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Synthesis and Theoretical Study of Molecular Structure of Some Novel Pyrazolone Derivatives

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Abstract
During the last two decades, the study of biological activities of pyrazolone derivatives has been the main focus area of many researchers. Looking to the importance and usefulness of pyrazolones, a series of 5-pyrazolone derivatives were synthesized by refluxing ethyl α-(4-chloro-2-methyl phenyl azo) aceto acetate and acid hydrazides of malon anilic acid in acetic acid medium or by heating under microwave irradiation. In this paper two of the newly synthesized compounds were characterized by elemental analysis, IR, 1H NMR spectroscopy. The synthesized compounds were used as efficient precursors for the synthesis of new heterocyclic compounds with expected biological activities. We have also concluded that the reactions described have proceeded to completion in a much shorter time when irradiated in a focused microwave oven. Theoretical study of the compounds and their IR spectra data have been determined by performing DFT molecular orbital calculations.
Keywords: Pyrazolone, refluxing, microwave, synthesis, biological activities

2.Introduction:

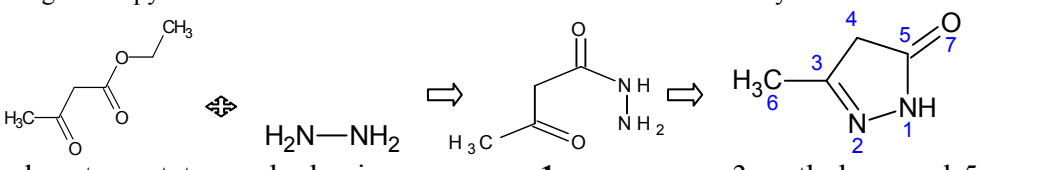
Pyrazolone is one of the important heterocyclic compounds having five membered ring lactam and an additional keto (C=O) group . It occurs in many drugs and synthetic products. The compounds having pyrazolone moiety are found to be remarkable anti tubercular, anti-inflammatory, antibacterial, antifungal and antitumor active[1-7]. The importance of azo derivatives of pyrazolones lies in their dyeing property. The biological activities of pyrazol-5-ones depend on the nature of the substituent groups. Heterocycles, containing the pyrazolone moiety, have attracted much attention and present a major scientific and applied interest due to their multiple possible applications as ligands in the chemistry of metalo-organic compounds, as chelating agents, as intermediates in the synthesis of new series of heterocyclic compounds, as biologically active compounds in agriculture and medicine. Pyrazolone and azopyrazolone compounds are also widely used as analytical reagents, they are capable of forming chelates with a number of metal cations [8,9], their formation is accompanied by change in physical properties like change in color, pH, conductivity, and absorption spectra [10]. 5-Pyrazolone azo-derivatives and their metal complexes have widely used in dye industry as well as in analytical field for determination of trace metals and they are predicted to have some medicinal and biological applications [11,12]. Derivatives of antipyrine or phenazone are mainly used as analgesic and antipyretic drugs [13]. 4-Aminoantipyrine, well known derivative of antipyrine, is used for the protection against oxidative stress and prophylactic of some diseases including cancer [14,15,16]. Therefore, it was trying to combine the above mentioned investigate to find out the additive effect towards microbial activities of the newly synthesized compounds

3.Materials and methods

The reagents were from commercial sources (Merck) and used as received, and the starting compounds were obtained according to the literature. All melting points are uncorrected. 1H-NMR spectra were measured by WP 400-NMR spectrophotometer, solvents such as dimethyl sulphoxide (DMSO) were used as solvents and the chemical shifts were quoted as δ-value relative to tetramethyl silane (TMS, δ=O) as an internal standard. Elemental analyses were carried out by the micro analysis. Starting Compounds were prepared following literature procedure.

