: CHAPTER - III :

SYNTHETIC APPLICATION OF PECHMANN CONDENSATION

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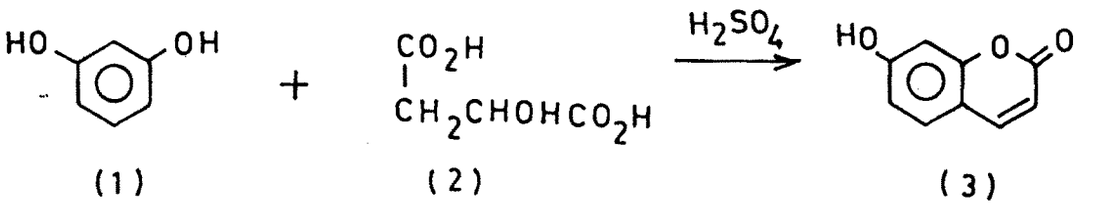
ABSTRACT

The Pechmann condensation of p-cresol (3.1) and 3,3-dimethyl acrylic acid (3.2) using methane sulphonic acid gave 4,4,6-trimethyl dihydrocoumarin (3.3). Reaction of p-hydroxy acetophenone with the same reactant using methane sulphonic acid yielded p-acetylphenyl-3,3-dimethyl acrylate (3.6). Condensation of p-hydroxy benzoic acid with 3,3-dimethyl acrylic acid using methanesulphonic acid did not give the desired product.

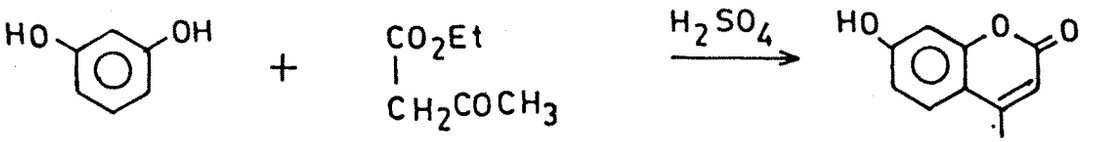
INTRODUCTION

Coumarine, Chromones and Chromanones together from an important group of natural products. We undertook the synthesis of some useful chromanones by using Pechmann and related reactions[1]. Variety of coumarin derivatives (1.3 and 1.5) have been reported firstly by Pechmann in 1883 by condensing malic acid (1.2) or β-Ketoesters (1.4) with phenols in presence of concentrated sulphuric acid. This reaction was modified by Simonis and his co-workers,who reported formation of chromanones[1] (1.6) rather than coumarins by using same reactants but phosphorus pentoxide as the condensing agent. The course of Pechmann condensation depends on the nature of phenol, the type of acid or ester and also on the condensing agent used.

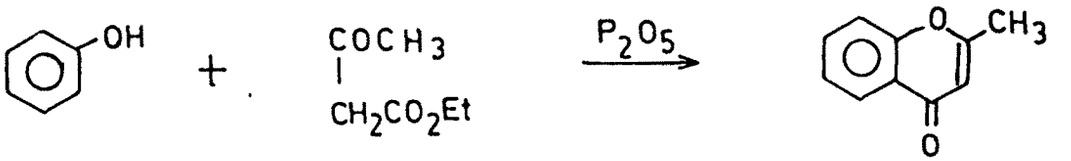
CHART-1



(1) (2) (3)



(1) (4) (5)



(6)

ACTIVITY OF PHENOLS :

The position and nature of the substituents present on the benzene ring definitely affect the reactivity of the phenol. Among mono-, di- and trihydric phenolic compounds, resorcinol is the most reactive. At the same time phenol, quinol and 2-naphthol give low yields of products. Alkyl groups in phenols have little inhibiting effect on the Pechmann condensation but halogens have more effect. In monohydric phenol substituent in the ortho position has a maximum inhibiting effect, less if it is in the para position and least with meta substituents. Substituents like nitro and carboxyl group may inhibit the reaction. The reactivity of the phenolic compound is increased by electron donating groups.

$$-CH_3 \rightarrow -OH \rightarrow -OCH_3$$

$$-NH_2 \rightarrow -NHCH_3 \rightarrow -NR_2$$

and is decreased by electron weithdrawing groups, i.e.,

$-NO_2$, $-SO_3H$, $-COOH$, $-COOCH_3$, $-COCH_3$, $-CN$ and $-CHO$

EFFECT OF CONDENSING AGENT :

