Triazines and Related Products. Part 19.[1] 4-Amino-2-[2-(piperidin-1-ylazo)phenyl]quinazoline and its Analogues

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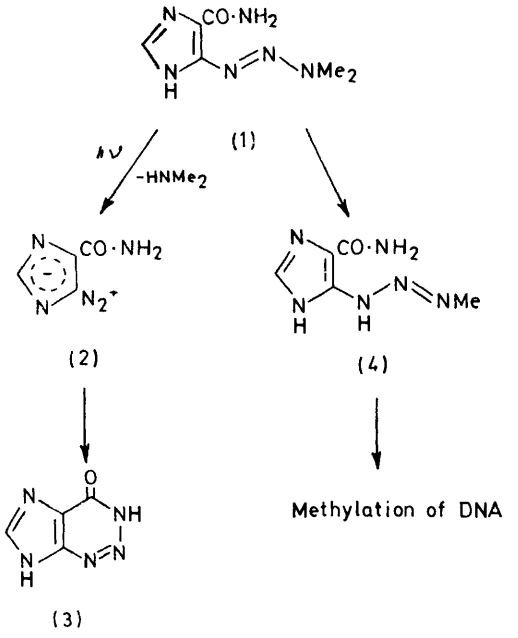
The reactions of anthranilonitrile and 5-bromoanthranilonitrile with sodium hydride in dimethyl sulphoxide yield 4-amino-2-(2-aminophenyl)quinazoline (7) and its dibromo-analogue (8), respectively. Nitrosation of the diamines affords unstable diazonium salts which cyclise to either quinazolino[3,2-*c*]- or quinazolino[1,2-*c*]-[1,2,3]benzotriazines. These tetracyclic triazines readily undergo ring opening in the presence of secondary-amines to form the title compounds. 1,3-Bis-(2-cyano-4-bromophenyl)triazene (12) is smoothly transformed into dibromoquinazolines (18) in boiling secondary amines.

4-Amino-2-[2-(piperidin-1-ylazo)phenyl]quinazoline (17a) behaves as a masked diazonium compound and decomposes in mineral acids, in acetic acid containing copper-bronze, in hot ethylene glycol, on photolysis in methanol or ethanol, or on reduction. The triazene linkage of (17a) is resistant to alcoholic potassium hydroxide but the 4-aminoquinazoline nucleus is hydrolysed to the corresponding quinazolin-4(3*H*)-one system. Methylation of (17a) with methyl iodide in tetrahydrofuran affords an N(1) methiodide (29) which is hydrolysed to the corresponding 1-methylquinazolin-4(1*H*)-one (30) in aqueous alkali. The unusual properties of this and other 1-methylquinazolin-4(1*H*)-ones can be attributed to their dipolar character. This renders the 1-methyl group liable to removal in acidic conditions.

5-(3,3-DIMETHYLTRIAZEN-1-YL)IMIDAZOLE-4-CARBOXAMIDE (1) (DTIC) is used in the treatment of human malignant melanoma,[2] although its mode of action is imperfectly understood. In light DTIC dissociates to give dimethylamine and the diazoimidazole (2),[3] which cyclises irreversibly to the imidazotriazinone (3) (Scheme 1). These latter two derivatives possess a wide range of biological activities,[4] but are probably not involved in the tumour-inhibitory process. *In vivo* (in the dark) DTIC is metabolised by oxidative demethylation in the liver [5] to generate the reactive monomethyltriazene (4) (MIC), which can methylate nucleic acid components, notably N(7) of guanine.[6]



SCHEME 1

The structurally related piperidinylazophenylquinazoline (17a) and the pyrrolidinyl- and morpholinyl-analogues (17b and c) are inhibitory towards human epidermoid carcinoma cells in tissue culture.[7] We have prepared a range of related derivatives, and examined their chemistry in an effort to gain an insight into their mode of action.

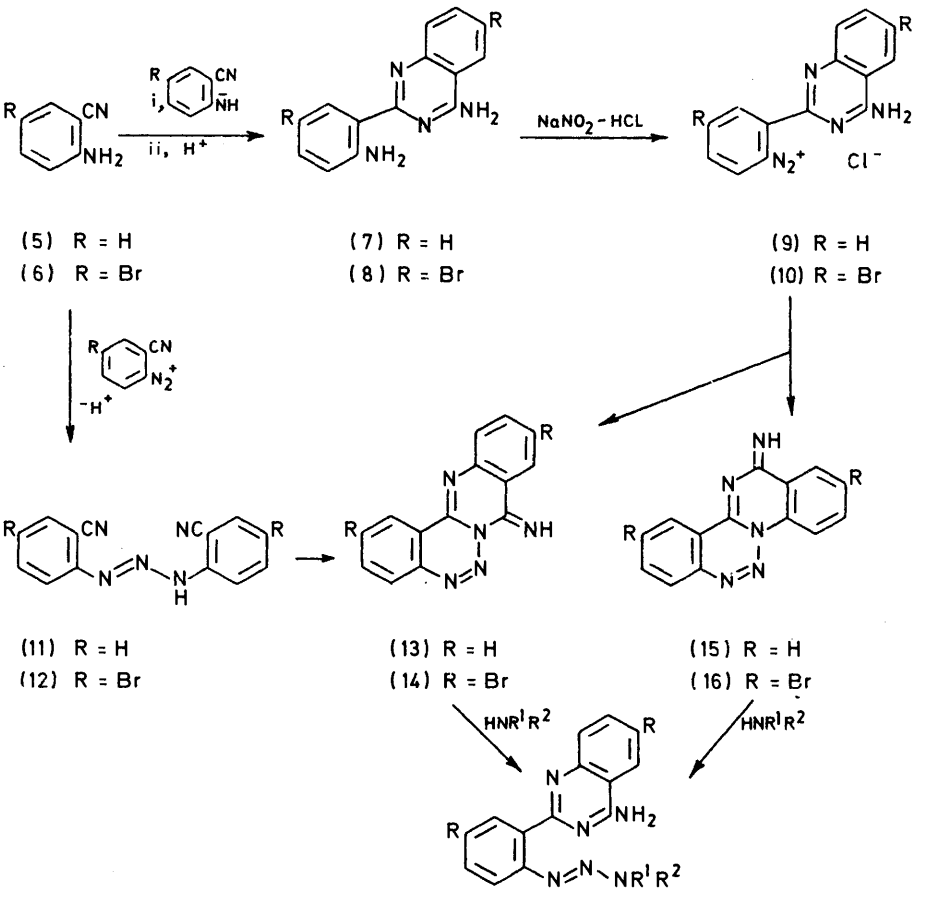
Two efficient routes are available for the synthesis of the title compounds, both starting from anthranilonitriles (Scheme 2). High yields of amidines can be obtained by reactions of nitriles with the anions of amines in dimethyl sulphoxide.[8] When anthranilonitrile (5) and its 5-bromo-derivative (6) were treated with sodium hydride in dimethyl sulphoxide the diaminoquinazolines (7) and (8), respectively, were isolated in near quantitative yields: in these special cases the intermediate amidines (which were not isolated) undergo a second intramolecular amine–nitrile addition in the anticipated manner.[9] Diazotisation of the diamine (7) in 2N-hydrochloric acid afforded an unstable diazonium chloride (9) ($\nu_{max.}$ 2 250 cm^{-1}), which cyclised on attempted crystallisation, or on basification, to a tetracyclic triazine. This triazine has been previously assigned structure (13) [10] on the basis of a similar preference for cyclisation at the quinazoline N(3) atom in the reactions of other 2-(2-aminophenyl)quinazolines with carbon-inserting reagents: [11] the isomeric structure (15) has not been rigorously excluded, however, and there seems no obvious way to distinguish between these isomers. The question of the structure of this product

