CHAPTER - 2

SYNTHESIS OF PHENACYL ESTERS BY USING MIXTURE OF TETRABUTYLAMMONIUM BROMIDE AND DIBENZO-[18]-CROWN-6.

ABSTRACT

O-alkylation of carboxylic acid by phenacyl bromide using the mixture of tetrabutylammonium bromide and dibenzo-(18)-crown-6 provides a simple and efficient procedure for the synthesis of phenacyl esters.

INTRODUCTION

Esterification is an important and fundamental reaction which is widely used in various fields of chemistry and a number of methods have been presented. Esterification of carboxylic acids with hydroxy compounds (R'OH) is usually effected by refluxing the acid and alcohol with small amount of sulfuric acid, hydrogen chloride or arylsulphonic acid (3.1). The equillibrium 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 esterification at room temperature[2].

Reactive hydrogen compounds (R'X) such as benzyl chloride[3], 2-bromoacetylthiophene (C_4H_3S) $COCH_2Br$[4], and 2-chloromethylthianaphthene (C_8H_5S) CH_2Cl[5] are readily converted to esters by treatment with sodium salt of

carboxylic acids (3.2). 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 (3.3). A rigorous 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].

Phenyl esters[8] are obtained by heating an acid and a phenol in polyphosphoric acid (PPA) (3.4). 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)[9]. The reaction is considered to involve intermediate formation of the acid anhydride (3.5).

Carboxylic acids and phenols can be converted into methyl esters[10] and ethers in yields > 90% by thermal decomposition of trimethyl anilinum salts in an inert refluxing solvent like toluene (3.6). This method is successful even with sterically hindered acids.

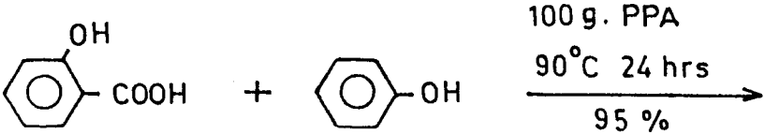
Shaw and Kunerth[11] have reported the esterification of sodium salt of carboxylic acids with alkyl halides in hexamethylphosphoric triamide (HMPT) at room temperature.

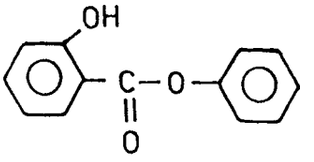
CHART-3

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

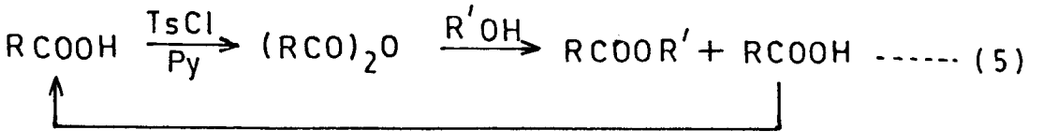
$$RCOONa + R'X \longrightarrow RCOOR' + NaX \quad \text{--------(2)}$$

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





---------(4)



$$RCOOH + (CH_3)_3\overset{+}{N}C_6H_5\bar{O}H \xrightarrow{\Delta}$$

$$RCOOCH_3 + (CH_3)_2NC_6H_5 \text{---(6)}$$

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

$$CH_2(COOC_2H_5)_2 \text{------ (7)}$$

$$C_6H_5COOH + CH_2Br_2 \xrightarrow[86\ \%]{NaOH,\ HMPT}$$

$$(C_6H_5COO)_2CH_2 \text{------(8)}$$

The method is applicable to the preparation of ethyl esters of hindered acids. In esterification of acids that undergo ready decarboxylation, anhydrous potassium carbonate rather than NaOH is used as base (3.7). Diesters[11] can be obtained by reaction of sodium salt of acids with dibromomethane (3.8).

Methyl and ethyl esters[12] of carboxylic acids can be prepared by the reaction of carboxylic acids with trialkyloxonium tetrafluoroborate. The reaction is rapid even with hindered acids.

Aryloxy-acetic acid esters are formed conveniently by using polymer supported aryloxy acetic acid anion and alkyl halide[13] (3.9).

Bram[14] and co-workers have reported a procedure for formation of aromatic carboxylic esters by alkylation of potassium carboxylate under solid-liquid phase transfer catalyst (TBAB or Aliquat 336) without using solvent.

The reaction of salt of hydroxy carboxylic acids with alkyl halide in the presence of PTC ($Bu_4N^+X^-$)[15] or crown ether (18-C-6)[16], (3.10) gives carboxylic esters. Non-quaternizable tertiary amines[17] also used as PTC, gives low yield of esters. However the yield is increased by using $Bu_4N^+Br^-$.

