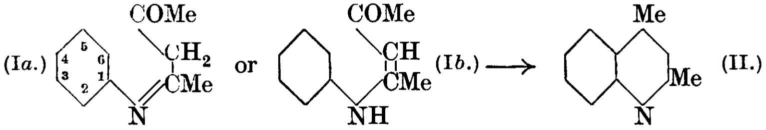
CCXXXIX.—*The Factors controlling the Formation of Some Derivatives of Quinoline, and a New Aspect of the Problem of Substitution in the Quinoline Series.*

By ELWYN ROBERTS and EUSTACE EBENEZER TURNER.

AN apparently excellent method for obtaining quinoline derivatives (II) is that devised by Combes (*Bull. Soc. chim.*, 1888, **49**, 90; *Compt. rend.*, 1887, **106**, 142), namely that of warming, with concentrated sulphuric acid, the condensation products (I*a* or I*b*) of acetylacetone with primary aromatic amines :

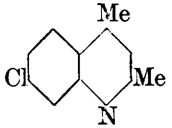


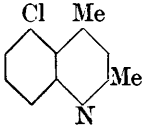
Previous work has shown that most simple substituted anilines condense readily with acetylacetone, even where, as in 2 : 6-dimethoxyaniline, a marked steric effect must be supposed to occur (Turner, J., 1917, **111**, 1), and it has now been found that, although *o*-, *m*-, and *p*-chloro-, 2 : 4-, 3 : 4-, and 3 : 5-dichloro-aniline do so, 2 : 5-dichloroaniline condenses only partially. The ease of condensation appears to be affected most by the basicity of the aniline used, for no nitroaniline, simple or complex, can be caused to condense with acetylacetone. It may be noted that acetylacetone condenses less well with most bases than does, for example, salicylaldehyde, which rapidly converts 2 : 5-dichloroaniline into the o-*hydroxybenzylidene* derivative.

The second stage of the Combes quinoline synthesis, namely, the intramolecular condensation of an anil of acetylacetone, is, however, much more definitely affected by the nature of the substituents present. Thus, whilst the condensation products, with acetylacetone, of aniline and *p*-toluidine (Combes, *loc. cit.*), those of 2 : 3-, 2 : 5-, and 3 : 4-dimethoxyaniline, that of 2-bromo-4 : 5-dimethoxyaniline (Lions, Perkin, and Robinson, J., 1925, **127**, 1158), and, as now shown, that of *m*-chloroaniline readily pass into the corresponding substituted 2 : 4-dimethylquinolines, a number of not very dissimilar anils do not, under corresponding conditions, undergo conversion into quinolines to any measurable extent. Into this second class fall the condensation *products*, with acetylacetone, now examined for the first time, of *o*- and *p*-chloroanilines, 2 : 4-, 2 : 5-, and 3 : 5-dichloroanilines, and *o*-anisidine. Koenigs and Mengel (*Ber.*, 1904, **37**, 1322) were similarly unable to obtain 6-methoxy-2 : 4-dimethylquinoline from β-*p*-methoxyanilinopropenyl methyl ketone. Marckwald and Schmidt (*Annalen*, 1893, **274**, 331) showed that, whilst both *m*- and *p*-phenylenediamines condensed with two molecules of acetylacetone, treatment of the products with concentrated sulphuric acid afforded an amino-2 : 4-dimethylquinoline (and not a phenanthroline) in the former case, and no quinoline at all in the second. Incidentally, Bülow and Issler (*Ber.*, 1903, **36**, 4013) effected the conversion of β-*m*-hydroxyanilinopropenyl methyl ketone into a mixture of hydroxy-2 : 4-dimethylquinolines by using, not concentrated sulphuric acid, but hydrogen chloride and glacial acetic acid as the condensing medium.

It appears possible to draw certain definite conclusions from these facts. For example, when a strongly ortho-para directing group is present in the meta-position to the nitrogen atom [3 or 5 in (I)], condensation proceeds readily, even if a similar group is present in an unfavourable position, as in 2 : 5-, 3 : 4-, and 2 : 3-dimethoxyaniline. On the other hand, a strongly ortho-para directing group present in position 4 (I), in absence of other substituents in favourable positions, appears to be sufficient to prevent quinoline formation (*o*- and *p*-anisidine). The effect of chlorine is what would be anticipated from our knowledge of its power as a directive influence. Thus, whilst one chlorine atom in a favourable position (meta to the nitrogen atom) is associated with exceptional ease of quinoline formation, a chlorine atom in another position prevents condensation (but compare the case of 3 : 4-dichloroaniline, below). It therefore seems that in these cases the ortho-directive influence of the nitrogen atom is, extraordinary though it may appear, feebler than the opposing ortho-para influence of a chlorine atom. Further, whilst steric factors do not prevent the operation of the directive influence of a methoxyl group, they appear to more than neutralise that of even two chlorine atoms. Thus, β-3 : 5-dichloroanilinopropenyl methyl ketone [chlorine in positions 3 and 5 in (I)] cannot be converted into the corresponding quinoline, although the two chlorine atoms and the nitrogen atom would be expected to favour condensation. From this fact, one might deduce that the dimethylquinoline formed from *m*-chloroaniline would be (III) rather than (IV), since the steric effect would operate against the formation of the latter. That this inference is correct is proved later. It would also appear to follow from this that the compound obtained by Marckwald and Schmidt (*loc. cit.*) from *m*-phenylenediamine is 7-amino-2 : 4-dimethylquinoline. The non-formation of a quinoline from *p*-phenylenediamine is of interest, for, since β-*p*-aminoanilinopropenyl methyl ketone is presumably present as the ion (V) in concentrated sulphuric acid solution, the most favoured position would appear to be that where condensation could occur, but does not.

(III.)





