Monoalkyltriazenes

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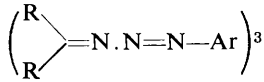
1 Introduction

Triazene, $HN{=}N.NH_2$, is an important member of the family of open-chain nitrogen compounds and, although not isolable, has been postulated as an intermediate in the one-electron oxidation of hydrazine to ammonia and nitrogen during pulse radiolysis.[1] Many derivatives of triazene have been synthesized, the most notable being the monoaryl-, 1,3-diaryl-, 1,3-dialkyl-, 1-aryl-3-alkyl-[$ArN{=}N.NHR$; 'monoalkyltriazenes' (1)], 1-aryl-3,3-dialkyl-[$ArN{=}N.NR_2$; 'dialkyltriazenes' (2)], and *N*-hydroxy-[$ArN{=}N.N(OH)R$] triazenes.[2] Recently reported novel triazenes are the 1,2,3-triazabutadienes  [3,4] and the closely related azidinium salts.[5] Monoalkyltriazenes merit separate consideration not only because of their abundant and distinctive chemistry, but also because of their important biological properties. The monoalkyltriazenes may be the active metabolites of the anti-tumour dialkyltriazenes (2) (Section 5). Synthetic applications of monoalkyltriazenes (Section 4) include esterification, deamination of primary amines, and the ability to act as bridging agents in co-ordination chemistry. The first sections, however, consider the synthetic and structural aspects of monoalkyltriazene chemistry.

2 Preparation

A. Grignard Method.—The formation of a monoalkyltriazene by the reaction of a Grignard reagent with an aryl azide was first demonstrated by Dimroth[6]

[1] E. Hayon and M. Simic, *J. Amer. Chem. Soc.*, 1972, **94**, 42.
[2] H. Zollinger, 'Azo and Diazo Chemistry', Interscience, New York, 1961, 179; P. A. S. Smith, 'Open-Chain Nitrogen Compounds', Vol. 2, 1966, Benjamin, 336—343.
[3] R. Ebisch and P. Niedermayer, *Z. Chem.*, 1975, **15**, 143.
[4] V. E. Fanghanel, R. Hansel, W. Ortman, and J. Hohlfeld, *J. prakt. Chem.*, 1975, **317**, 631; *ibid.*, 1976, **318**, 671.
[5] B. von Hellrung and H. Balli, *Helv. Chim. Acta*, 1976, **59**, 140.
[6] O. Dimroth, *Ber.*, 1903, **36**, 909.

$$ArN_3 + RMgX \longrightarrow [ArN(MgX).N{=}N.R] \xrightarrow{H_2O} Ar.NH.N{=}N.R \quad (1)$$

[equation (1)] and the importance of the reaction is well recognized.[7] The Grignard method is quite versatile with respect to variations in the alkyl group and has been applied recently to the preparation of monoalkyltriazenes labelled with ^{14}C in the alkyl group,[8] a novel ferrocenylmethyltriazene,[9] and monovinyltriazenes labelled with ^{14}C in the vinyl group.[10] An unusual variation on the Grignard theme is the reaction of the azides (3a) and (3b) with the sulphur ylide (4) to give vinyl triazenes.[11] Although mechanistically intriguing, this reaction is severely limited in scope since other azides give rise to dihydrotriazoles, not triazenes.

$$\underset{(3)}{R{-}N_3} + 2CH_2{=}\underset{(4)}{\overset{O}{\overset{\|}{S}}}Me_2 \longrightarrow R{-}N{=}N.NH.CH{=}CH_2 + 2Me_2SO$$

a: R = *p*-$O_2N.C_6H_4$
b: R = Bz

Unlike monoalkyltriazenes prepared by other routes, compounds generated from Grignard reagents are generally free from contamination by higher homologous open-chain nitrogen compounds. However, the Grignard method cannot be used when the aryl group contains substituents, *e.g.* CO_2R and CN, which themselves react with the Grignard reagent. Fortunately in the majority of such instances the diazonium coupling method is a practical alternative.

B. Diazonium Coupling.—*N*-Coupling of an aryl diazonium salt with a primary aliphatic amine is an obvious method of generating a monoalkyltriazene [equation (2)]. However, this apparently simple method, described in *Organic Syntheses*,[12] is fraught with difficulties, not the least of which is the propensity of the triazene (1) to react further with diazonium ion to give the penta-azadiene (5).[13] The

$$ArN_2^{\cdot} + RNH_2 \longrightarrow \underset{(1)}{ArN{=}N.NHR} \xrightarrow{ArN_2^+} \underset{(5)}{ArN{=}N.\overset{R}{\overset{|}{N}}.N{=}NAr} \quad (2)$$

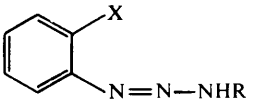
recommended [12] method of separation of (1) from (5) is vacuum sublimation, the penta-azadiene usually being involatile, although exploitation of fractional solubilities in methanol has been suggested as a satisfactory alternative.[14]

[7] V. Zverina and M. Matrka, *Chem. listy*, 1969, **63**, 51.
[8] A. N. Lotsova, T. N. Shatkina, and O. A. Reutov, *Doklady Akad. Nauk S.S.S.R.*, 1968, **183**, 1091.
[9] D. E. Bublitz, *J. Organometallic Chem.*, 1970, **23**, 225.
[10] C. C. Lee and E. C. F. Ko, *Canad. J. Chem.*, 1976, **54**, 3041.
[11] G. Gaudiano, C. Ticozzi, A. Umani-Ronhi, and P. Bravo, *Gazzetta*, 1967, **97**, 1411.
[12] E. H. White, A. A. Baum, and D. E. Eitel, *Org. Synth.*, 1973, Coll. Vol. **5**, 797.
[13] G. F. Kolar, in 'Mass Spectroscopy in Biochemistry and Medicine', ed. Frigerio and Castagnoli, Raven Press, New York, 1974, 267.
[14] C. S. Rondesvedt and S. J. Davis, *J. Org. Chem.*, 1957, **22**, 200.

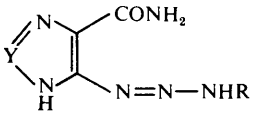
Proponents of sublimation appear to have overlooked the danger of explosion due to the thermal instability of triazenes and penta-azadienes.[14]

The tendency towards penta-azadiene formation is dependent on the nature of substituents in the aryl group; it has been shown[15] that diazonium salts with strongly electron-withdrawing substituents in the aryl group react with methylamine to give penta-azadiene-free triazenes. This specificity has been attributed to the resonance effect of the substituent in Ar, which reduces electron density at the N-3 nitrogen in (1) and prevents further coupling with diazonium ion.

Notwithstanding the difficulty involved, the *N*-diazo coupling method has been widely used to prepare a number of monomethyltriazenes with different aryl groups.[16,17] The method is also amenable to variations in the alkyl group, *e.g.* cyclohexyl-,[18] glucopyranosyl-,[19] galactopyranosylmethyl-,[20] and xylopyranosyl-triazenes;[21] significantly in all these cases the aryl group contained an electron-attracting substituent at the *para*-position. Although triazenes of type 1, with *ortho*-substituents in the aryl group, are susceptible to cyclization, a number of triazenes of this type have been isolated and characterized, such as the esters (6a),[22] the nitrile (6b),[23] and the analogous imidazole-(7a),[24] 1,2,3-triazole-(7b),[25] and pyrazole-carboxamides.[26]



(6) a; X = CO_2R'
b; X = CN, R = CH_2Ph
c; X = $COCH_3$

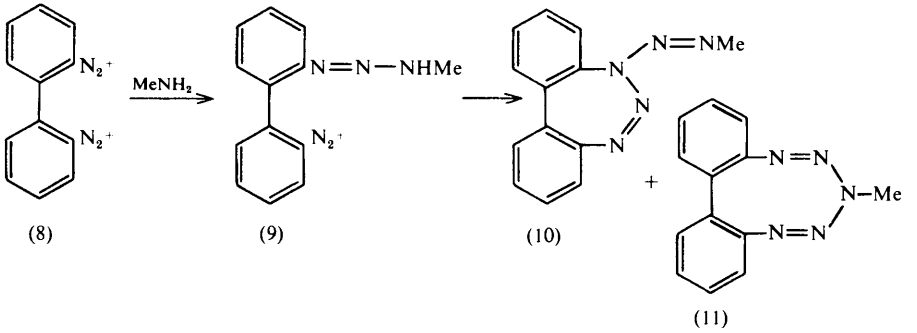


(7) a; Y = CH
b; Y = N

A novel diazo-coupling of this type is the reaction of the tetrazotized biphenyl (8) with methylamine, which initially generates the triazenido diazonium salt (9).[27] This triazene undergoes two distinct cyclizations to give the unstable penta-azadienes (10) and (11) (Scheme 1).

