CHAPTER - 2

MONOALKYLATION OF MELDRUM'S ACID UNDER PHASE TRANSFER CATALYZED CONDITIONS

ABSTRACT

Phase Transfer Catalyzed (PTC) monoalkylation of Meldrum's acid (2,2 dimethyl-1,3 dioxan-4,6-dione) (3.1) by benzyl and alkyl halides using tetra-n-butyl ammonium hydroxide provides a simple procedure for the preparation of various mono-substituted Meldrum's acids.

INTRODUCTION

Phase Transfer Catalysts have found wide applications in recent years in various fields, particularly in organic synthesis. Recently Meldrum's acid has attracted much attention as a versatile synthon[1] in organic synthesis. Our attention was focussed on Meldrum's acid by its high acidity (pKa = 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 synthesis[2,3] and it has strong tendency to undergo bis-alkylation[3].

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[4] and Davidson and Bernhard assigned the correct structure[5] (3.1) to Meldrum's acid as 2,2-dimethyl-1,3 dioxan-4,6-dione.

Meldrum's acid (pKa = 4.83)[6] is a strong organic acid comparable in strength to acetic acid (pKa = 4.76) and is around ten pK units more acidic than acyclic malonate esters. This can be explained as with dimedone (pKa = 5.2)[5] on the basis of the stability of the resultant anion

in which the pi 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 predominantly in the mono-enol form, whereas the latter is in the diketo tautomer (> 99.5%).[7] This is not surprising since esters are generally enolized to a much smaller extent than ketones.[8]

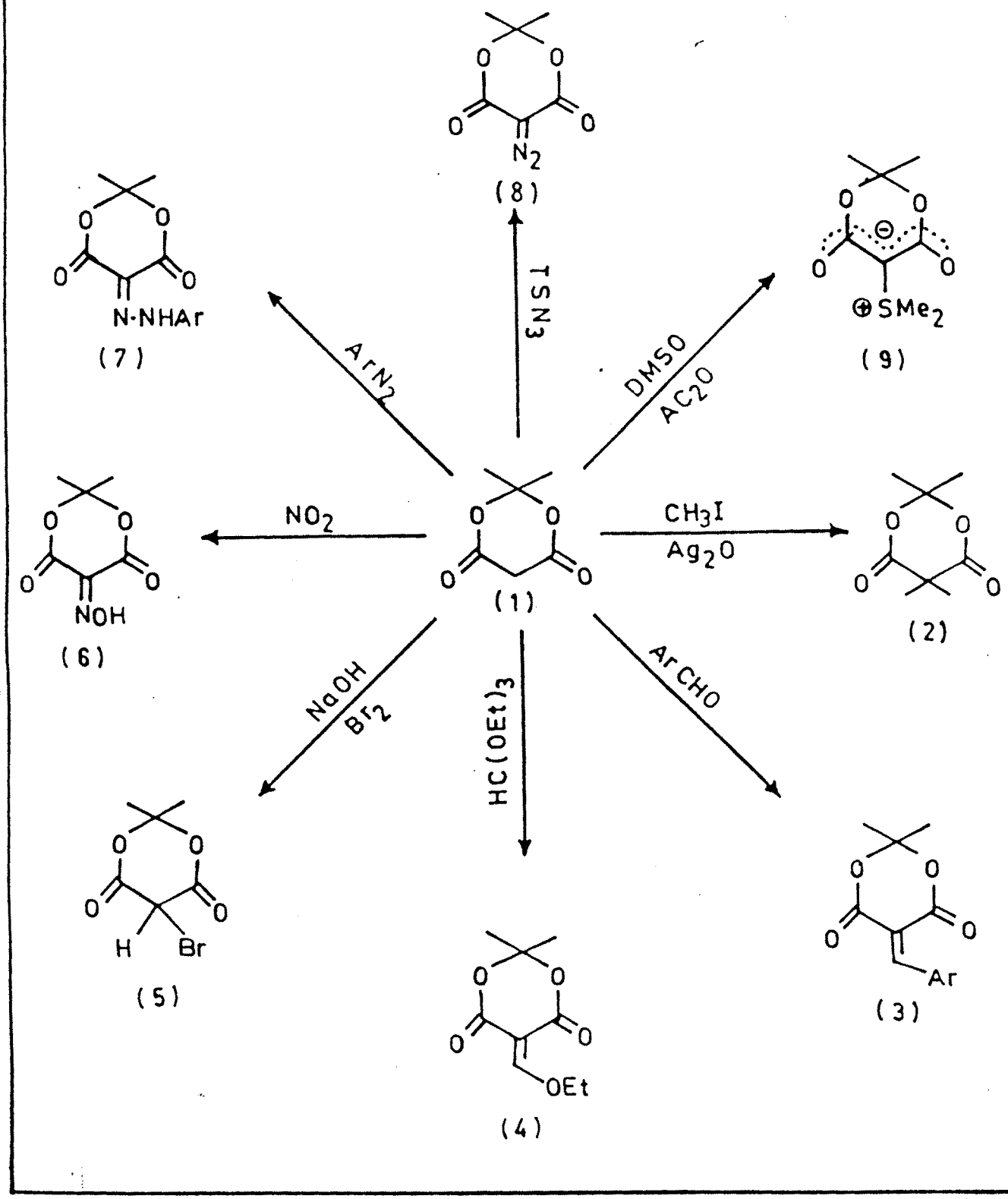
The conformation of 1,3-dioxan-4,6-dione system has been studied by N.M.R.[9], dipole moment measurements[10] and X-ray crystallography[11]. The majority opinion favours a boat structure for 2,2,5,5 - tetra substituted compounds. Other physical properties of the system which have been studied include U.V.[12], I.R.[13], Mass[14], ^{1}H-N.M.R.[15] and ^{13}C-NMR[16].

