SYNTHESIS AND STUDY OF BIOLOGICAL ACTIVITIES OF SOME CYCLIC NITROGEN COMPOUNDS

A THESIS

In Partial Fulfilment of the requirements
of M.Sc. Degree

By

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OF SOME CYCLIC NITROGEN COMPOUNDS

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A C K N O W L E D G E M E N T

This study has been carried out in the laboratories of the Faculty of Agriculture, Ain Shams University, Zagazig, A.R.E.

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N O T E

Beside the work carried out in this thesis, the candidate has attended post graduate course for two years in organic chemistry including the following topics:

1- Reaction Mechanism.

2- Electronic, Infrared, Raman, and N.M.R. Spectroscopy of organic chemistry.

3- Micro-analysis of organic compounds.

4- Heterocyclic compounds.

5- Reaction of organic compounds.

He has successfully passed an examination in these topics.

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PART II

BIOLOGICAL ACTIVITIES OF 2--PYRAZOLIN-5-ONES

Summary of the Original Work

Some Reactions with 2-Pyrazolin-5-one and The Biological Activities of Pyrazolones

3-Methyl-5-pyrazolone was condensed with aliphatic or aromatic aldehydes or ketones to give the corresponding 4-alkylidene- or 4-arylidene- derivatives. Thus the condensation of 3-methyl-5-pyrazolone with chloral, salicylaldehyde, acetone, and p-methylacetophenone yielded the corresponding 4-(2,2,2-trichloroethylidene-, 4-salicylidene-, 4-isopropylidene-, and 4-(1-methyl-1-p-methyl phenyl methylene)- derivatives.

3-Amino-1-phenyl-5-pyrazolone reacted with chloroacetyl chloride, 2-furylamine, and 2-aminopyridino to give the corresponding 3-substituted amino-1-phenyl-5-pyrazolone derivatives. The condensation of the same pyrazolone with aromatic aldehydes yielded the corresponding 4-arylidene- derivatives.

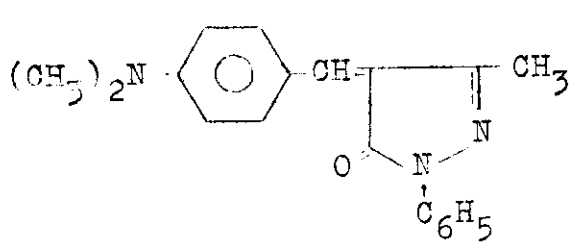
Bromination of 1-(2,4-dinitrophenyl-)-3-methyl-5-pyrazolone in hot chloroform yielded the 4-bromo-derivative. The same pyrazolone was condensed with aliphatic and aromatic aldehydes to give the corresponding 4-alkylidene- or 4-arylidene-derivatives.

Antipyrine was reacted with aromatic aldehyde to give the corresponding 4,4'-biantipyrine derivatives.

To study the relationship between chemical structure and biological activities, the plant growth regulating activity, the phytotoxicity and the fungitoxicity of 69 pyrazolone derivatives were compared at equimolar doses.

The following conclusions could be extracted from the experimental results.

1- All the minimum structural requirements for stimulant activity are contained in the following formulas:



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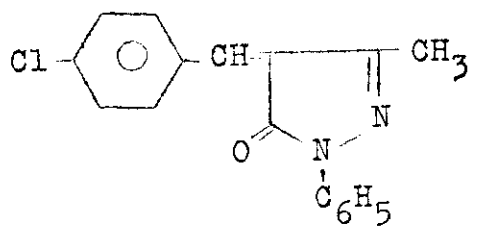
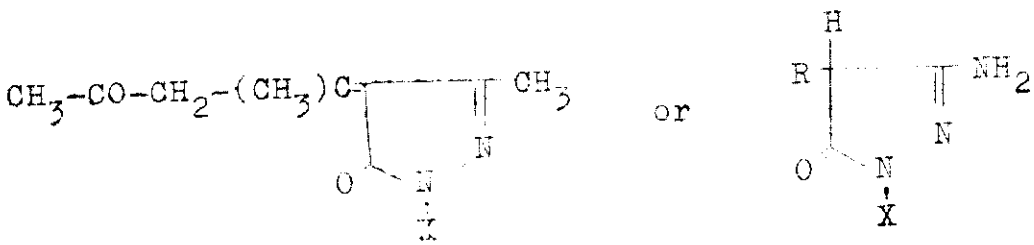


