Quinoxaline Derivatives. V.[1] Some Reactions of 2-Cyano-3-hydroxyquinoxaline 1-Oxide

By Yusuf AHMAD, M. S. HABIB,* M. IQBAL and ZIAUDDIN

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The presence of a nitrile group and an *N*-oxide function, side by side in the same molecule, confers some unusual properties on 2-cyano-3-hydroxyquinoxaline 1-oxide (Ia), as has been reported in an earlier paper.[2] It is recovered unchanged when it is refluxed with phosphorus trichloride. All atempts to deoxygenate it to 2-cyano-3-hydroxyquinoxaline (II: R=R'=H; R''=CN) by reduction with sodium dithionite in acetic acid (or aqueous ethanol), zinc and acetic acid, or by catalytic hydrogenation in the presence of Pd-C, were unsuccessful. Instead of the expected deoxygenated base (II: R=R'=H; R''=CN), the

* C/o Burroughs Wellcome & Co. (Pakistan), Ltd., D/43 S. I. T. E., Karachi, Pakistan.

1) Part IV: Y. Ahmad, M. S. Habib, Ziauddin and N. Bashir, *Tetrahedron*, **21**, April (1965).

2) Part III; Y. Ahmad, M. S. Habib and Ziauddin, ibid., **20**, 1107 (1964).

product isolated in each case was 2-hydroxyquinoxaline (II: R=R'=R''=H), indicating that although deoxygenation had been achieved, it was accompanied by a simultaneous loss of the nitrile group.

During the reaction of 3-hydroxyquinoxaline-2-carboxyamide 1-oxide (III) with aniline (or *N*-methylaniline) to obtain 3-hydroxyquinoxaline-2-carboxyanilide (or *N*-methylanilide) 1-oxide (III: CONHPh or CONMePh for $CONH_2$), it was observed that if the reactants were heated together for only a few minutes the product obtained in both cases was 3-hydroxyquinoxaline-2-carboxyamide (II: R=R'=H; R''=$CONH_2$), whereas if the heating was prolonged for 24 hr., 3-hydroxyquinoxaline-2-carboxyanilide (II: R=R'=H; R''=CONHPh) and 3-hydroxyquinoxaline-2-carboxy-*N*-methylanilide (II: R=R'=H; R''=CONMePh) respectively were obtained. This indicated that these amines deoxygenated the *N*-oxide (III) and that the resulting amide reacted further to give the corresponding anilides (II: R=R'=H; R''=CONHPh or CONMePh). This observation, combined with the fact that amines are known[3] to deoxygenate heterocyclic *N*-oxides, prompted us to try the action of amines on the *N*-oxide (Ia) to obtain 2-cyano-3-hydroxyquinoxaline (II: R=R'=H; R''=CN) which was needed in connection with another investigation.

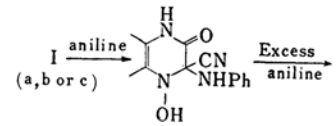
The *N*-oxide (Ia), on being heated with *N*-methylaniline, gave a product which also seemed to have lost the nitrile group (the infrared absorption peak at 2240 cm^{-1} for CN was missing). Its constitution was established as 3-hydroxy-2-(*N*-methylanilino)quinoxaline (IIb) on the basis of the following evidence:

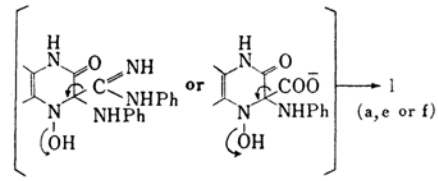
(i) Its elementary analysis agrees with $C_{15}H_{13}N_3O$.

(ii) On methylation with methyl sulphate in acetone in the presence of potassium carbonate, it was converted to 3,4-dihydro-4-methyl-2-(*N*-methylanilino)-3-oxoquinoxaline (IIc), identical (infrared spectra and mixed melting point) with an authentic sample prepared[4] by heating 2-chloro-3,4-dihydro-4-methyl-3-oxoquinoxaline and *N*-methylaniline together in methanol.

Aniline and cyclohexylamine also reacted similarly with the *N*-oxide (Ia) and yielded the corresponding amino-derivatives (IIa and d). 7-Chloro- and 7-ethoxy-derivatives (Ib and c) of 2-cyano-3-hydroxyquinoxaline 1-oxide also behaved similarly and with aniline gave anilino-derivatives (IIe and f) of the same type. The structures of these amino-derivatives (IIa and d-f) followed by analogy and on the basis of their elementary analysis. This reaction of bases on the *N*-oxides (Ia-c) can be compared to asimilar action of aqueous potassium hydroxide, described in Part III,[2] wherein the highly-developed electrophilicity of the $C_{(2)}$ of the *N*-oxide (Ia), on account of its attachment to two strong electron-withdrawing functions (i. e., CN and *N*-oxide), is considered to be responsible for the attack of the OH anion and, thereby, the displacement of the nitrile group.

