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Synthesis and Characterization of a Series of 1-Aryl-4-[aryldiazenyl]-piperazines. Part I. Isomers of N-(2,3-Dimethylphenyl)-N'-(Aryldiazenyl)-Piperazines

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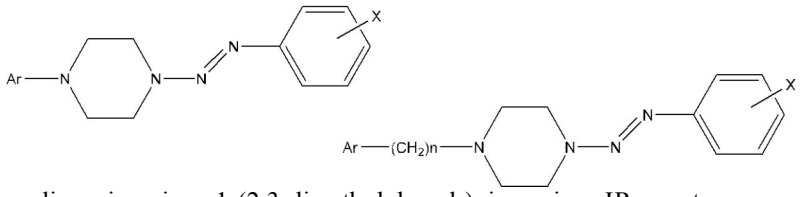
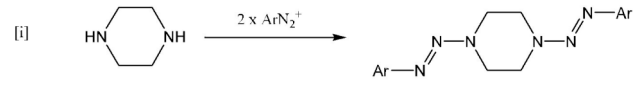
Abstract: This paper describes the synthesis of several new series of 1-(2-aryldiazen-1-yl-) 4-arylpiperazines and 1-(2-aryldiazen-1-yl-)4-arylalkylpiperazines by using diazonium coupling between arenediazonium ions with the appropriate 1-arylpiperazine or the 1-arylalkylpiperazine. The new compounds have a common thread in that they are isomers of the series of N-(2,3-dimethylphenyl)- N'-(aryldiazenyl)-piperazines. The new triazenes have been characterized by IR and NMR spectroscopy and mass spectrometry.



Keywords: Arylpiperazine; diazonium ion, 1-(2,3-dimethylphenyl-)piperazine, IR spectroscopy, Mass spectrometry, 1-(2-methylphenylmethyl-)piperazine, 1-(3-methylphenylmethyl-)piperazine, 1-(4-methylphenylmethyl-)piperazine, NMR spectroscopy, piperazine, triazene.

INTRODUCTION

Previous work in this laboratory has described the synthesis of the 1,4-bis-(2-aryl-diazen-1-yl-)piperazines (**1**)[1, 2] using the bis-diazonium coupling reaction with piperazine itself (equation (i)):



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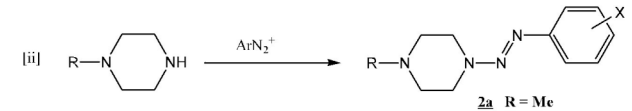
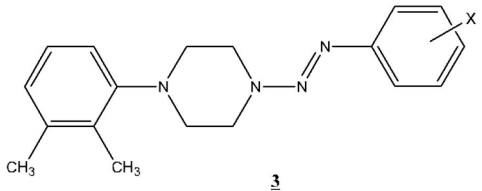
In a similar fashion, diazonium coupling with 1-methylpiperazine afforded a series of 1-(2-aryldiazen-1-yl-)4-methylpiperazines (**2a**) [3](equation ii):



2a R = Me
2b R = Et
2c R = acyl
2d R = Ar'

Subsequently, this work was extended to the synthesis of the 1-(2-aryldiazen-1-yl-) 4-ethylpiperazines (**2b**) [4]. Further investigation led to the synthesis of a large number of 1-(2-aryldiazen-1-yl-)4-acylpiperazines (**2c**); the paper describing these latter results has recently been published [5]. The next logical step in the pursuit of new molecules of the N-aryldiazenylpiperazines is to investigate the synthesis of the1-aryl-4-[aryldiazenyl] -piperazines (**2d**) by diazonium salt coupling with a series of 1-arylpiperazines.

In the present work, a series of N-(2,3-dimethylphenyl)-N'-(aryl-diazenyl)-piperazines (**3**) have been synthesized by diazonium coupling with N-(2,3-dimethylphenyl-)piperazine. These new triazenes represent the first ever piperazine derivatives to be reported with one N-aryl substituent at N4 opposite to the N-aryldiazenyl substituent at N1. The common thread of all the new compounds reported in this paper is that they are isomers of the compounds of series **3**.



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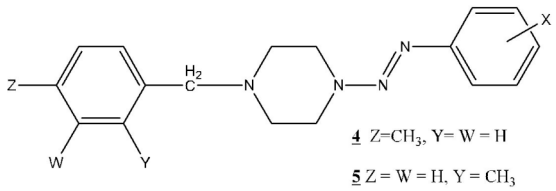
Isomeric compounds described as 1-(methylphenyl-methyl)-4-(aryldiazenyl)-piperazines (**4** , **5** and **6**) have also been prepared and characterized:



4 Z=CH_3, Y= W = H

5 Z = W = H, Y = CH_3

6 Z = Y = H, W = CH_3

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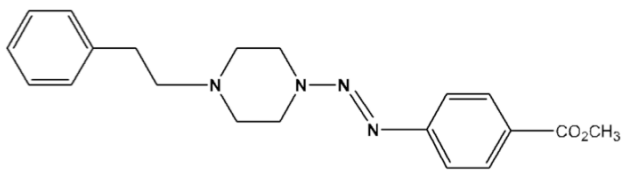
Also the isomer methyl 4-[2-(4-phenethylpiperazino)-1-diazenyl]benzoate (**7**) has been prepared and characterized.



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EXPERIMENTAL

Materials and Apparatus

The series of aromatic primary amines and the series of 1-arylsubstituted-piperazines were reagent-grade materials purchased from the Aldrich Chemical Co. Ltd., and were used without further purification. Melting points were determined on a Fisher-Johns Melting Point Apparatus and were uncorrected. Infrared spectra were obtained using nujol mulls on a Bruker Vector-22 IR spectrometer. ^{1}H and ^{13}C NMR spectra were obtained on Bruker AC 250MHz and 500MHz spectrometers at the Atlantic Regional Magnetic Resonance Center at Dalhousie University in Halifax, Nova Scotia. Chemical shifts were recorded in $CDCl_3$ solutions at room temperature, and were related to TMS internal standard. The NMR data were interpreted using the TOPSPIN software. The high resolution mass spectra were obtained at Dalhousie University in Halifax, Nova Scotia. Accurate mass measurements were made on a CEC 21-110B mass spectrometer operated at a mass resolution of 8000 (10% valley) by computer-controlled peak matching to appropriate PFK reference ions. Spectra were obtained using electron ionization at 70 volts and a source temperature of 175℃, with samples being introduced by means of a heatable quartz probe. The standard deviation of mass measurement is +/- 0.0008 amu, which is an average of 3.6 ppm over the mass range 100 to 300 amu.