2- All the minimum structural requirements for phytocidal activity are contained in the following formulas:



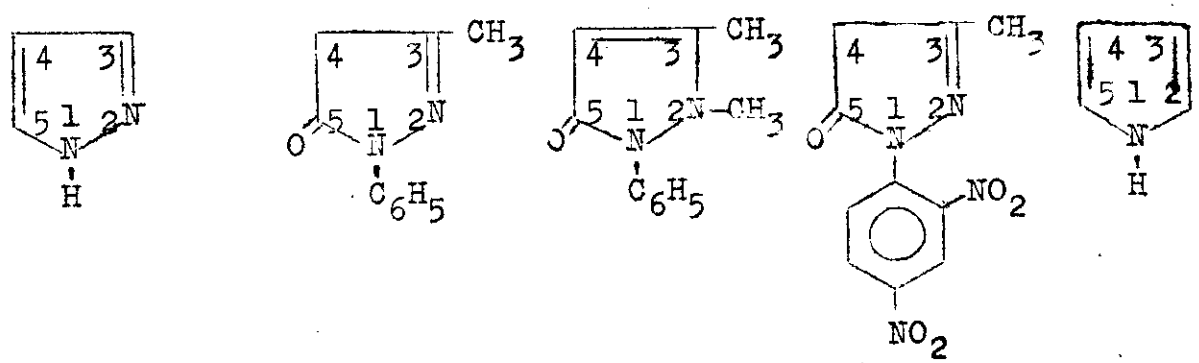
Where in X = H, or Br

R = H, Br or $CH(OH).CCl_3$

3- The 4-carboxaldehyde-, and the 4-(2,2,2-trichloro-1-hydroxy-ethyl-)-, derivatives of 3-methyl-1-phenyl-5-pyrazolone were the most toxic compounds tested against Myrothecium verrucaria (Alb. and Schw.) Ditm. ex. Fr.

GENERAL INTRODUCTION

The pyrazole ring system (I) consists of doubly unsaturated atoms. A compound containing this system was synthesised firstly by Knorr in 1883 (1) from the reaction of ethyl acetoacetate with phenylhydrazine which yielded 3-methyl-1-phenyl-5-pyrazolone (II).

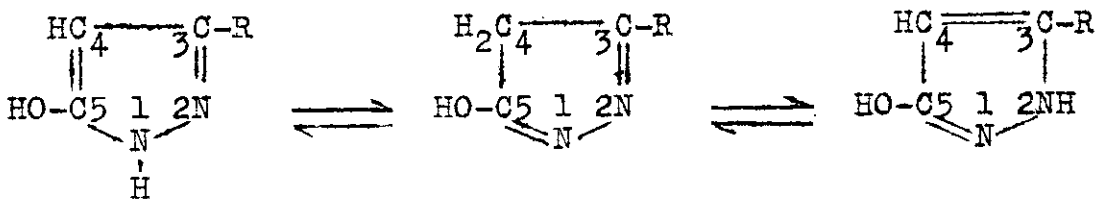


I II III IV V

The pyrazole name was introduced for this type of compounds by Knorr to denote that the nucleus was derived from pyrrole(V) by the replacement of a carbon atom by a nitrogen atom.

Gagon et al. (2) measured the ultraviolet absorption for 2-pyrazolin-5-one and a series of its 4-alkyl derivatives and found that they exhibit a high intensity of absorption maxima ($\epsilon_{max.} \sim 16{,}000$) at shorter wavelengths ($\lambda_{max.} \sim 250$ mu).

