NEW METHODS FOR THE SYNTHESIS OF BIOLOGICALLY ACTIVE COMPOUNDS

A THESIS

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(IN CHEMISTRY)

BY

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DECEMBER 1987

DEDICATED TO MY PARENTS

CERTIFICATE

Certified that the work incorporated in the thesis entitled **"New Methods for the Synthesis of Biologically Active Compounds"** submitted by Mr. N. K. Bhamare was carried out by the candidate under my supervision. Such material as has been obtained from other sources has been duly acknowledged in the thesis.

S N Kulkarni

(DR. S. N. KULKARNI)
Supervisor

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(N. K. BHAMARE)

National Chemical Laboratory
Pune 411 008
December 1987

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GENERAL REMARKS

1 The figure numbers, scheme numbers, chart numbers and reference numbers etc. given in each chapter refer to that particular chapter only. The references are given at the end of each chapter.

2 All melting and boiling points are uncorrected. Temperatures are recorded on centrigrade scale.

3 Petroleum ether refers to the fraction boiling in the range 60-80°C.

4 Column chromatography was carried out using silica gel (60-120 mesh) which was activated at 120°C for 5 hr. Unless otherwise mentioned alumina refers to neutral alumina.

5 The spots on TLC plates were visualised by exposing them to iodine vapours.

6 The IR spectra of liquids were recorded as smears and solids as nujol mulls on Perkin Elmer 'Infracord-137B', 599B and/or 683 Model spectrometer using NaCl optics.

7 PMR spectra were recorded on Varian T-60, Jeol-60, Bruker WH-90 or Varian FT-80 spectrometers using TMS as internal standard and chemical shifts are given in δ values.

8 Mass spectra were recorded on a CEC-2-110B double focussing spectrometer using direct inlet system at 70 eV.

9 Microanalyses were carried out in the Microanalytical Section of this laboratory. The analyses are given in % values.

10 GLC was run on Hewlett-Packard 5730A instrument using nitrogen as a carrier gas and flame ionisation detector.

11 UV spectra were recorded in spectroscopic methanol on "Specord" Cart-Zeiss UV-Vis-Spectrophotometer.

GENERAL INTRODUCTION

The present thesis describes the synthesis of various enamines and their utilisation for the synthesis of different types of compounds of biological interest and compounds which are inaccessible or difficult to prepare by other methods. The main aim is to develop a new methodology for the synthesis of the compounds of biological interest with the use of enamines. The use of enamines by Gilbert Stork and their utilisation in alkylation, acylation and other types of electrophilic substitutions has revolutionised the art of synthesis of various natural products. Excellent reviews on the enamines are now available.[1,2] However, there are not many syntheses of heterocyclic compounds using enamines as compared to its use in alycyclic and carbocyclic compounds, especially as key intermediates, in natural product synthesis. Our interest arose in developing new methodology, as it is one of the areas of research in our laboratory. With this in mind we have decided to utilise enamines as useful intermediates in synthesizing various types of compounds of current interest as well as new routes for the target compounds.

The thesis is divided into four chapters.

Chapter I: A Brief Review of Enamines

A brief account of the methods of preparation of enamines, structure and reactivity relationship, alkylation and acylation reactions have been described. The preparation of various carbocyclic and heterocyclic ring systems using enamines have also been described.

Chapter II:

Part A - Different Methods of Synthesis of Isatogens Using Enamines

Section (A): Introduction - This introductory part deals with the chemistry of isatogens, their nomenclature, structures, methods of synthesis, as well as chemical and biological properties.

Section (B): Synthesis of 2-Arylisatogens and its Limitations The styrene enamines were prepared by various routes and were further acylated with substituted o-nitrobenzoyl chlorides. These acylated enamines were converted to 2-arylisatogens and phenyl benzyl ketones. The limitations of this method of preparation of 2-arylisatogens are also described.

Part B - Synthesis of Nitro Substituted Alkyl Phenyl Ketones

In this part enamines prepared from various aliphatic aldehydes were acylated with substituted nitrobenzoyl chlorides and were further hydrolysed to nitro substituted alkyl phenyl ketones.

Chapter III: Hydrogenation Studies of Enamines for the Synthesis of Various Heterocyclic Compounds

α-(o-Nitrobenzoyl) - β—morpholinostyrenes were reductively cyclised to 4-hydroxyquinolines and 4-hydroxyquinoline N-oxides. The enamines prepared from o-nitroacetophenones were studied under various reductive conditions with different reagents.

Chapter IV: Some New Approaches for the Synthesis of Ibuprofen

In this chapter enamines have been utilised for the preparation of an anti-inflammatory drug, ibuprofen.

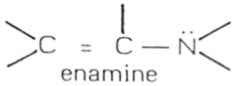
CHAPTER-I

A BRIEF REVIEW OF ENAMINES

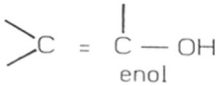
Enamine reactivity has been known since 1883 when, first Collie[3] and later Benary[4] and then Robinson[5] described the C-alkylation or acylation of amino crotonic esters. However the pioneering work on the reactions of enamines with electrophile has been done by Stork in 1954. The C-alkylation and acylation of a carbonyl compound via an enamine intermediate has consequently become known as the Stock reaction.[6]

Although much further work on enamine chemistry has been carried out by other chemists, majority of this work is conceptually no different than that exemplified by Stork.

The term enamine was coined by Wittig and Blumenthal in 1927, which implies an unsaturated amine structure analogous to familiar enol as follows.



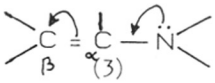
enamine
(1)



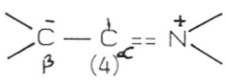
enol
(2)

The enamines are ambident, conjugated diene systems with high, but variable nucleophilicity at both the nitrogen and β-carbon atoms.

In enamine the orbital interaction between the loan pair on nitrogen and π-electrons of the double bond results in increased electron density at the β-carbon atom as shown by structure (3) and (4).



(3)

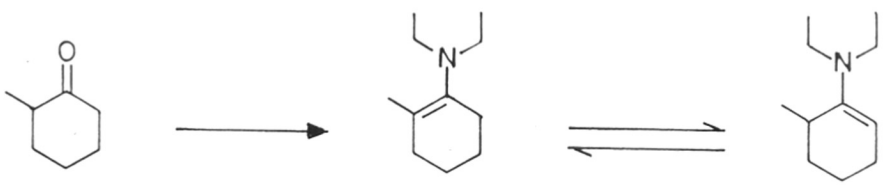


(4)

The contributing structure (4) makes the enamine susceptible to attack of an electrophile at β-carbon atom. This polarisation effect is permanent as shown by its PMR spectrum wherein the proton at β-carbon atom is considerably shielded and consequently appears at high field in the region of 4.1 to 4.6 δ, as compared to the usual olefinic signal at 5.5 δ. The shielding effect at carbon atom is due to p-π conjugation.[7]

Structure and Reactivity

Mixtures of structurally isomeric enamines are usually obtained from unsymmetrical ketones. These isomers undergo rapid acid catalysed equilibrium as shown below.

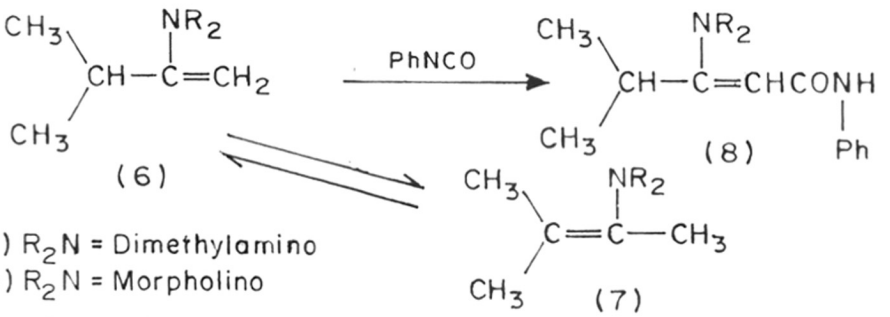


(5a) (5b)

The isomer distribution varies with the amine used. The pyrrolidine enamines of 2-methylcyclohexanones exist as less than 10% in more substituted form (5a) whereas in the case of morpholine isomer, (5a) may form 30-65% of enamine mixture.[8] These differences can be attributed to different conjugating ability and steric requirements of the amine moiety.

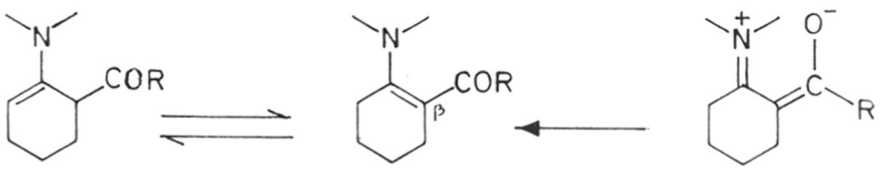
In case of acyclic enamines, an important investigation by Pocar et al.[9] has demonstrated unequivocally that (i) the less substituted enamine is more reactive isomer and (ii) interconversion of enamine isomers may, or may not, occur during the reaction,

depending upon the reagent and experimental conditions used. For example, dimethylamine, enamine of methyl isopropyl ketone exists as a 50:50 mixture of (6) and (7). However, reaction with phenylisocyanate gives only 3-dimethylamino-4-methyl-2-pentenoic acid anilide (8) in 100% yield. Under the reaction condition, the more substituted isomer (7), which is deactivated by $A^{1,3}$ strain, rearranges to more reactive, less substituted form (6). Similar results were obtained with morpholine enamine, which exists as a 30:70 mixture of (6b) and (7b), respectively.



a) R_2N = Dimethylamino
b) R_2N = Morpholino

Acylated enamine also exists as an equilibrium mixture containg more substituted (10) and less substituted (9) forms, and isomeric distribution again varies with the amine used.



(9) (10) (11)

However, in this case it is the pyrrolidine enamine which appears to exist mainly in more substituted or conjugated form (10) whereas

morpholine and piperidine enamines usually exist in the less substituted or non-conjugated form (9).[10,11] The other important difference is that, the more substituted acyl enamine (10) may undergo further reaction at the oxygen, rather than at the β-carbon as in (11).[12,13]

The reactivity of enamine depends on the amine moiety and on the degree of the substitution at the α- and β-positions. Alkyl substituents at the α-carbon increase the elecron density[14] and reactivity at β-carbon atom, by hyper-conjugative and inductive effects, provided that steric interactions do not impair the loan pair interactions. Conversely, the steric and electronic effects of β-substituents decrease the reactivity at the β-carbon atom.

The order of reactivity is therefore normally as follows.

$R_2N\ C(R) = CH_2 > R_2N\ C(R) = CHR > R_2NCH = CHR >$

$R_2NCH = CR_2$

Thus the cyclic and acyclic ketone enamines are more readily C-alkylated than aldehyde enamines which, unless proper precautions are taken, tend to react preferentially at nitrogen.

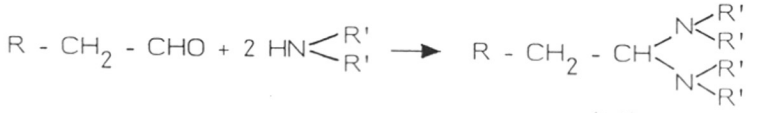
In the case of enamine from cyclic ketones, spectroscopic evidence suggest that reactivity may vary with ring size of ketone in the order $5 > 12 > 8 > 6 > 7$.[15]

Preparation of Enamines

Reaction of Carbonyl Compounds with Amines:

i) Ketones: Enamines of ketones are usually prepared by azeotropic procedures[16,17] which involve refluxing the carbonyl compound and amine in a suitable solvent such as benzene, toluene or xylene in the presence of acid catalyst.

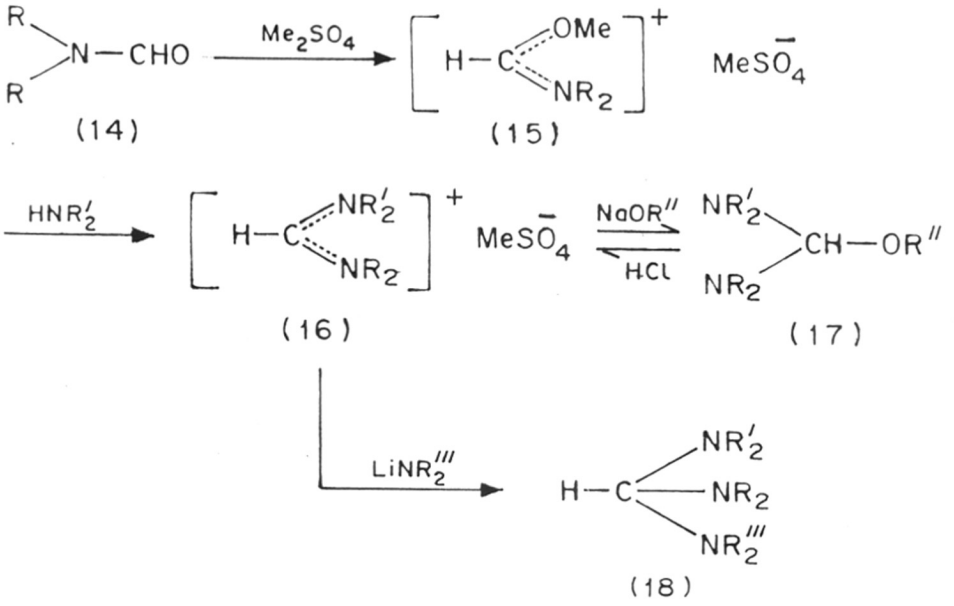
ii) Aldehydes: The first general method developed for the preparation of enamines involved the reaction of aldehyde with a secondary amine (two equivalents) in cold, in the presence of anhydrous postassium carbonate.[18] This gives a 1,1-diamine (aminal) (12) which affords enamine (13) on destructive distillation.



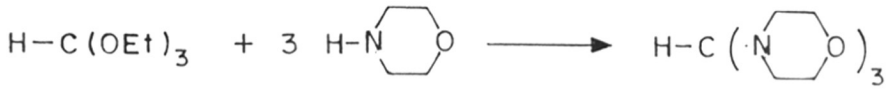
(12)

(13)

iii) Enamines from formamide acetals: Formamide acetals,[19] prepared by the reaction of dialkyl formamide (14) with dimethyl sulphate, afforded the adduct (15). This upon treatment with one mole of dialkyl amine gave the resonance stabilised amidinium cation (16) which when treated with sodium or potassium alkoxide gave the aminal ester (17). The amidinium ion (16) could be regenerated from the aminal ester (17) by treatment with acid. Similarly, when (16) was reacted with lithium dialkyl amide, the tris -(dialkylamino)methane (18) was obtained.

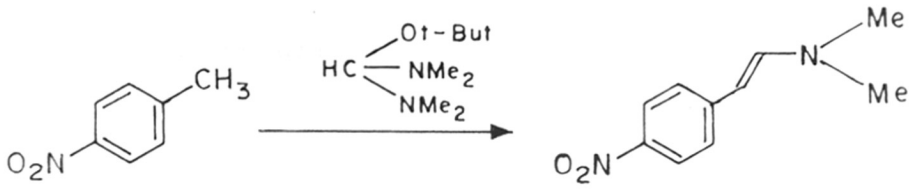


Tris-(dialkylamino)methane[20] can be alternatively prepared from orthoesters using secondary amines. Thus, triethyl orthoformate and morpholine were combined and refluxed using steam jacket condensor for the continuous removal of ethanol. The refluxing mixture on cooling, gave trimorpholinomethane (19).



(19)

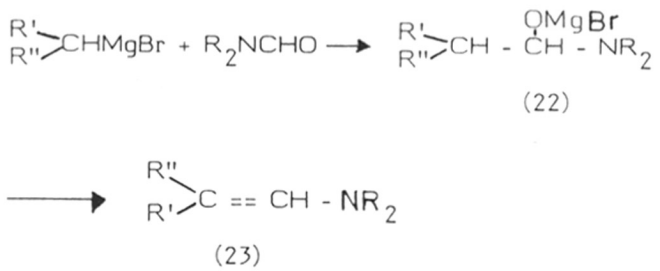
The reaction of substituted toluene (20) with formamide acetals, aminals, tris-(dialkylamino)methane proceeds in generally good yields[19] to enamine (21). The rection proceeds in highest yields with strongly electron-withdrawing substituents (nitro, cyano, sulphonamide) and in lower yields with weakly electron-withdrawing substituents.



(20) (21)

iv) The preparation of enamines by addition of Grignard reagent to N,N-dialkylformamide[21]

The reaction of N,N-dialkyl formamide with alkyl magnesium halide gives a primary addition product (22) which undergoes spontaneous elimination, forming enamine (23) in considerable yield.



(22)

(23)

Alkylation Reactions

The alkylation reactions are useful since the reaction at nitrogen of the enamine is reversible, whereas, reaction at carbon is rendered irreversible by proton transfer. Ketone and aldehyde enamines can therefore be alkylated in high yields by this method.

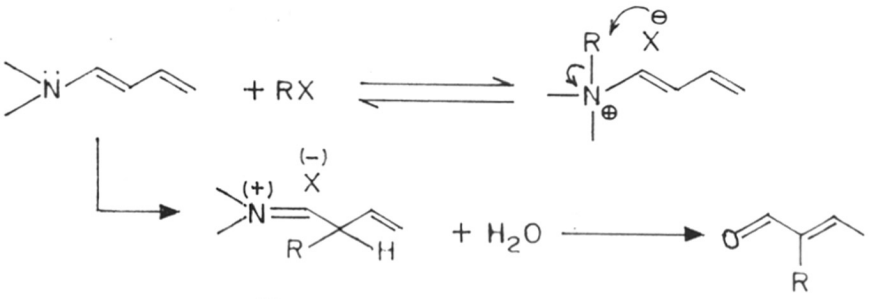
In general, alkylation of ketone with simple inactivated alkyl halides, is unsatisfactory since complex mixtures of unalkylated, monoalkylated, dialkylated and N-alkylated products are formed. Unalkylated iminium salt may be formed by proton exchange between

the starting enamine and C-alkylated imminium salt. Methylation has been reported to be especially bad in this respect.

The problem of N-alkylation versus C-alkylation has been investigated by Kuehne and Garbacik[22], but it was not found possible to establish any general predictive rules. For example, although the pyrrolidine enamine of cyclohexanone showed a greater ratio of C- to N-alkylation with methyl iodide at room temperature, than did the morpholine enamine. This situation was reversed for the reaction with benzyl bromide. However, in the majority of cases, there was an increase in the C- to N-alkylation ratio on heating the reaction mixtures from room temperature to 100°C for 18 hr. Due to N to C alkyl transfer, the facility of N-alkylated enamines to act as carbon alkylating agents, was found to vary with the structure of amine, the ketone used to form the enamines, and with the alkylating agent. On this basis, morpholine enamines were particularly poor (i.e. showed the least increase in C to N ratio on heating), whereas hexamethylene imine enamines were the best. As regards the alkylating agents, the more reactive ones such as benzyl bromide, showed the greatest increase in C to N alkylation ratio on heating.

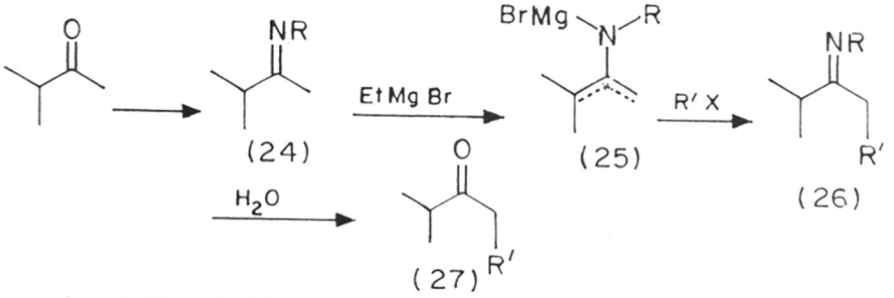
Regarding the mechanism of N to C alkyl transfer, Pandit et al.[23] have concluded that, direct intramolecular N⟶ C alkyl transfer does not take place and have interpreted the data availble from the alkylation of dienamines in favour of a dissociation to alkyl halide and subsequent C-alkylation rather than an intermolecular

alkyl transfer from an ene-ammonium salt to the enamine.



Stork and Dowd[24] have found out that a wide variety of imines derived from aliphatic primary amines and enolisable aldehydes were readily converted to magnesium derivatives, (25) by refluxing with ethyl magnesium bromide in tetrahydrofuran.

These readily prepared magnesium salts react with primary and secondary alkyl halides, to give, after aqueous acid hydrolysis, high yields of monoalkylated carbonyl compounds as shown below.



In similar fashion, the cyclohexylimine from cyclohexanone gave with butyl iodide, 78% of 2-butrylcyclohexanone.

This modification by Stork has the following advantages. (i) Some halides which are easily dehydrohalogenated by strong oxygen bases are not dehydrohalogenated by the magnesium salt of imines.

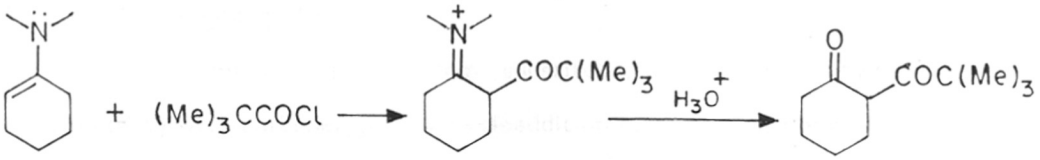
(ii) The formulation of magnesium complex of N-alkylimies may be carried out in the presence of alkyl bromides, since the latter react only slowly with Grignard reagents. This is helpful with imines which condense easily with their Grignard salts, such as the imines of the low molecular aldehydes.

(iii) Allylic halides give alkylation without rearrangement.

(iv) The reaction normally introduces the new alkyl group on the less alkylated side of an unsymmetrical ketone.

Acylation Reactions

Acylation of enamine is a well known synthetic method for α-acylation of aldehydes or ketones.[25] This is an elegant method of carbon-carbon bond formation, which in turn, is superior to Grignard, Aldol, Claisen, Michael and related reactions.[16] Acylation of enamines derived from an aldehyde having α-hydrogen atom, using acid chloride in the absence of an auxiliary base, essentially proceeds via C-acylation to furnish β-ketoaldehyde upon hydrolysis. The acylation of an enamine, with acid chloride bearing no α-hydrogen atom is straightforward and the acylated enamine gives on acid hydrolysis, the α-acyl derivatives of original aldehydes or ketones.[16] For example, the acylation of enamine derived from cyclohexanone, furnishes the corresponding 2-acylated product or β- diketone (29).



(28) (29)

With an acid halide containing ∝-hydrogen atom, the enamine will take up hydrogen chloride to form a ketene in situ, which in turn adds to enamine, furnishing an aminocyclobutanone intermediate,[26] which upon acid hydrolysis gives β-ketoaldehydes.

N-Acylation of enamines is reversible at low temperature. The use of hindered enamines derived from di-isopropylamine, for example, prevents N-acylation and results in good yields of C-acylated aldehydes.[27] With ketone enamines, there is less tendency for amide formation and morpholine enamines often give better yields of C-acylated product than do the more reactive pyrrolidine enamines.

Carbocyclic and Heterocyclic Synthesis

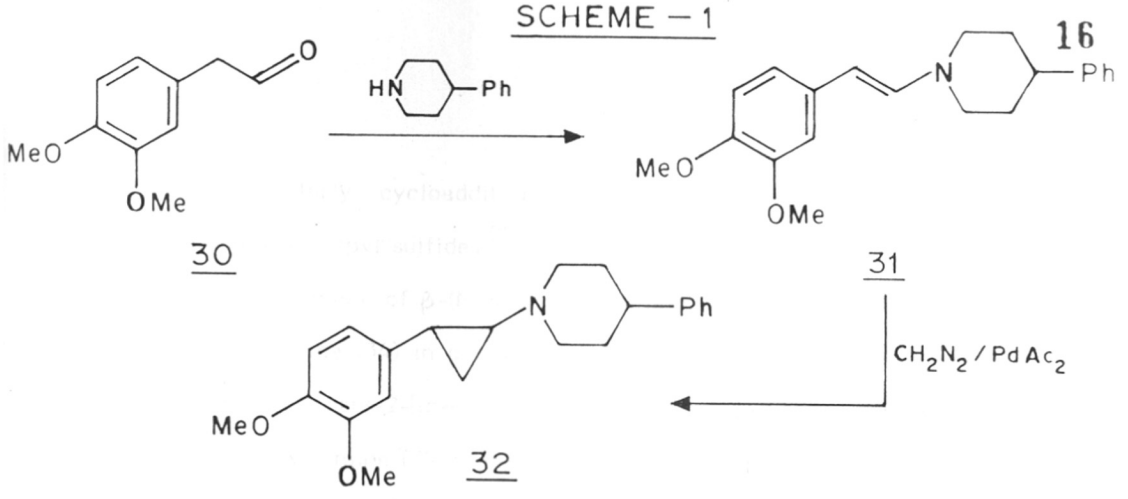
The enamines have been extensively used for the construction of various cyclic systems. The formation of new ring system involves, the introduction or elimination of one or more carbon atoms into an enamine moiety leading to carbocyclic or heterocyclic molecule. When enamine system contains one of the hetero atoms, it leads to heterocyclic compound.

Following types of the ring systems can be constructed with the use of enamines. It includes three-membered ring system to more than six-membered ring systems.

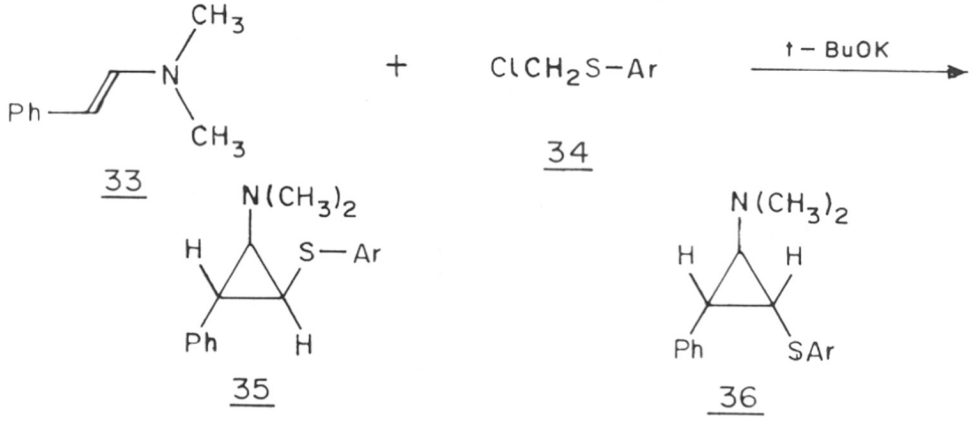
(A) Three-membered rings

The enamine prepared from substituted phenylacetaldehyde on reacting with carbene, gives a cycloaddition product. Cyclopropyl-dopamine analogue was prepared by this route.[28] (Scheme-1).

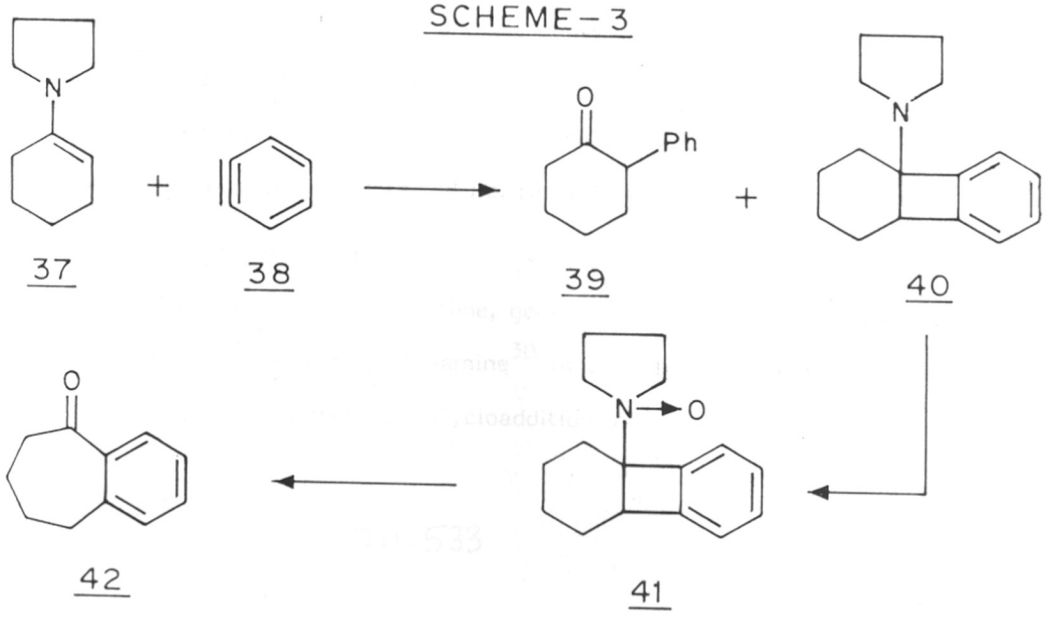
SCHEME – 1



SCHEME– 2



SCHEME– 3



Similarly cycloaddition of thiocarbenes to enamine gives aminocyclopropyl sulfides.[29]

Treatment of β-(N,N-dimethylamino)styrene (33) with p-chlorophenyl sulfide (34) in potassium tertiary butoxide afforded a mixture of cis and trans-2-[(p-chlorophenyl)thio]-N,N-dimethyl-trans-3-phenylcyclopropyl amine (35 & 36) in 41% yield. Adsorption chromatography on silica gel afforded (35) and (36) (3:2 ratio).

It was not possible to assign individual cyclopropyl protons, and, as a result, stereochemical assignment based on vicinal coupling constant, could not be made. A tentative stereochemical assignment based on the effect on the substituent, cis to the phenyl group in a phenylcyclopropane has on the PMR signal of phenyl group was made. Phenylcyclopropanes taking a substituent cis to the phenyl ring showed broad phenyl signal (relative to the compound with a cis substituent), because of increased shielding of the ortho protons. Since a significant difference in phenyl band widths was observed, the compound which possesses a broad phenyl signal was assigned strcuture (35) and cis compound with the sharp phenyl signal was assigned structure (36). The above assignment is based on the assumption that a trans relationship between the dimethylamino and phenyl group is maintained i.e. reaction is stereospecific.

(B) Four-membered rings

1,2-Cycloaddition of ketene, generated in situ from corresponding acid chloride and triethylamine[30] to enamines lead to the formations of cyclobutanones. Cycloaddition of olefines to enamines,

at a low temperature under aprotic conditions is also well documented method for the formation of cyclobutanes from aldehyde enamines.[1]

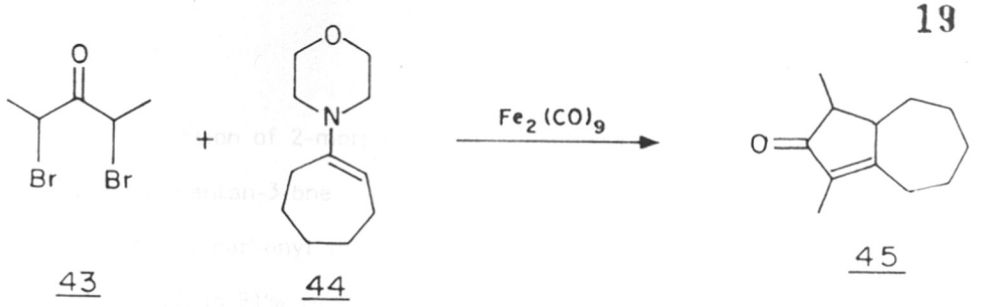
Addition of pyrrolidine enamine of cyclohexanone to benzyne, generated from o-bromo-fluorobenzene and magnesium, gives 2-phenyl-cyclohexanone (39) in 28% yield and aminocyclobutene (40) in 21% yield [31] (Scheme-3).

This difference in product ratio may reflect the formation of epimeric zwitterionic cis-1,3-diaxially substituted chair, or trans substituted boat intermediate in which the otherwise favoured, 1,5-proton transfer is hindred by a methyl substituent. Alternatively, this result may be rationalised by assuming electrophilic addition of a 1,4-dipolar benzyne coupling adduct to the enamine, followed by a 1,5-proton transfer to give conjugated enamine product. Thermolysis of amine oxides gave ketone (42).

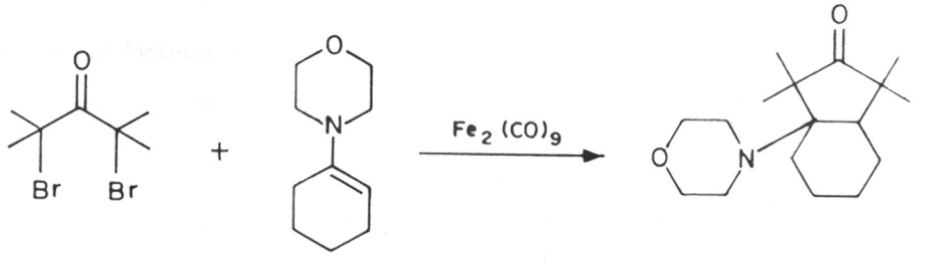
(C) Five-membered rings

The construction of five-membered carbocyclic systems have been generally accomplished by intramolecular condensation of an open chain carbonyl compound or carbocyclic acid derivative or ring contraction of six membered cyclic ketones. But enamines have been used for the cyclopentanone synthesis by the intra-molecular coupling of three or two carbon units. It consists of the reaction of dibromo ketones (43) and morpholine enamine (44) in the presence of iron carbonyls, followed by spontaneous elimination of morpholine. This was achieved under mild reactions conditions.[32]

SCHEME–4

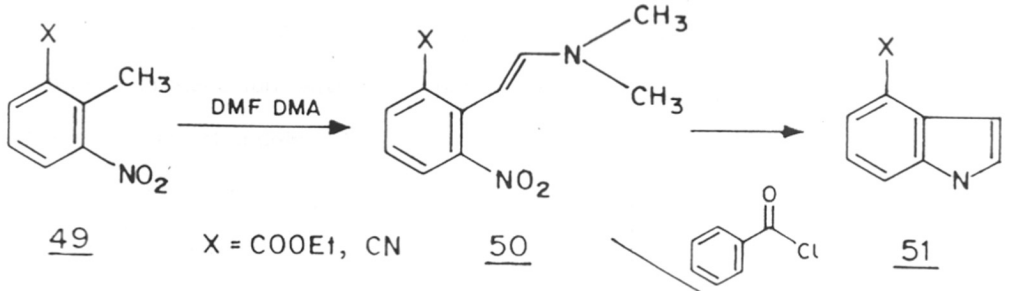


43 44 45



46 47 48

SCHEME–5



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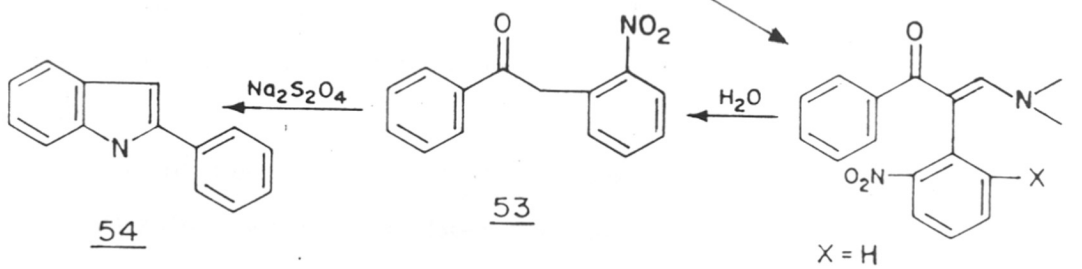

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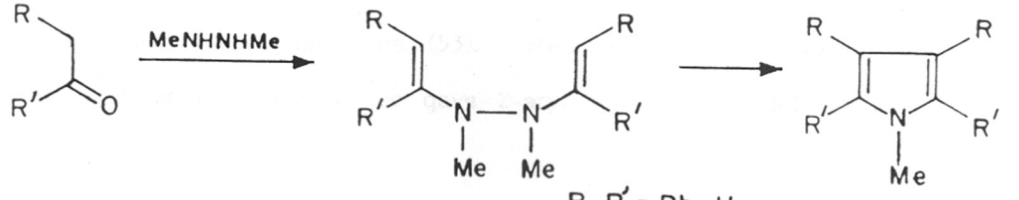
SCHEME–6



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The reaction of 2-morpholinocyclohexene (47) with 2,4-dibromo-2,4-dimethyl-pentan-3-one (46) bearing no hydrogen atom at a position ∝- to carbonyl function, gave rise to the stable β-morpholinoketone (48) in 91% yield (Scheme-4).

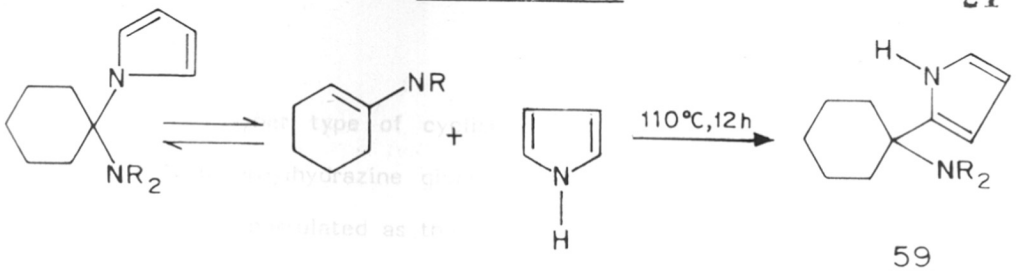
Preparation of Heterocyclic Compounds

Ponticello & Baldwin[33] prepared 4-substituted (4-COOEt, CN) indole derivatives, a precursor in the synthesis of ergot alkaloids, and related compounds. Treatment of susbtituted o-nitrotoluene with 2 equivalent of dimethylformamide dimethylacetal (DMFDMA) in DMF at 110°C for 2 days gave enamine (50). Reductive cyclisation of enamine (50) to the 4-substituted indole (51) was carried out in the presence of iron in acetic acid - ethanol, in about 63% yield. While hydrogenation with 10% palladium on carbon, provided only trace amount of indole (51).

A similar type of enamine (50) was prepared by Lloyd and Nicols.[34] When 2-benzyloxy-6-nitrotoluene was combined with 1.5 equivalents of tripiperidinomethane at 110°C for four hours, which was further cyclised to indole in the presence of titanium trichloride.

Edward Corcia and Ian Fryer[35] prepared similar enamine with (DMFDMA) which was acylated with benzoyl chloride, followed by direct hydrolysis of reaction mixture. This effected the desired three step sequence of acylation, hydrolysis, deformylation to give 2-(2-nitrophenyl) acetophenone (53). Reduction of acetophenone (53) with sodium hydrosulfide gave 2-aryl substituted indole (54), (Scheme-5).

SCHEME-7



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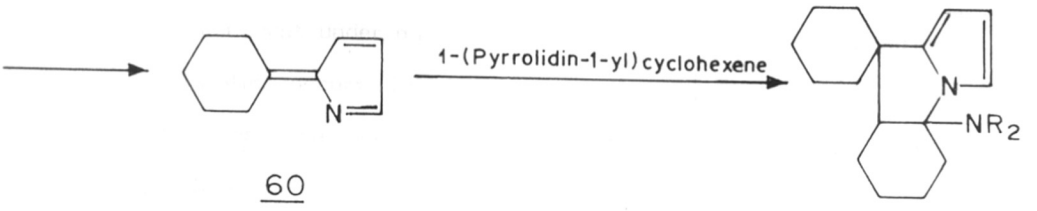

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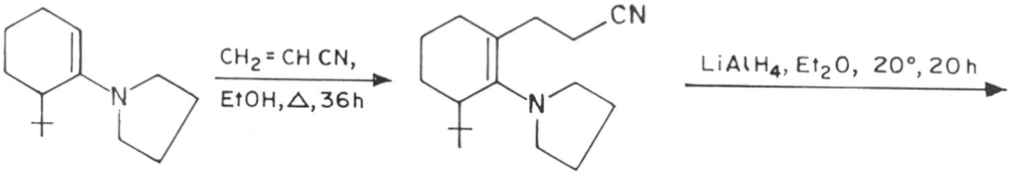
SCHEME-8



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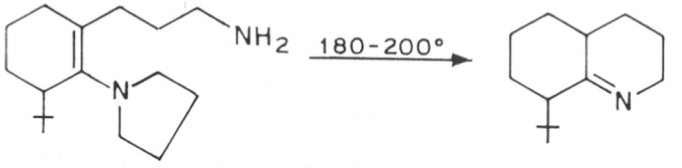

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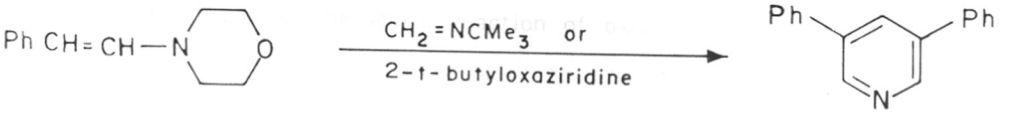
SCHEME-9



66 67

Fischer type of cyclisation of the carbonyl compound with N,N-dimethylhydrazine gives N-methylpyrroles.[36] Bis-enehydrazine (56) was postulated as the intermediate in this reaction (Scheme-6).

Pyrroles have been found to react with enamines by initial C-protonation of the enamine and N-alkylation of pyrrole by resulting imminium salt under mild conditions; under more forcing conditions, C-alkylation occurs (59), followed by elimination to give azafulvene (60) which then reacts with second equivalent of enamine to give pyrrolizine (61)[37] (Scheme-7).

Six-Membered Heterocylic Compounds

Pyrrolidino enamine of 2-t-butylcyclohexanone was alkylated with acrylonitrile to give cyanoethylated product (63). This cyanoethylated product was reduced with lithium aluminium hydride and was further cyclised to ocatahydro -Δ^{1-9} quinolines (65), in the presence of heat[38,39] (Scheme-8).

Aliphatic Schiffs bases react with aldehyde enamines (two equivalent) to give the pyridine (67). 2-t-Butyl-1-oxaziridine gives the same product (67)[40] (Scheme-9).

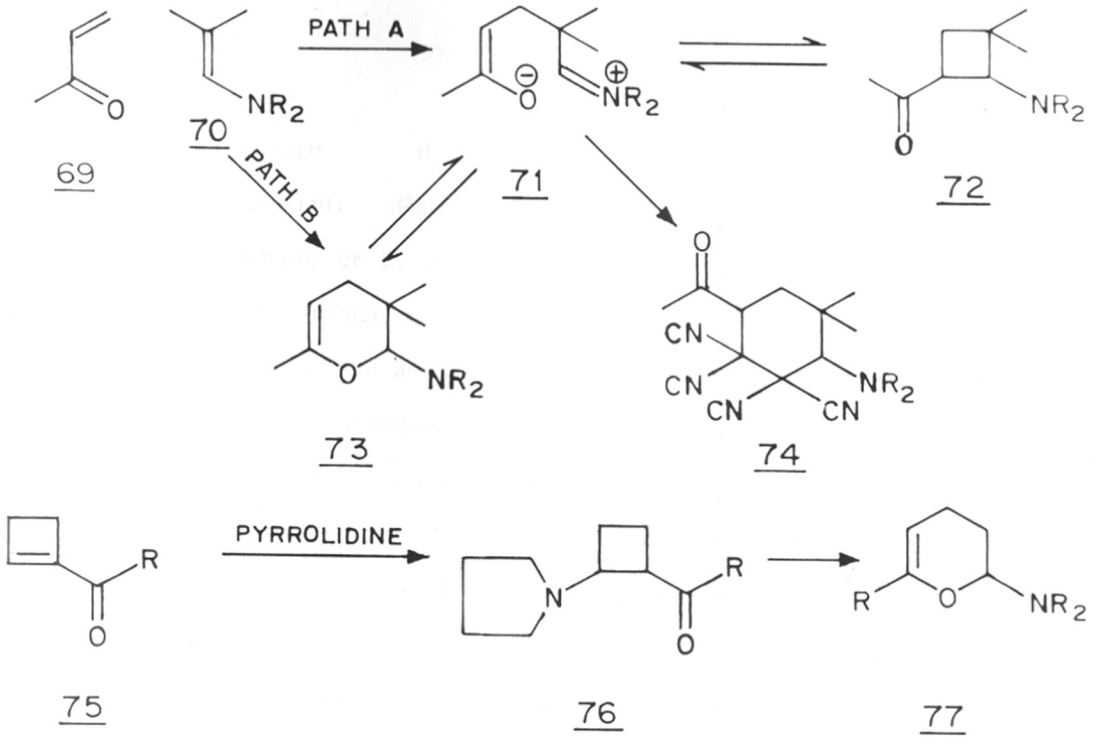
The formation of large amounts of N-tert-butylformamide ascribed to thermal rearrangement of the oxaziridine and benzaldehyde, implies oxidative decomposition of the enamine. Thus formation of unexpected pyridine derivative suggested that participation of Schiffs base (N-tert-butylformamide) which was formed from oxaziridine in the course of reaction. The intermediacy of the Schiff base in the above reaction of oxaziridine is established

by carrying out the reaction between enamine and the trimer of Schiffs base.

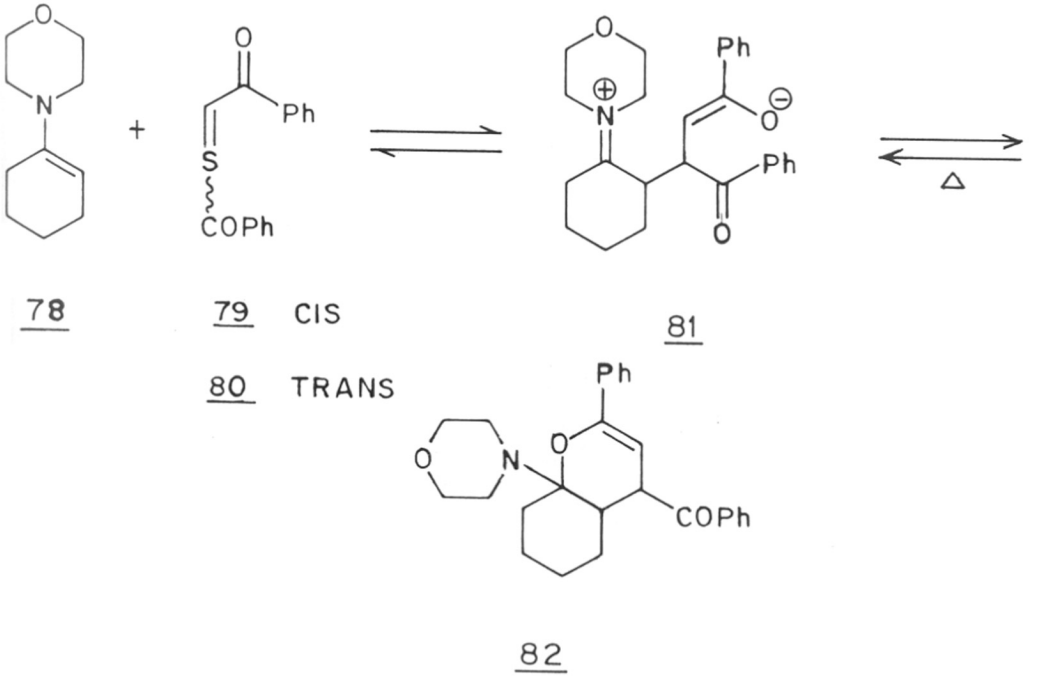
In contrast to the oxaziridine, the trimer of Schiffs base did not react with the enamine at 30°C. The formation of pyridine derivative at 110°C showed that the rate of dissociation of the trimer of Schiffs base is rather slow and oxaziridine is a better source of Schiffs base at lower temperature. The yield of pyridine derivative was increased up to 36% at 200°C. Though the rate of dissociation of the trimer becomes greater as the temperature increases, no improvement in the yield was observed at 250°C as compared with the result at 200°C. Decrease in the molar ratio of Schiffs base/enamine did not cause any increase in the yield of pyridine derivative. Longer reaction time has not significant effect on the yield either.

Dihydropyrans (73) have been found to be the initially formed products in the reaction of methyl vinyl ketone with enamines, but appears in some cases to form an equilibrium with the corresponding cyclobutylmethyl ketone (72) via the open chain imminium enolate (71). The later may be trapped with tetracyanoethylene to give (74).[41] It is not surprising that the cyclobutyl ketones (72) were not isolated since their independent synthesis from (75) has shown that they readily rearrange to the thermodynamically more stable dihydropyrans (77)[42] (Scheme-10).

SCHEME – 10



SCHEME – 11



The formation of dihydropyrans could occur by a concerted [4+2] cycloaddition (Path b, Scheme-10) of α,β-unsaturated ketone to the amine, or by a two step process involving cyclisation of the initially formed zwitterionic intermediate (Path a, Scheme-10).

Following an analogous procedure, it was shown that both cis and trans-dibenzoylethylene gave one and the same dihydropyran (82). Moreover, reaction of enamine (78) with an excess of cis (79) gave unchanged olefin, as the more stable trans-(80) under conditions (i.e. absence of free secondary amine at room temperature) which precluded interconversion of (79) and (80) (Scheme-11). This clearly constitutes unequivocal evidence, for two step mechanism involving the reversible formation of the zwitterionic intermediate (81). Unfortunately the stereochemistry of dihydropyrans (82) could not be ascertained.

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CHAPTER- II

SYNTHESIS OF 2-ARYLISATOGENS AND NITRO SUBSTITUTED ALKYL PHENYL KETONES

This Chapter is divided into two parts:

PART A: Different methods of synthesis of isatogens using enamines

PART B: Synthesis of nitro substituted alkyl phenyl ketones

CHAPTER-II, PART-A

DIFFERENT METHODS OF SYNTHESIS OF ISATOGENS USING ENAMINES

This part is divided into two sections.

Section A:

Introduction:

This introductory section deals with the chemistry of isatogens, their nomenclature, structure, methods of synthesis, chemical and biological properties.

Section B:

Synthesis of 2-Arylisatogens and its Limitations:

This section describes the new approaches to the synthesis of 2-arylisatogen. Three different methods have been explored.

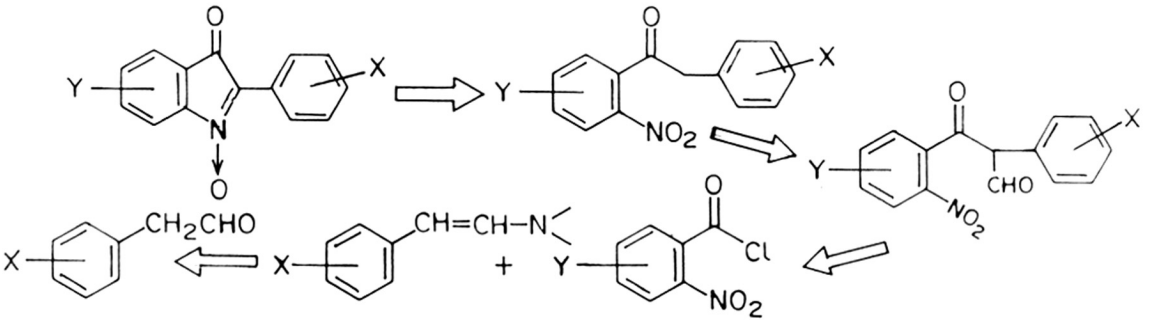
Part A:

Section A:

A Brief Review on Chemistry of Isatogens:

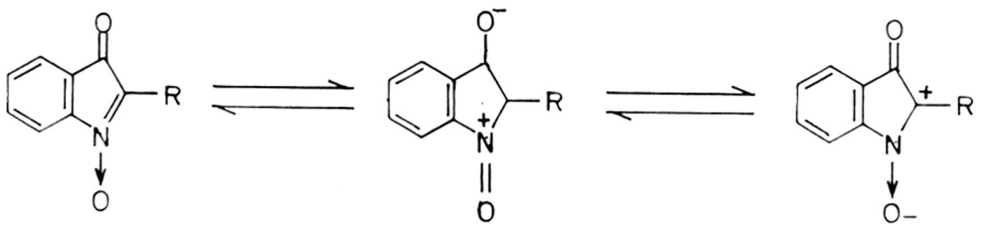
2-Substituted isatogens are of current interest since they possess antitubercular[1] and fungicidal activity[2] and also play a vital role in physiology.[3,4,5] Some time back we reported a new method for the synthesis of 2-arylisatogens, based on cyclodehydration of o-nitrophenyl benzyl ketones. The isatogens prepared in our laboratory by this method were screened for antitubercular activity. However, there is need to prepare these compounds by other routes depending on ready accessibility of starting materials. Our method

developed earlier, has been analysed by retrosynthetic scheme using enamines of phenylacetaldehydes.



From retrosynthetic scheme it is clear that, the preparation of substituted phenyl acetaldehyde and their enamines consist as one part and substituted o-nitrobenzoyl chlorides as the other part. Based on this retrosynthetic scheme, various methods of preparation of 2-arylisatogens have been developed by us. Since this part deals with preparation of isatogens, it is appropriate here to give a very brief review on this subject.

Isatogens are a class of compounds belonging to the indole group. The earlier literature refer them as isatogens while later, they are referred to as 3-oxo-3H-indole-1-oxide or 3H-indol-3-one-1-oxide (1). These are highly coloured compounds and are relatively



(1) (2) (3)

stable due to resonance stru ctures (2 & 3) involving the oxide substituent. These are not naturally occurring compounds.

Although the parent isatogen (1, R=H) is unknown, recently 2-alkyl isatogens (1, R = alkyl) have been reported[6]. The numbering is in accordance with the IUPAC system.

Synthesis of Isatogens

The first synthesis of isatogens was reported by Baeyer,[7,8] during the course of his classic research on indigo. The synthesis of isatogens can be broadly classified under the following categories based on the starting materials, with various reagents and reaction conditions.

I o-Nitrophenylacetylene derivatives or o-nitrotolans

II o-Nitrostilbenes and their derivatives

III Pyridinium ethanols and vinylpyridinium salts

IV Oxidation of 2-substituted indoles

V Deformylation-cum-cyclodehydration of 3-(2-nitrophenyl)3-oxo-2-phenyl-1-propanals (β-ketoaldehydes).

VI 1-Oximino-1-(heterocyclic)-2-phenylglyoxal

VII Miscellaneous preparations.

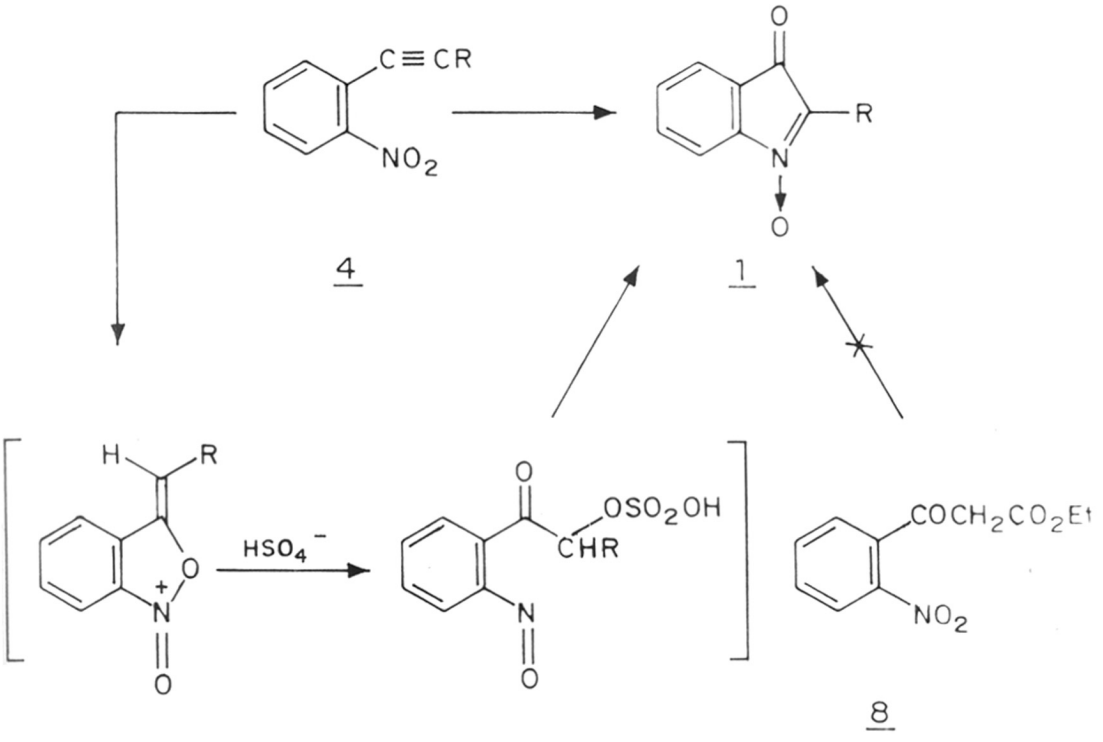
I. Synthesis of isatogens from o-nitrophenylacetylene derivatives or o-nitrotolans

The o-nitrophenylacetylene derivatives have been cyclised to isatogens under acidic, basic and neutral conditions.

(a) Cyclisation in acidic medium (Scheme-1): The first isatogen was reported by Baeyer[7,8] when he obtained ethyl isatogenate

SCHEME-1

CYCLISATION IN ACID MEDIUM



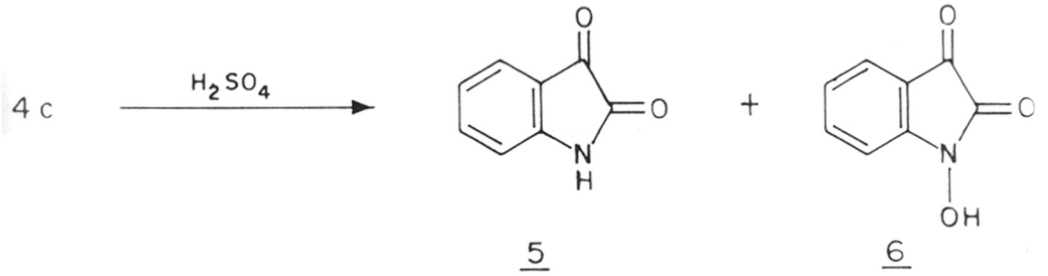
4 a : R = CO_2Et

4 b : R = (2-NO_2) C_6H_4

4 c : R = CO_2H

1 a : R = CO_2Et

1 b : R = 2-Isatogenyl



(1, R = COOEt) by treatment of o-nitrophenylpropiolate (4a) with cold sulphuric acid. Under the same conditions, (4b) gave the corresponding isatogen (1b). However, (4c) yielded a mixture of isatin (5) and 1-hydroxyisatin[9] (6). Loudon and Tennant[10] assumed that it is through the sulfonated product (7) that the isatogen is formed and the assumption of Baeyer[9] that the initial step is hydration of triple bond does not appear to be significant, since the resulting ethyl-2-nitrobenzoyl acetate (8) is readily hydrolysed by concentrated sulphuric acid. No further work seems to have been done.

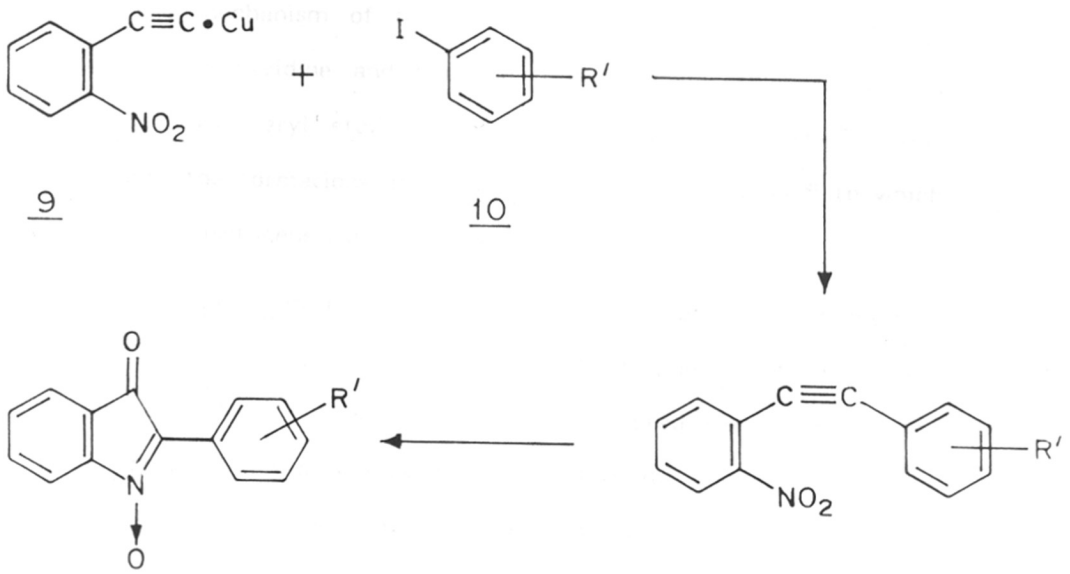
(b) Cyclisation in basic medium (Scheme-2): Pyridine and heat[11] as well as pyridine and light[12-16] are used to effect the formation of isatogens. Pfeiffer in 1916[12] discovered that pyridine solution of o-nitrophenylacetylene derivatives on irradiating or heating afford several substituted 2-phenylisatogens. Systems which can by elimination generate o-nitrophenylacetylenes, are also susceptible to this reaction but the available evidence[17] suggests that the acetylenes need not necessarily be the intermediates.

Pyridine and heat are used[18] to effect the formation of isatogens mainly from the o-nitrotolans (11). These o-nitrotolans (11) are obtained[19] in good yields by the reaction of copper (I) 2-nitrophenylacetylides (9) and substituted aromatic iodo compounds (10).

This reaction is influenced by both steric and electronic factors[18] and has limitations when acidic groups are present in the iodo compound (10). The tolans where o-nitrosubstitution is in iodo

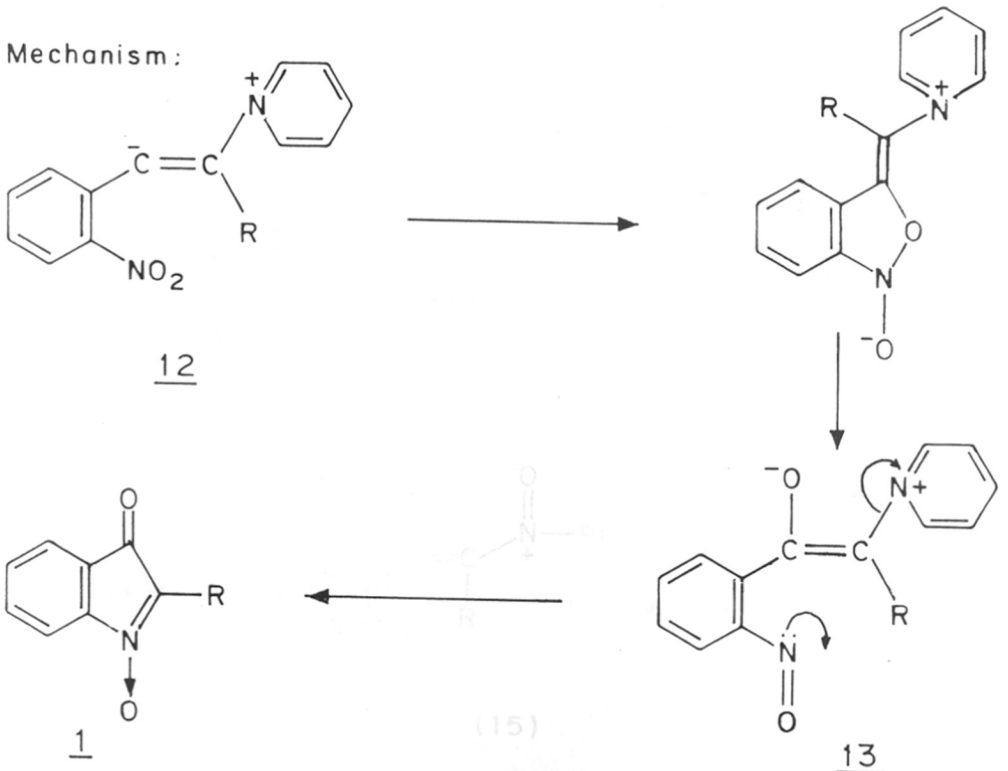
SCHEME-2

CYCLISATION IN BASIC MEDIUM



R = H, OCH_3 etc.

Mechanism:

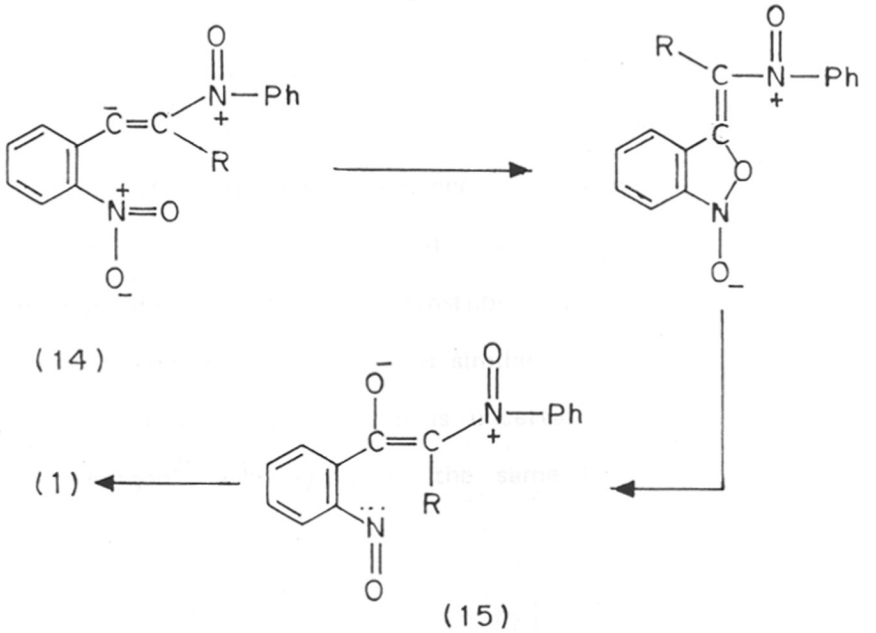


R= aryl or substituted aryl

compound, do not cyclise to isatogens easily. Further heating or irradiation in pyridine solution is required in such cases.