[1] Part 18, A. Gescher, M. F. G. Stevens, and C. P. Turnbull, preceding paper.
[2] S. K. Carter and M. A. Friedman, *European J. Cancer*, 1972, **8**, 85.
[3] Y. F. Shealy, C. A. Krauth, S. J. Clayton, A. T. Shortnacy, and W. R. Laster, *J. Pharm. Sci.*, 1968, **57**, 1562.
[4] M. F. G. Stevens, *Progr. Medicin. Chem.*, in the press.
[5] J. K. Skibba, D. D. Beal, G. Ramirez, and G. T. Bryan, *Cancer Res.*, 1970, **30**, 147.
[6] H. T. Nagasawa, F. N. Shirota, and N. S. Mizuno, *Chem.-Biol. Interactions*, 1974, **8**, 403.
[7] M. F. G. Stevens, unpublished results.
[8] B. Singh and J. C. Collins, *Chem. Comm.*, 1971, 498.
[9] E. C. Taylor and A. McKillop, 'The Chemistry of Cyclic Enaminonitriles and *o*-Aminonitriles,' Interscience, New York, 1970, p. 233.
[10] M. F. G. Stevens, *J. Chem. Soc.* (*C*), 1967, 1096.
[11] M. W. Partridge, S. A. Slorach, and H. J. Vipond, *J. Chem. Soc.*, 1964, 3670.

must remain open, particularly as the quinazoline (17a) undergoes methylation at N(1) (see later).

Diazotisation of the dibromoquinazoline (8) in 6N-hydrochloric acid gave a stable diazonium chloride (10) which, surprisingly, could be crystallised unchanged from 6N-hydrochloric acid. Subsequent crystallisation from ether–methanol led to cyclisation and the isolation of a hydrochloride salt of the tetracyclic triazine (14), or (less likely) the isomer (16). Cyclisation of (10) was accompanied by the disappearance of the diazo i.r. band at 2 260 cm^{-1}.

Triazine (13) is implicated as an intermediate in many of the reactions of 1,3-bis-*o*-cyanophenyltriazene (11).[12,13] For example, the reaction of (11) with piperidine, pyrrolidine and morpholine yields the piperidinyl-, pyrrolidinyl-, and morpholinyl-azophenylquinazolines (17a—c), respectively.[13] This synthesis has in the present work been extended to further examples in the series (17d—h). Yields are near quantitative with all



(5) R = H
(6) R = Br

(7) R = H
(8) R = Br

(9) R = H
(10) R = Br

(11) R = H
(12) R = Br

(13) R = H
(14) R = Br

(15) R = H
(16) R = Br

	R	R^1	R^2
(17) a;	H	$[CH_2]_5$	
b;	H	$[CH_2]_4$	
c;	H	$[CH_2]_2 \cdot O \cdot [CH_2]_2$	
d;	H	$CHMe \cdot [CH_2]_4$	
e;	H	$CH_2 \cdot CHMe \cdot [CH_2]_3$	
f;	H	$[CH_2]_2 \cdot CHMe \cdot [CH_2]_2$	
g;	H	$[CH_2]_6$	
h;	H	Me	Me

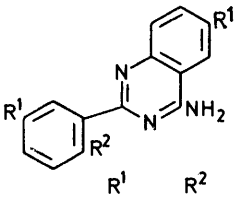
	R	R^1	R^2
(18) a;	Br	$[CH_2]_5$	
b;	Br	$[CH_2]_4$	
c;	Br	$[CH_2]_2 \cdot O \cdot [CH_2]_2$	
d;	Br	$CHMe \cdot [CH_2]_4$	
e;	Br	$CH_2 \cdot CHMe \cdot [CH_2]_3$	
f;	Br	$[CH_2]_2 \cdot CHMe \cdot [CH_2]_2$	

SCHEME 2

[12] H. N. E. Stevens and M. F. G. Stevens, *J. Chem. Soc.* (*C*), 1970, 765.
[13] M. F. G. Stevens, *J.C.S. Perkin I*, 1974, 615.

secondary amines examined with the exception of aziridine, which gave an intractable oil.

