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Research Paper

Coupling of Paba Diazonium Chloride with Active Methylenes And Their Microbial Evaluations

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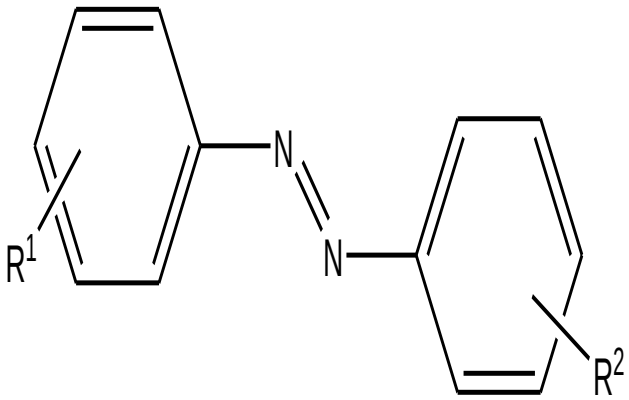
ABSTRACT: *Diazotization of P-amino benzoic acid was carried out in presence of sodiumnitrite and hydrochloric acid. Followed by couplingreaction with activated methylene group in presence of sodium acetate and ethanol to yield the corresponding substituted arylazo (I-V). The coupling adducts were reacted with hydrazine hydrate under reflux in ethanol in presence of tri ethyl amine to yield the pyrazolone derivatives (VI-VIII). Also acetylation of the coupling adducts with acetic anhydride gave only (IX) while the rest of compounds did not react .The compounds (I-IX) were tested against microorganisms such as gram negative bacteria(E-coli Neisseria and Salmonella) in comparable with different antibiotics, for example Ampicillin.*

Keywords: *dyes, PABA, diazoamino coupling, active methylene*

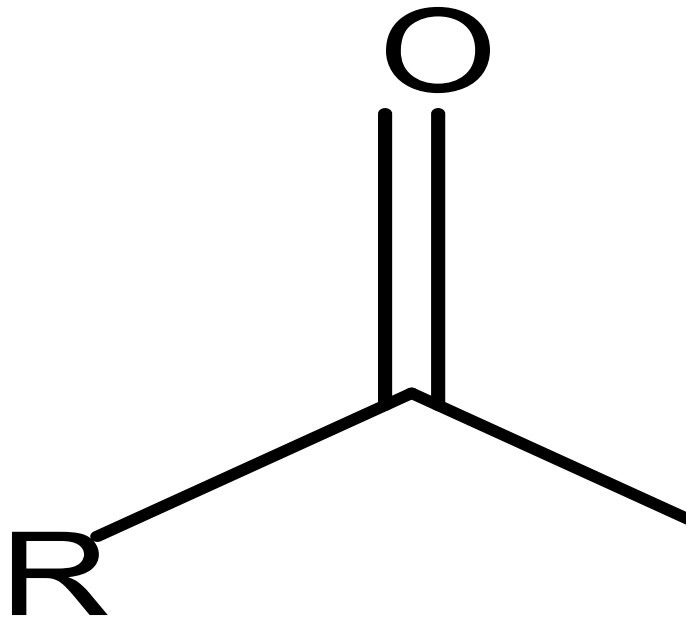
I. INTRODUCTION

Diazotization is a process by which an aromatic primary amine is converted to a diazonium compound. In diazotization, sodium nitrite is added to a solution of the amine in aqueous acid at 0–5°C. Reactions of the amine with nitrous acid give a nitrosamine. Tautomerization and loss of water lead to the diazonium ion, which is stabilized by delocalization of the positive charge at the ortho and para carbon atoms of the ring.Azo dyes form a large structural group of synthetic dyes. An azo dye has the general structure below:[1,2]

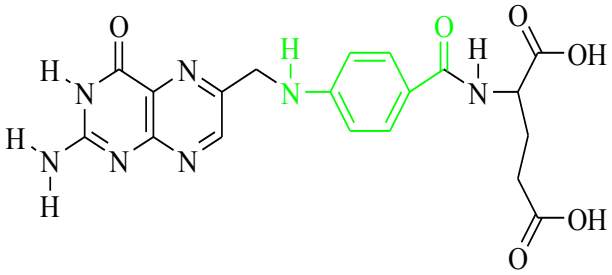


The azo groups form links or bridges between organic residues of which one is usually an aromatic nucleus and being a chromophore, azo groups impart colour to textile fiber. The depth of shade is influenced by the number of azo groups present in the structure of the azo dye. It has been found that the azo dyes are capable of forming hydrogen bonds with the fiber thereby enhancing dye –fiber binding forces. [3]

coupling reaction between active methylene and diazonium salts is generally conducted at room temperature and in protic organic solvent in presence of base. Acetylacetone (1a) , benzoylacetone (1b), diphenylpentanedione(1c), and other 1,3-diketones including cyclic ketones (3a and b) have been coupled with aromatic diazonium salts in ethanloic sodium acetate to yield corresponding products (2a-c)[4,5] and (4a and b)[6,7]



Para-amino benzoic acid (PAPA)is considered to be in the B-complex vitamin family.



