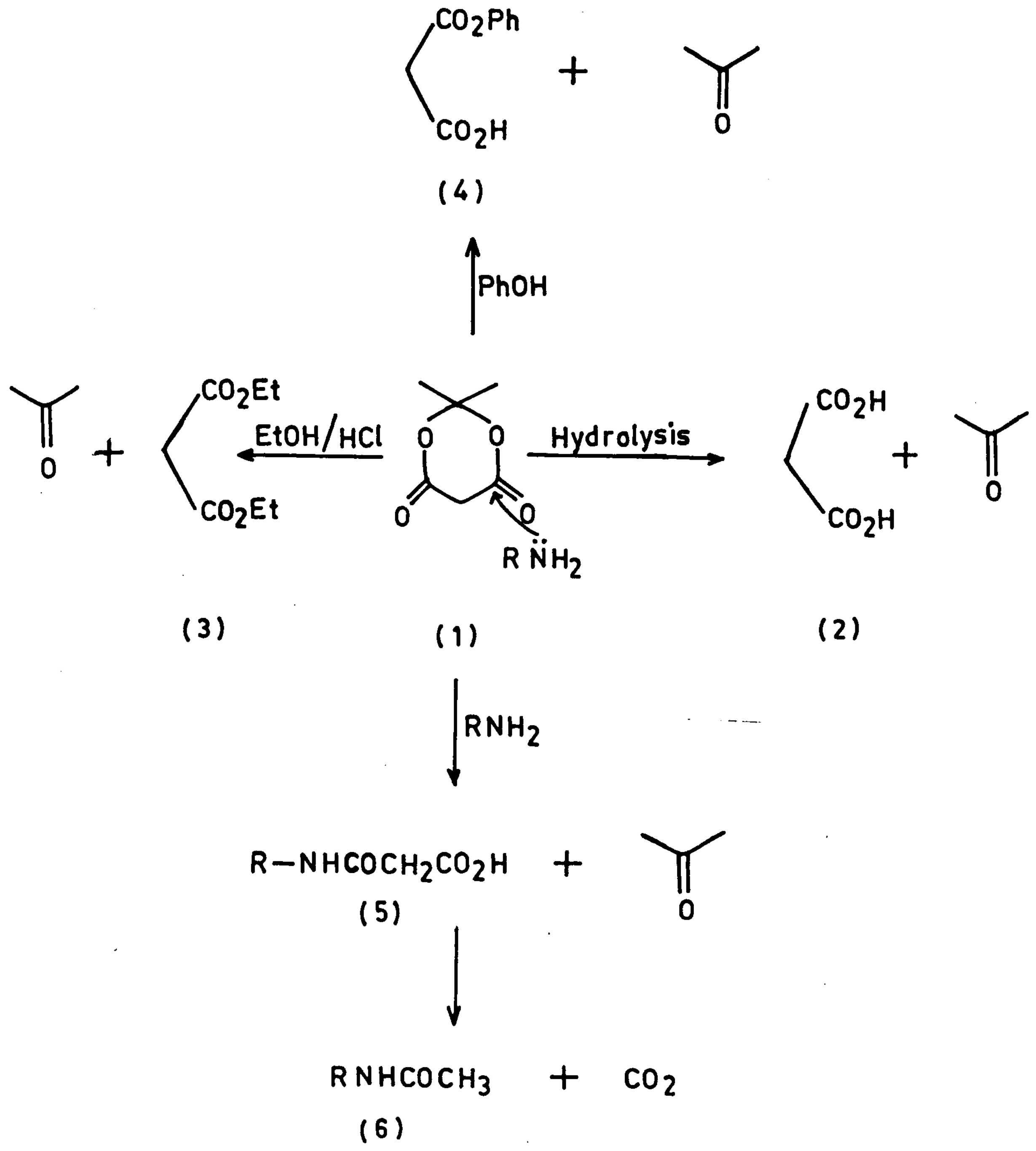

CHART-2

Properties :

