

THE SYNTHESIS OF 1,2-BIS-(4'-(TRIAZENYL)PHENYL)ETHANES*

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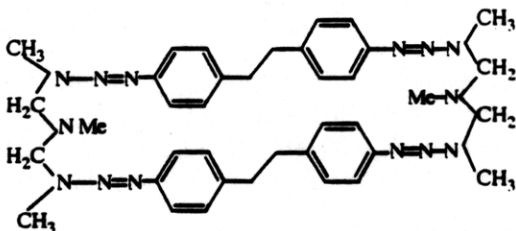
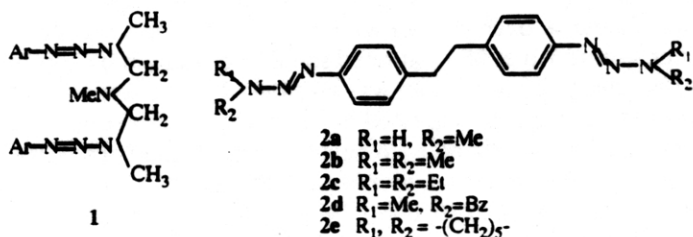
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A series of 1,2-bis-(4'-(triazenyl)phenyl)ethanes (2) has been synthesised by bis-diazotization of ethylene dianiline, and coupling of the resulting bis-diazonium salt with appropriate alkyl or dialkylamines. The bis-triazenes have been characterized by infrared (ir) and nuclear magnetic resonance spectroscopy (nmr), mass spectrometry and elemental analysis. Line broadening in the nmr spectra of the bis-triazenes is attributed to a combination of conformational equilibria and hindered rotation around the N¹-N² triazene bond and also around the C-C bond of the ethylene bridge.

On a synthésisé une série des éthanes de 1,2-bis-(4'-(triazenyl)phényl) (2) par la bis-diazotisation de l'éthylène dianiline et l'accouplement du sel de bis-diazonium avec des alkyl- ou des dialkyl-amines. On a caractérisé les bis-triazènes par la spectroscopie infrarouge, par la spectroscopie nucléaire magnétique, par la spectroscopie de masse, et par l'analyse élémentaire. On attribue l'élargissement des lignes des spectra (nmr) des bis-triazènes à la combinaison d'équilibres conformationnelles autour de la rotation retardée de la liaison N-N et aussi autour de la liaison C-C du pont d'éthylène.

Introduction

Triazenes, also known as diazoamino compounds, are molecules containing three contiguous nitrogen atoms, connected by one double and one single bond. 1-Aryl-3,3-dialkyltriazenes (Ar-N=N-NR₂) have been recognised as antitumour agents for some time (Vaughan, 1990) and several compounds of this type are currently in use for treatment of cancer (Lee, et al, 1994). A novel example of a 3,3-dialkyltriazene is the bis-triazene represented by the structure 1; such compounds are formed as byproducts during the synthesis of 3-hydroxymethyltriazenes (Ar-N=N-(CH₂)₃-CH₂OH) by the reaction of diazonium ions with formaldehyde and methylamine (Manning, et al., 1984).



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A different mode of bis-triazene connection is that represented by the group of compounds **2**, and 1,2-bis-(4'-(3,3-dimethyltriazen-1-yl)phenyl)ethane (**2b**) has been reported to have cytostatic properties (Foerster and Steinhoff, 1970).

A predominant topic in chemistry in recent years has been the discovery and exploitation of macrocyclic molecules, such as the crown ethers (Gokel and Durst, 1976). An interesting extension of this chemistry would be the synthesis of cyclic tetrakis-triazenes of the type **3**. Such compounds have not yet been reported and as a stepping stone to the synthesis of such compounds we have undertaken the study of the synthesis and properties of intermediates like **2a**.