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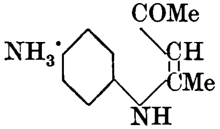


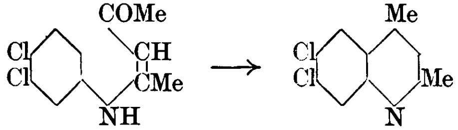
(V)

It is somewhat difficult, on the other hand, to explain why β-*p*-toluidinopropenyl methyl ketone [methyl in position 4 in (I)] is quantitatively converted into 2 : 4 : 6-trimethylquinoline (see Experimental). For, since *p*-chlorotoluene nitrates to roughly equal extents in the 2- and 3-positions (Holleman, *Rec. trav. chim.*, 1909, **28**, 408), the influence of a methyl group should approximate to that of a chlorine atom in type (I). The explanation may be, however, that just as replacement by chlorine, but not by methyl, diminishes the basicity of the aniline molecule, so it diminishes the ortho-para directive influence, already small, of the nitrogen atom in the acetylacetone anils.

Particular interest attaches to the action of sulphuric acid upon the condensation product of acetylacetone with 3 : 4-dichloroaniline (VI). Preliminary experiments showed no condensation, but then, on one occasion, a good conversion into a dichlorodimethylquinoline,

m. p. 119—120°, occurred. Attempted repetition of the successful experiment on at least a dozen occasions never gave an isolable quantity of this product, which, however, has been shown to be 6 : 7-*dichloro*-2 : 4-*dimethylquinoline* (VII).

(VI.)



(VII.)

We regard these results as indicating that in (VI) there is a very delicate balance between the antagonistic and the favourable influences, so that the slightest variation from the ideal conditions for condensation is sufficient to prevent ring closure.

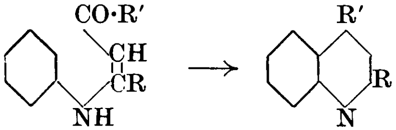
The non-formation of quinoline in the cases referred to above can hardly be due to an initial condensation to the extent of a few units %, the water formed then, with the sulphuric acid, hydrolysing the unchanged anil of a weak base, for if this were so, condensation should have been observed where absolute or slightly fuming sulphuric acid was used.

Partly in order to prove the constitution of the products (III) and (VII), and partly to institute a comparison of the Combes condensation with others leading to the same, and other, quinolines, we next directed our attention to the method first used by Reed (*J. pr. Chem.*, 1885, **32**, 630), but generally known as the Beyer condensation (*ibid.*, 1886, **33**, 393). When heated with a suitably aged mixture of paraldehyde, acetone, and hydrogen chloride at 100° in presence of nitrobenzene, *o*-, *m*-, and *p*-chloro-, 2 : 4-, 2 : 5-, 3 : 4-, and 3 : 5-dichloro-, and 2 : 4 : 5-trichloro-aniline were converted into dimethylquinolines, although in every case the yield was poor. On the other hand, *m*-nitroaniline was apparently unaffected, whilst *o*-nitroaniline was converted in good yield into a *compound* other than the expected 8-nitro-2 : 4-dimethylquinoline. Again, 3-chloro-6-nitro- and 3 : 4-dichloro-6-nitro-aniline were converted into tarry substances from which nothing could be isolated. The object of attempting the latter two condensations was to synthesise reference compounds needed for the elucidation of the structure of (III) and (VII).

When on one occasion 3 : 5-dichloroaniline was heated with a paraldehyde–acetone–hydrogen chloride mixture prepared 2 months previously, no 5 : 7-dichloro-2 : 4-dimethylquinoline was obtained, but, in good yield, a *substance* which has not yet been identified.

The above results become of even greater interest when the Combes and the Beyer condensation are compared with those of Doebner and von Miller and of Skraup. The last three of these condensations have been the subject of repeated investigation, but much uncertainty still exists as to the precise mechanism underlying them. Consideration of the papers of von Miller (*Ber.*, 1891, **24**, 1720; 1892, **25**, 2072), Jones and his collaborators (J., 1910, **97**, 632; 1911, **99**, 334; 1912, **101**, 1376), Blaise and Maire (*Compt. rend.*, 1907, **144**, 93; *Bull. Soc. chim.*, 1908, **3**, 658), and Simon (*Compt. rend.*, 1907, **144**, 138) suggests, however, that the four reactions under discussion are similar in one respect, namely, that in the last stage they all appear to conform to the general scheme of (VIII) passing into (IX):

(VIII.)



(IX.)

The Skraup, Doebner–Miller, Beyer, and Combes condensations are represented by this scheme when $R = R' = H$, $R = Me$ and $R' = H$, $R = R' = Me$, and $R = R' = Me$, respectively. The assumption is not invalidated by the observations of Knoevenagel and his collaborators (*Ber.*, 1922, **55**, 1923; 1923, **56**, 2414), nor can the fact that the so-called "aldol bases" are formed in the Doebner–Miller reaction be regarded as involving a conception essentially different from that represented by the above scheme.

Decker and Remfry (*Ber.*, 1905, **38**, 2773) concluded that both the Skraup and the Doebner–Miller reaction converted mono-meta-substituted anilines into 5-substituted quinolines. A closer examination of the facts, however, shows that this is hardly the case, since Skraup reactions with these compounds actually fall into two classes. Those in which the meta-substituent is meta-directing (NO_2, SO_3H, and CO_2H) give almost entirely 5-substituted quinolines (La Coste, *Ber.*, 1883, **16**, 669; Claus and Stiebel, *Ber.*, 1887, **20**, 3095; Knueppel, *Ber.*, 1896, **29**, 703; Decker, *J. pr. Chem.*, 1901, **63**, 573; **64**, 85; Lellmann and Lange, *Ber.*, 1887, **20**, 1446; Schlossen and Skraup, *Monatsh.*, 1881, **2**, 518: Skraup, *Ber.*, 1882, **15**, 893; Skraup and Bronner, *Monatsh.*, 1886, **7**, 139, 519; Lellmann and Alt, *Annalen*, 1887, **237**, 307), whilst, when the meta-substituent is ortho-para directing (Cl, Br, Me, OH), either a mixture of 5- and 7-derivatives results, or almost exclusively the 7-derivative (La Coste and Bodewig, *Ber.*, 1884, **17**, 926; La Coste, *Ber.*, 1885, **18**, 2940; Claus and Tornier, *Ber.*, 1887, **20**, 2872; Claus and Vis, *J. pr. Chem.*, 1889, **40**, 382; Skraup, *Monatsh.*, 1882, **3**, 381, 531; Skraup, *loc. cit.*; Skraup and Bronner, *loc. cit.*; von Braun, Gmelin, and Schultheiss, *Ber.*, 1923, **56**, 1341). On the other hand, *m*-