The bases similarly attack the electron-deficient $C_{(2)}$. However, no free CN anions were detected in the reaction mixture, as in the case of the action of aqueous potassium hydroxide on I (a, b or c). Therefore, the amines (e. g. aniline) probably react further with the nitrile group and result in a simultaneous deoxygenation, as is shown below: **





3-Hydroxy-2-phenylquinoxaline 1-oxide[1] (Ia: Ph for CN), when heated under reflux with fuming hydrobromic acid, is quantitativly deoxygenated[5] to 3-hydroxy-2-phenylquinoxaline (II: R=R'=H; R''=Ph). This interesting transformation led us to study the effect of fuming hydrobromic acid on the *N*-oxide (Ia). On being refluxed with this reagent for two hours, Ia gave, in a 30% yield, a product which contained bromine in a non-reactive form. Its infrared spectrum resembled that of 2,3-dihydroxyquinoxaline. Elementary analysis agreed well with a monobromo-derivative of 2,3-dihydroxyquinoxaline. The position of bromine was established as follows:

(a) Its infrared spectrum was identical with that of 6-bromo-2,3-dihydroxyquinoxaline (IVa), which was synthesised by the condensation of 4-bromo-*o*-phenylenediamine with ethyl oxalate as described by Curd et al.[6]

(b) The mono-bromo compound, on methylation with methyl sulphate and aqueous alkali,

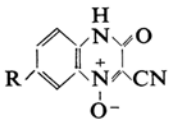
3) I. J. Pachter and M. C. Kloetzel, *J. Am. Chem. Soc.*, **74**, 971 (1952).

4) J. W. Clark-Lewis, *J. Chem. Soc.*, **1957**, 439.

** The authors wish to thank the referee for this suggestion, which accounts for the loss of the nitrile group with the simultaneous deoxygenation of the compounds.

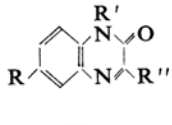
5) Unpublished work.

6) F. H. S. Gurd, D. G. Davey and G. J. Stacey, *J. Chem. Soc.*, **1949**, 1271.



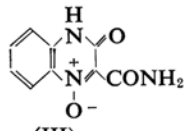
(I)

(a) R=H
(b) R=Cl
(c) R=EtO

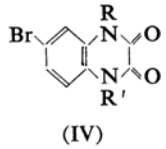


(II)

	R	R′	R″
(a)	H	H	NHPh
(b)	H	H	NMePh
(c)	H	Me	NMePh
(d)	H	H	HN(S)
(e)	Cl	H	NHPh
(f)	EtO	H	NHPh



(III)



(IV)

(a) R=R′=H
(b) R=R′=Me
(c) R=Me; R′=H

gave a dimethyl derivative, m. p. 205—207°C, which was identical (infrared spectra and mixed melting point) with an authentic sample of 6-bromo-1, 2, 3, 4-tetrahydro-1, 4-dimethyl-2, 3-dioxoquinoxaline (IVb) synthesised by the methylation of 6-bromo-2, 3-dihydroxyquinoxaline or 6-bromo-3, 4-dihydro-4-methyl-3-oxoquinoxaline (IVc). This unusual formation of 6-bromo-2, 3-dihydroxyquinoxaline from 2-cyano-3-hydroxyquinoxaline 1-oxide (Ia) probably takes place in two steps. The *N*-oxide (Ia) is first converted to 2, 3-dihydroxyquinoxaline through the sequence (cyano *N*-oxide (Ia) → amide *N*-oxide (III) → carboxylic acid *N*-oxide (III, CO_2H for $CONH_2$) → decarboxylation to 3-hydroxyquinoxaline 1-oxide → rearrange ment to 2, 3-dihydroxyquinoxaline) as was previously envisaged[2] in its reaction with a mixture of concentrated sulphuric acid and acetic acid. Bromination takes place later with bromine, which is either generated in situ by the consumption of a part of the *N*-oxide or by the aerial oxidation of hydrobromic acid itself. This is supported by the fact that 2, 3-dihydroxyquinoxaline (IVa: H for Br) itself gives 6-bromo-2, 3-dihydroxyquinoxaline (IVa) (a) on prolonged heating with fuming hydrobromic acid or (b), far more quickly and in a quantitative yield on the addition of an aqueous solution of potassium bromate (to generate one equivalent of bromine) to its solution in hydrobromic acid.