Meldrum's acid (pK 4.83)[16] is a strong carbon acid comparable in strength to acetic acid (pK 4.76) and is around ten pK units more acidic than acylic malonate esters. This can be explained as with dimedone (pK 5.2)[7] on the basis of the stability of the resultant anion (1.7) in which the π-orbitals are rigidly held in the ideal configuration for overlap. The tautomeric properties of dimedone and Meldrum's acid are quite different, the former exists predominatly in the mono-enol form, whereas the latter is the diketo tautomer ($>$ 99.5%)[17]. This is not surprising since esters are generally enolized to a much smaller extent than Ketones.[18]

Then conformation of 1, 3-dioxan-4,6-dione system has been studied by n.m.r.[19], dipole moment measurements.[20] and X-ray crystallography.[21] The majority opinion favours a boat structure for most derivatives, with a chair structure for 2, 2, 5,5-tetrasubstituted compounds. Other physical properties of the system which have been sutdied include u.v.[10], i.r.[22], mass,[23] ^{1}H-n.m.r.[24] and ^{13}C-n.m.r.[25]

The chemistry of Meldrum's acid is dominated by its susceptibility to nucleophilic attack at positions

Reactions with electrophiles

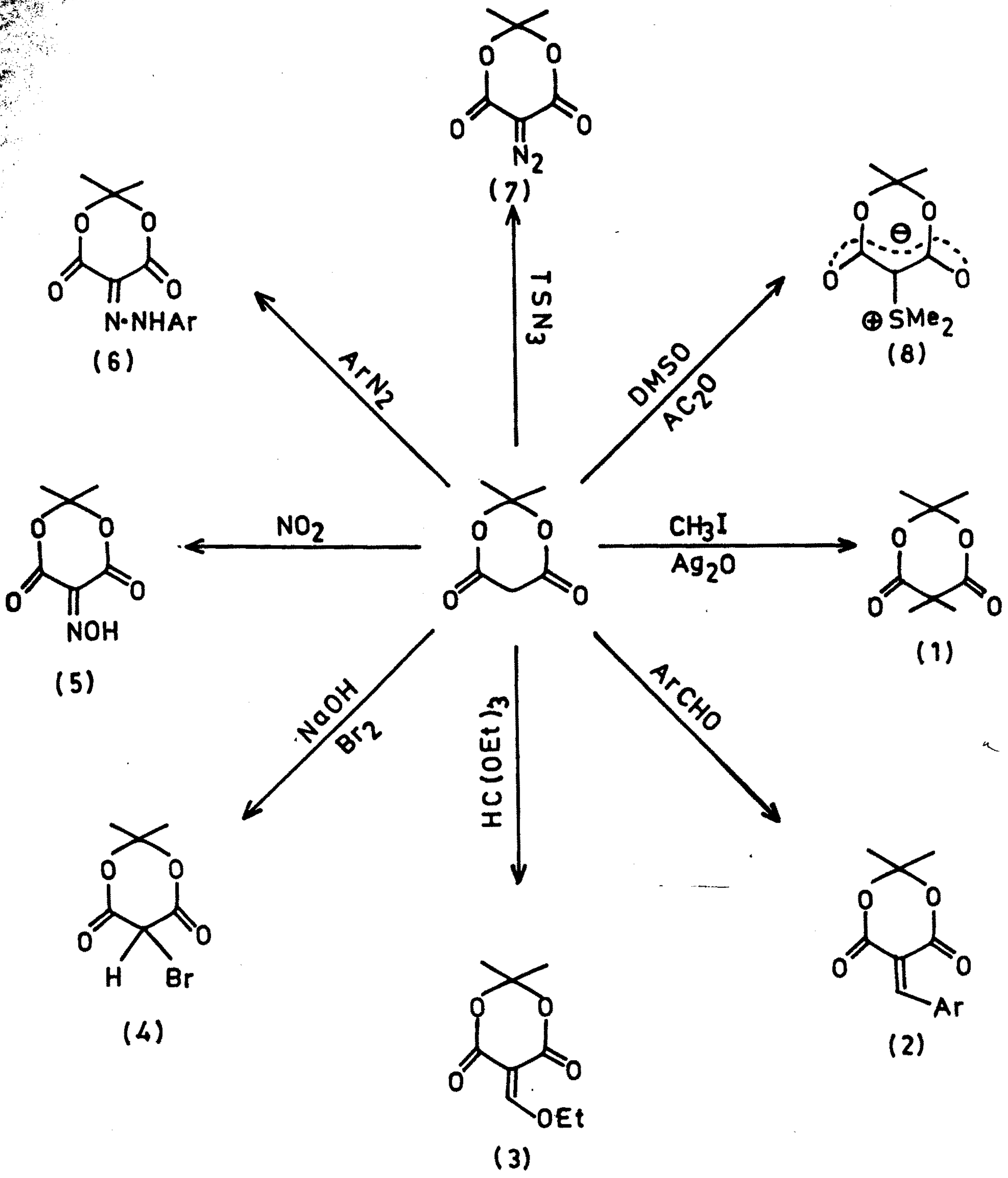