The chemistry of Meldrum's acid is dominated by its susceptibility to nucleophilic attack at positioins 4 and 6 and to electrophilic attack (via the anion) at position 5. Acid or base catalyzed hydrolysis leads to malonic acid[4]. Ethanolysis in the presence of hydrogen chloride leads to malonate diesters[12,19], while phenols give monoaryl esters[17] which can be easily converted to diaryl esters. Ketones react with Meldrum's acid by displacement of acetone to give 2,2-disubstituted-1,3-dioxan-4,6-diones[18]. Nitrogen nucleophiles yield monoamides of malonic acid, which can undergo decarboxylation, as in the case of aniline[4] to give anilide. 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.

CHART – 3

Reactions with electrophiles



The presence of a highly reactive methylene group and easily degradable ester function in Meldrum's acid makes it an attractive synthon in organic syntheses. Meldrum's acid can act as a methylene synthon by hydrolysis and exhaustive decarboxylation of its derivatives. The conditions needed for certain heterocyclic systems are surprisingly mild[20,21]. Dauben's two step synthesis of δ-damascone[22] is a beautiful example of the use of strong dienophile character of methylene Meldrum's acid. Under extreme conditions, cleavage of acetone may be followed by decarboxylation to give lactams[23], in these cases Meldrum's acid acts as the synthetic equivalent of ketene. McNab et.al. have reported a new synthesis of pyridazin-3-ones by the reaction of Meldrum's acid with α-dicarbonyl monohydrazones[24].

Meldrum's acid is widely used for the preparation of α-pyrones and 2-pyridones in heterocyclic chemistry[1]. Alkylation of Meldrum's acid with ethyl p-(α-bromoethyl) benzoate, followed by mild hydrolysis and decarboxylation yields the half acid ester[2]. A general β-ketoester synthesis[25] has been reported from Meldrum's acid and acid chlorides. The synthesis of 4-alkylated pyridines from 4-(1-H)-pyridones has been carried out using Meldrum's acid[20a]. 4-chloro quinoline and 4-chloropyridine react with Meldrum's acid to give substituted products which can be hydrolysed and decarboxylated to yield alkyl quinolines[20b] or pyridines[20c]. Y.Osamu and co-workers have prepared 2-substituted indoles from acyl Meldrum's acid and phenyl hydroxyl amines[26] along with poor yields of isoxazoles. An improved synthesis of 1,4-dithiaspiro decan-8-one[27] has been carried out by using Meldrum's acid. The Birch reduction of 4-methoxy phenol gave

4-methoxy-3-cyclohexan-1-ol. Lactone synthesis via the intramolecular alkylation of β-keto ester dianions has been reported by Weiler and co-workers[28] from acylated Meldrum's acid.

Procedures that involve the formation and subsequent reaction of anions derived from active methylene compounds constitute a very important and synthetically useful class of organic reactions. The presence of certain unsaturated functions like nitro, carbonyl, cyano, sulphone or phenyl groups at saturated carbon atoms renders any hydrogen atoms bonded to that carbon relatively acidic. The acidity of the C-H bond in these compounds, always called as active methylene compounds, is attributed to a combination of the inductive electron withdrawing ability of the unsaturated substituents and the ability of these substituents to delocalize the negative charge formed when the proton has been removed. The effectiveness of these unsaturated functions as activating groups follows the approximate order,

$$NO_2 > COR > CN \simeq CO_2R > SOR > Ph > R$$

Also the presence of two such unsaturated substituents further enhance the acidity of an active methylene compound. The high acidity of Meldrum's acid (pKa = 4.83) is attributed to the stability of the resultant anion in which the pi-orbitals are rigidly held in the ideal configuration for overlap.

Removal of a proton from the carbon atom alpha to a carbonyl group leads to the formation of anions, usually called enolate anions. The rate of proton attraction is quite high in the case of 1,3-dicarbonyl compounds. A qualitative relationship exists between the rate of proton

removal and the dissociation constant (pKa value) for active methylene compounds and in that proton removal is usually more rapid for more acidic compounds. Methylene groups activated by a single nitro group, two or more carbonyl, ester or cyano groups are quite acidic and may in large part to their enolate (or analogous) anions by treatment with relatively strong bases in aprotic solvents or with an anhydrous alcoholic solution of a metal oxide. The solutions of enolate anions thus obtained are allowed to react with alkyl halides or other alkylating agents. β-diketones are sufficiently acidic so that their anions may be formed with alkali metal hydroxides or alkali metal carbonates in water, aqueous alcohol or acetone.

These reactions share a common mechanism involving base catalyzed formation of a carbanion followed by nucleophilic attack via an S_N^2 mechanism. The alkylating agent must be a suitable substrate for an S_N^2 reaction. Primary halides and sulphonates are the best substrates. Secondary system usually give poorer yields because of competition from elimination reaction . Tertiary halides or sulphonates are unsatisfactory because elimination rather than substitution occurs[29]. These reactions are important means of synthesising a variety of ketones[30] and carboxylic acids[31,32].