Esters of hydroxy carboxylic acids are also prepared by using two phase system of H_2O and higher alcohol in the presence of inorganic salts[18]. The phase transfer

catalyzed esterification of salt of carboxylic acids with alkyl halide in two phase system (H_2O/CH_2Cl_2) gives carboxylic esters[19]. The α-Naphthalene acetic acid aryl esters are prepared by using PTC in which α-naphthalene-acetyl chloride is treated with ROH in presence of NaOH in two phase system[20]. (3.11).

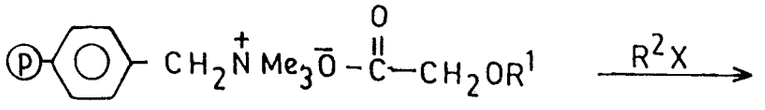
Very recently, the use of Phase-Transfer Catalysis for the synthesis of diacetate esters has been reported by Xiaojuan et. al.[21].

Aliphatic saturated and unsaturated acids, benzylic acids and aromatic acids in benzene are esterified by alkyl halides in the presence of aqueous solution of K_2CO_3 and Bu_4NBr as PTC[22] (3.12).

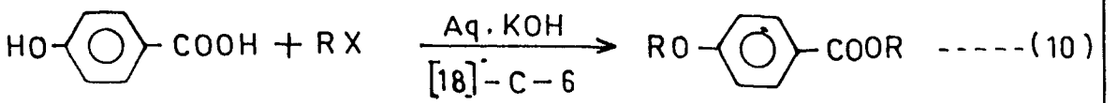
The reaction of salt of carboxylic acids with a halo derivative of an aliphatic or cycloaliphatic hydrocarbon in presence of phase transfer agent such as Bu_2NCH_2PhCl gives carboxylic esters.[23] An improved esterification of salt of carboxylic acids with alkyl halides under phase transfer condition without solvent has been reported by Vinczer et. al.[24]

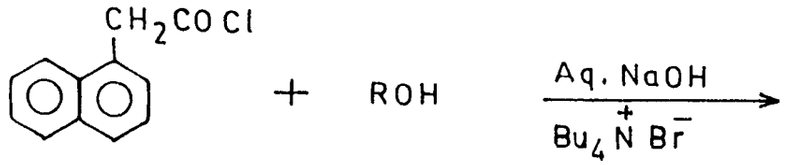
Numerous esters are prepared by using non-modified domestic microwave ovens as safe and convenient lab devices. High pressures are avoided by conducting the reaction with reactants impregnated on solid mineral supports in dry media or by PTC in absence of organic solvents[25].

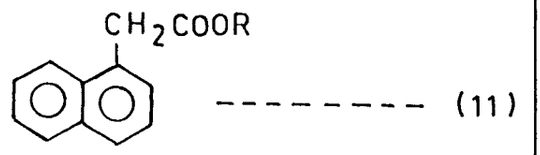
CHART-3 (contd)



$$R^1OCH_2COOR^2 + \text{(P)-C}_6\text{H}_4\text{-}CH_2\overset{+}{N}Me_3\bar{X} \quad \text{---(9)}$$

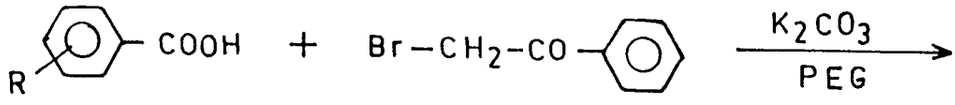


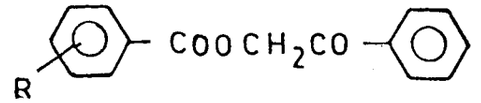




$$\text{-------- (11)}$$

$$RCOOH + R'X \xrightarrow[Bu_4\overset{+}{N}Br^-]{\text{Aq. } K_2CO_3} RCOOR' \quad \text{------- (12)}$$





$$\text{-------- (13)}$$

The utilization of phenacyl and p-bromophenacyl esters for identification and separation of acids have been indicated by Rather and Reid[26] and by Judifind and Reid[27]. p-Halogenophenacyl and phenacyl esters are in some cases superior to p-hitrobenzyl esters in the identification of acid[27]. The successful employment of these reagents for fruit acids has suggested the possibility of quantitative differentiation of fatty acids obtained from suponification of glycerides contained in fats and vegetable oils.

