CCLVII.—*Steric Hindrance in Reactions of Substituted Quinoxalines.*

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IT has long been known that a methyl group occupying the α- or the γ-position to the nitrogen atom of a pyridine or quinoline nucleus possesses a high reactivity towards aldehydes and other reagents, which in the β-position it does not possess. The methyl groups of 2 : 3-dimethylquinoxaline, $C_6H_4\langle^{N:CMe}_{N:CMe}$, are each in the α-position with respect to one nitrogen atom of the heterocyclic nucleus, but each is at the same time in the β-position with respect to the second nitrogen atom. It therefore seemed possible that these methyl groups would be of the non-reactive or at least of a less reactive type. The observation that in this dimethylquinoxaline both methyl groups have a high reactivity of the kind specified was of sufficient interest to warrant a detailed study.

We have examined the behaviour of 2-methyl-, 2 : 3-dimethyl-, and 2 : 3 : 6-trimethyl-quinoxalines, 2-phenyl-3-methylquinoxaline, 2-benzylquinoxaline, and 2-*p*-methoxy- and 2-*p*-chloro-benzyl-3-phenylquinoxaline with a number of aldehydes and with bromine. The 2 : 3-dimethyl base has also been condensed with ethyl oxalate.

Although a quantitative comparison was not practicable, it is clear that 2 : 3-dimethylquinoxaline reacts with aromatic aldehydes with approximately the same ease as does quinaldine. The reactivity is no doubt due to the simultaneous effects of general and alternating polar influences. Polarisations leading to reaction are possible if a methyl group is placed α- to a nuclear nitrogen atom and the second nitrogen atom does not interfere with this. Its general polar

effect will in fact tend to increase the reactivity of the molecule. The experiments of Mills and others (J., 1922, **121**, 2724; 1925, **127**, 2466) indicate that the polarisation in question here may proceed as far as complete tautomeric change into a more reactive isomeride. From this point of view it is not surprising that Lapworth and Higginbotham (J., 1922, **121**, 2823) found no reactivity in the methyl groups of *m*-methoxytoluene and 3 : 5-dimethoxytoluene and that we similarly failed to induce reaction between an aromatic aldehyde and *m*-dimethylaminotoluene. A possible reactive tautomeric form cannot in these cases be formulated.

It should, however, be pointed out that even if this reactivity of the methyl group arises only where tautomeric change is possible it does not follow that completed isomeric change precedes reaction. The activated molecule which reacts may, in fact, occupy an intermediate position between the methylene base $-NH\cdot\overset{|}{C}:CH_2$ and the methyl base $-N:\overset{|}{C}\cdot CH_3$. In the closely analogous case of keto-enolic tautomerism, where the enolic forms are known to be more reactive with bromine than the keto-forms, the experiments of Leuchs (*Ber.*, 1913, **46**, 2435: compare Robinson, J., 1917, **111**, 963) indicate that complete enolisation does not precede the reaction.

The products of condensation of 2 : 3-dimethylquinoxaline with aromatic aldehydes are distyrylquinoxalines (I), but in the reactions with certain aldehydes such as *o*- and *p*-methoxybenzaldehydes and *m*-nitrobenzaldehyde a monostyryl derivative was isolated in place of, or in addition to, the other. The formula (II) was a conceivable alternative to (III) for these substances, but the latter is undoubtedly correct, since the products decolorise cold solutions of bromine and permanganate. Moreover, the substance from *m*-nitrobenzaldehyde was shown to react further with the nitro-aldehyde with production of the distyrylquinoxaline of type (I), a reaction which points conclusively to the formula (III).

(I.) $C_6H_4\langle\begin{matrix}N:\overset{|}{C}\cdot CH:CHAr\\ N:\overset{|}{C}\cdot CH:CHAr\end{matrix}$ $\qquad$ $C_6H_4\langle\begin{matrix}N:\overset{|}{C}\cdot CH_2\\ N:\overset{|}{C}\cdot CH_2\end{matrix}\rangle CHAr$ (II.)

$$C_6H_4\langle\begin{matrix}N:\overset{|}{C}\cdot CH_3\\ N:\overset{|}{C}\cdot CH:CHAr\end{matrix} \quad \text{(III.)}$$

Condensation with benzaldehyde and piperonal was best brought about by heating the mixture to the boiling point in the absence of catalysts, but in all other cases the reactants were heated together in boiling acetic anhydride for a few hours. A comparison of the behaviour of some fifteen aromatic aldehydes with the 2 : 3-dimethyl base shows that those containing the nitro-group are distinguished by their rapid condensation, yielding styryl derivatives which are

easily isolated, as they crystallise directly from the reaction mixture. 2 : 3-Dimethylquinoxaline furnishes upwards of 50% of the calculated yield of product when condensed in acetic anhydride with *o*-, *m*-, or *p*-nitrobenzaldehyde, 2 : 4-dinitrobenzaldehyde, or *o*- or *p*-chlorobenzaldehyde. In particular, *p*-nitro- and 2 : 4-dinitrobenzaldehydes are convenient reagents for detecting the reactive methyl group of a base. There is little doubt that these aldehydes will react equally readily with other heterocyclic bases, and we have confirmed this in the case of three substituted quinolines.

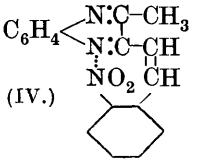
On the other hand, the products from the three methoxybenzaldehydes were obtained in lower yield. Although this may have been partly due to the greater difficulty of their isolation, there can be no doubt that the methoxy-aldehydes react more slowly. Moreover *o*-methoxybenzaldehyde yielded solely the monostyryl derivative (III; Ar = C_6H_4·OMe). This compound decolorises cold solutions of permanganate and bromine and yet was recovered unchanged after a second heating with *o*-methoxybenzaldehyde.

