CHAPTER - 3

SYNTHESIS OF ARYLOXYACETIC ACID ESTERS UNDER PHASE TRANSFER CATALYZED CONDITIONS

ABSTRACT

Phase Transfer Catalyzed (PTC) O-alkylation of aryloxyacetic acid by alkyl halide using tetra-n-butyl ammonium hydrogen sulfate provides a smiple and efficient procedure for the synthesis of aryloxy acetic acid esters. In addition to ease and simplicity of the method here the catalyst could be recovered.

INTRODUCTION

Esterification of carboxylic acids with hydroxy compounds (R'OH) is usually effected by refluxing the acid and alcohol with a small amount of sulfuric acid, hydrogen chloride or arylsulfonic acid (4.1). The equilli-brium is shifted to the right by an excess of the reactant or by removal of water either by azeotropic distillation or by means of a suitable drying agent. The necessity for continuous drying is eliminated when methylene or ethylene chlorides are used as solvents for the reaction[1]. A small amount of an acid chloride such as thionyl chloride, acetyl chloride or stearoyl chloride has proved superior to hydrogen chloride as a catalyst for certain esterifications at room temperature[2].

Reactive hydrogen compounds (R'x) such as benzyl chloride[3], 2-bromoacetylthiophene $(C_4H_3S)COCH_2Br$[4], and 2-chloromethylthianapthene $(C_8H_5S)CH_2Cl$[5] are readily converted to esters by treatment with sodium salt of carboxylic acids (4.2). A small amount of triethylamine has proved to be an effective catalyst.[5,6]

Reaction of alkylchlorosulfites or alkyl sulfates on salts of carboxylic acids has been developed as a method of esterification (4.3). A vigorous

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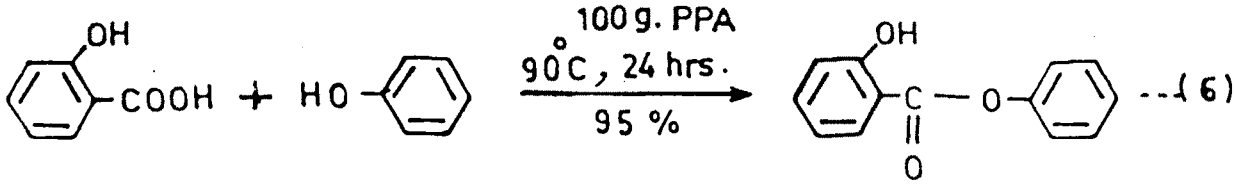
$$RCOOH + R'OH \rightleftharpoons RCOOR' + H_2O \quad \text{---(1)}$$

$$RCOONa + RX \longrightarrow RCOOR' + NaX \quad \text{-------(2)}$$

$$RCOONa + ROSOCl \longrightarrow RCOOR' + SO_2 + NaCl \quad \text{--(3)}$$

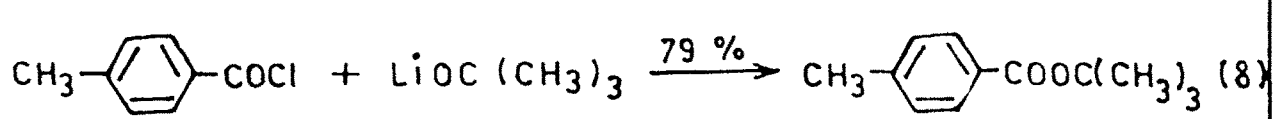
$$RCOOH \xrightarrow{H^+} R-C(=OH^+)-OH \xrightarrow[-N_2]{CH_2N\equiv N} R-C(=O^+CH_3)-OH \longrightarrow R-C(=O)-OCH_3 \quad \text{----------(4)}$$

$$C_6H_5COOH + (CH_3)_2NCH(OC_2H_5)_2 \xrightarrow[90\%]{} C_6H_5COOC_2H_5 + C_2H_5OH + (CH_3)_2NCHO \quad \text{----------(5)}$$



(6)

$$RCOOH \xrightarrow[Py]{TsCl} (RCO)_2O \xrightarrow{R^1OH} RCOOR^1 + RCOOH \quad \text{-----(7)}$$



exothermic reaction occurs between chlorosulfites and the acid salts. Further heating to 100-150°C results the evolution of sulfur dioxide and the formation of the esters. Aliphatic and aromatic acids including the hindered 2,4,6-trialkylbenzoic acids have been esterified.[7]

Esterification of carboxylic acids with diazomethane was discovered by Von Pechmann[8]. The fact that neutral alcohols do not react with diazomethane suggests that an acidic substance supplies a proton required for catalysis of the esterification (4.4). Dimethylformamide diethyl acetal $(CH_3)_2NCH(OC_2H_5)_2$ can be used as a reagent for esterification of carboxylic acids under mild conditions[9,10]. Thus benzoic acid (0.4 mole) reacts with 2 equivalents of the acetal to give ethyl benzoate (4.5) under the following conditions : in methylene chloride for 5 hrs at 40°C; in benzene for 1 hr at 80°C; in acetonitrile for 36 hrs at room temperature[10].

