

**SYNTHETIC STUDIES ON
SOME POLYCYCLIC AZA & OXAARENES OF
BIOLOGICAL IMPORTANCE**

**A THESIS SUBMITTED FOR THE DEGREE
OF**

DOCTOR OF PHILOSOPHY

**BY
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**DEPARTMENT OF CHEMISTRY
INDIAN INSTITUTE OF TECHNOLOGY
KHARAGPUR
1991**

**Dedicated To My Beloved
Sister Late Shaheen Perween**

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In my opinion, the thesis has fulfilled the requirements according to regulations and has reached the standard for submission. He has carried out research in the Department of Chemistry, Indian Institute of Technology, Kharagpur, for five years. To my knowledge these results have not been submitted for the award of any other degree or diploma.



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ACKNOWLEDGEMENT

The author acknowledges his highest regard and his indebtedness to Dr. J. K. Ray for his keen interest, valuable guidance, constant help and encouragement throughout the period of research work.

The author wishes his sincere thanks to Prof. S. K. Palit, Ex-Head, Department of Chemistry, for his inspiration and invaluable suggestions and for providing all the possible facilities for making this programme a success.

The author takes this opportunity to acknowledge the advice and suggestions extended to him by Prof. A. B. Sannigrahi (Head, Department of Chemistry), Prof. B. Nayak (Ex-Head, Department of Chemistry), Prof. K. B. De, Dr. T. K. Sarkar, Dr. D. Mal and Dr. K. C. Majumdar.

The author wishes to express his hearty thanks to Dr. Gandhi K. Kar (Jhargram Raj College, Jhargram) for his continued interest, constant help and encouragement during the course of work.

It is a sense of great pleasure for author to express his thankfulness to Dr. D. Ramesh, Dr. P. S. V. Subba Rao, Dr. A. C. Karmakar, Dr. A. Dutta, T. K. Satpathi, R. K. Pal, K. V. S. N. Murthy, M. Shrinivas and B. C. Roy for their help and co-operation throughout the course of work.

The author is grateful to Dr. A. Patra, University of Calcutta, Calcutta, for CMR and 2D NMR of a sample of lactam. IICB, Calcutta and CDRI, Lucknow, deserve special thanks for NMR, Mass and Elemental Analyses.

The author expresses his deep sense of gratitude to Dr. Patrick Carroll, University of Pennsylvania, Philadelphia, U.S.A., for the X-ray crystallography of the lactam.

Gracious thanks are extended to the Council of Scientific and Industrial Research, New Delhi, and Indian Institute of Technology, Kharagpur for the award of fellowships (JRF & SRF) and other financial assistance throughout the research programme.

Finally, the author wishes to express his sincere thanks to Mr. T. Maiti who patiently typed the manuscript and Mr. G. K. Bose for drawing the structures.

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PREFACE

Numerous studies carried out all over the world, during the past decade, indicated that "bay region" diol epoxides are the major ultimate carcinogenic metabolites of a large number of polycyclic aromatic hydrocarbons. The quest for ultimate carcinogenic metabolites of analogous azapolynuclear aromatic hydrocarbons (PAA) has only recently begun. The quantum chemical studies predict the 'bay region' diol epoxides of PAA are expected to be the most electrophilic and consequently mutagenic/tumorigenic metabolites. Amongst the PAAs, most extensively studied dihydrodiols or diol epoxides are benzacridines. However, dibenzacridines specially (a,h), (c,h) and (a,j) have also been synthesised and were converted to diol epoxides. This has stimulated considerable research interest in the synthesis of dibenzacridines having methoxy substitutions in the terminal ring for further elaboration to dihydrodiol.

Chloroaldehydes when reacted with arylamines, produce anils, the hydrochloride of which on heating has high preferential regioselectivity in cyclization to substituted quinolines. We have observed that the rates of reactions of polycyclic chloroaldehydes with 1 and 2-naphthyl amines are different, the former produces Schiff's base first which on heating with another equivalent of 1-naphthylamine generates a high yielding practical synthesis of dihydrodibenz acridines. The preferential regioselective cyclization of mixed anil hydrochlorides have also been taken up in the first chapter of this dissertation. Following the protocol of functional group transformations, methoxy $\rightarrow$ phenol $\rightarrow$ orthoquinone $\rightarrow$ dihydrodiol, dibenzacridines and other polycyclic azaarenes having methoxy group in

the terminal ring could be converted to the penultimate oxidative metabolite carcinogenic compounds of this series.

In the second chapter dihydro chromanones and dihydro benzchromanones have been converted to chloroaldehydes by Vilsmeier-Haack reaction. These chloroaldehydes have been converted to oxaazaarenes through their anil hydrochlorides, the resistivity in opening up of the pyran ring during thermal cyclization has been extensively studied, thus a useful synthesis of polycyclic oxaazaarenes have been developed. This method also represents a potentially general synthetic approach to both linear and angular polyarenes.

Polycyclic aromatic compounds in which the terminal ring (preferably in the "bay region") replaced by alpha pyranone moiety are found to inhibit induction of polycyclic hydrocarbon-induced tumorigenesis in rodents. To build up the qualitative structure activity relationship, (QSAR) systematic investigations of the effects of structural modifications on anticarcinogenic activity have been conducted recently by Harvey's group. As part of a related program with this objective, we have synthesised a series of polycyclic coumarin and oxa-coumarin derivatives. These compounds should be more effective in blocking tumor induction than their analogs having smaller aromatic ring systems. With this design concept in mind the syntheses of polycyclic coumarin derivatives were successfully carried out by the conversion of chloroaldehyde $\rightarrow$ methoxyaldehyde $\rightarrow$ chalcone derivatives $\rightarrow$ coumarin derivatives. Though there are many synthetic approaches known for coumarin syntheses but easy availability of the chloroaldehydes prompted us to take-up the synthesis by the above mentioned pathway. The yields are good to very good in all the steps.

Further, presence of the carbethoxy group alpha to carbonyl moiety will help in the synthesis of further annelated viz. alkylated coumarin derivatives. This has been discussed in the third chapter.

Versatility of chloroaldehydes in the synthesis of polycyclic aza, oxaazaarene and coumarins have been explored. In the fourth chapter of this thesis we have used the chloroaldehydes in the synthesis of isoxazoles via azidoaldehydes. The medicinal importance of polycyclic isoxazole derivatives have been reviewed.

Finally, in the reawakening of interest for the synthesis of new gamma-lactam antibiotics, we have developed a novel method of synthesis of A,B ring trans fused, tricyclic C-aryl gamma-lactams. Thus, the anilino-malonates were condensed with aryl acryloyl chloride to get the gamma-lactam derivatives.

Saponification followed by decarboxylation produced only the trans fused aryl gamma-lactam carboxylic acids. Extensive NMR & X-ray studies of one of the derivatives were taken up to establish the stereochemistry. Finally annulation through Arndt-Eistert reaction followed by cyclization of the resultant acid enabled us to develop a useful route for the synthesis of tricyclic gamma-lactams (viz. furo gamma-lactams). The novel syntheses described herein offer the advantages of fewer steps and superior yield over previous methods. These five chapters constitute an up-to-date and thorough exposition of the present state of the art of synthesis and biological importance of polycyclic heterocyclic compounds, named as "SYNTHETIC STUDIES ON SOME POLYCYCLIC AZA & OXAARENES OF BIOLOGICAL IMPORTANCE".

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- b) Synthesis and Thermolysis of Cycloalkenylazides. A simple route to polycyclic isoxazoles. Md. Izhar Sami, G. K. Kar & J. K. Ray, Org. Prepn.Proced.Int. (U.S.A), Vol.23, No. 2, 6 (1991).
- c) Synthesis of Polycyclic oxa-coumarins as an antitumor agents. Md. Izhar Sami, G. K. Kar & J. K. Ray, Tetrahedron - Communicated.
- d) A short synthesis of Dibenz[c,h]acridines - Md. Izhar Sami, G. K. Kar & J. K. Ray, Tetrahedron Lett., - Communicated,
- e) Cyclisation of Anil derivatives - A short and convenient synthesis of naphthopyrano quinolines - Md. Izhar Sami, G. K. Kar & J. K. Ray, Synthesis, - Communicated.

Abstract

Polycyclic aza and oxa-arenes have attracted organic chemists for their varied biological activities and interesting structural frameworks. In this dissertation we have presented the syntheses of polycyclic azaarenes viz. dibenz[c,h]acridines which are potent carcinogenic compounds and have two bay regions in their structures. Our synthetic approach involves regioselective thermal cyclisation of enamino-imines which have been obtained from various chloroaldehydes via Schiff's bases. Further to study the carcinogenicity/mutagenicity we have synthesised naphthopyrano quinolines from suitable chloroaldehydes. Chloroaldehydes on treatment with aniline or substituted anilines gave the enamino-imine hydrochlorides which on thermal cyclisation produced naphthopyrano quinolines in good to excellent yields. We have used the chloroaldehydes in synthesising the carcinogenic compounds in first two chapters. Then we thought to utilise the same chloroaldehydes in synthesising some polycyclic coumarins (antitumor) and isoxazoles which have varied biological activities. In third chapter the synthetic route is based on the transformation of functional groups from chloroaldehydes to methoxy aldehydes followed by treatment with cyanoacetic ester and finally intramolecular cyclisation with py.HCl to get the polycyclic coumarins.

In fourth chapter we have described two steps synthesis of polycyclic isoxazoles starting from chloroaldehydes of various ketones and then thermal cyclisation of azido aldehydes into isoxazoles in excellent yields.

Finally we have concentrated on the synthesis of various polycyclic Gamma Lactams. We synthesised some stereodefined novel Furo Gamma Lactams involving the intermolecular Michael addition of anilinomalonates to α, β -unsaturated acid chloride followed by intramolecular amidification. Hydrolysis of the resultant diester produced the mono-carboxylic acid where the stereo chemistry of the ring juncture was found to be trans which have been confirmed by X-ray analysis. The annelation of the acid through Arndt-Eistart reaction and cyclisation produced the tricyclic gamma lactams in good yield.

Key words : Azaarenes, dibenz[c,h]acridines, bay region, oxa-azaarenes, naphthopyrano quinolines, carcinogenesis, polycyclic coumarins, antitumor, isoxazoles, Furo Gamma Lactams.

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INTRODUCTION

In this dissertation entitled "SYNTHETIC STUDIES ON SOME POLY-CYCLIC AZA & OXAARENES OF BIOLOGICAL IMPORTANCE" we like to present some new and optimised synthetic methods for the preparation of biologically important aza- and oxaheterocycles. The present work has been classified mainly into five chapters which are being discussed below.

Chapter 1 describes the short and efficient synthetic routes to poly-aromatic azaarenes (PAA) which are potent carcinogenic compounds. Thus, dibenz[c,h]acridine and its derivatives which are important compounds in the study of mutagenic/carcinogenic activity has been prepared in high yield starting from suitable chloroaldehydes and 1-naphthylamine by regioselective thermal cyclisation method.

The chloroaldehydes on condensation with α -naphthylamine (1 equivalent) afforded the chlorovinylimines which on further heating at 140° - 180°C with 1-naphthylamine gave the dihydrodibenz[c,h]acridine derivatives in very good yields. Aromatisation of these dihydro derivatives with Pd/C in p-cymene gave the dibenz[c,h]acridine derivatives in excellent yield. One of the striking feature of the above method is that there is a methoxy group in the terminal ring of dibenz[c,h]acridine which can be transformed to dihydrodiol and diol epoxide by a method already developed in our laboratory.

A general programme involving the synthesis of potential carcinogenic compounds of polycyclic oxa-azaarenes has been described in Chapter 2 of this thesis. Our method involves the synthesis of naphthopyrano[4,3-b]quinoline derivatives and its isomer by thermal cyclisation of anil hydrochlorides. The anil derivatives were obtained from corresponding

chloroaldehydes by the reaction with aniline/substituted anilines in presence of 2N HCl in excellent yields. The anilhydrochlorides on brief heating at a temperature slightly above their melting points underwent ring closure with elimination of aryl aminohydrochlorides to afford the corresponding quinoline derivatives in moderate to excellent yield.

Coumarins constitute an important class of natural products many of which exhibit useful drug activity. 3 and 4-substituted coumarins are well known for their physiological properties. Pyrano coumarins are also biologically active. Recently it has been found that coumarin analogues inhibit the induction of polycyclic aromatic hydrocarbons induced tumorigenesis in the rodents and some of them are excellent antitumor agents. As a part of a programme with this objective we have undertaken the synthesis of some novel coumarin and oxa-coumarin derivatives in Chapter 3.

Our method involves the synthesis of various polycyclic coumarins starting from suitable chloroaldehydes. Chloroaldehydes on treatment with sodium methoxide led to methoxy aldehydes in high yields which on condensation with ethyl cyanoacetate in ethanol and 30% aqueous-alcoholic KOH produced the cyanoderivatives in very good yields. Briefly heating the latter with pyridine hydrochlorides afforded the coumarin derivatives in excellent yields.

Chapter 4 presents the synthesis of some novel polycyclic isoxazoles which are known to be very important class of heterocycles of diverse physiological activities. Our method involves the synthesis of polycyclic isoxazoles from the suitable chloroaldehydes via the thermolysis of azidoaldehydes. The azidoaldehydes were prepared in high yields by the reaction of chloroaldehydes with sodium azide in dimethyl sulfoxide

(DMSO). The thermal cyclisation of azides to polycyclic isoxazoles were achieved in excellent yields^{by} refluxing with dichloromethane.

Chapter 5 describes the synthesis of some stereodefined and novel furo gama-lactam derivatives involving the intermolecular Michael addition of anilinomalonates to α, β -unsaturated acid chloride followed by intramolecular amidification as the key step to produce the gama lactam moiety. Then gama lactam derivatives were subsequently converted to a tricyclic furo gama-lactams with trans juncture using standard procedures. The anilinomalonates were condensed with 3-(2'-furyl)acryloyl chloride in fashion which permitted intermolecular Michael addition followed by intramolecular amidification to give the desired gama-lactam diester derivatives. The resulting diesters on hydrolysis and concomitant decarboxylation yielded the mono acids. The hydrolysis of diester produced only the trans isomer as evident from the coupling constants of C_4 -H and C_5 -H.

The annelation of mono acids was done by Arndt Eistert reaction. Fresh mono acids were converted into acid chloride by the reaction of oxalyl chloride from sodium salt of acids. When acid chlorides were treated with diazomethane, it afforded the gama-lactam diazoketones in excellent yield. The esters were achieved by refluxing the diazoketones in freshly prepared Ag_2O and methanol. On hydrolysis of esters gave the annelated acids in good yield. The desired compounds i.e. tricyclic furo gama-lactams were achieved by cyclisation of acids with PPA in good yield.

All the IR spectra were recorded on a Perkin-Elmer 883 Infrared Spectrometer using potassiumbromide plates for solids. NMR spectra were recorded on Varian EM390 (90 MHz), JEOL (100 MHz) and Bruker 250 (250 MHz) instrument with TMS as internal standard.

CHAPTER 1

STUDIES ON POLYCYCLIC AZAARENES - A SHORT
SYNTHESIS OF DIBENZ[c,h]ACRIDINES

INTRODUCTION

One of the most feared disease now-a-days is cancer which is associated with the abnormal growth of cells. Many types of compounds are known to induce carcinogenesis and much work is actively going on all over the world to understand the relation between the structures of these compounds and its cancer inducing effects. Various theories have been proposed from time to time to explain the relationship between structural features and carcinogenic activities. Polycyclic azaarenes are widely spread in biosphere and are serious environmental pollutants. This has created tremendous interest towards synthesis of PAA and their probable oxidative metabolities. Hence, new synthetic methods were developed in the various laboratories which resulted in getting the desired compounds in pure form for biological assay. In this connection, we have also synthesised some dibenz[c,h]acridines which are potent carcinogens and hence at the beginning we have discussed and reviewed on polycyclic azaarenes and their available synthetic routes from recent literature.

DISCUSSION

In general cancer may be defined as "abnormal growth of cells", but what causes this abnormal growth, what is the prevention and what are the protections? These are a few questions which have been answered by scientists but not ambiguously.

In 1980 cancer was proved for the first time as a viral disease caused by human T-cell Leukemia virus (HTLV). This virus is distinct

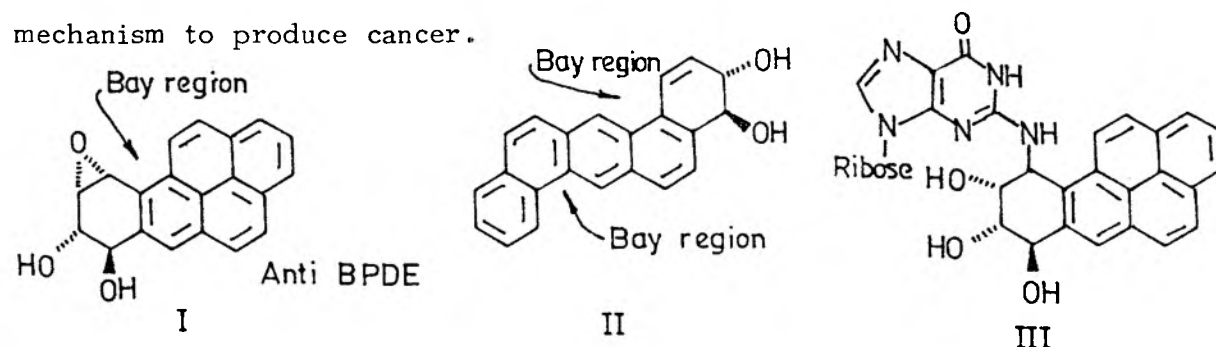
from all known animal tumor virus, infection with it is clearly associated with a type of T-lymphocytic human tumor, but how the virus causes the tumor is not clearly known. Various other viruses have been shown to cause cancer viz. BK and JC virus ¹.

Viruses probably cause a small fraction of human cancer, chemicals are thought to be culpable in large number of cases.

Chemical carcinogens have a very broad range of structures with no obvious unifying chemistry. Polycyclic aromatic hydrocarbons (PAH) are the major class of chemical carcinogens and have been extensively studied and reviewed ².

It has been established and reviewed by R. G. Harvey ^{2a,b} that PAH gets converted to diol epoxide by enzymes and other cofactors and these oxidative metabolites are the ultimate carcinogens in PAH series. The diol epoxide of PAHs having bay region are most potent carcinogens (I,II).

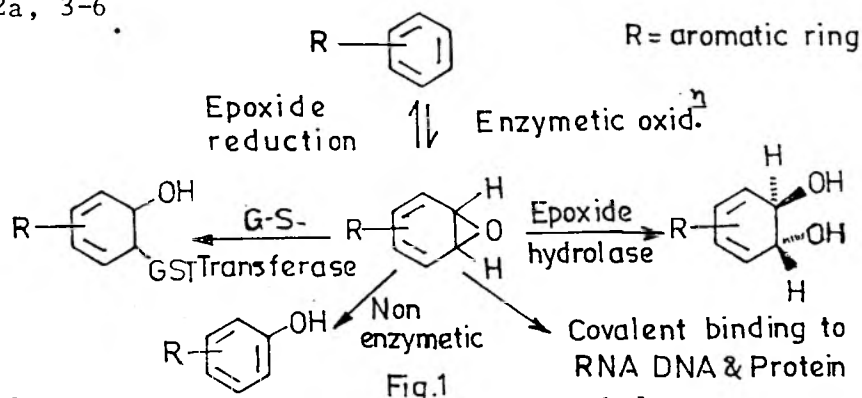
It has been established further that these diol epoxides form adduct (III) with nucleic acid (guanosine) and which then multiplies by an unknown mechanism to produce cancer.



In recent review Harvey and Geacintov ^{2b} have shown the detailed mechanism of binding of oxidative metabolites of PAH with nucleic acids. But how the single unit adduct multiplies have not yet been fully understood, because the direct alkylation of DNA can produce various

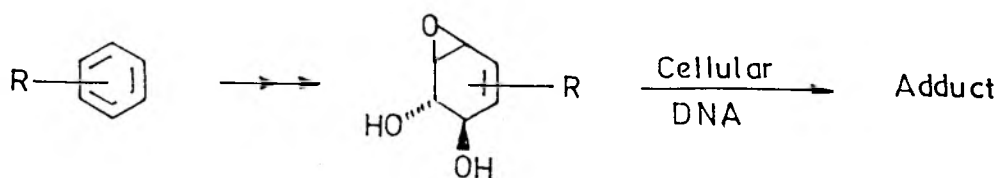
adducts at different base sites which forces to take an average of the picture and not the exact one. Probably DNA sequencing alkylation on specific base sites might produce some light in this field.

It was thought earlier that PAHs are direct acting carcinogens, but this idea was proved to be wrong in latter stage. It is now recognised that PAHs require metabolic activation in order to express tumorigenic activity^{2a, 3-6}.



It is believed that principal primary metabolites are arene oxides which are formed by enzymatic addition of an atom of oxygen to an aromatic-C=C-bond. These relatively unstable intermediates may then i) undergo hydration catalysed by epoxide hydrolase to form dihydro diols, ii) rearrange spontaneously to phenols, iii) undergo addition of glutathione catalysed by glutathione-s-transferase, iv) covalent bind to DNA, RNA and proteins (Fig. 1)

Current evidences indicate that principal biologically active metabolites are dihydrodiol epoxide derivatives^{2a, 3-6} which undergo adduct formation with cellular DNA to induce nonlethal mutation ultimately resulting in tumor formation.



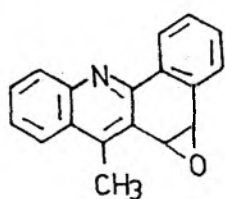
Synthesis has played an important role in all of these evidences. Several synthetic and biological studies have also established that the bay region dihydrodiol epoxide are much more mutagenic than the other regioisomers.

Though extensive studies with PAHs and their metabolites which bind them to DNA have been carried out in the last few decades. It is surprising that polycyclicazaarenes in contrast have not been thoroughly investigated in terms of their mutagenic and/or carcinogenic activities.

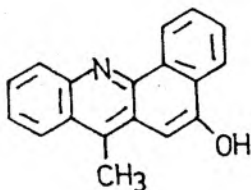
Recently it has been reported that several polycyclic azaarenes (PAA) like acridines, benzacridines and dibenzacridines etc. which are coming out from cigarette smoke, automobile exhaust⁷⁻¹⁰, industrial effluents are wide spread in biosphere and are serious environmental pollutants. This has created renewed interest in this class of compounds. Isolation of azaarenes in pure form from environmental pollutants is time consuming, laborious and difficult job and also not adequate amount of sample could be isolated by GC/MS technique. For testing more materials are required in pure form. This needs improved methods for the synthesis of these PAAs. As a result of this a significant number of synthesis and biological evaluation of several PAAs and their oxidative metabolites have come out in last few years.

In order to evaluate the carcinogenic/mutagenic activities of PAA, L. J. Boux et al¹¹ have reported the synthesis of K-region oxide (IV), phenol (V), dihydrodiols (VI and VII) of 7-methyl benz[c]acridine. However biological testing revealed that these oxidative products are less mutagenic than parent heterocycles^{11,12}.

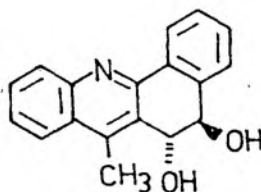




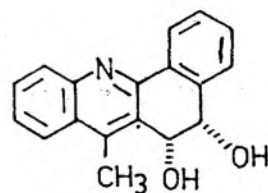
IV



V

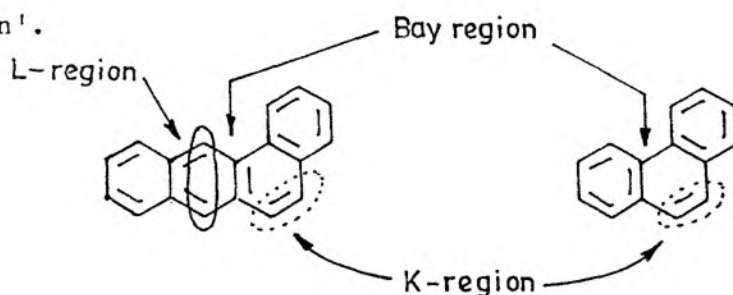


VI

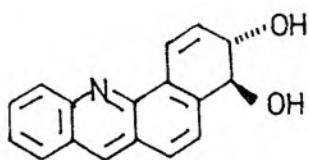


VII

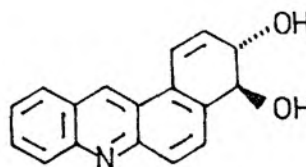
The K-region terminology derives from Pullmann's theory, according to which carcinogenic polycyclic aromatic hydrocarbons were considered to be distinguished by an electron rich bond such as the 4,5 bond of benzo[a]pyrene which is termed the K-region and excision of which leaves a fully aromatic polycyclic aromatic hydrocarbon ring system. Other regions which got investigated were 'bay' and 'L-region'.



The position of N-atom plays an important role towards the mutagenicity of the corresponding PAA. When the nitrogen atom presents in the bay region of PAAs, it increases their carcinogenicity. To test this hypothesis and rationalise the relationship between the position of nitrogen in a given azaarenes and its carcinogenicity, Ridder and Engelhardt¹³ designed a new synthesis of trans-3,4-dihydro diol (VIII) and (IX) via modified Birch reduction of the parent heterocycles.



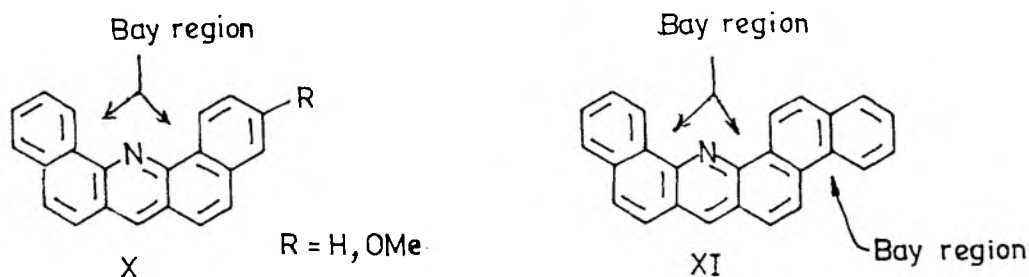
VIII



IX

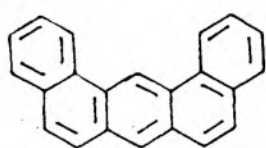
It has been proved that the dihydrodiol of benz[c]acridine (VIII) containing N-atom near the bay region was found to be more mutagenic¹⁴ than the corresponding benz[a]acridine (IX).

In dibenz[c,h]acridines (X and XI) the position of nitrogen is very interesting. The compound (X) possess two bay regions and on the other hand the compound (XI) have three bay regions as shown below.

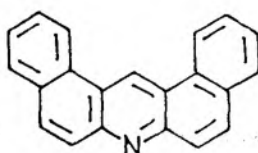


It is expected that these compounds (X & XI) will show enhanced carcinogenic activity as compared to their PAH analogue. In order to test the mutagenic/carcinogenic activity we undertook the synthesis of some dibenz[c,h]acridines in this chapter. Before discussion of our synthesis we will briefly review the synthesis and biological properties of some dibenzacridines which are more relevant to our present works.

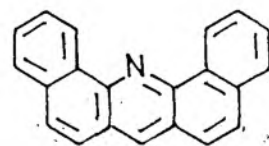
In contrast to the weak carcinogenicity of benz[a] and benz[c]acridines, dibenz[c,h]acridine (XIV) is a potent carcinogen¹⁵. Its activity is interesting from structure-activity stand point as contrast with the very weak carcinogenicity of the two closely related isosteric molecules dibenz[a,j]anthracene (XII) and dibenz[a,j]acridine (XIII)¹⁶.



XII

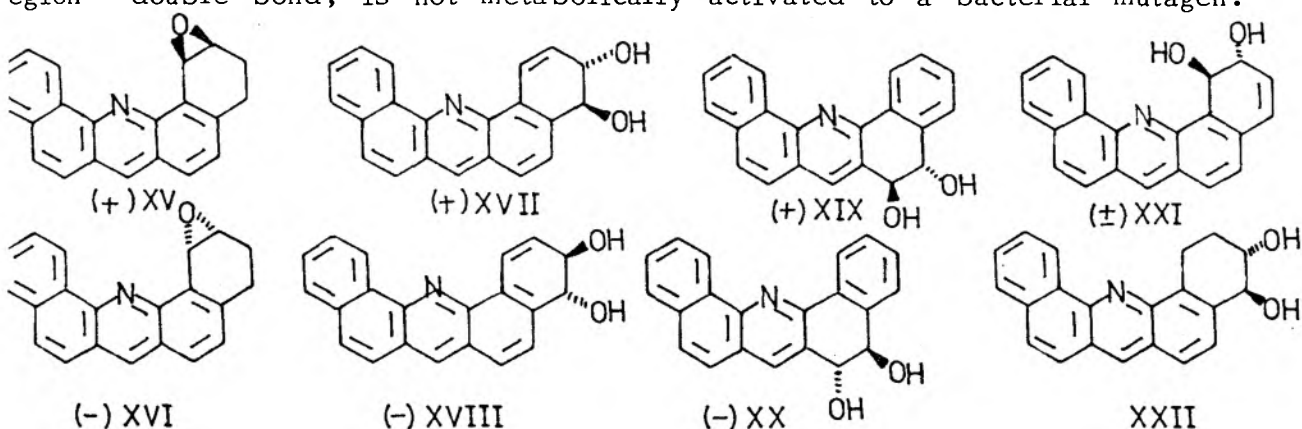


XIII



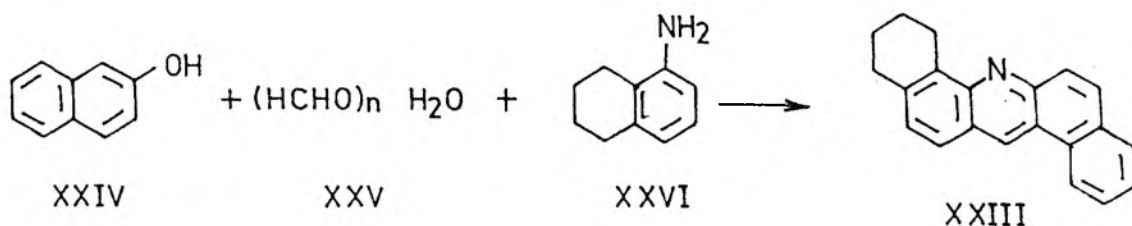
XIV

Recently it has been reported¹⁷ that enantiomeric pairs of bay region tetrahydro-1,2-epoxides of dibenz[c,h]acridine (XV & XVI) are at least times more mutagenic than the diol epoxide in the Salmonella assay and no difference in mutagenic activity is observed between enantiomers. ($\pm$)3,4-dihydrodiols (XVII & XVIII) are metabolised products which are several fold more mutagenic than the products of the metabolism of dibenz[c,h]acridine or its ($\pm$)5,6-dihydrodiols (XIX & XX) or 1,2-dihydrodiol (XXI) and the tetrahydro 3,4-diol (XXII) which lacks the isolated bay region double bond, is not metabolically activated to a bacterial mutagen.

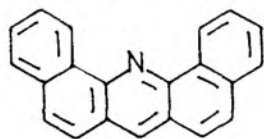


Though much work has been done in the field of acridines and benzacridines however survey of literature reveals that only a few synthetic methods have come out for dibenzacridine derivatives and also the methods suffer from the difficulty of poor yield and longer time of reaction.

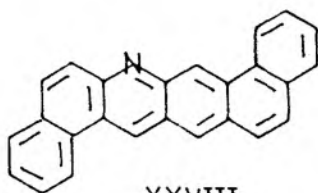
In 1956 N. P. Buü Hoi et al¹⁸ reported the synthesis of 8,9,10,11-tetrahydrodibenz[a,h]acridine (XXIII) in poor yields only by the action of paraformaldehyde (XXV) on a mixture of β -naphthol (XXIV) and 5,6,7,8-tetrahydro-1-naphthylamine (XXVI) using Skraup reaction.



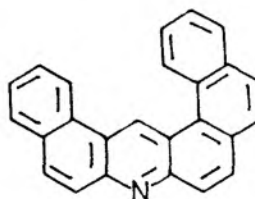
hey¹⁹ have also prepared the following compounds (XXVII-XXX) using the same procedure.



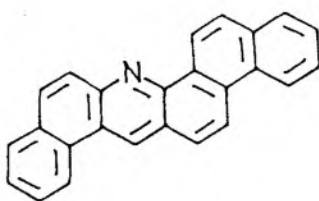
XXVII



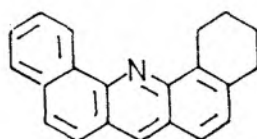
XXVIII



XXIX



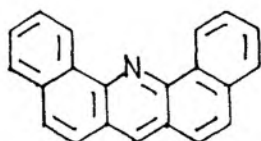
XXX



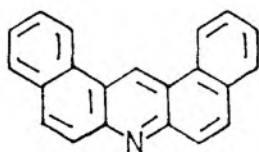
XXXI

Although the compound (XXXI) has been described in the literature²⁰ neither a detailed procedure nor a good yield was provided. Recently, S. Kumar et al²¹ have reported the synthesis of same compound using the same methodology.

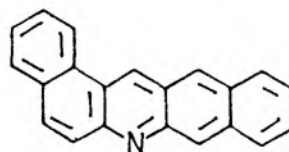
N. P. Buü Hoi et al²² have also reported that α -naphthisatine, and α -tetralone on refluxing in alcoholic 10N KOH for 120 hrs and the product on decarboxylation at 300°C with Cu_2CrO_4 followed by aromatisation with 5% Pd-C gave 28-30% dibenz[c,h]acridine (XXXII). Similarly starting from either α/β tetralone and suitable naphthisatine derivatives they prepared the dibenzacridines (XXXIII-XXXV) in poor yield.



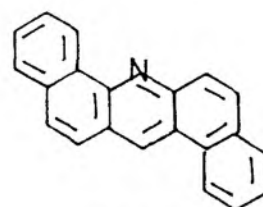
XXXII



XXXIII

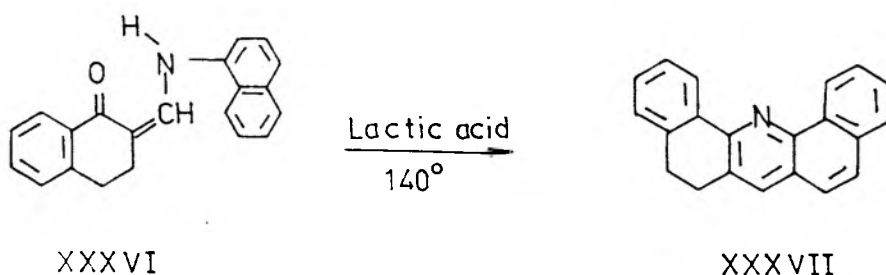


XXXIV

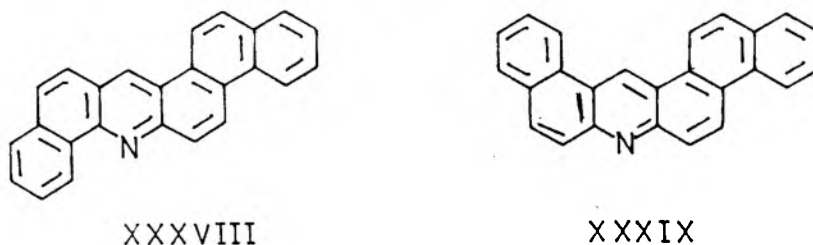


XXXV

In 1974 B. D. Tilak et al²³ have reported the synthesis of 8,9-dihydrodibenz[c,h]acridine (XXXVII) by the cyclodehydration of 2-(1-naphthylaminomethylene)-1-tetralone (XXXVI) in presence of lactic acid at 140° in only 10% yield. The dihydro compound on dehydrogenation with Se gave the dibenz[c,h]acridine (XXXII) in 38% yield.

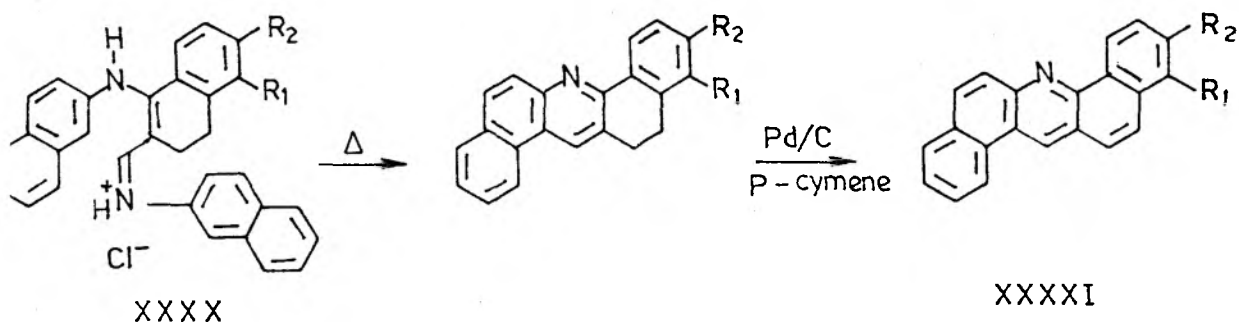


Earlier Ulmann-Fetvadjan condensation reaction was used for the synthesis of dibenzacridines²⁴ derivatives. Thus 2-aminophenanthrene on condensation with α and β -naphthols readily furnished benzo[c]naphth[1,2-j]-acridine (XXXVIII) and benzo[a]naphth[1,2-j]acridine (XXXIX) respectively.

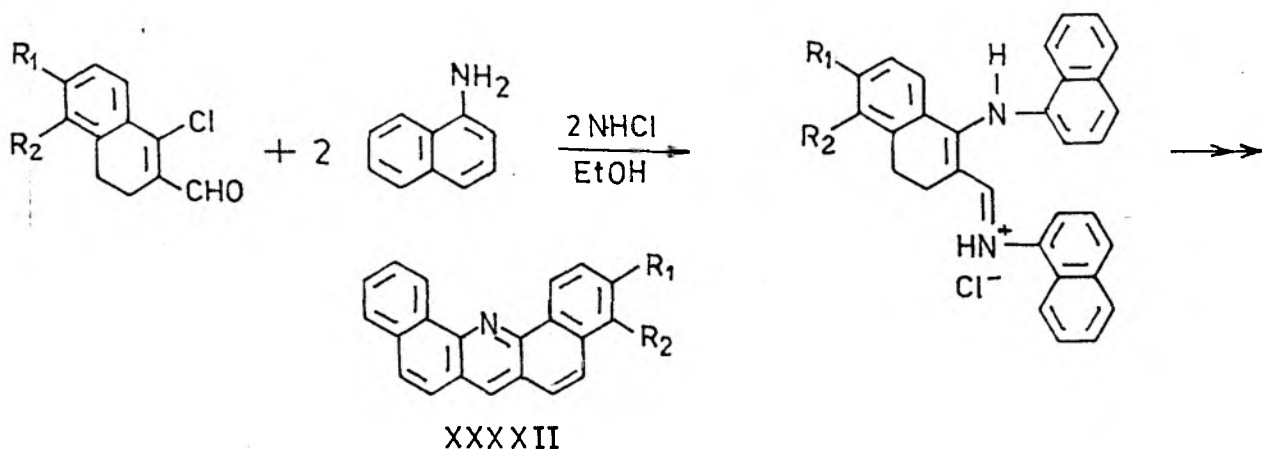


The literature survey reveals that only four synthesis of dibenzacridines have been reported so far as we have described earlier. In every synthesis the yields were poor and time consuming. So, recently Ray et al²⁵⁻²⁷ from this laboratory have developed a simple and convenient method for the synthesis of various polycyclic azaarenes by thermal cyclisation of anil hydrochlorides which were prepared by suitable chloroaldehydes and by reaction of various arylamines in presence of EtOH/2N·HCl. In most

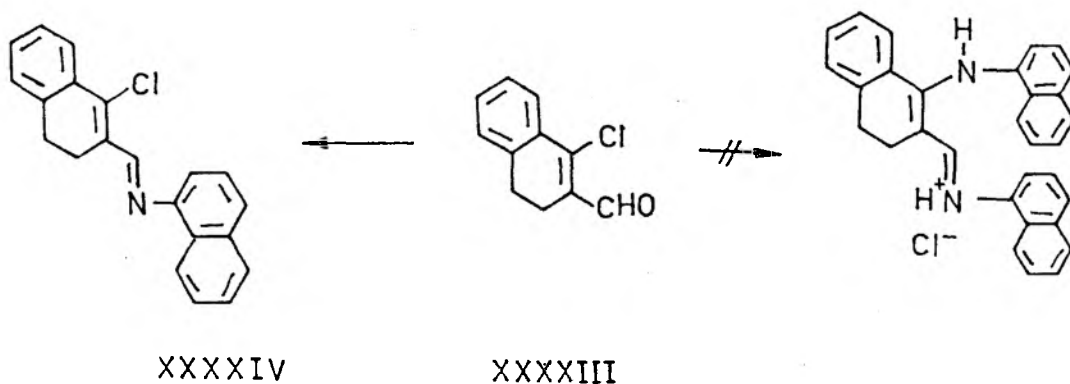
of the cases the yields of the final compounds were high and also the time of reaction was very short. Very recently Ray et al²⁸ have reported the synthesis of some dibenz[a,h]acridines (XXXXI) by regioselective cyclisation of anil derivatives (XXXX) in high yield.



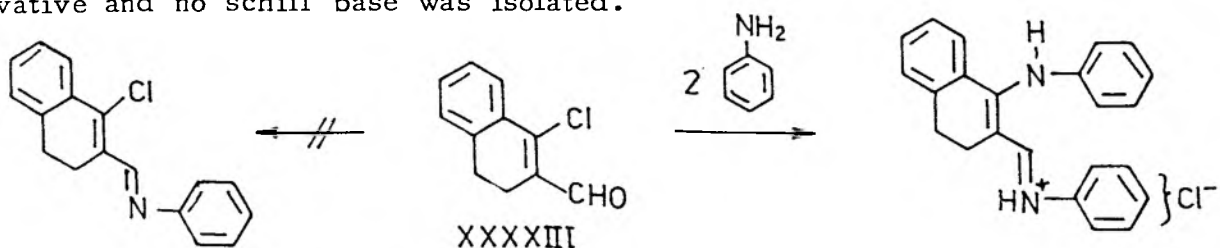
Following the same sequences of reactions we have also thought to synthesise dibenz[c,h]acridines (XXXXII) as per following scheme.



Interestingly when α -tetralone chloroaldehyde (XXXXIII) was treated with 2 moles of α -naphthyl amine in presence of 2N·HCl in EtOH, no anil-hydrochloride but only chlorovinylimine (XXXXIV) was isolated.

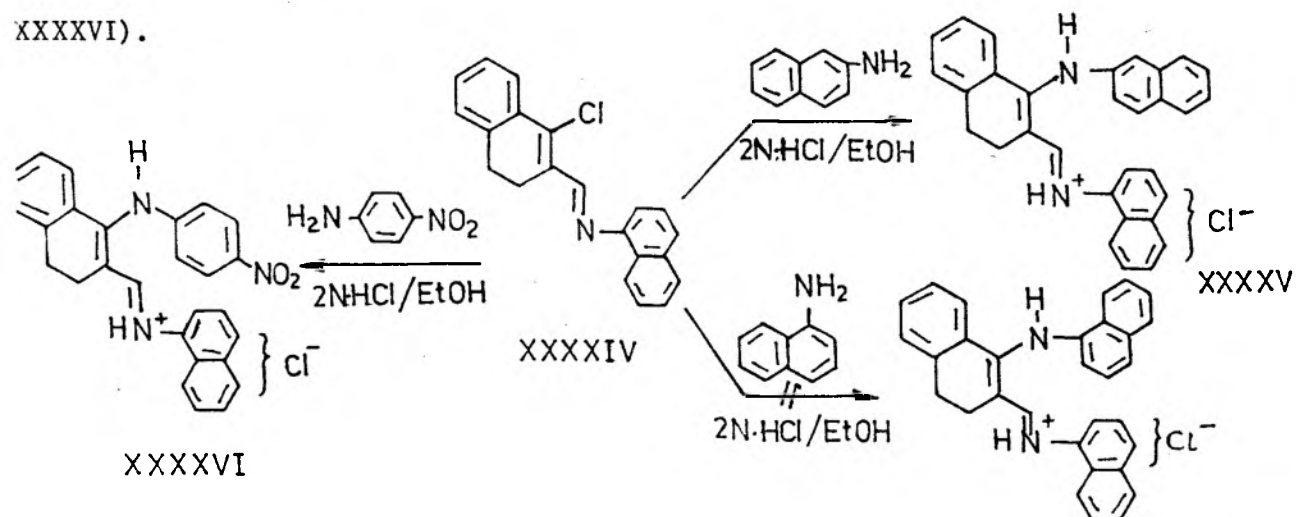


So, this is probable due to the increased 'perieffect' of α -naphthylamine which is evident from the following studies. When 1 equivalent of α -tetralone chloroaldehyde (XXXXIII) was refluxed with 2 equivalent of aniline in benzene (or in EtOH/2N HCl) it always produced the anil derivative and no schiff base was isolated.



Even when 1 equivalent of chloroaldehyde (XXXXIII) was treated with 1 equivalent of aniline then also anil derivative was formed as the only product and 0.5 equivalent of chloroaldehyde remained unreacted.

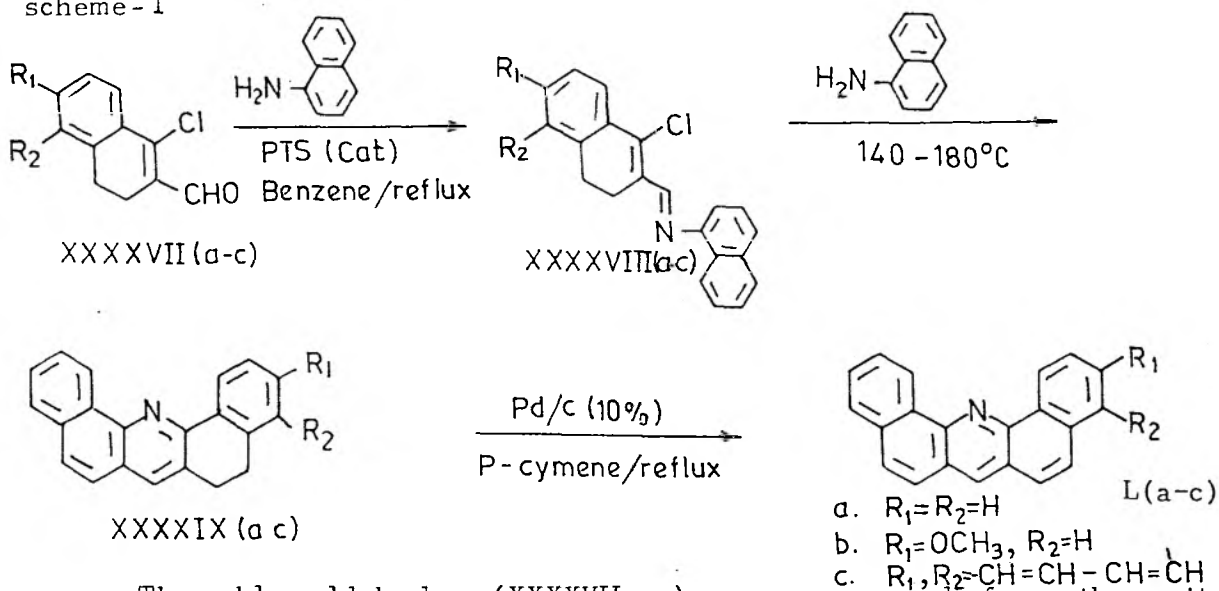
The schiff base (XXXXIV) however on reaction with a further 1 equivalent of p-nitroaniline or 2-naphthylamine (which is having comparable bulk with that of α -naphthylamine) afforded the anil derivatives (XXXXV-XXXXVI).



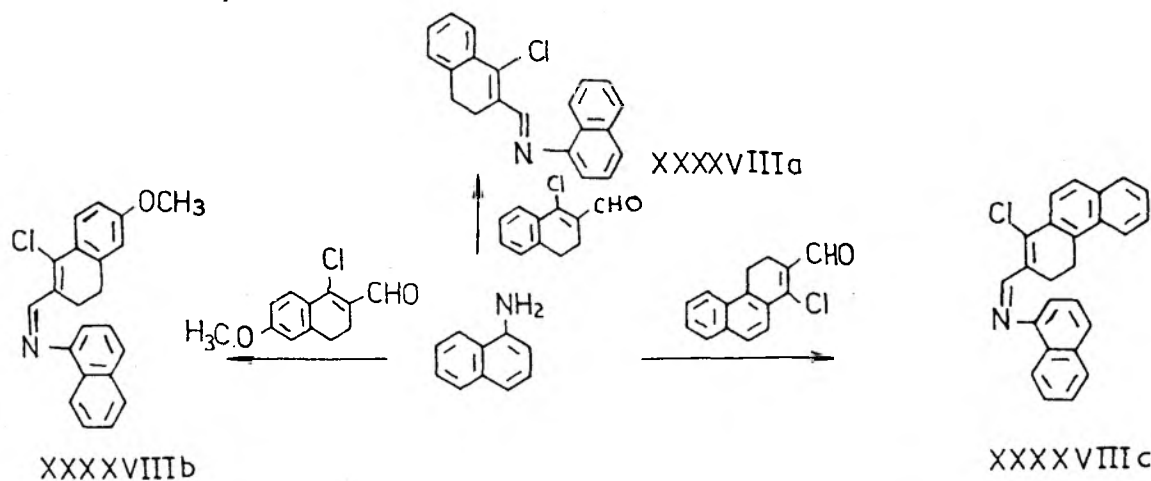
Previous results from this laboratory showed that in case of anil hydrochloride formation using o-substituted anilines resulted with poor yields as compared to the m/p substituted anilines where in general excellent yields were obtained. This clearly indicates that the anil derivative was not formed with α -naphthylamine due to increased periinteraction.



We were, however, able to synthesise the desired target compounds i.e., dibenz[c,h]acridines (La-c) via a modified procedure as shown in scheme - I

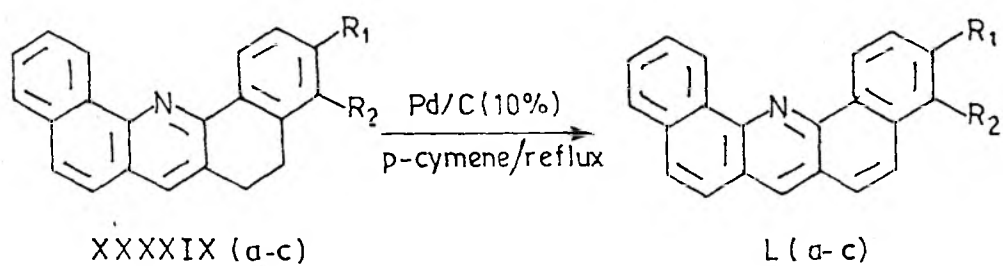
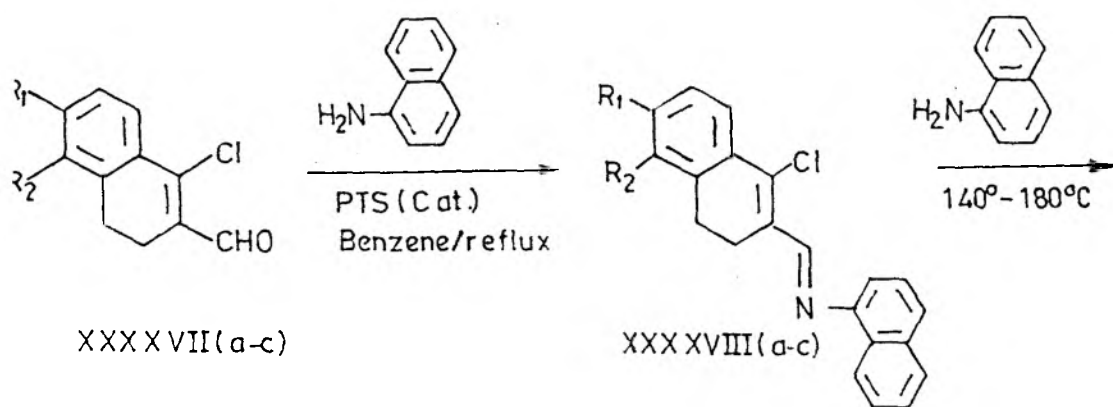


The chloroaldehydes (XXXXVIIa-c) were prepared from the suitable ketones by treatments with POCl_3/DMF (Vilsmeier Haack reagent). Refluxing of the chloroaldehydes (1 equivalent) with 1 equivalent of 1-naphthylamine in benzene produced the chlorovinylimines (XXXXVIIIa-c) as yellow solid in excellent yields.

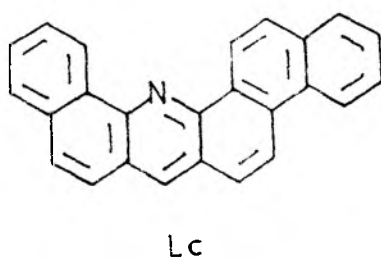
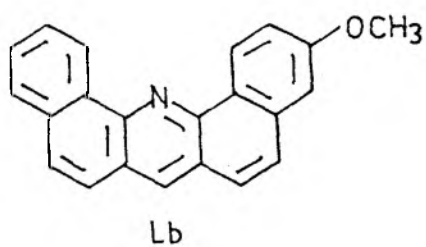
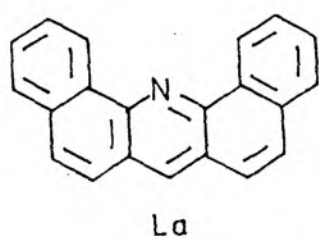


The Schiff bases (XXXXVIIIa-c) showed an absorption at $1590-1610\text{ cm}^{-1}$ and at about $3310-3400\text{ cm}^{-1}$ for $\nu_{\text{C=N}}$ and $\nu_{\text{N-H}}$ respectively.

SCHEME-I



- $\text{R}_1 = \text{R}_2 = \text{H}$
- $\text{R}_1 = \text{OCH}_3, \text{R}_2 = \text{H}$
- $\text{R}_1, \text{R}_2 = \text{CH}=\text{CH}-\text{CH}=\text{CH}$



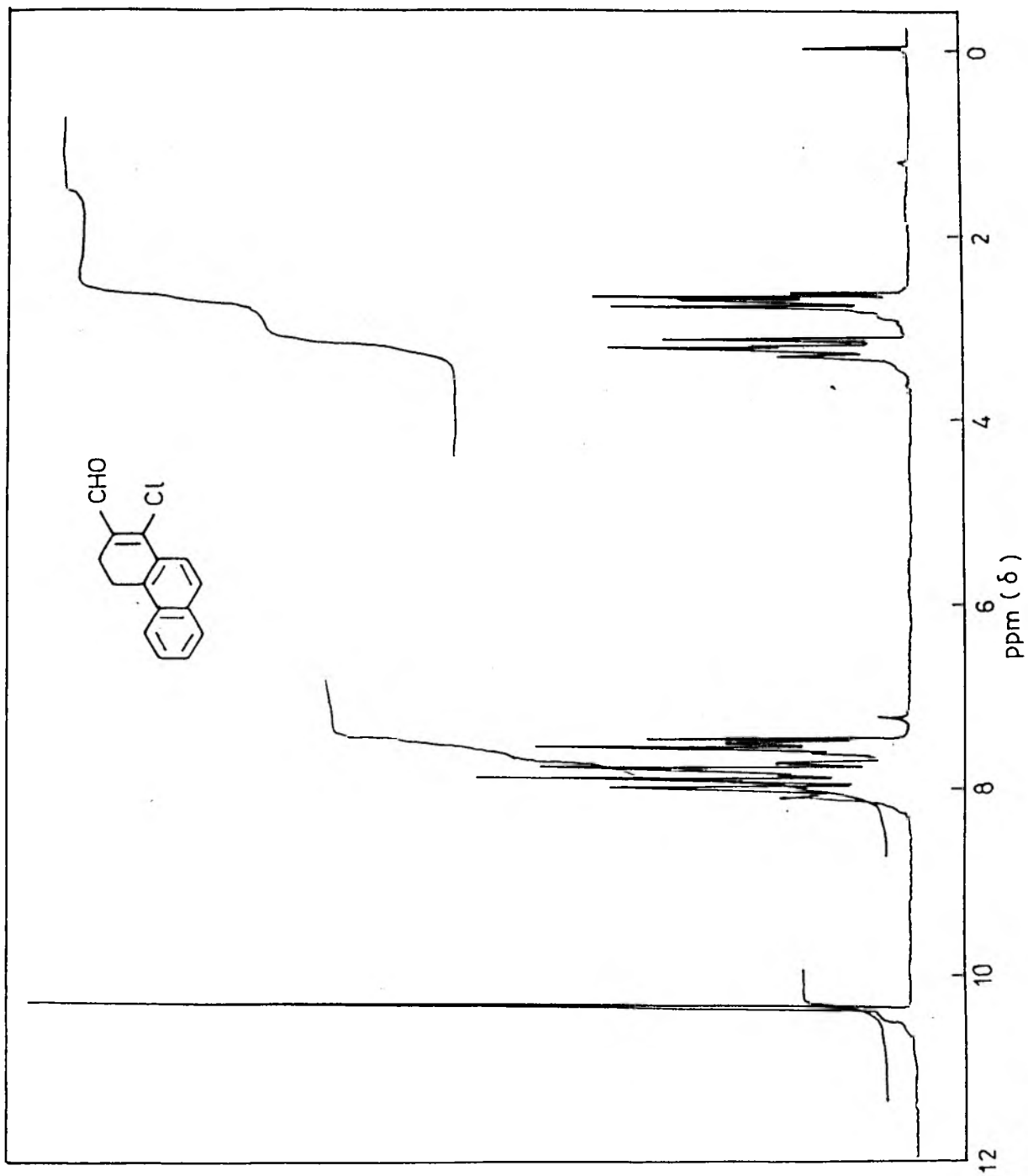
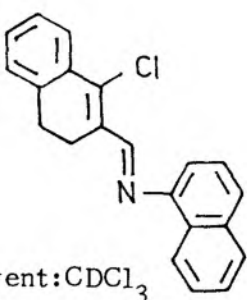


FIG. 1-1

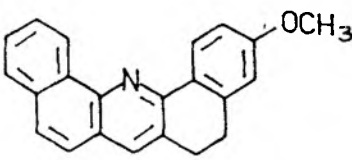
The ^1H NMR of the compound (XXXXVIIIa) is shown below.

	Position of peaks	Nature	Proton count	Assignment
	2.8-3.35	m	4H	$-\text{CH}_2-\text{CH}_2-$
	7.0-7.9	m	10H	Aromatic
	8.4	dd	1H	Aromatic
	9.0	s	1H	$-\text{CH}=\text{N}$

Solvent: CDCl_3

Fig. 1.3

The Schiff bases (XXXXVIIIa-c) on heating again with 1 mol of α -naphthylamine at $140-180^\circ\text{C}$ afforded the dihydrodibenz[c,h]acridine derivatives (XXXXIXa-c) in very good to excellent yield. All the compounds were characterised by usual spectral data as well as by elemental analysis. The compound (XXXXIXb) shows the following signals in ^1H NMR.