Result and discussion:

It has been reported that ethyl aceto acetate reacted with hydrazine hydrate in domestic microwave oven to give the pyrazolone derivatives **2** via the formation of intermediate hydrazide derivative **1.**

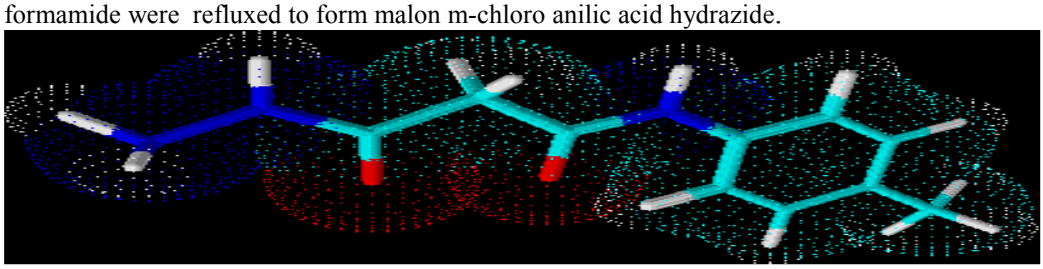


Ethyl aceto acetate hydrazine **1** 3-methyl pyrazol-5-one **2**

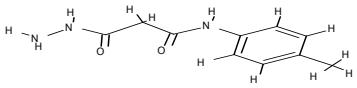
The compound 2 was examined as a key precursor of the many important pyrazolone derivatives. The series of malon anilic acid hydrazides have been prepared by the method reported in the literature[17,18].

It has been known for many years that the azo compounds are widely used as dye in various fields such as the dyeing of textile fibers, the coloring of different materials, in biological–medical field and in organic synthesis [19-23].

A mixture of p-toluidine, diethyl malonate and dimethyl formamide was refluxed, treated with hydrazine hydrate to form malon p- toluidic acid hydrazide. Similarly m-chloroaniline, diethyl malonate and dimethyl formamide were refluxed to form malon m-chloro anilic acid hydrazide.

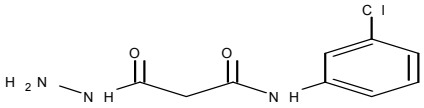


Malon p-toluidic acid hydrazide : 3D View



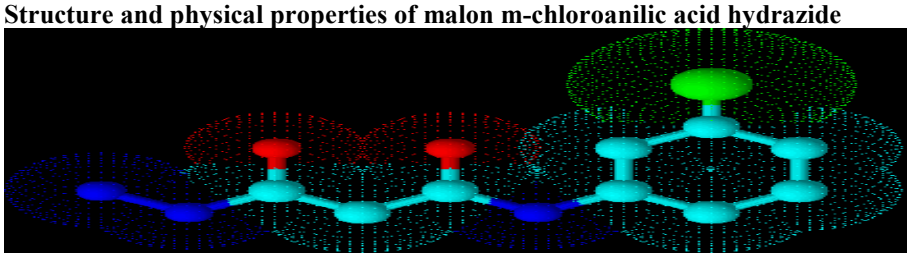
Molecular Formula	= $C_{10}H_{13}N_3O_2$
Formula Weight	= 207.22912
Composition	= C(57.96%) H(6.32%) N(20.28%) O(15.44%)
Molar Refractivity	= 57.14 ? 0.3 cm^3
Molar Volume	= 164.9 ? 3.0 cm^3
Parachor	= 450.5 ? 4.0 cm^3
Index of Refraction	= 1.609 ? 0.02
Surface Tension	= 55.6 ? 3.0 dyne/cm
Density	= 1.256 ? 0.06 g/cm^3
Dielectric Constant	= Not available
Polarizability	= 22.65 ? 0.5 $10^{-24}cm^3$
Monoisotopic Mass	= 207.100777 Da
Nominal Mass	= 207 Da
Average Mass	= 207.2291 Da