PABA has been used as a component of many commercially available sunscreens due to its ability to block damaging ultraviolet rays.

One very interesting application for this versatile substance is its potential to restore hair to its natural color. **(8)**

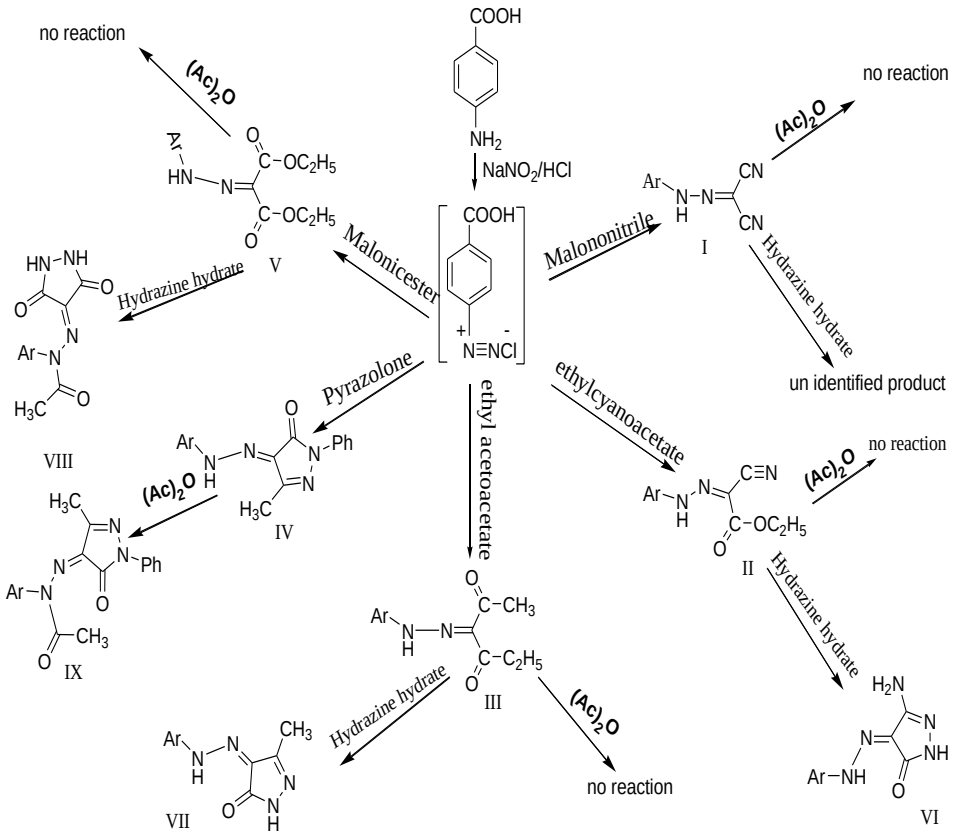
II . DISCUSSION

From the foregoing literature survey, it has been showed that when the diazonium salt of p-amino benzoic acid allowed to react with different compounds contain methylene group, which act as a nucleophilic center and attack the diazonium salt of p-amino benzoic acid to afford the following :

In 2007,Fikret Karel and Aykut Demircall synthesized different derivative through coupling reaction between 4- substituted benzene diazonium salt with malononitrile, ethyl cyano acetate and ethyl aceto acetate in sodium acetate as buffered solution.(9)

R= H , NO_2 ,O CH3

Compound (5 a-c) when allowed to react with hydrazine hydrate, cyclization occurs to give compound (8 a-c)



Scheme I

2.1. Reaction of 4- carboxy – benzene diazonium chloride with active methylene

2.1.1 synthesis of 4-[(N\ - Dicyano methylene) hydrazino] benzoic acid (I)

When p-amino benzoic acid was reacted with sodium nitrite and hydrochloric acid at 0 ^{0}C diazonium salts was obtaind which reacted in situ with malononitrile to afford compound I. The explanation of this reaction is a nuclophilic attack of the active methylene of malononitrile on the diazonium salt.

Compound (I) was obtained as a desired product and was confirmed by satisfactory spectroscopic analysis. The infra red spectrum showed strong bands at (2500 - 3500 cm^{-1}) correspond to carboxylic group , also conjugated cyano group at 2050cm^{-1} as sharp band , the carbonyl group of carboxylic acid appearse at 1680 cm^{-1}, stretching band corresponding to carbon-carbon double bond of aromatic ring at (1420 and 1610 cm^{-1}) .

The proton magnetic resonance spectrum showed two doublet signals at δ = 7.5 ppm and 7.9 ppm representing (4H, Ar-H). Also carbon magnetic resonance spectrum showed signal at 85.88 ppm indicating

olfenic carbon, signals at 109.9 and 114.3 ppm represent cyano group and signals at 116.2 and 145.4 ppm representing aromatic carbons and 166.56 ppm indicated to carbonyl group.