The conversion of carboxylic acid into its t-butyl esters by acid-catalyzed addition to isobutene is illustrated by a procedure for the preparation of di-t-butyl malonate[11]. Phenyl esters[12] are obtained by heating an acid and a phenol in polyphosphoric acid [PPA] (4.6). Esters are formed when a solution of an acid (1 equivalent) and an alcohol (1 equivalent in pyridine) is treated with p-toluenesulfonyl chloride (tosyl chloride; 2 equivalents)[13]. The reaction is considered to involve intermediate formation of the acid anhydride (4.7). Carboxylic acids are converted into their ethyl esters when heated with an excess of triethyl orthoformate, $HC(OC_2H_5)_3$. Even hindered acids such as 2,4,6-trimethylbenzoic acid are esterified[14]. Diphenyl diazomethane, $(C_6H_5)_2CN_2$ is

also used for esterification of carboxylic acids. Hindered tertiary acids, react with diphenyldiazomethane to give benzhydryl esters.

t-Butyl esters of carboxylic acids[15] and sulfonic acids[16] have been prepared by reaction of acid chlorides with alkoxides like lithium t-butoxide, $LiOC(CH_3)_3$. The method is particularly useful for preparation of highly hindered esters. The method is recommended for the preparation of t-butyl p-toluate[17] (4.8).

Carboxylic acids and phenols can be converted into methyl esters[18] and ethers in yields > 90% by thermal decomposition of trimethyl anilinum salts in an inert refluxing solvent like toluene (5.1). This method is successful even with sterically hindered acids. Trimethyl phosphate, $(CH_3)_3PO$ can also be used for esterification[19] of hindered carboxylic acids.

Carboxylic acids react with 6-chloro-1-p-chlorobenzene-sulfonyloxy-benzotriazole (5.2) in $CHCl_3$ or acetonitrile in the presence of 1 equivalent triethylamine to form an active ester (5.3), which can be isolated if desired. The esters (5.3) react with an alcohol, again in the presence of 1 equivalent of base, to form an ester of carboxylic acid (5.4). The esterification[20] can be carried out in one step by mixing the acid, the alcohol, the coupling reagent and 2 equivalent of base in ether. In either case, the reaction takes place at 20°C.

Shaw and Kunerth[21] have reported the esterification of sodium salt of carboxylic acids with alkyl halides in hexamethylphosphoric triamide (HMPT) at room temperature. The method is applicable to the preparation of ethyl esters of hindered acids. In esterification of acids that undergo

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$$RCOOH + (CH_3)_3\overset{+}{N}C_6H_5\bar{O}H \xrightarrow{\Delta} RCOOCH_3 + (CH_3)_2NC_6H_5 \quad ---(1)$$

$$RCOOH + \underset{OSO_2C_6H_4Cl(p)}{\text{(2)}} \xrightarrow[-ClC_6H_4SO_3H\cdot N(C_2H_5)_3]{N(C_2H_5)_3} \underset{OCOR}{\text{(3)}}$$

$$\xrightarrow[N(C_2H_5)_3]{R^1OH} RCOOR^1 \text{ (4)} + \underset{OH\cdot N(C_2H_5)_3}{\text{Cl}}$$

$$CH_2(COOH)_2 + C_2H_5Cl \xrightarrow[91\ \%]{K_2CO_3,\ HMPT} CH_2(COOC_2H_5)_2 \quad ------(5)$$

$$C_6H_5COOH + CH_2Br_2 \xrightarrow[86\ \%]{NaOH,\ HMPT} (C_6H_5COO)_2CH_2 \quad ------(6)$$

$$\underset{(7)}{\text{Br}} + RCOOH \xrightarrow{Base} \left[\text{RCOO}\right] \xrightarrow[Base]{R^1OH} RCOOR^1 + \text{O} + \text{Base·HI} \quad (8)$$

$$RX + R^1COOCs \xrightarrow[70-90\ \%]{DMF} R^1COOR + CsX \quad -------(9)$$

$$RCOOH + R^1X + DBU \xrightarrow{C_6H_6} RCOOR^1 + DBU\cdot HX \quad -----(10)$$

$$\text{(P)}-CH_2\overset{+}{N}Me_3\bar{O}-\overset{O}{\overset{\|}{C}}-CH_2OR^1 \xrightarrow{R^2X} R^1OCH_2COOR^2 + \text{(P)}-CH_2\overset{+}{N}Me_3\bar{X} \quad ---(11)$$

ready decarboxylation, anhydrous potassium carbonate rather than NaOH is used as base (5.5). Diesters[21] can be obtained by reaction of sodium salt of acids with dibromoethane (5.6).