The dibromotriazene (12) was prepared by half-diazotisation of 5-bromoanthranilonitrile in a weakly acid medium and had all the expected properties: it decomposed in hot 70% ethanol to afford 4-amino-6-bromo-2-(3-bromophenyl)quinazoline (20); with ethanol containing hydrazine and Raney nickel it gave the diamine (8); with 2-naphthol in ethanol the azo dye (21) was produced. All these high-yielding conversions probably involve the intermediate tetracyclic triazine



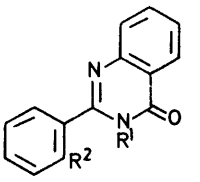
	R^1	R^2
(19)	H	H
(20)	Br	H
(21)	Br	2-hydroxy-1-naphthylazo

(14), and could be simply effected by employing this triazine as starting material. More important, the diaryltriazene (12) was smoothly transformed in boiling secondary amines into a series of triazenoquinazolines (18a—f) in high yields; selected examples of these derivatives were also prepared from the hydrochloride salt of the tetracyclic triazine (14).

No direct cleavage of the diaryltriazenes (11) and (12) was observed in their reactions with secondary amines. Similarly, 1,3-bis-*p*-nitro-, 1,3-bis-*p*-methyl-, and 1,3-bis-*p*-chloro-phenyltriazenes were unchanged after prolonged treatment in boiling piperidine or morpholine.

The reactions of the piperidinylazophenylquinazoline (17a) in acids all proceed with N–N bond cleavage. In 2N-hydrochloric acid (17a) cyclised to the hydrochloride salt of the tetracyclic triazine (13) [or its isomer (15)]. This salt was unstable and its synthesis and spectroscopic properties were sensitive to small changes in the reaction conditions. Its cyclic nature was confirmed by the absence of diazo i.r. absorption at 2 200—2 300 cm^{-1}. Treatment of (17a) with acetic acid followed by basification yielded the free base of (13). The dibromotriazene (18a) on the other hand in 6N-hydrochloric acid formed the diazonium chloride (10), identical with the product formed by diazotisation of the diamine (8) in 6N-hydrochloric acid. In boiling 4N-sulphuric acid the triazene (17a) decomposed extensively to yield 2-(2-hydroxyphenyl)quinazolin-4(3*H*)-one (23) in poor yield.

Although the triazene (17a) was stable in boiling ethanol in the dark, irradiation in methanol or ethanol afforded 4-amino-2-phenylquinazoline (19). This behaviour contrasts with the irradiation of DTIC, which gives the stable diazoimidazole (2).[3] In the present case the diazo intermediate presumably formed in the photolysis of (17a) cannot be stabilised by compensating ionisation of an acidic proton; instead, reductive



	R^1	R^2
(22)	H	H
(23)	H	OH
(24)	Me	H
(25)	H	piperidin-1-ylazo
(26)	H	pyrrolidin-1-ylazo
(27)	H	morpholin-4-ylazo
(28)	H	3,3-dimethyltriazen-1-yl

elimination of nitrogen occurs in the protic solvent. 4-Amino-2-phenylquinazoline (19) is also formed from the triazene (17a) in boiling ethylene glycol or by treatment with copper-bronze in acetic acid. Acetic acid is a particularly useful medium for promoting Sandmeyer-type displacements of nitrogen in 1,2,3-benzotriazines and triazenes.[1,14] Catalytic reduction of the piperidinylazophenylquinazolines (17a) and (18a) with Raney nickel and hydrazine in ethanol led to the diamines (7) and (8), respectively.

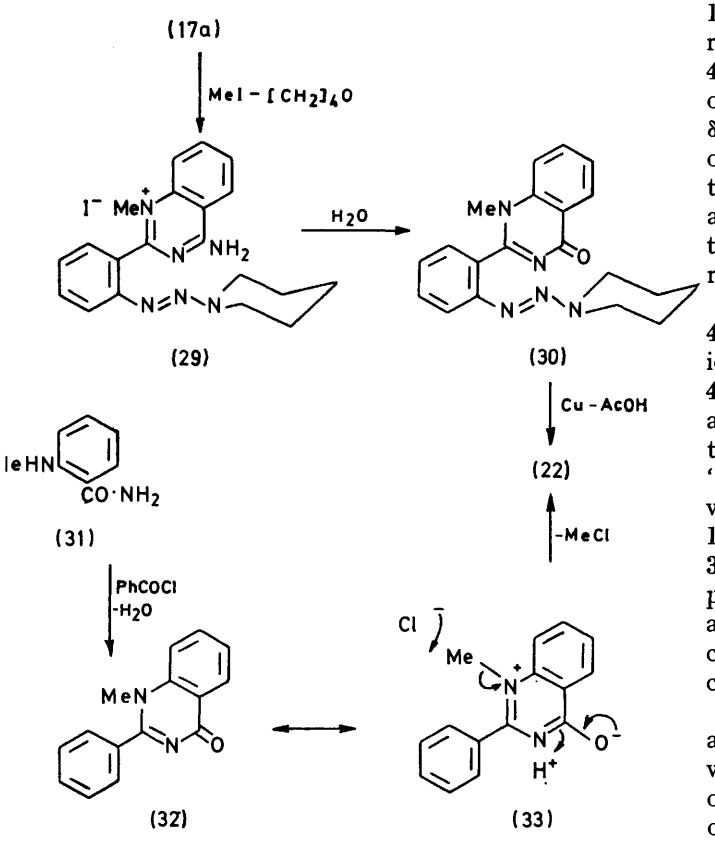
In complete contrast to the above observations the triazeno side-chains of the aminoquinazolines (17a—c and h) proved remarkably stable in 50% alcoholic potassium hydroxide—the products were the quinazolones (25)—(28), respectively. In boiling ethylene glycol or copper-bronze–acetic acid reductive elimination of the triazeno-fragment of the quinazolones (25)—(28) led to quantitative formation of 2-phenylquinazolin-4(3*H*)-one (22).

