The Reaction of Ethoxyquin (6-Ethoxy-1,2-dihydro-2,2,4-trimethylquinoline) with Nitrous Acid

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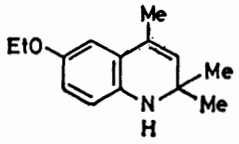
The reaction of ethoxyquin (6-ethoxy-1.2-dihydro-2.2.4-trimethylquinoline) with acidified sodium nitrite solution over a short period at room temperature gives the unstable 1-nitroso derivative together with smaller amounts of the 8-nitro derivative and a quinone imine which has lost the ethyl group. The 8-nitroso derivative is observed fleetingly as a very readily oxidised intermediate. On being kept on silica gel the 1-nitroso derivative is partly transformed into the 8-nitro derivative and ethoxyquin itself, but the main product is the quinone imine. The crystal structures of 8-nitroethoxyquin (2) and of 6-acetoxy-1.2-dihydro-2.2.4-trimethylquinoline (7), the product of reduction—acetylation of the quinone imine. have been determined by *X*-ray analysis.

ETHOXYQUIN, which is readily available from the condensation of acetone with *p*-phenetidine,[1] has structure (1), 6-ethoxy-1,2-dihydro-2,2,4-trimethylquinoline. It is



(1)

an antioxidant, and has found several applications. As an additive to animal feedstuffs it has a preservative action, and appears, for example, to protect carotenoids and vitamin A from oxidative breakdown.[2] It is also employed in the prevention of scald in pears and apples.[3]

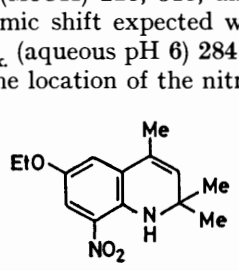
As a secondary amine, ethoxyquin might be expected to interact with nitrite (present naturally, or as a food additive) under mildly acidic conditions (such as obtain in the stomach) to generate an *N*-nitrosamine. Many *N*-nitrosamines have been shown to be potent carcinogens in experimental animals,[4] and it is reported that a nitrosation product (' polymerised *N*-nitroso-2,2,4-trimethyl-1,2-dihydroquinoline ') of the related compound 1,2-dihydro-2,2,4-trimethylquinoline is carcinogenic in rats.[5] Applications have even been reported for the nitroso derivatives themselves: the nitroso derivatives of 1,2-dihydro-2,2,4-trimethylquinolines (including ethoxyquin) appear to have found use industrially in controlling the vulcanisation of rubber.[6]

The nitrosation products of ethoxyquin have not been characterised. However, the nitrosation of 1,2-dihydro-2,2,4-trimethylquinoline has been reported to give an orange-red oil regarded as the *N*-nitroso derivative [7] (although also referred to as a polymer [6]). The oil was not subjected to elemental analysis. It appeared to us that the characterisation of these 1,2-dihydro-1-nitrosoquinoline derivatives was unsatisfactory. Because of this, and the environmental implications mentioned above for ethoxyquin, we have made a detailed chemical examination of the nitrosation of this substance.

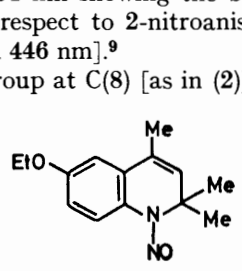
The nitrosation of ethoxyquin over a limited period was examined in aqueous acetic acid at 4°, and in an aqueous citrate–phosphate buffer (pH 2.2, 4°; the pH of normal gastric juice *in situ* is reported [8] to fall in the range 2.0—6.6 with a mean value near 3.0). Reaction proceeded less rapidly in the buffer solution, but the products, which were separated by preparative t.l.c., were the same in both cases.

The reaction in aqueous acetic acid gave four main products. The most mobile of these was isolated as maroon-red prisms, m.p. 120—121°. Elemental analysis and accurate measurement of the molecular ion accorded with the molecular formula $C_{14}H_{18}N_2O_3$. The presence of a nitro group was evident from the i.r. spectrum (ν 1 510 and 1 322 cm^{-1}) and the mass spectrum which showed a moderate molecular ion signal [*m/e* 262 (23%)] together with strong fragments corresponding to the loss of a methyl group [*m/e* 247 (100%)] and NO_2 + Me [*m/e* 201 (30%)]. The electronic spectrum had $\lambda_{max.}$(MeOH) 228, 318, and 494 nm showing the bathochromic shift expected with respect to 2-nitroanisidine [$\lambda_{max.}$ (aqueous pH 6) 284 and 446 nm].[9]

The location of the nitro group at C(8) [as in (2)] was



(2)



(3)

indicated by n.m.r. spectroscopy, the aromatic region showing an AB quartet with *J* 3 Hz, consistent with *meta* coupling. One of the protons, that at C(7) adjacent to the nitro group, was deshielded with respect to the aromatic protons of ethoxyquin itself.

Structure (2) was put beyond doubt by an *X*-ray crystal structure determination. The molecular structure found is shown in Figure 1, which also gives the numbering scheme used in the structure analysis, whilst bond lengths and angles are given in Tables 1 and 2. The bicyclic nucleus is nearly planar, with a maximum deviation from its least-squares plane (see Table 2) of 0.062 Å [C(2)]. In addition the nitro group also lies close to this plane, presumably due to a possible hydrogen-bond interaction between O(19) and H(1). A packing diagram of the crystal structure of (2) is given in Figure 2.

The main product from the nitrosation of ethoxyquin in aqueous acetic acid was a yellow unstable gum: it

underwent transformations on standing and on repeated chromatography and was not obtained sufficiently pure for analysis. It is regarded as the 1-nitroso derivative (3) of ethoxyquin on the basis of chemical analogy,[10] and

TABLE 1

Interatomic distances (Å) and angles (°) in compounds (2) and (7), with estimates of standard deviations in parentheses

