NOVEL ORGANIC INTERMEDIATES AND REACTIONS

A THESIS
SUBMITTED TO THE
SHIVAJI UNIVERSITY, KOLHAPUR
FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY
(IN CHEMISTRY)

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NOVEMBER 1990

Dedicated To

My Parents

And Teachers

CERTIFICATE

Certified that the work incorporated in the thesis entitled **"Novel Organic Intermediates and Reactions"** submitted by MR. THOMAS DANIEL was carried out by the candidate at the National Chemical Laboratory, Pune 411 008, India, under my supervision for the Degree of Doctor of Philosophy in Chemistry, Shivaji University, Kolhapur. This work was not submitted so far for any degree.

(N. R. AYYANGAR)
Research Guide

GENERAL REMARKS

1. All the temperatures are in °C unless otherwise mentioned. All the melting points and boiling points are in °C and are uncorrected.
2. Fluorescence spectra were recorded on SFM-25 Konitron Fluorometer.
3. IR spectra were recorded on Perkin-Elmer Infrared Spectrometer model 137B or 599B, Pye-Unicam Infrared Spectrophotometer model SP300. The IR frequencies are expressed in cm^{-1}.
4. UV/Visible spectra were recorded in Hitachi 330, UV/Vis or Beckman double beam spectrophotometer model 216 with 1 cm quartz cells. The wavelength maxima has been recorded in nanometers (nm).
5. GC analyses were carried out on Hewlett-Packard HP 5880.
6. ^{1}H-NMR spectra were recorded on Jeol PMX 60 SI, Varian T60 NMR, Varian 80A FT-NMR, Bruker FT90 or MSL 300 NMR spectrometers using tetramethylsilane as internal standard. The chemical shifts are cited in δ (ppm) scale. The following abbreviations are used: s = singlet; bs = broad singlet, d = doublet; t = triplet; q = quartet; m = multiplet; J = coupling constant in Hz.
7. Mass spectra were recorded on CEC-21-110B or Finnigan MAT-1020 automated GC/MS or AEI MS3074 GC/MS spectrometer.
8. Depths of the dyes on the polyester have been compared with the 1% standard shades.
9. The numbers assigned to the structures given in each chapter refer only to that particular chapter.

ABBREVIATIONS

Ac	Acetyl
Ar	Aryl
Et	Ethyl
FIG	Figure
IR	Infra-red
Me	Methyl
m.p.	Melting point
MS	Mass spectrum
NMR	Nuclear Magnetic Resonance
OMe	Methoxy
Ph	Phenyl
h	Hour/s

Patents:

BP	British Patent
Belg Pat.	Belgian Patent
Fr. Pat.	French Patent
Ger Offen	German Patent
Hung.	Hungarian Patent
Neth. P	Netherlands Patent
Japan Kokai	Japan Patent
USP	United States Patent

CONTENTS

CHAPTER-I

A NEW AND CONVENIENT SYNTHESIS OF 4-AMINO-3-NITROBENZOPHENONE AND 2-AMINO-5-NITROBENZOPHENONE AND THEIR N-ALKYL DERIVATIVES

INTRODUCTION

As a result of poor sanitation and lower standard of living, incidence of helminth infestations is alarmingly high in sub-tropical regions.[1,2] Non-availability of minimum medical facilities for the diagnosis of the specific helminth infestation aggravates the situation even further. Benzimidazoles are versatile heterocycles possessing a wide spectrum of biological activity. Methyl-[5-(benzoyl)-benzimidazol-2-yl]-carbamate known as mebendazole (1) (CHART 1) is one of the important benzimidazole carbamates currently in use as broad spectrum human and veterinary anthelmintic drug.[3,4,5]

A research and development programme was therefore initiated for a commercially viable process for the synthesis of 4-amino-3-nitrobenzophenone[6,7] (3), which can be easily converted into 3,4-diaminobenzophenone, the key intermediate required for the preparation of mebendazole (1) (CHART 2). This work also resulted in the preparation of 2-amino-5-nitrobenzophenone (5) (CHART 1) and their analogues. 2-Amino-5-nitrobenzophenone (5) is the key intermediate for the synthesis of nitrazepam (4), an important tranquilizer.

The hitherto known processes[8,9] for the preparation of 4-amino-3-nitrobenzophenone with or without N-alkyl substituents involves either the reaction of 4-fluoro-3-nitrobenzophenone or 4-chloro-3-nitrobenzophenone, with ammonia or alkyl amines and are covered by patents (CHARTS 3 and 4). In addition, there is a Japanese patent[10] in which aniline is used as the starting material (CHART 5).

Generally, the preparation of fluorobenzene, which is the starting material for 4-fluoro-3-nitrobenzophenone, is tedious and difficult to handle (German patent,[8] CHART 3). A multistep procedure is required for the preparation of p-chlorobenzoic acid (Hungarian patent,[9] CHART 4). Also, both the above patent procedures involve expensive starting materials. Moreover, it is clear that the Japanese patent has the inherent disadvantage of simultaneous benzoylation occurring at the amino function which introduces an additional unit process of selective alkaline hydrolysis of 4-benzamidobenzophenone.

Nitrazepam and its Intermediates:

1,3-Dihydro-7-nitro-5-phenyl-2H-1,4-benzodiazepin-2-one 4, known as nitrazepam[11] (CHART 1) is a well-known tranquilizer with relatively low toxicity. It is potentially useful as muscle relaxant, anticonvulsant as well as for depressed states and tension. A number of patents are known for the preparation of nitrazepam (vide infra).

A Netherlands patent[12] describes the preparation of nitrazepam from 2-amino-5-nitrobenzophenone (5) which in turn is prepared from p-nitroaniline (CHART 6).

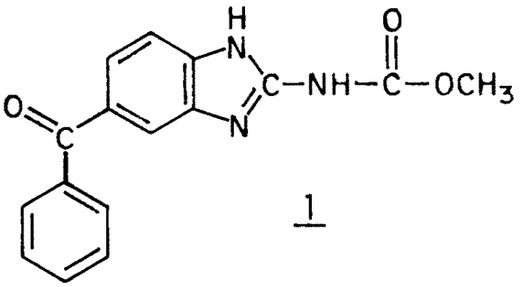
A German patent[13] describes the preparation of 2-benzoylamino-5-nitrobenzophenone from 4-benzoylaminonitrobenzene. In this process, benzoyl derivative of p-nitroaniline is condensed with 1.2-2.5 moles of benzoyl chloride in the presence of $ZnCl_2$ to give 2-benzoylamino-5-nitrobenzophenone which is then hydrolyzed in acidic or alkaline medium to yield 2-amino-5-nitrobenzophenone in 30% to 40% yield. In another

report[14] p-nitroaniline by itself or its acetyl or benzoyl derivative is benzoylated in presence of 3-fold excess of anhydrous zinc chloride at 200°C to produce 2-amino-5-nitrobenzophenone in 20% yield. In yet another German patent,[15] 2-chloro-5-nitrobenzophenone is treated with sodium salt of p-toluenesulfonamide in dimethylformamide to give 2-(p-toluenesulfonamido)-5-nitrobenzophenone. It was hydrolyzed by concentrated sulphuric acid at 55°C to yield 2-amino-5-nitrobenzophenone which in turn is treated with phthalimido acetyl chloride and then with hydrazine hydrate to yield nitrazepam (CHART 7).

A Belgium patent[16] also describes the preparation of 2-amino-5-nitrobenzophenone from p-nitroaniline and then its conversion to nitrazepam.

From the foregoing discussion, it is evident that 2-amino-5-nitrobenzophenone is an important intermediate for the preparation of nitrazepam. The present Chapter deals with the synthesis of 2-amino-5-nitrobenzophenone, 4-amino-3-nitrobenzophenone and their N-alkyl derivatives in high yield and high purity from easily accessible starting materials.

CHART-1



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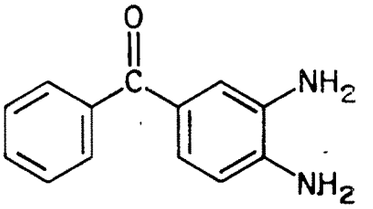

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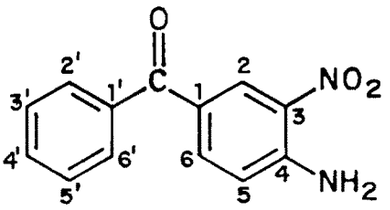

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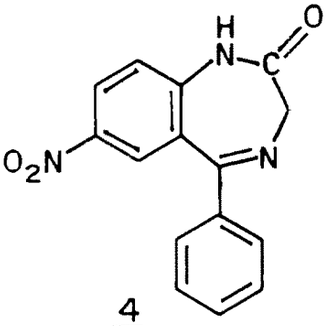

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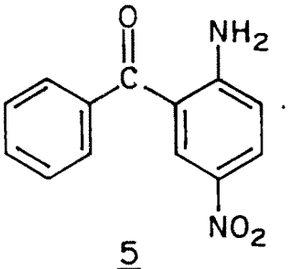

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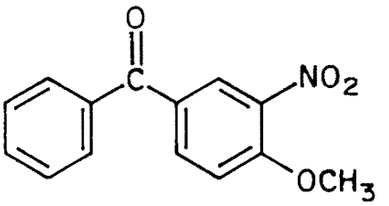

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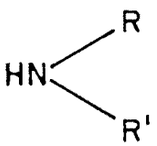

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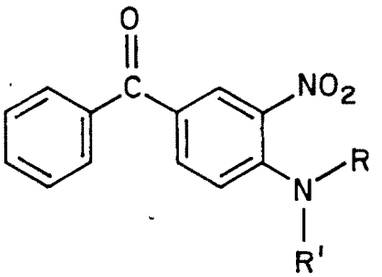

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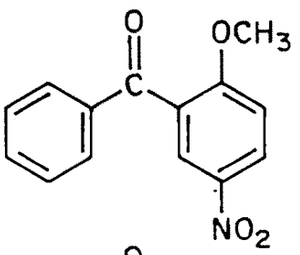

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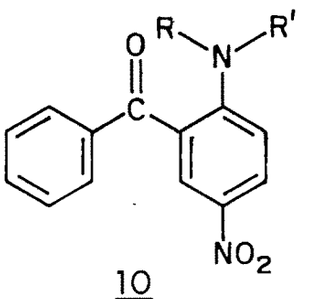

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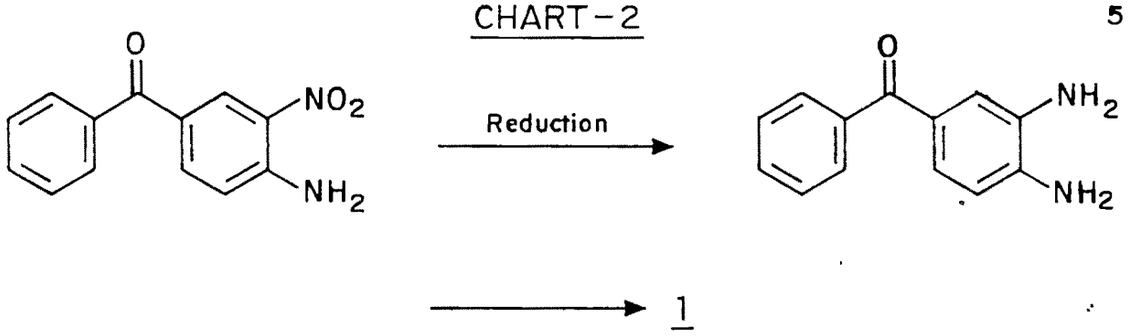

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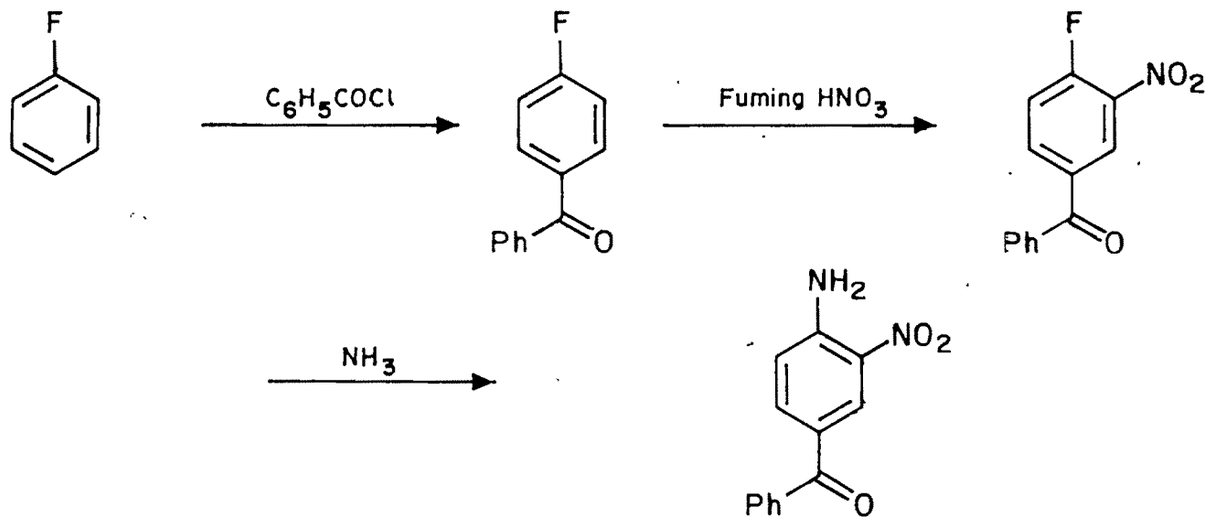

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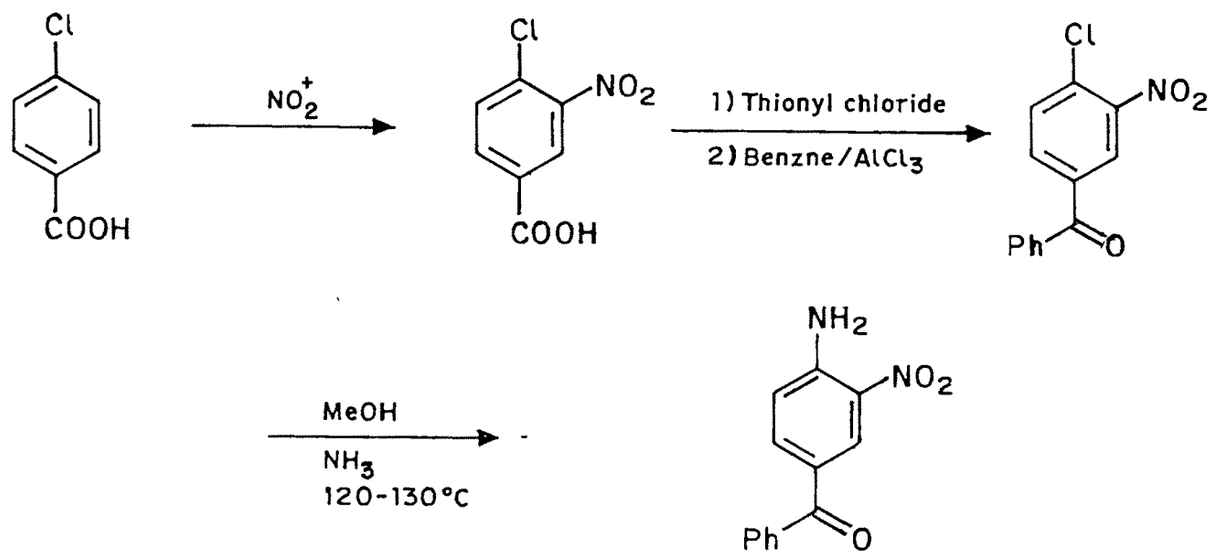

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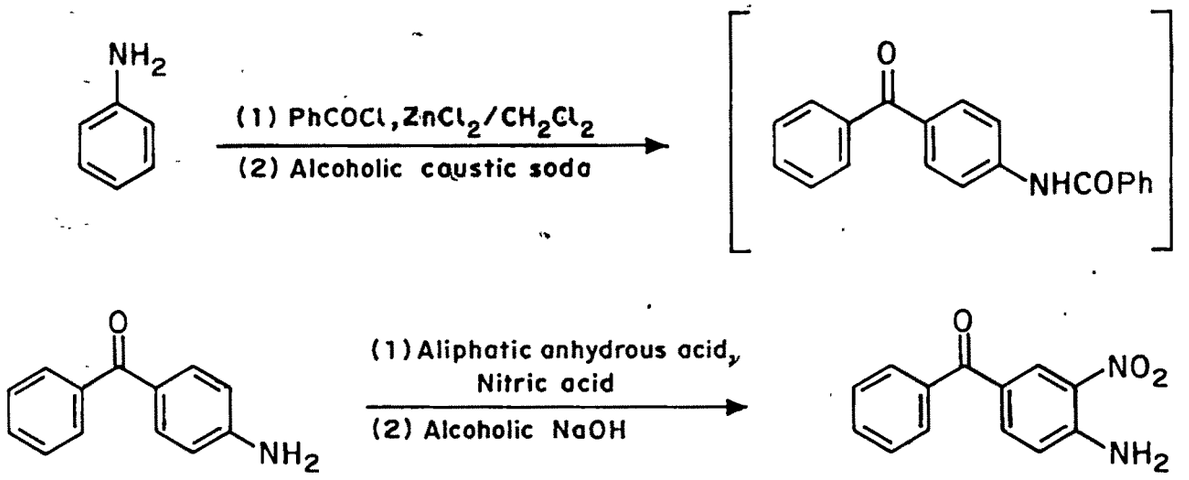

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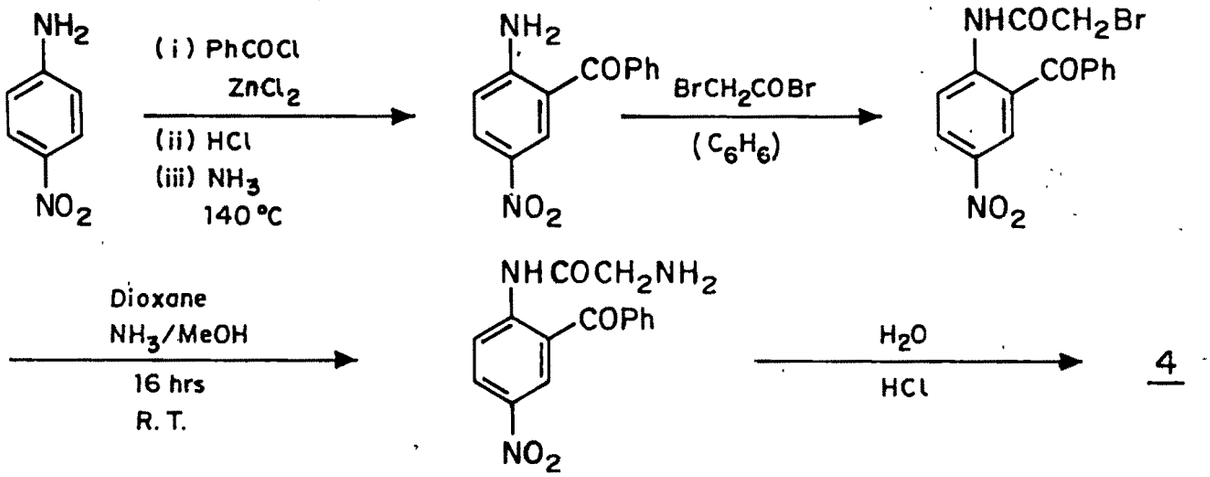

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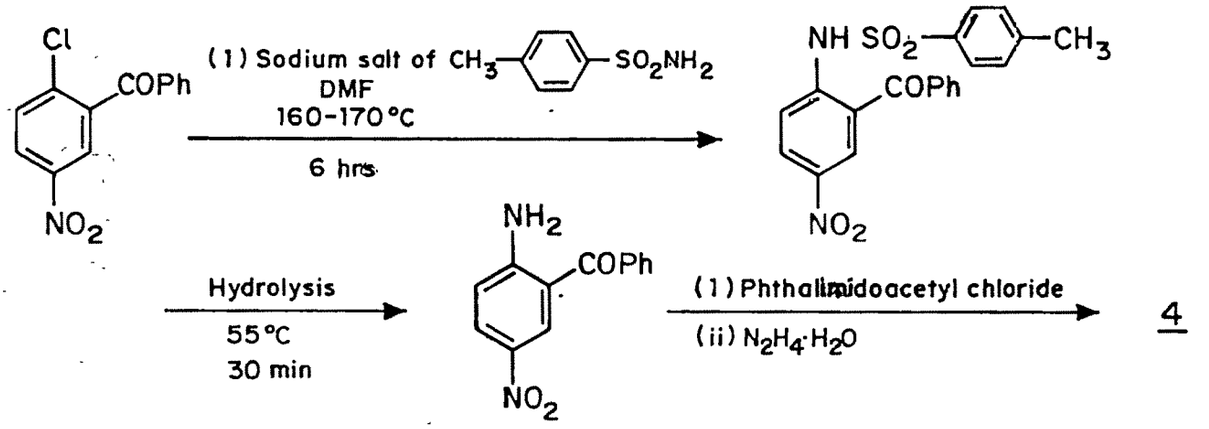


PRESENT WORK

The existing methods for the preparation of 4-amino-3-nitrobenzophenone, 2-amino-5-nitrobenzophenone and their N-alkyl derivatives demand either drastic conditions leading to poor yields or use of expensive starting materials. Therefore, there is a need to develop a new methodology by which the required intermediates could be produced in high yields and purity. In contrast to the existing processes, a convenient and cheaper process for the production of 4-amino-3-nitrobenzophenone and 2-amino-5-nitrobenzophenone was developed. o-Nitrochlorobenzene was envisaged as a suitable starting material in an attempt to prepare 4-chloro-3-nitrobenzophenone which can be ultimately converted to the desired intermediate, 4-amino-3-nitrobenzophenone. Contrary to the expectations, benzoylation of o-nitrochlorobenzene under different reaction conditions (catalysts like Fe, $FeCl_3$, $ZnCl_2$ and different reaction temperatures) did not proceed to yield 4-chloro-3-nitrobenzophenone.

Alternatively (in another approach) o-nitroanisole was successfully benzoylated using ferric chloride as the Friedel-Crafts catalyst to produce 4-methoxy-3-nitrobenzophenone in 60% yield (CHART 8). The reported method[17,18] involves benzoylation of anisole and its further nitration using fuming nitric acid in acetic anhydride to give 4-methoxy-3-nitrobenzophenone (**6**).

In another report[19] sodium methoxide is treated with 4-chloro-3-nitrobenzophenone to yield **6**.

4-Methoxy-3-nitrobenzophenone (**6**) prepared by the benzoylation of o-nitroanisole was characterized by spectral methods. Its IR spectrum displayed an absorption at 1650 cm^{-1} corresponding to a carbonyl group. ^{1}H-NMR Spectrum showed signals at 7.2 (d, J=8Hz) and 8.3 (d, J=1.5Hz) corresponding to 5-H and 2-H protons respectively. Thus, the spectral data are in agreement with the structure of the product formed.

There are instances where a suitably substituted methoxy group in aromatic system could be conveniently replaced by nucleophiles[20] such as NH_2, NHR, NR_1R_2. Accordingly, the compound 3-nitro-4-methoxybenzophenone was subjected to a nucleophilic reaction with liquor ammonia in a closed vessel at 130°C for 4 h to afford 4-amino-3-nitrobenzophenone (**8a**) in almost quantitative yield (CHART 8, R = R' = H).

The IR spectrum of 4-amino-3-nitrobenzophenone in $CHCl_3$ shows sharp absorption bands at 3260 cm^{-1} and 3200 cm^{-1} due to NH_2 stretching vibrations and an absorption at 1660 cm^{-1} corresponding to the benzoyl carbonyl group.

The ^{1}H-NMR spectrum of 4-amino-3-nitrobenzophenone showed the disappearance of the methoxy peak at 4.01 as in **6** and the appearance of the amino group at 6.3 . A doublet centred at 6.6 (J=9Hz) corresponds to the 5-H proton. The 2-H proton is deshielded due to the benzoyl and nitro groups in the ortho positions and appears as a meta coupled doublet centred at 8.26 (J=3Hz).

Aromatic nucleophilic substitutions are accelerated by electron-withdrawing groups especially in positions ortho and

para to the leaving group. Activating groups (like NO_2, -COPh) towards nucleophiles, by withdrawing electron density, are able to stabilize the intermediate **11** (CHART 9). The formation of methanol during the reaction was confirmed by gas liquid chromatography of an aliquot of the reaction mixture. Such a mechanism is responsible for the formation of of **8a-8g** and **10a-10h** (CHARTS 8 & 10).

The methodology for the preparation of 4-amino-3-nitrobenzophenone (**3**) from 4-methoxy-3-nitrobenzophenone (**6**) was extended for the preparation of other N-alkyl derivatives of 4-amino-3-nitrobenzophenone (**8a-8g**) in high yields (CHART 8 and Table 1). All the compounds synthesised have been characterized by spectral and elemental analysis.

IR Spectra of 8b-8g:

In the IR spectra of the compounds (**8b-8g**), the carbonyl stretching frequency is observed between 1630-1660 cm^{-1}. For compounds **8b-8g** an absorption between 3350-3370 cm^{-1} clearly indicates the presence of N-H bond. The presence of nitro group is indicated by the absorptions around 1520 and 1330 cm^{-1}. As an example, in the case of 4-isopropylamino-3-nitrobenzophenone (**8d**) carbonyl stretching frequency is observed at 1655 cm^{-1}. A sharp absorption at 3370 cm^{-1} confirms the presence of N-H bond (FIG. 1).

^{1}H-NMR Spectra (8b-8g):

The disappearance of the methoxy signal (4.01) and the appearance of the N-alkyl signal are noticed in the

aliphatic region. In the aromatic region, the 5-H proton which is shielded appears as an ortho coupled doublet around 6.7. The presence of electron-withdrawing groups at the ortho positions makes the 2-H proton highly deshielded and it appears around 8.2 as a meta coupled doublet. In most of the cases, the NH proton appears downfield. As an example, in the spectrum of 4-isopropylamino-3-nitrobenzophenone (**8d**) in $CDCl_3$, the methyl protons are seen as a doublet (J=8Hz) at 1.4. The CH proton is observed as a multiplet centred at 3.9. The aromatic 5-H proton appears as ortho-coupled doublet (J=9Hz) at 6.7 and the most deshielded 2-H proton appears as meta coupled doublet (J=3Hz) at 8.4. The NH proton is observed at 8.1 as a doublet (J=12Hz) (FIG. 2).

2-Amino-5-nitrobenzophenone and its alkyl derivatives:

The route employed for the synthesis of **10a** and **10b** from 2-methoxy-5-nitrobenzophenone[21] (**9**) is outlined in Chart 10. Compound **9** was transformed into the desired intermediates **10a** and **10b** in almost quantitative yields by treatment with liquor ammonia or cyclohexylamine in a closed vessel at 130°C for 5 h (Table 1). The compounds **10a** and **10b** were characterized by spectral and elemental analysis.

Spectral analysis of 10a and 10b:

The IR spectrum of **10a** shows the absorption bands at 3340 and 3400 cm^{-1} confirming the presence of amino function. For **10b**, a strong absorption at 3270 cm^{-1} corresponds to the N-H stretching and an absorption at 1630 cm^{-1} corresponds to the carbonyl stretching frequency (FIG. 3).

In ^{1}H-NMR spectrum (TFA) of **10a**, 3-H proton is observed as an ortho coupled doublet (J=9Hz) at 7.3 and 6-H proton is observed as a meta coupled doublet (J=2Hz) at 8.6. The 4-H appears as a doublet of doublet centred at 8.35. Similarly, in ^{1}H-NMR spectrum of **10b** in CCl_4, the methylene protons of cyclohexyl group is observed as a multiplet centred at 1.6. The C-H proton of the cyclohexyl group is observed as a multiplet centred at 3.4. The 3-H proton appears as an ortho coupled doublet (J=9Hz) at 6.4 and the 4-H proton is seen as dd at 7.7. The 6-H proton is observed as meta coupled doublet (J=1.5Hz) at 8.0. All other aromatic protons are observed between 7.3-7.1 as multiplet. The N-H proton is seen as a broad doublet at 8.96 (FIG. 4).

Analysis of Mass Spectra:

The major mass spectral fragmentation pattern for the compounds prepared is presented in Charts 11, 12 and 13. All the compounds exhibited molecular ion peaks of intensity varying from 15-100 per cent. In addition, virtually all the compounds showed peaks at 105 representing benzoyl cation (CHART 11, Path a). A peak corresponding to m/e, M-77 can also be explained (CHART 11, Path b).

The E.I. mass spectra of aromatic nitro compounds have been studied and the major features are well-known,[22] particularly the pronounced effects of ortho substitution.[23,24] Hydrogen transfer and oxygen migration are the main rearrangements which complicate the spectra of nitro arenes.[25]

In the present case, the mass spectra of **8a-8e** and **8g-8h** show a significant ortho effect. This is evidenced from the fact that hydrogen transfer on to the nitro group followed by cleavage of the N-O bond was observed in the spectra of these compounds (Chart 12). Chart 12 represents the fragmentation pattern typical of these compounds showing the ortho effect. The compounds **8f** and **10b** show the cleavage of cyclohexyl ring with the loss of C_3H_7 radical[22] as the main fragmentation leading to the most abundant ion (M-43, base peak) (CHART 13). The formation of this intense fragment is due to its special stability. Mass spectrum of **8d** shows a peak at 284 corresponding to the molecular ion. Loss of methyl group from the molecular ion gives rise to a peak at 269 and forms the base peak. The benzoyl cation and phenyl cation are shown by peaks at m/e 105 and 77 respectively (FIG. 5).

In the mass spectrum of **10b**, a peak at 324 corresponds to the molecular ion. The base peak is formed by the loss of C_3H_7 radical (M-43) and is seen at m/e 281 (FIG. 6).

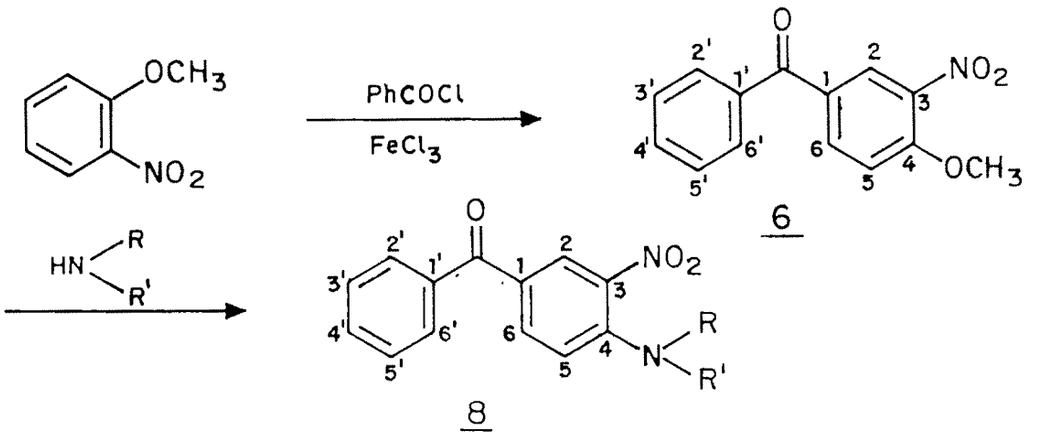
Conclusion:

In conclusion, this chapter has provided convenient and efficient methods for the preparation of 4-amino-3-nitrobenzophenone and their N-alkyl derivatives in high yields and good purity under mild reaction conditions. These compounds constitute important intermediates in the preparation of anthelmintic drugs exemplified by mebendazole; in addition 2-amino-5-nitrobenzophenone serves as a key intermediate in the synthesis of commercially important tranquilisers such as nitrazepam.

TABLE 1

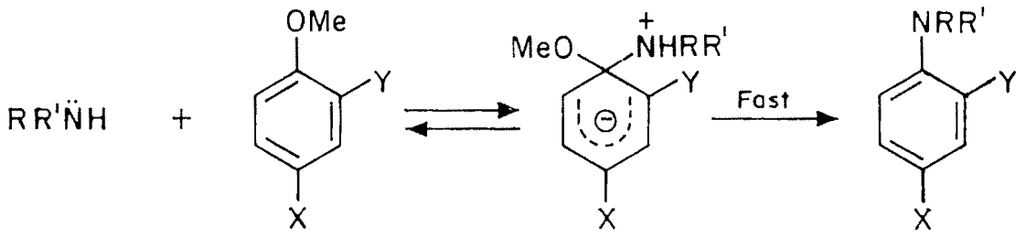
Sl.No.	Product	R	R'	Reaction Time(hr)	Yield (%)	m.p. Found	m.p. Reported
1	**8a**	H	H	5	98	140	140[26]
2	**8b**	H	Me	5	96	205	205[27]
3	**8c**	H	Et	5	96	99	-
4	**8d**	H	Me_2CH	5	88	88	-
5	**8e**	H	$n\text{-}C_4H_9$	5	98	65	-
6	**8f**	H	$c\text{-}C_6H_{11}$	5	98	170	-
7	**8g**	Me	Me	5	70	116	-
8	**10a**	H	H	5	96	161	161.5[28]
9	**10b**	H	$c\text{-}C_6H_{11}$	5	95	95	-

CHART – 8



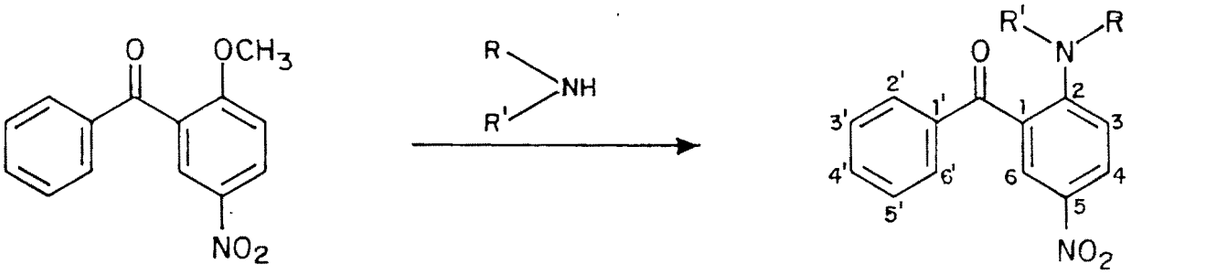
8a: R = R' = H
8b: R = H, R' = CH_3
8c: R = H, R' = Et
8d: R = H, R' = Me_2CH
8e: R = H, R' = n-C_4H_9
8f: R = H, R' = Cyclohexyl
8g: R = Me, R' = Me

CHART – 9



X = COPh
Y = NO_2

CHART – 10



10a: R = R' = H
10b: R = H, R' = Cyclohexyl

CHART – 11

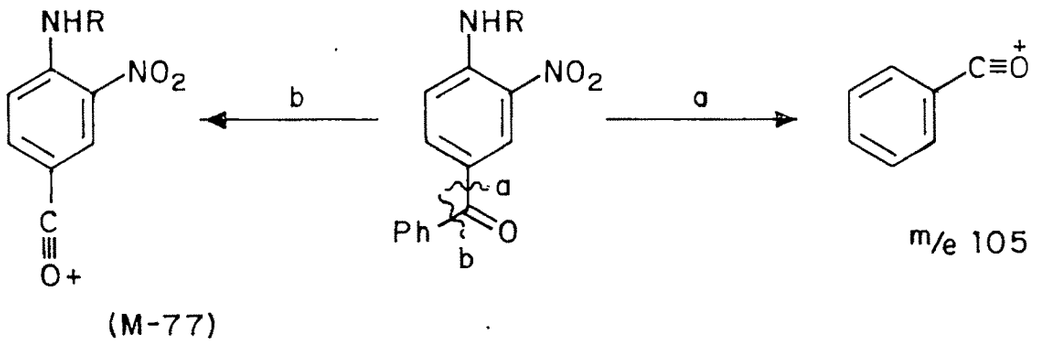


CHART – 12

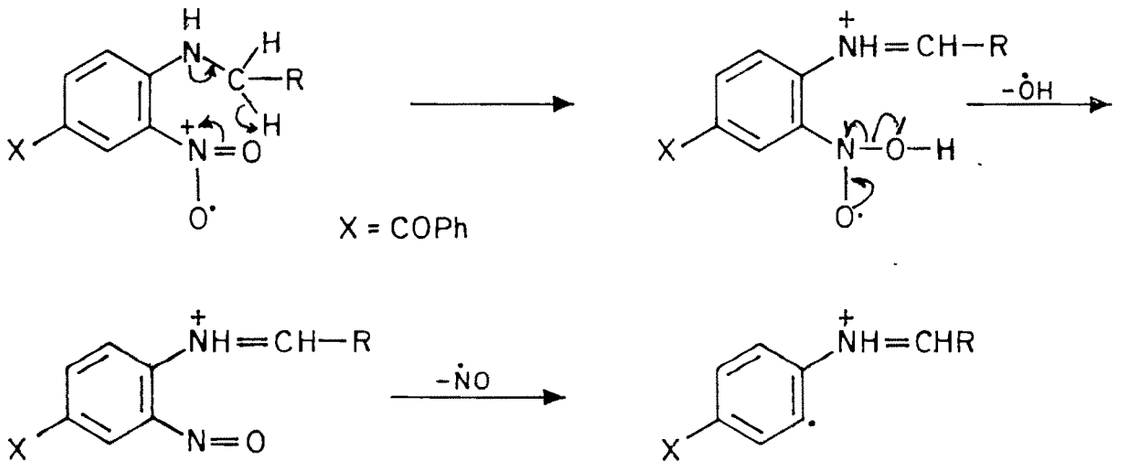
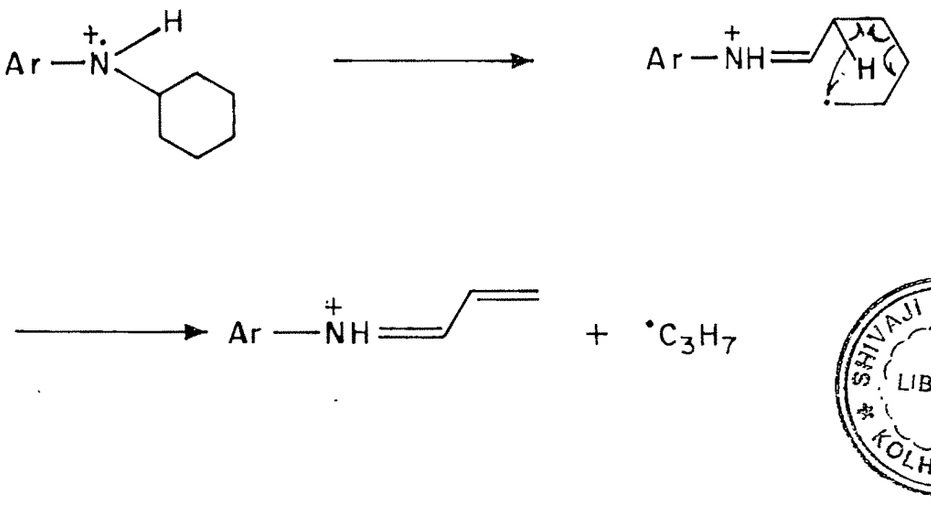


CHART – 13



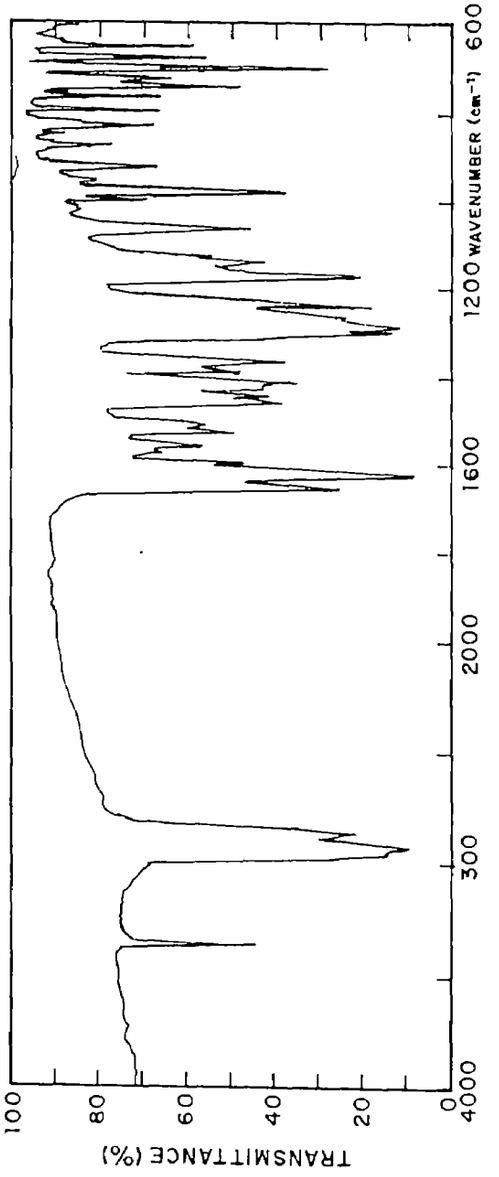
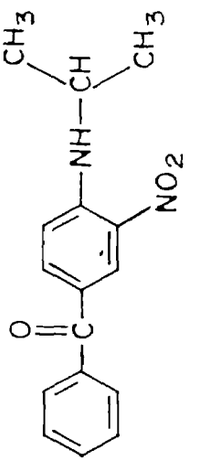

TRANSMITTANCE (%)
100
80
60
40
20
0
4000
3000
2000
1600
1200
600
WAVENUMBER (cm⁻¹)

FIG. 1


CH3
CH
CH3
NH
NO2
O
C

8d

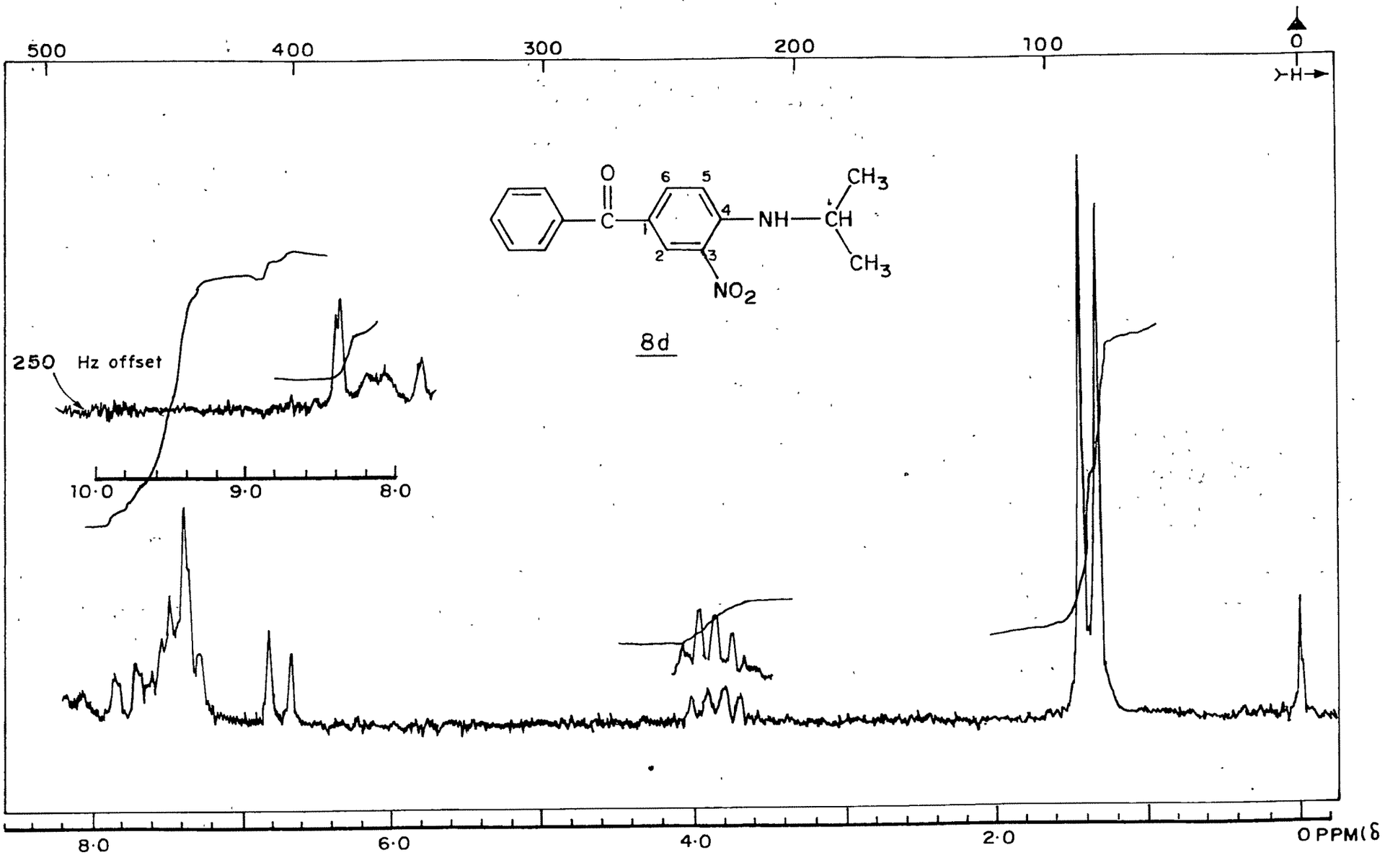

500
400
300
200
100
0
>H
O
6
5
4
1
2
3
C
NH
CH
CH3
CH3
NO2
8d
250 Hz offset
10·0
9·0
8·0
8·0
6·0
4·0
2·0
0 PPM(δ

FIG. 2

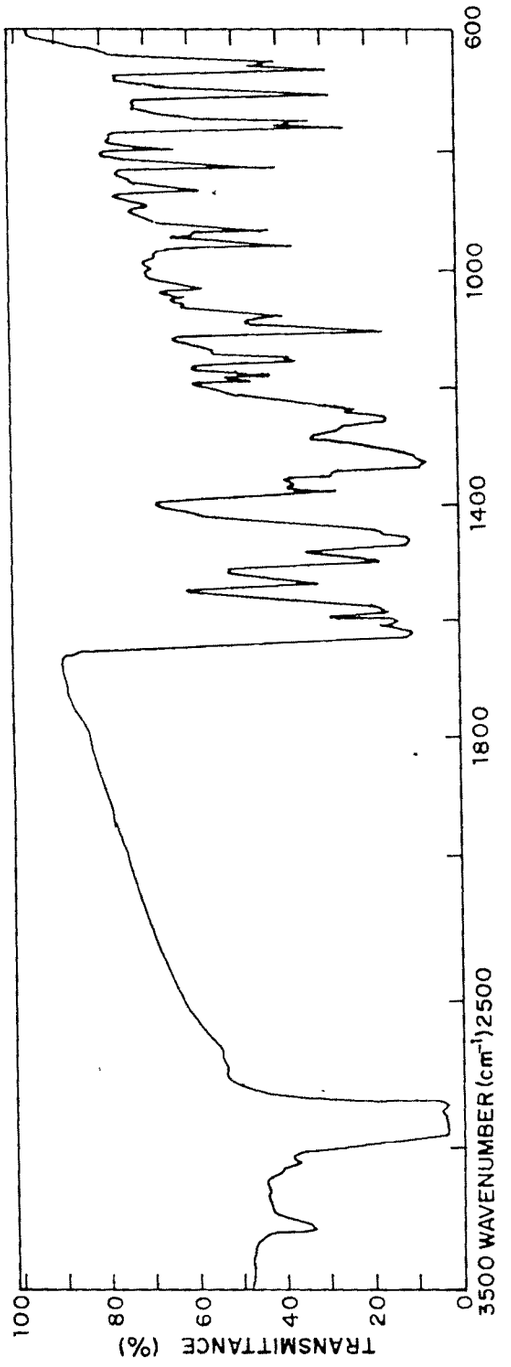
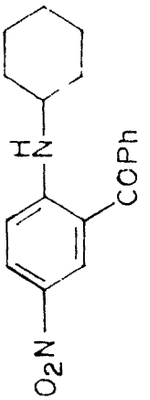

TRANSMITTANCE (%)
100
80
60
40
20
0
3500
2500
1800
1400
1000
600
WAVENUMBER (cm⁻¹)

FIG. 3


H
N
COPh
O2N

10 b

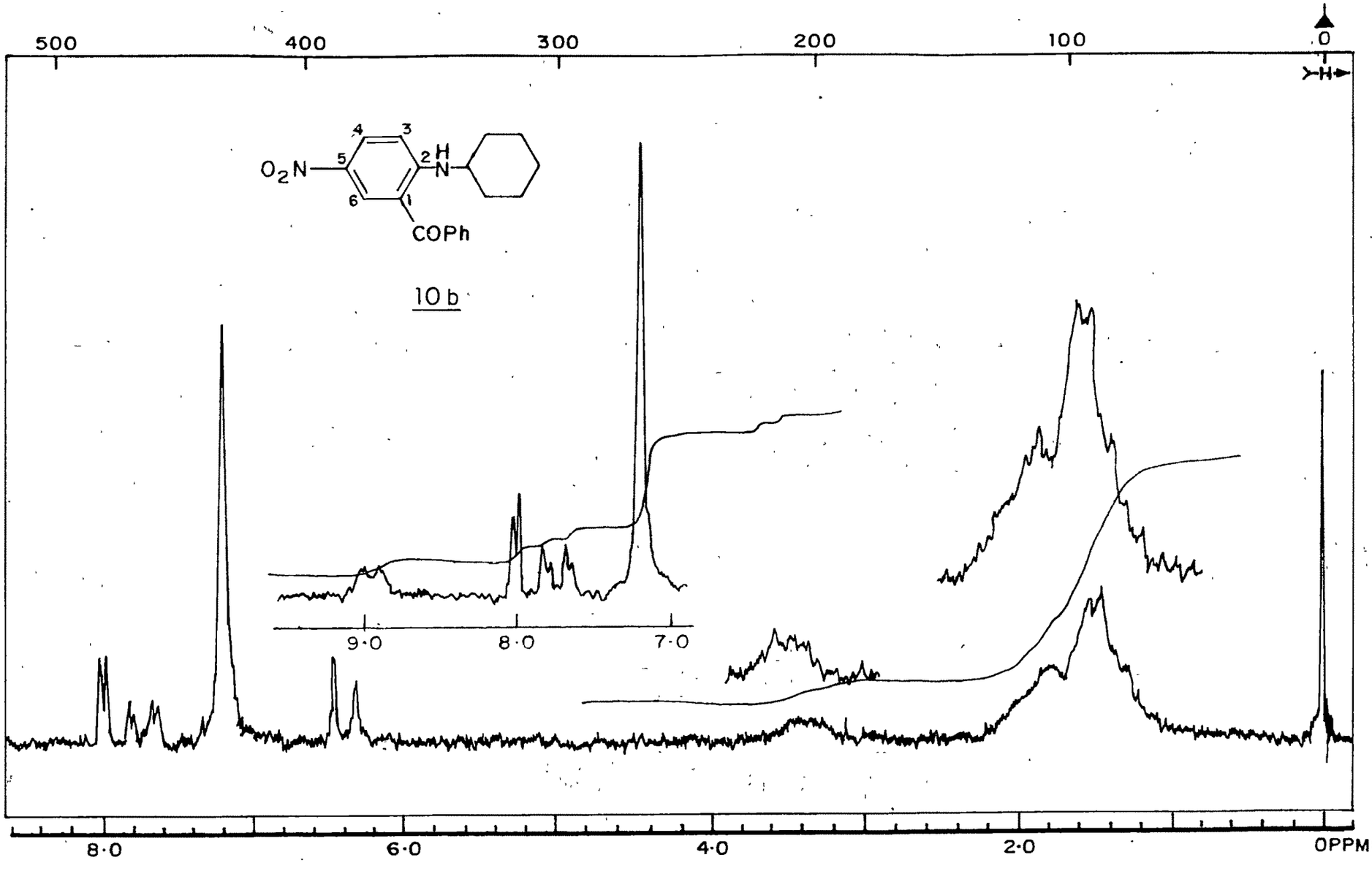

500
400
300
200
100
0
TMS
O2N
NH
COPh
10 b
9·0
8·0
7·0
8·0
6·0
4·0
2·0
0PPM(δ)

FIG. 4

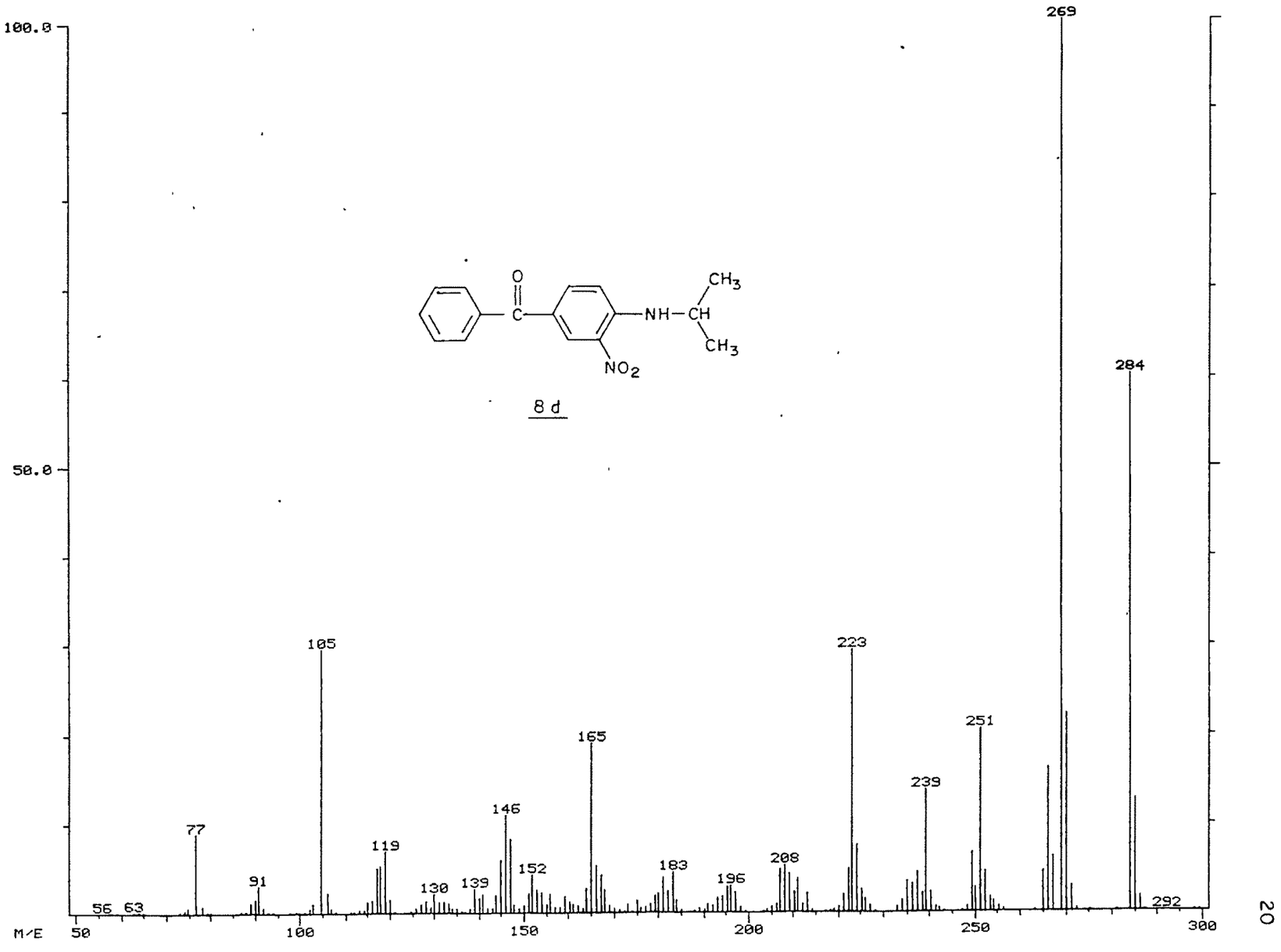

100.0
50.0
M/E
50
100
150
200
250
300
269
284
105
223
165
251
239
146
77
119
208
183
152
196
91
130
139
56
63
292
O
C
NH
CH
CH3
CH3
NO2
8 d

FIG 5

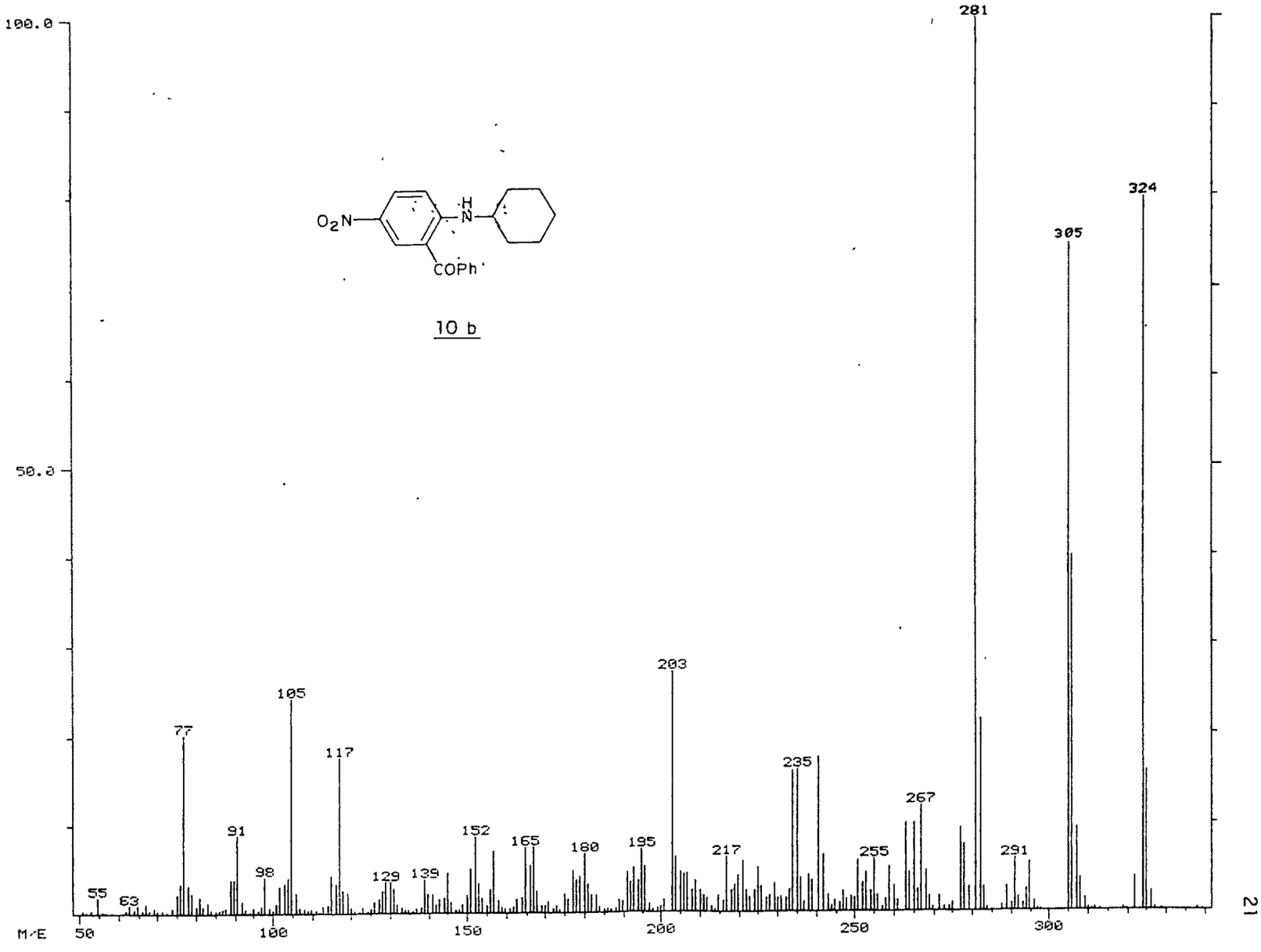

100.0
50.0
M/E
50
100
150
200
250
300
281
324
305
203
105
77
117
235
267
91
152
165
180
195
217
255
291
98
129
139
55
63
O_2N
NH
COPh
10 b

FIG 6

EXPERIMENTAL

Preparation of 4-methoxy-3-nitrobenzophenone (6):

Benzoyl chloride (34.8 g, 0.24 mol) was added dropwise over a period of 1 h to a stirred mixture of o-nitroanisole (30.6 g, 0.2 mol) and anhydrous ferric chloride (2 g) at 30°C. The temperature of the reaction mixture was slowly raised over 0.5 h to 130-140°C and maintained at this temperature for 5 h. The reaction mixture was cooled to 30° and poured into a mixture of 10N hydrochloric acid (5 ml) and crushed ice (300 g). The product was extracted with chloroform (200 ml). The organic layer was dried over anhydrous potassium carbonate. After removal of the drying agent, the organic filtrate was evaporated under vacuum to give the product **6**, yellow needles from methanol, m.p. 105°C (lit.[17] m.p. 105°C), yield 15.4 g (60%).

IR: (Nujol) cm^{-1} 1640, 1610, 1530, 1460, 1380, 1370, 1300, 1290, 1250, 1160, 1150, 1080, 1010, 980, 920, 860, 840, 790, 730, 700, 670.

^{1}H-NMR ($CDCl_3$): 4.01 (3H, s, CH_3), 7.2 (1H, d, 5-H, J=8Hz), 7.4-8.13 (6H, m, 2',3',4',5',6' & 6-H), 8.3 (1H, d, 2-H, J= 1.5Hz).

MS: m/e (rel. int. %), 257(80), 180(19), 133(9), 119(25), 105(100), 77(62), 63(7).

Anal. $C_{14}H_{11}NO_4$: Calc. C, 65.4; H, 4.3; N, 5.4
(257) Found: C, 65.7; H, 4.8; N, 5.5.

Preparation of 4-amino-3-nitrobenzophenone and its N-alkyl derivatives (8a-8g) (CHART 8):

General Procedure:

A mixture of 4-methoxy-3-nitrobenzophenone (**6**) (25.7 g, 0.1 mole) and excess of either aqueous ammonia (25%) or alkylamine (0.6 mole) was heated in a closed vessel at 120°C for 5 h. The reaction mixture was cooled to 30°C and diluted with water (500 ml). The product which separated out was filtered and crystallized to give the pure material (**8a-8g**).

4-Amino-3-nitrobenzophenone (8a):

Yellow needles from ethanol, m.p. 140°C (lit.[26] m.p. 140°C); yield 23.7 g (98%).

IR ($CHCl_3$) cm^{-1}: 3260, 3200, 1660, 1630, 1570, 1530, 1490, 1450, 1420.

^{1}H-NMR ($CDCl_3$): 6.3 (2H, s, NH_2), 6.66 (1H, d, 5-H, J=8Hz), 7.2-7.8 (6H, m, Ar-H), 8.26 (1H, d, 2-H, J=1.5Hz).

MS: m/e (rel. int. %): 242(18), 225(2), 207(2), 195(6), 179(3), 165(100), 151(3), 139(5), 119(44), 105(62), 91(14), 77(32).

Anal: $C_{13}H_{10}N_2O_3$: Calc. C, 64.45; H, 4.13; N, 11.57
(242) Found: C, 64.19; H, 4.48; N, 11.20

4-Methylamino-3-nitrobenzophenone (8b):

Yellow needles from ethanol, m.p. 205°C (lit.[27] m.p. 205°C); yield 24.6 g (96%).

IR (Nujol) cm^{-1}: 3370, 1650, 1620, 1570, 1520, 1460, 1400, 1370, 1330, 1290, 1230, 1180, 1150, 1120, 1050, 960, 920, 880, 860, 840, 770, 740, 700, 680, 620.

^{1}H-NMR (TFA): 3.2 (3H, s, CH_3), 7.1 (1H, d, 5-H, J=9Hz), 7.46-7.7 (5H, m, 2',3',4',5' & 6'-H), 7.9-8.16 (1H, q, 6-H), 8.66 (1H, d, 2-H, J=1.5Hz).

MS: m/e (rel. int. %): 256(18), 239(2), 223(2), 209(5), 193(2), 179(27), 161(16), 152(6), 133(9), 105(100), 91(5), 77(57), 63(6).