The mechanism of formation of isatogens using pyridine and sunlight or pyridine and heat on o-nitrophenylacetylenes (4, R = CO_2H, alkyl, aryl etc.) has been explained by Huisgen.[20] This involves the formations of betaine (12) as a key intermediate which yields the isatogens via the intermediate (13).

(c) Cyclisation in neutral medium: In the presence of nitrosobenzene, the chloroform solution of o-nitrophenylacetylenes yield isatogens.[15,21,22] This reaction can be effected even in the absence of light. The reaction takes several days for completion in cold, but if refluxed, only few hours are adequate. However, in some cases, the reaction of o-nitrophenylacetylenes with nitrosobenzene leads to complex mixtures. Patterson[3] has suggested intermediates (14) and (15) which are similar to the intermediates (12) and (13) suggested by Huisgen.[20] The intermediate (15) upon cyclisation to the corresponding isatogen, generates nitrosobenzene.



This method was successful in the preparation of 2-(2-pyridyl) isatogen[16] (1, R = 2-pyridyl) where the sulphonic acid method failed.

II. Synthesis of isatogens from o-nitrostilbenes and their derivatives (Scheme-3)

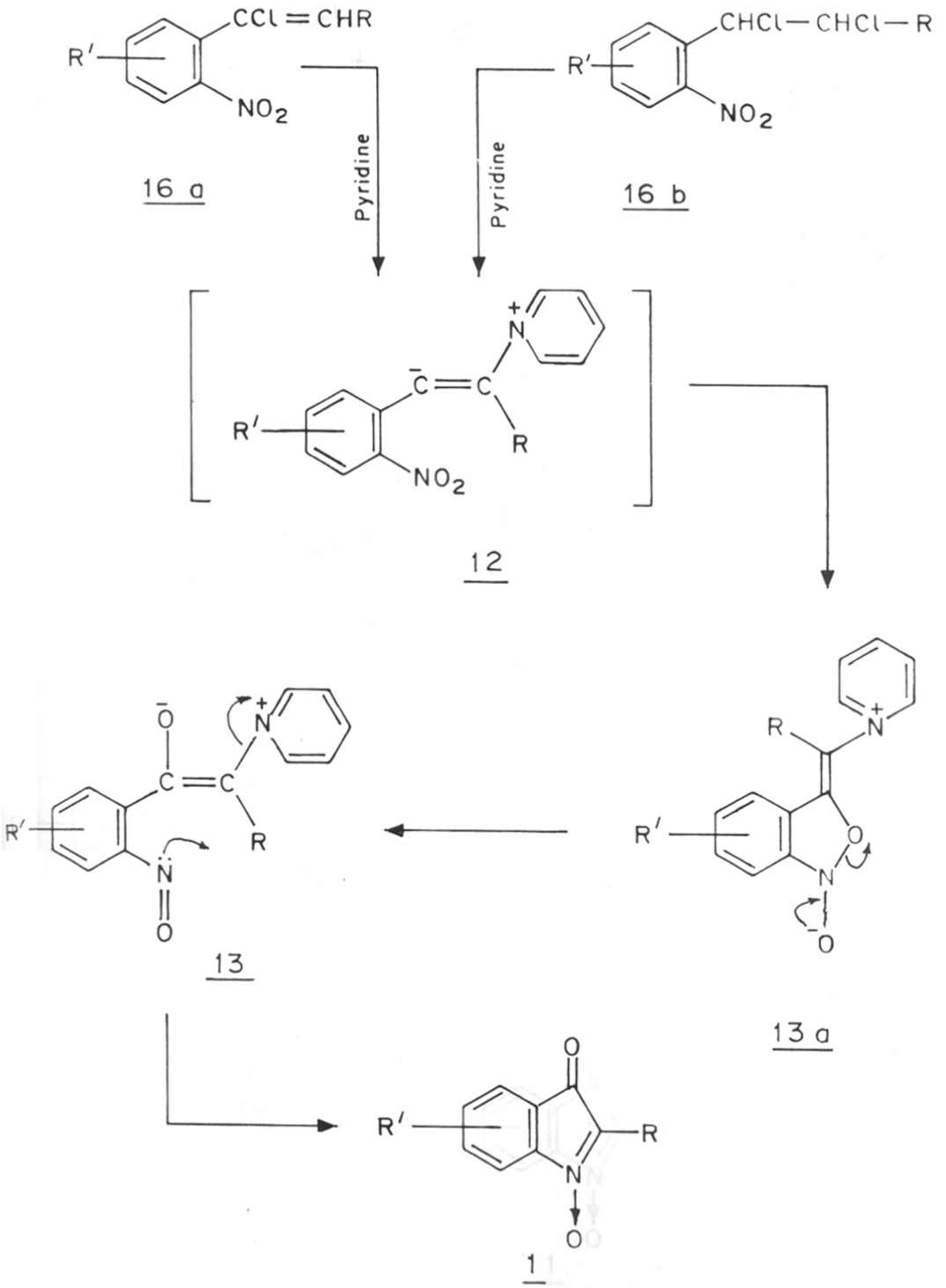
o-Nitrostilbenedihalides (16b) on treatment with strong base yield o-nitrophenylaceylenes which readily isomerise to the corresponding isatogens. When weak bases are used, 15 is initially converted into o-nitrostilbenemonohalide (16a). Further conversion to the isatogen is very slow, but when their pyridine solutions are exposed to sunlight, they readily yield the isatogens.

Adopting this method, a large number of isatogens have been synthesized by Ruggli.[15,23-27] The stereochemistry is quite important as only the dihalides formed from trans-stilbenes undergo dehydrohalogenation to the o-nitroacetylenes. Stilbenes with strongly electron-withdrawing group in a phenyl ring or stilbenes having a pyridine ring, cyclise to the corresponding isatogens on exposure to sunlight even in the absence of base.[28] Stilbenes with an extending conjugation (e.g. a styryl group) cyclises to isatogen when the solution of compound in benzene containing iodine is exposed to sunlight.[29] The formation of isatogen (1) from o-nitrostilbenemonohalides (16a) and o-nitrostilbenedihalides (16b) is limited to reaction occurring in pyridine or similar solvents.

The reaction mechanism is uncertain and has been criticised by Huisgen[20] who envisages the same betaine (12) intermediate.

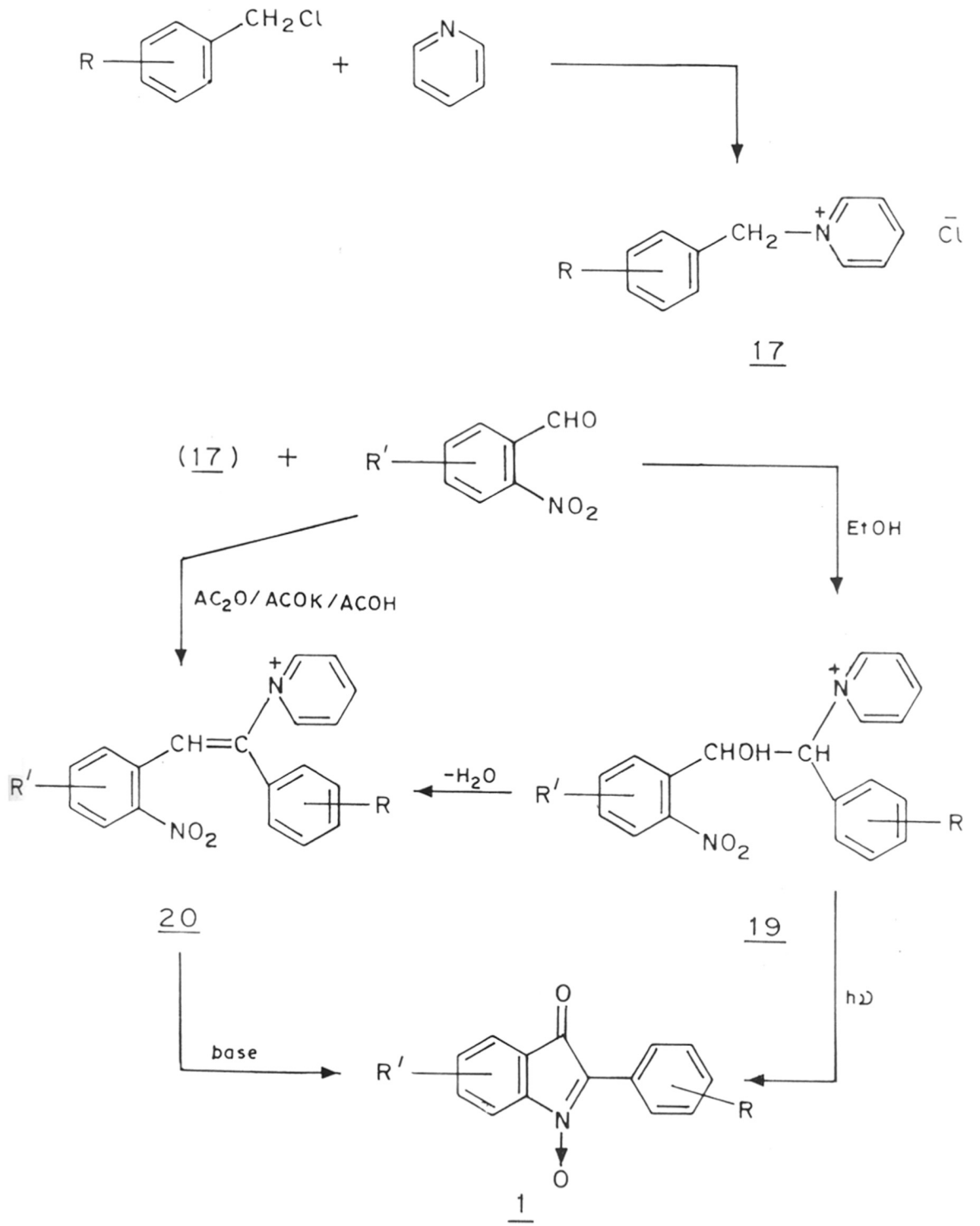
SCHEME-3

SYNTHESIS OF ISATOGEN BY METHOD II



SCHEME-4

SYNTHESIS OF ISATOGENS BY METHOD III



According to this mechanism, the catalysis by pyridine is likely to yield the 5-membered cyclic intermediate (13a). It is presumed that only the first step, namely the formation of betaine (12) is of photochemical nature, since the isatogen can be obtained spontaneously from pyridinium salt in the presence of sodium carbonate.

III. Synthesis of isatogens from pyridinium ethanols and vinylpyridinium salts (Scheme - 4)

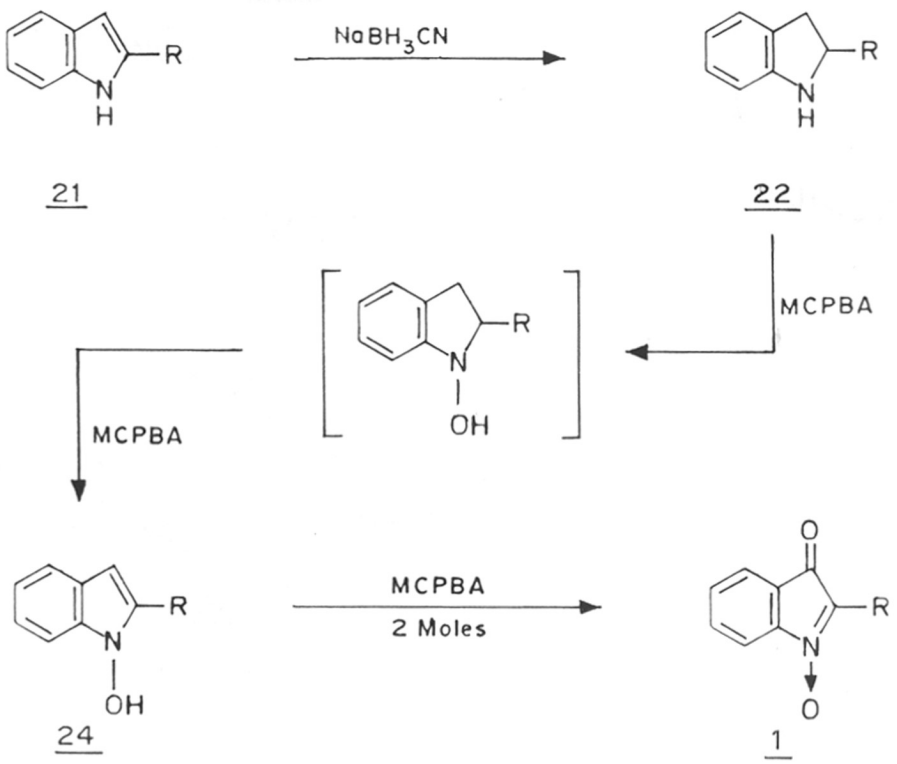
One of the most general methods is that of F. Krohnke,[17,30-32] which involves the condensation of benzylpyridinium salts (17) with substituted o-nitrobenzaldehyde (18) to yield the pyridinium ethanols (19). These compounds (19) on exposure to sunlight or UV light furnish the corresponding isatogens (1) in good yields. Dehydration of (19) leads to vinylpyridinium salts (20) which can also be cyclised to the isatogen in the presence of sodium carbonate or pyridine in combination with diethylamine. The vinylpyridinium salts (20) can also be prepared directly.[33-35] Here again, the same betaine (12) is envisaged in the formation of isatogen.

Pyrolysis[31] of vinylpyridinium salts (20) also yield isatogens, but in poor yields.

IV. Synthesis of isatogens from 2-substituted indoles

The most recent synthesis of isatogen starts from 2-substituted-1-hydroxyindoles.[6] Reduction of 2-substituted indoles (21) by sodium-cyanoborohydride[6,36] renders the corresponding indolines (22) which can be oxidised by metachloroperbenzoic acid (MCPBA) to the isatogen (1). M. Hooper et al.[6] have proposed a mechanism for

this conversion via N-hydroxylation of the indoline to 23 followed by dehydrogenation to 1-hydroxyindole (24) which is further oxidised to isatogens (1).

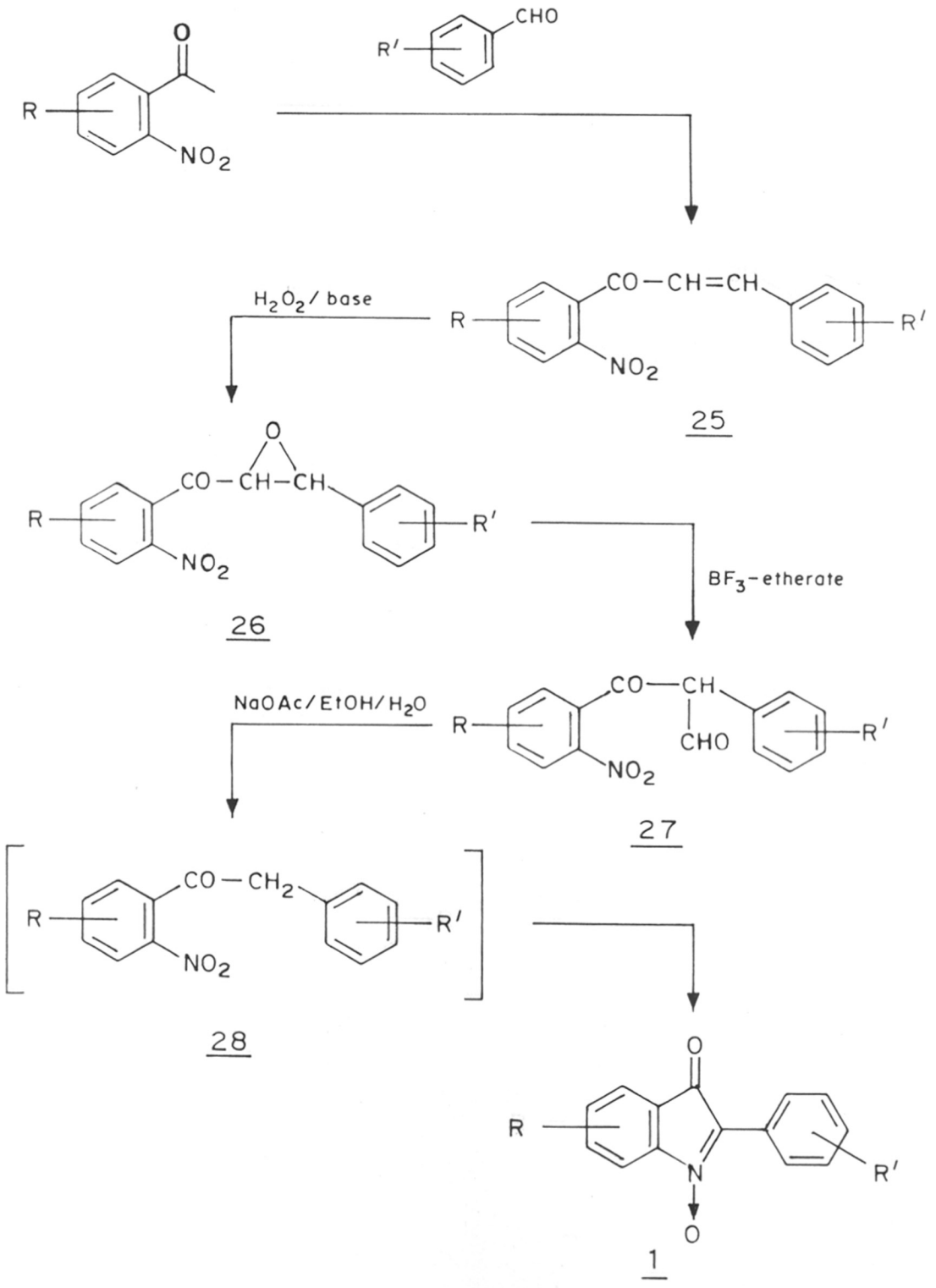


By this method 2-alkylisatogens (1) have been reported for the first time. This method requires the efficient synthesis of preparing 2-substituted 1-hydroxyindoles.

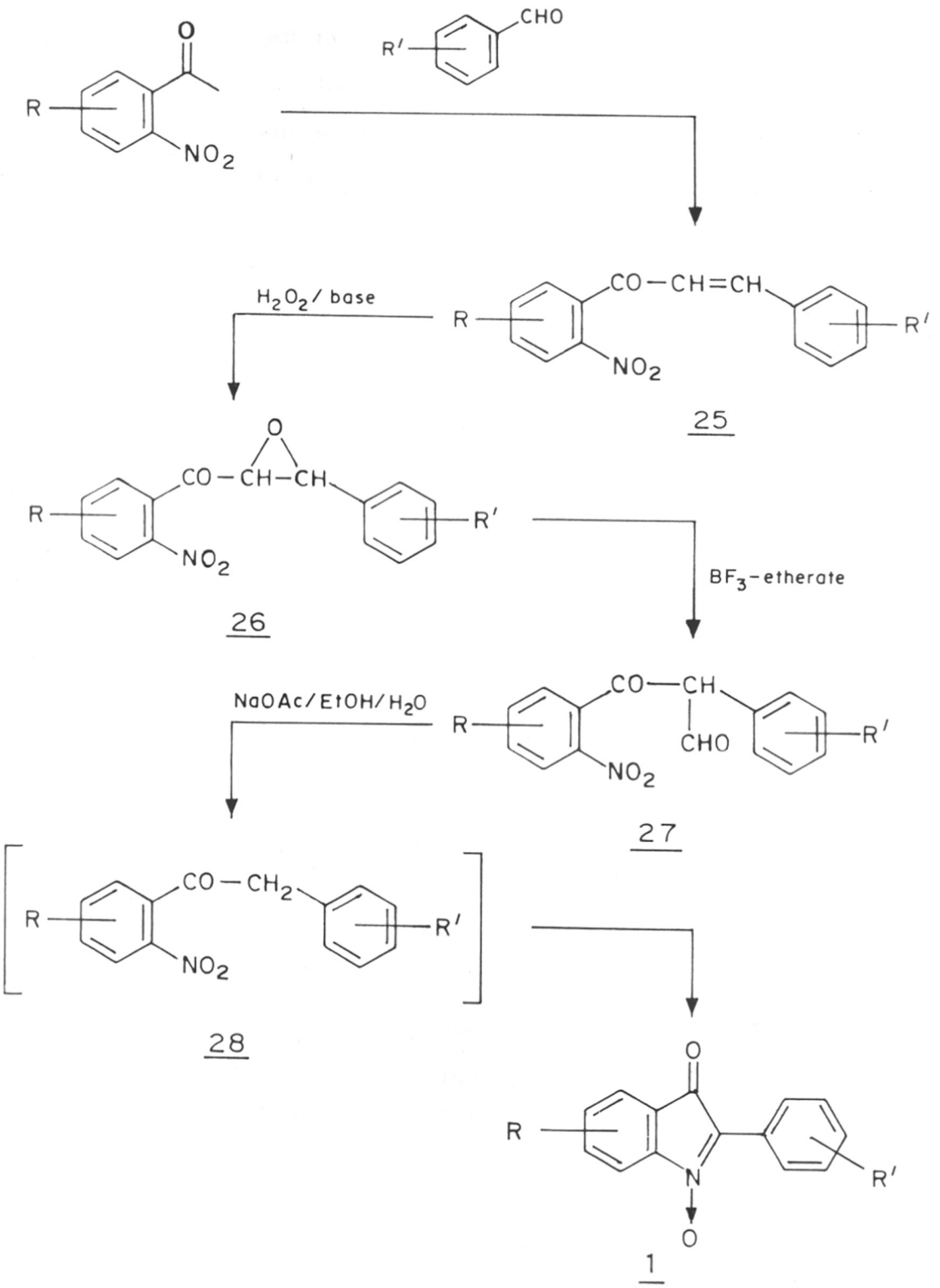
V. Deformylation and cyclodehydration of 3-(2-nitrophenyl) 3-oxo-2-phenyl-1-propanals (β-ketoaldehydes) (Scheme 5)

o-Nitroacetophenone on condensation with different aromatic aldehydes yielded the corresponding 1-(2-nitrophenyl)-3-phenyl-2-propen-1-ones (25, Chalcones). These were epoxidised to 2,3-epoxy-1-(2-nitrophenyl)-

SCHEME-5


CHO
R'
O
R
NO2
H2O2 / base
CO—CH=CH
R
R'
NO2
25
O
CO—CH—CH
R
R'
NO2
26
BF3-etherate
NaOAc/EtOH/H2O
CO—CH
CHO
R
R'
NO2
27
CO—CH2
R
R'
NO2
28
O
R
N
O
R'
1

SCHEME-5

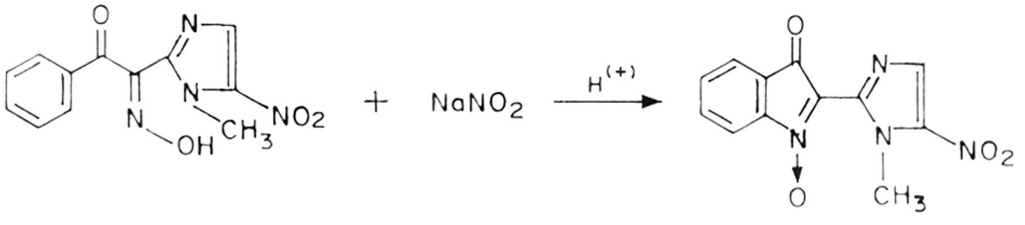

CHO
R'
O
R
NO2
H2O2 / base
CO—CH=CH
R
R'
NO2
25
O
CO—CH—CH
R
R'
NO2
26
BF3-etherate
NaOAc/EtOH/H2O
CO—CH
CHO
R
R'
NO2
27
CO—CH2
R
R'
NO2
28
O
R
N
O
R'
1

3-phenyl-1-propanones (26, Chalcone epoxides) which on treatment with BF_3-etherate, rearranged to 3-(2-nitrophenyl)-3-oxo-2-phenyl-1-propanals [β-ketoaldehydes (27)]. These β-ketoaldehydes (27) on deformylation and cyclodehydration with sodium acetate in aqueous ethanol furnished substituted-2-phenylisatogens [37] (1) and in some cases it was possible to isolate the intermediate 1-(2-nitrophenyl)-2-phenyl-ethanones (28) though in small quantities.

VI. Synthesis of isatogen from 1-oximino-1-(heterocyclic)-2-phenylglyoxal[38]

1-Oximino-1-(heterocyclic)-2-phenylglyoxal was treated with sodium nitrite in the presence of polyphosphoric acid to give 65% of isatogen.

A variety of 2-heterocyclic ring substituted isatogens were prepared and tested for fungicidal property.



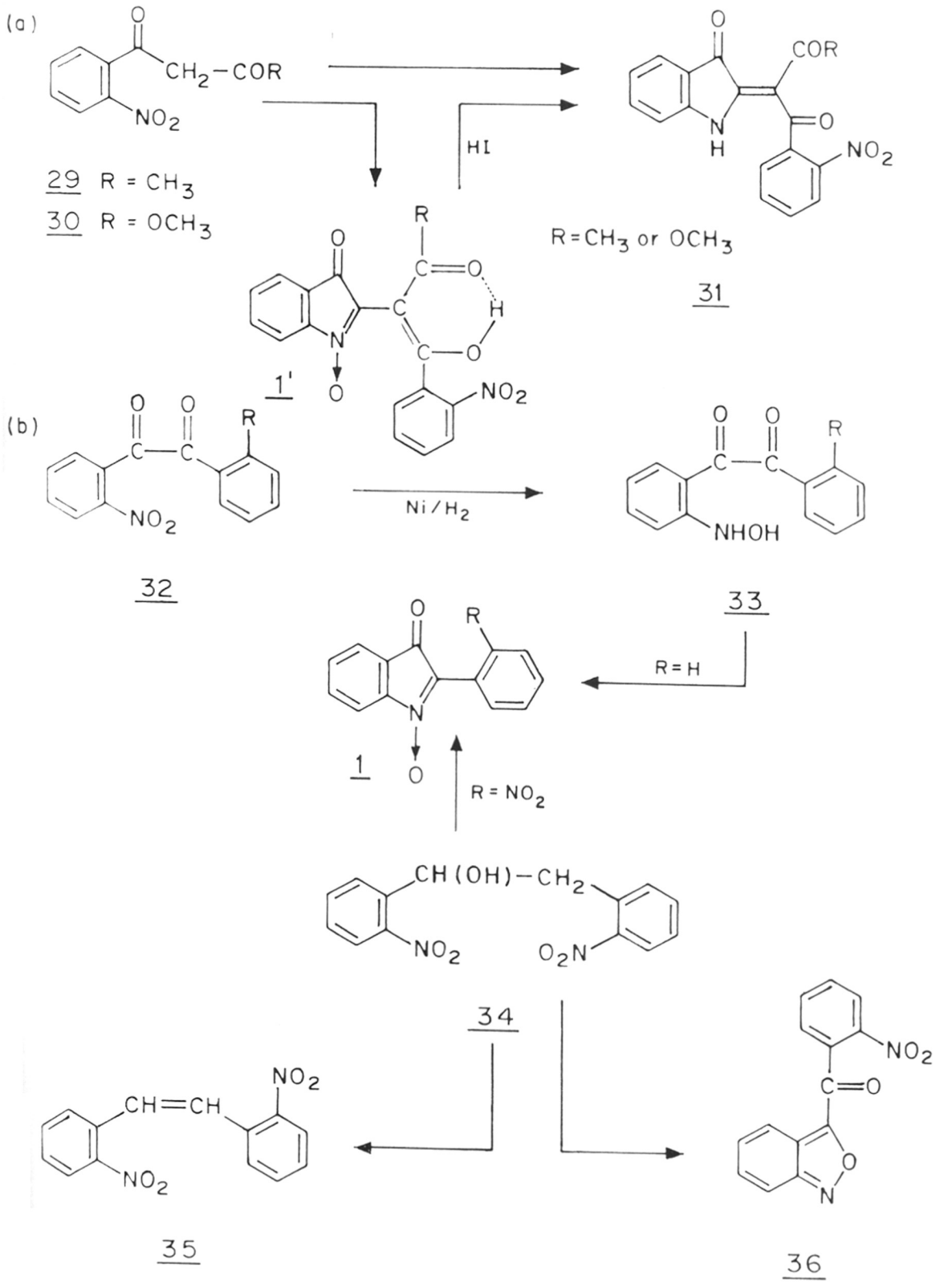
VII. Miscellaneous preparations (Schemes 6 and 7)

Isatogens have been isolated in low yields in several cases, along with various other products. Some of these are as follows:

a) Self condensation with cyclodehydration of 2-nitrobenzoylacetone (29) and 2-nitrobenzoylacetate (30) in presence of sodium bicarbonate or piperidine affords isatogen (1) along with indolinone[39] (31).

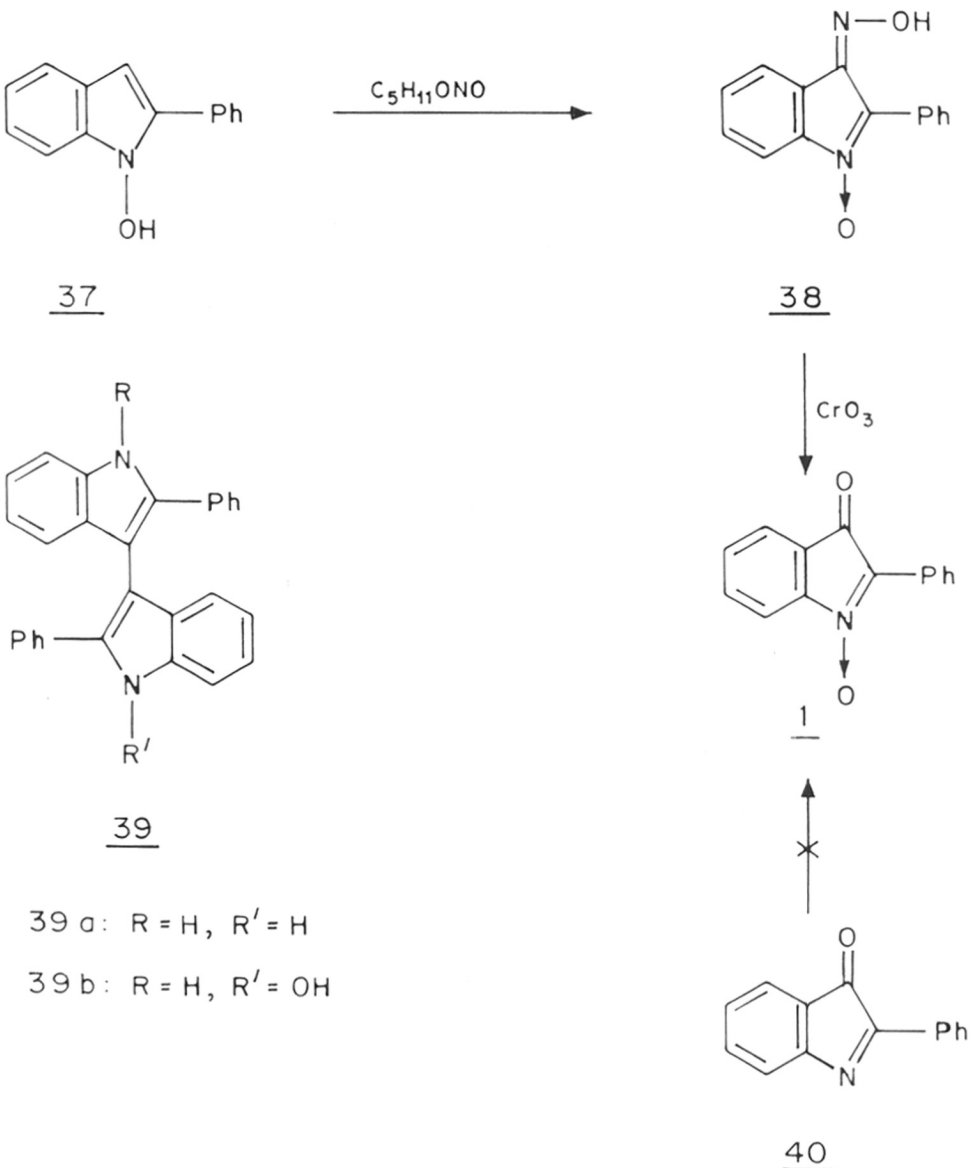
SCHEME-6

MISCELLANEOUS PREPARATIONS



SCHEME – 7

MISCELLANEOUS PREPARATION (CONTD.)



b) Reductive cyclisation of 2-nitrobenzil (32) by nickel and hydrogen yields isatogen[40] (1) through the intermediate hydroxylamino compound (33).

c) Recently Bakke[41,42] has reported that formation of isatogens (1) in low yield along with varying amounts of stilbene (35) and anthranil (36) by the acid catalysed rection on 1,2-di-(o-nitrophenyl)ethanol (34).

d) 2-Phenylisatogens have been reported, in small amounts in the reactions of 1-hydroxy-2-phenylindole (37) with various oxidising agents[43,45]. For example, amylnitrite[44,45] under alkaline conditions yields the oxime (38) which in turn was oxidised by chromic acid to isatogens (1). These reactions were accompanied by the formation of dimeric compounds (39) and various other byproducts.

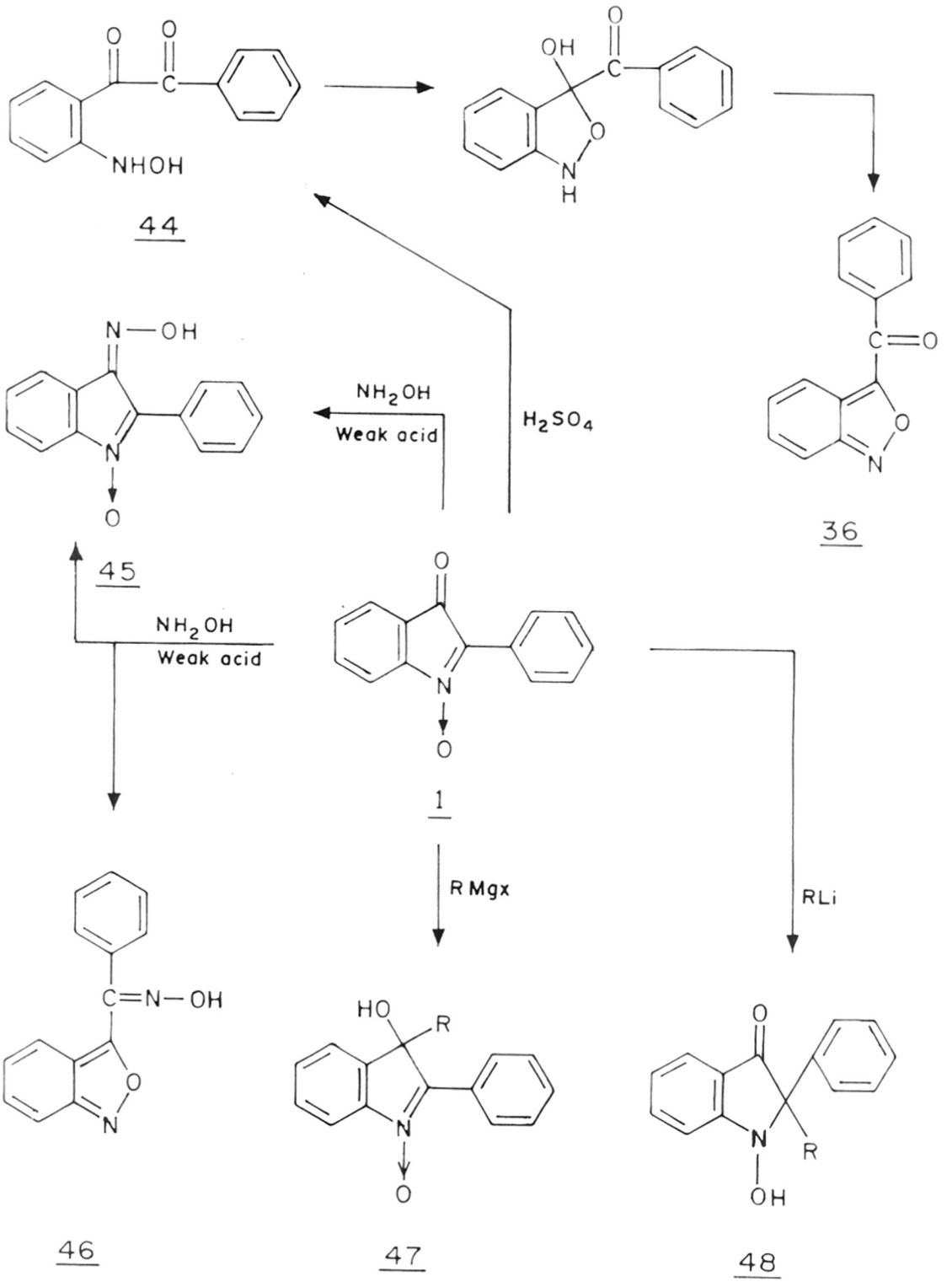
So far there is no suitable method for the direct oxidation of indolones (40) to isatogens[46] (1), Scheme-7.

Chemical properties of 2-phenylisatogens

The isatogens are reported[47] to exhibit the characteristics of quinones. They are deeply coloured solids and liberate iodine from hydroiodic acid. They form the quinhydrones with indoxyls (the indoxyl corresponding to the hydroquinone). It also behaves like quinones towards acetic anhydride in the presence of sulphuric acid giving a triacetate with one of the acetoxy groups in the benzene ring.

SCHEME–8

REACTIONS OF ISATOGEN



Reaction of 2-phenylisatogens (Scheme-8)

Isatogens contain a reactive nitrone as well as the carbonyl group and both the groups are prone to attack. Since it is not possible to depict all the ractions in details, only some of the important reactions are given below.

1. Reaction with acids:

2-Phenylisatogen on treatment with acids forms 3-benzoylanthranil[48-50] (36). The reaction proceeds through the initial addition of water across the nitrone system. Ring opening of the isatogen to 44 and subsequent cyclisation followed by 1,4-dehydration leads the anthranil (36).

2. Reaction at the carbonyl group:

In the presence of weak acid, 2-phenylisatogen (1) reacts with hydroxylamine to give both "C-oxime" (45) and the "N-oxime" i.e. the 3-benzoylanthraniloxime[47,48-50] (46). Grignard and organolithium compounds also attack the carbonyl group[47,51] to yield compound 47 and 48 in low yields. These structures have been established by IR and NMR spectra.

3. Reduction (Scheme-9):

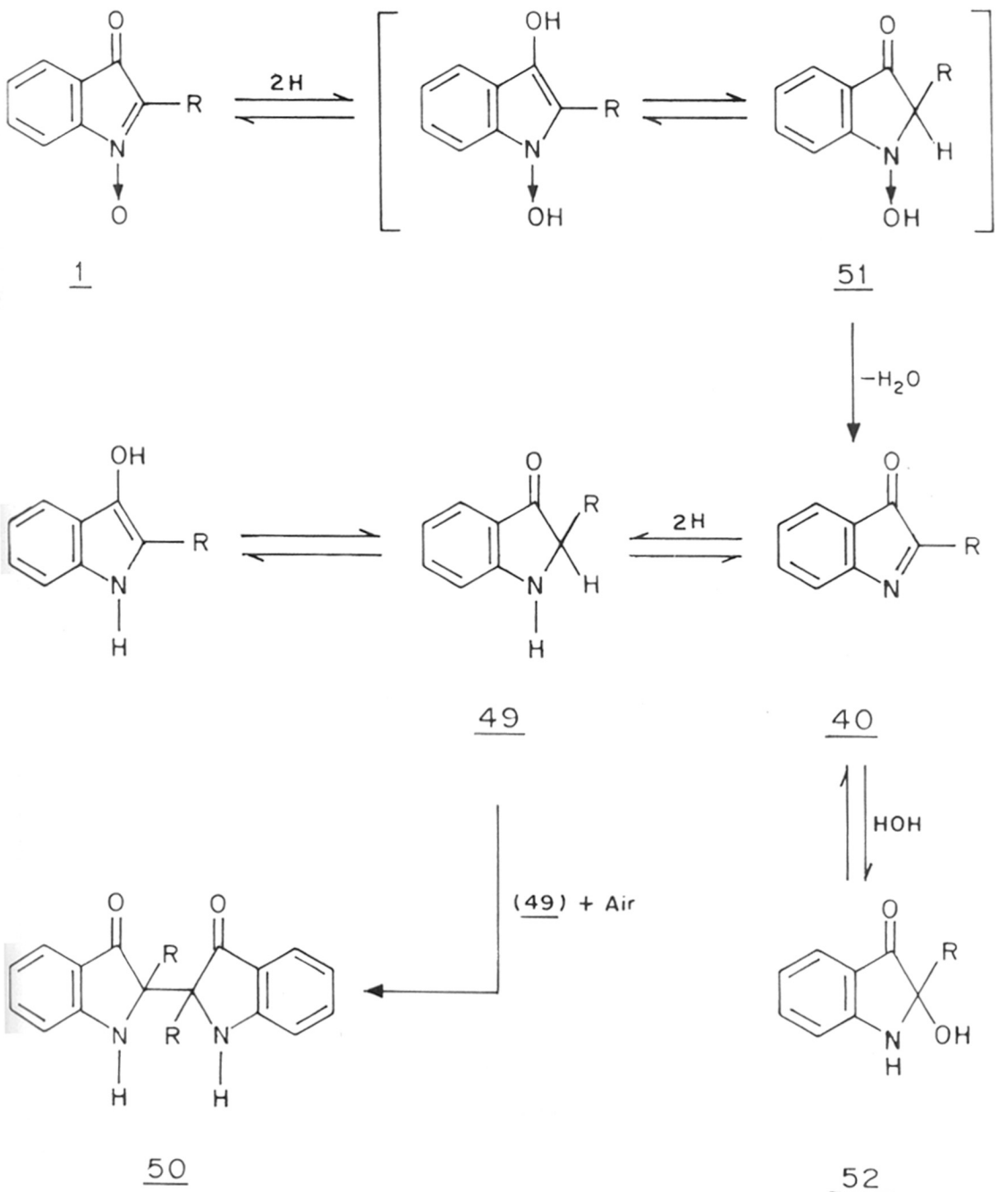
A variety of reagents have been used as reducing agents. These have been summarised.[3] The various products formed are indoxyl (49), diindoxyl (50), indolone (51) and indolone hydrate (52). The steps indicated are given in Scheme-9.

4. Addition to $\rangle C = N$ of isatogen

Isatogens (1) undergo addition to the 1,2 double bond.[52] Methanol

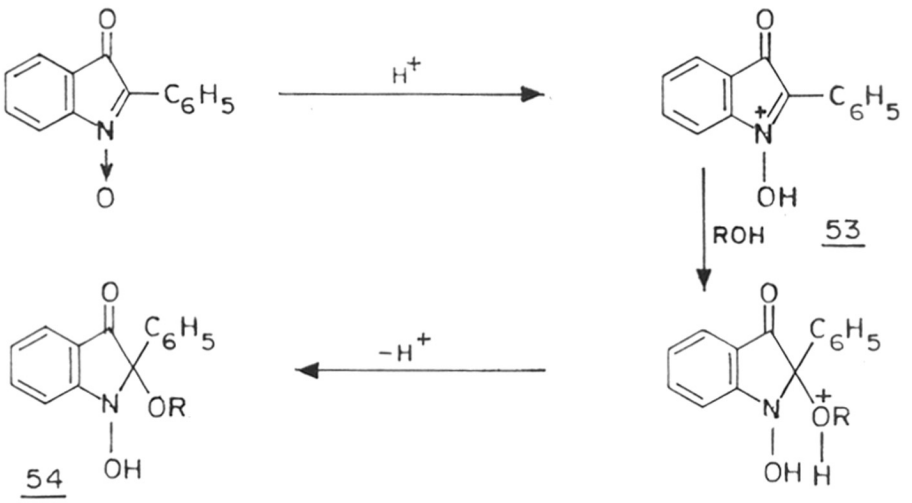
SCHEME-9

REDUCTION



R = Phenyl or substituted phenyl

or ethanol add in the presence of acid to give the corresponding 1-hydroxy-2-alkyloxyindoxyls (54). It is presumed that protonation of the oxygen atom on nitrogen occures first followed by nucleophilic addition to the resulting immonium ion (53). Acetylchloride and acetic anhydride also add to isatogens presumably by the initial acylation of oxygen on the nitrogen atom.[53]



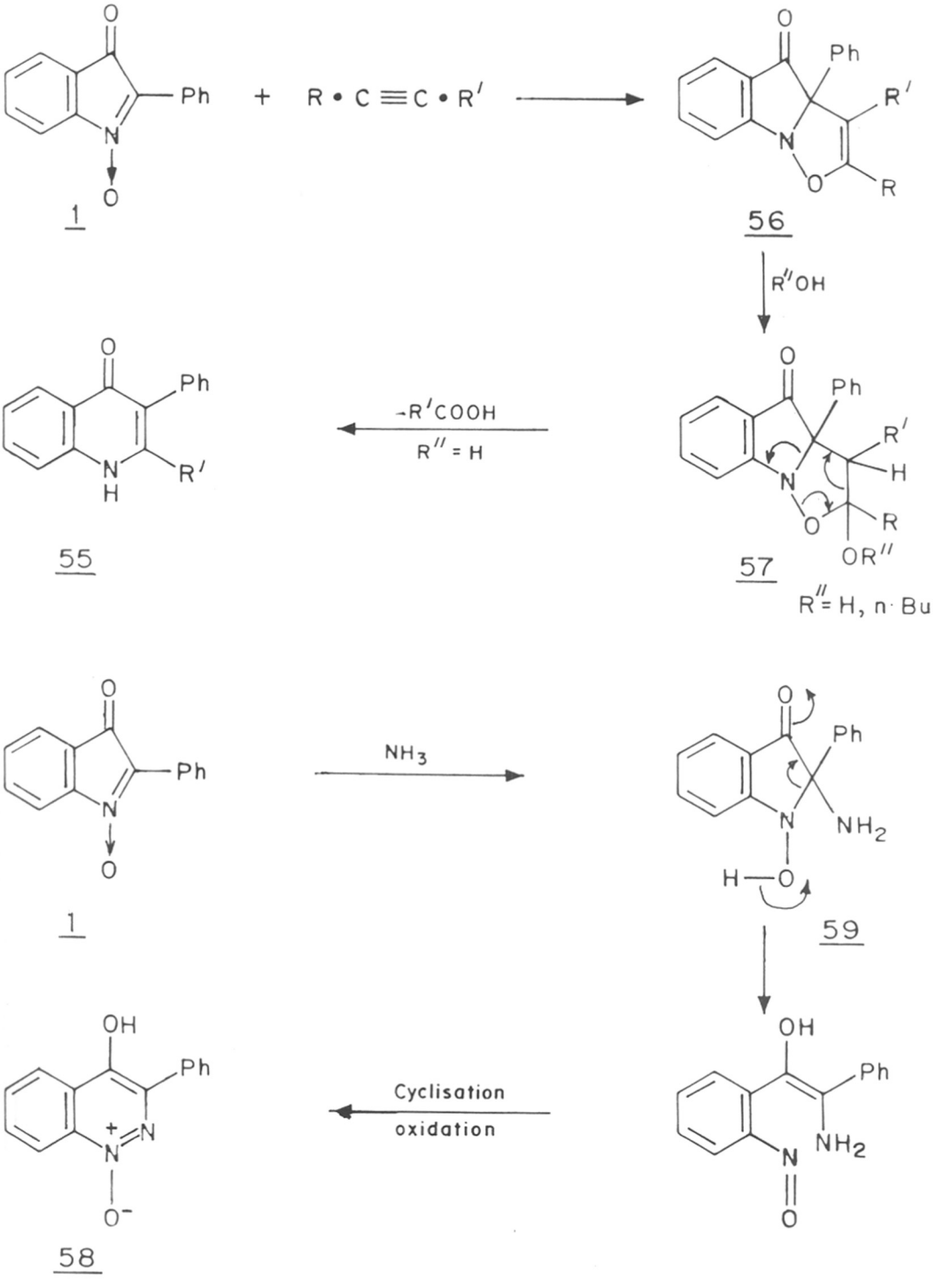
5. Ring expansion reactions (Scheme 10):

2-Phenylisatogen (1) can act as a 1,3-dipolar reagent in the presence of dipolarophiles such as substituted olefins and acetylenes,[54,55] and the products can undergo further reactions leading to isoxazolines and isoxazolidines. Thus 2-phenylisatogen (1) reacts with phenylacetylene or 2-nitrophenylacetylene[55] in boiling xylene in the presence of acid catalyst to yield the quinolone (55) along with benzoic or 2-nitrobenzoic acid. The reaction is presumed to proceed through the corresponding isoxazolines (56) and isoxazolidenes (57).

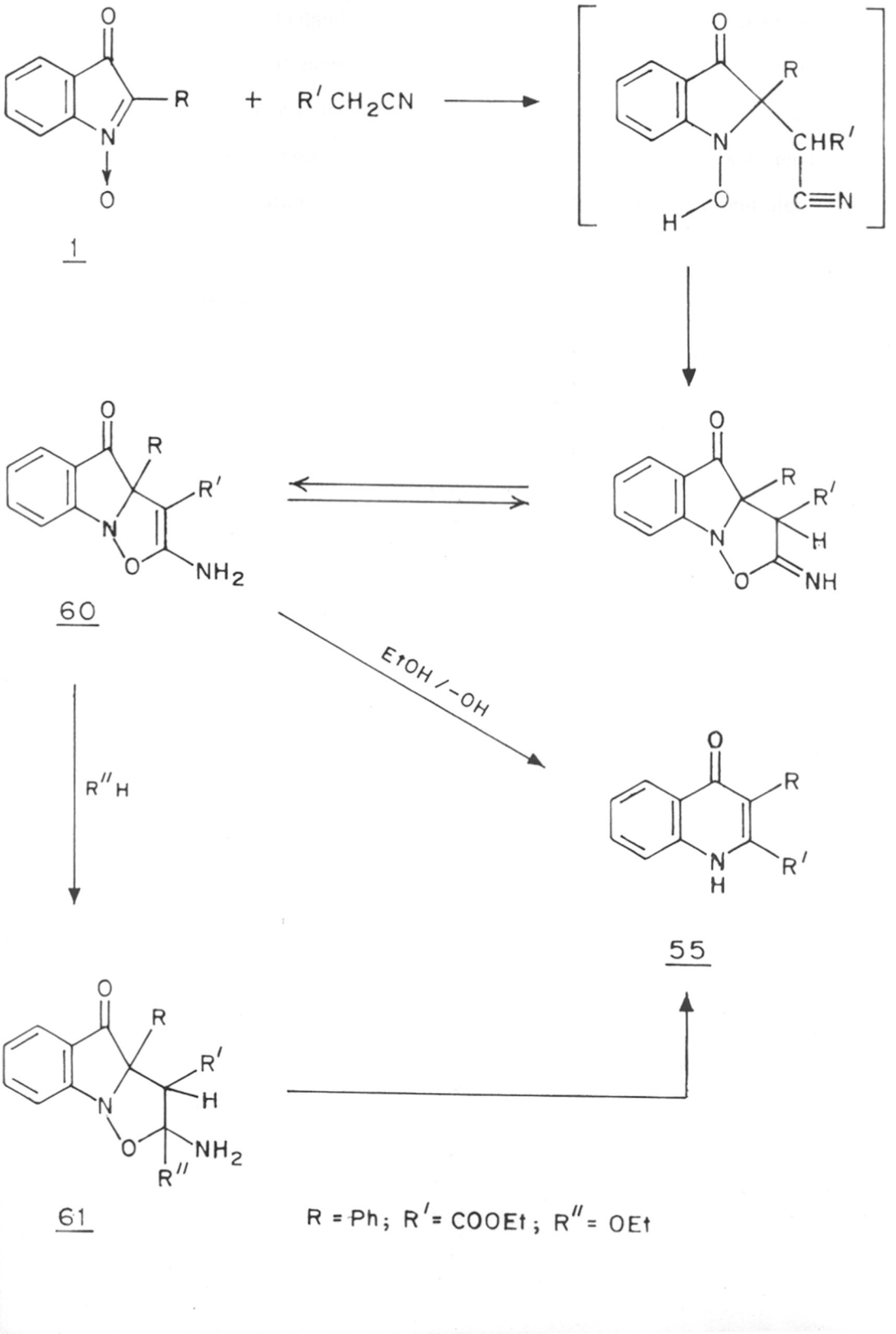
The ring expansion reaction also include the conversion of 2-phenyl-isatogen (1) to cinnolineoxides (58) on reaction with ammonia under

SCHEME-10

RING-EXPANSION REACTIONS



SCHEME-10 (CONTD.)



vigorous conditions. Noland[56] has proposed the mechanism to involve the initial formation of ammonia adduct (59) followed by ring expansion and oxidation. Various isoxazolines (60) and isoxazolidines (61) and quinolones (55) are formed[57,58] by the reaction of cold ethanolic solutions of isatogens with carbanions generated from substituted acetonitriles as in Scheme- 10.

Biological properties of isatogens

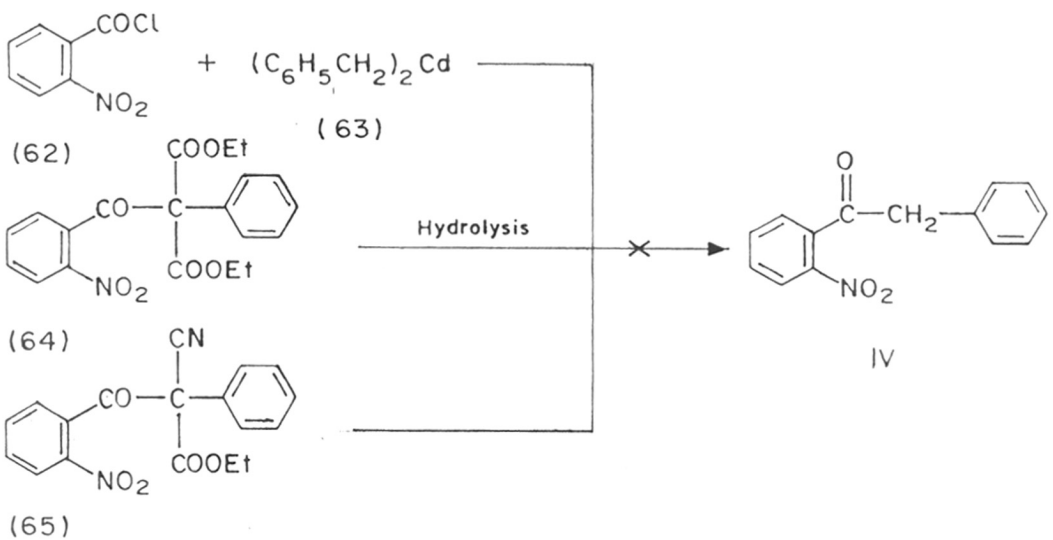
The in vitro antibacterial screening tests revealed that 2-phenyl-isatogen showed a broad spectrum of activity.[28] They also showed antimicrobial activity against mycoplasma organism and the mold candida albicans[3]. 2-Phenylisatogen was found to inhibit ADP-stimulated respiration in rat liver mitochondria.[59,60]

PART A: SECTION B

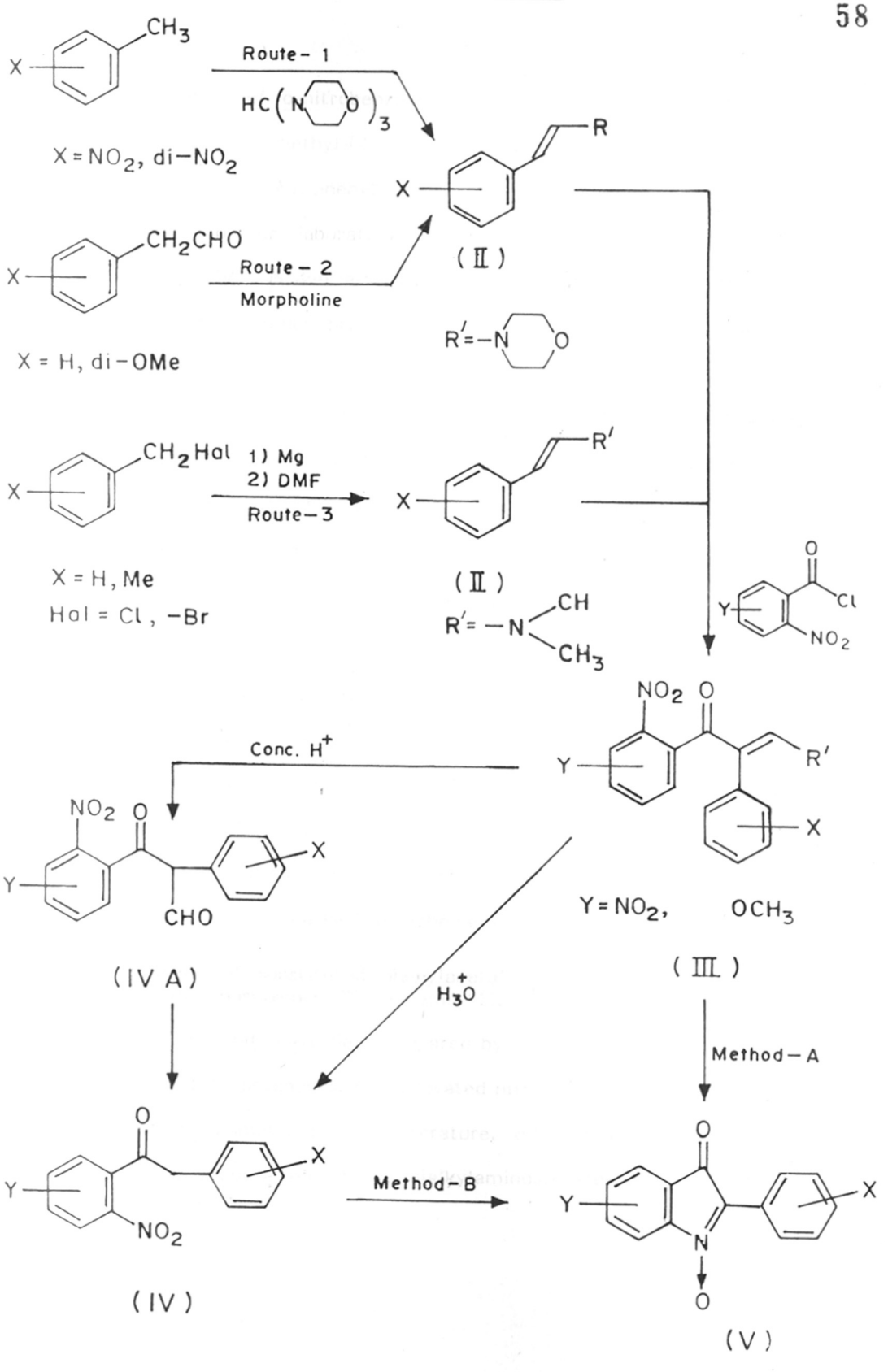
Present Investigation

Synthesis of 2-Arylisatogens and its Limitations

As seen from the various methods described in Section A, there seems to be the need for finding new methods, especially for the synthesis of isatogens having functional groups and also containing heterocyclic moiety. In this section we describe our approach based on retrosynthetic scheme given in Section A. Three different approaches for the preparation of enamines of phenylacetaldehyde have been described. These phenylacetaldehyde enamines were acylated with substituted o-nitrobenzoyl chlorides, followed by direct conversion of acylated products to isatogens or by initial conversion to o-nitrophenyl benzyl ketones and then further conversion to 2-arylisatogens. The key intermediates are substituted 1-(2-nitrophenyl)-2-substituted phenyl ethanones or o-nitrophenyl benzyl ketones. The unsuccessful attempts reported in literature of the synthesis of phenyl benzyl ketones are given below.



SCHEME– 11


Route – 1
X = NO2, di–NO2
Route – 2
Morpholine
X = H, di–OMe
1) Mg
2) DMF
Route–3
X = H, Me
Hal = Cl, –Br
(II)
(III)
Y = NO2, OCH3
Conc. H+
(IV A)
H3O+
Method – A
Method – B
(IV)
(V)

The reaction of o-nitrobenzoyl chloride with dibenzyl cadmium[61] and hydrolysis of diethyl-(2-nitrobenzoyl)-phenylmalonate[62] as well as ethyl-(2-nitrobenzoyl)-phenylcyanoacetate[15] have met with failure.

However, in our laboratory earlier workers were successful in deformylating the β-ketoaldehydes[37] to the required o-nitrophenyl benzyl ketones as minor products alongwith 2-arylisatogens (1) which are the major products.

In this section, the three different methods for the preparation of phenyl benzyl ketones and also the direct method of preparation of 2-arylisatogens through enamines have been described. This consists of the following steps.

1) Preparation of (phenylethenyl)dialkylamine or trans-β-dialkylaminostyrenes (II)
2) Preparation of α-(nitrobenzoyl)-β-dialkylaminostyrenes (III)
3) Preparation of 1-(nitroaryl)-2-arylethanones or phenyl benzyl ketones (IV)
4) Cyclodehydration of phenyl benzyl ketones (IV) to 2-arylisatogens (V)
5) Hydrolysis and cyclodehydration of α-(o-nitrobenzoyl)-β-dialkylaminostyrenes III to 2-arylisatogens (V).

All these steps are summarised in Scheme-11.

1. Preparation of substituted phenylacetaldehyde enamines or trans-β-dialkylaminostyrenes (II) (Scheme-12).

These compounds have been prepared by three different approaches.

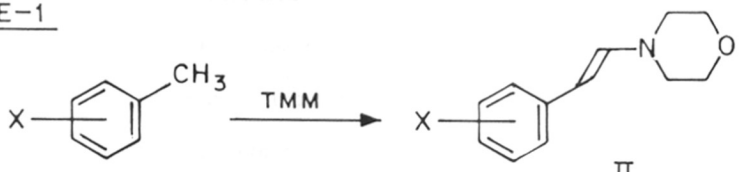
In one of the approaches, the activated nitrotoluenes were condensed with trimorpholinomethane. In literature, many reagents have been used for the preparation of β-dialkylaminostyrenes from activated

SCHEME-12

PREPARATION OF TRANS-β-DIALYLAMINOSTYRENES (II)

BY VARIOUS ROUTES

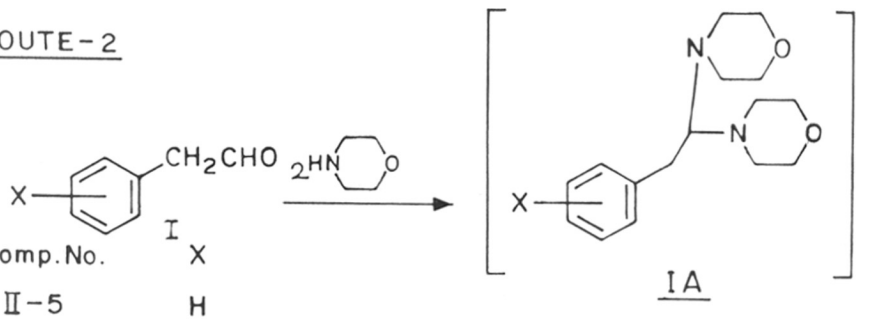
ROUTE-1



I TMM-Trimorpholinomethane II

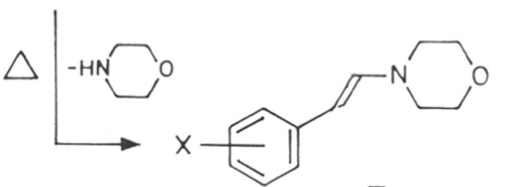
Comp. No.	X
II-1	4-NO_2
II-2	2-NO_2
II-3	2-NO_2, 5-OMe
II-4	2,4-di-NO_2

ROUTE-2

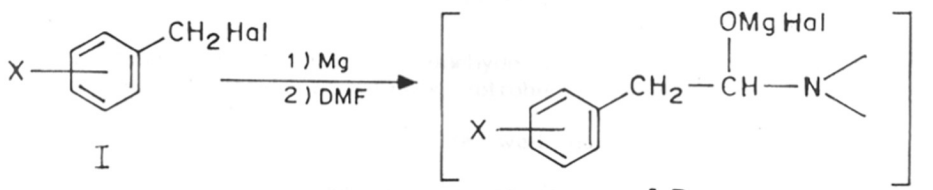


I IA

Comp. No.	X
II-5	H
II-6	3,4-di-OMe



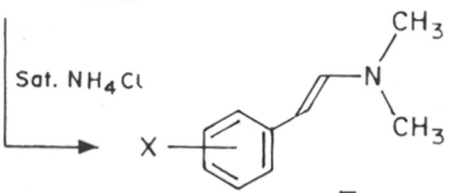
II



I IB

Hal = (Cl, Br)

Comp. No.	X
II-7	H
II-8	4-Me



II

3,4-dimethoxyphenylacetaldehyde were condensed with morpholine. The diamine formed was decomposed during vacuum distillation, but most of the β-morpholinostyrene remained undistilled. Hence, instead of distilling styrene enamine under reduced pressure, the morpholine was removed at low pressure after decomposition of diamine. The residue was crystallised from a suitable solvent.

The starting materials, phenylacetaldehyde was prepared by the oxidation of phenyl ethyl alcohol using pyridinium chlorochromate [73] while dimethoxyphenylacetaldehyde was prepared by ozonolysis of Eugenol after methylation of free hydroxyl group.

In the third approach of preparation of trans-β-dialkylaminostyrenes, the method of Christer Hansson and Borje Wickberg was followed.[74] It involves the reactions of alkylmagnesium halide with N,N-dialkylformamide to give the primary addition product which undergoes spontaneous elimination forming an enamine. Christer Hansson and Borje Wickberg used only alkyl halides, while in the present investigation, benzylhalides have been used to prepare benzylmagnesium halides. The primary adduct formed by the reaction of N,N-dimethylformamide was decomposed using saturated ammonium chloride solution to obtain enamine, instead of stirring the solution of primary adduct for 100-120 hr. to obtain the enamin as given in the literature.

