SYNTHESIS, REACTIONS AND PROPERTIES OF SOME HETEROCYCLIC COMPOUNDS

THESIS SUBMITTED TO THE UNIVERSITY OF CALICUT IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN CHEMISTRY

By

SOBHA.T.D

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF CALICUT
KERALA - INDIA
673 635

OCTOBER 1998

DEDICATED TO
THE FOND MEMORY
OF MY BELOVED MOTHER

CERTIFICATE

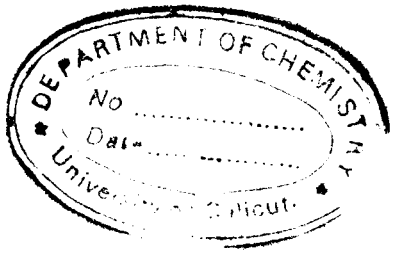
This is to certify that the thesis bound herewith is an authentic record of the research work carried out by Mrs.Sobha.T.D, under my supervision in partial fulfilment of the requirements for the Degree of Doctor of Philosophy in Chemistry of the University of Calicut, and further that no part thereof has been presented before for any other Degree.

Dr.P.MOHAMED SHAFI

Supervising Teacher.

Forwarded

13/10/98



DECLARATION

I hereby declare that the thesis bound herewith is an authentic record of the research work carried out by me under the supervision of Dr.P.Mohamed Shafi, M.sc, Ph.D, Reader, Department of Chemistry, University of Calicut in the partial fulfilment of the requirements for the Degree of Doctor of Philosophy in Chemistry of the University of Calicut, and further that, no part thereof has been presented before for any other Degree.

Sobha.T.D

SOBHA.T.D.

AKNOWLEDGEMENT

I wish to express my deep debt of gratitude and sincere thanks to Dr.P.Mohamed Shafi, Reader, Department of Chemistry, University of Calicut, my supervising teacher, for his able guidance and constant encouragement throughout the course of this work.

I am very grateful to Dr.N.Thankarajan, former Head of the Department of Chemistry and Dr.T.D.Radhakrishnan Nair, Professor and Head of the Department of Chemistry, University of Calicut, for providing necessary facilities.

I aknowledge with thanks Dr.Reiner Waibel, Frederich Alexander University, Germany, Dr.Leopold Jirovetz, Institute of Pharmaceutical Chemistry, University of Vienna, Dr.P.A.Joy, NCL, Pune and CDRI, Lucknow for Spectral Studies.

I am greately indebted to my teachers and colleagues at the University of Calicut and also at Sree Kerala Varma College Thrissur for their immense help which was essential for the completion of this work.

The financial assistance as Research Fellowship obtained from Council of Scientific and Industrial Research (Govt. of India) is greatefully aknowledged.

I am really greateful to the affections and co-operations of my husband, son, father, brother, sister, mother-in-law, brothers -in-law and sisters-in-law. Without their help I might not have completed this research work.

Finally I thank to Cyrix Computer Systems and D T P, Beach Road, Vatanappally for processing the manuscript of the thesis.

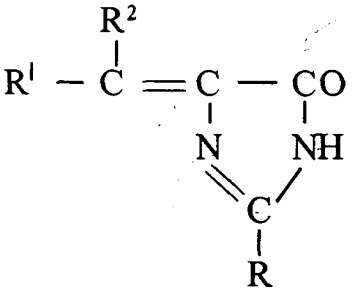
SOBHA.T.D

CONTENTS

PREFACE

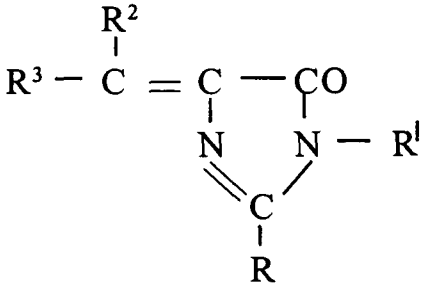
Heterocyclic chemistry is a wide and expanding area of chemistry. Out of the reserch work carried out in organic chemistry a substantial part is specifically devoted to the study of heterocyclic compounds.

The heterocyclic compounds studied and presented in this thesis belong to the imidazolinones. The 2,4 - disubstituted 2 - imidazolin - 5 - ones with an exocyclic double bond in the 4 - position are known as unsaturated 2,4 - disubstituted 2 - imidazolin - 5 - ones (I). They are the nitrogen analogs of the well known azlactones or unsaturated 2,4 - disubstituted - 2 - oxazolin - 5 - ones.



I

(I,-O-instead of - NH -). In 1962 Kidwai and Devasia developed a method for the synthesis of α amino acids and their derivatives starting from 2 - imidazolin - 5 - ones. The 1,2,4 - trisubstituted 2- imidazolin - 5 - ones (II) also are important



II

as many of them have proven biological properties.

One of the objectives of the work discribed in this thesis was to develop new methods for the synthesis of unsaturated 2,4 - disubstituted 2 - imidazolin - 5 - ones and to convert 2,4 - disubstituted 2 - imidazolin - 5 - ones into acylamino acid amides and acylamino acids. The synthesis of new 1,2,4 - trisubstituted 2 - imidazolin - 5 - ones, studies on dimerisation of unsaturated 2,4 - disubstituted - 2 - imidazolin - 5 - ones on heating with HI and acetic anhydride and the formation of hitherto unreported imidazolinones by the reaction between imidic acid esters and glycine ester were also the objectives of this work.

In the present work a new method for the synthesis of 4 - arylidene - 2 - phenyl - 2 - imidazolin - 5 - ones has been developed. Condensation of aromatic aldehydes with benzoylglycine amide in boiling potassium carbonate solution yielded the above compounds. The machanism of their formation also has been proved. Based on this work an article entitled " A new synthetic route to 4 - arylidene - 2 - phenyl - 2 - imidazolin - 5 - one " has been accepted for publication in Indian Journal of Chemistry (section B).

1,2,4 - Trisubstituted 2 - imidazolin - 5 - ones were synthesised by the reaction between azlactones and amines in glacial acetic acid. The amine used was p- aminobenzoic acid. The imidazolinones thus prepared contain a carboxylic acid group which could be esterified and also could be converted into an amide group by known methods. By this approch new imdazolinones were prepared. Based on this work an article entitled "Synthesis of 1,2,4 - trisubstituted 2 - imidazolin - 5 - ones" has been published in Asian J. Chem., **9 (4)** (1997), 881.

4 - Arylidene - 2 - aryl - 2 - imidazolin - 5 - ones can be converted to acyl amino acid amides and acylamino acids by reduction with HI - P followed by hydrolysis. But during HI - P reduction dimerisation of imidazolinones was ob-

served. It was also observed that treatment of unsaturated 2,4 -disubstituted 2 - imidazolin - 5 - ones with HI itself yielded 4,4^{1} - diarylmethyl - 2,2^{1} - diaryl - 4:4^{1} - biimidazolin - 5,5^{1} - diones. 4,4^{1} - Dibenzyl - 2,2^{1} - diphenyl - 4:4^{1} - biimidazolin - 5,5^{1} - dione underwent Mc Lafferty type rearrangement on heating.

Reaction between imidic acid ester and glycine ester yield 2 - substituted 2 - imidazolin - 5 - ones. But it was observed that this 2 - substituted imidazolinones further undergoes reaction with imidic acid ester giving 4 - (amino, arylmethylene) - 2 - aryl - 2 - imidazolin - 5 - ones. The amino group in these compounds could be acetylated to get their acetyl dervatives.

Unsaturated 2 - imidazolin - 5 - ones on simultaneous reduction and hydrolysis afford acylamino acid amides and acylamino acids. Devasia and Shafi synthesised a number of acylamino acid amides and acylamino acids by this method. They used 10% potassium hydroxide solution for this convertion. However the same procedure did not yield acylamino acid amide or acylamino acid in the case of 4 - arylidene - 2 - (m-tolyl) - 2 - imidazolin - 5 - ones. But, on using 5% KOH solution and zinc dust for simultaneous reduction and hydrolysis this imidazolinones yielded the corresponding acylamino acid amides and acylamino acids in the same experiment. Based on this work an article entitled "Synthesis of Acylamino Acid Amides and Acylamino Acids by the Simultaneous Reduction and Hydrolysis of Imidazolinones" has been published in Asian J. Chem., **10(4)** (1998), 1059.

PART I

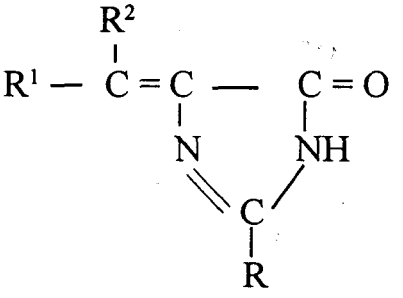
REVIEW

The work presented in this thesis is concerned with the synthesis and reactions, including reduction and hydrolysis to acylamino acid amides and acylamino acids, of unsaturated 2- imidazolin-5-ones. 2-Imidazolin-5-ones with an exocyclic double bond in the fourth position is known as unsaturated 2-imidazolin-5-ones. Therefore it is quiet appropriate to furnish the review of literature for the synthesis and reactions of unsaturated 2 - imidazolin - 5 -ones. The following review so prepared deals with synthesis of unsaturated 2,4- disubstituted and 1,2,4 - trisubstituted - 2 - imidazolin-5-ones and the synthesis of acylamino acid amides and acylamino acids by direct methods.

Section I

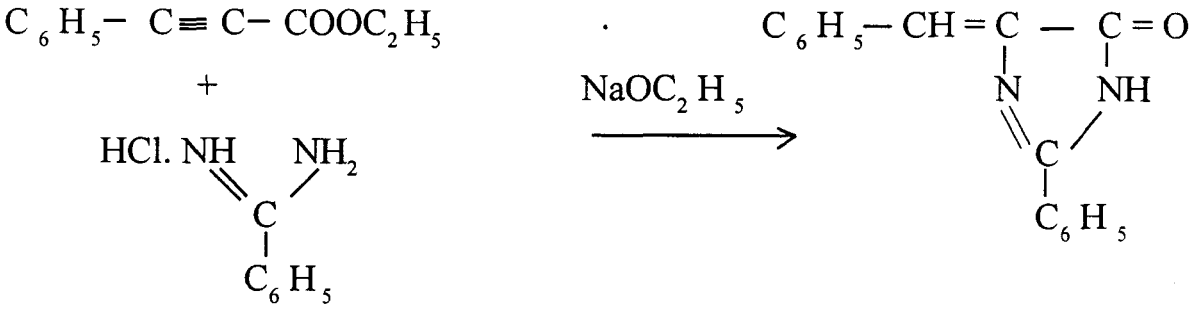
Synthesis of unsaturated 2-imidazolin -5-ones

Unsaturated 2,4 - disubstituted -2-imidazolin - 5-ones are also known as unsaturated 2,4 - disubstituted 5(4H)- imidazolones, unsaturated 2,4 - disubstituted 5-ketodihydroglyoxalines and unsaturated 2,5 - disubstituted 3,5 - dihydro-4-H-imidazole-4-ones.



Unsaturated 2,4-disubstituted-2-imidazolin-5-ones are usually called as unsaturated 2-imidazolin-5-ones for the sake of convenience.

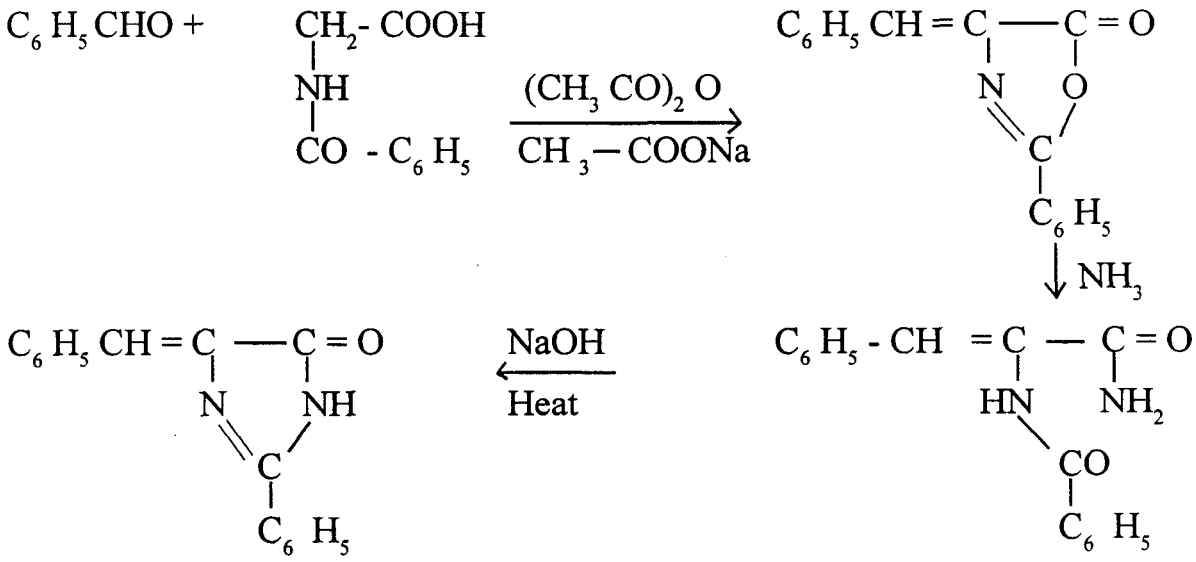
The synthesis of an unsaturated 2 - imidazolin - 5 - one was first reported in 1899 by Ruheman and Cunnington [1,2] . They synthesised 2 - phenyl - 4 - benzylidene -2-imidazolin - 5 - one by condensing phenylpropiolic ester with benzamidine hydrochloride in presence of sodium ethoxide. But no other unsaturated 2-imidazolin-5- one have been prepared by this method.



At present, however, there are four general methods for the synthesis of unsaturated 2- imidazolin - 5- ones namely azlactone, amidine - glyoxal, imidic acid ester - glycine ester and amidine - haloacetic ester method.

1. Azlactone method

Erlenmeyer [3-7] prepared 2 -phenyl -4-arylidene - 2 - imidazolin - 5- ones starting from azlactones. On heating a mixture of benzaldehyde and hippuric acid in presence of fused sodium acetate and acetic anhydride, the azlactone of α-benzoylaminocinnamic acid is formed. The azlactone readily affords α-benzoylaminocinnamic acid amide on heating with conc. ammonia in the presence of alcohol. The amide then cyclises to give 2-phenyl-4- benzylidene-2-imidazolin-5-one under the influence of hot dilute sodium hydroxide solution.

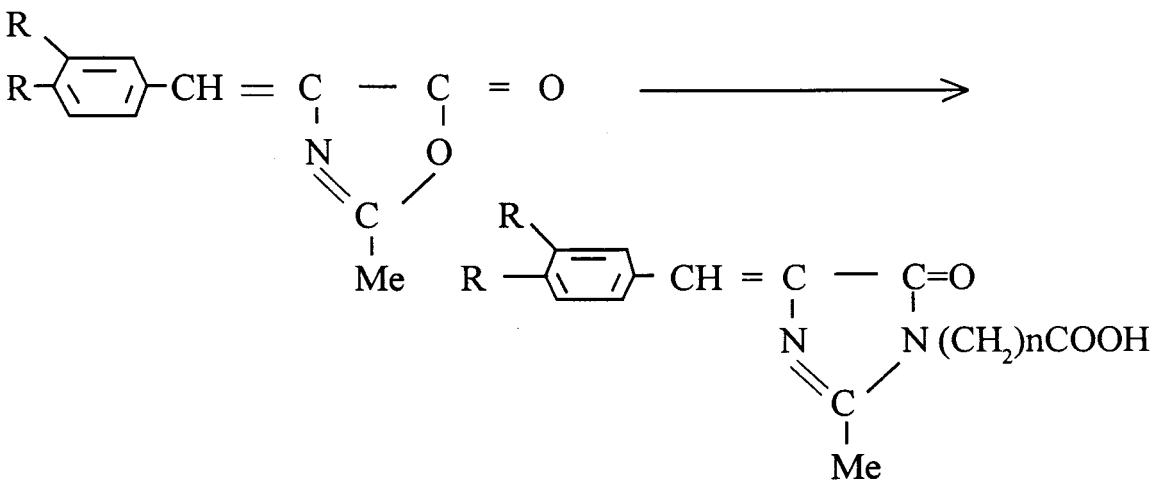


In 1946 Williams and Ronzio [8] obtained high yield of 2 - phenyl - 4-benzylidene -2- imidazolin-5-one from the corresponding azlactone by heating with aqueous alcoholic ammonia followed by treatment with potassium carbonate.

In 1948 Cornforth and Huang [9] prepared 2 - phenyl-4- benzylidene, anisylidene and furfurylidene-2-imidazolin-5- ones by dissolving appropriate azlactones in dioxan and warming with aqueous ammonia followed by boiling with potassium hydroxide.

In 1953 Kjaer [10] employed azlactone method in the synthesis of 2-phenyl-4-isobutylidene and 2-methyl - 4-benzylidene-2-imidazolin-5-ones. In 1971 Harhash and coworkers [11] prepared 2-benzyl -4- benzylidene-and anisylidene-2-imidazolin-5-ones by refluxing a mixture of the corresponding azlactones, concentrated ammonia and potassium carbonate in ethanol for 2 hours.

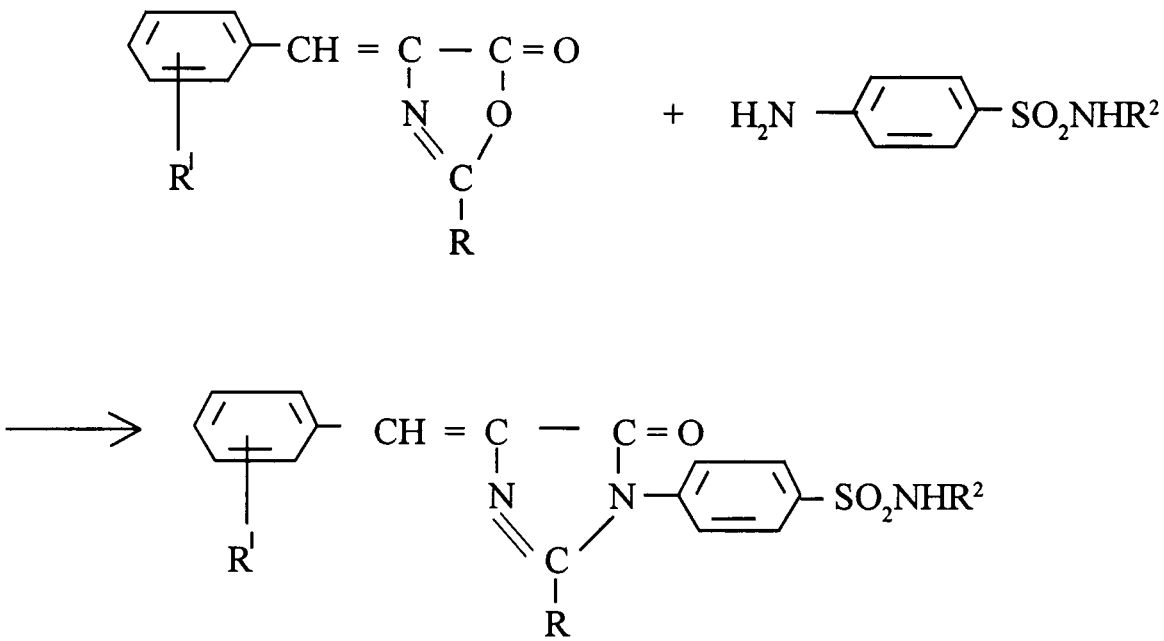
In 1979 Tiwari and Satsangi [12] synthesised piperazine - 1,4 - bis (2 - methyl - 4 - arylidene - 5 - oxoimidazolinyl -1 - alkyl carboxylate) by the reaction between piperazine and imidazoline as follows.



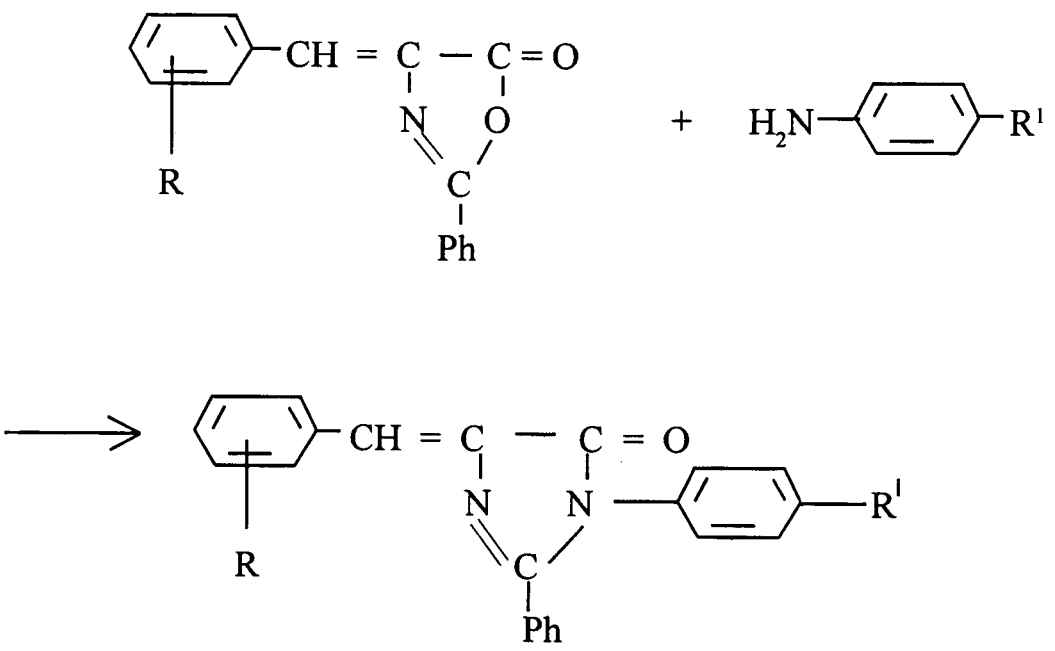
Piperazine ⟶ Piperazine - 1, 4 - bis (2 - methyl - 4 - arylidene - 5 - oximidazolinyl - 1 - alkyl - carboxylate)

Selected piperazine - 1, 4 - bis (2 - methyl - 4 - arylidene - 5 - oximidazolinyl - 1 - alkyl - carboxylate) possessed central nervous system depressant activity, but none had antiparkinsonian activity.

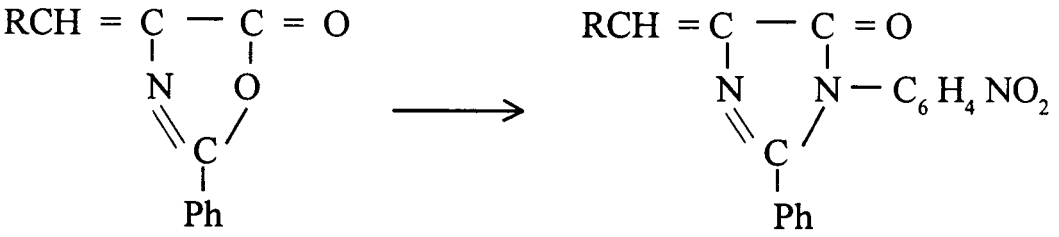
Gupta and coworkers [13] prepared 1 - (substituted sulfamidophenyl) - 2 - methyl /aryl - 4 (substituted benzylidene) - 5 - imidazolinones by the condensation of azlactones with p - aminobenzenesulphonamides.



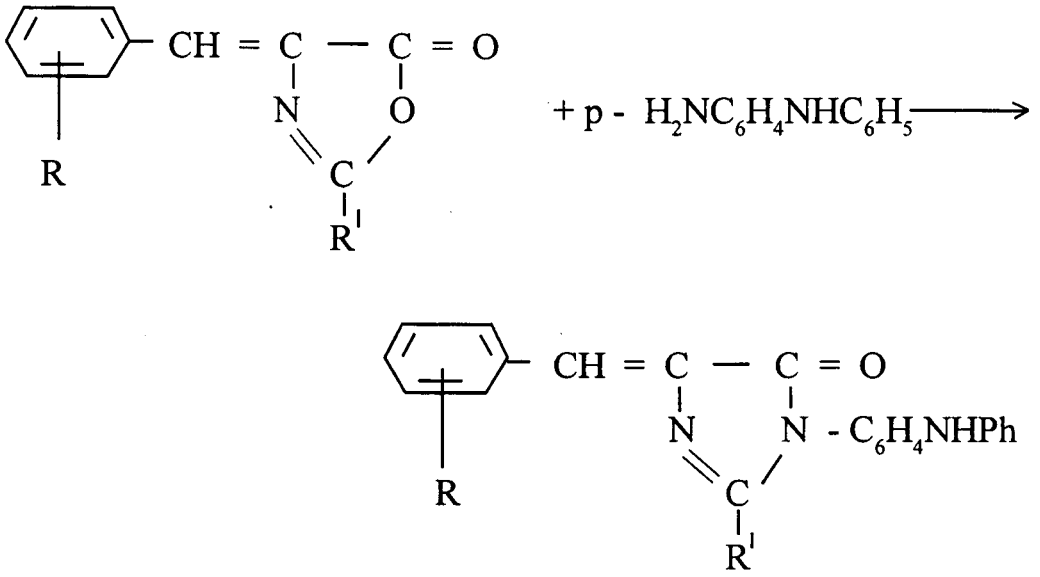
Badr and coworkers [14] prepared 2 - phenyl - 4 - arylidene - 2 - imidazolin - 5 - ones and their derivatives from 2 - phenyl - 4 - arylidene - 2 - oxazolin - 5 - ones.



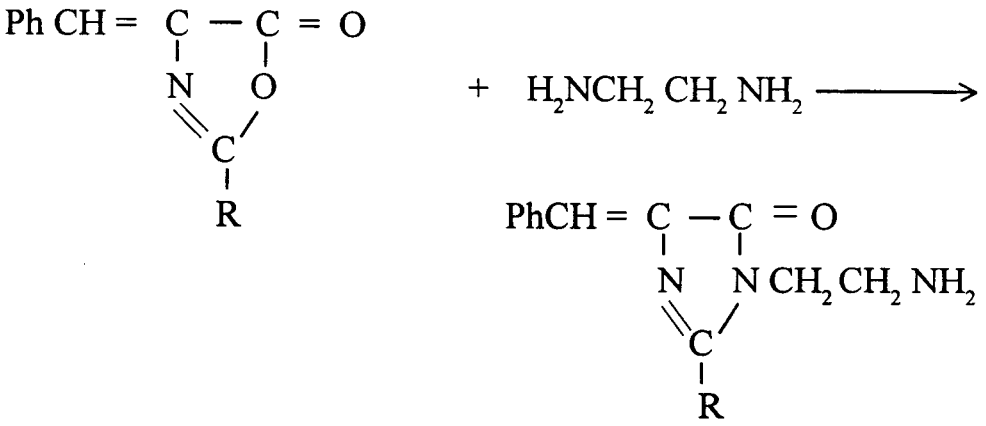
Mukerji and coworkers [15] synthesised 1,2,4- trisubstituted imidazolinones by treating oxazolones with substituted anilines.



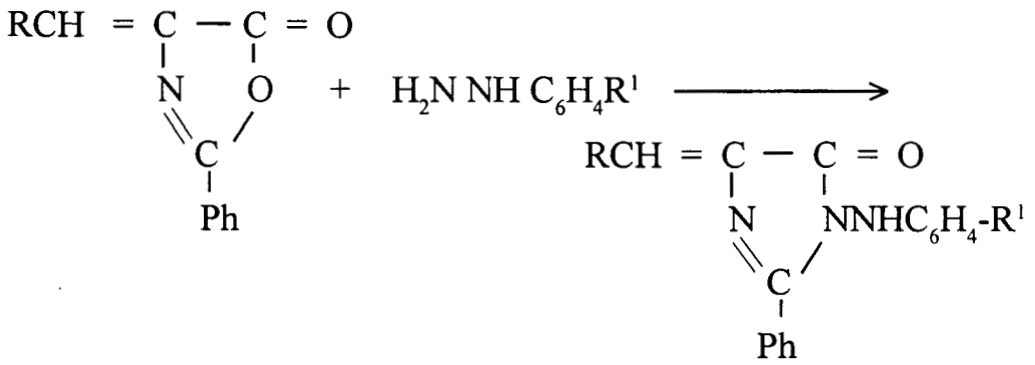
El- Sharief and Harb [16] synthesised 2- aryl - 4- arylidene - Δ^2 oxazolin-5 - ones and reacted them with p-aminodiphenylamine to prepare different derivatives of imidazolinones and studied their biological activity against Escherichia coli, Bacillus subtilis, and S.lutea.



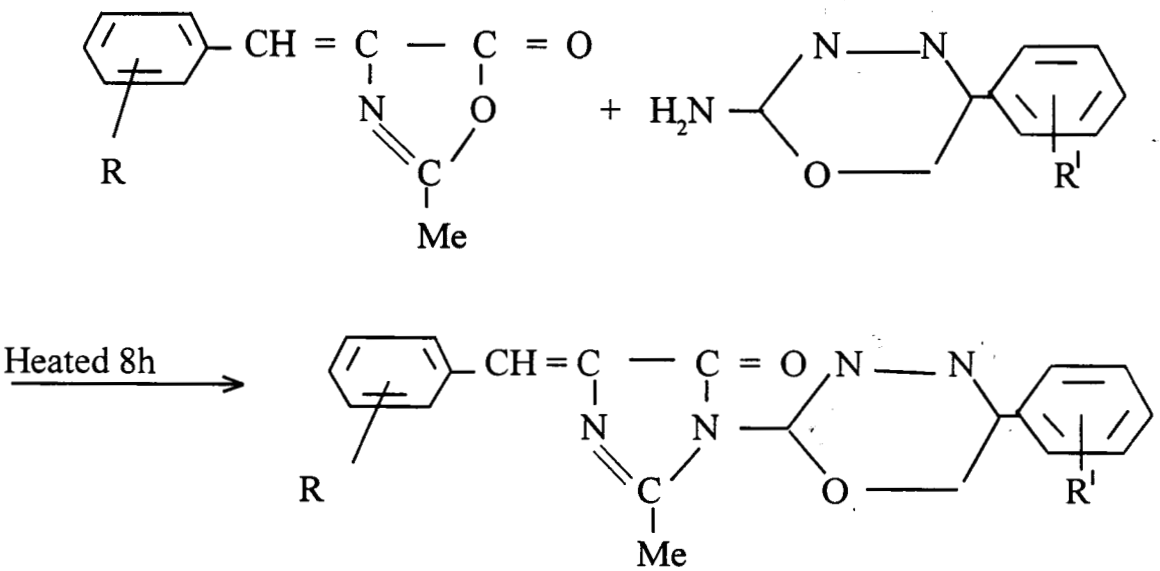
Pandey and Lohani [17] synthesised imidazolin- 5- ones by treating -2-methyl- and 2- phenyl-4-benzylidene oxazolin -5- one with ethylenediamine to give 2- methyl and 2- phenyl -4-benzylidene -1- (aminoethyl)imidazolin -5-one.



1,2,4-Trisubstituted -2- imidazolin -5- ones were synthesised [18] by heating oxazolin -5- ones with phenylhydrazine for 24 hours.

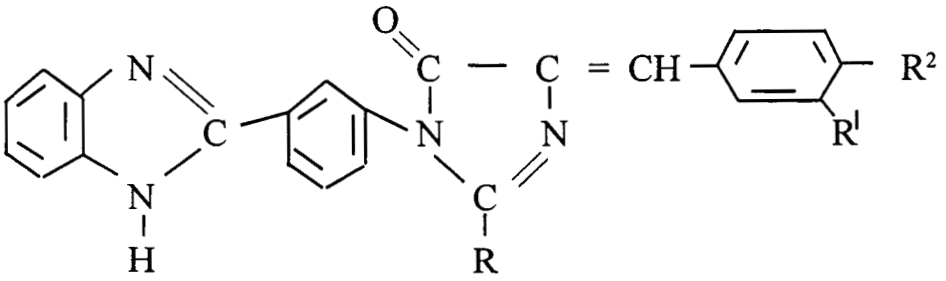


In 1982 Sengupta and coworkers [19] synthesised 1- (5^1-aryl-1^1,3^1,4^1-oxadiazol -2^1-yl) -2- methyl - 4 - (substituted benzylidene) imidazolin -5-ones, and screened for their antibacterial properties, by the condensation of oxazolinone with aminooxadiazoles.

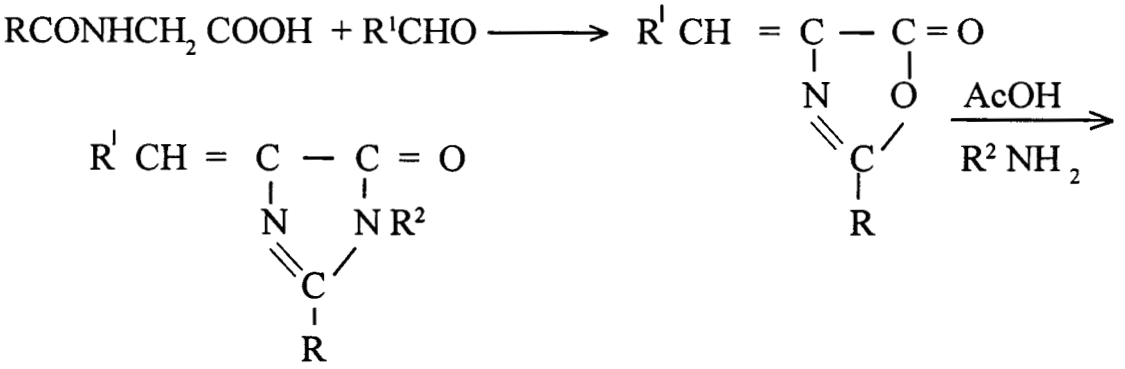


Mohan and coworkers [20] synthesised 1-[2/3-(2-phenyl benzimidazole] 2-methylphenyl-4 (3,4-disubstituted benzylidene) -5- oxoimidazoles and they showed CNS, anthelminitic and antiinflammatory activities. These compouds were synthesised by condensing (aminophenyl)benzimidazoles with benzylidene oxazolinones in dry pyridine and screened for toxicity and central nervous sys-

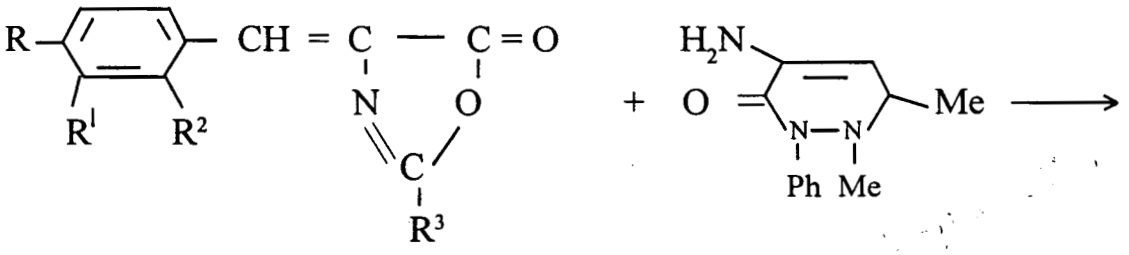
tem, anthelmintic and antiinflammatory activities.

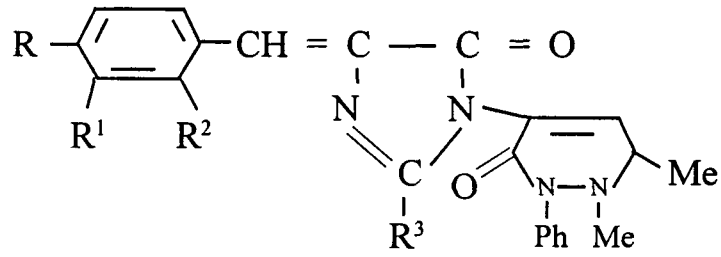


In 1983, Islam and coworkers synthesised [21] imidazolinones starting from arylidene -2- oxazolin -5-ones.

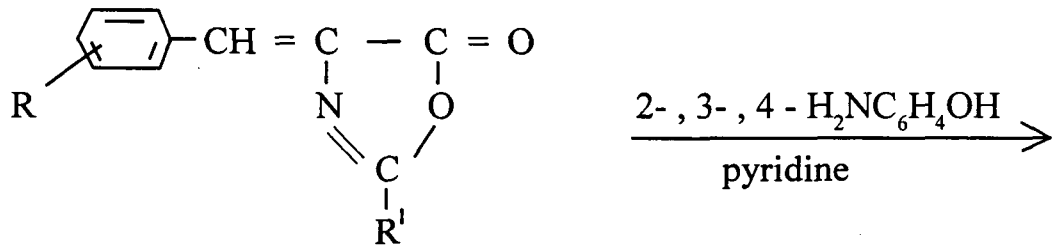


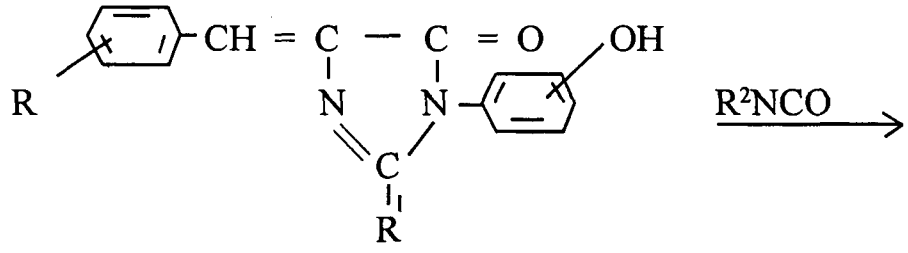
In 1984 Sengupta and coworkers [22] synthesised 4- [4,5-dihydro -4-(substituted benzylidene) -2- methyl /substituted aryl -5- oxo-1-H- imidazol-1-yl] -2,3- dimethyl-1- phenyl pyrazolin -5-ones as potential antimicrobial and AchE inhibitary agents.

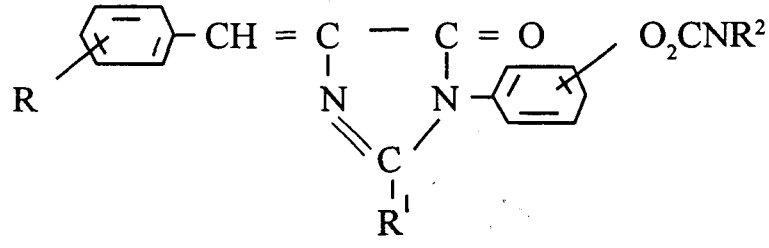




Sengupta and coworkers [23] synthesised and screened for antimicrobial properties of 1- (phenyl / methyl -carbamoyloxyphenyl)-2-methyl/phenyl -4-(substituted benzylidene) -5- imidazoline. Cyclocondensation of aldehyde with hippuric acid in acetic anhydride gave oxazolinones which were refluxed with 2-,3-,4-phenyl hydroxylamine in dry pyridine for 5- 8 hours to give imidazolinones.

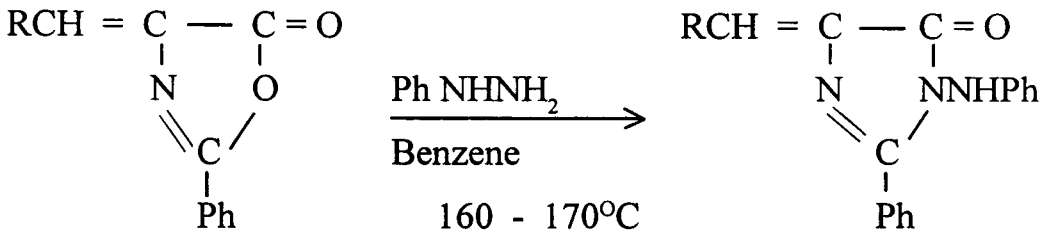




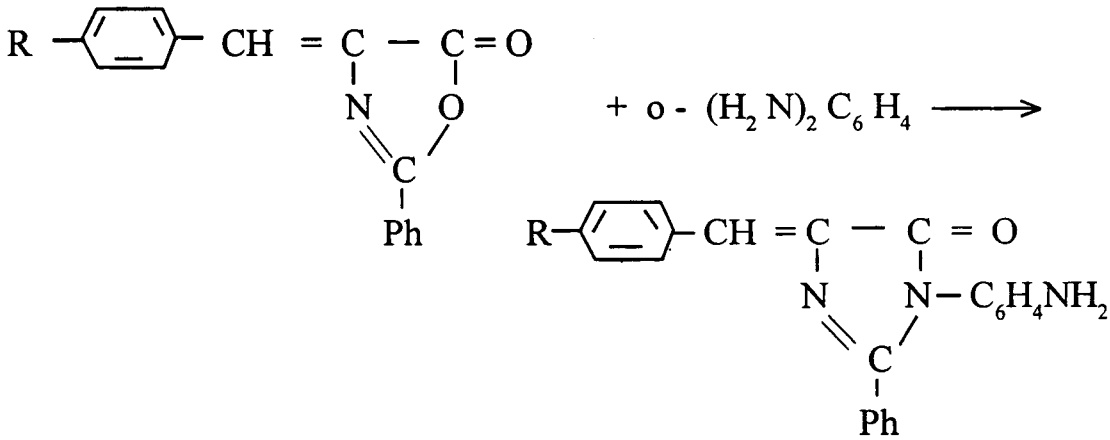


The imidazolinones were treated with R^2 NCO to give carbamates. Some of these carbamates were effective against Bacterium pamilus at 200 μg / 0.1 mL.

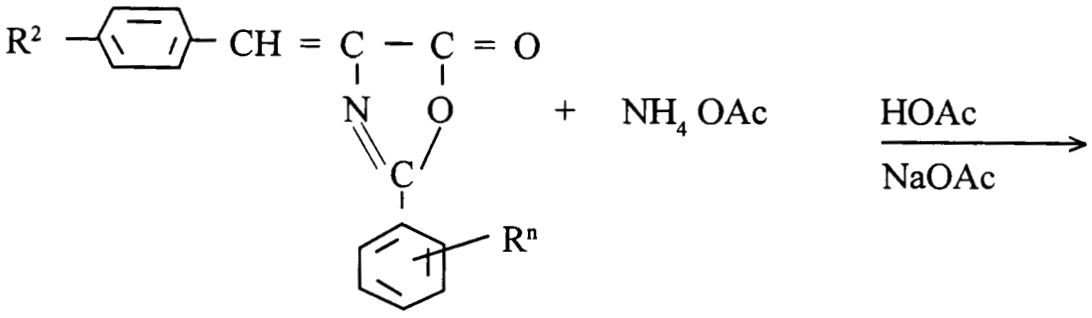
Kidwai and coworkers [24] prepared several imidazolinones by the reaction of oxazolinones with phenylhydrazine.

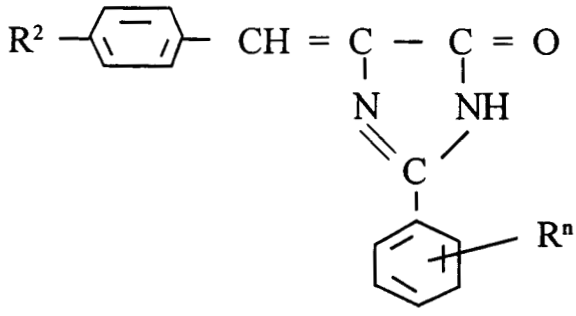


Hassan and coworkers [25] synthesised some imidazolinones by treating 2 - phenyl - 4 - arylmethylene - 2 - oxazolinones with o - aminoaniline and the newly formed imidazolinones were used as antioxidant additives for lubricant oils.

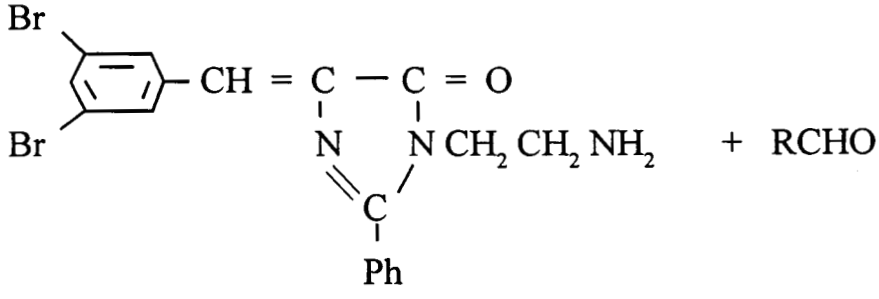


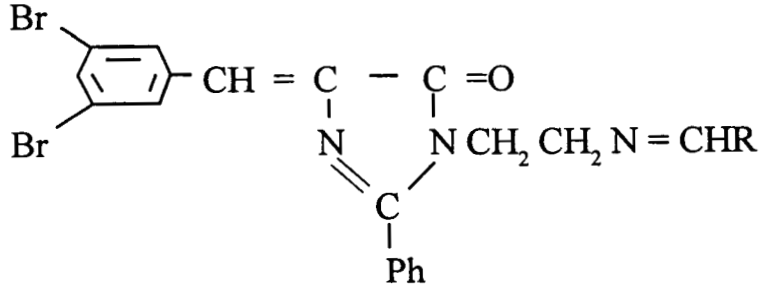
El - Sharief and coworkers [26] prepared new imidazolinones from corresponding oxazolinones by treatment with ammonium acetate in acetic acid in the presence of fused sodium acetate. They showed bactericidal activity.



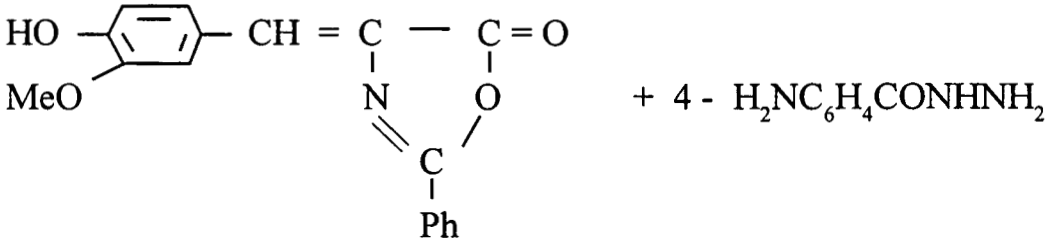


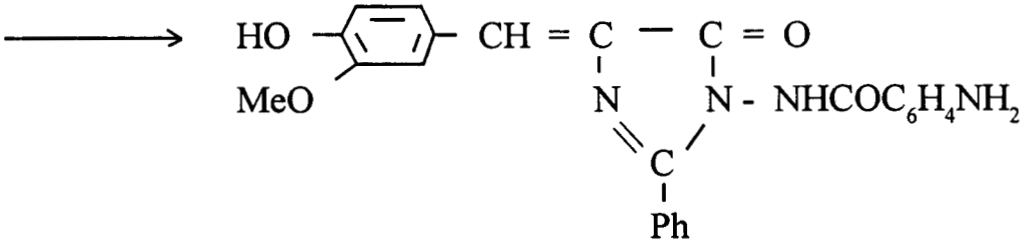
Dave and coworkers [27] synthesised 1 - (arylideneaminoethyl) - 2 - phenyl - 4 (3^{1}, 5^{1}- dibromo - 2 ^{1}- hydrobenzylidene) imidazolin - 5 - one by condensation of (amino ethyl) phenyl (dibromohydroxy benzylidene) imidazolinone with aldehyde.

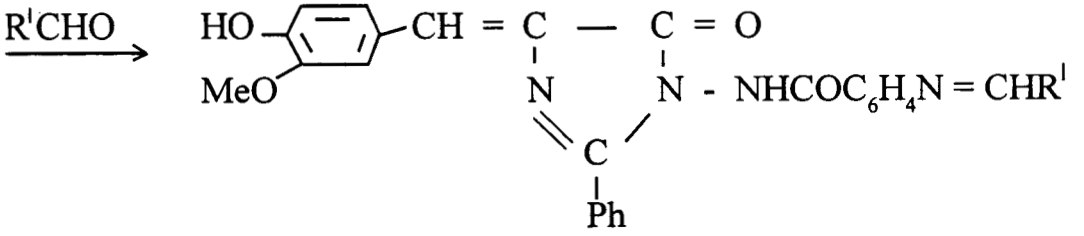




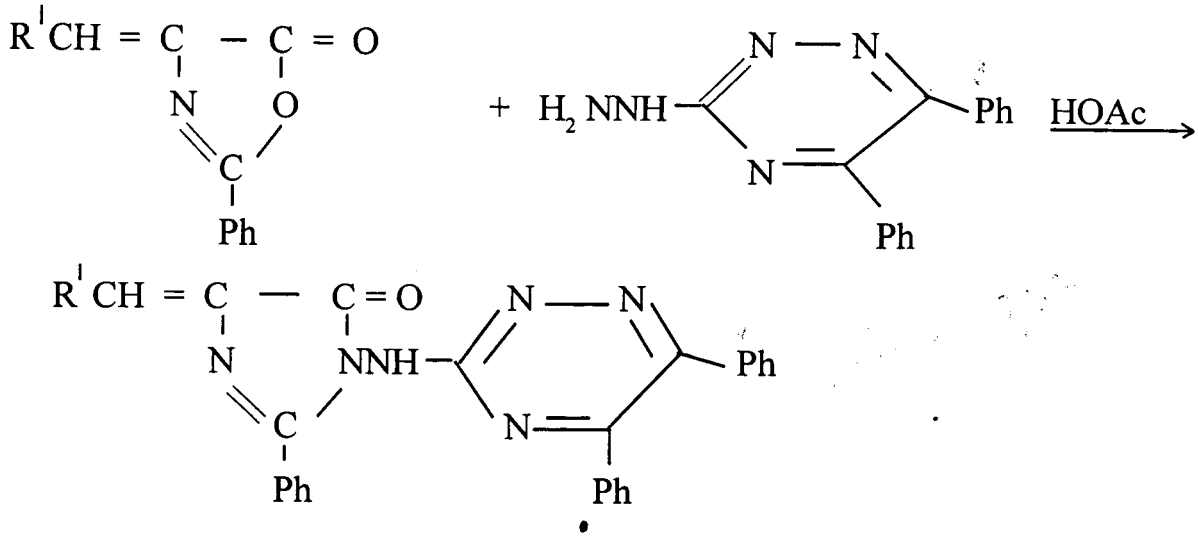
In 1988 Dave and coworkers [28] synthesised new imidazolinone by the treatment of 2 - oxazolin - 5 - one derivatives with 4 - $H_2NC_6H_4CONHNH_2$ and the product underwent a condensation reaction with R^1CHO to give [benzylidene (amino) benzamido] imidazolinones.





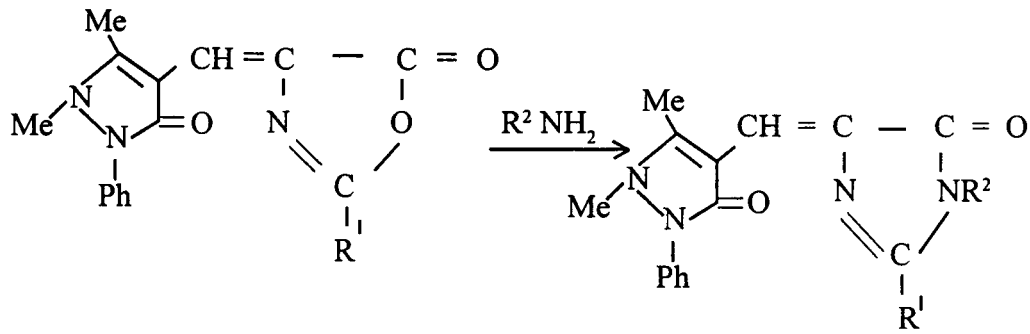


Reaction of 3 - hydrazino - 5, 6 - diphenyl - 1,2,4 - triazine with 4 - arylidene - 2 -phenyl - 5 (4H) oxazolinones yielded imidazolinones [29]

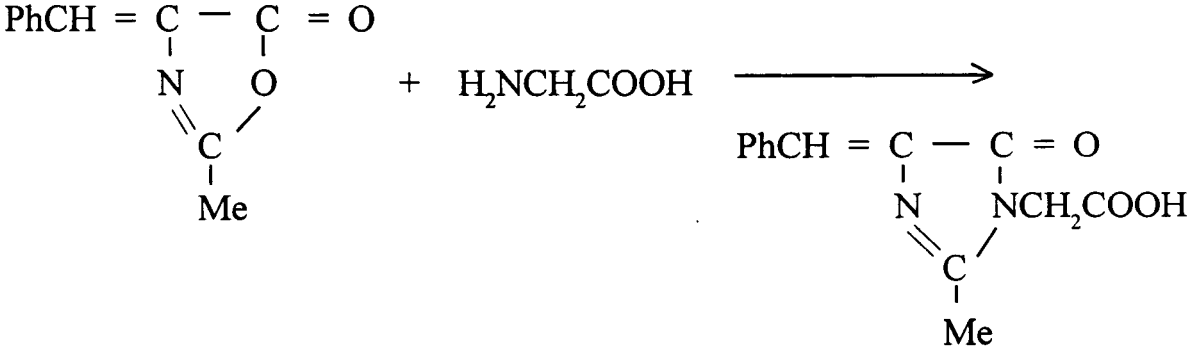


Imidazoline derivatives of antipyrine were prepared [30] by treating oxazolinones with amines.

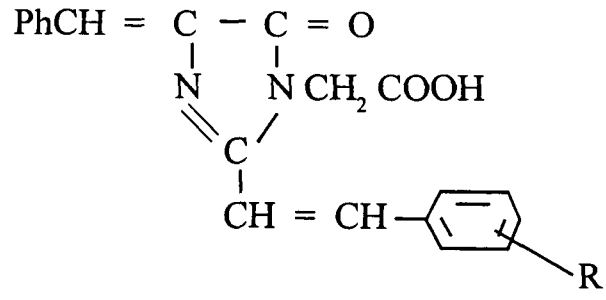
4-Formylantipyrine + $R^1CONHCH_2COOH$ ⟶



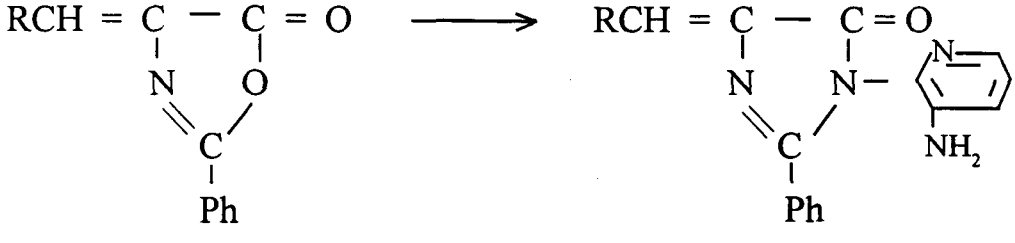
Kumar and coworkers [31] prepared new heterocyclic derivatives of amino acids and studied their antiinflammatory activity. Reactions of benzylidene methyloxazolinone with glycine gave benzylidene methyl imidazolinone derivatives which were converted to a series of aldol adducts.



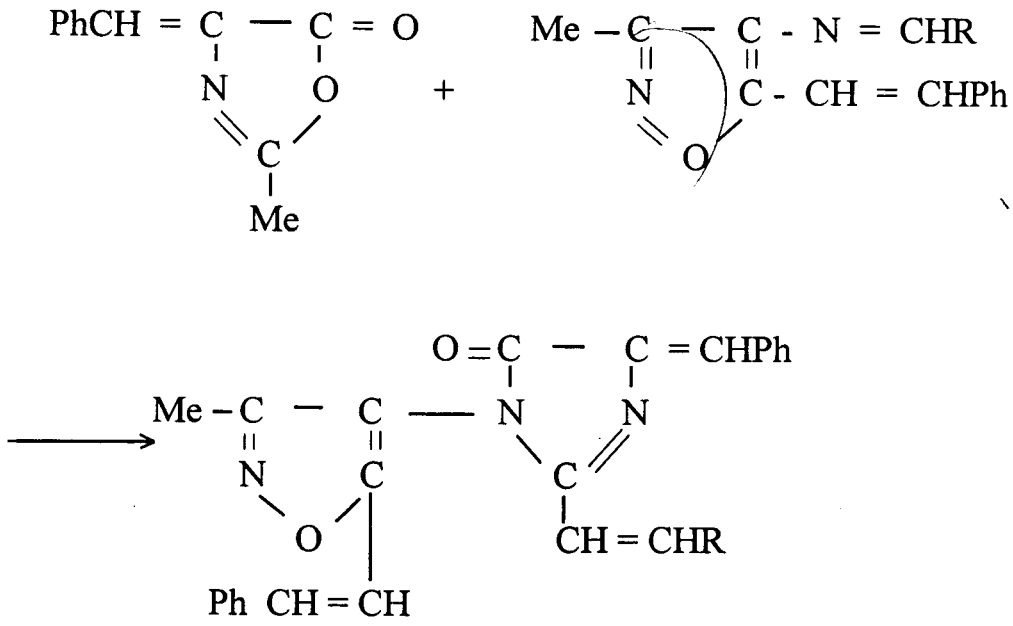
Aldol condensation



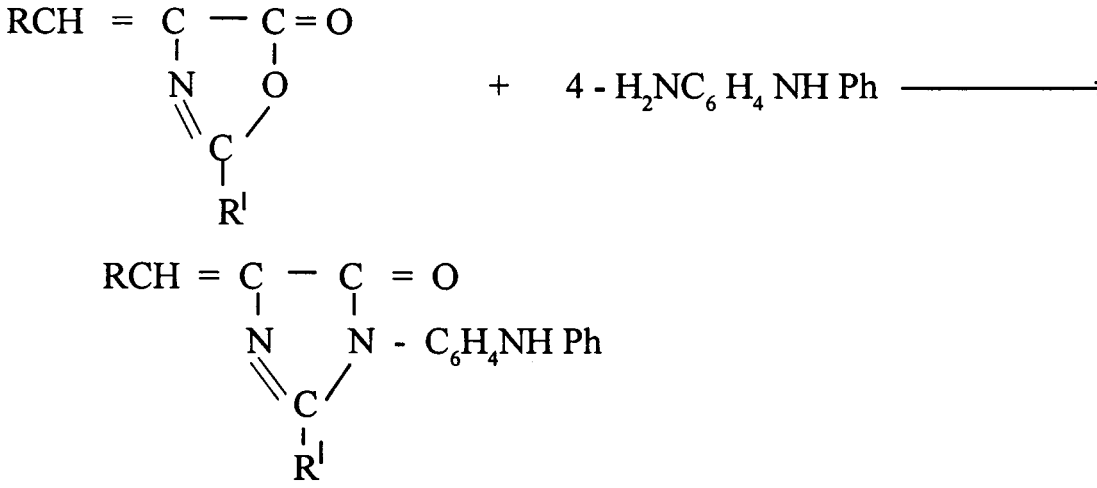
Girges and coworkers [32] synthesised and studied the biological activity of sulfonate ester containing imidazolyl pyridine, imidazo (4,5- b) pyridine and imidazo (5^{1}, 1^{1}, 2,3) imidazo (4,5-b) pyridine derivatives . Different ring systems containing imidazole and pyridine moieties and accommodating a sulfonate ester moiety in their structure were prepared via ring opening of 2-oxazolin-5-one derivatives under various reaction conditions. The antimicrobial activity of the synthesised compounds were investigated .