N-Diazo-coupling has also been used to prepare the novel 1,3-dialkyltriazene

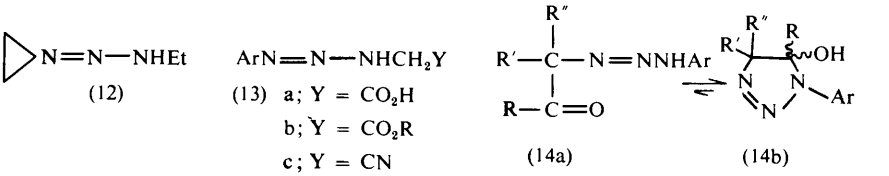
[15] T. P. Ahern and K. Vaughan, *J.C.S. Chem. Comm.*, 1973, 701.
[16] M. Remes, J. Divis, V. Zverina, J. Marhold, and M. Matrka, *Cesk. Farm.*, 1972, **21**, 442; J. Arient and K. Panus, *Coll. Czech. Chem. Comm.*, 1972, **37**, 1900.
[17] T. P. Ahern, H. Fong, and K. Vaughan, *Canad. J. Chem.*, 1977, **55**, 1701.
[18] H. Maskill and M. C. Whiting, *J.C.S. Perkin II*, 1976, 1462.
[19] O. Larm, K. Larsson, and M. Wannong, *Acta Chem. Scand. B*, 1977, **31**, 475.
[20] M. L. Sinnott and P. J. Smith, *J.C.S. Chem. Comm.*, 1976, 223.
[21] J. M. J. Tronchet and F. Rachidzadeh, *Helv. Chim. Acta*, 1976, **59**, 2855.
[22] R. J. LeBlanc and K. Vaughan, *Canad. J. Chem.*, 1972, **50**, 2544.
[23] H. N. E. Stevens and M. F. G. Stevens, *J. Chem. Soc.* (C), 1970, 765.
[24] Y. F. Shealy and C. A. Krauth, *J. Medicin. Chem.*, 1966, **9**, 34; Y. F. Shealy, C. A. Krauth, and C. A. O'Dell, *J. Pharm. Sci.*, 1975, **64**, 177.
[25] Y. F. Shealy and C. A. O'Dell, *J. Medicin. Chem.*, 1966, **9**, 733.
[26] Y. F. Shealy and C. A. O'Dell, *J. Pharm. Sci.*, 1971, **60**, 554.
[27] S. F. Gait, M. E. Peek, C. W. Rees, and R. C. Storr, *J.C.S. Perkin I*, 1974, 1248.



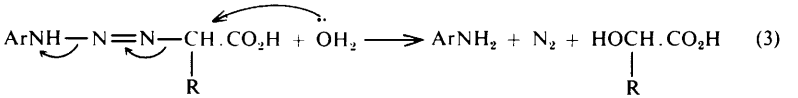
(8) (9) (10) (11)

Scheme 1

(12) from the unusually stable cyclopropyldiazonium ion,[28] and in the synthesis of triazabutadienes derived from iminoheterocyclic systems.[4] Diazotization of aromatic amines, in the presence of a primary aliphatic amine, and coupling with phenolic couplers, is reported to give azo-pigments with improved dispersal characteristics; presumably a monoalkyltriazene is generated *in situ*.[29]



Diazo-coupling with α-substituted alkylamines (NH_2CH_2Y, where Y is electron-withdrawing) gives rise to triazenes of type (13), which vary widely in stability. Thus, coupling with α-amino acids initially gives the unstable triazenes (13a), which hydrolyse spontaneously to give the α-hydroxy acid, N_2 and the associated arylamine [equation (3)], providing



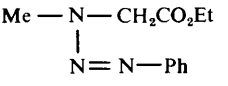
(3)

a valuable method of deamination of the amino acid.[30] A recent study [31] of the kinetics of the reaction has shown that there is no correlation between the rate of deamination and the pK_a of the amino acid.

By contrast the triazenes (13b) and (13c), derived from α-amino acid esters[32,33]

[28] W. Kirmse and U. Siepp, *Chem. Ber.*, 1974, **107**, 745.
[29] M. Rajewski, J. Korzeniowska, and W. Siwek, *Pol. P.*, 72853 (*Chem. Abs.*, 1977, **86**, 18349f).
[30] H. Zahn, B. Wollerman, and O. Waschka, *Z. Physiol. Chem.*, 1953. **294**, 100.
[31] M. Remes, J. Divis, V. Zverina, and M. Matrka, *Coll. Czech. Chem. Comm.*, 1976, **41**, 2566.
[32] R. J. Baumgarten, *J. Org. Chem.*, 1967, **32**, 484.
[33] J. F. McGarrity, *J.C.S. Chem. Comm.*, 1974, 558.

and nitriles[34] respectively, are quite stable and readily prepared. However, the keto-triazenes (14a), produced either by *N*-diazo-coupling with ω-aminoacetophenone[33] or by reaction of an aryl azide with a ketone,[35] prefer to exist in the 5-hydroxy-Δ^2-1,2,3-triazoline form (14b). Olsen has carried out a careful study of the triazene⇌triazoline tautomerism using i.r. and n.m.r. spectroscopy[36] and has shown that some of the triazolines exist in solution as an equilibrium mixture of diastereomers, most likely interconvertible *via* triazenes. Although the triazene-esters (13b) have not shown any tendency to cyclize, the related dialkyl triazene (15) cyclizes in thionyl chloride to give a mesoionic triazolium-oxide.[37]



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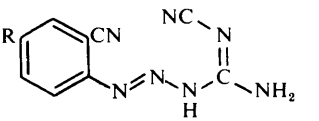


(16)

Conflicting claims have been made as to whether *N*-diazo-coupling occurs when a diazonium salt is treated with an amide; such a reaction, although inhibited by the weak nucleophilic character of the amido-nitrogen, would give rise to a monoacyltriazene (an oxidized form of a monoalkyltriazene). Oddo and Algerino[38] reported the synthesis of 1-phenyl-3-acetyltriazene by reaction of benzene diazonium chloride with acetamide in the presence of sodium hydroxide, whereas the same reaction in the presence of sodium acetate gave only 1,3-diphenyltriazene.[17] Failure to react with acetamide was also recorded in the case of the diazonium salt from sulphanilic acid ($^-O_3S.C_6H_4N_2^+$).[39] Nevertheless, the formation of the *N*-formyltriazenes (p-X.$C_6H_4N{=}N.NH.CHO$) by *N*-diazo-coupling with formamide appears to be unequivocal, since these triazenes could be dehydrated to give diazoisocyanides ($ArN{=}\overset{+}{N}{-}\overset{-}{N}{\equiv}C$)[40] Indeed, a number of monoacyltriazenes have been isolated in crystalline form by partial hydrolysis of hexa-azadienes[41] and are quite stable. 1-Phenyl-3-benzoyl-triazene has been obtained by reaction of phenylmagnesium bromide with benzoyl azide[42] and, more recently, by base-catalysed condensation of nitrosobenzene with benzhydrazide.[43]

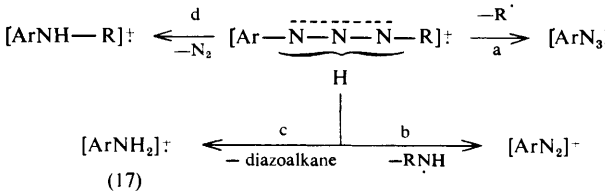
[34] T. A. Daniels, S. Sidi, and K. Vaughan, *Canad. J. Chem.*, 1977, **55**, 3751.
[35] C. E. Olsen, *Angew. Chem. Internat. Edn.*, 1974, **13**, 349.
[36] C. E. Olsen, *Acta Chem. Scand.*, 1973, **27**, 1987; C. E. Olsen and C. Pedersen, *Acta Chem. Scand.*, 1973, **27**, 2271.
[37] T. L. Gilchrist and G. E. Gymer, *Adv. Heterocyclic Chem.*, 1974, **16**, 58.
[38] G. Oddo and A. Algerino, *Chem. Ber.*, 1936, **69**, 279.
[39] H. Eagle and P. Vickers, *J. Biol. Chem.*, 1936, **114**, 193.
[40] T. Ignasiak, J. Suszko and B. Ignasiak, *J.C.S. Perkin I*, 1975, 2122.
[41] J. P. Horwitz and V. Grakauskas, *J. Amer. Chem. Soc.*, 1957, **79**, 1249.
[42] A. Bertho, *J. prakt. Chem.*, 1927, **116**, 101.
[43] S. Ito and T. Fukuyama, *J. Org. Chem.*, 1971, **36**, 2008.