(*a*) Distances	(2)	(7)
N(1)–C(2)	1.449(5)	1.467(3)
N(1)–C(9)	1.353(4)	1.382(3)
C(2)–C(3)	1.499(5)	1.512(3)
C(2)–C(11)	1.509(6)	1.526(3)
C(2)–C(12)	1.516(6)	1.521(3)
C(3)–C(4)	1.323(5)	1.327(3)
C(4)–C(10)	1.461(5)	1.470(3)
C(4)–C(13)	1.506(6)	1.504(3)
C(5)–C(10)	1.365(5)	1.390(3)
C(5)–C(6)	1.373(6)	1.374(3)
C(6)–C(7)	1.349(5)	1.369(3)
C(6)–O(14)	1.380(4)	1.418(2)
C(7)–C(8)	1.420(5)	1.378(3)
C(8)–C(9)	1.396(5)	1.395(3)
C(9)–C(10)	1.434(5)	1.406(3)
C(8)–N(17)	1.434(5)	
N(17)–O(18)	1.224(3)	
N(17)–O(19)	1.237(4)	
O(14)–C(15)	1.407(5)	1.340(2)
C(15)–C(16)	1.513(7)	1.491(4)
C(15)–O(17)		1.181(3)
N(1)–H(1)	0.82(6)	0.83(2)
C(3)–H(3)	1.00(4)	0.98(2)
C(5)–H(5)	0.88(4)	0.96(2)
C(7)–H(7)	0.92(3)	0.93(2)
C(8)–H(8)		0.96(2)
C–H(CH_2/CH_3)	0.91(4)—1.04(7)	0.84(4)—1.01(4)
(*b*) Angles		
C(2)–N(1)–C(9)	127.0(4)	118.5(2)
N(1)–C(2)–C(3)	110.1(4)	106.6(2)
N(1)–C(2)–C(11)	108.3(4)	111.8(2)
N(1)–C(2)–C(12)	109.3(4)	107.5(2)
C(3)–C(2)–C(11)	110.4(4)	109.5(2)
C(3)–C(2)–C(12)	109.4(4)	112.2(2)
C(11)–C(2)–C(12)	109.4(4)	109.3(2)
C(2)–C(3)–C(4)	126.0(4)	122.8(2)
C(3)–C(4)–C(10)	119.2(4)	118.6(2)
C(3)–C(4)–C(13)	121.5(4)	122.4(2)
C(10)–C(4)–C(13)	119.3(4)	119.0(2)
C(6)–C(5)–C(10)	123.5(4)	120.4(2)
C(5)–C(6)–C(7)	119.7(4)	121.4(2)
C(5)–C(6)–O(14)	115.2(4)	118.4(2)
C(7)–C(6)–O(14)	125.2(4)	120.0(2)
C(6)–C(7)–C(8)	119.0(4)	119.3(2)
C(7)–C(8)–C(9)	122.2(4)	120.7(2)
C(7)–C(8)–N(17)	115.5(3)	
C(9)–C(8)–N(17)	122.3(3)	
C(8)–C(9)–C(10)	116.6(3)	119.4(2)
N(1)–C(9)–C(8)	124.7(4)	121.2(2)
N(1)–C(9)–C(10)	118.7(3)	119.4(2)
C(4)–C(10)–C(5)	122.3(4)	123.8(2)
C(4)–C(10)–C(9)	118.8(3)	117.5(2)
C(5)–C(10)–C(9)	118.9(4)	118.7(2)
C(6)–O(14)–C(15)	117.4(3)	118.6(2)
O(14)–C(15)–C(16)	107.4(5)	110.5(3)
O(14)–C(15)–O(17)		122.7(2)
C(16)–C(15)–O(17)		126.8(3)
H(1)–N(1)–C(2)	118.2(3.6)	114.1(1.6)
H(1)–N(1)–C(9)	114.5(3.6)	115.6(1.6)

(*c*) Possible hydrogen bonds, intramolecular in (2) and intermolecular in (7)

(2)	(7)
N(1)–H(1) · · · O(19)	N(1)–H(1) · · · O(17)′
N(1) · · · O(19) = 2.62 Å	N(1) · · · O(17)′ = 3.12 Å
N(1)–$\widehat{H}$(1) · · · O(19) = 135.3°	N(1)–$\widehat{H}$(1) · · · O(17)′ = 154.2°

The primed atom is generated by symmetry, x, $-y$, $-\frac{1}{2} + z$.

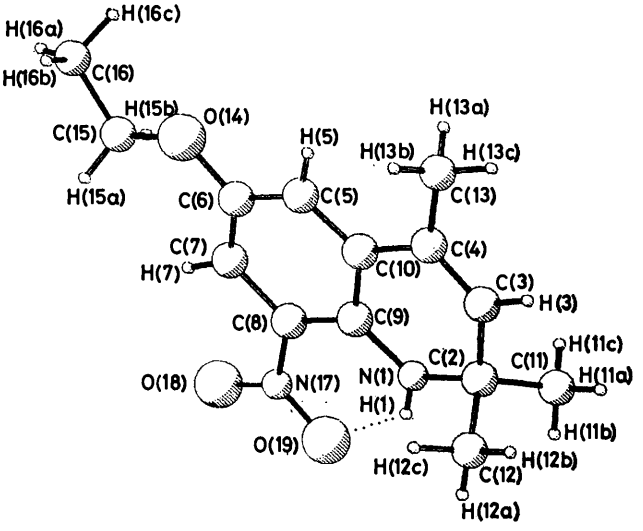


FIGURE 1 Molecular structure and atom numbering scheme of (2). The possible intramolecular hydrogen bond is indicated by the dotted line

this formulation is supported by the following evidence. (i) The substance gave a positive Liebermann test.

TABLE 2

(*a*) Least-squares planes in the form $Ax + By + Cz = D$, where x, y, and z are fractional co-ordinates. Deviations (Å) of the relevant atoms are given in square brackets

Compound (2)

Plane N(1)–C(10)

$$-3.6818x + 9.9813y + 6.9093z = -0.1126$$

[N(1) −0.018, C(2) 0.062, C(3) −0.002, C(4) −0.045, C(5) 0.025, C(6) 0.032, C(7) −0.005, C(8) −0.018, C(9) −0.017, C(10) −0.014, C(11) −1.092, C(12) 1.369, C(13) −0.121, O(14) 0.081, C(15) −0.037, C(16) −0.104, N(17) −0.037, O(18) −0.036, O(19) −0.043, H(1) 0.004, H(3) 0.010, H(5) −0.048, H(7) 0.015]

Compound (7)

Plane N(1)–C(10)

$$8.1128x - 3.2997y + 9.9315z = 1.8158$$

[N(1) 0.204, C(2) −0.393, C(3) 0.026, C(4) 0.184, C(5) −0.076, C(6) −0.129, C(7) −0.038, C(8) 0.076, C(9) 0.093, C(10) 0.051, C(11) −1.916, C(12) 0.141, C(13) 0.057, O(14) −0.382, C(15) 0.650, C(16) 0.190, O(17) 1.754, H(1) 0.120, H(3) 0.109, H(5) −0.154, H(7) −0.062, H(8) 0.075]

(*b*) Selected torsion angles (°)

The sign of the angle A–B–C–D is positive when a clockwise rotation about B–C is required to bring A–B–C into coincidence with B–C–D, viewed along B–C

