Synthesis, Structure, and Ambident Alkylation Reactions of 3-Aryl-1-(tetrazol-5′-yl)triazenes

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A series of 3-aryl-1-(tetrazol-5′-yl)triazenes was prepared by coupling tetrazole-5-diazonium ion with substituted anilines. The orientation of the ambident methylation reactions of the anion of these systems was investigated. ^{13}C N.m.r. spectra of the mono- and di-methyl derivatives provided information on the preferred tautomeric structure of the parent triazenyltetrazole system.

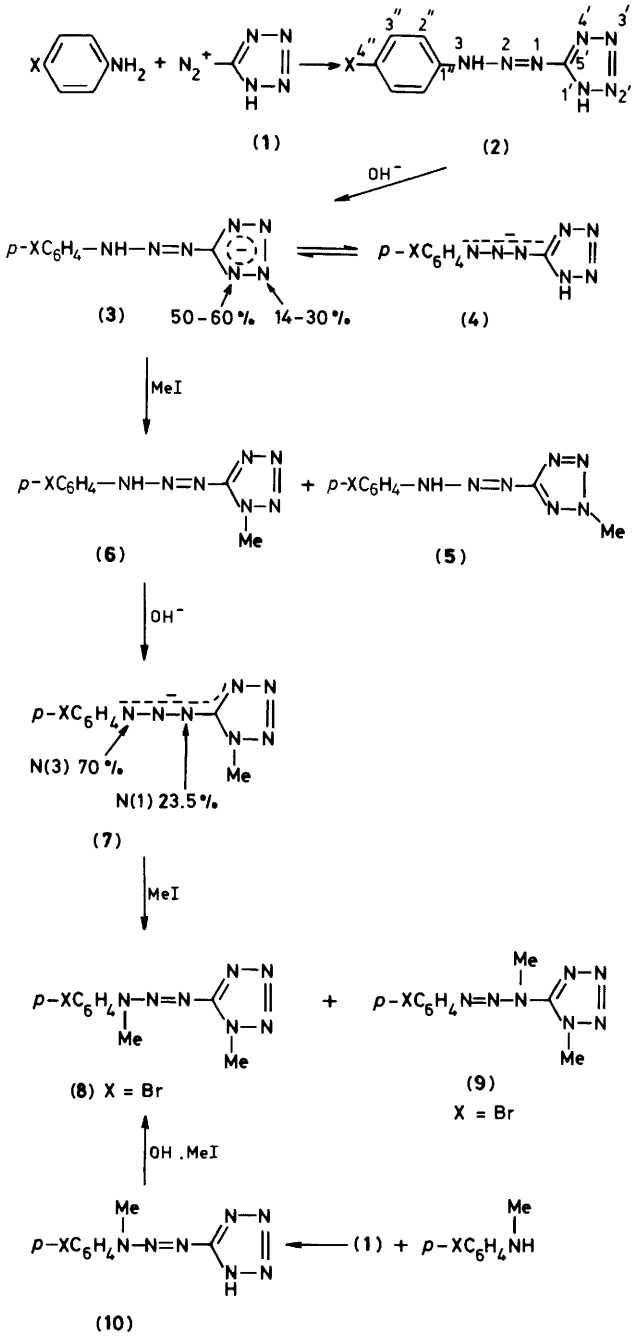
Triazene derivatives including heterocyclic triazenes have attracted recent attention because of their pharmacological properties including carcinogenic and anti-tumour activity.[1-4] However, only a few tetrazol-5-yltriazene derivatives have been reported.[5,6] These are mainly of the bis(substituted tetrazol-5-yl)triazene type formed in the diazotizations of some substituted aminotetrazole derivatives.[5,7,8]

