

Synthesis of 1-aryl-2-[3-methylpyrazolin-5'-oxo-1'-yl]-4-[phenyl/p-chlorophenyl]-imidazoles and their antihistamine activity

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Abstract : 1-Aryl-2-mercapto-4-(phenyl/n-chlorophenyl)-imidazoles (Ia-j) were condensed with hydrazine to get 1-aryl-2-hydrazino-4-(phenyl/p-chlorophenyl)-imidazoles (IIa-j). Later compounds were subsequently reacted with acetoacetic ester in presence of acetic acid to get the desired 1-aryl-2-(3-methylpyrazolin-5'-oxo-1'-yl)-4-(phenyl/2-chlorophenyl)-imidazoles (IIIa-j). These compounds were screened for anti-histaminic activity. All the compounds (IIIa-j) showed moderate anti-histaminic activity.

(Keywords : anti-histaminic activity, pyrazol moiety, insecticidal, herbicidal and fungicidal nature)

Introduction

The various broad spectrum physiological properties of imidazole derivatives have been discussed intensively. There are a number of compounds having pyrazole moiety which are of enormous biological importance e.g., 1,3-disubstituted-4-arylidene-pyrazolin-5-ones¹ and N-β-(aryloxy) propionyl-3-methyl-5-pyrazolone² are reported to be antifungal in nature.

4-[phenyl-3,5-dimethylpyrazolyl]-azo]-N-(substituted benzylidene) benzohydrazides have been reported to be insecticidal, herbicidal, fungicidal and having plant growth regulator activity³. Substituted pyrazol-6(2H)-ones are useful as bactericides, fungicides and antitumor agents⁴. Pyrazole sulphonamides derivatives in pre-emergence test gave above 90% control of *Echinochloa crusgalli* with little effect on wheat⁵.

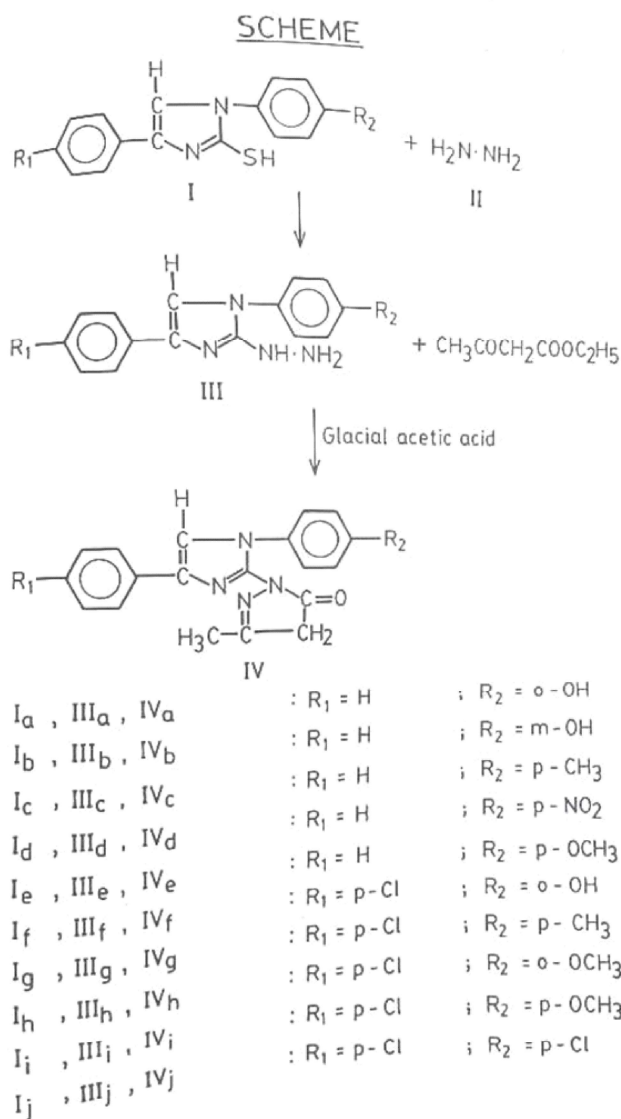
Oximino-pyrazolinones are useful against *Phytonhthora infestans* in tomato⁶. N-isonicotinoyl-3-methyl-4-(substituted arylidene)-2-Pyrazolin-5-one inhibited *Puccinia oxycae*⁷.