	Position of peaks	Nature	Proton Count	Assignment
	3.0-3.3	m	4H	$-\text{CH}_2-\text{CH}_2-$
	3.95	s	3H	$-\text{OCH}_3$
	6.81	d, $J=3$ Hz	1H	Aromatic
	7.0	dd, $J=3$ Hz	1H	Aromatic
	7.6-7.9	m	6H	Aromatic
	8.8	d, $J=9$ Hz	1H	Aromatic
	9.6	dd, $J=3$ Hz	1H	Aromatic

Solvent : CDCl_3

Fig. 1.5

We believe that Schiff bases (XXXXVIIIa-c) is being converted to dihydrodibenzacridines via the intermediate formation of enaminoimine-hydrochloride in the reaction mixture at higher temperature and is getting

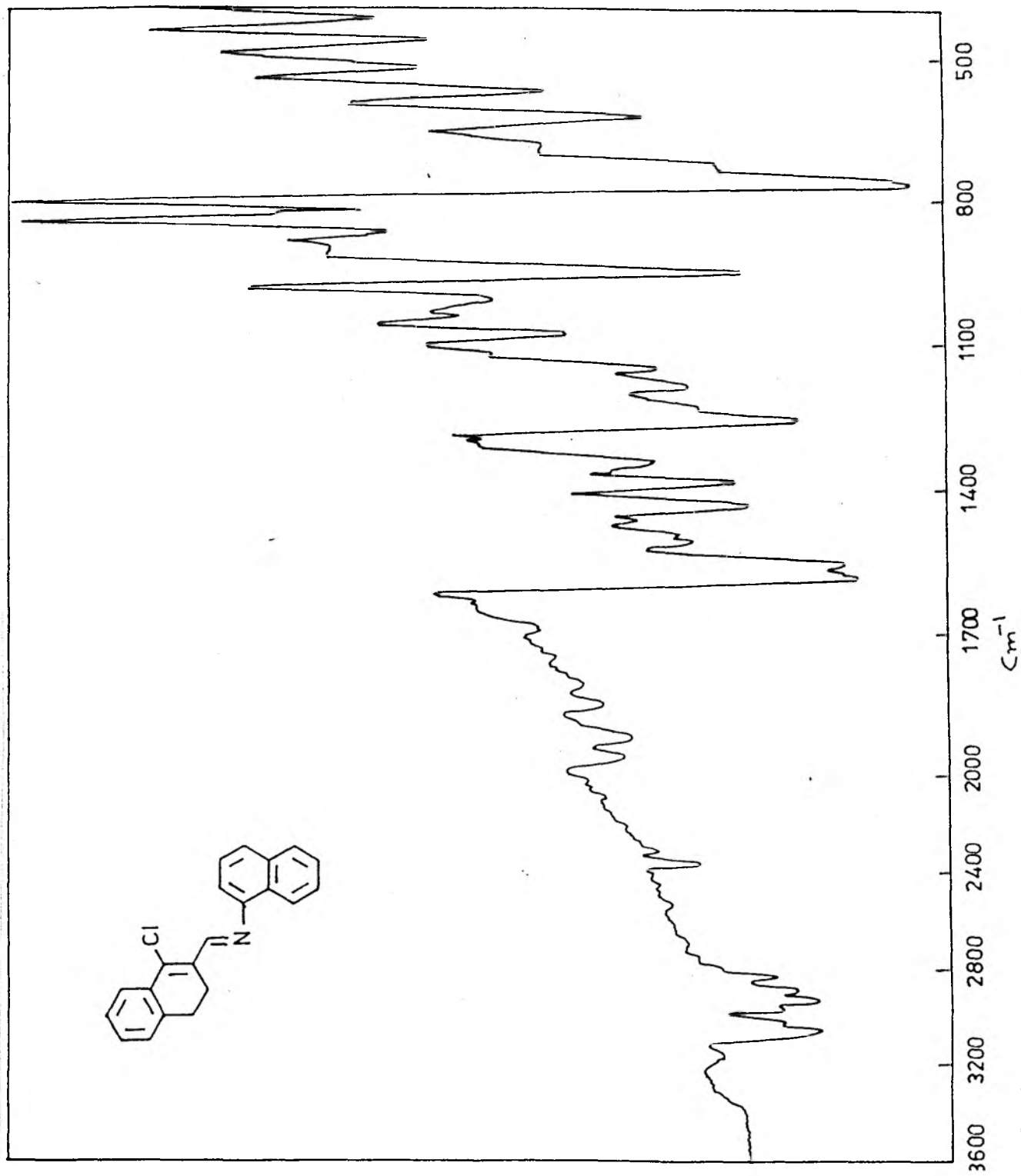
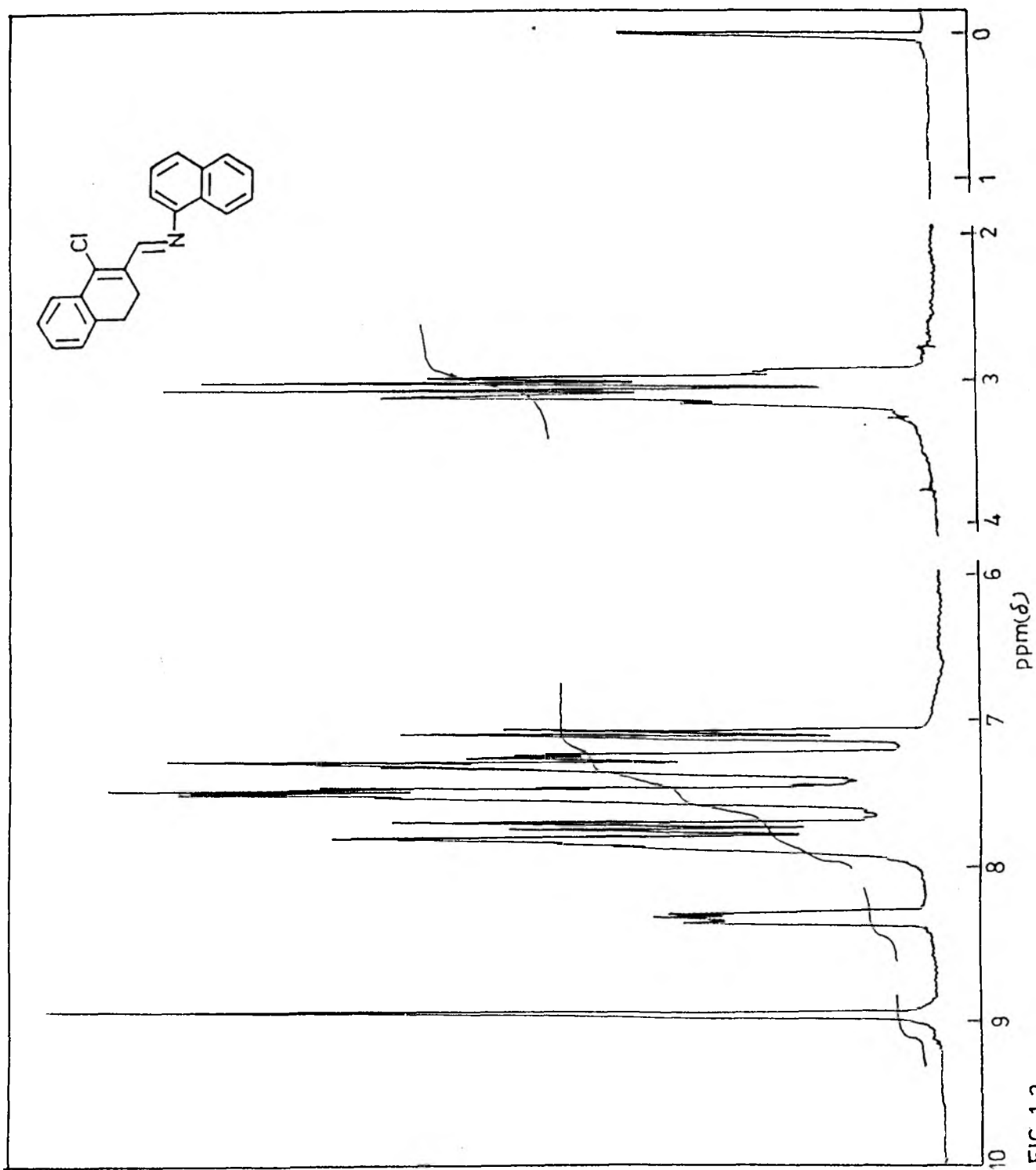
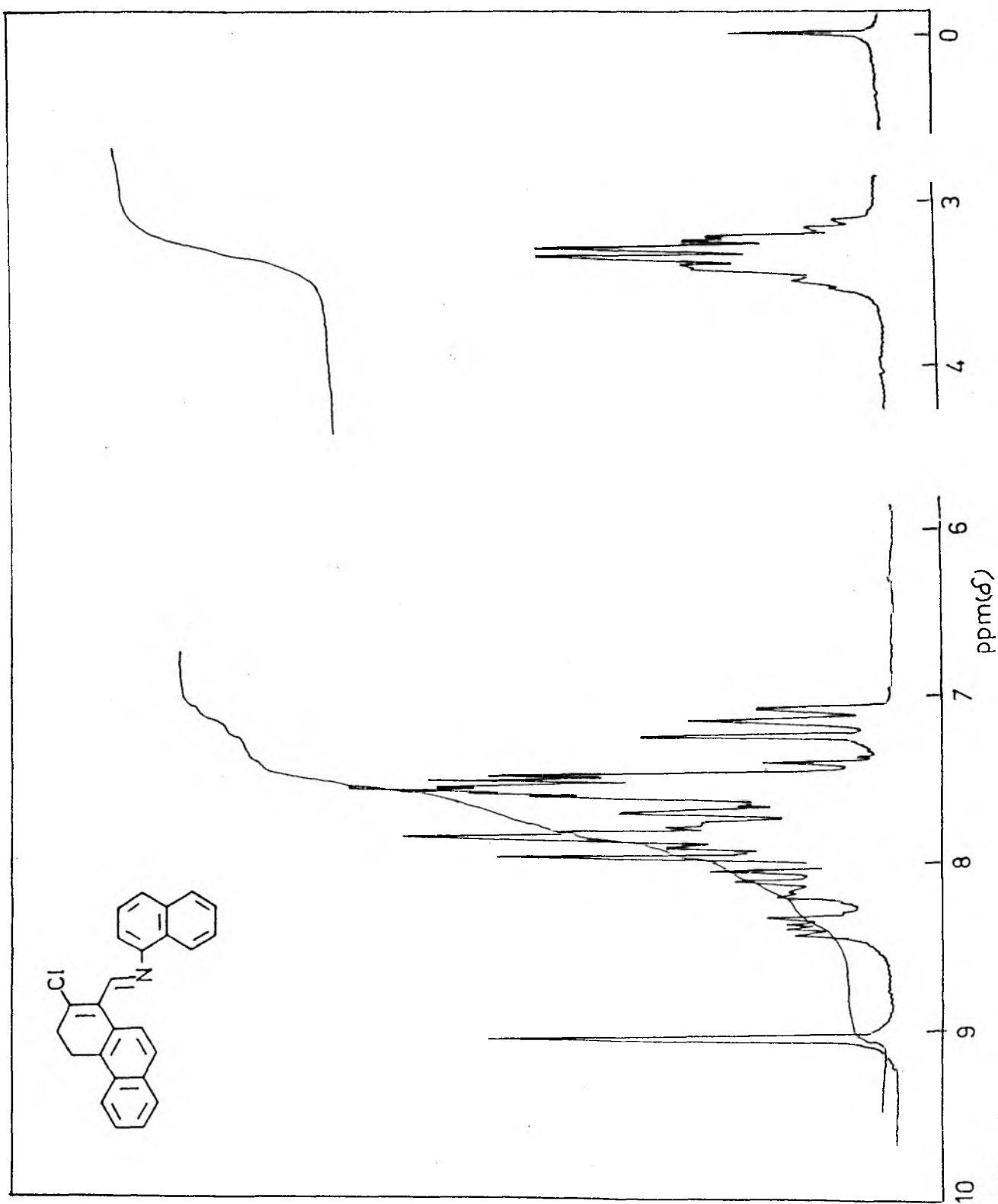
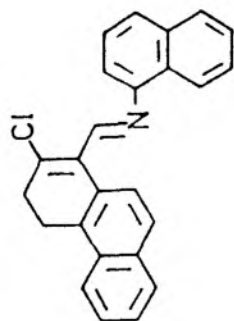
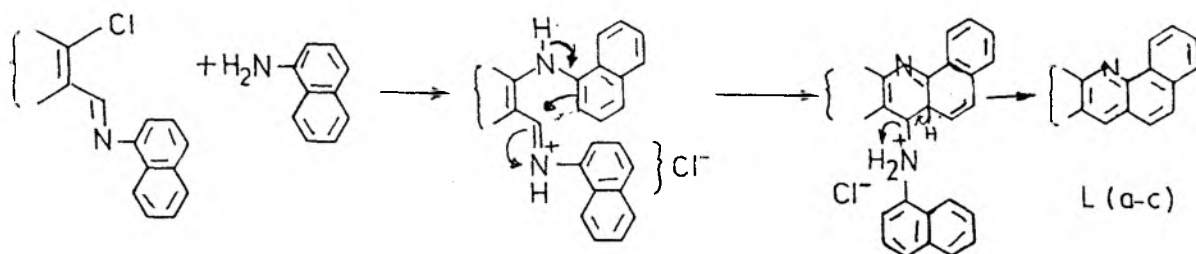


FIG. 1·2

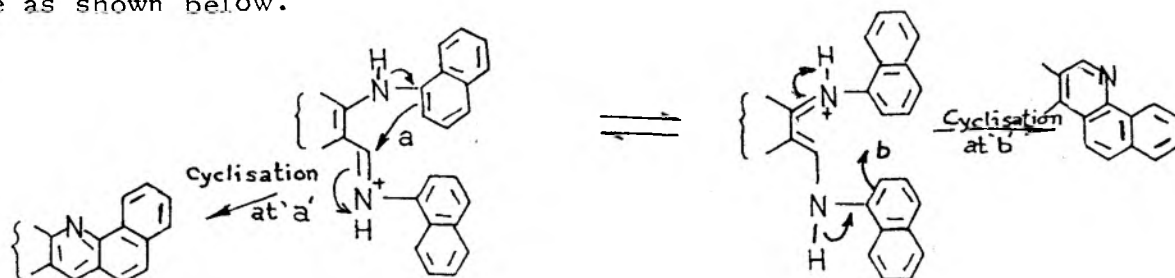




cyclised under this condition with elimination of 1-naphthylamine hydrochloride.

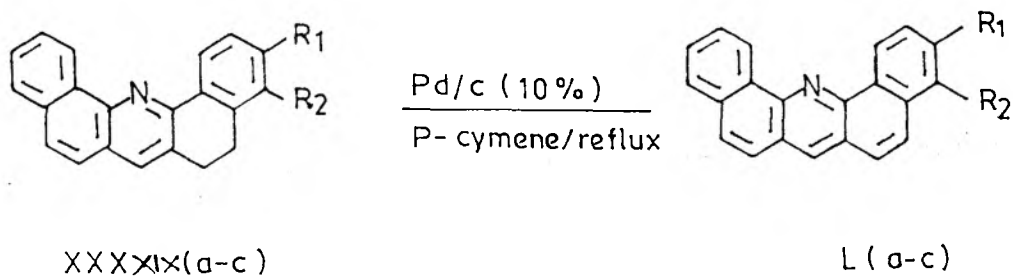


Theoretically cyclisation of anil hydrochloride leads to two possible isomeric products via the cyclisation of isomeric enaminoimine hydrochloride as shown below.



Interestingly, the anil hydrochlorides cyclised regioselectively to give the dihydrodibenz[c,h]acridine derivatives as a single isolable product (XXXXIXa-c) and no trace of other regioisomers were found in the reaction mixture as is evident by the spectral data and chromatographic analysis.

The aromatisation of the dihydro derivatives (XXXXIXa-c) was smoothly achieved by heating with Pd-C (10%) in p-cymene to produce the desired dibenz[c,h]acridine derivatives (La-c) in excellent yields.



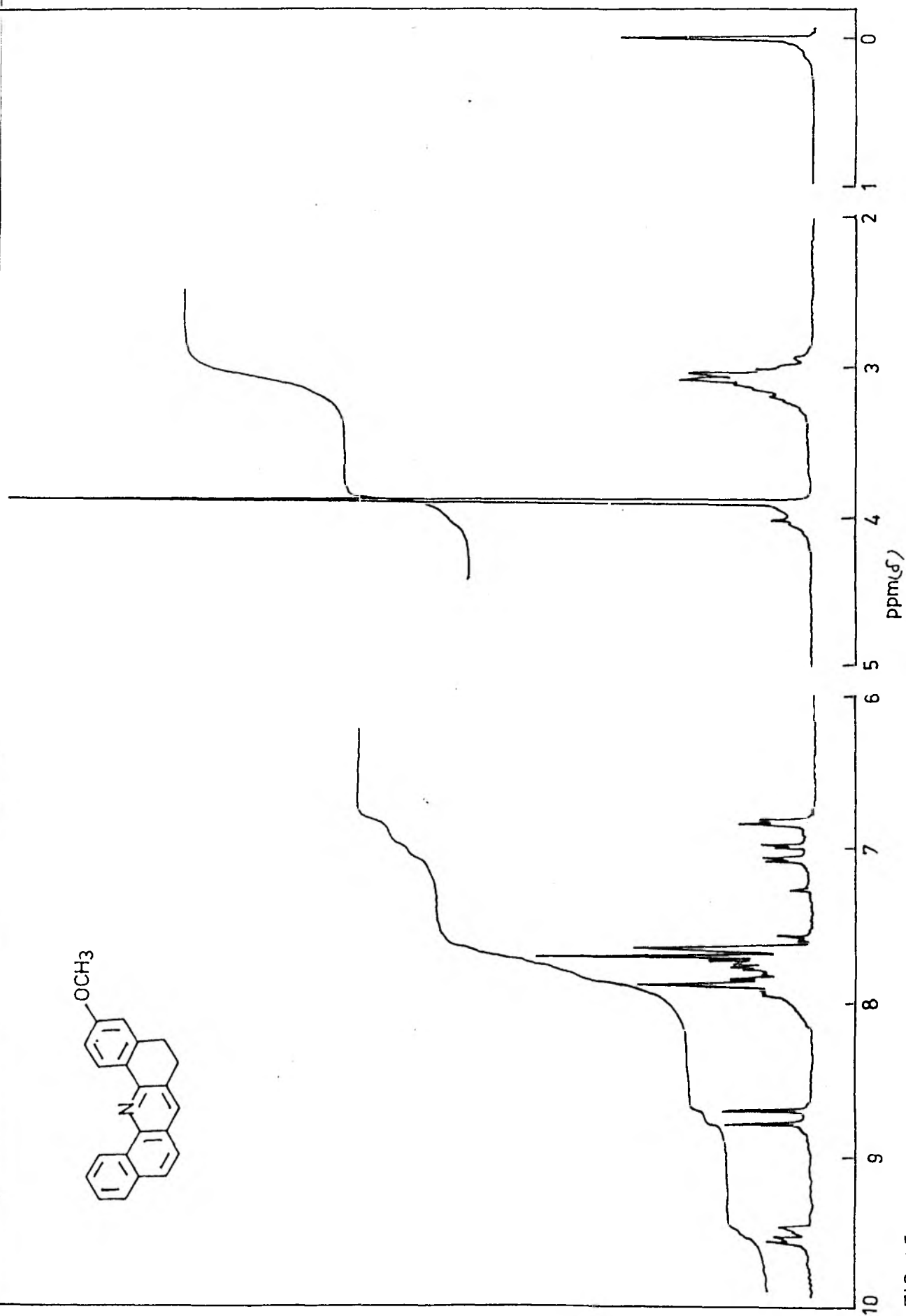
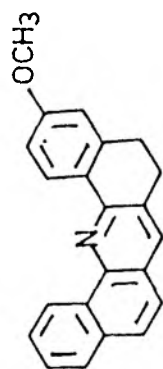
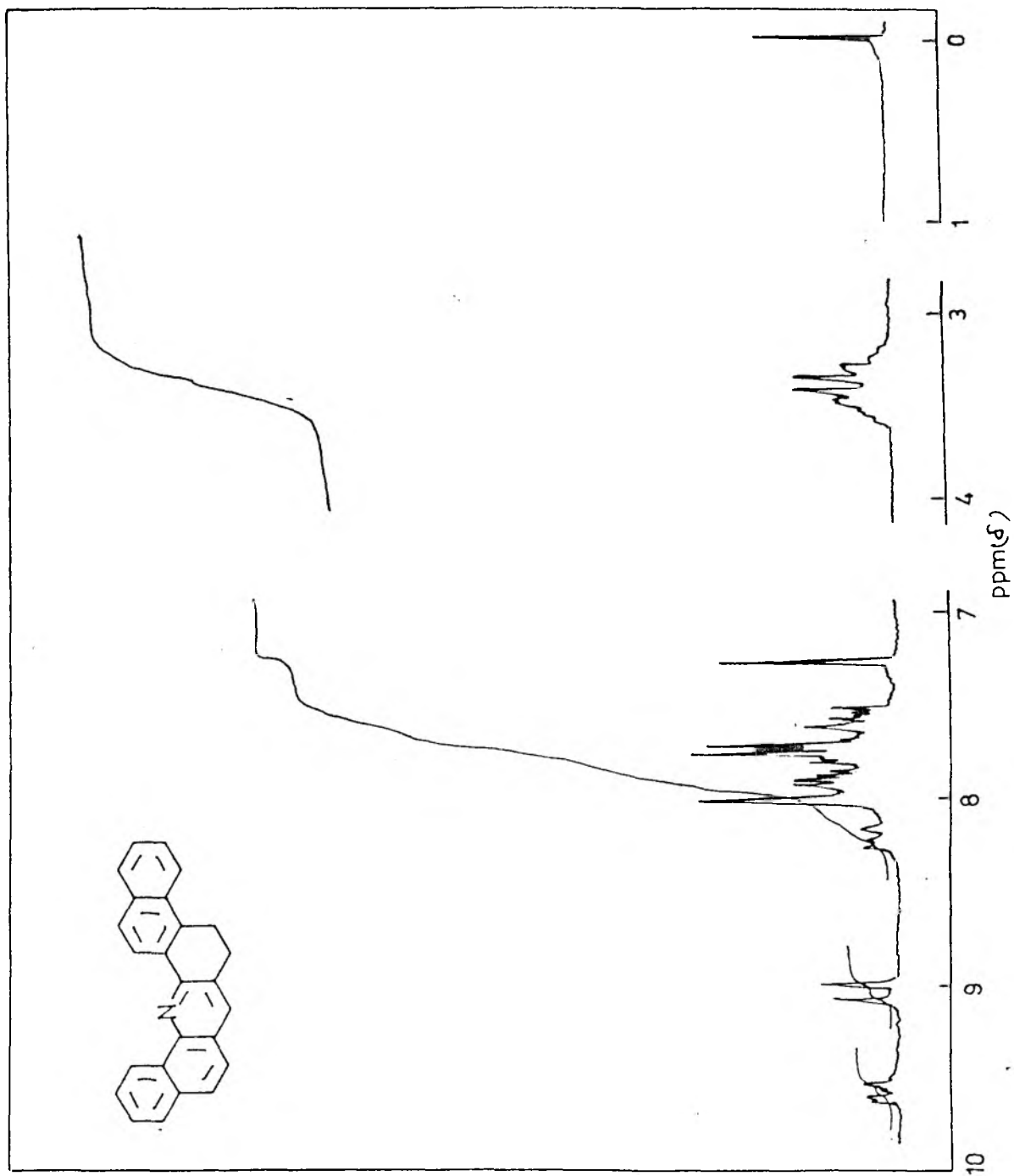
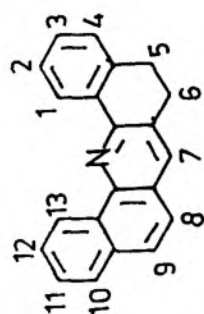
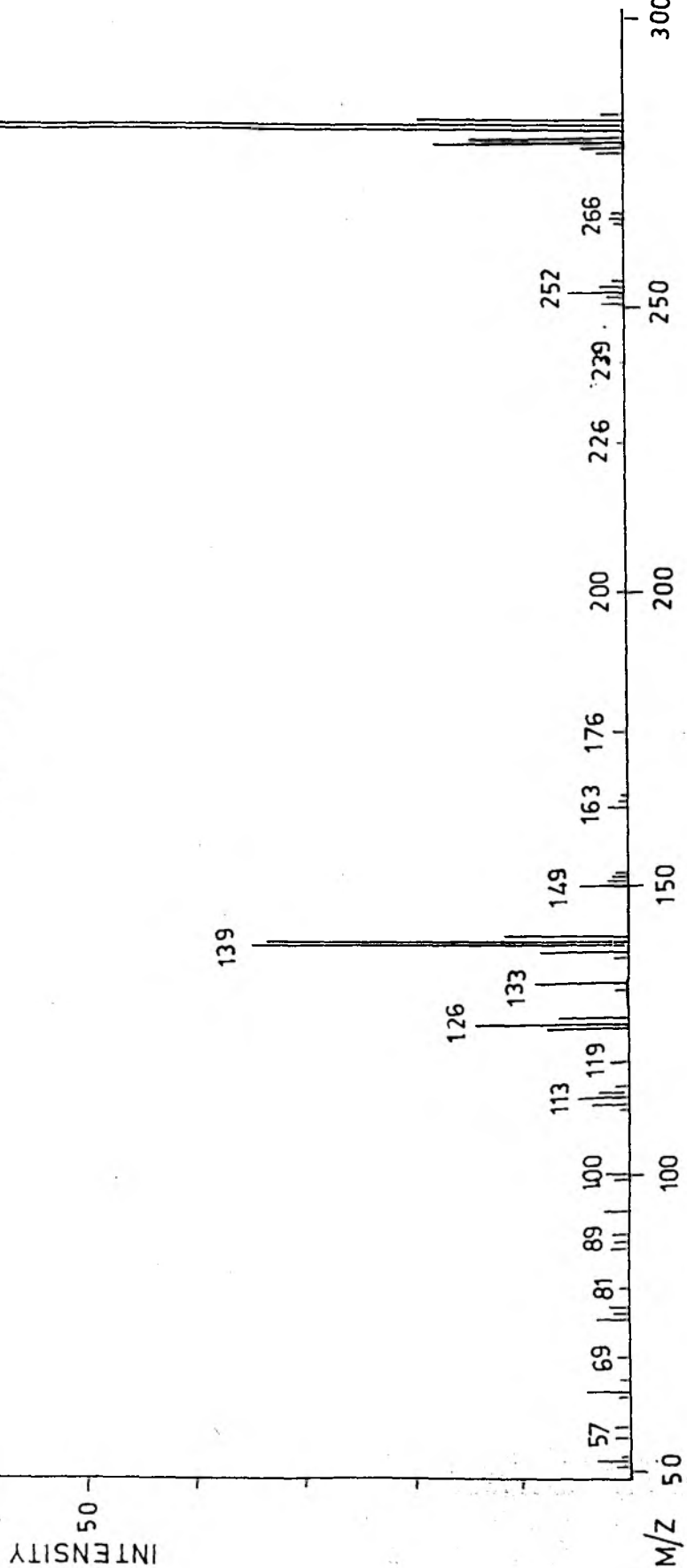


FIG. 1'5





(MW 281)

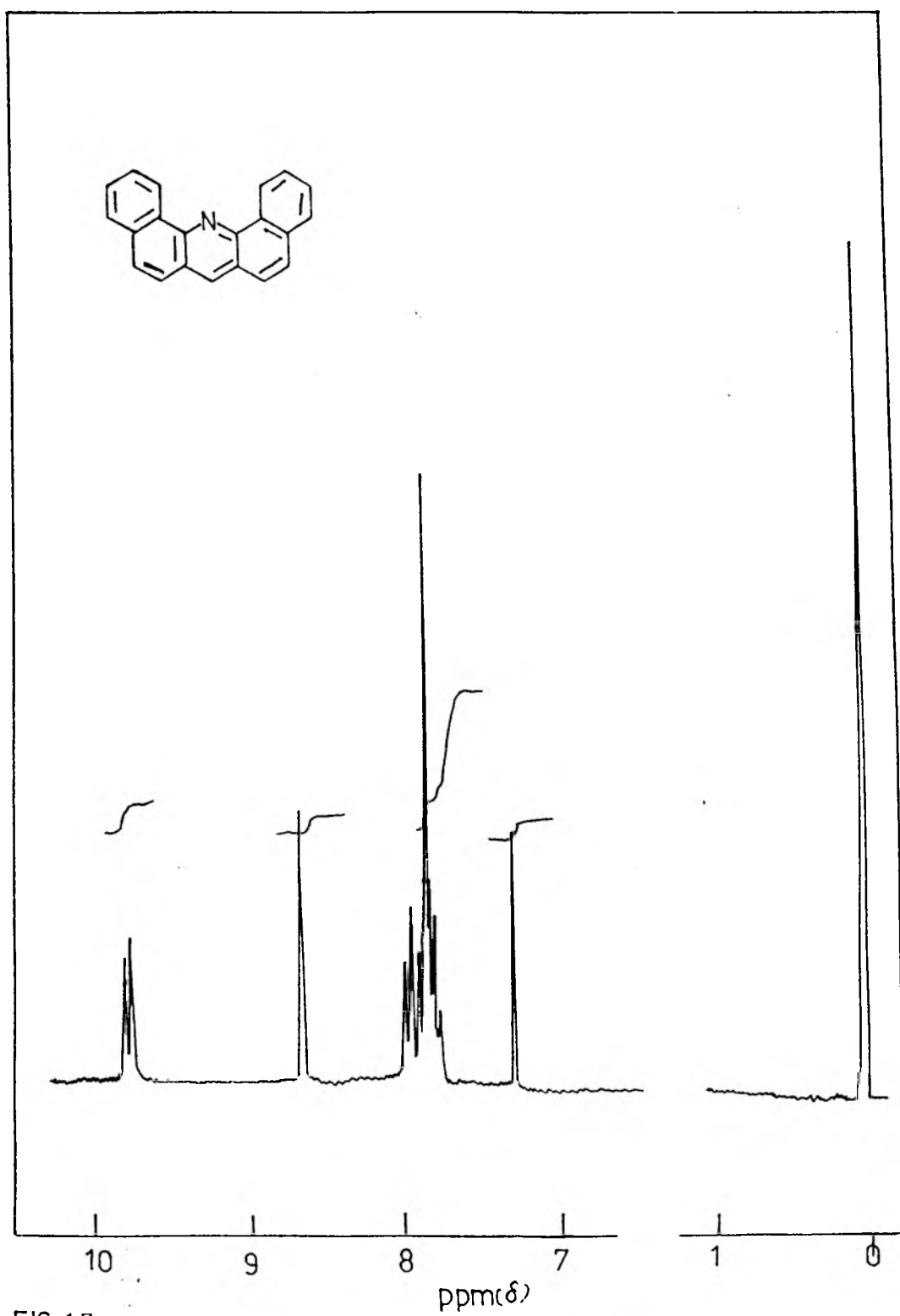


FIG. 17.



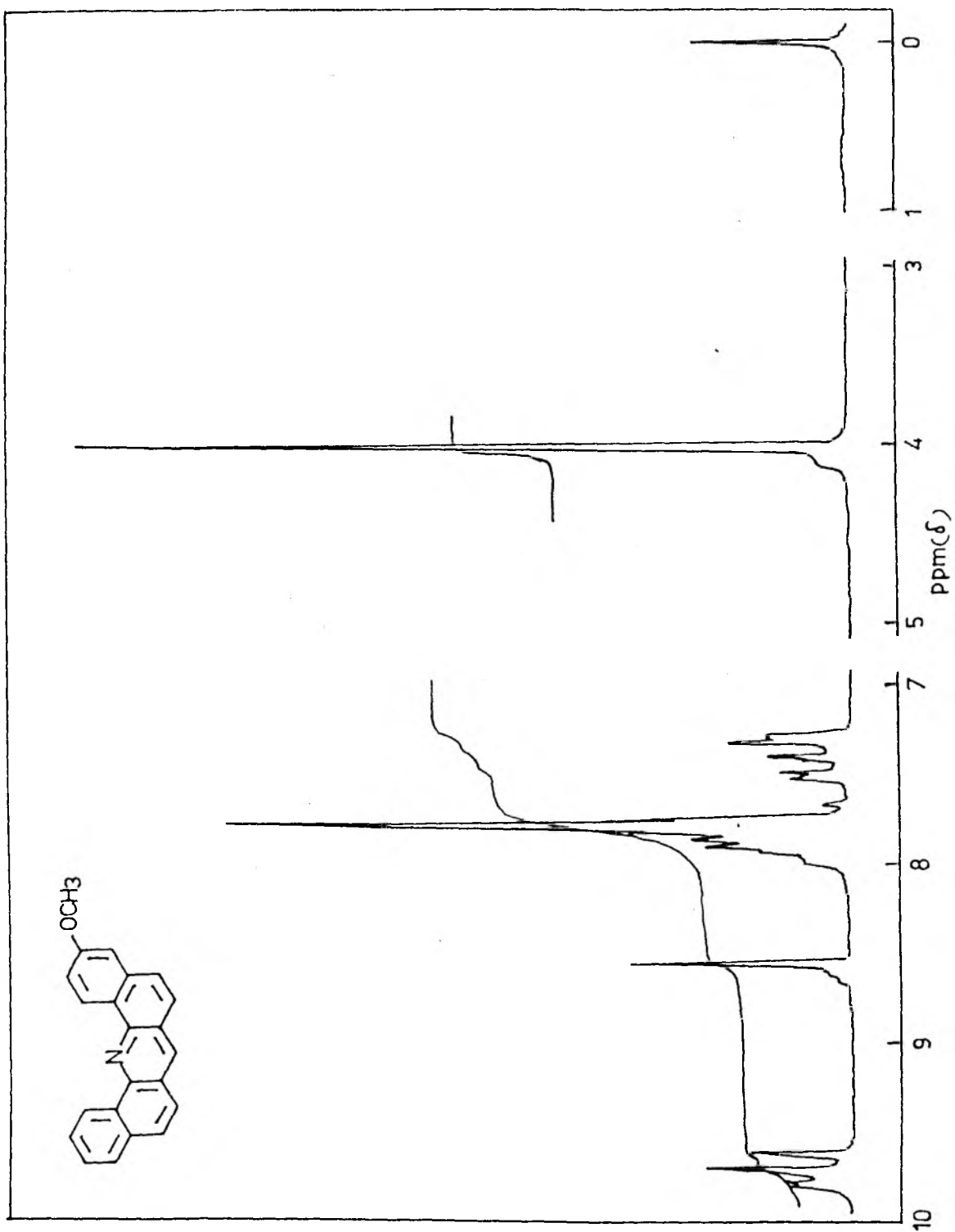
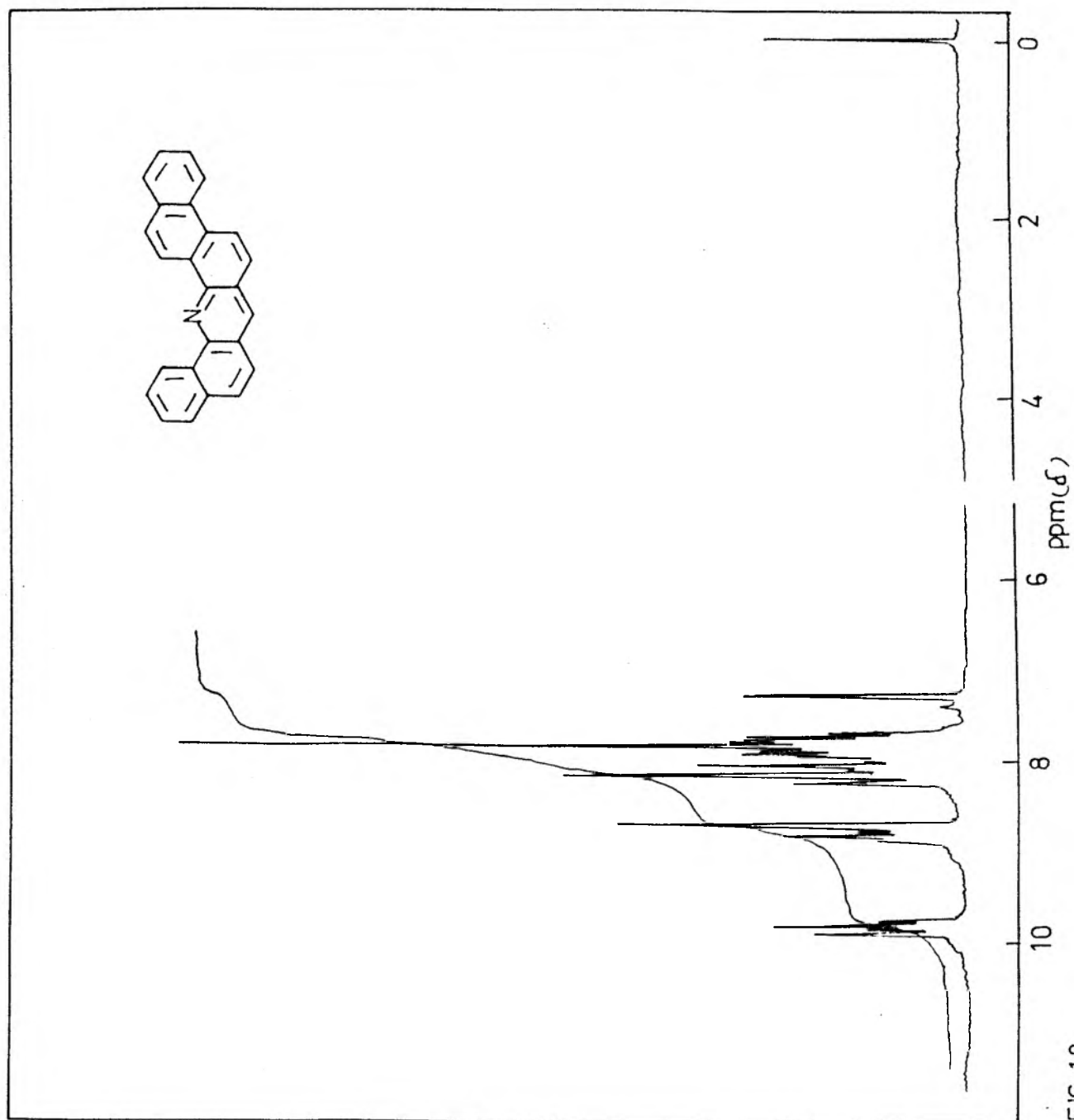
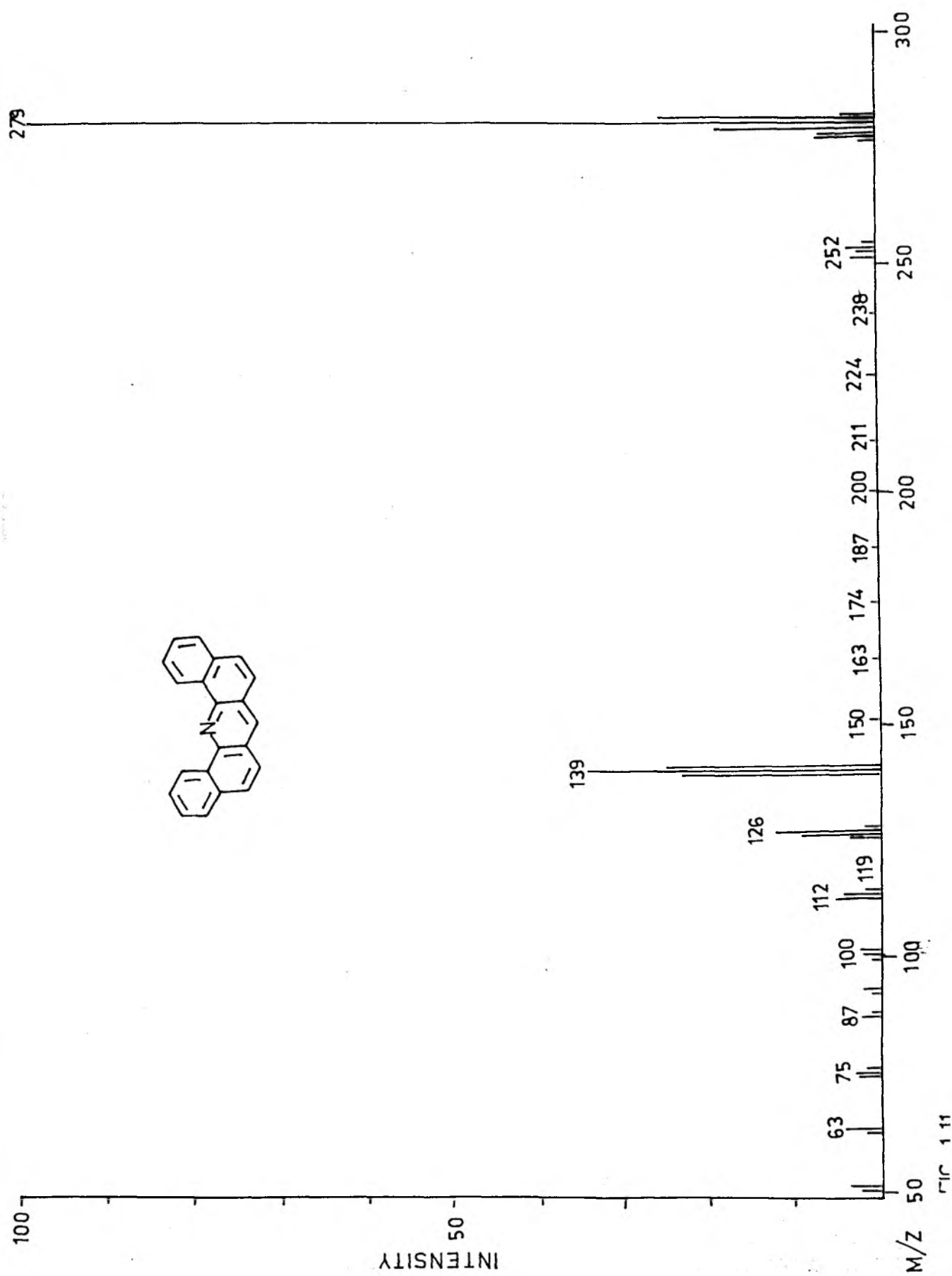
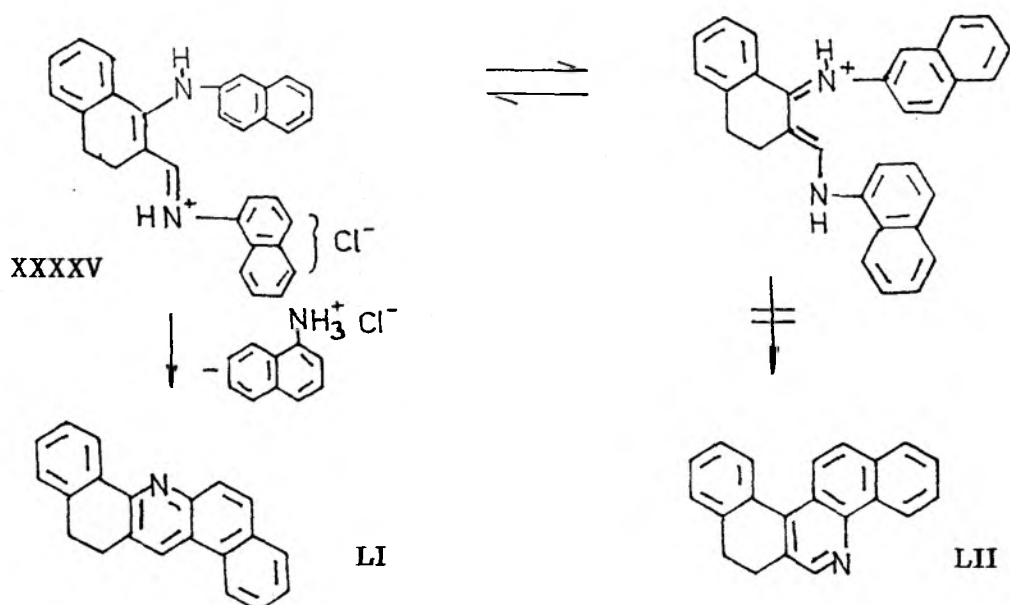


FIG. 18





Further to study the mechanism of cyclisation we have prepared various mixed anils (XXXXV & XXXXVI) from schiff base of 1-naphthylamine. Interestingly when the mixed anils were heated, it cyclised to give dibenzacridines (LI) and not the other isomer (LII). So it is clear from the study that after heating the mixed anils, the α -naphthylamino part condensed to the aldehyde molecule of chloroaldehyde is eliminating as a salt and β -naphthylamine part is cyclising to give the dihydrobenzacridines which confirm the mechanism of thermal cyclisation predicted by us earlier.

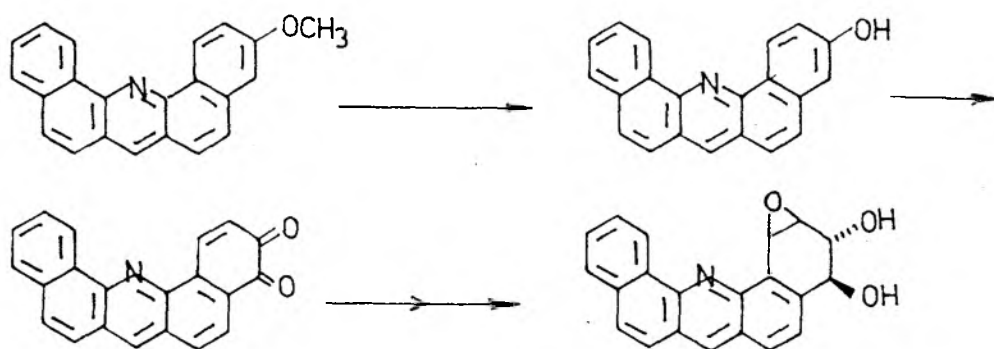


SCOPE OF FURTHER WORK

In this chapter we have described the synthesis of three classes of polycyclic azaarenes in high yield. PAH and polyazaarenes have been found to be carcinogenic by the diol epoxide moiety fused in the terminal rings of bay region polycycles.

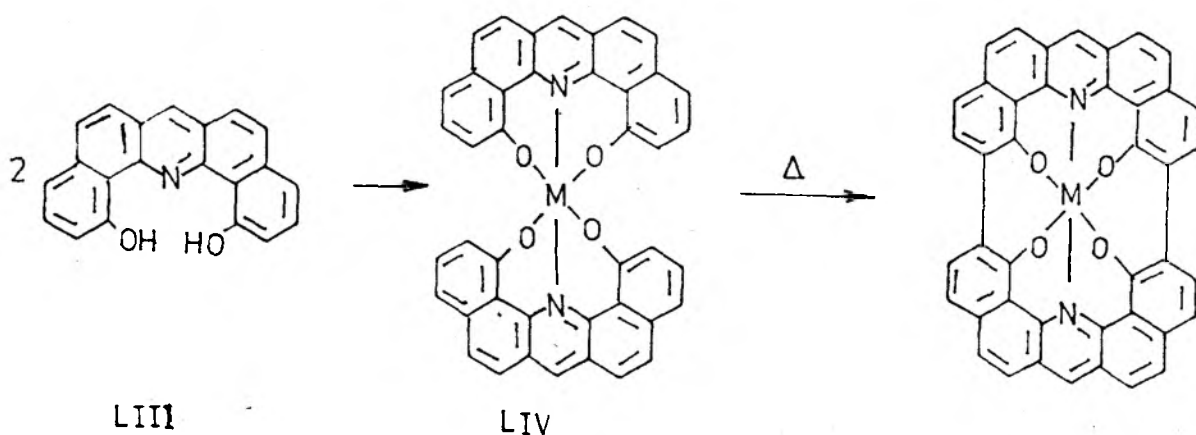
The present synthetic methodology has definitely produced routes for the preparation of dihydrodiol of dibenz[c,h]acridine.

Recently from this laboratory²⁹ a method has been developed to convert the methoxy group on either of the terminal ring into dihydrodiol/diol epoxide by the following method as shown below.



The above work is under progress in this laboratory to study the mutagenecity of dihydrodiol of benz[c,h]acridine.

Recently, it has been found that polycyclic azaarenes are good receptor for metal ions. Bell et al³⁰ have reported some interesting compounds in this series. We think that the compound (LIII) will be good metal ion receptor and macrocyclic molecule complex (LIV) can be prepared by the following method. Studies in this line are in progress in our laboratory.



EXPERIMENTAL

1-Chloro-3,4-dihydrophenanthrene-2-aldehyde (XXXXVIIC) :

To an ice cooled solution of DMF (5 ml), POCl_3 (4.0 gm, 26 m mol) was added dropwise. The mixture was stirred for 10 min. at $0-5^\circ\text{C}$. To this a solution of 1-oxo-1,2,3,4-tetrahydrophenanthrene (4 gm, 20.4 m mol) in 30 ml DMF was added dropwise maintaining the temperature at $0-5^\circ\text{C}$. The mixture was allowed to attain room temperature gradually and stirring was continued at 35°C for 7 hours. The mixture gradually became turbid and bright yellow in colour. The complex was then decomposed with ice cooled saturated solution of sodium acetate and extracted with ether. Organic layer washed with water, dried (Na_2SO_4) followed by removal of solvent afforded (XXXXVIIC) as brownish yellow solid. This on recrystallisation from pet.ether ($60-80^\circ\text{C}$) produced light yellow crystalline solid. Yield - 3.9 gm (79%), m.p. $65-66^\circ\text{C}$.

I.R. (KBr) ν_{max} : 1665 cm^{-1} .

$^1\text{H NMR}$ (CDCl_3) δ : 2.5 (t, 2H), 3.05 (t, 2H), 7.3-8.0 (m, 6H), 10.25 (s, 1H) ppm.

Analysis :	C	H
Found :	73.98	4.26 %
Calculated	74.22	4.54 %
$(\text{C}_{15}\text{H}_{11}\text{OCl})$		



1-Chloro-2-(α -naphthyliminomethyl)-3,4-dihydronaphthalene (XXXXVIIIa)

The mixture of chloroaldehyde (XXXXVIIa)²⁹ (5.8 gm, 0.03 mol) and α -naphthylamine (4.30 gm, 0.03 mol) in dry benzene (100 ml) was refluxed in presence of p-toluene sulfonic acid (Cat.) for 2 hrs using dean stark. The reaction mixture was cooled and washed well with water, solvent removed to get chlorovinyl imine (XXXXVIIIa) as a yellow solid. Recrystallisation from pet. ether (60-80° C) gave yellow crystalline solid. Yield 8.85 gm (92.4%), M.P. 106-107°C.

IR (KBr) $\lambda_{\max}$: 1590, 1610 cm^{-1} .

^1H NMR (CDCl_3) δ : 2.8-3.35 (m, 4H), 7.0-7.9 (m, 10H), 8.4 (dd, 1H), 9.0 (s, 1H) ppm.

MS (m/z) : 319(M^+), 316 262, 280, 175, 141, 127.

Analysis :	C	H	N
Found :	79.15	4.83	4.20 %
Calculated :	79.37	5.03	4.40 %

($\text{C}_{21}\text{H}_{16}\text{NCl}$)

1-Chloro-6-methoxy-2-(α -naphthyliminomethyl)-3,4-dihydronaphthalene (XXXXVIIIb)

A mixture of chloroaldehyde²⁹ (XXXXVIIb) (0.87 gm, 3.9 m mol) and α -naphthylamine (0.6 gm, 4.19 m mol) in 50 ml dry benzene was refluxed for 2 hrs in presence of PTS (Cat.). The reaction mixture was cooled and washed well with water. Removal of solvent gave yellow solid which was passed through a short column of alumina. Elution with benzene afforded (XXXXVIIIb) as a yellow solid. Yield - 1.5 gm (90%), M.P. 161-162°C.

IR (KBr) $\lambda_{\max}$: 1610, 1585 cm^{-1} .

^1H NMR (CDCl_3) δ : 2.9-3.21 (m, 4H), 3.85 (s, 1H), 6.9 (d, 1H), 7.2 (d, 1H),
7.4-7.9 (m, 7H), 8.4 (m, 1H), 9.0 (s, 1H) ppm.

Analysis :	C	H	N
Found :	75.67	5.14	3.72 %
Calculated :	75.97	5.17	4.02 %

($\text{C}_{22}\text{H}_{18}\text{NOCl}$)

1-Chloro-2-(α -naphthyliminomethyl)-3,4-dihydrophenanthrene (XXXXVIIIc)

A mixture of chloroaldehyde (XXXXVIIc) (121 mg, 0.5 m mol) and α -naphthylamine (72 mg, 0.503 m mol) in dry benzene (50 ml) was refluxed for 2 hrs in presence of PTS (Cat.). The reaction mixture was cooled and washed well with water. Removal of solvent gave 170 mg of shining yellow solid (XXXXVIIIc). Yield - 94.5%, M.P. 175-176°C (pet. ether [60-80°C] + benzene).

IR (KBr) $\lambda_{\max}$: 1610, 1690 cm^{-1} .

^1H NMR (CDCl_3) δ : 3.1-3.5 (m, 4H), 7.1 (d, 1H), 7.2 (d, 1H), 7.4-8.5 (m, 11H)
9.1 (s, 1H) ppm.

Analysis :	C	H	N
Found :	81.33	4.59	3.50 %
Calculated :	81.63	4.89	3.80 %

($\text{C}_{25}\text{H}_{18}\text{NCl}$)

5,6-Dihydrodibenz[c,h]acridine (XXXXIXa)

The mixture of chlorovinylimine (XXXXVIIIa) (160 mg, 0.5 m mol) and α -naphthylamine (75 mg, 0.52 mmol) was heated at 140-150°C for 4 hrs.

A white solid sublimed on the cooler part of the round bottom flask. The reaction mixture was cooled to room temperature and decomposed with water and extracted with chloroform. The organic layer was washed well with water, dried (Na_2SO_4) and the solvent evaporated to get crude product which was purified by silica gel column (pet. ether, 60-80°C) as a shining white solid (XXXXIXa). Yield - 110 mg (78.5%), M.P. 154-155°C.

^1H NMR (CDCl_3) δ : 3.0-3.3 (m, 4H), 7.26 (d, 1H), 7.42 (dd, 1H), 7.5 (dd, 1H), 7.6 (m, 2H), 7.84 (m, 2H), 7.9 (d, 1H), 7.95 (s, 1H), 8.85 (d, 1H), 9.5 (d, 1H) ppm.

MS (m/z) : 282(M+1), 281(M^+), 280(M-1), 252, 239, 226, 140, 139, 138.

Analysis :	C	H	N
Found :	89.46	5.11	4.72 %
Calculated :	89.68	5.34	4.98 %
(C ₂₁ H ₁₅ N)			

3-Methoxy-5,6-dihydrodibenz[c,h]acridine (XXXXIXb)

The mixture of chlorovinylimine (XXXXVIIIb) (0.35 gm, 1 m mol) and α -naphthylamine (145 mg, 1 m mol) was heated at 140-150°C for 4 hrs. After usual work up it gave dark viscous mass which was purified by passing through neutral alumina column (pet. ether, 60-80°C). Recrystallisation from EtOH gave white shining solid (XXXXIXb). Yield - 200 mg (64.5%), M.P. 115-116°C.

^1H NMR (CDCl_3) δ : 3.0-3.3 (m, 4H), 3.95 (s, 3H), 6.81 (d, 1H, J= 3 Hz), 7.0 (dd, 1H, J= 3 Hz), 7.6-7.9 (m, 6H), 8.8 (d, 1H, J= 9 Hz), 9.6 (dd, 1H, J= 3 Hz) ppm.

Analysis :	C	H	N
Found :	84.75	5.23	4.36 %
Calculated :	84.88	5.46	4.50 %
(C ₂₂ H ₁₇ NO)			

5,6-Dihydrobenzo[c]naphtho[2,1-h]acridine (XXXXIXc)

The mixture of chlorovinylimine (183 mg, 0.5 m mol) and α -naphthylamine (80 mg, 0.55 m mol) was heated at 140-150°C for 4 hrs. After usual work up it afforded the desired crude product (XXXXIXc) which was passed through a column of silica gel (pet. ether, 60-80°C) to get a shining colourless solid compound (XXXXIXc). Yield - 120 mg (73.1%), M.P. 206-207°C.

^1H NMR (CDCl_3) δ : 3.2-3.6 (m, 4H), 7.5-8.3 (m, 11H), 9.1 (d, 1H, $J = 9$ Hz), 9.6 (dd, 1H, $J = 3$ Hz) ppm.

Analysis :	C	H	N
Found :	90.46	4.82	4.03 %
Calculated :	90.63	5.13	4.23 %
$(\text{C}_{25}\text{H}_{17}\text{N})$			

Dibenz[c,h]acridine (La)

The dihydro compound (XXXXIXa) (0.4 gm, 1.42 m mol), Pd-C (10%) (400 mg) and p-cymene (20 ml) was refluxed for 5 hrs. The reaction mixture was filtered to remove Pd-C. Filtrate was distilled under vacuum to get the desired product (La) as a colourless solid which was further purified by recrystallisation from ethanol. Yield - 375 mg (94.4%), M.P. 193-194°C (lit.³¹ 189-190°C).

^1H NMR (CDCl_3) δ : 7.75-7.95 (m, 10H), 8.62 (s, 1H), 9.75 (d, 2H) ppm.

MS (m/z) : 280(M+1), 279(M⁺), 278(M-1), 252, 140, 139, 138, 126.

Analysis :	C	H	N
Found :	90.02	4.35	4.71 %
Calculated :	90.32	4.65	5.01 %
$(\text{C}_{21}\text{H}_{13}\text{N})$			

3-Methoxydibenz[c,h]acridine (Lb)

The dihydro derivative (XXXXIXb) (88 mg, 0.28 m mol), Pd-C (10%) (25 mg) and p-cymene (5 ml) was refluxed for 4 hrs. After usual work up it gave the desired product (Lb) which was purified by passing through a short column of neutral alumina (benzene) as a colourless solid. Yield - 73 mg (84%), M.P. 136-137°C.

$^1\text{H NMR}$ (CDCl_3) δ : 4.0 (s, 3H), 7.3 (d, 1H), 7.5 (dd, 1H), 7.8-8.0 (m, 8H), 8.6 (d, 1H, $J = 9$ Hz), 9.9 (dd, 1H, $J = 3$ Hz) ppm.

Analysis :	C	H	N
Found :	85.23	4.65	4.33 %
Calculated :	85.43	4.85	4.53 %

($\text{C}_{22}\text{H}_{15}\text{NO}$)

Benzo[c]naphtho[2,1-h]acridine (Lc)

The mixture of dihydro derivative (XXXXIXc) (60 mg, 0.18 m mol), Pd-C (10%) (50 mg) and p-cymene (5 ml) was refluxed for 12 hrs. After usual work up it gave the desired product (Lc) which was further recrystallised from benzene-ethanol to furnish greenish white solid.

Yield - 53 mg (90%), M.P. 206-207°C.

$^1\text{H NMR}$ (CDCl_3) δ : 7.8-8.2 (m, 10H), 8.9 (m, 3H), 9.9 (m, 2H) ppm.

Analysis :	C	H	N
Found :	90.33	4.84	3.93 %
Calculated :	90.63	5.14	4.23 %

($\text{C}_{25}\text{H}_{17}\text{N}$)

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CHAPTER 2

STUDIES ON POLYCYCLIC OXAAZAARENES - A SHORT SYNTHESIS OF NAPHTHOPYRANO QUINOLINES

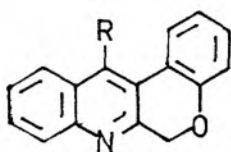


INTRODUCTION

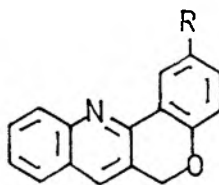
In the first chapter we have discussed the syntheses of dibenz[c,h]acridines which are potent carcinogenic compounds. In this chapter we have taken the synthesis of various naphtho pyrano quinoline derivatives to study their mutagenicity/carcinogenicity. A short synthesis of polycyclic oxaazaarenes where the azaarenes moiety was introduced in oxaarenes chloroaldehydes by reacting with aromatic amines followed by thermal cyclisation of resultant anil hydrochlorides have been developed.

DISCUSSION

Recently it has been shown by N. P. Buü Hoi et al¹ that benzo-pyrano quinolines (I,II) are carcinogenic compounds and preliminary testing indicates that benzoCpyrano quinolines are more carcinogenic than benzacridines².

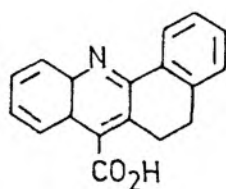


I



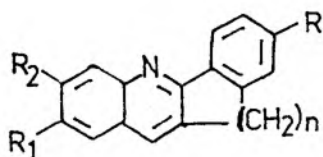
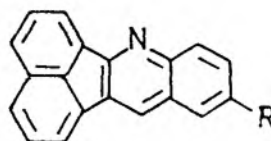
II

Polycyclic quinoline derivatives play an important role also in the field of medicinal chemistry. Thus, tetraphan (III), a dihydronaphthoquinoline derivative has been found to be active against muscle paralysis³.



III

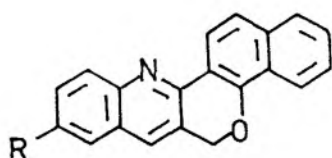
Recently Ray et al^{4,5} from this laboratory have developed simple and convenient syntheses of dihydronaphtho quinolines (IV) and some acenaphtho[1,2-b]quinolines (V) having semi bay region in their structures.

IV $n=1,2,3$ 

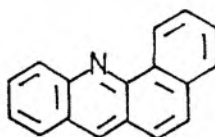
V

The compounds (IV) were found to be good flurochromes and have shown promise for vital staining of tumor cells and plant cells. On the other hand the four derivatives ($R=H$, OCH_3 , CH_3 , NO_2) of compound V were tested for their mutagenecity/carcinogenecity using Ames Test (salmonella assay). Compounds V ($R=H$) and V ($R=CH_3$) were found to be inactive. However the compound V ($R=OCH_3$) was active in TA-98 and TA-100 with metabolic activation whereas the compound V ($R=NO_2$) was very active in both strains with and without activation. The result confirms the fact that the electron withdrawing group (Nitro) increases the mutagenicity whereas the electron donating group (methyl) decreases its mutagenicity.

Though extensive studies with PAH and PAA and their binding to DNA have been carried out in last few decades, it is surprising that polycyclic oxaazaarenes in contrast have not been thoroughly investigated in terms of their mutagenicity and or carcinogenic activities until recently. So to study their mutagenicity we have taken the synthesis of various naphtho pyrano[4,3-b]quinolines (VI) and its isomers which are structural analogue of benzacridine (VII).



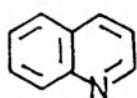
VI



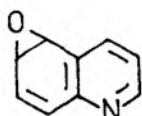
VII

Among the various potent carcinogens of aza PAHs, benzo(f)quinoline (BfQ) and benzo(h)quinoline (BhQ) have been detected in automobile exhaust, urban air particulates and cigarette smoke⁹.

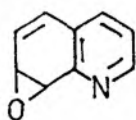
In order to investigate the metabolism of quinoline (VIII) by mammalian liver enzymes D. M. Jerina et al¹⁰ have reported the synthesis of quinoline 5,6(IX) and 7,8(X) oxides and the corresponding dihydrodiols (XI-XII).



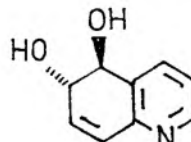
VIII



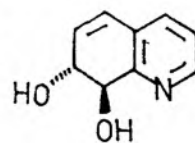
IX



X

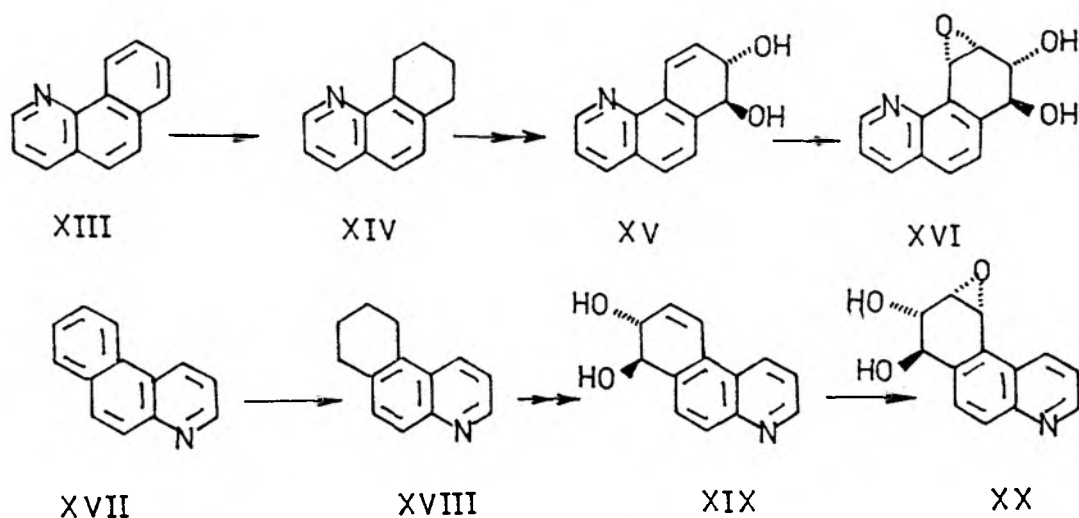


XI



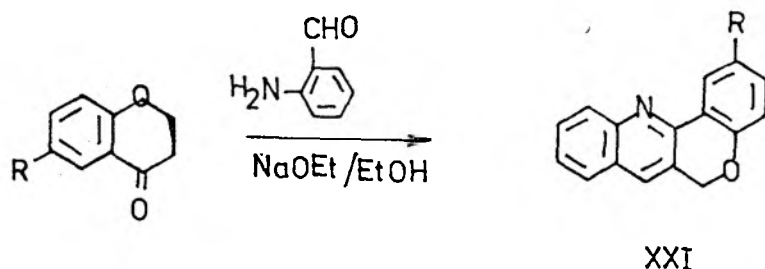
XII

To assess the role of aza substituents and the position of nitrogen in aza phenanthrenes and metabolism of these chemicals, S. Kumar et al¹⁷ have reported the synthesis of various dihydrodiol and diol epoxides of BfQ and BhQ (XIII-XX) starting from the corresponding tetrahydro derivatives (XIV).

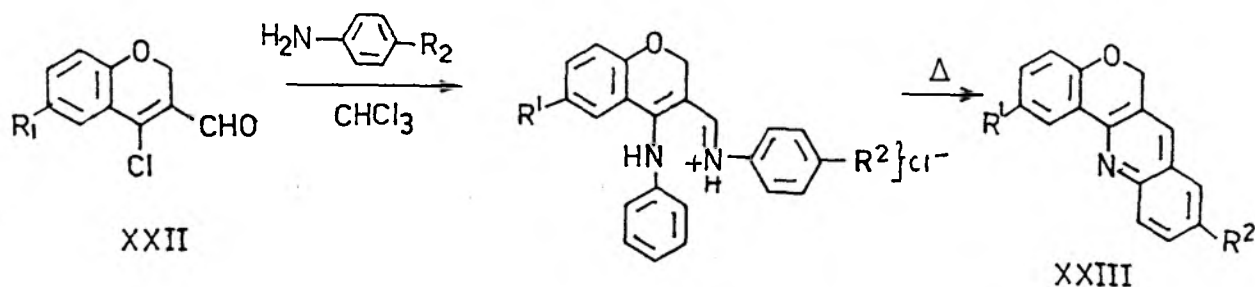


Keeping all the important facts about the biological activities of polyazaarenes and benzo pyrano quinolines, we present here a simple and convenient syntheses of naphthopyrano quinoline derivatives. Some of which are hitherto unreported. Though, the synthesis of naphtho pyrano quinolines have not been reported in the literature but 6-[H]-1-benzopyrano[4,3-b]quinolines are known and synthesised by various methods. Some synthetic methods are outlined below.

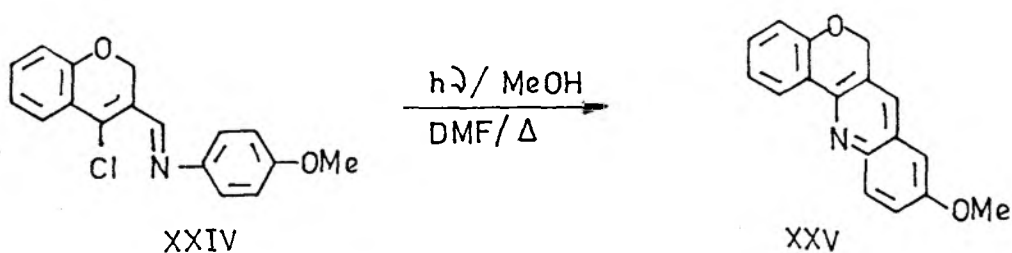
N. P. Buü Hoi et al¹² have synthesised benzo pyrano quinoline by condensing o-amino benzaldehyde with substituted benzo chromanone in presence of base to give quinoline derivatives (XXI) only in 20-30% yield.



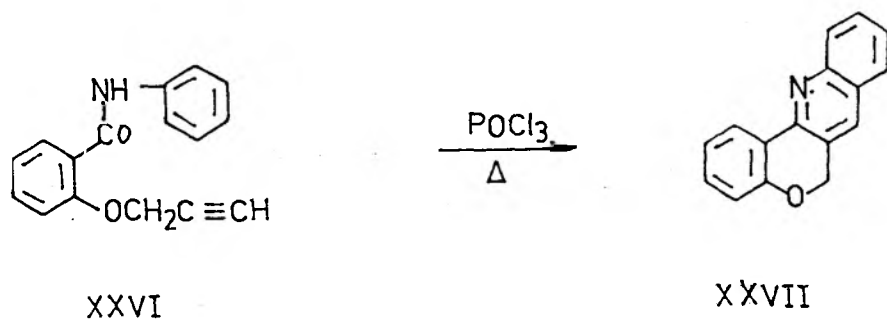
K. K. Balasubramanian et al¹³ have reported the synthesis of benzo-pyrano quinolines. The reaction of 4-chlorochromone-3-carboxyaldehyde (XXII) with p-substituted anilines in chloroform afforded the ^{hydrochloride of} enamino imines which were further cyclised by heating to get 6H-[1]-benzopyrano[4,3-b]quinolines (XXIII).



