Synthesis and Characterization of Novel Bis-Triazenes: 3,8-Di[2-aryl-1-azenyl]-1,3,6,8-tetraazabicyclo[4.4.1]undecanes and 1,3-Di-2-[(4-methoxyphenyl)-1-diazenyl]imidazolidine. The Reaction of Diazonium Ions with Ethylenediamine/Formaldehyde Mixtures

M. Brad Peori and Keith Vaughan*

Department of Chemistry, Saint Mary's University, Halifax, Nova Scotia, Canada B3H 3C3

Donald L. Hooper

Department of Chemistry, Dalhousie University, Halifax, Nova Scotia, Canada B3H 4J3

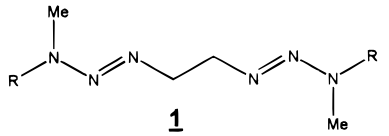
Received June 30, 1998

Reaction of a diazonium salt solution with a mixture of ethylenediamine and an excess of formaldehyde or 1,3,6,8-tetraazatricyclo[4.4.1.1^{3,8}]dodecane results in the formation of a novel class of bis-triazenes, the 3,8-di(2-aryl-1-azenyl)-1,3,6,8-tetraazabicyclo[4.4.1]undecanes (*6*), which have been fully characterized by spectroscopy, elemental analysis, and X-ray crystallography. The X-ray data show that the tetraazabicyclic cage is folded back so that the aryl groups interact by $\pi-\pi$-stacking. The proton NMR spectra are made complex by the presence of three sets of distinctly different diastereotopic methylene groups, which have been assigned by a combination of decoupling and 2D-NMR experiments. In the case involving coupling of the *p*-anisidine diazonium derivative to ethylenediamine and formaldehyde mixtures, 1,3-di-2-[(4-methoxyphenyl)-1-diazenyl]imidazolidine (*8*) was the only product isolated. Its structure has been assigned on the basis of ^{1}H and ^{13}C NMR spectra and X-ray crystallography.

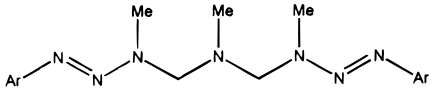
Introduction

1-Aryl-3,3-dimethyltriazenes (ArN═NNMe$_2$) have been shown to possess significant antitumor activity. Dacarbazine (DTIC) is a dimethyltriazenylimidazole that has been used for some time in the treatment of malignant melanoma,[1] but dacarbazine and other dimethyltriazenes have shown limited clinical effectiveness,[2] possibly because of the need for metabolic activation in the body. Recent studies have been aimed at the development of new triazene prodrugs such as the novel agent Temozolomide, developed in the U.K., which has exhibited promising activity in clinical trials against brain tumors[3] and malignant melanoma[4] with minimal side effects, and the novel tetraazepinones, Pyrcl and Quincl, developed in Canada.[5] Current research of our group is directed toward the synthesis of novel bis-triazenes, which may have the structural requirement for antitumor activity.

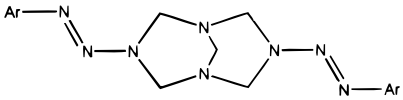
The trivial name "bis-triazene" has been used to describe a number of classes of organic compounds containing more than one triazene unit (N═NN) in a molecule. For example, reaction of the diazide N_3CH_2-CH_2N_3 with an alkyllithium reagent affords 1,2-bis-(alkyltriazeno)ethanes (1), which are potently cytotoxic due possibly to their ability to cross-link DNA.[6] Under appropriate conditions,[7] the reaction of a diazonium salt with a mixture of methylamine and formaldehyde affords the bis(triazenyl)methylamine (*2*), whereas similar diazonium coupling with a mixture of formaldehyde and ammonia produces the *bis*(triazenyl)tetraazabicyclononane (*3*).[8]



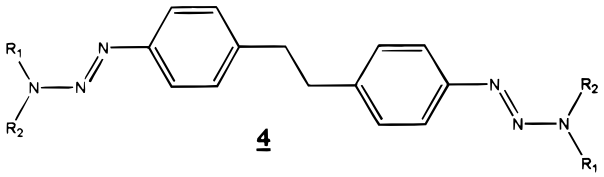
1



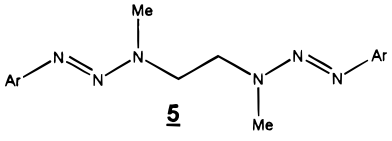
2



3



4



5

(1) Lucas, V. S., Jr.; Huang, A. T. Chemotherapy of Melanoma In *Developments in Oncology, Vol. 5, Clinical Management of Melanoma*; Siegler, H. F., Ed.; Martinus Nijhoff: The Hague, Netherlands, 1982; p 382.

(2) Bleeken, N. M.; Calvert, A. H.; Lee, S. M.; Harper, P.; Kaye, S. B.; Judson, I.; Brampton, M. *Br. J. Cancer* **1994**, *70*, 775.

(3) Newlands, E. S.; Stevens, M. F. G.; Wedge, S. R.; Wheelhouse, R. T. Brock, C. *Cancer Treat. Rep.* **1997**, *23*, 35.

(4) Bleehen, N. M.; Newlands, E. S.; Lee, S. M.; Thatcher, N.; Selby, P.; Calvert, H. A.; Rustin, G. J. S.; Brampton, M.; Stevens, M. F. G. *J. Clin. Oncol.* **1995**, *13*, 910.

(5) Jean-Claude, B. J.; Mustafa, A.; Damian, Z.; De Mark, J.; Chan, T. H.; Leyland-Jones, B. *Proc. Am. Assoc. Cancer Res.* **1995**, *36*, 349.

S0022-3263(98)01276-6 CCC: $15.00
Published on Web 09/10/1998

Table 1. Physical Data for 3,8-di[2-aryl-1-azenyl]-1,3,6,8-tetraazabicyclo[4.4.1]undecane (*6*)