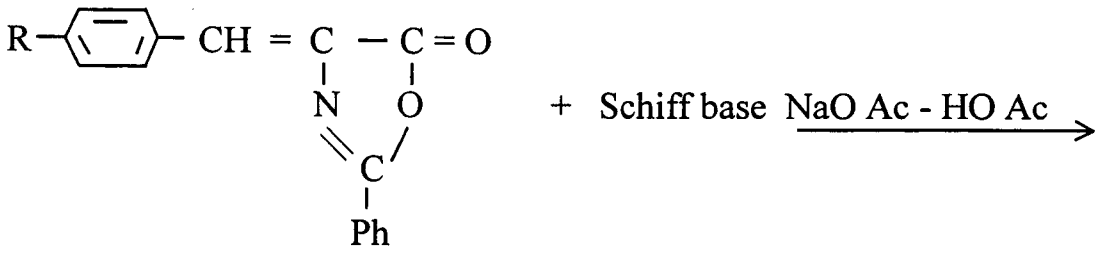
1989 Prameela and coworkers [33] synthesised isoxazolylimidazolin-5- ones by the cyclocondensation of isoxazole units with oxazoline.

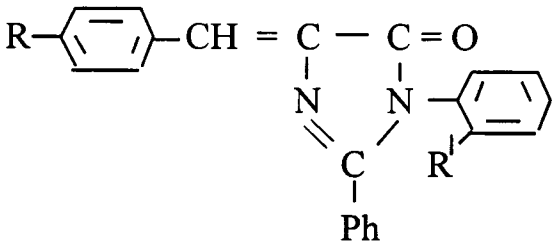


Moharram and coworkers [34] synthesised imidazolin -5-ones and screened their biological activity. Treatment of 5-oxazolinones with 4- $H_2N\ C_6H_4\ NHPh$ gave imidazolinone.

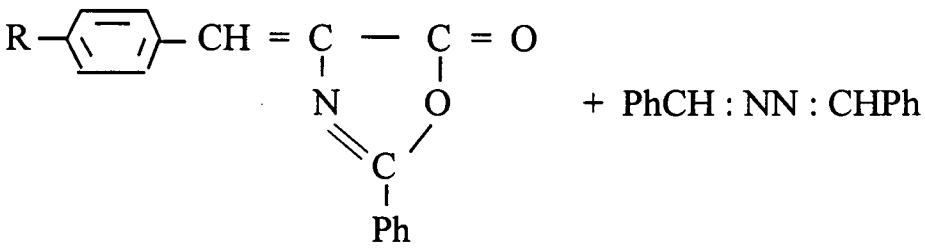


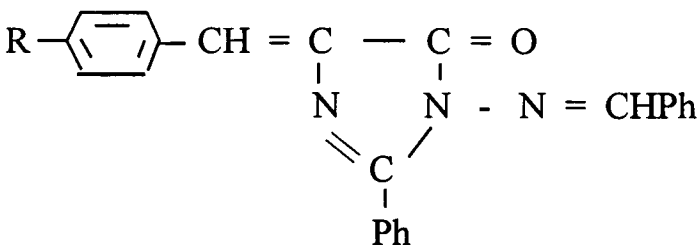
Reactions of 4 - (arylmethylene) - 2 - phenyl - 2- oxazolin - 5 - ones with schiff bases gave imidazolinones [35]. The oxazolinones reacted with schiff bases of aniline or o - toluidine in sodium acetate - acetic acid, to give imidazolinones.



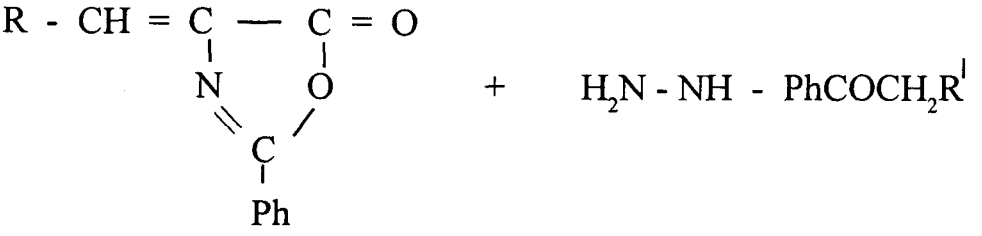


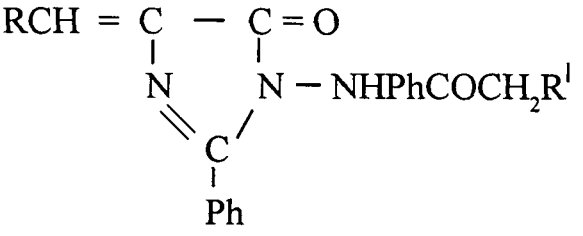
The reaction of oxazolinone with Ph CH : NN : CH Ph in the absence of solvent gave imidazolinone.





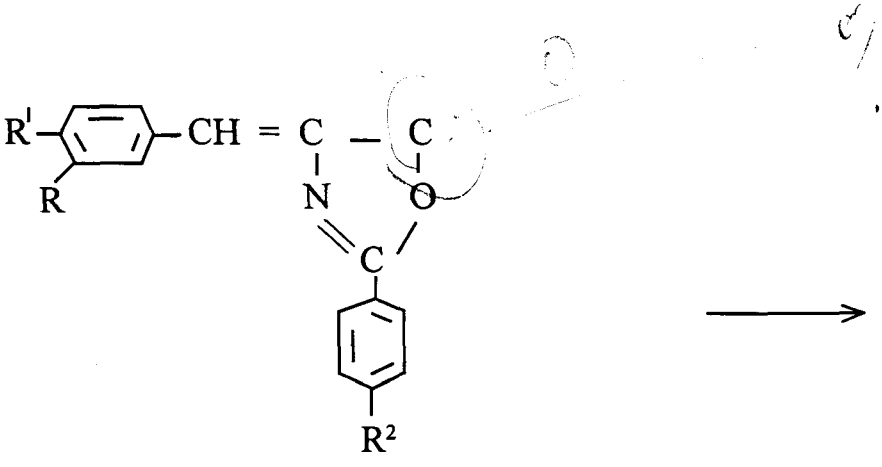
Various imidazolinones were prepared by the reactions between oxazolinones and amino compounds [36]. Reactions of these imidazolinones were also studied.

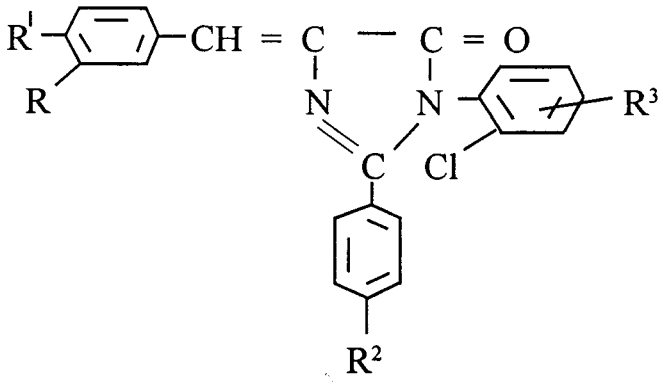




Sreevastava and coworkers [37] synthesised new substituted imidazolin - 5 - ones starting from oxazolones and their effect against sunhemp rostle virus on Cyanamopsis tetragonoloba was studied.

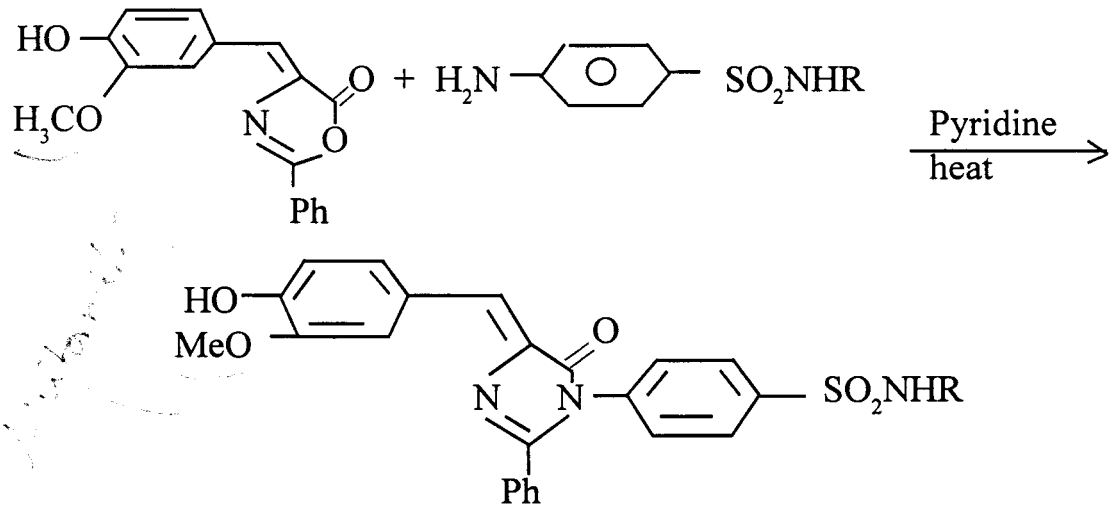
In 1990 Misra and coworkers [38] synthesised - 2 - aryl - 1 - (dichlorophenyl) - 4 - (3,4 - disubstituted benzylidene) imidazolin - 5 - ones as CNS active agents. The imidazolin - 5- one was prepared by the action of dichloraniline on appropriate oxazolin - 5 - ones in the presence of anhydrous $CaCl_2$.



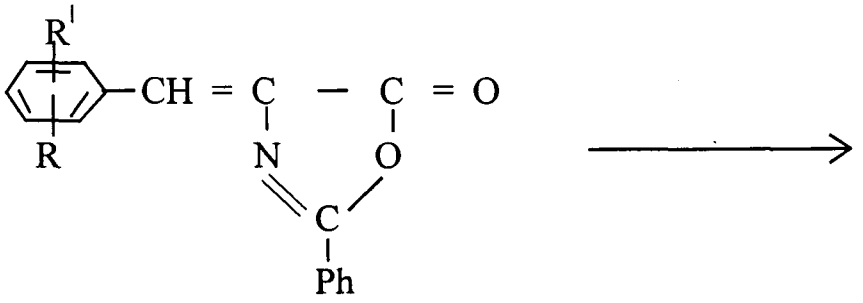


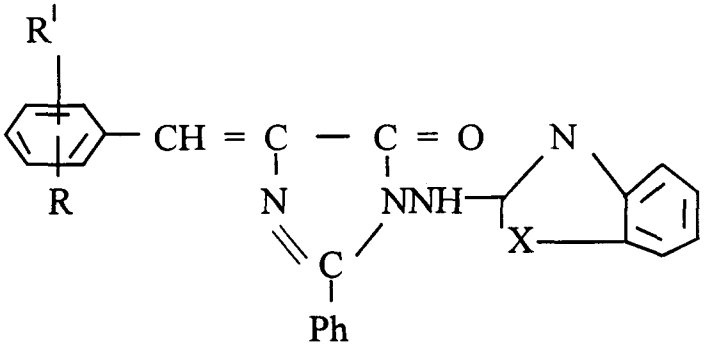
By Condensing Me - 4 - aminobenzoate with (indolylmethylene) oxazolone followed by the treatment with hydrazine gave the [(indolyl methylene) imidazolyl] benzoic acid hydrazides which condenses with aryl aldehyde, diazotised and aminated with aromatic amine to give imidazolinone [39]

Mathur and Sahay [40] synthesised and studied the biological activities of some imidazolones. Imidazolones which were biologically active were prepared by the condensation of 4 - $H_2NC_6H_4SO_2NHR$ with oxazolone.



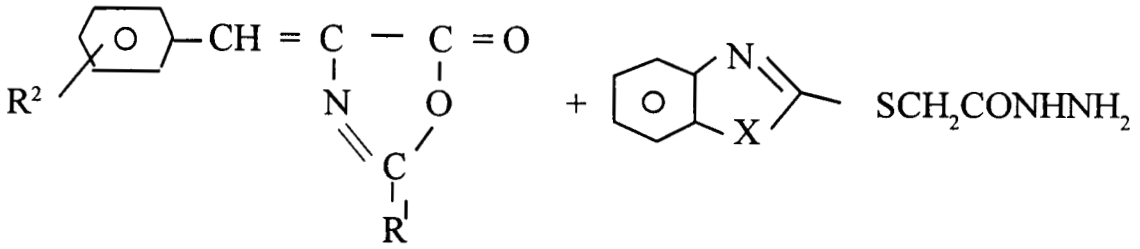
Husain and coworkers [41] prepared 1 - (2 - benzothiazolyl / benzoimidazolyl/ benzoxazolyl amino) - 4 - [(substituted - phenyl) methylene] - 2 - phenyl - 4 H - imidazol - 5 - one by the condensation of the hydrazines with benzylidene oxazolones.

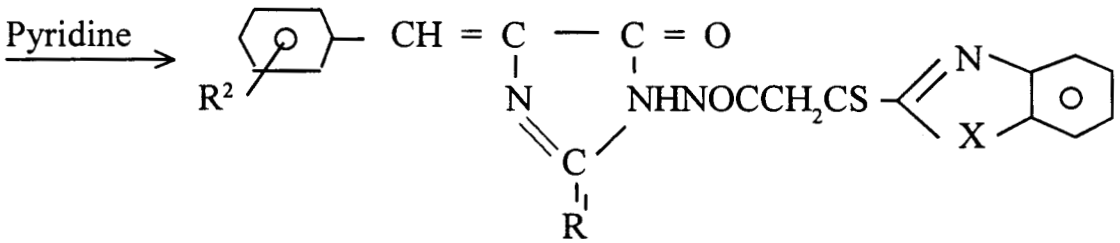




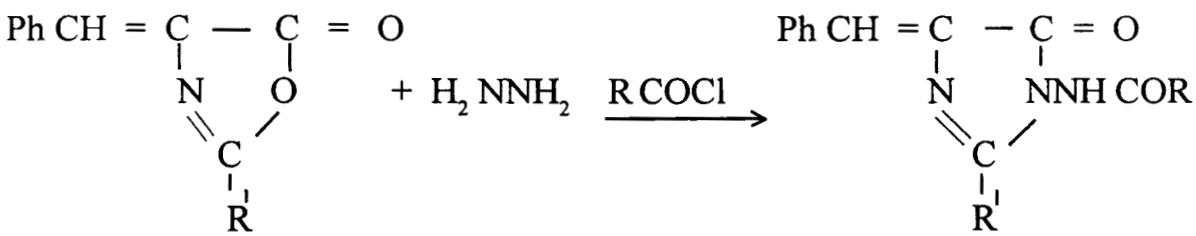
Upadhyay and coworkers [42] synthesised and studied the anticonvulsant activity of 1 - N (γ^1 - picolinyl) - 4 - substitutedbenzylidene - 2 - methyl / phenyl - 5 - imidazolinone. They were prepared by the condensation of oxazolones with p - picolinic acid hydrazide.

In 1992 Husian and coworkers [43] transformed oxazolones into imidazolones by condensing them with (2 - benzothiazolyl / benzoxazolylthio) acetic acid hydrazides in pyridine.





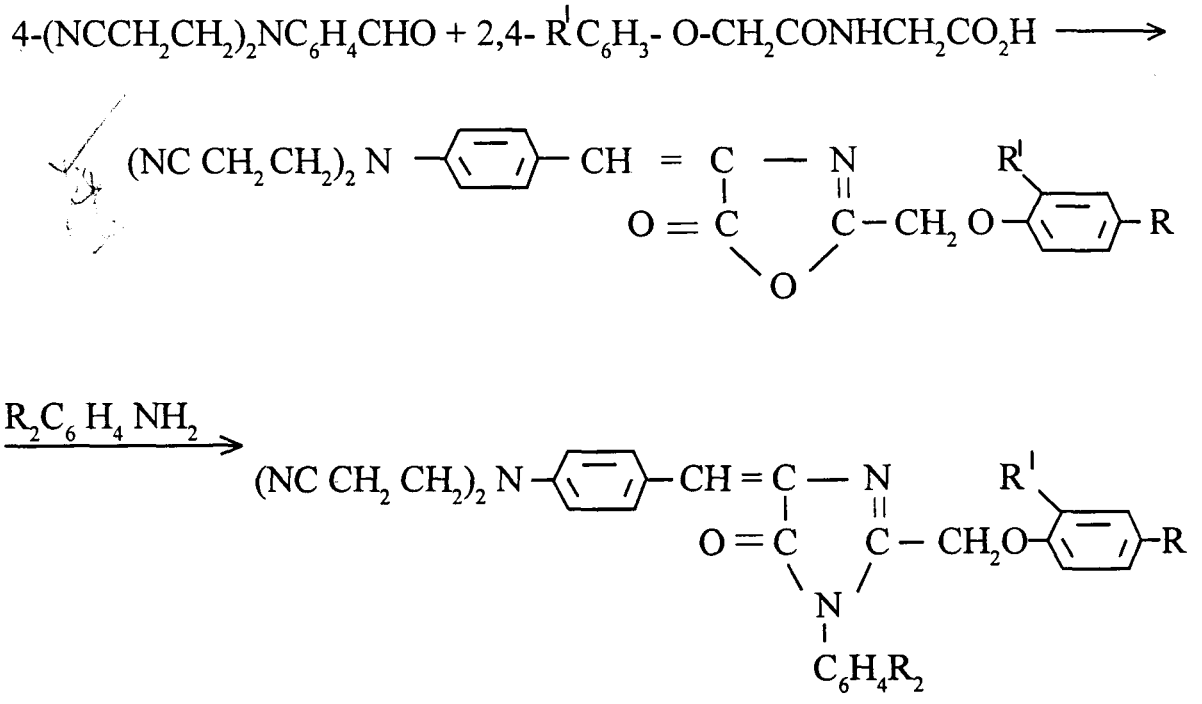
Upadhyay and coworkers [44] prepared benzoylbenzylideneimidazolinones by treating the oxazolinone with hydrazine followed by acylation with acid chloride.



They show good anticonvulsant activity against pentylenetetrazole induced convulsions.

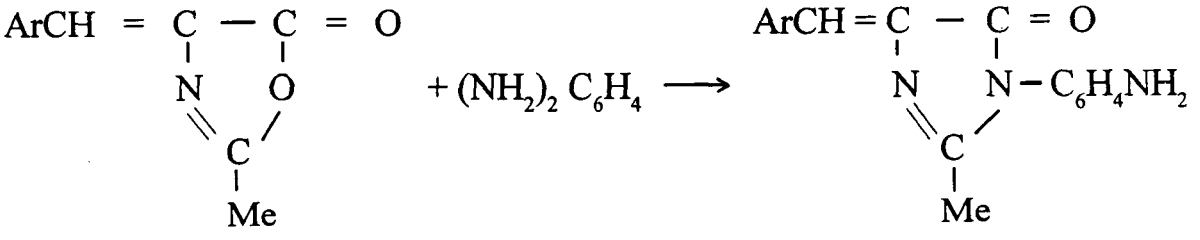
Jolly and Pathak Manish [45] synthesised imidazolinones by

cyclocondensation of derivatives of aryl aldehydes and glycine derivatives followed by the reaction of the oxazolone product with aryl amine.



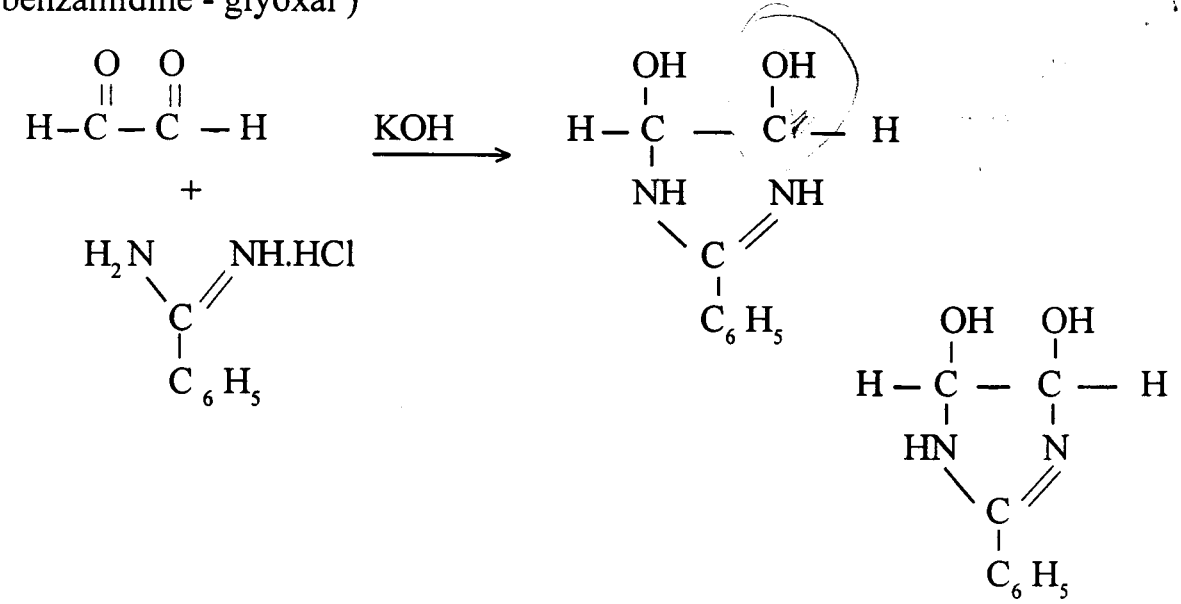
They showed the maximum anti-HIV activity and some of them showed moderate bactericidal activity.

Bhalla and coworkers [46] synthesised noval imidazole congeners as anti-inflammatory agents by condensing oxazolone with 1,2- diaminobenzene .

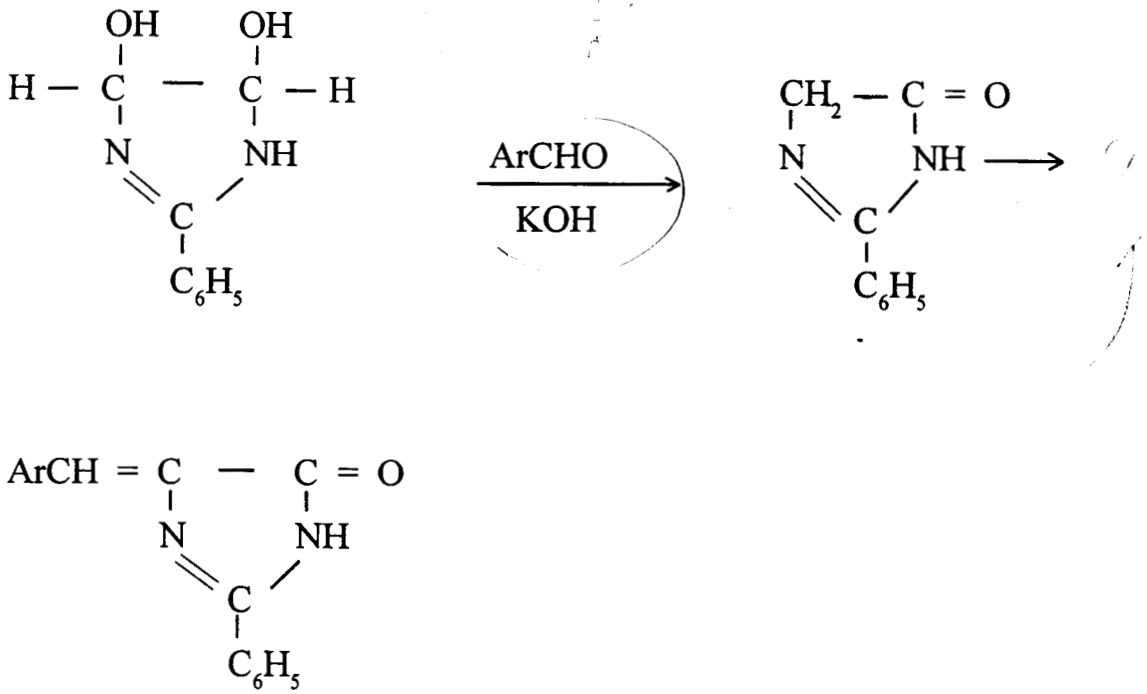


2 Amidine - glyoxal method

In 1935 Ekeley and Ronzio [2,47] developed a method for the synthesis of- 2 - aryl-4- arylidene-2-imidazolin - 5 - ones by condensing aromatic aldehydes with aromatic amidine-glyoxal addition products. Actually they thought that the condensation products obtained were either diaryl pyrimidones (or hydroxypyrimidines) or 2 - aryl - 4 - aroylglyoxalones. For example on treating a mixture of glyoxal and benzamidine hydrochloride with potassium hydroxide a labile basic substance is formed. It may be represented either as an open chain compound or preferably as a 2 - phenyl - 4,5 - dihydroxy - 2 - imidazolone (benzamidine - glyoxal) [2]

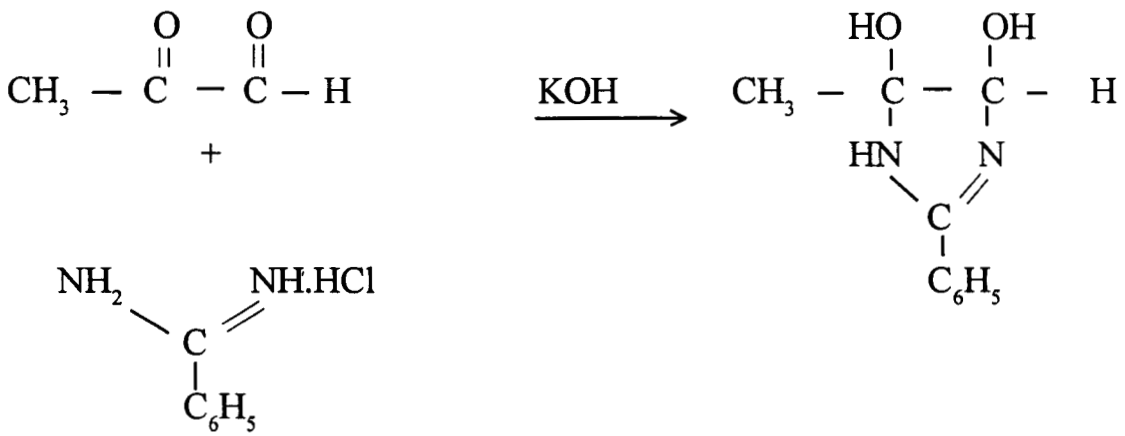


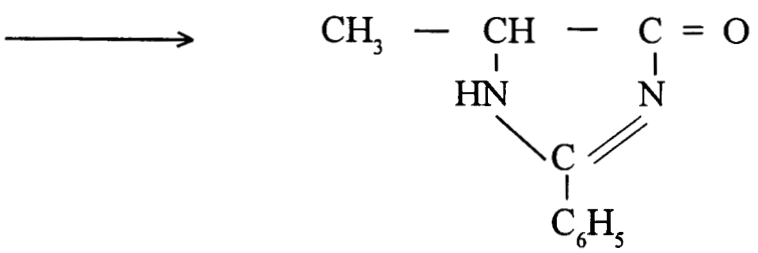
On condensing aromatic aldehydes with this substance in the presence of sodium or potassium hydroxide good yields of 2 - phenyl - 4 - arylidene - 2 - imidazolin - 5 - ones are obtained. The reaction may be formulated in the manner illustrated below using the more plausible 4,5 - dihydroxy - 2 - imidazoline structure for the benzamidine - glyoxal complex. It is assumed that the dihydroxy imidazoline loses a molecule of water under the influence of the base to form 2 - phenyl - 2 - imidazolin - 5 one containing a highly active methylene group. The 2- phenyl - 2 - imidazolin - 5 - one thus formed readily undergoes condensation with the aldehyde to give the final product.



Ekeley and coworkers [47,48] prepared numerous 2 - aryl - 4 - arylidene - 2 - imidazolin - 5 - ones by this method using the addition product of glyoxal with different aromatic amidines like benzamidine, p - toluamidine, m - toluamidine etc.

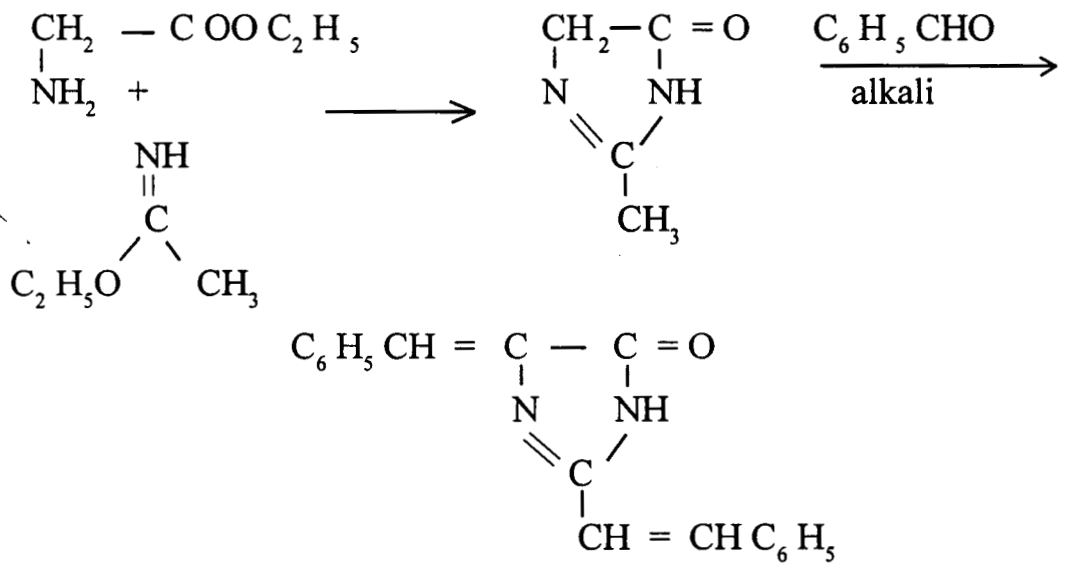
It is appropriate to mention here that saturated 2, 4 disubstitated 2 - imidazoline - 5 - ones were prepared by the condensation of substituted glyoxal with aromatic amidines [2,9].



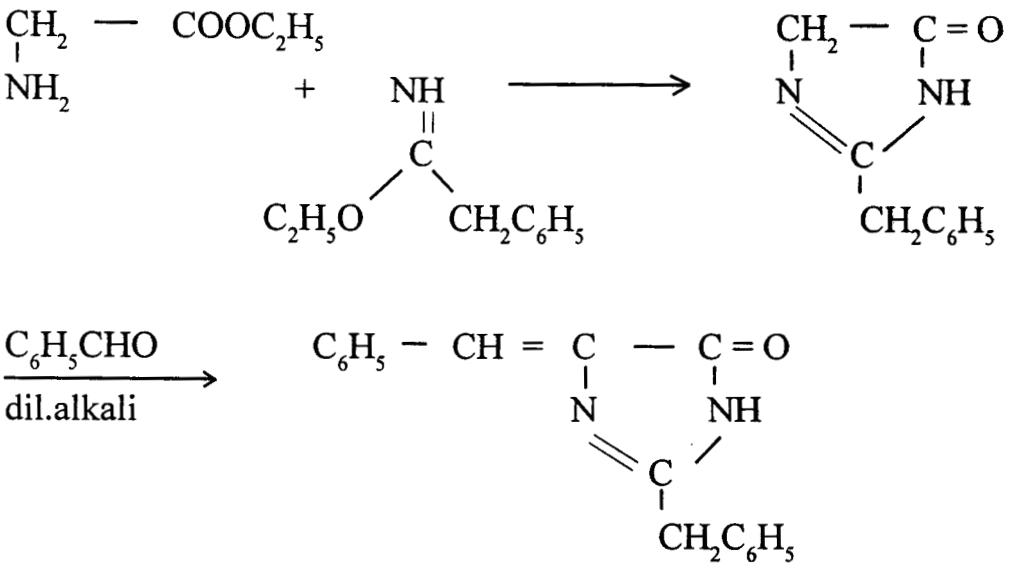


3. Imidic acid ester - glycine ester method

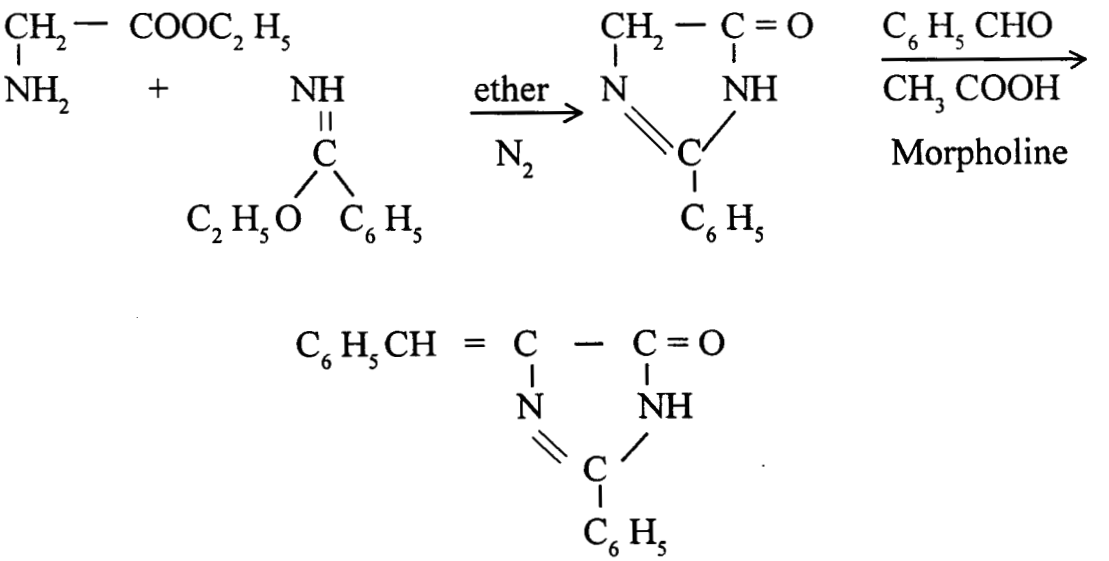
In 1907 Finger [49] obtained 2 - methyl - 2- imidazolin - 5 - one by condensing glycine ester with acetimidic acid ester at room temp. The 2 - methyl - 2 - imidazolin - 5 - one condensed with two moles of benzaldehyde to form 2 - benzylidenemethyl - 4 - benzylidene - 2 - imidazolin - 5 - one.



Finger and Zeh [50] obtained 2 - benzyl - 2 - imidazoline - 5 - one by condensing glycine ester with phenyl acetimidic acid ester and the condensation product in turn afforded 2 - benzyl - 4 benzylidene - 2 - imidazolin -5- one when it is condensed with benzaldehyde in presence of dilute alkali.

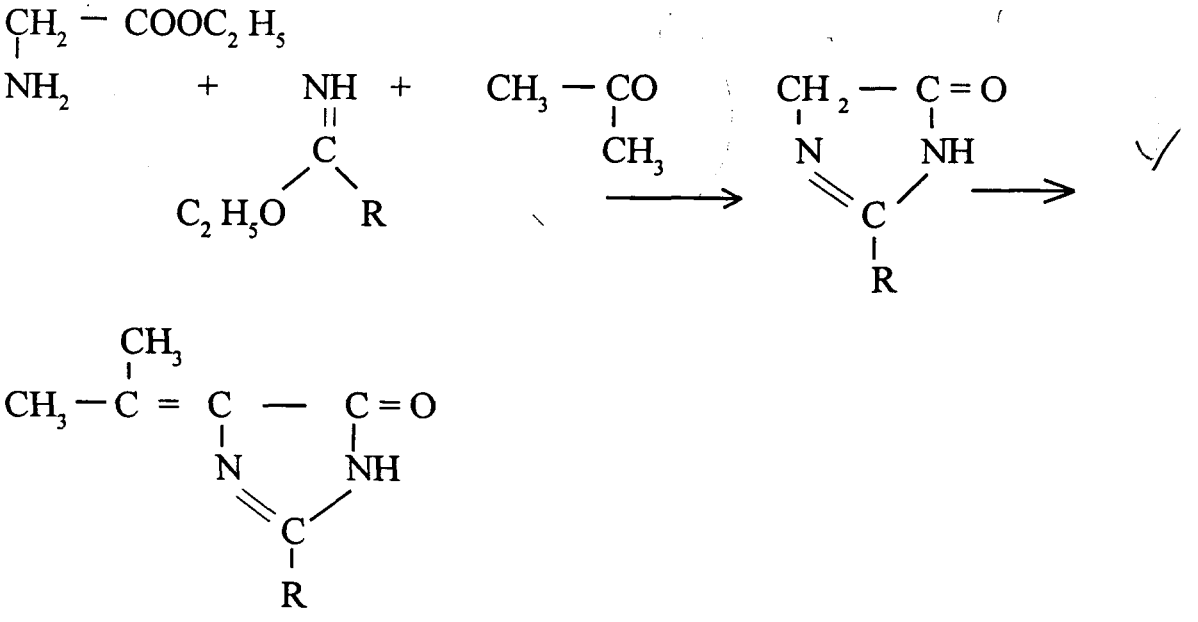


In 1953 Kjaer [51] prepared 2-phenyl-2- imidazolin - 5- one in 18.8% yield by condensing benzimidic acid ester with glycine ester in presence of anhydrous ether in nitrogen atmosphere. The product was recrystallised from benzene in an oxygen free atmosphere followed by sublimation. He obtained 2-phenyl- 4 - benzylidene - 2 - imidazolin - 5 one by condensing benzaldehyde with the 2 - phenyl - 2 - imidazolin -5 - one.



1 - Naphthaldehyde, furfuraldehyde, isatin and pyruvic acid were also condensed with 2 - phenyl - 2- imidazolin - 5 - one and obtained the corresponding unsaturated 2 - imidazolin - 5- ones.

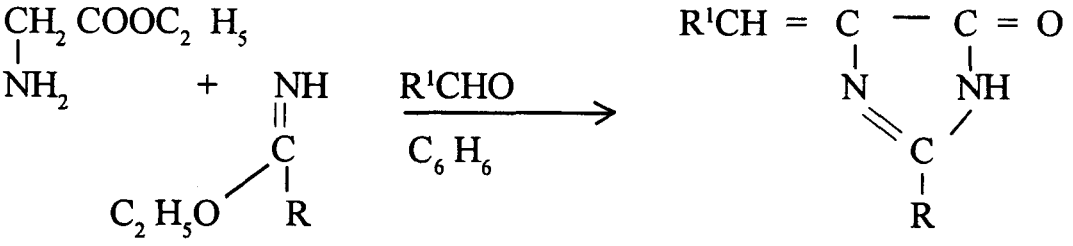
In 1953 Lehr and coworkers [52] obtained 2 - substituted 4 - isopropylidene - 2 - imidazolin - 5 - ones instead of the expected 2 - substituted 2 - imidazolin -5- ones when imidic acid esters were condensed with glycine ester using acetone as solvent. Glycine ester and imidic acid ester first condense to form 2 - substituted 2 - imidazolin - 5 - one which in turn reacts with acetone to form 2 - substituted - 4 - isopropylidene - 2 - imidazoline - 5 - one.



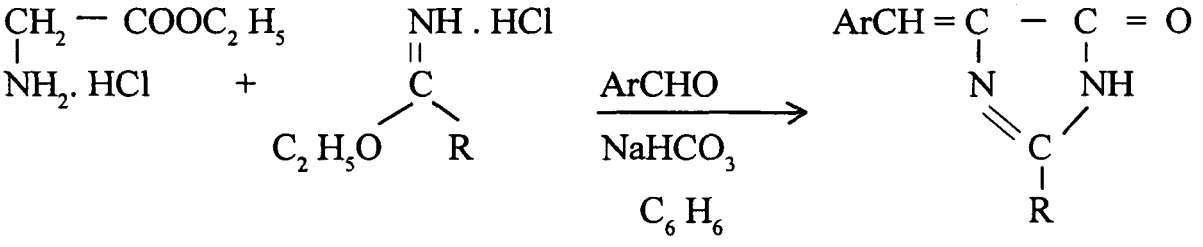
Lehr and coworkers [52] prepared a large number of unsaturated 2 - imidazolin - 5 - ones by refluxing aliphatic and aromatic ketones, acetoacetic ester, levulinic ester and acetophenone with a mixture of imidic acid ester and glycine ester. Benzene was used as solvent in the case of high boiling ketones while in the case of low boiling ketones exess of ketones themselves were the solvents. The structure of these compounds were confirmed by synthesising one

of them namely 2 - benzyl - 4 - cyclohexylidene - 2 - imidazolin - 5 - one by the simultaneous reaction of phenylacetimidic acid ester, glycine ester and cyclohexanone and also by the condensation of the preformed 2 - benzyl - 2 - imidazolin - 5 - one with cyclohexanone.

In 1962 Kidwai and Devasia [53] prepared a number of unsaturated 2 - imidazolin - 5 - ones by condensing aldehydes (aromatic aldehydes and isobutyraldehyde) with a mixture of an imidic acid ester and glycine ester in the presence of benzene at room temperature. When benzimidic acid ester was used they obtained very high yields of 2 - phenyl - 4 - arylidine - 2 - imidazolin - 5 - ones. Phenylacetimidic acid ester and acetimidic acid ester are other imidic acid esters used by them.

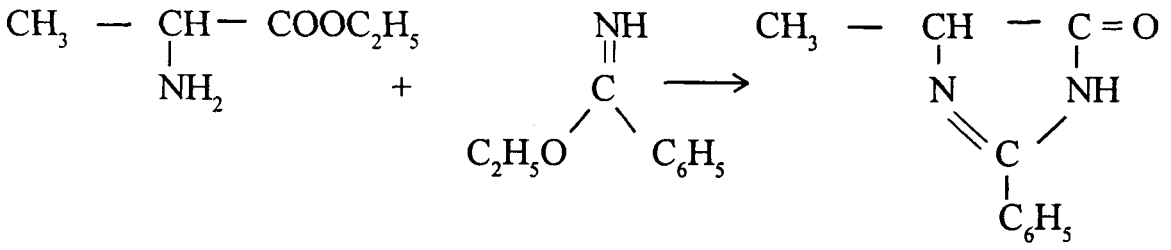


They further improved this method by condensing aromatic aldehydes directly with a mixture of the hydrochlorides of an imidic acid ester and glycine ester in presence of sodium bicarbonate in benzene at 72°C. Thus they prepared a few 2 - phenyl - 4 - arylidene - 2 - imidazolin - 5 - ones in very high yields.



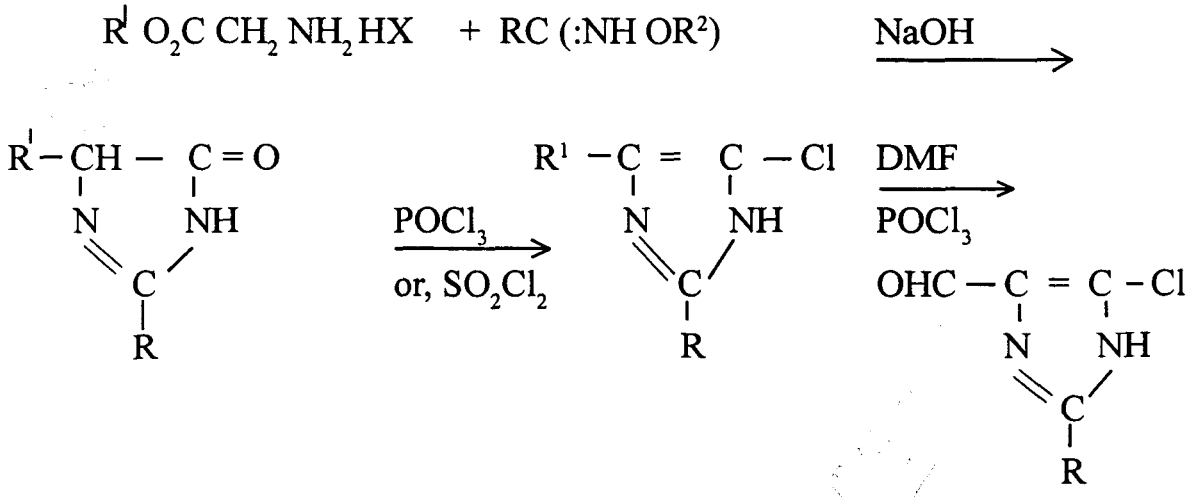
In 1975 Devasia and Pillai [54] prepared a few 2 - phenyl - 4 - arylidene - 2 - imidazolin - 5 - ones employing the above methods of Kidwai and Devasia.

It is relevent to mention here that saturated 2,4 - disubstituted - 2 - imidazolin - 5 - ones were prepared by condensing benzimidic acid ester with amino acid esters [9,55]



Imidazolinones having hypotensive activity were synthesised [56] by cyclocondensation of various imidic acid esters with glycine ethyl ester.

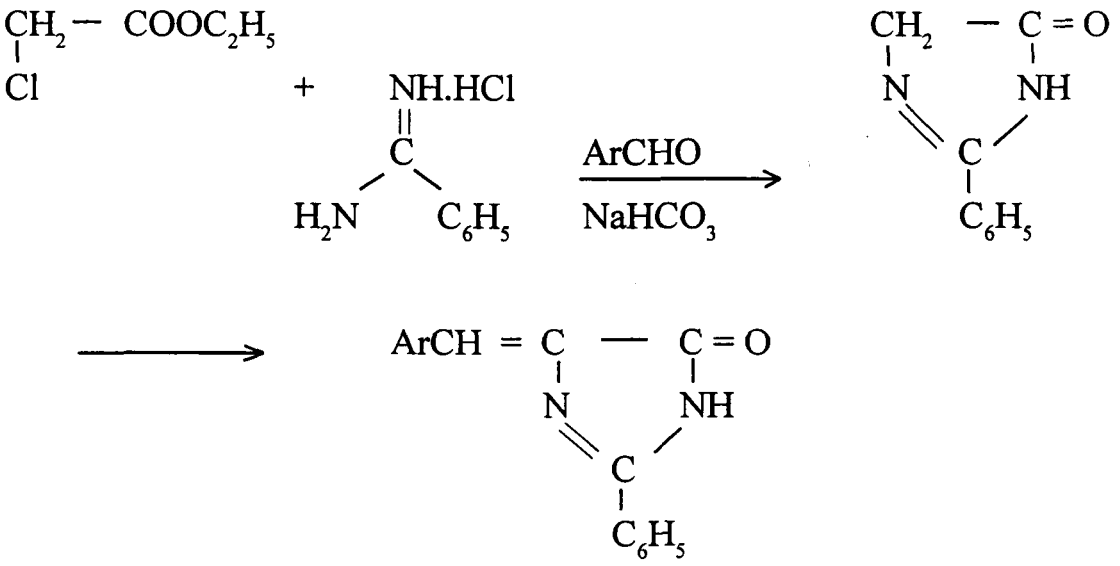
In 1994 Griffiths and coworkers [57] prepared imidazolones by the cyclocondensation of glycine ester hydrohalide (eg: glycine methyl ester hydrochloride) with imidic ester (eg: pentanimidic acid methylester) in presence of a base (eg: sodium hydroxide). These imidazolones were chlorinated with phosphorus oxychloride or thionyl chloride to get their chloro derivatives which on treatment with DMF and $POCl_3$ formed their formyl derivatives.



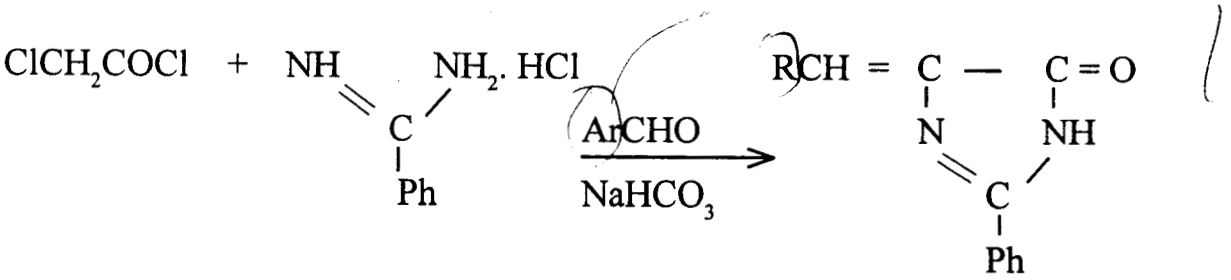
These compounds are useful as pharmaceutical and agrochemical intermediates.

4. Amidine - haloacetic ester method

In 1976 Devasia [58] developed the amidine-chloroacetic ester method for the synthesis of unsaturated 2 - imidazolin - 5 - ones .He obtained moderately good yields of 2 - phenyl - 4 - arylidene - 2 - imidazolin - 5 - ones by condensing aromatic aldehydes with a mixture of benzamidine hydrochloride and ethyl chloroacetate in the presence of sodium bicarbonate in n - propanol at reflux temparature. As in the cases of amidine - glyoxal and imidic acid ester - glycine ester methods, 2 - phenyl - 2 - imidazolin - 5 - one with a highly active methylene group may be formed as intermediate and the aldehyde condense with it to form the final product.

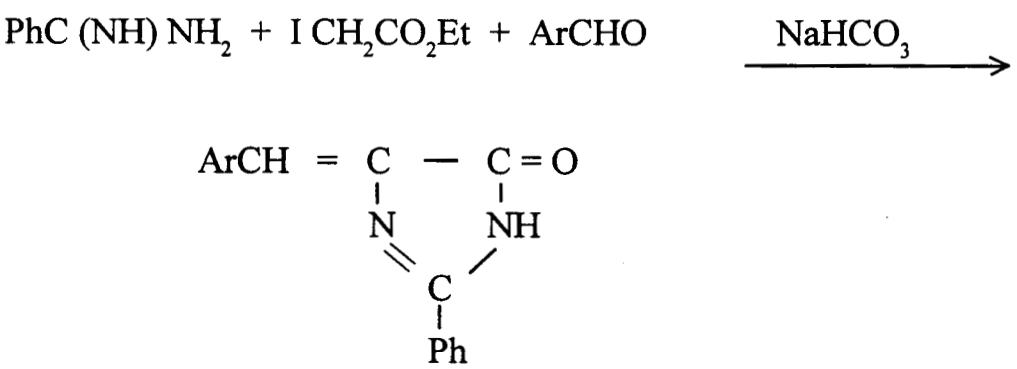


Devasia and Shafi [59] synthesised 4 - arylidene - 2 - phenyl - 2 - imidazolin - 5 - ones by condensing aromatic aldehydes with a mixture of chloroacetyl chloride and benzamidine in presence of sodium bicarbonate.



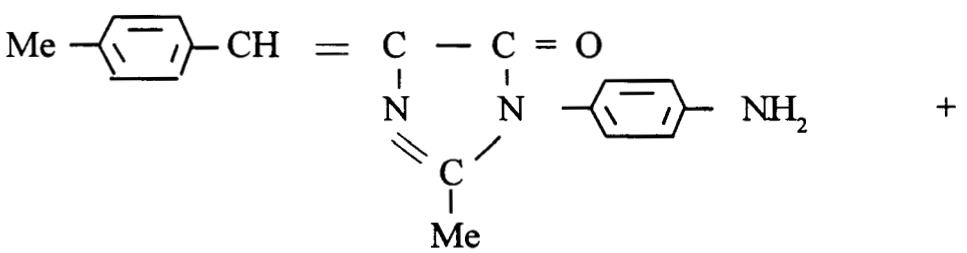
Davasia and Shafi [60] prepared a large number of unsaturated 2, 4 - disubstituted - 2 - imidazolin - 5 - ones employing the known amidine-haloacetic ester method.

2 - Aryl - 4 - arylidene - 2 - imidazolin - 5 - ones were prepared in quantitative yield [61] bycondensing aromatic aldehydes with benzamidine and ethyl iodoacetate in presence of sodium bicarbonate.

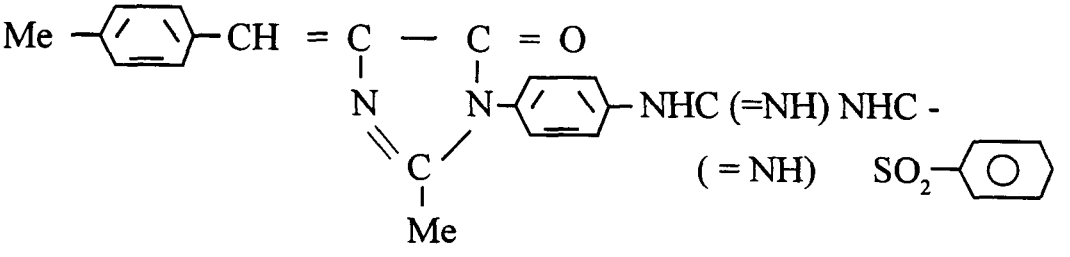


5. Other methods

Husain and coworkers [62] synthesised new imidazolinones by heating amine with $PhSO_2NHC$ (: NH) NHCN, water and concentrated hydrochloric acid at 130- 140^{0}C

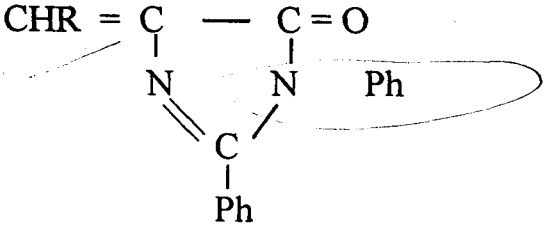


$PhSO_2NHC$ (: NH) NH. HCN Water - Conc. HCl →



In 1985 Ashare and coworkers [63] synthesised - 4 - (arylmethylene) - 1,2 - diphenyl - 2 - imidazolin -5 - ones by the reaction between hippuric acid, phenyl isothiocyanate and aromatic aldehydes.

$PhCONHCH_2COOH + RCHO + PhCNS$ Pyridine, 160 - 170°C →



Saxena and coworkers [64] prepared novel imidazole congeners as anti inflammatory agents. A number of furylmethylene imidazolone derivatives were prepared from furfuraldehyde and aroyl glycine via manich or cyclisation reactions of intermediate imidazolones and tested their antiinflammatery activity. It was found that they were strongly active.

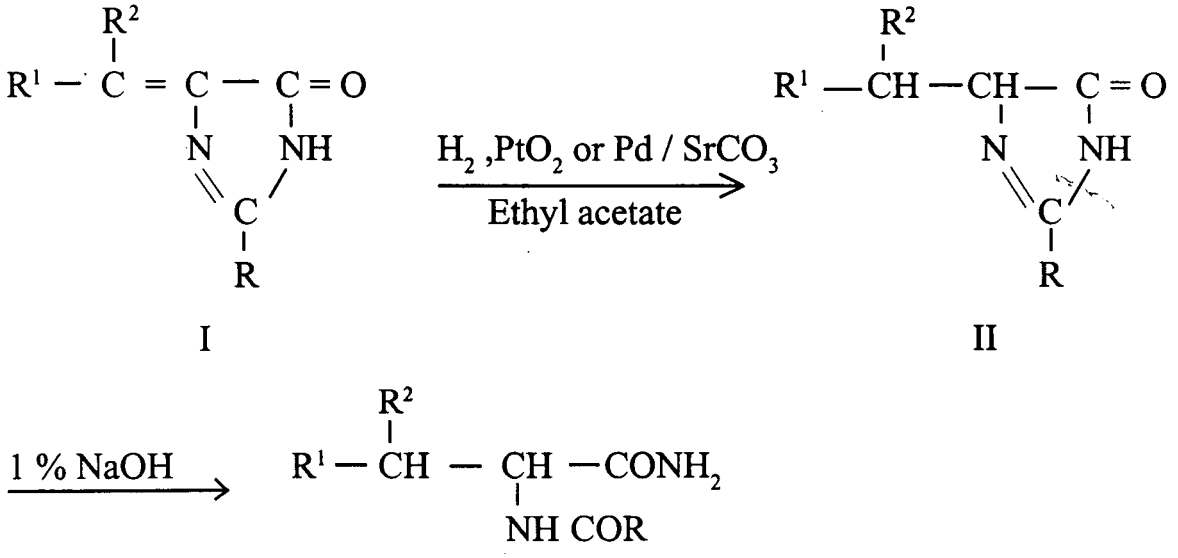
Section II

Synthesis of acylamino acid amides by direct methods

The acylamino acid amides are used as O-acylating reagents for serine [65]. They are usually prepared from aminoacids. However, a few of the several methods available for the synthesis of α- amino acids directly afford acylamino acid amides. The following is a review of these direct methods available for the synthesis of acylamino acid amides.

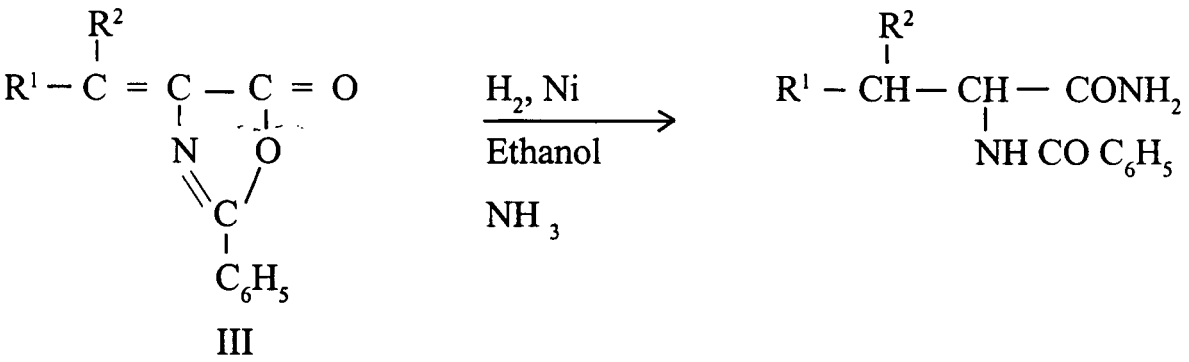
1. 2-Imidazolin -5- one-method

In 1962 Kidwai and Devasia [53] developed this method for the synthesis of acylamino acid amides. Unsaturated 2-imidazolin -5- ones (I) were hydrogenated to saturated 2- imidazolin -5- ones (II) which on heating with dilute alkali gave acylaminoacid amides in 27- 68% yields. The yields of acylaminoacid amides are not high since the heating with alkali further hydrolyses the amide to acylamino acid.



