A Search for Nonsteroidal Anti-Inflammatory Compounds

Part II

Department of Chemical Technology, Dr. Babasaheb Ambedkar Marathwada University
Ph.D. Thesis
Introduction

Pyridine is a six member ring with nitrogen as a hetero atom. In pyridine the unshared pair of electron is present in a Sp² orbital having an axis in the plane of the ring. Therefore, these electrons cannot be delocalised by interaction with the aromatic π-electrons. Since the electron density is somewhat greater at the nitrogen than the carbon atom it might be predicted that the total electron density at the nitrogen should make pyridine at least a strong base as the alkyl amines. Pyridine is much less basic than expected. The electron density of nitrogen atom of pyridine can be similar to that of alkyl amines but because of its increased electronegativity the electrons are less available for bond formation with an acid.

A small number of pyridine compounds are found in the nature, principally among the enzymes and alkaloids. They were derived from nicotinic acid or vitamin B6. Pyridines have proved to be active compounds, exhibiting activity such as anti-HIV¹, antibacterial², anti-fungal³, glucose-6-phosphatase catalytic site inhibitors⁴, analgesic⁵ etc.

Methods of preparation

Kingsberg⁷ have reported the details about different methods of synthesis of the pyridine. The important synthetic methods for the pyridine have been discussed below.

Hydrazine hydrate was allowed to react with a few 1,5-diketones giving 1-amino-1,4-dihydropyridines⁸ as shown in (Fig. I). The use of aryl hydrazines has been limited to 1,3,5-triketones⁹.

![Fig. I](image)

Knoevenagh¹⁰,¹¹ synthesised aromatic pyridines by reacting hydroxylamine hydrochloride with saturated 1,5-diketones in one pot with high yield as shown
in (Fig. II). The use of hydroxylamine hydrochloride in ethanol or aqueous alcohol above 120°C in sealed tube gives the same yield as obtained by reflux for longer time.

![Chemical Reaction Diagram]

Fig. II

1,3-Dioxo compounds have been condensed with malononitrile or cyano acetic ester in a which cyano group act as a nucleophile and provides the ring nitrogen. The reaction catalyzed by organic bases gives pyridinols (Fig. III). The reaction is also catalysed by small amount of ammonia.

![Chemical Reaction Diagram]

Fig. III

If the diketone and ammonia are allowed to react first, before addition of malononitrile a significant yield of the 2-amino pyridine is obtained, such being the exclusive product in the case of 2-hydroxy methylene cyclohexane. Sakuri and Latif have obtained 2-amino-3-cyano-4,6-disubstituted pyridines from the condensation of α,β-unsaturated ketones and malononitrile in presence of ammonium acetate. They have also synthesised 3-cyano-4,6-disubstituted-2-pyridine by condensing the α,β-unsaturated ketones with ethyl cyanoacetate.

Hantzsch reported the synthesis of dihydropyridins by the condensation of aldehyde, β-dicarbonyl compound in the presence of ammonia as shown in (Fig. IV). Mosher, H. S. and Shinde, D. B. et al. have synthesised dihydropyridins by using Hantzsch method.
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Fig. IV

Guareschi-Thorpe$^{18-19}$ carried out the condensation of cyanoacetic ester with acetoacetic ester in the presence of ammonia give pyridine derivatives (Fig. V).

Fig. V

Chichibabin$^{20}$ carried out the condensation of carbonyl compound with ammonia under pressure to form pyridine derivatives (Fig. VI). Sprung$^{21}$ and Farleyet al.$^{22}$ have synthesised various pyridine derivatives by using this method.

Fig. VI

Selection of Method

Considering the synthetic importance of Hantzsch method for the synthesis of pyridine moiety in pharmacologically active heterocycles, we have worked out the synthesis of various new pyridine derivatives for the first time using Hantzsch method and discussed it in section-A, section-B and section-C of this part.

