676. *The Oxidation of 3-Hydroxyquinoxaline-2-carboxyanilide and its N-Methyl Derivatives.*

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3,4-Dihydro-4-methyl-3-oxoquinoxaline-2-carboxy-*N*-methylanilide (Id) is oxidised by peracids to the 1-oxide, but on removal of either or both of the *N*-methyl groups [giving (Ia, b, or c)], the oxidation takes a different course, the carboxyamide groups being replaced by hydroxyl groups, the 2,3-dihydroxyquinoxaline is formed, and no *N*-oxides could be detected under a variety of conditions. The mechanism of these abnormal oxidations is discussed.

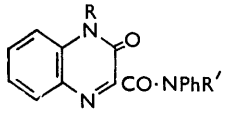
4-Acetyl-3,4-dihydro-3-oxoquinoxaline-2-carboxy-*N*-methylanilide forms an *N*-oxide (VIII) normally, which undergoes the sulphuric acid rearrangement described elsewhere.[1]

The isomeric mono-*N*-oxides of quinoxaline-2-carboxy-*N*-methylanilide have been prepared and characterised.

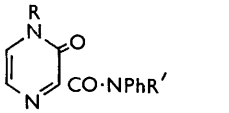
The mechanism of the acid-catalysed rearrangement of the *N*-oxides of 3,4-dihydro-4-methyl-3-oxoquinoxaline-2-carboxy-*N*-methylanilide (Id) and the corresponding pyrazine compound (IId) has been elucidated.[1] During attempted preparation of *N*-oxides of some closely related compounds, for comparison in this rearrangement, an anomalous reaction was encountered. 3,4-Dihydro-4-methyl-3-oxoquinoxaline-2-carboxy-*N*-methylanilide (Id) was oxidised directly to the 1-oxide in 50% yield with hydrogen peroxide and acetic

[1] Habib and Rees, *Chem. and Ind.*, 1959, **367**; *J.*, 1960, 3371.

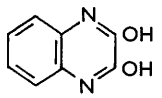
acid, as described by Clark-Lewis.[2] Similar oxidations of the anilides (Ia, b, and c), which were expected to give the corresponding 1-oxides, took a different course. These oxidations were then repeated under widely different conditions with hydrogen peroxide, peracetic acid, and perbenzoic acid (cf. Table). In all cases the only solid products were 2,3-dihydroxyquinoxaline (III) from (Ia and b), and 3,4-dihydro-2-hydroxy-4-methyl-



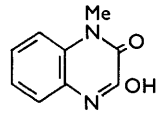
(I) a : R = R′ = H
b : R = H, R′ = Me
c : R = Me, R′ = H
d : R = R′ = Me



(II) a : R = R′ = H
b : R = H, R′ = Me
c : R = Me, R′ = H
d : R = R′ = Me



(III)



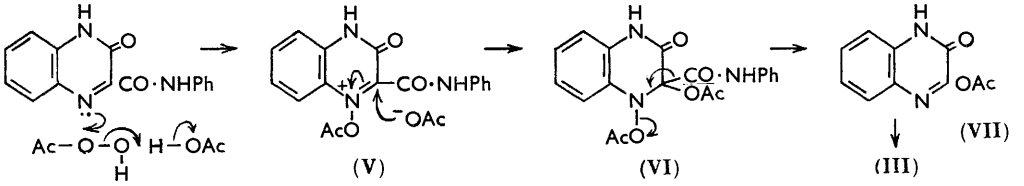
(IV)

