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SYNTHESIS AND BIOLOGICAL EVALUATION OF O-CHLORO PHENOL DERIVATIVES OF HETEROCYCLE AZOCINE

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ABSTRACT

Azocine is the chemical species of unsaturated eight membered heterocyclic ring with nitrogen as hetero atom. The IUPAC name of Azocine is Azacyclooctatetraene. The saturated or partially saturated azocine rings form the core structure of a group of opioid compounds sometimes known as Azocines. Azocine rings are found in many Natural products. The starting compounds for the synthesis of azocine is Ethyl-3-oxobutanoate. The structural assignments are supported by NMR, MASS, IR spectroscopy and chromatography Thin Layer Chromatography and Paper Chromatography. These include cyclazocine, pentazocine and phenazocine. The compounds possessing interesting biological and pharmacological properties as anti-inflammatory, anti-cancer, anti- bacterial, anti-fungal, anti-viral, anti-arrhythmic, tranquilizing, muscle relaxing and anti-diabetic agents.

KEYWORDS: Azocine, Ethyl-3-oxobutanoate, Anti fungal activity.

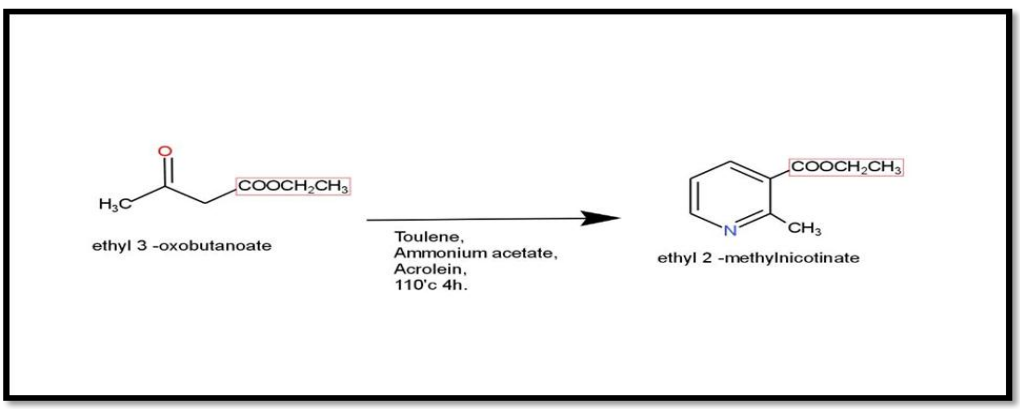
INTRODUCTION

The primary concern of this chapter is eight-membered aza heterocycles azocines. Azocines are a diverse class of compounds that frequently occur as biologically active compounds as well as being widely used in synthetic chemistry. Azocine is a heterocyclic organic compound with the molecular formula C_7H_7N. It consists of an unsaturated eight-membered ring having seven carbon atoms, one nitrogen atom and four double bonds. Saturated or

partially saturated azocine rings form the core structure of a group of opioid compounds sometimes known as azocines. These include cyclazocine, pentazocine and phenazocine. The fully saturated analog of azocine is azocane. Although foundations providing pioneering work on azocines had been started in the 1920s and 1930s, only limited systematic or comparative studies of azocines as a class have been done. In order to avoid repetition as well as to cover all the relevant literature available, some sections such as Azocines are a heterogeneous group of compounds. Most of the highly unsaturated azocines have been obtained from bi-or tri-cyclic precursors by bond reorganization processes which often consist of a single example. The properties and reactions of the azocines obtained by various approaches are in large measure characteristic of the substituents associated with a particular method, and for this reason, preparations and reactions have been discussed together. There has been little systematic or comparative study of azocines as a class, but questions of general interest include the relative stability of the eight-membered rings and bicyclic valence isomers and the potential aromaticity of 10π-electron systems.