General Procedure

The aromatic primary amine (0.006 mol) was dissolved in 6 mL of 3 mol/L hydrochloric acid, with the aid of heat if necessary, and the resulting solution cooled in an ice salt bath to below 5 ºC. The solution was diazotized with a solution of sodium nitrite (0.006mol) in 3mL water, with the temperature maintained below 5 ºC. Then, the solution was stirred for a further 30 min in the ice bath. A piperazine solution was prepared by mixing the 1-aryl-piperazine (0.005 mol) with 10 mL water; if necessary, a few drops of a dilute hydrochloric acid solution was added to get the arylpiperazine to dissolve. Then, the piperazine solution was added slowly to the diazonium salt solution. After stirring for an additional 30 min, the mixture was neutralized with a saturated sodium bicarbonate solution and then left to stir until precipitation was deemed to be complete (~1 hour). The solid product was filtered under suction, dried, and recrystallized from an appropriate solvent. Physical data (i.e. yield, m.p., recrystallization solvent) and spectroscopic analysis data (i.e. FT-IR, NMR, and high resolution MS data) were collected.

Synthesis of Series of N-(2,3-dimethylphenyl)-N'-(aryldiazenyl)-piperazines (3)

The compounds of series **3a-f** were prepared following the general procedure described above. However, during the experiments, there was a problem which may have affected the results. The diazo coupling reaction took place in an aqueous solution. One of the major starting materials, 1-(2,3-Xylyl)-piperazine monohydrochloride was not completely dissolved in water at room temperature even when extra hydrochloric acid was added. It could be dissolved in water with heat, but the reaction system had to be cooled all the time as described in the general procedure. Thus, the low solubility of the 1-(2,3-Xylyl)-piperazine may have limited the completion of the reaction. Nevertheless, the 1-(2,3-Xylyl)-piperazine monohydrochloride in water may have an equilibrium between the dissolved sample and the undissolved sample, when the dissolved 1-(2,3-Xylyl)-piperazine has been used in the reaction, then more of the undissolved piperazine will be dissolved in water. Nevertheless, the longer reaction time may have served to overcome the effect of this factor, as evident in the high yields of compounds of series **3** reported in Table **1**.

Synthesis of the Series of 1-(4-methylbenzyl)-4-(aryldiazenyl)-piperazines (4)

Following the general procedure described above, the experiments were performed in half scale due to the limit of the amount of starting materials. The same substituents of the aromatic amine were applied; the physical and IR data of the final products for this series are given in Table **2.**

Synthesis of the Series of 1-(2-methylbenzyl)-4-(aryldiazenyl)-piperazines (5)

The procedure follows the general procedure in the first several steps, until the mixture was neutralized with saturated sodium bicarbonate solution. After the neutralization, a sticky precipitate formed, which was isolated by filtration. The mother-liquor was stored in a fridge. In some cases, a further batch of solid product was isolated from the mother liquor after several days; the second batch was combined with the first batch for the purification. The oily sticky solid was dissolved in dichloromethane and transferred into an Erlenmeyer flask which then was placed in a fume hood for overnight or longer to allow the solvent to evaporate completely. The resulting sticky solid was dissolved in a minimum volume of the appropriate hot solvent (e.g. Ethanol) and then cooled slowly. The crystalline solid was precipitated, then filtered under suction and air dried. Physical data (i.e. yield, m.p., recrystallization solvent) and IR spectroscopic data are given in Table **3**.

Synthesis of Series of 1-(3-methylbenzyl)-4-(aryldiazenyl)-piperazines (6)

Following the general procedure described above for series **3**, the synthesis of the compounds of series **6** were performed in half scale due to the limit of the amount of starting materials. The same substituents of the aromatic

amine were applied; the physical and IR data of the final products for this series are given in Table **4**.

Synthesis of Methyl 4-[2-(4-phenethylpiperazino)-1-diazenyl]benzoate (7)

The synthetic procedure follows the general procedure described above. Due to the limited amount of the 1-(2-phenylethyl)-piperazine available, only one substituted aromatic amine (*p*-CO_2CH_3) was applied to the synthesis. The physical data is shown in Table **5**.

RESULTS AND DISCUSSION

Synthesis

The N-aryl-N'-(2-aryl-1-diazenyl-)piperazines (**3** to **7**) were synthesized by diazotization of an aromatic primary amine ($ArNH_2$) in hydrochloric acid, followed by coupling of the diazonium ion with the appropriate N-arylpiperazine or N-arylalkylpiperazines. Most of the crude products were obtained in good yield (57-100%) with the exception of compound **5c**. The compounds were purified by recrystallization in high recovery.

Infrared Spectral Analysis

The significant diagnostic results of the Infrared spectra of the new compounds are shown in Table **1** to Table **5**. All of the compounds show out-of-plane bending vibration modes of the substituted benzene rings. The para-disubstituted benzene ring, which is present in most of the compounds, except **3f**, **4f**, and **5e**, show out-of-plane bending vibration modes in the range of 825-859 cm^{-1}. Compounds **3f**, **4f**, and **5e** involve a monosubstituted benzene ring, which show two out-of-plane bending vibration modes in the ranges of 693-697 cm^{-1} and 761-765 cm^{-1}. The N-aryl group,

Table 1. Physical data for the N-(2,3-dimethylphenyl)-N'-(aryl-diazenyl)-piperazines (3).