Methylation of compound (17a) with methyl iodide in tetrahydrofuran gave two products, both of which contained an intact NNN linkage (red colour with 2-naphthol in acetic acid).[15] One compound (15%) was the hydroiodide salt of the starting material; analysis

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

[15] J. G. Erickson, ' The 1,2,3-Triazines ' in ' The Chemistry of Heterocyclic Compounds,' ed. A. Weissberger, Interscience, New York, 1956, vol. 10, pp. 12, 21, 25.

of the other (80%) indicated incorporation of the elements of methyl iodide. Basification of this methiodide with aqueous alkali led to hydrolysis and the isolation of a methylated quinazolone—this excluded methylation on the exocyclic 4-amino-group of (17a). The available evidence points to structure (29) for the methiodide and (30) for the corresponding methylated



SCHEME 3

quinazolone, since with copper-bronze–acetic acid the methylquinazolone underwent both demethylation and reductive elimination of the triazeno-side-chain to yield 2-phenylquinazolin-4(3*H*)-one (22). (This unexpected result initially led us erroneously to position the methyl group on the piperidine N atom.) An explanation was forthcoming when we re-examined a purported synthesis of 1-methyl-2-phenylquinazolin-4(1*H*)-one (32).[16] The reaction of benzoyl chloride with *o*-methylaminobenzamide (31) in boiling *p*-cymene gave not the 1-methylquinazolone (32) as claimed, but the demethylated 2-phenylquinazolin-4(3*H*)-one (22). Other alkylated heterocycles with dipolar character [as in (33)] readily undergo dealkylation:[17] in the present case this would involve a chloride-ion-initiated loss of methyl chloride (Scheme 3). Similar dipolar character in the unstable methylated quinazolone (30) accounts for its reaction with copper–acetic acid where acetate anion can promote demethylation; under the reaction conditions the piperidinylazo fragment is also reductively eliminated. The spectroscopic features of the methylated quinazolone (30) also support the assigned structure. αβ-Unsaturation shifts the carbonyl absorption to low frequency (1 643 cm^{-1}), close to the value (1 635) recorded for 1-methylquinazolin-4(1*H*)-one.[18] This contrast with the range (1 665—1 680 cm^{-1}) observed with the quinazolin-4(3*H*)-ones (22) and (25)—(28). The ^1H n.m.r. spectrum of (30) in deuteriochloroform shows broad singlets at δ 1.5 and 3.45 for the piperidine protons, the latter overlying the methyl singlet. The aromatic region of the spectrum shows a low-field multiplet at δ 8.35 attributable to the *peri*-proton, H(5), with the rest of the aromatic protons absorbing as a multiplet in the range δ 7.1—7.8.

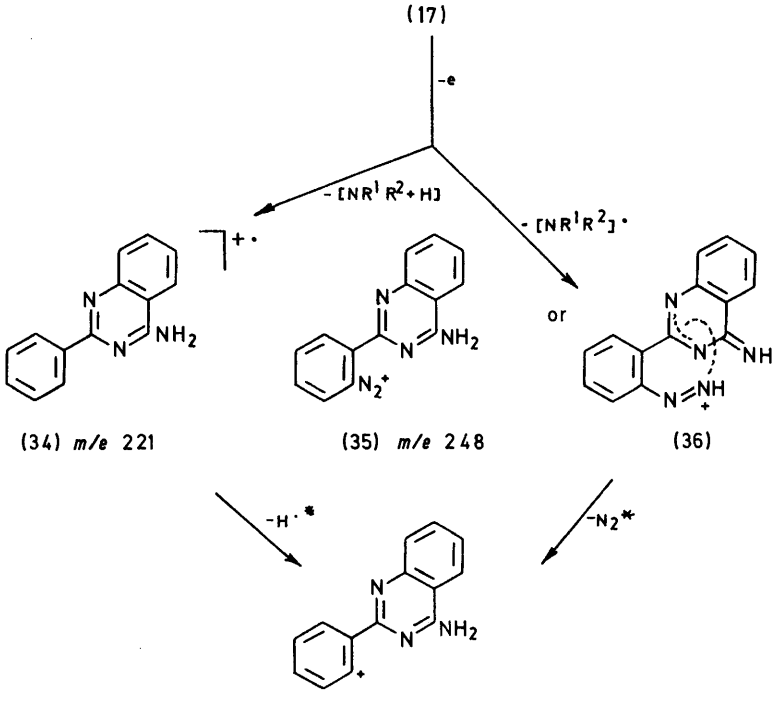
Two further reports support the above conclusions. 4-Aminoquinazoline is methylated at N(1) by methyl iodide [19] to afford the hydroiodide salt of 1,4-dihydro-4-imino-1-methylquinazoline; and the 1-methylquinazolone (32) is claimed [20] to rearrange thermally to the thermodynamically favoured 3-methyl isomer (24) by a '1,3-alkyl shift.' Unfortunately, in the latter paper it was not explained how a pure sample of the unstable 1-methyl isomer was obtained. A pure sample of the 3-methyl isomer (24) (ν_{CO} 1 670 cm^{-1}), prepared in the present work from benzoyl chloride and *N*-methylanthranilamide, was found to be stable under the conditions of its synthesis, and in boiling acetic acid containing copper-bronze.

The mass spectra of the isomeric methylpiperidinylazophenylquinazolines (17d—f) show features in common with those of the related derivatives (17a—c) [13] and other aryldialkyltriazenes.[21] The molecular ions are not observed and the most abundant peaks in all cases are derived from heteroalicyclic fragments (*m/e* 99 and 98). Of the aromatic ions those at *m/e* 221 and 220 are most important. The radical ion (34), *m/e* 221, is formed by cleavage of the triazene side-chain with H atom rearrangement, a reaction with a counterpart in the chemical reactions of this series. Alternative fragmentation of a methylpiperidinyl radical yields an unstable ion at *m/e* 248, which may be an acyclic diazonium ion (35) or a cyclic species (36): this loses nitrogen to form the arenium ion (37) at *m/e* 220, which may also be formed by H atom loss from the radical ion at *m/e* 221 (Scheme 4). The dimethyltriazene (17h) shows a very weak molecular ion (<1%) and significant ions at *m/e* 248 (55%), 221 (100), and 220 (86).

