Triazines and Related Products. Part 20.[1] Oxidation of 1-(Arylazo)-piperidines with Potassium Permanganate

By **Andreas Gescher, Colin P. Turnbull, and Malcolm F. G. Stevens,*** Cancer Chemotherapy Research Group, Department of Pharmacy, University of Aston in Birmingham, Birmingham B4 7ET

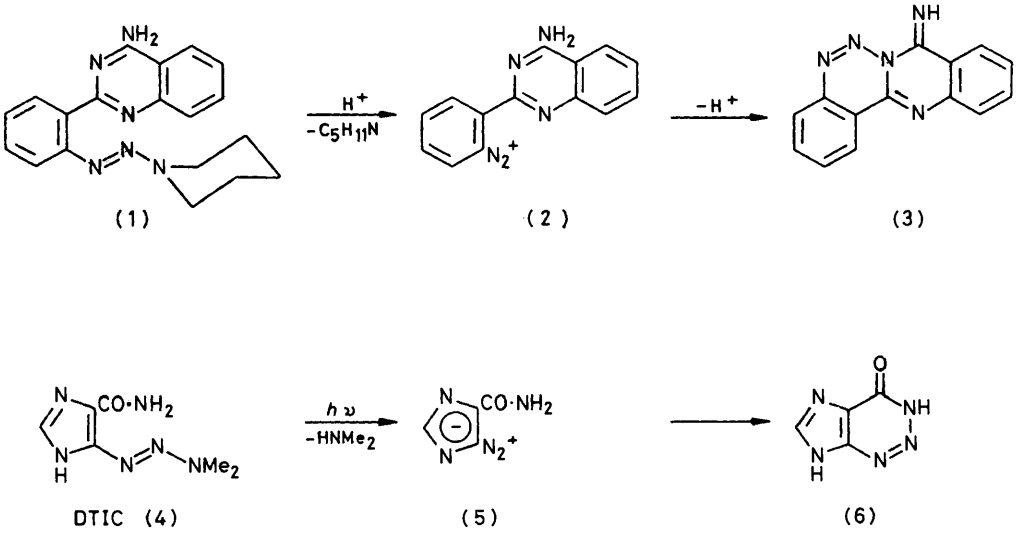
Oxidation of 1-(4-chlorophenylazo)piperidine with aqueous potassium permanganate afforded 4-chloroaniline, 1,3-bis-(4-chlorophenyl)triazene, and the oxidised triazenes 1-(4-chlorophenylazo)piperidin-2-one, -4-one, -3-ol, and -4-ol, and 1-(4-chlorophenylazo)-1,2,3,4-tetrahydropyridine. Oxidation of 4-amino-2-[2-(piperidin-1-ylazo)pheny]quinazoline yielded 4-amino-2-(2-aminophenyl)quinazoline and 1-[2-(4-aminoquinazolin-2-yl)phenylazo]piperidin-2-one.

Hydrolysis of 1-(4-chlorophenylazo)piperidin-2-one with 0.1N-potassium hydroxide in the dark yielded 4-chloroaniline and valerolactone. Valerolactone was also identified as an oxidation product from treatment of 4-amino-2-[2-(piperidin-1-ylazo)phenyl]quinazoline and *N*-nitrosopiperidine with permanganate. Oxidation at the α-position of the piperidine ring is an activating step in the development of alkylating activity in 1-(arylazo)piperidines: a mechanism for this process is proposed.

THE triazene 4-amino-2-[2-(piperidin-1-ylazo)phenyl]-quinazoline (1) and certain of its heteroalicyclic analogues are cytotoxic towards human epidermoid carcinoma cells in tissue culture.[2] In the search for a chemical explanation for this cytotoxicity we observed that the triazene (1) in acidic medium undergoes heterolytic fission to afford a diazonium intermediate (2) which can either be trapped by nucleophiles or induced to cyclise to a quinazolinobenzotriazine, probably the quinazolino[3,2-*c*][1,2,3]benzotriazin-8-imine (3).[1] In this aspect of its behaviour the triazine (1) is strikingly similar to the antitumour agent 5-(3,3-dimethyltriazen-1-yl)imidazole-4-carboxamide (DTIC) (4) which, in the presence of light, affords the diazoimidazole (5) and thence the hypoxanthine 2-aza-analogue (6) (Scheme 1).[3]

Although by no means conclusive[4] the available evidence suggests that *in vivo* DTIC acts as a pro-drug, being converted by oxidative *N*-demethylation in the liver to a chemically reactive monomethyl metabolite which can methylate biopolymers, notably nucleic acids.[5,6] The carcinogenic[7] 4-chlorophenyltriazene (7; $R^1 = R^2 = Me$) is also a substrate of the hepatic mixed-function oxygenases:[8] in this paper we describe the oxidation of two series of triazenes, (7) and (8), where R^1 and R^2 are conjoined in a heteroalicyclic ring.