No	X	Crude yield	Mp (℃)	Recryst. Solv.	Crystal Appearance	IR (cm^{-1})
		(%)				
3a	p-CN	87.3%	147-148	Ethanol	Red-brown	2220(CN)
					Needles	848(para)
						785&724
						(1,2,3-trisub)
3b	p-CO_2CH_3	63.7%	155-157	Ethanol	Small orange	1714(C=O)
					Plates	1275(C-O)
						856(para)
						780&724
						(tri-sub)
3c	p-Br	100.0%	103-103.5	Ethanol	Fibrous	833(para)
					Off-white	782&719
					Plates	(tri-sub)
3d	p-CH_3	81.8%	132-132.5	Ethanol	Needles	828(para)
						788&723
						(tri-sub)
3e	p-NO_2	100.0%	152-155	Ethanol	Red-brown	1507 &
					Needles	1341(NO_2)
						851(para)
						787&721
						(tri-sub)
3f	H	57.7%	102-102.5	Ethanol	Lustrous	697 & 763
					Gold plates	(mono-sub)
						788&724

Table 2. Physical data for series of 1-(4-methylbenzyl)-4-(aryldiazenyl)-piperazines (4).

No.	X	Crude yield (%)	mp(℃)	Recryst. Solv.	Crystal Appearance	IR (cm^{-1})
						(tri-sub)
4a	p-CN	99.6%	83-89	(a)	Dull orange	2225(CN)
					Powder	842&784(para)
				Hexanes &	Fibrous	1707(C=O)
					Pale yellow	1274(C-O)
4b	p-CO_2CH_3	95.7%	118-119	cyclohexane	Needles	827&799(para)
4c	p-Br	70.6%	91-92	Isopropanol	Pale yellow	832&801(para)
					Needles	
					Pink	
4d	p-CH_3	70.2%	93-94	Isopropanol	Plates	827&790(para)
					lustrous	1509 &
4e	p-NO_2	90.5%	124-125	Ethanol	Red-brown	1379(NO_2)
					needles	848&795(para)
					Off-white	695 & 765
4f	H	93.2%	94.5-95.5	Isopropanol	Needles	(monosub)
						798(para)

(a) This compound was soluble in a variety of solvents, but it did not recrystallize from any of them.

Table 3. Physical data for series of 1-(2-methylbenzyl)-4-(aryldiazenyl)-piperazines (5).

No.	X	Overall yield (%)	mp(℃)	Recryst. Solvent	Crystal appearance	IR (cm^{-1})
5a	p-CN	47%	73-74	Iso-Propanol	Off-white prisms	2218(CN) 840(para) 745(ortho)
5b	p-CO_2CH_3	52%	97.5-98.5	Iso-Propanol	Pale pink Needles	1714(C=O) 1274(C-O) 859(para) 746(ortho)
5c	p-Br	35%	65-66	Ethanol	Lustrous Brown plates	830(para) 744(ortho)
5d	p-NO_2	66.5%	92.5-93	Ethanol	Red-brown Prisms	1509 & 1378(NO_2) 853(para) 745(ortho)

Table 3. contd….

No.	X	Overall yield (%)	mp(℃)	Recryst. Solvent	Crystal appearance	IR (cm-1)
5e	H	72%	71-73	Hexanes (a)	Fibrous Pale yellow Prisms	693 & 761 (mono-sub) 743(ortho)

(a) By trituration

Table 4. Physical data for series of 1-(3-methylbenzyl)-4-(aryldiazenyl)-piperazines (6).

No.	X	Crude yield (%)	mp(℃)	Recryst. Solv.	Crystal appearance	IR (cm^{-1})
6a					Pale orange	2220(CN)
	p-CN	90%	105-106	iso-propanol	Needles	841(para)
						783 and 696(meta)
6b					Lustrous	1710(C=O)
					Flesh-colored	860(para)
	p-CO_2CH_3	93%	82-83	ethanol	Plates	775 & 698 (meta)
6c					Tiny buff	
	p-Br	87%	77-78	Iso-propanol	Colored	829(para)
					Needles	777 & 695 (meta)
6d					Pink	823(para)
	p-CH_3	62%	85-86	Iso-propanol	Needles	781 & 696 (meta)
6e					Tiny	1514 &
					Red-brown	1376(NO_2)
					Needles	853(para),
	p-NO_2	94%	82-83	Iso-propanol		781 & 694(m)

Table 5. Physical data for Methyl 4-[2-(4-phenethylpiperazino)-1-diazenyl]benzoate (7).

No.	X	Crude yield (%)	Mp (℃)	Recryst. Solv.	Crystal appearance	IR (cm^{-1})
						1722(C=O)
						1278(C-O)
						859(para)
					Creamy white	699&774
7a	p-CO_2CH_3	97.1%	98-99	Ethanol	prisms	(mono-sub)

Table 6. ^{1}H NMR Data for compounds 3a-f; chemical shifts in ppm relative to TMS(1%) at room temperature in $CDCl_3$.

No.	X	Aromatic	H_a	H_b	CH_3	X
		6.92(1H,d,J=8.0Hz)				
		6.96(1H,d,J=7.5Hz)				
3a	*p*-CN	7.10(1H,t,J=7.7Hz)	4.03(4H,br)	3.05(4H,br)	2.29(3H,s)	
		7.52(2H,d,J=8.5Hz)				
		7.62(2H,d,J=8.5Hz)			2.30(3H,s)	
		6.94(1H,d,J=8.0Hz)				
		6.97(1H,d,J=7.5Hz)				
3b	*p*-CO_2CH_3	7.12(1H,t,J=7.5Hz)	4.02(4H,br)	3.06(4H,br)	2.29(3H,s)	3.92(3H,s)
		7.52(2H,d,J=8.0Hz)				
		8.05(2H,d,J=8.5Hz)			2.31(3H,s)	
		6.93(1H,d,J=7.7Hz)				
		6.96(1H,d,J=6.5Hz)				
3c	*p*-Br	7.11(1H,t,J=7.5Hz)	3.95(4H,br)	3.05(4H,t,J=5.1Hz)	2.29(3H,s)	
		7.35(2H,d,J=9.0Hz)				
		7.48(2H,d,J=8.5Hz)			2.30(3H,s)	
		6.89(1H,d,J=7.3Hz)				
		6.91(1H,d,J=6.5Hz)				
3d	*p*-CH_3	7.06(1H,t,J=7.7Hz)	3.88(4H,br)	3.01(4H,t,J=5.0Hz)	2.25(3H,s)	2.32(3H,s)
		7.13(2H,d,J=8.1Hz)				
		7.34(2H,d,J=8.3Hz)			2.26(3H,s)	
		6.93(1H,d,J=8.3Hz)				
		6.97(1H,d,J=10.5Hz)				
3e	*p*-NO_2	7.12(1H,t,J=7.5Hz)	4.07(4H,br)	3.07(4H,br)	2.29(3H,s)	
		7.55(2H,d,J=9.0Hz)				
		8.23(2H,d,J=8.75Hz)			2.31(3H,s)	
		6.90(1H,d,J=8.0Hz)				
		6.91(1H,d,J=7.5Hz)				
3f	H	7.06(1H,t,J=7.8Hz)	3.92(4H,br)	3.01(4H,t,J=5.0Hz)	2.25(3H,s)	
		7.16(1H,t,J=7.4Hz)				
		7.33(2H,t,J=8.2Hz)				
		7.44(2H,d,J=7.4Hz)			2.26(3H,s)	