Very recently K. K. Balasubramanian et al¹⁴ have also synthesised benzo-pyrano quinolines (XXV) by photolysis of β-chlorovinylimine (XXIV).

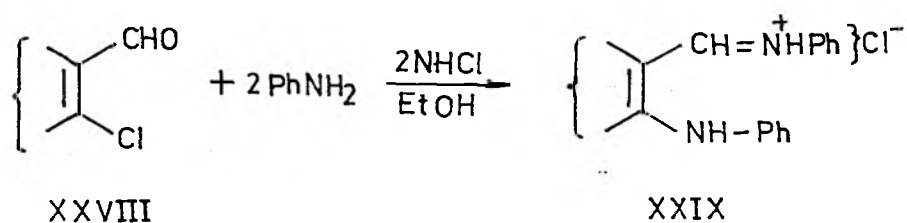


A facile synthesis of 6H-[1]-benzopyrano[4,3-b]quinoline (XXVII) is achieved from propargyloxysalicylanilide (XXVI) by Par Etienne Rougeot et al¹⁵ in 72% yield.

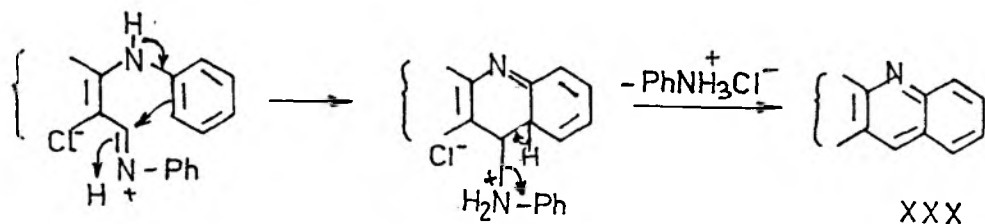


Our synthetic strategy is given in Scheme I and II.

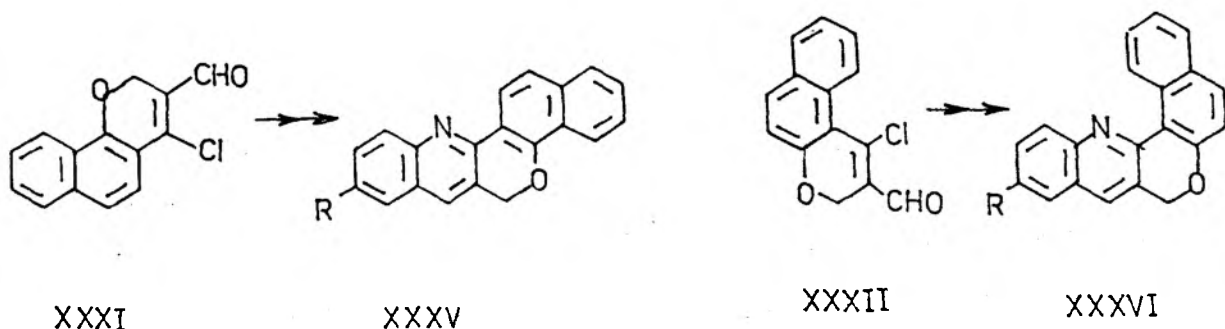
It is well known than when a compound such as (XXVIII) containing β -chloro acrolein moiety, is condensed with 2 moles of aniline in presence of 2N ethanolic HCl solution, the hydrochloride of anil derivative (XXIX) with suitably substituted amino function is formed in excellent yields¹⁶.



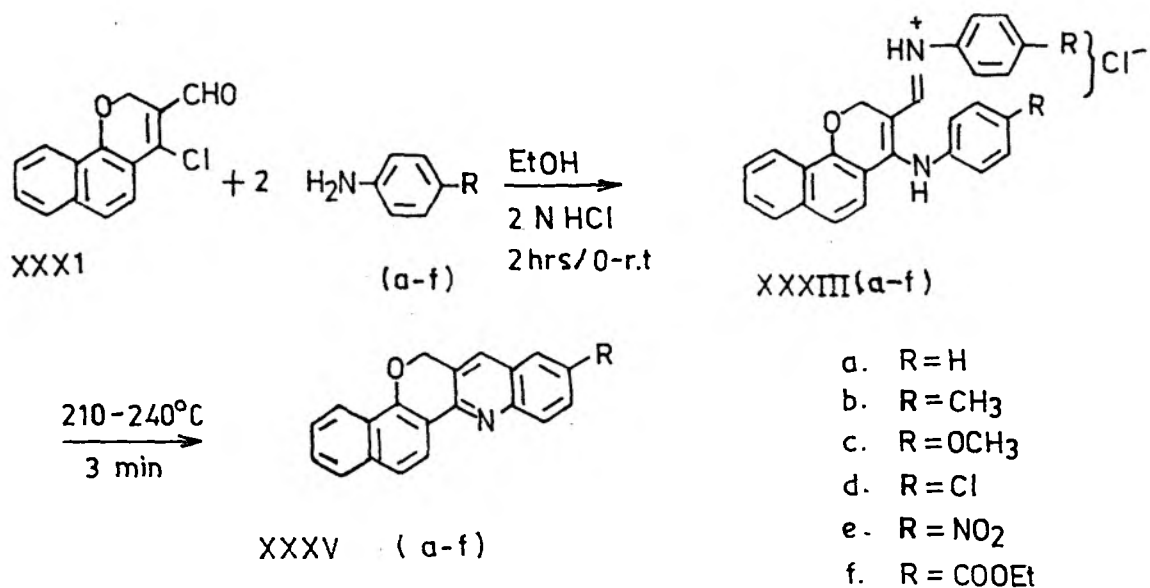
The anil derivative on brief heating, at 200-250° C readily cyclises to a quinoline derivative¹⁷ (XXX).



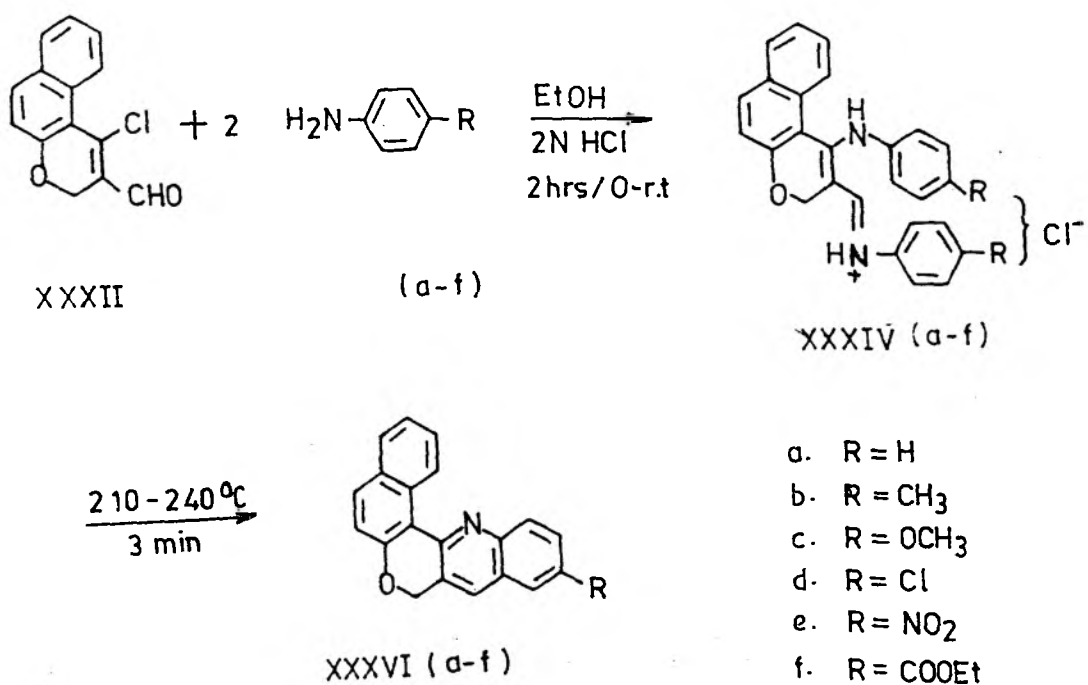
In order to synthesise the 6H-Naphthopyrano[4,3-b]quinoline and 8H-Naphthopyrano[4,3-b]quinoline derivatives (XXXV and XXXVI) we have utilized the above reaction sequence through chloroaldehydes, as the compound containing β -chloro acrolein moieties (XXXI and XXXII).



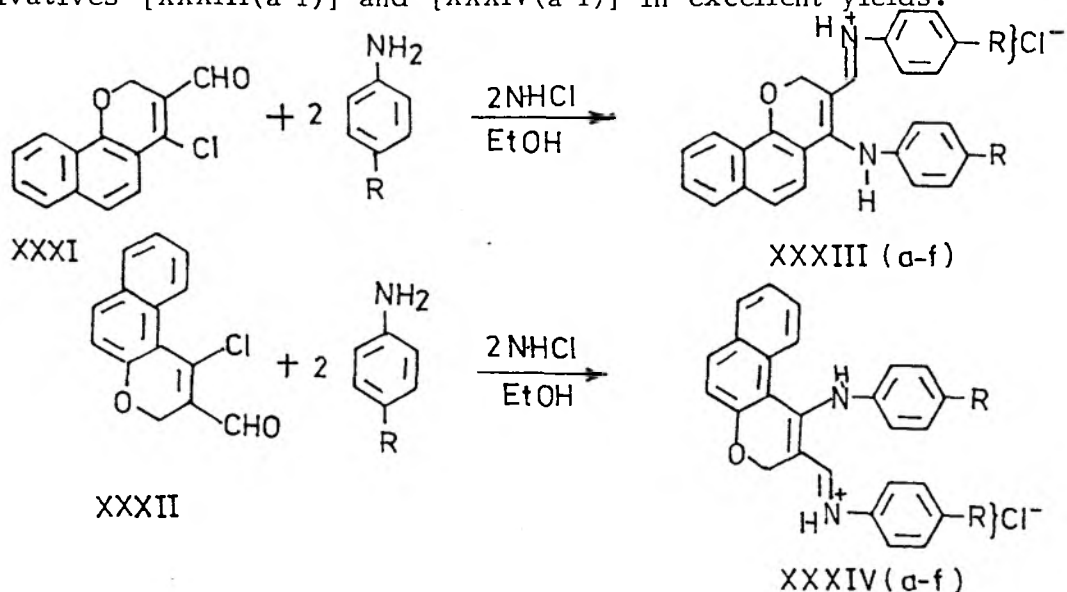
SCHEME -1



SCHEME -II

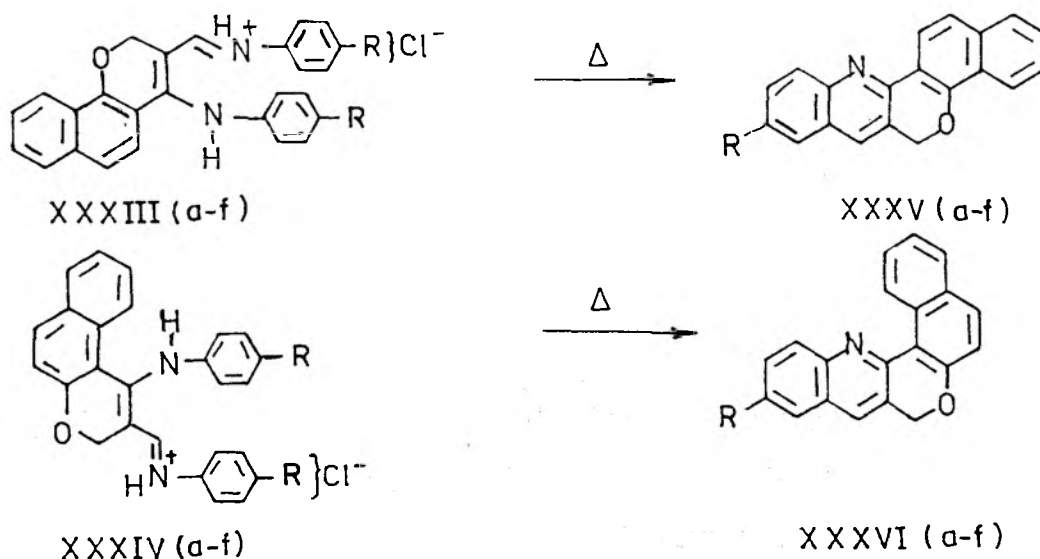


The chloroaldehydes (XXXI and XXXII) when treated with 2 moles of aniline or substituted anilines in presence of 2N HCl/EtOH gave anil hydrochloride derivatives [XXXIII(a-f)] and [XXXIV(a-f)] in excellent yields.



The I.R. spectra of these compounds showed absorption at 1615-1655 cm^{-1} and 3100-3400 cm^{-1} respectively for ν C=N and ν N-H. M.P., I.R., yields (%) etc. of these compounds are listed in Table - 1.

The anil derivatives [XXXIII(a-f)] and [XXXIV(a-f)] on brief heating (cf. 5-10 min.) at a temperature slightly above their melting points afforded the 6H-naphthopyrano[4,3-b]quinoline derivatives [XXXV(a-f)] and 8H-naphthopyrano[4,3-b]quinoline derivatives [XXXVI(a-f)] in good to excellent yields.



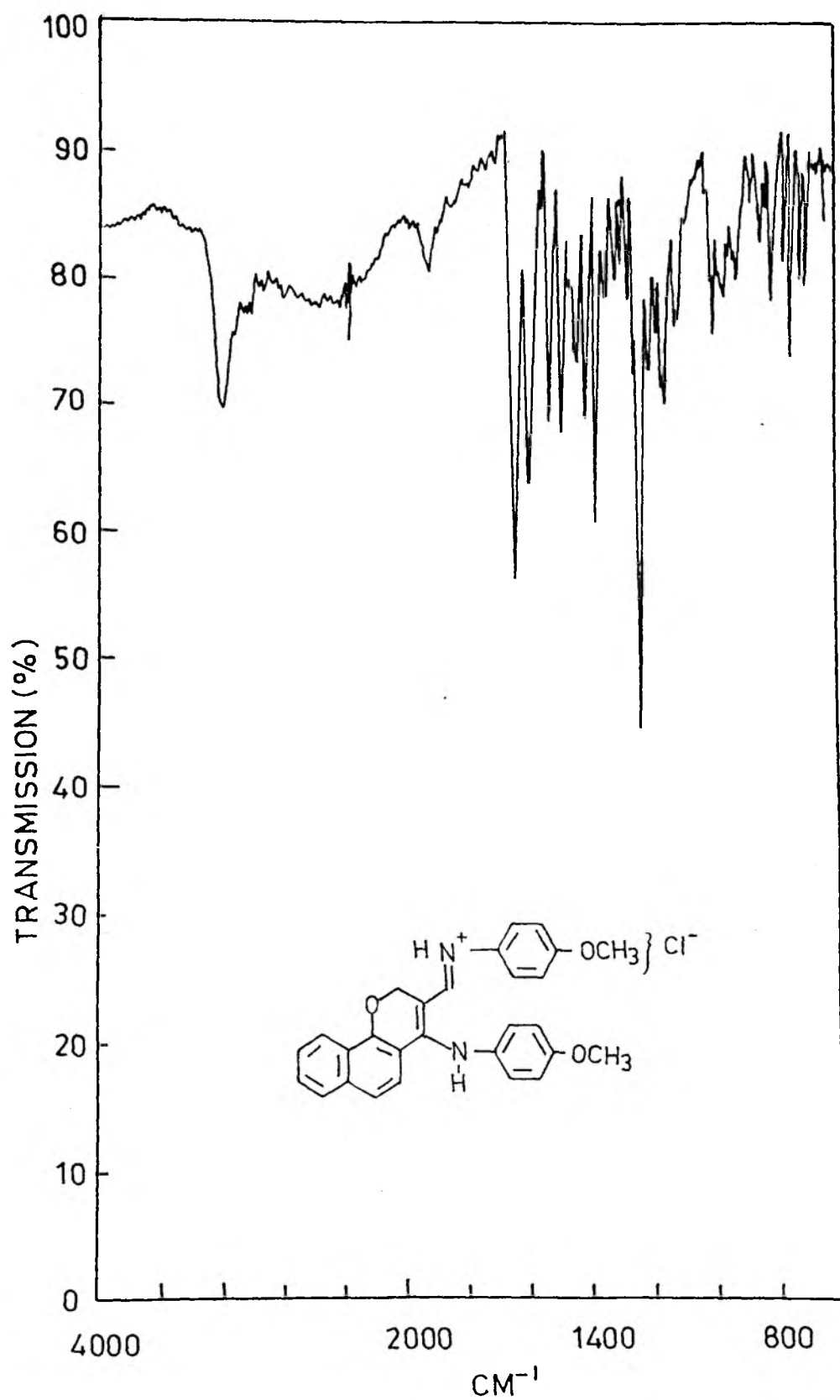
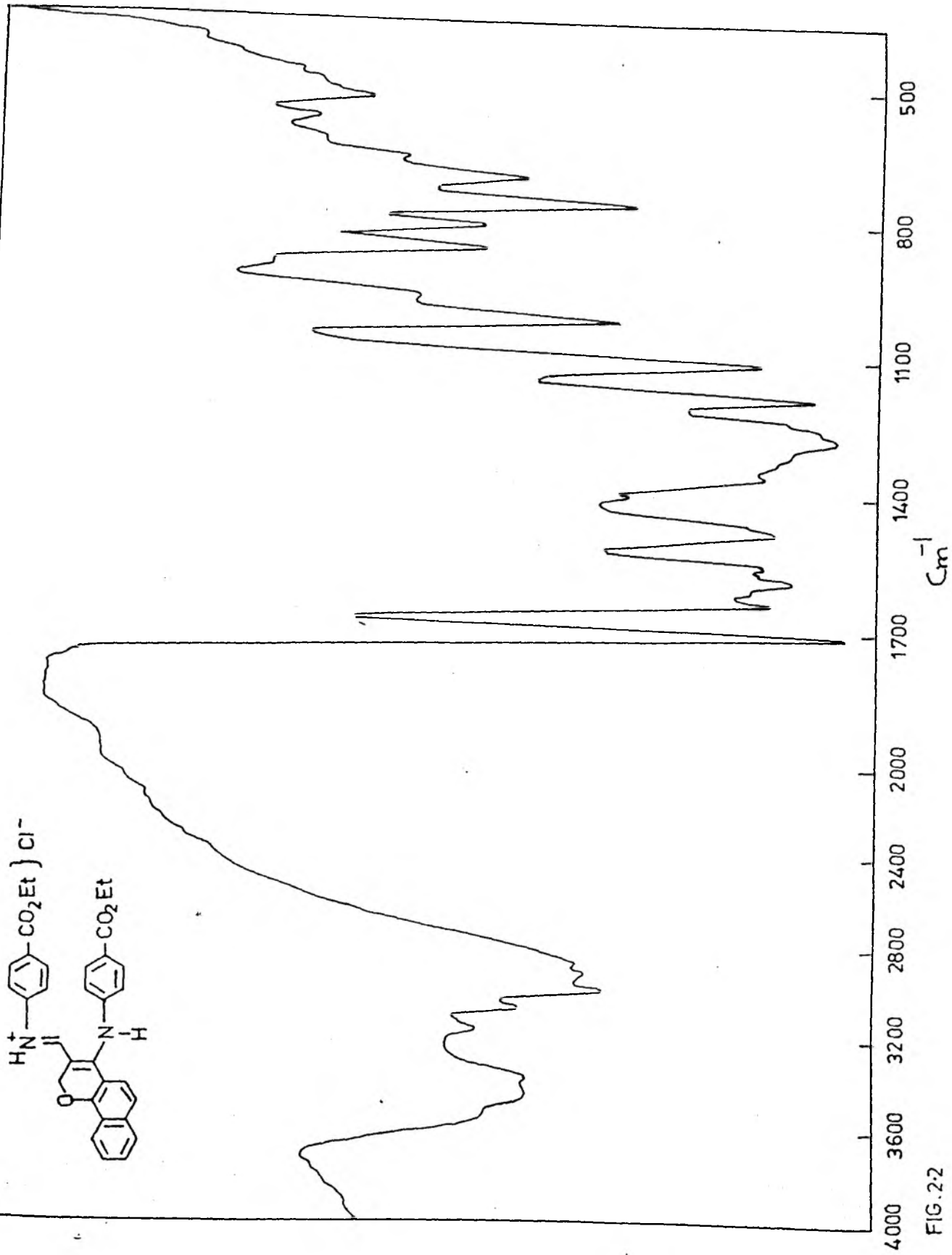
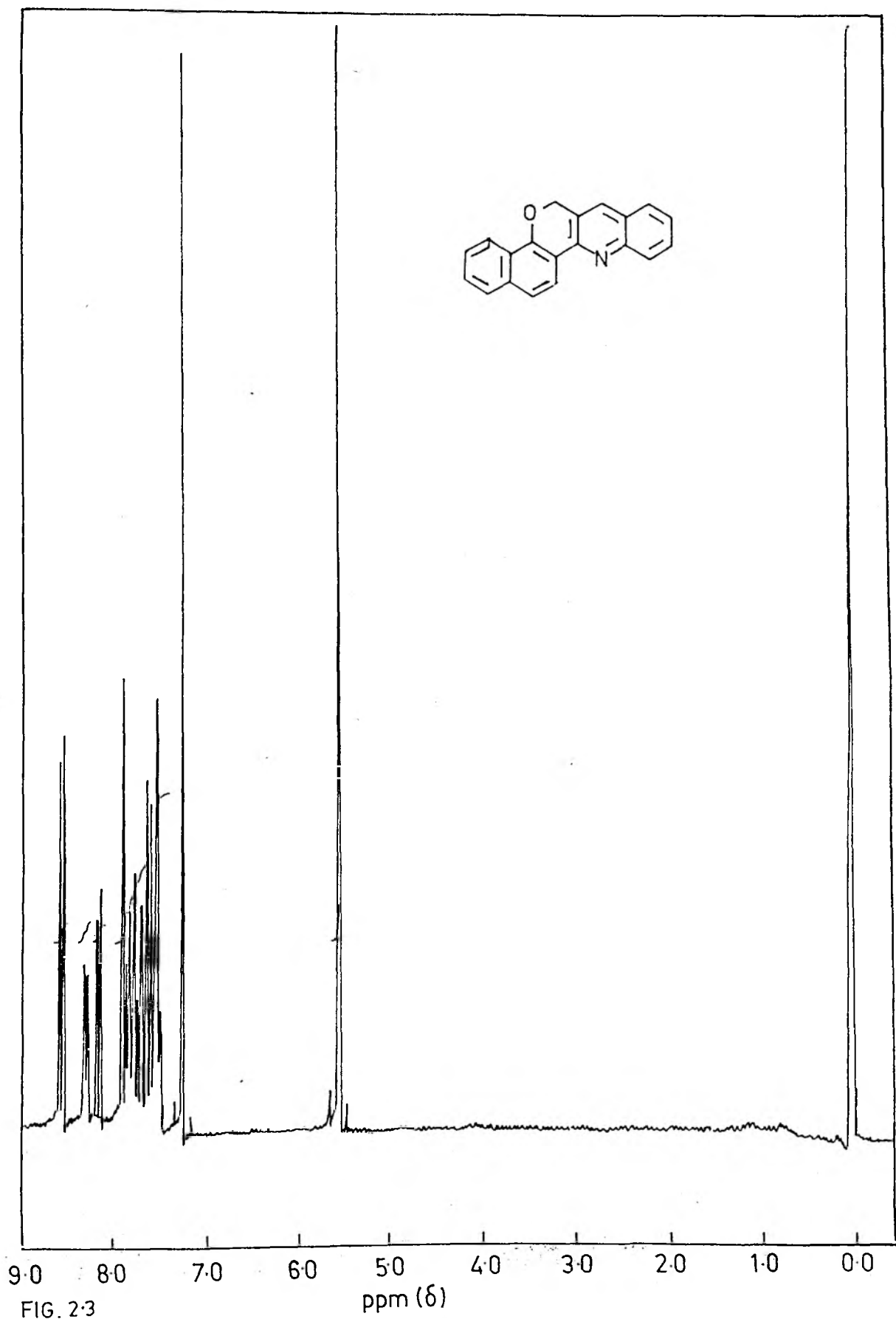


FIG. 2-1





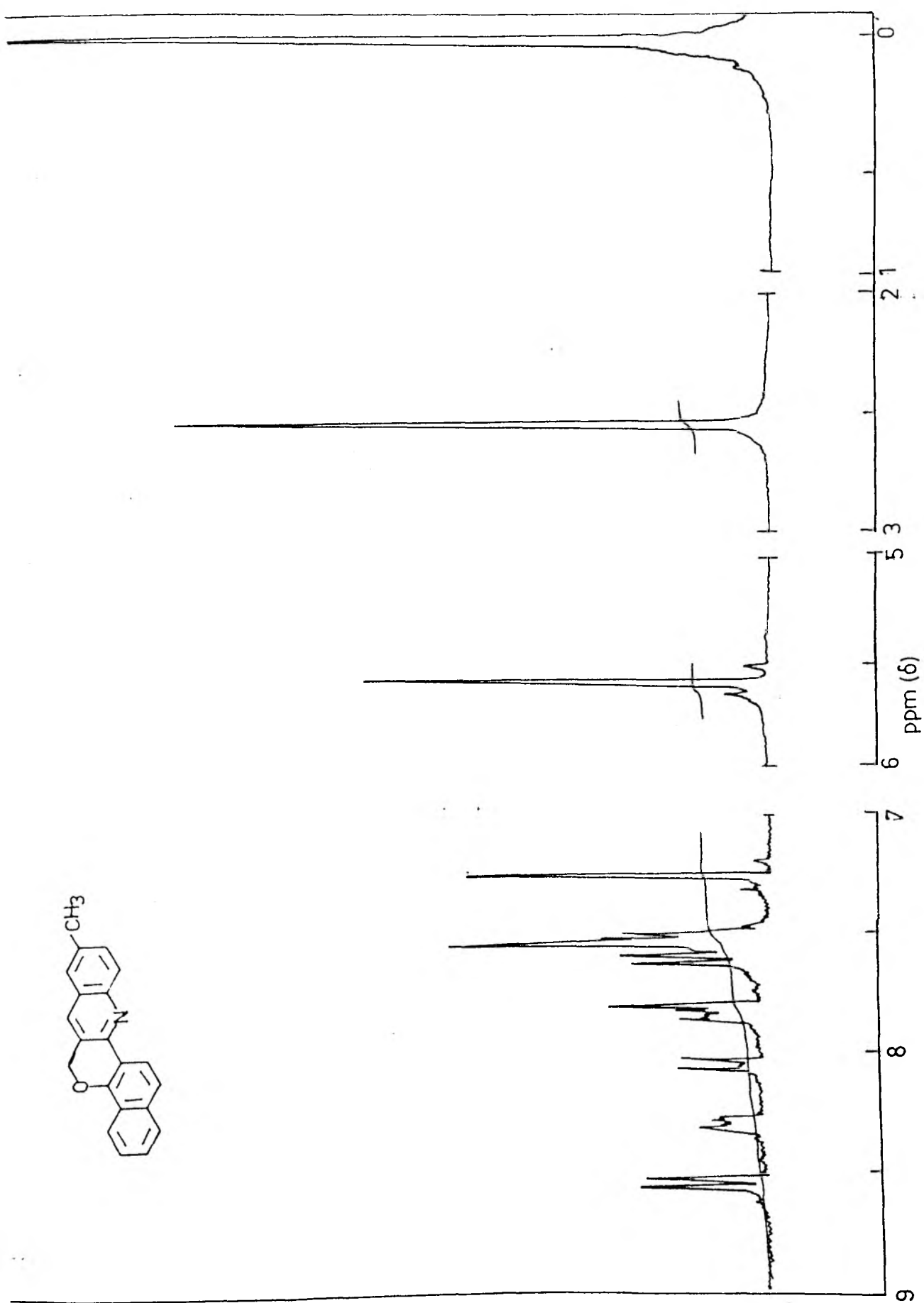


FIG. 2-5

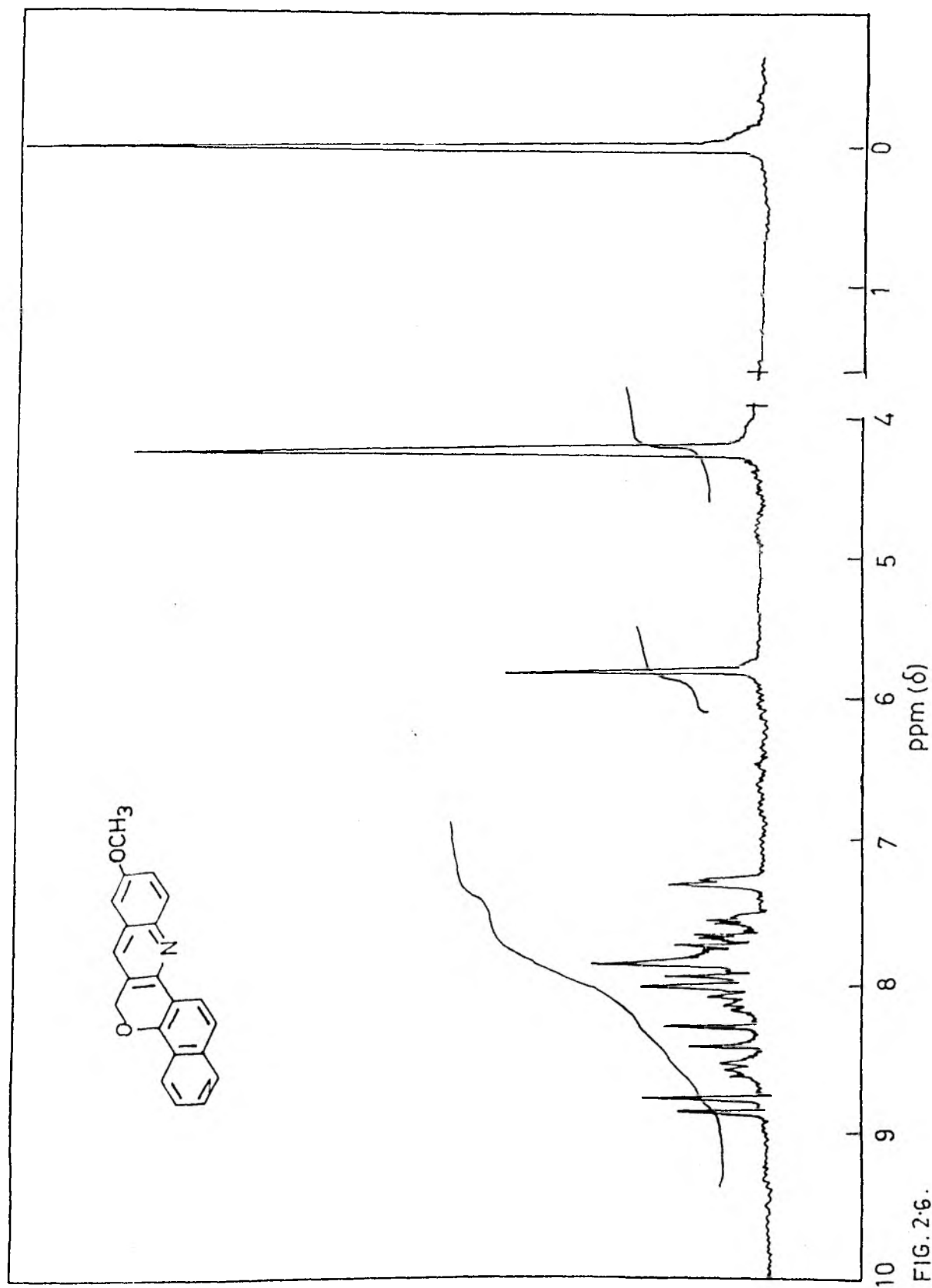
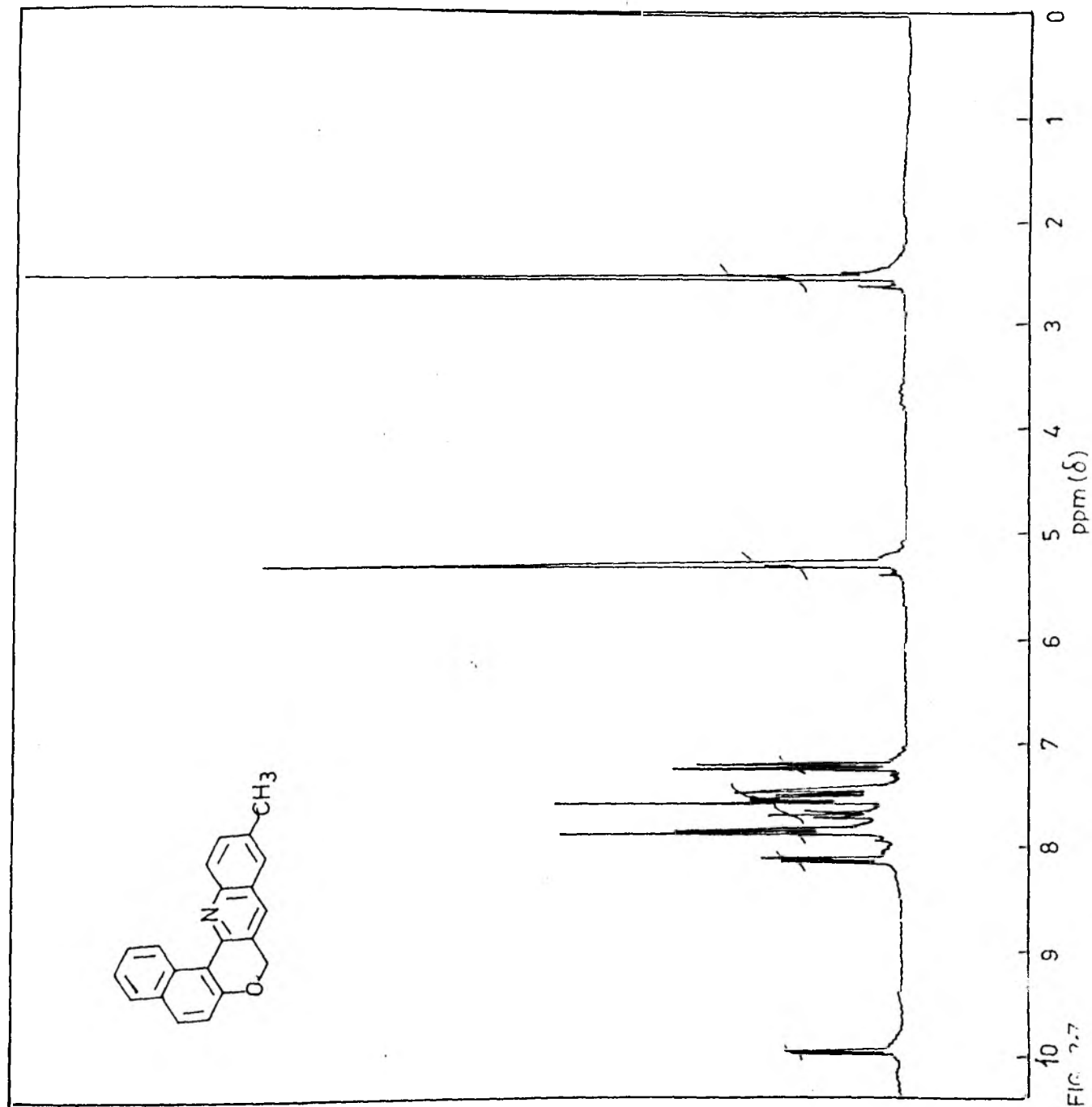
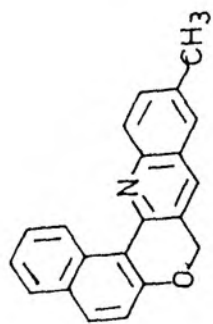


FIG. 2-6.



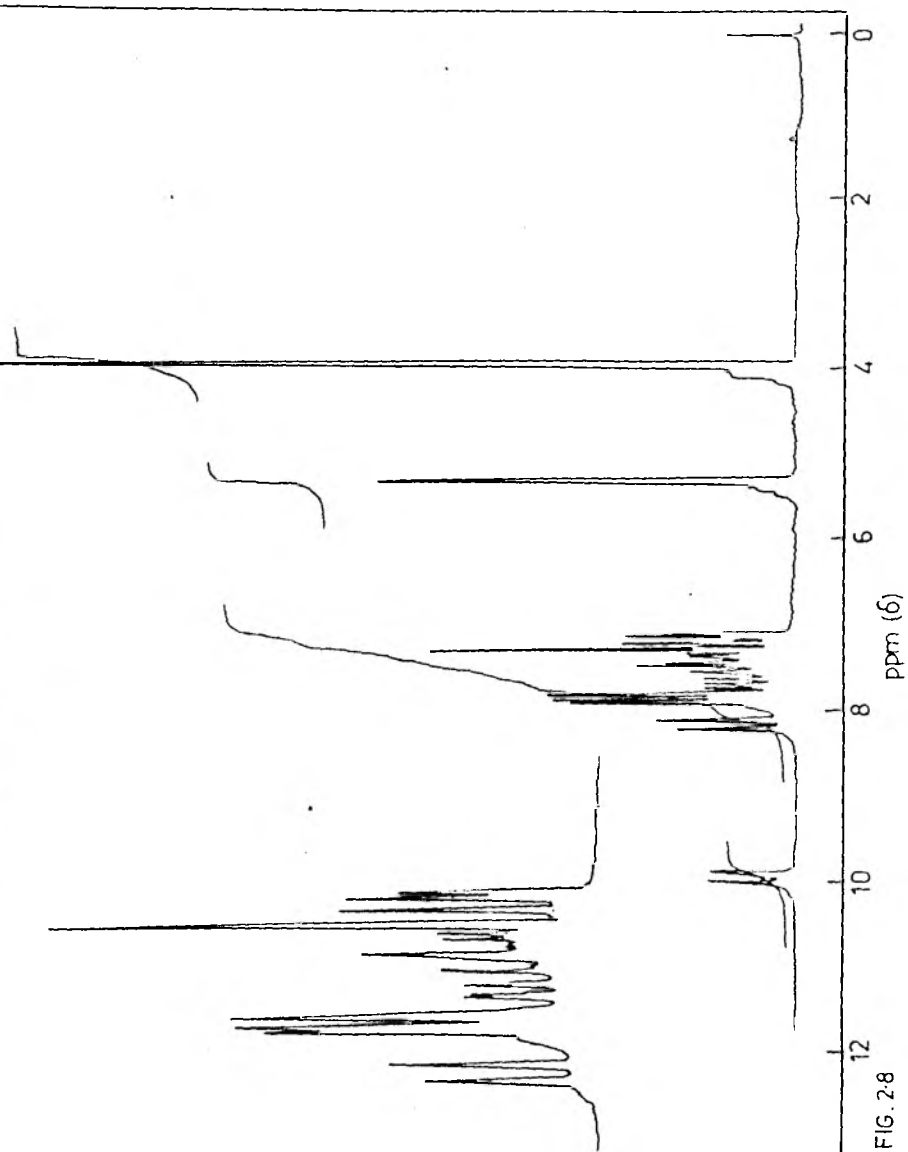
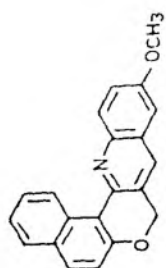


FIG. 2.8

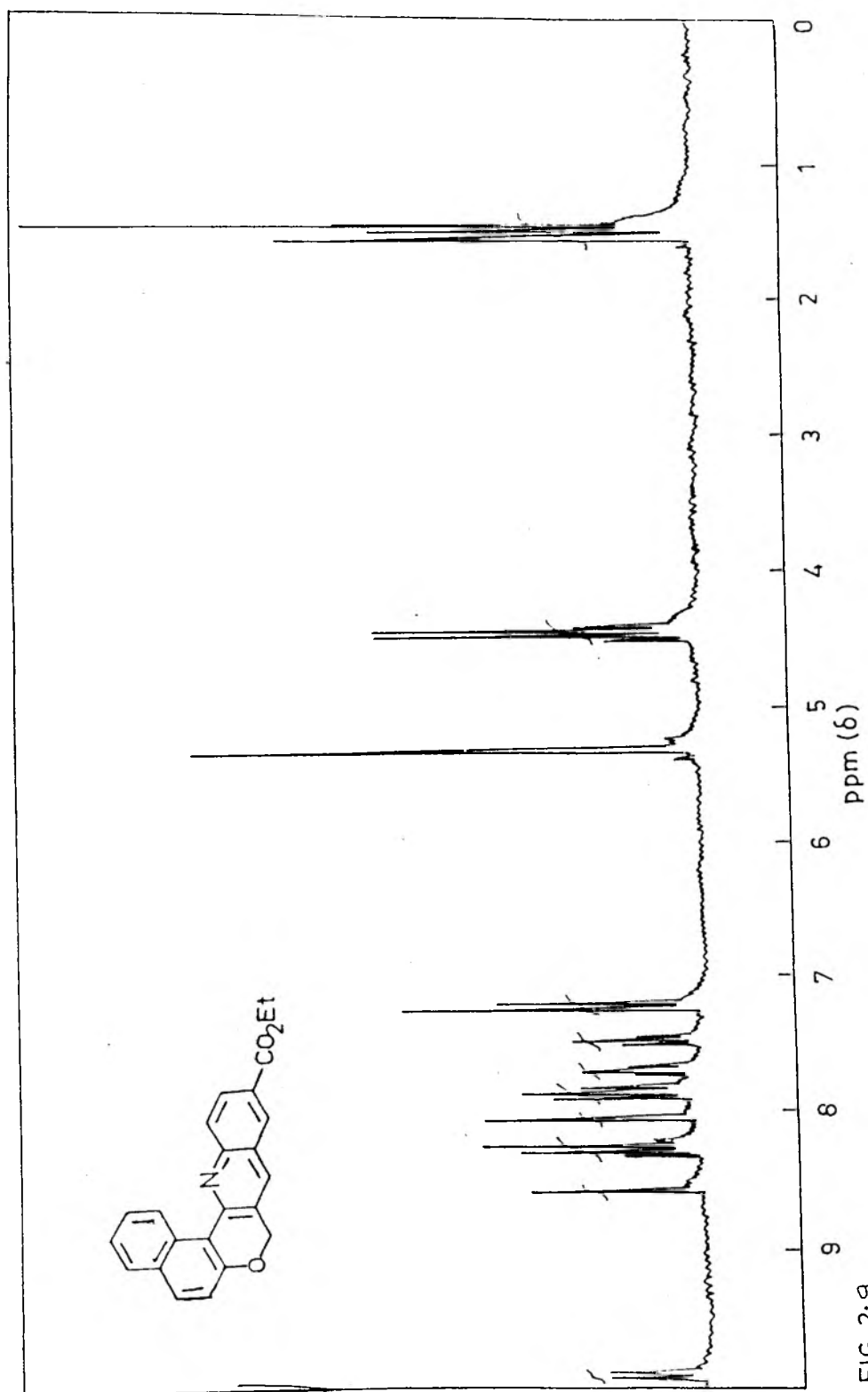
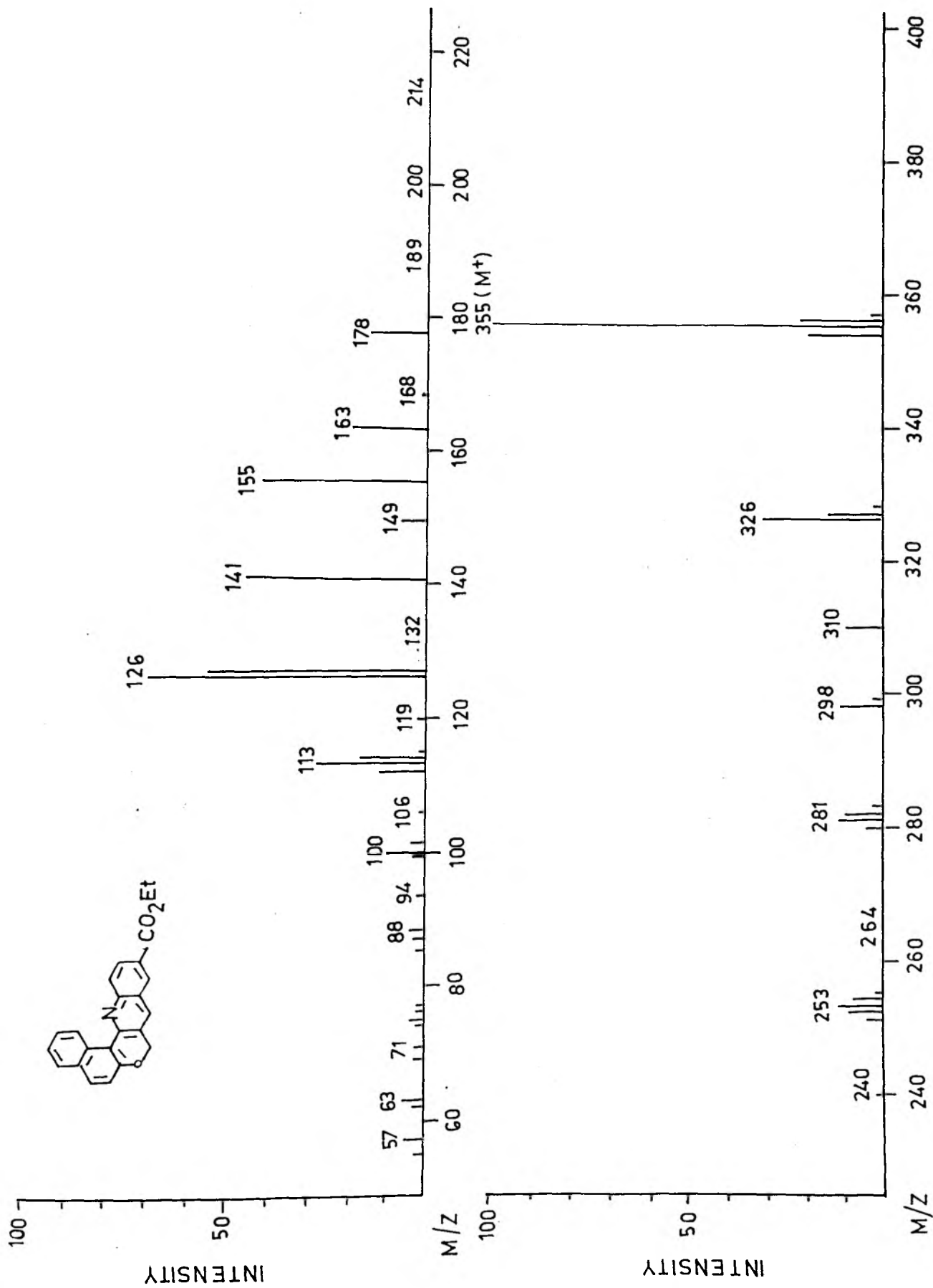
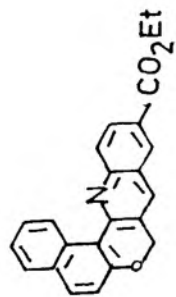


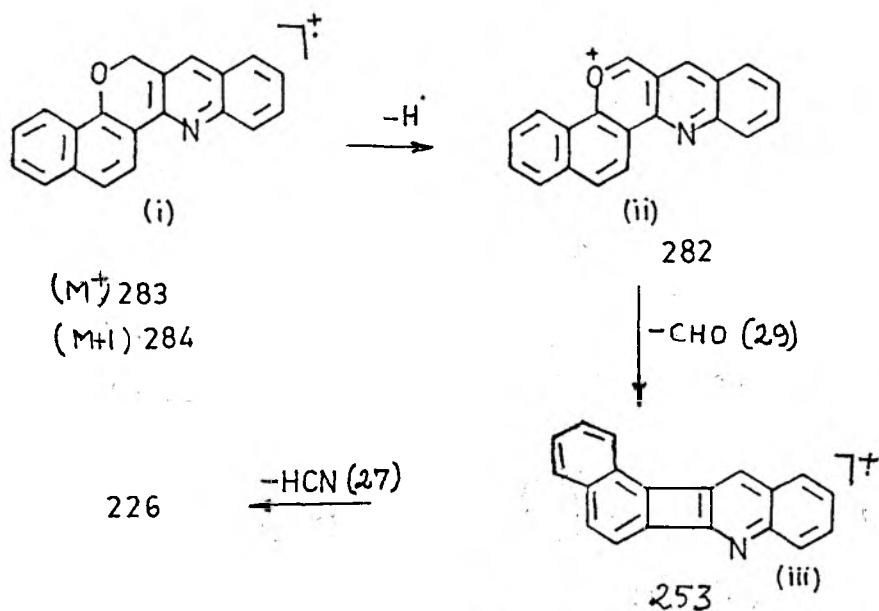
FIG. 2.9

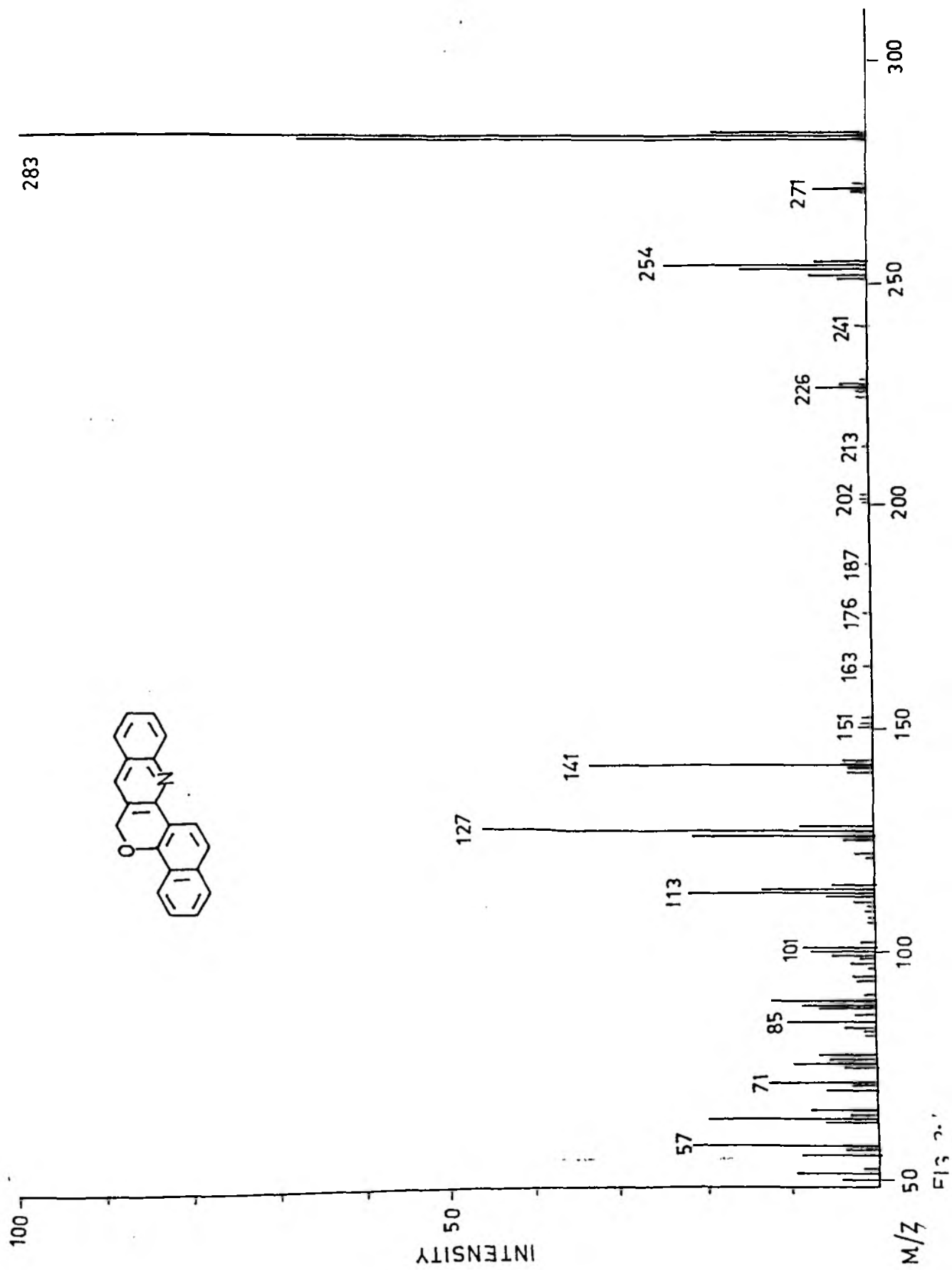
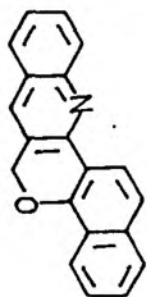


All the above compounds [XXXV(a-f)] and [XXXVI(a-f)] were characterised by usual spectral data and elemental analysis. The physical constants, I.R., ^1H NMR and mass spectral data etc. of the compounds are given in Table - 2A & 2B.

Thus, our method is simple and better than all the above synthesis of benzopyrano quinolines described earlier due to the easily availability of chloroaldehydes and aniline derivatives and ease of cyclisation to the desired product. Secondly, the alternate cyclisation of the anil derivatives to produce other isomer as previously reported by K. K. Balasubramanian et al¹³ did not occur. This was confirmed by spectral data, TLC and by analogy with other systems^{18,19}.

Mass Spectra Explanation of the compound (XXXVa)



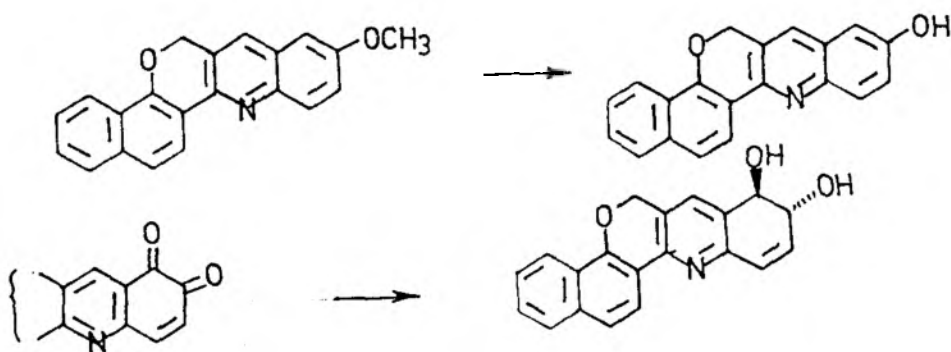


The molecule (i) is first dehydrogenated to the species (ii), which then extrudes carbon monoxide to an ion m/e 254 presumably ; this either eliminates HCN to give an ion m/e 227, or is dehydrogenated to the species (iii), which in turn extrudes HCN to give the hydrocarbon m/e 226.

Scope of further works

In this chapter we have described the synthesis of two isomers of naphthopyrano quinoline derivatives. It is well established that dihydrodiols and diol epoxides of PAH and polyazaarenes have been found carcinogenic. Surprisingly naphthopyrano quinolines have not yet been converted to trans-dihydrodiol or diol epoxides, penultimate and ultimate carcinogen respectively. Recently J. K. Ray et al²⁰ have developed a useful method following the protocol of functional group transformations methoxy→phenol→orthoquinone→dihydrodiol. For this the introduction of the methoxy group in either of terminal ring could be achieved by taking starting materials having the methoxy group in proper position in either the chloroaldehyde or the aromatic amines.

Thus utilizing the above methods the dihydrodiol of methoxy derivative of naphthopyrano quinoline can be achieved which will definitely shed new light in understanding the mechanism of cancer formation by quinoline derivatives as benzopyrano quinolines are carcinogenic. The scheme can be shown below :



-

Compounds	Nature	M.P.(°C)	Yield (%)	I.R. (KBr) $\gamma_{\max}^{-1}$ cm
XXXIIIa	Deep red solid	198-200 (d)	94.9	1600, 1622, 1640, 3050, 3150, 3400
XXXIIIb	Orange yellow solid	185-186(d)	70	1610, 1622, 1630, 3060, 3140, 3400
XXXIIIc	Red solid	205-206(d)	92.4	1602, 1625, 1640, 3060, 3142, 3400
XXXIIId	Deep yellow solid	203-204 (d)	79	1600, 1622, 1640, 3040, 3160, 3400
XXXIIIe	Deep red solid	210-212(d)	82.5	1332, 1376, 1522, 1572, 1590, 1620, 1640, 3060, 3400
XXXIIIf	Red solid	206-207(d)	94	1602, 1620, 1640, 1706, 3040, 3400
XXXIVa	Deep red solid	195-196(d)	54.5	1602, 1620, 3040, 3140, 3400
XXXIVb	Deep red solid	197-198(d)	68	1610, 1620, 3040, 3150, 3400
XXXIVc	Deep red solid	176-177(d)	88	1600, 1620, 3040, 3150, 3400
XXXIVd	Red solid	186-187(d)	82.5	1622, 3060, 3160, 3400
XXXIVe	Red solid	215-216(d)	68.5	1298, 1340, 1560, 1575, 1635, 3040, 3400
XXXIVf	deep red solid	186-187(d)	79	1600, 1620, 1635, 1712, 3050, 3140

TABLE - 2A

Compounds	Nature	M.P. (°C)	Yield (%)	I.R. (KBr) $\nu_{\max}$ cm ⁻¹	¹ H NMR (δ) ppm	Mass (m/z)
XXXVa	Colourless solid	195-196	55.4		5.5(s,2H), 7.3-7.9(m,8H), 8.05-8.35(m,2H), 8.55(d,1H),	284, 283, 282, 254, 253, 226, 141, 127, 113
XXXVb	Colourless solid	194-195	78.3		2.50(s,2H), 5.50(s,2H), 7.35-7.85(m,7H), 8.0(d,1H), 8.15-8.35(m,1H), 8.5(d,1H)	297, 296, 295, 269, 254, 241, 240, 227, 148, 142, 136
XXXVc	Faint yellow solid	201-202	32		3.9(s,3H), 5.55(s,2H), 7.05(d,1H), 7.25-7.9(m,6H), 8.1(d,1H), 8.2-8.4(m,1H), 8.55(d,1H)	
XXXVd	Colourless solid	222-223	90.9		5.52(s,2H), 7.4-8.8(m,7H), 8.08(d,1H), 8.2-8.4(m,1H), 8.52(d,1H)	
XXXVe	Yellow solid	203-204	63.4	1342, 1530, 1610	5.5(s,2H), 7.4-7.8(m,7H), 8.0-8.3(m,2H), 8.5(d,1H)	
XXXVf	Yellow solid	223-224	37	1622, 1718	1.45(t,3H), 4.5(q,2H), 5.55(s,2H), 7.3-7.7(m,3H), 7.8-8.0(m,2H), 8.15-8.4(m,3H), 8.45(s,1H), 8.55(d,1H)	355, 354, 325, 326, 298, 155, 140, 126

TABLE - 2B

Compounds	Nature	M.P. (°C)	Yield (%)	I.R. (KBr) $\bar{\nu}_{\max}$ cm	^1H NMR (δ) ppm	Mass (m/z)
XXXXVIa	Light orange solid	144-145	48		5.3(s,2H), 7.24(d,1H), 7.35-8.1(m,8H), 8.24(d,1H) 10.0(d,1H)	284, 283, 282, 254, 253, 226, 141, 127, 113.
XXXXVIb	Light orange yellow solid	162-163	42		2.55(s,2H), 5.28(s,2H), 7.24(d,1H), 7.4-7.85(m,8H), 8.1(d,1H), 9.95 (d,1H)	
XXXXVIc	Shining light brown solid	160-161	32.7		3.96(s,2H), 5.3(s,2H), 7.1-8.0(m,8H), 8.14(d,1H), 9.96 (d,1H)	
XXXXVI d	Light orange solid	205-206	38.6		5.3(s,2H), 7.2(d,1H), 7.3- 8.0(m,7H), 8.15(d,1H), 9.9 (d,1H)	
XXXXVIe	Brick brown solid	210-211	30.6	1340, 1520, 1580, 1610	5.3(s,2H), 7.2-8.76(m,9H), 9.88(d,1H)	
XXXXVIf	Yellow solid	171-172	39.3	1622, 1712	1.4(t,3H), 4.45(q,2H), 5.3(s,2H), 7.3(d,1H), 7.5(m,1H), 7.75(m,1H), 7.9(m,2H), 8.1(s,1H), 8.3(m,2H), 8.6(d,1H), 9.9(d,1H)	355, 354, 325, 289, 153, 140, 126

EXPERIMENTAL

1-Chloro-2-formyl-4-oxa-3,4-dihydrophenanthrene (XXXI) :

To a mixture of phosphorylchloride (5 gm, 32.6 m mol) in DMF (5 ml), 4-oxa-1,2,3,4-tetrahydrophenanthrenone²¹ (4.9 gm, 25 m mol) was added at 0 °C. The mixture was stirred and kept for 1 hr to attain the room temperature. The stirring was continued for whole night at room temperature. Next day, the reaction mixture was treated with a saturated solution of sodium acetate. The precipitate formed was filtered off, washed with water and air-dried to get 5.2 gm of (XXXI). This on recrystallisation with ethanol afforded yellow crystalline solid. M.P. 150-152°C (EtOH).

I.R. (KBr) $\lambda_{\max}$: 1660, 1600 cm^{-1} .

NMR (CDCl_3) δ : 5.20 (s, 2H), 7.53-8.25 (m, 6H), 10.16 (s, 1H) ppm.

M.S. m/e : 244(M^+)

Analysis :	C	H
Found :	68.5	3.7 %
Calculated :	68.6	3.7 %

1-Phenylamino-2-phenyliminomethyl-4-oxa-3,4-dihydrophenanthrenehydrochloride (XXXIIIa) :

The chloroformyl derivative (XXXI) (0.5 gm, 2.04 m mol) was added in one portion to a cooled stirred solution of freshly distilled aniline (0.5 gm 2.6 m mol) and 2N HCl (2.5 ml) in 25 ml ethanol. The solution was stirred for 15 min at 10-15°C and then 2 hrs at room temperature. The reaction mixture was cooled in an ice bath and the resulting solid filtered, washed

with little cold ethanol and dried to afford deep red solid (XXXIIIa). M.P. 198-200°C(d), Yield - (800 mg), 94.9%.

I.R. (KBr) $\nu_{\max}$: 1690, 1640 (C=N), 3150 (NH) cm^{-1} .

1-(p-Tolylamino)-2-(p-tolyliminomethyl)-4-oxa-3,4-dihydrophenanthrene hydrochloride (XXXIIIb) :

In a similar process (as mentioned above) 500 mg (2.04 m mol) of the chloroformyl derivative (XXXI) on reaction with 480 mg (2 m mol) of p-toluidine in 25 ml ethanol and 2.5 ml of 2N HCl gave 600 mg (70%) of (XXXIIIb) as orange yellow solid. M.P. 185-186°C.

I.R. (KBr) $\nu_{\max}$: 1610, 1630 (C=N); 3140 (NH) cm^{-1} .

1-(p-Methoxyphenylamino)-2-(p-methoxyphenyliminomethyl)-4-oxa-3,4-dihydrophenanthrene hydrochloride (XXXIIIc) :

Reaction of 650 mg (2.6 m mol) of the chloroformyl derivative (XXXII), 900 mg (3.75 m mol) of p-anisidine, 2.5 ml of 2N HCl in 25 ml ethanol gave 1.16 gm (92.3%) of (XXXIIIc) as dark red solid. M.P. 205-206°C(d).

I.R. (KBr) $\nu_{\max}$: 1602, 1640 (C=N), 3142 (NH) cm^{-1} .

1-(p-Chlorophenylamino)-2-(p-chlorophenyliminomethyl)-4-oxa-3,4-dihydrophenanthrene hydrochloride (XXXIIId) :

Chloroformyl derivative (XXXI) (0.5 gm, 2.0 m mol), p-chloroaniline (775 mg, 3.0 m mol) in 20 ml ethanol containing 2.5 ml 2N HCl on reaction gave 770 mg (79%) of the anil hydrochloride (XXXIIId) as deep yellow solid. M.P. 203-204°C(d).

I.R. (KBr) $\nu_{\max}$: 1600, 1622, 1640 (C=N), 3160 (NH) cm^{-1} .

1-(p-Nitrophenylamino)-2-(^p-nitrophenyliminomethyl)-4-oxa-3,4-dihydro-phenanthrene hydrochloride (XXXIIIe) :

Chloroformyl derivative (XXXI) (500 mg, 2 m mol), p-nitroaniline (620 mg, 2.2 m mol) in 20 ml ethanol containing 2.5 ml 2N HCl on reaction gave 850 mg (82.5%) of the anilhydrochloride (XXXIIIe) as bright red solid. M.P. 210-212°C(d).

I.R. (KBr) $\gamma_{\max}$: 875 (CN), 1332 (NO₂), 1572 (NO₂), 1640 (C=N), 3060 (NH) cm⁻¹.