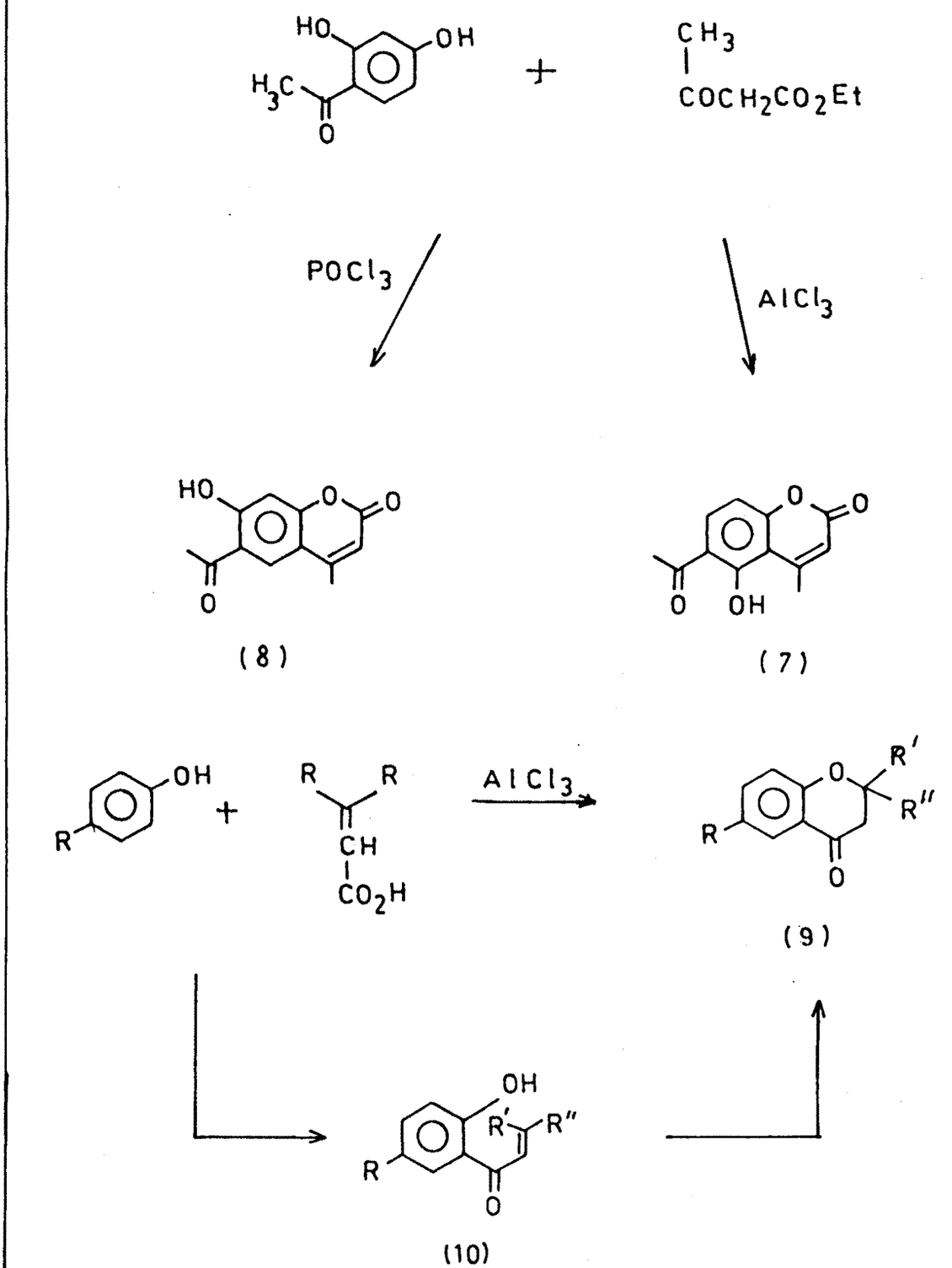
Various condensing agents that have been used for the Pechmann condensation are Phosphorous oxychloride, Phosphoric acid, Poly phosphoric acid, Zinc Chloride, anhydrous aluminium chloride, hydrogen chloride, hydrogen fluoride, boron trifluoride, stannic chloride, titanic chloride, sodium