Table 7. ^{1}H NMR Data for 4a-f; chemical shifts in ppm relative to TMS(1%) at room temperature in $CDCl_3$.

No.	X	Aromatic	H_a	H_b	CH_2	CH_3	X
		7.11(2H,d,J=7.8Hz)					
4a	p-CN	7.19(2H,d,J=7.9Hz)	3.84(4H,br)	2.56(4H,br)	3.51(2H,s)	2.31(3H,s)	
		7.43(2H,d,J=8.6Hz)					

Table 7. contd.....

No.	X	Aromatic	H_a	H_b	CH_2	CH_3	X
		7.55(2H,d,J=8.6Hz)					
		7.12(2H,d,J=7.8Hz)					
4b	p-CO_2CH_3	7.20(2H,d,J=7.9Hz)	3.83(4H,t,	2.56(4H,t,	3.51(2H,s)	2.32(3H,s)	3.86(3H,s)
		7.43(2H,d,J=8.5Hz)					
		7.98(2H,d,J=8.5Hz)	J=5.2Hz)	J=6.3Hz)			
		7.11(2H,d,J=7.8Hz)					
4c	p-Br	7.19(2H,d,J=7.9Hz)	3.76(4H,t,	2.55(4H,t,	3.51(2H,s)	2.31(3H,s)	
		7.27(2H,d,J=8.8Hz)					
		7.40(2H,d,J=8.7Hz)	J=5.3Hz)	J=5.2Hz)			
		7.13(2H,d,J=8.0Hz)					
4d	p-CH_3	7.14(2H,d,J=7.4Hz)	3.76(4H,t,	2.57(4H,t,	3.53(2H,s)	2.33(3H,s)	2.34(3H,s)
		7.23(2H,d,J=8.0Hz)					
		7.33(2H,d,J=8.3Hz)	J=5.3Hz)	J=5.2Hz)			
		7.12(2H,d,J=7.9Hz)					
4e	p-NO_2	7.20(2H,d,J=7.9Hz)	3.88(4H,br)	2.58(4H,br)	3.52(2H,s)	2.32(3H,s)	
		7.47(2H,d,J=9.1Hz)					
		8.16(2H,d,J=9.1Hz)					
		7.22(2H,d,J=7.9Hz)					
4f	H	7.32(2H,t,J=7.8Hz)	3.78(4H,t,	2.58(4H,t,	3.53(2H,s)	2.34(3H,s)	
		7.41(2H,d,J=8.2Hz)					
			J=5.2Hz)	J=5.2Hz)			
		7.17-7.13(3H,m)					

Table 8. ^{1}H NMR Data for 5a-e; chemical shifts in ppm relative to TMS(1%) at room temperature in $CDCl_3$.

No.	X	Aromatic	H_a	H_b	CH_2	CH_3	X
		7.24(1H,d,J=7.3Hz)					
5a	p-CN	7.45(2H,d,J=8.7Hz)	3.83(4H,t,	2.58(4H,br)	3.51(2H,s)	2.36(3H,s)	
		7.56(2H,d,J=8.7Hz)					
		7.21-7.14(3H,m)	J=4.75Hz)				
		7.24(1H,d,J=7.2Hz)					
5b	p-CO_2CH_3	7.43(2H,d,J=8.7Hz)	3.81(4H,t,	2.57(4H,t,	3.50(2H,s)	2.40(3H,s)	3.89(3H,s)
		7.97(2H,d,J=8.7Hz)					
		7.21-7.17(3H,m)	J=5.2Hz)	J=5.2)			
5c	p-Br	7.27(1H,d,J=7.1Hz)	3.77(4H,t	2.59(4H,t,	3.53(2H,s)	2.39(3H,s)	
		7.30(2H,d,J=8.8Hz)					
		7.43(2H,d,J=8.8Hz)					
		7.17-7.10(3H,m)	J=5.2Hz)	J=5.2Hz)			

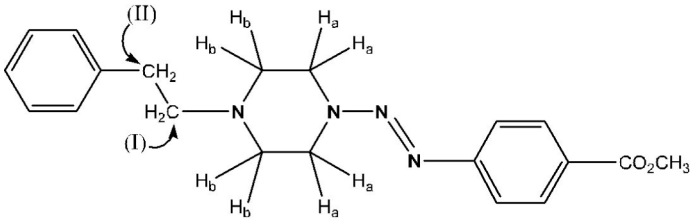
Table 8. contd.....