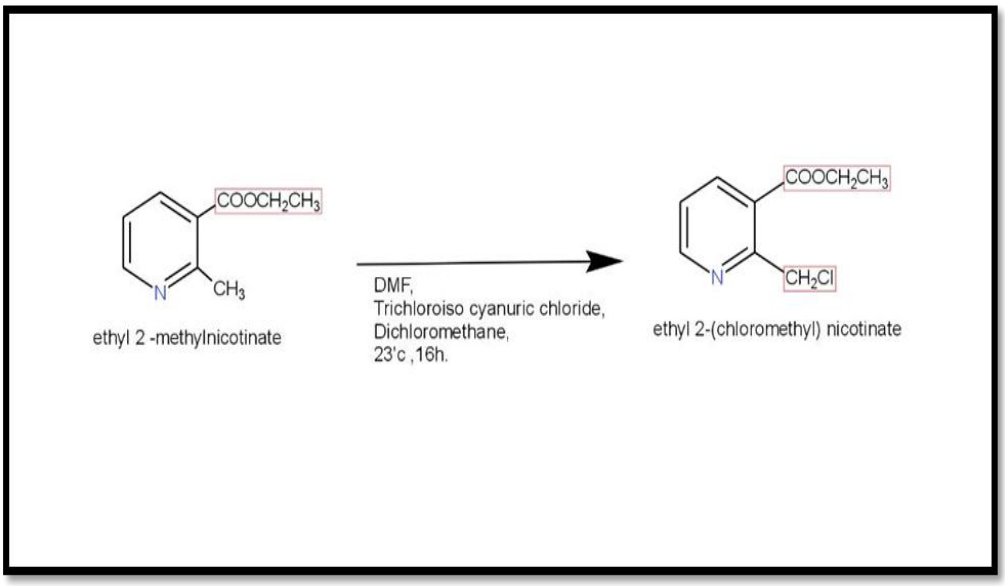
Molecular formula	-	C_7H_7N
Molecular weight	-	105.140 g·mol−1
Melting point	-	−37 °C
Boiling point	-	138 °C
Solubility	-	Acetone, chloroform

SCHEME AND MATERIALS METHOD



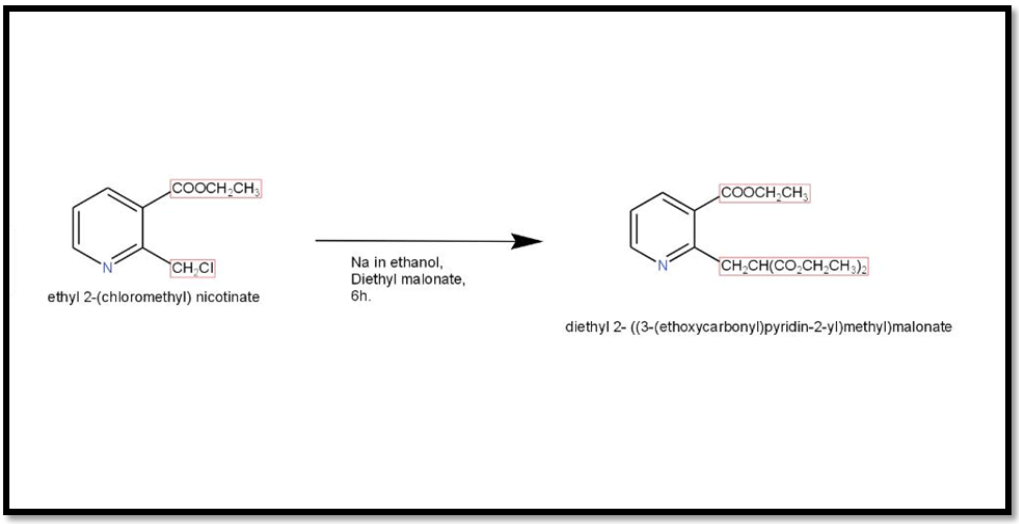
STEP-1: Synthesis of ethyl 2-methylnicotinate.

- A mixture of ethyl 3-oxo butanoate (0.1 mole), toluene (0. 1 mole), acrolein (0.1 mole) and ethanol (70 ml) reflex for 4 hours. Ammonum acetate (0.5M) solution add drop wise with vigorous stirring. The solution is washed with 0.1 N NaOH. The reaction mixture is poured into crushed ice, the product is wash with water repeatedly, dried and recrystallise from ethanol.



