Chapter 4

Section 1

Synthesis and Characterisation of Irganox 1076 homologue - A Novel observation

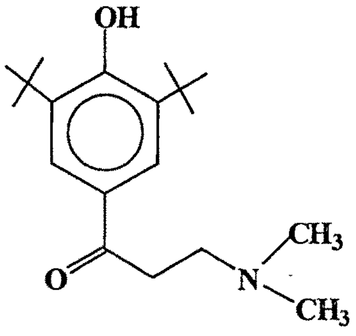
Antioxidants based on hindered phenols are of great importance because of their multiple applications ranging from foods to fuels, plastics as well as ultraviolet absorbing agents[1].

Literature data shows that introduction of long aliphatic chain in to stabiliser molecule decreases volatility and increases solubility in hydrocarbon polymer and hence improves the performance[2]. *Miller and Quackenbush*[3] reported that electron releasing group at para position of the hydroxyl group would enhance the antioxidant activity in alkyl phenolic types of antioxidants. On the other hand electron withdrawing group at same position has been reported to retard or completely eliminate the antioxidant activity.

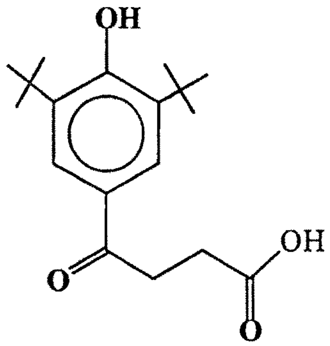
Among the hindered phenols, octadecyl-3-(3',5'-di-tert-butyl-4'-hydroxyphenyl) propionate commonly known as Irganox 1076 is widely used in food packaging, pharmaceutical formulations, polymer stabilisation and as UV and heat stabilisers.

It was therefore thought worthwhile to synthesise new antioxidants by increasing the alkyl chain length between phenol ring and electron withdrawing ester group. Better performance due to increasing the distance between electron withdrawing ester group and phenol ring was anticipated.

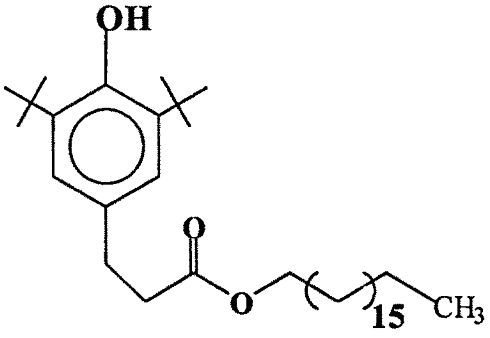
Ershov et al.[4] reported the synthesis of 3-(3',5'-di-tert-butyl-4'-hydroxy benzoyl) propanoic acid **II** from methiodide of compound **I** in several steps. They have synthesised compound **II** independently in 12% yield by acylation of 2,6-di-tert-butyl phenol with monochloro succinoyl chloride.



[I]



[II]



**Octadecyl-3-(3',5'-di-tert-butyl-4'-hydroxyphenyl)
propanoate [IRGANOX - 1076]**

Present work[*]

Present work deals with the synthesis of homologue of Irganox 1076 by introducing one more methylene group in the alkyl chain between ester group and phenol ring. This synthesis was achieved by performing Friedel-Crafts

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[*] Accepted for publication [14]

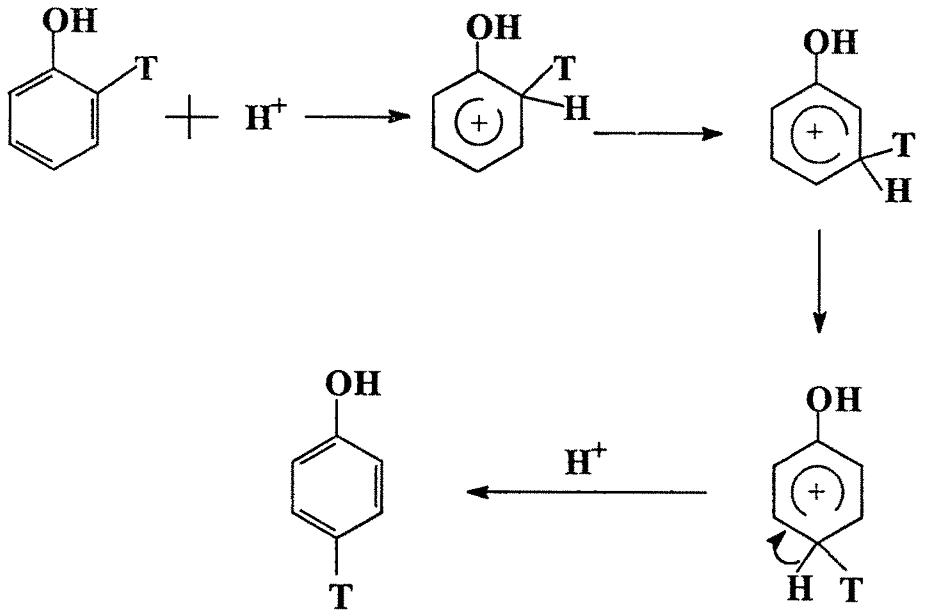
succinolyation on 2,6-di-tert-butyl phenol in the presence of anhydrous aluminum chloride followed by Clemmenson reduction and subsequent esterification using appropriate alcohol.

During the Friedel-Crafts succinolyation, we observed de-tert-butylation involving C-C bond rupture without tert-butyl acceptor, isomerisation of tertiary butyl group from 1,2 position in phenol ring to 1,4 position in the same ring along with *O*-and *C*-succinolylated products.

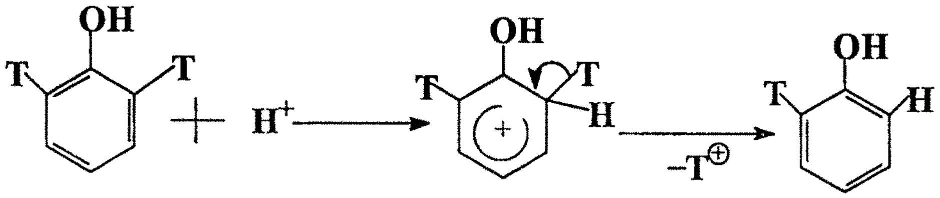
The literature data showed Lewis acid catalysed Friedel-Crafts isomerisation[5] and de-tert-butylation[6]. The de-tert-butylation is also catalysed by metal oxide[7] and mineral acids[8]. Normally de-tert-butylation involves the treatment of tert-butyl arenes with Lewis acid in the presence of tert-butyl acceptor[9]. De-tert-butylation of phenols without tert-butyl acceptor using TFA is also known, but it employed harsh conditions[10].

Migration or isomerisation of alkyl group from one position in the ring to another position in the same ring is known to occur via 1,2 shifts. Any 1,3 or 1,4 shift takes place by series of two or more 1,2 shifts[11].

This new process for the synthesis of octadecyl-4-(3',5'-di-tert-butyl-4'-hydroxy phenyl) butanoate is convenient, it envisages the use of cheaper starting materials and could be implemented for large scale preparation. In the presence of Lewis acid, one of the tert-butyl groups was detached from the aromatic ring and second was isomerised from 1,2 to the 1,4 position in the same ring (Scheme 1). In the absence of tert-butyl acceptor intra-molecular isomerisation was observed. In this case as isomerisation is fast, it is reasonable to suggest that the tert-butyl group is not completely detached from the aromatic ring but stays in the interaction through



Isomerisation of tert-butyl group in the presence of acid



De-tert-butylation in the presence of acid

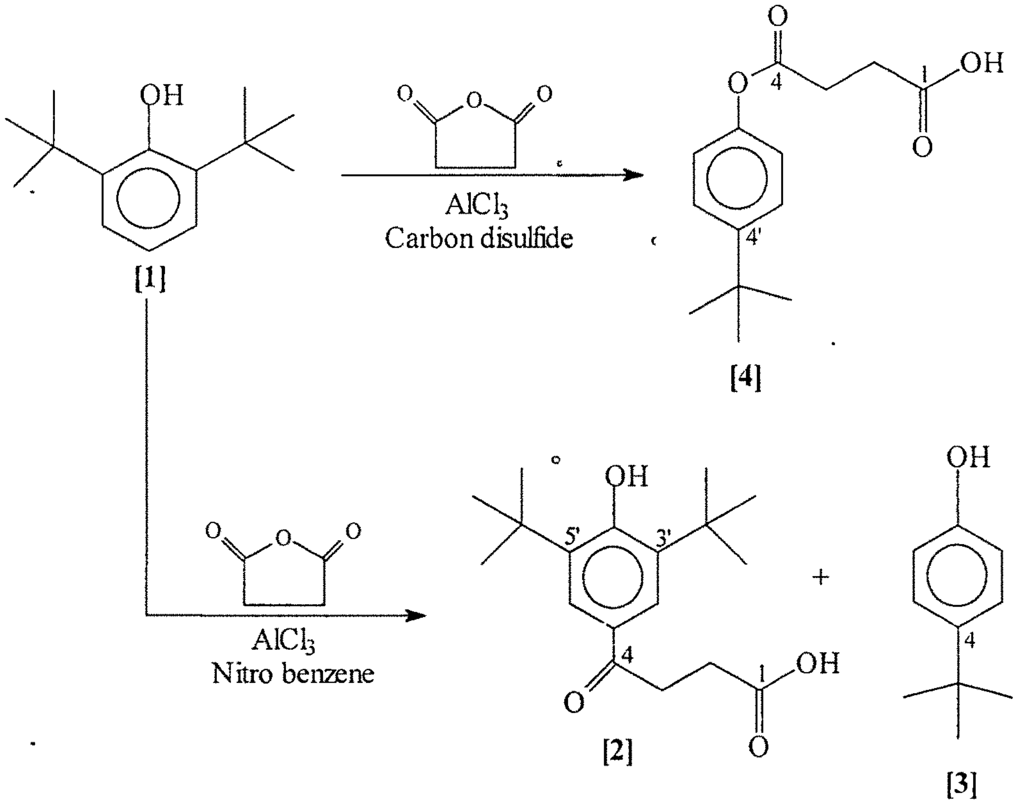
T = Tert- butyl group

Scheme 1

π type of intermediate. Complete detachment of the tert-butyl group in alkylation-dealkylation process would be expected to be much slower process.

2,6-Di-tert-butyl phenol on Friedel-Crafts succinolyation in the presence of anhydrous aluminium chloride in nitrobenzene gave desired *C*-succinoylated 3-(3',5'-di-tert-butyl-4'-hydroxy benzoyl) propanoic acid **2** along with 4-tert-butyl phenol **3** (Scheme 2). Phenol **3** was formed due to de-tert-butylation and isomerisation of tert-butyl group. Products **2** and **3** were separated through column chromatography. IR spectrum (Fig. 1) recorded as KBr pellets for keto acid **2** showed band at 3520 cm^{-1} due to OH stretching frequency of hindered phenolic group. Band for OH stretching frequency for an acid appeared at 3120 cm^{-1}. Band observed at 1720 cm^{-1} is due to carbonyl stretching frequency of acid. Carbonyl stretching frequency of ketone was observed at 1690 cm^{-1}. ^{1}H NMR spectrum recorded in $CDCl_3$ using TMS as internal standard for keto acid **2** (Fig. 2) showed singlet at δ 1.46 for eighteen protons is due to the presence of two tert-butyl groups. Triplet observed at δ 2.78 for two protons with J value 6.46 Hz and triplet at δ 3.28 for two protons with same J value correspond to $-CH_2-CH_2-$ group present in the side chain. Phenolic proton resonated at δ 5.73. Two aromatic protons of phenol ring appeared at δ 7.86.

IR spectrum of phenol **3** (Fig. 3) taken using KBr pellets showed band at 3240 cm^{-1} for OH stretching frequency of free hydroxyl group. ^{1}H NMR spectrum (Fig. 4) recorded in $CDCl_3$ using TMS as internal standard showed singlet at δ 1.29 for nine protons is due to one tert-butyl group. Phenolic proton appeared at δ 4.60. Double doublet observed at δ 6.75 ($J_{5,6}$ = 8.7 Hz & $J_{2,6}$ = 1.9 Hz) and at δ 7.3 ($J_{2,3}$=8.7 Hz & $J_{3,5}$= 2.1 Hz) for two protons each showed the presence of aromatic protons. From the value of coupling constant, conclusion can be drawn that the substituents present in the aromatic ring are para to each other. ^{13}C NMR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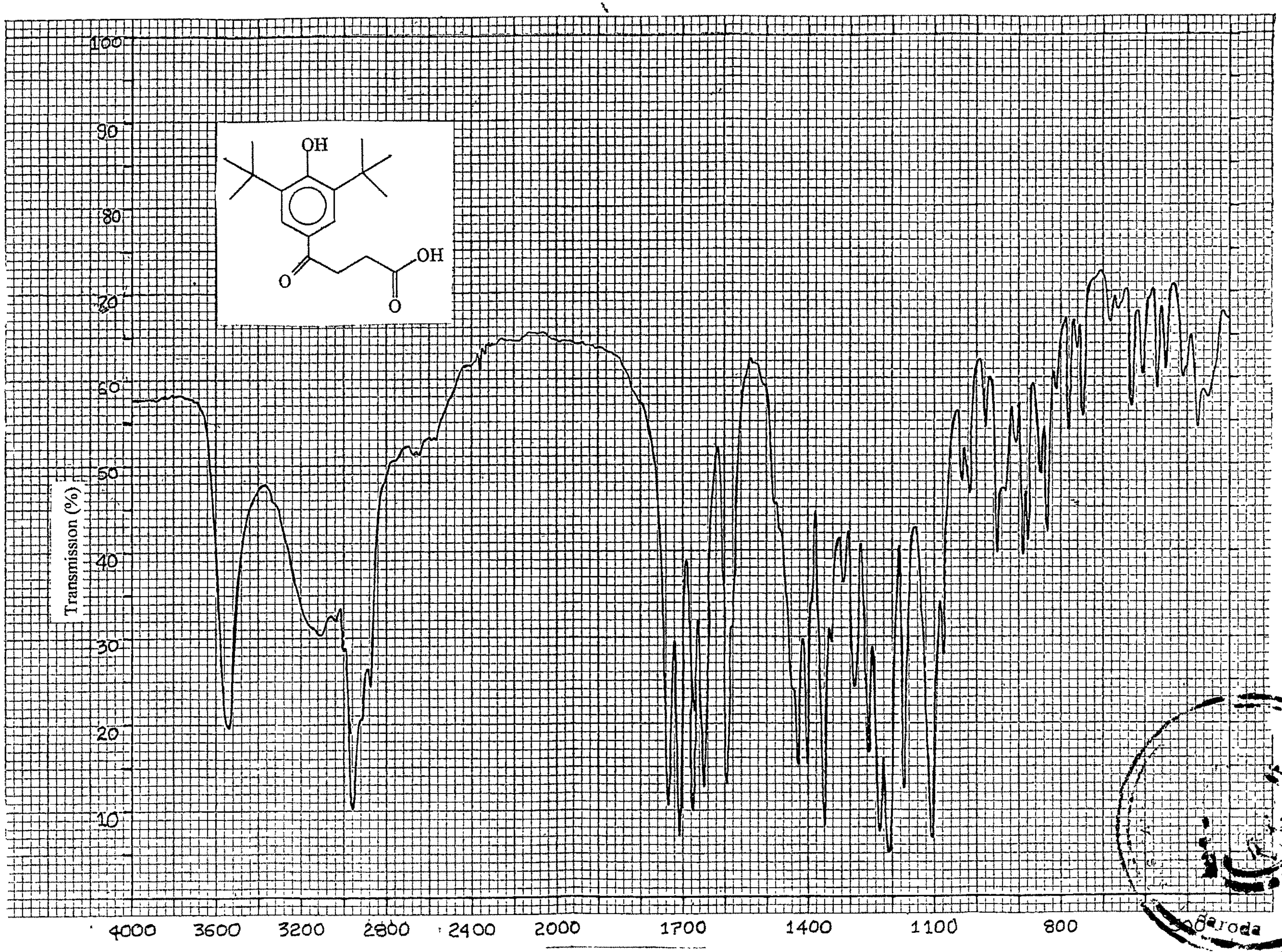
O
O
AlCl3
Carbon disulfide
O
O
4
1
OH
O
4'
[4]
O
O
O
AlCl3
Nitro benzene
OH
5'
3'
4
O
1
OH
O
[2]
+
OH
4
[3]