The selection of this method was made on the basis of following facts

1. Starting materials are easily available.
2. Yields are quantitative.
3. Product is unambiguous.
Section-A

[4-(2,6-Dimethyl-3,5-disubstituted-4-aryl-4H-pyridin-1-yl)-phenyl]-acetic acid

Drugs are grouped according to the structure of the carbon skeleton or chemical classification e.g. steroids, penicillins and peptides. Most drugs act at a specific site such an enzyme or receptor. Dihydropyridins are hydrogen transferring co-enzymes of utmost importance in biological system\textsuperscript{23,24}. The dihydropyridins of Nefedipine type belong to the most studied class of calcium antagonist used in clinical treatment of hypertension\textsuperscript{25}. They have also been reported to possess analgesic\textsuperscript{26}, antitumor\textsuperscript{27} properties.

Present work

Although a large number of heterocyclic alkanoic acids and related compounds have been reported for their anti-inflammatory activity. No work seems to have been reported so far on the anti-inflammatory activity of dihydropyridines. These findings prompted us to undertake synthesis of some new dihydropyridines bearing acetic acid moiety with an objective of studying their anti-inflammatory activity.

The synthetic routes of compounds are outlined in scheme IIA. [4-(2,6-dimethyl-3,5-disubstituted-4-aryl-4H pyridin-1-yl)-phenyl]-acetic acids (IIA\textsubscript{1-15}) were synthesized by reacting different aromatic aldehyde with dicarbonyl compound and p-amino phenyl acetic acid in ethanol.

General procedure

To synthesise the title compounds following starting materials have been used.

1. Dicarbonyl compound
   a. Acetonyl acetone
   b. Ethyl acetoacetate
   c. Methyl acetoacetate

2. Aldehyde
   a. Benzaldehyde
   b. 4-Chlorobenzaldehyde
c. 4-Methoxybenzaldehyde
d. Furfuraldehyde
e. Nicotinaldehyde

3. p-amino phenyl acetic acid

[4-(2,6-dimethyl-3,5-disubstituted-4-aryl-4H- pyridin-1-yl)-phenyl]-acetic acid (IIA1-15):

To a solution of dicarbonyl compound (0.02 m) and aldehyde (0.01 m) in dry ethanol, p-amino phenyl acetic acid (0.01 m) was added. The resulting mixture was refluxed and the reaction was monitored by TLC. After completion of reaction, the reaction mixture was allowed to cool to room temperature. Excess of the solvent was removed under vacuum. The solid thus obtained was filtered washed with cold ethanol, dried and recrystallised from suitable solvent. Purity of the compound was checked by TLC. Structure of the newly synthesised compounds was established by the spectral analysis.
Present Work

\[ 2\text{ MeCO}_2\text{R} + \text{ R}_1\text{CH} + \text{ NH}_2\text{HOOC} \rightarrow \text{ Scheme IIA} \]

Where
- \( R = \text{Me, OMe, OEt} \)
- \( R_1 = \text{Aryl} \)
Discussion of IR

IR spectra of some of the representative compounds of this series have been scanned on JASCO spectrophotometer using KBr pellets.

All the compounds showed absorption bands in the region 1690-1730 cm\(^{-1}\) due to >C=O stretching, 1600-1650 cm\(^{-1}\) due to C=C stretching in aromatic nucleus and 1200-1300 cm\(^{-1}\) due to C-N stretching. Broad absorption band in the region 2700-3400 cm\(^{-1}\) are attributed to acidic -OH.

The spectrum No.7 represents the IR spectrum of [4-(3,5-Diacetyl-2,6-dimethyl-4-phenyl-4H pyridin-1-yl)-phenyl]-acetic acid (IIA\(_1\)).