3,5-Diaryl pyrazoles are reported to inhibit the growth of *Staphylococcus aureus*⁸. β-Aryl-(1,3-disubstituted-5-oxo-2-pyrazolin-4-yl)-propionic acid have been found active against gram +ve and gram -ve bacteria⁹⁻¹⁸.

Pyrazol-[4,3-d]-pyridine-3-one derivatives are reported to be useful as antixoliotics, anticonvulsants and cognitive performance enhancers.

1-(n-Decyl)-3-pyrazolidinone showed anticonvulsant activity¹⁹. 3-(4',4'-Dimethyl-2'-piperidon-6'-yl)-methyl-2-pyrazolin derivative decreased the spontaneous motor activity in mice²⁰. A number of pyrazole derivatives have been reported to be anti-inflammatory in nature. Indruch et al. reported 4-substituted-1,2-diphenyl-3,5-pyrazolidine diones to be useful in arthritis. Styryl pyrazoles are also reported to be useful as 5-lipoxygenase inhibitor.

Keeping in view the above mentioned activities of pyrazole derivatives, as well as pharmacodynamic properties of imidazole, it was considered worthwhile to synthesize the compounds in which both imidazole and pyrazole moiety are present in single compound



Antihistaminic Activity

The antihistaminic activity (H_1) was measured on the isolated terminal part of ileum (5 cm long) of a guinea pig. This part of ileum was kept in a bath containing aerated Tyrode solution (20 ml) at 35 °C. Spasm of the ileum was induced with 3×10^{-8} g/ml of histamine. The percentage inhibition was plotted at different concentration

of the compound and the concentration corresponding for 50% inhibition (IC_{50}) was calculated. These values are listed in Table VI. with their standard errors.

The antihistaminic activity in vivo was tested in guinea pig by the Kongzett-Rossler

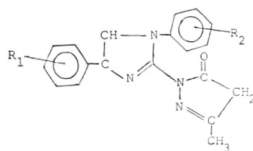
preparation²¹ against histamine (2.10 mg/kg i.v.) induced bronchoconstriction. The i.v. ED₅₀ value was calculated graphically by plotting percent inhibition of histamine bronchoconstriction versus dose of the compound.

- (1) The compounds exhibited a moderate antihistaminic activity.
- (2) The compound (IIIc) with 4-CH₃ group showed the strongest, activity.
- (3) No structure activity relationship could be established because of the irregular pattern of activity shown by the compounds.

Results and Discussion

The antihistaminic activity of the compounds is recorded in the Table. The following conclusion were drawn:

Table- No. 1 - Physical characteristics of 1-aryl-2-[3-methylpyrazolin-5' oxo-1'-YL] 4-(phenyl/p-chlorophenyl)-imidazoles



Compound No.	R1	R2	Melting Point (°C)	Yield (%)
IIIa	H	2-OH	124	59
IIIb	H	3-OH	121	59
IIIc	H	4-CH ₃	115	63
IIId	H	4-NO ₂	145	65
IIIe	H	4-OCH ₃	128	68
IIIf	Cl	2-OH	151	63
IIIg	Cl	4-CH ₃	162	71
IIIh	Cl	2-OCH ₃	132	62
IIIi	Cl	4-OCH ₃	151	55
IIIj	Cl	4-Cl	205	62

Table No. 2
Antihistaminic activity of 1-aryl-2[3-methylpyrazolin-5 cxo-1-yl] 4-phenyl/4-chlorophenyl imidazoles (VIIIa-j)

Compound No.	H1 Receptor blocking activity
IIIa	0.19±0.06
IIIb	0.41±0.02
IIIc	0.24±0.048
IIId	0.15±0.02
IIIe	0.17±0.05
IIIf	0.14±0.03
IIIg	0.09±0.03
IIIh	0.18±0.04
IIIi	0.20±0.02
IIIj	0.07±0.00

Table No. - 3
Antihistaminic activity of 1-aryl-2[3-methylpiazolin-5 exo-1-yl]
4-phenyl/4-chlorophenyl imidazoles (VIIIa-j)

Compound No.	H1 Receptor blocking activity
IIIa	0.19±0.06
IIIb	0.41±0.02
IIIc	0.24±0.048
IIId	0.15±0.02
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IIIg	0.09±0.03
IIIh	0.18±0.04
IIIi	0.20±0.02
IIIj	0.07±0.00

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