Nesynov[44] reported the reaction of diazonium salts with secondary amides and thioamides and found that *O*- or *S*-arylation occurred, together with *N*-coupling to afford triazenium salts [*e.g.* $ArN{=}N{-}N^{+}(Ar^{1}){=}C(Me)OAr.\ AcO^{-}$], whereas the analogous reaction with selenourea[45] resulted in *N*- and *Se*-coupling giving triazenes of type, $ArN{=}N.NHC(=NH)Se.N{=}N.Ar$. The novel cyanotriazenes (16), obtained by similar *N*-diazo coupling with cyanoguanidine, were found to be explosive when dry[46] and did not lend themselves to cyclization to iminobenzotriazines.

This area of triazene chemistry continues to be of interest, as indicated by a recent communication,[47] which describes new sulphonyl triazenes ($ArN{=}N.NHSO_2Ar^{1}$) as the *N*-diazo-coupling products of sulphonamides.

3 Structure: Application of Physical Methods

Detailed studies of the mass spectra of monoalkyltriazenes are few.[13,17] Frequently observed fragmentation pathways (Scheme 2) are (a) loss of alkyl radical; (b) loss of alkylamino radical; and (c) loss of a diazoalkane moeity. Surprisingly direct loss of N_2 (path d) is not a normal mode of fragmentation unless the aryl group contains an electron-withdrawing group.[17] The presence of these groups also appears to promote breakage of the *N*-alkyl linkage (path a), which is not prominent in the spectra of 3-alkyl-1-phenyltriazenes;[13] the outstanding feature of the spectrum of 3-methyl-1-phenyltriazene is a very intense peak at *m/e* 93 which has been assigned to the radical ion of aniline (17), arising by fission of the triazene group between N-1 and N-2, followed by hydrogen transfer.

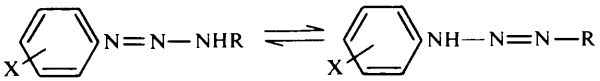


Mass Spectral Fragmentation of Monoalkyltriazenes

Scheme 2

Applications of i.r. and n.m.r. spectroscopy to the structural elucidation of monoalkyltriazenes are more numerous and these techniques have proved invaluable in the elaboration of the tautomeric equilibrium (Ia)⇌(Ib). Indeed, the tautomeric structure of triazenes in general has been the subject of a long-standing debate.[48]

[44] E. P. Nesynov and M. M. Besprozvannaya, *Ukrain. khim. Zhur.*, 1974, **40**, 182. (*Chem. Abs.*, 1974, **80**, 133326j); E. P. Nesynov, M. M. Besprozvannaya, and P. S. Pel'kis, *Dopovidi Akad. Nauk Ukrain. R.S.R., Ser. B.*, 1969, **31**, 27 (*Chem. Abs.*, 1969, **71**, 30134e).
[45] E. P. Nesynov and T. F. Aldokhina, *Zhur. obshchei Khim.*, 1976, **46**, 1098. (*Chem. Abs.*, 1976, **85**, 77803b).
[46] S. M. MacKenzie and M. F. G. Stevens, *J. Chem. Soc.* (*C*), 1970, 2298.
[47] R. Kreher and R. Halpaap, *Tetrahedron Letters*, 1977, 3147.
[48] T. W. Campbell and B. F. Day, *Chem. Rev.*, 1951, **48**, 299.



(Ia) (Ib)

The i.r. spectra of monoalkyltriazenes generally show two NH stretching vibration bands, one at 3480—3440 cm.$^{-1}$ assigned to tautometer (Ia), and the other near 3338 cm^{-1} assigned to (Ib).[49] Unambiguous assignment of these bands was made possible by observing the shift of the low frequency band to lower frequency when ^{15}N is introduced at N-1. The relative intensities of these bands are influenced by the substituent (X), implying that the substituent influences the tautomeric equilibrium; electron-withdrawing substituents shift the equilibrium in favour of form (Ib). A similar substituent effect has been observed, also by i.r. measurement, in the tautomerism of 1,3-diaryltriazenes.[50] From the temperature dependence of the intensity ratio of the i.r. bands, ΔH of the tautomeric reaction (Ia)⇌(Ib) was estimated to be 0.3 kcal mol^{-1},[49] which is in agreement with the value obtained for diaryltriazenes. Low temperature p.m.r. spectra of the *p*-tolyltriazenes (I; X = *p*-Me, R = Me or $PhCH_2$) in [$^2H_6$]acetone solution[51] exhibit two resonances for the α-protons in the R-group; a low-field singlet was assigned to form (Ib) and the high-field doublet, arising from coupling of α-protons with the adjacent NH proton, was assigned to form (Ia). By careful measurement of integrations of *N*-alkyl group proton signals, K_T values for these triazenes were evaluated as 0.46 (R = $PhCH_2$) (−40 °C) and 0.11 (R = Me) (−55 °C); thus the proportion of tautomers (Ia) and (Ib) of 3-methyl-1-*p*-tolyltriazene is approximately 9:1 at −55 °C in acetone solution. ΔH for the tautomeric equilibrium of the methyl-*p*-tolyltriazene was estimated to be 1.1 kcal mol^{-1}; the analogous measurement for the *p*-nitrophenyltriazenido-sugars (I; X = *p*-NO_2, R = Xylopyranosyl) was even greater, 3.03 kcal mol^{-1}.[21] These ΔH values are significantly greater than those estimated from i.r. measurements, but no explanation has been offered for the discrepancy.

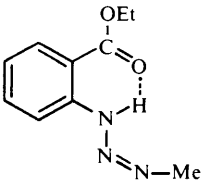
Further ^1H n.m.r. studies with monoalkyltriazenes have shown that the tautomerism is both solvent-dependent and influenced strongly by substituents in the aryl group. For example, the ^1H n.m.r. spectrum of 3-methyl-1-*p*-tolyltriazene, measured in dichloromethane at −65 °C[52] or in chloroform at −55 °C,[53] exhibits only one resonance, a doublet, for the *N*-methyl protons, indicating that only tautomer (Ia) is detectable under these conditions. However, tautomer (Ib) of the same *p*-tolytriazene has been detected in $CDCl_3$ by ^{13}C

[49] D. Hadzi and J. Jan, *Spectroscopy Letters*, 1968, **1**, 139.
[50] S. Weckherlin and W. Luttke, *Tetrahedron Letters*, 1964, 1711; T. Mitsuhashi, Y. Osamura, and O. Simamura, *Tetrahedron Letters*, 1965, 2593.
[51] R. Curci and V. Lucchini, *Spectroscopy Letters*, 1973, **6**, 293.
[52] N. S. Isaacs and E. Rannala, *J.C.S. Perkin II*, 1974, 899.
[53] K. Vaughan, *J.C.S. Perkin II*, 1977, 17.

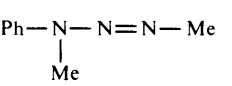
n.m.r. spectroscopy[54] and the failure to detect the ^1H n.m.r. signals of form (Ib) of this triazene has been ascribed[55] to low intensities of these signals which may well be considerably broadened.

However, clear distinction of tautomers (Ia) and (Ib) can be seen in the ^1H n.m.r. spectrum when the aryl group contains electron-withdrawing groups.[53] Thus the ^1H n.m.r. spectrum of 1-(*p*-cyanophenyl)-3-methyltriazene in $CDCl_3$ at -30 °C shows the singlet methyl resonance (δ 3.62) and the doublet methyl resonance (δ 3.22) in approximately equal intensities, indicating that the presence of the cyano-group shifts the tautomeric equilibrium towards (Ib), in agreement with the i.r. results previously discussed. The ^1H n.m.r. spectrum of 1-(*o*-ethoxycarbonylphenyl)-3-methyltriazene (6a; R = Me) exhibits only one *N*-methyl resonance, which is a singlet (δ 3.57). The explanation[53] of this observation is that intramolecular hydrogen bonding with the *o*-ethoxycarbonyl group holds the triazene in form (Ib) (see 18).

