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Synthesis of some Phthalazine from Hydrazone of Amino Acids

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Abstract:

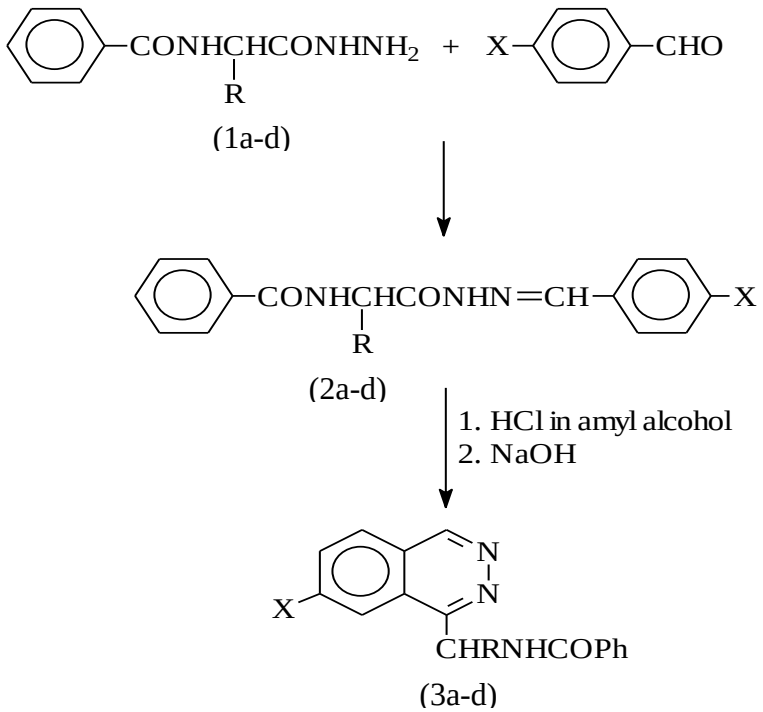
A number of hydrazone (2a-h) were synthesiszed from the reaction of protected amino acid hydrazide and substituted benzaldehyde. The obtained products then treated with amyl alcohol saturated with HCl gas to give a number of substituted phthalazine (3a-h). The structures of the synthesized compounds were confirmed by IR spectra methods.

Keywords: Phthalazine, hydrazone, amino acids

Introduction:

2,3-Dihydrophthalazine-1,4-diones are commonly used as intermediates in the synthesis of drug molecules with 1,4-disubstituted phthalazine substructure, such as antihypertensive agent dihydralazine (1,4-dihydrazinophthalazine)[(1)]. Tricyclic pyrido phthalazine dione derivatives was tested for antagonistic effects at the strychnine-insenstive modulatory site of the N-methyl-D-aspartate receptor glycine B[(2)]. Moreover, these compounds have attracted considerable attention because they can be easily oxidized to phthalazine 1,4-diones. The later diones exhibit interesting chemiluminescence phenomena[(3)]. They have pronounced (diaza) dienophilic properties[(4)]. Phthalazines are obtained by condensation of appropriate phthalic acid derivatives like esters or anhydrides with hydrazine[(5)]. Phthalazine was prepared by cyclization of $o(CN)_2C_6H_4$ with hydrazine followed by oxidation with oxygen[(6)]. Pyridazino [4,5-d] pyridazine has been employed as azadienes in cycloaddition reactions with electron rich dienophiles like enamine to afford phthalazine[(7-9)].

In the present work, the synthesis of some new substituted phthalazine and hydrazone were carried out (Scheme 1).



	R	X
a	$CH_3SCH_2CH_2$	OCH_3
b	$HSCH_2$	OCH_3
c	$(CH_3)_2CHCH_2$	OCH_3
d	4-OH-$C_6H_4CH_2$	OCH_3
e	$CH_3SCH_2CH_2$	NO_2
f	$HSCH_2$	NO_2
g	$(CH_3)_2CHCH_2$	NO_2
h	4-OH-$C_6H_4CH_2$	NO_2

Scheme (1)

Experimental:

Uncorrected melting point were determined using Electrothermal 9300 melting point apparatus. I.R. spectra were recorded by Infrared Spectrophotometer Model Tensor 27 Bruker Co. using KBr discs. Benzoyl amino acid hydrazides (1a-d) were prepared according to the reported procedure[10].

Synthesis of 4-substituted benzaldehyde benzoyl amino acid hydrazone (2a-h):

A mixture of (0.01 mole) of compounds (1a-d) with (0.01 mole) of aldehydes and (2) drops of (10%) sodium hydroxide in (20 ml) ethanol were refluxed for (2 hrs.). The reaction mixture was cooled, filtered and recrystallized from ethanol. The melting point and I.R. spectral data were shown in Table (1).

