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Synthesis of Some Bis-Hydrazones Derived from Benzilic Acid Hydrazide and Study Antibacterial Activity

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ABSTRACT

In this paper the synthesis of bis-hydrazones derivatives has been achieved by the reaction of terphthaldehyde with some primary aromatic amines yielded mono hydrazones (2a-g), the later reacted with benzilic acid hydrazide to afford the new of bis- hydrazones (3a-g). The synthesized mono and bis-hydrazones were characterized on the bases of their physical properties and spectroscopic data .Bis-hydrazone compounds were tested for biological activities as antibacterial and showed significance to moderate activity

Keywords: *Benzilic acid, hydrazide ,bis hydrazone, terphthldehyde, antibacterial*

INTRODUCTION

Hydrazones are a class of organic compounds have the structure $RHC=NNH_2$ [1]. They are related to ketones and aldehydes by the replacement of the oxygen with the NNH_2 functional group. They are formed usually by the action of hydrazine on ketones or aldehydes [2,3] The interest in the chemistry of hydrazones are a consequence of the fact that they undergo a wide The design and synthesis of new bis-hydrazones for the many particular pieces of research that have contributed to the spectacular. Hydrazone moiety plays an important key role in heterocyclic chemistry [4-6]. As we have already known, hydrazone compounds are important of multiple uses. The symmetric and asymmetric hydrazones represent one of the most important types of these compounds. Some bis- hydrazones have been used as anti-inflammatory agents and painkillers [7]. Some of them have also been found to be effective against certain bacterial and fungal species [8].

While others have been used as antimicrobials as they have been shown to be more effective than the effectiveness of mono hydrazones [9], and recently it has been shown that some bis-hydrazones do not cause ulcers when used in relieving pain [10]. Moreover, bis-hydrazones represent good fecundates for the preparation of different organic complexes [11-14]. Other bis-hydeazone compounds showed significant anti-inflammatory activity, while some of them exhibited potent analgesic activity [15]

EXPERIMENTAL SETUP

Melting point were determined in open capillary type on Stuart melting pointSMP30.The IR spectra using KBr disk were recorded on FTIR-600 Bio Tec. Engineering Management Co.Ltd. (UK) using KBr discs.^{1}H-NMRand ^{13}C-NMR spectra were recorded on JEOLEEA400MHz FT-NMR. All chemicals used were of high purity as the manufactures supplied starting chemical compounds were obtained from BDH, Sigma Aldrich, Fluka and used as received.

Preparation of 4 ((Substitutedimino) Methyl) Benzaldehyde (2a-G)[16]

Reflux of (0.001 ml, 0.134 g) Terfethaldehyde with 0.001 mol of appropriate primary aromatic amines in (30 ml) of ethanol for 5 hours. Leave to the next day at room temperature. The reaction mixture is poured into a quantity of water (20 ml) and stirring for one hour separates the filtration precipitation, re-crystallized using an appropriate solvent. Physical and spectral data are listed in tables (1 and 3) for compounds (2a-g).

Table1. *Physical data for compounds (2a-g)*

Comp. No.	X	Molecular formula	m.p °C	Yield %	Color	Crys. solvent
2a	4-CH_3	$C_{15}H_{13}NO$	190-192	80	pale yellow	Ethanol
2b	2-CH_3	$C_{15}H_{13}NO$	228-230	84	dark yellow	Ethanol+H_2O
2c	3-CH_3	$C_{15}H_{13}NO$	98-100	47	yellow	Methanol
2d	4-OCH_3	$C_{15}H_{13}NO$	173-175	94	olive green	Acetone
2e	2-OH	$C_{14}H_{11}NO_2$	113-115	40	brown	Ethanol
2f	2-Cl,4-NO_2	$C_{14}H_9N_2O_3Cl$	83-85	90	white	Methanol
2g	4-Cl	$C_{14}H_{10}NOCl$	172-174	60	pale yellow	Ethanol+H_2O

Preparation of 4 (substitute diphenylimino) benzylidine) 2- hydroxy- 2, 2-diphenyl acetohydrazide (2a- g) [17]

To equimolar of benzilic acid hydrazide (0.24g, 0.001mole) and hydrazones(2a-g) (0.001mole)in absolute ethanol (30ml). The mixture was refluxed for 6 hours, Then stirring the reaction mixture for (12 hours) at room temperature; The solid precipitate was filtered off and re-crystallized from ethanol. Physical and spectral data are listed in tables (2 and 4) for compounds (3a-g)

