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BISTRIAZENES: MULTIFUNCTIONAL ALKYLATING AGENTS

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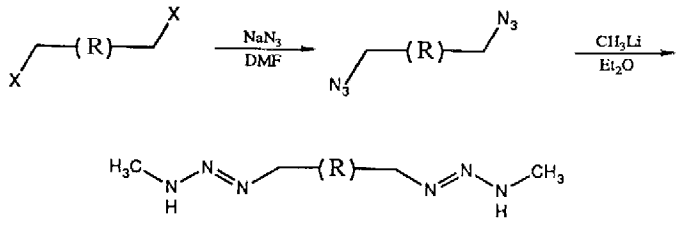
Abstract: The synthesis of bis(methyltriazeno)alkanes is readily accomplished by reaction of methyllithium with the appropriate diazidoalkane. These compounds possess interesting properties in solution, suggestive of an array of intermolecular hydrogen bonding.

Various triazenes, including 1,3-dialkyltriazenes[1], 1,3,3-trialkyltriazenes[2] and 1-aryl-3-alkyltriazenes[3] have been shown to undergo proteolytic decomposition to produce alkyldiazonium ions, which are known to be potent biological alkylating agents. Consistent with this property, many triazenes have been shown to be mutagenic[4], carcinogenic[5] and cytotoxic[6]. The aromatic triazenes, such as the clinically useful drug 5-(N,N-dimethyltriazeno)imidazole-4-carboxamide (DTIC)[7], require metabolic demethylation to produce the active metabolites which alkylate DNA (methylate in the case of DTIC). Methylating agents, such as DTIC or procarbazine, while useful as chemotherapeutic agents, are also potent mutagens and carcinogens[8]. We have recently reported on a new class of triazenes, 1,3-dialkyl-3-acyltriazenes[9]. These compounds, particularly 1-(2-chloroethyl)-3-methyl-3-acyltriazenes[10], possess significant antitumor properties. The 2-chloroethyl moiety, also present in anti-tumor drugs such as bis-(2-chloroethyl)-nitrosourea (BCNU), is thought to exert its cytotoxic activity by forming lethal, interstrand crosslinks in genomic DNA[11]. We report here the synthesis of a new class of multifunctional dialkyltriazenes, bis(methyltriazeno)alkanes (or trivially, bistriazenes), which upon hydrolytic decomposition can, in principle, produce bis(diazonio)alkanes with the ability to crosslink DNA.

The synthesis of the bistriazenes is accomplished readily by the reactions shown in Figure 1. An alkyl dihalide is allowed to react with 2.5 equivalents of NaN_3 in DMF overnight. Simple alkyldibromides require warming to 50°C, but allylic or benzylic dichlorides react readily at room temperature. The DMF solution is diluted with two volumes of pentane and an equal volume of water. The organic layer is then washed three times with water to remove traces of DMF. The pentane solution is dried over Na_2SO_4 and then concentrated. **[CAUTION: Low molecular weight azides are explosive and the diazides should not be isolated in neat form nor should one attempt to purify them].** The diazide solutions are diluted with anhydrous ether (ca. 10 ml/mmol diazide) and then cooled to -20°C under argon. A solution of methyllithium (ca. 2.5 equivalents, 1.4M in diethylether, low halide) is added dropwise at -20°C over 2 hours. Initial gas evolution, due to the presence of residual water, ceases quickly and the temperature is allowed to



R	X	Yield
-	Cl	32%
CH_2	Br	46%
$(CH_2)_2$	Br	58%
$(CH_2)_4$	Br	73%
	Cl	20%
	Cl	50%
	Cl	55%
	OTs	29%

Figure 1

rise to ambient. Stirring is continued for an additional 3 hours. A precipitate begins to form soon after the addition of methyl lithium is complete. The reaction is quenched by careful addition of half-saturated NH_4Cl with rapid stirring and cooling. Vigorous gas evolution and heating is caused by neutralization of the excess methyllithium. It is imperative, however, that this step be carried out as rapidly as possible because of the proteolytic instability of the product. The organic layer is separated, washed with cold water, dried over Na_2SO_4, and the solvent evaporated to dryness. The residue is crystallized from ether/petroleum ether. The compounds prepared in this fashion are shown in Figure 1.

In contrast to simple 1,3-dialkyltriazenes, the bistriazenes are solids. X-ray crystallographic analysis of 1,2-bis(methyltriazeno)ethane shows the molecules in string-like polymeric structures held together by intermolecular hydrogen bonds[12]. Variable temperatures H^1-NMR experiments suggest that these polymeric interactions may also exist in solution in aprotic solvents. Figure 2 shows the broadened H^1-spectra of 1,2-bis(methyltriazeno)ethane. The spectrum failed to sharpen as the temperature was elevated to 70°C. Presumably the intermolecular interactions still prevent coalescence to be reached at that temperature. Individual tautomers begin to freeze out at ~-40°C (panel II) and are partially resolved at -80°C (panel IV). This temperature is lower than these reported for simple 1,3-dialkyltriazenes.[13] Similarly, the ^{13}C NMR spectrum at -60°C

