675. *The Reduction of 3-Hydroxyquinoxaline-2-carboxylic Acid and Derivatives with Sodium Dithionite.*

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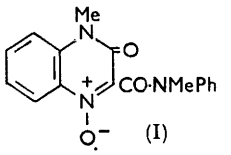
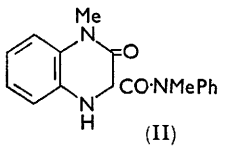
The reactivity of 3-hydroxyquinoxaline-2-carboxylic acid derivatives towards sodium dithionite is parallel to that of the corresponding 1-oxides towards sulphuric acid.[1] The ready formation of the corresponding 1,2-dihydro-compounds provides further evidence of the powerfully electrophilic nature of $C_{(2)}$ in certain of these compounds.

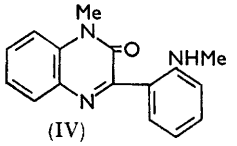
The very rapid reaction of 3,4-dihydro-4-methyl-3-oxoquinoxaline-2-carboxy-*N*-methylanilide 1-oxide (I) in cold concentrated sulphuric acid was attributed[1] to the presence of a powerfully electrophilic centre at $C_{(2)}$ in the conjugate acid; further experimental support might be obtained by investigation of the reduction of this and related compounds at the $N_{(1)}$–$C_{(2)}$ double bond. Formation of the 1,2-dihydro-compound involves addition of hydrogen, presumably as hydride ion at $C_{(2)}$ and a proton at $N_{(1)}$. As expected on the above assumption, this addition occurred most readily with those bases the 1-oxides of which are degraded by sulphuric acid.



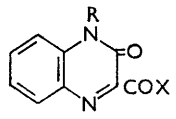
(I)



(II)



(IV)



(IIIa) ; R = H, X = OH
(IIIb) ; R = H, X = NHPh
(IIIc) ; R = Me, X = NHPh
(IIId) ; R = Me, X = NMePh

Sodium dithionite converted both the *N*-oxide (I) and the corresponding base into 1,2,3,4-tetrahydro-4-methyl-3-oxoquinoxaline-2-carboxy-*N*-methylanilide (II). This compound has been prepared by reduction of the *N*-oxide (I) by Usherwood and Whiteley,[2] who established its structure. The 1,2-dihydro-structure of the present reduction products follows by analogy and by the ready reversal of this reduction by heat. The bases prepared earlier[1] for conversion into their *N*-oxides were therefore treated with aqueous ethanolic sodium dithionite under standard conditions. 1,2-Dihydro-derivatives were formed from certain of the quinoxaline compounds only; for example, 3,4-dihydro-4-methyl-3-oxopyrazine-2-carboxy-*N*-methylanilide was recovered, and its 1-oxide was reduced only to the corresponding base. Six 3-oxoquinoxaline-2-carboxylic acid derivatives (III, I, and the corresponding diphenyl-amide) were all reduced to the 1,2-dihydro-compounds. If the oxo-group was removed or replaced by an amino-group no reduction was observed. Similarly, if the 2-carboxylic acid function was removed or replaced by a substituted phenyl ring there was again no reduction. Thus the minimum structural requirements for reduction under our conditions are summarised in formula (III), where the $N_{(1)}$–$C_{(2)}$ double bond is seen to be conjugated with the benzene ring and the two amide oxo-groups. This is the structure whose *N*-oxide undergoes the sulphuric acid rearrangement described earlier.[1] All the other bases, which were not reduced by sodium dithionite, yielded *N*-oxides which did not rearrange in acid, with the exception of 3,4-dihydro-4-methyl-3-oxopyrazine-2-carboxy-*N*-methylanilide whose 1-oxide rearranges,[1] but very much more slowly than the quinoxaline compound (I). The closely related structural requirements of

[1] Habib and Rees, *Chem. and Ind.*, 1959, 367; preceding paper.
[2] Usherwood and Whiteley, *J.*, 1923, 1069.

these two apparently dissimilar reactions suggest an underlying mechanistic similarity. The driving force of the acid-catalysed rearrangements was attributed [1] to the highly electrophilic nature of $C_{(2)}$ of the conjugate acids. This polarisation, less developed in the neutral molecules, would likewise promote nucleophilic attack by hydride ions at $C_{(2)}$ in the reduction reactions.