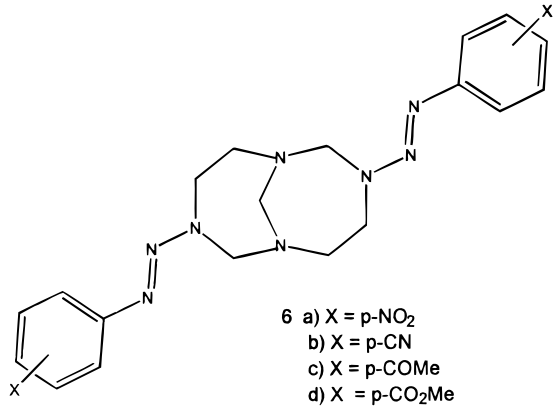
compd	X	methd	% yield	mp (°C)	IR (cm^{-1})	recryst solv
6a	*p*-NO_2	A	54	198−200	1560, 1350, (NO_2), 835 (*p*-sub OOP)	hexanes/EtOAc
6b	*p*-CN	A	33	214−216	2160 (CN) 815 (*p*-sub OOP)	EtOAc
6c	*p*-$COCH_3$	A	25	174−176	1645 (C═O) 790 (*p*-sub OOP)	EtOH
6d	*p*-CO_2CH_3	A	28	170−172	1680 (C═O) 1250,1135 (C−O) 750 (*p*-sub OOP)	hexanes/EtOAc
6e	*p*-$CO_2C_2H_5$	A	18	125−128	1670 (C═O) 1125, 1255 (C−O) 745 (*p*-sub OOP)	hexanes/EtOAc
6f	*p*-Br	A	26	173−175	1075 (Ar−Br) 800 (*p*-sub OOP)	hexanes/EtOAc
		B	55			
6g	*o*-NO_2	A	33	199−201	1550, 1380 (NO_2) 725 (*o*-sub OOP)	hexanes/EtOAc
6h	*o*-CN	A	26	229−231	2180 (CN) 735 (*o*-sub OOP)	EtOH/EtOAc

Table 2. ^{1}H NMR Data for 3,8-di[2-aryl-1-azenyl]-1,3,6,8-tetraazabicyclo[4.4.1] Undecane 6a−h[a]

compd	X	H_a, H_b	H_c, H_d	H_e, H_f, H_g	H_h	aromatic	X
6a	*p*-NO_2	4.14(s)	5.04, 4.98, 4.92, 4.86	3.51−3.26 (m)	4.51−4.38 (m)	7.96, 7.92, 7.19, 7.15	−
6b	*p*-CN	4.19(s)	5.01, 4.95, 4.90, 4.84	3.47−3.29 (m)	4.45−4.35 (m)	7.41, 7.38, 7.14, 7.11	−
6c	*p*-$COCH_3$	4.18(s)	5.00, 4.94, 4.88, 4.82	3.46−3.31 (m)	4.44−4.37 (m)	7.70, 7.66, 7.15, 7.11	2.52, s (CH_3)
6d	*p*-CO_2CH_3	4.15(s)	4.99, 4.93, 4.88, 4.82	3.47−3.29 (m)	4.33−4.17 (m)	7.79, 7.76, 7.14, 7.11	3.89
6e	*p*-$CO_2C_2H_5$	4.15(s)	5.01, 4.95, 4.90, 4.84	3.49−3.30 (m)	4.39−4.31 (m)	7.82, 7.79, 7.16, 7.13	3.49−3.30,m (CH_2) 1.39, t (CH_3)
6f	*p*-Br	4.15(s)	4.95, 4.89, 4.83, 4.77	3.39−3.22 (m)	4.35−4.31 (m)	7.27, 7.23, 6.99, 6.96	−
6g	*o*-NO_2	4.18(s)	4.98, 4.92, 4.88, 4.82	3.54−3.23 (m)	4.46−4.31 (m)	7.40−6.94 (m)	−
6h	*o*-CN	4.22(s)	5.00, 4.95, 4.86, 4.80	3.59−3.30 (m)	4.63−4.50 (m)	7.56−6.91 (m)	−

[a] Chemical shifts in ppm relative to TMS (1%) at 22 °C in $CDCl_3$. Refer to Figure 1 for assignment of proton labels.

We have reported[9] the synthesis of a different type of bis-triazene; bis-diazotization of ethylene dianiline and coupling of the resulting bis-diazonium salt with the appropriate alkylamine affords the 1,2-bis{4′-(triazenyl)-phenyl}ethanes (*4*), and we have recently completed a study[10] of the synthesis of the novel bis-triazenes, the 1,2-bis(1-aryl-3-methyltriazen-3-yl)ethanes (*5*), by the reaction of the appropriate diazonium salt with *N*,*N*′-dimethylethylenediamine. We now report the synthesis of a new type of bis-triazene, the 3,8-di[2-aryl-1-azenyl]-1,3,6,8-tetraazabicyclo[4.4.1]undecanes (*6*), which are obtained by the reaction of a diazonium salt with a mixture of formaldehyde and ethylenediamine:



6 a) X = p-NO_2
b) X = p-CN
c) X = p-COMe
d) X = p-CO_2Me
e) X = p-CO_2Et
f) X = p-Br
g) X = o-NO_2
h) X = o-CN

Experimental Section

All reagents were reagent grade materials purchased from the Aldrich Chemical Co. Ltd. and were used without further purification. Yields are based on recrystallization with the appropriate solvent (Table 1). Melting points were determined on a Reichert hot-stage microscope and are uncorrected. Infrared spectra were obtained using Nujol mulls, unless otherwise stated, on a Perkin-Elmer 299 spectrophotometer. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker 250-MHz spectrophotometer at the Atlantic Region Magnetic Resonance Center at Dalhousie University in Halifax, Nova Scotia. Chemical shifts were recorded in $CDCl_3$ solutions at 20 °C and are relative to TMS internal standard. Crystal structures were determined on an Enraf-Nonius CAD-4 diffractometer. Elemental analysis was performed by the Canadian Microanalytical Service Ltd., Delta, B.C.

3,8-Di[2-aryl-1-azenyl]-1,3,6,8-tetraazabicyclo[4.4.1]-undecane (*6*). General Procedure. Method A. An appropriate arylamine (0.0165 mol) was dissolved in 40 mL of 3 M HCl and gently heated, if necessary, to obtain a clear solution. This solution was then cooled and kept at 0−5 °C while diazotized with sodium nitrite (0.020 mol) dissolved in deionized water (10 mL). The resulting solution was stirred for 30 min, and any insoluble impurities were removed by vacuum filtration. A mixture of ethylenediamine and formaldehyde was prepared by adding 2.9 mL of a 50% ethylenediamine solution to 40.5 mL of a 37% formaldehyde aqueous solution at 0 °C. This ethylenediamine and formaldehyde mixture was then slowly added dropwise to the diazotized arylamine, being careful to keep the temperature of the reaction at 0−5 °C. This solution was stirred for 30 min, and then the pH adjusted to the alkaline region using saturated $NaHCO_3$. The product then precipitated out of solution as an oil or a solid. Solid precipitates were isolated by vacuum filtration and purified by recrystallization from an appropriate solvent (see Table 1). Oils were recovered by extraction into

(6) Blumenstein, J. J.; Michejda, C. J. *Tetrahedron Lett.* **1991**, 32, 183.
(7) Manning, H. W.; Hemens, C. M.; LaFrance, R. J.; Tang, Y.; Vaughan, K. *Can. J. Chem.* **1984**, *62*, 749.
(8) Singer, R. D.; Vaughan, K.; Hooper, D. L. *Can. J. Chem.* **1986**, *64*, 1567.
(9) Brown, D. S.; Merrin, M. P.; Vaughan, K. *Proc. N. S. Inst. Sci.* **1995**, *40*, 67.
(10) Hooper, D. L.; Pottie, I. R.; Vacheresse, M.; Vaughan, K. *Can. J. Chem.* **1998**, *76*, 125.