The spectrum of the related dimethyltriazenylquinazolone (28) also shows the features described above, but these are only minor pathways: instead, the

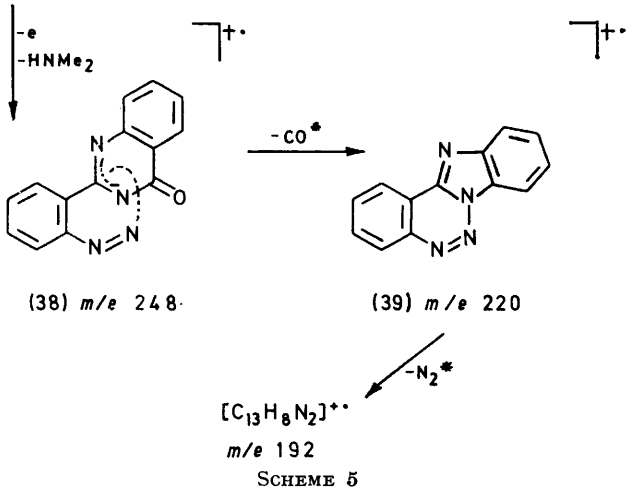
[16] R. N. Chakravarti and R. N. Adhya, *Bull. Calcutta School Trop. Med.*, 1963, **11**, 148.
[17] H. N. E. Stevens and M. F. G. Stevens, *J. Chem. Soc.* (*C*), 1970, 2289.
[18] S. C. Pakrashi, J. Bhattacharyya, L. F. Johnson, and H. Budzikiewicz, *Tetrahedron*, 1963, **19**, 1011.
[19] D. J. Brown and B. T. England, *Austral. J. Chem.*, 1968, **21**, 2813.
[20] Y. Hagiwara, M. Kurihara, and N. Yoda, *Tetrahedron*, 1969, **25**, 783.
[21] G. F. Kolar in 'Mass Spectrometry in Biochemistry and Medicine,' eds. A. Frigerio and N. Castagnoli, Raven Press, New York, 1974, p. 267.

dominating cleavage is loss of dimethylamine from the molecular ion to form a radical ion at *m/e* 248 (13%), which then expels carbon monoxide to form the radical ion at *m/e* 220 (100%). These ions are possibly cyclic species, (38) and (39) respectively (Scheme 5); subsequent fragmentations are identical with those of the molecular ion of benzimidazo[1,2-*c*][1,2,3]benzotriazine.[22]



SCHEME 4

(28)



SCHEME 5

The biological activities of the triazenes prepared in this work will be reported elsewhere. The piperidinyl-azophenylquinazoline (17a) clearly resembles DTIC in its ability to form a diazonium species and a cyclic 1,2,3-triazine, depending on the conditions, but it is unlikely that these intermediates account for its cytotoxic properties: all the degradation products of (17a), in fact, proved inactive. Our recent work on the chemical and metabolic oxidation of related triazenes suggests that (17a) is oxidatively transformed into an *alkylating* agent. This work will be reported in a future paper.

EXPERIMENTAL

4-Amino-2-(2-aminophenyl)quinazoline (7).—Anthranilonitrile (3.0 g) and sodium hydride (0.6 g) were stirred in dimethyl sulphoxide (13 ml) for 3 h at 0 °C and then for 21 h at 25 °C. 6N-Hydrochloric acid (100 ml) was added and the diaminoquinazoline dihydrochloride (3.0 g) collected. It was identical (i.r. and mixed m.p.) with an authentic sample.[23]

Quinazolino[3,2-c][1,2,3]*benzotriazin-8*(7H)-*imine* (13) [*or its Isomer* (15)].—4-Amino-2-(2-aminophenyl)quinazoline dihydrochloride (1.38 g) in 2N-hydrochloric acid (30 ml) was treated with sodium nitrite (0.35 g) in water (3 ml) at 0 °C. After 30 min an off-white solid (0.8 g) was collected. This was probably the crude diazonium chloride (9), $\nu_{max.}$ (KBr) 2 250 cm^{-1} (N_2^+). Basification of the diazonium chloride with ice–aqueous ammonia afforded the imine (0.55 g), identical (i.r.) with an authentic sample.[10]

4-Amino-2-[2-(2-methylpiperidin-1-ylazo)phenyl]quinazoline (17d).—1,3-Bis-*o*-cyanophenyltriazene (11) (2.0 g)

[22] R. A. W. Johnstone, D. W. Payling, P. N. Preston, H. N. E. Stevens, and M. F. G. Stevens, *J. Chem. Soc.* (*C*), 1970, 1238.

[23] M. W. Partridge and M. F. G. Stevens, *J. Chem. Soc.*, 1964, 3663.

was boiled for 2 h in 2-methylpiperidine (5 ml). Evaporation furnished a gum which was triturated with benzene–light petroleum. The *quinazoline* (81%) crystallised from acetone as buff prisms, m.p. 181—183° (Found: C, 69.1; H, 6.5; N, 24.4. $C_{20}H_{22}N_6$ requires C, 69.4; H, 6.35; N, 24.3%).

Similarly prepared from 1,3-bis-*o*-cyanophenyltriazene (11) and the appropriate amines were: 4-*amino*-2-[2-(3-*methylpiperidin*-1-*ylazo*)*phenyl*]*quinazoline* (17e) (88%), m.p. 158—160° (from benzene–light petroleum) (Found: C, 69.3; H, 6.4; N, 24.55%); 4-*amino*-2-[2-(4-*methylpiperidin*-1-*ylazo*)*phenyl*]*quinazoline* (17f) (90%), m.p. 146—147° (from toluene) (Found: C, 69.8; H, 6.2; N, 24.2%); and 4-*amino*-2-[2-(*hexahydroazepin*-1-*ylazo*)*phenyl*]*quinazoline* (17g) (85%), m.p. 72—73° (from toluene) (Found: C, 69.8; H, 6.5. $C_{20}H_{22}N_6$ requires C, 69.4; H, 6.35%).

4-*Amino*-2-[2-(3,3-*dimethyltriazen*-1-*yl*)*phenyl*]*quinazoline* (17h).—1,3-Bis-*o*-cyanophenyltriazene (2.0 g) was dissolved in anhydrous dimethylamine (10 ml) and kept at 4 °C for 30 days. The mixture, diluted with ice–water, slowly deposited the *dimethyltriazenylphenylquinazoline* (1.3 g), which was recrystallised from hot water; m.p. 154—156° (Found: C, 65.8; H, 5.35; N, 29.0. $C_{16}H_{16}N_6$ requires C, 65.75; H, 5.5; N, 28.8%); δ ($CDCl_3$) 3.02 (6 H, s, 2 × CH_3), 6.8br (2 H, s, NH_2), and 7.2—7.9 (8 H, m, ArH).