2. Acylation of phenylacetaldehyde enamine with nitro-substituted benzoylchlorides to obtain α-(nitrobenzoyl)-β-dialkylaminostyrenes (III) (Scheme-13).

Acylations of enamines are well documented synthetic routes for α-acylation of aldehydes. In the present investigation the method of Edward E. Carcia and R. Ian Fryers[64] was followed.

toluenes.[63-68] Amongst many reagents available, trimorpholinomethane was more suitable due to its easy method of preparation and considerable stability as it is a solid. Trimorpholinomethane has been prepared, from chloroform, methanoic sodium methoxide and morpholine.[69] The other method of preparation of trimorpholinomethane is by the reaction of ortho-ester with morpholine.[70]

Thus, 0.63 mole of morpholine and 0.42 mole of triethylorthoformate in the presence of catalytic amount of acetic acid[70] were refluxed for 2 hr. The solid trimorpholinomethane was collected by filtration.

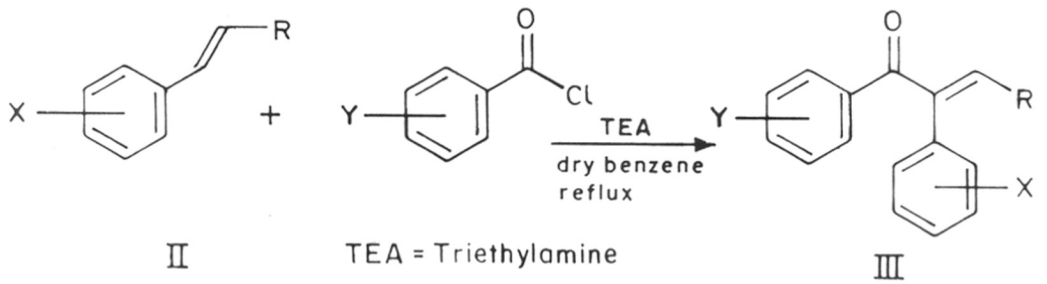
Trans-β-morpholinonitrostyrenes were prepared by Lloyd & Nichols method.[68]

One equivalent of nitrotoluene and 1.5 equivalent of trimorpholinomethane were heated at 120-130°C, with stirring under water aspiration vacuum for 3-4 hr. The red coloured solids were crystallized from solvents, while liquids were purified by column chromatography using alumina. Trans-stereochemistry of these enamines was confirmed by the PMR: α-H, 5.2 - 5.4, J = 14Hz. One of the starting materials 2-nitro-5-methoxytoluene was prepared by methylation of p-nitro-m-cresol.[71]

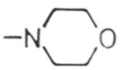
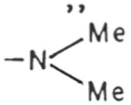
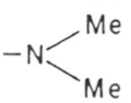
The method of preparation of trans-β-morpholinostyrene using trimorpholinomethane and nitrotoluenes has its own limiations, as it requires the presence of strong electron withdrawing groups on toluene moiety and hence cannot be used for toluenes without such substituents. To overcome this difficulty, the trans-β-morpholinostyrenes were prepared by Ziegenbein[72] method. Thus phenylacetaldehyde and

SCHEME – 13

PREPARATION OF α-(NITROBENZOYL)-β-DIALKYLAMINOSTYRENES (III)



II TEA = Triethylamine III

Comp. No.	X	Y	R
III – 1	4-NO_2	2-NO_2	
III – 2	2-NO_2	2-NO_2	,,
III – 3	4-NO_2	2-NO_2, 5-OMe	,,
III – 4	4-NO_2	2-NO_2, 4,5-di-OMe	,,
III – 5	2-NO_2, 5-OMe	2-NO_2	,,
III – 6	4-NO_2	2,4-di-NO_2	,,
III – 7	4-NO_2	H	,,
III – 8	4-NO_2	4-NO_2	,,
III – 9	2-NO_2	4-NO_2	,,
III – 10	2-NO_2	2,4-di-NO_2	,,
III – 11	2,4-di-NO_2	2-NO_2	,,
III – 12	2,4-di-NO_2	2,4-di-NO_2	,,
III – 13	2-NO_2, 5-OMe	2,4-di-NO_2	,,
III – 14	H	2-NO_2	,,
III – 15	3,4-di-OMe	2-NO_2	,,
III – 16	H	2-NO_2	
III – 17	4-CH_3	2-NO_2	

The starting materials were prepared as follows:

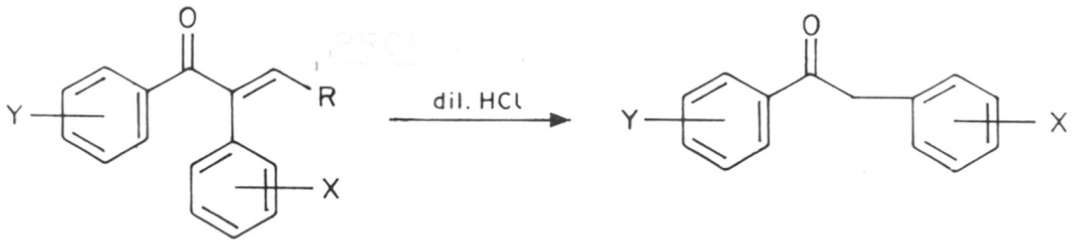
Nitrotoluenes were oxidised to corresponding o-nitrobenzoic acid by oxidation[75] using potassium permanganate. The nitro-benzoyl chlorides were prepared by refluxing the dry benzene solution of nitrobenzoic acid with thionyl chlorides for 4-8 hr. Purification of product by vacuum distillation was avoided, as it was reported that in some distillation explosion occurred.[76]

2,4-Dinitrobenzoic acid was prepared by the chromic acid[77] oxidation of 2,4-dinitrotoluene, while 2-nitro-4,5-dimethoxy benzoic acid was obtained by potassium permanganate oxidation of 2-nitro-4,5-dimethoxy toluene. When acylation reaction of trans-β-dialkylaminostyrene was carried out at room temperature, it was observed that the addition of substituted benzoyl chlorides to the enamine solution, resulted in poor yields of acylated product, especially when there are two nitro groups on β-dialkylaminostyrene ring. Hence acylation was carried out at 0°C.

Most of the acylated products were yellow coloured, high melting solids, while few were thick yellow coloured liquids, which were separated by silica gel column chromatography. The structure of these compounds were confirmed by the disappearance of the signal for the α-proton in PMR and by M^+ in mass spectra. These acylated compounds were used for the preparation of various heterocyclic compounds (described in Chapter III).

SCHEME-14

PREPARATION OF 1-(ARYL)-2-(ARYL) ETHANONE (IV)

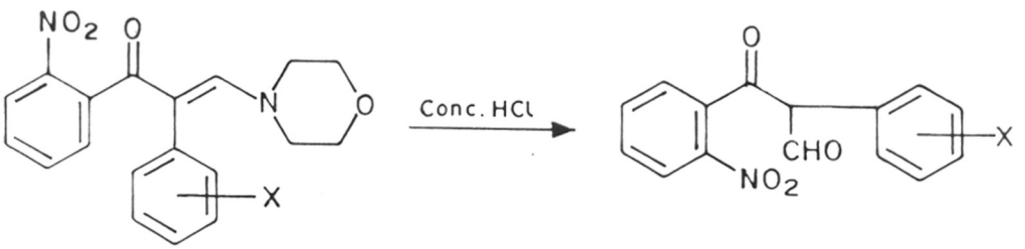


III IV

Comp. No.	X	Y
IV - 1	4-NO_2	2-NO_2
IV - 2	2-NO_2	2-NO_2
IV - 3	4-NO_2	2-NO_2,5-OMe
IV - 4	4-NO_2	2-NO_2,4,5-di-OMe
IV - 5	2-NO_2,5-OMe	2-NO_2
IV - 6	4-NO_2	2,4-di-NO_2
IV - 7	4-NO_2	H
IV - 8	4-NO_2	4-NO_2
IV - 9	2-NO_2	4-NO_2
IV - 10	2-NO_2	2,4-di-NO_2
IV - 11	2,4-di-NO_2	2-NO_2
IV - 12	2,4-di-NO_2	2,4-di-NO_2
IV - 13	2-NO_2-5-OMe	2,4-di-NO_2
IV - 14	H	2-NO_2
IV - 15	3,4-di-OMe	2-NO_2
IV - 16	4-Me	2-NO_2

SCHEME-15

PREPARATION OF 3-(2-NITROPHENYL)3-OXO-2-PHENYL-1-PROPANAL (IV A)



III IV A

Comp. No	X
IV A-2	2-NO_2
IV A-14	H

3. **Hydrolysis of compound (III) with dilute hydrochloric acid to give 1-(nitrophenyl)-2-phenylethanones or nitrophenyl benzyl ketones-(IV) (Scheme-14)**

The ∝-(nitrobenzoyl)-β-dialkylaminostyrenes (III) were hydrolysed to phenyl benzyl ketones (IV) in the presence of dilute (5-10%) hydrochloric acid. (Scheme-14).

The concentrated hydrochloric acid hydrolysis of compounds III gave mainly β-ketoaldehydes (IVA) (Scheme-15) along with minor quantities of phenyl benzyl ketones. The β-ketoaldehydes were separated from the reaction mixture, by washing the ethyl acetate solution of the reaction mixture with sodium bicarbonate solution (pH 7.5-8.5) till the bicarbonate washings were colourless. The bicarbonate washings were collected and acidified with hydrochloric acid to regenerate β-ketoaldehydes. In the initial experiments some of the β-ketoaldehydes were isolated, but in the later cases, dilute acid hydrolysis of compound III were followed to obtain phenyl benzyl ketones. The minor quantities of β-ketoaldehydes were removed by washings with sodium bicarbonate solution to obtain pure phenyl benzyl ketones in about 80-90% yield.

The IR showed band around 1709-1721 cm^{-1} due to $\rangle C = O$.

All the phenyl benzyl ketones showed PMR signals around 3.85--4.2 δ for the $COCH_2$ protons.

Preparation of 2-Arylisatogens (V)

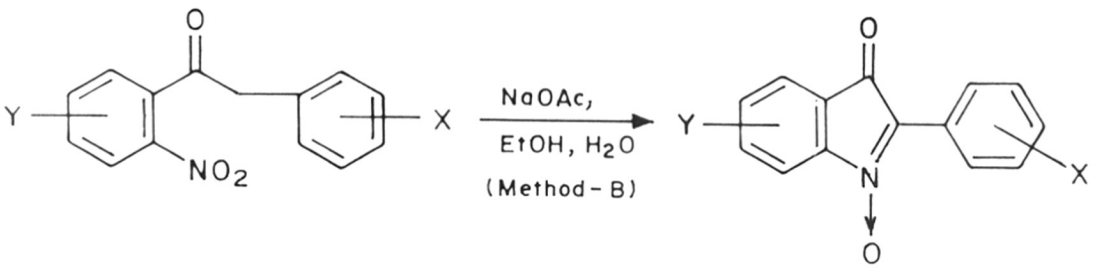
Preparation of isatogens (V) were carried out from two different starting materials.

4. **Cyclodehydration of o-nitrophenyl benzyl ketones IV to 2-aryl-isatogens (V) (Scheme-16).**

o-Nitrophenyl benzyl ketones (IV) were converted to isatogens (V) according to the method of House.[78] The compound (IV) was refluxed

SCHEME – 16

CYCLODEHYDRATION OF 1-(2-NITROARYL)-2-ARYL ETHANONES (IV) TO 2-ARYLISATOGENS (V)

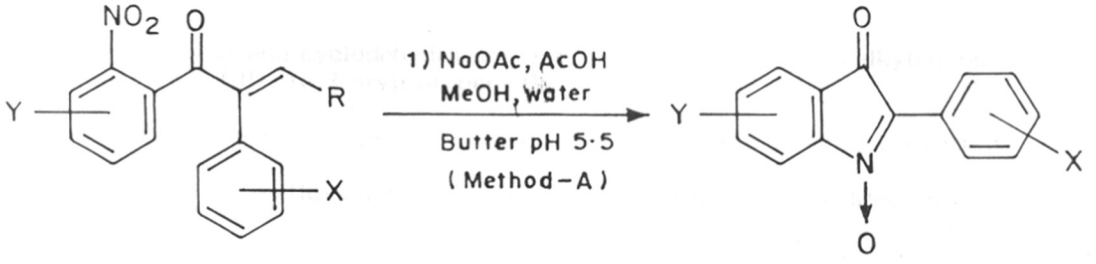


IV V

Comp. No.	X	Y
V – 1	4-NO_2	H
V – 2	2-NO_2	H
V – 3	4-NO_2	5-OMe
V – 4	4-NO_2	5,6-di-OMe
V – 5	2-NO_2, 5-OMe	H
V – 6	H	H
V – 7	3,4-di-OMe	H
V – 8	4-Me	H

SCHEME - 17

HYDROLYSIS AND CYCLODEHYDRATION OF α-(2-NITROBENZOYL) -β- DIALKYLAMINO STYRENES III TO 2-ARYLISALAGENS (V)



III V

Comp. No.	X	Y
V - 1	4-NO_2	H
V - 2	2-NO_2	H
V - 3	4-NO_2	5-OMe
V - 4	4-NO_2	5, 6-di-OMe
V - 5	2-NO , 5-OMe	H
V - 6	H	H
V - 7	3,4-di-OMe	H
V - 8	4-Me	H

with sodium acetate/ethanol/water for 3-4 hr (Method-B). The solvent was removed and the solid separated was collected by filtration. The coloured isatogens were crystallized from respective solvents to give ~90% yield.

5. **Hydrolysis and cyclodehydration of α-(o-nitrobenzoyl)-β-dialkylamino-styrenes (III) to 2-arylisatogens (V)** (Scheme-17).

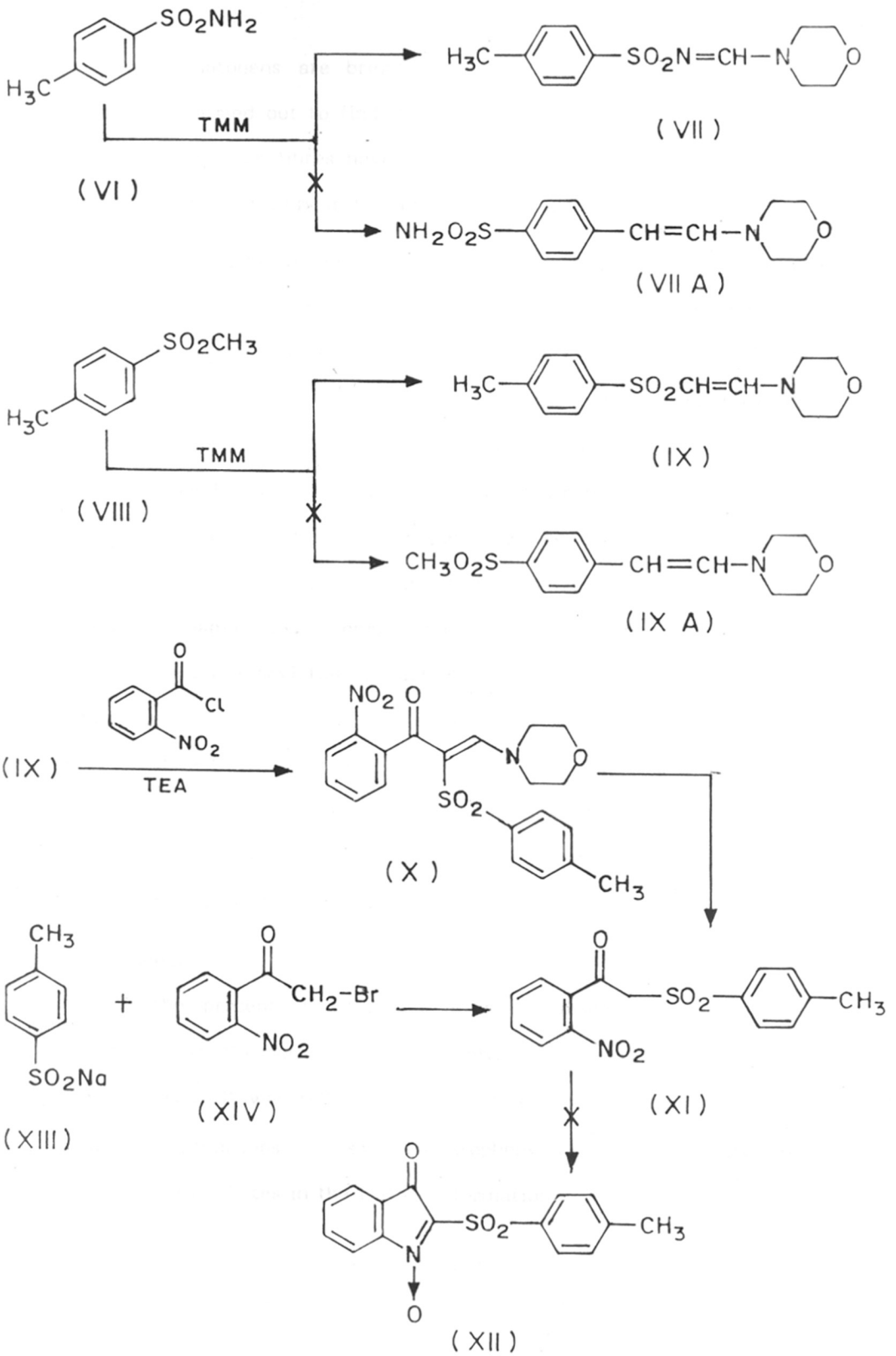
α-(o-Nitrobenzoyl)-β-dialkylaminostyrenes III were directly converted to isatogen by refluxing with sodium acetate/ethanol/water (Method-B). However, the yields obtained by this method were less, 40-50% and that in the case of compound III obtained from trans-β-dialkylamino-2-nitro-styrene could not be cyclized to isatogens by this method.

Hence, compound (III) was cyclized to isatogens in the presence of sodium acetate/acetic acid/methanol/water (pH 5.5, Method-A). The yields obtained by Method-A were better than the yields obtained by Method-B.

Spectral properties of isatogens: The important feature of the IR spectrum of isatogens is the strong carbonyl absorption from 1700 to 1720 cm^{-1} (conjugated $\rangle C = O$ in 5-membered ring) and a band at 1175 cm^{-1} which has been assigned to the N ⟶ O stretching vibration.

UV and visible spectra: The main absorption of 2-arylisatogen is reported[3] to occur around 280 nm (Log E 4.2-4.6). The band is usually broad and often shows more than one maxima. Substituents in 2-position of aryl ring tend to displace the band towards lower wavelength as the size of the substituent increases and the co-planarity of the two ring systems is lost.

SCHEME-18
ATTEMPTED SYNTHESIS OF 2-(p-TOSYL) ISATOGEN



These isatogens are brightly coloured solids, some experiments have been carried out to find the dyeing properties of these compounds. Thus the polyester fibres have been successfully dyed with these compounds and further work in this direction is in progress.

It was thought worthwhile to replace the nitro group in the toluene moiety by sulfonamide group and prepare the corresponding enamines using trimorpholinomethane (Scheme-18). However, when p-toluenesulfonamide was condensed with trimorpholinomethane, the condensation took place at nitrogen and not at the methyl carbon on benzene ring to yield the compound VII. Similarly when methyl-p-toluene sulfonate (VIII) was condensed with trimorpholinomethane, the condensation took place at the sulfonylmethyl, and not at the benzene methyl group; thus affording enamine IX. Compound IX was acylated using o-nitrobenzoyl chloride and the acylated product X was hydrolysed with dilute hydrochloric acid to obtain XI. The structure of XI was confirmed by comparing it with the authetic sample of XI which was synthesised by the condensation of sodium p-toluenesulfinate with ω-bromoacetophenone. Both the compounds X and XI failed to cyclize to the isatogen (XII) by either Method A or Method B.

Conclusion:

In the present investigation it is established that the isatogen formation is through the base catalysation of o-nitrophenyl benzyl ketones (IV). It was felt at this stage that in Krohnke's method, under the basic conditions, the same o-nitrophenyl benzyl ketones (IV) might be the intermediates in the isatogen formation.

It is also established that the isatogen formation in acidic medium is through the same intermediate o-nitrophenyl benzyl ketones (IV) as described by Baeyer.[4]

EXPERIMENTAL

PART A - SECTION B:

Section B of Part A deals with the preparation of substituted 2-arylisatogens.

The steps involved in the preparation are as follows:

1. Preparation of (phenylethenyl)dialkylamine or trans- β -dialkylaminostyrenes (II).
2. Preparation of α-(nitrobenzoyl)- β -dialkylaminostyrenes (III)
3. Preparation of 1-(nitroaryl)-2-(aryl)ethanones or phenyl benzyl ketones (IV)
4. Cyclodehydration of phenyl benzyl ketones (IV) to 2-arylisatogens (V)
5. Hydrolysis and cyclodehydration of α-(o-nitrobenzoyl)- β -dialkylaminostyrenes III to 2-arylisatogens (V).

Step 1: Preparation of (phenylethenyl)dialkylamines or trans- β -dialkylaminostyrenes (II)

Trans- β -dialkylaminostyrenes were prepared by three different routes.

Route 1: Preparation of trans- β -morpholinonitrostyrenes from nitro-substituted toluenes.

Route 2: Preparation of trans- β -morpholinostyrenes from phenylacetaldehydes.

Route 3: Preparation of trans- β -dimethylaminostyrenes from benzyl halides.

Route 1 : Preparation of trans-β-morpholinonitrostyrenes from nitro-substituted toluenes.

This requires preparation of trimorpholinomethane.

Preparation of trimorpholinomethane[70]

Morpholine (54.9 g, 0.63 mole), triethylorthoformate (62.2 g, 0.42 mole) and glacial acetic acid (1.26 g, 0.021 mole) were placed in 250 ml round bottom flask and heated to reflux, using steam jacket condensor for continous removal of ethanol. After two hours at reflux, the internal temperature had risen to 165°C, and heating was terminated. The mixture was allowed to stand at room temperature for 12 hr. The resulting crystals were collected by filtration, washed with ether and dried under vacuum to yield 35.2 g (61.8%) of trimorpholinomethane; m.p. 139°C (lit.[70] 137-153°C).

PMR ($CDCl_3$) showed signals at: δ 2.75 (t, 12H, $[-N(C\underline{H}_2)_2]_3$), 3.27 (s, $\underline{H}$-$C(N<)_3$), 3.65 (t, 12H, $[O(C\underline{H}_2)2]3$).

General procedure for the preparation of trans-β-morpholino nitrostyrenes (II) from nitro substituted toluenes. [68]

In a 100 ml round bottom flask, 0.1 mole of nitrotoluene and 0.15 mole of trimorpholinomethane were placed and heated together at 120-130°C under water pump suction with stirring, for continuous removal of morpholine, until the disappearance of nitrotoluene [4 hr, monitored by TLC; benzene : pet. ether (1:1)]. The reaction mixture was allowed to cool to room temperature. The reaction products in case of solids were crystallised from appropriate solvents and liquids were purified by neutral alumina chromatography, using benzene: pet. ether (1:1) mixture as an eluate.

Following compounds were prepared according to the general procedure with the quantities given.

1. Preparation of (4-nitrophenylethenyl)morpholine or trans-β-morpholino-4-nitrostyrene (II-1)

4-Nitrotoluene	13.7 g (0.1 mole)
Trimorpholinomethane	40.65 g (0.15 moles)

The mixture was heated under stirring at 130°C for 4 hr.

Yield :	17.55 g (75%)
M.p.	112°C (benzene, petroleum ether)

IR (nujol) spectrum showed band at 1640 cm^{-1} (HC=CH-N<)

PMR ($CDCl_3$) showed signals at δ 3.1 (t, 4H, $-N(\underline{CH_2})_2$); 3.7 (t, 4H, $O(\underline{CH_2})_2$); 5.3 (d, 1H, J = 14Hz, H>C = C<N<H); 6.85 (d, 1H, J = 14Hz, H>C = C<N<H); 7.1 & 7.95 (4H, p-disubstituted aromatic pattern).

Analysis found :	C, 61.4; H, 6.10; N, 12.57.
Analysis required for $C_{12}H_{14}N_2O_3$:	C, 61.53; H, 5.98; N, 11.96.
Mass spectrum :	M^+ 234.

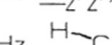
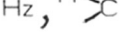
2. Preparation of (2-nitrophenylethenyl)morpholine or trans-β-morpholino 2-nitrostyrene (II-2).

2-Nitrotoluene	13.7 g (0.1 mole)
Trimorpholinomethane	40.65 g (0.15 mole)

The mixture was heated under stirring at 120°C for 4.5 hr. This compound was purified over neutral alumina column (1:50 ratio), using benzene: petroleum ether (1:1) mixture as an eluate. Attempts to distil under reduced pressure resulted in polymerisation of this compound. Hence, distillation was avoided.

Yield : 16.85 g (72%)

IR (neat) spectrum showed band at 1640 cm^{-1} (-CH=CH-N<).

PMR ($CDCl_3$) displayed peaks at δ 3.4 (t, 4H, -N($\underline{CH_2}$)$_2$); 3.85 (t, 4H, O($\underline{CH_2}$)$_2$); 5.4 (d, 1H, J = 14Hz, ) ; 6.8 (d, 1H, J = 14 Hz, ); 7.2 - 8.0 (aromatic protons).

Analysis found : C, 61.95; H, 6.38; N, 12.25

Analysis required for $C_{12}H_{14}N_2O_3$: C, 61.53; H, 5.98; N, 11.96.

Mass spectrum : M^+ 234.

3. Preparation of (2-nitro-5-methoxyphenylethenyl)morpholine or trans-β-morpholino-2-nitro-5-methoxystyrene (II-3).

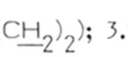
2-Nitro-5-methoxytoluene 16.7 g (0.1 mole)

Trimorpholinomethane 40.65 g (0.15 mole)

This compound was purified over neutral alumina chromatography (1:50 ratio), using benzene : pet. ether (1:1) mixture as an eluate.

Yield : 13.72 g (52 %)

IR (neat) spectrum showd band at 1645 cm^{-1} (-CH=CH – N<).

PMR ($CDCl_3$) displayed peaks at δ 3.2 (t, 4H, -N($\underline{CH_2}$)$_2$); 3.6 (t, 4H, O($\underline{CH_2}$)$_2$); 3.9 (s, 3H, O-$\underline{CH_3}$); 5.5 (d, 1H, J = 14Hz, ); 6.5 (d, 1H, J = 14Hz,); 7.2 - 8.2(aromatic protons).

Analysis found : C, 58.62; H, 6.58; N, 11.10

Analysis required for $C_{13}H_{16}N_2O_4$: C, 59.09; H, 6.06; N, 10.60

Mass spectrum : M^+ 264.

The starting material 2-nitro-5-methoxytoluene was prepared from p-nitro-m-cresol.[71]

M.p. 48-50°C (lit. 53-57°C).[85]

4. Preparation of (2,4-dinitrophenylethenyl)morpholine or trans-β-morpholino-2,4-dinitrostyrene (II-4)

2,4-Dinitrotoluene	18.2 g (0.1 mole)
Trimorpholinomethane	40.65 g (0.15 mole)

Reaction mixture was heated under stirring at 130°C, for 3 hr.

m.p. 186-88°C (ethanol)

Yield: 24.02 g (86.1%)

IR (nujol) showed band at 1645 cm^{-1} (-CH = CH - N<)

PMR ($CDCl_3$) spectrum showed signals at δ 3.3 (t, 4H, $-N(\underline{CH_2})_2$); 3.6 (t, 4H, $O(\underline{CH_2})_2$); 5.5 (d, 1H, J = 14Hz, $\underline{H}C = C$<N, H); 7.4-8.2 (aromatic protons); 6.9 (d, 1H, J = 14Hz, $H-C = C$<N, $\underline{H}$)

Analysis found : C, 51.50; H, 4.21; N, 14.88.

Analysis required for $C_{12}H_{13}N_3O_5$: C, 51.61; H, 4.66; N, 15.05.

Mass spectrum: M^+ 279.

Route 2: Preparation of trans-β-morpholinostyrenes from phenylacetaldehyde

General procedure: To a stirred ice cold solution of phenylacetaldehyde (0.1 mole) and 3-4 g of anhydrous potassium carbonate, was added dropwise morpholine (0.2 mole) over 30 minutes. After completion of addition, reaction mixture was allowed to come to the room temperature and stirred for 8 hr. Potassium carbonate was removed by filtration and filtrate of diamine was heated at 120-130°C/30 mm, to remove the liberated morpholine. The residue, after removal of morpholine, was crystallised from suitable solvent.

Following compounds were prepared according to this general procedure with the quantities given.

1 **Preparation of phenylethenylmorpholine or trans-β-morpholino-styrene (II-5).**

Phenylacetaldehyde 12.0 g (0.1 mole)

Anhydrous potassium carbonate 4.0 g

Morpholine 17.4 g (0.2 mole)

M.p. 76-77°C (carbon tetrachloride)

Yield: 12.38 g (65.5%)

IR (Nujol) spectrum showed band at 1645 cm^{-1} (-CH = CH - N<).

PMR ($CDCl_3$) spectrum showed signals at δ 3.2 (t, 4H, $-N(\underline{CH_2})_2$); 3.7 (t, 4H, $O(\underline{CH_2})_2$); 5.4 (d, 1H, J = 14Hz, $\underline{H}>C = C<^{N<}_{H}$); 6.6 (d, 1H, 14 Hz, $H>C = C<^{N<}_{\underline{H}}$); 7.0-7.2 (aromatic protons).

Analysis found : C, 75.95; H, 8.32; N, 7.67.

Analysis required for $C_{12}H_{15}NO$: C, 76.19; H, 7.94; N, 7.40.

Mass spectrum: M^+ 189.

The starting material phenylacetaldehyde was prepared from phenethyl-alcohol.[73]

2. **Preparation of (3,4-dimethoxyphenylethenyl)morpholine or trans-β-morpholino-3,4-dimethoxystyrene (II-6)**

3,4-Dimethoxyphenylacetaldehyde 18.0 g (0.1 mole)

Anhydrous potassium carbonate 4 g

Morpholine 17.4 g (0.2 mole)

M.p. 80°C (carbon tetrachloride - petroleum ether)

Yield: 14.94 g (60%)

IR (Nujol) showed band at 1640 cm^{-1} (-CH = CH - N<).

PMR ($CDCl_3$) spectrum showed signals at δ 3.2 (t, 4H, $N(\underline{CH_2})_2$); 3.6 (t, 4H, $O(\underline{CH_2})_2$); 3.8 (s, 6H, $(-O-\underline{CH_3})_2$); 5.4 (d, 1H, J = 14Hz,

$\underline{H}>C = C<^{N<}_{H}$); 6.4 (d, 1H, J = 14Hz, $H>C = C<^{N<}_{\underline{H}}$); 6.6 (aromatic protons).

Analysis found: C, 67.55; H, 8.12; N, 5.35.

Analysis required for $C_{14}H_{19}NO_3$: C, 67.47; H, 7.63; N, 5.62.

Mas spectrum: M^{+} 249.

The starting material 3,4-dimethoxyphenylacetaldehyde was prepared as follows.

The reaction was carried out in seven batches due to limited capacity of ozonalysis apparatus.

3-(3,4-Dimethoxyphenyl)-1-propene, (3.56 g, 0.02 mole), was dissolved in 100 ml of methanol and was subjected to ozonalysis for 2 hr. The ozonide was decomposed in ice cold condition by addition of dimethyl-sulfide. Reaction mixture was further stirred for 1 hr, the solvent was removed under reduced pressure. The residue of all the batches were combined and distilled at 120°/10 mm.

IR (Neat) spectrum showed bands at 1720 cm^{-1} ($>\overset{O}{\overset{\|}{C}}-$), 2700 cm^{-1} ($-\overset{O}{\overset{\|}{C}}-H$).

PMR (CCl_4) spectrum showed signals at δ 3.4 (d, 2H, $-\underline{CH_2}-$); 3.8 (s, 6H, $(O-\underline{CH_3})_2$); 6.5 - 6.6 (aromatic protons); 9.1 (d, 1H, $-\overset{O}{\overset{\|}{C}}-\underline{H}$).

Route 3: Preparation of trans-β-dimethylaminostyrenes from benzyl halides[74]

To a three necked 250 ml round bottom flask fitted with reflux condensor and a dropping funnel, were placed magnesium (5.4 g, 0.22 mole) in 50 ml dry ether and a pinch of iodine to initiate a reaction.

To the stirred solution, benzyl halide (0.2 mole) in dry ether (20 ml) was added dropwise at such a rate as to keep the solution at gentle reflux. After addition, the reaction mixture was refluxed for 3 hr. until all the magnesium dissolved. An additional 100 ml ether was introduced and the flask was cooled in ice salt mixture. Dimethylformamide (17.52 g, 0.24 mole) was added dropwise through dropping funnel, over 45 minutes. The sticky solid formed was stirred further for 12 hr. at room temperature. The Grignard complex was decomposed with saturated ammonium chloride solution. Ether layer separated was washed with water, dried over anhydrous sodium sulphate. Solvent evaporated and residue was distilled under reduced pressure.

Following compounds were prepared according to this general procedure, with the quantities given.

1. **Preparation of (phenylethenyl)dimethylamine or trans-β-dimethylaminostyrene (II-7).**

Magnesium	5.4 g (0.22 mole)
Benzyl chloride	25.30 g (0.2 mole)
Dimethylformamide	17.52 g (0.24 mole).
Distilled at	110-115°/0.5 mm
Yield:	15.58 g (53%).

IR (neat) showed band at 1640 cm^{-1} (-CH = CH - N$\lesssim$)

PMR (CCl_4) spectrum showed peaks at δ 2.8 (s, 6H, -N($\underline{CH_3}$)$_2$); 5.15 (d, 1H, J = 14Hz, $\underline{H}\!>\!C = C\!<^{H}_{N\lesssim}$); 6.75 (d, 1H, J = 14Hz, $H\!>\!C = C\!<^{\underline{H}}_{N\lesssim}$); 6.9 - 7.3 (aromatic protons).

Analysis found : C, 81.40; H, 8.82; N, 9.10

Analysis required for $C_{10}H_{13}N$: C, 81.63; H, 8.84; N, 9.52.

Mass spectrum : M^{+} 147.

2. **Preparation of (4-methylphenylethenyl) dimethylamine or trans-β--dimethylamino-4-methylstyrene (II-8).**

Magnesium	5.4 g (0.22 mole)
4-Methylbenzyl bromide	36.4 g (0.2 mole)
Dimethylformamide	17.52 g (0.24 mole)
Distilled at	125-130°/0.5 mm
Yield :	14.81 g (46%)

IR (Neat) showed band at 1640 cm^{-1} (-CH = CH - N<)

PMR(CCl_4) spectrum showed signals at δ 2.8 (s, 6H, $-N(\underline{CH_3})_2$); 5.0 (d, 1H, J = 14Hz, $\underline{H}>C=C<^{H}_{N<}$); 6.5 (d, 1H, J = 14Hz, $H>C=C<^{N<}_{\underline{H}}$); 6.9 - 7.3. (aromatic protons).

Analysis found : C, 82.12; H, 9.15; N, 8.86.

Analysis required for $C_{11}H_{15}N$: C, 81.98; H, 9.31; N, 8.70.

Mass spectrum: $M^{+\cdot}$ 161.

The starting material 4-methylbenzylbromide was prepared from 4-methylbenzyl alcohol.[86]

Step 2: Preparation of α-(nitrobenzoyl)- β -dialkylaminostyrenes (III)

This step involves the preparation of following acids and their corresponding acid chlorides.

a) o-Nitrobenzoic acid from o-nitrotoluene[75]

b) p-Nitrobenzoic acid from p-nitrotoluene[75]

c) 6-Nitro-3-methoxybenzoic acid[87] from 6-nitro-3-methoxytoluene[75]

d) 2-Nitro-4,5-dimethoxybenzoic acid from 2-nitro-4,5-dimethoxytoluene[75]

e) 2,4-Dinitrobenzoic acid from 2,4-dinitrotoluene[77]

Acid chlorides were prepared from corresponding carboxalic acids[75,76]

General procedure: In a 500 ml three necked flask, fitted with reflux condensor, having calcium chloride guard tube and a dropping funnel, was dissolved trans-β-dialkylaminostyrene II (0.05 mole) and triethylamine (0.05 mole) in dry benzene (100 ml). To the stirred solution of II, was added dropwise at ice cold condition, a solution of benzoyl chloride (0.05 mole) in dry benzene (25 ml). The reaction mixture was stirred at room temperature for 1 hr. and then refluxed with stirring for 15 hr. Reaction mixture was cooled to room temperature, solid separated was collected on Buckner funnel and washed with sufficient amount of water to dissolve triethylamine hydrochloride salt, dried and crystallised from solvent.

When solid was not separated, the benzene solution was washed thoroughly with water, dried over anhydrous sodium sulphate. Solvent was removed under reduced pressure and residue was purified by silica gel column chromatography (1:40 ratio), using benzene : ethyl acetate (80:20) mixture as an eluate.

Following compounds were prepared according to this generl procedure with the quantities given.

1. **Preparation of α-(2-nitrobenzoyl)-β-morpholino-4-nitrostyrene (III-1).**

Trans-β-morpholino-4-nitrostyrene	11.70 g (0.05 mole)
Triethylamine	5.05 g (0.05 mole)
2-Nitrobenzoyl chloride	9.28 g (0.05 mole)

M.p. 195°C (ethanol)

Yield: 13.98 g (73%)

IR (Nujol) showed band at 1640 cm^{-1} ()

PMR ($CDCl_3$) spectrum showed signals at δ 3.2 (t, 4H, $-N(\underline{CH_2})_2$); 3.6 (t, 4H, $O(\underline{CH_2})_2$), 6.9-8.1 (- C = $\underline{CH}$ - N< and aromatic protons)

Analysis found: C, 59.39; H, 4.68; N, 10.25.

Analysis required for $C_{19}H_{17}N_3O_6$: C, 59.53; H, 4.44; N, 10.96.

Mass spectrum: M^+ 383.

2. **Preparation of α-(2-nitrobenzoyl)- β -morpholino-2-nitrostyrene (III-2)**

Trans-β-morpholino-2-nitrostyrene	11.70 g (0.05 mole)
Triethylamine	5.05 g (0.05 mole)
2-Nitrobenzoyl chloride	9.28 g (0.05 mole)

M.p. 208°C (ethanol)

Yield : 15.51 g (81%)

IR (Nujol) showed band at 1640 cm^{-1} ()

PMR ($CDCl_3$) showed signals at δ 3.3 (t, 4H, $-N(\underline{CH_2})_2$); 3.6 (t, 4H, $O(\underline{CH_2})_2$); 6.9-8.1 (-C = $\underline{CH}$ - N< and aromatic protons)

Analysis found: C, 59.42; H, 4.69; N, 10.35

Analysis required for $C_{19}H_{17}N_3O_6$: C, 59.53; H, 4.44; N, 10.96

Mass spectrum: M^+ 383.

3. **Preparation of α-(2-nitro-5-methoxybenzoyl)- β -morpholino-4-nitrostyrene (III-3)**

Trans-β-morpholino-4-nitrostyrene	11.70 g (0.05 mole)
Triethylamine	5.05 g (0.05 mole)
2-Nitro-5-methoxybenzoyl chloride	10.78 (0.05 mole)

M.p. 183°C (ethyl acetate - petroleum ether)

Yield: 14.45 g (70%).

IR (Nujol) showed band at 1645 cm^{-1} (-C(=O)-N<)

PMR ($CDCl_3$) spectrum showed signals at δ 3.1 (t, 4H, -N($\underline{CH_2}$)$_2$); 3.5 (t, 4H, O($\underline{CH_2}$)$_2$); 3.8 (s, 3H, O$\underline{CH_3}$), 6.8 - 8.0 (-C = $\underline{CH}$ - N< and aromatic protons).

Analysis found: C, 57.72; H, 4.75; N, 10.12

Analysis required for $C_{20}H_{19}N_3O_7$: C, 58.11; H, 4.60; N, 10.17

Mass spectrum: M^+ 413 .

4. **Preparation of α-(2-nitro-4,5-dimethoxybenzoyl)- β-morpholino-4-nitrostyrene (III-4).**

Trans-β-morpholino-4-nitrostyrene	11.70 g (0.05 mole)
Triethylamine	5.05 g (0.05 mole)
2-Nitro-4,5-dimethoxybenzoyl chloride	12.28 g (0.05 mole)

M.p. 205°C (ethanol)

Yield : 7.3 g (33%)

IR (Nujol) showed band at 1640 cm^{-1} ()

PMR ($CDCl_3$) spectrum showed signals at δ 3.2 (t, 4H, -N($\underline{CH_2}$)$_2$); 3.6 (t, 4H, O($\underline{CH_2}$)$_2$); 3.9 (s, 6H, (O-$\underline{CH_3}$)$_2$); 6.8-8.1 (-C=$\underline{CH}$-N< and aromatic protons)

Analysis found: C, 56.48; H, 4.62; N, 9.52.

Analysis required for $C_{21}H_{21}N_3O_8$: C, 56.88; H, 4.74; N, 9.48.

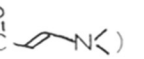
Mass spectrum: M^+ 443.

5. **Preparation of α-(2-nitrobenzoyl)- β -morpholino-2-nitro-5-methoxystyrene (III-5)**

Trans-β -morpholino-2-nitro-5-methoxystyrene	13.20 g (0.05 mole)
Triethylamine	5.05 g (0.05 mole)
2-Nitrobenzoyl chloride	9.28 g (0.05 mole)

This compound was purified by silica gel chromatography (1:40 ratio), using benzene : ethyl acetate (90:10) mixture as an eluate.

Yield : 8.88 g (43%0

IR (Neat) showed band at 1640 cm^{-1} (- )

PMR ($CDCl_3$) spectrum showed signals at δ 3.2 (t, 4H, $-N(\underline{CH_2})_2$); 3.6 (t, 4H, $O(\underline{CH_2})_2$); 3.9 (s, 3H, $O-\underline{CH_3}$); 6.9-8.1 ($C = \underline{CH} - N<$ and aromatic protons).

Analysis found: C, 57.65; H, 4.90; N, 10.35.

Analysis required for $C_{20}H_{19}N_3O_7$: C, 58.11; H, 4.60; N, 10.17.

Mass spectrum: M^+ 413.

6. Preparation of α-(2,4-dinitrobenzoyl)- β -morpholino-4-nitrostyrene (III-6).

Trans-β-morpholino-4-nitrostyrene	11.70 g (0.05 mole)
Triethylamine	5.05 g (0.05 mole)
2,4-Dinitrobenzoyl chloride	11.53 g (0.05 mole)

M.p. 224°C (acetonitrile)

Yield : 19.90 g (93%)

IR (Nujol) showed band at 1645 cm^{-1} ()

PMR ($CDCl_3$) spectrum showed signals at δ 3.4 (t, 4H, $-N(\underline{CH_2})_2$); 3.8 (t, 4H, $O(\underline{CH_2})_2$); 7.2 - 8.6 ($-C = \underline{CH} - N<$ and aromatic protons).

Analysis found: C, 53.49; H, 3.30; N, 13.00 .

Analysis required for $C_{19}H_{16}N_4O_8$: C, 53.27; H, 3.73; N, 13.08 .

Mass spectrum: M^+ 428.

7. **Preparation of ∝-(benzoyl)- β -morpholino-4-nitrostyrene (III-7).**

Trans-β-morpholino-4-nitrostyrene	11.70 g (0.05 mole)
Triethylamine	5.05 g (0.05 mole)
Benzoyl chloride	7.03 g (0.05 mole)

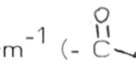
This compound crude as such was used for the acid hydrolysis.

8. **Preparation of ∝-(4-nitrobenzoyl)- β -morpholino-4-nitrostyrene (III-8).**

Trans-β-morpholino-4-nitrostyrene	11.70 g (0.05 mole)
Triethylamine	5.05 g (0.05 mole)
4-Nitrobenzoyl chloride	9.28 g (0.05 mole)

M.p. 383°C (acetone)

Yield: 16.85 g (88%)

IR (Nujol) showed band at 1650 cm^{-1} (- )

PMR ($CDCl_3$) showed signals at δ 3.4 (t, 4H, $-N(\underline{CH_2})_2$); 3.8 (t, 4H, $-O(\underline{CH_2})_2$); 7.1-8.4 (-C = $\underline{CH}$ - N< and aromatic protons).

Analysis found: C, 59.10; H, 4.68; N, 11.2.

Analysis required for $C_{19}H_{17}N_3O_6$: C, 59.53; H, 4.44; N, 10.96.

Mass spectrum: M^+ 383.

9. **Preparation of ∝-(4-nitrobenzoyl)-β-morpholino-2-nitrostyrene (III-9)**

Trans-β-morpholino-2-nitrostyrene	11.27 g (0.05 mole)
Triethylamine	5.05 g (0.05 mole)
4-Nitrobenzoyl chloride	9.28 g (0.05 mole)

M.p. 207-208°C (ethanol)

Yield: 14.94 g (78%).

IR (Nujol) showed band at 1640 cm^{-1} (-C(=O)- )

PMR ($CDCl_3$) displayed peaks at δ 3.3 (t, 4H, $-N(\underline{CH_2})_2$); 3.7 (t, 4H, $O(\underline{CH_2})_2$); 7.2 - 8.5 (-C = $\underline{CH}$ - N< and aromatic protons).

Analysis found: C, 59.80; H, 4.90; N, 11.30

Analysis found for $C_{19}H_{17}N_3O_6$: C, 59.53; H, 4.44; N, 10.96

Mass spectrum : M^+ 383.

10. Preparationof α-(2,4-dinitrobenzoyl)- β -morpholino-2-nitrostyrene (III-10).

Trans-β-morpholino-2-nitrostyrene	11.27 g (0.05 moles)
Triethylamine	5.05 g (0.05 mole)
2,4-Dinitrobenzoyl chloride	11.53 g (0.05 mole)

M.p. 212°C (ethanol)

Yield: 16.0 g (75%)

IR (Nujol) showed band at 1645 cm^{-1} (-C(=O)- )

PMR ($CDCl_3$) showed signals at δ 3.4 (t, 4H, $-N(\underline{CH_2})_2$); 3.7 (t, 4H, $O(\underline{CH_2})_2$); 7.2 - 8.7 (-C = $\underline{CH}$ - N< and aromatic protons)

Analysis found: C, 52.80; H, 3.90; N, 12.95.

Analysis required for $C_{19}H_{16}N_4O_8$: C, 53.27; H, 3.73; N, 13.08

Mass spectrum: M^+ 428.

11. Preparation of α-(2-nitrobenzoyl)-β-morpholino-2,4-dinitrostyrene (III-11)

Trans-β-morpholino-2,4-dinitrostyrene	13.95 g (0.05 mole)
Triethylamine	5.05 g (0.05 mole)
2-Nitrobenzoyl chloride	9.28 g (0.05 mole)

M.p. 207°C (ethanol)

Yield: 12.41 g (58%).

IR (Nujol) showed band at 1645 cm^{-1} (-)

PMR ($CDCl_3$) showed signals at δ 3.4 (t, 4H, $N(C\underline{H}_2)_2$); 3.7 (t, 4H, $O(C\underline{H}_2)_2$); 7.1 - 8.6 (-C = C<u>H</u> - N< and aromatic protons).

Analysis found: C, 52.70; H, 4.05; N, 13.15

Analysis required for $C_{19}H_{16}N_4O_8$: C, 53.27; H, 3.73; N, 13.08

Mass spectrum: M^+ 428.

12 **Preparation of α-(2,4-dinitrobenzoyl)-β-morpholino-2,4-dinitrostyrene (III-12)**

Trans-β-morpholino-2,4-dinitrostyrene	13.95 g (0.05 mole)
Triethylamine	5.05 g (0.05 mole)
2,4-Dinitrobenzoyl chloride	11.53 g (0.05 mole)

M.p. 262°C (ethanol)

Yield: 15.85 g (67%)

IR (Nujol) showed band at 1650 cm^{-1} (-)

PMR ($CDCl_3$) showed signals at δ 3.5 (t, 4H, $-N(C\underline{H}_2)_2$); 3.8 (t, 4H, $O(C\underline{H}_2)_2$), 7.2-8.7 (C = C<u>H</u> - N< and aromatic protons).

Analysis found: C, 48.55; H, 3.30; N, 14.40.

Analysis required for $C_{19}H_{15}N_5O_{10}$: C, 48.20; H, 3.17; N, 14.80

Mass spectrum: M^+ 473.

13. **Preparation of α-(2,4-dinitrobenzoyl)-β-morpholino-2-nitro-5-methoxystyrene (III-13)**

Trans-β -morpholino-2-nitro-5-methoxystyrene	13.20 g (0.05 mole)
Triethylamine	5.05 g (0.05 mole)
2,4-Dinitrobenzoyl chloride	11.53 g (0.05 mole)

M.p. 155°C (benzene - carbon tetrachloride)

Yield: 18.0 g (79%)

IR (Nujol) showed band at 1640 cm^{-1} (-C(=O)-Ar-N<)

PMR ($CDCl_3$) spectrum showed signals at δ 3.4 (t, 4H, $-N(\underline{CH_2})_2$); 3.6 (t, 4H, $O(\underline{CH_2})_2$); 3.9 (s, 3H, $O-\underline{CH_3}$); 7.1-8.5 (-C = $\underline{CH}$ - N< and aromatic protons).

Analysis found: C, 52.10; H, 4.20; N, 11.90.

Analysis required for $C_{20}H_{18}N_4O_9$: C, 52.40; H, 3.93; N, 12.22

Mass spectrum: M^+ 458.

14. Preparation of α-(2-nitrobenzoyl)- β -morpholinostyrene (III-14)

Trans-β-morpholinostyrene	9.45 g (0.05 mole)
Triethylamine	5.05 g (0.05 mole)
2-Nitrobenzoyl chloride	9.28 g (0.05 mole)

This compound was purified over silica gel chromatography, using benzene : ethyl acetate (80:20) mixture as an eluate.

Yield: 7.1 g (42%)

IR (Neat) showed band at 1640 cm^{-1} (-C(=O)-Ar-N<)

PMR ($CDCl_3$) showed signals at δ 3.3 (t, 4H, $-N(\underline{CH_2})_2$); 3.6 (t, 4H, $O(\underline{CH_2})_2$); 7.0 - 8.4 (-C = $\underline{CH}$ - N< and aromatic protons)

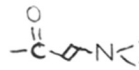
Mass spectrum: M^+ 338.

15. Preparation of α-(2-nitrobenzoyl)-β-morpholino-3,4-dimethoxystyrene (III-15).

Trans-β-morpholino-3,4-dimethoxystyrene	12.45 g (0.05 mole)
Triethylamine	5.05 g (0.05 mole)
2-Nitrobenzoyl chloride	9.28 g (0.05 mole)

This compound was purified over silica gel chromatography, using benzene:ethyl acetate (80:20) mixture as an eluate.

Yield : 11.74 g (59%)

IR (Neat) showed band at 1640 cm^{-1} ()

PMR ($CDCl_3$) showed signals at δ 3.2 (t, 4H, $-N(\underline{CH_2})_2$), 3.6 (t, 4H, $O(\underline{CH_2})_2$), 3.9 (s, 3H, $O-\underline{CH_3}$), 7.1-8.3 ($-C=\underline{CH}-N<$ and aromatic protons).

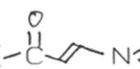
Mass spectrum: $M^{+\cdot}$ 398.

16. Preparation of α-(2-nitrobenzoyl)-β-dimethylaminostyrene (III-16)

Trans-β-dimethylaminostyrene	7.35 g (0.05 mole)
Triethylamine	5.05 g (0.05 mole)
2-Nitrobenzoyl chloride	9.28 g (0.05 mole)

M.P. : 115°C (carbon tetrachloride)

Yield : 11.10 g (75%)

IR (Nujol) showed band at 1640 cm^{-1} ()

PMR ($CDCl_3$) showed signals at δ 2.9 (s, 6H, $-N(\underline{CH_3})_2$), 6.9-8.1 ($-C = \underline{CH} - N<$ and aromatic protons).

Analysis found: C, 67.70; H, 5.80; N, 9.20

Analysis required for $C_{17}H_{16}N_2O_3$: C, 68.92; H, 5.41; N, 9.45.

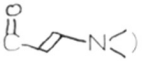
Mass spectrum: $M^{+\cdot}$ 296.

17. Preparation of α-(2-nitrobenzoyl)-β-dimethylamino-4-methylstyrene (III-17)

Trans-β-dimethylamino-4-methylstyrene	8.05 g (0.05 mole)
Triethylamine	5.05 g (0.05 mole)
2-Nitrobenzoyl chloride	9.28 g (0.05 mole)

M.P. 147°C (benzene-carbon tetrachloride)

Yield 8.84 g (57%)

IR (Nujol) showed band at 1640 cm^{-1} ()

PMR ($CDCl_3$) showed signals at δ 2.2 (s, 3H, $\underline{CH_3}$), 2.8 (s, 6H, $-N(\underline{CH_3})_2$), 7.0-8.6 (-C = $\underline{CH}$ - N< and aromatic protons)

Analysis found: C, 69.40; H, 5.45; N, 8.88 ·

Analysis required for $C_{18}H_{18}N_2O_3$: C, 69.68; H, 5.8; N, 9.03 ·

Mass spectrum: M^+ 310.

Preparation of 3-(2-nitrophenyl)-3-oxo-2-phenyl-1-propanal (IVA)

General Procedure: In a 100 ml round bottom flask, was dissolved 0.01 mole of α-(2-nitrobenzoyl)-β-dialkylaminostyrene, in 50 ml dioxane, to that 2 ml conc. hydrochloric acid was added and mixture was refluxed for 2 to 3 hr. Solvent was evaporated under reduced pressure and residue was extracted with ethyl acetate (3 x 15 ml). Ethyl acetate layer was washed with sodium bicarbonate solution (pH 7.5-8.5) till bicarbonate washings were colourless. Bicarbonate washings were combined and acidified with conc. hydrochloric acid. Solid separated was collected by filtration and crystallised from solvent.

1. **Preparation of 3-(2-nitrophenyl)-3-oxo-2-(2-nitrophenyl)-1-propanal (IVA - 2)**

This compound was prepared according to the general procedure with the following quantities.

α-(2-Nitrobenzoyl)-β-morpholino-2-nitrostyrene	: 3.83 g (0.01 mole)
Dioxane	: 50 ml
Conc. hydrochloric acid	: 2 ml

This compound was crystallised from ethanol.

Yield 2.07 g (66%)

M.P.

Analysis found: C, 57.15; H, 3.35; N, 8.60

Analysis required for $C_{15}H_{10}N_2O_6$: C, 57.33; H, 3.18; N, 8.92.

Mass spectrum: M^+ 314.

2. Preparation of 3-(2-nitrophenyl)-3-oxo-2-phenyl-1-propanal (IVA-14)

This compound was prepared according to the general procedure with the following quantities.

∝-(2-Nitrobenzoyl)-β-morpholinostyrene : 3.38 g (0.01 mole)

Dioxane : 50 ml

Conc. hydrochloric acid : 2 ml

This compound was crystallised from benzene - pet. ether.

Yield : 1.94 g (72%)

M.P. 136°C [1]

Analysis found: C, 66.52; H, 4.40; N, 5.45

Analysis calculated for $C_{15}H_{11}NO_4$: C, 66.91; H, 4.09; N, 5.20.

Mass spectrum: M^+ 269.

Step-3 : Preparation of 1-(nitroaryl)-2-(nitroaryl) ethanones or phenyl benzyl ketones (IV)

General Procedure: In a 100 ml round bottom flask, 0.01 mole of ∝-(nitrobenzoyl)-β-dialkylaminostyrene (III) was dissolved in 50 ml of dioxane, to that was added 5 ml dilute (5%) hydrochloric acid and the mixture was refluxed for 4 hr, until the starting material was disappeared from rection mixture (monitored by TLC, benzene).

Solvent was evaporated under reduced pressure. Residue was extracted with ethyl acetate. The ethyl acetate layer was washed with dilute sodium bicarbonate solution, until bicarbonate washings were colourless. Ethyl acetate layer was dried over anhydrous sodium sulfate. Solvent was evaporated under reduced pressure and residue was crystallised from solvent. The following compounds were prepared according to this general procedure with the quantities given.

1. **Prparation of 1-(2-nitrophenyl)-2-(4-nitrophenyl)ethanone (IV-1)**

   ∝-(2-Nitrobenzoyl)-β-morpholino-4-nitrostyrene : 3.83 g (0.01 mole)

   Dioxane : 50 ml

   5% Hydrochloric acid : 5 ml

   M.P. 135°C (ethanol)

   Yield : 2.40 g (84%)

   IR (Nujol) showed band at 1710 cm^{-1} (-C-)

   PMR ($CDCl_3$) showed signals at δ 4.2 (s, 2H, -CO-CH_2-); 7.2-8.5 (aromatic protons)

   Analysis found: C, 58.78; H, 3.88; N, 9.51.

   Analysis required for $C_{14}H_{10}N_2O_5$: C, 58.74; H, 3.50; N, 9.79.

   Mass spectrum: M^+ 286.

2. **Preparation of 1-(2-nitrophenyl)-2-(2-nitrophenyl)ethanone (IV-2)**

   ∝-(2-Nitrobenzoyl)-β-morpholino-2-nitrostyrene : 3.83 g (0.01 mole)

   Dioxane : 50 ml

   5% Hydrochloric acid : 5 ml

   M.P. 150°C (ethanol)

   Yield : 2.57 g (90%).

IR (Nujol) showed band at 1715 cm^{-1} ($\rangle C=O$)

PMR ($CDCl_3$) showed signals at δ 4.2 (s, 2H, -CO-CH_2-); 7.2-8.6 (aromatic protons).

Analysis found: C, 58.60; H, 3.98; N, 10.10

Analysis required for $C_{14}H_{10}N_2O_5$: C, 58.74; H, 3.50; N, 9.79.

Mass spectrum: M^+ 286.

3. **Preparation of 1-(2-nitro-5-methoxyphenyl)-2-(4-nitrophenyl) ethanone (IV-3).**

α-(2-Nitro-5-methoxybenzoyl)-β-morpholino-4-nitrostyrene: 4.13 g (0.01 mole)

Dioxane 50 ml

5% Hydrochloric acid 5 ml

M.P. 155°C (ethanol)

Yield 2.84 g (90%)

IR (Nujol) showed band at 1720 cm^{-1} ($\rangle C=O$)

PMR ($CDCl_3$) showed signals at δ 4.2 (s, 2H, $-C(=O)-CH_2-$); 3.9 (s, 3H, -O-CH_3); 7.2-8.5 (aromatic protons).

Analysis found: C, 56.45; H, 4.08; N, 9.15.

Analysis required for $C_{15}H_{12}N_2O_6$: C, 56.96; H, 3.80; N, 8.86.

Mass spectrum: M^+ 316.

4. **Preparation of 1-(2-nitro-4,5-dimethoxyphenyl)-2-(4-nitrophenyl) ethanone (IV-4)**

α-(2-Nitro-4,5-dimethoxybenzoyl)-β-morpholino-4-nitrostyrene 4.43 g (0.01 mole)

Dioxane 50 ml

5% Hydrochloric acid 5 ml

M.P. 195°C (ethanol)[89]

Yield : 2.80 g (81%)

IR (Nujol) showed band at 1715 cm^{-1} ($-\overset{O}{\overset{\|}{C}}-$)

PMR ($CDCl_3$) showed signals at δ4.2 (s, 2H, -CO-$\underline{CH_2}$-); 3.9 (s, 6H, (O-$\underline{CH_3}$)$_2$); 7.2-8.4 (aromatic protons).

Analysis found C, 55.10; H, 4.22; N, 8.20

Analysis calculated for $C_{16}H_{14}N_2O_7$: C, 55.49; H, 4.05; N, 8.09.

Mass spectrum: M^+ 346.

5. **Preparation of 1-(2-nitrophenyl)-2-(2-nitro-5-methoxyphenyl)ethanone (IV-5).**

α-(2-Nitrobenzoyl)-β-morpholino-2-nitro-5-methoxystyrene: 4.13 g (0.01 mole)

Dioxane 50 ml

5% Hydrochloric acid 5 ml

M.P. 95°C (ethanol)

Yield : 2.75 g (87%)

IR (Nujol) showed band at 1710 cm^{-1} ($-\overset{O}{\overset{\|}{C}}-$)

PMR ($CDCl_3$) showed signals at δ 3.9 (s, 3H, O-$\underline{CH_3}$); 4.15 (s, 2H, -CO-$\underline{CH_2}$-); 7.2-8.5 (aromatic protons).

Analysis found: C, 56.89; H, 3.89; N, 9.15.

Analysis required for $C_{15}H_{12}N_2O_6$: C, 56.96; H, 3.80; N, 8.86.

Mass spectrum: M^+ 316.

6. **Preparation of 1-(2,4-dinitrophenyl-2-(4-nitrophenyl) ethanone (IV - 6).**

α-(2,4-Dinitrobenzoyl)-β-morpholino-4-nitrostyrene: 4.28 g (0.01 mole)

Dioxane 50 ml

5% Hydrochloric acid 5 ml

M.P. 108°C (ethanol)

Yield : 3.08 g (93%)

IR (Nujol) showed band at 1710 cm^{-1} (>C=O)

PMR ($CDCl_3$) showed signals at δ4.2 (s, 2H, -CO-CH_2-); 7.2-8.8 (aromatic protons).

Analysis found: C, 50.30; H, 2.45, N, 12.20

Analysis required for $C_{14}H_9N_3O_7$: C, 50.76; H, 2.72; N, 12.69.

Mass spectrum: M^+ 331.

7. **Preparation of 1-(phenyl)-2-(4-nitrophenyl)ethanone (IV-7).**

α-(Benzoyl)-β-morpholino-4-nitrostyrene	3.38 g (0.01 mole)
Dioxane	50 ml
5% Hydrochloric acid	5 ml

M.P. 139°C (ethanol)[35]

Yield : 1.50 g (62%)

IR (Nujol) showed band at 1720 cm^{-1} (>C=O)

PMR ($CDCl_3$) showed signals at 4.1 (s, 2H, -CO-CH_2-); 7.2-8.2 (aromatic protons).

Analysis found: C, 69.95; H, 4.40; N, 5.72 ·

Analysis calculated for $C_{14}H_{11}NO_3$: C, 69.7; H, 4.56; N, 5.80 ·

Mass spectrum: M^+ 241.

8. **Preparation of 1-(4-nitrophenyl)-2-(4-nitrophenyl)ethanone (IV-8).**

α-(4-Nitrobenzoyl)-β-morpholino-4-nitrostyrene	3.83 g (0.01 mole)
Dioxane	50 ml
5% Hydrochloric acid	5 ml

M.P. 122°C (ethanol)[35,88]

Yield : 2.69 g (94%)

IR (Nujol) showed band at 1720 cm^{-1} (- $\overset{O}{\overset{\|}{C}}$ -)

PMR ($CDCl_3$) showed signals at δ 4.2 (s, 2H, -$\overset{O}{\overset{\|}{C}}$-$\underline{CH_2}$-), 7.3-8.6 (aromatic protons).

Analysis found C, 58.50; H, 3.30; N, 10.10 ·

Analysis calculated for $C_{14}H_{10}N_2O_5$: C, 58.74; H, 3.50; N, 9.79 ·

Mass spectrum: M^+ 286.

9 **Preparation of 1-(4-nitrophenyl)-2-(2-nitrophenyl)ethanone (IV-9)**

α-(4-Nitrobenzoyl)-β-morpholino-2-nitrostyrene 3.83 g (0.01 mole)

Dioxane 50 ml

5% Hydrochloric acid 5 ml

M.P. 130°C (ethanol)

Yield : 2.72 g (95%)

IR (Nujol) showed peak at 1710 cm^{-1} (- $\overset{O}{\overset{\|}{C}}$ -)

PMR ($CDCl_3$) showed signals at δ 4.2 (s, 2H, -CO-$\underline{CH_2}$-), 7.3-8.5 (aromatic protons).

Analysis found: C, 58.80; H, 3.70; N, 9.40

Analysis required for $C_{14}H_{11}N_2O_5$: C, 58.74; H, 3.50; N, 9.79

Mass spectrum: M^+ 286.

10 **Preparation of 1-(2,4-dinitrophenyl)-2-(2-nitrophenyl)ethanone (IV - 10).**

α-(2,4-Dinitrobenzoyl)-β-morpholino-2-nitrostyrene 4.28 g (0.01 mole)

Dioxane 50 ml

5% Hydrochloric acid 5 ml

M.P. 136°C (ethanol)

Yield : 2.88 g (87%)

IR (Nujol) showed band at 1710 cm^{-1} (>C=O)

PMR ($CDCl_3$) showed signals at δ 4.2 (s, 2H, -CO-CH_2-), 7.3-8.5 (aromatic protons).

Analysis found: C, 50.56; H, 2.90; N, 12.66 ·

Analysis required for $C_{14}H_9N_3O_7$: C, 50.76; H, 2.72; N, 12.69.

Mass spectrum: M^+ 331.

11. Preparation of 1-(2-nitrophenyl)-2-(2,4-dinitrophenyl)ethanone (IV - 11)

α-(2-Nitrobenzoyl)-β-morpholino-2,4-dinitrostyrene	4.28 g (0.01 mole)
Dioxane	50 ml
5% Hydrochloric acid	5 ml

M.P. 142°C (ethanol)

Yield: 2.84 g (86%)

IR (Nujol) showed band at 1715 cm^{-1} (>C=O)

PMR ($CDCl_3$) showed signals at δ 4.2 (s, 2H, -CO-CH_2-); 7.3-8.5 (aromatic protons).

Analysis found: C, 50.30; H, 3.05; N, 12.10

Analysis required for $C_{14}H_9N_3O_7$: C, 50.76; H, 2.72; N, 12.69.

Mass spectrum: M^+ 331.