The chlorophenyl derivatives (7a—f) were synthesized by reactions of a suspension of 4-chlorobenzenediazonium tetrafluoroborate in ethyl acetate at 5 °C with the appropriate secondary amines. Products were usually subjected to column chromatography on silica

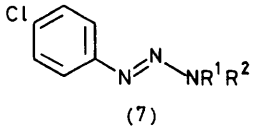


SCHEME 1

[1] Part 19, A. Gescher, M. F. G. Stevens, and C. P. Turnbull, *J.C.S. Perkin I*, 1977, 107.
[2] A. Gescher and M. F. G. Stevens, unpublished results.
[3] Y. F. Shealy, C. A. Krauth, and J. A. Montgomery, *J. Org. Chem.*, 1962, **27**, 2150.
[4] M. F. G. Stevens, *Progr. Medicin. Chem.*, 1976, **13**, 205.
[5] N. S. Mizuno, R. W. Decker, and B. Zakis, *Biochem. Pharmacol.*, 1975, **24**, 615.
[6] N. S. Mizuno and R. W. Decker, *Biochem. Pharmacol.*, 1976, **25**, 2643.
[7] R. Preussmann, S. Ivankovic, C. Landschuetz, J. Gimmy, E. Flohr, and U. Griesbach, *Z. Krebsforsch. Klin. Onkol.*, 1974, **81**, 285 (*Chem. Abs.*, 1975, **82**, 983r).
[8] R. Preussmann, A. von Hodenberg, and H. Hengy, *Biochem. Pharmacol.*, 1969, **18**, 1.

gel before crystallisation; the 2-methylpiperidino-derivative (7f) was obtained as an oil which was not further purified. All the triazenes migrated on t.l.c. as single spots which were located by spraying with 2-naphthol in acetic acid; the red colour of 1-chloro-4-(2-hydroxy-1-naphthylazo)benzene rapidly develops when the plates are heated. The mass spectra of the triazenes were consistent with their assigned structures, showing molecular ions of low abundance with major common ions at *m/e* 139/141 and 111/113 attributable to the 4-chlorobenzenediazonium ion and the 4-chlorophenylium ion respectively (see Table). Similar features have been noted in the mass spectra of the triazenoquinazoline series (8a—c and f—h).[9]

Oxidation of the triazenoquinazoline (1) with perbenzoic acid in benzene yielded only the benzoic acid salt of the starting material. Also, attempted oxidation of the chlorophenyltriazene (7a) in ether or methanol afforded only benzoic acid and unchanged triazene; with hydrogen peroxide in acetic acid an inseparable mixture was formed. [Apparently, only triazenes with a free NH group give *N*-oxides: although 1,3-bis-(4-chlorophenyl)triazene (9a) gave an 88% yield of an *N*-oxide, its *N*-methyl analogue (9b) did not react with perbenzoic acid in ether.[10]] An alternative route to



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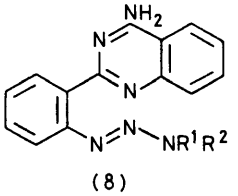
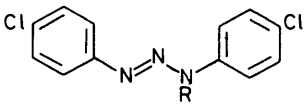


(8)

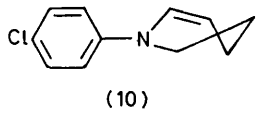
	R^1R^2		R^1R^2
a;	$[CH_2]_5$	j;	$CH_2 \cdot CH(OH) \cdot [CH_2]_3$
b;	$[CH_2]_4$	k;	$[CH_2]_2 \cdot CH(OH) \cdot [CH_2]_2$
c;	$[CH_2]_2 \cdot O \cdot [CH_2]_2$	l;	$C(:O) \cdot [CH_2]_4$
d;	$CHMe \cdot [CH_2]_3 \cdot CHMe$	m;	$CH:CH \cdot [CH_2]_3$
e;	$CMe_2 \cdot [CH_2]_3 \cdot CMe_2$	n;	$CH_2 \cdot CH:CH \cdot [CH_2]_2$
f;	$CHMe \cdot [CH_2]_4$	o;	$C(:O) \cdot [CH_2]_3$
g;	$CH_2 \cdot CHMe \cdot [CH_2]_3$	p;	$CH_2 \cdot CH(OH) \cdot O \cdot [CH_2]_2$
h;	$[CH_2]_2 \cdot CHMe \cdot [CH_2]_2$	q;	$CH(OH) \cdot CH_2 \cdot O \cdot [CH_2]_2$
i;	$[CH_2]_2 \cdot C(:O) \cdot [CH_2]_2$		

triazene *N*-oxides involves coupling between diazonium salts and *N*-arylhydroxylamines.[11] However, when benzenediazonium chloride was treated with *N*-hydroxypiperidine in sodium acetate buffer a dark brown oil was obtained. Only biphenyl and terphenyl were identified as components of the mixture: the origin of the phenyl radicals implicated as reactive species is uncertain.