nitroaniline gives mainly 5-nitroquinaldine (Decker and Remfry, *loc. cit.*), whilst it does not condense to any observable extent under the conditions of the Beyer synthesis.

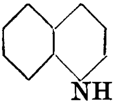
m-Chloroaniline gives rise to a mixture of 5- and 7-derivatives in the Skraup reaction (La Coste, 1885, *loc. cit.*; Claus and co-workers, *J. pr. Chem.*, 1893, **48**, 253, 270), mainly to the 7-derivative in the Beyer reaction, and to the 7-derivative only in the Combes condensation. An inspection of (VIII) and (IX) suggests that the difference in position of condensation in the three reactions mentioned is due to the steric effect of R′. Possibly the same effect prevents the formation of 5-nitro-2 : 4-dimethylquinoline by the Beyer process, since for some reason, not clear at present, the quinoline ring apparently prefers to form in the ortho-position with respect to a nitro-group rather than in the para-position. This point is of considerable interest, since in the nitration of nitrobenzene, more ortho- than para-substitution occurs.

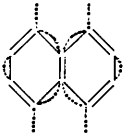
Which constitution (I*a* or I*b*) more accurately represents the constitution of the condensation products of acetylacetone with anilines cannot now be discussed, but we have observed that dibenzoylmethane condenses with freshly distilled aniline to give, as one product, a compound identical with that obtained by Watson (J., 1903, **83**, 1326) by the addition of aniline to benzoylphenylacetylene, CPh⋮C·COPh. Watson regarded his compound as being either CHPh:C(NHPh)·COPh or NHPh·CPh:CH·COPh, and the formation of the same compound from dibenzoylmethane shows that the latter reacts in the enolic form, to give the second of the two substances formulated, *i.e.*, to give the anilino-derivative and not the phenylimino-compound, COPh·CH_2·CPh:NPh. One of us has previously observed (Turner, *loc. cit.*) that when acetylacetone is heated with excess of aniline it undergoes scission, giving acetanilide. We have now found that benzanilide is formed as a second product when aniline reacts with dibenzoylmethane.

The factors governing substitution in quinoline compounds are apparently less complex than would be assumed from first considerations. Quinoline and 2-methylquinoline both nitrate simultaneously in the 5- and 8-positions (Claus and Kramer, *Ber.*, 1885, **18**, 1243, etc.), whilst 4-methylquinoline, on the other hand (Busch and Königs, *Ber.*, 1890, **23**, 2687), gives only the 8-nitro-derivative, an effect almost certainly due to the steric influence of the methyl group in position 4. 2 : 4-Dimethylquinoline would therefore also be expected to nitrate in position 8, and has actually been found to do so. The *nitro*-compound on reduction gives 8-*amino*-2 : 4-*dimethylquinoline*, and the latter is converted by the Gattermann diazo-method into 8-*chloro*-2 : 4-*dimethylquinoline*, identical with the product of the Beyer condensation, using *o*-chloroaniline.

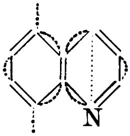
It would be thought that most of the substitution reactions of quinoline could be referred to the presence of the nitrogen atom, but actually this is not the case. Nor is it quite clear by what process conditions of nitration affect the proportion of 5- and 8-substitution in quinoline itself. For example, when quinoline nitrate is added to fuming sulphuric acid, 5-nitroquinoline results (Dufton, J., 1892, **61**, 783), whilst mixed acid converts quinoline itself mainly into the 8-isomeride (Königs, *Ber.*, 1879, **12**, 449). If the former nitration were explained as that of the ion (X), and the latter as that of the free base, then it would be difficult to explain why *iso*quinoline does not nitrate in position 7 (Claus and Hoffmann, *J. pr. Chem.*, 1893, **47**, 253), and even more so why quinolinium methonitrate also nitrates in positions 5 and 8 (Decker, *Ber.*, 1905, **38**, 1274). A comparison of quinoline and naphthalene appears to solve these difficulties, for, just as the behaviour of naphthalene is tolerably well explained by Thiele's formula (XI), so that of quinoline should be explained, at least to a considerable extent, by (XII), the following two facts being borne in mind: (1) Mills and Smith (J., 1922, **121**, 2724) concluded that in the naphthalene molecule the two central (*i.e.*, un-numbered) carbon atoms are joined by a double bond, (2) the pyridine molecule is markedly non-reactive, a property capable of explanation by formulating it as (XIII), since the highly unsaturated nitrogen atom may be assumed to take up residual affinity from the 4-position. That is, one would expect to find reactivity in the 5- and 8-positions in quinoline, corresponding to the reactivity of the *four* α-positions in naphthalene.

(X.)

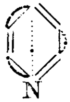




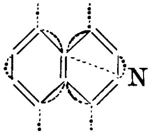
(XI.)



(XII.)



(XIII.)



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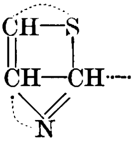

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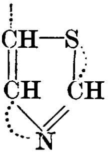

(XVI.)