A	B	C	D	Compound (2)	Compound (7)
C(8)	C(9)	N(1)	C(2)	−176.1	−151.5
C(10)	C(9)	N(1)	C(2)	3.9	31.1
C(9)	N(1)	C(2)	C(3)	6.2	46.6
N(1)	C(2)	C(3)	C(4)	−3.7	−34.0
C(2)	C(3)	C(4)	C(10)	0.0	4.9
C(2)	C(3)	C(4)	C(13)	−180.0	−175.6
C(15)	O(14)	C(6)	C(5)	174.2	101.2

(ii) The sharp absorption at 3 360 cm^{-1} in the i.r. spectrum of ethoxyquin was absent, but a strong band appeared at 1 445 cm^{-1} consistent with the presence of

an *N*-nitroso function (ν 1 430—1 500 cm^{-1}).[11] (iii) The n.m.r. spectrum was sharp, and consistent with a

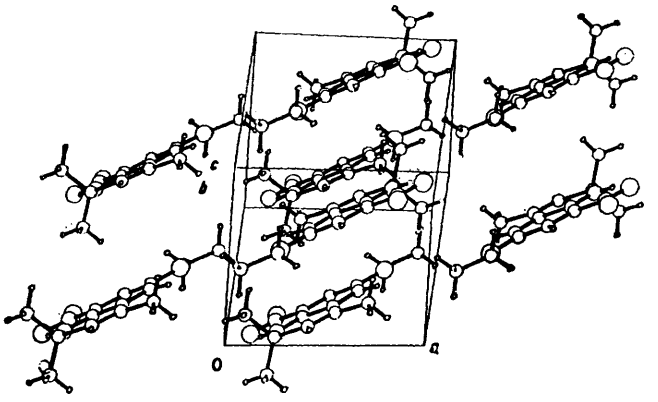
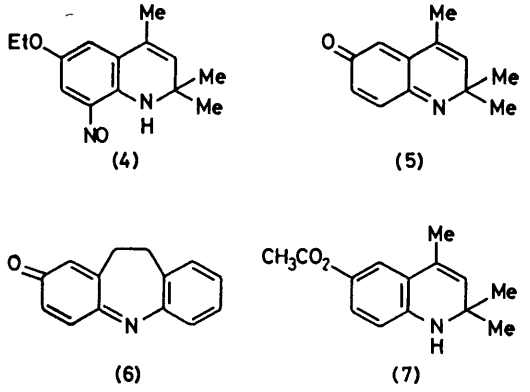


FIGURE 2 Molecular packing of (2)

monomeric formulation. The aromatic region corresponded to three protons. One of these [δ 7.78, assigned to H(8)] was considerably deshielded by the nitroso group in the *peri*-position. (iv) When set aside on silica gel in air for 40 h it furnished some 8-nitroethoxyquin (see below). (v) Transnitrosation to diphenylamine was observed, albeit in low yield. (vi) On reduction (Raney nickel–sodium hydroxide) ethoxyquin, characterised as the benzoyl derivative, was regenerated. Although the mass spectrum did not show a molecular ion corresponding to (3), peaks appeared corresponding to $(M - NO)^+$ and $(M - NO)_2^+$. We suppose that the latter arose by thermolysis to give $(M - NO)^{\cdot}$ which then dimerised on the probe. The evidence does not, however, exclude the possibility that dimeric species are present in the impure nitrosamine.

The third component was even more unstable—too unstable, indeed, for reliable spectroscopic data to be obtained. As the plate dried out, the band (originally yellowish) corresponding to this component gradually turned red. Rapid extraction with ether gave a low yield of a compound regarded as crude 8-nitrosoethoxyquin (4) since attempted further chromatographic



(4) (5) (6) (7)

purification revealed that it had been converted into the 8-nitro derivative (2).

The fourth component was formed in low yield. It was not crystalline, but was obtained as a yellow amorphous solid. Accurate mass measurements on the molecular ion corresponded to $C_{12}H_{13}NO$ and the n.m.r. spectrum showed that the ethoxy group was no longer present. This product was formulated as the quinone imine (5). The evidence for this unusual structure is as follows. (i) The substance showed an extended chromophore [yellow solution, $\lambda_{max.}$ (aqueous MeOH) 241, 284, and 374 nm] which, in a spectroscopic experiment, was bleached with sodium dithionite to give a reduction product with a chromophore ($\lambda_{max.}$ 230 and 345 nm) similar to that of ethoxyquin [$\lambda_{max.}$(MeOH) 228 and 355 nm]. (ii) Although there does not appear to be a record of the electronic absorption spectra of simple alkyl-*p*-quinone imines (presumably because such compounds are usually too unstable [12]) the aryl substituted compound (6) has been described,[13] and in the i.r. the carbonyl region is very similar to that of (5): 1 640

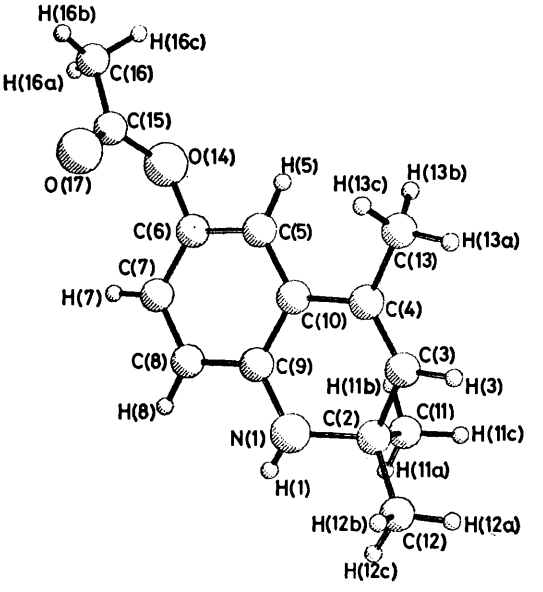


FIGURE 3 Molecular structure and atom numbering scheme of (7)

(strong, conjugated C=O), 1 603 (weaker, conjugated C=N), and 1 580 cm^{-1} (weaker still, conjugated C=C). (iii) The n.m.r. spectrum (see Experimental section) could be interpreted on the basis of structure (5). (iv) The quinone imine could not be acetylated, but reduction–acetylation gave a crystalline product which was shown to be the monoacetyl derivative (7) on the basis of elemental analysis, spectroscopic properties, and an *X*-ray crystal structure determination.