Scheme 2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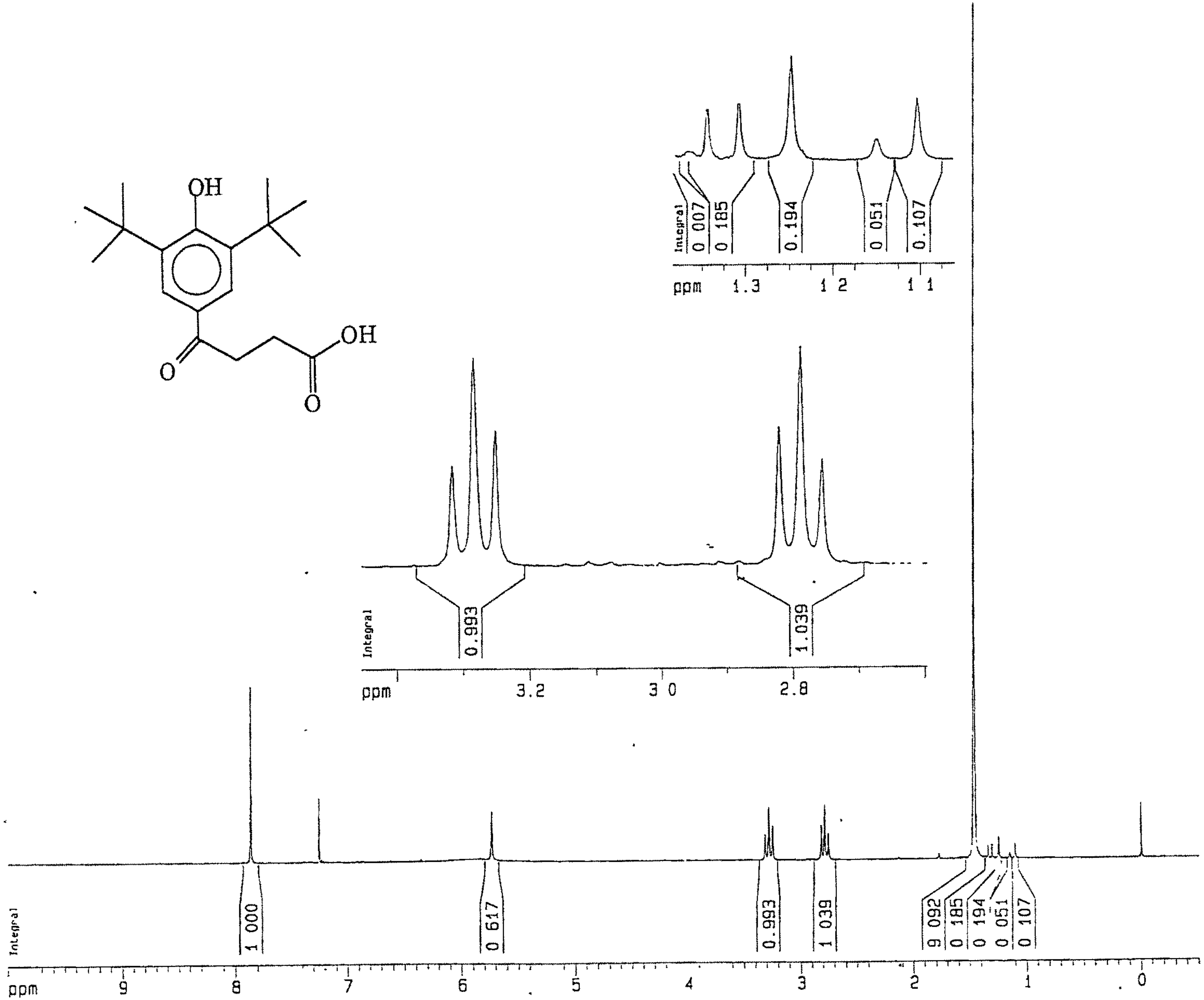
80
70
60
50
40
30
20
10
Transmission (%)
4000
3600
3200
2800
2400
2000
1700
1400
1100
800
Wavenumber (cm-1)
OH
OH
O
O

Figure 1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O
O
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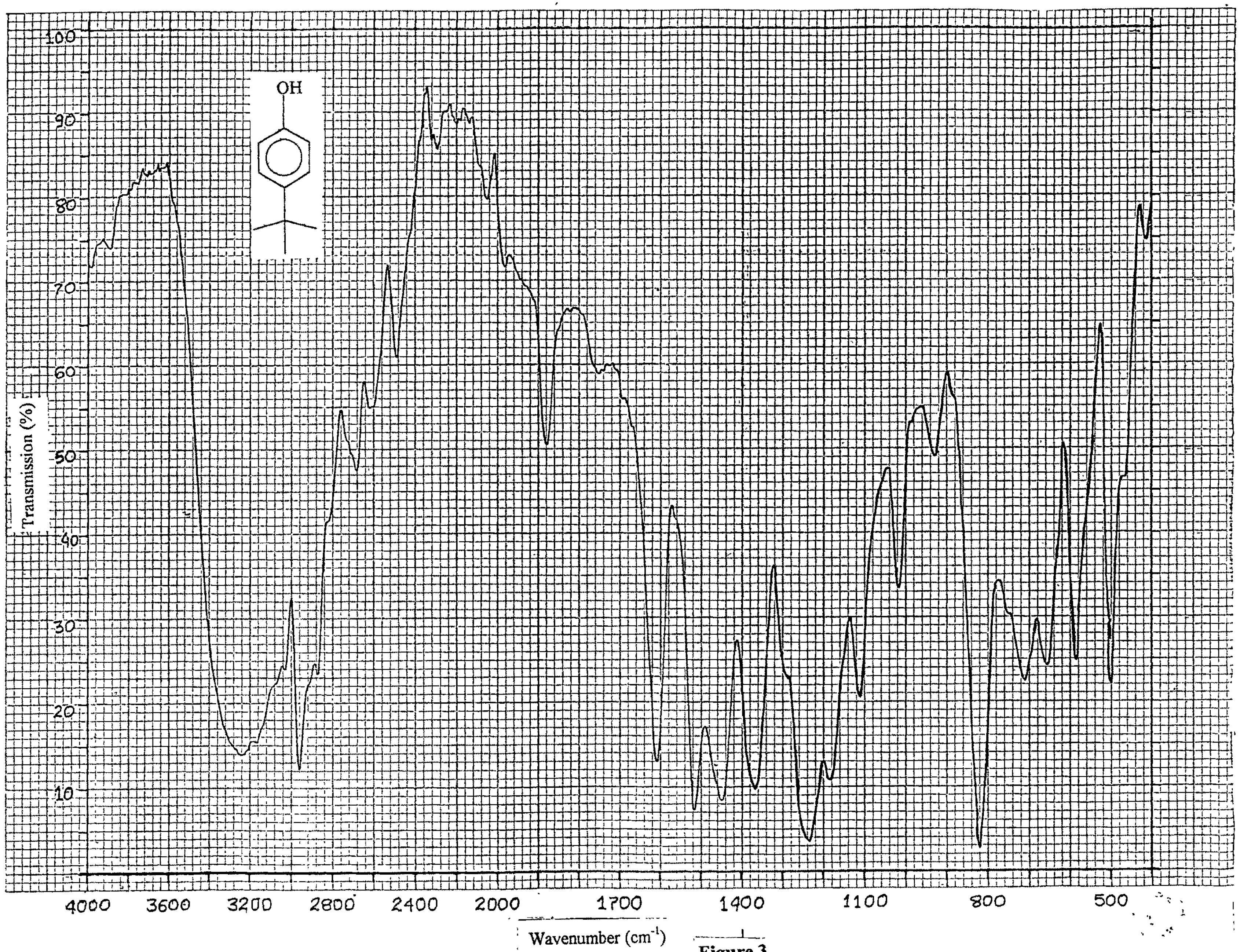
0.194
0 051
0.107
ppm
1.3
1 2
1 1
Integral
0.993
1.039
ppm
3.2
3 0
2.8
Integral
1 000
0 617
0.993
1 039
9 092
0 185
0 194
0 051
0 107
ppm
9
8
7
6
5
4
3
2
1
0

Figure 2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60
50
40
30
20
10
OH
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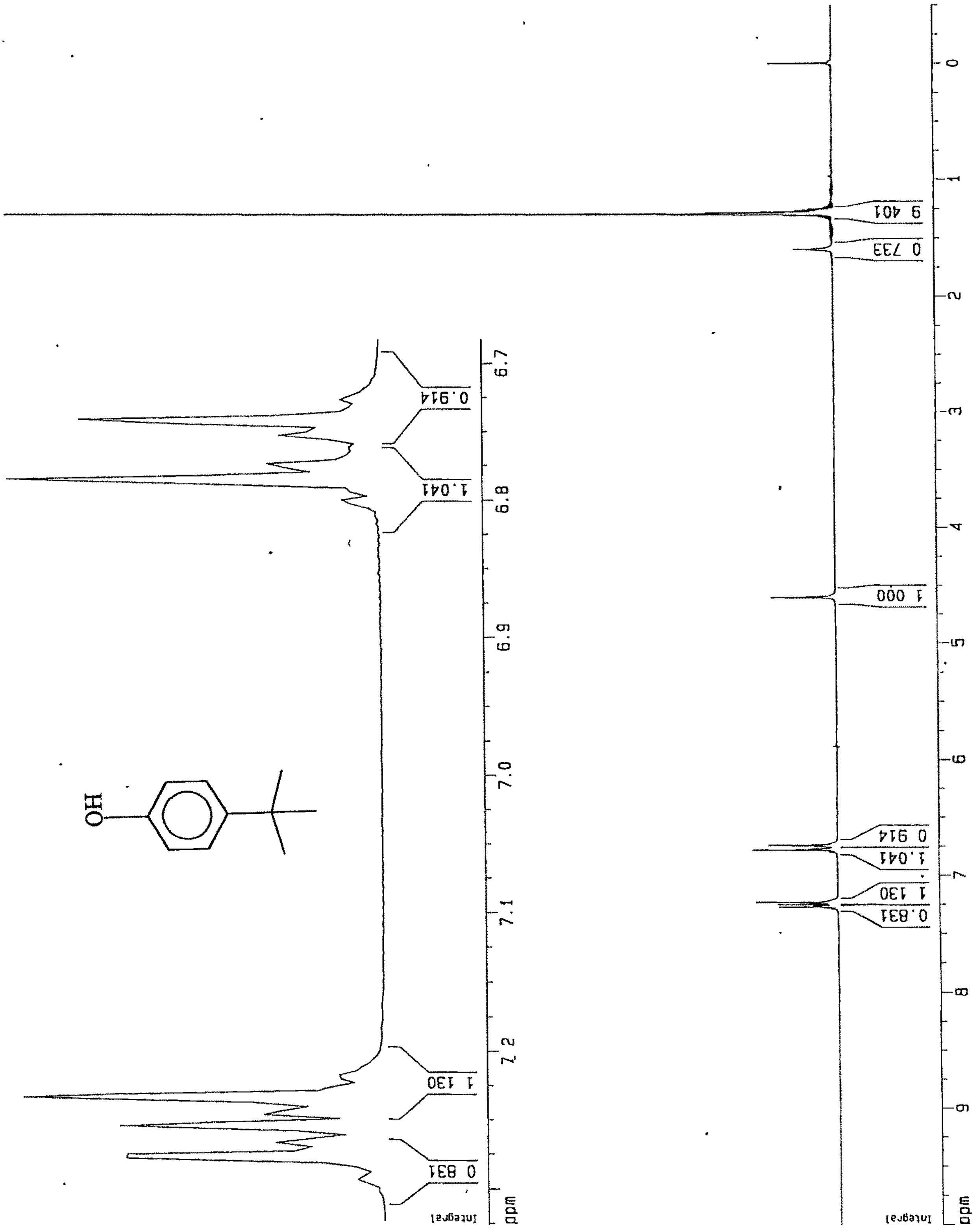
3600
3200
2800
2400
2000
1700
1400
1100
800
500
Wavenumber (cm⁻¹)

Figure 3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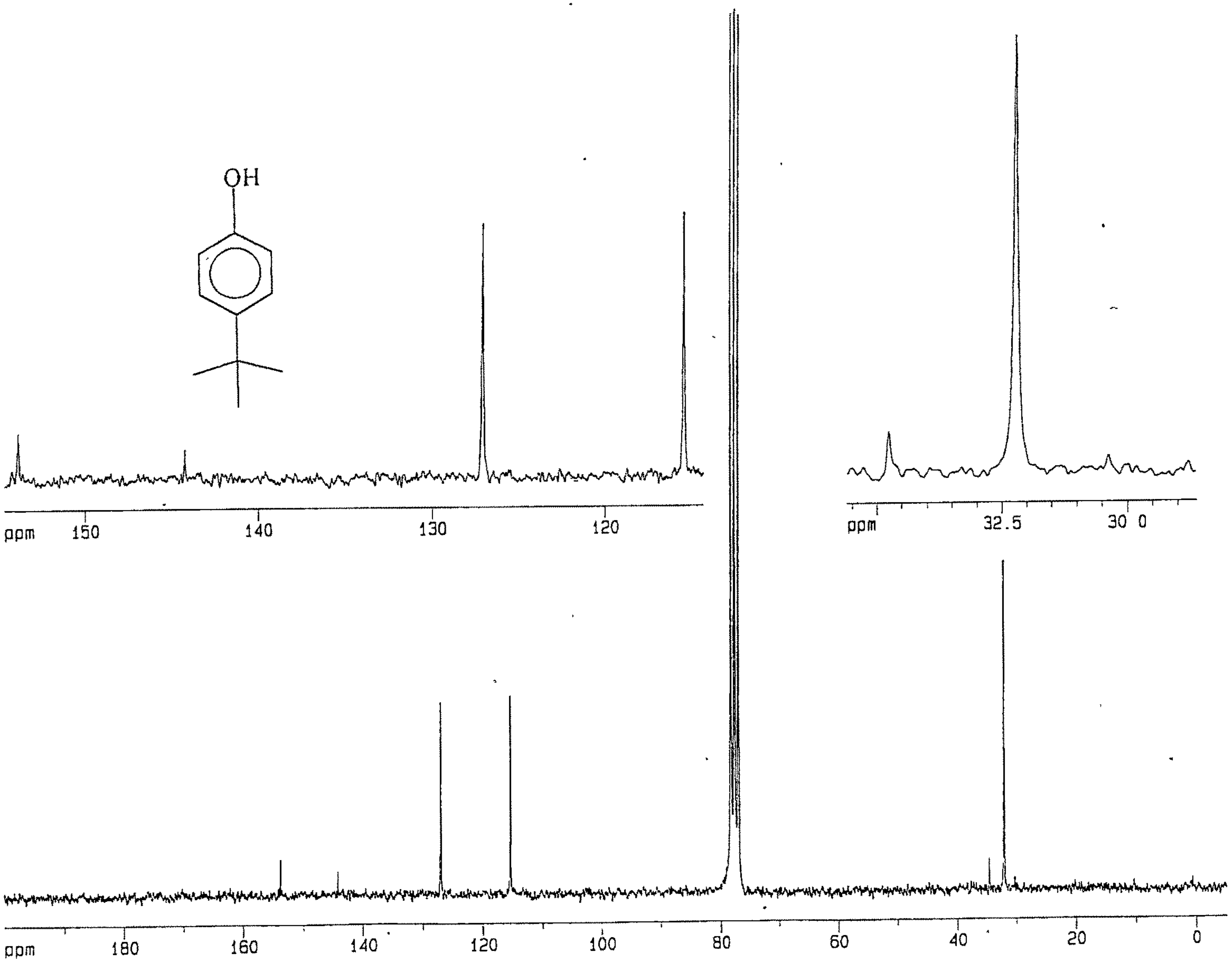
0.733
1.000
0.914
1.041
1.130
0.831
Integral
0
1
2
3
4
5
6
7
8
9
ppm
0.914
1.041
1.130
0.831
Integral
6.7
6.8
6.9
7.0
7.1
7.2
ppm

Figure 4

(Fig. 5) spectrum recorded using $CDCl_3$ as solvent showed singlet at δ 160 for C_1. Singlet observed at δ 144 is due to C_4. Signal observed at δ 127 is due to C_3, C_5 and signal at δ 115.4 is due to C_2, C_6 carbon atoms. Signal obtained at δ 34.76 is due to the presence of tertiary carbon present in tert-butyl group. The carbon of methyl group resonated at δ 32.31. DEPT (Fig. 6) indicated that compound contains quaternary aliphatic carbon, methyl carbon and two different aromatic carbon atoms.

Friedel-Crafts succinoylation of 2,6-di-tert-butyl phenol in carbon disulphide afforded 3-(4'-tert-butyl carbphenoxy) propanoic acid **4** formed due to de-tert-butylation, isomerisation and *O*-succinoylation (Scheme 2). IR spectrum taken using KBr pellets for compound **4** (Fig. 7) showed band at 3120 cm^{-1} for OH stretching frequency of an acid. Band observed at 1730 cm^{-1} is due to carbonyl stretching frequency of an acid. C=O stretching frequency of an ester appeared at 1710 cm^{-1}. ^1H NMR spectrum (Fig. 8) recorded in $CDCl_3$ using TMS as internal standard showed singlet at δ 1.30 for nine protons is due to tert-butyl group. Multiplet observed at δ 2.85 for four protons is due to the presence of $-CH_2-CH_2-$ group present in side chain. Two doublets observed at δ 7.0 ($J_{5',6'}$= 8.7 Hz & $J_{2',6'}$= 2.0 Hz) and at 7.38 ($J_{2',3'}$= 8.7 Hz & $J_{3',5'}$=1.9 Hz) for two protons, each is due to the presence of four aromatic protons. From the coupling constant values it can be concluded that two functional groups attached to benzene ring are para to each other. ^{13}C NMR spectrum (Fig. 9) recorded using $CDCl_3$ showed signals at δ 178.01 and at δ 170.87 for two CO groups. Signals for $C_{3'}$, $C_{2'}$, $C_{1'}$ and $C_{4'}$ appeared at δ 143.73, 148.20, 126.20 and at 120.71 respectively. Tertiary carbon of tert-butyl group appeared at 34.43. Signals for methyl carbon appeared at δ 31.36. Signals observed at δ 29.07 and 28.92 are due to two methylene carbons in the side chain having different environment. DEPT (Fig. 10) indicated the presence of three methyl groups, two methylene groups, two different carbonyl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ppm
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140
130
120
ppm
32.5
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ppm
180
160
140
120
100
80
60
40
20
0