3-oxoquinoxaline (IV), also prepared by monomethylation of (III), from (Ic). Thus when either or both of the *N*-methyl groups in (Id) are replaced by hydrogen, the 2-carboxyanilide group is replaced by a hydroxyl group. With the corresponding pyrazine compounds, both methylanilides (IIb and d) furnished *N*-oxides (68% and 46% respectively) with hydrogen peroxide and acetic acid, but the anilides (IIa and c) did not.[1] Similar unsuccessful attempts to prepare the *N*-oxides of analogous pyridazine compounds have also been reported.[1] Newbold and Spring [3] also found that 2,3-dihydroxyquinoxaline (III) was the product of oxidation of 2-hydroxyquinoxaline, 3-hydroxyquinoxaline-2-carboxylic acid, and 2,3-quinoxaline dicarboxylic acid with hydrogen peroxide and acetic acid. We find that this oxidation extends to the esters of these acids; ethyl 3,4-dihydro-4-methyl-3-oxoquinoxaline-2-carboxylate gives 3,4-dihydro-2-hydroxy-4-methyl-3-oxoquinoxaline in 50% yield and no *N*-oxide. Landquist [4] has also described the formation of compound (IV) from 3,4-dihydro-4-methyl-3-oxoquinoxaline with peracetic acid. A mechanism has not yet been proposed for these oxidations. When the >NH groups of the quinoxaline compounds (Ib and c) were protected by acetylation, 4-acetyl-3,4-dihydro-3-oxoquinoxaline-2-carboxy-*N*-methylanilide (I; R = Ac, R′ = Me) gave an *N*-oxide (50%) but 3,4-dihydro-4-methyl-3-oxoquinoxaline-2-carboxy-*N*-acetylanilide (I; R = Me, R′ = Ac) did not. Thus for *N*-oxide formation, the anilide-nitrogen atom must be alkylated, whilst the milder protection by acylation suffices for the heterocyclic nitrogen. This parallels the situation with the pyrazine compounds and indicates the greater sensitivity of the molecule to oxidation when the acyclic, rather than the cyclic, amide-nitrogen is not protected.

This unusual oxidation has approximately the same, limited scope among similar heterocyclic systems as that reported for the acid-catalysed *N*-oxide rearrangement [1] and the formation of 1,2-dihydro-compounds with sodium dithionite.[5] For example, the corresponding pyridine- and quinoline-carboxyanilides were oxidised to *N*-oxides [1] in high yield, and in the absence of the 3-oxo-substituent quinoxalinecarboxyanilides gave *N*-oxides normally. Quinoxaline-2-carboxy-anilide and -methylanilide yielded 1,4-dioxides with excess of peracetic acid and mono-oxides with one equivalent of this reagent; the structure of these mono-oxides is discussed below. Thus it was considered probable that these " abnormal " oxidations are controlled by the driving force invoked [1,5] for the above reactions—the marked electrophilicity of the 2-position of the quinoxaline, and to a smaller extent of the pyrazine. A reasonable mechanism is illustrated here for the peracetic acid oxidation of 3-hydroxyquinoxaline-2-carboxyanilide. The *N*-acetoxy-derivative (V), if hydrolysed, yields the *N*-oxide in the normal manner. However, alternative nucleophilic substitution of the quinoxaline ring can occur (cf. V) if $C_{(2)}$ is sufficiently electrophilic.

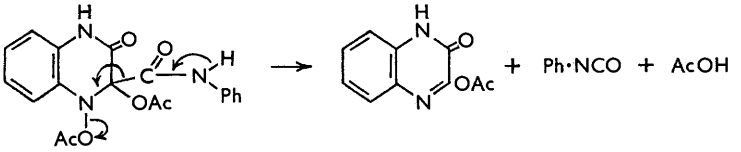
[2] Clark-Lewis, *J.*, 1957, 439.
[3] Newbold and Spring, *J.*, 1948, 519.
[4] Landquist, *J.*, 1953, 2830.
[5] Habib and Rees, preceding paper.

Elimination as shown in (VI) would then give the very unstable acetyl derivative [6] (VII) which would be rapidly hydrolysed to 2,3-dihydroxyquinoxaline (III).