Quinoxaline-2-carboxy-*N*-methylanilide 1,4-dioxide was reduced under the standard conditions to quinoxaline-2-carboxy-*N*-methylanilide, and no mono-oxide could be isolated.

Experimental

Standard Procedure for Reduction (cf. Newbold and Spring [3]).—A solution of the compound (0·2 g.) and sodium dithionite (0·3 g.) in 50% aqueous ethanol (10 ml.) was heated under reflux for ¾ hr.; more sodium dithionite (0·3 g.) was then added and the heating continued for a further ¾ hr. The ethanol was removed and the solid which separated on cooling was crystallised from aqueous ethanol. The yields were 72—98%.

3,4-*Dihydro*-4-*methyl*-3-*oxopyrazine*-2-*carboxy*-N-*methylanilide*.—3,4-Dihydro-4-methyl-3-oxopyrazine-2-carboxy-*N*-methylanilide 1-oxide gave the corresponding base, m. p. 188°, identical with an authentic sample.[1]

Quinoxaline-2-*carboxy*-N-*methylanilide*.—Quinoxaline-2-carboxy-*N*-methylanilide 1,4-dioxide [1] gave this base, m. p. 128°, identical with an authentic sample.[1] With use of the quantity of sodium dithionite calculated for removal of one oxygen atom, a mixture of starting material and free base was isolated, and no mono-oxide could be detected.

1,2-*Dihydro*-3-*hydroxyquinoxaline*-2-*carboxylic Acid*.—3-Hydroxyquinoxaline-2-carboxylic acid [1,4] (IIIa) gave, after adjusting the mixture to pH 2·5, 1,2-*dihydro*-3-*hydroxyquinoxaline*-2-*carboxylic acid hydrate*, m. p. 152° (decomp., depending on the rate of heating) (Found: C, 51·0; H, 4·8. $C_8H_8O_3N_2,H_2O$ requires C, 51·4; H, 4·8%).

1,2-*Dihydro*-3-*hydroxyquinoxaline*-2-*carboxyanilide*.—3-Hydroxyquinoxaline-2-carboxyanilide [6] (IIIb) gave pale yellow needles of 1,2-*dihydro*-3-*hydroxyquinoxaline*-2-*carboxyanilide*, m. p. 208° (Found: C, 66·9; H, 4·9. $C_{15}H_{13}O_2N_3$ requires C, 67·4; H, 4·9%). This dihydro-compound was reconverted into the starting material in air at 240° for ½ hr.; the 3-hydroxyquinoxaline-2-carboxyanilide (61%) crystallised as leaflets, m. p. and mixed m. p. 336—338°, from dimethylformamide.

1,2,3,4-*Tetrahydro*-4-*methyl*-3-*oxoquinoxaline*-2-*carboxyanilide*.—3,4-Dihydro-4-methyl-3-oxoquinoxaline-2-carboxyanilide (IIIc) (see below) gave pale yellow needles of the *tetrahydro-compound*, m. p. 161° (Found: C, 68·4; H, 5·4. $C_{16}H_{15}O_2N_3$ requires C, 68·3; H, 5·4%).

1,2,3,4-*Tetrahydro*-4-*methyl*-3-*oxoquinoxaline*-2-*carboxy*-N-*methylanilide*.—3,4-Dihydro-4-methyl-3-oxoquinoxaline-2-carboxy-*N*-methylanilide (IIId) and its 1-oxide (I) both yielded the tetrahydro-compound, m. p. 188°, identical with the product of zinc-dust reduction of the base reported by Clark-Lewis [5] and of the 1-oxide reported by Usherwood and Whiteley.[2]

1,2,3,4-*Tetrahydro*-4-*methyl*-3-*oxoquinoxaline*-2-*carboxy*-NN-*diphenylamide*.—3,4-Dihydro-4-methyl-3-oxoquinoxaline-2-carboxy-*NN*-diphenylamide 1-oxide [1] gave needles of the *tetrahydroquinoxaline* derivative, m. p. 179° (Found: C, 73·5; H, 5·5. $C_{22}H_{19}O_2N_3$ requires C, 73·9; H, 5·4%).