Figure 5

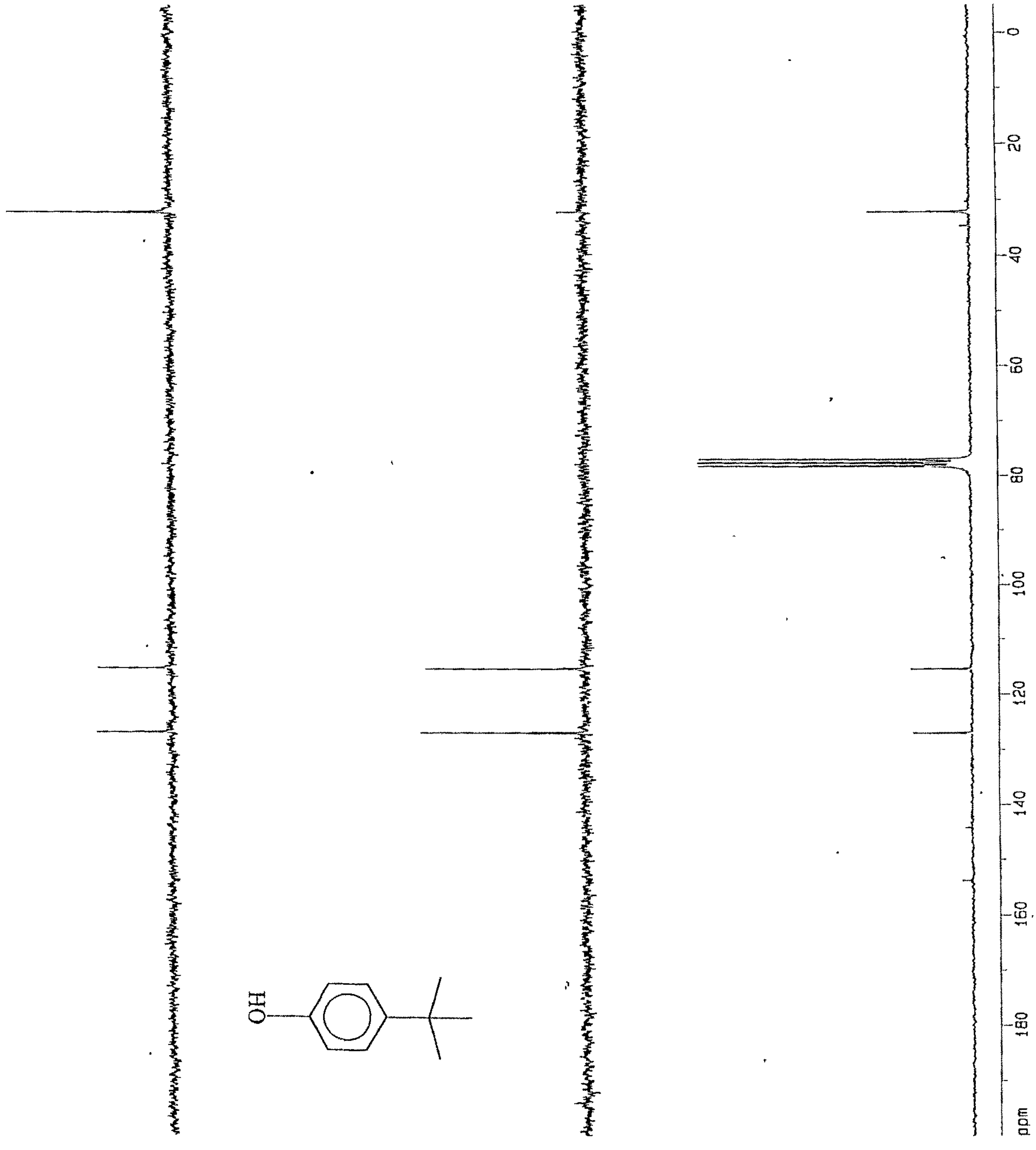
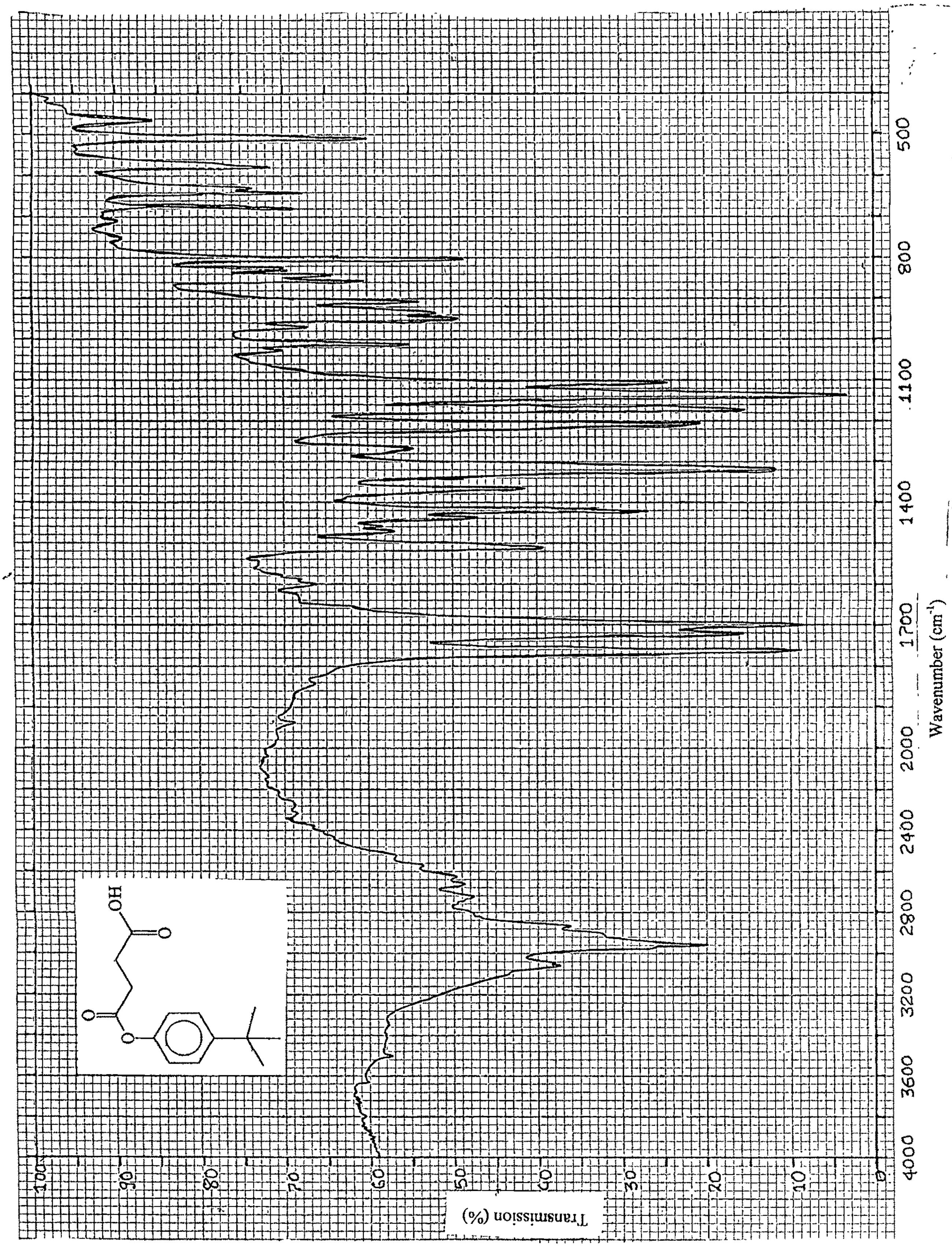


Figure 6


Transmission (%)
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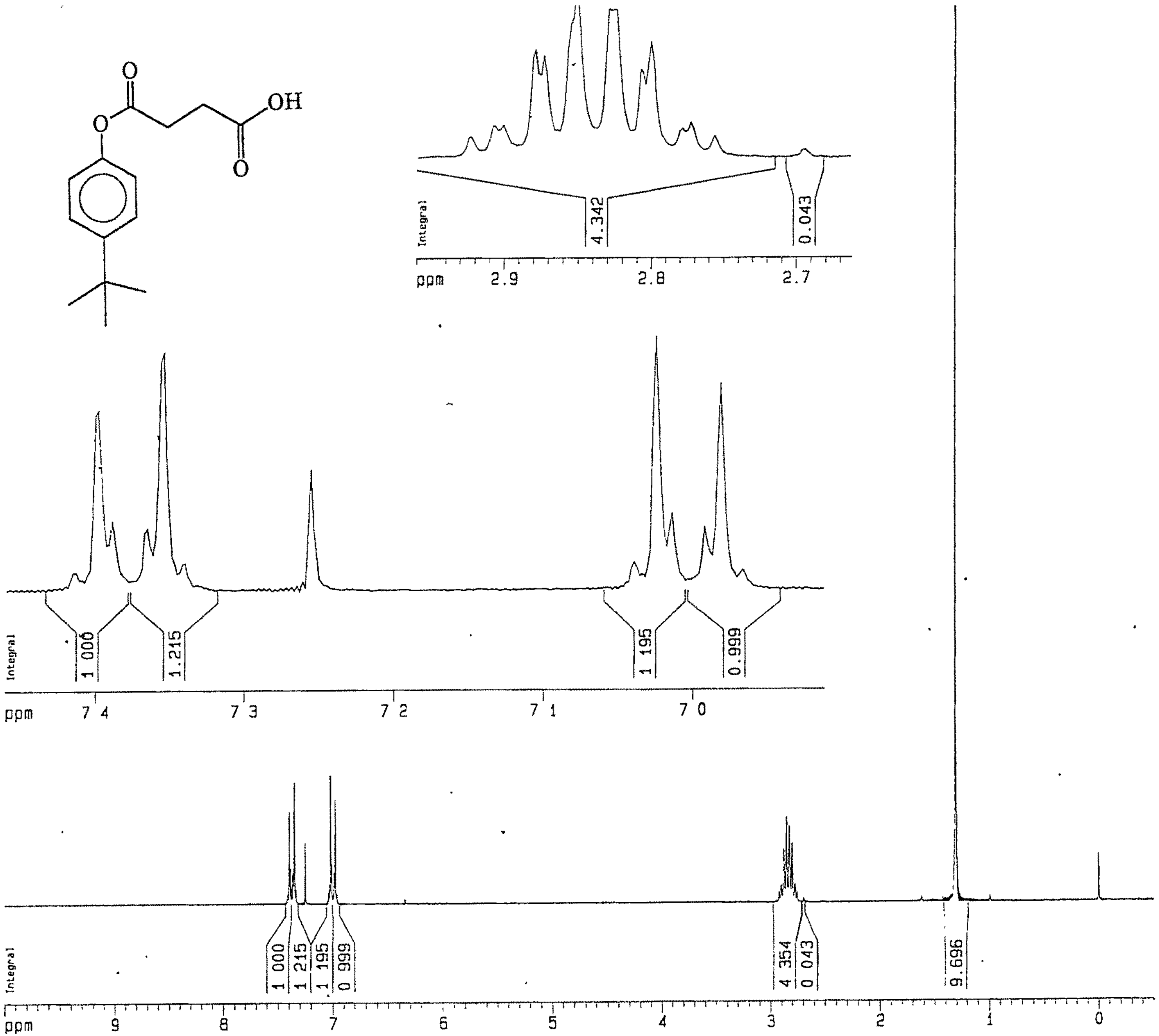
90
80
70
60
50
40
30
20
10
0
4000
3600
3200
2800
2400
2000
1700
1400
1100
800
500
Wavenumber (cm^{-1})
OH
O
O
O

Figure 7


OH
O
O
O
Integral
4.342
0.043
ppm
2.9
2.8
2.7
Integral
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1.215
1 195
0.999
ppm
7 4
7 3
7 2
7 1
7 0
Integral
1 000
1 215
1 195
0 999
4 354
0 043
9.696
ppm
9
8
7
6
5
4
3
2
1
0