The increasing importance of this nuclear substitution, relative to *N*-oxide formation, as $C_{(2)}$ becomes more electrophilic is clearly demonstrated by Landquist's results.[7] He showed that, under conditions where quinoxaline yields its di-*N*-oxide exclusively, 6-substituted quinoxalines yield less *N*-oxide and more of the corresponding 2,3-dihydroxy-compound as the substituent, which is conjugated with $C_{(2)}$, becomes more powerfully electron-withdrawing. 6-Nitroquinoxaline, for example, is oxidised to 2,3-dihydroxy-6-nitroquinoxaline in 60% yield, with only traces of *N*-oxides. Further support for this mechanism is provided by the susceptibility [8] of the 1-oxide of (Id) to nucleophilic attack at $C_{(2)}$ by ethoxide ions: warm ethanolic sodium ethoxide rapidly converts this compound into methylaniline, formic acid, and the 1-oxide of (IV), the product of hydroxyl substitution at $C_{(2)}$. 3,4-Dihydro-4-methyl-3-oxoquinoxaline-2-carboxy-*N*-methylanilide 1-oxide is also somewhat unstable under the conditions of its preparation by the oxidation of (Id); the yields are never high and tarry by-products are formed. It was recovered in 66% yield, together with a red tar, after being heated with 10% peracetic acid for 24 hours at 65°. Further, 3,4-dihydro-4-methyl-3-oxoquinoxaline-2-carboxyanilide (Ic), under conditions where it is largely decomposed by hydrogen peroxide and acetic acid, is stable to neutral and alkaline hydrogen peroxide and to sodium hydroxide alone, that is, where no *N*-oxide is formed. This mechanism (*e.g.*, V ⟶ VI ⟶ VII) also explains the difference in behaviour of the anilides (IIb) and (Ib) towards oxidation. The former gives the oxide in high yield, whilst the latter is hydroxylated at $C_{(2)}$ to give 2,3-dihydroxyquinoxaline (III) and no *N*-oxide. This accords with the greater electrophilicity of $C_{(2)}$ in the quinoxaline ring, as previously demonstrated [1,5] for very similar compounds.

Finally, the rôle of the *N*-methyl groups in controlling the direction of oxidation of the quinoxaline compounds (I) requires comment. The obvious explanations are unsatisfactory, and the situation is complicated since the exact fate of the ejected carboxyanilide or methylanilide group is not known. Electron-release by the *N*-methyl groups would cause a slight reduction in the electrophilicity of $C_{(2)}$ and so could reduce the amount of "abnormal" oxidation, but the similar effect of the *N*-acetyl group in (I; R = Ac, R′ = Me) argues against this explanation. The unsubstituted >NH groups can hardly be considered as sites of initial oxidative degradation since many carboxyanilides and 3-hydroxypyrazine-2-carboxy-*N*-methylanilide (IIb) give *N*-oxides in high yield. An attractive explanation of the oxidation of the anilides (IIa and c) and (Ia and c) would be the elimination of the side chain, *e.g.*, in (VI), as phenyl isocyanate:

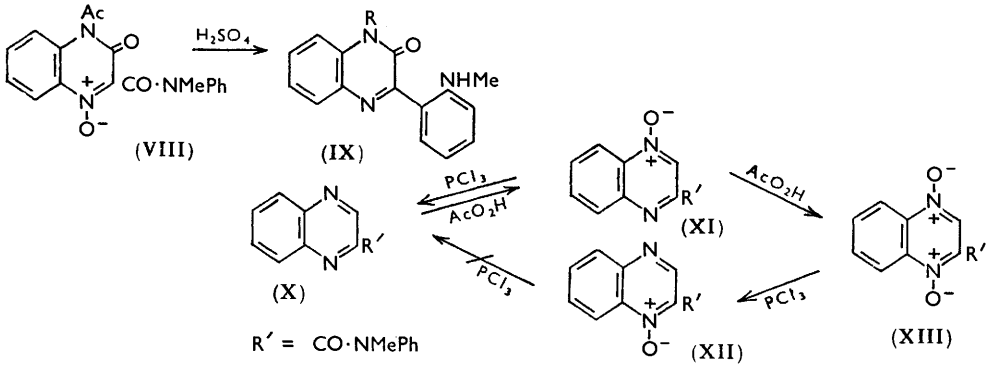


[6] Cf. Heller, Buchwaldt, Fuchs, Kleinicke, and Kloss, *J. prakt. Chem.*, 1925, **111**, 1.
[7] Landquist, *J.*, 1953, 2816.
[8] Usherwood and Whiteley, *J.*, 1923, **123**, 1069.