ethoxide, sodium acetate, cation exchange resdin, methane sulphonic acid, delomite powder etc. The nature of the condensing agent may decide the type of product and the yield of the reaction. The most commonly used reagent is sulphuric acid, which leads to the formation of coumarin.[2] 70-80% sulphuric acid is preferred to decrease the tendency of sulphonation. By using hydrogen chloride instead of sulphuric acid sulphonation can be avoided. Sometimes phosphorus oxychloride gives better yield than sulphuric acid. Phenols that do not form coumarins at all or give poor yields with sulphuric acid generally give chromones in the presence of phosphorus pentoxide. Anhydrous Aluminium chloride in presence of dry ether or nitrobenzene is most efficient also it alters the course of some reactions. In resorcinol if 4-position is occupied by carboxyl, carbmethoxy, acetyl or nitro group, condensation product mainly obtained is 5-hydroxy coumarin derivatives (2.8) instead of 7-hydroxy derivatives (2.7).

Condensation of phenols with unsaturated acids or acid chlorides using aluminium chloride in nitrobenzene or carbon disulphide has been used for the preparation of 4-chromanone[3] (2.9). Phenolic esters of unsaturated acids yield chromanones on reaction with aluminium chloride. Phloroglucinol[4] on reaction with 3,3-dimethyl acrylic acid in presence of polyphosphoric acid gives various types of chromanones.

For the Pechmann reaction, polyphosphoric acid is an

CHART-2


HO
OH
H_3C
O
+
CH_3
$COCH_2CO_2Et$
$POCl_3$
$AlCl_3$
HO
O
O
O
(8)
O
O
O
OH
(7)
OH
R
+
R
R
CH
CO_2H
$AlCl_3$
R
O
R'
R''
O
(9)
OH
R'
R''
R
O
(10)

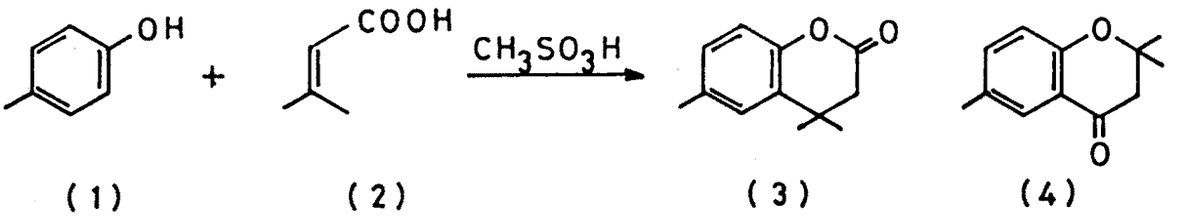
excellent condensing agent[5] than sulphuric acid. Zinc chloride-phosphorus oxychloride[6] is found to be useful in the preparation of 4-chromanone. The use of trihydric phenol i.e. phloroglucinol has also been reported[7] in the synthesis of 5,7-dihydroxy-2-methyl chromanone by reacting it with crotonic anhydride in presence of anhydrous aluminium chloride. Now-a-days resins like zeocarb 325, Amberlite IR-120 have been used as condensing agent[8] effectively. The main advantages are that these resins can be recovered and reused and also simple work-up methods. Recently it has been reported that methane sulphonic acid[9] used as condensing agent which also provides solvent medium for the reaction. It has been reported that montmorillonite clay[10] can act as an excellent condensing agent in Pechmann condensation reaction for the synthesis of various coumarin derivatives.

PRESENT WORK :

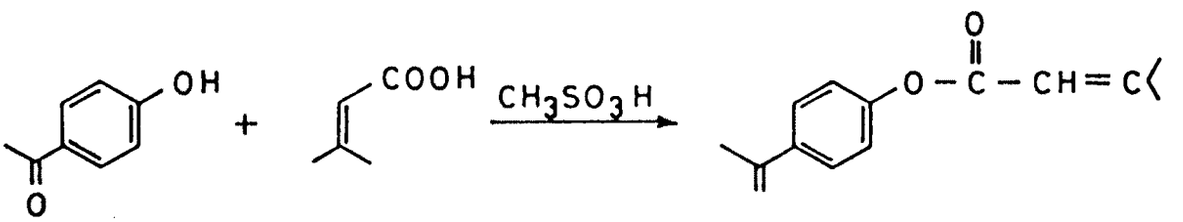
The chromanones like, 6-methyl-2,2-dimethyl-4-chromanone (3.4), 6-acetyl-2,2-dimethyl chromanone (3.7) and 5,7-dihydroxy -2,2-dimethyl chromanones form a group of natural products which are also useful as important intermediates for the synthesis of other natural products.