Discussion of PMR

\(^1\)H NMR spectra of some representative compounds were scanned on a sophisticated multinuclear FT-NMR spectrophotometer model Ac-300 F (Bruker) 300 MHz using TMS as an internal standard in CDCl\(_3\). Chemical shifts in \(\delta\) (ppm) scale. The spectrum No.8 represents the PMR spectrum of [4-(3,5-Diacetyl-2,6-dimethyl-4-phenyl-4H pyridin-1-yl)-phenyl]-acetic acid (IIA\(_1\)) as it displayed following PMR signal 1.8 (s, 6H, -CH\(_3\)), 2.6 (s, 6H, -CH\(_3\)), 3.5 (s, 2H, -CH\(_2\)-COOH), 4.5 (s, 1H, -CH=), 7.0-7.6 (m, 9H, Ar-H), 10.8 (s, 1H, -OH br).

Experimental Protocol

[4- (3,5 - Diacetyl - 2,6 dimethyl - 4 - phenyl - 4H pyridin-1-yl) - phenyl]- acetic acid (IIA\(_1\)) :

To a solution of acetylacetone (0.02 m) and benzaldehyde (0.01 m) in dry ethanol, p-amino phenyl acetic acid (0.01 m) was added. The resulting reaction mixture was refluxed for 6 hrs and the reaction was monitored by TLC. After completion of reaction, reaction mixture was allowed to cool to room temperature. Excess of the solvent was removed under vacuum. The solid thus obtained was filtered, washed with cold ethanol, dried and recrystallised from methanol to get IIA\(_1\). M.P.-197\(^{\circ}\)C, Yield-70%.

All other compounds (IIA\(_{1-15}\)) of the series were synthesized by following above procedure and are summarised in Table IIA.
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Table IIA: Characterisation data of for [4-(2,6-Dimethyl-3,5-disubstituted-4-aryl-4H pyridin-1-yl)-phenyl]-acetic acid (IIA1-15)

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* Recrystallised from methanol  # Recrystallised from acetone  + Recrystallised from ethanol

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Section-B

[4-[1,7-Disubstituted -4-(4-substituted aryl)-3,5-dimethyl-4,7-dihydro-1H-dipyrazolo[3,4-b;4',3'-e]pyridin-8-yl]-phenyl]-acetic acid

Nitrogen containing heterocyclic compounds eg. alkaloids, amides, nucleosides/nucleotides etc. are widely distributed in nature and play a vital role in the metabolism of all living cells. However, very few pyrazoles particularly 1,2 pyrazoles and their derivatives are naturally occurring. This may be due to the difficulty of living organisms to construct the N-N bond. Like other nitrogen heterocycles, pyrazoles also exhibit range of biological activities viz, antioxidant28, antiinvasive29, antiviral30, antipyretic31, anti-inflammatory32, antidepressant33 and blood pressure lowering34. Besides this pyrazoles are also used in agrochemicals35, dyestuff36, in sunscreen materials37 etc. Owing to the wide spread application of pyrazoles and their derivatives it was decided to undertake the synthesis of pyrazolopyridines.

Present work

Pyrazolopyridines are well known molecule exhibiting pharmacological activities like anxiolytic38,39, anticonvulsants40 and tested for their ability to displace flunitrazepam binding from bovine brain membranes41. Patel J. B. et al.42 studied the pharmacology of pyrazolopyridines. Bare T. M. et al.43 worked on the structure-activity relationships of a series of anxioselective pyrazolopyridine. It is also useful in the study of metabolites in serum and urine, was determined after intravenous and oral administration in experimental animals like mice, rats, rabbits & dogs44-48 and human volunteers49.

The synthetic routes of the title compounds are outlined in Scheme IIB. The title compounds [4-[1,7-Di substituted -4-(4-substituted aryl)-3,5-dimethyl-4,7-dihydro-1H-dipyrazolo [3,4-b;4',3'-e]pyridin-8-yl]-phenyl]-acetic acids (IIB1-12) are prepared by using Hantzsch method.

General procedure

To synthesise the title compounds following starting materials have been used.