Results and Discussion

(*a*) *Synthesis and Alkylation.*—Herein a series of new 3-aryl-1-(tetrazol-5′-yl)triazenes (**2**) (Table 1) was prepared by coupling tetrazole-5-diazonium salts (**1**) with substituted anilines. Proton abstraction from the compounds (**2**) could occur at the triazene chain or the tetrazole ring giving the anions (**3**) or (**4**) and these could interchange *via* tautomerism (Scheme). Monoalkylation could occur at the 1-, 3-, 1′, or 2′-nitrogen atoms (Scheme). In the event mono-alkylations with methyl iodide occurred preferentially at positions 1′ and 2′ giving the products (**6**) and (**5**) respectively (Scheme). The dominant reaction occurred at the 1′-position. The mono-anion (**7**) of the *N*(1′)-methyl derivatives (**6**) is also an ambident system with five viable sites for attack, the 1-, 3-, 2′-, 3′-, and 4′-nitrogen atoms. Attack at the 3′-position would give a meso-ionic product. Introduction of a second methyl group to this anionic system with methyl iodide occurred on the exocyclic triazene chain giving the products (**8**) and (**9**) with the main reaction occurring at the 3-position (Scheme).

The structure of the *N*-methyl isomers (**5**) and (**6**), and (**8**) and (**9**), were indicated from their ^1H and ^{13}C n.m.r. spectra (Table 2). The N–Me signals followed the patterns which we have previously established[9] for *N*-alkylazoles where the N–Me group is less shielded in an N–N(Me)–N unit, structure (**5**), as compared with a C–N(Me)–N unit, structure (**6**), thereby allowing a distinction to be made between the two. The tetrazole C-5′ shift which is known[9] to be about 10 p.p.m. downfield in a 2,5-disubstituted tetrazole [structure (**5**)] relative to a 1,5-disubstituted ring [structure (**6**)] also agreed with the assigned structure (Table 2). These assignments were confirmed for the series (**6**) through unequivocal syntheses by coupling of arene diazonium salts with 5-amino-1-methyltetrazole and for the series (**5**) by coupling diazotized 5-amino-2-methyltetrazole with *p*-substituted anilines. The structures of the dimethyl derivatives (**8**) and (**9**) were similarly established from ^1H and ^{13}C n.m.r. spectra and by unequivocal synthesis of the compound (**8**) from the corresponding *N*-methylaniline (Scheme) (Table 2).

(*b*) *Structure and Tautomerism.*—The parent triazenes (**2**), with two tautomeric N–H bonds, represent an interesting tautomeric system with six possible covalent tautomeric forms, excluding the possible meso-ionic forms and the extra forms arising from *E*–*Z* isomerism of the azo group. The possible



Scheme. X = (a), H; (b), Cl; (c), Br; (d), NO_2; (e), CO_2H; (f), Me

Table 1. Triazene derivatives

Compound	Yield (%)	M.p. (°C)	Found (%) (Required) C	H	N	Formula
(i) Parent triazene						
(2a)	73	78—80	44.0 (44.4)	3.6 (3.7)	51.3 (51.8)	$C_7H_7N_7$
(2b)	96	123—124	37.4 (37.6)	2.7 (2.7)	43.3 (43.8)	$C_7H_6ClN_7$
(2c)	96	112—113	29.4 (29.4)	2.8 (2.9)	33.8 (34.3)	$C_7H_6BrN_7 \cdot H_2O$
(2d)	87	168	35.3 (35.9)	2.6 (2.6)	47.5 (47.9)	$C_7H_6N_8O_2$
(2e)	90	204—206	38.1 (38.2)	3.75 (3.6)	38.6 (39.0)	$C_8H_7N_7O_2 \cdot H_2O$
(2f)	64	72—74	43.8 (43.4)	5.2 (4.9)	43.8 (44.3)	$C_8H_9N_7 \cdot H_2O$
(ii) *N*-Methyl derivatives						
(6b)	50	154—155	40.4 (40.4)	3.4 (3.4)	41.0 (41.3)	$C_8H_8ClN_7$
(6c)	60	166—167	34.1 (34.1)	2.9 (2.8)	34.7 (34.8)	$C_8H_8BrN_7$
(6d)	60	185—186	38.4 (38.7)	3.3 (3.2)	45.3 (45.2)	$C_8H_8N_8O_2$
(5b)	20	126—128	40.6 (40.4)	3.4 (3.4)	41.0 (41.3)	$C_8H_8ClN_7$
(5c)	29	134—135	34.0 (34.1)	2.8 (2.8)	34.2 (34.8)	$C_8H_8BrN_7$
(5d)	14	128—130	38.5 (38.7)	3.3 (3.2)	44.9 (45.2)	$C_8H_8N_8O_2$
(8)	70	170—171	36.8 (36.5)	3.5 (3.4)	33.2 (33.1)	$C_9H_{10}BrN_7$
(9)	23.5	165—166	36.7 (36.5)	3.7 (3.4)	33.2 (33.1)	$C_9H_{10}BrN_7$
(10a)	85	141—142	46.8 (47.3)	4.4 (4.4)	47.8 (48.3)	$C_8H_9N_7$
(10c)	87	161—162	33.7 (34.2)	2.7 (2.85)	34.5 (34.8)	$C_8H_8BrN_7$