Indeed, the application of similar reasoning to the *iso*quinoline and thiazole molecules suggests an alternative explanation of the interesting results obtained by Mills and Smith (*loc. cit.*), *viz.*, in *iso*quinoline, chlorine * should be more reactive (towards hydriodic acid and red phosphorus) in position 1 than in position 3, and in thiazole, since the nitrogen atom is less saturated than the sulphur atom (compare XV and XVI), reactivity should be associated more with position 2 than with position 4—which is actually the case. If this explanation is correct, reactivity should also be greater in position 5 than in position 4.

If (XIV) accurately represents the *iso*quinoline molecule, the known nitro-derivative might be expected to be the 5- rather than the 8-compound.

Quinoline actually resembles naphthalene very strongly in its substitution reactions, since α-nitronaphthalene corresponds with either 5- or 8-nitroquinoline. The analogy becomes even more striking when it is realised that, just as naphthalene-α-sulphonic acid is converted by concentrated sulphuric acid under definite conditions into the β-isomeride, so quinoline-5-sulphonic acid is converted by the same reagent at 250—300° into the 6-isomeride (Lellmann and Reusch, *Ber.*, 1889, **22**, 1391).

Nitration of 6-, 7-, and 8-chloro-2 : 4-dimethylquinoline appears to be controlled almost entirely by 5 : 8 reactivity, and by the ortho-para directive influence of the chlorine atom, which can act partly in the same sense. These overcome the steric effects which must be assumed in the case of the 6- and the 7-chloro-compound [compare the nitration, by Armstrong and Wynne, of β-chloronaphthalene, where the α-position *could* be avoided, and is (*Chem. News*, 1889, **59**, 225)]. For example, 6-chloro- and 7-chloro-2 : 4-dimethylquinoline nitrate in positions 5 and 8, respectively. The 8-chloro-compound nitrates in position 5, as is shown by the fact that the *nitro*-compound, on reduction, affords an *amino*-compound which is convertible into 5 : 8-*dichloro*-2 : 4-*dimethylquinoline*, identical with the product of Beyer condensation on 2 : 5-dichloroaniline.

That the ortho-para directive influence of the chlorine atoms in these compounds operates is shown by the results of nitrating 6- and 7-chloro-2 : 4-dimethylquinoline. The effect of 5 : 8-reactivity in the quinoline series is shown very clearly by the fact that 6-bromoquinoline sulphonates in position 8 (Edinger, *Ber.*, 1908, **41**, 937), whilst 6-chloroquinoline sulphonates either in 5 or in 8, according to conditions (Claus and Schedler, *J. pr. Chem.*, 1894, **49**, 355). An even more striking case is that recorded by Kaufmann and Hussy (*Ber.*, 1908, **41**, 1735), who showed that 6- and 7-nitroquinoline nitrate to give, respectively, 5 : 6- and 6 : 8-, and 5 : 7- and 7 : 8-

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* The chlorine atom here appears to be of the positive type.

dinitroquinoline, *i.e.*, 5 : 8-reactivity causes some nitration to occur in the ortho-position to a nitro-group.

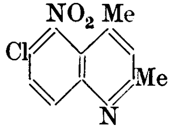
Dichloro-derivatives of 2 : 4-dimethylquinoline also nitrate quantitatively to give only one product. Thus the 5 : 8-dichloro-derivative gives 5 : 8-*dichloro*-6-*nitro*-2 : 4-*dimethylquinoline*, whose constitution is proved by its conversion, through the corresponding 6-*amino*-compound, into 5 : 6 : 8-*trichloro*-2 : 4-*dimethylquinoline*, also obtained by Beyer condensation of 2 : 4 : 5-trichloroaniline. Nitration of other dichloro-compounds undoubtedly occurs in position 5 or 8, but it has been impossible to prove the constitutions of the products, since the amines obtained by reduction could not be converted into the corresponding chloro-compounds. We have confirmed the observation made by Claus (compare *J. pr. Chem.*, 1894, **49**, 355) that the Sandmeyer reaction is unsuitable in the quinoline series, whereas the Gattermann method gives good results. On the other hand, the success of a replacement of an amino-group by chlorine depends also on the basicity of the amino-compound, and on the rate of diazotisation of the hydrochloride; for example, whilst 8-amino-, 6-*chloro*-5-*amino*-, 8-chloro-5-amino-, and 7-*chloro*-8-*amino*-2 : 4-*dimethylquinoline* diazotise readily, 5 : 8-dichloro-6-amino-2 : 4-dimethylquinoline diazotises slowly, 6 : 8-*dichloro*-5(?)-*amino*- still more slowly, and 5 : 6-*dichloro*-8(?)-*amino*- hardly at all. 5 : 6 : 8-Trichloro-2 : 4-dimethylquinoline does not undergo nitration under the conditions employed.

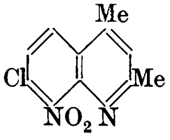
It was stated above that 3 : 4-dichloroaniline was converted by the Combes reaction into 6 : 7-dichloro-2 : 4-dimethylquinoline, but this fact was only established with considerable difficulty. *o*-Dichlorobenzene was found to condense readily with acetyl chloride under Friedel–Crafts conditions to give 3 : 4-*dichloroacetophenone*, but the nitration of the latter caused unexpected difficulties. These were finally overcome, and the 3 : 4-*dichloro*-2-*nitroacetophenone* obtained was converted into the corresponding *amino*-compound, which, when heated with acetone and a trace of alkali, gave an almost quantitative yield of 6 : 7-dichloro-2 : 4-dimethylquinoline, m. p. 119—120°, identical with the product from 3 : 4-dichloroaniline. The proof of the constitution of this product enabled us to deduce the constitution of the product of nitration of 6-chloro-2 : 4-dimethylquinoline. When this was reduced and the resulting amine was submitted to the Gattermann reaction, a dichlorodimethylquinoline was obtained, also melting at 119—120°; this depressed the m. p. of the synthetic 6 : 7-isomeride, and was therefore 5 : 6-dichloro-2 : 4-dimethylquinoline, since the 6 : 8-isomeride, obtained by Beyer condensation of 2 : 4-dichloroaniline, melted at 148—148·5°.