We undertook the synthesis of some of these chromanones using Pechmann condensation of suitable phenols with 3,3-dimethyl acrylic acid and methane sulphonic acid as condensing agent.

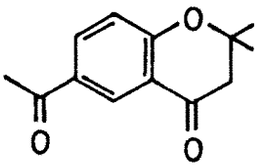
CHART — 3



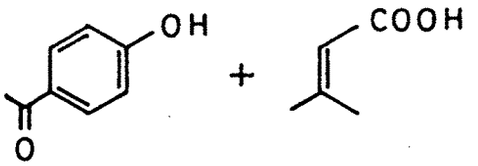
(1) (2) (3) (4)



(5) (2) (6)

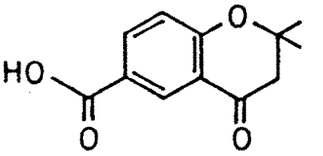


(7)



CH_3SO_3H → Starting material recovered

(8) (2)



(9)

The condensation of p-cresol with 3,3-dimethylacrylic acid (3.2) using methanesulphonic acid yielded 4,4,6-trimethyl dihydro coumarin (3.3) rather than expected chromanone (3.4). The structure (3.3) for the dihydrocoumarin has been assigned on the basis of spectral data. IR (nujol, fig.1) showed a strong band at 1775 cm^{-1} due to lactone carbonyl. The PMR ($CDCl_3$, fig.2) was in complete agreement with the structure. A strong singlet for six protons at δ 1.33 is assigned to the gem-dimethyl group, a singlet at 2.30 is due to aromatic methyl and a singlet for two protons at 2.50 is due to methylene protons. The three aromatic protons appeared as a multiplate between 6.6 and 7.2.

The reaction of p-hydroxyacetophenone and 3,3-dimethyl acrylic acid using methane sulphonic acid was carried out with a view to get the chromanone (3.7). This reaction gave p-acetyl phenyl-3,3-dimethyl acrylate (3.6). The I.R. spectrum of this product (fig.3) showed bands at 1710 cm^{-1} (ester) and 1670 cm^{-1} (ketone). The PMR spectrum (fig.4) showed two doublets for vinyl methyls at δ 1.94 and 2.18 a singlet for ketomethyl at 2.56, the olefinic proton at 5.7 and two doublets for aromatic protons at 6.92 (meta to ketone) and 7.9 (ortho to ketone).

Next, p-hydroxy benzoic acid was treated with 3,3-dimethyl acrylic acid and methane sulphonic acid with a view to getting the chromanone (3.9). The PMR indicated that the starting material was recovered.

All above experiments indicate that phenols deactivated by electron withdrawing groups like $-COCH_3$, $-COOH$ do not give chromanones under the above reaction conditions.