CHART-3

4 and 6 and to electrophilic attack (via the anion) at position 5. Acid or base catalyzed hydrolysis leads to malonic acid[6] (2.2). Ethanolysis in the presence of hydrogen chloride leads to the malonate diester[10,11] (2.3) while phenols give monoaryl esters (2.4) which can be easily converted to diaryl esters.[26] Ketones react with Meldrum's acid by displacement of acetone to give 2,2-disubstituted-1,3-dioxan-4,6-diones.[27] Nitrogen nucleophiles yield monoamides of malonic acid (2.5)[28] which can undergo decarboxylation, as in the case of aniline[6] to give anilide (2.6). The ring also undergoes fragmentation by pyrolysis.

In contrast to these examples, the reactions of Meldrum's acid with electrophiles generally leave the ring intact. Chart 3 gives the outline of the reactions involved.

Alkyl Derivatives of Meldrum's Acid :

5,5-Dialkyl derivatives (3.1) have been prepared by the reaction of the anion of Meldrum's acid (1.7) with alkyl[3,29] or activated heterocyclic[30] halides. The bases used for the preparation of anion are sodium ethoxide, silver oxide or sodium hydride. Meldrum's acid has a stong tendency to undergo bisalkylation and one isolates dialkyl derivatives invariably.[2,29]