The chloro-2 : 4-dimethylquinoline obtained by the Combes reaction from *m*-chloroaniline, and therefore either the 5- or the 7-derivative, gave a nitro-compound which was converted into a chloroamino-compound, and thence into a dichloro-compound melting at 104—104·5°. The latter could only be 5 : 6-, 5 : 7-, 5 : 8-, 6 : 7-, or 7 : 8-dichloro-2 : 4-dimethylquinoline. Of these compounds, three were already known, and 5 : 7-*dichloro*-2 : 4-*dimethylquinoline*, obtained by Beyer condensation from 3 : 5-dichloroaniline, was found to melt at 84—86°. It therefore follows that the above chlorodimethylquinoline is the 7-derivative, and the derived dichlorodimethylquinoline the 7 : 8-derivative.

6-*Chloro*-5-*nitro*-2 : 4-*dimethylquinoline* was found not to react with piperidine, and this led us to consider again the work of Mills and Smith (*loc. cit.*). If, with these authors, we assume the presence of a central double bond in the quinoline molecule, the 6-chlorine atom and the 5-nitro-group will be attached to carbon atoms joined by a double bond (XVII), a condition assumed by Borsche and his co-workers (*Annalen*, 1913, **402**, 81; 1926, **447**, 1) to be associated with diminished reactivity of chlorine. One of these assumptions—we think that due to Borsche—appears to be incorrect, since 7-*chloro*-8-*nitro*-2 : 4-*dimethylquinoline* (XVIII), in which almost similar conditions obtain, reacts readily with piperidine to give 8-*nitro*-7-*piperidino*-2 : 4-*dimethylquinoline*.

(XVII.)





(XVIII.)

We have also investigated the chlorination of various chloro-derivatives of 2 : 4-dimethylquinoline in presence of glacial acetic acid and anhydrous sodium acetate. 7-Chloro-2 : 4-dimethylquinoline gave a *trichloro*-derivative, whilst 6- and 8-chloro- and 5 : 6-dichloro-2 : 4-dimethylquinoline gave *tetrachloro*-2 : 4-*dimethylquinolines*, all different. 5 : 8-Dichloro-2 : 4-dimethylquinoline, however, gave a *pentachloro*-2 : 4-*dimethylquinoline*, identical with the product of chlorinating the 6 : 8-compound. All these compounds contain mobile chlorine (of the negative type), showing that chlorination has occurred partly in the methyl groups. Similar compounds were obtained by Königs from 8-nitro-4-methylquinoline (*Ber.*, 1898, **31**, 2368) and later by Hammick (J., 1923, **123**, 2882). Little can be said with regard to the constitutions of our compounds, except that the pentachloro-compound must, because of its dual origin, contain chlorine atoms in the 5-, 6-, and 8-positions. The extent to which chlorination occurs is apparently determined neither by the amount of sodium acetate used, nor by the solubility of the compounds actually isolated.

EXPERIMENTAL.

Condensation of Substituted Anilines with Acetylacetone.—The general method adopted was to allow a mixture of the substituted aniline (1 mol.) with 1·1 mols. of acetylacetone to boil gently under reflux for 1—2 hours. The cooled product was then thoroughly shaken with water, benzene added, and the two layers separated. The benzene solution was shaken twice or thrice with water, dried over anhydrous sodium sulphate, and heated at 100° until free from benzene. In most cases, the anil was then pure enough to solidify when cooled.

p-Toluidine.—The anil was obtained in almost theoretical yield, and after one crystallisation from light petroleum (b. p. 40—60°) formed massive prisms, m. p. 68—69°. Combes (*loc. cit.*) gave m. p. 39—40°, whereas in D.R.-PP. 363,582 and 363,583 the m. p. is given as 65·5°. Ferriss and Turner (J., 1920, **117**, 1140) stated that the anil was converted, under the conditions now given for its formation, into 2 : 4 : 6-trimethylquinoline. This, however, is not the case. The anil, β-*p*-toluidinopropenyl methyl ketone, when treated with sulphuric acid by the usual method (see below) was quantitatively converted into 2 : 4 : 6-trimethylquinoline, m. p. 43—45°. The m. p. (63—64°) quoted by Pfitzinger (*J. pr. Chem.*, 1888, **38**, 40) is evidently that of the hydrate, which we have found to melt at 63—65°. The concentrated sulphuric acid solution of the crude quinoline, when treated with potassium dichromate, remained a clear reddish-brown colour after some minutes' boiling, indicating the absence of even small quantities of *p*-toluidine. Such quantitative conversion into a quinoline was not observed with the product from any other substituted aniline.

o-*Chloroaniline.*—β-o-*Chloroanilinopropenyl methyl ketone* was readily formed, and separated from light petroleum (b. p. 40—60°) in small plates, m. p. 66—67° (Found : Cl, 17·1. $C_{11}H_{12}ONCl$ requires Cl, 16·9%).

p-*Chloroaniline.*—β-p-*Chloroanilinopropenyl methyl ketone* was readily obtained, and crystallised from light petroleum (b. p. 40—60°) in rectangular prisms, m. p. 60—61° (Found : Cl, 17·0%).

m-*Chloroaniline.*—β-m-*Chloroanilinopropenyl methyl ketone*, readily formed, crystallised from light petroleum (b. p. 40—60°) in plates; it had m. p. 42°, and b. p. 187°/13 mm. (Found : N, 6·9. $C_{11}H_{12}ONCl$ requires N, 6·7%).

o-*Hydroxybenzylidene*-3-*chloroaniline* was readily obtained, and separated from alcohol in bright yellow needles, m. p. 99° (Found : N, 6·1. $C_{13}H_{10}ONCl$ requires N, 6·0%).