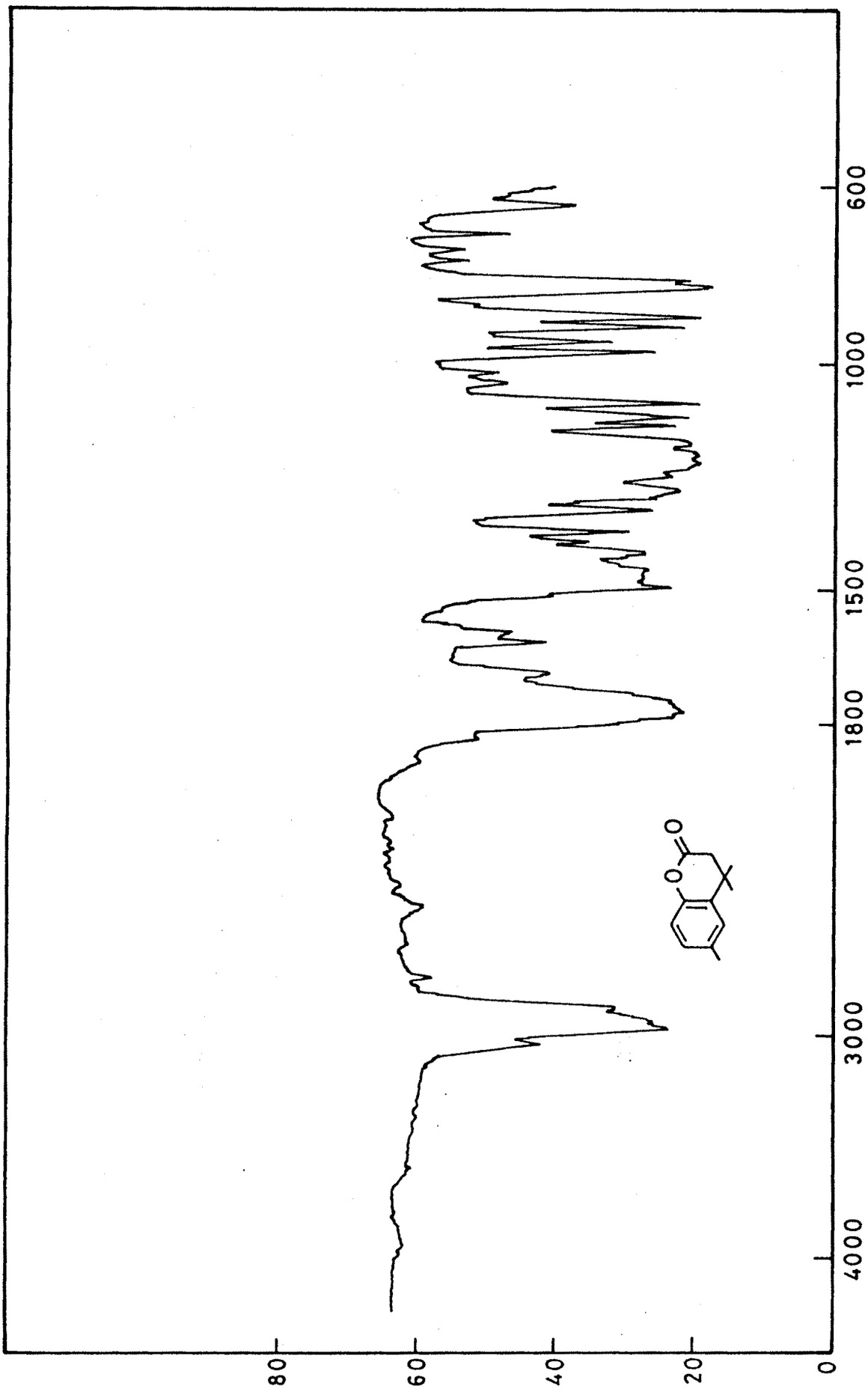

TRANSMITTANCE (%)
0
20
40
60
80
4000
3000
1800
1500
1000
600
