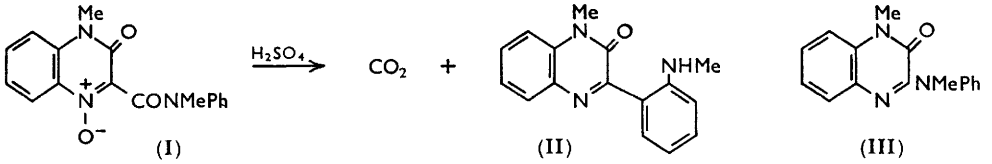
## 674. *The Mechanism and Scope of an* N*-Oxide Rearrangement.*

By M. S. Habib and C. W. Rees.

The mechanism of the very rapid reaction of 3,4-dihydro-4-methyl-2-(*N*-methyl-*N*-phenylcarbamoyl)-3-oxoquinoxaline 1-oxide (I) in concentrated sulphuric acid at 0° has been elucidated. A novel *N* ⟶ *ortho*-rearrangement of the heterocyclic aroyl group occurs with simultaneous loss of carbon dioxide. This proceeds by intramolecular electrophilic substitution of an *ortho*-position of the anilide by the carboxyamide-bearing carbon in the conjugate acid (I*a* ⟶ XII ⟶ XIII). This carbon atom proved to be insufficiently electrophilic for the rearrangement to occur in most heterocyclic systems investigated; thus the scope of the reaction is severely limited and it was extended only to the corresponding pyrazine compounds.

*The Rearrangement.*—The extremely rapid elimination of carbon dioxide from 3,4-dihydro-4-methyl-2-(*N*-methyl-*N*-phenylcarbamoyl)-3-oxoquinoxaline 1-oxide (I) on treatment with concentrated sulphuric acid at 0° was described by Usherwood and Whiteley [1] who considered the product to be 3,4-dihydro-4-methyl-2-*N*-methylanilino-3-oxoquinoxaline (III). Clark-Lewis [2] confirmed by synthesis the structure (I) for the *N*-oxide but showed that the rearrangement product was a secondary amine, 3,4-dihydro-4-methyl-2-*o*-methylaminophenyl-3-oxoquinoxaline (II). The reaction thus involves migration of an aroyl group from the nitrogen atom to an *ortho*-position of methylaniline with concomitant




(I) (II) (III)

loss of carbon dioxide. As this is an unusual reaction and one which could have synthetic value, its mechanism and scope have been elucidated.

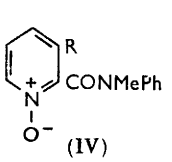
The carbon atom in position 2 of the quinoxaline ring will be rendered strongly

[1] Usherwood and Whiteley, *J.*, 1923, **123**, 1069.
[2] Clark-Lewis, *J.*, 1957, 439.

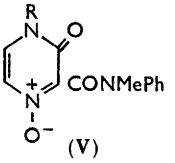
 



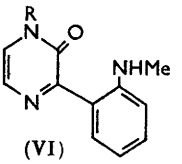
electrophilic by protonation of the *N*-oxide group in sulphuric acid, and a new bond is formed between this carbon atom and an *ortho*-position of the methylaniline. It therefore seemed probable that the reaction involves electrophilic attack at this position by $C_{(2)}$. The simplest heterocyclic molecule with the functional groups necessary for this rearrangement is the methylanilide 1-oxide (IV; R = H) of picolinic acid. This was found to be stable to concentrated sulphuric acid up to 60° and at higher temperatures was sulphonated, but no carbon dioxide was liberated. The 3-hydroxy-analogue (IV; R = OH), with an electron-withdrawing oxonium group (in concentrated sulphuric acid) *ortho* to $C_{(2)}$ of the pyridine ring, was also unchanged by sulphuric acid at 60°. Thus it seemed



(IV)

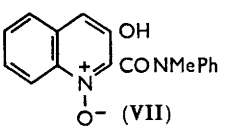


(V)

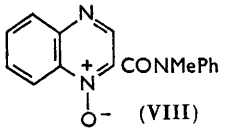


(VI)

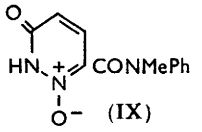
that in these pyridine compounds the carboxyamide-bearing carbon atom was not sufficiently electrophilic for the rearrangement to occur. Next the pyrazine derivatives (V; R = H and Me) were synthesised; in concentrated sulphuric acid both liberated carbon dioxide and developed a red colour [like the quinoxaline (I)]. However, these reactions were slow, requiring 2 hr. at 55° for completion compared with <10 min. at 0° for (I). Each of the pyrazine *N*-oxides rearranged to one product only (VI; R = H and Me respectively), in almost quantitative yield, in contrast to the quinoxaline *N*-oxide where the yield of the corresponding product (II) is considerably lower and a second product [1] can be isolated. The slower, uncomplicated reactions of the pyrazine compounds made them more suitable for use in experiments designed to establish the rearrangement mechanism. In view of the marked accelerating effect on this reaction of the fused benzene ring in the quinoxaline compound (I) it was hoped to investigate the action of concentrated sulphuric acid on 3-hydroxy-2-(*N*-methyl-*N*-phenylcarbamoyl)-quinoline 1-oxide (VII), but our attempts to prepare this compound were unsuccessful. 2-(*N*-Methyl-*N*-phenylcarbamoyl)quinoline 1-oxide itself did not rearrange.



(VII)



(VIII)



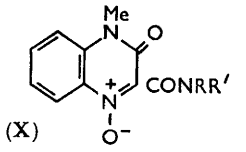
(IX)

The 1-oxide (VIII) was then prepared: it was stable in concentrated sulphuric acid at 55° for 16 hr. Thus both the ring nitrogen atom *meta*, and the potential hydroxyl group *ortho*, to the anilide groups are necessary for rearrangement at a detectable rate. Moreover, the oxide (IX), where the second heterocyclic nitrogen atom was in the alternative *meta*-position, did not rearrange in concentrated sulphuric acid at 55° for 24 hr. In this instance the recovery of starting material was low but this was presumably caused by sulphonation and not by rearrangement since none of the rearrangement product was isolated. Therefore the (potential) hydroxyl group, which is essential, must be *ortho* to the anilide group, in agreement with the postulated electron-withdrawal from $C_{(2)}$ by the oxonium ion, by its powerful inductive effect.

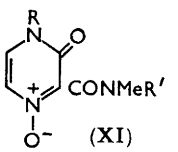
These results show that the carboxyamide-bearing carbon must be markedly electrophilic in the protonated form of the molecule in concentrated sulphuric acid, and this severely limits the scope of the reaction, which has only been effected with hydroxypyrazine and hydroxyquinoxaline derivatives. In contrast to this limitation on the structure of the heterocyclic part of the molecule, various anilide derivatives of the pyrazine and

quinoxaline acids were rearranged successfully. It is probable that any anilide of these acids with a free *ortho*-position would rearrange.

With the scope of the rearrangement broadly defined, the following results, which establish its mechanism, were obtained.



(X)



(XI)

(i) The oxide (X; R = R′ = Me) was recovered unchanged from concentrated sulphuric acid at 20° showing that the phenyl ring of the anilide is necessary for reaction. The corresponding diphenylamide rearranged completely in 5 min. in the acid in an ice–salt bath.

(ii) The *N*-oxide (X; R = Me, R′ = 2,6-$C_6H_3Me_2$) was unaffected by concentrated sulphuric acid at 20°, showing that the anilide must have a free *ortho*-position; migration to the *para*-position did not occur.

(iii) The oxide (X; R = Me, R′ = *p*-$NO_2{\cdot}C_6H_4$) required 24 hr. at 55° for complete rearrangement, compared with less than 10 min. at 0° for the analogous compound without the nitro-group. This powerful retarding effect of an electron-withdrawing substituent in the anilide ring confirms the electrophilic nature of the attack on this ring. The nitro-group is too remote to exert an appreciable steric effect.

(iv) 3,4-Dihydro-4-methyl-2-*N*-methylanilino-3-oxoquinoxaline (III), originally thought to be the reaction product,[1] was stable to concentrated sulphuric acid at 20°. This precludes mechanisms requiring loss of carbon dioxide to give this "unrearranged" product (III), followed by an $N \longrightarrow$ *ortho*-migration of the heterocyclic residue.

(v) The oxide (XI; R = H, R′ = *p*-$C_6H_4$Me) rearranged at a rate very similar to that of the isomer (XI; R = Me, R′ = Ph), and also yielded one product almost quantitatively; further, a mixture of their rearrangement products could be separated with aqueous alkali. A mixture of equimolecular amounts of these two *N*-oxides was rearranged in sulphuric acid and only two products, 3-hydroxy-2-(5-methyl-2-methylaminophenyl)-pyrazine and 3,4-dihydro-4-methyl-2-(*o*-methylaminophenyl)-3-oxopyrazine (VI; R = Me), were isolated, in the same high yield (93—94%) as when the two oxides were rearranged separately. Since neither of the "crossed" products could be detected the rearrangements are intramolecular and do not involve initial fission, for example by hydrolysis of the amide bond.