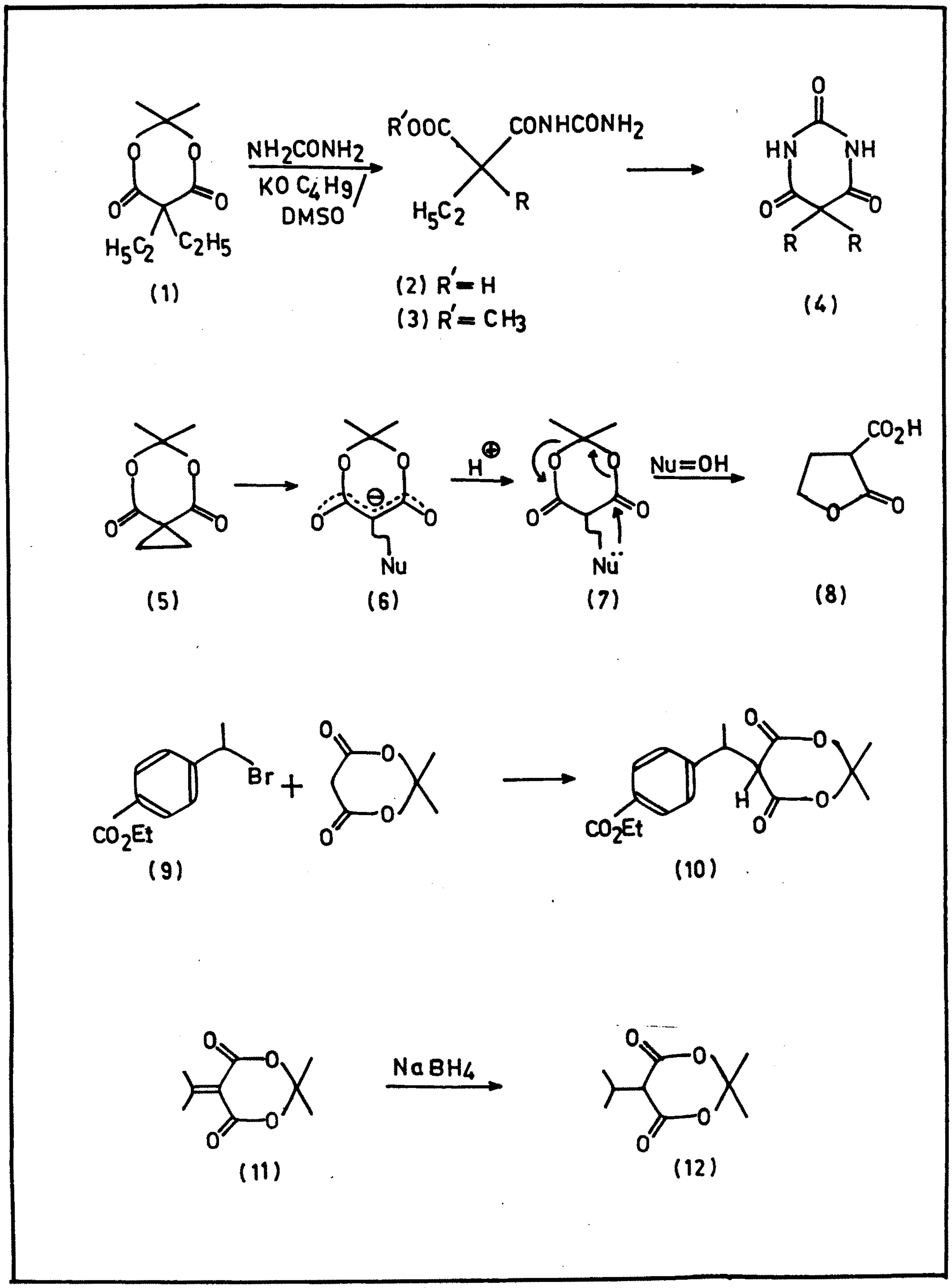
NH$_2$CONH$_2$
KO C$_4$H$_9$/
DMSO
R'OOC
CONHCONH$_2$
H$_5$C$_2$
R
HN
NH
R
R
H$_5$C$_2$
C$_2$H$_5$
(1)
(2) R' = H
(3) R' = CH$_3$
(4)
H$^{\oplus}$
Nu=OH
CO$_2$H
Nu
(5)
(6)
(7)
(8)
Br
+
CO$_2$Et
H
(9)
(10)
NaBH$_4$
(11)
(12)

CHART-4

This reaction is important from the point of view of preparation of spiro compounds from dibromoalkanes.[29]

Since the formation of anions such as (1.7) cannot compete, hydrolysis of diakyl derivatives is almost instantaneous under basic conditions.[31] Ethanolysis gives malonate mono- and di- esters. Reaction with urea yields dialkylmalonuric acid which can be converted into barbituric acid[32] (4.1 → 4.4).

The spiro cyclopropyl derivatives[33] (4.5) are of particular interest since they undergo Michael-type reactions with nucleophiles (4.5 → 4.6). Further intramolecular reaction may lead to lactones[33,34] (4.5 → 4.8) or lactams.[33]

Monoalkylation of Meldrum's acid with ethyl p-(α-bromoethyl) benzoate (4.9) has been reported.[2] Monoalkyl derivatives are easily obtained by the reduction of 5-methylene derivaties with sodium borohydride[35] (4.11 → 4.12), lithium aluminium hydride[36] or by catalytic reduction.[37]

PRESENT WORK :

In alkylations, Meldrum's acid (5.1) exhibits an overwhelming propersity to undergo bis-alkylation despite the use of one mole of alkyl halide.[2,29] Mono and bis-alkylated Meldrum's acids are important synthetic intermediates. In continuation with our work[2,4,5] on Meldrum's acid and with a view to studying the monoalkylation we present here some alkylation studies with it.