Table 3. ^{13}C NMR Data for 3,8-di[2-aryl-1-azenyl]-1,3,6,8-tetraazabicyclo[4.4.1] Undecane 6a−h[a]

compd	X	C1/C5	C2/C4	C3	C4	aromatic	X
6a	*p*-NO_2	47.43	47.03	71.06	73.84	154.77, 144.79, 124.30, 120.64	−
6b	*p*-CN	47.21	47.06	71.12	73.74	153.19, 132.61, 121.02, 119.31	108.1
6c	*p*-$COCH_3$	46.98	46.94	71.01	73.48	153.60, 133.85, 129.10, 120.45	197.44(C=O) 26.51(CH_3)
6d	*p*-CO_2CH_3	46.99	46.92	71.12	73.43	153.53, 130.23, 126.65, 120.32	167.01(C=O) 51.90(CH_3)
6e	*p*-$CO_2C_2H_5$	46.99	46.86	71.17	73.4	153.47, 130.17, 127.03, 120.28	166.51(C=O) 60.65 (−CH_2-) 14.37(CH_3)
6f	*p*-Br	46.92	46.51	71.01	73.2	148.92, 131.45, 122.08, 118.70	−
6g	*o*-NO_2	47.08	46.84	71.08	73.45	132.17, 124.89, 123.18, 118.92	−
6h	*o*-CN	47.59	46.84	not obs.	73.58	133.05, 132.38, 124.99, 116.64	108.14

[a] Chemical shifts are in ppm relative to TMS (1%) at 22 °C in $CDCl_3$ unless otherwise stated. Refer to Figure 1 for carbon assignments.

Table 4. Elemental Analysis for Selected 3,8-Di[2-aryl-1-azenyl]-1,3,6,8-tetraazabicyclo[4.4.1]undecanes

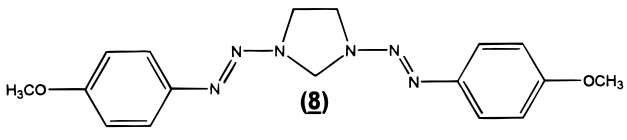
		calculated			found		
compd	X	C	H	N	C	H	N
6a	*p*-NO_2	50.21%	4.88%	30.82%	50.32%	4.92%	30.58%
6c	*p*-$COCH_3$	61.59%	6.29%	24.97%	61.57%	6.22%	24.86%
6d	*p*-CO_2CH_3	57.49%	5.87%	23.31%	57.45%	5.93%	23.24%
6e	*p*-$CO_2C_2H_5$	59.04%	6.34%	22.02%	59.14%	6.33%	21.79%
6f	*p*-Br	43.70%	4.25%	21.45%	43.63%	4.26%	21.27%
6h	*o*-CN	60.86%	5.35%	33.78%	60.87%	5.33%	33.88%

dichloromethane (3 × 20 mL aliquots), and the extract was dried over anhydrous Na_2SO_4. The extract was then filtered and rotoevaporated under vacuum to remove the solvent. Solids and oils were recrystallized using the appropriate solvent (Table 1). Solid products were then isolated and analyzed. The data collected for compounds **6a**−**h** can be found in Tables 1−4.

Method B. *p*-Bromoaniline (0.015 mol) was dissolved in 40 mL of 3 M HCl and gently heated, if necessary, to obtain a clear solution. This solution was then cooled and kept at 0−5 °C while diazotized with $NaNO_2$ (0.017 mol) dissolved in deionized water (10 mL). The resulting solution was stirred for 30 min, and any insoluble impurities were removed by vacuum filtration. 1,3,6,8-Tetraazatricyclo[4.4.1.1^{3,8}]dodecane (*7*) (0.0125 mol), which was prepared using the method described below, was then dissolved in 10 mL of a 37% formaldehyde solution. This solution was then slowly added dropwise to the diazotized arylamine, being careful to keep the temperature of the reaction at 0−5 °C. This solution was stirred for 30 min, and then the pH was adjusted to the alkaline region using saturated $NaHCO_3$. The product then precipitated out of solution as a solid. The solid precipitate was isolated by vacuum filtration and purified by recrystallization from an appropriate solvent (see Table 1). The solid product was then isolated and analyzed. The data collected for compound **6f** prepared via method B matches the analysis for **6f** prepared via method A and is represented in Tables 1−4.

1,3,6,8-Tetraazatricyclo[4.4.1.1^{3,8}]dodecane (*7*). A slurry of paraformaldehyde was created by adding 45 g of paraformaldehyde (1.50 mol) to 70 mL of *N*,*N*-dimethylformamide. The slurry was heated to 80 °C using a water bath, at which point 45 g of ethylenediamine (0.750 mol) was added to the slurry carefully with stirring. The reaction mixture was then heated to reflux for 2 h, over which time the solid slurry of paraformaldehyde dissolved to give a clear solution. At this point, the solution was left to cool, and at about 60 °C large amounts of needlelike crystals began to form. After it had cooled to room temperature, the solid was isolated via vacuum filtration and analyzed. This yield, along with a second crop of crystals obtained from concentrating the reaction mixture via evaporation, gave a cumulative yield of the tetraazatricyclododecane (*7*) of 35 g (21%): mp 205−206 °C; ^{1}H NMR δ 3.98 (s, 8H), 3.26 (s, 8H); ^{13}C NMR δ 73.74, 58.57.

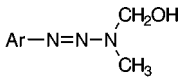
1,3-Di-2-[(4-methoxyphenyl)-1-diazenyl]imidazolidine (*8*). *p*-Anisidine (0.0165 mol) was dissolved in 40 mL of 3 M HCl. After a clear solution was obtained, this amine was then cooled and kept at 0−5 °C while being diazotized with $NaNO_2$ (0.020 mol) dissolved in deionized water (10 mL). The resulting solution was stirred for 30 min. An ethylenediamine and formaldehyde mixture was prepared by adding 2.9 mL of a 50% ethylenediamine solution to 40.5 mL of a 37% formaldehyde solution at 0 °C. This ethylenediamine/formaldehyde mixture was then slowly added dropwise to the diazotized arylamine, with the temperature of the reaction being carefully maintained at 0−5 °C. This solution was stirred for 30 min, and then the pH was adjusted to the alkaline region using saturated $NaHCO_3$. The product then precipitated out of solution as an oil. The oil was recovered by extraction into dichloromethane (3 × 15 mL aliquots), and the extract was dried over anhydrous Na_2SO_4. The extract was then filtered and evaporated under aspirator vacuum to remove the solvent. The resulting oil appeared to contain trace amounts of solid crystals. An attempt to remove these crystals using hexanes and ethyl acetate failed as the crystals dissolved. The entire compound was then dissolved by adding toluene. The compound was left for possible recrystallization. After several weeks in refrigeration, a trace amount of solid material was isolated and identified as the diaryldiazenylimidazolidine (*8*): yield 11%; mp 153−155 °C (hexanes/ethyl acetate/toluene); IR 1215, 1015 (C−O), 805 (*p*-sub OOP); ^{1}H NMR: δ 3.84 (s, 6H, OCH_3), 4.12 (s, 4H, NCH_2CH_2N), 5.43 (s, 2H, NCH_2N), 7.45−7.48 (AA′BB′, 8H, aromatic); ^{13}C NMR δ 46.58 (NCH_2CH_2N), 55.68 (OCH_3), 65.87 (NCH_2N), 114.35, 122.3, 144.1, 158.9 (aromatic).