Table2. *Physical data for compounds (3a-g)*

Comp. No.	X	Molecular Formula	m.p°C	Yield %	Color
3a	4-CH_3	$C_{28}H_{25}N_3O$	288-290	45	pale yellow
3b	2-CH_3	$C_{28}H_{25}N_3O$	268-270	52	Green
3c	3-CH_3	$C_{28}H_{25}N_3O$	256-258	55	Yellow
3d	4-OCH_3	$C_{23}H_{20}N_3O_3$	278-280	40	Green
3e	2-OH	$C_{28}H_{22}N_3O_3$	293-295	62	Brown
3f	2-Cl,4-NO_2	$C_{28}H_{20}N_4O_4Cl$	88-90	95	Yellow
3g	4-Cl	$C_{28}H_{20}N_4O_4Cl$	283-285	53	Brown

RESULTS AND DISCUSSION

Hydrazones were found to be an important structural unite to construct a large number of organic compounds through their various reactions with different organic reagents .Thus, due to the possession of the terphethaldehyde compound two carbonyl group, it has the ability to condense with two groups to form symmetric or asymmetric bis-hydrazones which as we have mentioned, have great importance in many fields .The mono hydrazone compounds (2a-g) synthesize from condensation of one mole of terphethaldehyde (1) with one mole of some aromatic amines. An efficient procedure is described for the synthesis of bis-hydrazone derivatives (3a-g) via reaction of benzilic acid hydrazide with hydrazones (2a-g) as shown in the scheme.

All products were characterized by physical and spectral data. The IR spectra for compounds (2a-g) showed characteristic absorption peak in the region (1688-1701cm^{-1}) stretching for (C=O

amide) group, at (1593-1649 cm^{-1}) stretching group for (C=N) group, (2976-3052 cm^{-1}) due to (ArCH) group.

The ^{1}H-NMR spectra for compounds (2a-g) in (DMSO-d_6) in ppm showed significant peaks as the following. .singlet in the range (7.015-8.066ppm) due to HC=N group, at the range (8.69-9.579ppm) due to HC=O group, in addition the aromatic of part showed multiplet and other groups as shown in table 3.

^{13}C-NMR Spectra showed peaks for compounds (2a-g) at the following ,these compounds containing(CH=N) were characterized by the presence of the signals in the range of δ(151.7-161.11 ppm),the carbon signal of C=O group for aldehyde appeared at δ values between(190.6-192.2ppm),while CH_3 group in some compounds appeared at δ values between(20.90-21.75 ppm),finally these Compounds have aromatic part were characterized by the presence of the signals as shown in table 3.