Anal: $C_{14}H_{12}N_2O_3$: Calc. C, 65.6; H, 4.7; N, 10.93
(256) Found: C, 66.1; H, 5.0; N, 11.25

4-Ethylamino-3-nitrobenzophenone (8c):

Pale yellow needles from hexane, m.p. 99°C; yield 26 g (96%).

IR (Nujol) cm^{-1}: 3360, 1660, 1640, 1580, 1530, 1450, 1420, 1370, 1330, 1300, 1280, 1240, 1170, 1080, 890, 800, 780, 710.

^{1}H-NMR ($CDCl_3$): 1.4 (3H, t, CH_3), 3.36 (2H, m, CH_2), 6.7 (1H, d, 5-H, J=9Hz), 7.2-7.9 (6H, m, Ar-H), 8.4 (1H, d, 2-H, J=1.5Hz), 8.1 (1H, t, NH, exchangeable with D_2O).

MS: m/e (rel. int. %): 270(100), 264(1), 255(74), 235(15), 223(12), 210(45), 193(35), 181(23), 166(8), 146(6), 118(6), 105(11), 77(4).

Anal. $C_{15}H_{14}N_2O_3$: Calc. C, 66.66; H, 5.18; N, 10.37
(270) Found: C, 67.00; H, 5.32; N, 10.36

4-Isopropylamino-3-nitrobenzophenone (8d):

Yellow needles from methanol, m.p. 88°C; yield 27.3 g (96%).

IR (Nujol) cm^{-1}: 3370, 1655, 1625, 1560, 1540, 1520, 1460, 1420, 1370, 1330, 1310, 1290, 1250, 1180, 1140, 1070, 980, 930, 840, 800, 770, 730, 700, 680, 650, 600, 530.

^{1}H-NMR ($CDCl_3$): (6H, d, CH_3), 3.9 (1H, m, CH), 6.7 (1H, d, 5-H), J=8Hz), 7.2-7.9 (6H, m, 2',3',4',5',6' and 6-H), 8.4 (1H, d, 2-H, J=1.5Hz), 8.1 (1H, d, NH, J=12Hz).

MS: m/e (rel. int. %): 284(61), 269(100), 251(21), 239(14), 223(30), 208(5), 196(4), 165(20), 146(11), 119(7), 105(30), 91(3), 77(9).

Anal. $C_{16}H_{16}N_2O_3$: Calc. C, 67.6; H, 5.6; N, 9.86
(284) Found C, 68.04; H, 5.82; N, 10.1

4-Butylamino-3-nitrobenzophenone (8e):

Yellow needles from methanol, m.p. 65°C, yield 29.2 g (98%).
IR (Nujol) cm^{-1}: 3360, 1640, 1610, 1570, 1510, 1460, 1440, 1400, 1360, 1320, 1270, 1220, 1160, 1120, 1080, 960, 880, 830, 790, 740, 700, 670, 630, 520.

^{1}H-NMR (CCl_4): 1.1 (3H, t, CH_3), 1.3-2.1 (4H, m, $-CH_2$), 3.3-3.7 (2H, m, $NHCH_2$), 7.2 (1H, d, 5-H, J=9Hz), 7.7-8.4 (6H, m, 2',3',4',5',6' and 6-H), 8.7 (1H, t, NH), 8.9 (1H, d, 2-H, J=1.5Hz).

MS: m/e (rel. int. %): 298(58), 292(1), 275(1), 263(5), 255(100), 238(8), 210(12), 197(9), 161(4), 120(2), 105(11), 91(1), 77(4).

Anal. $C_{17}H_{18}N_2O_3$ Calc. C, 68.45; H, 6.04; N, 9.40
(298) Found C, 68.83; H, 6.39; N, 9.34

4-Cyclohexylamino-3-nitrobenzophenone (8f):

Pale yellow needles from acetone, m.p. 170°C, yield 31.8 g (98%).

IR (Nujol) cm^{-1}: 3350, 1650, 1620, 1570, 1520, 1450, 1410, 1380, 1370, 1320, 1300, 1230, 1160, 1140, 1110, 1070, 960, 890, 840, 800, 740, 710, 640.

^{1}H-NMR ($CDCl_3$): 1.2-2.3 (10H, m, CH_2's of cyclohexyl), 3.7 (1H, m, CH of cyclohexyl), 7.1 (1H, d, 5-H, J=8Hz), 7.5-8.3 (6H, m, 2',3',4',5',6' and 6-H), 8.8 (1H, d, 2-H, J=1.5Hz).

MS: m/e (rel. int. %), 324(77), 289(47), 281(100), 261(5), 251(8), 235(16), 223(6), 203(4), 161(15), 152(2), 130(2), 119(2), 105(11), 77(5).

Anal. $C_{19}H_{20}N_2O_3$ (324) Calc. C, 70.37; H, 6.17; N, 8.64
Found C, 69.70; H, 6.41; N, 8.72

4-N,N-Dimethylamino-3-nitrobenzophenone (8g):

Purified by column chromatography using a mixture of pet. ether and ethylacetate (v/v 9.5:0.5). Yellow crystals from pet. ether, m.p. 116°C.

IR (Nujol) cm^{-1}: 1645, 1605, 1580, 1540, 1520, 1470, 1460, 1420, 1390, 1360, 1330, 1270, 1220, 1170, 1130, 1090, 1000, 980, 840, 810, 720.

^{1}H-NMR ($CDCl_3$): 3.07 (6H, s, CH_3), 7.07 (1H, d, 5-H, J=9Hz), 7.47-7.80 (5H, m, 2',3',4',5' and 6'-H), 7.95 (1H, dd, 6-H), 8.27 (1H, d, 2-H, J=1.5Hz).

MS: m/e (rel. int. %): 270(18), 253(87), 238(5), 223(57), 208(8), 195(100), 181(10), 167(62), 159(9), 146(53), 132(50), 119(44), 105(68), 77(9).

Anal. $C_{15}H_{14}N_2O_3$ Calc. C, 66.60; H, 5.10; N, 10.37
(270) Found C, 66.63; H, 5.30; N, 10.04

Preparation of 2-amino-5-nitrobenzophenone and its N-alkyl derivatives (10a, 10b) (CHART-10):

These compounds are prepared by the general procedure described for 4-amino-3-nitrobenzophenone and its N-alkyl derivatives (**8a-8g**). Here, 2-methoxy-5-nitrobenzophenone (**9**) was reacted with ammonia or alkylamine to yield the respective products (**10a, 10b**):

2-Amino-5-nitrobenzophenone (10a):

Yellowish red prisms from ethylacetate, m.p.161°C (lit.[22] m.p. 161.5°C), yield 23.2 g (96%).

IR (Nujol) cm^{-1}: 3460, 3360, 1640, 1615, 1600, 1560, 1500, 1480, 1450, 1440, 1380, 1310, 1260, 1160, 1100, 960, 925, 850, 840, 805, 770, 750, 710, 660, 645.

^{1}H-NMR (TFA): 7.3 (1H, d, 3-H, J=8Hz), 7.5-7.8 (5H, m, 2',3', 4',5' and 6'-H), 8.2-8.5 (1H, dd, 4-H), 8.6 (1H, d, 6-H, J=1.5Hz).

MS: m/e (rel. int. %): 242(78), 241(100), 225(7), 195(18), 165(13), 139(7), 119(22), 105(40), 91(7), 77(7).

Anal. $C_{13}H_{10}N_2O_3$ Calc. C, 64.46; H, 4.13; N, 11.57
(242) Found C, 64.59; H, 4.63; N, 11.64

2-Cyclohexylamino-5-nitrobenzophenone (10b):

Yellow plates from acetone, m.p. 95°C, yield 29.1 g (90%).

IR (Nujol) cm^{-1}: 3270, 1630, 1610, 1580, 1535, 1460, 1380,

1260, 1150, 1110, 1080, 960, 940, 830, 760, 710, 610.

^{1}H-NMR (CCl_4): 1.1-2.1 (10H, m, CH_2's of cyclohexyl group), 3.23-3.7 (1H, m, CH of cyclohexyl), 6.4 (1H, d, 3-H, J=9Hz), 7.1-7.3 (5H, m, Ar-H),8.0 (1H, d, 6-H, J=1.5Hz)8.96 (1H, bd, NH).

MS: m/e (rel. int. %): 324(80), 305(76), 281(100), 267(12), 235(16), 203(27), 117(18), 105(24), 77(20).

Anal. $C_{19}H_{20}N_2O_3$ (324) Calc. C, 70.40; H, 6.20; N, 8.64
Found C, 70.44; H, 6.71; N, 8.79

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CHAPTER - II

PART-A

BENZOTRICHLORIDE-A VERSATILE REAGENT FOR THE PREPARATION OF SUBSTITUTED BENZOPHENONES

INTRODUCTION

It may be recapitulated that the preceding chapter described a route for the synthesis of 4-amino-3-nitrobenzophenone (1) and related compounds. As already pointed out, 1 is the key intermediate in the industrial preparation of mebendazole, a widely used anthelmintic drug. The salient features of the method were benzoylation of o-nitroanisole using benzoyl chloride under Friedel-Crafts conditions followed by the nucleophilic displacement of the methoxy group by ammonia or different alkylamines. Although the route appears attractive, a re-examination revealed that benzoylation occurred in a moderate yield and subsequent reaction involved the use of pressure and comparatively high temperature. In this context, devising an alternate method which could be more efficient and use milder reaction conditions becomes necessary. The current industrial method[1-3] for 4-acetamidobenzophenone 2 involves the transformation of 4-nitrobenzoic acid 6, to its acid chloride and Friedel-Crafts reaction with benzene using aluminium chloride as the catalyst. p-Nitrobenzophenone 7, thus obtained is reduced to the corresponding amino derivative 8 and subsequently acetylated with acetic anhydride (CHART 2). It is apparent that 2 can be conveniently utilized in the synthesis of 4-amino-3-nitrobenzophenone 1. As the above method for 1 involves a multistep procedure, it was thought worthwhile to investigate the benzoylation of readily accessible acetanilide 3 to obtain 2 in a single step.

However, the reaction of acetanilide (3) with equimolar quantity of benzoyl chloride (4) at 0-25°C in presence of three equivalents of aluminium chloride using ethylene dichloride as a solvent failed to afford 4-acetamidobenzophenone 2 (CHART 3). On the other hand, most of the starting material was recovered along with some polymeric products; benzoyl chloride had hydrolyzed to benzoic acid (CHART 3).

Substituted benzophenones constitute important organic intermediates and therefore various methods are available in literature for their synthesis. The most commonly employed method[4] is the Friedel-Crafts acylation of aromatics with benzoyl chloride as the acylating agent inspite of its hygroscopic and lachrymatory nature.

Other methods for the preparation of benzophenones include oxidation of diphenylmethanes,[5] Grignard reactions[6] and Fries migration.[7]

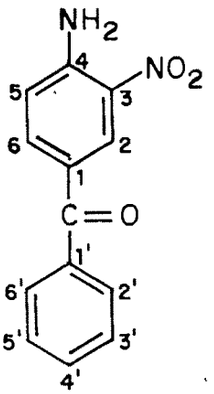
Although benzoylation is practised as an industrial method for benzophenones, there are certain inherent limitations. In the benzoylation of an aromatic ring using an acid, acid halide, anhydride or a ketene in presence of acid catalysts, high temperatures[8] are generally employed. Besides this, the presence of certain sensitive functional groups such as hydroxyl and amino or acetylamino on the aromatic ring leads to undesirable side reactions and therefore the main reaction is not productive. In this context, the choice of a suitable benzoylating agent which is compatible with sensitive functionalities

becomes very important. It is interesting to note that the use of benzotrichloride 5, a precursor to benzoyl chloride as a benzoylating agent has been mentioned by Newman et al.[9,10] in early fifties. A mixture of 2-hydroxy-5-methylbenzophenone (40%) and 6,12-diphenyl-2,8-dimethyl-6,12-epoxy-6H,12H-dibenzo-[b,f]dioxocin was obtained by the reaction of benzotrichloride with p-cresol (CHART 4). It may be mentioned that benzoyl chloride is manufactured[11] by the reaction of benzotrichloride with an equimolar amount of water or benzoic acid.

In addition to these isolated reports, there have been a few patents[12-20] indicating the use of benzotrichloride as a benzoylating agent. These have been mostly restricted to reactive phenols probably due to the industrial importance of the products as intermediates for sun-screen agents[21] (CHART 5). A cursory look at Chart 5 which may summarize the patent literature on the use of benzotrichloride shows that in one case[13] hydrofluoric acid and benzotrichloride are used in the benzoylation of resorcinol at -10°C. In another patent[14] resorcinol is similarly benzoylated using benzotrichloride in presence of N-methyl-2-pyrrolidone. Although the yields in the above methods have been satisfactory, benzoylation of p-tert-butyl phenol[16] with benzotrichloride in aqueous sodium hydroxide furnished a mixture of O- and C-acylated products. As already mentioned, this type of benzoylation has been resorted to essentially in the case of phenols. However, a systematic development of benzotrichloride as a benzoylating agent for

aromatics and hetero-aromatics in general does not appear to have been made so far. This prompted us to undertake an investigation on the use of benzotrichloride as a benzoylating agent and develop a practical and convenient method by optimizing the various parameters involved.

CHART – 1



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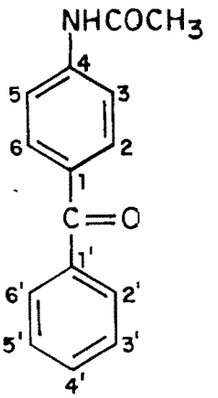

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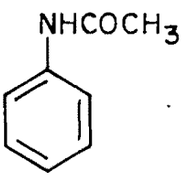

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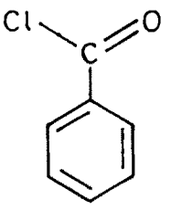

4

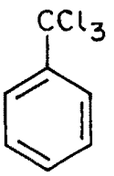

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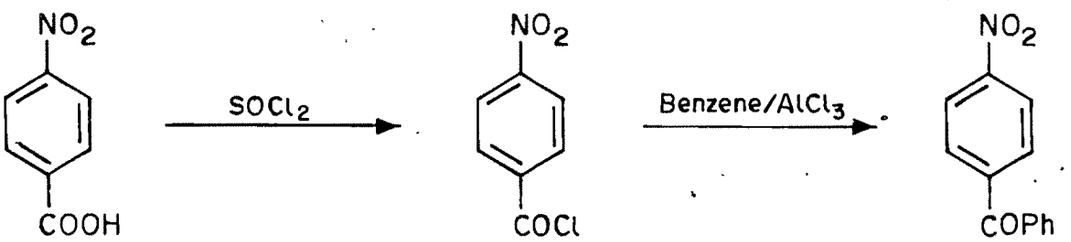
CHART – 2



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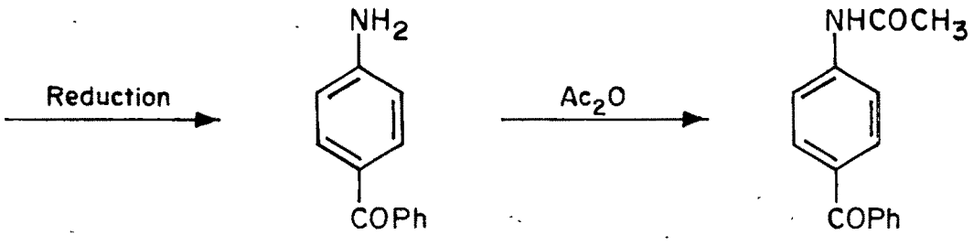

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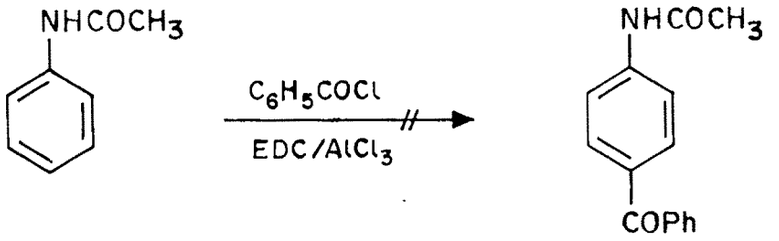
CHART – 3



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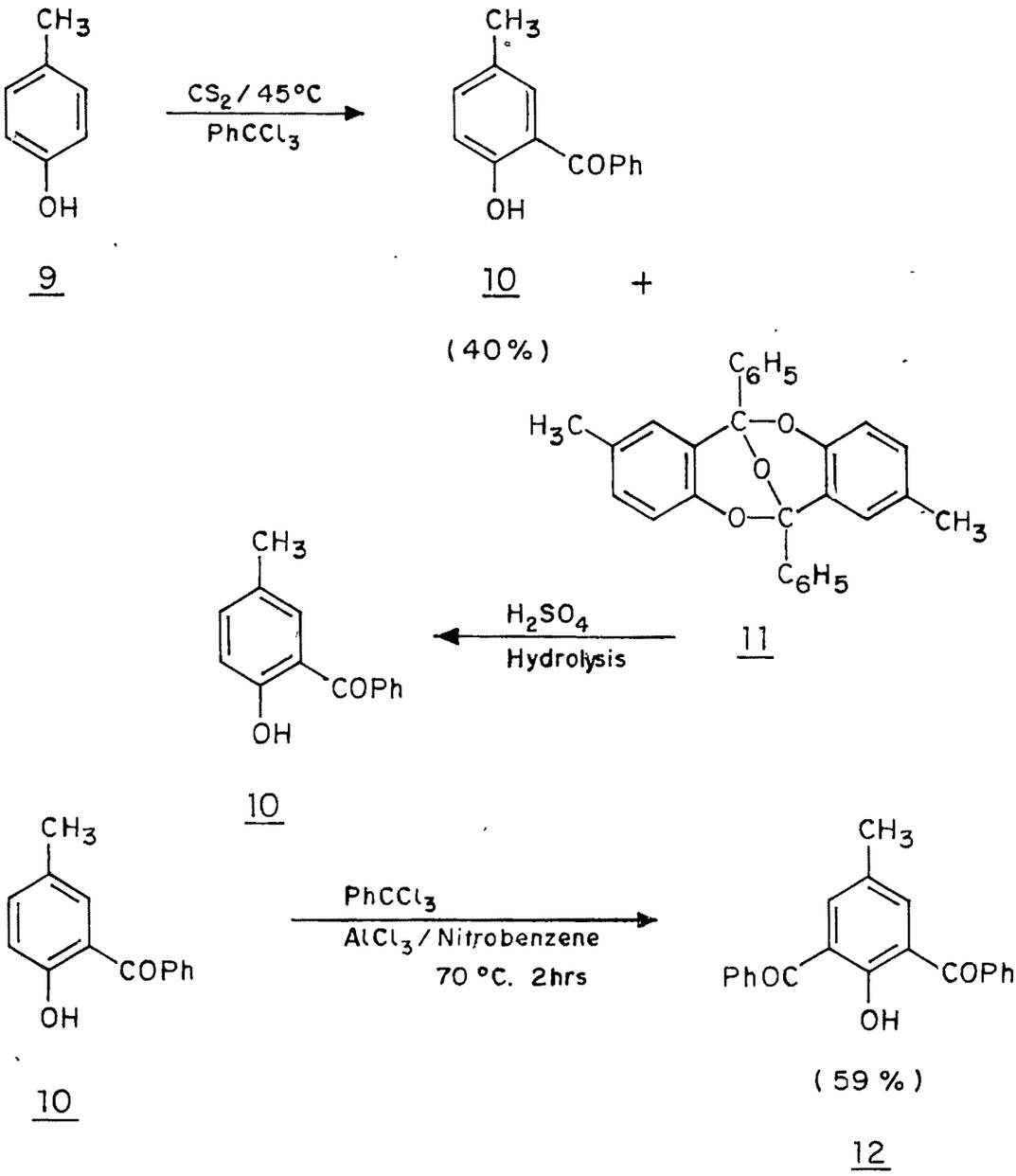
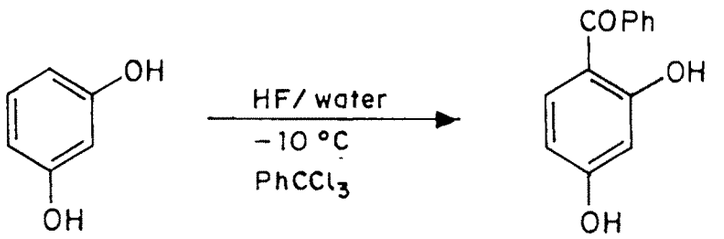
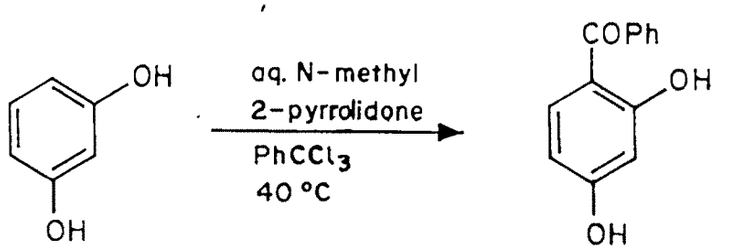


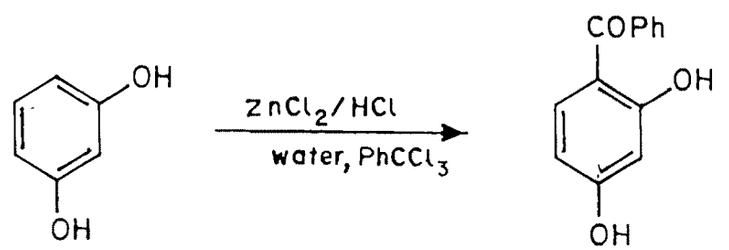
CHART – 5

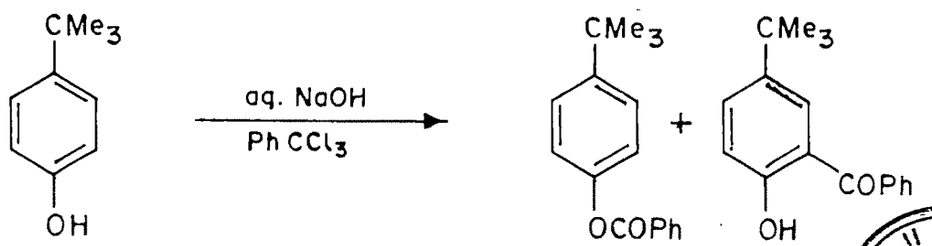
USE OF $PhCCl_3$ AS BENZOYLATING AGENT



13 14







(54·1%) (33·8%)

15 17

PRESENT WORK

It may be recalled that attempts to prepare benzoylated derivatives of acetanilide and similar anilides with benzoyl chloride were not successful. Therefore, a more reactive reagent for benzoylation was sought for. The literature survey indicated a possible potential of benzotrichloride for its development as an efficient benzoylating agent.

The reaction of benzotrichloride with acetanilide was examined in great detail. This reaction is similar to the Friedel-Crafts alkylation reaction. This class of reactions has been extensively studied[22] and the conditions in terms of the right solvent, the catalyst and its molar proportion and temperature have been generally established. Nevertheless, the efficiency of the reaction appears to depend on the substrate used. Employing the generally-followed conditions, the reaction of acetanilide with equimolar quantity of benzotrichloride was carried out in EDC as a solvent and using three equivalents of aluminium chloride as a catalyst and maintaining the temperature in the range of 0-25°C. After a standard work up, nearly a quantitative yield of 4-acetamidobenzophenone (2), was obtained. The homogeniety of the product was determined by Gas Liquid Chromatography (FIG. 1) and ^{1}H-NMR and other spectral characteristics. GLC of a mixture of acetanilide and a standard sample of 4-acetamidobenzophenone was taken separately (FIG. 2).

It may be pointed out here that the reaction of parent compound aniline with benzotrichloride under similar conditions

did not yield the C-acylated product; instead led to a complex polymeric mixture suggesting the necessity of protecting the amino group. Encouraged by the result obtained, different parameters that govern the reaction were varied and their effect on the course of the reaction studied.

Solvent effect:

The reaction was carried out using other solvents such carbon disulphide and nitrobenzene in place of ethylenedichloride. They are also generally employed in Friedel-Crafts reactions. The use of chloroform as a solvent was checked. The results have been tabulated (Table 1). The table clearly shows that the best yield has been obtained when EDC was used as the solvent. This may be attributed to the high solubility of benzotrichloride-aluminium chloride complex in ethylene dichloride.

Catalyst:Substrate Ratio and Temperature Variations:

Attempts were made to reduce the quantity of aluminium chloride necessary for the reaction without adversely affecting the yields. Various experiments were carried out using equimolar amounts of acetanilide and aluminium chloride and varying the temperature in the range 25-150°C. Similarly, the use of 2:1 ratio of aluminium chloride to acetanilide was made and the reaction carried out at different temperatures. The findings from these experiments have been depicted in Table 2. It is evident from the table that use of equimolar amounts of aluminium chloride is not sufficient for the reaction to occur irrespective of the reaction temperature. It is also apparently

seen that an enhancement of reaction temperature leads to lowering of yield of the benzoylated product. However, yields in the range of 72% and 82% of the product could be realized when two equivalents of $AlCl_3$ was used. A dramatic increase in the yields could be accomplished with 3:1 equivalents of aluminium chloride:acetanilide and that too at ambient temperature (FIG. 3).

From the foregoing discussion it becomes apparent that treatment of acetanilide with three molar equivalents of aluminium chloride in ethylenedichloride as solvent at room temperature leads to nearly quantitative yield of the required 4-acetamidobenzophenone. Evidently, the stability factor of the protecting groups under our reaction conditions is also responsible for the high selectivity and yield of 2.

The various parameters optimized for the reaction of acetanilide and benzotrichloride were studied for their suitability for the synthesis of various benzoyl derivatives of different aromatic and heteroaromatic systems (SCHEME 1) (Table 3). It may be pointed out that the conditions described above could be satisfactorily employed for numerous substrates (3a-3s). At the same time, it may be added that the reactions of phenols had to be performed at lower temperatures. The purity and characterizations of all the products were established on the basis of their melting points and comparison of the spectral data, wherever known.

Spectral Characteristics of the Products (2a-2s):

It has been already mentioned that the products from these

benzoylation reactions were characterized on the basis of their spectral features. The compounds **2c, 2d, 2o, 2r** and **2s** (Table 1) have not been reported so far; while the compounds **2a, 2b** although reported in literature are not backed up by spectral data.

IR Spectra:

The general features of the IR spectra of all these compounds are indicated below:

1. A strong absorption in the range 1620-1660 cm^{-1} typical of the benzophenone carbonyl chromophore.
2. The compounds **2a-2d** display NH stretching vibration in the range 3260-3340 cm^{-1}.

The IR spectrum of **2r** indicated the presence of two carbonyl absorptions at 1620 and 1745 cm^{-1}. The latter absorption clearly indicated the presence of a five-membered lactam. The IR spectrum of **2d** besides showing the typical NH stretching at 3310 cm^{-1} displayed distinct carbonyl absorptions at 1640 and 1735 cm^{-1} (FIG. 4).

^{1}H-NMR Spectra:

All the compounds showed satisfactory NMR chemical shifts for the structures assigned. In fact, they were conspicuous by their simplicity and very few signals. For example, the spectrum of **2d** exhibited a 3H singlet at 3.73 indicating the presence of ester methyl group and a number of signals in the range 6.7-7.8 integrating for ten protons. Obviously, the NH resonance is masked (FIG. 5).

The occurrence of H-bonding is beautifully reflected in the NMR of **2s**. This results in two magnetically unequivalent methyl and methylene groups leading to separate resonances for both the methyls and methylenes of the carbethoxy groups (1.2 and 1.36, methyl triplets; 4.2 and 4.3, methylene quartets). The other notable feature of the spectrum is the downfield doublet at 8.5 (J=15Hz) typical of β-proton of an unsaturated system and the NH doublet at 11.0 (J=15Hz).

Mass Spectra:

The general features of the mass spectra of all these compounds (**2a-2s**) are briefly outlined below.

Besides showing the molecular ion peaks, the compounds displayed the base peaks, in most of the cases at M-77 due to the expected fragmentation leading to a loss of phenyl group. Another common fragmentation leads to the loss of the benzoyl group (105) itself. Obviously, prominent peaks were noticed at m/e 77 and 105. The rest of the fragmentation appears to be dependent on the other structural features of the products.

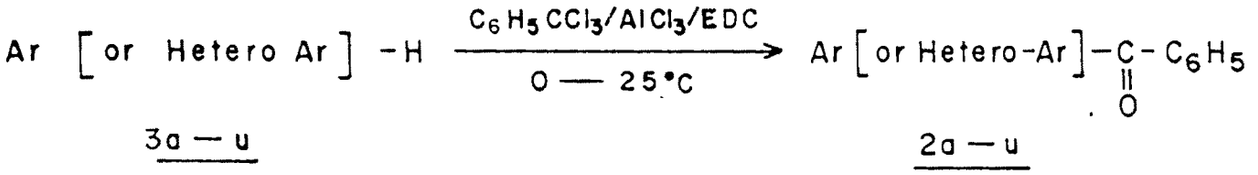
The mass spectrum of **2c** presents some interesting aspects. Although the base peak is formed by the loss of phenyl group, there is a prominent peak at 155 indicating a radical ion representing p-toluene sulphonyl group. The latter readily fragments with a loss of neutral molecule of sulphur dioxide leading to tropilium ion at 91. For **2d**, a facile loss of phenyl group has led to an additional base peak at 178 (100%) besides that of the molecular ion at 255 (100%). The radical ions corresponding to the phenyl and benzoyl groups are also prominently

observed (FIG. 6). The spectra of compounds containing halogen atoms exhibited peaks due to the presence of the isotopic atoms.

Conclusion:

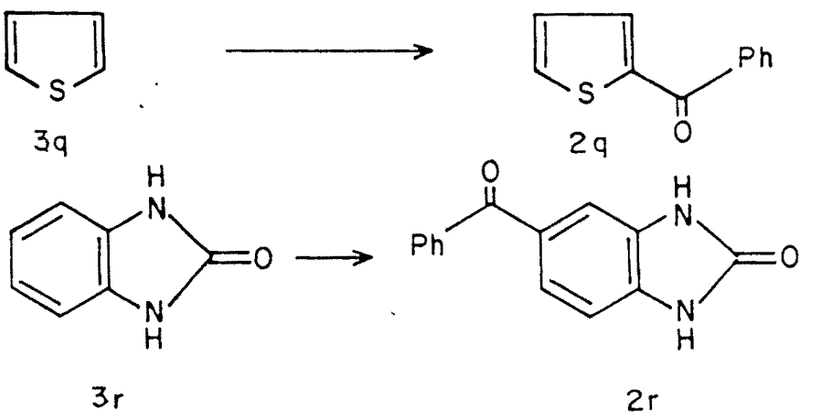
The work described here represents an extremely convenient and high yielding methodology for the preparation of various substituted benzophenones which are industrially important. The salient features of this methodology are indicated below.

(i) Benzoylation occurs under extremely mild conditions. This may be attributed to the fact that benzotrichloride, the precursor of benzoyl chloride is a more reactive benzoylating agent under milder reaction conditions. It may be emphasized that substrates such as acetanilide, benzanilide which do not react with benzoyl chloride undergo facile benzoylation with benzotrichloride, (ii) By virtue of the non-hygroscopic and non-lachrymatory nature, the large scale handling of benzotrichloride does not present problems; (iii) The work up procedures are easy. (iv) The yields of the products are excellent and in many cases almost quantitative.



3a — u

2a — u



3q 2q

3r 2r

SCHEME 1 (see table 3)

Table 1: Benzoylation of 3a to 2a in various solvents

Solvent	Yield[a] (%)
Ethylene dichloride	98
Carbon disulfide	95
Chloroform	89
Nitrobenzene	64

[a]Isolated yield of 2a

Table 2: Benzoylation of 3a to 2a at various temperatures

Molar ratio $AlCl_3$: 3a	Temperature (°C)	Solvent	Yield[a] (%)
1:1	25-150	-	Nil
2:1	25	Ethylene dichloride	82
	75	Ethylene dichloride	72
	100	Nitrobenzene	50
	150	Nitrobenzene	25
3:1	25	Ethylene dichloride	98

[a]Isolated yield of 2a

Table 3: Benzoylation of aromatic substrate 3 to the benzoyl compound 2

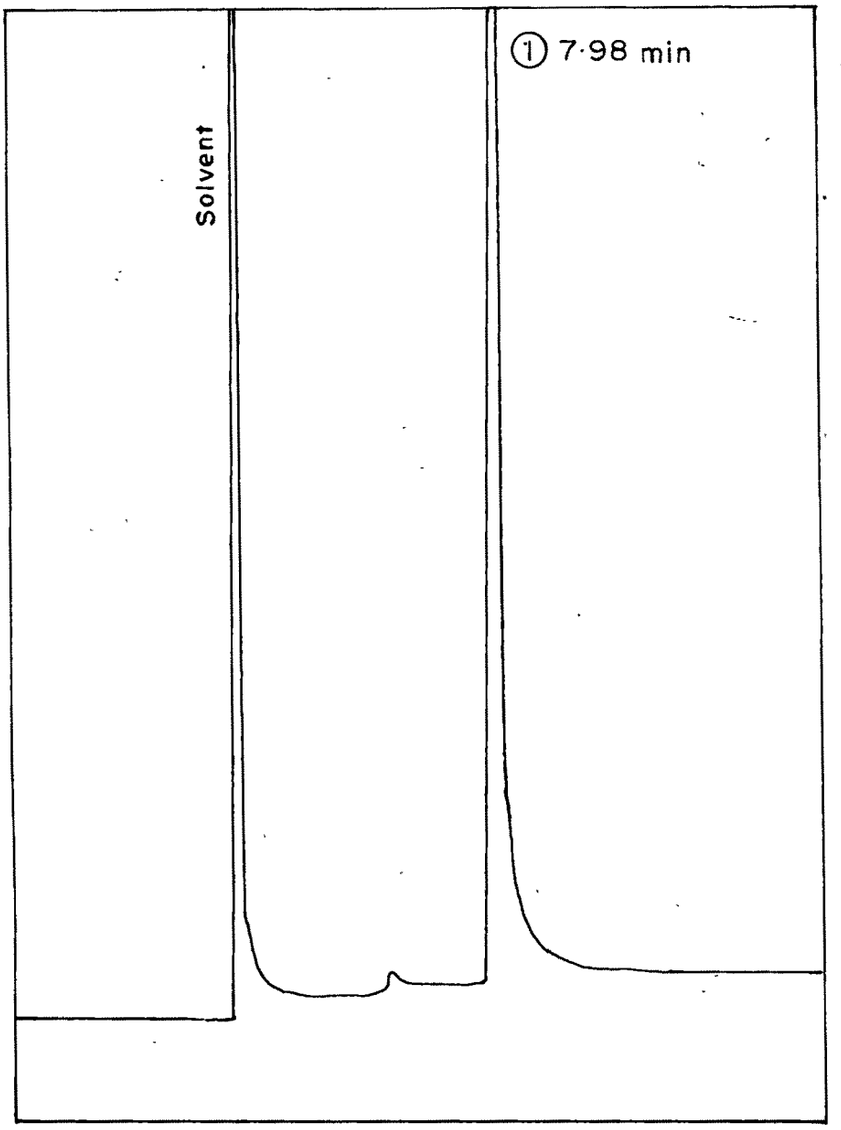
No.	Substrate 3 Ar (or Het-Ar)	No.	Product 2 Benzoyl Der.	Yield[a] (%)	m.p./b.p.(°C) Found	Rep.[f]
3a	Acetanilide	2a	4-Benzoyl	98	156	156[9]
3b	Benzanilide	2b	4-Benzoyl	96	152	152[10]
3c	p-Toluenesulphonanilide	2c	4-Benzoyl[b]	84	175	-
3d	N-(Phenyl)carbamic acid methyl ester	2d	N-[(4-Benzoyl)phenyl]carbamic acid methyl ester[b]	98	160	-
3e	Chlorobenzene	2e	4-Benzoyl	88	75	75-76[11]
3f	o-Dichlorobenzene	2f	4-Benzoyl	72	104	104[12]
3g	Bromobenzene	2g	4-Benzoyl	93	82	82.5[11]
3h	Benzene	2h	Benzophenone	95[c]	48	48.5[13]
3i	Toluene	2i	4-Benzoyl	95[e]	59	59[14]
3j	o-Xylene	2j	4-Benzoyl	95	47	47[15]
3k	m-Xylene	2k	4-Benzoyl	95	186	186-90[15]
3l	Anisole	2l	4-Benzoyl	93[e]	61	61[8]
3m	Phenol	2m	4-Benzoyl	93[e]	135	135[16]
3n	Resorcinol	2m	4-Benzoyl	94[d]	144	144[6]
3o	4-Methylacetanilide	2o	2-Benzoyl[b]	74	120	-
3p	Naphthalene	2p	1-Benzoyl	85[e]	75	75[17]
3q	Thiophene	2q	2-Benzoyl	98	56	56[18]
3r	Benzimidazolin-2-one	2r	5-Benzoyl[b]	98	303	-
3s	Ethyl-α-(carbethoxy-β-(anilino)acrylate	2s	Ethyl-α-(carbethoxy)-β-[p-(benzoyl)anilino]acrylate[b]	95	55	-

[a]Isolated yield based on 3; [b]Unreported benzoyl derivatives 2

[c]Yield based on limiting benzotrichloride; [d]The reaction was carried out at -20°C

[e]The reaction was carried out at 0 - 5°C

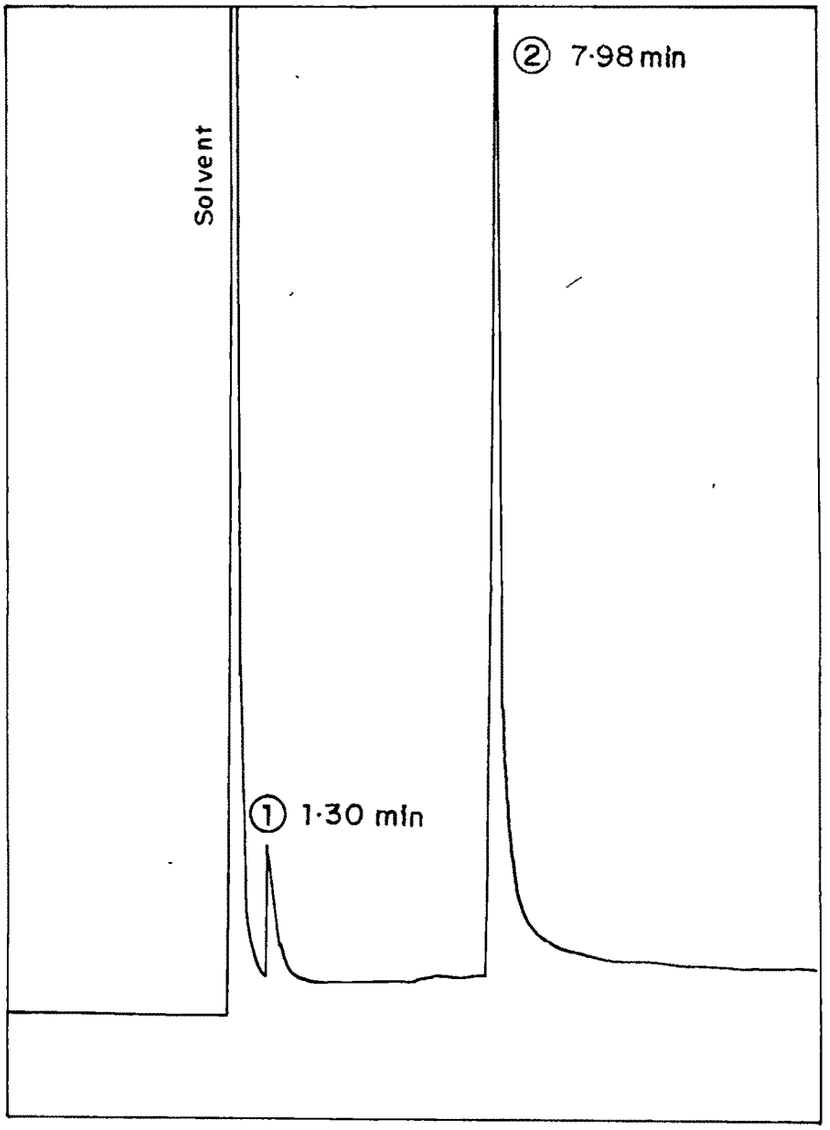
[f]The superscript refers to references of literature.



① 4-ACETAMIDO BENZOPHENONE (synthesised)

Column	SE-30.	loading 0·3 %
Column Temp.	180°	$\xrightarrow{20°/min}$ 240° for 10 min
Flow of N_2	30 ml / min	
Chart sweep	0·5 cm / min	

FIG. 1



① ACETANILIDE

② 4-ACETAMIDO BENZOPHENONE (authentic)

Column SE-30. loading 0·3 %

Column Temp. 180° $\xrightarrow{20°/\text{min}}$ 240° for 10 min

Flow of N_2 30 ml / min

Chart sweep 0·5 cm / min

FIG. 2

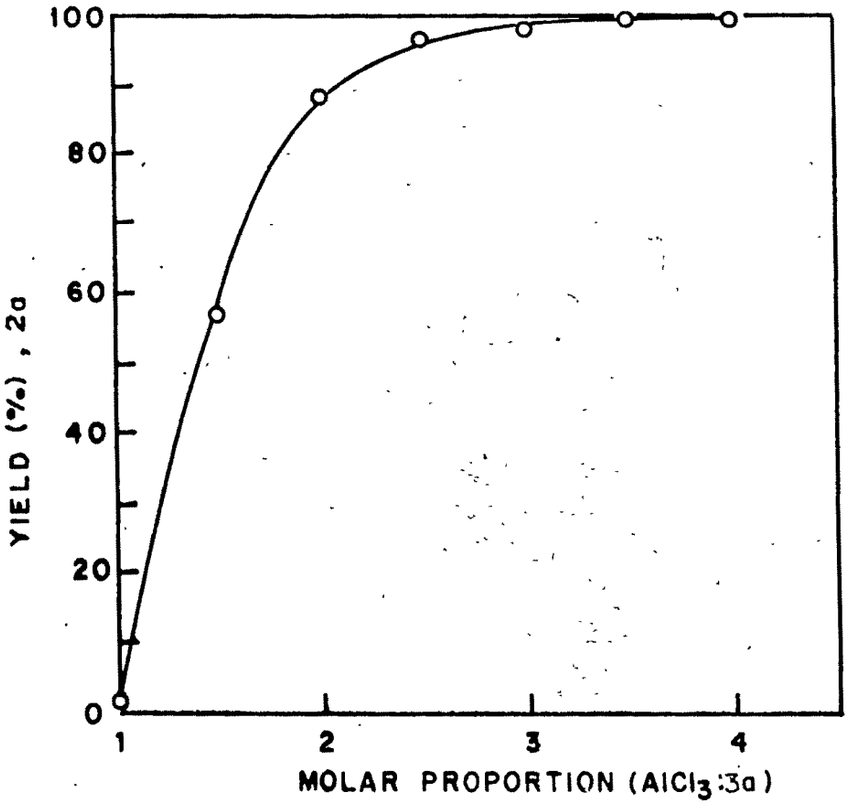


FIGURE 3. EFFECT OF MOLAR PROPORTION OF ALUMINIUM CHLORIDE AND 3a ON THE YIELD OF 2a

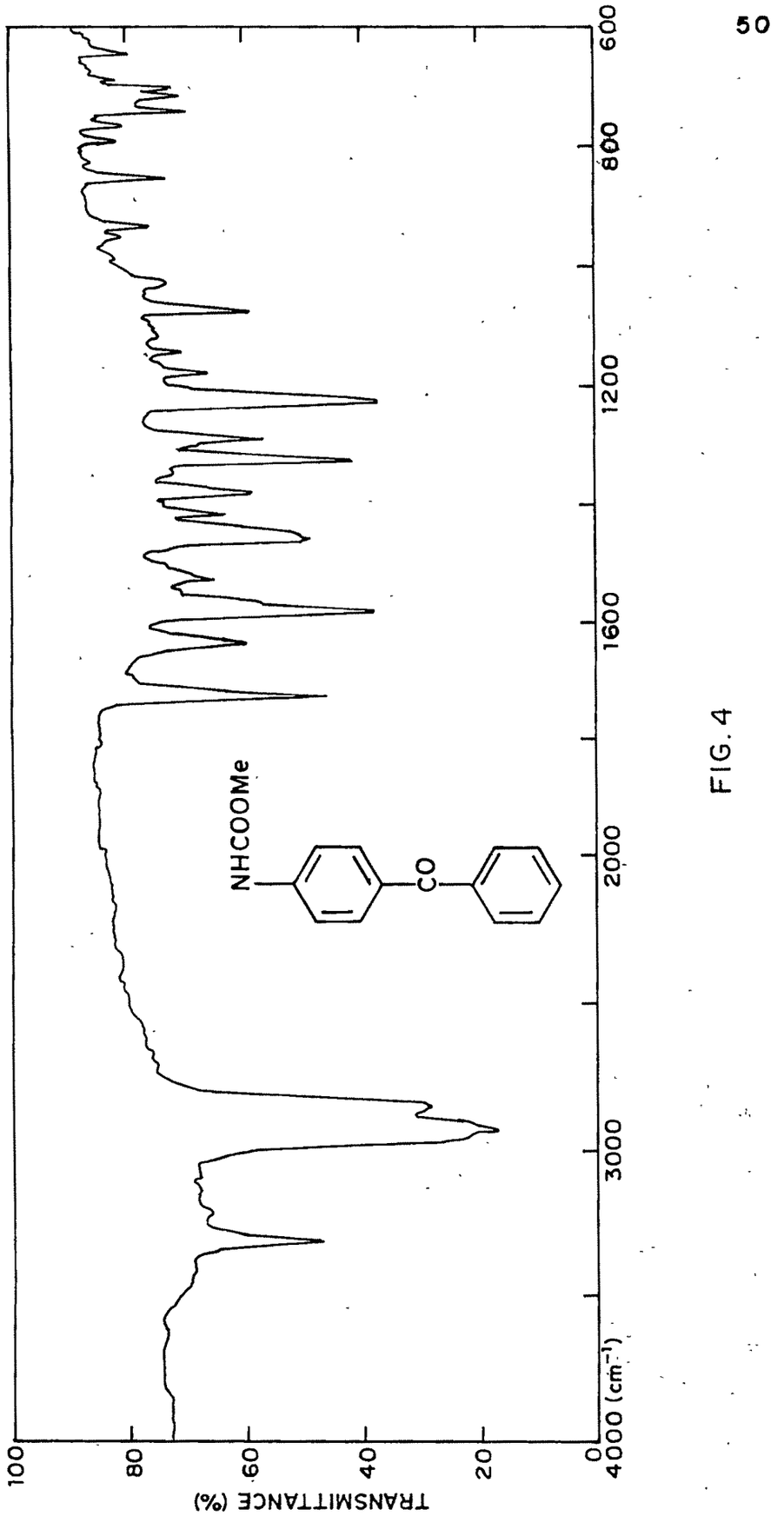

TRANSMITTANCE (%)
100
80
60
40
20
0
4000 (cm⁻¹)
3000
2000
1600
1200
800
600
NHCOOMe
CO

FIG. 4

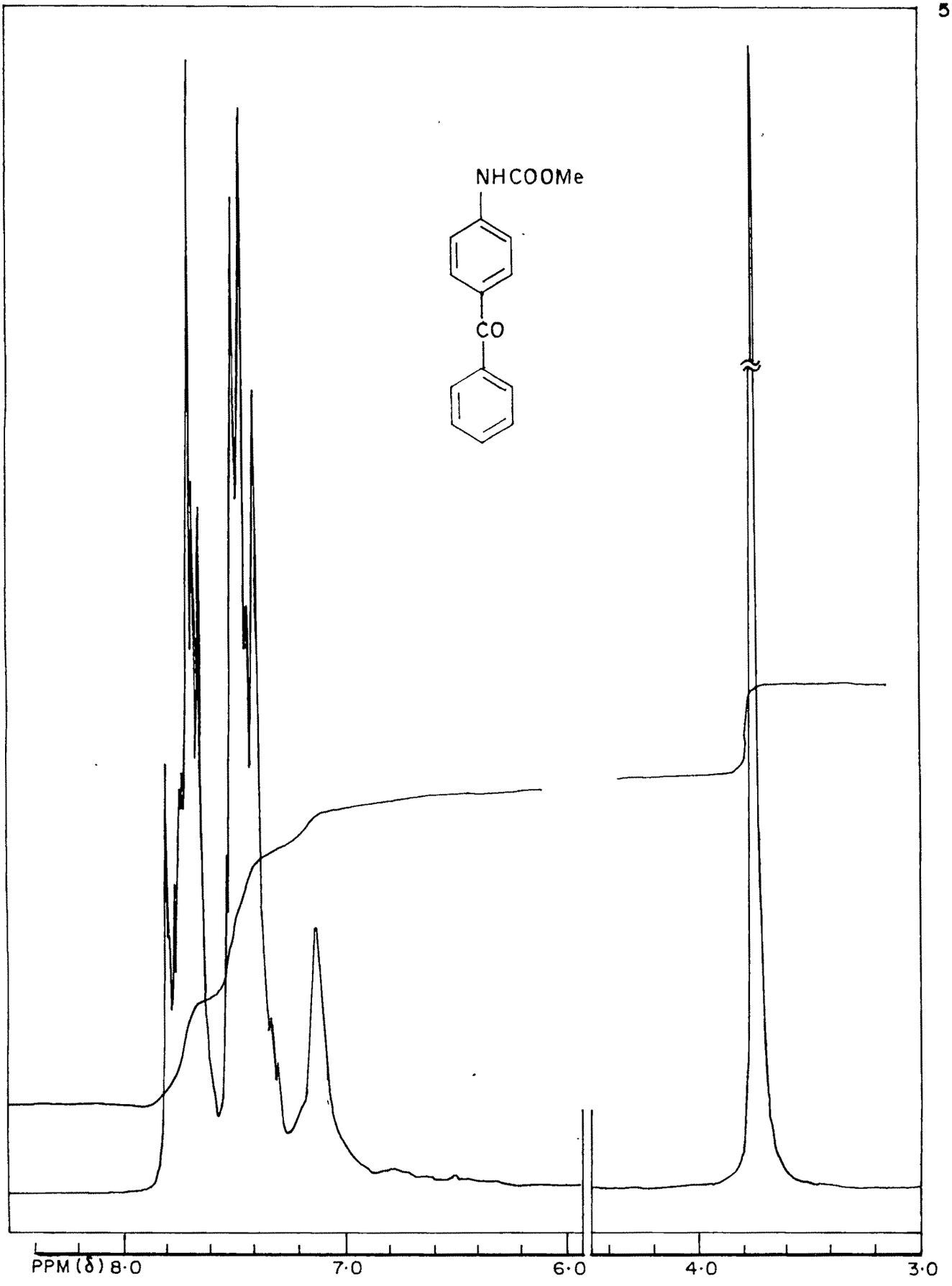


FIG. 5

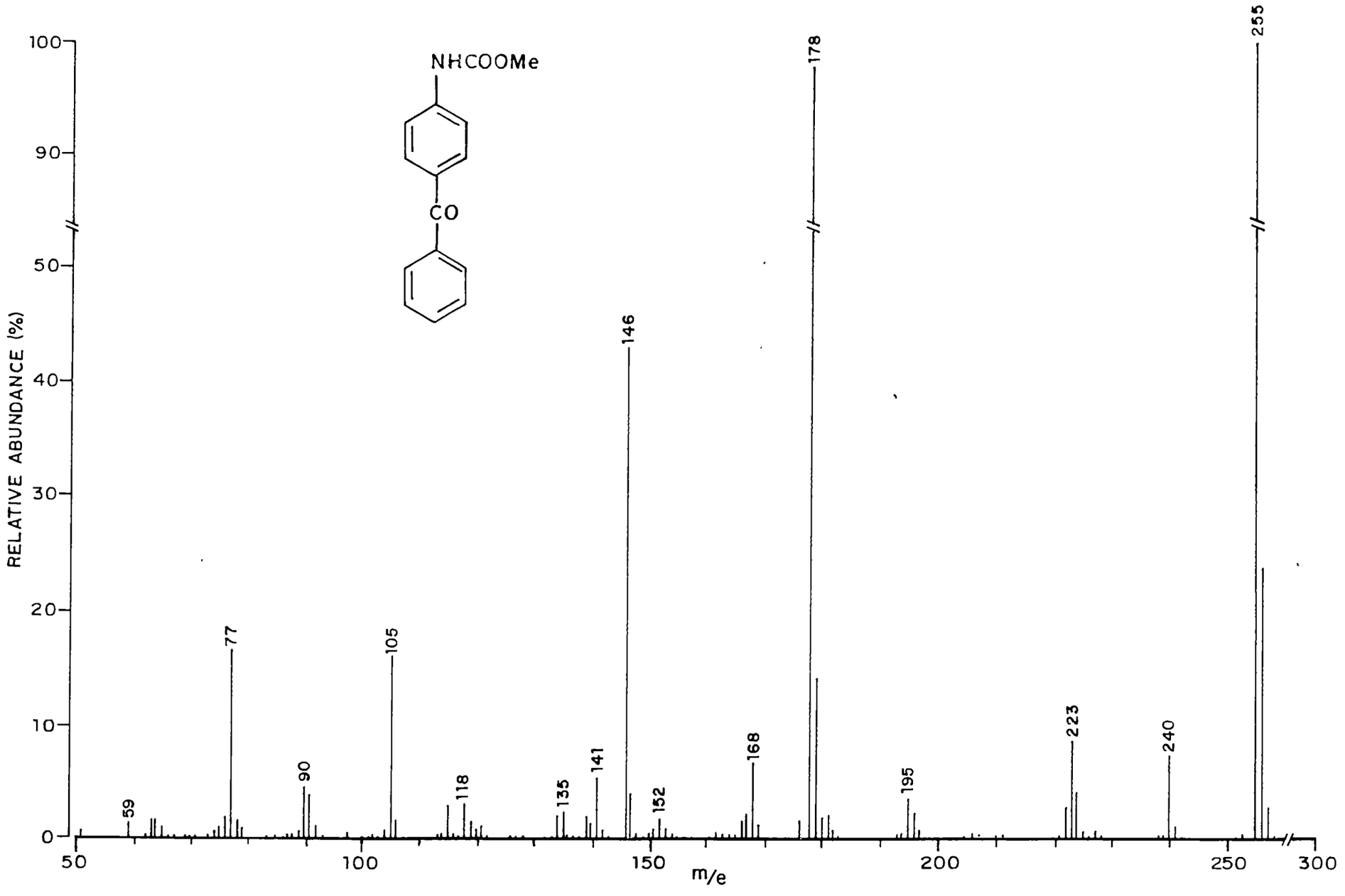

NHCOOMe
CO
RELATIVE ABUNDANCE (%)
m/e
100
90
50
40
30
20
10
0
50
100
150
200
250
300
59
77
90
105
118
135
141
146
152
168
178
195
223
240
255

FIG. 6

EXPERIMENTAL

General Procedure for the Synthesis of 2a-2s using Benzotrichloride:

To a cooled solution (0-5°C) of anhydrous aluminium chloride (40 g, 0.3 mol) in ethylene dichloride (150 ml), benzotrichloride (21.5 g, 0.11 mol) was added over 15 min. Acetanilide (or the substrate to be benzoylated) (0.1 mol) was added over 15 min. The reaction mixture was stirred for 5 h. Completion of the reaction was checked by TLC on silica-gel using petroleum ether (b.p. 60-80°C) and ethyl acetate (4:1) as the eluent. Care was taken to maintain anhydrous conditions throughout the course of the reaction. The dark-brown reaction mixture was poured into crushed ice (500 g) and 10 ml hydrochloric acid. The resulting mixture was stirred at 70°C for 0.5 h. After cooling, EDC layer was separated, washed with water (3 x 250 ml) and dried. The solvent was removed by distillation and the resulting product **2** was crystallized from a suitable solvent.

4-Acetamidobenzophenone (2a):

White needles from aqueous ethanol, yield 23.4 g (0.98 mol, 98%), m.p. 156°C (lit.[23] m.p. 156°C).

IR (Nujol, cm^{-1}): 3340, 1700, 1620, 1575, 1450, 1375, 1310, 1250, 1160, 1020, 860, 740.

^{1}H-NMR ($CDCl_3$): 2.12 (3H, s, CH_3), 7.2-7.9 (9H, m, Ar-H), 8.12 (1H, bs, NH, exchangeable with D_2O).

MS: m/e (rel. int. %): 239 (M^+, 68), 197(62), 180(3), 162(10), 141(14), 120(100), 105(15), 92(8), 77(3).

Anal. $C_{15}H_{13}NO_2$: Calc. C, 75.31; H, 5.43; N, 5.85
(239) Found: C, 74.90; H, 5.75; N, 5.60

4-Benzoylbenzanilide (4-Benzamidobenzophenone) (2b):

White needles from ethanol, m.p. 152°C (lit.[24] m.p. 152°C), yield, 28.9 g (96%).

IR (Nujol, cm^{-1}): 3380, 1650, 1590, 1460, 1380, 1320, 1280, 1170, 940, 920, 840, 740, 720, 700.

^{1}H-NMR ($CDCl_3$): 7.23-8.00 (14H, m, Ar-H), 8.3 (1H, s, NH, exchangeable with D_2O).

MS m/e (rel. int. %): 301 (M^+, 100), 196(4), 168(6), 141(6), 105(100), 91(3), 77(39).

Anal. $C_{20}H_{15}NO_2$ Calc. C, 79.73; H, 4.98; N, 4.65
(301) Found: C, 79.52; H, 4.87; N, 4.37

(p-Toluene sulphonamido)benzophenone (2c)

Yellowish white crystals from ethanol, m.p. 175°C, yield 29.5 g (84%).
IR (Nujol, cm^{-1}): 3260, 1650, 1590, 1570, 1465, 1420, 1390, 1350, 1330, 1300, 1290, 1240, 1150, 1100, 930, 860, 820, 730, 710, 690.

^{1}H-NMR ($CDCl_3$): 2.3 (3H, s, CH_3), 7-7.9 (13H, m, Ar-H), 10.1 (1H, bs, NH, exchangeable with D_2O).

MS m/e (rel. int. %): 351 (M^+, 30): 274(13), 222(7), 197(14), 165(25), 155(29), 141(12), 120(31), 105(28), 91(78), 83(100), 77(29), 65(19), 57(16).

Anal. $C_{20}H_{17}NO_3S$: Calc. C, 68.37; H, 4.84; N, 3.98; S, 9.11
(351) Found: C, 68.23; H, 5.05; N, 3.54; S, 8.92

N-[4(Benzoyl)phenyl]carbamic acid Methyl Ester (2d):

2d was prepared in two steps.

Step 1: Preparation of N-(phenyl)carbamic acid methyl ester:

It was prepared by treating equimolar amounts of aniline with methylchloroformate in presence of a base (triethylamine). Leaflets from aq. ethanol, m.p. 51°C (lit.[25] m.p. 51°C), yield 146.5 g (0.97 mol) (97%).

IR (Nujol, cm^{-1}): 3340, 1720, 1600, 1530, 1510, 1450, 1370, 1310, 1220, 1100, 1080, 1040, 940, 900, 850, 760, 740, 700.

^{1}H-NMR ($CDCl_3$): 3.73 (3H, s, CH_3), 6.7 - 7.56 (6H, m, Ar-H and NH).

MS m/e (rel. int. %): 151(83), 135(17), 119(100), 106(71), 92(61), 91(86), 77(54), 65(73), 64(80), 51(55), 44(54).

Anal. $C_8H_9NO_2$: Calc. C, 63.57; H, 5.90; N, 9.27
(151) Found: C, 63.50; H, 6.22; N, 9.33

Step 2: Preparation of **2d**:

N-Phenylcarbamic acid methyl ester was reacted with benzotrichloride as in the general procedure, to yield **2d**.
Cream-white crystals from a mixture of acetone and petroleum ether (b.p. 60-80°C) (v/v, 1:1), m.p. 160°C, yield 24.9 g (98%).

IR (Nujol, cm^{-1}): 3310, 1730, 1640, 1590, 1460, 1420, 1380, 1330, 1290, 1230, 1080, 930, 850.

^{1}H-NMR ($CDCl_3$): 3.73 (3H, s, CH_3), 6.77 - 7.88 (10H, m, Ar-H and NH).

MS m/e (rel. int. %): 255 (M^+, 100), 239(20), 222(71), 178(100), 168(20), 141(21), 118(40), 105(89), 77(86), 63(44), 51(44), 44(60).

Anal. $C_{15}H_{13}NO_3$: Calc. C, 70.58; H, 5.09; N, 5.49
(255) Found: C, 70.34; H, 5.20; N, 5.32

4-Chlorobenzophenone (2e):

Purified by column chromatography using column silica gel. The eluent used was a mixture of chloroform and petroleum ether (v/v, 1:1). White needles from hexane, m.p. 75-76°C (lit.[26] m.p. 75-76°C), yield 19 g (88%).

IR (Nujol, cm^{-1}): 1640, 1580, 1440, 1360, 1300, 1280, 1140, 1080, 1000, 920, 840, 790, 720, 690.

^{1}H-NMR ($CDCl_3$): 7.33-7.82 (9H, m, Ar-H).

MS m/e (rel. int. %): 218 [$(M+2)^+$, 18]: 216 (M^+, 58), 181(21), 152(10), 139(92), 105(100), 77(47).

Anal. $C_{13}H_9ClO$: Calc. C, 72.22; H, 4.16; Cl, 16.20
(216) Found: C, 72.14; H, 3.98; Cl, 15.92

3,4-Dichlorobenzophenone (2f):

2f was purified by column chromatography using silica gel column. The eluent used as a mixture of chloroform and petroleum ether (v/v, 1:1). Needles from hexane, m.p. 104°C (lit.[27] m.p. 104°C), yield 18 g (72%).

IR (Nujol, cm^{-1}): 1640, 1565, 1440, 1380, 1300, 1280, 1260, 1230, 1150, 1030, 950, 890, 820, 790, 720, 690.

^{1}H-NMR ($CDCl_3$): 7.26-7.84 (8H, m, Ar-H).

MS m/e (rel. int. %): 250 (M^+, 70), 215(18), 173(58), 145(33), 105(100), 77(55).

Anal. $C_{13}H_8Cl_2O$: Calc. C, 62.40; H, 3.20; Cl, 28.00
(250) Found: C, 62.32; H, 3.20; Cl, 27.80

4-Bromobenzophenone (2g):

White plates from ethanol, m.p. 82.5°C (lit.[26] m.p. 82.5°C), yield 24.2 g (93%).

IR (Nujol, cm^{-1}): 1650, 1610, 1440, 1370, 1310, 1290, 1160, 1070, 1010, 940, 920, 850, 800, 730, 700.

^{1}H-NMR ($CDCl_3$): 7.4-8.0 (9H, m, Ar-H).

MS m/e (rel. int. %): 262 [$(M+2)^+$, 100], 260 (M^+, 100), 181(27), 182(27), 183(27), 184(68), 151(17), 152(10), 154(23), 156(23), 121(12), 105(60), 93(29), 77(24).

Anal. $C_{13}H_9BrO$: Calc. C, 55.93, H, 3.81; Br, 33.47
(260) Found: C, 55.78; H, 3.84; Br, 33.16

Benzophenone (2h):

White prisms from alcohol, m.p. 48°C (lit.[28], m.p. 48.5°C), yield 16.9 g (93%).

IR (Nujol, cm^{-1}): 1660, 1610, 1590, 1560, 1450, 1380, 1320, 1270, 1170, 1140, 1070, 1030, 1010, 950, 920, 810, 760, 700, 640.

^{1}H-NMR ($CDCl_3$): 7.36-7.60 (6H, m, 2,4,6,2',4' and 6'-H), 7.72-7.90 (4H, m, 3,5,3' and 5'-H).

MS m/e (rel. int. %): 182 (M^+, 100), 152(7), 105(94), 77(94), 74(10), 51(61).