2.1.2 Synthesis of 4-[N\ -(cyano-ethoxy-carbonyl -methylene)hydrazino] benzoic acid (II)

4-[N\ -(cyano-ethoxy-carbonyl -methylene) hydrazino] benzoic acid (II) was obtained when p-amino benzoic acid was diazotized in presence of sodium nitrite and hydrochloric acid , after the diazotization has been completed , ethyl cyano acetate was added followed by addition of sodium acetate to activate the nuclophilic attack of active methylene on diazonium salt giving nuclophilic adduct , as yellowish green crystals. The infra red of compound (II) showed strong bands at (2500 -3500 cm^{-1}) owing to carboxylic group , also an indication of conjugated cyano group with sharp band at 2050cm^{-1}, appearance of characteristic band of carbonyl group of ester at 1740 cm^{-1} was noticed beside a lower frequency band of carbonyl group of carboxylic acid at 1680 cm^{-1}. Also proton magnetic resonance spectrum showed a typical ethyl ester group with triplet and quartet at 1.3 ppm and 4.3 ppm respectively, as well as two doublets at 7.5 ppm and 7.97 ppm representing two sets of aromatic protons in addition to acidic protons at 12.34 possibly hydroxyl group. Carbon magnetic resonance spectrum showed signals at 14 ppm indicated methyl group , signal at 62 ppm for methylene group and signal at 105.6 ppm represents cyano group.

2.1.3 Synthesis of 4-[N\ - (1-ethoxycarbonyl-2-oxo- propylidene)- hydrazino)] Benzoic acid (III)

A diazonium salt of p-amino benzoic acid when allowed to react with ethyl aceto acetate in the presence sodium acetate at room temperature the desired compound (III) was obtained. All spectroscopic data , that is infra-red , proton magnetic resonance and carbon magnetic resonance agreed with the proposed structure because of the characteristic proton magnetic resonancesignals of ethyl ester group at 1.3 ppm and 4.3 ppm as well as the acidic proton of the carboxylic group at 11.57 ppm , also the presence of ketonic group at 193.7 ppm in carbon magnetic resonance, the infra red spectral data showed the bands of carboxylic group , the characteristic carbonyl band of ester and the lower frequency of the ketonic group due to conjugation.

2.1.4 Synthesis 4-[N\ - (3-methyl-5-oxo-1-phenyl-1,5-dihydro-4H- pyrazol-4-ylidene) hydrazino] benzoic acid (IV).

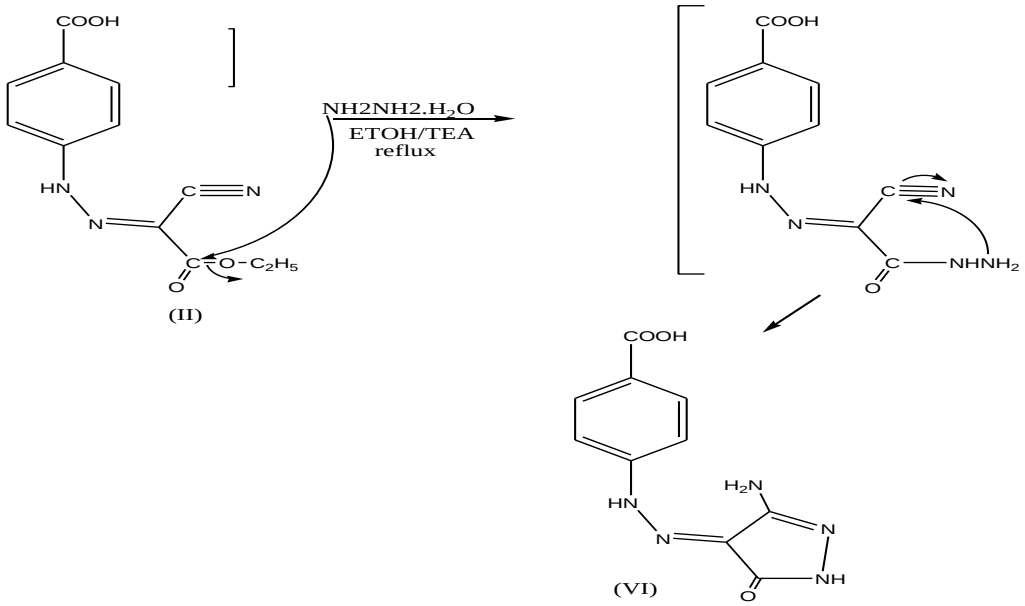
The basic ethanolic solution of 1-phenyl-3-methyl-5-pyrazolone was added to the preformed diazonium salt of p-amino benzoic acid to enable the nucleophilic addition of the active methylene of the pyrazolone to the diazonium salt, the reaction was completed giving the desired product in excellent yield as orange crystals.With respect to the spectral data, very important information was obtained simply absence of aliphatic protons and carbons except methylgroup at position three of the pyrazolone ring which gave an idea that there is no NN double bond while the CN double bond is conjugated with the carbonyl group of the pyrazoline , at position three of the pyrazolone ring 13ppm represinting hydroxyl group which indicate the enolization of the product , the aryl part of the compound showed signals and bands comparable with the other synthesized compounds.

