The Structure of Aryldialkyltriazene *N*-Oxides

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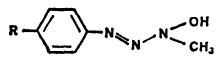
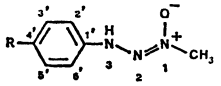
Synopsis. The structure of 3-aryl-1,3-dimethyltriazene 1-oxides has been demonstrated by comparison with other triazenes and triazene *N*-oxides by mass spectrometry and ^1H and ^{13}C NMR.

Aryldimethyltriazene *N*-oxides exhibit interesting pharmacological properties. 1-Aryl-3-hydroxy-3-methyltriazenes, **1a**, which are the proton tautomers of 3-aryl-1-methyltriazene 1-oxides, **1b**, have been described as immunosuppressive[1,2] and antiinflammatory agents.[3]

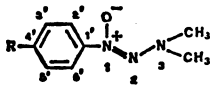


1a



1b

Some 1-aryl-3,3-dimethyltriazene 1-oxides, **2**, were found useful in the treatment of phlogistic processes.[4] The same activity was observed for a third class of triazene *N*-oxides, **3**, obtained from the methylation of 3-aryl-1-methyltriazene 1-oxides, **1b**, with methyl iodide in the presence of the irreversible proton acceptor sodium hydride.[3]



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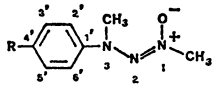
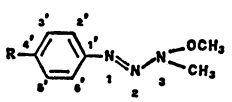


3

In view of preparing new derivatives of **3**, we wished to establish the actual structure of this reaction product; no such evidence could in fact be found in the literature. Bamberger and Renauld[5] reacted the *p*-nitro derivative of **1b** with methyl iodide and potassium hydroxide and postulated structure **4** for the isolated reaction product. Later, Boese *et al.*[6] assumed the same structure for the product resulting from the reaction of *N,O*-dimethylhydroxylamine with *p*-nitrobenzenediazonium chloride; evidence for the assignment was obtained by hydrolyzing the product to the starting amine with hydrochloric acid. The melting point of Bamberger's compound differed widely (142 °C *vs.* 66 °C) from that of Boese's. In a recent review this assignment was deemed reasonable on a synthetic basis and structure **4** and **5** were then proposed for Bamberger's compound.[7] We set up to establish the actual structure of the compound on firmer grounds. Incidentally, structure **2** and **5** are of interest, being potential oxidative metabolites of the antitumor agents aryldimethyltriazenes, **6**.[8]



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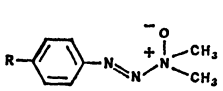

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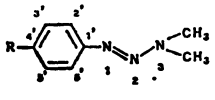


6

Experimental

The following compounds were synthesized for comparative purposes according to reported procedures: 3-aryl-1-methyltriazene 1-oxide (**1b**; R=*p*-nitro,[5] and *p*-chloro,[9] mp 149 °C after recrystallization from methanol, lit,[9] unreported), 1-(*p*-chlorophenyl)-3,3-dimethyltriazene 1-oxide (**2**, R=*p*-chloro[3]), 1-(*p*-chlorophenyl)-3-methoxy-3-methyltriazene (**4**, R=*p*-chloro, mp 18—19 °C after recrystallization from petroleum ether at low temperature), 1-(*p*-nitrophenyl)-3-methoxy-3-methyltriazene (**4**, R=*p*-nitro[6]), Bamberger's triazene[5] and its *p*-chloro analog, synthesized according to the same procedure using four equivalents of potassium hydroxide and methyl iodide in order to drive the reaction to completion, mp 90.5—91.5 °C after recrystallization from hexane.

The ^1H and ^{13}C NMR spectra were recorded using TMS as internal standard with JEOL JNM-C60HL and JNM-FX-90Q FT spectrometers respectively. Mass spectra here reported were recorded with an LKB mass Spectrometer, *via* sublimation at room temperature into the ion source kept at 200 °C; ionization energies were at nominal 20 and 70 eV. Reported mp's are uncorrected.