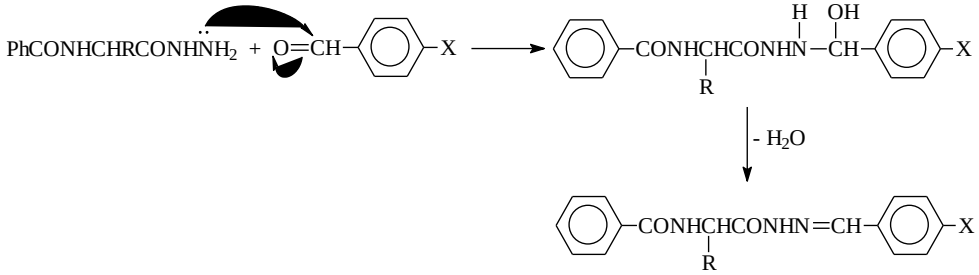


Table (1): Some of the physical properties of compounds (2a-h)

Comp. No.	m.p. (°C)	Yield (%)	I.R. ν (cm^{-1}) KBr dis		
			C=O	C=N	N-H
2a	180-182	81	1670	1635	3294
2b	159-161	87	1645	1619	3263
2c	161-163	80	1647	1627	3243
2d	205-207	92	1668	1637	3260
2e	205-207	78	1683	1637	3250
2f	85-87	84	1661	1647	3323
2g	240-242	79	1688	1636	3301
2h	135-137	80	1660	1639	3260

Table (2): Some of the physical properties of compounds (3a-h)

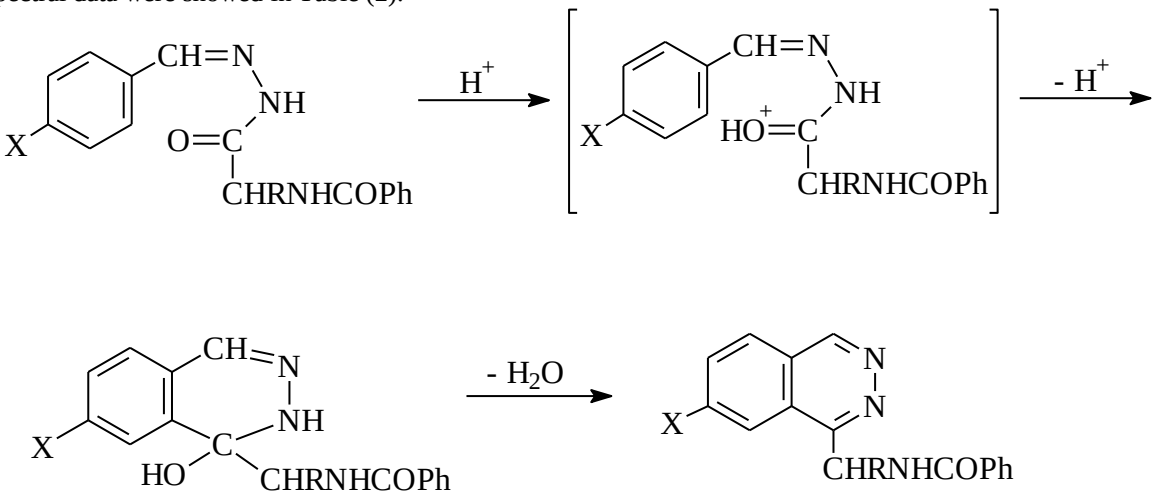
Comp. No.	m.p. (°C)	Yield (%)	I.R. ν (cm^{-1}) KBr dis		
			C=O	C=N	N-H
3a	157-159	43	1653	1625	3246
3b	64-66	51	1645	1638	3242
3c	160-162	44	1646	1604	3310
3d	169-171	47	1683	1624	3246
3e	298-300	50	1640	1610	3231
3f	> 300	42	1676	1619	3290
3g	283-285	53	1653	1622	3220
3h	250 d	47	1635	1598	3243

Synthesis of 1-(benzoyl amino alkyl)-7-substituted phthalazine (3a-h):

(1 gm) of compounds (2a-h) in (10 ml) of amyl alcohol (saturated with HCl gas) was heated on steam bath for (1.5 hrs.) and then refluxed for (1 hr.). The reaction mixture was cooled, washed with (10 ml) of (20%) sodium hydroxide and with water until neutralized, evaporation of the solvent and recrystallization from ethanol to afforded the product. The melting point and I.R. spectral data were showed in Table (2).