The structure of a single molecule of (7) and the atom numbering scheme used are shown in Figure 3, whilst details of molecular geometry are given in Tables 1 and 2. The bicyclic nucleus in this molecule is considerably less flattened than in molecule (2), and this may well be due to the absence of the nitro group and the associated intramolecular O · · · H–N(1) hydrogen bond found in

(2). Thus the maximum deviation from the N(1)–C(10) least-squares plane is now 0.393 Å [C(2)].

The differences between the conformations of the heterocyclic ring in the two molecules are highlighted by comparing the relevant dihedral angles (see Table 2) and the ring angles, particularly at N(1) and C(2). Differences between the two molecules also show up in the carbocyclic ring [*e.g.* in the bond length C(7)–C(8)], and these may be attributed to the effects of the nitro group and, possibly, of the different substituents at C(6). In this context, it is worth commenting that in (2) the

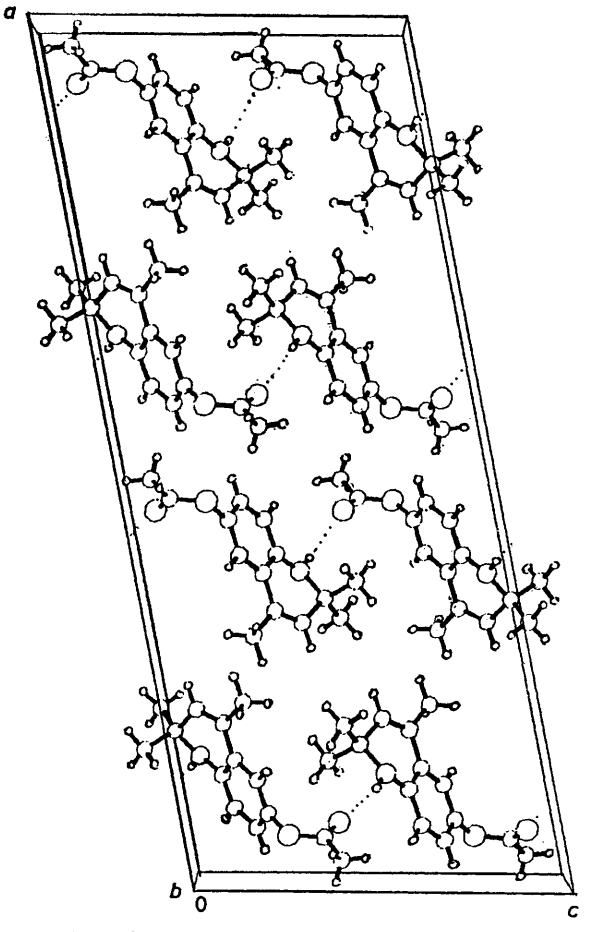
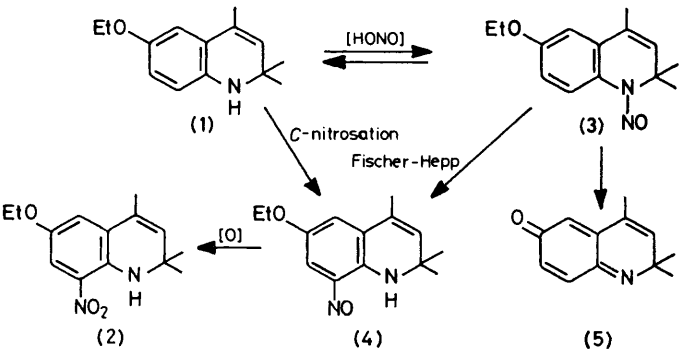


FIGURE 4 Molecular packing of (7). Possible intermolecular hydrogen bonds are indicated by dotted lines

ethoxy group also lies in the plane of the nucleus with C(6)–O(14) 1.380 Å, whereas in (7) the acetyl group makes an angle of 80° with the nuclear plane and C(6)–O(14) is 1.418 Å.

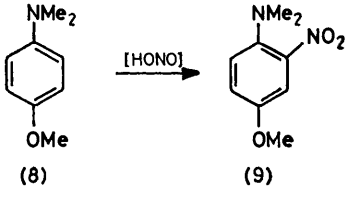
In the crystal, molecules of (7) are connected by hydrogen bonds between N(1) on one molecule and O(17) on another. A packing diagram of the crystal structure of (7) is given in Figure 4.

A parallel nitrosation reaction was carried out with 1-methylethoxyquin. While this gave a mixture containing several minor components, it gave no product comparable with the substance formulated above as 1-nitrosoethoxyquin (3). The major product (33% isolated) was 1-methyl-8-nitroethoxyquin, which was also prepared by the methylation (dimethyl sulphate; 100°) of 8-nitroethoxyquin (2).



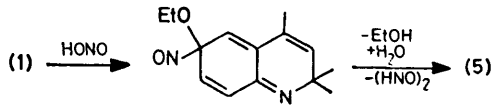
SCHEME 1 Proposed reaction pathways in the nitrosation of ethoxyquin

Under the conditions described (aqueous acetic acid–ether; 6 min; 4°) the yields of products isolated from ethoxyquin were as follows: the 8-nitro compound (2) (5%); the 1-nitroso compound (3) (52%); the crude 8-nitroso compound (4) (1%); and the quinone imine (5) (0.3%). If the preparation was carried out over a longer period the proportion of the 1-nitroso compound (3) dropped, and the yields of the nitro compound (2) and the quinone imine (5) increased. The 8-nitroso derivative was not detected in large amount under any conditions. The crude 8-nitroso derivative readily oxidises during the isolation process to give the 8-nitro derivative, and it is presumed that a major pathway to the latter compound follows this route (Scheme 1). As shown in Scheme 1 the *C*-nitrosation could occur (i) indirectly, from the 1-nitroso derivative by a Fischer–Hepp rearrangement or (ii) directly as it does presumably in the nitrosation of 1-methylethoxyquin and in the simpler but analogous reaction (8) ⟶ (9).[10] (It is conceivable, however, that these examples involve an intermediate *N*-nitroso quaternary ammonium ion.) Possibly both pathways are followed, for when 1-nitrosoethoxyquin (3) was left on the silica gel absorbent for 40 h at room temperature it was transformed into 8-nitroethoxyquin (2) (8%), ethoxyquin (1) (30%), and the quinone imine (5) (57%). The formation of (2) and (1) here can be explained in terms of the silica gel support acting as an acidic medium: both the Fischer–Hepp rearrangement and the hydrolysis of *N*-nitro-



