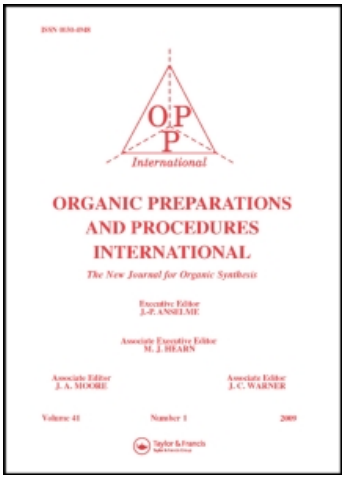


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# RECENT PROGRESS IN THE SYNTHESIS OF *bis*-TRIAZENES

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# RECENT PROGRESS IN THE SYNTHESIS OF *bis*-TRIAZENES

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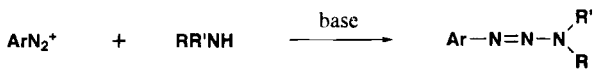
## INTRODUCTION

A triazene is a molecule containing three contiguous nitrogen atoms, with a double bond between N1 and N2, *i.e.* –N=N-N- . A "*bis*-triazene" is any compound containing two such triazene units in the same molecule. This paper describes recent progress in the design of *bis*-triazenes in which the triazene units are connected in a variety of configurations. Previous reports have reviewed much of the chemistry of triazenes relevant to a discussion of *bis*-triazene chemistry.[1] "Monoalkyltriazenes" is the trivial term used commonly to designate a 1-aryl-3-alkyltriazene, Ar-N=N-NHR; the chemistry of monoalkyltriazenes has been reviewed.[1] More recently, the chemistry of antitumour triazenes has been reviewed[2] with the emphasis on chemistry of interest to the medicinal chemist.

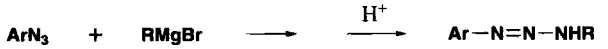
### 1. *Triazene Synthesis*

1-Aryl-3,3-dialkyltriazenes are readily synthesized by the coupling of the appropriate diazonium ion with secondary amines (*Eq. 1*, R, R' ≠ H).[3]




(1)

Monoalkyltriazenes can also be prepared by the diazonium coupling method using a primary alkylamine (*Eq. 1*, R = H, R' ≠ H)[4] but are also available from the reaction of aryl azides with Grignard reagents (*Eq. 2*).[5]

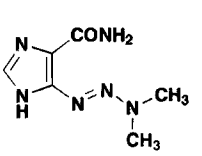



(2)

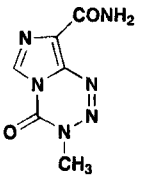
### 2. *Antitumour Activity*

The antitumour activity of 1-aryl-3,3-dimethyltriazenes has been known for many years,[6] and at least one member of this family, *Dacarbazine*® (DTIC; 5-(3,3-dimethyl-1-triazeno)imidazole-4-carboxamide, **1**), is clinically useful in the treatment of malignant melanoma.[7] It has been recog-

nized that the dimethyltriazene (**1**) is simply a pro-drug for the cytotoxic metabolite monomethyltriazene. The cytotoxic action of the drugs is thought to arise from DNA methylation by the monomethyltriazene.[8,9]



**1**



**2**

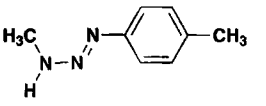
The pro-drug approach to triazene design led to the discovery of *Temozolomide*,[10] an imidazolotetrazinone (**2**), which is a novel broad spectrum antitumour agent. Although *temozolomide* itself is not an acyclic triazene, its mode of action is thought to involve hydrolysis of the tetrazinone ring to afford the cytotoxic monomethyltriazene.



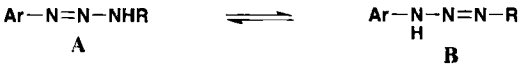
### 3. *Structure*

The structure of the triazene moiety is influenced by the resonance arising from delocalization of the electron lone-pair on N-3.

X-Ray crystallography of a typical triazene, 1-(*p*-carbamoylphenyl)-3,3-dimethyltriazene,[11] shows that the N2-N3 bond is significantly shorter [1.312(8)Å] than expected for an isolated N-N single bond [*ca.* 1.45Å]. The crystal structure of the monomethyltriazene, 3-methyl-1-p-tolyltriazene,[12] shows similar bond lengths, and also shows that these molecules are linked by N-H .... N hydrogen bonding. However, the most significant feature of this structure is that it confirms that the monoalkyltriazene prefers the "conjugated" tautomer (**3**). Tautomerism in the monoalkyltriazenes has been extensively studied by nmr spectroscopy.[13] At low temperature, the signals of the alkyl groups in tautomers A and B are clearly distinguished. When R = Me, the methyl group of tautomer B is a singlet, whereas the methyl group of tautomer A shows as a doublet due to coupling with the neighbouring NH proton.