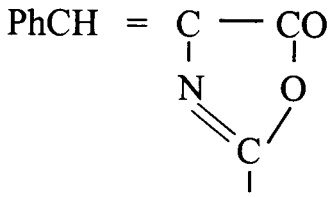
2. Azlactone method

Badshah and coworkers [66] prepared benzoylamino acid amides by hydrogenation of azlactones III in the presence of alcoholic ammonia using Raney nickel catalyst at room temperature and high pressure. Thus they prepared a number of benzoylaminoacid amides like N- benzoylphenyl alanine, N- benzoyl - O - methyltyrosine amide, N-benzoyltyrosine amide, N- benzoyl valine amide, N - benzoylisoleucine amide, N - benzoylleucine amide etc in 73- 100% yields.



Ali and coworkers [67] obtained acylamino acid amides by the hydrogenation of azlactones in the presence of alcoholic ammonia using Raney nickel or better palladium - carbon catalyst at room temperature but under high pressure. Use of tetrahydrofuran or dioxan instead of alcohol as solvent minimised the time of reduction with little variation in the yields of products.

The acylamino acid amide, V1 was prepared by Ali and Khan [68] as follows. One mole of hydroxylamine in methanol containing sodium at room temperature for 24 hours to produce 51% of V which was hydrogenated using Pd/C as cataylyst to give 95% of VI



IV

PhCH (NHOH) CH (NHB_2) CONHOH

V

Ph CH (NH_2) CH (NH B_2) $CONH_2$

VI

3. Substituted acylamino acid amides

Acylamino acid amides were prepared [69] by the reaction of aldehydes or ketones with a mixture of ammonia and an isonitrile in the presence of a carboxylic acid or its salt as illustrated by the synthesis of N- acetylaminoisovaleric acid -N- cyclohexylamide by the following scheme.

$$(CH_3)_2\,CH\,CHO + C_6H_{11}\,NC + NH_3 + NH_4\,OAC \longrightarrow (CH_3)_2\,CH\,\underset{\displaystyle NHAC}{\underset{|}{CH}}\,CONH\,C_6H_{11}$$

Section III

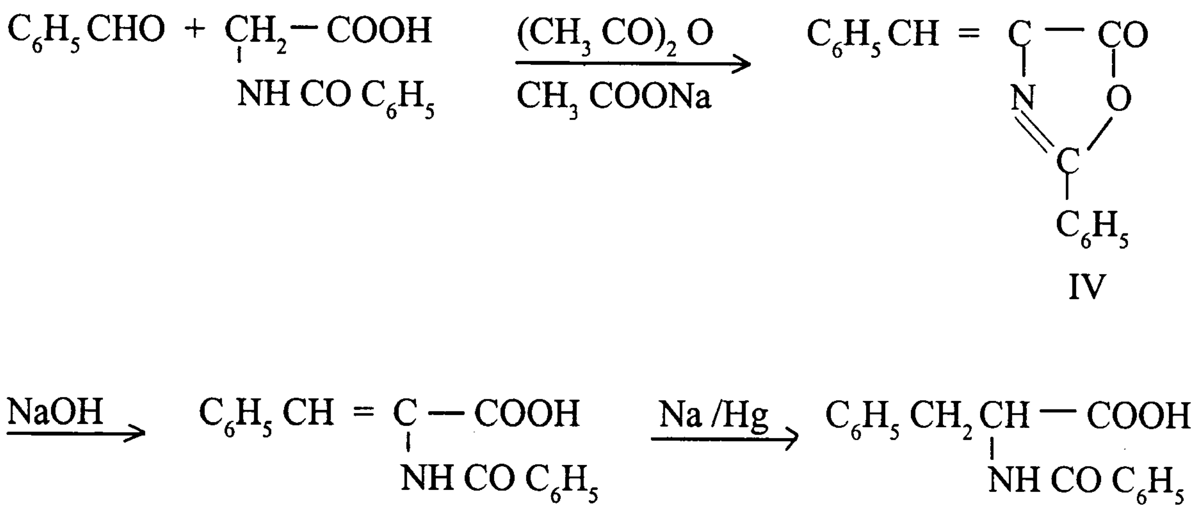
Synthesis of acylamino acids by direct methods

Acylamino acids are largely used for the resolution of amino acids [70] and for the synthesis of peptides [71]. Acylamino acids are mainly prepared from amino acids. However, a few of the several methods available for the synthesis of α- amino acids directly afford acylamino acids.

1. Azlactone method

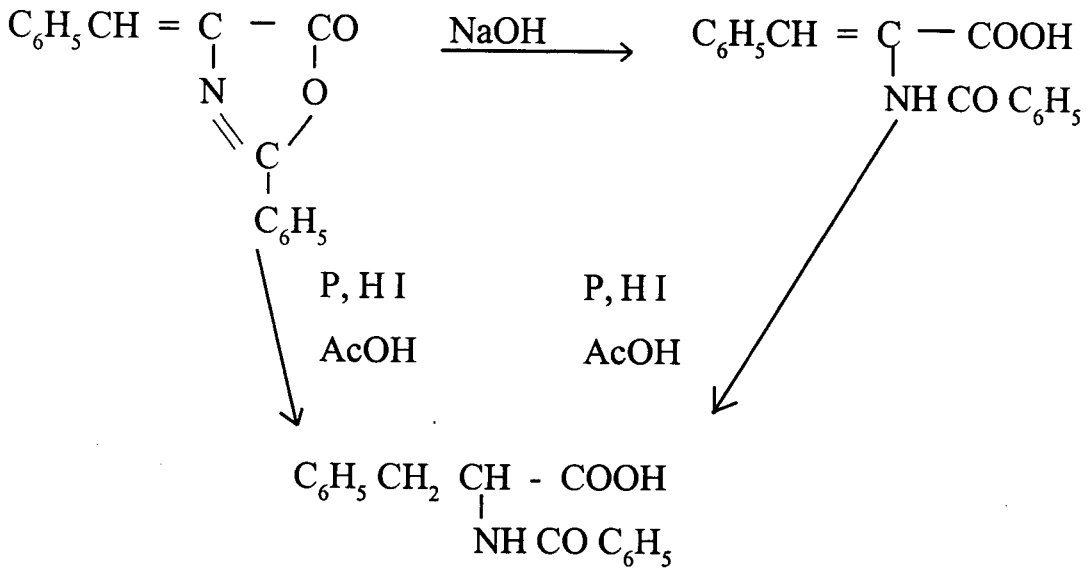
The azlactone method is an excellent and well exploited method for the synthesis of acylamino acids. In 1883 Plochl [72] obtained the so called azlactone (IV) on condensation of benzaldehyde with hippuric acid in the presence of acetic anhydride. After ten

years Erlenmeyer [73] improved very much this synthesis of azlactone and prepared benzoylphenylalanine starting from it acccording to the following scheme.

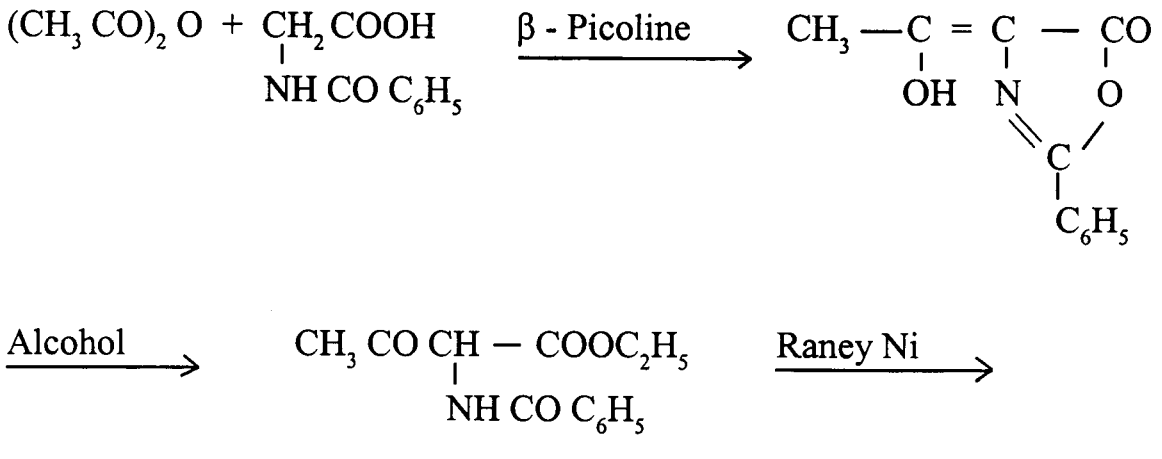


Employing this method benzoyltyrosine and benzoylleucine were also prepared by Erlenmeyer and coworkers [74-76]. In the synthesis of benzoylphenylalanine and benzoyltyrosine the yields were excellent except in the last stage. Fischer [77,78] improved this stage and obtained 80% yield of benzoyl phenylalanine and 65-70% yield of benzoyltyrosine. Ellinger and Flamand [79,80] used sodium amalgam and absolute alcohol instead of water for the reduction of the acrylic acid in the synthesis of benzoyltryptophan by this method. Pyman [81] prepared benzoylhistidine by employing this method.

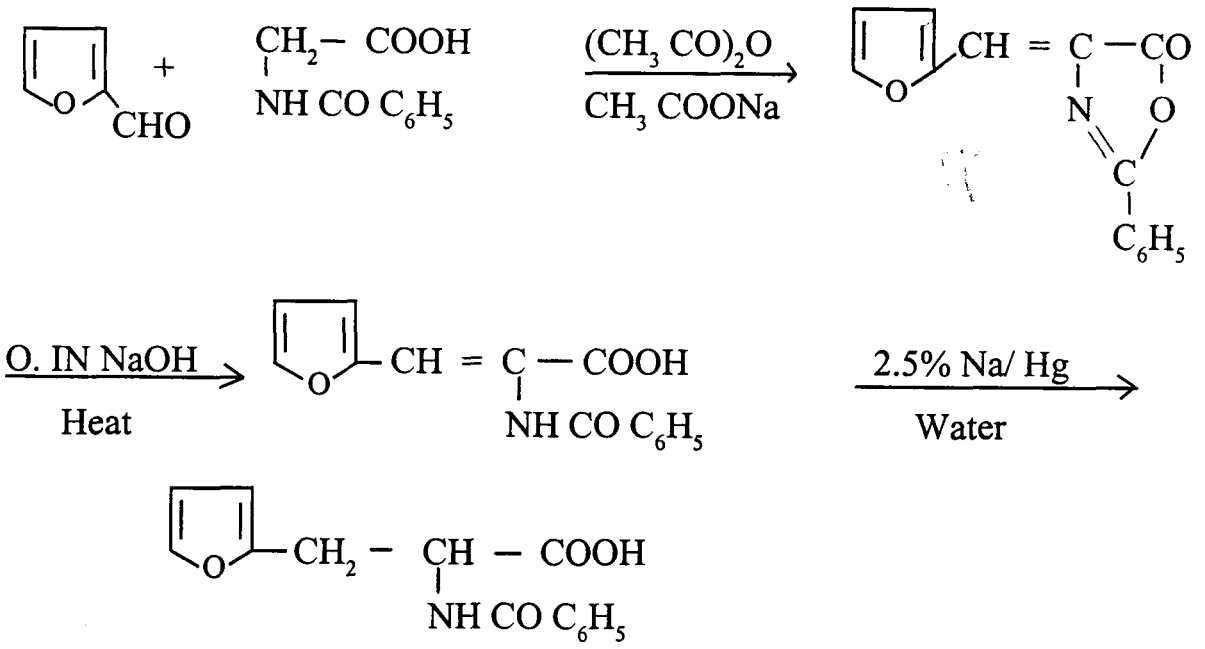
In 1931 Lamb and Robson [82] prepared benzoyl derivatives of phenyl alanine and tyrosine by the reduction of azlactones with small quantity of hydroiodic acid and red phosphorus in the presence of acetic acid. Benzoylphenylalanine and benzoyltyrosine were also prepared from the corresponding acrylic acids by using this reducing agent. The following scheme illustrates the preperation of benzoylphenylalanine by the methods.



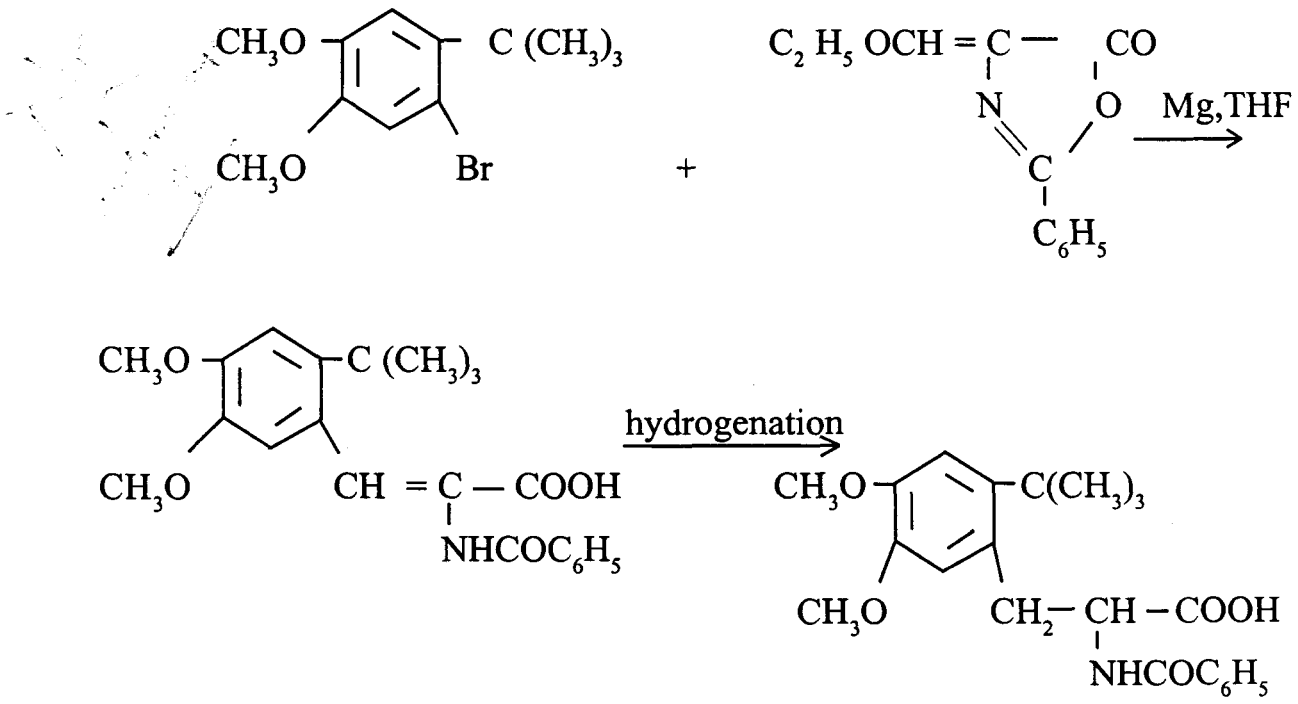
In 1948 Attenburrow and coworkers [83] prepared benzoylthreonine as shown in the following scheme:



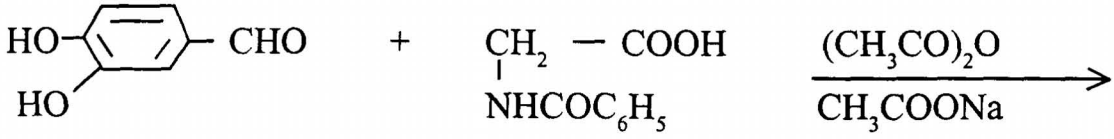
Terentev and coworkers [84] in 1963 synthesised N- benzoyl -β -(2- furyl) - α- alanine by the azlactone method as follows.

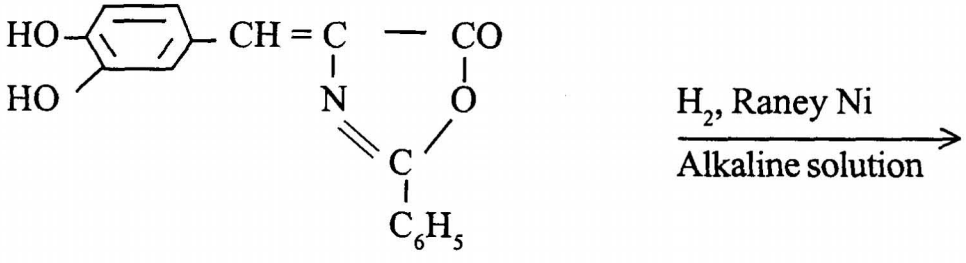


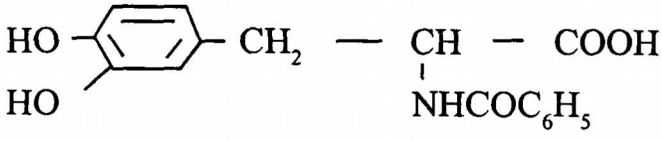
In 1971 Morgenstern and coworkers [85] synthesised N- benzoyl-β- (2-tertiarybutyl - 4,5 dimethoxyphenyl) alanine by the Grignard reaction of 4- bromo -5- tertiarybutylveratrole with 4-(ethoxymethylene) -2-phenyl -5- oxazolone followed by hydrogenation as shown below.



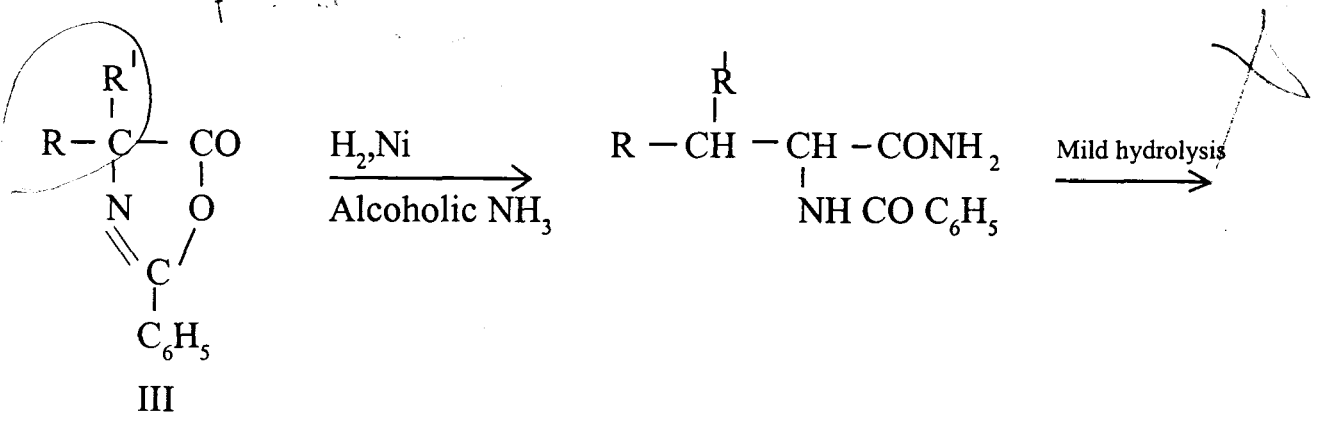
Schubel and coworkers [86] in 1972 prepared N- benzoyldopa by the azlactone method as follows



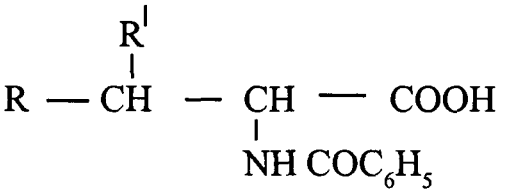




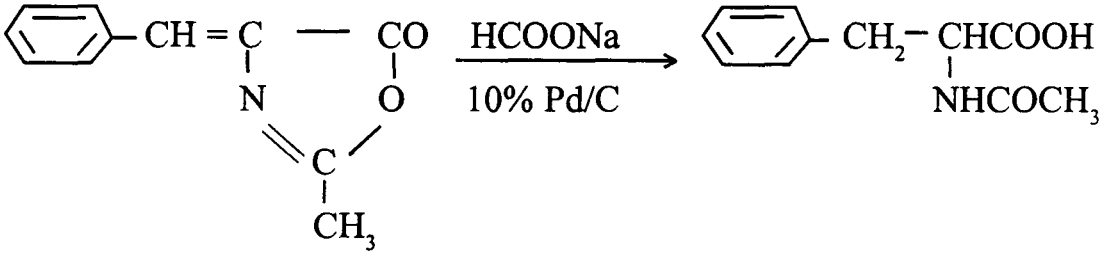
In 1972 Badshah and coworkers [66] efficiently employed the azlactone (III) for the synthesis of one dozen benzoylamino acids. The azlactones on catalytic reduction in the presence of alcoholic ammonia using Raney nickel catalyst at room temperature but under high pressure afforded benzoylamino acid amides in excellent yields. The benzoylamino acids were obtained from the latter in very high yields by mild hydrolysis with hydrochloric acid.



III



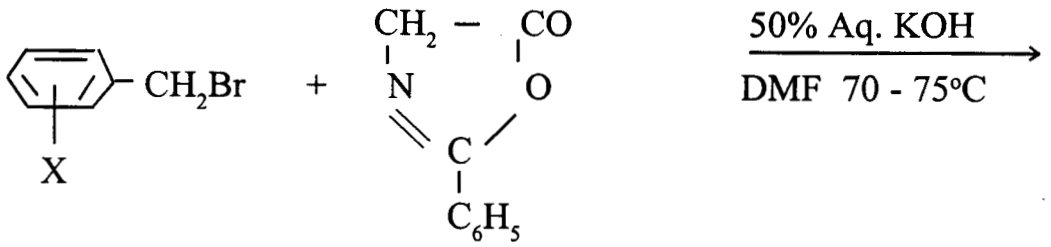
Hamaguchi [87] in 1973 prepared N- acetylphenylalanine in 91% yield by stirring 2- methyl -4- benzylidene -5-oxazolinone and sodiumformate in acetic acid for 4 - 5 hours at 65-70^{0}C with 10% Pd/C catalyst.

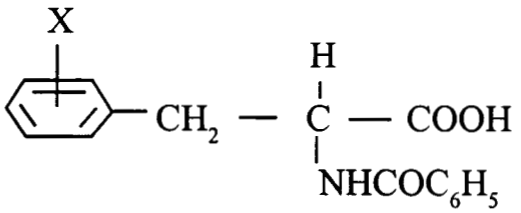


By employing this method N-benzoylphenylalanine (90% yield), N - benzoyltryptophan (85 % yield), N - benzoylvaline and N-acetyl - p-methylphenyl-alanine were also prepared.

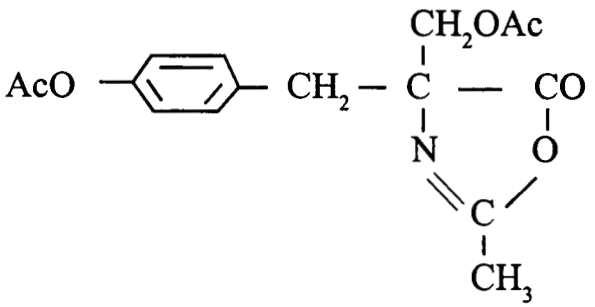
Berntsson and coworkers [88] in 1973 prepared N-acylphenylalanines by the electrolytic reduction of azlactones in alkaline medium using mercury cathode in an electrolytic cell with an electrode separating cation exchanger membrane.

In 1973 Akashi [89] prepared a number of N- benzoylphenylalanines by the action of benzoyl halides on hippuric acid azlactone as shown below.



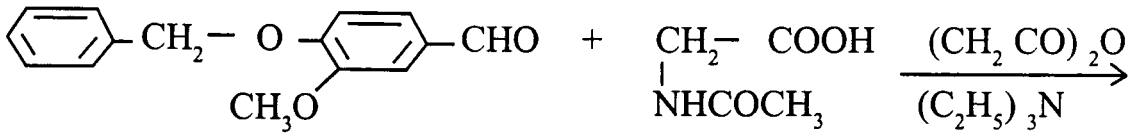


In 1975 Schnettler and Sah [90] developed a method for the synthesis of O,N - diacetyl (p-acteoxybenzyl)serine as follows. Tyrosine upon reaction with a mixture of sodium acetate, acetic anhydride and formaldehyde gave the azlactone VII which on hydrolysis with water afforded O,N - diacetyl α- (p-acetoxybenzyl)-serine

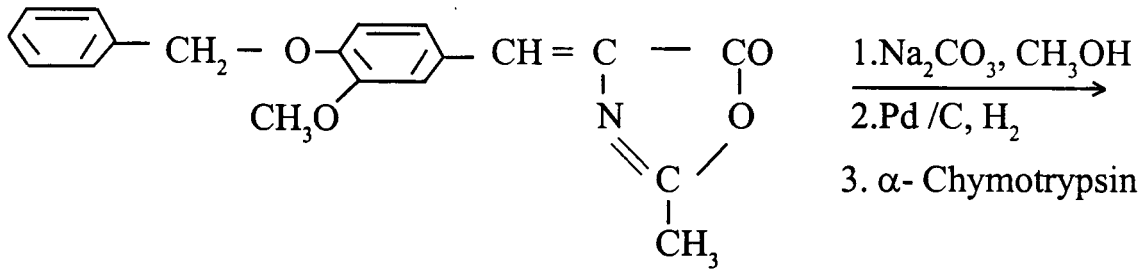


VII

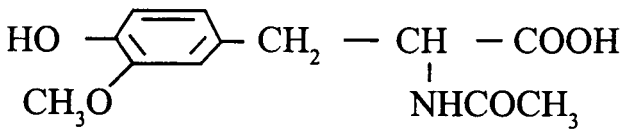
Matta and coworkers [91] in 1975 prepared N- acyldopa of optical purity by the azlactone method. The aldehyde VIII was heated with aceturic acid in the presence of acetic anhydride and triethyl amine at 70°C for two hours to give the azlactone IX. The azlactone IX was then heated under reflux with sodium carbonate in the presence of methanol, hydrogenated using pd/C catalyst and selectively hydrolysed with α- Chymotrypsin to yield N-acetyl - 3 - (4-hydroxy - 3 - methoxyphenyl) - L - alanine.



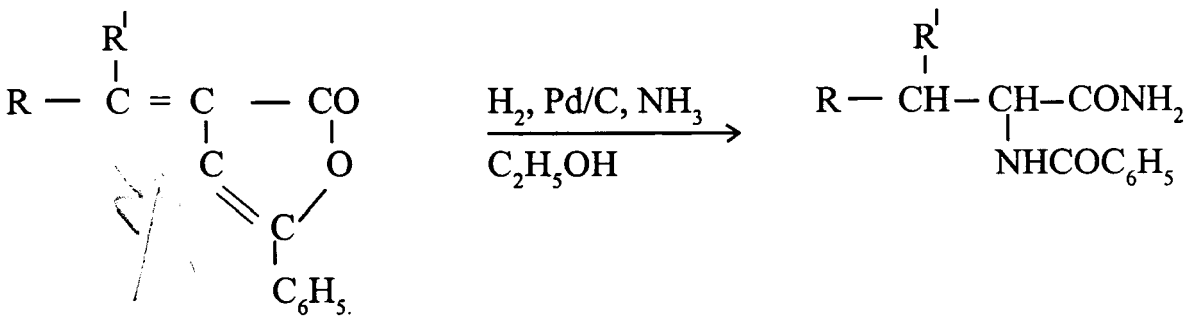
VIII



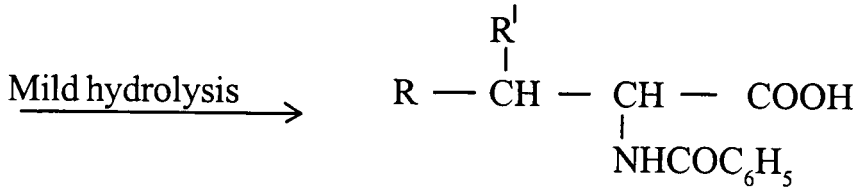
IX



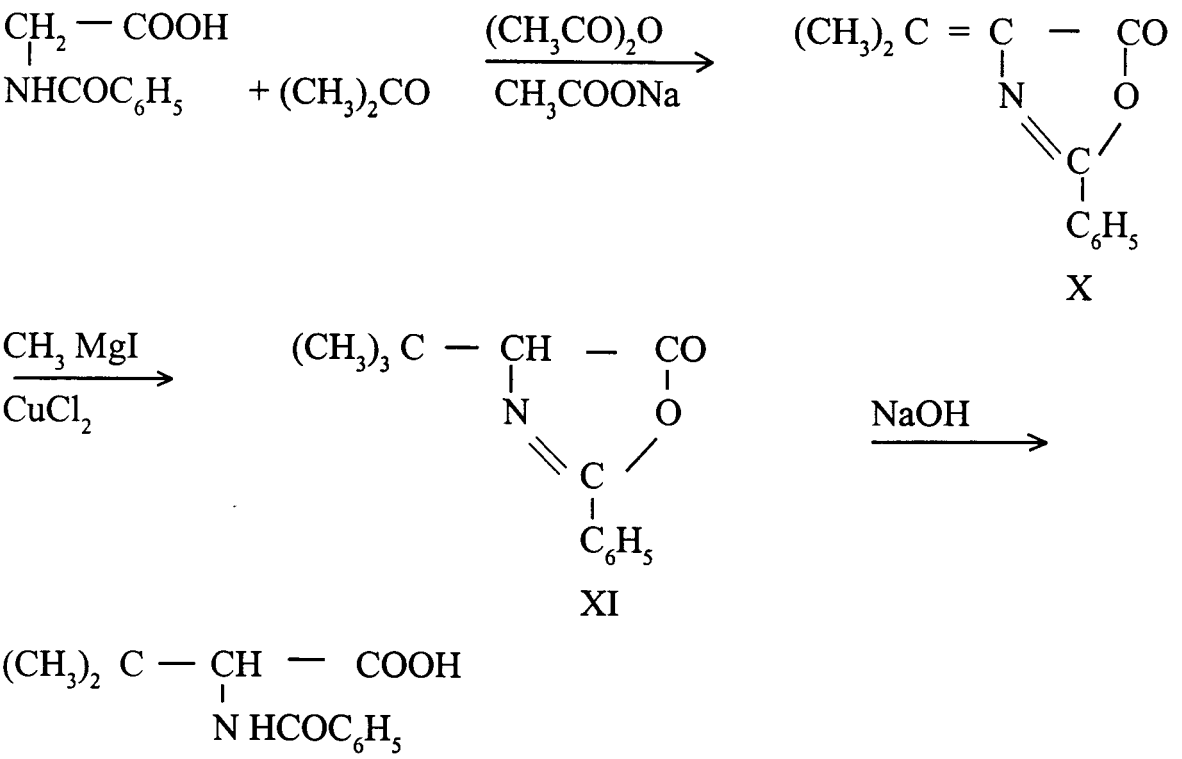
In 1976 Ali and coworkers [67] employed the azlactone method for the synthesis of a large number of benzoylamino acids in very high yields. Azlactones (III) on catalytic reduction in the presence of alcoholic ammonia using Raney nickel or better pd/C catalyst at room temparature but under high pressure yielded benzoyl amino acid amides. Use of tetrahydrofuran or dioxan as solvent instead of alcohol minimised the time of reduction with little variation in the yields of products. The benzoylamino acid amides afforded the benzoylamino acids on mild hydrolysis with hydrochloric acid.



III



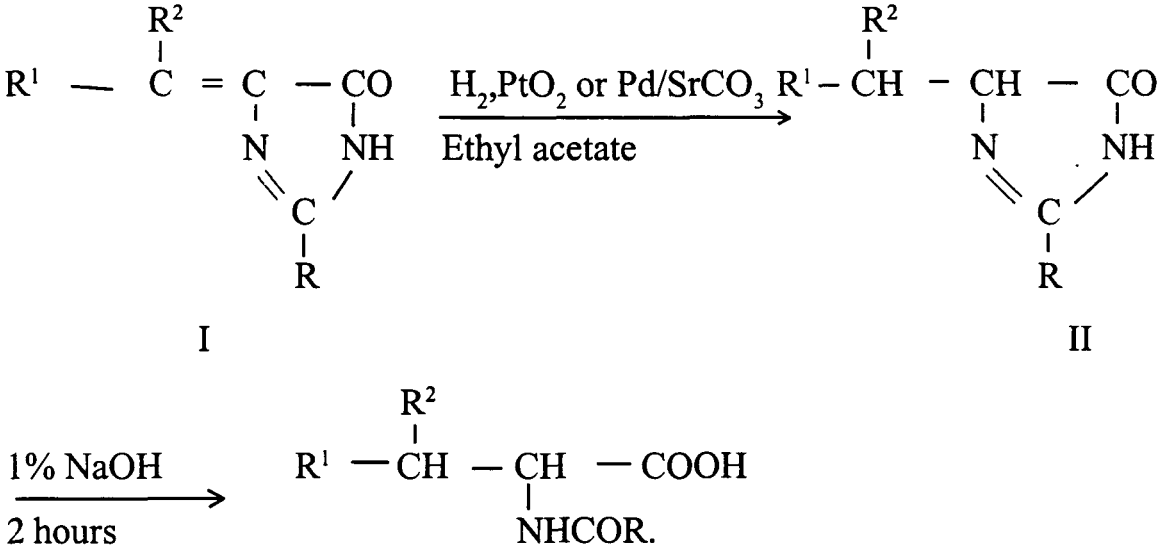
In 1979 Miyazawa and coworkers [92] prepared N-benzoyltertiaryleucine by the azlactone method. The benzoylglycine was treated with acetone in the presence of acetic anhydride and sodium acetate to give the azlactone X. On treatment with methyl magnesium iodide in the presence of copper chloride X afforded the azlactone XI. This azlactone was treated with sodium hydroxide to get benzoyl tertiary leucine.



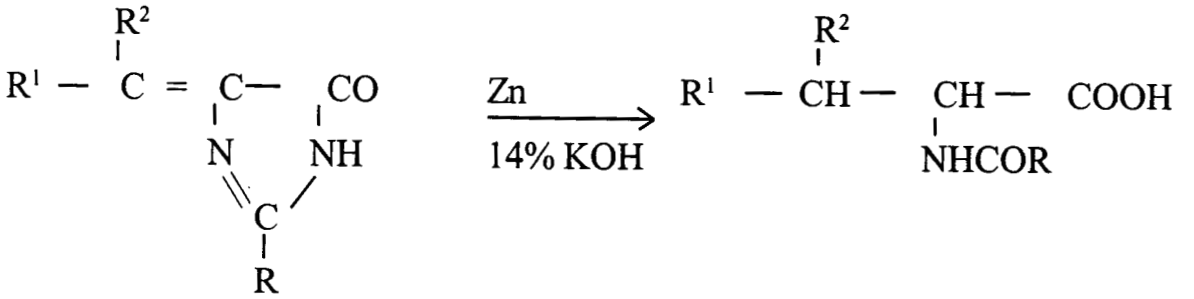
Furuya and Hirowata in 1980 [93] prepared N-(1 - diacetyl - DL - tryptophan) by hydrolysing 2 - methyl 4 - (1 - acetyl - 3 - indolylmethylene) - 5 - oxazolone and reducing the resulting α- acetamino - β - (1 - acetyl- 3 - indolyl) acrylic acid.

2- Imidazolin - 5 - one method

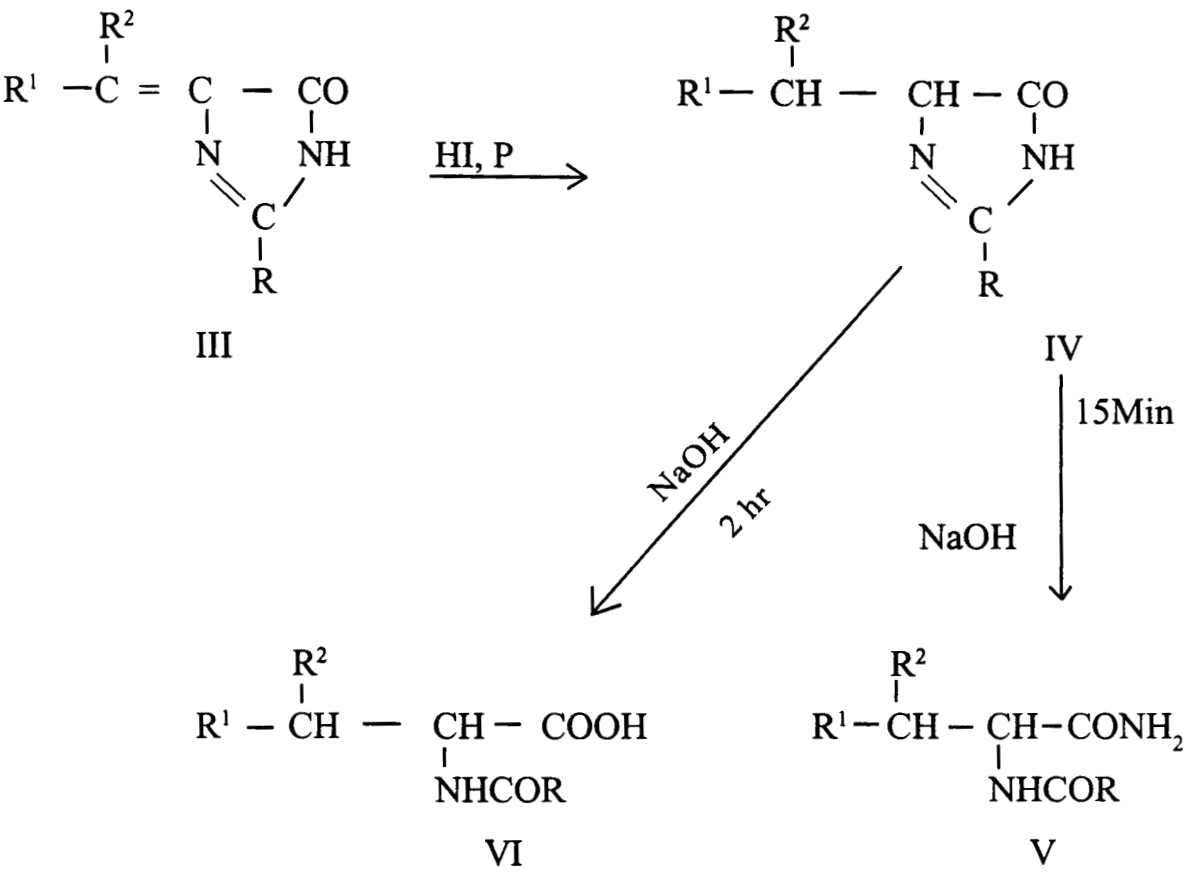
In 1962 Kidwai and Devasia [53] developed the 2 - imidazolin - 5 - one method for the synthesis of acylamino acids. Unsaturated 2 - imidazolin - 5 - ones (I) were hydrogenated to saturated 2 - imidazolin - 5 - ones (II) at room temparature and pressure using platinum oxide or palladium - strontium carbonate as catalyst and ethyl acetate as solvent. The saturated 2 - imidazolin - 5 - ones afforded acylaminoacids on heating under reflux with 1% sodium hydroxide solution for 2 hours. Thus they prepared three benzoylamino acids and two phenyl acetylamino acids in good yields.



In 1975 Devasia and Pillai [54] converted unsaturated 2 - imidazolin - 5 - ones to acylamino acids in a single step by the simultaneous reduction and hydrolysis with a mixture of zinc dust and 14% aqueous potassium hydroxide solution. Thus they prepared five benzoylamino acids in good yields.



In 1979 Devasia and Shafi [94] synthesised acylamino acids and acylaminoacid amides from 2,4 - disubstituled 2- imidazolin - 5 - ones. Unsaturated 2,4 - disubstituted 2 - imidazolin -5 - ones (III) have been reduced with a mixture of hydroiodic acid and red phosphrous in the presence of acetic anhydride to give the saturated 2,4 - disubstituted 2 - imidazolin - 5 - ones (IV) which have been hydrolysed to acyl amino acid amides (V) and acylamino acids (VI) with sodium hydroxide solution under different conditions.



CHAPTER I

Synthesis of 4 - arylidene - 2 - phenyl - 2 - imidazolin - 5 - ones

4 - Arylidene - 2 - phenyl - 2 - imidazolin - 5 - ones are the nitrogen analogues of the well known azlactones. Azlactones are converted into amino acids and acylamino acids by reduction and hydrolysis using HI-P or by catalytic reduction and hydrolysis. However 4 - arylidene - 2 - phenyl - 2 - imidazolin-5-ones can be converted into acylamino acids and acylamino acid amides by simultaneous reduction and hydrolysis [54,60,94] using zinc dust and alkali which are relatively cheap. Therefore, it is worthwhile to develop more methods for the synthesis of this class of compounds. In this chapter a new method for their synthesis is described.

Results and discussion :

In the present work 0.01 mole of an aromatic aldehyde and 0.011 mole of benzoylglycine amide were heated under reflux with saturated aqueous solution of potassium carbonate for 3 hours. Eight aldehydes were thus condensed with benzoylglycine amide to get 4 - arylidene -2 - phenyl - 2 - imidazolin - 5 - ones in 44 - 60% yields (Table - 1)

Table - I

Physical data of 4 - arylidene - 2 - phenyl - 2 - imidazolin - 5 - ones(III)

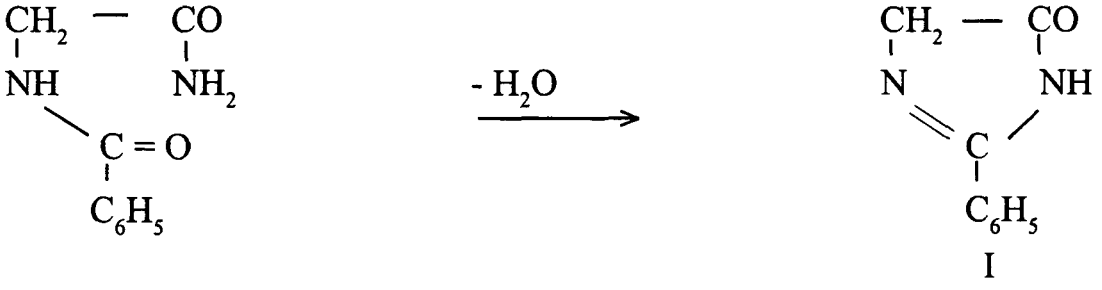
Ar	m.p(^{o}C)	Yield(%)	$\upsilon_{C=O}$(cm^{-1})	λ_{max}(nm)
Phenyl	282-83	44	1697.6	382
4 - chlorophenyl	310	48	1701.4	386

PART II

4 - Methoxyphenyl	300	58	1699.5	398
2-Chlorophenyl	267	52	1718.0	383
3,4-Dimethoxyphenyl	269-70	57	1701.4	405
3,4-Methylenedioxy phenyl	295-96	60	1705.3	406
3-Nitrophenyl	261-62	44	1705.1	389
4-Nitrophenyl	313	46	1711.1	402

Mechanism :

Wieland and Biener [95] obtained 2 - phenyl - 2 - imidazolin - 5 - one (I) by heating benzoylglycine amide to 170 °C in presence of a base. This is the crucial compound in the synthesis of 4 - arylidene - 2 - phenyl - 2 - imidazolin - 5 - ones. Aromatic aldehydes condense with I to give 4 - arylidene - 2 - phenyl

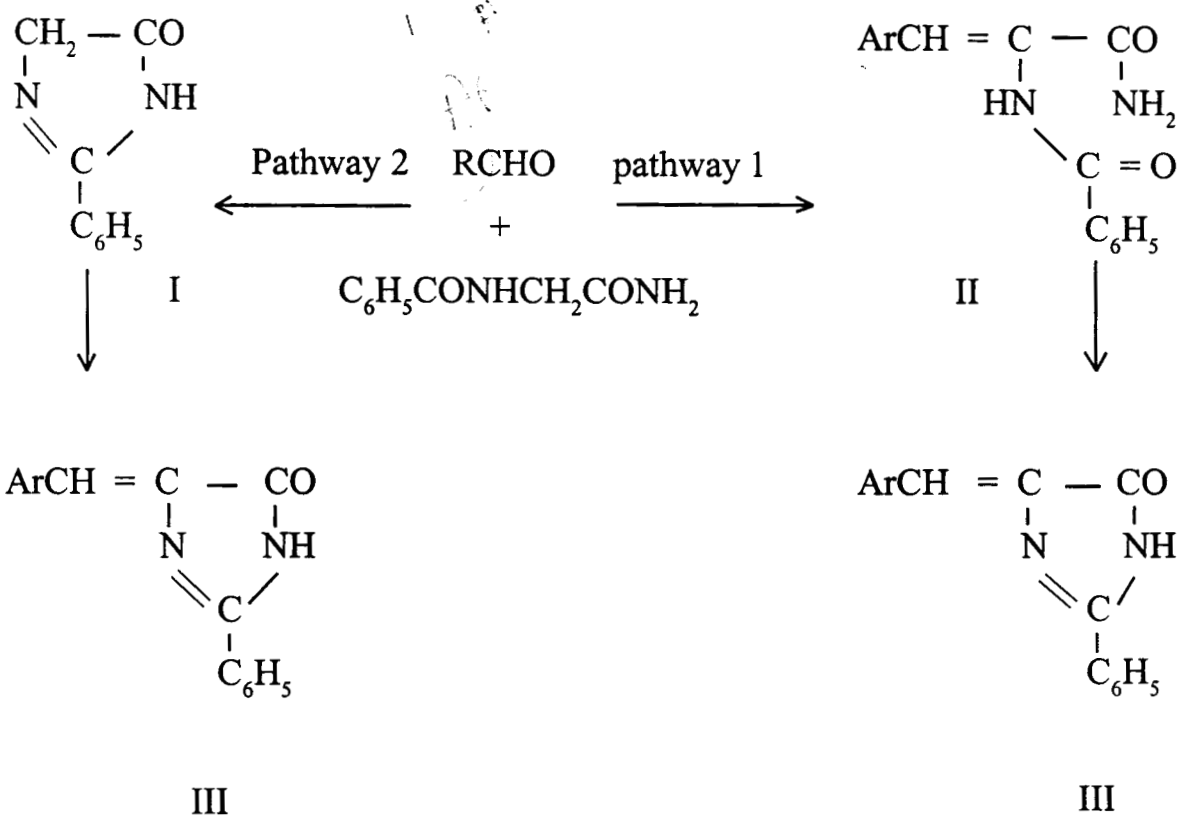


I

2 - imidazolin - 5 - ones [50,53,95]. An attempt was therefore made to condense aromatic aldehydes with benzoylglycine amide at 170°C in presence of bases like sodium bicarbonate or potassium bicarbonate. Very little yields of the products were obtained. More over they were contaminated with red coloured impurities. Hence condensation was tried in aqueous solutions like saturated solutions of sodium carbonate or potassium carbonate and dilute solutions of sodium hydroxide or potassium hydroxide. Better yields were obtained with a

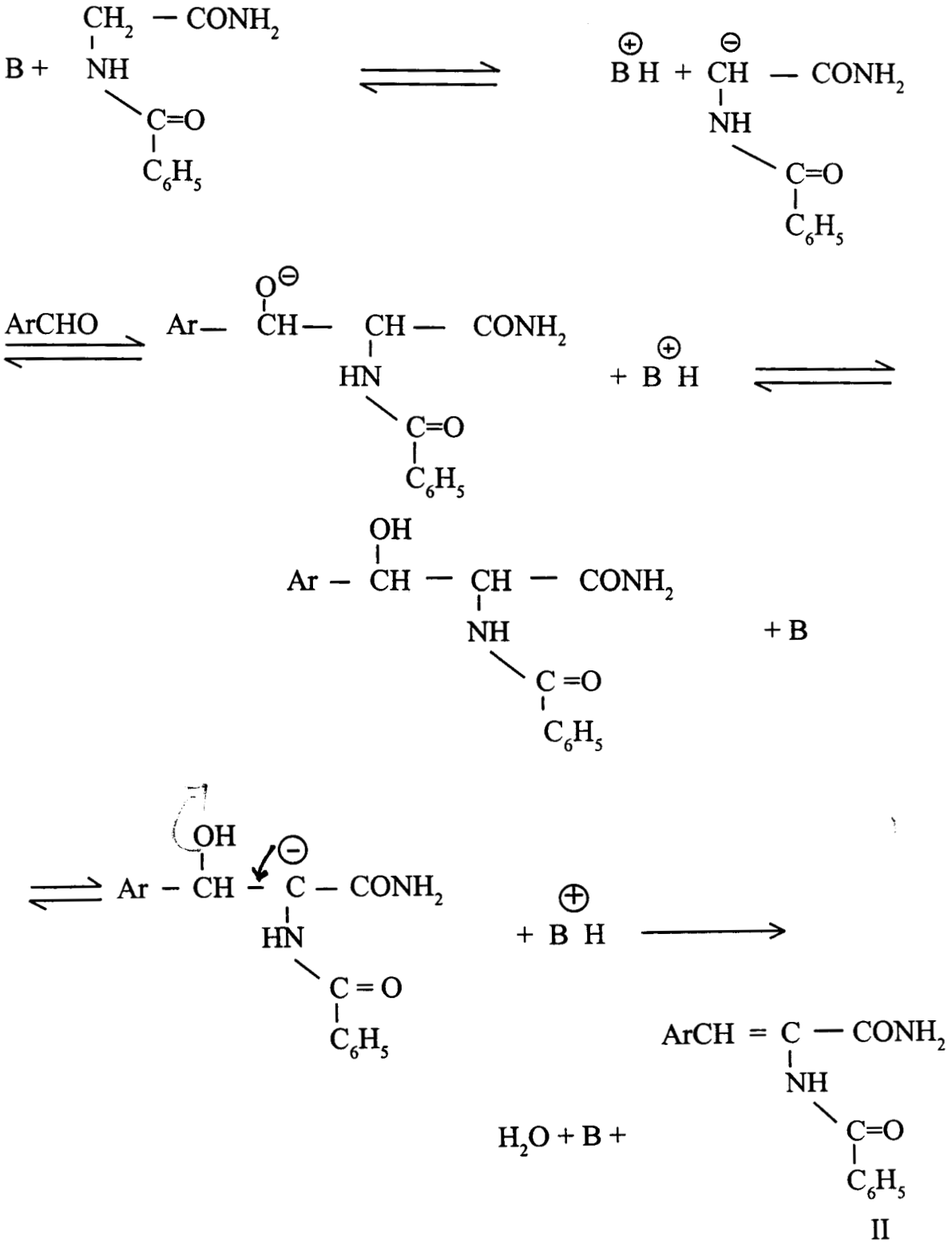
saturated solution of potassium carbonate. Benzoylglycine amide is likely to be hydrolysed when sodium hydroxide or potassium hydroxide is used as the base, lowering the yields of imidazolinones.

The reaction may follow two pathways given below. In pathway 1 condensation of the aromatic aldehyde with benzoylglycine amide takes place



first giving α - benzoylaminocinnamic (substituted cinnamic) acid amide (II). This is a typical Knoevenagel condensation in which the methylene group is activated by a benzoylamino group on one side and by an amide carbonyl on the other. II Cyclises to the product III [2-7]. In the pathway 2 cyclisation of benzoylglycine amide to 2 - phenyl - 2 - imidazolin - 5 - one (I) is the first step of reaction [95]. In the second step, the aromatic aldehyde condenses with it to give the product (III).

During this study it could be proved that pathway 1 was followed in the reaction. This mechanism was proved by isolating II from the reaction mixture

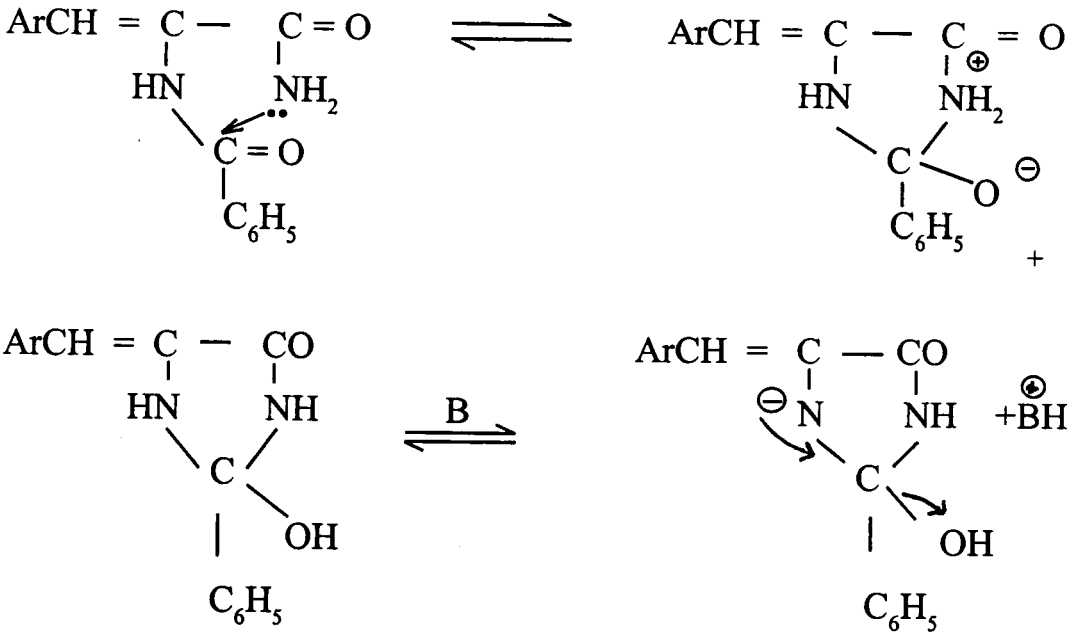


and elucidating its structure. It is well known [2,3,4] that II cyclises in aqueous alkaline solutions giving 4 - arylidene - 2 - phenyl - 2 - imidazolin - 5 - ones. The intermediate II was isolated by condensing benzaldehyde with benzoylglycine amide. It was also prepared by heating azlactone of α-aminocinnamic acid with methanolic ammonia [3]. Both the compounds melted at the same temperature of 223°C. Their mixed melting point was undepressed.

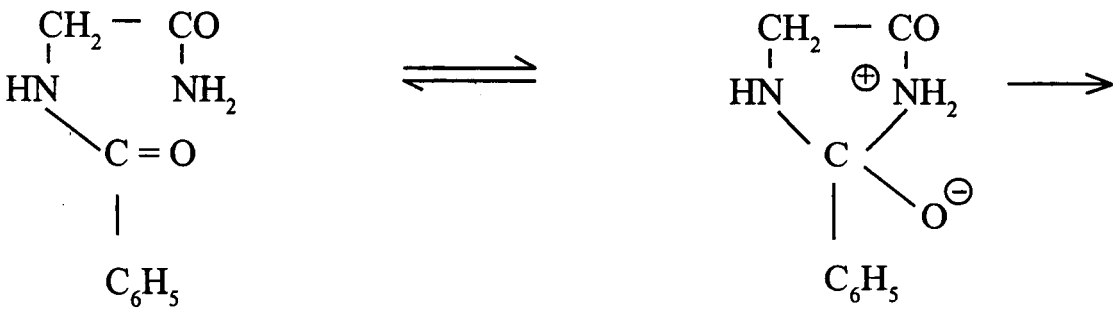
Formation of I via pathway 2 was disproved as follows. Benzoylglycine amide alone was heated in saturated solution of potassium carbonate for 3 hours. Formation of I would result in red colouration due to further reactions [95]. But no red colour was formed showing the absence of I. In another experiment benzoylglycine amide alone was heated under reflux in saturated solution of potassium carbonate for 3 h . After cooling to room temparature benzaldehyde was added to it and stirred for one hour. No yellow compound got precipitated. Presence of I would have resulted in the formation of yellow coloured 4 - benzylidene - 2 - phenyl - 2 - imidazolin - 5 - one as I condenses with aromatic aldehydes even at room temparature [53].

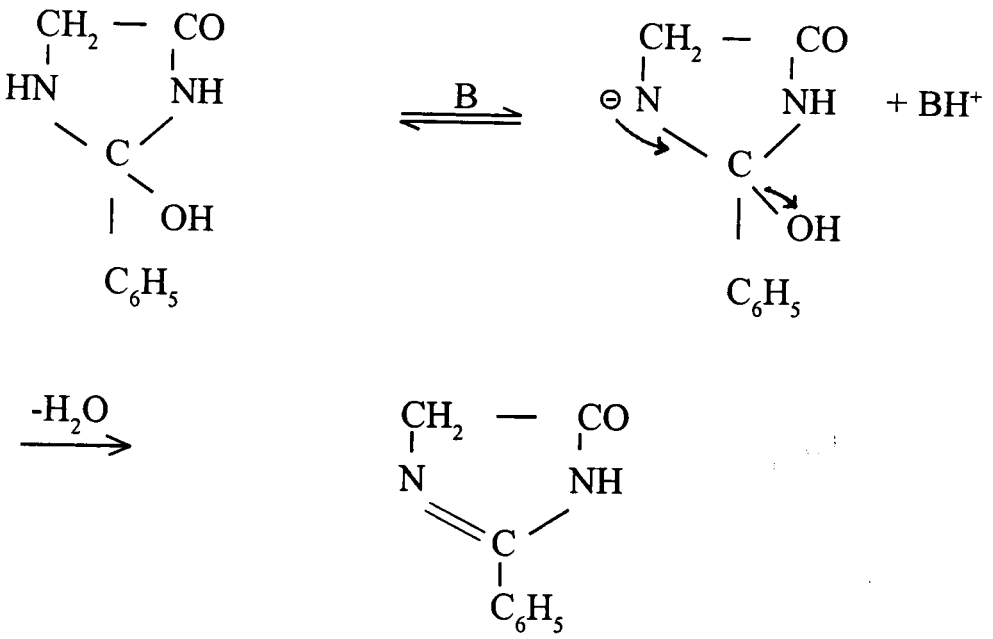
But wieland and Biener [95] had obtained I by heating benzoylglycine amide at 170°C with a base. It might be possible at an elevated temparature of 170°C while under mild conditions adopted in this work the alternate path followed. It can be noted that cyclisation occurs via the attack at the carbonyl carbon of benzoyl group by the amide nitrogen using its lone pair electrons

Pathway 1



Pathway 2





The lone pair electrons will be more available for nucleophlic attack in pathway 1 as the amide carbonyl is in conjugation with the double bond at the α,β - position rendering the amide carbonyl less electronegative . Dehydration after cyclisation also will be favoured in this case as it produces fully conjugated system starting from the phenyl group at position 2 of the imidazolinone ring and ending at the aromatic ring of the benzylidene group at position 4 .