Anal. $C_{13}H_{10}O$: Calc. C, 85.69; H, 5.53
(182) Found: C, 85.48; H, 5.46

4-Methylbenzophenone (2i):

White crystals from pet.ether, m.p. 59°C (lit.[29] m.p. 59-60°C), yield 18.6 g (95%).

IR (Nujol, cm^{-1}): 1660, 1610, 1470, 1440, 1390, 1330, 1290, 1200, 1160, 1090, 950, 940, 880, 840, 800, 780.

^{1}H-NMR ($CDCl_3$): 2.23 (3H, s, CH_3), 7.03-7.83 (9H, m, Ar-H).

MS m/e (rel. int. %): 196 (M^+, 76%), 181(46), 165(19), 152(14), 119(100), 105(52), 91(39), 77(27), 65(12).

Anal. $C_{14}H_{12}O$: Calc. C, 85.71; H, 6.12
(196) Found: C, 85.46; H, 6.24

3,4-Dimethylbenzophenone (2j):

Needles from pet. ether, m.p. 47°C (lit.[30] m.p. 47-48°C), yield 20.1 g (95%).

IR (Nujol, cm^{-1}): 1650, 1600, 1590, 1560, 1450, 1410, 1320, 1300, 1270, 1170, 1120, 1030, 980, 970, 870, 800, 780, 720, 700.

^{1}H-NMR ($CDCl_3$): 2.3 (6H, s, CH_3), 7.1-8.0 (8H, m, Ar-H).

MS m/e (rel. int. %): 210 (M^+, 49), 195(11), 133(100), 105(48), 94(29), 77(17), 57(21), 45(84), 40(79).

Anal. $C_{15}H_{14}O$: Calc. C, 85.71; H, 6.66
(210) Found: C, 85.46; H, 6.38

2,4-Dimethylbenzophenone (2k):

Distilled under vacuum, $b.p._{15}$ 188°C (lit.[30] $b.p_{15}$ 186-90°C).

IR (Nujol, cm^{-1}): 1640, 1610, 1600, 1580, 1440, 1370, 1310, 1290, 1270, 1240, 1180, 1160, 1020, 940, 890, 830, 800, 750, 730, 700.

^{1}H-NMR ($CDCl_3$): 2.3 (6H, s, CH_3), 6.8-7.9 (8H, m, Ar-H).

MS m/e (rel. int. %): 210 (M^+, 93), 209(100), 195(6), 178(14), 165(25), 133(62), 105(68), 77(63), 51(41).

Anal. $C_{15}H_{14}O$: Calc. C, 85.71; H, 6.66
(210) Found: C, 85.64; H, 6.72

4-Methoxybenzophenone (2l):

Yellowish white needles from diethyl ether, m.p. 61°C (lit.[8] m.p. 61-62°C), yield 19.7 g (93%).

IR (Nujol, cm^{-1}): 1650, 1600, 1580, 1510, 1460, 1470, 1330, 1290, 1260, 1180, 1160, 1120, 1030, 950, 800.

^{1}H-NMR ($CDCl_3$): 3.84 (3H, s, OCH_3), 6.9 (2H, d, 3-H & 5-H), 7.4-7.86 (7H, m, Ar-H).

MS m/e (rel. int. %): 212 (M^+, 31), 135(100), 105(14), 92(10), 77(21).

Anal. $C_{14}H_{12}O_2$: Calc. C, 79.24; H, 5.66
(212) Found: C, 79.12; H, 5.54

4-Hydroxybenzophenone (2m):

Plates from aq. ethanol, m.p. 134°C (lit.[31] m.p. 134°C), yield 18.6 g (94%).

IR (Nujol, cm^{-1}): 3120, 1645, 1610, 1580, 1560, 1480, 1470, 1390, 1340, 1330, 1250, 1190, 1170.

^{1}H-NMR ($CDCl_3$): 6.88 (2H, d, 3-H and 5-H), 7.28-7.88 (7H, m, Ar-H), 8.8 (1H, b, OH, exchangeable with D_2O).

MS m/e (rel. int. %): 198 (M^+, 56), 121(100), 105(18), 93(9), 77(11).

Anal. $C_{13}H_{10}O_2$: Calc. C, 78.78; H, 5.05
(198) Found: C, 78.46; H, 4.94

2,4-Dihydroxybenzophenone (2n):

The reaction was carried out at -20°C. Faint yellow needles from aqueous ethyl alcohol, m.p. 144°C (lit.[14] m.p. 141-144°C), yield 20.1 g (94%).

IR (Nujol, cm^{-1}): 3300, 1630, 1590, 1500, 1450, 1440, 1370, 1290, 1190, 1100, 1060, 980, 940, 920, 850, 800, 760, 690.

^{1}H-NMR ($CDCl_3$): 6.36-6.68 (2H, m, 3-H & 5-H), 7.36-7.64 (6H, m, Ar-H), 11.64 (2H, bs, OH).

MS m/e (rel. int. %): 214 (M^+, 83), 213(83), 144(27), 137(100), 105(81), 94(69), 77(56), 57(55).

Anal. $C_{13}H_{10}O_3$: Calc. C, 72.89; H, 4.67
(214) Found: C, 72.56; H, 4.79

2-Benzoyl-4-methylacetanilide (20):

White plates from methanol, m.p. 120°C, yield 13.2 g (74%).

IR (Nujol, cm^{-1}): 3220, 1660, 1600, 1590, 1540, 1500, 1460, 1440, 1370, 1310, 1290, 1220, 1170, 1150, 1030, 980, 940, 850, 830, 820, 730.

^{1}H-NMR ($CDCl_3$): 2.04 (3H, s, CH_3), 2.24 (3H, s, OCH_3), 7 - 7.80 (8H, m, Ar-H), 8.72 (1H, bs, NH, exchangeable with D_2O).

MS m/e (rel. int. %): 253 (M^+, 53), 235(5), 224(4), 210(62), 193(47), 180(9), 165(15), 152(6), 134(16), 105(68), 77(100), 63(11).

Anal. $C_{16}H_{15}NO_2$: Calc. C, 75.88; H, 5.92; N, 5.53
(253) Found: C, 75.64; H, 6.16; N, 5.67

1-Benzoylnaphthalene (2p):

Crystals from ethanol, m.p. 75°C (lit.[32] m.p. 75-76°C), yield 19.7 g (85%).

IR (nujol, cm^{-1}): 1660, 1600, 1450, 1430, 1370, 1340, 1320, 1290, 1250, 1200, 1170, 1150, 1010, 920, 880, 810, 800, 780.

^{1}H-NMR ($CDCl_3$): 7.24 - 8.28 (12H, m, Ar-H).

MS m/e (rel. int. %): 232 (M^+, 86), 155(91), 127(82), 105(79), 77(100), 51(61), 44(66).

Anal. $C_{17}H_{12}O$: Calc. C, 87.93; H, 5.17
(232) Found: C, 87.68; H, 4.98

2-Benzoylthiophene (2q):

Needles from petroleum ether (b.p. 60-80°C), m.p. 56°C (lit.[33] m.p. 56-57°C), yield 18.4 g (98%).

IR (Nujol, cm^{-1}): 1630, 1600, 1580, 1510, 1450, 1410, 1380, 1360, 1320, 1300, 1250, 1190, 1140, 1080, 1050, 1030, 1010, 990, 950, 940, 900, 860, 810, 720, 700, 650.

^{1}H-NMR ($CDCl_3$): 7.0-7.8 (8H, m, Ar-H and 3,4 & 5-H of thiophene).

MS m/e (rel. int. %): 188 (M^+, 100), 171(15), 160(24), 148(24), 111(85), 105(62), 83(23), 77(64), 51(56), 43(18).

Anal. $C_{11}H_8OS$: Calc. C, 70.21; H, 4.25; S, 17.02
(188) Found: C, 70.26; H, 4.34; S, 16.84

Benzimidazoline-2-one(5-benzoyl) (2r):

Benzimidazoline-2-one was prepared from urea and orthophenylene diamine as reported.[34] It was benzoylated using benzotrichloride to get 5-benzoyl benzimidazoline-2-one.

Plates from methanol, m.p. 303°C, yield 23.3 g (98%).

IR (Nujol, cm^{-1}): 3140, 3040, 1745, 1620, 1440, 1430, 1430, 1360, 1310, 1280, 1190, 960, 860.

^{1}H-NMR (DMSO d_6): 7.0-7.8 (8H, m, Ar-H), 10.86 (1H, s, NH), 11.08 (1H, bs, OH exchangeable with D_2O).

MS m/e (rel. int. %): 238 (M^+, 90), 161(100), 133(27), 105(37), 77(12).

Anal. $C_{14}H_{10}N_2O_2$: Calc. C, 70.58; H, 4.20; N, 11.76
(238) Found: C, 70.62; H, 3.92; N, 11.44

Ethyl-α-(carbethoxy)-β-[(p-benzoyl)anilino] acrylate (2s): Ethyl-α-(carbethoxy)-β-(anilino)acrylate was prepared by reacting aniline with diethylethoxymethylene malonate.[35] This compound was reacted with benzotrichloride as described in the general procedure to yield the product **2s**. Yellow plates from petroleum ether, m.p. 55°C, yield 34.8 g (95%).

IR (Nujol, cm^{-1}): 1730, 1700, 1660, 1620, 1590, 1460, 1420, 1390, 1310, 1250, 1180, 1150, 1090, 1040, 940.

^{1}H-NMR ($CDCl_3$): 1.20 (3H, t, CH_3), 1.36 (3H, t, CH_3 of H-bonded carbethoxy group), 4.2 (2H, q, $\underline{CH_2}$-CH_3), 4.3 (2H, q, $\underline{CH_2}$-CH_3 of H-bonded carbethoxy group), 7.0-7.9 (9H, m, Ar-H), 8.5 (1H, d, $\underline{CH}$, J=15Hz), 11 (1H, d, NH, J=15Hz).

MS m/e (rel. int. %): 367 (M^+, 38), 321 (38), 265(38), 221(14), 172(8), 144(23), 129(10), 116(15), 105(100), 89(9), 77(19).

Anal. $C_{21}H_{21}NO_5$: Calc. C, 68.66; H, 5.72; N, 3.81
(367) Found: C, 68.28; H, 5.92; N, 3.70

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PART-B

A CONVENIENT SYNTHESIS OF 3,4-DIAMINOBENZOPHENONE AND MEBENDAZOLE

INTRODUCTION

A successful methodology for the synthesis of 4-acetamidobenzophenone **1a** and [(4-benzoyl)phenyl]carbamic acid methyl ester **1b** (CHART 1) using benzotrichloride as a benzoylating agent has been described in Part A of this chapter. These compounds are important intermediates in the synthesis of mebendazole[1] **5**, a well-known anthelmintic drug. This part of the chapter briefly outlines important methods practised in the synthesis of **5**. It also describes the preparation of 3,4-diaminobenzophenone **4**. The synthesis of **4** comprises the standardisation of the nitration of **1a** and **1b** to give **2a** and **2b** respectively, with fuming nitric acid, alkaline hydrolysis of **2a** and **2b**, followed by reduction with sodium sulphide to yield the required 3,4-diaminobenzophenone **4**. The three chemical transformations involved have been investigated and the reaction parameters are optimized for realization of 3 and **4** in excellent overall yields. This has culminated in the synthesis of mebendazole **5**.

Of the various anthelmintic agents known, benzimidazole carbamates[1] occupy an important place. Mebendazole, viz methyl [5-benzoylbenzimidazole-2-yl]carbamate, (**5**), in particular, is widely used in the treatment of parasitic infestations. A few drugs belonging to this class have been shown in Table-1 along with their generic names. Owing to its clinical importance and wide application, the synthesis of mebendazole, particularly its method of preparation on a commercial scale, has attracted the attention of the drug industry.

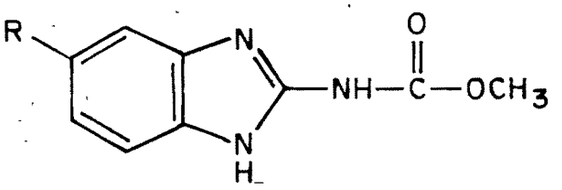
Bulk of the available literature is in the form of patents and there have been a few publications which appear to be more of an academic nature. They have no commercial utility. The patented literature is invariably sketchy, devoid of detailed reaction conditions and yields at the various stages of reactions involved. Nonetheless, a brief survey of the available literature has been provided below and an elegant method for the synthesis of **5** is described. A German patent[2] outlines the synthesis of **5** by the reaction of 3-nitro-4-aminobenzophenone **3** with methoxycarbonyl isothiocyanate (**6**) to give **7** which, when heated gives methyl-7-benzoyl-1H-2,1,4-benzothiazin 3-yl-carbamate, **8**. The compound **8** on treatment with methanolic hydrochloric acid gives **5** in an overall yield of 52% (CHART 2). In a Hungarian patent,[3] calcium cyanamide was treated with methylchloroformate and the resulting product was reacted with 3,4-diaminobenzophenone leading to an improved yield of **5** (CHART 3). Similar approaches with minor modifications have been given in a few British patents[4,5] also.

A Japanese patent[6] utilizes the monosulphate of S-methylated thiourea and condenses the salt with methylchloroformate The resulting ester is then reacted with 3,4-diaminobenzophenone to furnish **5** in 73% yield. The treatment of 3,4-diaminobenzophenone with MeOOC-NHC-(SMe) = N COOMe (condensed product of S-methyl thiourea with 2 molecules of methylchloroformate) is also reported[7] to yield **5**. In a recent report,[8] the reaction of 3,4-diaminobenzophenone with methoxycarbonyl isothiocyanate in

presence of N,N-dicyclohexyl carbodiimide (DCC) as a base afforded **5** in a moderate yield (CHART 4). A synthesis of **5** reported recently,[9] involves diacylation of 2-amino-5-benzoyl benzimidazole **12**, with methylchloroformate and subsequent methanolysis of the diacylated derivative **13**. In addition, the monoacyl derivative **14**, has also been rearranged to **5** (CHART 5). A Spanish patent[10] describes the benzoylation of methyl N-(cyano)-N-(o-nitrophenyl)carbamate **15** and the reductive cyclization of the ensuing product **16** to get the monoacylated **17**. A base-promoted rearrangement of **17** has been shown to yield mebendazole **5** (CHART 6).

TABLE -1

CHEMICAL STRUCTURES OF BENZIMIDAZOLE CARBAMATE ANTHELMINTICS



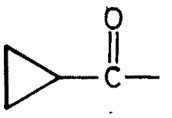
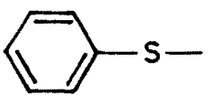
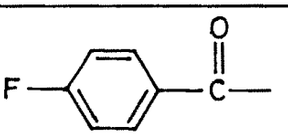
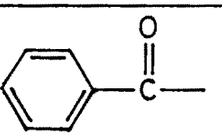
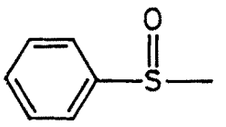
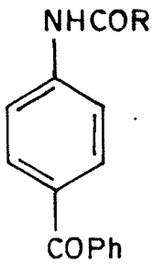
GENERIC NAME	R
ALBENDAZOLE	$CH_3-CH_2-CH_2-S-$
CICLOBENDAZOLE	
FENBENDAZOLE	
FLUBENDAZOLE	
MEBENDAZOLE	
OXFENDAZOLE	
OXIBENDAZOLE	$CH_3-CH_2-CH_2-O-$
PARABENDAZOLE	$CH_3-CH_2-CH_2-CH_2-$

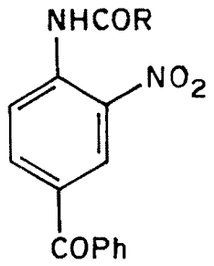
CHART-1



1

1a : R = CH_3

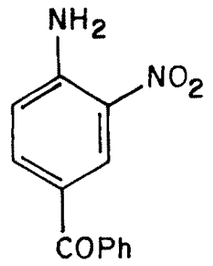
1b : R = OCH_3



2

2a : R = CH_3

2b : R = OCH_3



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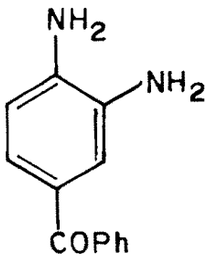

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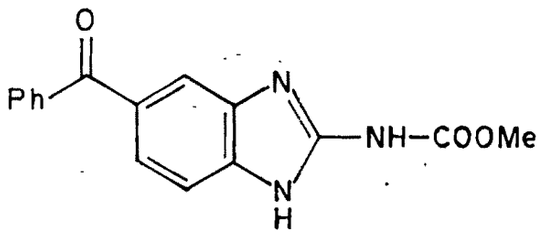
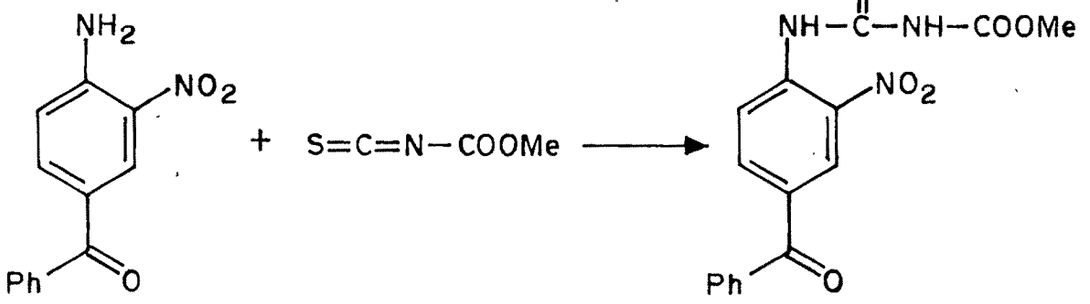
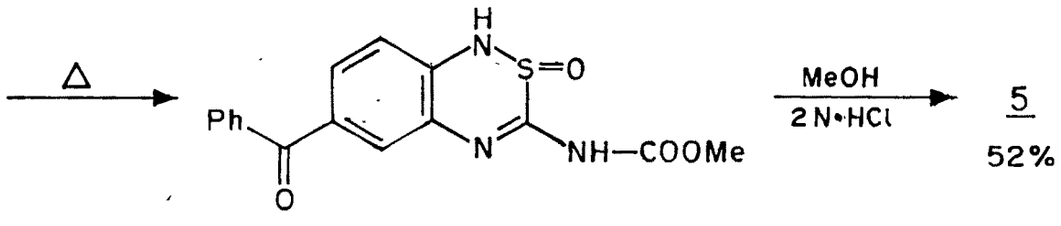


5

CHART-2



3 6 7



8 5

52%

CHART -3

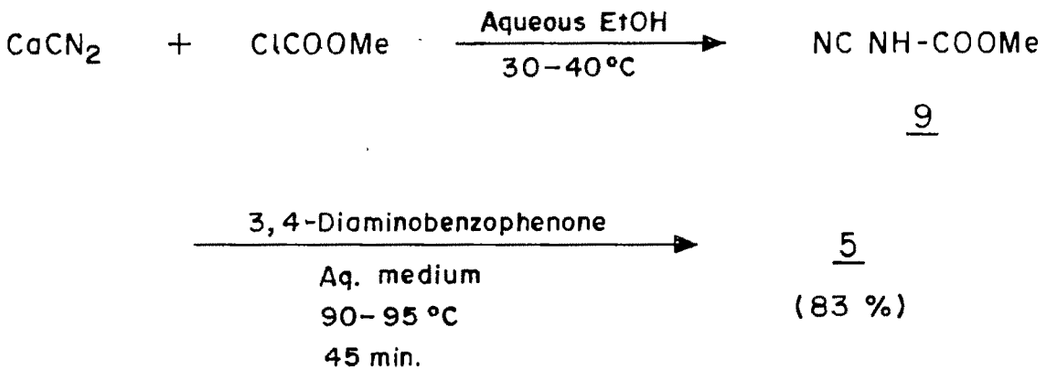
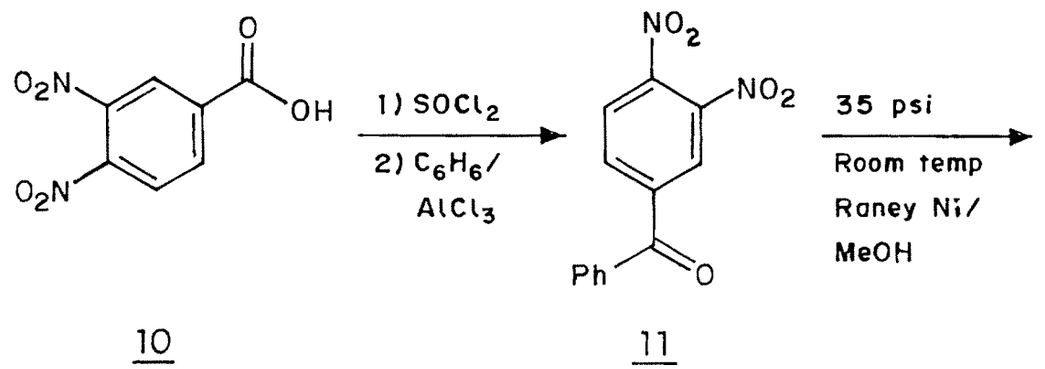


CHART - 4



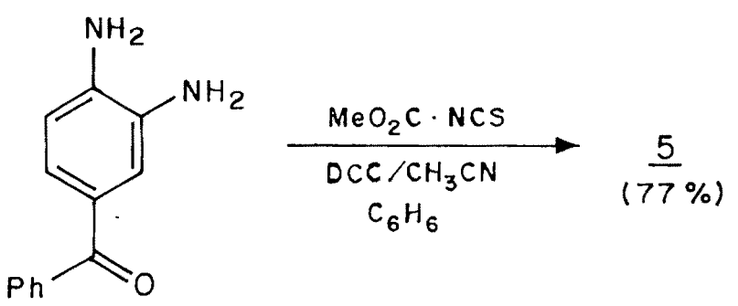


CHART – 5

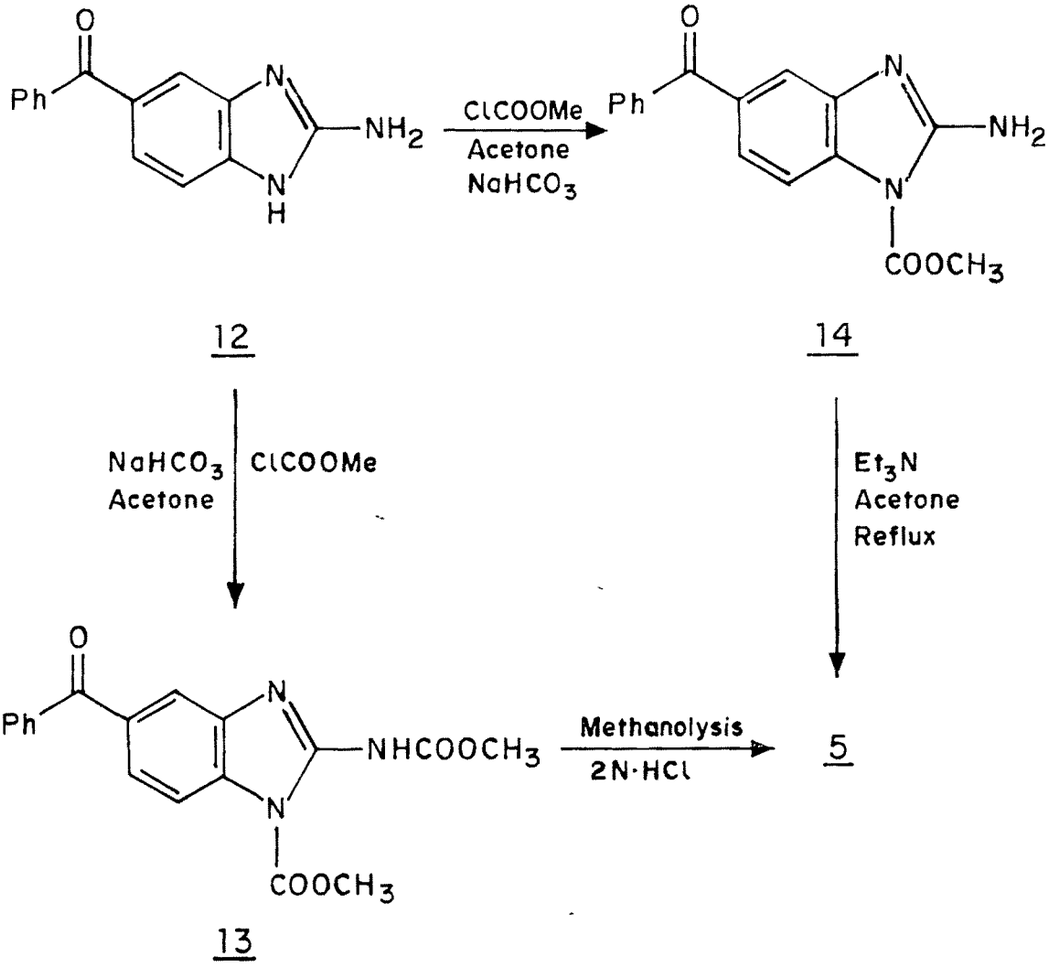
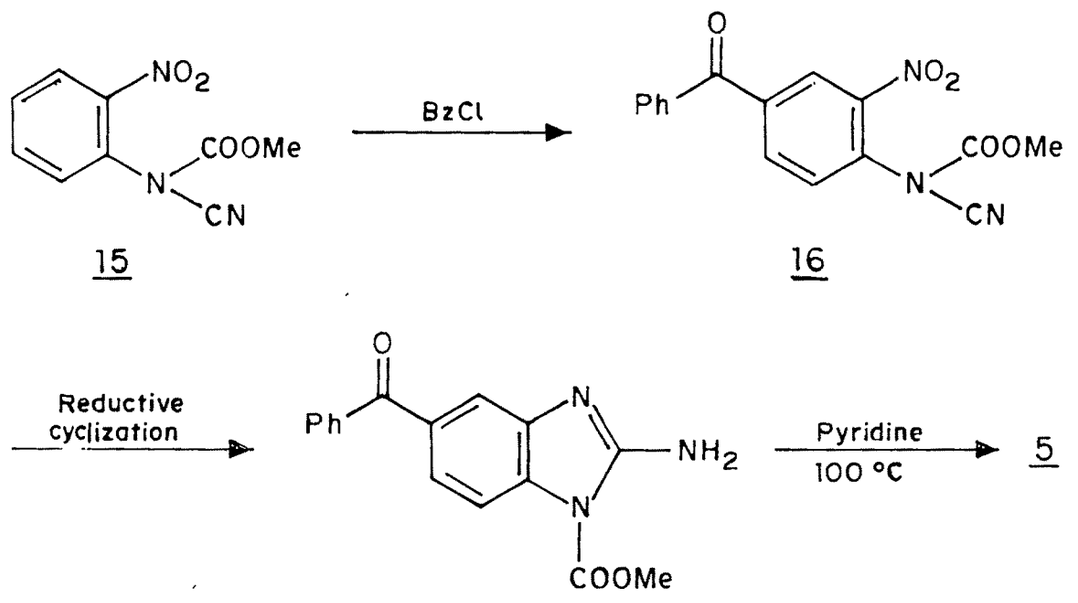


CHART – 6



PRESENT WORK

The preparation of 4-acetamidobenzophenone (**1a**) and [(4-benzoyl)phenyl]carbamic acid methyl ester (**1b**) have already been described in Part A of this chapter. The nitration of **1a**, the hydrolysis of the nitro derivative and finally the reduction of the nitro to amino group have been shown in SCHEME 1. p-Acetamidobenzophenone (**1a**) was conveniently nitrated by fuming nitric acid in acetic anhydride at 0-5°C.[11] By virtue of the meta directing benzoyl group and ortho directing acetamido group present in the molecule, almost quantitative yield of the nitro derivative was obtained. The compound was satisfactorily identified by its spectral data and elemental microanalysis. The IR spectrum exhibited the typical absorption bands at 1510 and 1380 cm^{-1} for the nitro group and two sharp bands at 1640 and 1700 cm^{-1} for the benzoyl carbonyl and acetamido carbonyl groups, respectively. The ^{1}H-NMR spectrum displayed a 3H singlet for the methyl on the carbonyl, a 5H multiplet in the region 7.2-7.8 and separate 1H multiplets centered at 8.0, 8.62 and 8.86 besides showing a broad signal at 10.4 for the NH proton. The mass spectrum displayed the molecular ion peak at m/e 284, base peak at 165 and other prominent peaks at 105 and 77. It is necessary to point out that the spectroscopic analytical data of this compound have not been reported although the compound is known.

The hydrolysis of this nitro derivative **2a** was carried out with alcoholic sodium hydroxide under reflux conditions to obtain an almost quantitative yield of 3-nitro-4-aminobenzophenone.

The spectral data of this product was identical with that obtained earlier (vide infra, Chapter 1).

The transformation of the nitro derivative into 3,4-diaminobenzophenone could be easily accomplished by its treatment with an aqueous solution of sodium sulphide over 8-10 h. The product thus obtained was characterized in the usual manner.

The IR spectrum was conspicuous by the absence of the typical nitro group absorptions and showed the expected NH_2 stretching frequencies as well as the carbonyl stretching frequency. The ^{1}H-NMR spectrum showed a broad 4H signal at 3.4 partially exchangeable with D_2O, and a 6H multiplet in the region 6.76-7.38 and 1H signals at 6.32 and 7.43 for the aromatic protons.

The mass spectrum indicated the facile loss of a phenyl group giving rise to the base peak at m/e 135. The other peaks worthy of mention are at 107 and 91 arising by the subsequent losses of amino groups.

[4-(Benzoyl)phenyl]carbamic acid methyl ester (**1b**) as an alternate starting material for the preparation of 3,4-diaminobenzophenone was checked for its feasibility (SCHEME 2). This involved in the first place the preparation of methyl ester of phenyl carbamic acid, **1b**. This could easily be done by the reaction of aniline with methylchloroformate (vide infra; part A) following a reported procedure.[12] Benzoylation of (**1b**) using benzotrichloride as described in Part A afforded the 4-benzoyl derivative in a good yield. Nitration of this compound

with fuming nitric acid furnished the required **2b** in almost quantitative yield. It may be mentioned here that this compound has not so far been reported in literature and its characterization has been based on the spectral data; the salient spectral features are indicated below.

The IR spectrum displayed characteristic bands at 3340, 1740 and 1660 cm^{-1} for the NH, the ester carbonyl and the benzoyl carbonyl groups respectively; in addition, the nitro group was clearly seen by its typical absorption bands (FIG.1). The ^{1}H-NMR spectrum showed a 3H singlet at 3.88 for the ester methyl group and the aromatic protons were seen in the range 7.4 - 7.88 (6H). Other characteristic signals were a downfield 1H quartet at 8.12 and another 1H doublet at 8.72. As expected, the NH proton appeared as a broad singlet at 10.12 and exchanged with D_2O (FIG. 2).

A prominent molecular ion was noticed at 300 (87%) in its mass spectrum and the loss of the benzoyl cation was clearly seen by the base peak at 105 (FIG. 3).

Alkaline hydrolysis of **2b** readily afforded **3** in good yield. This product was identical in all respects with the one obtained from the hydrolysis of **2a**. The compound **3** on reduction with sodium sulphide led to **4**.

This alternate approach was undertaken with the object of improving the yield of the final product so that it may become commercially important. However, a comparison of the two approaches in terms of the number of operations and the yields

therein revealed that one is as good as the other. Nevertheless, this provides an alternative approach for the synthesis of **4**.

One pot synthesis of mebendazole (5) (SCHEME 3):

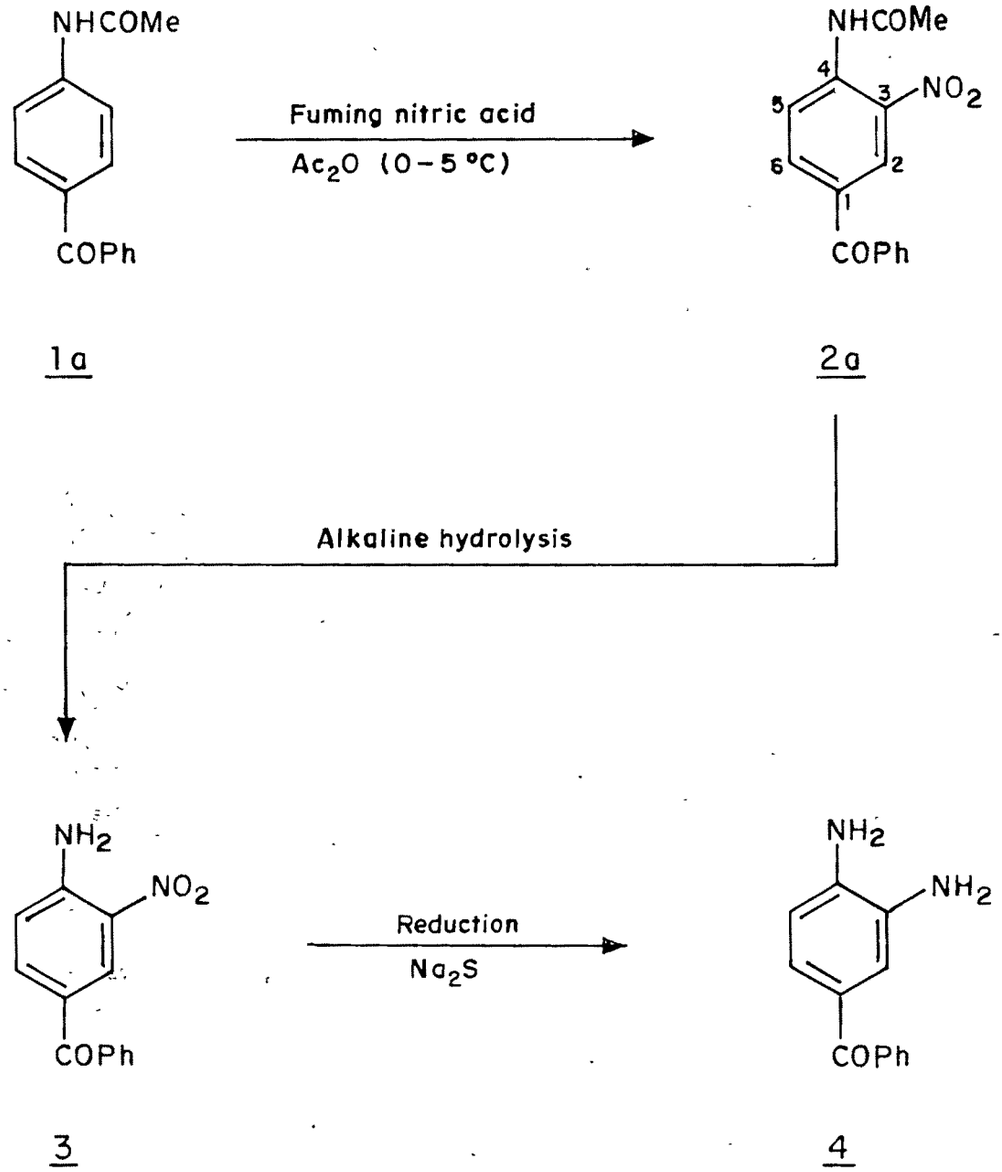
The introduction of this chapter described various methods of synthesis of mebendazole. It may be noted that the synthesis involves separate preparations of the reagents thereby increasing the number of operations. We have standardised a preparative method in which **5** can be obtained in a single pot operation starting from 3,4-diaminobenzophenone.

As indicated in SCHEME 3, the synthesis of mebendazole involves the treatment of 3,4-diaminobenzophenone with the reagent **20** in acidic medium as the key reaction. The reaction of potassium thiocyanate with methylchloroformate readily yielded methoxycarbonylisothiocyanate[13] (**18**). Addition of ammonia followed by S-methylation by dimethylsulphate gave the required reagent **20**. The key reaction carried out as indicated above furnished the target molecule **5** in a very good yield (94%) based on 3,4-diaminobenzophenone). Crystallization from acetic acid offered the product in pure form. The spectral data (experimental) of the product **5** was in conformity with its structure and this assignment was corroborated by comparison of the data with those reported in literature.[8]

Conclusion:

The work presented in this part comprises the preparation of 3,4-diaminobenzophenone from 4-acetamidobenzophenone and [4-benzoyl)phenyl]carbamic acid methyl ester. An important achievement has been the synthesis of mebendazole in one pot operation.

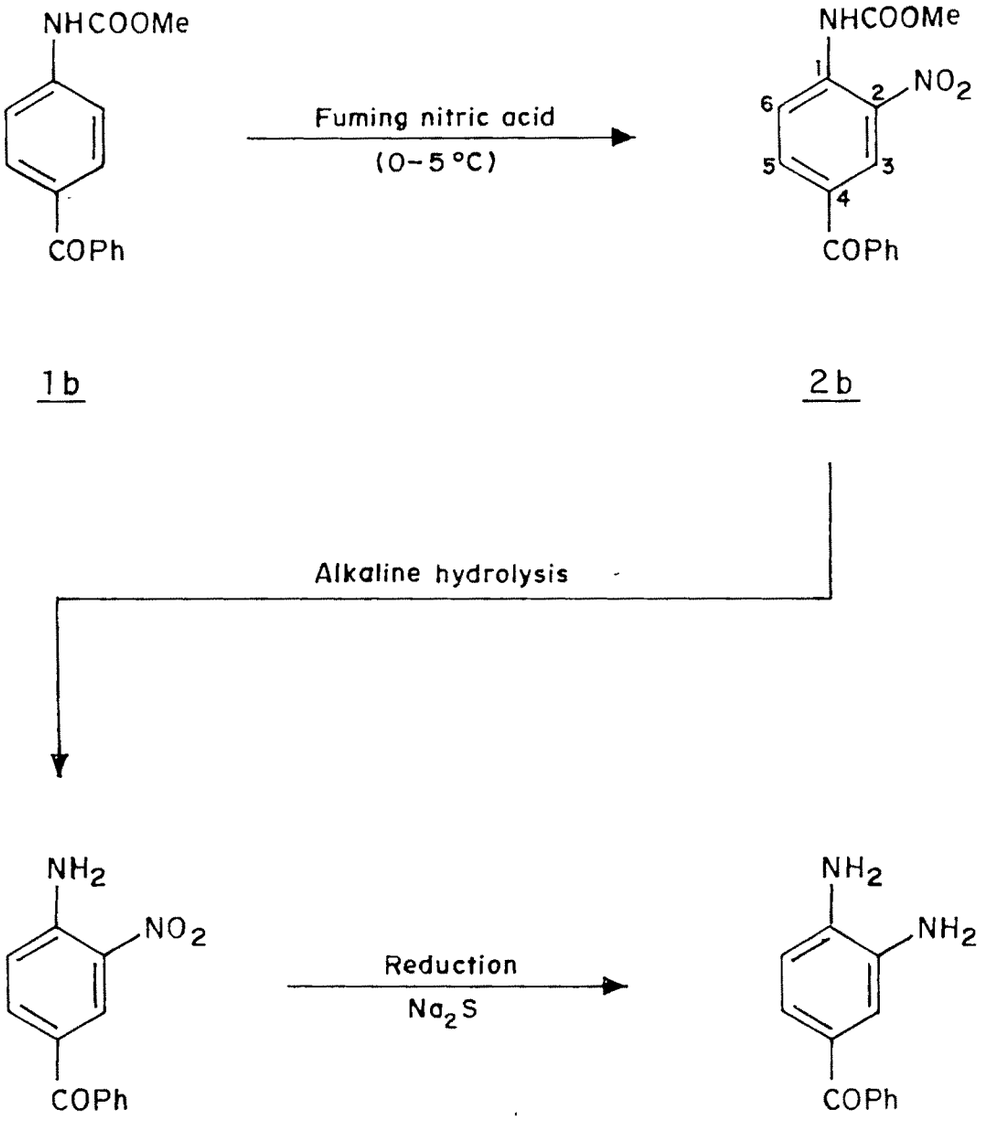
SCHEME – 1



1a 2a

3 4

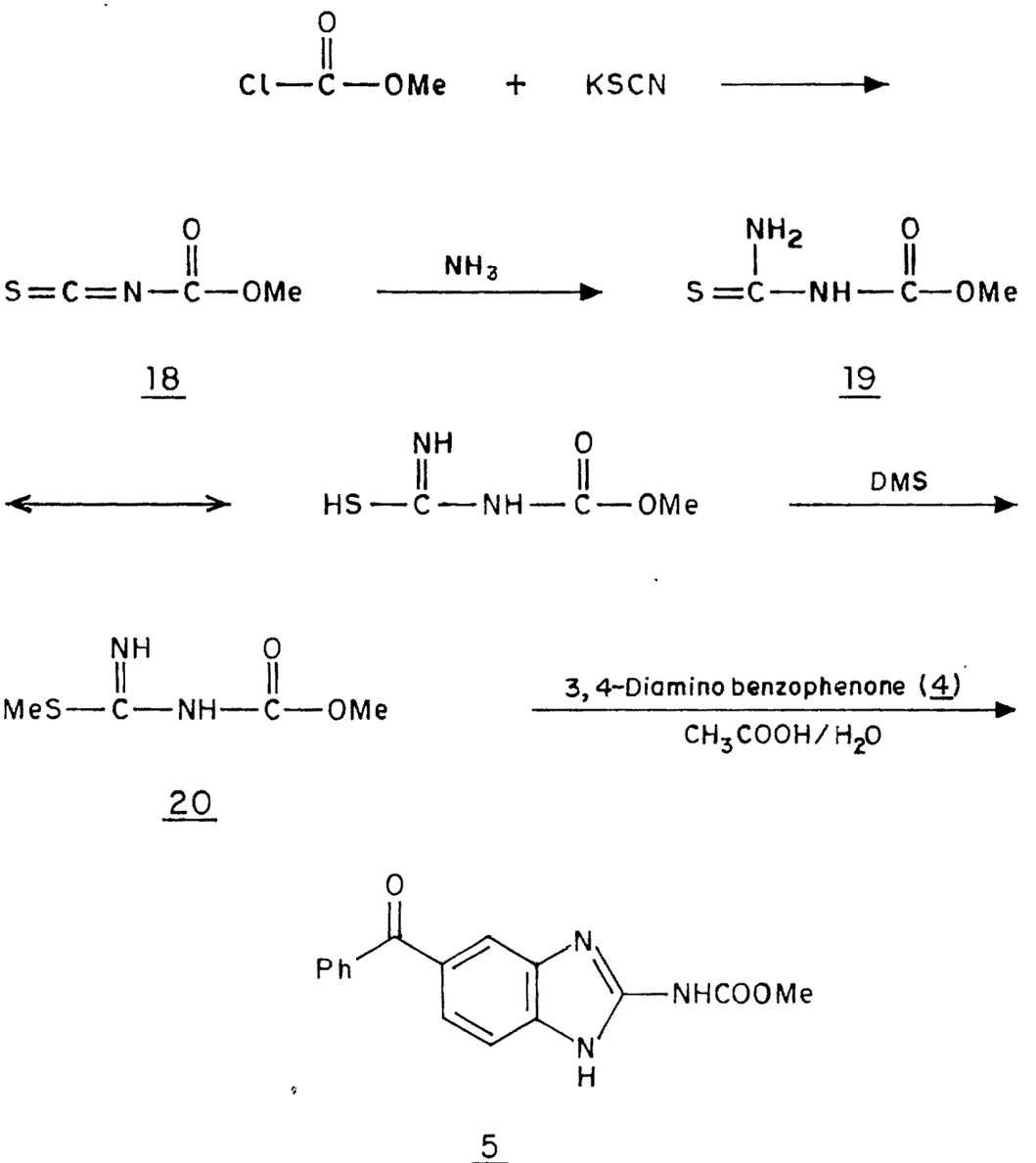
SCHEME – 2



1b 2b

3 4

SCHEME – 3


Cl—C(=O)—OMe + KSCN
S=C=N—C(=O)—OMe
NH3
S=C(NH2)—NH—C(=O)—OMe
18
19
HS—C(=NH)—NH—C(=O)—OMe
DMS
MeS—C(=NH)—NH—C(=O)—OMe
3, 4-Diamino benzophenone (4)
CH3COOH/H2O
20
Ph
NHCOOMe
5

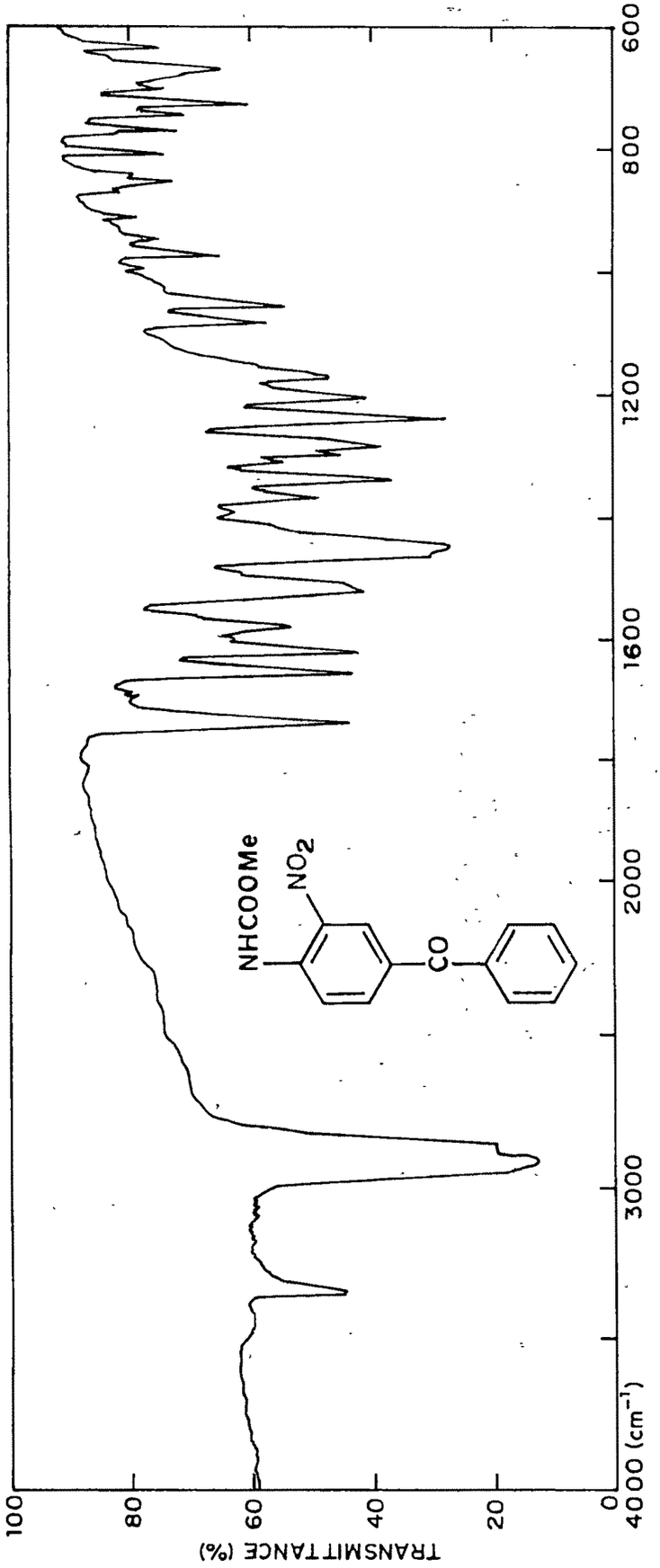

TRANSMITTANCE (%)
100
80
60
40
20
0
4000
3000
2000
1600
1200
800
600
(cm⁻¹)
NHCOOMe
NO2
CO

FIG. 1

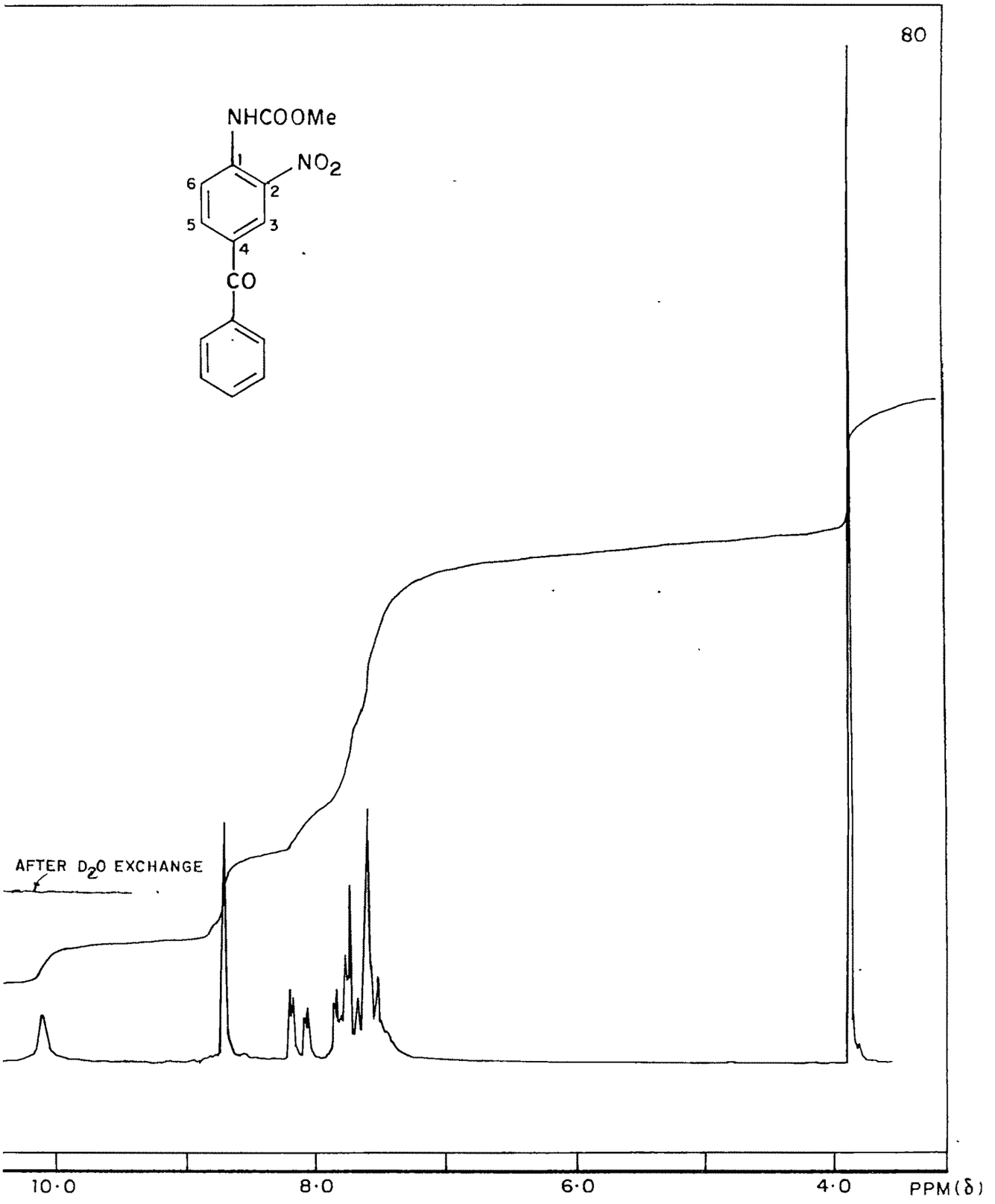


FIG. 2

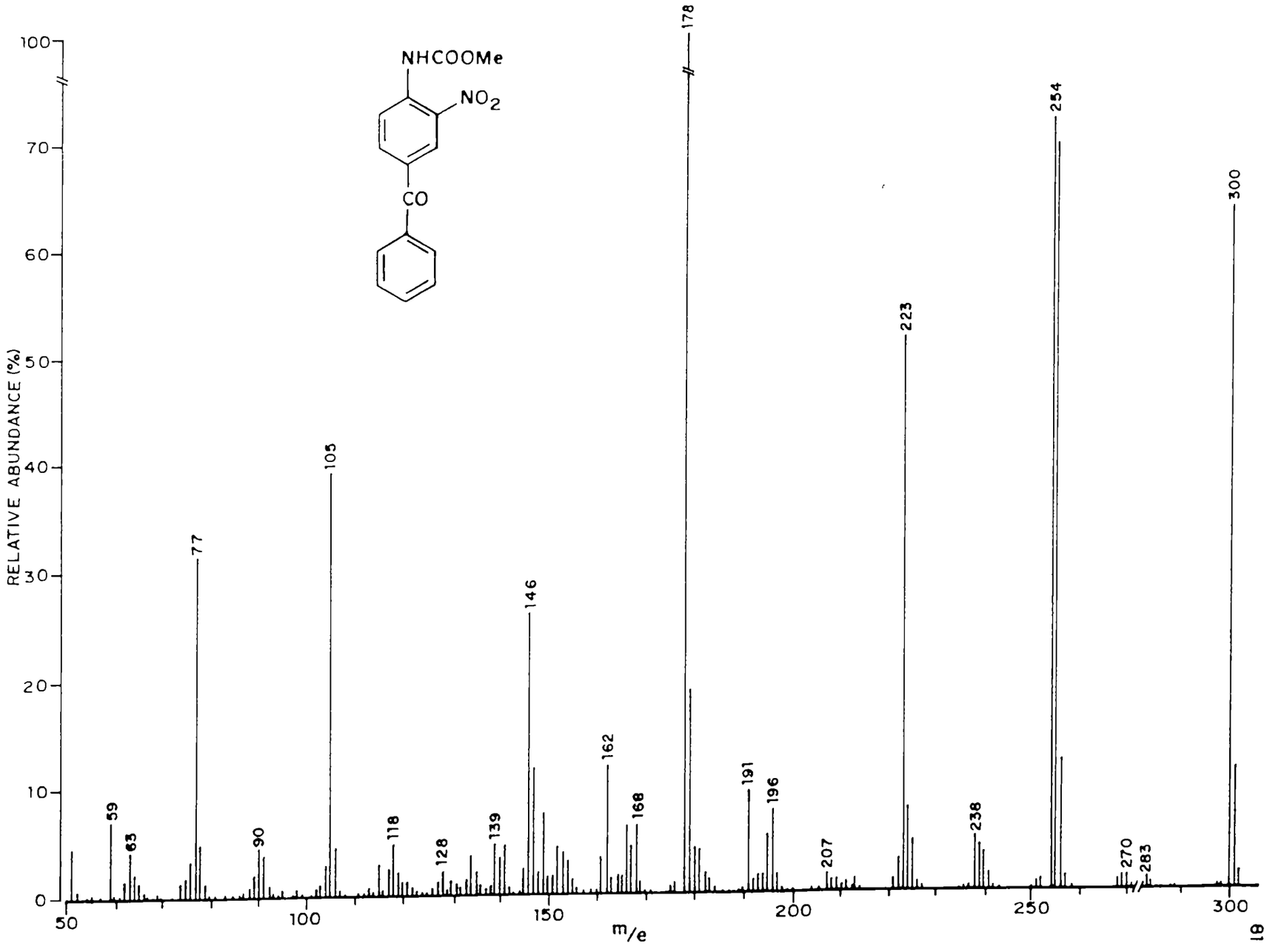

NHCOOMe
NO2
CO
RELATIVE ABUNDANCE (%)
m/e
100
70
60
50
40
30
20
10
0
50
100
150
200
250
300
59
63
77
90
105
118
128
139
146
162
168
178
191
196
207
223
238
254
270
283
300

FIG. 3

EXPERIMENTAL

General Remarks:

Many reactions were carried out to optimize the conditions for different reactions such as nitration, hydrolysis, reduction etc. However, only those reactions with optimized conditions have been included.

Preparation of 4-acetamido-3-nitrobenzophenone (2a) (SCHEME 1):

To an ice-cooled (0-5°C) solution of 4-acetamidobenzophenone (23.9 g, 0.1 mol) in acetic anhydride (51 g) was added fuming nitric acid (9.45 g, 0.15 mol) in a dropwise manner (0.5 h). The temperature was slowly allowed to reach 25°C in 15 min. It was maintained at 25°C for 30 min, poured into ice, filtered to collect the product. Crystallized from methanol in brownish yellow needles, yield 26.9 g (95%), m.p. 144-45°C.

IR (Nujol, cm^{-1}): 1700, 1640, 1605, 1570, 1510, 1440, 1360, 1330, 1280, 1220, 1160, 980, 840, 730, 690.

^{1}H-NMR ($CDCl_3$): 2.33 (3H, s, OCH_3), 7.2-7.8 (5H, m, Ar-H), 7.93-8.11 (1H, dd, 6-H), 8.62 (1H, d, 2-H; J=3Hz), 8.86 (1H, d, 5-H; J=9Hz), 10.4 (1H, bs, NH, exchangeable with D_2O).

MS m/e (rel. int. %): 284 (M^+, 10), 242(59), 165(100), 138(19), 119(16), 105(32), 91(9), 77(42).

Anal. $C_{15}H_{12}N_2O_4$: Calc. C, 63.36; H, 4.22; N, 9.40
(284) Found: C, 63.80; H, 4.64; N, 9.85

Preparation of 3-nitro-4-aminobenzophenone (3):

4-Acetamido-3-nitrobenzophenone (28.4 g, 0.1 mol) was added into 100 ml of 6% methanolic sodium hydroxide solution

containing 5 ml of water under stirring. The reaction mixture was refluxed (3 h) and excess methanol was distilled out. The residue was poured into water and the product that separated out was filtered, crystallized from methanol as yellow needles, yield 22.7 g (94%), m.p. 140°C (lit.[14] m.p. 140°C). The spectral properties of this product have already been described in Chapter 1.

Preparation of 3,4-diaminobenzophenone (4):

Sodium sulphide hexahydrate (60.1 g, 0.25 mol) was dissolved in 250 ml of hot water and was filtered to get a clear solution. 4-Amino-3-nitrobenzophenone 3 (24.2 g, 0.1 mol) in 50 ml water was taken in a 4-necked flask equipped with stirrer, thermometer well, reflux condenser and addition funnel. This was warmed to 85°C and sodium sulphide solution was added in a dropwise manner (4 h). It was refluxed with stirring for 5 more hours and then cooled, diluted with water and the product that separated was filtered to get 3,4-diaminobenzophenone. It was crystallized from a mixture (1:1, v/v) of benzene and pet. ether (b.p. 60-80°C), yield 19.1 g (90%), m.p. 112-14°C.

IR (Nujol, cm^{-1}): 3460, 3380, 3210, 1660, 1610, 1590, 1560, 1450, 1320, 1290, 1160, 1140, 1080, 990, 920, 850, 820, 800, 750, 720, 710.

^{1}H-NMR ($CDCl_3$): 3.40 (4H, bs, NH_2, exchangeable with D_2O); 6.32 (1H, d, 5-H; J=8Hz), 6.76-7.38 (6H, m, Ar-H), 7.43 (1H, d, 2-H, J=3Hz).

MS m/e (rel. int. %): 135 (M^+, 100), 107(27), 91(18), 80(14), 77(21).

Anal. $C_{13}H_{12}N_2O$: Calc. C, 73.58; H, 5.66; N, 13.21
(212) Found: C, 73.90; H, 6.60; N, 13.25

UV/Visible: λ_{max} (MeOH) 253 nm, (ϵ = 13165), 364 nm (ϵ = 9680)

Preparation of [4-(benzoyl)2-nitrophenyl]carbamic acid methyl ester 2b (SCHEME 2):

To an ice-cooled (0-5°C) solution of 4-(benzoyl)phenyl carbamic acid methyl ester (25.59 g, 0.1 mol) in acetic anhydride (51 g) was added furming nitric acid (9.45 g, 0.15 mol) in a dropwise manner (0.5 h). The temperature was slowly allowed to reach 25°C in 15 min. It was maintained at 25°C for 30 min, poured into ice and filtered to collect the product. Crystallization from methanol gave **2b** in yellow needles, 28.8 g (96%), m.p. 300°C.

IR (Nujol, cm^{-1}): 3340, 1740, 1660, 1620, 1580, 1450, 1340, 1280, 1240, 1200, 1170, 1080, 1060, 970, 850, 810, 730.

^{1}H-NMR ($CDCl_3$): 3.88 (3H, s, OCH_3), 7.4-7.88 (6H, m, Ar-H), 8.12 (1H, dd, 5H), 8.72 (1H, d, 3H; J=3Hz), 10.12 (1H, bs, NH, partially exchangeable with D_2O).

MS m/e (rel. int. %): 300 (M^+, 87), 285(5), 269(5), 254(56), 238(35), 223(71), 191(24),179(26), 162(37), 161(39), 105(100), 94(52), 77(62), 63(38), 59(52), 57(52), 44(98), 43(83), 41(55), 40(84).

Anal. $C_{15}H_{12}N_2O_5$: Calc. C, 60.00; H, 4.00; N, 9.33
(300) Found: C, 59.81; H, 4.15; N, 9.10

Alkaline hydrolysis of 2b:

2b (30 g, 0.1 mol) was slowly added into 100 ml of 6% methanolic sodium hydroxide solution containing 5 ml of water under stirring. The reaction mixture was refluxed (3 h) and excess methanol was distilled out. The residue was poured into water when the product **3** separated out. It was filtered and crystallized from methanol in yellow needles, yield 22.7 g (94%), m.p. 140°C (lit.[15] m.p. 140°C).

The spectral data of the product has already been given in Chapter 1.

Preparation of mebendazole 5 (SCHEME 3):

A solution of potassium thiocyanate (10.2 g, 0.11 mol) in ethyl acetate (70 ml) was taken in a four-necked flask equipped with a mechanical stirrer, thermowell, reflux condenser and an addition funnel. To the stirred solution was added methyl chloroformate (8.9 g, 0.094 mol) in about 10 min. After stirring the reaction at 60°C for 1 h, it was cooled to 0-5°C and aqueous ammonia (25%, 7.3 g) was slowly added and stirring continued for 15 min. The residue obtained on removal of ethyl acetate was warmed with dimethyl sulphate (15.1 g, 0.12 mol) and 50 ml of water (30 min). The pH of the solution was brought to 6.0 by the addition of aqueous sodium hydroxide. Afterwards 3,4-diaminobenzophenone (13 g, 0.09 mol) was introduced and the mixture was heated between 85-90°C for 3 h. The product that separated out on cooling was collected by filtration and pressed dry. Crystallization from acetic acid gave **5** as a colourless amorphous product, yield 16.91 g (94%), m.p. 303°C (lit. m.p.>300°C).

IR (Nujol, cm^{-1}): 3360, 1715, 1620, 1580, 1520,1450, 1390, 1250, 1220, 1190, 1080.

^{1}H-NMR (TFA): 4.06 (3H, s, CH_3), 7.4-8.3 (8H, m, Ar-H).

MS m/e (rel. int. %): 295 (M^+, 100), 279(21), 263(56), 237(30), 218(83), 186(87), 160(22), 130(7), 105(12), 77(10).

Anal. $C_{16}H_{13}N_3O_3$: Calc. C, 65.08; H, 4.41; N, 14.23

(295) Found: C, 64.70; H, 4.70; N, 14.14

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CHAPTER-III

EXCEPTIONALLY STABLE PHENYL-DICHLOROCARBENIUM ION AS A FRIEDEL-CRAFTS INTERMEDIATE : A HIGH-FIELD MULTINUCLEAR NMR-STUDY

INTRODUCTION

In the previous chapter the use of benzotrichloride as an efficient Friedel-Crafts reagent for the synthesis of benzophenones has been described. The results prompted us to study the nature of the intermediate species in the reactions. The study is based essentially on multinuclear NMR spectroscopy.

The present chapter describes for the first time, based on a high field multinuclear NMR study, that it is possible to obtain exceptionally stable phenyldichlorocarbenium ion (**10**) (CHART 1) under milder Friedel-Crafts reaction conditions. The phenyldichlorocarbenium ion species (**10**) has been shown to be stable for atleast two weeks at 25°C. Thus, it is not an exaggeration to call it "Off-the-Shelf" carbenium ion. As the investigation pertains to the study of carbenium ion intermediate species such as **10** generated under Friedel-Crafts conditions, it is apt to present in a concise manner, the generation of carbocations, their stabilities, different methods for their detection, and mechanistic aspects of Friedel-Crafts reactions.