2 : 4-*Dichloroaniline.*—This base condensed readily with acetylacetone. β-2 : 4-*Dichloroanilinopropenyl methyl ketone* separated from aqueous alcohol in needles, m. p. 100·5° (Found : N, 5·8. $C_{11}H_{11}ONCl_2$ requires N, 5·7%). o-*Hydroxybenzylidene*-2 : 4-*dichloroaniline* separated from alcohol in brilliant yellow needles, m. p. 90·5° (Found : N, 5·3. $C_{13}H_9ONCl_2$ requires N, 5·3%).

2 : 5-*Dichloroaniline.*—The condensation of this base with acetylacetone presents two interesting features. When any other of the substituted anilines dealt with was heated with acetylacetone at 100° (the approximate b. p. of such mixtures), water was seen to separate after a few minutes. In the case of 2 : 5-dichloroaniline, however, water only separated from the condensation mixture when the latter was boiling briskly. On cooling it a few degrees, the water redissolved. The second peculiarity observed was the small yield obtained, so that the β-2 : 5-*dichloroanilinopropenyl methyl ketone* was only isolable by distillation under diminished pressure (b. p. 190—200°/15 mm.) of the purified reaction product. It finally crystallised from light petroleum (b. p. 40—60°) in octahedra, m. p. 46°. *o*-Hydroxybenzylidene-2 : 5-dichloroaniline, on the other hand, was readily obtainable in good yield; the crude product crystallised from alcohol in bright yellow needles, m. p. 107° (Found : N, 5·4%).

3 : 5-*Dichloroaniline.*—Condensation occurred readily, but the β-3 : 5-*dichloroanilinopropenyl methyl ketone* was not obtained crystalline. The 3 : 5-dichloroaniline required was obtained by reducing 3 : 5-dichloronitrobenzene by the iron method, the nitro-compound being prepared as follows (compare Holleman and Reiding, *Rec. trav. chim.*, 1904, **23**, 366) : A mixture of 85 g. of 2 : 6-dichloro-4-nitroaniline and 170 c.c. of concentrated sulphuric acid was diazotised at −5° with 56 g. of solid sodium nitrite. The dark paste obtained was slowly run into 600 c.c. of boiling 96% alcohol; immediate decomposition then took place, with the formation of an orange solution. Some sodium sulphate separated, and on diluting the mixture largely with water, the nitro-compound was precipitated. It had m. p. 62—65°, whereas the pure substance melts at 65°.

3 : 4-*Dichloroaniline.*—This base condensed smoothly with acetylacetone to give β-3 : 4-*dichloroanilinopropenyl methyl ketone,* which separated from alcohol in almost colourless needles, m. p. 73° (Found : N, 5·7%). o-*Hydroxybenzylidene*-3 : 4-*dichloroaniline* crystallises from alcohol in long, yellow needles, m. p. 113°

(Found : N, 5·4%). The 3 : 4-dichloroaniline required was prepared by reducing the corresponding nitro-compound by the iron method.

o-*Anisidine.*—Condensation occurred readily to give β-o-*methoxyanilinopropenyl methyl ketone*, which separated from light petroleum (b. p. 40—60°) in plates, m. p. 51—52·5°.

3-*Chloro*-6-*acetamidoaniline.*—This also was found to condense with acetylacetone, but the product, like that from *o*-anisidine, was not further examined, since it gave no quinoline derivative when treated with concentrated sulphuric acid.

3 : 4-*Dichloro*-6-*nitroaniline.*—This base was recovered unchanged after being heated with excess of acetylacetone in a closed tube for 6 hours at 200°. The dichloro-base was readily obtainable by hydrolysing (90% sulphuric acid at 120° for 20 minutes) the corresponding acetyl derivative, the latter being prepared as described by Beilstein and Kurbatow (*Annalen*, 1879, **196**, 225).

Attempted Preparation of 2 : 3-*Dichloroaniline.*—(*a*) The nitration of 3 : 4-dichloroaniline in presence of a large excess of sulphuric acid led to a mixture of products, from which only unchanged base was isolated. It had been hoped that 3 : 4-dichloro-5-nitroaniline would be obtained, and thence, by removal of the amino-group, 2 : 3-dichloronitrobenzene. (*b*) *o*-Chloroacetanilide sulphonated readily when added to cold fuming sulphuric acid (25% SO_3). The solution was treated with nitric acid, and then evidently contained 3-chloro-5-nitro-4-acetamidobenzenesulphonic acid (compare D.R.-P. 206,345, dealing with a similar treatment of *m*-chloroacetanilide). The solution of the nitrosulphonic acid, when diluted slightly and boiled, contained acetic acid, but various methods tried did not give detectable quantities of 2-chloro-6-nitroaniline, from which it had been hoped to prepare 2 : 3-dichloronitrobenzene.

Conversion or Attempted Conversion of Anils of Acetylacetone into Substituted 2 : 4-*Dimethylquinolines.*—The most satisfactory method of effecting this condensation was as follows : The anil was slowly added, as a fine powder, or as a thin stream of liquid, to six times its weight of concentrated sulphuric acid, the latter being kept well shaken, and cooled below 5°. As soon as solution occurred, the mixture was heated for 0·5 hour on the boiling water-bath. The extent of condensation was readily diagnosed by diluting a little of the sulphuric acid solution. In cases of unsuccessful condensation, the odour of acetylacetone became apparent at once, and, usually, the sulphate of the unchanged base separated. Neither of these observations was made in the case of a successful condensation, and the further addition of potassium dichromate then gave an immediate precipitate of the quinoline dichromate (see above under *p*-toluidine). The isolation of the quinolines presented no difficulty.

