Triazenes; III. A Convenient Synthesis of Triazenes with Potential Anti-Tumour Activity

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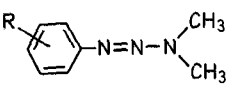
Recently, it has been reported that 1-aryl-3,3-dimethyltriazenes **1**, although inactive *in vitro*, develop anti-tumour properties *in vivo* or after incubation with liver fractions[1,2]. In these cases 1-aryl-3-methyltriazenes **2** are implicated as the cytotoxic species. It is possible that the methylating activity of monomethyltriazenes **2** is responsible for their action but 1-aryl-3-hydroxymethyl-3-methyltriazenes **3** are also candidates[3] since oxidative metabolic demethylation of dimethylamino compounds generally is known to proceed via hydroxymethyl intermediates. The report[4] of the synthesis of four triazenes **3**, which failed in other cases, prompted us to describe a convenient method which affords good yields of 1-aryl-3-hydroxymethyl-3-methyltriazenes **3**.



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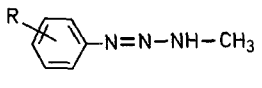

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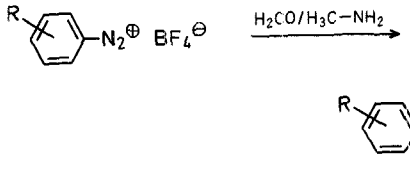

3a-f

The structure of all triazenes **3** were determined on the basis of microanalyses, ^{1}H-N.M.R., and I.R. spectral data and, in some cases, also by mass spectrometry. The purity of the products was checked by T.L.C. on silica gel 60 F 254, eluent: chloroform/ether (3:1).

The thermal and photochemical decomposition of triazenes **3** in 1:1 methanol/water leads to the formation of 4-substituted anilines **4** not *N*-methylarylamines **5**. The reaction is thus assumed to proceed via intermediate formation of aryl radicals as formulated below.