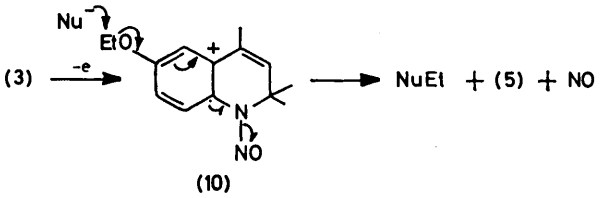
amines (amides of nitrous acid) are acid catalysed reactions. The formation of the quinone imine finds a structural analogy in the dealkylation of monoethers of

hydroquinone with nitrous acid [14] to furnish the corresponding benzoquinones. The present reaction may follow a course analogous to that demonstrated for hydroquinone monoethers [14] (Scheme 2). However,



SCHEME 2

since the reaction appears to proceed effectively from the nitrosamine (3), an alternative mechanism may operate, *e.g. via* a one-electron oxidation to the radical cation (10) (Scheme 3). Such a process, which can also be formu-



SCHEME 3

lated as an acid-catalysed reaction or as a homolytic reaction of (3), would mean that 1-nitrosoethoxyquin might behave as an ethylating agent. This possibility is thought to be important in view of the established link between alkylation and carcinogenesis.[15]

EXPERIMENTAL

General experimental directions have been given previously.[16]

Reaction of Nitrous Acid with Ethoxyquin.—Ethoxyquin (6-ethoxy-1,2-dihydro-2,2,4-trimethylquinoline) (147 mg) and acetic acid (0.8 ml) were shaken with sodium nitrite (100 mg) in water (1 ml) at 4° under nitrogen. After 3 min ether (1 ml) was added, and the mixture was shaken for a further 3 min. The mixture was neutralised with saturated sodium hydrogencarbonate and extracted with ether (60 ml). The ether extract was dried (Na_2SO_4), concentrated, and subjected without delay to preparative t.l.c. (petroleum–ether 4 : 1) to give the following components in order of decreasing mobility.

(i) 6-*Ethoxy*-1,2-*dihydro*-2,2,4-*trimethyl*-8-*nitroquinoline* (9.5 mg, 5%), R_F 0.58, red prisms, m.p. 120—121° (from ether–petroleum) (Found: C, 64.5; H, 7.05; N, 10.9. $C_{14}H_{18}N_2O_3$ requires C, 64.1; H, 6.9; N, 10.7%), *m/e* (105°) 262 (23%), 247 (100), 231 (5), 217 (8), 201 (30), 186 (11), 173 (15), 144 (5), 108 (14), 91 (4), 77 (5), and 45 (5), ν 3 310s, 3 110, 1 580, 1 510, 1 500, 1 390, 1 365, 1 340, 1 322, 1 060, 995, 890, and 765 cm^{-1}, λ(MeOH) 228 (ε 28 500), 318 (7 700), and 494 nm (12 400), δ 8.45br (NH), 7.38 (d, *J* 3 Hz, 7-H), 6.91 (d, *J* 3 Hz, 5-H), 5.54 (s, 3-H), 3.98 (q, *J* 7 Hz, CH_2O), 1.98 (s, $=CCH_3$), 1.38 (t, *J* 7 Hz, CH_2CH_3), and 1.38 (s, 2-Me_2). The structure was confirmed by *X*-ray analysis (see below). (ii) A yellow component, R_F 0.44, which on extraction with anhydrous ether gave an unstable viscous oil (87 mg, 52%) which could not be obtained crystalline and which is formulated as 6-ethoxy-1,2-dihydro-2,2,4-trimethyl-1-nitrosoquinoline, λ(MeOH) 227, 256, and 318 nm, ν(film) 3 360w, 1 640, 1 603, 1 550, 1 445, 1 285, 1 205, 1 052, and 758 cm^{-1}, δ 7.78 (dd, *J* 9 and 2 Hz, 8-H), 6.7—7.0 (m, 7-, 5-H), 5.90br (s, 3-H), 4.08 (q, *J* 7 Hz, CH_2O), 2.04br (s, 4-Me), 1.67 (s, 2-Me_2), and 1.40 (t, *J* 7 Hz, CH_3CH_2), *m/e* (102°) 432 [2(*M* − NO), 19%], 417 [2(*M* − NO) − Me, 100], 216 (*M* − NO, 8), and 202 (*M* − NO − Me + H, 35). Reduction with Raney nickel and aqueous sodium hydroxide furnished ethoxyquin (38%), which was characterised as its 1-*benzoyl derivative*, m.p. 85—86° (Found: *M*, 321.174. $C_{21}H_{23}NO_2$ requires *M*, 321.173), identical with a sample prepared from ethoxyquin. (iii) A pale yellow component, R_F 0.19, which turned red on the plate. Rapid extraction with ether and evaporation gave a compound (1.7 mg, 1%) regarded as crude 6-ethoxy-1,2-dihydro-2,2,4-trimethyl-8-nitrosoquinoline since on rechromatography this material was converted almost quantitatively to the corresponding 8-nitro derivative (above). (iv) A yellow polar component, R_F 0.05, formed in low yield (0.4 mg, 0.3%). Further quantities of this were obtained by repeating the experiment, and from the transformation of 1-nitrosoethoxyquin on silica gel (see below). It was obtained as a yellow resin, but could not be induced to crystallise. It is formulated as the quinone imine (2,6-*dihydro*-2,2,4-*trimethyl*-6-*oxoquinoline*) (Found: M^+, 187.100. $C_{12}H_{13}NO$ requires *M*, 187.100), *m/e* (62°) 187 (37%), 172 (17, *M* − Me, accurately measured), 159 (56, *M* − CO, accurately measured), 144 (100, *M* − CO − Me, accurately measured), 115 (34), 102 (19), 91 (35), 76 (34), and 63 (41), λ(MeOH) 243 (ε 10 100), 253 (9 800), 281 (12 400), and 366 nm (4 200), ν(film) 3 450, 1 640, 1 615, 1 580, 1 300, 1 110, 1 040, 890, 820, and 810 cm^{-1}, δ 7.16 (d, *J* 10 Hz, 8-H), 6.62 (dd, *J* 10 and 2 Hz, 7-H), 6.42br (s, 5-H), 6.3br (s, 3-H), 1.97 (s, 4-Me), and 1.38 (s, 2-Me_2).

In a similar experiment the reaction was carried out (4°; N_2; 10 min) in a vigorously stirred two-phase system consisting of McIlvaine's citric acid–phosphate buffer (pH 2.2) and ether. The products were worked up in the same way to give the 8-nitro derivative (3%), the 1-nitroso derivative (29%), recovered ethoxyquin (R_F 0.38; 38%), the 8-nitroso derivative (0.6%), and the quinone imine (trace).