(vi) The *N*-oxide function was necessary for this reaction where carbon dioxide is lost. The corresponding unoxidised bases were inert to sulphuric acid, except for certain quinoxaline anilides which underwent a similar rearrangement but without the final decarboxylation. These reactions will be described later.

(vii) Rearrangement of the quinoxaline *N*-oxide (I) was catalysed by polyphosphoric acid at 55°, to give the same products as sulphuric acid.

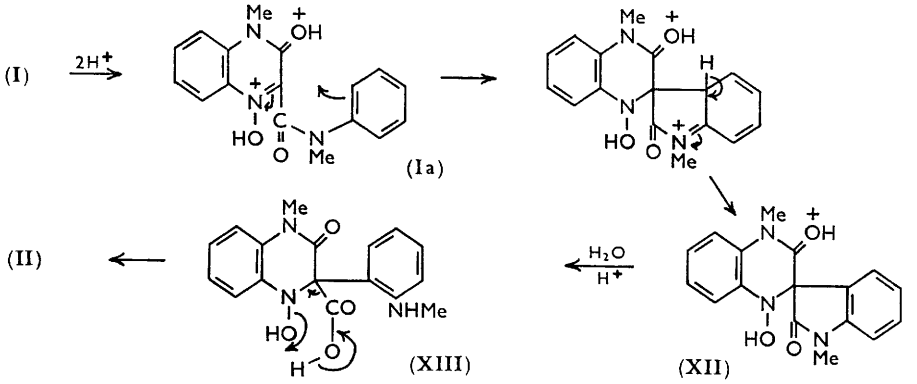
These results show that the rearrangement must be caused by intramolecular electrophilic substitution of the anilide *ortho*-position by $C_{(2)}$ of the heterocyclic ring, as shown for the quinoxaline oxide (I). The very ready decarboxylation and dehydration of the acid (XIII) is presumably due to the availability of the cyclic transition state shown, analogous to that for β-keto-acids [3] and βγ-unsaturated acids.[4] This mechanism is also supported by the stability of the product, analogous to (XIII), formed from the corresponding unoxidised base in concentrated sulphuric acid, for this base rearranges without decarboxylation. Certain observations in the literature agree with the view that $C_{(2)}$ of quinoxaline

[3] Westheimer and Jones, *J. Amer. Chem. Soc.*, 1941, **63**, 3283.
[4] Arnold, Elmer, and Dodson, *J. Amer. Chem. Soc.*, 1950, **70**, 4359; Barton and Brooks, *J.*, 1951, 257.



is particularly electrophilic, a property sufficiently developed in the conjugate acid (I*a*) to initiate this very rapid sequence of reactions. Chapman and Russell-Hill,[5] for example, have measured the reactivity of chlorine in heterocyclic systems towards nucleophilic displacement by ethoxide ions, which is strongly accelerated if the carbon bearing the chlorine atom is electrophilic. They found that 2-chloroquinoxaline was even more reactive than 2-chloroquinazoline where the chlorine atom is *ortho* to both the activating




nitrogen atoms. Clark-Lewis [2] has also demonstrated the same reactivity to nucleophilic substitution in the very ready formation of the anilinoquinoxaline (III) from 2-chloro-3,4-dihydro-4-methyl-3-oxoquinoxaline and methylaniline. The considerable acid strength of 2-nitromethylquinoxaline, which dissolves in 5% aqueous sodium hydrogen carbonate,[6] can be similarly explained. Further evidence of this marked reactivity of quinoxalines to nucleophilic attack in various reactions will be presented later.

An attempt to extend this rearrangement to a five-membered heterocyclic system failed because the compound chosen, 2-(*N*-methyl-*N*-phenylcarbamoyl)benzoxazole 3-oxide, could not be prepared.

*Materials.*—The anilides and methylanilides were prepared from the carboxylic acids: (*a*) *via* the acid chloride prepared with thionyl chloride; (*b*) by conversion of the amine into the " phosphazo "-derivative [*e.g.*, Ph·NH·P=NPh, $(PhMeN)_3P$] and reaction of this with the acid; and (*c*) by direct interaction of the acid or amide with the required amine. Method (*b*) generally was most satisfactory in providing pure products which were readily isolable, particularly where method (*a*) gave intractable tars, but the yields were sometimes higher by method (*a*) when purified thionyl chloride was used. Wide variation of reaction time (5 min.—3 hr.) was noted for method (*b*); this method was extended to the preparation of *N*-methyl-*p*-toluidides with phosphorus tri-(*N*-methyl-*p*-toluidide). When the acid amide was readily available, the anilides were often obtained in high yield by method (*c*).

The *N*-oxides were usually prepared with peracetic acid, but a mixture of hydrogen peroxide and acetic acid, which required longer reaction times, caused less tar-formation when the base was sensitive to oxidation.

Picolinic acid was prepared by a modification of Clemo and Ramage's method [7] and 3-hydroxypicolinic acid was prepared by diazotisation of 3-aminopicolinic acid.[8] 3-Hydroxyquinaldine, m. p. 260°, was prepared from *o*-aminobenzaldehyde and chloroacetone by the method due to Koenigs and Stockhausen,[9] and from 3-aminoquinaldine.[10] Kulisch,[11]

[5] Chapman and Russell-Hill, *J.*, 1956, 1563.
[6] Fanta, Stein, and Rickett, *J. Amer. Chem. Soc.*, 1958, **80**, 4578.
[7] Clemo and Ramage, *J.*, 1931, 440.
[8] Sucharda, *Ber.*, 1925, **58**, 1728; Blicke and Jenner, *J. Amer. Chem. Soc.*, 1942, **64**, 1722.
[9] Koenigs and Stockhausen, *Ber.*, 1902, **35**, 2556.
[10] Bargellini and Berlingozzi, *Gazzetta*, 1923, **53**, 3.
[11] Kulisch, *Monatsh.*, 1895, **16**, 355.

however, assigned this structure to a compound, m. p. 203—205°, obtained from *o*-toluidine and ethyl pyruvate. Support for Koenigs and Stockhausen's structure for the compound, m. p. 260°, is provided here by its ready condensation with benzaldehyde to give 3-hydroxy-2-styrylquinoline. This styryl compound should be readily converted into the corresponding acid; however, no 3-hydroxyquinaldinic acid was isolated from oxidations of the quinoline or its acetate or benzoate. Since benzoic acid was isolated in good yield the difficulty was thought to be isolation of the hydroxy-acid free from inorganic material. 3-Methoxy-2-styrylquinoline was therefore prepared and oxidised to 3-methoxyquinaldinic acid hydrate in low yield. Attempts to prepare this acid anhydrous resulted in decarboxylation to 3-methoxyquinoline, and demethylation with hydriodic acid was accompanied by decarboxylation to 3-hydroxyquinoline.

The methylanilide of 6-hydroxypyridazine-3-carboxylic acid [12] was methylated to 1,6-dihydro-1-methyl-3-(*N*-methyl-*N*-phenylcarbamoyl)-6-oxopyridazine and also oxidised to the *N*-oxide and 3,6-dihydroxypyridazine. Oxidation of the 1-methyl-compound with peracetic acid or hydrogen peroxide in acetic acid gave only 1,6-dihydro-3-hydroxy-1-methyl-6-oxopyridazine.

4,5-Diamino-2,6-dihydroxypyrimidine was prepared by Bogert and Davidson's method [13] but we obtained the free base and not the sulphate. This was converted [14] into 2,4-dihydroxypteridine which was hydrolysed [15] to 3-hydroxypyrazine-2-carboxylic acid in high yield; 2,4-dihydroxypteridine [16] gave much lower yields of the pyrazine acid. Aminomalonamide was obtained by ammonolysis [17] of ethyl aminomalonate prepared [18] by the reduction of ethyl nitrosomalonate.[19] Condensation of aminomalonamide with glyoxal consistently gave much lower yields (20—35%) of 3-hydroxypyrazine-2-carboxyamide than that (92%) claimed by Jones.[17] Hofmann degradation [20] of this amide gave 2-amino-3-hydroxypyrazine which was converted into 2,3-dihydroxypyrazine required for comparison with a product isolated in the oxidation of 3-hydroxypyrazine-2-carboxyanilide. 3-Hydroxy-2-(*N*-methyl-*N*-phenylcarbamoyl)pyrazine and the corresponding *p*-toluidide and 3,4-dihydro-4-methyl-2-(*N*-methyl-*N*-phenylcarbamoyl)-3-oxopyrazine yielded *N*-oxides normally.