No.	X	Aromatic	Ha	Hb	CH2	CH3	X
		7.26(1H,d,J=7.2Hz)					
5d	p-NO_2	7.49(2H,d,J=9.0Hz)	3.89(4H,br)	2.61(4H,br)	3.54(2H,s)	2.39(3H,s)	
		8.18(2H,d,J=9.0Hz)					
		7.21-7.15(3H,m)					
		7.25(1H,d,J=7.0Hz)					
5e	H	7.30(2H,t,J=7.9Hz)	3.75(4H,t,	2.57(4H,t,	3.50(2H,s)	2.36(3H,s)	
		7.40(2H,d,J=8.4Hz)					
		7.18-7.12(4H,m)	J=5.2Hz)	J=5.3Hz)			

Table 9. ^{1}H NMR Data for 6a-e; chemical shifts in ppm relative to TMS(1%) at room temperature in $CDCl_3$.

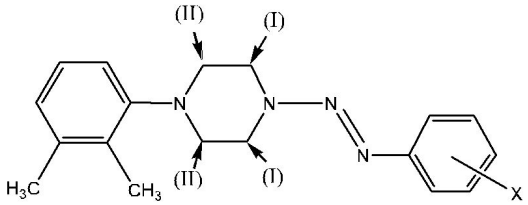
No.	X	Aromatic	H_a	H_b	CH_2	CH_3	X
		7.10(1H,d,)					
		7.15(2H,m)					
6a	*p*-CN	7.23(1H, dd)	3.89(4H,t,	2.60(4H,br)	3.55(2H,s)	2.36(3H,s)	-
		7.47(2H,d)					
		7.59(2H,d)	J=5Hz)				
		7.09(1H,d)					
		7.14(1H,d)					
		7.16(1H,br)					
		7.22(1H,dd)					
		7.46(2H,d)					
6b	*p*-CO_2CH_3	8.01(2H,d)	3.87(4H,t)	2.59(4H,t)	3.54(2H,s)	2.36(3H,s)	3.89(3H,s)
		7.27(1H,d,J=7.1Hz)					
6c	*p*-Br	7.30(2H,d,J=8.8Hz)	3.79(4H,t)	2.58(4H,t)	3.53(2H,s)	2.35(3H,s)	-
		7.43(2H,d,J=8.8Hz)					
		7.17-7.10(3H,m)					
		7.08(1H,d)					
		7.13(4H,m)					
		7.22(1H,t)					
6d	*p*-CH_3	7.33(2H,d)	3.77(4H,t)	2.58(4H,t)	3.53(2H,s)	2.33(3H,s)	-
		7.09(1H,d)					
		7.15(2H,m)					
6e	p-NO_2	7.23(1H,d)	3.92(4H,br)	2.62(4H,br)	3.56(2H,s)	2.35(3H,s)	-
		7.49(2H,d)					
		8.18(2H,d)					

Table 10. ^{1}H NMR Data for 7a; chemical shifts in ppm relative to TMS(1%) at room temperature in $CDCl_3$.



No.	X	Aromatic	H_a	H_b	CH_2(I)	CH_2(II)	X
		8.01(2H,d,J=8.5Hz)	3.89(4H,t,				
7a	*p*-CO_2CH_3	7.46(2H,d,J=8.5Hz)	J=7.5Hz)	2.67(4H,br)	2.83(2H,t,J=8.0Hz)	2.68(2H,t,J=8.0Hz)	3.89(3H,s)
		7.28(2H,t,J=7.5Hz)					
		7.21(2H,d,J=7.5Hz)					
		7.20(1H,t,J=7.0Hz)					

Table 11. ^{13}C NMR Data for 3a-f; chemical shifts in ppm relative to TMS(1%) at room temperature in $CDCl_3$.



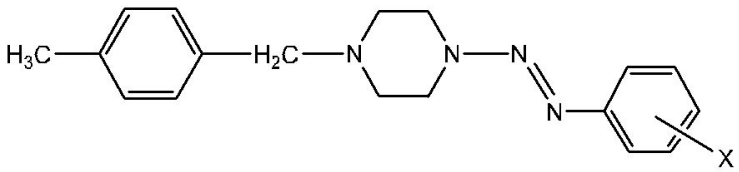
No.	X	Aromatic	Piperazine I	Piperazine II	Me1	Me2	X
3a	*p*-CN	153.8, 150.8, 138.3, 133.1, 131.4	51.6	(a)	20.6	13.9	108.6(CN)
		126.0, 125.8, 121.2, 119.4, 116.8					
3b	*p*-CO_2CH_3	154.1, 150.9, 138.2, 131.4, 130.6	(b)	(a)	20.6	13.9	51.9(OMe)
		127.2, 126.0, 125.7, 120.5, 116.9					167.0(C=O)
3c	*p*-Br	151.0, 149.4, 138.2, 131.9, 131.4	51.7	(a)	20.6	13.9	
		125.9, 125.6, 122.3, 119.3, 116.8					
3d	p-CH3	151.1, 148.2, 138.1, 135.9, 131.3	51.7	47.9	20.6	13.9	21.0(Me)
		129.5, 125.9, 125.5, 120.6, 116.8					
3e	p-NO2	155.5, 150.7, 145.2, 138.3, 131.4	(a)	(a)	20.6	13.9	
		126.0, 125.8, 124.9,					

Table 11. Contd…..

No.	X	Aromatic	Piperazine I	Piperazine II	Me1	Me2	X
		120.8, 116.9					
		150.7, 150.1, 137.8,					
3f	H	130.9, 128.5	51.4	48.9	20.3	13.5	
		125.8, 125.5, 125.1,					
		120.4, 116.4					

(a) Not detected
(b) Masked by O-methyl carbon signal

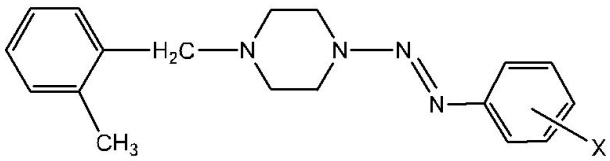
Table 12. ^{13}C NMR Data for 4a-f; chemical shifts in ppm relative to TMS(1%) at room temperature in $CDCl_3$.