Results and Discussion

^1H Spectral characteristics of *p*-chloro- and *p*-nitro-substituted triazenes are summarized in Table 1; the corresponding ^{13}C NMR spectral characteristics are shown in Table 2. The methyl groups in 1-(*p*-chlorophenyl)-3,3-dimethyltriazene, **6** (R=*p*-Cl), appeared as a singlet at δ=3.25 (in $CDCl_3$) and δ=3.26 (in acetone-d_6 at room temperature, whereas in the corresponding 1-(*p*-nitrophenyl)-3,3-dimethyltriazene, **6** (R=*p*-NO_2), the methyl groups appeared as two signals at δ=3.26 and δ=3.60 (in acetone-d_6) or δ=3.28 and 3.50 (in $CDCl_3$) because of the restricted rotation around N_2–N_3 bond, which coalesced at higher temperatures. Similarly, both methyl groups in 1-(*p*-chlorophenyl)-3,3-dimethyltriazene 1-oxide, **2**, appeared as a singlet at room temperature. On the other hand, two methyl groups appeared as two singlets at δ=4.13 and 3.29

TABLE 1. ^1H NMR (δ) DATA

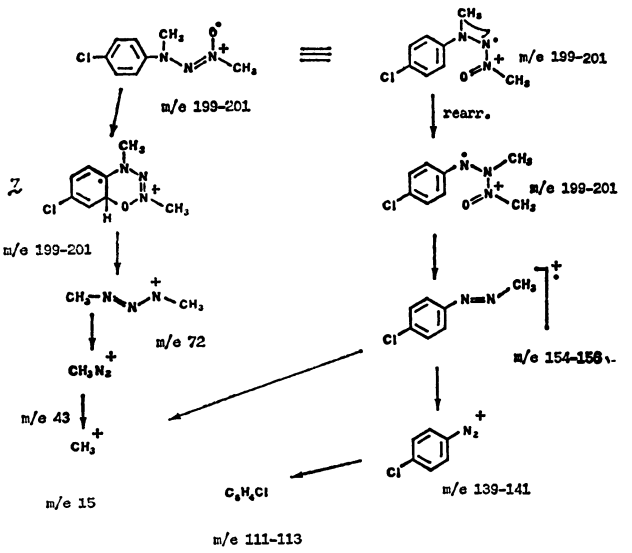
Compound	Solvent	N_3-CH_3	N_1-CH_3	O-CH_3	NH	Ar
6 (R=*p*-Cl)	$CDCl_3$	3.25 s				7.25 br s
	CD_3COCD_3	3.26 br s				7.32 s
2 (R=*p*-Cl)	$CDCl_3$	3.22 s				7.88 d, 7.28 d
						$J_{2',3'}=J_{5',6'}$=9.0 Hz
4 (R=*p*-Cl)	$CDCl_3$	3.84 s		3.30 s		7.40 d, 7.25 d
						$J_{2',3'}=J_{5',6'}$=8.0 Hz
1b(R=*p*-Cl)	$CDCl_3$		3.90 s		10.9 br s	7.22 d, 6.95 d
						$J_{2',3'}=J_{5',6'}$=9.0 Hz
3 (R=*p*-Cl)	$CDCl_3$	3.30 s	3.95 s			7.20 d, 6.88 d
						$J_{2',3'}=J_{5',6'}$=9.0 Hz
6 (R=*p*-NO_2)	CD_3COCD_3	3.26 s				8.23 d, 7.54 d
		3.60 s				$J_{2',3'}=J_{5',6'}$=9.0 Hz
	$CDCl_3$	3.28 s				8.10 d, 7.42 d
		3.50 s				$J_{2',3'}=J_{5',6'}$=9.0 Hz
4 (R=*p*-NO_2)	$CDCl_3$	3.88 s		3.65 s		8.15 d, 7.50 d
						$J_{2',3'}=J_{5',6'}$=9.0 Hz
1b(R=*p*-NO_2)	DMSO-d_6		3.98 s		11.85 br s	8.18 d, 7.39 d
						$J_{2',3'}=J_{5',6'}$=9.0 Hz
3 (R=*p*-NO_2)	DMSO-d_6	3.29 s	4.13 s			8.10 d, 7.08 d
						$J_{2',3'}=J_{5',6'}$=9.0 Hz

Table 2. ^{13}C NMR data[a)]