0039-7881/80/0232-0116 $ 03.00

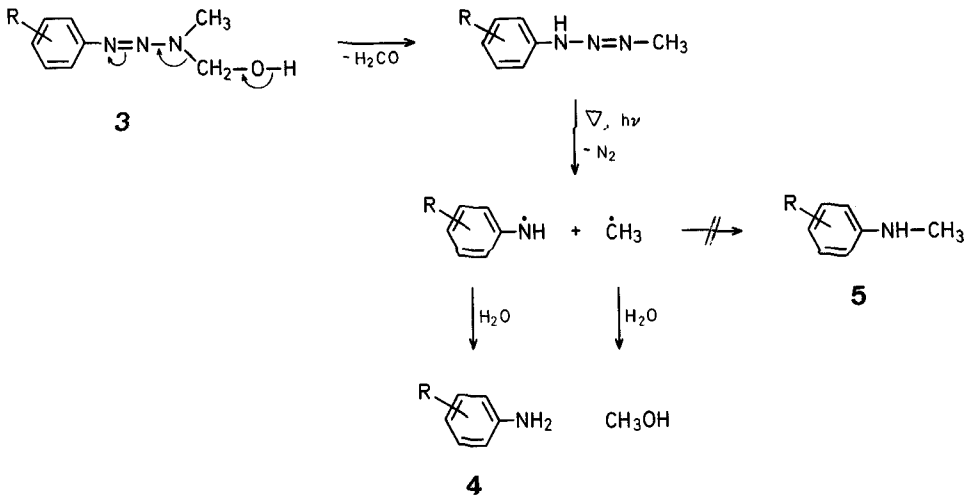

Table. 1-Aryl-3-hydroxymethyl-3-methyltriazenes **3a–f**

Product[a] No.	R	Yield [%][b]	m.p. [°C]	Molecular formula[c,d]	R_f[e]	^{1}H-N.M.R. (CDCl$_3$/TMS)[f] δ [ppm]	I.R. (nujol) ν [cm^{-1}][g]
3a	4-Cl	40	110	$C_8H_{10}ClN_3O$ (199.64)	0.90	7.36 (d, 2H); 7.33 (d, 2H); 4.70 (s, 2H); 3.32 (s, 3H); 2.52 (s, 1H)	3440
3b	4-Br	55	128	$C_8H_{10}BrN_3O$ (244.09)	0.90	7.50 (d, 2H); 7.35 (d, 2H); 4.70 (s, 2H); 3.30 (s, 3H); 2.52 (s, 1H)	3440
3c	4-NC—	75	102	$C_9H_{10}N_4O$ (190.20)	0.78	7.54 (s, 2H); 7.52 (s, 2H); 4.70 (s, 2H); 3.32 (s, 3H); 2.49 (s, 1H)	3440
3d	4-H_3C—CO—	65	115	$C_{10}H_{13}N_3O_2$ (207.23)	0.57	7.99 (d, 2H); 7.55 (d, 2H); 4.75 (s, 2H); 3.32 (s, 3H); 2.62 (s, 3H); 2.50 (s, 1H)	3440
3e	4-C_2H_5OOC—	60	126	$C_{11}H_{15}N_3O_3$ (237.26)	0.78	8.04 (d, 2H); 7.48 (d, 2H); 4.66 (s, 2H); 4.38 (q, 2H); 3.28 (s, 3H); 2.43 (s, 1H); 1.39 (t, 3H)	3440
3f	4-O_2N—	70	108	$C_8H_{10}N_4O_3$ (215.23)	0.71	8.22 (d, 2H); 7.57 (d, 2H); 4.76 (s, 2H); 3.32 (s, 3H); 2.50 (s, 1H)	3440

[a] These products are white or pale yellow. Storage in the dark is not necessary.
[b] Yield of isolated product after washing with hexane; m.p.'s measured on a Kofler Heizbank.
[c] All products gave satisfactory microanalyses with the following maximum deviations from the calculated values: C ±0.2, H ±0.25, N ±0.25.
[d] The analysis were carried out by Microanalytical Service, University of St.Jérôme, Marseille.
[e] The purity of the triazenes **3** was checked by T.L.C. on silica gel 60 F 254, eluent: 3:1 chloroform/ether.
[f] *In most cases aromatic protons appear as two doublets.*
[g] Measured with a Perkin-Elmer 237 spectrophotometer.

The triazenes **3** undergo thermal or photochemical decomposition with initial loss of formaldehyde according to the hypothesis of Stevens and Vaughan[3], elimination of nitrogen, and formation of arylamino radicals which then migrate out of the solvent cage abstracting a hydrogen atom to give the anilines **4**. The anilines **4** were identified by comparison of their ^{1}H-N.M.R. spectra and their R_f values (*T.L.C. on silica gel 60 F 254*, eluent chloroform/ether, 3:1) with those of commercial authentic samples. ^{1}H-N.M.R. spectra were recorded at 90 MHz using a Perkin Elmer R-32 spectrometer.

1-Aryl-3-hydroxymethyl-3-methyltriazenes 3; General Procedure:
An aqueous solution of the arenediazonium tetrafluoroborate (5 mmol) is added to a premixed solution of 35% aqueous formaldehyde (12 ml) and 33% aqueous methylamine (2.5 ml) at 0 °C. The mixture is stirred for 12 h. The hydroxymethyltriazene **3** which crystallises is collected, washed with water, and dried under vacuum. The crude product can be purified by washing with several portions of hexane.

Pyrolysis of 1-Aryl-3-hydroxymethyl-3-methyltriazenes 3:
A solution of triazene **3a–f** (200 mg) in 1:1 methanol/water (200 ml) is heated at 60 °C for one day. The solvent is then removed in vacuo. The residue is diluted with benzene and purified by preparative T.L.C. on silica gel (PF 254+366) using chloroform as eluent to give **4**; yield: 39–45%.

Photolysis of 1-Aryl-3-hydroxymethyl-3-methyltriazenes 3:
A solution of triazene **3a–f** (200 mg) in 1:1 methanol/water (200 ml) is irradiated through a pyrex filter under a steam of nitrogen, using a Mazda 400 W U.V. lamp until all the starting material was consumed. The solvent is then removed in vacuo and the residue is purified as described above to give **4**; yield: 46–71%.

Received: September 19, 1979

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[4] A. Gescher et al., *Tetrahedron Lett.* **1978**, 5041.