Phenacyl esters can be prepared by the action of the phenacyl bromide on the sodium salt of an acid in aqueous alcoholic solution[28]. Phenacyl esters serve very well for synthetic purposes because they are much more readily cleaved by nucleophiles than other esters. Phenacyl esters are stable to acidic hydrolysis e.g. The reaction of acid with phenacyl bromide in the presence of bases[29,30] gives phenacyl esters, which can be cleaved by treatment with Zn/HOAc or H_2/Pd-C[29,31]. Huang et. al.[32] have reported the phenacyl esters, under phase transfer catalyzed condition using polyethylene glycol and in presence of K_2CO_3 with phenacyl bromide and carboxylic acids (3.13). The esters can be cleaved by hydrolysis with NaTeH to give acid. Phenacyl carboxylates and thiocarboxylates are also cleaved by metal alkoxides[33].

PRESENT WORK

The synthesis of phenacyl esters has many uses in organic chemistry. Hendrickson and Kandall[31] have reported the use of phenacyl esters as protecting groups in which they are specially attractive as they are stable to many reactive conditions used in organic synthesis and are released under very mild conditions, such as treatment of the derivative with zinc in acetic acid. The majority of phenacyl esters are solids and as such, they provide a useful means for characterizing acids or phenols. Earlier Hendrickson has reported that the phenacyl esters can be synthesized according to traditional methods[34] or by treating the sodium salt of the acid with the appropriate phenacyl bromide in DMF. The problems with the classical procedure are that slow reaction times[34], hydrolysis of the alkylating agent[35], low yields of product and contamination of product with starting alkylating agent.

In 1974 Durst[36] has overcome some of these problems by carrying out the reaction using the potassium salt of an acid, p-bromophenacyl bromide and dicyclohexano[18]-crown-6 as the stabilizing catalyst under reflux conditions in acetonitrile. Clark and Miller[37] utilized potassium fluoride in glacial acetic acid for the quantitative preparation of phenacyl esters. Subsequently these reactions are developed as general methods for fatty acids[38] and biologically important dicarboxylic acids and

their separation and determination by HPLC. Salunkhe et. al.[39] used polymer supported reagent for synthesis of phenacyl esters.

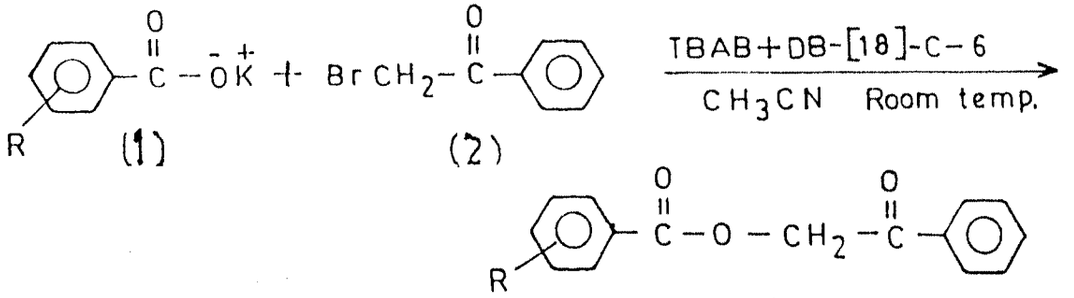
Bartsch and Philips[40] introduced tris-(3, 6-dioxaheptyl) amine (TDA-1) as phase transfer catalyst for substitution by strongly nucleophilic reagent such as thiocyanate, methoxide and phenoxide. However reactions of weaker nucleophilies such as carboxylate were not examined. He used Durst's[36] procedure, a reaction mixture of equimolar potassium carboxylate and ∝-p-dibromoacetopheone (0.1 mmol) and TDA-1 (0.06 m mol) instead of crown ether, was refluxed in acetonitrile for 15 minutes. However for carboxylate derived from certain highly ramified carboxylic acids the reaction appeared to be significantly slower than when the crown ether catalyst was utilized. Huang et al[32] utilized PEG as PTC with K_2CO_3, they also used same procedure as Durst, i.e. reaction mixture of equimolar carboxylic acid, phenacyl bromide, potassium carbonate (5.5 m mol) polyethylene glycol (1 m mol) and acetonitrile was stirred at room temperature for 20 minutes and refluxed about 50 minutes.

The reported results shown in Table-1 suggest that even by using PTC drastic reaction conditions are required for synthesis of phenacyl esters.