Quinoxaline-2-carboxylic acid [21] was converted into its methylanilide which was oxidised to the 1,4-dioxide with excess of peracetic acid. 2-(*N*-Methyl-*N*-phenylcarbamoyl)quinoxaline 1-oxide was prepared from this by partial deoxygenation with phosphorus trichloride in chloroform; evidence for the structure of this mono-oxide and the 4-isomer will be presented later. 3-Hydroxyquinoxaline-2-carboxylic acid, prepared by the method of Gowenlock *et al.*[22] or more readily by alkaline hydrolysis of alloxazine, was converted into the methylanilide and the *N*-methyl-*p*-nitroanilide which were then methylated. Ethyl 3-hydroxyquinoxaline-2-carboxylate [22] was methylated and hydrolysed to 3,4-dihydro-4-methyl-3-oxoquinoxaline-2-carboxylic acid, thus avoiding the need for the inaccessible *N*-methyl-*o*-phenylenediamine required in King and Clark-Lewis's [23] preparation of this acid. Its acid chloride was allowed to react separately with dimethylamine, methylaniline, diphenylamine, and *N*-methyl-2,4- and -2,6-xylidine, to yield the corresponding amides which were converted into their *N*-oxides in the usual way, except for the two xylidides. The 2,6-isomer gave a small yield of the corresponding *N*-oxide with peracetic acid at 100°, but attempts to oxidise the 2,4-isomer were unsuccessful.

[12] Evans and Wiselogle, *J. Amer. Chem. Soc.*, 1945, **67**, 60.
[13] Bogert and Davidson, *J. Amer. Chem. Soc.*, 1933, **55**, 1667.
[14] Weijlard, Tishler, and Erickson, *J. Amer. Chem. Soc.*, 1945, **67**, 802.
[15] McDonald and Ellingson, *J. Amer. Chem. Soc.*, 1947, **69**, 1034.
[16] Albert, Brown, and Cheeseman, *J.*, 1951, 474.
[17] Jones, *J. Amer. Chem. Soc.*, 1949, **71**, 78.
[18] Locquin and Cerchez, *Compt. rend.*, 1928, **186**, 1360.
[19] Snyder and Smith, *J. Amer. Chem. Soc.*, 1944, **66**, 351.
[20] Muehlmann and Day, *J. Amer. Chem. Soc.*, 1956, **78**, 242.
[21] Maurer and Boettger, *Ber.*, 1938, **71**, 1383.
[22] Gowenlock, Newbold, and Spring, *J.*, 1945, 622.
[23] King and Clark-Lewis, *J.*, 1951, 3381.

Benzoxazole-2-carboxylic acid was prepared by Skraup and Moser's method [24] and converted into the anilide and methylanilide; oxidation of these bases with the usual reagents yielded tars from which no crystalline products were isolated.

## Experimental

Benzene and toluene were dried with sodium wire. Phosphorus tri-(*N*-methylanilide) [25] was stored at room temperature in the absence of moisture. Phenylphosphazoanilide was prepared by the method of Grimmel, Guenther, and Morgan [26] except that the mixture was finally heated on a steam-bath for 30 min., the anilinium chloride was filtered off, and the solvent removed under reduced pressure; the product was ready for use.

*General Method for the Preparation of* N-*Oxides*.—Unless otherwise stated *N*-oxides were prepared by heating a mixture of the base (1·0 g.), acetic acid (2 ml.), and peracetic acid (40%; 3 ml.) at 60° for 16 hr. The acetic acid was then removed under reduced pressure and the residue dissolved in chloroform and neutralised with solid sodium carbonate. The solution was filtered and dried ($Na_2SO_4$), the chloroform removed, and the *N*-oxide purified by crystallisation.

*Picolinanilide*.—(*a*) Prepared directly from picolinic acid [7] (3·1 g.) and aniline (8 g.) at 120—125° for 8·5 hr., and crystallised from light petroleum (b. p. 60—80°), the anilide formed pale yellow needles (2·65 g., 53%), m. p. 76°. Engler [27] reports m. p. 76°.

(*b*) Prepared from the acid (3 g.), through the acid chloride,[28] the anilide formed colourless needles (2·0 g., 40%), m. p. 76°. This yield was increased to 90% if the acid chloride was distilled before addition of aniline.

(*c*) Phenylphosphazoanilide [from aniline (37·4 g.)] was heated under reflux with picolinic acid (10 g.) in dry toluene (100 ml.) for 3 hr.; picolinanilide (8 g., 48%) again had m. p. 76°.

*Picolinanilide* 1-*Oxide*.—Crystallisation from ethyl acetate gave needles of the *oxide* (84%), m. p. 143—145° (Found: C, 67·2; H, 5·1; N, 13·1. $C_{12}H_{10}O_2N_2$ requires C, 67·3; H, 4·7; N, 13·1%).

N-*Methylpicolinanilide*.—(*a*) To the acid chloride [from picolinic acid (20 g.) and thionyl chloride (45 ml.)] in benzene (100 ml.), methylaniline (65 ml.) in benzene was added dropwise, the temperature being kept below 30°. The solution was then heated under reflux for 3 hr., cooled, neutralised with a solution of sodium hydroxide, and extracted with chloroform. Excess of methylaniline and chloroform were removed and the residue was distilled at 140° (bath)/0·02 mm. Crystallisation of the distillate from light petroleum (b. p. 40—60°) gave needles of N-*methylpicolinanilide* (20·1 g., 58·6%), m. p. 54° (Found: C, 73·3; H, 5·7; N, 13·2. $C_{13}H_{12}ON_2$ requires C, 73·6; H, 5·7; N, 13·2%) [*picrate*, m. p. 161° (Found: C, 51·5; H, 3·5; N, 16·0. $C_{19}H_{15}O_8N_5$ requires C, 51·7; H, 3·4; N, 15·9%)].

(*b*) Phosphorus tri-(*N*-methylanilide), obtained from methylaniline (10·7 g.) and phosphorus trichloride (2·3 g.) in dry toluene, and picolinic acid (4·5 g.) in dry toluene (100 ml.) were heated under reflux for 2 hr. The hot solution was filtered and the toluene was removed. The residue, on crystallisation from light petroleum (b. p. 60—80°), gave needles of the methylanilide (1·5 g., 19·5%), m. p. 54° alone or on admixture with the product obtained by method (*a*).

N-*Methylpicolinanilide* 1-*Oxide* (IV; R = H).—Crystallisation from ethyl acetate gave cubes of the *oxide* (84%), m. p. 144° (Found: C, 68·0; H, 5·4; N, 12·3. $C_{13}H_{12}O_2N_2$ requires C, 68·4; H, 5·3; N, 12·3%) [*picrate*, m. p. 152° (Found: C, 49·6; H, 3·4; N, 15·0. $C_{19}H_{15}O_9N_5$ requires C, 49·9; H, 3·3; N, 15·3%)].

3-*Hydroxypicolinic Acid*.—3-Aminopicolinic acid (9 g.) was diazotised. The mixture was boiled and then cooled to room temperature, and the pH was adjusted to 3—4 with sodium hydroxide solution. Water was distilled off and the yellow-red mass dried at 100° and extracted with alcohol until a white insoluble solid remained. Concentration of the alcoholic solution gave pale yellow needles of 3-hydroxypicolinic acid (7·8 g., 75%), m. p. 211—212° (decomp.). Kirpal [29] reports m. p. 205—215° but gives no details for the preparation.

3-*Hydroxypicolinanilide*.—The phosphazo-compound, from aniline (7·5 g.) and phosphorus

[24] Skaup and Moser, *Ber.*, 1922, **55**, 1090.
[25] Abramovitch, Hey, and Long, *J.*, 1957, 1787.
[26] Grimmell, Guenther, and Morgan, *J. Amer. Chem. Soc.*, 1946, **68**, 539.
[27] Engler, *Ber.*, 1894, **27**, 1786.
[28] Späth and Spitzer, *Ber.*, 1926, **59**, 1481.
[29] Kirpal, *Monatsh.*, 1908, **29**, 231.

trichloride (1·8 g.), and 3-hydroxypicolinic acid (1·8 g.) in dry toluene (50 ml.), were boiled under reflux for 2 hr. The solution was filtered, the toluene removed, and the residue extracted with light petroleum (b. p. 80—100°; 400 ml.). On concentration, *3-hydroxypicolinanilide* (2 g., 18%) crystallised as small needles, m. p. 89° (Found: C, 67·1; H, 5·0; N, 12·9. $C_{12}H_{10}O_2N_2$ requires C, 67·3; H, 4·7; N, 13·1%).