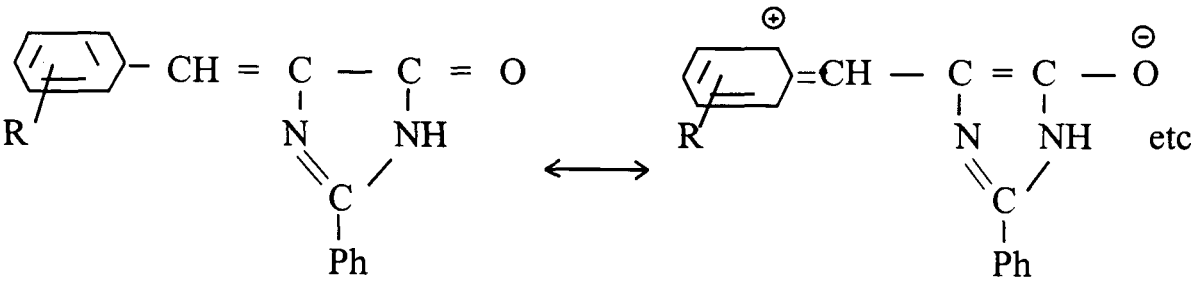
Spectral properties

The infrared (IR) spectra of the samples were recorded as KBr pellets.

The important bands observed in the infrared sepectra of 4 - arylidene - 2 - phenyl - 2 - imidazolin - 5 - ones are due to the C = O, C = N, C = C and N-H vibrations. These compounds are similar to cyclic five membered lactams. The carbonyl group is in conjugation with the exocyclic double bond at α,β - position. This exocyclic double bond extends the conjugation to the aromatic ring of the arylidene group. Hence the substituent in this aromatic ring influences the

carbonyl absorption frequency. The carbonyl absorption frequencies of the eight compounds synthesised fall in the range 1697.6 to 1718.0 cm^{-1} (Table I).

In this α, β - unsaturated carbonyl system the carbonyl absorption frequency decreases due to slight single bond character arising by the following resonating structures.



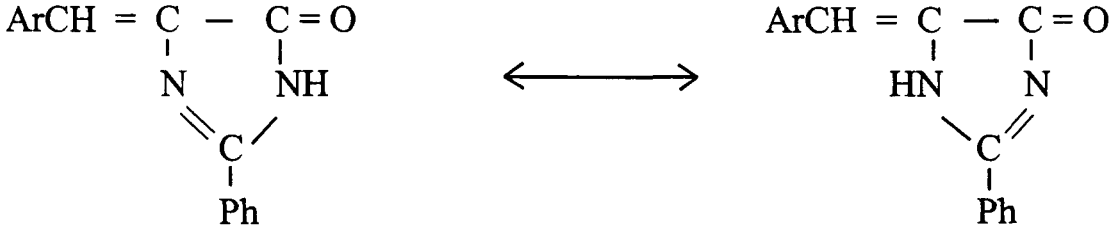
Therefore if the substituent in the aromatic ring of the arylidene group is electron donating either by mesomeric or inductive effects, the carbonyl absorption frequency will decrease on the contrary it will increase. In this study the carbonyl absorption frequency of all imidazolinones with substituted aryl group was higher than the unsubstituted one. That is the net result of inductive and mesomeric effects was electron withdrawing. These compounds are comparable to five membered cyclic lactams which have a carbonyl absorption frequency 1700 - 1750 cm^{-1} [96].

The highest carbonyl absorption frequency (1718 cm^{-1}) was exhibited by 4 - o - chlorobenzylidene - 2 - phenyl - 2 - imidazolin - 5 - one. In this case the electron withdrawing inductive effect is very much greater than the mesomeric effect due to the proximity of the chlorine atom to the carbonyl group. The corresponding p - chloro derivative absorbed at 1701.4 cm^{-1}. In the case of p- and m - nitrobenzylidene derivatives the former compound had higher C = O absorption frequency than the latter. The p - nitro group has - I effect. Its mesomeric effect also reduces the electron density in the aryl group leading to

higher bond order of the carbonyl group. On the other hand, the mesomeric effect of the m - nitrogroup, by virtue of its position will not induce higher bond order in the carbonyl group. The methoxy group and methylene dioxy group also increased the carbonyl absorption frequency than the unsubstituted ones showing electron withdrawing character.

The C = N stretching absorption frequency ranged between 1637.8 - 1645.5 cm^{-1}. It is known that C = N absorption frequency is about $1640cm^{-1}$ in compounds where this bond is conjugated with C = C [97].

The N - H stretching absorption is appearing as a group of slightly broad, medium intensity peaks in the regions 3061 - 3150 cm^{-1} apparently due to the tautomeric structures below.



In UV - Vis. spectra of these compounds showed an absorption maximum in the range 382 - 406 nm. This is attributed to the n - π^* transitions of the carbonyl group perturbed by intramolecular charge - transfer from arylidene residue to the polarised carbonyl group [104]. All the substituents in the arylidene ring was found to produce a red shift. A substituent at the para position resulted in higher red shift than the ortho or meta substituted counterparts. This can be due to the increase in chromophore length when the substituent occupies the para position.

EXPERIMENTAL

I R spectra were recorded as KBr pellets using Shimadzu 8101A FT IR equipment

Abbreviations s,m,br stand for strong, medium and broad

UV - Vis. spectra were recorded in ethanol solution using a Shimadzu 1601 UV - Vis. spectrometer.

The melting points recorded in open capillaries are uncorrected.

Synthesis of starting materials

Glycine ethyl ester hydrochloride

Glycine ethyl ester hydrochloride was prepared according to the method developed by Curtius and Geoble [98] and improved by others [53,99,100]

In a 2 - litre round bottomed flask with ground - glass joint was placed a mixture of glycine (75g, 1 mole) and absolute ethanol (750 mL) and the flask was fitted with a rubber cork carrying an inlet tube and a calcium chloride guard tube. Hydrogen chloride gas dried by bubbling through concentrated sulphuric acid was passed into the mixture till 100 g (2.7 mole) of the gas was absorbed. The flask was fitted with a reflux condenser carrying a calcium chloride guard tube and the mixture was heated under reflux. The glycine completely went into solution within about 30 minutes. After a total refluxing of two hours the flask was allowed to cool and the solution was transferred into a 1000 - mL conical flask for the sake of convenience. The solution was seeded to induce crystallisation, when a lot of glycine ester hydrochloride crystals separated. The flask was tightly stoppered and placed in the refrigerator overnight to effect complete crystallisation of the product. The crystals were quickly filtered on a large Buchner funnel, washed with two 50 mL portions of ice cold absolute ethanol and dried in the oven at 80^{o}C for one hour. The colourless glycine ethyl

ester hydrochloride weighed 118 g (84%) and melted at 144 - 146°C. Kidwai and Devasia [53] reported m.p. 144 - 145°C for this compound.

Glycine ethyl ester

Glycine ethyl ester hydrochloride was converted to glycine ethyl ester according to the method developed by Fischer [101,102] and improved by Kidwai and Devasia [53].

A saturated solution of glycine ethyl ester hydrochloride (25g, 0.18 mole) in 30mL of water was placed in a 500 mL conical flask. To this solution was added ether (100 mL) and the mixture was cooled in icebath and neutralised with 20mL of ice cold sodium hydroxide solution (40%). The aqueous layer was saturated with potassium carbonate by keeping the flask in icebath. The contents of the flask was transferred into a separatory funnel, shaken well and the ether layer was collected in a 500 - mL conical flask. The aqueous layer was extracted twice more with 50mL portions of ether. To dry the combined ether extracts anhydrous potassium carbonate was added , the flask was stoppered and placed in the refrigerator for 6 hours. The ether solution of glycine ester was filtered through a fluted filter paper by decantation and the residue was washed with dry ether. The ether was evaporated under reduced pressure from a cold water bath. The yield of colourless glycine ethyl ester thus obtained was 16.1 g (87%).

Hippuric acid amide (Benzoylglycine amide)

In a 500 - mL conical flask glycine ester obtained as above and methyl alcohol (100 mL) saturated with 5.1g (0.3 mole) of ammonia were stirred with a magnetic stirrer for one hour at 0°C and then at room temparature for 20 hours. Excess of methyl alcohol was removed by vacuum evaporation. The glycine

amide formed was dissolved in 10% sodium hydroxide solution (100mL) and transfered into a 250- mL conical flask. Benzoyl chloride (25mL, 0.21 mole) was then added in portions of 5mL to this solution and shaken well cooling the flask under tap. When the reaction was complete, the flask was placed in the refrigerator for 5 hours. The white crystals of hippuric acid amide formed was filtered, washed thrice with 10mL portions of water and dried. The product weighed 9 g (25.3%) and melted at 180 - 82°C. Reported melting point is 183°C [103].

Synthesis of imidazolinones

4 - Benzylidene -2 - phenyl - 2 - imidazolin - 5 - one

Benzoylglycine amide (1.96g, 0.011 mole), benzaldehyde (1.01mL, 0.01 mole) and saturated solution of potassium carbonate (20mL) were taken in a 50-mL round bottomed flask and heated under reflux for 3 hours. On heating for half an hour, the yellow crystals began to separate. After 3 hours, the flask was cooled. The yellow crystals of 4 - benzylidene -2 - phenyl - 2 - imidazolin - 5 - one was filtered, washed twice with 10mL of water and then with 10mL of ethanol and dried. The yellow product weighed 1.62g (43.5%) and melted at 280°C.

4 - Benzylidene -2 - phenyl - 2 - imidazolin - 5 - one (0.5g) was recrystallised from isobutanol (50mL). The recrystallised product melted at 282 - 83°C. The reported m.p is 284°C [60].

Analysis

N(%)

Found : 11.67

Calculated : 11.29

$C_{16}H_{12}N_2O$

IR

υ (Cm^{-1}) 3180 (m, br), 3080 (m), 1697.6 (m)
1639.7 (s), 1595.3(m) , 1267.4 (s), 1178.3 (s)

U.V - Vis

λ_{max} - 382nm

4 - (p - Chlorobenzylidene) -2 - phenyl - 2 - imidazolin - 5 -one

Benzoylglycine amide (1.96g, 0.011 mole) and p - chlorobenzaldehyde (1.4g, 0.01 mole) were heated under reflux in saturated potassium carbonate solution (20mL) for 3 hours. The yellow crystals of 4 - (p - chlorobenzylidene) -2 - phenyl - 2 - imdazolin - 5 - one formed was filtered, washed with water (10mL) and alcohol (10mL) and dried. The product weighed 2.03g (48.1%) and melted at 310°C.

4 - (p - Chlorobenzylidene) - 2 - phenyl - 2 - imdazolin - 5 -one (0.5g) was recrystallised from isobutanol (45 mL). It melted at 310°C. The reported melting point is 313 - 14°C [60].

Analysis

N(%)
Found : 9.64
Calculated : 9.92
$C_{16}H_{11}N_2OCl$

IR

υ (Cm^{-1}) 3180 (m,br), 3080 (m),1701.4 (m),
1641.6 (m), 1601 (s), 1261.6(s), 1180.6(s)

U.V -Vis

λ_{max} = 386nm

4- (p- Methoxybenzylidene) -2- phenyl - 2- imidazolin -5- one

Benzoylglycine amide (1.96g, 0.011 mole) and anisaldehyde (1.21mL, 0.01 mole) were heated under reflux in saturated potassium carbonate solution (20 mL). The yellow crystals of 4-(p- methoxybenzylidene) -2- phenyl -2-imidazolin-5- one formed was filtered, washed with water (10 mL) and alcohol (10mL) and dried. The product weighed 2.41g (57.8%) and melted at 300°C.

4- (p- Methoxybenzylidene) -2-phenyl -2- imidazolin -5- one (0.5g) was recrystallised from isobutanol (45mL). The yellow crystals melted at 300°c. The reported m.p is 301-2°C [60].

Analysis

N(%)

Found : 9.79

Calculated : 10.07

$C_{17}H_{14}N_2O_2$

I.R

$\upsilon(cm^{-1})$ 3180(m, br), 3065.3(m), 1699.5(s), 1641.6(m), 1597.3(m), 1265.5(s),1172.9(s)

U.V -Vis

λ_{max} = 398nm

4- (o-Chlorobenzylidene) -2- phenyl -2- imidazolin -5- one

Benzoylglycine amide (1.96g, 0.011mole) and o-chlorobenzaldehyde (1.12mL, 0.01 mole) were heated under reflux in saturated potassium carbonate

solution (20mL). The yellow crystals of 4-(o-chlorobenzylidene) -2- phenyl -2-imidazolin -5- one formed was filtered, washed with water (10mL) and alcohol (10mL) and dried. The product weighed 2.2g (52%) and melted at 267°c.

The unsaturated 2- imidazolin -5- one (0.5g) was recrystallised from isobutanol (40 mL). The yellow crystals melted at 267°c. Devasia and Shafi [60] reported m.p 267- 268°c for this compound.

Analysis

N(%)

Found : 9.99

Calculated : 9.92

$C_{16}H_{11}N_2OCl$

I.R

$\upsilon(cm^{-1})$ 3180 (m,br), 3080 (m), 1718.0 (s), 1637.8(m), 1603 (m), 1286.7(s), 1199(s).

U.V- Vis

λ_{max} = 383nm

4- (3,4- Dimethoxybenzylidene) -2-phenyl- 2- imidazolin -5-one

Benzoylglycine amide (1.96g,0.011 mole) and veratraldehyde (1.66g, 0.01mole) were heated under reflux in saturated potassium carbonate solution (20mL). The yellow crystals of 4-(3,4 - dimethoxybenzylidene) -2- phenyl- 2-imidazolin -5- one formed was filtered, washed with water (10mL) and alcohol (10mL) and dried. The product weighed 1.84g (57%) and melted at 268- 70°c

4 - (3,4- Dimethoxybenzylidene) -2- phenyl -2- imidazolin -5- one (0.5g) was recrystallised from isobutanol (35mL). The yellow crystals melted at 269-70°c. The reported m.p is 269- 70°C [60] .

Analysis

N(%)

Found : 9.17

Calculated : 9.09

$C_{18}H_{16}N_2O_3$

I.R

υ (cm^{-1}) 3180 (m,br), 3080 (m), 1701.4(s), 1637.8 (m), 1593.4 (m), 1272 (s), 1185 (s).

U.V- Vis

λ_{max} - 405nm

4- (3,4- Methylenedioxybenzylidene) -2- phenyl -2- imidazolin -5- one

Benzoylglycine amide (1.96g, 0.011 mole) and piperonaldehyde (1.5g, 0.01mole) were heated under reflux in saturated potassium carbonate solution (20mL). The yellow crystals of 4 - (3,4- methylenedioxybenzylidene) -2- phenyl - 2- imidazolin -5- one formed was filtered, washed with water (10mL) and alcohol (10mL) and dried. The product weighed 1.92g (60%) and melted at 295°C.

4- (3,4- Methylenedioxybenzylidene) -2- phenyl -2- imidazolin -5- one (0.5g) was recrystallised from isobutanol (40mL). The yellow crystals formed melted at 295- 96°c. The reported m.p is 296- 97°C [60] .

Analysis

N(%)

Found : 9.69

Calculated : 9.56

$C_{17}H_{12}N_{12}O_3$

IR

υ (cm^{-1}) 3180 (m,br), 3061.4 (m), 1705.3 (s), 1639.7 (m)
1601.1 (m), 1263.5 (s), 1188.3 (s)

U.V-Vis

λ_{max} = 406 nm

4 - (m - Nitrobenzylidene) -2 - phenyl - 2 - imidazolin - 5 - one

Benzoylglyine amide (1.96g, 0.011 mole) and m - nitrobenzaldehyde (1.51g, 0.01 mole) were heated under reflux in saturated potassium carbonate solution (20mL). The yellow crystals of 4 - (m - nitrobenzylidene) - 2 - phenyl - 2 - imidazolin - 5 - one formed was filtered, washed with water (10mL) and alcohol (10mL) and dried. The product weighed 1 .42g (44%) and melted at 260°C.

4 - (m - Nitrobenzylidene) - 2 - phenyl - 2 - imidazolin - 5 - one (0.5g) was recrystallised from 1:2 mixture of nitrobenzene and toluene (20mL). The yellow crystals melted at 261 - 62°C. The reported m.p is 262°C [60].

Analysis

N(%)

Found : 13.95

Calculated : 14 .33

$C_{16}H_{11}N_3O_3$

IR

υ(cm-1) 3180 (m,br), 3080(m), 1705.1 (s), 1645.5 (m),
1599.2 (m), 1268 (s), 1175 (s)

U.V - Vis

λ_{max} - 389.0nm

4 (p - Nitrobenzylidene) -2 - phenyl -2 - imidazolin - 5 - one

Benzoylglycine amide (1.96g, 0.011 mole)and p - nitrobenzaldehyde (1.51g, 0.01 mole) were heated under reflux in saturated potassium carbonate solution (20mL). The yellow crystals formed was filtered, washed with water(10mL), and alcohol (10mL) and dried. The product weighed 1.48g (46%) and melted at 312 - 313°C.

4 - (p - Nitrobenzylidene) -2- phenyl - 2 - imidazolin - 5 - one (0.5g) was recrystallised from a mixture of nitrobenzene (22mL) and toluene (15 mL). The yellow crystals melted at 313°C. The reported m.p is 313°C [60].

Analysis

N(%)

Found : 14.17

Calculated : 14.33

$C_{16}H_{11}N_3O_3$

IR

υ (cm^{-1}) 3180 (m,br), 3080 (m), 1711.1 (s), 1641.6 (m), 1595.3 (m), 1342 (s), 1298.3 (s), 1199.9(s)

U.V - Vis

λ_{max} - 402nm

α - Benzoylaminocinnamic acid amide

Finely powdered benzoylglycine amide (1.96g, 0.011 mole), benzaldehyde (1.01mL, 0.01 mole) and saturated potassium carbonate solution (20mL) were taken in a 50 - mL round bottomed flask and heated under reflux for 15 minutes. The reaction mixture was cooled and filtered, washed with water to get dull white crystals melting at 223°C.

Alternatively it was prepared by heating azlactone of α - benzoylamino cinnamic acid and alcoholic ammonia. Dull white crystals of α - benzoylamino cinnamic acid amide formed was filtered, washed with water and dried. It melted at 223^{O}C .

Analysis

N(%)

Found : 10.42

Calculated ; 10.53

$C_{16}H_{14}N_2O_2$

CHAPTER II

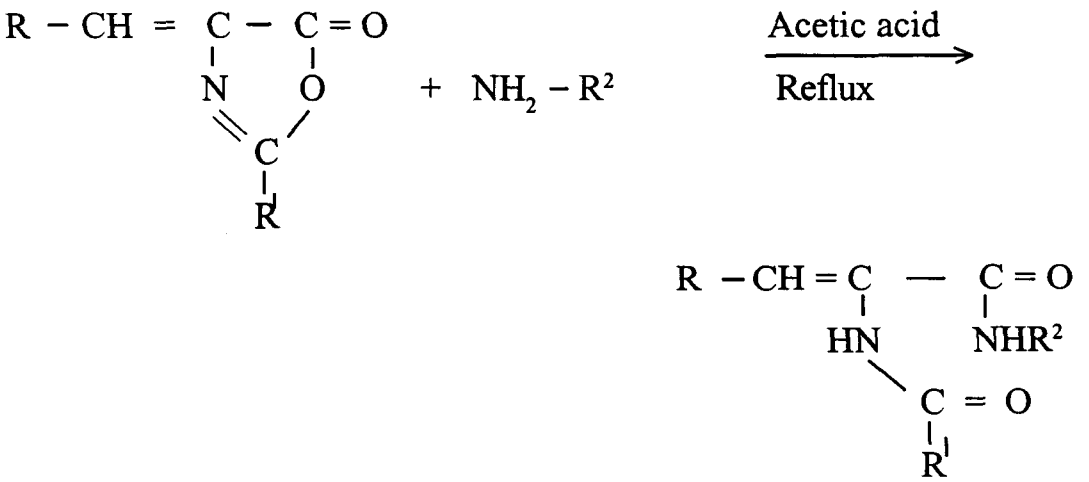
Synthesis of 1,2,4- trisubstituted - 2- imidazolin -5 -ones

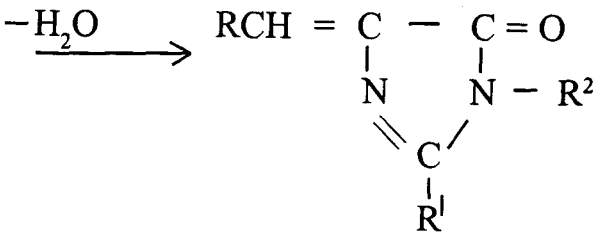
Imidazolinones have been found to possess various biological properties like antimicrobial, anthelmintic, antiparkinsonian, central nervous system depressant, anticonvalescent and monoamineoxidase inhibitor properties [40,105-111]. Hence it is worthwhile to synthesise and characterise new imidazolinones. In this chapter the synthesis of 1,2,3 - trisubstituted - 2- imidazolin - 5- ones is presented.

A. Synthesis of 2- aryl - 4- arylidene - 1 -(4'- carboxyphenyl) -2- imidazolin - 5- ones

Results and Discussion

It is well known that 4- arylidene - 2- phenyl - 2- oxazolin - 5- ones (azlactones) undergo ring opening at C - 5 by interaction with amines to yield α - benzoylaminocinnamic acid amides [112]. These amides, under suitable conditions, undergo cyclisation to give 2- aryl - 4- arylidene - 2- imidazolin - 5- ones [113]. These two reactions can be made to occur in a single experiment by heating the oxazolinone with a primary amino compound in acetic acid under reflux for a few hours [114]. The reaction can be depicted as follows.





In this work 4- arylidene - 2- phenyl - 2- oxazolin - 5-ones and 4- arylidene - 2- p- chlorophenyl - 2- oxazolin - 5- ones were converted to the corresponding imidazolinones by heating them with p - aminobenzoic acid under reflux in acetic acid for five hours.

In the general procedure the oxazolinone and p- aminobenzoic acid (0.01 mole each) were heated under reflux with 25 mL of acetic acid for five hours. Within a few minutes of boiling, the solid compound went into solution to give a practically colourless solution. After half an hour colourless solid began to deposition in the sides of the flask which can be the substituted amide formed by the ring opening of oxazolinone due to its reaction with p - aminobenzoic acid. On prolonged heating the solid gradually went into solution giving a yellow coloured solution. After five hours of heating the reaction mixture was cooled and poured into water in order to precipitate the product formed. After filtration and washing with water the product was dried in the oven. The compound thus prepared are given in table II - 1

Table II- 1

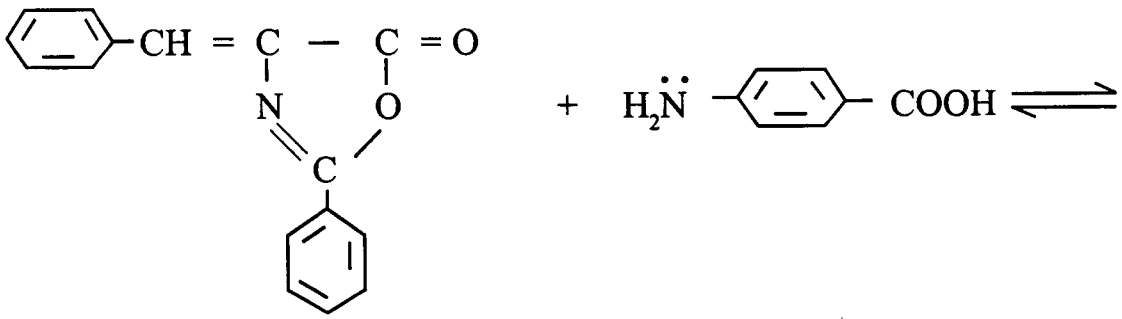
2- Aryl - 4- arylidene - 1- (4^1- carboxyphenyl) - 2- imidazolin - 5-ones

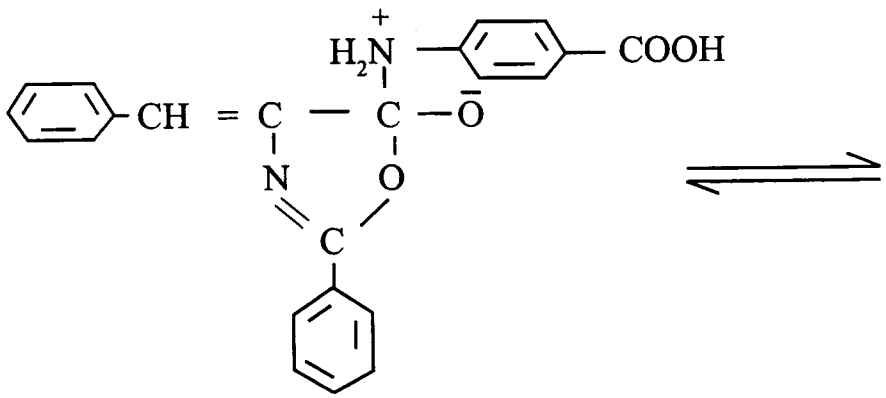
Name	m.p (°C)	Yield (%)	λ max (nm)
1. 4 - Benzylidene - 1 - (4^1- carboxyphenyl) - 2 - phenyl - 2 - imidazolin - 5 one	270	81	379

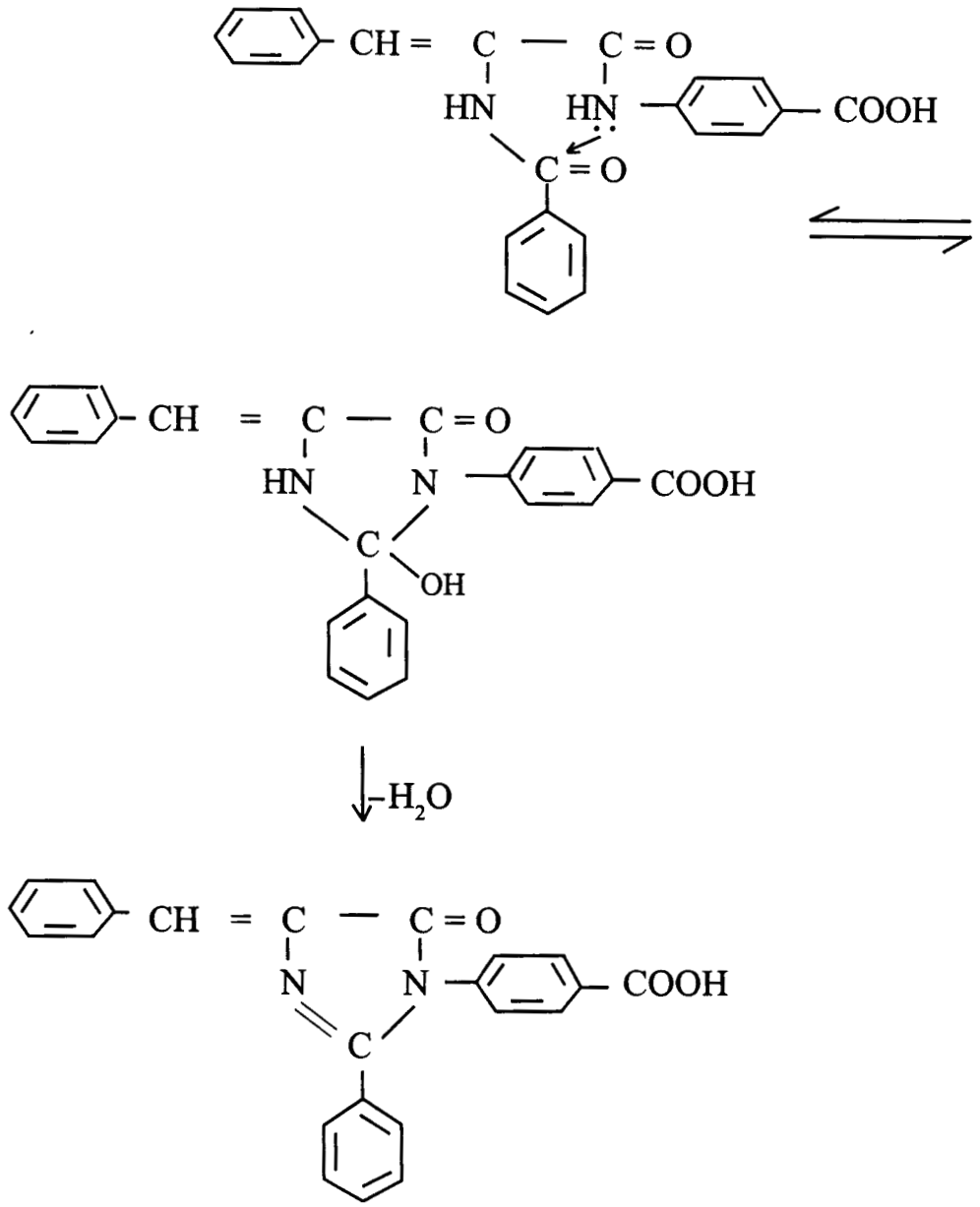
2. 1 - (4 I - Carboxyphenyl) - 4 - (p - methylbenzylidene) - 2 - phenyl - 2 -imidazolin - 5 - one	234	79	385
3. 1 - (4 I - Carboxyphenyl) - 4 - (p - chlorobenzylidene) - 2 - phenyl - 2 - imidazolin - 5 - one	220	53	380.5
4. 1 - (4 I - Carboxyphenyl) - 4 - (o - chlorobenzylidene) - 2 - phenyl - 2 - imidazolin - 5 - one	275	90	382.5
5. 1 - (4 I - Carboxyphenyl) - 4 - (p - methoxybenzylidene) - 2 - phenyl - 2 - imdazolin - 5 - one	282	75	381.5
6. 4 - Benzylidene - 1 - (4 I - carboxyphenyl) - 2 - (p - chlorophenyl) - 2 - imidazolin- 5 - one	269	64	381.5
7. 1 - (41 - Carboxyphenyl) - 4 - (p - chlorobenzylidene) - 2-(p- chlorophenyl) - 2 - imidazolin - 5 - one	242	100	393
8. 1 - (4 I - Carboxyphenyl) - 4 - (o - chlorobenzylidene) - 2 - (p - chlorophenyl) - 2 - imidazolin - 5 - one	233	100	376.5
9. 1 - (4 I - Carboxyphenyl) - 4 - (p - chlorobenzylidene) - 2 - (p - chlorphenyl) - 2 - imidazolin - 5 - one	226	83	384
10. 1 - (4 I Carboxyphenyl) - 4 - (p -methoxybenzylidene) - 2 - (p - chlorophenyl) - 2 - imidazolin - 5 - one	251	100	389.5

The identity of all the compounds were confirmed by elemental analysis. The mass spectrum of one of the compounds [4 - benzylidene - 1 - (4' - carboxyphenyl) - 2 - phenyl - 2 - imidazolin - 5 - one] was recorded. It gave M^+ at m/z = 368 corresponding to the expected structure. Other significient peaks were at m/z = 247 (57%), 121 (40%), 105 (80%) and 77 (100%).

The mechanism of formation of imidazolinones in this case is similar to the one given under chapter one. The mechanism of reaction between 4 - benzylidene - 2 - phenyl - 5 - oxazolinone and p - aminobenzoic acid can be shown as follows.







The UV - Vis spetra of these compounds had an absorption maximum in the range 376.5 to 393 nm. Comparison of these values with those of 4- arylidene - 2 - phenyl - 2 - imidazolin - 5 - ones (Chapter I) shows that introduction of p - carboxyphenyl group at position 1 of the imidazolinone ring has very little influence on the absorption maximum of these compounds. This can be justified on the basis that the absorption is due to the n - π^* transition of the carbonyl

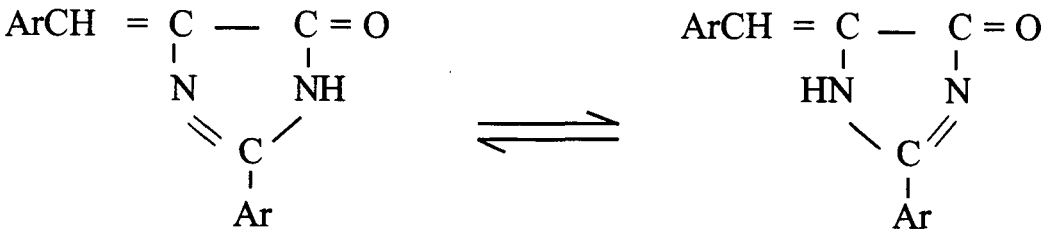
Table II - 2

UV - Vis absorption maximum of 1- substituted and unsubstituted imidazolinones

Unsubstituted	λ max (nm)	Substituted	λ max (nm)
4 - Benzylidene - 2 - phenyl - 2 - imidazolin - 5 - ones	382	4 - Benzylidene - 1 - (4 -carb-oxyphenyl) - 2 -phenyl - 2 - imidazolin - 5 - one	379
4 - p - Chlorobenzylidene- 2 - phenyl - 2 - imidazolin - 5 - one	386	1 - (4 ^{1}- Carboxyphenyl) - 4 - p -chlorobenzylidene- 2 - phenyl - 2 - imidazolin - 5 - one	382.5
4 - o -Chlorobenzylidene- 2-phenyl-2-imidazolin - 5 - one	383	1 - (4 ^{1}-Carboxyphenyl) - 4-(o-chlorobenzylidene)- 2-phenyl-2-imidazolin - 5 - one	380.5
4 - (p -Methoxybenzylidene) - 2 - phenyl - 2 - imidazolin - 5 - one	398	1 - (4^{1} -Carboxyphenyl) - 4- (p - methoxybenzylidene) - 2 - phenyl - 2 - imidazo-lin - 5 - one	395

group perturbed by the intramolecular charge transfer from arylidene residue to the polarised carbonyl group [104]. The lone pair electron on the adjacent nitrogen can influence the electronic environment of the carbonyl group. The availability of the electron pair on the nitrogen at position 1 of the imidazoline ring for

conjugation with the C = O bond can be practically the same in the unsubstituted and substituted imidazolinones. In the unsubstituted imidazolinones this electon pair will be utilised for bond formation due to the following tautomeric structures.



In the case of 1 - (4 ^{1}- carboxyphenyl) - imidazolinones, this electron pair can overlap with the p - orbitals in the phenyl ring bonded to nitrogen making it less available for conjugation with the >C = O bond of the imidazolinone ring.

B. <u>Esterification of the carboxyl group in 4 - arylidene 1 - (4^{1} - carboxyphenyl) - 2 - aryl - 2 - imidazolin - 5 - ones</u>

In an attempt to synthesise and characterise new imidazolinones, the carboxyl group in 4 - arylidene - 1 - (4^{1} - carboxyphenyl) 2 - aryl - 2 - imidazolin - 5 - ones was esterified with methanol.

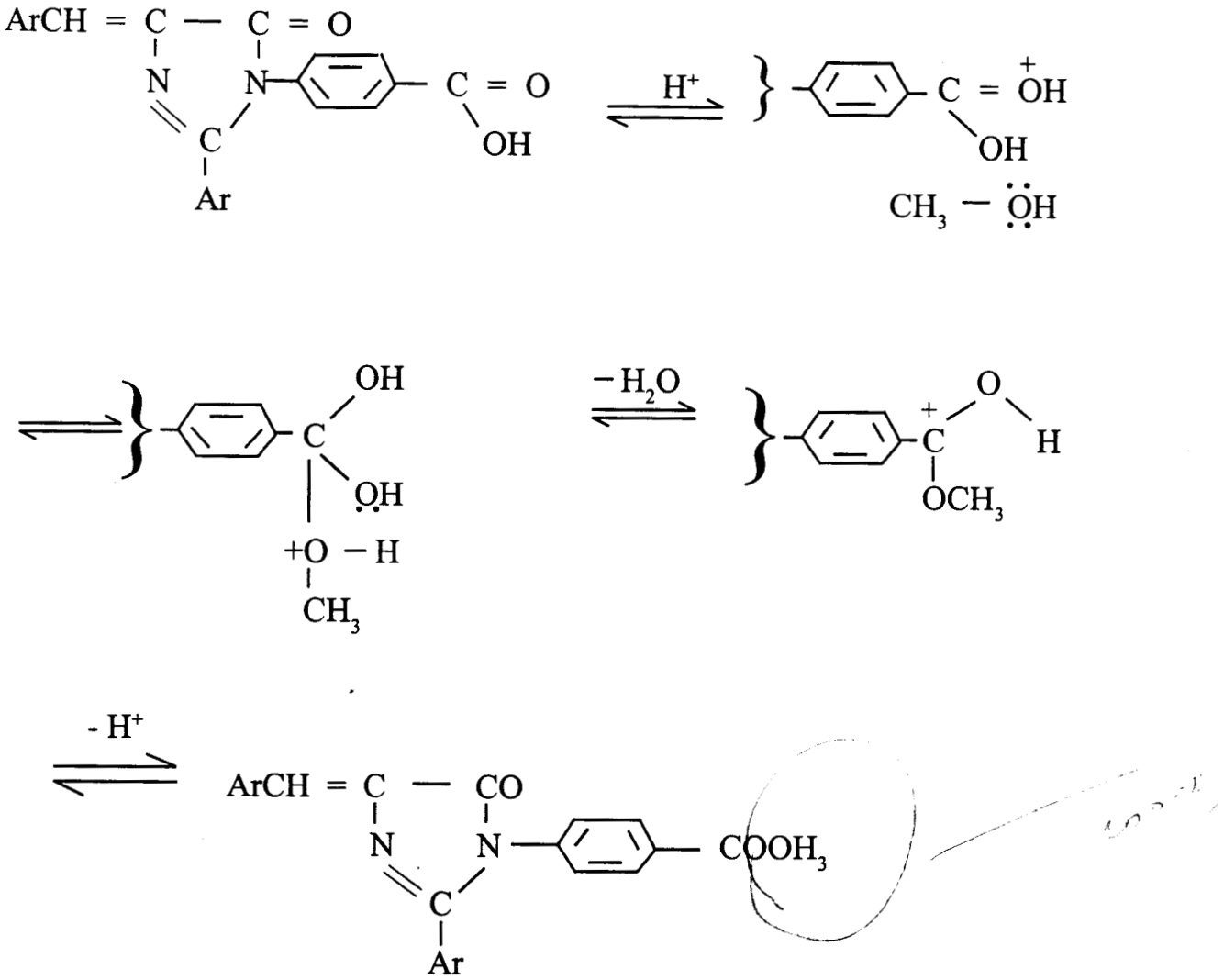
In every case 2g of the imidazolinone was heated under reflux with 0.5 mL of concentrated sulphuric acid and 10mL methanol for 2h. On boiling, the imidazolinone went into solution. The colour of the solution remained yellow throughout the reaction. After two hours of refluxing the reaction mixture was cooled to room temparature. The solidified product was filtered, washed twice with 5 mL portions of methanol and dried. The compounds thus prepared are given in the table II - 3

Table II - 3

2 - Aryl - 4 - arylidene - 1 - (4 ^{l}- carbomethoxyphenyl) - 2 - imidazolin - 5 - ones

Name	m.p (^{o}C)	Yield (%)	λ max(nm)
1. 4 - Benzylidene - 1 - (4 ^{l}- carbomethoxy phenyl) - 2 - phenyl - 2 - imidazolin - 5- one	174	61	380.5
2. 1 - (4 ^{l}- Carbomethoxyphenyl) - 4 - (o - chlorobenzylidene) - 2 - phenyl - 2 - imi- dazolin - 5 - one	189	73	380.5
3. 1 - (4 ^{l}- Carbomethoxyphenyl) - 4 - (p - methoxybenzylidene) - 2 - phenyl - 2 - imidazolin - 5 - one	182	87	397
4. 1 - (4 ^{l}- Carbomethoxyphenyl) - 4 - (p - chlorobenzylidene) - 2 - phenyl - 2 - imi- dazolin - 5 - one	189	73	381
5. 1 - (4 ^{l}- Carbomethoxyphenyl) - 4 - (p- methylbenzylidene) - 2 - phenyl - 2 - imidazoline - 5 - one	193	72	380

4 - Arylidene - 1 - (4 ^{l}carboxyphenyl) - 2 - aryl - 2 - imidazolin -5-one can be considered as p - substituted benzoic acids. Their esterification with methanol using acid catalyst will, therefore, fellow $A_{AC}2$ mechanism as follows.



All the esters synthesised as above gave satisfactory analytical result for nitrogen. The mass spectrum of 4 - p - chlorobenzylidene - 2 - phenyl - 1 - (4^{l} - carbomethoxyphenyl) - 2 - imidazolin - 5 - one was recorded. It had M^{+}peak at m/z = 416 (12.5%) in accordeance with the structure proposed. Due to the presence of ^{37}Cl atom a peak at 418 (6%) was also present. Other peaks present were at m/z = 385 (13%), 368 (100%), 301 (40%) , 276 (18%), 105 (30%), and 77.

The U.V - Vis absorption maxima of these esters were very close to their precursors (Table II - 3) showing the negligible influence of esterification on electon transfer energy responsible for this transition mentioned above.

C. Conversion of 4 - arylidene - 1 - (4 ^{1}- carboxyphenyl) - 2 - phenyl - 2 - imidazolin - 5 - ones to the corresponding amides.

As in the conversion of the carboxylic group to the ester group under section B of this chapter, the carboxylic groups could also be converted to amide group. This reaction yielded imidazolinones hitherto unreported. The method used was the well known two step process. That is conversion of the acid group to acid chloride group by reacting with thionyl chloride followed by reaction with liquor ammonia. Imidazolinones are cyclic amides. Eventhough amides are susceptible to thionyl chloride, imidazolinones are resistant to it [57]

In the general procedure one gram of 4- arylidene - 1(4 -^{1}carboxyphenyl)2-phenyl -2- imidazolin -5- one was heated under reflux with thionyl chloride (3mL) for 2 hours. Within one hour of heating the imidazolinone went into yellow solution. The round - bottomed flask containing the reaction mixture was cooled in ice and 10mL of ammonia solution added in portions with shaking. After complete addition of ammonia solution the reaction mixture was kept at room temperature for one hour and the products formed filtered. It was washed thoroughly with water and dried. The compounds synthesised are given in the table II- 4.

Table II - 4

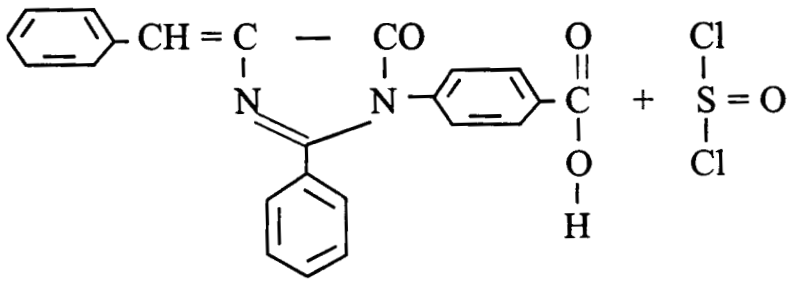
2- Aryl -4- arylidene -1-(4 - carboxamidophenyl) -2- imidazolin -5- one

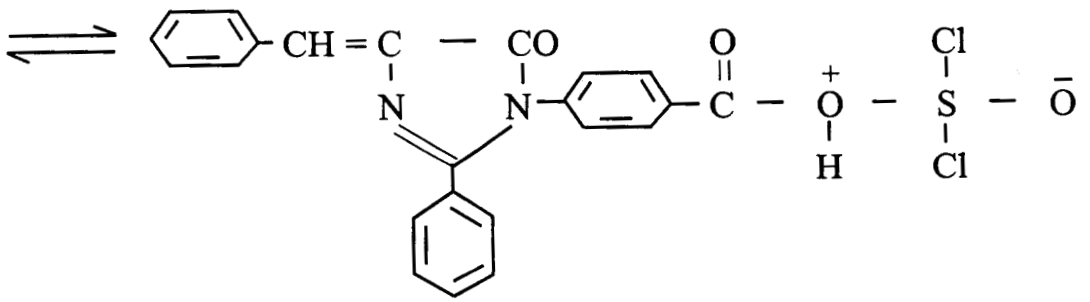
Name	m.p (^{0}C)	Yield(%)	λmax (nm)
1. 4- Benzylidene-1- (4^{1}- carboxamido phenyl) -2- phenyl-2- imidazolin -5-one154	80	377.5	
2. 1-(4 ^{1}Carboxamidophenyl) -4- (methyl benzylidene) -2-phenyl-2- imidazolin -5-one.	100	100	383.5

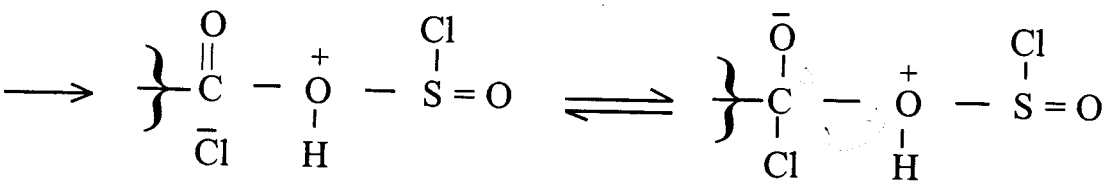
3. 1- (4 ¹-Carboxamidophenyl) -4-(o- chloro phenyl) -2-phenyl -2- imidazolin -5- one	134	100	380
4. 1-(4¹- Carboxamidophenyl) - 4 -(p- metho- xybenzylidene)-2- phenyl - 2- imidazolin -5-one.	197	91	395
5. 1- (4 ¹ Carboxamidophenyl) -4- (p - chlo- robenzylidene) -2- phenyl -2-imidazolin -5- one.	189	100	381

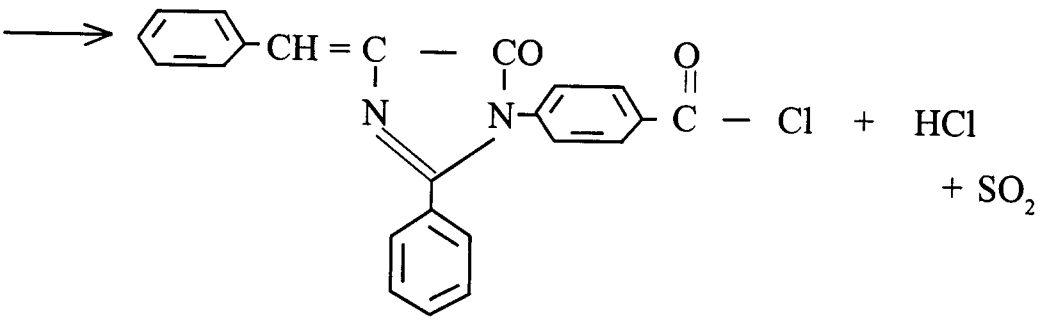
Mechanism

Step 1

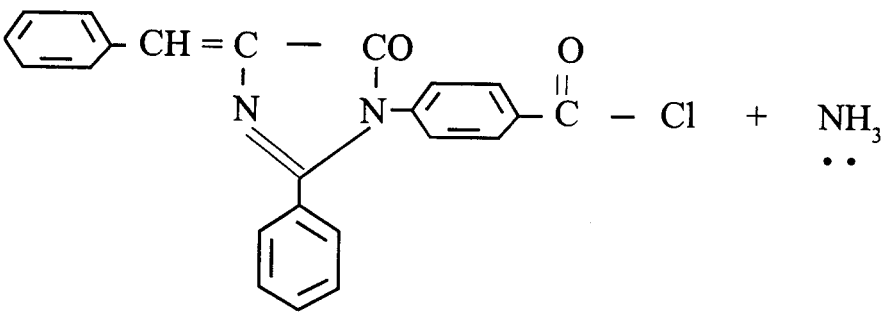


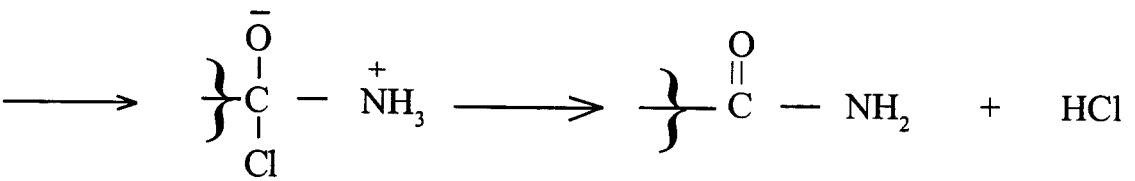






Step II





All the compounds synthesised above gave satisfactory analysis for nitrogen. The E.I mass spectrum of one typical compound was also recorded to confirm the structure. 4- Benzylidene - (4' - carboxamido phenyl) -2- phenyl -2- imidazolin -5- one gave molecular ion peak at m/z 365 (37%) confirming its identity. Other important peaks were at m/z = 382(17%), 263(18%), 247(62%), 120(60%), 104 (100%), and 87 (80%).

The UV - Vis. spectra of the above amide derivatives showed absorption maxima very close to their ester counter parts.(table II - 5).

Table II- 5

UV - Vis. absorption maxima of esters and amides

Parent imidazolinone	Ester	Amide
4 - Benzylidene - 1 - (carboxyphenyl) - 2 - phenyl - 2 - imidazolin - 5 - one	380.5 nm	379.5nm
1 - (Carboxyphenyl) - 4 - (p-methylbenzylidene) - 2 - phenyl - 2 - imidazolin - 5 - one	380nm	380.5nm
1 - (Carboxyphenyl) - 4 - (p- chlorobenzylidene) - 2 - phenyl - 2 - imidazolin - 5 - one	381nm	381nm
1- (Carboxyphenyl) - 4 - (o-chlorobenzylidene) - 2 - phenyl - 2 - imidazolin - 5 - one	380.5nm	380nm
1- (Carboxyphenyl) - 4 - (methoxybenzylidene) - 2 - phenyl - 2 - imidazolin- 5- one	397nm	395nm

EXPERIMENTAL

Melting points recorded using open capillary are uncorrected. Mass spectra were recorded on Jeol D - 300 spectrometer and the UV - Vis. spectra on Shimadzu 1601 UV - Vis. spectrometer.

Synthesis of starting materials

Benzoylglycine

Benzoylglycine was prepared by benzoylating glycine. Glycine (25g, 0.33 mole) was dissolved in 250mL of 10% sodium hydroxide solution contained in a conical flask. Added 45 mL (0.385 mole) of benzoylchloride in five portions to this solution, stoppered the vessel and shook vigorously after each addition until all the chloride had reacted. Transferred the solution to a beaker and rinsed the conical flask with little water. A few grams of crushed ice was put in the solution and added con. HCl slowly and with stirring until the mixture was acidic to congored. The crystals formed were filtered on a bunchner funnel and air dried. The melting point was found to be 188°C. The reported m.p is 187°C. [115]

p - Chlorobenzoylglycine

Dry powdered p - chlorobenzoic acid (38.4g, 0.246 mole) was placed in a 250 - mL R.B. flask fitted with a condenser. Thionyl chloride (22mL, 0.306 mole) was added and heated the flask on a boiling water bath for one hour until the evolution of HCl stopped. The contents were left to cool and transferred into a separatory funnel. Ice - cold water (50mL) and solvent ether (100mL) were added into the funnel and shaken well. The ether layer was separated and dried using anhydrous sodium sulphate. Ether was removed by distillation and the crude product again distilled to get pure p - chlorobenzoylchloride [116].

Glycine (12g, 0.16 mole) was dissolved in 150 mL of 10% sodium hy-

droxide solution contained in a conical flask, added the p - chlorobenzoyl chloride prepared in five portions to this solution, stoppered the vessel and shook vigorously after each addition until all the chloride had reacted. Transfered the solution to a beaker and rinsed the conical flask with a little water. A few grams of crushed ice was put in the solution and added conc.HCl solwly and with stirring until the mixture was acidic to congored. The crystals formed were filtered on a buchner funnel and air dried. The melting point was found to be 142°C. The reported m.p is 143°C [103].

Azlactones : Azlactones were prepared following the known method [117] . Aromatic aldehyde and benzoylglycine or p - chlorobenzoylglycine were taken in a dry 250 mL conical flask in equimolar proportions (0.04 mole). 12mL of acetic anhydride and 3.5g of anhydrous sodium acetate were also added and the mixture heated over a flame with shaking. When the mixture liquified it was transferred over to a boiling water bath and heated. After one hour. 20mL of alcohol was added to the flask and allowed the mixture to stand for one and half hours. The crystalline product formed was filtered, washed with 5mL portions of cold alcohol, small portions of boiling water and dried at 100°C. The different azlactones thus prepared are given in table II - I

Table II - I

2 - Aryl - 4 - arylidene -2 - oxazolin - 5 - ones

Name	m.p (°C)	yield (%)	% of N Found	% of N Calculated
1. 4 - Benzylidene - 2 - phenyl - 2 - oxazolin - 5 - one	169°C	56	5.5	5.6

2. 4(- p Methylbenzylidene) 2 - phenyl - 2 - oxazoline - 5 - one	203	46	5.1	5.3
3. 4 (o - Chlorobenzylidene) - 2 - phenyl - 2 - oxazolin - 5 - one	195	52	4.7	4.94
4. 4 - (p - Chlorobenzylidene) - 2 - phenyl - 2 - oxazolin - 5 - one	145	49	4.81	4.94
5. 4 (p - Methoxybenzylidene) - 2 - phenyl - 2 - oxazolin - 5 - one	164	48	5.0	5.03
6. 4 - Benzylidene -2 - (p - chlorophenyl) - 2 - oxazolin - 5 - one	163	45	4.9	4.94
7. 4 - p - (Methylbenzyilidene) - 2 - (p - Chlorophenyl) - 2 - oxazolin - 5 - one	133	48	4.6	4.71
8. 4 - (p - Chlorobenzylidene) - 2 - (p - chlorophenyl) - 2 - oxazolin - 5 - one	199	47	4.4	4.41
9. 4 - (o - Chlorobenzylidene) - 2 - (p - chlorophenyl) - 2 - oxazolin - 5 - one	202	49	4.3	4.41
10. 4 - (p- Methoxybenzylidene) - 2 - (p - chlorophenyl) - 2 - oxazolin - 5 - one	117	41	4.5	4.47

Synthesis of 1, 2, 4 - trisubstituted - 2 - imidazolin - 5 - ones.

4 - Benzylidene -1-(4^{1}- carboxyphenyl) - 2 - phenyl - 2 - imidazolin - 5 -one

4 - Benzylidene - 2 - phenyl - 2 - oxazolin - 5 - one (2.49g, 0.01 mole), p - aminobenzoic acid (1.37g, 0.01 mole) and acetic acid (25mL) were taken in a

round bottomed flask and heated under reflux on a sand bath. Within half an hour the oxazolin dissolved completely giving a pale yellow solution. The colour of this solution got deepened as the reaction progressed. After 5 hours, it was cooled and poured into ice - cold water. The product was filtered, washed with water (2 x 10mL) and dried. The yellow product weighed 2.8 g (81%).

The unsaturated 2 - imidazolin - 5 - one (0.5g) was recrystallised from methanol (50mL). The recrystallised yellow product melted at 270°C.

Analysis

N(%)

Found : 7.3

calculated : 7.4

$C_{23}H_{16}N_2O_3$

U.V - Vis

λ max : 379 n.m

1 - (4' - Carboxyphenyl) - 4 - (p - methylbenzylidene) - 2 - phenyl 2 - imidazolin - 5 - one:

4 - (p - Methyl benzylidene) - 2 - phenyl - 2 - oxazolin - 5 - one (2.63g, 0.01 mole), p - amino benzoic acid (1.37g, 0.01 mole) and 25 mL of acetic acid were taken in a round bottomed flask and heated under reflux for 5h. After cooling, the contents were poured into ice cold water, filtered, washed with water (2 x 10 mL) and dried. The yellow product weighed 2.5g (79%).

The unsaturated 2 - imidazolin - 5 - one (0.5g) was recrystallised form methanol (50mL) , the yellow crystals melted at 234°C.

Analysis

N(%)

found : 7.1

Calculated : 7.2

$C_{24}H_{18}N_2O_3$

U.V - Vis

λ max : 385 n.m.

1 - (4' - Carboxyphenyl) - 4 - (p - chlorobenzylidene) - 2 - phenyl - 2 - imidazolin - 5 - one)

4 - p - Chlorobenzylidene - 2 - phenyl - 2 - oxazolin - 5 - one (2.84g, 0.01 mole), p - aminobenzoic acid (1.37g, 0.01 mole) and 25 mL of acetic acid were taken in a round bottomed flask and heated under reflux for 5h, after cooling the contents, poured into ice - cold water filtered, washed with water (2 x 10 mL) and dried. The yellow product weighed 3.6g (90%)

The unsaturated 2 - imidazolin - 5 - one (0.5g) was recrystallised from methanol (50ml). The yellow crystals melted at 275°C.

Analysis

N(%)

found : 6.8

calculated : 6.96

$C_{23}H_{18}N_2O_3Cl$

U.V- Vis

λ max : 382.5 n.m

1 - (4' - Carboxyphenyl) - 4 - (o - chlorobenzylidene) - 2 - phenyl - 2 - imidazolin - 5 - one

4 - (o - chlorobenzylidene) - 2 - phenyl - 2 - oxazolin - 5 - one (2.84g, 0 .01 mole), p - aminobenzoic acid (1.37g, 0.01 mole) and acetic acid (25mL), were taken in a round bottomed flask, heated under reflux for 5h on a sand bath. After cooling the contents were poured into ice - cold water. The product formed was filtered, washed with water (2 x 10 mL) and dried. The yellow product weighed 2.53g (53%).

The unsaturated 2 - imidazolin - 5 - one (0.5) was recrystallised from methanol (50mL). The yellow crystals melted at 220° C.

Analysis

N(%)

Found : 7.0

Calculated : 6.96

$C_{23}H_{16}N_2O_3Cl$

U.V- Vis

λ max - 380.5 n.m.

1 - (4' - Carboxyphenyl) - 4 - (p - methoxybenzylidene) - 2 - phenyl - 2 - imidazolin - 5 - one

4 - (p - Methoxybenzylidene) - 2 - phenyl - 2 - oxazolin - 5 - one (2.79g, 0.01 mole), p - aminobenzoic acid (1.37g, 0.01 mole) and acetic acid (25mL) were taken in a round bottomed flask and heated under reflux for 5h on a sand bath . After cooling the contents were poured into ice - cold water,

filtered, washed with water (2 x 10ml) and dried. The yellow product weighed 2.99g (75%)

The unsaturated 2 - imidazolin - 5 - one (0.5g) was recrystallised from methanol (50mL). The yellow crystals melted at 282 °C.