Structure and physical properties of malon p-toluidic acid hydrazide



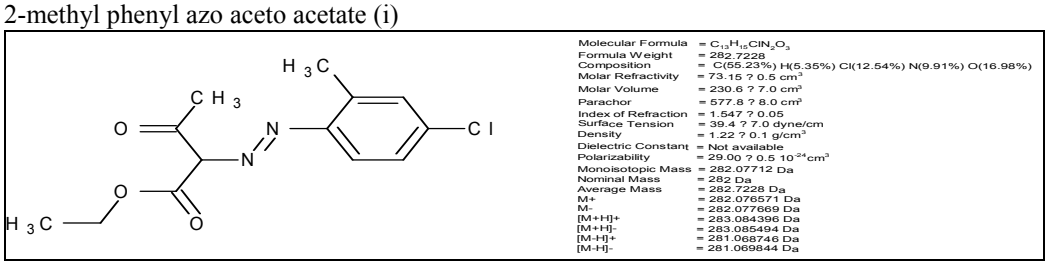
Molecular Formula	= $C_9H_{10}ClN_3O_2$
Formula Weight	= 227.6476
Composition	= C(47.48%) H(4.43%) Cl(15.57%) N(18.46%) O(14.06%)
Molar Refractivity	= 57.21 ? 0.3 cm^3
Molar Volume	= 160.5 ? 3.0 cm^3
Parachor	= 448.7 ? 4.0 cm^3
Index of Refraction	= 1.631 ? 0.02
Surface Tension	= 60.9 ? 3.0 dyne/cm
Density	= 1.417 ? 0.06 g/cm^3
Dielectric Constant	= Not available
Polarizability	= 22.68 ? 0.5 $10^{-24}cm^3$
Monoisotopic Mass	= 227.046154 Da
Nominal Mass	= 227 Da
Average Mass	= 227.6476 Da
M+	= 227.045606 Da
M-	= 227.046703 Da
[M+H]+	= 228.053431 Da
[M+H]-	= 228.054528 Da
[M-H]+	= 226.037781 Da
[M-H]-	= 226.038878 Da

Structure and physical properties of malon m-chloroanilic acid hydrazide



Malon m-chloro anilic acid hydrazide : 3D View

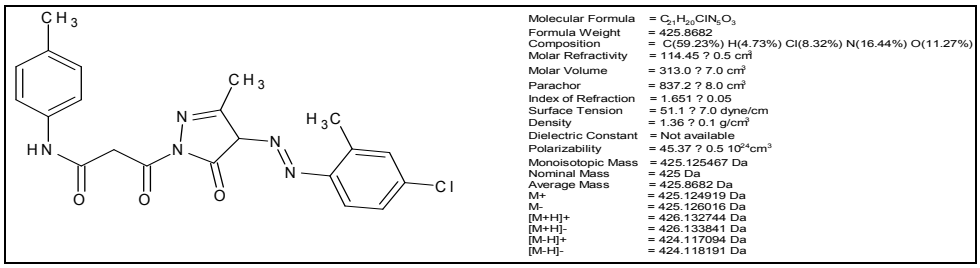
2-Amino-5-chloro toluene was diazotized and condensed with ethyl aceto acetate which gave ethyl α-4-chloro-2-methyl phenyl azo aceto acetate (i)