The reaction of carboxylic acids and alcohols in presence of 1.2 equivalent of 1-methyl-2-bromopyridinium iodide (5.7) and 2.4 equivalent of tri-n-butyl amine affords esters[22] (5.8) in 60 to 90% yield. Optimum yields are obtained in refluxing toluene or dichloromethane. The method is useful for synthesis of sterically hindered esters. Esters of protected amino acids and peptides can be prepared by treatment of cesium salt of acids with an alkyl halide in DMF (5.9). The reaction proceeds without observable racemization[23].

Carboxylic acids can be esterified[24] by reaction with alkyl halides and 1,5-diazobicyclo [5,4,0] undecene-5 (DBU) in benzene at 25 or 80° (5.10). The reaction is widely applicable to hindered or unstable acids. Presumably the hydrogen bonded complex of DBU and the acid plays a significant role in the reaction. The DBU can be recovered by treatment of the hydrochloride with sodium hydroxide[25].

Esters[26] can be prepared by the reaction of an acid and an alcohol in the presence of pyridine (3 equivalents) and N,N-dimethylphosphoramidic dichloride, $(CH_3)_2NPOCl_2$ (1.5 equivalents) at room temperature. Phenyl dichlorophosphate, $C_6H_5OPOCl_2$, can also be used as the activating agent, often with somewhat improved yields. This esterification is applicable even to tertiary alcohols.

Methyl and ethyl esters[27] of carboxylic acids can be prepared by the reaction of carboxylic acids with trialkyloxonium tetrafluoroborate. The reaction is rapid even with hindered acids.

Dimethylchloroformiminium chloride generated in situ for DMF and oxalyl chloride, converts carboxylic acids into an activated derivative, which reacts with alcohols or phenols in presence of pyridine to form esters[28] in 70-90% yield. The method is also useful for preparation of active esters for N-protected amino acids, since no racemization is observed.

Chemiabsorption of dicarboxylic acid on alumina or silica can be used to effect selective esterification[29] of one acid group with diazomethane. The method was demonstrated by conversion of terepthalic acid, C_6H_4-1,4-$(COOH)_2$, into the monomethyl ester in quantitative yield.

Acids can be esterified at 25°C and in yields of 85-95% by treatment with 2-fluoro-1,3,5-trinitrobenzene (1 equivalent), 4-dimethyl aminopyridine (DMAP; 2 equivalents) and an alcohol in acetonitrile for 2-24 hrs. The method is successful with hindered acids but t-butyl esters cannot be prepared under these mild conditions. Presumably a trinitrophenyl ester is an intermediate[30].

PRESENT WORK

Under normal displacement conditions in protic solvents carboxylate anions are weakest nucleophiles due to their strong solvation, while in nonpolar aprotic solvents under PTC conditions the presence of ionpairs may show enhanced reactivity of the carboxylate anion.

Brandstrom's standard procedure for esterification[31] consists of neutralising equivalent amounts of acid and tetra-n-butyl ammonium hydrogen sulfate with sodium hydroxide solution, adding an excess of alkylating agent in dichloromethane and refluxing for 30 minutes. By this method yields obtained are upto 90% even in case of sterically hindered o,o'-dimethyl or dimethoxy substituted benzoic acids.

Earlier reports show that the synthesis of aryloxy acetic acid esters have been carried out by using polymer supported aryloxyacetic acid anion and alkyl halide.[37](5·11).

In view of the importance of aryloxyacetic acid esters as flavouring agents, a simple and efficient method is now reported for the O-alkylation of aryloxyacetic acids under PT catalyzed conditions. We have synthesized the aryloxy methyl acetates which are potential biological active compounds particularly in the pesticide field[32]. This procedure for O-alkylation consists of neutralising equivalent amounts of aryloxyacetic acid and tetra-n-butyl ammonium hydrogen sulfate with sodium hydroxide solution, adding an excess of methyl iodide dissolved in dichloromethane and refluxing for 2 to 4 hrs. Here the products were obtained in higher yields and purity.

$$\underset{\text{I}}{Ar\text{-}O\text{-}CH_2COOH} \xrightarrow[CH_3I,\ CH_2Cl_2 \text{ reflux, 2-4 hr}]{\text{aq. NaOH, } n\text{-}Bu_4N.\ HSO_4} \underset{\text{II}}{Ar\text{-}O\text{-}CH_2COOCH_3}$$

a) Ar = C_6H_5 -

b) Ar = $C_{10}H_7$ -

c) Ar = o-CH_3-C_6H_4 -

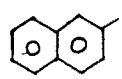
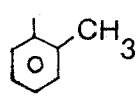
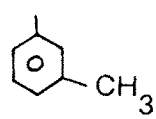
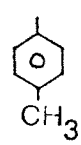
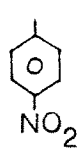
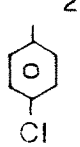
d) Ar = m-CH_3-C_6H_4 -

e) Ar = p-CH_3-C_6H_4 - f) Ar = p-NO_2-C_6H_4 -

g) Ar = p-Cl-C_6H_4 -

The results of the synthesis of various aryloxy methyl acetates are given in Table-1. The products were characterised by B.P., ^{1}H-NMR spectra (Table-2) and IR spectra.

TABLE - 1 : Different Aryloxymethyl Acetates (II) Synthesized.