Table3. *Spectral data for compounds (2a-g)*

Comp. No.	FTIR (KBr) cm^{-1}			^{1}H-NMR δ (ppm) DMSO-d6	^{13}C-NMR δ (ppm) DMSO-d6
	C=O	C=N	ArCH		
2a	1701	1593	2997	2.345 (s, 3H, CH_3), 8.707 (s, 1H, HC=O), 7.246-7.249 (m, 6H, ArH),8.058 (m, 3H, ArH, HC=N)	21.4(CH_3),[122.3, 129.8, 130.4,131. ,137.1,139.3,142.4,149.1] aromatic carbon,160,11(CH=N),192.1(CHO)
2b	1694	1649	3024	2.364 (s, 3H, CH_3), 8.71(s, 1H, HC=O), 7.196-7.251 (m, 6H, ArH),8.057 (m, 3H, ArH, HC=N)	20.98(CH_3),[122.4,129.3,130.2,131. 3,136.7,139.3,142.2,149] aromatic carbon,160,2(CH=N),192.2(CHO)
2c	1701	1618	2976	2.354 (s, 3H, CH_3), 8.69 (s, 1H, HC=O), 7.233-7.246 (m, 6H, ArH), 8.066 (m, 3H, ArH, HC=N)	21.75(CH_3),[122.2,129.5,130.3,131. 4,137.2,139.1,142.4,149] aromatic carbon,161,1(CH=N),190.9(CHO)
2d	1693	1623	3022	3.787 (s, 3H, OCH_3), 9.578 (s, 1H, HC=O), 7.135-7.284 (m, 4H, ArH), 7.638-7.812(m, 4H, ArH), 7.015 (bs, 1H, HC=N)	55.8(OCH_3),[115.4,122.5,129.4,130 ,139.8,142.4,145.1,159.3]aromatic carbon,161.1(CH=N),190.8(CHO)
2e	1688	1637	3030	9.841 (s, 1H, OH 9.443 (s, 1H, HC=O), 7.135-7.284 (m, 4H, ArH), 7.638-7.812(m, 4H, ArH), 7.019 (bs, 1H, HC=N)	[114.9,119.7,122.5,128.4,129.7,130. 1,139.2,141.1]aromatic carbon, 151.2(C-OH) 151.7(CH=N),191.3(CHO)
2f	1698	1653	3066	8.710 (s, 1H, HC=O), 7.244-7.251 (m, 6H, ArH), 8.052(m, 3H, ArH, HC=N)	[122.8,125.1,128.8,129.9,130.1,131. 2,139.3,142.4]aromatic carbon. 155.7(C-N),147.8(C-NO_2),161(CH=N),191.3(CHO)
2g	1695	1642	3052	8.722 (s, 1H, HC=O), 7.241-7.248 (m, 6H, ArH), 8.063(m, 3H, ArH, HC=N)	[122.8,125.1,128.8,129.9,130.1,131. 2,139.3,142.4]aromatic carbon. 145.7(C-N) ,160(CH=N),190.6 (CHO)

The IR spectra for compounds (3a-g) showed characteristic absorption peak in the region (1630-1655 cm^{-1}) stretching for (C=O amide) group, at (1598-1618 cm^{-1}) stretching for (C=N) group, at (3198-3318 cm^{-1}) due to (NH) group. and at (3041-3066 cm^{-1}) stretching for (ArH) group. The ^{1}H-NMR spectra for compounds (3a-g) in (DMSO-d_6) in ppm showed significant peaks as the following. Singlet in the range (4.789-6.122 ppm) due to OH group, at the range (8.707-9.518ppm) due to HC=O group and singlet in the range (7.015-8.063ppm) due to HC=N group, in addition the aromatic of part showed multiplet and other groups as shown in table 4. ^{13}C-NMR Spectra showed peaks for compounds (3a-g) at the following, these compounds containing (C-OH) were characterized by the presence of the signals in the range of δ (82.9-83.8 ppm), The presence of (CH=N) group adjacent to Whose origin

monohydrazone (CH=N) were characterized by the presence of the signals in the range of δ(159.8-160.7 ppm) while the (CH=N) group adjacent to Whose origin benzilic acid hydrazide were characterized by the presence of the signals in the range of δ(144.1-144.7 ppm),also some of compounds appeared at δ values between(20.9-21.5 ppm)due to CH_3 group, finally these Compounds have aromatic part were characterized by the presence of the signals as shown in table 4.