Analysis

N(%)

Found : 6.9

Calculated : 7.03

$C_{24}H_{18}N_2O_4$

U.V. - Vis

λ max : 395 n.m.

4 - Benzylidene - 1 - (4' - carboxyphenyl) - 2 - (p- chlorophenyl) - 2 - imidazolin- 5 - one

4 -Benzylidene - 2 - (p - chlorophenyl) - 2 - oxazolin - 5 - one (2.83g, 0.01 mole), p-aminobenzoic acid (1.37g, 0.01 mole), and acetic acid (25mL) were taken in a round bottomed flask and heated under reflux for 5h on a sand bath. After cooling the contents were poured into ice - cold water, filtered washed with water (2 x 10mL) and dried. The yellow product weighed 2.5g (64%).

The unsaturated 2 - imidazolin - 5 - one (0.5g) was recrystallised from methanol (45mL). The yellow crystals melted at 269°C.

Analysis

N(%)

Found : 6.7

Calculated : 6.96

$C_{23}H_{16}N_2O_3Cl$

U.V. - Vis

λ max - 381.5 n.m

1 - (4^{1}- Carboxyphenyl) - 4 - (p - chlorobenzylidene) - 2 -(p -chlorophenyl) - 2 - imidazolin - 5 - one

4 - (p - Methylbenzylidene) - 2 - p - (chlorophenyl) - 2 - oxazolin - 5 - one (2.97g, 0.01 mole), p - aminobenzoic acid (1.37g, 0.01 mole) and acetic acid (25mL) were taken in a round bottomed flask, and heated under reflux on a sandbath for 5h. After cooling the contents were poured into ice - cold water, filtered, washed with water (2 x 10mL) and dried. The yellow product weighed 4.16g (100%).

The unsaturated - 2 - imidazolin - 5 - one was recrystallised from methanol (45mL). The yellow crystals formed melted at 242°C.

Analysis

N(%)

Found : 6.6

Calculated : 6.72

$C_{24}H_{17}N_2O_3Cl$

U.V. Vis

λ max - 393 n.m.

1 - (4^{1}- Carboxyphenyl) - 4 - (o - chlorobenzylidene) - 2 - (p - chlorophenyl) - 2 - imidazolin - 5 - one

4 - (o - Chloro benzylidene) - 2 - (p- chlorophenyl) - 2 - oxazolin -5 - one (3.18g, 0.01 mole), p - aminobenzoic acid (1.37g), 0.01 mole) and acetic

acid (25mL) were taken in a round - bottomed flask and heated under reflux on a sand bath for 5h. After cooling the contents were poured into ice - cold water, filtered, washed with water (2 x 5mL) and dried. The yellow product formed weighed 4.37g (100%).

The unsaturated 2 - imidazolin - 5 - one was recrystallised from methanol (50mL). The yellow crystals formed melted at 233°C .

Analysis

N(%)

Found : 6.2

Calculated : 6.4

$C_{23}H_{14}N_2O_3Cl_2$

U.V- Vis

λ max - 376.5n.m.

1 - (4^1- Carboxyphenyl) -4 - (p - chlorobenzylidene) - 2 - (p - chlorophenyl) 2 - imidazolin - 5 - one.

4 - (p - Chlorobenzylidene) - 2 - (p - chlorophenyl) 2 - oxazolin - 5 - one (3.18g, 0.01 mole), p - aminobenzoic acid (1.37g, 0.01 mole) and acetic acid (25mL) were taken in a round bottomed flask and heated under reflux on a sand bath for 5h,. After cooling the contents were and poured into ice - cold water, filtered,washed with water (2 x 10 mL), and dried. The yellow product weighed 3.62g (83%).

The unsaturated - 2 - imidazolin - 5 - one (0.5g) was recrystallised from methanol (40mL). The yellow crystals melted at 226°C.

Analysis

N(%)

Found : 6.3

Calculated : 6.4

$C_{23}H_{14}N_2O_3Cl_2$

U.V - Vis

λ max - 384 n.m.

1 - (4' - Carboxyphenyl) - 4 - (p - methoxybenzylidene) - 2 - (p - chlorophenyl) - 2 - imidazolin -5 - one

4 - (p - Methoxybenzylidene) - 2 - (p - chlorophenyl) - 2 - oxazolin - 5 - one (3.13g, 0.01 mole), p - aminobenzoic acid (1.37g, 0.01 mole) and acetic acid (25mL) were taken in a round bottomed flask and heated under reflux for 5h on a sand bath. After cooling the contents were poured into ice - cold water filtered, washed with water and dried. The yellow product weighed 4.32g (100%)

The unsaturated - 2 - imidazolin - 5 - one (0.5g) was recrystallised from methanol (50mL) . The yellow crystals formed melted at 251°C.

Analysis

N(%)

Found : 6.4

Calculated : 6.48

$C_{24}H_{17}N_2O_4Cl$

U.V - Vis

λ max - 389.5 n.m.

1 - (4^{I}- Carbomethoxyphenyl) - 4 - benzylidene - 2 - phenyl - 2 - imidazolin - 5 - one

Two grams (0.0057 mole) of 1 - (4^{I}- carboxyphenyl) - 4 - benzylidene 2 - phenyl - 2 - imidazolin - 5 - one, conc. sulphuric acid (0.5mL) and methanol (10mL) were taken in a round bottomed flask and heated under reflux for 2h over a water bath. The product formed was filtered after cooling, washed with methanol (2 x 5 mL) and dried. The yellow product formed weighed 1.25g (61%).

The ester (0.5g) was recrystallised from methanol (20mL). The yellow crystals melted at 174^{o}C.

Analysis

N(%)

Found : 7.2

Calculated : 7.33

$C_{24}H_{18}N_2O_3$

U.V. - Vis

λ max - 380.5 n.m.

1 - (4^{I}- Carbomethoxyphenyl) - 4 - (p - methylbenzylidene) - 2 - phenyl - 2 - imidazolin - 5 - one

1 - (4^{I}- Carboxyphenyl) - 4 - (p - methylbenzylidene) - 2 - phenyl - 2 - imidazolin - 5 - one (2g, 0.0055 mole), conc. sulphuric acid (0.5mL) and methanol (10mL) were taken in a round bottomed flask, heated under reflux over water bath for 2h. The product formed was filtered after cooling, washed with methanol (2 x 5 mL) and dried. The yellow product weighed 1.53g (72%).

The ester (0.5g) was recrystallised from methanol (15mL). The yellow crystals formed melted at 193°C

Analysis

N(%)

Found : 7.0

Calculated : 7.07

$C_{25}H_{20}N_2O_3$

U.V - Vis

λ max - 380 n.m.

1 - (4'- Carbomethoxyphenyl) - 4 - (o - chlorobenzylidene) - 2 - phenyl - 2 - imidazolin - 5 - one

1 - (4' - Carboxyphenyl) - 4 - (o - chlorobenzylidene) - 2 - phenyl - 2 - imidazolin - 5 - one (2g, 0.0052 mole), conc. sulphuric acid (0.5 mL) and methanol (10mL) were taken in a round bottomed flask, heated under reflux for 2h over a boiling water bath. The product formed was filtered after cooling, washed with methanol (2 x 5 mL) and dried. The yellow product weighed 1.47 g (73%).

The ester (0.5g) was recrystallised from methanol (20mL). The yellow crystals formed melted at 189 °C.

Analysis

N(%)

Found : 6.8

Calculated : 6.72

$C_{24}H_{17}N_2O_3Cl$

U.V. - Vis

λ max - 380.5 n.m.

1 - (4'- Carbomethoxyphenyl) - 4 - (p - methoxybenzylidene) - 2 - phenyl - 2 - imidazolin - 5 - one.

1 - (4'- Carboxyphenyl) - 4 - (p - methoxybenzylidene) - 2 - phenyl - 2 - imidazolin - 5 - one (2g, 0.00523 mole), conc. sulphuric acid (0.5mL) and methanol (10mL) were taken in a round bottomed flask, heated under reflux over a boiling water bath for 2h. The product formed was filtered after cooling, washed with methanol (2 x 5 mL) and dried. The yellow product formed weighed 1.74g (87%)

The ester (0.5g) was recrystallised from methanol (50mL). The yellow crystals formed melted at 182^{o} and weighed 0.43g (76%)

Analysis

N(%)

Found : 6.8

Calculated : 6.8

$C_{25}H_{20}N_2O_4$

U.V. - Vis

λ max 397 n.m

1 - (4'- Carbomethoxyphenyl) - 4 - (p- chlorobenzylidene) - 2 - phenyl - 2 - imidazolin - 5 - one

1 - (4'- Carboxyphenyl) - 4 - (p- chlorobenzylidene) - 2 - phenyl - 2 - imidazolin - 5 - one (2g, 0.0052 mole), conc. sulphuric acid (0.5mL) and methanol (10mL), were taken in a round bottomed flask, heated under reflux over a

boiling water bath for 2h. The product formed was filtered after cooling, washed with methanol (2 x 5mL) and dried. The yellow product weighed 1.52g (73%).

The ester (0.5g) ws recrystallised from methanol (20 mL). The yellow crystals formed melted at 189°C.

Analysis

N(%)

Found : 6.9

Calculated : 6.72

$C_{24}H_{17}N_2O_3Cl$

U.V - Vis

λ max - 381 n.m.

1 - (4^{l}- Carbomethoxyphenyl)- 4 - benzylidene - 2 - (p - chlorophenyl) - 2 - imidazolin - 5 - one.

1 - (4^{l}- Carboxyphenyl) - 4 - (benzylidene) 2 - (p- chlorophenyl) - 2 - imidazolin - 5 -one (2g, 0.0052 mole), conc. H_2SO_4 (0.5mL), methanol (10mL) were taken in a round bottomed flask, heated under reflux for 2h over a boiling water bath. The product formed was filtered after cooling, washed with methanol (2 x 5 mL) and dried. The yellow product weighed 1.69g (78%)

The ester (0.5g) was recrystallised from methanol (20mL). The yellow crystals formed melted at 235°C

Analysis

N(%)

Found : 7.0

Calculated : 6.72

$C_{24}H_{17}N_2O_3Cl$

U.V- Vis

λ max - 379 n.m.

1 - (4^{l} - Carbomethoxyphenyl) - 4 - (p-methylbenzylidene) - 2 - (p-chlorophenyl) - 2 - imidazolin - 5 - one

1 - (4^{l} - Carboxyphenyl) - 4 - (p-methylbenzylidene) - 2 - (p-chlorophenyl) - 2 - imidazolin - 5 - one (2g, 0.0048mole), conc. Sulphuric acid (0.5mL) and methanol (10mL) were taken in a round bottomed flask, heated under reflux over a boiling water bath for 2h. The product formed was filtered after cooling, washed with methanol (2 x 5 mL) and dried. The yellow product weighed 1.82g (88%).

The ester (0.5g) was recrystallised from methanol (50mL). The yellow crystals formed melted at 185^{o}C.

Analysis

N(%)

Found : 6.3

Calculated : 6.5

$C_{25}H_{19}N_2O_3Cl$

U.V - Vis

λ max = 386.5 n.m.

1 - (4^{l} - Carbomethoxyphenyl) - 4 - (o - chlorobenzylidene) - 2 - (p - chlorophenyl) - 2 - imidazolin - 5 - one

1 - (4^{l} - Carboxyphenyl) - 4 - (o - chlorobenzylidene) - 2 - (p - chloro phenyl) - 2 - imidazolin - 5 - one (2g, 0.0046 mole), conc. sulphuric acid (0.5mL) and methanol (10 mL) were taken in a round bottomed flask ,heated under reflux for 2h. over a boiling water bath. The product formed were filtered after cooling, washed with methanol (2 x 5mL) and dried. The yellow product weighed 1.8g (87%).

The ester (0.5g) was recrystallised from methanol (25mL). The yellow crystals formed melted at 220°C.

Analysis

N(%)

Found : 6.2

Calculated : 6.2

$C_{24}H_{16}N_2O_3Cl_2$

U.V - Vis

λ max - 382.5 n.m.

1 - (4^{l} - Carbomethoxyphenyl) - 2 - (p - chlorophenyl) - 4 - (p - methoxybenzylidene) - 2 - imidazolin - 5 -one.

1 - (4^{l} - Carboxyphenyl) - 2 - (p- chlorophenyl) - 4 - (p - methoxy benzylidene) - 2 -imidazolin - 5 - one (2g,0.0046 mole), conc. sulphuric acid

(0.5mL) and methanol (10mL) were taken in a round bottomed flask, heated under reflux over a boiling water bath 2h. The product formed were filtered after cooling, washed with methanol (2 x 50) and dried. The yellow product weighed 2.05g (100%).

The ester (0.5g) was recrystallised from methanol (50mL). The yellow crystals formed melted at 229°C.

Analysis

N(%)

Found : 6.3

Calculated : 6.26

$C_{25}H_{18}N_2O_4Cl$

U.V - Vis

λ max - 401 n.m.

1 - (4' Carbomethoxyphenyl) - 4 - (p- chlorobenzylidene) -2-(p-chlorophenyl) - 2 - imidazolin - 5 - one

1- (4 '- Carboxyphenyl) -4- (p-chlorobenzylidene) - 2 - (p -chlorophenyl) -2- imidazolin -5- one (2g, 0.0046 mole), conc. sulphuric acid(0.5 mL) and methanol (10mL), were taken in a round bottomed flask, heated under reflux for 2h. over a boiling water bath. The product formed was filtered after cooling,washed with methanol (2 x 5mL) and dried. The yellow product weighed 1.62g (78%)

The ester (0.5g) was recrystallised from methanol (50mL). The yellow crystals formed melted at 214°C.

Analysis

N(%)

Found: 6.1

Calculated: 6.2

$C_{24}H_{16}N_2O_3Cl_2$

U.V - Vis

λ max - 382 n.m.

1- (4^1 - Carboxamidophenyl) - 4 - benzylidene -2 - phenyl -2- imidazolin - 5 -one.

1- (4^1- Carboxyphenyl) - 4 - benzilidene -2- phenyl -2- imidazolin - 5- one (1g, 0.00285 mole) and thionyl chloride (3mL) were heated under reflux in a round - bottomed flask for 2h. After cooling 10 mL of ammonia solution was added and the products formed filtered and dried, weighed 0.84g (80%)

The amide (0.5g) was recrystallised from ethanol (25mL). The yellow crystals formed melted 154^0 C.

Analysis

N(%)

Found : 11.4

Calculated: 11.44

$C_{23}H_{18}N_3O_2$

U.V - Vis

λ max - 379.5 n.m.

1- (4'- Carboxamidophenyl) - 4 - (p-methylbenzylidene) - 2 - phenyl - 2 - imidazolin - 5 - one

1- (4'- Carboxyphenyl) - 4 - (p-methylbenzylidene) - 2 - phenyl - 2 - imidazolin -5- one (1g, 0.00285mole) , and thionyl chloride (3mL) were taken in a round bottomed flask, heated under reflux for 2h. After cooling 10mL ammonia solution was added and the products formed filtered and dried; weighed 1.05g (100%).

The amide (0.5) was recrystallised from ethanol (50mL). The yellow crystals formed melted at 100°C.

Analysis

N(%)

Found : 11.1

Calculated : 11.00

$C_{24}H_{20}N_3O_2$

U.V - Vis

λ max - 380.5 n.m.

1- (4'- Carboxamidophenyl) - 4 - (o - chlorobenzylidene) - 2 - phenyl - 2 - imidazolin - 5 - one

1- (4' - Carboxyphenyl) - 4 - (o - chlorobenzylidene) - 2 - phenyl - 2 - imidazolin - 5 - one (1g, 0.0026g), thionyl chloride (3ml) were taken in a round bottomed flask, heated under reflux for 2h. After cooling 10mL ammonia solution was added, the product formed filtered and dried. It weighed 1.04g (100%).

The amide (0.5g) was recrystallised from ethanol (20mL). The yellow

crystals formed melted at 134°C.

Analysis

N(%)

Found : 10.3

Calculated : 10.46

$C_{23}H_{17}N_3O_2Cl$

U.V - Vis

λ max - 380 n.m.

1- (4'- Carboxamidophenyl) - 4 - (p- methoxybenzylidene) -2- phenyl - 2- imidazolin -5- one

1- (4'- Carboxyphenyl - 4 - (p - methoxybenzylidene) -2- phenyl -2- imidazolin -5- one (1g, 0.00262 mole) and thionyl chloride (3mL) were taken in a round bottomed flask, heated under reflux for 2h. After cooling added 10mL ammonia. The product formed was filtered, washed and dried. It weighed 0.95g (91%).

The amide (0.5g) was recrystallised from ethanol (50mL). The yellow crystals formed, melted at 197°C.

Analysis

N(%)

Found : 10.6

Calculated : 10.57

$C_{24}H_{20}N_3O_3$

U.V - Vis

λ max - 395 n.m.

1- (4' - carboxamidophenyl) - 4 - (p - chlorobenzylidene) - 2 - phenyl - 2 - imidazolin - 5 - one

1- (4' - Carboxyphenyl) - 4 - p - (chlorobenzylidene) - 2phenyl - 2 - imidazolin -5- one (1g, 0.0026) and thionyl chloride (3mL) were taken in a round bottomed flask, heated under reflux for 2h. After cooling 10mL ammonia was added. The product formed was filtered washed and dried. It weighed 1.04g (100%).

The amide (0.5g) was recrystallised from ethanol (50mL), The yellow crystals formed melted at 189°C.

Analysis

N(%)

Found : 10.4

Calculated : 10.46

$C_{23}H_{17}N_3O_2Cl$

U.V - Vis

λ max - 381 n.m.

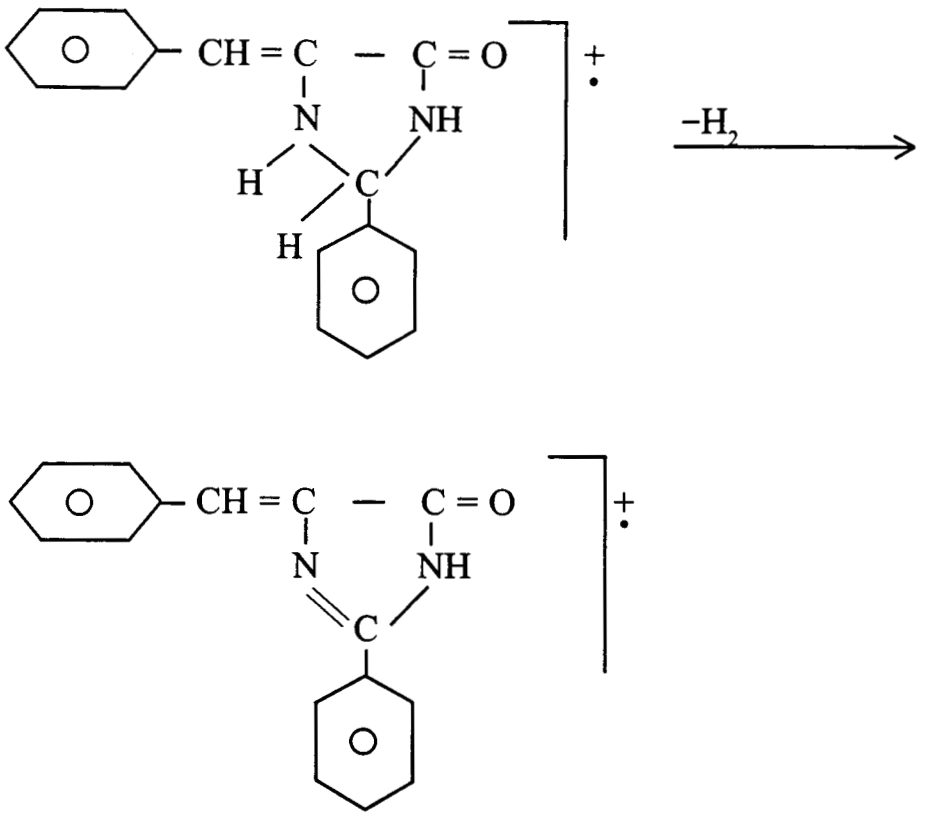
CHAPTER III

Synthesis and thermal rearrangement of 4, 4^{1} - diarylmethyl - 2, 2^{1} - diaryl - 4; 4^{1} - biimidazolin - 5, 5^{1} - diones

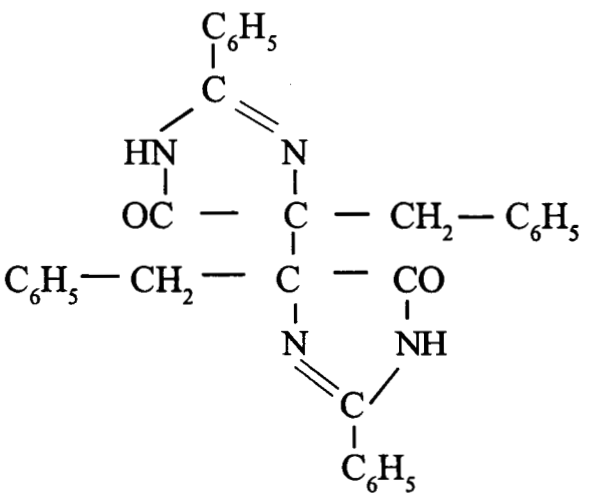
Unsaturated 2 - imidazolin - 5 - ones are the nitrogen analogs of azlactones. In the Erlenmeyer azlactone synthesis, amino acids and acylamino acids are obtained by the simultaneous reduction and hydrolysis of azlactones with hydriodic acid and red phosphorus. Unsaturated imidazolinones undergo only reduction under these reaction conditions [53]. Devasia and Shafi [94] synthesised acylamino acid amides and acylamino acids by the alkaline hydrolysis of reduced imidazolinones. The reduction was effected using hydriodic acid and red phosphorus.

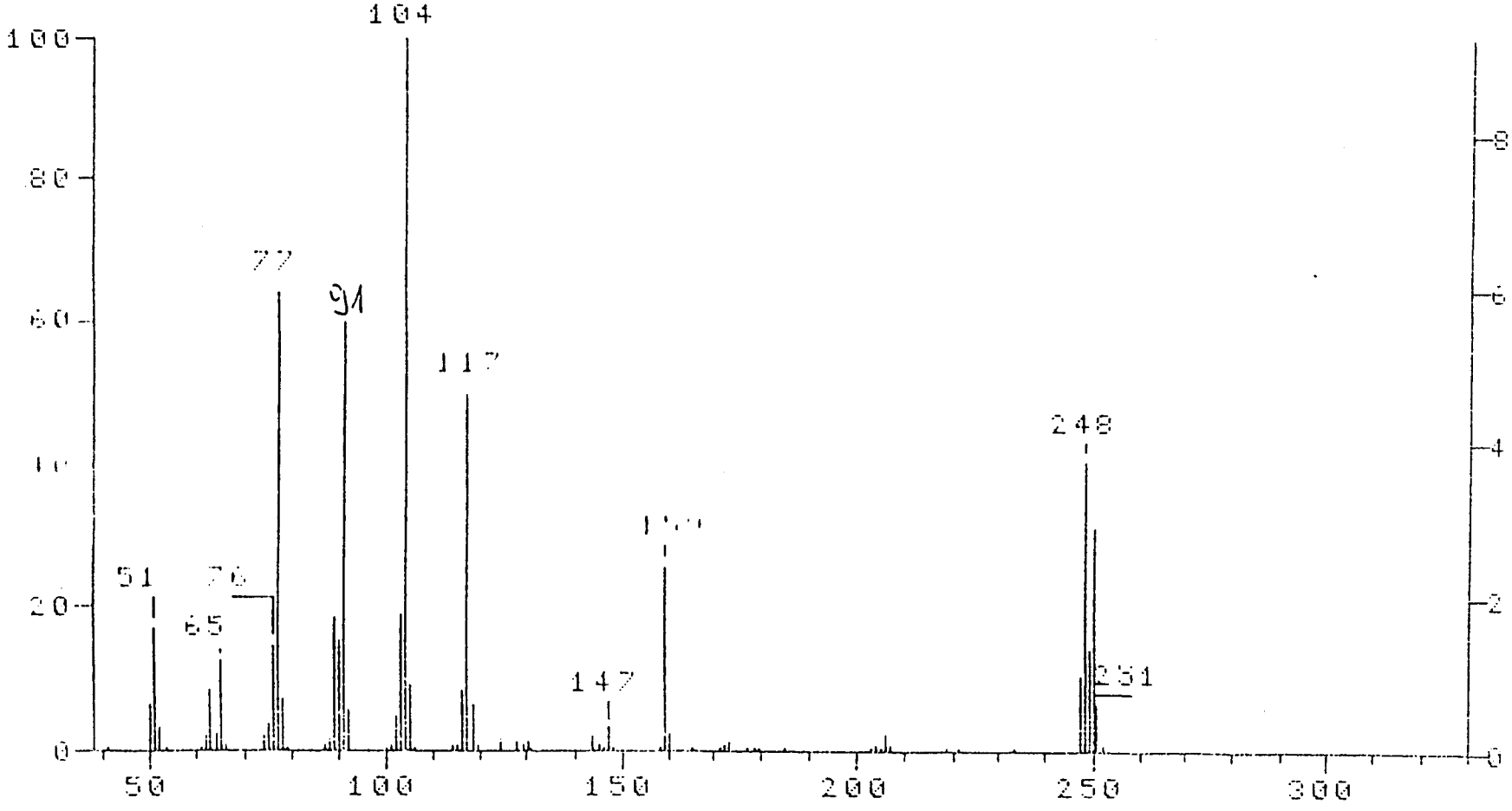
Results and discussion

In an attempt to isolate the HI-P reduction product of 4- benzylidene - 2 - phenyl - 2 - imidazolin - 5 - one by crystallising from ethanol an unexpected product got separated. It did not undergo hydrolysis to give acylamino acid like the reduced product. Mass spectrum of this compound gave M^{+} peak at m/z 250. This suggested a structure to have formed by the reduction of the C = N bond of the ring. An intense peak (40%) at m/z 248 by elimination of hydrogen supported this observations. Taking the case of 4 - benzylidene - 2-phenylimidazolinone the spectrum can be explained as follows. The elimination of hydrogen, though not very common under EI mass studies, can be expected as the resultant radical ion has a highly conjugated structure and hence



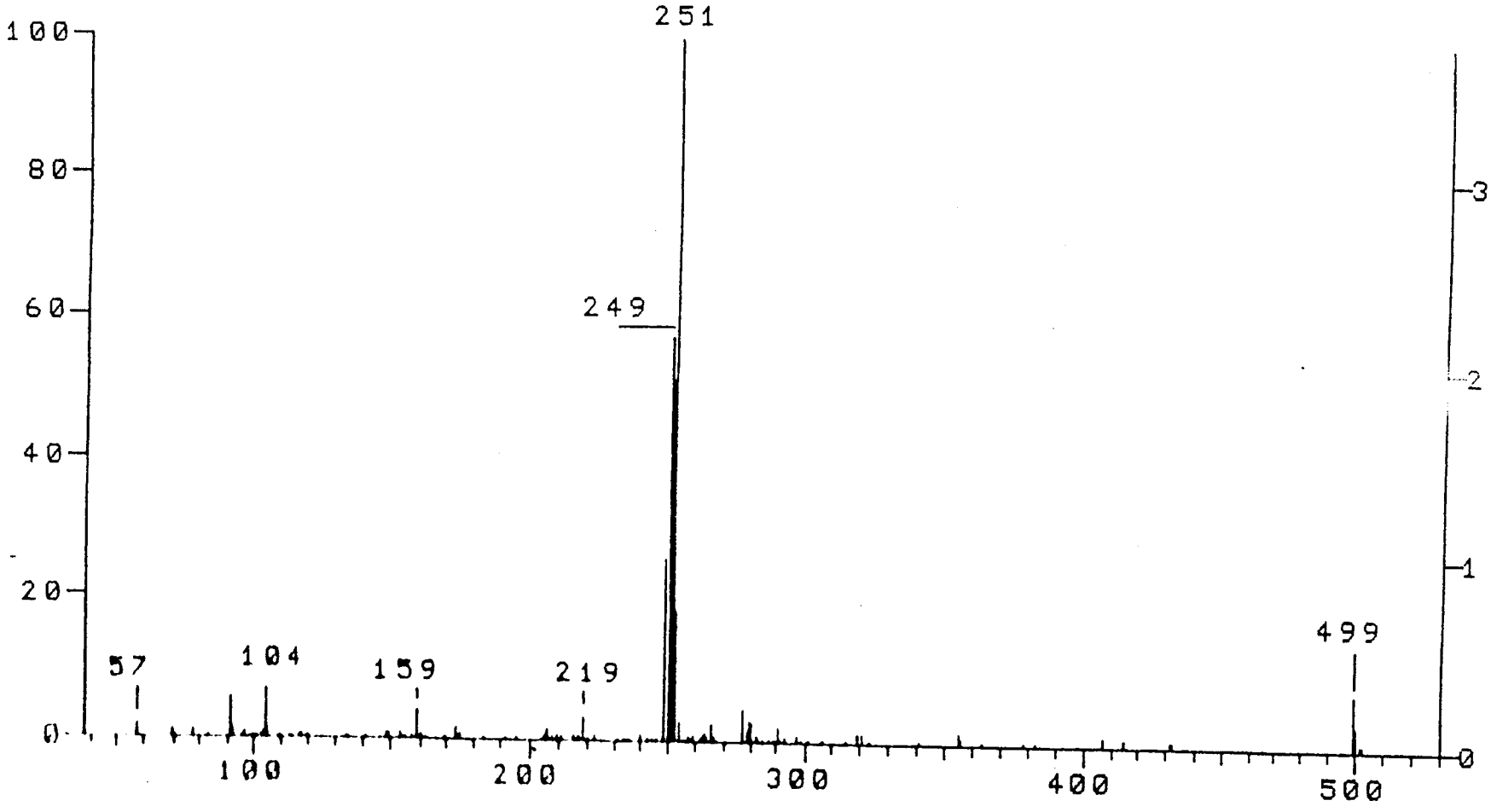
stable. However the peak at m/z = 91 (60%) could not be explained based on this structure and is therefore ruled out. The CI - mass spectrum showed a peak at m/z = 499 with intensity 10%. If this is taken to be the quasimolecular ion $[M+1]^+$ the molecular mass of the compound is 498 corresponding to a dimer of the following structure





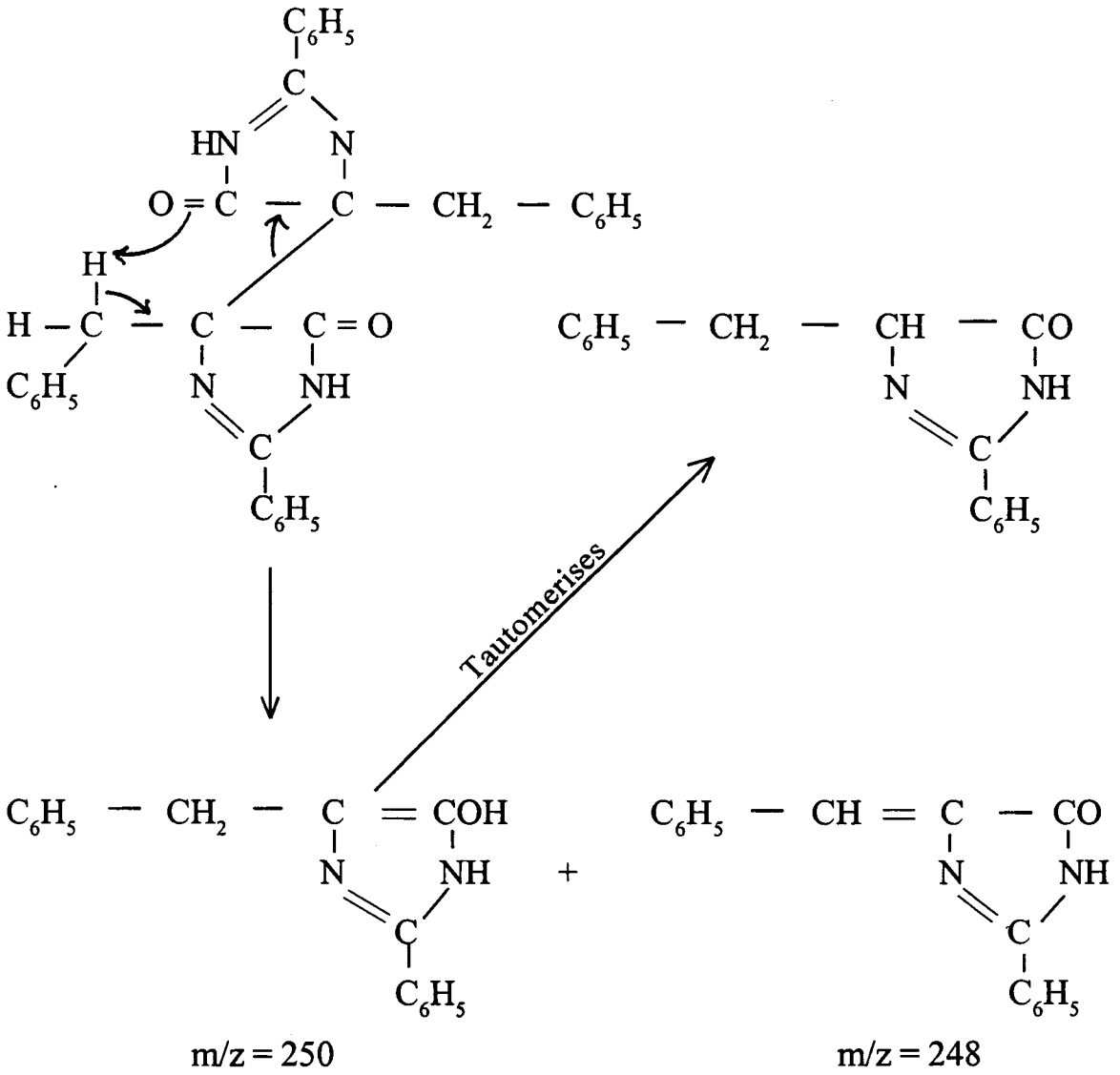
104

EI - MS of 4, 4 ^{1}- dibenzyl - 2.2 ^{1}- diphenyl -4:4^{1} - biimidazolin - 5,5^{1} - dione



CI - MS of 4, 4^{1}- dibenzyl - 2,2 ^{1}- diphenyl -4:4^{1}- biimidazolin - 5,5^{1} - dione

This structure can account for the base peak at m/z = 251 and another peak at m/z 249 (60%). The peak at m/z 91 in the EI mass spectrum can also be explained based on this structure as it contains the benzyl group. The peaks in the EI mass spectrum at m/z = 251 and 249 have arisen by the Mc Lafferty rearrangement



These two fragments with masses 250 and 248 units give rise to peaks at m/z = 251 and 249 as they had accepted H^+ during chemical ionisation

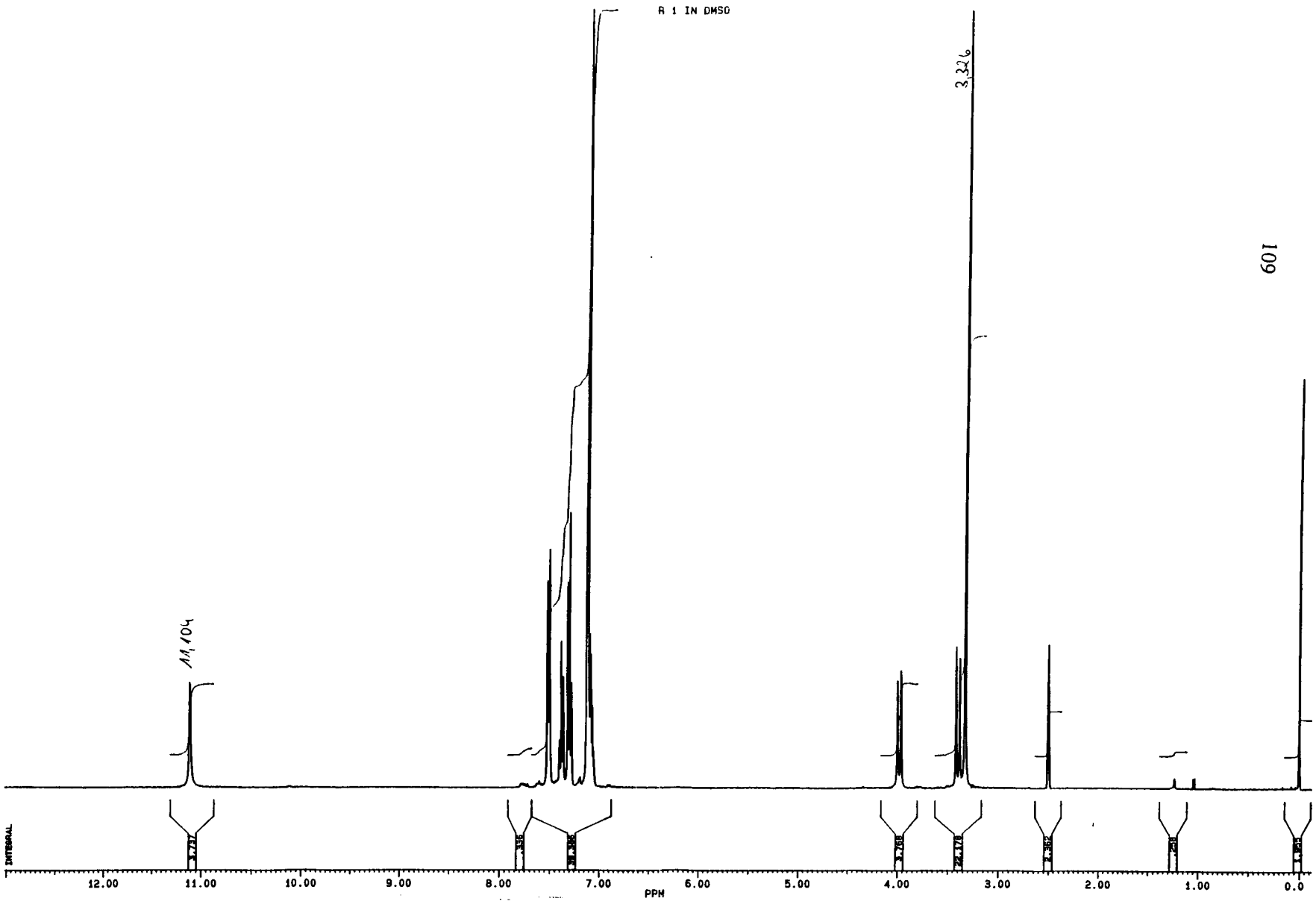
The ^1H nmr spectrum of this dimer compound showed a singlet at δ 11.1(2H) corresponding to the -NH - protons in the heterocyclic ring, multiplets in the region δ 7.75 (20H) corresponding to the aromatic protons and two doublets at δ 3.98 and 3.4 corresponding to two protons each. The coupling constant of these doublets was found to be 12Hz. This can be attributed to the geminal coupling of the two protons of the methylene group. These two protons are magnetically nonequivalent due to the presence of the adjacent chiral carbon atom (carbon at fourth position of the imidazolinone ring is chiral). The exchangeable nature of the protons absorbing at δ 11.10 was evident from the ^1H nmr spectrum after deuterium wash. The noise decoupled ^{13}C nmr spectrum had 12 peaks in consistence with the proposed structure. The ^{13}C nmr of the quaternary carbon atoms alone also could be recorded. It had 5 peaks supporting the proposed structure.

Further the complete ^{13}C values of all carbon atoms in the molecule were assigned by the help of different nmr analyses like distortionless enhancement by polarisation transfer (DEPT, $\theta = 135^0$), heteronuclear multiple quantum correlation (HMQC) and heteronuclear multiple - bond correlation (HMBC).

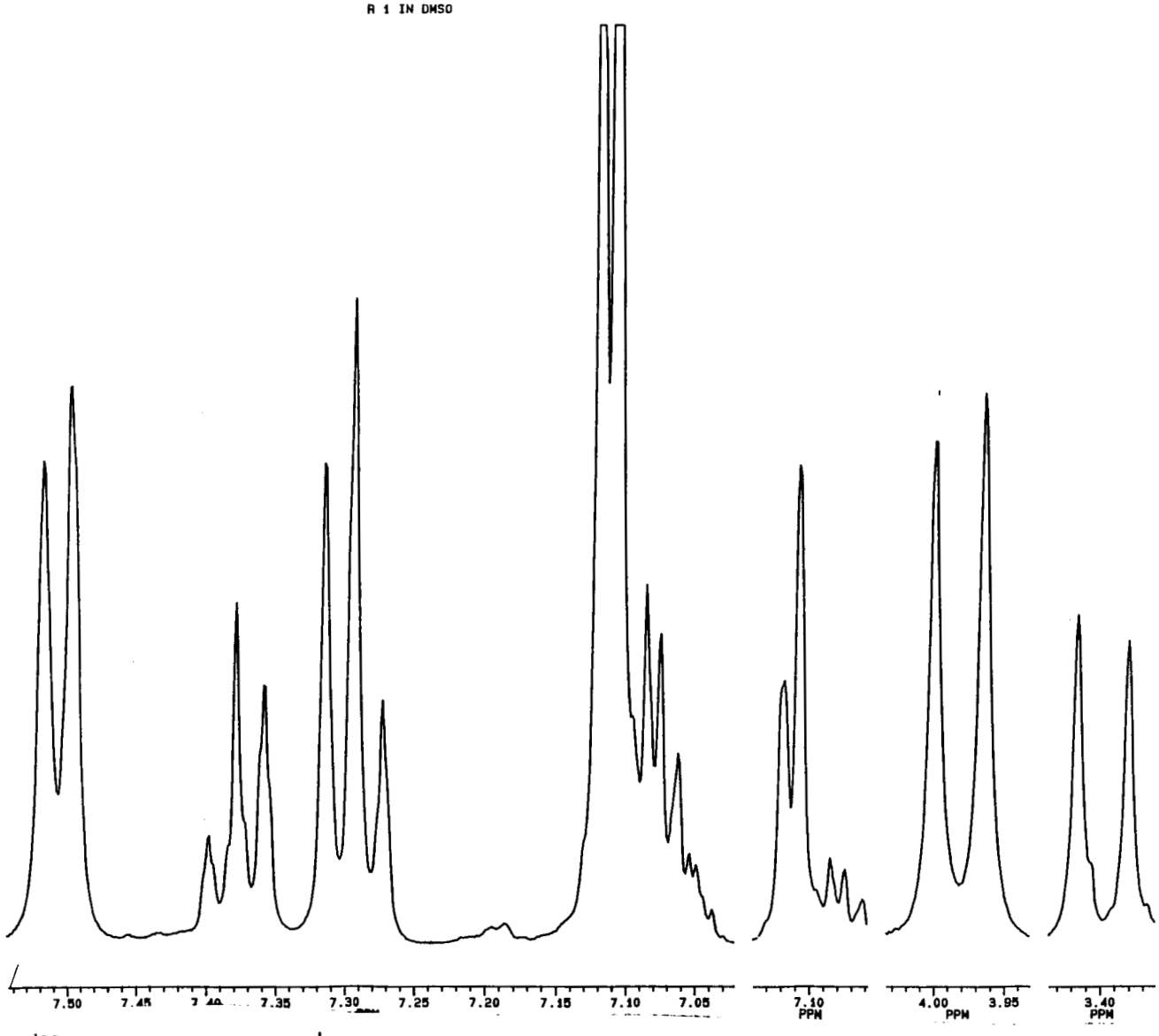
In the ^{13}C nmr spectrum of quaternary carbon atoms there were only five peaks with δ values 76.9, 128 .4, 135.3 , 160 and 183.7 . Of these values 183.7 and 160 can unambiguously be assigned to the carbonyl carbon atom and the -N = C'- in the heterocyclic ring respectively . Similarly the absorption at δ 76.9 is due to the carbon at 4th position of the imidazolinone ring while the aromatic quaternary carbon atoms at δ 128.4 and 135.3 can be those of either benzene ring. In the DEPT, $\theta = 135^0$ spectrum only the protonated carbons appear with - CH_3 and CH carbons having positive amplitude and CH_2 carbons with negative amplitude. Hence the CH_2 carbon absorption could be assigned a chemical shift value of δ 35.3 from the DEPT, $\theta = 135^0$ spectrum. In the

HMQC spectrum protons directly bonded to the ^{13}C nuclei alone produce cross - peaks in the 2D spectrum [126] while in the HMBC spectrum protons interacting through two - bond ($^2J_{CH}$), three - bond ($^3J_{CH}$) and occasionally four - bond ($^4J_{CH}$) interactions give cross peaks [127]. In the HMQC spectrum of this compound both the protons absorbing at δ 3.98 and 3.4 gave cross peaks with the carbon atom absorbing at δ 35.3. This confirmed the identity of the methylene carbon atom. These methylene protons gave cross peaks with the carbon atoms at δ 76.9, 130.3, 135.3 and 183.7 in the HMBC spectrum. From this the δ values 135.3 and 130.3 can be respectively assigned to the carbon atom (quaternary carbon) of the phenyl group bonded to the methylene group and the ortho - carbon atoms of the same phenyl group. These results in combination with the spectrum of quaternary carbons enable us to assign a δ value 128.4 to the carbon atom of the other phenyl group bonded at position 2 of the imidazolinone ring. The quaternary carbon at δ 135.3 has cross peaks with the one proton triplet at δ 7.08 but not with the triplet at δ 7.05 in the HMBC spectrum. That is, the triplet at δ 7.08 is that of the m - proton of the phenyl moiety of the benzyl group. This proton has cross peak with the carbon at δ 127.4 in the HMQC spectrum proving the chemical shift of this meta carbon atom. This proton also has cross peak with the carbon at δ 130.3 and 126.3 in the HMBC spectrum. The carbon at δ 130.3 being already assigned the one at δ 126.3 is the paracarbon of this phenyl ring. It has cross peak with the one proton triplet at δ 7.05 in the HMQC spectrum.

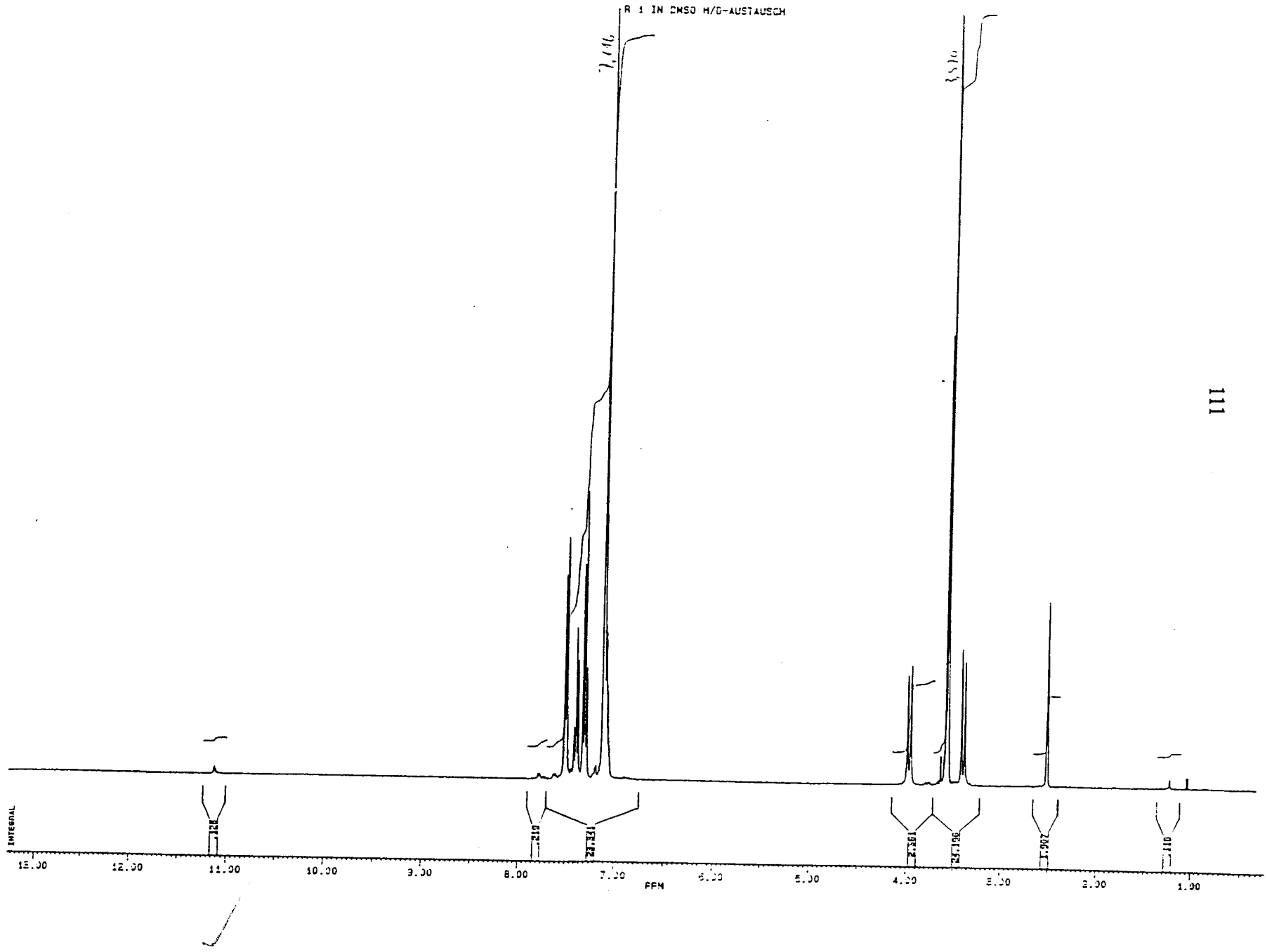
The quaternary carbon atom in the phenyl ring at 2nd position of the imidazolinone ring has already been assigned (δ 128.4). The single proton doublet at δ 7.51 has cross peak with the carbon at δ 126.4 in the HMQC spectrum which assigns the ortho carbons in this phenyl ring. The ^1H nmr spectrum has two single proton triplets at δ 7.29 and 7.38. These are the



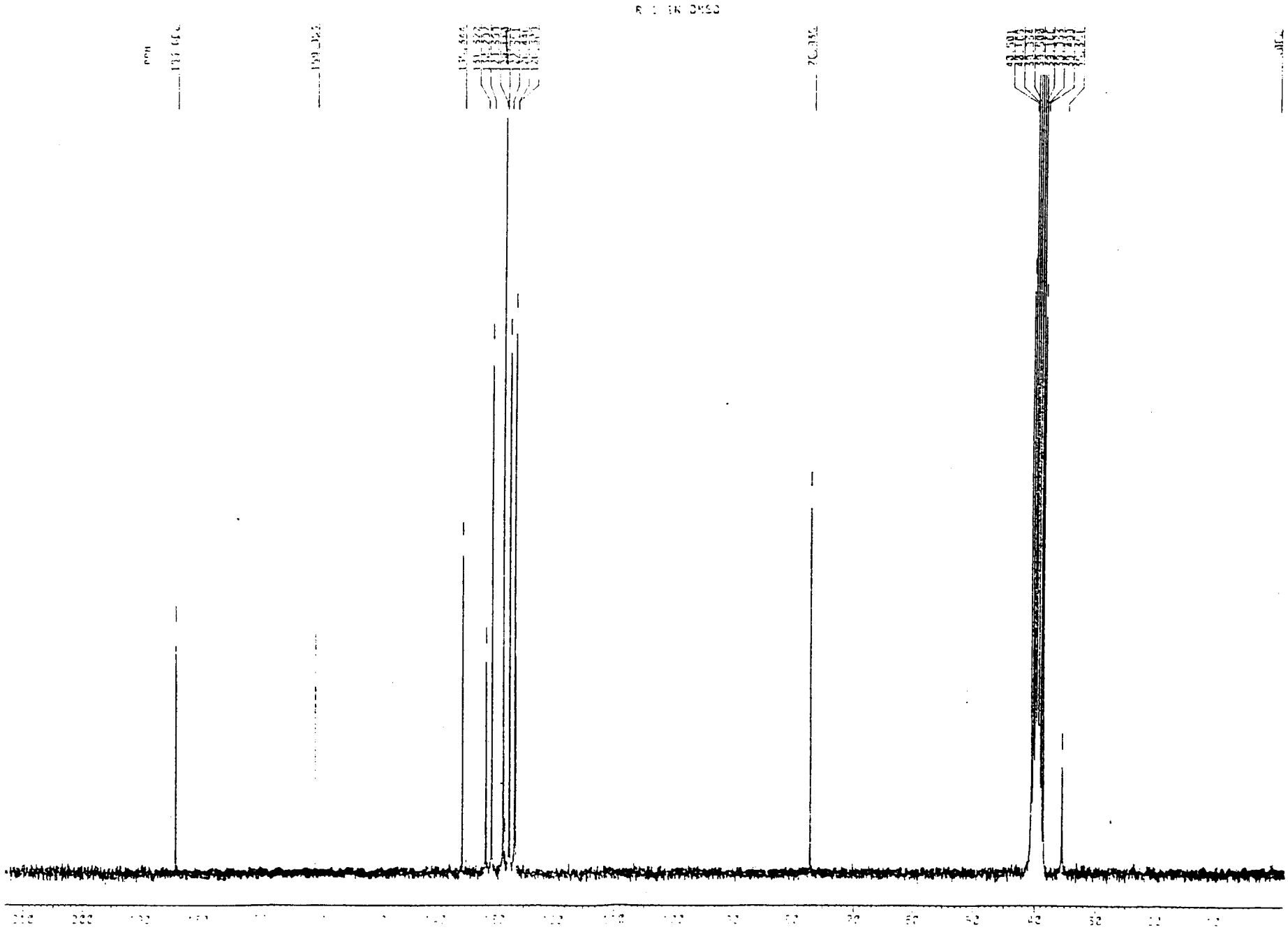
^{1}H nmr spectrum of 4, 4^{1}- dibenzyl - 2,2^{1}- diphenyl -4:4^{1}- biimidazolin - 5,5^{1}- dione



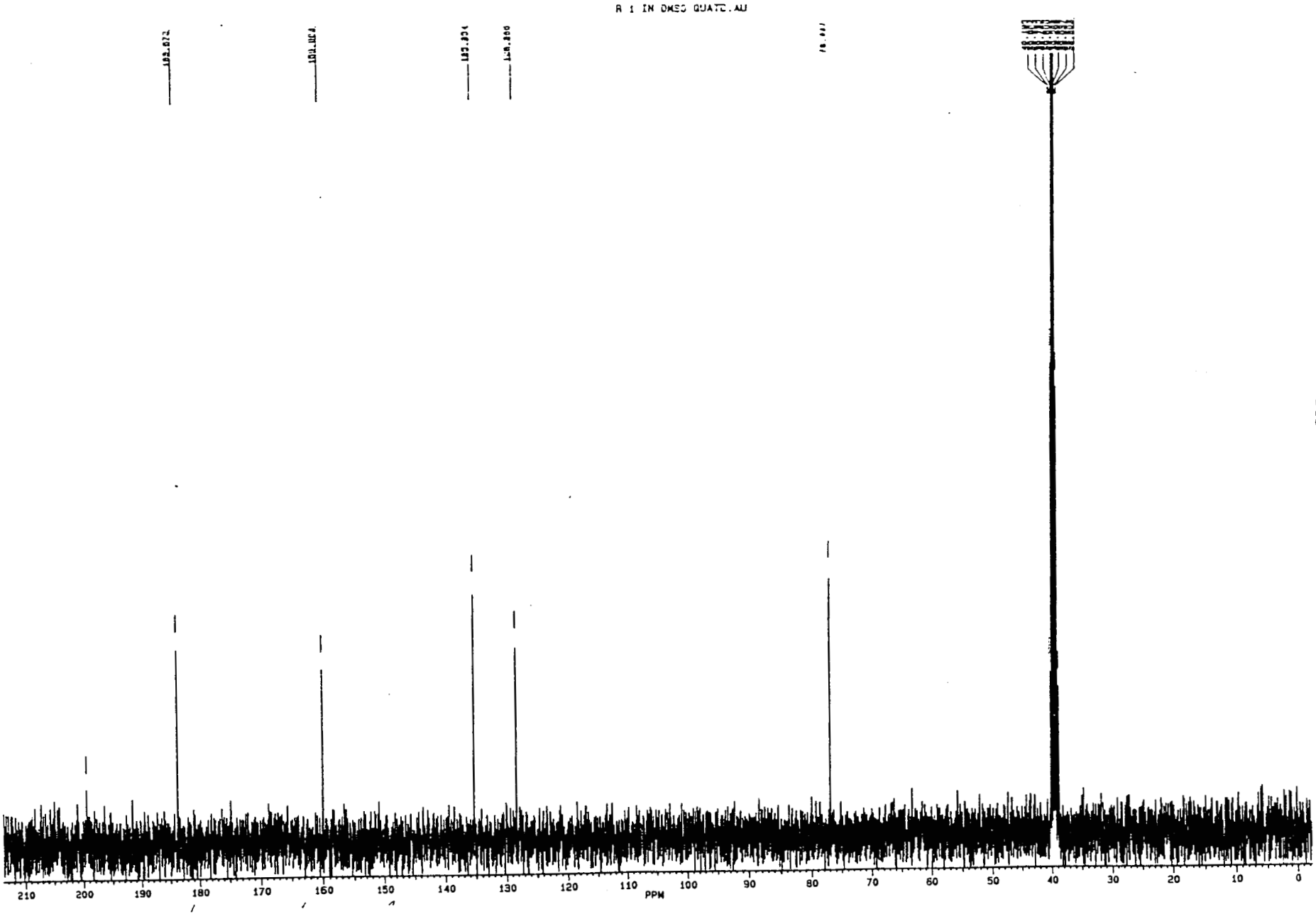
^{1}H nmr spectrum of 4, 4^{1}- dibenzyl - 2,2^{1}- diphenyl -4:4^{1}- biimidazolin - 5,5^{1} - dione (expanded)