Preparation of 8-*Nitroethoxyquin and the Quinone Imine from* 1-*Nitrosoethoxyquin.*—Ethoxyquin (251 mg) was nitrosated in acetic acid (1.3 ml) with sodium nitrite (171 mg) in water (1 ml) as before. After preparative t.l.c. the 1-nitrosoethoxyquin component was left on the silica gel support (40 h) before being extracted and rechromatographed. This gave the following products, the identities of which were confirmed by t.l.c.–u.v.: (i) the 8-nitro derivative, R_F 0.58, maroon crystals (11.3 mg); (ii) ethoxyquin, R_F 0.38, as a yellow oil (34 mg); and (iii) the quinone imine, R_F 0.05, extracted from the silica gel with ethyl acetate, to give a yellow amorphous solid (56 mg). No 1-nitrosoethoxyquin remained.

Reduction–Acetylation of the Quinone Imine.—On attempted acetylation (pyridine–acetic anhydride) the quinone imine was recovered.

The quinone imine (95 mg), anhydrous sodium acetate (79 mg), zinc dust (277 mg), and acetic anhydride (2.2 ml) were heated at *ca.* 60° for 1.6 h. The mixture was taken to dryness under reduced pressure and extracted with chloroform (20 ml). After filtration and concentration the extract was subjected to t.l.c. (petroleum–ether 8 : 3). The main product had R_F 0.25 and after extraction (anhydrous ether) gave a gum (55 mg) which crystallised from petroleum to give plates (37 mg, 32%) of 6-*acetoxy*-1,2-*dihydro*-2,2,4-*trimethylquinoline*, m.p. 60—61° (Found: C, 72.75; H, 7.55;

N, 6.1. $C_{14}H_{17}NO_2$ requires C, 72.7; H, 7.4; N, 6.05%), λ 234 (ε 31 800), 277 (2 670), and 352 nm (2 730), ν(Nujol) 3 360, 1 740, 1 642, 1 610, 1 370, 1 358, 1 220, 895, and 804 cm^{-1}, δ 6.21—6.80 (m, 5-, 7-, and 8-H), 5.32br (s, 3-H), 3.51br (s, NH), 2.25 (s, CH_3CO), 1.96 (d, *J* 2 Hz, 4-Me), and 1.28 (s, 2-Me_2), *m/e* 41°)(231 (*M*, 15%), 216 (41), 174 (44), 115 (53), 113 (59), 87 (97), and 85 (100). The structure was confirmed by *X*-ray analysis (see below).

6-*Ethoxy*-1,2-*dihydro*-1,2,2,4-*tetramethylquinoline* (1-*Methylethoxyquin*).—Ethoxyquin (2.5 g) was heated with dimethyl sulphate (2 g) for 2.5 h at 100°. The mixture was worked up with excess aqueous sodium hydroxide and extracted with ether. Fractional distillation under nitrogen of the dried extract gave 6-*ethoxy*-1,2-*dihydro*-1,2,2,4-*tetramethylquinoline* (1.8 g, 66%), b.p. 182° at 0.05 mmHg (Found: *M*, 231.162. $C_{15}H_{21}NO$ requires *M*, 231.162), λ(MeOH) 232 (ε 36 200) and 365 nm (2 900), ν(film) 2 820, 1 663w, 1 610, 1 575, 1 392, 1 382, 870, and 800 cm^{-1}, δ 6.35—6.80 (m, 5-, 7-, and 8-H), 5.36 (s, 3-H), 3.96 (q, *J* 7 Hz, CH_2O), 2.74 (s, NMe), 1.93 (s, 4-Me), 1.33 (t, *J* 7 Hz, CH_3CH_2), and 1.20 (s, 2-Me_2).

6-*Ethoxy*-1,2-*dihydro*-1,2,2,4-*tetramethyl*-8-*nitroquinoline* (1-*Methyl*-8-*nitroethoxyquin*).—(a) *From* 1-*methylethoxyquin*. 1-Methylethoxyquin (326 mg) in aqueous N-HCl (1.4 ml) was treated (4°; N_2) with sodium nitrite (250 mg) in water (2 ml) and ether (1 ml). The solution was agitated for 7 min, and then quenched with an excess of sodium hydrogencarbonate solution. The ether extract (50 ml) was dried, concentrated, and chromatographed (t.l.c., petroleum–ether 8 : 1.5). The major component (R_F 0.72) gave maroon-red prisms (129 mg, 33%) of 6-*ethoxy*-1,2-*dihydro*-1,2,2,4-*tetramethyl*-8-*nitroquinoline*, m.p. 59—60° (from petroleum). The carbon analysis was low (nitro compound) (Found: C, 64.3; H, 7.5; N, 10.0%; M^+, 276.147. $C_{15}H_{20}N_2O_3$ requires C, 65.2; H, 7.3; N, 10.15%; *M*, 276.147), λ(MeOH) 232 (ε 54 900), 335i (2 100), and 470 nm (3 200), ν 1 612, 1 560, 1 510, 1 384, 1 360, 1 343, 1 298, 1 132, 1 050, and 770 cm^{-1}, δ 7.11 (d, *J* 3 Hz, 7-H), 6.90 (d, *J* 3 Hz, 5-H), 5.57 (s, 3-H), 3.98 (q, *J* 7 Hz, CH_2O), 2.60 (s, NMe), 2.00 (s, 4-Me), 1.38 (t, *J* 7 Hz, CH_3CH_2), and 1.25 (s, 2-Me_2), *m/e* (36°) 276 (21%), 261 (100), 246 (2), 231 (10), 215 (50), 185 (23), 171 (4), and 157 (7).

(b) *From* 8-*nitroethoxyquin*. 8-Nitroethoxyquin was methylated in a way analogous to that described for ethoxyquin to give 1-methyl-8-nitroethoxyquin (14%) identical (t.l.c., u.v.) with the above sample.

Transnitrosation Experiments.—(a) *From* 1-*nitrosoethoxyquin to diphenylamine*. A freshly prepared sample of 1-nitrosoethoxyquin (16 mg; yellowish resin) was kept in the dark in air in tetrahydrofuran (2 ml) with diphenylamine (37 mg) for 4.5 h at 20°. Preparative t.l.c. (toluene; two developments) gave *N*-nitrosodiphenylamine, R_F 0.55 (1.0 mg, 8% estimated spectroscopically), $\lambda_{max.}$ 295 nm (ε 6 050). The identity of this material was confirmed by mixed t.l.c.