12. Preparation of 1-(2,4-dinitrophenyl)-2-(2,4-dinitrophenyl)ethanone (IV - 12).

α-(2,4-Dinitrobenzoyl)-β-morpholino-2,4-dinitrostyrene :	4.73 g (0.01 mole)
Dioxane	50 ml
5% Hydrochloric acid	5 ml

M.P. 150°C (ethanol)

Yield : 2.22 g (59%)

IR (Nujol) showed band at 1720 cm^{-1} (>C=O)

PMR ($CDCl_3$) showed signals at δ 4.2 (s, 2H, -CO-CH_2-), 7.3-8.7 (aromatic protons).

Analysis found: C, 44.40; H, 2.30; N, 14.50

Analysis required for $C_{14}H_8N_4O_9$: C, 44.68; H, 2.13; N, 14.89.

Mass spectrum: M^+ 376.

13. Preparation of 1-(2,4-dinitrophenyl)-2-nitro-5-methoxyphenyl)ethanone (IV - 13).

α-(2,4-Dinitrobenzoyl)- β -morpholino-2-nitro-5-methoxystyrene 4.58 g (0.01 mole)

Dioxane 50 ml

5% Hydrochloric acid 5 ml

M.P. 202°C (ethanol)

Yield : 3.21 g (89%)

IR (Nujol) showed band at 1715 cm^{-1} (>C=O)

PMR ($CDCl_3$) showed signals at δ 4.2 (s, 2H, - CO - CH_2-); 3.9 (s, 3.9 (s, 3H, O-CH_3); 7.2-8.5 (aromatic protons).

Analysis found: C, 49.60; H, 2.90; N, 11.40

Analysis required for $C_{15}H_{11}N_3O_8$: C, 49.86; H, 3.04; N, 11.63.

Mass spectrum: M^+ 361.

14. Preparation of 1-(2-nitrophenyl)-2-phenylethanone (IV-14)

This compound was prepared from the following two different starting materials.

i) From α-(2-nitrobenzoyl)-β-morpholinostyrene using the following quantities

α-(2-Nitrobenzoyl)-β-morpholinostyrene	3.38 g (0.01 mole)
Dioxane	50 ml
5% Hydrochloric acid	5 ml

M.P. 73°C (petroleum ether)[37]

Yield : 2.05 g (85%)

ii) From α-(2-nitrobenzoyl)- β -dimethylaminostyrene using the following quantities

α-(2-(nitrobenzoyl)-β-dimethylaminostyrene	2.96 g (0.01 mole)
Dioxane	50 ml
5% Hydrochloric acid	5 ml

Yield : 2.10 g (87%)

IR (Nujol) showed band at 1720 cm^{-1} ($-\overset{O}{\overset{\|}{C}}-$)

PMR ($CDCl_3$) showed signals at δ 4.2 (s, 2H, -CO-$\underline{CH_2}$-)

Analysis found : C, 69.55; H, 4.30; N, 5.40.

Analysis calculated for $C_{14}H_{11}NO_3$: C, 69.70; H, 4.56; N, 5.80

Mass spectrum: M^+ 241.

15. Preparation of 1-(2-nitrophenyl)-2-(3,4-dimethoxyphenyl)ethanone (IV - 15)

α-(2-Nitrobenzoyl)-β-morpholino-3,4-dimethoxystyrene	3.98 g (0.01 mole)
Dioxane	50 ml
5% Hydrochloric acid	5 ml

M.P. 127-28°C (benzene)

Yield : 2.17 g (72%)

IR (Nujol) showed band at 1720 cm^{-1} (>C=O)

PMR ($CDCl_3$) showed signals at δ 3.9 (s, 6H, $(O-CH_3)_2$); 4.2 (s, 2H, $-CO-CH_2-$); 7.1 - 8.4 (aromatic protons).

Analysis found: C, 63.35; H, 4.80; N, 4.38.

Analysis required for $C_{16}H_{15}NO_5$: C, 63.78; H, 4.98; N, 4.65 ·

Mass spectrum : M^+ 301.

16. Preparation of 1-(2-nitrophenyl)-2-(4-methylphenyl)ethanone (IV-16)

α-(2-Nitrobenzoyl)-β-dimethylamino-4-methylstyrene: 3.10 g (0.01 mole)

Dioxane	50 ml
5% Hydrochloric acid	5 ml

M.P. 61°C (carbon tetrachloride)[1]

Yield : 1.78 g (70%).

IR (Nujol) showed band at 1715 cm^{-1} (>C=O)

PMR ($CDCl_3$) showed signals at δ 2.2 (s, 3H, $-CH_3$), 4.2 (s, 2H, $-COCH_2-$), 7.2-8.4 (aromatic protons).

Analysis found: C, 70.44; H, 4.80; N, 5.30

Analysis calculated for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.09; N, 5.49.

Mass spectrum: M^+ 255.

Step-4 : Preparation of substituted 2-arylisatogens V

These compounds were prepared by two different general methods, using different starting materials.

General Method A:

Hydrolysis and cyclodehydration of α-(2-nitrobenzoyl)-β-dialkylamino styrene III to 2-arylisatogens (V)

In a 100 ml round bottom flask, α-(2-nitrobenzoyl)-β-dialkylamino-styrene (0.005 mole) was dissolved in a mixture of 9.2 ml water, 3.6 ml

methanol, 2.4 ml acetic acid, 2.4 g sodium acetate (buffer, pH 5.5) and was refluxed on water bath for 4 - 5 hr, until the starting material spot disappeared from the reaction mixture (monitored by TLC, benzene: ethyl acetate (80:20) mixture as solvent). Solvent was removed under reduced pressure. Solid separated was filtered, washed with water, dried and crystallized from solvent.

General Method B:

Cyclodehydration of 1-(2-nitroaryl)-2-(aryl)ethanones IV to 2-arylisatogens V

1-(2-Nitroaryl)-2-(aryl)-ethanone (0.005 mole) was dissolved in 25 ml of ethanol, to that sodium acetate (1.64 g, 0.02 mole) in water (5 ml) was added and mixture was refluxed for 4 hr, until the starting material spot disappeared from the reaction mixture (monitored by TLC, benzene : ethyl acetate (80:20) mixture as solvent). After completion of the reaction, solvent was removed under reduced pressure, solid separated was filtered, washed with water, dried and crystallized from solvent.

The following compounds were prepared according to the General Methods A & B, with the quantities given.

UV and Visible Spectra of these compounds were taken in spectroscopic grade methanol. Due to insufficient solubility of these compounds in methanol, absorption (ϵ values) were not taken.

1. Preparation of 2-(4-nitrophenyl)isatogen (V-1)

Method A:

α-(2-Nitrobenzoyl)-β-morpholino-4-nitrostyrene 1.915 g (0.005 mole)

M.P. 254°C (acetone)[89]

Yield : 1.19 g (89%)

Method B:

1-(2-Nitrophenyl)-2-(4-nitrophenyl)ethanone 1.43 g (0.005 mole)

Sodium acetate 1.64 g (.02 mole)

Ethanol 25 ml

Yield : 1.23 g (92%)

IR (Nujol) showed bands at 1715 cm^{-1} (C=O) and 1175 cm^{-1} (N→O)

PMR ($CDCl_3$) showed aromatic protons at δ 7.2-8.5

Analysis found: C, 62.38; H, 3.49; N, 10.66

Analysis calculated for $C_{14}H_8N_2O_4$: C, 62.67; H, 2.99; N, 10.45

UV & Visible Spectra - λ_{max} 415 nm

Mass spectrum: M^+ 268.

1 **Preparation of 2-(2-nitrophenyl)isatogen (V-2)**

Method A:

α-(2-Nitrobenzoyl)-β-morpholino-2-nitrostyrene 1.915 g (0.005 mole)

Crystallised from acetone[90]

M.P. 202°C

Yield 1.20 g (90%).

Method B:

1-(2-Nitrophenyl)-2-(2-nitrophenyl)ethanone 1.43 g (.005 mole)

Sodium acetate 1.64 g (0.02 mole)

Ethanol 25 ml

Yield : 1.20 g (90%)

IR (Nujol) showed bands at 1715 cm^{-1} (C = O), 1180 cm^{-1} (N→O)

PMR ($CDCl_3$) showed signals at δ 7.3 - 8.5 (aromatic protons).

Analysis found: C, 62.67; H, 3.46; N, 10.70.

Analysis calculated for $C_{14}H_8N_2O_4$: C, 62.67; H, 2.99; N, 10.45.

UV & Visible Spectra: λ_{max} 410 nm

Mass spectum: M^+ 268.

3. Preparation of 2-(4-nitrophenyl)-5-methoxyisatogens (V-3)

Method A:

α-(2-Nitro-5-methoxybenzoyl)- β-morpholino-4-nitrostyrene 2.065 g (0.005 mole)

This compound was crystallized from acetone.

M.P. 205°C

Yield : 1.27 g (85%)

Method B:

1-(2-Nitro-5-methoxyphenyl)-2-(4-nitrophenyl)ethanone 1.58 g (0.005 mole)

Sodium acetate 1.64 g (0.02 mole)

Ethanol 25 ml

Yield : 1.39 g (93%)

IR (Nujol) showed bands at 1710 cm^{-1} (C = O) and 1175 cm^{-1} (N→O)

PMR ($CDCl_3$) showed signals at δ3.9 (s, 3H, -O$\underline{CH_3}$) and 7.2 - 8.5 (aromatic protons).

Analysis found: C, 60.60; H, 3.47; N, 9.01.

Analysis required for $C_{15}H_{10}N_2O_5$: C, 60.40; H, 3.36; N, 9.39.

UV & Visible spectra: λ_{max} 478-491 nm

Mass spectrum : M^+ 298.

4. Prepartion of 2-(4-nitrophenyl)-5,6-dimethoxyisatogen (V-4)

Method A:

-(2-Nitro-5-methoxybenzoyl)- -morpholino-4-nitrostyrene: 2.215 g (0.005 mole)

This compound was crystallized from ethanol.[89]

M.P. 255°C

Yield : 0.98 g (60%)

Method B:

1-(2-Nitro-4,5-dimethoxyphenyl)-2-(4-nitrophenyl)ethanone :

1.73 g (0.005 mole)

Sodium acetate 1.64 g (0.02 mole)

Ethanol 25 ml

Yield : 1.38 g (84%)

IR (Nujol) showed bands at 1712 cm^{-1} (C = O) and 1170 cm^{-1} (N→O).

PMR ($CDCl_3$) showed signals at δ3.9 (s, 6H ($-OC\underline{H}_3)_2$) and 7.2-8.5 (aromatic protons).

Analysis found: C, 58.30; H, 3.60; N, 8.66 .

Analysis calculated for $C_{16}H_{12}N_2O_6$: C, 58.54; H, 3.66; N, 8.53 .

UV & Visible Spectra : λ_{max} 330-334 nm

Mass spectrum: M^+ 328.

5. **Preparation of 2-(2-nitro-5-methoxyphenyl)isatogen (V-5)**

Method A:

α-(2-Nitrobenzoyl)-β-morpholino-2-nitro-5-methoxystyrene:

2.065 g (0.005 moles)

This compound was crystallized from methanol

M.P. 105°C

Yield 0.625 g (42%)

Method B:

1-(2-Nitrophenyl)-2-(2-nitro-5-methoxyphenyl)ethanone

1.58 g (0.005 mole)

Sodium acetate	1.64 g (0.02 mole)
Ethanol	25 ml

Yield : 1.37 g (92%)

IR (Nujol) showed bands at 1715 cm^{-1} ($\geq C = O$) and 1180 cm^{-1} ($N \rightarrow O$)

PMR ($CDCl_3$) showed signals at δ 3.9 (s, 3H, $-OC\underline{H}_3$); 7.3 - 8.9 (aromatic protons)

Analysis found: C, 60.35; H, 3.62; N, 9.42.

Analysis required for $C_{15}H_{10}N_2O_5$: C, 60.40; H, 3.36; N, 9.39.

UV & Visible Spectra: λ_{max} 420-422 nm

Mass spectrum: M^+ 298.

6. Preparation of 2-phenylisatogen (V-6)

Method A:

Two different starting materials were used to prepare this compound.

1) α-(2-Nitrobenzoyl)-β-morpholinostyrene	1.69 g(0.005 mole)

Yield : 0.82 g (74%)

M.P. 140°C (ethanol) [37]

2) α-(2-Nitrobenzoyl)-β-dimethylaminostyrene	1.48 g (0.005 mole)
Sodium acetate	1.64 g
Ethanol	25 ml

Yield : 0.870 g (78%)

Method B:

1-(2-Nitrophenyl)-2-phenylethanone	1.205 g (0.005 mole)
Sodium acetate	1.64 g (0.02 mole)
Ethanol	25 ml

Yield : 0.90 g (81%)

IR (Nujol) showed bands at 1710 cm^{-1} (C = O) and 1175 cm^{-1} (N→O)

PMR ($CDCl_3$) showed signals at δ 7.0-8.2 (aromatic protons).

Analysis found: C, 74.90; H, 4.20; N, 6.15.

Analysis calculated for $C_{14}H_9NO_2$: C, 75.33; H, 4.04; N, 6.28.

UV & Visible Spectra: λ_{max} 435-438 nm

Mass spectrum: M^+ 223.

7. Preparation of 2-(3,4-dimethoxyphenyl)isatogen (V-7)

Method A:

α(2-Nitrobenzoyl)-β-morpholino-3,4-dimethoxystyrene	1.99 (0.005 mole)

This compound was crystallized from ethanol - acetic acid.[1,89]

M.P. 226°C

Yield : 0.76 g (54%)

Method B:

1-(2-Nitrophenyl)-2-(3,4-dimethoxyphenyl)ethanone	1.505 g (0.005 mole)
Sodium acetate	1.64 g (0.02 mole)
Ethanol	25 ml

Yield : 1.13 g (80%)

IR (Nujol) showed bands at 1715 cm^{-1} (⁻C = O) and 1178 cm^{-1} (N→O)

PMR ($CDCl_3$) showed signals at δ 3.9 (s, 6H $(-OC\underline{H}_3)_2$) and 7.1 to 8.2 (aromatic protons).

Analysis found: C, 67.60; H, 4.80; N, 5.10.

Analysis required for $C_{16}H_{13}NO_4$: C, 67.84; H, 4.59; N, 4.95.

Mass spectrum: M^+ 283.

8. Preparation of 2-(4-methylphenyl)isatogen (V-8)

Method A:

α-(2-Nitrobenzoyl)-β-dimethylamino-4-methylstyrene 1.55 g (0.005 mole)

This compound was crystallized from acetone

M.P. 206°C

Yield : 0.85 g (72%)

Method B:

1-(2-Nitrophenyl)-2-(4-methylphenyl)ethanone	1.275 (0.005 mole)
Sodium acetate	1.64 g (0.02 mole)
Ethanol	25 ml

Yield : 1.00 g (84%)

IR showed bands at 1710 cm^{-1} ($\geq C = O$) and 1170 cm^{-1} ($N \rightarrow O$)

PMR ($CDCl_3$) showed signals at δ 2.2 (s, 3H, $-CH_3$) and 7.2-8.3 (aromatic protons).

Analysis found C, 76.20; H, 4.80; N, 5.65.

Analysis calculated for $C_{15}H_{11}NO_2$: C, 75.95; H, 4.64; N, 5.90

UV & Visible Spectra: λ_{max} 448 nm

Mass spectrum: M^+ 237.

Attempted Synthesis of 2-(p-Tosyl)Isatogen:

1. Preparation of enamine of p-toluenesulfonamide (VII)

In a 50 ml round bottom flask, p-toluenesulfonamide (8.55 g, 0.05 mole) and trimorpholinomethane (20.3 g, 0.075 mole) were placed and heated at 130°C under stirring for 4 hr, using water aspirator vacuum to remove morpholine. Reaction mixture was cooled to room temperature,

solid separated was filtered and crystallized from benzene.

M.P. 173-74°C

Yield : 9.11 g (68%)

IR (Nujol) showed bands at 1625 cm^{-1}, ($\rangle N - CH = N - SO_2$), 1305 cm^{-1}, 1150 cm^{-1} ($-SO_2-$).

PMR ($CDCl_3$) showed signals at δ 2.3 (s, 3H, $-CH_3$); 3.4 (t, 4H, 4H, $-N(CH_2)_2$); 3.6 (t, 4H, $O(CH_2)_2$); 7.15 and 7.75 (aromatic p-disubstituted pattern); 8.1 (s, 1H, $-N=CH-N\langle$).

Analysis found: C, 53.58; H, 6.31; N, 10.27; S, 12.15

Analysis required for $C_{12}H_{16}N_2O_3S$: C, 53.73; H, 5.97; N, 10.44; S, 11.94.

Mass spectrum: M^+ 268.

2. **Preparation of p-tosylethenyl morpholine (IX)**

In a 50 ml round bottom flask, methyl p-toluenesulfonate (8.6 g, 0.05 mole) and trimorpholinomethane (20.3 g, 0.075 mole) were placed and heated at 130°C under stirring for 4 hr, using water aspirator vacuum to remove morpholine. Reaction mixture was cooled, solid separated was collected by filtration and crystallized from ethanol.

M.P. 128°C

Yield : 8.74 g (65.5 %)

IR (Nujol) showed bands at 1605 cm^{-1} ($\rangle N-CH=CH-SO_2$), 1310 cm^{-1}, 1125 cm^{-1} ($-SO_2-$)

PMR ($CDCl_3$) showed signals at δ 2.3 (s, 3H, CH_3); 3.1 (t, 4H, $-N(CH_2)_2$); 3.6 (t, 4H, $O(CH_2)_2$); 4.9 (d, 1H, J = 14Hz, $H\rangle C = CH - N\langle$), 6.9 - 7.6 ($H\rangle C = CH - N\langle$ and aromatic protons).

Analysis found: C, 57.95; H, 6.32; N, 4.87; S, 12.30.

Analysis required for $C_{13}H_{17}NO_3S$: C, 58.42; H, 6.37; N, 5.24; S, 11.99.

Mass spectrum: $M^{\ddagger}$ 267.

3. Preparation of 2-(2-nitrobenzoyl)-2-(p-tosyl)ethenylmorpholine (X)

To the stirred solution of p-tosylethenylmorpholine (5.34 g, 0.02 mole) and triethylamine (2.01 g, 0.02 mole) in dry benzene (50 ml), was added dropwise 2-nitrobenzoyl chloride (3.71 g, 0.02 mole) in benzene (10 ml). After completion of addition, the mixture was refluxed under stirring for 15 hr. Solid separated was collected by filtration, washed with water and crystallized from ethanol.

M.P. 214-215°C

Yield : 7.0 g (85%)

IR (Nujol) showed bands at 1605 cm^{-1} ($\geq N - CH = CH - \overset{O}{\overset{\|}{C}}-$), 1330 cm^{-1}, 1155 cm^{-1} ($-SO_2-$).

PMR ($CDCl_3$) showed signals at δ 2.3 (s, 3H, $-CH_3$), 3.6 (broad singlet, 4H, $-N(CH_2)_2$): 3.8 (broad singlet, 4H, $-O(CH_2)$; 6.8-7.8 ($-C = C\overset{\diagdown N \diagup}{\underset{H}{}}$ and aromatic protons).

Analysis found: C, 60.31; H, 4.68; N, 7.20; S, 8.31.

Analysis required for $C_{20}H_{20}N_2O_6S$: C, 57.69; H, 4.8 ; N, 6.73; S, 7.69.

Mass spectrum: $M^{\ddagger}$ 416.

4. Preparation of 1-(2-nitrophenyl)-2-(p-tosyl)ethanone (XI)

In a 100 ml round bottom flask, 2-(2-nitrobenzoyl)-2-(p-tosyl)ethenyl-morpholine X, (4.16 g, 0.01 mole) dissolved in a mixture of dioxane

(50 ml), 5% hydrochloric acid (5 ml) and was refluxed for 4 hr. Solvent evaporated under reduced pressure. Solid obtained was filtered, washed with water and crystallized from benzene.

M.P. 150°C

Yield : 2.42 g (76%)

IR (Nujol) showd bands at 1640 cm^{-1} (-C(=O)-), 1320 cm^{-1}, 1140 cm^{-1} ($-SO_2-$)

PMR ($CDCl_3$) showed signals at δ 2.4 (s, 3H, CH_3), 3.9 (s, 2H, -C(=O)-CH_2-), 7.1-7.8 (aromatic protons).

Analysis found: C, 56.18; H, 3.92; N, 4.61; S, 14.08.

Analysis required for $C_{15}H_{13}NO_5S$: C, 56.43; H, 4.08; N, 4.39; S, 10.03.

Mass spectrum: $M^{+\cdot}$ 319.

Same compound XI was prepared from sodium p-toluenesulfinate and ω-Bromo-2-nitroacetophenone as follows.

Sodium p-toluenesulfinate 1.78 g (0.01 mole) and ω-bromo-2-nitroacetophenone were added in absolute methanol (20 ml) and was refluxed for 4 hr, cooled and poured in 100 ml water, extracted in ether (3 x 20 ml). Ether layer was dried over anhydrous sodium sulfate, solvent evaporated and residue was purified over silica gel chromatography, using benzene : petroleum ether (1:1) mixture as an eluate.

Yield : 1.28 g (40%)

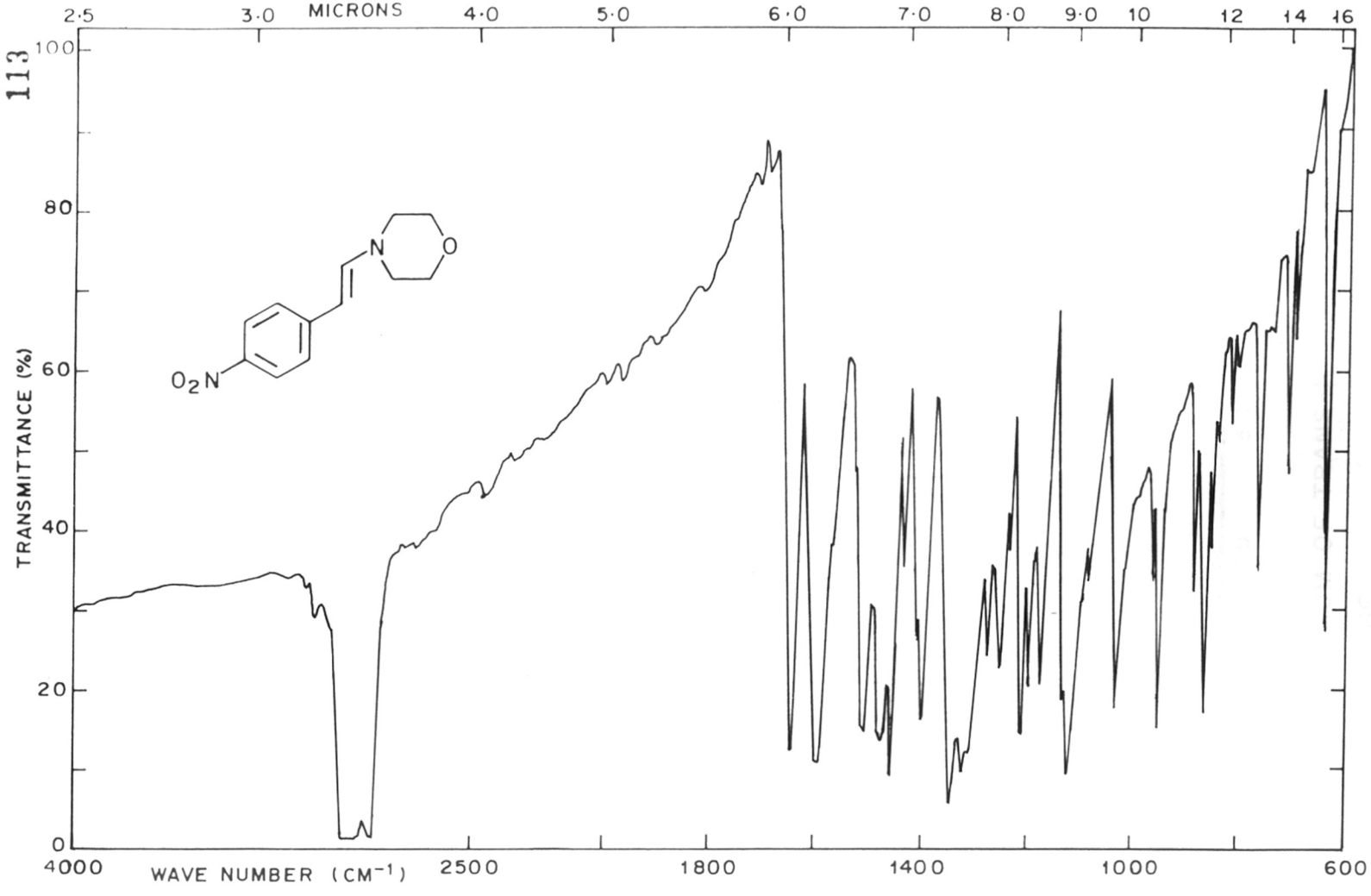


FIG. 2·1. IR SPECTRUM OF TRANS-β-MORPHOLINO-4-NITROSTYRENE

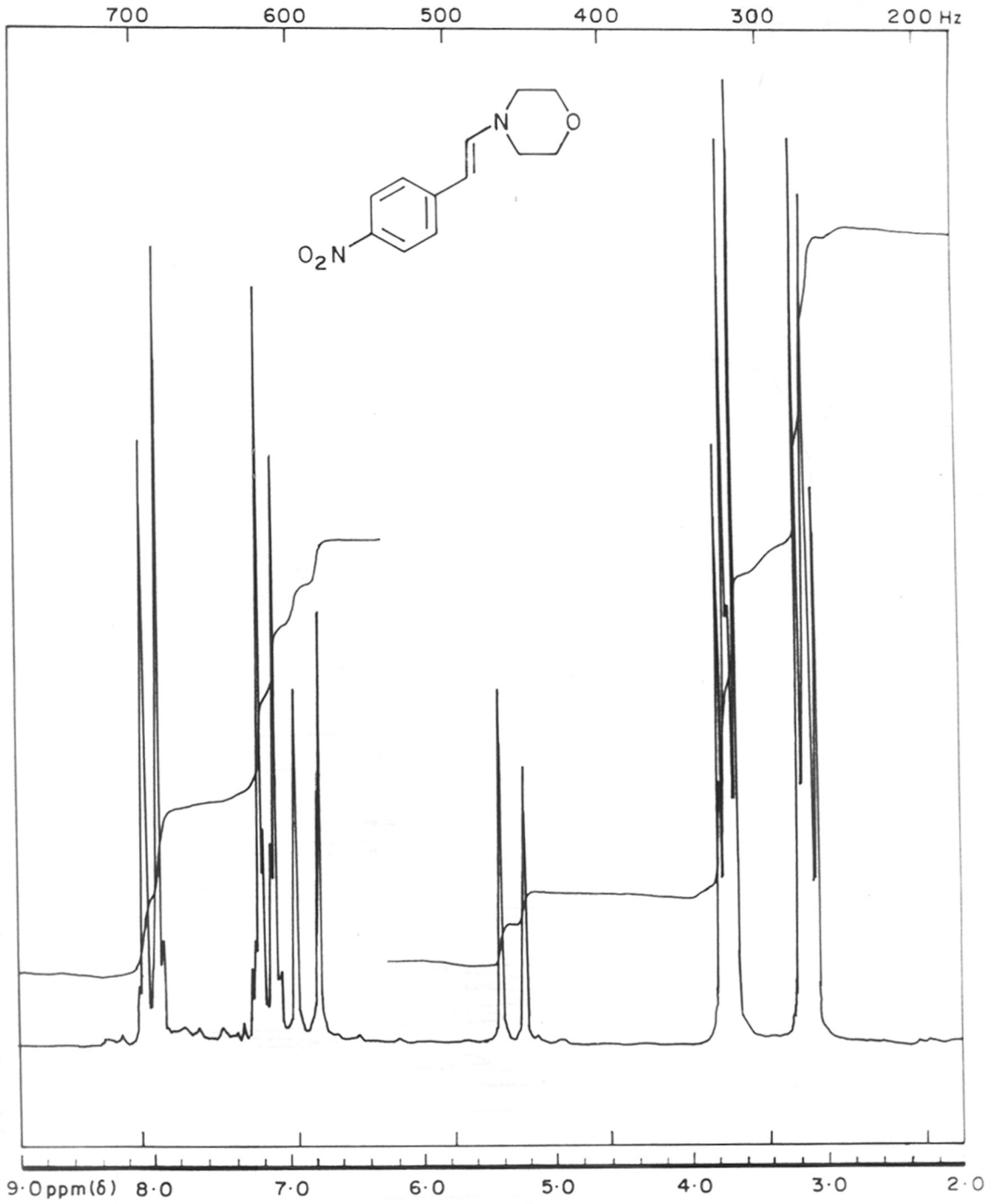


FIG. 2·2. PMR SPECTRUM OF TRANS-β-MORPHOLINE-4-NITROSTYRENE

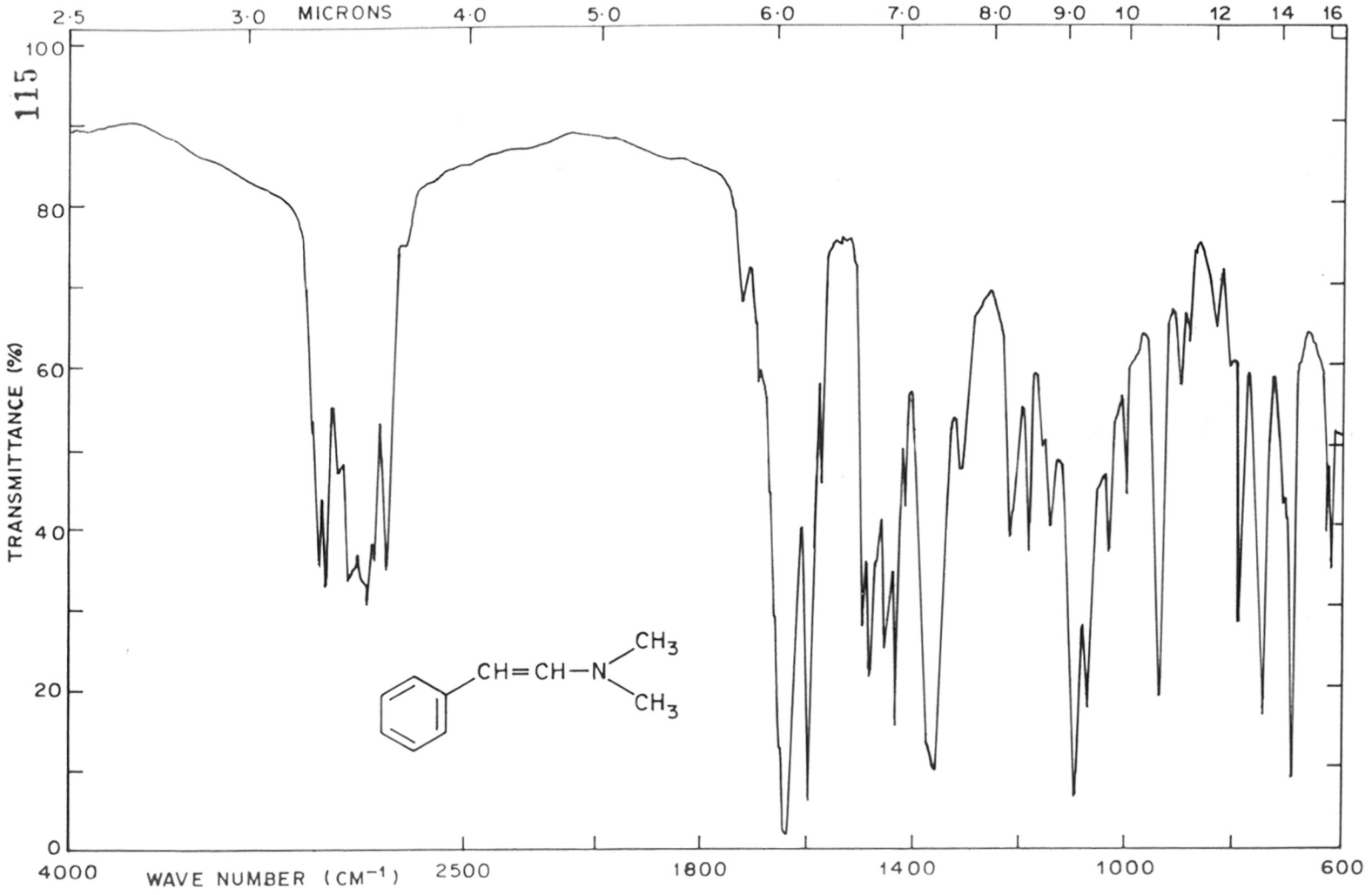


FIG. 2·3. IR SPECTRUM OF TRANS-β-DIMETHYLAMINOSTYRENE

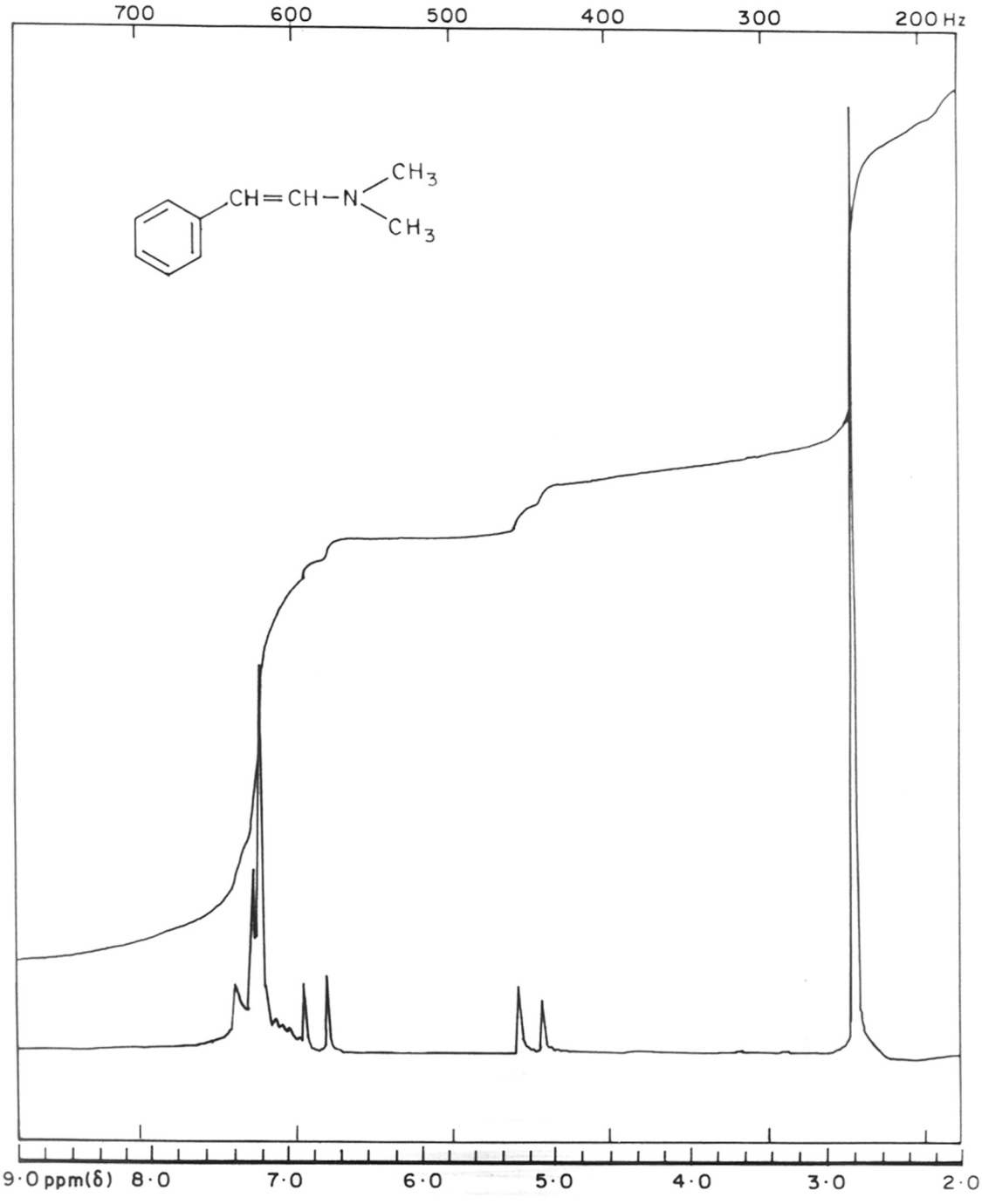


FIG. 2·4. PMR SPECTRUM OF TRANS–β–DIMETHYLAMINOSTYRENE

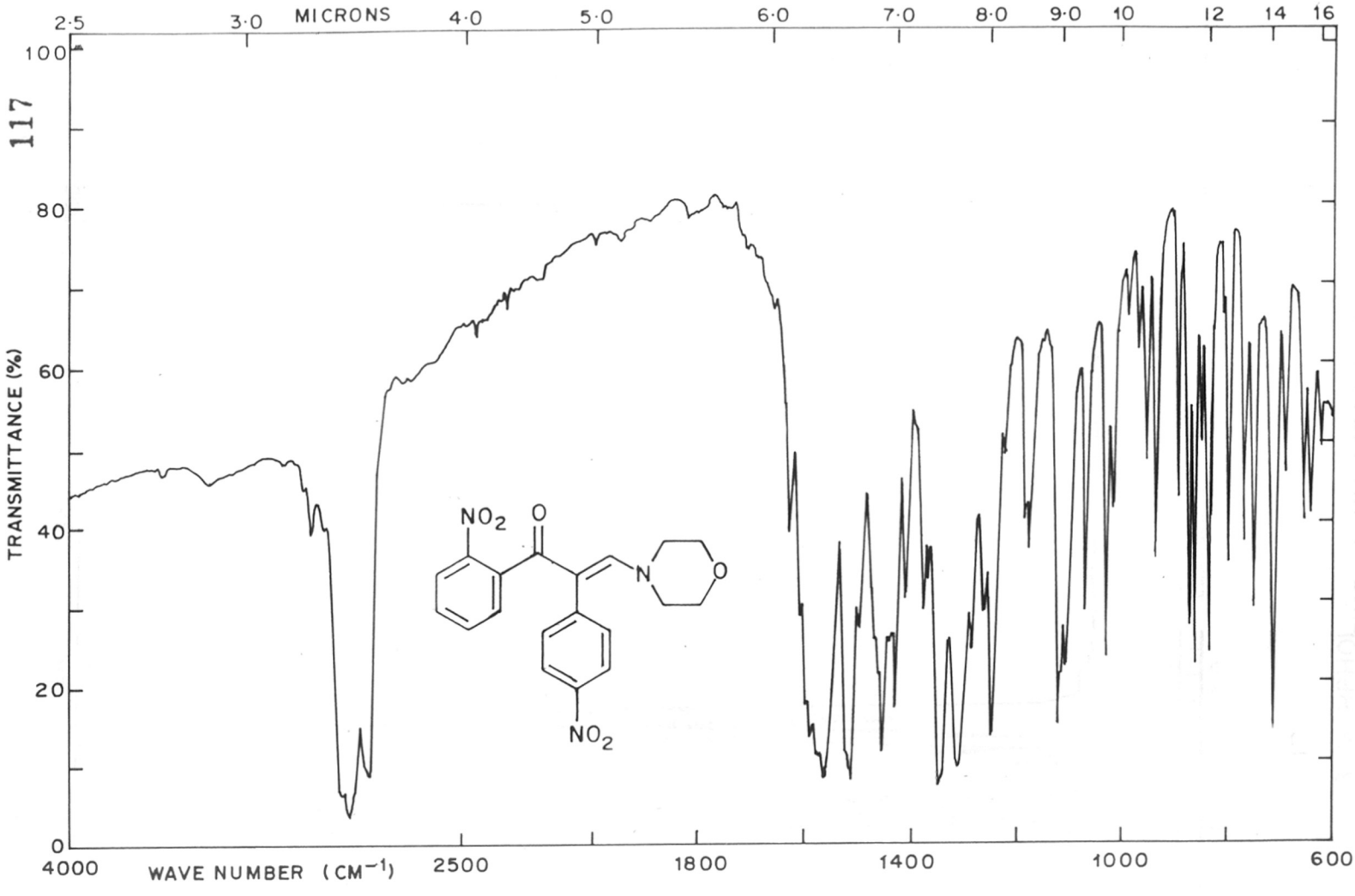


FIG. 2·5. IR SPECTRUM OF α-(2-NITROBENZOYL) β-MORPHOLINO-4-NITROSTYRENE

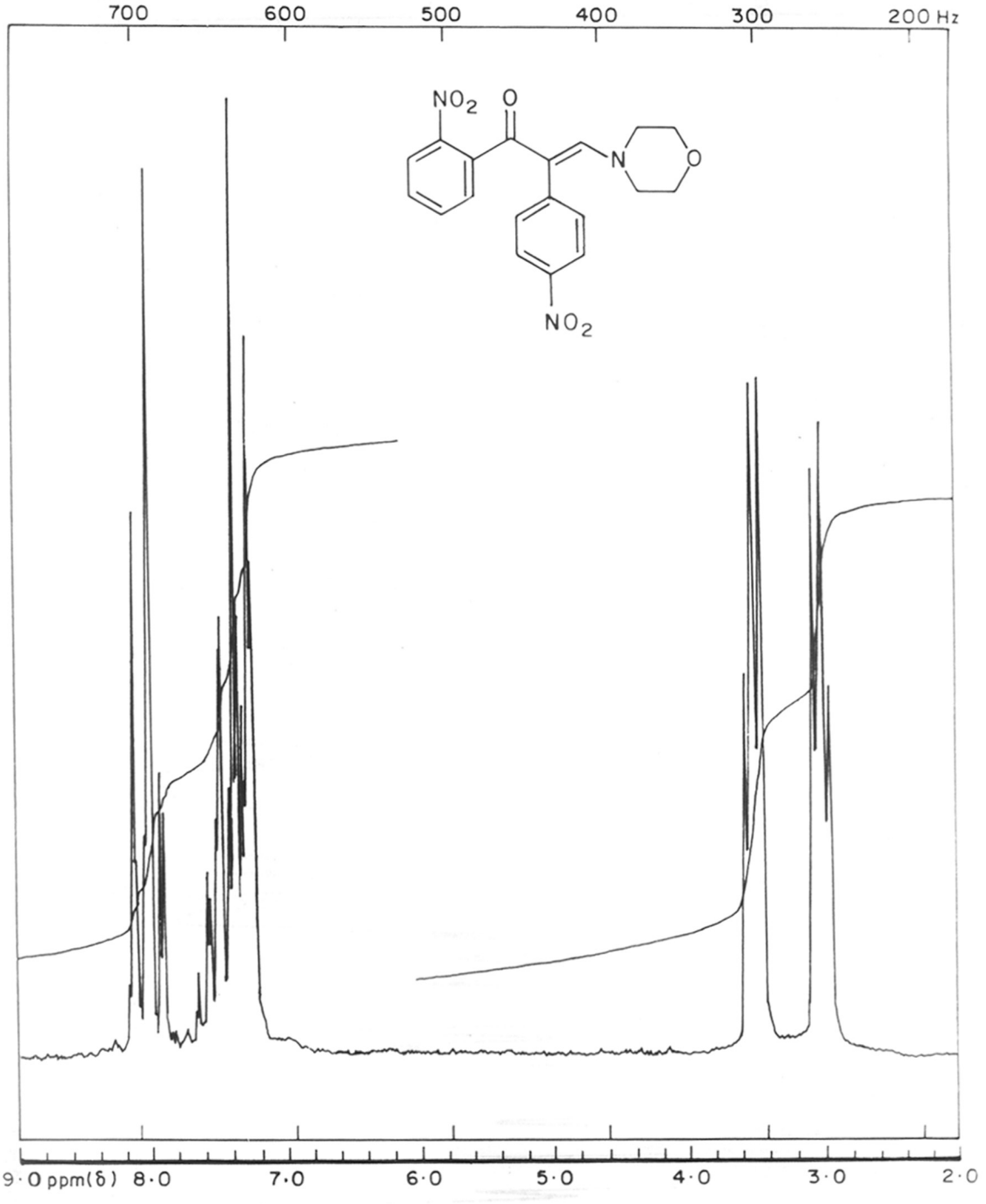


FIG. 2·6. PMR SPECTRUM OF α-(2-NITROBENZOYL) β-MORPHOLINO-4-NITROSTYRENE

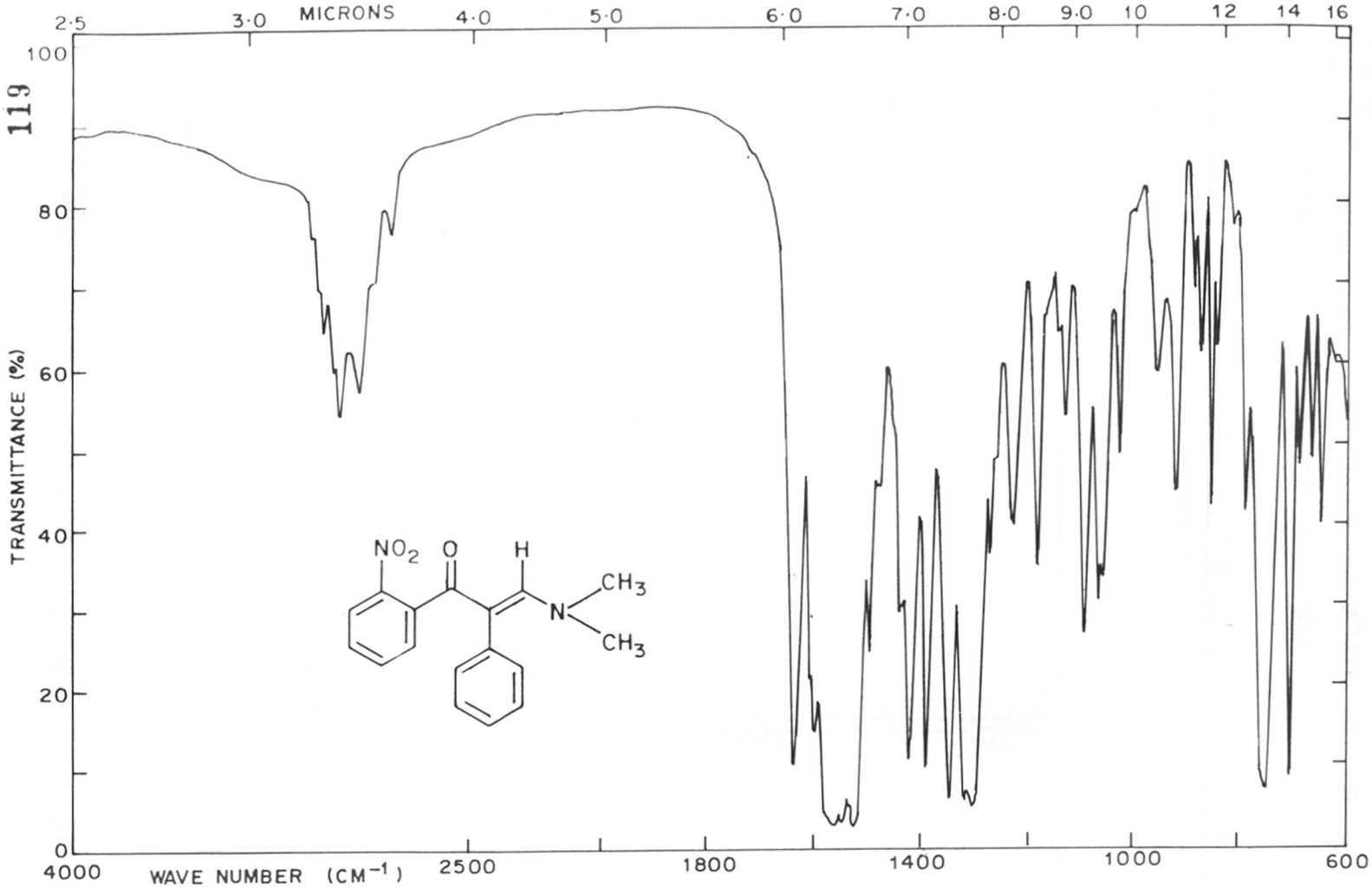


FIG. 2·7. IR SPECTRUM OF α-(2-NITROBENZOYL) β-DIMETHYLAMINOSTYRENE

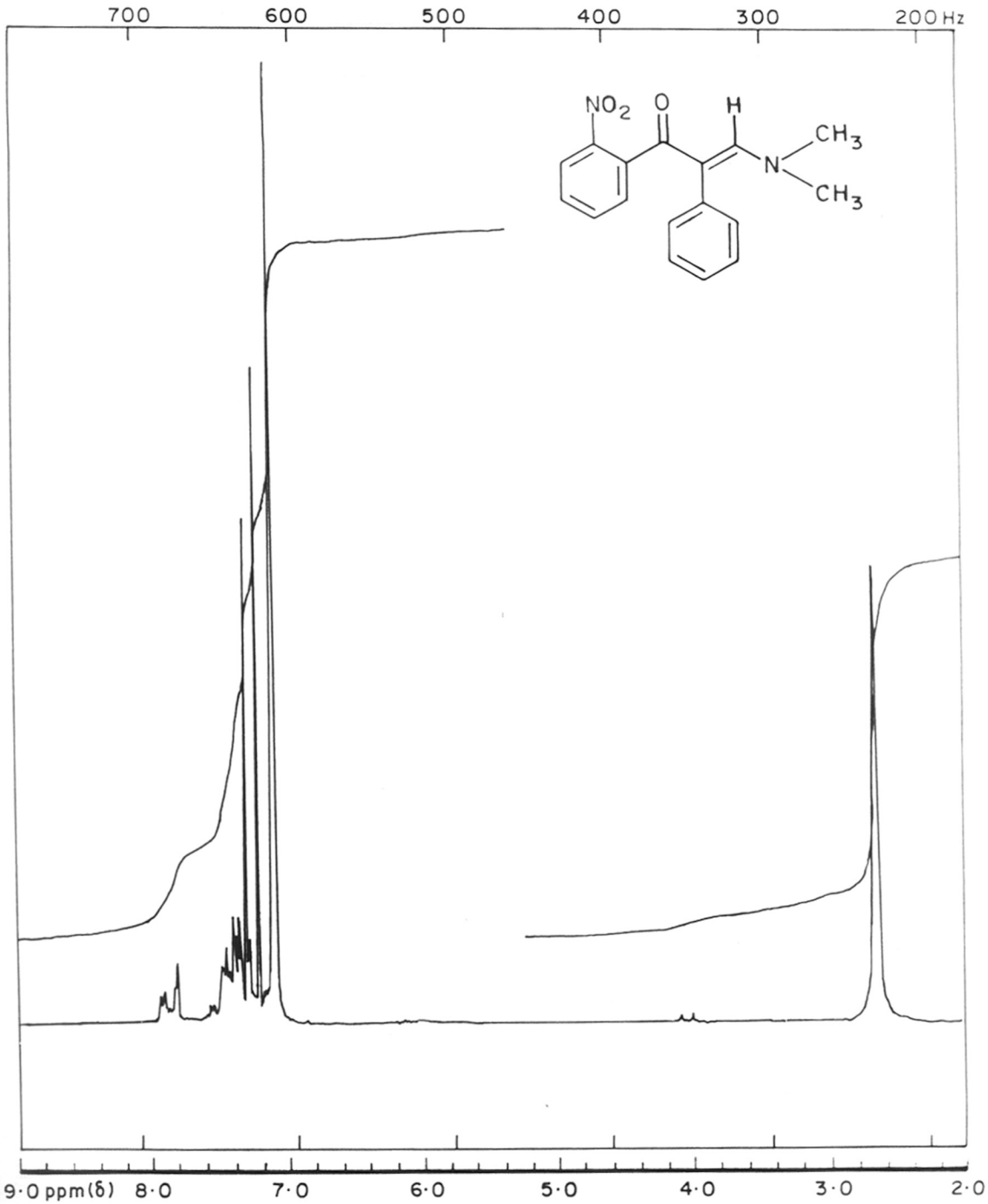


FIG. 2·8 PMR SPECTRUM OF α-(2-NITROBENZOYL) β-DIMETHYLAMINOSTYRENE

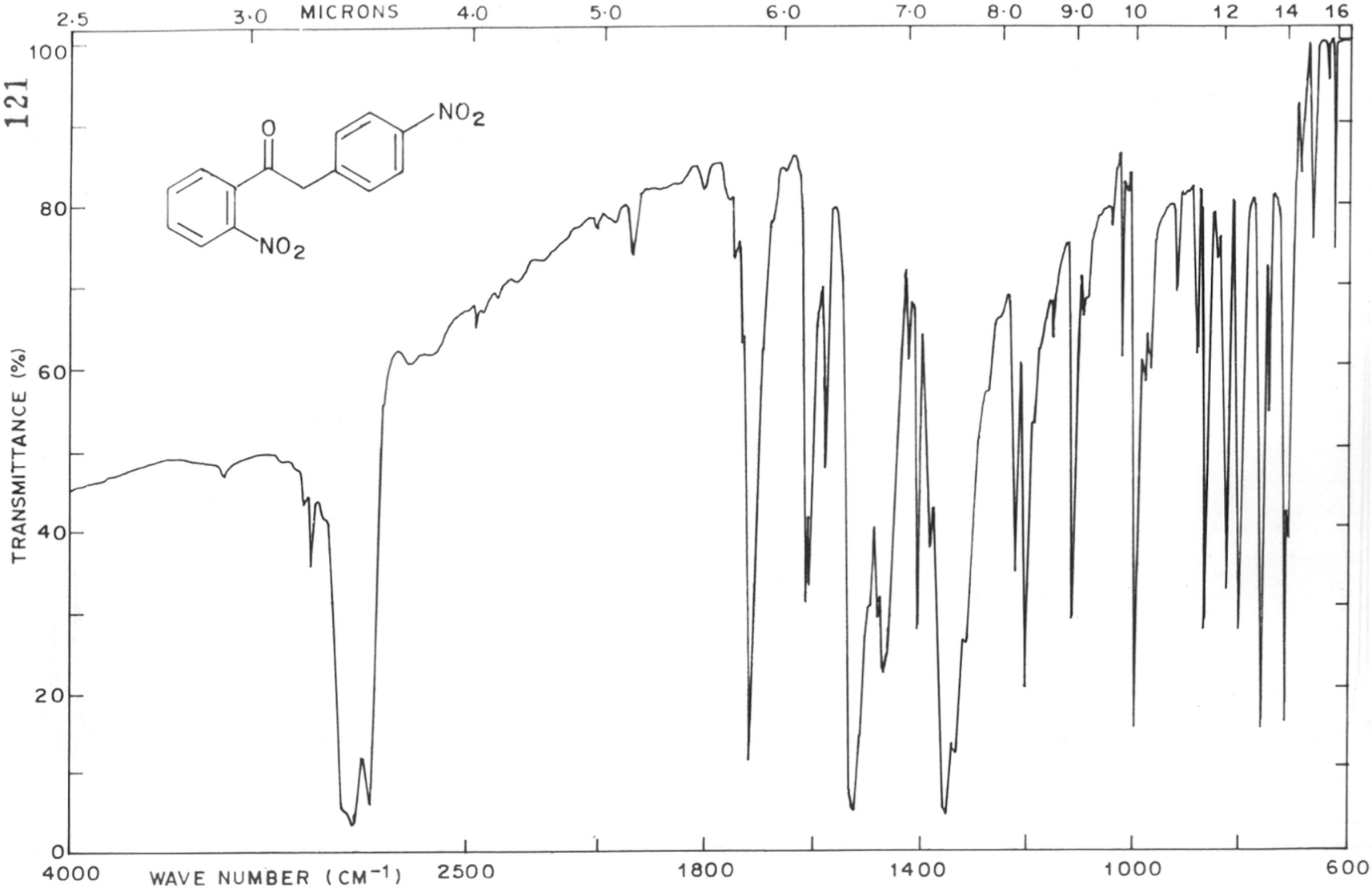


FIG. 2·9. IR SPECTRUM OF 1-(2-NITROPHENYL)-2-(4-NITROPHENYL) ETHANONE

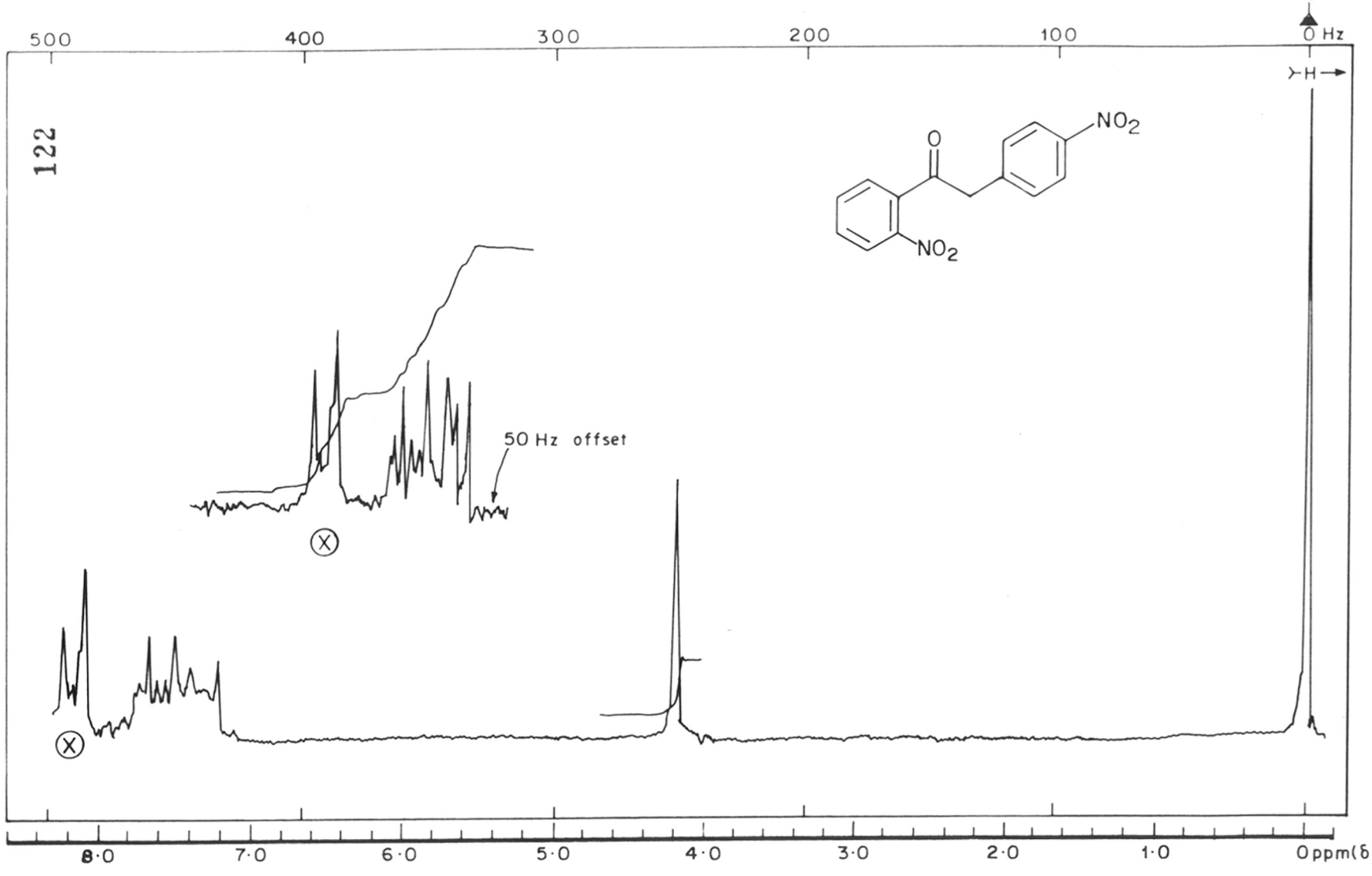


FIG. 2·10. PMR SPECTRUM OF 1-(2-NITROPHENYL)-2-(4-NITROPHENYL) ETHANONE

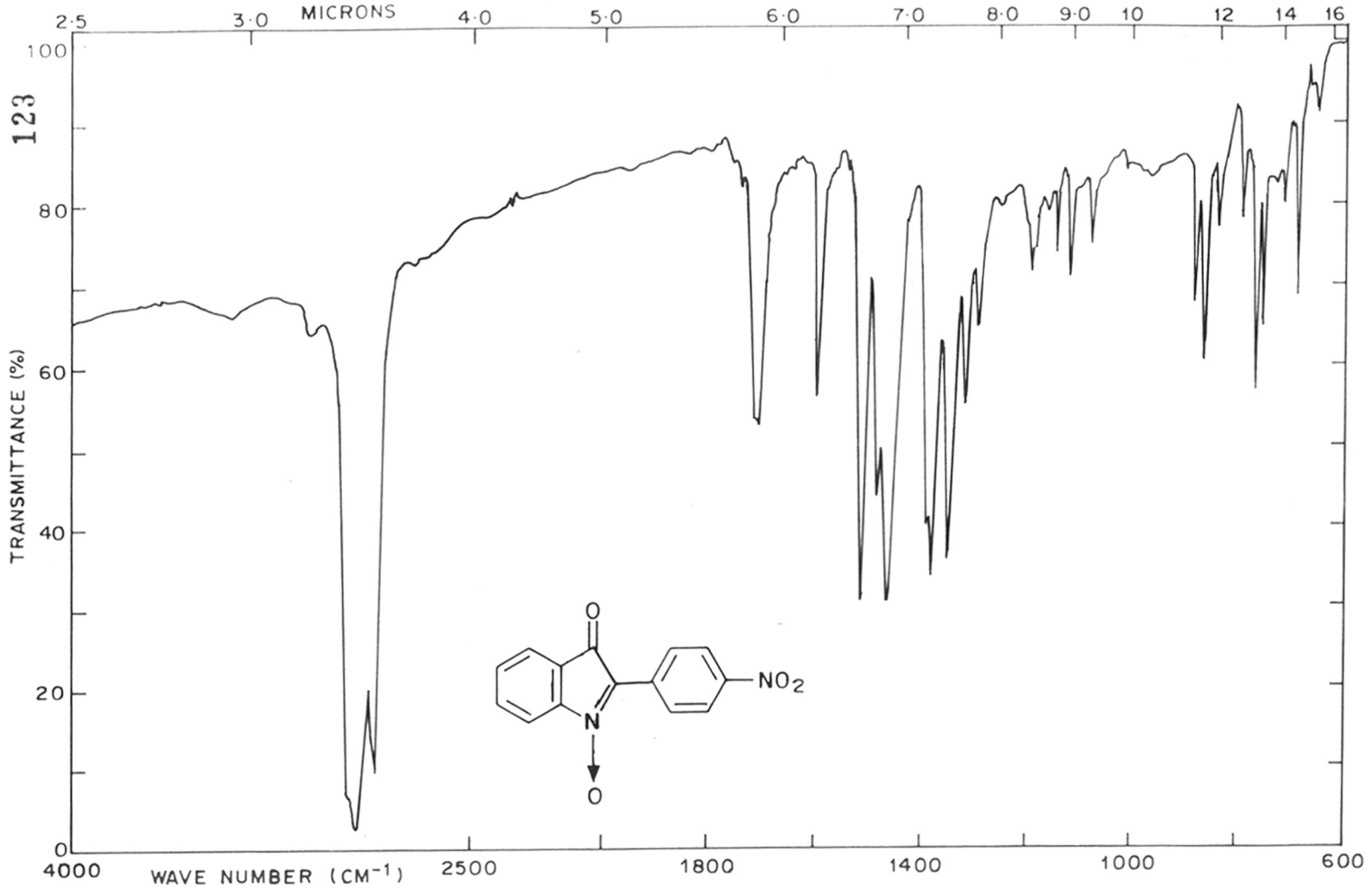


FIG. 2·11· IR SPECTRUM OF 2-(4-NITROPHENYL) ISATOGEN

CHAPTER-II, PART-B

SYNTHESIS OF NITRO SUBSTITUTED ALKYL PHENYL KETONES

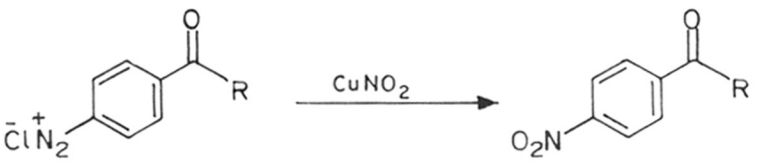
Introduction:

The literature survey revealed that only a few nitro-ketones were prepared mainly by the nitration of corresponding ketones.[79,80] The well-known Grignard reaction is also of limited application because of its interference with nitro group in an aromatic nucleus.

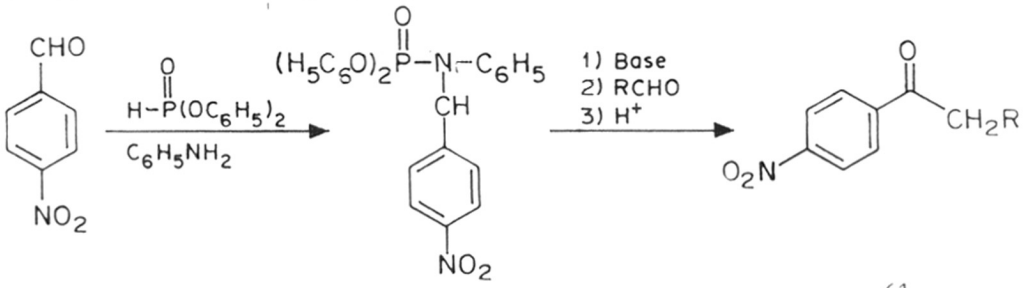
The o-nitrophenyl alkyl ketones and their substituted derivatives have found immense use as the starting as well as intermediate compounds in the field of dyes, drugs and heterocyclic compounds.