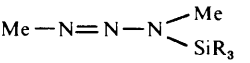
The assignments of singlet and doublet methyl resonances in the spectra of monoalkyltriazenes to tautomers (Ib) and (Ia) respectively has been confirmed by chemical shift correlation with model compounds. The well known 3,3-dimethyltriazenes (2; R = Me) serve as an excellent model for tautomer Ia of the monoalkyltriazenes; the observed chemical shifts are δ3.23[56] and δ3.17—3.22.[52,53] 1-Methyltriazenes (*e.g.* 19), which would be useful model compounds for tautomer (Ib), were until recently unreported; however Pochinok[57] has reported a chemical shift at δ3.98 for the 1-methyl-group in 1,3-dimethyl-3-phenyltriazene (19) although the source or method of preparation of (19) is not clear. Other mode compounds of potential application are the 1,3-dimethyl-3-silyltriazenes (20),[58] which undergo silyl-group migration analogous to the prototropy in monoalkyl- and diaryl-triazenes.



(18)



(19)

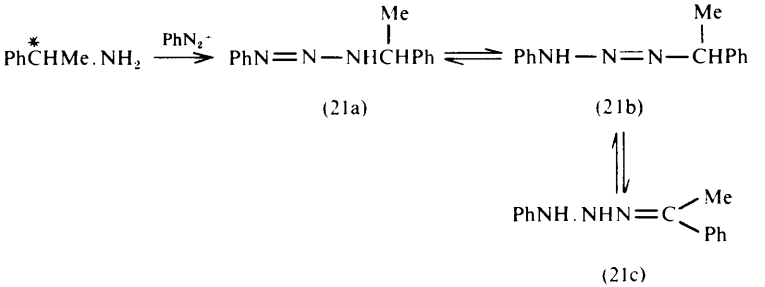


(20)

A surprising result was obtained when optically active α-methylbenzylamine was coupled with a benzene diazonium salt;[59] the resulting triazene (21) was

[54] K. Albert, K-M. Dangel, A. Rieker, H. Iwamura, and Y. Imahashi, *Bull. Chem. Soc. Japan*, 1976, **49**, 2537.
[55] H. Iwamura, K. Albert, and A. Rieker, *Tetrahedron Letters*, 1976, 2627.
[56] *Sadtler Index of N.M.R. Spectra*, 1968, 4499M.
[57] V. Ya Pochinok, *Ukrain. khim. Zhur.*, 1977, **43**, 180. (*Chem. Abs.*, 1977, **86**, 188927j).
[58] N. Wiberg and H. J. Pracht, *Chem. Ber.*, 1972, **105**, 1377. 1388.
[59] A. P. Terent'ev, E. G. Rukhadze, T. V. Ershova, and S. A. Burkhova, *Zhur. org. Khim.*, 1968, **4**, 125. (*Chem. Abs.*, 1968, **68**, 86923s).

optically inactive. This observation was accounted for by the extended tautomerism [(21a)⇌(21b)⇌(21c)] whereby the mobility of the α-proton causes racemization. The driving force for the shift to tautomer (21c) may be the conjugation of the C=N group with the benzene ring. Analogous reaction of optically active *N*-ethyl-α-methyl-benzylamine gave the optically active dialkyltriazene [PhN=N.N(C_2H_5).$\overset{*}{C}$HMe.Ph], which cannot undergo prototropy. A similar phenomenon has been observed when diazotized methyl anthranilate was coupled to L-phenylalanine ethyl ester to afford an optically inactive 3-alkylbenzotriazinone.[60] The optical inactivity of the product was rationalized by the formation of the intermediate triazene [6a; R = —CH(CO_2Et)CH_2Ph], in which the α-CH group is acidic relative to that in simple 3-alkyl triazenes (*e.g.* 21) and which could readily ionize under the conditions used to give a trigonal planar, resonance stabilized anion. Reprotonation and cyclization would then afford the racemic benzotriazinone.



4 Reactions

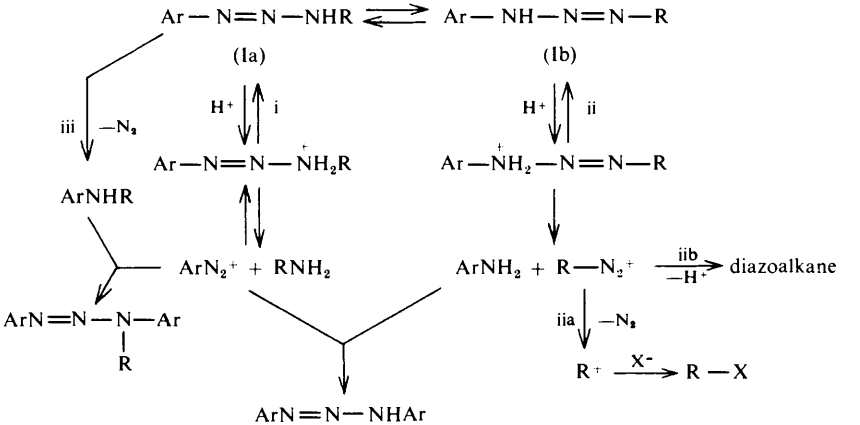
An aspect of triazene chemistry of quite recent origin, but of growing importance, is their ability to act as ligands in co-ordination compounds, although one could look upon this property as an extension of their nucleophilic character, and this topic is treated as such in this review. However this Section is primarily concerned with the synthetic applications of monoalkyltriazenes, particularly with respect to the deamination of primary amines, the esterification of carboxylic acids and the formation of 1,2,3-benzotriazines. The first two types of reaction are manifestations of the facile release of the alkyl group during degradation of the triazene, whereas cyclization reactions require strict control over degradative side-reactions to optimize the yield of cyclic triazine. Thus, a sound knowledge of the degradative properties of monoalkyltriazenes will aid the synthetic chemist and we begin this section with an appraisal of recent studies of the acid-catalysed and thermolytic reactions of monoalkyltriazenes.

A. Acid-catalysed Degradation.—(i) *Protolysis.* Degradation of monoalkyltriazenes in protic media leads to products arising from protonation mainly at

[60] A. C. Mair and M. F. G. Stevens, *J. Chem. Soc.* (*C*), 1971, 2317.

N-3 of the tautomeric form Ib (Scheme 3, path ii). Thus hydrolysis of 1-phenyl-3-methyltriazene in water gives a mixture of aniline and methanol, but not phenol.[6,61a] Significant evidence for the involvement of both tautomers (Ia, Ib) is adduced by the formation of diaryltriazenes during degradation of monomethyl-[17] and monobutyl-[61b] triazenes in protic media; the diaryltriazene can arise by coupling of the diazonium ion $Ar.N_2^+$ (path i) with the arylamine $ArNH_2$ (path ii). The formation of 1,3-diaryl-3-alkyltriazenes in these degradations is evidence for the formation of secondary amines by loss of nitrogen (path iii) before diazo-coupling. Matrka *et al.*[62] established a significant correlation between the rate of protolysis and the σ-value of the substituent in the aryl group; in a predictable manner, electron-withdrawing groups slow down the protolysis. The greater reactivity of the non-conjugated tautomer (Ib) has been suggested by a kinetic study of the hydrolysis of the vinyl ethers of hydroxyethyltriazenes ($PhN{=}N.NHCH_2CH_2OCH{=}CH_2$).[63]

Evidence of carbonium-ion involvement (path iia, Scheme 3) in the mechanism of protolysis has been obtained from the decomposition of 1-phenyl-3-n-propyltriazene in aqueous sulphuric acid; analysis of the resulting mixture of alcohols showed a significant amount of 2-propanol, in addition to 1-propanol, implying formation and rearrangement of the n-propyl cation.[8] Indeed acidic hydrolysis of monovinyltriazenes has been used as a method of generating and



Scheme 3

studying vinyl cations. 1,2-Aryl shifts across the double bond of the vinyl group were observed in the case of unsymmetrically substituted vinyltriazenes, *e.g.* 3-(1-phenyl-2,2-di-*p*-tolylvinyl)-1-phenyltriazene decomposes in acetic acid at

[61] (*a*) V. Y. Andakushkin, B. A. Dolgoplosk, and I. I. Radchenko, *Zhur. obshchei Khim.*, 1956, **26**, 2972 (*Chem. Abs.*, 1957, **51**, 8674a); (*b*) V. H. Oelschlager and H. Blume, *Arzneim. Forsch.*, 1976, **26**, 303.