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67
1. 5-methyl-2-substituted-2,4-dihydro-pyrazol-3-one  
   a. 5-Methyl-2,4-dihydro-pyrazol-3-one  
   b. 5-Methyl-2-phenyl-2,4-dihydro-pyrazol-3-one  
2. Aldehyde  
   a. Benzaldehyde  
   b. 4-Chlorobenzaldehyde  
   c. 4-Methoxybenzaldehyde  
   d. Nicotinaldehyde  
   e. Furfuraldehyde  
   f. Thiophene-2-carboxylic aldehyde  
3. p-amino phenyl acetic acid  

[4-[1,7-Disubstituted-4-(4-substituted aryl)-3,5-dimethyl-4,7- dihydro-1H-dipyrazolo[3,4-b:4',3'-e]pyridin-8-yl]-phenyl] - acetic acid (IIB1-12) :  
To a solution of 5-methyl-2-substituted-2,4-dihydro-pyrazol-3-one (0.02 m) and aldehyde (0.01 m) in dry ethanol, p-amino phenyl acetic acid (0.01 m) was added and resulting reaction mixture was refluxed. After completion of the reaction, the reaction mixture was allowed to cool to room temperature. The solid thus obtained was filtered. Excess of the solvent was removed under vacuum. The solid thus obtained was filtered, washed with cold ethanol, dried and recrystalised from suitable solvent. Purity of the compound was checked by TLC. Structure of the newly synthesised compounds was established by the spectral analysis.
Present Work

Scheme IIB

Where
R = H, Phenyl
R₁=Aryl
Discussion of IR

IR spectra of some of the compounds from this series have been scanned on JASCO spectrophotometer using KBr pellets.

All the compounds showed absorption bands in the region 1680-1710 cm\(^{-1}\) >C=O stretching, 1430-1600 cm\(^{-1}\) due to C=C/C=N stretching in aromatic nucleus and 1150-1350 cm\(^{-1}\) due to C-N stretching. Broad absorption band in the region 2800-3500 cm\(^{-1}\) are due to acidic -OH. The spectrum No.9 represents the IR spectrum of [4-(3,5-Dimethyl-1,4,7-triphenyl-4,7-dihydro-1H-dipyrazolo[3,4-b;4',3'-e]pyridin-8-yl]-phenyl]-acetic acid (IIB\(_1\)).

Discussion of PMR

\(^1\)HNMR spectra in CDCl\(_3\) on a sophisticated multinuclear FT-NMR spectrophotometer model Ac-300 F (Bruker) 300 MHz using TMS as an internal standard. Chemical shifts in \(\delta\) (ppm) scale. The spectrum No.10 represents the PMR spectrum of [4-(3,5-Dimethyl-1,4,7-triphenyl-4,7-dihydro-1H-dipyrazolo [3,4-b;4',3'-e]pyridin-8-yl]-phenyl]-acetic acid (IIB\(_1\)) as it displayed following PMR signal 2.7 (s, 6H, -CH\(_3\)), 3.3 (s, 2H, -CH\(_2\)-COOH), 5.5 (s, 1H, -CH-), 6.5-7.5 (m,19H, ArH), 10.9 (s, 1H, -OH br).

Experimental Protocol

[4-(3,5-Dimethyl-1,4,7-triphenyl-4,7-dihydro-1H-dipyrazolo[3,4-b;4',3'-e]pyridin -8-yl]-phenyl]-acetic acid (IIB\(_1\)) :

To a solution of 5-methyl-2-substituted-2,4-dihydro-pyrazol-3-one (0.02 m) and aldehyde (0.01 m) in dry ethanol, p-amino phenyl acetic acid (0.01 m) was added and resulting reaction mixture was reflux for 8 hrs. The reaction was monitored by TLC. After completion of the reaction, reaction mixture was allowed to cool to room temperature. The solid thus obtained was filtered. Excess of the solvent was removed under vacuum. The solid thus obtained was filtered, washed with cold ethanol, dried and recrystallised from methanol to get IIB\(_1\). M.P.-212\(^\circ\)C, Yield-65%.