**3**

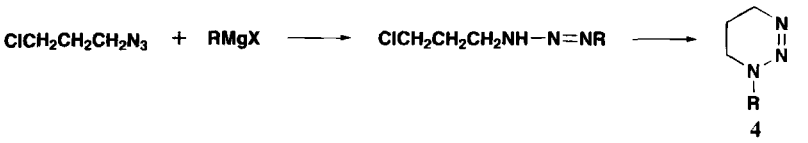


**A** **B**

### 4. *Cyclic Triazenes ("Triazinines")*

Reaction of 1-azido-3-chloropropane with an alkyl Grignard reagent, followed by work-up with Dowex or ammonia buffer leads to the immediate formation of the 1-alkyl-3-(3-

chloropropyl)triazene. When a solution of this triazene is concentrated, it undergoes self-catalyzed cyclization to the triazinine **4**,[14] which is a unique example of a cyclic triazene (*Eq. 3*). The cyclic nature of **4** constrains the triazene group to a Z-configuration (as opposed to the E-form[11] found in acyclic triazenes, *e.g.* **3**), and therefore triazinines present an opportunity to explore the chemistry of the Z-triazene moiety.

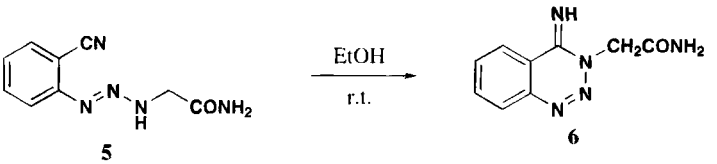



(3)

**4**

### 5. *Triazene Precursors of Heterocyclic Systems*

1-Aryl-3-alkyltriazenes (Ar-N=N-NHR) with appropriate substituents in the aryl and alkyl groups have been used as precursors for a variety of nitrogen-containing heterocycles.[2] For example, 3-(carbamoylmethyl)-1-(*o*-cyanophenyl)triazene (**5**) cyclizes in ethanol at room temperature to give the 4-imino-1,2,3-benzotriazine (**6**).[15]




(4)

**5** **6**



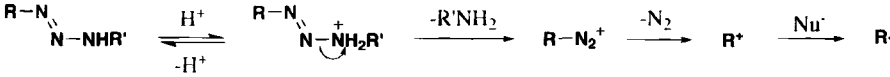
## I. *bis*-3-(ARYLTRIAZEN-1-YL)ETHANES

An earlier documented molecule of the *bis*-triazene type is the *bis*-(3-phenyltriazen-1-yl)ethane (**7**), obtained by Pochinok *et al.*,[16] by the addition of phenylmagnesium bromide to 1,2-diazidoethane (*Eq. 5*). The same method was also used more recently by Blumenstein and Michejda[17]


(5)

**7**

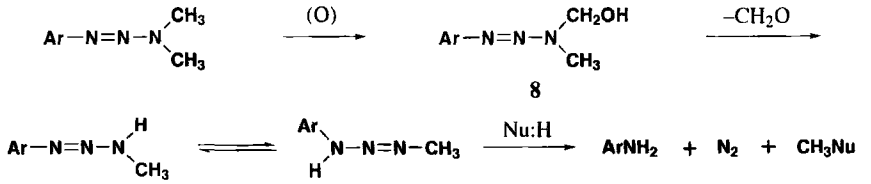
to prepare a series of 1,2-*bis*(alkyltriazeno)ethanes,(R-NH-N=N-$CH_2CH_2$-N=N-NH-R). These *bis*-triazenes are potent cytotoxic agents due to their apparent ability to cause cross-linking of DNA by alkylation. Various triazenes, including 1,3-dialkyltriazenes, 1,3,3-trialkyltriazenes and 1-aryl-3-alkyl-triazenes have been shown to undergo proteolytic decomposition to produce alkyl diazonium ions, which are known to be potent biological alkylating agents. A typical mechanism is shown in Eq. 6




(6)

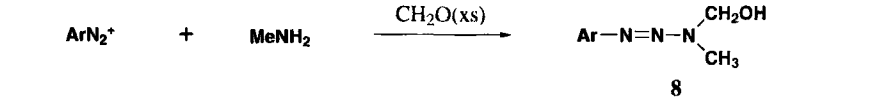
## II. HYDROXYMETHYLTRIAZENES

The biological activity of *dacarbazine* (**1**) and analogous 1-aryl-3,3-dimethyltriazenes is thought to arise from metabolic activation to a cytotoxic species and the course of the metabolism is presumed to involve hepatic oxidation to give the hydroxymethyltriazene (**8**) (*Scheme 1*).