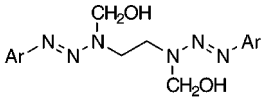
(8)

Discussion

Previous studies[7,11] have shown that diazonium coupling with mixtures of methylamine and formaldehyde affords either the bis-triazene (*2*), the hydroxymethyltriazene (*9*), or a mixture of both under appropriate reaction conditions. By analogy with these previous studies, diazonium coupling with a mixture of ethylenediamine and formaldehyde might be expected to afford the bis-hydroxymethyltriazene (*10*), the hydroxymethyl analogue of the bis-triazene (*5*). Instead, the products



9



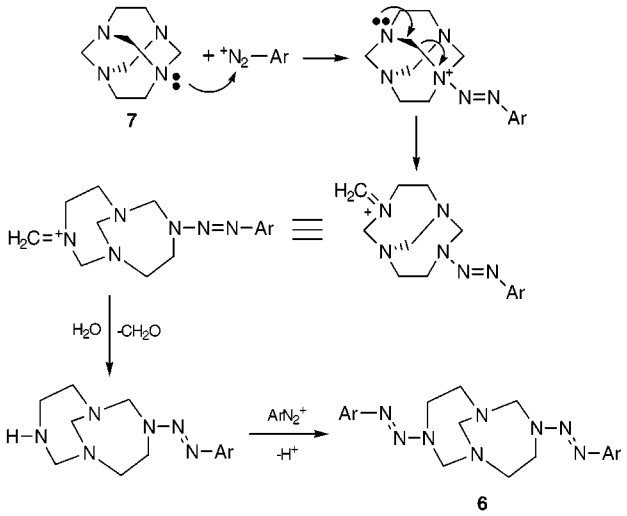
10

recovered from diazotization of the appropriate arylamine and the coupling of the diazonium ions with a mixture of formaldehyde/ethylenediamine were the bicyclic bis-triazenes, 3,8-di[2-aryl-1-azenyl]-1,3,6,8-tetraazabicyclo-[4.4.1]undecanes **6a**−**h**. These 3,8-di[2-aryl-1-azenyl]-1,3,6,8-tetraazabicyclo[4.4.1]undecanes (*6*) were isolated in moderate to good yields of 18−54%, depending on the substituent, via the synthetic procedure defined in method A. The optimum ratio of arylamine:formaldehyde:ethylenediamine for method A was observed to be 1:20:1 by varying composition mixtures of formaldehyde and ethylenediamine.

The formation of the 3,8-di[2-aryl-1-azenyl]-1,3,6,8-tetraazabicyclo[4.4.1]undecanes (*6*) is believed to arise from the coupling of the diazonium salt to a molecule of 1,3,6,8-tetraazatricyclo[4.4.1.1^{3,8}]dodecane (*7*). 1,3,6,8-Tetraazatricyclo[4.4.1.1^{3,8}]dodecane (*7*) has been shown via X-ray crystal structure[12] to be the condensation product of ethylenediamine with formaldehyde in the solid state. Therefore, the reaction mechanism for the formation of 3,8-di[2-aryl-1-azenyl]-1,3,6,8-tetraazabicyclo-[4.4.1]undecanes is believed to be the route shown in Scheme 1, which is analogous to the mechanism for bis-(arylazo)tetraazabicyclononane (*3*) formation previously reported.[8] Supporting evidence for the mechanism in Scheme 1 is the fact that direct diazonium coupling with the dodecane (*7*) results in a higher yield of **6**.

Infrared Spectral Analysis. Infrared spectral analysis of the new bis-triazenes confirms the presence of the functional group attached to the aryl moiety. The carbonyl group of the esters **6d** and **6e** and ketone **6c** show stretching vibrations between 1645 and 1680 cm^{-1}. Two carbon−oxygen single bond stretching bands for **6d** and **6e** were found at 1135, 1250 cm^{-1} and 1125 and 1255 cm^{-1} respectively. Nitrile group stretching vibrations were observed in the spectra of **6b** and **6h** at 2160 and 2180 cm^{-1}, respectively. The spectra of **6a** and **6g** contained the symmetric and asymmetric vibrations of the nitro group at 1350 and 1560 cm^{-1}, and 1380 and 1550 cm^{-1}, respectively. **6f** showed a strong absorption at 1075 cm^{-1} which can be assigned to an Ar−Br stretch.

Scheme 1. Synthetic Pathway for 3,8-Di-2-[2-aryl-1-azenyl]-1,3,6,8-tetra-azabicyclo[4.4.1]undecanes



NMR Spectral Analysis: ^{1}H NMR. Proton NMR provided unequivocal evidence for the structure of the bis-triazenes. The aromatic resonance signals of compounds containing *para* substituents, **6a**−**f**, were found between δ 7.79 and 6.96 and exhibited the general splitting pattern of an AA′BB′ system. Compounds **6g** and **6h** contained complex aromatic splitting patterns due to the *ortho* substituent at δ 7.56−6.91. Methyl protons that were adjacent to an oxygen atom in the ester **6d** had a singlet signal at δ 3.89. The ethyl ester substituent **6e** had the general splitting of a triplet at δ 1.39 representing the methyl protons of the ethyl group; however, the methylene protons of the ethyl group were observed at δ 4.40−4.30, overlapping a multiplet in this range. The methyl protons for the acetyl group of compound **6c** where found to resonate at δ 2.52 as a singlet.

The protons of the bicyclic component of compound *6* give a surprisingly complex series of splitting patterns. The complexity of the ^{1}H NMR spectra was puzzling because at first glance the molecule appeared to have symmetry. However, unambiguous structural information collected via X-ray crystal structures of a number of these compounds gave structural information which could be related to the complex splitting patterns observed in these compounds. X-ray analysis revealed that the molecule adopts a folded geometry about the bicyclic basket portion of the molecule. However, it is believed that this folded geometry exists only in the solid state and that in solution a more "stretched out" geometry is adopted by the molecule. Analysis of the crystallographic data obtained for select compounds supported the extensive NMR evidence gathered as the geometry of the molecules explains the diastereotopicity of a number of the methylene protons.