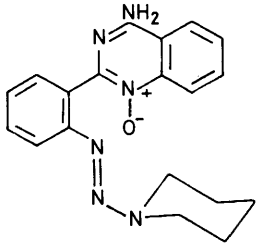
Oxidation of 1-(*Arylazo*)*piperidines with Potassium Permanganate.*—The triazene (7a) was oxidized with permanganate in buffered aqueous acetone (pH 7.5) or aqueous acetone containing sodium hydrogen carbonate



(9) a; R=H
b; R=Me



(10)



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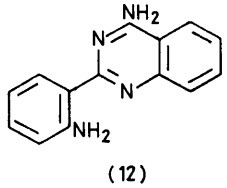


(12)

(pH 9) in the dark. The range of products was the same in each case and the mixtures were separated either by preparative layer chromatography or by g.l.c. and identified by combined g.l.c.–mass spectrometry; in most cases structures were confirmed by comparison with authentic synthetic materials. Of the eight products identified six were characterised as triazenes on t.l.c. by spraying with 2-naphthol. One product ($\lambda_{max.}$ 296 and 358 nm) was identical with authentic 1,3-bis-(4-chlorophenyl)triazene (9a). Three other triazenes proved to be the oxidised piperidines (7i and j and k), which were prepared independently by coupling 4-chlorobenzenediazonium tetrafluoroborate with piperidin-4-one, -3-ol, and -4-ol, respectively; these products had the expected physical characteristics (Table). The most polar triazene, which was also the major oxidation product (5%), crystallised from benzene–light petroleum and had a u.v. maximum at 305 nm. The mass spectrum of the product confirmed the molecular formula $C_{11}H_{12}ClN_3O$ with a molecular ion at *m/e* 237/239 and further characteristic ions at *m/e* 139 and 111—this establishes that the site of oxidation is not in the 4-chlorophenyl group, and this was confirmed by a carbonyl absorption (1 690 cm^{-1}) in the i.r. spectrum. The ^1H n.m.r. spectrum of this triazene (in deuteriochloroform) showed, in the aliphatic region, two triplets at τ 6.22 and 7.38 and a multiplet at τ 8.20: these absorptions closely parallel those of 1-benzoylpiperidin-2-one (two triplets at τ 6.21 and 7.43 and a multiplet at τ 8.09). The above evidence conclusively points to this triazene being the piperidin-2-one (7l), and although an independent synthesis could not be achieved by coupling 4-chlorobenzenediazonium tetrafluoroborate with valerolactam, the triazene prepared by oxidation of (7a) was

[9] M. F. G. Stevens, *J.C.S. Perkin I*, 1974, 615.
[10] T. Mitsuhashi and O. Simamura, *J. Chem. Soc.* (*B*), 1970, 705.
[11] E. Bamberger, *Ber.*, 1896, **29**, 102.

reduced (hydrazine–Raney nickel) to valerolactam, which was identified as δ-aminovaleric acid. The sixth triazene decomposed slowly on a silica gel t.l.c. plate; rapid extraction of the adsorbent gave an oil which was a mixture of two components (g.l.c.–mass spectrometry). One component showed an apparent molecular ion at *m/e* 221/223 with major ions at *m/e* 139 and 111 and is tentatively identified as 1-(4-chlorophenylazo)-1,2,3,4-tetrahydropyridine (7m); it differed from a sample of its isomer 1-(4-chlorophenylazo)-1,2,3,6-tetrahydropyridine (7n) prepared by coupling 4-chlorobenzenediazonium tetrafluoroborate and 1,2,3,6-tetrahydropyridine (Table). In light or in polar solvents the first component or the mixture was slowly transformed into a second product which was not a triazene. The mass spectrum showed a molecular ion at *m/e* 193/195 and other significant ions iron(III) chloride; peaks in the mass spectrum at *m/e* 139 and 111]. The small amount of material available mitigated against a conclusive structure determination, but the compound must be either the morpholin-2-ol (7p) or the isomeric -3-ol (7q).

Oxidation of the triazenoquinazoline (1) with permanganate in alkaline aqueous acetone gave the piperidin-2-one (8l) (25%) as the only identified triazene in addition to starting material. This regiospecificity of oxidation contrasts markedly with the more random oxidation of 1-(4-chlorophenylazo)piperidine, and can be explained if the initial oxidation product is the quinazoline 1-oxide (11). This oxide could selectively transfer its oxygen to the piperidine 2-position; models show this to be feasible. In support of this suggestion it may be recalled that the triazene (1) also undergoes

Triazenes prepared by coupling 4-chlorophenyldiazonium tetrafluoroborate with amines