Product No.	Ar -	Reaction Time [hr]	Yield [%]	B.P.(Lit) [°C]
II_a *		4	90	245(245)[33]
II_b *		2.5	85	77(78)[34]
II_c *		2.5	88	210(210)[33]
II_d		3.5	89	208(208)[33]
II_e		2.5	90	207(207)[33]
II_f *		4	90	99(100)[34]
II_g *		4	85	145

* Some illustrative NMR spectra of esterification are given just after the experimental part.

TABLE - 2 : ^{1}H-NMR Spectral Data

Product No.	^{1}H-NMR (CCl_4) δ (ppm)
II_a	3.65 (3H,s,-CH_3), 4.5 (2H,s,-CH_2-COO), 6.71-7.3 (5H, m, Ar-H).
II_b	3.75 (3H, s, -O-CH_3), 4.8 (2H, s, -OCH_2 - CO), 6 - 7.5 (7H, m, Ar-H).
II_c	2.3 (3H, s, Ar-CH_3), 3.7 (3H, s, - OCH_3), 4.5 (2H, s, -O-CH_2), 6.6-7.3 (4H, m, Ar-H).
II_d	2.3 (3H, s, Ar-CH_3), 3.7 (3H, s, -OCH_3), 4.5 (2H, s, -O-CH_2), 6.6-7.3 (4H, m, Ar-H).
II_e	2.3 (3H, s, Ar-CH_3), 3.7 (3H, s, -OCH_3), 4.5 (2H, s, -O-CH_2), 6.6-7.3 (4H, m, Ar-H).
II_f	3.7 (3H, s, -O-CH_3), 4.8 (2H, s, -O-CH_2-CO), 7.2 (2H, d, Ar-H meta to -NO_2), 8.3 (2H, d, Ar-H ortho to -NO_2).
II_g	3.65 (3H, s, -OCH_3), 4.55 (2H, s, -OCH_2-CO), 6.7 - 7.3 (4H, m, Ar-H).

IR Spectral Data :

All aryloxyesters show absorption bands at 1730-1670 cm^{-1} ester carbonyl and 1100-1050 cm^{-1} C-O-C symmetrical stretching of aryl alkyl ethers. The asymmetrical stretching of C-O-C shown at 1260-1240 cm^{-1}. Micro compounds show absorption bands at 1560 cm^{-1} and 1380 cm^{-1}.

EXPERIMENTAL

General :

Methyl iodide (SRL), tetra-n-butyl ammonium hydrogen sulfate (SRL) were commercially available.

Phenoxyacetic acid ($C_6H_5OCH_2COOH$), o-methylphenoxyacetic acid (o-CH_3-$C_6H_4OCH_2COOH$), m-methyl phenoxyacetic acid (m-CH_3-$C_6H_4OCH_2$ COOH), p-methyl phenoxyacetic acid (p-CH_3-C_6H_4O-CH_2COOH), β-napthoxy acetic acid, p-chloro phenoxyacetic acid (p-Cl-C_6H_4O-CH_2COOH) were prepared according to the procedure given in the 'Text Book of Organic Chemistry' by A.I. Vogel. p-nitro phenoxyacetic acid was prepared by polymer supported method.[35]

The ^{1}H-NMR spectra were recorded on Perkin-Elmer 783 spectrophotometer.

General Procedure for Synthesis of Aryloxymethyl Acetates :

Aryloxyacetic acid (5 m mole) and tetra-n-butyl ammonium hydrogen sulfate (1.7 gms, 5 m mole) was added to sodium hydroxide (0.200 gms, 5 m mole) in 2.5 ml. water. To this stirred solution methyl iodide (0.37 ml, 6 m mole) in 5 ml dichloromethane was added. The resultant reaction mixture was refluxed with stirring for 2-4 hrs. 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. The tetra-n-butyl ammonium iodide separated out as a solid was filtered off. The etheral solution was dried

with anhydrous sodium sulfate. After removal of the solvent, the product was purified by chromatography over silica gel eluting with benzene.

Recovery of Tetra-n-Butyl Ammonium Hydrogen Sulfate :

The tetra-n-butyl ammonium iodide separated as a solid was converted into tetra-n-butyl ammonium hydrogen sulfate[36].

$$\underset{\text{toluene}}{Bu_4\overset{+}{N}I} + \underset{H_2O}{H_2SO_4} + (C_8H_{17})_3N \longrightarrow \underset{\text{toluene}}{(C_8H_{17})_3N{:}HI} + \underset{H_2O}{Bu_4N^+HSO_4^-}$$

Tetra-n-butylammonium iodide (0.01 mole, 3.69 gm), trioctylamine (0.0113 mole, 4.0 g), toluene (20 ml) and 1 M H_2SO_4 (10 ml) were mixed and stirred until all solid had disappeared. The layers were separated and the organic layer washed with three 10 ml portions of water. The combined aqueous layer was washed with two 5 ml portions of methylene chloride. This removed an excess of tetra-n-butyl ammonium iodide, or an excess of H_2SO_4 as an ion pair with trioctylamine. The water was removed at reduced pressure (60° and 1 torr at the end). The residue was almost pure tetra-n-butyl ammonium hydrogen sulfate.