Table4. *Spectral data for compounds (3a-g)*

Comp.No.	FTIR (KBr) cm^{-1}				^{1}H-NMR δ (ppm) DMSO-d6	^{13}C-NMR δ (ppm) DMSO-d6
	C=O	C=N	NH	ArH		
3a	1655	1610	3258	3066	2.127 (s, 3H, CH3), 4.825 (bs,, 1H, OH), 11.542 (s, 1H, NH), 8.718 (s, 1H, HC=N), 8.554(s, 1H, HC=N), 6.981-7.457 (m, 10H, ArH), 7.711-8.065 (m, 8H, ArH)	21.5(CH3),83.8(COH),[122.2,126.4,127.1,129.3,132.2,133.4,140.8,142.8,154.1]aromatic carbon,144.2(CH=N),160(CH=N)
3b	1649	1598	3198	3057	2.132 (s, 3H, CH3), 4.867 (bs,, 1H, OH), 11.431 (s, 1H, NH), 8.698 (s, 1H, HC=N), 8.501(s, 1H, HC=N), 6.942-7.401 (m, 10H, ArH), 7.723-8.059 (m, 8H, ArH)	21.2(CH3),83.1(COH),[121.4,125.99,128.1,129.65,132.45,133.25,140.2,142.5,153.9] aromatic carbon,144.6(CH=N),160.7(CH=N)
3c	1641	1618	3318	3064	2.202 (s, 3H, CH3), 4.798 (bs,, 1H, OH), 11.486 (s, 1H, NH), 8.715 (s, 1H, HC=N), 8.508(s, 1H, HC=N), 6.908-7.511m, 10H, ArH), 7.721-8.165 (m, 8H, ArH)	20.9(CH3),82.9(COH),[121.1,125.95,127.7,129.55,132.3,133.4,140.4,141.95,154.4] aromatic carbon,144.5(CH=N),160.2(CH=N)
3d	1643	1608	3305	3042	3.754 (s, 3H, OCH3), 5.025 (bs, 1H, OH), 11.232 (s, 1H, NH), 8.924 (s, 1H, HC=N), 8.702 (s, 1H, HC=N), 7.073-7.520(m, 10H, ArH), 7.641-7.922(m, 8H, ArH)	55.75(OCH3),83.1(COH),[114.2,121.1,125.95,127.7,129.5,132.3,133.4,140.4,141.95,154.4]aromatic carbon,141.3(CH=N),159.8 (CH=N)
3e	1630	1602	3292	3052	11.09 (s,1H, OH), 6.122 (bs, 1H, OH), 11.198 (s, 1H, NH), 8.921 (s, 1H, HC=N), 8.698 (s, 1H, HC=N), 7.055-7.496(m, 10H, ArH), 7.637-7.913(m, 8H, ArH)	83.8(COH),[117.3,121.2,126.6,127.1,129.1,132.7,133.1,141.1,142.4,154.4] aromatic carbon,144.2(CH=N),160(CH=N), 162.1(COH)
3f	1648	1612	3242	3041	5.341 (bs, 1H, OH), 11.142 (s, 1H, NH), 8.911 (s, 1H, HC=N), 8.712 (s, 1H, HC=N), 7.044-7.533(m, 10H, ArH), 7.629-7.898(m, 8H, ArH)	82.9(COH),[118.2,122.8,123.9,125.4,128.8,129.9,131.2,139.3,142.4]aromatic carbon. 156.4(C-N),147.4(C-NO2), 144.1(CH=N),160.2(CH=N)
3g	1642	1605	3285	3052	5.234 (bs, 1H, OH), 11.197 (s, 1H, NH), 8.908 (s, 1H, HC=N), 8.688 (s, 1H, HC=N), 7.042-7.499(m, 10H, ArH), 7.634-7.906(m, 8H, ArH)	83.4(COH),[116.2,122.5,125.1,128.4,129.8,130,131.6,139.1,142.6] aromatic carbon. 145.35(C-N) ,144,7(CH=N)160.3(CH=N),

BIOLOGICAL ACTIVITY

All bis-hydrazones synthesized compounds (3a-g) were screened for *in vitro* antibacterial activity by adopting the disc diffusion method. For antibacterial studies the microorganisms employed were *Esherichia coli, Staphylococcus aurous, Micrococcus, Pseudomonas, Bacillius11 and Bacillius12.*

From the obtained data, it is evident that compounds (3a, 3d and 3g) possess a very good activity against bacteria Strains like *E. coli* and Staphylococcus as shown in table 5.

Table5. *Antibacterial activity of (3a-g) compounds*

Compd.No.	Inhibition zone"%")mm(					
	E. coli	***Staphylococcus aurous***	***Micrococcus***	***Pseudomonas***	***Bacillius 11***	***Bacillius12***
3a	17	11	-------	-------	-------	-------
3b	7	10	-------	-------	-------	-------
3c	------	-------	8	8	6	6
3d	6	17	-------	-------	-------	-------
3e	------	-------	6	7	6	6
3f	9	6	-------	-------	-------	-------
3g	9	18	-------	-------	-------	-------

Inhibition zone diameter (mm) (%inhibition): 6-10 (27-45%); 10-14 (45-64); 18-22(82-100).

CONCLUSION

As part of continuous program directed toward the studies with benzilic acid hydrazide,In this work the synthesis and characterization of the bis-hydrazones derived from has been realized advantages of this work were obtained mono and bis-hydrazones with a good product yield, short reaction time using the benzilic acid hydrazide The structure of the obtained compound was confirmed by spectroscopic analysis These compounds are stable compounds, which renders them beneficial substances for antibacterial activities .

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