Compound	Yield(%)	M.p.(°C)	Recrystallisation	Formula	% Found (required) C	H	N	Cl	Relative intensities of important ions (% of base peak) [a] M^+	*m/e* 139 (141)	*m/e* 111 (113)	τ Values [b]	R_F values [c]	G.l.c. retention times (min) [d]
(7a)	60	43—44	Ethanol–water	$C_{11}H_{14}ClN_3$	59.3 (59.1)	6.1 (6.3)	18.6 (18.8)	15.8 (15.9)	23 (*m/e* 223)	82	100	2.82 (4 H, m, ArH), 6.36br (4 H), 8.45br (6 H)	0.71	8.9
(7b)	55	60—61	Ethanol–water	$C_{10}H_{12}ClN_3$	57.3 (57.1)	5.9 (5.7)	20.3 (20.0)	17.3 (17.2)	12 (*m/e* 209)	37	100	2.68 (4 H, m, ArH) 6.23 (4 H, m), 8.0 (4 H, m)	0.64	8.7
(7c)	75	57—58 [e]	Light petroleum	$C_{10}H_{12}ClN_3O$					10 (*m/e* 225)	43	100	2.65 (4 H, ArH) 6.20 (8 H, s)	0.60	9.2
(7d)	38	44—45	Ethanol–water	$C_{13}H_{18}ClN_3$	61.8 (61.9)	7.2 (7.2)	16.6 (16.7)	14.1 (14.3)	5 (*m/e* 251)	31	100			
(7e)	46	64—66	Methanol–water	$C_{15}H_{22}ClN_3$	64.0 (64.3)	7.9 (7.9)	15.3 (15.0)	13.1 (12.9)	6 (*m/e* 279)	43	100			
(7f)	63	Oil [f]		$C_{12}H_{16}ClN_3$					8 (*m/e* 237)	35	100			
(7i)	45	84—85	Benzene–light petroleum	$C_{11}H_{12}ClN_3O$	55.7 (55.5)	5.1 (5.1)	17.8 (17.7)	14.9 (15.1)	5 (*m/e* 237)	28	100	2.63 (4 H, m, ArH), 5.88 (4 H, t), 7.40 (4 H, t)	0.35	9.4
(7j)	60	Oil [f]		$C_{11}H_{14}ClN_3O$					9 (*m/e* 239)	50	100		0.20	10.7
(7k)	50	63—64	Benzene–light petroleum	$C_{11}H_{14}ClN_3O$	54.9 (55.0)	5.9 (5.8)	17.7 (17.5)	15.0 (15.0)	3 (*m/e* 239)	31	100		0.09	11. [g]
(7n)	50	30—32	Benzene–light petroleum	$C_{11}H_{12}ClN_3$	59.6 (59.4)	5.6 (5.4)	18.5 (18.9)	16.1 (16.2)	8 (*m/e* 221)	48	100	2.62(4 H, m, ArH), 4.13 (2 H, m, CH:CH), 5.75 (2 H, m), 6.05 (2 H, t), 7.60 (2 H, m)	0.65	
(9a)	90	128—130 [h]	Light petroleum	$C_{12}H_9Cl_2N_3$					5 (*m/e* 265)	54	100		0.57	

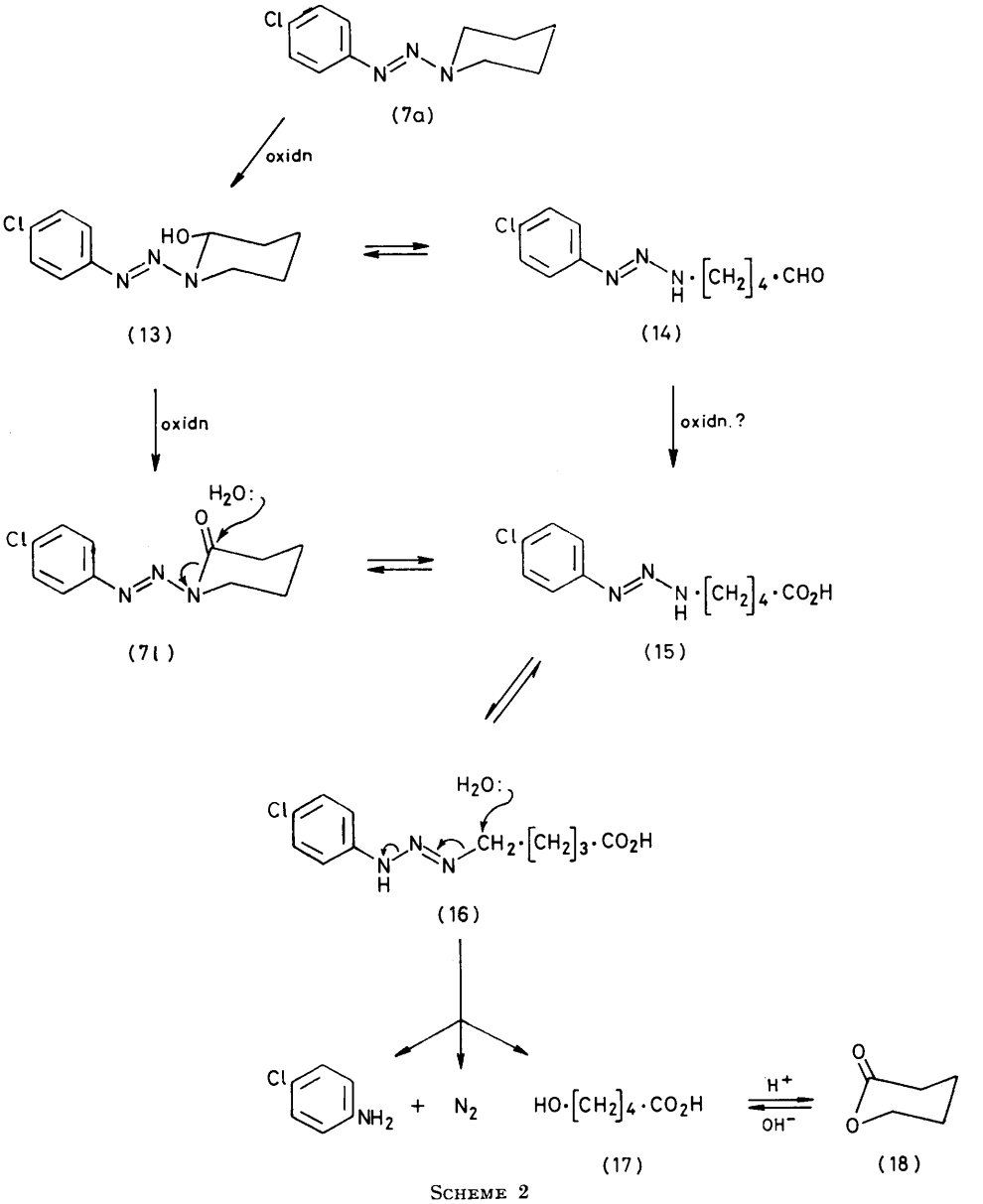
[a] Recorded on a V.G. Micromass 12B; direct insertion probe (150°); ionisation potential 70 eV. [b] Recorded on a Varian HA-100 spectrometer; solutions in deuteriochloroform. [c] 0.25 mm Kieselgel GF_{254}(Merck); plates developed with benzene–ether (9 : 1); spots detected by spraying with 3% 2-naphthol in acetic acid followed by heating at 100 ° for 10 min. [d] Pye Unicam 104; triazenes separated on a 1.5 m column of 3% OV17 on Chromosorb W.AW–DMCS, 80–120 mesh (Phase Separations Ltd.); nitrogen gas flow rate 50 ml min^{-1}; column oven temperature 178°; FID; retention times relative to 4-chloroaniline as zero. [e] R. A. Henry and W. M. Dehn, *J. Amer. Chem. Soc.*, 1943, **65**, 479, m.p. 54—55°. [f] Unstable on heating. [g] TMS ether has retention time of 8.2 minutes. [h] R. Meldola and F. W. Streatfield, *J. Chem. Soc.*, 1888, 664, m.p. 130°.