*3-Hydroxypicolinic Acid 1-Oxide.*—Crystallised from light petroleum (b. p. 80—100°), the *oxide* (76%) formed needles, m. p. 94·5° (Found: C, 62·7; H, 4·4; N, 12·2. $C_{12}H_{10}O_3N_2$ requires C, 62·6; H, 4·4; N, 12·2%).

*3-Hydroxy-N-methylpicolinanilide.*—Phosphorus tri-(*N*-methylanilide) [from phosphorus trichloride (1·15 g.) and methylaniline (5·5 g.)] and 3-hydroxypicolinic acid (2·0 g.) in dry toluene (100 ml.) were boiled under reflux for 3 hr. The toluene was distilled off and the solid was boiled with water for 15 min. The dried residue was extracted with light petroleum (b. p. 80—100°), and the aqueous filtrate was neutralised with solid hydrogen carbonate and extracted with chloroform. The solution was dried ($Na_2SO_4$) and the chloroform removed. The oily residue was extracted with light petroleum (b. p. 80—100°), and the combined petroleum solutions concentrated, giving needles of *3-hydroxy-N-methylpicolinanilide* (1·9 g., 58%), m. p. 154° (Found: C, 68·5; H, 5·6; N, 12·4. $C_{13}H_{12}O_2N_2$ requires C, 68·4; H, 5·3; N, 12·3%).

*1-Oxide* (IV; R = OH). This *oxide* (95%) crystallised from alcohol as needles, m. p. 263—265° decomp. (Found: C, 64·3; H, 5·0; N, 11·5. $C_{13}H_{12}O_3N_2$ requires C, 63·9; H, 4·9; N, 11·5%).

*N-Methylquinaldinanilide.*—A mixture of phosphorus tri-(*N*-methylanilide) [from phosphorus trichloride (1·2 ml.) and methylaniline (8 ml.)] and quinaldinic acid (3·5 g.) in dry toluene (30 ml.) was heated under reflux for 1 hr. The hot toluene solution was decanted off and the residue extracted with boiling toluene (2 × 25 ml.). The original solution and extracts were combined and the toluene was removed under reduced pressure. The *anilide* crystallised from light petroleum (b. p. 80—100°) as needles (4 g., 67·6%), m. p. 109° (Found: C, 78·1; H, 5·4. $C_{17}H_{14}ON_2$ requires C, 77·8; H, 5·4%).

*1-Oxide.* The *oxide* crystallised from water as needles, m. p. 153—154° (Found: C, 73·7; H, 5·4. $C_{17}H_{14}O_2N_2$ requires C, 73·4; H, 5·1%).

*3-Acetoxy-2-styrylquinoline.*—3-Hydroxy-2-methylquinoline (3·2 g.), acetic anhydride (6 g.), and benzaldehyde (6·4 g.) were heated for 3 hr. at 155—160°. The cooled mixture was diluted with ethanol (50 ml.), and the yellow precipitate crystallised from ethanol, forming pale yellow needles of the *quinoline* (3·2 g., 55·2%), m. p. 130° (Found: C, 78·5; H, 5·3. $C_{19}H_{15}O_2N$ requires C, 78·9; H, 5·2%).

*3-Hydroxy-2-styrylquinoline.*—3-Acetoxy-2-styrylquinoline (3·2 g.) and 6N-hydrochloric acid (32 ml.) were heated under reflux for 1 hr. The mixture was cooled and added to an excess of hot aqueous sodium hydroxide. The alkaline solution was filtered and neutralised; the yellow precipitate crystallised from ethanol, forming orange beads of *3-hydroxy-2-styrylquinoline* (2·5 g., 91·5%), m. p. 206—207° (decomp.) (Found: C, 81·8; H, 5·4. $C_{17}H_{13}ON$ requires C, 82·6; H, 5·3%).

*2-Styryl-3-quinolyl Benzoate.*—3-Hydroxy-2-styrylquinoline (7 g.) was benzoylated with benzoyl chloride (5·5 ml.) in dry pyridine (24 ml.). The *ester* (8·3 g., 83·8%) formed needles, m. p. 178° (from ethanol) (Found: C, 81·2; H, 4·8. $C_{24}H_{17}O_2N$ requires C, 82·0; H, 4·9%).

*3-Methoxy-2-methylquinoline.*—3-Hydroxy-2-methylquinoline (2·0 g.) was methylated in dry methanol with ethereal diazomethane,[30] from *N*-toluene-*p*-sulphonylmethylnitrosamine (21 g.). The product was a gum (2·0 g., 92%), b. p. 172—174°/16 mm. [the *picrate*, prepared in ethanol, had m. p. 227° (decomp.) (Found: C, 50·7; H, 3·8. $C_{17}H_{14}O_8N_4$ requires C, 50·8; H, 3·5%)].

*3-Methoxy-2-styrylquinoline.*—The styryl-compound was similarly prepared by methylation of 3-hydroxy-2-styrylquinoline (6·5 g.) in ethanol (300 ml.); it formed a syrup (6·2 g., 93%) which was used without further purification. The *picrate* (prepared in ethanol) formed yellow needles, m. p. 228° (Found: C, 58·9; H, 3·5. $C_{24}H_{18}O_8N_4$ requires C, 58·8; H, 3·7%).

*3-Methoxyquinoline-2-carboxylic Acid.*—A solution of 3-methoxy-2-styrylquinoline (2·2 g.) in pyridine (70 ml.) and water (10 ml.) was stirred and cooled (ice–salt) while potassium permanganate (2·5 g.) in water (45 ml.) was added at a rate which kept the temperature at 2—5°. The mixture was stirred for 45 min. at 2—5° and for 2·5 hr. at room temperature.

[30] Boer and Backer, *Rec. Trav. chim.*, 1954, **73**, 229.



Manganese dioxide was filtered off and extracted twice with hot 0·1N-sodium hydroxide (2 × 50 ml.). The combined filtrates were concentrated to 50 ml. and cooled. The low-melting solid was filtered off and the filtrate concentrated to 10 ml. The solution was brought to pH 2·5 with concentrated hydrochloric acid. The precipitate, collected after 16 hr., was washed with boiling ether and then crystallised from water, forming pale yellow needles of *3-methoxyquinoline-2-carboxylic acid hydrate* (0·3 g., 15%), m. p. 112·5° (decomp.) (Found: C, 59·8; H, 5·2. $C_{11}H_9O_3N,H_2O$ requires C, 59·7; H, 5·0%). Demethylation with hydriodic acid was accompanied by decarboxylation to give 3-hydroxyquinoline, m. p. 196°.

*3-Methoxyquinoline.*—3-Methoxyquinoline-2-carboxylic acid was easily decarboxylated at its melting point. 3-Methoxyquinoline was identified as its picrate, m. p. 220—222°, prepared in ethanol. Alford and Schofield [31] report m. p. 220—222°.

*3-Hydroxy-6-(N-methyl-N-phenylcarbamoyl)pyridazine.*—Phosphorus tri-(*N*-methylanilide) [from methylaniline (7·1 ml.) and phosphorus trichloride (1·1 ml.)] was heated under reflux for 1 hr. with 1,6-dihydro-6-oxopyridazine-3-carboxylic acid [12] (2·5 g.) in dry toluene (22 ml.). The toluene was removed under reduced pressure and the residue extracted with ethanol (2 × 100 ml.). Concentration of the extract and crystallisation of the residue from water gave needles of the N-*methylanilide* (2·0 g., 50%), m. p. 158° (Found: C, 63·4; H, 4·9. $C_{12}H_{11}O_2N_3$ requires C, 62·9; H, 4·8%).

1-*Oxide* (IX). The *N*-methylanilide (4·5 g.) and 40% peracetic acid (10 ml.) were heated on a water-bath for 4 hr. More peracetic acid (3 × 1 ml.) was added at hourly intervals. The excess of acetic acid was then distilled off under reduced pressure and the residual gum treated with boiling benzene (2 × 20 ml.), from which starting material (1·5 g.) was recovered. The residue was then extracted with ethanol (30 ml.), and the solid was obtained on cooling crystallised from ethanol, forming needles of the 1-*oxide* (0·9 g., 28·1%), m. p. 221° (decomp.) (Found: C, 58·4; H, 4·6; N, 17·4. $C_{12}H_{11}O_3N_3$ requires C, 58·8; H, 4·5; N, 17·1%).

After removal of the *N*-oxide the ethanol was evaporated, giving an orange-red solid which crystallised from water as orange beads of 3,6-dihydroxypyridazine (0·6 g., 43%), m. p. 256° (Found: C, 43·0; H, 3·1. Calc. for $C_4H_4O_2N_2$: C, 42·9; H, 3·6%). The m. p. reported [32] is 299—300° (the yields are calculated after allowing for recovered starting material).