The bases that have been used so far by various workers for the alkylation of Meldrum's acid are strong and are not bulky so as to cause steric hindrance for the abstraction of proton from the monoalkylated Meldrum's acid. We thought of using weak, bulkier organic bases so that after formation of the monoalkyl derivative the abstraction of the proton would be difficult and the reaction will stop at the monoalkylation stage.

First we selected triethylamine as the base and benzyl Chloride as the halide. Alkylation using one mole each of the above and slightly excess than one mole of Meldrum's acid in methylene chloride yielded only dibenzyl Meldrum's acid (5.2) which was characterized by N.M.R. (Fig. 1) and comparison with authetic speciman. The monoalkylated product (5.3) was

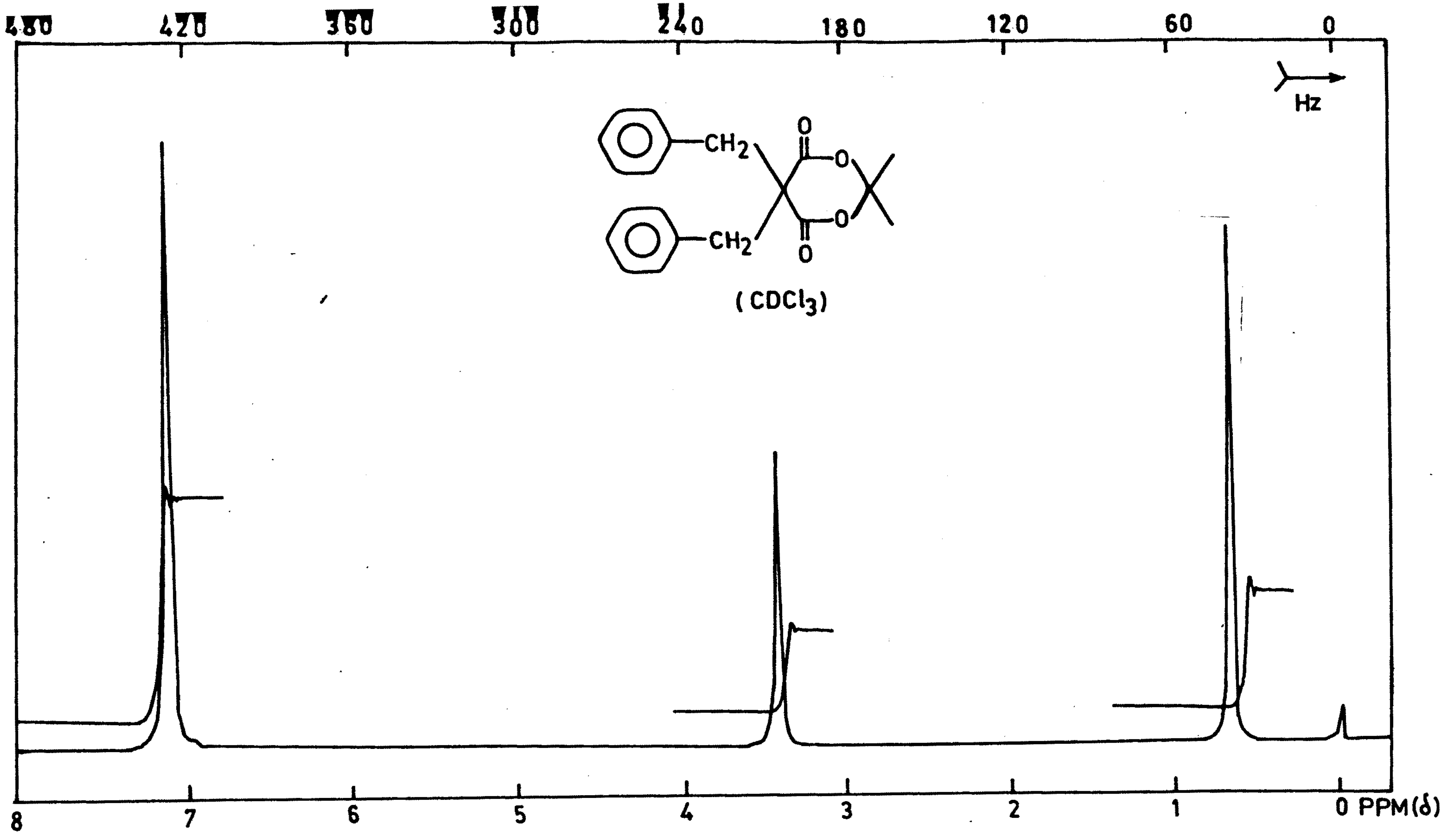
480
420
360
300
240
180
120
60
0
Hz
CH2
CH2
O
O
O
O
(CDCl3)
8
7
6
5
4
3
2
1
0 PPM(δ)