(b) *From* N-*nitrosodiphenylamine to ethoxyquin*. Ethoxyquin (140 mg) and *N*-nitrosodiphenylamine (39 mg) were heated (*ca.* 55°) in tetrahydrofuran (2 ml) and citric acid–phosphate buffer (pH 2.2; 3 ml) for 4 h in air. The mixture was subjected to preparative t.l.c. (petroleum–ether 8.5 : 1.5) to give 1-nitrosoethoxyquin (R_F 0.44; crude yield 19 mg, 39%) and ethoxyquin (R_F 0.38; 65 mg). Diphenylamine, 8-nitroethoxyquin, and the quinone imine were also detected.

* For details of Supplementary Publications see Notice to Authors No. 7 in *J.C.S. Perkin I*, 1978, Index issue.

X-*Ray Crystallography*

Structure Determination of 8-*Nitroethoxyquin* (2).—The compound was crystallised from petroleum–ether. A single crystal of size 0.30 × 0.20 × 0.15 mm was used for oscillation and Weissenberg photography and later for data collection. Preliminary unit-cell parameters and the crystal system were determined from photographic measurements. Accurate cell parameters were obtained from least-squares refinement of 15 setting angles automatically centred on a Nonius CAD4 diffractometer at the beginning of data collection. The centrosymmetric space group was indicated by intensity statistics and confirmed by structure analysis.

Crystal data. $C_{14}H_{18}N_2O_3$, $M = 262.3$. Triclinic, $a = 8.410(4)$, $b = 8.612(3)$, $c = 10.000(4)$ Å, $\alpha = 95.44(2)$, $\beta = 99.44(2)$, $\gamma = 73.60(3)°$, $U = 684.5$ Å^3, $D_m = 1.26$ g cm^{-3} (flotation), $D_c = 1.27$ g cm^{-3}, $Z = 2$, $F(000) = 280$, space group $P\bar{1}$ $\mu(Cu\text{-}K_\alpha) = 6.5$ cm^{-3}, $\lambda(Cu\text{-}K_\alpha) = 1.541\,8$ Å. The intensity data were collected out to $\theta = 60°$ using Ni-filtered Cu-K_α radiation and an ω—2θ scan technique. The scan rate was variable and was determined by a fast prescan. All the reflections yielding a net count >10 in the prescan were rescanned slowly to give a total count of 3 000 subject to a maximum time of 60 s. The scan width was determined as scan = 0.8 + 0.2tanθ and the aperture settings as apt. = 3.0 + 0.5tanθ. Two intensity-control reflections monitored after every 50 reflections did not show any decay of the crystal during data collection. In each 96 step scan, the outer 16 steps on each side constituted left (B_L) and right (B_R) backgrounds, and the 'central' 64 steps the peak count (*C*). The integrated intensity (I_0) of a reflection and its estimated standard deviation $|\sigma(I_0)|$ were calculated from the equations: $I_0 = |C - 2(B_L + B_R)|$ and $\sigma(I_0) = |C + 4(B_L + B_R)|^{\frac{1}{2}}$. The intensities were corrected for the Lorentz and polarisation factors and variable measuring time, but not for absorption or extinction. The data reduced to a total of 2 041 unique reflections of which only 1 207 obeying the condition $I_0 > 1.5\sigma(I_0)$ were used in the structure refinement.

Attempts to solve the structure using multisolution Σ_2 sign expansion (SHELX [17] program) yielded a repeating planar hexagonal pattern which proved difficult to interpret, although in retrospect the correct atoms could be identified. The incorporation of trio relations [18] yielded a double image [19] of the complete molecule except for three atoms, the two images being separated by the vector −0.120, −0.206, 0.054. A difference electron density synthesis calculated from a molecule placed exactly half-way between the two images revealed the remaining atoms. Isotropic and anisotropic least squares refinement of all the non-hydrogen atoms reduced the *R* values to 0.15 and 0.098 respectively. The hydrogen atoms were located from a difference map and included in the refinement with isotropic temperature factors. The weighting scheme used was $w = (\sigma^2|F_o| + 0.000\,86F_o^2)^{-1}$, which gave reasonably flat analysis of variance with sinθ, $(F_o/F_{max.})^{\frac{1}{2}}$, parity groups, and reflection indices. The refinement converged at *R* 0.061 and R_w 0.059. The fractional co-ordinates for all the atoms and isotropic temperature factors for the hydrogen atoms are given in Tables 3 and 4. Anisotropic temperature factors for the non-hydrogen atoms, and the observed and calculated structure factors are listed in Supplementary Publication No. SUP 22359 (12 pp.).* The interatomic distances and angles are presented in Tables 1 and 2.

Structure Determination of 6-Acetoxy-1,2-dihydro-2,2,4-trimethylquinoline (7).—Crystals of (7) were grown from petroleum. As before, the unit-cell parameters were initially derived from single crystal *X*-ray photographs and subsequently refined on the diffractometer. Systematic absences, *hkl* for $h + k$ = odd and *h0l* for *l* odd, indicated the space group as *Cc* or *C2/c*, the latter being confirmed by structure analysis.

Crystal data. $C_{14}H_{17}NO_2$, $M = 231.3$. Monoclinic, $a = 32.581(9)$, $b = 5.847\ 8(10)$, $c = 13.707(3)$ Å, $\beta = 101.09(2)°$, $U = 2\ 562.8$ Å^3, $D_m = 1.19$ g cm^{-3} (flotation), $Z = 8$, $D_c = 1.20$ g cm^{-3}, $F(000) = 992$, space group *C2/c*, μ(Mo-K_α) = 0.46 cm^{-1}, λ(Mo-K_α) = 0.710 69 Å. The intensities were recorded from a crystal measuring 0.35 × 0.22 × 0.10 mm, using the procedure mentioned for compound (2). In the present case, however, monochromated Mo-K_α radiation was used and the θ limit was set to 28°. Data reduction gave a total of 3 091 unique reflections; of these 1 177 had $I_0 > 1.5\sigma(I_0)$ and were used in the refinement. Absorption corrections were not considered necessary. The structure was solved by automatic direct methods routine in SHELX [17] and refined by least-squares. Isotropic and anisotropic refinement of the non-hydrogen atoms gave an *R* value of 0.124 and 0.096 respectively. The positions of the hydrogen atoms were determined from difference synthesis and included in the refinement. The structure finally refined to *R* 0.035 and R_w 0.028 (the hydrogen atoms isotropic, others anisotropic). At the final stage, an empirical isotropic extinction parameter *x* in the modified expression for the calculated structure factor $F_c' = F_c(1 - xF_c^2/\sin\theta)$ was also varied in the least-squares, and this refined to a value of $85(\pm 11) \times 10^{-5}$. The weighting scheme employed was $w = 1/\sigma^2(F_o)$. The final atomic fractional co-ordinates and isotropic temperature factors for the hydrogen atoms are given in Tables 5 and 6. Anisotropic temperature factors for the non-hydrogen atoms, and the observed and calculated structure factors are listed in Supplementary Publication No. SUP 22359.* The interatomic distances and angles are presented in Tables 1 and 2. Neutral atom scattering