1,6-*Dihydro-1-methyl-3-(N-methyl-N-phenylcarbamoyl)-6-oxopyridazine.*—1,6-Dihydro-3-(*N*-methyl-*N*-phenylcarbamoyl)-6-oxopyridazine (8 g.) was methylated with potassium carbonate (8 g.) and dimethyl sulphate (3·2 ml.) in boiling acetone (125 ml.). The 1-*methyl*-N-*methylanilide* (6·5 g., 76·5%) formed needles, m. p. 108° (Found: C, 63·9; H, 5·1. $C_{13}H_{13}O_2N_3$ requires C, 64·2; H, 5·4%).

*Oxidation.* Attempted *N*-oxidation with hydrogen peroxide and acetic acid or peracetic acid at various temperatures (55—100°) gave either starting material or a mixture of starting material and 1,6-dihydro-3-hydroxy-1-methyl-6-oxopyridazine (40%), m. p. 244° (decomp.) (Found: C, 47·2; H, 3·9. Calc. for $C_5H_6O_2N_2$: C, 47·6; H, 4·8%). The m. p. reported [33] is 210—211°.

2,3-*Dihydroxypyrazine.*—2-Amino-3-hydroxypyrazine [20] (1·5 g.) was diazotised. The reaction mixture was boiled for 2 min. and then cooled in ice. 2,3-Dihydroxypyrazine (50%), m. p. >350°, was crystallised from acetic acid (Found: N, 24·85. Calc. for $C_4H_4O_2N_2$: N, 25·0%). Karmas and Spoerri report [34] m. p. >320° for this compound, prepared by demethylation of 2,3-dimethoxypyrazine.

3-*Hydroxy-2-phenylcarbamoylpyrazine.*—(*a*) A mixture of 3-hydroxypyrazine-2-carboxyamide [17] (1 g.) and aniline (10 ml.) was heated under reflux for 9 hr. The cooled mixture was poured into 2N-hydrochloric acid (100 ml.). The insoluble anilide was washed with boiling water (50 ml.) and crystallised from dimethylformamide, forming yellow needles of the *carboxyanilide* (1·35 g., 97%), m. p. 287—288° (decomp.) (Found: C, 61·1; H, 4·2; N, 19·55. $C_{11}H_9O_2N_3$ requires C, 61·4; H, 4·2; N, 19·5%).

(*b*) 3-Hydroxypyrazine-2-carboxylic acid [15] (2 g.) was converted into the acid chloride by use of thionyl chloride and benzene under reflux. This was suspended in benzene (20 ml.), and a solution of aniline (10 ml.) in benzene (10 ml.) added dropwise. After 2 days the anilide was filtered off and washed with water and acetone. Crystallisation from dimethylformamide gave

[31] Alford and Schofield, *J.*, 1953, 1813.
[32] Mizzoni and Spoerri, *J. Amer. Chem. Soc.*, 1951, **73**, 1873.
[33] Eichenberger, Staehelin, and Druey, *Helv. Chim. Acta*, 1954, **37**, 845.
[34] Karmas and Spoerri, *J. Amer. Chem. Soc.*, 1957, **79**, 680.

yellow crystals (1·3 g., 43%), m. p. and mixed m. p. with the product obtained by method (*a*) 287—288° (decomp.).

*Oxidation.* Oxidation of this anilide (0·3 g.) with hydrogen peroxide (30%; 2 ml.) and acetic acid (10 ml.) at 50° for 96 hr. did not yield *N*-oxide, but only a tar and 2,3-dihydroxypyrazine, m. p. >350°.

3,4-*Dihydro*-4-*methyl*-3-*oxo*-2-*phenylcarbamoylpyrazine*.—3-Hydroxy-2-phenylcarbamoylpyrazine (0·5 g.) was methylated with dimethyl sulphate and potassium carbonate in boiling acetone. The yellow needles of 3,4-*dihydro*-4-*methyl*-3-*oxo*-2-*phenylcarbamoylpyrazine* (0·25 g., 49·5%) had m. p. 186°, after recrystallisation from acetone (Found: C, 62·7; H, 5·2; N, 18·2. $C_{12}H_{11}O_2N_3$ requires C, 62·9; H, 4·8; N, 18·3%).

*Oxidation.* Oxidation with hydrogen peroxide and acetic acid under various conditions also led to the formation of tars only.

3-*Hydroxy*-2-(N-*methyl*-N-*phenylcarbamoyl*)*pyrazine*.—A mixture of phosphorus tri-(*N*-methylanilide) [from phosphorus trichloride (3·2 ml.) and methylaniline (21·2 ml.)] and 3-hydroxypyrazine-2-carboxylic acid (7 g.) in dry toluene (60 ml.) was heated under reflux for 1 hr. The toluene was removed and the residue extracted with ethanol (3 × 100 ml.). Concentration of the extract gave cubes of the N-*methylanilide* (4·5 g., 39·5%), m. p. 217·5° after further crystallisation (Found: C, 62·8; H, 4·6. $C_{12}H_{11}O_2N_3$ requires C, 62·9; H, 4·8%).

1-*Oxide* (V; R = H). A mixture of the *N*-methylanilide (2 g.), acetic acid (10 ml.), and 30% hydrogen peroxide (2 ml.) was heated at 55°. Two further quantities of hydrogen peroxide (each 1 ml.) were added at intervals of 24 hr. After the mixture had been heated for 72 hr. in all, it was diluted with water (10 ml.) and kept at 0° for 24 hr. The solid crystallised from acetic acid as cubes of the 1-*oxide* (1·5 g., 68·3%), m. p. 289° (decomp.) (Found: C, 59·0; H, 4·3; N, 17·2. $C_{12}H_{11}O_3N_3$ requires C, 58·8; H, 4·5; N, 17·1%).

3,4-*Dihydro*-4-*methyl*-2-(N-*methyl*-N-*phenylcarbamoyl*)-3-*oxopyrazine*.—3-Hydroxy-2-(*N*-methyl-*N*-phenylcarbamoyl)pyrazine (2 g.) was methylated with dimethyl sulphate and potassium carbonate in boiling acetone. The 4-*methyl*-N-*methylanilide* (1·0 g., 46·0%) formed needles, m. p. 190—190·5° (from ethanol) (Found: C, 64·8; H, 5·4; N, 17·5. $C_{13}H_{13}O_2N_3$ requires C, 64·2; H, 5·4; N, 17·3%).

1-*Oxide* (V; R = Me). (*a*) The 4-methyl-*N*-methylanilide (0·5 g.) was oxidised with acetic acid (3 ml.) and hydrogen peroxide (30%, 0·5 ml.) as before. The 1-*oxide* formed needles (from ethanol) (0·25 g., 46·7%), m. p. 225° (decomp.) (Found: C, 59·8; H, 4·8; N, 15·9. $C_{13}H_{13}O_3N_3$ requires C, 60·2; H, 5·05; N, 16·2%).

(*b*) 3-Hydroxy-2-(*N*-methyl-*N*-phenylcarbamoyl)pyrazine 1-oxide (0·5 g.) was methylated with dimethyl sulphate and potassium carbonate in boiling acetone. The product was treated as in (*a*), yielding 0·4 g. (77%) of material, m. p. and mixed m. p. with that obtained by method (*a*) 218°.

3-*Hydroxy*-2-(N-*methyl*-N-p-*tolylcarbamoyl*)*pyrazine*.—An ice-cold solution of phosphorus trichloride (1·4 g.) in toluene (10 ml.) was added dropwise to a stirred solution of *N*-methyl-*p*-toluidine (8 g.) in toluene (20 ml.). After 30 min. at room temperature the mixture was heated on a steam-bath for 45 min. 2-Hydroxypyrazine-3-carboxylic acid (2 g.) was added and the mixture was heated under reflux for 5 min. The resulting solution (two layers) was chilled for 12 hr. and the yellow crystals collected and washed with water and with alcohol. Crystallisation from ethanol gave cubes of the p-*toluidide* (1·6 g., 46·1%), m. p. 205° (Found: C, 64·0; H, 5·6; N, 17·4. $C_{13}H_{13}O_2N_3$ requires C, 64·2; H, 5·4; N, 17·3%).

1-*Oxide* (XI; R = H, R′ = *p*-$MeC_6H_4$). The *p*-toluidide (0·5 g.) was oxidised with hydrogen peroxide in acetic acid, as already described. The crystalline product was recrystallised from ethanol, forming needles of the 1-*oxide* (0·26 g., 48·5%), m. p. 248° (decomp.) (Found: C, 60·2; H, 4·7; N, 16·2. $C_{13}H_{13}O_3N_3$ requires C, 60·2; H, 5·05; N, 16·2%).