Experimental

All reagents were reagent grade materials and were used without further purification. Melting points were determined on a Reichert hot-stage microscope and are uncorrected. Infrared (ir) spectra were obtained using Nujol mulls, on a Perkin-Elmer 299 spectrophotometer. ^1H and ^{13}C nuclear magnetic resonance (nmr) spectra were obtained on C^2HCl_3 solutions at 20° using a Bruker 250 MHz spectrophotometer. Chemical shifts are reported in ppm downfield from the signal of tetramethylsilane. Electron impact mass spectra of compounds **2c** and **2d** were obtained on a Finnigan quadrupolar 4500 machine with a temperature-programmed solids probe. The mass spectrum of compound **2a** was obtained by chemical ionization (isobutane) on a DuPont 21-100 mass spectrometer. Mass spectral data are reported with m/z values followed by the relative abundances in parentheses.

General procedure for preparation of 1,2-bis-(4'-(triazenyl)phenyl)ethanes (2a-e)
4,4'-Ethylenedianiline (1.4 g, 0.007 mole) was dissolved in a hot premixed solution of concentrated hydrochloric acid (4 mL) and distilled water (25 mL). The solution was allowed to cool to room temperature and was then filtered to remove insoluble impurities. The ethylene dianiline solution was treated at 0° with a saturated solution of sodium nitrite (1 g, 0.014 mole) over a period of 30 min. The resulting solution was then treated dropwise over 10 min with methylamine or a secondary amine (0.02 mole). After stirring 1 h at 0° a saturated solution of sodium bicarbonate was added dropwise until the reaction mixture was alkaline. The mixture was then stirred for 2 h at 0° when the triazene precipitated from the reaction mixture. The triazene was filtered, dried and recrystallized from hexanes unless stated otherwise.

1,2-bis-(4'-(3-Methyltriazen-1-yl)-phenyl)-ethane (2a) - Yield 57%; m. p. $\approx 230^\circ$; m/z 254 (58%), $[\text{M}+\text{H}-\text{MeN}_2]^+$, 240 (84%), $[\text{M}+\text{H}-\text{CH}_3\text{N}_3]^+$, 198 (100%); ν_{max} 3400-3100 (NH), 830 (*p*-disub.) cm^{-1} ; δ_{H} 3.00 (4H, ArCH_2), 3.81 (6H, s, NMe), 7.21, 7.24, 7.61, 7.64 (8H, AA'BB', arom.); δ_{C} 28.36 (NCH_3), 37.56 (CH_2Ar), 115.28, 122.11, 125.84, 129.29 (arom.).

1,2-bis-(4'-(3,3-Dimethyltriazen-1-yl)-phenyl)-ethane (2b) - Yield 80%, m. p. $152-154^\circ$; (Found: C, 66.9; H, 7.4; N, 25.8. Calc. for $\text{C}_{18}\text{H}_{24}\text{N}_6$ C, 66.7; H, 7.4; N, 25.9%); ν_{max} 810, 830 (*p*-disub.) cm^{-1} ; δ_{H} 2.89 (4H, ArCH_2), 3.32 (12H, NMe), 7.10, 7.13, 7.31, 7.34 (8H, AA'BB', arom.); δ_{C} 37.69 (CH_2Ar), 41.0 (br, NCH_3), 120.38, 128.98, 139.07, 149.04 (arom.).

1,2-bis-(4'-(3,3-Diethyltriazen-1-yl)-phenyl)-ethane (2c) - Yield 79%, m. p. $76-77^\circ$; (Found: C, 69.4; H, 8.3; N, 21.9. $\text{C}_{22}\text{H}_{32}\text{N}_6$ requires C, 69.5; H, 8.4; N, 22.1%); ν_{max} 840 (*p*-disub.) cm^{-1} ; δ_{H} 1.27 (12H, 3J 7.17 Hz, Me), 2.91 (4H, CH_2Ar), 3.76 (8H, 3J 7.17 Hz, NCH_2), 7.10, 7.13, 7.30, 7.34 (8H, AA'BB', arom.); δ_{C} 13.02 (CH_3), 37.75 (CH_2Ar),

44.66 (NCH_2), 120.32, 128.93, 138.80, 149.39 (arom.); m/z 380 (86) M^+ , 308 (28) $[\text{M-Et}_2\text{N}]^+$, 280 (66) $[\text{M-Et}_2\text{N}_3]^+$, 208 (72) $[\text{M-Et}_2\text{N-Et}_2\text{N}_3]^+$, 190 (97), 180 (100), 165 (82), 118 (14), 90 (87), 76 (20), 72 (79).