Fig. 1

not formed. N.M.R. ($CDCl_3$) δ : 0.68 (6H, S, $(CH_3)_2 - C$), 3.45 (4 H, S, ($Ph-C\underline{H}_2$ $)_2$), 7.16(10H, S, Ar-$\underline{H}$).

The above alkylation reaction was then tried with benzene as the solvent instead of methylene chloride but again dibenzyl Meldrum's acid was the only product. Experiment using pyridine as the base also yielded dibenzyl Meldrum's acid.

These results support earlier observations that the Meldrum's acid has a great tendency to undergo bis-alkylation despite the use of one mole of alkyl halide[2,29].

Use of two moles of benzyl chloride and three moles of base in the alkylation increased the yield of the dibenzyl Meldrum's acid considerably. This represents a new procedure for the bis-alkylation of Meldrum's acid using bases like triethylamine and pyridine.

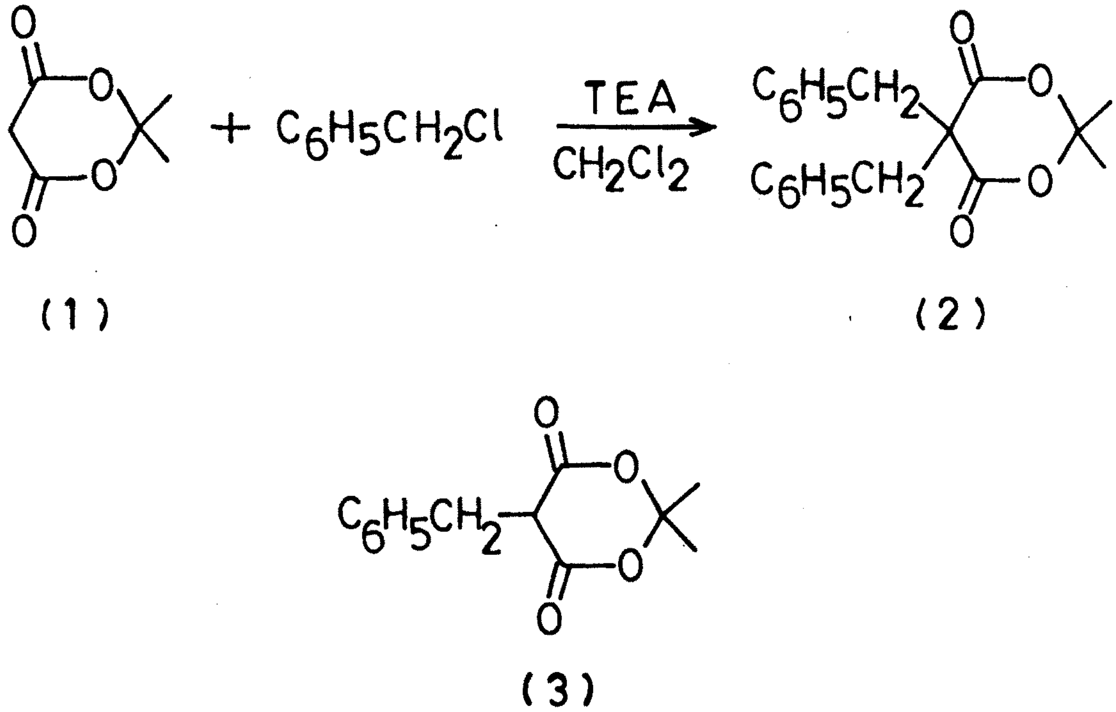

CHART-5

EXPERIMENTAL :

General :

Triethylamine and pyridine were kept over KOH pellets and then distilled and stored over KOH pellets, Methylene chloride was distilled over a small amount of P_2O_5 before use. Benzene was distilled and then dried by pressing sodium wire in it.

The P.M.R. spectrum was recorded on Varian T-60 instrument and the I.R. on Perkin-Elmer Infracord.

MELDRUM'S ACID :

It was prepared according to the procedure of Davidson and Bernhard[7].

To a suspension of powdered malonic acid (52 g) in acetic anhydride (60 ml), was added, with stirring, concentrated sulphuric acid (1.5 ml). Most of the malonic acid dissolved with spontaneous cooling. To the resulting solution, acetone (40 ml) was added while cooling, to maintain the temperature between 20 - 25°c. The reaction mixture was allowed to stand over night in the refrigerator and the resulting crystals filtered by suction and washed three times with sifficient ice water; yield of air dried product (35 g; 49%). Recrystallization is conveniently effected without heating by dissolving the crude product (10 g) in acetone (20 ml), filtering and adding water (40 ml). The recovery is about 70%, m.p. 94-95° (decomposition).

