N,N-Bis-(1-aryl-3-methyltriazen-3-ylmethyl)methylamines (1,9-Diaryl-3,5,7-trimethyl-1,2,3,5,7,8,9-hepta-azanona-1,8-dienes): Novel Coupling Products from the Reaction of Arenediazonium Ions with Methylamine and Formaldehyde

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The reaction of arenediazonium ions with aqueous formaldehyde–methylamine solutions affords mixtures of the 3-hydroxymethyltriazenes, $ArN{=}NN(Me)CH_2OH$, and the previously unreported bis(triazenylmethyl)methylamines, $ArN{=}NN(Me)CH_2N(Me)CH_2N(Me)N{=}NAr$.

Reaction of formaldehyde–methylamine mixtures with arenediazonium chlorides carrying $-M$ substituents has been shown[1] to afford the pharmacologically important[2] hydroxymethyltriazenes (**1**). Recently it has been claimed[3] that other hydroxymethyltriazenes, including *p*-chloro- and *p*-bromo-compounds, may be obtained by reaction of the formaldehyde–methylamine mixture with arenediazonium fluoroborates. We now report that this diazonium coupling reaction can afford both (**1**) and the previously unreported bis(triazenylmethyl)-methylamines (**2**) and that the compounds reported by Julliard *et al.*[3] are in fact examples of (**2**), a novel class of hepta-azanona-1,8-dienes.

$$XC_6H_4{-}N{=}N{-}N(Me)CH_2OH$$
(**1**)

$$[p\text{-}XC_6H_4{-}N{=}N{-}N(Me)CH_2]_2NMe$$
(**2**)

Table 1. Physical data of the hydroxymethyltriazenes (**1**) and hepta-azanona-1,8-dienes (**2**).

Compound	X	Yield (%)	M.p. (*t*/°C)	I.r., ν (cm^{-1})	δ (^{1}H n.m.r.) in $(CD_3)_2SO$				
					Arom. (AA'BB')	CH_2	OH	$N-CH_3$	X
(**1a**)	*p*-Br	47	71—73	3320	7.2—7.7	5.13(d)	6.33(t)	3.20(s)	—
(**1b**)	*p*-NO_2	57	103—104	3370,1515,1340	7.5—8.4	5.18(d)	6.50(t)	3.23(s)	—
(**1c**)	*p*-CN	100	114	3400, 2220	7.4—8.0	5.17(d)	6.43(t)	3.20(s)	—
(**1d**)	*p*-MeO_2C	53	126—127	3440, 1700	7.5—8.0	5.15(d)	6.39(t)	3.17(s)	3.84(s)
(**1e**)	*o*-CF_3	75	58—59	3240	7.4—7.9(m)	5.13	6.36	3.13(s)	—
					δ (^{1}H n.m.r.) in $CDCl_3$				
					Arom. (AA'BB')	CH_2	CH_3-N-5	CH_3-N-3 and -7	
(**2a**)	Br	15	134	—	7.3—7.6	4.63(s)	2.43(s)	3.23(s)	
(**2b**)	NO_2	15	134—136	1510, 1340	7.5—8.2	4.73(s)	2.48(s)	3.31(s)	
(**2c**)	CN	67	123—124	2225	7.6—7.7	4.73(s)	2.46(s)	3.32(s)	
(**2d**)	Cl	33	116	—	7.36	4.63(s)	2.40(s)	3.23(s)	

In such a reaction the ratio (**1**):(**2**) is strongly dependent on (a) the nature of the substituent in the aryl group, and (b) the molar ratio of formaldehyde and methylamine in the reaction mixture. If the arenediazonium salt has a strongly electron-withdrawing substituent (CO_2R, CN, NO_2, $COCH_3$, $CONH_2$, or CF_3) and is treated with an excess of formaldehyde–methylamine (12:1), the only product is of type (**1**). If, on the other hand, either the molar ratio of formaldehyde to methylamine is reduced (for electron-withdrawing substituents in the arenediazonium salt) or the arenediazonium salt has a substituent which is not $-M$ or strongly $-I$ in character, products of type (**2**) are obtained. When an arenediazonium salt with a strongly electron-withdrawing substituent is treated with formaldehyde–methylamine in lower molar ratios (6:1, 1:1, or 1:2) mixtures of (**1**) and (**2**) are obtained.