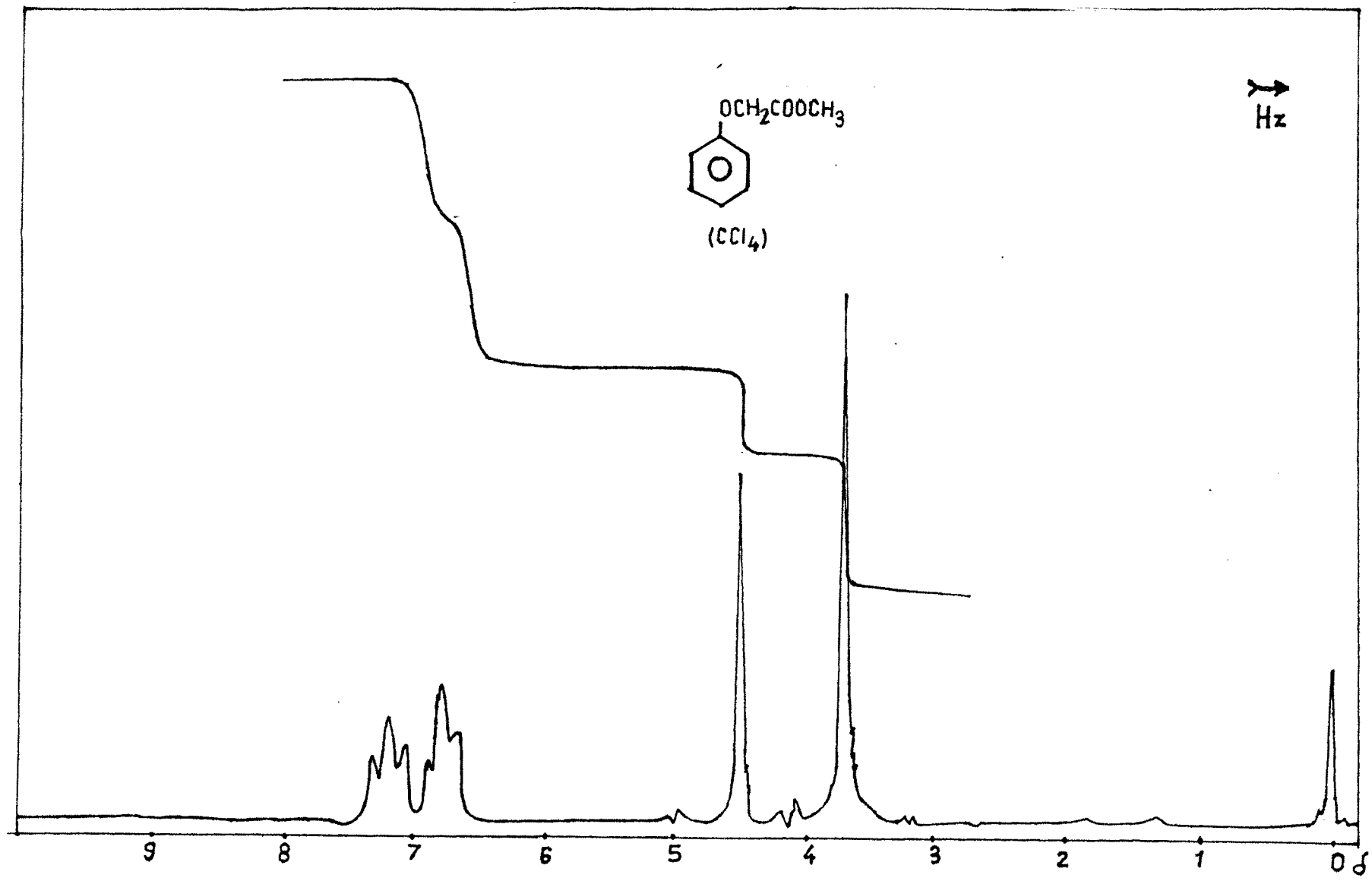


Fig. 1

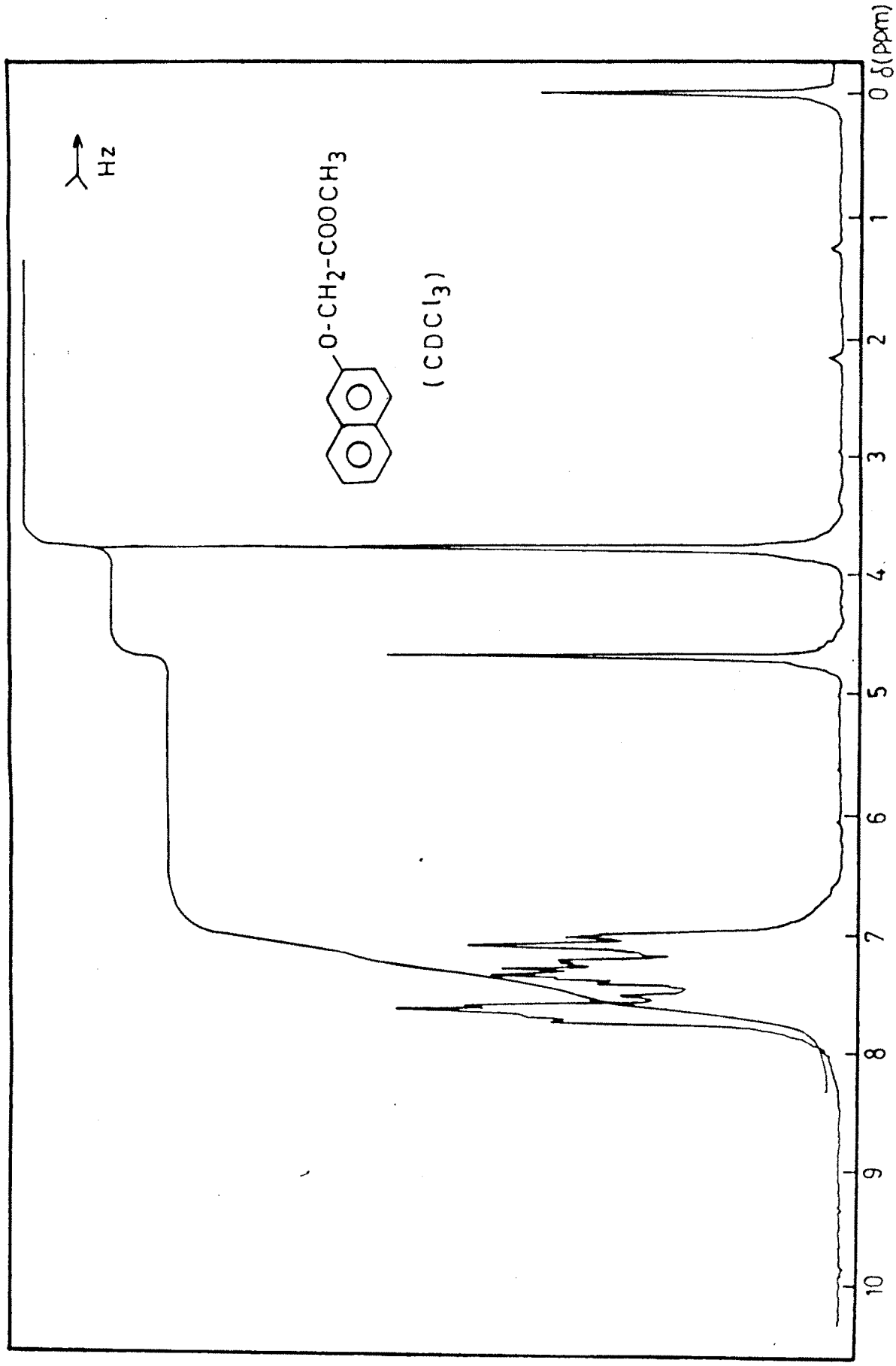