1-(p-Carbethoxyphenylamino)-2-(p-carbethoxyphenyliminomethyl)-4-oxa-3,4-dihydrophenanthrene hydrochloride (XXXIIIIf) :

500 mg (2 m mol) chloroformyl derivative (XXXI), 820 mg (2.5 m mol) 4-aminoethyl benzoate, 2.5 ml 2N HCl in 15 ml of ethanol on reaction gave (XXXIIIIf), a dark red solid 1.07 gm (92%). M.P. 206-207°C(d).

I.R. (KBr) $\gamma_{\max}$: 1602, 1640 (C=N), 1706 (CO₂Et), 3400 (br) cm⁻¹.

6H-Naphtho[2', 1:5,6]pyrano[4,3-b]quinoline (XXXVa) :

0.5 gm of the anil hydrochloride (XXXIIIa) taken in a large test tube and heated at 210-240°C for 3-5 min. Aniline hydrochloride deposited in the cooler part of the test tube. The cooled mass was extracted with chloroform, washed with water, dried (Na₂SO₄). Removal of solvent afforded dark coloured mass which was then passed through a short column of alumina. Elution with pet. ether (60-80°C) gave a colourless solid which was further recrystallised from ethanol. Yield of colourless shining solid (XXXVa) was 190 mg (55.4%), M.P. 195-196°C.

^1H NMR (CDCl_3) δ : 3.5 (s,2H), 7.3-7.9 (m,3H), 8.05-8.35 (m,2H), 8.5 (d,1H)
ppm.

MS (m/z) : 284, 283, 282, 254, 253, 226, 141, 127, 113.

Analysis :	C	H	N
Found :	84.65	4.25	4.53 %
Calculated :	84.80	4.59	4.94 %

($\text{C}_{20}\text{H}_{13}\text{NO}$)

9-Methyl -6H-naphtho[2',1:5,6]pyrano[4,3-b]quinoline (XXXVb) :

The anil hydrochloride (XXXIIIb) (0.58 gm) was heated in a long test-tube at 210-240°C for 3-5 min. The fused mass was extracted with choloform, washed with water, dried (Na_2SO_4). Removal of solvent afforded dark colour residue which was purified by passing through a short column of neutral alumina. Elution with pet. ether (60-80°C) gave colourless shining solid. Recrystallisation from ethanol gave 300 mg (78.3%) of the desired product (XXXVb). M.P. 194°C.

^1H NMR (CDCl_3) δ : 2.50 (s,3H), 5.50 (s,2H), 7.35-7.85 (m,7H), 8.0 (d,1H),
8.15-8.35 (m,1H), 8.55 (d,1H) ppm.

MS (m/z) : 297, 296, 295, 269, 254, 241, 240, 227, 148, 142, 136.

Analysis :	C	H	N
Found :	84.64	4.74	4.30 %
Calculated :	84.84	5.05	4.71 %

($\text{C}_{20}\text{H}_{13}\text{NO}$)

9-Methoxy-6H-naphtho[2',1:5,6]pyrano[4,3-b]quinoline (XXXVc) :

850 mg of the anil hydrochloride (XXXIIIc) was heated at 210-240°C for 5 min. The fused residue was extracted with chloroform and after usual procedure afforded dark coloured solid which was passed through a column of n-alumina. Elution with pet-ether+benzene (9:1) gave yellow solid. Recrystallisation with ethanol afforded (XXXVc) as a light yellow solid. Yield - 180 mg (32%). M.P. 201-202°C.

^1H NMR (CDCl_3) δ : 3.9 (s,3H), 5.55 (s,2H), 7.05 (d,1H), 7.5-7.9 (m,6H),
8.1 (d,1H), 8.2-8.4 (m,1H), 8.55 (d,1H) ppm.

Analysis :	C	H	N
Found :	80.30	4.56	4.27 %
Calculated :	80.57	4.79	4.47 %

($\text{C}_{21}\text{H}_{15}\text{NO}$)

9-Chloro-6H-naphtho[2',1:5,6]pyrano[4,3-b]quinoline (XXXVd) :

500 mg of the anil hydrochloride (XXXIIId) was heated at 210-240°C for 5 min. After usual work up it gave dark coloured residue which was purified by column chromatograph (Elution with pet-ether 60-80°C). Recrystallisation with ethanol gave 300 mg (90.9%) of the desired product (XXXVd) as light yellow solid. M.P. 222-223°C.

^1H NMR (CDCl_3) δ : 5.52 (s,2H), 7.4-8.0 (m,7H), 8.08 (d,1H), 8.2-8.4 (m,1H),
8.52 (d,1H) ppm.

Analysis :	C	H	N
Found :	75.39	3.36	4.42 %
Calculated :	75.59	3.77	4.40 %

($\text{C}_{20}\text{H}_{12}\text{ONCl}$)

9-Nitro-6H-naphtho[2',1:5,6]pyrano[4,3-b]quinoline (XXXVe) :

500 mg of the anil hydrochloride (XXXIIIe) was heated at 210-240°C for 5 min. After usual work up it gave dark residue which was purified by column. Elution with pet. ether+benzene (1:1) gave yellow solid. Recrystallisation with ethanol afforded (XXXVe) as a light yellow solid 200 mg (63.4%). M.P. 203-204°C.

^1H NMR (CDCl_3) δ : 5.5 (s, 2H), 7.4-7.8 (m, 7H), 8.0-8.3 (m, 2H), 8.5 (d, 1H) ppm.

Analysis :	C	H	N
Found :	72.98	3.35	4.0 %
Calculated :	73.17	3.65	4.26 %

($\text{C}_{20}\text{H}_{12}\text{N}_2\text{O}_3$)

9-Carbethoxy-6H-naphtho[2',1:5,6]pyrano[4,3-b]quinoline (XXXVf) :

700 mg of the anil hydrochloride (XXXIIIIf) was heated at 210-240°C for 5 min. After usual work up it gave dark coloured residue which was passed through a column of neutral alumina. Elution with pet. ether (60-80°C)+benzene (9:1) afforded yellow solid. Recrystallisation with ethanol gave the desired product (XXXVf) 165 mg (37%) as yellow solid. M.P. 223-224°C.

I.R. (KBr) $\tilde{\nu}_{\text{max}}$: 1622, 1718 cm^{-1} .

^1H NMR (CDCl_3) δ : 1.45 (t, 3H), 4.5 (q, 2H), 5.55 (s, 2H), 7.3-7.7 (m, 3H), 7.8-8.0 (m, 2H), 8.15-8.4 (m, 3H), 8.45 (s, 1H), 8.55 (d, 1H) ppm.

MS (m/z) : 355, 354, 326, 325, 298, 155, 140, 126.

Analysis :	C	H	N
Found :	77.45	4.53	3.44 %
Calculated :	77.74	4.78	4.94 %
(C ₂₃ H ₁₇ NO ₃)			

4-Chloro-3-formyl-1-oxa-1,2-dihydrophenanthrene (XXXII) :

To a cold stirred solution of phosphoryl chloride (5.37 gm, 35 m mol) and DMF (5 ml) added the ketone²¹ (5.5 gm, 27 m mol). The mixture was stirred at room temperature for whole night. Next day, the reaction mixture was treated with saturated solution of sodium acetate. The separated yellow solid was filtered, washed with water and air dried to get (XXXII) as a yellow solid. Yield - 5.7 gm (84%). M.P. 129-130°C (EtOH)

I.R. (KBr) $\lambda_{\max}^{-1}$: 1650 cm⁻¹.

4-Phenylamino-3-phenyliminomethyl-1-oxa-1,2-dihydrophenanthrene hydrochloride (XXXIVa) :

The chloroformyl derivative (XXXII) (980 mg, 4.0 m mol) was added in one portion to a cooled stirred solution of freshly distilled aniline (850 mg, 4.56 m mol) and 2N HCl (2.5 ml) in 25 ml ethanol. The solution was stirred for 2 hrs at room temperature and then the reaction mixture was cooled in ice bath and filtered, the solid was washed with little cold ethanol and dried in air to afford (XXXIVa) as a deep red solid.

Yield - 900 mg (54.5%), M.P. 195-196°C(d).

I.R. (KBr) $\lambda_{\max}^{-1}$: 1602, 1635 (C=N), 3140, 3400 cm⁻¹.



4-(p-Tolylamino)-3-(p-tolyliminomethyl)-1-oxa-1,2-dihydrophenanthrene hydrochloride (XXXIVb) :

In a similar process (as mentioned above) 450 mg (1.84 m mol) of the chloroformyl derivative (XXXII) on reaction with 450 mg (2.1 m mol) of p-toluidine in 25 ml ethanol and 2.5 ml of 2N HCl gave 550 mg (67.9%) of (XXXIVb) as a dark red solid. M.P. 197-198°C(d).

I.R. (KBr) $\lambda_{\max}$: 1610, 1620, 3150, 3400 cm^{-1} .

4-(p-Methoxyphenylamino)-3-(p-methoxyphenyliminomethyl)-1-oxa-1,2-dihydrophenanthrene hydrochloride (XXXIVc) :

Chloroformyl derivative (XXXII) (0.5 gm, 2 m mol), p-anisidine (0.7 gm, 3 m mol) in 20 ml ethanol containing 2.5 ml 2N HCl on reaction gave 0.85 gm (88%) of the anil hydrochloride (XXXIVc) as a deep red solid. M.P. 176-177°C(d).

I.R. (KBr) $\lambda_{\max}$: 1600, 1620, 3040, 3150 cm^{-1} .

4-(p-Chlorophenylamino)-3-(p-chlorophenyliminomethyl)-1-oxa-1,2-dihydrophenanthrene hydrochloride (XXXIVd) :

Reaction of (1 gm, 4 m mol) of the chloroformyl derivative (XXXII) 2 gm (4.66 m mol) of p-chloroaniline, 2.5 ml of 2N HCl in 25 ml ethanol gave 1.6 gm (82.5%) of (XXXIVd) as a red solid. M.P. 186-187°C.

I.R. (KBr) $\lambda_{\max}$: 1622, 3060, 3160, 3400 cm^{-1} .

4-(p-Nitrophenylamino)-3-(p-nitrophenylimino)-1-oxa-1,2-dihydrophenanthrene hydrochloride (XXXIVe) :

Chloroformyl derivative (XXXII) 0.98 gm (4 m mol), 1.2 gm (4.3 m mol) p-nitroaniline, 2.5 ml 2N HCl in 15 ml of ethsanol on reaction gave (XXXIVe) as a red solid. Yield - 1.72 gm (68.5%), M.P. 215-216°C(d).

I.R. (KBr) $\nu_{\max}$: 1575, 1635, 3040, 3400 cm^{-1} .

4-(p-Carbethoxyphenylamino)-3-(p-carbethoxyphenyliminomethyl)-1-oxa-1,2-dihydrophenanthrene hydrochloride (XXXIVf) :

500 mg (2 m mol) chloroformyl derivative (XXXII), 820 mg (2.5 m mol) 4-aminoethyl benzoate, 2.5 ml 2N HCl in 20 ml of ethanol on reaction gave 0.9 gm (79%) of (XXXIVf) as a deep red solid. M.P. 186-187°C.

I.R. (KBr) $\nu_{\max}$: 1600, 1620, 1635, 1712, 3050, 3140 cm^{-1} .

8H-Naphtho[1',2':5,6]pyrano[4,3-b]quinoline (XXXVIa) :

0.7 gm of the anil hydrochloride (XXXIVa) taken in a large test tube was heated at 210-240°C for 3-5 minutes. Aniline hydrochloride deposited in the cooler part of the test tube. The cooled mass was extracted with chloroform, washed with water, dried (Na_2SO_4). Removal of solvent afforded dark coloured mass which was then passed through a short column of neutral alumina. Elution with pet. ether (60-80°C) gave a light orange solid which was further recrystallised from ethanol. The yield of the compound (XXXVIa) was 230 mg (48%).

M.P. 144-145°C(d). ^1H NMR (CDCl_3) δ : 5.3 (s,2H), 7.24 (d,1H), 7.35-8.1 (m,8H), 8.24 (d,1H), 10.0 (d,1H) ppm.

11-Methyl-8H-naphtho[1',2':5,6]pyrano[4,3-b]quinoline (XXXVIb) :

The anil hydrochloride (XXXIVb) (650 mg. 1.47 m mol) was heated in large test tube at 210-240°C for 3-5 min. After usual work it gave dark coloured residue which was purified by column (pet. ether, 60-80°C). Recrystallisation with ethanol afforded 180 mg (42%) of the desired product (XXXVIb). M.P. 162-163°C.

^1H NMR (CDCl_3) δ : 2.55 (s,3H), 5.28 (s,2H), 7.24 (d,1H), 7.4-7.85 (m,8H) 8.1 (d,1H), 9.95 (d,1H) ppm.

11-Methoxy-8H-naphtho[1',2':5,6]pyrano[4,3-b]quinoline (XXXVIc) :

100 mg of the anilhydrochloride (XXXIVc) was heated at 210-240°C for 5 min. The fused residue was extracted with chloroform and after usual work up afforded dark coloured solid which was passed through a column of neutral alumina. Elution with pet. ether (60-80°C) gave light brown solid. Recrystallisation with ethanol gave 130 mg (32%) of the desired compound (XXXVIc). M.P. 160-161°C(d).

^1H NMR (CDCl_3) δ : 3.96 (s,3H), 5.3 (s,2H), 7.1-8.0 (m,8H), 8.14 (d,1H), 9.96 (d,1H) ppm.

11-Chloro-8H-naphtho[1',2':5,6]pyrano[4,3-b]quinoline (XXXVIId) :

750 mg of the anil (XXXIVd) was heated in a long neck test tube at 210-240°C for 5 min. The fused residue was extracted with chloroform and after usual work up it gave dark coloured solid which was passed through a column of neutral alumina. Elution with pet. ether + benzene (9:1) afforded light yellow solid. Recrystallisation with ethanol gave (XXXVIId) as a shining light yellow solid. Yield - 220 mg (38.6%). M.P. 205-206°C(d).

^1H NMR (CDCl_3) δ : 5.3 (s, 2H), 7.2 (d, 1H), 7.3-8.0 (m, 7H), 8.15 (d, 1H), 9.9 (d, 1H) ppm.

11-Nitro-8H-naphtho[1',2':5,6]pyrano[4,3-b]quinoline (XXXVIe) :

750 mg of the anil (XXXIVe) was heated at 210-240°C for 5 min. and after usual work up it gave brown coloured solid which was passed through a short column of neutral alumina. Elution with pet. ether + benzene (1:4) it gave brown solid of (XXXVIe). Yield 150 mg (30.6%). M.P. 210-211°C (benzene + pet. ether).

I.R. (KBr) $\bar{\nu}_{\text{max}}$: 1340, 1520, 1580, 1610 cm^{-1} .

^1H NMR (CDCl_3) δ : 5.3 (s, 2H), 7.2-8.76 (m, 9H), 9.88 (d, 1H) ppm.

11-Carbethoxy-8H-naphtho[1',2':5,6]pyrano[4,3-b]quinoline (XXXVIf) :

500 mg of the anil (XXXIVf) was heated in a test tube at 210-240°C for 5 min. After usual work up it gave dark coloured residue which was passed through a column of neutral alumina. Elution with pet. ether + benzene (4:1) gave (XXXVIf) as a yellow solid. Yield 125 mg (39%). M.P. 171-172°C (EtOH). IR (KBr) $\bar{\nu}_{\text{max}}$: 1622, 1712 cm^{-1} .

^1H NMR (CDCl_3) δ : 1.4 (t, 3H), 4.45 (q, 2H), 5.3 (s, 2H), 7.3 (d, 1H),
7.5 (m, 1H), 7.75 (m, 1H), 7.9 (m, 2H), 8.1 (s, 1H),
8.3 (m, 2H), 8.6 (d, 1H), 9.9 (d, 1H) ppm.

MS (m/z) : 355, 354, 325, 298, 153, 140, 126.

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CHAPTER 3

SYNTHESIS OF POLYCYCLIC COUMARINS

AND OXA-COUMARINS



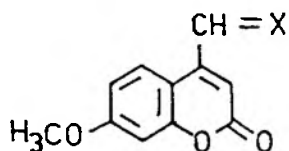
INTRODUCTION

Polycyclic coumarin derivatives are found to inhibit mutagenesis induced by polyaromatic hydrocarbons. Recent reports emphasise that replacement of a benzene ring of carcinogenic polyaromatic hydrocarbons (PAH) by a pyranone moiety produce an anticarcinogenic effect. Chapter 3 describes a three step synthesis of several polycyclic coumarin and oxacoumarin derivatives. The synthetic route is based on the transformation of functional groups from chloroaldehydes to methoxy aldehydes followed by condensation with cyanoacetic ester and intramolecular cyclisation of the resulting cyano derivatives to produce the coumarin derivative in good to excellent yields. Firstly we have discussed the biological activities of coumarins and some important synthetic routes available in the literature.

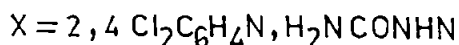
DISCUSSION

Coumarins constitute an important class of natural products¹. Several coumarin derivatives have attracted the attention of medicinal chemists for their wide variety of physiological activities².

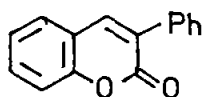
R. D. Shridhar et al³ have shown that compound (I) is effective as antibacterial, antifungal, amebicidal and anthelmintic agents.



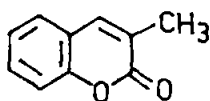
I



3-Phenyl and 3-methyl coumarins (II,III) have been reported to possess anticoagulants⁴, anthelmintic⁵ and hypnotic activities⁶.

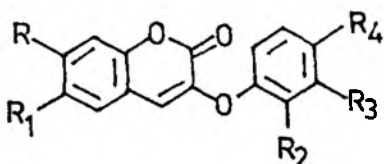


II



III

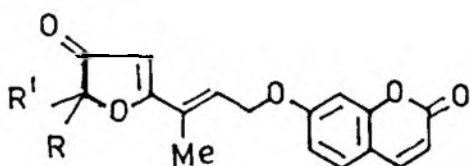
It is further reported that 3-phenoxy coumarin⁷ (IV) possess significant antimicrobial and antitubercular activities.



IV

1. $R=H$, $R^1=Cl$, $R^2=H, Cl, Me, OMe$
 $R^3, R^4=H, Cl, Me, OMe, NO_2$
2. $R=R^2=R^3=H$, $R^1=R^4=Cl$

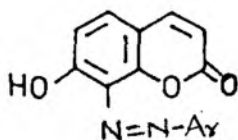
Recently, Baraldi and M. Guarneri⁸ have synthesised Geiparverin (V) which is active in inhibiting the proliferation of murin and human tumor cell lines in vitro and have cytostatic activity in vitro.



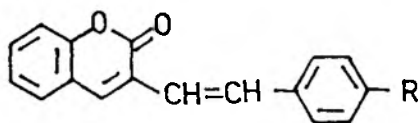
V

- i. $R=Me$, $R^1=Et$
- ii. $R=R^1=Me$

Coumarin derivatives (VI,VII) have been found to be used as a good dye⁹ and whiteners¹⁰ for polyesters also.



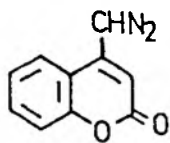
VI



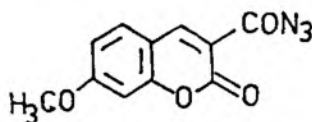
$R=H, OMe$

VII

The compounds (VIII)¹¹ and (IX)¹² have been found to be highly sensitive fluorescent labelling reagents for alcohols and carboxylic acid in high pressure liquid chromatograph (HPLC).

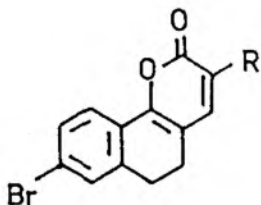


VIII



IX

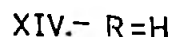
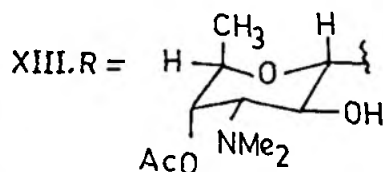
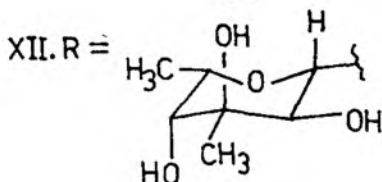
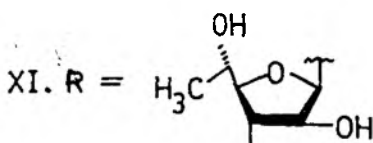
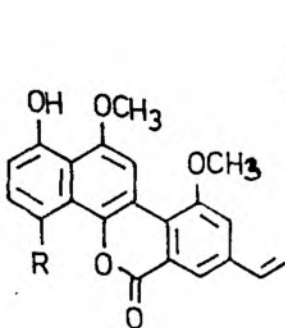
The antimicrobial activity of some tricyclic pyranone derivatives¹³ (X) were tested against bacillus activities and it was found that the compound Xc was the most active.



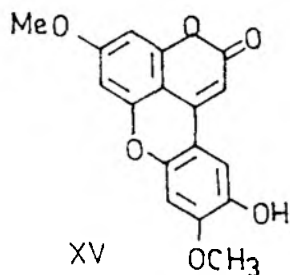
X

- a. R = CN
- b. R = CO₂Et
- c. R = CO₂H

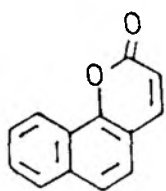
Very recently it has been reported that tetracyclic pyranone derivatives such as Gilvocarcin^{14, 15} (XI) also known as toromycin¹⁶ and anandimycin¹⁷ which are representative of a new class of aromatic c-glycoside antibiotics possess significant antitumor activity¹⁸. Other members of this family include chrysomycin (XII) and ravidomycin (XIII) which incorporate the same aromatic aglycon attached to various glycosidic substituents. The glycon of these antitumor antibiotics defucogilvocarcin¹⁹ (XIV) has recently been isolated as a natural product.



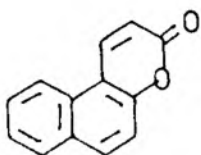
Recently, R. Mata et al²⁰ have isolated a novel oxacoumarin derivative (XV) from *emostima carbacum*. The compound has shown to act as an anti-microbial agent.



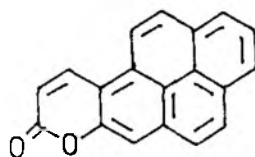
Coumarin analogs have shown to inhibit induction of polycyclicaromatic-hydrocarbon induced tumorigenesis in rodents^{21,22}. Very recently R. G. Harvey et al²³ have synthesised a series of polycyclic coumarins (XVI-XIX) and they showed that polycyclic coumarins act as anticancer agents. The compounds were chosen for specific study on the basis of evidence which suggested that coumarin derivatives structurally related to the carcinogenic polycyclic benzo[a]pyrene and 7,12-dimethyl benz[a]anthracene may be more effective in blocking tumor induction than their analogues having fewer number of aromatic ring systems. Preliminary bioassays confirms the anticarcinogenic activity of the polycyclic coumarins and the compound(XVIII) exhibit highest activity, showing strong potency as an inhibitor of DMBA induced skin tumors in mice and as an inducer of the aryl hydroxylase enzyme.



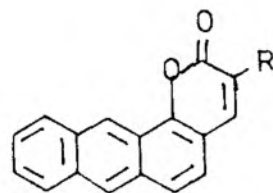
XVI



XVII



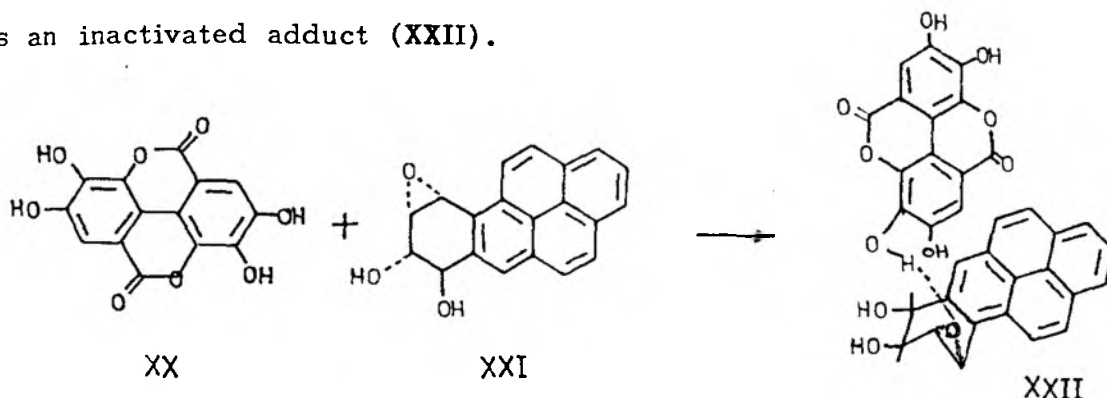
XVIII



XIX

In 1982 it has been shown by D. M. Jerina et al²⁴ that the ellagic acid (XX) which is isolated from green plant, coffee, nuts and grapes, is anticarcinogen and it neutralises the epoxide dihydrodiol of benz[a]pyrene

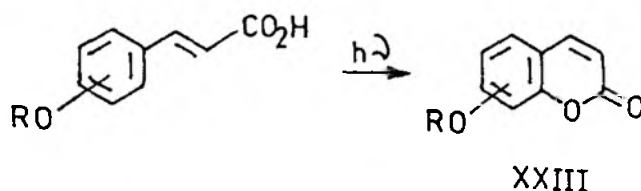
(XXI) which is potential carcinogenic as an environmental pollutant in vitro as an inactivated adduct (XXII).



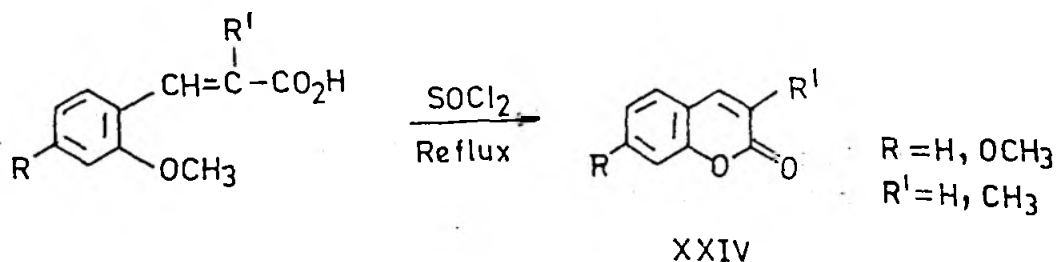
These discoveries attracted many organic chemists to take up the synthesis and design of various coumarin derivatives and to study their role in eliminating carcinogens from the environment.

As a part of a program with these objectives we have also undertaken to synthesise a series of polycyclic coumarin and oxacoumarin derivatives. Although many synthetic routes to coumarins are known²⁵⁻²⁷. Some syntheses of these classes of compounds are summarised below.

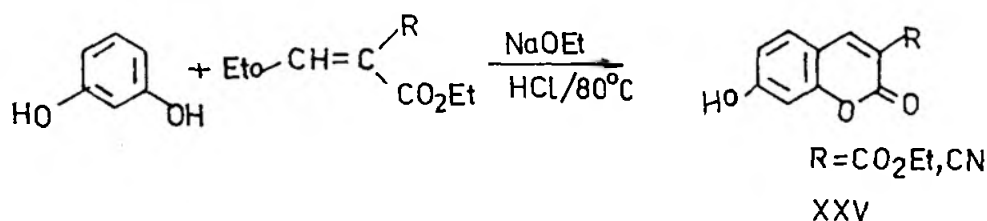
G. Pandey et al²⁸ have synthesised the coumarins (XXIII) from substituted cinnamic acids by single electron transfer process.



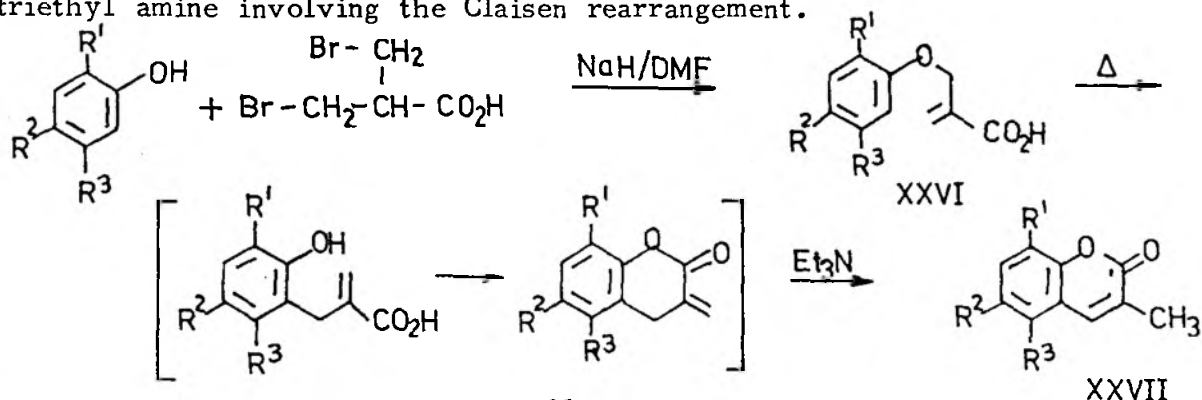
F. D. Popp et al²⁹ have synthesised 3-substituted coumarin derivatives (XXIV) by refluxing a mixture of thionyl chloride and o-methoxy- α -methyl cinnamic acid or o-cinnamic acid in very poor yield.



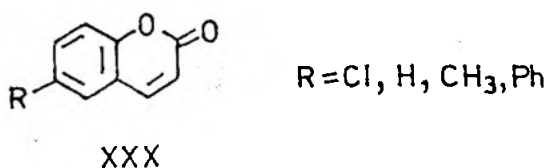
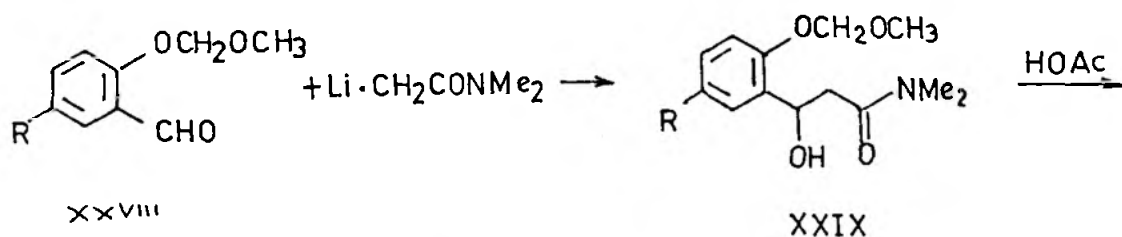
S. B. Lokhande et al⁹ have reported the synthesis of 3-substituted coumarins (XXV) by condensation of resorcinol with conjugated enol ethers in presence of sodium ethoxide followed by cyclisation of the resulting compounds in situ with HCl.



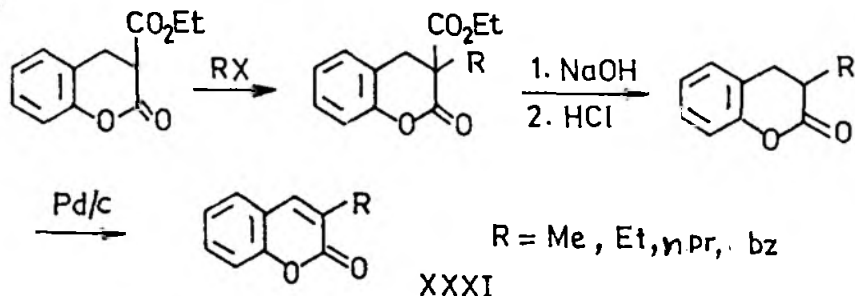
A new synthesis of 3-methyl coumarins (XXVII) was developed by S. Swaminathan et al³⁰ from α -aryloxymethyl acrylic acids (XXVI) in presence of triethyl amine involving the Claisen rearrangement.



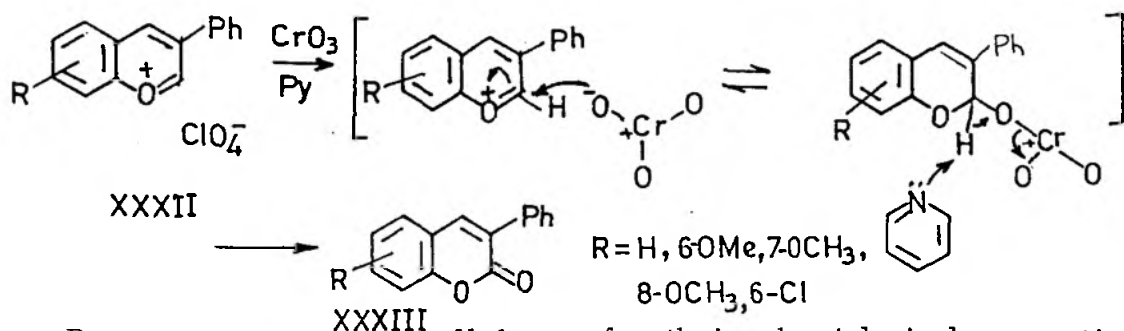
Recently R. G. Harvey et al³¹ have reported the synthesis of various polycyclic coumarin derivatives (XXX) ortho-methoxymethyl aryl aldehydes (XXVIII) yield (XXIX) which on heating in refluxing acetic^{acid} undergoes smooth conversion to the coumarin derivatives.



A new synthesis of 3-alkyl coumarins (XXXI) was achieved by the catalytic μ hydrogenation of 3-carbethoxy-3,4-dihydro coumarins by A. K. Mitra et al³².



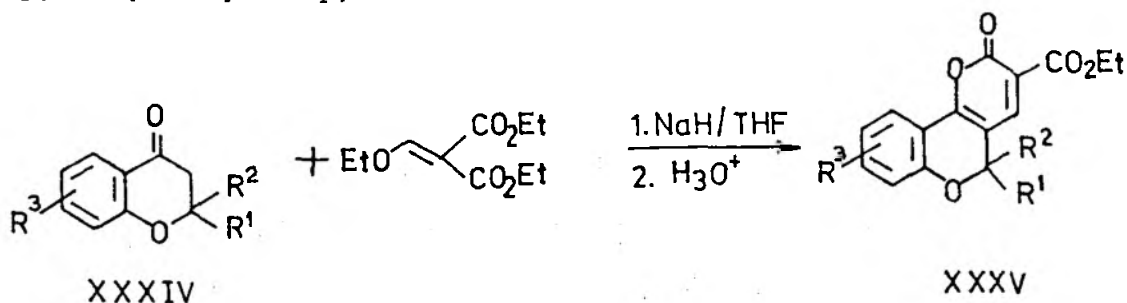
A very typical synthesis of 3-phenyl coumarins (XXXIII) have been represented by C. D. Vallet et al³³ by the oxidation of isoflavylum salts (XXXII) with pyridine CrO_3 complex.



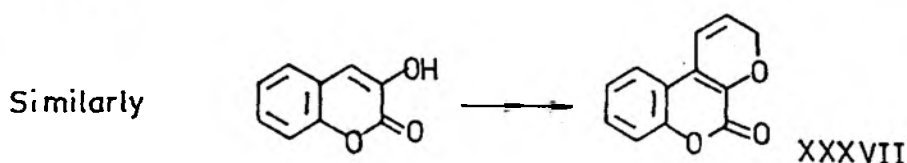
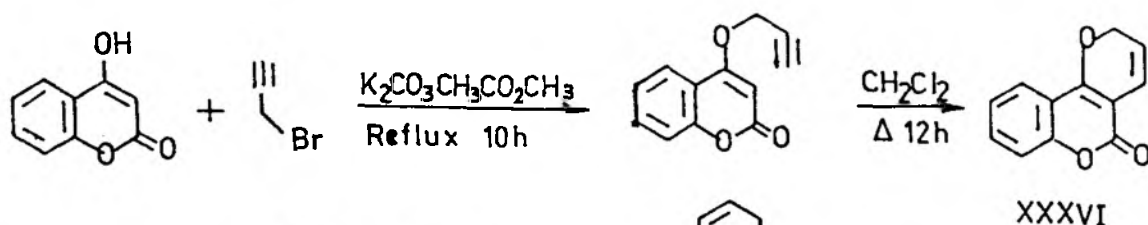
Pyrano coumarins are well known for their physiological properties³⁴.

A very few report has come on the synthesis of fused pyrano coumarins. Some of them are discussed below.

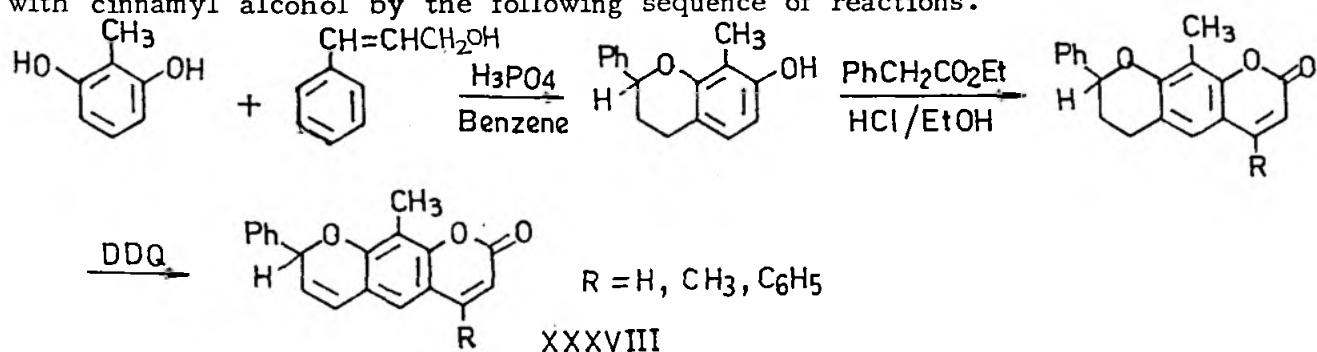
In 1985, a french group³⁵ has reported the synthesis of 2-oxopyrano-[3,2-c]benzopyran. When chromanones (XXXIV) were treated with conjugated enol ethers in presence of sodium hydride in THF gave 3-substituted 2-oxopyrano[3,2-c]benzopyranone (XXXV).



Recently, K. C. Majumder et al³⁶ have reported the regioselective synthesis of 2H-pyrano[3,2-c]benzopyran-5H-one (XXXVI) and 3H-pyrano[2,3-c]-benzopyran-5H-one (XXXVII) in 55 and 60% yield by the sigmatropic rearrangement of 4-2-propynyloxy coumarin and 3-2-propynyloxy coumarin respectively.



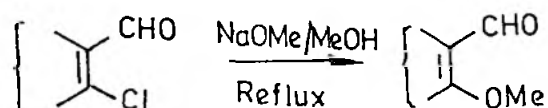
V. K. Ahluwalia et al³⁷ have also synthesised linearly fused pyrano coumarins (XXXVIII) by acid catalysed condensation of 2-methyl resorcinol with cinnamyl alcohol by the following sequence of reactions.



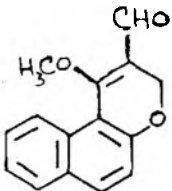
Chemoprotection against cancer have been the subject matter of many recent researchers. Some chemical compounds containing electrophilic centres that can function as Michael reaction acceptor, raises the level of enzymes³⁸ protective against electrophilic chemical carcinogens. Coumarin analogs are found to inhibit induction of polyaromatic hydrocarbon induced tumorigenesis in rodents which we have discussed previously. Thus several coumarin derivatives related to polycyclic arenes are needed to establish the structure activity relationships in the series of compounds. Systematic investigation of structural modification of molecules of this type in relation to anticarcinogenic activity have not been reported.

Thus, in this chapter we like to present the synthesis of polycyclic umarins and oxa-coumarin derivatives starting from suitable chloroaldehydes per Schemes (I-IV).

The chloroaldehydes (XXXIX-XXXXII) were converted to the methoxy derivatives by refluxing with sodium methoxide in methanol for 2 hrs. The methoxy aldehydes show a strong peaks at 1640 to 1650 cm^{-1} characteristics of β -methoxy α, β -unsaturated aldehyde groups whereas peaks at 1610 cm^{-1} are due to C=C. The compounds also show a singlet at about 10.2 to 10.5 due to -CHO protons and strong singlet at 3.5 to 3.8 due to methoxy groups.



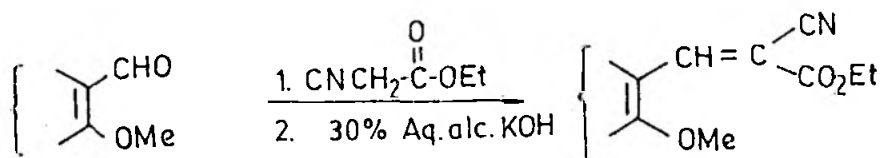
The ^1H NMR of the compound (XXXXVI) is given below :

	Position of peaks (δ) ppm	Nature	Proton count	Assignment
	3.7	s	3H	-OCH ₃
	5.0	s	2H	-OCH ₂
	7.15	d	1H	Aromatic
	7.3-7.95	m	4H	Aromatic
	8.5	d	1H	Aromatic
	10.2	s	1H	-CHO

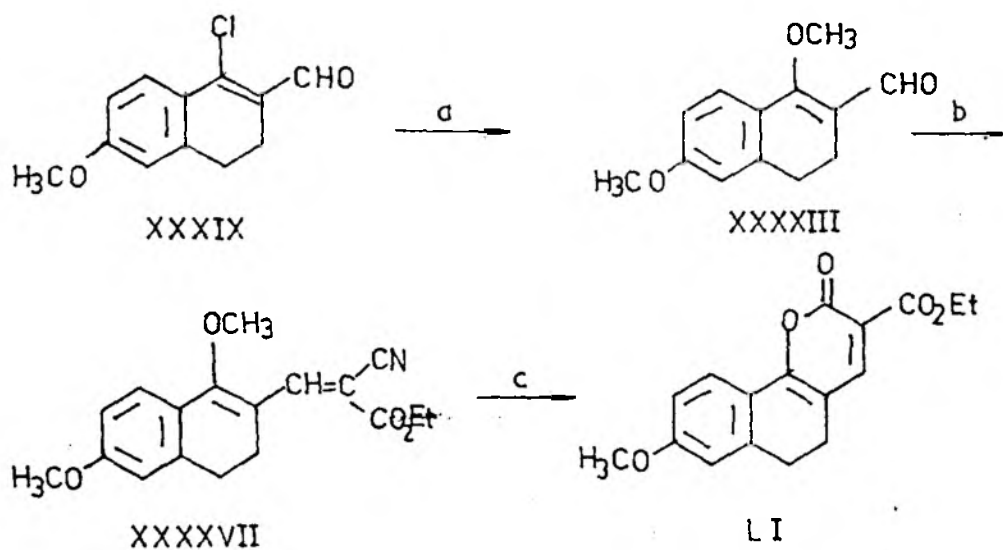
Solvent: CDCl_3

Fig. 3.3

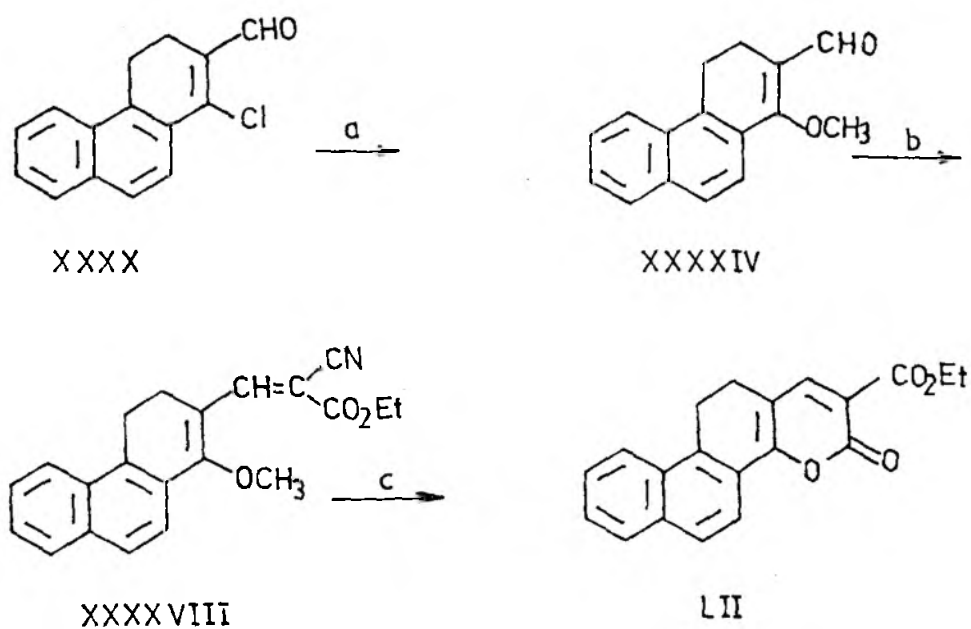
The methoxy aldehydes (XXXXIII-XXXXVI) were condensed with cyanoacetic ester in presence of 30% aqueous alcoholic KOH to produce the nitrile derivatives as yellow to deep red solids.



SCHEME - I



SCHEME- II

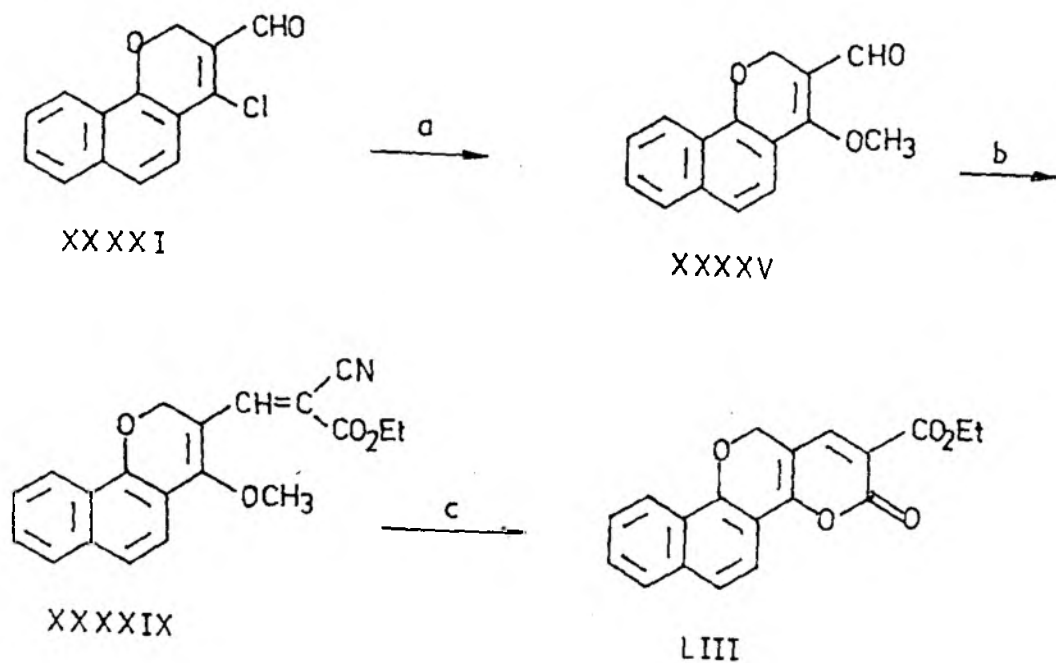


a. $\text{NaOCH}_3/\text{MeOH}$ / Reflux/ 2hr

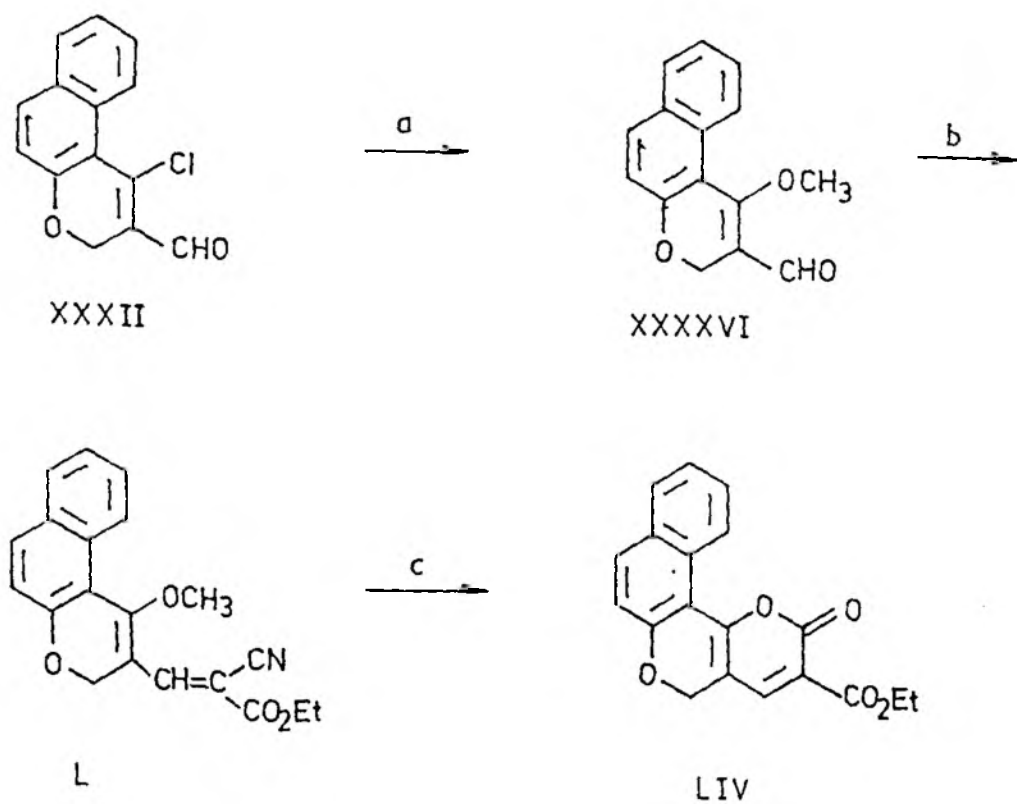
b. $\text{CNCH}_2\text{CO}_2\text{Et}$ / EtOH / aq. ethanolic / KOH / Reflux

c. $\text{Py. HCl} / \Delta$

SCHEME-III



SCHEME - IV



- a. NaOCH_3 / MeOH / Reflux / 2 hr
 b. $\text{CNCH}_2\text{CO}_2\text{Et}$ / EtOH / aq. Ethanolic KOH / Reflux
 c. $\text{Py. HCl} / \Delta$

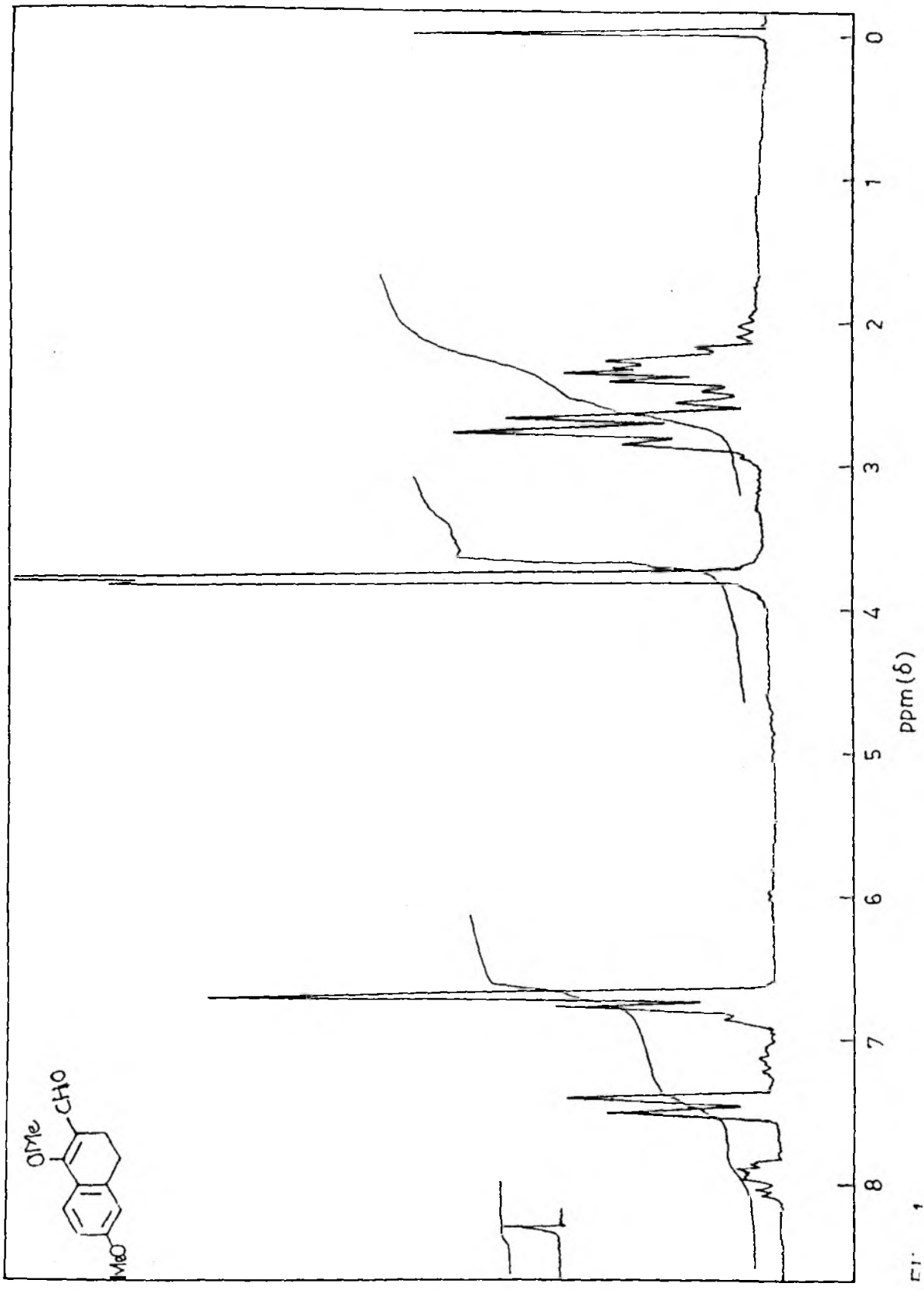




FIG. 3-2.

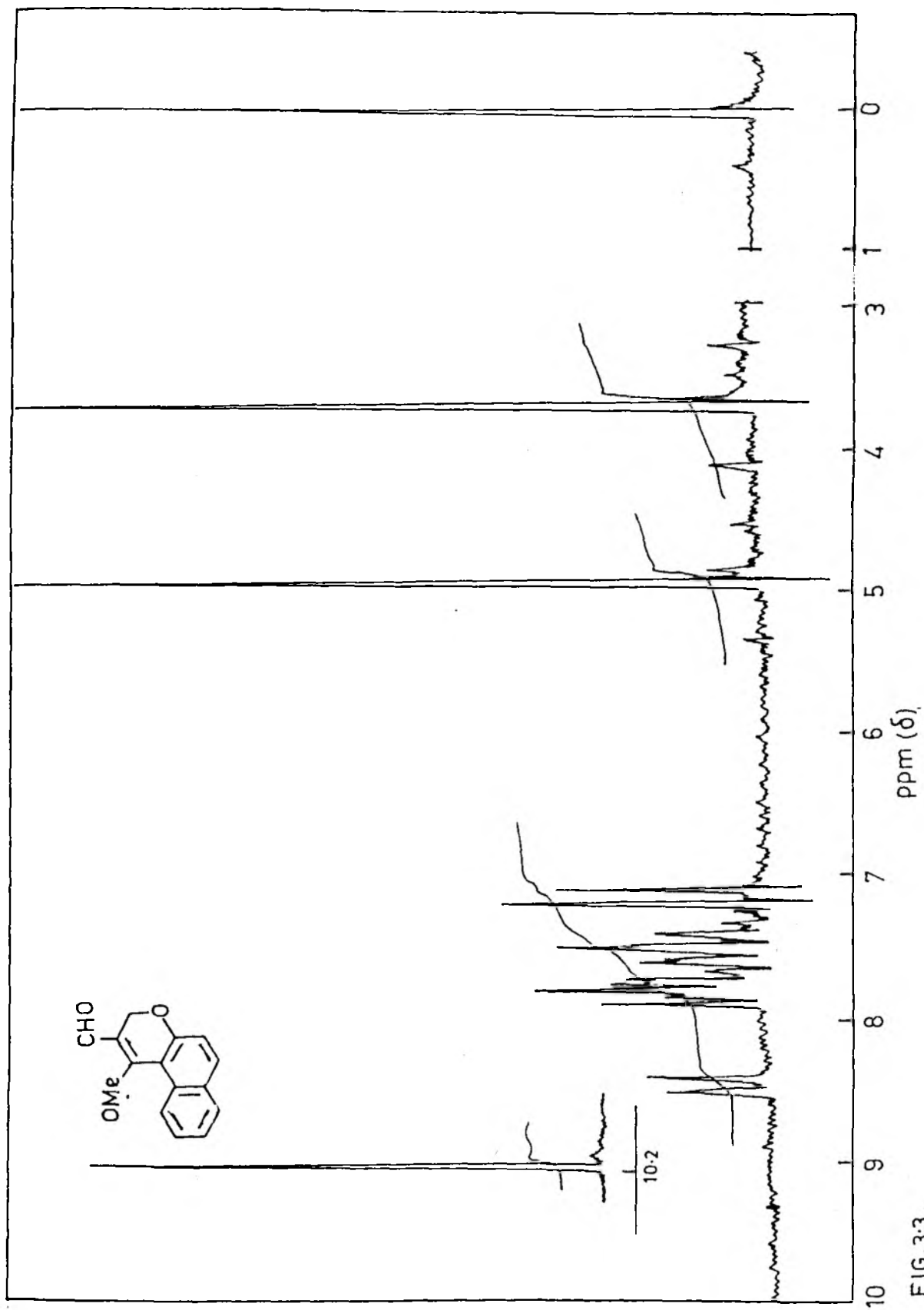


FIG. 3.3.

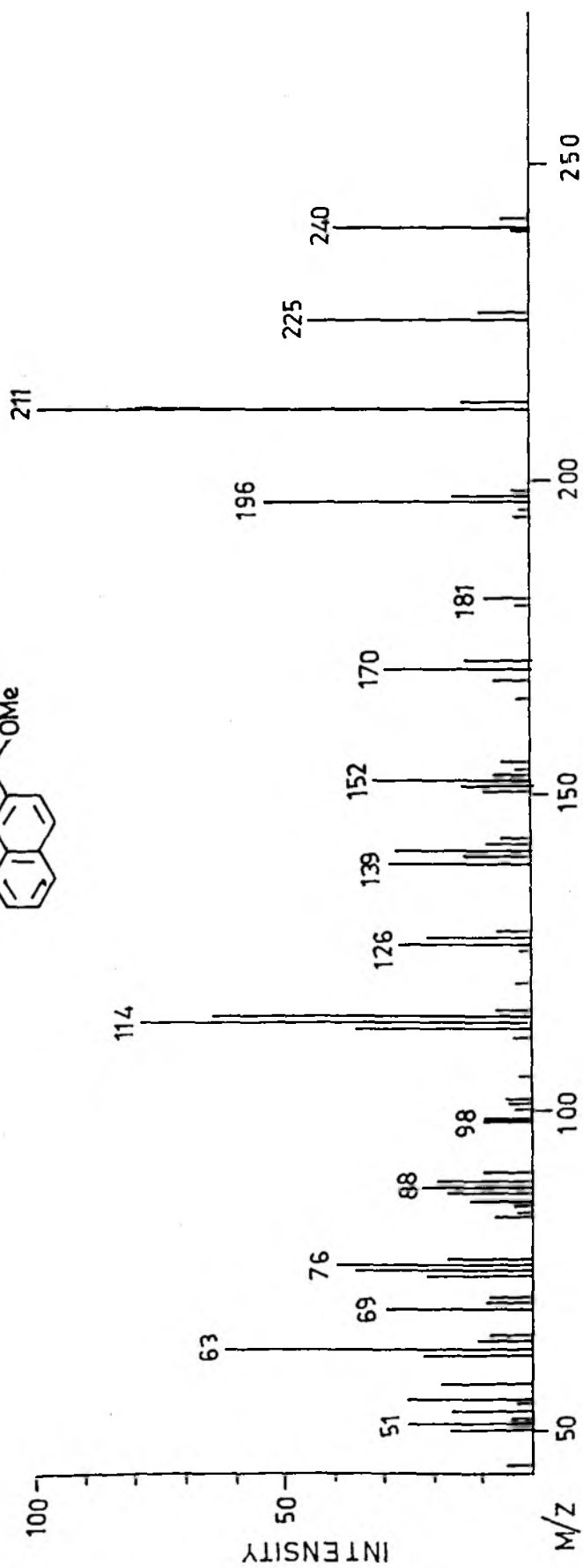
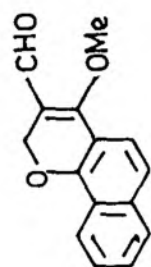
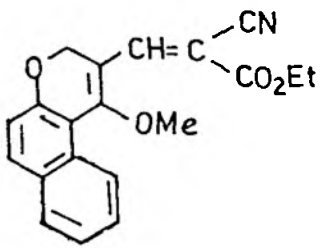


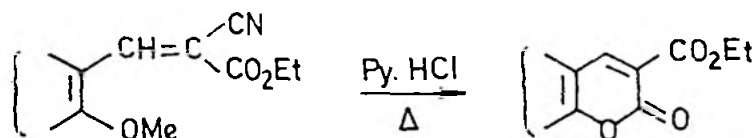
FIG. 3-4.

The absence of peaks at 1640-1650 ($-\text{CHO}$) and appearance of peaks at 1720 cm^{-1} ($-\text{CO}_2\text{Et}$) and 2200 cm^{-1} ($\text{C}\equiv\text{N}$) indicate the formation of the cyano derivatives. The nmr splitting pattern is also in agreement of the assigned structures.

The ^1H NMR of the compound (L) is given below :

	Position of peaks (δ) ppm	Nature	Proton count	Assignment
 Solvent : CDCl_3 Fig. 38	1.35	t	3H	$-\text{OCH}_2-\text{CH}_3$
	3.65	s	3H	$-\text{OCH}_3$
	4.35	q	2H	$-\text{OCH}_2\text{CH}_3$
	5.4	s	2H	$-\text{OCH}_2$
	7.2	d	1H	Aromatic
	7.3-8.0	m	4H	Aromatic
	8.4	d	1H	Aromatic
	8.6	s	1H	$-\text{CH}=\text{C}-\text{CN}$ $\quad\quad\quad\text{CO}_2\text{Et}$

The conversion of the nitrile derivatives (XXXXVII-L) to the coumarin derivatives (LI-LIV) were achieved in excellent yield by heating the nitriles with py.HCl under nitrogen atmosphere.



The 3-carbethoxy coumarin derivatives absorb at $1740-1767\text{ cm}^{-1}$ characteristic of γ -pyranone carbonyl groups and $1700-1715\text{ cm}^{-1}$ for ester groups. The nmr splitting pattern is also in agreement with the assigned structures.