This must be discounted, however, since diphenylurea, separately shown to be the transformation product of phenyl isocyanate under the reaction conditions, could not be detected in a typical oxidation of the anilide (Ic).

The non-heterocyclic oxidation products, when isolated, were obtained as tars which were not characterised. The tars are probably the oxidation products of the anilines liberated during the reaction, possibly by decarboxylation of arylcarbamic acid formed by nucleophilic attack of the acyclic carboxyamide group.

Since attempts to prepare the oxides of the quinoxaline amides (Ia, b, and c) were not successful, it is not known whether they would undergo the same rearrangement in sulphuric acid as that of the amide (Id). 4-Acetyl-3,4-dihydro-3-oxoquinoxaline-2-carboxy-*N*-methylanilide 1-oxide (VIII), however, did rearrange analogously, to give some 4-acetyl-3,4-dihydro-2-(*o*-methylaminophenyl)-3-oxoquinoxaline (IX; R = Ac) but largely the hydrolysis product, 3-hydroxy-2-*o*-methylaminophenylquinoxaline (IX; R = H).



The two mono-oxides of quinoxaline-2-carboxy-*N*-methylanilide (X) have been prepared and characterised as follows. Oxidation with one mol. of peracetic acid gave one mono-oxide, m. p. 150°, which was readily deoxygenated with cold phosphorus trichloride to (X). Oxidation with an excess of peracetic acid gave the dioxide (XIII) which on reduction gave a second mono-oxide, m. p. 198—199°, which resisted deoxygenation by cold phosphorus trichloride. The former oxide, which is more readily formed and more readily reduced, is assigned the 4-oxide structure (XI) where steric compression in the transition states for both reactions will be considerably less than for reaction at $N_{(1)}$. Here the bulky *ortho*-substituent hinders both direct oxidation to the 1-oxide (XII), and reduction of this oxide. Quinoxaline-2-carboxyanilide was similarly oxidised to the di-*N*-oxide, which was reduced to the 1-oxide with cold phosphorus trichloride.

Experimental

Anilides.—The preparations of 3-hydroxy-[1] (Ia) and 3,4-dihydro-4-methyl-3-oxo-quinoxaline-2-carboxyanilide [2] (Ic) and 3,4-dihydro-4-methyl-3-oxoquinoxaline-2-carboxy-*N*-methylanilide [1] (Id) have been described.

3-*Hydroxyquinoxaline-2-carboxy*-N-*methylanilide* (Ib).—3-Hydroxyquinoxaline-2-carboxylic acid chloride, from the acid [1] (3·0 g.) and thionyl chloride, was suspended in benzene, and a solution of methylaniline (10 ml.) in benzene (15 ml.) was slowly added. The mixture was washed with 2N-hydrochloric acid (2 × 100 ml.) to yield a pink solid which crystallised from ethanol (charcoal) as pale yellow needles of 3-*hydroxyquinoxaline-2-carboxy*-N-*methylanilide* (3·1 g., 71%), m. p. 242° (Found: C, 68·8; H, 5·0; N, 15·1. $C_{16}H_{13}O_2N_3$ requires C, 68·8; H, 4·7; N, 15·05%).