All other compounds of the series were synthesized by following above procedure and are summarised in Table IIB.
Table IIB: Characterisation data of for \([4-[1,7\text{-bis-}(substituted)-4-(4\text{-substituted ary1})-3,5\text{-dimethyl-4,7-dihydro-1H-}
\text{dipyrazolo}[3,4-b;4',3'-e]\text{pyridin-8-yl]}\text{-phenyl]acetic acid (IIB}_{1-12})\)

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<th>No.</th>
<th>R</th>
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<th>MP &lt;sup&gt;(°C)&lt;/sup&gt;</th>
<th>Yield (%)</th>
<th>Molecular formula</th>
<th>Molecular Weight</th>
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A Search for Nonsteroidal Anti-Inflammatory Compounds: Pyridine

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* Recrystallised from ethanol    # Recrystallised from ethyl acetate    + Recrystallised from methanol

Department of Chemical Technology, Dr.Babasaheb Ambedkar Marathwada University

Ph.D. Thesis
Section-C

[4-[1,7-Bis-(4-substituted phenyl)-2,6-diimino-8-substituted aryl-1,2,6,7-tetrahydro-8H-3,5-dithia-1,4,7-triaza-s-indacen-4-yl]-phenyl]-acetic acid

A number of scientists in the past have tried to find out some relationship between chemical structure and physiological or biological properties of the chemical compounds. It is now established fact that the activity of a compound depends upon structure and functional group.

Many fused pyridines are reported showing important medicinal properties such as antibiotics\textsuperscript{50-58}, beta3-adrenoceptor agonists\textsuperscript{59}, phosphodiesterase inhibitors\textsuperscript{60}, anti-HIV\textsuperscript{61} and antifungal\textsuperscript{62}.

In continuation of efforts to incorporate pyridine moiety in pharmacologically active heterocycles and while referring the literature of the pyridine and thiazolidinone it was found that they are associated with physiological and biological properties like antimicrobial\textsuperscript{63,64}, antibacterial\textsuperscript{65}, central nervous system active agents\textsuperscript{66} (Briefly discussed in part-2 & 3 ). Taking this fact in to consideration it was thought worth while to synthesise a series of fused pyridines.

Present work

The synthetic routes of compounds are outlined in scheme-IIC. The compounds \{4-[1,7-Bis-(4-substituted phenyl)-2,6-diimino-8-substituted aryl-1,2,6,7-tetrahydro-8H-3,5-dithia-1,4,7-triaza-s-indacen-4-yl]-phenyl\}-acetic acid (II C\textsubscript{1,15}) which were prepared by the reaction of 3-(4-substituted phenyl)-2-imino-thiazolidin-5-one and p-amino phenyl acetic acid with appropriate aldehyde in the presence of ethanol.

General procedure

To synthesise the title compounds following starting materials have been used.

1. 3-(4-Substituted phenyl)-2-imino-thiazolidin-5-one
   a. 2-Imino-3-phenyl-thiazolidin-5-one
   b. 3-(4-Chloro-phenyl)-2-imino-thiazolidin-5-one
c. 2-Imino-3-p-tolyl-thiazolidin-5-one

2. Aldehyde
   a. Benzaldehyde
   b. 4-Chlorobenzaldehyde
   c. 4-Methoxybenzaldehyde
   d. Furfuraldehyde
   e. Nicotinaldehyde

3. p-amino phenyl acetic acid

\[4-[1,7-Bis-(4 - substituted phenyl)-2,6 - di imino - 8 - substituted aryl-1,2,6,7-\text{tetrahydro-8H-3,5-dithia -1,4,7- triaza-s-indacen-4-yl]- phenyl}] - acetic acid (\text{IIIC}_{1-15}) :\]