**Scheme 1**

Loss of formaldehyde from **8** affords the "monomethyltriazene", which is presumed to be the active metabolite due to its proclivity for methylation of DNA.[18] It was assumed for many years that hydroxymethyltriazenes (**8**) were inherently unstable, until a remarkably simple synthesis of a series of hydroxymethyltriazenes was achieved[19] by diazonium coupling with a mixture of methylamine and excess formaldehyde (*Eq. 7*):

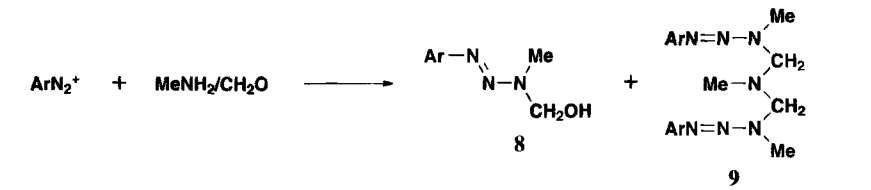



(7)

Further studies[20] with the hydroxymethyltriazenes clearly showed that they are "activated" triazenes which inhibit tumour cell growth without metabolic activation, unlike 1-aryl-3,3-dimethyltriazenes which show no *in vitro* activity.

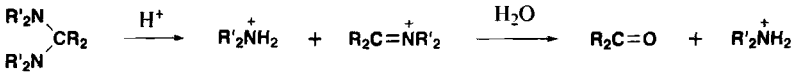
## III. *bis*-(1-ARYL-3-METHYLTRIAZEN-3-YLMETHYL)METHYLAMINES

An unexpected development in *bis*-triazene chemistry came from studies of the diazonium coupling reaction with methylamine/formaldehyde mixtures. The major product of this reaction is the antitumor hydroxymethyltriazene (**8**), as described above, but many of the reaction mixtures afforded a second product, identified as the novel *bis*-triazene, the N,N-*bis*-(1-aryl-3-methyltriazen-3-ylmethyl)methylamine (**9**).[21] The proportion of the *bis*-triazene (**9**) in the product mixture is enhanced when the aryl group does not contain an electron-withdrawing group and by decreasing the ratio of formaldehyde:methylamine in the reaction mixture.[22]




(8)

*bis*-Triazenes of type **9** have significant antitumour activity against the TLX5 lymphoma in mice;[22] the level of antitumor activity had maximum increase in life span (ILS) of 190% (Test/Control) at a dose level of 160 mg/kg/day for 5 days. With analogous dimethyltriazenes, the ILS is comparable but a higher dosage is needed to achieve the results. In a further study of the biological properties of these *bis*-triazenes, antitumor activity was demonstrated versus the PC6 mouse tumor and it was shown that these compounds inhibit the growth of tumor cells growing in culture, without metabolic activation.[23] This latter observation is significant since it suggests that the *bis*-triazene (**9**) may be a good pro-drug form for the cytotoxic "monomethyltriazenes" (ArN=N-NHMe). Kinetic studies of the *bis*-triazene hydrolysis in pH 7.5 buffer show that they decompose with half-lives comparable to the analogous monomethyltriazenes.[23] The relative ease of decomposition of the *bis*-triazenes (**9**) is probably due to the "aminal" moiety, N-$CH_2$-N (*gem*-diamine) in the structure. Cleavage of *gem*-diamines is catalysed by protic conditions into an imine and an ammonium salt (*Eq. 9*).[24]

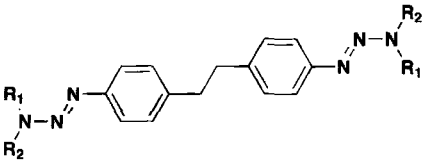


(9)



## IV. *bis*-(4'-TRIAZENYLPHENYL) ETHANES

Aqueous diazotization of 1,2-*bis*(*p*-aminophenyl)ethane, followed by treatment with two equivalents of methylamine or a dialkylamine led to the formation of the series of 1,2-*bis*-(4'-(triazen-1-yl)phenyl)ethanes (**10 a-e**) in 57-91% yields.[25] These *bis*-triazenes were characterized by IR, NMR and mass spectrometry. The NMR spectra were normal in showing characteristic AA'BB' couplings in the aromatic region and the methylene protons of the ethylene bridge appear (in $CHCl_3$) as a singlet at $\delta \sim 2.9$. The N-Me resonance of **10a** appears at $\delta$ 3.32, broadened by hindered rotation around the N2-N3 bond, whereas the N-Me resonance of **10d** is shifted up-field to $\delta$ 3.81, probably due to tautomerism.[13] *bis*-Triazene (**10d**) has been shown to possess cytostatic properties.[26]