4-*Acetyl*-3,4-*dihydro*-3-*oxoquinoxaline*-2-*carboxy*-N-*methylanilide* (I; R = Ac, R′ = Me).—A mixture of 3-hydroxyquinoxaline-2-carboxy-*N*-methylanilide (0·5 g.) and acetyl chloride (5 ml.) was heated under efficient reflux for 24 hr. The excess of acetyl chloride was distilled and the residue crystallised from ethanol as colourless needles of the *acetyl derivative* (0·5 g.,

86%), m. p. 216° (Found: C, 67·6; H, 4·5; N, 12·8. $C_{18}H_{15}O_3N_3$ requires C, 67·3; H, 4·7; N, 13·1%).

4-Acetyl-3,4-dihydro-3-oxoquinoxaline-2-carboxy-N-methylanilide 1-Oxide (VIII).—A mixture of the acetyl derivative (1·2 g.), acetic acid (6 ml.) and 30% hydrogen peroxide (1·2 ml.) was heated at 55° and two further quantities of hydrogen peroxide (0·6 ml.) were added after 20 and 40 hr. After 60 hours' heating in all, the acetic acid was removed under reduced pressure and the residual gum extracted with ethanol. The ethanolic solution, on concentration and dilution with water, gave a pale yellow precipitate which crystallised from benzene–chloroform as cubes of *4-acetyl-3,4-dihydro-3-oxoquinoxaline-2-carboxy-N-methylanilide 1-oxide* (0·6 g., 47%), m. p. 216—217° (Found: C, 63·8; H, 4·4. $C_{18}H_{15}O_4N_3$ requires C, 64·1; H, 4·5%). The mixed m. p. with starting material was depressed by 20°.

3,4-Dihydro-4-methyl-3-oxoquinoxaline-2-carboxy-N-acetylanilide (I; R = Me, R′ = Ac).—3,4-Dihydro-4-methyl-3-oxoquinoxaline-2-carboxyanilide (0·5 g.) and acetic anhydride (5 ml.) were heated under reflux for 24 hr. On cooling, crystals separated and recrystallised from benzene and light petroleum (b. p. 60—80°) to give yellow needles of the *acetyl derivative* (0·4 g., 69%), m. p. 254° (Found: N, 13·1. $C_{18}H_{15}O_3N_3$ requires N, 13·1%). Oxidation of this anilide with hydrogen peroxide and acetic acid at 55° for 72 hr. gave 3,4-dihydro-2-hydroxy-4-methyl-3-oxoquinoxaline (IV) (50%), m. p. 283—284°, alone and on admixture with an authentic sample (see below). The same product was obtained in 50% yield by a similar oxidation of ethyl 3,4-dihydro-4-methyl-3-oxoquinoxaline-2-carboxylate.[1]

Attempted Preparation of the 1-Oxides of the Quinoxaline-anilides (Ia, b, and c).—The anilide (1·0 g.) was treated with the oxidising agent at the temperature and for the time shown in the Table. The products were isolated by removing volatile components under reduced pressure

Temp.	Time (hr.)	AcOH (ml.)	30% H_2O_2 (ml.)	AcO_2H (40% in AcOH) (ml.)	B_3O_2H (6% in $CHCl_3$) (ml.)	Products
3-Hydroxyquinoxaline-2-carboxyanilide (Ia)						
20°	48	2	—	3	—	Starting material 80%
36	36	4	—	1·5	—	,, ,, 65%
45	28	—	—	2 [a]	—	,, ,, 67%
76	2	—	—	1·5 [b]	—	,, ,, 78%
56	60	5	2	—	—	2,3-Dihydroxyquinoxaline 75%
65	20	4	—	4	—	,, ,, 80%
100	0·3	—	—	5	—	,, ,, 55%
3-Hydroxyquinoxaline-2-carboxy-N-methylanilide (Ib)						
20	48	8	—	3	—	Starting material 70%
43	18	10	—	1·5	—	,, ,, 70%
55	18	—	—	3 [c]	—	,, ,, 80%
40	72	10	3·5	—	—	2,3-Dihydroxyquinoxaline 50%
40	72	9·5	—	3·5	—	Starting material and 2,3-dihydroxyquinoxaline
20	72	—	—	—	30	Starting material 40% and dihydroxyquinoxaline 10%
20	240	—	—	—	35	2,3-Dihydroxyquinoxaline and tar
65	50	5	4	—	—	2,3-Dihydroxyquinoxaline 75%
3,4-Dihydro-4-methyl-3-oxoquinoxaline-2-carboxyanilide (Ic)						
20	48	4	—	4	—	Starting material 100%
40	72	10	2·5	—	—	3,4-Dihydro-2-hydroxy-4-methyl-3-oxoquinoxaline 60%
56	72	5	2	—	—	70%
65	42	5	2	—	—	75%