Fig. 2

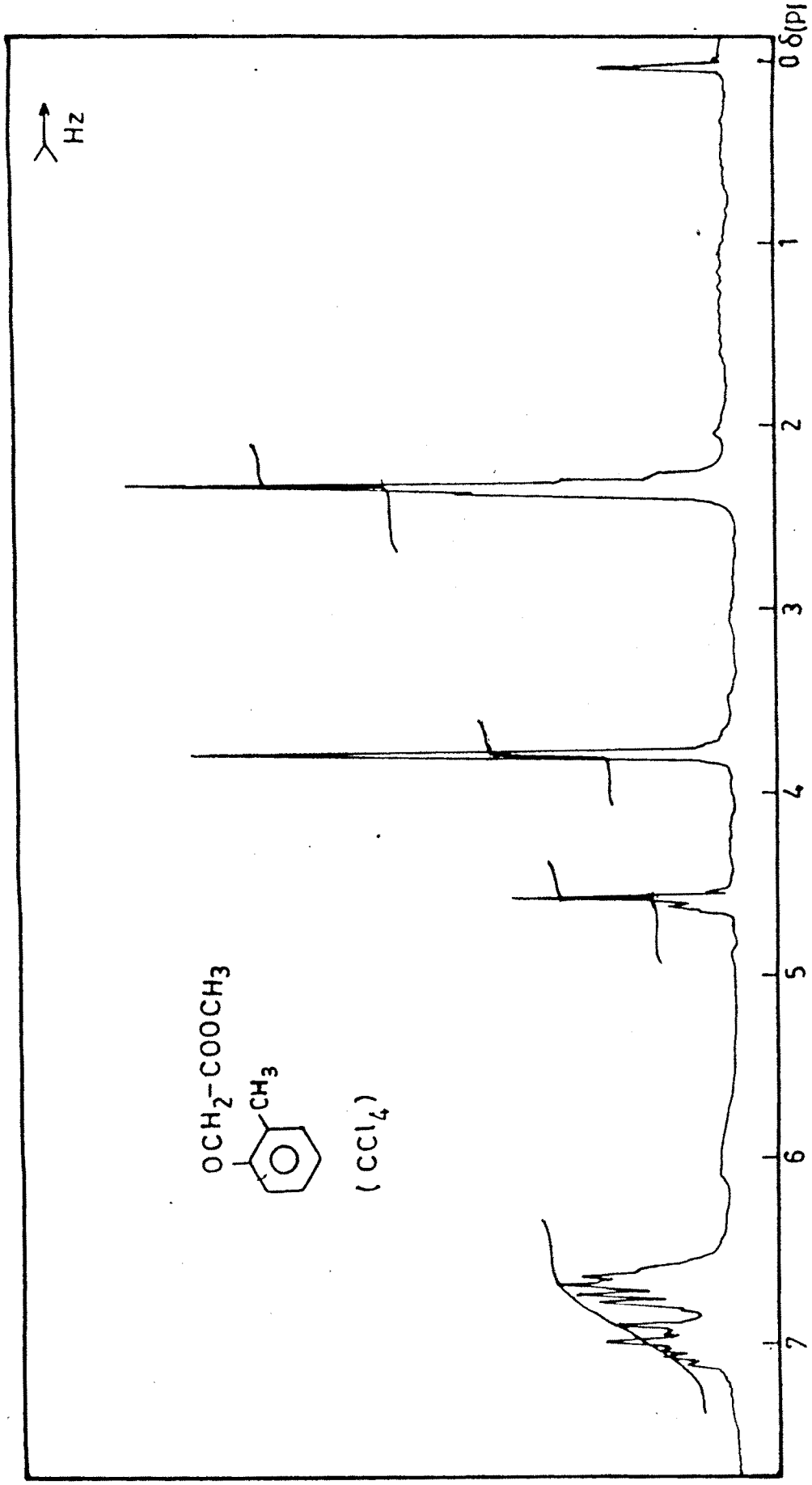


Fig. 3