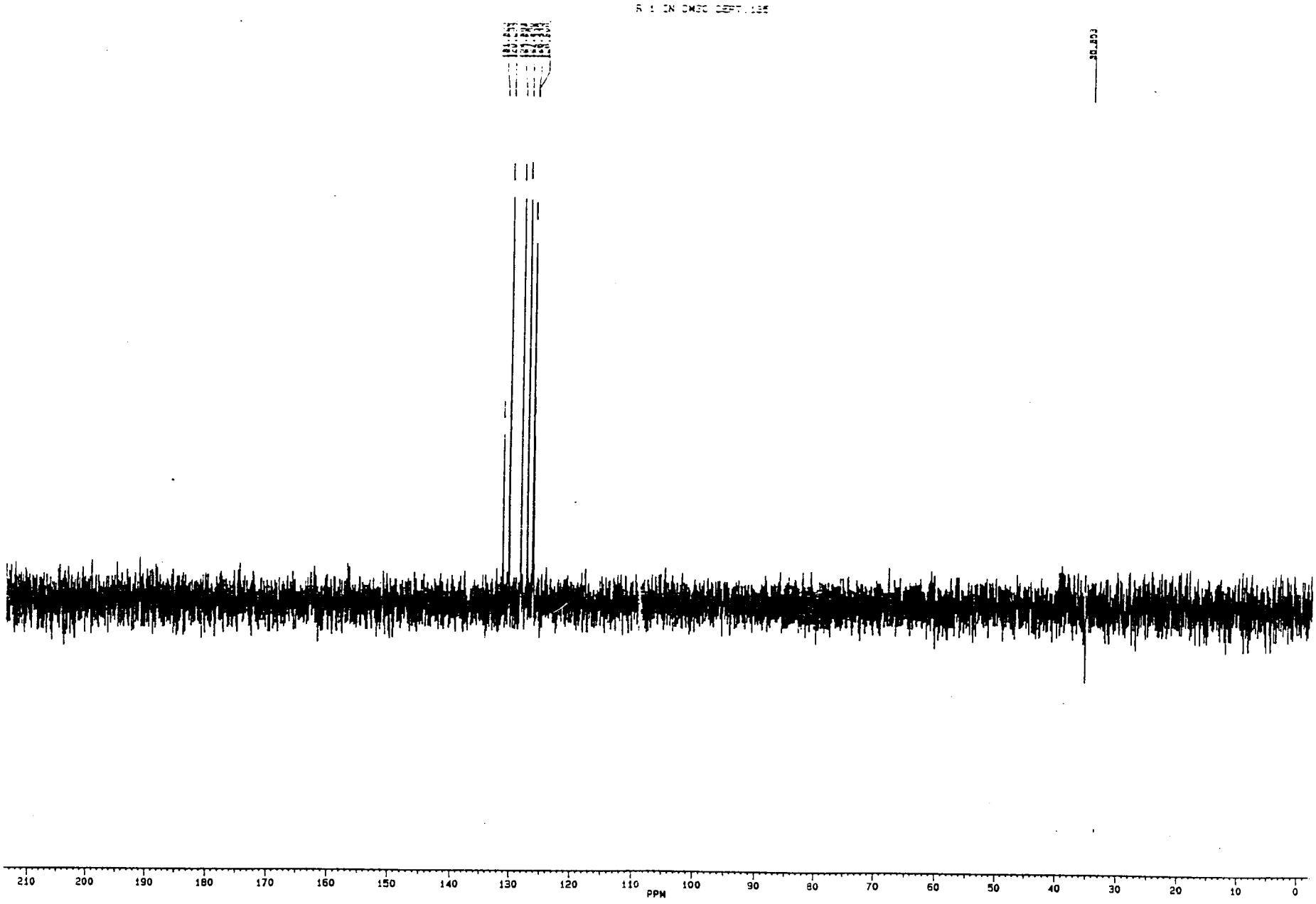
H - D exchange ^{1}H nmr spectrum of 4, 4 ^{1}- dibenzyl - 2,2 ^{1}- diphenyl -4:4^{1} - biimidazolin - 5,5^{1} - dione



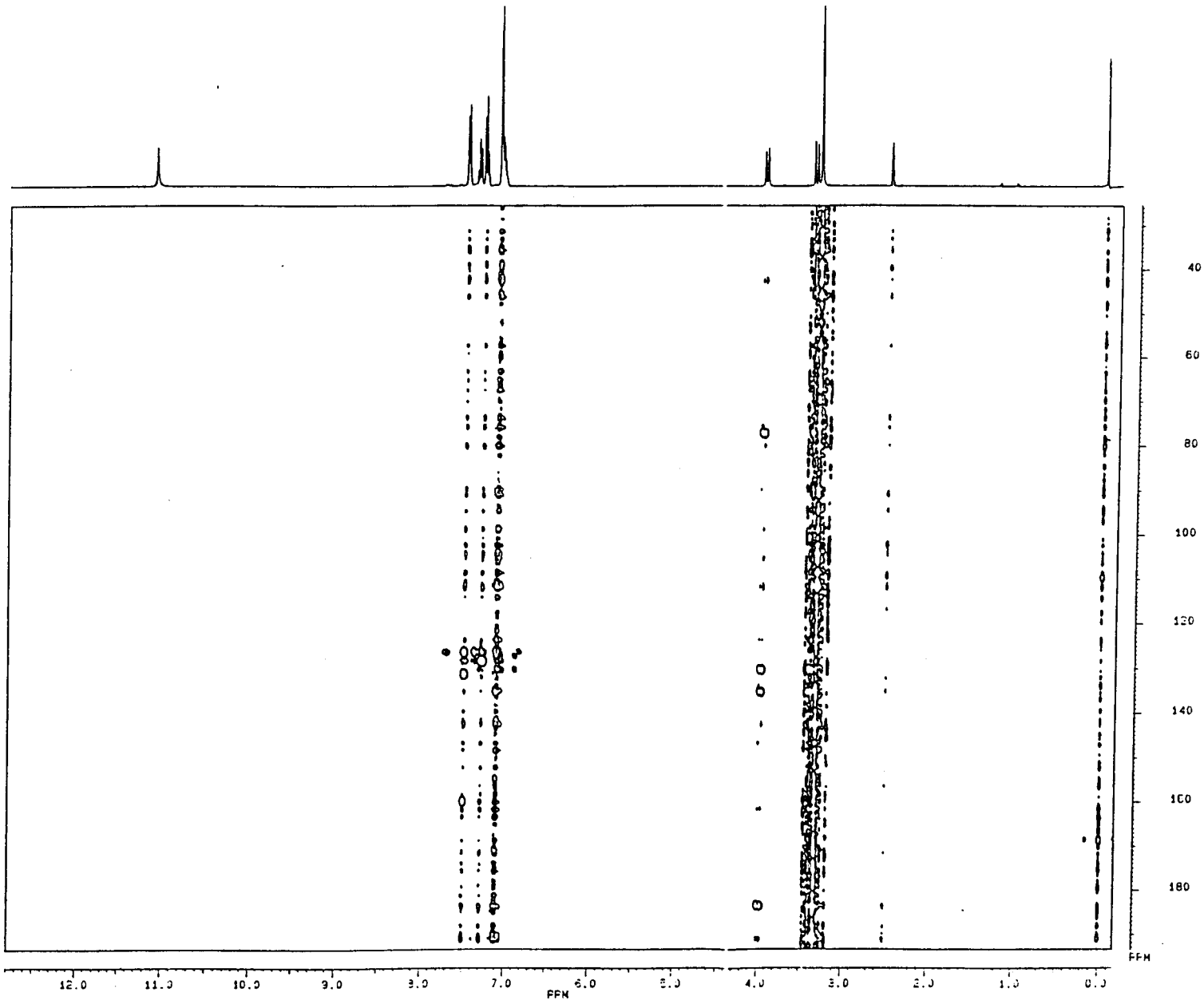
^{13}C nmr spectrum of 4, 4^{1} - dibenzyl - 2,2^{1} - diphenyl -4:4^{1} - biimidazolin - 5,5^{1} - dione



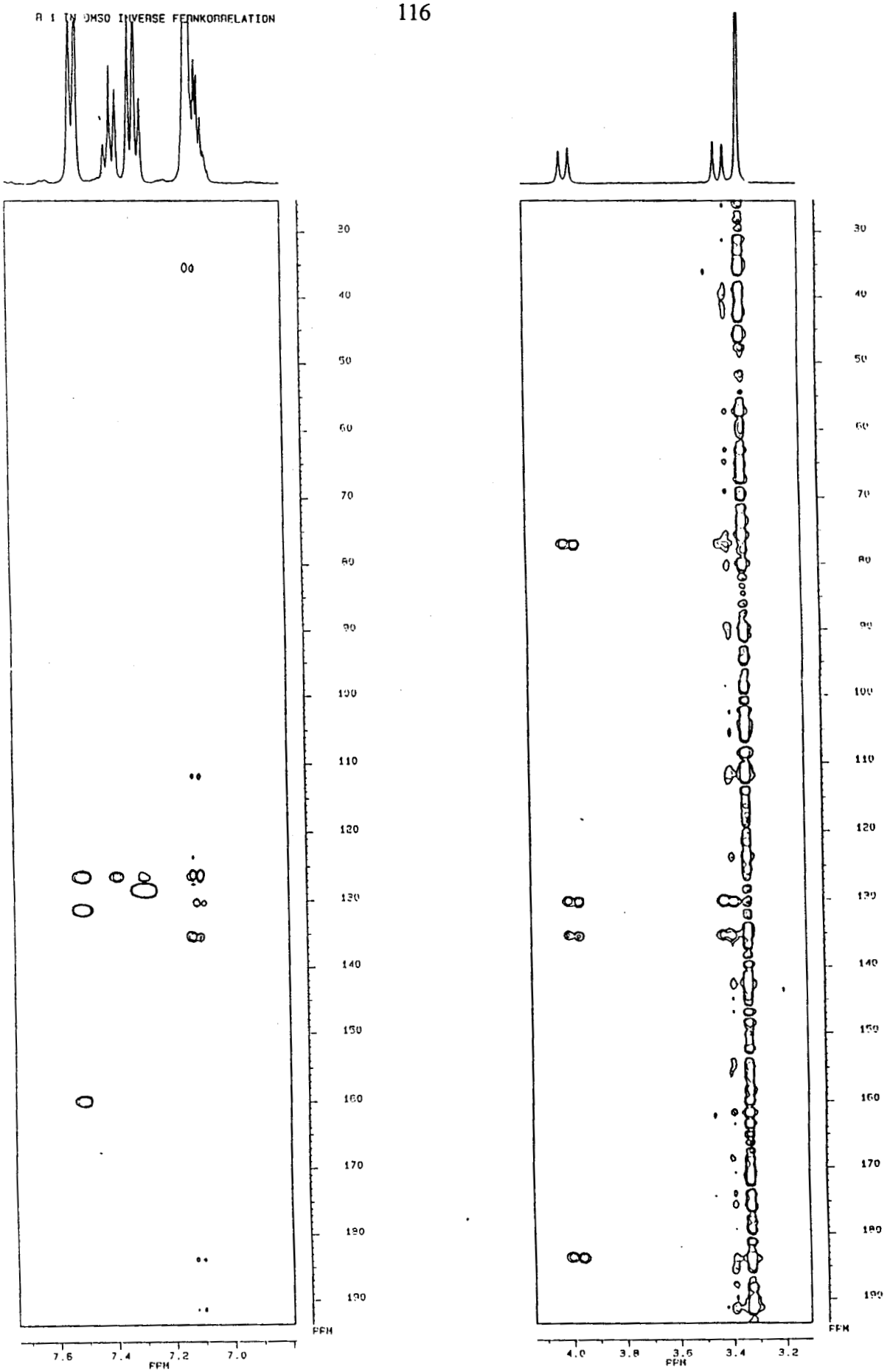
^{13}C nmr spectrum of quaternary carbon atoms of 4,4^{1}- dibenzyl - 2.2^{1}- diphenyl -4:4^{1}- biimidazolin - 5,5 - dione



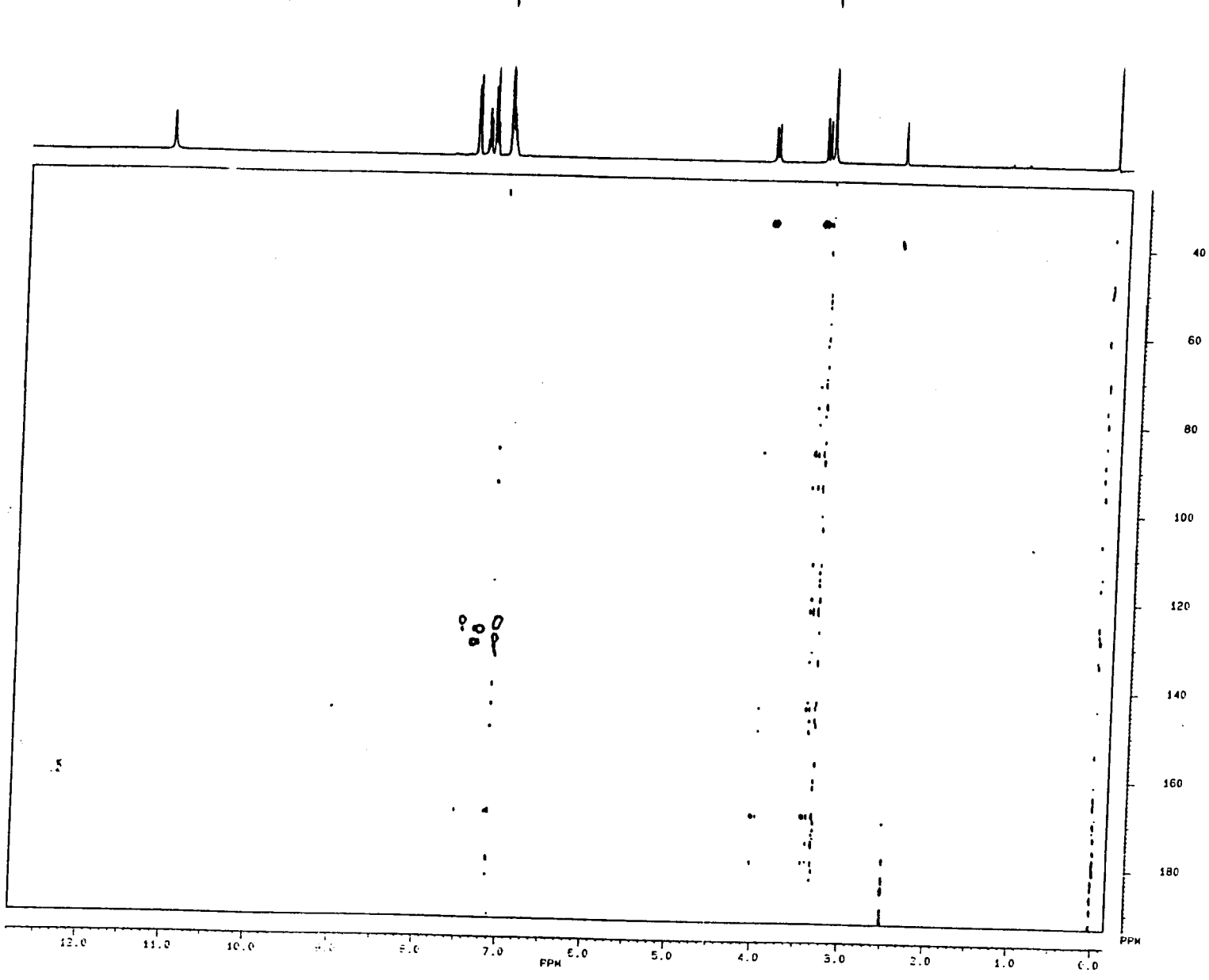
DEPT, θ = 135^0 ^{13}C nmr spectrum of 4, 4 ^{1}- dibenzyl - 2,2 ^{1}- diphenyl -4:4 ^{1}- biimidazolin - 5,5 - dione



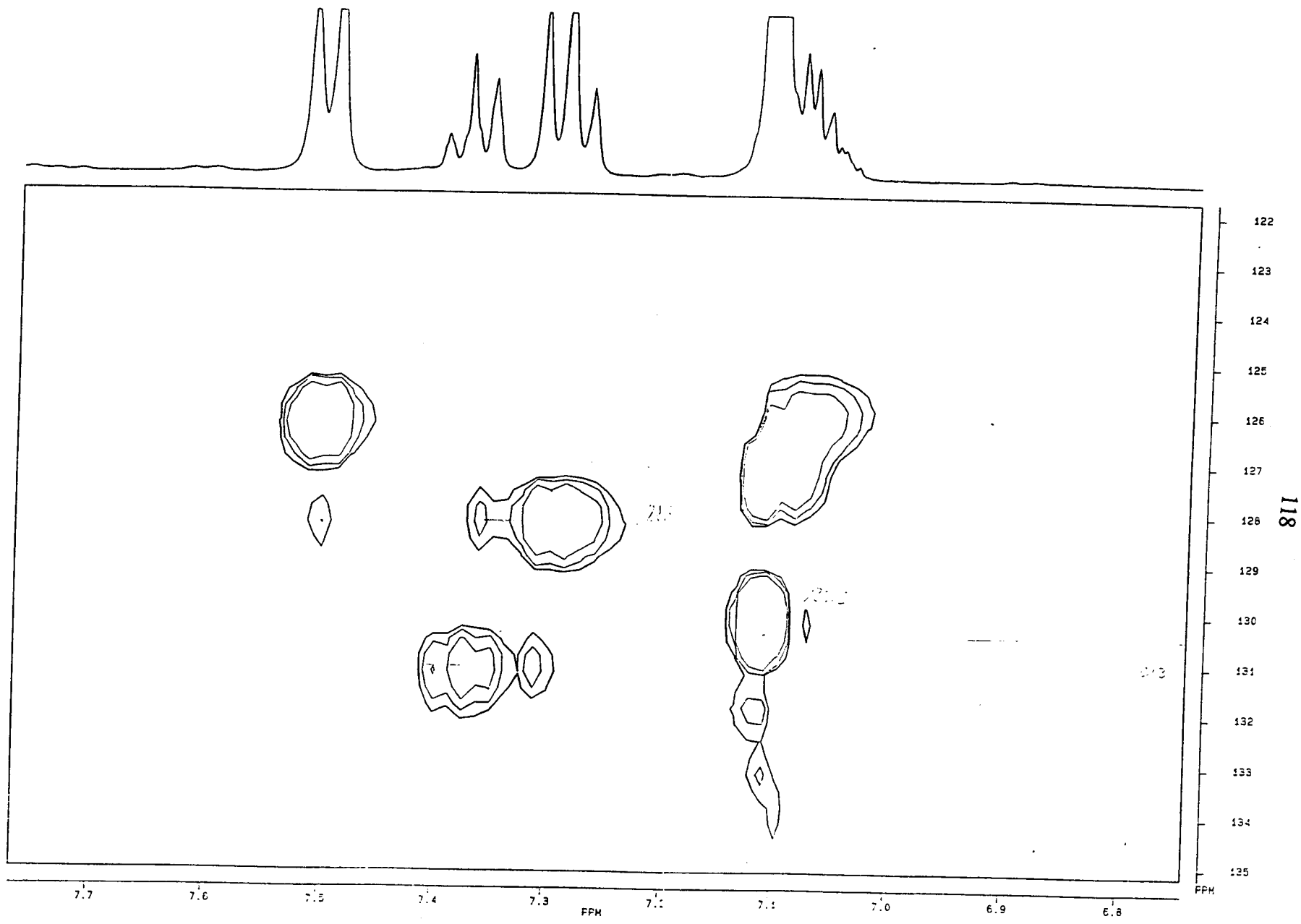
HMBC spectrum of 4,4^{1} - dibenzyl - 2,2^{1} - diphenyl - 4:4^{1} - biimidazolin - 5,5^{1} - dione



HMBC spectrum (expanded) of 4,4^{1} - dibenzyl - 2,2^{1} - diphenyl - 4:4^{1} - biimidazolin - 5,5^{1} - dione

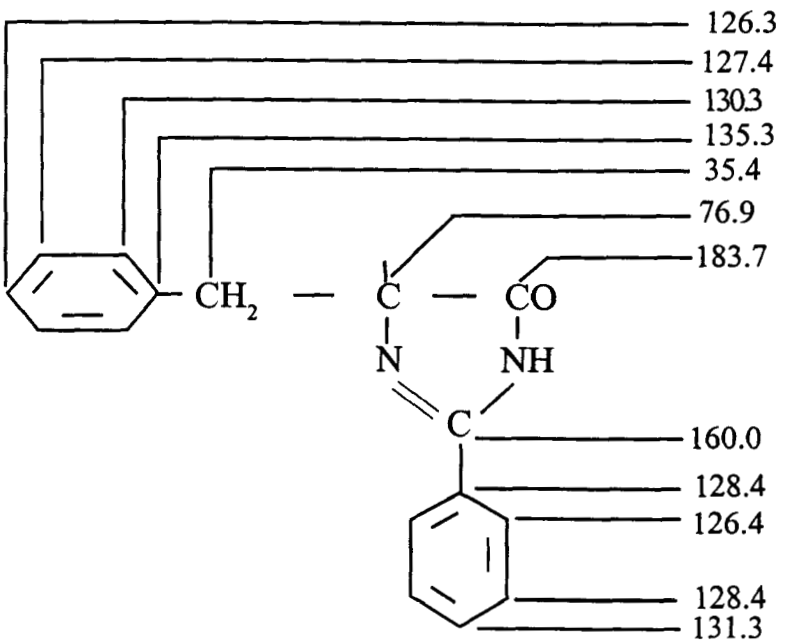


HMQC spectrum of 4,4^{1}- dibenzyl - 2,2^{1}- diphenyl - 4:4^{1}- biimidazolin - 5,5^{1}- dione



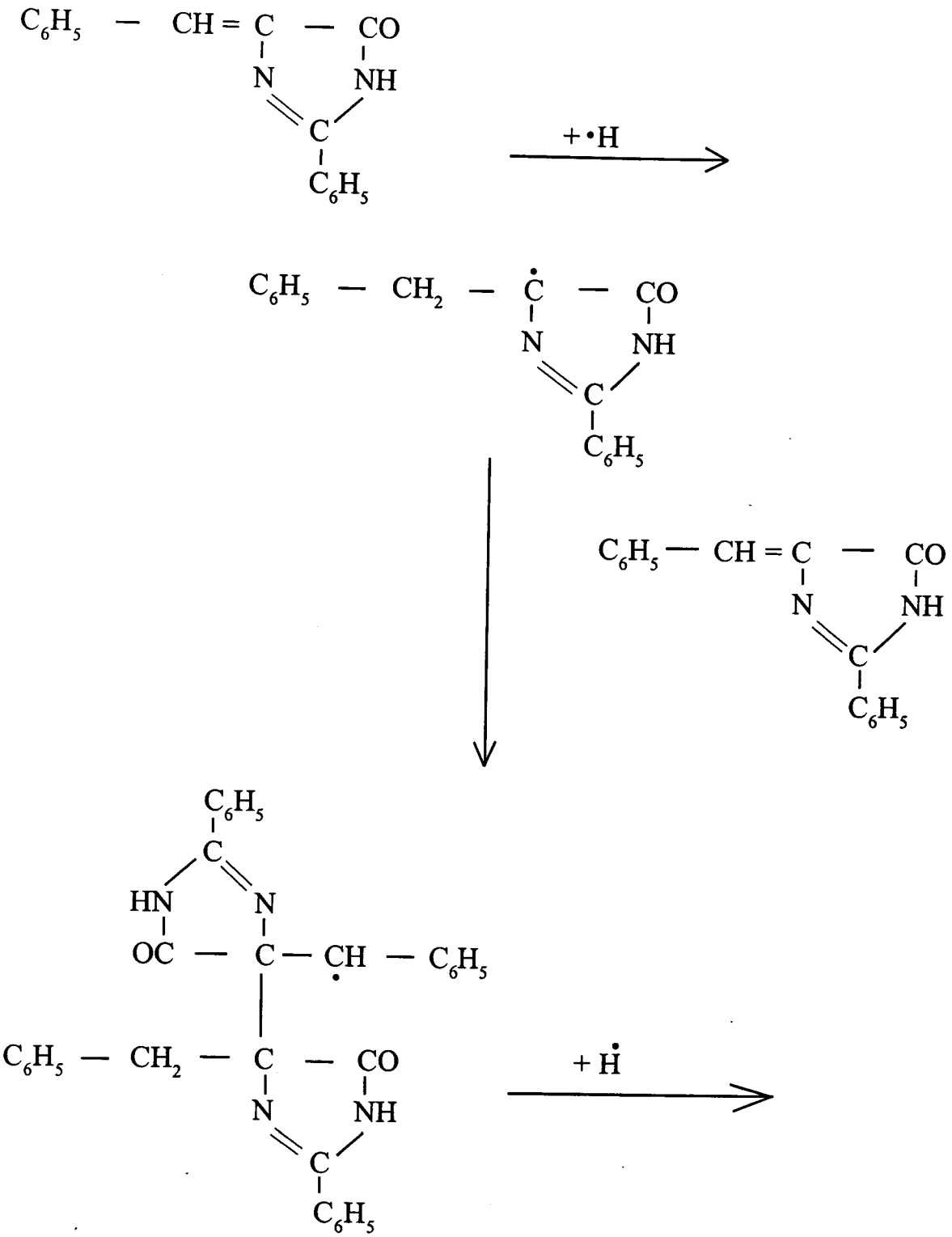
HMQC spectrum (expanded) of 4,4 ^{1}- dibenzyl - 2,2 ^{1}- diphenyl - 4:4 ^{1} - biimidazolin - 5,5^{1} - dione

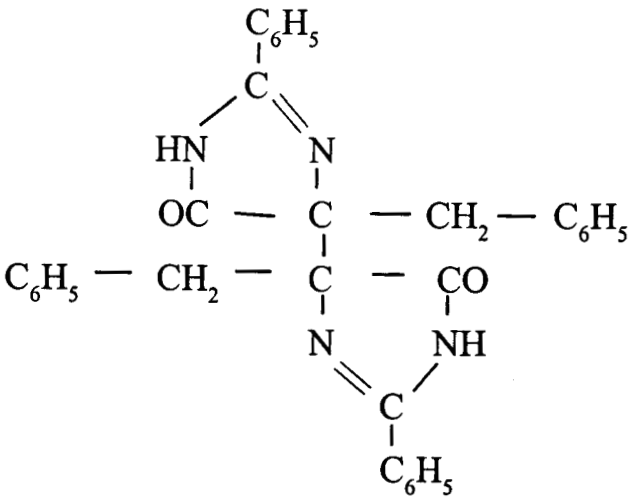
protons at meta or para positions of this ring. The triplet at δ 7.29 has cross peaks with the carbons at δ 128.4 and 126.4 in the HMBC spectrum. The carbon at δ 126.4 being already assigned as the ortho carbon atom, the meta carbon atom can be assigned a value of δ 128.4. In the HMQC spectrum the triplet at δ 7.29 has cross peak at δ 128.4 and the triplet at δ 7.38 has cross peak at δ 131.3. Thus the para carbon atom also is assigned a chemical shift value of δ 131.3. The complete assigment is as follows.



This compound was found to be optically inactive showing its racemic nature.

By heating 4 - benzylidene - 2 - phenyl - 2 - imidazolin - 5 - one with hydriodic acid and acetic anhydride yielded the same compound as above. This observation proved that red phosphorus has no role in the formation of this compound. The following radical mechanism is therefore proposed for its formation. At the reflux temparature employed in this method HI can undergo homolytic bond cleavage giving rise to hydrogen radical.





The compounds synthesised by this method are given in table III - 1

Table III - 1

4, 4^{1} - Diarylmethyl - 2, 2^{1} - diaryl - 4:4^{1} - biimidazolin - 5, 5^{1} - diones

Name	Yield(%)	m.p(^{0}C)
1. 4, 4^{1} - Dibenzyl - 2, 2^{1} - diphenyl - 4:4^{1} - biimidazolin - 5,5^{1} - dione	40	261
2. 4, 4^{1} - Di(p-tolylmethyl) - 2, 2^{1} - diphenyl - 4:4^{1} -biimidazolin - 5,5^{1} - dione	41	256
3. 4, 4^{1} - Di(p-chlorophenylmethyl) - 2, 2^{1} - diphenyl - 4:4^{1} -biimidazolin - 5,5^{1} - dione	38	252
4. 4, 4^{1} - Dibenzyl - 2, 2^{1} - di (m - tolyl) - 4:4^{1} -biimidazolin - 5,5^{1} - dione	33	236

5.	4, 4 ^{l}- Di(p-chlorophenylmethyl) - 2, 2 ^{l}- di (m - tolyl) - 4:4^{l} - biimidazolin - 5,5^{l} - dione	34	248

Thermal rearrangement of 4,4^{l} - diarylmethyl - 2,2^{l} - diaryl - 4:4^{l} - biimidazolin - 5,5^{l} - diones

4 - Benzylidene - 2 - phenyl - 2 - imidazolin - 5 - one is reported [94] to have converted to N - benzoylphenylalanine in 70% yield by reduction with HI - P followed by alkali hydrolysis. In the present work it was found that when this unsaturated imidazolinone was heated under reflux with hydroiodic acid in acetic anhydride major portion of it was converted to the dimer which cannot be hydrolysed to N - benzoylphenylalanine. That is, these two observations does'nt go hand in hand. An encouraging clue in this connection was available from the mass spectral data that the dimer undergoes Mc Lafferty rearrangement. During the Mc Lafferty rearrangement the dimer is converted to one molecule of 4 - benzyl - 2 - phenyl - 2 - imidazolin - 5 - one (reduced product) and 4 - benzylidene - 2 - phenyl - 2 - imidazolin - 5 - one. The former compound of these two on hydrolysis give N- benzoylphenylalanine.

The same kind of rearrangement took place on heating this dimer just above its melting point and keeping at that temparature for two minutes. The two compounds thus obtained were isolated by boiling with benzene and filtering hot. The reduced product remained in hot benzene while the unsaturated imidazolinone was practically insoluble in benzene. The identity of both the compounds were verified by comparing their melting points with authentic samples and by mixed melting point method. The identity of the reduced product could further be confirmed by hydrolysis of it to N - benzoylphenylalanine with so-

dium hydroxide solution [53].

The imidazolinone dimer was also heated under reflux in acetic anhydride alone. The colourless compound first dissolved and within 15 minutes the colour of the solution turned yellow indicating its decomposition to the unsaturated imidazolinone, which is coloured yellow, and the saturated imidazolinone. After one hour of refluxing the solution was subjected to TLC examination. On TLC comparison with authentic samples of 4 - benzyl - 2 - phenyl - 2 - imidazolin - 5 -one and 4 - benzylidene - 2 - phenyl - 2 - imidazolin - 5 - one, it could be proved that the acetic anhydride solution contained both of these compounds. This experiment proved beyond doubt that even if the dimer is formed during HI - P reduction it will get decomposed to the reduced and unsaturated imidazolinones. The latter on further reduction will give the saturated imidazolinone. Due to this reason major portion of 4 - benzylidene - 2 - phenyl - 2 - imidazolin - 5 - one will get converted to 4 - benzyl - 2 - phenyl - 2 - imidazolin - 5 - one on reduction with HI - P mixture. This clearly justified the high yield of N - benzoylphenylalanine reported by Devasia and Shafi [94].

This work has culuminated in the finding that 4,4' - dibenzyl - 2,2' - diphenyl - 4:4' - biimidazolin - 5,5' - dione undergose Mc Lafferty type rearrangement under thermal conditions which is a rare observation.

EXPERIMENTAL

Melting points recorded using open capillary are uncorrected. ^{13}C nmr (broad band decoupled) spectrum was recorded on Bruker AC 250 spectroscope at 62.5 MHz. All other nmr experiments were conducted using Bruker AM 360 at 360 MHz for ^{1}H and 90.5 MHz for ^{13}C. Optical activity was checked using Rudolf Autopol III polarimeter.

Synthesis of starting materials

Glycine ester was prepared as discribed in chapter I. Imidic acid ester hydrochlorides were prepared according to the method originated by pinner [118] and improved by others [52, 119-125].

Benzimidic acid methyl ester hydrochloride

In a 500 mL filter flask with a cork carrying an inlet tube was placed a mixture of benzonitrile (51mL, 0.5 mole) and absolute methanol (22 mL, 0.54 mole). A calcium chloride guard tube was attached to the side arm and the flask was cooled in freezing mixture of ice and salt. Hydrogen chloride gas bubbling through concentrated sulphuric acid was passed into the mixture till 22g (0.6 mole) of the gas was absorbed. The flask was stoppered and left in the freezing mixture. Within 3 hours the reaction mixture solidified into a colourless crystalline mass. The flask was placed in the refrigerator overnight. The hard solid mass of product was carefully broken up, transferred into a dry mortar, quickly powdered and taken in a 500mL conical flak. Dry ether (150mL) was added and the flask was stoppered and allowed to stand in the refrigerator overnight. The imidic acid ester hydrochloride was collected in a large sintered glass funnel and washed with two 50mL portions of dry ether. It was dried in a vacuum desiccator over potassium hydroxide pellets and phosphorus pentoxide. The benzimidic acid methyl ester hydrochloride weighed 82.5g (96%) and melted at 98- 99^{0}C with

decomposition. Being not very stable at room temperature it was collected in a tightly stoppered bottle and kept in the refrigerator.

m- Toluimidic acid ethyl ester hydrochloride

A mixture of m- tolunitrile (29.85 mL 0.25mole) and absolute ethanol (15.75mL 0.27 mole) was placed in a filter flask with a cork carrying an inlet tube. A calcium chloride guard tube was attached to the side arm and the flask was cooled in freezing mixture of ice and salt. Dry hydrogen chloride gas was passed into the mixture until 11g (0.3 mole) of the gas was absorbed. The flask was stoppered and left in the freezing mixture. After six hours the imidic acid ester hydrochloride began to seperate as colourless crystals. Then the flask was placed in the refrigerator for one day. The hard solid mass of the imidic acid ester hydrochloride formed was powdered and filtered through a sintered glass funnel and washed twice with 25mL portions of dry ether. It was dried in a vacuum desiccator over solid sodium hydroxide. The colourless m-toluimidic acid ethyl ester hydrochloride melting at 143- 44°C weiged 45g (89%). Being not verystable at room temperature it was stored in the refrigerator.

4- Benzylidene - 2 - phenyl - 2 - imidazolin - 5- one

Benzimidic acid methyl ester hydrochloride (4.63g, 0.027 mole), glycine ester hydrochloride (5g, 0.036 mole) and sodium bicarbonate (5.88g, 0.07 mole) were quickly mixed in a dry mortar and the mixture was immediately transferred into a 250mL round bottomed flask with long neck. Benzaldehyde (2.5mL, 0.024mole) and benzene (10mL) were soon added to the mixture and the flask was heated at once at 72°C with constant shaking in a pre - heated water bath. There was separation of esters with vigorous evalution of carbon dioxide. Within 10 minutes of heating the unsaturated - 2- imidazolin -5- one began to separate as yellow crystals. Shaking was stopped and the flask was kept vertically clamped

in the water bath for another 50 minutes while the temperature of the bath was maintained at about 72°C. The mixture solidified into a yellow mass which gradually turned slightly red. It was broken with a glass rod, heated with ethanol (25mL) and filtered hot on a sintered glass funnel. The filtrate was red coloured. The product was washed thrice with 10mL ethanol, thrice with 10mL portions of water and dried in the oven at 90°C for 1 hour. The yellow 4 - benzylidene -2- phenyl -2- imidazolin -5- one weighed 4.16 g (70%) and melted at 284- 285°C. Reported m.p is 284°C [60] .

4 - (p- Chlorobenzylidene) - 2 - phenyl - 2 - imidazolin - 5 - one

p- Chlorobenzaldehyde (6.72g, 0.048 mole) was condensed with a mixture of benzimidic acid methyl ester hydrochloride (9.26g,0.054 mole) and glycine ethyl ester hydrochloride (10g,0.072 mole) in the presence of sodium bicarbonate(11.76g,0.14 mole) and benzene (20 mL) by heating at about 72°C for 1 hour. The yellow product weighed 9.25g (69%) and melted at 313-314°C. The reported m.p. is 313 - 14°C [60] .

4 - (p- Methylbenzylidene) - 2 - phenyl - 2 - imidazolin - 5 - one

p- Tolualdehyde (2.83mL, 0.024 mole) was condenced with a mixture of benzimidic acid methyl ester hydrochloride (4.63g,0.027 mole) and glycine ethyl ester hydrochloride (5g, 0.036 mole) in the presence of sodium bicarbonate (5.88g,0.07 mole) and benzene (10mL) by heating at about 72°C for 1 hour. The yellow product melting at 312°C weighed 5.12g(81%) . The reported m.p is 312 - 13°C [60].

4 - Benzylidene - 2 - m-tolyl - 2 - imidazolin - 5 - one

m- Toluimidic acid ethyl ester hydrochloride (4.78g,0.024 mole) , glycine ethyl ester hydrochloride (4.17g,0.03 mole) and sodium bicarbonate (4.8g, 0.057

mole) were quickly mixed in a dry mortar and the mixture was immediately transferred into a 250mL round - bottomed flask with long neck. Benzaldehyde (2.02mL, 0.02mole) and benzene (10mL) were soon added to the mixture and the flask was heated at once at 72°C with constant shaking in a pre - heated water bath. There was separation of esters with vigorous evolution of carbondioxide. Within 10 minutes of heating the unsaturated 2- imidazolin -5- one began to separate as yellow crystals. Shaking was stopped and the flask was kept vertically clamped in the water bath for another 50 minutes while the temperature of the bath was maintained at about 72°C. The mixture solidified into a yellow mass which gradually turned slightly red. When the flask was removed from the water bath the solid mass became more red. It was broken with a glass rod, heated with ethanol (50mL) and filtered hot on a sintered glass funnel. The filterate was red coloured. The product was washed thrice with 20mL portions of ethanol, thrice with 20mL portions of water and finally with 10mL of ethanol and dried in the oven at 90°c for 1 hour. The yellow 4- benzylidene - 2- m- tolyl - 2- imidazolin -5- one weighed 4.03g(77%) and melted at 254-255 °C. The reported m.p is 255- 256°C [60]

4 - (p- Chlorobenzylidene) - 2 - m - tolyl - 2 - imidazolin - 5 - one

p- Chlorobenzaldehyde (2.8g,0.02 mole) was condensed with a mixture of m- tolumidic acid ethyl ester hydrochloride (4.78gm, 0.024mole) and glycine ethyl ester hydrochloride (4.17g, 0.03mole) in the presence of sodium bicarbonate (4.8g, 0.057 mole) and benzene (10mL) by heating about 72°C for 1 hour. The yellow product melting at 269-270°C weighed 4.3g (73%).The reported m.p is 270 - 271°C [60]

Synthesis of 4,4^{1} - diarylmethyl - 2, 2^{1} - diaryl - 4:4^{1} - biimidazolin - 5,5^{1} - diones

4,4^{1}- Dibenzyl - 2,2^{1} - diphenyl - 4:4^{1} - biimidazolin - 5,5^{1} - dione

4- Benzylidene -2- phenyl -2-imidazolin -5- one (2g, 0.008mole) was taken in a 100mL round bottomed flask and acetic anhydride (12mL) added. A reflux condenser was fitted to the flask and cooled in water. Hydriodic acid (12mL) was added in portions through the condenser. After complete addition of hydriodic acid it was heated under reflux for 2 hours. After cooling it was filtered and the filtrate neutralised with saturated sodium carbonate solution. The precipitate obtained was collected and dissolved in ethanol (50mL) by heating and filtered. After keeping the solution overnight the white crystals of 4,4^{1}- dibenzyl - 2,2^{1} - diphenyl - 4:4^{1} -biimidazolin - 5,5^{1} - dione formed was filtered, washed with 5mL of ethanol and dried. Weighed 0.8g (40%) and melted at 259^{o}C.

4,4^{1} - Dibenzyl - 2,2^{1} - diphenyl - 4:4^{1}-biimidazolin - 5,5^{1} - dione was recrystallised from isopropanol (30mL). The colourless crystals formed melted at 261^{o}c.

Analysis

N(%)

Found : 11.2

Calculated : 11.24

$C_{32}H_{26}N_4O_2$

4,4^{1}- Di (p-tolylmethyl) - 2,2^{1} - diphenyl - 4:4^{1} - biimidazolin - 5,5^{1} -dione

4- p- Methylbenzylidene -2- phenyl -2- imidazolin -5- one (2.2g, 0.008 mole) was taken in a 100mL round bottomed flask and acetic anhydride (12mL) added. A reflux condenser was fitted to the flask and cooled in water. Hydriodic

acid (12 mL) was added in portions through the condenser. After complete addition of hydriodic acid it was heated under reflux for 2 hours. After cooling it was filtered and the filtrate neutralised with saturated sodium carbonate solution. The precipitate obtained was collected and dissolved in ethanol (50 -mL). After keeping overnight the white crystals of 4,4' - di(p - tolylmethyl) - 2,2' - diphenyl - 4:4' - biimidazolin - 5,5'-dione formed was filtered, washed with 5mL of ethanol and dried. It weighed 0.85g (41%) and melted at 255°C.

4,4'- Di(p - tolylmethyl) - 2,2' -diphenyl - 4:4' - biimidazolin - 5,5' - dione was recrystallised from isopropanol. The colourless crystals formed melted at 256°C.

Analysis

N(%)

Found : 10.6

Calculated : 10.64

$C_{34}H_{30}N_4O_2$

4, 4'- Di(p -chlorophenylmethyl) - 2,2' - diphenyl - 4:4' - biimidazolin - 5,5' - dione

4 - p - Chlorobenzylidene -2- phenyl -2- imidazolin 5- one (2.26g, 0.008 mole) was taken in a 100 - mL round bottomed flask and acetic anhydride (12mL) added. A reflux condenser was fitted to the flask and cooled in water. Hydriodic acid (12mL) was added in portions through the condenser. After complete addition of hydriodic acid it was filtered and the filtrate neutralised with saturated sodium carbonate solution. The precipitate obtained was collected and dissolved in ethanol (50mL). After keeping overnight the white crystals of 4 , 4'- di(p -chlorophenylmethyl) - 2,2' - diphenyl - 4:4' - biimidazolin - 5,5' - dione formed was filtered, washed with 5 mL of ethanol and dried. It weighed 0.85g (38%) and melted at 250 °C.

4 , 4^{l}- Di(p -chlorophenylmethyl) - 2,2^{l} - diphenyl - 4:4^{l} - biimidazolin - 5,5^{l}-dione was recrystallised from isobutanol. The colourless crystals formed melted at 252^{o}C.

Analysis

N(%)

Found : 10.0

Calculated : 9.89

$C_{32}H_{24}N_4O_2Cl_2$

4, 4^{l}- Dibenzyl - 2,2^{l}-di(m - tolyl) - 4:4^{l} -biimidazolin - 5,5^{l} -dione

4 - Benzylidene -2- m - tolyl -2- imidazolin -5- one (2.1g, 0.008 mole) was taken in a 100 - mL round bottomed flask and acetic anhydride (12mL) added. A reflux condenser was fitted to the flask and cooled in water. Hydriodic acid (12 mL) was added in portions through the condenser. After complete addition of hydriodic acid it was heated under reflux for 2 hours. After cooling it was filtered and the filtrate neutralised with saturated sodium carbonate solution. The precipitate obtained was collected and dissloved in ethanol (50mL). After keeping overnight the white crystals of 4, 4^{l}- dibenzyl - 2,2^{l} - di -(m-tolyl) - 4:4^{l} - biimidazolin - 5,5^{l} - dione formed was filtered, washed with 5 mL of ethanol and dried. It weighed 0.7g (33%) and melted at 236^{o}C.

4,4^{l} - Dibenzyl - 2,2^{l} - di(m -tolyl) - 4:4^{l} - biimidazolin - 5,5^{l} - dione was recrystallised from isopropanol. The white crystals melted at 236^{o}C.

Analysis

N(%)

Found : 10.6

Calculated : 10.68

$C_{34}H_{30}N_4O_2$

4, 4^{1}- Di(p -chlorophenylmethyl) - 2, 2^{1}- di(m -tolyl) - 4;4^{1} - biimidazolin - 5,5^{1} - dione

4 - p - Chlorobenzylidene - 2 - m - tolyl - 2 - imidazolin - 5 - one (2.39g, 0.008 mole) was taken in a 100 mL round bottomed flask and acetic anhydride (12 mL) added. A reflux condenser was fitted to the flask and cooled in water. Hydriodic acid (12mL) was added in portions through the condenser. After complete addition of hydriodic acid it was heated under reflux for 2 hours. After cooling it was filtered and the filtrate neutralised with saturated sodium carbonate solution. The precipitate obtained was collected and dissolved in ethanol (50mL) . After keeping overnight the white crystals of 4,4^{1}-di(p - chlorophenylmethyl) - 2,2^{1} - di(m - tolyl) - 4:4^{1} - biimidazolin - 5,5^{1} - dione formed was filtered, washed with 5mL of ethanol and dried. It weighed 0.81g (34%)and melted at 247^{0}C .

4,4^{1}-Di(p - chlorophenylmethyl) - 2,2^{1} - di(m - tolyl) - 4:4^{1}- biimidazolin - 5,5^{1} - dione was recrystallised from isopropanol. The white crystals formed melted at 248^{0}C.

Analysis

N(%)

Found : 9.5

Calculated : 9.45

$C_{34}H_{28}N_4O_2Cl_2$

Thermal rearrangement of 4,4^{1} - dibenzyl - 2,2^{1} - diphenyl - 4:4^{1} - biimidazolin - 5,5^{1} - dione

4 ,4^{1}- Dibenzyl - 2,2^{1} - diphenyl - 4:4^{1} - biimidazolin - 5,5^{1} - dione (0.5g) was taken in a clean dry test tube and heated in an oil bath. When the temperature reached 261^{0}C it melted. Heating was stopped when the temperature reached

263^{0}C. The test tube was kept at this temperature for two minutes. By this time the imidazolinone dimer had dissolved and the colour turned to yellow. The test tube was taken out and allowed to cool. Benzene (5mL) was then added, boiled and filtered hot. 4- Benzylidene - 2 - phenyl - 2 - imidazolin - 5 - one formed due to rearrangement remained in the filter paper. It was recrystallised from isobutanol and melted at 284 - 85^{0}C. The reported m.p is 284^{0}C [60].

To the filtrate petroleum ether (5mL) was added while 4 - benzyl - 2-phenyl - 2 - imidazolin - 5 - one precipitated (0.15g). It melted at 167 - 170^{0}C. Its reported m.p is 168 - 169^{0}C [53].

Hydrolysis of 4 - benzyl - 2 - phenyl - 2 - imidazolin - 5 - one

4 - Benzyl - 2 - phenyl - 2 - imidazolin - 5 - one (0.1g) was heated under reflux with 4% sodium hydroxide solution (10mL) for one hour. Evolution of ammonia, due to its hydrolysis could be felt from its smell at the top of the condenser. After one hour the solution was acidified with conc. hydrochloric acid to precipitate N - benzoylphenylalanine. The product was filtered after cooling in ice for one hour. It was washed with water and dried. After recrystallisation from 50% ethanol it melted at 187 - 188^{0}C. The reported m.p of this compound is 188 - 189^{0}C [94].

Rearrangement of 4,4^1 - dibenzyl - 2,2^1-diphenyl - 4:4^1 -biimidazolin - 5,5^1 - dione in boiling acetic anhydride.

4,4^1 -dibenzyl - 2,2^1-diphenyl - 4:4^1-biimidazolin - 5,5^1- dione in boiling acetic anhydride (0.5g) was heated under reflux in acetic anhydride (5mL). It went into solution on boiling and colourless solution turned pale yellow within 15minutes. After refluxing for one hour the solution was subjected to comparative thin layer chromatography with authentic samples of 4 - benzylidene - 2 - phenyl - 2 -imidazolin - 5 - one and 4 - benzyl - 2 - phenyl - 2 - imidazolin - 5 -

one. Thin layer chromatographic plate was prepared using silica gel G(Qualigens) and activated at 100°C for 30 minutes. This acetic anhydride reaction mixture, solution of 4 - benzylidene - 2 - phenyl - 2 - imidazolin - 5 - one and 4 - benzyl - 2 - phenyl - 2 - imidazolin - 5 - one were spotted on the same plate and eluted with benzene. After development the plate was sprayed with 50% sulphuric acid and heated in the oven at 110°C for one hour. Charred spots corresponding to 4 - benzylidene - 2 - phenyl - 2 -imidazolin - 5 - one and 4 - benzyl - 2 - phenyl - 2 - imidazolin - 5 - one were present in the acetic anhydride solution.

4 - Benzyl - 2 - phenyl - 2 - imidazolin - 5 - one

In a 100-mL round bottemed flask with ground glass joint were placed crude 4 - benzylidene - 2 - phenyl - 2 - imidazolin - 5 - one (2g), red phosphorus (1.8g) and acetic anhydride (12mL). The flask was fitted with a reflux condenser and hydriodic acid (7.5mL) was added through the condenser in small portions while the flask was being shaken and cooled in water. The mixture was heated under reflux with occassional shaking for 2 hours. The flask was allowed to cool and the reaction mixture was filtered through a fluted filter paper and the unreacted phosphorus on the filter was washed with two 2mL portions of glacial acetic acid. The combined filtrate and washings were diluted with water (50mL) and purified by extracting twice with 20mL portions of benzene. The aqueous solutions was taken in a separatory funnel, benzene(20mL) was added to it and then 20% sodium hydroxide solution (20mL) was added in portions with shaking. The benzene layer was collected. Again benzene (20mL) was added to the aqueous layer and treated with 20% sodium hydroxide solution (20mL). The combined benzene extracts were added to 25mL of petroleum ether (60 -80°C) when pale yellow crystals of the saturated 2 - imidazolin - 5 -one separated. The crystals were filtered and washed twice with 3mL portions of petroleum ether and

dried by suction. The pale yellow 4 - benzyl - 2 - phenyl - 2 - imidazolin - 5 - one melting at 165 - 170^{0}C(rapid heating) weighed 0.8g (40%) Kidwai and Devasia [53] reported m.p 168 - 169^{0}C (rapid heating) for this compound.

Analysis

N(%)

Found :11.47

Calculated :11.19

$C_{16}H_{14}N_2O$

CHAPTER IV

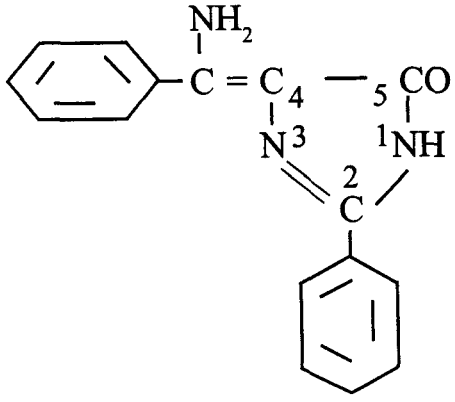
Synthesis of 4 - (amino, arylmethylene) - 2 - aryl - 2 imidazolin - 5 - ones and their acetylated products

Synthesis of 4 - (amino, arylmethylene) - 2 - aryl - 2 imidazolin - 5 - ones

The formation of red coloured products during the reaction between benzimidic acid ester and glycine ester have been thoroughly investigated [49,5195]. A reinvestigation of this reaction resulted in the isolation and structural elucidation of 4 - (amino, arylmethylene) - 2 - aryl- 2 - imidazolin - 5 - ones.

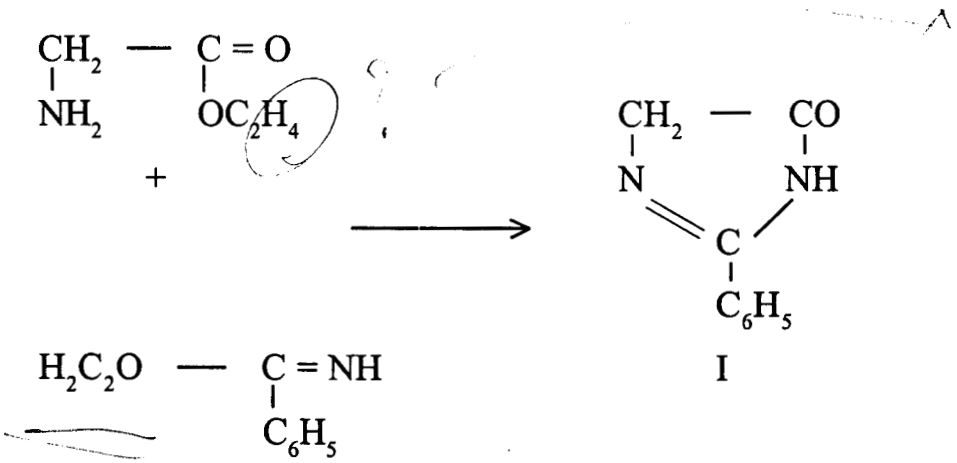
Results and discussion

Benzimidic acid methyl ester and glycine ethyl ester on heating under reflux in pyridine turned red within a few minutes. After heating for three hours the reaction mixture was left as such for two days. On the second day reddish yellow crystals were found to have deposited. After recrystallisation from ethanol this compound was analysed using spectral methods and the structure (II) assigined to it.



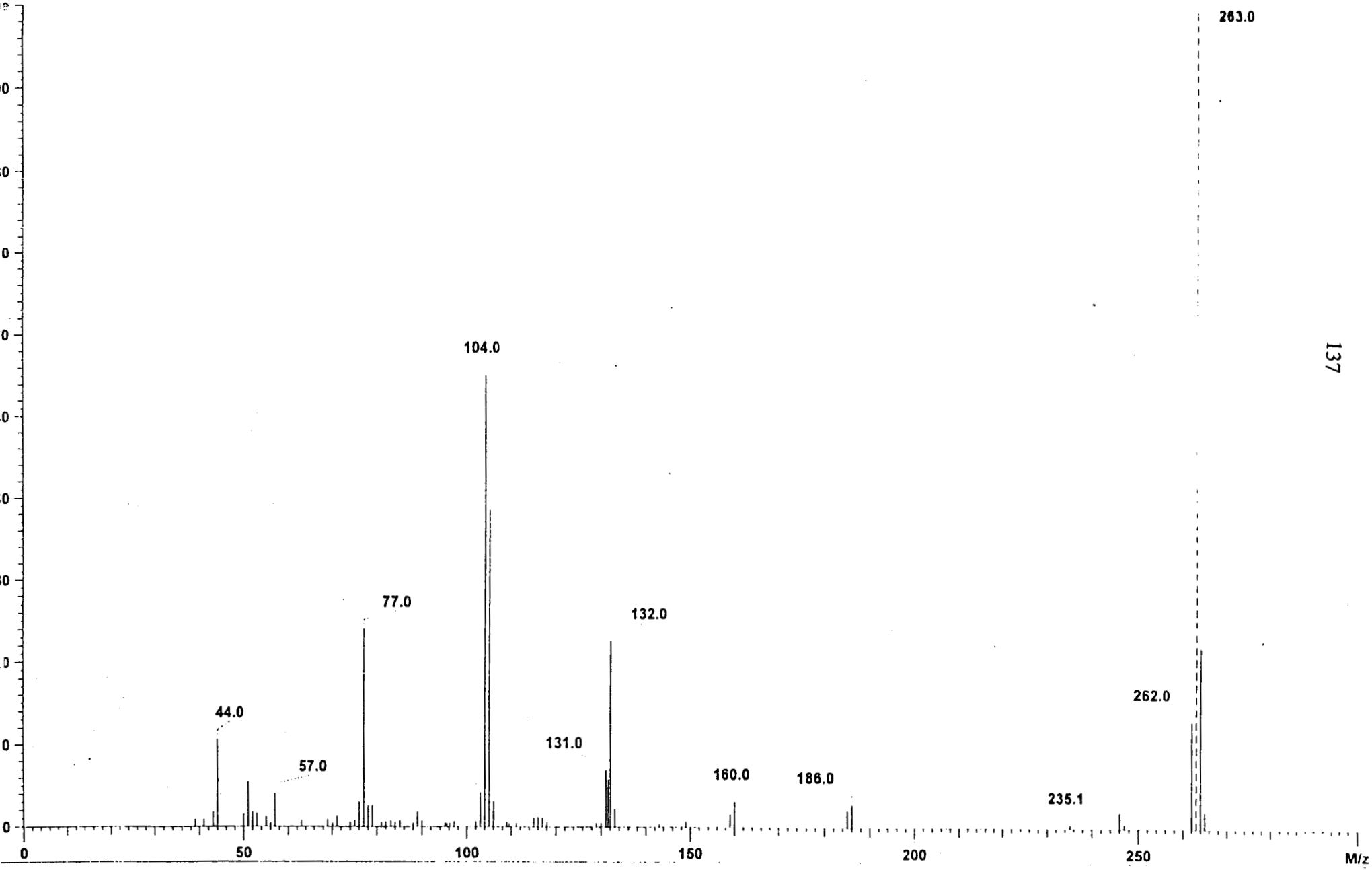
II

This structure was arrived at as follows. Its mass spectrum had M^+ peak at 263, which is also the base peak corresponding to this structure. The odd mass justified the presence of odd number of nitrogen atoms. The reaction between benzimidic acid ester and glycine ester yields 2 - phenyl - 2 - imidazolin - 5- one [49 51 95] (I) which contains two nitrogen atoms. Therefore it was assumed that the product (II) should contain at least three nitrogen atoms to



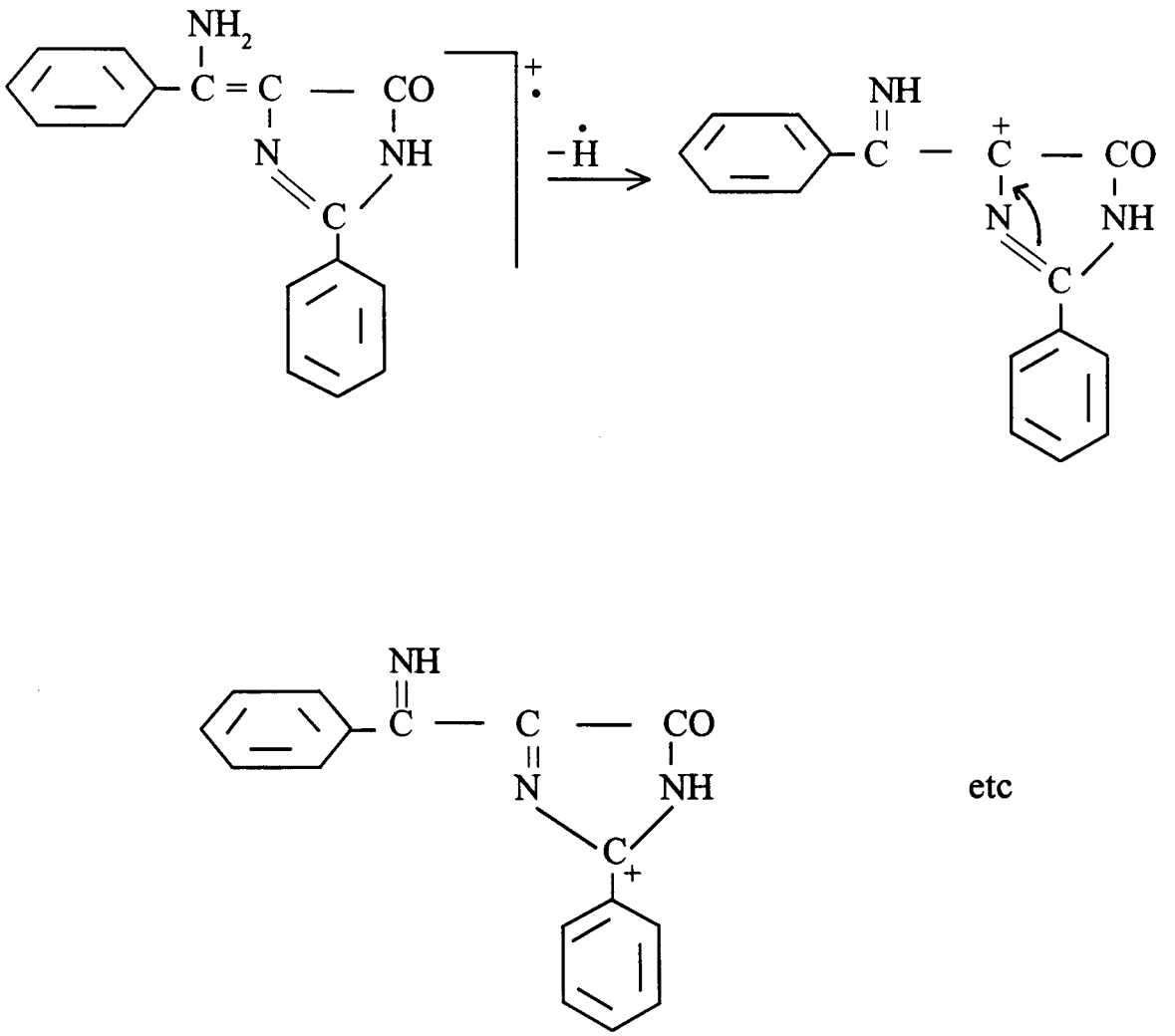
give an odd mass number. The logic behind this assumption was that II was the resulting compound due to the reaction between I and one of the starting compounds which contain one nitrogen each. Other important peaks in the mass spectrum were at m/z = 262, 235, 186, 160, 132, 131, 104 and 77 which further supported the proposed structure.