Table-1 : Synthesis of phenacyl ester of benzoic acid using different phase transfer catalysts:

PTC used	Temperature condition	Time (h)	Yield (%)	Refer-ence No
Dicyclohexano-[18]-C-6	Reflux	0.25	93	36
TDA-1	Reflux	0.25	96	40
PEG	Reflux	0.75	100	32

In view of the importance of phenacyl esters as protecting groups[31], we have carried out synthesis of phenacyl esters by reaction of potassium salt of benzoic acid with phenacyl bromide in two phase system (CH_2Cl_2/H_2O) in presence of the mixture of tetrabutylammonium bromide and dibenzo-[18]-crown-6. The reaction was completed after 5h indicating transport of carboxylate ion from aqueous phase into organic phase is slow. Therefore we thought that the reaction may be facile under solid-liquid phase transfer catalyzed condition which promted us to report here a simple and efficient method for the synthesis of phenacyl esters, where the reaction of equimolar potassium salt of an acid (1) with phenacyl bromide (2) was carried out within very short time and high yield under mild reaction conditions in acetonitrile using mixture of tetrabutylammonium bromide (TBAB) and a catalytic amount of dibenzo-[18]-crown-6. (Scheme).



(SCHEME)

The esterification of potassium salt of benzoic acid (0.05 m mol) with phenacyl bromide (0.05 m mol) using tetrabutylammonium bromide and dibenzo-[18] - crown-6 is monitored by varying the amount of both catalysts (Table-2)

Table-2: Effect on synthesis of phenacyl ester of benzoic acid (0.05 m mol) using different combinations of PTC (TBAB) and dibenzo-[18]-crown-6.

Expt	Dibenzo-[18]-crown-6 (mg)	PTC [TBAB] (mg)	Time (h)	Tempera- (°C)	Yield (%)
1	0	16	4.00	R.T.	86
2	4	0	3.00	R.T.	90
3	2	16	2.25	R.T.	90
4	2	32	1.75	R.T.	91
5	3	32	1.25	R.T.	93
6	4	16	1.50	R.T.	93
7	4	24	1.25	R.T.	95
8	4	32	0.75	R.T.	98
9	4	48	0.75	R.T.	98
10	4	32	0.08	80	98
11	6	48	0.75	R.T.	98

It is observed that by using the mixture of 4mg dibenzo-[18]-crown-6 with 32 mg of tetrabutylammonium bromide, reaction requires very short time as compared to the other combinations of the mixture (Expt No. 8, Table-2) Conducting the reaction without either of tetrabutylammonium bromide or dibenzo-[18]-crown-6 resulted in more reaction time and lower chemical yields than with both catalysts. The nucleophilicity of alkoxyanions is enhanced by both catalysts and hence O-alkylation reaction is completed within very short time, indicating solid liquid phase transfer catalysis is more effective than liquid-liquid phase system.

The results of the syntheses of phenacyl esters of various acids are given in Table-3. The products were characterized by ^{1}H-NMR spectra (Table-4) and IR spectra. Some illustrative ^{1}H-NMR and IR spectra of esterification are given just after the experimental part.

Table-3: Synthesis of phenacyl esters.

Acid	Time [h]	Yield [%]	M.P. (Lit.) [°C]
Benzoic	0.75	98	118 (119-120)[41]
p-Nitrobenzoic	3.00	90	128 (128)[26]
o-Chlorobenzoic	2.00	94	84 - 86
p-Methoxybenzoic	0.75	95	136 - 138 (136)[43]
o-Methylbenzoic	1.00	92	140 (138.5)[26]
m-Methylbenzoic	1.75	92	94 - 96
∝ -Furoic	2.25	95	84 - 86(84 - 85)[43]

As expected, for the reaction with acids containing electron withdrawing substituents, the rate was slow, while for the acids containing electron donating substituents, the rate was fast (Table-3).

It is noteworthy to see when dibenzo-[18]-crown-6 was used, the reaction was completed within 0.75 h for potassium salt of benzoic acid. However by using [15]-crown-5 the reaction required 7.5 h under similar conditions. This shows that the spatial coordination of ion and ligand cavity plays important role in using crown ethers. Obviously the effective cavity volume of the 18-membered crown ether ring is better suited to the ion diameter of K^+ (2.66 A°). By using [15]-crown-5 the reaction was completed within 3h for sodium salt of benzoic acid.

EXPERIMENTAL

General:

Potassium hydroxide (Merck), benzoic acid (Qualigens), p-nitrobenzoic acid (SRL), o-chlorobenzoic acid (SRL), m-methyl benzoic acid (Merck), furoic acid (Merck), p-methoxy benzoic acid (SRL), o-methyl benzoic acid (Merck), acetonitrile (Merck), methanol (Qualigens), tetrabutylammonium bromide (Loba), dibenzo-[18]-crown-6 (Merck), [15]-crown-5 (Merck), sodium hydroxide (Merck) are commercially available.