To a solution of 3-(4-substituted phenyl)-2-imino-thiazolidin-5-one (0.02 m) and aldehyde (0.01m) in dry ethanol, p-amino phenyl acetic acid (0.01m) was added and the reaction mixture was refluxed. The mixture was allowed to cool to room temperature. Excess of the solvent was removed under vacuum. The solid thus obtained was filtered, washed with cold ethanol, dried and recrystalised from suitable solvent. Purity of the compound was checked by TLC. Structure of the newly synthesised compounds was established by the spectral analysis.
Present Work

\[
2 \text{HN} = \text{S} \quad + \quad \text{R}_1 \text{H} \quad + \quad \text{NH}_2 \\
\text{HOOC} \quad \text{HOOC} \\
\text{HN} = \text{S} \quad \text{R} \quad \text{R}_1 \quad \text{R} \quad \text{NH} \\
\text{HN} = \text{S} \quad \text{R} \quad \text{R}_1 \quad \text{R} \quad \text{NH} \\
\text{HOOC} \quad \text{HOOC}
\]

Where
R = Ph, p-ClPh, p-MePh
R$_1$ = Aryl

Scheme IIC

Department of Chemical Technology, Dr. Babasaheb Ambedkar Marathwada University
Ph.D. Thesis
Discussion of IR

IR spectra of some of the compounds from this series have been scanned on JASCO spectrophotometer using KBr pellets.

All the compounds showed absorption bands in the region 1680-1740 cm⁻¹ >C=O stretching, 1600-1675 cm⁻¹ due to C=C stretching in aromatic nucleus, 1600-1650 cm⁻¹ due to C=N stretching. It is observed that absorption band 3200-3400 cm⁻¹ region are due to -NH- stretching, 1100-1180 cm⁻¹ due to C-S stretching and 1200-1350 cm⁻¹ due to C-N stretching. The broad absorption band in the region 2600-3300 cm⁻¹ is due to acidic -OH. The spectrum No.11 represents the IR spectrum of [4-(2,6-Diimino-1,7,8-triphenyl-1,2,6,7-tetralhydro-8H-3,5-dithia-1,4,7-triaza-s-indacen-4-yl)-phenyl]-acetic acid (IIC₁).

Discussion of PMR

¹HNMR spectra in CDC₃ on a sophisticated multinuclear FT-NMR spectrophotometer model Ac-300 F (Bruker) 300 MHz using TMS as an internal standard. Chemical shifts in δ (ppm) scale. The spectrum No.12 represents the PMR spectrum of [4-(2,6-Diimino-1,7,8-triphenyl-1,2,6,7-tetralhydro-8H-3,5-dithia-1,4,7-triaza-s-indacen-4-yl)-phenyl]-acetic acid (IIC₁) as it displayed following PMR signal 3.5 (s 2H, -CH₂-COOH), 4.4 (s, 1H, -CH-), 6.6-7.6 (m, 19H, Ar-H), 8.8 (s, 2H, -NH br), 11 (s, 1H, -OH br).

Experimental Protocol

[4-(2,6-Diimino-1,7,8-triphenyl-1,2,6,7-tetralhydro-8H-3,5-dithia-1,4,7-triaza-s-indacen-4-yl)-phenyl]-acetic acid (IIC₁):

To a solution of 2-Imino-3-phenyl-thiazolidin-5-one (0.02 m), benzaldehyde (0.01 m) in dry ethanol, p-amino phenyl acetic acid (0.01 m) was added and the reaction mixture was refluxed for 9 hrs. The mixture was allowed to cool to room temperature. Excess of the solvent was removed under vacuum. The solid thus obtained was filtered, washed with cold ethanol, dried and recrystalised from ethanol to get IIC₁. M.P.-217°C, Yield-60%.

All other compounds of the series were synthesized by following above procedure are summarised in Table IIC.
Table IIC: Characterisation data of \([4\text{-}[1,7\text{-Bis-(4-substituted phenyl)}-2,6\text{-diimino-8-substituted aryl}-1,2,6,7\text{-tetrahydro-8H-3,5-dithia-1,4,7-triaza-s-indacen-4-yl]}\text{-phenyl]}\text{-acetic acid (IIC1-15)}

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* Recrystallised from ethanol  # Recrystallised from ethyl acetate  + Recrystallised from acetone

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Department of Chemical Technology, Dr. Babasaheb Ambedkar Marathwada University

Ph.D. Thesis
A Search for Nonsteroidal Anti-Inflammatory Compounds: References

References

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