Figure 1 shows the labeling of the protons of the bicyclic basket portion of compounds **6a**−**h**. The bicyclic basket is made up of two equivalent ethylene bridges (C1/C2 and C4/C5) which, together with the nitrogens attached, are the ethylenediamine portions of the basket. These ethylene bridges contain two equivalent sets of diastereotopic methylene groups. The eight protons of these diastereotopic methylene groups, labeled H_e, H_f, H_g, and H_h, surprisingly give two complex multiplets,

(11) Hemens, C. M.; Manning, H. W.; Vaughan, K.; LaFrance, R. J.; Tang, Y. *Can. J. Chem.* **1984**, *62*, 741.

(12) Murray-Rust., P. *J. Chem. Soc., Perkin Trans. 2* **1974**, 1075.

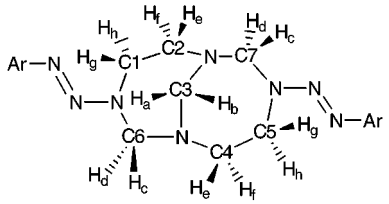


Figure 1. Proton and carbon labels for the bicyclic basket structure of 3,8-di[2-aryl-1-azenyl]-1,3,6,8-tetraazabicyclo-[4.4.1]undecane (*6*).

which integrate in the ratio 6:2. The two proton multiplet in the range δ 4.63−4.17 is assigned to the proton labeled H_h in Figure 1. The chemical shift of H_h is more than a full ppm downfield from the other three protons, H_e, H_f, and H_g, observed in a 6-proton multiplet in the range δ 3.22−3.59. The explanation for the downfield shift of the protons H_h is that somehow the H_h protons are in an entirely different chemical environment in which they are deshielded. A close inspection of many of these low-field multiplets reveals eight lines suggesting the signal is a doublet of a doublet of doublets (see inset in Figure 2). This pattern can be explained if H_g and H_h are diastereotropic and experience geminal coupling to one another as well as different couplings to their two neighboring diastereotopic protons H_e and H_f. An example of this multiplet can be observed at δ 4.33−4.17 in the ^{1}H NMR spectrum of the *p*-CO_2CH_3 derivative **6d**, Figure 2, which is a typical 250-MHz ^{1}H NMR spectrum of *6*. In the case of **6e**, the signal for H_h at δ 4.39−4.31 is overlapped by the quartet of the CH_2 group of the ethyl ester which has the same chemical shift to give a signal with an integration of six rather than two.

The second 6-proton multiplet caused by the remaining protons of the ethylene bridges is a more complex 6-proton multiplet found in the range δ 3.59−3.22 of the ^{1}H NMR of *6*. This more complex multiplet is assigned to the H_e, H_f, and H_g protons of the ethylene bridge and is the result of the overlapping and second-order spectral effects of three nonequivalent protons, H_g, H_e, and H_f, with different but almost identical chemical shifts (H_e and H_f are diastereotopic). The line count of this multiplet varies from 14 to 24 uneven and disproportioned lines (see inset Figure 2). Slight variations in the chemical shifts of these three protons determine the degree of overlap and second-order spectra of the multiplet and therefore the size and number of lines of the multiplet. In Figure 2 this complex multiplet can be observed in the range δ 3.47−3.29.

The bicyclic basket portion of *6*, Figure 1, also contains three single-carbon methylene linkages, two of which are nonbridging (C6 and C7) and one which is bridging (C3); these are the original formaldehyde carbon atoms. Protons H_a and H_b of the bridging methylene (C3) are enantiotopic and give rise to a singlet in the range δ 4.22−4.15 with an integration of two protons. In Figure 2 this singlet can be observed at δ 4.15. On the other hand, protons H_c and H_d of the equivalent nonbridging methylene groups C6 and C7 are diastereotopic. The chemical shift values of H_c and H_d turn out to be close to one another, giving rise to a second-order spectra AB system of doublets resulting in H_c and H_d being observed as a quartet-like signal in the proton NMR in the range δ 5.01−4.77, depending on the substituent. In Figure 2 this four- line AB system is observed at δ 4.99, 4.93, 4.88, and 4.82.

^{13}C NMR. ^{13}C NMR spectroscopy supported the conclusions from the ^{1}H NMR data. The aromatic resonances of *para*-substituted compounds **6a**−**f** were observed as four signals that were found between δ 154.77 and δ 118.70. The *ortho*-substituted compounds **6g** and **6h** produced four aromatic resonances between δ 132.17 and 118.92 which represented the hydrogen-bearing aromatic carbons. The signals for the *ipso* carbons of the aromatic ring are believed not to be detected due to a nuclear Overhauser enhancement observed in the proton-decoupled spectrum. As the signal intensities for the carbons bearing hydrogens in compounds **6g** and **6h** increase, the *ipso* carbons of the aromatic ring which bear no hydrogens do not experience a nuclear Overhauser enhancement. This leads to the drowning out of the *ipso* carbon's signal in the background noise of the spectrum. The methyl carbon bonded to the oxygen atom in methyl ester **6d** had a signal of δ 51.90. The ethyl ester substituent **6e** created two signals within the proton-decoupled ^{13}C NMR spectra at δ 60.65 (CH_2) and δ 14.37 (CH_3). The acetyl group in compound **6c** had two resonances, one for the carbonyl carbon (δ 197.44) and one for the methyl group (δ 26.51). The cyano substituted compounds **6b** and **6h** gave cyano-carbon resonances at δ 108.10−108.14. The carbonyl carbon of esters **6d** and **6e** and the acetyl group of **6c** gave resonances at δ 197.44−166.51.

Carbon atoms C1 and C5 of the bicyclotetraamine basket (Figure 1), which are equivalent carbons of the ethyl linkages closest to the triazene moiety, were found to resonate in the range δ 47.06−46.51. C2 and C4, which are equivalent carbons of the ethylene moiety farthest from the triazene moiety, resonate in the range δ 47.43−46.92. The resonance for the methylene bridging carbon C3 had signals from δ 73.84 to 73.40. The resonances of the equivalent methylene groups which are nonbridging, C6 and C7, had signals from δ 71.12 to 71.01. These assignments were confirmed by the following DEPT experiments.