2.1.5 Synthesis of 4-[N\- (diethoxy-dicarbonyl-mathylene) hydrazino] benzoic acid (V)

Reaction of the basic ethanolic solution of diethylmalonate with the diazonium salt of p-amino benzoic acid gave 4-[2-(1,3-diethoxy-1,3-dioxopropan-2-ylidene) hydrazinyl] benzoic acid (V) in lower yield when compared with other active methylenes , all the spectral data obtained were consistent with the proposed structure.

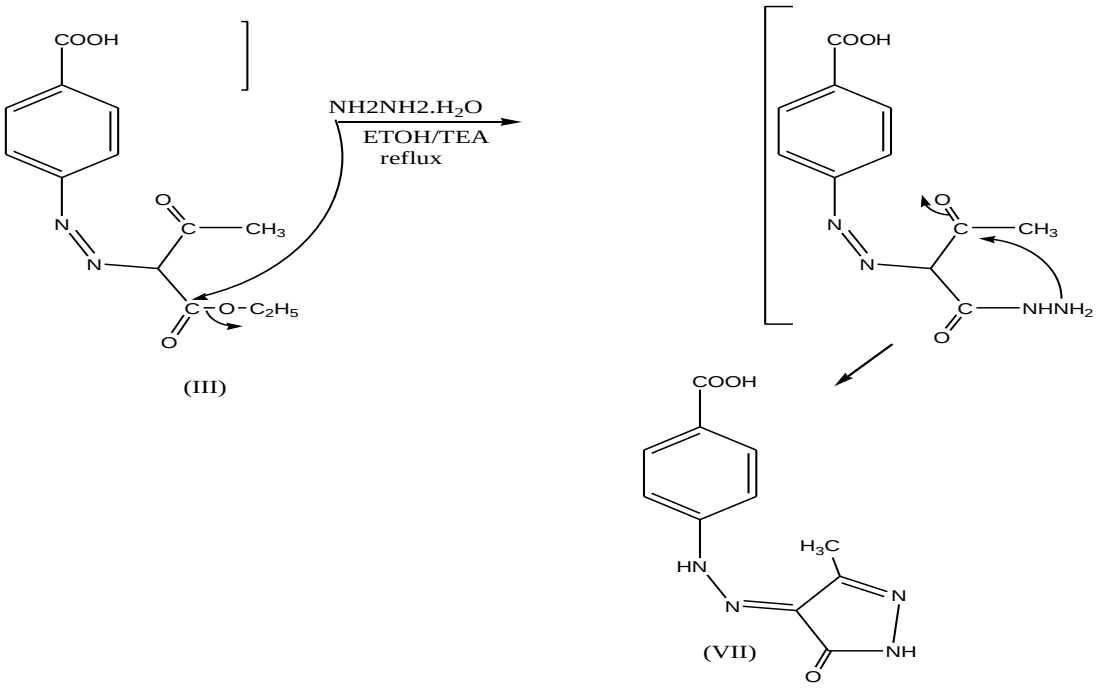
2.2. Reaction of compouneds II, III, and V with hydrazine hydrate

Compounds I, II, III, and V were expected to give the pyrazoline ring, only unexpectedly compound I gave unidentified mixture when reacted with the hydrazine hydrate in the same reaction conditions. Reaction of compound (II) with hydrazine hydrate gave4-[N\ - (3-amino-5-oxo-1,5-dihydro-4*H*-pyrazol-4-ylidene) hydrazino] benzoic acid (VI) forming pyrazolone derivatives (VI) as brown crystals.



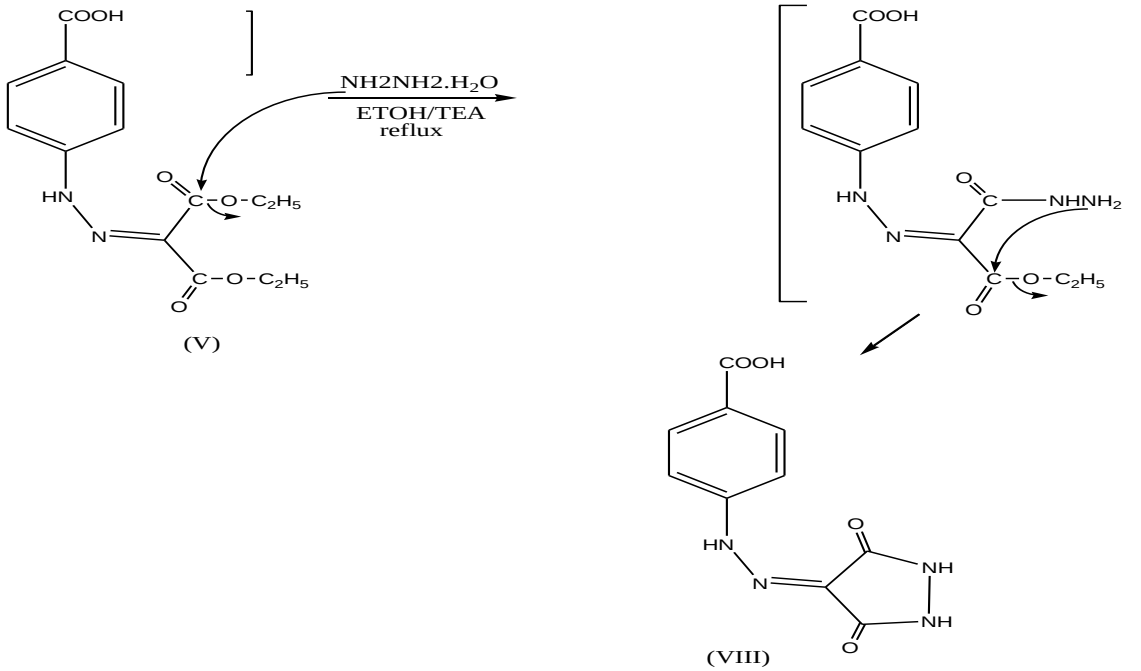
The structure of compound (VI) was confirmed by satisfactory spectroscopic analysis. IR spectrum showed strong bands to COOH at (2500-3500) cm^{-1}, CO of carboxylic acid at 1680 cm^{-1}, CO of Ketone at 1630 cm^{-1}, the stretching corresponding to C═C aromatic ring at 1400-1600 cm^{-1}. The H^1-NMR spectrum showed two doublets at 7.4ppm and 7.8 ppm representing 4H for aromatic protons, the acidic proton of the carboxylic acid appears at 10.5 ppm.