[a] Also 15 ml. of NMe_2Ac. [b] Also 6 ml. of MeOH. [c] Also 10 ml. of Pr^iOH.

and were separated and purified by crystallisation. 2,3-Dihydroxyquinoxaline was identified by comparison of its infrared spectrum (in Nujol mull) with that of a sample, m. p. 360°, prepared by the condensation of *o*-phenylenediamine and ethyl oxalate.[3] 3,4-Dihydro-2-hydroxy-4-methyl-3-oxoquinoxaline (IV) was identified by mixed m. p. and infrared comparison with an authentic sample,[9] m. p. 286—288°. The latter compound was also prepared in low yield by monomethylation of 2,3-dihydroxyquinoxaline (below).

[9] Cheeseman, *J.*, 1955, 1804.

Further Oxidations with Peracetic acid.—The following results were obtained on heating the compounds with 10% peracetic acid in acetic acid at 65° for 24 hr. 2,3-Dihydroxyquinoxaline (III) was recovered almost quantitatively. 3,4-Dihydro-4-methyl-3-oxoquinoxaline-2-carboxy-*N*-methylanilide 1-oxide was recovered in 66% yield, the residue being a tar. Phenyl isocyanate was converted, almost quantitatively, into diphenylurea, m. p. 240°. 3,4-Dihydro-4-methyl-3-oxoquinoxaline-2-carboxyanilide (Ic) was converted into 3,4-dihydro-2-hydroxy-4-methyl-3-oxoquinoxaline (IV), m. p. 286—287°, in high yield [no diphenylurea was detected in this product; the presence of diphenylurea in prepared mixtures with (IV) was readily detected by m. p. behaviour]. 3-Hydroxyquinoxaline-2-carboxyanilide (Ia) was converted into 2,3-dihydroxyquinoxaline and a tar.

Further Reactions of 3,4-*Dihydro-4-methyl-3-oxoquinoxaline-2-carboxyanilide* (Ic).—This anilide was treated severally with excess of 10% aqueous hydrogen peroxide, 10% hydrogen peroxide in 2N-sodium hydroxide, and 2N-sodium hydroxide at 65° for 24 hr. and was recovered in each experiment in >90% yield.

3,4-*Dihydro-2-hydroxy-4-methyl-3-oxoquinoxaline* (IV).—2,3-Dihydroxyquinoxaline (3 g.), dimethyl sulphate (1 ml.) and 2N-sodium hydroxide (75 ml.) were shaken together at room temperature for 2 hr. The solid precipitated on acidification was collected, dried at 100°, and extracted with dry acetone (100 ml.). The acetone was removed and the residue, largely starting material, was dissolved in the minimum volume of hot acetic acid. On cooling, 2,3-dihydroxyquinoxaline crystallised, and the mother-liquor yielded the monomethylated product on addition of water. This crystallised from dilute acetic acid as colourless needles, m. p. 286—288° (12%, after allowance for recovered starting material). Cheeseman [9] reports m. p. 286—287° for this compound.