The compounds of types (**1**) and (**2**) are best characterised by ^{13}C n.m.r. spectroscopy. The *p*-bromo-compounds (**1a**) and (**2a**) show distinctive ^{13}C patterns: (**1a**) in $(CD_3)_2SO$ has δ 32.99 (CH_3), 77.99 (CH_2OH), and 118.00, 122.41, 131.78, and 149.39 p.p.m. (aromatic-C); (**2a**) in $CDCl_3$ has δ 34.36 (CH_3), 37.65 (CH_3), 74.17 (CH_2), and 119.01, 122.33, 131.84, and 149.61 p.p.m. (aromatic-C) in the fully decoupled spectrum. The ^{13}C n.m.r. spectrum of (**2a**), recorded with gated decoupling, shows a C–H directly bonded coupling constant for the methylene carbon of 149 Hz, in the range expected for an $N-CH_2-N$ group.

The triazenes (**1**) and (**2**) are also distinguished by their i.r. and ^{1}H n.m.r. spectra (see Table 1). Hydroxy-group absorption is evident at 3300—3450 cm^{-1} in the i.r. spectra of (**1**), but is absent in the i.r. spectra of (**2**). The ^{1}H n.m.r. spectra of type (**2**) compounds in $CDCl_3$ all show two *N*-methyl signals, in the ratio 2:1, and the signal from the two equivalent CH_2 groups, in addition to the signals from the aromatic AA'BB' system. The ^{1}H n.m.r. spectra of the hydroxymethyltriazenes (**1**) are diagnostically different. These spectra were recorded in $(CD_3)_2SO$ to minimise exchange and show a sharp singlet for NCH_3 at δ 3.2, a doublet at 5.2 for CH_2, and a triplet at *ca.* 6.5 for OH. Addition of D_2O to the solution of (**1**) causes the disappearance of the triplet and the collapse of the doublet to a singlet, confirming the assignment of these signals to the CH_2OH moiety.

Two possible mechanisms for the formation of the bis-triazenes (**2**) may be considered. The initial coupling of a diazonium ion with the carbinolamine CH_3NHCH_2OH, formed *in situ*, leads logically to the hydroxymethyltriazene (**1**). A possible route to (**2**) would involve formation of a tris(methylamino)–formaldehyde adduct, equation (i), followed by coupling (ii) with two moles of diazonium ion. Alternatively, a condensation of two moles of (**1**) with methylamine could also yield (**2**), equation (iii). Since both possible routes to (**2**) would be favoured by a lower ratio of formaldehyde to methylamine, it is not yet possible to determine which is the preferred mechanism.

$$3\,MeNH_2 + 2\,CH_2O \rightleftharpoons MeNHCH_2N(Me)CH_2NHMe + 2\,H_2O \quad (i)$$

$$MeNHCH_2N(Me)CH_2NHMe + 2\,ArN_2^+ \rightarrow (2) + 2\,H^+ \quad (ii)$$

$$2\,ArN{=}NN(Me)CH_2OH + MeNH_2 \rightarrow (2) + 2\,H_2O \quad (iii)$$

Finally, comparison of the physical characteristics and ^{1}H n.m.r. spectra of the bis(triazenylmethyl)methylamines (**2a**—**d**) described here with the data reported by Julliard *et al.*[3] for a series of hydroxymethyltriazenes shows clearly that the products described by them have structure (**2**), not (**1**). Furthermore, the observation[3] that these products do not have significant *in vitro* activity is not surprising. Compounds of type (**2**) should, by analogy with other methylalkyltriazenes,[4] be antitumour agents, but will require methabolic activation to exhibit a cytotoxic effect. In contrast, the hydroxymethyltriazenes (**1**) can lose formaldehyde without metabolic intervention and have been shown to exhibit cytotoxicity *in vitro*.[5]

Note added in proof: while this communication was in the press, the authors were made aware of a paper in the most recent issue of *J. Chem. Res.* (ref. 6). The results of Cheng *et al.* agree with those reported here, although the mechanistic interpretation may be different.

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