It is thus clear that the reaction of 2 : 3-dimethylquinoxaline proceeds easily with most substituted benzaldehydes, including those with a nitro-group or a chlorine atom in the *o*-position, yet the second stage of the reaction is inhibited when an *o*-methoxy-group is present. If this effect were solely due to steric hindrance, the nitro-group would be expected to have at least as great an influence as the methoxy-group. We suggest that the explanation is to be found in the polar characters of the various atoms and groups and in the forces of attraction and repulsion which arise between them. It is known that nitro-compounds are able to unite with bases, union presumably taking place between the nitro-group and the nitrogen atom of the base, and an attraction must therefore exist between a nitro-group of the mono- or di-nitrobenzaldehyde and the nitrogen atom of the quinoxaline. Direct confirmation of this was obtained by the isolation of a " molecular " *compound*,

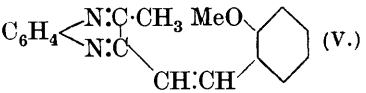
$$C_{10}H_{10}N_2,2C_6H_3(NO_2)_2\cdot CHO,$$

from the two reactants in a case where high reactivity had been found. This is of interest as affording evidence of direct union of the reacting molecules as a prelude to the condensation. Moreover it appears probable that this attraction of the nitro-group to the tertiary nitrogen atom will continue to operate within the molecule of the nitrostyryl derivative first formed. Consequently the latter substance will for a large proportion of the time assume a configuration such as (IV), in which the large nitrostyryl residue is held remote from the second methyl group in the quinoxaline nucleus. Reaction of (IV) with a second molecule of *o*-nitrobenzaldehyde will be unhindered, a similar force operating between the second nitrogen

atom of the base and the nitro-group of this aldehyde so as to keep this nitro-group also away from the region of reaction, and a di(*o*-nitrostyryl)quinoxaline results.



(IV.)



(V.)

The force which is involved in the condensation with *o*-methoxybenzaldehyde, on the other hand, should be one of repulsion between the methoxy-group and the basic nitrogen atoms. The reaction is therefore slower and the monostyrylquinoxaline first produced tends for the greater portion of the time to adopt a spatial arrangement such as (V). Access of a second molecule of the aldehyde to the remaining methyl group of the base will now be very difficult. If further reaction were to take place, the adjacent nitrogen atom would tend to force the methoxy-group of this aldehyde molecule into the space around the methyl group already crowded in (V). The second stage of the reaction is thus completely arrested by a steric hindrance depending for its operation on the polar nature of the groups involved.

In order to test this conception we examined the reaction of the quinoxaline with *o*-iodobenzaldehyde. The iodine atom is known to have a large steric effect in such reactions as the esterification of acids, but it has the same type of general polar effect as the nitro-group and might be expected to have a similar attraction for a basic nitrogen atom. Experiment confirmed the expectation that steric hindrance would therefore be absent, for a good yield of di(*o*-iodostyryl)quinoxaline was isolated.

The effect here discussed is seen to be a true steric hindrance, although its operation may depend on the control of configuration by polar forces. The apparent steric hindrance of a reaction may arise from at least three distinct causes, namely (*a*) true steric hindrance, (*b*) the influence (other than steric) of the hindering group on the reactivity of the active group, (*c*) direct chemical action between the groups of the kind suggested by Sidgwick and Callow (J., 1924, **125**, 527). The distinction between these may be uncertain in some cases, and a polar force may, as above suggested, be involved in evoking effects of type (*a*). A similar explanation may be offered of the observation of Remsen and Reid (*Amer. Chem. J.*, 1899, **21**, 340) that *o*-methoxybenzamide is hydrolysed faster than *o*-chlorobenzamide, a true steric hindrance (*a*) being controlled by a repulsion and an attraction respectively between the groups involved.

The variations in reactivity recorded by Dyson, George, and Hunter (J., 1927, 436), however, are apparently due to effects of type (*b*) and not to steric hindrance.

A less extended series of experiments with 2 : 3 : 6-trimethylquinoxaline served on the whole to confirm the conclusions arrived at with the dimethyl base. The third methyl group is not in a position to be reactive, but it shows its presence by a distinct increase of reactivity in the other two methyl groups. The 6-methyl group no doubt exerts an effect on the nitrogen atoms similar to that which causes *m*- and *p*-toluidines to be stronger bases than aniline. The nitrogen atoms of the quinoxaline consequently cause a somewhat greater activation of the 2- and 3-methyl groups.

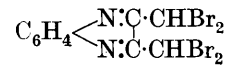
The base 2-phenyl-3-benzylquinoxaline was included in our study because the methylene group of the benzyl group seemed likely to show an enhanced reactivity due to the attached phenyl nucleus (compare Skraup and Böhm, *Ber.*, 1926, **59**, 1007). Substituted benzyl bases could easily be prepared by the method of Malkin and Robinson (J., 1925, **127**, 369), but we found that neither the benzyl nor the *p*-methoxy- nor *p*-chloro-benzyl bases reacted at all under the conditions of our experiments. The reaction is here inhibited by the combined steric hindrance of the phenyl radicals in position 2 and in the benzyl group of position 3, for we obtained good yields of styryl derivatives from 2-phenyl-3-methylquinoxaline on the one hand and from 2-benzylquinoxaline on the other. That a single *o*-methyl group exerts little or no steric hindrance in this reaction is shown by the easy condensation with 2 : 3-dimethylquinoline.