1,2-bis-(4'-(3-benzyl-3-methyltriazene-1-yl)-phenyl)-ethane (2d) - Yield 91%, *m. p.* 117-118°, hexanes-ethyl acetate, (Found: C, 75.4; H, 6.75; N, 17.6. $\text{C}_{30}\text{H}_{32}\text{N}_6$ requires C, 75.6; H, 6.7; N, 17.65%); ν_{max} 820 (*p*-disub.), 730, 690 (monosub.) cm^{-1} ; δ_{H} 2.91 (4H, CH_2Ar), 3.12 (6H, NMe), 4.92 (4H, NCH_2), 7.40-7.19 (18H, arom.); δ_{C} 34.76 (NCH_2), 37.72 (CH_2Ar), 58.97 (PhCH_2), 120.61, 128.99, 139.31, 148.96 (*p*-disub.), 127.65, 127.67, 128.73, 136.96 (Ph); m/z 476 (55) M^+ , 356 (23) $[\text{M-MeBzN}]^+$, 328 (10) $[\text{M-(MeBz)}_2\text{N}_3]^+$, 238 (92) $[\text{MeBzN}_3\text{C}_7\text{H}_6]^+$ 208 (22), 180 (98), 165 (71), 120 (98), 91 (100) $[\text{C}_7\text{H}_7]$, 90 (85).

1,2-bis-(4'-(3,3-pentamethylenetriazen-1-yl)-phenyl)-ethane (2e) - Yield 87%, *m. p.* 155-157°, ν_{max} 840 (*p*-disub.) cm^{-1} ; δ_{H} 1.68 (12H), 2.91 (4H, CH_2Ar), 3.74 (8H, NCH_2), 7.09, 7.13, 7.32, 7.35 (8H, AA'BB', arom.); δ_{C} 25.28, 24.45 (CH_2), 38.0 (CH_2Ar), 44.51 (NCH_2), 120.39, 128.51, 128.97 and 139.5 (arom.).

Results and Discussion

Aqueous bis-diazotization of 4,4'-ethylenedianiline followed by reaction with two equivalents of methylamine or a dialkylamine led to the production of 1,2-bis-(4'-(triazen-1-yl)-phenyl)ethanes (**2a-e**) in 57-91% yields. The dialkyltriazenes (**2b-e**) were obtained pure by recrystallization and **2b-d** gave satisfactory elemental analyses. The monoalkyltriazene (**2a**) was not recrystallized but good ir and nmr spectra of this compound were obtained. The ir spectra of all of these compounds showed absorption in the range 810-841 cm^{-1} , as expected, due to out-of-plane bending vibrations of a *para*-disubstituted benzene derivative. Compound **2d** also had additional absorption bands at 690 and 730 cm^{-1} due to the presence of a benzyl moiety.