WAVENUMBER (cm⁻¹)
O
O

FIG. 1

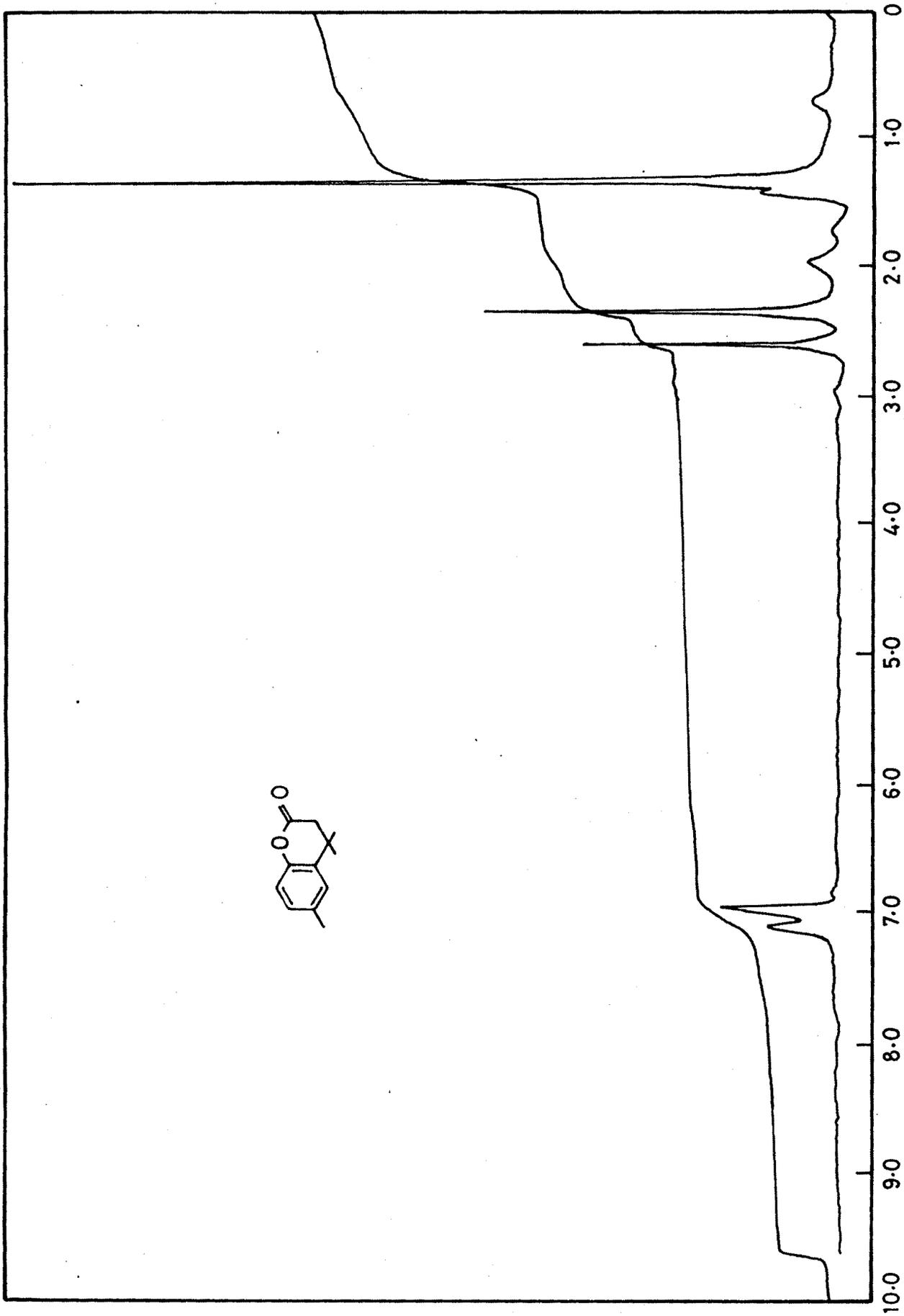


FIG. 2

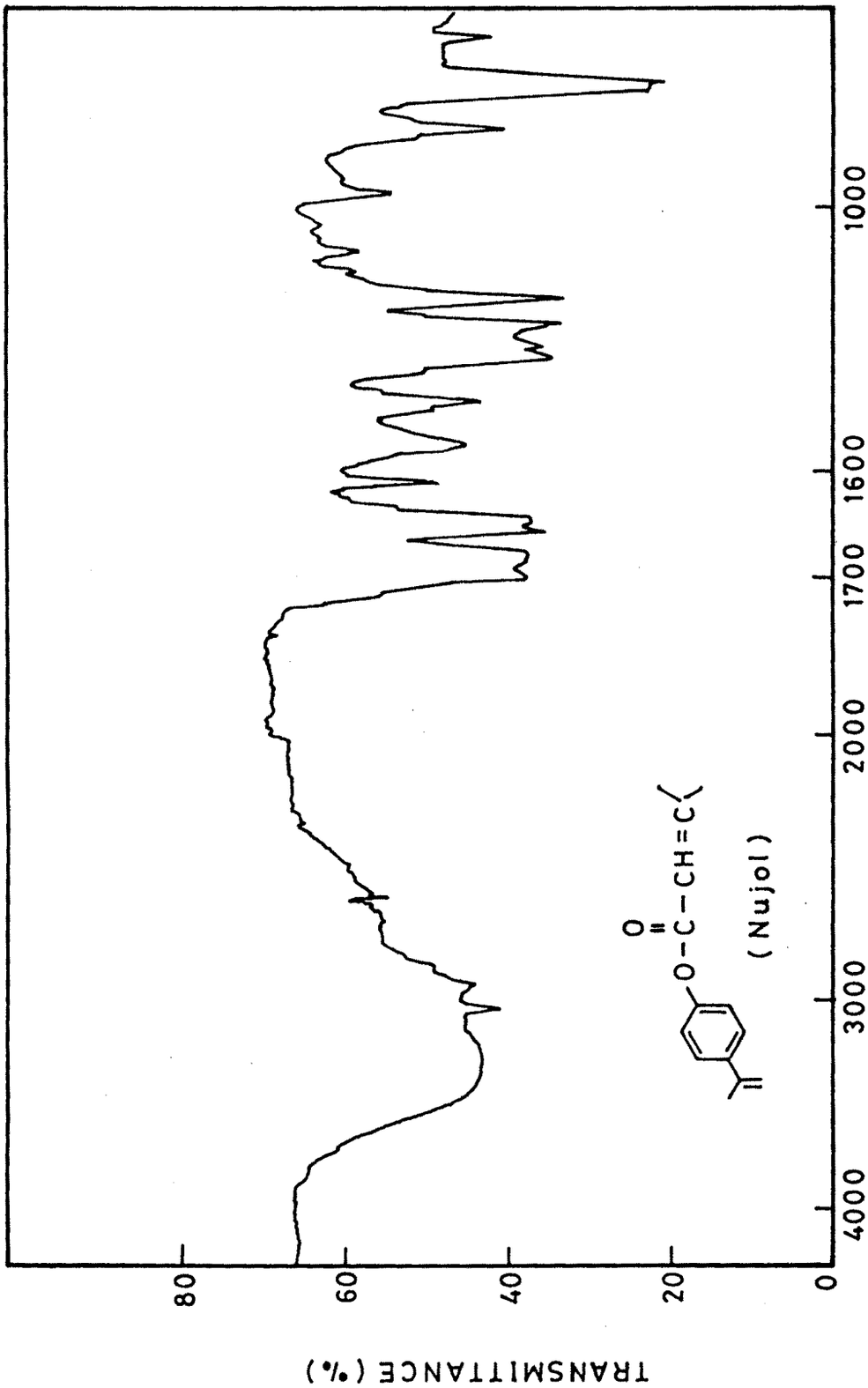

TRANSMITTANCE (%)
0
20
40
60
80
4000
3000
2000
1700
1600
1000
WAVENUMBER (cm⁻¹)
O
O-C-CH=C
(Nujol)