PRESENT WORK

Monoalkylation of Meldrum's Acid :

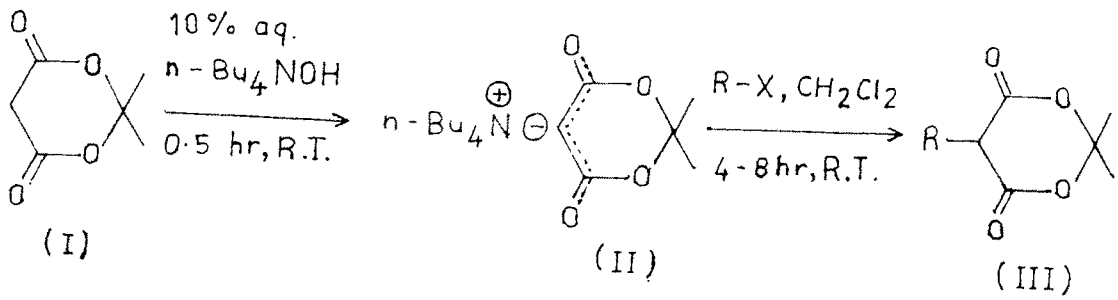
Mono-alkylated Meldrum's acids are important synthetic intermediates. They can be easily converted into malonic esters or acids, ketones and barbiturates. They have also been used for generation of ketenes. In view of the importance of mono-alkylated Meldrum's acid

in pharmaceuticals, a simple method is now reported for the mono-alkylation of Meldrum's acid.

In alkylation Meldrum's acid exhibits an overwhelming propensity to undergo bis-alkylation, despite the use of one mole proportion of alkyl halide[31]. Ott[33] has reported the alkylation of Meldrum's acid with methyl iodide in ether using silver oxide which is quite expensive. This gave only dimethyl Meldrum's acid in low yield (40%). The change of solvent from ether to acetonitrile improved the yield (67%). Hedge et.al.[31] studied the benzylation of Meldrum's acid using metal alkoxides in different solvent. The treatment of Meldrum's acid with benzyl chloride using sodium methoxide in methanol gave dimethyl-Meldrum's acid in 19% yield, whereas the reaction with sodium ethoxide in ethanol gave 16% yield of the product. The same reaction using sodium ethoxide in dimethyl formamide (DMF) improved the yield to 35%. Also, the reaction of the monosodium salt of Meldrum's acid in DMF gave somewhat better yield (42%). The above procedure has been extended for the preparation of spiro compounds[31] from dibromoalkanes in low yield (30-35%). Mane and Krishna Rao[2] have reported bis-alkylation with ethyl bromoacetate and ethyl p-bromomethyl benzoate. Beres et.al.[34] have reported the preparation of diethyl Meldrum's acid in low yield from diethyl malonic acid. Recently the bis alkylation of Meldrum's acid has been carried out by alkyl halides in dimethyl formamide (DMF) using anhydrous potassium carbonate[35]. C.Chan and X. Huang have reported the bisalkylation of Meldrum's acid under phase transfer catalyzed conditions[36] by using solid-liquid phase system.

Earlier reports show the preparation of monoalkyl derivatives of Meldrum's acid by using different methods. A.D.Wright et al.[37] have reported the monoalkyl derivatives of Meldrum's acid by borohydride reduction of its methylene derivatives. The monoalkylation of Meldrum's acid had also been carried out by conjugate Grignard addition which have been reported by Haslego et al.[38] Nutaitis et.al.[39] have reported the monoalkylation by cyanoborohydride reduction of acyl derivatives of Meldrum's acid. Mane and K.Rao[2] have reported its exceptional mono-alkylation in DMF using potassium carbonate. Meldrum's acid can also be reductively mono alkylated by using borane-dimethylamine and aldehyde or ketone[40].

We now report here a simple method for the monoalkylation of Meldrum's acid under phase transfer catalyzed conditions by using liquid-liquid phase system. Here the anion which is linked with PTC(II) was added slowly to the alkyl halide in dichloromethane to give monoalkylated products (III). The tetra-n-butyl ammonium hydroxide acts as a weak base as well as a PTC. This procedure avoids the excess of anion in the alkylating medium preventing bisalkylation. It is observed that the secondary and higher primary halides gave exclusively monoalkylated products, whereas lower as well as highly reactive halides give a mixture of bis alkylated products.



(I) (II) (III)

(a) R = $C_6H_5CH_2$; (b) R = C_2H_5; (c) R = iso-C_3H_7;

(d) R = n-C_4H_9; (e) R = iso-C_4H_9; (f) R = iso-amyl.

The results of the syntheses of various monoalkylated products are given in Table-1. The products were characterized by ^{1}H-NMR spectra (Table-2).

TABLE - 1 : Monoalkylated Meldrum's Acids Synthesized.

Product No.	R	X	Reaction time [hr]	Yield [%]	M.P. [°C]
III_a	$C_6H_5CH_2$ -	Cl	4	30 *	80
III_b	C_2H_5 -	Br	6	30 *	106
III_c	iso-C_3H_7-	I	6	40	109
III_d	n-C_4H_9 -	Br	8	30	118
III_e	iso-C_4H_9-	I	7	40	120
III_f	iso-amyl-	Br	7	40	67

* 10 % bis-alkylated product was also observed.