Figure 8

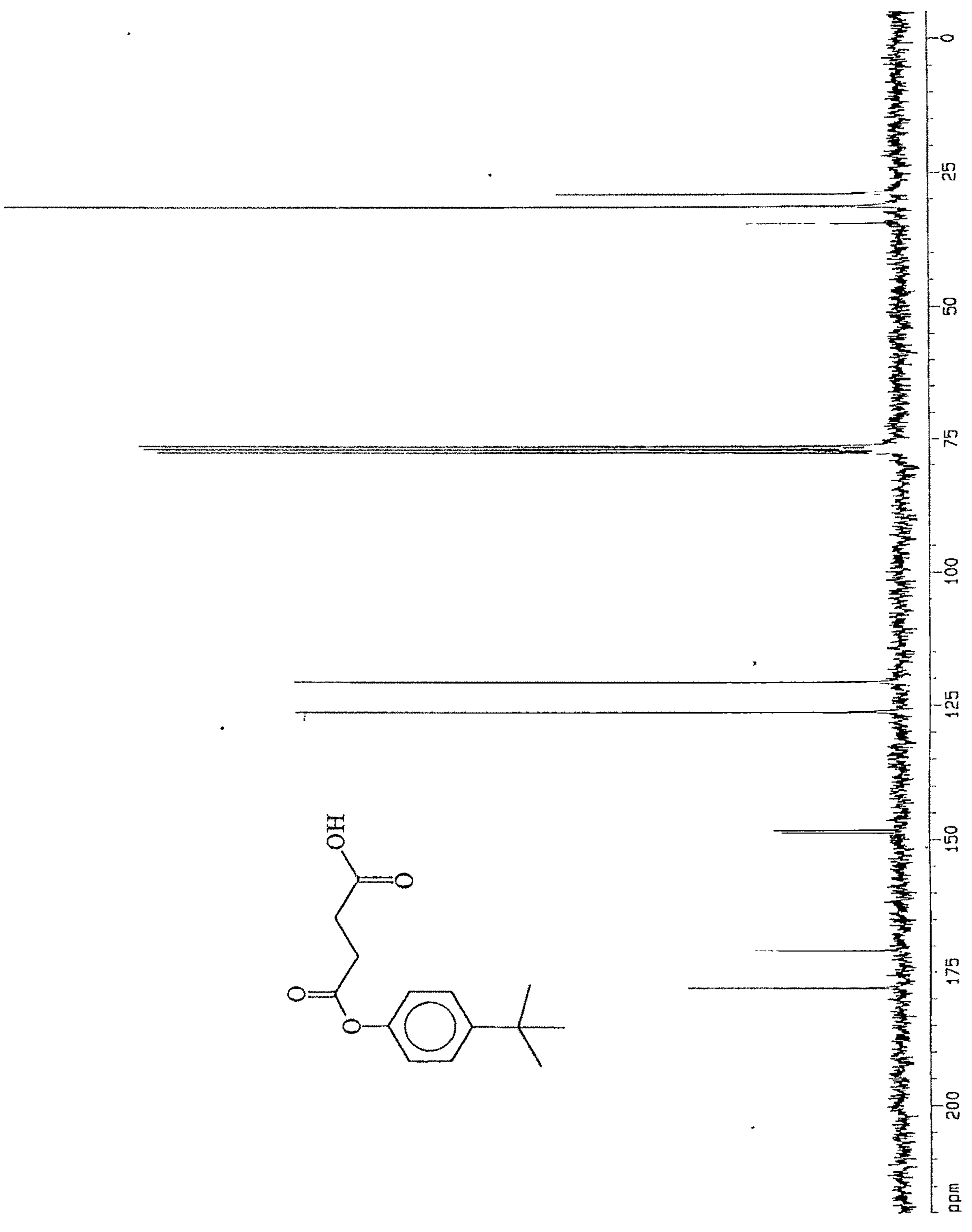


Figure 9

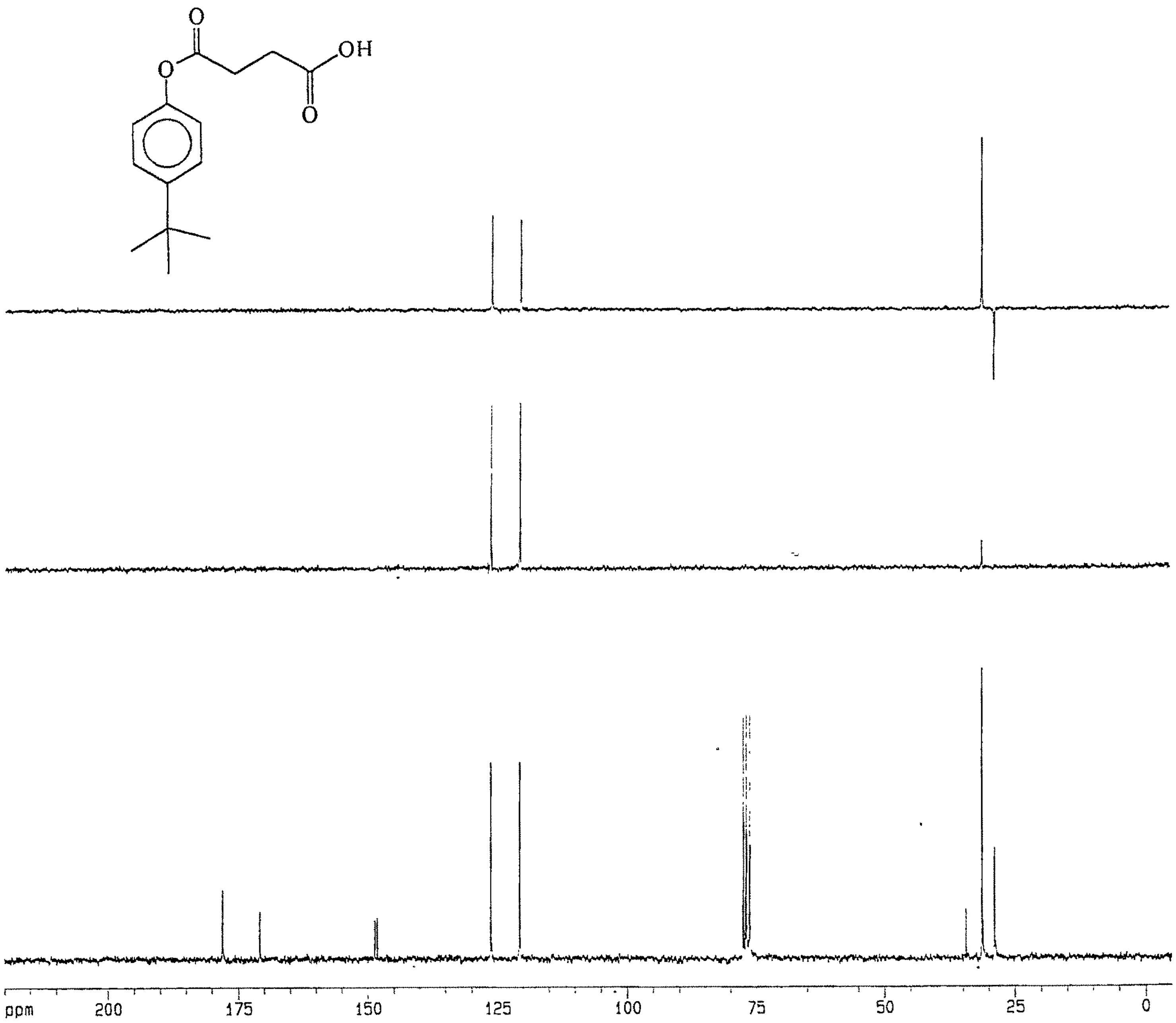


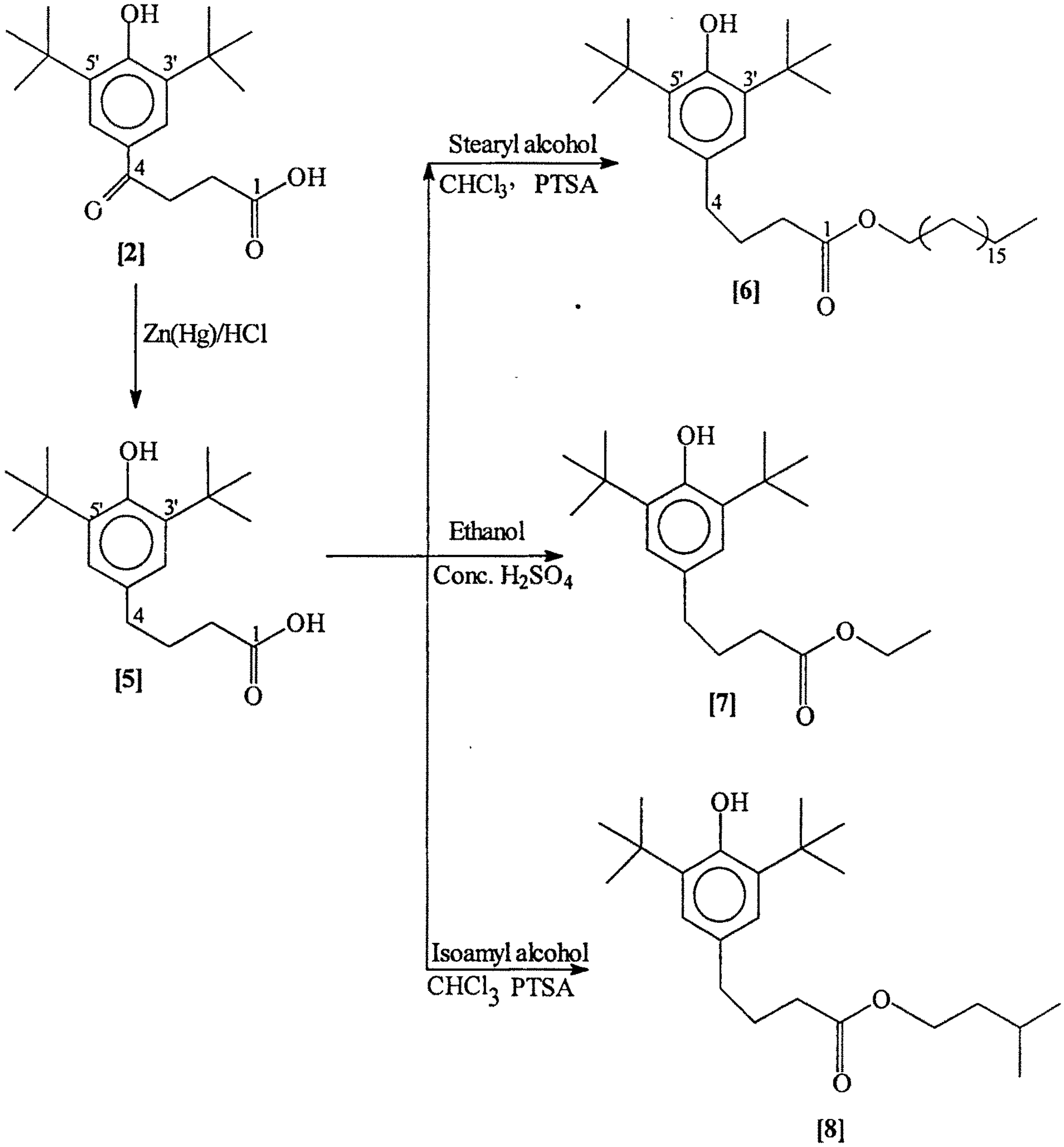
Figure 10

groups, two different aromatic methine groups, two aromatic quarternary carbon atoms and one aliphatic quarternary carbon atom. Mass spectrum (Fig. 11) showed the molecular ion peak at m/e 150. Base peak was observed at m/e 135.

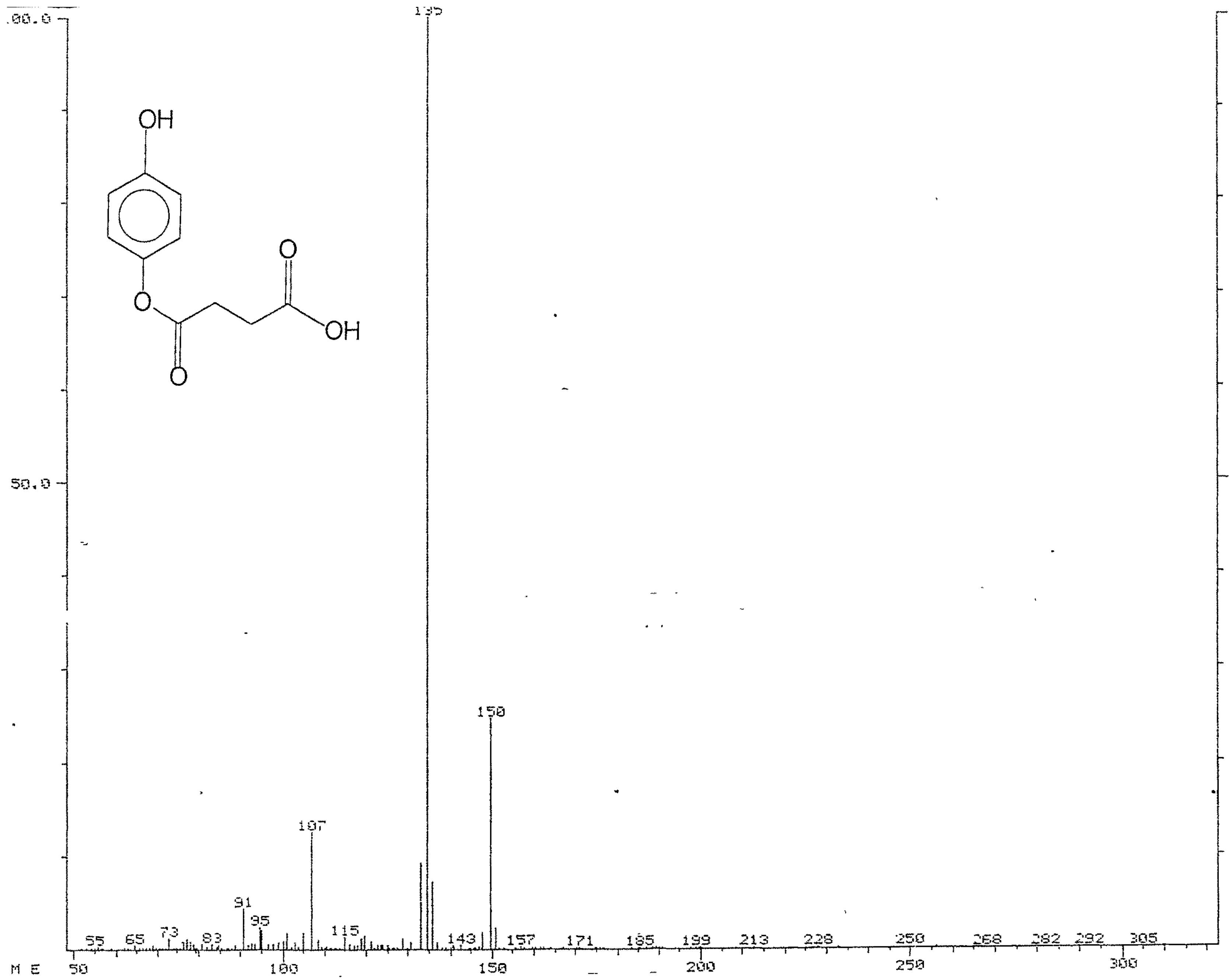
It is observed that in case of nitrobenzene as solvent, amount of *C*-acylated product is more along with some amount of **3** indicating that de-tert-butylation and isomerisation is less in this solvent. The use of carbon disulfide as solvent leads to product **4** in major quantity suggesting that the extend of isomerisation and de-tert-butylation is more.

3-(3',5'-Di-tert-butyl-4'-hydroxybenzoyl)propanoic acid **2** on Clemmenson reduction using Zn(Hg) and conc. HCl afforded 4-(3',5'-di-tert-butyl-4'-hydroxy phenyl) butanoic acid **5** (Scheme 3). IR spectrum taken using KBr pellet showed band at 3520 cm^{-1} due to hindered phenolic OH stretching frequency. OH stretching frequency of an acid appeared at 3118 cm^{-1}. CO stretching frequency of an acid appeared at 1710 cm^{-1}. ^1H NMR spectrum (Fig. 12) recorded in $CDCl_3$ using TMS as internal standard showed singlet at δ 1.43 for eighteen protons. This is due to two tert-butyl groups. Multiplet observed at δ 1.8 for two protons is due to methylene group present in side chain $-CH_2-\underline{CH_2}-CH_2-$. Two triplets observed at δ 2.3 and at δ 2.6 for two protons each, due to two CH_2 groups, one attached to aromatic ring and another attached to acid group. Phenolic proton resonated as singlet at δ 5.1. Two aromatic protons appeared as singlet at δ 7.0.

4-(3',5'-Di-tert-butyl-4'-hydroxyphenyl) butanoic acid **5** on esterification with stearyl alcohol in the presence of *p*-toluene sulfonic acid (PTSA) afforded octadecyl-4-(3',5'-di-tert-butyl-4'-hydroxyphenyl) butanoate, an Irganox 1076 homologue (Scheme 3). IR spectrum (neat) (Fig. 13) showed band at 3518 cm^{-1} for hindered phenolic OH stretching frequency. CO stretching frequency of an


OH
5'
3'
4
1
OH
O
O
[2]
Zn(Hg)/HCl
[5]
Stearyl alcohol
$CHCl_3$, PTSA
[6]
15
Ethanol
Conc. H_2SO_4
[7]
Isoamyl alcohol
$CHCl_3$ PTSA
[8]

Scheme 3


00.0
50.0
M E
135
150
107
91
95
55
65
73
83
115
143
157
171
185
199
213
228
250
268
282
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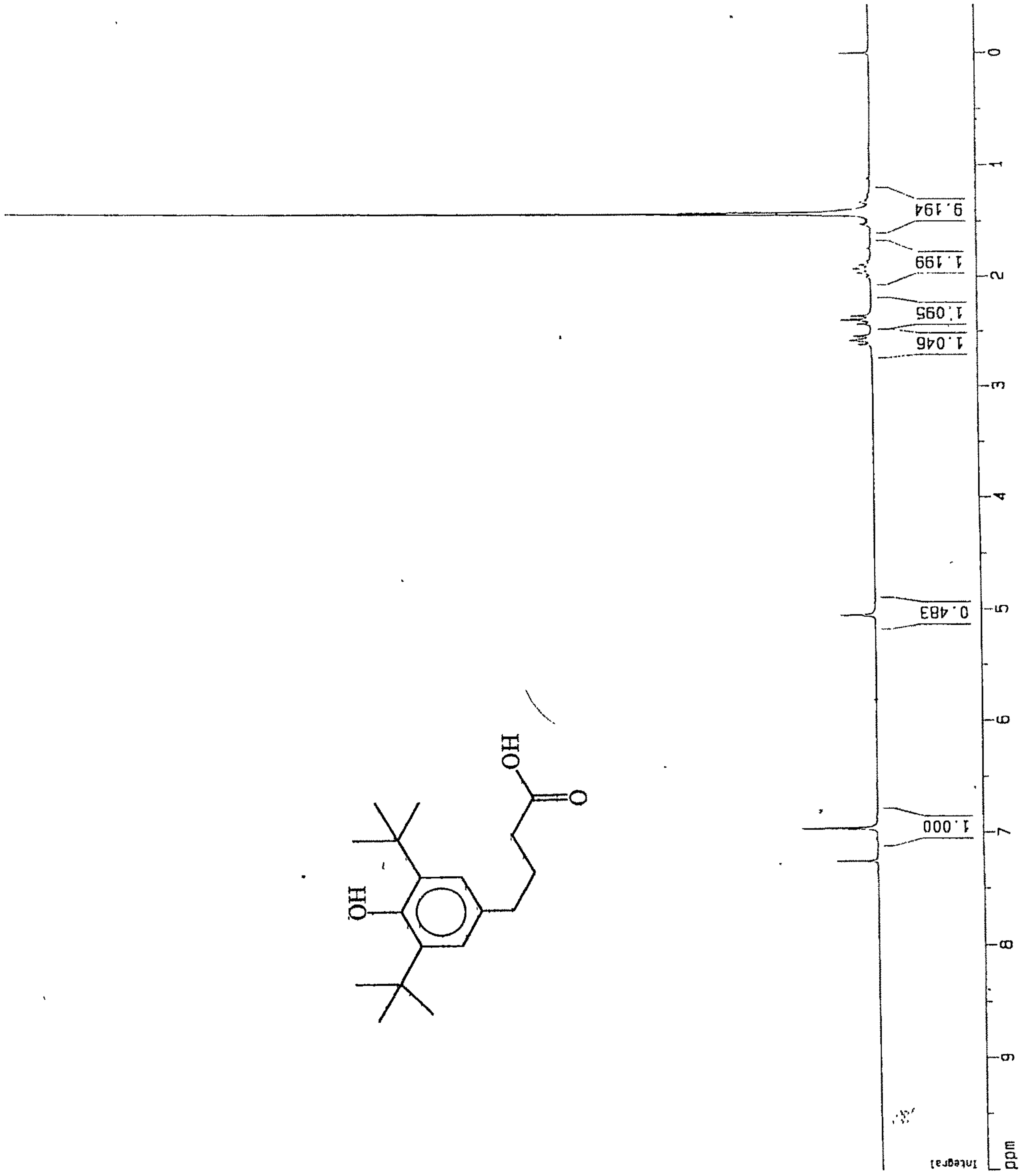
50
100
150
200
250
300
11816Se.
10.
OH
O
O
O
OH

Figure 11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HO
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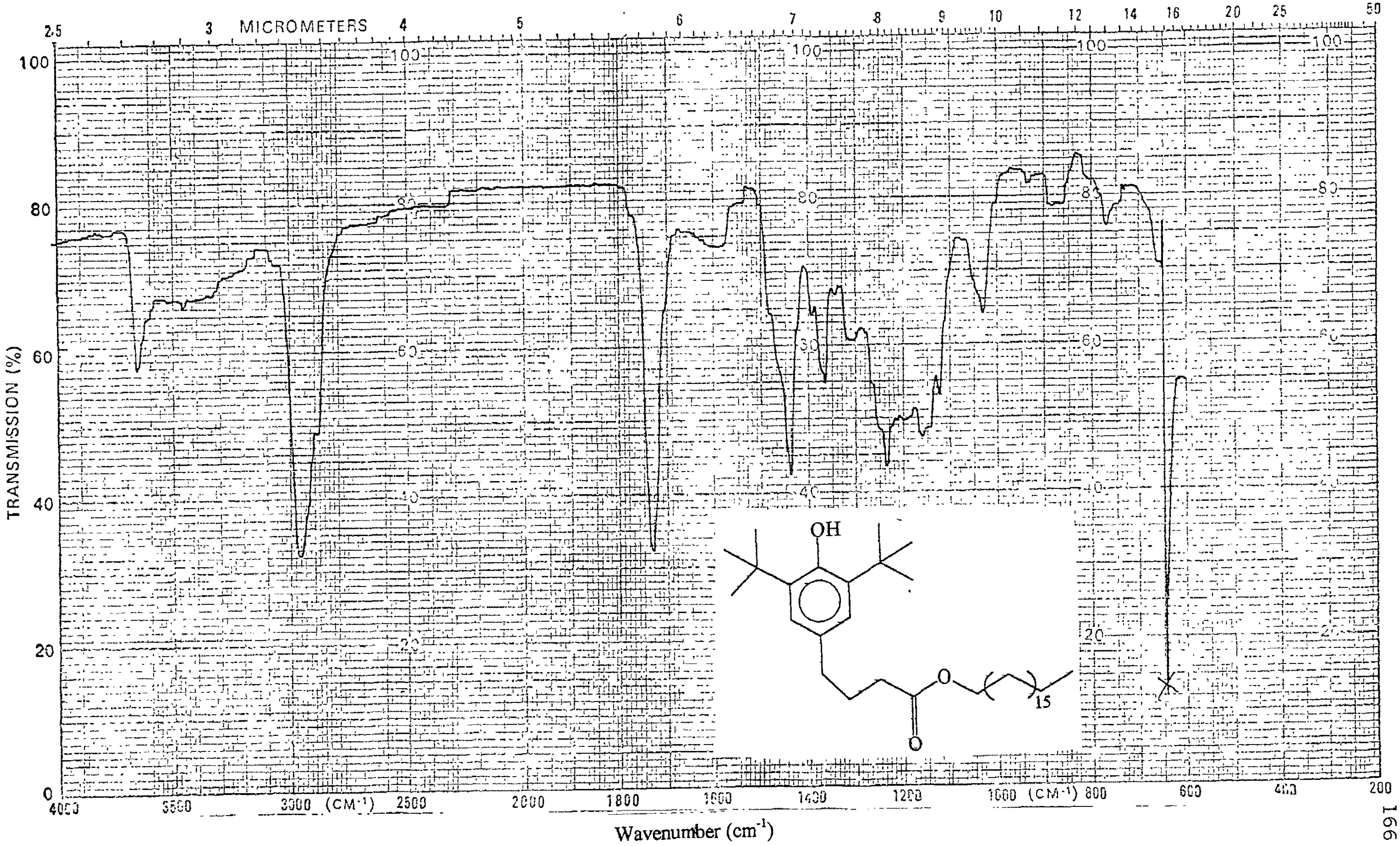
6
7
8
9
ppm