All of the triazenes showed characteristic AA'BB' couplings in their ^1H nmr spectra with $^3J_{\text{HH}} \approx 8.4\text{Hz}$ (**2a** = 8.55Hz; **2d** = 8.24Hz). The methylene protons of the ethylene bridge fortuitously appeared (in CHCl_3) as a singlet, $\delta_{\text{H}} \approx 2.9$ in all the cases examined. The triazene **2b** had predictable N-Me resonance at δ_{H} 3.32, broadened by hindered rotation around the $\text{N}^2\text{-N}^3$ bond (Akhtar, et al., 1968), whereas the NMe resonance of **2a** appeared at δ_{H} 3.81, probably due to tautomerism (Hooper and Vaughan, 1981). Such tautomerism probably accounts for the difficulty experienced in detecting the signal of the NH proton in **2a**. The ^1H nmr spectrum of the piperidine derivative **2e** was, as expected complex and the multiple couplings of the ring CH_2 groups were not determined. However, the broad resonance at δ_{H} 3.74 was assigned to the N-CH_2 moieties and that centered on δ_{H} 1.68 to the remaining ring CH_2 groups.

Further confirmation of the structures assigned to the triazenes **2a-e** was provided by ^{13}C nmr data and assignments are given in the experimental section of this paper. Signals for the bridging ethylene carbon atoms were found in the region δ_{C} 25.3-44.6 and in some cases these were broadened considerably, possibly due to hindered rotation about the C-C bond.

The electron impact mass spectra of the triazenes **2a**, **2c** and **2d** could be interpreted in terms of the structures proposed for these compounds, though no molecular ion was found in the spectrum of **2a**. Abundant molecular ions at m/z 380 and 476 were observed in the mass spectra of **2c** and **2d** respectively and the further fragmentations of these ions were similar. Both compounds showed the following fragmentation reactions: cleavage of the $\text{N}^2\text{-N}^3$ bond, the N^1 -aryl bond and the bridging C-C bond.

Fragmentation of both triazene units was also observed and gave the ions common to both spectra at m/z 208 and 180. Chemical ionization mass spectroscopy, of compound **2a** using isobutane as the ionizing gas, did not provide the expected $[M+H]^+$ ion at m/z 297 but did produce an abundant ion at m/z 254 possibly arising by protonation of N^1 and subsequent fission of the N^1-N^2 bond. Another abundant ion at m/z 240 probably involves loss of the fragment CH_3N_3 .

The experiments described show that bis-triazenes of type **2** can be prepared in good yield and that their physical and spectral characteristics are consistent with those of known simpler triazenes. This knowledge will be useful in the endeavor to synthesize macrocyclic tetrakis-triazenes e.g. **3**.

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References

- Akhtar, M.H., McDaniel, R.S., Fraser, M. and Oehlschlager, A.C. 1968. NMR study of hindered rotation in 1-aryl-3,3-dimethyltriazenes. *Tetrahedron*, 24: 3899-3906.
- Foerster, H. and Steinhoff, D. 1970. Cytostatic mono- and bis-dialkyltriazenes. South African Patent 69 04,895; *Chem. Abs.*, 73: 55823h.
- Gokel, G.W. and Durst, H.D. 1976. Principles and Synthetic Applications in Crown Ether Chemistry. *Synthesis*. 168-184.
- Hooper, D.L. and Vaughan, K. 1981. ^{13}C and 1H Nuclear magnetic resonance study of solvent effects on tautomerism in 1-aryl-3-methyltriazenes. *J. Chem. Soc. (Perkin Trans. II)*. 1161-1165.
- Lee, S.M., Thatcher, N., Crowther, D. and Margison, G.P. 1994. Inactivation of O^6 -alkylguanine-DNA alkyltransferase in human peripheral blood mononuclear cells by temozolomide. *Brit. J. Cancer.*, 69: 452-456.
- Manning, H.W., Hemens, C.M., LaFrance, R.J., Tang, Y. and Vaughan, K. 1984 Open-chain nitrogen compounds. Part VI. The formation of bis(1-aryl-3-methyltriazene-3-ylmethyl)methylamines in the reaction of diazonium ions with mixtures of formaldehyde and methylamine. *Can. J. Chem.*, 62: 749-754.
- Vaughan, K. 1990. Triazenes. In *The chemistry of antitumour agents* (Ed. D.E.V. Wilman), Chapman and Hall, New York, pp. 159-186.

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