TABLE - 2 : Spectral Data

Product No.	^{1}H-NMR ($CDCl_3$) δ (ppm)
III_a	1.4 (3H,s,CH_3), 1.6 (3H,s,CH_3), 3.32 (2H,d,CH_2), 3.8 (1H,t,CH), 7.2 (5H,m,Ar-H).
III_b	1.05 (3H,t,CH_3), 1.75 (6H,s, gem dimethyl), 2.15 (2H,m,CH_2), 3.35 (1H,t,CH).
III_c	1.15 (6H,d,CH_3), 1.73 and 1.75 (3H each, s, gem dimethyl), 2.73 (1H,m, $\underline{CH}CH_3$), 3.42 (1H,d, CH flanked by CO).
III_d	0.9 (3H,t,CH_3), 1.35 (4H,m,CH_2CH_2), 1.73 and 1.75 (3H each, s, gem dimethyl), 1.9 (2H,m,CH_2), 3.5 (1H,t,CH).
III_e	0.95 (6H,d,CH_3), 1.73 and 1.75 (3H each, s, gem dimethyl), 1.9 to 2.2 (3H,m,CH & CH_2), 3.45 (1H,t,CH flanked by CO).
III_f	0.90 (6H,d,CH_3), 1.3 (2H,m,CH_2), 1.8 (6H,s, gem dimethyl), 2.0 (3H,m,CH_2 & CH), 3.55 (1H,t,CH).

We have also carried out the monoalkylation of Meldrum's acid by using isopropyl iodide with different PTCs such as tetra-n-butyl ammonium hydrogen sulfate and benzyl triethyl ammonium chloride in presence of aqueous sodium hydroxide.

The results of the synthesis of monoalkylated products are given in the Table-3.

TABLE - 3 : Monoalkylation of Meldrum's Acid by Isopropyl Iodide with Different PT Catalysts.

	Catalyst	Reaction Time [hr]	Yield [%]
i)	Tetra-n-butyl ammonium hydroxide	6	40
ii)	Tetra-n-butyl ammonium hydrogen sulfate	6	30
iii)	Benzyl triethyl ammonium chloride	6	25

Thus, tetra-n-butyl ammonium hydroxide is a better catalyst as it acts as a PTC as well as a weak base.

EXPERIMENTAL

General :

Benzyl chloride (SDS), ethyl bromide (SRL), isopropyl iodide (SRL), n-butyl bromide (SRL), isobutyl iodide (SRL) and isoamyl bromide (SRL) were commercially available.

All the mono-alkylation reactions were performed at room temperature. Methylene chloride (MERCK) was distilled before use. ^{1}H-NMR spectra were recorded on Perkin-Elmer 783 Spectrophotometer.

Meldrum's acid :

It was prepared according to the procedure of Davidson and Bernhard.[5]

To a suspension of powdered malonic acid (52 g) in acetic anhydride (60 ml) was added, with stirring, concentrated A.R. grade 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 overnight in the refrigerator and the resulting crystals filtered by suction and washed three times with sufficient ice water. Yield of air dried product is (35 g) 49%. Recrystallisation 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°C (decomposition).

General Procedure for Monoalkylation of Meldrum's Acid :

Meldrum's acid (I, 0.360 gm, 2.5 m mole) was added to 10% aq. solution of tetra-n-butyl ammonium hydroxide (6.475 ml, 2.5 m mole) and stirred for 0.5 hr. Then it was added dropwise with stirring to a solution of alkyl halide (2.7 m mole) in dichloromethane (7 ml) during 4-5 hr. After completion of the addition, the resultant reaction mixture was stirred for 4-8 hr. at room temperature until TLC analysis (silica gel G, benzene/ethyl acetate) indicated completion of the reaction. Then the two layers were separated. The organic layer was evaporated. To the residue 7 ml. ether was added (if the halide used is iodide, the tetra-n-butyl

ammonium iodide separates out as a solid which may be filtered off). The etheral solution was washed with water. Then it was dried with anhydrous sodium sulfate. After removal of the solvent, the product was purified by chromatography over silica gel eluting with benzene.

In case of synthesis of monoalkylated products with PTCs such as tetra-n-butyl ammonium hydrogen sulfate (2.5 m mole, 0.848 gm) and benzyl triethyl ammonium chloride (2.5 m mole, 0.569 gm), sodium hydroxide (2.5 m mole, 0.100 gm) in 2.5 ml water was used.