Reactions of 4-*Amino*-2-[2-(*piperidin*-1-*ylazo*)*phenyl*]*quinazoline* (17a) *Hydrate*.—(i) The quinazoline hydrate (0.5 g) was stirred in 2N-hydrochloric acid (15 ml) for 1 h. The precipitated solid crystallised from methanol–ether to afford the *hydrochloride salt* of quinazolino[3,2-*c*][1,2,3]-benzotriazin-8(7*H*)-imine (13) [or its isomer (15)] as off-white micro-needles (0.3 g), m.p. 188° (decomp.) (Found: C, 59.0; H, 3.9; N, 24.6. Calc. for $C_{14}H_9N_5$,HCl: C, 59.2; H, 3.5; N, 24.7%). Basification of the salt with ice–aqueous ammonia afforded the free base of (13) [or its isomer (15)], identical (i.r.) with an authentic sample.[10]

(ii) The quinazoline hydrate (2.0 g) was heated at 100 °C in acetic acid (10 ml) for 40 min. Basification of the mixture with ice–aqueous ammonia liberated the free base (1.2 g) of the tetracyclic triazine (13) [or its isomer (15)], identical with the aforementioned sample.

(iii) The quinazoline hydrate (1.5 g) was boiled in 4N-sulphuric acid (25 ml) for 2 h and cooled. The product, 2-(2-hydroxyphenyl)quinazolin-4(3*H*)-one (23) deposited (0.25 g) from the cooled solution was identical (m.p. and i.r.) with an authentic sample.[24]

(iv) The quinazoline hydrate (0.1 g) was irradiated in methanol (1 l) with a 100 W medium-pressure lamp in a Hanovia photochemical reactor equipped with a Pyrex filter. After 24 h the u.v. spectrum of the photolysate was identical with that of pure 4-amino-2-phenylquinazoline (19) [$\lambda_{max.}$ (EtOH) 254, 285infl, 304, 321infl, and 333infl nm].[13,23] T.l.c. of the concentrated solution on silica gel [ether–chloroform–methanol (10 : 2 : 1)] confirmed the identification of the photoproduct.

(v) The quinazoline hydrate (0.1 g) in ethanol (25 ml) was exposed to laboratory light for 75 days. T.l.c. of the solution (as above) showed it to contain starting material and 4-amino-2-phenylquinazoline (19).

The quinazoline hydrate was unchanged by boiling methanol or ethanol in the dark (5 h).

(vi) The quinazoline hydrate (1.0 g) was boiled in ethylene glycol (15 ml) for 1 h and the solution diluted with water (50 ml). The chilled solution slowly deposited 4-amino-2-phenylquinazoline (0.6 g).

(vii) Copper-bronze (0.5 g) produced a vigorous effervescence when added to a solution of the quinazoline hydrate (1.0 g) in boiling acetic acid (10 ml). After 1 h the mixture was filtered and basified with ice–aqueous ammonia. The product (78%) was identical (i.r.) with 4-amino-2-phenylquinazoline.

(viii) The quinazoline hydrate (1.0 g) in ethanol (20 ml) containing Raney nickel (1.0 g) was treated over 1 h at 60—65 °C with hydrazine hydrate (5 × 1 ml). The mixture was filtered through Kieselguhr and evaporated, and the residue triturated with 6N-hydrochloric acid. The product, 4-amino-2-(2-aminophenyl)quinazoline dihydrochloride (92%), was identical (i.r.) with an authentic specimen.[23]

2-[2-(*Piperidin*-1-*ylazo*)*phenyl*]*quinazolin*-4(3H)-*one* (25).—4-Amino-2-[2-(piperidin-1-ylazo)phenyl]quinazoline hydrate (17a) (1.0 g) was boiled (3 h) in ethanol (20 ml) containing potassium hydroxide (10 g) and diluted with water (50 ml). The precipitated quinazolinone (0.6 g) was identical (i.r.) with an authentic sample.[25]

Similarly prepared from the quinazolines (17b) and (17c) respectively were 2-[2-(pyrrolidin-1-ylazo)phenyl]quinazolin-4(3*H*)-one (26) (65%) and 2-[2-(morpholin-4-ylazo)-phenyl]quinazolin-4(3*H*)-one (27) (70%), identical with authentic samples.[25]

2-[2-(3,3-*Dimethyltriazen*-1-*yl*)*phenyl*]*quinazolin*-4(3H)-*one* (28).—The dimethyltriazene (17 h) (1.5 g) in ethanol (20 ml) containing potassium hydroxide (10 g) was boiled (3.5 h); the mixture was diluted with water (50 ml), and organic products were extracted into ether (4 × 25 ml). The dried (Na_2SO_4) extract was evaporated and the residue crystallised from ethanol. The *dimethyltriazenylquinazolone* (93%) had m.p. 212—213° (Found: C, 65.1; H, 5.15; N, 24.1. $C_{16}H_{15}N_5O$ requires C, 65.5; H, 5.1; N, 23.9%); $\nu_{max.}$ (KBr) 1 665 cm^{-1} (C=O).

The aforementioned quinazolones (25)—(28) were boiled in ethylene glycol for 1 h. In each case the product, formed by diluting the mixture with water, was 2-phenylquinazolin-4(3*H*)-one (22) [20] (60, 57, 70, and 65% yield, respectively).

1,3-*Bis*-(2-*cyano*-4-*bromophenyl*)*triazene* (12).—Finely powdered 5-bromoanthranilonitrile (3.94 g) [26] in 2N-hydrochloric acid (25 ml) was treated at 0 °C with sodium nitrite (0.7 g) in water (5 ml) over 30 min. The mixture was diluted with ice–water (75 ml), stirred at 0 °C for a further 2 h, and kept at 4 °C overnight. The precipitated *triazene* (80%) crystallised from toluene as yellow needles, m.p. 185° (decomp.) (Found: C, 41.7; H, 1.9; N, 17.2. $C_{14}H_7Br_2N_5$ requires C, 41.5; H, 1.7; N, 17.3%); $\nu_{max.}$ (KBr) 3 220 (NH) and 2 239 and 2 220 cm^{-1} (C≡N).