The fragment at m/z 262 is formed by the elimination of hydrogen radical from the molecular ion radical. This cation is stabilised by conjugation with adjacent double bond which is in conjigation with the C = N in the heterocyclic ring.

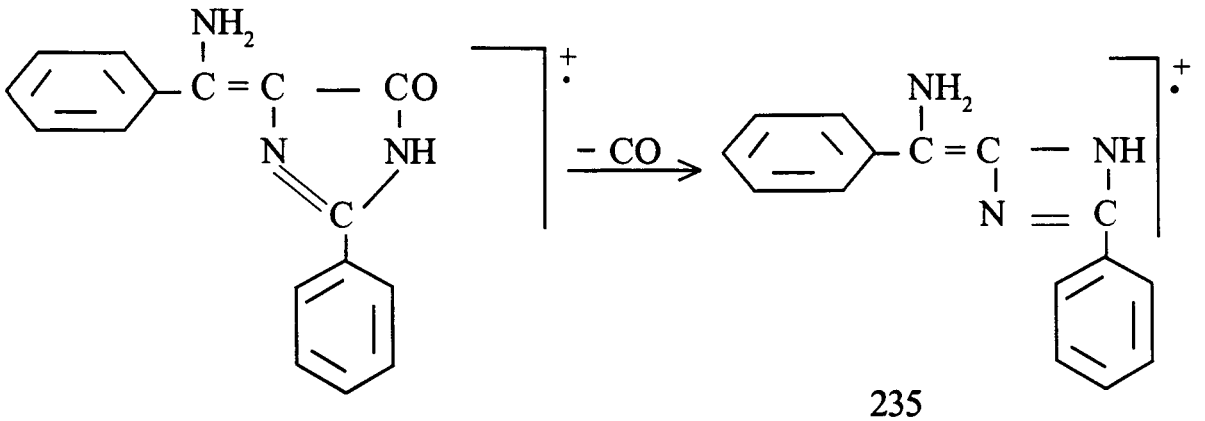


137

EI - MS of 4 - (Amino, phenylmethylene) - 2 - phenyl - 2 - imidazolin - 5 - one

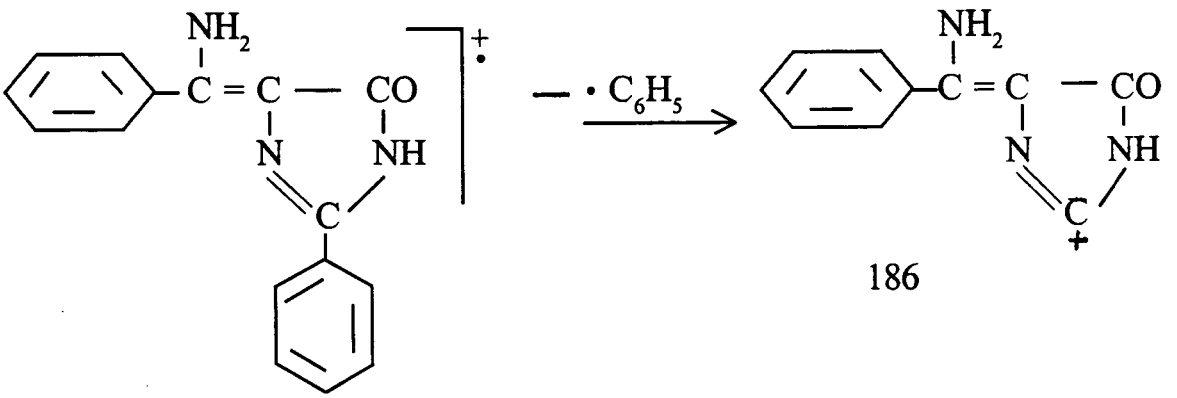


The mass peak at 235 units correspond to the radical ion formed by the elimination of a neutral molecule of CO from the molecular ion.



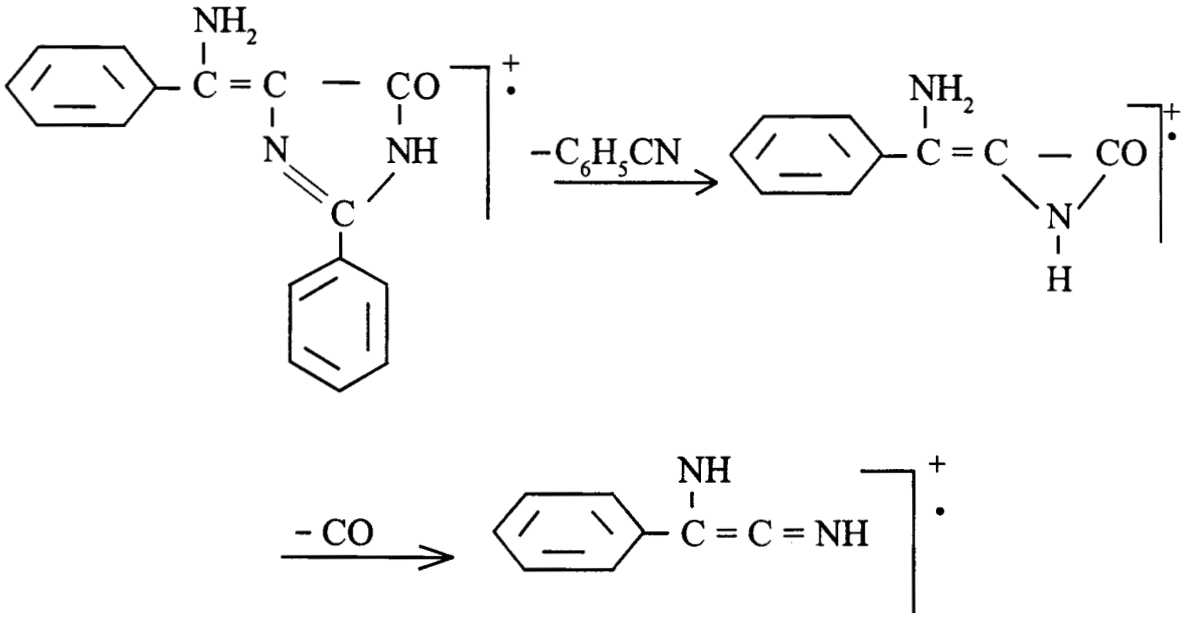
235

An alternate fragmentaion pathway gives rise to the peak at m/z = 186. It is due to the removal of phenyl radical in the heterocyclic ring of the molecular ion

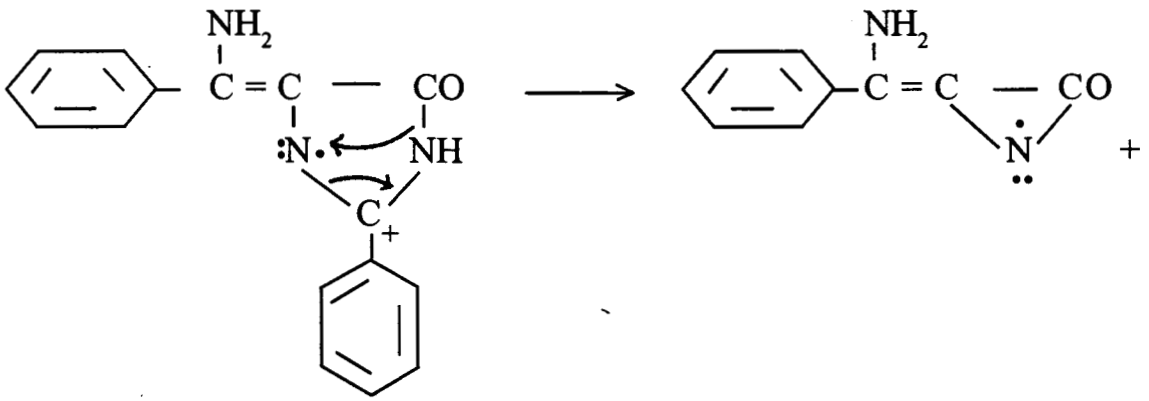


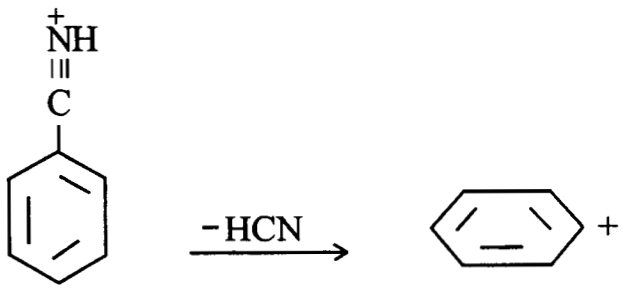
186

Removal of a neutral benzonitrile molecule from the molecular ion results in the peak at 160 mass units which eliminates a neutral molecule of CO giving the fragment ion at m/z = 132.



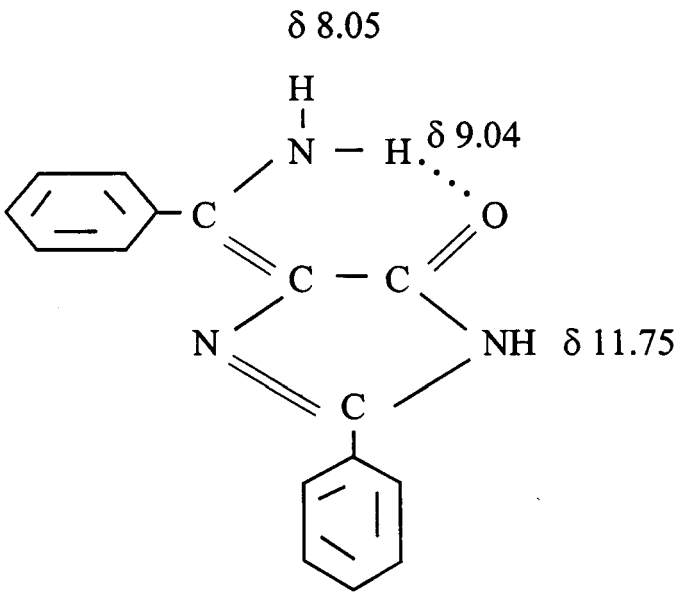
Intense peaks at m/z = 104 and 77 are due to fragmentations given below



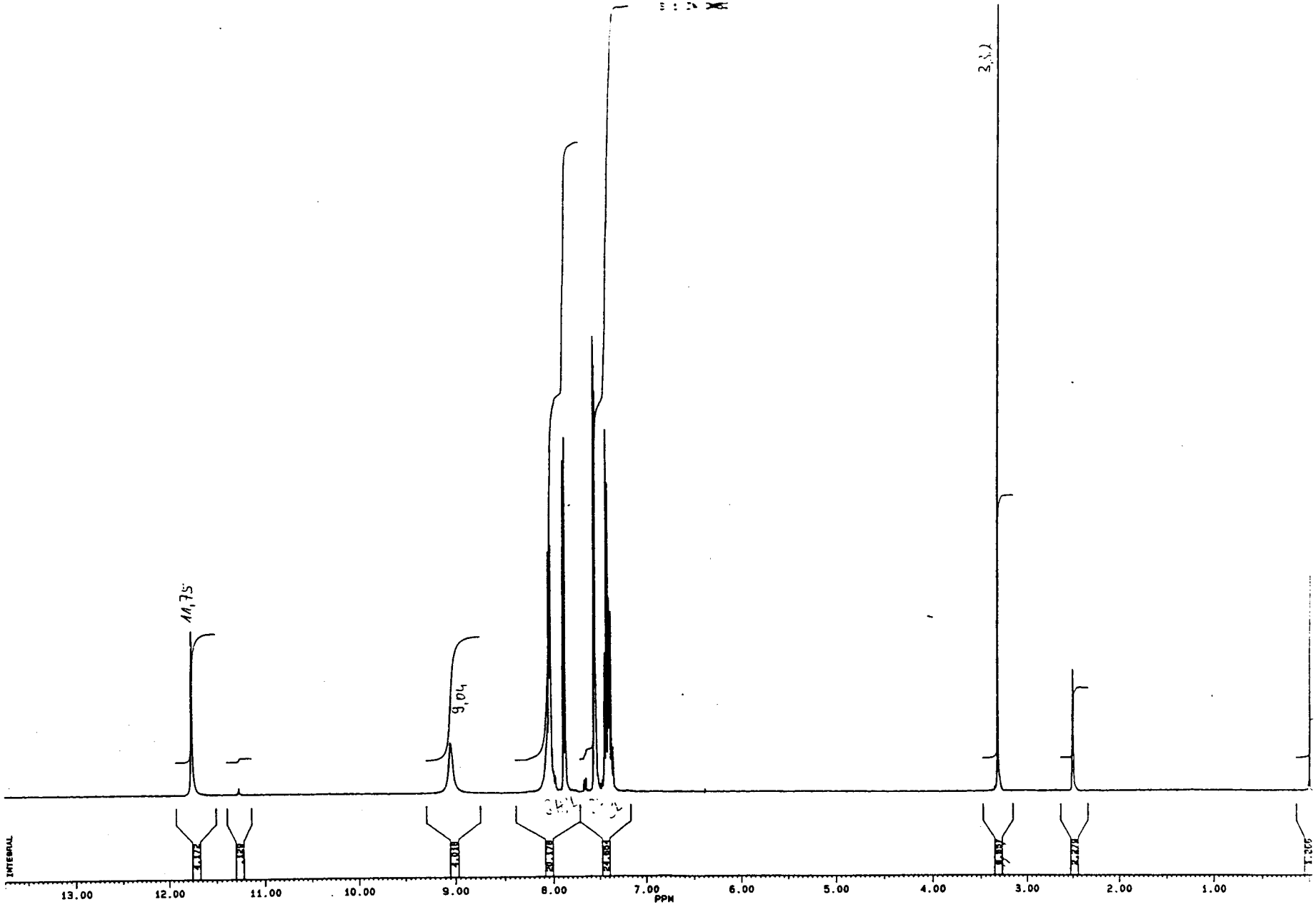


104 77

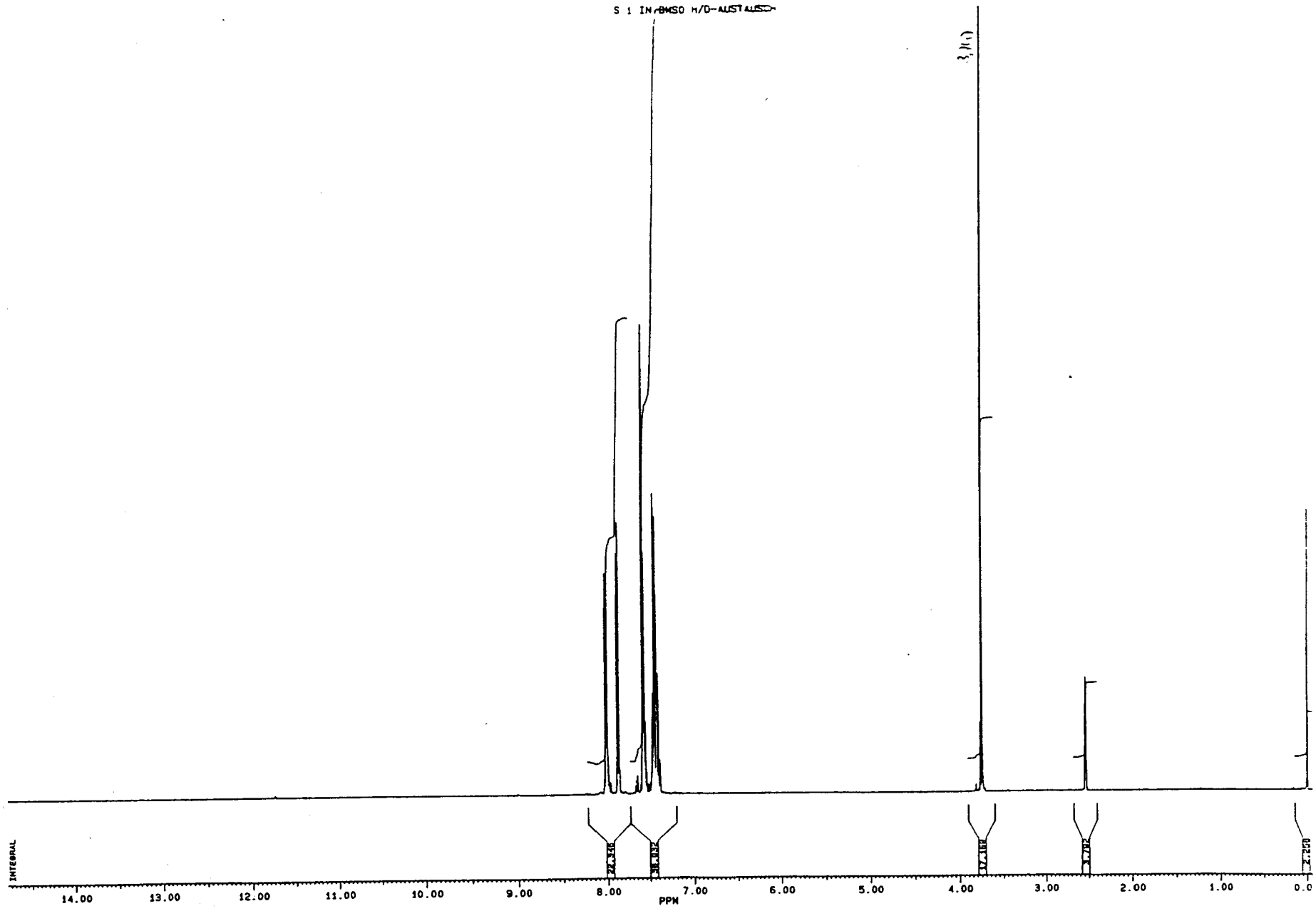
The ^1H nmr spectrum also supported this structure. The - NH - proton in the heterocyclic ring absorbed at a low field of δ 11.75. This is reasonable as - NH - is flanked by the carbonyl group on one side and > C = N - group on the other. It also showed absorptions due to ten aromatic protons and one of the amino protons in the region δ 7.35 - 8.05. The second amino proton absorbed at δ 9.04 as it is engaged in intramolecular hydrogen bonding with the carbonyl group. The proton absorbing at δ 8.05 is burried among the aromatic protons. This fact was confirmed as follows



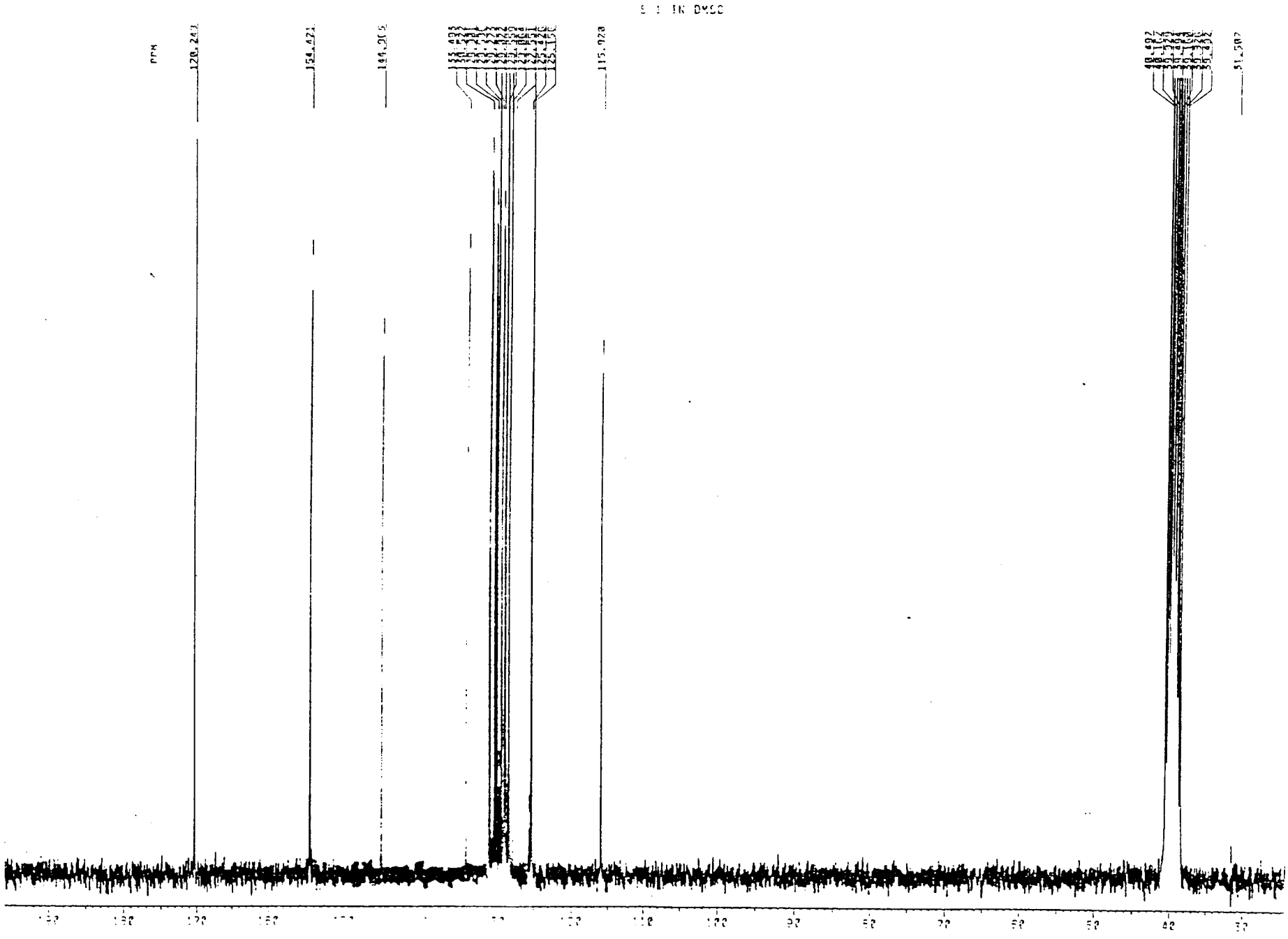
The line of integration in the ^1H nmr spectrum at about δ 8 has two steps, one corresponding to three protons and the other to two protons. The same integration in the nmr spectrum after deuterium exchange also has two steps, but corresponding to two protons each showing the exchangable nature of one of the protons. This test proved the absorption position of this proton at δ 8.05. The other two amino proton absorptions at δ 9.04 and 11.75 also vanished after deuterium wash.



^{1}H nmr spectrum of 4 - (Amino, phenylmethylene) - 2 - phenyl - 2 - imidazolin - 5 - one.



H - D exchange ^{1}H nmr spectrum of 4 - (Amino, phenylmethylene) - 2 - phenyl - 2 - imidazolin - 5 - one.



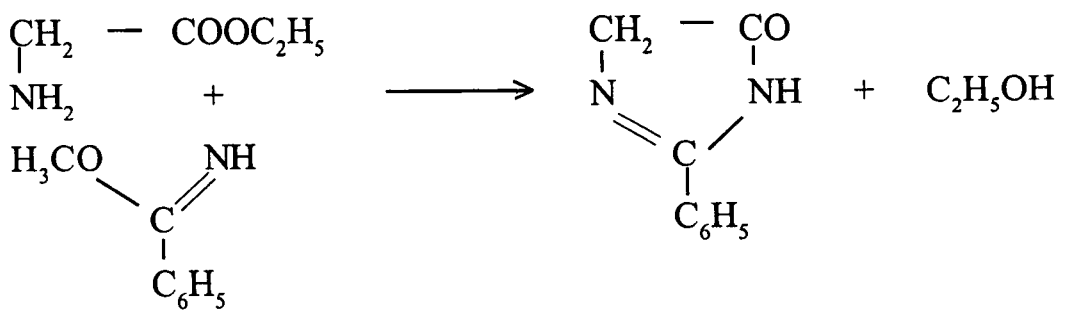
^{13}C nmr spectrum of 4 - (Amino, phenylmethylene) - 2 - phenyl - 2 - imidazolin - 5 - one.

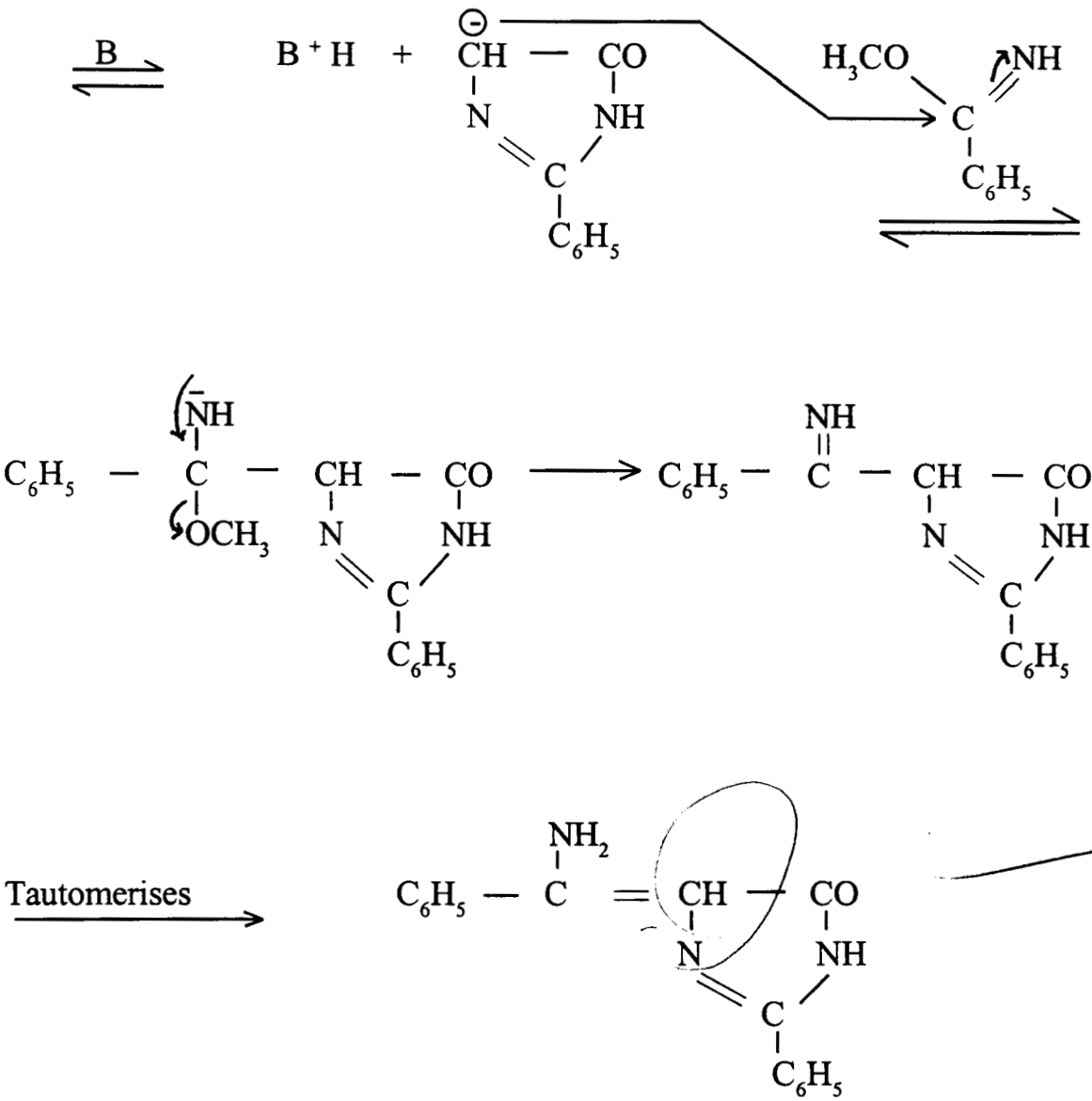
As we find the two protons of the amino group magnetically nonequivalent they are expected to exhibit geminal coupling. But it is not observed. This can be either due to rapid exchange of these two protons or the quadrupole moment of nitrogen. Fast exchange will lead to broadening of the proton absorption which is not observed. Hence this observation can be attributed to the quadrupole moment of nitrogen atom to which the protons are bonded.

The ^{13}C nmr spectrum has 15 peaks in the region δ 115.9 - 170.2 while this compound has only 12 equivalent carbon atoms. This observation can be due to the presence of slight impurity. The carbonyl carbon absorbs at δ 170.2 while the carbon at the second position of the imidazolinone ring which is double bonded to nitrogen at the third position of the ring absorbs at δ 154.4. All other carbons also are sp^2 hybridised and hence absorb between δ 115.9 - 144.9.

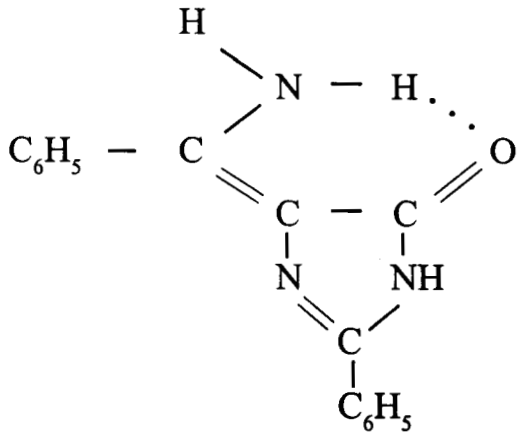
The IR spectrum also is in consistance with the above observations. The doublet expected for a free - NH_2 group is absent, instead a broad peak in the region 3700 - 3000 cm^{-1} with the maximum at 3445 cm^{-1} is observed. The carbonyl absorption is also at a lower frequency of 1666.7 cm^{-1} due to intramolecular hydrogen bonding [The carbonyl absorption frequency of 4 - benzylidene - 2 - phenyl - 2 - imidazolin - 5 - one is 1697.6 cm^{-1} (chapter I)] .

Once the structure of the compound was establised the following mechanism could be proposed for its formation.

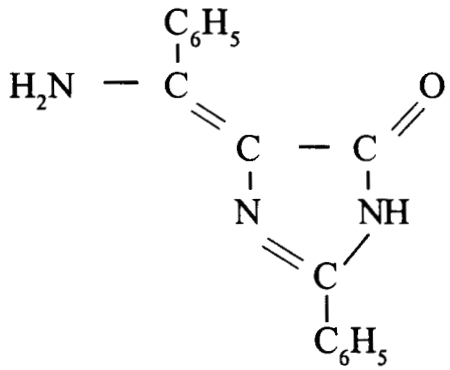




Due to this possible tautomerism two geometrical isomers II A and IIB are possible. However only II A was found to have formed. This can be due to the high thermodynamic stability of this intramolecularly hydrogen bonded isomer



II A



II B

In the synthesis of II given above glycine ester itself can act as the base. In order to increase the yields of the products the general procedure was modified as follows.

Imidic acid ester and glycine ester were taken in the molar ratio 2:1 and heated under reflux in toluene in presence of anhydrous sodium acetete as the base. After 5 hours of refluxing the reaction mixture was kept overnight and filtered. The product was washed twice with 20mL portions of distilled water and finally with 10mL of ether. The imidazolinones thus prepared are given in the table IV - 1. All the three compounds synthesised gave satisfactory analytical data for nitrogen

Table IV - 1

4 - (Amino, arylmethylene) - 2 - aryl - 2 - imidazolin - 5 - ones

Name	Yield (%)	m.p(^{0}C)
1. 4 - (Amino, phenylmethylene) - 2 - phenyl - 2- imidazolin - 5 - one	64	199

2. 4 - (Amino, p - methylphenylmethylene) - 2 - (p - methylphenyl) - 2- imidazolin - 5 - one	63	259
3. 4 - (Amino, m - methylphenylmethylene) - 2 - (m - methylphenyl) - 2 - imidazolin - 5 - one	72	258

Acetylation of 4 - (amino, arylmethylene) - 2 - aryl - 2 - imidazolin - 5 - ones

As amino groups can be easly acetylated by reacting with acetic anhydride it was proposed to attempt it on 4 - (amino, arylmethylene) - 2 - aryl - 2 - imidazolin - 5 - ones. This resulted in the synthesis of three more new compounds.

Results and discussion

In all the three cases 2g of the imidazolinone was stirred with acetic anhydride (2mL) and pyridine (10mL) for 6 hours and poured into ice - cold water and kept in the refrigerator for 4 hours. The product was filtered and washed with water and dried. The three acetyl derivatives synthesised are given in the table IV - 2.

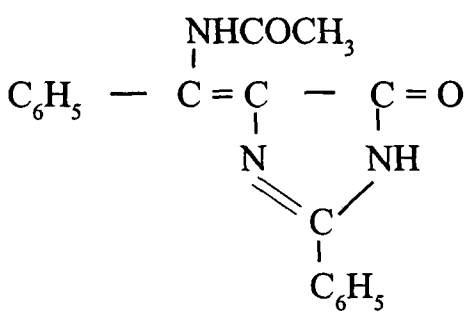
Table IV - 2

4 - (Acetylamino, arylmethylene) - 2 - aryl - 2 - imidazolin - 5 - ones

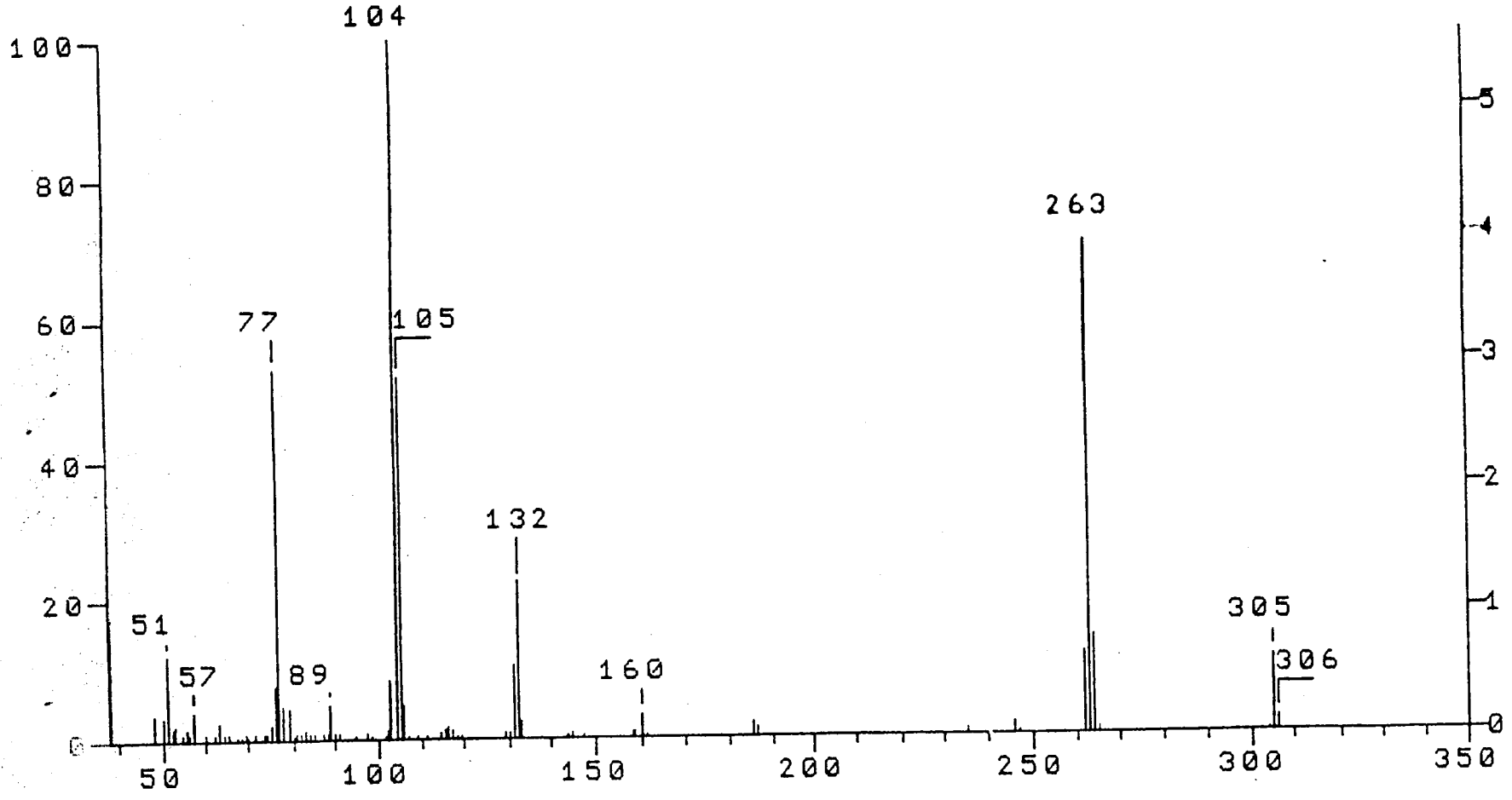
Name	Yield (%)	m.p(^{0}C)
1. 4 - (Acetylamino, phenylmethylene) - 2 - phenyl - 2 - imidazolin - 5 - one	72	275

2. 4 - (Acetylamino, p - methylphenylmethylene) - 2 - (p -methylphenyl) - 2 - imidazolin - 5 - one	65	276
3. 4 - (Acetylamino, m - methylphenylmethylene) - 2 - (m - methylphenyl) -2 - imidazolin - 5 - one	75	273

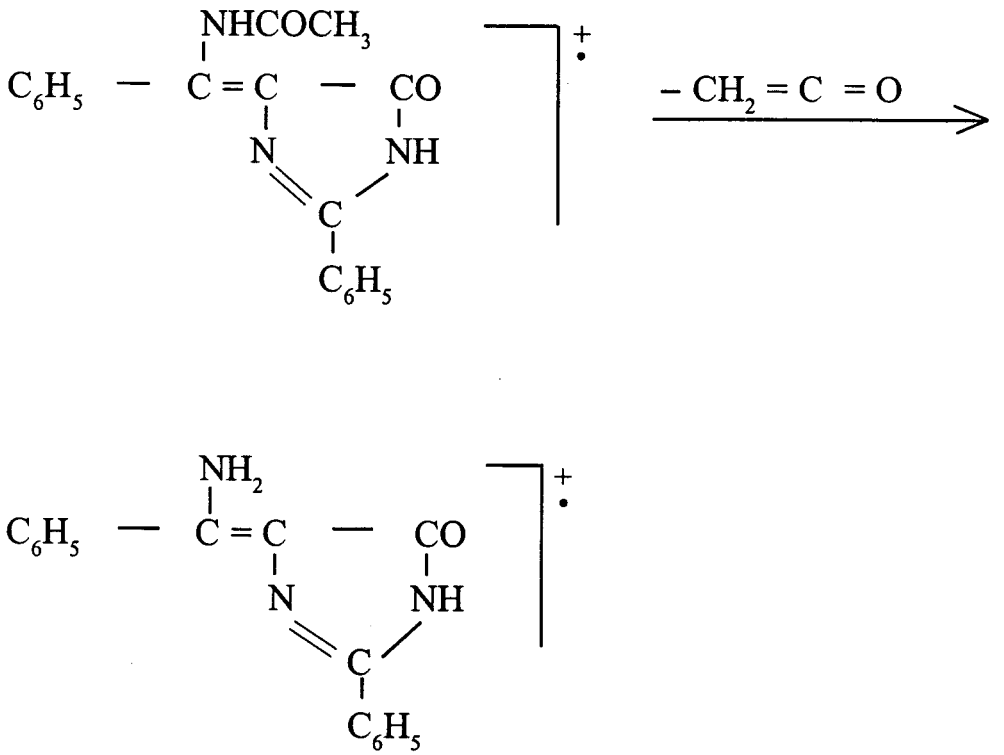
The structure of 4 - (acetylamino, phenylmethylene) - 2 - phenyl - 2 - imidazolin - 5 - one was elucidated from its spectral data. Its mass spectrum gave M^+ peak at m/z = 305 corresponding to the expected structure III. Other peaks are at m/z = 263, 160, 132, 105, 104 (base peak) and 77.



The formation of the fragment with m/z = 263 is as follows. This radical ion is the same as that formed from - 4 - (amino, phenylmethylene) - 2 - phenyl - 2 - imidazolin - 5 - one. other fragment ions were the same as that observed for the unacetylated product. This observation proved its identity.

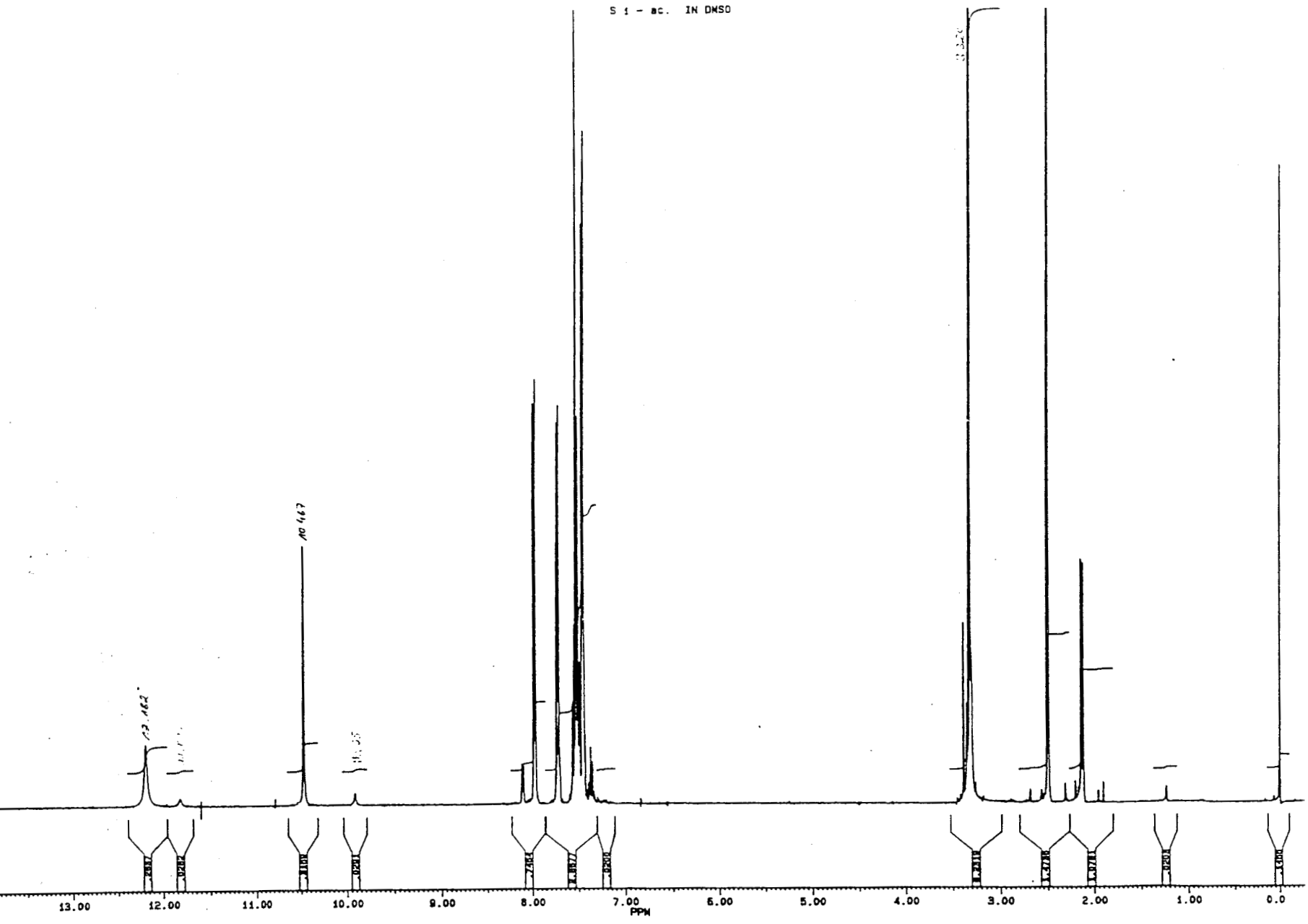


EI - MS of 4 - (Acetylamino, phenylmethylene) - 2 - phenyl - 2 - imidazolin - 5 - one.



The ^1H nmr spectrum showed absorption due to 10 aromatic protons in the region δ 7.4 - 8. A singlet integrating to 3 protons is observed at δ 2.14 corresponding to - CH_3 of the acetyl group. The proton bonded to the nitrogen in the ring absorbs at δ 12.18 and the proton on the amino nitrogen absorbs at δ 10.47 (it is hydrogen bonded to the carbonyl oxygen). These observations also strongly support the proposed structure. All the acetyl derivatives gave satisfactory analytical data for nitrogen.

Wieland and Biener[95] pherographically studied the pigment formed by the reaction between benzimidic acid ester and glycine ester. They observed a whole series of red pigments by this study. But they could not identify their structures. The present work illuminates on this previous report elucidating the structure of one of those compounds or probably two (II A and II B).



^{1}H nmr spectrum of 4 - (Acetylamino, phenylmethylene) - 2 - phenyl - 2 - imidazolin - 5 - one .

Experimental

Melting points recorded using open capillary are uncorrected. All the ^{1}H nmr spectra were recorded on a Bruker AM 360 spectroscope and ^{13}C nmr on a Bruker AC 250 spectroscope using TMS as reference standard. Chemical shifts are recorded in δ values. The mass spectra were recorded on Finnigan TSQ 70 or Finnigan MAT 8200 spectrometers. IR spectra were recorded as KBr pellets using Shimadzu 8101 A FT IR equipment.

Synthesis of starting materials

Glycine ethyl ester, benzimidic acid methyl ester hydrochloride, m-Toluimidic acid ethyl ester hydrochloride were prepared as described in chapter III.

Benzimidic acid methyl ester

Benzimidic acid methyl ester hydrochloride was converted into the free ester essentially according to the method employed by Lehr and coworkers [52] and improved by Kidwai and Devasia [53].

A solution of benzimidic acid methyl ester hydrochloride, (22.2g, 0.13 mole) in 30 mL of water, was placed in a 500mL conical flask. To this ether (60mL) was added, cooled in ice bath and neutralised by slowly adding 16mL of ice cold sodium hydroxide solution(40%). The aqueous layer was saturated with potassium carbonate by keeping the flask in ice bath. The contents of the flask was transferred into a seperatory funnel, shaken well and the ether layer was collected in a 250mL conical flask. The aqueous layer was extracted twice more with 50mL portions of ether. To dry the combined ether extracts anhydrous potassium carbonate was added, the flask was stoppered and placed in the refrigerator for 6 hours. The ether solution of benzimidic acid methyl ester was filtered through a fluted filter paper by decantation and the residue was washed with dry ether. The ether was evapourated under reduced pressure from a cold water bath. The yield of slightly coloured benzimidic acid methyl ester was 17.4g

(100%).

m- Toluimidic acid ethyl ester

A saturated solution of m- toluimidic acid ethyl ester hydrochloride (5g,0.025 mole) in 6 mL of water, was placed in a 250mL conical flask. To this ether (12mL) was added,cooled in ice bath and neutralised by slowly adding 4mL of ice cold sodium hydroxide solution (40%). The contents of the flask was transferred into a seperatory funnel, shaken well and the ether layer was collected in a 250mL conical flask. The aqueous layer was saturated with potassium carbonate and extracted twice more with 6 mL portions of ether. The combined ether extracts were dried with anhydrous potassium carbonate by keeping the flask in the refrigerator for 6 hours. The ether solution of m- toluimidic acid ethyl ester was filtered through a fluted filter paper by decantation and the residue was washed with dry ether. The ether was evaporated under reduced pressure from a cold water bath. The yield of slightly coloured m- toluimidic acid ethyl ester was 4.1g (100%).

p- Toluimidic acid methyl ester hydrochloride

A mixture of p- tolunitrile (35.8mL, 0.3 mole) and absolute methanol (13.3 mL,0.33 mole) was taken in a 250 mL filter flask fitted with a cork carrying an inlet tube. A calcium chloride guard tube was attached to the side arm of the flask and the mixture was cooled in cold water (ice - salt bath cannot be used since the mixture solidifies). Dry hydrogen chloride gas was passed into the mixture till 14g (0.38 mole) of the gas was absorbed. The flask was closed and kept in cold water. Within 30 minutes the reaction mixture solidified into a colourless crystalline mass. Then the flask was allowed to stand in the refrigerator overnight. The hard solid mass of product was powdered and transferred into a 250-mL conical flask. Dry ether (100 mL) was added, the flask was stoppered and placed in the refrigerator overnight. The imidic acid ester hydrochloride was filtered on a sintered glass funnel and washed twice with 25- mL portions of dry

ether. It was dried in a vacuum desiccator over solid potassium hydroxide and phophorous pentoxide. The colourless p- toluimidic acid methyl ester hydrochloride melting at 164- 165°C weighed 55g (99%). Being not very stable at room temperature it was stored in the refrigerator.

p - Toluimidic acid methyl ester

A saturated solution p - toluimidic acid methyl ester hydrochloride (5g,0.027 mole) in 6mL water was placed in a 250mL conical flask. To this ether (12ml) was added, cooled in ice bath and neutralised by slowly adding 4mL of ice cold sodium hydroxide solution (40%). The contents of the flask was transferred into a seperatory funnel, shaken well and the ether layer was collected in a 250mL conical flask. The aqueous layer was saturated with potassium carbonate and extracted twice more with 6 mL portions of ether. The combined ether extracts were dried with anhydrous potassium carbonate by keeping the flask in the refrigerator for 6 hours. The ether solution of p- toluimidic acid methyl ester was filtered through a fluted filter paper by decantation and the residue was washed with dry ether. The ether was evaporated under reduced pressure from a cold water bath. The yield of slightly coloured p- toluimidic acid methyl ester was 4g (100%).

Synthesis of 4 - (amino, arylmethylene) - 2 - aryl - 2 - imidazolin - 5 -one

4 - (Amino, phenylmethylene) -2-phenyl 2- imidazolin -5- one.

Benzimidic acid methyl ester (3.92g, 0.029 mole), glycine ethyl ester (1.49g, 0.0145 mole), anhydrous sodium acetate (3g, 0.0037 mole) and toluene (10 mL) were taken in a 100 mL round bottomed flask, heated under reflux for 5 hours. The product formed was kept as such for a day and filtered, washed twice with 20 mL portions of water and then with 10 mL of ether and dried in the oven at

90°C for one hour. The yellow crystals of 4 - (amino, phenylmethylene) - 2 - phenyl - 2 - imidazolin - 5 - one weighed 4.85g (64%) and melted at 197°C .

Recrystallisation of the imidazolinone from toluene gave yellow crystals melting at 199°C.

Analysis

N(%)

Found : 16.0 , Calculated : 15.96

$C_{16}H_{13}N_3O$

I.R υ (cm^{-1}) 3445, 1666.7, 1639.7, 1603

4 - (Amino, p- methylphenylmethylene) - 2 - (p- methylphenyl) - 2 - imidazolin - 5 - one.

P - Toluimidic acid methyl ester (4.32g, 0.029g), glycine ethyl ester (1.49g, 0.0145 mole), sodium acetate (3g, 0.037 mole), and toluene (15mL) were taken in a 100mL R.B. flask, heated under reflux for 5 hours. The product formed was kept for a day and filtered, washed twice with 20mL portions of water and then with 10mL of ether and dried in the oven at 90°C for one hour. The yellow crystals of 4- (amino, p - methylphenylmethylene) -2-(p- methylphenyl) -2-imidazolin -5- one weighed 4.92g (63%). Recrystallisation of the unsaturated 2 - imidazolin- 5 - one (2.5g) from xylene (50 mL) gave yellow crystals melting at 259°C.

Analysis

N(%)

Found : 14.3

Calculated : 14.38

$C_{18}H_{18}N_3O$

4 - (Amino, m - methylphenylmethylene) - 2 - (m- methylphenyl) - 2 - imidazolin - 5 - one.

m - Toluimidic acid ethyl ester (4.73g, 0.029 mole), glycine ethyl ester (1.49g, 0.0145 mole) and toluene (15mL) were taken in a 100 mL round bottomed flask, heated under reflux for 5 hours. The product formed was kept for a day and filtered, washed twice with 20 mL portions of water and then with 10mL of ether and dried in the oven at 90°C for one hour. The yellow crystals of 4-(amino, m - methylphenylmethylene) - 2 - (m - methylphenyl) - 2 - imidazolin - 5 one weighed 5.02 gm (72 %).

3 gm of 4 - (Amino, m - methylphenylmethylene) - 2 - (m - methylphenyl) - 2 - imidazolin - 5 - one was recrystallised from ethanol. Yellow crystals melted at 258°C.

Analysis

N(%)

Found : 14.4

Calculated : 14.38

$C_{18}\ H_{18}\ N_3O$

Synthesis of 4 - (acetyl amino, aryl methylene) - 2 - aryl - 2 - imidazolin - 5 - one

4 - (Acetylamino, phenylmethylene) -2- phenyl -2- imidazolin -5- one

4 - (Amino, phenylmethylene) -2- phenyl -2- imidazolin -5- one (2g, 0.0076 mole) was taken in a 100mL conical flask. To this pyridine (10mL) and acetic anhydride (2 mL, 0.02 mole) were added and stirred using a magnetic stirrer for

6 hours and then poured into ice - cold water and kept in the refrigerator for 4 hours. The product formed was filtered, washed thrice with 10mL portions of water and dried. The yellow crystals of 4- (acetylamino, phenylmethylene) - 2- phenyl - 2- imidazolin -5- one weighed 1.68g (72%)

4 - (Acetylamino, phenylmethylene) -2- phenyl -2- imidazolin -5- one (1g) was recrystallised from ethyl alcohol (40mL) to give yellow crystals melting at 275°C.

Analysis

N(%)

Found : 14.0

Calculated : 13.77

$C_{18}H_{15}N_3O_2$

4 - (Acetyl amino, p - methylphenylmethylene) -2- (p - methylphenyl) -2- imidazolin - 5 - one

4- (Amino, p - methylphenylmethylene) -2 - (p -methylphenyl) - 2- imidazolin - 5 - one (2g, 0.0069 mole) was taken in a 100 mL conical flask. To this acetic anhydride (2 mL, 0.02 mole) and pyridine (10mL) were added and stirred continously for 6 hours using a magnetic stirrer. Then it was poured into ice cold water and kept in the refrigerator for 4 hours. The yellow crystals of 4 - (acetylamino, p - methylphenylmethylene) - 2 - (p - methylphenyl) - 2 - imidazolin -5 - one formed was filtered, washed thrice with 10 mL portions of water and dried. It weighed 1.5g (65%).

4 - (Acetylamino, p - methylphenylmethylene) - 2 - (p - methylphenyl) - 2 - imidazolin - 5 - one (1gm) was recrystallised from ethanol (30mL). It melted at 276°C.

Analysis

N(%)

Found : 12.6

Calculated : 12.57

$C_{20}H_{20}N_3O_2$

4 - (Acetylamino, m - methylphenylmethylene) - 2 - (m -methylphenyl) - 2 -imidazolin - 5- one

4- (Amino, m - methylphenylmethylene) - 2 - (m- methylphenyl) - 2 - imidazolin- 5- one (2 g 0.0069 mole) was taken in a 100 mL conical flask. To this acetic anhydride (2mL 0.02 mole) and pyridine (10 mL) were added. Stirred continously for 6 hours using a magnetic stirrer. It was then poured into ice - cold water (50 mL) and placed in the refrigerator for 4 hours.The yellow product formed was filtered, washed thrice with 20 mL portions of water and dried. 4-(Acetylamino, m -methylphenylmethylene) - 2 - (m - methylphenyl) - 2- imidazolin - 5 - one weighed 1.5g (75%).

4 - (Acetylamino, m - methylphenylmethylene) - 2- (m - methylphenyl) - 2 -imidazolin - 5 - one (1g) was recrystallised from ethanol (30mL). The yellow crystals melted at 273°C.