β-*Anilinopropenyl Methyl Ketone.*—The yield of pure 2 : 4-dimethylquinoline obtained was 90% on the weight of anil taken, or 75% on the weight of aniline. The success of this condensation appears to depend largely on the purity of the anil, the distillation of which (Combes, *loc. cit.*) is not only unnecessary, but disadvantageous.

The anils from acetylacetone and *o*- and *p*-chloroaniline, 2 : 4-, 2 : 5-, and 3 : 5-dichloroaniline, *o*-anisidine and 3-chloro-6-acetamidoaniline were not converted into the corresponding quinolines by the sulphuric acid method. Use of absolute sulphuric acid, or of slightly fuming acid, or variation of the temperature of heating made no difference to the result.

The anil from 2 : 5-dimethoxyaniline behaved exactly as described by Lions, Perkin, and Robinson (*loc. cit.*), the yield of 5 : 8-dimethoxy-2 : 4-dimethylquinoline being almost quantitative.

β-m-*Chloroanilinopropenyl Methyl Ketone.*—This anil (compare that last mentioned) was converted almost quantitatively into 7-*chloro*-2 : 4-*dimethylquinoline*, the *hydrate* of which separated from aqueous alcohol in colourless needles, m. p. 61° (Found : Cl, 16·7. $C_{11}H_{10}NCl$ requires Cl, 18·5%. $C_{11}H_{10}NCl,H_2O$ requires Cl, 16·9%). Crystallisation of the hydrate from light petroleum afforded the anhydrous base in prismatic needles, m. p. 46·5—48·5° (Found : Cl, 17·9%). The quinoline is obtained in almost theoretical yield if the anil–sulphuric acid solution is heated, not at 100°, but at 130—140°.

7-*Chloro*-2 : 4-*dimethylquinoline hydrochloride* forms colourless needles, m. p. 277° (decomp.), soluble in water [Found : Cl (ionisable), 15·8. $C_{11}H_{10}NCl,HCl$ requires Cl (ionisable), 15·6%]. The *sulphate* separates from water in rhombohedra, and the *dichromate* in brilliant yellow needles. The *silver nitrate additive compound*, colourless needles [Found : Ag, 17·8. $(C_{11}H_{10}NCl)_2,AgNO_3$ requires Ag, 17·6%] melts at 197° (decomp.).

In an attempt to synthesise this quinoline, various experiments were carried out on the preparation of 4-chloro-2-aminoacetophenone. (1) This substance could not be isolated from the product of interaction of *p*-chloroaniline with acetic anhydride in presence of zinc chloride, although aniline, under similar conditions, is known to afford *p*-aminoacetophenone (Klingel, *Ber.*, 1885, **18**, 2688). (2) 2 : 4-Dinitroethylbenzene was not converted into 2 : 4-dinitroacetophenoneoxime when kept at room temperature in presence of amyl nitrite and piperidine, although Reich and Nicolaeva (*Helv. Chim. Acta*, 1919, **2**, 84) obtained a small yield of the oxime by using sodium ethoxide as the condensing agent. (3) 2 : 4-*Dichloroacetophenone* was not converted into 4-chloro-2-aminoacetophenone when heated for 6 hours at 180° with alcoholic ammonia. The 2 : 4-dichloroacetophenone was obtained in 15% yield by condensing *m*-dichlorobenzene with acetyl chloride in presence of aluminium chloride. The majority of the dichlorobenzene was recovered unchanged. 2 : 4-Dichloroacetophenone has m. p. 33—34°, and b. p. 140—150°/15 mm. (Found : Cl, 37·2. $C_8H_6OCl_2$ requires Cl, 37·5%). To a boiling suspension of 1 g. of the ketone in 100 c.c. of 1·5% aqueous sodium hydroxide, were added 2·23 g. of potassium permanganate dissolved in 50 c.c. of water. Immediate oxidation occurred, and the sole product obtained, after crystallisation from aqueous alcohol, was 2 : 4-dichlorobenzoic acid, m. p. 161—162°.

β-3 : 4-*Dichloroanilinopropenyl Methyl Ketone.*—The only successful condensation of this compound was carried out by slowly adding the anil to five times its weight of cooled concentrated sulphuric acid, and heating the resulting solution at 130—140° for 4 hours. On cooling and pouring the mixture into water, a little 3 : 4-dichloroaniline sulphate separated; this was collected. The filtrate was rendered alkaline with ammonia, the precipitated quinoline was removed and dissolved in dilute sulphuric acid, and dilute potassium dichromate solution added. The precipitated *dichromate* (yellow needles, soluble in hot, but insoluble in cold water) was collected, and converted into the free base, which, after crystallisation from alcohol or light petroleum (b. p. 80—100°), formed colourless needles, m. p. 119—120° (Found : Cl, 31·5. $C_{11}H_9NCl_2$ requires Cl, 31·4%). Repetition of this condensation some dozen times under apparently similar conditions never gave rise on any second occasion to isolable quantities of the quinoline. Variation of the concentration of sulphuric acid, or of temperature or of time of heating, or of the conditions of mixing of anil and acid, also led to the same negative result. Saturation of a glacial acetic acid solution of the anil with dry hydrogen chloride (compare Bülow and Issler, *loc. cit.*) or treatment of a similar solution with acetic anhydride, or with acetyl chloride, did not cause ring-closure. The anil was also heated with syrupy phosphoric acid at 130—145° and then at 200° for 2 hours, but after this treatment, only 3 : 4-dichloroaniline was isolated. In the case of the acetyl chloride experiment, a crystalline solid separated after 5 minutes, but then redissolved. Treatment of the anil with a mixture of acetic anhydride and acetyl chloride merely led to the production of 3 : 4-dichloroacetanilide.