at *m/e* 178/180, 164/166, 139/141, and 138/140. Possibly this product is 1-(4-chlorophenyl)-1,2,3,4-tetrahydropyridine (10) formed from its triazene precursor (7m) by homolytic loss of nitrogen.

Surprisingly, 4-chloroaniline was isolated as a product of the oxidation of the triazene (7a) by permanganate; it was not formed in the absence of oxidant. Similarly oxidation of 1-(4-chlorophenylazo)pyrrolidine (7b) gave starting material, 4-chloroaniline, 1,3-bis-(4-chlorophenyl)triazene (9a), and 1-(4-chlorophenylazo)pyrrolidin-2-one (7o). The last-named derivative was characterised by its spectroscopic properties: $\lambda_{max.}$ 305 nm, ν_{CO} 1 725 cm^{-1}, and an ^1H n.m.r. spectrum strikingly similar in the aliphatic region to that of 1-benzoylpyrrolidin-2-one. The morpholino-analogue (7c) on oxidation by permanganate yielded 4-chloroaniline, the bis-triazene (9a), and a triazene hydroxylated in the morpholine ring [ν_{OH} 3 410 cm^{-1}; no phenolic function as indicated by a negative colour reaction with methylation at N-1.[1] 4-Amino-2-(2-aminophenyl)-quinazoline (12) was also identified as an oxidation product from the triazene (1), the dimethyltriazene (8; $R^1 = R^2 = Me$), and the heteroalicyclic analogues (8b, c, and f—h). The diamine (12) corresponds to the 4-chloroaniline formed on oxidation in the chlorophenyl series.

Hydrolysis of 1-(*Arylazo*)*piperidin*-2-*ones*.—We suggest that the arylamines originate from the corresponding 1-(arylazo)piperidin-2-ones by the process outlined in Scheme 2 [the chlorophenyltriazene (7a) is used as an example]. The crucial intermediate is presumably the piperidin-2-ol (13), which may well exist in equilibrium with the ring-opened form (14). Elimination of water from the piperidin-2-ol is a probable route to the unsaturated piperidine (7m), but the major pathway involves further oxidation to the piperidin-2-one (7l). [A less likely route to (7l) follows the reaction sequence (13) ⟶ (14) ⟶ (15) ⟶ (7l).] The piperidin-2-one

(7l) is stable in buffered aqueous ethanol (pH 7.5) in the dark, but under laboratory illumination yields chlorobenzene, 4-chlorophenol, 4-chloroaniline, and other, unidentified products. However, in 0.1N-potassium hydroxide in the dark, the piperidin-2-one decomposed by a different route to yield 4-chloroaniline and (following acidification) valerolactone (18). We interpret this result as follows: the piperidin-2-one (7l) undergoes hydrolytic cleavage in aqueous alkali to form the unstable monoalkyltriazene (15) [*cf.* the active monomethyl metabolite of DTIC];[5,12] the unconjugated tautomer (16) of this triazene then *alkylates* water. This is depicted as an S_N2 process in Scheme 2. The products of the alkylation are 4-chloroaniline, nitrogen, and the hydroxy-acid (17), which is isolated as valerolactone. 1,3-Bis-(4-chlorophenyl)triazene (9a), also formed on oxidation of (7a—c), could be formed by coupling between 4-chloroaniline and a 4-chlorobenzenediazonium species generated by heterolytic cleavage of the monoalkyltriazene (15). This latter process has been described as ' diazo-migration ' by Zollinger.[13]



SCHEME 2

The recovery of 4-chloroaniline in the oxidations of (7a) and (7; $R^1 = R^2 = Me$) was low (1.3 and 1.7%, respectively, as estimated by quantitative g.l.c.): this may be explained by the observation that 4-chloroaniline itself is rapidly consumed by oxidation with potassium permanganate in aqueous buffer. Significantly, no 4-chloroaniline was detected in the oxidation of

[12] R. C. S. Audette, T. A. Connors, H. G. Mandel, K. Merai, and W. C. J. Ross, *Biochem. Pharmacol.*, 1973, **22**, 1855.