Phenacyl bromide was prepared by earlier reported method[42].

NMR: ^{1}H-NMR spectra were recorded on Brucker MSL 300 spectrometer.

IR: IR spectra were recorded on Perkin Elmer-783 spectrophotometer.

TLC: TLC was carried out using Kodak 13181 silica gel with fluorescent indicator precoated plates.

Procedure for preparation of phenacyl bromide:

A solution of 12.5 gms (12.14 ml. 0.105 M) acetophenone in 12.5 ml dry ether was placed in dry three necked flask fitted with a separating funnel, mechanical stirrer and reflux condensor. The solution was cooled in ice bath. 0.125 gms. of anhydrous $AlCl_3$ was introduced and 16.75 gms (5.35 ml, 0.105 M) of Br_2 was added gradually from separating funnel with stirring at rate of about 1 ml per minute. The bromine colour disappears rapidly although very little hydrogen bromide was evolved, towards the end of reaction solution becomes pink.

After the bromine has been added, the ether and dissolved HBr were removed at once under reduced pressure with slight current of air. The phenacyl bromide remains as a solid mass as brownish yellow crystals. The colour was removed by shaking with mixture of 1 ml of H_2O and 5 ml of petroleum ether. The crystals were filtered with suction and washed several times with fresh portion of solvent mixture until white product was obtained. The crude

product was recrystalized from methanol.

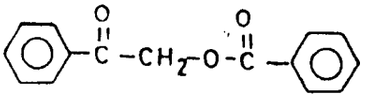
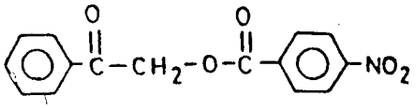
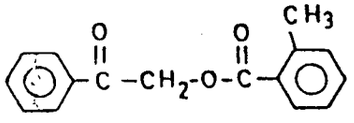
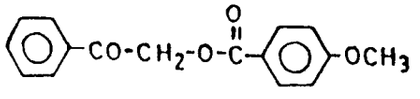
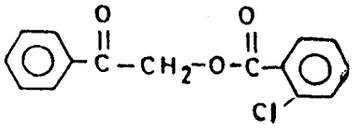
Procedure for the preparation of potassium salt of an acid:

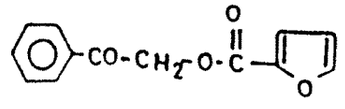
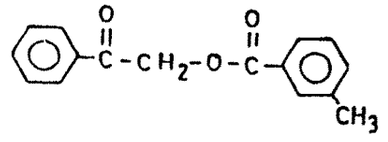
A sample of organic acid (0.05 m mol) dissolved in methanol (2 ml) was neutralised to phendph thalein end point by the equimolar potassium hydroxide in methanol. The solvent was removed under reduced pressure to get white or slight pink solid.

General procedure for the synthesis of phenacyl esters:

To a solution of potassium salt of an acid (0.05 m mol) in acetonitrile (5 ml) tetrabutylammonium bromide (32 mg), dibenzo-[18]-crown-6 (4 mg) and phenacyl bromide (0.05 m mol) were added and the reaction mixture was stirred at room temperature until TLC analysis (Pet ether: EtOAc, 9:1, V/V) indicated completion of the reaction. Solvent was removed under reduced pressure and the residue was taken up in dichloromethane (10 ml) and washed with water (2 x 10 ml). The organic layer was separated and dried over anhydrous sodium sulphate. The solvent was evaporated and the product was purified by column chromatography (Pet ether: EtOAc, 9:1, V/V).

Table-4: ^{1}H-NMR Spectral data

Sr. No.	Phenacyl Ester	^{1}H-NMR ($CDCl_3$) δ (ppm)
1.		5.42 (S, 2H,-$COOCH_2$) 7.28-7.51 (m, 6H, Ar-H, meta and para to -COO and CO) 7.78-7.91 (m, 4H, Ar-H ortho to-COO and CO)
2.		5.6 (S, 2H, -$COOCH_2$) 7.5 (d, 3H, Ar-H, meta & para to CO) 7.83 (d, 2H,Ar-H, ortho to-CO) 8.26 (S, 4H, Ar-H)
3.		2.6 (S, 3H, Ar-CH_3) 5.5 (S, 2H,-$COOCH_2$) 7.2 - 8.15 (m, 9H, Ar-H)
4.		3.8 (S, 3H, -OCH_3) 5.5 (5, 2H, -$COOCH_2$) 6.9 (d, 2H, Ar-H, ortho to -OCH_3 7.5 (m, 3H, Ar-H, meta & para to CO group) 7.95 (m, 4H, Ar-H, ortho to -COO and CO group)
5.		5.57 (S, 2H,-$COOCH_2$) 7.33-7.62 (m, 6H, Ar-H, meta & para to -COO and -CO) 7.82-8.08 (m, 3H, Ar-H, ortho to -COO and -CO)