Ordinary aldehydes cannot be acylated at the ∝-position in the presence of base due to the self condensation and hence the enamines are ideal for such acylation reactions. Nitration of simple alkyl phenyl ketones always gives a mixture, the separation of which is rather tedious. Further, it has not been possible to obtain alkyl p-nitrophenyl ketones by this route. The other methods[81] available for the preparation of alkyl p-nitrophenyl ketones involve:

(i) Diazotisation of p-aminophenyl alkyl ketones followed by replacement of diazo group by treatment with cuprous nitrite.

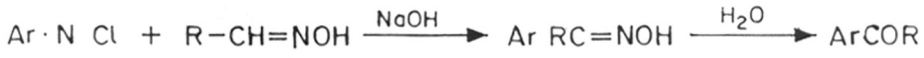


(ii) Use of Schiff bases of nitrosubstituted benzaldehydes, diphenyl phosphites and aliphatic aldehydes.[82] However, other methods cannot be applied when o-nitro group is present.



Some time back our earlier workers developed a direct method[61] employing dialkyl cadmium and o-nitrobenzoyl chloride. The yields however were moderate.

Some of the methods, which are used for the preparation of alkyl phenyl ketones cannot be used where there is nitro substituent, such as Friedel-Crafts reaction and distillation of calcium salt of aromatic acids. The only method which is useful is the Beech method which consists of reaction of aryldiazonium salts with oximes of aliphatic aldehydes.



Present Investigation:

o-Nitrobutyrophenone, a plant growth regulator[83] and p-nitro isobutyrophenone, which is a planned intermediate for the synthesis of ibuprofen, prompted us to prepare nitro-substituted alkyl phenyl ketones.

A general method for the synthesis of nitro-substituted alkyl phenyl ketones has been reported here (Scheme-19) using enamine acylation reactions. The method involves the acylation of morpholine enamines of aliphatic aldehydes with nitro-substituted benzoyl chlorides in the presence of triethylamine.

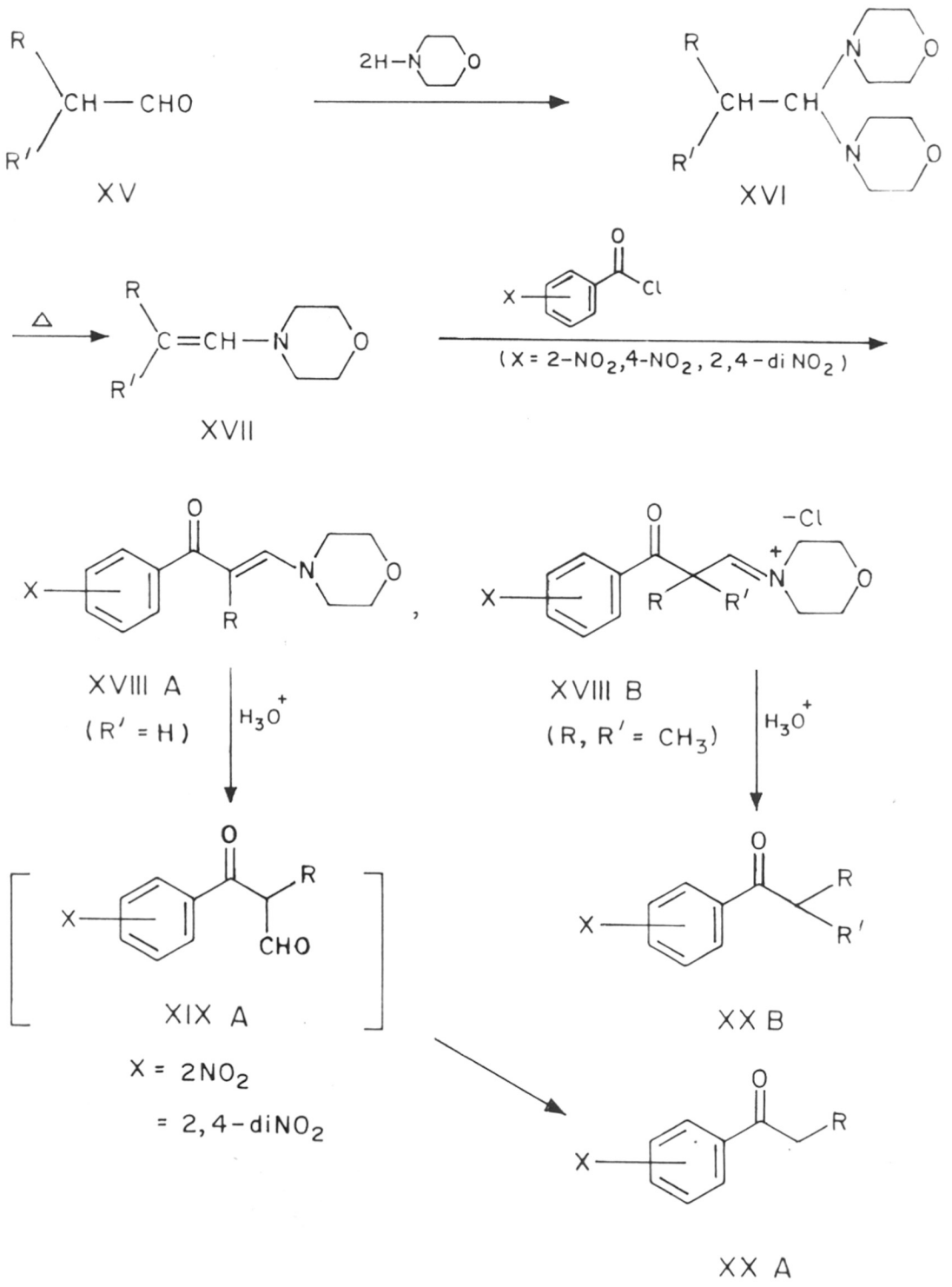
Morpholine enamine of aliphatic aldehydes were prepared by Davidsen's[84] method i.e. one mole of aliphatic aldehyde and two moles of morpholine were reacted in presence of anhydrous potassium carbonate at room temperature for 8 hours. The diamine formed, was decomposed during vacuum distillation to get enamine (XVII) (Scheme-20).

These enamines showed characteristic band in IR at 1650-1660 cm^{-1}. The PMR spectrum of isobutyraldehyde enamine showed β-proton at 5.4 δ, while in case of butyraldehyde enamine β-proton was shown at 5.3 δ (d, J = 14Hz) and the α-proton at 4.0 δ as multiplet. The hexaldehyde enamine showed β-proton at δ 5.6 (d, J = 14Hz) and α-proton at 4.15 δ as multiplet.

Attempts to acylate aliphatic aldehyde enamines with nitrobenzoyl chlorides at room temperature resulted in poor yields of acylated enamines. Hence, addition of nitrobenzoyl chlorides to the solution

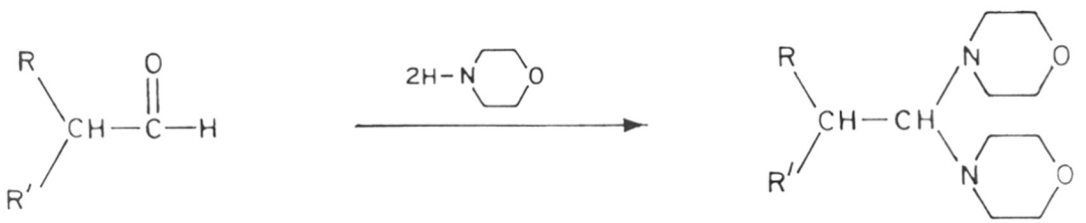
SCHEME - 19

PREPARATION OF NITRO SUBSTITUTED ALKYL PHENYL KETONES

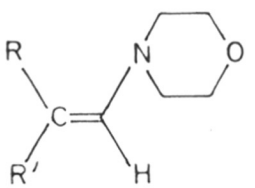


SCHEME-20

PREPARATION OF MORPHOLINOENAMINES OF ALIPHATIC ALDEHYDES (1-MORPHOLINOALKENES)



XV XVI

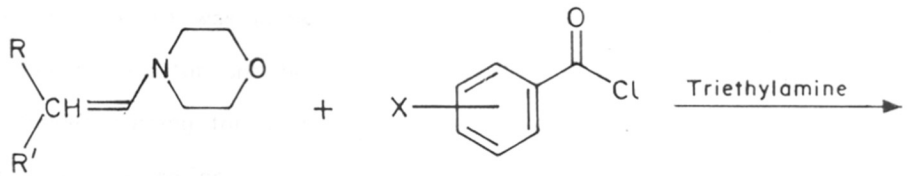


XVII – 1

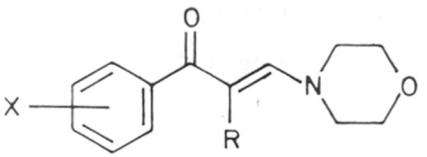
Comp. No	R	R′
XVII-1	CH_3	CH_3
XVII-2	C_2H_5	H
XVII-3	C_4H_9	H

SCHEME-21

PREPARATION OF 1-MORPHOLINO-2-(NITROBENZOYL) ALKENES

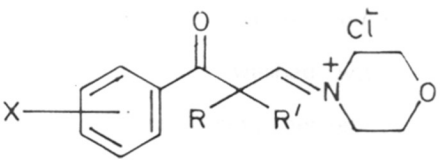


XVII



XVIII A

(When R′ = H in comp. XVII)



XVIII B

(When R′ = CH_3 in comp. XVII)

Comp No.	X	R	R′
XVIII B-1	2-NO_2	CH_3	CH_3
XVIII B-2	4-NO_2	CH_3	CH_3
XVIII B-3	2, 4 di-NO_2	CH_3	CH_3
XVIII A-4	2-NO_2	C_2H_5	No substituent
XVIII A-5	4-NO_2	C_2H_5	,,
XVIII A-6	2, 4 di-NO_2	C_2H_5	,,
XVIII A-7	2-NO_2	C_4H_9	,,
XVIII A-8	4-NO_2	,,	,,
XVIII A-9	2, 4 di-NO_2	,,	,,

of enamine was carried out at 0°C. After completion of addition, the reaction mixture was allowed to come to room temperature and was further stirred for one hour at room temperature. Then it was refluxed under stirring for 8 hours. The reaction mixture was cooled to room temperature and the acylated enamines (XVIIIA) in case of solids were filtered and washed with sufficient amount of water to remove the hydrochloride salt of triethylamine, and in case of liquid (XVIIIA) acylated enamines, the benzene solution was washed with water and chromatographed over silica gel column, using benzene: pet. ether as an eluant. In the case of acylated products of isobutyraldehyde enamine, the crude acylated products (XVIIIB) were subjected to hydrolysis directly.

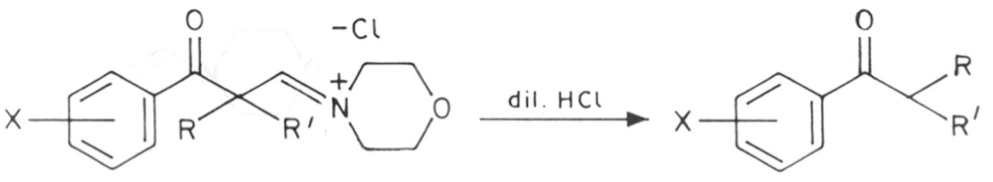
The acylated enamines (XVIIIA) showed absence of α-proton in PMR and exhibited IR band at 1620 - 1640 cm^{-1}.

The acylated enamines were hydrolysed with dilute hydrochloric acid in dioxane. After completion of the reaction, solvent was removed under reduced pressure and the residue was extracted in ethyl acetate, washed with water. Evaporation of ethyl acetate gave nitro-substituted alkyl phenyl ketones (XX).

Solid alkyl phenyl ketones were purified by crystallization, whereas liquids were either distilled under reduced pressure or were purified by chromatography over silica gel. However, in case of 2-nitro and 2,4-dinitro-substituted enamines (XVIIIA), the hydrolysis gave β-keto-aldehydes (XIXA) as major products as judged by their elemental analysis

SCHEME – 22

HYDROLYSIS OF MORPHOLINIUM SALTS (XVIII B) TO ALKYL PHENYL KETONES (XX B)

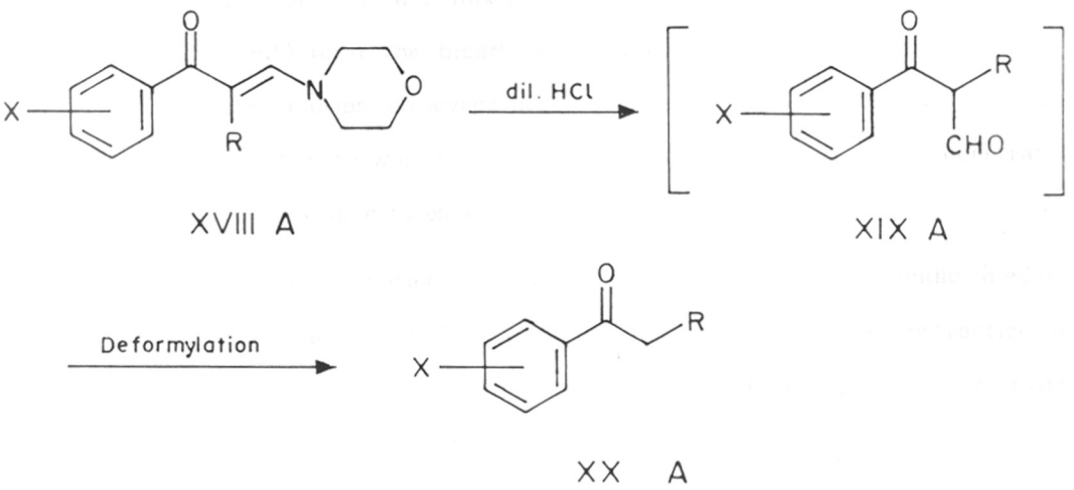


XVIII B XX B

Comp No.	X	R	R'
XX B-1	2-NO_2	CH_3	CH_3
XX B-2	4-NO_2	CH_3	CH_3
XX B-3	2, 4 di-NO_2	CH_3	CH_3

SCHEME-23

HYDROLYSIS OF 1-MORPHOLINO-2-(NITROBENZOYL) ALKENES TO ALKYL PHENYL KETONES VIA β-KETOALDEHYDES



XVIII A

XIX A

XX A

Comp. No.	X	R
XIX A-1	2-NO_2	C_2H_5
XIX A-2	2,4 di- NO_2	C_2H_5
XIX A-3	2-NO_2	C_4H_9
XIX A-4	2,4 di-NO_2	C_4H_9
XX A-4	4-NO_2	C_2H_5
XX A-5	4-NO_2	C_4H_9
XX A-6	2-NO_2	C_2H_5
XX A-7	2,4 di-NO_2	C_2H_5
XX A-8	2-NO_2	C_4H_9
XX A-9	2,4 dl-NO_2	C_4H_9

and mass spectral data ($M^{+\cdot}$). The β-ketoaldehydes (XIXA) were separated from the reaction mixture by thoroughly shaking the ethyl acetate solution of reaction mixture with sodium bicarbonate solution (pH 7.5 - 8.5) until the bicarbonate washings were colourless. The ethyl acetate solution on evaporation gave alkyl phenyl ketones (XXA) and the bicarbonate washings were combined and acidified with concentrated hydrochloric acid to obtain β-ketoaldehydes (XIXA).

The formation of β-ketoaldehydes (XIXA) in acidic medium in the presence of 2-nitro group may be due to the interaction of nitro group with enolic form of (XIXA). However, β-ketoaldehydes (XIXA) were directly converted to alkyl phenyl ketones (XXA) by sodium acetate hydrolysis. Hydrolysis of (XVIIIA) including 2-nitro derivatives with sodium acetate gave directly alkyl phenyl ketones (XXA), but the yields obtained were poor.

The IR spectra of alkyl phenyl ketones showed characteristic peak of >C = O at 1710 - 1720 cm^{-1}.

Conclusion:

The literature methods of preparation of nitro-substituted alkyl phenyl ketones have their own limitations. The method established in the present investigation, viz., by acylation of aliphatic aldehyde enamines with nitro-substituted benzoyl chlorides, is a general method, with a considerable improvement in yields. This method can be extended for the synthesis of various substituted alkyl phenyl ketones.

EXPERIMENTAL

PART B: Synthesis of Nitro Substituted Alkyl Phenyl Ketones

This involves the following steps:

Step 1: Preparation of 1-Morpholinoalkenes (XVII)

Step-2: Preparation of 1-Morpholino-2-(nitrobenzoyl)alkenes (XVIII) (Acylation of 1-Morpholinoalkenes with Nitrobenzoyl Chlorides)

Step-3: Hydrolysis of 1-Morpholino-2-(nitrobenzoyl)alkenes (XVIIIA) to 3-(Nitrophenyl)-3-oxo-2-alkyl-1-propanals (XIXA, β-Ketoaldehydes) and alkyl phenyl ketones (XX).

Step-4: Preparation of alkyl phenyl ketones (XXA) from 3-(Nitrophenyl)-3-oxo-2-alkyl-1-propanals (XIXA).

Step-1: **Preparation of 1-Morpholinoalkenes (XVII)**

General Procedure:

To the stirred solution of aliphatic aldehyde (1 mole) and anhydrous potassium carbonate (20 g) in 500 ml round bottom flask, was added dropwise at 0°C, morpholine (2 moles) over 30 minutes. After completion of addition, the mixture was allowed to come to the room temperature and stirred further for 8 hr. Potassium carbonate was removed by filtration and filtrate was distilled under reduced pressure.

The following compounds were prepared according to this general method with the quantities given.

1. **Preparation of 1-morpholino-2-methyl-prop-1-ene (XVII-1)**

Isobutyraldehyde	72 g (1 mole)
Anhydrous potassium carbonate	20 g
Morpholine	174 g (2 mole)

Distilled at 90-91°C/100 mm

Yield : 100 g (71%)

IR (Neat) showd band at 1650 cm^{-1} ($>C = CH-N<$)

PMR (CCl_4) showed signals at δ 2.6 (t, 4H, $-N(\underline{CH_2})_2$); 3.5 (t, 4H, $O(\underline{CH_2})_2$); 5.4 (s, 1H, $>C = C<^{N}_{\underline{H}}$).

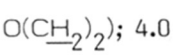
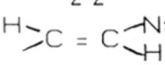
2. **Preparation of 1-morpholino-but-1-ene (XVII-2)**

Butyraldehyde	72 g (1 mole)
Anhydrous potassium carbonate	20 g
Morpholine	174 g (2 mole)

Distilled at 95.100°/95 mm.

Yield : 90.2 g (64%)

IR (Neat) showed band at 1640 cm^{-1} (-CH = CH - N<)

PMR (CCl_4) showed signals at δ 2.6 (t, 4H, -N($\underline{CH_2}$)$_2$); 3.5 (t, 4H, O($\underline{CH_2}$)$_2$); 4.0 (m, 1H, ); 5.3 (d, 1H, J = 14Hz, )

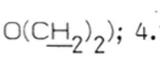
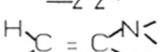
3. **Preparation of 1-morpholino-hex-1-ene (XVII-3)**

n-Hexaldehyde	100 g (1 mole)
Anhydrous potassium carbonate	20 g
Morpholine	174 g (2 mole)

Distilled at 145-50°/25 mm

Yield : 138.6 g (82%)

IR (Neat) showed band at 1660 cm^{-1} (-CH = CH - N<)

PMR (CCl_4) showed signals at δ 2.5 (t, 4H, N($\underline{CH_2}$)$_2$); 3.5 (t, 4H, O($\underline{CH_2}$)$_2$); 4.15 (m, 1H, ); 5.6 (d, 1H, J = 14Hz, ).

Step-2: **Preparation of 1-Morpholino-2-(nitrobenzoyl)alkenes (XVIII)**

General Procedure:

In a three necked 250 ml round bottom flask, fitted with dropping funnel and reflux condensor with $CaCl_2$ guard tube, was taken a mixture of 1-morpholinoalkene (XVII) (0.05 mole) and triethylamine (0.05 mole) in dry benzene (50 ml). To the stirred solution of enamine at 0°C was added dropwise a solution of nitrobenzoyl chloride (0.05 mole) in dry benzene (15 ml). After completion of addition, the reaction mixture was allowed to come to room temperature and was further stirred for 1 hour at room temperature. It was refluxed under stirring

for 8 hours. Half of the solvent was removed under reduced pressure and reaction mixture was cooled to room temperature. The acylated compounds (XVIII), in case of solids, were collected by filtration, washed with sufficient amount of water to remove the triethylammonium hydrochloride salt, while in case of liquids, the benzene solution was washed thoroughly with water, dried over anhydrous sodium sulfate, Solvent was removed under reduced pressure and compound was purified by silica gel chromatography. The acylated compounds obtained from isobutyraldehyde enamines were directly hydrolysed to alkyl phenyl ketones without isolating the acylated compounds.

The following compounds were prepared according to this general procedure with the quantities given.

1. **Preparation of morpholinium salt by acylation of 1-morpholino-2-methyl-prop-1-ene with 2-nitrobenzoyl chloride (XVIII B-1)**

1-Morpholino-2-methyl-prop-1-ene	7.05 g (0.05 mole)
Triethylamine	5.05 g (0.05 mole)
2-Nitrobenzoyl chloride	9.28 g (0.05 mole)

This compound without purification was used for the next step of acid hydrolysis.

2. **Preparation of morpholinium salt by acylation of 1-morpholino-2-methyl-prop-1-ene with 4-nitrobenzoyl chloride (XVIII B-2)**

1-Morpholino-2-methyl-prop-1-ene	7.05 g (0.05 mole)
Triethylamine	5.05 g (0.05 mole)
4-Nitrobenzoyl chloride	9.28 g (0.05 mole)

This compound without purification was used for the next step of acid hydrolysis.

3. **Preparation of morpholinium salt by acylation of 1-morpholino-2-methyl-prop-1-ene with 2,4-dinitrobenzoyl chloride (XVIII B-3)**

1-Morpholino-2-methyl-prop-1ene	7.05 g (0.05 mole)
Triethylamine	5.05 g (0.05 mole)
2,4-Dinitrobenzoyl chloride	11.53 g (0.05 mole)

This compound without purification was used for the next step of acid hydrolysis.

4. **Preparation of 1-morpholino-2-(2-nitrobenzoyl)-but-1-ene (XVIIIA-4)**

1-Morpholino-but-1-ene	7.05 g (0.05 mole)
Triethylamine	5.05 g (0.05 mole)
2-Nitrobenzoyl chloride	9.28 g (0.05 mole)

This compound was purified over silica gel chromatography (1:40 ratio), using benzene : petroleum ether (1:1) mixture as an eluate.

Yield 9.86 g (68%)

IR (Neat) showed band at 1620 cm^{-1} (-C(=O)-  -N<)

PMR (CCl_4) showed signals at δ 3.4 (t, 4H, $-N(\underline{CH_2})_2$); 3.7 (t, 4H, $O(\underline{CH_2})_2$); 1.1 (t, 3H, $-\underline{CH_3}$); 2.73 (q, 2H, $-\underline{CH_2}-$); 6.5 (s, 1H, $-C=C(N<)\underline{H}$); 7.3-8.2 (aromatic protons).

Analysis found: C, 62.15; H, 6.55; N, 9.65.

Analysis required for $C_{15}H_{18}N_2O_4$: C, 62.07; H, 6.2; N, 9.66.

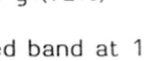
Mass spectrum: $M^{\ddagger}$ 290.

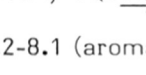
5. **Preparation of 1-morpholino-2-(4-nitrobenzoyl)-but-1-ene (XVIIIA-5)**

1-Morpholino-but-1-ene	7.05 g (0.05 mole)
Triethylamine	5.05 g (0.05 mole)
4-Nitrobenzoyl chloride	9.28 g (0.05 mole)

M.P. 201-202°C (benzene)

Yield : 10.44 g (72%)

IR (Nujol) showed band at 1620 ()

PMR ($CDCl_3$) showed signals at δ 1.05 (t, 3H, $-\underline{CH_3}$); 2.7 (q, 2H, $-\underline{CH_2}-$); 3.4 (t, 4H, $N(\underline{CH_2})_2$); 3.7 (t, 4H, $O(\underline{CH_2})_2$); 6.6 (s, 1H, ); 7.2-8.1 (aromatic protons).

Analysis found: C, 62.2; H, 6.4; N, 9.8

Analysis required for $C_{15}H_{18}N_2O_4$: C, 62.07; H, 6.2; N, 9.66.

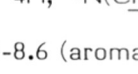
6. **Preparation of 1-morpholino-2-(2,4-dinitrobenzoyl)-but-1-ene (XVIIIA-6)**

1-Morpholino-but-1-ene	7.05 (0.05 mole)
Triethylamine	5.05 g (0.005 mole)
2,4-Dinitrobenzoyl chloride	11.53 g (0.005 mole)

M.P. 153-54°C (methanol-acetone)

Yield: 11.22 g (67%)

IR (Nujol) showed band at 1630 cm^{-1} ()

PMR ($CDCl_3$) showed signals at δ 1.1 (t, 3H, $-\underline{CH_3}$), 2.75 (q, 2H, $-\underline{CH_2}-$), 3.4 (t, 4H, $-N(\underline{CH_2})_2$), 3.7 (t, 4H, $O(\underline{CH_2})_2$), 6.6 (s, 1H, ), 7.3-8.6 (aromatic protons)

Analysis found: C, 53.2; H, 5.3; N, 12.6

Analysis reuired for $C_{15}H_{17}N_3O_6$: C, 53.73; H, 5.75; N, 12.53.

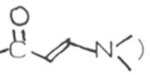
Mass spectrum: M^+ 335.

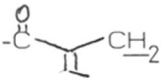
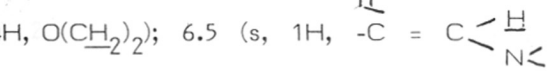
7. **Preparation of 1-morpholino-2-(2-nitrobenzoyl)-hex-1-ene (XVIIIA-7)**

1-Morpholino-hex-1-ene	8.45 g (0.05 mole)
Triethylamine	5.05 g (0.05 mole)
2-Nitrobenzoyl chloride	9.28 g (0.05 mole)

M.P. 96°C (carbon tetrachloride - petroleum ether)

Yield: 10.33 g (65%)

IR (Nujol) showed band at 1620 cm^{-1} ()

PMR ($CDCl_3$) showed signals at δ 0.95 (broad, 3H, $-\underline{CH_3}$); 1.45 (m, 4H, $-\underline{CH_2}-\underline{CH_2}-CH_3$); 2.5 (broad, 2H, ); 3.3 (t, 4H, $N(\underline{CH_2})_2$); 3.6 (t, 4H, $O(\underline{CH_2})_2$); 6.5 (s, 1H, ); 7.0-8.1 (aromatic protons).

Analysis found: C, 64.0; H, 6.5; N, 8.9.

Analysis required for $C_{17}H_{22}N_2O_4$: C, 64.15; H, 6.91; N, 8.8.

Mass spectrum: M^+ 318.

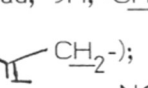
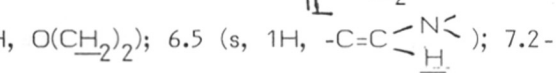
8. Preparation of 1-morpholino-2-(4-nitrobenzoyl)-hex-1-ene (XVIIIA-8)

1-Morpholino-hex-1-ene	8.45 g (0.05 mole)
Triethylamine	5.05 g (0.05 mole)
4-Nitrobenzoyl chloride	9.28 g (0.05 mole)

This compound was purified over silica gel chromatography, using benzene:pet. ether (1:1) mixture as an eluate.

Yield: 8.90 g (56%)

IR (Neat) showed band at 1620 cm^{-1} ()

PMR ($CDCl_3$) showed signals at δ 0.9 (broad, 3H, $-\underline{CH_3}$); 1.4 (m, 4H, $-\underline{CH_2}-\underline{CH_2}-CH_3$), 2.5 (broad, 2H, ); 3.3 (t, 4H, $-N(\underline{CH_2})_2$); 3.6 (t, 4H, $O(\underline{CH_2})_2$); 6.5 (s, 1H, ); 7.2-8.2 (aromatic protons).

9. Preparation of 1-morpholino-2-(2,4-dinitrobenzoyl)-hex-1-ene (XVIIA-9)

1-Morpholino-hex-1-ene	8.45 g (0.05 mole)
Triethylamine	5.05 g (0.05 mole)
2,4-Dinitrobenzoyl chloride	11.53 g (0.05 mole)

M.P. 138-140°C (benzene - petroleum ether)

Yield : 14.70 g (81%)

IR (Nujol) showed band at 1620 cm^{-1} (-C(=O)-N<)

PMR ($CDCl_3$) showed signals at δ 1.0 (broad, 3H, $-CH_3$); 1.5 (m, 4H, $-CH_2-CH_2-CH_3$); 2.5 (broad, 2H, -C(=O)-CH_2); 3.4 (t, 4H, $-N(CH_2)_2$); 3.7 (t, 4H, $O(CH_2)_2$); 6.5 (s, 1H, -C = C<N-H), 7.5-8.8 (aromatic protons).

Analysis found: C, 56.3; H, 5.9; N, 11.4.

Analysis required for $C_{17}H_{21}N_3O_6$: C, 56.2; H, 5.79; N, 11.57.

Mass spectrum: M^+ 363.

Step 3 : Hydrolysis of 1-Morpholino-2-(Nitrobenzoyl) alkenes (XVIII) to 3-(Nitrophenyl)-3-oxo-2-alkyl-1-propanals (β-Ketoaldehydes) (XIXA) and Alkyl Phenyl Ketones (XX).

General Procedure:

1-Morpholino-2-(nitrobenzoyl)alkenes (0.01 mole) was dissolved in dioxane (25 ml), to that 50% hydrochloric acid (5 ml) was added and the mixture was refluxed for 4 hours. Solvent was removed under reudced pressure. The residue was extracted in ethyl acetate (25 ml). Ethyl acetate layer was washed with sodium bicarbonate solution (pH 7.5-8.5), until the bicarbonate washings were colourless. Bicarbonate washings were combined and acidified with conc. hydrochloric acid. Solid separated was filtered, dried and crystallised from solvent to obtain pure β-ketoaldehydes.

The ethyl acetate layer was dried over anhydrous sodium sulfate, solvent was removed under reduced pressure to obtain alkyl phenyl ketones XXA.

The following β-ketoaldehydes (XIXA) were prepared according to this general procedure.

1. Preparation of 3-(2-nitrophenyl) 3-oxo-2-ethyl-1-propanal (XIXA-1)

1-Morpholino-2-(2-nitrobenzoyl)-but-1-ene	2.90 g (0.01 mole)
Dioxane	25 ml
50% Hydrochloric acid	5 ml

M.P. 131°C (carbon tetrachloride - petroleum ether)

Yield : 0.93 g (42%)

IR (Nujol) showed bands at 2640 cm^{-1} (-C(=O)-H), 1650 cm^{-1} (-C(=O)-CHO)

PMR ($CDCl_3$) showed signals at δ 1.0 (t, 3H, $C\underline{H}_3$); 2.0 (m, 2H, -$C\underline{H}_2$-); 7.2-8.2 (aromatic protons); 9.2 (d, 1H, -C(=O)-$\underline{H}$).

Analysis found : C, 59.8; H, 5.2; N, 6.6.

Analysis required for $C_{11}H_{11}NO_4$: C, 59.73; H, 4.98; N, 6.33.

Mass spectrum: M^+ 221.

Ethyl acetate layer was concentrated and 2-nitrobutyrophenone (yield 25%)was obtained.

2. Preparation of 3-(2,4-dinitrophenyl)-3-oxo-2-ethyl-1-propanal (XIXA-2)

1-Morpholino-2-(2,4-dinitrobenzoyl)-but-1-ene	3.35 g (0.01 mole)
Dioxane	25 ml
50% Hydrochloric acid	5 ml

M.P. 140-41°C (benzene - petroleum ether)

Yield : 1.49 g (56%)

IR (Nujol) showed bands at 2650 cm^{-1} (-C(=O)-H), 1640 cm^{-1} (-C(=O)-CHO)

PMR ($CDCl_3$) showed signals at δ1.0 (t, 3H, $C\underline{H}_3$); 2.1 (m, 2H, -$C\underline{H}_2$-); 7.3-8.4 (aromatic protons); 9.2 (d, 1H, -C(=O)-$\underline{H}$).

Analysis found: C, 49.9; H, 3.9; N, 11.0

Analysis required for $C_{11}H_{10}N_2O_6$: C, 49.62; H, 3.76; N, 10.53.

Mass spectrum: M^+ 266.

Ethyl acetate layer after concentration gave 2,4-dinitrobutyrophenone (Yield 22%).

3. **Preparation of 3-(2-nitrophenyl)-3-oxo-2-(n-butyl)-1-propanal (XIXA-3)**

1-Morpholino-2-(2-nitrobenzoyl)-hex-1-ene	3.18 g (0.01 mole)
Dioxane	25 ml
50% Hydrochloric acid	5 ml

M.P. 95°C (benzene - petroleum ether)

Yield 1.97 g (79%)

IR (Nujol) showed bands at 2650 cm^{-1} (-C(=O)-H), 1640 cm^{-1} (-C(=O)-CHO)

PMR ($CDCl_3$) showed signals at δ 0.8 - 2.1 (-$\underline{CH_2}$-$\underline{CH_2}$-$\underline{CH_2}$-$\underline{CH_3}$), 7.4 - 8.2 (aromatic protons), 9.5 (d, 1H, -C(=O)-$\underline{H}$).

Analysis found: C, 62.7; H, 6.1; N, 5.4.

Analysis required for $C_{13}H_{15}NO_4$: C, 62.65; H, 6.02; N, 5.62.

Mass spectrum: M^+ 249.

Ethyl acetate layer after concentration gave 2-nitrohexophenone (Yield 15%).

4. **Preparation of 3-(2,4-dinitrophenyl)-3-oxo-2-(n-butyl)-1-propanal (XIXA-4)**

1-Morpholino-2-(2,4-dinitrobenzoyl)-hex-1-ene	3.63 g (0.01 mole)
Dioxane	25 ml
50% Hydrochloric acid	5 ml

M.P. 142°C (carbon tetrachloride - petroleum ether)

Yield : 1.80 g (61%).

IR (Nujol) showed bands at 2650 cm^{-1} (-C(=O)-H); 1645 cm^{-1} (-C(=O)-CHO)

PMR ($CDCl_3$) showed signals at δ 0.8-2.0 (-$\underline{CH_2}$-$\underline{CH_2}$-$\underline{CH_2}$-$\underline{CH_3}$); 7.3-8.5 (aromatic protons); 9.3 (d, 1H, -C(=O)-$\underline{H}$).

Analysis found: C, 53.4; H, 4.62; N, 9.6.

Analysis required for $C_{13}H_{14}N_2O_6$: C, 53.06; H, 4.76; N, 9.52.

Mass spectrum: M^+ 294.

Ethyl acetate layer after concentration gave 2,4-dinitrohexophenone (Yield 12%).

The following alkyl phenyl ketones ($\underline{XX}$) were prepared according to this general procedure with the quantities given.

(In the following preparations β-ketoaldehydes were not isolated).

1. Preparation of 2-nitroisobutyrophenone (XXB-1)

Morpholinium salt XVIIIB-1	2.90 g (0.05 mole)
Dioxane	25 ml
50% Hydrochloric acid	5 ml

Ethyl acetate layer was dried over anhydrous sodium sulfate. Solvent was removed under reduced pressure and residue was crystallised from carbon tetrachloride - petroleum ether.

M.P. 65-66°C

Yield 0.96 g (50%)

IR (Nujol) showed band at 1680 cm^{-1} (-C(=O)-)

PMR ($CDCl_3$) showed signals at δ1.2 (d, 6H, -CH($\underline{CH_3}$)$_2$); 2.9 (m, 1H, -$\underline{CH}$(CH_3)$_2$; 7.2-8.2 (aromatic protons).

Analysis found: C, 61.6; H, 5.9; N, 8.0.

Analysis required for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.7; N, 7.25

Mass spectrum: M^+ 193.

2. **Preparation of 4-nitroisobutyrophenone** (XXB-2)

Morpholinium salt XVIIIB-2	2.90 g (0.01 mole)
Dioxane	50 ml
50% Hydrochloric acid	5 ml

Ethyl acetate layer was concentrated and residue was crystallised from carbon tetrachloride - petroleum ether.

M.P. 51°C[91]

Yield : 1.12 g (58%)

IR (Nujol) showed band at 1690 cm^{-1} (-$\overset{O}{\overset{\|}{C}}$-)

PMR ($CDCl_3$) showed signals at δ1.3 (d, 6H, -CH($\underline{CH}_3$)$_2$); 3.1 (m, 1H, -$\underline{CH}$(CH_3)$_2$); 7.3-8.4 (aromatic protons).

Analysis found: C, 62.6; H, 5.8; N, 7.1.

Analysis calculated for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.7; N, 7.25.

Mass spectrum : M^+ 193.

3. **Preparation of 2,4-dinitroisobutyrophenone (XXB-3)**

Morpholinium salt XVIIB-3	3.35 g (0.01 mole)
Dioxane	25 ml
50% Hydrochloric acid	5 ml

Ethyl acetate layer was concentrated and residue was crystallised from benzene - petroleum ether.

M.P. 45-46°C

Yield 1.15 g (48%)

IR (Nujol) showed band at 1680 cm^{-1} (-$\overset{O}{\overset{\|}{C}}$-)

PMR ($CDCl_3$) showed signals at δ1.3 (d, 6H, -CH($\underline{CH}_3$)$_2$); 3.1 (m, 1H, -$\underline{CH}$(CH_3)$_2$); 7.3-8.5 (aromatic protons).

Analysis found: C, 50.8; H, 4.1; N, 11.7 ·

Analysis reuired for $C_{10}H_{10}N_2O_5$: C, 50.42; H, 4.2; N, 11.76.

Mass spectrum: M^+ 238.

4. **Preparation of 4-nitrobutyrophenone (XXA-4)**

1-Morpholino-2-(4-nitrobenzoyl)-but-1-ene	2.90 g (0.01 mole)
Dioxane	25 ml
50% Hydrochloric acid	5 ml

Ethyl acetate layer was concentrated and residue was crystallised from benzene - petroleum ether,

M.P. 57°C

Yield : 1.73 g (90%)

IR (Nujol) showed band at 1680 cm^{-1} (-C(=O)-)

PMR ($CDCl_3$) showed signals at δ1.0 (t, 3H, -CH_3); 1.8 (m, 2H, -CH_2-CH_3); 2.8 (t, 2H, -C(=O)- CH_2-); 7.2-8.2 (aromatic protons).

Analysis found: C, 61.8; H, 5.6; N, 7.4

Analysis required for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.7; N, 7.25.

Mass spectrum: M^+ 193.

5. **Preparation of 4-nitrohexophenone (XXA-5)**

1-Morpholino-2-(4-nitrobenzoyl)-hex-1-ene	3.18 g (0.01 mole)
Dioxane	25 ml
50% Hydrochloric acid	5 ml

Ethyl acetate layer was concentrated and residue was crystallised from carbon tetrachloride - petroleum ether.

M.P. 44°C[94]

Yield: 1.60 g (73%)

IR (Nujol) showed band at 1680 cm^{-1} ($-\overset{O}{\overset{\|}{C}}-$)

PMR ($CDCl_3$) showed signals at δ 0.8 - 1.9 ($-\underline{CH_2}-\underline{CH_2}-\underline{CH_2}-\underline{CH_3}$); 2.8 (t, 2H, $-\overset{O}{\overset{\|}{C}}-\underline{CH_2}-$); 7.2-8.2 (aromatic protons).

Analysis found: C, 65.45; H, 6.65; N, 6.86.

Analysis calculated for $C_{12}H_{15}NO_3$: C, 65.16; H, 6.79; N, 6.33.

Mass spectrum: M^+ 221.

Step 4: **Preparation of Alkyl Phenyl Ketones XXA from 3-(Nitrophenyl)-3-oxo-2-alkyl-1-propanals (β-Ketoaldehydes) XIXA.**

General Procedure:

3-(Nitrophenyl)-3-oxo-2-alkyl-1-propanal XIXA (0.005 mole) was dissolved in ethanol (10 ml). To that, sodium acetate (0.82 g, 0.01 mole) in water (2 ml) was added and the mixture was refluxed for 3 hours. Solvent was removed under reduced pressure. The residue was extracted in ethyl acetate (10 ml), washed with water and dried over anhydrous sodium sulfate. Ethyl acetate was removed under reduced pressure and compound was purified either by crystallization or by vacuum distillation.

The following compounds were prepared according to this general procedure, with the quantities given.

1. **Preparation of 2-nitrobutyrophenone (XXA-6)**

3-(2-Nitrophenyl)-3-oxo-2-ethyl-1-propanal	1.105 g (0.005 mole)
Sodium acetate	0.82 g (0.01 mole)
Ethanol	10 ml

Distilled at 170-75°C/8 mm[93]

Yield : 0.87 g (90%)

IR (Neat) showed band at 1680 cm^{-1} (-C(=O)-)

PMR ($CDCl_3$) showed signals at δ0.9 - 1.9 (-CH_2-CH_3); 2.8 (t, 2H, -C(=O)-CH_2-); 7.1-8.2 (aromatic protons).

Mass spectrum: M^+ 193.

2. **Preparation of 2,4-dinitrobutyrophenone (XXA-7)**

3-(2,4-Dinitrophenyl)-3-oxo-2-ethyl-1-propanal	1.33 g (0.005 mole)
Sodium acetate	0.81 g (0.01 mole)
Ethanol	10 ml

M.P. 88°C (benzene - petroleum ether)

Yield: 0.87 g (73%)

IR (Nujol) showed band at 1680 cm^{-1} (-C(=O)-)

PMR ($CDCl_3$) showed signals at δ0.8 - 1.8 (-CH_2-CH_3); 2.9 (t, 2H, -C(=O)-CH_2-); 7.3-8.4 (aromatic protons).

Analysis found: C, 50.2; H, 4.0; N, 11.9

Analysis required for $C_{10}H_{10}N_2O_5$: C, 50.42; H, 4.2; N, 11.76.

Mass spectrum : M^+ 238.

3. **Preparation of 2-nitrohexophenone (XXA-8)**

3-(2-Nitrophenyl)-3-oxo-2-phenyl-1-propanal	1.245 g (0.005 mole)
Sodium acetate	0.82 g (0.005 mole)
Ethanol	10 ml

Distilled at 152-155°C/4 mm

Yield: 1.00 g (90%)

IR (Neat) showed band at 1690 cm^{-1} (-C(=O)-)

PMR ($CDCl_3$) showed signals at δ0.8-2.0 (-CH_2-CH_2-CH_2-CH_3); 2.8 (t, 2H, -C(=O)-CH_2-); 7.1-8.1 (aromatic protons).

Mass spectrum : M^+ 221.

4. **Preparation of 2,4-dinitrohexophenone (XXA-9)**

3-(2,4-Dinitrophenyl)-3-oxo-2-(n-butyl-1-propanal	1.47 g (0.005 mole)
Sodium acetate	0.82 g (0.005 mole)
Ethanol	10 ml

M.P. 102-103°C (benzene-petroleum ether)

Yield : 1.10 g (83%)

IR (Nujol) showed band at 1680 cm^{-1} ($-\overset{O}{\overset{\|}{C}}-$)

PMR ($CDCl_3$) showed signals at 0.9-2.0 ($-C\underline{H}_2-C\underline{H}_2-C\underline{H}_2-C\underline{H}_3$); 2.6 (t, 2H, $-\overset{O}{\overset{\|}{C}}-C\underline{H}_2-$); 7.2-8.2 (aromatic protons).

Analysis found: C, 54.4; H, 5.72; N, 10.3.

Analysis required for $C_{12}H_{14}N_2O_5$: C, 54.14; H, 5.26; N, 10.53.

Mass spectrum: $M^{+\cdot}$ 266.

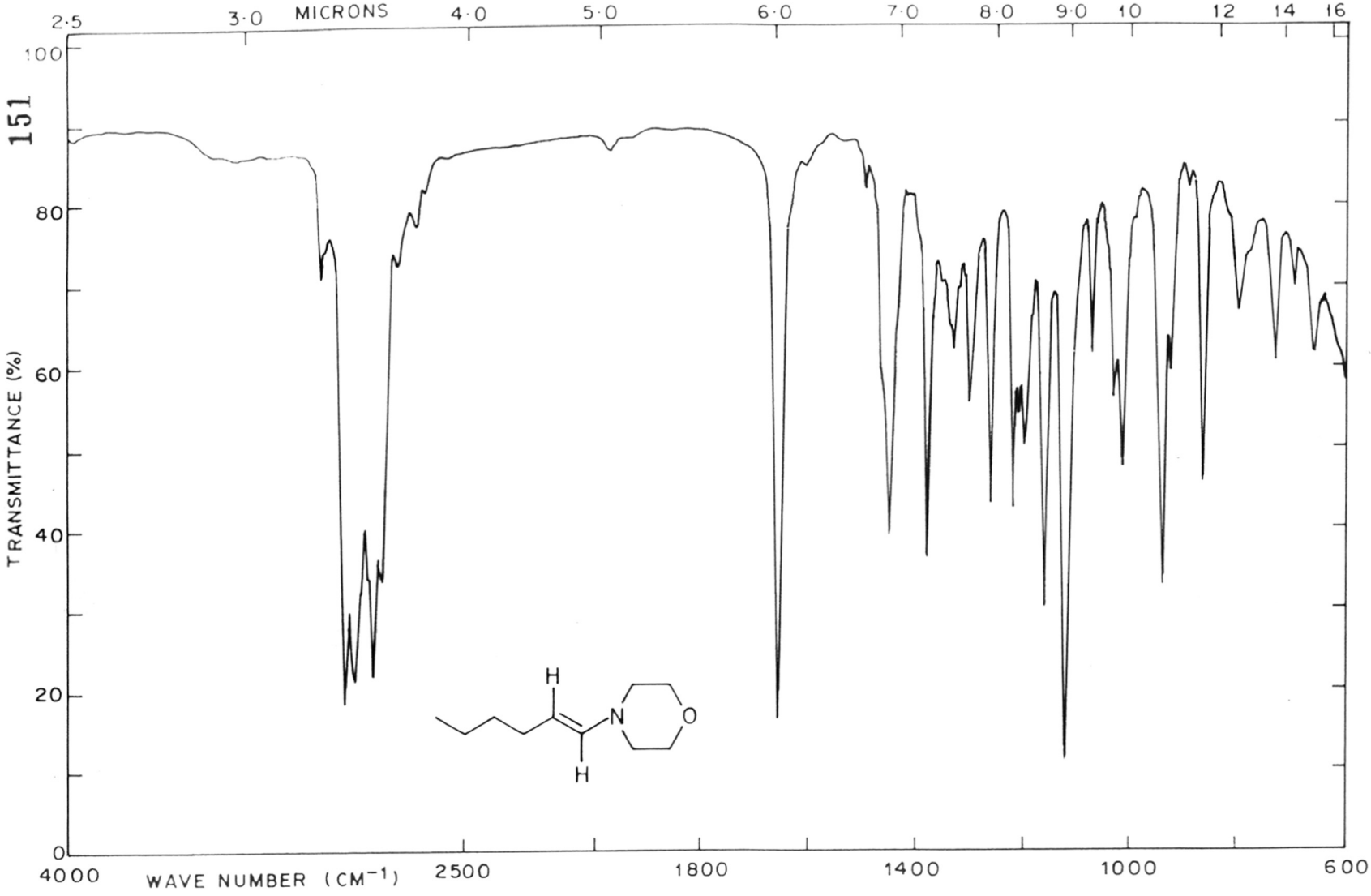


FIG. 2·12. IR SPECTRUM OF 1-MORPHOLINO-HEX-1-ENE

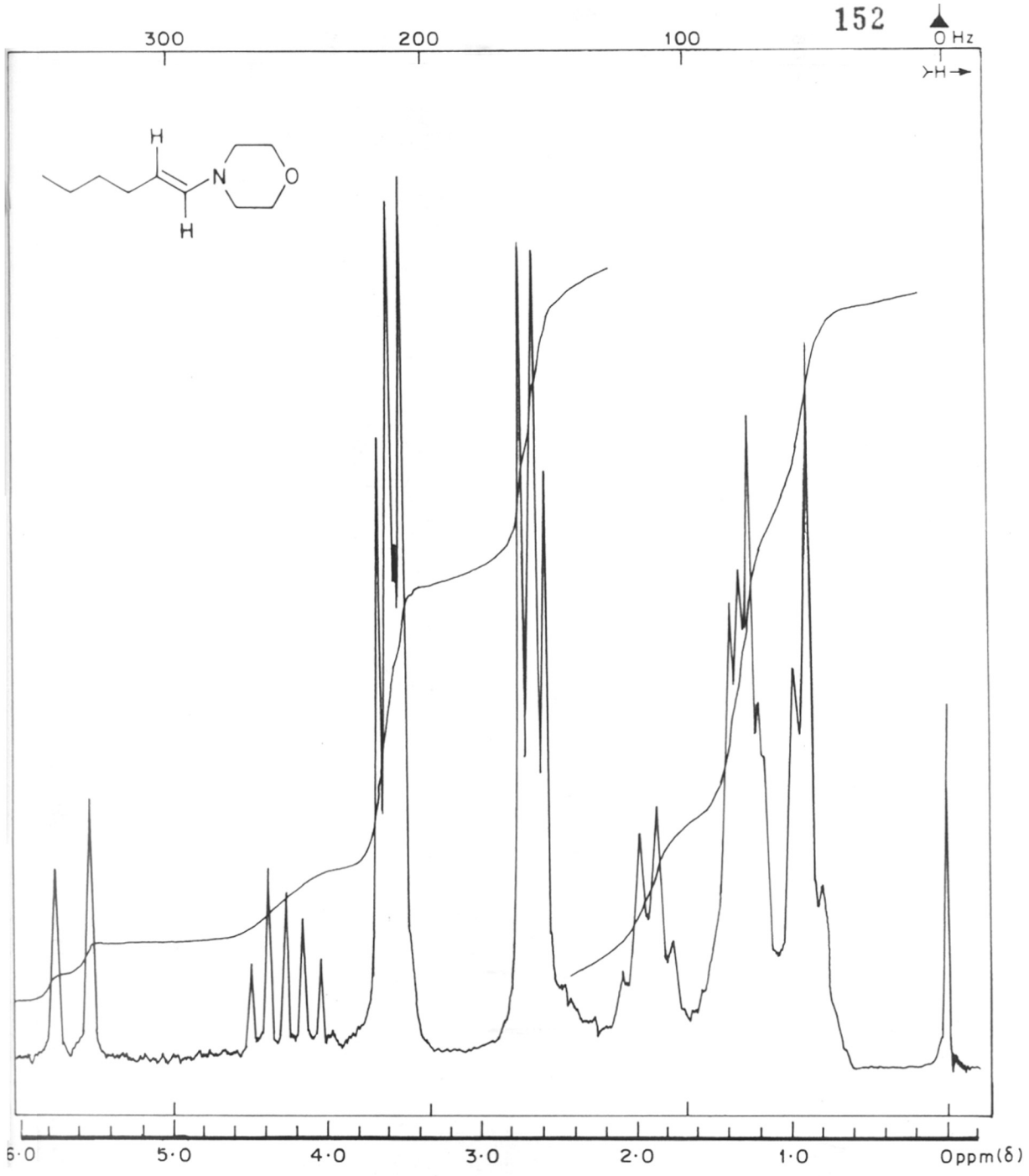


FIG. 2·13. PMR SPECTRUM OF 1-MORPHOLINO-HEX-1-ENE

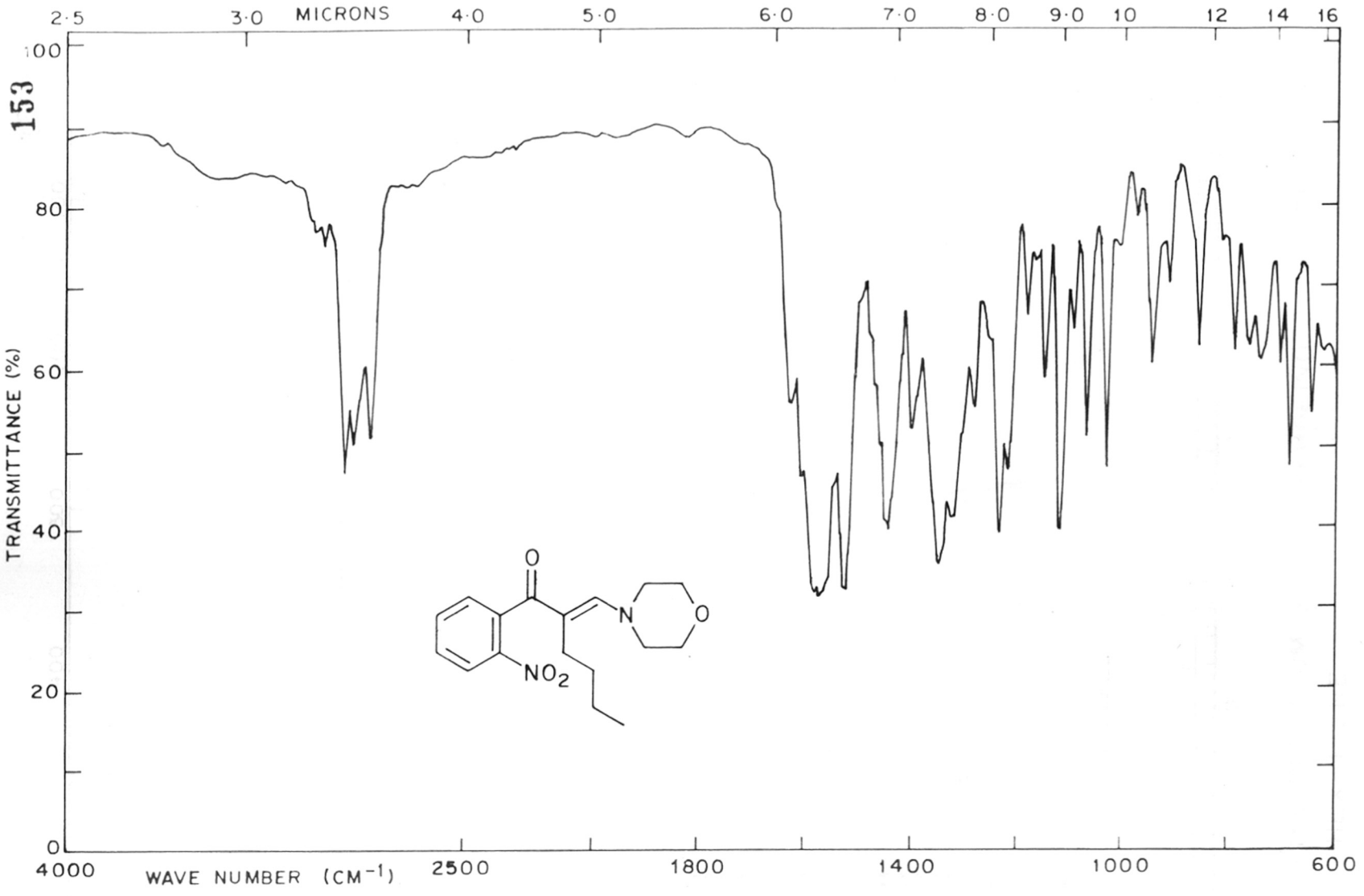


FIG. 2·14. IR SPECTRUM OF 1-MORPHOLINO-2-(2-NITROBENZOYL)-HEX-1-ENE

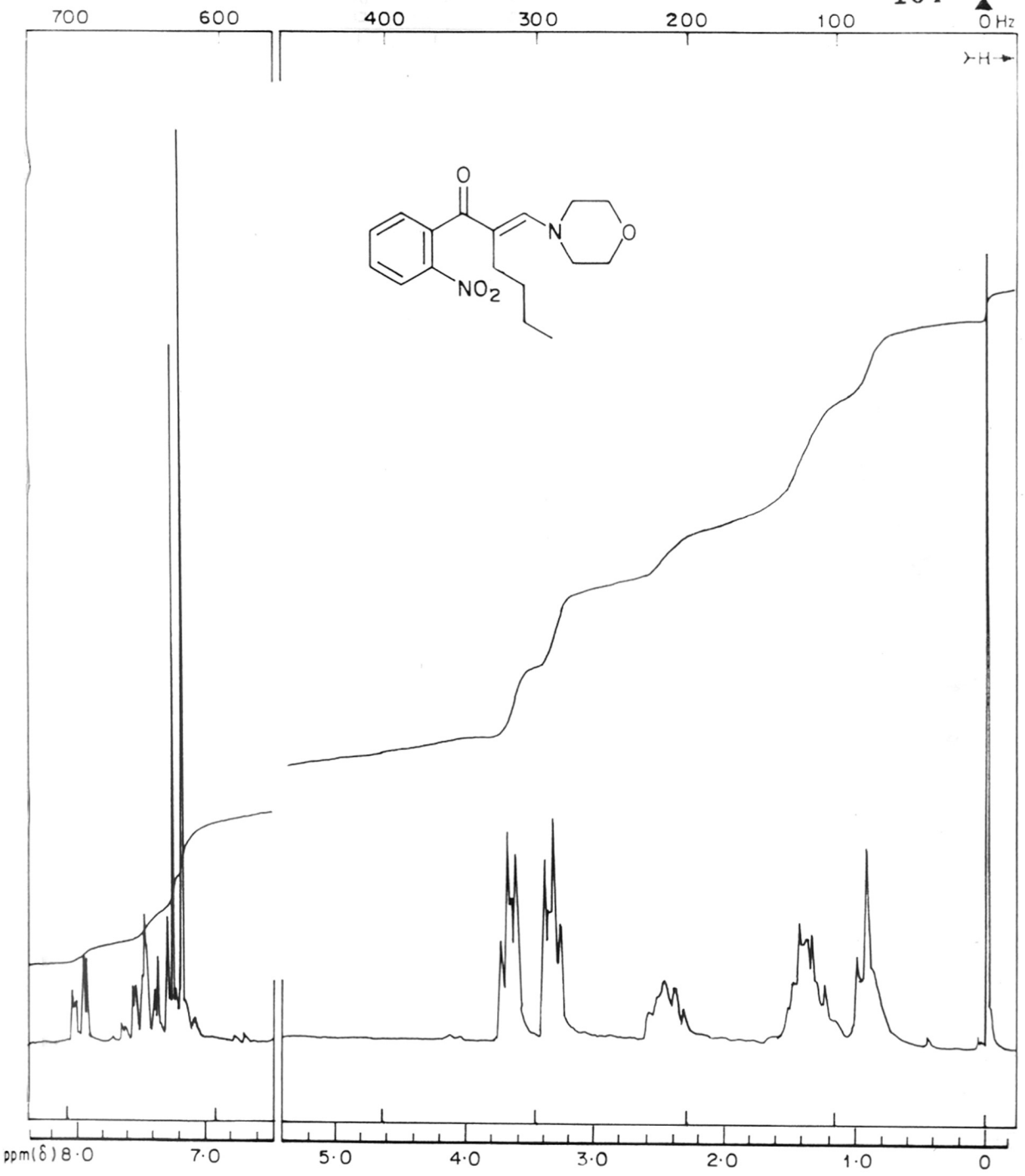


FIG 2·15. PMR SPECTRUM OF 1-MORPHOLINO-2-(2-NITROBENZOYL) -HEX-1-ENE

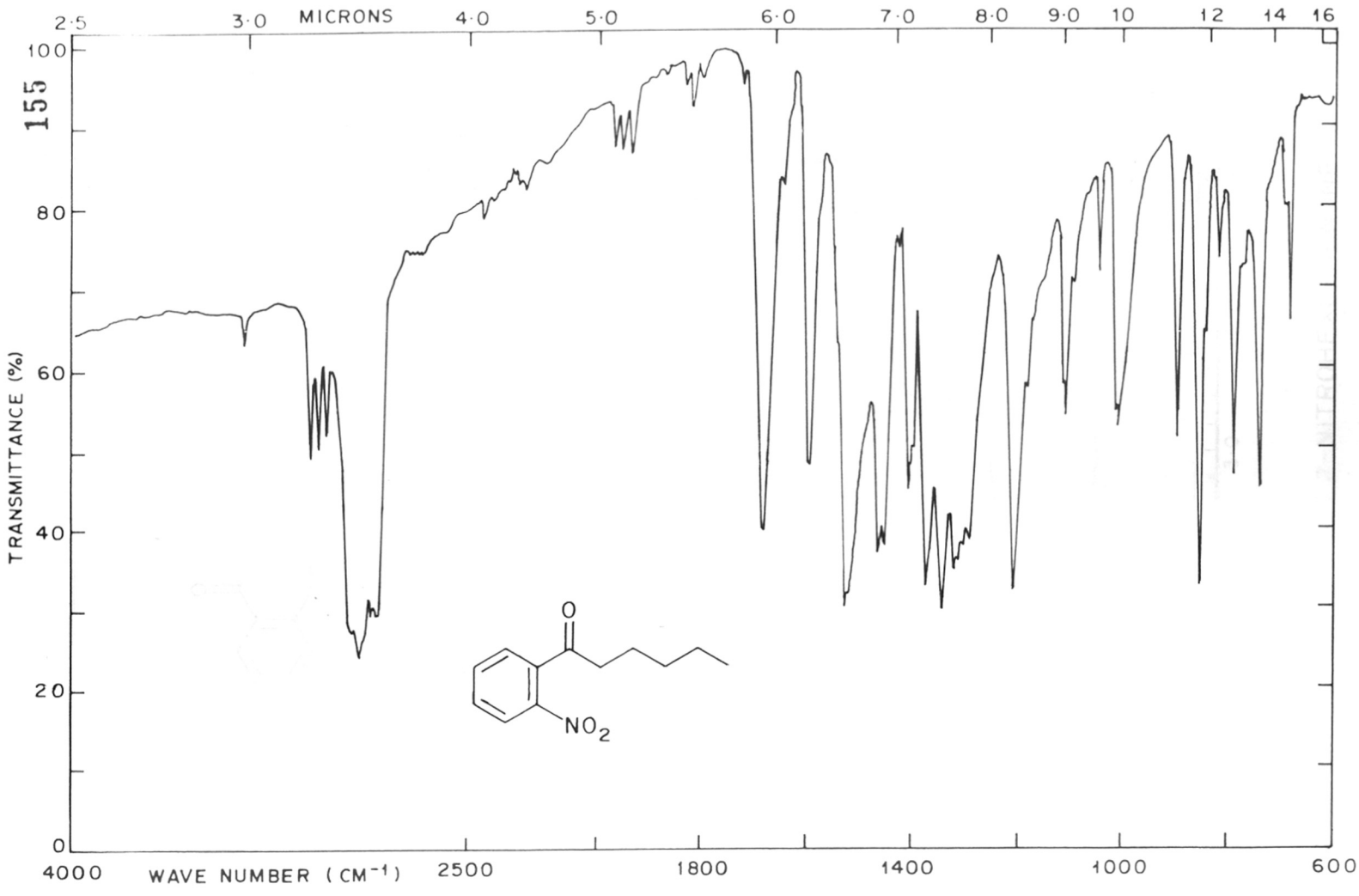


FIG. 2·16. IR SPECTRUM OF 2-NITROHEXOPHENONE

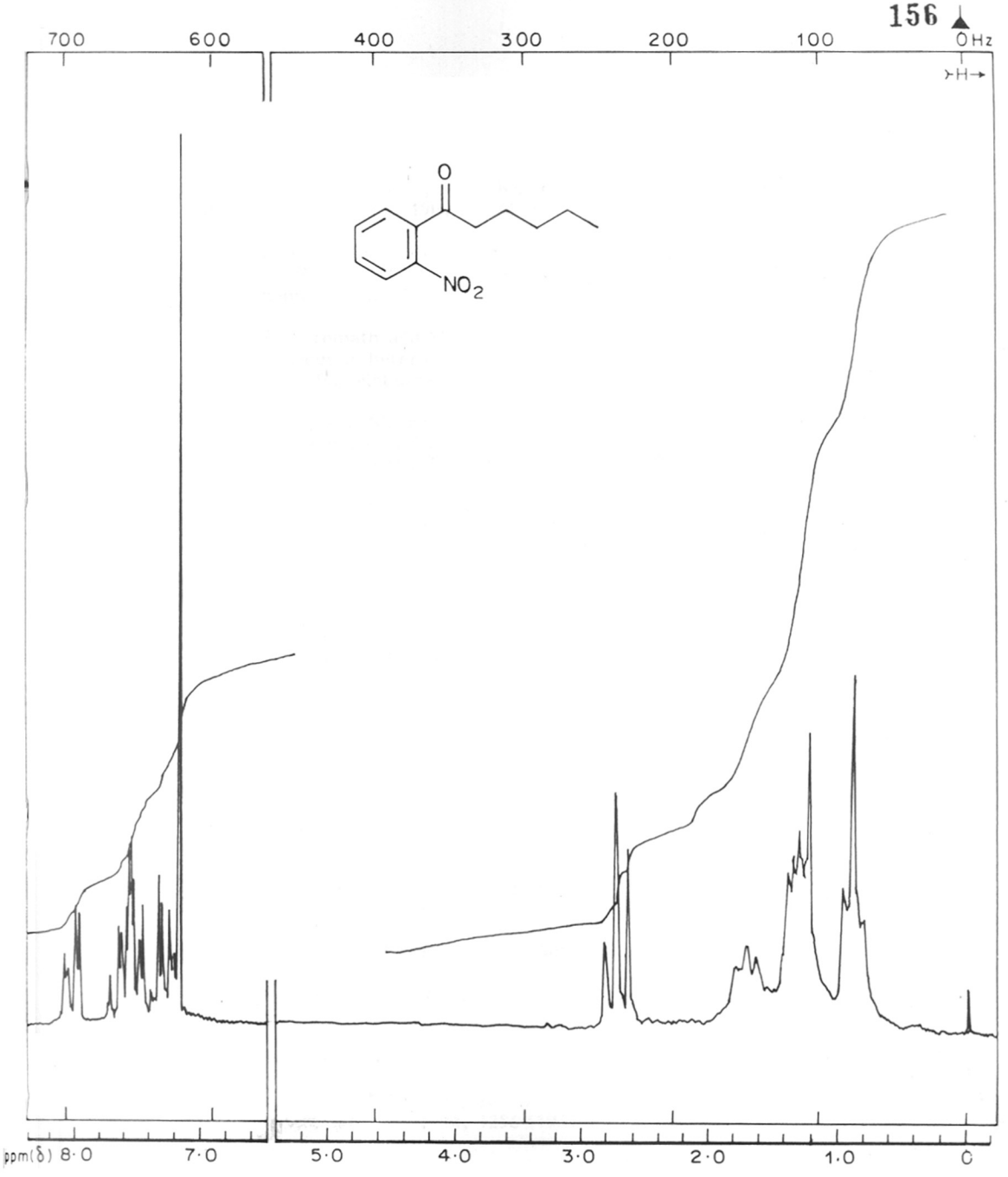


FIG. 2·17. PMR SPECTRUM OF 2-NITROHEXOPHENONE

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CHAPTER-III

HYDROGENATION STUDIES OF ENAMINES FOR THE SYNTHESIS OF VARIOUS HETEROCYCLIC COMPOUNDS

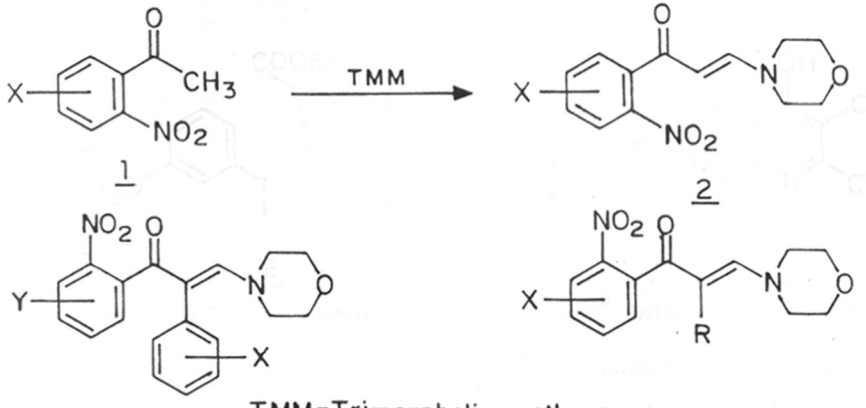
Introduction

A brief review of the chemistry of enamines and their use in the preparation of various heterocyclic compounds is given in Chapter 1. The utilisation of enamines for the synthesis of 2-arylisatogens is described in Chapter II. In this chapter, the hydrogenation studies of enamines and their utilisation for the synthesis of 4-hydroxyquinolines and 4-hydroxyquinoline N-oxides are described. The 4-hydroxyquinolines can be readily converted to the desired drugs, having an alkylamino side chain attached at 4-positions. These compounds have promising antimalarial activity.[1] Conard an d L. Limpach[2] first prepared 4-hydroxyquinoline by condensation of aniline with acetoacetic ester at room temperature, followed by cyclisation at 250°C. Limpach[3] later on increased the yield from 30 to 90-95% by use of mineral oil as a diluent in the cyclisation step. It has been found that in the reaction reported by Gould and Jacob,[4] the thermal cyclisation of ethyl β-anilino-α-carbethoxyacrylate has many general applications.