In contrast to this is the observation that the *N*-oxide (Ia) is recovered unchanged even after eight hours boiling with a mixture of concentrated hydrochloric acid and acetic acid.

7) A. H. Cowenlock, G. T. Newbold and F. S. Spring, jbid., **1945**, 622.

Experimental

Infrared spectra were measured in Nujol mull. The light petroleum used had a 60—80°C boiling range.

2-Anilino-3-hydroxyquinoxaline (IIa).—2-Cyano-3-hydroxyquinoxaline 1-oxide[2] (Ia) (1g.) and aniline (20 ml.) were heated together under reflux for 4 hr. The reaction mixture was allowed to cool and then diluted with light petroleum. The solid thus separated was crystallised from ethanol as pale yellow micro-needles of the anilinoquinoxaline (IIa), yield, 90%; m. p. 247—248°C (Found: C, 69.6; H, 4.4; N, 17.5. Calcd. for $C_{14}H_{11}N_3O$: C, 70.8; H, 4.6; N, 17.7%).

3-Hydroxy-2-(*N*-methylanilino)quinoxaline (IIb).—Similarly, the *N*-oxide (Ia) in an excess of *N*-methylaniline gave, in a 40% yield, colourless cubes (from ethanol) of the *N*-methylanilinoquinoxaline (IIb), m. p. 180—182°C (Found: N, 16.5. Calcd. for $C_{15}H_{13}N_3O$: N, 16.7%). The compound IIb (0.13 g.), on methylation with methyl sulphate (0.1 ml.) in the presence of anhydrous potassium carbonate (0.5 g.) and acetone (heated under reflux), gave, in a 50% yield, 3, 4-dihydro-4-methyl-2-(*N*-methylanilino)-3-oxoquinoxaline (IIc), m. p. 145—146°C (Found: N, 15.95. Calcd. for $C_{16}H_{15}N_3O$: N, 15.8%). Its melting point was not depressed by admixture with a sample (m. p. 143—144°C) prepared by the method of Clark-Lewis[4] by the condensation of 2-choro-3, 4-dihydro-4-methyl-3-oxoquinoxaline with *N*-methylaniline in boiling methanol.

2-Cyclohexylamino-3-hydroxyquinoxaline (IId).—Similarly, the *N*-oxide (Ia), on being treated with cyclohexylamine, gave, in a 90% yield, yellow needles (from ethanol) of the cyclohexylaminoquinoxaline (IId), m. p. 246°C (Found: C, 63.8; H, 7.1; N, 16.3. Calcd. for $C_{14}H_{17}N_3O \cdot H_2O$: C, 64.3; H, 7.2; N, 16.1%).

2-Anilino-7-chloro-3-hydroxyquinoxaline (IIe).—7-Chloro-2-cyano-3-hydroxyquinoxaline 1-oxide[2] (Ib) with aniline gave, in a good yield, yellow cubes (from glacial acetic acid) of the anilinochloroquinoxaline (IIe), m. p. 318—319°C (Found: Cl, 13.15; N, 15.3. Calcd. for $C_{14}H_{10}ClN_3O$: Cl, 13.1; N, 15.5%).

2-Anilino-7-ethoxy-3-hydroxyquinoxaline (IIf).—2-Cyano-7-ethoxy-3-hydroxyquinoxaline 1-oxide[2] (Ic) with aniline gave in a good yield, yellow needles (from ethanol) of the anilinoethoxyquinoxaline (IIf), m. p. 260—261°C (Found: C, 67.65; H, 5.4; N, 15.0. Calcd. for $C_{16}H_{15}N_3O$: C, 68.3; H, 5.4; N, 14.9%).

The Reduction of 3-Hydroxyquinoxaline-2-carboxyamide (III).—The amide *N*-oxide[2] (III), on being heated under reflux with aniline or *N*-methylaniline for 3 min., gave 3-hydroxyquinoxaline-2-carboxyamide (II: R=R′=H; R″=$CONH_2$), m. p. 308—310°C (decomp.) in a quantitative yield. Its melting point was not depressed by admixture with a sample[7] (m. p. 308—310°C) obtained by the action of concentrated ammonium hydroxide on ethyl 3-hydroxyquinoxaline-2-carboxylate. The infrared spectra of the compounds obtained by the two methods were also identical.