**10**

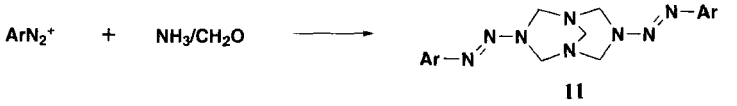
a) $R_1 = R_2 = Me$ b) $R_1 = R_2 = Et$ c) $R_1 = R_2 = PhCH_2$ d) $R_1 = H, R_2 = Me$ e) $R_1, R_2 = -(CH_2)_5-$

## V. 3,7-*bis*-ARYLAZO-1,3,5,7-TETRAAZABICYCLO[3.3.1]NONANES

### *1. Synthesis*

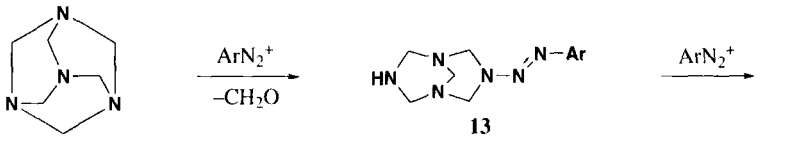
As noted earlier, hydroxymethyltriazenes (**8**) are formed by diazonium coupling with formaldehyde/methylamine mixtures. In principle, diazonium coupling with an ammonia/formalde-

hyde mixture would be expected to afford a new type of triazene, Ar-N=N-NH-$CH_2OH$; however, to date this type of triazene has not been reported. In reality,[27] this coupling reaction affords a novel type of *bis*-triazene, 3,7-*bis*-(arylazo)-1,3,5,7-tetraazabicyclo[3.3.1]nonanes (**11**).




**11** (10)

The formation of molecules of type **11** is rationalized by diazonium attack at any one of four equivalent nitrogen atoms in the molecule of hexamethylenetetramine (**12**) (formed *in situ* from ammonia and formaldehyde), with subsequent ring cleavage and loss of one methylene unit as formaldehyde to give an intermediate with one free NH group (**13**). Subsequent diazonium coupling at the free NH leads to the observed *bis*-triazene (**11**); indeed the same product is formed if the diazonium salt is coupled directly to hexamethylenetetramine (**12**) (*Eq. 11*).[27]




**12** **13** (11)

Analysis of the low temperature NMR spectra of the *p*-ethoxycarbonyl substituted member of this series (**11**, Ar = *p*-$EtO_2CC_6H_4$) shows that the bicyclic system prefers the chair-chair conformation in solution, in contrast to the solid state structure (see below). The *bis*(arylazo)tetraazabicyclononanes, which are stable in pH 7.5 buffer, undergo slow decomposition at slightly acidic pH in an acetone-buffer mixture. The apparent products of the decomposition of **11** are the arylamines, isolated as the Mannich adducts, $ArNHCH_2CH_2COCH_3$.[27]

### 2. *X-ray Crystallography*

The X-ray crystal structures of a number of 3,3-dialkyl-1-aryltriazenes[11] provide an important basis for comparison with the structures of *bis*-triazenes. The X-ray crystal structures of each new *bis*-triazene series have been studied systematically. Recently, the X-ray crystal structure of four of the 3,7-*bis*-(arylazo)-1,3,5,7-tetraazabicyclo[3.3.1] nonanes (**11**) was determined.[28] All four compounds have the same feature in that the tetraazabicyclononane unit assumes a cage-like structure with the aryltriazene moieties lying parallel to one another so that the aryl rings are held together by π–π stacking. The interplanar distance between the benzene rings is *ca.* 3.8-4.0 Å. Close study of the X-ray structure reveals that in two of the compounds the triazene units lie parallel to one another, *i.e.* the N=N-N moieties eclipse one another when viewed at an orthogonal angle to the plane of the benzene rings. An example of a structure of this type, with a *o*-cyano substituent, is shown in Fig. 1, which shows the eclipsing of the triazene moieties and also shows the near-perfect overlap of