I. CARBOCATIONS:

(a) The General Concepts:

Owing to the industrial importance of Friedel-Crafts reactions and the pioneering work of G.A. Olah,[1] the study of carbocations has received tremendous attention. At the outset, a clear distinction has to be made between a carbonium ion and a carbenium ion. The general concept of carbocations encompasses all cations of carbon containing compounds which can be differentiated into two distinct classes: (i) trivalent

or classical carbocations (carbenium ions) and (ii) penta- or tetra-coordinated or non-classical carbocations (carbonium ions (CHART 1, 2a & 2b).

As essential feature of a carbenium ion is the presence of trivalent carbon bearing positive charge and possessing only six valence electrons. In the absence of serious steric problems, the carbenium ion has a planar configuration as shown in 1, arising from the sp^2 hybridization of the carbenium centre. The positive charge could be reasonably associated with the vacant p-orbital perpendicular to the plane of the three substituents. On the other hand, carbonium ions are electron deficient in the sense that they possess insufficient valence electrons to allow their formulation in terms of electron pair bonds alone. Hence, the formation of a two electron three centre bond is the notable necessary feature (CHART 1). Trivalent carbenium ions play a vital role in electrophilic reactions of 'π' and 'n' donors while penta-coordinated carbonium ions are involved in the similar reactions of σ donor saturated systems.

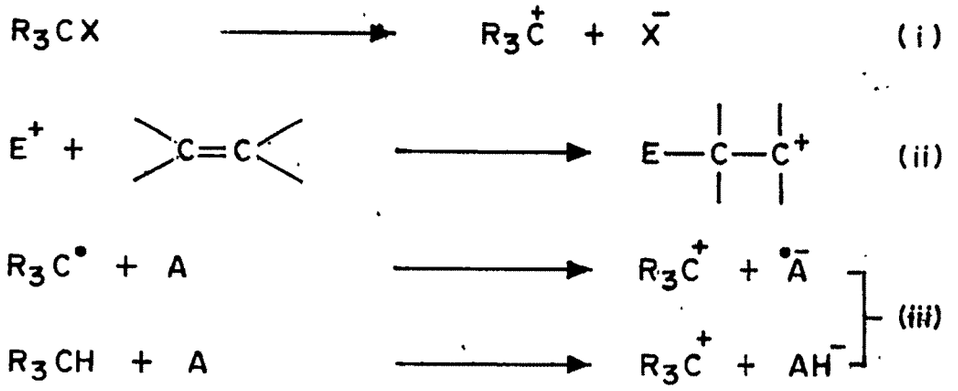
(b) A Brief Historical Perspective of Carbocation Chemistry[2]

The formation of coloured solutions with the dissolution of compounds such as triphenyl carbinol in sulphuric acid and salt-like behaviour of triphenylmethyl chloride in sulphur dioxide led the earlier chemists[3] to lay the foundation of carbocation chemistry. Although the term "carbonium" ion was used to denote the electron deficient ionic carbocations, it was later on modified by Dilthey[4] and subsequently such intermediates were referred to as carbenium ions. With the

advent of methanonium ion (CH_5^+) arising from the reaction of methane with super acids and from mass spectral investigations, the more rational nomenclature of carbenium ion, carbonium ion and carbocation was advocated by Olah. Carbocation chemistry developed rapidly from 1930 onwards and rationalized the different rates of reactions in terms of structures and properties of the transient intermediates and also the proportion and structure of products. With the advent of super acid media,[5] organic chemists got an opportunity to generate carbocations in "stable solutions" which were known to have fleeting existence so far.

(c) Generation of Carbocations:

The most common chemical processes that lead to the generation of carbocations are: (i) the heterolysis of a σ bond, (ii) addition of an electrophile to an unsaturated linkage, (iii) the transfer of hydride ion or an electron from a neutral species and finally (iv) the rearrangement of a carbocation to a more stabilized one. The first three processes are represented by the following equations.



The heterolytic process is generally favoured by polar solvents owing to the stabilization of the resulting ionic charges by solvent molecules.[6,7] Similarly, carbenium ion formation is promoted by those leaving groups which form the most stable anions. An experimentally observed order of leaving groups is ClO_4^- > $CF_3SO_3^-$ > $ArSO_3^-$ > Br^- > Cl^- > $\underline{p}$-NO_2-$C_6H_4CO_2^-$. The best leaving groups are thus the anions of strong acids. In the case of poorer leaving groups such as OH^- (anions derived from much weaker acids), the assistance from Lewis acids makes the heterolysis more favourable. This may be exemplified by the generation of carbocations from alkyl and acyl halides with the use of aluminium chloride BF_3-etherate etc.[8]

(d) Stability and Structure of Carbocations:

Although usually classified as reactive intermediates, carbocations span a wide range of stability, some occurring as indefinitely stable salts while others have lifetimes of a few nanoseconds. In solution these carbocations may either be free or be associated with counter ions, resulting in ion pairs. A stability order of tertiary > secondary > primary has been observed and this has been rationalized by invoking hyperconjugation. Resonance contributions also confer stabilities to carbocations.

(e) Halogenated Carbocations:

As the term implies halogenated carbocations are those ions which carry halogen atoms directly attached to the carbocation centre or as more remote substituents. Substituted

halocarbenium ions are generally stable and have been directly observed by NMR spectroscopy in stable ion conditions. In terms of inductive effect, halogens are electronegative atoms and should destabilize the carbenium ions. However, long-lived stable alkyl halocarbenium ions like $CH_3-C^+(X).CH_3$ have been directly observed by NMR spectroscopy.[11] The high stability of these ions can be accounted for by the back donation from the unshared electron pairs of the halogen into the empty p-orbital of carbenium ion. This is generally referred to as 2p-2p interaction and has been extensively studied by ^{13}C NMR spectroscopy.[9]

The back donation of halogens show an order of F>Cl>Br and this order has been understood in terms of the increasing size of the halogen atoms. Obviously such p-p interaction is more feasible in case of fluorine because of the similar size of the charged carbon (empty p-orbital) and fluorine atoms.

Dimethylfluorocarbenium ion[10] 3a was the first directly observed halocarbenium ion and was obtained by the ionization of 2,2-difluoropropane in SbF_5-SO_2 solution at -60°C. It can also be generated by protonation of 2-fluoropropene with $FSO_3H-SbF_5-SO_2$ at -60°C (CHART 2). Similarly, methyl difluorocarbenium ion 3b and many monocyclic halocarbenium ions 3c could be obtained by the ionization of their corresponding halogenated precursors[9-12] in strong acidic media (FSO_3H-SO_2, SbF_5-SO_2ClF etc.)

at very low temperatures ranging from -60° to -120°C. Similarly, halogenated arylcarbenium ions (3d and 3e) could be directly observed by NMR spectroscopy under comparable conditions at -30° to -80°C[13,14] (CHART 2).

(f) The Study of Carbocations (Methods and Results):

Different techniques have been used to characterize carbocations of different classes. There are theoretical methods,[15] gas phase methods[16] and methods that involve the solid salts. Particularly, the absolute configuration of carbocations can be established by their X-ray crystallography of solid salts. It is found that carbenium ions in general assume a planar configuration while the acyl cations prefer a linear geometry. Various spectroscopic techniques such as infra-red,[17] Raman and X-ray photo-electron spectroscopy[18] have been employed in the study of carbocations. The triphenylcarbenium ion represents not only the first stable carbenium ion to be discovered but also to be studied by X-ray diffraction.[18b]

The single most powerful spectroscopic method for investigating the structures of carbocations in solution is NMR spectroscopy. Although ^{1}H-NMR has been used for a long time, the ^{13}C and ^{19}F NMR have contributed considerably in the investigation of carbocations.[19] For NMR experimental studies, carbenium ion solutions are generally prepared in strongly acidic media such as FSO_3H-SbF_5-SO_2, HF-SbF_5-SO_2ClF and SbF_5-SO_2 at low temperatures to minimize the reactions of the ions and particularly their rearrangements. At the outset, as the NMR behaviour of a compound

is a function of the available electron density around the nucleus, the downfield shift is a clear indication of electron deficiency; chemical shifts, especially of carbon and to a smaller extent internuclear coupling constants are studied to gauge the charge distribution in the ions.

It is also observed[20] that the coupling constant between a ^{13}C nucleus and a directly attached proton is enhanced with the increasing "s" character of the carbon atom. Thus ($^{1}J_{CH}$) for sp^2 carbon is greater than that for sp^3 carbon.

II. FRIEDEL-CRAFTS REACTIONS

The alkylation or acylation of aromatic/aliphatic compounds in the presence of aluminium chloride or other Lewis acid catalysts is called Friedel-Crafts reactions. The alkylating agents may be alkyl halides, olefins or alcohols. The acylating agents can be aliphatic or aromatic acyl halides or anhydrides.

(a) Friedel-Crafts Alkylation:

Among various Friedel-Crafts catalysts aluminium chloride occupies a unique place because of its extensive use. Owing to different intereactions of arene, electrophile and reaction conditions, it is difficult to draw a general order of catalyst reactivity. Nevertheless, the following reactivity order has been observed.[21] Al(III) > Ga(III) > Fe(III) > Sb(V) > Zn(IV) B(III) > Sb(III). Among the reactivity order of halides in alkylhalides, a reactivity order of F > Cl > Br > I has been generally noticed. Similarly, a reactivity order of allyl ≡benzyl > tertiary alkyl > secondary alkyl > primary alkyl has also been noticed.

It is clear that carbenium ions are involved in the majority of Friedel-Crafts reactions.[22] The borontrifluoride-catalysed reaction of benzene with [2-^{14}C] ethyl fluoride results in scrambling of the label in the ethylbenzene when the reaction is carried out in non-polar solvents. These results were taken to indicate the intermediacy of carbenium ions.[23] With primary alkylating agents, entirely free carbenium ions do not appear to be involved. The ion may then exist as a dipolar complex or as a tight ion pair (CHART 3).

Although the mechanistic picture of Friedel-Crafts alkylation may be quite complex, two extreme mechanisms that might be operating are shown in CHART 3. The first one involves the generation of a carbocation by the reaction of aluminium chloride on the alkyl halide followed by an electrophilic attack on the aromatic substrate. The second mechanism implicates a separate complexation of the catalyst with the alkyl halide followed by different steps indicated in CHART 3.

(b) Friedel-Crafts Acylation:

Friedel-Crafts acylations constitute a general methodology for the synthesis of aryl ketones. This type of reaction is applicable to a wide variety of aromatics. Since the reaction involves nucleophilic attack by the aromatic system on the carbonyl carbon, enhancement of electrophilicity of the carbonyl carbon is the main role of the catalyst. The use of Lewis acids leads to the formation of acylium ions or their equivalents. Normally,[24] very strong acids are the best (e.g. CF_3-SO_3H, $AlCl_3$)

and with their use acylating species is rapidly formed which react with the aromatic ring in a rate determining step, presumably via a σ complex.

Exact details of the mechanism have been the subject of much discussion,[25,26] particularly on the nature of the acylating species. Stable acylium (oxo-carbenium) hexafluoroantimonate salts have been isolated. Their crystal structure shows a linear $R - C^{+} = O$ grouping.[27] These salts are very powerful acylating agents.[28] Complexes of aluminium chloride and benzoyl chloride, however, have also been examined by crystallographic methods and coordination was shown to be between the aluminium and oxygen rather than involving chlorine.[29] It is likely that the acylating species varies from case to case. They are likely to be one of the species formulated in CHART 3.

(c) Donor-Acceptor Interactions in Friedel-Crafts Systems:

The concept of donor-acceptor interactions has been extremely useful in rationalizing organic reaction mechanisms. This is particularly true in Friedel-Crafts reactions. Such interactions are illustrated by the formation of complexes of Lewis acids with both the alkyl and acyl halides and the aromatic substrates; complexes thus formed are known to possess varied stabilities.

$$R - X + AlCl_3 \longrightarrow R - X \ldots AlCl_3$$

$$R - \overset{O}{\overset{\|}{C}} - X + AlCl_3 \longrightarrow RCOX \ldots AlCl_3$$

The complex formation leads to the weakening of the C-X bond and in quite a few cases ionization occurs as indicated below.[30]

$$CH_3COF + SbF_5 \rightarrow CH_3CO^+SbF_6^-$$

Aluminium chloride and bromide which generally are used as Friedel-Crafts catalysts are known to exist in monomeric or dimeric form predominantly, depending upon the nature of the solvent. Both the entities complex with a donor molecule (D). The dimer does it so after opening one of the halogen bridges (CHART 4). The predominance of a particular type of complex is governed by the chemical nature of the donor and acceptor, solvent, temperature and free energies of complex formation. Since complex formation consists of Lewis acid Lewis base interaction, relative complex stabilities of various acceptors with a given donor are proportional to the basicity of donor. Complex formation between a catalyst and a product, may in certain cases, provide the driving force of an otherwise thermodynamically unfavourable reaction.

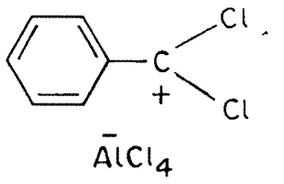
There are two types of complexation of aromatic compounds with either the reagent or the catalyst. The first type involves the entire sextet acting as an electron donor. A complex thus obtained is known as a π complex. The other type involves the complexation between the acceptor molecule and a particular carbon atom of the aromatic system through a σ bond (CHART 4).

Perrier reported[31] the formation of a complex $C_6H_5COCl---AlCl_3$ in carbon disulphide as colourless needles. Reaction of the complex with an aromatic hydrocarbon resulted in the formation of a crystalline complex of aluminium chloride with the resulting ketone (4a) (CHART 4).

Infra red spectrum of benzoyl chloride - $AlCl_3$ complex showed a lowering of the frequency of the free carbonyl group at 1783 cm^{-1} when compared to that of free benzoyl chloride. This indicates that the Lewis acid interacts with the carbonyl group as shown in **4b**[25] (CHART 4).

After having considered the general concept of carbocations essential for the understanding of the mechanistic aspects of Friedel-Crafts reactions, our work regarding direct observation of a highly stable, long-lived carbocation **10** under Friedel-Crafts conditions at ambient temperature is discussed in the following section.

CHART-1

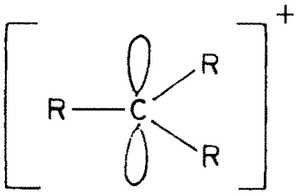


10

CARBOCATION

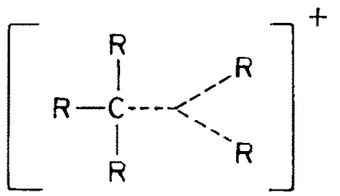
CARBENIUM IONS — TRIVALENT — "CLASSICAL"

CARBONIUM IONS — PENTA OR TETRA-COORDINATED — "NONCLASSICAL"



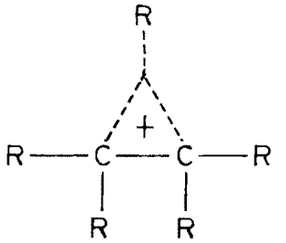
1

R = H or ALKYL



PENTA-COORDINATED

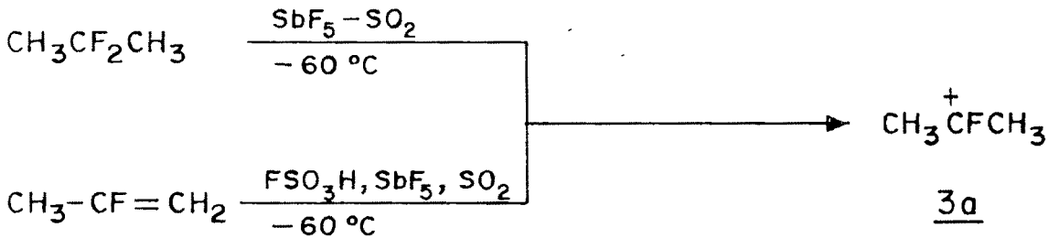
2a

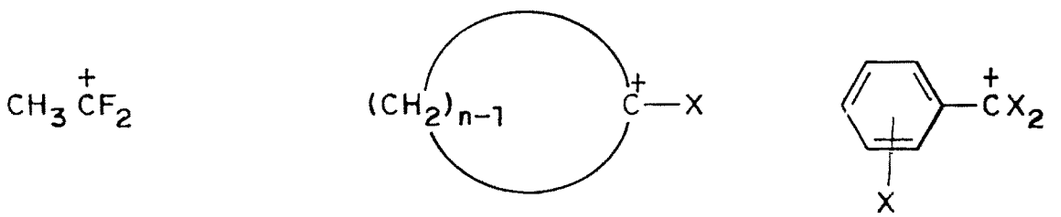


TETRA-COORDINATED

2b

CHART-2


CH3CF2CH3
SbF5 – SO2
– 60 °C
CH3–CF=CH2
FSO3H, SbF5, SO2
– 60 °C
CH3CFCH3
3a
+ SbF5X⁻
(X = F or FSO3H)


CH3CF2
(CH2)n–1
C—X
CX2
X
3b
3c
3d
X = F, Cl, Br

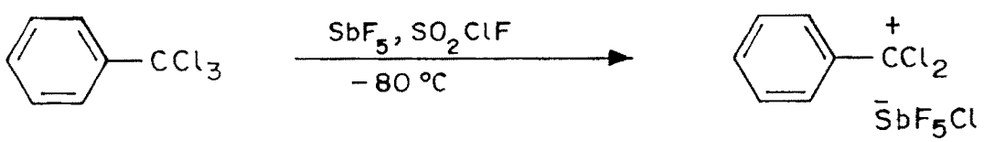
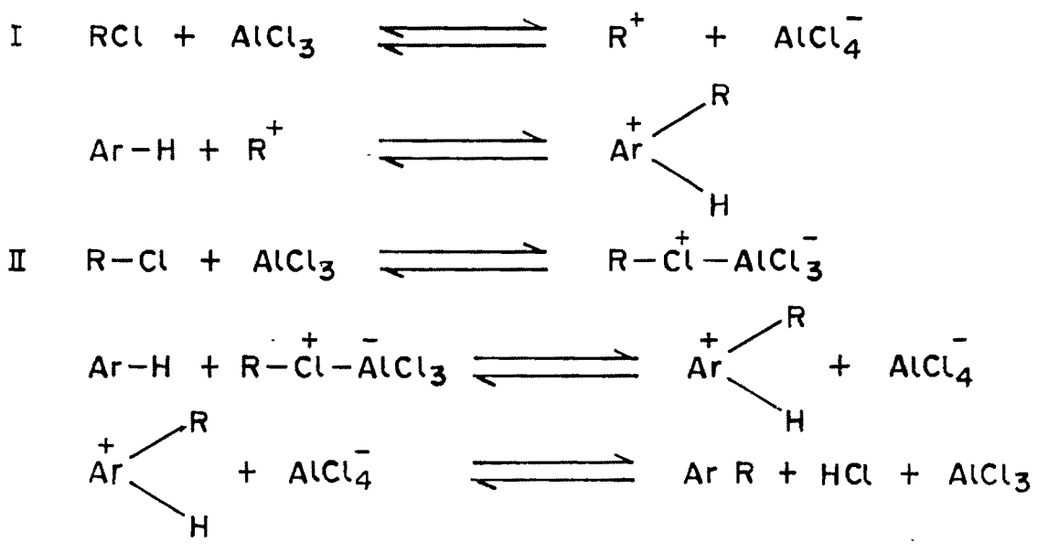
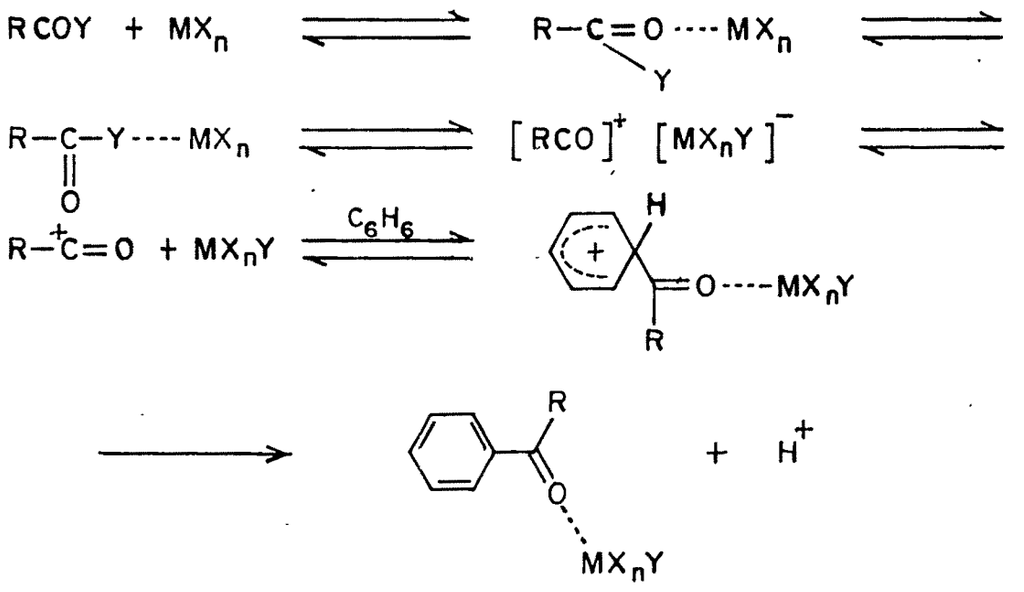

CCl3
SbF5, SO2ClF
– 80 °C
CCl2
SbF5Cl
3e

CHART-3

MECHANISM OF ALKYLATION :



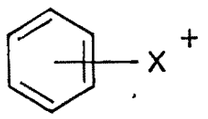
MECHANISM OF ACYLATION :



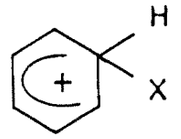
M = Al, Zn, B, Sn etc.

X = Halogen

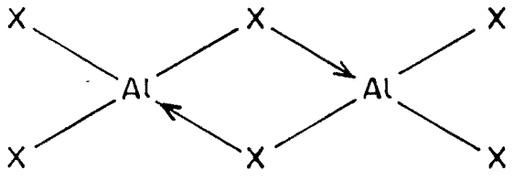
CHART–4



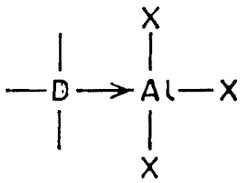
π – complex



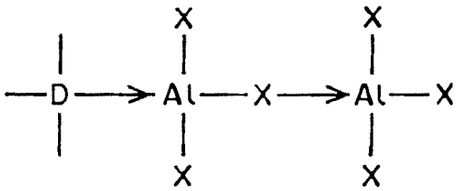
σ – complex



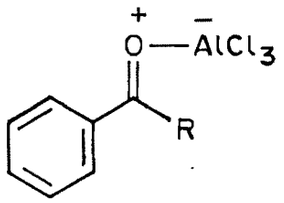
Dimer



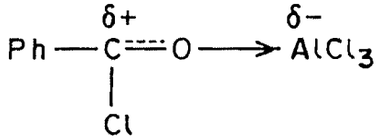
Complex



Dimer complex



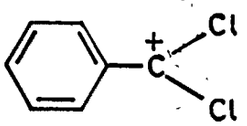
4a



4b

PRESENT WORK

Halogenated carbocations play an important role as intermediates in a variety of organic reactions such as the electrophilic addition to halo olefins,[32] electrophilic substitutions of halo aromatics[33] and the hydrolysis of gem-dihalides.[34] Although halogenated aryl carbenium ions are assumed to be the reaction intermediates in many industrially valuable Friedel-Crafts reactions,[35,36] their existence has never been confirmed. Thus, nothing is known regarding the stability of halogenated aryl carbenium ions in common organic solvents at ambient temperature. We report herein for the first time, the intermediacy of an exceptionally stable phenyldichlorocarbenium tetrachloroaluminate complex (**10**) involved in Friedel-Crafts

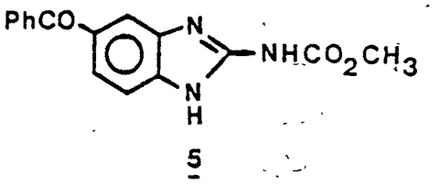


$\bar{A}lCl_4$

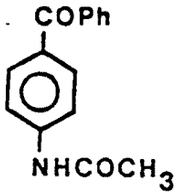
10

reaction of acetanilide with benzotrichloride and aluminium chloride in ethylene dichloride at 25°C and its characterization by high field ^{1}H, ^{13}C and ^{27}Al NMR spectroscopy.

Methyl(5-benzoylbenzimidazol-2-yl) carbamate, known as mebendazole, (**5**) is an important broad spectrum human and veterinary anthelmintic drug (Chapter 2, Part B). During our research on potential anthelmintic drugs which are structural analogues of mebendazole, we required 4-acetamidobenzophenone (**6**).



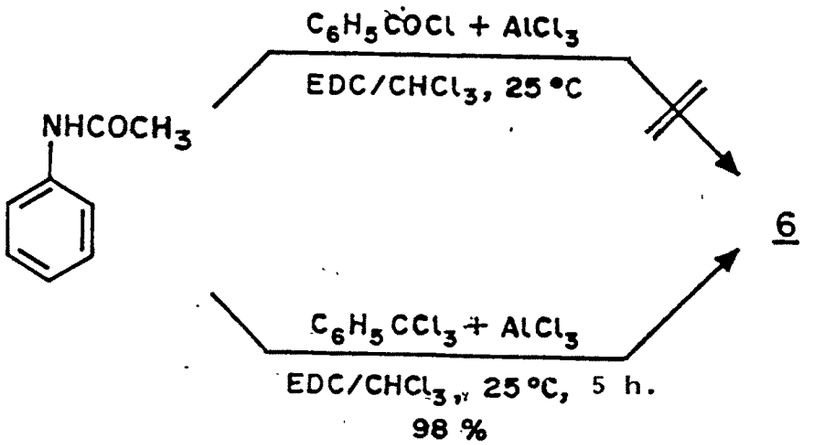
5



6

In this regard, we made an interesting observation that while acylation of acetanilide with benzoyl chloride and aluminium chloride (3 eqv) in ethylene dichloride at 25°C fails, the reaction of acetanilide with benzotrichloride and aluminium chloride (3 eqv.) followed by hydrolysis affords 4-acetamido-benzophenone (6) (Chapter 2, Part A) in a quantitative manner (SCHEME 1). Intrigued, we systematically examined the reaction

SCHEME-1



intermediates obtained in each case (before the addition of acetanilide) by high field NMR spectroscopy. Our object was to understand why the benzotrichloride-aluminium chloride system is far more reactive than the benzoyl chloride-aluminium chloride combination.

Results and Discussion:

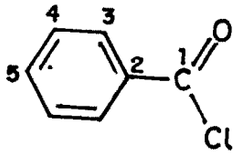
It has been widely accepted and experimentally proved that to obtain a stable complex under Friedel-Crafts conditions, excess of Lewis acid is required.[37,38] Hence, initially we concentrated mainly on the characterization of species present in the complex of benzoyl chloride and benzotrichloride with three equivalents of aluminium chloride. Though the reaction of these organic reagents were carried out either in ethylene dichloride (EDC) or chloroform, for the ease of detection of the proton NMR signals, the complexes were characterized in deutero-chloroform.

In FIG.1, the ^{1}H-NMR spectrum of the complex of benzoyl chloride with thrice the stoichiometric equivalent of aluminium chloride in deutero chloroform is presented along with that of benzoyl chloride alone in the same solvent. The observed changes in the chemical shifts after the complex formation appear to be quite evident. The meta, para and ortho protons of the complex are deshielded by 0.25, 0.45 and 0.32 ppm respectively. These changes indeed implied the decrease of π-electron density from the aromatic ring or in other words, these changes indicated the acquisition of positive charge by the carbonyl carbon of the complex and delocalization of the π-electron charge from the phenyl ring by mesomeric interaction.

It is of great importance to us, in the present context, to have an in depth knowledge about the nature of species present in solution for the benzotrichloride-aluminium chloride case. The proton NMR spectrum obtained for the benzotrichloride-

aluminium chloride complex is compared with that of benzotrichloride alone in FIG. 2. The ^{1}H chemical shifts obtained (Table 1) shows that the ortho, meta and para protons of this particular complex are deshielded to a greater extent (2.5 to 3 times) than in the case of benzoyl chloride-aluminium chloride complex. When compared with benzotrichloride, the meta, para and ortho protons of its complex with aluminium chloride showed a deshielding of 0.60, 1.3 and 0.94 respectively. The magnitudes of the aromatic proton chemical shifts (Table 1) are themselves sufficient to show that the nature of the complex formed in this case is entirely different from what is obtained in the case of benzoyl chloride-aluminium chloride complex. This result also clearly suggests that the carbon atom containing the ionizable chlorine atoms of the complex has a significantly higher degree of "carbocation character" compared to the carbonyl carbon of the complex of benzoyl chloride. Incidentally, the chemical shifts observed for the benzotrichloride-aluminium chloride complex are almost similar to what is reported by Olah[12] at very low temperatures in stable ion conditions as phenyl dichlorocarbenium ion (3e) (CHART 2). This clearly demonstrates the existence of a fully developed carbenium ion under Friedel-Crafts conditions for benzotrichloride - alumnium chloride system. It is for the first time that the generation and observation of carbocation of this class is made under conditions of Friedel-Crafts reaction at ambient temperature using aluminium chloride. The benzoyl chloride-aluminium chloride complex is more like a donor-acceptor complex (8).

The difference in the character of the complex **8** and **10** is even more remarkably observed in the ^{13}C-NMR spectra. The ^{13}C-NMR spectra of the compounds **7-10** could be recorded both in ethylene dichloride and $CDCl_3$. As can be seen from Table 1, the differences in carbon chemical shifts observed in going from $CDCl_3$ (top row of chemical shifts) to ethylene dichloride (bottom row of chemical shifts) for any given compound are insignificant. Clearly there is no solvent effect (FIG.3). For the sake of consistency, the ^{13}C-NMR spectral data in $CDCl_3$ only will be used for the discussion. The ^{13}C-NMR spectrum of benzoyl chloride (7) shows five peaks at δ 128.80, 131.20, 133.22, 135.12 and 168.07 ppm corresponding to the carbon atoms C-4, C-3, C-2, C-5 and C-1 respectively (the numbering is as shown),



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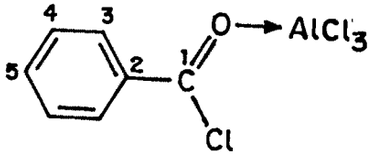
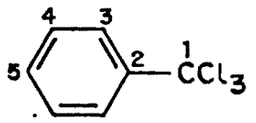


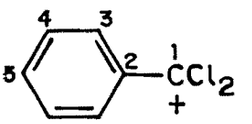
8

while the benzoyl chloride-aluminium chloride complex (8) shows five peaks at δ 130.53, 130.74, 135.71, 143.73 and 192.05 ppm corresponding to the carbon atoms C-2, C-4, C-3, C-5 and C-1 respectively (FIG. 4). The two important features in the above ^{13}C-NMR spectral data are that the carbonyl carbon C-1 of the benzoyl chloride-aluminium chloride complex (8) is deshielded, while the quaternary carbon C-2 of the complex is shielded. The difference in ^{13}C chemical shift values are: $\Delta\delta^{7,8}(C_1)$=23.98ppm, $\Delta\delta^{7,8}(C_2)$= -2.69ppm, $\Delta\delta^{7,8}(C_3)$=4.51ppm, $\Delta\delta^{7,8}(C_4)$=1.94ppm

and $\Delta\delta^{7,8}(C_5)$=8.61ppm (FIG.6). The ^{13}C-NMR spectrum of benzotrichloride (**9**) shows five peaks at δ 97.55, 125.29, 128.14, 130.09 and 144.10 ppm corresponding to the carbon atoms C-1, C-4, C-3, C-5 and C-2 respectively, while the ^{13}C spectrum of benzotrichloride-aluminium chloride complex (**10**) shows five new peaks[18] at δ 134.11, 140.53, 144.08, 160.0 and 209.76 ppm corresponding



9



$\bar{A}lCl_4$

10

to the carbon atoms C-4, C-2, C-3, C-5 and C-1 respectively (FIG. 5). The most remarkable feature in the ^{13}C spectral data of the complex **10** is the enormous deshielding (112.21 ppm) experienced by the carbon atom C-1, which strongly supports the proposed carbocation structure. Furthermore, it was observed that the ^{13}C spectrum of the complex **10** did not undergo any change (FIG. 5) even after two weeks at 25°C, demonstrating its exceptionally high stability. The complete list of differences in the ^{13}C chemical shift values is as follows: $\Delta\delta^{9,10}$ (C_1) = 112.21 ppm, $\Delta\delta^{9,10}$ (C_2) = -3.57 ppm, $\Delta\delta^{9,10}$ (C_3) = 15.94 ppm, $\Delta\delta^{9,10}$ (C_4) = 8.82 ppm and $\Delta\delta^{9,10}$ (C_5) = 29.91 ppm. A comparison of the differences in the ^{13}C chemical shift values, $\Delta\delta^{9,10}$ (C_n, n = 1-5) with that of $\Delta\delta^{7,8}$ (C_n, n = 1-5) clearly demonstrates the much higher degree of the positive charge associated with the carbocation center C-1 in the complex **10** as compared to that of the complex **8**.

Just like the ^{13}C spectra, the ^{27}Al spectra recorded for the complexes **8** and **10** (Table 1) in either ethylene dichloride or $CDCl_3$ showed no solvent effect. More importantly, the ^{27}Al chemical shift of the benzoyl chloride-aluminium chloride complex (**8**) viz., 98 ppm,(FIG.7) is less shielded compared to the ^{27}Al chemical shift of phenyldichlorocarbenium tetrachloroaluminate complex (**10**) viz., 92 ppm (FIG. 8) in additional support of the donor-acceptor type structure[39] for the complex **8** and the carbenium ion structure for the complex **10**.

It has been already mentioned that three molar excess of aluminium chloride is required for the Friedel-Crafts reactions to proceed smoothly. We have systematically carried out ^{13}C-NMR measurements of the 1:1 $AlCl_3$ complex, for both benzoyl chloride and benzotrichloride. The spectra obtained for benzotrichloride at different intervals of time are given in FIG.9 along with benzotrichloride and its complex with 3 equivalents of $AlCl_3$.

These spectra already show the unstable nature of the species formed. The nature of the spectra changes with time. It can also be noted that in the 1:1 complex of benzotrichloride-aluminium chloride, unlike in the case of 1:3 complex (FIG.9), a carbenium ion is not formed at all as no signals could be detected at the expected positions. In FIG. 10, the ^{13}C-NMR spectra obtained for the 1:1 complex of benzoyl chloride and $AlCl_3$ at two time intervals are presented. For comparison, the spectra obtained for 1:3 complex and benzoyl chloride are also given. It has been observed that the 1:1 complex does not change very much with time. It is also important to note that

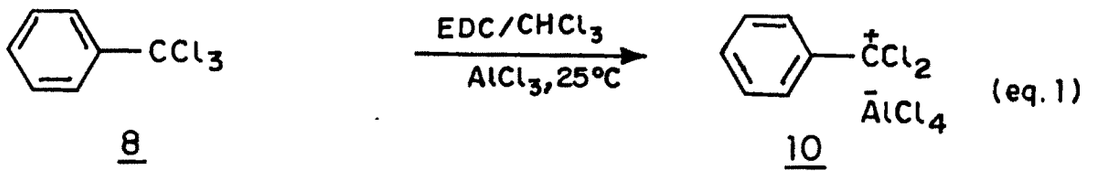
the chemical shift observed for the carbonyl carbon of 1:1 complex (δ 184.2 ppm) is different from what is observed for the 1:3 complex (δ 191.2 ppm). This seems to indicate localization of more positive charge on the carbonyl carbon of the 1:3 complex. This indeed demonstrates that 3 equivalents of $AlCl_3$ is a minimum requirement for the formation of a stable carbenium ion or a stable donor-acceptor complex.

In a nutshell, the ^{1}H , ^{13}C and ^{27}Al-NMR data unequivocally show that the nature of complex formed by benzoyl chloride and benzotrichloride with three equivalents of $AlCl_3$ are not the same. It is clear that the carbon atom C-1 of the phenyldichlorocarbenium tetrachloroaluminate complex (**10**) possesses a remarkably high degree of positive charge compared to the carbonyl carbon C-1 of the benzoyl chloride-aluminium chloride complex (**8**). The complex (**8**) is more like a donor-acceptor complex while the complex (**10**) is a carbenium ion. This in turn provides an unambiguous answer to the question of reactivity of these complexes with acetanilide. The NMR evidence clearly points out the intermediacy of **10** in the Friedel-Crafts reaction of acetanilide with benzotrichloride and aluminium chloride in ethylene dichloride at 25°C.

The present work reports for the first time ^{1}H, ^{13}C, and ^{27}Al-NMR spectral data for benzoyl chloride-aluminium chloride complex **8**. Previously the structure of this particular complex was investigated by IR spectroscopy[40] and X-ray analysis.[29,41]

While it is known that the carbenium ion **3e** (CHART 2) could be observed in strongly acidic media such as SbF_5-SO_2ClF

at -80°C, the present study demonstrates for the first time, that it is also possible to obtain stable aryldihalocarbenium ions such as **10** under milder Friedel-Crafts reaction conditions in ethylene dichloride at 25°C. However, the fact that **3e** (CHART 2) could be observed at -80°C in strongly acidic media such as SbF_5-SO_2ClF does not guarantee the existence of such ions as **10** in common organic solvents such as ethylene dichloride (EDC) or chloroform at 25°C (eqn. 1), or that such ions can be exceptionally stable (stable for 2 weeks at 25°C) or even that such ions are amenable to NMR investigations in an unusual solvent like ethylene dichloride.



8 **10** (eq. 1)

Thus, there is an enormous difference between the formation of **3e** in SbF_5-SO_2ClF at -80°C and the formation of **10** under extremely mild conditions. In this context, the formation of a highly stable phenyldichlorocarbenium ion **10** at ambient temperature and its amenability to NMR investigations is highly remarkable. This is precisely the novelty of this work and this also can have a significant effect on carbocation chemistry which can stimulate future research in this area.

Table 1: The ^{1}H, ^{13}C and ^{27}Al Spectral Data for 7-10[a]

Compd.	^{1}H[b]	^{13}C[f]					^{27}Al[i]
		C_1	C_2	C_3	C_4	C_5	
7	7.50(dt,J=1.5,7.8Hz,2H)	168.07	133.22	131.20	128.80	135.12[g]	
	7.67(tt,J=1.4,7.5Hz,1H)	167.51	132.60	130.72	128.46	134.88[h]	
	8.12(m,2H)[c]						
8	7.75(t,J=8Hz,2H)	199.05	130.53	135.71	130.74	143.73[g]	98[g]
	8.12(t,J=7.5Hz,1H)	191.62	129.33	134.76	129.64	143.01[h]	99[h]
	8.44(dd,J=1.2,8.5Hz,2H)[d]						
9	7.42(m,3H),7.92(m,2H)[c,e]	97.55	144.10	128.14	125.29	130.09[g]	
		97.32	143.65	128.00	124.94	130.01[h]	
10	8.02(t,J=8Hz,2H)	209.76	140.53	144.08	134.11	160.00[g]	92[g]
	8.78(t,J=7.4Hz,1H)	209.53	140.06	143.43	133.43	159.39[h]	93[h]
	8.86(d,J=7.8Hz,2H)[d]						

[a]The ^{1}H NMR spectra were recorded in $CDCl_3$ only whereas the ^{13}C and ^{27}Al spectra were recorded in both ethylene dichloride and $CDCl_3$. [b]The chemical shifts (in ppm) correspond to meta, para and ortho protons, respectively. [c]Referred to internal TMS. [d]Referred to TMS of the corresponding uncomplexed parent compounds. [e]The meta and para protons are grouped together. [f]Referred to external capillary TMS. [g]Recorded in $CDCl_3$. [h]Recorded in ethylene dichloride. [i] ^{27}Al chemical shifts are with reference to $Al(H_2O)_6^{3+}$ at 0 ppm.

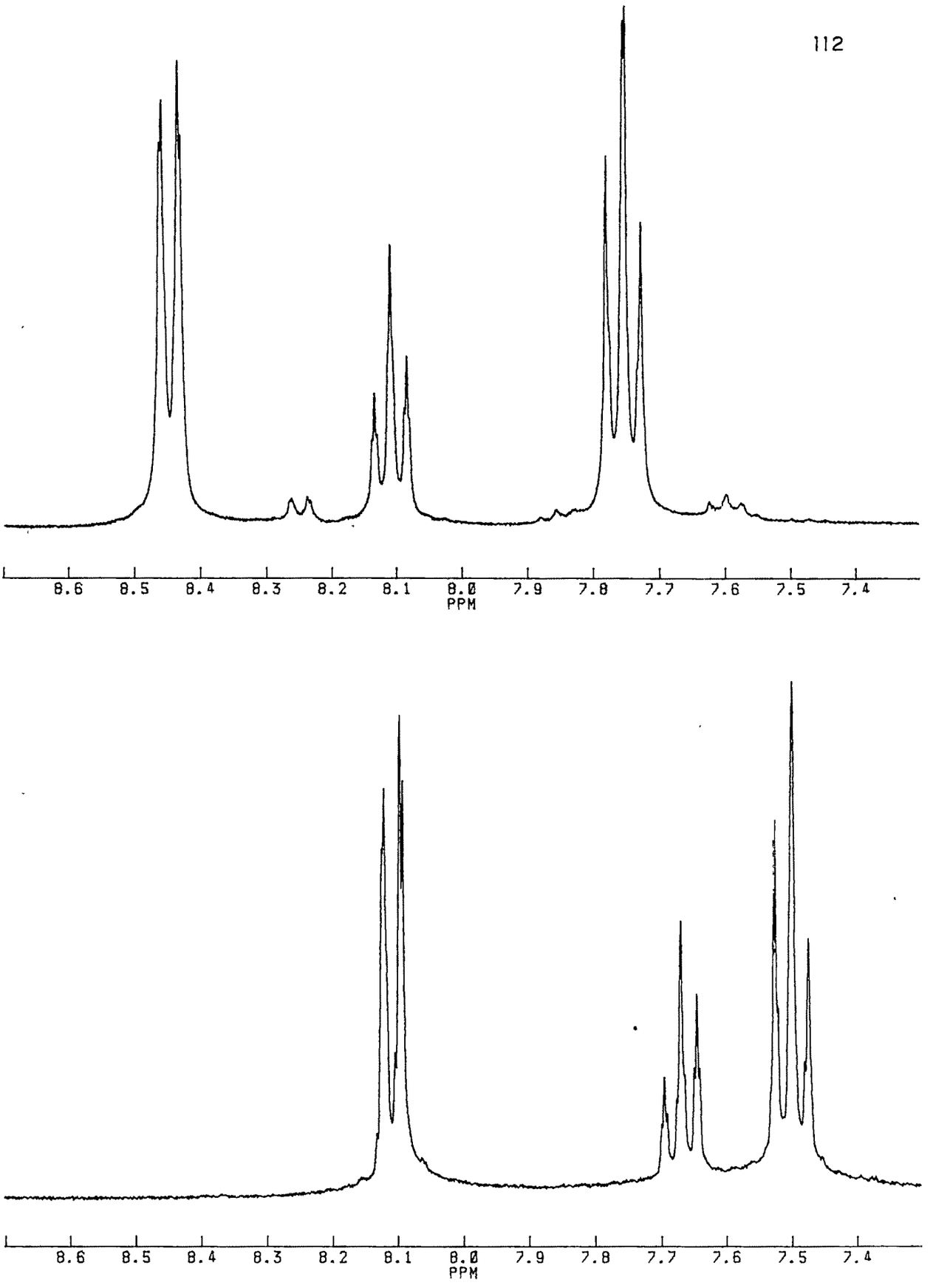


FIG.1. 300-MHz ^{1}H NMR SPECTRA OF BENZOYL CHLORIDE (7, BOTTOM) AND AND BENZOYL CHLORIDE - ALUMINIUM CHLORIDE COMPLEX (8, TOP)

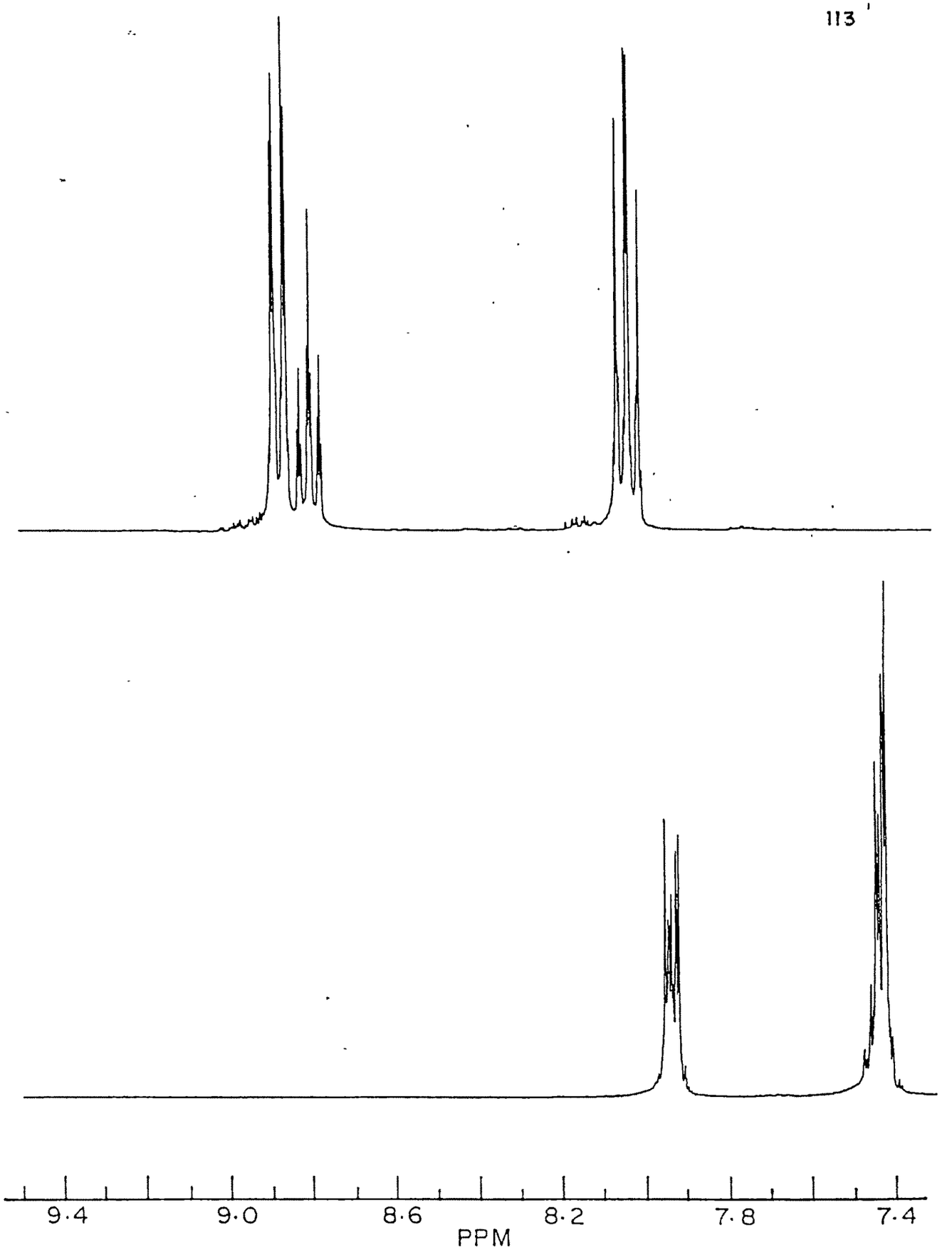


FIG.2. 300-MHz ^{1}H NMR SPECTRA OF BENZOTRICHLORIDE (9, BOTTOM) AND BENZOTRICHLORIDE-ALUMINIUM CHLORIDE COMPLEX (10, TOP)

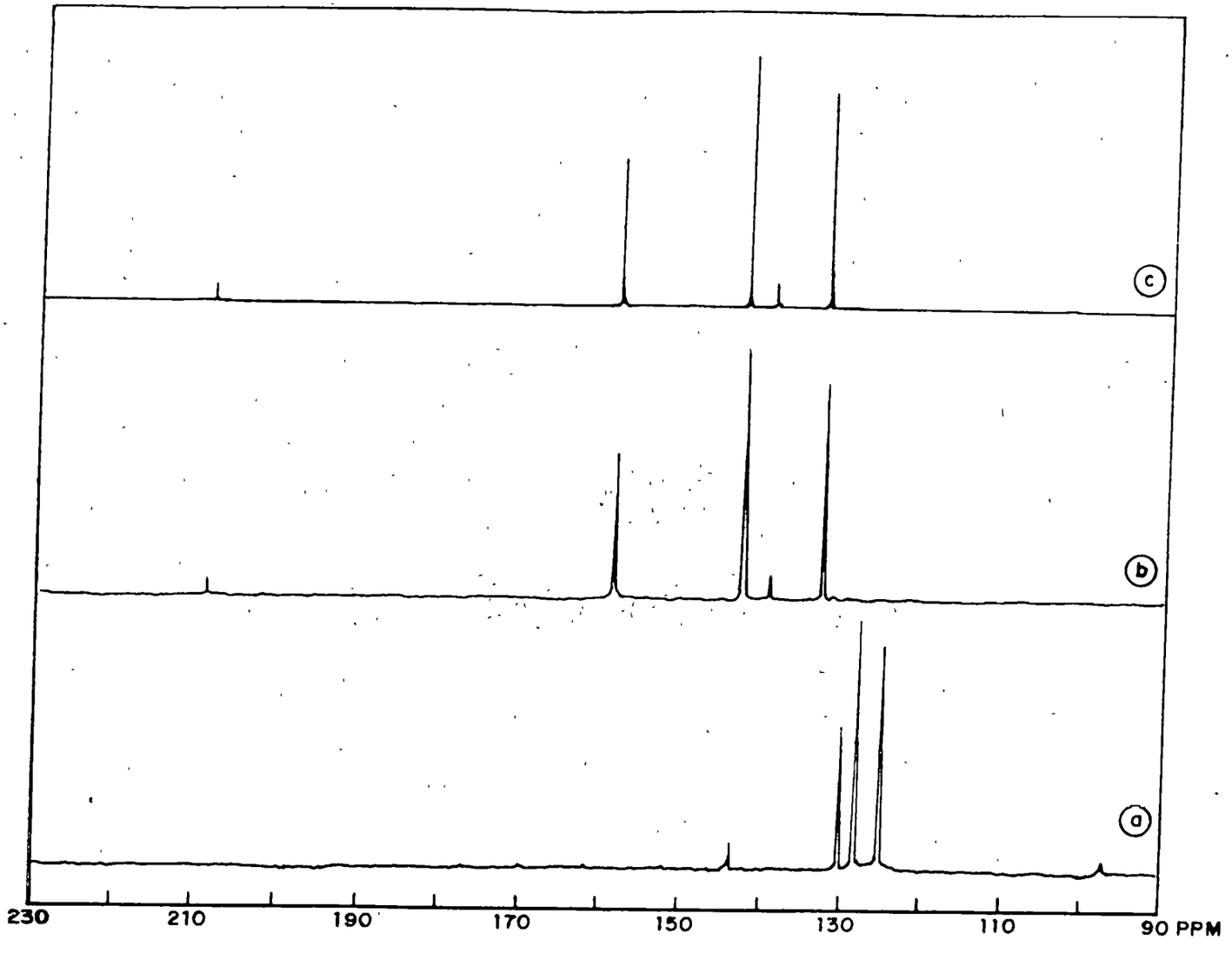


FIG. 3. COMPARISON OF ^{13}C NMR OF (10) IN DIFFERENT SOLVENTS

(a) BENZOTRICHLORIDE (in EDC), (b) (10) in EDC, (c) (10) in $CDCl_3$

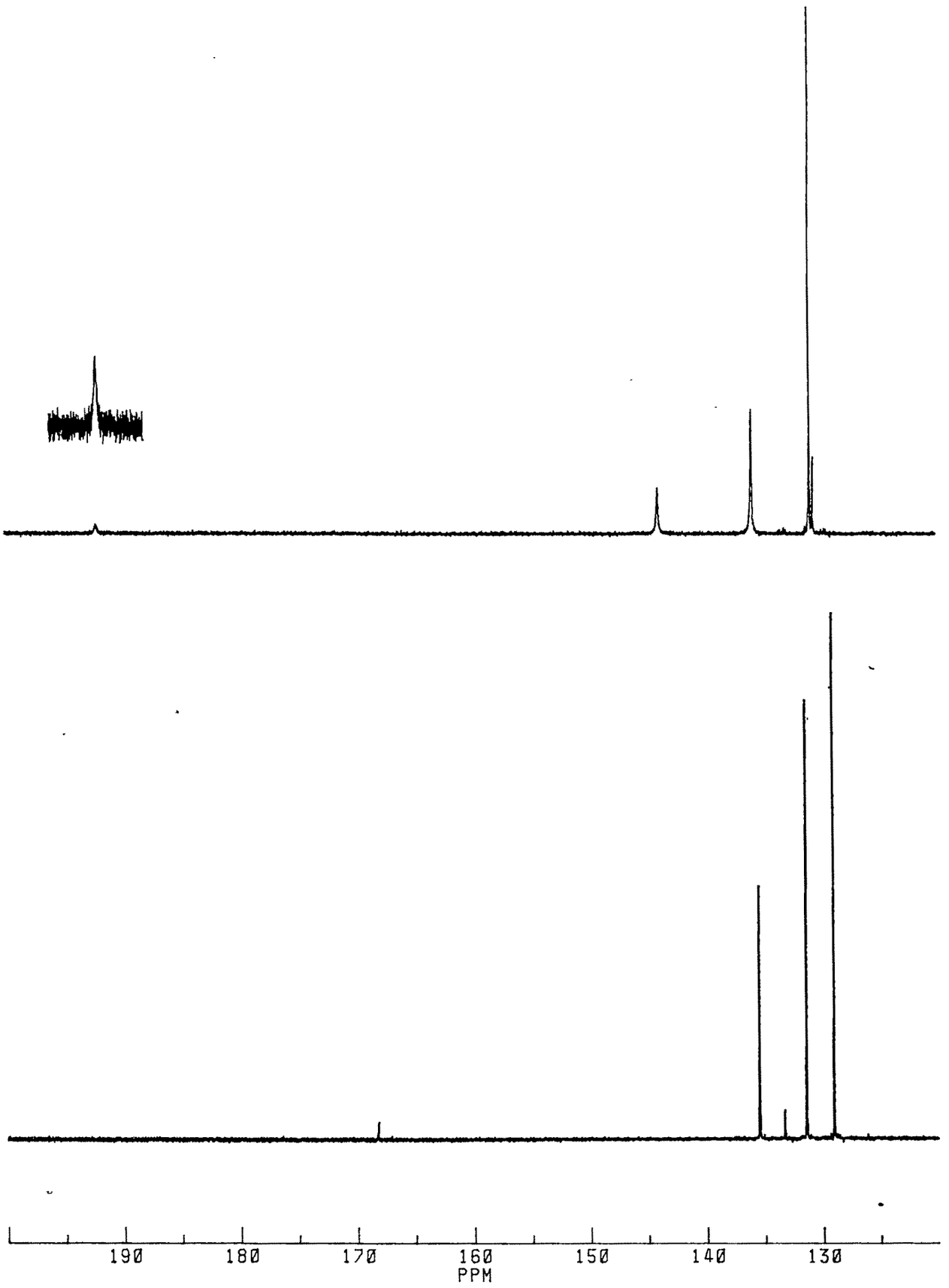


FIG. 4. 75-MHz ^{13}C NMR SPECTRA OF BENZOYLCHLORIDE (7, BOTTOM) AND BENZOYL CHLORIDE-ALUMINIUM CHLORIDE COMPLEX (8, TOP) IN $CDCl_3$

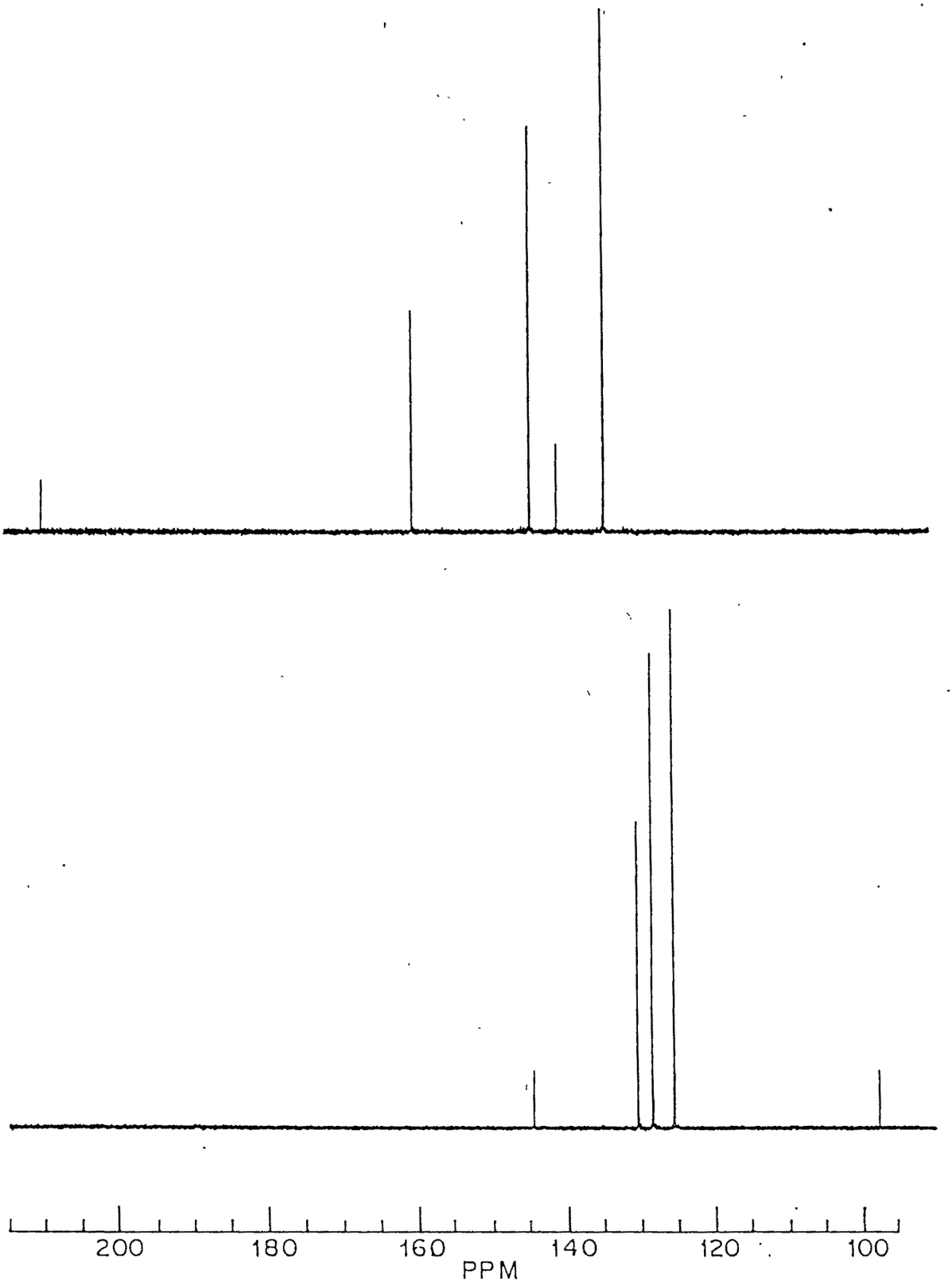


FIG. 5. 75-MHz ^{13}C NMR SPECTRA OF BENZOTRICHLORIDE (9, BOTTOM) AND BENZOTRICHLORIDE-ALUMINIUM CHLORIDE COMPLEX (10, TOP) IN $CDCl_3$

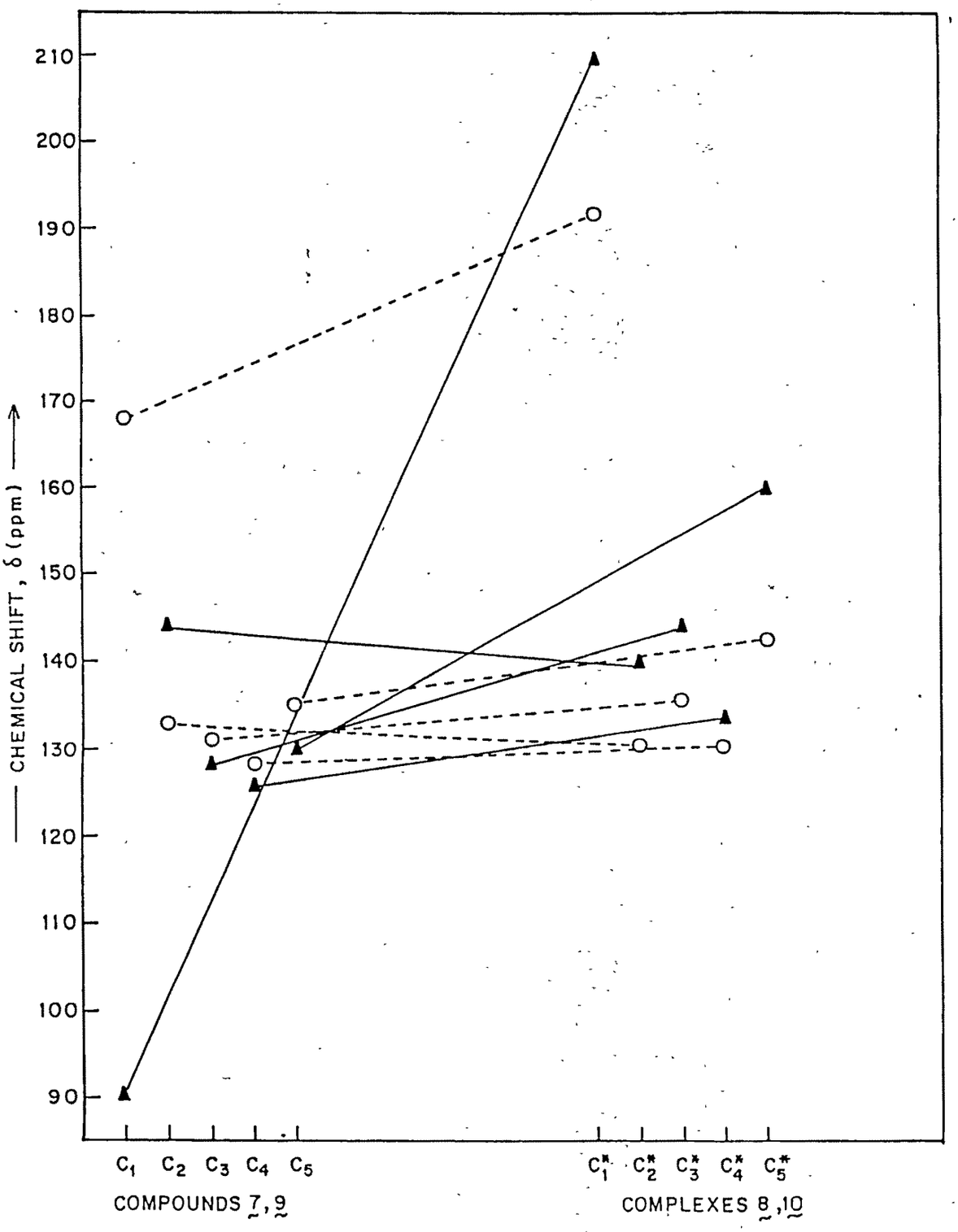


FIG. 6. THE DIFFERENCE IN ^{13}C NMR CHEMICAL SHIFTS OF (a) BENZOYL CHLORIDE (7) AND ITS COMPLEX 8 (o----o). (b) BENZOTRICHLORIDE (9) AND ITS COMPLEX 10 (▲——▲)