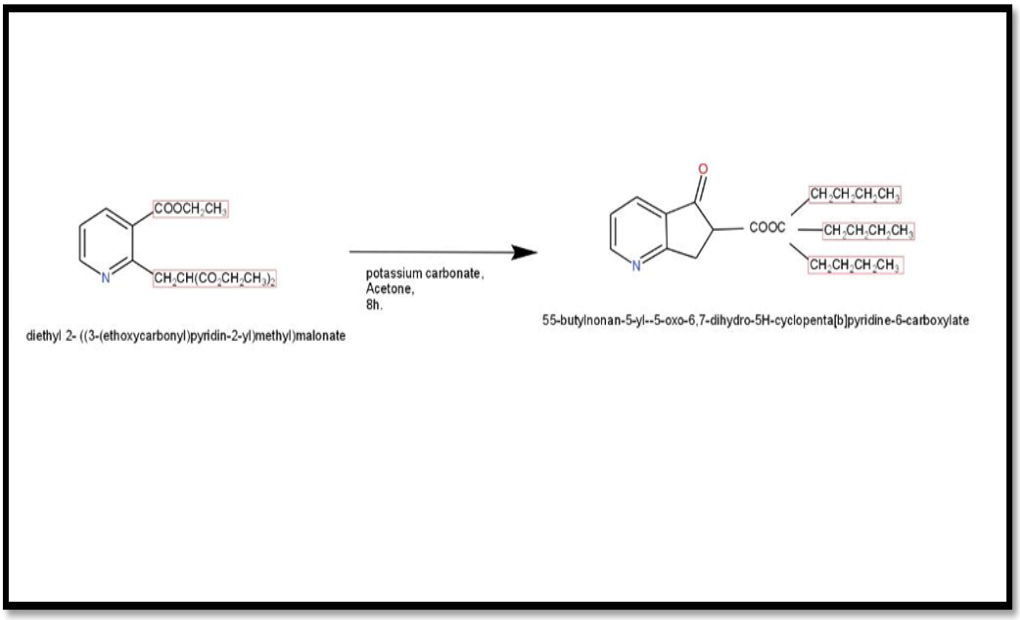
STEP 2: Synthesis of ethyl 2-(chloromethyl)nicotinate.

- Equimolar quantities of compound 1, dimethyl formamide and tri chloro cyanuric chloride were reflux in ethanol using dichloro methane as a catalyst for 16 hours. The solution mixture is concentrated and poured on crushed ice. The compound thus obtained is filter, dry and recrystallise from ethanol.



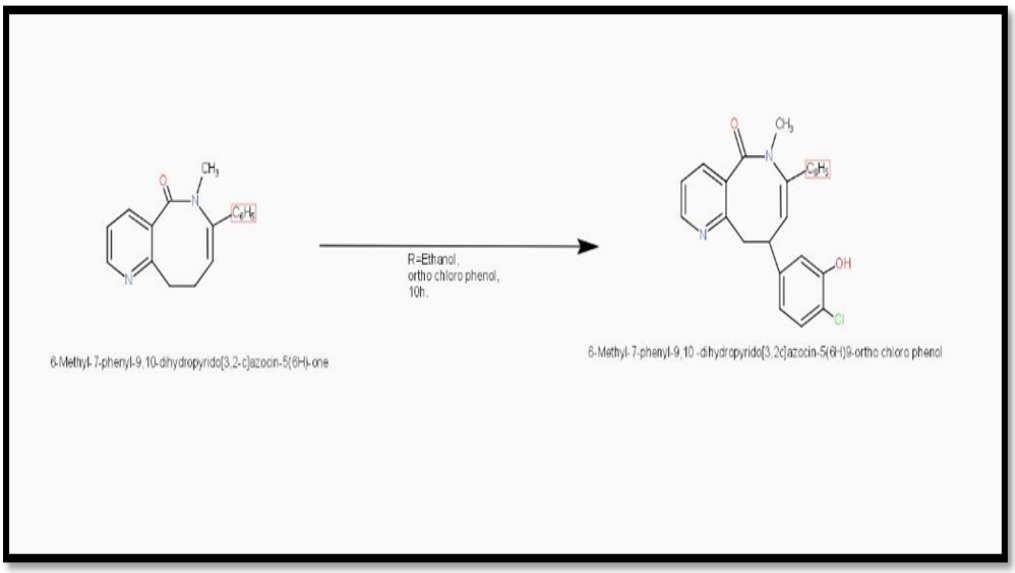
Step 3: Synthesis of diethyl 2-((3-(ethoxycarbonyl)pyridin-2-yl)methyl) malonate.

- Compound 2 (0.1 mole) is to be dissolve in diethyl malonate (0.1 water repeatedly and recrystallised mole) is reflexed sodium in ethanol for 5 hours. The content is evaporated to dryness and the product so obtained is washed with from ethanol.



Step 4: Synthesis of 5-butylnonan-5yl 5-oxo-6,7-dihydo-5H-cyclopentapyridine-6-carboxylate.

- Compound 3 (0.1 mole) is to be dissolve in tetra hydro furan (50ml) which is to be added to sodium hydride (0.1 mole) in acetone (50ml) and the contents to be refluxed in ethanol in for5 hours. The reaction mixture is reduced to half of its volume and poured onto crushed ice. The product so obtain is wash with water repeatedly, dried and recrystallised from ethanol.



Step 5: 6-methyl-7-methyl-9,10-dihydropyrido(3,2c)azocine-5(6H)9-o-chloro phenol.

• Compound 4 (0.1 mole) is to be dissolved in potassium carbonate (0.5M) is refluxed in acetone for 8 hours. The content is evaporated to dryness and the product so obtained is washed with water repeatedly and recrystallised from ethanol.