ALKYLATION OF MELDRUM'S ACID :

(1) Using one mole of each of the reactants :

Meldrum's acid (1.5 gm.) was dissolved in dry methylene chloride (15 ml.) and triethylamine (1 ml) was added to it with magnetic stirring. After stirring for 10 min., benzyl chloride (1 ml.) in methylene chloride (5 ml.) was added dropwise during 15 min. The solution was then refluxed on a water bath for 6 hr. and left overnight. It was then diluted with ether (50 ml) and the ether layer was successively washed with water and aqueous sodium carbonate and again with water. The sodium carbonate washing was cooled and carefully acidified with dil. HCl to precipitate any monoalkylated product that is formed since monoalkylated product is quite acidic due to the presence of acidic proton. No ppt. or oily product was detected indicating the absence of monoalkylated product. The above ether layer was dried over anhydrous sodium sulphate and the solvent removed. A solid product was obtained contaminated with small amount of unreacted benzyl chloride (T.L.C.) Pet. ether (10 ml.) was added and the solid was filtered. It was crystallised from pet. ether-chloroform, m.p. 228-229^{o} (Lit.^{4}. 229-30^{o}). yield 1.1 gm. The yield is low due to the use of only one mole of benzyl chloride. I.R. (Nujol) : 1762, 1734 cm^{-1}. P.M.R. (Fig. 1, $CDCl_3$, 60 MH_z) : δ 0.68 (6H, S, $(CH_3)_2$-C), 3.45 (4 H, S, $\underline{CH_2}$), 7.16 (10 H, S, Ar-$\underline{H}$).

Experiment using above reactants in benzene instead of methylene chloride gave similar results. The same observations were also made using pyridine as the base in the above experiment.

(2) Using two moles of benzyl chloride :

The experiment was performed exactly as described in (1) using the following quantities. Meldrum's acid 1.5 g, benzyl chloride 2 ml. and triethylamine (3 ml.). The yield of the dibenzyl Meldrum's acid was 2.5 g.

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