No.	X	Aromatic	Piperazine I	Piperazine II	CH_2	CH_3	X
		153.5, 136.7,					
4a	p-CN	134.1, 132.6	51.0(br)	(a)	62.1	20.7	108.0(CN)
		128.7, 128.7,					
		120.7, 119.0					
		153.8, 136.6,					
4b	p-CO_2CH_3	134.2, 130.2	52.0(br)	(a)	62.1	20.7	51.5(OMe)
		128.7, 128.7,					
		126.7, 119.9					166.7(C=O)
		149.5, 136.9,					
4c	p-Br	134.6, 131.8	52.2	48.0(br)	62.5	21.1	
		129.1, 129.0,					
		122.2, 119.1					
		148.2, 136.9,					
4d	p-CH_3	135.8, 134.8	52.3	47.4(br)	62.6	21.1	21.0(Me)
		129.5, 129.1,					
		129.0, 120.5					
		155.6, 145.0,					
4e	p-NO2	137.1, 134.4	52.3(br)	(a)	62.4	21.1	
		129.1, 129.0,					
		124.8, 120.7					
4f	H	150.5, 136.9,	52.2	48.0(br)	62.5	21.1	
		134.7, 129.1					
		129.0, 128.9,					
		126.0, 120.7					

(a) Not detected

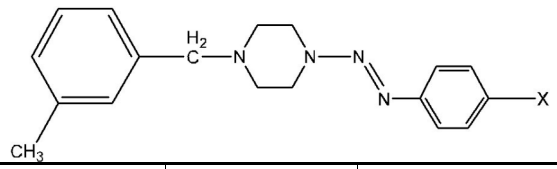
Table 13. ^{13}C NMR Data for 5a-e; chemical shifts in ppm relative to TMS(1%) at room temperature in $CDCl_3$.



				Piperazine			
No.	**X**	**Aromatic**	**Piperazine I**	**II**	**CH_2**	**CH_3**	**X**
5a	p-CN	153.9,137.6,135.8, 133.1, 130.5	52.2(br)	(a)	60.7	19.3	108.4(CN)
		129.9,127.5,125.7, 121.2, 119.5					
		154.2,137.6,135.9,					
5b	p-CO_2CH_3	130.6, 130.4	52.4(br)	(a)	60.7	19.2	51.9(OMe)
		129.9,127.4,127.1,					
		125.6, 120.4					167.1(C=O)
5c	p-Br	149.2,137.3,135.6, 131.5, 130.1	52.0(br)	(a)	60.4	18.9	
		129.5,126.9,125.2, 121.9, 118.7					
		155.6,145.0,137.6,					
5d	p-NO_2	135.7, 130.5	52.2(br)	43.0(br)	60.6	19.2	
		129.9,127.4,125.6, 124.8, 120.7					
5e	H	150.6,137.7,136.1, 130.4, 129.8	52.2(br)	(a)	60.7	19.0	
		128.9,127.3,126.1, 125.6, 120.7					

(a) Not detected

Table 14. ^{13}C NMR Data for 6a-e; chemical shifts in ppm relative to TMS(1%) at room temperature in $CDCl_3$.



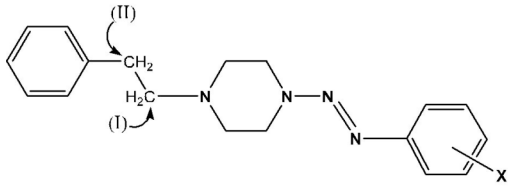
			Piperazine	Piperazine			
No.	**X**	**Aromatic**	**I**	**II**	**CH_2**	**CH_3**	**X**
6a	p-CN	153.8, 138.0, 137.5, 133.0, 129.8	52.1(br)	(a)	62.75	21.4	108.4(CN)
		128.3, 128.1, 126.2,					
		121.1,119.4					

Table 14. Contd…..

			Piperazine	Piperazine			
No.	**X**	**Aromatic**	**I**	**II**	**CH_2**	**CH_3**	**X**
		154.1, 138.0, 137.6,					
6b	p-CO_2CH_3	130.6,129.8	52.3(br)	(a)	62.8	21.4	51.9(OMe)
		128.73,128.0,127.0,					
		126.2,120.4					167.0(C=O)
		149.5, 138.0, 137.7,					
6c	p-Br	131.8,129.8	52.3	(a)	62.8	21.4	-
		128.3, 128.1, 126.2,					
		122.3,119.1					
		148.2, 137.9, 137.7,					
6d	p-CH_3	135.8,129.8	52.4	47.4(br)	62.9	21.4	21.0(Me)
		129.5, 128.2, 128.0,					
		126.2,120.5					
		155.6, 145.1,					
6e	p-NO_2	138.1, 128.3	52.7(br)	51.6(br)	62.7	21.4	-
		128.2, 126.2,					
		124.8, 120.7					

(a) Not detected

Table 15. ^{13}C NMR Data for 7a; chemical shifts in ppm relative to TMS(1%) at room temperature in $CDCl_3$.



			Piperazine	Piperazine			
No.	**X**	**Aromatic**	**I**	**II**	**CH_2(Ⅰ)**	**CH_2(Ⅱ)**	**X**
		153.6,139.5,					
7a	p-CO_2CH_3	130.1, 128.2	51.4	(a)	59.6	33.2	51.9(OMe)
		127.9,126.7,					
		125.7, 119.9					166.5(C=O)

(a) not detected

Table 16. High-resolution electron-ionization mass spectral (EI-MS) data for 3a-f.

No.	**X**	**Molecular**	**Calculated**	**Experimental**
		Formula	**Mass**	**Mass**
3a	p-CN	C19H21N5	319.1797 amu	319.1785 amu
3b	p-CO_2Me	C20H24N4O2	352.1899 amu	352.1914 amu

Table 16. Contd…..

No.	X	Molecular Formula	Calculated Mass	Experimental Mass
3c	p-Br	C18H21N4Br	372.0949 amu	372.0957 amu
3d	p-CH_3	C19H24N4	308.2001 amu	308.1994 amu
3e	p-NO_2	C18H21N5O2	339.1695 amu	339.1702 amu
3f	H	C18H22N4	294.1844 amu	294.1830 amu

Table 17. High-resolution electron-ionization mass spectral (EI-MS) data for 4a-f.