[13] H. Zollinger, 'Azo and Diazo Chemistry,' Interscience, New York, 1961, pp. 185—187.

1-(4-chlorophenylazo)-2,2,6,6-tetramethylpiperidine (7e) which has no α-CH group available for oxidation.

Valerolactone (18) was also identified in acidified extracts from the oxidation of the triazenoquinazoline (1) and the carcinogen *N*-nitrosopiperidine by permanganate. α-Oxidation is considered to be an important metabolic activating step in the development of the carcinogenic potential of *N*-nitrosopiperidine,[14] and subsequent transformations, although not yet elucidated, may parallel those of the structurally related 1-(arylazo)-piperidines.

A comparison between the oxidation of 1-(4-chlorophenylazo)piperidine by permanganate and oxidations by the Udenfriend process,[15] Fenton's reagent, and rat liver microsomes will be reported elsewhere.

EXPERIMENTAL

Conditions for t.l.c., g.l.c., and mass and ^{1}H n.m.r. spectral examination of products were as given in the Table unless otherwise stated. 4-Chloroaniline was detected (t.l.c.) by spraying with a saturated solution of 4-dimethylaminobenzaldehyde in 10N-hydrochloric acid. I.r. spectra were recorded on a Perkin-Elmer 157G spectrometer (KBr disc). Light petroleum refers to the fraction of b.p. 40—60 °C.

Interaction of 4-Chlorobenzenediazonium Tetrafluoroborate with Amines.—A suspension of powdered 4-chlorobenzenediazonium tetrafluoroborate (0.03 mol) in ethyl acetate (50 ml) was added dropwise to a stirred solution of the amine (0.03 mol) in ethyl acetate (50 ml) at 5 °C. After 2 h unchanged diazonium salt was filtered off and the filtrate was evaporated. The products were purified by column chromatography on silica gel with benzene–light petroleum as eluting solvent. The physical characteristics of the triazenes are recorded in the Table.

Oxidation of Triazenes with Peroxy-acids.—(i) A solution of 4-amino-2-[2-(piperidin-1-ylazo)phenyl]quinazoline (1) hydrate [9] (3.32 g) in tetrahydrofuran (60 ml) mixed with a solution of perbenzoic acid (1.38 g) in benzene (30 ml) was kept at 4 °C for 12 days. Evaporation afforded a gum which solidified when triturated with acetone. The product, *4-amino-2-[2-(piperidin-1-ylazo)phenyl]quinazolinium benzoate* (65%) crystallised from acetone; m.p. 139—141° (Found: C, 68.3; H, 5.6; N, 17.3. $C_{19}H_{20}N_6,C_7H_6O_2$ requires C, 68.7; H, 5.7; N, 17.5%). The salt was converted into the free base (hydrate) in aqueous ammonia.

(ii) Oxidation of 1-(4-chlorophenylazo)piperidine (7a) with peracetic acid according to the method of Belov and Savich [16] gave an inseparable oily mixture. Oxidation of (7a) with perbenzoic acid in either ether or methanol according to the procedure used for the oxidation of 1,3-diphenyltriazene [10] gave a small yield of benzoic acid and unchanged starting material.

Coupling of Benzenediazonium Chloride and N-Hydroxypiperidine.—Aniline (1.0 g) in 2N-hydrochloric acid (10 ml) was diazotised at 0 °C by dropwise addition of sodium nitrite (0.8 g) in water (5 ml). The solution was added dropwise at 5 °C to a stirred mixture of *N*-hydroxypiperidine (1.0 g) and water (50 ml) containing sodium acetate trihydrate (1.7 g). After 2 h a brown oil was extracted with ether (3 × 25 ml). The dried (Na_2SO_4) extracts were evaporated to dryness. T.l.c. of the residue [silica gel; toluene–acetone (3 : 1)] showed the presence of biphenyl; chromatography fractionation on an alumina column (benzene) gave a solid (5%) which crystallised from light petroleum as white crystals, m.p. 216—218°, identical with authentic terphenyl (lit.,[17] m.p. 212—213°).