4-*Amino*-2-(2-*amino*-5-*bromophenyl*)-6-*bromoquinazoline* (8).—(i) 1,3-Bis-(2-cyano-4-bromophenyl)triazene (2.0 g) in ethanol (50 ml) containing Raney nickel (1.0 g) was treated at 60—65 °C over 1 h with hydrazine hydrate (5 × 1 ml). The filtered solution was evaporated to yield the *quinazoline* (1.8 g), which crystallised as yellow needles (from aqueous ethanol or butanol), m.p. 285—287° (Found: C, 42.8; H, 2.5; N, 14.1. $C_{14}H_{10}Br_2N_4$ requires C, 42.6; H, 2.5; N, 14.2%).

(ii) 5-Bromoanthranilonitrile (9.8 g) and sodium hydride (0.6 g) in dimethyl sulphoxide (13 ml) were stirred at 0 °C

[24] J. L. Rodgers and J. P. Milionis, U.S.P., 3,169,129.
[25] M. S. S. Siddiqui and M. F. G. Stevens, *J.C.S. Perkin I*, 1974, 611.
[26] S. M. Mackenzie and M. F. G. Stevens, *J. Chem. Soc.* (*C*), 1970, 2298.

(3 h) and then at 25 °C (21 h). Dilution of the mixture with water (300 ml) afforded the quinazoline (7.0 g), identical (i.r.) with the above sample.

2-(4-Amino-6-bromoquinazolin-2-yl)-4-bromobenzenediazonium Chloride Dihydrochloride (10).—A suspension of 4-amino-2-(2-amino-5-bromophenyl)-6-bromoquinazoline (2.0 g) in 6N-hydrochloric acid (40 ml) was treated at 0 °C with sodium nitrite (0.35 g) in water (3 ml). After 90 min the crude *diazonium chloride dihydrochloride* (70%) was collected; it crystallised from 6N-hydrochloric acid as yellow prisms, m.p. 210° (decomp.) (Found: C, 33.3; H, 2.3; N, 13.7. $C_{14}H_8Br_2ClN_5,2HCl$ requires C, 33.3; H, 1.9; N, 13.6%), $\nu_{max.}$ (KBr) 2 260 cm^{-1} (N_2^+).

2,10-Dibromoquinazolino[3,2-c][1,2,3]benzotriazin-8(7H)-imine (14) [*or its Isomer* (16)].—Crystallisation of the diazonium chloride dihydrochloride (10) from ether–methanol (1 : 1) afforded the *benzotriazinimine monohydrochloride* (95%) as pink needles, m.p. 213° (decomp.) (Found: C, 38.4; H, 2.3; N, 15.5. $C_{14}H_7Br_2N_5,HCl$ requires C, 38.05; H, 1.8; N, 15.85%).

4-Amino-6-bromo-2-(3-bromophenyl)quinazoline (20).—1,3-Bis-(2-cyano-4-bromophenyl)triazene (0.2 g) in 75% aqueous ethanol (5 ml) was boiled for 1 h and diluted with water. The precipitated *quinazoline* crystallised (53%) from toluene; m.p. 257—258° (Found: C, 44.7; H, 2.3; N, 10.9. $C_{14}H_9Br_2N_3$ requires C, 44.4; H, 2.1; N, 11.1%).

4-Amino-6-bromo-2-[5-bromo-2-(2-hydroxy-1-naphthylazo)-phenyl]quinazoline (21).—2-Naphthol (0.15 g) and 1,3-bis-(2-cyano-4-bromophenyl)triazene (0.4 g) were boiled in ethanol (10 ml) for 1 h. The precipitated *naphthylazoquinazoline* (89%) crystallised from dimethylformamide as red microrosettes, m.p. 316—318° (Found: C, 52.8; H, 2.9; N, 12.85. $C_{24}H_{15}Br_2N_5O$ requires C, 52.5; H, 2.7; N, 12.75%).

4-Amino-6-bromo-2-[5-bromo-2-(piperidin-1-ylazo)phenyl]-quinazoline (18a).—(i) 1,3-Bis-(2-cyano-4-bromophenyl)-triazene (0.8 g) in piperidine (3 ml) was boiled for 2 h and diluted with water (30 ml). The *quinazoline* (62%) deposited when the mixture was cooled to 0 °C, crystallised from acetone as white microprisms, m.p. 198—200° (Found: C, 46.7; H, 3.9; N, 17.1. $C_{19}H_{18}Br_2N_6$ requires C, 46.5; H, 3.6; N, 17.2%).

(ii) 2,10-Dibromoquinazolino[3,2-*c*][1,2,3]benzotriazin-8(7*H*)-imine hydrochloride (1.0 g) in piperidine (5 ml) was boiled for 1 h. Dilution of the cooled solution with ice-water (50 ml) afforded an off-white solid (0.65 g), identical (i.r.) with the aforementioned sample.