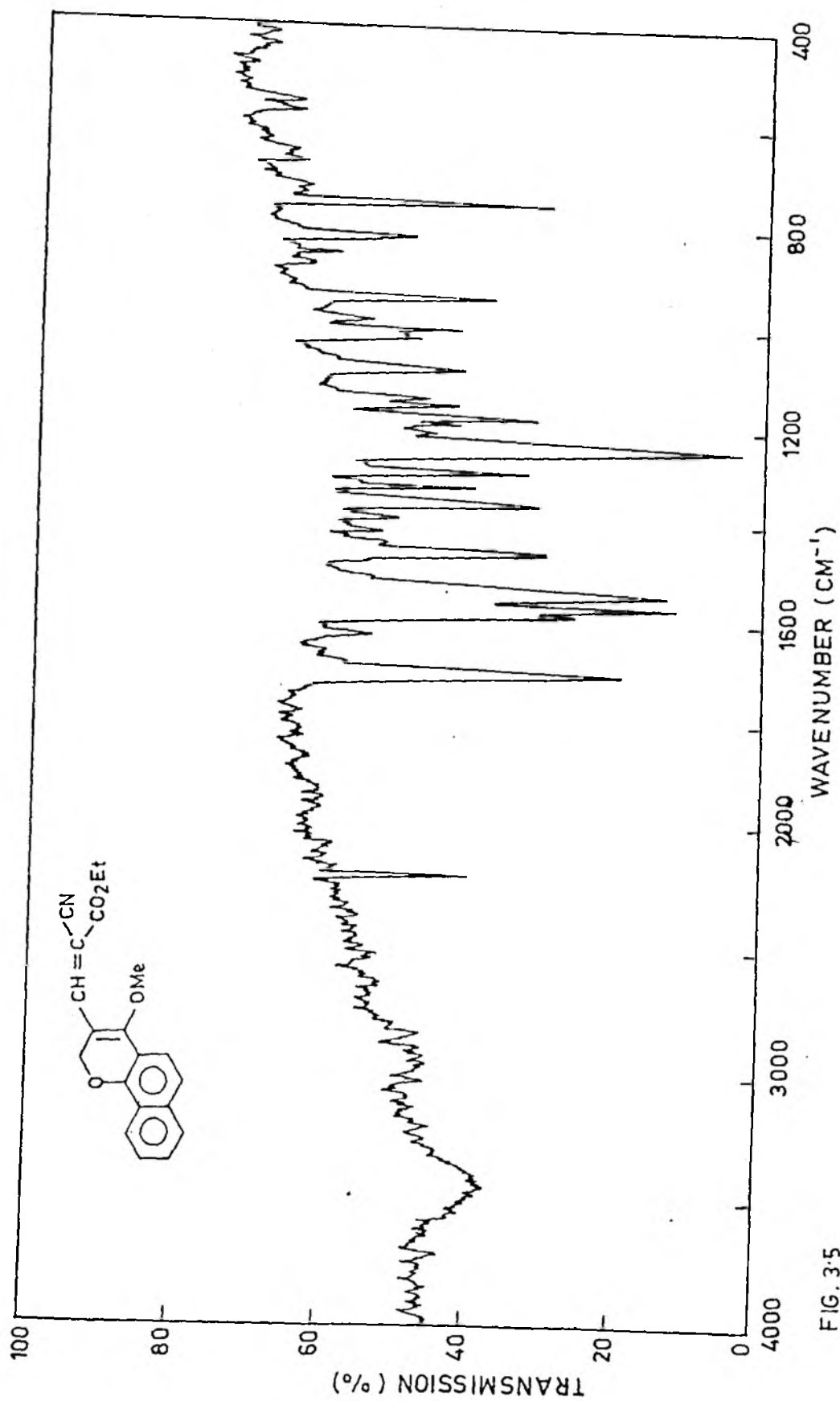


FIG. 3.5

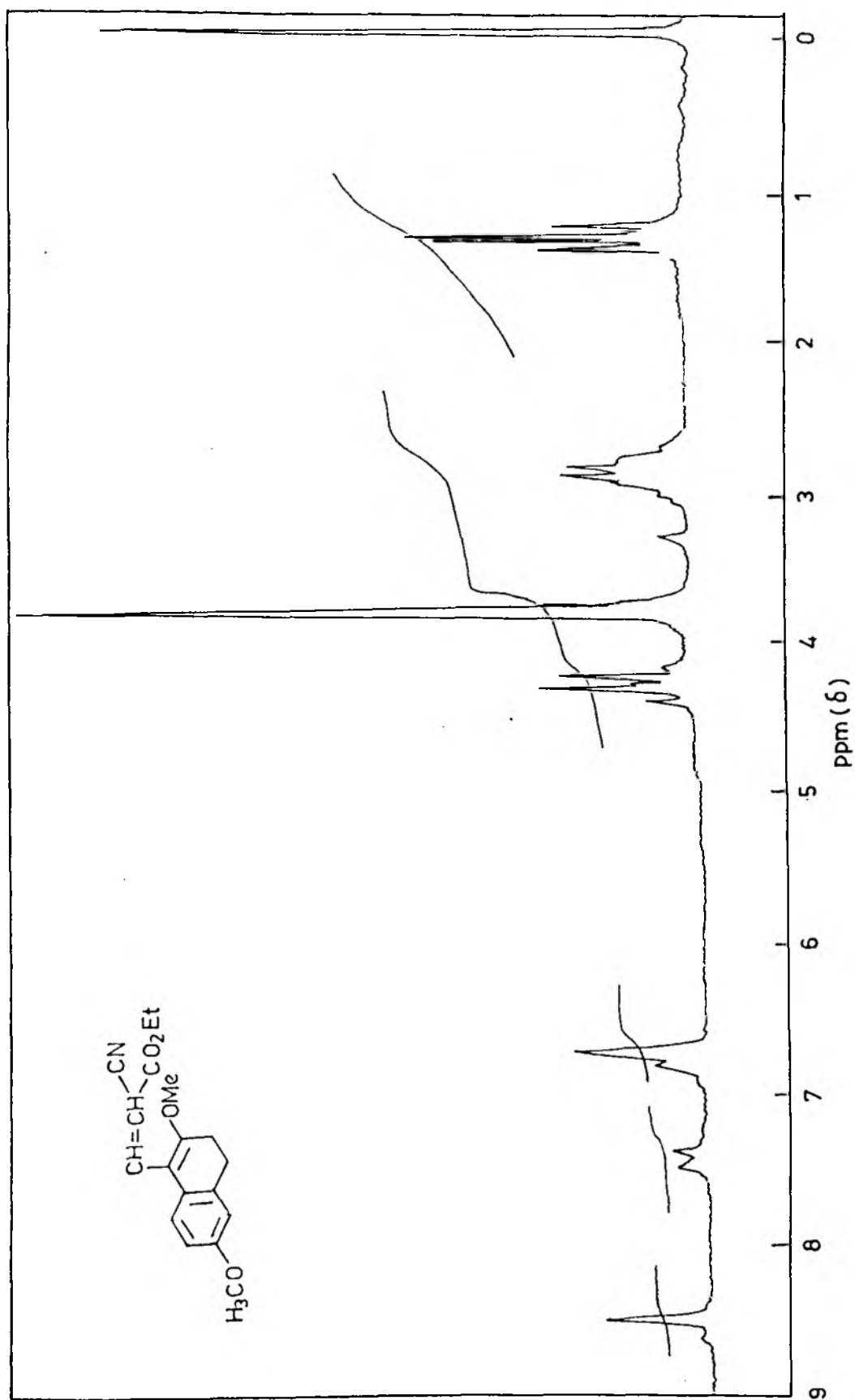


FIG. 3-6

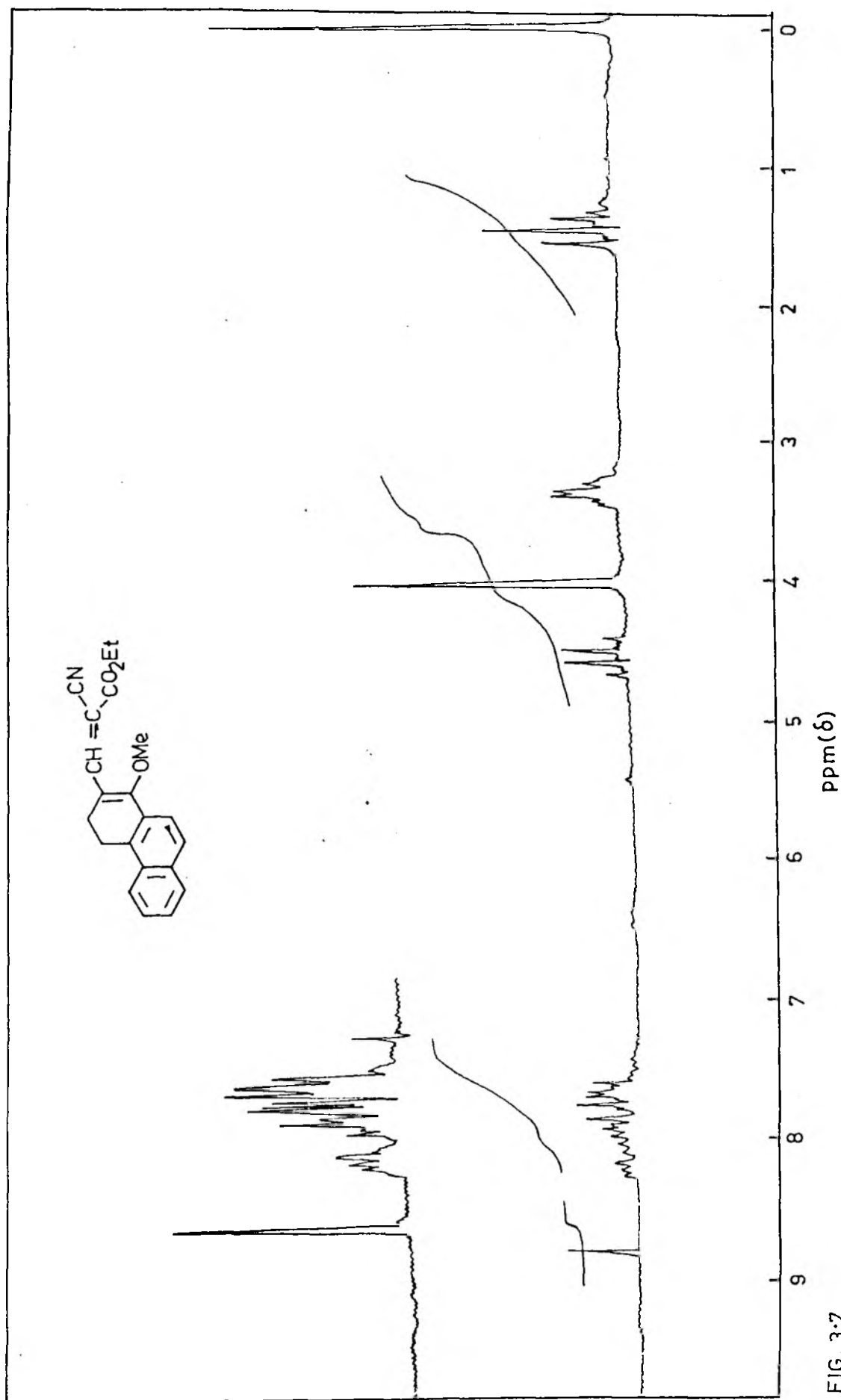
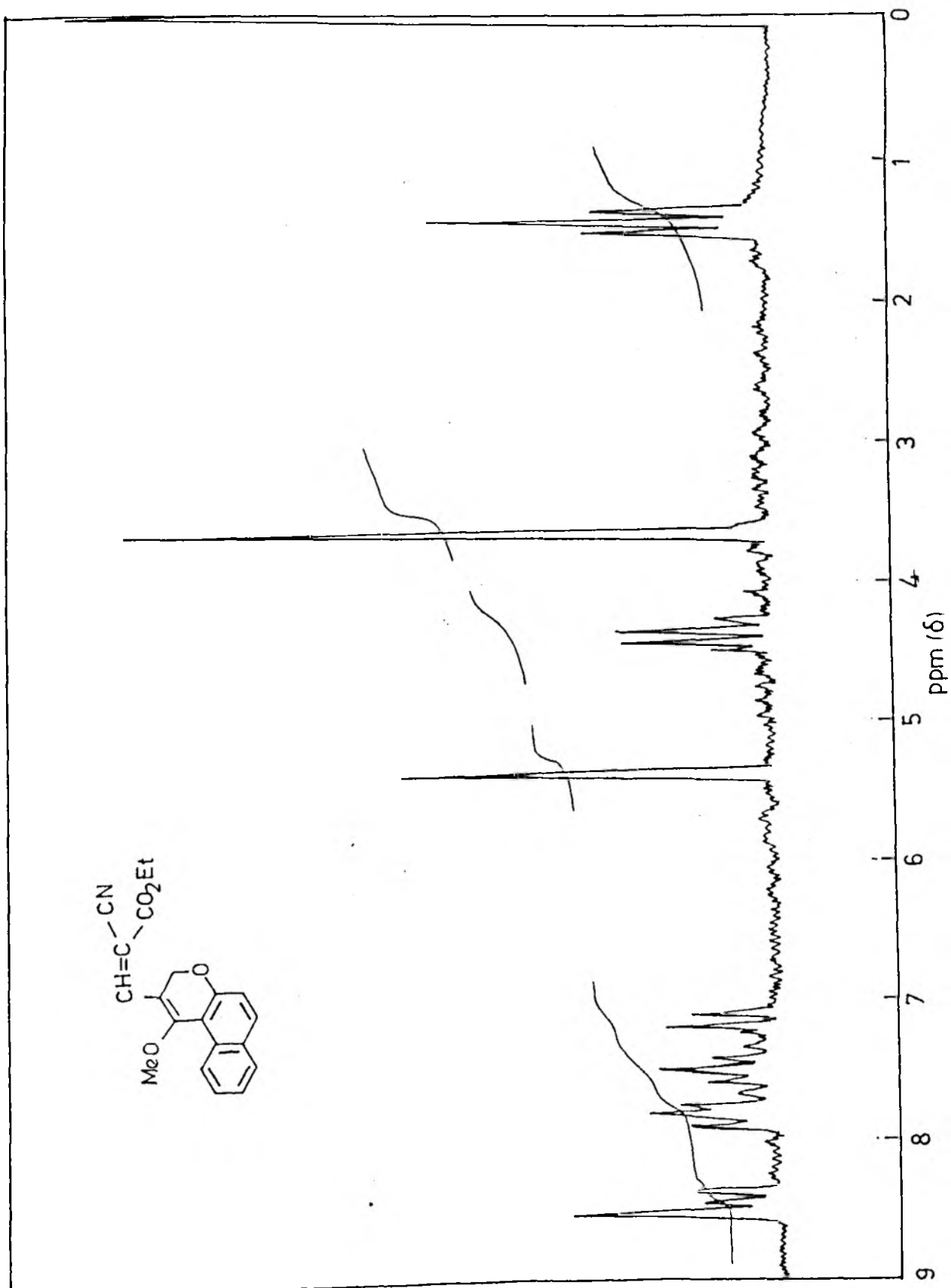
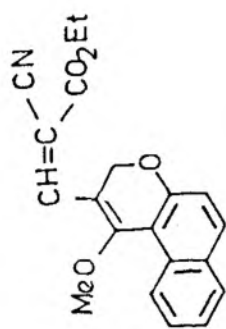


FIG. 3-7.



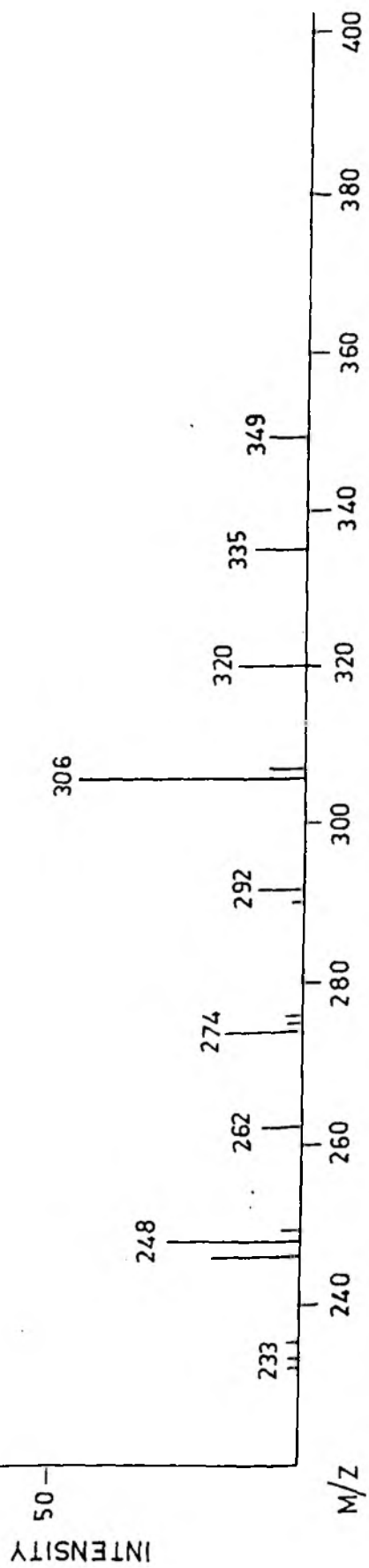
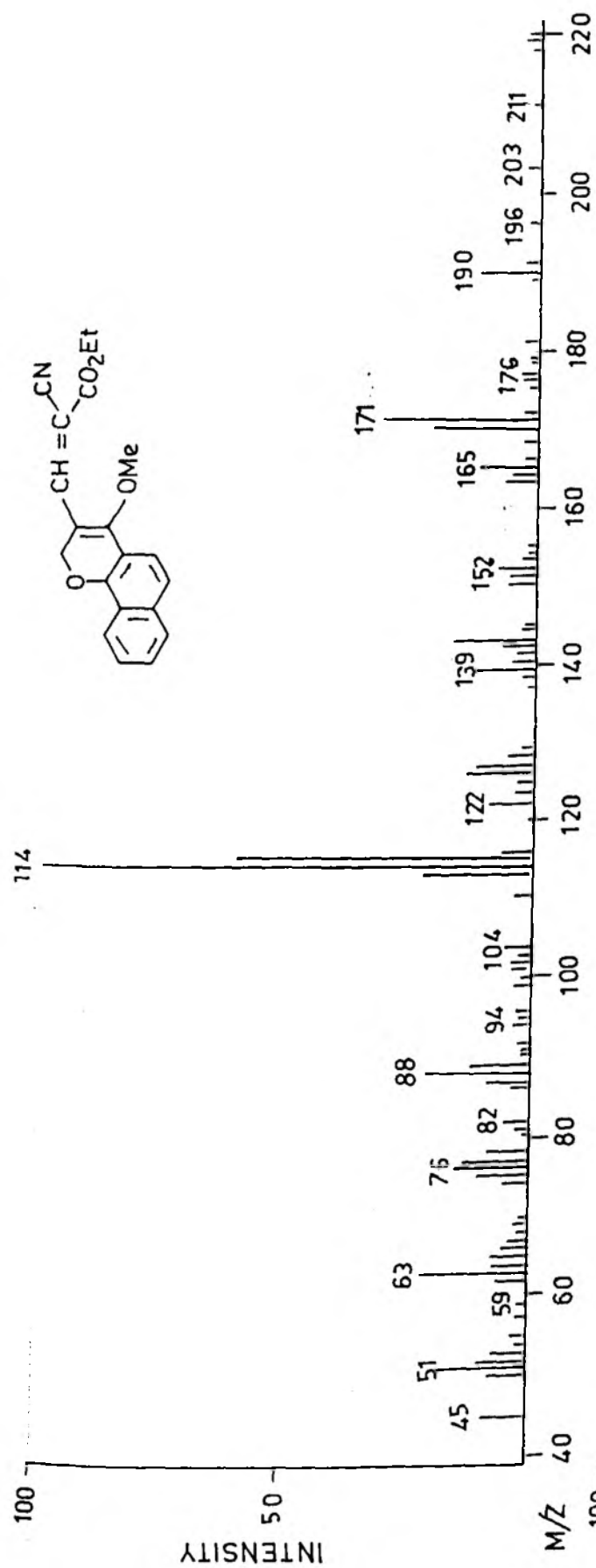


FIG. 3-9

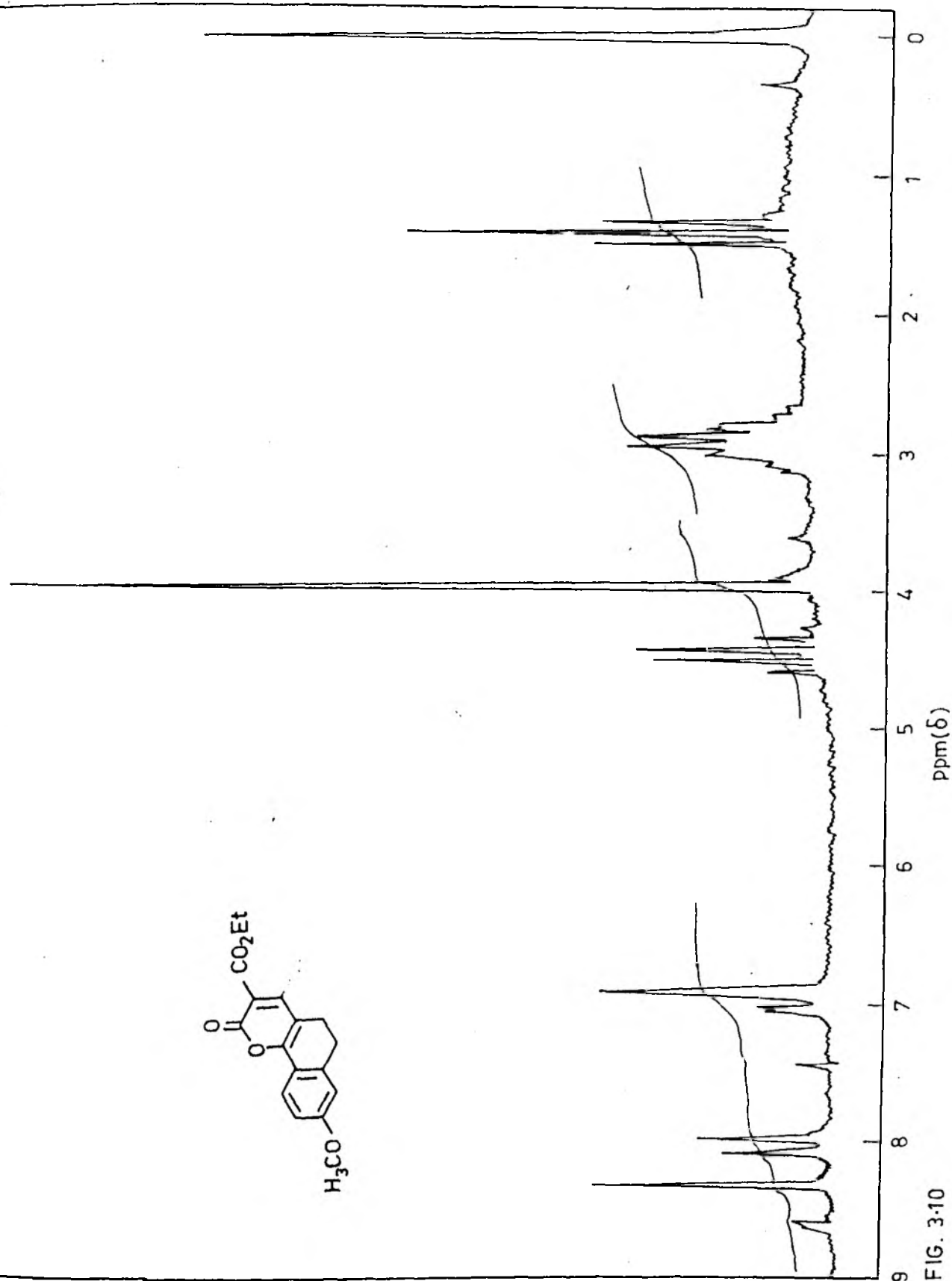
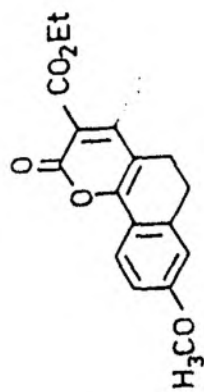
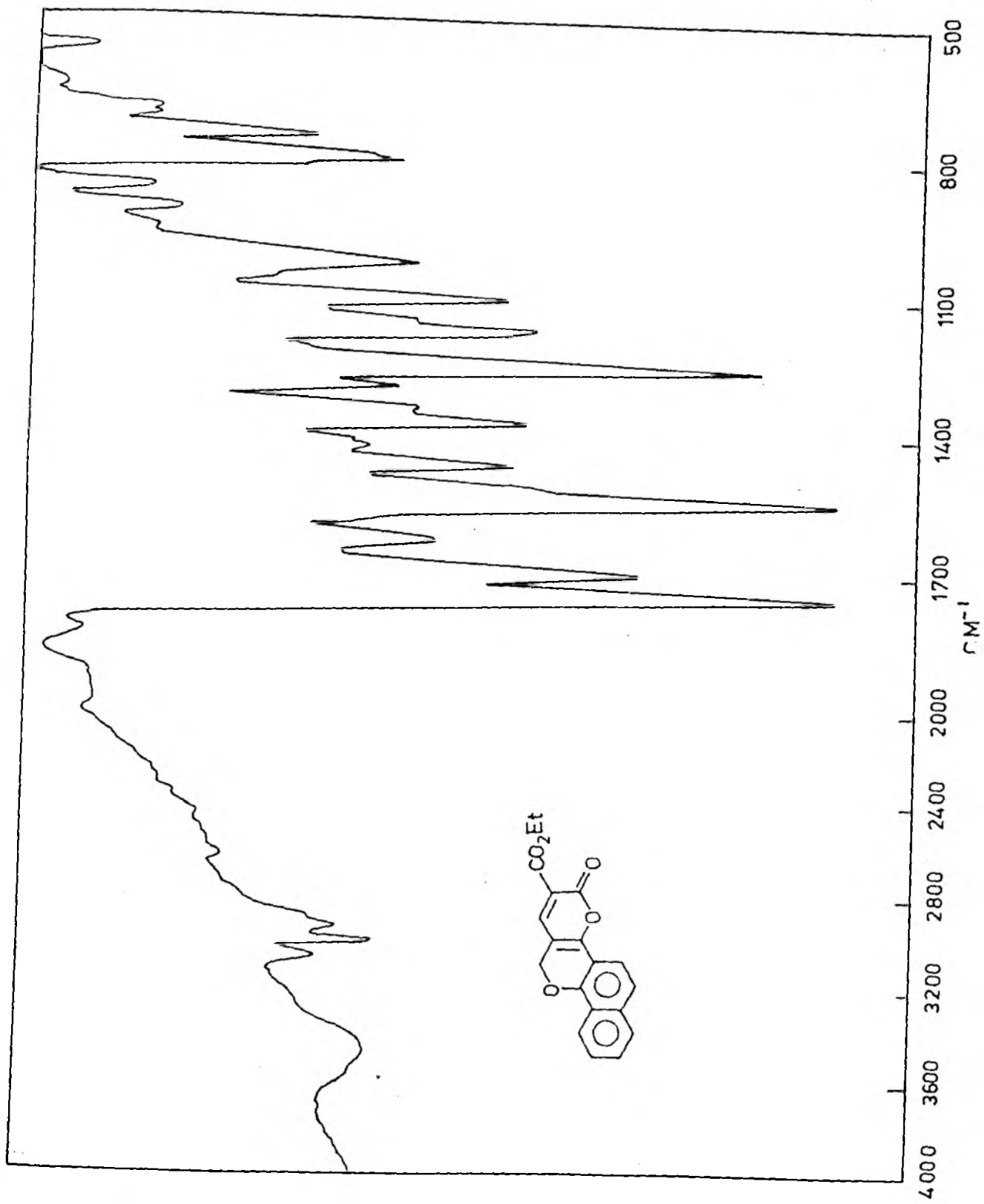


FIG. 3-10

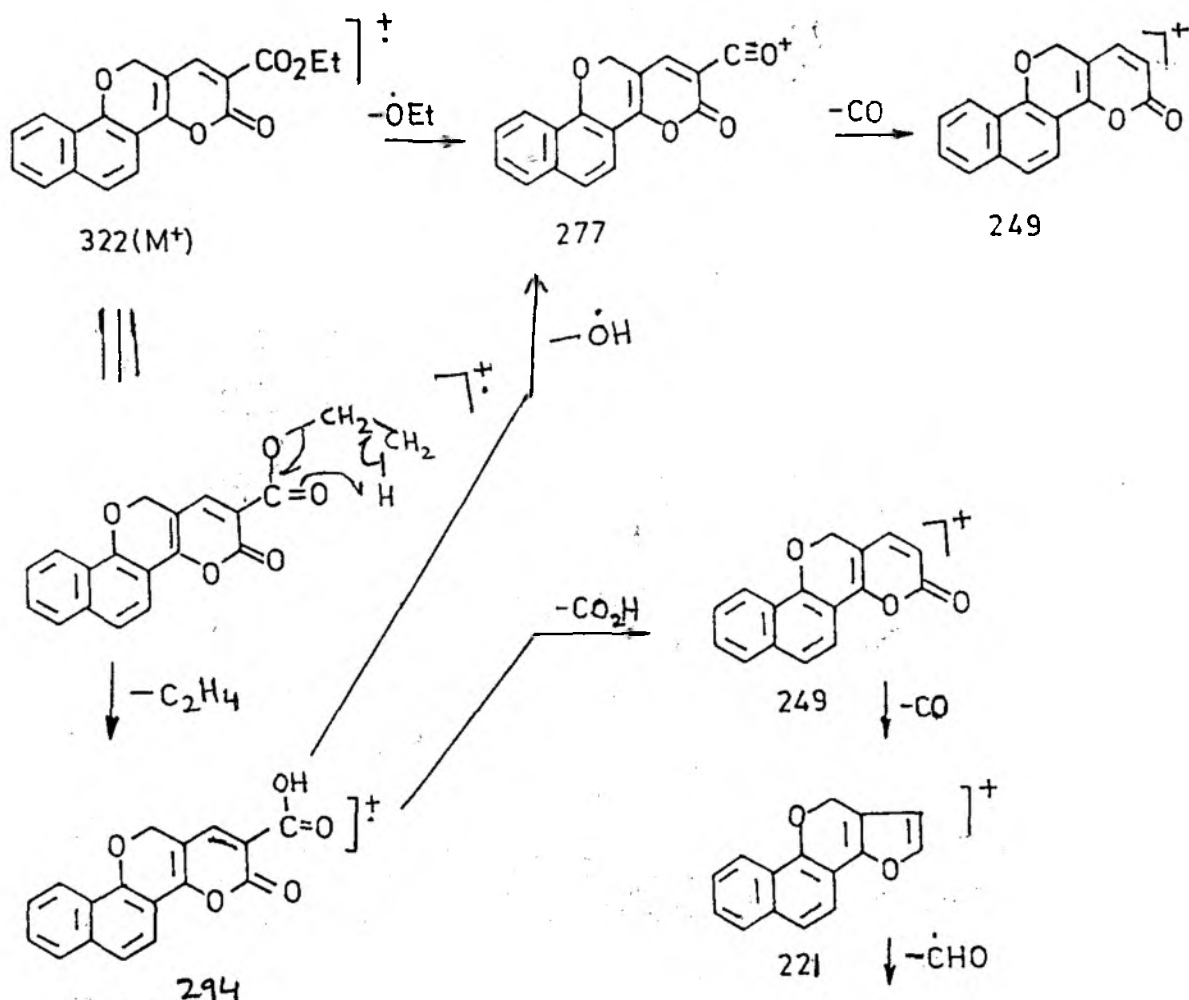


The ^1H NMR of the compound (LIII) is given below :

	Position of peaks (δ) ppm	Nature	Proton count	Assignment
	1.4	t	3H	$-\text{OCH}_2-\text{CH}_3$
	4.2	q	2H	$-\text{OCH}_2-\text{CH}_3$
	5.35	s	2H	$-\text{OCH}_3$
	7.4-7.9	m	5H	Aromatic
Solvent : CDCl_3	8.08-8.35	m	2H	Aromatic

Fig. 3-12

Mass Spectra Explanation of the compound (LIII) :



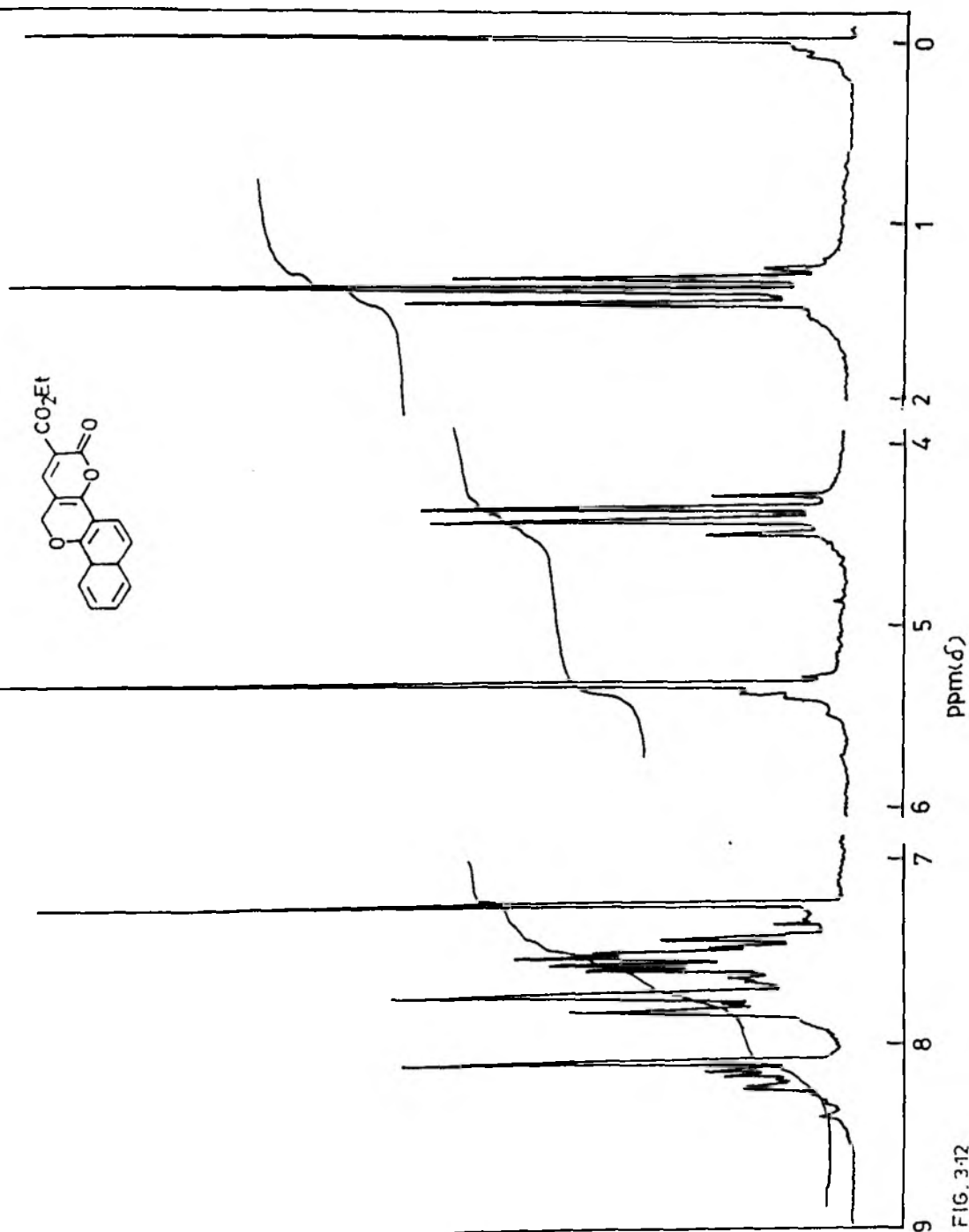
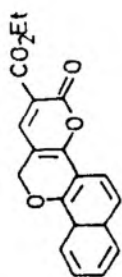


FIG. 3-12



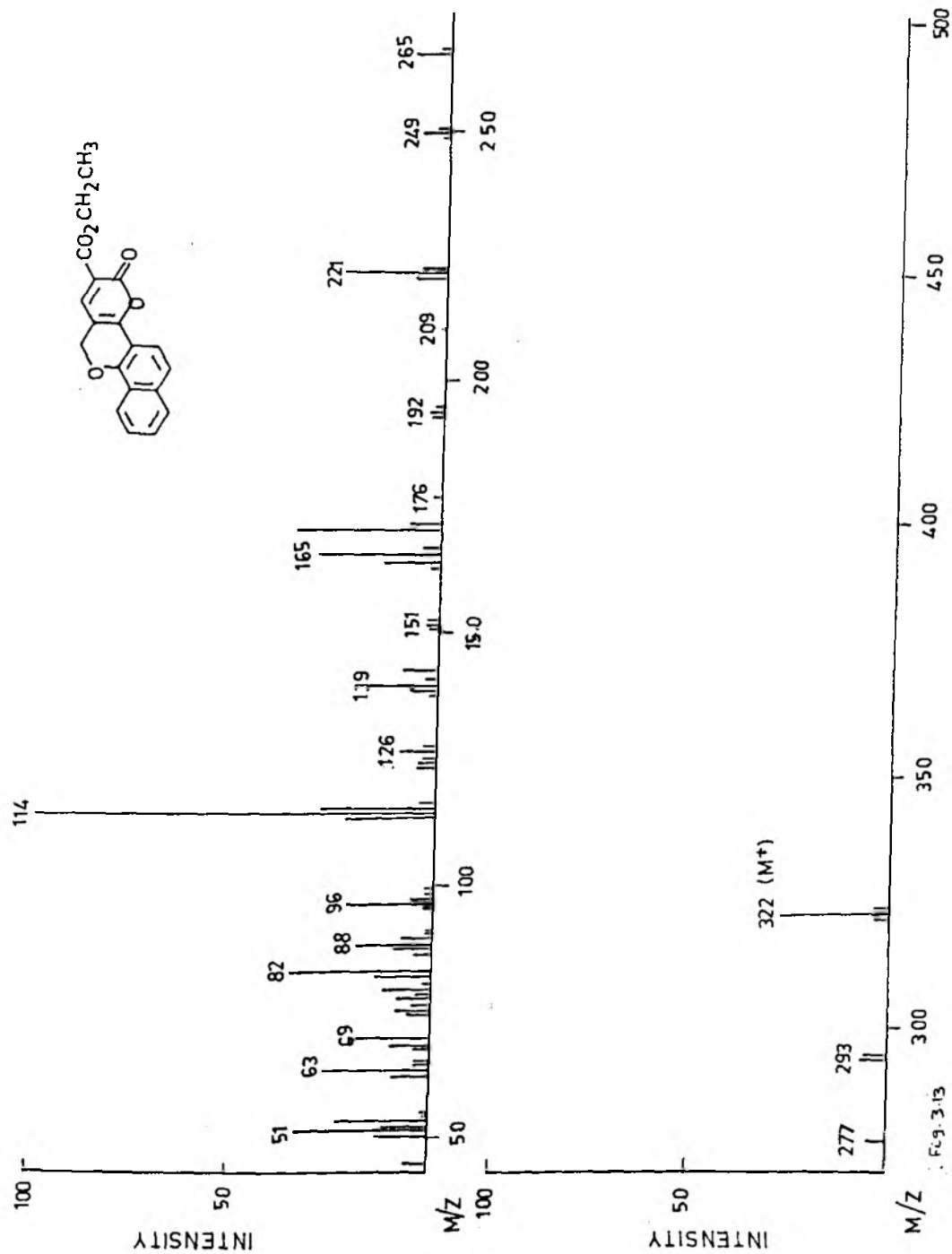
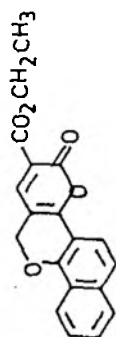


Fig. 3-13

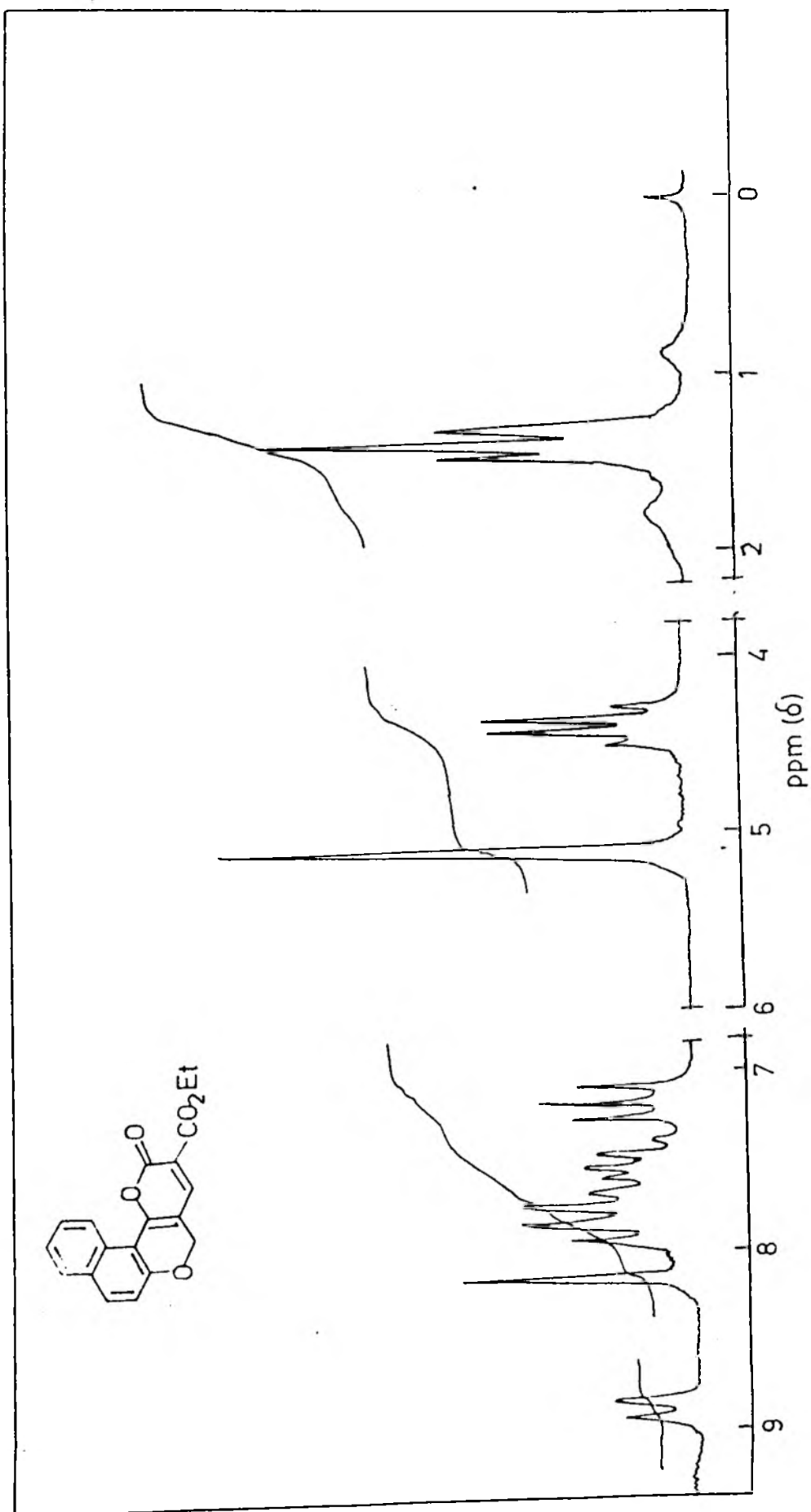


FIG. 3-14

EXPERIMENTAL

Preparation of methoxy aldehyde derivatives (XXXXIII-XXXXVI)

1,6-Dimethoxy-2-formyl-3,4-dihydronaphthalene (XXXXIII) :

6-Methoxy-1-chloro-2-formyl-3,4-dihydronaphthalene (XXXIX) (2 gm, 9 m mol) was added to a solution of sodium methoxide (0.24 Na, 10.4 m mol/40 ml dry methanol) and the contents were refluxed on a water bath for 2 hr. Methanol was evaporated and the mixture cooled. Ice water was added. The organic oily layer was extracted with ether, dried (Na_2SO_4). Removal of solvent afforded viscous oil which was distilled under reduced pressure to get 1.5 gm of (XXXXIII) (64.5%) as a light yellow liquid, b.p. $110^\circ/10$ mm.

IR (KBr) ν_{max} : 1610, 1640 cm^{-1} .

^1H NMR (CDCl_3) δ : 2.35 (t,2H), 2.8 (t,2H), 3.85 (s,6H), 6.7 (s,1H), 6.75 (d,1H), 7.45 (d,1H), 10.2 (s,1H) ppm.

1-Methoxy-2-formyl-3,4-dihydrophenanthrene (XXXXIV) :

5 m mol of metallic sodium was dissolved in 40 ml of anhydrous methanol and chloroaldehyde (XXXX) (1 gm, 4 m mol) was added to it. The mixture was refluxed for 2 hrs. After usual work up (as described above) it afforded the methoxy aldehyde (XXXXIV) as a yellow solid. Yield - 0.8 gm (88.8%), m.p. $50-52^\circ\text{C}$ (ether). IR (KBr) ν_{max} : 1610, 1640 cm^{-1} . ^1H NMR (CDCl_3) δ : 2.4 (t,2H), 2.9 (t,2H), 3.6 (s,3H), 7.0-8.4 (m, 6H), 10.25 (s,1H) ppm.

1-Methoxy-2-formyl-4-oxa-3,4-dihydrophenanthrene (XXXXV) :

Sodium (250 mg, 11 m mol) was dissolved in 100 ml of dry methanol and the chloroaldehyde (XXXXI) (2.45 gm, 10 m mol) was added in one lot. The mixture was refluxed for 2 hrs. Excess methanol was evaporated off, diluted with ice water and extracted with ether. After usual work up it afforded the methoxyaldehyde (XXXXV) as a yellow solid. Yield 1.8 gm (75%), m.p. 107-108°C (ether).

IR (KBr) $\nu_{\max}$: 1610, 1640 cm^{-1} .

^1H NMR (CDCl_3) δ : 4.1 (s, 3 H), 5.2 (s, 2H), 7.4-7.7 (m, 4H), 7.8 (d, 1H), 8.2 (d, 1H), 10.2 (s, 1H) ppm.

MS (m/z) : 240(M^+), 225 (M-15), 211, 196, 181, 170, 114.

Analysis :	C	H
Found :	74.8	4.75%
Calculated :	75.0	5.0 %

4-Methoxy-3-formyl-1-oxa-1,2-dihydrophenanthrene (XXXXVI) :

The chloro aldehyde (XXXXII) (1.82 gm, 10 m mol) was added to a solution of sodium methoxide (0.20 gm Na/40 ml methanol) and the contents were refluxed for 2 hrs. Excess methanol was evaporated and the mixture cooled. After usual work up it afforded the methoxy aldehyde (XXXXVI) as yellow viscous oil which was passed through a neutral alumina column (pet. ether, 40-60°C) to get light yellow solid. Yield - 1.2 gm (73%), m.p. 80-85°C.

IR (KBr) $\nu_{\max}$: 1610, 1640 cm^{-1} .

^1H NMR (CDCl_3) δ : 3.7 (s, 3H), 5.0 (s, 2H), 7.15 (d, 1H), 7.3-7.95 (m, 4H), 8.5 (d, 1H), 10.2 (s, 1H) ppm.

Preparation of acrylonitrile derivatives (XXXXVII-L) :

α -Carbethoxy- β -[1,6-dimethoxy 3,4-dihydro-2-naphthyl]acrylonitrile (XXXXVII) :

To a mixture of methoxy aldehyde (XXXXIII) (1.5 gm, 6.88 m mol) and ethyl cyanoacetate (7.2 m mol) in 15-20 ml of ethanol was added few drops of 30% aqueous ethanolic KOH and the mixture was refluxed on water bath for 15-20 min. The resulting deep red solution was filtered, washed well with water and dried to get yellow solid, 1.2 gm (56%) of (XXXXVII), m.p. 130-132°C (ethanol).

IR (KBr) $\lambda_{\max}$: 1610, 1720, 2114 cm^{-1} .

^1H NMR (CDCl_3) δ : 1.3 (t, 3H), 2.85 (t, 2H), 2.95 (t, 2H), 3.85 (s, 6H),
4.3 (q, 2H), 6.75 (s, 1H), 6.8 (d, 1H), 7.45 (d, 1H),
8.5 (s, 1H) ppm.

α -Carbethoxy- β -[1-methoxy-3,4-dihydro-2-phenanthryl]acrylonitrile (XXXXVIII) :

A mixture of methoxy aldehyde (XXXXIV) (0.25 gm, 1.05 m mol), ethyl cyanoacetate (125 mg, 1.10 m mol) and 2-3 drops of 30% ethanolic aqueous KOH in ethanol was refluxed for 15 min. The mixture was cooled to room temperature and ice water was added to it. The mixture was extracted with dichloromethane and washed with water, dried (Na_2SO_4). Solvent evaporated to get yellow viscous mass which was passed through a neutral alumina column (pet. ether, 40-60°C). Further it was recrystallised with pet ether to furnish 240 mg (70.5%) of (XXXXVIII), m.p. 122-125°C (pet-ether).

IR (KBr) $\lambda_{\max}$: 1610, 1720, 2200 cm^{-1} .

^1H NMR (CDCl_3) δ : 1.5 (t, 3H), 3.25–3.55 (m, 4H), 4.0 (s, 3H), 4.55 (q, 2H),
7.5–8.4 (m, 6H), 8.85 (s, 1H) ppm.

**α -Carbethoxy- β -[1-methoxy-4-oxa-3,4-dihydro-2-phenanthryl]acrylonitrile
(XXXXIX) :**

The methoxy aldehyde (XXXXV) (1 gm, 4 m mol) was dissolved in 15 ml of ethanol and to this cyanoacetic ester (520 mg, 4.5 m mol) was added. After this few drops of 30% ethanolic aqueous KOH was added and the mixture was refluxed for 15–25 min. The resulting deep red solution was then cooled and poured in ice water. The solid separated was filtered, washed well with water, dried to get 1.15 gm (82.4%) of (XXXXIX) as a deep red solid. m.p. 140–141°C (ethanol).

IR (KBr) $\lambda_{\max}$: 1615, 1700, 2200 cm^{-1} .

^1H NMR (CDCl_3) : 1.4 (t, 3H), 3.9 (s, 3H), 4.3 (q, 2H), 5.6 (s, 2H),
7.5–7.6 (m, 4H), 7.8 (d, 1H J = 8.5 Hz), 8.2 (d, 1H
 J = 7.5 Hz), 8.40 (d, 1H J = 8.5 Hz) ppm.

MS (m/z) : 335(M^+) 320, 306, 274, 248, 171, 114.

Analysis :	C	H	N	
Found :	71.4	5.8	3.9	%
Calculated :	71.64	5.07	4.18	%
(C ₂₀ H ₁₇ NO ₄)				

α -carbethoxy- β -[4-methoxy-1-oxa-1,2-dihydro-3-phenanthryl]acrylonitrile (L)

A mixture of methoxy aldehyde derivative (XXXXVI) (1 gm, 4 m mol) ethyl cyanoacetate (520 mg, 4.5 m mol) and 2-3 drops of 30% ethanolic aqueous KOH in 15-20 ml of ethanol was refluxed for 15-20 min. After usual work up (as given above) afforded 850 mg (60.9%) of (L) as a yellow solid. m.p. 166-167°C (ethanol).

IR (KBr) $\lambda_{\max}$: 1610, 1720, 2200 cm^{-1} .

^1H NMR (CDCl_3) δ : 1.35 (t, 3H), 3.65 (s, 3H), 4.35 (q, 2H), 5.4 (s, 2H),
7.2 (d, 1H), 7.3-8.0 (m, 4H), 8.4 (d, 1H), 8.6 (s, 1H)
ppm.

Preparation of Polycyclic Coumarin derivatives (LI-LIV)

3-Carbethoxy-8-methoxy-5,6-dihydronaphtho[1,2-b]pyran-2-one (LI) :

165 mg (0.53 m mol) of the nitrile (XXXXVII) was heated with 400 mg of dry pyridine hydrochloride for 10 min. The mixture was cooled and poured into dil.HCl. The yellow solid separated was filtered, washed with dil.HCl followed by water several times and dried to get yellow solid 100 mg (63%) of (LI), m.p. 140-141°C (ethanol).

IR (KBr) $\lambda_{\max}$: 1620, 1710, 1750 cm^{-1} .

^1H NMR (CDCl_3) : 1.4 (t, 3H), 2.7 (t, 2H), 3.0 (t, 2H), 3.9 (s, 6H),
4.45 (q, 2H), 6.8 (s, 1H), 7.1 (d, 1H), 8.0 (s, 1H),
8.35 (s, 1H) ppm.

MS (m/z) : 300(M^+), 272 (M-28), 244, 228, 198.

3-Carbethoxy-5,6-dihydrophenanthro [1,2-b]pyran-2-one (LII) :

The nitrile (XXXXVIII) 125 mg (0.37 m mol) was boiled with 600 mg of dry py.HCl for 10 min. After usual work (as mentioned above) afforded 75 mg (83%) of (LII) as a yellow solid. M.P. 176-177°C (ethanol).

IR (KBr) $\lambda_{\max}$: 1620, 1710, 1750 cm^{-1} .

^1H NMR (CDCl_3) : 1.4 (t,3H), 2.92 (t,2H), 3.4 (t,2H), 4.4 (q,2H),
7.4-7.9 (m,4H), 8.1-8.35 (m,2H) ppm.

3-Carbethoxy-6-oxa-5,6-dihydrophenanthro [1,2-b]pyran-2-one (LIII) :

The cyanoderivative (XXXXIX) (0.5 gm, 1.5 m mol) was heated with pyridine hydrochloride (2.5-3.0 gm) for 10-15 min. After cooling to room temperature it was poured into ice cooled dil.HCl. The solid separated was filtered off and washed well with water and dried to get 330 mg (68.75%) of the compound (LIII) as a yellow solid.

M.P. 213-214°C (ethanol).

IR (KBr) $\lambda_{\max}$: 1626, 1697, 1747 cm^{-1} .

^1H NMR (CDCl_3) δ : 1.4 (t,3H), 4.2 (q,2H), 5.35 (s,2H), 7.4-7.9 (m,5H),
8.08-8.35 (m,2H) ppm.

MS (m/z) : 322(M^+), 293, 277, 265, 245, 221, 169, 165, 139, 114.

Analysis : C H

Found : 70.60 4.20 %

Calculated : 70.81 4.35 %

($\text{C}_{19}\text{H}_{14}\text{O}_5$)

3-Carbethoxy-6-oxa-5,6-dihydrophenanthro [4,3-b]pyran-2-one (LIV) :

90 mg (0.26 mmol) of the nitrile derivative (L) was heated with py.HCl (2.5-3.0 gm) for 10-15 min. After usual work up it afforded 72 mg (75%) of the desired product (LIV) as a orange yellow solid which was purified by preparative TLC/ Al_2O_3 (benzene-ethyl acetate), 9:1). IR (KBr) λ_{max} : 1623, 1700, 1767 cm^{-1} .

^1H NMR (CDCl_3) δ : 1.4 (t, 3H), 4.4 (q, 2H), 5.1 (s, 2H), 7.12 (d, 1H), 7.36-8.04 (m, 4H), 8.16 (s, 1H), 8.9 (d, 1H) ppm.

MS (m/z) : 322(M^+), 293, 277, 265, 245.

Analysis :	C	H
Found :	70.65	4.25 %
Calculated :	70.81	4.35 %
(C ₁₉ H ₁₄ O ₅)		



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CHAPTER 4

SYNTHESIS OF SOME POLYCYCLIC ISOXAZOLES

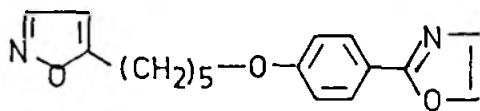
INTRODUCTION

In this chapter we have described the synthesis of some polycyclic isoxazoles from chloroaldehydes via azidoaldehydes by thermal cyclization. The rational in taking up this project was initiated from the utilization of chloroaldehydes in the synthesis of polycyclic isoxazoles. This initiative was further authenticated because of the biological activities of polycyclic isoxazoles. And so, at the beginning we have discussed and reviewed the importance of polycyclic isoxazoles and their available synthetic routes from recent papers.

DISCUSSION

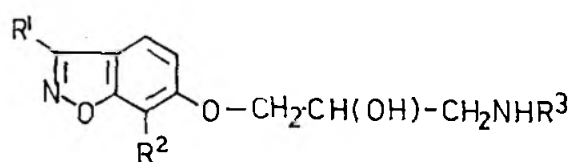
Isoxazoles (Anthranils) are important nitrogen-oxygen containing heterocycles possessing diverse biological activities. Many isoxazole derivatives have been found to possess antiinflammatory¹, analgesic¹, antiviral², antifungal³, herbicidal⁴ and many other biological activities.

G. D. Diana et al⁵ showed that disubstituted phenylisoxazoles (I) are active against picorna virus and also effective in preventing the paralysis in mice infected with coxsackie virus A-9.

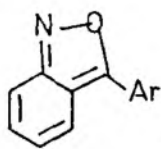


I

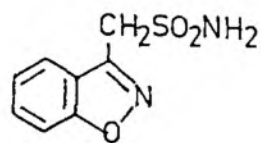
3-Substituted benzisoxazoles (II,III) are very important drugs, and are effective as diuretics, antihypertensive⁶ and antiinflammatory agents⁷. 3-Islamoyl methyl 1,2-benzisoxazole (IV) is a new type of anticonvulsant and neurotoxic agent⁸.



II

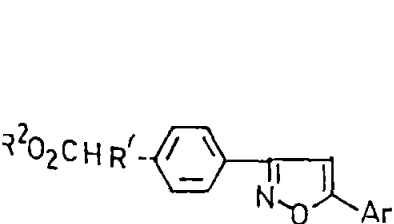


III

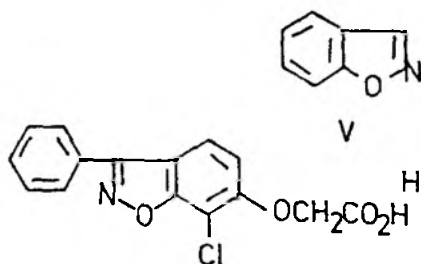


IV

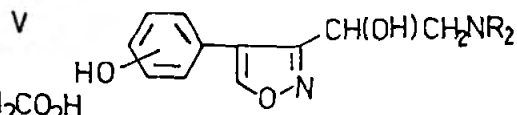
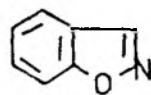
1,2-Benzisoxazole⁹ (V) have appreciable physiological activities. Recently, D. R. Shridhar et al showed that 4-(5-arylisoxazole-3-yl)phenyl propanoic acids and their methyl esters (VI) are antiinflammatory agents¹¹. 1,2-Benzisoxazolyl acetic acid (VII) has diuretic, antihypertensive and uricolytic activities¹¹ whereas the compound (VIII) is effective as antipyretic, analgesic, antiinflammatory and anticonvulsant agents¹².



VI

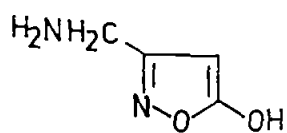


VII



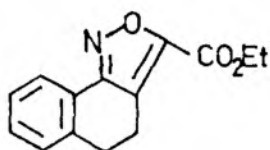
VIII

Muscimol¹³ (3-hydroxy-5-aminomethyl isoxazole) (IX) is a powerful inhibitor of central nervous system, it reinforces the action of narcotics and possess sedative and antienetic properties. Recently, a series of reports have come in Brain Research Bulletin¹⁴ regarding the physiological properties of muscimol.

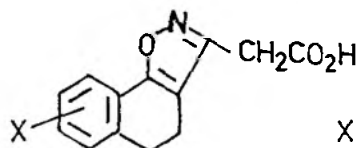


IX

Suzuki Yashushi et al¹⁵ showed that condensed isoxazole derivatives like naphth[1,2-c]isoxazole-3-carboxylate (X) and naphth[2,1-d]isoxazole-3-acetic acid (XI) have analgesic, antipyretic, antiinflammatory, antisecretion and antiulcer properties.



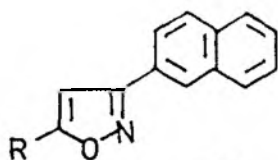
X



XI

X = H, Pr, 6-OMe
Et, PhCH₂, naphthyl

Recently it has been shown by A. A. Regaila Harsan et al¹⁶ that 5-naphthyl isoxazole (XII) is a potential pesticide.

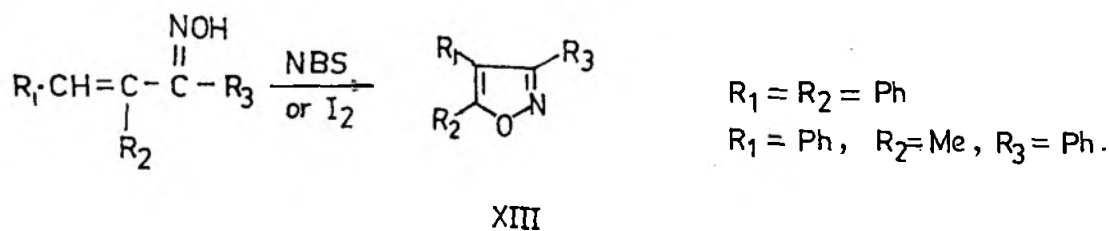


XII

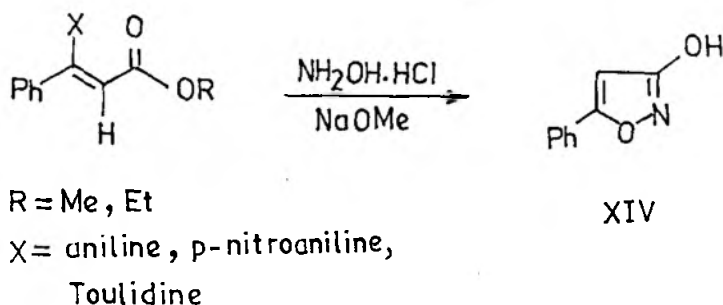
R = H, CH₃

As a consequence of the importance of these types of compounds a number of syntheses on substituted isoxazoles have come out in the last few decades. Most of these synthesis involves the suitably substituted oximes as the precursor of isoxazoles.

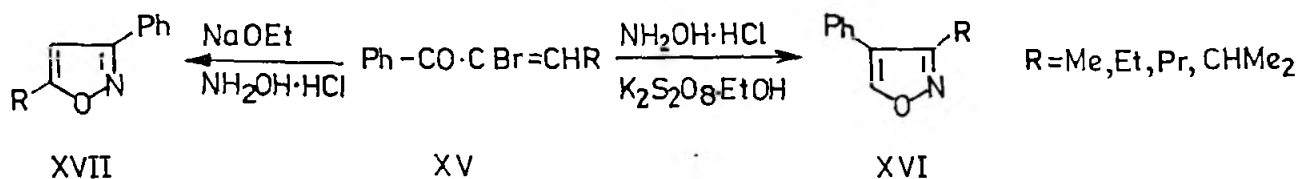
The synthesis of isoxazole derivatives (XIII) was achieved in poor yield by John F. Hansen et al¹⁷ by the reaction of several α, β unsaturated ketoximes with NBS.



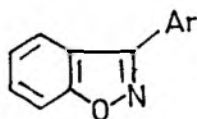
Kashima et al¹⁸ have reported the regioselective synthesis of 3-hydroxy isoxazole derivatives (XIV) from β -amino- α, β -unsaturated esters with NH_2OH HCl in presence of base in 12-40% yield.



Kashima et al¹⁹ have also reported the regioselective synthesis of some 3,4- and 3,5-disubstituted isoxazoles (XVI & XVII). By the reaction of α -bromo enones (XV) with NH_2OH HCl in presence of $\text{K}_2\text{S}_2\text{O}_8$ in EtOH gave (XVI) in only 30-49% yield, whereas XV on reaction with NH_2OH HCl in presence of NaOEt produces the isomeric 3,5-disubstituted isoxazole (XVII) in about 25-30% yield.

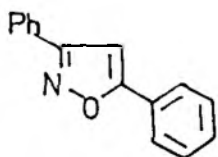


A similar type of synthesis of 3-aryl-1,2-benzisoxazole (XVIII) via oxidative cyclisation was carried out by Russian chemists²⁰. When oxime of o-iodo and o,m p-bromo benzophenones were treated with K₂S₂O₈ in conc. H₂SO₄ isoxazoles were obtained in good yield.



XVIII

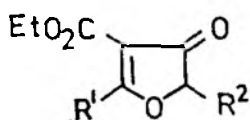
F. G. Bettinetti et al²¹ have reported the synthesis of 3,5-diphenyl isoxazole (XIX) from benzonitrile oxide which was obtained from PhCH=NOH·HCl and PhC≡CNa.



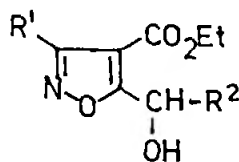
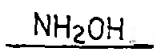
XIX

A very typical synthesis was done by Deshayes Christian et al²² by taking furanones (XX) as a starting material. When ethoxy carbonyl-3(2H)-furanones were refluxed with NH₂OH HCl and NaOAc in EtOH, the isoxazoles

(XXI) was obtained in excellent yields.

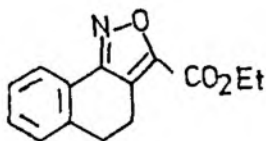


XX



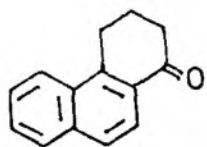
XXI

Naphth[1,2-c]isoxazole-3-carboxylate (XXII) were prepared by Suzuki Yashuji et al¹⁵ by treatment of methyl-1-hydroxyimino-1,2,3,4-tetrahydronaphthalene-2-glyoxalate in EtOH with HCl (g).

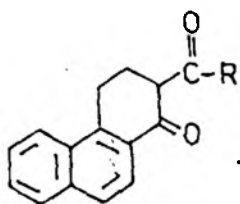
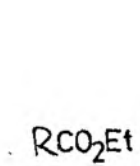


XXII

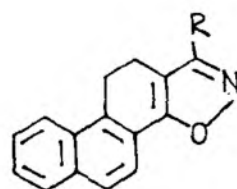
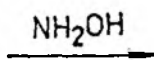
S. Kumar et al²³ have reported the synthesis of 10,11-dihydrophenanthro[2,1-d]isoxazole from dihydrophenanthrenone (XXIII). Treatment of (XXIII) with ethyl formate and diethyl oxalate in the presence of sodium ethoxide produced 2-formyl-1-oxo-1,2,3,4-tetrahydrophenanthrene in 54% yield which on reaction with NH_2OH HCl afforded the isoxazole (XXIV) in 57% yield.