Oxidations with Potassium Permanganate.—(i) *1-(4-Chlorophenylazo)piperidine* (7a). The triazene (0.352 g, 1.6 mmol) dissolved in acetone (10 ml) and 0.05M-phosphate buffer (10 ml) was stirred in the dark for 12 h with potassium permanganate (3.2 mmol) at 25 °C. Manganese dioxide was filtered off and the filtrate vacuum-evaporated at 40 °C. Fractions of the residue (in dichloromethane) were separated on t.l.c. plates and compared with reference materials (Table). The following compounds were identified: starting material (R_F 0.71); 1,3-bis-(4-chlorophenyl)-triazene (0.57); 1-(4-chlorophenylazo)piperidin-4-one (0.35); 1-(4-chlorophenylazo)piperidin-3-ol (0.20); 1-(4-chlorophenylazo)piperidin-4-ol (0.09); 4-chloroaniline (0.41). The identity of the foregoing compounds was established by g.l.c.–mass spectrometry (for data see Table) and by a comparison of the i.r. and mass spectra (samples separated by preparative t.l.c.) with those of authentic materials.

The dichloromethane solution of the oxidation mixture was evaporated to dryness. A light-petroleum-insoluble fraction (R_F 0.16) crystallised from benzene–light petroleum as white crystals of *1-(4-chlorophenylazo)piperidin-2-one* (7l) (5%), m.p. 105—106° (Found: C, 55.9; H, 5.3; N, 18.0. $C_{11}H_{12}ClN_3O$ requires C, 55.5; H, 5.1; N, 17.7%); $\nu_{max.}$ (KBr) 1 690 cm^{-1} (C=O); $\lambda_{max.}$ (EtOH) 304 nm; *m/e* 237 (M^+, 5%), 139 (28), and 111 (100); τ ($CDCl_3$) 2.63 (4 H, m, ArH), 6.22 (2 H, t), 7.38 (2 H, t), and 8.20 (4 H, m).

The dichloromethane-soluble fraction gave a further oxidation product (R_F 0.36) which was a triazene (red colour with 2-naphthol and acetic acid). Rapid extraction in the dark of the band at R_F 0.36 with dichloromethane afforded an oil which was examined by g.l.c.–mass spectrometry. The first peak (retention time 4.4 min) exhibited *m/e* 193 (M^+, 100%), 178 (24), 164 (33), 139 (27), 138 (31), and 130 (49); this compound was possibly 1-(4-chlorophenyl)-1,2,3,4-tetrahydropyridine (10). A further fraction had a retention time of 9.6 min and showed *m/e* 221 (M^+, 6%), 139 (45), and 111 (100). This is tentatively identified as 1-(4-chlorophenylazo)-1,2,3,4-tetrahydropyridine (7m). In light, the oil (R_F 0.36) was completely transformed in 3 h to the product of *M* 193.

(ii) *1-(4-Chlorophenylazo)pyrrolidine* (7b). Oxidation of this triazene was accomplished similarly. Identified products (t.l.c.) were 1,3-bis-(4-chlorophenyl)triazene and 4-chloroaniline. A product (R_F 0.24) obtained by crystallisation of the dichloromethane-soluble residue from benzene–light petroleum was *1-(4-chlorophenylazo)pyrrolidin-2-one* (7o) (5%), m.p. 154—156° (Found: C, 53.7; H, 4.7; Cl, 16.2; N, 19.0. $C_{10}H_{10}ClN_3O$ requires C, 53.6; H, 4.5; Cl, 16.1; N, 18.8%); $\nu_{max.}$ (KBr) 1 725 cm^{-1} (C=O); $\lambda_{max.}$ (EtOH) 305 nm; *m/e* 223 (M^+, 9%), 139 (44), and 111 (100); τ ($CDCl_3$) 2.47 (4 H, m, ArH), 6.06 (2 H, t), 7.28 (2 H, t), and 7.76 (2 H, m).

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(iii) 4-(4-*Chlorophenylazo*)*morpholine* (7c).—Oxidation with aqueous permanganate (as above) afforded 4-chloroaniline and 1,3-bis-(4-chlorophenyl)triazene (t.l.c.). The dichloromethane-soluble products crystallised from benzene–light petroleum to give 4-(4-chlorophenylazo)morpholin-2- or -3-ol (<5%), m.p. 120—122° (Found: C, 50.0; H, 4.9; Cl, 15.0; N, 17.6. Calc. for $C_{10}H_{12}ClN_3O_2$: C, 49.6; H, 5.0; Cl, 14.9; N, 17.4%); $\nu_{max.}$ 3 410 cm^{-1} (OH); $\lambda_{max.}$ (EtOH) 285 and 310infl. nm; *m/e* 224 (M^+ — OH, 10%), 139 (57), 111 (100); R_F 0.19; retention time of trimethylsilyl ether 16.6 min).

(iv) 4-*Amino*-2-[2-*piperidin*-1-*ylazo*)*phenyl*]*quinazoline* (1) *hydrate*. The quinazoline hydrate[9] (0.8 g) in acetone (60 ml) was added to a mixture of potassium hydrogen carbonate 0.6 g) and potassium permanganate (0.9 g) in water (60 ml) and the resulting mixture was stirred at 25 °C in the dark for 10 h. Manganese dioxide was filtered off through kieselguhr and the products were extracted into chloroform (3 × 80 ml). The extracts were concentrated to 5 ml and stored at 4 °C overnight; the precipitated 1-[2-(4-*amino*-*quinazolin*-2-*yl*)*phenylazo*]*piperidin*-2-*one* (25%) had m.p. 202—204° (from chloroform) (Found: C, 65.8; H, 5.1; N, 24.0. $C_{19}H_{18}N_6O$ requires C, 65.9; H, 5.2; N, 24.3%); $\nu_{max.}$ (KBr) 3 460, 3 320, 3 210 (NH), and 1 655 cm^{-1} (C=O); τ (CD_3OD) 1.95 (1 H, d, ArH), 2.2—2.6 (7 H, m, ArH), 6.45 (2 H, t), 7.40 (2 H, t), and 8.25 (4 H, m). The residual chloroform solution was examined by t.l.c. [ether–chloroform–methanol (10 : 2 : 1)]. The band which ran concurrently with 4-amino-2-(2-aminophenyl)quinazoline (12) was removed and the silica extracted with ethanol. A u.v. spectrum of this solution revealed peaks at 240, 265infl., 303, 337infl., and 360infl., identical with those from the authentic quinazoline (12).[9]