Table 2. ^{13}C N.m.r. shifts (p.p.m. from TMS)

Compound	C-5′	C-1″	C-2″	C-3″	C-4″	N-Me δ_C	N-Me (δ_H)
(2a)	160.15	141.7	116.9	129.4	125.6		
(2b)	159.8	140.9	118.6	129.4	129.4		
(2c)	159.9	141.1	119.0	132.3	117.8		
(2d)	161.0	146.05	115.8	125.5	143.45		
(2e)[a]	160.9	144.35	115.9	131.05	126.95		
(2f)[b]	159.65	139.95	117.3	129.9	135.3		
(5b)	168.4	140.6	117.6	129.5	129.5	39.8	(4.3)
(5c)	168.5	141.4	118.05	132.3	116.75	39.8	(4.4)
(5d)	168.9	146.4	115.1	125.1	142.95	39.9	(4.4)
(6b)	157.75	139.4	117.7	129.55	129.3	33.65	(3.9)
(6c)	157.75	139.75	117.9	132.4	117.3	33.65	(4.0)
(6d)	157.75	145.55	115.8	125.8	143.7	33.85	(4.1)
(8)	158.1	142.6	120.9	132.2	118.7	33.4[c]	(4.1)[c]
						34.4[d]	(3.75)[d]
(9)	161.9	151.4	123.7	131.3	114.6	32.2[c]	(4.15)[c]
						35.2[e]	(3.7)[e]
(10a)	161.5	143.3	118.8	129.3	126.05	34.4	(3.8)

[a] *p*-CO_2H, 166.9 p.p.m. [b] *p*-Me, 20.5 p.p.m. [c] *N*(1′)-Me. [d] *N*(3)-Me (unprimed locant refers to the systematic numbering given for the particular compound). [e] N(1)-Me.

covalent tautomers are the (1*H*, 1′*H*), (1*H*, 2′*H*), (1′*H*, 4′*H*), (1′*H*, 2′*H*), (3*H*, 1′*H*), and (3*H*, 2′*H*) forms (Scheme). There have been extensive studies of triazene tautomerism[10–16] and it has been established[10,11] that electron-withdrawing substituents in the aryl ring favour the non-conjugated (XAr–NH–N=N–) form. Recently the NH ^1H n.m.r. signals of both forms of some alkylaryltriazenes have been directly detected allowing an accurate quantitative assessment to be made.[10] With the substrates (**2**), as is often the case with acidic 5-aminotetrazole derivatives, reliable NH signals could not be