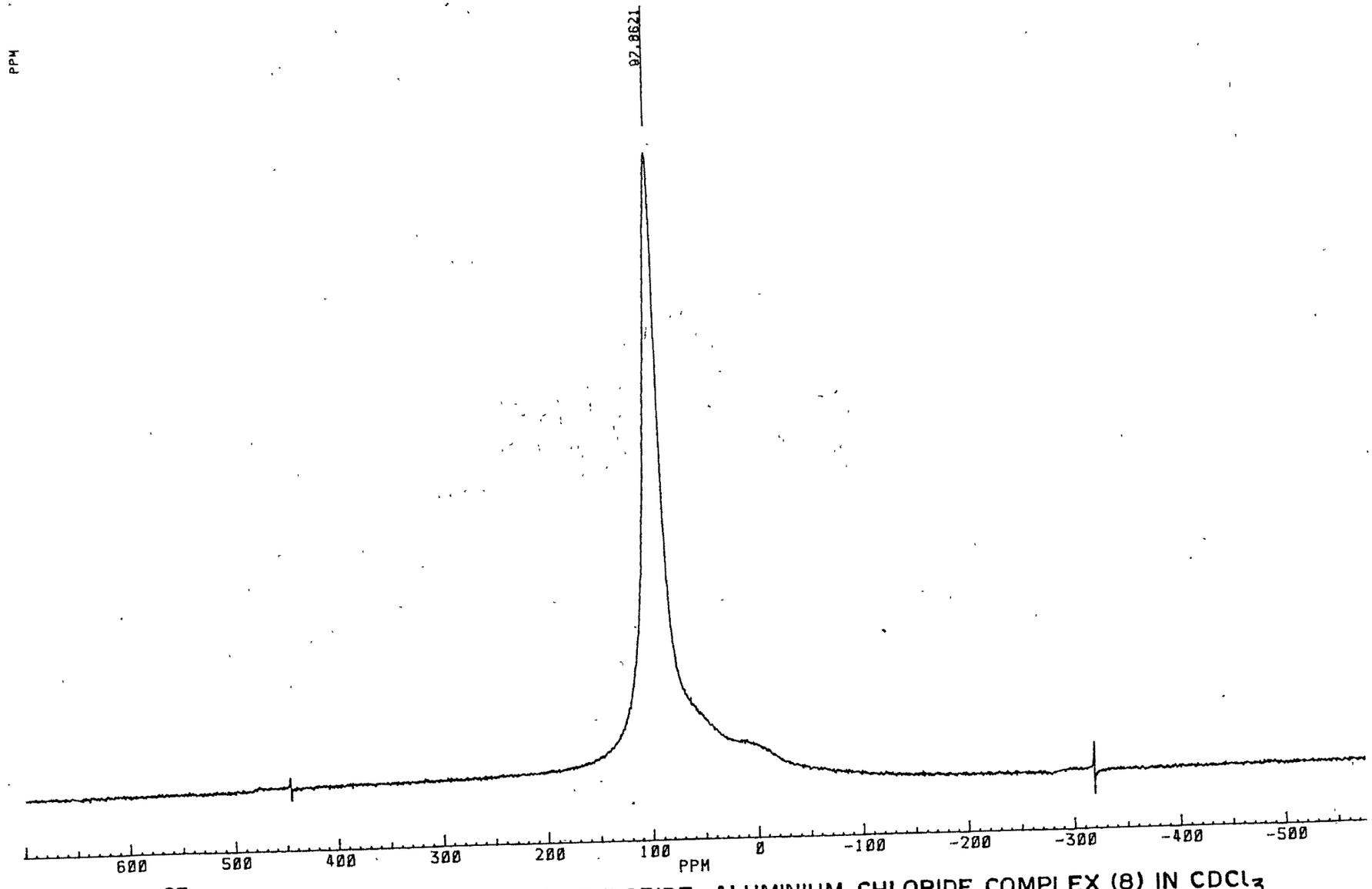


FIG.7. 78-MHz ^{27}Al NMR SPECTRUM OF BENZOYL CHLORIDE–ALUMINIUM CHLORIDE COMPLEX (8) IN $CDCl_3$

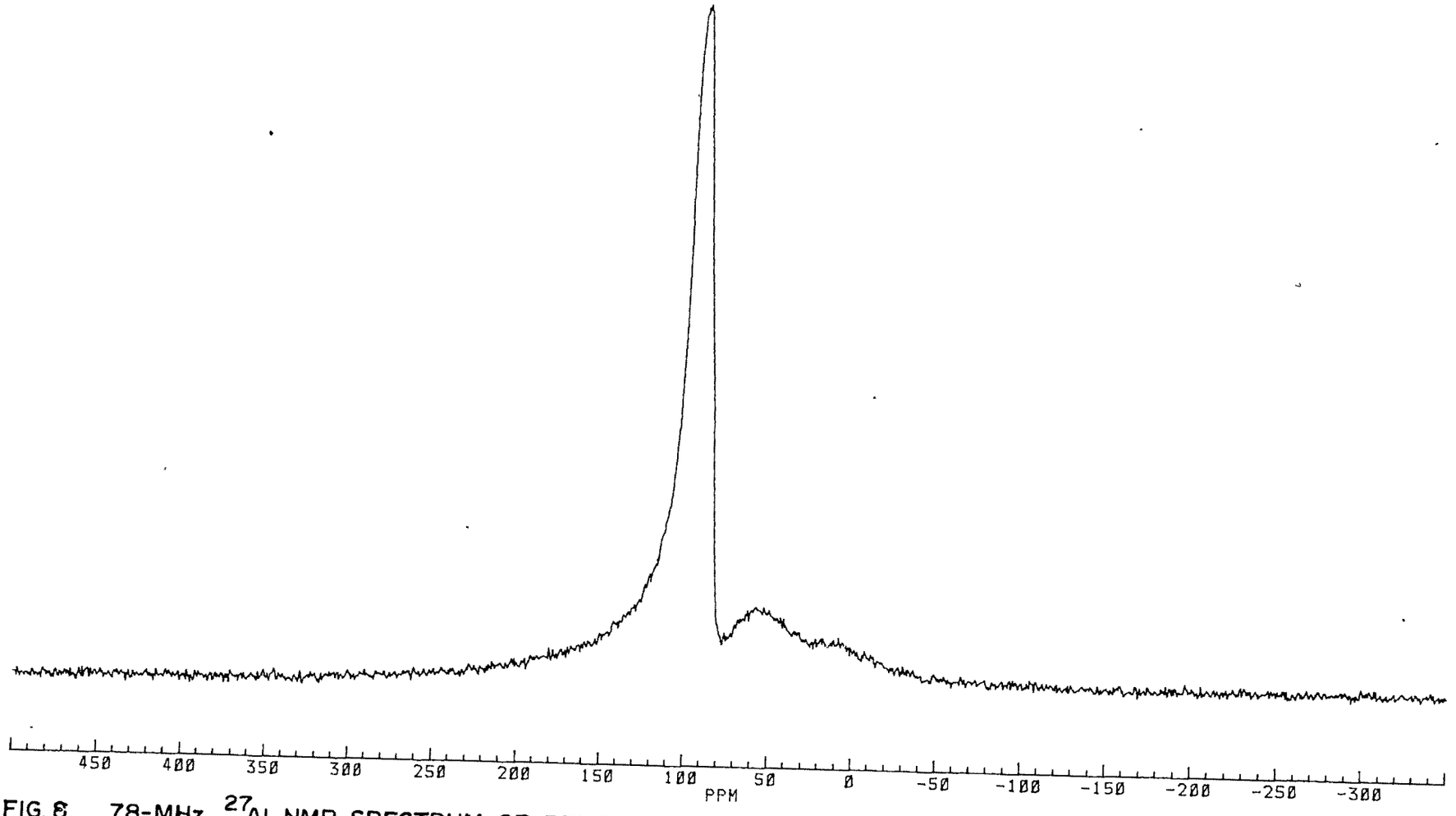
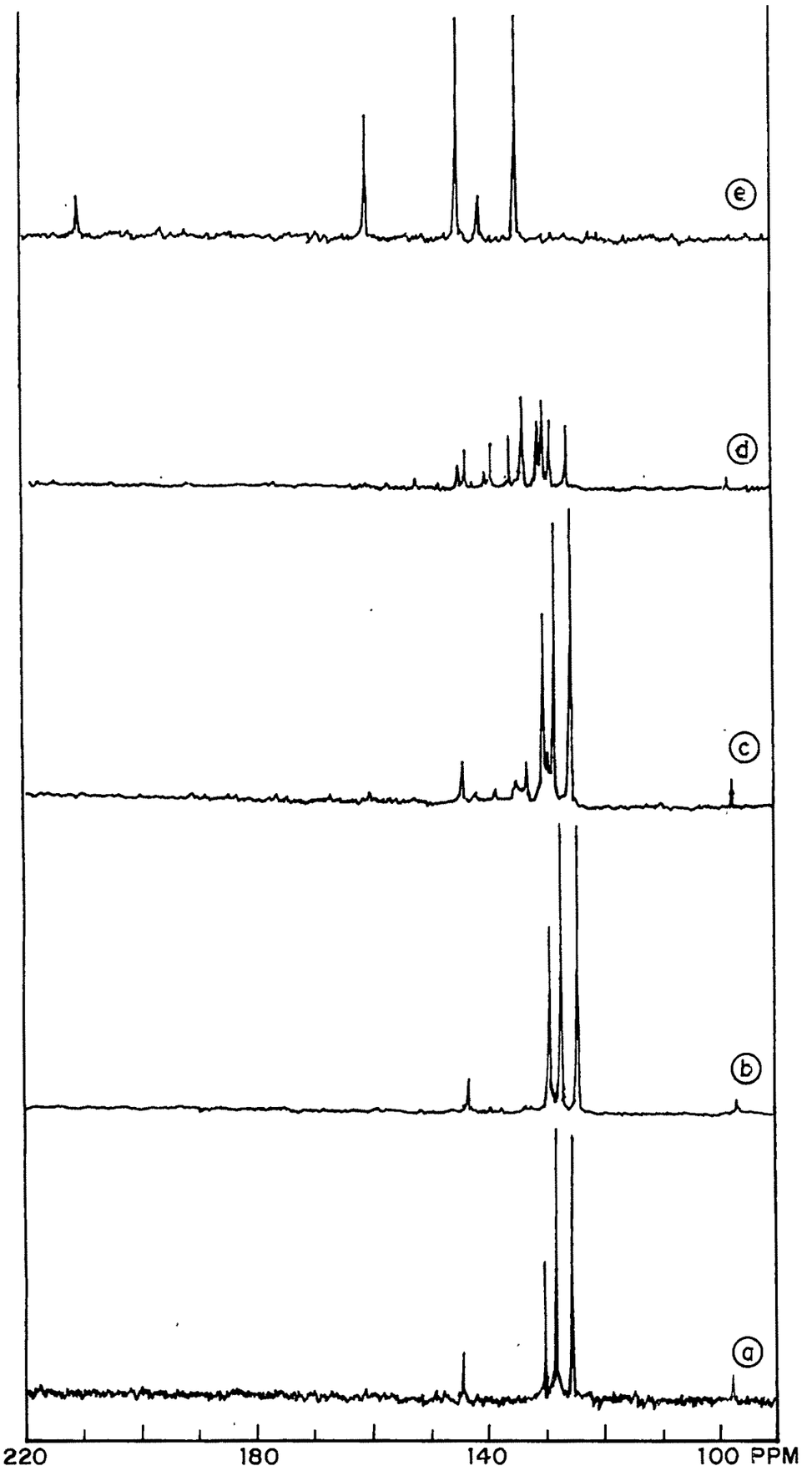


FIG. 8. 78-MHz ^{27}Al NMR SPECTRUM OF BENZOTRICHLORIDE-ALUMINIUM CHLORIDE COMPLEX (10) IN EDC



.9. COMPARISON OF ^{13}C NMR SPECTRA OF COMPLEXES OF BENZOTRICHLORIDE WITH ONE AND THREE EQUIVALENTS OF $AlCl_3$ IN $CDCl_3$
(a) BENZOTRICHLORIDE, (b) 1:1 COMPLEX (IMMEDIATELY AFTER MIXING)
(c) AFTER 2 HRS, (d) AFTER 4 HRS, (e) 1:3 COMPLEX

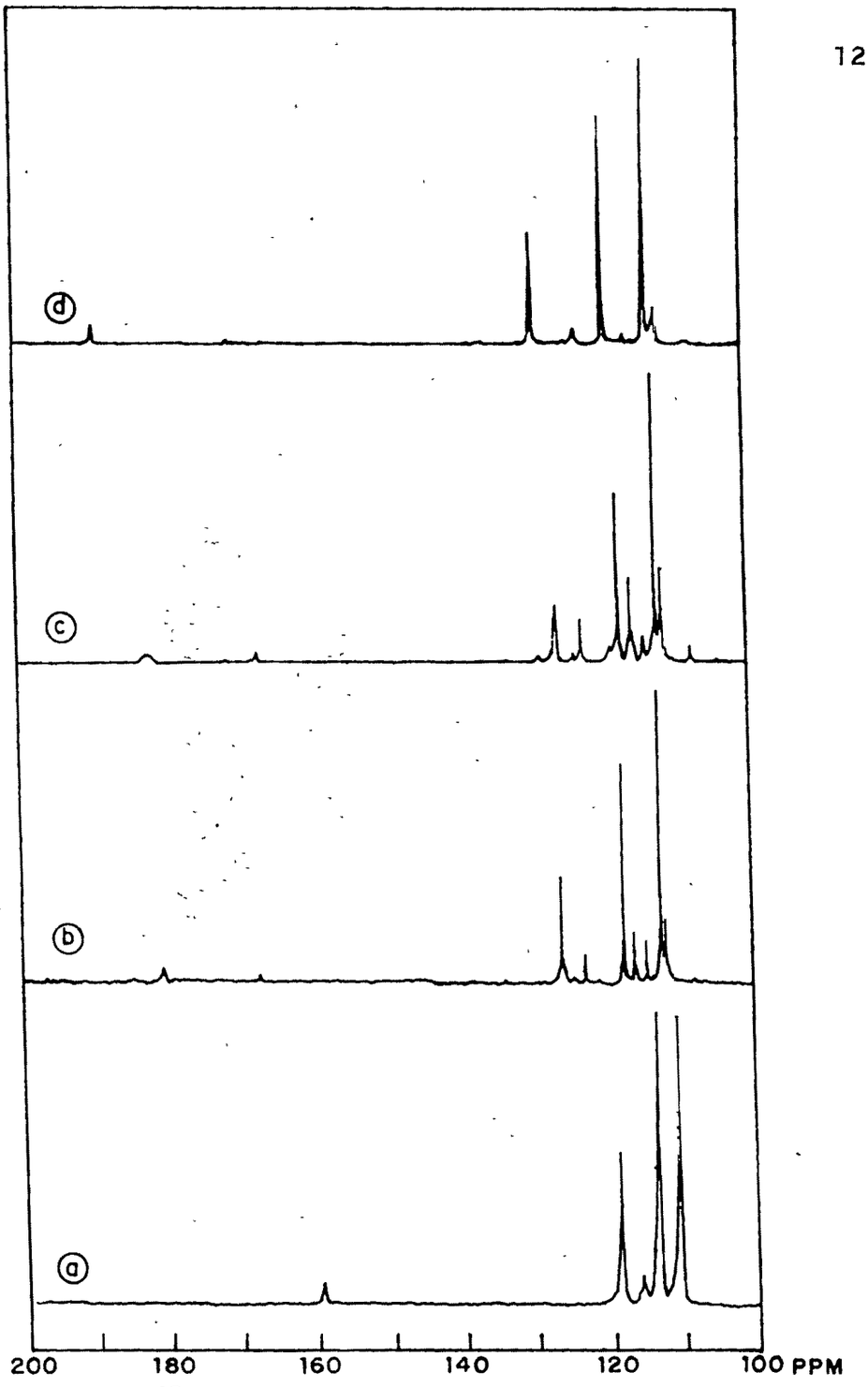


FIG. 10. COMPARISON OF ^{13}C NMR SPECTRA OF COMPLEXES OF BENZOYL CHLORIDE WITH ONE AND THREE EQUIVALENTS OF $AlCl_3$ IN EDC

(a) BENZOYLCHLORIDE, (b) 1:1 COMPLEX (IMMEDIATELY AFTER MIXING)
(c) AFTER 30 MINUTES, (d) 1:3 COMPLEX

EXPERIMENTAL

General Remarks:

The NMR experiments were performed on a Bruker MSL 300 spectrometer with superconducting magnets, operating at 300, 78.2 and 75.46 MHz for ^{1}H, ^{27}Al, and ^{13}C nuclei, respectively. For ^{13}C and ^{1}H measurements 32K data points were used and the chemical shifts in δ ppm were referred to TMS as 0 ppm. An aqueous solution of $AlCl_3$ (1M) was used as external reference for ^{27}Al measurements. All the spectra were recorded at ambient temperature (25°C). A capillary containing D_2O was used for field frequency locking for the measurements in EDC. The ^{13}C-NMR spectra were obtained under broad band noise decoupling conditions.

Purification of Starting Materials:

Aluminium chloride was purified by sublimation of anhydrous C.P. grade material at about 150°C around 10 mm vacuum. Resublimation afforded still refined material which was stored in a stoppered bottle and preserved in a dessicator. Both benzoyl chloride (b.p. 197.2°C) and benzotrichloride ($b.p._{10}$ 89°C) were freshly distilled before use. Ethylene dichloride (EDC) was purified by a standard procedure.

Preparation of Samples for the NMR Experiments:

General Procedure:

Aluminium chloride was weighed in a stoppered weighing bottle and carefully transferred into the NMR tube. The required amount of benzoyl chloride or benzotrichloride was weighed and

transferred using the solvent ($CDCl_3$ or EDC) into the NMR tube and the tube was vigorously shaken.

^{1}H-NMR Spectra:

A solution of 10-12 mg of benzoyl chloride or benzotrichloride in about 0.5 ml of $CDCl_3$ was taken in a 5 mm NMR tube to get a satisfactory proton NMR.

^{13}C-NMR and ^{27}Al-NMR Spectra:

A 10 mm (o.d.) NMR tube was employed for recording the spectrum in EDC. But for recording spectra in $CDCl_3$ both 5 mm and 10 mm NMR tubes were used. About 2.5 ml of EDC or $CDCl_3$ was needed to obtain a satisfactory solution containing about 100-150 mg of benzoyl chloride or benzotrichloride with corresponding amount of aluminium chloride.

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CHAPTER – IV

GENERAL INTRODUCTION

Structure determination of dyes is relatively a difficult task because of the complexity involved. Disperse dyes, being water insoluble, can be purified by extraction with suitable solvents and subsequently subjected to other methods of purification such as chromatography for structure determination. Methods based on chemical degradation have been used for years to convert the original dye molecule to simpler products of known structures. The combination of instrumental and chemical methods and integrated application of each at suitable stages is the efficient approach to tackle the structural problems of synthetic dyes. Reasonable and careful interpretation of the results gives the complete structural features of an unknown dye.

Amongst the four principal methods of instruments analysis, UV-visible spectrum gives the information about the chromophoric groups present in the molecule. Infra-red spectrum indicates the functional groups and acts as a characteristic property of a compound serving as a fingerprint. Mass spectrum gives the molecular weight with its characteristic fragmentation pattern. Nuclear magnetic resonance allows the direct observation of carbon skeleton carrying the protons and functional groups such as alkoxy and acetyl groups. These methods are complementary to each other. Their proper interpretation leads to the correct structure of an unknown dye sample.

Thus, chemical examination of an unknown dye involves a number of steps, such as (a) determination of its application

class, (b) separation of the pure dye from dispersing agents and other diluents, (c) thin layer chromatography to check its homogeneity, (d) isolation and purification of individual components if it is a mixture, (e) determination of its elementary composition, (f) determination of functional groups and basic carbon skeleton and (g) synthesis. (In a multistep synthesis each intermediate is fully characterized before going for the next step).

Application of these methods is illustrated by structural elucidation of two commercial dyes, C.I. Disperse Violet-33 (Part A) and C.I. Disperse Yellow-232 (Part B). One of the dyes, disperse yellow 232 showed interesting laser properties besides being a fluorescent disperse dye. This prompted us to look into the synthesis of similar dyes comprising fluorophores, which might possess better lasing properties. From this point of view, quite a few dyes were synthesized and this work is included in Part C of this chapter. The investigations of both the dyeing characteristics as well as the laser characteristics were also carried out.

PART - A

STRUCTURAL FEATURES OF

C.I. DISPERSE VIOLET 33

INTRODUCTION

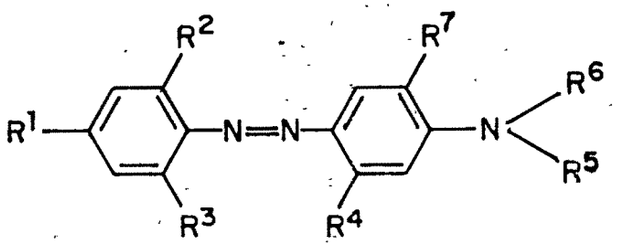
In continuation of the efforts[1] initiated in this laboratory to deduce the chemical constitution of commercial disperse dyes and their synthesis, C.I. Disperse Violet-33 (Navilene Rubine 3B) was taken up for structure elucidation. The dye has been reported[2] to have a monoazo constitution with good fastness properties. A detailed study of the spectral and elemental analysis aided by literature survey of similar compounds indicated the structure of the dye as 3. Further, the structure of the dye was unambiguously established by its synthesis from readily available starting materials and direct comparison.

In view of the above observations, it becomes pertinent to present an overview of violet disperse dyes[3,4,5] belonging to azo class.

Although the majority of violet-disperse dyes are either anthraquinone and azo compounds, attention will be given only to the latter class. A list of commercial violet azo disperse dyes of known constitution is shown in CHART 1. The substitution pattern in violet disperse dyes in general, aims at: (i) increasing the fastness properties, (ii) making the dyes substantive towards substrate, (iii) getting level dyeings and (iv) confering dispersion stability. The diazo components used are usually mono- or di-substituted nitro-anilines, substituents being at the 2 and 6 positions with respect to the amino group. The substituents are generally auxochromes such as the nitro, chloro and bromo groups. The coupling

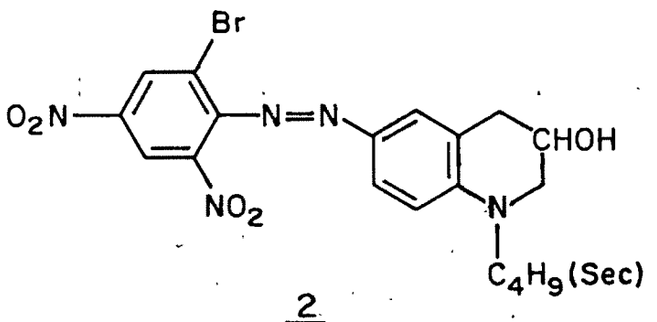
components consist of substituted dialkyl anilines. One of the substituents may be alkyl groups ranging from methyl to butyl or alkoxy groups. The other substituents are either β-hydroxy or β-acetoxyalkyl groups such as hydroxyethyl or acetoxyethyl groups. These groups confer dispersing stabilities to the dyes. The substituents in the ring of the coupling components of the compounds may be alkyl such as methyl and/or an acetyl-amino function.

CHART - 1



1

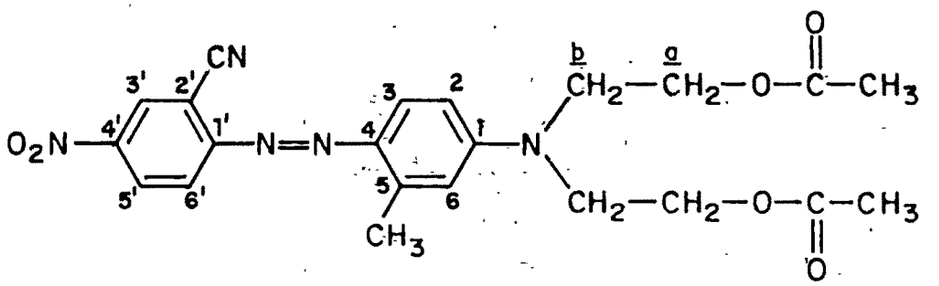
No.	C.I. Disperse violet	C.I.	R^1	R^2	R^3	R^4	R^5	R^6	R^7
1a	12	11120	NO_2	NO_2	H	H	CH_2CH_2OH	$C_4H_9(n)$	H
1b	13	11195	NO_2	NO_2	H	CH_3	CH_2CH_2OH	$C_4H_9(n)$	H
1c	24	11 200	NO_2	Br	NO_2	CH_3	CH_2CH_2OH	$C_4H_9(n)$	H
1d	58	11340	NO_2	Cl	Cl	NHAc	CH_2CH_2OAc	CH_2CH_2OAc	OMe



2

C.I. Disperse violet-7 (C.I. 11410)

CHART-2



3

PRESENT WORK

C.I. Disperse Violet-33 (Navilene Rubine 3B) is a commercial disperse dye used for dyeing of polyester fibre. A sample of commercial C.I. disperse violet 33 was dried to constant weight. The weight decreased by 4% due to the evaporation of moisture present in the dye. A dry sample was extracted with benzene in a soxhlet extractor to free it from inorganic and other impurities. The dark brown benzene extract on evaporation left a powdered material which on repetitive TLC on silica gel using pet. ether (b.p. 60-80°C) and acetone (v/v 9:1) showed a reddish violet spot with Rf value 0.3. The solution of the dye in acetone was adsorbed on silica gel and chromatographed. The column was eluted with a mixture of pet. ether and acetone (v/v 9:1). The purified product was crystallized from benzene.

A part of the purified dye 0.25 g was dissolved in DMF and heated to 80°C. Alkaline sodium dithionite solution was then added dropwise till the colour of the dye solution disappeared. Subsequent air oxidation did not regenerate the colour. So, the anthraquinone structure for the dye was ruled out. On the basis of elemental analysis and molecular weight obtained from the mass spectrum, the molecular formula of the dye was computed as $C_{22}H_{23}N_5O_6$. The detailed spectral analysis of the dye aided by literature survey based on the derived molecular formula led to the elucidation of its chemical constitution as the azo dye 3.

The electronic spectrum of 3 showed λ_{max} 515 nm ($\log \epsilon$ = 3.64). The IR spectrum in nujol revealed a strong carbonyl

stretching frequency at 1730 cm^{-1} attributable to ester group and 2240 cm^{-1} to a cyano group in the dye molecule. The absorption bands at 1520 cm^{-1} and 1330. cm^{-1} may be attributed to a nitro group (FIG. 1).

In ^{1}H-NMR, the singlet at 2.05 accounts for six protons. That indicates the presence of two acetate moieties. Another signal at 2.7 (3H, s) could be attributed to aromatic methyl adjacent to an electron-withdrawing group. It may be possibly ortho to the azo linkage (FIG. 2).

The methylenes adjacent to nitrogen (CH_2-b) appear as a triplet at 3.75. Another triplet 4.32 corresponding to the methylenes adjacent to acetate group (CH_2-a) is observed. A close observation of the aromatic protons shows that at 6.75 an overlapping multiplet integrating for two protons is observed. The protons 2-H and 6-H have these chemical shifts due to electron-donating substituents such as dialkylamino and methyl groups at 1 and 5 positions. The ortho-coupled doublet (J=9Hz) corresponding to 3-H merges with the ortho-coupled doublet (J=9Hz) of 6'-H and appears at 7.8-8.0. The 5'-H proton appears as a quartet (doublet of doublets) centred at 8.42. The most-deshielded proton in the NMR spectrum at 8.6 which appeared as a meta-coupled doublet was attributed to the 3'-H proton of the dye. The presence of the electron-withdrawing nitro and cyano groups has the effect on the chemical shift of 3'-H proton which is in conjugation (FIG. 2). These NMR values are in agreement with reported values of related compounds in literature.[6]

The mass spectrum showed the molecular ion at 453 (M^+). The base peak at 87 is probably due to ion [CH_2-CH_2-O-$COCH_3$]$^+$. The loss of [CH_2-O-$COCH_3$] from the molecular ion gives rise to the m/e ion at 380. A further loss of CH_3COOH due to Mac-Lafferty rearrangement gives peak at 320 (FIG. 3). Thus, by all accounts the structure of the dye was found to be 3 and was confirmed by an unambiguous multistep synthesis as shown in SCHEME 1.

The synthesised dye was found to be identical with the dye isolated from the commercial sample by tlc, mixed melting point, and superimposable visible and IR spectra (FIG. 1).

Synthesis of Disperse Violet 33:

The synthesis of disperse violet 33 involves three steps as in the SCHEME 1. In the first step, N,N'[3-methylphenyl) imino]-bis-ethanol (5) is prepared from meta-toluidine (4) and ethylenechlorohydrin in aqueous alkaline medium. The literature survey for the preparation of 5 reveals that it can be prepared either by using ethylene oxide[7] under pressure or by using ethylene chlorohydrin.[10,11] The dye intermediate 6 was prepared[12] in the second step by coupling 5 with diazotized 2-amino-5-nitrobenzonitrile. In step 3, the compound 6 was acetylated using acetic anhydride in presence of a base to give the dye 3.

The IR spectrum of 5 shows the disappearance of the amino function and appearance of a broad signal between 3190 cm^{-1} and 3260 cm^{-1} confirming the presence of hydroxy group.

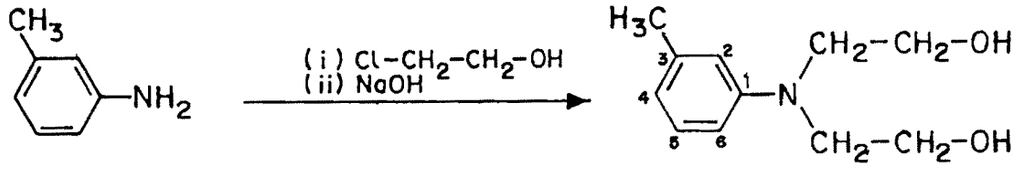
^{1}H-NMR spectra of **5** also shows the presence of OH protons at 4.16 and exchange with D_2O. The methylenes adjacent to nitrogen appear as a triplet at 3.4 and adjacent to hydroxyl group appears at 3.6 in a similar way.

In the mass spectrum of **5**, the molecular ion (M^+) peak is seen at 195. A peak at 164, which is formed by the loss of CH_2-OH group forms the base peak.

For the azo compound **6** the IR spectrum shows the presence of cyano group at 2240 cm^{-1} and hydroxyl groups as a broad signal at 3540 cm^{-1}. The mass spectrum of **6** showed the molecular ion peak at 369. As in the case of **5**, the base peak is observed by the loss of [CH_2-OH] radical and is seen at 338. The peak at 265 is obtained by the loss of the disubstituted amino function from the molecular ion (CHART 3).

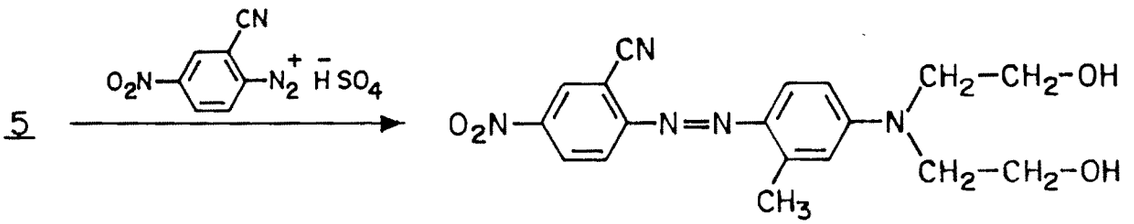
SCHEME-1

STEP-1



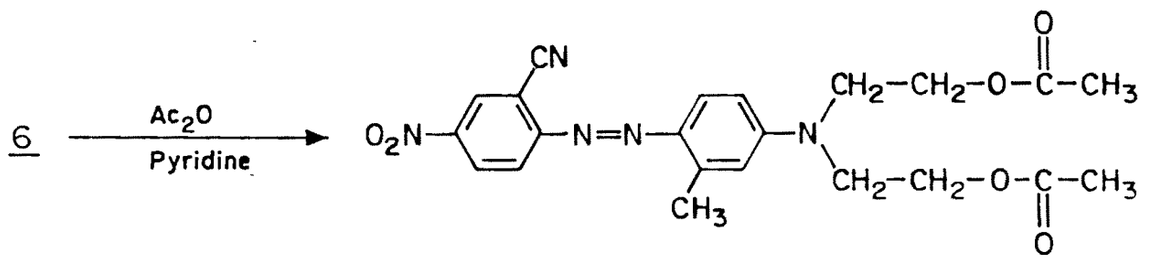
4 5

STEP-2



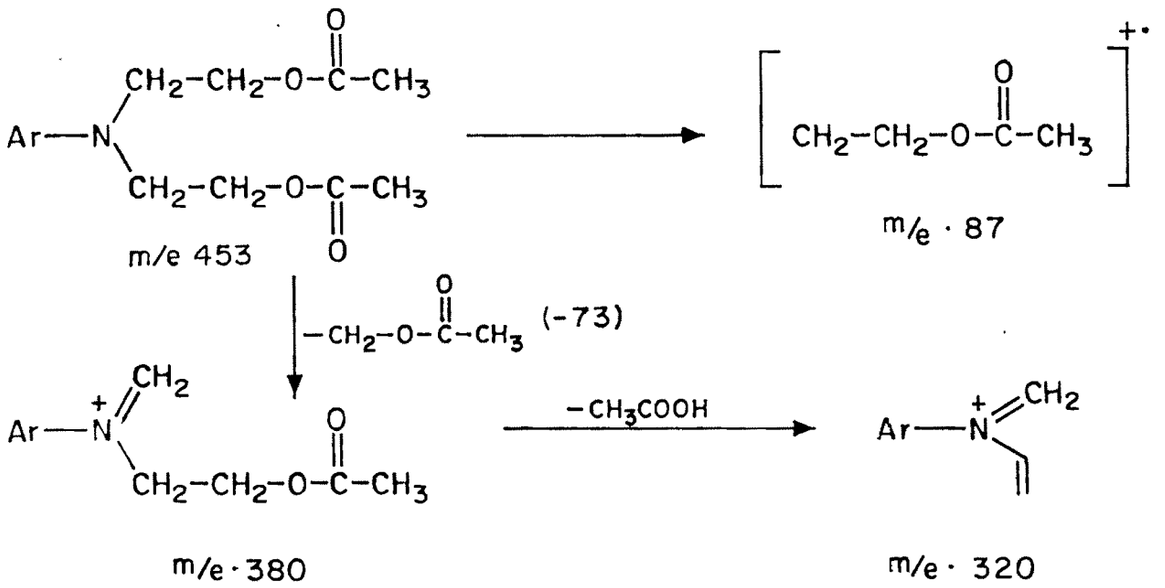
6

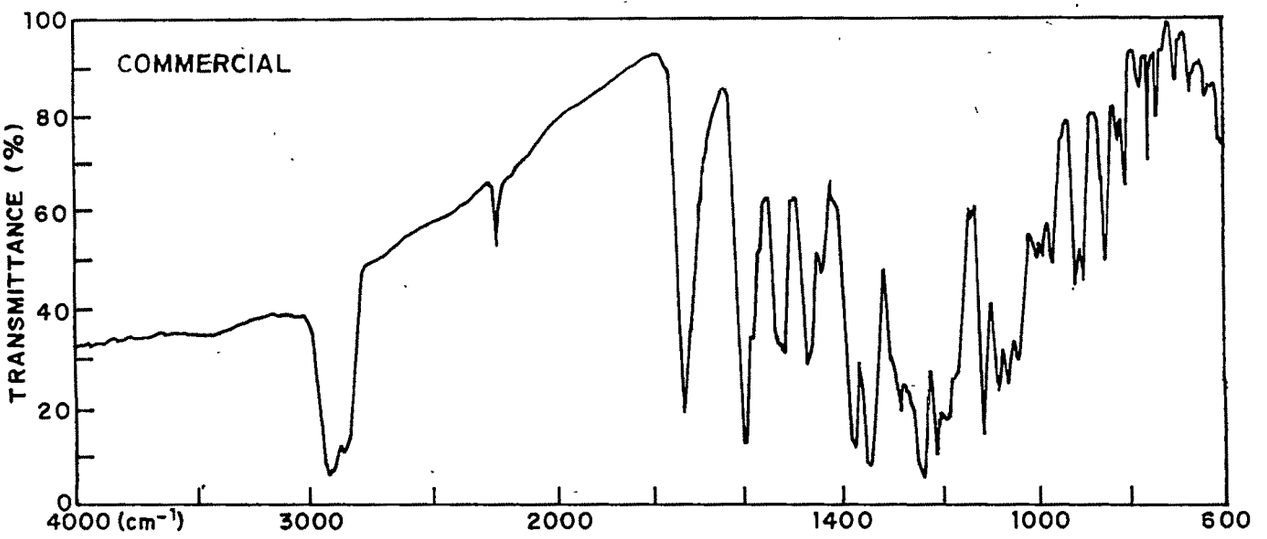
STEP-3



3

CHART-3




COMMERCIAL
TRANSMITTANCE (%)
100
80
60
40
20
0
4000 (cm⁻¹)
3000
2000
1400
1000
600

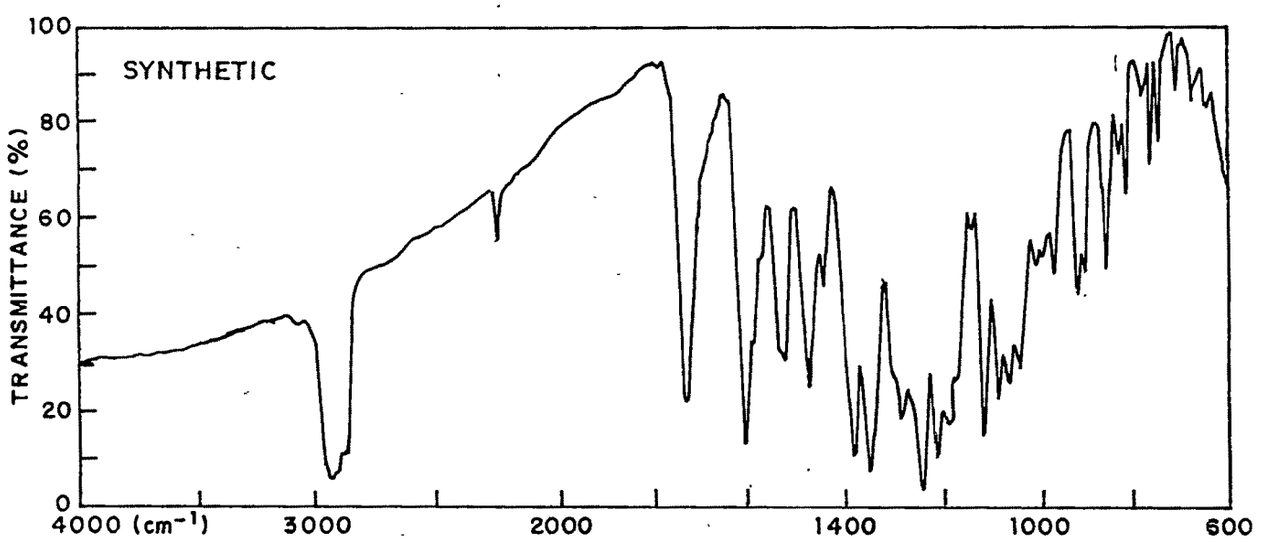
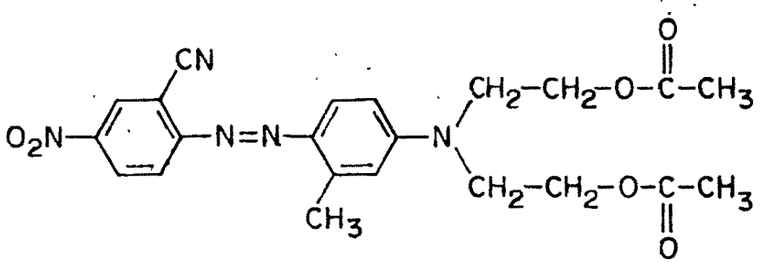

SYNTHETIC
TRANSMITTANCE (%)
100
80
60
40
20
0
4000 (cm⁻¹)
3000
2000
1400
1000
600

FIG. 1


CN
O2N
N=N
N
CH2–CH2–O–C–CH3
CH2–CH2–O–C–CH3
O
O
CH3

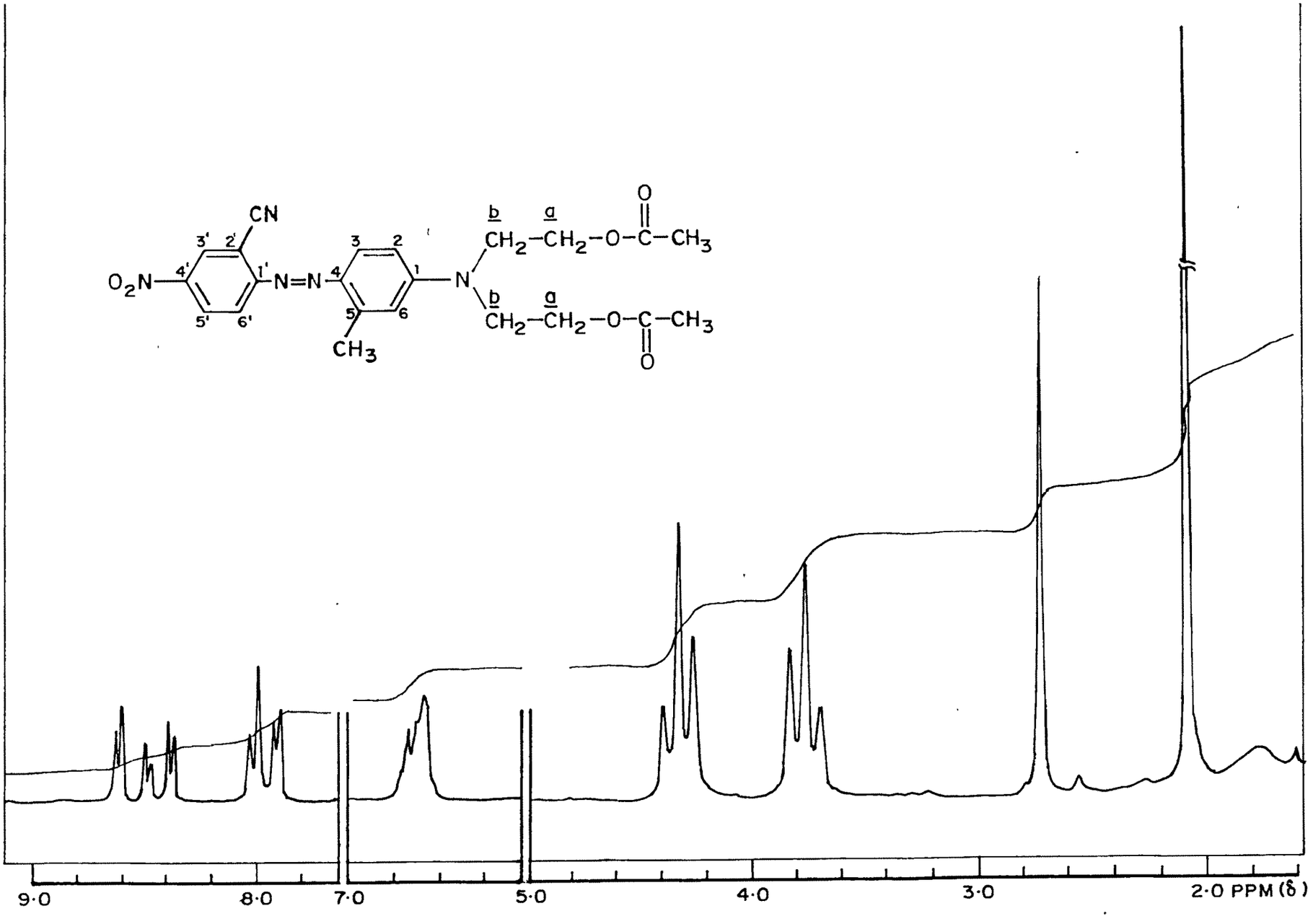

CN
3'
2'
3
2
b
a
O
CH2–CH2–O–C–CH3
4'
1'
N=N
4
1
N
O2N
5'
6'
5
6
CH3
b
a
CH2–CH2–O–C–CH3
O
9·0
8·0
7·0
5·0
4·0
3·0
2·0 PPM (δ)

FIG. 2

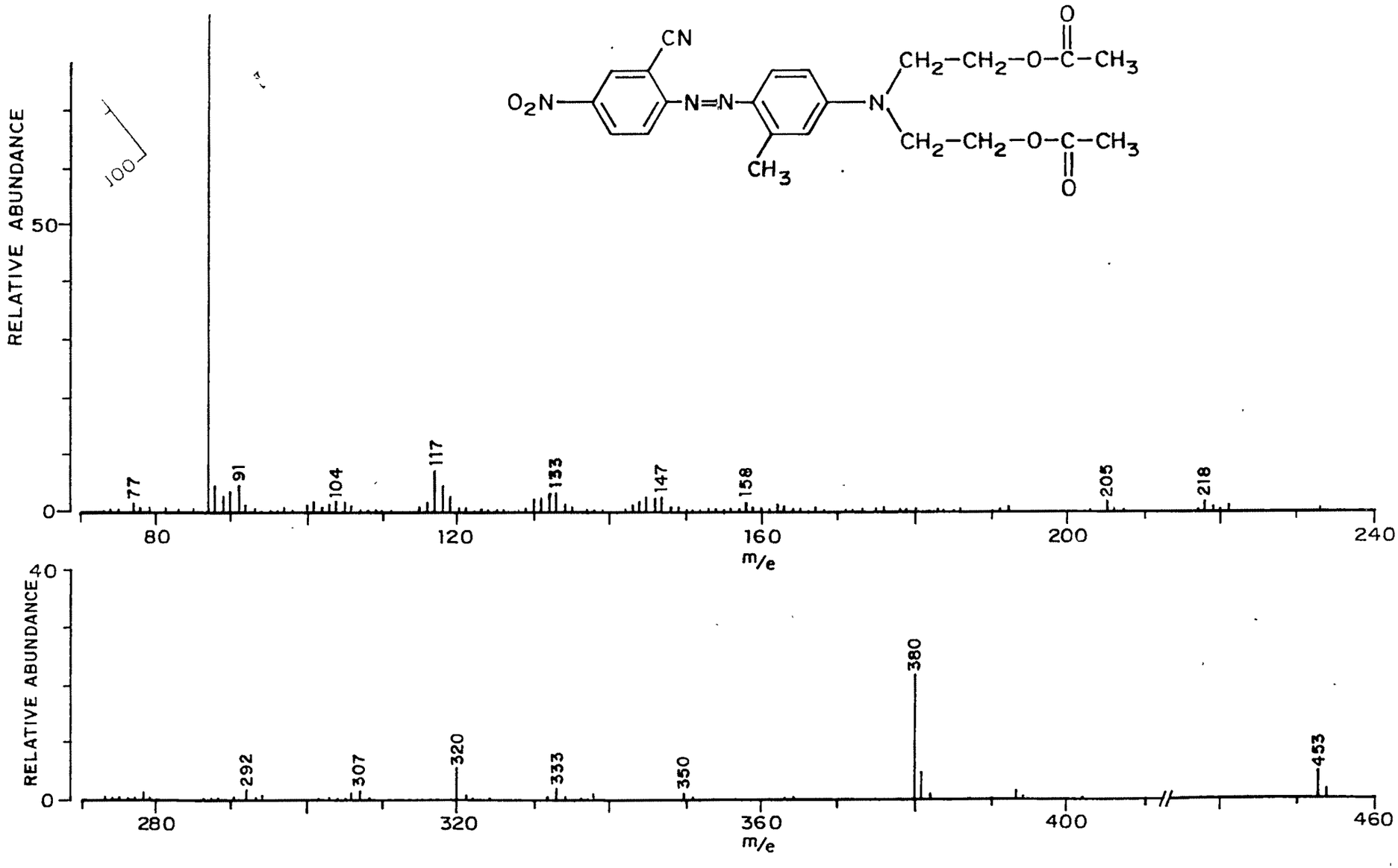

RELATIVE ABUNDANCE
100
50
0
77
91
104
117
133
147
158
205
218
80
120
160
200
240
m/e
CN
O_2N
N=N
N
$CH_2-CH_2-O-C-CH_3$
O
CH_3
RELATIVE ABUNDANCE
40
0
292
307
320
333
350
380
453
280
320
360
400
460
m/e

FIG. 3

EXPERIMENTAL

Isolation and purification of the commercial dye C.I. Disperse Violet 33:

The commercial dye (5 g) was dried at 50°C under reduced pressure and dry weight (4.8 g) gave the moisture content to be 4%. The dried sample was extracted with benzene in a soxlect extractor to free it from inorganic and other diluents. The dark brown benzene extract after removal of solvent gave a dark powdered material. Thin layer chromatography in pet. ether and acetone (9:1) shows a reddish violet spot having Rf value 0.3. It was purified by column chromatography. The dye was taken in acetone and adsorbed on silica gel. The column was eluted with a mixture of pet. ether (b.p. 60-80°C) and acetone (v/v, 9:1). The product was crystallized from benzene to give light fluffy material weighing 1.5 g, m.p. 168°C.

λ_{max} (u/v): 290 nm (ϵ = 10785)

λ_{max} (visible): 516 nm (ϵ = 36401).

IR (Nujol, cm^{-1}): 2240, 1730, 1600, 1580, 1510, 1520, 1410, 1430, 1360, 1330, 1270, 1230, 1200, 1180, 1100, 1080, 1060, 1030, 960, 910, 900, 850, 810, 700, 740.

^{1}H-NMR ($CDCl_3$): 2.07 (6H, s, $COCH_3$), 2.72 (3H, s, Ar-CH_3), 3.75 (4H, t, -CH_2-b), 4.32 (4H, t, CH_2-a), 6.75 (2H, m, 2-H & 6-H), 7.88 (1H, d, 3-H, J=9Hz), 8.0 (1H, d, 6'-H, J=9Hz), 8.42 (1H, dd, 5'-H), 8.6 (1H, d, 3'-H, J=3Hz), (FIG. 2).

MS m/e (rel. int. %): 453 (M^+, 4), 380(8), 320(3), 117(9), 91(7), 87(100).

Anal. $C_{22}H_{23}N_5O_6$: Calc. C, 58.28; H, 5.07; N, 15.45
(453) Found: C, 57.90; H, 5.10; N, 15.12

Synthesis of Disperse Violet 33 (SCHEME 1):

Step 1: Synthesis of 2,2'[3-methylphenyl]imino]bis-ethanol (5):

m-Toluidine (10.7 g, 0.1 mol), NaOH (10 g, 0.25 mol), water (40 ml) and potassium iodide (0.5 g) were taken in a 4-necked flask fitted with stirrer, thermometer well, reflux condenser and addition funnel. Ethylenechlorohydrin (20.13 g, 0.25 mol) was added drop by drop during 2 h. The temperature was raised to 95°C and kept at that temperature for 16 h. The reaction mixture was poured into ice and treated with dil. sodium bicarbonate solution. It was then extracted with chloroform, washed with water and distilled to get the product 5. Yield 12.5 g (64%). Crystallized from pet. ether - ethyl acetate (1:1) mixture, m.p. 71°C (lit.[8] m.p. 71°C).

IR (Nujol, cm^{-1}): 3190 - 3260 (broad), 1600, 1510, 1490, 1460, 1380, 1360, 1280, 1180, 1040, 1020, 1000, 880, 840, 770, 700.

^{1}H-NMR ($CDCl_3$): 2.16 (s, 3H, CH_3), 3.4 (4H, t, N-CH_2-), 3.6 (4H, t, -CH_2-OH), 4.16 (2H, s, OH), 6.26-6.60(3H, m, 2-H, 4-H & 6-H), 7.1 (1H, dd, 5-H).

MS m/e (rel. int. %): 195 (M^+, 15), 164(100), 120(96), 105(15), 91(64), 77(14), 65(9).

Anal. $C_{11}H_{17}NO_2$: Calc. C, 67.69; H, 8.71; N, 7.17
(195) Found: C, 67.66; H, 8.94; N, 7.14

Step 2: Preparation of the azo intermediate (6):

Sulphuric acid (5 ml) was taken in a 50 ml beaker. Into that, sodium nitrite (0.165 g, 0.24 mol) was added very slowly to make a uniform solution of sodium nitrite in sulphuric acid in half an hour. It was warmed to 50°C on a water bath carefully and then kept aside. To this solution was added 2-cyano-4-nitroaniline (3.26 g, 0.02 mol) slowly with stirring during 30 min. To that, 5 ml acetic acid was added to attain a uniform paste. Thus, diazotization of 2-cyano-4-nitroaniline was completed. For coupling, diazotized solution was added at 0°C to 3.9 g (0.02 mol) of 2,2'-[(3-methylphenyl)amino]bis-ethanol in 5 ml of 0.5 N hydrochloric acid. Sodium acetate (10 g) also was added, stirred for a few hrs. The azo compound (**6**) that separated was filtered. Thin layer chromatography of the compound in a mixture of chloroform and methanol (9:1) showed a single spot. It was crystallized from ethyl acetate, yield 6.6 g (90%), m.p. 194°C.

λ_{max} (uv): 292 (ϵ = 9483)

λ_{max} (visible) 532 (ϵ = 37530)

IR (Nujol, cm^{-1}): 3540, 2240, 1600, 1580, 1510, 1460, 1360, 1325, 1290, 1260, 1240, 1200, 1160, 1110, 1080, 1040, 980, 900, 840, 810, 760, 740.

MS m/e (rel. int. %): 369 (M^+, 12), 338(100), 294(43), 277(3), 265(40), 254(3), 83(10).

Anal. $C_{18}H_{19}N_5O_4$: Calc. C, 58.53; H, 5.14; N, 18.97
(369) Found: C, 58.10; H, 5.60; N, 18.60

Step-3: Acetylation of the azo intermediate (6):

The compound 6 (3.69 g, 0.01 mol), pyridine (0.79 g, 0.01 mol) and acetic anhydride (10 ml) was mixed and refluxed on a water bath for 5 h. The reaction mixture was poured into ice. The separated product was collected by filtration and its purity was checked by TLC in chloroform. The product was crystallized from ethyl acetate, yield 4.3 g (95%), m.p. 168°C.

The dye synthesised as above was identical in all respects (UV-visible, IR, NMR, Mass and elemental analysis) with the isolated commercial dye 3. The mixed m.p. remained undepressed.

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PART-B

STRUCTURAL FEATURES OF C.I. DISPERSE YELLOW 232 AND ITS SYNTHESIS

INTRODUCTION

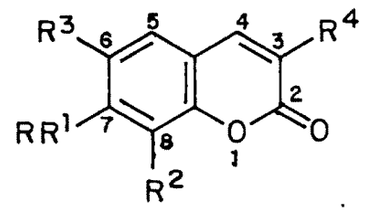
All fluorescent brightening agents[1] known upto the present time are derived from aromatic compounds or pseudoaromatic (unsaturated) heterocyclic components linked together by direct bonds or small bridges such as CO-, NHCO, NHCONH, -CH = N- or -CH = CH-. According to physical conception, their molecules possess extensive resonance or possess electron system which can be excited sufficiently in the range of 340-400 nm. They can be classified in definite fluorescence system corresponding to the empirical or physical conception. These are, in particular, the systems derived from stilbene, coumarin, 1,3-diphenyl pyrazoline, naphthalimide and aryloxazoles, all of which allow numerous variations based on chemical principles.

Coumarins with an electron-donating substituents in position 7, with electron withdrawing or electron delocalizing substituents in position 3 are known to exhibit particularly strong fluorescence. These fluorescent dyes[2,3] (1, CHART 1) are used in safety clothing and in warning and signalling colours. They are also used as photographic sensitizers.[4]

A number of coumarin derivatives (2, CHART 2) have found widespread applications as optical brighteners[5,6,7] for polyester and polyamide fibres, and for poly(vinyl chloride) substrates. An introduction of a strong fluorophore like benzoxazolyl radical at the 3-position of coumarin with additional auxochromic amino group at position-7 can shift the absorption into the visible region and can be used as greenish

yellow fluorescent dyestuff.[8] This is also supported by another German patent[9] where similar type of dyes (4, 5, CHART 3) are prepared and used for dyeing polyester fibres in brilliant greenish yellow shades.

CHART-1



1

R, R^1 = C_{1-4} alkyl or C_{1-3} phenyl alkyl

R^2, R^3 = H; or RR' = $(CH_2)_2Z(CH_2)_2$

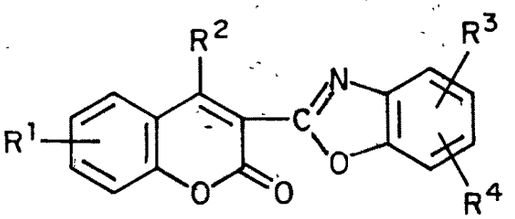
RR^3 = $(CH_2)_2$, $(CH_2)_3$ or Me_2CCH_2CHMe;

R^1R^2 = $(CH_2)_3$

Z = O, NH, NMe, CH_2 or a direct bond

and R^4 = heterocyclic ring

CHART-2



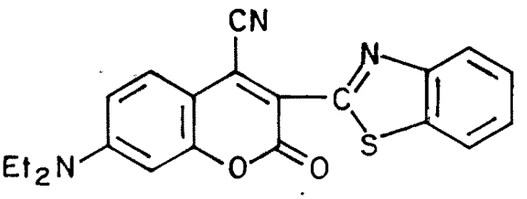
2

R^1 = H, 6-Me or 6-Cl

R^2 = H or Me

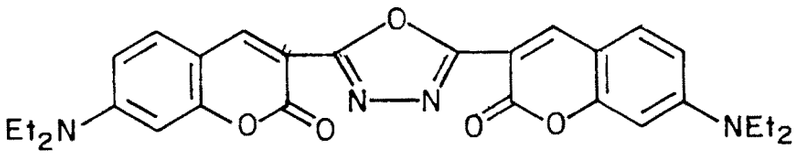
R^3 = H, 5 or 6-Me, or 5-Cl

R^4 = H or 6-Me

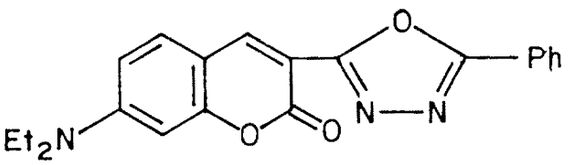


3

CHART-3

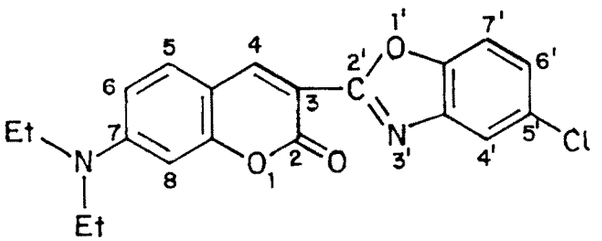


4



5

CHART-4



6

PRESENT WORK

In continuation of the efforts[10] to deduce the chemical constitution of commercial fluorescent systems which may have applications as dye lasers and in luminescent solar concentrators, study towards the elucidation of the structure of Intrasil Brilliant Yellow 10GF (Crompton-Knoweles Corporation) was taken up. It is classified in 'Colour Index' as an azo dye, C.I. Disperse Yellow 232 with brilliant greenish yellow hue on polyester with no constitution number. It is also reported to have a good light (4-5), sublimation (5) and washing fastness properties.[11]

Eventhough it has been described to have an azo constitution, it is confirmed now that the dye does not possess azo group but possesses an aryloxazole and a coumarin ring, contributing to the fluorescence exhibited by the dye. A detailed study of the spectral and elemental analyses, aided by literature survey of similar compounds, established the structure of the dye to be 3-(5'-chloro-2'-benzoxazolyl)-7-diethylamino-2H-1-benzopyran-2-one (**6**). Further, the structure of the dye was unambiguously established by its synthesis from readily available starting materials. The structure was finally confirmed by X-ray crystallography.

A sample of the commercial product, Intrasil Brilliant Yellow 10GF (C.I. Disperse Yellow 232) was extracted with chloroform in a soxhlet extractor to free it from inorganic and other diluents. The fluorescent greenish yellow pasty

extract on removal of the solvent by distillation left a solid material (20% of the commercial dye), which on TLC examination using chloroform as the eluent showed only one spot. After purification by column chromatography and crystallization from acetone, the spectral and elemental analyses were recorded.

The anthraquinone or the azo constitution for the dye (Disperse Yellow 232) was discounted by subjecting it to the treatment of alkaline dithionite (vatting), when neither decolourisation nor any colour change was observed. This prompted us to look for other structures such as coumarins, naphthalimides, benzoxazoles and other heterocycles which normally exhibit fluorescence in daylight. On the basis of elemental analysis and molecular weight obtained from the mass spectrum, the molecular formula of the dye was derived as $C_{20}H_{17}ClN_2O_3$. The detailed spectral analysis of the dye aided by literature survey based on the derived molecular formula led to the elucidation of its chemical constitution as the coumarin derivative, 3-(5'-chloro-2'-benzoxazolyl)-7-diethylamino-2H-1-benzopyran-2-one (**6**).

The electronic spectrum of **6** in the UV region revealed a characteristic wavelength maximum of low intensity at 282 nm corresponding to a coumarin nucleus. The high intensity wavelength maximum at 452 nm was indicative of the brilliant greenish yellow colour of the dye. The IR spectrum (FIG. 1) revealed a strong carbonyl stretching frequency at 1720 cm^{-1} attributable to the α,β-unsaturated lactone of the dye molecule.

The ^{1}H-NMR spectrum (FIG. 2) revealed a triplet and a quartet centred at 1.16 and 3.37 respectively, corresponding to the methyl and methylene protons of the diethylamino substituent. A meta-coupled doublet at 6.42 (J=2Hz) integrating for one proton was assigned to 8-H, taking into consideration the proximity of the electron-donating nitrogen and oxygen atoms at ortho positions. The doublet of a doublet centred at 6.75 was indicative of a 6-H proton ortho to the diethylamino substituent. The ortho-coupled doublet at 7.22 (J=9Hz) was ascribed to the more shielded 7'-H proton of the benzoxazole ring; and the doublet at 7.40 (J=10Hz) was assigned to the deshielded 5-H of the coumarin skeleton. The 6'-H proton of the benzoxazole ring appeared as a quartet (doublet of doublet) centred at 7.15. The magnetic resonance signal due to 4'-H appeared as a meta-coupled doublet at 7.64 (J=2Hz). The most deshielded proton in the NMR spectrum at 8.5 which appeared as a singlet, was attributed to the 4-H proton of the coumarin nucleus which is in conjugation with the electron-withdrawing C = O and C = N linkages.

The mass spectrum (FIG. 3) showed the molecular ions at 368 (M^{+}) and 370 $(M+2)^{+}$ corresponding to the typical ^{35}Cl and ^{37}Cl isotopes present in the dye. The first facile loss of a methyl group from the dialkylamino substituent to give a peak at 353 in good relative abundance was in agreement with such a fragmentation reported for 7-diethylamino-4-methyl coumarin.[13] The fragment ion at 325 ($M-CH_3-CO$), 311 ($M-C_2H_5$ – CO), 296

(M-CH_3-CO-COH), 282 (M-C_2H_5-CO-COH), 269 (M-CH_3-2CO-C_2H_4) and 268 (M-CH_3-CO-COH-C_2H_4) were in good agreement with **6**, the structural assignment made for the dye.

The elucidated structure **6** of the dye was confirmed by synthesis. The synthetic dye was found to be identical with the sample isolated from commercial dye by TLC, mixed melting points and superimposable visible and IR spectra (FIG. 1).

The elucidated structure of the dye **6** was confirmed by its unambiguous syntheses by **Methods A and B.**

The Method-A involves condensation of the 2H-1-benzopyran-2-one acid or the ester derivatives (**7a, 7b**) with 4-chloro-2-aminophenol (SCHEME 1).[8] The benzopyran-2-one **7** was prepared from the commercially available diethyl meta-aminophenol (DEMAP) either by a multistep process as in SCHEME 2 or by a reported single step process[12] (SCHEME 3).

In the Method-B, N-(3-methoxypropyl)cyano acetamide (**16**) (SCHEME-3) prepared by the condensation of ethylcyanoacetate with methoxypropylamine (**15**) was reacted with **8** to yield benzoxazolylacetamide **17**. The acetamide **17** was condensed with 4-diethylaminosalicylaldehyde **12** as prepared in SCHEME 2 in the presence of catalytic amount of piperidine to yield the dye **6**. The process is illustrated in SCHEME 4.[3,4]

The condensation involving o-aminophenol **8** was performed in an atmosphere of nitrogen to suppress its autoxidation to the undesired products. The key intermediate in the synthesis of the dye **6** by Method-A is the benzopyran ethylester **7b**.