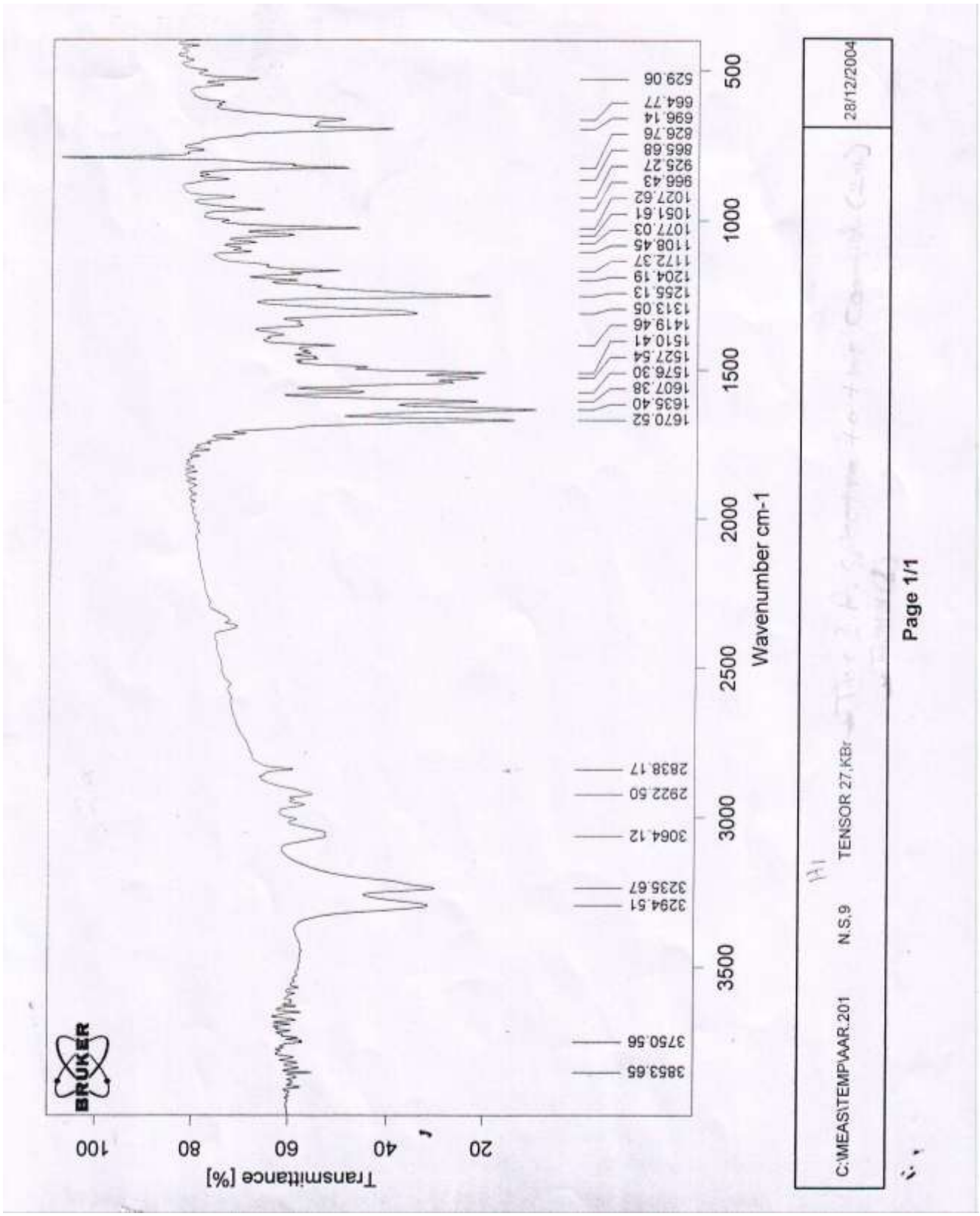
Results And Discussion:

Hydrazone compounds (2a-h) were prepared by the condensation reaction of benzoyl amino acid hydrazide with aldehyde. The mechanism of the substituted hydrazone formation can be illustrated as below. Phthalazine compounds (3a-h) were prepared through ring closure of hydrazone by Skraup synthesis[11] using hydrochloric acid in amyl alcohol. The cyclization mechanism could be illustrated as follows:

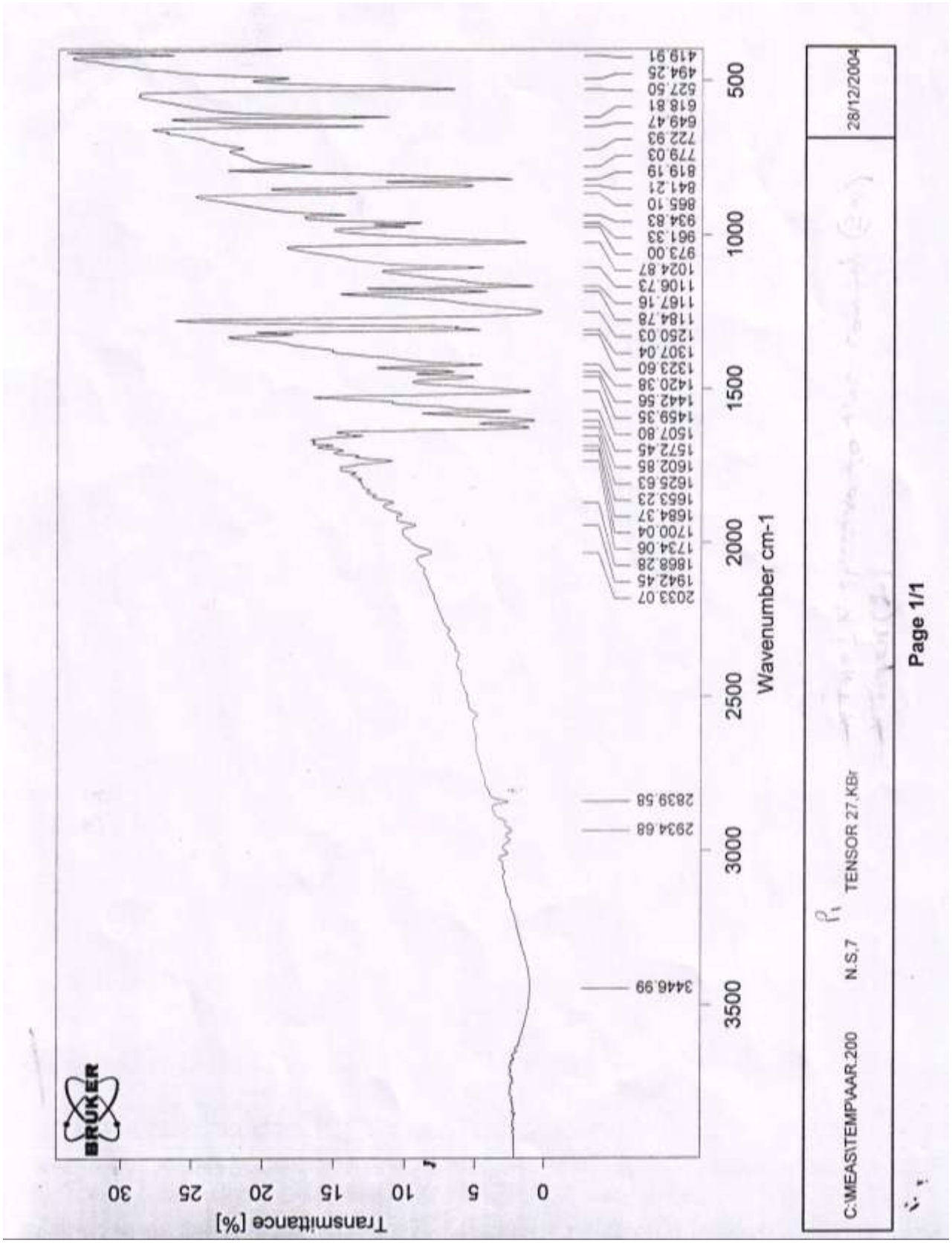


The IR characterization absorption bands of the hydrazone compounds (2a-h) were given in Table (1) and (Fig. 1). The main absorption bands for imine and amide groups appeared at (1619-1647 cm^{-1}) and (1645-1688

cm^{-1}) for (C=N) and (C=O). While at (3243-3323 cm^{-1}) represent (N-H). Table (2) shows the main absorption bands of substituted phthalazine compounds (3a-h) which includes stretching vibrations of (C=N) and (C=O) at (1598-1638 cm^{-1}) and (1635-1683 cm^{-1}) respectively. While the absorption bands at (3220-3246 cm^{-1}) were assigned to (N-H) stretching vibrations (Fig. 2).



Fig(1): The IR spectra of the compound (2a)



Fig(2): The IR spectra of the compound (3a)

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تحضير عدد من مركبات الفثالازين من هيدرازونات الاحماض الامينية

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الملخص:

يتضمن البحث تحضير عدد من الهيدرازونات (2a-h) من تفاعل هيدرازيدات الاحماض الامينية المحمية مع البنزالديهايد المعوض ثم عوملت النواتج بعد ذلك بالكحول الاميلي المشبع بغاز HCl مكونة عدد من معوضات الفثالازين (3a-h) . شخصت المركبات الناتجة بطيف الأشعة تحت الحمراء.