Figure 12


MICROMETERS
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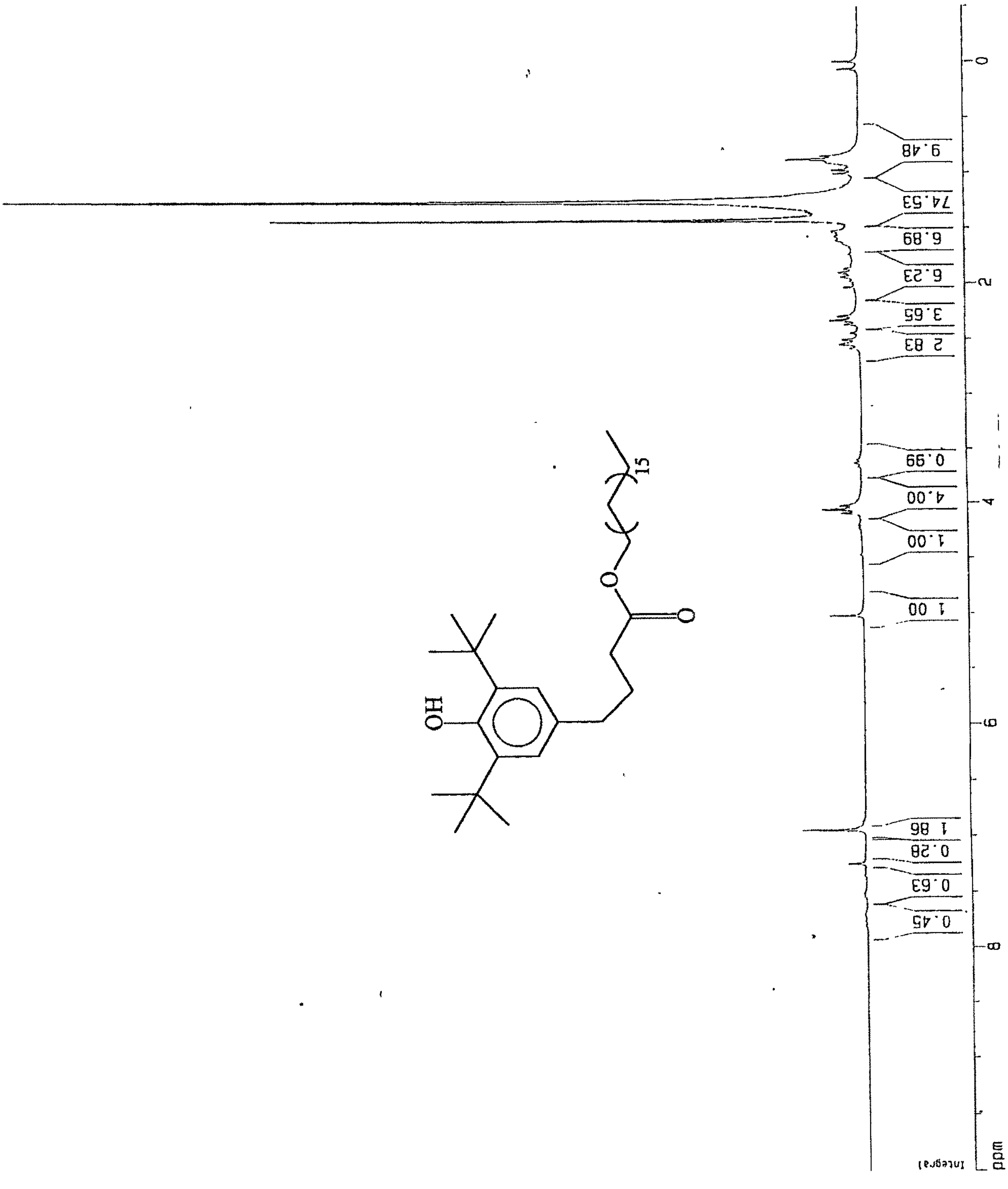
3
4
5
6
7
8
9
10
12
14
16
20
25
50
TRANSMISSION (%)
100
80
60
40
20
0
4000
3500
3000 (CM⁻¹)
2500
2000
1800
1600
1400
1200
1000 (CM⁻¹) 800
600
400
200
Wavenumber (cm⁻¹)
OH
O
O
15

Figure 13

ester appeared at 1738 cm^{-1}. Unequal bands observed at 1385, 1375 cm^{-1} are due to CH bending for tert-butyl group. ^1H NMR spectrum (Fig. 14) recorded using $CDCl_3$ as solvent and TMS as internal standard showed triplet at δ 0.9 for three protons. This is due to the methyl group present at the terminal position in stearyl chain. Multiplet observed in the range of δ 1.0 to 1.7 for fifty protons is due to eighteen protons of two tert-butyl groups along with methylene protons of stearyl chain. Multiplet at δ 1.95 for two protons is due to $-CH_2-C\underline{H_2}-CH_2-CO-$. Triplet observed at δ 2.35 for two protons is due to $Ph-C\underline{H_2}-$ protons. Two triplets observed at δ 2.60 and at δ 4.10 for two protons, each due to two methylene protons attached to carbonyl carbon of ester and oxygen of ester respectively. Phenolic proton resonated at δ 5.10. Two aromatic protons appeared at δ 7.0 as singlet.

The work was extended by replacing octadecyl group in Irganox 1076 homologue by ethyl, n-propyl, isopropyl and isoamyl groups.

4-(3',5'-Di-tert-butyl-4'-hydroxyphenyl) butanoic acid **5** on esterification with ethyl alcohol in the presence of sulfuric acid afforded ethyl-4-(3',5'-di-tert-butyl-4'-hydroxyphenyl) butanoate (Scheme 3). IR spectrum of the compound **7** (neat) showed band at 3620 cm^{-1} due to the presence of hindered phenolic OH stretching frequency. Carbonyl carbon of ester group vibrated at 1740 cm^{-1}. ^1H NMR spectrum (Fig. 15) recorded in $CDCl_3$ using TMS as internal standard showed triplet at δ 1.24 for three protons and quartet at δ 4.10 for two protons indicated the presence of ethyl group. Eighteen tert-butyl protons appeared at δ 1.44. Two triplets observed at δ 2.35 and at δ 2.51 for two protons each showed the presence of two methylene groups, one attached to phenol ring and the other attached to carbonyl carbon of ester linkage. Multiplet observed at δ 1.90 for two protons is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74.53
6.89
6.23
3.65
2.83
0.99
4.00
1.00
1.00
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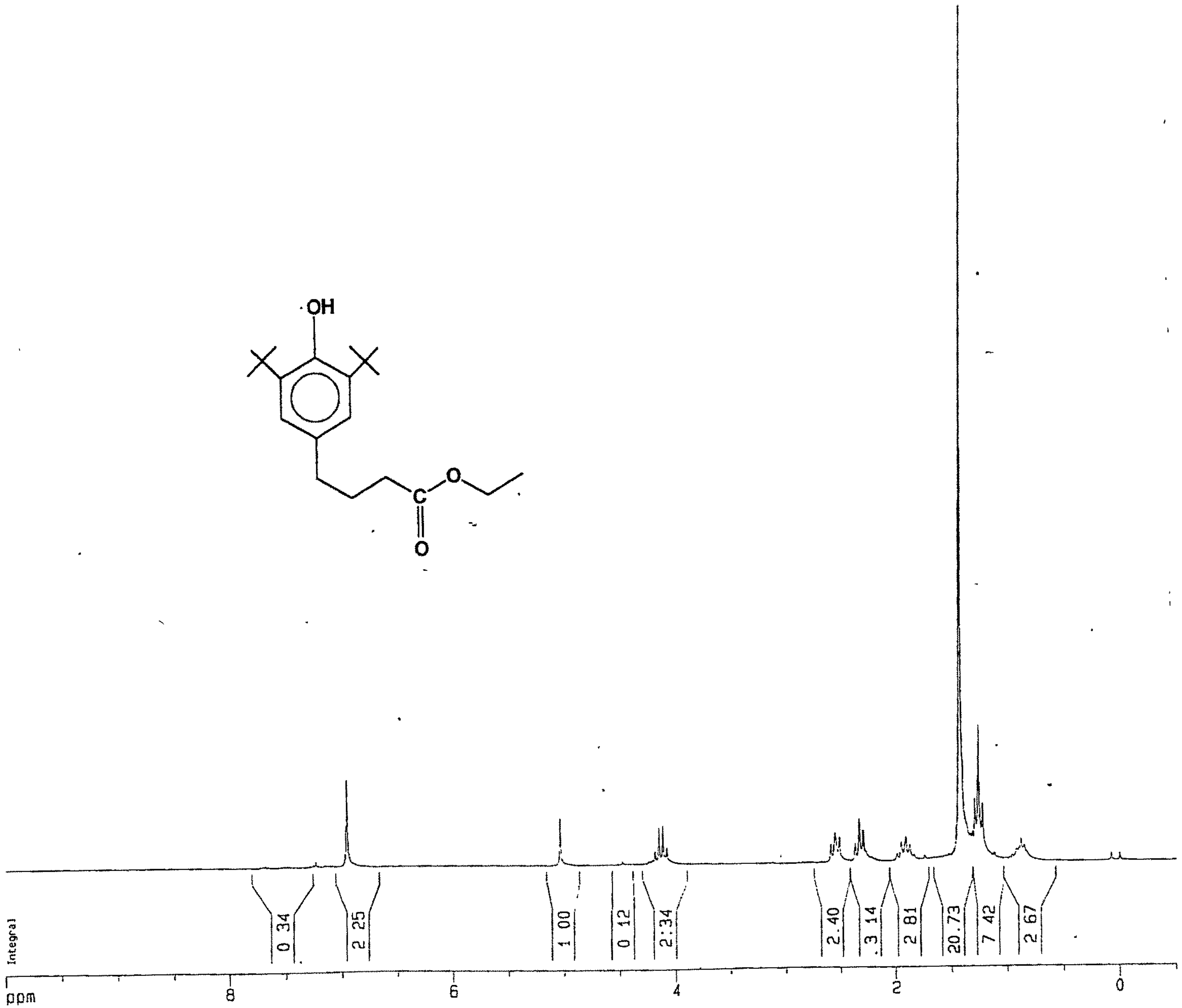
0.28
0.63
0.45
Integral
0
2
4
6
8
ppm

Figure 14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C
O
O
Integral
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2 25
1 00
0 12
2:34
2.40
.3 14
2 81
20.73
7 42
2 67
ppm
8
6
4
2
0

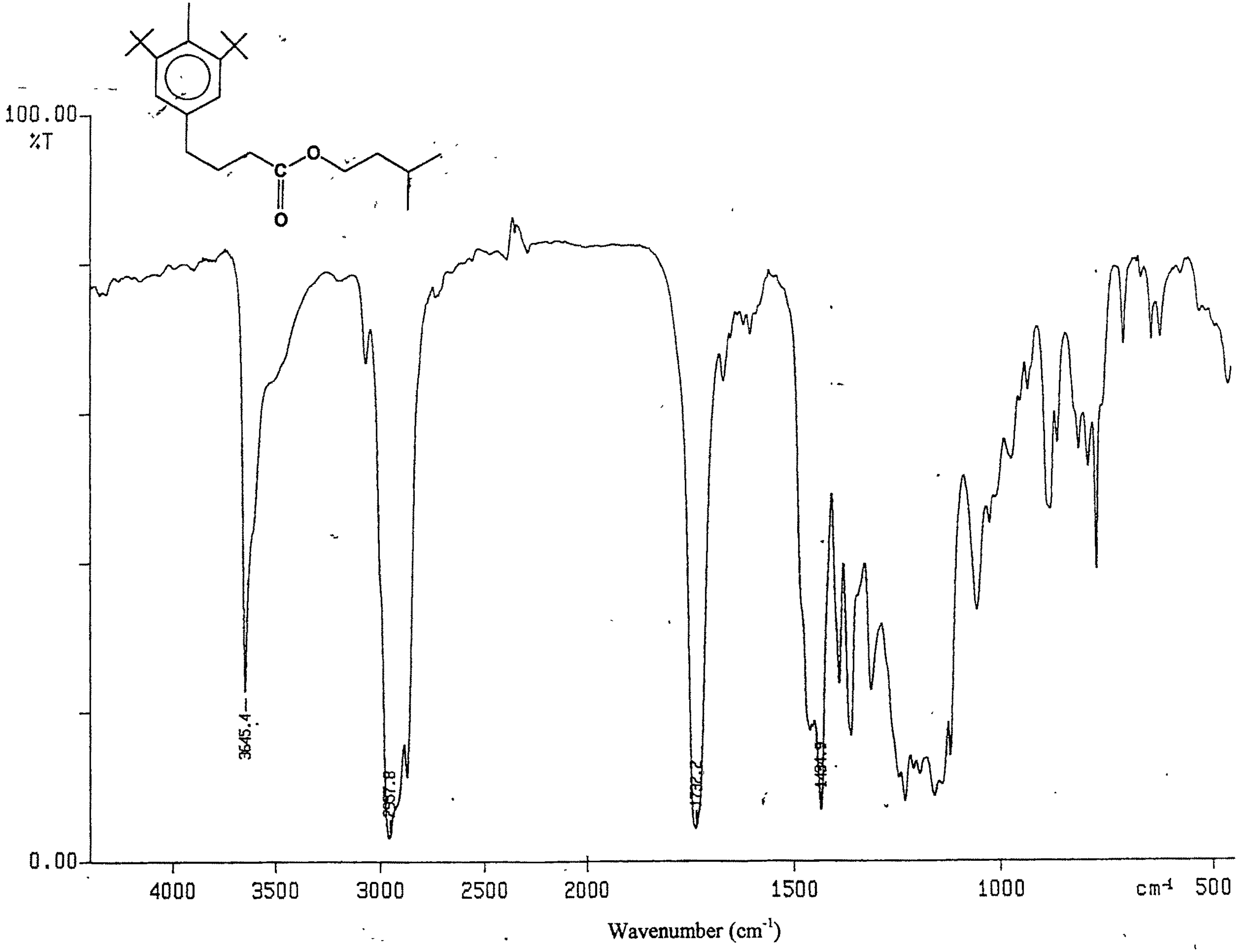
Figure 15

due to methylene group attached to two other methylene groups. Phenolic protons resonated at δ 5.0 as singlet. Two aromatic protons appeared at δ 6.95 as singlet.

Butanoic acid **5** on reaction with different alcohols afforded alkyl-4-(3',5'-di-tert-butyl-4'-hydroxyphenyl) butanoate **[8-10]** (Scheme 3). IR spectrum (neat) of compound (Fig. 16) **8** showed band at 3645 cm^{-1} due to hindered phenolic OH group. Band observed at 1732 cm^{-1} is due to the presence of carbonyl stretching frequency of ester group. ^1H NMR spectrum (Fig. 17) recorded in $CDCl_3$ showed doublet at δ 0.83 is due to presence of two methyl groups in aliphatic side chain. Eighteen tert-butyl protons appeared as singlet at δ 1.35. Quartet observed at δ 1.45 is due to the presence of methylene ($-CH_2-C\underline{H}_2-CH-$) protons. Methine proton present in the side chain appeared as multiplet at δ 1.59. Multiplet at δ 1.86 is due to the presence of methylene ($-CH_2-C\underline{H}_2-CH_2-$) protons. Triplets observed at δ 2.26 and at δ 2.47 are due to the presence of two methylene groups ($Ph-C\underline{H}_2-CH_2-CH_2-$) and ($-CH_2-CH_2-C\underline{H}_2-CO$) respectively. Triplet observed at δ 4.03 is due to the presence of methylene group attached to oxygen of ester group. Phenolic proton resonated at δ 4.97. Two aromatic protons observed at δ 6.89.

Experimental

Melting points were determined using open capillary paraffin bath and were uncorrected. IR spectra were recorded on Perkin-Elmer IR -781 spectrophotometer as KBr Pellet or using Nujol. ^1H NMR spectra were determined on Brucker-200 MHz spectrometer and CMR spectra were recorded on Bruker-50MHz spectrophotometer using $CDCl_3$ as solvent and TMS as internal reference. Mass spectrum was recorded on Fillisinnigan Mat-1020B instrument. Elemental analysis was performed on Coleman C, H analyser. Reaction was monitored by TLC, carried out on E-Merck silica gel plates (60 F_{254}) precoated on aluminium sheet.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%T
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1732.2
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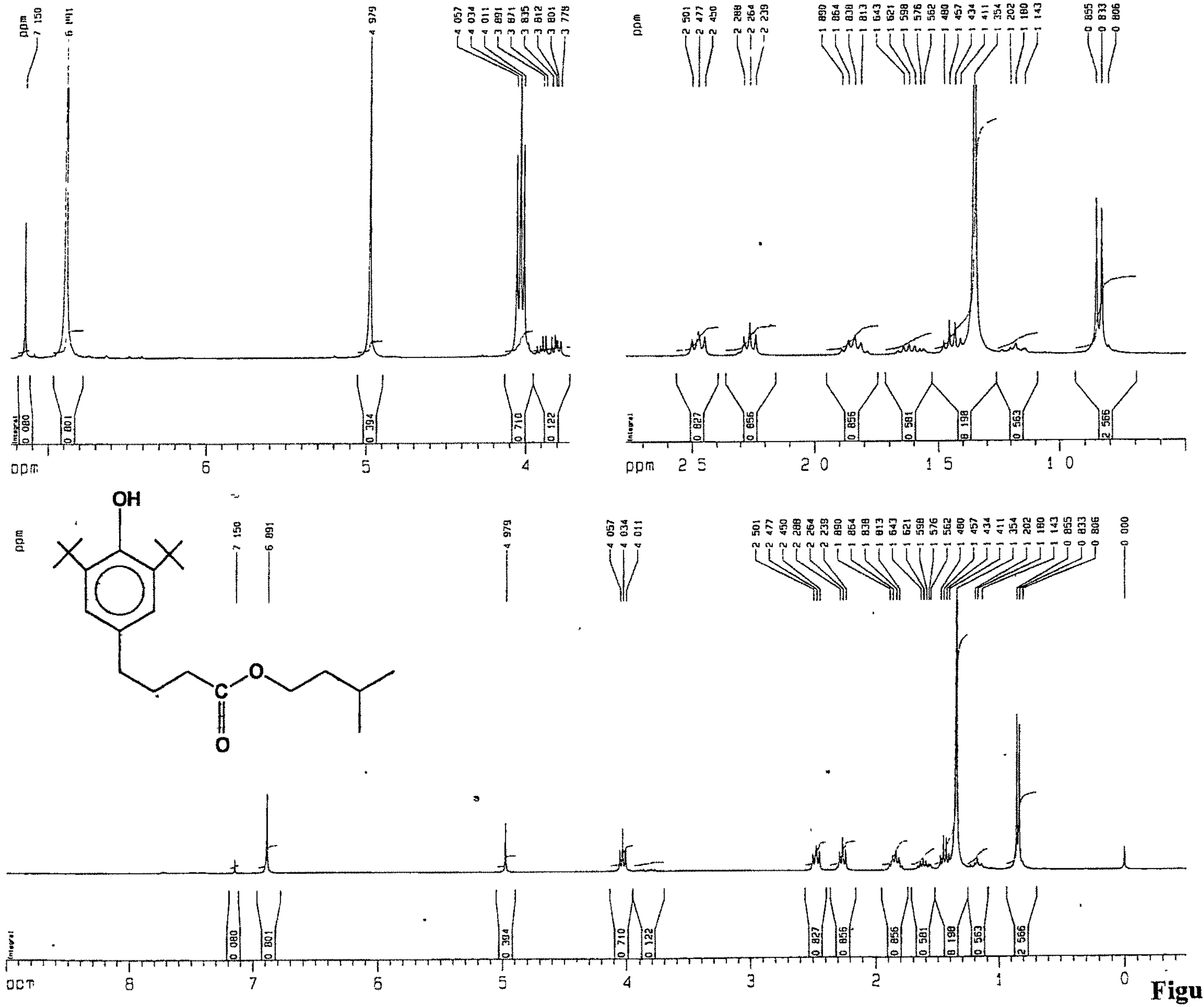
3000
2500
2000
1500
1000
cm-1
500
Wavenumber (cm-1)

Figure 16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4 979
4 057
4 034
4 011
3 891
3 871
3 835
3 812
3 801
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0 801
0 394
0 710
0 122
ppm
6
5
4
ppm
2 501
2 477
2 450
2 288
2 264
2 239
1 890
1 864
1 838
1 813
1 643
1 621
1 598
1 576
1 562
1 480
1 457
1 434
1 411
1 354
1 202
1 180
1 143
0 855
0 833
0 806
Integral
0 827
0 856
0 856
0 581
8 198
0 563
2 566
ppm
2 5
2 0
1 5
1 0
OH
C
O
O
ppm
0 000
8
7
6
5
4
3
2
1
0

Figure 17

Friedel-Crafts succinolyation on 2,6-di-tert-butyl phenol

(Process A)

To the stirring solution of 2,6-di-tert-butyl phenol (0.01mol) and succinic anhydride (0.015mol) in nitrobenzene (100 ml), $AlCl_3$ (0.02mol) was added in parts at temperature 0-5^{0}C. The reaction mixture was stirred for 6 hr. The mixture was quenched in cold water and HCl. Nitrobenzene layer was washed with water and was removed using Dean-Stark apparatus. The dark brown pasty mass obtained was stirred with petroleum ether (5 ml) and the solid obtained was filtered, dried and crystallised from the mixture of benzene and petroleum ether to get compound **2.** m.p. 164-165^{0}C (lit^4 163-165^{0}C), yield 55%. Compound **3** was isolated from the surface of the Dean-Stark apparatus and was crystallised from petroleum ether in white needles. m.p. 95-97^{0}C (lit^{12} 96-98^{0}C), yield 10%.