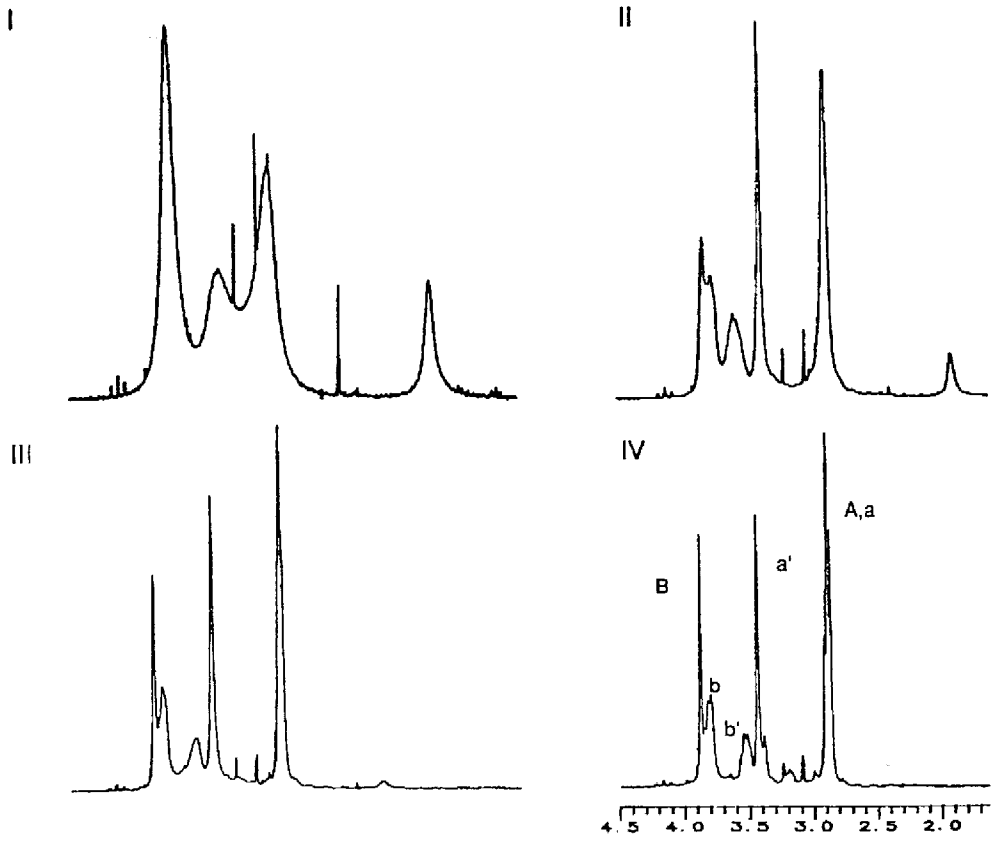


Figure 2: Variable temperature ^{1}H-NMR (200MH$_z$, CD_2Cl_2) of bis(methyltriazeno)ethane. I) 0°C, II) -40°C. III) -60°C, IV) -80°C. Labeled peaks in IV correspond to designated atoms in Figure 4.

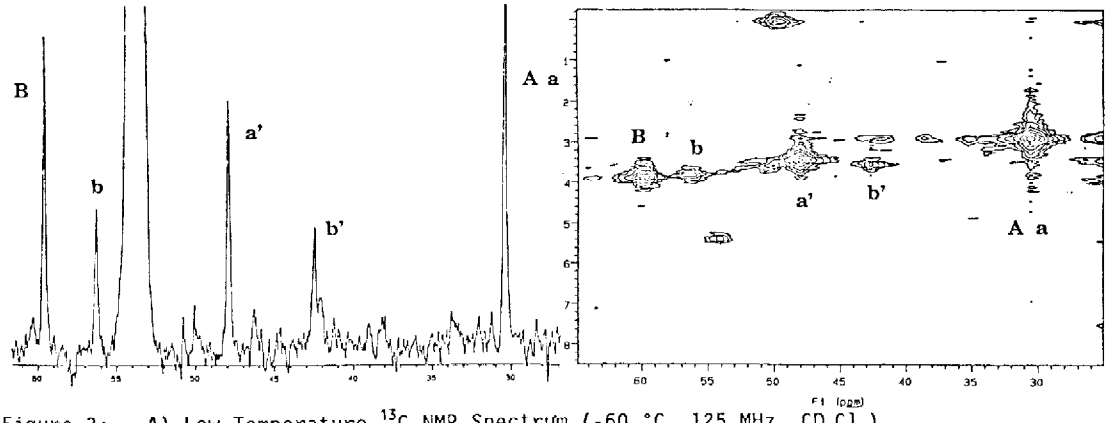


Figure 3: A) Low Temperature ^{13}C NMR Spectrum (-60 °C, 125 MHz, CD_2Cl_2).
B) Low Temperature ^{1}H-^{13}C HMQC Correlation NMR Spectrum (-60 °C, CD_2Cl_2).

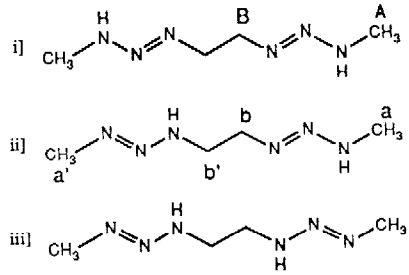


Figure 4:
Bis(methyltriazeno)ethane tautomers

is partially resolved (Figure 3) and consists of five resonances which are consistant with those observed in the ^{1}H spectrum. An HMQC ^{1}H-^{13}C correlation spectrum[14] confirms the assignments as noted in Figure 3.

It is interesting to note the presence of two out of the possible three tautomers of the bistriazene in the -80°C NMR spectrum. The predominant tautomer appears to be "in-out" (Figure 4, form ii). The second visible tautomer is the "out-out" (Figure 4, form i). The "in-in" isomer is not discernible, but a small amount may be hidden in the relatively broad lines of the spectrum. In contrast, the only tautomer seen in the solid state is "out-out".

The unusual physical and chemical characteristics of the bistriazenes suggest that these compounds may possess some interesting biological properties. Indeed, preliminary data suggest that several of these compounds may interact directly with biological macromolecules and some are potently cytotoxic. Additional investigations of the chemical and biological properties of these new compounds are underway.

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