2-(N-*Methyl*-N-*phenylcarbamoyl*)*quinoxaline*.—Quinoxaline-2-carboxylic acid [21] (3·5 g.), thionyl chloride (20 ml.), and benzene (10 ml.) were heated under reflux for 2 hr., and the mixture was evaporated to dryness under reduced pressure. The residue was dissolved in a mixture of methylaniline (16 ml.) and benzene (20 ml.), and shaken for 5 min. The benzene solution was washed successively with 2N-hydrochloric acid (3 × 25 ml.), aqueous sodium hydrogen carbonate, and water, and then evaporated. The residue crystallised from aqueous ethanol as needles of the N-*methylanilide* (4 g., 75%), m. p. 128° (Found: C, 72·5; H, 5·15. $C_{16}H_{13}ON_3$ requires C, 73·0; H, 5·0%).

1,4-*Dioxide*. A mixture of the *N*-methylanilide (1 g.), acetic acid (2 ml.), and 40% peracetic



acid (5 ml.) was heated at 55° for 24 hr., and the residue, obtained by evaporation to dryness under reduced pressure, was crystallised from ethanol forming needles of the 1,4-*dioxide* (1 g., 90%), m. p. 223° (Found: C, 65·25; H, 4·6; N, 13·85. $C_{16}H_{13}O_3N_3$ requires C, 65·1; H, 4·4; N, 14·2%).

1-*Oxide* (VIII). Chloroform (2 ml.), 2-(*N*-methyl-*N*-phenylcarbamoyl)quinoxaline 1,4-dioxide (0·2 g.), and phosphorus trichloride (0·4 ml.) were kept at room temperature for 16 hr. and then poured on ice. The mixture, on basification with aqueous sodium hydroxide and evaporation of the chloroform, gave a solid which crystallised from ethanol as needles of the 1-*oxide* (0·2 g., 95%), m. p. 198—199° (Found: C, 68·3; H, 4·4; N, 15·4. $C_{16}H_{13}O_2N_3$ requires C, 68·8; H, 4·7; N, 15·05%).

3-*Hydroxyquinoxaline-2-carboxylic Acid.*—Alloxazine (4·7 g.), prepared [35] by the condensation of *o*-phenylenediamine with alloxan, was heated in 20% aqueous sodium hydroxide (20 ml.) in an autoclave at 170° for 4 hr. The mixture was then heated to boiling, treated with animal charcoal, and filtered. On acidification of the filtrate, 3-hydroxyquinoxaline-2-carboxylic acid (3·1 g., 73·5%), m. p. 268° (decomp.), separated.

3,4-*Dihydro-4-methyl-3-oxoquinoxaline-2-carboxyamide.*—3-Hydroxyquinoxaline-2-carboxyamide (80%), m. p. 306—308°, was prepared by the addition of aqueous ammonium hydroxide to ethyl 3-hydroxyquinoxaline-2-carboxylate [22] and was then methylated to give 3,4-dihydro-4-methyl-3-oxoquinoxaline-2-carboxyamide, m. p. 254°, in 80% yield, as described by Clark-Lewis.[36]

3,4-*Dihydro-4-methyl-3-oxoquinoxaline-2-carboxylic Acid.*—Methylation of ethyl 3-hydroxyquinoxaline-2-carboxylate [22] (dimethyl sulphate, anhydrous potassium carbonate and acetone) gave *ethyl 3,4-dihydro-4-methyl-3-oxoquinoxaline-2-carboxylate* (2·5 g., 80% yield), m. p. 125·5° (from ethanol) (Found: C, 61·85; H, 5·1. $C_{12}H_{12}O_3N_2$ requires C, 62·1; H, 5·2%). This ester was hydrolysed by hot 3N-sodium hydroxide for ½ hr. The acid was obtained in nearly quantitative yield as yellow needles, m. p. 172·5—173° (decomp.). The m. p. recorded by King and Clark-Lewis [23] is 173—174° (decomp.).

3,4-*Dihydro-4-methyl-2-(N-methyl-N-phenylcarbamoyl)-3-oxoquinoxaline.*—3-Hydroxy-2-(*N*-methyl-*N*-phenylcarbamoyl)quinoxaline (1·0 g.) was methylated (dimethyl sulphate, potassium carbonate, and acetone). 3,4-Dihydro-4-methyl-2-(*N*-methyl-*N*-phenylcarbamoyl)-3-oxoquinoxaline formed needles, m. p. 162—163° (70%), from benzene–petroleum (b. p. 60—80°.) Clark-Lewis [36] records m. p. 165°.

1-*Oxide* (I). (*a*) The direct oxidation of 3,4-dihydro-4-methyl-2-(*N*-methyl-*N*-phenylcarbamoyl)-3-oxoquinoxaline with hydrogen peroxide (30%) and acetic acid afforded the *N*-oxide, m. p. 189—190°, in 50% yield, as described by Clark-Lewis.[2]

(*b*) The oxidation [1] of hydroxyimino-*NN'*-dimethylmalondianilide [2] with chromic acid also gave the *N*-oxide (33%), m. p. 187°. The mixed m. p. with the product by method (*a*) was the same.

2-*Dimethylcarbamoyl-3,4-dihydro-4-methyl-3-oxoquinoxaline.*—3,4-Dihydro-4-methyl-3-oxoquinoxaline-2-carboxylic acid (1·2 g.), thionyl chloride (10 ml.), and benzene (20 ml.) were heated under reflux for 2 hr. The solid obtained after the removal of thionyl chloride and benzene under reduced pressure was suspended in benzene and added to alcoholic dimethylamine (30%; 20 ml.) at 0°. The solution was allowed to warm to room temperature, and after 10 min. was evaporated to dryness under reduced pressure and extracted with benzene (5 × 10 ml.). The benzene solution was dried ($Na_2SO_4$) and concentrated to 15 ml. Needles of 2-dimethylcarbamoyl-3,4-dihydro-4-methyl-3-oxoquinoxaline (1·2 g., 88·2%), m. p. 129°, were obtained (Found: N, 17·9. Calc. for $C_{12}H_{13}O_2N_3$: N, 18·2%).

Clark-Lewis [35] reports m. p. 115° for this compound; however, the ultraviolet absorption of the product, m. p. 129°, was identical with that reported by Clark-Lewis.

1-*Oxide* (X; R = R' = Me). The dimethyl-carboxyamide (2 g.) was oxidised with hydrogen peroxide in acetic acid, as in previous experiments. When the acetic acid was removed under diminished pressure and the residue crystallised from ethanol pale yellow rosettes of the 1-*oxide* (1·3 g., 62%), m. p. 182—183°, were obtained (Found: C, 58·3; H, 5·2; N, 16·7. $C_{12}H_{13}O_3N_3$ requires C, 58·3; H, 5·3; N, 17·0%).

2-*Diphenylcarbamoyl-3,4-dihydro-4-methyl-3-oxoquinoxaline.*—3,4-Dihydro-4-methyl-3-oxoquinoxaline-2-carboxyl chloride (from 1·5 g. of acid) and diphenylamine (7 g.) in benzene (70 ml.). were heated for 5 min. The benzene was then removed under reduced pressure, the residue

[35] Kuhling, *Ber.*, 1891, **24**, 2364.
[36] Clark-Lewis, *J.*, 1957, 422.

extracted with petroleum (b. p. 60—80°) until diphenylamine was no longer recovered, and the residue crystallised from benzene, forming microcrystals of 2-*diphenylcarbamoyl*-3,4-*dihydro*-4-*methyl*-3-*oxoquinoxaline* (1·7 g., 64%), m. p. 209° (Found: C, 74·4; H, 4·7. $C_{22}H_{17}O_2N_3$ requires C, 74·35; H, 4·8%).

1-*Oxide* (X; R = R′ = Ph). The diphenylcarboxyamide (0·5 g.) was oxidised with 30% hydrogen peroxide and acetic acid as before. The 1-*oxide* crystallised from ethanol as pale yellow needles (0·35 g., 67%), m. p. 226° (Found: C, 70·8; H, 4·6. $C_{22}H_{17}O_3N_3$ requires C, 71·15; H, 4·6%).

3-*Hydroxy*-2-(N-*methyl*-N-p-*nitrophenylcarbamoyl*)*quinoxaline*.—The acid chloride, from the acid (3·0 g.) and thionyl chloride (15 ml.), was treated with a hot solution of *N*-methyl-*p*-nitroaniline (5·0 g.) in benzene (200 ml.). Unchanged *N*-methyl-*p*-nitroaniline separated on cooling; the filtrate was evaporated to dryness under reduced pressure and the residue crystallised from ethanol, forming yellow prisms of the N-*methyl*-p-*nitroanilide* (4·6 g., 90·9%), m. p. 226° (Found: C, 59·5; H, 3·9; N, 17·1. $C_{16}H_{12}O_4N_4$ requires C, 59·3; H, 3·7; N, 17·3%).