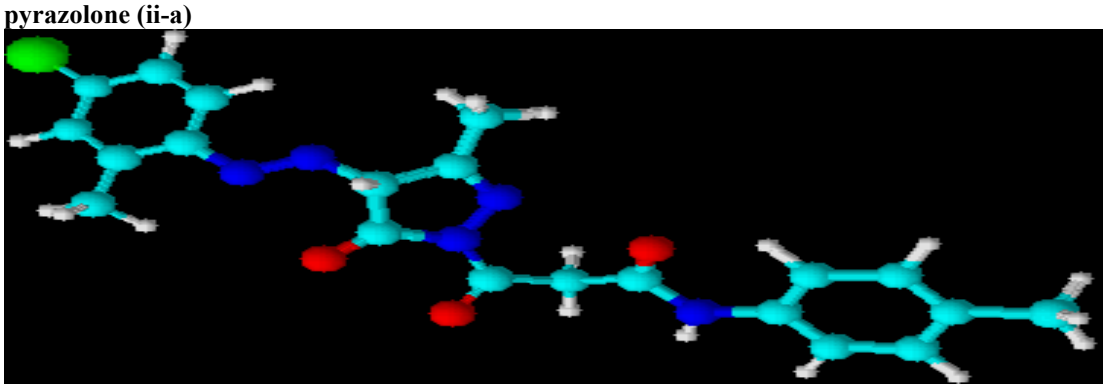
Molecular Formula	= $C_{13}H_{15}ClN_2O_3$
Formula Weight	= 282.7228
Composition	= C(55.23%) H(5.35%) Cl(12.54%) N(9.91%) O(16.98%)
Molar Refractivity	= 73.15 ? 0.5 cm^3
Molar Volume	= 230.6 ? 7.0 cm^3
Parachor	= 577.8 ? 8.0 cm^3
Index of Refraction	= 1.547 ? 0.05
Surface Tension	= 39.4 ? 7.0 dyne/cm
Density	= 1.22 ? 0.1 g/cm^3
Dielectric Constant	= Not available
Polarizability	= 29.00 ? 0.5 $10^{-24}cm^3$
Monoisotopic Mass	= 282.07712 Da
Nominal Mass	= 282 Da
Average Mass	= 282.7228 Da
M+	= 282.076571 Da
M-	= 282.077669 Da
[M+H]+	= 283.084396 Da
[M+H]-	= 283.085494 Da
[M-H]+	= 281.068746 Da
[M-H]-	= 281.069844 Da

Ethyl α-4-chloro-2-methyl phenyl azo aceto acetate (i)

The ester (i) on refluxing with malon anilic acid hydrazides in acetic acid medium or by heating in microwave gave pyrazolone azo derivatives of the type (ii-a &b).

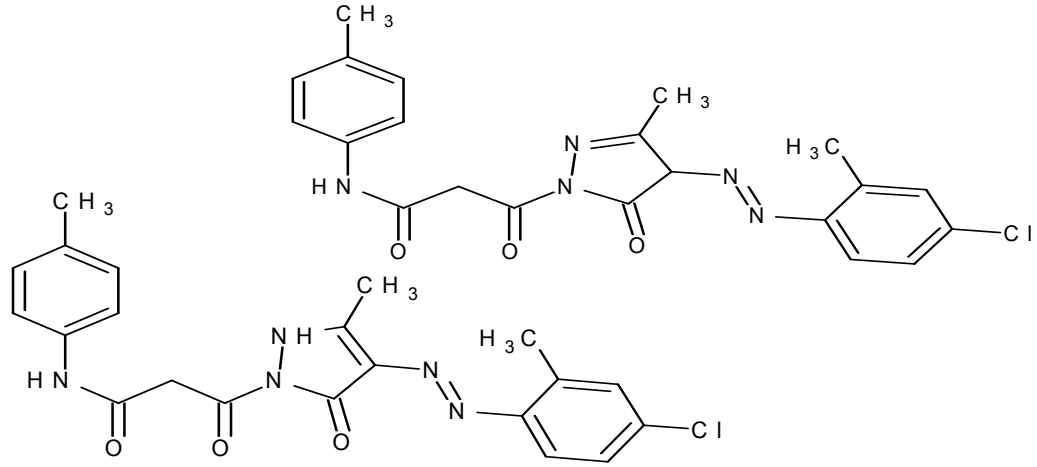


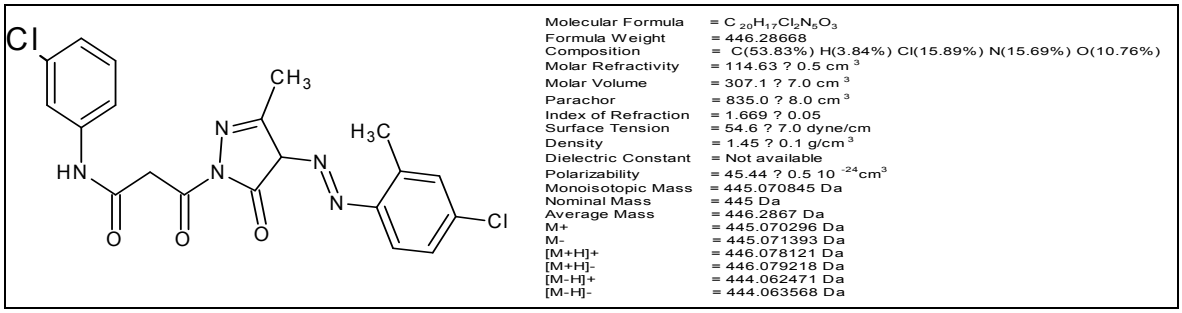
Structure and properties of 1-(p-toludic malonyl)-3-methyl-4-(4'-chloro-2-methyl phenyl azo)-5-pyrazolone (ii-a)