[62] V. Zverina, M. Remes, J. Divis, J. Marhold, and M. Matrka, *Coll. Czech. Chem. Comm.*, 1973, **38**, 251.

[63] V. S. Sukhinin and A. P. Kozlov. *Zhur. obshchei Khim.*, 1975, **45**, 145. (*Chem. Abs.*, 1975, **82**, 97332p).

room temperature in a matter of seconds giving a 20% yield of the rearranged decomposition product 2-phenyl-1,2-di-*p*-tolylvinyl acetate.[64] Recent studies by Lee and Ko[10] with ^{14}C labelled vinyltriazenes have shown that about 38% scrambling of the label, attributable to 1,2-anisyl shifts, can occur but that analogous 1,2-phenyl shift does not operate. Triazenes of type (13b) do not degrade in acid to give carbonium ions but instead give stable diazoacetates [path (iib), Scheme 3], *e.g.* $N_2CH_2CO_2Et$;[32] this reaction is also base-catalysed.[33]

(ii) *Reaction with Lewis Acids.* Monoalkyltriazenes degrade when in contact with Lewis Acids; consequently, purification by standard chromatographic methods is not always possible. The reaction of 1-phenyl-3-alkyltriazenes with aluminium trihalides in benzene affords *N*-alkylanilines, with nitrogen evolution, together with alkylbenzenes from alkylation of the solvent,[65] whereas the esters (6a) decomposed over alumina in benzene, to give the primary arylamine (o-$RO_2C.C_6H_4NH_2$) in almost 80% yield.[22] The facility with which the esters (6a) convert to the arylamine is possibly a consequence of the preference of these triazenes to exist as the unconjugated tautomer (ArNH.N=NR).[53] The specific involvement of this tautomeric form is also implicated by the products observed when triazene decomposition is initiated by silica gel in benzene.[66] These authors favour a carbonium-ion pair mechanism [equation (4)] on grounds that:

$$ArNH.N{=}N{-}R \longrightarrow \underset{\downarrow}{Ar\bar{N}H} + \bar{N}_2R \longrightarrow \underset{\text{(ion pair)}}{Ar\bar{N}H.R^-} + N_2 \qquad (4)$$
$$\downarrow$$
$$ArNH_2\,(61\%) \qquad ArNHR\,(36\%)$$

(*a*) R migrates to N with retention of configuration;

(*b*) The reaction is intramolecular and no crossed products are formed;

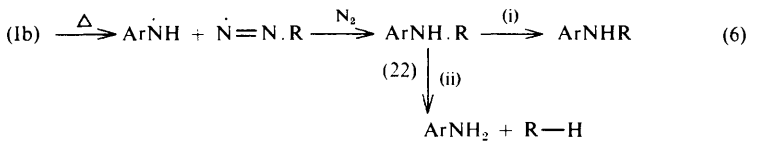
(*c*) The reaction is suppressed entirely in ethanol. Furthermore, analogous 1,3-diphenyl- and 3,3-dialkyltriazenes do not decompose under the same conditions, suggesting that the formation of tautomer (Ib) is essential for reaction to occur.

B. Thermolysis.—The formation of secondary amines in the reaction of diazomethane with primary amines[67] may well be the first reported example of thermal breakdown of a monoalkyltriazene; although this reaction has found little synthetic application, the possible intermediacy of a triazene in the conversion [equation (5)] has not been discounted.

$$CH_2N_2 + RNH_2 \longrightarrow [RNH{-}N{=}N{-}CH_3] \longrightarrow RNHCH_3 + N_2 \qquad (5)$$

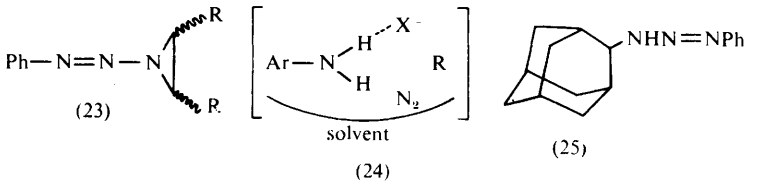
[64] W. M. Jones and F. W. Miller. *J. Amer. Chem. Soc.*, 1967, **89**, 1960.
[65] R. Kreher and K. Goth, *Z. Naturforsch.*, 1976, **31b**, 217.
[66] M. Kawanisi, I. Otani, and H. Nozacki, *Tetrahedron Letters*, 1968, 5575.
[67] L. I. Smith, *Chem. Rev.*, 1938, **23**, 202.

Cserhegyi *et al.*[68] followed the kinetics of the pyrolysis of 3-methyl-1-phenyltriazene in unlabelled and in tritiated cyclohexane by measurement of the CH_4:N_2 ratio in the gaseous products. Although a kinetic isotope effect was observed for hydrogen abstraction, no firm conclusions were apparent regarding the mechanism of the reaction. Recent ^1H- and ^{13}C-CIDNP investigations[54] of the thermolysis of 3-alkyl-1-*p*-tolyltriazenes at 125—135 °C have shown that although tautomer (Ia) is predominant in the tautomeric mixture, the major products ($ArNH_2$, ArNHR, and RH) arise from homolysis of tautomer (Ib) [equation (6)]:



(6)

The CIDNP results show polarization of the nuclei in $ArNH_2$, ArNHR, RH, and in minor products, in agreement with the formation of an intermediate arylaminyl–alkyl radical pair (22), which may collapse (i) to the cage recombination products, ArNHR and ring-alkylated anilines, or undergo H-abstraction (ii) to give the escape products, $ArNH_2$ and RH. Thermolysis of dialkyltriazenes, which cannot tautomerize to a form like (Ib), follows a different route; for example, thermal breakdown of the novel azo-aziridines (23) gives phenyl azide and alkenes, specifically with retention of configuration in the alkene.[69]



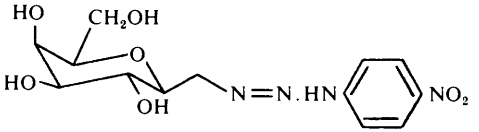
C. Deamination of Primary Amines.—Conventional methods for the deamination of primary aliphatic amines include the nitrous acid–amine reaction and the decomposition of nitrosoamides. The use of triazenes as intermediates in deamination, which is a consequence of the facile degradation of monoalkyltriazenes discussed earlier, has been recognized for some time[30,70] and has been used with sufficient frequency to be regarded now as almost conventional. The triazene method is useful for the conversion of amines into esters, alkyl halides, ethers and related derivatives, and yields are usually superior to other methods.

Although the triazene method of deamination leads to considerable racemization in the product RX, suggesting that the carbonium ion mechanism

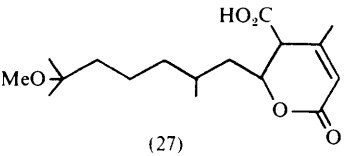
[68] A. Cserhegyi, G. Szentgyorggyi, and O. Bobis, *Magy. Kem. Foly.*, 1971, **77**, 607 (*Chem. Abs.*, 1972, **76**, 71793r).
[69] R. E. Clark and R. D. Clark, *J. Org. Chem.*, 1977, **42**, 1136.
[70] E. H. White and H. Scherrer, *Tetrahedron Letters*, 1961, 758.