The reaction of compound (III) with hydrazine hydrate gave compound 4-[N\ -(3-methyl-5-oxo-1,5-dihydro-4*H*-pyrazol-4-ylidene) hydrazino] benzoic acid (VII)showing the same route of the reaction , forming pyrazolone derivative (VII) as orange crystals.



The structure of compound (VII) was confirmed by satisfactory spectroscopic analysis, all spectroscopic nformation agreed with the proposed structure.

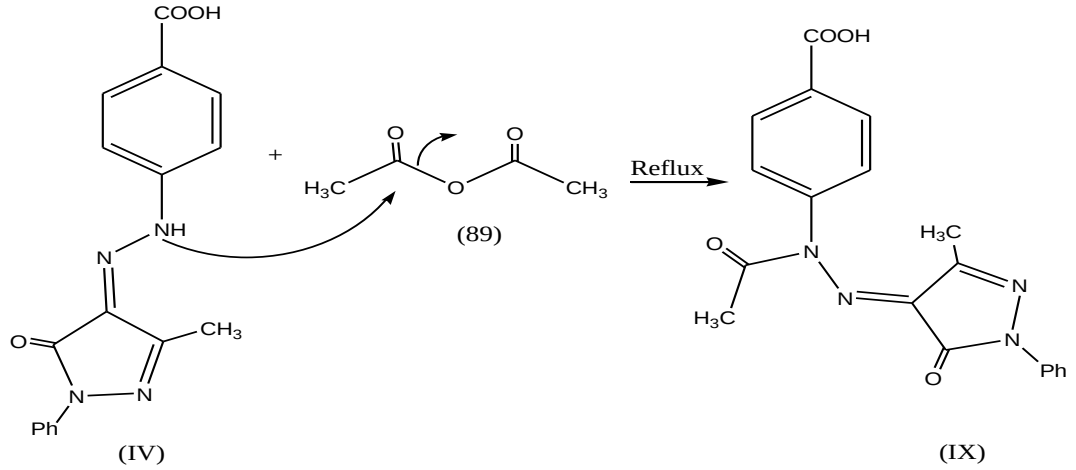
The compound (V) was reacted with hydrazine hydrate to give 4-[N\ - (3,5-dioxopyrazolidin-4-ylidene) hydrazino] benzoic acid (VIII) , as yellow crystals.



The spectrum of compound (VIII) show mostly the same spectra of compound (VI) only differ in the position of hydroxyl group at 13.8 ppm acidic proton , which indicate the enolization of the product.

2.3. Reaction of compound (IV) with acetic anhydride

Refluxing of compound (IV) with acetic anhydride for 2.5 hours gave an identified product, greenish –yellow yield.

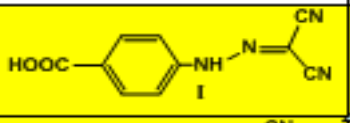
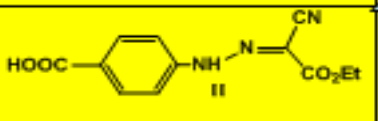
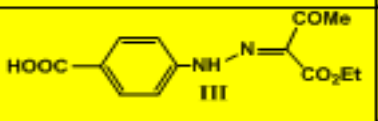
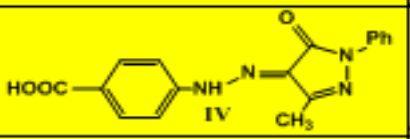
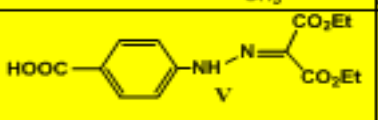
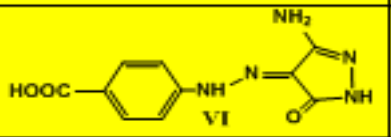
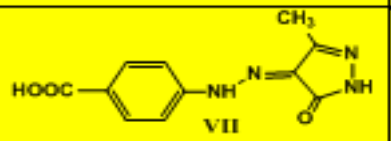
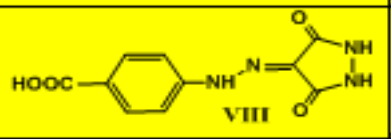
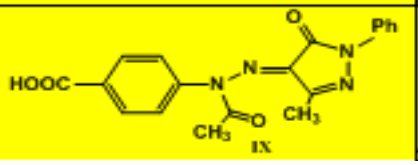