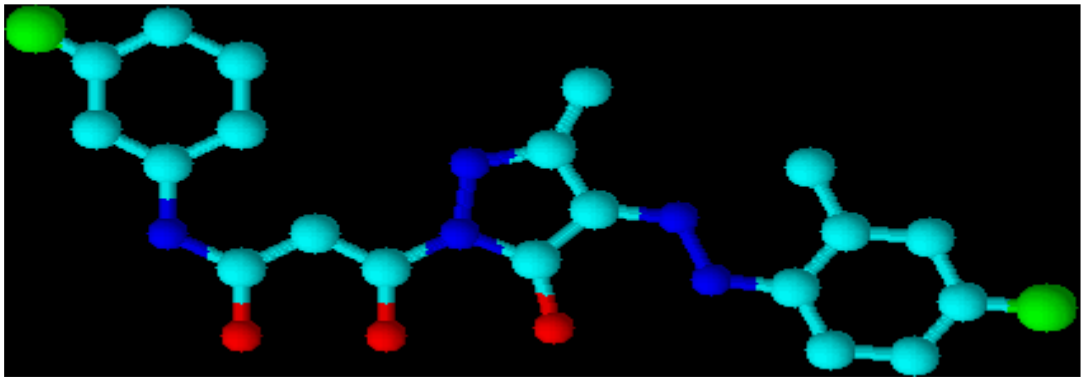
Balls and sticks 3d view of 1-(p-toludic malonyl)-3-methyl -4-(4'-chloro-2-methyl phenyl azo)-5-pyrazolone(ii-a)

Two possible tautomeric forms of the above compound were suggested, which are as follows:





Structure and properties of 1-(m-chloro anilino malonyl)-3-methyl-4-(4'-chloro-2-methyl phenyl azo)-5-pyrazolone (ii-b)



Balls and sticks 3d view of 1-(m-chloro anilino malonyl)-3-methyl -4-(4'-chloro-2-methyl phenyl azo)-5-pyrazolone(ii-b)

Spectral properties of 1-(p-toludic malonyl)-3-methyl-4-(4'-chloro-2-methyl phenyl azo)-5-pyrazolone: (ii-a)
IR (KBr,v max cm^{-1}), 3236 (N-H-str), 1717 (C=O), 820(1,2,4 tri substituted aromatic), 714 (C-Cl str), 1589(-N=N),1457(-CH_2), 1H NMR(400 MHz): 2.21(s 3H, CH_3), 6.7-7.6(m, Ar-H), 3.23(OCH_3 proton).
Spectral properties of 1-(m-chloro anilino malonyl)-3-methyl-4-(4'-chloro-2-methyl phenyl azo)-5-pyrazolone: (ii-b) IR (KBr,v max cm^{-1}): 3013(C-H stretching), 749(1,3 di substituted aromatic), 1647(C=O stretching), 809(1,2,4 tri substituted aromatic, 698 (C-Cl stretching),1H NMR(400 MHz): 2.08(s 3H, CH_3), 5.47(CH_2 proton), 7.32-7.6(m, Ar-H)

4. Conclusions

In conclusion, the synthesized compounds were used as efficient precursors for the synthesis of new heterocyclic compounds including the pyrazolone moiety with expected biological activities and that may be used as dyes also. We have also revealed that the reactions described have done to completion in a much shorter time when irradiated in a focused microwave oven. Product's yield is found to be higher under microwave irrradiation than those obtained by conventional heating. Theoretically predicted IR and NMR were in agreement with the experimental data.

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