Sr. No.	Phenacyl Ester	^{1}H-NMR ($CDCl_3$) δ(ppm)
6.		5.57 (S, 2H, $-COCH_2$) 6.6 (dd,1H, Ar-H J = 2.5 and J = 3.7 β' to cyclic O) 7.3 - 7.73 (m, 5H, Ar-H, meta and para to -CO and α' and β to cyclic O) 7.9 - 8.15 (m, 2H, Ar-H, ortho to CO)
7.		2.37 (S, 3H, $Ar-CH_3$) 5.53 (S, 2H, $-COOCH_2$) 7.22 - 7.6 (m, 5H Ar-H, meta and para to -COO & -CO) 7.8 - 8.04 (m, 4H, Ar-H, ortho to -COO and -CO)

IR SPECTRA : ν max (Nujol) cm^{-1}

I.R. Spectra of phenacyl esters were recorded on Perkin Elmer 783 Spectrometer and show characteristic absorption bands at 1705-1740 cm^{-1} (ester C = O) and 1680 - 1700 cm^{-1} (keto C = O). Esters of NO_2 acids at 1510 - 1520 cm^{-1} and 1345 - 1355 cm^{-1}

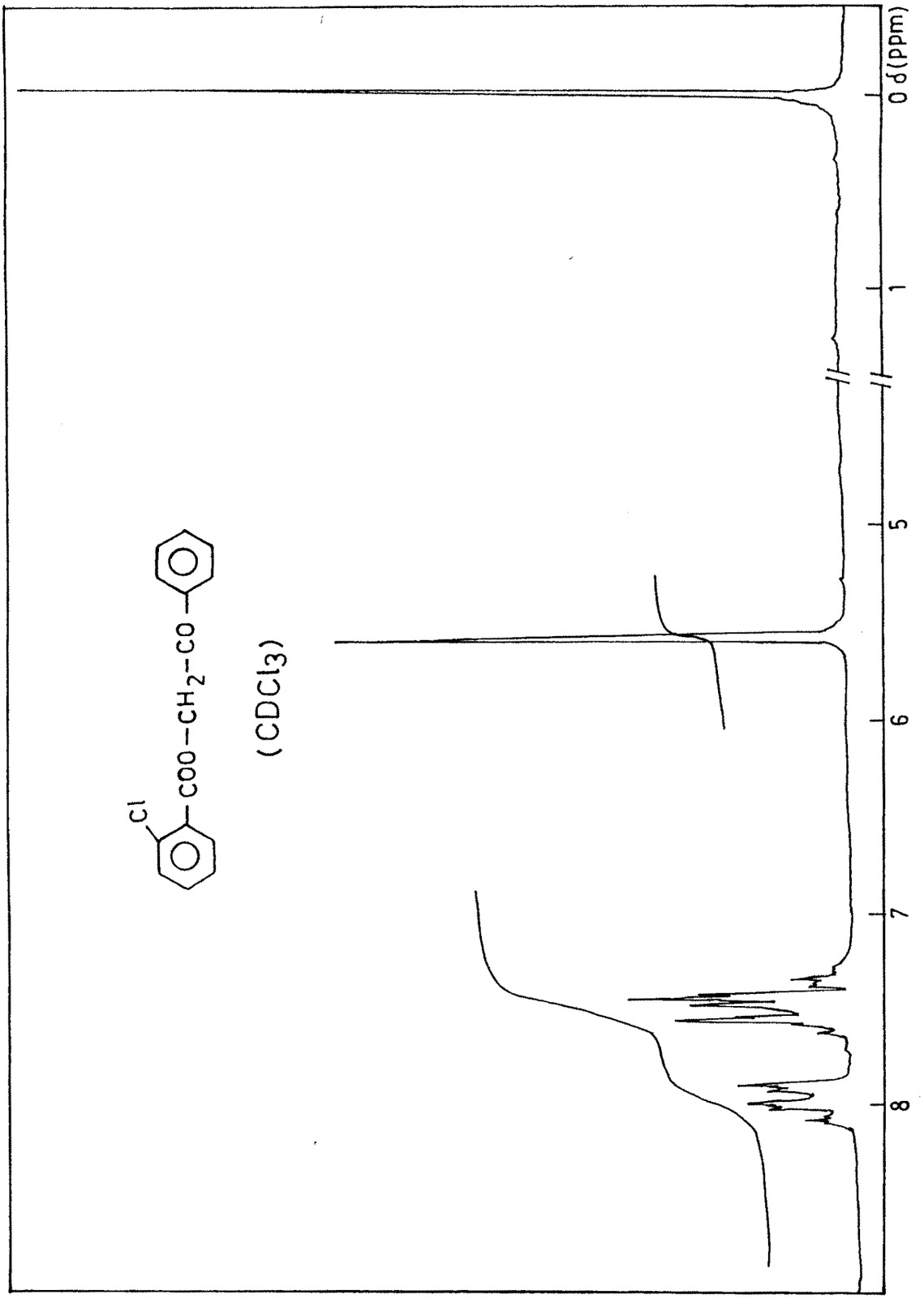


Fig. 1

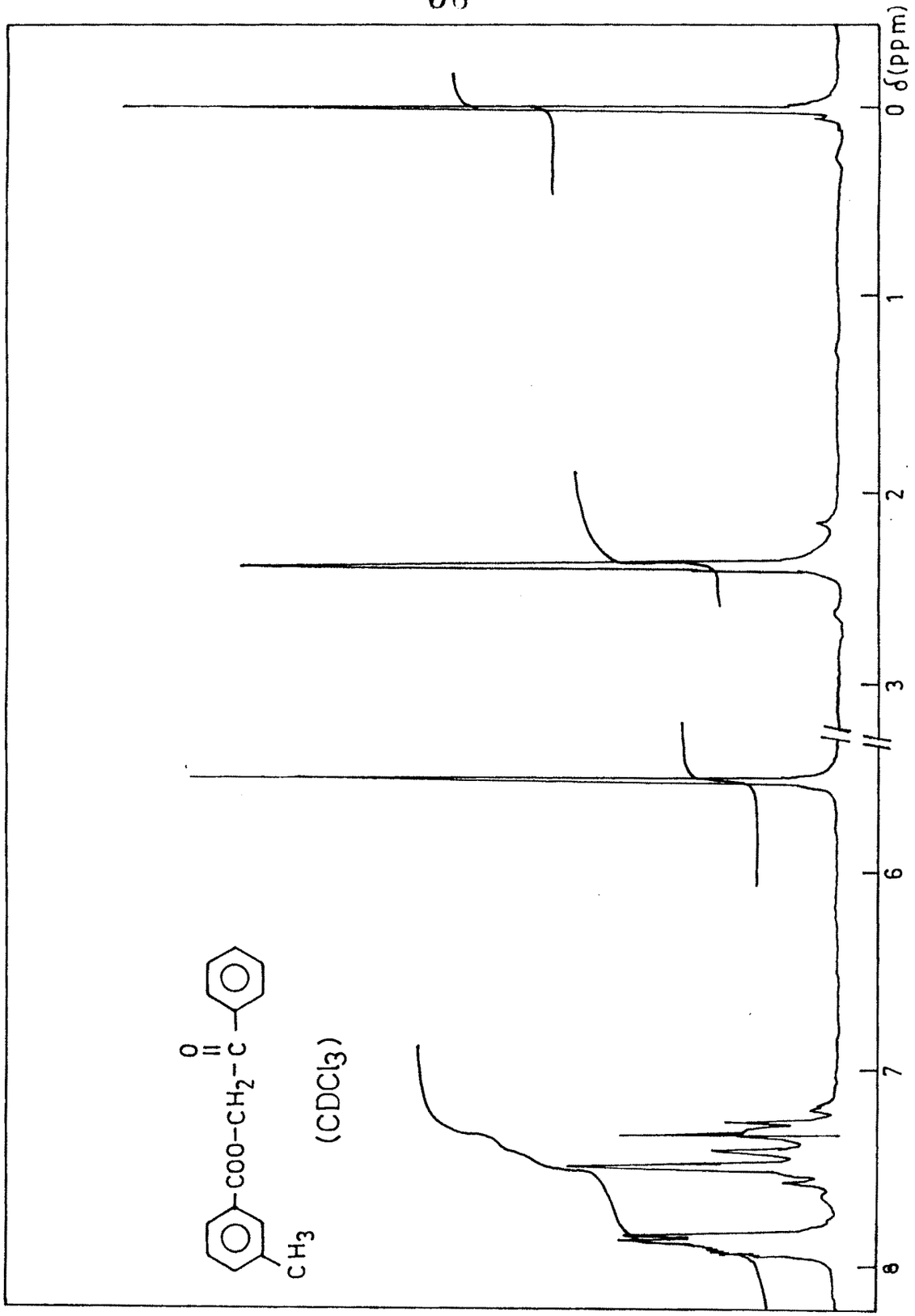


Fig. 2

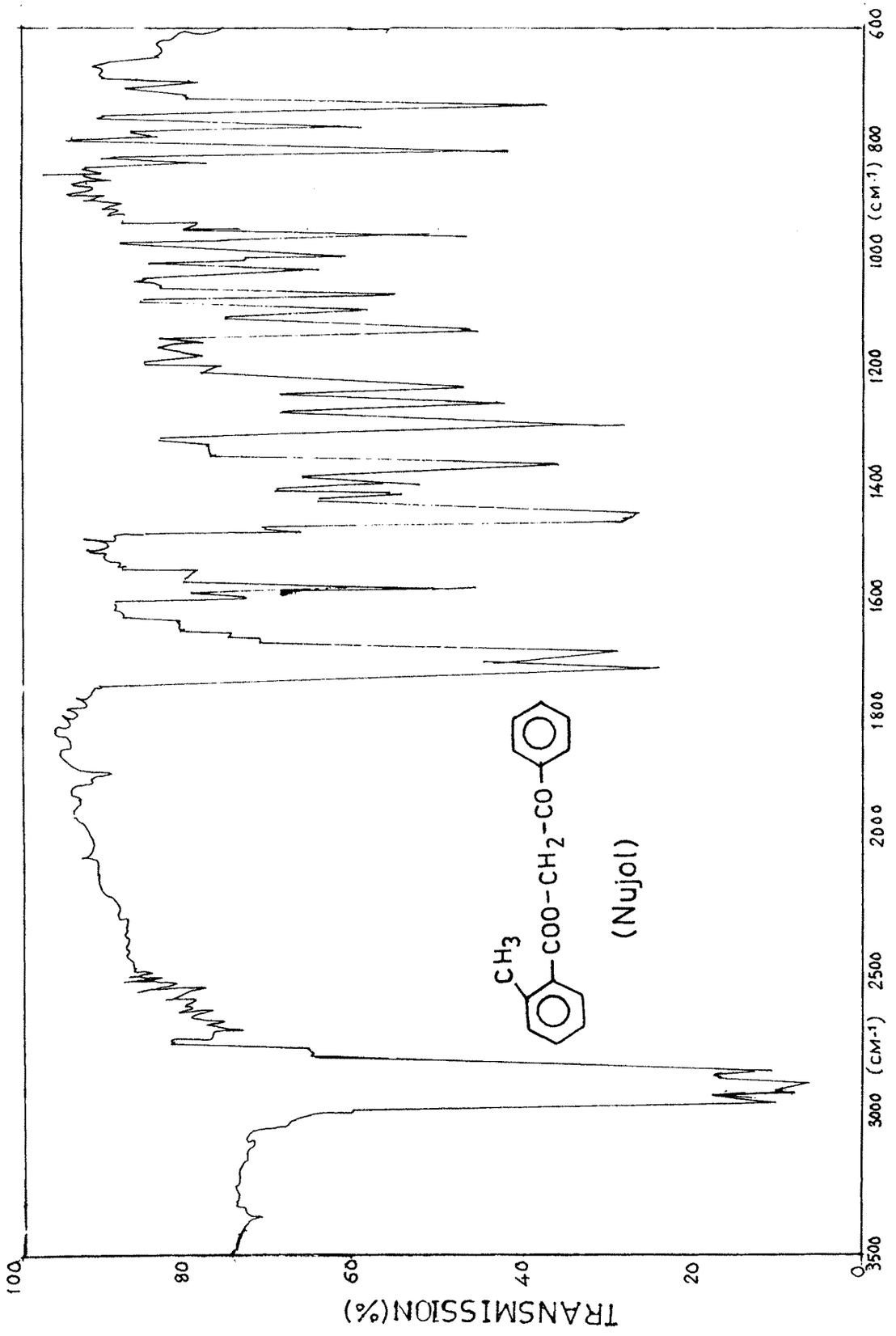

TRANSMISSION(%)
100
80
60
40
20
0
3500
3000 (CM-1)
2500
2000
1800
1600
1400
1200
1000 (CM-1)
800
600
WAVENUMBER
CH3
COO-CH2-CO
(Nujol)

Fig. 3

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