No.	X	Molecular Formula	Calculated Mass	Experimental Mass
4a	p-CN	C19H21N5	319.1797 amu	319.1803 amu
4b	p-CO_2Me	C20H24N4O2	352.1899 amu	352.1896 amu
4c	p-Br	$C_{18}H_{21}N_4Br$	372.0949 amu	372.0952 amu
4d	p-CH_3	C19H24N4	308.2001 amu	308.1997 amu
4e	p-NO_2	C18H21N5O2	339.1695 amu	339.1708 amu
4f	H	C18H22N4	294.1844 amu	294.1853 amu

Table 18. High-resolution electron-ionization mass spectral (EI-MS) data for 5a-e.

No.	X	Molecular Formula	Calculated Mass	Experimental Mass
5a	p-CN	C19H21N5	319.1797 amu	319.1791 amu
5b	p-CO_2Me	C20H24N4O2	352.1899 amu	352.1892 amu
5c	p-Br	$C_{18}H_{21}N_4Br$	372.0949 amu	372.0963 amu
5d	p-NO_2	C18H21N5O2	339.1695 amu	339.1683 amu
5e	H	C18H22N4	294.1844 amu	294.1845 amu

Table 19. High-resolution electron-ionization mass spectral (EI-MS) data for 6a-e.

No.	X	Molecular Formula	Calculated Mass	Experimental Mass
6a	p-CN	C19H22N5	320.1876 amu	320.1857 amu
6b	p-CO_2Me	$C_{20}H_{24}N_4O_2Na$	375.1797 amu	375.1791 amu
6c	p-Br	C18H22N4Br	373.1028 amu	373.1022 amu

Table 19. Contd…..

No.	X	Molecular	Calculated	Experimental
		Formula	**Mass**	**Mass**
6d	p-CH_3	$C_{19}H_{24}N_4Na$	331.1899 amu	331.1893 amu
6e	p-NO_2	C18H22N5O2	340.1774 amu	340.1767 amu

Table 20. High-resolution electron-ionization mass spectral (EI-MS) data for 7a.

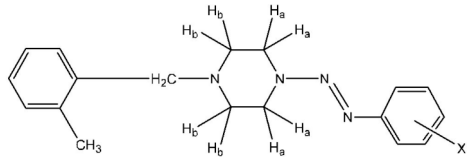
No.	X	Molecular	Calculated	Experimental
		Formula	**Mass**	**Mass**
7a	p-CO_2Me	C20H24N4O2	352.1899 amu	352.1890 amu

which is attached on the piperazine ring in **3a-f**, is a 1,2,3-trisubstituted benzene ring system. Predictably this ring system shows two out-of-plane bending vibration modes in the ranges of 719-724 cm^{-1} and 780-788 cm^{-1}. The aryl group, which is linked to the piperazine ring in **4a-f**, is a para-disubstituted benzene ring, which shows one out-of-plane bending vibration band in the range of 784-801 cm^{-1}. The aryl group, which is connected to the piperazine ring in **5a-e**, is an ortho-substituted benzene ring. Compounds **5a-e** show one ortho-substituted out-of-plane bending vibration band in the range of 743-746 cm^{-1}. The monosubstituted benzene ring, which joined with the piperazine ring in **7a**, shows two out-of-plane bending vibration bands at 699 and 744 cm^{-1}. The carbonyl group of the ester group, which is present in compounds **3b**, **4b**, **5b**, **6b** and **7a**, shows a stretching vibration band in the range of 1707-1722 cm^{-1}. In the same compounds, carbon oxygen single bond stretching bands of the ester groups were in the range of 1274-1278 cm^{-1}. Nitrile group stretching vibration bands were observed in **3a**, **4a**, **5a** and **6a** in the range of 2218-2225 cm^{-1}. Nitro groups, which were contained in **3e**, **4e**, **5d** and **6e**, show symmetric stretching vibration modes in the range of 1341-1379 cm^{-1} and asymmetric stretching vibration modes in the range of 1507-1509 cm^{-1}.

^{1}H NMR Spectroscopic Analysis

The ^{1}H NMR results are shown in Table **6** to Table **10**. These results are expressed as chemical shift in ppm relative to TMS(1%) at room temperature in $CDCl_3$. All of the compounds contained two benzene rings; the aromatic signals appeared in the range of δ 8.23-6.90 with a coupling constant (J) in the range of 7.0-9.0 Hz. One of the two benzene rings was initially from aniline derivatives, which are most of the para-substituted anilines except **3f**, **4f**, and **5e**; such that they show two doublet peaks characteristic of an AA'BB' system in the range of aromatic protons. The highest chemical shift peaks are always due to the two equivalent aromatic protons which are close to the triazene subunit. Some aromatic protons were not resolved due to overlapping peaks in the range of δ 7.20-6.90. The starting material, the aryl piperazine, was studied by NMR spectroscopy as a model compound to distinguish the protons in the two aryl groups, and the protons on the aryl group were matched with the same proton in the final triazene product in an approximate range.

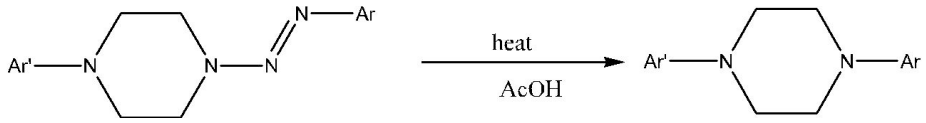
[iii]



The most significant peaks are the methylene protons on the piperazine ring protons H_a and H_b (see schematic [iii] above). As shown in tables 6 to 10, H_a has a higher chemical shift than that of H_b. due to the closer proximity of H_a to the triazene subunit. In general, the methylene protons are represented by two triplet peaks each integrating for 4H. However, some of the triplet peaks were not resolved resulting in broad peaks, especially for H_a. Such observation was due to the restricted rotation of the nitrogen-nitrogen single bond in the triazene subunit [6]. The H_a protons have representative peaks in the range of δ 4.07-3.75 with integration for 4H and coupling constants in the range of 4.8-5.3 Hz for the resolving triplet peaks. The H_b protons have representative peaks in the range of δ 3.07-2.55 with coupling constants in the range of 5.1-6.3 Hz for the resolving triplet peaks. Signals arising from the substituents on the benzene ring are consistent with the substituents present, such as the O-methyl protons arising as singlets in the range δ 3.08 -3.92 in the spectra of **3b**, **4b**, **5b**, **6b** and **7a**. The ethylene bridge linking the piperazine and aryl rings in compound **7**a is manifested by two 2H triplet peaks at δ 2.68 ppm and δ 2.83 ppm with a coupling constant J = 8.0 Hz. The full analysis of the ^{1}H spectrum of **7a** was complicated by the coincidence of the signals of H^a and the O-methyl protons at 3.89 ppm and the (considerable overlap of the triplets of CH_2 (II) and proton H^b.