XXIII

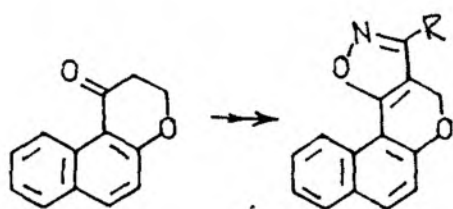


R = H, CO_2Et

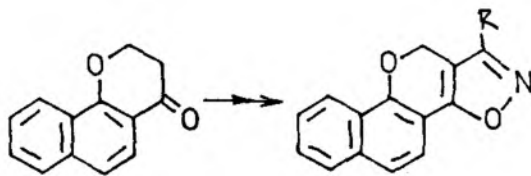


XXIV

A similar type of synthesis has been reported by G. S. Mishra et al ²⁴. They have prepared naphthopyranoisoxazoles (XXV & XXVI) by taking two different ketones following the same sequence of reaction as described above.

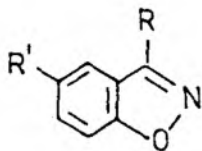


XXVI

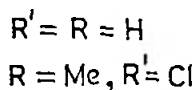


XXV

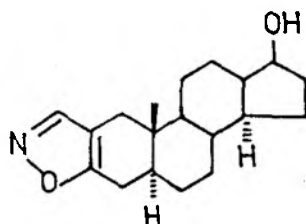
1,2-benzisoxazoles ²⁵ (XXVII) were prepared by thermal decomposition of 2,5-HOR'-C₆H₃CR=NOAc in presence of silica gel or alumina in good yield. These isoxazoles are useful intermediate for pesticides and dyes.



XXVII

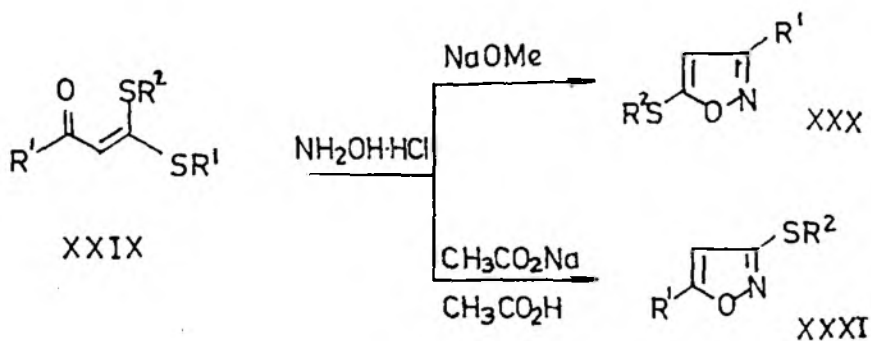


The synthesis and endocrinological activities of steroidal[2,3-d]isoxazoles have been reported by R. O. Clinton et al ²⁶. The reaction of 2-hydroxy methylene androstan 17 β -ol-3-one with NH₂OH HCl in ethanolic solution gave 17 β -hydroxy androstano[2,3-d]isoxazole (XXVIII). Similarly they have prepared two more steroidal [2,3-d]isoxazoles. The compounds proved to be very active when tested for myotrophic and anatrolic activities and in addition they have low androgene activity. Some of them have very potent progestational activity.



XXVIII

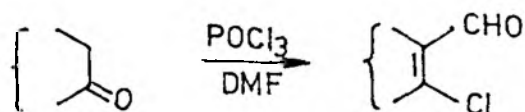
Very recently a regioselective synthesis of isomeric 5-alkyl thio and 3-alkyl thio isoxazoles (XXX-XXXI) has been reported by H. Junjappa et al ²⁷ from acyl ketenedithio acetals (XXIX). Thus the reaction of (XXIX) with hydroxylamine hydrochloride in presence of strong base sodium methoxide (PH9) in refluxing methanol afforded 3-substituted 5-alkyl thio-isoxazoles (XXX) in good yields. When (XXIX) were treated with $\text{NH}_2\text{OH HCl}$ in the presence of sodium acetate acetic acid (PH 2.2) in refluxing ethanol/benzene gave 5-substituted 3-alkyl thio isoxazoles (XXXI) in good yields.



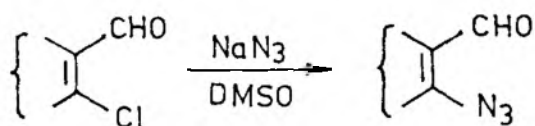
Pursuing our interest in new heterocyclic compounds which might exhibit physiological activities because of their structural resemblance to the above mentioned compounds, we developed a simple and convenient two steps synthesis of several polycyclic isoxazoles (XXXV & XXXVIII) from the various chloroaldehydes [XXXIII(a-c) and XXXVI]. In the above mentioned schemes most of the isoxazoles were synthesised by the classical methods using NH_2OH and also in most of the cases the yields were poor. Our method involves

the direct formation of isoxazole moiety in very good to excellent yields by the thermal cyclisation of azido aldehydes (XXXIV & XXXVII). The synthetic strategy is given in Scheme I.

The chloroaldehydes required for this purpose were prepared from the corresponding ketones by Vilsmeier Haack reaction.



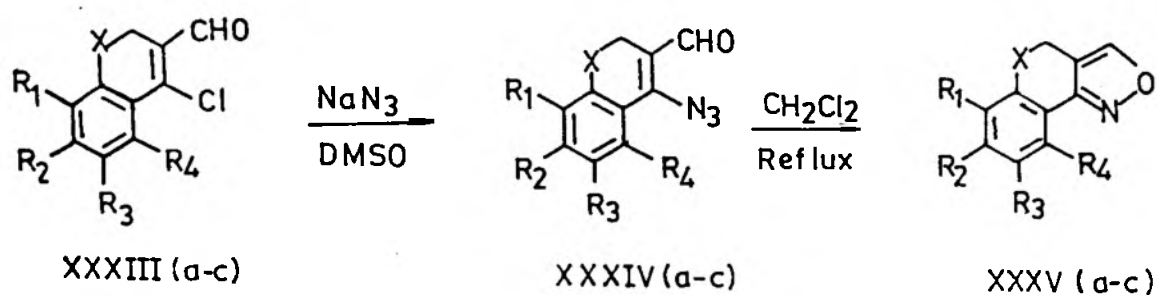
When chloroaldehydes were treated with sodium azide in DMSO gave the azido aldehydes (XXXIV & XXXVII) in 97-68% yields.



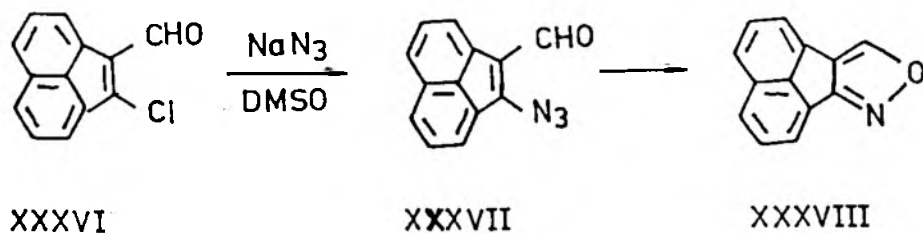
The IR spectra show strong absorption between 2100-2120 and 1650 cm^{-1} for compounds (XXXIV & XXXVII) which are characteristics of N_3 and CHO groups.

The thermal cyclisation of azides into isoxazoles (XXXV & XXXVII) has been achieved in excellent yield by refluxing with dichloromethane.

SCHEME - I



- a. $R_1 = R_2 = R_3 = R_4 = \text{H}$, $X = \text{CH}_2$
- b. $R_1, R_2 = \text{CH}=\text{CH}-\text{CH}=\text{CH}$, $R_3 = R_4 = \text{H}$, $X = \text{CH}_2$
- c. $R_1 = R_2 = \text{H}$, $R_3, R_4 = \text{CH}=\text{CH}-\text{CH}=\text{CH}$, $X = \text{O}$



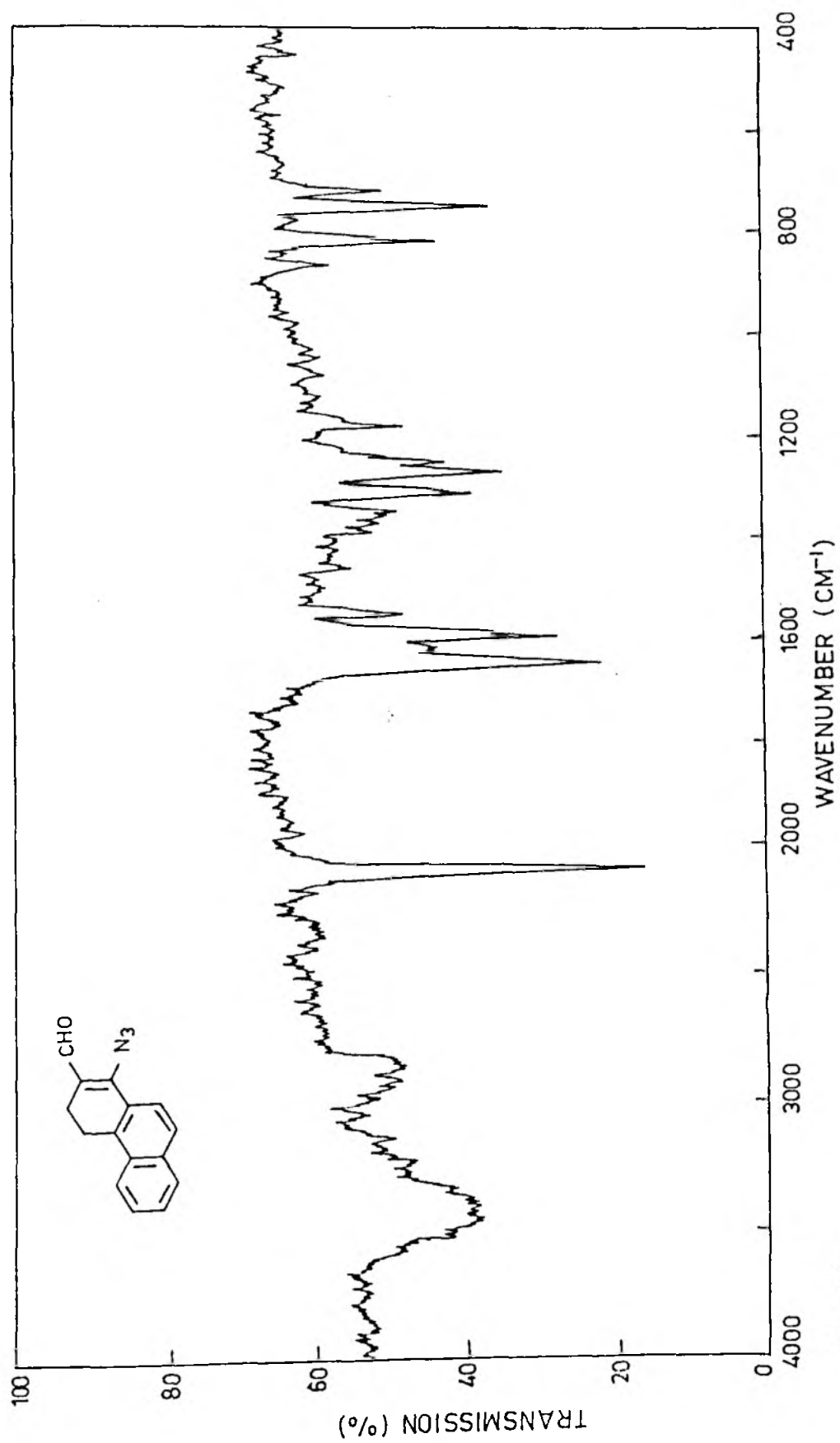


FIG. 4.1.

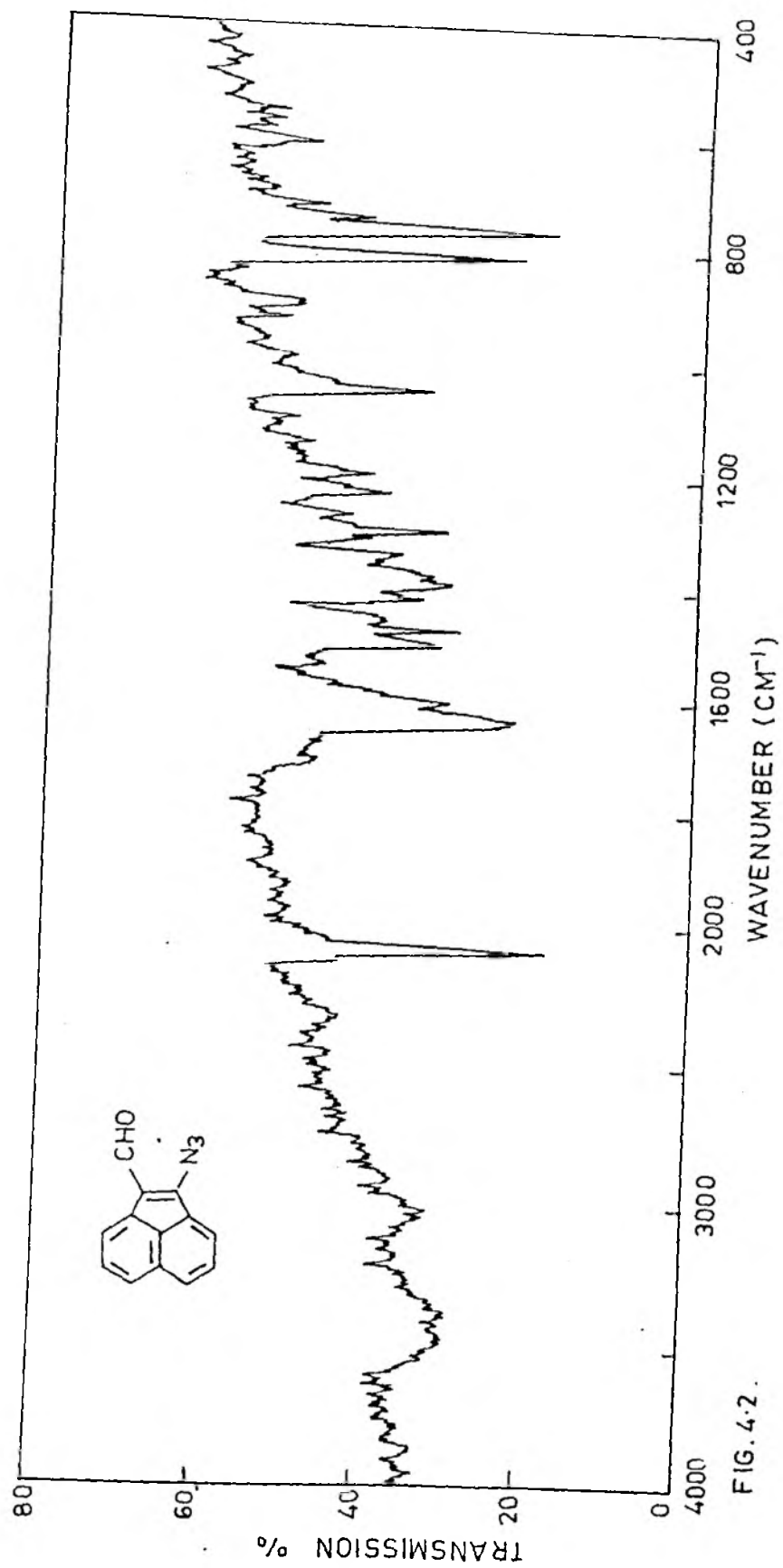
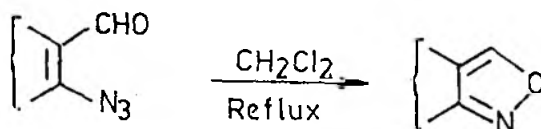
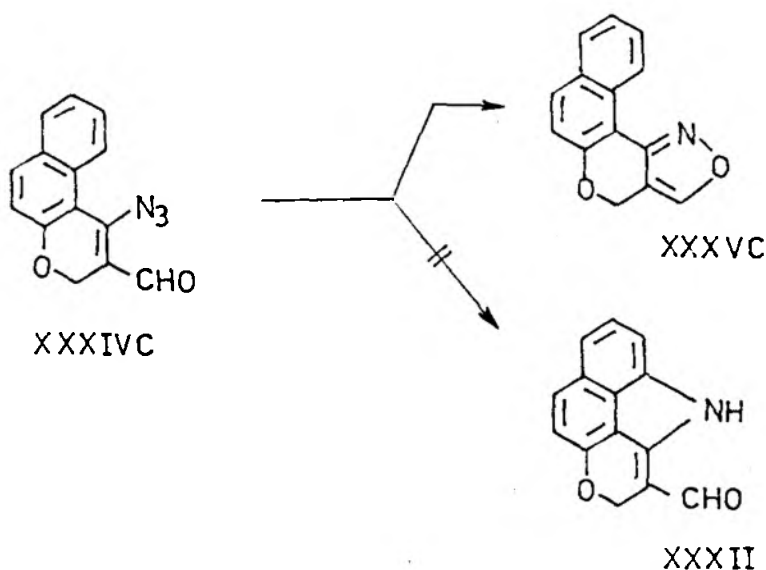


FIG. 4.2.



The spectral data, m.p. and yields have been summarised in Table I. The data are in agreement with the assigned structure.

The interesting feature of the scheme is ready availability of the starting materials, extremely good yield in most of the steps and also the product formed were of high purity. Interestingly, the nitrene generated from azido aldehydes preferred to add aldehydes to form isoxazoles as the sole reaction product instead of inserting to C-H bond of the proximate benzene ring to form pyrrole ring (XXXII). The high yield of isoxazoles demonstrate further that ring opening ring closure²⁸ reaction was not preferred in these azides. Thus, our method is superior in every respect to the previously reported synthesis of isoxazoles.



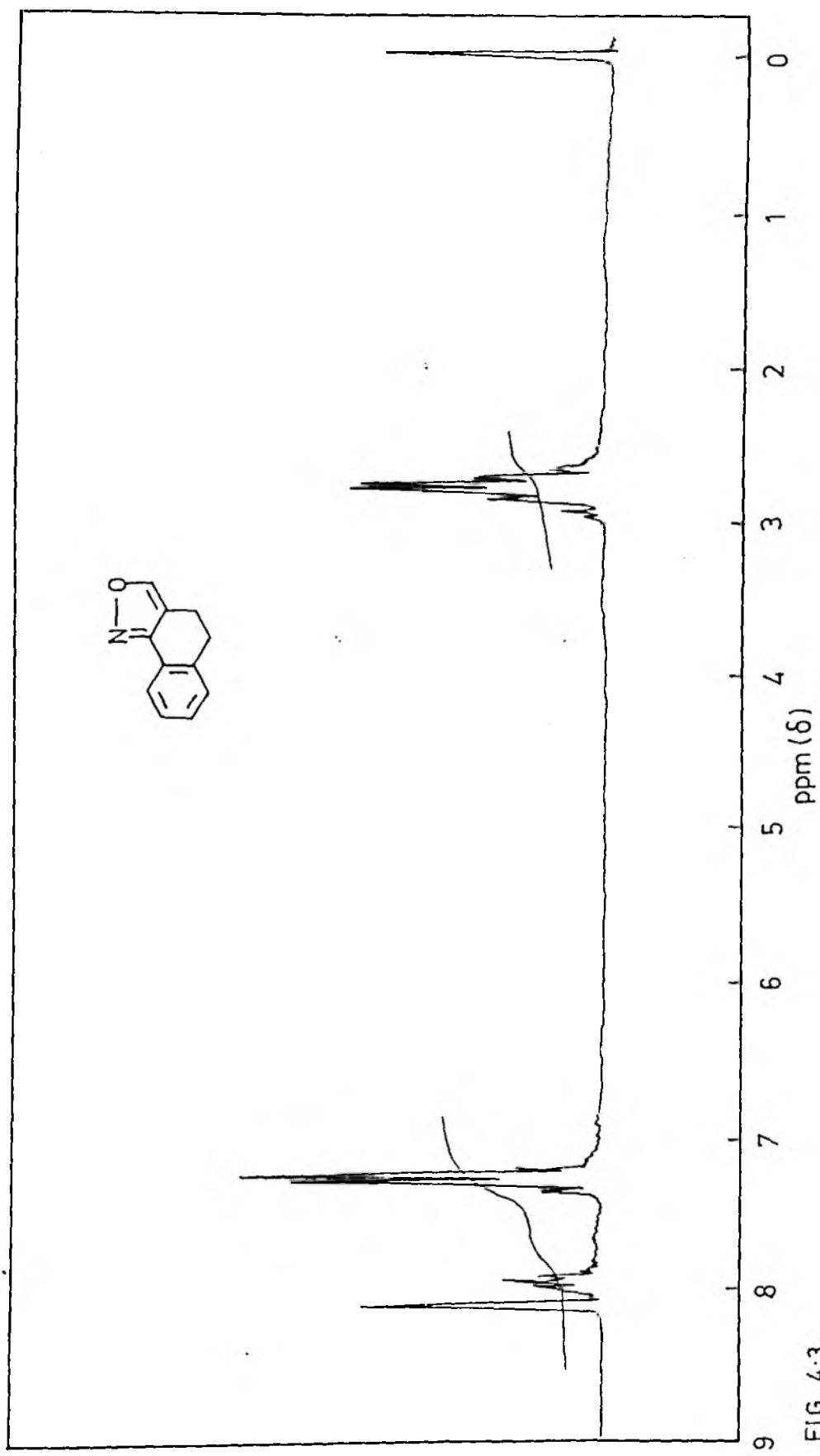


FIG. 4.3.

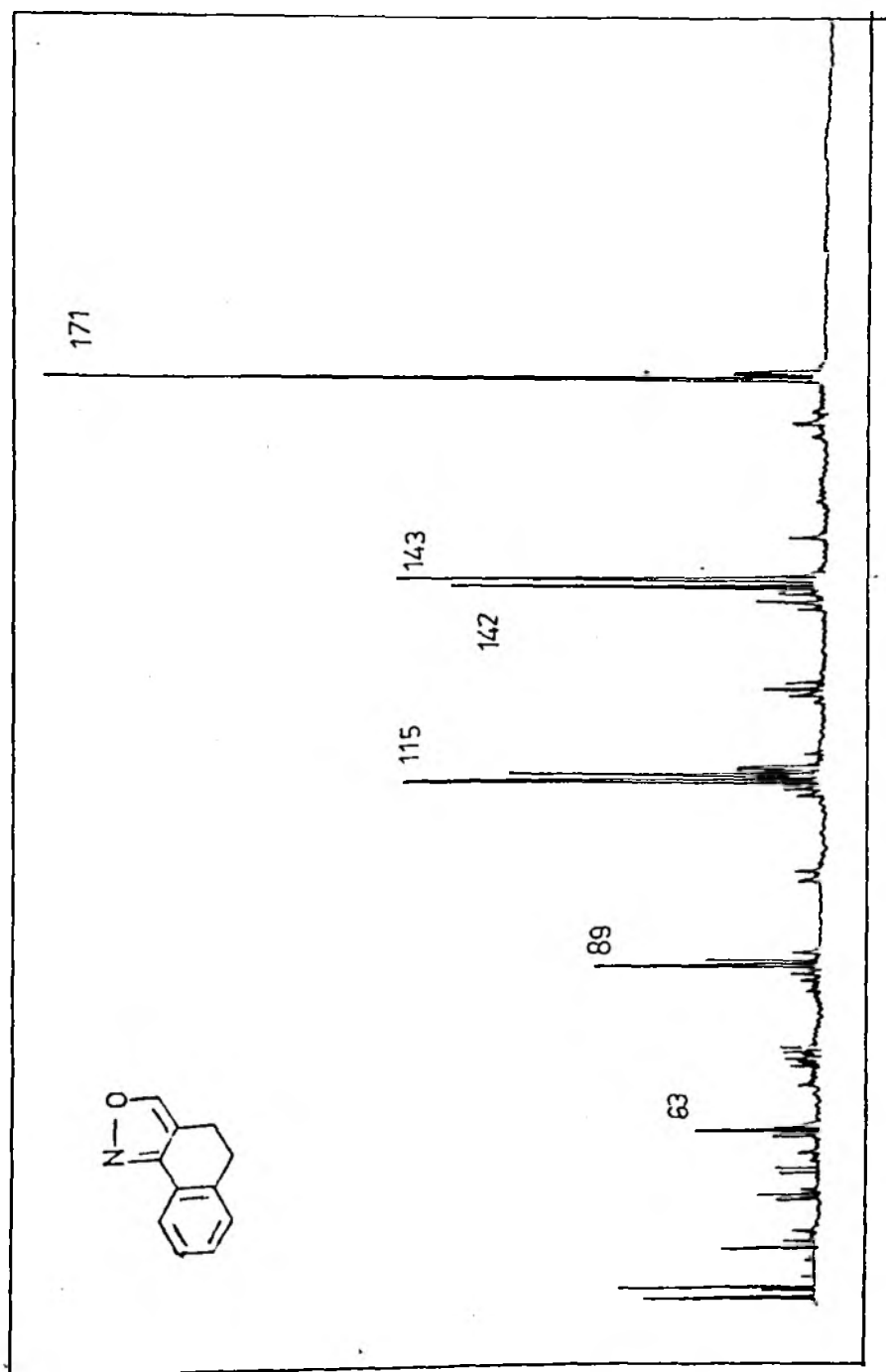


FIG. 4.4.



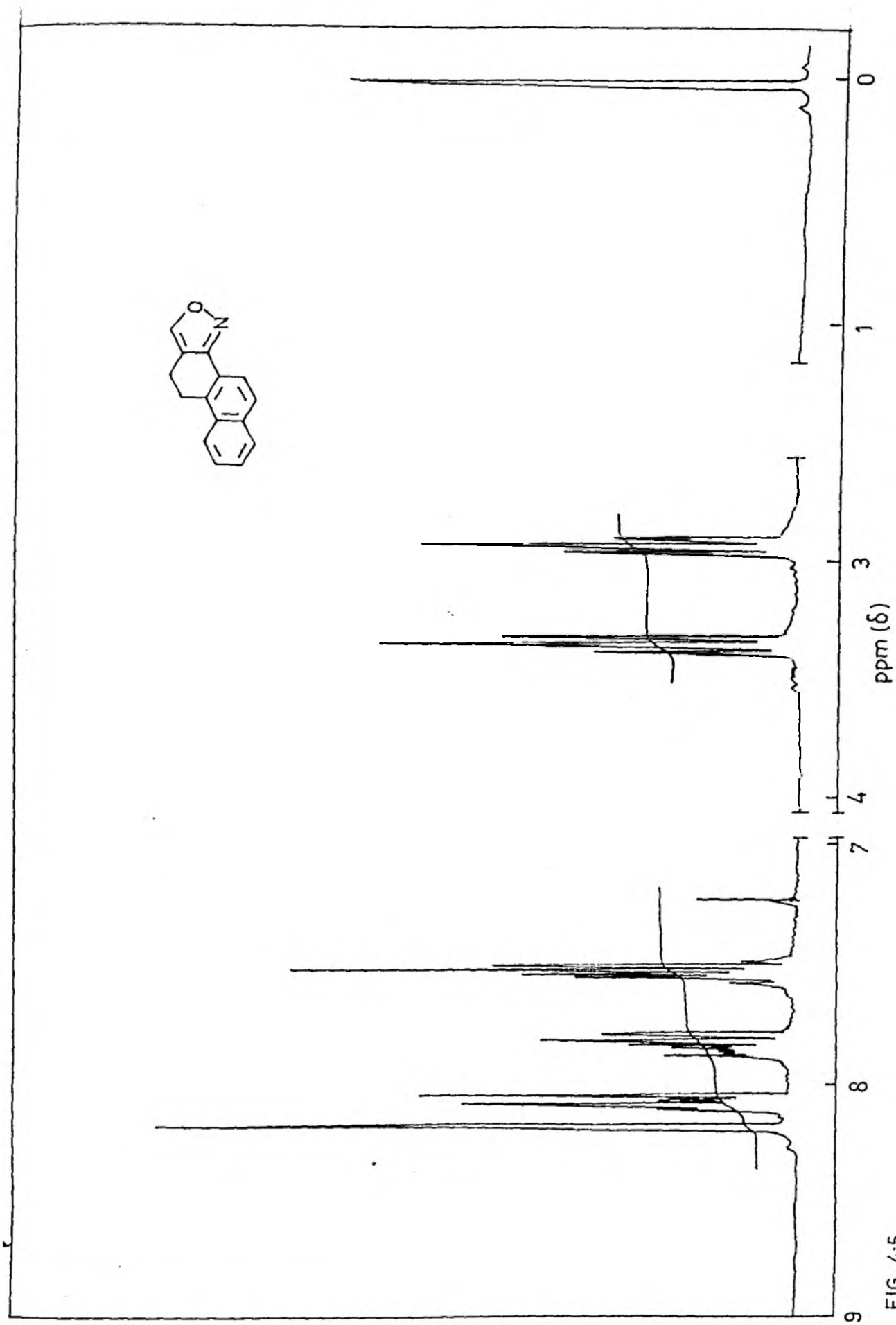
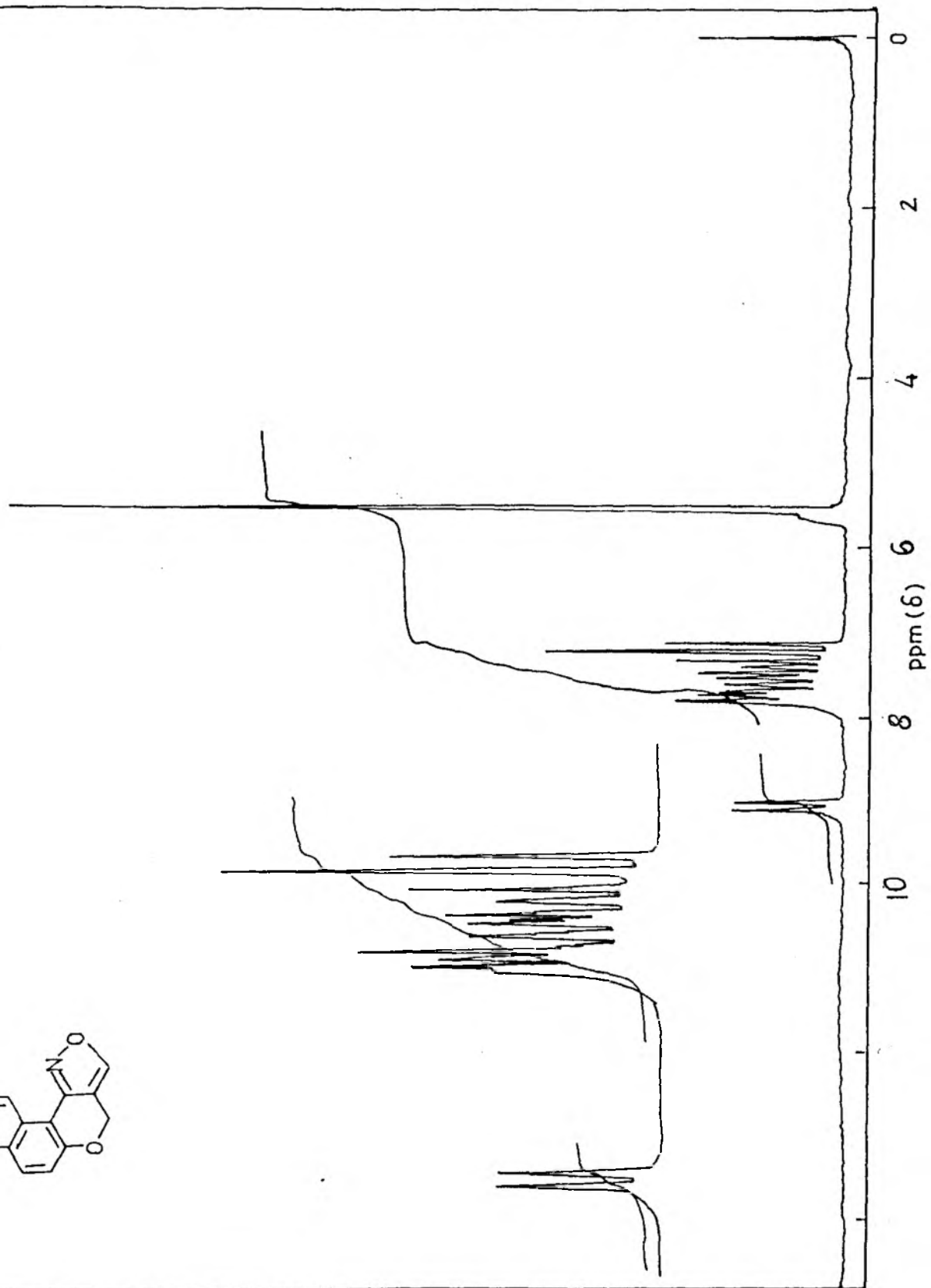
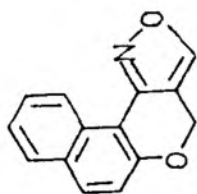


FIG. 4-5.



Compounds	Nature	M.P. (°C)	Yield (%)	IR (KBr) (cm ⁻¹)	NMR (δ) ppm (CDCl ₃)	MS (M ⁺)
XXXIVa	Yellow oil	Oil	87	2120, 1650	9.5 (s, 1H), 7.1-7.9 (m, 4H), 2.5-3.5 (m, 4H)	-
XXXIVb	Light yellow solid	101-102	97	2100, 1650	-	-
XXXIVc	Yellow solid	119-120	68	2120, 1625	-	-
XXXVII	Orange red solid	106-108	84	2100, 1650	-	-
XXXVa	Yellow oil	Oil	72	3040, 2980, 1608, 1672, 1402, 1269	8.1 (s, 1H), 7.8-8.1 (m, 1H) 7.1-7.4 (m, 4H), 2.6-3.0 (m, 4H) 63	171, 143, 142, 116, 115, 89, 63
XXXVb	Colourless solid	110-111	98	3052, 2968, 1611, 1561, 1401, 1264	7.5-8.2 (m, 7H), 3.4 (t, 2H), 2.9 (t, 2H)	221, 192, 178, 165, 139
XXXVc	Pink solid	181-182	75	3077, 2940, 1606, 1571 1379, 1268	9.1 (d, 1H), 7.1-7.8 (m, 6H) 5.5 (s, 2H)	223, 222, 194, 168, 166, 111
XXXVIII	Light yellow	98-99	67	2960, 1610, 1575, 1408, 1270	8.5 (s, 1H), 7.5-8.2 (m, 6H)	193, 166, 165, 164, 149, 139, 138, 137, 87

EXPERIMENTAL

Preparation of azidoaldehydes (XXXIV(a-c) & XXXVII)

1-Azido-2-formyl-3,4-dihydronaphthalene (XXXIVa) :

The chloroformyl derivative ²⁹ (XXXIIIa) (1.5 gm, 7.79 m mol) in dimethyl sulfoxide (DMSO) was added dropwise to an ice cooled solution of sodium azide (1 gm, 15.3 m mol) in 10 ml DMSO. The mixture was stirred for 1 hr at 5-10°C and then for 5 hrs at room temperature (the completion of the reaction was monitored by TLC). Then the reaction mixture was poured in ice cold water and extracted with ether. The organic layer was washed well with water, dried (Na₂SO₄) and solvent removed in vacuo to get the azide (XXXIVa) as a yellow viscous oil 1.35 gm (87%).

I.R. (KBr) $\nu_{\max}$: 1650, 2120 cm⁻¹.

¹H NMR (CDCl₃) δ : 2.5-3.5 (m,4H), 7.1-7.9 (m,4H) & 9.5 (s,1H)

1-Azido-2-formyl-3,4-dihydrophenanthrene (XXXIVb) :

To an ice cooled solution of sodium azide (170 mg, 7.6 m mol) in 10 ml DMSO, a solution of chloroaldehyde (XXXIIIb) (0.5 gm, 2.06 m mol) in DMSO was added dropwise. The mixture was stirred for 1 hr at 5-10°C and then 4 hours at the room temperature. After usual work up (as mentioned above) gave 0.5 gm (97.4%) of the azide (XXXIVb) as a light yellow solid, m.p. 101-102°C.

I.R. (KBr) $\nu_{\max}$ 1650, 2100 cm⁻¹.



1-Azido-2-formyl acenaphthalene (XXXVII) :

In a similar process (as mentioned above) 1.5 gm (6.9 m mol) of chloroformyl derivative³⁰ (XXXVI) on reaction with 0.6 gm (9.2 m mol) of sodium azide in 10 ml DMSO gave 1.3 gm (84%) of the azide (XXXVII) as an orange-red solid, m.p. 106-108°C.

I.R. $\nu_{\max}$: 1650, 2100 cm^{-1} .

4-Azido-3-formyl-1-oxa-3,4-dihydrophenanthrene (XXXIVc) :

1.5 gm (6.19 m mol) of chloroformyl derivative³¹ (XXXIIIc) on treatment with 0.8 gm (4.6 m mol) of sodium azide in 10 ml DMSO afforded 1.05 gm (68.2%) of (XXXIVc) as a light yellow solid, m.p. 119-121°C.

I.R. (KBr) $\nu_{\max}$: 1625, 2120 cm^{-1} .

Preparation of isoxazole derivatives [XXXV(a-c) & XXXVIII] :

3,4-dihydronaphtho [1,2-c]isoxazole (XXXVa) :

A solution of azide (XXXIVa) (0.8 gm) was refluxed for 24 hrs in dry dichloromethane (50 ml). The solvent was then removed by distillation and the residue was chromatographed over neutral alumina (benzene) to furnish the isoxazole (XXXVa) as a light yellow oil. Yield 500 mg (72.7%).

I.R. (KBr) $\nu_{\max}$: 3040, 2980, 1608, 1672, 1402, 1264 cm^{-1} .

¹H NMR (CDCl_3) δ : 2.6-3.0 (m, 4H), 7.1-7.4 (m, 4H), 7.8-8.1 (m, 1H),
8.1 (s, 1H) ppm.

MS (m/z) : 171(M^+), 143, 142, 116, 115, 89, 63.

Analysis :	C	H	N
Found :	77.1	5.1	7.9 %
Calculated :	77.2	5.3	8.2 %
(C ₁₁ H ₉ NO)			

3,4-dihydrocphenanthro[1,2-c]isoxazole (XXXVb) :

Following the same procedure (as mentioned above) 200 mg of the azide (XXXIVb) afforded the isoxazole (XXXVb) as a light brown solid which was purified by column chromatography on neutral alumina (benzene + pet.ether, 3:7). Recrystallisation with pet.ether (60-80°C) gave a colourless solid. Yield - 175 mg (98.9%), m.p. 110-111°C.

I.R. (KBr) $\nu_{\max}$: 3052, 2968, 1611, 1561, 1401, 1264 cm⁻¹.

¹H NMR (CDCl₃) δ : 2.9 (t, 2H), 3.4 (t, 2H), 7.5-8.2 (m, 7H) ppm.

MS (m/z) : 221(M⁺), 192, 178, 165, 139.

Analysis :	C	H	N
Found :	81.3	4.7	6.1 %
Calculated :	81.5	4.9	6.3 %
(C ₁₅ H ₁₁ NO)			

Acenaphtho[1,2-c]isoxazole (XXXVIII) :

In a similar process 800 mg of the azide (XXXVII) gave a dark red solid which was purified by recrystallisation with pet.ether (60-80°C) to furnish isoxazole (XXXVIII) as a light pink solid. Yield - 450 mg (66.4%), m.p. 98-99°C.

I.R. (KBr) $\nu_{\max}$: 2960, 1610, 1575, 1408, 1270 cm⁻¹.

^1H NMR (CDCl_3) δ : 7.5-8.0 (m, 6H), 8.5 (s, 1H) ppm.

MS (m/z) : 193(M^+), 166, 165, 164, 149, 139, 138, 137, 87.

Analysis :	C	H	N
Found :	80.5	3.3	6.9 %
Calculated :	80.8	3.6	7.2 %

($\text{C}_{13}\text{H}_7\text{NO}$)

1-Oxa-1,2-dihydrophenanthro[4,3-c]isoxazole (XXXVc) :

A solution of azide (XXXIVc) 150 mg in dichloromethane was refluxed for 24 hrs. The solvent was removed to get yellow solid which on recrystallisation with benzene afforded the isoxazole (XXXVc) as a light yellow solid.

Yield - 100 mg (75.2%), m.p. 181-182°C.

I.R. (KBr) ν_{max} : 3077, 2940, 1606, 1571, 1379, 1268 cm^{-1} .

^1H NMR (CDCl_3) δ : 5.5 (s, 2H), 7.1-7.8 (m, 6H), 9.1 (d, 1H) ppm.

MS (m/z) : 223(M^+), 222, 194, 168, 166, 111.

Analysis :	C	H	N
Found :	75.1	3.8	6.1 %
Calculated :	75.3	4.0	6.3 %

($\text{C}_{14}\text{H}_9\text{NO}_2$)

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CHAPTER 5

STUDIES ON GAMA-LACTAMS - SYNTHESIS OF SOME POLYCYCLIC FURO GAMA-LACTAMS

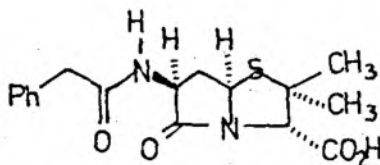
INTRODUCTION

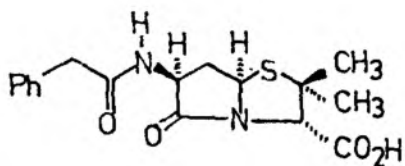
The first four chapters of this dissertation describe the use of chloroaldehyde derivatives in the synthesis of various polycyclic heterocyclic compounds. These compounds are useful to determine the carcinogenic activities and antitumor properties. As a change from the main theme in this concluding chapter we like to present the synthesis of a completely different class of heterocyclic compounds viz. polycyclic gamma-lactams, e.g. furo gamma-lactams. Many of the analogues in this series are found to be biologically active. So, initially we have discussed the biological properties of various gamma-lactams and some important synthetic routes to pyrrolidinone moieties from the literature.

DISCUSSION

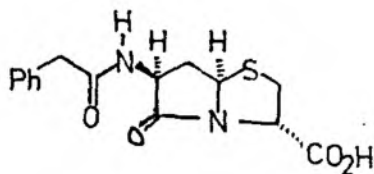
The interest generated in the 4-membered cyclic amides after the discovery of penicillin and other γ -lactam antibiotics led workers in various laboratories¹ to prepare homologues and analogues of penicillin. These works were undertaken since the proposed homologues and analogues will be more amenable to synthesis than penicillin and information obtained from a study of their properties might be useful in the penicillin problems.

Thus, this led to the synthesis of γ -lactams of the following homopenicilloic acid derivatives (I-III).



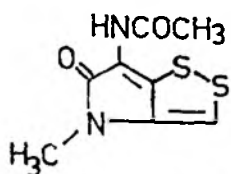


II



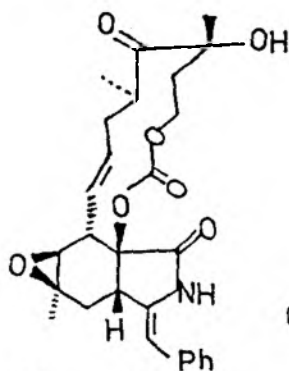
III

The interest in these 5-membered ring amides was further spurred with the discovery of antibiotics like thiolutin (IV)², holomycin³, aureothricin⁴, oleficine (V)⁵ and the complex metabolic products, cytochalasins (VI)⁶⁻⁹. All of them possess γ -lactam ring. The structures of few of these compounds are given below.

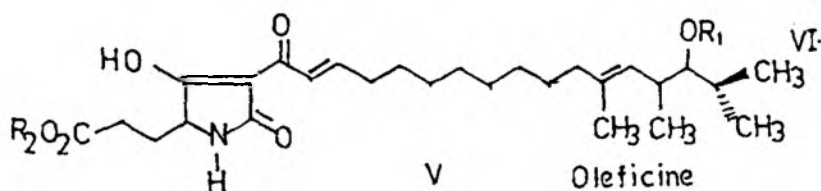


Thiolutin

IV



Cytochalasin-A



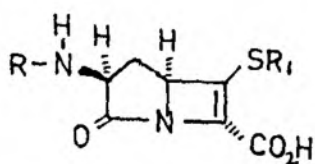
V

Oleficine

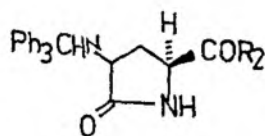
VI

Though the derivatives of pyrrolidine seldom show activities that differ greatly in kind from the corresponding open chain tertiary amines, formal oxidation of compounds containing this moiety to pyrrolidinone or succinimide endows the derivatives with biological activities.

Thus, the following γ -lactams (VII & VIII) possess antibacterial activity against a wide range of bacterial pathogens¹⁰.

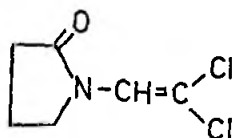


VII

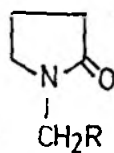


VIII

Certain N-substituted pyrrolidinones (IX & X) were found to be effective as bactericides and virusides¹¹ and in treatment of acute hypoxia in mice¹².



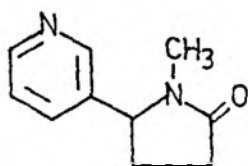
IX



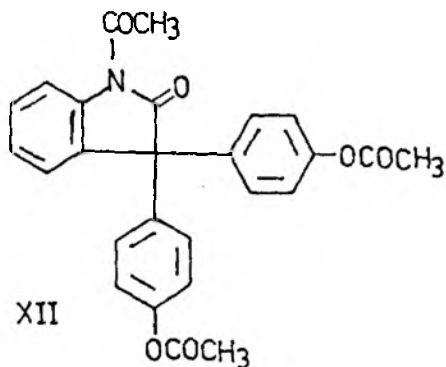
X

A recent report by Japanese workers¹³ states the application of γ -lactams in differentiation of Friend Leukemia cells.

Cotinine (XI)¹⁴ shows psychomotor stimulation, triacetyl diphenolisatin (XII)¹⁵ shows marked catharactic effect.

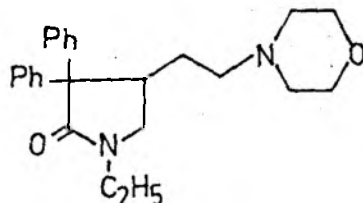


XI



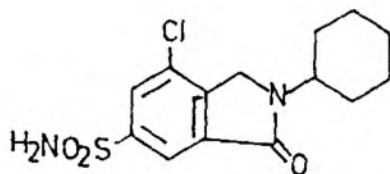
XII

Doxapram (XIII)¹⁶, a monocyclic γ -lactam derivative, is used as a respiratory stimulant, particularly in patients susceptible to postanesthetic respiratory depression.



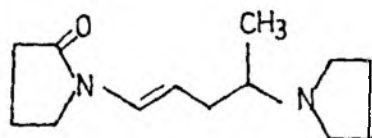
XIII

A patent¹⁷ awarded to May & Baker, 1963 for the synthesis of clorexolane (XIV) mentions important diuretic properties of the drug.

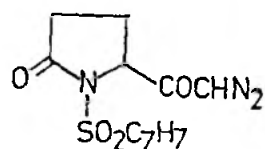


XIV

The pyrrolidinone (XV)¹⁸ is an oxotremoric antagonist and the γ -lactam (XVI)¹⁹ is a potent antineoplastic agent against Ehrlichascites carcinoma and lymphocytic leukemia.

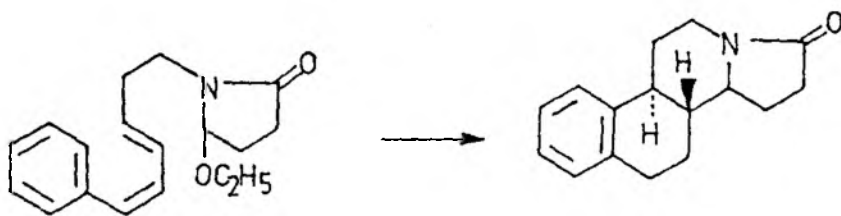


XV

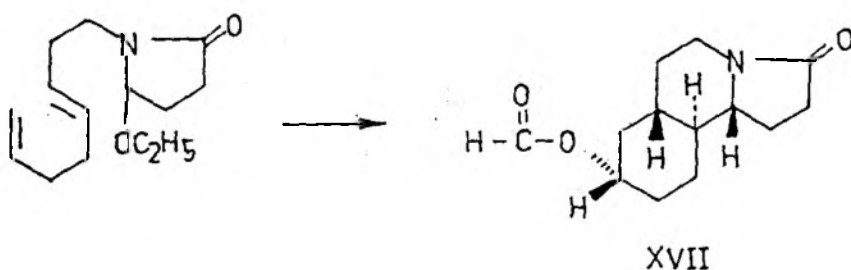


XVI

A recent report²⁰ describes the biomimetic carbocyclisation leading to the synthesis of the following azasteroid.

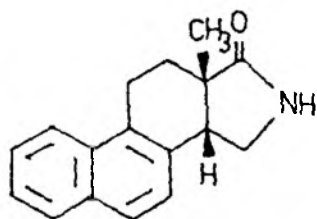


This method was extended to the synthesis of the compound (XVII) which stimulates the BCD ring of azasteroid.

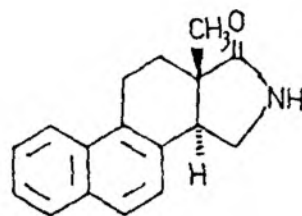


XVII

In 1950, W. E.. Bechmann et al²¹ have synthesised some stereodefined azasteroid, i.e. 14-aza-equilenins (XVIII & XIX) which have pyrrolidinone in their structures.



XVIII

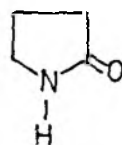
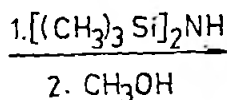
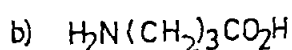
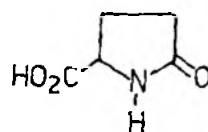
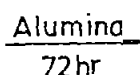
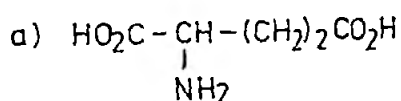


XIX

Since 1949, many γ -lactam derivatives have been synthesised so far. Some important methods of the syntheses are summarised below.

1) From aminoacids :

Many γ -lactam derivatives have been synthesised from aminoacids using a variety of reagents such as alumina²², silica gel²³, catechol boranes²³ and hexamethyl disilazane²⁴ etc.



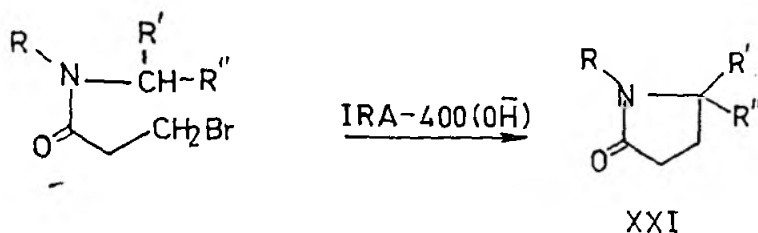
2) Acyl-N bond formation :

The formation of 1,5-dimethyl-2-pyrrolidone (XX) is an example of acyl-nitrogen bond formation, catalytic hydrogenation of a mixture of Levulinic acid and methyl amine gives the desired product²⁵.

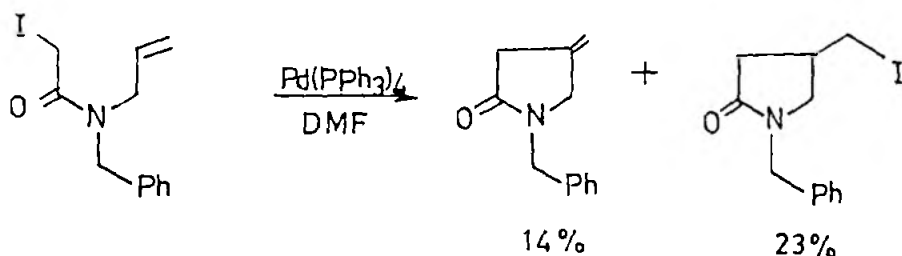


3) Carbon-carbon bond formation :

Chatterjee et al²⁶ reported a method for the synthesis of γ -lactam (XXI) through the C-C bond formation. They used IRA-400(OH⁻) as catalyst to cyclise the following compound.



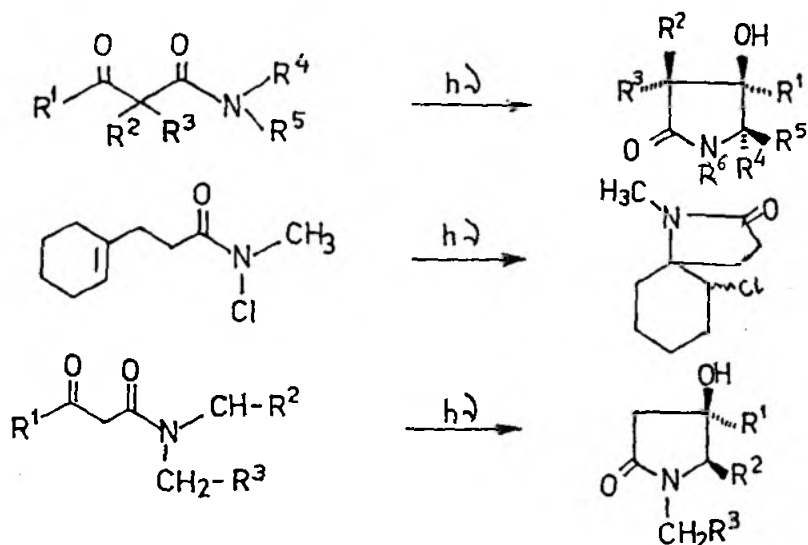
Some other methods of γ -lactam formation by C-C bond include a novel preparative method of γ -butyrolactams using Ruthenium or copper catalyst²⁷ or α -haloamide having internal double bond in presence of catalytic amount of $\text{Pd(PPh}_3)_4$ ²⁸.



4) By Photochemical methods :

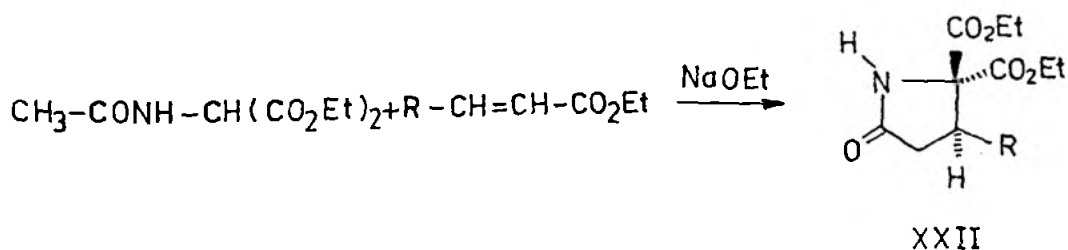
Literature survey shows a number of examples for the synthesis of γ -lactams by photochemical methods. Various starting materials like N,N-

disubstituted β -keto amides²⁹, N-Iodoamides³⁰, N,N-dialkylbenzoylacetamides³¹ and N-chloroamides³² have been successfully employed for the preparation of 2-pyrrolidinones.

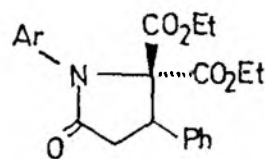
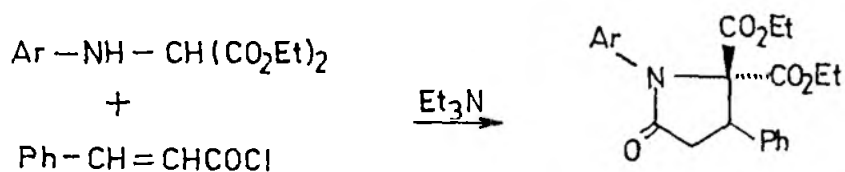


5) **By intramolecular condensation :**

A novel synthesis of γ -lactam by intermolecular Michael addition followed by intramolecular amidification was first reported by Cocolas and Hartung³³ by diethylacetamidomalonate and ethyl acrylate in refluxing ethanol.

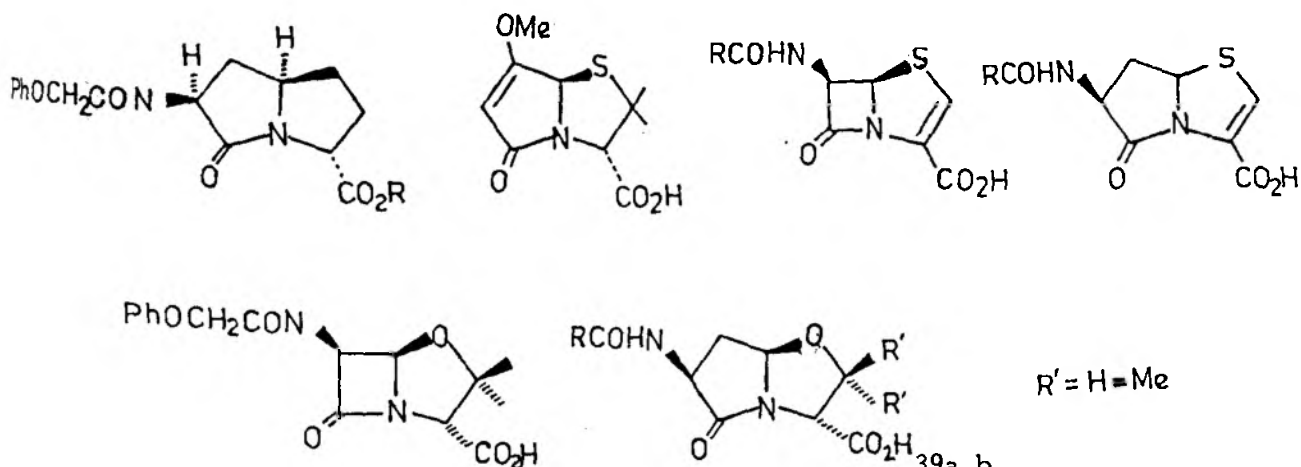


The above method was modified by Chatterjee et al³⁴ to develop γ -lactam derivatives (XXIII) in improved yield by replacing acrylic ester derivatives by α, β -unsaturated acid chloride which was found to be a better Michael acceptor.

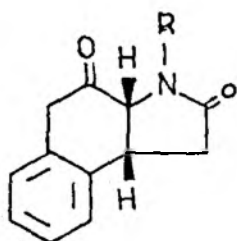


XXIII

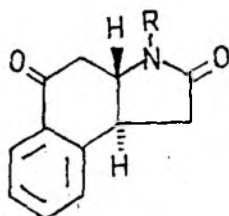
J. E. Baldwin et al have synthesised various stereodefined fused γ -lactam analogues of carbapenicillanic acids, penicillanic acids³⁵, penams³⁶, penems³⁷, 1-oxapenams³⁸ and other potential γ -lactams antibiotics containing a cycloserine nucleus. Most of them show antibacterial activities.



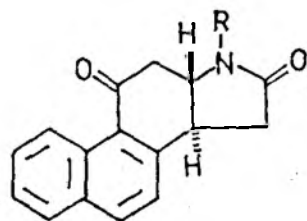
Recently from this laboratory Chatterjee et al^{39a,b} have synthesised tricyclic and tetracyclic γ -lactams (XXIV-XXVI) which have got the nitrogen atom in an isolated position. These compounds also stimulate the BCD ring structures of aza-steroid.



XXIV

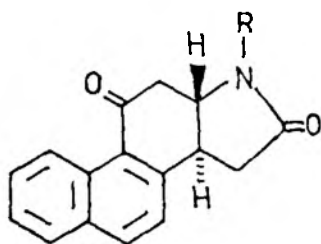


XXV

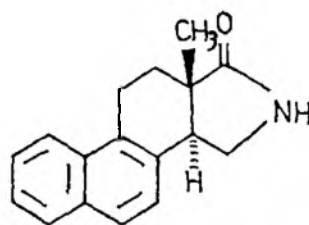


XXVI

The structure of the compound (XXVI) is very similar to 14-aza equilenin an aza-steroid (XXVII).

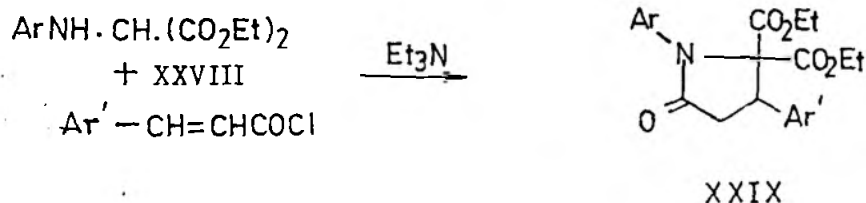


XXVI



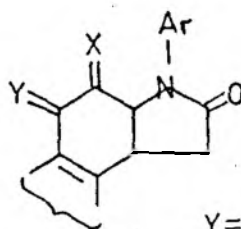
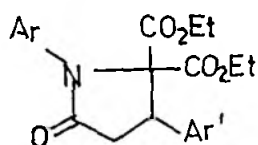
XXVII

The key step for the synthesis of polycyclic γ -lactams (XXIV-XXVI) was the development of the suitably substituted γ -lactam moiety in the first step involving the intermolecular Michael addition of suitably α, β -unsaturated acid chloride with aryl anilinomalonate (XXVIII) in presence of Et_3N followed by intramolecular amidification of the resulting Michael adduct.



XXIX

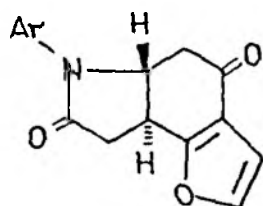
Then, γ -lactam derivatives were further annelated to the tricyclic/tetracyclic frame work following a sequence of reactions like hydrolysis, decarboxylation, side chain annelation of the acid by Arndt Eistert synthesis and finally the cyclisation of acid was achieved by PPA.



$\text{Y} = \text{H}, \text{H}, \text{X} = \text{O}$

$\text{Y} = \text{O}, \text{X} = \text{H}, \text{H}$

Further investigation was undertaken by us to synthesise γ -lactams [XXX(a,b)] having a furan moiety in place of phenyl or naphthyl groups. The furo γ -lactam is a novel heterocyclic system and to our surprise the furo γ -lactams have not been reported in the literature.

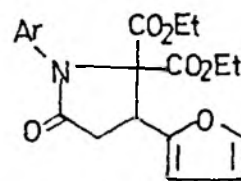
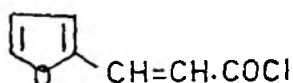
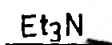
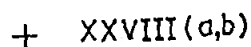
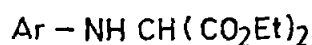


XXX (a,b).

XXXa. Ar = p-chlorophenyl

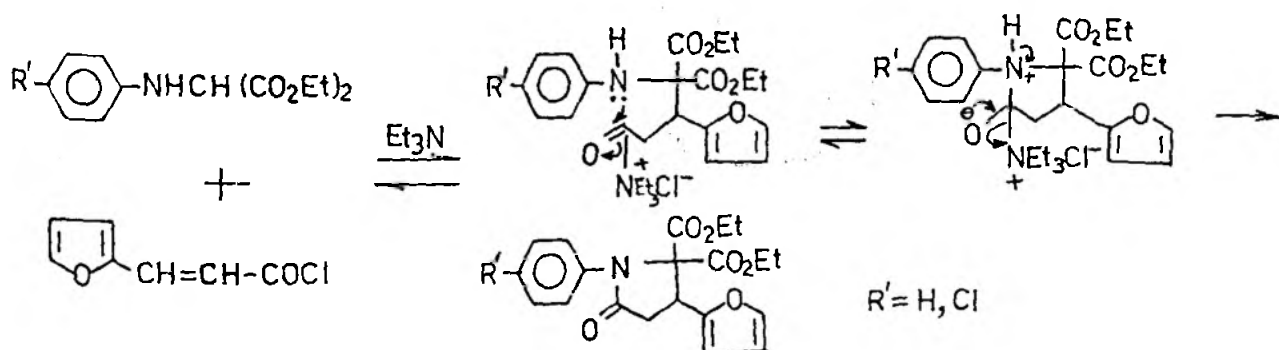
XXXb. Ar = phenyl

We have utilised the above methods for constructing the γ -lactam derivatives (XXXI) which have suitable substituents, that could be exploited in building up the desired polycyclic furo γ -lactam.



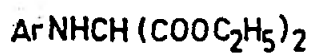
XXXI

The mechanism of the condensation is shown below.