Its structure was established on the basis of the ^{1}H-NMR spectra which showed a singlet signal at δ= 2.25 ppm representing methyl of acetyl group. Also ^{13}C-NMR showed signal at 171.8 of carbonyl of acetyl group.

2.4. Biological evaluation

Antibacterial activities of the synthesized compounds were examined in vitro by the known agar diffusion technique. All compounds were tested for activity against gram-negative bacteria Escherichia coli-Neisseria and Salmonella, compared with antibiotic. All compound under study showed activity against gram-negative bacteria except compound (IV). Compound VII exhibited higher activity than others against two selected microorganisms.It was observed that azo compounds I, III and IX showed moderate activity against bacteria. While the remaining compounds displayed weaker activity against all microbes under investigation table I.

Table(I) :Azo compound and antibiotic results of the tested on nesseria , E-coli and salmonella cm

Azo compound	Neiseria	E-coli	Salmonella	Anti biotic
 I	1.3 / 1.2	1 / 1.5	0.6 / 1.2	A10
 II	1 / 0	0 / 1.2	1 / 3.5	Ch30
 III	1.6 / 1	1.2 / 1	1 / 0	CX10
 IV	0 / 2	0 / 3.2	0 / 0	AM25
 V	0.8 / 1.3	0 / 0	1 / 0	T30
 VI	0 / 0.8	0 / 0	1.3 / 2.4	MET5
 VII	1.2 / 3.6	2 / 2	0	Va5
 VIII	1 / 0.6	1 / 1	3.1	Cb100
 IX	1 / 1	0.8 / 1.2	1.9 / 0	FD10

III . EXPERMENTAL

All chemicals were purchased from Sigma-Aldrich (St. Louis, Mo, USA). All melting points (mps) were determined by SMP3 stuart scientific melting point apparatus (stuart, Staffordshire, UK) and are uncorrected. All the reactions were monitored by thin-layer chromatography (TLC) using silica gel 60 F254 TLC plates (Merck KGaA, Darmstadt, Germany). Spectroscopic data were recorded with the following instruments: IR,Perkin Elmer model spectrum100spectrophotometer (Waltham, Massachusetts, USA); NMR, Brucker 300 MHz instrumentsin deuterochloroform ($CDCl_3$) or hexadeuterodimethylsulfoxide (DMSO-d_6) solution using TMS as internal standard (Brucker Company, Elk GroveVillage, USA).

3.1. Synthesis of products

3.1.1. Reaction diazonium salt of P-amino benzoic acid with active methylenes

General procedure[7]

P-amino benzoic acid (0.03mol) was dissolved in 30mLof concentrated HCl and 20mL of water cooled in ice and then (0.03mol) of sodium nitrite in 50mL of water was added in portions .Amixture of (0.03mol) of active methylenes , 20g of sodium acetate ,15mL of ethanol , and 50mL of water was prepared separately and cooled in ice. The diazonium salt solution was added slowly to the second solution ,with ice cooling .The cooled reaction mixture was stirred for 30 mins., filtered, washed with cold water and re-crystallized from ethanol.

Compound Number	Yield (%)	m.p.(C°)

I	77	253-255
II	32	264-265
III	36	208-210
IV	81	298-299
V	35	219-222

3.1.1.1 4-[(N\ -Dicyano methylene) hydrazino] benzoic acid (I)
Mol. Formula $C_{10}H_6N_4O_2$ (214)
IR (KBr) : v = 2500-3500 (COOH) , 2050 (CN) , 1680 (CO) , 1420-1610 (C=C).
^{1}H-NMR (DMSO-d_6) δ = 7.5 (d , 2H , Ar-H) ,7.9 (d , 2H , Ar-H).
^{13}C– NMR (DMSO-d_6) : δ = 85.88 (s ,1C) , 109.9(s ,1C) , 114.3 (s,1C) , 116.2 (d ,2C) , 127.2 (s , 1C) , 130.8 (d ,2C) , 145.4 (s , 1C) ,166.56 (s , 1C).