^{13}C NMR

The structures of all new compounds have been investigated by ^{13}C NMR spectroscopy (see Tables **11** to **15**). For compounds **3a-f**, there are ten magnetically non-equivalent aromatic carbon atoms in each molecule. The aromatic carbons resonate in the range of δ 116-155 ppm. The mono- or para-substituted benzene ring has four

(iv) 

magnetically non-equivalent carbon atoms, since two carbon atoms on the ortho position are magnetically equivalent and the same goes for the two carbon atoms on the meta position. The 1,2,3-trisubstituted benzene ring has six carbon atoms that are all magnetically non-equivalent. The carbon atoms in the piperazine ring were often difficult to resolve due to the dynamic equilibrium in the triazene moiety. The carbon atoms in the piperazine ring are represented by the two peaks (both are usually broad peaks, if observed) in the range of δ 52.4-43.0 ppm. The two methyl groups on the 1,2,3-trisubstituted benzene ring were represented by the two peaks in the ranges of δ 20.6-20.3 ppm and δ 13.9-13.5 ppm. The nitrile group carbons resonate at δ 108.6 ppm. The carbonyl carbon in the ester subunit was represented by a peak at δ 167.0 ppm; the methyl group in the ester group was represented by a peak at δ 51.9 ppm. In **3d**, the p-tolyl methyl group resonates at δ 21.0 ppm.

For the compounds **4a-f**, there are two benzene rings, one mono-substituted and one para-disubstituted. Therefore, there are eight magnetically non-equivalent aromatic carbons in each compound, which are represented by eight peaks in the range of δ 155.6-119.0 ppm. For the piperazine carbons and the substituents on the aniline derivatives, chemical shifts similar to those seen previously in compounds **3a-f** were observed. The two carbons linked to the aryl group, in which the aryl group is attached to the piperazine ring, is represented by two peaks in the ranges of δ 62.6-62.1 ppm and δ 21.1-20.7 ppm. The carbons of the methylene groups between the benzene ring and the piperazine ring resonate in higher frequency (δ 62.6-62.1 ppm).

For the compounds **5a-e**, there are ten magnetically non-equivalent aromatic carbons for each compound, which include six carbons from the ortho substituted benzene ring and four carbons from the para- or mono-substituted benzene ring. The ten aromatic carbons resonated in the range of δ 155.6-118.7 ppm. All other carbons located in the piperazine ring and the substituents have similar chemical shifts as described previously for compounds **3a-f**.

For the compounds **6a-e**, there are ten magnetically non-equivalent aromatic carbons for each compound, which include six carbons from the meta substituted benzene ring and four carbons from the para- or mono-substituted benzene ring. The ten aromatic carbons resonated in the range of δ 155.6-118.7 ppm. All other carbons located in the piperazine ring and the substituents have similar chemical shifts as described previously for compounds **3a-f**.

For the compound **7a**, eight magnetically non-equivalent aromatic carbons were involved in each compound, due to the fact that the two benzene rings were para- and mono-substituted rings. The two methylene groups between the benzene ring and the piperazine ring were represented by two peaks at δ 59.6 and δ 51.4 ppm. The higher chemical shift accounts for the methylene group linked to the piperazine ring. All the other carbons in the molecule resonated in the reasonable range as described previously for compounds **3a-f**.

MASS SPECTRAL ANALYSIS

The high resolution mass spectrometry (MS) results are shown for all new compounds in Tables **16** to **20**. Mass spectroscopy (MS) is an important tool in synthetic organic chemistry, especially high resolution MS. Although MS can be used to predict the conformation of the molecule by matching the peaks to the small fragments of the molecule, the MS results can not be used because it is not capable of distinguishing the isomers in this project. The main use of the MS is to provide the evidence of the formation of the target molecule by matching the actual molecular weight with the experimental molecular ion mass. In the high resolution MS, the results were obtained with the standard deviation of +/-0.0008 amu. According to the MS results, all the molecular ions have been found in the spectra and matched with the actual mass of the molecule within the standard deviation.

CONCLUSION

The series of isomers of N-(2,3-dimethylphenyl)-N'-(aryldiazenyl)-piperazines were prepared in this study. The physical data of all the compounds were measured. All the compounds were extensively characterized through infrared, NMR, and mass spectral analysis. It is always interesting to speculate on the potential applications of new compounds like those reported in this paper. The new 1-aryl-4-[aryldiazenyl]-piperazines (**2d**) have the potential to undergo thermal cleavage under appropriate conditions to provide a route to unsymmetrically substituted N-aryl-N'-arylpiperazines (**8**). In a previous report [7], it was shown that the synmmetrical 1,4-bis-(2-aryldiazen-1-yl-)piperazines (**1**) undergo thermal cleavage in acetic acid to afford symmetrical N,N'-diarylpiperazines. The analogous reaction of **2d** would afford the unsymmetricaly substituted piperazines (**8**) thus:

Further work in this laboratory will be undertaken to try to make this idea a reality.

Aryldiazenylpiperazines have also been utilized as a means to the immobilization of a diazonium ion by covalent linkage to piperazine attached to a (Merrifield-)resin. The resin bound 1-aryldiazenyl)piperazine was used as a substrate for a Wallach reaction with hydrogen [18F]fluoride to produce radio-labelled 2-fluorophenyl phenyl ether [8].

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

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