(Scheme 3, path iia) is dominant, later studies by White *et al.*[71] showed that the carbonium ion could be intercepted by the arylamine. The arylamine substitution products, *e.g.* $RNHC_6H_4Y$ and $NH_2C_6H_3YR$, retain configuration in the R-group which suggests that the carbonium ion is formed in the same solvent cage with the counterion and the aromatic amine, *i.e.* [24; R = $-\dot{C}H(CH_3)Ph$], related to that proposed for the nitrosoamide decomposition.[72]

The triazene method does offer some advantage over other methods of deamination. For example, Storesund and Whiting[73] were unable to prepare the nitrosoamide derived from 2-amino-adamantane. However, the related triazene (25), although unstable when crystalline, could be obtained with difficulty and was used to study the acetolysis of the 2-adamantyl group. Similarly *cis*- and *trans*-4-*t*-butylcyclohexyltriazenes were used in the deamination of cyclohexylamines in order to study the derived carbonium ions.[18] A more exotic application of the method is the use of the β-D-galactopyranosylmethyl-*p*-nitrophenyl-triazene (26) to generate 'hot' carbonium ions which can act as 'affinity labels' in blocking the active site of liganding enzymes (in particular *E. coli* β-galactosidase).[20]



(26)



(27)

$HO(CH_2)_2CH(NHCO_2CMe_3)CO_2CH_2Ph$

(28)

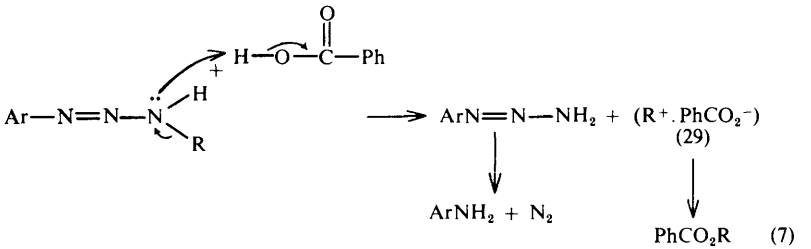
D. Esterification.—By virtue of the facility with which monoalkyltriazenes release the alkyl fragment, alkylation of organic species is perhaps their most important synthetic function. In particular, the esterification of carboxylic acids has been applied to derivitization of benzoic acids,[12] fatty acids,[74] insect hormone derivatives [(*e.g.* (27)],[75] bilirubin,[76] pyrrole carboxylic acids,[77] *N*-blocked α-amino acids,[78] polymethacrylic acid,[79] and other polymeric carboxylic acids.[80] The use of a monobenzyltriazene for the synthesis of an *N*-blocked homoserine benzyl ester (28) was found[78] to be the best compromise to overcome the

[71] E. H. White, H. Maskill, D. J. Woodcock, and M. A. Schroeder, *Tetrahedron Letters*, 1969, 1713.
[72] E. H. White and C. Aufdermarsh, *J. Amer. Chem. Soc.*, 1961, **83**, 1179.
[73] H. J. Storesund and M. C. Whiting, *J.C.S. Perkin II*, 1975, 1452.
[74] C. A. Henrick, U.S. P. 3873586. (*Chem. Abs.*, 1975, **82**, 170098y).
[75] C. A. Henrick, W. E. Willy, J. W. Baum, T. A. Baer, B. A. Garcia, T. A. Mastre, and S. M. Chang, *J. Org. Chem.*, 1975, **40**, 1.
[76] D. W. Hutchinson, B. Johnson, and A. J. Knell, *Biochem. J.*, 1973, **133**, 493.
[77] E. Campaigne and G. M. Shutske, *J. Heterocyclic Chem.*, 1975, **12**, 67.
[78] T. Fickel and C. Gilvarg, *J. Org. Chem.*, 1973, **38**, 1421.
[79] R. Blumstein, G. J. Murphy, A. Blumstein, and A. C. Watterson, *J. Polymer. Sci., Polymer Letters Edn.*, 1973, **11**, 21.
[80] L. H. Cohen, *J. Polymer Sci., Polymer Letters Edn.*, 1976, **14**, 7.

problems of the interfering lactonization of *N*-blocked homoserine in acid media and of the benzyl ester in the presence of base. However the aromatic amine, which is a by-product of esterification by triazenes, can induce base-catalysed lactonization and the neutral conditions employed in the triazene method do not entirely eliminate cyclization.

Application of the triazene method to the esterification of polymethacrylic acid[79] eliminated the possibility of polyethylene contamination, thus leaving the polymer tactility unchanged. Other advantages of this method, compared to the conventional method using diazomethane, were seen to be: (*a*) the triazenes are non-explosive under the conditions used; (*b*) they are readily available (some commercially), are reasonably stable and do not have to be freshly prepared (*cf.* diazomethane), and (*c*) the triazene method is faster. However the advantages of monoalkyltriazenes must be weighed against their potent carcinogenic activity (see Section 5). Moreover, comparisons of the triazene method with other alkylation procedures are not always favourable.[80]

A kinetic study of the reactions of a series of 3-alkyl-1-aryltriazenes with benzoic acids supports a mechanism in which proton transfer and departure of an alkyl cation are rate determining and synchronous [equation (7)].[52]



(7)

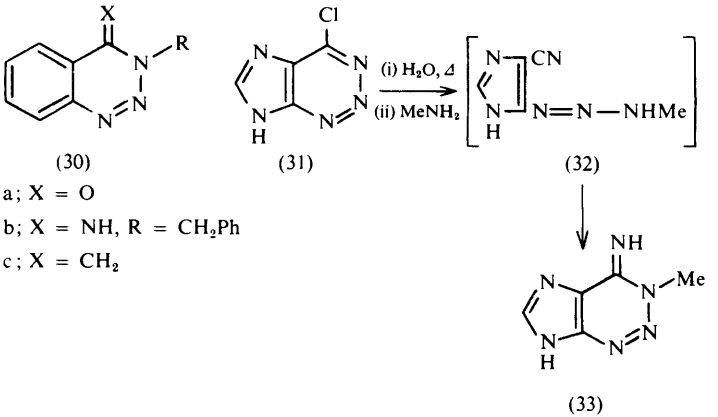
The occurrence of Wagner–Meerwein rearrangements, the extent of which were dependent on solvent polarity, in all cases examined, supported the carbonium ion-carboxylate ion-pair (29) hypothesis, whereas White *et al.*[71] dismissed the suggestion of intimate carbonium ion-carboxylate ion-pairs on the basis of stereochemical studies (see earlier discussion, Section 4-C). Clearly there is an unresolved contradiction here, which may have arisen because of the different solvents employed.

Alkylation of other organic functional groups by triazenes has not been so thoroughly studied. Succinimide and phenols are methylated by monomethyltriazenes, but the alkylation of alcohols and mercaptans requires aluminium alcoholate catalysis.[81] Evidently, alkylation by monoalkyltriazenes requires acid catalysis, but further studies appear to be necessary in this area.

[81] V. Ya. Pochinok and L. P. Limarenko, *Ukrain. khim. Zhur.*, 1955, **21**, 496. (*Chem. Abs.*, 1956, **50**, 5549i); V. Ya. Pochinok and O. I. Shevchenko, *Ukrain. khim. Zhur.*, 1954, **20**, 289. (*Chem. Abs.*, 1956, **50**, 272e).

E. Cyclization Reactions.—Although monoalkyltriazenes possess the necessary structural requirement to act as precursors for cyclic 1,2,3-triazines, there are no reported examples of the conversion of a monoalkyltriazene to a monocyclic triazine. However the synthesis of 1,2,3-benzotriazine derivatives from *ortho*-substituted 3-alkyl-1-aryltriazenes (6) is well documented and quite versatile. Although the *o*-alkoxycarbonyl derivatives (6a) can be isolated,[22,82] cyclization of these esters to benzotriazinones (30a) is extremely facile and is sometimes observed spontaneously.[60,83] The conversion (6a)→(30a) is catalysed by protic media or by alumina in organic solvents. Cyclization of the *o*-acetylphenyltriazenes (6c) is also catalysed by alumina and affords 4-methylene-benzotriazines (30c).[84]

Whereas many 1-(*o*-cyanophenyl)-3-aryltriazenes undergo cyclization to 4-iminobenzotriazines,[85] the only unequivocal example of a monoalkyltriazene undergoing such cyclization is that of the benzyl derivative (6b) which produces the unusually stable 4-imino-3-alkylbenzotriazine (30b).[23] The analogous monomethyltriazenoimidazole (32) is possibly an intermediate in the conversion of the chlorotriazine (31) to the iminotriazine (33) by the successive action of water and methylamine.[86]



(30)
a; X = O
b; X = NH, R = CH_2Ph
c; X = CH_2

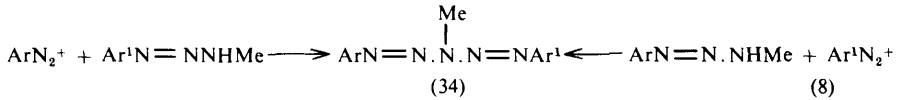
(31)