Compound solvent and t/°C	δ	J/Hz
6 (R=Cl) $CDCl_3$	C_1' 149.6 t	J=6.1
	C_4' 130.4 t	J=7.9
	C_3' 128.8 dd	J^1=166.4 J^2=5.0
	C_2' 121.7 dd	J^1=163.6 J^2=5.0
	NCH_3 39.3 broad q	J=142
2 (R=Cl) $CDCl_3$	C_1' 144.0 broad m	
	C_4' 136.0 m	
	C_3' 128.7 dd	J^1=170.0 J^2=5.9
	C_2' 122.2 dd	J^1=170.0 J^2=5.0
	NCH_3 43.5 qq	J^1=138.6 J^3=3.6
4 (R=Cl) $CDCl_3$	C_1' 147.9 broad m	
	C_4' 133.4 broad m	
	C_3' 129.1 dd	J^1=167.1 J^2=5.0
	C_2' 123.0 dd	J^1=164.3 J^2=5.0
	OCH_3 61.2 q	J=145.0
	NCH_3 41.9 q	J=140.7
1b(R=Cl) $CDCl_3$	C_1' 138.6 broad m	
	C_4' 129.4 dd	J^1=166.4 J^2=5.0
	C_3' 127.6 m	
	C_2' 115.6 dd	J^1=164.3 J^2=6.0
	NCH_3 50.1 q	J=144.3
3 (R=Cl) $CDCl_3$	C_1' 146.1 broad m	
	C_4' 128.7 dd	J^1=166.4 J^2=5.4
	C_3' 127.9 broad m	
	C_2' 117.9 dd	J^1=162.9 J^2=6.4
	N_1CH_3 53.1 q	J=144.3
	N_3CH_3 37.3 q	J=140.0
6 ($R=NO_2$) $CDCl_3$, 24 °C	C_1' 155.8 m	
	C_4' 144.4 m	
	C_3' 124.5 dd	J^1=170.0 J^2=5.0
	C_2' 120.3 dd	J^1=168.9 J^2=6.0
	NCH_3 43.3 deg qq	J^1=140.7 $J^3\simeq$3.5
	NCH_3 36.0 deg qq	J^1=140.7 $J^3\simeq$3.5
4 ($R=NO_2$) $CDCl_3$, 24 °C	C_1' 153.7 m	
	C_4' 145.7 m	
	C_3' 124.1 dd	J^1=170.0 J^2=5.0
	C_2' 121.4 dd	J^1=167.9 J^2=6.0
	OCH_3 61.1 q	J=146.4
	NCH_3 41.0 q	J=142.1
1b($R=NO_2$) DMSO-d_6, 50 °C	C_1' 143.8 m	
	C_4' 138.2 m	
	C_3' 122.7 dd	J^1=170.7 J^2=5.0
	C_2' 111.0 dd	J^1=169.3 J^2=6.0
	NCH_3 84.3 q	J=144.3
3 ($R=NO_2$) DMSO-d_6, 24 °C	C_1' 151.5 m	
	C_4' 140.5 m	
	C_3' 125.0 deg dd	J^1=167.1 $J^2\simeq$5.0
	C_2' 113.9 deg dd	J^1=165.7 $J^2\simeq$5.0
	N_1CH_3 53.6 q	J=145.0
	N_3CH_3 36.7 q	J=142.9

a) The ^{13}C chemical shifts of the aryl carbon atoms have been assigned on the basis of literature references: T. Axenrod, P. Mangiaracina, and P. S. Pregosin, *Helv. Chim. Acta*, **59**, 1655 (1976).

in the compound obtained by Bamberger by methylation of the corresponding 3-(*p*-nitrophenyl)-1-methyltriazene 1-oxide, **1b**. The large chemical shift difference observed for these methyl groups ($\Delta\delta$=0.84 ppm) and the absence of coalescence at higher temperatures, indicated that they were attached at different positions, leaving thus the 1-(*p*-nitrophenyl)-1,3-dimethyltriazene 1-oxide (structure **3**) as the most plausible one. Analogous evidence could be found also for the product obtained by methylation of 3-(*p*-chlorophenyl)-3-methyltriazene 1-oxide, **1b**. In ^{13}C NMR spectra, long range coupling constants $J^3_{H-C-N-}{}^{13}C$=



3.6 Hz were observed for all compounds having both methyl groups attached to the same nitrogen atom, *i.e.* in 1-(*p*-nitrophenyl)-3,3-dimethyltriazene, **6** (R=*p*-NO_2), 1-(*p*-chlorophenyl)-3,3-dimethyltriazene, **6** (R=*p*-Cl), and in the corresponding N_1-oxide (**2**, R=*p*-Cl). Since this coupling was not observed for the Bamberger's methylation product and its *p*-chloro analogue, structure **5** had to be excluded, leaving thus the nitrogen close to the phenyl ring as the only possible position at which methylation could occur. Mass spectrometry supported this evidence. Bamberger's *p*-chloro derivative under electron impact at 20 eV showed intense peaks for the parent ions (*m/e* 201 and 199), and doublets separated by two mass units at *m/e* 154—156, 139—141, and 111—113. This fragmentation is clearly incompatible with structure **5**, but could be readily reconciled with structure **3**, by postulating a 3,2-methyl shift in the parent cation radical produced upon ionization. Any thermal rearrangement prior to ionization in the course of sublimation into the ion source could be ruled out by the fact that the process occurred at room temperature. A second pathway could be given by rebonding of the parent ion to the bicyclic system **7**, which eventually collapsed to the dimethyltriazenyl ion (*m/e* 72), then cascading to methane diazonium (*m/e* 43) and methyl (*m/e* 15) cations.

References

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