The following compounds were not reduced under the standard conditions: 3,4-dihydro-4-methyl-3-oxopyrazine-2-carboxy-*N*-methylanilide,[1] quinoxaline-2-carboxy-*N*-methylanilide,[1] 3-aminoquinoxaline-2-carboxy-*N*-methylanilide (see below), 2-hydroxyquinoxaline,[4] and 3,4-dihydro-4-methyl-2-*o*-methylaminophenyl-3-oxoquinoxaline (IV).[5]

3-*Hydroxyquinoxaline*-2-*carboxyanilide* (IIIb).—This anilide, prepared from 3-hydroxyquinoxaline-2-carboxylic acid by standard methods,[1] crystallised from dimethylformamide as yellow needles, m. p. 340—343° (decomp.). Clark-Lewis [6] records m. p. 343—345° (decomp.).

3,4-*Dihydro*-4-*methyl*-3-*oxoquinoxaline*-2-*carboxyanilide* (IIIc).—(*a*) 3,4-Dihydro-4-methyl-3-oxoquinoxaline-2-carboxyamide [6] (2 g.) was heated under reflux with aniline (15 ml.) until no more ammonia was evolved (13 hr.), and the cooled mixture was poured into an excess of 2N-hydrochloric acid. The *anilide* crystallised from ethanol as yellow needles (1·9 g., 67%), m. p.

[3] Newbold and Spring, *J.*, 1948, 519.
[4] Gowenlock, Newbold, and Spring, *J.*, 1945, 622.
[5] Clark-Lewis, *J.*, 1957, 439.
[6] Clark-Lewis, *J.*, 1957, 422.

193—195° (Found: C, 68·8; H, 4·7; N, 14·9. $C_{16}H_{13}O_2N_3$ requires C, 68·8; H, 4·7; N, 15·05%).

(*b*) 3-Hydroxyquinoxaline-2-carboxyanilide was methylated with dimethyl sulphate to give a product (73%) identical with that of method (*a*).

(*c*) 3,4-Dihydro-4-methyl-3-oxoquinoxaline-2-carboxyl chloride, prepared by heating the acid [7] (7·0 g.), thionyl chloride (30 ml.), and benzene (40 ml.) under reflux for 2 hr. and then evaporating to dryness, was added portionwise to an excess of aniline in benzene, and the mixture heated for 15 min. The precipitate was washed with 2N-hydrochloric acid and then with water. The anilide (96%) was identical with the above products.

3-*Aminoquinoxaline-2-carboxyanilide*.—Phenylphosphazoanilide,[1] from aniline (3·9 ml.) and phosphorus trichloride (0·64 ml.), was heated under reflux with 3-aminoquinoxaline-2-carboxylic acid [9] (2·0 g.) in dry toluene for 1 hr. The hot mixture was rapidly filtered and the residue was extracted twice with hot toluene. The volume of the combined filtrate and extracts was reduced (10 ml.); on cooling a crystalline solid (1·2 g., 41%), m. p. 211—212°, separated. Recrystallisation from ethanol gave yellow needles of 3-*aminoquinoxaline-2-carboxyanilide*, m. p. 213° (Found: C, 68·0; H, 4·4. $C_{15}H_{12}ON_4$ requires C, 68·2; H, 4·6%).

3-*Aminoquinoxaline-2-carboxy*-N-*methylanilide*.—Phosphorus tri-(*N*-methylanilide),[8] from methylaniline (4·3 ml.) and phosphorus trichloride (0·64 ml.), was heated under reflux with 3-aminoquinoxaline-2-carboxylic acid [9] (2·0 g.) in dry toluene (40 ml.) for 20 min. The toluene was removed, the tarry residue was extracted with ethanol, and the ethanolic solution (charcoal) evaporated to dryness. The solid gave yellow needles (from water) of 3-*aminoquinoxaline-2-carboxy*-N-*methylanilide* (0·69 g., 23%), m. p. 157° (Found: C, 68·6; H, 4·9. $C_{16}H_{14}ON_4$ requires C, 69·0; H, 5·1%).

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[7] King and Clark-Lewis, *J.*, 1951, 3381.
[8] Abramovitch, Hey, and Long, *J.*, 1957, 1787.
[9] Weijlard, Tishler, and Erickson, *J. Amer. Chem. Soc.*, 1944, **66**, 1957.