(32)

(33)

F. Nucleophilic Properties.—The nucleophilic character of a monoalkyltriazene is at once evident from the fact that formation of penta-azadienes often accompanies triazene formation during *N*-diazo coupling. Indeed, Dimroth[87] showed that the same unsymmetrical penta-azadiene (34) arises from two different coupling reactions of diazonium salt with monomethyltriazene [equation (8)]:

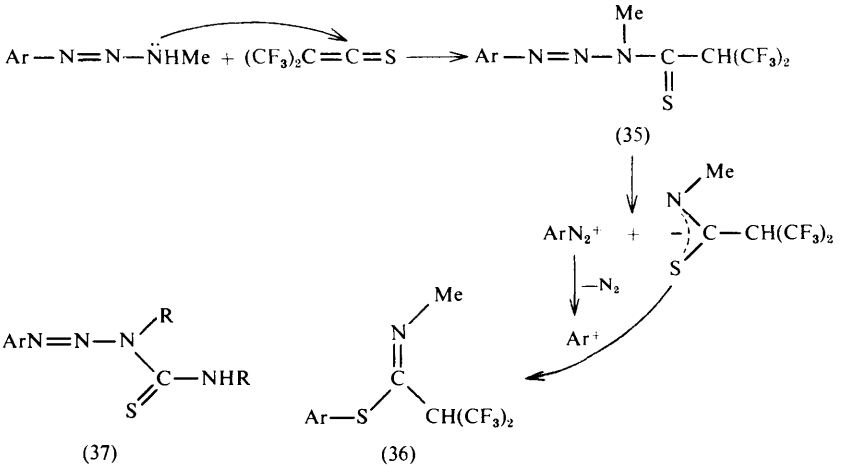
[82] W. F. Gilmore and R. N. Clark, *J. Heterocyclic Chem.*, 1969, **6**, 809.
[83] E. van Heyningen, *J. Amer. Chem. Soc.*, 1955, **77**, 6562.
[84] H. Fong and K. Vaughan, *Canad. J. Chem.*, 1975, **53**, 3714.
[85] M. S. S. Siddiqui and M. F. G. Stevens, *J.C.S. Perkin I*, 1974, 609.
[86] V. S. Mokrushin, V. I. Ofitserov, T. V. Rapakova, A. G. Tsaur, and Z. V. Pushkareva, *Khim. geterotsikl. Soedinenii*, 1976, 556. (*Chem. Abs.*, 1976, **85**, 46590a).
[87] O. Dimroth, *Ber.*, 1907, **40**, 2390.



(34) (8)

Significantly, diazo-coupling occurs at the *N*-atom adjacent to the methyl, not the aryl, group. The greater nucleophilicity of N-3 is also evident during acetylation with acetic anhydride, which affords 3-acyl derivatives.[88]

Recent studies reinforce these observations. Reaction of 3-methyl-1-*p*-tolyltriazene with thioketenes affords the *S*-aryl thioimide (36), *via* the thioacylated triazene (35)[89] (Scheme 4; Ar = *p*-MeC_6H_4). An analogous reaction takes place when a thioketene is treated with a diaryltriazene but not with 1-aryl-3,3-dimethyltriazenes, which instead induce dimerization of the thioketene. Although the thioacyl triazene (35) is not stable, the analogous reaction of monoalkyltriazene with isothiocyanates affords stable *N*-arylazothioureas (37), which have useful miticidal properties.[90]



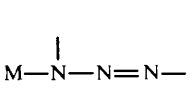
(37) (36)

Scheme 4

G. Complex Formation.—The nucleophilic character of triazenes lends itself well to the formation of triazenido-metal bonds, which offer a variety of bonding arrangements in transition metal (M) complexes. Three fundamental co-ordination modes have been identified. Although the monodentate mode (38) has been disputed, two instances of complex formation by diaryltriazenes with platinum[91]

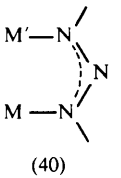
[88] O. Dimroth, *Ber.*, 1905, **38**, 670.
[89] M. S. Raasch, *J. Org. Chem.*, 1972, **37**, 1347.
[90] S. Kano, E. Takeuchi, T. Noguchi, and M. Asada, Jap. P. 74/28188. (*Chem. Abs.*, 1975, **82**, 155909r).
[91] L. D. Brown and J. A. Ibers, *J. Amer. Chem. Soc.*, 1976, **98**, 1957.

and palladium[92] in this mode have been verified by *X*-ray analysis. The bidentate mode of complexation (chelation) (39) occurs more commonly, as in the ruthenium[91] and cobalt[93] complexes of 1,3-diphenyltriazene. The third type of triazene complex (40) has the triazenido-group acting as a bridging ligand between two metal atoms, which are sometimes bonded to each other; this mode has been characterized for complexes of 1,3-dimethyltriazene with rhodium/copper[94] and for diaryltriazenes with copper[95] and palladium.[96]



(38)

(39)



(40)

Not all of these co-ordination modes have been observed in complexes of monoalkyltriazenes. Chelation of molybdenum and tungsten by 1-(*p*-chlorophenyl)-3-iso-propyltriazene has been reported,[97] and these complexes were unusual in being non-fluxional, unlike diaryl complexes. 3-Methyl-1-*p*-tolyltriazene serves as a bridging ligand in complexes with silver/rhodium, silver/indium, and mercury/iridium.[98] Complexes of 3-t-butyl-1-aryltriazenes with Ag^{I}, Hg^{I}, Hg^{II}, and Cu^{II} are known,[99] but their structures have not been defined. The *in situ* formation of an aluminium complex of 3-methyl-1-phenyltriazene has been reported,[100] but this 'complex' may be simply a salt of Al^{3+}. The monodentate mode of complex formation has not been observed for monoalkyltriazenes.

5 The Role of Monoalkyltriazenes in the Metabolism of Anti-tumour Dialkyltriazenes

Monoalkyltriazenes are cytotoxic agents and have carcinogenic,[101] mutagenic,[102] teratogenic,[103] anti-fungal,[104] and anti-tumour activity.[105] The intense interest in

[92] G. Bombieri, A. Immirzi, and L. Toniolo, *Inorg. Chem.*, 1976, **15**, 2428.
[93] M. Corbett and B. F. Hoskins, *Chem. Comm.*, 1968, 1602.
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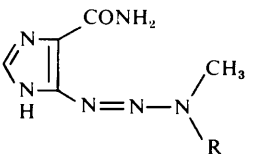
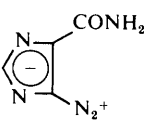
these triazenes revolves around their (possible) role as the active metabolites and proximate carcinogens of the anti-tumour 3,3-dialkyltriazenes and interpretation of their mode of action offers a challenge to the chemist interested in reactive chemical species. Anti-tumour activity in dimethyltriazenes was first reported more than twenty years ago,[106] but their clinical use originated from the search for inhibitors of *de novo* purine synthesis.[107,108] 5-(3,3-Dimethyl-1-triazeno)imidazole-4-carboxamide (DTIC; 'Dacarbazine®') (41a), a product of this search, is clinically useful in the treatment of malignant melanoma.[109]

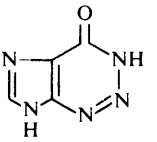
It has been suggested that DTIC is a stabilized form of Diazo-IC (42) and that the diazo derivative is liberated in target cells.[110] The inhibitory activity of DTIC against bacterial systems[111] and against Chinese hamster ovary cells and malignant melanoma cells in culture[112–114] is certainly enhanced in the presence of light which transforms DTIC to Diazo-IC and thence to 2-azahypoxanthine (43). The comparative biological activities of these three imidazole derivatives have been reviewed.[115] However, simple 3,3-dialkyl-1-aryltriazenes (44) not bearing an imidazole moeity are equally effective as DTIC as anti-tumour agents. The diazonium ions derived from these compounds are not always active[116] although



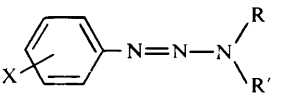
(41) a; R = Me (DTIC)
b; R = H (MTIC)



(42)



(43)



(44) a; R = R′ = Me
b; R = Me, R′ = Et
c; R = R′ = Et
d; R = Me, R′ = Bu^{t}

[106] D. A. Clarke, R. K. Barclay, C. C. Stock, and C. S. Rondestvedt. *Proc. Soc. Exp. Biol. Med.*, 1955, **90**, 484.
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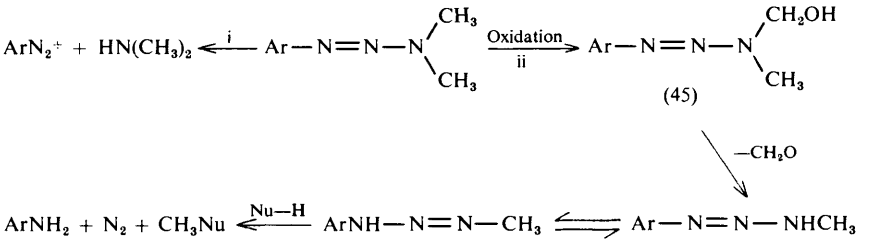
this has been attributed to unfavourable transport characteristics of the diazonium compounds.[117]

The recognition of a correlation between the rate of hydrolysis of dimethyltriazenes and the ability to induce local tumours at the site of administration,[118] lends support to the hypothesis that triazenes may be transport forms of reactive diazonium species [Scheme 5, route (i)].