Although **7b** was hydrolyzed to the new carboxylic acid **7a** in good yield, it was found that both **7a** and **7b** react with 4-chloro-2-aminophenol to give **6** in comparable yields (~75%). The compound **7b** could be synthesized in four steps (SCHEME 2) or in one step (SCHEME 3). The synthesis of **7b** by SCHEME 2 involves the use of diethylethoxymethylene malonate and titanium tetrachloride. But in SCHEME 2 comparatively cheaper reagents such as diethyl malonate are used. Titanium tetrachloride poses material handling problem in scale-up operations of the commercial process. The relative importance of SCHEME 2 is also enhanced by the fact that it allows the synthesis of diethylaminosalicylaldehyde **12** which can be utilized for the alternative synthesis of **6** by Method-B. A salient feature of Method-B is that it enables us to recover and reuse one of the reactants viz. 3-methoxypropylamine (**15**). The process economics can be further improved if ethylamine or propylamine can be used instead of **15**.

Diethylmetaaminophenol (DEMAP) **9** (SCHEME 2) was methylated using dimethylsulphate and alkali to give the methyl ether **10**. The appearance of the methoxy proton at 3.7 as a singlet confirms the formation of **10**. The methyl ether **10** was formylated using $DMF/POCl_3$ to give the aldehyde **11**. For compound **11**, in IR spectrum the typical overtone band of the aldehyde group is seen at 2670 cm^{-1}. The ^1H-NMR spectrum also shows the aldehyde proton at 9.9 as a singlet. The compound **11** was demethylated using anhydrous aluminium chloride in ethylene dichloride to give 4-diethylaminosalicylaldehyde **12**. For **12**, in IR spectrum

the typical overtone band of the aldehyde function is observed at 2360 cm^{-1}. The OH stretching probably is not seen due to the hydrogen bonding with the carbonyl oxygen. The ^{1}H-NMR spectra shows the absence of the methoxy group. The appearance of the OH proton at 11.6 as a broad singlet confirmed the formation of **12**. The compound **12** on treatment with diethylmalonate in presence of piperidine gave the benzopyran derivative **7b**. The IR spectrum of **7b** shows the lactone group at 1710 cm^{-1}.

In ^{1}H-NMR spectrum of **7b**, the methyl protons of the carbethoxy group and N-ethyl group are seen as triplets centred at 1.4 and 1.2 respectively. The quartet centred at 3.43 and 4.36 can be assigned to the methylene protons of N-ethyl and carbethoxy groups respectively. The 8-H proton of the aromatic ring is seen as a doublet at 6.63 (J=8Hz). The 4-H proton is observed at 8.33 as a singlet. The ester **7b** on hydrolysis yielded the free carboxylic acid **7a**. In the case of **7a**, IR spectrum shows the cyclic keto group at 1730 cm^{-1}. In ^{1}H-NMR spectrum of **7a**, the methyl and methylene protons are seen centred at 1.24 and 3.48 as a triplet and quartet respectively. The 6-H proton is seen at 6.48 as multiplet. The 8-H proton is seen as a doublet at 6.76 (J=8Hz) and 5-H is seen as a doublet at 7.44 (J=9Hz). The 4-H proton is observed as a singlet at 8.68. In the mass spectra[13] of all compounds, viz. **10**, **11**, **12**, **7a** and **7b**, the loss of methyl group from the diethylamino group (M^+ -15) occurs spontaneously and gives rise to the base

peak. The rest of the fragmentation is in accordance with the structure of each compound.

X-Ray Data:

The structure 6 of Intrasil Brilliant Yellow 10GF was confirmed by X-ray crystallography[15] and was found to be 3-(5'-chloro-2-benzoxazolyl)-7-(diethylamino)-2H-1-benzopyran-2-one $C_{20}H_{17}ClN_2O_3$, Mr = 369, crystallizes in monoclinic systems. The space group is $P2_1/a$. The cell dimensions are: a = 9.262(2), b = 13.282(2), c = 14.453(a), A°, β = 104.16 (2)°. Density by floatation method using potassium iodide solution is 1.43 g/cc and then calculated density by X-ray method is 1.47 g/cc. A crystal of a size 0.2 x 0.05 x 1.00 mm was used for X-ray data. Collection was done on Nonius CAD-4F-11M X-ray diffractometer. MoK α radiation wavelength = 0.7107 A° was used. Structure was solved by direct methods using MULTAN 78. The dihedral angle between the benzoxazoline and the benzopyrone moieties is 5.9° showing significant deviation from planarity. The ring systems are planar.

A perspective view of the molecule along with the crystallographic numbering of atoms is given in FIG. 4. Bond distances and bond angles are given in Table 1.

Table 1: Bond distances (A) and bond angles (°) with e.s.d.'s in parentheses

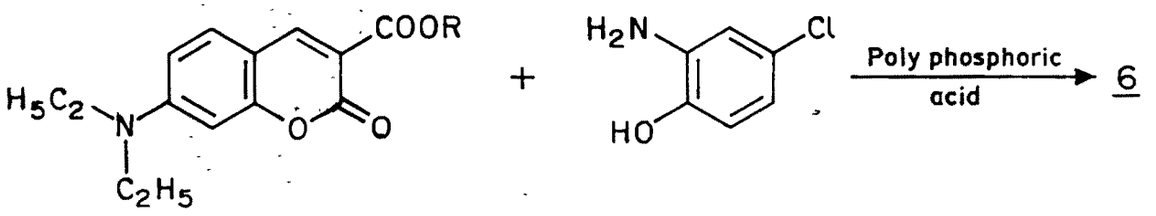
Cl-C(5')	1.735(9)		
O(1)-C(2')	1.364(9)		
O(1)-C(7')	1.363(8)		
		C(2')-O(1)-C(7')	103.7(5)
O(2)-C(1)	1.353(8)		
O(2)-C(2)	1.378(8)		
		C(1)-O(2)-C(2)	124.0(5)
O(3)-C(2)	1.185(9)		
C(1')-C(2')	1.402(11)		
C(1')-C(6')	1.361(11)		
C(1')-N(1)	1.443(9)		
		C(2')-C(1')-C(6')	121.8(7)
		C(2')-C(1')-N(1)	106.2(6)
		C(6')-C(1')-N(1)	132.0(7)
C(2')-C(3')	1.358(10)		
		O(1)-C(2')-C(1')	109.2(6)
		O(1)-C(2')-C(3')	129.8(7)
		O(1')-C(2')-C(3')	121.0(7)
C(3')-C(4')	1.406(11)		
		C(2')-C(3')-C(4')	117.9(7)
C(4')-C(5')	1.368(13)		
		C(3')-C(4')-C(5')	119.2(7)
C(5')-C(6')	1.371(12)		
		Cl-C(5')-C(4')	117.4(7)
		Cl-C(5')-C(6')	118.7(7)
		C(4')-C(5')-C(6')	123.8(8)
		C(1')-C(6')-C(5')	116.3(8)
C(7')-C(3)	1.469(10)		
C(7')-N(1)	1.283(9)		
		O(1)-C(7')-C(3)	119.7(6)
		O(1)-C(7')-N(1)	117.0(6)
		C(3)-C(7')-N(1)	123.3(6)
C(1)-C(8)	1.385(10)		
C(1)-C(9)	1.387(10)		
		O(2)-C(1)-C(8)	117.0(6)
		O(2)-C(1)-C(9)	121.0(6)
		O(3)-C(7')-N(1)	123.3(6)
C(2)-C(3)	1.451(9)		
		O(2)-C(2)-O(3)	116.5(6)
		O(2)-C(2)-C(3)	115.9(6)
		O(8)-C(1)-C(9)	122.0(7)
C(3)-C(4)	1.357(9)		
		C(7')-C(3)-C(2)	121.5(6)
		C(7')-C(3)-C(4)	119.3(6)
		C(2)-C(3)-C(4)	119.2(6)

contd....

Table 1 contd..

C(4)-C(9)	1.408(10)		
		C(3)-C(4)-C(9)	123.2(6)
C(5)-C(6)	1.396(10)		
C(5)-C(9)	1.401(10)		
		C(6)-C(5)-C(9)	120.4(7)
C(6)-C(7)	1.419(10)		
		C(5)-C(6)-C(7)	120.0(7)
C(7)-C(8)	1.401(10)		
C(7)-N(2)	1.361(10)		
		C(6)-C(7)-C(8)	119.0(7)
		C(6)-C(7)-N(2)	119.3(7)
		C(8)-C(7)-N(2)	121.6(7)
		C(1)-C(8)-C(7)	119.7(7)
		C(1)-C(9)-C(4)	116.6(7)
		C(1)-C(9)-C(5)	118.8(7)
		C(4)-C(9)-C(5)	124.5(7)
C(10)-C(11)	1.475(11)		
C(10)-N(2)	1.496(10)		
		C(11)-C(10)-N(2)	111.4(6)
C(12)-C(13)	1.509(11)		
C(12)-N(2)	1.456(9)		
		C(13)-C(12)-N(2)	114.4(6)
		C(1')-N(1)-C(7')	103.9(6)

SCHEME-1

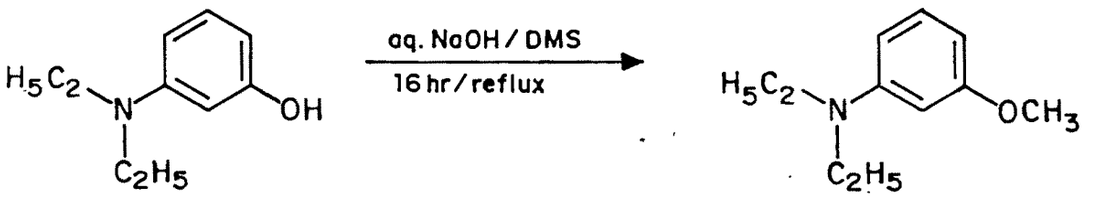


8

7a: R = H

7b: R = C_2H_5

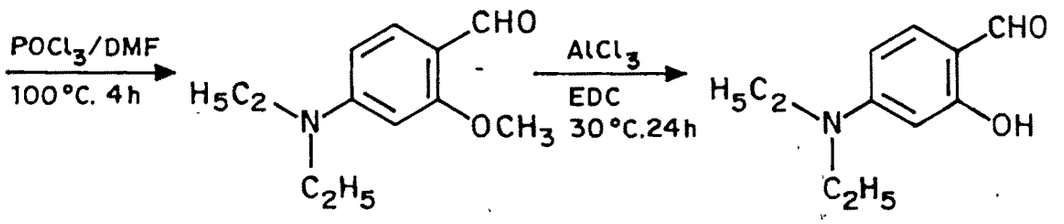
SCHEME-2



9

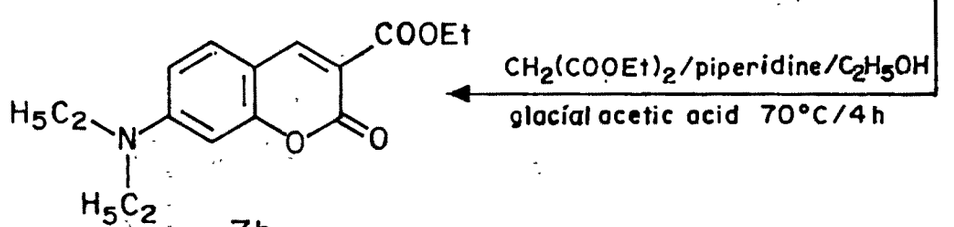
10

(90 %)

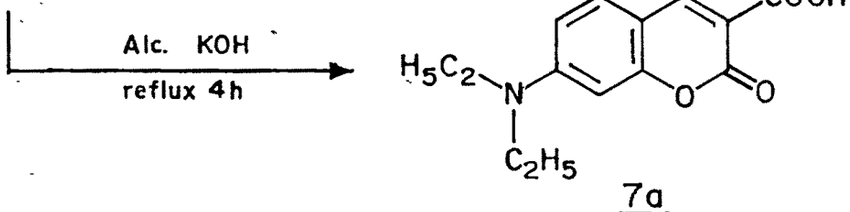


11

12

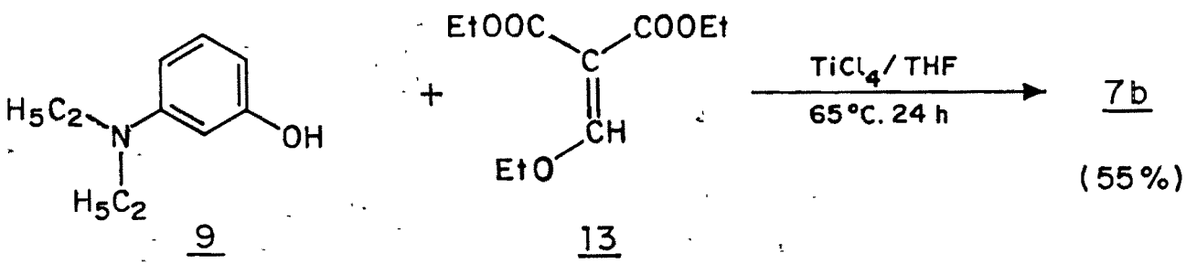


7b

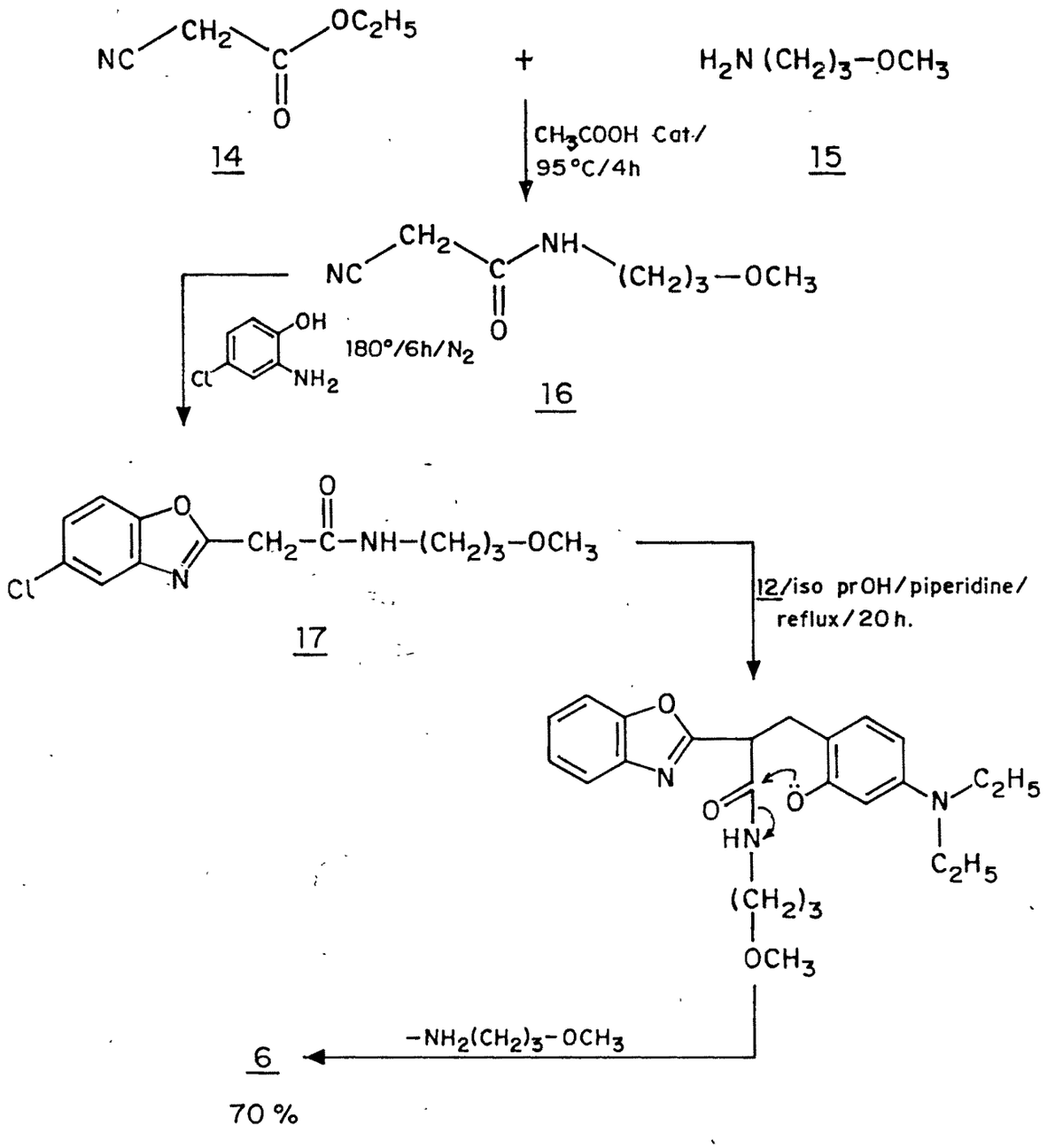


7a

SCHEME - 3



SCHEME - 4



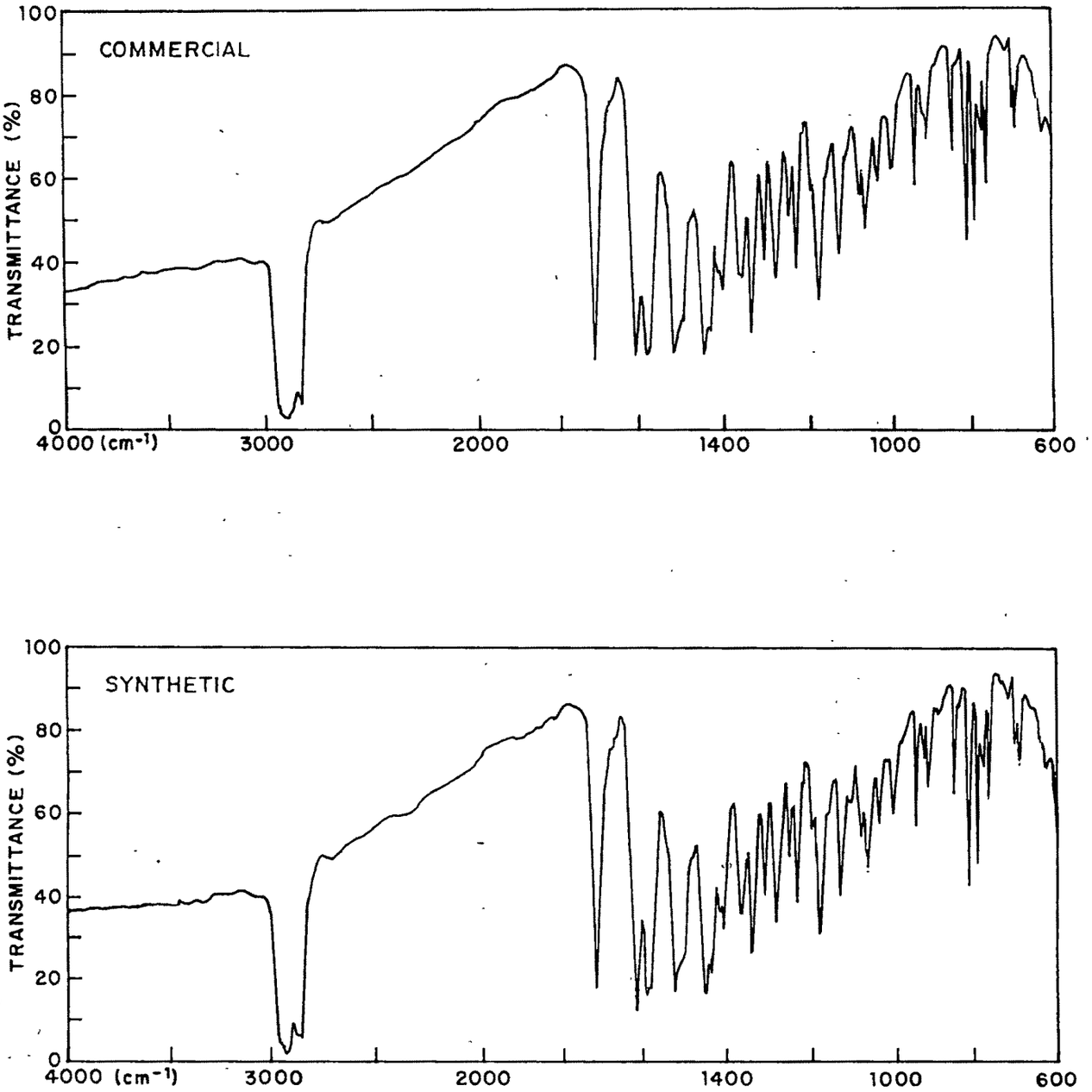
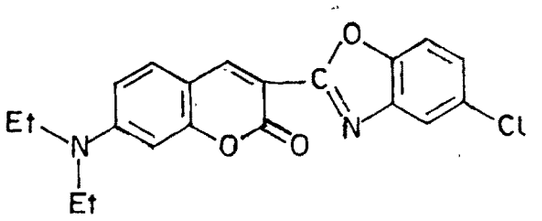

COMMERCIAL
TRANSMITTANCE (%)
100
80
60
40
20
0
4000 (cm⁻¹)
3000
2000
1400
1000
600
SYNTHETIC
TRANSMITTANCE (%)
100
80
60
40
20
0
4000 (cm⁻¹)
3000
2000
1400
1000
600

FIG. 1


Et
N
Et
O
O
C
N
O
Cl

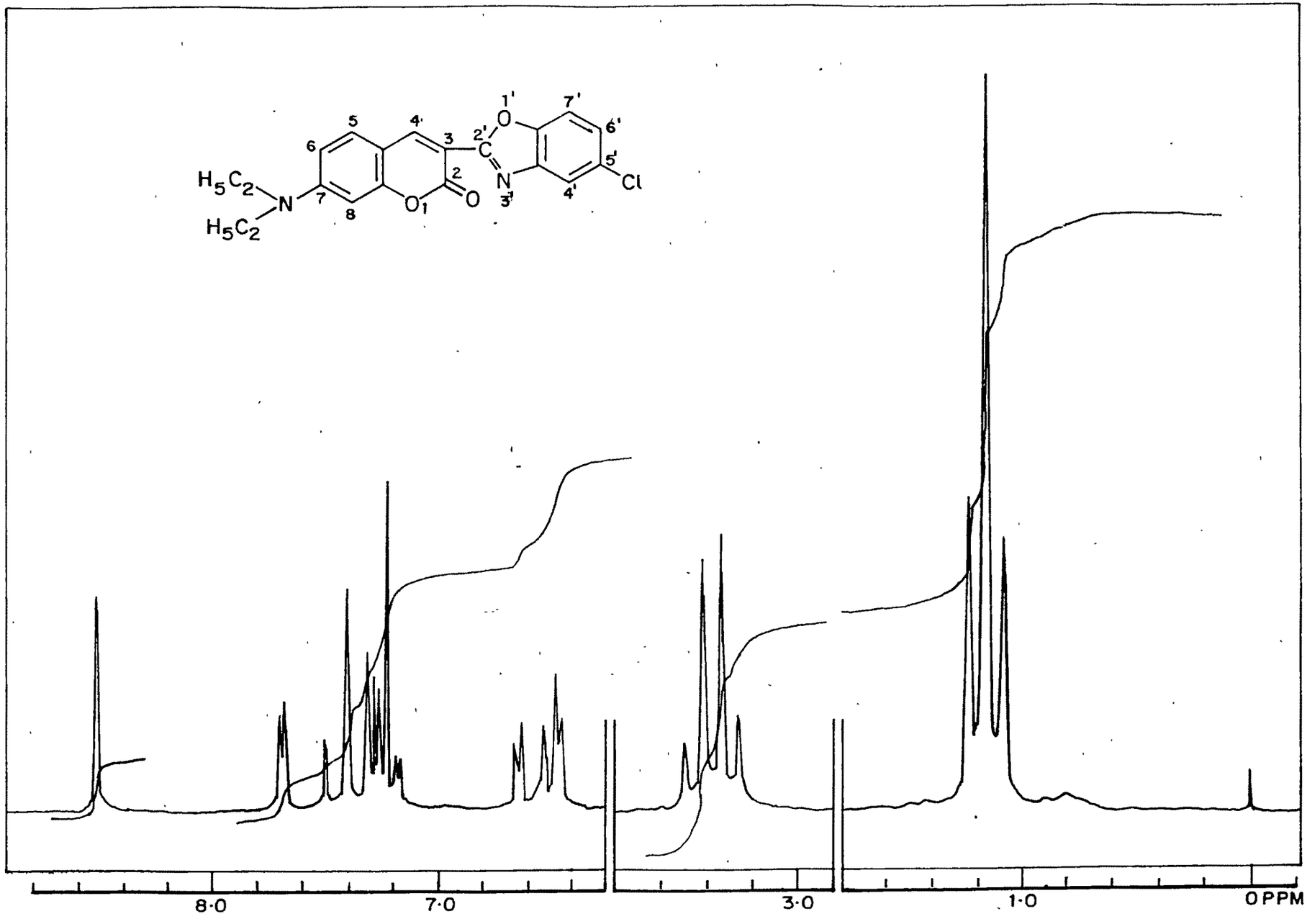


FIG. 2

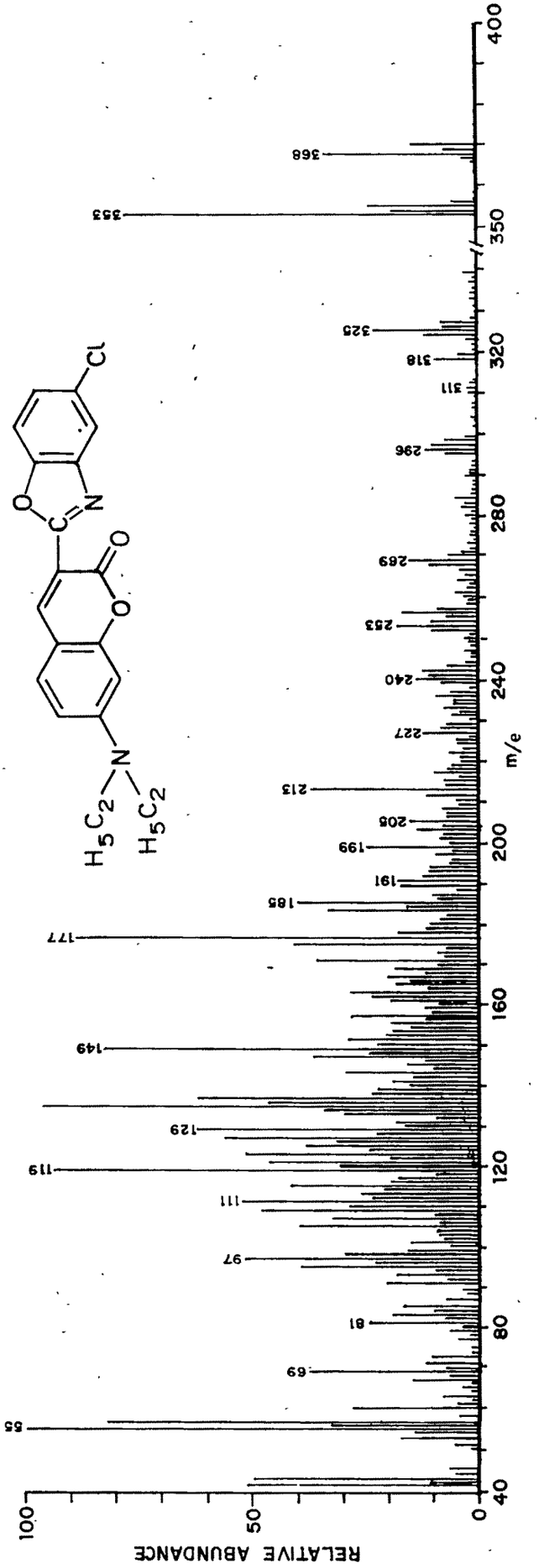

RELATIVE ABUNDANCE
100
50
0
m/e
40
80
120
160
200
240
280
320
350
400
55
69
81
97
111
119
129
149
177
185
191
199
205
213
227
240
253
269
296
311
318
325
353
368
Cl
O
N
O
O
H_5C_2
N
H_5C_2

FIG. 3

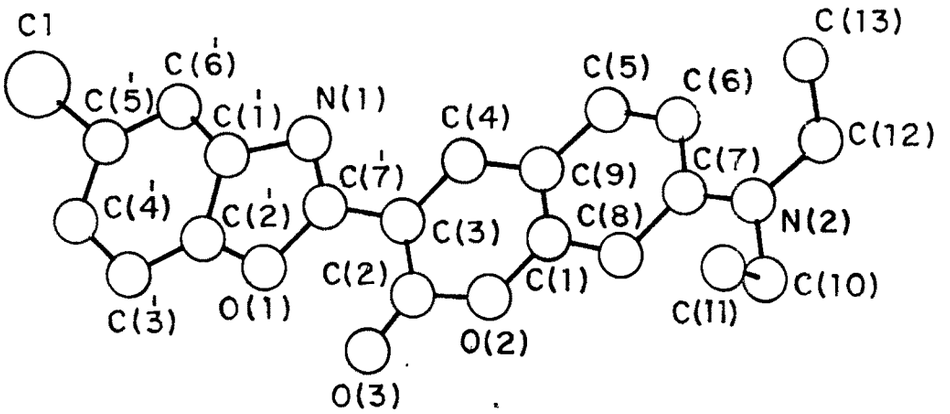


FIG. 4 A PERSPECTIVE VIEW OF THE MOLECULE WITH ATOMIC NUMBERING.

EXPERIMENTAL

Isolation and purification of the commercial Disperse Yellow 232 (6):

The commercial dye (5 g) was dried at 50°C under reduced pressure and the dry sample was extracted with chloroform (500 ml) for 24 h. Removal of the solvent from chloroform extract yielded a brown solid (0.88 g), TLC of which on silica gel showed a single brilliant greenish yellow spot with Rf value of 0.5 when eluted with chloroform. The extracted dye (0.88 g) was purified by chromatography through a silica gel column using a mixture of chloroform and pet. ether (v/v, 4:1) as eluent. The chromatographed dye was crystallized from acetone, m.p. 195°C.

IR (Nujol, cm^{-1}): 1720, 1620, 1520, 1450, 1340, 1240, 1180, 1140, 1070, 1050, 1010, 960, 920, 835, 800, 785, 760.

^{1}H-NMR ($CDCl_3$): 1.16(6H, t, $N-CH_2-\underline{CH}_3$), 3.37 (4H, q, $N-\underline{CH}_2-CH_3$), 6.42 (1H, d, 8H, J=2Hz), 6.75 (1H, dd, 6-H), 7.15 (1H, q, 6'-H), 7.22 (1H, d, 7'-H, J=9Hz), 7.40 (1H, d, 5-H, J=10Hz), 8.5 (1H, s, 4-H).

MS: m/e (rel. int. %) 368 (M^+, 33), 353 (76), 325(23), 213 (37), 185(39), 177(88), 149(83), 135(96), 129(62), 119(94), 111(53), 97(52), 69(38), 55(100).

^{13}C Spectra ($CDCl_3$): 161.10, 157.59, 152.24, 148.77, 145.56 142.73, 130.67, 129.87, 125.07, 119.61, 111.03, 110.17, 108.47, 105.79, 97.30, 45.34, 12.22.

Anal. $C_{20}H_{17}ClN_2O_3$: Calc. C, 65.23; H, 4.61; N, 7.60; Cl, 9.61
(368) Found: C, 65.32; H, 4.21; N, 7.75; Cl, 9.15

UV-Visible: λ_{max} (DMF) 282 nm (ϵ = 4121); 452 nm (ϵ = 61618)

Synthesis of 3-(5'-chloro-2'-benzoxazolyl)-7-diethylamino-2H-1-benzopyran-2-one (I) (Intrasil Brilliant Yellow 10 GF)

Method A:

The dye was synthesised by the condensation of 7-diethylamino-2H-1-benzopyran-2-one-3-carboxylic acid or its ethyl ester (**7a, 7b**) with 4-chloro-2-aminophenol (**8**) (SCHEME 1). The benzopyran-2-one (**7**) was synthesised starting from diethyl-m-aminophenol (DEMAP) (**9**) in five steps (SCHEME 2) or in a single step (SCHEME 3).

Preparation of DEMAP methyl ether (10) (Scheme 2):

To a solution of DEMAP 16.5 g (0.1 mol) in aqueous sodium hydroxide (5% w/v, 100 ml), dimethyl sulphate 27.7 g, (0.022 mol) was added dropwise with stirring over 1 h. The reaction mixture was heated at 95-98°C for 5 h. and then poured into ice-cold water. The aqueous mixture was extracted with chloroform, then the chloroform layer was repeatedly washed with water and dried. Removal of chloroform gave the methyl ether **10**. Distilled under vacuum as a colourless liquid; $b.p._{14}$ 147-148°C (lit.[16] $b.p._{14}$ 146-148°C); yield, 16.1 g (90%).

IR (Neat, cm^{-1}): 1600, 1570, 1500, 1470, 1370, 1350, 1320, 1280, 1220, 1180, 1145, 1070, 830, 750, 700.

^{1}H-NMR ($CDCl_3$): 1.13 (6H, t, N-CH_2-$\underline{CH_3}$), 3.33 (4H, q, N-$\underline{CH_2}$-CH_3), 3.8 (3H, s, OCH_3), 6.26 (3H, m, 2-H, 4-H & 5-H), 7.2 (1H, m, 6-H).

MS: m/e (rel. int. %), 179 (M^+, 23), 164(100), 150(30), 136(39), 121(3).

Anal. $C_{11}H_{17}NO$ Calc: C, 73.74; H, 9.49; N, 7.82.
(179) Found: C, 73.13; H, 9.70; N, 7.60.

Preparation of 4-diethylamino-2-methoxybenzaldehyde (11):

Phosphorous oxychloride 18.4 g (0.12 mol) was slowly added over 1 h. into cooled dimethylformamide 36.5 g(0.5 mol) at 0°C and the mixture was stirred further for 1 h. at 0°C. Then DEMAP methyl ester (**10**) 17.9 g (0.10 mol) was added dropwise over 1 h. and the mixture heated on a boiling water bath for 4 h. It was cooled and poured into ice cold water. The pH of the slurry was adjusted to 4-4.5 and filtered. After cooling, the separated solid product was dried, crystallized from pet. ether; m.p. 76°C (lit.[17] m.p. 73-76°C), yield 10.3 g (50%).

IR (Nujol, cm^{-1}): 2670, 1640, 1470, 1400, 1360, 1270, 1220, 1180, 1150, 1080, 1020.

^{1}H-NMR: ($CDCl_3$): 1.16 (6H, t, N-CH_2-$\underline{CH_3}$), 3.33, 4H, q, N-$\underline{CH_2}$-CH_3), 3.7 (3H, s, OCH_3), 5.93 (1H, m, 5-H), 6.13 (1H, d, 3-H, J=3Hz), 7.46 (1H, d, 6-H, J=9Hz), 9.9 (1H, s, -$\underline{CH}$O).

MS m/e (rel. int. %): 207 (M^+, 52), 192(100), 164(33), 148(6), 136(15), 121(8), 108(7), 91(3), 77(3).

Anal. $C_{12}H_{17}NO_2$ Calc: C, 69.60; H, 8.22; N, 6.81.
207 Found: C, 69.41; H, 8.12; N, 6.70.

Preparation of 4-diethylaminosalicylaldehyde (12):

4-Diethylamino-2-methoxybenzaldehyde (11) 4.14 g (0.02 mol) was stirred in ethylenedichloride (60 ml) and powdered anhydrous aluminium chloride (2.66 g, 0.4 mol) was then added rapidly. Care was taken to perform the reaction under strictly anhydrous conditions. The reaction mixture was stirred at room temp. for 24 h. and the product was isolated by pouring into water, extraction with chloroform and removal of the solvent; m.p. 67°C (lit.[18] m.p. 65-67°C), yield 3.2 g (89%).

IR (Nujol, cm^{-1}): 2360, 1620, 1550, 1520, 1450, 1340, 1240, 1120, 1080, 840, 800, 770, 700.

^{1}H-NMR ($CDCl_3$): 1.20 (6H, t, N-CH_2-$\underline{CH_3}$), 3.40 (4H, q, N-$\underline{CH_2}$-CH_3), 6.12 (1H, dd, 5-H), 6.33 (1H, d, 3-H, J=2.5Hz), 7.28 (1H, d, 6-H, J=9Hz), 9.53 (1H, s, $\underline{CH}$O), 11.64 (1H, bs, OH, exchangeable with D_2O).

MS m/e (rel. int. %): 193 (M^+, 34), 178(100), 162(5), 150(67), 136(7), 122(9), 104(4), 94(8), 77(3) and 54(4).

Anal. $C_{11}H_{15}NO_2$: Calc. C, 68.41; H, 7.80; N, 7.25.
(193) Found: C, 68.52; H, 8.0; N, 7.12.

Preparation of 7-diethylamino-2H-1-benzopyran-2-one-3-carboxylic acid ethyl ester (7b):

To a mixture of the aldehyde 12 (2.89 g, 0.015 mol), diethyl malonate (2.40 g, 0.015 mol) and piperidine (1.27 g, 0.015 mol) in ethanol (40 ml), a drop of glacial acetic acid was added. The reaction mixture was refluxed for 4 h and ethanol was then removed by distillation. The residual mass

was poured into ice-cold water and the pH of the aqueous slurry was adjusted to 4.5-5.0 by careful addition of conc. hydrochloric acid. After cooling, the solid product which separated was filtered and dried. The crude product was dissolved in acetone, adsorbed on silica gel and chromatographed through a column of silica gel, using acetone petroleum ether mixture (1:10, v/v) as the eluting solvent to give pure **7b**; m.p. 87°C (lit.[7] m.p. 87°C).

IR (Nujol, cm^{-1}): 1710, 1630, 1610, 1520, 1450, 1380, 1240, 1200, 1140, 1120, 1030, 930, 830.

^{1}H-NMR ($CDCl_3$): 1.2 (6H, t, $N-CH_2-\underline{CH_3}$), 1.4 (3H, t, $OCH_2-\underline{CH_3}$), 3.43 (4H, q, $N-\underline{CH_2}-CH_3$), 4.36 (2H, q, $O-\underline{CH_2}-CH_3$), 6.40 (1H, d, 8-H, J=2Hz), 6.63 (1H, dd, 6-H), 7.30 (1H, d, 5-H, J=9Hz), 8.33 (1H, s, 4-H).

MS m/e (rel. int. %): 289 (M^+, 45), 274(100), 246(14), 200(8), 188(4), 174(6), 160(5), 144(4), 116(5), 77(3), 43(3).

Anal. $C_{16}H_{19}NO_4$: Calc. C, 66.41; H, 6.62; N, 4.80.
(289) Found: C, 66.40; H, 6.41; N, 4.52.

Preparation of 7-diethylamino-2H-1-benzopyran-2-one-3-carboxylic acid (7a):

The ethyl ester **7b** (1.44 g, 0.005 mol) was added to a solution of potassium hydroxide (0.35 g, 0.006 mol) in ethanol (100 ml) and the mixture refluxed on a water bath for 4 h. Ethanol was removed by distillation and the residual mass was poured into ice-cold water, the pH of the resulting slurry adjusted to 2-3 by addition of dilute hydrochloric acid (10% w/v) and then extracted with chloroform. Further work-up in

the usual manner after the removal of chloroform yielded **7a**. Crystallized from pet. ether-ethylacetate mixture (1:1); m.p. 220°C. Yield 1.15 g (88.5%).

IR (Nujol, cm^{-1}): 1730, 1600, 1560, 1490, 1440, 1390, 1260, 1180, 1120, 1070, 1000, 795.

^{1}H-NMR ($CDCl_3$): 1.24 (6H, t, CH_2-$\underline{CH_3}$), 3.48 (4H, q, $\underline{CH_2}$-CH_3), 6.48 (1H, d, 8H, J=2Hz), 6.66 (1H, dd, 6-H), 7.44 (1H, d, 5-H, J=9Hz), 8.68 (1H, s, 4-H).

MS m/e (rel. int. %): 261 (M^+, 55), 246(100), 202(15), 174(33), 145(14), 116(16), 89(23), 77(19), 63(21), 45(30).

Anal. $C_{14}H_{15}NO_4$: Calc: C, 64.43; H, 5.75; N, 5.42.
(261) Found: C, 64.72; H, 5.90; N, 5.01.

One step preparation of 7-diethylamino-2H-1-benzopyran-2-one-3-carboxylic acid ethyl ester 12 (7b) (Scheme 3):

To a cooled solution (0°C) of a mixture of DEMAP (7.95 g, 0.05 mol) and diethylethoxymethylenemalonate (11.8 g, 0.055 mol) in dry tetrahydrofuran (40 ml), titanium tetrachloride (6 ml) was added rapidly. The temperature was slowly raised to 65°C over 0.5 h and the mixture stirred for 24 h at 65°C.The crude material, obtained after pouring into ice and extraction with chloroform was subjected to column chromatography on silica gel using chloroform as eluent to afford 7b, yield 7.9 g (55%). The compound was characterized by spectral and elemental analysis.

Preparation of 3-(5'-chloro-2'-benzoxazolyl)-7-diethylamino-2H-1-benzopyran-2-one (6)[7] (Scheme 1):

A mixture of the benzopyran-3-carboxylic acid **7a** (0.261

g, 0.001 mol) or its ethyl ester 7b (0.289 g, 0.001 mol), 4-chloro-2-aminophenol (0.143 g, 0.001 mol) and polyphosphoric acid (1.0 g) was stirred at 180°C for 3 h in an inert atmosphere (nitrogen). The mixture was poured into ice-cold water (50 ml), the pH adjusted to 8.5 by sodium carbonate solution (10% w/v) and extracted with chloroform (300 ml). The chloroform layer was washed with water and dried over anhydrous sodium sulfate. After removal of chloroform by distillation, the residual crude dye was purified by column chromatography using chloroform-pet. ether (4:1) as eluent. The dye was crystallized from acetone in yellow needles; m.p. 195°C, yield 0.276 g (75%). The dye synthesised as above was identical in all respects (IR, NMR, mass and elemental analysis) with the isolated commercial dye **6**. The mixed m.p. remained undepressed.

Method B:

Alternative synthesis of 6 (Disperse Yellow 232) (Scheme 4):

A mixture of ethylcyanoacetate (14) (1.13 g, 0.01 mol), 3-methoxypropylamine (0.89 g, 0.01 mol) and glacial acetic acid (0.1 ml) was heated with stirring at 95°C for 4 h. in an inert atmosphere (nitrogen). The reaction mixture was cooled to 29°C and 4-chloro-2-aminophenol (1.43 g, 0.01 mol) was added. It was heated at 180°C for 6 h. under stirring under nitrogen and then cooled to 29°C. 4-Diethylaminosalicylaldehyde (12) (1.93 g, 0.01 mol) in isopropanol (25 ml) was added and the mixture was refluxed for 20 h, maintaining the nitrogen

atmosphere. The reaction mixture was poured into ice-cold water (200 ml) and the pH of the slurry adjusted to 3 by the addition of dilute hydrochloric acid (10%, w/v). The precipitated crude dye was filtered and further purified by column chromatography using chloroform - pet. ether (4:1) mixture. Yield 2.5 g (70%). The dye was identical in all respects to the dye prepared by Method A and isolated commercial dye.

X-Ray crystallography:

The structure of Disperse Yellow 232 was confirmed by X-ray crystallography.

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PART-C

SYNTHESIS, LASER CHARACTERISTICS AND DYEING BEHAVIOUR OF NOVEL 7-DIETHYLAMINO-2H-1-BENZOPYRAN-2-ONES

INTRODUCTION

It may be recalled that the preceding part (Part B) described the structure elucidation of C.I. Disperse Yellow 232 as 3-(5'-chloro-2'-benzoxazolyl)-7-diethylamino-2H-1-benzopyran-2-one (**5g**) and its synthesis[1] (CHART 1). An extremely interesting aspect that emerged was the fluorescence exhibited by the dye **5g**. This observation prompted us to check its laser property as well. In addition to this, syntheses of a few more fluorescent dyes which might possess better lasing properties were planned. In designing such dyes, maintaining similar fluorophores was considered necessary. Therefore, variations were made by either having a benzoxazole or a benzimidazole moiety at position 3 of the coumarin ring. In addition, changes were made at 5' position of both the systems (CHART 1). These resulted in the synthesis of a few fluorescent dyes, the majority of which possessed good laser properties. Substituted coumarin derivatives to which class the dye **5g**, belongs constitute a group of widely used laser dyes emitting in the blue-green region of the spectrum.[2] Some members of this class rank among the most efficient laser dyes in recent times.[3] In particular, heterocyclic substituents such as in the dye **5g** may give rise to dyes with wider range of optimum lasing wavelength.

A study of the laser properties of the dyes is discussed in this chapter. It is relevant to give a brief account of the laser phenomenon.

Laser:

The abbreviation LASER stands for "Light Amplification by Stimulated Emission of Radiation". In practice, lasers are used as generators of radiation possessing intense energy. Generally, laser action is possible only if the material can be placed in a condition of amplification called negative absorption for some particular wavelength region. Negative absorptions occur in a stationary non-equilibrium state that depends on the rate at which excitation is achieved and also on the rates of relaxation and transition.

Organic dye lasers:

Lasers are available with different compounds and in this section, a small account is given of organic dye lasers. By virtue of possessing lasing properties (vide infra), laser dyes have become technologically very important. These dyes are referred to as tunable dyes as they can be tuned over a large wavelength range. The inherent requirement for a laser dye to find a practical application is that the dye must lase intensively in a desired spectral range and must have a long life. Laser dyes are finding extensive application in television pictures, large visual displays and calculators generated by light source. Another important application lies in the area of isotope separation wherein selective excitation is utilized.

The active component of an organic dye laser is an organic fluorescent dye dissolved in a common solvent. This may be

exemplified by Rhodamine 6G in alcohol or Fluorescein in water. These substances derive their colours from strong absorptions in the visible region. They are excited by a process called optical pumping which uses solid state lasers or flash lamps that deliver short pulses. The output of the dye laser is a short pulse of broad spectral content. Such dye lasers display a considerable gain. The excitation and emission cycle of organic dyes is a function of the material that is used. But all these materials possess certain basic structural features in common which determine the main character of their optical processes. The characteristic feature is the presence of a lone pair of electrons having certain freedom of motion within the molecule. This motion of the electron pair determines the electronic configuration of the molecule. Generally, most of the molecules in the ground state are in singlet states wherein the spins of the electrons are opposite. When the molecules are excited, the electrons are transferred to higher singlet excited states and they cross over into the corresponding triplet excited lower states. In addition, there are different vibrational levels in each electronic state. The transition from singlet state to the corresponding triplet state is called intersystem crossing. While the radiative process of the singlet state returning to the ground state is termed as 'fluorescence' and that from a triplet to the ground state is called 'phosphorescence'. This situation is depicted in the Jablonski diagram[5] (FIG. 1).

Laser phenomenon:

The phenomenon of lasing can be understood with the help of the pictorial presentation shown in FIG. 2. This picture is a plot of the energy of the molecule as a function of the interatomic distances. The horizontal lines in each electronic level represents the molecular vibrational bands. Absorption and emission occur where there is a transition from one level to the other. With reference to the dye molecules, the promotion from the lowest lying bands of the ground singlet state to one of the lower bands of the first singlet excited state requires the absorption of one quantum of light energy. Both the absorption and emission spectra of these dyes are affected by the different atomic distances corresponding to the minimum m_o and m_1 of the singlet states of s_o and s_1. Of special interest to lasers, are the fluorescent dyes which emit light after a short lapse of time and thereby the emission spectrum get shifted with respect to the absprption spectrum. Being governed by Frank Condom Principles, these transitions occur at the highest rate which needs minimal rearrangement of inter-atomic distances. With reference to the FIG. 2, the transition $\mathfrak{v}'=0 \longrightarrow \mathfrak{v}''=1$ may be more likely than $\mathfrak{v}'=0 \longrightarrow \mathfrak{v}''=0$ The opposite transition may be weak because the $\mathfrak{v}'' = 1$ is not sufficiently populated. The initial level of the transition $\mathfrak{v}' = 0 \longrightarrow \mathfrak{v}'' = 1$ may become populated when the molecule is pumped optically into $\mathfrak{v}' = 1$ level as the energy is rapidly redistributed among adjacent vibrational levels and also because of the fact that the population tends to favour the lowest level.

In dye lasers, optical pumping is generally done from the lowest vibrational level ($\nu''= 0$) of s_o into some of the s_1 bands. Stimulated radiation is emitted from $\nu' = 0$ into one of the bands above $\nu'' = 0$. In this manner the lasing occurs with the involvement of energy at four different levels. The above description provides a glimpse into the phenomenon of lasing.

Reported methods of synthesis of 3-(benzimidazolyl) or 3-(benzoxazolyl)-2H-1-benzopyran-2-ones:

Due to the commercial importance of these fluorescent dyes, the literature available for the synthesis of the dyes of this class are in the form of patents.

A German patent[6] indicates the condensation of malononitrile or ethylcyanoacetate with o-phenylenediamine and the resulting product **6** was reacted with 4-dialkylaminosalicylaldehyde **7**. Neither the detailed reaction conditions nor the yields are mentioned. In another German patent[7], a similar sequence of reactions was applied to o-aminophenol resulting in 3-benzoxazolyl coumarin derivative. In yet another report,[8] the same procedure was followed. In this case 4-diethylaminosalicylaldehyde was prepared utilizing the trimethylsilyl ether of m-diethylaminophenol (**10**) and further condensed with 2-cyanomethylbenzimidazole to form the dye. In a Japanse patent,[9] minor changes in reaction conditions such as utilizing a high boiling solvent are made to improve the yield [CHART 2). These dyes are used[10] in the dyeing of acetate, polyester or or polyamide fibres to obtain fluorescent yellow shades. A few dyes of this class can find use as fluorescent pigments.[11-12]

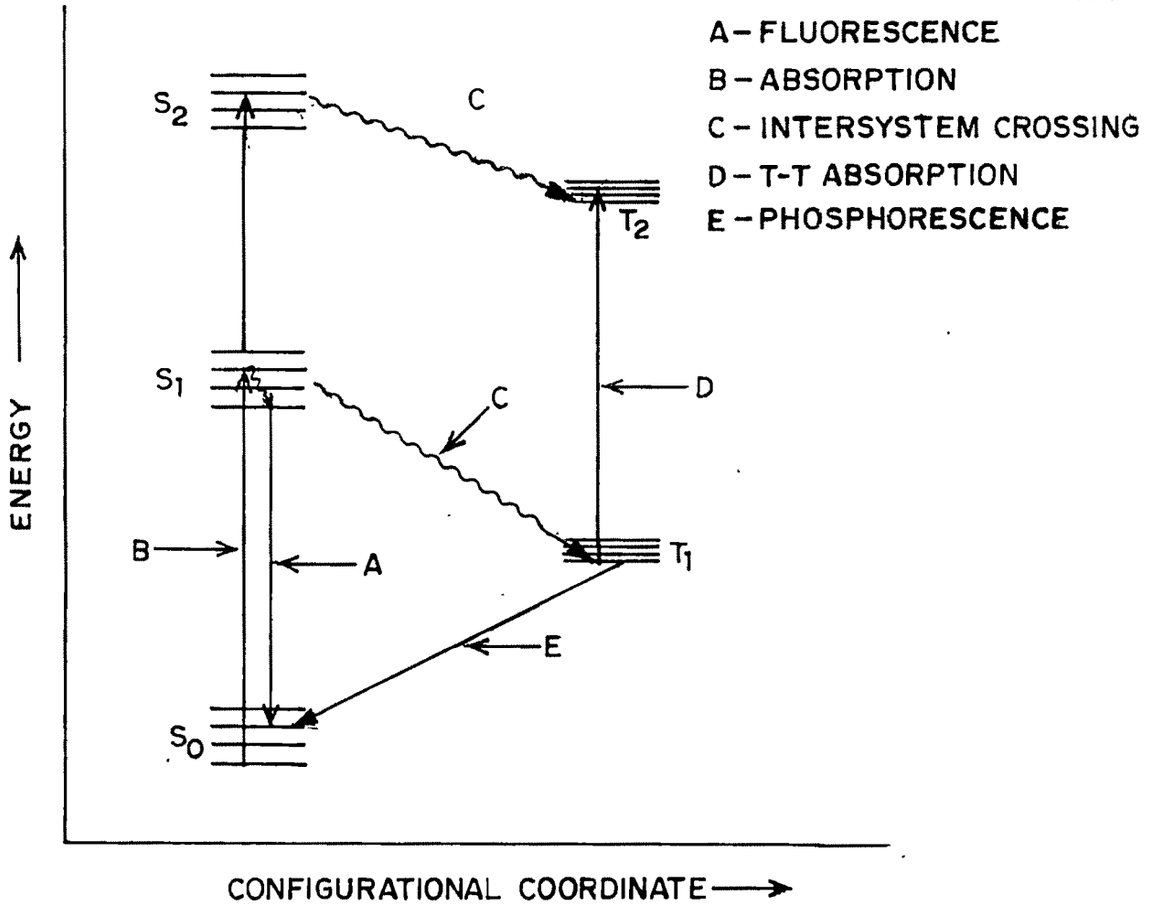


FIG. 1 (Jablonski diagram)

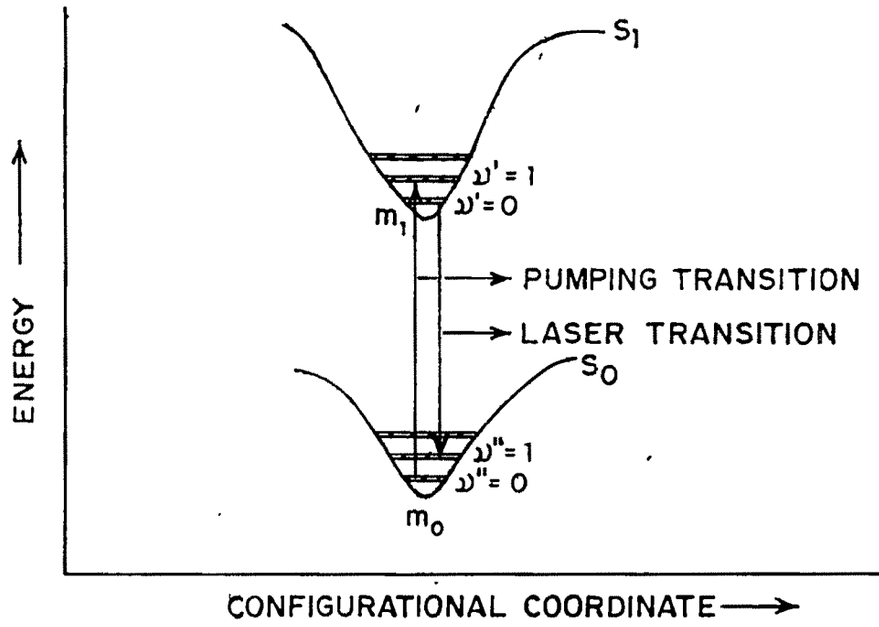
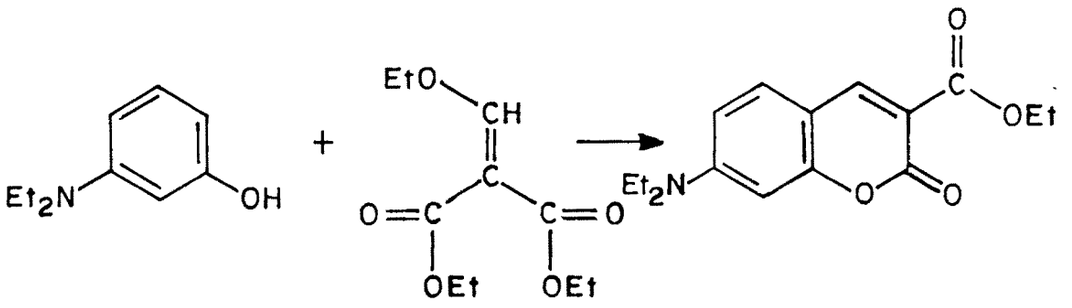
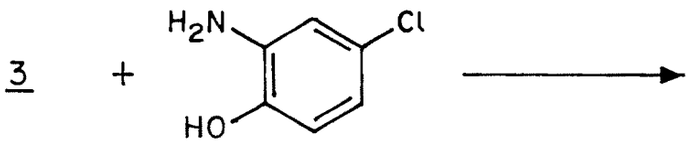


FIG. 2. PARTIAL ENERGY LEVEL DIAGRAM OF A DYE LASER MATERIAL

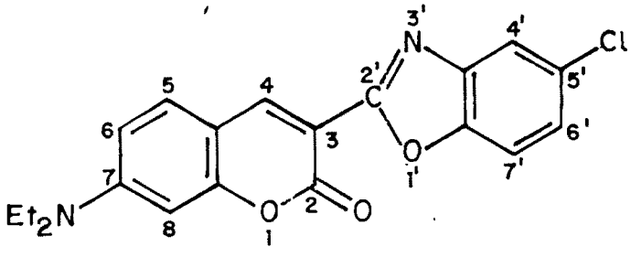
CHART – 1



1 2 3



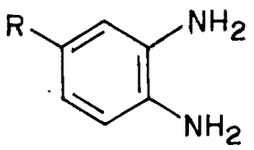
3 4g



5g

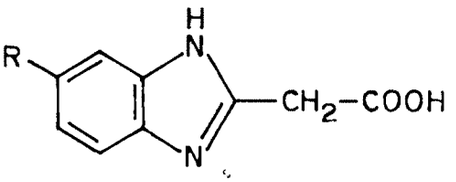
CHART-2

(1)



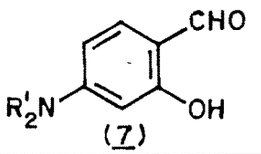
+ $CN-CH_2-R'$ —(50% H_2SO_4, 10 hr. Reflux)→

$R = H, CH_3$ ($R' = CN$ or $COOEt$)



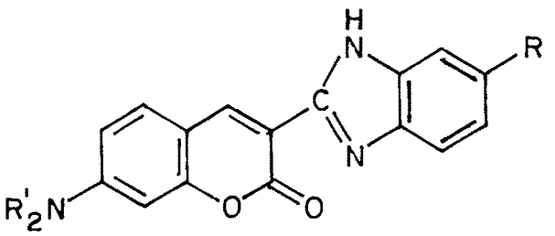
6

+

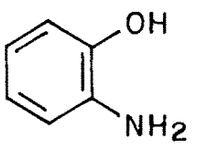


(7)

—(1 hr, (90-5 °C))→

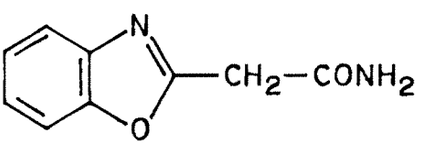


(2)

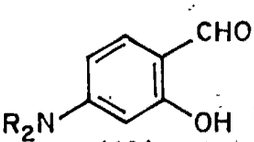


+ $NC-CH_2-CONH_2$ —(170 °C)→

8



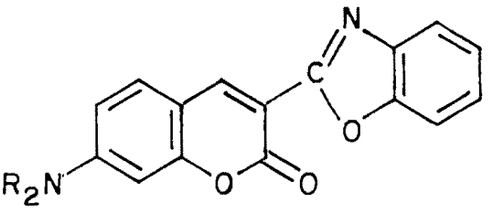
+



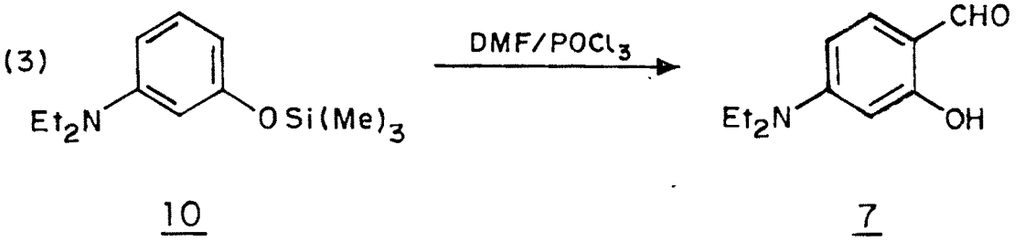
(11) (R = Me or Et) →

9

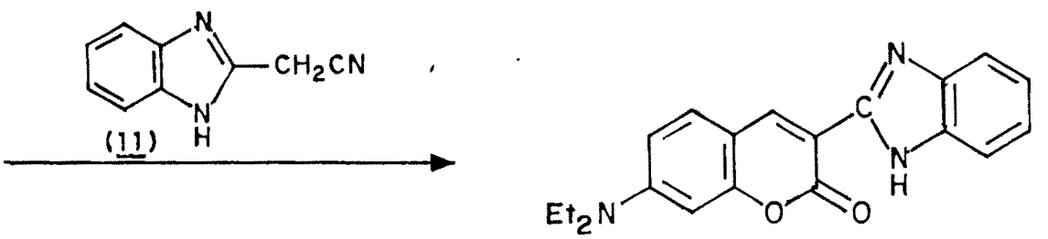
CHART-2 (contd.)



R = Me or Et



10 7



PRESENT WORK

The work described in this part concerns the synthesis of a few dyes belonging to the class of benzimidazolyl and benzoxazolyl coumarins. As already described in the preceding section, reaction of N,N-diethyl-m-aminophenol (DEMAP) with diethyl ethoxymethylene malonate (2) led to the synthesis of the coumarin ester 3 (CHART 1). This section gives an account of the reaction of 3 with differently substituted o-phenylenediamines and o-aminophenols as well (**4a-4f**) using polyphosphoric acid as the condensing agent (SCHEME 1). These reactions led to the efficient synthesis of **5a-5f**.

The readily available 2-nitro-4-chloroaniline was reduced by using sodium sulphide to yield 4-chloro-o-phenylenediamine (**4c**) required for the preparation of **5c**. The intermediate **4f** was prepared from 4-methoxy-3-nitrobenzophenone in two steps. The operations involved the demethylation of 4-methoxy-3-nitro benzophenone in ethylene dichloride using anhydrous aluminium chloride and subsequent reduction of the nitro function with sodium sulphide.

The products **5a-5f** were generally purified by column chromatography and the structures were determined by spectral and elemental analytical data. The salient spectral features are furnished below.

Absorption Spectral Characteristics:

All the dyes revaled a characteristic wavelength maximum of a coumarin nucleus at 270-288 nm in the UV region. In the

visible region, the absorption maxima ranged from 437-456 nm. The presence of electron-withdrawing benzoyl and chloro substituents in the dyes **5b** and **5c** has brought about bathochromic shifts of the order of 19 and 5 nm respectively, as compared to the unsubstituted dye **5a**. Similar behaviour is seen for the benzoxazole dyes **5e-5g**. The benzoyl groups have also brought about a marked increase in the tinctorial power of the dyes **5b** and **5f** in comparison to the unsubstituted dyes **3a** and **3e** respectively, as indicated by the molar extinction coefficient values (Table 1). Although this is not seen for the chloro substituted benzimidazole dye **5c**, considerable increase in the ϵ -value for the chlorobenzoxazole dye **5g** as compared to **5e** has been observed.

Emission Spectral Characteristics:

The fluorescence spectra were recorded by exciting the solutions of the dyes **5a-5g** in methanol at their respective absorption wavelength maxima in the visible region. The dyes exhibited fluorescence emission wavelength maxima ranging from 490-495 nm depending upon the substituent. The relative intensities of fluorescence of these dyes were evaluated under identical concentrations of the dye solutions assuming the relative intensity of the dye **5g** to be **1** (Table 1). In general, the dyes **5a-5d** in the benzamidazole series have better fluorescence intensities as compared to those in the benzoxazole series. The absorption and fluorescence spectra of the dye **5c** is shown in FIG. 3 (fluorescence spectrum is normalized to same intensity as corresponding absorption curve by adjusting concentratios).