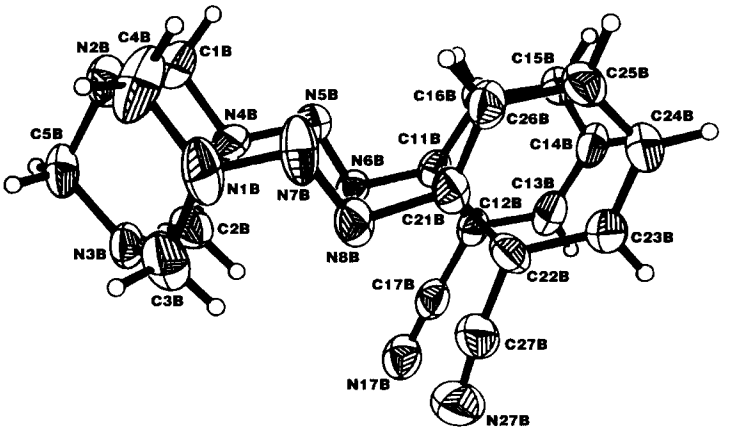



**Fig. 1** ORTEP diagram of 3,7-*bis*-(o-cyanophenylazo)-1,3,5,7-tetraazabicyclo[3.3.1]nonane (**11**, substituent = *o*-CN) viewed from above the plane of the benzene rings

the two benzene rings. In the other two molecules in this series, the N=N groups are aligned in opposite directions with respect to this orthogonal axis, as seen in the structure of the p-nitro substituted compound in Fig. 2. The solid-state structure of these *bis*-arylazo-tetraazabicyclo[3.3.1]nonanes is

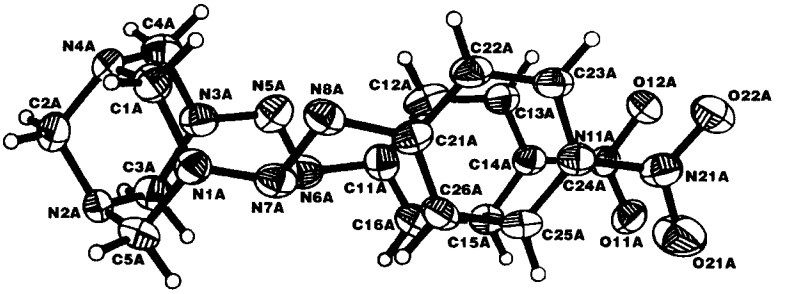
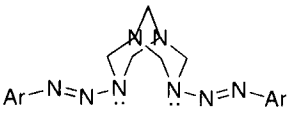



**Fig. 2** ORTEP diagram of 3,7-bis-(p-nitrophenylazo)-1,3,5,7-tetraazabicyclo[3.3.1]nonane (**11**, substituent = *p*-$NO_2$) viewed from above the plane of the benzene rings

significantly different than the structures observed in solution by VT NMR studies;[27] the NMR solution studies suggested that these molecules (**11**) prefer a structure described as "extended di-equatorial" with the triazene units extended in the di-equatorial positions (structure **14**).

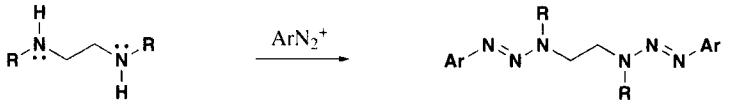



**14**

## VI. 1,2-*bis*-(1-ARYL-3-METHYLTRIAZEN-3-YL)ETHANES

### 1. *Synthesis*

A series of new *bis*-triazenes, the 1,2-*bis*-(1-aryl-3-alkyltriazen-3-yl)ethanes (**16**), have been synthesized by diazonium coupling with N,N'-dimethyl- and N,N'-diethyl-ethylenediamine.[29] These compounds are obtained readily without any special conditions as reasonably pure crystals (*Eq. 12*).

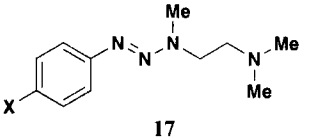


**15** **16** (12)

a) R = Me, Ar = *o*-$CNC_6H_4$ b) R = Me, Ar = *o*-$MeOC_6H_4$

c) R = Me, Ar = *p*-$CNC_6H_4$ d) R =E t, Ar = *p*-$CNC_6H_4$

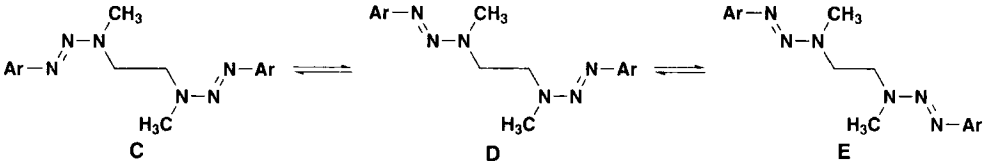
As model compounds for spectroscopic analysis, a series of related triazenes, the 1-(1-aryl-3-methyltriazen-3-yl)-N,N'-dimethyl-2-ethanamines (**17**) were prepared by diazonium coupling with N,N,N'-trimethylethylenediamine. The N-methyl chemical shifts in the model compounds (**17**) provide useful data for assigning chemical shifts in the NMR spectra of the series of *bis*-triazenes (**16**).