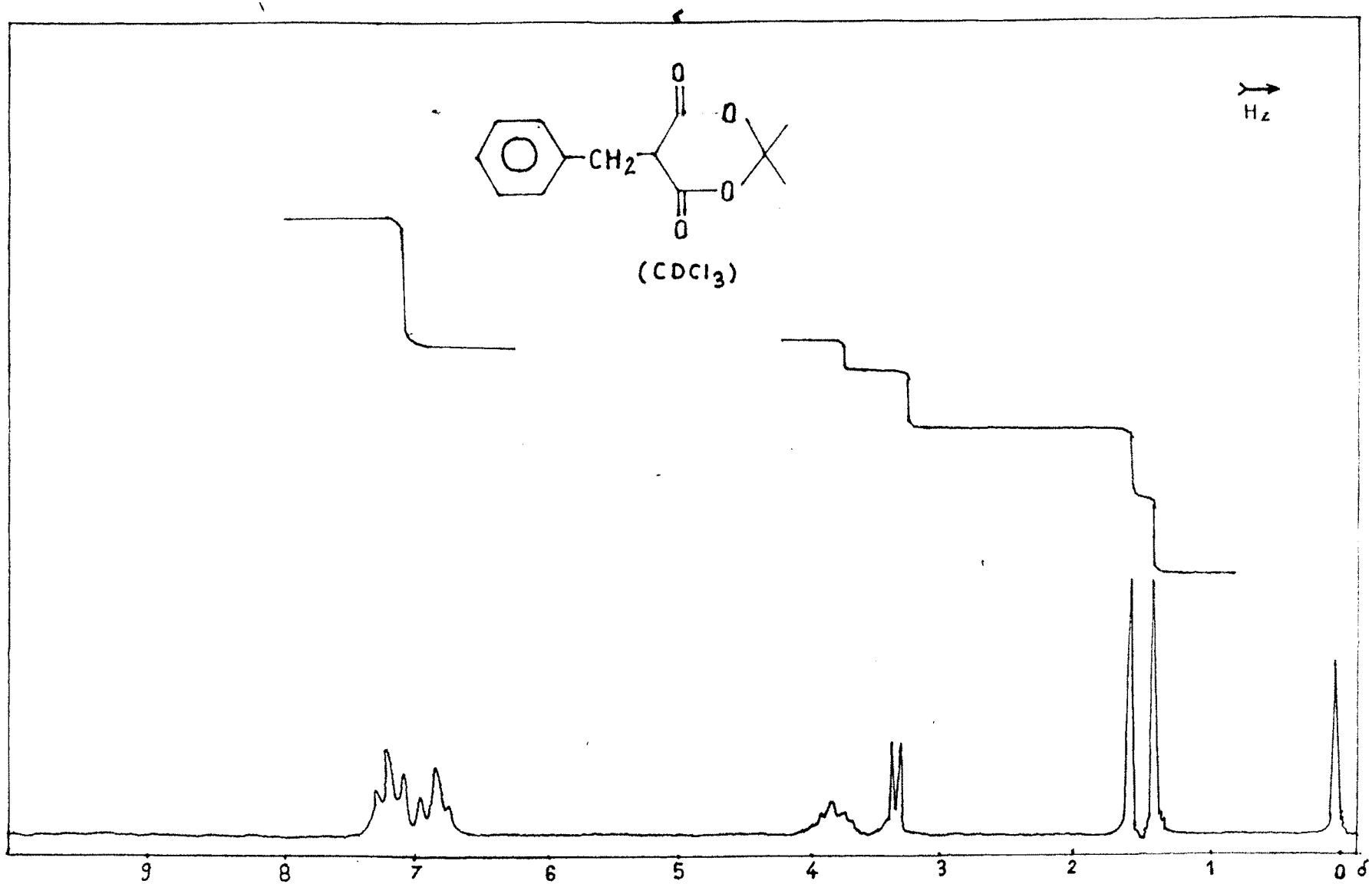


Fig. 1

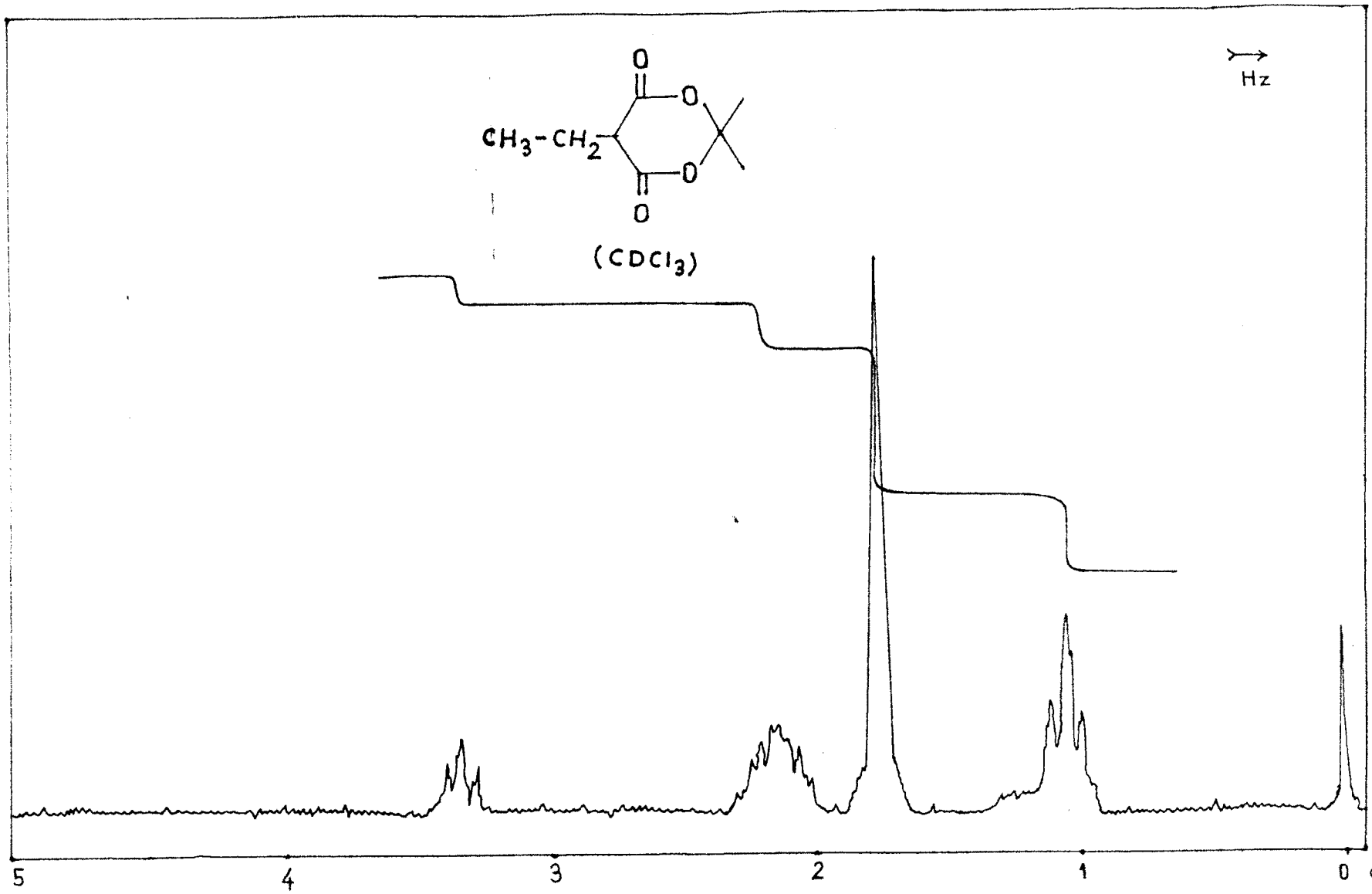