Chemicals

Ethyl 3-oxobutanoate, Acrolein, Toluene, Ethanol, Ammonium acetate, Sodium hydroxide, Dimethyl formamide, Tri chloro cyanuric chloride, Dichloromethane, Diethyl malonate, Tetra hydro furan, Acetone, Sodium hydride, Potassium carbonate.

Apparatus

Round bottom flask, Reflex condenser, Measuring Cylinder, Beakers, Funnel, Petri plates, Glass rods, Water bath, Weighing balance, Tripod stand.

Physical characterisation

Molecular formula	-	$C_{19}H_{17}N_2O_2Cl$
Molecular weight	-	340.5gm/mole
Melting point	-	+40°C
Boiling point	-	137 °C
Solubility	-	Acetone, Ethanol, Methanol, Water.

BIOLOGICAL SCREENING

Antifungal Activity

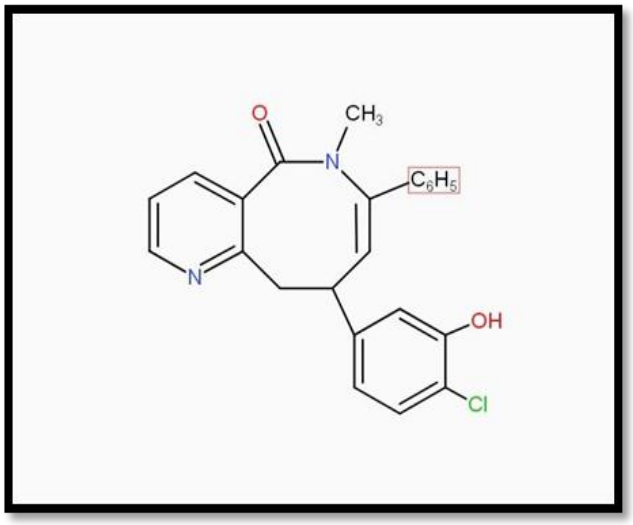
Antifungal activity Turbidometric method by using Sabouraund dextrose broth The synthesized compounds were screened for invitro antimicrobial activity by Turbidometric method. This method was used for determining the selective effectiveness of the antifungal activity. The standard antibiotic selected for study of the antifungal activity was ketoconazole. The activity was compared with standard ciprofloxacin drug.

Materials Used

Sabouraud dextrose broth, sterile borosil boiling test tube, sterile test tube, sterile pipettes and sterile cotton swabs.

Fungal

In the percent study the following fungi were used.



Aspergillus niger

IUPAC Name

6-methyl-7-methyl-9,10-dihydropyrido(3,2) azocine-5(6H)9-o-chloro phenol.

IR Interpretation

I.R. Spectral data (KBr discs) (in Cm-1)

N-H str_	3389.59
C=N str_	1769.58
=C-H str_	3196.36
C=O str_	1766.69
C-N str_	1386.09
=C-H bending	1524.30

^{1}HNMR INTERPRETATION

^{1}HNMR Spectral data Absorption position (in PPM)

6.39-7.8	m, 24H, ArH
4.4	s, 1H, NH
2.38	s, 3H, CH3
4.14	d, 1H, CH
4.19	t,1H, CH
3.22	q, 1H, CH
3.19, 2.84	d, 2H, CH_2
1.15	d, 3H, CH_3

RESULTS AND DISCUSSION

Synthesis

The present study reports the synthesis of azocine derivatives. Electrophillic addition of Ethyl 3-oxo butanoate in acrolein was carried out stepwise at different temperatures by various

acids. The final azocine derivative in the synthesized compound-5 was replaced by o-chloro phenol. Since the report regarding this compound suggest a azocine possesses a good biological activity.

Physical Characterization

At room temperature of newly synthesized compound were determined by various organic solvents and it was found that all compounds were freely soluble in ethanol, methanol, DMF, DMSO and carbon tetra chloride.

Anti Fungal Activity

The below table revealed that activity increase with concentration

Sample	Bacteria	Concentration	% inhibition of growth
Control	Aspergillus niger		0
6-methyl-7-methyl-9,10-dihydropyrido(3,2) azocine-5(6H)9-o-chloro phenol	Aspergillus niger	50 µg/ml 100 µg/ml 150 µg/ml 200 µg/ml 250 µg/ml	17.15 24.16 31.25 38.52 55.26
Ortho chlorophenol	Aspergillus niger	100 µg/ml	85.69

CONCLUSION

In the present study we concluded that the azocine derivative of synthesized compound having good anti-fungal activity.

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