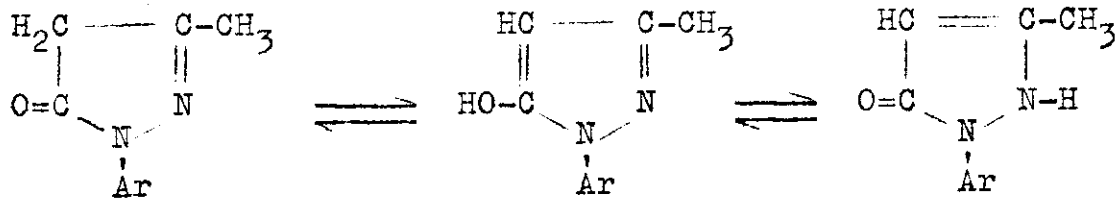
This finding indicated the presence of a double bond between two carbon atoms. From this and from the fact that pyrazolones did not exhibit the carbonyl stretching frequency, the above authors suggested their existence in an enolic form. Accordingly 2-pyrazolin-5-one and similar compounds are believed to exist as a mixture of the three most probable tautomeric structures (a), (b) and (c).



(a) (b) (c)

Randol et al. (3) studied the infrared absorption spectra of 3-methyl-5-pyrazolone in nujol, potassium bromide, and chloroform, and found that the stretching frequency of carbonyl group is expected to be influenced by its presence as a part of the 5-membered ring, and its conjugation with the adjacent nitrogen. However, there is no way of predicting exactly in which region it will absorb, and finding the presence of such a band at about 1610 cm^{-1}.

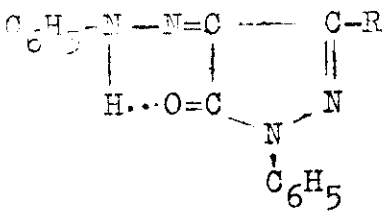
Stevens (4) found that 3-methyl-1-aryl-5-pyrazolone (II) exists as a mixture of the three most propable tautomeric structures (VIa-c).



VIa VIb VIc

5-Pyrazolones lacking a substituent at position-1, had a carbonyl absorption band at 1710-45 cm^{-1}, and at 3460-3580 cm^{-1} (NH), visible only in solution. The band at 1610 cm^{-1}, present in the spectrum was assigned to the (C=N) group, since the nuclear magnetic resonance spectrum of 3-methylpyrazolone showed the presence of a vinylic methyl. The 1-substituted pyrazolones had bands at 1710 and 1620 cm^{-1} assigned to (C=O) and (C=N) groups, respectively. Owing to insufficient solubility, some nuclear magnetic resonance spectra were determined in solvents (C_5H_5N, D_2O, 3:2 C_5H_5N··D_2O) other than $CDCl_3$. 4-Arylazo-5-pyrazolone showed a highly deshielded (δ 3.8-4.2) proton, exchangable with D_2O, assignable only to an intramolecularly

hydrogen bonded -NH or -OH in view of the infrared spectroscopic evidence for a hydrogen bonded carbonyl group (VII).



(VII)

This type of compounds plays an important part in many drugs, dyes and pesticides. Accordingly, pyrazolones have been widely studied and the field continues to be active to day even through antipyrine and related medicals (1,5,6,7).

Antipyrine(2,3-dimethyl-1-phenyl-5-pyrazolone)and its 4-acylamino analogues in which the acyl group is acetyl-, propionyl-, butyryl-, isovaleryl-, benzoyl-, cinnamoyl- and salicyl- were found to have febrifugal, analgesic, antiphlogistic and antiduritic activity in rabbits (8). Novalgene (the 4-$N(CH_3)_2CH_2SO_3Na$- derivative of antipyrine), the well known analgesic drug, as well as 1-(4-pyridyl)-5-pyrazolone have good analgesic and antipyritic properties (1,9).