Elemental analysis **[2]**	Found:	C, 71.00	H, 8.09
$C_{18}H_{26}O_4$/306	Expected:	C, 70.59	H, 8.50%

Elemental analysis **[3]**	Found:	C, 79.49	H, 8.94
$C_{10}H_{14}O$/150	Expected:	C, 80.00	H, 9.33%

(Process B)

Succinic anhydride (0.015mol) was dissolved in carbon disulfide (100ml). To this, 2,6-di-tert-butyl phenol (0.01mol) was added and the mixture was cooled to 0-5^{0}C. Aluminium chloride (0.02mol) was added in parts at this temperature and the mixture was stirred for 6 hr at 0-5^{0}C. The reaction mixture was decomposed in cold water and HCl. Carbon disulfide layer was removed by simple distillation. The pasty mass obtained was stirred with petroleum ether. The solid on crystallisation from petroleum ether gave 3-(4'-tert-butyl carbphenoxy) propanoic acid **4.** m.p. 88-90^{0}C, yield 40%.

Elemental analysis	Found:	C, 67.60	H, 7.33
$C_{14}H_{18}O_4$/250	Expected:	C, 67.20	H, 7.20%

Synthesis of 4-(3',5'-di-tert-butyl-4'-hydroxyphenyl)butanoic acid ***5.***

A solution of keto acid **2** (0.01mol) in toluene (25 ml) was added to a freshly prepared mixture of amalgamated zinc (from mossy zinc), water (20 ml) and conc. HCl (20 ml). The resulting mixture was refluxed vigorously for 12 hr with 5 ml portion of HCl being added every 4 hr. After cooling toluene layer was separated. White crystalline solid obtained after removal of toluene was dried and crystallised from petroleum ether. m.p. 100-102^{0}C (lit[13] 119-120^{0}C), yield 90%.

Elemental analysis	Found:	C, 74.38	H, 9.69
$C_{18}H_{28}O_3$/292	Expected:	C, 73.97	H, 9.58%

Synthesis of octadecyl-4-(3',5'-di-tert-butyl-4'-hydroxyphenyl) butanoate ***6.***

Butanoic acid **5** (0.01mol) was dissolved in dry chloroform (50 ml). To this octadecyl alcohol (0.01mol) was added followed by catalytic amount of *P*-toluene sulfonic acid. The reaction mixture was refluxed for 6 hr using Dean-Stark apparatus. After cooling, the chloroform layer was washed with water and was removed by distillation. Product obtained was purified by column chromatography (elution: petroleum ether) as thick viscous liquid, yield 84%.

Elemental analysis	Found:	C, 79.21	H, 11.56
$C_{36}H_{64}O_3$/544	Expected:	C, 79.41	H, 11.76%

Synthesis of ethyl-4-(3',5'-di-tert-butyl-4'-hydroxyphenyl) butanoate.

Butanoic acid 5 (0.01mol) was dissolved in dry ethanol (50ml). To this sulfuric acid (0.2ml) was added. The reaction mixture was refluxed for 6 hr. After cooling, excess of ethanol was removed by distillation. Product obtained was purified using column chromatography (elution : Pet.ether) as thick viscous liquid. yield 80%.

Elemental Analysis	Found :	C, 74.50	H, 10.08
$C_{20}H_{33}O_3$/321	Expected:	C, 74.76	H, 10.28%

Synthesis of isoamyl-4-(3',5'-di-tert-butyl-4'-hydroxyphenyl) butanoate.

Isoamyl alcohol (0.01mol) was added to a solution of butanoic acid **5** (0.01mol) in chloroform (50ml). To this, catalytic amount of PTSA was added and the mixture was refluxed for 8 hr using Dean Stark apparatus. Excess of chloroform was removed by distillation and washed with water. The crude slurry was purified by column chromatography using Pet. ether as eluent. The product was obtained as viscous liquid, yield 70%.

n-Propyl-4-(3',5'-di-tert-butyl-4'-hydroxyphenyl) butanoate and isopropyl-4-(3',5'-di-tert-butyl-4'-hydroxyphenyl) butanoate were also prepared by following the same procedure.

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Chapter 4

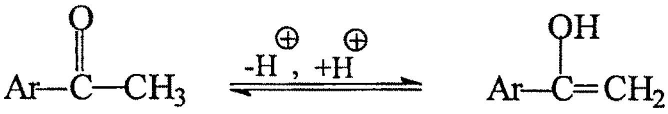
Section 2

Preparation and Reactions of 1-(3',5'-Di-tert-butyl-4'-hydroxy phenyl)-2-bromoethanone

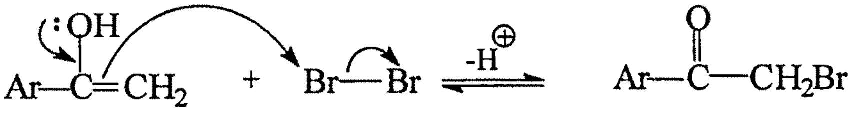
The reaction of carboxylic acid chloride or anhydride with aromatic hydrocarbon in the presence of aluminum chloride generally gives good yield of aromatic ketone. This Friedel-Crafts acylation requires at least one molar equivalent of aluminum chloride for each carbonyl group present in the acylating agent. This is because $AlCl_3$ is capable of forming rather stable complex with carbonyl group. This complex formation requires an equivalent quantity of metal halide and hence a slight excess of this amount is employed. Excess of benzene or toluene is used as a solvent when either of these substances constitutes one of the reactants, otherwise carbon disulfide or nitrobenzene is generally employed as solvent. Polysubstitution or rearrangement is not observed in Friedal-Crafts acylation. The mechanism of Friedal-Crafts reaction involves the attack of acylium ion or electrophile to aromatic compounds.

Ershov, Volodkin[1] and *Cook, Gilmour*[2] reported the synthesis of 3,5-di-tert-butyl-4-hydroxyacetophenone **1** by introducing acetyl group at the position para to hydroxy group in 2,6-di-tert-butyl phenol using acetyl chloride in the presence of aluminum chloride at 0 to 5^0C .

Phenacyl bromide derivatives are important intermediate in the synthetic organic chemistry due to its high reactivity towards amines, phenols and alcohols.
Bromination of methyl group can be restricted to mono substitution when the reaction is carried out in acidic media. The mechanism involves protonation of carbonyl oxygen, followed by proton loss to give enol. After mono bromination, protonation of the bromo ketone is less favourable owing to the presence of electron withdrawing halogen atom. Further enolisation does not occur easily and therefore halogination ceases, the product is aryl bromomethyl ketone or phenacyl bromide.

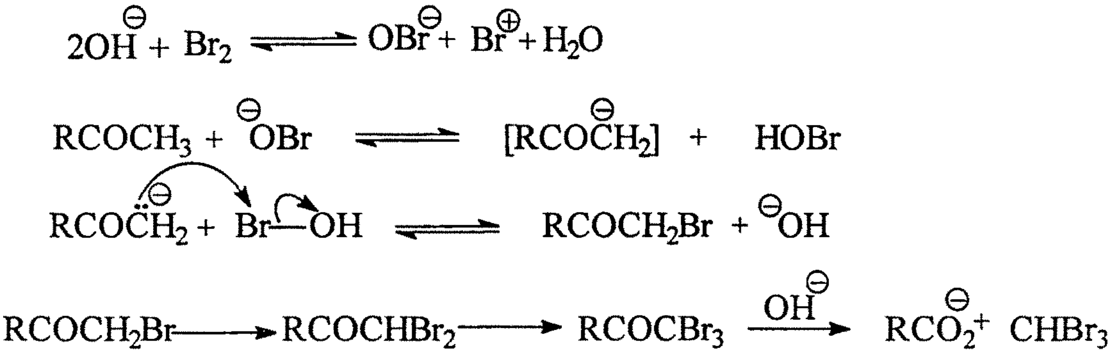


$$\mathrm{Ar{-}\overset{\displaystyle O}{\overset{\|}{C}}{-}CH_3 \underset{}{\overset{-H^{\oplus},\ +H^{\oplus}}{\rightleftharpoons}} Ar{-}\overset{\displaystyle OH}{\overset{|}{C}}{=}CH_2}$$



$$\mathrm{Ar{-}\overset{\displaystyle OH}{\overset{|}{C}}{=}CH_2 + Br{-}Br \overset{-H^{\oplus}}{\rightleftharpoons} Ar{-}\overset{\displaystyle O}{\overset{\|}{C}}{-}CH_2Br}$$

Bromination of methyl group in the presence of base results in the oxidation of methyl ketone to a carboxylic acid. This involves treatment of the methyl ketone with an alkaline hypohalide reagent. A trihalomethyl ketone is initially formed which then undergoes hydrolysis under the basic conditions used.

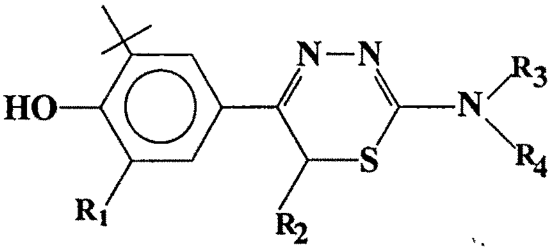


$$\mathrm{2OH^{\ominus} + Br_2 \rightleftharpoons OBr^{\ominus} + Br^{\oplus} + H_2O}$$
$$\mathrm{RCOCH_3 + {}^{\ominus}OBr \rightleftharpoons [RCOCH_2^{\ominus}] + HOBr}$$
$$\mathrm{RCO\ddot{C}H_2^{\ominus} + Br{-}OH \rightleftharpoons RCOCH_2Br + {}^{\ominus}OH}$$
$$\mathrm{RCOCH_2Br \longrightarrow RCOCHBr_2 \longrightarrow RCOCBr_3 \xrightarrow{OH^{\ominus}} RCO_2^{\ominus} + CHBr_3}$$

Volod'kin et al.[3] prepared the 1-(3',5'-di-tert-butyl-4'-hydroxyphenyl)-2-bromoethanone **2** by adding bromine to 3,5-di-tert-butyl-4-hydroxyacetophenone **1** in octane at 70^{0}C in 80% yield.

Werner et al.[4] synthesized compound **2** by refluxing ketone **1** in dichloromethane using bromine in 67% yield. They have reported the synthesis and testing of 5-(3'-

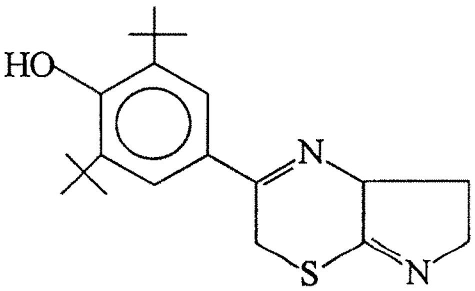
alkyl-5'-tert-butyl-4'-hydroxyphenyl)-2-amino-6[H],1,3,4-thiadiazines(R_1=CMe_3, R_2=H, R_3R_4=Me) **4** by refluxing bromoethanone **2** and $Me_2NCSNHNH_2$ in ethanol, as drug.



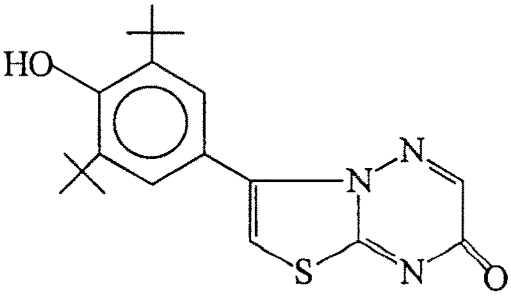
[4]

Werner et al.[5] reported the synthesis and testing of imidazo and triazolo thiadiazines as 5-lipoxygenase inhibitors. They obtained compound **5** by heating bromoethanone **2** with 1-amino-2-thioxoimidazolidine in ethanol.

Synthesis of 3-(3',5'-di-tert-butyl-4'-hydroxyphenyl) phenyl-7H-thiazolo [3,2,b] [1,2,4] triazine-7-one **6** and it's anti-inflammatory activity was reported by *Werner et al*[6]. They prepared compound **6** by treating bromoethanone **2** with 3-mercapto-2 [H]-1,2,4-triazine-5-one in 80% yield.

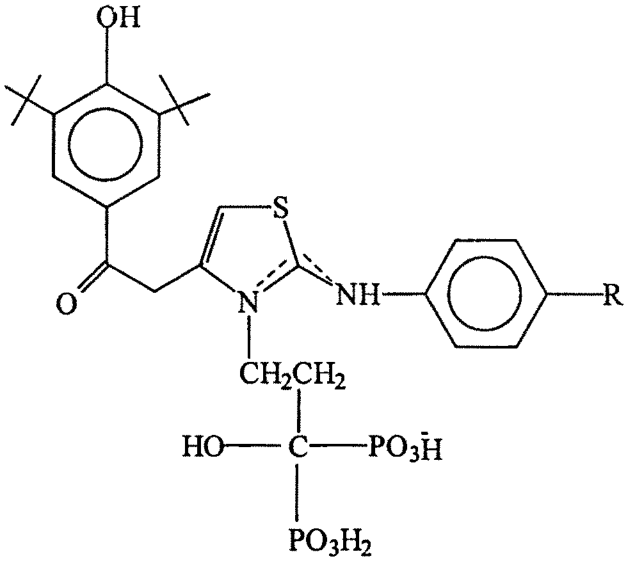


[5]



[6]

Lozinskii et al.[7] reported the synthesis of thiazolium-substituted alkylidene-1,1-bis phosphonic acid **7** by Hantzsch cyslisation of bromoethanone **2** with 4-RC_6H_4-NH-$C(S)CH_2CH_2C(OH)(PO_3H_2)_2$. NEt_2. nH_2O, (n=1,3), (R=H, Br, Cl, NO_2) in aqueous ethanol containing triethylamine.



[7]

From the literature search it has been observed that the various heterocyclic moieties formed from the 1-(3',5'-di-tert-butyl-4'-hydroxyphenyl)-2-bromoethanone **2** has remarkable potential to act as drugs. It is also reported in literature that low molecular weight antioxidants like BHT are preferred for polymer because they are capable of migrating freely through out the polymer bulk so as to reach large number of initiation sites that are generated at elevated temperature.[8] However BHT suffers from a major drawback viz. high volatility. In more demanding long-term heat exposure, however, the choice is almost always in favour of high molecular weight antioxidants. High molecular weight of an antioxidant may ensure low volatility.[9]

Considering the above mentioned facts,2-amino thaizole and benzofuran moieties were synthesised using bromoethanone **2.** The bromoethanone **2** was allowed to react with various substituted phenols to form antioxidants of high molecular weight.