3,4-*Dihydro*-4-*methyl*-2-(N-*methyl*-N-p-*nitrophenylcarbamoyl*)-3-*oxoquinoxaline*.—3-Hydroxy-2-(*N*-methyl-*N*-*p*-nitrophenylcarbamoyl)quinoxaline (2·5 g.) was methylated (dimethyl sulphate, potassium carbonate, and acetone). 3,4-*Dihydro*-4-*methyl*-2-(N-*methyl*-N-p-*nitrophenylcarbamoyl*)-3-*oxoquinoxaline* (2·0 g., 77%) formed needles, m. p. 198°, from ethanol (Found: C, 59·9; H, 4·5. $C_{17}H_{14}O_4N_4$ requires C, 60·35; H, 4·2%).

1-*Oxide* (X; R = Me, R′ = *p*-$NO_2$·$C_6H_4$). Prepared by oxidation with hydrogen peroxide in acetic acid, the 1-*oxide* formed needles (63·7%), m. p. 204—205°, from ethanol (Found: C, 57·6; H, 3·7. $C_{17}H_{14}O_5N_4$ requires C, 57·6; H, 4·0%).

N-*Methyl*-2,6-*xylidine*.—2,6-Xylidine (12·1 g.), water (50 ml.), and dimethyl sulphate (9·5 ml.) were shaken for 45 min., and concentrated hydrochloric acid (25 ml.) was then added at 0°. A concentrated solution of sodium nitrite (10 g.) was added dropwise at <10°. 15 min. later the nitroso-derivative was extracted with ether, the ethereal extract dried ($Na_2SO_4$), the ether removed, and the residual liquid gradually added to a well-stirred solution of stannous chloride hydrate (68 g.) in concentrated hydrochloric acid (66 ml.). The temperature was kept below 60°. After 1 hr. at room temperature, excess of aqueous sodium hydroxide was added to the mixture, which was then extracted with benzene. The benzene solution was dried ($Na_2SO_4$) and evaporated under reduced pressure to yield *N*-methyl-2,6-xylidine (4·0 g., 30%); this was used without further purification.

N-*Methyl*-2,4-*xylidine*.—*N*-Methyl-2,4-xylidine was prepared similarly from 2,4-xylidine in 35% yield.

3,4-*Dihydro*-4-*methyl*-2-(N-*methyl*-N-2,6-*xylylcarbamoyl*)-3-*oxoquinoxaline*.—3,4-Dihydro-4-methyl-3-oxoquinoxaline-2-carboxyl chloride (from 1·2 g. of acid) was added portionwise to a solution of *N*-methyl-2,6-xylidine (1·8 g.) in benzene (10 ml.). The mixture was shaken for 10 min. and then washed with 2N-hydrochloric acid (2 × 25 ml.); the *anilide* crystallised from ethanol as needles (1·86 g., 93%), m. p. 264° (Found: C, 71·0; H, 6·0. $C_{19}H_{19}O_2N_3$ requires C, 71·0; H, 6·0%).

3,4-*Dihydro*-4-*methyl*-2-(N-*methyl*-N-2,4-*xylylcarbamoyl*)-3-*oxoquinoxaline*.—This *anilide* (68%) (Found: C, 70·9; H, 6·1%) was prepared similarly and had m. p. 213°.

3,4-*Dihydro*-4-*methyl*-2-(N-*methyl*-N-2,6-*xylylcarbamoyl*)-3-*oxoquinoxaline* 1-*Oxide* (X; R = Me, R′ = 2,6-$Me_2C_6H_3$).—The anilide (1·0 g.) was treated with 40% peracetic acid (10 ml.) as already described. The 1-*oxide* formed cubes (0·2 g., 20%), m. p. 274° (decomp.), from ethanol (Found: N, 12·3. $C_{19}H_{19}O_3N_3$ requires N, 12·5%).

*Attempted Preparation of* 3,4-*Dihydro*-4-*methyl*-2-(N-*methyl*-N-2,4-*xylylcarbamoyl*)-3-*oxoquinoxaline* 1-*Oxide* (X; R = Me, R = 2,4-$Me_2C_6H_3$).—The oxidation of the anilide with 30% hydrogen peroxide and acetic acid or peracetic acid at various temperatures (55—100°) gave either starting material or a gum, or the mixture of these two, from which *N*-oxide could not be isolated.

*Benzoxazole*-2-*carboxyanilide*.—This anilide, m. p. 155—157°, was prepared by Skraup and Moser's method [24] in good yield.

2-(N-*Phenyl*-N-*phenylcarbamoyl*)*benzoxazole*.—Potassium benzoxazole-2-carboxylate [24] (2·0 g.) and thionyl chloride (10 ml.) in dry benzene (10 ml.) were heated under reflux for 1·25 hr. The mixture was evaporated to dryness under diminished pressure and the residue was suspended in benzene (10 ml.). A solution of methylaniline (4 ml.) in benzene (10 ml.) was then added. The reaction mixture was shaken for 10 min. and washed first with 2N-hydrochloric

acid and then with water. The dried ($Na_2SO_4$) benzene layer gave the N-*methylanilide* (0·9 g., 36%), as needles, m. p. 83° [from light petroleum (b. p. 60—80°)] (Found: C, 70·8; H, 4·45. $C_{15}H_{12}O_2N_2$ requires C, 71·4; H, 4·8%).

*Oxidation.*—Oxidation of both anilides with hydrogen peroxide and acetic acid or peracetic acid or perbenzoic acid by the usual methods yielded only tars from which solid could not be isolated.

## Treatment of *N*-oxides with sulphuric acid

3-*Hydroxy*-2-o-*methylaminophenylpyrazine* (VI; R = H).—3-Hydroxy-2-(*N*-methyl-*N*-phenylcarbamoyl)pyrazine 1-oxide (1·0 g.) and concentrated sulphuric acid (8 ml.) were heated at 55° for 2 hr. The cooled mixture was poured on ice, then neutralised with aqueous sodium hydroxide and extracted with chloroform; the extracts were dried ($Na_2SO_4$) and the chloroform removed. The residue crystallised from benzene–light petroleum (b. p. 60—80°) as yellow leaflets of 3-*hydroxy*-2-o-*methylaminophenylpyrazine* (0·84 g., 93%), m. p. 193° (Found: C, 65·0; H, 5·7; N, 20·8. $C_{11}H_{11}ON_3$ requires C, 65·7; H, 5·5; N, 20·9%).

3,4-*Dihydro*-4-*methyl*-2-o-*methylaminophenyl*-3-*oxopyrazine* (VI; R = Me).—(*a*) 3,4-Dihydro-4-methyl-2-(*N*-methyl-*N*-phenylcarbamoyl)-3-oxopyrazine 1-oxide (0·1 g.) and sulphuric acid (1 ml.) were heated at 55° for 2 hr. The cooled mixture was poured on ice, and the solution basified with aqueous sodium hydroxide and extracted with chloroform. The extract was dried ($Na_2SO_4$) and distilled under reduced pressure and the residue crystallised from benzene–light petroleum (b. p. 60—80°), giving orange leaflets of 3,4-*dihydro*-4-*methyl*-2-o-*methylaminophenyl*-3-*oxopyrazine* (0·077 g., 93%), m. p. 135° (Found: C, 66·7; H, 5·9; N, 19·7. $C_{12}H_{13}ON_3$ requires C, 66·95; H, 6·1; N, 19·5%).

(*b*) 3-Hydroxy-2-*o*-methylaminophenylpyrazine (0·2 g.), dimethyl sulphate (0·1 ml.), acetone (10 ml.), and potassium carbonate (0·2 g.) were heated under reflux for 0·5 hr. The acetone was removed, the residue dissolved in dilute hydrochloric acid, and the solution basified with aqueous sodium hydroxide. 3,4-Dihydro-4-methyl-2-*o*-methylaminophenyl-3-oxopyrazine (0·05 g.) formed leaflets, m. p. and mixed m. p. 130—131°.

3-*Hydroxy*-2-(5-*methyl*-2-*methylamino*)*phenylpyrazine.*—3-Hydroxy-2-(*N*-methyl-*N*-*p*-tolylcarbamoyl)pyrazine 1-oxide (0·1 g.) and concentrated sulphuric acid (1 ml.) were heated at 55° for 2 hr.; the mixture was allowed to cool and then poured on ice. The solution was neutralised with aqueous sodium hydroxide and extracted with chloroform. The chloroform extract gave a residue, which crystallised from benzene–light petroleum (b. p. 60—80°) as cubes of 3-*hydroxy*-2-(5-*methyl*-2-*methylaminophenyl*)*pyrazine* (0·078 g., 94%), m. p. 144° (Found: C, 66·2; H, 5·9; N, 19·15. $C_{12}H_{13}ON_3$ requires C, 66·95; H, 6·1; N, 19·5%).