Valerolactone was identified as follows. (*a*) The oxidation mixture, filtered to remove manganese dioxide, was shaken with aqueous 1% sodium hydrogen carbonate (100 ml) for 2 h at 25 °C and extracted with chloroform (2 × 100 ml). The aqueous layer was acidified with 10N-hydrochloric acid. A dried ($MgSO_4$) chloroform extract of the acidic solution was concentrated to 5 ml; the i.r. spectrum of this solution was identical (ν_{CO} 1 723 cm^{-1}) with that of a chloroform solution of valerolactone. (*b*) The concentrate described above was evaporated and the oily residue was mixed with 0.5N-hydroxylamine hydrochloride in 95% ethanol (5 ml) and 6N-sodium hydroxide (1 ml).[18] The mixture was heated to boiling, cooled, acidified with N-hydrochloric acid (10 ml), and extracted with ether (3 × 25 ml). T.l.c. fractionation of the ethereal solution on silica gel [ethanol as developing solvent with 5% iron(III) chloride solution spray] showed a magenta spot which ran concurrently with authentic valerolactone that had been similarly treated. (*c*) G.l.c. analysis of the chloroform extract described above was performed on a 1 m column of 3% SE30 on Chromosorb W.AW-DMCS (100—120 mesh) (Phase Separations Lt.) (oven temperature 150 °C, injection temperature 180 °C, nitrogen gas flow rate of 40 ml min^{-1}). The retention time of the valerolactone (7.3 min relative to 4-chloroaniline at zero) was identical with that of an authentic sample.

(v) N-*Nitrosopiperidine*. A solution of *N*-nitrosopiperidine (0.28 g) in acetone (60 ml) was treated with potassium permanganate (0.9 g) and potassium hydrogen carbonate (0.6 g) in water (60 ml) and stirred at 25 °C for 20 h. The presence of valerolactone was confirmed by the three methods described above.

Properties of 1-(4-*Chlorophenylazo*)*piperidin*-2-*one* (7l).—(i) The piperidinone (0.05 g) in ethanol (10 ml) and phosphate buffer (pH 7.5; 10 ml) was exposed to laboratory light for 48 h at 25 °C. Ethanol was removed by vacuum evaporation at 40 °C and the aqueous solution was extracted with chloroform. G.l.c. showed the presence of chlorobenzene (24%; internal standard toluene), 4-chlorophenol (1%; internal standard phenol), and 4-chloroaniline (8%; internal standard 4-methoxyaniline). There was no decomposition when the experiment was repeated in the dark.

(ii) The piperidinone (0.015 g) was kept at 25 °C in the dark for 1 week in acetone (10 ml) and 0.1N-potassium hydroxide (10 ml). Acetone was removed at 40 °C under reduced pressure and the aqueous residue was extracted with ether. T.l.c. of the ethereal layer confirmed the presence of 4-chloroaniline. The aqueous phase was acidified with 10N-hydrochloric acid and extracted with chloroform, and the chloroform-soluble products were examined for the presence of valerolactone. The lactone was characterised by the g.l.c. and t.l.c. methods described previously.

(iii) The piperidinone (0.02 g) in ethanol (30 ml) was heated (60 °C) with Raney nickel (0.5 g) and hydrazine hydrate (4 ml; in 1 ml portions) for 2 h. Catalyst was removed by filtration through Kieselguhr and the filtrate was vacuum-evaporated. The residue was acidified with 10N-hydrochloric acid (1 ml) and heated for 5 min at 100 °C. The solution was examined by paper chromatography [mobile phase butanol–acetic acid–water (4 : 1 : 1)]. The paper was sprayed with a solution prepared by mixing alcoholic 0.2% ninhydrin (50 ml), acetic acid (10 ml), and collidine (2 ml) with aqueous 1% copper(II) acetate. A yellow-brown spot ran concurrently with that due to authentic valerolactam which had been similarly treated.

Semi-quantitative Determination of 4-*Chloroaniline from Oxidation of Triazenes by Permanganate*.—The triazenes (7; $R^1 = R^2 = Me$), (7a), and (7e) were oxidised with permanganate in buffered aqueous acetone as previously described and manganese dioxide was removed. Solutions of the evaporated mixtures in dichloromethane were examined by g.l.c. (for conditions see Table; 4-methoxyaniline as internal standard). Yields of 4-chloroaniline (mean of three oxidations on each triazene) were 1.7%, 1.3%, and nil, respectively.

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