Fig. 2

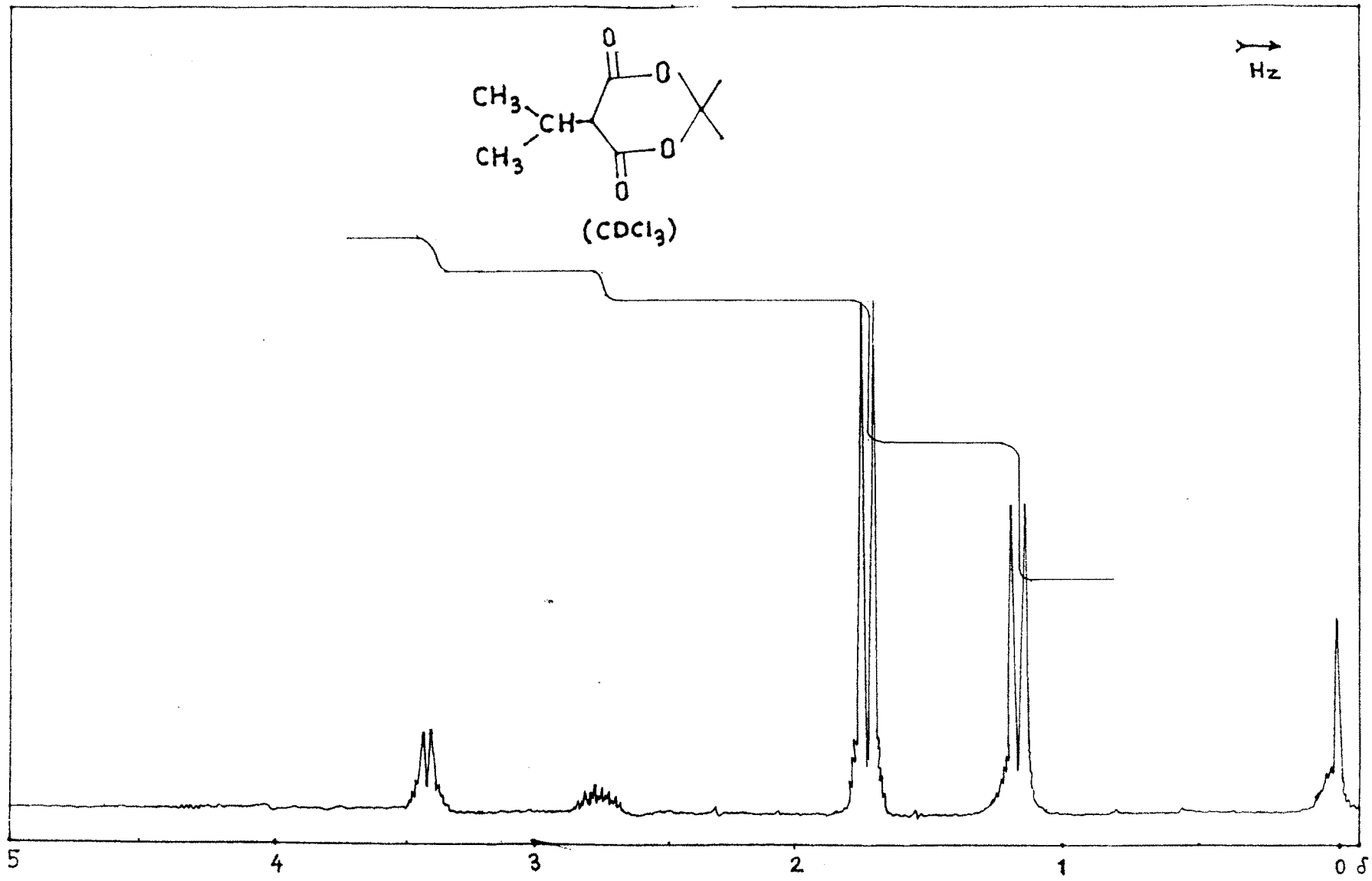


Fig. 3

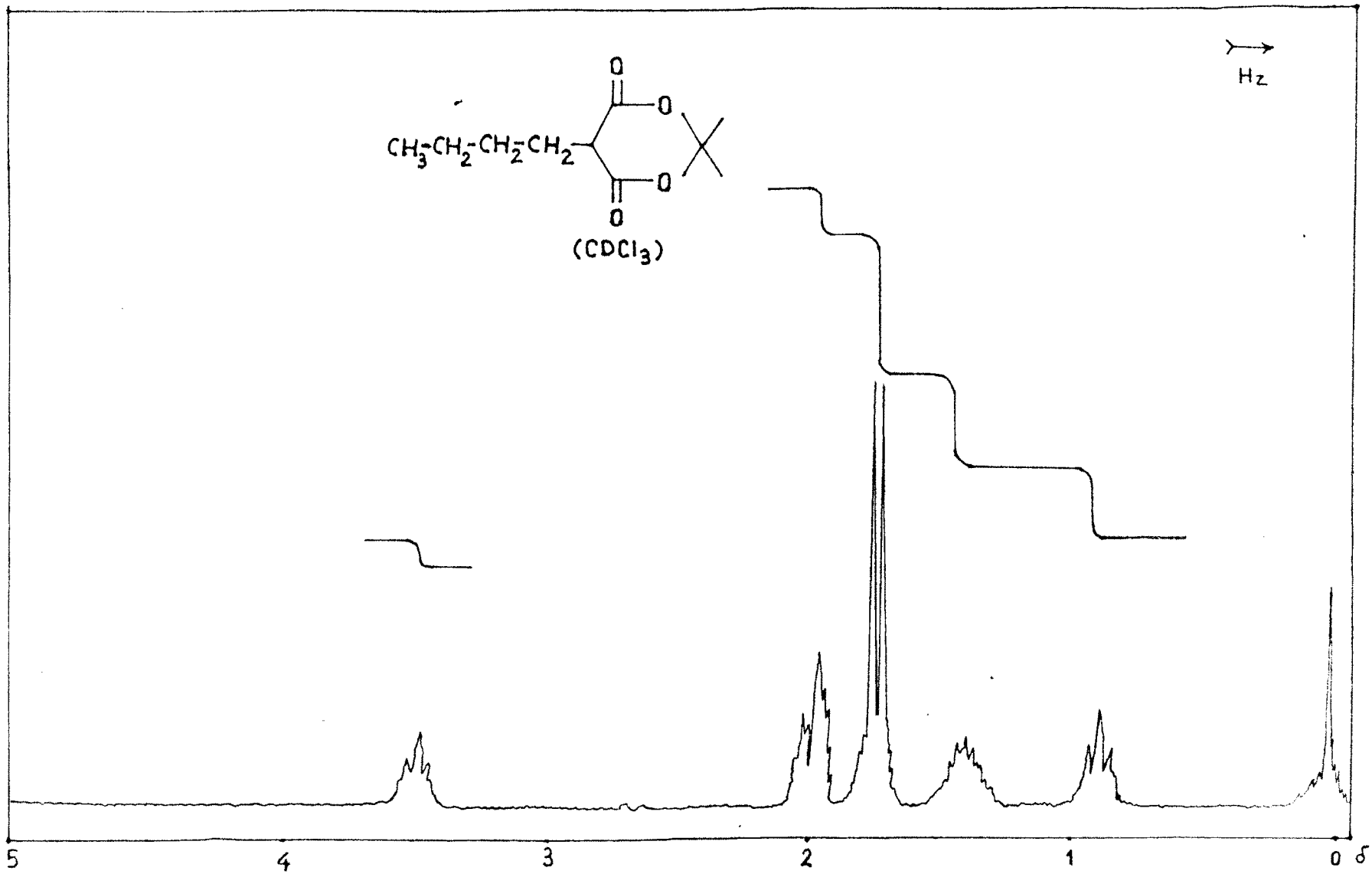