IR Spectra:

The prominent chromophoric groups present in these molecules are the α,β-unsaturated lactone present in the coumarin moiety and NH group in the benzimidazolyl derivatives. These chromophores were conspicuously observed as strong bands between 1680-1740 cm^{-1} and between 3350-3370 cm^{-1} respectively. Additional carbonyl absorptions were noticed at 1660 cm^{-1} in the case of **5b** and **5f** indicating the benzoyl carbonyl functions. These characteristic absorptions have been exemplified by the IR of **5c** (FIG. 4).

^{1}H-NMR Spectra:

The ^{1}H-NMR of all these compounds displayed both the triplet and the quartet signals (centered around 1.1 and 3.4 respectively) indicating the diethylamino functionality. A typical characteristic of the spectra was the downfield absorption of 4-H proton around 8.5 as a singlet. Invariably, the NH proton (for **5a-5d**) was observed around 11.2 as a broad singlet and could be exchanged with D_2O. These prominent features are seen in the NMR of **5c** (FIG. 5).

Mass Spectra:

All the compounds showed the corresponding molecular ion peaks. The general fragmentation pattern observed has been exemplified by mass spectrum of **5c** (FIG. 6). The chloro substituted **5c** displayed two molecular ions at m/e 367 and 369 indicating the presence of chlorine. The base peak arose by the loss of a methyl group leading to the ion at m/e 352.

LASER SPECTRAL PROPERTIES:

The solution of the dyes **5** in concentrations of the order of 2×10^{-2}M were pumped by a pulsed nitrogen laster at λ=337 nm. The optimum lasing wavelength range (band width), lasing maxima and relative intensities (on an arbitrary scale) are recorded in Table 2. Generally, the benzimidazole dyes **5a-5d** exhibited superior lasing properties compared to the benzoxazole dyes **5e-5g**. The dyes **5b** and **5d** possessing strong electron-withdrawing benzoyl group and electron-donating methyl group respectively have a longer lasing wavelength tunability range of 30-40 nm as compared to a range of 8 nm of the dye **5a** which is a known commercial laser dye.[13] In addition, the dyes **5b** and **5d** exhibited greater relative intensities in comparison to **5a** making them more efficient laser dyes. The laser efficiency (laser output, arbitrary units) of **5c** versus wavelength is depicted in FIG. 7.

The benzoxazole dyes **5e** and **5f** did not lase although they showed intense fluorescence. The coumarin dyes **5a-5d** in the benzimidazole series showed more or less similar relative intensities of lasing and were better than chlorobenzoxazole dye **5g** (Table 2).

DYEING CHARACTERISTICS:

The dyes were applied on polyester by high pressure high temperature dyeing technique and were found to impart greenish yellow to orange hue on the fibre. The pick up and fastness properties are recorded in Table 3. All the dyeings showed

depths comparable to that of standard 1% lemon yellow and orange shades on polyester except for the dye **3d** which was weaker in comparison. The light fastness was determined by exposing the dyed polyester on an Atlas Fadometer for 24 h. All the dyes had moderate light fastness and moderate to good sublimation fastness properties (Table 3).

Conclusion:

Since we were able to prepare quite a few new efficient laser dyes, the methodology described in this part for the synthesis of these dyes assumes great importance. Considering the fact that fluorescent dyes constitute only a small fraction of thousands of known dyes and among these fluorescent systems only a few are effective as dye lasers, the dyes **5b**, **5c**, **5d**, and **5g** show great promise as efficient laser dyes with strong possibilities of commercial exploitation. Moreover the dyes **5** gave rise to brilliant greenish yellow shades on polyesters with moderate to good fastness properties making them suitable for use as disperse dyes.

Table 1

ELECTRONIC SPECTRA OF THE DYES 5*

Dye No.	λ_{max} (nm); (ϵ) (Lit/mol^{-1}/cm^{-1}) Absorption UV	Absorption VIS	Emission fluorescence	Rel. intensity of fluorescence
5a	286(13105)	437(43934)	492	1.6
5b	274(24320)	456(55670)	495	1.1
5c	288(11927)	442(43673)	493	1.8
5d	288(13295)	438(43873)	494	1.6
5e	278(7314)	444(35022)	490	1.2
5f	270(14292)	450(45887)	493	0.5
5g	278(11103)	452(48739)	493	1.0

* Methanol was used as the solvent.

Table 2

LASER PROPERTIES OF THE DYES 5*

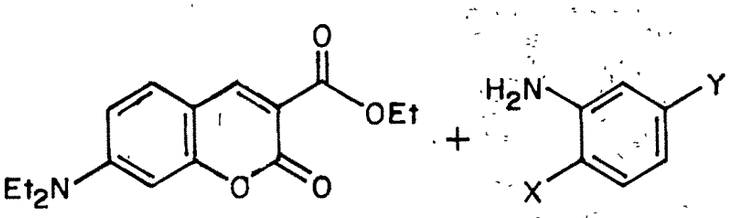
Dye No.	Lasing region (nm)	Bandwidth (nm)	Lasing maxima (nm)	Rel. intensity (arbitrary scale where for 5a intensity is 1)
5a	523-531	8	526	1.0
5b	540-570	30	550	1.1
5c	517-524	7	520	1.1
5d	500-540	40	520	1.1
5e	-	-	No lasing	-
5f	-	-	No lasing	-
5g	523-534	11	528	0.7

* Chloroform was used as the solvent except for 5b where 1:1 mixture of EDC and ethanol was used.[14]

Table 3

Dye No.	Reference Depth	Shade (1%)	Light fastness Xeno Test 24 h. exposure	Sublimation fastness at 200°C for 1 min.		
				Loss in Depth	Change in Tone	Staining on adjacent fibre
5a	1/1		2	3	3	2-3
5b	1/1		3	3-4	3	4
5c	1/1		3	3-4	3-4	2-3
5d	1/3		3	3-4	3	3
5e	1/1		3	3	3	2
5f	1/1		3	3	3	3-4
5g	1/1		3	3	3	2-3

SCHEME —1



3 4

4a : X = NH_2 , Y = H

4b : X = NH_2 , Y = COPh

4c : X = NH_2 , Y = Cl

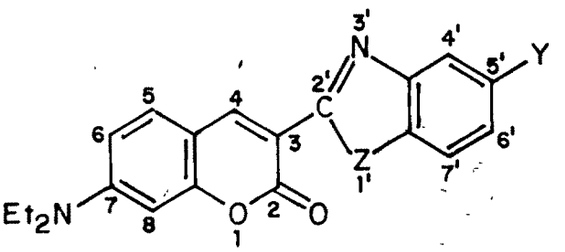
4d : X = NH_2 , Y = CH_3

4e : X = OH , Y = H

4f : X = OH , Y = COPh

4g : X = OH , Y = Cl

PPA
180–190 °C



5

5a : Z = NH, Y = H

5b : Z = NH, Y = COPh

5c : Z = NH, Y = Cl

5d : Z = NH, Y = CH_3

5e : Z = O , Y = H

5f : Z = O , Y = COPh

5g : Z = O , Y = Cl

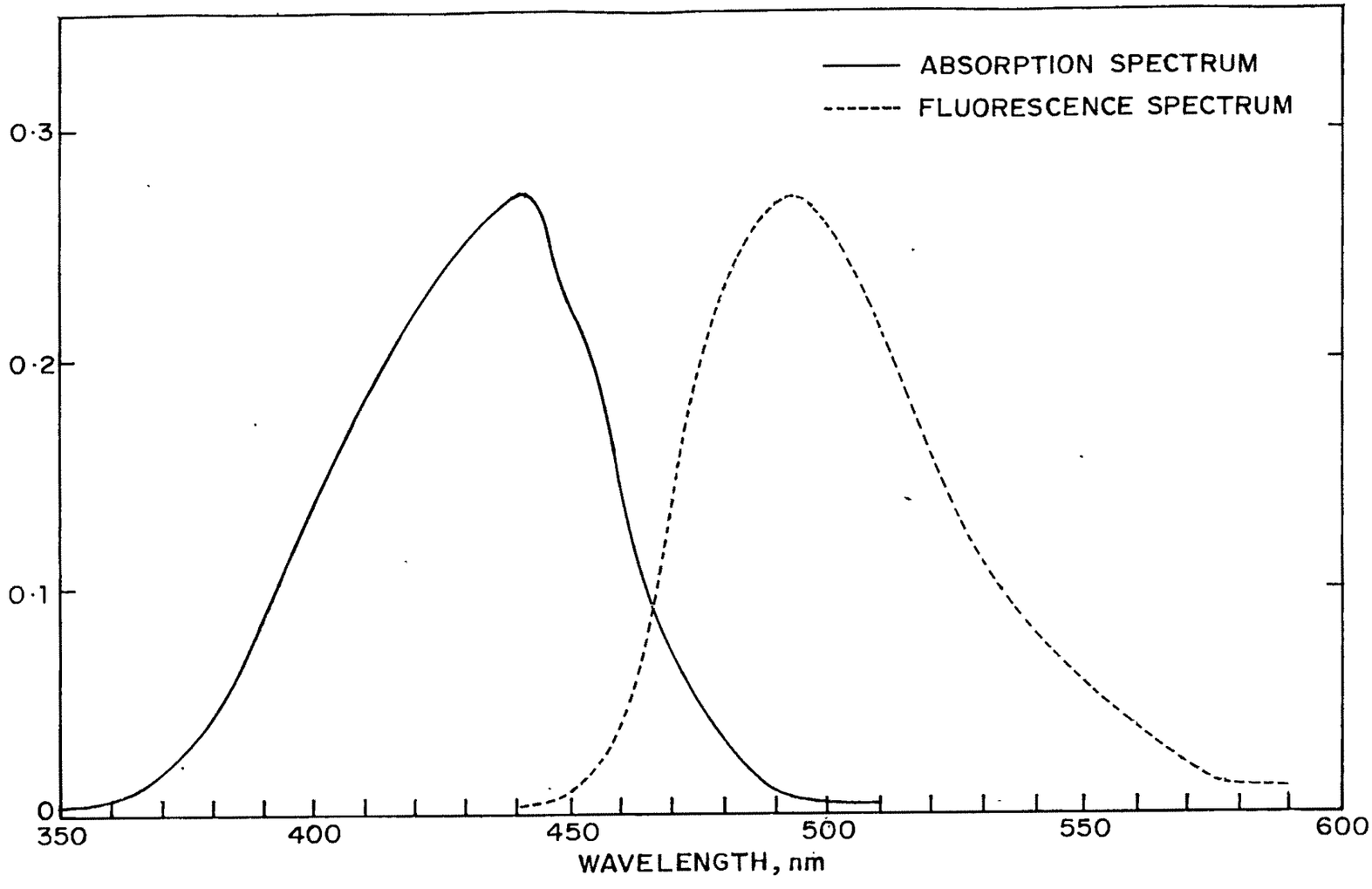


FIG. 3. ABSORPTION AND FLUORESCENCE SPECTRA OF 5c IN METHANOL; FLUORESCENCE SPECTRUM IS NORMALIZED TO SAME INTENSITY AS ABSORPTION CURVE.

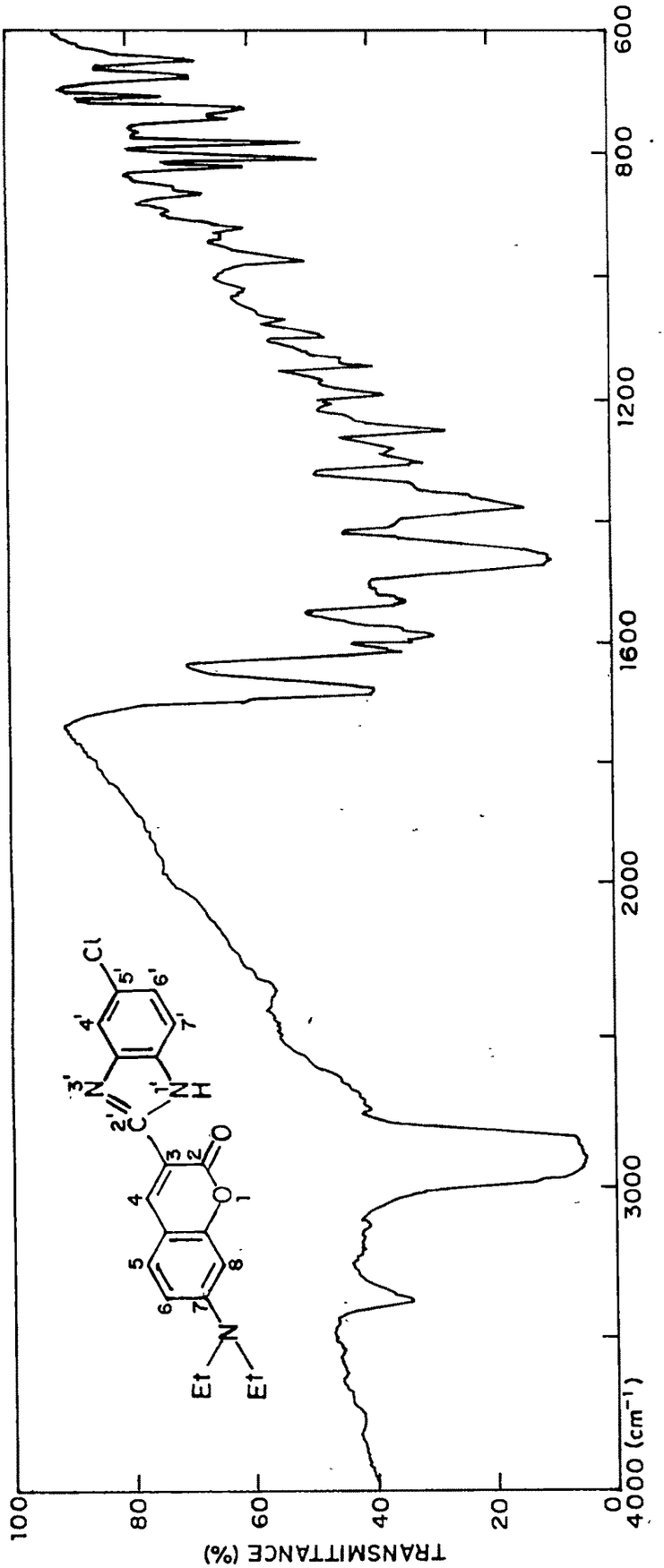

TRANSMITTANCE (%)
100
80
60
40
20
0
4000 (cm⁻¹)
3000
2000
1600
1200
800
600
Cl
5'
6'
4'
7'
3'
N
1'
NH
2'
C
3
2
O
4
O
1
5
8
6
7
N
Et
Et

FIG. 4

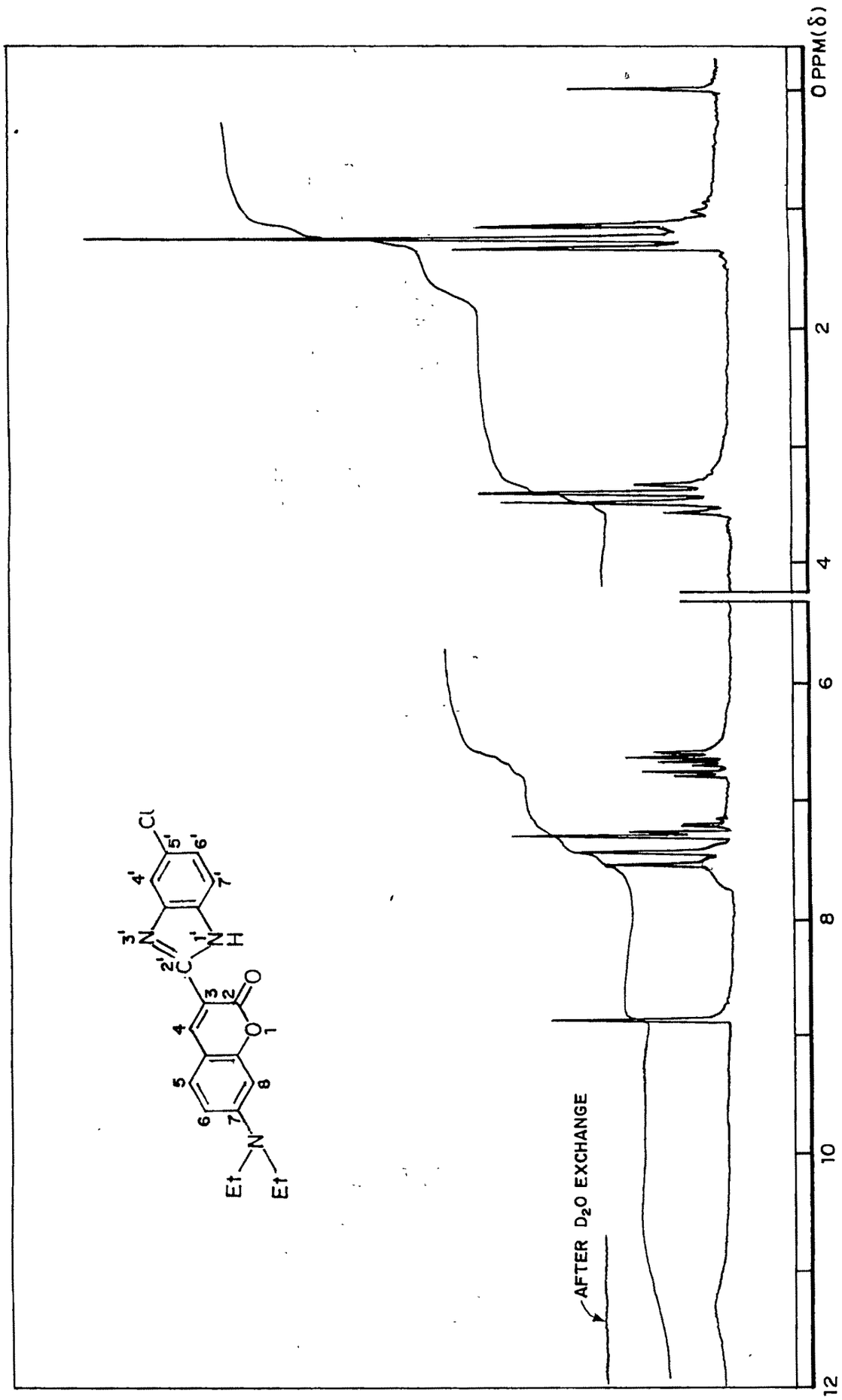

0PPM(δ)
2
4
6
8
10
12
AFTER D_2O EXCHANGE
Cl
5'
6'
4'
7'
3'
N
1'
N
H
2'
C
3
2
O
4
O
1
5
8
6
7
N
Et
Et

FIG. 5

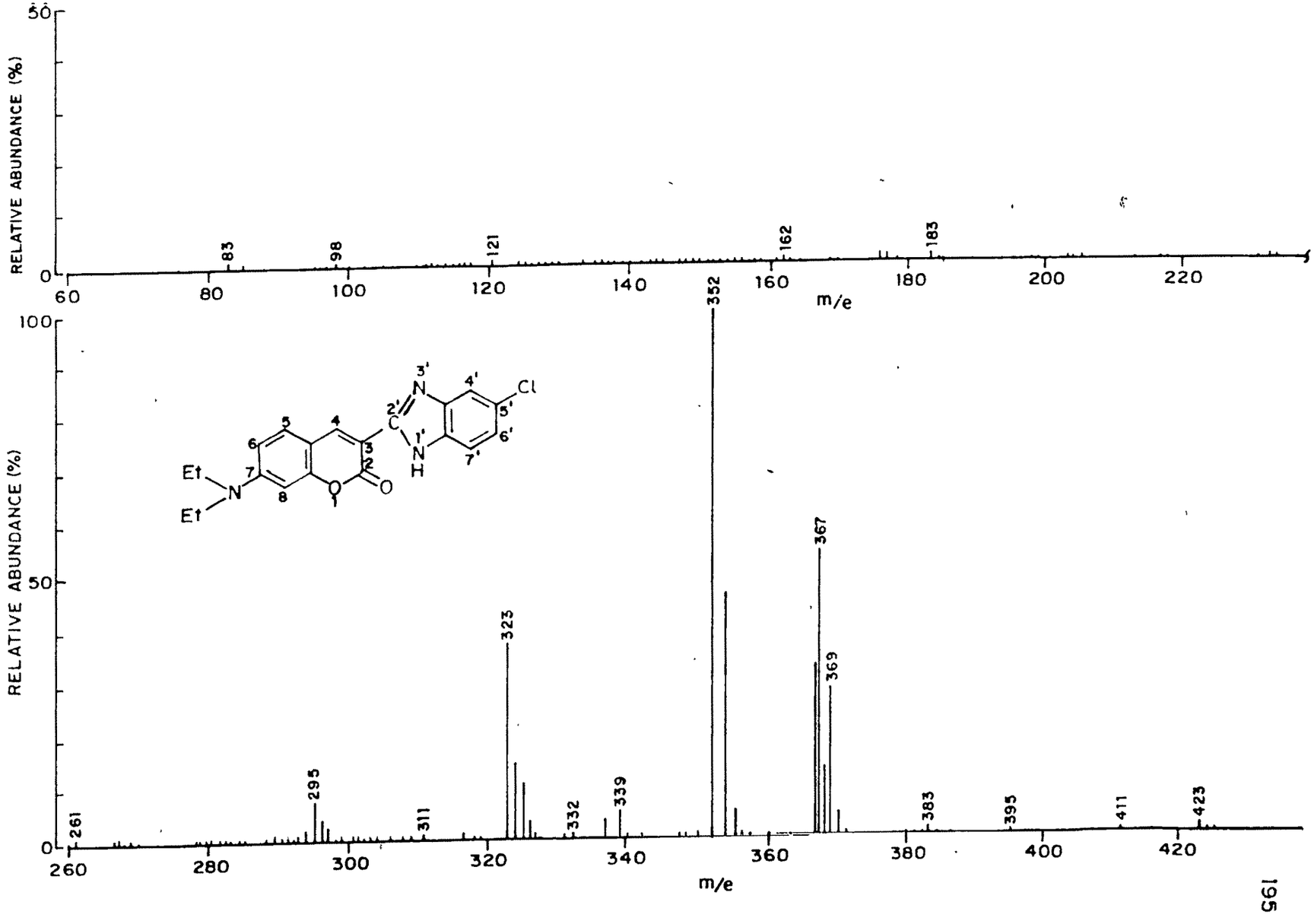

RELATIVE ABUNDANCE (%)
50
0
83
98
121
162
183
60
80
100
120
140
160
180
200
220
m/e
100
50
0
352
367
323
369
295
311
332
339
383
395
411
423
261
260
280
300
320
340
360
380
400
420
m/e
Et
Et
N
O
O
Cl
H
1
2
3
4
5
6
7
8
1'
2'
3'
4'
5'
6'
7'
195

FIG. 6

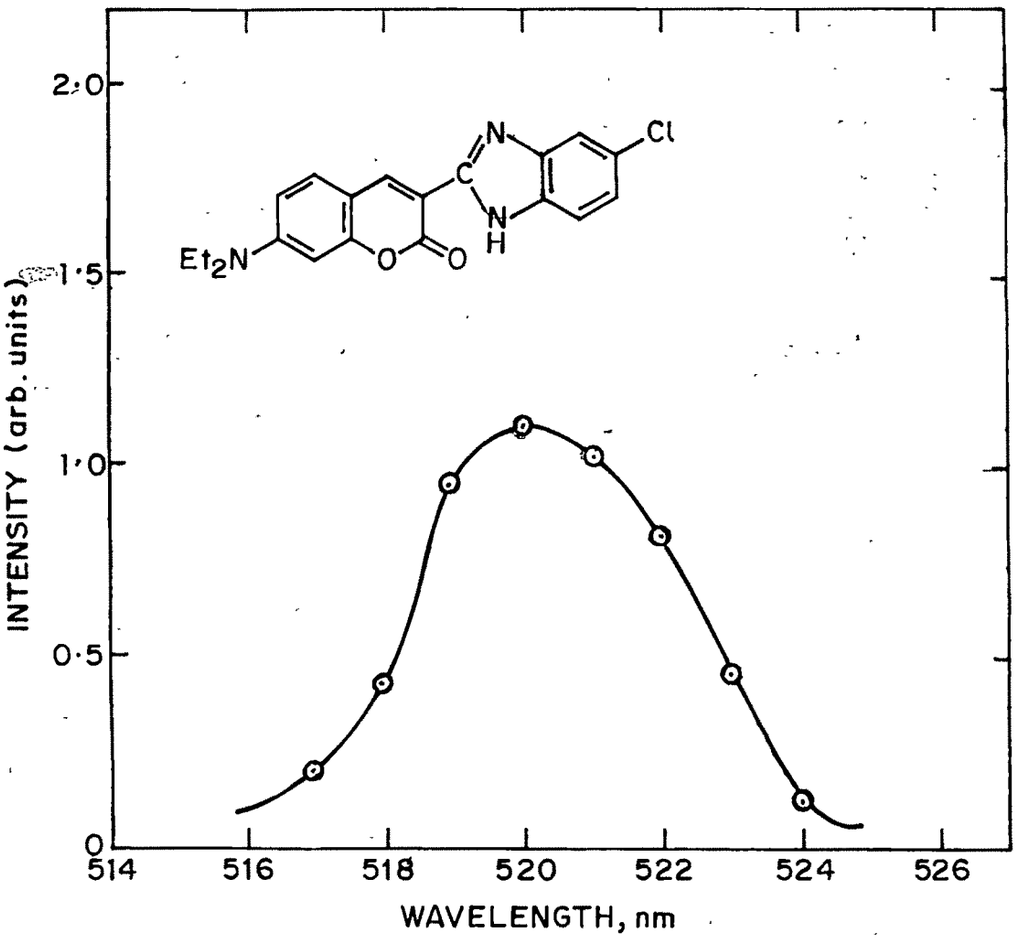
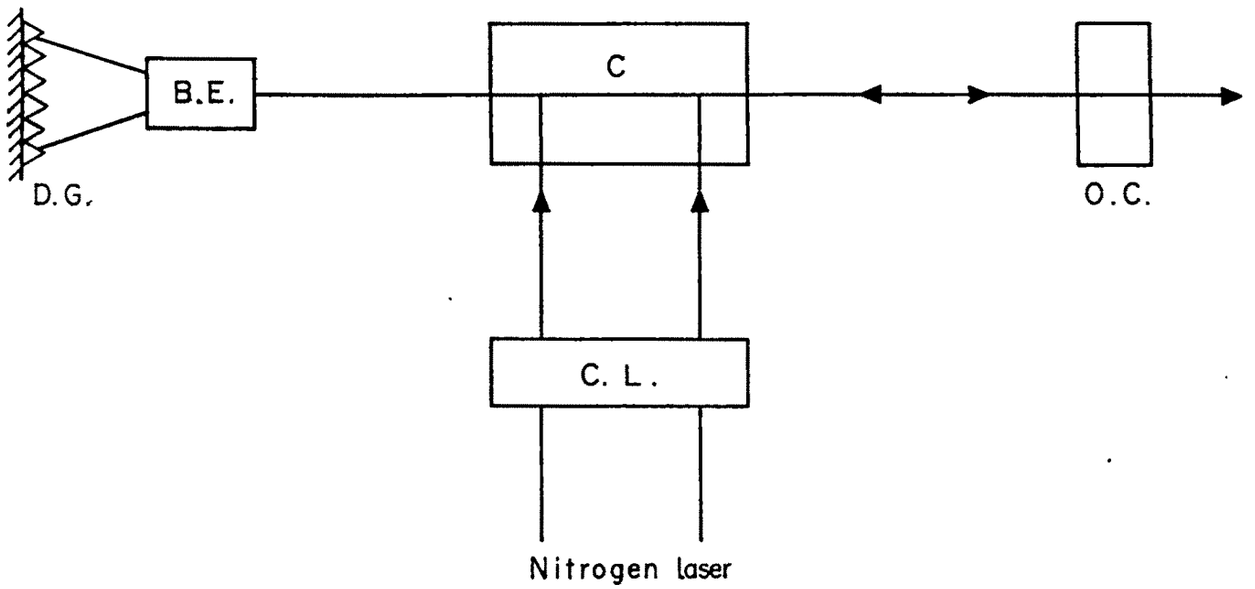

2·0
1·5
1·0
0·5
0
INTENSITY (arb. units)
514
516
518
520
522
524
526
WAVELENGTH, nm
Et2N
O
O
N
H
C
N
Cl

FIG. 7



D.G. — Diffraction grating
C — Cuvette
C.L. — Cylindrical lens
O.C. — Output coupler
B.E. — Beam expander

FIG. 8: Experimental set-up for evaluation of laser spectral characteristics

EXPERIMENTAL

Preparation of the dyes 5a-5f: General Procedure:

A mixture of 7-diethylamino-2-oxo-2H-1-benzopyran-3-carboxylic acid ethyl ester 3 (0.01 mol) (CHART 1, prepared by the method reported in Part B), 4-substituted o-phenylenediamine or o-aminophenol (4a-4f) (0.01 mol) and polyphosphoric acid (10 g) was stirred at 180°C for 3 h in an inert atmosphere (nitrogen). The mixture was poured into ice-cold water (250 ml), the pH adjusted to 8.5 by addition of sodium carbonate solution (10% w/v) and extracted with chloroform (2 x 250 ml). The chloroform layer was washed with water and dried over anhydrous sodium sulphate. After removal of chloroform by distillation, the residual crude dye was purified by column chromatography on silica gel using a mixture of chloroform : pet. ether (1:1, v/v), as eluent.

Characterization and identification of dyes 5a-5f (Scheme 1):

3-(1H-Benzimidazol-2'-yl)-7-diethylamino-2H-1-benzopyran-2-one (5a):

Yellow needles from acetone, m.p. 240°C, yield 2.79 g (84%).

IR (Nujol, cm^{-1}): 3370, 1690, 1610, 1590, 1530, 1460, 1430, 1400, 1380, 1350, 1310, 1270, 1250, 1190, 1150, 1090, 980, 920, 820, 780.

^{1}H-NMR ($CDCl_3$): 1.2 (6H, t, N-CH_2-CH_3), 3.4 (4H, q, N-CH_2-CH_3), 6.55 (1H, d, 8-H, J=2Hz), 6.66 (1H, dd, 6-H), 7.20-7.32 (2H, m, 4-H and 7'-H), 7.44 (2H, d, 5'-H & 6'-H, J=9Hz), 8.91 (1H, s, 4-H), 11.28 (1H, bs, NH, exchangeable with D_2O).

MS m/e (rel. int. %): 333 (M^+, 92), 318(100), 303(6), 289(71), 261(32), 233(12), 205(14), 167(9), 159(12).

Anal. $C_{20}H_{19}N_3O_2$: Calc. C, 72.07; H, 5.71 ; N, 12.61
(333) Found: C, 71.92; H, 5.60; N, 13.01

3-[5'-Benzoyl-(1H-benzimidazol-2'-yl)]-7-diethylamino-2H-1-benzopyran-2-one (5b):

Yellow needles from chloroform, m.p. 265°C, yield 3.71 g (85%). IR (Nujol, cm^{-1}): 3360, 1720, 1625, 1610, 1540, 1390, 1360, 1310, 1250, 1200, 1150, 1120, 1100, 1040, 990, 980, 920, 860, 830, 810.

^{1}H-NMR ($CDCl_3$): 1.24 (6H, t, N-CH_2-CH_3), 3.83 (4H, q, N-CH_2-CH_3), 6.48 (1H, d, 8-H, J=2Hz), 6.68 (1H, dd, 6-H), 7-8.1 (9H, m, Ar-H), 8.93 (1H, s, 8-H), 11.24 (1H, bs, NH, exchangeable with D_2O).

MS m/e (rel. int. %): 437 (M^+, 100), 422(94), 393(27), 317(70), 288(24), 261(22), 105(64), 77(63).

Anal. $C_{27}H_{23}N_3O_3$: Calc. C, 74.14; H, 5.26; N, 9.61
(437) Found: C, 73.92; H, 5.45; N, 9.62

3-[5'-Chloro-(1H-benzimidazol-2'-yl)]-7-diethylamino-2H-1-benzopyran-2-one (5c):

The dye 5c was prepared in two steps.

Step 1: Preparation of 4-chloro-o-phenylenediamine (4c):

To a solution of 4-chloro-2-nitroaniline (17.2 g, 0.1 mol) in 50 ml ethanol was added a solution of sodium sulphide hexahydrate (50 g) in water (500 ml) in 4 h at 80°C. The solution was refluxed for another 5 h. After removal of ethanol, the residue was digested in chloroform and this extract was

washed with water and dried. The product obtained on evaporation of the solvent was crystallized from a mixture of pet. ether and ethylacetate (2:1, v/v), m.p. 81°C (lit.[15] m.p.81°C), yield 13.5 g (95%).

IR (Nujol, cm^{-1}): 3420, 3400, 3340, 1620, 1590, 1500, 1470, 1380, 1270, 1320, 1100, 920, 900, 850, 810.

^{1}H-NMR ($CDCl_3$): 3.85 (4H, bs, $N\underline{H}_2$), 7.8 (3H, m, Ar-H).

MS m/e (rel. int. %): 144 $[(M+2)]^+$, 142 (M^+, 100), 124(65), 107(48), 80(74), 78(50), 63(39), 53(38), 52(42), 51(40), 40(25), 32(100).

Anal. $C_6H_7ClN_2$: Calc. C, 50.70; H, 4.92; N, 19.70; Cl, 24.65
(142) Found: C, 50.40; H, 5.10; N, 19.80; Cl, 24.24

Step 2: Preparation of **5c**:

The product **5c** was prepared as in the general procedure by the condensation of **3** and **4c**. Crystallized from chloroform, m.p. 271°C, yield 3.23 g (88%).

IR (Nujol, cm^{-1}): 3370, 1680, 1610, 1530, 1460, 1370, 1300, 1280, 1250, 1190, 1150, 1090, 1020, 975, 920, 860, 825, 790, 780, 740, 700.

^{1}H-NMR ($CDCl_3$): 1.2 (6H, t, N CH_2-$C\underline{H}_3$), 3.4 (4H, q, N $C\underline{H}_2$-CH_3), 6.53 (1H, d, 8-H, J=2Hz), 6.64 (1H, dd, 6-H), 7.13 (1H, q, 6'-H), 7.4-7.71 (3H, m, 4'-H, 7'-H & 5'-H), 8.84 (1H, s, 4-H), 11.24 (1H, bs, NH, exchangeable with D_2O).

MS m/e (rel. int. %): 369 $(M+2)^+$, 367 (M^+, 54), 352(100), 339(6), 323(36), 295(8).

Anal. $C_{20}H_{18}ClN_3O_2$: Calc. C, 65.39; H, 4.90; N, 11.44; Cl, 9.53
(376) Found: C, 65.60; H, 4.80; N, 11.36; Cl, 9.42

3-[5'-Methyl-(1H-benzimidazol-2'-yl)]-7-diethylamino-2H-1-benzopyran-2-one (5d):

Yellow needles from methanol, m.p. 235°C, yield 3.23 g (95%).

IR (Nujol, cm^{-1}): 3350, 1690, 1620, 1600, 1540, 1470, 1380, 1360, 1260, 1100, 1080, 1030, 820, 800, 790.

^{1}H-NMR ($CDCl_3$): 1.24 (6H, t, N-CH_2-$C\underline{H}_3$), 2.46 (3H, s, Ar-$C\underline{H}_3$), 3.44 (4H, q, N-$C\underline{H}_2$-CH_3), 6.48 (1H, d, 8-H), J=2Hz), 6.7 (1H, dd, 6-H), 7.11 (1H, q, 6'-H), 7.2-7.62 (3H, m, 4'-H, 7'-H & 5-H), 9.28 (1H, s, 4-H), 11.2 (1H, bs, NH, exchangeable with D_2O).

MS m/e (rel. int. %): 347 (M^+, 100), 332(89), 303(50), 275(8), 174(13), 166(43), 152(69), 138(20), 109(12).

Anal. $C_{21}H_{21}N_3O_2$: Calc. C, 72.62; H, 6.05; N, 12.10
(347) Found: C, 72.54; H, 6.24; N, 11.71

3-(2'-Benzoxazolyl)-7-diethylamino-2H-1-benzopyran-2-one (5e):

Yellow needles from acetone, m.p. 170°C, yield 2.73 g (82%).

IR (Nujol, cm^{-1}): 1730, 1605, 1580, 1530, 1490, 1440, 1410, 1370, 1350, 1310, 1280, 1230, 1180, 1120, 1070, 1010, 940, 855, 820, 790, 770.

^{1}H-NMR ($CDCl_3$): 1.2 (6H, t, N-CH_2-$C\underline{H}_3$), 3.42 (4H, q, N-$C\underline{H}_2$-CH_3), 6.46 (1H, d, 8-H, J=2Hz), 6.66 (1H, dd, 6-H), 7.2-7.95 (5H, m, Ar-H), 8.73 (1H, s, 4-H).

MS m/e (rel. int. %): 334 (M^+, 72), 319(100), 291(33), 262(16), 234(7), 206(6), 159(9).

Anal. $C_{20}H_{18}N_2O_3$: Calc. C, 71.86; H, 5.38; N, 8.38
(334) Found: C, 71.43; H, 5.55; N, 7.91

3-(5'-Benzoyl-2'-benzoxazolyl)-7-diethylamino-2H-1-benzopyran-2-one (5f):

The synthesis of 5f was achieved in three steps.

Step 1: Preparation of 4-hydroxy-3-nitrobenzophenone:

To a solution of 4-methoxy-3-nitrobenzophenone, (2.57 g, 0.01 mol) in dry ethylene dichloride (50 ml) was added powdered anhydrous aluminium chloride (13.3 g, 0.1 mol). The reaction mixture was stirred for 24 h at room temperature. Completion of the reaction was ensured by TLC using a mixture of chloroform and pet. ether (1:4, v/v). The reaction mixture was poured into ice (250 g) containing 10 ml hydrochloric acid. The EDC layer was separated out, washed and distilled to yield the product. The product was purified by alkali treatment (10% NaOH solution) and regenerating the product with dilute hydrochloric acid (10%). Crystallized from methanol as yellow plates, m.p. 120-21°C (lit.[16] m.p. 121°C).

IR (Nujol, cm^{-1}): 3300,, 1650, 1610, 1580, 1530, 1450, 1430, 1380, 1320, 1250, 1160, 1120, 1080, 980.

^{1}H-NMR ($CDCl_3$): 7.2-7.7 (6H, m, Ar-H), 8.06 (1H, q, 6-H), 8.53 (1H, d, 2-H, J=3Hz), 10.8 (1H, bs, OH, exchangeable with D_2O).

MS m/e (rel. int. %): 243 (M^+, 84), 226(4), 197(22), 166(91), 139(26), 120(55), 105(96), 92(40), 77(91), 63(40), 51(63), 44(33).

Anal. $C_{13}H_9NO_4$: (243) Calc. C, 64.19; H, 3.70; N, 5.76
Found: C, 63.60; H, 3.98; N, 5.83

Step 2: Preparation of 3-amino-4-hydroxybenzophenone (4f):

3-Nitro-4-hydroxybenzophenone (24.3 g, 0.1 mol) was reduced

by sodium sulphide hexahydrate solution as reported in the preparation of 4c from 2-nitro-4-chloroaniline. Crystallized from methanol, m.p. 161°C (lit.[17] m.p. 161°C), yield 19.17 g (90%).

IR (Nujol, cm^{-1}): 3500, 3400, 1640, 1610, 1590, 1570, 1520, 1460, 1450, 1370, 1320, 1300, 1220, 1140, 1000, 990, 890, 880, 830, 810, 750, 730.

^{1}H-NMR ($CDCl_3$): 4.2 (2H, bs, NH_2, exchangeable with D_2O), 6.62-7.70 (9H, m, Ar-H & OH).

MS m/e (rel. int. %): 213 (M^+, 100), 196(33), 185(20), 168(26), 156(37), 130(100), 126(24), 115(14), 108(78), 105(84), 80(74), 77(81), 51(55), 53(51), 43(48).

Anal. $C_{13}H_{11}NO_2$: (213) Calc. C, 73.24; H, 5.16; N, 6.57
Found: C, 73.10; H, 5.24, N, 6.42

Step 3: Preparation of 5f:

The product 5f was prepared as in the general procedure by the condensation of 3 and 4f. Yellow needles from chloroform, m.p. 188°C, yield 3.15 g (72%).

IR (Nujol, cm^{-1}): 1740, 1660, 1590, 1520, 1500, 1450, 1380, 1360, 1290, 1250, 1190, 1130, 1070, 960.

^{1}H-NMR ($CDCl_3$): 1.22 (6H, t, $N-CH_2-\underline{CH_3}$), 3.42 (4H, q, $N-\underline{CH_2}-CH_3$), 6.46 (1H, d, 8-H, J=2Hz), 6.66 (1H, dd, 6-H), 7.2-8.2 (9H, m, Ar-H), 8.55 (1H, s, 4-H).

MS m/e (rel. int. %): 438(M^+, 68), 423(100), 410(6), 395(17), 105(10)

Anal. $C_{27}H_{22}N_2O_4$: Calc. C, 73.97; H, 5.02; N, 6.39
(438) Found: C, 73.64; N, 5.14; N, 6.22

EVALUATION OF LASER PROPERTIES:

The solution containing the dyes 5 was excited (or pumped) by a pulsed nitrogen laser; output power 60KW, pulse duration, 15 nsec, pulse rep. freq. 1Hz. The schematic diagram of the experimental set up is shown in the FIG. 8. The output from the nitrogen laser is line focussed on the cuvette containing dye solution (2×10^{-2} M) with the help of a cylindrical lens. The fluorescence of the dye is expanded with the help of a beam expander and allowed to fall on the diffraction grating held in a littrow position. The grating selects a particular wavelength to pass through the dye cell depending upon the grating angle. The reflecting mirror or the output coupler partially reflects the beam back into the cell and partially transmits it. This forms the laser oscillator cavity. Once the back and forth oscillations were set, a laser output was obtained from the output coupler.

The lasing range of the dye was monitored with the help of a grating monochromator (Model 218, Mephereson, USA). The laser output was allowed to fall on the entrance slit of the monochromator and detected at the exit slit with the help of a photo-diode. The intensity of the laser output was plotted against wavelength to give the tuning curve of the dye.

DYE DISPERSION AND APPLICATION:

Dye Dispersion: Dispersions of the dyes (**5a-5g**) were prepared by

milling 1 g. of the dye, 1 g. of Tamol NNO (dispersing agent) in water (25 ml), in a glass tube containing steel rods for 48 h. The 1% dispersion of these dyes were used as stock solution for dyeing polyester fibre.

Dye application by high temperature high pressure method: The dye bath was set with 1% dispersion, 5% unisperse P (a heat resistant levelling agent of HICO) and 1% acetic acid, keeping the material liquor ratio 1:100. The material was entered at 60°C and the temperature raised to 130°C in 30 min. The dyeing was continued at 130°C for one more hour. After cooling, the dyeings were taken out and given a treatment of 2% sodium bi-sulphite and 4% sodium hydroxide at 70° for 15 min. Finally, they were rinsed and dried at 60°C.

Determination of fastness properties:

Sublimation fastness: The dyed polyester fibre was stitched between the two pieces of undyed polyester fibres (stain cloth) of equal lengths. This system was subjected to pass through a chamber at 200°C for one minute. Any staining on the undyed piece, change in tone or loss in depth were assessed with the following ratings, using standard procedures.[18]

1 - Poor; 2 - Fair; 3 - Moderate; 4 - Good; 5 - Excellent.

Light fastness: This was determined by exposing the dyed polyester on Atlas Fadometer equipment for 24 h. Any fadings of the shades were assessed with the following ratings:

1 - Poor; 3 - Moderate; 5 - Good; 6 - Very good; 7 - Excellent; 8 - Maximum.

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CHAPTER-V

SYNTHESIS OF ETHYL-α-CARBETHOXY-β-(ARYLAMINO) ACRYLATES AND RELATED COMPOUNDS

INTRODUCTION

Ethyl-α-(carbethoxy)-β-(arylamino) acrylates represent valuable class of intermediates[1,2,3] in the synthesis of biologically active molecules. For example, this class of intermediates are utilized in the synthesis of antimalarial agents such as chloroquine,[4] anti-infectives such as nalidixic acid, and quinoline antibiotics like norfloxacin (CHARTS 1&2). In addition, this class of compounds derive their importance from their ability to confer extra stability to a variety of polymers such as polystyrene and polyolefins against the undesirable effects of ultra-violet light.[5] Their industrial importance makes the synthesis and economical process of manufacture of this type of acrylates interesting and challenging.

The synthetic utility of ethyl-α-(carbethoxy)-β-(m-chloroanilino) acrylate (3) has been exemplified[6,7] in the efficient synthesis of chloroquine phosphate, (9) a well-known antimalarial agent (CHARTS 1&2). Although CHARTS 1&2 are self explanatory, a few reactions are worthy of mention. The basic step is the synthesis of 3 from the reaction of m-chloroaniline with diethyl ethoxymethylenemalonate 2. The thermal cyclization of 3 affords the intermediate 4 which on subsequent chemical transformations indicated in the chart leads to the target molecule 9. We thought of devising a short and convenient route for the synthesis of ethyl-α-(carbethoxy)-β-(arylamino) acrylates owing to their industrial importance. An exhaustive literature survey was carried out and the available

methods for their preparations have been briefly indicated below. As shown in CHART 1, the conventional method involves the reaction of m-chloroaniline with diethyl ethoxymethylene malonate or ethoxymethylene malonic ethyl ester (EMME). An Organic Synthesis[8] procedure for the preparation of EMME involves the reaction of diethyl malonate (DEM) with triethyl orthoformate (TEOF) under reflux conditions along with acetic anhydride/ zinc chloride. The method involved refluxing for unduly long periods and isolating the product by fractional distillation under vacuum in 50-60% yield (CHART 3). In another patent[9], a comparable process to the above is described wherein acetic acid was used as the catalyst. Subsequently, a different method[2] was developed in which bis(m-chlorophenyl) formamidine was used as a starting material which on reaction with DEM afforded ethyl-α-(carbethoxy)-β-(m-chloroanilino) acrylate. Surprisingly, this method resulted in the formation of the undesirable acrylanilide 12 as a major product (CHART 4). Similarly, the method developed by Snyder and Jones[1] suffered from the same disadvantage of predominantly yielding the unwanted side product. They obtained 3 from the reaction of m-chloroaniline, TEOF and DEM, although in poor yields.

A recent Hungarian patent[10] utilises the preformed bis-(3-chlorophenyl) formamidine as a starting material and obtains the desired 3 by its reaction with TEOF and DEM using zinc chloride or magnesium chloride hydroxide as a catalyst. However, neither the yield nor the catalyst quantities have been mentioned.

Similarly, unspecified yields of 3 were obtained[11] by the reaction of m-chloroformanilide with phosphorous oxychloride and ethoxy magnesio derivative of diethylmalonate at low temperature (0-10°C). A similar procedure is outlined in a German patent[12] wherein m-chloroaniline and formic acid were utilised and the product arising therefrom was treated with DEM and m-chloroaniline for 2 days. However, the desired product could not be obtained in sufficient purity.

An improved synthesis of 3 has been reported[13] in which a preformed bis-(m-chlorophenyl) formamidine is made to react with TEOF and DEM. In this case, the reaction was sluggish and required 70 hrs of heating and the product was isolated by vacuum distillation. An examination of the methods outlined above for the preparation of 3 reveals the following points:

(i) Many of the available methods are patented and very sketchy in information without specifying the yields that are obtainable.

(ii) Wherever detailed procedures are available, the yields are not very satisfactory and in most of the cases the reaction involves long hours of heating.

(iii) Owing to the formation of by-products, the yields of the desired product have not been attractive.

In view of the commercial importance of the compound 3 and related compounds and the non-availability of satisfactory preparative methods, it was thought worthwhile to devise a suitable route for their synthesis.

CHART – 1

SYNTHESIS OF 4,7-DICHLORO QUINOLINE

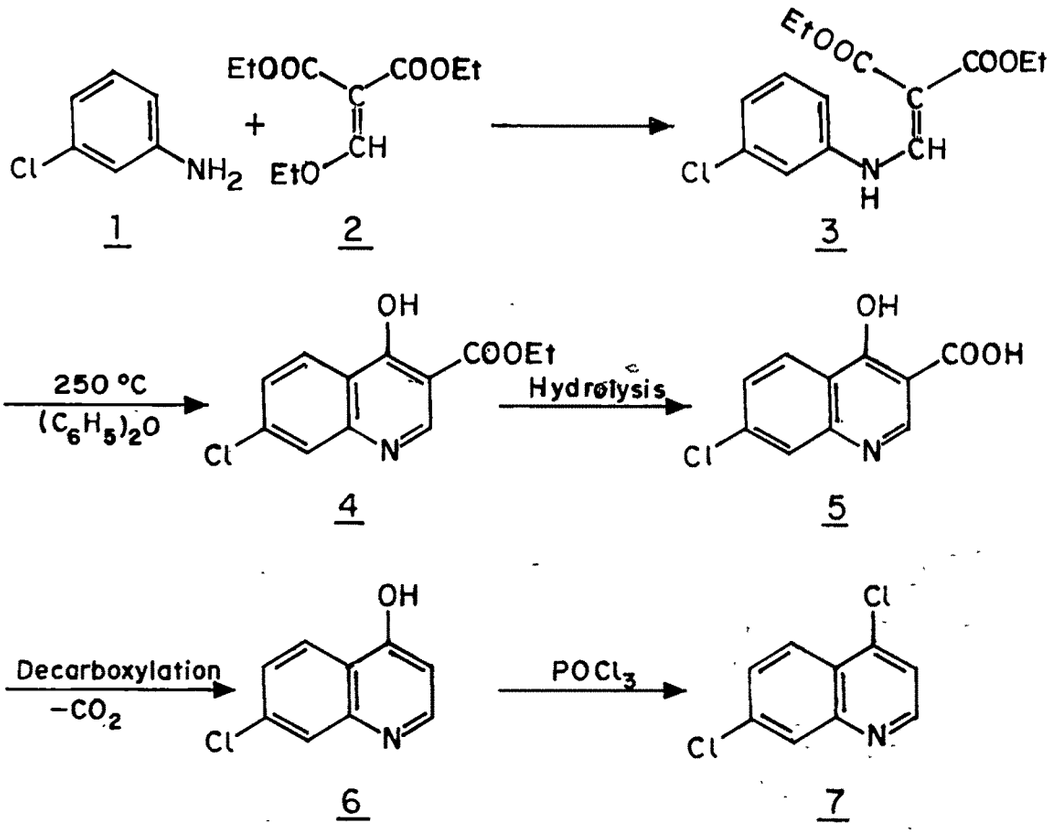


CHART – 2

SYNTHESIS OF CHLOROQUINE PHOSPHATE

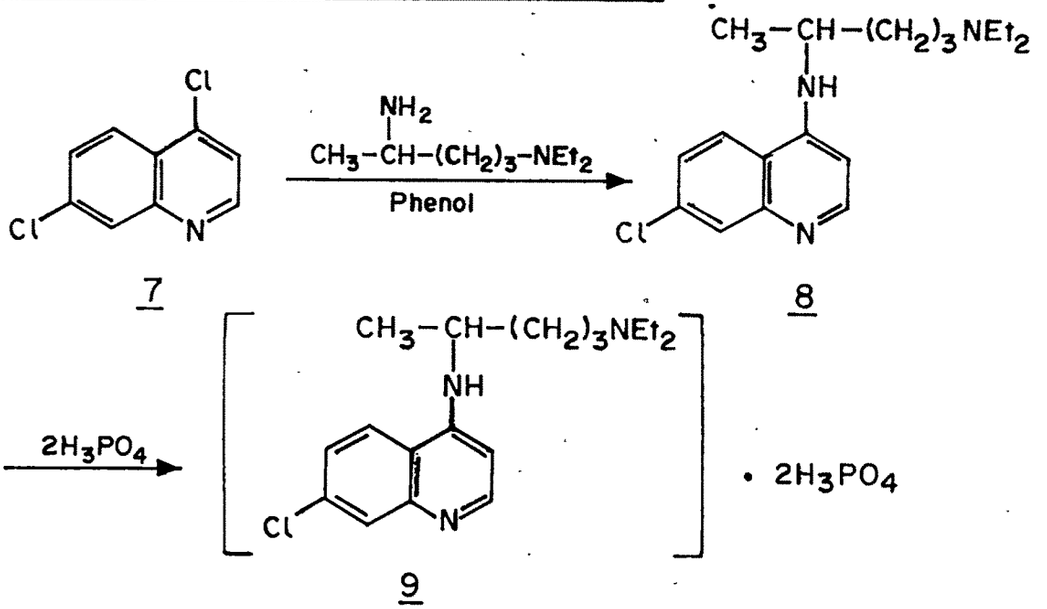
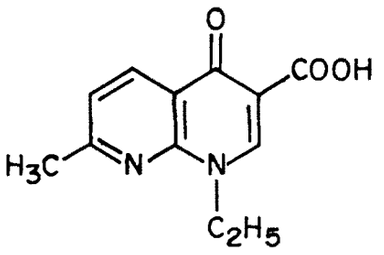


CHART-2 (Contd.)

NALIDIXIC ACID



NORFLOXACIN

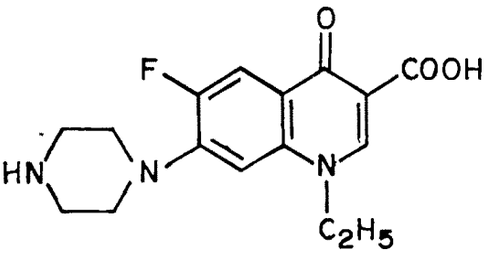
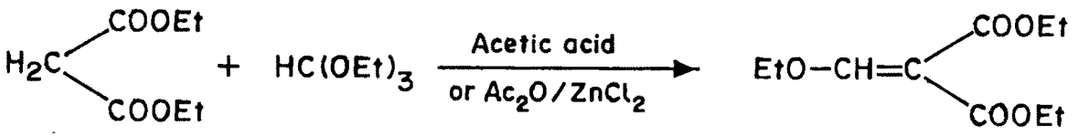
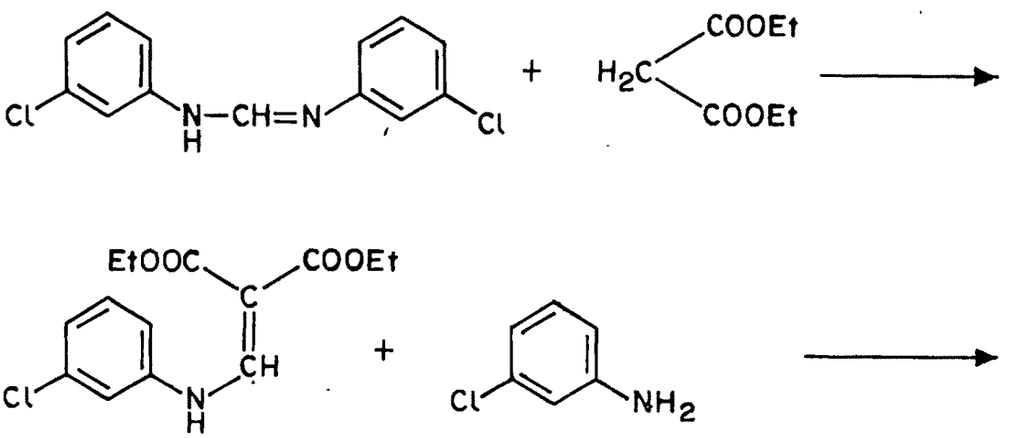


CHART-3

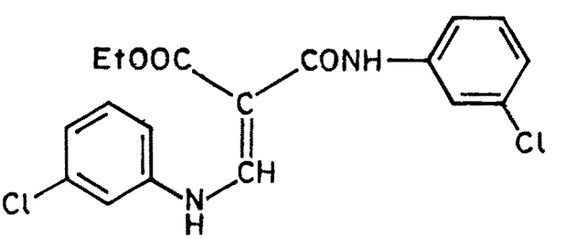


(50-60 %)

CHART-4



3 1



12

PRESENT WORK

In order to improve the yield of the desired product (3) the overall stoichiometry of the reaction was examined. It involved the reaction of m-chloroaniline, DEM and TEOF as shown in CHART 5. Although the reaction sequence (CHART 6) appears extremely simple, the simultaneous presence of all the reactants does not lead to the exclusive formation of the desired product owing to different competing reactions. The situation has been explained by steps 1, 2 and 3 (CHART 5). The reaction of TEOF with m-chloroaniline should lead to almost quantitative yields of formamidine **10**. As one can see, the reaction of the latter with DEM leads to the equimolar quantities of the desired acrylate, regenerating equimolar amounts of m-chloroaniline which is also known to react with the final product **3** leading to the formation of the undesired anilide **12**. To avert this process, it was thought of ensuring an excess of TEOF so that there will be a continuous formation of formamidine. At the same time, it was thought useful to make the addition of DEM in instalments, so that the formation of semianilide with DEM is also precluded. This strategy of sequential and moderated addition of TEOF and DEM is based on the different kinetics of the reaction of m-chloroaniline with the three esters. While the reaction with TEOF is the most rapid and that with acrylate, **3**, is the slowest, the reaction with DEM is intermediate in rate.[13] In other words, the rate of reaction of m-chloroaniline is known to be in the order TEOF > DEM > acrylate **3**.

This strategy was found to be extremely successful and led to the formation of the required acrylate in excellent yields (exceeding 90%) with the suppression of the side products.

Use of Lewis Acid as a Catalyst:

A plausible reaction mechanism for the formation of the acrylate by the reaction of formamidine with DEM is indicated in CHART 7. The nitrogen lone pair (from the imidine link of 10) abstracts a proton from the doubly-activated methylene of DEM and the resulting enolate and the protonated formamidine react and lead to a new C-C bond formation. The driving force is the stabilisation of the iminium ion. The resulting intermediate leads to the ethylαcarbethoxyβarylamino acrylate in a facile manner by virtue of the conjugation that is realized. This mechanistic proposition suggests that the use of a Lewis acid such as zinc chloride might accelerate the reaction in which a proton is abstracted from the active methylene group, by complexing with the estér carbonyl and making the methylene proton more acidic. This expectation turned out to be true and good yields of acrylates of type 3 could be obtained using catalytic amounts of zinc chloride in relatively shorter reaction times.

The sequential and moderated addition of TEOF and DEM as described above and the use of zinc chloride as a catalyst resulted in an efficient synthesis of 3 in almost quantitative yields. The product was well characterized by spectral and analytical methods.

We report that ethyl-α-(carbethoxy)-β-(acrylamino)acrylates and related compounds (3a-3o) (SCHEME 1) can be produced in less than 24 hours in high yield and purity in one pot operation. Thus, a mixture of an arylamine such as m-chloroaniline and half the stoichiometric quantity of TEOF was heated at 130-135°C for 2 h, the intermediate bis-aryl formamide (10), without isolation, was treated with the remaining half of TEOF and half the stoichiometric amount of DEM in the presence of catalytic amount of zinc chloride and the heating was continued for 5 hours. This was followed by further addition of the remaining quantity of DEM and stirring for 15 hours under identical conditions. The products such as 3c were isolated in almost quantitative yields by pouring the reaction mixture into ice-cold acidified water followed by filtration (Table 1).

Generality of the Reaction:

The success that was realized in the synthesis of 3 prompted us to check the generality of this reaction in the preparation of various substituted acrylates. Differently substituted arylamines and various types of active methylene compounds were employed (SCHEME 1). The results obtained have been depicted in Table 1. A perusal of the results indicates that the reaction was very facile in the case of malononitrile and was complete in 8 hours. Generally, almost quantitative yields of substituted acrylates are obtained. On the other hand, the reaction failed with methylphenyl acetate and methyl ethyl ketone.

These acrylates, it may be mentioned, serve as intermediates in the preparation of substituted quinolines. The experimental conditions and the characterization of these products are given in a separate section.

Spectral Characterization of Acrylates (3a-3o):

The purity of the products was established in all the cases by thin layer chromatography. Although most of these compounds are known in literature, they had been prepared from a commercial point of view and were not fully spectroscopically analysed. Wherever such data are available, we found that the compounds synthesized in the present study displayed comparable spectral data with those reported. The salient spectral features of these compounds are briefly outlined below:

IR Spectra:

The typical skeletal absorptions of the aromatic CH bonds were noticed in all these spectra around 1600, 1580 and 1500 cm^{-1}. The olefinic linkage displayed a weak band around 1650. The α, β-unsaturated carbonyl functionality was evidenced by a shifting of the ester carbonyl band to 1670-1680 cm^{-1}. Another significant feature was a relatively poor NH stretching which can be attributed to the intramolecular hydrogen bonding that arises by a favourable six-membered transition state, easily possible in these compounds. The above-mentioned characteristics have been exemplified by the IR data of 3b. The NH stretching frequency is observed as a weak absorption at 3150 cm^{-1}.

The ester carbonyl and CH=C are seen at 1680 and 1650 cm^{-1} respectively. The aromatic CH bands are seen at 1600, 1570 cm^{-1} (FIG. 1). The compounds **3j** and **3k** exhibited distinct bands at 2200 and 2210 cm^{-1} respectively confirming the presence of the nitrile group.

PMR Spectra:

The PMR spectral data for all the products were satisfactory. Spectrum of **3b** for example, exhibited a methyl triplet at 1.31 (J=7Hz), a methylene quartet at 4.2 (J=7Hz), a doublet at 8.3 (J=13Hz), typical of a β-proton of an α,β-unsaturated system and a downfield N-H doublet at 9.7 (J=13Hz) and 3 protons multiplet in the range of 6.7-7.3 for the aromatic protons. An additional feature of this spectrum was the appearance of another methyl triplet and a methylene quartet at 1.38 and 4.27 suggesting the occurrence of a strong hydrogen bonding between the ester carbonyl and NH bond. This facet was also evidenced by the large coupling constant observed[14] for the olefinic and NH protons (FIG. 2). This phenomenon of intramolecular hydrogen bonding[15] was observed in the IR and ^{1}H-NMR spectra of all the compounds.

Mass Spectra:

The mass spectra of all these compounds (**3a-3o**) showed the molecular ions clearly. The prominent peaks observed were due to the expected fragmentation leading to the loss of 46 units (C_2H_5OH), and a further loss of 45 units (OC_2H_5). In some cases, the loss of CO (28) were also noticeable. Another

feature of the mass spectra of these compounds is the presence of a peak corresponding to the basic aromatic amino moiety. In the case of the dicyano compound **3n**, the base peak was due to the loss of 27 (HCN).

As a typical example, in the case of **3b**, the molecular ion is observed at m/e 297. The presence of chlorine is confirmed by the M+2 ion present. The first loss of EtOH (46) forms the base peak at 251 (100%). The next loss of OEt (45) forms the ion at 206 (27%). A peak observed at 178 (70%) may be due to the further loss of CO (28). There is also a peak at 127 (28%) corresponding to the ion formed from ortho-chloroaniline moiety (FIG. 3).