Scheme 5

Set against these results, there is now compelling evidence that an alternative mechanism—enzymic activation—is responsible for the systemic carcinogenic activity and, possibly, anti-tumour activity of dialkyltriazenes, and that alkylating metabolites formed following oxidative *N*-dealkylation are the bioactive species [Scheme 5, route (ii)].

Considerable support for this hypothesis has been obtained from experiments with isotopically labelled triazenes. Thus incorporation of radioactivity in the DNA of human melanoma cells was observed after incubation with DTIC labelled with ^{14}C at the side-chain methyl groups.[119] The primary site of methylation has been identified as N-7 of guanine residues from *in vivo* studies with labelled DTIC in man and 1-phenyl-3,3-[^{14}C]-dimethyltriazene in rats,[120] *in vitro* alkylation of nucleic acids and nucleotides by phenylmonomethyltriazene,[121] and by *in vitro* treatment of calf-thymus DNA with tritium-labelled MTIC (41b), the proposed active metabolite of DTIC.[122] In the latter case, however, less than 0.5% of the added ^{3}H was recovered in DNA because most of the tritiated MTIC was hydrolysed rapidly in the aqueous medium to form methanol, which contained 96% of the added label. It is also significant that MTIC inhibits DNA and protein synthesis in cultures of Novikoff hepatoma cells.[123] The [*Me*-$^{2}H_3$]-guanine isolated after incubation of [*Me*-$^{2}H_3$]-MTIC with calf thymus DNA *in vitro* displayed (chemical ionization mass spectrometry) a quasi-molecular ion (MH^+) at *m/e* 169 which was three mass units higher than the comparable

[117] W. J. Dunn, M. J. Greenberg, and S. S. Callejas, *J. Medicin. Chem.*, 1976, **19**, 1299.
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ion for an undeuterated sample of 7-methylguanine; major fragment ions also occurred at m/e values three mass units higher than fragment ions in the standard. These important observations confirm that methylation of biological macromolecules by MTIC must involve the transfer of an *intact* methyl group and exclude the involvement of diazomethane (or methylene).[124]

As a consequence of the methylating reaction of MTIC the imidazole fragment is liberated as the primary amine 5-aminoimidazole-4-carboxamide.[125,126]

Although many of the biological effects of DTIC can be satisfactorily accounted for by invoking an MTIC intermediate[127] monomethyltriazenes are, in general, no better as anti-tumour agents than their dimethyl counterparts. This is due to the greater toxicity and shorter biological half-life of the monomethyltriazenes:[128] direct administration of the monomethyltriazene is less effective than using the dimethyltriazene because the latter serves as a stabilized slow-release ('prodrug') form of the active metabolite. A monomethyltriazene (p-$CH_3SO_2.C_6H_4N{=}N.NHMe$) with a relatively long half-life has comparable anti-tumour activity to that of its dimethyl homologue.[128]

A classical study by Connors and his co-workers on structure-activity relationships for the dialkyltriazenes (44), with variations in X, R, and R′, suggested that only chemicals which can be converted enzymatically to a monomethyltriazene have anti-tumour properties.[116,128] Thus the methyl-ethyl analogue (44b) is active because de-ethylation is preferred to demethylation and the active monomethyltriazene is formed. Although the diethyl analogue (44c) is dealkylated as readily as the dimethyl (44a), the former is inactive, clearly because it cannot metabolize to monomethyltriazene. Mixed methylalkyltriazenes are active only if the higher alkyl group can suffer α-hydroxylation and removal to leave the monomethyltriazene; this cannot occur with the t-butylmethyltriazene (44d) since the higher alkyl group has no α-hydrogen and the compound is preferentially demethylated by liver microsomes to give the mono-t-butyltriazene.

Even though the methylating activity of monomethyltriazenes is conceded, the mechanism by which they methylate components of DNA is still obscure. From chemical studies (Section 4-D) it is apparent that monomethyltriazenes alkylate acidic sites more effectively and that acid catalysis is often necessary. Significantly the *in vitro* alkylation of guanosine by phenylmonoalkyltriazenes requires catalysis by acetic acid.[121] What is certain is that a *free methylcarbonium ion* cannot be involved in the process although this has been repeatedly claimed in the literature. Apart from strictly chemical objections to such a fugitive intermediate, there is no possibility that such a reactive species could

[124] H. T. Nagasawa, F. N. Shirota, and N. S. Mizuno, *Chem.-Biol. Interactions*, 1974, **8**, 403.
[125] J. L. Skibba, D. D. Beal, G. Ramirez, and G. T. Bryan, *Cancer Research*, 1970, **30**, 147.
[126] N. S. Mizuno and E. W. Humphrey, *Cancer Chemother. Rep.*, Part 1, 1972, **56**, 465. (*Chem. Abs.*, 1973, **78**, 11411w).
[127] N. S. Mizuno, R. W. Decker, and B. Zakis, *Biochem. Pharmacol.*, 1975, **24**, 615.
[128] T. A. Connors, P. M. Goddard, K. Merai, W. C. J. Ross, and D. E. V. Wilman, *Biochem. Pharmacol.*, 1976, **25**, 241.

achieve the necessary biological selectivity. Furthermore the methylation hypothesis of anti-tumour activity can be criticized on other grounds:

(i) The hypothesis does not explain why dimethyltriazenes are selectively cytotoxic *in vivo* (*i.e.* after metabolism to a monomethyltriazene) to a tumour cell line (TLX5 lymphoma) which has natural resistance to classical alkylating agents such as cyclophosphamide.[129]

(ii) Diethyltriazenes are not anti-tumour agents despite the fact that they are metabolized to monoethyltriazenes which have alkylating capability.[121,128]

It is possible that the methylating activity of monomethyltriazenes is responsible for their carcinogenic properties and general cytotoxicity, and that different reactive metabolites are involved in *selective* anti-tumour action: the hydroxymethyltriazenes (45) are obvious candidates since oxidative metabolic demethylation of dimethylamino compounds generally is known to proceed *via* hydroxymethyl intermediates.[130] Studies of the time course of oxidative *N*-demethylation of DTIC and dimethyltriazenes showed that the process levels off within five minutes of incubation and indicated the occurrence of concomitant metabolic conversion to compounds other than monomethyltriazenes.[131] Traces of water soluble triazenes tentatively identified as conjugates of 3-hydroxymethyl-3-methyl-1-phenyltriazene (45; Ar = Ph) have been isolated from the urine of rats treated with 3,3-dimethyl-1-phenyltriazene.[132,133] When DTIC was administered intravenously to man 43% of the dose was recovered unchanged in the urine after 6 hours. One unidentified metabolite which gave a positive Bratton–Marshall test (*i.e.* contained an intact triazene linkage) was detected in trace amounts.[134] Possibly this metabolite is a hydroxymethyltriazene or a conjugate thereof.

Future synthetic studies in the triazene field might be aimed at the synthesis of hydroxymethyltriazenes of type (45). It is possible that such compounds may be more stable than hitherto assumed, and have interesting biological properties.

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[133] G. F. Kolar, *Xenobiotica*, 1977, **7**, 100.
[134] Ti Li Loo, J. K. Luce, J. H. Jardine, and E. Frei, *Cancer Research*, 1968, **28**, 2448.