Through the kindness of Dr. F. M. Hamer, who supplied us with a specimen of the quinoxaline of *cyclo*pentadione, we were able to examine this base also. It reacts readily with aldehydes, although markedly less rapidly than the 2 : 3-dimethyl base, and the products have the structure $C_6H_4\langle\begin{matrix}N{:}C\cdot C(:CHAr)\\ N{:}C\cdot C(:CHAr)\end{matrix}\rangle CH_2$.

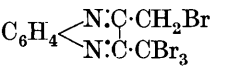
The *methiodide* of 2 : 3-dimethylquinoxaline was prepared in order to test its capacity to undergo condensations similar to those of quinaldine methiodide. Unexpected difficulty was found in its preparation, only resinous products being at first produced. Subsequently a good yield of a monomethiodide was obtained by heating the base in a large excess of methyl iodide. It is possible that this method would yield quaternary salts in some other cases of recorded difficulty (*e.g.*, the substituted quinazolines; Bogert and Clark, *J. Amer. Chem. Soc.*, 1924, **46**, 1294). The methiodide reacted with aldehydes and with nitrosodimethylaniline, but the products were black, insoluble solids which it was found impossible to purify. Repeated trials showed no reaction between the methiodide and

quinoline methiodide in alkaline solution to yield a dye of the *iso*cyanine type, nor with formaldehyde present to give a carbocyanine.

The bromination of these quinoxalines was studied under the standard conditions of heating the substance at 100° in acetic acid with bromine and sodium acetate. 2-Methylquinoxaline yielded the expected ω-tribromo-compound analogous to that obtained from quinaldine. In other cases, steric hindrance supervened, 2 : 3-dimethylquinoxaline being converted into a tetrabromo-derivative which resisted further bromination. This may be compared with the tetrabromo-compound from *o*-xylene (Gabriel and Müller, *Ber.*, 1895, **28**, 1830). It has the symmetrical structure (VI) and not the alternative (VII), for on hydrolysis with silver acetate it is converted into a substance giving an immediate precipitate with *p*-nitrophenylhydrazine. A similar steric hindrance is apparent in the formation of the dibromo-derivative (VIII) from phenylmethylquinoxaline.



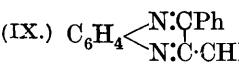
(VI.)

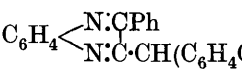


(VII.)

(VIII.)

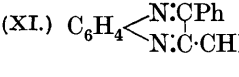
When benzyl- and chlorobenzyl-phenylquinoxalines were subjected to the same reaction, the products isolated were free from bromine, and were identified as the acetoxy-compounds (IX) and (X). These substances must evidently have been produced by the

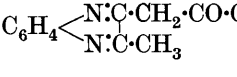
(IX.) 



(X.)

interaction of a monobromo-compound with the sodium acetate present. The bromo-compound (XI), which must thus be an intermediate product, would have a particularly reactive bromine atom similar to that of diphenylmethyl bromide.

(XI.) 



(XII.)

2 : 3-Dimethylquinoxaline reacts with ethyl oxalate, in the presence of either sodium or potassium ethoxides (compare the reactions of quinaldine examined by Wislicenus, *Ber.*, 1897, **30**, 1479; 1909, **42**, 1140) to yield *ethyl 2-methylquinoxaline-3-pyruvate* (XII), the structure of which is confirmed by the formation of a p-*nitrophenylhydrazone*.

The 2 : 3-dimethyl base did not react with amyl nitrite, Michler's hydrol, *p*-nitrosodimethylaniline, or a 2 : 4-dinitrobenzenediazonium salt.

EXPERIMENTAL.

Preparation of the Quinoxalines.—The method of Böttcher (*Ber.*, 1913, **46**, 3084) for preparing 2-methylquinoxaline was modified as follows: *iso*Nitrosoacetone (37 g.) and *o*-phenylenediamine (44 g.) were boiled in a mixture of hydrochloric acid (15 g.; *d* 1·19), glacial acetic acid (25 c.c.), and water (75 c.c.). The resultant mixture was made alkaline and benzoylated by means of benzoyl chloride (50 g.). The product was removed in a current of steam, and the distillate extracted with ether. The extract was dried over anhydrous sodium sulphate, the ether removed, and the residue distilled in a vacuum. The substance had b. p. 118°/16 mm. (yield, 13 g. or 45%).

2 : 3-Dimethylquinoxaline was obtained from methyl ethyl ketone through the *iso*nitroso-compound (compare Gabriel and Sonn, *Ber.*, 1907, **40**, 4850), the latter being used in the form of the crude oil which separates on acidification of the alkaline reaction mixture (yield, 70%).

2 : 3 : 6-Trimethylquinoxaline was readily obtained by a similar process.

2-Phenyl-3-methylquinoxaline (Auwers, *Ber.*, 1917, **50**, 1182) was not detected in the products of interaction of *iso*nitrosopropiophenone and *o*-phenylenediamine, but was prepared by heating the diketone (Smedley, J., 1909, **95**, 218) and the diamine together in ethyl alcohol for ½ hour.

Benzylglyoxal was prepared as described by Dakin and Dudley (*J. Biol. Chem.*, 1914, **18**, 42), except that the presence of any large amount of dibenzyl was avoided by preparing the magnesium benzyl chloride as recommended by Gilman and Myers (*J. Amer. Chem. Soc.*, 1923, **45**, 2462). Hydrolysis of the acetal (b. p. 131°/4 mm., 148—151°/18 mm.) from 20 g. of diethoxyacetopiperidide yielded at once the practically pure benzylglyoxal of m. p. 117—118° (3·8 g.).

2-*Benzylquinoxaline* was obtained as a dark oil, which did not solidify, by heating benzylglyoxal and *o*-phenylenediamine (1 mol.) for 20 minutes in ethyl alcohol. The *picrate* forms yellow needles, m. p. 117°, from ethyl alcohol (Found: N, 15·9. $C_{21}H_{15}O_7N_5$ requires N, 15·6%).