3.1.1.2 4-[N\ - (cyano--ethoxy-carbonyl -methylene) hydrazino] benzoic acid (II)
Mol. Formula $C_{12}H_{11}N_3O_4$ (261)
IR(KBr): v = 2500-3500 (COOH) , 2050 (CN) 1740 (CO) , 1680(CO) , 1610-1430 , (C=C) , 1250 (O-C_2H_5).
^{1}H-NMR(DMSO-d_6) δ = 1.3 (t , 3H , CH_3) ,4.3 (q , 2H , CH_2) , 7.5 (d , 2H ,Ar-H) ,7.9 (d , 2H , Ar-H) , 12.34 (s , 1H , COOH).
^{13}C– NMR (DMSO-d_6) δ = 14 (q ,1C) ,62 (t , 1C) , 105.6 (s , 1C) , 111 (d , 2C) ,115.7 (s ,1C) , 126.4 (d ,2C) ,130.8 (s , 1C) ,145.3 (s ,1C) , 160.5 (s , 1C) , 166.68 (s ,1C).

3.1.1.3 4-[N\ - (1-ethoxycarbonyl-2-oxo- propylidene)-hydrazino)] benzoic acid (III) Mol. Formula $C_{13}H_{14}N_2O_5$ (278)
IR(KBr) :v = 2500-3500 (COOH) ,1710 (CO) ,1680 (CO) , 1630(CO) , 1620-1430 (C=C) ,1190 (CH_3).
^{1}H-NMR (DMSO-d_6): δ = 1.3 (t , 3H , CH_3) , 2.4 (s , 3H , $COCH_3$) , 4.3 (q ,2H , CH_2) , 7.5 (d , 2H , Ar-H) ,7.9 (d ,2H , Ar-H) ,11.57 (s , 1H , COOH).
^{13}C– NMR(DMSO- d_6): δ =14(q ,1C) , 25 (q , 1C) , 60.6 (t , 1C) , 115 (d , 2c) ,125 (s ,1C) , 130.9 (d ,2C) ,133 (s ,1C) ,145.3 (s ,1C) , 162 (s ,1C) , 166.8 (s ,1C) ,193.7 (s ,1C).

3.1.1.4 4-[N\ - (3-methyl-5-oxo-1-phenyl-1,5-dihydro-4*H*-pyrazol-4-ylidene) hydrazino] benzoic acid (IV)
Mol. Formula $C_{17}H_{14}N_4O_3$ (322)
IR (KBr) :v = 2500-3500 (COOH) ,1690 (CO) ,1660 (CO) , 1610-1420 (C=C) ,1375 (CH_3).
^{1}H-NMR (DMSO-d_6) : δ = 2.2 (s , 3H , CH_3), 7 (d , 2H , Ar-H) ,7.3 (dd , 1H , Ar -H) 7.5(dd , 2H , Ar-H) , 7.8 (dd , 2H , Ar-H) , 7.9 (d , 2H , Ar-H) , 13 (s ,1H , OH).
C^{13} – NMR (DMSO-d_6) : δ =11(q,1C) , 115.6 (d , 2C) , 117.6 (s ,1C) ,120.6 (d ,2C) , 124.8 (d ,1C) , 127 (d ,2C) ,128.8 (d ,2C)130.8 (s ,1C) , 137.6 (s ,1C) , 144.7 (s ,1C) , 148.5 (s ,1C) ,156 (s ,1C) ,166.6 (s ,1C).

3.1.1.5 4-[N\ -(diethoxy-dicarbonyl-mathylene) hydrazino] benzoic acid (V) Mol .Formula $C_{14}H_{16}N_2O_6$ (308)
IR (KBr) : v = 2500-3500 (COOH) , 1720 (CO) ,1680 (CO) , 1610 - 1430 (C=C) , 1260 (OC_2H_5).
^{1}H-NMR (DMSO-d_6) δ := 1.2 (t ,6H , CH_3) ,4.2 (q , 4H , CH_2) 7.4 (d , 2H , Ar-H) ,8 (d , 2H , Ar-H) , 11.9 (s ,1H , COOH).
C^{13} – NMR (DMSO-d_6) : δ=13.7(q, 2C) , 61(t , 2C) , 114.5 (d , 2C) , 123.8 (s ,1C) ,125.3 (s ,1C) , 130. 8(d ,2C) ,145.8 (s,1C),161.3 (s , 2C) ,166.7 (s ,1C).

3.1.2. Reaction of compounds II , III and V with hydrazine hydrate General procedure

In 5o mL round –bottomed flask equipped with condenser and magnetic stirrer. (0.01mol) of compounds (II , III and V) respectively was refluxed with (0.01mol) hydrazine hydrate in 30mL ethanol , and few drops of triethyl amine , the formed precipitate was filtered ,washed with cold water and re-crystallized from toluene.

Cmopound Number	Reaction Time (Hour)	Yield (%)	m.p. (C°)
VI	3 hrs.	24.29	> 3oo
VII	6 hrs.	45.8	> 3oo
VIII	8 hrs.	40.32	242-245

3.1.2.1 4-[N\ - (3-amino-5-oxo-1,5-dihydro-4*H*-pyrazol-4-ylidene) hydrazino] benzoic acid (VI)

Mol. Formul $C_{10}H_9N_5O_3$ (247)
IR (KBr) : v = 2500-3500 (COOH) ,1680 (CO) ,1630 (CO) , 1600 -1400 (C=C).
^{1}H-NMR (DMSO-d_6) δ = 7.4 (d ,2H , Ar-H) , 7.8 (d , 2H , Ar-H) ,10.5 (s , 1H , COOH).