3,4-*Dihydro*-4-*methyl*-2-o-*methylaminophenyl*-3-*oxoquinoxaline* (II).—(*a*) 3,4-Dihydro-4-methyl-2-(*N*-methyl-*N*-phenylcarbamoyl)-3-oxoquinoxaline 1-oxide decomposed in concentrated sulphuric acid to give 3,4-dihydro-4-methyl-2-*o*-methylaminophenyl-3-oxoquinoxaline in 70% yield as described by Clark-Lewis.[2] A second product [1] was also obtained.

(*b*) 3-Hydroxy-2-*o*-methylaminophenylquinoxaline (to be described in a later communication) was methylated with methyl sulphate. The product (orange needles from aqueous methanol), m. p. 130°, was identical with that from preparation (*a*).

3,4-*Dihydro*-4-*methyl*-2-o-*phenylaminophenyl*-3-*oxoquinoxaline.*—2-Diphenylcarbamoyl-3,4-dihydro-4-methyl-3-oxoquinoxaline 1-oxide (0·1 g.) was stirred gradually into cooled concentrated sulphuric acid (1 ml.), and after 5 min. the solution was poured on ice (5 g.) and filtered. The filtrate was basified and extracted with chloroform. The chloroform was dried ($Na_2SO_4$) and the solvent removed. Crystallisation from ethanol gave needles of 3,4-*dihydro*-4-*methyl*-2-o-*phenylaminophenyl*-3-*oxoquinoxaline* (0·035 g., 39%), m. p. 297° (Found: C, 76·4; H, 5·1. $C_{21}H_{17}ON_3$ requires C, 77·0; H, 5·2%).

3,4-*Dihydro*-4-*methyl*-2-(2-*methylamino*-5-*nitrophenyl*)-3-*oxoquinoxaline.*—3,4-Dihydro-4-methyl-2-(*N*-methyl-*N*-*p*-nitrophenylcarbamoyl)-3-oxoquinoxaline 1-oxide (0·2 g.) and concentrated sulphuric acid (3 ml.) were heated at 55° for 24 hr. The mixture was allowed to cool to room temperature and then poured on ice (10 g.). The yellow precipitate was washed with water and then with ethanol; crystallisation from dimethylformamide gave yellow cubes of 3,4-*dihydro*-4-*methyl*-2-(2-*methylamino*-5-*nitrophenyl*)-3-*oxoquinoxaline* (0·14 g., 77%), m. p. 280° (Found: C, 62·2; H, 5·2; N, 17·65. $C_{16}H_{14}O_3N_4$ requires C, 61·9; H, 4·55; N, 18·1%).

*Rearrangement of a Mixture of* 3-*Hydroxy*-2-(N-*methyl*-N-p-*tolylcarbamoyl*)*pyrazine* 1-*Oxide*

(XI; R = H, R′ = *p*-$MeC_6H_4$) *and* 3,4-*Dihydro*-4-*methyl*-2-(N-*methyl*-N-*phenylcarbamoyl*)-3-*oxopyrazine* 1-*Oxide* (XI; R = Me, R′ = Ph).—An intimate mixture of these finely-powdered *N*-oxides (0·10 g. of each) was heated in concentrated sulphuric acid (2 ml.) at 55° for 2 hr. The dark red solution was cooled and poured on ice (10 g.). The solution was made strongly alkaline with aqueous sodium hydroxide and extracted with chloroform (3 × 25 ml.). The chloroform solution was dried ($Na_2SO_4$) and then evaporated to dryness under reduced pressure. The residue crystallised from benzene–light petroleum (b. p. 60—80°) as orange leaflets of 3,4-dihydro-4-methyl-2-*o*-methylaminophenyl-3-oxopyrazine (0·0767 g., 93%), m. p. and mixed m. p. 135°.

The original alkaline solution was then adjusted to pH 6 and extracted with chloroform. The chloroform extract was worked up as before, giving cubes of 3-hydroxy-2-(5-methyl-2-methylamino)phenylpyrazine (0·0775 g., 94%), m. p. and mixed m. p. 144°.

*Compounds not rearranged by Sulphuric Acid.*—Experiments in which rearrangement in concentrated sulphuric acid could not be detected are summarised in the Table. The amides or *N*-oxides were dissolved in 10—15 times their weight of concentrated sulphuric acid and heated under the conditions shown. After the acid solution had been poured on ice the starting material was recovered. In no case was any of the product to be expected from rearrangement detected.

| Expt. No. | Compound | Temp. | Time (hr.) | % recovery |
|---|---|---|---|---|
| 1. | *N*-Methylpicolinanilide 1-oxide (IV; R = H) | 60° | 4 | 90 |
| 2. | 3-Hydroxy-*N*-methylpicolinanilide 1-oxide (IV; R = OH) | 60 | 3 | 90 |
| 3. | *N*-Methylquinaldinanilide 1-oxide | 55 | 14 | 70 |
| 4. | 1,6-Dihydro-3-(*N*-methyl-*N*-phenylcarbamoyl)-6-oxopyridazine | 55 | 24 | 90 |
| 5. | ,, ,, ,, 2-oxide | 55 | 24 | 40 |
| 6. | 3-Hydroxy-2-*N*-phenylcarbamoylpyrazine | 20 | 1 | 80 |
| 7. | 3-Hydroxy-2-(*N*-methyl-*N*-phenylcarbamoyl)pyrazine | 20 | 1 | 80 |
| 8. | 3,4-Dihydro-4-methyl-3-oxo-2-*N*-phenylcarbamoylpyrazine | 20 | 1 | 70 |
| 9. | 3,4-Dihydro-4-methyl-2-(*N*-methyl-*N*-phenylcarbamoyl)-3-oxopyrazine | 20 | 1 | 80 |
| 10. | 2-(*N*-Methyl-*N*-phenylcarbamoyl)quinoxaline 1-oxide (VIII) | 55 | 16 | 80 |
| 11. | 3-Hydroxyquinoxaline-2-carboxylic acid | 20 | 0·5 | 100 |
| 12. | 3-Hydroxyquinoxaline-2-carboxyamide | 20 | 0·5 | 100 |
| 13. | 3,4-Dihydro-4-methyl-3-oxoquinoxaline-2-carboxyamide | 20 | 0·5 | 95 |
| 14. | 2-Dimethylcarbamoyl-3,4-dihydro-4-methyl-3-oxoquinoxaline | 20 | 0·25 | 80 |
| 15. | ,, ,, ,, 1-oxide (X; R = R′ = Me) | 20 | 0·25 | 83 |
| 16. | 3,4-Dihydro-4-methyl-2-*N*-methylanilino-3-oxoquinoxaline (III) | 20 | 0·25 | 100 |
| 17. | 3,4-Dihydro-4-methyl-2-(*N*-methyl-*N*-2,6-xylylcarbamoyl)-3-oxoquinoxaline 1-oxide | 20 | 0·25 | 70 |

(i) Experiments No. 1, 2, and 16 were repeated at higher temperatures; the products were completely water soluble and gave white crystalline precipitates with *S*-benzylthiouronium chloride. Sulphonation had presumably occurred, but this was not further investigated.
(ii) The low yield in experiment No. 5 is also presumably due to sulphonation.

*Treatment with Polyphosphoric Acid.*—3,4-Dihydro-4-methyl-2-(*N*-methyl-*N*-phenylcarbamoyl)-3-oxoquinoxaline 1-oxide (I) (0·5 g.) and polyphosphoric acid (10 g.) were heated at 55° for 13 hr. The mixture was allowed to cool and then diluted with water (20 ml.) and filtered. Basification of the filtrate with aqueous sodium hydroxide and crystallisation of the residue from aqueous methanol gave orange needles of 3,4-dihydro-4-methyl-2-*o*-methylaminophenyl-3-oxoquinoxaline (50%), m. p. and mixed m. p. 135°.

The solid removed from the reaction mixture was identical with the second product obtained by sulphuric acid treatment.[1]

A brief summary of this work has appeared.[37]

We are grateful to Messrs. Laporte Chemicals Ltd., for a generous supply of peracetic acid and to Professor D. H. Hey, F.R.S., and Professor W. G. Overend, D.Sc., for their interest and encouragement.

KING'S COLLEGE AND BIRKBECK COLLEGE, LONDON. [*Received, September 21st*, 1959.]

[37] Habib and Rees, *Chem. and Ind.*, 1959, 367.