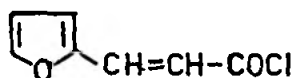
The scheme undertaken by us for the synthesis of 9-aryl-9-aza-3, di-oxa-4,5-furobicyclo[4.3.0]nonane is outlined in Scheme I.

SCHEME-I

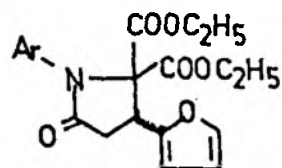


XXVIII (a,b)

+

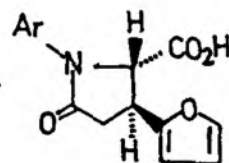
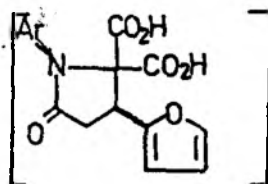


$\xrightarrow{\text{Et}_3\text{N}}$



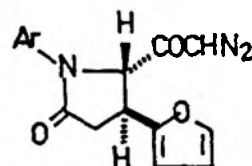
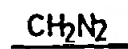
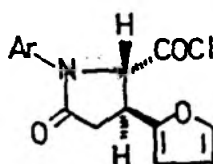
XXIX (a,b)

$\xrightarrow[2. \text{EtOH}/\text{H}_2\text{O}]{1. 2\text{KOH}}$



XXXII (a,b)

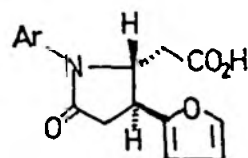
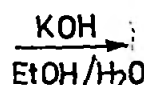
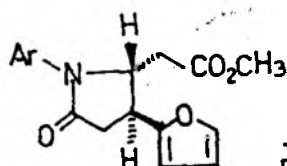
$\xrightarrow[2. \text{COCl}]{1. \text{MeONa}}$
 COCl



XXXIII (a,b)

XXXIV (a,b)

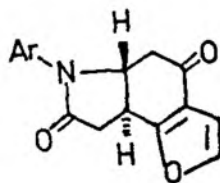
$\xrightarrow[\text{MeOH}]{\text{Ag}_2\text{O}}$



XXXV (a,b)

XXXVI (a,b)

$\xrightarrow[100^\circ\text{C}]{\text{PPA}}$



XXX (a,b)

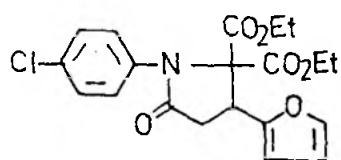
XXXa. Ar=p-chlorophenyl

XXXb. Ar=phenyl



The anilinomalonates [XXVIII(a,b)] were condensed separately under the condition as described by Chatterjee et al³⁴ with 3-(2'-furyl)acryloyl chloride in presence of Et₃N to give the γ -lactam derivatives (XXXIa) and (XXXIb) respectively in 67.6^{and} 62.8% yield respectively. IR spectra of the compounds are consistent with the assigned structures. Peaks at 1740 and 1725 cm⁻¹ for p-chloro derivatives (XXXa) are due to two ester groups and γ -lactams carbonyl function respectively. The phenyl derivatives shows absorption at 1745 and 1720 cm⁻¹ for two esters and γ -lactam carbonyl functions.

The ¹H NMR spectra of the compounds also fit well with the proposed structures. Thus the spectrum of N-(p-chloroanilino)-5,5-dicarbethoxy-4-furyl-pyrrolidin-2-one shows the following peaks.

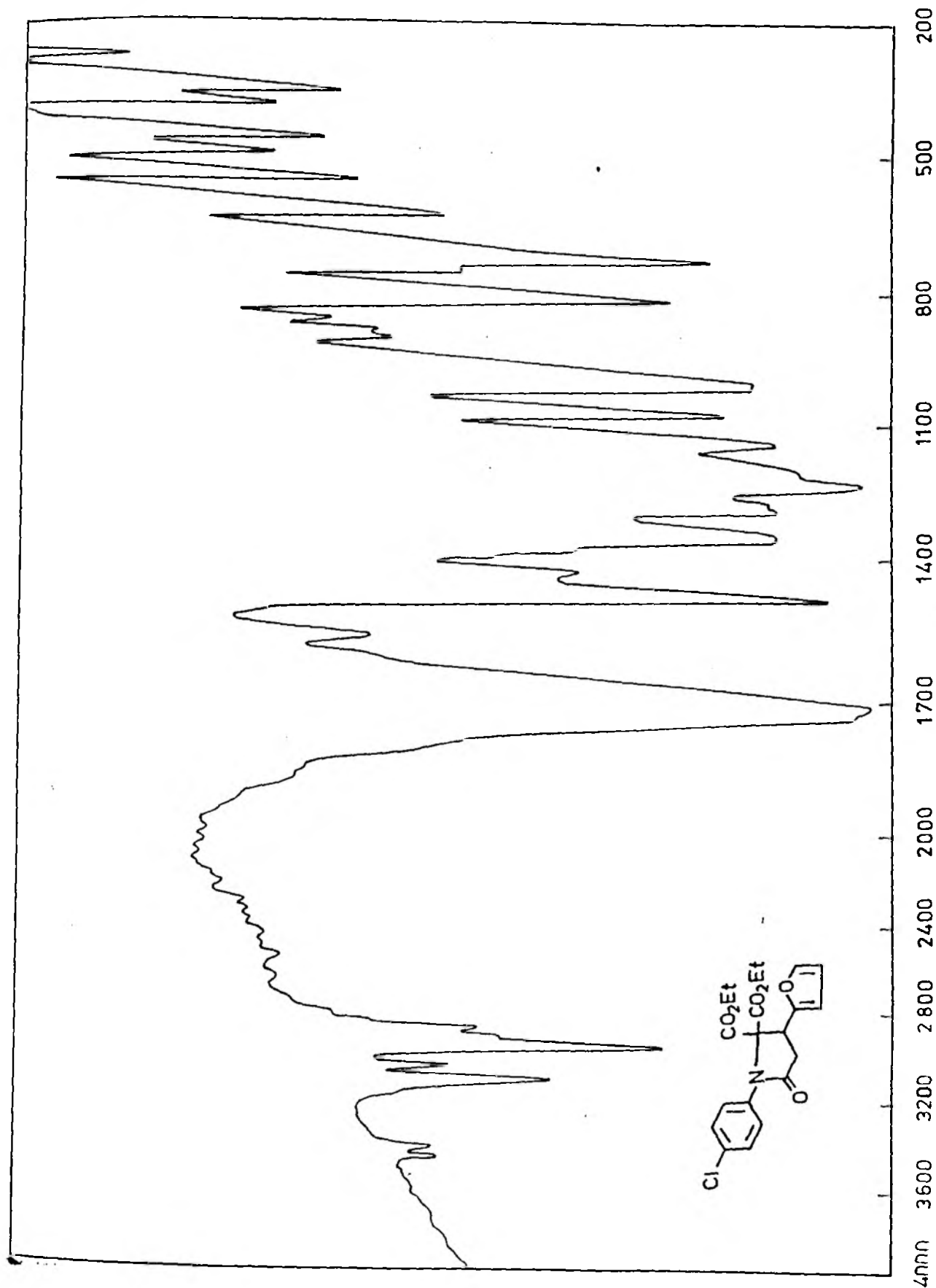


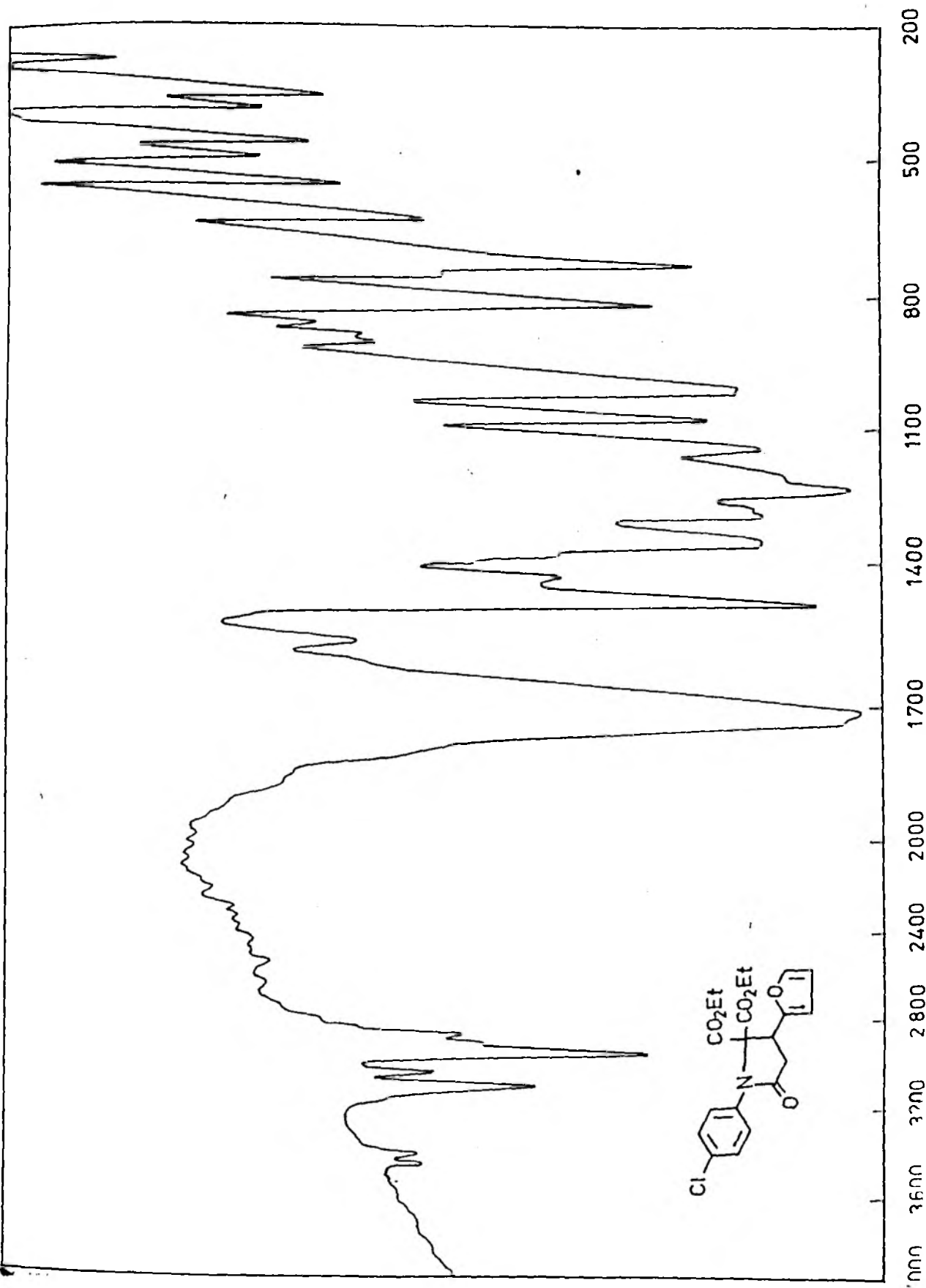
Solvent: CDCl₃

Fig. 5-2

Position of peak (δ) ppm	Nature	Proton count	Assignment
0.85	t	3H	- CH ₃
1.2	t	3H	- CH ₃
2.75-3.5	d (J=9 Hz)	2H	CH ₂ CON
3.6-4.2	m	4H	- OCH ₂ CH ₃
4.6	t (J= 9 Hz)	1H	- CH
6.3-6.5	m	2H	Aromatic
7.1-7.5	m	5H	Aromatic

It is interesting to note that the methyl protons and the methylenes of the two ester groups do not have same chemical shifts since the C₅ ester group which is trans to C₄ phenyl ring is deshielded by the neighbouring furan groups³⁴.





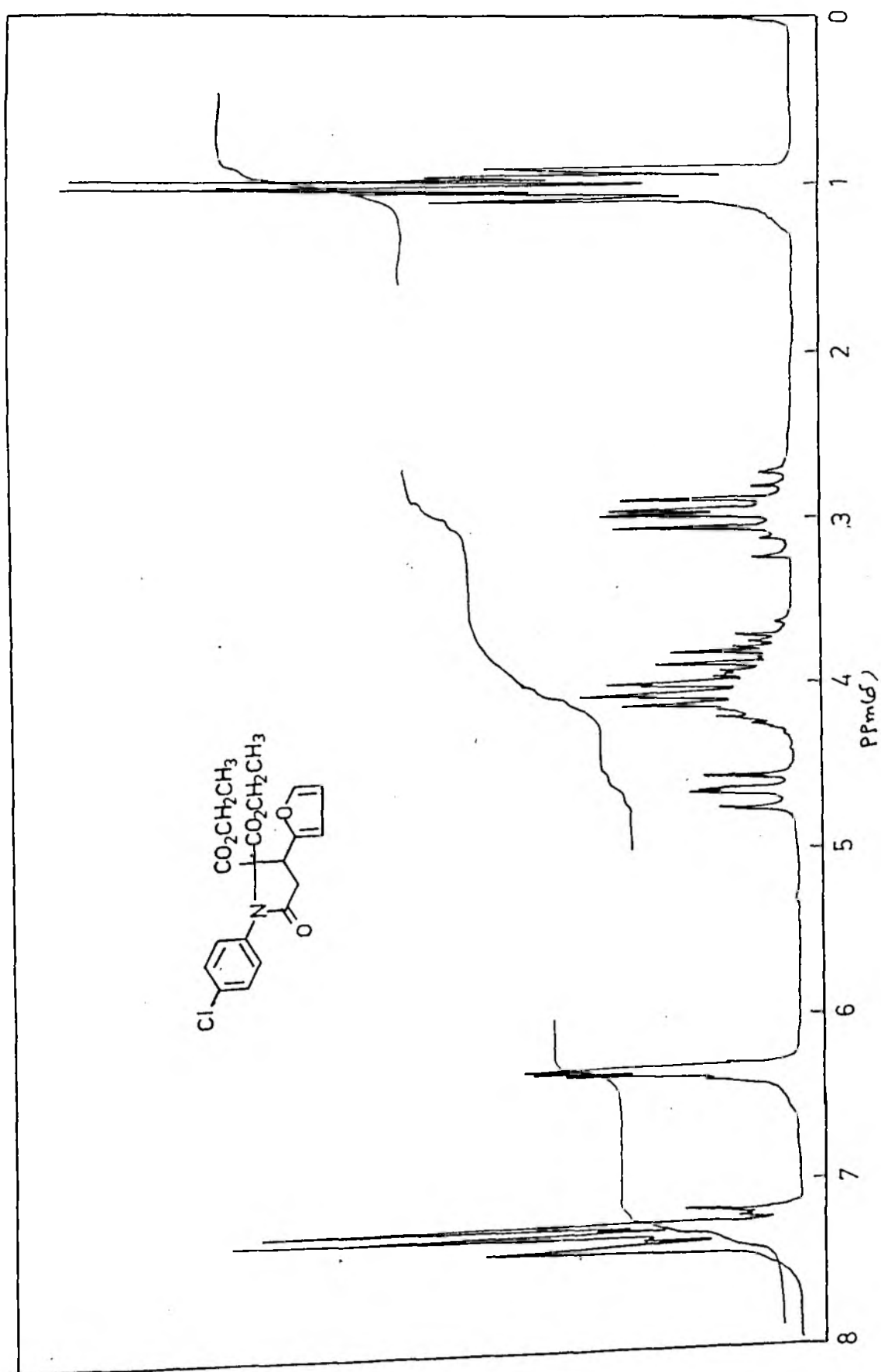
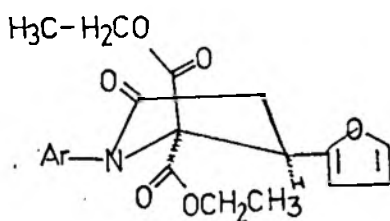
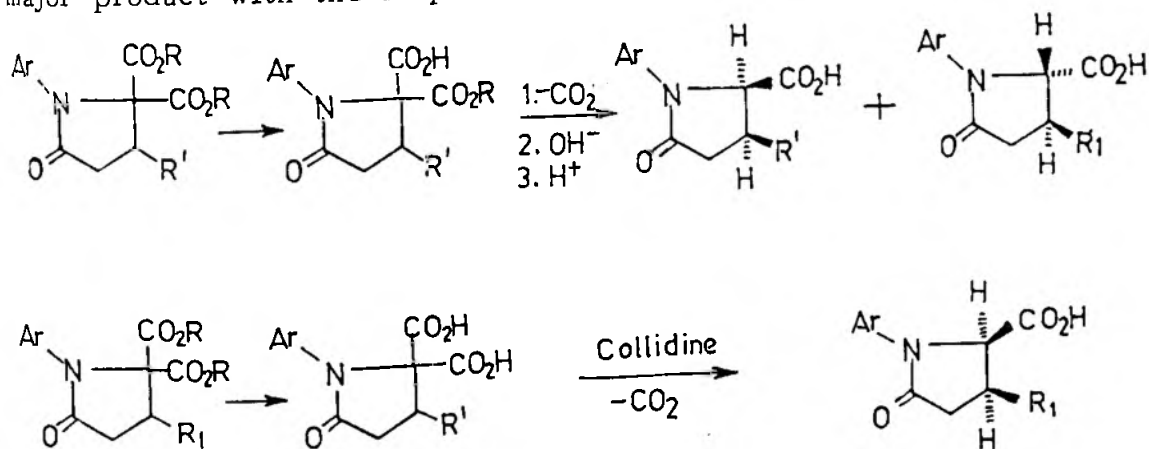


FIG. 52

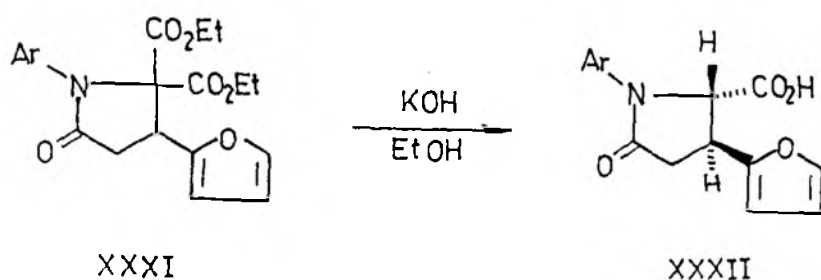


Though the partial saponification of γ -lactam diesters followed by sequential decarboxylation leads to a mixture of cis and trans γ -lactam monocarboxylic acid derivatives^{39a}. Pachalley⁴⁰ has shown that a pyrrolidine dicarboxylic acid could be stereo selectively decarboxylated to cis as a major product with the help of collidine.

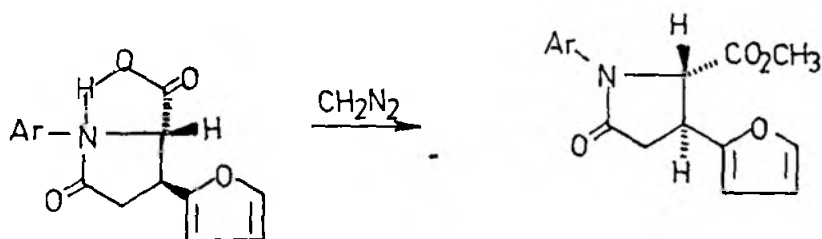


However the pyrrolidinone derivatives [XXXI(a,b)] when refluxed with 2 molar alcoholic KOH solution and the reaction mixture worked up, the products were found to be exclusively trans mono acid (XXXII) as evident from the coupling constant of C_4 -H and C_5 -H ($J \sim 5$ Hz) in ^1H NMR, a single spot in TLC and finally by X-ray analysis. It is also well known from the literature⁴¹ that when a diester is drastically saponified it always gives exclusively trans isomer in which coupling constant ($J \sim 5$ Hz) is always lower than the cis isomer ($J \sim 8$ Hz) particularly in this type of systems.





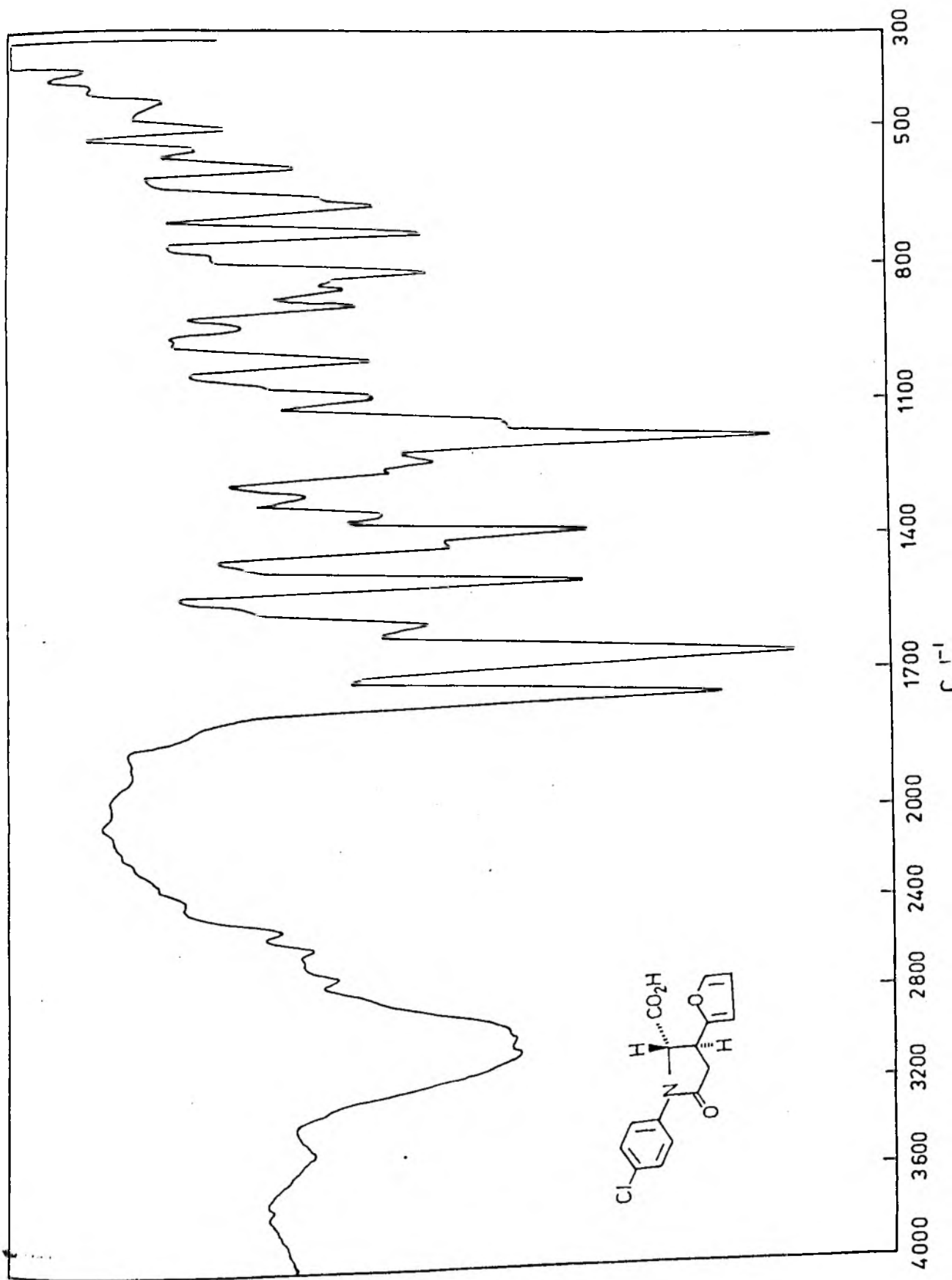
The marked bathochromic shift in the I.R. carbonyl band of the mono acids from the normal 1700 cm^{-1} to 1650 cm^{-1} is attributed to a probable hydrogen bonded structure (A) which would permit greater interaction between oxygen p-electrons and carbonyl π -electrons. This is supported by the observation that the esters obtained on treatment with CH_2N_2 shows carbonyl absorption in I.R. spectra at the expected place.

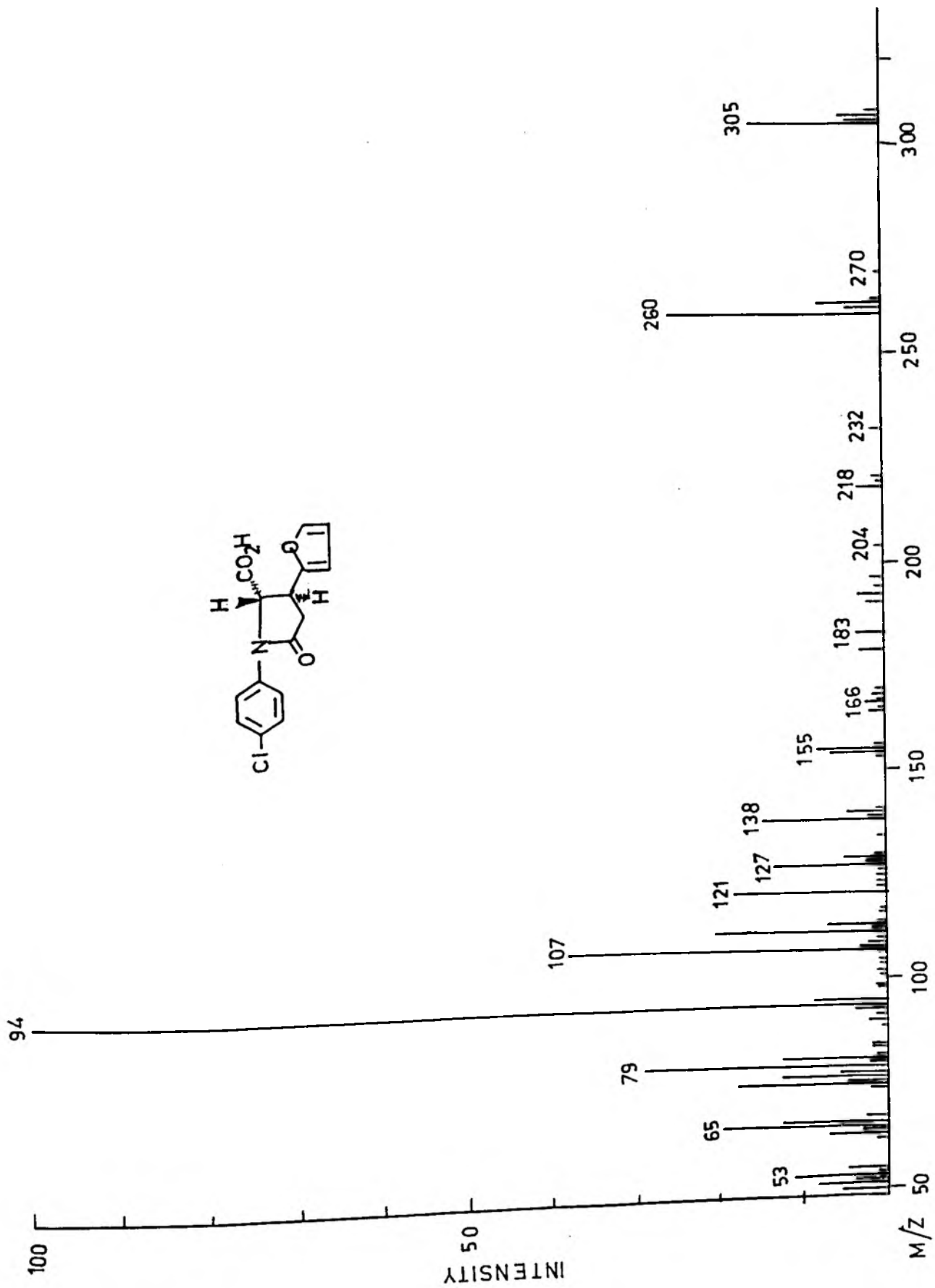
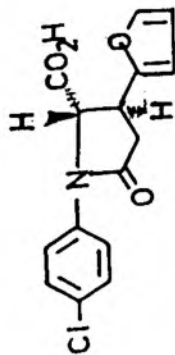


The ^1H NMR spectra of one mono acid derivative (XXXIIa) is described below :

	Position of peaks (δ) ppm	Nature	Proton Count	Assignment
	2.75-2.83	dd ($J = 4\text{ Hz}$)	1H	H^c
	3.03-3.13	dd ($J = 9\text{ Hz}$)	1H	H^d
	3.75-3.85	m	1H	H^b
	4.77	d ($J = 3.3\text{ Hz}$)	1H	H^a
	6.23	d ($J = 3.2\text{ Hz}$)	1H	H^g
	6.32	t	1H	H^f
	7.3-7.45	m	5H	H^e
Solvent: DMSO- d_6				

The acid proton was not observed in ^1H NMR, however treatment of compound with CH_2N_2 showed the formation of $-\text{COOCH}_3$ (Fig.5.5).





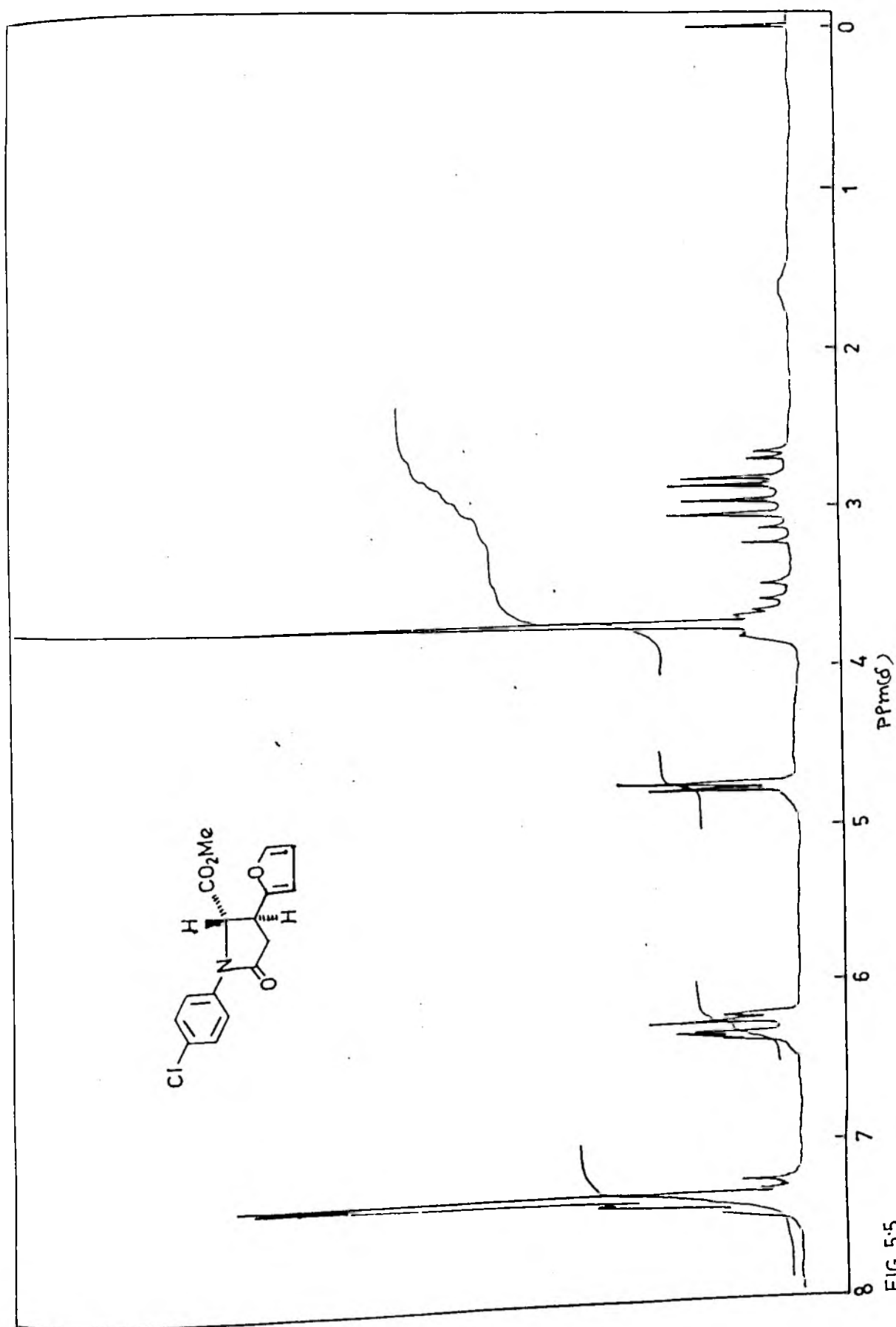
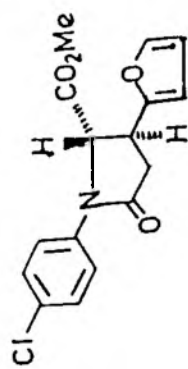
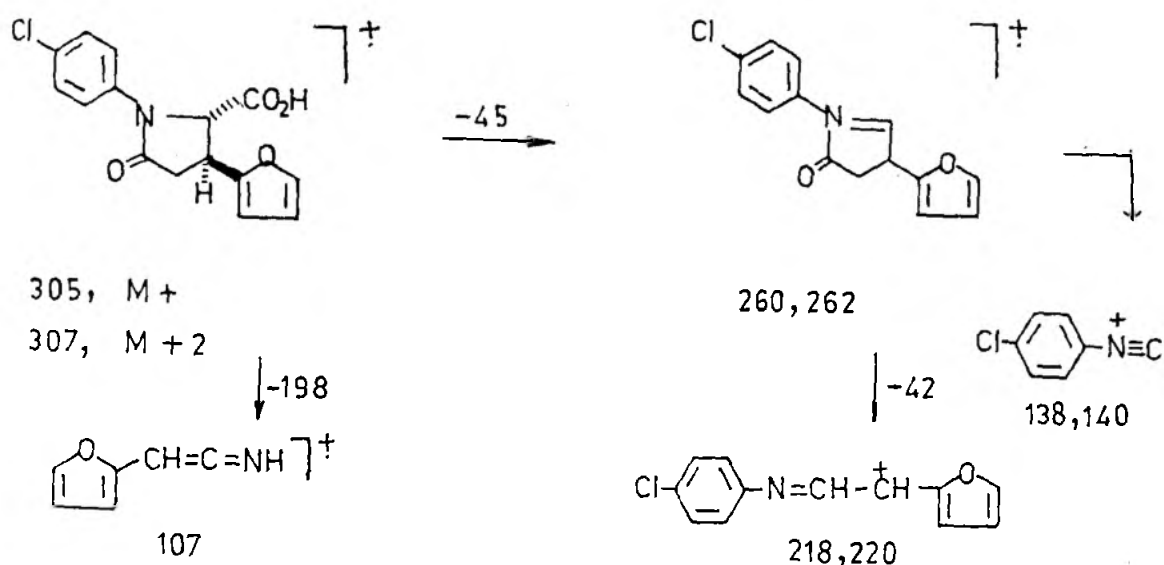


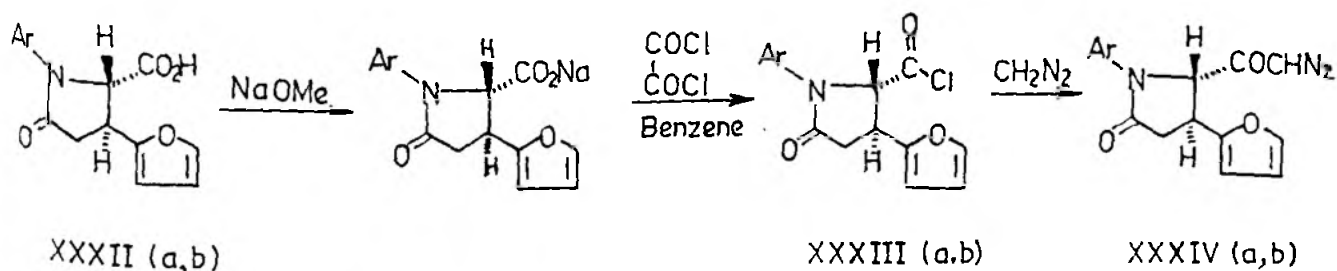
FIG. 5.5

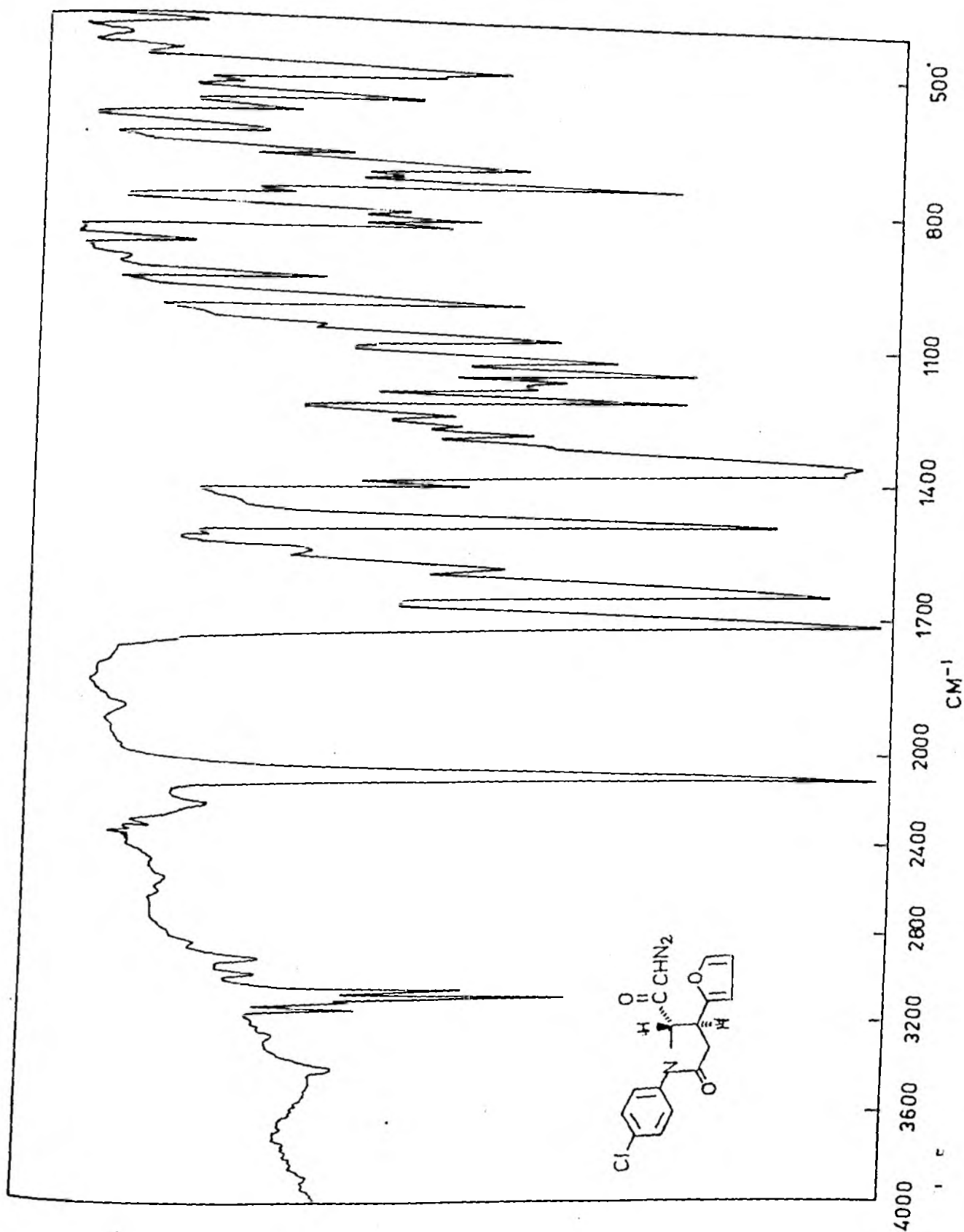
The mass spectrum of the mono acid (XXXIIa) shows the following fragmentation pattern (Fig.5.4).



The γ -lactam mono acids [XXXII(a,b)] were then converted to the corresponding acid chlorides [XXXIII(a,b)] by treatment with oxalyl chloride to the sodium salt of acids prepared from sodium methoxide in presence of phenolphthalein as an indicator. The crude acid chlorides show absorptions at about 1794 cm^{-1} and 1705 cm^{-1} for $\nu_{C=O}$ (acid chloride and $\nu_{C=O}$ (γ -lactam) respectively.

The reaction of the acid chlorides [XXXIII(a,b)] with excess of CH_2N_2 gave the diazo ketones [XXXIV(a,b)] in excellent yields. IR spectrum of XXXIV(a,b) shows strong band at 2110 , 1708 and 1638 cm^{-1} due to diazo group, γ -lactam carbonyl and carbonyl function of COCHN_2 respectively.





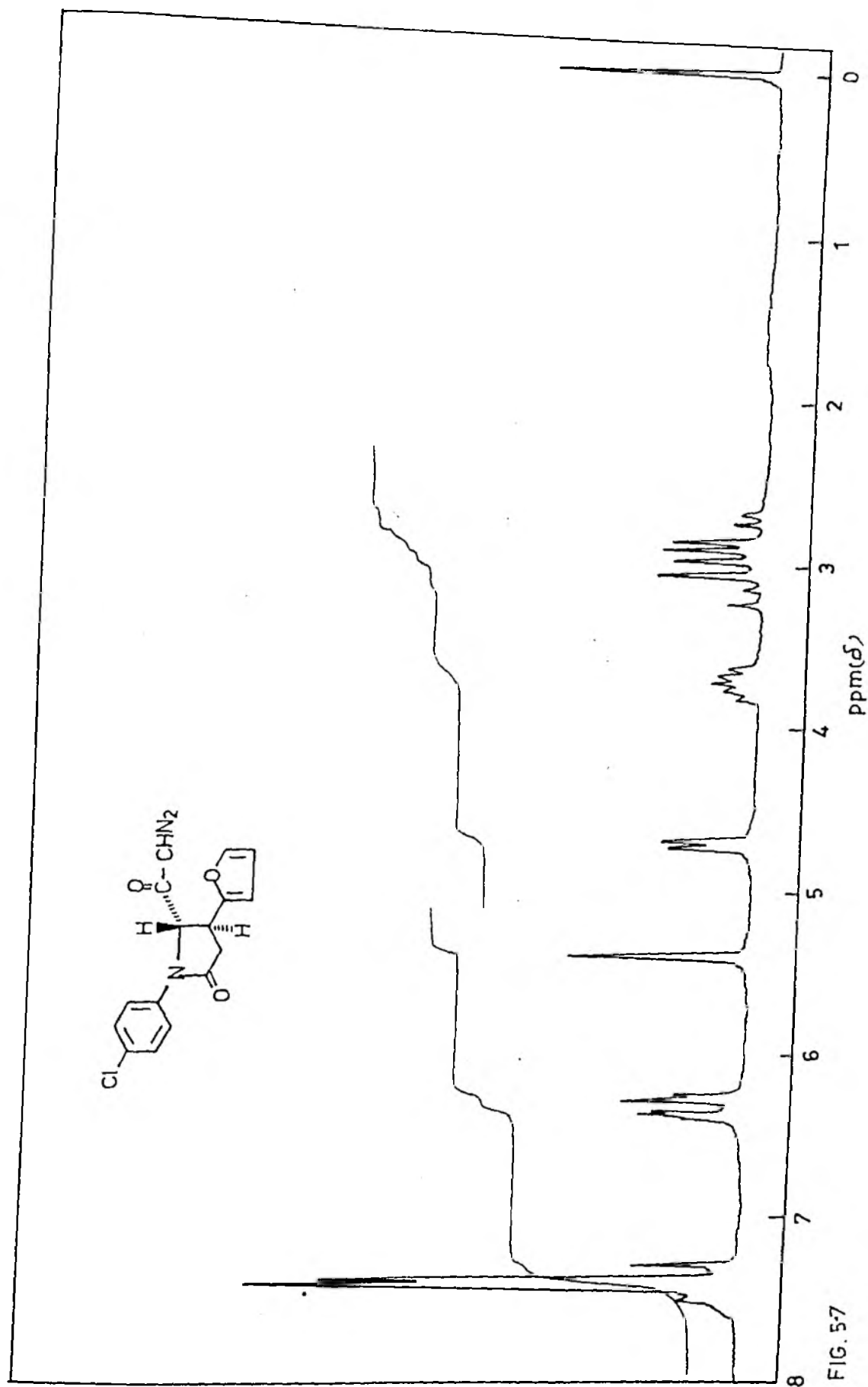
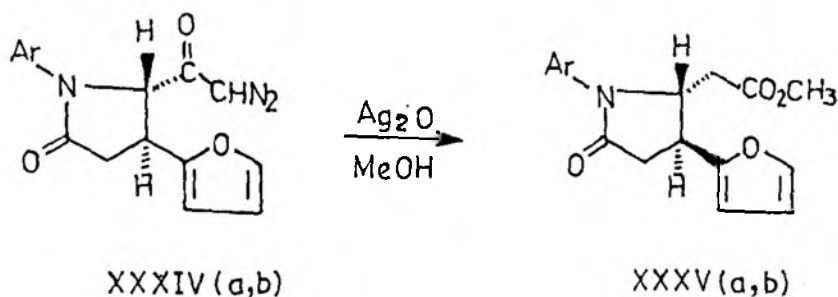


FIG. 5-7

The diazo ketones XXXIV(a,b) on treatment with $\text{Ag}_2\text{O}/\text{MeOH}$ gave the γ -lactam esters (XXXV) in quantitative yield.



The authenticity of these esters were established by spectral and elemental analyses. The IR spectra of the compounds show absorption at 1740 cm^{-1} for ester groups and 1706 cm^{-1} for γ -lactam carbonyl functions respectively. To confirm the stereochemistry of ring juncture we have taken the X-ray of the compound (368) and 2D NMR. The X-ray data and an ORTEP X-ray of the ester are given in Table-1 and Fig.5.17

The ^1H NMR spectra of one ester derivatives (XXXVa) is discussed below.

	Position of peaks (δ) ppm	Nature	Proton count	Assignment
	2.52-2.68	dd	2H	H^b, H^c
	2.76-3.16	dd	2H	H^e, H^f
	3.40-3.68	m	1H	H^d
	3.52	s	3H	$-\text{OCH}_3$
	4.48-4.8	m	1H	H^a
	6.2	d	1H	H^g
	6.28-6.36	dd	1H	H^h
	7.25-7.5	m	5H	H^i

Solvent: CDCl_3

Fig. 5.9

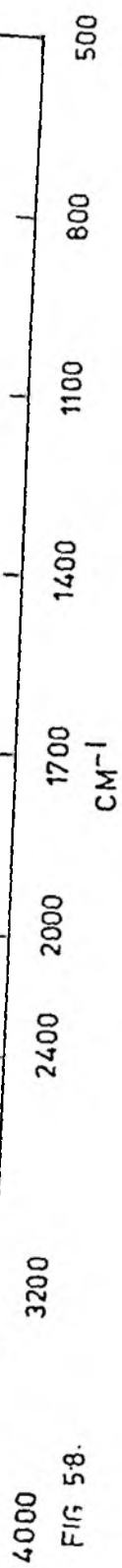
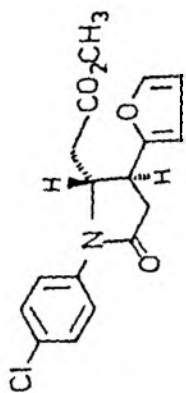


FIG 58.

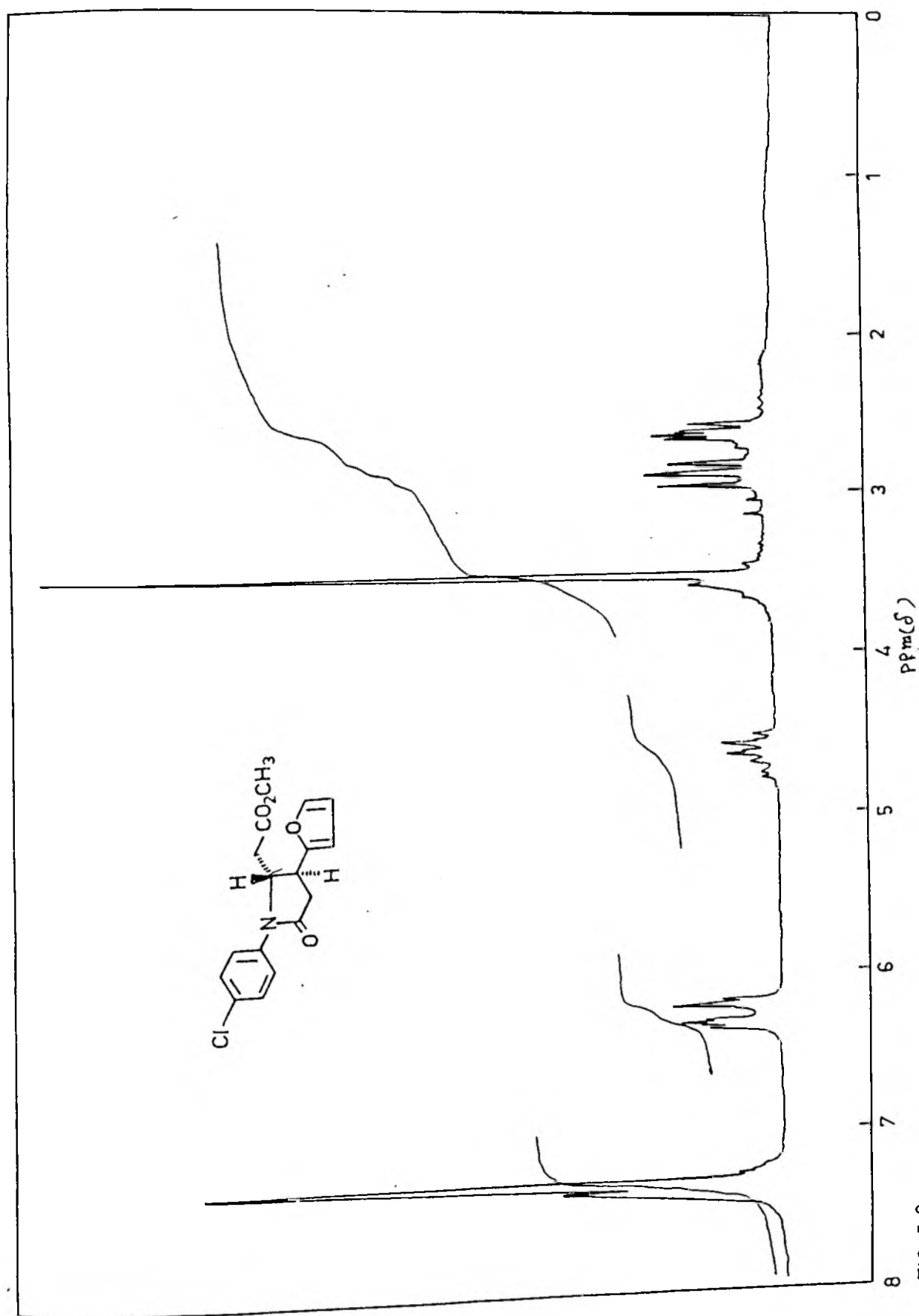
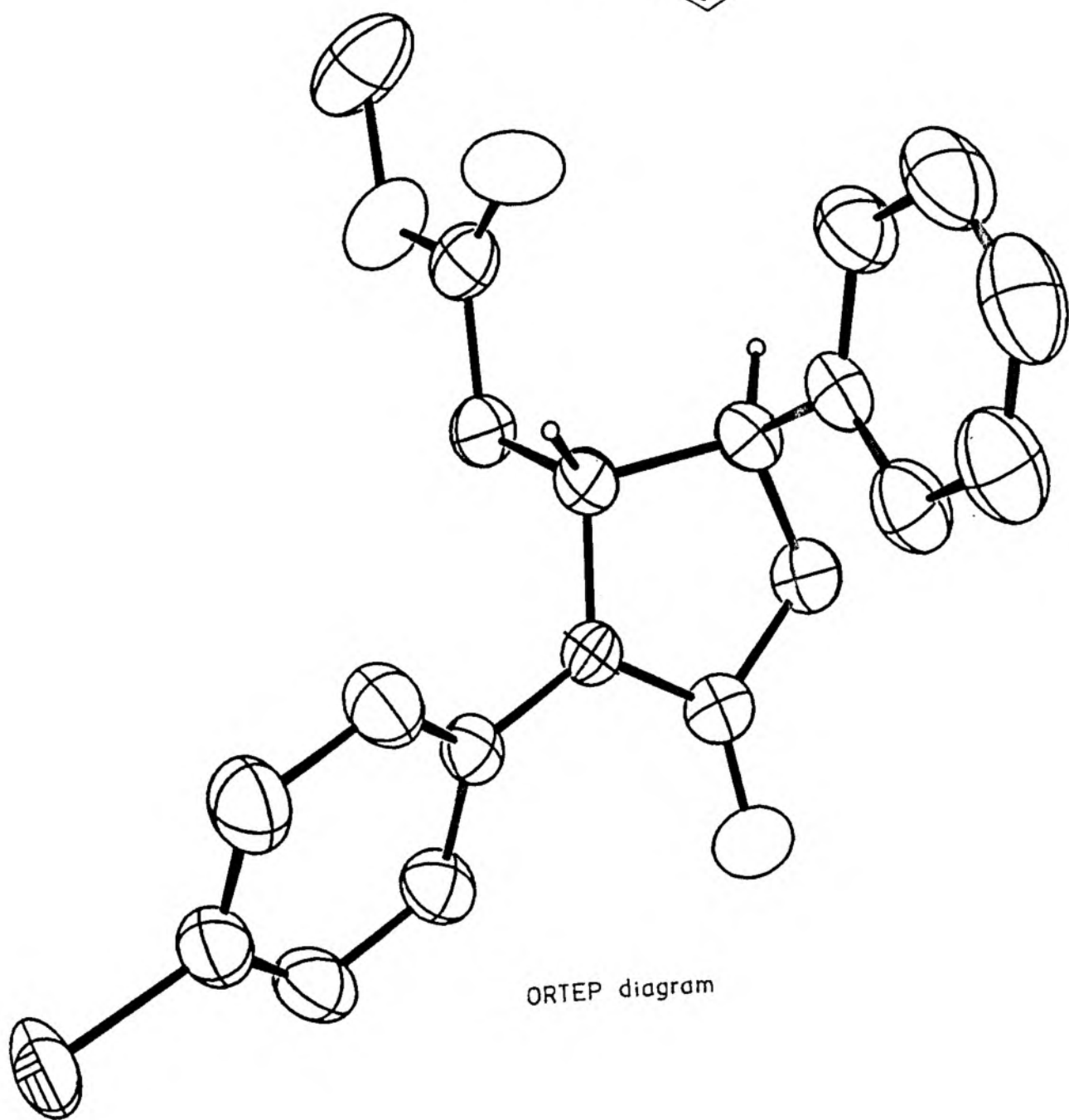
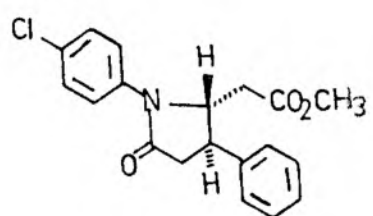


FIG. 5-9

Compound 968



ORTEP diagram

FIG. 5-17

TABLE-1

Crystal Data - Compound 968

Formula	$C_{19}H_{18}NO_3Cl$
Formula weight	343.81
Crystal class	monoclinic
Space group	$P2_1/c$, $Z=4$
Cell constants:	
a , Å	10.052(2)
b , Å	18.215(3)
c , Å	9.728(1)
β , °	100.49(2)
μ , cm^{-1}	20.7
D_{calc} , g/cm^3	1.304
Radiation	$Cu-K_{\alpha}$ 1.54184 Å
θ range, °	2-65
hkl ranges	$-11 \leq h \leq 11$, $0 \leq k \leq 21$, $0 \leq l \leq 11$
No. reflections measured	3286
No. reflections used in refinement	2433 [$F_o^2 > 3\sigma(F_o^2)$]
R	0.058
R_w	0.088

Refined Positional Parameters for Compound 968

Atom	x	y	z	B _{eq} , Å ²
C1	0.95563(8)	0.13617(5)	0.44807(8)	9.49(2)
C1	1.0750(3)	0.1517(2)	0.5977(3)	6.30(6)
C2	1.0709(3)	0.2139(2)	0.6755(3)	6.66(7)
C3	1.1674(2)	0.2263(2)	0.7934(3)	5.85(6)
C4	1.2704(2)	0.1762(1)	0.8327(2)	4.67(4)
C5	1.2745(3)	0.1140(2)	0.7525(3)	6.71(7)
C6	1.1765(3)	0.1021(2)	0.6366(3)	7.55(8)
C7	1.4284(2)	0.1284(1)	1.0469(2)	4.65(4)
C8	1.5554(2)	0.1643(1)	1.1371(2)	4.90(5)
C9	1.5196(3)	0.2457(1)	1.1312(3)	5.51(5)
C10	1.4237(2)	0.2562(1)	0.9955(2)	5.00(5)
C11	1.6813(2)	0.1468(1)	1.0788(2)	5.27(5)
C12	1.7180(3)	0.1861(2)	0.9698(3)	6.90(7)
C13	1.8303(3)	0.1680(2)	0.9146(3)	8.62(9)
C14	1.9099(3)	0.1113(2)	0.9677(4)	9.29(9)
C15	1.8789(3)	0.0714(2)	1.0779(4)	9.03(9)
C16	1.7630(3)	0.0889(2)	1.1345(4)	7.19(7)
C17	1.3240(2)	0.1010(1)	1.1309(3)	5.31(5)
C18	1.3723(3)	0.0355(1)	1.2175(3)	5.84(6)
C19	1.3231(5)	-0.0478(2)	1.3861(4)	11.1(1)
N	1.3716(2)	0.1886(1)	0.9525(2)	4.71(4)
O1	1.3973(2)	0.31368(9)	0.9329(2)	6.43(4)
O2	1.2845(2)	0.0150(1)	1.2957(2)	7.97(5)

Refined Positional Parameters for Compound 968 (cont.)