Table 1

Sr. No.	Compd. No.	R	R^1	R^2	Yield	M.P.	Lit. M.P.
1	**3a**	H	COOEt	COOEt	94	50	50[17]
2	**3b**	2-Cl	COOEt	COOEt	96	90	91[18]
3	**3c**	3-Cl	COOEt	COOEt	94	56	57[17]
4	**3d**	4-Cl	COOEt	COOEt	90	81	82[17]
5	**3e**	4-OMe	COOEt	COOEt	86	Oil	38[19]
6	**3f**	3-CH_3	COOEt	COOEt	88	41	41[18]
7	**3g**	4-NO_2	COOEt	COOEt	96	142	142[17]
8	**3h**	2,4-Cl_2	COOEt	COOEt	86	112	112[20]
9	**3i**	2-naphthyl (= Ar)	COOEt	COOEt	88	78	78[16]
10	**3j**	2-Cl	COOEt	CN	92	170	-
11	**3k**	3-Cl	COOEt	CN	96	126	126[1]
12	**3l**	3-Cl	COOEt	COMe	85	87	88[1]
13	**3m**	4-OCH_3	COOEt	COMe	88	88	88[21]
14	**3n**	3-Cl	CN	CN	96	198	198[22]
15	**3o**	3-Cl	COMe	COMe	80	92	92[1]

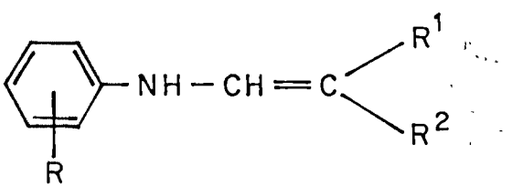


CHART-5

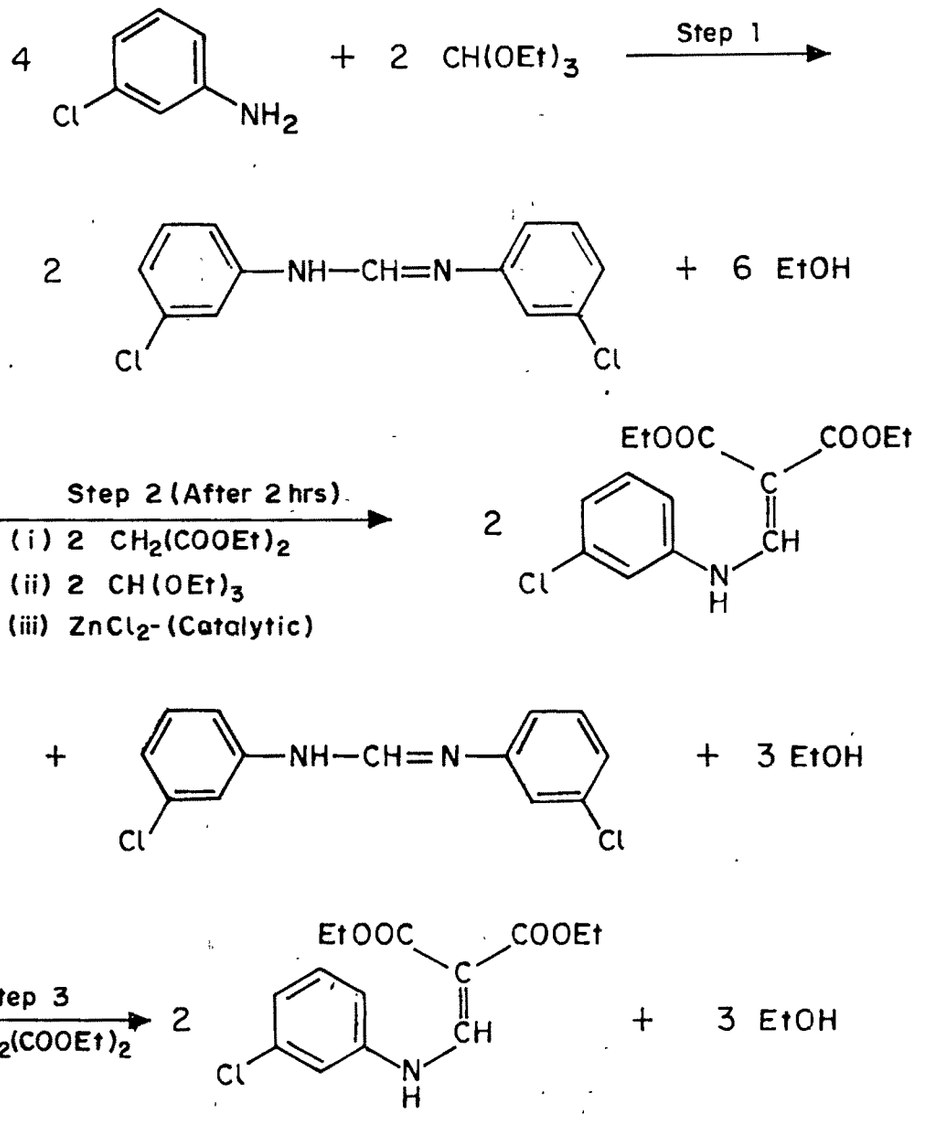


CHART-6

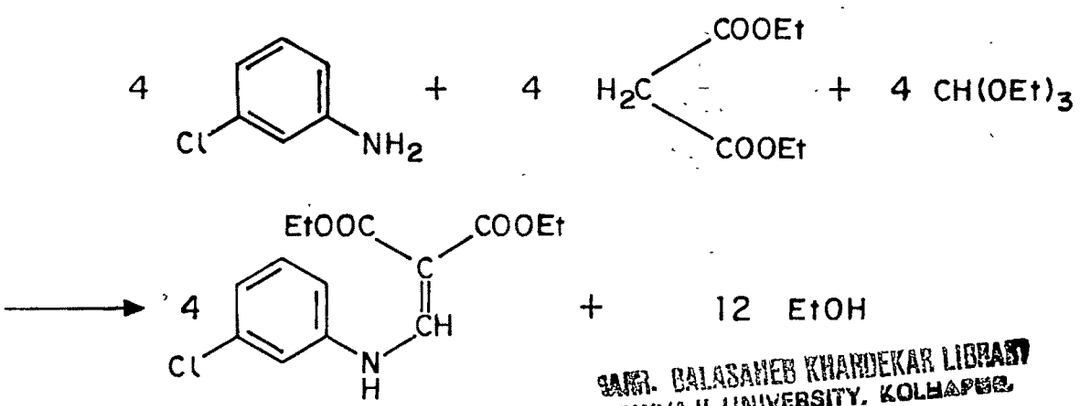
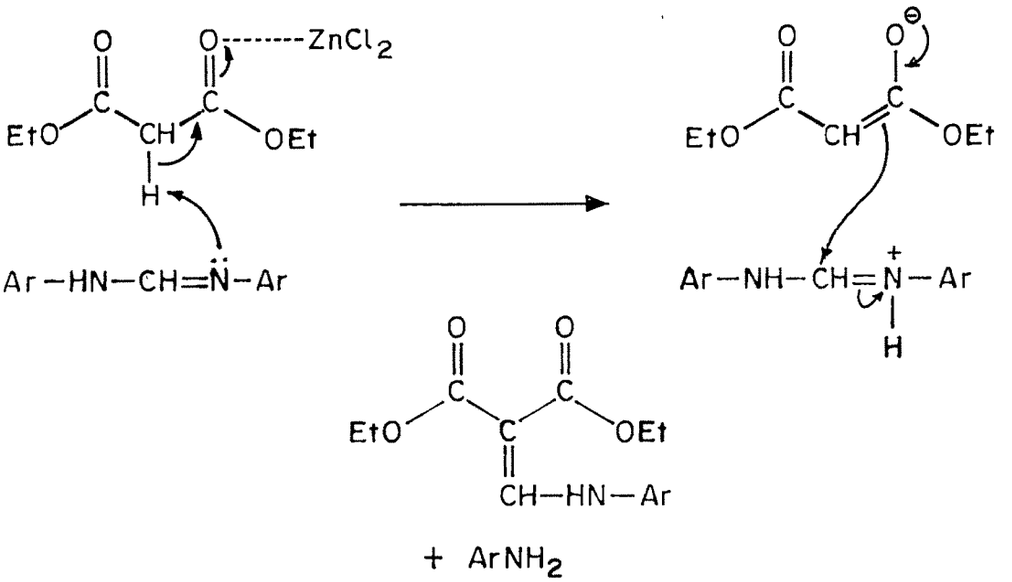
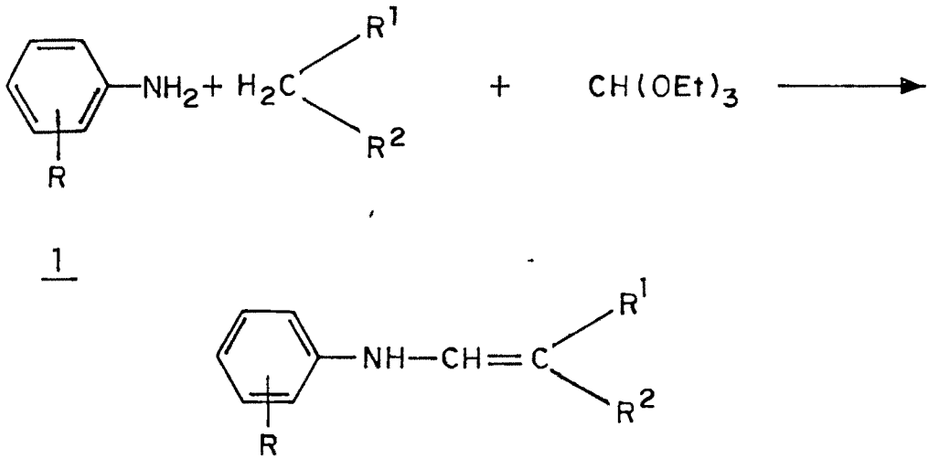


CHART – 7



SCHEME – 1



Ar—NH—CH=N—Ar

10

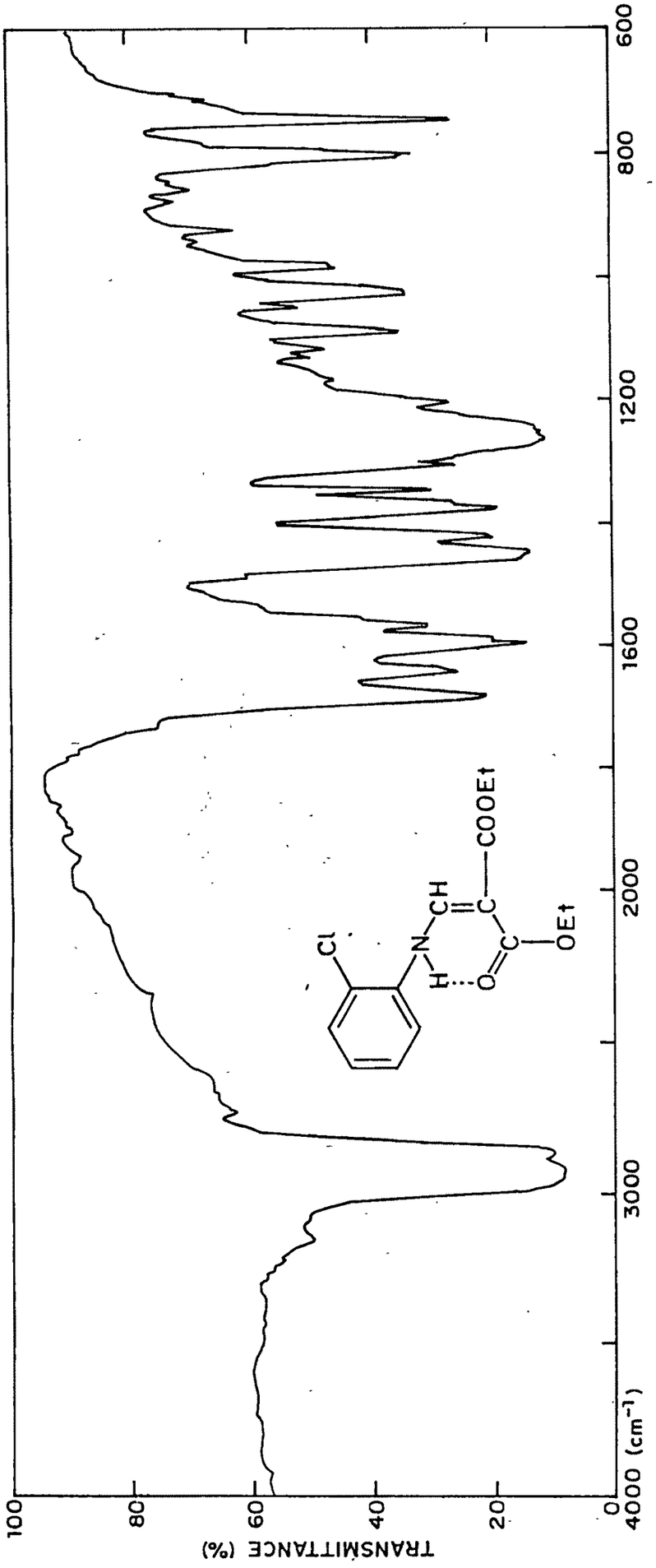

TRANSMITTANCE (%)
100
80
60
40
20
0
4000 (cm⁻¹)
3000
2000
1600
1200
800
600
Cl
N
CH
C
COOEt
C
OEt
O
H
O

FIG. 1

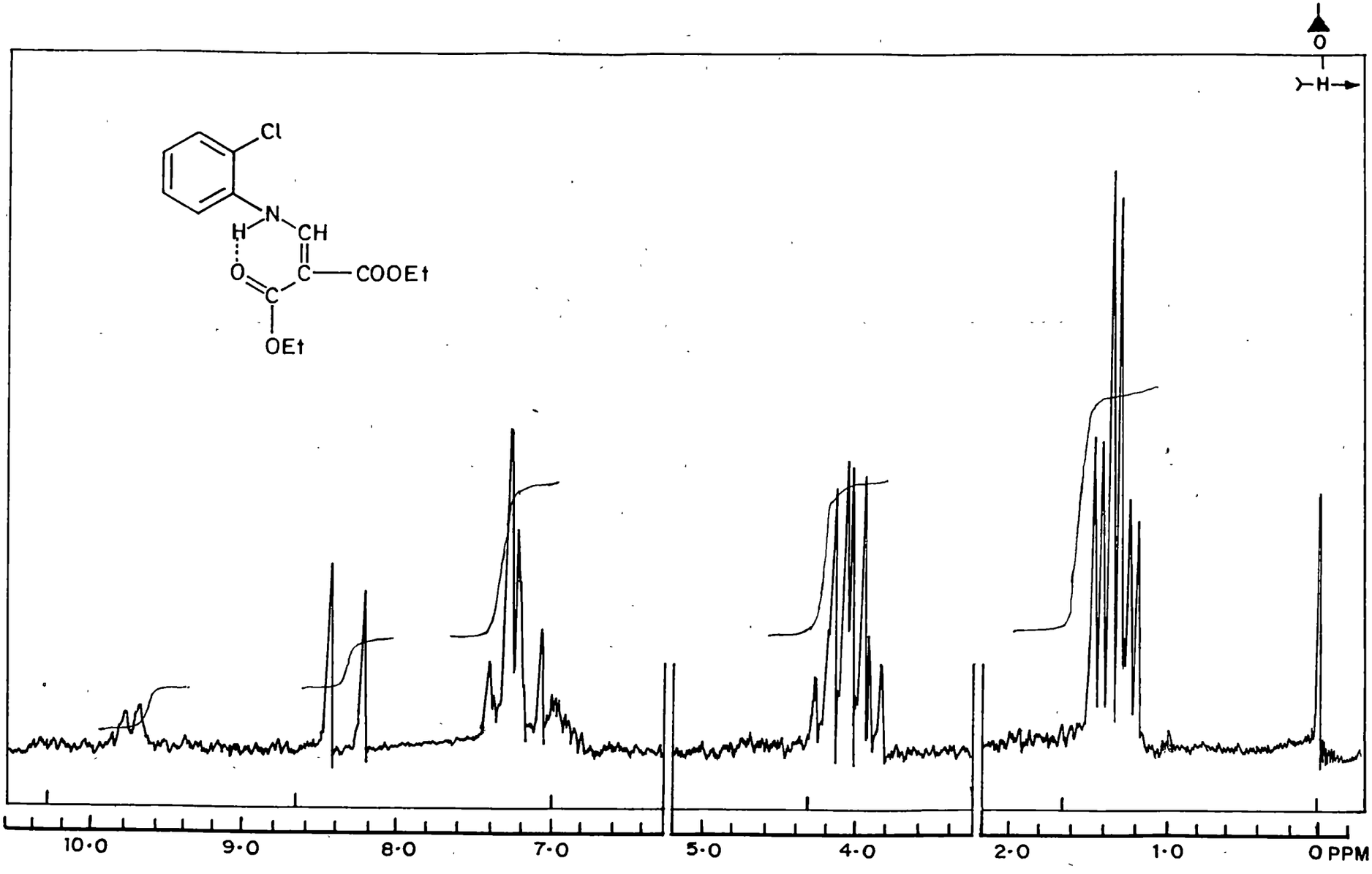


FIG. 2

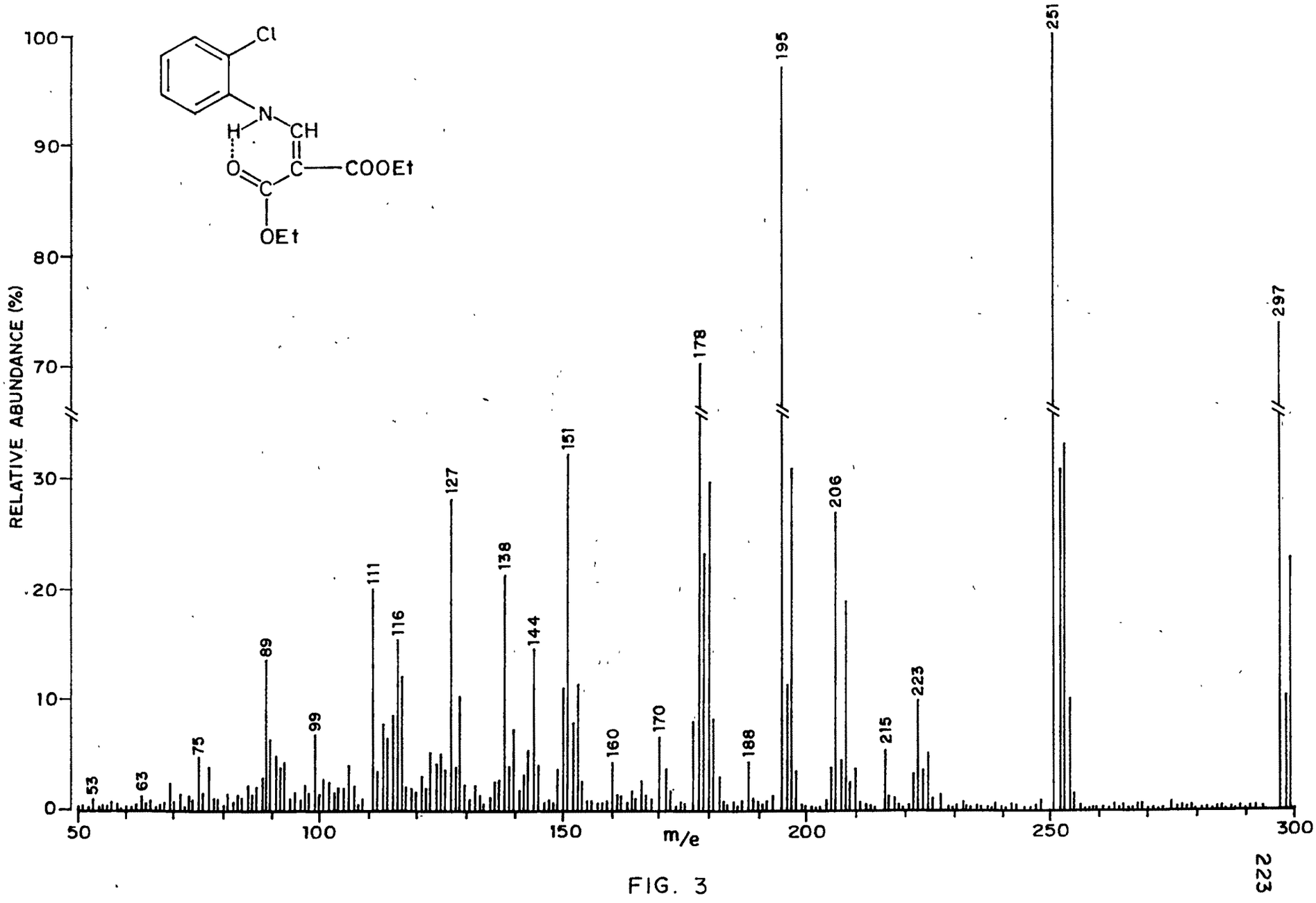

Cl
N
H
CH
O
C
COOEt
C
O
OEt
RELATIVE ABUNDANCE (%)
100
90
80
70
30
20
10
0
50
100
150
200
250
300
m/e
53
63
75
89
99
111
116
127
138
144
151
160
170
178
188
195
206
215
223
251
297
223

FIG. 3

EXPERIMENTAL

General Procedure for the Preparation of 3:

Ethyl-α-(carbethoxy)-β-(anilino)acrylate (3a):

A mixture of aniline (37.2 g, 0.4 mol) and triethyl orthoformate (TEOF) (29.6 g, 0.2 mol) were stirred at 135°C for 2 h and ethanol as it was being generated, was distilled off. To the resulting bis-(anilino) formamidine, which was not isolated, were added in the same flask, TEOF (32.6 g, 0.22 mol) diethyl malonate (32 g, 0.2 mol) and freshly fused anhydrous zinc chloride (0.25 g) and heating was continued for 5 h. Then, an additional (32 g, 0.2 mol) DEM was added and stirring was continued for further 15 h at 135°C. The reaction mixture was poured into 10% aqueous hydrochloric acid (50 ml) cooled in an ice bath. The separated product was collected by filtration. (In the case of low melting product, it is extracted with chloroform and then solvent was distilled out). The product was crystallized from pet. ether (b.p. 60-80°C) as white needles, yield 99 g (94%), m.p. 50°C [lit.[17] m.p. 50°C).

IR (Nujol, cm^{-1}): 3180, 1720, 1690, 1620, 1600, 1570, 1460, 1370, 1250, 1100, 1080, 1040, 990, 800, 760, 700.

^{1}H-NMR (CCl_4): 1.32 (3H, t, CH_3), 1.39 (3H, t, CH_3, H-bonded COOEt), 4.2 (2H, q, $\underline{CH_2}$-CH_3), 4.27 (2H, q, $\underline{CH_2}$-CH_3, H-bonded COOEt), 6.93-7.5 (5H, m, Ar-H), 8.4 (1H, d, $\underline{CH}$, J=13Hz), 11.0 (1H, d, NH, J=13Hz).

MS: m/e (rel. int. %): 263 (M^+, 33), 217(100), 172(36), 161(96), 144(75), 117(38), 104(15), 93(15), 77(18).

Anal. $C_{14}H_{17}NO_4$: Calc. C, 63.87; H, 6.46; N, 5.32
(263) Found: C, 63.60; H, 7.00; N, 5.80

Ethyl-α-carbethoxy-β-(o-chloroanilino)acrylate (3b):
White needles from pet. ether, m.p. 90°C (lit.[18], 91°C), yield 114 g (96%).

IR (Nujol, cm^{-1}): 3150, 1680, 1650, 1600, 1570, 1450, 1420, 1380, 1340, 1270, 1200, 1090, 1030, 980, 920, 800, 750.

^{1}H-NMR (CCl_4): 1.31 (3H, t, CH_3), 1.38 (3H, t, CH_3, H-bonded), 4.2 (2H, q, $C\underline{H}_2$), 4.27 (2H, q, CH_2, H-bonded), 7.1-7.4 (4H, m, Ar-H), 8.3 (1H, d, CH, J= 13Hz), 9.7 (1H, d, NH, J=13Hz).

MS m/e (rel. int.%): 297 (M^+,73), 251(100), 206(27); 195(97), 178(70), 151(32), 138(21), 127(28), 111(20), 89(13).

Anal. $C_{14}H_{16}ClNO_4$: Calc. C, 56.47; H, 5.37; N, 4.70; Cl, 11.93
(297) Found: C, 56.52; H, 5.47; N, 4.72, Cl, 11.50

Ethyl-α-(carbethoxy)-β-(m-chloroanilino)acrylate (3c):
Slender white needles from pet. ether, m.p. 57°C (lit.[17] 57°C), yield, 112 g (94%).

IR (Nujol, cm^{-1}): 3160, 1680, 1650, 1620, 1600, 1460, 1410, 1380, 1260, 1100, 1030, 860, 810, 780, 680.

^{1}H-NMR (CCl_4): 1.30 (3H, t, CH_3), 1.38 (3H, t, CH_3, H-bonded), 4.15 (2H, q, $C\underline{H}_2$), 4.21 (2H, q, $C\underline{H}_2$, H-bonded), 6.7-7.3 (4H, m, Ar-H), 8.13 (1H, d, CH, J=13Hz), 10.73 (1H, d, NH, J=13Hz).

MS m/e (rel. int. %): 297 (M^+, 56), 251(100), 206(27), 195(91), 178(87), 151(37), 138(27), 128(30), 116(18), 111(44), 99(9), 89(23).

Anal. $C_{14}H_{16}ClNO_4$: Calc. C, 56.47; H, 5.37; N, 4.70; Cl, 11.93
(297) Found: C, 56.91; H, 5.62; N, 4.80; Cl, 11.75

Ethyl-α-(carbethoxy)-β-(p-chloroanilino)acrylate (3d):

White needles from pet. ether, m.p. 81°C (lit.[17] 82°C), yield 107 g, (90%).

IR (Nujol, cm^{-1}): 3160, 1670, 1640, 1600, 1450, 1420, 1300, 1260, 1200, 1100, 1030, 800, 750.

^{1}H-NMR (CCl_4): 1.3 (3H, t, CH_3), 1.39 (3H, t, CH_3, H-bonded), 4.18 (2H, q, CH_2-), 4.25 (2H, q, CH_2, H-bonded), 6.72-7.2 (m, 4H, Ar-H), 8.3 (1H, d, CH, J=13Hz), 10.33 (1H, d, NH, J=13Hz).

MS m/e (rel. int. %): 297(43), 251(81), 206(27), 195(100), 178(75), 151(43), 138(16), 127(24), 89(12).

Anal. $C_{14}H_{16}ClNO_4$: Calc. C, 56.47; H, 5.37; N, 4.70
(297) Found: C, 56.14; H, 5.75; N, 4.84

Ethyl-α-(carbethoxy)-β-(p-anisidino)acrylate (3e):

Oil (lit.[19] m.p. 38°C), yield 101 g (86%).

IR (Nujol, cm^{-1}): 3180, 1710, 1640, 1580, 1510, 1450, 1370, 1300, 1250, 1200, 1070, 1020, 830.

^{1}H-NMR (CCl_4): 1.3 (3H, t, CH_3), 1.37, (3H, t, CH_3, H-bonded), 3.8 (3H, s, OMe), 4.15 (2H, q, CH_2), 4.21 (2H, q, CH_2, H-bonded), 6.6-7.2 (4H, m, Ar-H), 8.33 (1H, d, CH, J=13H_z), 10.96 (1H, d, NH, J=13H_z).

MS m/e (rel. int. %): 293(M^+, 17), 247(49), 233(60), 217(100), 189(23), 151(39), 115(50), 103(100), 75(64).

Anal. $C_{15}H_{19}NO_5$: Calc. C, 61.43; H, 6.48; N, 4.77
(293) Found: C, 61.22; H, 6.48; N, 4.50

Ethyl-α-(carbethoxy)-β-(m-toluidino)acrylate (3f):

Fine white needles from pet. ether, m.p. 41°C (lit.[18] m.p. 41°C), yield 97.5 g (88%).

IR (Nujol, cm^{-1}): 3190, 1690, 1640, 1610, 1590, 1440, 1370, 1250, 1215, 1080, 1020, 1010, 980, 795, 750, 675.

^{1}H-NMR (CCl_4): 1.3 (3H, t, CH_3), 1.37 (3H, t, CH_3, H-bonded), 4.15 (2H, q, CH_2), 4.21 (2H, q, CH_2, H-bonded), 6.6-7.1 (4H, m, Ar-H), 8.26 (1H, d, CH, J=13Hz), 9.46 (1H, d, NH, J=13Hz).

MS m/e (rel. int. %): 277 (M^+, 79), 231(100), 186(22), 175(62), 158(38), 130(30), 91(17).

Anal. $C_{15}H_{19}NO_4$: Calc. C, 64.98; H, 6.85; N, 5.05
(277) Found: C, 64.53; H, 7.07; N, 5.15

Ethyl-α-(carbethoxy)-β-(p-nitroanilino)acrylate (3g):

Yellow needles from ethylacetate, m.p. 142°C (lit.[17] m.p. 142°C), yield 118.3 g (96%).

IR (Nujol, cm^{-1}): 3160, 1675, 1630, 1610, 1560, 1500, 1440, 1410, 1370, 1230, 1090, 1010, 850.

^{1}H-NMR (CCl_4): 1.31 (3H, t, CH_3), 1.38 (3H, t, CH_3, H-bonded), 4.18 (2H, q, CH_2), 4.25 (2H, q, CH_2, H-bonded), 6.93-7.50 (4H, m, Ar-H), 8.4 (1H, d, CH, J=13Hz), 11.0 (1H, d, NH, J=13Hz).

MS m/e (rel. int. %): 308 (M^+, 55), 262(86), 206(100), 189(68), 143(38), 116(21), 89(28), 69(31).

Anal. $C_{14}H_{16}N_2O_6$: Calc. C, 54.54; H, 5.19; N, 9.09
(308) Found: C, 54.50; H, 5.37; N, 8.92

Ethyl-α-(carbethoxy)-β-(2,4-dichloroanilino)acrylate (3h):
White needles from ethanol, m.p. 112°C (lit.[20] m.p. 112°C), yield 114 g (86%).

IR (Nujol, cm^{-1}): 1670, 1640, 1600, 1455, 1410, 1360, 1330, 1235, 1200, 1090, 1020, 800.

^{1}H-NMR (CCl_4): 1.31 (3H, t, CH_3), 1.38 (3H, t, CH_3, H-bonded), 4.15 (2H, q, CH_2), 4.22 (2H, q, CH_2, H-bonded), 6.76-7.5 (3H, m, Ar-H), 8.4 (1H, d, CH, J=13Hz), 11.1 (1H, d, NH, J=13Hz).

MS m/e (rel. int. %): 331 (M^+, 48), 285(100), 242(22), 229(79), 212(66), 204(15), 185(33), 172(26), 161(32), 150(19), 123(15), 111(13), 97(11), 73(7), 69(9).

Anal. $C_{14}H_{15}ClNO_4$: Calc. C, 50.60; H, 4.50; N, 4.20; Cl, 21.38
(331) Found: C, 50.92; H, 4.82; N, 4.10; Cl, 20.94

Ethyl-α-(carbethoxy)-β-(2-naphthylamino)acrylate (3i):
White plates from petroleum ether, m.p. 78°C (lit.[16] m.p. 78°C).

IR (Nujol, cm^{-1}): 3250, 1670, 1610, 1580, 1500, 1430, 1410, 1370, 1350, 1340, 1230, 1200, 1080, 1020, 980, 950, 780, 720.

^{1}H-NMR ($CDCl_3$): 1.5 (3H, t, CH_3), 1.57 (3H, t, CH_3, H-bonded), 4.5 (2H, q, CH_2), 4.6 (2H, q, CH_2, H-bonded), 7.2-8.1 (7H, m, Ar-H), 8.5 (1H, d, CH, J=13Hz), 11.3 (1H, d, NH, J=13Hz).

MS m/e (rel. int. %): 313(92), 267(100), 221(81), 211(64), 194(75), 167(89), 143(61), 127(64), 94(76), 58(94).

Anal. $C_{18}H_{19}NO_4$: Calc. C, 69.01; H, 6.07; N, 4.47
(313) Found: C, 68.82; H, 5.80; N, 4.34

Ethyl-α-(cyano)-β-(o-chloroanilino)acrylate (3j):

Yellowish white needles from methanol, m.p. 170°C, yield 92 g (92%).

IR (Nujol, cm^{-1}): 3190, 2200, 1660, 1620, 1450, 1410, 1370, 1310, 1240, 1170, 1020, 975, 780, 755.

^{1}H-NMR (CCl_4): 1.35 (3H, t, CH_3), 4.23 (2H, q, CH_2), 6.8-7.63 (4H, m, Ar-H), 7.8 (1H, d, CH, J=13Hz), 9.53 (1H, d, NH, J=13Hz).

MS m/e (rel. int. %): 250 (M^+, 64), 222(9), 204(100), 177(23), 138(59), 111(24), 99(8), 75(9).

Anal. $C_{12}H_{11}ClN_2O_2$: Calc. C, 57.49; H, 4.39; N, 11.17; Cl, 14.14
(250) Found: C, 57.78; H, 4.51; N, 10.90; Cl, 14.00

Ethyl-α-cyano-β-(m-chloroanilino)acrylate (3k):

Yellowish white needles from methanol, m.p. 126°C (lit.[1] m.p. 126°C), yield 96 g (96%).

IR (Nujol, cm^{-1}): 3180, 2210, 1670, 1620, 1580, 1450, 1370, 1310, 1240, 1170, 1140, 1080, 1010, 860, 780.

^{1}H-NMR (CCl_4): 1.3 (3H, t, CH_3), 4.3 (2H, q, CH_2), 7.13-7.76 (4H, m, Ar-H), 8.3 (1H, d, CH, J=13Hz), 11.1 (1H, d, NH, J=13Hz).

MS m/e (rel. int. %): 250 (M^+, 32), 222(7), 204(70), 177(51), 151(12), 138(100), 111(57), 99(11).

Anal. $C_{12}H_{11}ClN_2O_2$: Calc. C, 57.49; H, 4.39; N, 11.17; Cl, 14.17
(250) Found: C, 56.98; H, 4.56; N, 10.90; Cl, 14.02

Ethyl-α-(acetyl)-β-(m-chloroanilino)acrylate (3l):

Yellow needles from methanol, m.p. 87°C (lit.[1] m.p. 88°C), yield 91 g (85%).

IR (Nujol, cm^{-1}): 1705, 1630, 1590, 1560, 1450, 1370, 1305, 1240, 1200, 1060, 980, 900, 850, 790, 770, 670.

^{1}H-NMR (CCl_4): 1.3 (3H, t, CH_3), 2.36 (3H, s, $COCH_3$), 4.15 (2H, q, CH_2), 6.73-7.23 (4H, m, Ar-H), 8.16 (1H, d, CH, J=13Hz), 10.33 (1H, d, NH, J=13Hz).

MS m/e (rel. int. %): 267 (M^+, 38), 252(13), 222(15), 206(27), 193(100), 178(58), 151(16), 142(33), 111(24), 89(16).

Anal. $C_{13}H_{14}ClNO_3$: Calc. C, 58.30; H, 5.23; N, 5.23; Cl, 13.27
(267) Found: C, 58.80; H, 5.31; N, 5.16; Cl, 13.06

Ethyl-α-(acetyl)-β-(p-anisidino)acrylate (3m):

Yellowish white needles from methanol, m.p. 88°C (lit.[21] m.p. 88°C), yield 92.5 g (88%).

IR (Nujol, cm^{-1}): 3180, 1705, 1640, 1580, 1510, 1450, 1370, 1300, 1250, 1200, 1070, 1020, 980, 830, 770.

^{1}H-NMR (CCl_4): 1.3 (3H, t, CH_3) 2.43 (3H, s, $COCH_3$), 3.8 (3H, s, OMe), 6.73-7.23 (4H, m, Ar-H), 8.3 (1H, d, CH, J=13Hz), 12.93 (1H, d, NH, J=13Hz).

MS m/e (rel. int. %): 263(M^+,35), 217(25), 202(15), 189(100), 174(75), 142(20), 132(20), 104(12), 77(18).

Anal. $C_{14}H_{17}NO_4$: Calc. C, 63.87; H, 6.40; N, 5.32
(263) Found: C, 64.30; H, 6.58; N, 5.24

α-(Cyano)-β-(m-chloroanilino)acrylonitrile (3n):

White powder from methanol, m.p. 198°C (lit.[22] m.p.198-99°C).

IR (Nujol, cm^{-1}): 3300, 2210, 1650, 1600, 1500, 1470, 1380, 1350, 1100, 1040.

^{1}H-NMR ($CDCl_3$): 6.8-7.4 (5H, m, Ar-H), 7.8 (1H, d, CH, J=13Hz), 8.5 (1H, d, NH, J=13Hz).

MS m/e (rel. int. %): 203(M^+,92), 176(50), 158(100), 168(48), 127(58), 111(79), 94(34), 75(55), 65(41), 44(76).

Anal. $C_{10}H_6ClN_3$: Calc. C, 58.96; H, 2.94; N, 20.63; Cl, 17.44
(203) Found: C, 58.64; H, 2.82; N, 20.54; Cl, 17.22

3-(m-Chloroanilinomethylene)acetylacetone (3o):

Pale yellow needles from methanol, m.p. 92°C (lit.[1] m.p. 92°C), yield 76 g (80%).

IR (Nujol, cm^{-1}): 1680, 1600, 1560, 1440, 1380, 1340, 1300, 1270, 1240, 1180, 1160, 1140, 1080, 1020, 970, 960, 930, 890.

^{1}H-NMR ($CDCl_3$): 2.36 (3H, s, OCH_3), 2.46 (3H, s, $COCH_3$, H-bonded), 6.8-7.6 (4H, m, Ar-H), 8.16 (1H, d, CH, J=13Hz), 10.3 (1H, d, NH, J=13Hz).

MS m/e (rel. int. %): 237(M^+,94), 222(94), 214(55), 194(38), 182(69), 180(100), 152(38), 127(61), 94(37), 85(53), 70(60), 44(67), 43(94).

Anal. $C_{12}H_{12}ClNO_2$: Calc. C, 60.60; H, 5.05; N, 5.89; Cl, 14.94
(237) Found: C, 60.34; H, 5.24; N, 5.96; Cl, 14.62

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SUMMARY

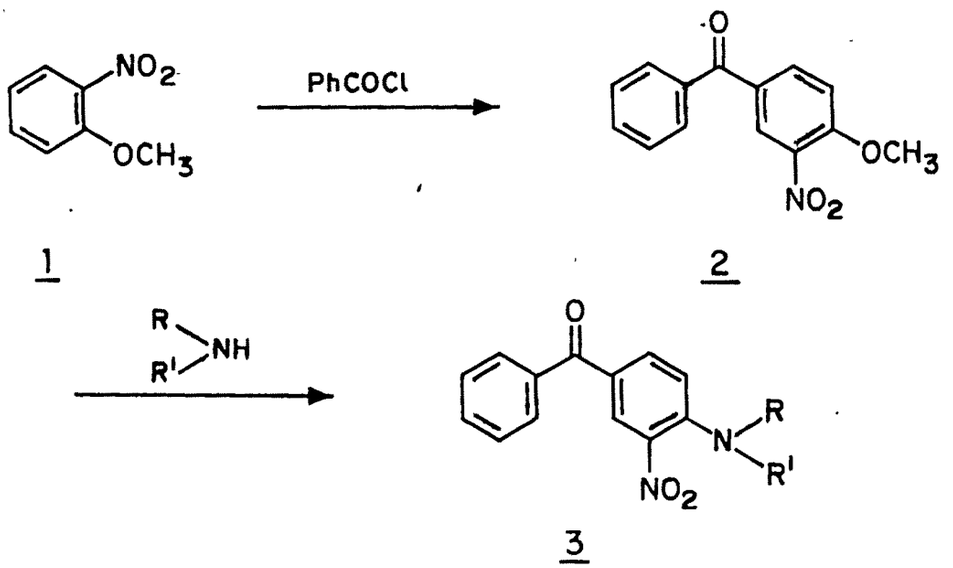
SUMMARY

The work presented in this thesis entitled **"Novel Organic Intermediates and Reactions"** comprises five chapters. A concise summary of the work distributed among five chapters is furnished below:

CHAPTER I: A New and Convenient Synthesis of 4-Amino-3-Nitrobenzophenone and 2-Amino-5-nitrobenzophenone and their N-Alkyl Derivatives:

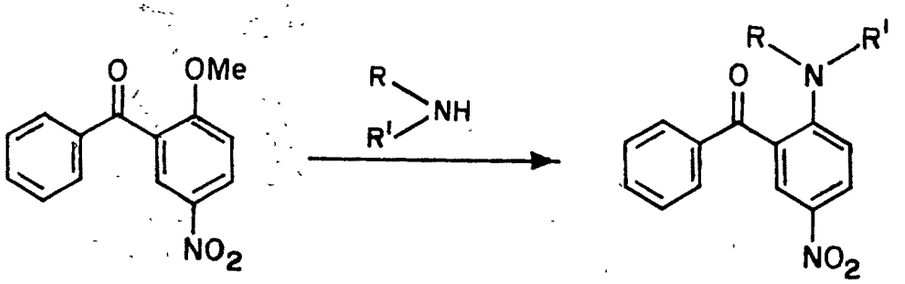
4-Amino-3-nitrobenzophenone is an important intermediate in the synthesis of mebendazole, a valuable anthelmintic drug. This chapter deals with a convenient synthesis of 4-amino-3-nitrobenzophenone, 2-amino-5-nitrobenzophenone and their N-alkyl derivatives in high yield and purity. The present method

SCHEME - 1



3a, R = H, R' = H,
3b, R = H, R' = CH_3,
3c, R = H, R' = C_2H_5,
3d, R = H, R' = $CH(CH_3)_2$,
3e, R = H, R' = n-C_4H_9,
3f, R = H, R' = Cyclohexyl,
3g, R = CH_3, R' = CH_3

SCHEME - 2



4 5

5a, R = H, R' = H
5b, R = H, R' = Cyclohexyl

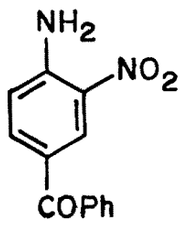
consists of treating 4-methoxy-3-nitrobenzophenone (2) and 2-methoxy-5-nitrobenzophenone (4) with aqueous ammonia, or with aqueous or non-aqueous alkylamines, in a closed vessel at 120°C for 5 h (SCHEMES 1 and 2). The compound **2** in turn was synthesized by a hitherto unreported route involving benzoylation of o-nitroanisole. The compounds **3a-3g** and **5a-5b** were characterized by spectral and elemental analysis.

CHAPTER II:

PART A: Benzotrichloride - A Versatile Reagent for the Preparation of Substituted Benzophenones:

This part describes an efficient method for the preparation of 4-acetamido benzophenone (**8**) which is an important intermediate for the synthesis of 4-amino-3-nitrobenzophenone (**6**) starting from acetanilide. While the benzoylation of acetanilide with benzoyl chloride failed, the use of benzotrichloirde, a precursor of benzoyl chloride led to an almost

quantitative yield of 4-acetamido benzophenone (8). This method was employed to prepare a number of substituted benzophenones (8a-8s) in high yields under extremely mild conditions (SCHEME 3).



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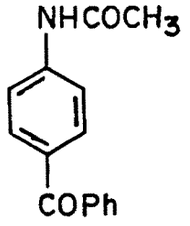
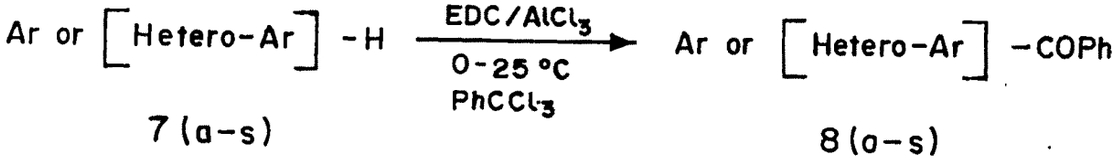


8

SCHEME - 3



7 (a-s)

8 (a-s)

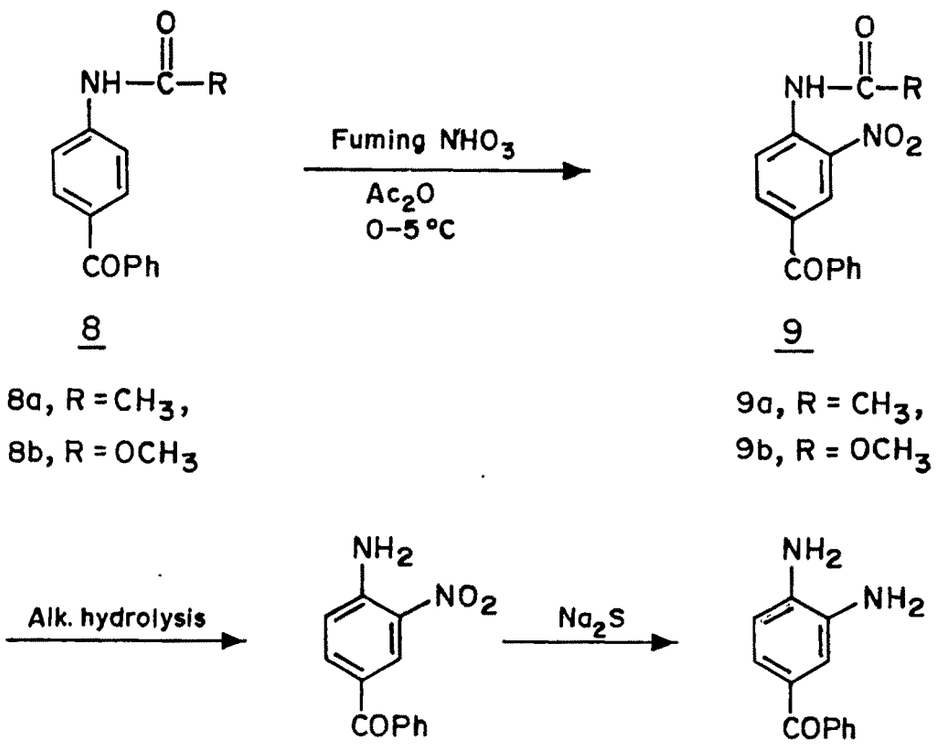
The following compounds (8a-8s) were prepared and characterized by spectral and elemental analysis: 4-Acetamidobenzophenone (8a), [4-(Benzoyl)- phenyl]carbamic acid methyl ester (8b), 4-Benzoyl benzanilide (8c), 4-Benzoyl(p-toluene-sulfonalide) (8d), 4-Chlorobenzophenone (8e), 3,4-Dichlorobenzophenone (8f), 4-Bromobenzophenone (8g), Benzophenone (8h), 4-Methylbenzophenone (8i), 3,4-Dimethyl benzophenone (8k), 4-Methoxybenzophenone (8l), 4-Hydroxy-benzophenone (8m), 2,4-Dihydroxybenzophenone (8n), 2-Acetamido-5-methyl-benzophenone (8o), 1-Benzoylnaphthalene (8p), 2-Benzoyl thiophene (8q), 5-Benzoyl benzimidazolin-2-one (8r), Ethyl-α-(carbethoxy)-β-(4-benzoyl anilino)acrylate (8s).

The efficacy of the method can be judged by the following observations: (i) Benzotrichloride is more reactive than benzoyl chloride under mild reaction conditions, (ii) Being a cheaper, non-hygroscopic and non-lachrymatory reagent, use of benzotrichloride on a large scale is easy and economical; (iii) The selectivity and high yields of this method are noteworthy.

PART B: A Convenient Synthesis of 3,4-Diaminobenzophenone and Mebendazole:

This part describes the conversion of **8a** and **8b** into 3,4-diaminobenzophenone, as detailed in SCHEME 4. All the steps were carried out under mild reaction conditions. The yields were almost quantitative. The intermediates were characterized by spectral and elemental analysis. Finally, mebendazole (**10**) was

SCHEME – 4



8

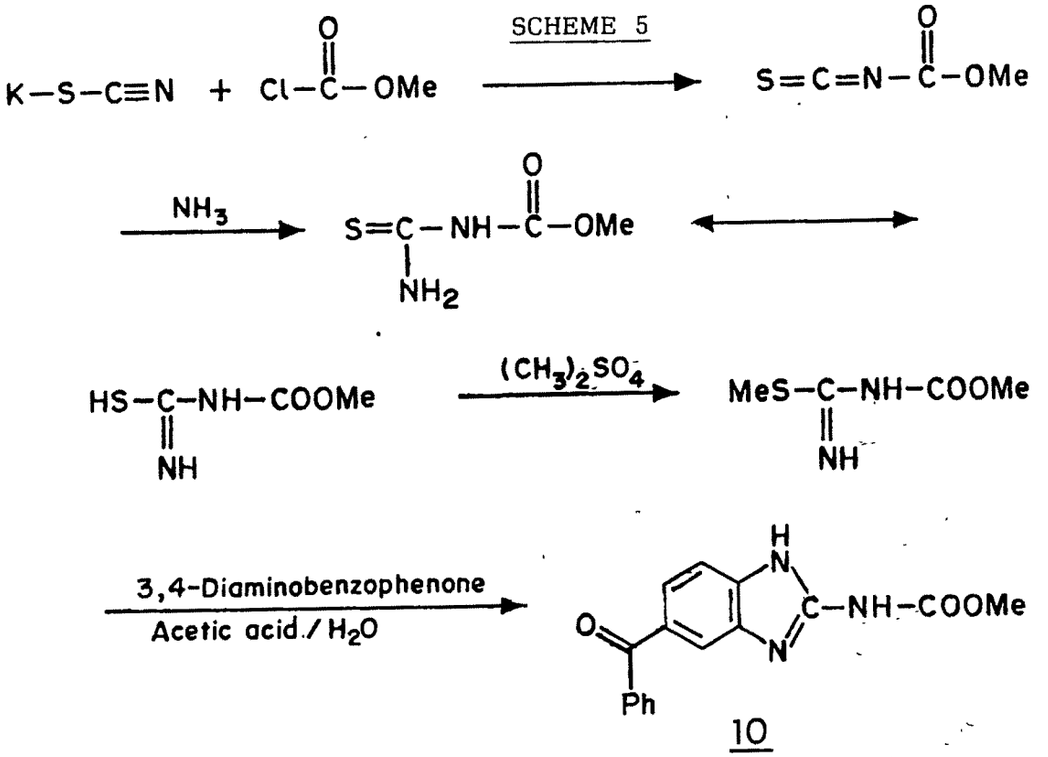
8a, R = CH_3,
8b, R = OCH_3

9

9a, R = CH_3,
9b, R = OCH_3

synthesized in one pot operation by an improved method in good yield and purity as shown in SCHEME 5.

SCHEME 5

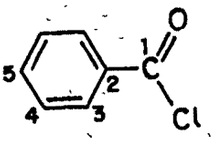


10

CHAPTER III: Exceptionally Stable Phenyldichlorocarbenium Ion as a Friedel-Crafts Intermediate: A High-Field Multinuclear NMR Study.

In this chapter we report, for the first time, the intermediacy of an exceptionally stable phenyl dichlorocarbenium tetrachloroaluminate complex **14** in the Friedel-Crafts reaction of acetanilide with benzotrichloride and aluminium chloride in ethylene dichloride at 25°C and its characterization by high field ^{1}H, ^{13}C and ^{27}Al NMR spectroscopy.

The ^{1}H, ^{13}C and ^{27}Al NMR spectral data for benzoyl chloride (**11**) benzoyl chloride-aluminium chloride complex (**12**), benzotrichloride (**14**) in ethylene dichloride (EDC) and $CDCl_3$ at 25°C was studied. The reactivity of **12** and **14** on acetanilide



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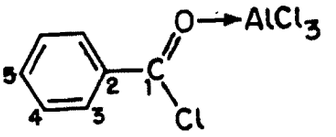

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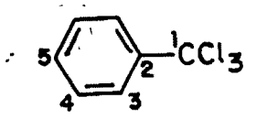

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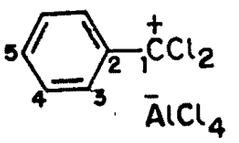


14

under Friedel-Crafts reaction conditions was explained by this study. A donor-acceptor structure (12) and the carbenium ion structure (14) was also suggested. The NMR evidence clearly points out the intermediacy of 14 in Friedel-Crafts reaction of acetanilide with benzotrichloride and $AlCl_3$ at 25°C. The present study also demonstrates for the first time, that it is possible to obtain exceptionally stable aryldihalocarbenium ions such as 14 under milder Friedel-Crafts reaction conditions at ambient temperature. This can have a significant effect on carbocation chemistry which can stimulate future research in this area.

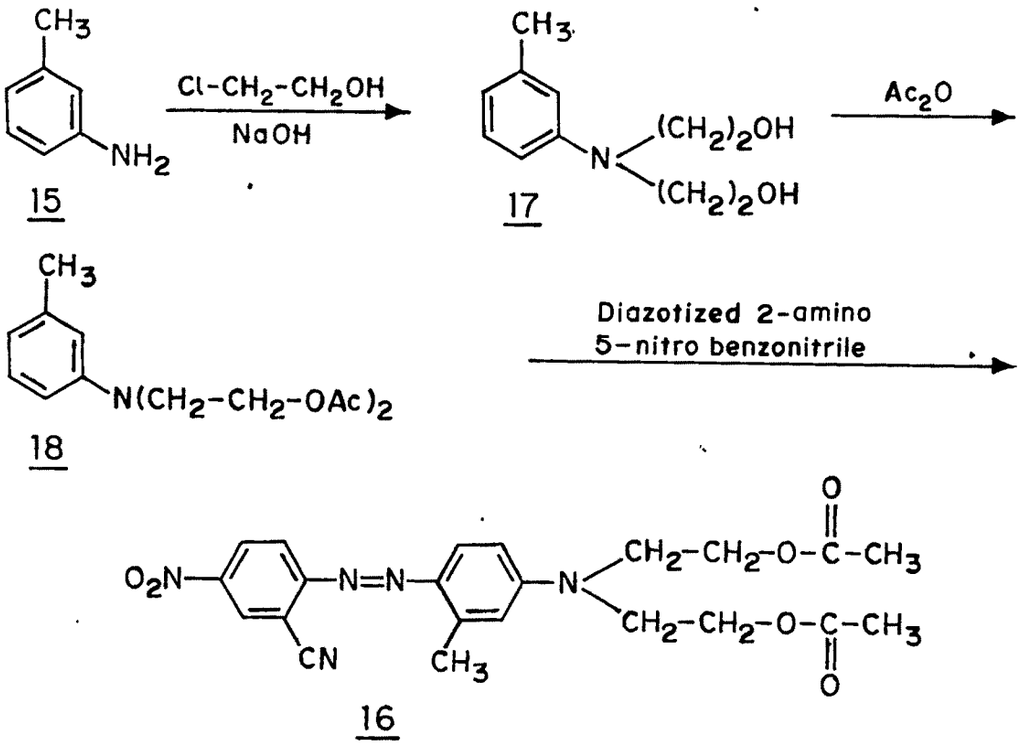
CHAPTER IV:

PART A: Structural Features of C.I. Disperse Violet 33:

Structural elucidation of commercial dyes is extremely important not only for the understanding of the structural features, but also for innovative research in the area. This part describes the structural elucidation of C.I. Disperse Violet 33 as 16 on the basis of spectral and elemental

analysis. This assignment was confirmed by an unambiguous multistep synthesis (SCHEME 6).

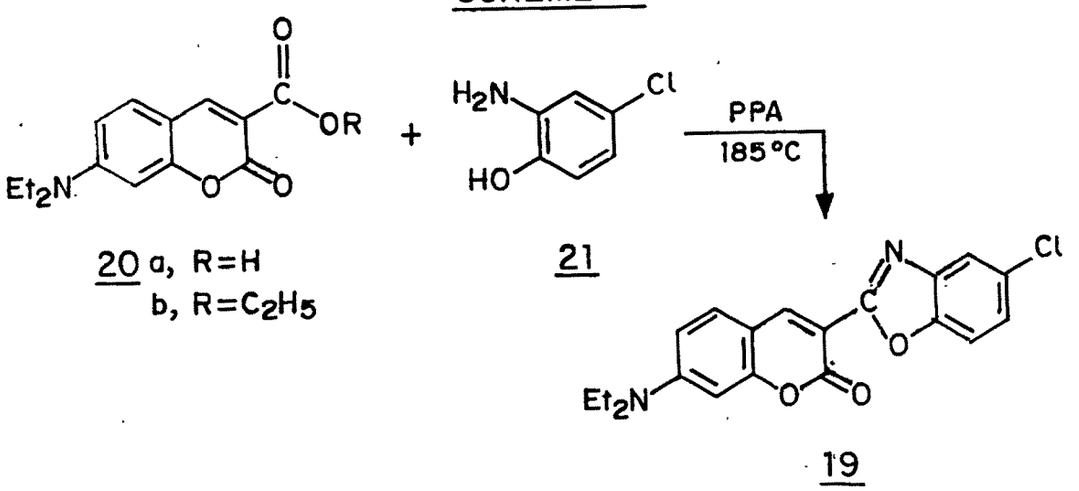
SCHEME-6



PART B: Structural Features of C.I. Disperse Yellow 232 and its Sytnthesis.

In continuation of the work described in Part A, the chemical constitution of C.I. Disperse Yellow 232 (Intrasil Brilliant Yellow 10GF) has been established as 3-(5'-chloro-2-benzoxazolyl)-7-diethylamino-2H-1-benzopyran-2-one **19**. This was further confirmed by its synthesis. The key step in this synthesis consists of the condensation of 7-diethylamino-2H-1-benzopyran-2-one-3-carboxylic acid or its ethyl with 2-amino-4-chlorophenol in presence of polyphosphoric acid (SCHEME 7). The benzopyran-2-one **20** was synthesized starting from commercially

SCHEME-7



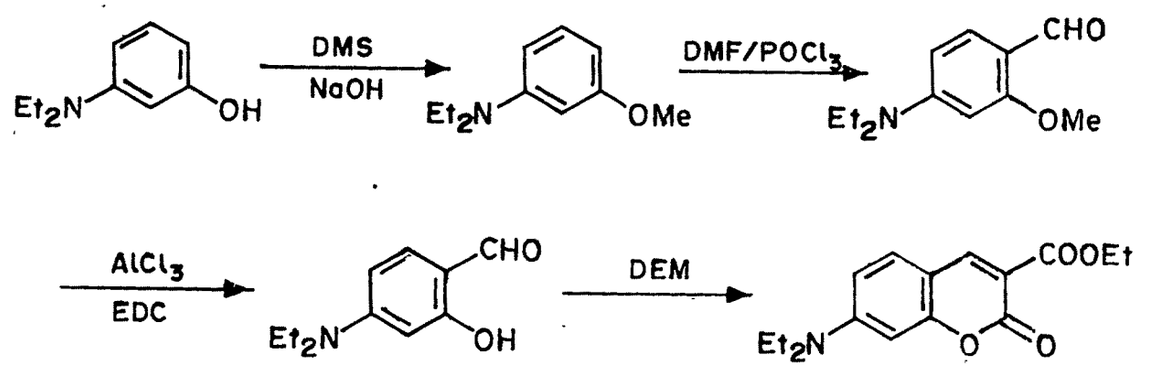
20 a, R=H
b, R=C_2H_5

21

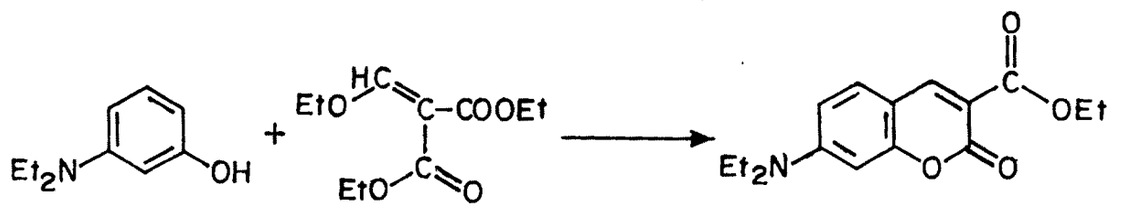
19

available diethyl meta-aminophenol (DEMAP) in a multistep process or alternatively by a single step process (SCHEMES 8 and 9). Further the structure of the dye was confirmed with X-ray crystallographic analysis.

SCHEME-8



SCHEME-9

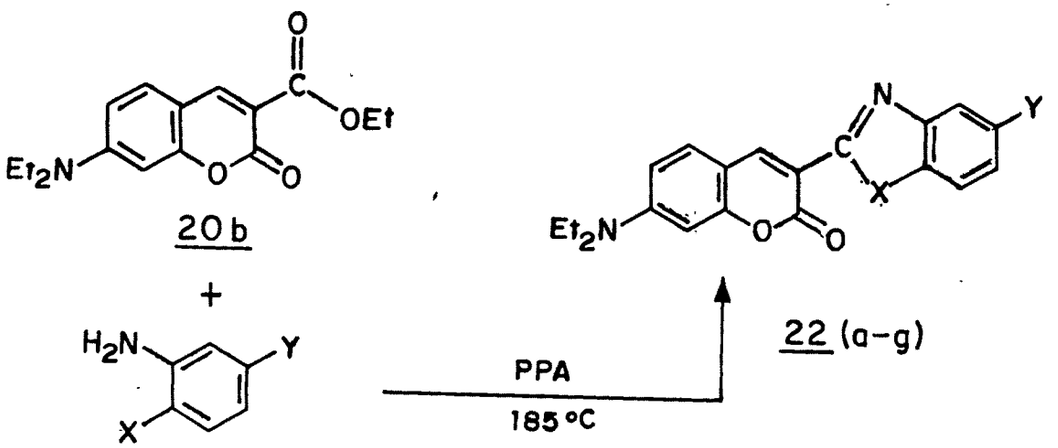


PART C: Synthesis, Laser Characteristics and Dyeing Behaviour of Novel 7-Diethylamino-2H-1-Benzopyran-2-ones.

In Part C, the synthesis of several new analogues (22a-22f) of the dye 19 and their evaluation as laser dyes are reported. The spectral properties and the dyeing characteristics of the new dyes (22a-22g) are also described. These dyes were prepared by the condensation of 7-diethylamino-2H-1-benzopyran-2-one-3-carboxylic acid ethyl ester (20b) with substituted o-aminophenol or o-phenylenediamines (21a-21f). In general these dyes (22) are found to lase in the region 500 nm to 570 nm.

Considering the fact that fluorescent dyes constitute only a small fraction of thousands of known dyes and among these fluorescent systems only a few are effective as dye lasers, the

SCHEME-10



21 (a-g)

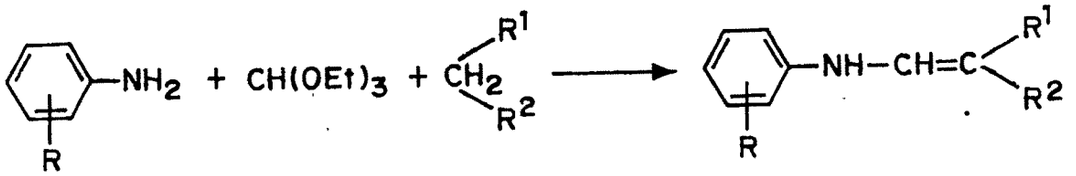
a: X = NH_2, Y = H
b: X = NH_2, Y = COPh,
c: X = NH_2, Y = Cl
d: X = NH_2, Y = CH_3
e: X = OH, Y = H
f: X = OH, Y = COPh
g: X = OH, Y = Cl

a: X = NH, Y = H
b: X = NH, Y = COPh
c: X = NH, Y = Cl
d: X = NH, Y = CH_3
e: X = O, Y = H
f: X = O, Y = COPh
g: X = O, Y = Cl

dyes **22b-22d** and **22g** show great promise as efficient laser dyes with strong possibilities for commercial exploitation. Moreover, these dyes **(22a-22g)** give rise to brilliant greenish yellow shades on polyester with moderate to good fastness proeprties making them suitable for use as disperse dyes.

CHAPTER V: Synthesis of Ethyl-α-(carbethoxy)-β-(arylamino) acrylates and Related Compounds.

Ethyl-α-(carbethoxy)-β-(arylamino) acrylates **(26)** are valuable intermediates for the synthesis of biologically important quinoline derivatives. In this chapter ethyl-α-(carbethoxy)-β-(arylamino) acrylates and related compounds **(26)** are produced in high yield and purity in one pot operation using $ZnCl_2$ as a catalyst. Thus a mixture of arylamine **23** was heated with half the stoichiometric quantity of TEOF **(24)** to form the intermediate bis-arylformamide **(27)**. The compound **(27)** without isolation was treated with the remaining **24** and **25** by a sequential and controlled addition gave **26** in high yield. The following compounds **(26a-26o)** were prepared and characterized :



23 **24** **25** **26**

Ar–NH–CH=N–Ar

27

26: R,R^1,R^2; **26a**: H, COOEt, COOEt; **26b**: 2-Cl, COOEt, COOEt; **26c**: 3-Cl, COOEt, COOEt; **26d**: 4-Cl, COOEt, COOEt; **26e**: 4-OMe, COOEt, COOEt; **26f**: 4-Me, COOEt, COOEt, **26g**: 4-NO_2, COOEt, COOEt; **26h**: 2,4-Cl_2, COOEt, COOEt, **26i**: 2-Naphthyl, COOEt, COOEt; **26j**: 2-Cl, COOEt, CN; **26k**: 3-Cl, COOEt, CN; **26l**: 3-Cl, COOEt, COMe; **26m**: p-OMe, COOEt, COMe; **26n**: 3-Cl, CN, CN; **26o**: 3-Cl, COMe, COMe.

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