DEPT Experiment. DEPT experiments were run on compounds **6d**, **6c**, and **6f** in order to confirm the ^{13}C NMR assignments. The DEPT spectrum for the *para*-methyl ester compound **6d** had positive peaks at δ 51.90, 120.32, and 130.23, indicating a methine or methyl groups. The positive signal at δ 51.90 was assigned to the methyl group on the methyl ester substituent. The two remaining positive signals in the DEPT spectrum of **6d**, δ 120.32 and 130.23, were assigned to the *meta* and *ortho* methine groups of the aromatic rings. The DEPT spectrum of **6d** also gave inverse peaks at δ 46.99 and 46.92, which were assigned to carbons C1/C5 and C2/C4 (Figure 1), respectively, confirming these carbons as methylene carbons. The inverse peaks at δ 73.42 and 71.11 of **6d**'s DEPT spectrum were assigned to C6/C7 and C3, respectively, and confirmed their identity as methylene carbons. The DEPT spectrum for the *para* bromo compound **6f** revealed positive peaks at δ 122.12 and 118.74, which were assigned to the aromatic *meta* and *ortho* methine carbons. Inverse peaks at δ 46.98 and 46.55 of the DEPT spectrum of **6f** were assigned to the methylene carbons of C1/C5 and C2/C4, respectively, while the inverse peaks at δ 73.26 and 71.06 were assigned to the methylene carbons of C6/C7 and C3, respectively. For the DEPT spectrum of the *para* methyl ketone compound **6c**, there were three positive peaks observed. The first of these positive peaks, observed at

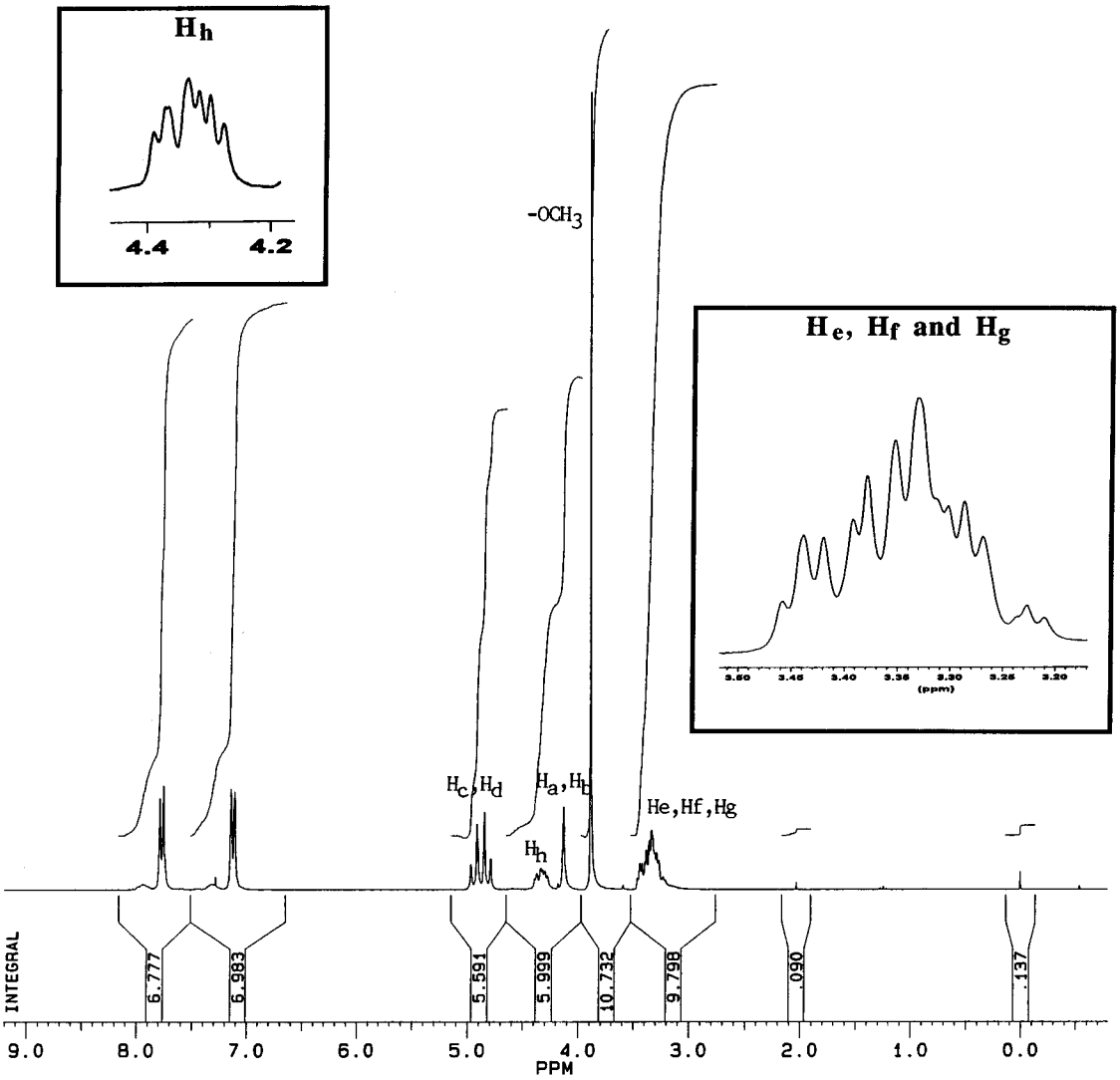


Figure 2. ^{1}H NMR spectrum (250 MHz) of **6d** (X = *p*-CO_2CH_3).

δ 26.51, was assigned to the methyl carbon on the methyl ketone substituent. The remaining two positive peaks at δ 129.09 and 120.45 were assigned to the *meta* and *ortho* aromatic methine carbons. An inverse peak at δ 46.98 in the DEPT spectrum of **6c** was assigned to confirm the methylene of carbons C1/C5; however, no peak was observed for the methylene carbons of C2/C4. Inverse peaks at δ 73.48 and 71.01 confirmed the methylene carbons of C6/C7 and C3, respectively.

2D-NMR Experiments: HETCOR. To support the analysis of the ^{13}C and ^{1}H NMR spectra, a series of 2D-NMR experiments were run for compound **6d**. The first of these experiments involved a heteronuclear correlation spectroscopy (HETCOR) experiment. The peaks of the carbon spectrum were already assigned using DEPT experiments and correlation of carbon spectral data of compounds with similar structural features, such as *5*[10] and *3*.[8]

The HETCOR spectrum of **6d** shows the following correlations: (a) The O-methyl carbon signal at δ 51.9 correlates with the proton singlet at δ 3.89. (b) The carbon signal of C3 at δ 71.1 correlates with the 2-proton singlet at δ 4.15 assigned to the enantiotopic protons H_a and H_b. (c) The carbon signal of C6/C7 at δ 73.43 correlates with the quartet-like signal in the proton spectrum at δ 4.82−4.99 assigned to the diastereotopic protons H_c and H_d. (d) The carbon signal of C2/C4 at δ 46.99 correlates with the high-field segment of the proton multiplet at δ 3.29−3.47, which enables the exact chemical shift of the diastereotopic protons H_e and H_f to be assigned as δ 3.24. (e) The carbon signal of C1/C5 at δ 46.92 correlates with two proton multiplets, those at δ 4.17 assigned to H_h and at ca. δ 3.48 assigned to H_g. This crucial observation confirms that H_g and H_h are diastereotopic but does not provide an explanation for the downfield shift of H_h by 0.77 ppm relative to H_g. Figure 3 shows an expanded plot of the HETCOR spectrum of **6d** in the region of the chemical shift for C1/C5 and C2/C4, which reveals the carbon signal to be two signals, and confirms that the protons attached to C1/C5, H_g and H_h, are responsible for these multiplets observed in the proton spectrum.