Analysis

N(%)

Found : 12.5

Calculated : 12.57

$C_{20}H_{20}N_3O_2$

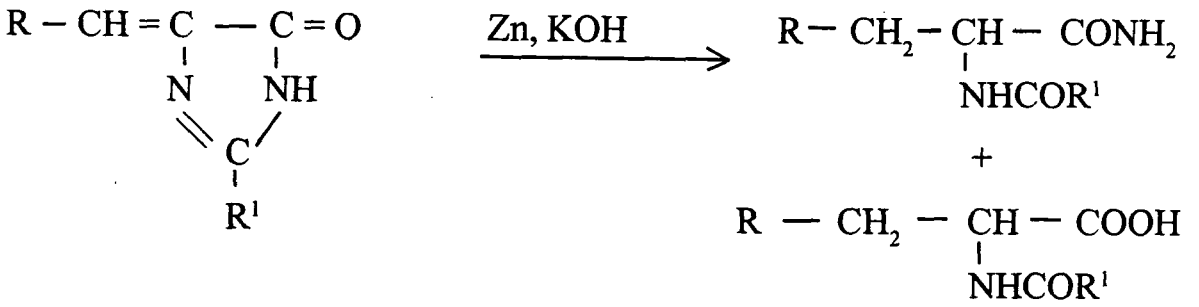
CHAPTER V

Synthesis of acylamino acid amides and acylamino acids

Results and Discussion

In 1975 Devasia and Pillai [54] prepared five benzoylamino acids in 41 - 67 % yields by the simultaneous reduction and hydrolysis of the unsaturated 2 - imidazolin - 5 - ones with a mixture of zinc dust and potassium hydroxide solution. In every case, 2g of the unsaturated 2 - imidazolin - 5 - one was refluxed with a mixture of zinc dust (5g) and 50mL of 14% potassium hydroxide solution for one hour. They observed copious evolution of ammonia due to the hydrolysis of the reduced 2 - imidazolin - 5 - ones, to acylamino acids. After removing the unreacted zinc dust, carbon dioxide was passed through the solution. The mixture of zinc carbonate and impurities precipitated were removed and the solution further purified by extraction with ethyl acetate. The acylamino acid was precipitated from the solution by acidification with hydrochloric acid. It was filtered, washed with ether and recrystallised from glacial acetic acid. Devasia and Shafi [94] improved and employed this method for the synthesis of acylamino acids and acylamino acid amides.

In the present work, several experiments have been carried out by changing the reaction conditions to improve this method and the yields of acylamino acid amides and acylamino acids. But the attempts have not been much successful. However, fairly good conversion of the imidazolinones to the products could be achieved by the reduction and hydrolysis of the unsaturated 2- imidazolin -5- ones. In every case 2g of 4- arylidene-2-m-tolyl-2-imidazolin-5-one was heated under reflux with a mixture of 5g of zinc dust and 100mL of 5% potassium hydroxide solution for one hour.



After cooling to room temperature the precipitated acylamino acid amide along with the zinc dust were filtered off. The acylamino acid amide was recovered from zinc by dissolving in ethanol. The aqueous solution after removal of zinc dust and acylamino acid amide was acidified with concentrated hydrochloric acid to precipitate acylamino acid. This product had a very pale yellow colour, probably due to the presence of small quantities of unhydrolysed imidazolinones, both reduced and unreduced. In order to purify the product it was redissolved in sodium carbonate solution and filtered to remove impurities. The filterate on acidification yielded pure acylamino acids. Table V. I gives the list of the acylamino acid amides and acylamino acids prepared by this method.

It is noteworthy that in the case of the four imidazolinones studied both acylamino acid amides and acylamino acids could be isolated in the same experiment.

TABLE V. 1

Acylamino acid amides and acylamino acids

	Name	Yield(%)	m.p(°C)
	Acylamino acid amides		
1.	N-m-Toluylphenylalanine amide	46	236
2.	N-m-Toluyl(p-methoxyphenyl)-alanine amide	42	258

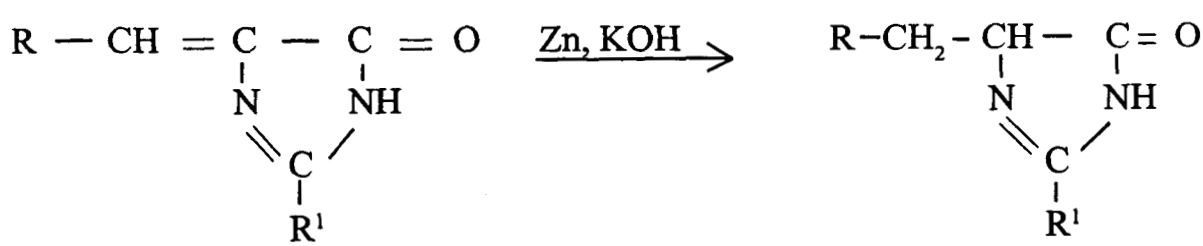
3.	N-m-Toluyl(p-chlorophenyl)-alanine amide	38	262
4.	N-m- Toluyl(3,4- methylene-dioxyphenyl)alanine amide	32	289

Acylamino acids

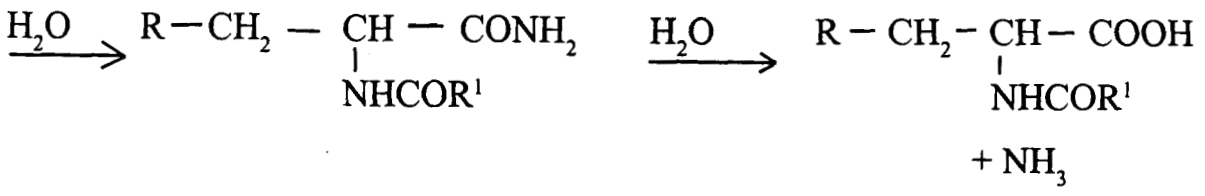
1.	N-m- Toluylphenylalanine	22	165
2.	N-m-Toluyl -O-methyltyrosine	19	196
3.	N-m- Toluyl(p-chlorophenyl)-alanine	24	191
4.	N-m- Toluyl(3,4-methylenedioxy-phenyl)alanine	13	198

Mechanism

Reduction with zinc dust and potassium hydroxide solution provides a typical example of dissolving metal reduction. The exocyclic double bond which is at α, β- position of the carbonyl group is reduced to form the corresponding saturated 2- imidazolin -5- ones. The saturated 2-imidazolin -5- ones (II) then undergo hydrolysis to form acylamino acid amides which on further hydrolysis yield the corresponding acylamino acid.

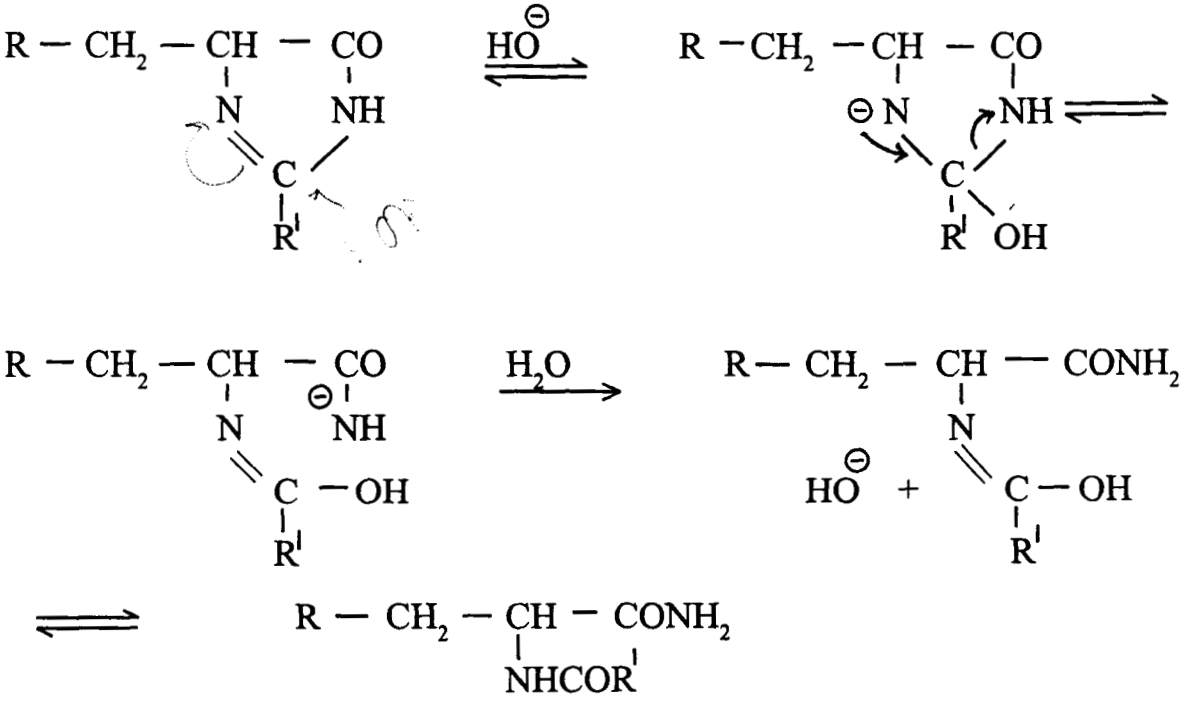


I II

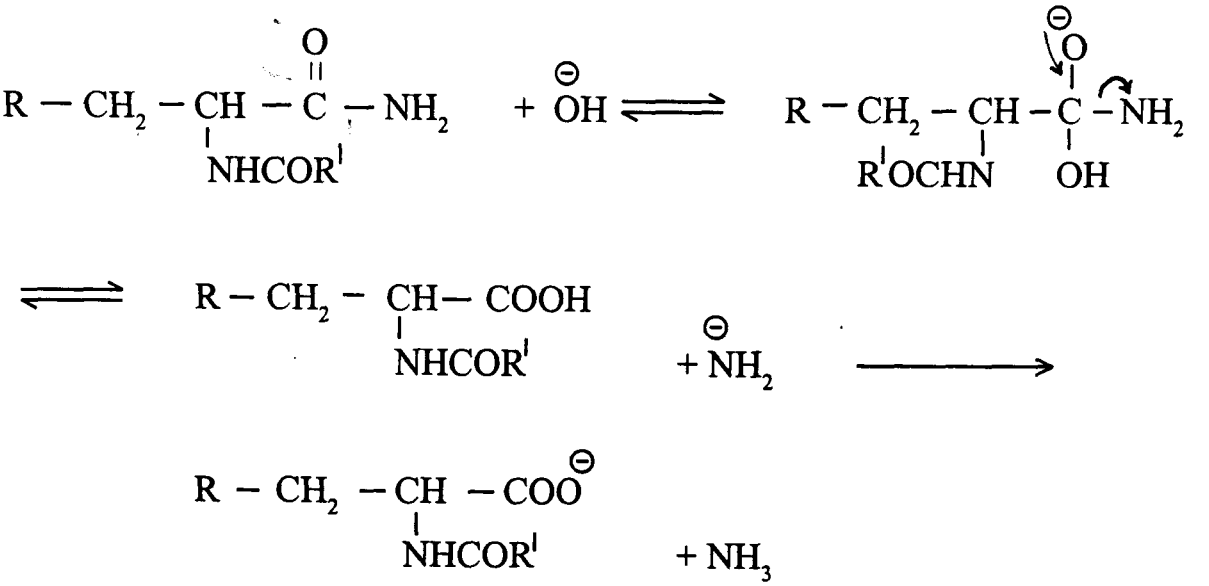


The acylamino acid amides are hydrolysed by the strong alkali used for the reaction. Further this sequence of reduction and hydrolysis is already known in the synthesis of acylamino acid amides and acylamino acids by the hydrolysis of the saturated 2- imidazolin -5- ones obtained from the unsaturated 2- imidazolin-5-ones by catalytic hydrogenation [53] or by hydriodic acid reduction [94]. The mechanism of the hydrolysis of saturated 2- imidazolin -5- ones to acylamino acid amides and that of the hydrolysis of the latter to acylamino acids are as follows.

The formation of acylamino acid amides by the hydrolysis of the saturated 2- imidazolin -5-ones show that the cleavage of the ring takes place at 1-2 linkage. Hence the mechanism can be formulated as follows.



Just like acid amides the acylamino acid amides formed by the hydrolysis of the saturated 2- imidazolin -5-ones undergo further hydrolysis to form acylamino acids and ammonia. The mechanism of the hydrolysis may be formulated as follows.



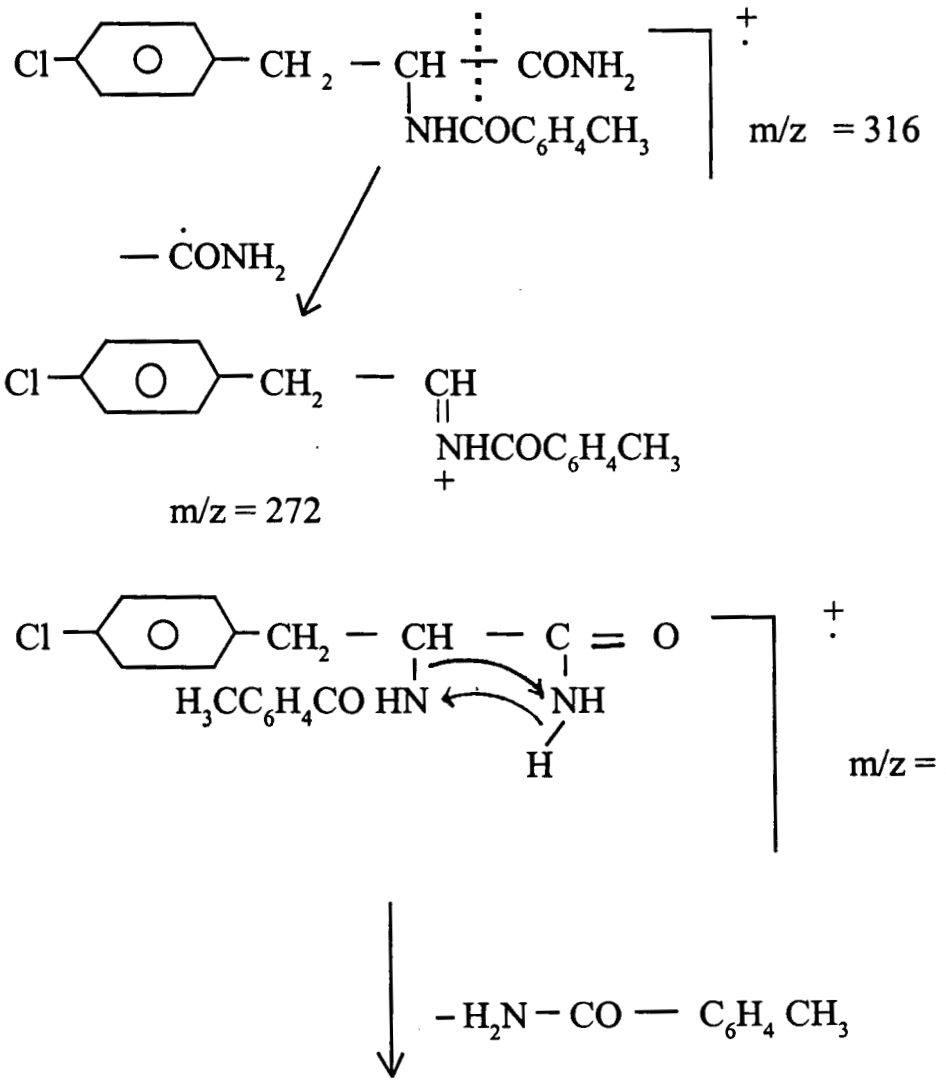
Both potassium and sodium hydroxide solutions were found to be suitable for the reaction but the former gave better yields. In the case of potassium hydroxide best yields were obtained when 2g of the unsaturated 2- imidazolin -5-one was refluxed with a mixture of 5g of zinc dust and 100mL of 5% solution of potassium hydroxide for 1 hour. As per the sequence of hydrolysis higher yields of the acylamino acid could be expected by increasing the time of hydrolysis. However, due to the hydrolysis of the acylamino acids themselves, this result could not be acheived.

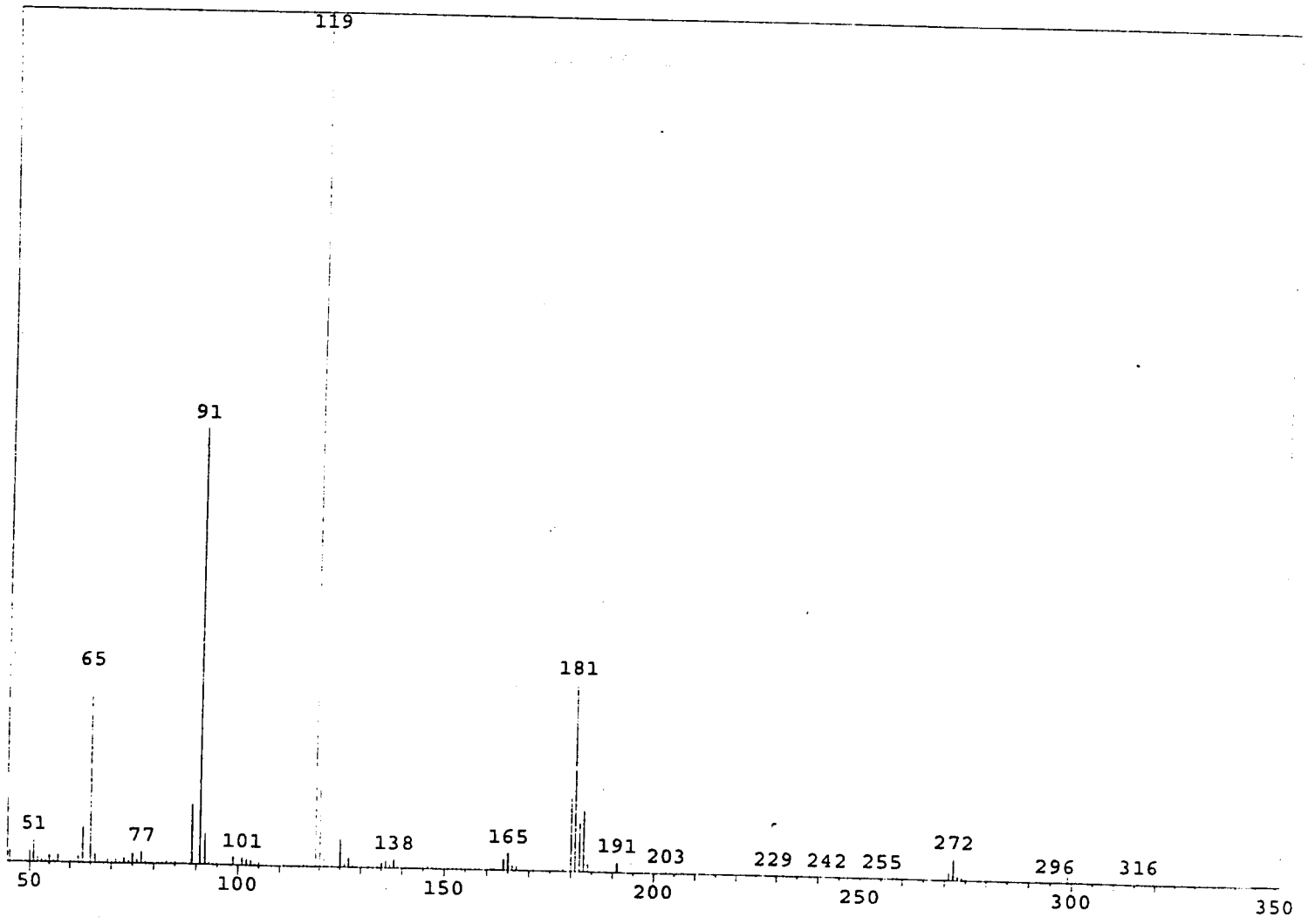
Metals like zinc, tin and aluminium were tried but only zinc was found to be suitable for reduction. The yields of products depended on the purity of zinc dust used for the reaction. When an old stock of zinc dust was used, the yields of products were very low. Hence purification of zinc dust can be recommended for this reaction.

All the acylamino acid amides and acylamino acids prepared are new compounds and gave satisfactory analytical data for nitrogen. In order to confirm the identity of the compounds synthesised, the mass spectra of one acylamino acid amide (N-m - toluyl (p - chlorophenyl) alanine amide) and one acylamino acid (N - m - toluyl - 0 - methyltyrosine) were recorded and found to agree with their structures. The fragmentation patterns were as follows.

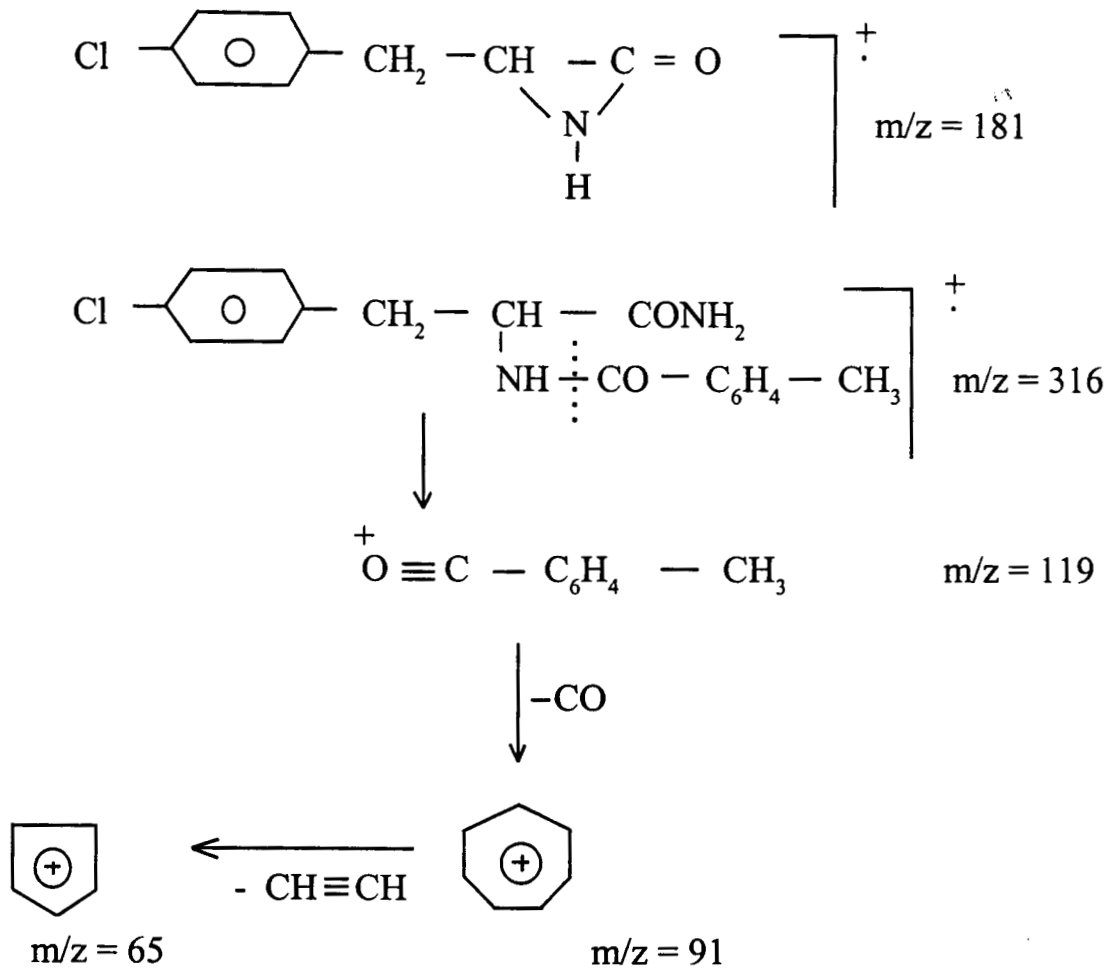
N - m - Toluyl(p - chlorophenyl)alanine amide, $C_{17}H_{17}N_2O_2Cl$

m/z: 316 (M^+, O.19%), 272 (2.5%), 181 (22%)
119 (100%), 91 (51%), 65 (22%) and 51 (2.7%)



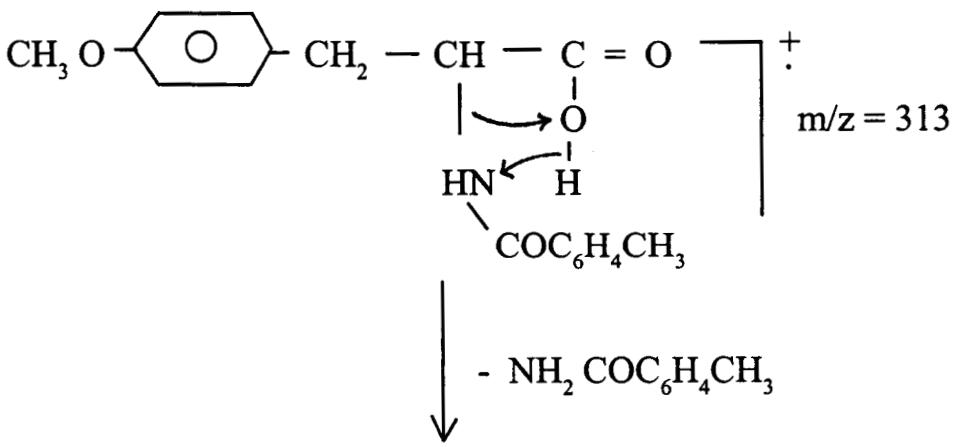


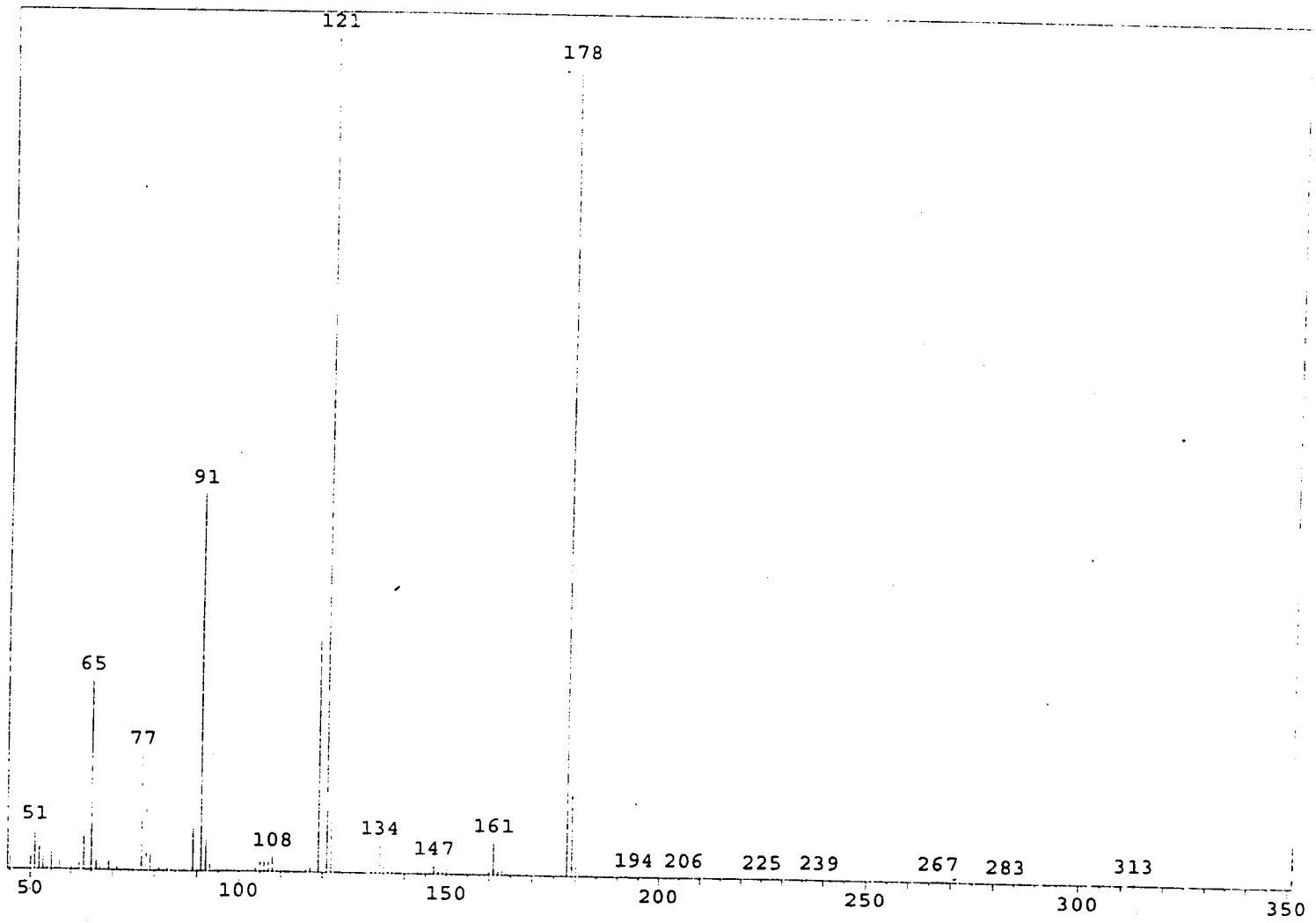
EI - MS of N - m - Toluyl (p-Chlorophenyl) alanine amide.



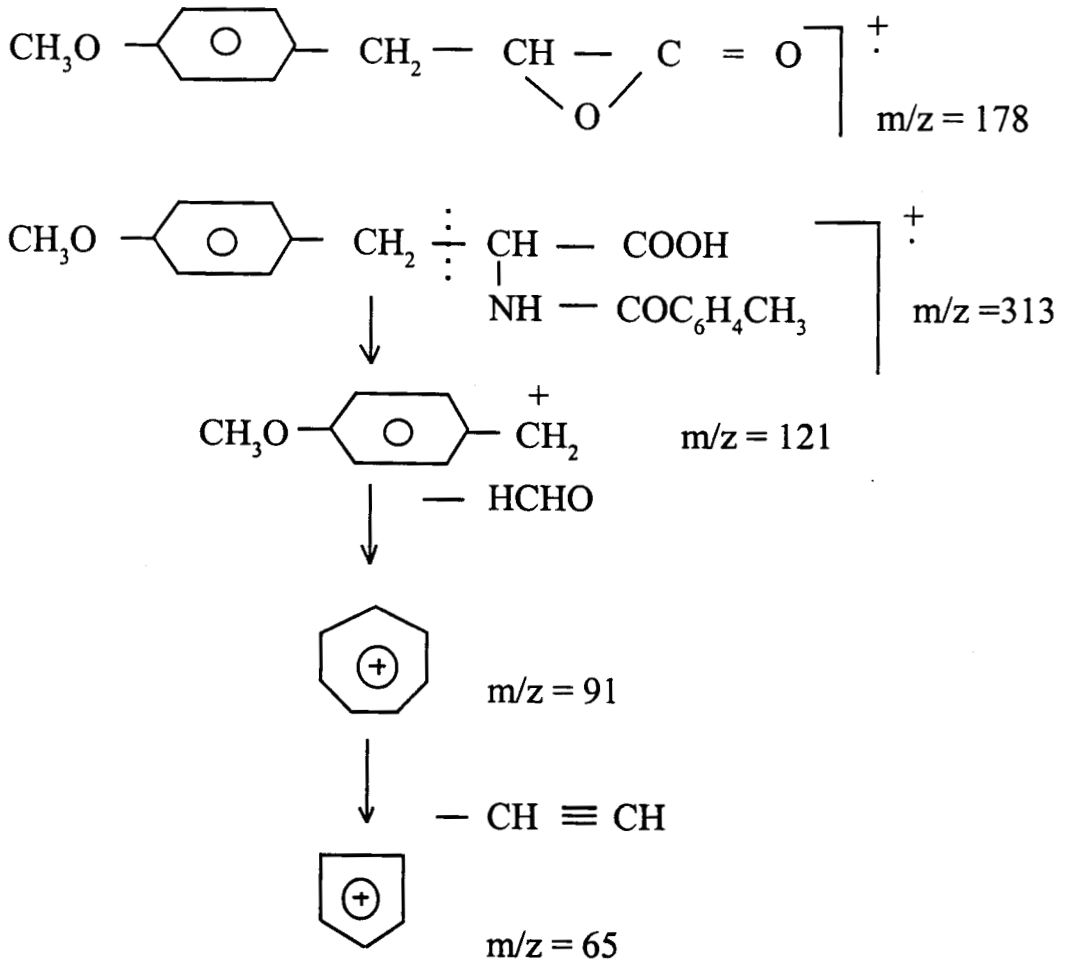
N - m - Toluyl- O -methyltyrosine: $C_{18}H_{17}NO_4$

m/z : 313 (M^+, 0.41%), 178 (94%), 121 (100%), 91 (44%), 65 (22%)





EI - MS of N - m - Toluyl - O - methyltyrosine.



4-Arylidene-2-m-tolyl-2-imidazolin-5-ones if subjected to reduction and hydrolysis under the condition used in earlier works [54, 94] no product could be isolated. However, by this modified method both acylamino acid amide and acylamino acid could be isolated in the same experiment.

Experimental

Melting points recorded using open capillary are uncorrected. Electron impact mass spectra were recorded on finnigan MAT 70 spectrometer.

Synthesis of starting materials

m- Toluimidic acid ethyl ester and glycine ethyl ester were prepared as discribed in chapter IV. The imidazolinones were prepared according to the method of Kidwai and Devasia [53].

4- Benzilydene-2-m- tolyl -2- imidazolin -5-one

m-Toluimidic acid ethyl ester hydrochloride (4.78 g, 0.024 mole), glycine ethyl ester hydrochloride (4.17g,0.03 mole) and sodium bicarbonate (4.8g, 0.057 mole) were quickly mixed in a dry mortar and the mixture was immediately transferred into a 250- mL round- bottomed flask with long neck. Benzaldehyde (2.02 mL, 0.02 mole) and benzene (10mL) were soon added to the mixture and the flask was heated atonce at 72°C with constant shaking in a preheated water bath. There was seperation of esters with vigorous evolution of carbondioxide. Within 10 minutes of heating the unsaturated 2- imidazolin -5-one began to seperate as yellow crystals. Shaking was stopped and the flask was kept vertically clamped in the water bath for another 50 minutes while the temperature of the bath was maintained at about 72°C. The mixture solidified into a yellow mass which turned slightly red. When the flask was removed from the water bath, the solid mass became more red. It was broken with a glass rod, heated with ethanol (50mL) and filtered hot on a sintered glass funnel. The filterate was red coloured. The product was washed thrice with 20mL portions of water and finally with 10 mL of ethanol and dried in the oven at 90°C for one hour. The yellow 2- m-tolyl -4-benzylidene -2- imidazolin -5- one weighed 4.03g (77%) and melted at 254-255°C

4 - (p-Chlorobenzylidene) - 2 - m - tolyl - 2 - imidazolin - 5 - one

p-Chlorobenzaldehyde (2.8 g, 0.02 mole) was condensed with a mixture of m- toluimidic acid ethyl ester hydrochloride (4.78 g, 0.024 mole) and glycine ethyl ester hydrochloride (4.17 g, 0.03 mole) in presence of sodium bicarbonate (4.8g, 0.057 mole) and benzene (10 mL) by heating at about 72°C for one hour. The yellow product melting at 269-270°C weighed 4.3g (73%).

4-p- Methoxybenzylidene -2-m- tolyl- 2- imidazolin -5- one

Anisaldehyde (2.42 mL, 0.02 mole) was condensed with a mixture of m-toluimidic acid ethyl ester hydrochloride (4.78g, 0.024 mole) and glycine ethyl ester hydrochloride (4.17g, 0.03 mole) in the presence of sodium bicarbonate (4.8g, 0.057 mole) and benzene (10 mL) by heating at about 72°C for one hour. The yellow product weighed 4.55g (78%) and melted at 272- 273°C.

4 - (3,4- Methylenedioxybenzylidene) -2- m- tolyl- 2-imidazolin -5-one

Piperonaldehyde (3 mL, 0.02 mole) was condensed with a mixture of m-toluimidic acid ethyl ester hydrochloride (4.78g, 0.024 mole) and glycine ethyl ester hydrochloride (4.17g, 0.03 mole) in the presence of sodium bicarbonate (4.8g, 0.057 mole) and benzene (10 mL) by heating at about 72°C for one hour. The yellow product melting at 232°C weighed 7.34g (65.39%).

Synthesis of acylamino acid amides

N-m- Toluylphenylalanine amide

In a 250-mL round- bottomed flask with ground glass joint was placed a mixture of crude 4- benzylidene -2- m- tolyl -2- imidazolin -5- one (2g), pure zinc dust (5g) and 5% KOH solution (100mL). The mixture was heated under reflux. On boiling the unsaturated 2-imidazolin - 5- one dissolved completely and the flask was shaken occasionally. After one hour of refluxing, the flask was allowed to cool, the acylamino acid amide containing the unreated zinc was

collected by filtration. The amide was dissolved in boiling ethanol (100 mL) and filtered to remove the zinc dust. The solution was then concentrated to about 50 mL and it was allowed to cool. The crystals of amide seperated were filtered and dried. The colourless N- m- Toluylphenylalanine amide weighing 1g (46%) melted at 236°C.

Recrystallisation

N - m- Toluylphenylalanine amide (0.4g) was dissolved in boiling ethanol (40 mL) and filtered. The crystals seperated during the filteration were redissolved and the solution was allowed to stand. White crystals seperated were filtered and dried. It melted sharply at 236°C.

Analysis

N(%)

Found : 10.02

calculated : 9.93

$C_{17}H_{18}N_2O_2$

N- m Toluyl (p - methoxyphenyl)alanine amide

4 - (p - Methoxybenzylidene) - 2 - m - tolyl - 2 - imidazolin - 5 - ones (2g), zinc dust (5g) and 5% potassium hydroxide solution (100 mL) were taken in a 250 - mL round- bottomed flask fitted with a reflux condenser and heated under reflux for one hour. The acylamino acid amide formed was filtered along with the unreacted zinc dust and washed twice with 10mL portions of water. The amide was dissolved in boiling ethanol (100mL) and the solution was filtered to remove the zinc dust. The filtrate was concentrated to about 50mL and allowed

to cool. The amide separated was filtered and dried, The colourless crystals of N-m - toluyl (p - methoxyphenyl) alanine amide weighing 0.88g (42%) melted at 255°C.

The acylamino acid amide was recrystallised from ethanol. The colourless crystals melted at 258°C

Analysis

N(%)

Found : 8.83

Calculated : 8.97

$C_{18}H_{20}N_2O_3$

N-m- Toluyl(p-chlorophenyl)alanine amide

4 - (p - Chlorobenzylidene) - 2 - m - tolyl - 2 - imidazolin - 5 - one (2g), zinc dust (5g) and 5% potassium hydroxide (100mL) were taken in a 250 mL round bottomed flask. Heated under reflux for one hour. The acylamino acid amide formed was filtered together with the unreacted zinc. The amide was then dissloved in boiling ethanol (100mL) and filtered to remove zinc dust. The filtrate was then concentrated to 50 mL and kept for some time. White crystals of N - m - toluyl (p - chlorphenyl) alanine amide weighing 0 .8g (38%) melted at 260°C.

N - m - Toluyl (p - chlorophenyl) alanine amide (0.4g) was dissolved in boiling ethanol (40mL) and filtered, the crystals separated during the filtration

were redissolved and the solution was allowed to stand. White crystals separated were filtered and dried. It melted sharply at 262°C.

Analysis

N(%)

Found : 8.90

Calculated : 8.86

$C_{17}H_{17}N_2O_2Cl$

N - m - Toluyl (3,4 - methylenedioxyphenyl) alanine amide

4 - (3, 4 - Methylenedioxyphenyl) - m - tolyl - 2 - imidazolin - 5 -one (2g), zinc dust (5g), 5% potassium hydroxide solution (100 mL) were taken in a 250-mL round bottomed flask. Heated under reflux for one hour. The acylamino acid amide formed was filtered together with the unreacted zinc. The amide was then dissolved in boiling ethanol (150 mL) and was filtered to remove the zinc dust and the filtrate was concentrated to 75 mL and kept for some time. Colourless crystals of N - m- toluyl (3,4 - methylenedioxyphenyl) alanine amide formed weighing 0.68g (22%) melted at 285°C.

The N - m - Toluyl (3,4 - methylenedioxyphenyl) alanine amide (0.4g) was recrystallised from ethanol, the colourless crystals formed were filtered and dried. It melted sharply at 289°C.

Analysis

N(%)

Found : 8.62

Calculated : 8.59

$C_{18}H_{18}N_2O_4$

Synthesis of acylamino acids

N - m - Toluylphenylalanine

The filtrate obtained after the removal of N - m - Toluylphenylalanine amide and zinc dust was neutralised with conc. HCl. The product formed was filtered and stirred with saturated sodium carbonate solution. The insoluble materials were recovered by filteration. The filtrate was acidified with conc. HCl to precipitate acylamino acid. It was then filtered, washed twice with 10mL portions of water and dried. The colourless crystals of N - m - toluylphenylalanine weighed 0.48g and melted at 162°C.

N - m - Toluylphenylalanine was recrystallised from 50% ethanol. The colourless crystals melted at 165°C.

Analysis

N(%)

Found : 4.97

Calculated : 4.95

$C_{17}H_{17}NO_3$

N - m - Toluyl - O - methyltyrosine

The filtrate obtained after removal of N - m - toluyl (p-methoxyphenyl) alanine amide and zinc dust was neutralised with conc. hydrochloric acid. The product formed was filtered and stirred with saturated sodium carbonate solution. The insoluble materials were removed by filtration. The filtrate was acidified with conc. HCl to precipitate acylamino acid. It was filtered, washed twice with 10 mL portions of water and dried. The colourless crystals of N - m - toluyl

- O - methyltyrosine weighed 0.4g and melted at 195°C.

The acylamino acid was recrystallised from 50% ethanol. The crystals melted at 196°C

Analysis

N(%)

Found : 4.47

Calculated : 4.50

$C_{18}H_{17}NO_4$

N- m - Toluyl(p-chlorophenyl)alanine

The filtrate obtained after removal of N-m - toluyl (p - chlorophenyl) alanine amide and zinc dust was neutralised with conc. hydrochloric acid. The product formed was filtered and stirred with saturated sodium carbonate solution. The insoluble materials were removed by filtration. The filtrate was acidified with conc. HCl to precipitate acylamino acid. It was filtered, washed twice with 10 mL portions of water and dried. The colourless crystals of N - m - toluyl (p - chlorophenyl) alanine weighed 0.52g and melted 190°C.

N - m - Toluyl(p - chlorophenyl)alanine was recrystallised from 50 % ethanol. The colourless crystals melted at 191°C.

Analysis

N(%)

Found : 4.46

Calculated : 4.42

$C_{17}H_{16}NO_3Cl$

N - m - Toluyl(3,4 - methylenedioxyphenyl)alanine

The filtrate obtained after removal of N - m - toluyl (3,4 methylene dioxyphenyl) alanine amide and zinc dust was neutralised with conc. HCl. The product formed was filtered and stirred with saturated sodium carbonate solution. The insoluble materials were removed by filtration. The filtrate was acidified with conc. HCl to precipitate acylamino acid. It was filtered, washed with 10mL portions of water and dried. The colourless crystals of N - m - toluyl (3,4 - methylenedioxyphenyl) alanine weighed 0.32g and melted at 195°C.

N - m - Toluyl(3,4 - methylenedioxyphenyl)alanine was recrystallised from 50% ethanol. The colourless crystals melted at 198°C.

Analisis

N(%)

Found : 4.28

Calculated : 4.30

$C_{18}H_{17}O_5N$

REFERENCES

1. Ruheman, S; cunnington. A.V; J. Chem. Soc., **75** (1899), 954.
2. Hofmann, K., " The chemistry of heterocyclic compounds," Vol VI, edited by A. Weissberger (Interscience, New York), 1953, 93.
3. Erlenmeyer, E; Ber, **33** (1900), 2036.
4. Erlenmeyer, E; Ann, **337** (1904), 265.
5. Erlenmeyer, E; Matter, O; Ann, **337** (1904), 271.
6. Erlenmeyer, E; Staldin, W; Ann, **337** (1904) 283.
7. Erlenmeyer, E; Weittenberg, F; Ann, **337** (1904) , 294.
8. Williams, D.L; Ronzio, A.R; J.Am. Chem.Soc, **68** (1946), 647.
9. Cornforth, J.W; Huang, H.T; J.Chem. Soc, (1948) , 731
10. Kjaer, A; Acta. Chem.scand, **7** (1953), 900.
11. Harhash; A.H., Latif, N.A; Aziz, A.A; Indian J. Chem, **9** (1971) 789
12. Tiwari S.S; Satsangi, R.K; J. Indian. Chem. Soc **56** (1979), 526.
13. Gupta; Anil. K. Sen Gupta; Anurag Ateet; J.Indian. Chem. Soc, **58** (1981), 279.
14. Badr M.Z; El - Sharief; H.A.H; Tadros, M.E; Indian. J. Chem. Sect B, **20B (2)** (1981), 1093.
15. Mukerji; Dev.Das; Nautiyal; Sudha Rani; Prasad; Chinta Ram; Pol.J. Parmacol. Pharm., **33(6)** (1981), 633.
16. El - Sharief, A.M.S; Harb; A.A; Ind.J. Chem Sect. B, **21B (5)**, 1982, 449
17. Pandy V.K; Lohani, H.C; Curr. Sci **51 (9)** (1982), 460
18. Nelepa; Karel; Metala, Leopold; Acta Univ. Dalacki, Olomac, Fac. Rerun, Nat, **69** (chem 20) 1981, 95.
19. Sengupta, Anil. K; Gupta, M.M; Gupta, Anurag Ateet; Indian. Drugs, **20(2)** (1982), 55.

20. Mohan, Raji, V.R; Agarwal , Chapla; Agarwal, Rajesh; Misra, Vinay. S; Pharmacol. Res. Commun, **16 (4)** (1984) 321.

21. Islam, A.M; El- Sharief, A.M.S; Ismail, I.M; Harb. A.A; Egypt. J. Chem, **26 (3)** (1983), 221.

22. Sengupta, Anil K; Rastogi , Anita; Acta. Prarm. Jugol; **34 (4)** 1984, 215.

23. Sengupta, Anil. K ; Gupta, Anurag Ateet ; J. Ind. Chem .Soc., **61 (8)** (1984), 724.

24. Kidwai, Muzahir; M, Khan; Naseem, A ; J. Nepal. Chem. Soc, **1 (1)** (1981), 39.

25. Hassan, H.M; El - Fedawy, M; El - Zimity. M.T; Indian J. Technol., **23(12)** (1985) , 473.

26. El - Sharief, A.M.S; Abd - El - Maged, M.F; Hammad, N.I.S; Ammar Y.A; Harb. A.A; J. Chem., **28 (1)** (1985), (pub 1986), 1.

27. Dave, A.M ; Bhatt, K.N; Undavia, N.K; Trivedi, P.B; J.Indian. Chem.Soc., **64 (6)** (1987), 348

28. Dave, A.M; Bhatt, K.N; Undavia, N.K; Trivedi. P.B; J. Indian. Chem. Soc., **65 (4),** (1988), 294

29. Eld, Mohga, M; Badawag, M.A; Mansour, A.K; J. Heterocycl. Chem, **25(6)** (1988), 1813.

30. Harb, A.A; Elagamy, A.A; Khodeir. M.N.M; Egpt. J. Pharm. Soc, **29 (1 - 4)** (1988), 279.

31. Kumar, Atal; Verma, M; Indian J. Chem. Sect B, **27 B (3)** (1988), 301.

32. Girges, Margret; Mansour; El - Zahab; Mohamed Mahmoud Abou; Hanna, Moktar, Ayad; Collect, Czech. Chem. Commun, **54 (4)** (1989), 1096.

33. Prameela, B; Rajanavendar, E; Murthy, A, Krishna; Collect, Czech. Chem. Commun., **54 (4)** (1989), 1092.

34. Moharram; Hussieny Hamed; J. Serb. Chem. Soc., **54 (2)** (1989), 75.

35. Ismail, M, Fakry; Kandile, N, Garib; Asian. J. Chem., **1 (3),** (1989), 254.

36. Badr, Mohmoud ; Zarief, amin; Tadros; Magda, Ebeid; J. Chem. Soc., Pak.**11 (2),** (1989), 150.

37. Sree Vastava, Archan Jyothi ; Swaroop, Sanjay; Saxena, V.K; Chowdhury, B.L ; Sree vastava; P ponam; Indian .J. Pharm. Sci, **51 (6)** (1989), 238.

38. Misra, Upma; Pathk. A.K; Tiwari, D.C; Singh, Amarika; Indian Drugs, **27 (12),** (1990), 607.

39. Shrimali, Menakoshi; Kalsi; Reena, Sah; Renu, Barthwal. J.D; J. Indian. Chem Soc., **67 (9)** (1990), 748.

40. Mathur. K.C ; Sahay, R; J. Indian. Chem. Soc., **67 (10)** (1990), 856.

41. Husian, M. Imtiaz ; Kumar, Vinay; J. Indian. Chem. Soc., **68 (2)** (1991), 102.

42. Upadhyay, Parekh; Pandya, Ajay; Parekh, Hansa; J. Indian. Chem. Soc., **68(5)** (1991), 296

43. Husian, M. Imtaiz; Kumar, Vinay; Indian. J, Chem. Sect. B, **31 B (4)** (1992), 285.

44. Upadhyay. P.S; Joshi. H.D; Baxi. A.J; Parekh. A.R ; Indian. J. Herocycl. Chem, **1 (2)** (1991) , 71.

45. Jolly. V.S; Pathak, Manish; J. Indian Chem. Soc., **68 (11)** (1991), 1388.

46. Bhalla, Manish; Naithani, P.K; Bhalla. T.N; Sexena. A.K ; Shankar. K ; J. Indian. Chem. Soc., **69 (19),** (1992), 594.

47. Ekeley, J.B; Ronzio, A.R; J.Am. Chem. Soc, **57** (1935), 1353

48. Ekeley, J.B; Elliot, J.L. J.Am. Chem. Soc, **58** (1936), 163

49. Finger, H; J. Prakt. Chem, (2) **76** (1907), 93.

50. Finger, H ; Zeh, W; J. Prakt. Chem, (2) **82** (1910), 50.

51. Kjaer, A; Acta. Chem. Scand; 7 (1953), 1030.
52. Lehr, H; Karlan, S; Goldberg, M.W; J. Am. Chem.Soc., **75** (1953), 3640.
53. Kidwai, A.A; Devasia, G.M; J. Org. Chem, **27** (1962), 4527.
54. Devasia, G.M ; Pillai, C.R; Tetrahedron Lett, (1975) 4053
55. Previero, A; Barry, L.G ; Previero, M.A; Febs. Lett, (1969), 225.
56. Daiichi, Seiyaka, Co Ltd; Jpn Kokai Tokkyo Koho JP 8253, 466 (Cl Co 7D 233 / 58) 30 March 1982, Apl 80/128, 744, 17, Sep 1980; 3 PP,C.A.Vol. 97,1982, 922842.
57. Griffiths, Gareth ; Imwinkelried, Rane ; Gosteli Jacques, (Lonza AG) Evr. Pat. Appl. EP. 614892 (Cl Co 7 D 233/68), 14 Sep (1994) CH Appl. 93 / 749, 12 Mar, (1993), 8 PP, C.A. Vol. 121,1994, 2307722.
58. Devasia, G.M; Tetrahedron Lett, (1976), 571.
59. Devasia,G.M ; Shafi. P.M; Indian J. Chem., Sect B, **17 B (5)** (1979), 526.
60. Devasia, G.M; Shafi; P.M; Indian. J.Chem. Sect. B, **20B (8)** (1981), 657.
61. Shafi. P. Mohammed; Curr. Sci, **54 (23)** (1985) 1231.
62. Husain, M.I; Gupta, Kiran Bala ; Indian Drugs, **20 (8)** (1983) , 311.
63. Ashare, Ram ; Mukerjee, Arya. K; Chem. Ind. (London), **18** (1985), 627.
64. Saxena, Sushama; Verma. M; Sexna. A.K ; Sanker. K; Indian. J. Hetrocycl. Chem., **1 (1)** (1991) , 34.
65. Previero, A ; Barry, L.G; previero, M.A ; Febs. Lett., (1969), 225.
66. Badshah, A; Khan. N.H; Kidwai, A.R. J. Org. Chem., **37** (1972), 2916.
67. Ali. M; Khan, N.H; Siddiqui, A.A; Synth. Commun, **6** (1976), 227.
68. Ali. R.M; Khan. N.H; Synth. Commun, **8 (7)** (1978), 497.
69. Aktiebolaget, A.A. K.F ; Ger. 1, 141, 281, Chem. Abstr. **58**(1963), 1282 B.

70. Greenstein, J.P ; Winitz, M; "Chemistry of the ameino acids" **Vol. II** (John. Wiley , Nwe York), 1961, 715.

71. Greenstein, J.P; winitz, M. " Chemistry of the armino acids" **Vol. II** (John Wiley, New York), 1961, 804.

72. Plochl .J; Ber, **16** (1883), 2815.

73. Erlenmeyer, E; Ann, **275** (1893), 1

74. Erlenmeyer, E; Halsey, J.T; Ber ; **30** (1897), 2981

75. Erlenmeyer, E; Halsey, J.T; Ann, **307** (1899), 138.

76. Erlenmeyer, E ; Kunlin, J; Ann, **316** (1901), 145.

77. Fischer, E; Mouneyrat, A; Ber., **33** (1900), 2383.

78. Fischer, E; Ber., **32** (1899), 3638.

79. Ellinger, A; Flamand, C; Ber., **40** (1907), 3029.

80. Ellinger, A; Flamand, C; Z. Physiol. Chem, **55** (1908), 8.

81. Pyman, F.L; J.Chem. Soc, **109** (1916), 186.

82. Lanb, J; Robson, W; J. Biochem, **25** (1931), 1231

83. Attenburrow, J; Elliot, D.F; Penny, G.F; J.Chem. Soc, (1948), 310.

84. Terentev, A.P; Gracheva, R.A; Mikhailova, N.M; Zh. Obsch.Khim,**33** (1963), 58.

85. Morgenstern, A.P; Suchijit C; Nauta, W. Th; J. Chem. Soc.,**22** (1971)3706

86. Schubel, H; Jansem, P; Ratz, H; Fr. Damande; 2, 081, 389; C.A. Vol.77,1972 , 3706.

87. Hamaguchi. H ; Japan Kokai, 7238, 919; C.A Vol., **78** (1973), 98015.

88. Berntsson, P.B; Vastra, F; Gaarder, J.O; Lamm,B.B; Ger. Offen. 2, 243,665; C.A, Vol. 79, 1973, 19116.

89. Akashi, H; Yuki, Gosei Kagaliu Kyokai Shi, **32 (3)** (1973), 200.

90. Schnettler, R.A; Sah, J.T; U.S 3, 856, 854; C.A. Vol. **82** 1975 112251

91. Matta, M.S ; Kelly, J.A; Rohde, M.F; U.S. 3, 878, 043;C.A. Vol. **83** 1975, 164578.

92. Miyazawa, J; Nagai, T; Yarnada, T; Kuwata, S; Watanabe, H; Mem. Konan. Univ. Sci. Ser **23** (1979), 51.

93. Furuya.Y; Hirowata. N; Japan. Kokai Tokkyo Kcho, 8027, 129; C.A. Vol. **93,** 1980, 47202.

94. G.M. Devasia; P.M. Shafi; Indian J. Chem. Sec. B **19** (1980) 70.

95. Wieland, T ; Biner, H ; Tetrahedron, **15** (1961), 1

96. Bellamy, L.J ; "The infra red spetra of complex molecules" Vol. I, Edn. 3 (Chapman and Hall) London, 1975, p.242.

97. Bellamy, L.J ; " The infra red spectra of complex molecules" Vol. I, Edn. 3 (Chapman and Hall) London, 1975, p.300

98. Curtius, T ; Goebel, F ; J. Prakt. Chem., (2) **37** (1888), 150

99. Harries, C ; Wiess, M ; Ann.**327** (1903), 355.

100. Chambers, R.W ; Carpenter, F.H ; J. Am. Chem. Soc., **77** (1955), 1522.

101. Fischer, E ; Sitzungsber ; Akad. Wiss. Berlin, **48** (1900), 1062.

102. Fischer, E ; Ber ; **34** (1901), 433.

103. "Dictionary of Organic Compounds", Vol. 3 (Eyre & Spottiswoode publishers Ltd. E & FN SPON Ltd.), London.

104. M.Z.A, Bads etal ; Ind. J. Chem. **18B**, (1979).

105. I.R, Dushinsky ; V.S. Appl. **2**, 707, 186, C.A. Vol. 50, 1956, 5766.

106. S.S, Tiwari ; Agarwal ; R.K, Satsangi ; Ind. J.Chem., **56** (1979), 627.

107. S.S, Tiwari ; Agarwal ; R.K, Satsangi ; Ind. J.Chem., **57** (1979), 1040.

108. S.S, Tiwari ; R, Agarwal ; R.K, Satsangi ; Ind. J. Chem., **57** (1980), 1040.

109. D. Mukerji ; S.R, Nautiyi ; C.K. Prasad ; Indian Drugs, **18** (1981), 125.

110. M, Verma ; A.K, Chaturvedi ; A, Chaudhari ; S.S, Parmar ; J. Pharm. Sci, **63**(1974), 1740.

111. S.S, Tiwari ; R.K, Satsangi ; J. Ind. Chem. Soc., **56** (1979), 627.

112. Cranacher, C ; Mahler, M ; Helv. Chim. Acta, **10** (1927), 246.

113. Narang, K.S ; Raj, J.N ; J. Chem. Soc., (1931), 976.

114. S.S, Tiwari ; R.K, Satsangi ;Ind. J. Chem. **56** (1979), 1979.

115. A.I. Vogel, " A Text book of Practical Organic Chemistry " 3rd Edn. (ELBS & Longman Group Ltd.), 1956, p. 584.

116. A.I. Vogel, " A Text book of Practical Organic Chemistry " 3rd Edn. (ELBS & Longman Group Ltd.), 1956, p. 246.

117. R. Adams " Organic Reactions " Vol. III, Wiely, NewYork, 1947, p. 198.

118. Pinner ; A; Ber ; **61** (1883), 1643.

119. Hill, A.J ; Rabinowitz, I ; J. Am. Chem. Soc., **48** (1926), 732.

120. Mc Elvain, S.M ; Nelson, J.W ; J. Am. Chem. Soc., **64** (1942), 1852.

121. Vila, J.P ; Jarque. R.G ; Anales fis. y. quim., **40** (1944), 248

122. Mackenzia, C.A ; Schmidt, G.A ; Webb, L.R ; J. Am. Chem. Soc., **73** (1951), 4990

123. Holly ,F.N ; Stammer, C.H; U.S. Pat. **2**, 772, 281 ; C.A. Vol. 51, 1957, 8145.

124. Thomas, P.R ; Tylor, G.J ; J. Chem. Soc., (1957) 2197, 125.

125. Cuvigny, T ; Bull . Soc. Chim. France, (1957), 655.

126. Atta - ur - Rahaman & M.I, Chaudhary ; "Solving problems with NMR spectroscopy ", Academic press (NewYork), 1996 p. 271 .

127. Atta - ur - Rahaman & M.I, Chaudhary ; "Solving problems with NMR spectroscopy ", Academic press (NewYork), 1996 p. 273.