6-Bromo-2, 3-dihydroxyquinoxaline (IVa).—a) The *N*-oxide (Ia) (1 g.) or amide *N*-oxide (III) (1 g.) in fuming hydrobromic acid (30 ml.) was heated under reflux for 2 hr. The reaction mixture was then allowed to cool. On dilution with water, a yellow solid separated which crystallised from dimethylformamide-ethanol as colourless cubes of the bromoquinoxaline (IVa), m. p. >350°C, yield 30% (Found: N, 11.8. Calcd. for $C_8H_5BrN_2O_2$; N, 11.6 %). This was identical (infrared spectra) with an authentic sample of 6-bromo-2, 3-dihydroxyquinoxaline.[6] The *N*-oxide (Ia) was recovered unchanged on being heated under reflux for 8 hr. with a mixture (1 : 1) of HCl and AcOH or on being heated under reflux with acetylchloride in a sealed tube at 100°C for 72 hr. The amide *N*-oxide (III), on the other hand, gave 2, 3-dihydoxyquinoxaline on being heated with a mixture (1 : 1) of HCl and AcOH.

b) A mixture of 2, 3-dihydroxyquinoxaline (1 g.) and fuming hydrobromic acid (50 ml.) was heated under reflux for 8 hr. The solid separated during the reaction was collected and crystallised from dimethylformamide-ethanol as colourless cubes of the monobromo-2, 3-dihydroxyquinoxaline (20% yield, m.p. >350°C, identical (infrared spectra) with a sample obtained under a). Curd, Davey and Stacey[6] have reported this compound, but have not given any melting point for it.

c) The addition of a calculated amount of aqueous potassium bromate to a solution of 2, 3-dihydroxyquinoxaline in hot fuming hydrobromic acid immediately precipitated, in a quantitative yield, the monobromo-2, 3-dihydroxyquinoxaline, which was then collected and crystallised from dimethylformamide-ethanol as colourless cubes, m. p. >350°C (The infrared spectrum was identical with that of 6-bromo2, 3-dihydroxyquinoxaline.).

6-Bromo-1, 2, 3, 4-tetrahydro-1, 4-dimethyl-2, 3-dioxoquinoxaline (IVb).—6-Bromo-2, 3-dihydroxyquinoxaline (obtained under a, b or c; see above) (1 g.), anhydrous potassium carbonate (2 g.) and methyl sulphate (0.5 ml.) in acetone (50 ml.) were heated under reflux for 3 hr. The reaction mixture was then filtered, and the filtrate on concentration gave a solid which crystallised from ethanol as white needles of the tetrahydroquinoxaline (IVb), m. p. 205—206°C, in a good yield. It was identical (infrared spectra and mixed melting point with a synthetic sample prepared by the methylation of 6-bromo-3, 4-dihydro-2-hydroxy-4-methyl-3-oxoquinoxaline (IVc) (see below) with methyl sulphate and aqueous sodium hydroxide. Curd, Davey and Stacey[6] recorded its m. p. as 205—206°C.

6-Bromo-3, 4-dihydroxy-2-hydroxy-4-methyl-3-oxoquinoxaline (IVc).—Without being isolated from its ethanolic solution, 4-bromo-2-methylaminoaniline prepared by the hydrogenation of 4-bromo-2-methylamino-1-nitrobenzene (5 g.) in ethanol (60 ml.) over Pd-C was condensed with ethyl oxalate (20 g.) by heating them together under reflux for 3.5 hr. The solid which separated was collected and crystallised from acetic acid as colourless micro-needles of the bromoquinoxaline (IVc), m. p. 325—327°C (Found: Br, 31.05; N, 10.7. Calcd. for $C_9H_7BrN_2O_2$: Br, 31.4; N, 11.0%).

Summary

2-Cyano-3-hydroxyquinoxaline 1-oxide (Ia), and its 7-chloro- or 7-ethoxy-derivatives (Ib, c), on treatment with aniline, are deoxygenated, with a simultaneous displacement of the nitrile group, resulting in the formation of 2-anilinoquinoxalines (IIa, e and f). Ia undergoes similar transformations with *N*-methylaniline and cyclohexylamine.

The *N*-oxide (Ia), on being heated with fuming hydrobromic acid, yields 6-bromo-2, 3-dihydroxyquinoxaline (IVa), the mechanism of formation of which has been outlined.

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Chemical Research Division
Central Laboratories
Pakistan Council of Scientific and Industrial Research
Karachi, Pakistan