The methods reported in literature for the synthesis of 4-hydroxyquinoline derivatives are mainly by condensation of aniline with various reagents like ethoxymethylenemalonic ester,[5] formylpropionic ester,[6] alkyl arylacetals,[7] ethyl α-formylphenylacetate,[8] and acetoacetic ester.[9] Very few methods for preparation of 3-aryl, 3-alkyl substituted 4-hydroxyquinolines are reported.[6,8,9]

The main interest in the present investigation was the utilisation of enamines (2) obtained from the condensation of o-nitroacetophenone

with trimorpholinomethane[10] and use of intermediates ∝-(2-nitrobenzoyl) β-dialkylaminostyrenes (III) and 1-morpholino-2-(o-nitrobenzoyl) alkenes (XVIIIA) prepared in Chapter II for the various hydrogenation studies.



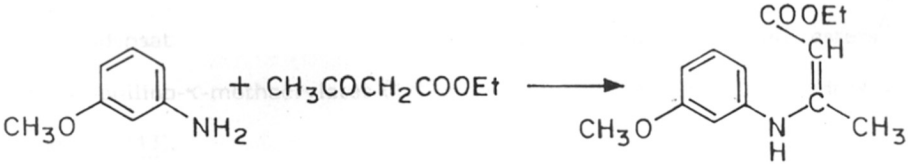
TMM=Trimorpholinomethane

(III) XVIII A

As visualised from the structures of enamines, they could be easily converted to 4-hydroxyquinoline and 4-hydroxyquinoline N-oxide derivatives during hydrogenation. This is a new approach which has not been explored probably because the functional groups like nitro group are reduced simultaneously leading to amino substituted 4-hydroxyquinolines.

Some of the known methods for the preparation of 4-hydroxyquinoline derivatives are as follows:

1. m-Anisidine was condensed with one equimolar quantity of acetoacetic ester[9] in presence of an acid catalyst to give ethyl β-methoxyanilino-crotonate (5) which was alkylated with heptyl iodide. Cyclisation of alkylated crotonate was effected in presence of diphenyl ether at 250°C.



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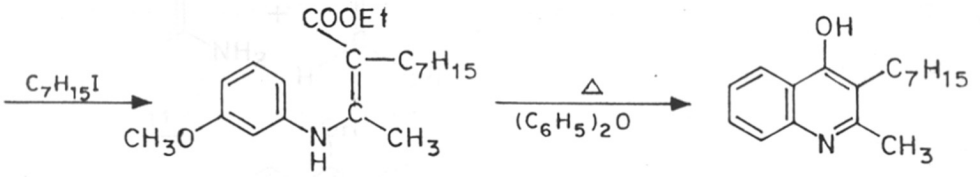

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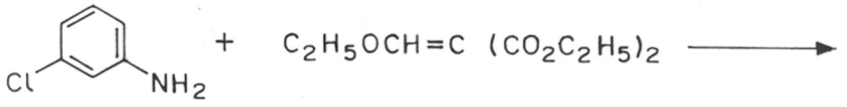
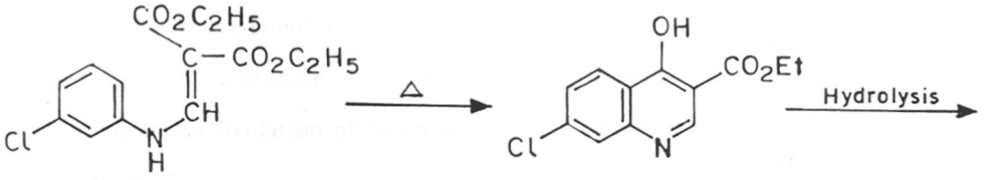
2. The reaction of ethoxymethylenemalonic ester[5] with m-chloroaniline gave anilinoacrylate (8) which was cyclised at high temperature to 3-ethylate (9). Hydrolysis and decarboxylation of ester gave 7-chloro-4-hydroxy-quinoline (42).





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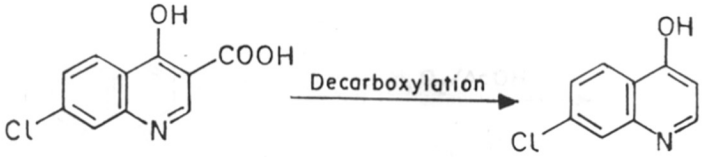
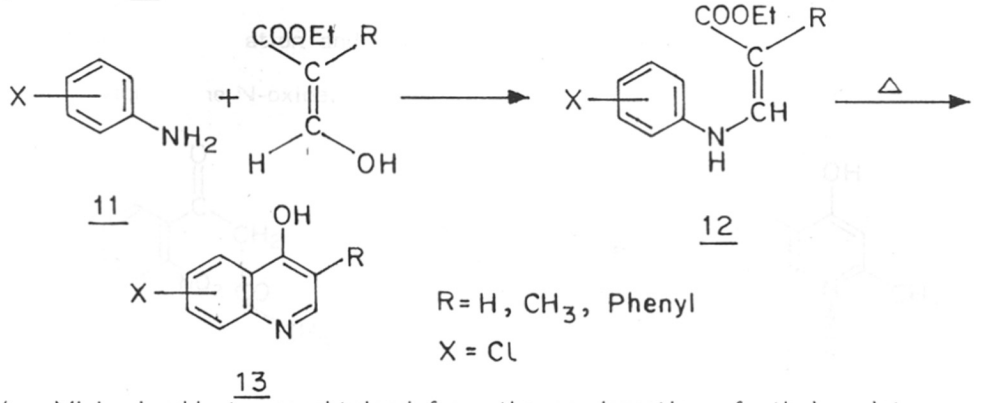
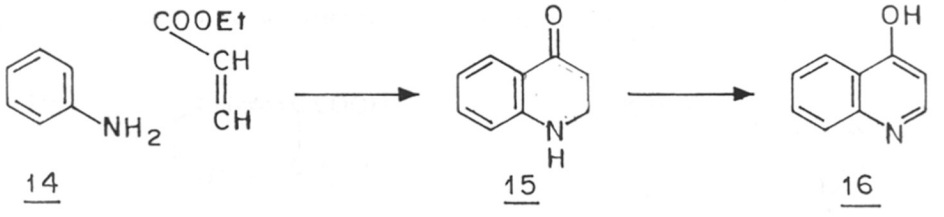


10 42

3. Condensation of substituted aniline with sodioformylpropionic esters[6] gave β-anilino-ϰ-methacrylates (12) and was further cyclised to 4-hydroxy-quinolines (13).

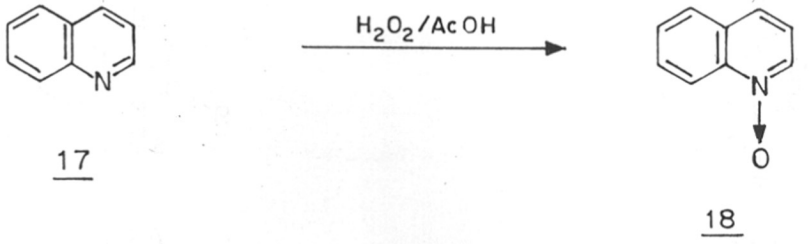


4. Michael adduct was obtained from the condensation of ethylacrylate and aniline,[11] which was aromatised to 4-hydroxyquinoline.

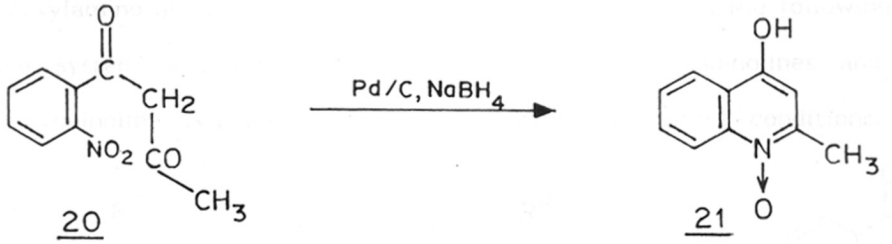


Synthesis of 4-hydroxyquinoline N-oxides

1. The common literature method for the preparation of quinoline N-oxides consist of oxidation of quinoline by hydrogen peroxide in presence of acetic acid.[12]

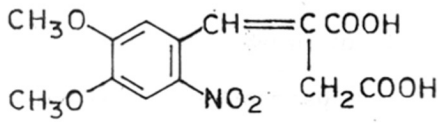


2. There is a report[13] indicating the formation of 4-hydroxyquinoline N-oxide during the cyclisation step. Hence, when o-nitrobenzoylacetone dissolved in either sodium hydroxide or methanol, was added to the suspension of palladium charcoal in aqueous sodiumborohydride solution followed by filtration and acidification of the filtrate, gave 4-hydroxy-2-methylquinoline N-oxide.



20 21

3. When 6-nitroveratrylidenesuccinic acid was heated with 20% aqueous potassium hydroxide for 30 min, it cyclised to quinoline N-oxide which was retrieved by acidification of the reaction mixture.[14]



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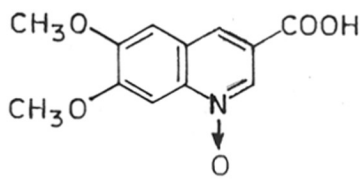
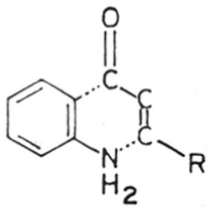


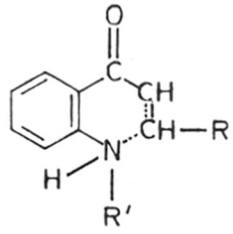
23

Present Investigation

It is evident from above methods of preparation of 4-hydroxyquinolines that the quinoline nucleus is built up mainly by addition of aniline to to the α,β conjugated carbonyl system followed by cyclisation.

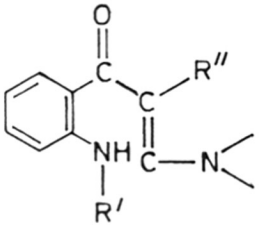


24 A



24 B

while 4-hydroxyquinoline N-oxides are prepared by partial reduction of nitro group and cyclisation with elimination of R group in (24A). It was therefore visualised that the (24B, R' = H) system could be explored for building up of 4-hydroxyquinoline through cyclisation at amino group. 4-Hydroxyquinoline N-oxide can also be obtained through cyclisation at hydroxylamino group in (24B, R' -OH). With this intention, the following enamine system was utilised to prepare the 4-hydroxyquinolines and 4-hydroxyquinoline N-oxides in one step, under very mild conditions.



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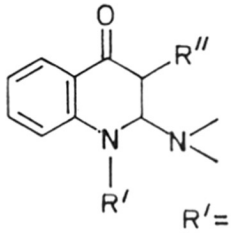

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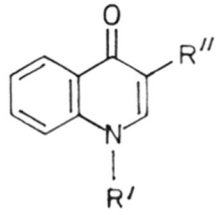
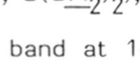
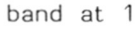
R'= H,OH

R''= Alkyl, Aryl



27

For this purpose the compound α-(o-nitrobenzoyl)-β-morpholinoethene was studied in detail for various hydrogenation reactions with different reagents as summarised in Scheme-1.

The α-(o-nitrobenzoyl)-β-morpholinoethene (2) prepared by the condensation of o-nitroacetophenone with trimorpholinomethane[10] showed m.p. 150°C (benzene); PMR spectrum ($CDCl_3$) showed signals at δ 3.3 (t, 4H, $-N(CH_2)_2$); 3.75 (t, 4H, $O(CH_2)_2$); 5.3 (d, 1H, J = 14Hz, ). IR spectrum (Nujol) showed band at 1660 cm^{-1} (- ); Mass spectrum: M^+ 262.

The results of hydrogenation studies are described below:

(a) Reduction with titanium trichloride

α-(o-Nitrobenzoyl)-β-morpholinoethene and 15% titanium trichloride

was stirred in presence of ammonium acetate solution for 30 min. 2-Amino acetophenone (28) formed was extracted in ether and purified by silica gel column chromatography using pet. ether-benzene (95:5%) eluate

2-Aminoacetophenone[15] was characterised by its spectral data. IR spectrum (Nujol) showed bands at 1710 cm^{-1} (-C-), 3380, 3230 cm^{-1} ($-NH_2$). PMR spectrum (CCl_4) showed signals at δ 2.5 (s, 3H, $-CH_3$), 6.1 ($-NH_2$. D_2O exchangeable).

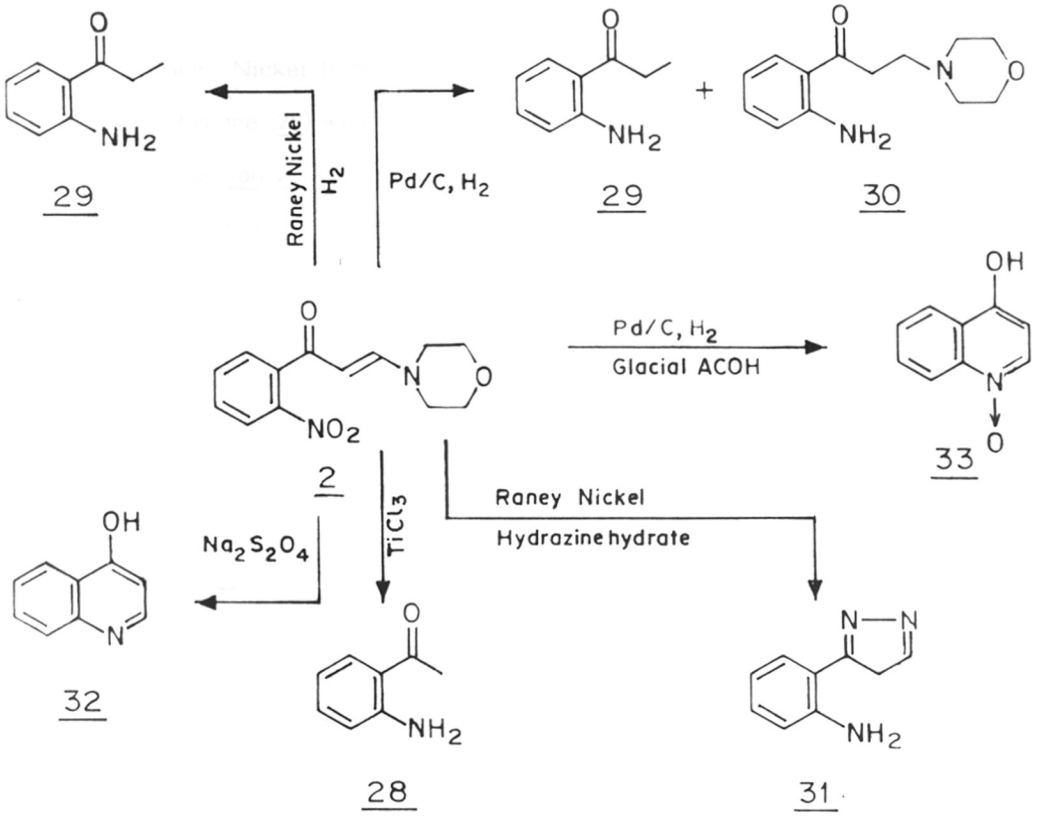
(b) Reduction with palladium charcoal

Reduction of α-(o-nitrobenzoyl)- β-morpholinoethene with 10% palladium charcoal at 3 atmospheric pressure gave the mixture of two compounds, which were separated over silica gel chromatography. Fraction eluted in petroleum ether : benzene (95:5) was 2-aminopropiophenone[15] (29) which was confirmed by its spectra data. IR spectrum (Neat) showed bands at 1710 cm^{-1} (-C-); 3240, 3350 cm^{-1} ($-NH_2$). PMR spectrum (CCl_4) showed signals at δ 1.15 (t, 3H, $-CH_3$), 2.95 (q, 2H, $-CH_2-$), 5.85 ($-NH_2$, D_2O exchangeable).

The fraction eluted in petroleum ether : benzene (85:15) mixture was 1-(2-aminobenzoyl)-2-morpholinoethane (30) which was characterised by its spectral data; m.p. 170°C (benzene); IR spectrum (Nujol) showed 3245, 3390 cm^{-1} ($-NH_2$). PMR spectrum ($CDCl_3$) showed signals at δ 2.5 (t, 4H, $-N(CH_2)_2$); 3.7 (t, 4H, $O(CH_2)_2$); 2.8 (t, 2H, $-CH_2\ N(CH_2)_2$); 3.15 (t, 2H, $-C-CH_2-$); 6.3 ($-NH_2$. D_2O exchangeable). Mass spectrum: M^+ 234.

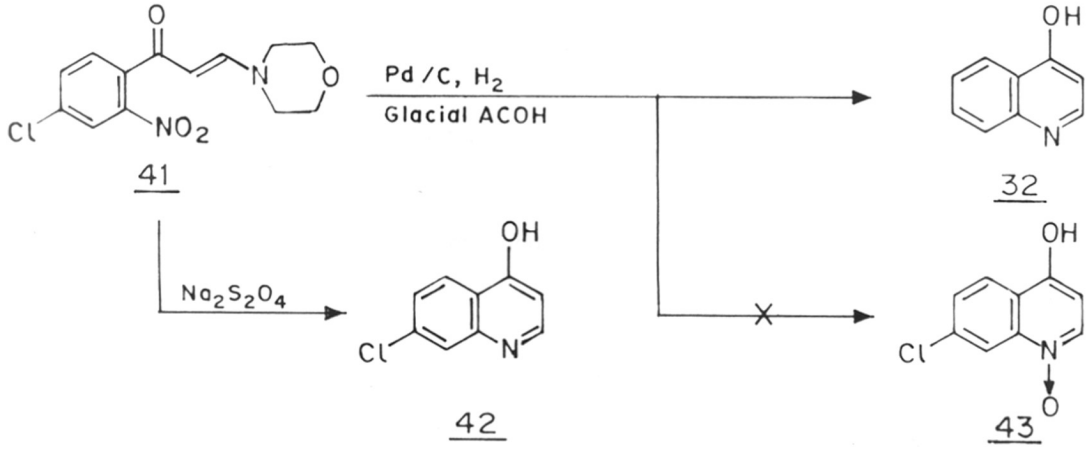
SCHEME – 1

VARIOUS REDUCTION REACTIONS OF α-(O-NITROBENZOYL)-β-MORPHOLINO ETHENYL.



SCHEME – 2

PREPARATION OF 7-CHLORO-4-HYDROXYQUINOLINE (42)



(c) Reduction with Raney Nickel

Raney Nickel hydrogenation at 3 atmosphere pressure gave 2-amino-propiophenone (29) which was characterised by its spectral data.

(d) Reduction with Raney Nickel and hydrazine hydrate

To a mixture of ∝-(o-nitrobenzoyl)- β-morpholinoethene and Raney Nickel in methanol, hydrazine hydrate was added slowly to obtain 3-(2-aminophenyl)pyrazole[16] (31). It is therefore evident that enamine is first decomposed to β-ketoaldehyde which then reacts with hydrazine hydrate to give the pyrazole derivative. This compound was crystallised from dichlorethane : petroleum ether; m.p. 128°C (lit.[16] 128°C); IR spectrum (Nujol) showed band at 3250-3380 cm^{-1} (-NH_2. >N<u>H</u>). PMR spectrum ($CDCl_3$) showed signals at δ 5.9 (-N<u>H</u>$_2$, D_2O exchangeable); 6.5 - 7.8 (pyrazole ring and phenyl ring protons). Mass spectrum: M^+ 159. Analysis showed correct values.

(e) Reduction with sodium hydrosulfite[17]

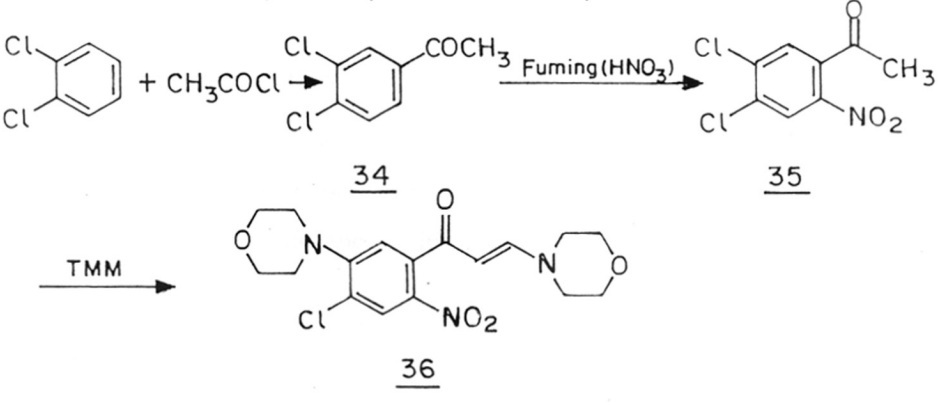
Sodium hydrosulfite was portionwise added to the solution of ∝-(o-nitrobenzoyl)- β -morpholinoethene in ethanol : THF (1:1) mixture. The desired 4-hydroxyquinoline (32) was obtained by acidification of the reaction mixture; m.p. 199°C (lit.[18] 201°C); IR (Nujol) showed bands at 3320- 3500 cm^1 (-OH). PMR spectrum (Acetone-d_6) showed signals at δ 7.6-9.1 (aromatic protons). Mass spectrum: M^+ 145. UV spectrum (methanol) showed λ_{max} 330 (ϵ_{max} 9753.3).

(f) Reduction with palladium charcoal in acid medium

∝-(o-nitrobenzoyl)- β -morpholinoethen was hydrogenated in prsence of 10% palladium charcoal and catalytic amount of acetic acid at 3

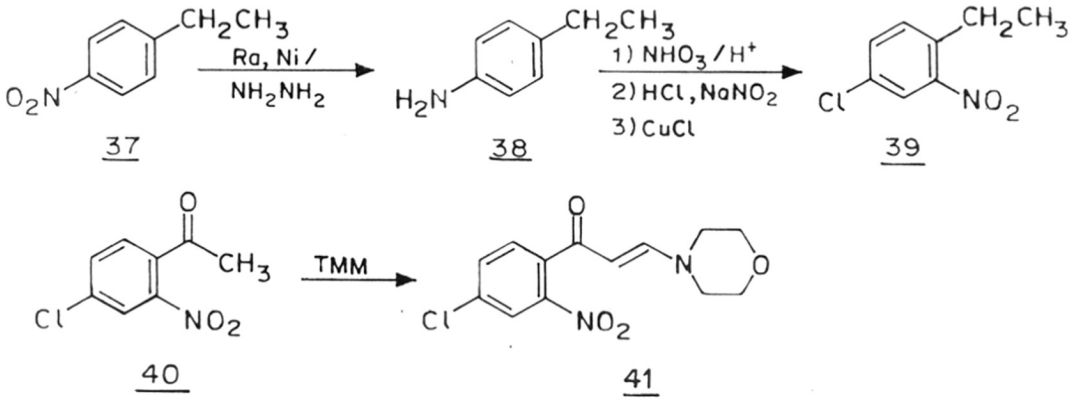
atmosphere pressure to obtain 4-hydroxyquinoline N-oxide[18,19] (33). This compound was characterised by its spectral data. IR spectrum (Nujol) showed bands at 3330-3480 cm^{-1} (-OH). PMR spectrum (TFA) showed signals at δ 7.1-8.9 (aromatic protons). Mass spectrum: M^{+} 161. UV spectrum (methanol) showed λ_{max} 343 nm (ϵ_{max} 10885.7).

The main object of the reduction studies was utilisation of these results for the preparation of 7-chloro-4-hydroxyquinoline which is an intermediate in the synthesis of chloroquine, an antimalarial drug. This was obtained from the enamine of 2-nitro-4-chloroacetophenone. For this purpose a model compound, 2-nitro-4,5-dichloroacetophenone, which is easy to prepare[20]. was studied for enamine formation and further hydrogenation. The condensation of 2-nitro-4,5-dichloroacetophenone with trimorpholinomethane gave a compound which showed m.p. 218°C. Microanalysis and mass (M^{+} 382) gave the compound of molecular formula $C_{17}H_{20}N_3O_5Cl$ which indicated that the chlorine atom para to nitro group was replaced by morpholine (36). This was supported by PMR ($CDCl_3$) signals at δ 3.2 [m, 8H, $((-N(CH_2)_2)_2)$]; 3.85 [m, 8H, $((O(CH_2)_2)_2)$]; 5.35 (d, 1H, J = 14Hz, $\frac{H}{}\!\!>C = C\!<^{N}_{H}$), 7.45 (d, 1H, J = 14Hz, $H\!>C = C\!<^{N}_{H}$); 6.15, 8.15 (aromatic protons). IR showed bands at 1640 cm^{-1} (- $C(=O)\!-\!C=C\!-\!N<$) etc. This result was not suprising as such displacement reaction was observed previously in this laboratory.[20]



The reduction studies of this enamine (36) with sodium hydrosulfite and with 10% palladium charcoal in acidic medium did not give the expected compounds. Products obtained require further studies to assign the structures beyond doubt.

2-Nitro-4-chloroacetophenone[20,21] was prepared from 4-nitroethylbenzene.



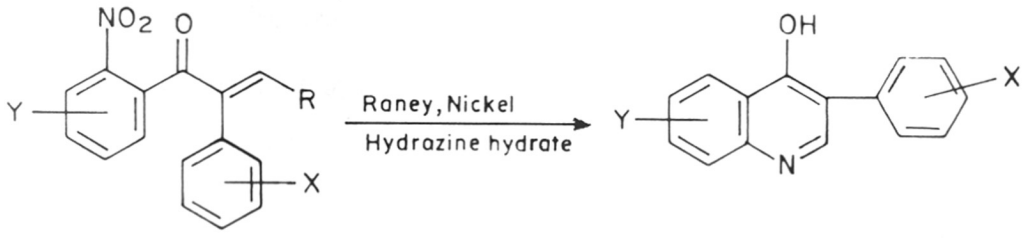
p-Nitroethylbenzene was reduced to p-aminoethylbenzene by Raney Nickel and hydrazine hydrate.[22] p-Aminoethylbenzene was nitrated to 2-nitro-4-aminoethylbenzene which was diazotised and the diazo group was displaced by cuprous chloride to obtain 2-nitro-4-chloroethylbenzene.[23] 2-Nitro-4-chloroethylbenzene was oxidised with potassium permanganate in presence of aluminium sulfate[24] to give 2-nitro-4-chloroacetophenone.

This compound was confirmed by its spectral data, PMR spectrum ($CDCl_3$) showed signals at δ 2.5 (s, 3H, -$\overset{O}{\overset{\|}{C}}$ - CH_3); 7.35, 7.45, 8.66 (aromatic protons). IR showed band at 1695 cm^{-1} (-$\overset{O}{\overset{\|}{C}}$-).

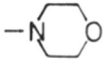
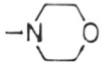
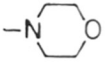
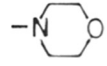
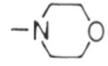
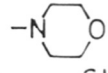
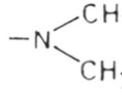
2-Nitro-4-chloroacetophenone was condensed with 1.5 equivalents of trimorpholinomethane[10] to give α-(2-nitro-4-chlorobenzoyl)-β-morpholinoethene (41); m.p. 148°C (benzene). IR spectrum (Nujol) showed band

SCHEME–3

PREPARATION OF 3-ARYL–4–HYDROXYQUINOLINES (XXXXIV)



III XXXXIV

Comp. No	X	Y	R	Comp. No.	X	Y
III–1	4–NO_2	H		XXXXIV–1	4–NH_2	H
III–2	2–NO_2	H		XXXXIV–2	2–NH_2	H
III–3	2–NO_2 5–OMe	H		XXXXIV–3	2–NH_2 5–OMe	H
III–4	4–NO_2	4–NO_2		XXXXIV–4	4–NH_2	7–NH_2
III–5	2–NO_2	4–NO_2		XXXXIV–5	2–NH_2	7–NH_2
III–6	H	H		XXXXIV–6	H	H
III–7	4–CH_3	H		XXXXIV–7	4–CH_3	H

at 1640 cm^{-1} (-C(=O)-C=C-N<). PMR spectrum ($CDCl_3$) showed signals at δ 3.3 (t, 4H, $-N(CH_2)_2$); 3.6 (t, 4H, $O(CH_2)_2$), 5.3 (d, 1H, J = 14Hz, H-C = C(-H)-N<). Mass spectrum: M^+ 296.

Reduction of α-(2-nitro-4-chlorobenzoyl)- β -morpholinoethene with sodium hydrosulfite followed by usual work-up gave 4-hydroxy-7-chloroquinoline (42); m.p. 272°C (lit.[5] 278°C). IR spectrum (Nujol) showed band at 3310-3490 cm^{-1} (-OH). UV spectrum (methanol) showed λ_{max} 330 (ϵ_{max} 9965.5). Mass spectrum: M^+ 179. Analysis showed the correct values within the range of 0.5% error. (Scheme-2).

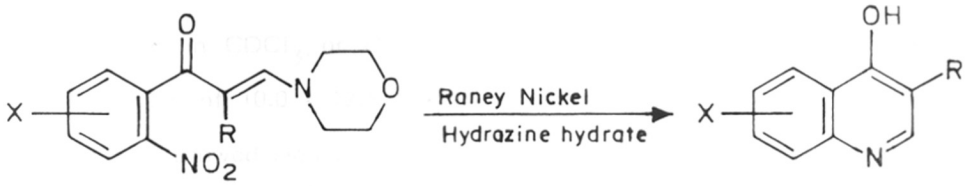
10% Palldium charcoal hydrogenation of the same compound at 3 atmosphere pressure in presence of acetic acid gave 4-hydroxyquinoline (32) instead of the expected 4-hydroxy-7-chloroquinoline N-oxide (43).

From the above hydrogenation studies it is evident that three reagents seems to be worth studing. They are: 1) Ra/Ni,-NH_2NH_2; 2) Pd/C, H_2. Cat. HOAc; and 3) Sodium hydrosulfite. The enamines prepared from o-nitroacetophenones gave pyrazole derivative when they were reacted with Raney Nickel, hydrazine hydrate while the acylated enamines namely α-(2-nitrobenzoyl)- β -dialkylaminostyrenes (III) prepared in Chapter II, Part A, when reacted with Raney Nickel, hydrazine hydrate , surprisingly gave 3-aryl substituted 4-hydroxyquinolines (XXXXIV) instead of pyrazole derivative. (Scheme-3).

IR of these compounds showed bands at 3350-3500 cm^{-1} (OH); while $-NH_2$ (if present) showed two bands in between 3200-3390 cm^{-1}.

SCHEME – 4

PREPARTION OF 3-ALKYL-4-HYDROXYQUINOLINES (XXXXV)



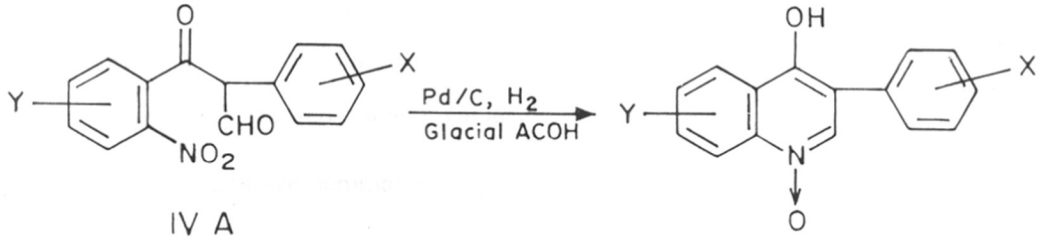
XVIII A XXXXV

Comp. No.	X	R
XVIII A-1	H	$-C_2H_5$
XVIII A-2	4-NO_2	$-C_2H_5$
XVIII A-3	H	$-C_4H_9$
XVIII A-4	4 NO_2	$-C_4H_9$

Comp. No.	X	R
XXXXV-1	H	$-C_2H_5$
XXXXV-2	7-NH_2	$-C_2H_5$
XXXXV-3	H	$-C_4H_9$
XXXXV-4	7-NH_2	$-C_4H_9$

SCHEME – 5

PREPARATION OF 3-ARYL-4-HYDROXYQUINOLINE N-OXIDES (XXXXVI)



IV A XXXXVI

Comp. No.	X	Y
IV A-2	2-NO_2	H
IV A-14	H	H

Comp. No.	X	Y
XXXXVI-2	2-NH_2	H
XXXXVI-14	H	H

PMR either in $CDCl_3$ or DMSO d_6 or Acetone d_6 showed OH signal in the region of 10.0 - 12.4 δ which exchanged with D_2O. NH_2 group (if present) showed signals in between 3.6 - 4.2 δ, exchangeable with D_2O. Due to nonavailability of dueterated solvents, PMR of some of the compounds were not taken. Ultra Violet absorption showed λ_{max} between 275 - 234 nm. Microanalysis and mass spectra showed correct values. The results are summarised in Scheme-2.

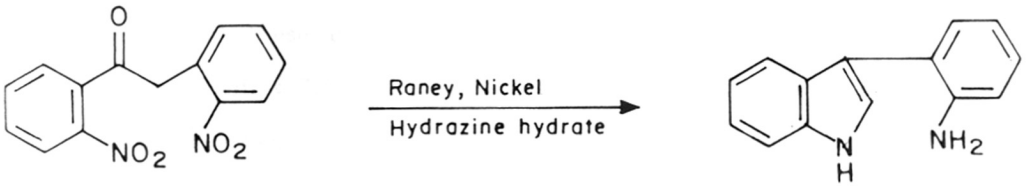
Similarly 1-morpholino-2-(o-nitrobenzoyl)alkenes (XVIIIA) prepared in Chapter II, Part B were reductively cyclised to 3-alkyl substituted 4-hydroxyquinolines (XXXXV) in presence of Raney Nickel and hydrazine hydrate. IR of these compounds showed bands in between 3100-3500 cm^{-1} (-OH & $-NH_2$). UV spectra showed λ_{max} in the region of 323-339 nm. PMR showed signals of OH in the region of 10.7 - 12.05 δ which is exchanged with D_2O. 3-Ethyl substituted 4-hydroxyquinolines showed signal at δ 1.0 - 1.2 (t, 3H, $-CH_3$), 2.5 (q, 2H, $-CH_2-$) while 3-butyl substituted 4-hydroxyquinoline showed signal in the region of 0.9 - 2.5 δ, each group of proton could not be assigned separately. Microanalysis and mass spectra showed correct values.

The results are summarised in Scheme-4.

The reduction studies of β-ketoaldehydes IVA in presence of Raney Nickel and hydrazine hydrate was carried out, because presumably they might form pyrazone derivatives. However, 3-(2-nitrophenyl)-3-oxo-2-phenyl-1-propanal (IVA) prepared in Chapter II, Part A were

SCHEME – 6

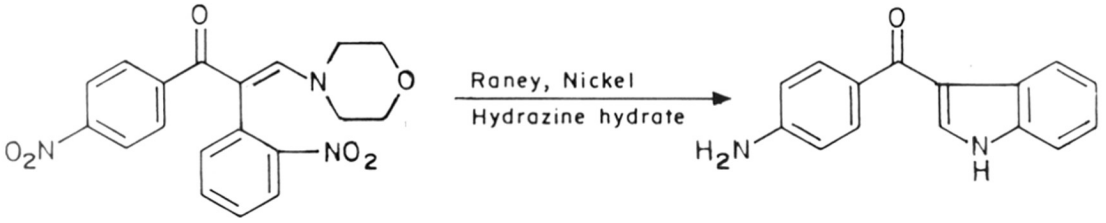
PREPARATION OF 3-(2-AMINOPHENYL)INDOLE (XXXXVII)



IV – 2 XXXXVII

SCHEME – 7

PREPARATION OF 3-(4-AMINOBENZOYL)INDOLE (XXXXVIII)



III – 9 XXXXVIII

hydrogenated at 3 atmosphere pressure with Pd/C in presence of acetic acid to give 3-aryl substituted 4-hydroxyquinoline N-oxides (XXXXVI).

PMR of these compounds showed signals of aromatic protons in the region of δ 7.2 - 8.5. IR showed bands in between 3280-3450 cm^{-1} corresponding to NH_2 and OH and bands in between 1185-1190 cm^{-1} corresponding to (N $\rightarrow$ O). UV showed λ_{max} in the range of 320 - 328 nm. Microanalysis and mass spectra showed correct values. The results are indicated in Scheme-5.

1-(2-Nitrophenyl)-2-(2-nitrophenyl)ethanone (IV-2) was cyclised to 3-(2-aminophenyl)indole (XXXXVII) in presence of Raney Nickel and hydrazine hydrate (Scheme-6). This compound showed PMR signals at δ 3.1 (-NH_2, D_2O exchangeable); 4.3 (>NH, D_2O exchangeable); 6.6 - 7.7 (aromatic protons). IR showed bands between 3150-3380 cm^{-1} (-NH_2, NH). UV showed λ_{max} 330 nm (ϵ_{max} 6825); Mass spectrum: M^+ 208; m.p. 138°C.

The compound α-(4-nitrobenzoyl)-β-morpholino-2-nitrostyrene (III-9) was cyclised to 3-(4-aminobenzoyl)indole (XXXXVIII) in prsence of Raney Nickel and hydrazine hydrate (Scheme-7); m.p. 207°C (ethanol). PMR showed signals at δ 2.95 (-NH_2, D_2O exchangeable); 4.0 (>NH, D_2O exchangeable), 3180-3310 cm^{-1} (-NH_2, >NH). UV spectrum showed λ_{max} at 333-334 nm (ϵ_{max} 13422.5). Mass spectrum: M^+ 236.

Conclusion

Enamines are very useful intermediates for the synthesis of various heterocyclic compounds. Depending upon the reducing agents 3-alkyl, 3-aryl substituted 4-hydroxyquinoline, 4-hydroxyquinoline N-oxides and indoles are prepared in one step.

EXPERIMENTAL

Preparation of α-(2-nitrobenzoyl)-β-morpholinoethene

The following starting materials were prepared:

1. 2-Nitroacetophenone
2. 2-Nitro-4,5-dichloroacetophenone
3. 2-Nitro-4-chloroacetophenone

1. Preparation of 2-nitroacetophenone (1)

This was prepared according to the literature[24] method as follows:

A three necked, two litre round bottom flask equipped with a mechanical stirrer, a thermometer and a reflux condensor was charged with water (500 ml), o-nitroethylbenzene (90.6 g, 0.6 mole) and aluminium sulfate (90.6 g). The mixture was heated to 60°C and potassium permanganate (160.03 g) was added in ten portions at an interval of 1 hour, with vigorous stirring. The temperature of the reaction mixture was maintained at 60-62°C on a heated waterbath. After the last portion of oxidising agent was added, the reaction mixture was stirred at the same temperature until the reaction terminated. After 14 hr from the start of reaction, samples of the reaction mixture were taken at intervals of 30 min. The completion of reaction was indicated by the absence of violet colour on the filter paper, when a drop of the reaction mixture was placed on it. The duration of the process was about 20 hr.

The 2-nitroacetophenone was isolated as follows:

At the end of the reaction, 500-700 ml of ethyl acetate was added to the reaction mixture and it was stirred at the same temperature (60-62°) for 1 - 1.5 hr, cooled to room temperature and was filtered through a Buchner funnel. The residue which was a mixture of manganese dioxide and aluminium hydroxide was washed on the filter with about 150 ml of ethyl acetate. The filtrate was transferred to a separating funnel and the ethyl acetate layer was separated from the aquous layer. The solvent was distilled off to yield a mixture of nitro compounds (88.4 g) which was fractionally distilled under vacuum.

Fr. 1, b.p. 76-83°/1.5 mm - unreacted o-nitroethyl benzene 36.4 g

Fr. 2, b.p. 117-125°/1.5 mm - 2-nitroacetophenone 39.6 g

Yield of pure 2-nitroacetophenone 66.8%.

2. **Preparation of 2-nitro-4,5-dichloroacetophenone** (35)

To a well stirred suspension of anhydrous $AlCl_3$ (44.3 g, 0.34 mol) and o-dichlorobenzene (30 ml, 0.26 mole) was added acetylchloride (10.8 ml, 0.15 mole) in 1 hr at 20-25°C temperature. After the initial reaction was subsided, the mixture was heated on steam bath for 2 hr. Then it was cooled and poured on ice containing conc. HCl. This was extracted with 2 x 100 ml ether. The extract was washed with water till free of acid, dried over anhydrous sodium sulfate and concentrated. The oily residue subjected to distillation. The fraction collected at 130-132°/15 mm gave crude 4,5-dichloroacetophenone (24 g). This was purified by crystallization from benzene - pet. ether when pure 4,5-dichloroacetophenone (m.p. 75-76°C) was obtained (21 g).

4,5-Dichloroacetophenone (8 g) was added o fuming HNO_3 (d 1.5, 50 ml) at temperature between 35° - 38°C in 10 min. with stirring. This was further stirred for 15 min. at this temperature and poured on ice. The precipitated nitroketone was collected and digested with aqueous sodiumbicarbonate (10%) for 10 min. The product was filtered, washed with water till free of alkali and purified it by crystallisation from ethanol.

Yield 5.8 g (57.5%)

M.P. 100-101°C

3. Preparation of 2-nitro-4-chloroacetophenone (40)

This involves the following steps:

(a) Preparation of 4-aminoethylbenzene from 4-nitroethylbenzene [22]

To a mechanically stirred solution of 4-nitroethylbenzene (45. 3 g, 0.3 mole) in ethanol (300 ml), at 50°C was added Raney Nickel (4.8 g), followed by addition of hydrazine hydrate (75 g) at such a rate as to maintain the temperature 50-55°C. When effervescence had ceased, the catalyst was removed by filtration, solvent evaporated at reduced pressure and residue distilled at 82-90°/0.5 mm.

Yield 30.75 g (85%)

IR spectrum (Neat) showed bands at 3360 and 3440 cm^{-1} ($-NH_2$)

PMR spectrum (CCl_4) showed signals at δ 1.8 (t, 3H, $-C\underline{H}_3$); 3.0 (q, 2H, $-C\underline{H}_2-$), 3.95 (NH_2, D_2O exchangeable), 7.1-7.6 (aromatic protons).

(b) Preparation of 2-nitro-4-chloroethylbenzene [23]

To a stirred solution of conc. sulphuric acid at 10°C was added 4-aminoethylbenzene (30.25 g). Then it was cooled to-5°C, followed by addition

of a mixture of nitric acid (d 1.50, 17.5 g) and conc. sulphuric acid (50 g) over 1 hr, keeping the ice salt bath temperature between 0°-5°C. After 20 min. of addition, the reaction mixture was poured into 1000g of ice. The solid obtained was filtered, dissolved in the mixture of hydrochloric acid (100 cc) and water (500 cc); to that a solution of sodium nitrite (14 g) in water (40 cc) was added dropwise over 30 min. at 0°C. It was then treated with urea (2 g), filtered and the filtrate was poured slowly at 80°C into occasionally stirred solution of cuprous chloride (32 g) in 25 % hydrochloric acid (150 cc). After completion of addition, it was kept for 0.5 hr at 80°C, cooled to room temperature, extracted in ether (3 x 100 ml), ether layer was washed with water, dried over anhydrous sodium sulphate, solvent removed and the residue was distilled at 105°C/0.5 mm.

Yield 18.3 g (42.77%)

PMR spectrum (CCl_4) showed signals at δ 1.15 (t, 3H, $\underline{CH_3}$), 2.95 (q, 2H, -$\underline{CH_2}$-), 7.2-7.9 (aromatic protons).

(c) Preparation of 2-nitro-4-chloroacetophenone

This compound was prepared according to the procedure of the preparation of 2-nitroacetophenone with the following quantities.

2-Nitro-4-chloroethylbenzene	18.55 g (0.1 mole)
$Al_2(SO_4)_3$	12.5 g
$KMnO_4$	22 g

This compound was purified by fraction distillation.

Fr. 1, b.p. 82-90°/.5 mm, unreacted 2-nitro-4-chloroethylbenzene (12 g)

Fr. 2, b.p. 115-120°/.5 mm, 2-nitro-4-chloroacetophenone (4 g)

Yield 4 g (20%)

M.P. 55°C

IR spectrum (Neat) showed band at 1695 cm^{-1} (-C-)

PMR spectrum ($CDCl_3$) showed signals at δ 2.5 (s, 3H, -C-CH_3), 7.35, 7.45, 8.66 (aromatic protons).

Preparation of α-(2-nitrobenzoyl)-β-morpholinoethene

General Procedure:

In a 100 ml round bottom flask, 2-nitroacetophenone (.02 mole) and trimorpholinomethane (8.13 g, 0.03 mole) were placed and the mixture was heated at 120-130°C, under water-pump suction with stirring for 2 hr. The resultant mixture was cooled to room temperature, solid obtained was crystallized from appropriate solvent.

The following compounds were prepared according to this general method, with the quantities given.

1. **Preparation of α-(2-nitrobenzoyl)-β-morpholinoethene** (2)

2-Nitroacetophenone 3.30 g (0.02 mole)

Trimorpholinomethane 8.13 g (0.03 mole)

M.P. 150-152°C (benzene)

Yield 4.24 g (81%)

IR spectrum (Nujol) showed band at 1660 cm^{-1} (-C-C=C-N<)

PMR spectrum ($CDCl_3$) showed signals at δ 3.3 (t, 4H, -N(CH_2)$_2$), 3.75 (t, 4H, O(CH_2)$_2$), 5.3 (d, 1H, J = 14Hz, H>C = C<N<H), 7.1-7.8 (H>C = C<N<H and aromatic protons).

Analysis, Found: C, 59.25; H, 5.71; N, 9.79.

$C_{13}H_{14}N_2O_4$ requires: C, 59.54; H, 5.34; N, 10.68.

Mass spectrum: M^+ 262.

2. **Preparation of α-(2-nitro-4-chloro-5-morpholinobenzoyl) -β-morpholinoethene (36)**

2-Nitro-4,5-dichlorophenone 4.68 g (0.02 mole)

Trimorpholinomethane 8.13 g (0.03 mole)

M.P. 218°C (methanol)

Yield 5.96 g (78%).

IR spectrum (Nujol) showed band at 1640 cm^{-1} (-C(=O)-C=C-N<)

PMR spectrum ($CDCl_3$) showed signals at δ 3.2 [m, 8H, $(-N(CH_2)_2)_2$] 3.85 [m, 8H, $(O(CH_2)_2)_2$], 5.35 (d, 1H, J = 14Hz, H-C = C(-N<)-H), 7.45 (d, 1H, J = 14Hz, H-C = C(-N<)-H), 6.15, 8.15 (aromatic protons).

Analysis, Found: C, 52.89; H, 5.51; N, 10.94; Cl, 9.19.

$C_{17}H_{20}N_3O_5Cl$ requires: C, 53.40; H, 5.24; N, 11.0; Cl, 9.29.

Mass spectrum: M^+ 382.

3. **Preparation of α-(2-nitro-4-chlorobenzoyl)- β -morpholinoethene (41)**

2-Nitro-4-chloroacetophenone 4.01 g (0.02 mole)

Trimorpholinomethane 8.13 g (0.03 mole)

M.P. 148°C (benzene)

Yield 4.91 g (83%)

IR spectrum (Nujol) showed band at 1640 cm^{-1} (--C(=O)-C=C-N<)

PMR spectrum ($CDCl_3$) showed signals at δ 3.3 (t, 4H, $-N(CH_2)_2$), 3.6 (t, 4H, $O(CH_2)_2$), 5.3 (d, 1H, J = 14Hz, H-C = C(-N<)-H), 7.2-7.9 H-C = C(-N<)-H and aromatic protons).

Mass spectrum: M^+ 296.

a) **Reduction of α-(2-nitrobenzoyl)-β-morpholinoethene with titanium trichloride to 2-aminoacetophenone[15] (28)**

To a solution of titanium trichloride (15%, 30 ml, 8 mole) and ammonium acetate (60 ml, 4 molar) was added a solution of α-(2-nitrobenzoyl)- β-morpholinoethene (1.31 g, 0.005 mole) in acetone (2 ml). The mixture was stirred for 30 min, extracted in ether (3 x 20 ml), ether layer was washed with water, dried over anhydrous sodium sulphate. The solvent was evaporated and the residue was chromatographed over silica gel using pet. ether - benzene (95:5) mixture as an eluent.

Yield 0.216 g (32%)

IR spectrum (Neat) showed bands at 1710 cm^{-1} ($-\overset{O}{\overset{\|}{C}}-$), 3380, 3230 cm^{-1} ($-NH_2$).

PMR spectrum (CCl_4) showed signals at δ 2.5 (s, 3H, $-\underline{CH_3}$), 6.1 (NH_2, D_2O exchangeable), 6.4-7.7 (aromatic protons).

b) **Reduction of α-(2-nitrobenzoyl)- β-morpholinoethene with palladium charcoal to 2-aminopropionone (29) and 1-(2-aminobenzoyl)-2-morpholinoethane (30).**

α-(2-Nitrobenzoyl)- β-morpholinoethene (1.31 g, 0.005 mole) was dissolved in ethanol (20 ml), to that 10% palladium charcoal (10 mg) was added and the mixture was hydrogenated at 3 atmospheric pressure for 4 hr. The catalyst was removed by filtration, the filtrate was concentrated under reduced pressure, and the residue was chroamtographed over silica gel. Fraction eluted in petroleum ether : benzene (95:5) mixture was 2-aminopropiophenone, while fraction eluted in petroleum ether : benzene (85:15) mixture was 1-(2-aminobenzoyl)-2-morpholinoethane.

Yield of 2-aminopropiophenone[15] 0.171 g (23%)

IR spectrum (Neat) showed bands at 3240, 3350 cm^{-1} ($-NH_2$), 1710 cm^{-1} (-C-).

PMR spectrum (CCl_4) showed signals at δ 1.15 (t, 3H, CH_3), 2.95 (q, 2H, $-CH_2-$), 5.85 (NH_2, D_2O exchangeable), 6.65-7.85 (aromatic protons).

Yield of 1-(2-aminobenzoyl)-2-morpholinoethane 0.386 g (33%)

M.P. 170°C (benzene)

IR spectrum (Nujol) showed bands at 3245, 3390 cm^{-1} ($-NH_2$), 1710 cm^{-1} (-C-).

PMR spectrum ($CDCl_3$) showed signals at δ 2.5 (t, 4H, $-N(CH_2)$, 3.7 (t, 4H, $O(CH_2)$, 2.8 (t, 2H, $-CH_2-N<$), 3.15 (t, 2H, -C- CH_2-), 6.3 (NH_2, D_2O exchangeable), 6.45-7.85 (aromatic protons).

Mass spectrum: M^+ 234.

c) **Reduction of α-(2-nitrobenzoyl-β-morpholinoethene with Raney Nickel hydrogenation to 2-aminopropiophenone[15] (29)**

α-(2-Nitrobenzoyl)-β-morpholinoethene (1.31 g, 0.005 mole) was dissolved in ethanol (20 ml), to that Raney Nickel (300 mg) was added and the mixture was hydrogenated for 10 hr. Raney Nickel was removed by filtration, the filtrate was concentrated and the residue was chromatographed over silica gel using benzene: pet.ether (5:95) mixture as an eluent.

Yield 0.342 g (46%).

d) **Reduction of α-(2-nitrobenzoyl)-β-morpholinoethene with Raney Nickel hydrazine hydrate to 3-(2-aminophenyl)pyrazole[16] (31)**

To a stirred solution of α-(2-nitrobenzoyl)-β-morpholinoethene

(1.31 g, 0.005 mole) dissolved in methanol (20 ml) at 50°C, was added Raney Nickel (300 mg), followed by addition of hydrazine hydrate (2.5 ml) at such a rate as to maintain the reaction temperature between 50 - 55°C. The reaction mixture was stirred further for 2 hr. The catalyst was removed by filtration, the filtrate was concentrated and the residue was crystallised from dichloroethane - pet. ether.

M.P. 128°C

Yield 0.445 g (56%)

IR spectrum (Nujol) showed band at 3250-3380 cm^{-1} ($-NH_2$, >N-H).

PMR spectrum ($CDCl_3$) showed broad signal at δ 5.9 (NH_2, D_2O, exchangeable), 6.5-7.8 (pyrazole ring and phenyl ring protons).

Analysis, Found: C, 68.81; H, 5.38; N, 25.92.

Calculated for $C_9H_9N_3$: C, 68.92; H, 5.66; N, 26.42.

Mass spectrum: M^+ 159.

e) **Reduction of α-(2-nitrobenzoyl)-β-morpholinoethene with sodium hydrosulfite to 4-hydroxyquinoline**

Literature method[17] was followed for the reduction with sodium hydrosulfite.

General Procedure:

To α-(2-nitrobenzoyl)-β-morpholinoethene (0.005 mole) dissolved in a mixture of 15 ml THF, 15 ml ethanol and 10 ml water, was added portionwise, 2.4 g of sodium hydrosulfite. The mixture was stirred and heated on steam bath for 10 min. and after an additional 10 ml of water was added, stirring was continued at room temperature for 20 min. At this point more sodium hydrosulfite (1.6 g) was added portion-

wise and after warming, the mixture was stirred at room temperature for 20 min. and evaporated at reduced pressure to remove the organic solvents. The residue was acidified with 6N hydrochloric acid, the solid obtained was filtered and crystallised.

The following compounds were prepared according to this general method with the quantities given.

1. **Preparation of 4-hydroxyquinoline** (32)

α-(2-Nitrobenzoyl-β-morpholinoethene	1.31 g (0.005 mole)
THF : Ethanol (1:1)	30 ml
Sodium hydrosulfite	4 g

This compound was crystallised from water

M.P. 199°C (lit. 201°C)

Yield 0.565 g (78%)

IR spectrum (Nujol) showed band at 3320-3500 cm^{-1} (OH).

PMR spectrum (Acetone-d_6) showed signals at δ 7.6-9.1 (aromatic protons).

UV spectrum (methanol) showed λ_{max} at 330 (ϵ_{max} 9753.3)

Analysis, Found: C, 73.83; H, 4.76; N, 9.38.

Calculated for $C_{19}H_7NO$: C, 74.48; H, 4.83; N, 9.66.

Mass spectrum: M^+ 145.

2. **Preparation of 4-hydroxy-7-chloroquinoline** (42)

α-(2-Nitro-4-chlorobenzoyl)-β-morpholinoethene	1.48 g (0.005 mole)
Sodium hydrosulfite	4 g

This compound was crystallised from ethanol-water.

M.P. 272°C (lit.[5] 278°C)

Yield 0.483 g (54%)

IR spectrum (Nujol) showed band at 3310-3490 cm^{-1} (OH^-).

Analysis, Found: C, 59.85; H, 3.40; N, 7.52; Cl, 20.10.

Calculated for C_9H_6NOCl: C, 60.33; H, 3.35; N, 7.82; Cl, 19.83.

UV spectrum (methanol) showed λ_{max} 330 nm (ϵ_{max} 9965.5)

Mass spectrum: $M^{\ddagger}$ 179.

f) **Preparation of 4-hydroxyquinoline-1-oxide:**

General Procedure

α-(2-Nitrobenzoyl)-β-morpholinoethene (0.005 mole) was dissolved in methanol (20 ml). To that glacial acetic acid (0.2 ml) and palladium charcoal (10%, 100 mg) was added and the mixture was hydrogenated at 3 atmospheric pressure for 4-5 hr. The catalyst was removed by filtration, solvent evaporated under reduced pressure and the residue was crystallised from the appropriate solvent.

The following compounds were prepared according to this general method with the quantities given.

1. **Preparation of 4-hydroxyquinoline-1-oxide** (33)

α-(2-Nitrobenzoyl)-β-morpholinoethene	1.31 g (0.005 mole)
10% Palladium charcoal	100 mg
Glacial acetic acid	0.2 ml

This compound was crystallised from methanol.

M.P. 236°C (lit.[6] 268°C)

Yield 0.475 g (59%)

IR spectrum (Nujol) showed band at 3330-3480 cm^{-1} (-OH).

PMR spectrum (TFA) showed signal at δ 7.1-8.9 (aromatic protons).

Analysis, Found: C, 67.58; H, 4.10; N, 8.73.

$C_9H_7NO_2$ requires: C, 67.08; H, 4.35; N, 8.7.

UV spectrum (methanol) showed λ_{max} at 343 nm (ϵ_{max} 10885.7)

Mass spectrum: M^+ 161.

2. **Reduction of ∝-(2-nitro-4-chlorobenzoyl)-β-morpholinoethene with Pd/C in acidic medium to 4-hydroxyquinoline** (33)

∝-(2-Nitro-4-chlorobenzoyl)-β-morpholinoethene	1.48 g (0.005 mole)
10% Palladium charcoal	100 mg
Glacial acetic acid	0.2 ml

Instead of expected 4-hydroxy-7-chloroquinoline-1-oxide, unexpected 4-hydroxyquinoline was obtained.

M.P. 197°C (methanol)

Yield 0.319 g (44%).

Preparation of 3-aryl-4-hydroxyquinolines and 3-alkyl-4-hydroxyquinolines

General Procedure:

To a stirred solution of α-(2-nitrobenzoyl)-β-dialkylaminostyrene (III, 0.01 mole) or 1-morpholino-2-(2-nitrobenzoyl)alkenes (XVIII-A, 0.01 mole) in acetone (50 ml) at 50°C was added Raney Nickel (1.5g). Then hydrazine hydrate (80%, 5-6 ml) was added at such a rate as to maintain the temperature of reaction mixture between 50-55°C. Stirring was continued at room temperature until the effervences were ceased (3 hr). Catalyst was removed by filtration, solvent was removed under reduced pressure and residue was crystallized from solvents.

Following compounds were prepared according to this general procedure, with the quantities given.

Due to insolubility of some of the compounds in common deuterated solvents, PMR were not taken.

1. **Preparation of 3-(4-aminophenyl)-4-hydroxyquinoline** (XXXXIV-1)

α-(2-Nitrobenzoyl)-β-morpholino-4-nitrostyrene	3.83 g (0.01 mole)
Raney Nickel	1.5 g
Acetone	50 ml
Hydrazine hydrate	5 ml

M.P. 301°C (methanol)

Yield 1.88 g (79.7%)

IR (Nujol) showed bands at 3290, 3380 ($-NH_2$), 3490 cm^{-1} (OH). PMR spectrum (Acetone-d_6) showed signals at δ 3.8 ($-NH_2$, D_2O exchangeable); 10.4 (-OH, D_2O exchangeable); 6.5-8.1 (aromatic

protons).

Analysis, Found: C, 75.80; H, 5.15; N, 12.0

$C_{15}H_{12}N_2O$ requires: C, 76.27; H, 5.08; N, 11.86.

UV spectrum (methanol) showed λ_{max} at 280 nm (ϵ_{max} 28686.2)

Mass spectrum: $M^{\ddagger}$ 236.

2. **Preparation of 3-(2-aminophenyl)-4-hydroxyquinoline** (XXXXIV-2)

α-(2-Nitrobenzoyl)-β-morpholino-2-nitrostyrene	3.83 g (0.01-mole)
Raney Nickel	1.50 g
Hydrazine hydrate	5 ml
Acetone	50 ml

M.P. 264-66°C (methanol)

Yield 1.99 g (84.2%)

IR spectrum (Nujol) showed bands at 3310 cm^{-1}, 3410 cm^{-1} ($-NH_2$); 3500 cm^{-1} (-OH).

PMR spectrum (Acetone-d_6) showed signals at δ 4.1 ($-NH_2$), D_2O, exchangeable); 10.1 (-OH, D_2O, exchangeable); 6.7-8.2 (aromatic protons).

Analysis, Found: C, 75.90; H, 5.28; N, 11.30

$C_{15}H_{12}N_2O$ requires: C, 76.27; H, 5.08; N, 11.86

UV spectrum (methanol) showed λ_{max} at 333-334 nm (ϵ_{max} 9596.3)

Mass spectrum: $M^{\ddagger}$ 236.

3. **Preparation of 3-(2-amino-5-methoxyphenyl)-4-hydroxyquinoline** (XXXXIV-3)

α-(2-Nitrobenzoyl)-β-morpholino-2-nitro-5-methoxystyrene	4.13 g (0.01 mole)
Raneyl Nickel	1.50 g

Hydrazine hydrate	5 ml
Acetone	50 ml

M.P. 235°C (ethanol-benzene)

Yield 1.86 g (69.8%).

IR spectrum (Nujol) showed bands at 3280 cm^{-1}, 3390 cm^{-1} ($-NH_2$); 3490 cm^{-1} (-OH).

PMR spectrum ($CDCl_3$) showed signals at δ 3.6 ($-NH_2$, D_2O exchangeable); 3.9 (s, 3H, $O-CH_3$); 11.2 (-OH, D_2O exchangeable); 6.7-8.1 (aromatic protons).

Analysis, Found: C, 71.85; H, 5.10; N, 10.3.

$C_{16}H_{14}N_2O_2$ requires: C, 72.18; H, 5.26; N, 10.52.

UV spectrum (methanol) showed λ_{max} at 318-320 nm (ϵ_{max} 14911.7)

Mass spectrum: M^+ 266.

4. **Preparation of 3-(4-aminophenyl)-4-hydroxy-7-aminoquinoline** (XXXXIV-4)

α-(2,4-Dinitrobenzoyl)-β-morpholino-4-nitrostyrene	4.28 g (0.01 mole)
Raney Nickel	1.5 g
Hydrazine hydrate	6 ml
Acetone	50 ml

M.P. 329-331°C (methanol)

Yield 2.00 g (79.7%)

IR spectrum (Nujol) showed bands at 3290 cm^{-1}, 3370 cm^{-1} ($-NH_2$); 3480 cm^{-1} (OH).

Analysis, Found: C, 71.95; H, 4.80; N, 17.2.

$C_{15}H_{13}N_3O$ requires: C, 71.71; H, 5.17; N, 16.73.

UV spectrum (methanol) showed λ_{max} at 323 nm (ϵ_{max} 13446.4)

Mass spectrum: M^+ 251.

5. **Preparation of 3-(2-aminophenyl)-4-hydroxy-7-aminoquinoline** (XXXXIV-5)

α-(2,4-Dinitrobenzoyl)-β-morpholino-2-nitrostyrene	4.28 g (0.01 mole)
Raney Nickel	1.50 g
Hydrazine hydrate	6 ml
Acetone	50 ml

M.P. 312°C (methanol)

Yield 1.92 g (76.4%)

IR spectrum (Nujol) showed bands at 3295 cm^{-1}, 3380 cm^{-1} ($-NH_2$); 3490 cm^{-1} (-OH).

Analysis, Found: C, 71.50; H, 5.32; N, 16.6.

$C_{15}H_{13}N_3O$ requires: C, 71.71; H, 5.17; N, 16.73.

UV spectrum (methanol) showed λ_{max} at 323 nm (ϵ_{max} 16475.9)

Mass spectrum: M^+ 251.