Phenyl β-*methoxy*-p-*chlorostyryl ketone*, $Ph{\cdot}CO{\cdot}C(OMe){:}CH{\cdot}C_6H_4Cl$, was obtained from ω-methoxyacetophenone (4·6 g.) by condensation with *p*-chlorobenzaldehyde and was isolated as an oil, b. p. 238°/16 mm. (yield, 5·7 g.), which solidified on keeping and was crystallised (m. p. 45°) from light petroleum (Found: Cl, 13·0. $C_{16}H_{13}O_2Cl$ requires Cl, 13·0%).

Phenyl p-*Chlorobenzyl Diketone.*—A solution of the foregoing substance (2 g.) in acetic acid (9 c.c.) and concentrated hydrobromic acid (4 c.c.) was heated until the yellow solution acquired a greenish

hue; it was then cooled and diluted. The product (1·8 g.) was isolated by means of ether and recrystallised from light petroleum; m. p. 85° (Found: Cl, 13·4. $C_{15}H_{11}O_2Cl$ requires Cl, 13·7%). This substance differs from the corresponding methoxybenzyl compound (Malkin and Robinson, *loc. cit.*) in not being appreciably extracted from its ethereal solution by aqueous alkalis.

2-p-*Chlorobenzyl*-3-*phenylquinoxaline*.—The diketone condensed with *o*-phenylenediamine in alcoholic solution to yield this quinoxaline, but a more convenient mode of procedure was as follows: To the solution obtained by heating phenyl β-methoxy-*p*-chlorostyryl ketone (5 g.) in acetic acid (22 g.) and hydrobromic acid (10 c.c.), as previously described, *o*-phenylenediamine (2 g.) was added, and the mixture boiled with addition of ethyl alcohol until a homogeneous solution resulted. Crystals of the quinoxaline separated as the solution cooled, and after recrystallisation from ethyl alcohol had m. p. 142° (yield, 5·5 g.) (Found: Cl, 10·6. $C_{21}H_{15}N_2Cl$ requires Cl, 10·7%).

Phenyl β : 3-*Dimethoxystyryl Ketone*.—The product from ω-methoxyacetophenone (27·2 g.) and *m*-methoxybenzaldehyde was an oil of b. p. 245°/18 mm. (27·8 g.) (Found: C, 75·5; H, 6·0. $C_{17}H_{16}O_3$ requires C, 76·1; H, 6·0%). Hydrolysis of this with acetic and hydrobromic acids yielded a pinkish solid which, after being crystallised from light petroleum, melted at 175—180° (decomp.) when rapidly heated. This *substance* was not the expected diketone but apparently a polymeride, which did not react with *o*-phenylenediamine and was not further investigated (Found: C, 75·6; H, 5·7; *M*, 474. $C_{16}H_{14}O_3$ requires C, 75·6; H, 5·5%; *M*, 254).

Condensation of 2-*Methylquinoxaline with Aldehydes*.—In each case a solution of the base (1 mol.) and an aldehyde (1 mol.) in acetic anhydride (5—6 mols.) was boiled for a certain period of time; the product separated in the crystalline condition on cooling.

2 : 4-Dinitrobenzaldehyde gave 2-(2 : 4-*dinitrostyryl*)*quinoxaline* (yield, after 1 hour, 80%), which was recrystallised from hot aqueous acetic acid; m. p. 219—220° (decomp.) (Found: N, 17·6. $C_{16}H_{10}O_4N_4$ requires N, 17·4%).

2-o-*Nitrostyrylquinoxaline*, formed from *o*-nitrobenzaldehyde (yield, after 3 hours, 78%), crystallised from toluene in pale yellow needles, m. p. 156° (Found: N, 15·1. $C_{16}H_{11}O_2N_3$ requires N, 15·2%).

2-m-*Nitrostyrylquinoxaline*, from *m*-nitrobenzaldehyde (yield, after 4 hours, 68%), crystallised from equal volumes of benzene and petroleum (b. p. 60—80°) in almost colourless needles, m. p. 199·5° (Found: N, 15·3%).

2-p-*Nitrostyrylquinoxaline*, from *p*-nitrobenzaldehyde (yield, after

¾ hour, 65%), crystallised from toluene in pale yellow needles, m. p. 200° (Found: N, 15·3%).

The base appeared to react with benzaldehyde, but the product was not obtained crystalline.

Condensation of 2 : 3-Dimethylquinoxaline with Aldehydes.—2 : 3-Dimethylquinoxaline was boiled in solution in excess of benzaldehyde for 2 hours. On cooling, 2 : 3-*distyrylquinoxaline* was deposited as a yellow solid which crystallised from a mixture of equal proportions of xylene and light petroleum (b. p. 90—120°) in yellow monoclinic needles, m. p. 190·5° (yield, 50—70%) (Found: C, 86·2; H, 5·3; N, 8·5; *M*, 363. $C_{24}H_{18}N_2$ requires C, 86·25; H, 5·4; N, 8·4%; *M*, 334). No monostyrylmethylquinoxaline could be detected whatever the conditions of the reaction. Oxidation of the substance in acetone solution by potassium permanganate yielded no crystalline product other than benzoic acid. The action of bromine in boiling chloroform produced after 3 hours a *tetrabromide*, which was isolated by evaporation of the solvent and obtained in silvery plates, m. p. 190° (depressed to 177° by admixture of distyrylquinoxaline), by crystallisation from benzene (Found: Br, 48·1. $C_{24}H_{18}N_2Br_4$ requires Br, 48·3%).