observed in $(CD_3)_2SO$. Solvents such as $CDCl_3$ and CD_3CN which have been successful for studying triazene tautomerism did not prove suitable due to the high insolubility of the compounds (**2**). However, the *N*-methyl isomers provided models for the most likely of the various tautomeric forms using ^{13}C n.m.r. spectroscopy. Other techniques such as i.r. and u.v. spectroscopy were not informative due to inadequate differences between the model spectra. For example, the $\lambda_{max.}$ values in acetic acid for the series (**2c**), (**5c**), (**6c**), and (**8**) were 342, 343, 353, and 340 nm respectively. The tetrazole C-5′ shift of compounds (**2**) was close to that of the *N*(1′)-methyl isomers (**6**) and (**8**) and significantly different from that of the *N*(2′)-methyl isomers (**5**). The tetrazole C-5′ shift is highly sensitive to the substituent pattern of the tetrazole ring and has been established as a reliable probe of the tautomeric location of the tetrazole proton,[17,18] which in compounds (**2**) is at the N-1′ position. The location of the other proton is indicated at the triazene N-3 position by comparison of the carbon shifts of the aryl ring (Table 2) with those of appropriate models such as substituted anilines and azobenzenes.[19] Thus compound (**8**), containing an N–Me unit bonded to the aryl ring, provided a model for the N(3)–H form and compound (**9**) with an azo group in direct conjugation with the aryl ring, provided a model for the N(1)–H form. The similarity of the aryl carbon shifts of compound (**2c**) (Table 2) with those of compound (**8**) (*cf.* the important C-1″ and C-4″ positions), and the contrast with those of compound (**9**), suggest that the dominant tautomer in perdeuteriodimethyl sulphoxide solution is the (3*H*, 1′*H*) form (**2**).

Experimental

M.p.s were measured with an Electrothermal apparatus. I.r. spectra were measured for Nujol mulls with a Perkin-Elmer 377 spectrophotometer. U.v. spectra were measured on a Beckman DBGT Grating u.v. spectrophotometer. ^1H and ^{13}C N.m.r. spectra were measured for solutions in $(CD_3)_2SO$ with Me_4Si as internal reference on JEOL JNM-100 and CFT-20 spectrometers.

Synthesis of 3-*Aryl*-1-(*tetrazol-5′-yl*)*triazenes* (**2**).—The following procedure was followed in each case. A solution of 5-aminotetrazole hydrate (0.04 mol) in conc. hydrochloric acid (11.5 ml) and water (120 ml) at 0 °C was treated by dropwise addition of a solution of sodium nitrite (2.8 g, 0.04 mol) in water (25 ml) **(CARE: safety shield and full safety precautions required)** and the mixture was stirred for 10 min at 0—5 °C and then slowly added to a prepared solution of the substituted aniline (0.04 mol) in 6M HCl (20 ml) which had been diluted with water (300 ml) and cooled with crushed ice (*ca.* 100 g) prior to the addition. (It may be necessary to heat the aniline–hydrochloric acid mixture to obtain a clear solution at first.) The triazene (**2**) (Table 1) separated immediately. After the mixture had been stirred for 20 min the product was collected, washed with several small portions of cold water, and recrystallised from ethanol–water. The compounds proved to be hygroscopic on being kept under normal conditions.

Methylation of the Triazenes.—(*a*) The following is a typical example. A solution of compound (**2c**) (5.36 g, 0.02 mol) and sodium hydroxide (800 mg, 0.02 mol) in aqueous ethanol (1:1 v/v) (80 ml) was treated with methyl iodide 5.68 g, 0.04 mol), and the mixture was stirred at 47 °C for 2 h and cooled at 0 °C for 12 h. The yellow solid (from filtrate A), a mixture of compounds (**6c**) and (**5c**), was stirred in diethyl ether and the insoluble fraction was recrystallised and shown to be 3-(p-*bromophenyl*)-1-(1′-*methyltetrazol-5′-yl*)*triazene* (**6c**) (3.33 g, 59%), m.p. 166—167 °C (from aqueous alcohol); $\nu_{max.}$ 3 180 (NH) and 1 600 cm^{-1} (C=N); $\nu_{max.}$(HOAc) 353 nm. The ether-soluble fraction was recovered by evaporation and proved to be the 2-methyl isomer, 3-(p-*bromophenyl*)-1-(2′-*methyltetrazol-5′-yl*)*triazene*, (**5c**) (490 mg), m.p. 134—135 °C (from aqueous alcohol); $\nu_{max.}$ 3 200 (NH) and 1 600 cm^{-1} (C=N); $\lambda_{max.}$(HOAc) 343 nm. The mother filtrate (A) was extracted with diethyl ether (1 × 100; 2 × 50 ml) (remaining aqueous solution B). The combined etheral extract was washed with water, dried (Na_2SO_4), and evaporated to yield a further crop (1.09 g) of compound (**5c**) (overall yield 1.58 28%). The aqueous solution (B) was acidified with conc. hydrochloric acid (2 ml) and the starting triazene (**2c**) (490 mg, 9.2%), m.p. 112—113 °C (from aqueous alcohol) was recovered (overall recovery 96%). The other alkylations (Table 1) were carried out in a similar manner.