6. **Preparation of 3-(phenyl)-4-hydroxyquinoline** (XXXXIV-6)

α-(2-Nitrobenzoyl)-β-morpholinostyrene	3.83 g (0.01 mole)
Raney Nickel	1.50 g
Hydrazine hydrate	5 ml
Acetone	50 ml

M.P. 254°C (ethanol)

Yield 1.60 g (72%)

IR spectrum (Nujol) showed bands at 3480 cm^{-1} (-OH).

Analysis, Found: C, 80.8; H, 4.80; N, 6.95.

Calculated for $C_{15}H_{11}NO$: C, 81.44; H, 4.97; N, 6.33.

UV spectrum (methanol) showed λ_{max} at 270 nm, (ϵ_{max} 13128.6)

Mass spectrum: M^{+} 221.

7. **Preparation of 3-(4-methylphenyl)-4-hydroxyquinoline** (XXXXIV-7)

α-(2-Nitrobenzoyl)-β-dimethylamino-4-methylstyrene	3.10 g (0.01 mole)
Raney Nickel	1.50 g
Hydrazine hydrate	5 ml
Acetone	50 ml

M.P. 260°C (methanol)

Yield 2.00 g (85.2%)

IR spectrum (Nujol) showed band at 3490 cm^{-1} (-OH).

PMR spectrum (Acetone-d_6) showed signals at δ 2.5 (s, 3H, -$\underline{CH_3}$); 10.8 (OH, D_2O exchangeable), 7.3-8.6 (aromatic protons).

Analysis, Found: C, 81.58; H, 5.25; N, 5.66.

$C_{16}H_{13}NO$ requires: C, 81.70; H, 5.53; N, 5.95.

UV spectrum (methanol) showed λ_{max} at 275 nm (ϵ_{max} 11362.3)

Mass spectrum: M^{+} 235.

8. **Preparation of 3-ethyl-4-hydroxyquinoline** (XXXXV-1)

1-Morpholino-2(2-nitrobenzoyl)-but-1-ene	2.90 g (0.01 mole)
Raney Nickel	1.50 g
Hydrazine hydrate	5 ml
Acetone	30 ml

M.P. 185-86°C (chloroform-benzene)

Yield 1.18 g (68.6%)

IR spectrum (Nujol) showed bands at 3300-3490 cm^{-1} (-OH)

PMR spectrum ($CDCl_3$) showed signals at δ 1.2 (t, 3H,-$C\underline{H}_3$), 2.5 (q, 2H, -$C\underline{H}_2$-), 7.2-8.4 (aromatic protons), 12.05 (-OH, D_2O exchangeable).

Analysis, Found: C, 75.80; H, 6.70; N, 7.75.

$C_{11}H_{11}NO$: requires: C, 76.30; H, 6.36; N, 8.09.

UV spectrum (methanol) showed λ_{max} at 339 nm (ϵ_{max} 7294.7)

Mass spectrum: M^+ 173.

9. **Preparation of 3-ethyl-4-hydroxy-7-aminoquinoline** (XXXXV-2)

1-Morpholino-2-(2,4-dinitrobenzoyl)-but-1-ene	3.35 g (0.01-mole)
Raney Nickel	1.50 g
Hydrazine hydrate	6 ml
Acetone	30 ml

M.P. 235-36°C (methanol-chloroform)

Yield 1.18 g (62.5%)

IR spectrum (Nujol) showed bands at 3100-3480 (-NH_2& OH)

PMR spectrum (Acetone-d_6) showed signals at δ1.0 (t, 3H, -$C\underline{H}_3$); 2.5 (q, 2H, -$C\underline{H}_2$-), 5.0 (NH_2, D_2O exchangeable), 6.5-7.9 (aromatic protons), 10.7 (OH, D_2O exchangeable).

Analysis, Found: C, 70.35; H, 6.20; N, 14.60.

$C_{11}H_{12}N_2O$ requires: C, 70.21; H, 6.38; N, 14.89.

UV spectrum (methanol) showed λ_{max} at 326 nm (ϵ_{max} 8633.8)

Mass spectrum: M^+ 188.

10. **Preparation of 3-(n-butyl)-4-hydroxyquinoline** (XXXXV-3)

1-Morpholino-2-(2-nitrobenzoyl)-hex-1-ene	3.18 g (0.01 mole)
Raney Nickel	1.50 g

Hydrazine hydrate	5 ml
Acetone	30 ml

M.P. 138-39°C (benzene - petroleum ether)

Yield 1.21 g (60.3%)

IR (Nujol) showed band at 3300-3490 cm^{-1} (-OH)

PMR ($CDCl_3$) showed signals at δ 1.0-2.5 (-$\underline{CH_2}$-$\underline{CH_2}$-$\underline{CH_2}$-$\underline{CH_3}$); 7.2 - 8.4 (aromatic protons); 11.2 (OH, D_2O exchangeable).

Analysis, found: C, 77.15; H, 7.80; N, 6.65

$C_{13}H_{15}NO$ requires: C, 77.61; H, 7.46; N, 6.97.

UV spectrum (methanol) showed λ_{max} at 338 nm

(ϵ_{max} 12432.5)

Mass spectrum: M^{+} 201.

11. Preparation of 3-(n-butyl)-4-hydroxy-7-aminoquinoline (XXXXV-4)

1-Morpholino-2-(2,4-dinitrobenzoyl)-hex-1-ene	3.63 g (0.01 mole)
Raney Nickel	1.50 g
Hydrazine hydrate	6 ml
Acetone	50 ml

M.P. 207-208°C (ethanol - benzene)

Yield 1.22 g (56.5%)

IR spectrum (Nujol) showed band at 3100-3480 cm^{-1} ($-NH_2$ and -OH).

PMR spectrum (Acetone d_6) showed signals at δ 0.9-2.4 ($-\underline{CH_2}-\underline{CH_2}-\underline{CH_2}-\underline{CH_3}$); 5.1 ($NH_2$, D_2O exchangeable); 6.6, 7.5, 8.0 (aromatic protons); 10.4 (OH, D_2O exchangeable).

Analysis, Found: C, 71.90; H, 7.12; N, 12.72.

$C_{13}H_{16}N_2O$ requires: C, 72.22; H, 7.40; N, 12.96.

UV spectrum (methanol) showed λ_{max} at 323 nm (ϵ_{max} 12544.3)

Mass spectrum: M^+ 216.

Preparation of 3-aryl-4-hydroxyquinoline -1-oxide

General Procedure:

3-(2-Nitrophenyl)-3-oxo-2-phenyl-1-propanal (β -ketoaldehyde IVA, 0.001 mole), was dissolved in methanol (20 ml), to that glacial acetic acid (0.2 ml) and palladium charcoal (10%, 100 mg) were added. The mixture was hydrogenated at 3 atmospheric pressure for 4 hr. Catalyst was removed by filtration, solvent removed under reduced pressure and residue crystallized from appropriate solvent.

The following compounds were prepared according to this general procedure with the quantities given.

1. **Preparation of 3-(2-aminophenyl)-4-hydroxyquinoline-1-oxide (XXXXVI-2)**

3-(2-Nitrophenyl)-3-oxo-2-(2-nitrophenyl)-1-propanal
0.314 g (0.001 mole)

Glacial acetic acid 0.2 ml

10% Palladium charcoal 0.1 g

M.P. 206-207°C (methanol)

Yield 0.170 g (6 7.4%)

IR spectrum (Nujol) showed bands at 3110 cm^{-1}, 3240 cm^{-1} ($-NH_2$); 3350 cm^{-1} (-OH); 1170 cm^{-1} ($N\rightarrow O$)

Analysis, Found: C, 71.98; H, 5.10; N, 10.92.

$C_{15}H_{12}N_2O_2$ requires: C, 71.42; H, 4.76; N, 11.11.

UV spectrum (methanol) showed λ_{max} at 320 nm (ϵ_{max} 11312.5)

Mass spectrum: M^{+} 252

2. **Preparation of 3-phenyl-4-hydroxyquinoline-1-oxide** (XXXXVI-9)

3-(2-Nitrophenyl)-3-oxo-2-phenyl-1-propanal 0.269 g (0.001 mole)

Glacial acetic acid 0.2 ml

10% Palladium charcoal 0.1 g

M.P. 242°C (ethanol)

Yield 0.123 g (52%)

IR spectrum (Nujol) showed band at 3380 cm^{-1} (-OH), 1165 cm^{-1} ($N\rightarrow O$)

PMR spectrum (Acetone-d_6) showed signals at δ 10.3 (-OH, D_2O, exchangeable); 7.2-8.5 (aromatic protons).

Analysis, Found: C, 76.20; H, 4.82; N, 5.60.

$C_{15}H_{11}NO_2$ requires: C, 75.94; H, 4.64; N, 5.90.

UV spectrum (methanol) showed λ_{max} 328 nm (ϵ_{max} 9674.8).

Mass spectrum: M^{+} 237.

1. **Preparation of 3-(2-aminophenyl) indole** (XXXXVII)

This compound was prepared according to the general procedure of preparation of 3-aryl-4-hydroxyquinolines, with the quantities given below.

1-(2-Nitrophenyl)-2-(2-nitrophenyl)ethanone	2.68 g (0.01 mole)
Raney Nickel	1.5 g
Hydrazine hydrate	5 ml
Acetone	30 ml

M.P. 138°C (carbon tetrachlorice)

Yield 1.18 g (56.5%)

IR spectrum (Nujol) showed bands at 3150-3310 cm^{-1} ($-NH_2$, $>NH$)

PMR spectrum (DMSO-d_6) showed signals at δ 2.90 ($-NH_2$, D_2O exchangeable); 6.8-7.6 (aromatic protons), 5.2 (NH, D_2O, exchangeable)

Analysis, Found: C, 80.20; H, 5.90; N, 13.92.

$C_{14}H_{12}N_2$ requires: C, 80.76; H, 5.76; N, 13.46.

UV spectrum (methanol) showed λ_{max} 330 nm (ϵ_{max} 6825).

Mass spectrum: M^+ 208.

2. **Preparation of 3-(4-aminobenzoyl) indole** (XXXXVIII)

This compound was prepared according to the general procedure of preparation of 3-aryl-4-hydroxyquinolines, with the following quantities.

α-(4-Nitrobenzoyl)-β-morpholino-2-nitrostyrene	3.83 g (0.01 mole)
Raney Nickel	1.50 g
Hydrazine hydrate	6 ml
Acetone	50 ml

M.P. 207°C (ethanol)

Yield 1.96 g (83%)

IR spectrum (Nujol) showed bands at 1660 cm^{-1} (); 3180-3310 cm^{-1} ($-NH_2$, $>NH$).

PMR spectrum (DMSO-d_6) showed signals at δ 2.95 (NH_2, D_2O, exchangeable), 4.0 (NH, D_2O exchangeable), 6.8-8.6 (aromatic protons).

Analysis, found: C, 75.75; H, 4.90; N, 11.40

$C_{15}H_{12}N_2O$ requires: C, 76.27; H, 5.08; N, 11.86

UV Spectrum (methanol) showed λ_{max} at 333-334 nm

(ϵ_{max} 13422.5)

Mass spectrum: M^+ 236.

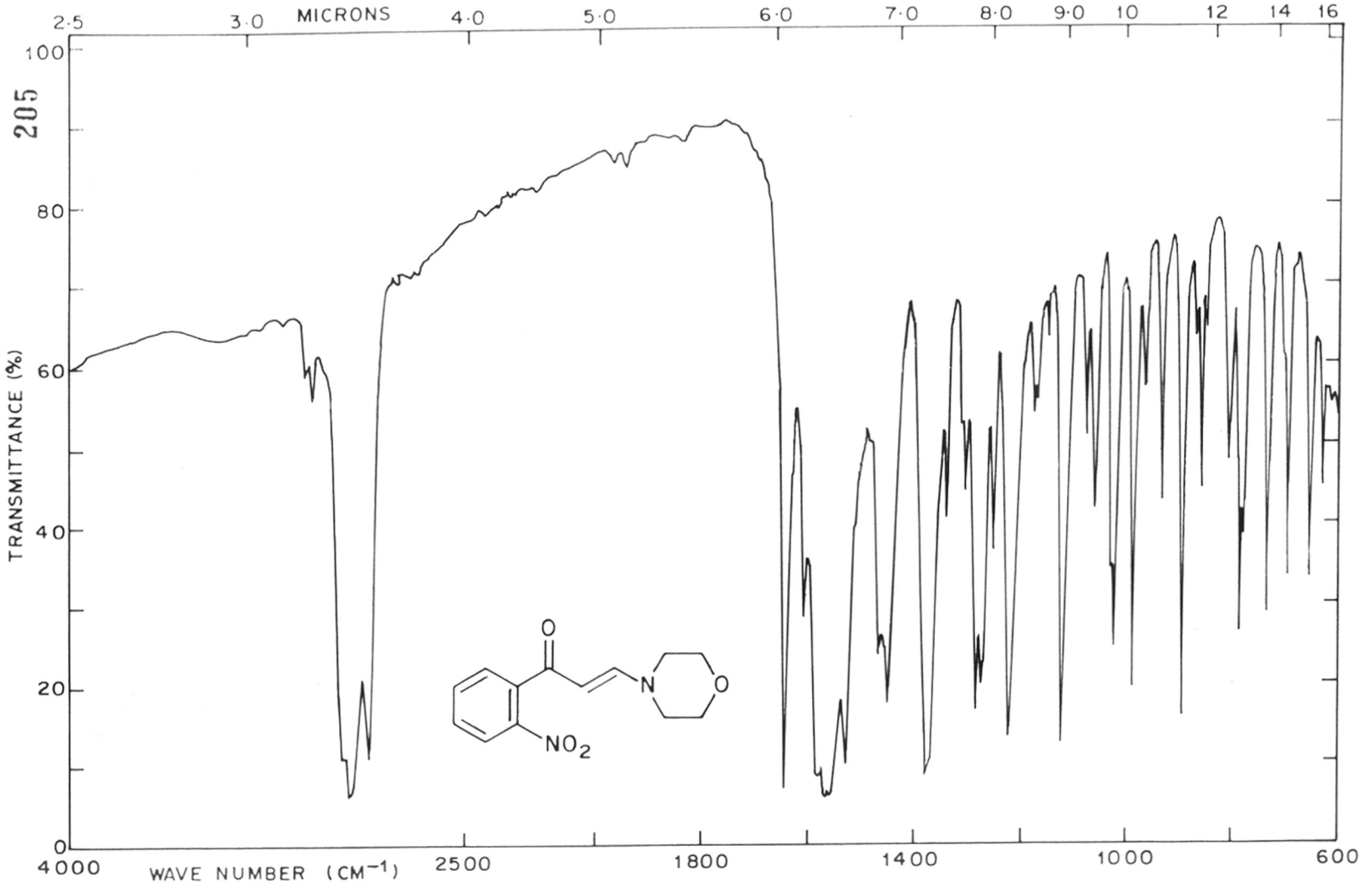


FIG. 3·1. IR SPECTRUM OF α-(2-NITROBENZOYL)-β-MORPHOLINOETHENE

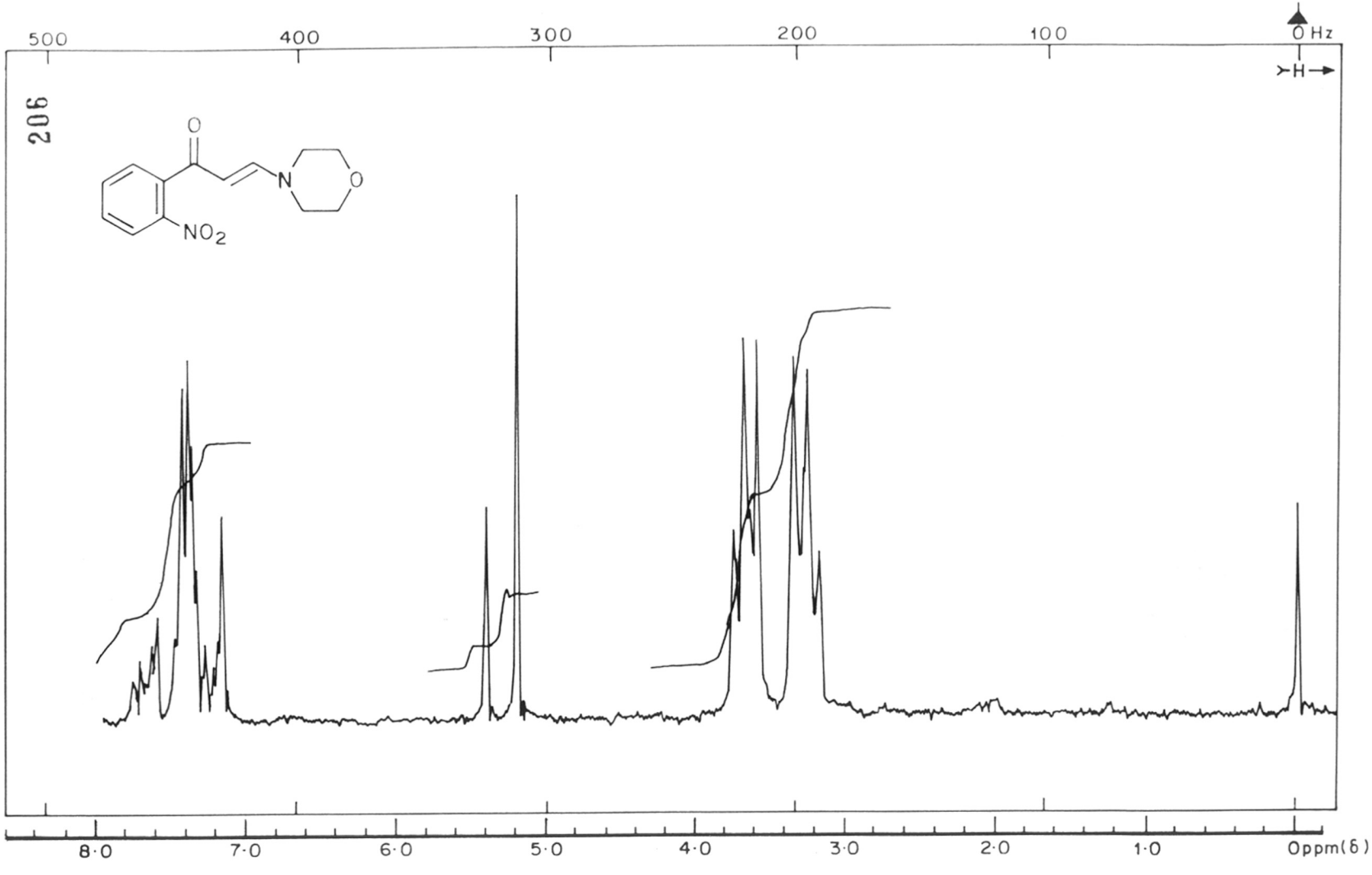


FIG. 3·2. PMR SPECTRUM OF α-(2-NITROBENZOYL)-β-MORPHOLINOETHENE

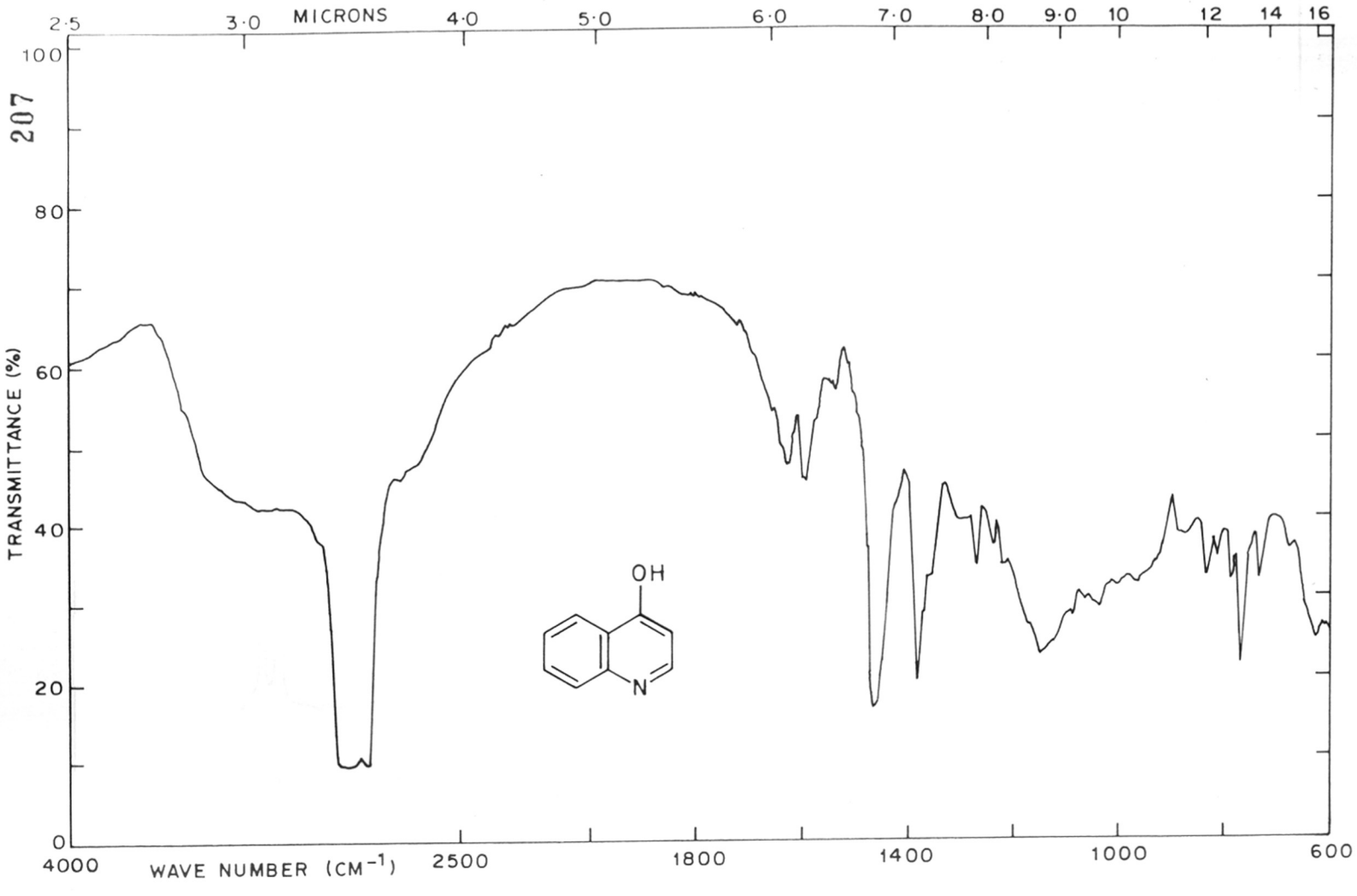


FIG. 3·3. IR SPECTRUM OF 4-HYDROXYQUINOLINE

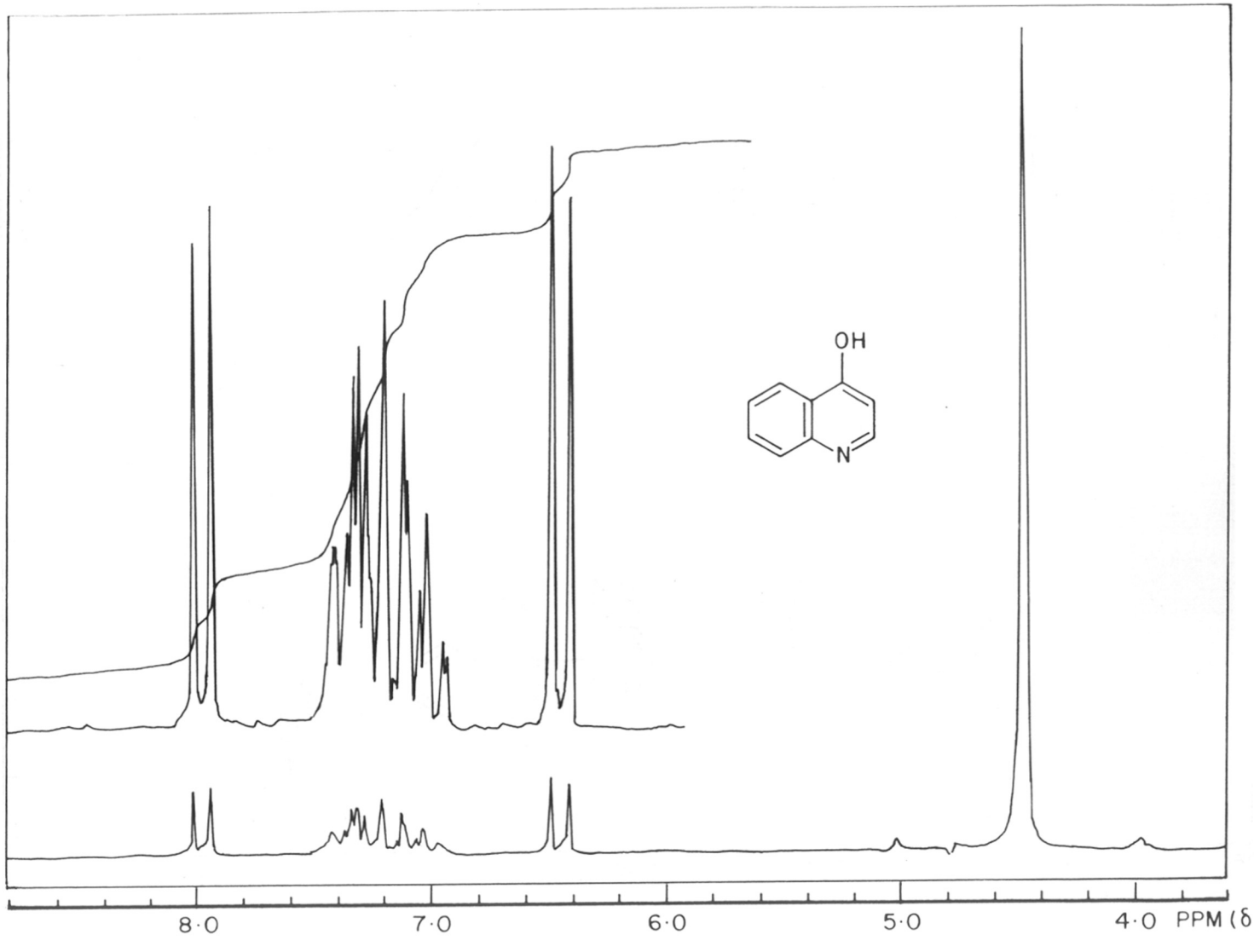


FIG. 3·4. PMR SPECTRUM OF 4-HYDROXYQUINOLINE

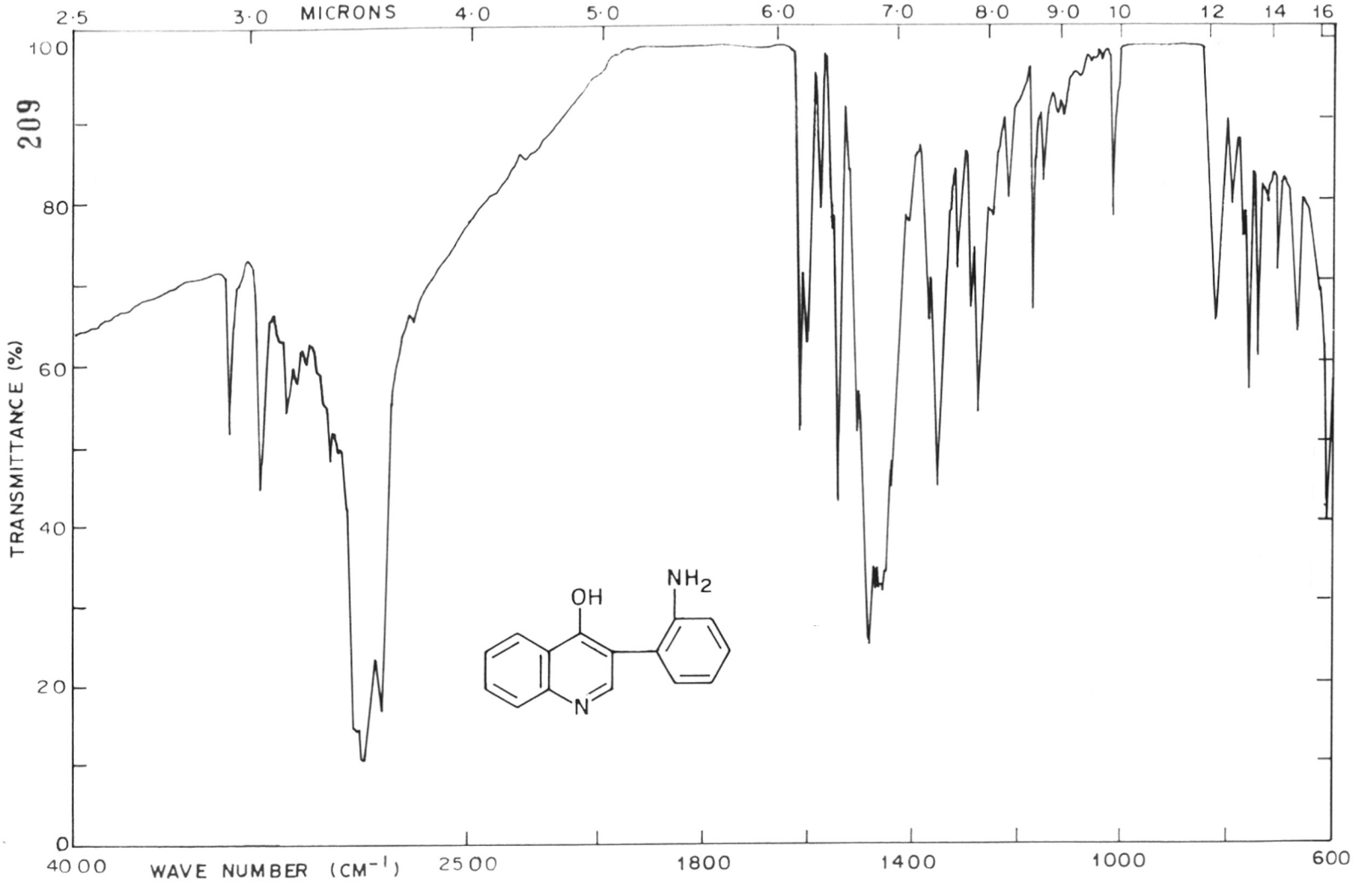


FIG. 3·5. IR SPECTRUM OF 3-(2-AMINOPHENYL)-4-HYDROXYQUINOLINE

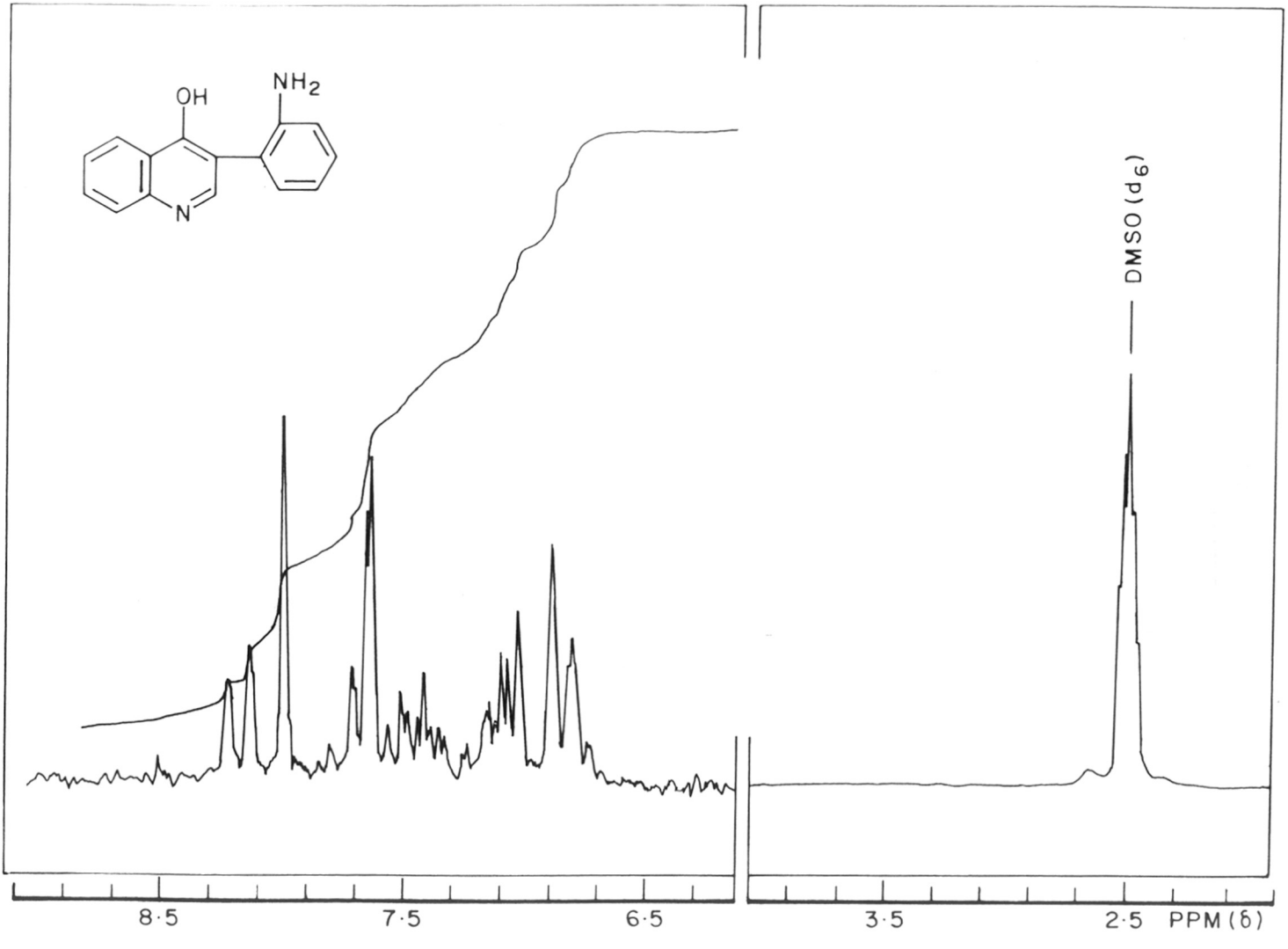


FIG. 3·6. PMR SPECTRUM OF 3-(2-AMINOPHENYL)-4-HYDROXYQUINOLINE

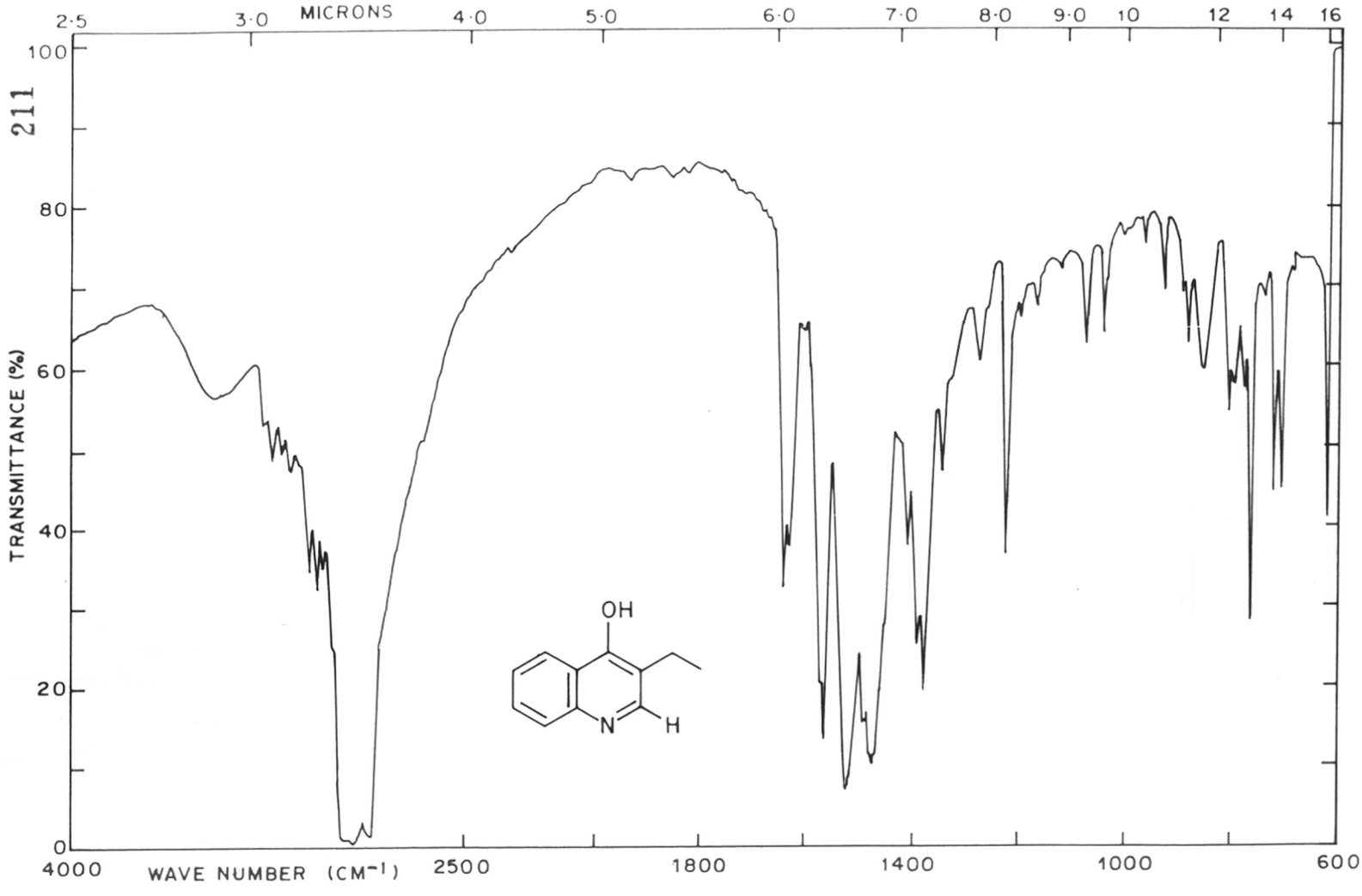


FIG. 3·7. IR SPECTRUM OF 3-ETHYL-4-HYDROXYQUINOLINE

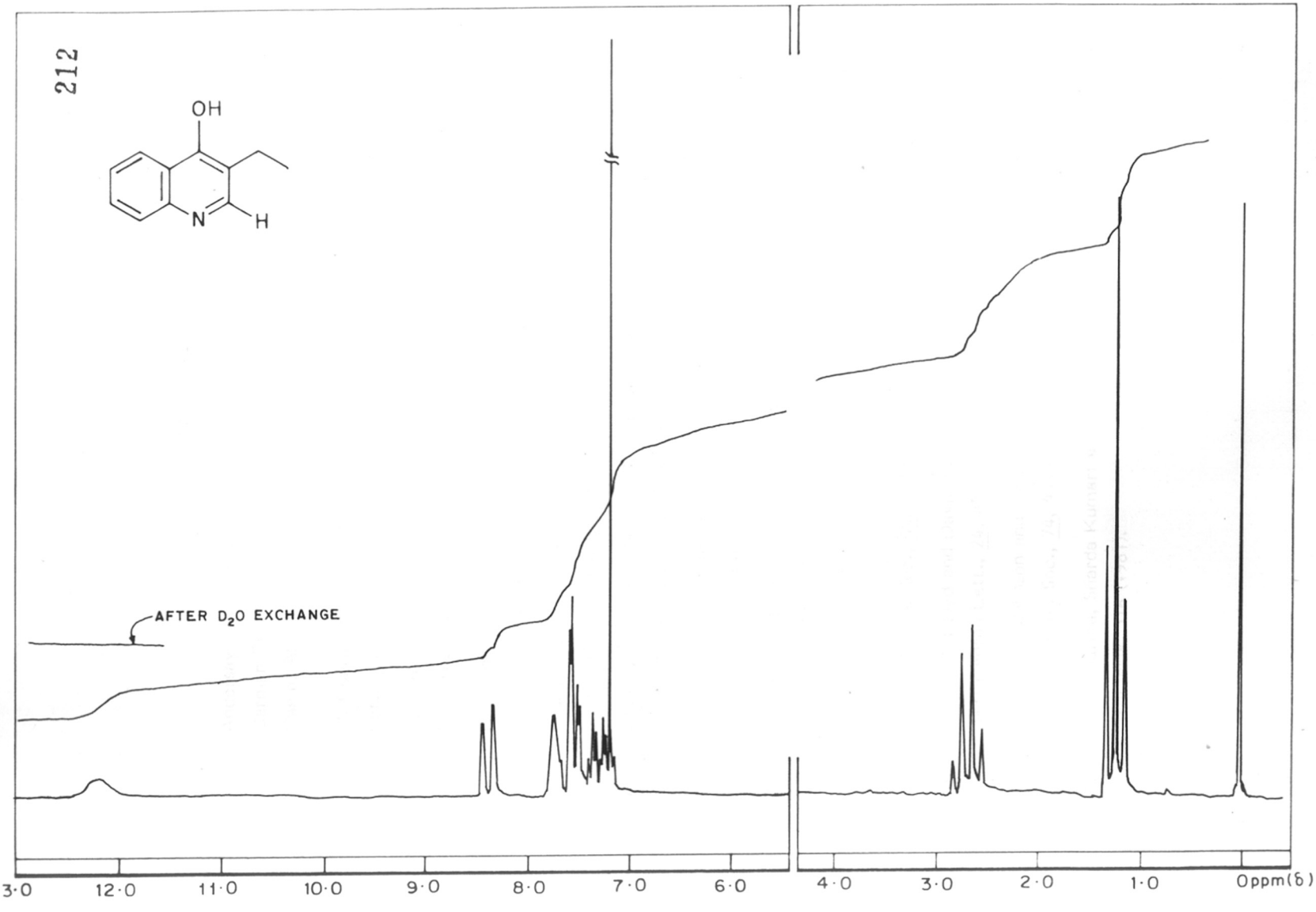


FIG. 3·8. PMR SPECTRUM OF 3-ETHYL-4-HYDROXYQUINOLINE

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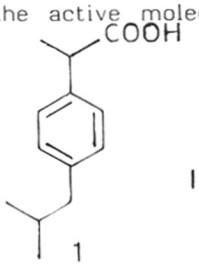
CHAPTER-IV

SOME NEW APPROCHES FOR THE SYNTHESIS OF IBUPROFEN

Introduction

Anti-inflammatory drugs are increasingly used for relief of pain due to rheumatism. Steroids[1] were one of the first compounds to be used for its treatment. The main disadvantage of using steroids is their gastrointestinal intolerence. This necessitated the discovery of nonsteroidal anti-inflammatory drugs, which have similar therapeutic activity devoid of side effects. The action of nonsteroidal drugs is due to cycloxygenase inhibition as they stop the arachidonic acid cascade to prostaglandins and thromboxane A2 which are responsible for the inflamation mechanism.

Attempts have been made in the past for the design of new non-steroidal drugs and out of this ibuprofen, 2-(4-isobutylphenyl) propionic acid has emerged as one of the active molecules in this respect.[2]



IBUPROFEN

1

Now this is marketed throughout the world under the trade name 'Brufen'. It is found to be 28 times more active than aspirin. The mode of action is through inhibition of the prostaglandin biosynthesis. Since then many new compounds have been prepared and marketed. The main type of compounds can be broadly classified as follows: 1) Benzoic acid derivatives as exemplified by salicylic acid group diflunisil, anthranilic acid compounds with mefencemic and niflumic acid,

2) Arylacetic acid compounds, such as endomethacien, salindae, ibufunae and diclofinae,

3) ∝-Arylpropionic acid with ibuprofen as the first representative compound.

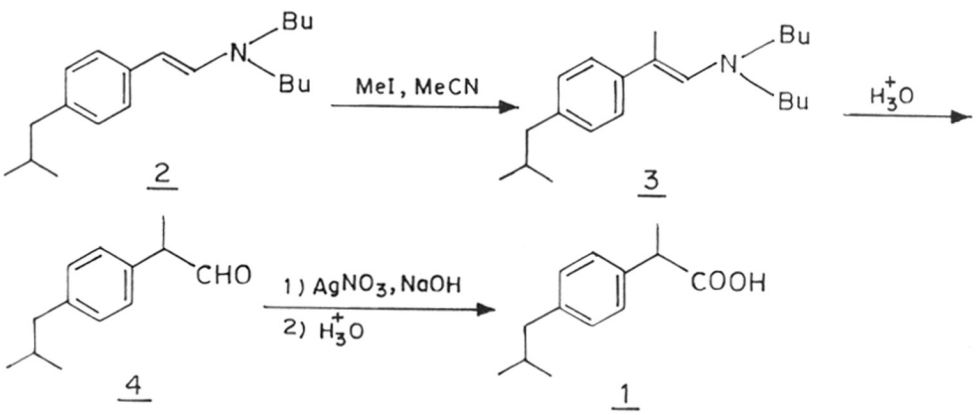
It is the synthesis of the last type of compounds we are mainly concerned with.

Methods of Preparation of Ibuprofen

There are many methods reported in literature for the synthesis of ibuprofen, most of which start from isobutylbenzene. However, the methods vary in the introduction of propionic acid side chain. There are various approaches described in a recent review.[3] For the present discussion we shall describe only those methods, which use enamines as their intermediates or involve aromatisation of substituted cyclohexane ring.

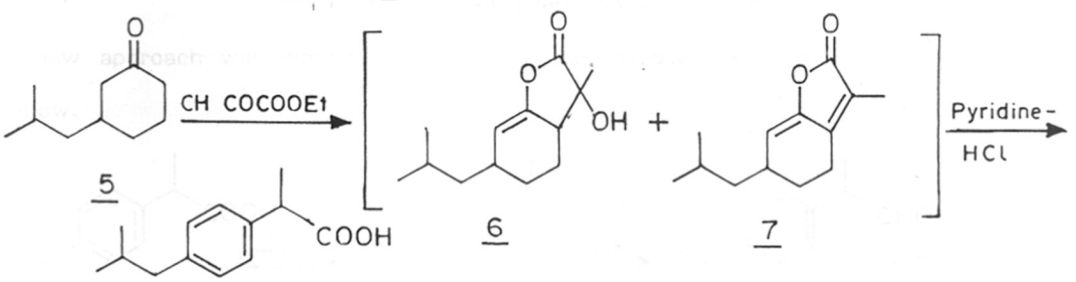
1. Using Ethylarenes[4]

P-Iso-BuC_6H_4CH=CHNBu_2 was refluxed with methyl iodide in methylcyanide, which was further refluxed in 1N hydrochloric acid to give aldehyde (4). The aldehyde (4) was added to an aqueous mixture of silver nitrate and sodium hydroxide. The resulting mixture was further refluxed and then acidified to give ibuprofen (1).



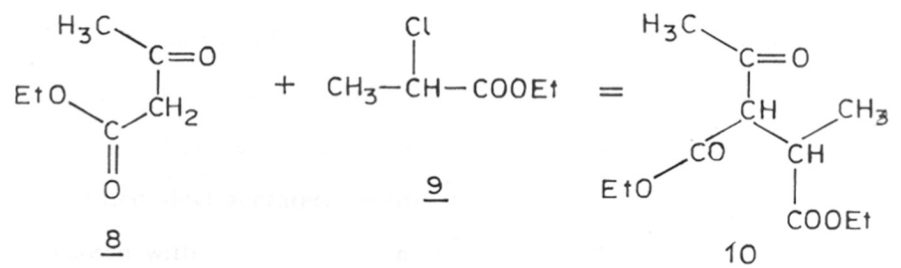
2. Aromatisation of Isobutylcyclohexanone[5]

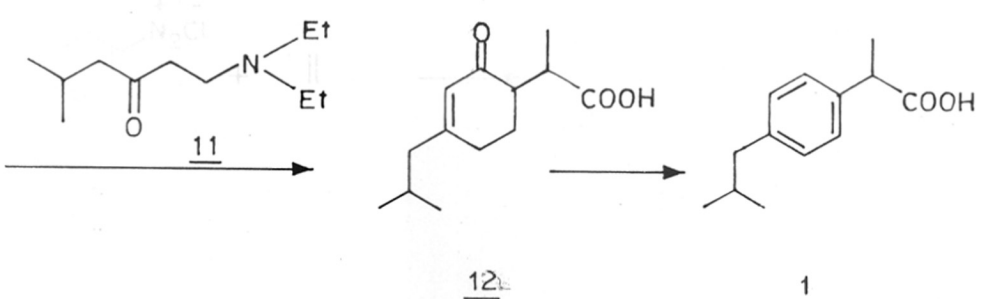
When 3-isobutylcyclohexanone (5) was refluxed with ethyl pyruvate, the intermediate 6 and 7 obtained was satisfactorily aromatised.



3. Using Diethyl α-methyl-β-acyl succinate[6]

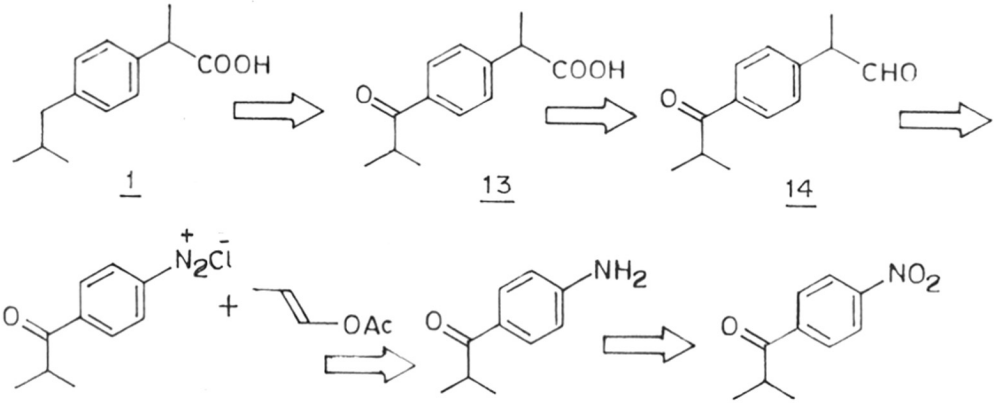
(2-Diethylaminoethyl)-isobutyl ketone (11), a precursor of vinyl isobutyl ketone, was selectively condensed with diethyl α-methyl-β-acyl succinate (10) using potassium carbonate to give 2-(4-isobutyl 2-oxo-3-cyclohexenyl)propionic acid (12) whose aromatisation with succinic anhydride produce ibuprofen.



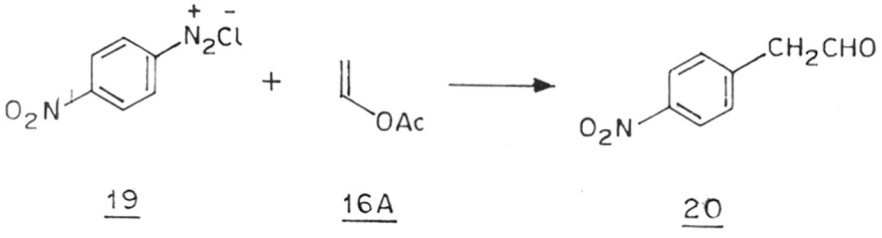


Present Investigation

As seen from various reported syntheses, the use of enamines or aromatisation of cyclohexane has not been explained fully. Initially a new approach was planned as given by the retrosynthetic scheme below.

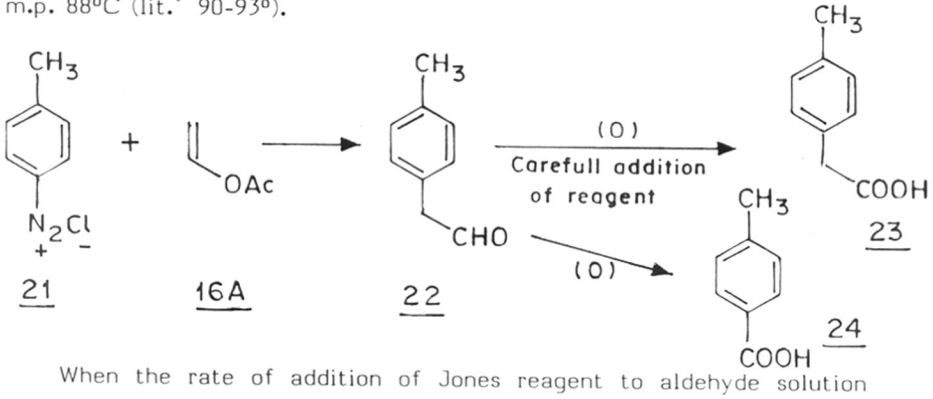


It was envisaged that (1) can be obtained by Wolf Kishner reduction of (13) which in turn can be obtained from (14) and (15). The preparation of compound (18) is described in Chapter-II, Part-B. The success of this reaction depends on condensation of the diazo compound (15) with substituted vinyl acetates. In literature[7] p-nitrodiazonium chloride was condensed with vinyl acetate to obtain p-nitrophenylacetaldehyde.



As a model study, diazo compound from p-toluidine was condensed with vinyl acetate.[8] The solution of diazo compound, previously neutralised to pH 5 by sodium bicarbonate, was added dropwise to the stirred solution of vinyl acetate followed by addition of $CuCl_2$. The resultant compound was extracted in solvent and the residue was steam distilled after removal of the solvent to obtain phenyl-acetaldehyde derivative (22), which was further oxidised with Jones reagent to carboxylic acid.

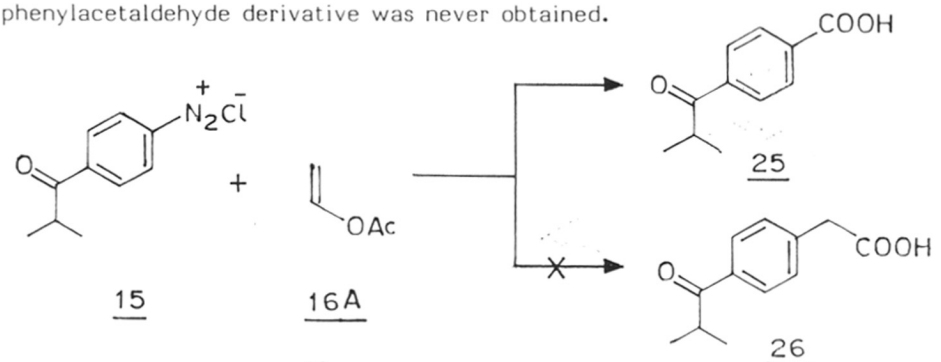
It was observed that when the addition of Jones reagent to the aldehyde solution was carried out over a period of about one hour, the desired p-methyl phenylacetic acid (23) was obtained which was confirmed by its spectral data. Mass spectrum M^+ 150; PMR in ($CDCl_3$) showed signals at δ 2.20 (s, 3H, $C\underline{H}_3$), 3.6 (s, 2H, -$C\underline{H}_2$-COOH), and m.p. 88°C (lit.[9] 90-93°).



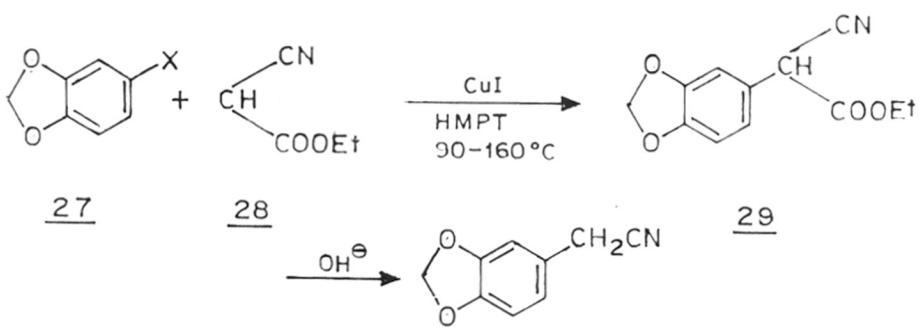
When the rate of addition of Jones reagent to aldehyde solution was increased (in 10 minutes), the unexpected p-toluic acid was obtained (24), which showed m.p. 179-80°C (lit.[10] 180-182°C); Mass spectrum M^+ 136, PMR in $CDCl_3$ showed signal at δ2.4 (s, 3H, $C\underline{H}_3$).

Reduction of p-nitroisobuterophenone by Raney Nickel and hydrazine hydrate gave p-aminoisobuterophenone, m.p. 107-108°C (lit.[11] m.p. 108°C). When p-aminoisobuterophenone was subjected to the above described series of reaction, it gave p-carboxyisobuterophenone (25), m.p. 137°C. IR spectrum (nujol) showed bands at 3150-3400 cm^{-1} (-OH), 1680, 1670 cm^{-1} (-C-, -C-OH). PMR ($CDCl_3$) showed signals at δ 1.25 (d, 6H, J = 6Hz, $-CH(\underline{CH_3})_2$), 3.6 (m, 1H, $-\underline{CH}(CH_3)_2$); Mass spectrum showed M^+ 192.

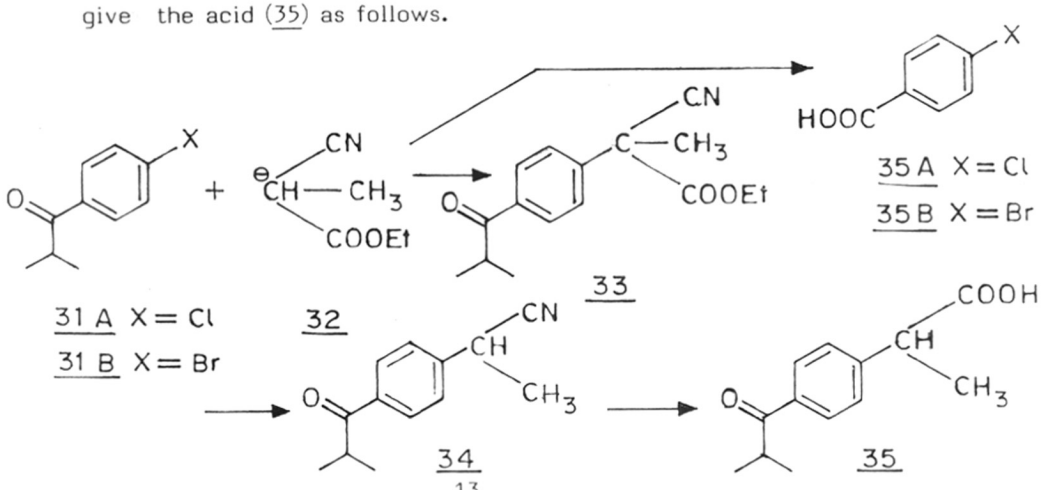
Even under different set of conditions i.e. rate of addition of diazo compound, rate of addition of Jones reagent, the expected phenylacetaldehyde derivative was never obtained.



In a recent report[12] it was stated that aromatic halogen can be easily replaced by a nucleophile.



Based on the above reaction strategy it was envisaged that p-chloro-isobuterophenone (31) on reaction with ethyl-2-cyanopropionate should give the acid (35) as follows.

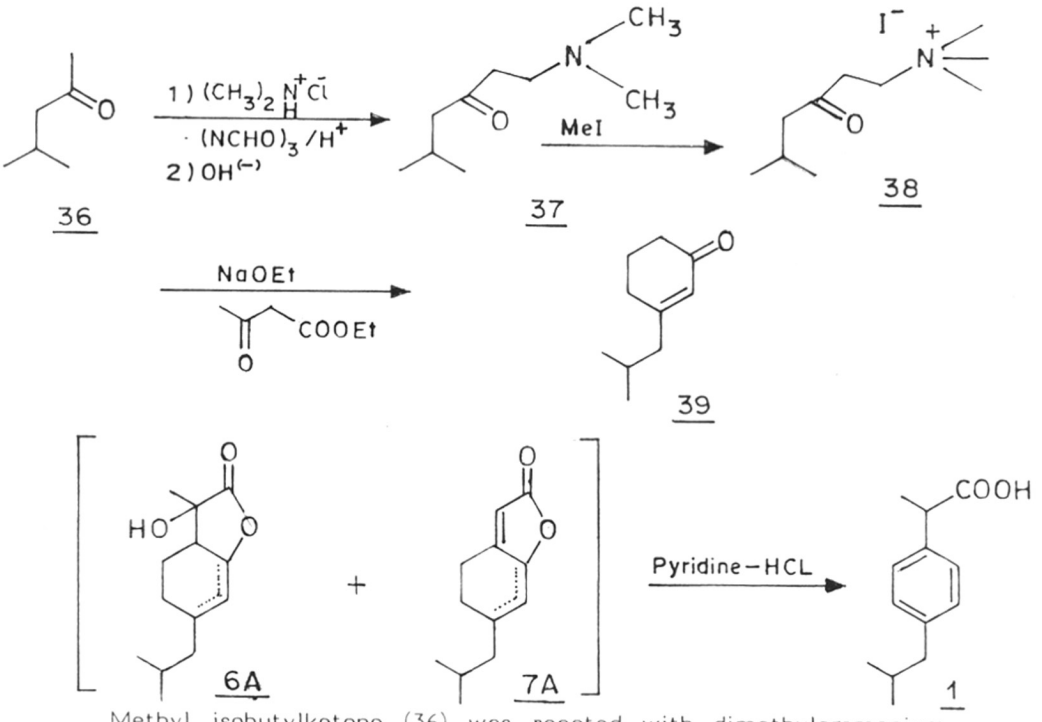


p-Chloroisobuterophenone[13] was prepared by acylation of isobuteraldehyde enamine with p-chlorobenzoyl chloride, followed by acid hydrolysis. When p-chloroisobuterophenone (31A) on reaction with ethyl-2-cyanopropionate (32) gave p-chlorobenzoic acid (35A), m.p. 238°C (lit.[14] m.p. 239-241°C), Mass spectrum M^{+} 156.

Similarly when p-bromoisobuterophenone[15] (31B) prepared by Friedel Crafts[13] reaction of bromobenzene with isobuteroyl chloride was reacted with ethyl-2-cyanopropionate gave p-bromobenzoic acid (35B), m.p. 252°C (lit.[16] m.p. 252-254°C), Mass spectrum M^{+} 201.

This reaction was tried under various parameters like reaction time, use of catalytic amount of crown ether, replacement of ethyl-2-cyanopropionate by ethylcyanoacetate and the desired compound was not obtained.

In an another approach 3-isobutyl-cyclohex-2-en-1-one (39)[17,18] an intermediate for the synthesis of ibuprofen was prepared. The reaction sequence is outlined below.



Methyl isobutylketone (36) was reacted with dimethylammonium hydrochloride in presence of paraformaldehyde to give a Mannich base[19] (37). PMR (CCl_4) of this compound showed signals at δ 1.0 (d, 6H, J = 6.5 Hz, $-CH(\underline{CH_3})_2$) 1.9-2.5 (m, $\underline{CH_2}-N(\underline{CH_3})_2$) and $\underline{CH_2}-CO-\underline{CH_2}-\underline{CH}$). IR of this compound showed the carbonyl band at 1730 cm^{-1}.

This Mannich base (37) was treated with methyl iodide to give the salt (38) which was further reacted with ethylacetoacetate to give 3-isobutyl-cyclohex-2-en-1-one (39)[17]. PMR of this compound

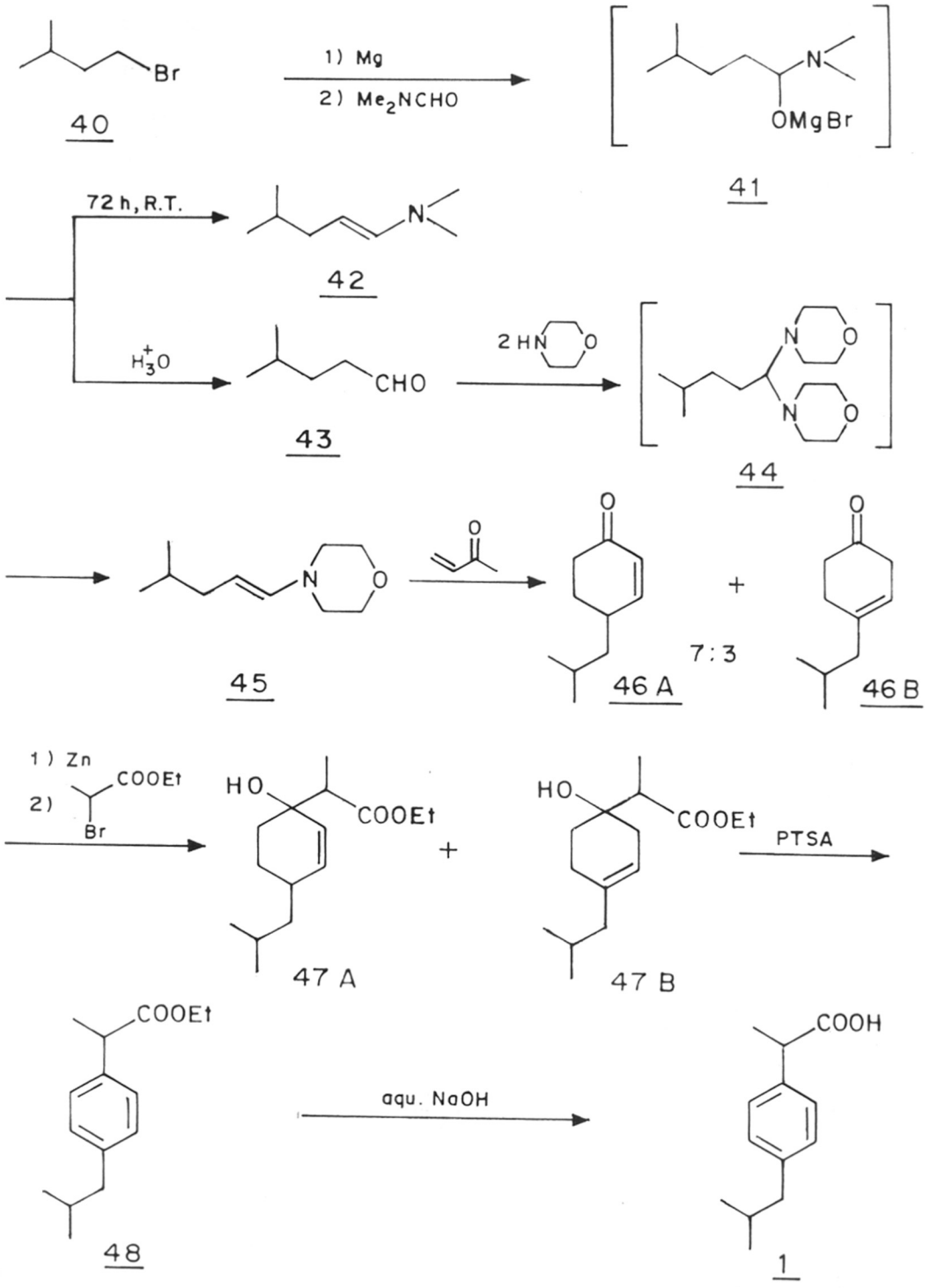
showed signals at δ 0.95 (d, 6H, J = 6Hz, -CH $(CH_3)_2$); 5.75 (s, 1H, olefinic proton). IR showed carbonyl band at 1680 cm^{-1} corresponds to α,β unsaturated ketone. Fruther sequence for the conversion of this compound to ibuprofen is known in literature.[5]

In the next approach we have utilized enamine of 4-methylpentaldehyde as a starting material for the synthesis of ibuprofen as given in Scheme-1. In this approach, isoamylbromide (40) was reacted with magnesium in dry ether to form a Grignard complex of isoamylbromide, which was further condensed with dimethylfomamide to give the intermediate salt[20] (40). After completion of addition of dimethylformamide to the Grignard solution the sticky salt was stirred at room temperature for 72 hr. IR of the supernatant solution of the reaction mixture showed weak peak of enamine at 1640 cm^{-1}. After 72 hr, the reaction mixture was removed and the residue was distilled at 82-85°/ 90 mm to give 25% of enamine (42). This enamine (42) showed PMR (CCl_4) signals at δ 0.9 (d, 6H, J = 6Hz, -CH$(CH_3)_2$ 1.85 (m, 2H, allylic CH_2), 2.5 (s, 6H, -N$(CH_3)_2$); 4.05 (m, 1H, H-C=C-N) 5.7 (d, 1H, J = 14Hz, H-C=C-N-H).
IR showed a characteristic enamine peak at 1640 cm^{-1}.