2 : 3-Dimethylquinoxaline was boiled with piperonal (1 mol.) in acetic anhydride (5—6 mols.) for 5 hours, and the mixture distilled in a current of steam. The residue of 2-*methylenedioxystyryl*-3-*methylquinoxaline* solidified on keeping (yield, 20%) and after crystallisation from benzene–light petroleum and again from methyl alcohol was obtained in lemon-yellow needles, m. p. 150° (Found: N, 9·5. $C_{18}H_{14}O_2N_2$ requires N, 9·7%). When the heating was prolonged, a trace of a substance of higher melting point was observed among the products. This was prepared in quantity by boiling 2 : 3-dimethylquinoxaline with an excess of piperonal for 4 hours, removing the latter in boiling water, and crystallising the crude solid product from ethyl alcohol. 2 : 3-*Di(methylenedioxystyryl)quinoxaline* was then obtained in yellow monoclinic needles, m. p. 208° (yield, 30%) (Found: C, 73·8; H, 4·4; N, 6·8. $C_{26}H_{18}O_4N_2$ requires C, 73·9; H, 4·3; N, 6·6%). Addition of zinc chloride to the reaction mixture in this preparation did not improve the yield and made the purification less easy.

In the following preparations the base (1 mol.) and the required aldehyde (1 mol.) were heated in boiling acetic anhydride (5—6 mols.) for varying periods. The mixture was distilled in a current of steam, and the residue dried and crystallised.

The product obtained with *m*-nitrobenzaldehyde after 6 hours' heating was fractionally crystallised from benzene. The larger and more insoluble portion was recrystallised from this solvent and

2 : 3-*di*(m-*nitrostyryl*)*quinoxaline* obtained in small yellow bipyramids, m. p. 237° (yield, 10%) (Found : C, 67·8; H, 3·8; N, 13·3. $C_{24}H_{16}O_4N_4$ requires C, 67·9; H, 3·8; N, 13·2%). The smaller, more soluble, fraction was 2-m-*nitrostyryl*-3-*methylquinoxaline*, which crystallised from aqueous methyl alcohol in almost colourless needles, m. p. 184° (yield, 1—2%) (Found : C, 70·0; H, 4·4; N, 14·5. $C_{17}H_{13}O_2N_3$ requires C, 70·1; H, 4·5; N, 14·4%). This substance rapidly decolorised solutions of potassium permanganate and of bromine. When it was heated in boiling acetic anhydride with *m*-nitrobenzaldehyde it was converted into the foregoing di(*m*-nitrostyryl)quinoxaline of m. p. 237°.

The oily product from *p*-methoxybenzaldehyde, after 7 hours' heating, solidified on keeping. It was separated into two fractions by means of methyl alcohol. The less soluble portion was 2 : 3-*di*(p-*methoxystyryl*)*quinoxaline*, which crystallised from light petroleum (b. p. 90—120°) in yellow needles, m. p. 163° (yield, 10%) (Found : N, 7·3. $C_{26}H_{22}O_2N_2$ requires N, 7·1%). The more soluble fraction was 2-p-*methoxystyryl*-3-*methylquinoxaline*, which crystallised in rosettes of yellow needles, m. p. 122·5° (yield, 10%) (Found : N, 10·3. $C_{18}H_{16}ON_2$ requires N, 10·1%).

The following preparations were carried out as before, except that two molecular proportions of aldehyde were used.

2 : 3-*Di*(m-*methoxystyryl*)*quinoxaline* was obtained with *m*-methoxybenzaldehyde after 4 hours' heating and crystallised from ethyl alcohol in yellow prisms, m. p. 126° (yield, 10%) (Found : N, 7·3. $C_{26}H_{22}O_2N_2$ requires N, 7·1%).

2-o-*Methoxystyryl*-3-*methylquinoxaline* was isolated with some difficulty from the reaction with *o*-methoxybenzaldehyde after 6½ hours' heating. It was extracted in light petroleum, and crystallised from methyl alcohol in microscopic yellow crystals, m. p. 112° (yield, 1—2%) (Found : N, 10·1. $C_{18}H_{16}ON_2$ requires N, 10·1%). This compound rapidly decolorises solutions of permanganate and of bromine. It was recovered entirely unchanged after being heated in boiling acetic anhydride for 12 hours with *o*-methoxybenzaldehyde (2 mols.).

2 : 3-*Di*(3 : 4-*dimethoxystyryl*)*quinoxaline* was obtained from 3 : 4-dimethoxybenzaldehyde in a similar manner. It crystallised from ethyl alcohol in yellow needles, m. p. 208° (yield, 10%) (Found : N, 6·3. $C_{28}H_{26}O_4N_2$ requires N, 6·2%).

2 : 3-*Di*(β-*furylvinyl*)*quinoxaline* was obtained from furfural after 5 hours' heating, and crystallised from light petroleum (b. p. 90—120°) in yellow crystals, m. p. 169° (yield, 5%) (Found : N, 9·0, $C_{20}H_{14}O_2N_2$ requires N, 8·9%).

In the following preparations with nitro- and halogenated benz-

aldehydes distillation in steam was unnecessary, as the product crystallised when the mixture cooled.

2 : 3-*Di*(o-*nitrostyryl*)*quinoxaline* (yield, after 3 hours, 80%) crystallised from benzene in star-shaped groups of needles, m. p. 194·5° (Found : N, 13·5. $C_{24}H_{16}O_4N_4$ requires N, 13·2%).

2 : 3-*Di*(p-*nitrostyryl*)*quinoxaline* (yield, after 1½ hours, 75% crystallised from nitrobenzene in deep yellow crystals, m.p. 288° (decomp.) (Found : N, 13·3%).