FIG. 3

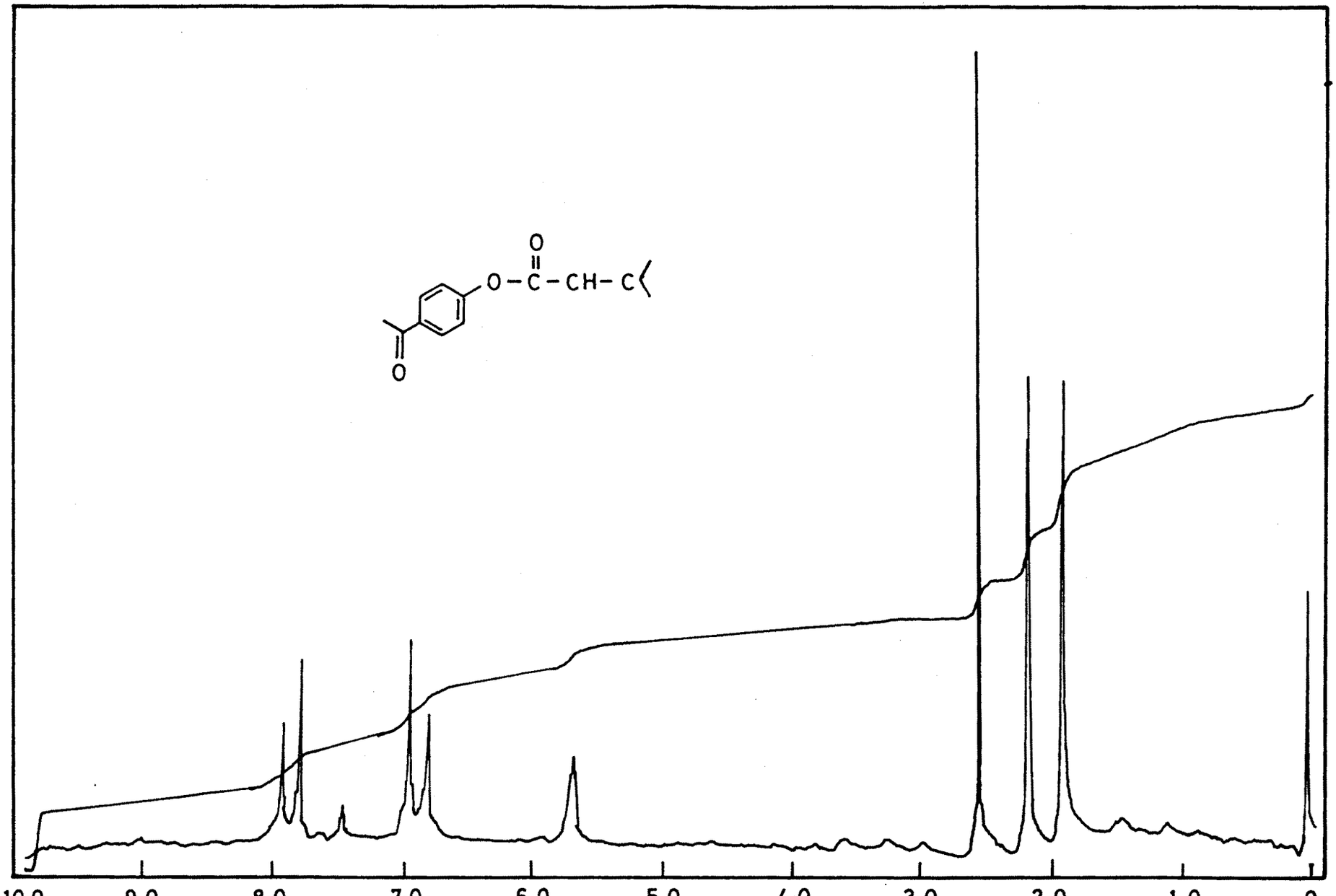


FIG. 4

EXPERIMENTAL

General :

p-Cresol (BDH), 3,3-dimethyl acrylic acid (SRL), methane sulphonic acid (Fluka), p-hydroxy acetophenone (SRL), p-hydroxy benzoic acid (BDH) were used.

CONDENSATION OF p-CRESOL WITH 3,3-DIMETHYL ACRYLIC ACID :

p-Cresol (2.614 g, 25 m mol) and 3,3-dimethyl acrylic acid (2.501 g, 25 m mol) were added simultaneously to a flask containing methane sulphonic acid (10 ml, 1.30 m mol). The reaction mixture was stirred for 1.5 hr. at 80°C, cooled poured on to crushed ice and extracted with ether. The combined ether layer was successively washed with sodium hydroxide solution, water and dried. Removal of solvent furnished the crude product, 3.3 (2.2 g) which was purified by column chromatography over silica gel to give crystalline product (1.750 g) (m.p. 67-8°C). IR (Nujol, fig.1) 1775 cm^{-1}. PMR ($CDCl_3$, fig.2) : δ 1.33 (6 H,s, gem-dimethyl), 2.30 (3H,s,Ar-CH_3), 2.50 (2H, s, -CH_2-), 6.9-7.2 (3H,m, Ar-H).

Analysis Found : C, 75.6; H, 7.5 %

$C_{12}H_{14}O_2$ requires : C, 75.8; H, 7.4 %.

p-ACETYL PHENYL 3,3-DIMETHYL ACRYLATE (3.6) :

p-Hydroxy acetophenone (3.4 g) and 3,3-dimethyl acrylic acid (2.5 g) were added to a flask containing methanesulphonic acid (10 ml). This reaction mixture was stirred at 80°C for 1.5 hr. After cooling the reaction mixture was poured on crushed ice and extracted with ether. The organic extract was sucessi-

vely washed with sodium hydroxide, water and dried. After removal of solvent crude product 3.6 (2.5 g) was obtained. It was purified by column chromatography over silica gel (1.9 g) m.p. 68-70°C. IR (nujol, fig.3) : 1710 cm^{-1} (ester), 1670 cm^{-1} (ketone). PMR ($CDCl_3$, fig.4) : δ 1.94 and 2.18 (3H each bs, vinyl methyl groups), 2.53 (3H, s - $COCH_3$), 5.7 (1H, m, vinyl -H), 6.92 (2H, d, J = 8 Hz, Ar-H meta to ketone) and 7.9 (2H, d, J = 8 Hz, Ar-H ortho to ketone).

Analysis found : C, 71.45; H, 6.32 %

$C_{13}H_{14}O_3$ requires : C, 71.55; H, 6.42 %.

CONDENSATION OF p-HYDROXY BENZOIC ACID AND 3,3-DIMETHYL ACRYLIC ACID USING METHANE SULPHONIC ACID :

p-Hydroxy benzoic acid (3.4 g) and 3,3-dimethyl acrylic acid (2.5 g) were added simultaneously to a flask containing methane sulphonic acid (10 ml). Reaction mixture was stirred at 80°C for 1.5 hr then cooled, poured onto crushed ice and extracted with ether. After usual work up and removal of solvent gave crude product (2.4 g). It was purified over column chromatography over silica gel (1.5 g), the desired product (3.9) was not obtained.

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