COSY Experiments. An H−H correlation spectroscopy (COSY) experiment for **6d** was also performed, Figure 4, which shows an off-diagonal peak correlating between the two multiplets in the proton NMR at δ 4.33−4.17 and 3.47−3.29. As shown in the HETCOR experiments, the multiplet at δ 4.33−4.17 represents the proton H_h, while the multiplet at δ 3.47−3.29 represents protons H_e, H_f, and H_g. The off-diagonal peak between these two multiplets in the COSY experiment further supports the analysis that these two multiplets are caused by neigh-

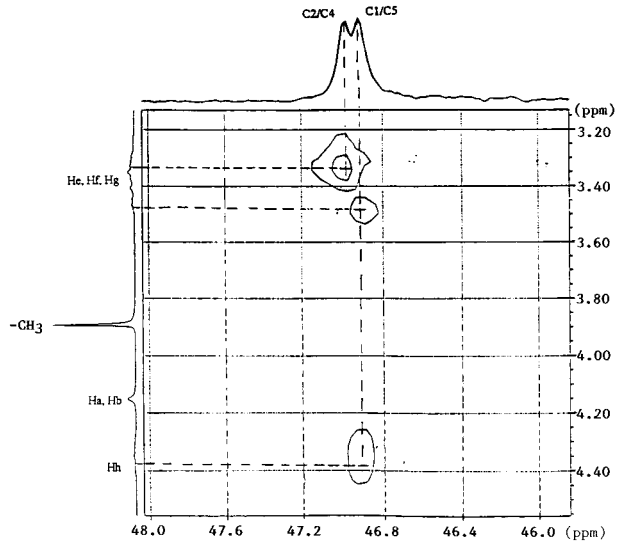


Figure 3. Enlargement of **6d** 2D HETCOR spectrum, showing C1/C5 and C2/C4 correlations.

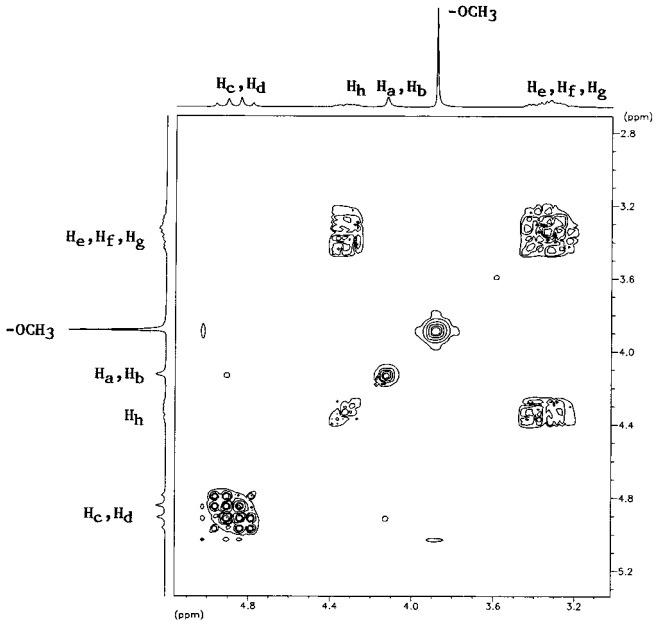
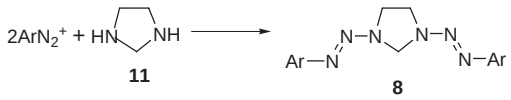


Figure 4. COSY Spectrum of **6d**, showing coupling between protons H_e, H_f, H_g, and H_h.

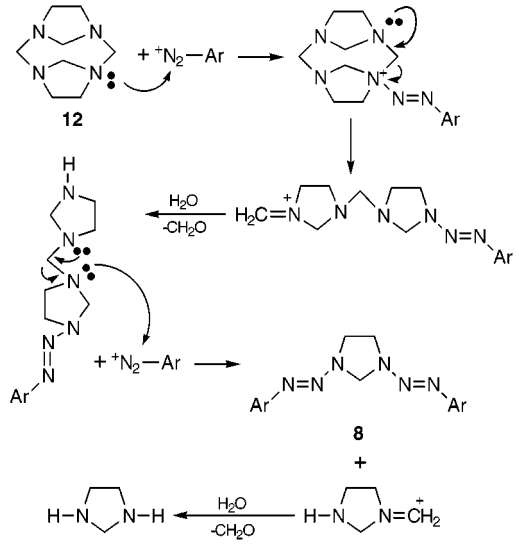
boring protons and supports the analysis that H_h is shifted downfield from H_e, H_f, and H_g.

1,3-Di-2-[(4-methoxyphenyl)-1-diazenyl]imidazolidine (*8*). The diazonium salt from *p*-anisidine, instead of coupling to 1,3,6,8-tetraazatricyclo[4.4.1.1^{3,8}]dodecane (*7*) as depicted in Scheme 1, followed an alternative pathway and afforded the bis-arylazoimidazolidine *8*. The structure of *8* is corroborated by ^{1}H and ^{13}C NMR data and by X-ray crystallography. The X-ray crystal structure will be published elsewhere.[14] The proton NMR of **8** is straightforward with aromatic resonance of the AA′BB′ system between 7.48 and 7.45 ppm, an *O*-methyl 6-proton singlet at 3.88 ppm, a four-proton singlet at 4.12 ppm assigned to the equivalent methylene groups at C4/C5 of the ring, and a 2-proton singlet at 5.43 ppm arising from the NCH_2N group. In the supporting ^{13}C NMR spectrum, the two equivalent carbons of the ethylene carbons, C4/C5, resonate at 46.58 ppm, while the carbon at C2 resonates at 65.87 ppm and the *O*-methyl carbon is found at 55.68 ppm. Aromatic carbons in the spectrum of **8** appear between 114.35 and 158.90 ppm.