The following compounds in series (18) were prepared by treating 1,3-bis-(2-cyano-4-bromophenyl)triazene (12) with saturated heterocyclic amines at reflux temperature (2 h) and diluting the solutions with water: *4-amino-6-bromo-2-[5-bromo-2-(pyrrolidin-1-ylazo)phenyl]quinazoline* (18b) (70%), m.p. 225—227° (from aqueous ethanol) (Found: C, 45.5; H, 3.2; N, 17.7. $C_{18}H_{16}Br_2N_6$ requires C, 45.4; H, 3.4; N, 17.6%); *4-amino-6-bromo-2-[5-bromo-2-(morpholin-4-ylazo)phenyl]quinazoline* (18c) (78%), m.p. 203—205° (needles from toluene) (Found: C, 43.8; H, 3.6; N, 17.5. $C_{18}H_{16}Br_2N_6O$ requires C, 43.9; H, 3.25; N, 17.1%); *4-amino-6-bromo-2-[5-bromo-2-(2-methylpiperidin-1-ylazo)-phenyl]quinazoline* (18d) (85%), m.p. 225—227° (from aqueous dimethylformamide) (Found: C, 47.8; H, 4.2; N, 16.6. $C_{20}H_{20}Br_2N_6$ requires C, 47.6; H, 4.0; N, 16.7%); *4-amino-6-bromo-2-[5-bromo-2-(3-methylpiperidin-1-ylazo)-phenyl]quinazoline* (18e) (72%), m.p. 230—231° (from aqueous methanol) (Found: C, 47.6; H, 4.2; N, 16.9%); *4-amino-6-bromo-2-[5-bromo-2-(4-methylpiperidin-1-ylazo)-phenyl]quinazoline hydrate* (18f) (84%), m.p. 198—200° (with sintering at 105°) (from aqueous methanol) (Found: C, 46.1; H, 4.5; N, 15.8. $C_{20}H_{20}Br_2N_6,H_2O$ requires C, 45.9; H, 4.2; N, 16.1%).

Reactions of 4-Amino-6-bromo-2-[5-bromo-2-(piperidin-1-ylazo)phenyl]quinazoline (18a).—(i) The quinazoline (18a) (0.6 g) stirred at 25 °C in 6N-hydrochloric acid (15 ml) for 5 h gave a yellow solid (0.5 g), identical (i.r.) with 2-(4-amino-6-bromoquinazolin-2-yl)-4-bromobenzenediazonium chloride dihydrochloride.

(ii) Reduction of the quinazoline (18a) with Raney nickel and hydrazine hydrate at 60—65 °C afforded 4-amino-6-bromo-2-(2-amino-5-bromophenyl)quinazoline (85%), m.p. 285—287° (from butanol), identical (i.r.) with the sample previously synthesised.

(iii) The quinazoline (18a) (0.8 g) was boiled in ethylene glycol (15 ml) for 1 h and the solution diluted with ice–water (50 ml). The precipitated solid, crystallised from toluene, afforded 4-amino-6-bromo-2-(3-bromophenyl)quinazoline (50%), m.p. 257—258°, identical (i.r.) with the aforementioned specimen.

Reactions of 1,3-Diaryltriazenes in Piperidine and Morpholine.—(i) 1,3-Bis-*p*-nitrophenyltriazene was recovered (95%) from either boiling piperidine or morpholine (3 h). There was no change in the u.v. spectrum of the solutions during reaction, and no new products were detected (t.l.c.).

(ii) No changes in the u.v. spectra of solutions of 1,3-bis-*p*-tolyltriazene or 1,3-bis-*p*-chlorophenyltriazene in either boiling piperidine or morpholine (3 h) were detected. Starting materials were recovered (over 90%) in each case.

4-Amino-1-methyl-2-[2-(piperidin-1-ylazo)phenyl]quinazolinium Iodide (29).—The quinazoline hydrate (17a) (3.0 g) was boiled in tetrahydrofuran (20 ml) containing methyl iodide (3 ml) for 45 min. The precipitate was collected and fractionally crystallised from ethanol. The least-soluble fraction (15%) was *4-amino-2-[2-(piperidin-1-ylazo)phenyl]-quinazoline hydroiodide*, m.p. 177° (yellow needles) (Found: C, 50.0; H, 4.8; N, 17.95. $C_{19}H_{20}N_6,HI$ requires C, 49.6; H, 4.6; N, 18.3%). Basification of the hydroiodide with aqueous ammonia liberated the quinazoline hydrate free base (17a). The second crystalline fraction (prisms) was the *methylquinazolinium iodide* (80%), m.p. 234—236° (Found: C, 50.4; H, 4.9; N, 17.6. $C_{20}H_{23}IN_6$ requires C, 50.6; H, 4.85; N, 17.7%).

1-Methyl-2-[2-(piperidin-1-ylazo)phenyl]quinazolin-4(1H)-one (30).—The methylquinazolinium iodide (29) (2.0 g) in boiling ethanol (20 ml) was poured into an excess of aqueous ammonia and the mixture was stirred at 25 °C for 1 h. The precipitated *methylquinazolinone* (1.4 g) crystallised from aqueous ethanol as white needles, m.p. 213—215° (Found: C, 69.2; H, 6.2; N, 20.5. $C_{20}H_{21}N_5O$ requires C, 69.2; H, 6.05; N, 20.2%); $\nu_{max.}$ (KBr) 1 643 cm^{-1} (C=O).

2-Phenylquinazolin-4(3H)-one (22).—(i) The methylquinazolinone (30) (0.5 g), acetic acid (5 ml), and copper-bronze (0.3 g) were boiled (2 h). The solution was filtered and concentrated; dilution of the residue with water afforded 2-phenylquinazolin-4(3*H*)-one (63%), identical (i.r.) with an authentic sample.[20]

(ii) 2-Methylaminobenzamide (31) (0.4 g),[27] dissolved in boiling *p*-cymene (5 ml), was treated dropwise (5 min) with

[27] I. M. Heilbron, F. N. Kitchen, E. B. Parkes, and G. D. Sutton, *J. Chem. Soc.*, 1925, **127**, 2167.

benzoyl chloride (0.6 ml). The white product (0.7 g) which immediately formed was identical (i.r.) with the above sample of 2-phenylquinazolin-4(3*H*)-one.

3-*Methyl*-2-*phenylquinazolin*-4(3H)-*one* (24).—This quinazolone was prepared by cyclisation of 2-benzamido-*N*-methylbenzamide; it had m.p. 134—135° (lit.,[28] 136—138°). A solution of the quinazolone (0.3 g) and copper-bronze (0.1 g) was boiled in acetic acid (5 ml) for 1 h and then diluted with an excess of aqueous sodium hydroxide. The precipitate (0.28 g) was identical (i.r.) with the starting material.

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[28] G. B. Jackman, V. Petrow, and O. Stephenson, *J. Pharm. Pharmacol.*, 1960, **12**, 529.