**17**

### 2. *NMR Spectroscopy*

The $^1H$ NMR spectra of the *bis*-triazene series (**16**) show significant line broadening of the N-methyl resonances arising from the restricted rotation around the N2-N3 bond of the triazene units. The presence of strongly electron-withdrawing groups on the aryl ring restricts the rotation to the point where the N-methyl signals of the rotamers are distinct even at room temperature; four resonances of the N-methyl signal are clearly evident and these can be assigned to the anti-anti (**C**), the syn-anti (**D**) and the syn-syn (**E**) conformations of the *bis*-triazene.



**C** **D** **E**

### 3. *X-ray Crystallography*

The structures of two compounds in the *bis*-triazene series (**16**) have been confirmed by X-ray crystallography.[30] The *o*-cyanophenyl *bis*-triazene (**16a**) adopts the anti-anti conformation (**A**) in the crystal consistent with the NMR data of this compound[29] and the molecule adopts a staggered

conformation with an extended structure in which the aryl rings are essentially at opposite ends of the plane of the molecule (*Fig. 3*). In contrast, the *o*-methoxyphenyl analogue (**16b**) adopts the gauche

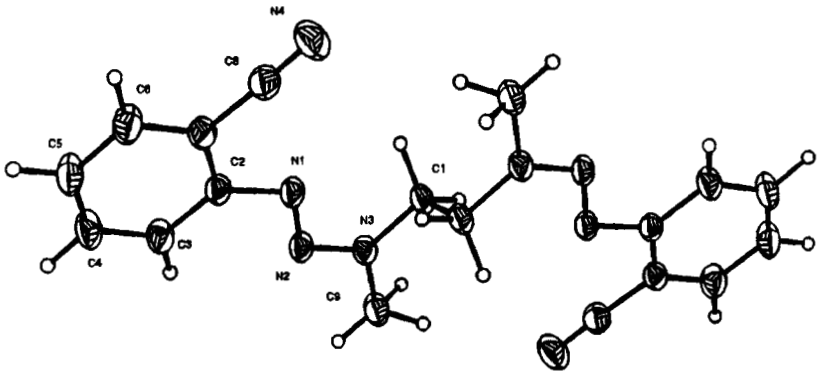



**Fig. 3** ORTEP diagram of 1,2-*bis*-(1-*o*-cyanophenyl-3-methyltriazen-3-yl)ethane (**16a**)



conformation around the C-C bond of the ethane unit and the syn-syn configuration around the N2-N3 bonds of the triazene units; this results in a folded, cage-like structure for the molecule in which the triazene units are only separated by 3.25 Å (*Fig. 4*). The folded structure of **16b** is surprising in view

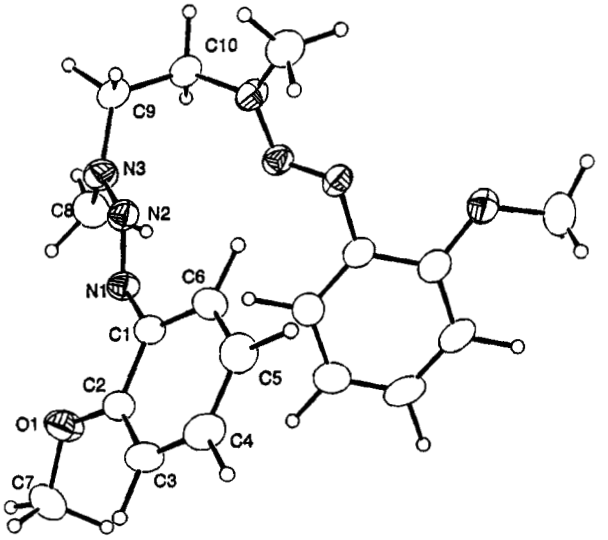


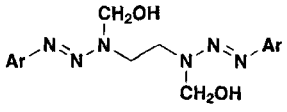

**Fig. 4** ORTEP diagram of 1,2-*bis*-(1-*o*-methoxyphenyl-3-methyltriazen-3-yl)ethane (**16b**)

of the amount of steric crowding compared with the structure of **16a**. The folded structure of **16b** appears to be held in this conformation by interaction of the *ortho*-hydrogen on each benzene ring with the N2 atom of the opposite triazenyl moiety.