Atom	x	y	z	B _{eq} , Å ²
O3	1.4761(2)	0.0041(1)	1.2176(3)	9.13(6)
H7	1.4527	0.0854	1.0008	6*
H8	1.5757	0.1457	1.2304	6*
H2	0.9994	0.2482	0.6483	6*
H3	1.1643	0.2710	0.8461	6*
H5	1.3441	0.0779	0.7808	6*
H6	1.1786	0.0584	0.5821	6*
H9a	1.5982	0.2749	1.1345	6*
H9b	1.4770	0.2587	1.2083	6*
H12	1.6641	0.2284	0.9323	8*
H13	1.8508	0.1971	0.8368	6*
H14	1.9853	0.0977	0.9255	6*
H15	1.9380	0.0312	1.1141	8*
H16	1.7398	0.0601	1.2115	6*
H17a	1.2419	0.0890	1.0683	6*
H17b	1.3041	0.1401	1.1909	6*
H19a	1.3650	-0.0840	1.3405	6*
H19b	1.3831	-0.0326	1.4697	6*
H19c	1.2435	-0.0683	1.4143	6*

Starred atoms were not refined.

$$B_{eq} = 4/3(\beta_{11}a^2 + \beta_{22}b^2 + \beta_{33}c^2 + \beta_{12}ab\cos\gamma + \beta_{13}accos\beta + \beta_{23}bccos\alpha).$$

Bond Distances In Compound 988

Atom 1	Atom 2	Distance	Atom 1	Atom 2	Distance	Atom 1	Atom 2	Distance
C1	C1	1.733(3)	C7	C17	1.526(3)	C12	C13	1.375(4)
C1	C2	1.367(4)	C7	N	1.477(3)	C13	C14	1.351(5)
C1	C6	1.364(4)	C8	C9	1.524(4)	C14	C15	1.377(6)
C2	C3	1.379(3)	C8	C11	1.513(3)	C15	C16	1.413(5)
C3	C4	1.382(3)	C9	C10	1.499(3)	C17	C18	1.490(3)
C4	C5	1.380(4)	C10	N	1.374(3)	C18	O2	1.320(4)
C4	N	1.419(3)	C10	O1	1.215(3)	C18	O3	1.189(4)
C5	C6	1.373(4)	C11	C12	1.384(4)	C19	O2	1.451(4)
C7	C8	1.555(3)	C11	C16	1.384(4)			

Bond Angles in Compound 968

Atom 1 =====	Atom 2 =====	Atom 3 =====	Angle =====	Atom 1 =====	Atom 2 =====	Atom 3 =====	Angle =====	Atom 1 =====	Atom 2 =====	Atom 3 =====	Angle =====
C1	C1	C2	120.9(2)	C17	C7	N	110.5(2)	C12	C13	C14	120.4(3)
C1	C1	C6	119.6(2)	C7	C8	C9	103.0(2)	C13	C14	C15	119.9(3)
C2	C1	C6	119.5(2)	C7	C8	C11	110.9(2)	C14	C15	C16	120.2(3)
C1	C2	C3	120.6(3)	C9	C8	C11	113.5(2)	C11	C16	C15	119.5(3)
C2	C3	C4	120.0(3)	C8	C9	C10	105.5(2)	C7	C17	C18	112.2(2)
C3	C4	C5	119.0(2)	C9	C10	N	107.5(2)	C17	C18	O2	111.6(2)
C3	C4	N	120.8(2)	C9	C10	O1	126.8(2)	C17	C18	O3	125.5(3)
C5	C4	N	120.3(2)	N	C10	O1	125.7(2)	O2	C18	O3	122.9(2)
C4	C5	C6	120.2(3)	C8	C11	C12	122.4(2)	C4	N	C7	122.1(2)
C1	C6	C5	120.8(3)	C8	C11	C16	119.4(2)	C4	N	C10	124.7(2)
C8	C7	C17	114.2(2)	C12	C11	C16	118.2(3)	C7	N	C10	113.2(2)
C8	C7	N	102.9(2)	C11	C12	C13	121.8(3)	C18	O2	C19	116.0(3)

Refined Thermal Parameters (Beta's) for Compound 968

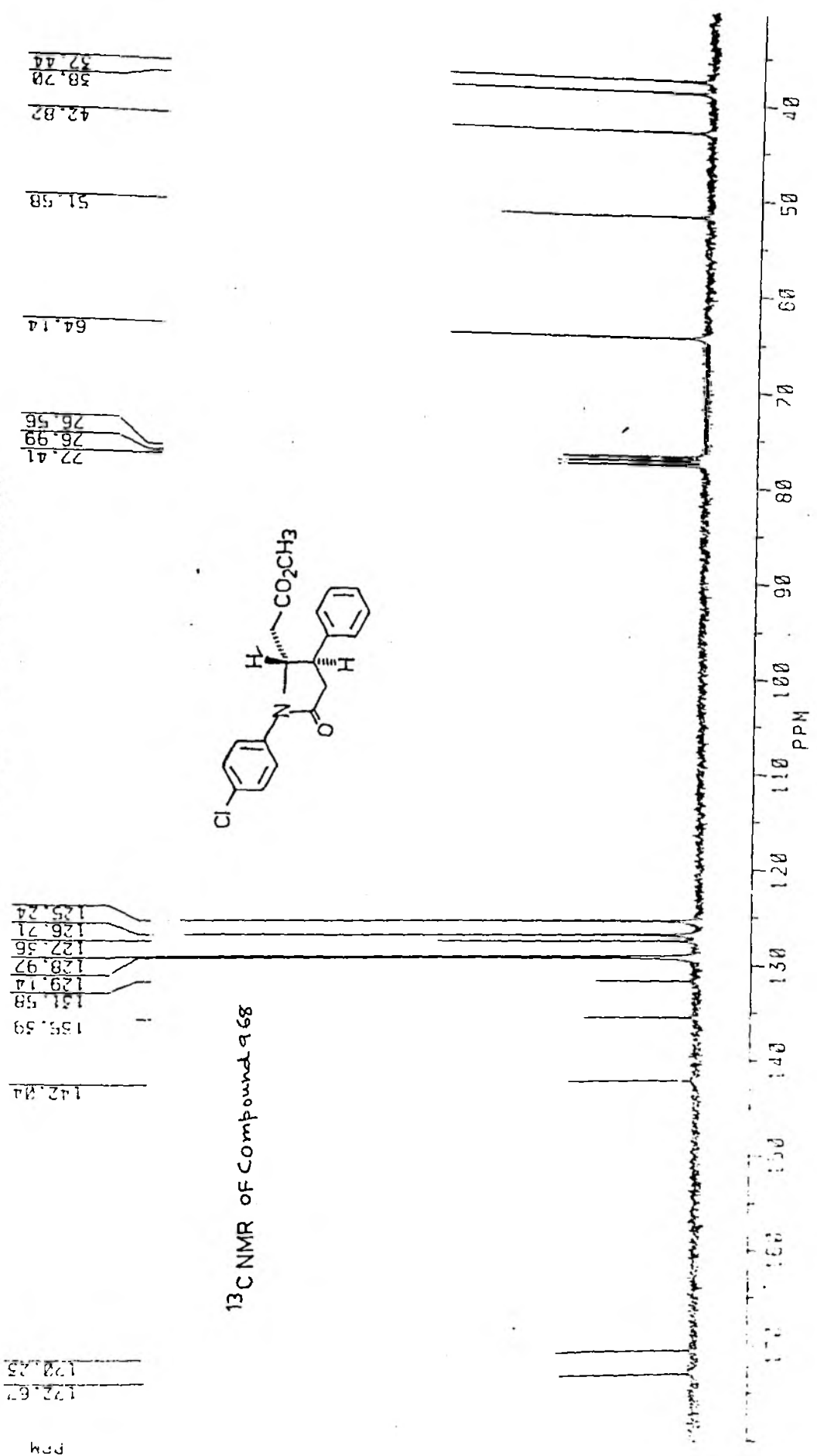
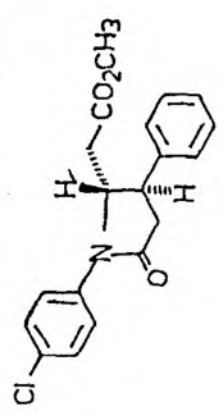
Name	B(1,1)	B(2,2)	B(3,3)	B(1,2)	B(1,3)	B(2,3)
C1	0.01949(9)	0.00910(4)	0.0204(1)	-0.0101(1)	-0.0110(2)	0.0053(1)
C1	0.0134(3)	0.0060(1)	0.0148(3)	-0.0042(3)	0.0009(5)	0.0034(3)
C2	0.0113(3)	0.0066(1)	0.0179(3)	0.0013(3)	0.0018(5)	0.0052(3)
C3	0.0124(2)	0.00505(9)	0.0166(3)	0.0024(3)	0.0060(5)	0.0009(3)
C4	0.0103(2)	0.00410(7)	0.0126(2)	-0.0000(2)	0.0052(4)	0.0005(2)
C5	0.0159(3)	0.00471(9)	0.0192(4)	0.0022(3)	-0.0029(6)	-0.0033(3)
C6	0.0186(4)	0.0056(1)	0.0198(4)	-0.0018(4)	-0.0023(7)	-0.0040(4)
C7	0.0106(2)	0.00377(7)	0.0130(2)	0.0007(2)	0.0037(4)	0.0001(2)
C8	0.0115(2)	0.00434(8)	0.0117(2)	0.0005(2)	0.0019(4)	-0.0005(2)
C9	0.0148(3)	0.00433(8)	0.0138(3)	-0.0002(3)	0.0056(4)	-0.0019(3)
C10	0.0136(2)	0.00366(7)	0.0136(2)	0.0010(2)	0.0073(4)	-0.0007(2)
C11	0.0098(2)	0.00476(8)	0.0145(3)	0.0001(2)	-0.0005(4)	-0.0026(3)
C12	0.0122(3)	0.0073(1)	0.0173(3)	0.0000(3)	0.0077(5)	-0.0005(4)
C13	0.0138(3)	0.0097(2)	0.0218(4)	-0.0012(4)	0.0112(6)	-0.0038(5)
C14	0.0137(3)	0.0087(2)	0.0305(5)	-0.0017(4)	0.0110(7)	-0.0119(5)
C15	0.0146(3)	0.0064(1)	0.0337(6)	0.0049(3)	0.0004(8)	-0.0072(5)
C16	0.0141(3)	0.0054(1)	0.0236(4)	0.0024(3)	0.0029(6)	-0.0019(4)
C17	0.0125(2)	0.00414(8)	0.0157(3)	0.0003(2)	0.0076(4)	0.0006(3)
C18	0.0173(3)	0.00408(8)	0.0152(3)	-0.0012(3)	0.0093(5)	-0.0001(3)
C19	0.0443(7)	0.0059(1)	0.0251(5)	-0.0086(5)	0.0272(9)	0.0049(4)
N	0.0115(2)	0.00367(6)	0.0126(2)	0.0006(2)	0.0026(3)	0.0000(2)
O1	0.0205(2)	0.00383(6)	0.0167(2)	0.0004(2)	0.0057(4)	0.0010(2)
O2	0.0255(3)	0.00488(7)	0.0234(2)	-0.0043(2)	0.0240(4)	0.0010(2)
O3	0.0223(3)	0.00654(8)	0.0291(3)	0.0087(3)	0.0187(5)	0.0107(3)

The form of the anisotropic thermal parameter is:

$$\exp[-(\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + \beta_{12}hk + \beta_{13}hl + \beta_{23}kl)]$$

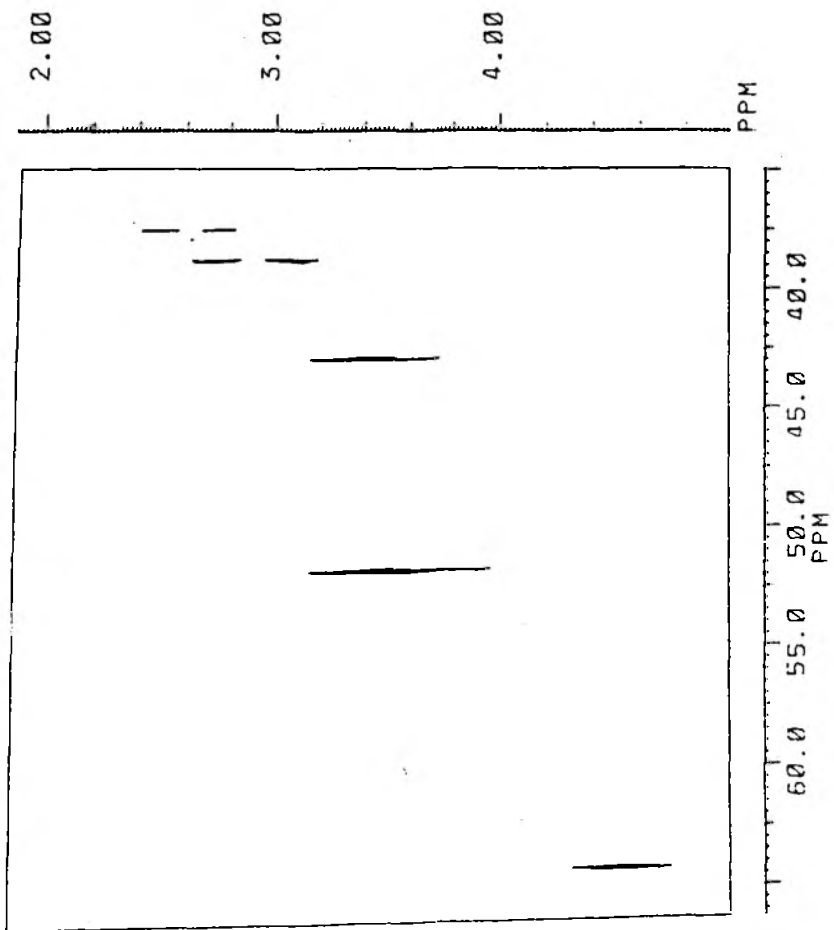
100 MHz CDCl₃ TMS

¹³C NMR of Compound 968

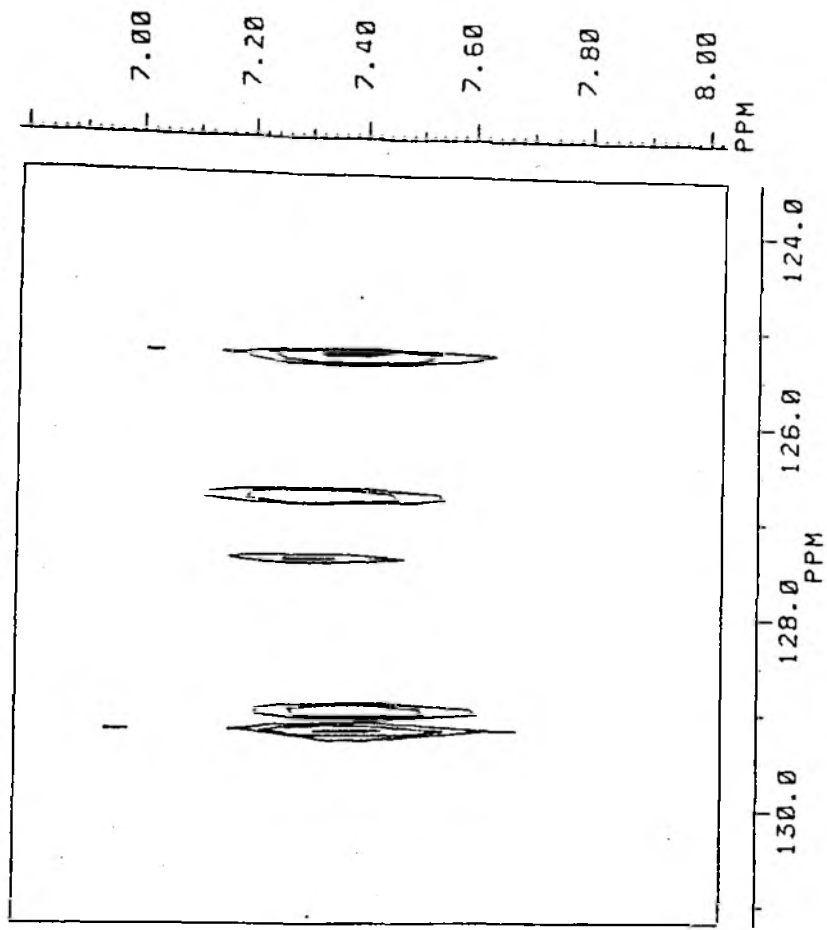


2DNMR OF Compound 968

JR-1 XHCORR F4TR6 C4L UNIV 13/7/83



JR-1 XHCORR F4TR6 C4L UNIV 13/7/83



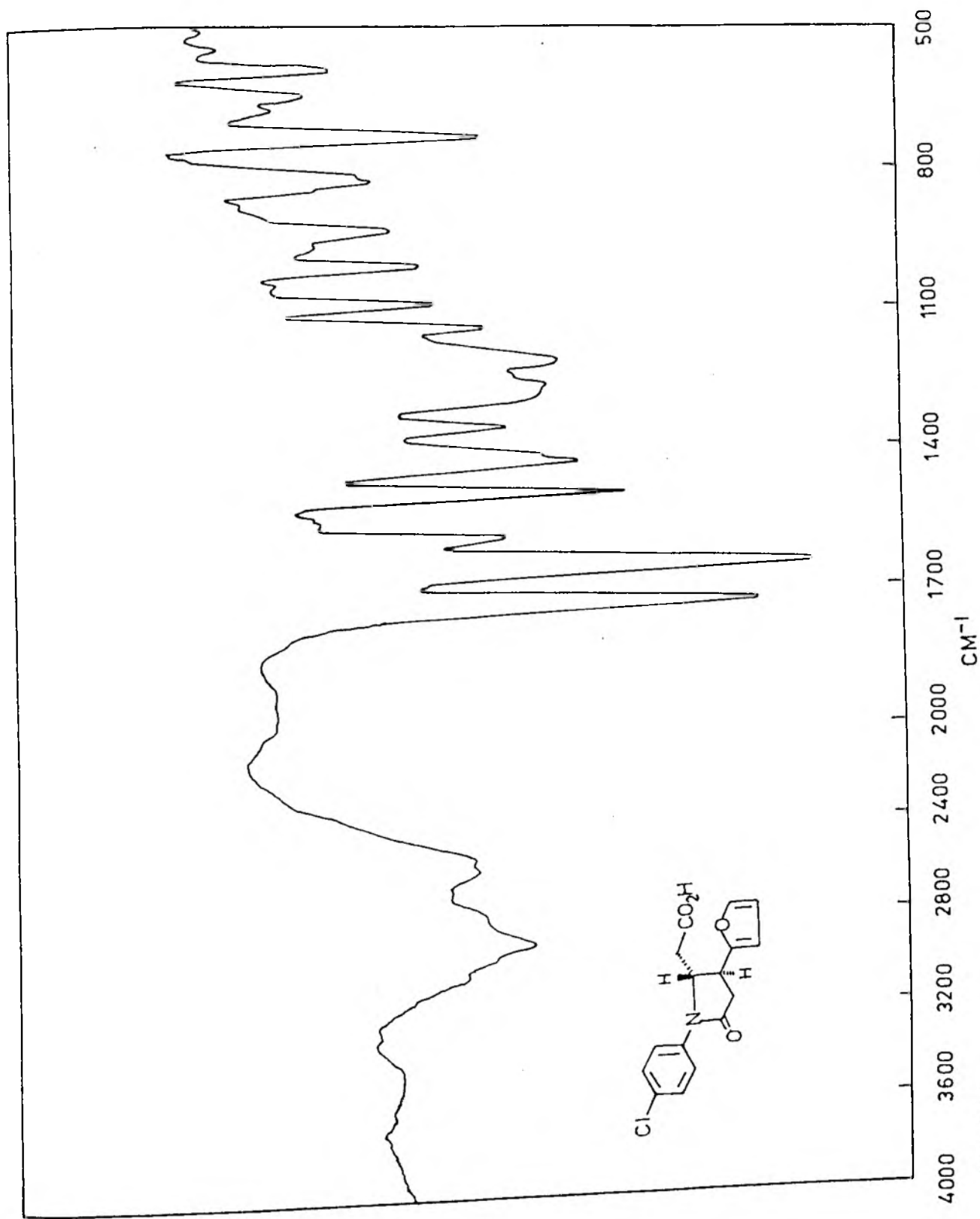


FIG 5.10

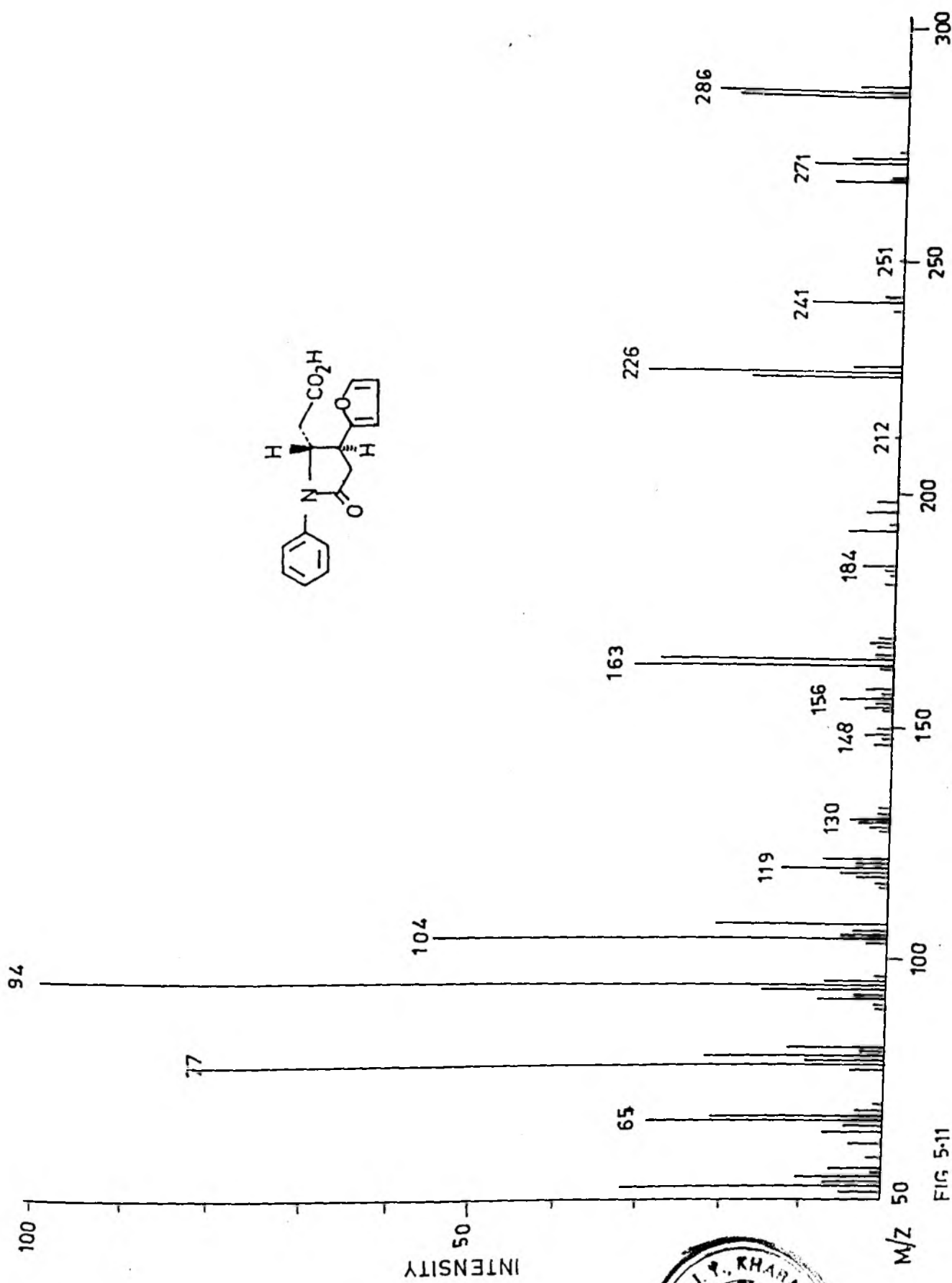
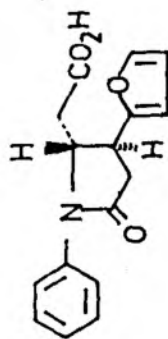
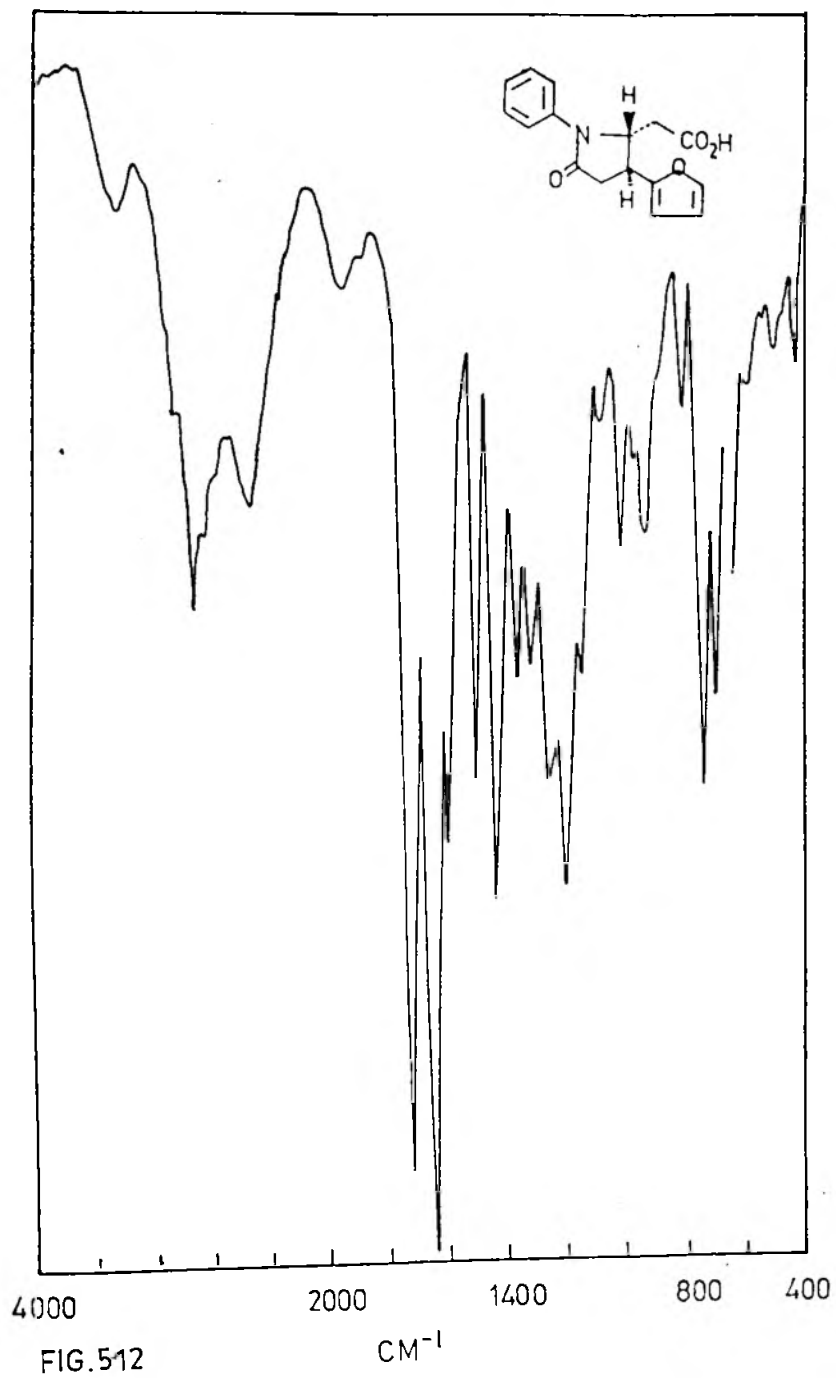
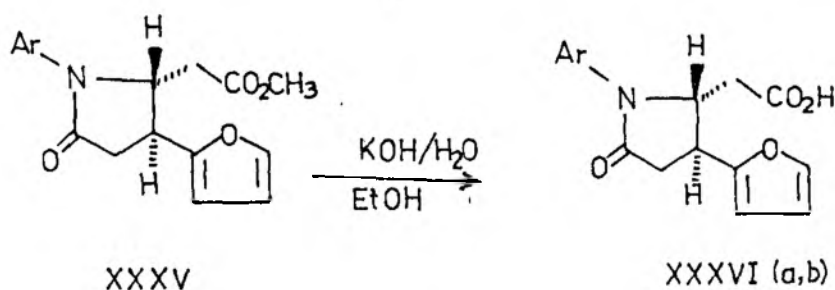


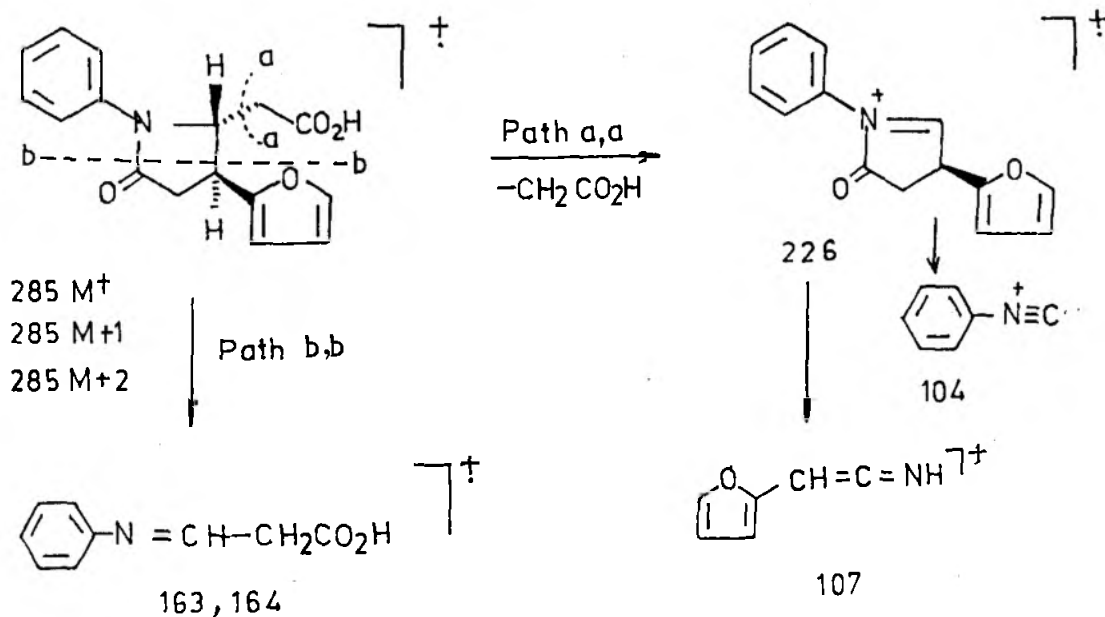
FIG 5-11



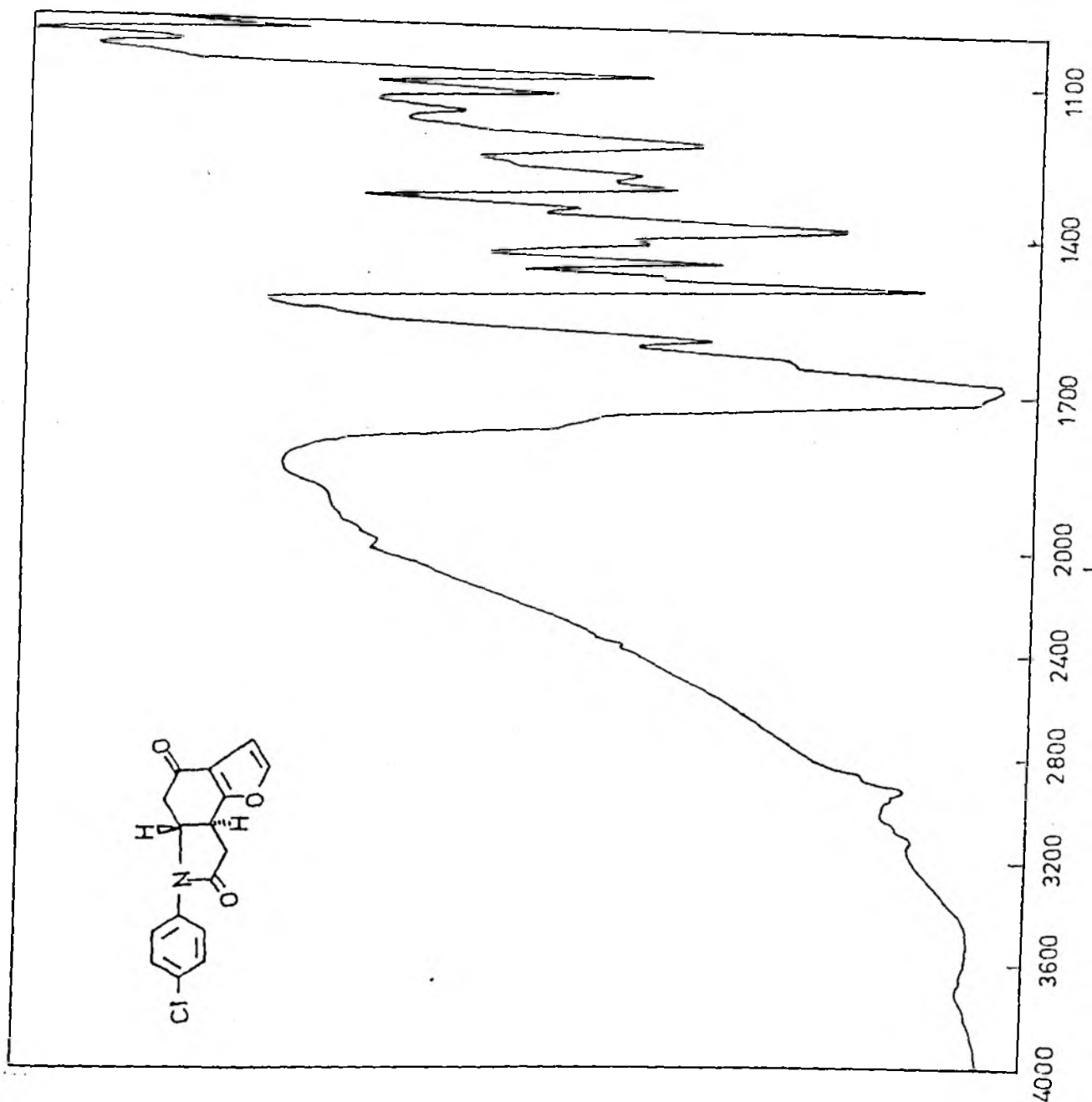
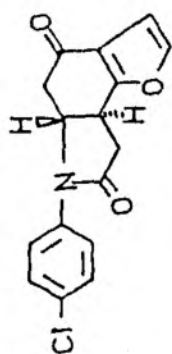
Alkaline hydrolysis of the esters [XXXV(a,b)] gave the acids in excellent yields. I.R. spectra of the compounds show $\nu_{C=O}$ absorptions at 1650-1644 cm^{-1} due to acid carbonyl and 1730-1720 cm^{-1} due to γ -lactam carbonyl functions respectively. Here also bathochromic shift in IR absorption is observed for the γ -lactam mono acids XXXVI(a,b). The compounds were characterised by usual spectral data as well as elemental analysis.



The mass spectra of the compound (XXXVIb) is explained as follows.



Cyclisation of the acids [XXXVI(a,b)] to the polycyclic furo γ -lactam derivatives [XXX(a,b)] was achieved by the treatment of acids with polyphosphoric (PPA) at 100°C. The final compounds were characterised by IR, NMR and mass spectral data and also by comparison with the CMR of the compound (XXV).



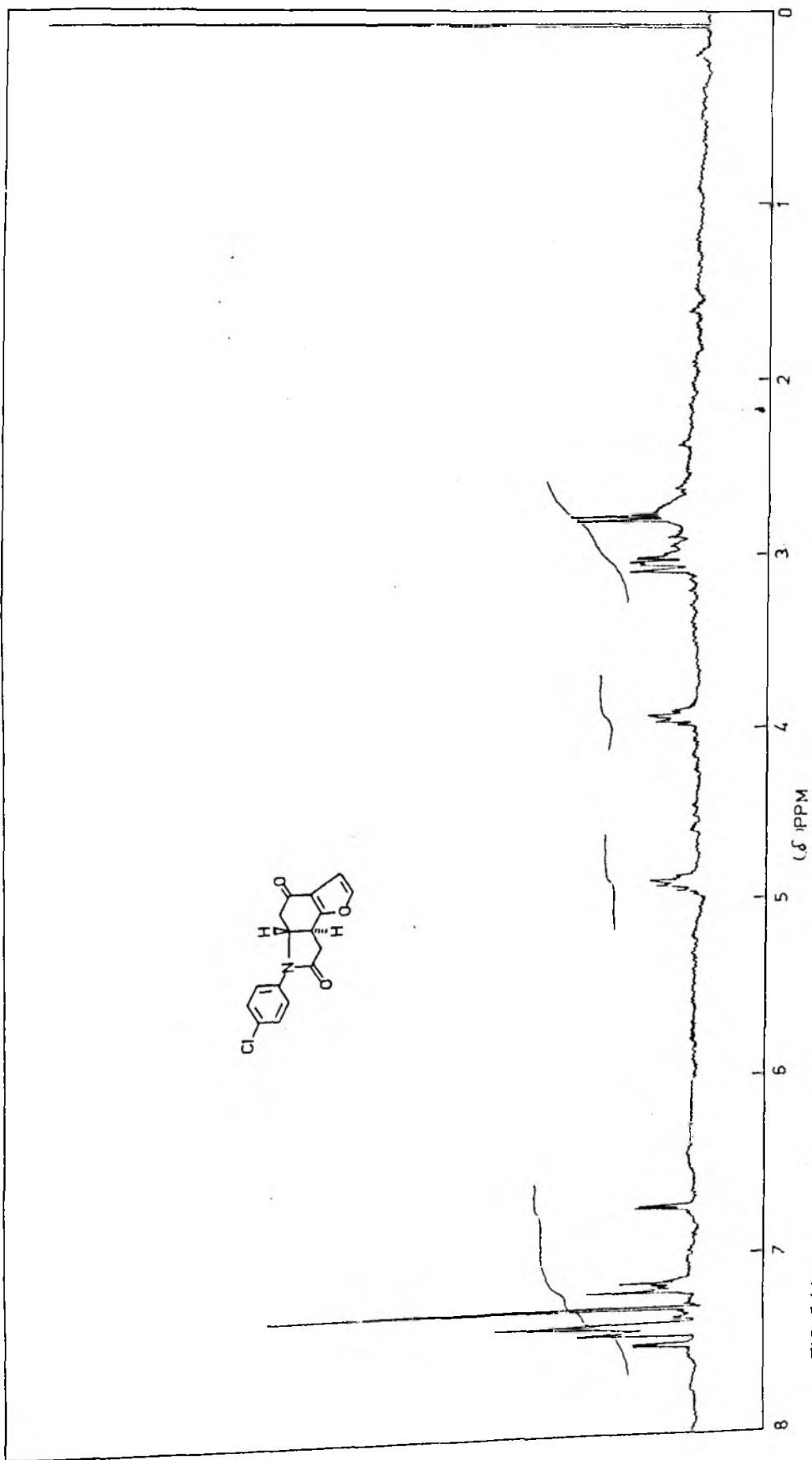
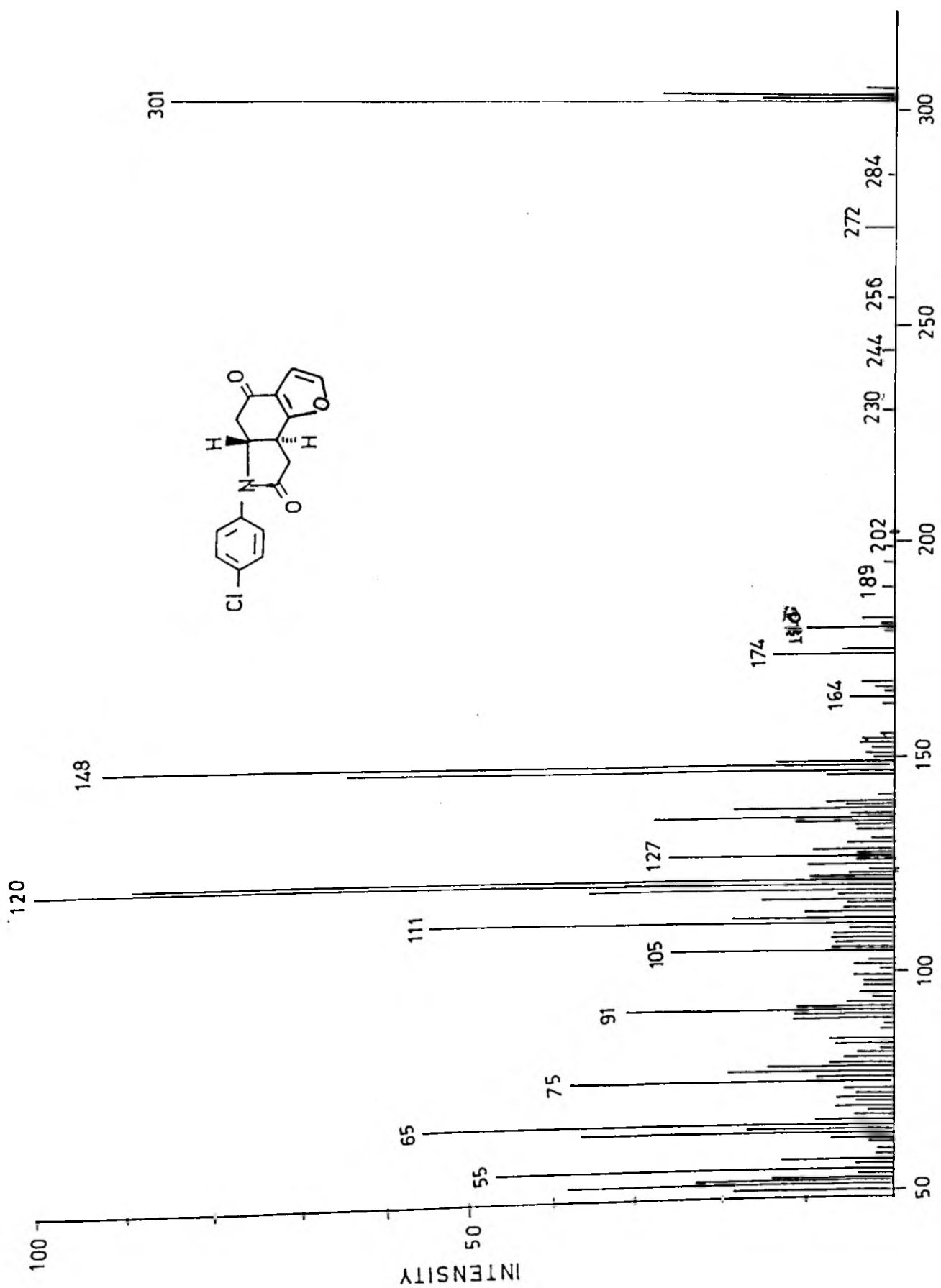
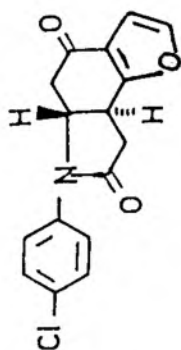


FIG. 5-14



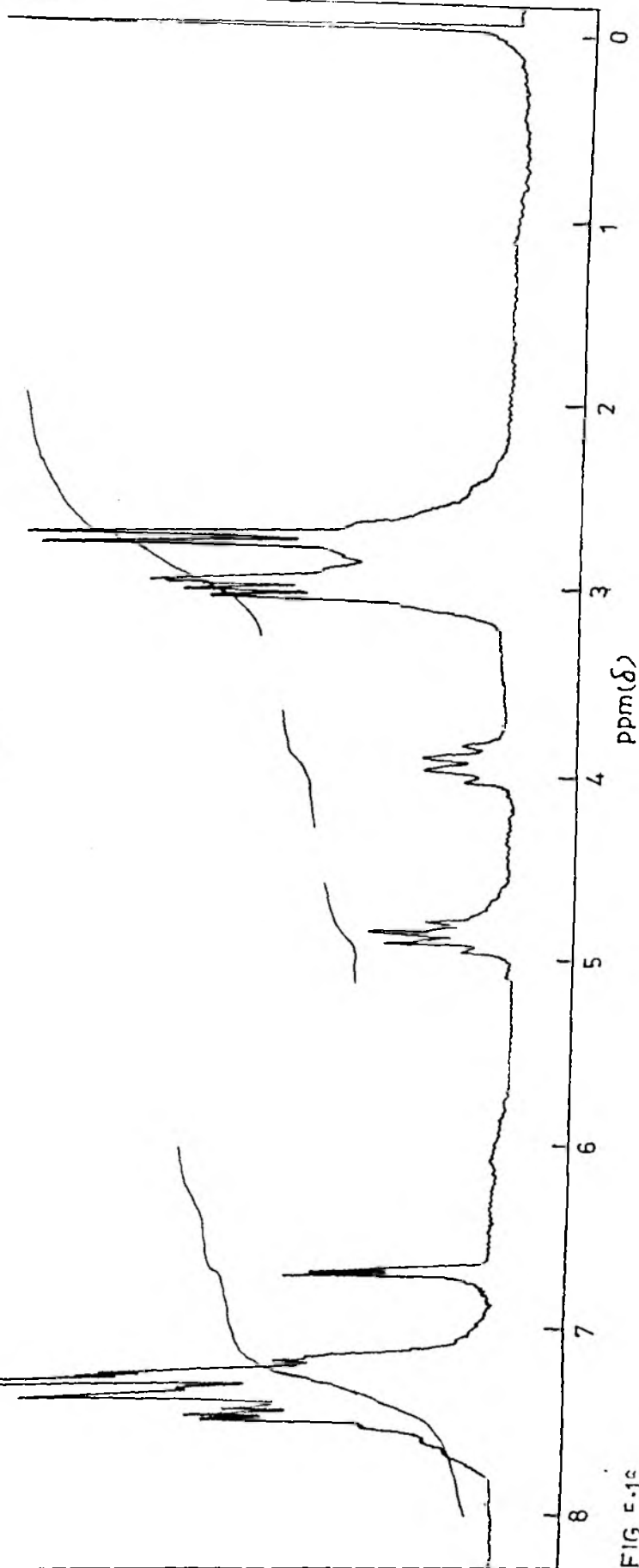
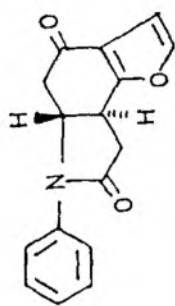
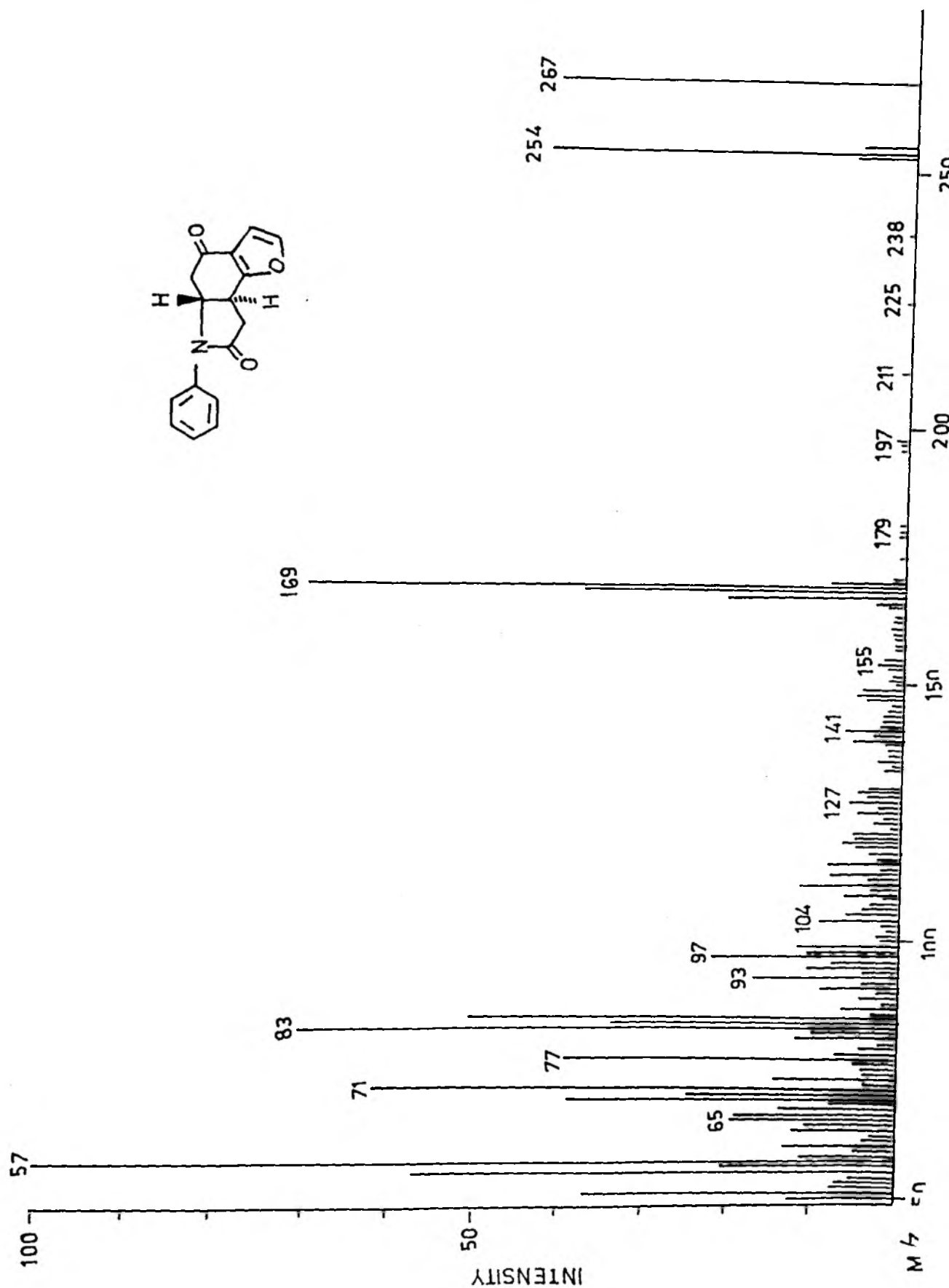
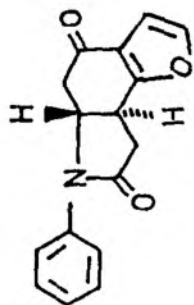


FIG 5.1s



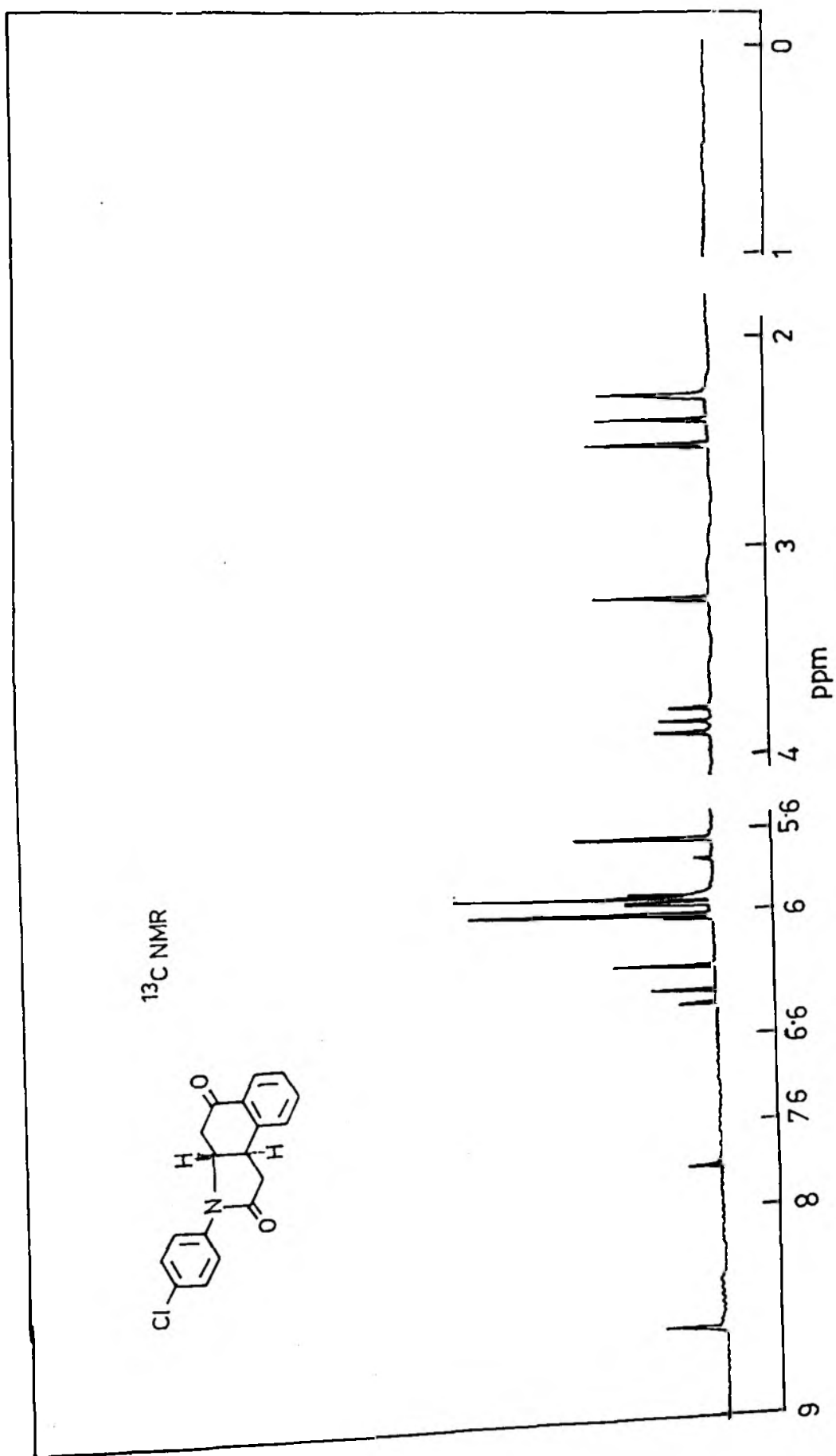


FIG. 5-18

EXPERIMENTAL

Diethyl p-chloroanilinomalonate (XXVIIIa) :

A mixture of p-chloroaniline (25.5 gm, 200 m mol) and diethyl bromomalonate (23 gm, 100 m mol) was taken in a round bottomed flask fitted with a two way stop cock. The flask was evacuated to 40 mm pressure and kept in an oven maintained at 70°C for 8 hr. The resulting solid cake was powdered and extracted with ether. Ether layer was washed with dil.HCl, water and dried (Na_2SO_4). Removal of solvent and recrystallisation (pet. ether) afforded 28 gm (98%) of white shining needle shaped crystals of anilinomalonate (XXVIIa), m.p. 91-92°C.

1-(p-Chlorophenyl)-4-furyl-5,5-dicarbethoxy pyrrolidin-2-one (XXXIa) :

To a mixture of diethyl p-chloroanilinomalonate (5.7 gm, 20.9 m mol) and triethylamine (4 gm, 36.3 m mol) in 50 ml of dry benzene, 3-(2-furyl)-acryloyl chloride (3.8 gm, 20.9 m mol, which was prepared from 3-furylacrylic acid)⁴¹ in 25 ml dry benzene was added dropwise with stirring. The reaction mixture was warmed up and the precipitate of triethylamine hydrochloride was separated out. The reaction mixture was refluxed on a water bath, protecting from moisture for 6 hrs. Then it was cooled to room temperature and the reaction mixture was washed successively with water, cold 2N.HCl solution and 5% sodiumbicarbonate solution and finally with water for several times. After drying the benzene layer over anhydrous Na_2SO_4 , solvent was evaporated at reduce pressure. The brown viscous oil was obtained which became solid after four or five days. The crude solid product was recrystallised twice from isopropyl alcohol to afford big colourless crystalline solid, m.p. 71-72°C, Yield - 5.75 gm (67.6%).

I.R. (KBr) $\bar{\nu}_{\max}$: 1740, 1725, 1588 cm^{-1} .

^1H NMR (CDCl_3) δ : 0.85 (t,3H), 1.2 (t,3H), 2.7-3.5 (dd,2H, $J = 9$ Hz), 3.6-4.2 (m,4H), 4.52-4.8 (dd,1H, $J = 9$ Hz), 6.3-6.5 (m,2H), 7.15-7.5 (m,5H).

Elemental analysis :	C	H	N
Found :	59.15	4.53	3.25 %
Calculated :	59.18	4.93	3.45 %
$(\text{C}_{20}\text{H}_{20}\text{NO}_6\text{Cl})$			

1-(p-Chlorophenyl)-4-furyl-5-carboxy pyrrolidine-2-one (XXXIIa) :

3.0 gm (7.3 m mol) of γ -lactam diester (XXXIa) was dissolved in 30 ml in ethanol. To this aqueous solution of KOH (0.9 gm, 15.7 m mol) in 10 ml of water was added. The mixture was refluxed for four hours. Ethanol was distilled off. The residue was diluted with water and then acidified with cold dil.HCl. The solid separated was extracted with ethyl acetate for several times, dried (Na_2SO_4) and solvent removed, crude product obtained on recrystallisation with ethylacetate-pet.ether (60-80° C) mixture gave shining colourless solid, m.p. 159-160°C, Yield - 2.1 gm (93%).

I.R. (KBr) $\bar{\nu}_{\max}$: 1748, 1659, 1588 cm^{-1} .

^1H NMR (CDCl_3) δ : 2.73-2.83 (dd,1H, $J = 4$ Hz), 3.03-3.13 (dd,1H, $J = 9$ Hz), 3.75-3.85 (m,1H), 4.78 (d,1H, $J = 3.3$ Hz), 6.23 (d,1H, $J = 3.2$ Hz), 6.36 (t,1H), 7.3-7.45 (m,5H).

MS (m/z) : 307 (M+2), 306 (M+1), 305 (M^+), 262, 261, 260, 220, 218, 107.

1-(p-Chlorophenyl)-4-furyl-5-carbonyl chloride pyrrolidin-2-one (XXXIIIa) :

The acid (XXXIIa) (1.9 gm, 6 m mol) was dissolved in dry methanol (10 ml) and was converted to its sodio-salt by neutralising with a dilute solution of (2%) sodium methoxide in methanol using phenolphthalein as indicator. The solvent was removed under reduced pressure. The sodium salt thus obtained was dried by distilling benzene thrice from it (25ml x 3) and finally dried in vacuum for half hr. The dry sodio-salt was suspended in dry benzene (50 ml) containing catalytic amount of anhydrous pyridine (Ca.0.3 ml) and cooled in ice bath. Oxalyl chloride (1.1 gm, 8 m mol) was added to the reaction mixture with constant shaking. After 30 min in ice bath, the reaction mixture was kept at room temperature for 1 hr and 30 min at 60°C. The sodium chloride filtered off and the filtrate was concentrated in vacuum. The acid chloride obtained as a off white solid which was directly used for next step.

I.R. (KBr) $\nu_{\max}$: 1704, 1794 cm^{-1} .

1-(p-Chlorophenyl)-4-furyl-5-diazoacetyl pyrrolidin-2-one (XXXIVa) :

The crude acid chloride (XXXIIIa) was dissolved in dry ether dichloromethane mixture. This was added dropwise in about 30 min to an ice cooled solution of CH_2N_2 (generated from 10 gm of N-methylnitrosomethyl urea). The mixture was kept for overnight at room temperature. Removal of solvent and excess of diazomethane gave a yellowish brown oil. This was dissolved in dry ether and passed through a short column of neutral alumina. Evaporation of solvent gave yellow viscous oil which solidified on standing. Sample recrystallised from ether gave shining white solid, m.p. 120-121°C, Yield - 2.0 gm (quantitative).

I.R. (KBr) $\nu_{\max}$: 1647, 1708, 2110 cm^{-1} .

^1H NMR (CDCl_3) δ : 2.64-2.96 (dd, 1H, $J = 5.5$ Hz), 2.92-3.28 (dd, 1H, $J = 8.5$ Hz), 3.6-3.84 (m, 1H), 4.72 (d, 1H, $J = 4$ Hz), 5.4 (s, 1H), 6.26 (d, 1H, $J = 4$ Hz), 6.32-6.4 (dd, 1H), 7.36-7.6 (m, 5H)

1-(p-Chlorophenyl)-4-furyl-5-carbomethoxy methyl pyrrolidin-2-one (XXXVa) :

To a stirred solution of diazoketone (0.875 gm, 2 mmol) in 25-30 ml dry methanol at 50°C , 1.5 gm of freshly prepared Ag_2O was added in 2-3 batches. Immediate evolution of N_2 took place. When the evolution of N_2 ceased a further quantity of Ag_2O (~1 gm) was added and the mixture was refluxed for 2 hrs on water bath. Then it was filtered and solvent removed. The brownish yellow oil was purified by passing through short column of neutral Al_2O_3 . Elution with ether afforded a viscous oil which solidified on standing for a long time, m.p. $60-61^\circ\text{C}$. Yield - 0.86 gm (quantitative).

I.R. (KBr) $\nu_{\max}$: 1498, 1592, 1706, 1740 cm^{-1} .

^1H NMR (CDCl_3) δ : 2.52-2.68 (dd, 1H), 2.76-3.16 (dd, 2H), 3.40-3.68 (m, 1H), 3.52 (s, 3H), 4.5-4.8 (m, 1H), 6.2 (d, 1H), 6.28-6.36 (dd, 1H), 7.25-7.5 (m, 5H)

Elemental analysis : C H N

Found : 61.14 4.48 4.16 %

Calculated : 61.16 4.79 4.19 %

($\text{C}_{17}\text{H}_{16}\text{NO}_4\text{Cl}$)

1-(p-Chlorophenyl)-4-furyl pyrrolidin-2-one-5-acetic acid (XXXVIa) :

0.7 gm (2 m mol) of γ -lactam ester (XXXVa) in 20 ml ethanol and 10 ml water was refluxed with 6% KOH (aq.) solution (2.4-2.6 ml) for 4 hrs. The ethanol was removed as much as possible by distillation and the residue was diluted with water. The neutral matter was extracted with ether. The basic aqueous part was then acidified with chilled dil.HCl and extracted with ethylacetate. After usual work up it gave viscous oil which on keeping in vacuum for whole night it became white solid, m.p. 166-167°C. Yield - 0.62 gm (89.8%).

I.R. (KBr) $\nu_{\max}$: 1589, 1650, 1730 cm^{-1} .

9-(p-Chlorophenyl)-9-aza-3,8-dioxo-4,5-furobicyclo[4.3.0]nonane (XXXa) :

The acid (XXXVIa) (260 mg, 0.81 m mol) was stirred with 8 gm poly-phosphoric acid at 100°C for 30 min. After cooling it was decomposed with ice water and extracted with chloroform. The chloroform layer was then washed successively with NaHCO_3 solution, water and dried over anhydrous Na_2SO_4 . Removal of solvent gave a light brown solid which was further purified by passing through a column of basic alumina (benzene + ethyl acetate, 8:2) as a colourless solid, m.p. 140-141°C. Yield - 150 mg (61%).

I.R. (KBr) $\nu_{\max}$: 1690, 1702 cm^{-1} .

^1H NMR (CDCl_3) δ : 2.73-2.80 (m, 2H), 2.85-3.15 (m, 2H), 3.84-3.99 (m, 1H, $J = 4.5$ Hz), 4.8-4.89 (m, 1H, $J = 4.5$ Hz), 6.68 (d, 1H, $J = 1.9$ Hz), 7.1-7.45 (m, 4H), 7.52 (d, 1H, $J = 1.9$ Hz)

MS (m/z) : 303 ($M+2$), 302 ($M+1$), 301 (M^+), 272, 189, 180, 174, 148, 147, 121, 120, 111, 105, 91, 75, 65, 55.

Anilinomalonate (XXVIIIb) :

A mixture of aniline (27.6 gm, 296.7 m mol) and 36 gm (150 m mol) of diethylbromomalonate was evacuated to 40 mm pressure in a stopped round bottom flask. The reaction mixture was then allowed to stand at 70°C in an oven for 8 hrs. The resulting solid cake was powdered and extracted with ether. Ether layer was washed with dil.HCl and water several times, dried (Na_2SO_4). Removal of solvent and recrystallisation from ether gave 34.8 gm (95%) white colourless crystal of anilinomalonate (XXVIIb), m.p. 45-46°C.

1-Phenyl-4-furyl-5,5-dicarbethoxy pyrrolidin-2-one (XXXIb) :

To a mixture of diethyl anilinomalonate (7 gm, 18.86 m mol) and triethylamine (8 ml, 79 m mol) in 50 ml dry benzene, a solution of 3-2'-furyl acryloyl chloride (5 gm, 31 m mol) in benzene was added dropwise with stirring. The reaction mixture was refluxed on a water bath for 6 hrs. It was cooled to room temperature and washed successively with water, dil.HCl, 5% sodium bicarbonate solution and water. The organic layer was dried over sodium sulphate and the solvent was removed to get 5.6 gm of diester (XXXIb) in 62.8% yield, m.p. 95-96°C (isopropanol).

I.R. (KBr) ν_{max} : 1745, 1720, 1710, 1410 cm^{-1} .

^1H NMR (CDCl_3) δ : 0.81-0.93 (t,3H), 0.99-1.09 (t,3H), 2.81-2.96 (dd,1H, J = 8.6 Hz), 3.01-3.18 (dd,1H, J = 8.6 Hz), 3.72-4.17 (m,4H), 4.60-4.75 (dd,1H), 6.24 (d,1H), 6.41 (dd,1H), 7.18-7.48 (m,6H)

Elemental analysis :	C	H	N
Found :	64.29	5.22	3.35 %
Calculated :	64.69	5.66	3.77 %
(C ₂₀ H ₂₁ NO ₆)			

1-Phenyl-4-furyl-5-carboxy pyrrolidin-2-one (XXXIIb) :

2.6 gm (7.0 m mol) of the γ -lactam diester (XXXIb) was dissolved in 35 ml of ethanol. To this added a solution of KOH (1.8 ml, 18 m mol) in 10 ml water and refluxed for four hours. After usual work up it gave 1.48 gm (62.8%) of (XXXIIb) as white solid, m.p. 171-172°C (ethylacetate-benzene).

I.R. (KBr) $\nu_{\max}$: 1656, 1707 cm^{-1} .

NMR (DMSO- d_6) δ : 2.6-2.82 (dd,1H), 2.95-3.2 (dd,1H), 3.75-3.85 (m,1H), 4.80 (d,1H), 6.5 (m,2H), 7.1-7.5 (m,6H)

Elemental analysis :	C	H	N
Found :	70.28	4.79	5.19 %
Calculated :	70.58	5.09	5.49 %
(C ₁₅ H ₁₃ NO ₃)			

1-Phenyl-4-furyl-5-carbonyl chloride pyrrolidin-2-one (XXXIIIb) :

The acid (XXXIIb) (1.35 gm, 5 m mol) was dissolved in dry methanol (10 ml) and was converted to its sodio-salt by neutralising with a dilute solution of (2%) sodium methoxide in methanol using phenolphthalein as indicator. The dry sodio-salt was suspended in dry benzene (50 ml) containing catalytic amount of anhydrous pyridine (Ca.0.3 ml) and cooled in ice bath. Oxalyl chloride (0.9 gm, 7 m mol) was added to the reaction mixture with constant shaking. Following the same procedure as described for (XXXIIIa) the acid chloride was obtained as a white off solid, m.p. 126-127°C. The crude acid chloride was used directly for next step.

I.R. (KBr) $\nu_{\max}$: 1704, 1794 cm^{-1} .

1-Phenyl-4-furyl-5-diazoacetyl pyrrolidin-2-one (XXXIVb) :

The above acid chloride was dissolved in dry ether (60 ml) and added dropwise to a magnetically stirred ice cooled dry excess ethereal diazomethane (generated from N-methyl nitrosomethyl urea, 7 gm, dried over potassium hydroxide). The reaction mixture was left over night at room temperature and then filtered through a sintered glass funnel. Ether and excess of diazomethane was removed under reduced pressure to afford the crude diazoketone as brown viscous oil. This was dissolved in dry ether and passed through a shortcolumn of neutral alumina to get white solid of (XXXIVb), m.p. 121-122°C. Yield - 1.35 gm (91.8%).

I.R. (KBr) $\nu_{\max}$: 2107, 1708, 1638 cm^{-1} .

^1H NMR (CDCl_3) δ : 2.65-2.96 (dd, 1H, $J = 6$ Hz), 2.92-3.28 (dd, 1H, $J = 8.5$ Hz), 3.65-3.85 (m, 1H), 4.72 (d, 1H), 5.4 (s, 1H), 6.24 (d, 1H, $J = 4$ Hz), 6.26 (d, 1H, $J = 4$ Hz), 6.32-6.4 (dd, 1H), 7.34-7.6 (m, 6H)

1-Phenyl-4-furyl-5-carbomethoxy methyl pyrrolidin-2-one (XXXVb) :

460 mg (1.55 mmol) of (XXXIVb) on reaction with excess of freshly prepared Ag_2O (1.0 gm) in anhydrous methanol under the condition as described for (XXXIVa) gave as faint yellow viscous oil which was purified by passing a short column of neutral alumina. Elution with ether afforded a viscous yellow oil, Yield - 450 mg (97.8%).

I.R. (KBr) $\nu_{\max}$: 1706, 1740 cm^{-1} .

^1H NMR (CDCl_3) δ : 2.5-2.68 (dd, 1H), 2.76-3.18 (m, 2H), 3.4-3.68 (dd, 1H), 3.52 (s, 3H), 4.5-4.7 (m, 1H), 6.2 (d, 1H), 6.3-6.4 (dd, 1H), 7.2-7.5 (m, 6H)

1-Phenyl-4-furyl pyrrolidin-2-one-5-acetic acid (XXXVIb) :

390 mg (1.30 m mol) of γ -lactam ester (XXXVb) on hydrolysis with an aqueous alcoholic solution of KOH (140 mg, 2.4 m mol) gave, after usual workup, 300mg(80.8%) of the acid (XXXVIb) as a colourless oil which solidified on keeping for whole night in vacuum, m.p. 147-148°C.

I.R. (KBr) $\nu_{\max}$: 1644, 1720, 3436 cm^{-1} .

^1H NMR (CDCl_3) δ : 2.5-2.7 (m,2H), 2.85-3.2 (m,2H), 3.5-3.8 (m,1H), 4.5-4.8 (m,1H), 6.2 (d,1H), 6.4 (d,1H), 7.2-7.5 (m,6H) ppm.

MS (m/z) : 287 (M+2), 286 (M+1), 285 (M^+), 271, 241, 226, 225, 164, 163, 107, 104, 94, 77, 65.

9-Phenyl-9-aza-3,8-dioxo-4,5-furobicyclo[4.3.0]nonane (XXXb) :

210 mg (0.73 m mol) of the acid (XXXVIb) was heated with 8 gm of polyphosphoric acid at 100 °C with stirring. After usual workup it afforded a light brown solid which was passed through a short column of basic alumina. Elution with (benzene + E.A.; 8:2) gave a colourless solid, m.p. 171-172°C, Yield - 110 mg (56%).

I.R. (KBr) $\nu_{\max}$: 1692, 1701 cm^{-1} .

^1H NMR (CDCl_3) δ : 2.6-2.8 (m,2H), 2.85-3.1 (m,2H), 3.8-4.05 (m,1H), 4.8-4.9 (m,1H), 6.7 (d,1H), 7.1-7.6 (m,5H)

MS. (m/z) : 257(M^+ 254, 211, 197, 169, 168, 167, 83, 77, 71, 57.

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