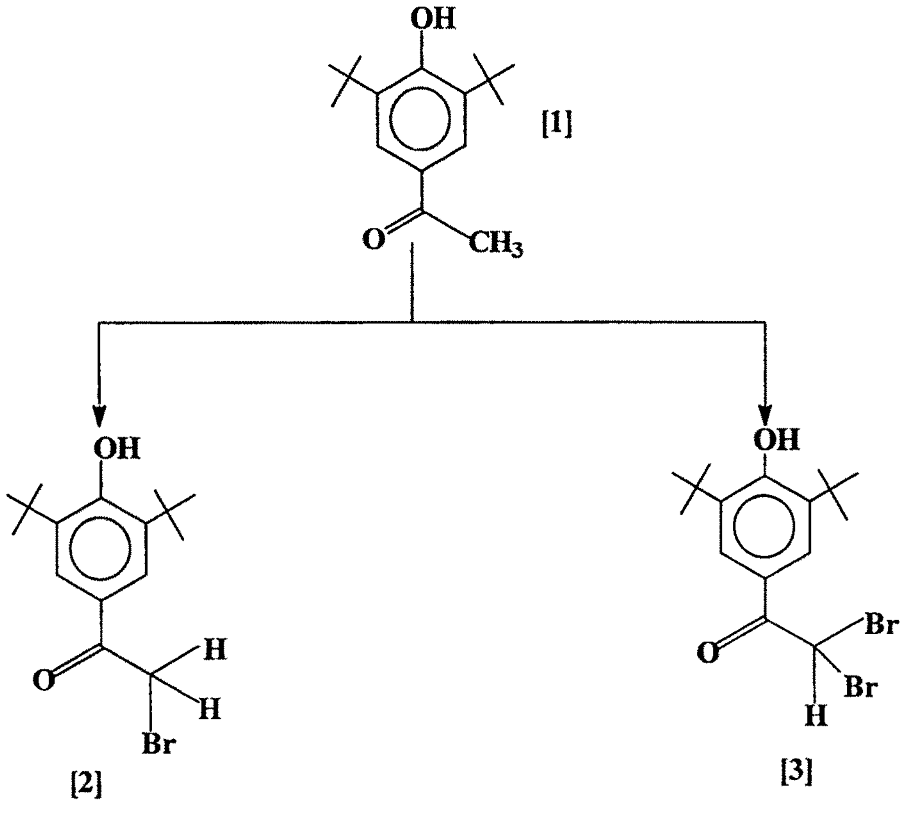
Present work

3,5-Di-tert-butyl-4-hydroxyacetophenone was synthesized from 2,6-di-tert-butyl phenol according to reported method.[10]

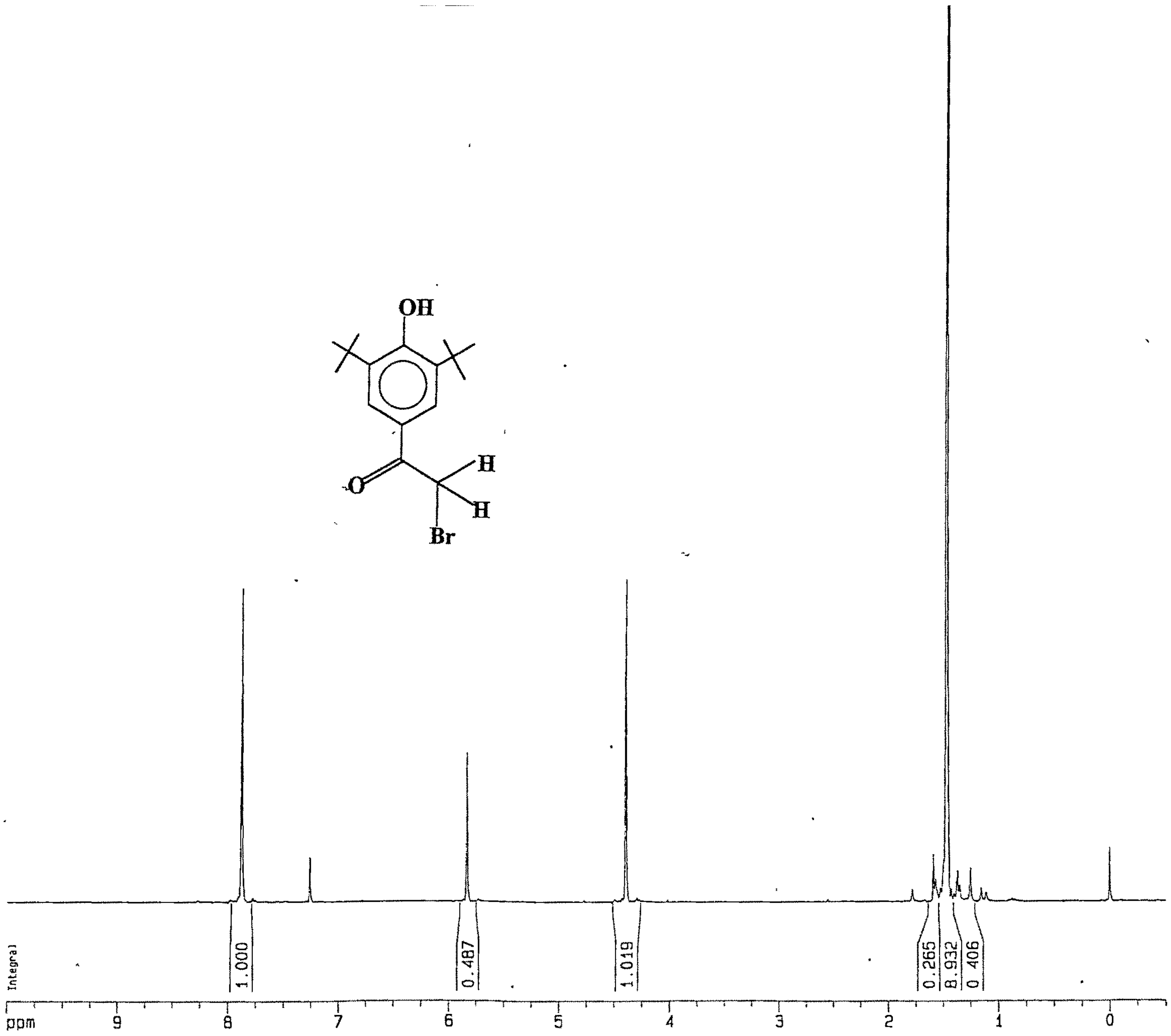
Bromination of 3,5-di-tert-butyl-4-hydroxyacetophenone 1

Liquid bromine was added to a homogeneously stirred mixture of acetophenone **1** in glacial acetic acid. 1-(3',5'-Di-tert-butyl-4'-hydroxyphenyl)-2-bromoethanone **2** and 1-(3',5'-Di-tert-butyl-4'-hydroxyphenyl)-2,2-dibromoethanone **3** were isolated from the reaction mixture (Scheme1). Both these compounds were purified through column chromatography. The structures of **2** and **3** were established on the basis of IR and NMR spectral techniques. IR spectrum of compound **2** taken using KBr showed band at 3620 cm^{-1} due to OH stretching frequency of hindered phenolic group. Band observed at 1680 cm^{-1} is due to CO stretching frequency of carbonyl group attached to aromatic ring. ^{1}H NMR spectrum (Fig. 1) of compound **2** recorded in CDCl$_3$ using TMS as internal standard showed singlet at δ 1.50 for eighteen protons due to the presence of two tert-butyl groups. Singlet that observed for two protons at δ 4.40 indicated the presence of methylene group. Phenolic proton appeared as singlet at δ 5.82. Two aromatic protons resonated at δ 7.90 as singlet.

The IR spectrum taken using KBr pellet of compound **3** showed band at 3618 cm^{-1} for OH stretching frequency of hindered phenolic group. Stretching vibration of carbonyl group appeared at 1660 cm^{-1}. ^{1}H NMR spectrum (Fig. 2) of compound **3** recorded in CDCl$_3$ using TMS as internal standard showed singlet at δ 1.50 correspond to eighteen protons of two tert-butyl groups. Phenolic proton appeared at δ 5.80 as singlet. Singlet observed at δ 6.40 for one proton is due to methine proton. The peak for methine proton is in lower region and elemental analysis results confirmed the dibromination of acetyl group in acetophenone **1.** Two aromatic protons resonated at δ 7.92 as singlet.



Scheme 1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H
H
O
Br
Integral
1.000
0.487
1.019
0.265
8.932
0 406
ppm
9
8
7
6
5
4
3
2
1
0

Figure 1

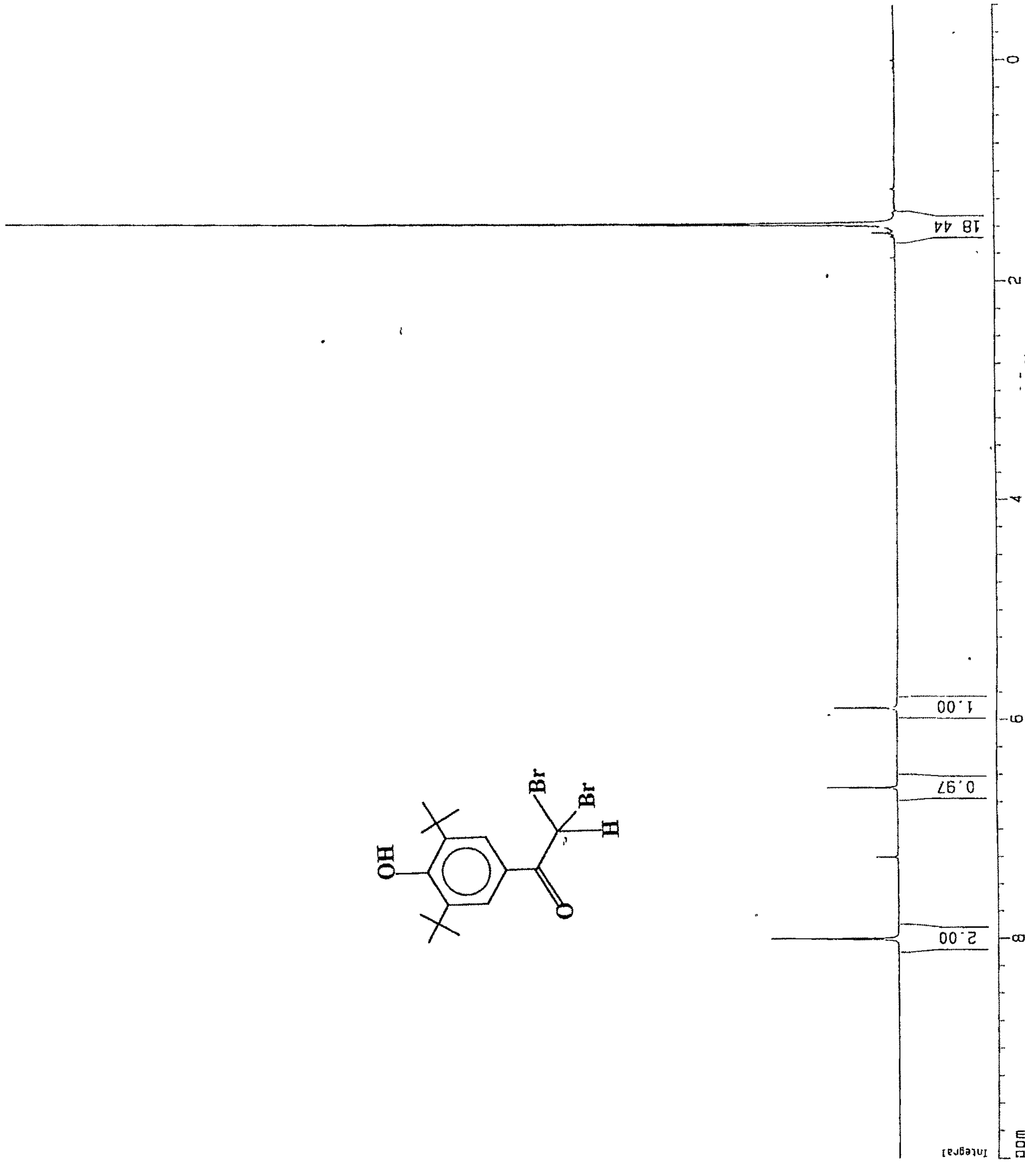
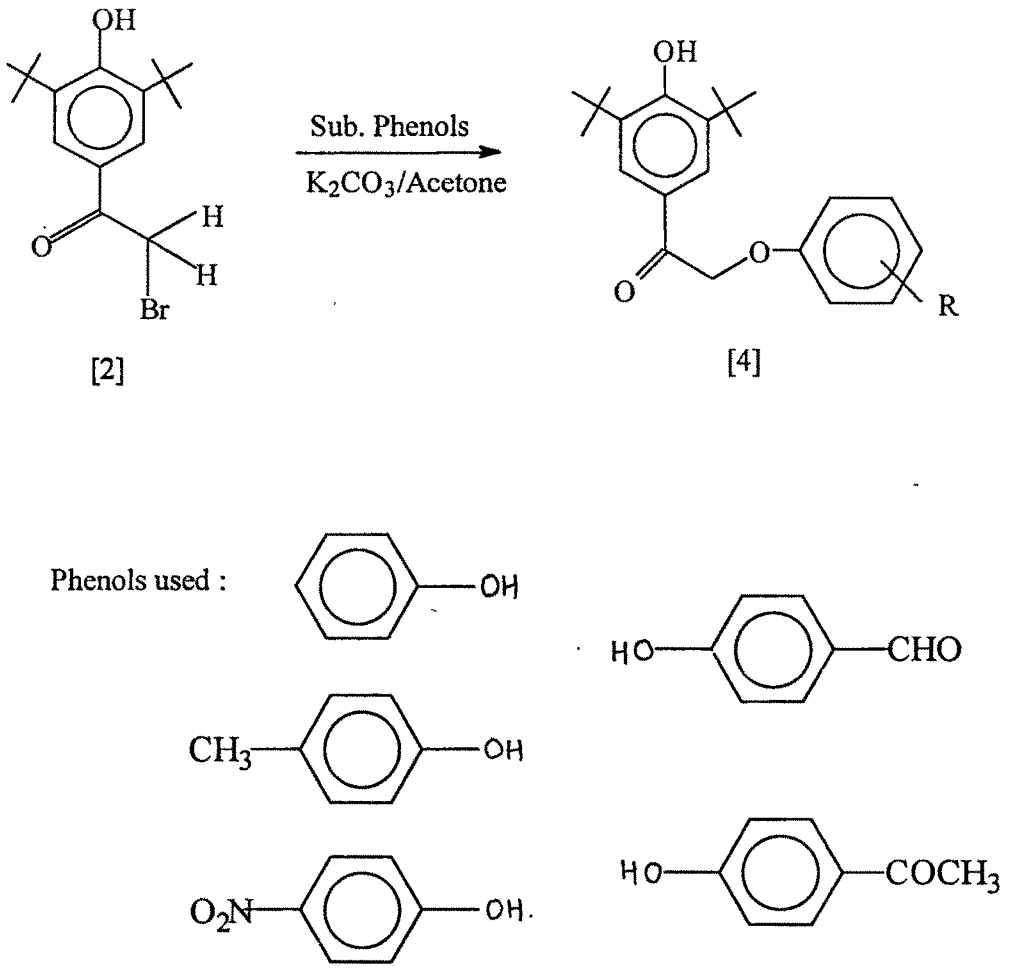


Figure 2

Condensation of 1-(3',5'-di-tert-butyl-4'-hydroxyphenyl)-2-bromoethanone with substituted phenols [P1-P5]

1-(3',5'-Di-tert-butyl-4'-hydroxyphenyl)-2-bromoethanone **2** on reaction with various substituted phenols in the presence of anhydrous K_2CO_3 using acetone as solvent gave corresponding 1-(3',5'-di-tert-butyl-4'-hydroxyphenyl)-2-(substituted phenoxy) ethanone (Scheme 2). Elemental analysis and spectral studies are used to establish the structure of these synthesised compounds. IR and NMR spectra of the representative compound **4P₃** are discussed here. IR spectrum taken using KBr showed band at 3610 cm^{-1} due to OH stretching frequency of hindered phenolic group. Ketonic group vibrated at 1690 cm^{-1}. ^1H NMR spectrum (Fig. 3) recorded in $CDCl_3$ using TMS as internal standard showed singlet at δ 1.50 for two tert-butyl groups. Methylene protons appeared at δ 5.40 as singlet. Phenolic protons resonated at δ 5.8 as singlet. Doublet observed at δ 7.0 and at δ 8.25 for two protons, each with same J=10Hz confirmed the presence of four aromatic protons of *p*-cresol. Two aromatic protons of phenol resonated at δ 7.8.


OH
Sub. Phenols
K_2CO_3/Acetone
H
H
O
Br
[2]
OH
O
O
R
[4]
Phenols used :
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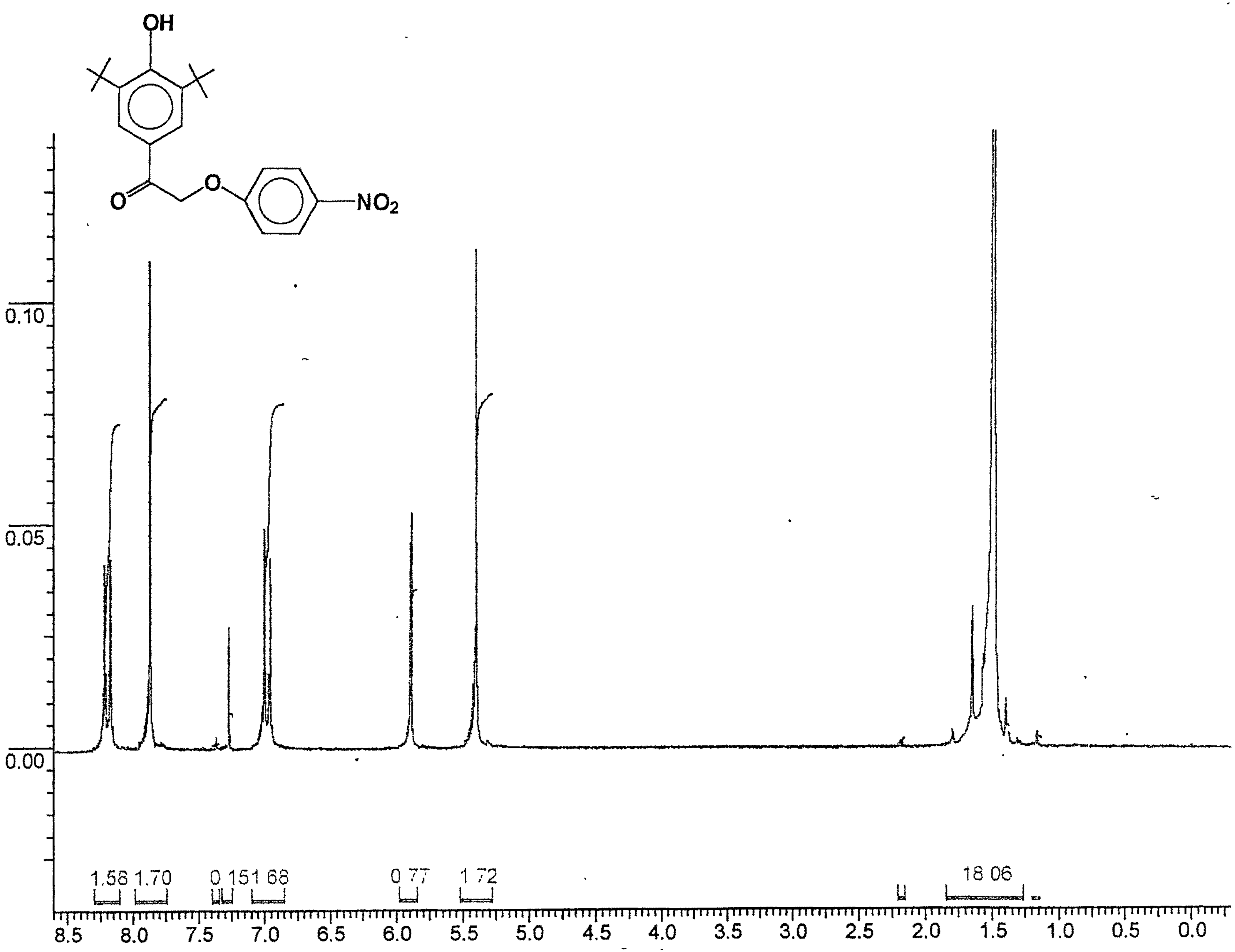
HO
CHO
CH_3
OH
HO
$COCH_3$
O_2N
OH.