Rearrangement of 4-*Acetyl*-3,4-*dihydro*-3-*oxoquinoxaline*-2-*carboxy*-N-*methylanilide* 1-*Oxide* (VIII) *in Sulphuric Acid.*—The oxide was added portionwise with stirring to concentrated sulphuric acid (2 ml.), and the mixture left at room temperature for 20 min. and then poured on ice (5 g.) and filtered. The filtrate, on neutralisation with aqueous sodium hydroxide, gave an orange precipitate which was collected, dried, and extracted with benzene. The residue was crystallised from a large volume of benzene as yellow needles of 4-*acetyl*-3,4-*dihydro*-2-(*o-methylaminophenyl*)-3-*oxoquinoxaline* (0·02 g., 11%), m. p. 204—205° (Found: C, 69·5; H, 5·9. $C_{17}H_{15}O_2N_3$ requires C, 69·6; H, 5·15%). The original benzene extract was evaporated and the residue crystallised from aqueous dimethylformamide as orange needles of 3-*hydroxy*-2-(*o-methylaminophenyl*)*quinoxaline* (0·102 g., 73%), m. p. 221—222° (Found: C, 71·3; H, 5·1. $C_{15}H_{13}ON_3$ requires C, 71·7; H, 5·2%). The last compound was methylated with dimethyl sulphate in the usual manner to give 3,4-dihydro-4-methyl-2-(*o*-methylaminophenyl)-3-oxoquinoxaline, m. p. 130°, alone and on admixture with an authentic specimen.[2]

Quinoxaline-2-carboxyanilide 1,4-*Dioxide.*—Quinoxaline-2-carboxyanilide [10] (1 g.), acetic acid (2 ml.), and 40% peracetic acid (5 + 2 ml.) were treated as described for the oxide (VIII) above, to yield a gum which solidified on trituration with ethanol. The yellow *di*-N-*oxide* crystallised from dimethylformamide as leaflets (0·67 g., 60%), m. p. 211° (Found: C, 63·65; H, 3·7. $C_{15}H_{11}O_3N_3$ requires C, 64·05; H, 3·9%).

Quinoxaline-2-carboxyanilide 1-*Oxide.*—To quinoxaline-2-carboxyanilide-1,4-dioxide (0·2 g.) in chloroform (2 ml.), phosphorus trichloride (0·4 ml.) was added and the mixture left at room temperature overnight and then poured on ice (10 g.). Aqueous sodium hydroxide was added in slight excess, the chloroform removed, and the yellow solid which separated crystallised from ethanol to give needles of *quinoxaline-2-carboxyanilide* 1-*oxide* (0·15 g., 79%), m. p. 159° (Found: C, 67·7; H, 4·3; N, 15·65. $C_{15}H_{11}O_2N_3$ requires C, 67·9; H, 4·2; N, 15·8%).

Quinoxaline-2-carboxy-*N*-methylanilide (X) and its 1-oxide (XII) and 1,4-dioxide (XIII) were prepared as before.[1]

Quinoxaline-2-carboxy-N-*methylanilide* 4-*Oxide* (XI).—A mixture of quinoxaline-2-carboxy-*N*-methylanilide (0·8 g.), acetic acid (2·5 ml.), and 30% peracetic acid (1·27 ml., 1 equiv.) was heated at 55° for 16 hr. and then evaporated under reduced pressure. The residue of 4-*oxide* crystallised from ethanol as light yellow needles (0·55 g., 65%), m. p. 150° (Found: C, 68·5; H, 4·8; N, 15·3. $C_{16}H_{13}O_2N_3$ requires C, 68·8; H, 4·7; N, 15·05%).

Reaction of Quinoxaline-2-carboxy-N-*methylanilide Mono-oxides with Phosphorus Trichloride.*—The 4-oxide (XI) (0·2 g.), chloroform (2 ml.), and phosphorus trichloride (0·4 ml.) were left together at room temperature for 16 hr. and then poured on ice. Excess of aqueous sodium

[10] Maurer and Boettger, *Ber.*, 1938, **71**, 1383.

hydroxide was added and the chloroform removed. Quinoxaline-2-carboxy-*N*-methylanilide which separated on cooling crystallised from aqueous ethanol as needles (0·14 g., 80%), m. p. and mixed m. p. 124°. The 1-oxide (XII), treated identically, was unchanged.

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