Fig. 4

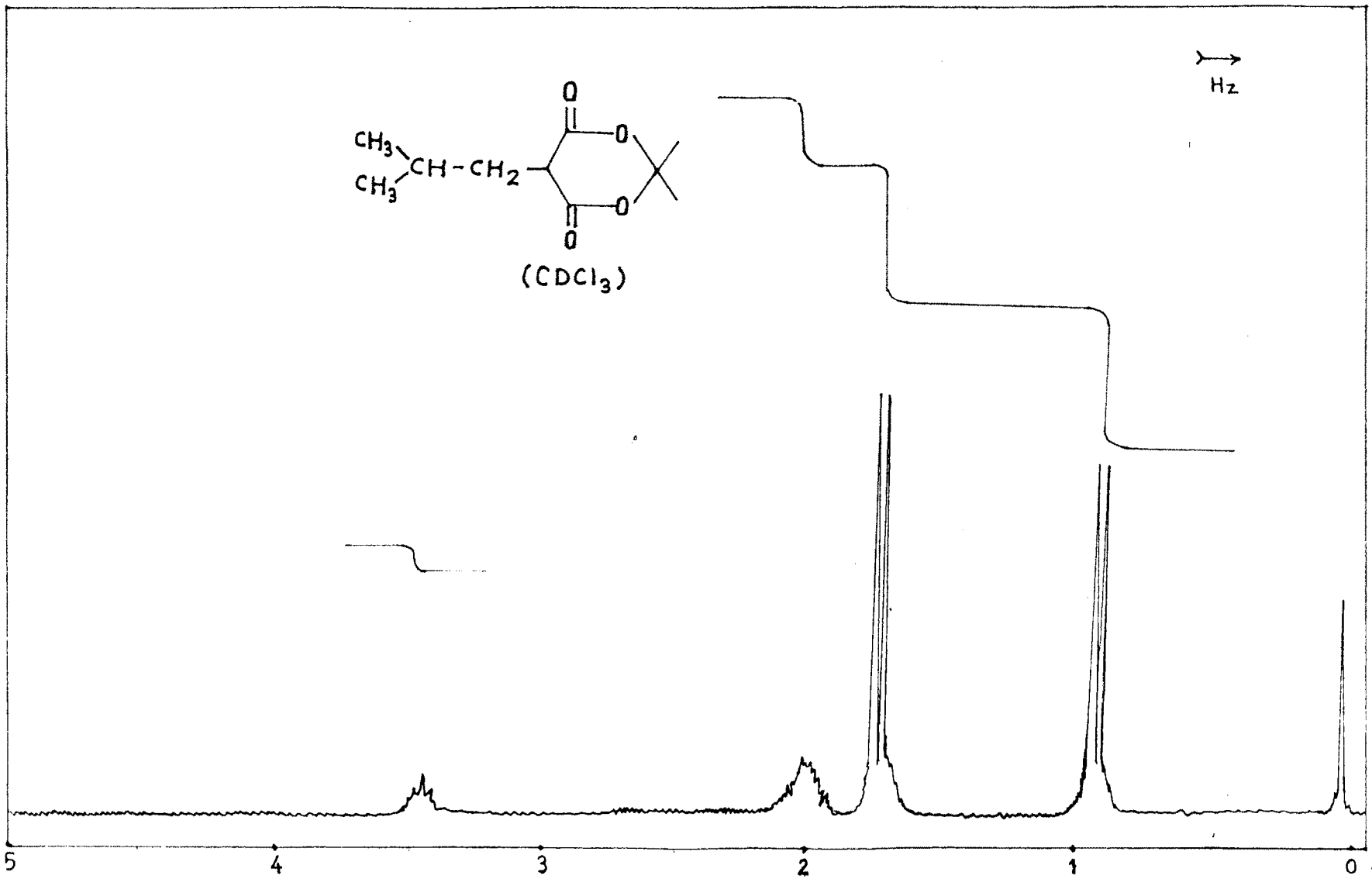


Fig. 5