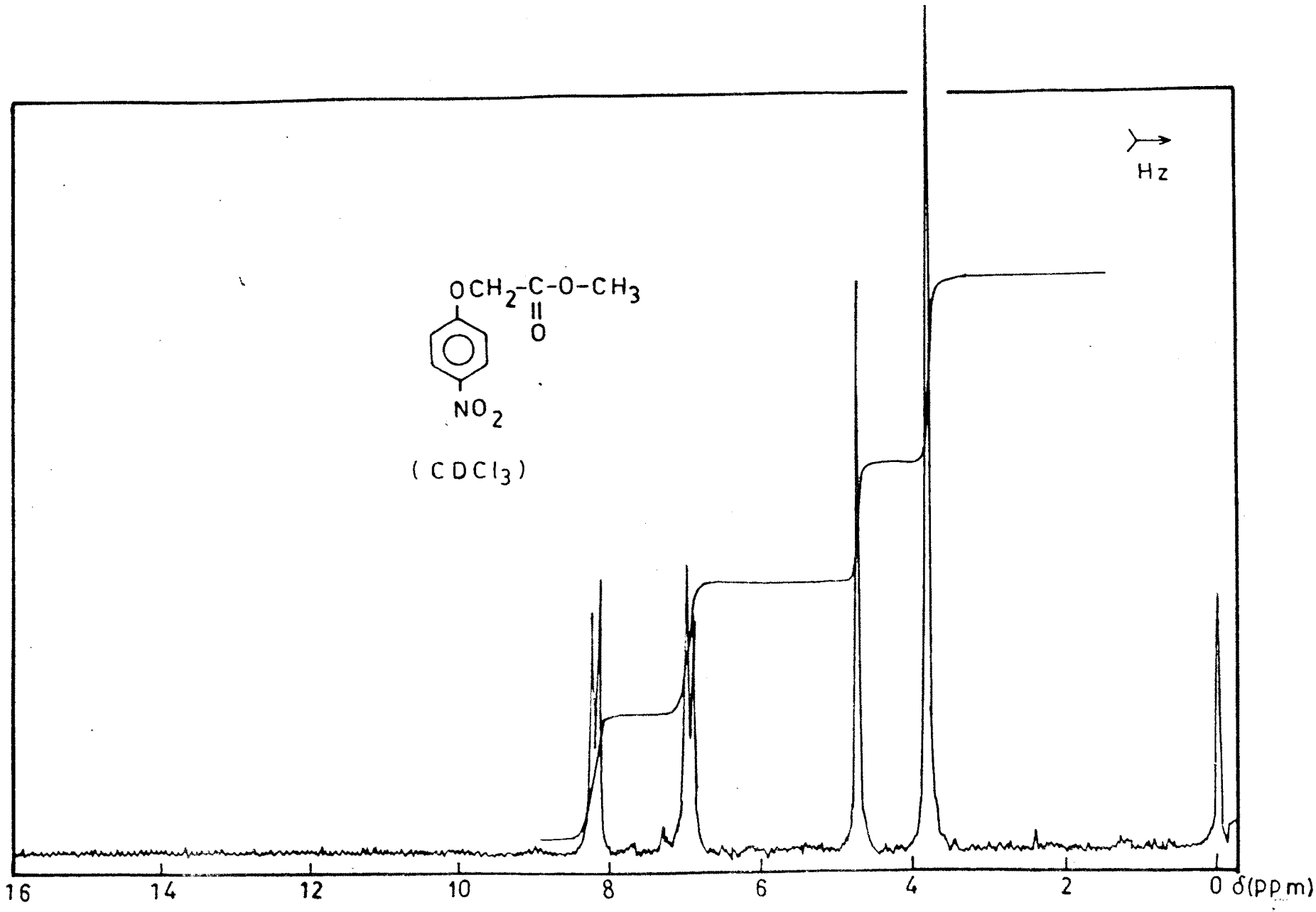


Fig. 4

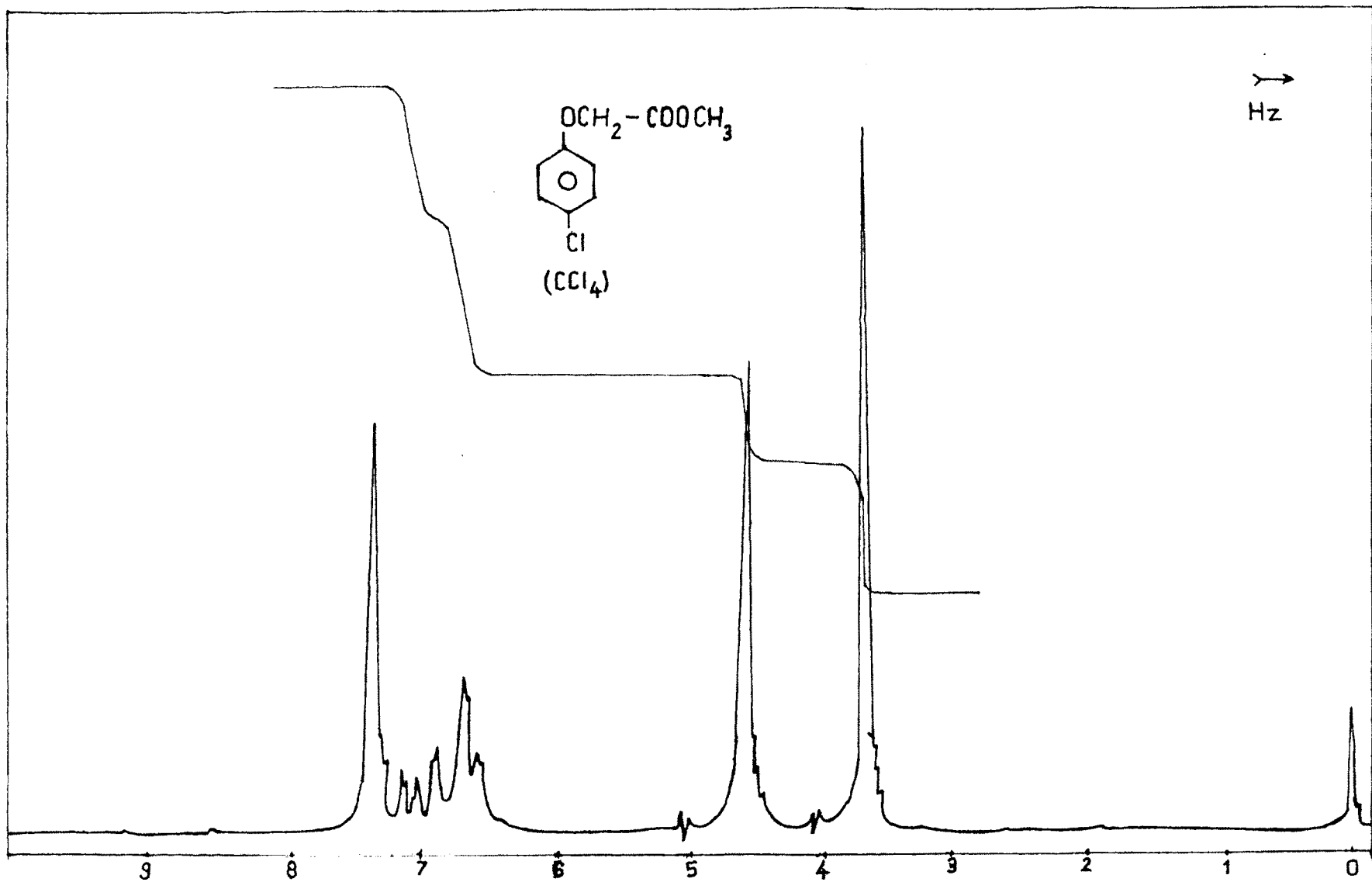


Fig. 5

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