TABLE 3

Fractional co-ordinates (× 10⁴) for the non-hydrogen atoms in (2), with estimates of standard deviations in parentheses

Atom	*x*	*y*	*z*
N(1)	2 558(5)	−1 175(4)	1 851(4)
C(2)	2 497(5)	−2 452(5)	2 670(4)
C(3)	4 064(5)	−2 904(5)	3 673(4)
C(4)	5 295(5)	−2 196(5)	3 859(4)
C(5)	6 335(5)	19(5)	3 238(4)
C(6)	6 256(5)	1 288(5)	2 474(4)
C(7)	4 965(5)	1 748(5)	1 468(4)
C(8)	3 692(5)	928(4)	1 243(4)
C(9)	3 742(4)	−360(4)	2 013(4)
C(10)	5 161(4)	−830(4)	3 045(4)
C(11)	2 317(8)	−3 894(7)	1 736(6)
C(12)	994(7)	−1 866(10)	3 423(6)
C(13)	6 827(7)	−2 762(8)	4 891(7)
O(14)	7 554(3)	2 002(3)	2 825(3)
C(15)	7 617(8)	3 207(8)	1 994(6)
C(16)	9 230(8)	3 667(10)	2 493(9)
N(17)	2 354(4)	1 508(4)	169(3)
O(18)	2 362(4)	2 642(4)	−479(3)
O(19)	1 197(4)	854(4)	−79(3)

TABLE 4

Fractional co-ordinates (× 10⁴) and isotropic thermal parameters (× 10³) for the hydrogen atoms * in (2), with estimates of standard deviations in parentheses

Atom	*x*	*y*	*z*	U_{iso}
H(1)	1 759(70)	−836(63)	1 261(58)	111(21)
H(3)	4 149(46)	−3 808(45)	4 257(39)	64(12)
H(5)	7 237(48)	−347(40)	3 823(37)	51(11)
H(7)	4 804(42)	2 595(38)	923(34)	43(11)
H(11a)	2 274(51)	−4 734(50)	2 203(44)	72(14)
H(11b)	1 341(54)	−3 601(45)	1 046(43)	67(13)
H(11c)	3 234(75)	−4 194(63)	1 186(58)	122(23)
H(12a)	69(67)	−1 490(57)	2 737(55)	100(17)
H(12b)	959(69)	−2 647(67)	4 088(63)	123(21)
H(12c)	1 044(55)	−805(58)	3 940(50)	85(18)
H(13a)	7 796(63)	−3 125(54)	4 388(50)	95(18)
H(13b)	6 916(66)	−1 936(64)	5 538(58)	111(22)
H(13c)	6 931(58)	−3 825(58)	5 268(47)	98(17)
H(15a)	6 689(56)	4 099(53)	1 947(42)	70(16)
H(15b)	7 623(56)	2 665(52)	1 078(53)	89(17)
H(16a)	9 437(71)	4 218(67)	1 868(59)	115(22)
H(16b)	9 177(75)	4 188(69)	3 468(71)	142(27)
H(16c)	149(68)	2 654(62)	2 598(50)	97(19)

* Hydrogen atoms are numbered according to the parent atom, distinguished by suffixes a—c if more than one is present.

TABLE 5

Fractional co-ordinates (× 10⁵) for the non-hydrogen atoms in (7), with estimates of standard deviations in parentheses

Atom	*x*	*y*	*z*
N(1)	13 769(7)	−8 330(34)	6 318(15)
C(2)	16 865(6)	1 291(39)	981(15)
C(3)	19 612(7)	17 049(40)	8 185(16)
C(4)	18 180(7)	29 208(37)	14 995(16)
C(5)	11 717(7)	40 559(43)	21 426(16)
C(6)	7 709(7)	35 689(41)	22 548(14)
C(7)	5 705(8)	16 223(45)	18 635(17)
C(8)	7 710(7)	1 502(46)	13 252(16)
C(9)	11 735(6)	6 286(36)	11 727(15)
C(10)	13 820(7)	25 871(37)	16 105(14)
C(11)	14 792(10)	14 826(56)	−8 169(20)
C(12)	19 310(12)	−18 564(58)	−2 240(28)
C(13)	20 867(9)	46 064(60)	21 647(21)
O(14)	5 544(4)	52 153(27)	27 236(10)
C(15)	5 284(7)	48 960(49)	36 781(17)
C(16)	3 029(11)	68 389(67)	40 440(28)
O(17)	6 684(7)	32 707(35)	41 356(12)

TABLE 6

Fractional co-ordinates (× 10⁴) and isotropic thermal parameters (× 10³) for the hydrogen atoms * in (7), with estimates of standard deviations in parentheses

Atom	*x*	*y*	*z*	U_{iso}
H(1)	1 230(7)	−1 863(40)	324(16)	71(9)
H(3)	2 250(6)	1 848(30)	714(12)	46(5)
H(5)	1 289(6)	5 457(37)	2 433(14)	59(7)
H(7)	302(7)	1 324(35)	1 959(14)	63(7)
H(8)	625(6)	−1 160(35)	1 007(14)	56(6)
H(11a)	1 287(7)	538(39)	−1 273(17)	84(9)
H(11b)	1 329(7)	2 789(37)	−600(15)	67(8)
H(11c)	1 708(7)	2 104(35)	−1 139(16)	69(7)
H(12a)	2 131(7)	−1 344(37)	−596(16)	75(8)
H(12b)	2 072(8)	−2 779(45)	332(19)	95(10)
H(12c)	1 728(10)	−2 859(54)	−656(22)	126(14)
H(13a)	2 348(8)	4 587(41)	2 052(16)	89(8)
H(13b)	1 973(8)	6 198(45)	2 049(17)	92(10)
H(13c)	2 078(7)	4 353(39)	2 827(17)	79(8)
H(16a)	49(13)	6 840(57)	3 780(26)	163(18)
H(16b)	332(9)	6 710(48)	4 685(21)	111(12)
H(16c)	405(13)	8 351(64)	3 830(26)	187(19)

* See footnote in Table 4.

* See footnote on p. 493.

factors were taken from ref. 20 (C, N, and O) and ref. 21 (H) for both (7) and (2). The crystallographic computations were done on the Queen Mary College ICL 1904S and University of London CDC 7600 computers, using the SHELX program and the University of Cambridge IBM 370/165 using further programs written by G. M. S.

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