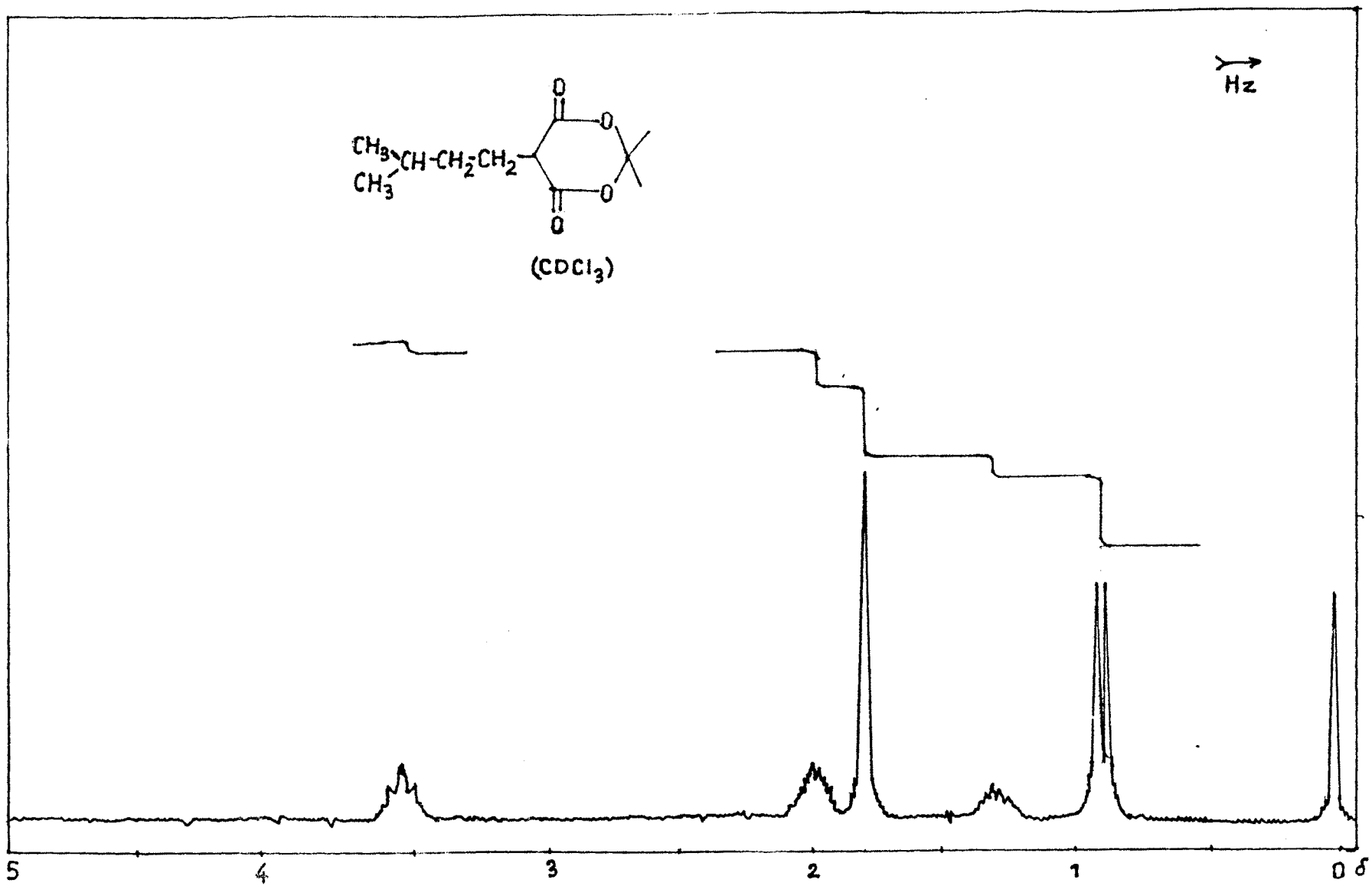


Fig. 6

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