Scheme 2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O
O
NO2
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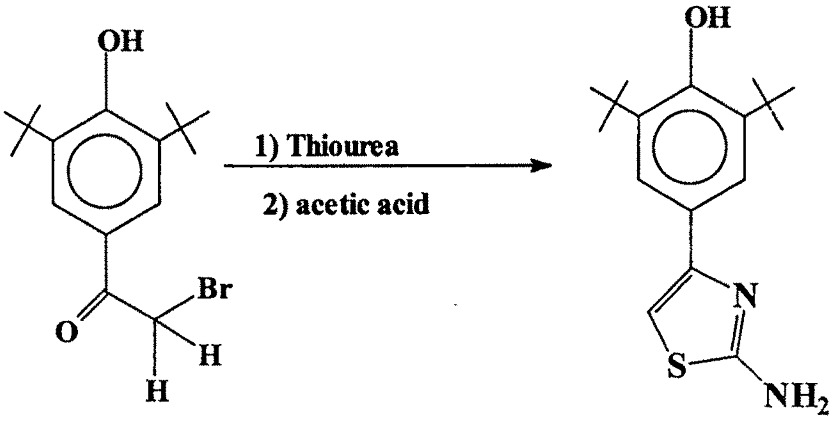
0.05
0.00
1.58
1.70
0 15
1 68
0 77
1 72
18 06
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

Figure 3

Synthesis of 2-amino-4-(3',5'-di-tert-butyl-4'-hydroxyphenyl) thiazole

1-(3',5'-Di-tert-butyl-4'-hydroxyphenyl)-2-bromoethanone **2** on cyclocondensation with thiourea in the presence of glacial acetic acid afforded thiazole derivative (Scheme 3). Structure of this compound was established on the basis of elemental analysis and NMR spectral study. ^{1}H NMR spectrum (Fig. 4) recorded in $CDCl_3$ using TMS as internal standard showed singlet at δ 1.47 for eighteen protons of two tert-butyl groups. Two NH_2 protons appeared at δ 5.01 as singlet. Phenolic proton resonated at δ 5.10 as singlet. Methine proton present in thiazole ring was observed at δ 6.50 as singlet. Singlet that appeared at δ 7.55 for two protons showed the presence of aromatic ring in the molecule.



Scheme 3

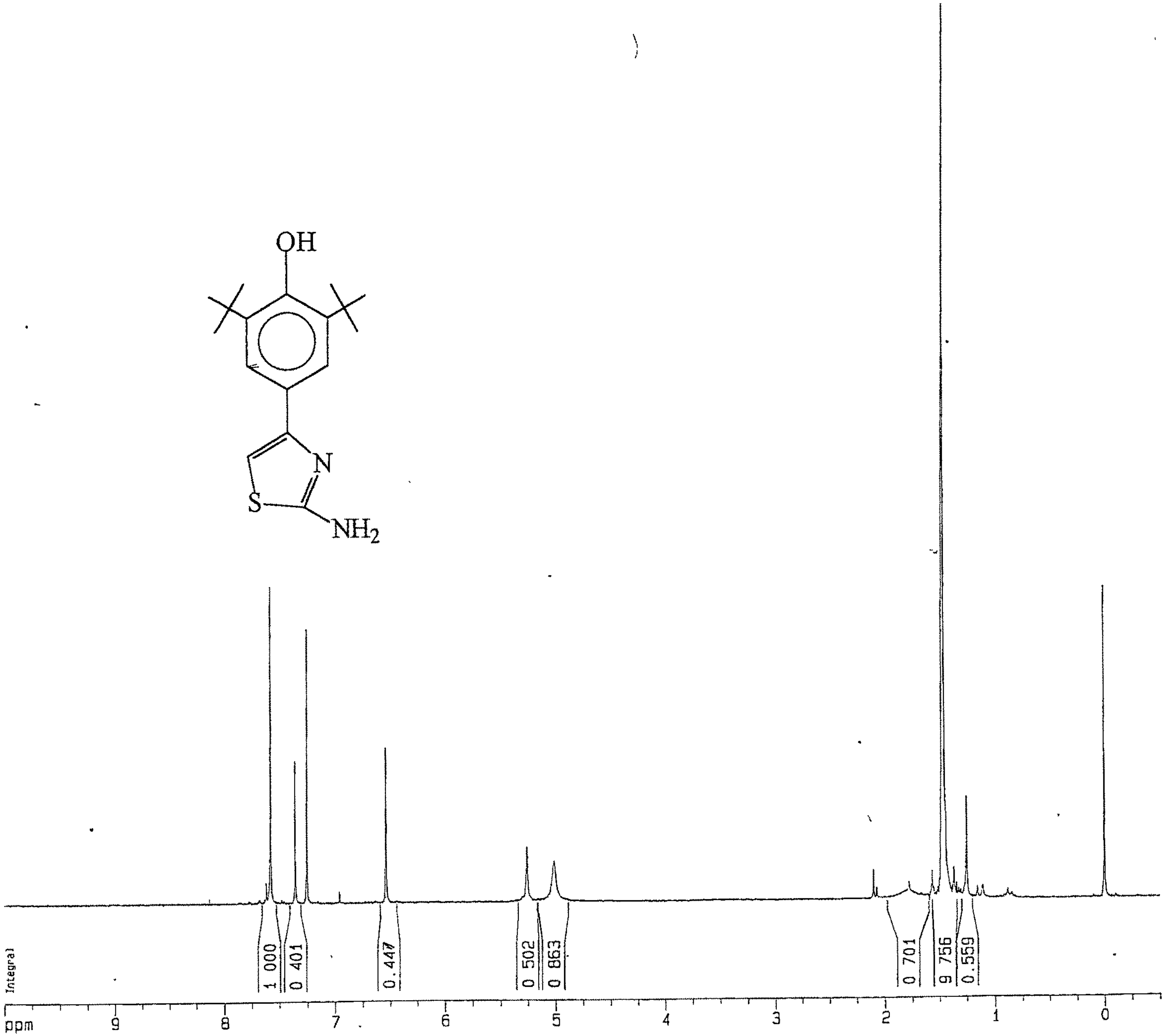
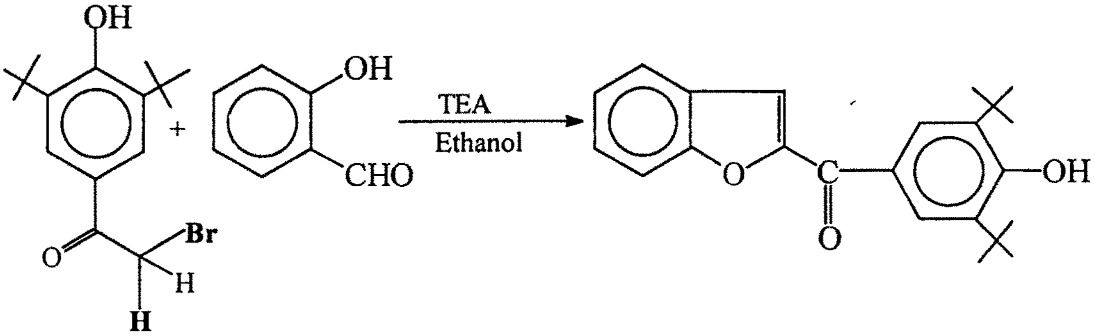

OH
N
S
NH$_2$
Integral
1 000
0 401
0.447
0 502
0 863
0 701
9 756
0.559
ppm
9
8
7
6
5
4
3
2
1
0

Figure 4

Synthesis of 2-(3',5'-di-tert-butyl-4'-hydroxybenzoyl) benzofuran

1-(3',5'-Di-tert-butyl-4'-hydroxyphenyl)-2-bromoethanone **2** on reaction with *o*-hydroxybenzaldehyde in the presence of triethylamine and ethanol afforded 2-(3',5'-di-tert-butyl-4'-hydroxybenzoyl) benzofuran (Scheme 4). The structure of the synthesised compound was established on the basis of elemental analysis, IR and NMR spectral studies. IR spectrum taken using KBr pellets showed band at 3622 cm $^{-1}$ due to OH stretching frequency of hindered phenolic group. ^{1}H NMR spectrum (Fig. 5) recorded in $CDCl_3$ using TMS as internal standard showed singlet at δ 1.51 for eighteen protons due to presence of two tert-butyl groups. Phenolic proton appeared at δ 5.80 as singlet. Signal observed at δ 7.75 is for the proton present at position $C_{7'}$. Signal at δ 7.65 is due to the presence of proton at $C_{4'}$. Protons of $C_{5'}$ and $C_{6'}$ appeared as multiplet along with two aromatic protons of phenol ring in the region of δ 7.27 to 7.53. Methine protons of furan ring resonated at δ 8.01 as singlet.



Scheme 4

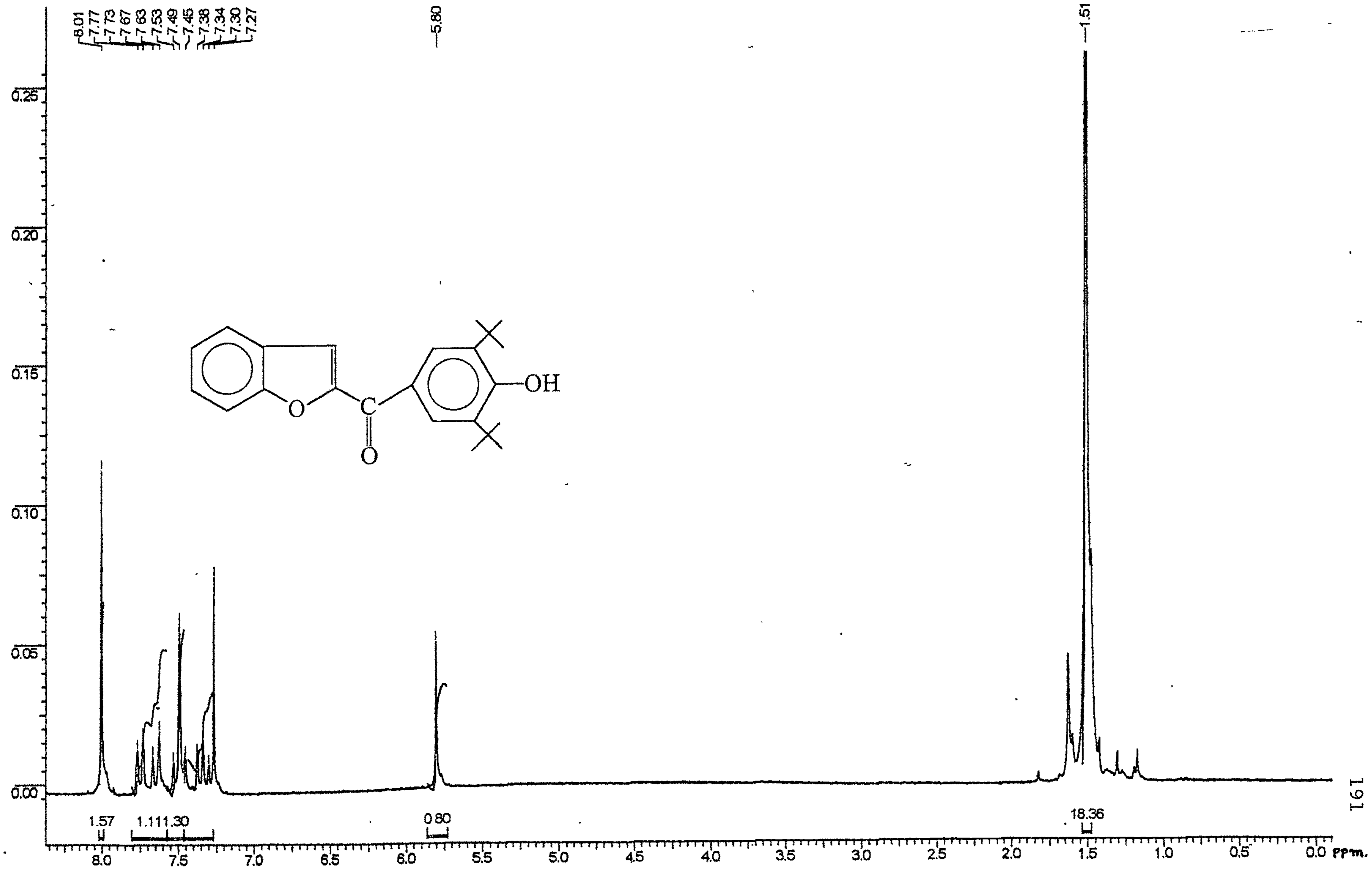

8.01
7.77
7.73
7.67
7.63
7.53
7.49
7.45
7.38
7.34
7.30
7.27
5.80
1.51
0.25
0.20
0.15
0.10
0.05
0.00
OH
C
O
O
1.57
1.11
1.30
0.80
18.36
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0 ppm.

Figure 5

Experimental

Elemental analyses were performed using Perkin-Elmer-2400 (Norwalk, CT) C, H, N and S analyser. IR spectra were recorded on Shimadzu - IR 408 (Japan) spectrophotometer as KBr pellet. ^{1}H NMR spectra were recorded on Brukers-200mHz (Wissenbourg-France) spectrophotometer using $CDCl_3$ as solvent and TMS as internal standard. Signal positions (δ value) were measured relative to the TMS signal (δ 0). Coupling constant values are given in Hz. Acme's silica gel with mesh size 60-120 was used for column chromatography. Analytical TLC was performed on precoated E. Merck silica gel 60 F_{254} aluminum plates.

3,5-Di-tert-butyl-4-hydroxyacetophenone **1** was prepared according to a known procedure[10].

Bromination of acetophenone 1

To a stirring solution of 3,5-di-tert-butyl-4-hydroxyacetophenone (0.01mol) in glacial acetic acid (30ml), liquid bromine (0.009mol) in acetic acid (5ml) was added dropwise over a period of half an hour. After complete addition, reaction mixture was stirred at room temperature for 4 hr. The product obtained by pouring the reaction mixture in to ice cold water was filtered and dried. Two different products **2** and **3** were isolated from this reaction, both of them were separated through column chromatography using petroleum ether as eluent.

1-(3',5'-Di-tert-butyl-4'-hydroxyphenyl)-2-bromoethanone **2** m.p. 94-96^{0}C (Lit[3] m.p. 95-97^{0}C), yield 60%.

Elemental analysis	Found:	C, 59.04	H, 6.91
$(C_{16}H_{23}BrO_2)$/327	Calc.:	C, 58.71	H, 7.03%

1-(3',5'-Di-tert-butyl-4'-hydroxyphenyl)-2,2-dibromoethanone **3**. m.p. 102-104^{0}C, yield 38%.

Elemental analysis	Found:	C, 47.82	H, 5.20
($C_{16}H_{22}Br_2O_2$)/404	Calc.:	C, 47.52	H, 4.95%

Preparation of 1-(3',5'-di-tert-butyl-4'-hydroxyphenyl)-2-(substituted phenoxy) ethanone

Anhydrous potassium carbonate (0.1mol) was added to homogeneously stirred mixture of substituted phenol (0.01mol) in dry acetone (25ml) followed by 1-(3',5'-di-tert-butyl-4'-hydroxyphenyl)-2-bromoethanone **2** (0.01mol). The reaction mixture was refluxed for 6 hr. The solid obtained by pouring the mixture in ice-cold water was filtered, dried and crystallised using appropriate solvents.

Melting point, yield and elemental analysis results of the synthesised compounds are shown in Table 1.

Code.	Phenols	Yield (%)	M.P. (°C)	M.F. (Mol. Wt.)	Elemental Analysis (Calc./ Obs.) (%)		
					C	H	N
$P1^{P}$	C_6H_5OH	69	86	$C_{22}H_{28}O_3$ (340)	78.49 78.90	7.95 8.37	--
$P2^{B+P}$	4-$CH_3C_6H_4OH$	75	108	$C_{23}H_{30}O_3$ (354)	77.96 78.20	8.47 8.87	--
$P3^{B}$	4-$NO_2C_6H_4OH$	80	140	$C_{22}H_{27}NO_5$ (385)	68.57 68.20	7.01 7.11	3.63 3.76
$P4^{B}$	4-$CHOC_6H_4OH$	60	120	$C_{23}H_{28}O_4$ (368)	75.00 74.82	7.60 7.45	--
$P5^{B+P}$	4-$COCH_3C_6H_4$ OH	70	110	$C_{24}H_{30}O_4$ (382)	75.39 75.02	7.85 7.90	--

* Solvent used for crystallisation

A= Alcohol, B= Benzene, P= Petroleum ether.

Table 1.

Synthesis of 2-amino-4-(3',5'-di-tert-butyl-4'-hydroxyphenyl) thiazole

1-(3',5'-Di-tert-butyl-4'-hydroxyphenyl)-2-bromoethanone **2** (0.01mol) was added to a mixture containing thiourea (0.02mol) and ethanol (30ml) followed by acetic acid (0.2ml). The reaction mixture was refluxed on sand bath for 6 hr. The mixture was cooled and excess of ethanol was removed by distillation. Product obtained by pouring the reaction mixture in cold water was crystallized from ethylacetate-petroleum ether. m.p. 200-202°C, yield 65%.

Elemental Analysis	Found:	C, 67.74	H, 7.79	N, 9.14
($C_{17}H_{24}N_2OS$)/304	Calc.:	C, 67.35	H, 7.89	N, 9.21%

Preparation of 2-(3',5'-di-tert-butyl-4'-hydroxybenzoyl)benzofuran

To a homogenous mixture of *o*-hydroxybenzaldehyde (0.1mol) in ethanol (30ml), bromoethanone **2** (0.01mol) was added followed by triethylamine (0.02mol). The reaction mixture was refluxed for about 12 hr. Yellow pasty mass obtained by pouring the reaction mixture in water was purified by column chromatography using ethylacetate : petroleum ether (80:20) as eluent. m.p. 122-124°C, yield 72%.

Elemental Analysis	Found:	C, 79.19	H, 7.47
($C_{23}H_{26}O_3$)/350	Calc.:	C, 78.85	H, 7.42%

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