Scheme 2. Possible Alternative Diazonium Coupling with Tetrahydroimidazole



Scheme 3. Synthetic Pathway for 1,3-Di-2-[(4-methoxyphenyl)-1-diazenyl]imidazolidine



There are two possible alternative diazonium coupling pathways which would explain the formation of *8*. The first is diazonium coupling to an ethylenediamine/formaldehyde condensation product, tetrahydroimidazole (*11*), as shown in Scheme 2. A second pathway to the formation of *8* is via coupling of the diazonium to 1,3,6,8-tetraazatricyclo[6.2.1.1^{3,6}]dodecane (*12*) as shown in Scheme 3. This second pathway to the formation of *8* appears to the more likely as 1,3,6,8-tetraazatricyclo-[6.2.1.1^{3,6}]dodecane (*12*) has been reported[16] as a possible structural isomer to 1,3,6,8-tetraazatricyclo[4.4.1.1^{3,8}]-dodecane (*7*) for the condensation product of ethylenediamine with formaldehyde.

The reaction involving the isolation of 1,3-di-2-[(4-methoxyphenyl)-1-diazenyl]imidazolidine (*8*) involved the same reaction conditions as the preparation of 3,8-di[2-aryl-1-azenyl]-1,3,6,8-tetraazabicyclo[4.4.1]undecanes **6a**−**h** via method A. This suggests it may be possible that both *7* and *12* are present in the aqueous reaction mixture and there may be a competitive reaction of diazonium coupling among the two structural isomers *7* and *12*. A competitive coupling among these structural isomers may account in part for the low yields obtained for *6* and would also account for the poor yield of *8*.

X-ray Crystallography. The structures of the *p*-nitro **6a**, *p*-methyl ester **6d**, *p*-ethyl ester **6e**, *o*-nitro **6g**, and

(13) Jorgensen, W. L.; Severance, D. L. *J. Am. Chem. Soc.* **1990**, *112*, 4768. Zhang, J.; Moore, J. S. *J. Am. Chem. Soc.* **1996**, *118*, 1019. Hunter, C. A. *Chem. Soc. Rev.* **1994**, *23*, 101.

(14) Peori, M. B.; Biradhar, K.; Vaughan, K. Unpublished results.

(15) Bullerwell, W. L.; MacGillivray, L. R.; Zaworotko, M. J.; Vaughan, K.; Wilman, D. E. V. *Acta Crystallogr.* **1995**, *C51*, 2624.

(16) Bischoff, C. A. *Ber. Dtsch. Chem. Ges.* **1898**, *31*, 3248.

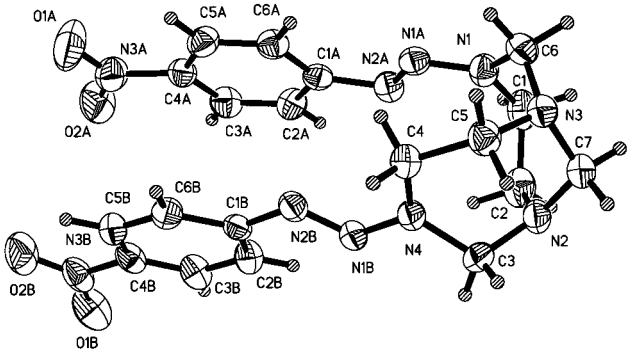


Figure 5. ORTEP diagram of compound **6a**.

o-cyano **6h** substituted bis-triazenes have been confirmed by X-ray crystallography. In the solid state, four of these compounds, **6a**, **6e**, **6g**, and **6h**, adopt a folded configuration in which the molecule folds about the bicyclic "basket" portion of the molecule to give a parallel or nearly parallel face-to-face overlap of the aromatic rings. An ORTEP diagram of the *p*-nitro compound **6a** is shown in Figure 5 as an example. The *p*-methyl ester **6d** seems to be the exception to this behavior; although the molecule still folds about the "basket" portion of the molecule, its aromatic rings seem to swing away from one another. In the case of compounds **6a**, **6e**, **6g**, and **6h**, the nearly parallel facial overlap of the aromatic rings suggests that there may be a $\pi-\pi$ stacking interaction between the aromatic rings. Compounds **6a**, **6e**, **6g**, and **6h** have aromatic ring facial distances of 3.606, 3.798, 3.876, and 3.777 Å, respectively, which are within the distance considered for a $\pi-\pi$ stacking interaction, 3.50−4.00 Å.[13] Compound **6d**, which appears to have no intramolecular $\pi-\pi$ stacking interaction, turns out to have an intermolecular face-to-face $\pi-\pi$ stacking between two adjacent molecules with an average face-to-face distance of 3.589 Å. Full details of the X-ray crystal structures of these compounds will be published elsewhere.[14] Bond lengths in the crystal structure of **6a** compare favorably with those reported for simple 1-aryl-3,3-dimethyltriazenes.[15]

Upon examination of all five crystal structures for any type of interaction involving either of the two hydrogens about the carbons C2 and C4 which would explain the deshielding of one of these hydrogens, resulting in the proton NMR pattern described earlier, none could be found. Examination of the crystal structures shows that either the protons about C2 and C4 are in similar chemical environments or the C2 and C4 carbons themselves are oriented differently from one another, resulting in their sets of protons being in completely different chemical environments, which would not be explainable via the proton NMR. Thus, it may be surmised that these compounds, rather than adopting a folded configuration, may adopt an unfolded configuration in solution. It is also possible that this unfolded configuration of the molecule may better explain the proton NMR patterns observed.

Conclusions

From this study of the NMR, infrared, and elemental analysis data presented in this report, it is concluded that the reaction of aryldiazonium salts with ethylenediamine and formaldehyde mixtures via method A results not in the formation of bis-dihydroxymethyltriazene (*10*) but in the production of the 3,8-di[2-aryl-1-azenyl]-1,3,6,8-tetraazabicyclo[4.4.1]undecanes (*6*) and the 1,3-di-2-[(4-methoxyphenyl)-1-diazenyl]imidazolidine (*8*) in the case of the *p*-methoxy substituent. X-ray crystallographic analysis confirms the structure of compound (*6*) and also shows that the molecule adopts a folded configuration about the basket portion of the molecule in the solid state. The structure of *8* has also been derived via NMR spectral evidence and X-ray crystallography.

3,8-Di[2-aryl-1-azenyl]-1,3,6,8-tetraazabicyclo[4.4.1]-undecanes (*6*) are believed to be the result of diazonium coupling to 1,3,6,8-tetraazatricyclo[4.4.1.$1^{3,8}$]dodecane (*7*), which is the condensation product of ethylenediamine and formaldehyde via method A synthesis. Method B synthesis of *6*, which is a direct coupling of the diazonium to *7*, results in a significantly higher yield of *6*. Future work with these molecules may show promising biological activity or may reveal the potential for use as a building block for macrocycles or as a ligand in the chelation of metals.

Acknowledgment. The authors are grateful to the Senate Research Committee of Saint Mary's University and the Nova Scotia Department of Education and Culture N.S. Links Program for financial support.

JO981276G