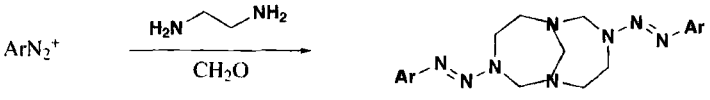
## VII. 3,8-DI-(2-ARYL-1-AZENYL)-1,3,6,8-TETRAAZABICYCLO[4.4.1]UNDECANES

### 1. *Synthesis*

As described earlier in this review, diazonium coupling with methylamine/formaldehyde mixtures affords the hydroxymethyltriazene (**8**).[19] In analogy with this result, diazonium coupling with a mixture of ethylenediamine and formaldehyde might be expected to afford the *bis*-hydroxymethyltriazene (**18**), the hydroxymethyltriazene analogue of the *bis*-triazene (**16**). Instead, the products recovered from diazonium coupling with a mixture of ethylenediamine and formaldehyde were identified as the heterobicyclic *bis*-triazenes, the 3,8-di-(2-aryl-1-azenyl)-1,3,6,8-tetraazabicyclo[4.4.1]undecanes (**19**).[31]

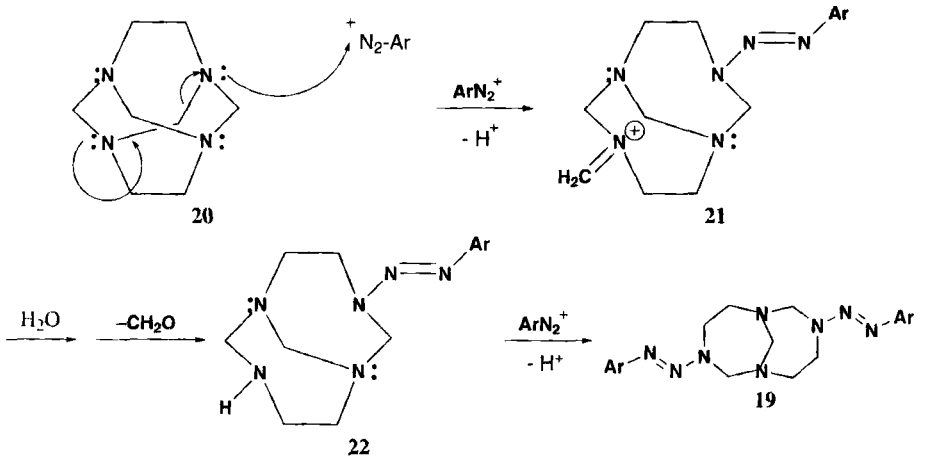


**18**



**19** (13)

The formation of these novel *bis*-triazenes stems from the coupling of the diazonium ion to a molecule of 1,3,6,8-tetraazatricyclo[4.4.1.1$^{3,8}$]dodecane (**20**), the known condensation product of ethylenediamine and formaldehyde.[32] Diazonium coupling at a bridging nitrogen in **20** sets off a sequence of reactions with ring-opening leading as shown in Scheme 2 to the observed product.



**Scheme 2**

### 2. *NMR Spectroscopy*

The NMR spectra of the heterobicyclo-*bis*-triazenes (**19**) provide a wealth of information about the stereochemistry of the various methylene protons in the bicyclic moiety (refer to *Fig. 5* for proton assignments). Protons $H_a$ and $H_b$ of the bridging methylene are enantiotopic and give rise to a

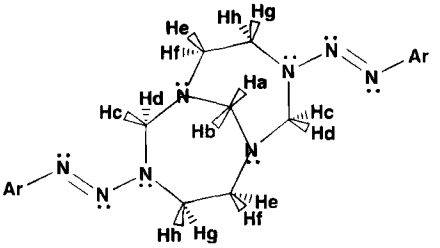



**Fig. 5**

two-proton singlet at ca. δ 4.2. On the other hand, protons $H_c$ and $H_d$ of the equivalent non-bridging methylene groups are diastereotopic, and since the chemical shift values of $H_c$ and $H_d$ are close to one another, they give rise to a second-order AB system of doublets. Thus, $H_c$ and $H_d$ are observed as a quartet-like signal in the range δ 4.77-5.01. The nmr signals of the protons of the two equivalent ethylene bridges, $H_e$, $H_f$, $H_g$, and $H_h$, are much more complex since these protons are in diastereotopic methylene groups with four unique chemical shifts, appearing as two complex multiplets integrating in the ratio 6:2. The two-proton eight-line multiplet arising from $H_h$ at δ 4.17-4.63 is a full ppm downfield from the multiplet of the other three protons, $H_e$, $H_f$ and $H_g$, observed as a 6-proton multiplet at δ 3.22-3.59. Further NMR experiments, including $^{13}C$ nmr, DEPT, HETCOR, and COSY experiments[31] provided further confirmation of the structure of the *bis*-triazene series **19** and confirmed the proton assignments described above.