2-(2 : 4-*Dinitrostyryl*)-3-*methylquinoxaline* (yield, after 1 hour, 80%) separated from *cyclo*hexanol in orange-yellow crystals, m. p. 224—225° (decomp.) (Found : C, 60·5; H, 3·4; N, 16·9. $C_{17}H_{12}O_4N_4$ requires C, 60·7; H, 3·6; N, 16·7%). This substance rapidly decolorised solutions of permanganate and of bromine. The only product isolated after oxidation with potassium permanganate in acetone solution was 2 : 4-dinitrobenzoic acid (m. p. 177—179°). It was found possible also to produce the above compound by condensation in glacial acetic acid, or in xylene in the presence of a trace of zinc chloride. On the other hand, molecular proportions of the base and dinitrobenzaldehyde in solution in benzene were found to yield, after the expiration of 10 days, a considerable quantity of crystals of m. p. 96—97°. Admixture with a little of the base lowered the m. p. Fractional crystallisation from light petroleum yielded the quinoxaline and the aldehyde. The substance is, in fact, an *addition compound* of the base and the aldehyde, decomposed in hot petroleum. The variation of m. p. with composition of a mixture of the two substances shows the compound to contain 2 molecules of aldehyde to 1 molecule of base :

Dinitrobenzaldehyde (mols. %)	100	97·6	75	66·7	52·4
M. p.	71°	71°	75°	91°	80·5°
Dinitrobenzaldehyde (mols. %)	50	47·6	33·3	25·0	0
M. p.	72°	74°	81°	88°	106°

In view of the direct formation of a di-(2 : 4-dinitrostyryl) derivative from 2 : 3 : 6-trimethylquinoxaline (p. 1972) it seemed likely that an analogous compound would be formed from the 2 : 3-dimethyl base. The isolation of the above monostyryl derivative might be accounted for by its relative insolubility and its consequent removal from the reaction by crystallisation. This was confirmed as follows. The 2 : 3-dimethyl base, heated for 8 hours with the dinitro-aldehyde (3 mols.) in an excess of acetic anhydride, furnished 2 : 3-*di*(2 : 4-*dinitrostyryl*)*quinoxaline* (yield, 75%), which crystallised in brown needles from hot nitrobenzene and melted at 295—297° (decomp.) (Found : C, 56·1; H, 3·0. $C_{24}H_{14}O_8N_6$ requires C, 56·0; H, 2·7%).

2-(2 : 4 : 6-*Trinitrostyryl*)-3-*methylquinoxaline* (yield, after 1½

hours, 25%) crystallised from *cyclo*hexanol in brown crystals, m. p. 250—251° (decomp.) (Found: C, 53·6; H, 3·0. $C_{17}H_{11}O_6N_5$ requires C, 53·5; H, 2·9%).

2 : 3-*Di*(o-*chlorostyryl*)*quinoxaline* (yield, after 2½ hours, 60%) crystallised from benzene in long, yellow needles, m. p. 189·5° (Found: Cl, 17·5. $C_{24}H_{16}N_2Cl_2$ requires Cl, 17·6%). A careful search gave no indication of the presence of any monostyryl derivative among the products of this reaction.

2 : 3-*Di*(m-*chlorostyryl*)*quinoxaline* (yield, after 5 hours, 30%) was obtained solid with difficulty; the product was distilled in steam, purified by means of ethyl alcohol, and crystallised from light petroleum, forming yellow needles, m. p. 149° (Found: Cl, 17·5%).

2 : 3-*Di*(p-*chlorostyryl*)*quinoxaline* (yield, after 2½ hours, 60%) crystallised from benzene in small, star-shaped clusters of needles, m. p. 218° (Found: Cl, 17·4%).

2 : 3-*Di*(o-*iodostyryl*)*quinoxaline* (yield, after 5 hours, 40%) crystallised from light petroleum (b. p. 90—120°) in pale yellow plates, m. p. 179° (Found: I, 43·4. $C_{24}H_{16}N_2I_2$ requires I, 43·3%).

No crystalline product was isolated when condensations were attempted between 2 : 3-dimethylquinoxaline and dimethylaminobenzaldehyde, chloral, cinnamaldehyde, phenylacetaldehyde, benzil, glyoxal, phthalic anhydride, *p*-nitrosodimethylaniline, Michler's hydrol, or xanthydrol.

Condensation of 2 : 3 : 6-*Trimethylquinoxaline with Aldehydes.*—The base was boiled with benzaldehyde in excess for 2 hours; 2 : 3-*distyryl*-6-*methylquinoxaline* crystallised from the cooled reaction mixture (yield, 81%) and by recrystallisation from xylene was obtained in small, yellow needles, m. p. 193° (Found: N, 8·3. $C_{25}H_{10}N_2$ requires N, 8·3%).

The following condensations were carried out in acetic anhydride, and the products worked up as described on p. 1968.

2 : 3-*Di*(*methylenedioxystyryl*)-6-*methylquinoxaline* (yield, after 4 hours, 10%) was crystallised from dilute alcohol; m. p. 168° (Found: N, 6·6. $C_{27}H_{20}O_4N_2$ requires N, 6·4%).

2-p-*Methoxystyryl*-3 : 6-*dimethylquinoxaline* (yield, after 5 hours, 1—2%) separated from methyl alcohol in small yellow crystals, m. p. 116° (Found: N, 9·8. $C_{19}H_{18}ON_2$ requires N, 9·7%), and 2 : 3-*di*(p-*methoxystyryl*)-6-*methylquinoxaline* (yield, after 10 hours, 15%) in yellow needles, m. p. 136° (Found: N, 7·1. $C_{27}H_{24}O_2N_2$ requires N, 6·9%).

2 : 3-*Di*(3 : 4-*dimethoxystyryl*)-6-*methylquinoxaline* (yield, after 5 hours, 5%) separated from light petroleum (b. p. 90—120°) in orange-yellow crystals, m. p. 205° (Found: N, 6·1. $C_{29}H_{28}O_4N_2$ requires N, 6·0%).