3.1.2.2 4-[N\- (3-methyl-5-oxo-1,5-dihydro-4*H*-pyrazol-4-ylidene) hydrazino] benzoic acid (VII)
Mol. Formul $C_{11}H_{10}N_4O_3$ (246)
IR (KBr) : v = 2500-3500 (COOH) , 1640 (CO) , 1610 (CO) , 1580 -1450(C=C) , 1370 (CH_3).
^{1}H-NMR (DMSO-d_6) : δ = 2 (s , 3H , CH_3) , 7.4 (d , 2H , Ar-H) , 8 (d , 2H , Ar-H).
^{13}C– NMR(DMSO-d_6) : δ =11.8 (q ,1C) , 115 (d ,2C) , 128 (s , 1C) , 130.5 , (s ,1C) , 132.9 (d ,2C) , 144.4 (s , 1C) , 146.6 (s , 1C) , 159.9 (s , 1C) , 169 (s , 1C).

3.1.2.3 4 -[N\- (3,5-dioxopyrazolidin-4- ylidene) hydrazino] benzoic acid(VIII) Mol. Formul $C_{10}H_8N_4O_4$(248)
IR(KBr) : v = 2500-3500 (COOH) , 1670 (CO) , 1610 (CO) , 1500-1390 (C=C).
^{1}H-NMR (DMSO-d_6) : δ = 7.4 (d , 2H , Ar-H) , 7.8 (d , 2H , Ar-H) , 13.8 (s , 1H , OH).
^{13}C– NMR (DMSO-d_6) : δ = 114 (d , 2C) , 114.7 (s , 1C)) , 121.34 (d ,2C) , 130.7 (s , 1C) , 144.5 (s ,1C) , 161.8 (s , 2C) , 163.4 (s , 1C).

3.1.3. Reaction of compound IV with acetic anhydride General procedure
In 5o mL round –bottomed flask equipped with condenser and magnetic stirrer, (0.01mol) of compound (IV) was refluxed with acetic anhydride for 2.5 hrs. , the acetylated product was separated, filter, and re-crystallized from toluene, m.p.(225-228) , yield 27.77%.

3.1.3.1 4-[N- acetyl-N\ -(3-methyl-5-oxo-1-phenyl-1,5-dihydro-4*H* pyrazol-4-ylidene) hydrazino] benzoic acid (IX)
Mol. Formul $C_{19}H_{16}N_4O_4$ (364)
IR (KBr) : v = 2500-3500 (COOH) , 1780 (CO) , 1730 (CO) , 1670 (CO) , 1560 -1420 (C=C) , 1375 (CH_3).
^{1}H-NMR (DMSO-d_6): δ = 2.2 (s ,3H , CH_3) , 2.4 (s ,3H , $COCH_3$) 7 (dd , 1H ,Ar-H) 7.3 (dd ,2H , Ar -H) 7.5 (dd , 2H , Ar-H) ,7.8 (d , 2H ,Ar-H) , 7.9 (d , 2H , Ar-H) ,12.48 (s , 1H , COOH).
^{13}C– NMR (DMSO-d_6) : δ = 11.5 (q ,1C) , 21.9 (q ,1C) , 115.6 (d , 2C) , 117.6 (d ,2C) , 124.8 (d ,1C) , 127 (s ,1C) , 128.8 (s ,1C) ,129 (d , 2C) , 131.9 (d , 2C) , 137.7 (s , 1C) , 144.76 (s , 1C) , 148.5 (s , 1C) , 156.2 (s , 1C) , 166.6 (s , 1C) , 171.8 (s , 1C)

3.2. The sensitivity test of the azo compound
The newly synthesized products were dissolved 3mg in1mL of acetone then saturated disk of filter paper then the dried this disk and distribution on agar containing the gram-negative bacteria , Escherichia coli – Neisseria and Salmonella 24hrs. at 37C^o

Antibiotic
Antibiotic carried out using the agar diffusion technique containing the gram-negative bacteria , Escherichia coli –Neisseria and Salmonella shown in table I.

IV . CONCLUSION

p-aminoazobenzoic acid was first reacted with sodium nitrite and hydrochloric acid in order to prepare diazonium salts which was then reacted insitu with malononitrile , ethyl cyano acetate , ethyl aceto acetate , pyrazoline and diethylmalonate giving hydrazinyl derivatives. Compounds (II), (III) and (V) gave a moderate yield. While compounds (I) and (IV) gave a high yield.Their structures were established on the basis of the IR , ^{1}H-NMR and ^{13}C-NMRspectra.Refluxing of compound (II , III ,and V) in hydrazine hydrate gave a good yield of compound (VI ,VII and VIII) , the structure of compounds was substantiated from IR , ^{1}H-NMR and 13C-NMRspectra .

All the compounds were tested for activity against gram-negative bacteria Escherichia coli- Neisseria and Salmonella compared with antibiotic, excepted compound (IV) no effected. The compound VII exhibited higher activity than others against two selected microorganisms. It is observed that azo compounds I and III showed moderate activity against bacteria. The remaining compounds displayed weak activity against all microbes.

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