### 3. *X-ray Crystallography*

The structures of the *p*-nitro-, *p*-methoxycarbonyl-, *p*-ethoxycarbonyl, *o*-nitro- and *o*-cyano-substituted *bis*-triazenes of type **19** have been confirmed by X-ray crystallography.[33] Prior to this work, folded structures had been observed for the *bis*-arylazo-tetraazabicyclo[3.3.1]nonanes (**11**) and in the structure of the *bis*-(1-aryl-3-methyltriazen-3-yl)ethane (**16b**). Thus, it was no surprise that the crystal structure of the heterobicyclo-*bis*-triazenes (**19**) show the now-familiar, typical folded structures held together by π–π stacking. Figure 6 shows an ORTEP plot of one of the compounds from this

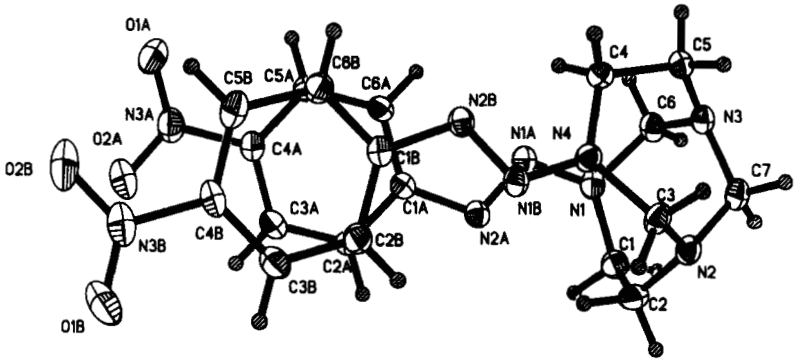



**Fig. 6** ORTEP diagram of 3,8-di-[2-(*p*-nitrophenyl)-1-azenyl]-1,3,6,8-tetra-azabicyclo[4.4.1] undecane (**22**, substituent = *p*-$NO_2$) viewed from above the plane of the benzene rings

series, namely the 3,8-di-[2-(p-nitrophenyl)-1-azenyl]-1,3,6,8-tetraazabicyclo[4.4.1]undecane, showing the almost 100% overlap of the two benzene rings. An alternate view of the same molecule, looking between the planes of the rings, is shown in Figure 7.



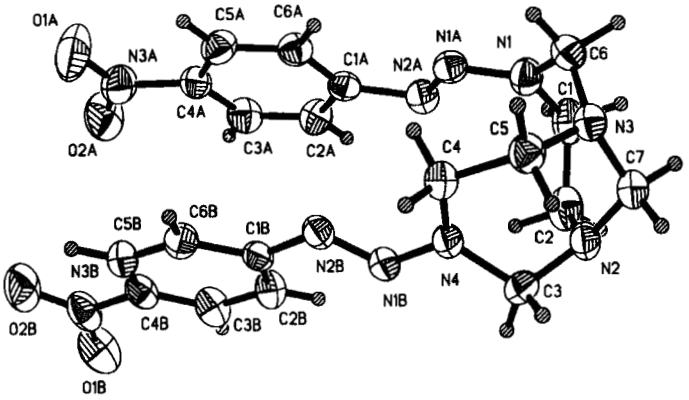
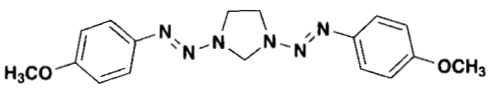



**Fig. 7** ORTEP diagram of 3,8-di-[2-(*p*-nitrophenyl)-1-azenyl]-1,3,6,8-tetra-azabicyclo[4.4.1] undecane (**22**, substituent = *p*-$NO_2$) looking between the planes of the benzene rings

### 4. *1,3-bis-2-[(4-Methoxyphenyl)-1-diazenyl]imidazolidine*

The diazonium coupling of *p*-methoxyphenyldiazonium ion with ethylenediamine/formaldehyde led to a different product identified by spectroscopy as 1,3-*bis*-2-[(4-methoxyphenyl)-1-diazenyl]imidazolidine (**23**).[31] The structure of this product has been confirmed by X-ray crystallography.[34]

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