In the following preparations steam distillation was dispensed with, as the product crystallised from the cooling reaction mixture.

The product from *m*-nitrobenzaldehyde (after 5 hours' heating) was separated into two portions by means of benzene. The less soluble portion was 2 : 3-*di*(m-*nitrostyryl*)-6-*methylquinoxaline*, which was crystallised from *cyclo*hexanol; m. p. 244·5° (yield, 10%) (Found: N, 12·9. $C_{25}H_{18}O_2N_4$ requires N, 12·8%). The more soluble portion was 2-m-*nitrostyryl*-3 : 6-*dimethylquinoxaline* and was crystallised from light petroleum; m. p. 165° (yield, 1—2%) (Found: N, 13·5. $C_{18}H_{15}O_2N_3$ requires N, 13·8%).

2 : 3-*Di*(2 : 4-*dinitrostyryl*)-6-*methylquinoxaline* (yield, after 1¼ hours, 80%) separated from *cyclo*hexanol in orange-yellow crystals, m. p. 251—255° (decomp.) (Found: C, 57·0; H, 3·4; N, 15·7. $C_{25}H_{16}O_8N_6$ requires C, 56·75; H, 3·0; N, 15·9%).

Condensation of 3-*Phenyl*-2-*methylquinoxaline with Aldehydes.*—The base was heated with boiling benzaldehyde (4 mols.) for 1 hour. 2-*Styryl*-3-*phenylquinoxaline* crystallised as the mixture cooled (yield, 90%) and separated, on recrystallisation from ethyl alcohol, in pale yellow needles, m. p. 149° (Found: N, 9·3. $C_{22}H_{16}N_2$ requires N, 9·1%).

2-p-*Nitrostyryl*-3-*phenylquinoxaline* was prepared from the base and *p*-nitrobenzaldehyde in acetic anhydride (yield, after 2 hours, 80%). It crystallised from benzene–light petroleum in bright yellow needles, m. p. 233° (Found: N, 12·1. $C_{22}H_{15}O_2N_3$ requires N, 11·9%).

2-(2 : 4-*Dinitrostyryl*)-3-*phenylquinoxaline* (yield, 90%) separated from light petroleum in yellow needles, m. p. 215° (Found: N, 14·1. $C_{22}H_{14}O_4N_4$ requires N, 14·1%).

Behaviour of Phenylbenzylquinoxaline with Aldehydes.—The substances were recovered unchanged when 3-phenyl-2-benzylquinoxaline and *p*-nitrobenzaldehyde; 3-phenyl-2-*p*-methoxybenzylquinoxaline and *p*-nitro- or 2 : 4-dinitro-benzaldehyde; 3-phenyl-2-*p*-chlorobenzylquinoxaline and *p*-nitro- or 2 : 4-dinitro-benzaldehyde or dimethylaminobenzaldehyde were heated together for 6—10 hours in boiling acetic anhydride. The phenylchlorobenzylquinoxaline was unaffected by boiling with benzaldehyde for 3 hours.

Condensation of 2-*Benzylquinoxaline with Aldehydes.*—The crude benzylquinoxaline was heated with an excess of *p*-nitrobenzaldehyde in boiling acetic anhydride for 5 hours.

2-(β-*Phenyl*-p-*nitrostyryl*)*quinoxaline* separated from the cooling mixture (yield, 1·2 g. from 1·4 g. of benzylglyoxal). It crystallised from ethyl alcohol in pale yellow needles, m. p. 149° (Found: N, 12·0. $C_{22}H_{15}O_2N_3$ requires N, 11·9%).

Condensation of the crude base with dinitrobenzaldehyde (7 hours'

heating) yielded a trace of a crystalline product, m. p. 261—262°, which was insufficient for analysis, but was probably the corresponding 2-(β-*phenyl*-2 : 4-*dinitrostyryl*)*quinoxaline*.

*Condensation of Quinoxalino*cyclo*pentane with Aldehydes.*—Quinoxalino*cyclo*pentane was converted by heating in boiling benzaldehyde for 2 hours into the *dibenzylidene* derivative (yield, 40%), brownish crystals, m. p. 213°, from ethyl alcohol (Found : N, 8·4. $C_{25}H_{18}N_2$ requires N, 8·1%), and by heating with *p*-nitrobenzaldehyde in acetic anhydride into the *di*-p-*nitrobenzylidene* derivative (yield, after 1 hour, 85%), which crystallised from hot nitrobenzene in yellow needles, decomp. 268—270° (Found : N, 12·8. $C_{25}H_{16}O_4N_4$ requires N, 12·8%). This base also condensed rapidly with 2 : 4-dinitrobenzaldehyde, but the product was so insoluble that it was impossible to purify it.

Condensation of Some Quinoline Bases with 2 : 4-*Dinitrobenzaldehyde.*—The products were obtained crystalline in 60—80% yield in 1—2 hours' heating. Quinaldine yielded 2-(2 : 4-*dinitrostyryl*)-*quinoline*, crystallising from benzene in pale yellow needles, m. p. 200° (Found : N, 13·1. $C_{17}H_{11}O_4N_3$ requires N, 13·1%). 2 : 8-Dimethylquinoline was converted into 2-(2 : 4-*dinitrostyryl*)-8-*methylquinoline*, crystallising from benzene in bright yellow needles, m. p. 198° (Found : C, 64·5; H, 4·5. $C_{18}H_{13}O_4N_3$ requires C, 64·5; H, 3·9%). 2 : 3-Dimethylquinoline gave 2-(2 : 4-*dinitrostyryl*)-3-*methylquinoline*, crystallising from benzene in brown needles, m. p. 257° (Found : C, 64·6; H, 3·7%). The same base, heated in excess of benzaldehyde at 150—160° for 6 hours, was converted into 2-*styryl*-3-*methylquinoline*, which separated as almost colourless crystals, m. p. 102°, from light petroleum (yield, 50%) (Found : C, 88·2; H, 6·4. $C_{18}H_{15}N$ requires C, 88·2; H, 6·1%).