(*b*) A solution of compound (**6c**) (1.41 g, 5 mmol) and sodium hydroxide (200 mg, 5 mmol) in 50% (v/v) aqueous ethanol was treated with methyl iodide (0.62 ml, 0.01 mol) and the mixture was stirred at 47 °C for 2 h and cooled at 0 °C for 12 h. The yellow solid which separated (1.39 g, 94%) was a 3:1 mixture of the compounds (**8**) and (**9**). These were separated on a column of alumina made up in light petroleum (b.p. 40—60 °C)–diethyl ether and eluted with toluene–ethyl acetate (9:1 v/v). The early fractions eluted 3-(p-*bromophenyl*)-1-*methyl*-1-(1′-*methyltetrazol-5′-yl*)*triazene* (**9**), m.p. 165—166 °C (from aqueous alcohol); $\nu_{max.}$ no NH, 1 585 cm^{-1} (C=N); while 3-(p-*bromophenyl*)-3-*methyl*-1-(1′-*methyltetrazol-5′-yl*]*triazene* (**8**), m.p. 170—171 °C (from aqueous alcohol) was collected from the later fractions, $\nu_{max.}$ no NH, 1 585 cm^{-1} (C=N); $\lambda_{max.}$(HOAc) 340 nm.

Unequivocal Syntheses of Methyl Isomers.—The following are typical examples. (i) A stirred solution of *p*-chloroaniline (1.27 g, 0.01 mol) in conc. hydrochloric acid (3 ml) and water (30 ml) was diazotized at 0 °C by dropwise addition of a solution of sodium nitrite (0.69 g, 0.01 mol) in water (6 ml) and the mixture, after being stirred for 10 min, was quickly added to a cooled solution of 5-amino-1-methyltetrazole (0.99 g, 0.01 mol) in water (70 ml). Careful addition of dilute aqueous sodium carbonate to the resulting mixture gave separation of yellow crystals of 3-(p-*chlorophenyl*)-1-(1′-*methyltetrazol-5′-yl*)*triazene* (**6b**) (1.045 g, 44%), m.p. 155—156 °C, identical (mixed m.p.; i.r. and ^1H n.m.r. spectra) with the sample obtained from methylation of compound (**2b**).

(ii) A solution of 5-amino-2-methyltetrazole (0.99 g, 0.01 mol) in conc. hydrochloric acid (3 ml) and water (30 ml) was treated at 0 °C with a solution of sodium nitrite (0.69 g, 0.01 mol) in water (16 ml) and the mixture was added to a stirred solution of *p*-bromoaniline (1.72 g, 0.01 mol) in conc. hydrochloric acid (2 ml) and water (100 ml) at 0 °C. Careful addition of dilute aqueous sodium carbonate caused separation of orange crystals of 3-(*p*-bromophenyl)-1-(2′-methyltetrazol-5′-yl)triazene (**5c**) (0.52 g, 19%), m.p. 134—135 °C, identical (mixed m.p.; i.r. and ^1H n.m.r. spectra) with the sample obtained from methylation of compound (**2c**).

(iii) Coupling of substituted *N*-methylanilines with tetrazole-5-diazonium chloride as described gave the compounds (**10**) (Table 1). Methylation of compound (**10c**) gave compound (**8**) which was identical (mixed m.p.; i.r. and ^1H n.m.r. spectra) with the sample obtained from the methylation of compound (**6c**).*

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