The yield of enamine obtained by stirring the solution of the salt (34) was only 25%, hence the solution of salt (34) as converted to the aldehyde (43) by treatment with 3N hydrochloric acid. The yield of aldehyde[21] was 76.2%. IR of this aldehyde showed bands at 2700 cm^{-1} for (-C(=O)-H) stretching and 1722 cm^{-1} for carbonyl. PMR (CCl_4) showed signals at δ 9.7 (s, 1H, -C(=O)-H), 0.9 (d, 6H, -CH$(CH_3)_2$), 3.4 (m, 1H, -CH$(CH_3)_2$).

SCHEME – 1

TOTAL SYNTHESIS OF IBUPROFEN



The aldehyde was condensed with two equivalent of morpholine to give the diamine intermediate (44) which was decomposed during fractional distillation to give morpholine enamine of 4-methylpentaldehyde (45). The enamine (45) was purified by distillation at 67-70°/2 Yield 65.4% and was characterised by its spectra data. PMR (CCl_4) showed signals at δ 0.9 (d, 6H, J = 6Hz, $-CH(\underline{CH_3})_2$); 1.8 (m, 2H, $-\underline{CH_2}-CH=CH-$); 2.7 (t, 4H, $-N(\underline{CH_2})_2$); 3.6 (t, 4H, $O(\underline{CH_2})_2$), 4.2 (m, 1H, $\underline{H}>C=C<\underline{N}<$); 5.6 (d, 1H, J = 14Hz, $H>C=C<\underline{N}<$). IR showed characteristic enamine peak at 1650 cm^{-1}.

Enamine (45) was condensed with methylvinylketone in dry ether and worked out in usual manner to give a mixture of two isomers of 4-isobutyl-cyclohex-2-en-1-one (46A) and 4-isobutyl-cyclohex-3-en-1-one (46B). GLC showed (column OV-101, temp. 160°C) 70:30 mixture of (46A) and (46B).

Thease isomers showed PMR (CCl_4) signals at δ 1.0 (d, 6H, J = 6.5 Hz, $-CH(\underline{CH_3})_2$); 5.45 (triplet of β-proton in isomer 46B), 5.85 (d, J = 12Hz, CH in isomer 46A), 6.8 (d, J = 12Hz, β-proton in isomer 46A). IR showed bands at 1685 cm^{-1} and 1715 cm^{-1} for carbonyl absorption in isomer 46A and 46B respectively.

The mixture of compound 46A and 46B was as such subjected to Reformatsky reaction[22] in presence of zinc and 2-bromoethyl propionate to give the hydroxy compound 47A and 47B, which was purified by distillation at 95-105°/5 mm; Yield 67%. This compound showed PMR ($CDCl_3$) signals at δ 0.9 (d, 6H, J = 6.5 Hz, $-CH(\underline{CH_3})_2$); 1.1 (t, 3H, $O-CH_2-\underline{CH_3}$); 4.05 (q, 2H, $-O-\underline{CH_2}-CH_3$); 5.1-5.7 (olefinic

protons of both the isomers 47A and 47B), 3.15 (bs, 1H, OH, D_2O exchangeable). IR showed band at 3500 cm^{-1} (-OH); 1725 cm^{-1} ester carbonyl.

The hydroxy compound 47A and 47B was aromatised with p-toluene sulphonic acid by refluxing in toluene to give ester (48) which was purified by distilling at 105-110°/1 mm, yield 57.26%. This compound showed PMR (CCl_4) signals at δ 0.9 (d, 6H, J = 6.5 Hz, $-CH(CH_3)_2$), 4.0 (q, 2H, $-O-CH_2-CH_3$), 7.0 (4H, aromatic protons). IR showed band at 1740 cm^{-1} corresponding to ester carbonyl.

The ester 48 was hydrolysed with 30% sodium hydroxide solution to give ibuprofen, m.p. 76°C, Yield (90.29%).

Ibuprofen was characterised by its spectral data, PMR ($CDCl_3$) showed signals at δ 0.9 (d, 6H, J = 6.5 Hz, $-CH(CH_3)_2$), 1.4 (d, 3H, $CH_3 - \overset{1}{C}H - COOH$), 1.85 (m, 1H, $-CH(CH_3)_2$), 2.4 (d, 2H, $-CH_2-CH(CH_3)_2$), 3.65 (q, 1H, $CH_3-\overset{1}{C}H-COOH$), 7.0 (4H, aromatic protons). IR showed band at 1680 cm^{-1} for carbonyl group of carboxylic acid and broad band between 3210-3460 cm^{-1} for carboxylic OH. Mass spectrum showed $M^{+\cdot}$ 206. Mixed melting point with the authentic sample showed no depression in meling point.

CONCLUSION

Few methods are known in the literature, for the synthesis of ibuprofen via enamines. Out of many methods tried in our laboratory for the synthesis of ibuprofen, using enamines, the method involving the enamine derived from isoamylbromide was successful. Although the yield in the aromatisation step was not very satisfactory, nevertheless this is a new method for the synthesis of ibuprofen.

CHAPTER IV

EXPERIMENTAL

The experimental part of this chapter is divided into two sections.

Section IVA

This describes the attempted synthesis of following compounds:

1. Preparation of 4-methylphenylacetic acid
2. Formation of p-toluic acid
3. Attempted synthesis of p-(carboxymethyl)phenyl isopropyl ketone (Formation of p-carboxyphenyl isopropyl ketone).
4. Attempted synthesis of p-(1-cyanoethyl)phenyl isopropyl ketone from:
   (a) p-Chlorophenyl isopropyl ketone
   Formation of p-chlorobenzoic acid
   (b) p-Bromophenyl isopropyl ketone
   Formation of p-bromobenzoic acid

Section IVB

This section describes the preparation of 2-(4-isobutylphenyl) propionic acid (Ibuprofen) and its intermediate 3-isobutyl cyclohex-2-en-1-one.

1. Preparation of 3-isobutyl cyclohex-2-en-1-one
   (a) Preparation of Mannich base of methyl vinyl ketone and its quaternary salt.
   (b) Preparation of 3-isobutyl cyclohex-2-en-1-one from quaternary salt of Mannich base.

2. Preparation of 2-(4-isobutylphenyl)propionic acid

Step I : Preparation of enamine

(a) Preparation of 1-(N,N-dimethylamino) 4-methyl-pent-1-ene

(b) Preparation of 4-methyl pentaldehyde

(c) Preparation of 1-morpholino-4-methyl-pent-1-ene

Step II : Preparation of 4-isobutyl substituted cyclohexenones

Step III: Reformatsky reaction of cyclohexenone with bromo-propionate.

Step IV : Aromatisation of 1,4-disubstituted cyclohexenol

Step V : Hydrolysis of ester to carboxylic acid.

Section IVA:

1. **Preparation of 4-methylphenylacetic acid (p-tolylacetic acid)** (23)

This comprises of two steps:

A) Preparation of 4-methylbenzenediazonium chloride

To a mixture of hydrochloric acid (5 ml) and water (5 ml) was dissolved p-toluidine (2.67 g, 0.025 mole), the resulting solution was cooled to 0°C. To the stirred solution of hydrochloride at 0°C, a solution of sodium nitrite (1.66 g) in water (5 ml) was added dropwise, the mixture was stirred further for 5 min, until there was no evolution of gaseous product. The resulting 4-methylbenzenediazonium chloride was neutralised with sodium bicarbonate solution to pH 5.

B) Condensation of 4-methylbenzenediazonium chloride with vinyl acetate[8]

In a 50 ml round bottom flask calcium carbonate (0.26 g), acetone (12 ml) and vinyl acetate (4 ml) was placed. The resulting mixture was stirred vigorously and to it a solution of 4-methylbenzenediazonium chloride was added dropwise over 1 hr. A cooled solution of $CuCl_2$, H_2O (0.84 g) in water (1 ml) was added to it. Uniform evolution of gaseous product (3-5 bubbles per second) occurred at 20-22°C. Three hours after the evolution of nitrogen completely ceased. The reaction mixture was extracted with ethyl acetate. The ethyl acetate extract was washed with water and the solvent was removed under reduced pressure, the residue was mixed with water (30 ml) and was steam-distilled.

The condensate was extracted with ether (20 ml) and the residue after evaporation of ether was dissolved in acetone (5 ml). Jones reagent (2 ml) was added dropwise over 1 hr to the stirred solution of residue in acetone, which was further stirred for 20 min. The resulting mixture was extracted with ethyl acetate (3 x 20 ml). The ethyl acetate extracts were combined and washed with water (10 ml), then with 5% sodium bicarbonate solution (2 x 10 ml). Bicarbonate washings were combined and acidified with conc. hydrochloric acid. The solid separated was filtered, dried and crystallised from ethanol.

M.P. 88°C (lit.[9] 90-93°C)

Yield 0.5 g (13.36 %)

IR spectrum (Nujol) showed band at 3340-3500 cm^{-1} (-COOH) and 1690 cm^{-1} (- $\overset{O}{\overset{\|}{C}}$ -).

PMR spectrum ($CDCl_3$) showed signals at δ 2.2 (s, 3H, -$\underline{CH_3}$); 3.6 (s, 2H, -$\underline{CH_2}$-); 7.1, s, 4H, aromatic protons); 10.6 (1H, -COO$\underline{H}$, D_2O, exchangeable).

Analysis: found: C, 71.63; H, 6.18.

Calculated for $C_9H_{10}O_2$: C, 72.00; H, 6.66.

Mass spectrum: M^+ 150.

2. Formation of p-toluic acid (24)

This compound was obtained according to the procedure of the preparation of 4-methylphenylacetic acid with the same quantities, but the addition of Jones reagent was done within 10 min.

M.P. 179-80°C (ethanol) (lit.[10] 180-82°C).

Yield 1.12 g (38.0%).

IR spectrum (Nujol) showed broad band at 3000-3400 cm^{-1} (-COOH) and 1675 cm^{-1} (- $\overset{O}{\overset{\|}{C}}$ -).

PMR spectrum ($CDCl_3$) showed signals at δ 2.4 (s, 3H, -CH_3); 7.25 and 8.0 (aromatic protons); 9.5 (1H, -COOH, D_2O exchangeable).

Analysis; found: C, 70.21; H, 5.67.

Calculated for $C_8H_8O_2$: C, 70.59; H, 5.88.

Mass spectrum: M^+ 136.

3. Attempted synthesis of p(carboxymethyl)phenyl isopropyl ketone (26) (Formation of p-carboxyphenyl isopropyl ketone (25)

This consist of two steps:

A) Preparation of 4-aminoisobuterophenone (17)

This was prepared by the reduction of 4-nitroisobuterophenone.

4-Nitroisobuterophenone (5.79 g, 0.03 mole) was dissolved in ethanol (50 ml), to that Raney Nickel (1.2 g) was added and the mixture stirred at 50°C. Hydrazine hydrate (7 ml) was added to it, at such a rate as to keep the temperature between 50-55°C. After completion of addition, the reaction mixture was further stirred for 2 hrs, filtered, solvent removed under reduced pressure and residue crystallised from benzene.

M.P. 107-108°C[11]

Yield 4.15 g (85%).

IR spectrum (Nujol) showed bands at 3300, 3390 cm^{-1} (-NH_2), 1680 cm^{-1} (- $\overset{O}{\overset{\|}{C}}$ -).

PMR spectrum ($CDCl_3$) showed signals at δ 1.1 (d, 6H, J = 6Hz, -CH(CH_3)$_2$); 3.5 (m, 1H, -CH(CH_3)$_2$); 4.15 (-NH_2, D_2O exchangeable); 6.65 and 7.8 (aromatic protons).

Analysis; found: C, 73.45; H, 8.31; N, 8.25.

Calculated for $C_{10}H_{13}NO$: C, 73.62; H, 7.98; N, 8.59.

Mass spectrum: $M^{+\cdot}$ 163.

B) Formation of p-carboxyphenyl isopropyl ketone (25)

This was obtained according to the procedure of preparation of 4-methylphenylacetic acid with the following quantities:

4-Aminoisobuterophenone	4.07 g (0.025 mole)
Sulphuric acid : water (1:1)	12 ml
Sodium nitrite	1.66 g
Calcium carbonate	0.26 g
Vinyl acetate	4 ml

This compound was crystallised from methanol.

M.P. 137°C

Yield 1.2 g (25%).

IR spectrum (Nujol) showed band at 3150-3400 cm^{-1} (-OH); 1680, 1760 cm^{-1} (-C-, -C-OH)

PMR spectrum ($CDCl_3$) showed signals at δ 1.25 (d, 6H, J = 6Hz, -CH $(CH_3)_2$); 3.6 (m, 1H, $CH(CH_3)_2$); 8.0-8.4 (aromatic protons).

Analysis; found: C, 68.55; H, 5.90.

Requires for $C_{11}H_{12}O_3$: C, 68.75; H, 6.25.

Mass spectrum: $M^{+\cdot}$ 192.

4. Attempted synthesis of p(1-cyanoethyl)phenyl isopropyl ketone

This was attempted from two starting materials

A) 4-Chlorophenyl isopropyl ketone

B) 4-Bromophenyl isopropyl ketone

This consist of following steps:

A) Preparation of 4-chlorophenyl isopropyl ketone (31A)

This compound was prepared by acylation of 1-morpholino-2-methyl-prop-1-ene with 4-chlorobenzoyl chloride followed by acid hydrolysis.

Preparation of 1-morpholino-2-methyl-prop-1-ene is described in Chapter II, Part B. The acylation procedure was as follows:

In a three necked 250 ml round bottom flask fitted with reflux condensor with calcium chloride guard tube and a dropping funnel, a mixture of 1-morpholino-2-methyl-prop-1-ene (7.05 g, 0.05 mole) and triethylamine (5.05 g, 0.05 mole) in dry benzene (50 ml) was taken. To the stirred solution of above mixture at 0°C, a solution of 4-chloro-benzoyl chloride (8.75 g, 0.05 mole) in dry benzene (15 ml) was added dropwise. After completion of addition the reaction mixture was stirred for 1 hr at room temperature. Then it was refluxed under stirring for 8 hr, and the solvent was removed under reduced pressure. The residue was dissolved in dioxane (100 ml) and to that 50% hydrochloric acid (10 ml) was added. This mixture was refluxed for 4 hr. Dioxane was removed under reduced pressure and the residue was extracted in ethyl acetate (3 x 20 ml). The combined ethyl acetate layers were washed with bicarbonate solution (pH 8.5) until the bicarbonate washings

were colourless. Solvent was removed under vacuum and the residue was distilled under reduced pressure (120-122°C/3.5 mm[13]).

Yield 5.66 g (62%)

IR spectrum (Neat) showed band at 1680 cm^{-1} (- $\overset{O}{\overset{\|}{C}}$ -).

PMR spectrum (CCl_4) showed signals at δ 1.0 (d, 6H, J = 6Hz $CH(C\underline{H}_3)_2$); 3.2 (m, 1H, $C\underline{H}(CH_3)_2$); 7.15, 7.65 (aromatic protons).

C) Attempted synthesis of p-(1-cyanoethyl)phenyl isopropyl ketone from 4-chloroisobuterophenone
Formation of 4-chlorobenzoic acid (35A)

The literature procedure[12] was followed.

A commercial 60% sodium hydride dispersion (0.160 g, 4 mmol) was placed in 25 ml flask and parafin oil was removed by washing with dry hexane (3 x 2 ml). The remaining solid was covered with hexamethyl phosphoric triamide (HMPA, 1ml) and solution of ethyl-2-cyanopropionate (0.542 g, 4 mmol) in the same solvent (2.5 ml) was added with stirring. After 20 min, 4-chlorophenyl isopropyl ketone (0.365 g, 2 mmol) was added, followed by addition of copper (I) iodide (0.762 g, 4 mmol) and the mixture was heated to 120-125°C. The colour turned gray to black as the temperature increased. The progress of the reaction was monitored by TLC. After 8 hr, a solution of sodium hydroxide (0.144 g, 3.6 mmol) in water (3 ml) was introduced and heated at 80-90°C for an additional 2 hr. After cooling, the solution was neutralised with dilute hydrochloric acid and extracted with ethyl acetate (3 x 20 ml). The ethyl acetate layers were combined and dried over anhydrous sodium sulfate. Evaporation of the solvent gave a residue which was crystallised from ethanol.

M.P. 238°C (lit.[14] 239-241°C).

Yield 0.120 g (38.45%)

IR spectrum (Nujol) showed bands at 3050-3400 cm^{-1} (-COOH) and 1685 cm^{-1} (- $\overset{O}{\overset{\|}{C}}$ -).

Analysis; found: C, 53.20; H, 3.20; Cl, 22.44.

Calculated for $C_7H_5O_2Cl$: C, 53.84; H, 3.21; Cl, 22.75.

Mass spectrum: M^+ 156.

B) Preparation of 4-bromophenyl isopropyl ketone (31B)

This was prepared according to the literature[15] procedure. To a freshly distilled bromobenzene (18.84 g, 0.12 mole) and anhydrous aluminium chloride (4.8 g, 0.036 mole), under stirring was added dropwise 2-methylpropionyl chloride (3.26 g, 0.03 mole) at 0°C and stirred further for 6 hrs until no more HCl was evolved. It was poured in a mixture of conc. hydrochloric acid and ice (1:1, 250 g). The organic phase was extracted with ether (2 x 50 ml), dried over calcium chloride and the residue was fractionated under reduced pressure (128-138°C/13 mm[13]).

Yield 4.04 g (58%)

IR spectrum (Neat) showed band at 1685 cm^{-1} (- $\overset{O}{\overset{\|}{C}}$ -)

PMR spectrum (CCl_4) showed signals at δ 1.15 (d, 6H, J = 6Hz, $CH(\underline{CH_3})_2$); 3.45 (m, 1H, $-\underline{CH_3})_2$); 7.3-7.8 (aromatic protons).

C) Attempted synthesis of p-(1-cyanoethyl)phenyl isopropyl ketone from p-chloroisobuterophenone
Formation of 4-bromobenzoic acid (35B)

This was obtained according to the procedure used for the formation of 4-chlorobenzoic acid with the following quantities:

Sodium hydride	0.160 g (4 mmol)
Ethyl cryanopropionate	0.542 g (4 mmol)
4-Bromophenyl isopropyl ketone	0.452 g (2 mmol)

This compound was crystallised from ethanol-carbon tetrachloride.

M.P. 252°C (lit.[16] 252-254°C).

Yield 0.210 g (52.5%)

IR spectrum (Nujol) showed bands at 3090-3450 cm^{-1} (-COOH) and 1675 cm^{-1} (- $\overset{O}{\overset{\|}{C}}$ -)

Analysis; found: C, 41.72; H, 2.40; Br, 39.26.

Calculated for $C_7H_5O_2Br$: C, 41.8; H, 2.49 Br, 39.80.

Mass spectrum: M^+ 201.

Section IVB:

5. **Preparation of Mannich base of methyl isobutyl ketone** (37)

Methyl isobutyl ketone (10.0 g, 0.1 mole), dimethylammonium chloride (8.45 g, 0.1 mole), paraformaldehyde (9.0 g, 0.1 mole) and 0.25 ml of concentrated HCl in absolute alcohol (25 ml) were refluxed on water bath for 10 hr. Alcohol was removed under vacuum. To this, water (20 ml) was added and the mixture shaken with ether (20 ml) to remove unreacted ketone. The aqueous layer was then basified with 50% aqueous KOH solution. The separated amine was taken in ether and the ether layer washed with water. Solvent was evaporated and the residue distilled under reduced pressure.

120-125°C/140 mm

Yield 8.5 g (54.84%)

IR spectrum (Neat) showed band at 1730 cm^{-1} (- $\overset{O}{\overset{\|}{C}}$ -)

PMR spectrum (CCl_4) showed peaks at δ 1.0 (d, 6H, J = 6.5Hz, $-CH(\underline{CH_3})_2$); 1.9-2.5 ($-\underline{CH_2}-\overset{O}{\overset{\|}{C}}-\underline{CH_2}-\underline{CH}(CH_3)_2$, $-\underline{CH_2}-N(\underline{CH_3})_2$).

6. Preparation of quaternary salt of Mannich base (38)

To the stirred mixture of Mannich base (7.75 g, 0.05 mole) in dry ether (100 ml), methyl iodide (8.52 g, 0.06 mole) was added dropwise at 0°C. An exothermic reaction ensured the formation of quaternary salt. This was then allowed to stand at room temperature for 3 hr and then the separated solid was filtered in exclusion of moisture and dried in a vacuum decicator.

Yield 13.5 g, (90.9%).

This salt was used for the next step immediately.

7. Preparation of 3-isobutyl cyclohex-2-en-1-one[17,18] (39)

To a warm ethanolic solution of ethyl sodium acetoacetate (prepared from 0.92 g, 0.04 mole sodium in 100 ml of ethanol and 5.2 g (0.04 mole) of ethyl acetoacetate was added dropwise absolute ethanolic solution of quaternary salt (38) (11.88 g, 0.04 mole) over 20 min, while ethyl sodioacetoacetate solution was kept stirring. After completion of addition the mixture was refluxed for 4 hr, then KOH (4 g) in water (6 ml) was added and the mixture refluxed further for 8 hr. Solvent was removed under vacuo and water (50 ml) was added to the residue which was extracted with ether (50 ml). The ether layer was washed with water (20 ml), dried over anhydrous sodium sulphate, and the solvent removed. The residue was distilled under reduced pressure.

90-100°C/5 mm[17].

Yield 4.43 g (73%)

IR spectrum showed bands at 1680 cm^{-1} (- $\overset{O}{\overset{\|}{C}}$ -) and 1630 cm^{-1} (olefinic bond).

PMR spectrum showed signals at δ 0.95 (d, 6H, J = 6Hz, $-CH(\underline{CH_3})_2$); 5.75 (s, 1H, $>C=C\underline{H}$).

Analysis, found: C, 79.32; H, 10.15

Calculated for $C_{10}H_{16}O$: C, 78.95; H, 10.53.

Mass spectrum: M^{+} 152.

8. Preparation of 4-methyl pentaldehyde (43)

To a three necked 250 ml flask fitted with reflux condensor and dropping funnel, magnesium (5.4 g, 0.22 mole) in dry ether (50 ml) were stirred and a piece of iodide was added to initiate the reaction. This was followed by dropwise addition of isoamyl bromide (30.2 g, 0.2 mole) in dry ether (20 ml). The rate of addition was such as to keep the solution at gentle reflux. After the completion of the addition, the reaction mixture was warmed to reflux for 3 hr, until all the magnesium was dissolved. An additional 100 ml ether was introduced and then the flask was cooled in ice-salt mixture and dimethylformamide (17.52 g, 0.24 mole) was added slowly over 45 min. The sticky solid formed was stirred for 12 hr at room temperature. The Grignard complex was decomposed with 3N HCl. The organic layer was washed with 5% sodium bicarbonate solution and dried over anhydrous sodium sulfate. Solvent was evaporated and the residue was distilled at atmospheric pressure

115-120°C[21]

Yield 18.3 g(76.2%)

IR spectrum (Neat) showed band at 2700 cm^{-1} (-C(=O)-H), 1722 cm^{-1} (-C(=O)-)

PMR spectrum (CCl_4) showed signals at δ 0.9 (d, 6H, $-CH(C\underline{H}_3)_2$); 1.5 (m, 2H, $-C\underline{H}_2-$); 2.2 (m, 2H, $-C\underline{H}_2-C(=O)-$); 3.4 (m, 1H, $-C\underline{H}(CH_3)_2$); 9.7 (1H, -C(=O) - H).

9. Preparation of 1-morpholino-4-methyl-pent-1-ene (45)

To a stirred ice cooled solution of 4-methyl pentaldehyde (14.00 g, 0.14 mole) and anhydrous potassium carbonate (7-8 g) was added dropwise morpholine (24.36 g, 0.28 mole). After completion of the addition, the mixture was stirred for 8 hr. at room temperature. Potassium carbonate was removed by filtration and the filtrate was distilled under reduced pressure.

67-70°C/20 mm

Yield 15.47 g (65.4%)

IR spectrum (Neat) showed band at 1650 cm^{-1} (-CH=CH-N<).

PMR spectrum (CCl_4) showed signals at δ 0.9 (d, 6H, J = 6Hz, $-CH(C\underline{H}_3)_2$); 1.8 (m, 2H, $-C\underline{H}_2-CH=CH-$); 2.3 (m, 1H, $-C\underline{H}(CH_3)_2$); 2.7 (t, 4H, $-N(C\underline{H}_2)_2$); 3.6 (t, 4H, $O(C\underline{H}_2)_2$); 4.2 (m, 1H, J = 14Hz, $\underline{H}>C=C<^{N<}_{\underline{H}}$); 5.6 (d, 1H, J = 14Hz, $H>C=C<^{N<}_{\underline{H}}$).

10. Preparation of 1-N,N-dimethylamino-4-methyl-pent-1-ene (42)

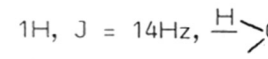
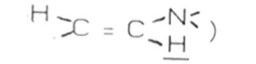
To a three necked 250 ml flask, fitted with reflux condensor and dropping funnel, magnesium (5.4 g, 0.22 mole) in dry ether (50 ml) was stirred, a piece of iodine was added to initiate the reaction,

followed by dropwise addition of isoamyl bromide (30.2 g, 0.2 mole) in dry ether (20 ml). After completion of the addition the reaction mixture was heated and refluxed for 3 hr, until all magnesium dissolved. An additional 100 ml of ether was introduced at this stage and the flask was cooled in an ice salt mixture. N,N-Dimethylformamide (17.52 g, 0.24 mole) was added slowly over 45 min. The reaction mixture was stirred further for 72 hr. The progress of enamine formation was judged by IR of the supernatant liquid. After 72 hr, the mixture was filtered and the solvent was removed from filtrate. The residue was distilled under reduced pressure.

82-85°C/90 mm

Yield 6.35 g (25%)

IR spectrum (Neat) showed band at 1640 cm^{-1} ()

PMR spectrum (CCl_4) showed signals at δ 0.9 (d, 6H, $-CH(\underline{CH_3})_2$, J = 6Hz); 1.85 (m, 2H, $\underline{CH_2}$ ); 2.5 (s, 6H, $-N(\underline{CH_3})_2$); 4.05 (m, 1H, J = 14Hz, ); 5.7 (d, 1H, J = 14Hz, )

11. Preparation of 4-isobutyl cyclohex-2-en-1-one (46A) and 4-isobutyl cyclohex-3-en-1-one (46B)

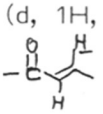
To a stirred ice cooled solution of 1-morpholino-4-methyl-pent-1-ene (15.21 g, 0.09 mole) in dry ether (50 ml) was added dropwise, under nitrogen atmosphere, methyl vinyl ketone (6.3 g, 0.09 mole) over 30 min. After 22 hr of stirring at room temperature the mixture was decomposed by addition of 190 ml of 15% HCl; the mixture was further stirred at room temperature for 30 hr. The organic layer

was separated and washed with dilute HCl, then with water, dried over anhydrous sodium sulfate. The solvent was evaporated and the residue was distilled under reduced pressure.

140-143°C/120 mm.

Yield 12.47 g (90%).

IR spectrum (Neat) showed bands at 1685 cm^{-1} (-  isomer) 1715 cm^{-1} (-  isomer)

PMR spectrum (CCl_4) showed signals at δ 1.0 (d, 6H, J = 6.5Hz, $-CH(\underline{CH_3})_2$); 5.45 (t, 1H,  in comp. 46B); 5.85 (d, 1H, J = 12Hz,  in comp. 46A); 6.8 (d, 1H, J = 12Hz,  in comp. 46A)

GLC (column: OV 101, temp. 160°C) showed 70:30 mixture of 46A : 46B respectively.

Analysis, found: C, 78.54; H, 10.44.

Requires for, $C_{10}H_{16}O$: C, 78.95; H, 10.53.

Mass spectrum: M^+ 152.

12. Preparation of 4-isobutyl-1-(2-ethyl propionate)cyclohex-2-en-1-ol (47A) and 4-isobutyl-1-(2-ethyl propionate)cyclohex-3-en-1-ol (47B)

This compound was prepared according to Vogels[22] procedure. In a three necked flask, fitted with reflux condensor with calcium chloride guard tube, a dropping funnel, a zinc dust (previously dried at 100°C, 4 g, 0.0610 mole) was placed. A solution of ethyl bromo-acetate (8.35 g, 0.050 mole) and a mixture of 46A and 46B (9.12g, 0.06 mole) in dry benzene (8 ml) and dry ether (2 ml) was added through the dropping funnel.

Initially 1 ml solution was added to zinc dust, the flask was warmed gently until the reaction started. When reaction has commenced but not before the mixture was stirred and the reminder of the solution was added at such a rate that moderate refluxing occurred. The reaction mixture was refluxed for further 30 min and then cooled in an ice bath, sulphuric acid (10%, 20 ml) was added with vigorous stirring. Solution was transferred to separatory funnel, the aqueous layer was removed. The benzene layer was washed twice with 5 ml portion of 5% sulphuric acid, once with 3 ml 10% sodium carbonate solution and finally with 2-3 ml portion of water. It was dried over anhydrous sodium sulfate, the solvent removed and the residue was distilled under reduced pressure.

95-105°C/5 mm

Yield 10 g (67%)

IR spectrum (Neat) showed bands at 3500 cm^{-1} (-OH), 1725 cm^{-1} (- $\overset{O}{\overset{\|}{C}}$ -)

PMR spectrum (CCl_4) showed signals at δ 0.9 (d, 6H, J = 6.5Hz, $-CH(\underline{CH_3})_2$); 1.1 (t, 3H, $-CH_2-\underline{CH_3}$); 4.05 (q, 2H, $O-\underline{CH_2}-$); 5.1-5.7 (2H, olefinic protons of 47A and 47B); 3.15 (1H, -OH, D_2O exchangeable).

Analysis, found: C, 70.45; H, 10.38

Requires for $C_{15}H_{26}O_3$: C, 70.87; H, 10.24.

Mass spectrum: M^+ 254.

13. Preparation of 2-(4-isobutylphenyl) ethyl propionate (48)

2.54 g (0.01 mole) of compounds 47A and 47B was dissolved in dry toluene (100 ml), to that p-toluene sulphonic acid (2 g) was added and the mixture was refluxed for 6 hr. The organic layer was washed with water and dried over anhydrous sodium sulfate. The solvent removed under reduced pressure and the residue was distilled under vacuum.

105-110°C/1 mm^2.

Yield 1.34 g (57.26%)

IR spectrum (Neat) showed band at 1740 (-C(=O)-)

PMR spectrum (CCl_4) showed signals at δ 0.9 (d, 6H, J = 6Hz, $-CH(C\underline{H}_3)_2$); 1-1.5 (m, $O-CH_2-C\underline{H}_3$ and $C\underline{H}_3$ - CH<COOEt); 2.35 (d, 2H, $-C\underline{H}_2-CH(CH_3)_2$); 1.85 (m, 1H, $-C\underline{H}(CH_3)_2$); 3.6 (q, 1H, -CH-COOEt); 7.0 (aromatic protons); 4.0 (q, 2H, $-O-C\underline{H}_2-CH_3$)

Analysis, found: C, 77.18; H, 9.63.

Requires for $C_{15}H_{22}O_2$: C, 76.92; H, 9.40.

Mass spectrum: M^+ 234.

14. Preparation of 2-(4-isobutylphenyl) propionic acid (Ibuprofen) (1)

2-(4-Isobutylphenyl)ethyl propionate (0.936 g, 0.004 mole) was dissolved in methanol (20 ml) and to that 30% NaOH solution (4 ml) was added. The mixture was refluxed for 4 hr. Methanol was removed under reduced pressure. The residue was acidified with 3N HCl. The solid separated was filtered and crystallised from benzene.

M.P. 76°C (lit.[2] 75-77°C)

Yield 0.744 g (90.29%)

IR spectrum (Nujol) showed bands at 1680 cm^{-1} (- $\overset{O}{\overset{\|}{C}}$ -), 3210-3460 (-OH).

PMR spectrum ($CDCl_3$) showed signals at δ 0.9 (d, 6H, J = 6Hz, $-CH(\underline{CH_3})_2$); 1.4 (d, 3H, $\underline{CH_3}-CH<^{COOH}$), 2.4 (d, 2H, $-\underline{CH_2}-CH(CH_3)_2$); 1.85 (m, 1H, $-\underline{CH}(CH_3)_2$); 3.65 (q, 1H, $CH_3-\underline{CH}-\overset{O}{\overset{\|}{C}}OH$); 7.0 (aromatic protons).

Analysis, found: C, 75.40; H, 8.48.

Calculated for $C_{13}H_{18}O_2$: C, 75.73; H, 8.74.

Mass spectrum: M^+ 206.

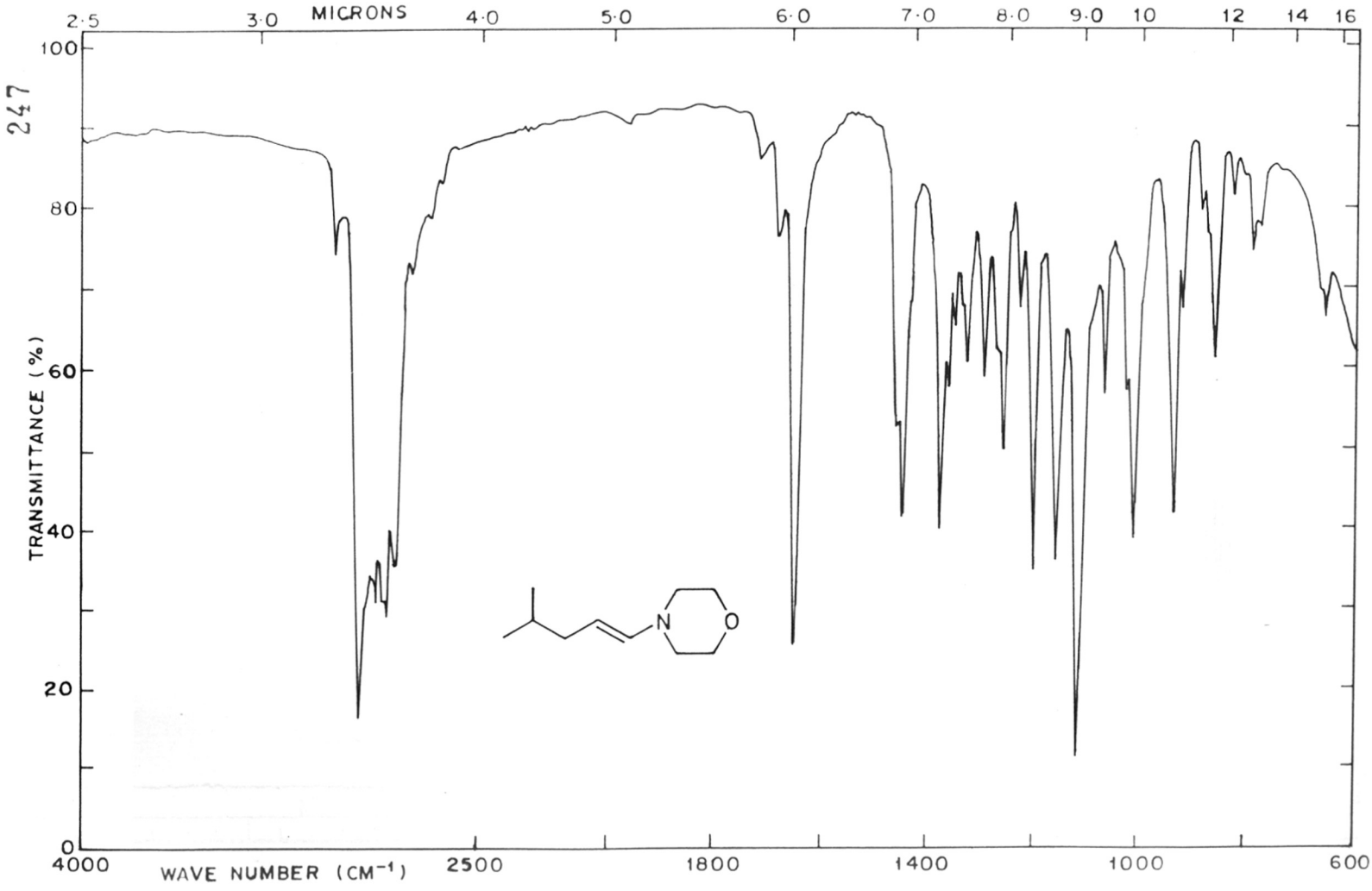


FIG. 4-1. IR SPECTRUM OF 1-MORPHOLINO-4-METHYL-PENT-1-ENE

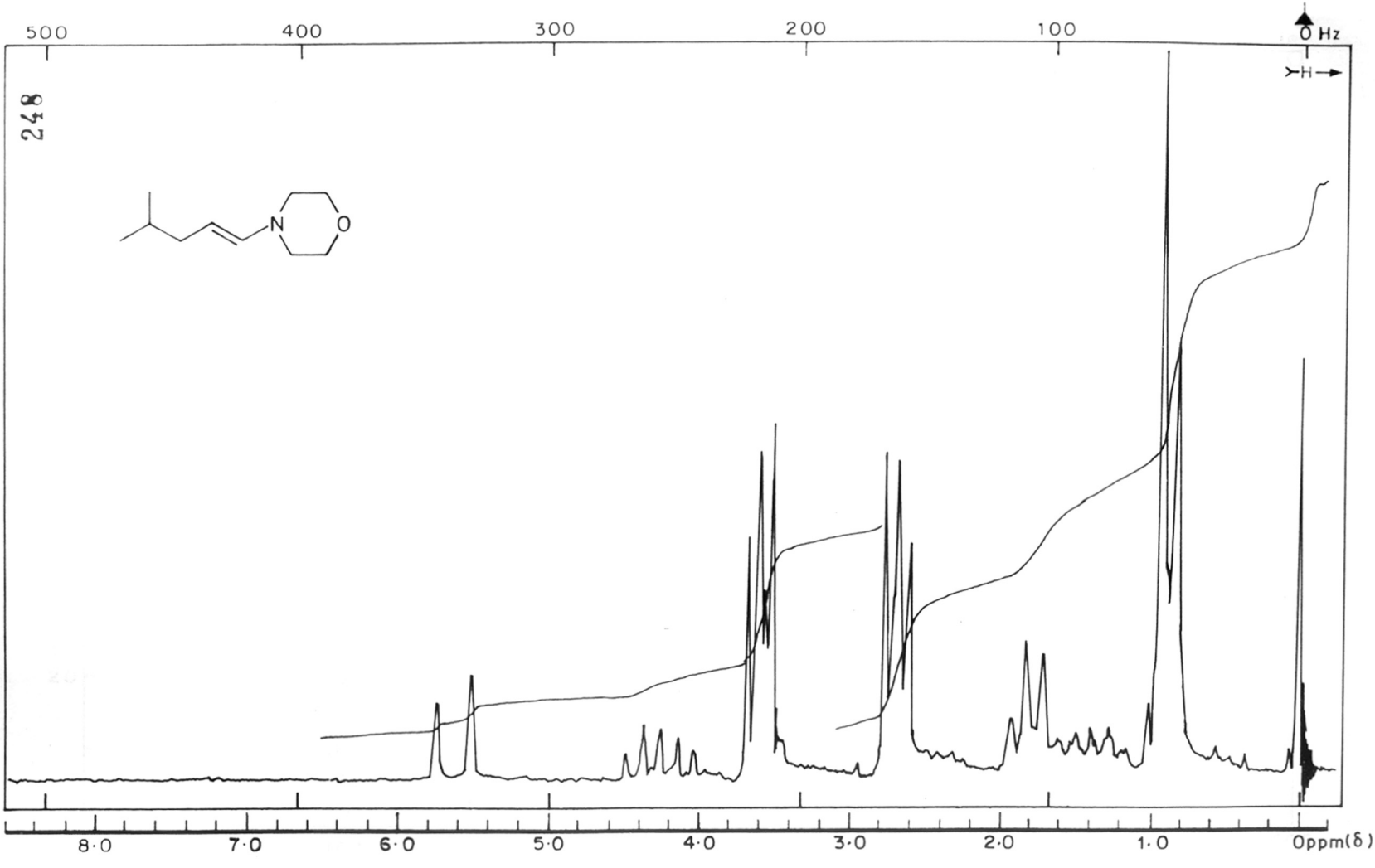


FIG. 4·2. PMR SPECTRUM OF 1-MORPHOLINO-4-METHYL-PENT-1-ENE

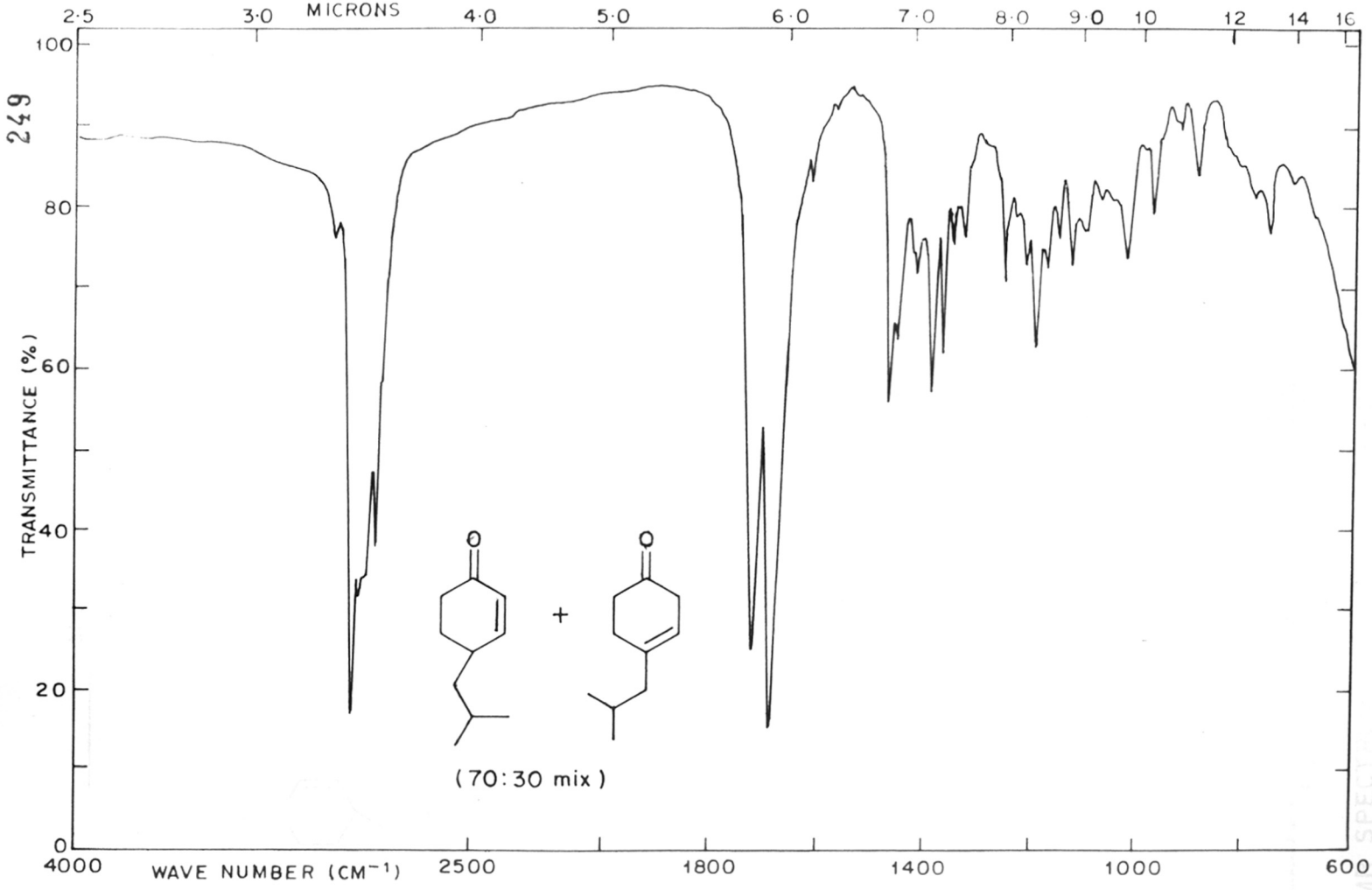


FIG. 4·3. IR SPECTRUM OF MIXTURE OF 4-ISOBUTYL CYCLOHEX-2-EN-1-ONE AND 4-ISOBUTYL CYCLOHEX-3-EN-1-ONE

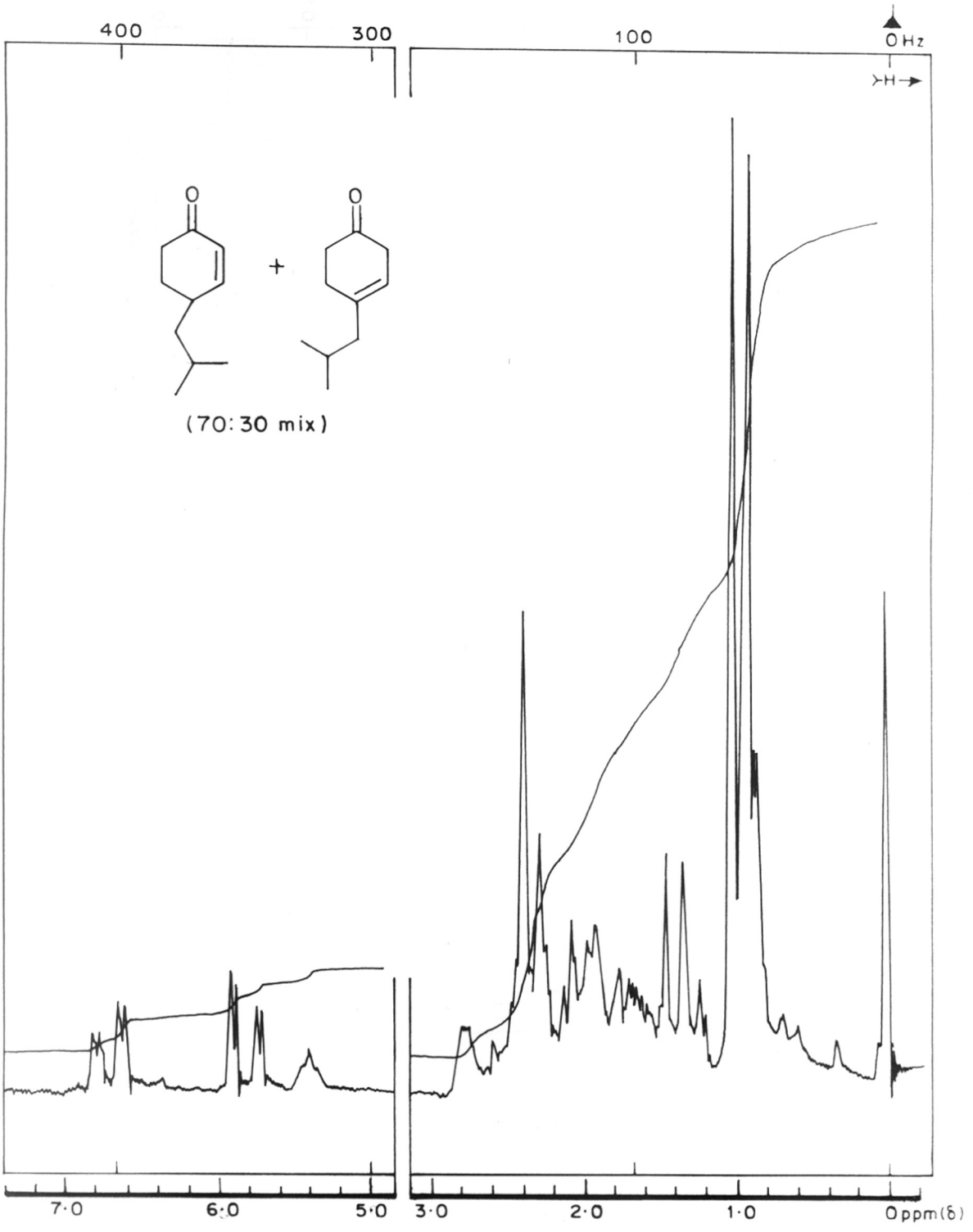


FIG 4·4. PMR SPECTRUM OF MIXTURE OF 4-ISOBUTYL CYCLOHEX-2-EN -1-ONE AND 4-ISOBUTYL CYCLOHEX-3-EN-1-ONE

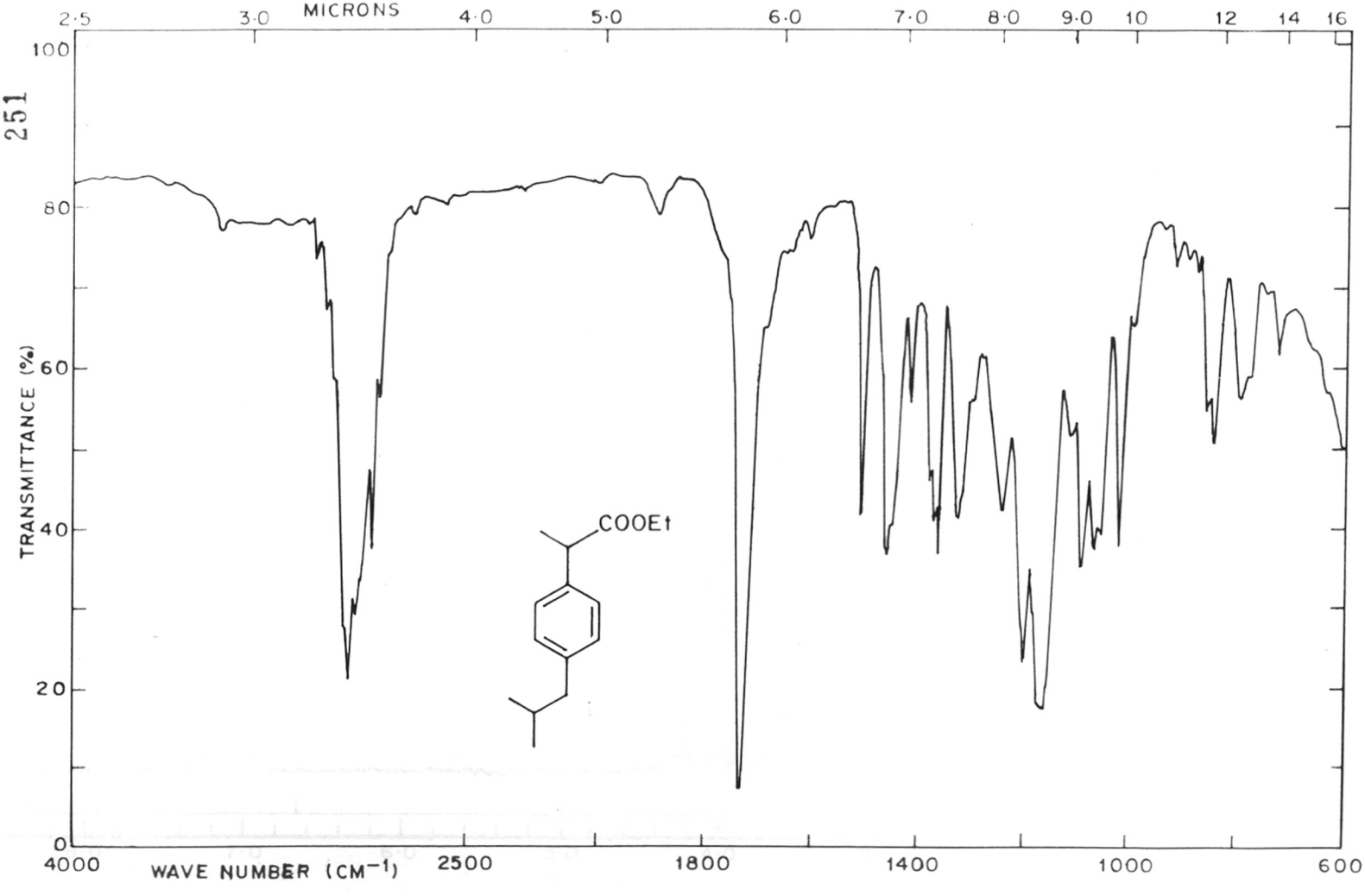


FIG. 4·5. IR SPECTRUM OF 2-(4-ISOBUTYLPHENYL) ETHYL PROPIONATE

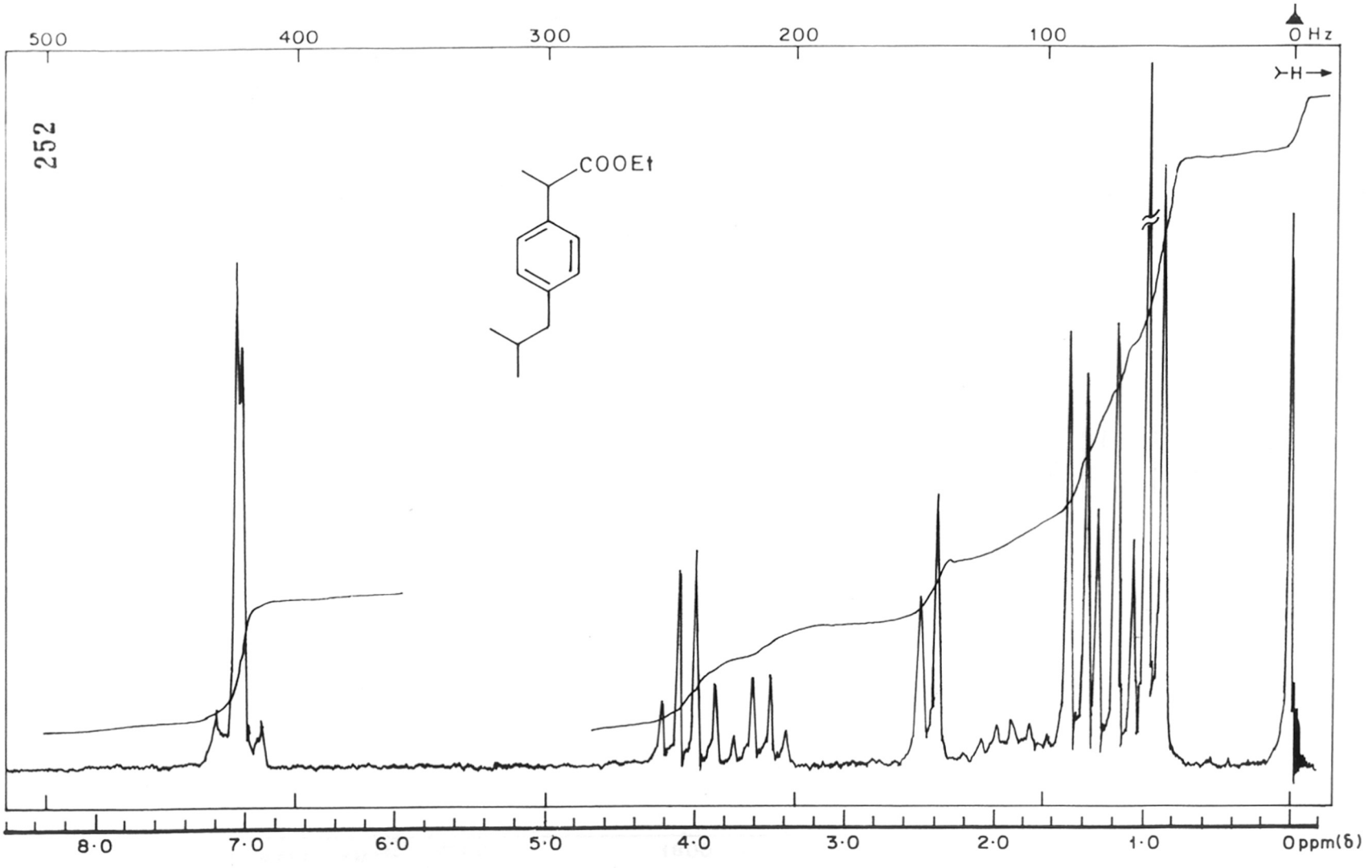


FIG. 4·6. PMR SPECTRUM OF 2-(4-ISOBUTYLPHENYL) ETHYL PROPIONATE

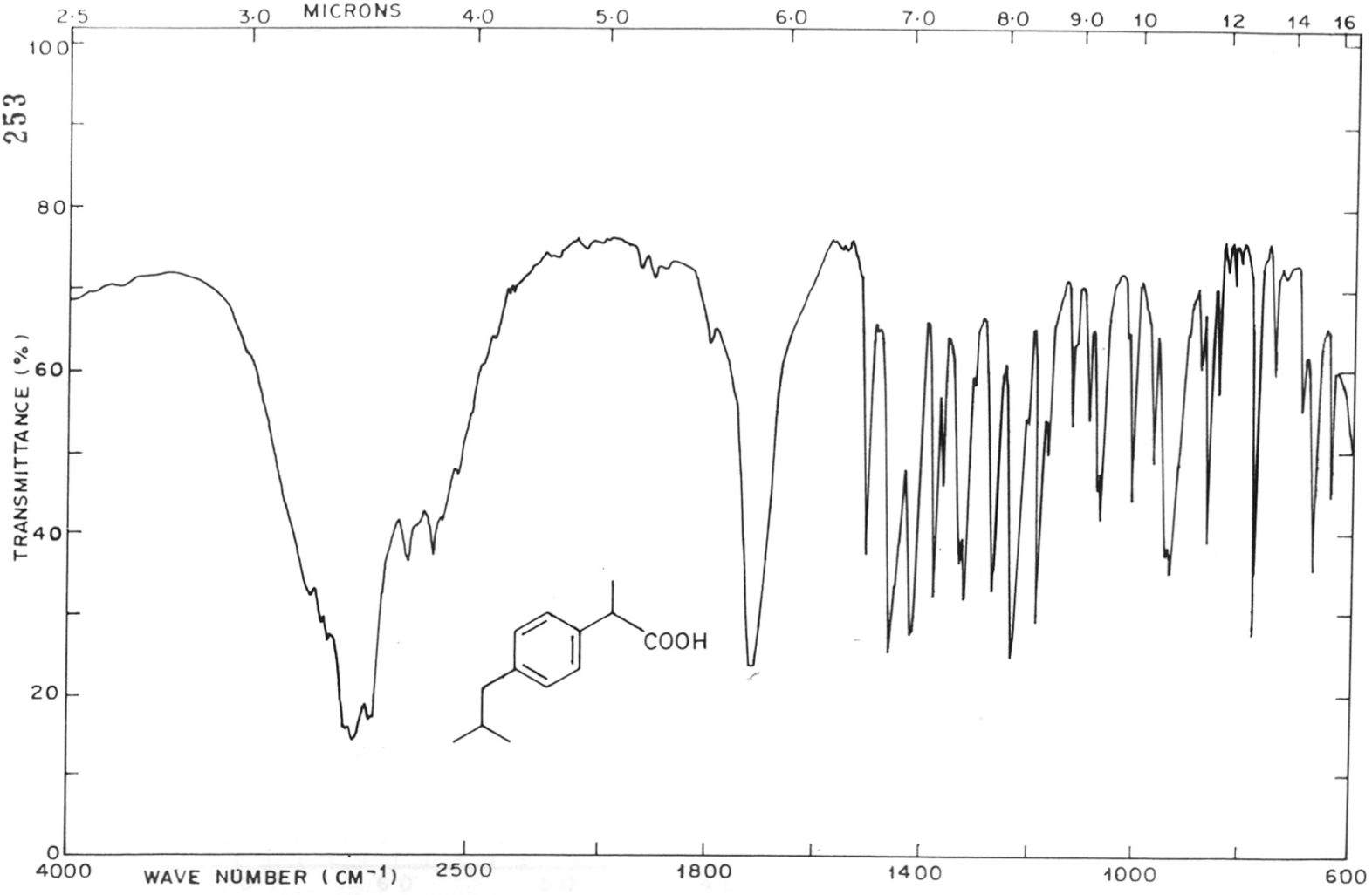


FIG. 4·7. IR SPECTRUM OF IBUPROFEN

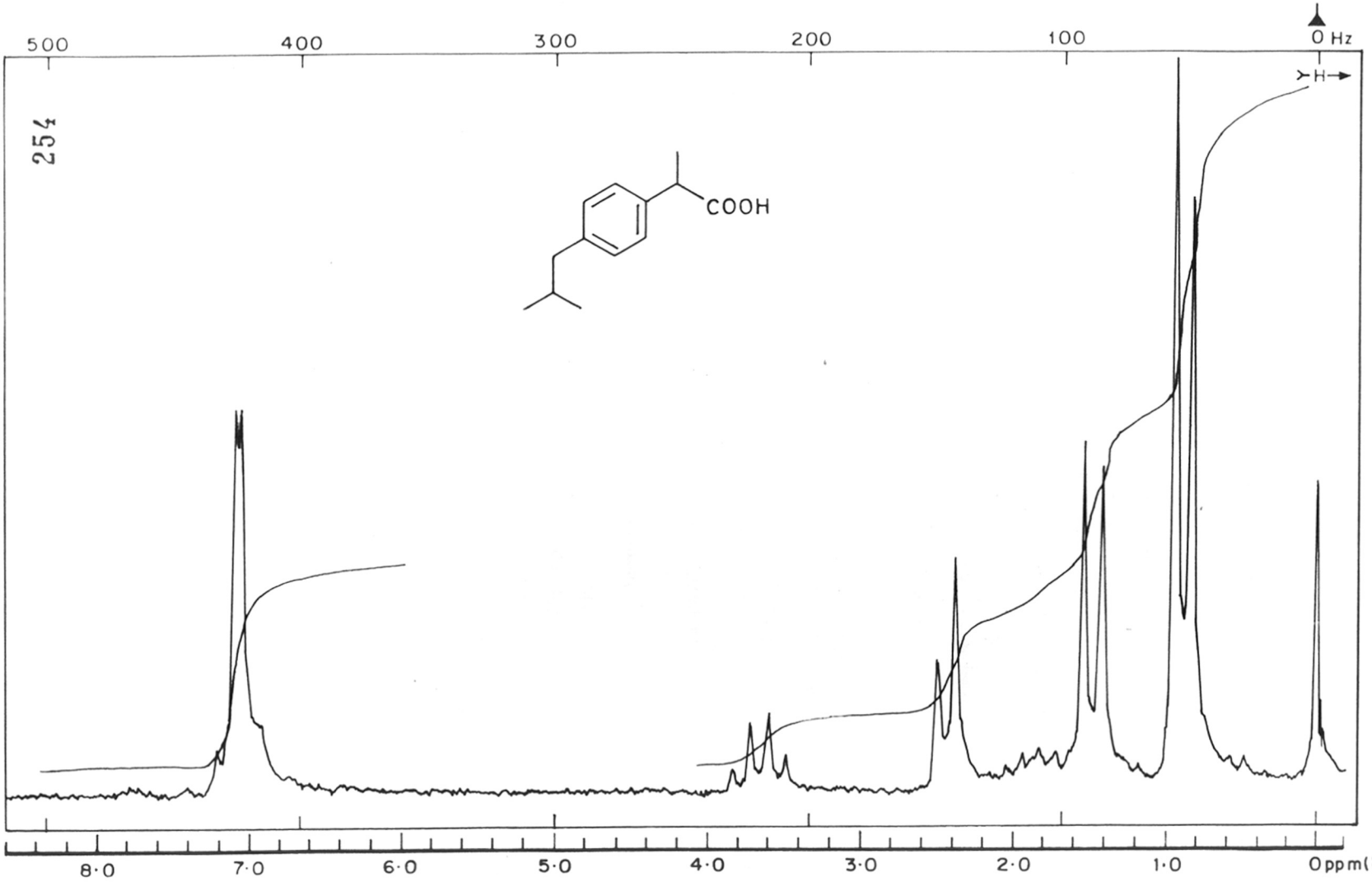


FIG. 4·8. PMR SPECTRUM OF IBUPROFEN

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