Condensation of 2 : 3-*Dimethylquinoxaline with Ethyl Oxalate.*—To a suspension of sodium ethoxide (2 mols.) in dry ether, mixed with a little xylene, was added an ethereal solution of 2 : 3-dimethylquinoxaline (1 mol.) and ethyl oxalate (2 mols.). At the end of 12 hours a pale yellow colour had developed and traces of a solid were to be seen separating. After 4 weeks, the accumulated solid was collected and washed thoroughly with dry ether. It crystallised from acetic acid or ethyl alcohol in orange-yellow needles, m. p. 129° (yield, 2·5 g. from 4·7 g. of base). This was *ethyl* 2-*methylquinoxaline*-3-*pyruvate* (Found : C, 65·6; H, 5·5. $C_{14}H_{14}O_3N_2$ requires C, 65·2; H, 5·5%). When potassium ethoxide was substituted for sodium ethoxide in the preparation (compare Wislicenus, *Ber.*, 1909, **42**, 1140), the yield was improved (3·2 g. from 4·7 g. of base). The p-*nitrophenylhydrazone* crystallised in orange needles, m. p. 189°, from ethyl alcohol (Found : N, 18·0. $C_{20}H_{19}O_4N_5$ requires N, 17·8%).

After dimethylquinoxaline had been kept with amyl nitrite and sodium or potassium ethoxide for 12 days, no condensation product could be detected.

Bromination of the Quinoxaline Bases.—2-Methylquinoxaline, brominated as described by Hammick (J., 1923, **123**, 2883), yielded an oil which solidified 2 days later. After several recrystallisations from ethyl alcohol, 2-ω-*tribromomethylquinoxaline* was obtained (yield of pure substance, 10%) in pink plates, m. p. 109° (Found : Br, 62·7. $C_9H_5N_2Br_3$ requires Br, 63·0%).

2 : 3-Dimethylquinoxaline, brominated with 6 molecular proportions of bromine under similar conditions, gave a quantitative yield of 2 : 3-*di*(ω-*dibromomethyl*)*quinoxaline*, which crystallised from glacial acetic acid in colourless needles, m. p. 228° (Found : Br, 66·9. $C_{10}H_6N_2Br_4$ requires Br, 66·95%). This substance was recovered unchanged after boiling in glacial acetic acid for 1 hour with a large excess of bromine. When this compound was boiled in glacial acetic acid solution with silver acetate, the halogen was removed. The resulting solution gave a precipitate with *p*-nitrophenylhydrazine which was sparingly soluble in the common solvents and could not be obtained pure. The di-aldehyde was too unstable to be isolated by evaporation even under reduced pressure in an inert atmosphere.

Bromination of 3-phenyl-2-methylquinoxaline gave 3-*phenyl*-2-ω-*dibromomethylquinoxaline* (yield, 90%), which separated from light petroleum in clusters of needles, m. p. 148° (Found : Br, 42·1. $C_{15}H_{10}N_2Br_2$ requires Br, 42·25%).

To 3-phenyl-2-benzylquinoxaline (1·5 g.), dissolved in glacial acetic acid containing sodium acetate (2·3 g.), was added bromine (1·5 g.; 2 mols.) in a little acetic acid at 70°. After the reaction had been completed on the water-bath, the product obtained on pouring the mixture into water proved to be 3-*phenyl*-2-*phenylacetoxymethylquinoxaline* (yield, 90%), which crystallised from light petroleum in colourless prisms, m. p. 126°. It was free from halogen and after hydrolysis gave a test for acetic acid (Found : C, 78·3; H, 5·3. $C_{23}H_{18}O_2N_2$ requires C, 78·0; H, 5·1%).

3-Phenyl-2-*p*-chlorobenzylquinoxaline underwent a similar change with bromine and sodium acetate in glacial acetic acid solution, giving in quantitative yield the bromine-free product, 3-*phenyl*-2-p-*chlorophenylacetoxymethylquinoxaline*, colourless prisms from light petroleum, m. p. 119° (Found : Cl, 9·4. $C_{23}H_{17}O_2N_2Cl$ requires Cl, 9·1%).

3-Phenyl-2-*p*-methoxybenzylquinoxaline did not react with bromine under similar conditions to the above, nor when the reaction mixture was boiled for 1 hour.

Action of Methyl Iodide on Dimethylquinoxaline.—When 2 : 3-di-

methylquinoxaline was heated at various temperatures with methyl iodide (2 or 3 mols.), no crystalline product could be isolated, nor could the methosulphate be obtained by means of methyl sulphate. However, the base, heated in a sealed tube at 90° for 6½ hours with methyl iodide (10 mols.), furnished a *monomethiodide* (yield, 80%) which crystallised from ethyl alcohol in greenish-yellow needles, m. p. 192° (Found : I, 42·6. $C_{11}H_{13}N_2I$ requires I, 42·4%). Addition of sodium hydroxide to the aqueous solution precipitated an oil which could not be obtained crystalline.

The methiodide was boiled in ethyl alcohol with benzaldehyde or nitrosodimethylaniline and a trace of piperidine. In each case a brilliant colour change occurred and a black solid was precipitated, which, however, was insoluble in all solvents including phenol, nitrobenzene, *cyclo*hexanone, and acetic acid.

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