6 : 7-*Dichloro*-2 : 4-*dimethylquinoline hydrochloride* forms white needles, m. p. 235°, sparingly soluble in water [Found : Cl (ionisable), 13·6. $C_{11}H_9NCl_2,HCl$ requires Cl (ionisable), 13·5%]. The

chloroaurate forms twig-like, yellow needles, sparingly soluble even in hot water; the *sulphate* forms white needles; the *silver nitrate additive compound* is precipitated when an alcoholic solution of the base is treated with an aqueous solution of silver nitrate. It forms colourless needles, m. p. 218—219°, soluble in hot, but sparingly soluble in cold, alcohol [Found: Ag, 17·7. $(C_{11}H_9NCl_2)_2,AgNO_3$ requires Ag, 17·4%].

Nitration of 6 : 7-*Dichloro*-2 : 4-*dimethylquinoline.*—The method used for nitrating this base, and for all the other quinoline bases mentioned, unless otherwise stated, was as follows: The base was added slowly to five times its weight of a mixture, kept at −5°, of 1 part by weight of fuming nitric acid (*d* 1·5) and 2 parts by weight of concentrated sulphuric acid (*d* 1·84). The resulting solution was kept at the ordinary temperature for 1—2 hours and then poured on ice, and the nitro-compound was isolated either as the sulphate or as the free base.

In the case of 6 : 7-*dichloro*-8(?)-*nitro*-2 : 4-*dimethylquinoline*, the base was crystallised from alcohol, and then formed white needles, m. p. 197° (Found: N, 10·6. $C_{11}H_8O_2N_2Cl_2$ requires N, 10·4%). Nitration of 6 : 7-dichloro-2 : 4-dimethylquinoline with mixed acid at 60° also gave the nitro-compound described above.

Consideration of the other results obtained in this work suggests that the nitro-compound is of the 8- rather than of the 5-type.

Preparation of Substituted 2 : 4-*Dimethylquinolines by the Beyer Process.*—The method adopted was essentially that used by Beyer (*loc. cit.*), but in detail as follows: (*a*) A mixture of 96 g. of paraldehyde and 160 g. of acetone was saturated with dry hydrogen chloride, and left for 3 days. Such a mixture then weighed approximately 425 g. (*b*) The substituted aniline (1 mol.) was thoroughly ground with 3 mols. of concentrated hydrochloric acid, and the mixture added to one of 0·5 mol. of nitrobenzene and 255 g. of the acetone–paraldehyde–hydrogen chloride mixture. The whole was heated at 100° under reflux for 10 hours, and then worked up by an appropriate method, as described under individual compounds.

8-*Chloro*-2 : 4-*dimethylquinoline.*—The reaction mixture obtained from *o*-chloroaniline by the process just mentioned was poured into water; the resulting mixture was repeatedly extracted with ether, and the aqueous-acid layer rendered alkaline with sodium hydroxide. It was then thoroughly extracted with ether, and the ethereal extract was washed with brine and dried over anhydrous sodium sulphate. Evaporation of the ether and distillation of the residue under diminished pressure afforded two fractions, the first consisting of 40% of the original chloroaniline used; the second, b. p. 170—190°/15 mm. (mainly 185°/15 mm.), was 8-*chloro*-

2 : 4-*dimethylquinoline* (yield 25%), which solidified on cooling. After being twice crystallised from light petroleum (b. p. 40—60°), it formed stout, white prisms, m. p. 74° (Found : Cl, 18·6. $C_{11}H_{10}NCl$ requires Cl, 18·6%). The quinoline separates anhydrous from aqueous alcohol in small, rectangular plates. It was unaffected by piperidine after 1 hour's heating at 100°.

Nitration of 8-*Chloro*-2 : 4-*dimethylquinoline.*—The last-named quinoline nitrated readily, and on pouring the nitration mixture on ice a copious white precipitate of the *sulphate* of 8-chloro-5-nitro-2 : 4-dimethylquinoline was obtained. This was collected and treated with aqueous ammonia, and the reddish-brown solid obtained was crystallised from alcohol. The nitro-compound forms pale yellowish-brown prisms, m. p. 107—108° (Found : Cl, 15·1. $C_{11}H_9O_2N_2Cl$ requires Cl, 15·0%) (yield, more than 90%).

8-*Chloro*-5-*amino*-2 : 4-*dimethylquinoline* was prepared by the reduction of the 5-nitro-compound with iron, water, and ferric chloride. The reaction mixture was cooled and filtered. The residue of iron and amino-compound was dried and extracted with benzene. The *amino-compound* separated from the cooled benzene solution in brown prisms, m. p. 170—172° (Found : Cl, 17·1. $C_{11}H_{11}N_2Cl$ requires Cl, 17·2%) (yield, 33%).

Conversion of 8-*Chloro*-5-*amino*- *into* 5 : 8-*Dichloro*-2 : 4-*dimethylquinoline.*—The chloroamino-compound (4 g.) was ground with 12 c.c. of concentrated hydrochloric acid, and the stiff reddish-brown paste so obtained cooled to −5°. A solution of 1·4 g. of sodium nitrite in 4·5 c.c. of water was slowly added. Diazotisation was rapid, and to the clear solution obtained was added a suspension of 5 g. of copper powder in hydrochloric acid (1 vol. of concentrated acid : 1 vol. of water). A brisk evolution of nitrogen occurred. Removal of the copper left a yellowish solution, which when treated with aqueous ammonia gave an almost theoretical yield of 5 : 8-dichloro-2 : 4-dimethylquinoline as a white precipitate. This, after being twice crystallised from alcohol, formed prismatic needles, m. p. 117—118°, alone or when mixed with 5 : 8-dichloro-2 : 4-dimethylquinoline prepared from 2 : 5-dichloroaniline (see below).

Chlorination of 8-*Chloro*-2 : 4-*dimethylquinoline.*—A solution of 1 g. of the quinoline in 20 c.c. of glacial acetic acid was heated at 60°, saturated with chlorine, and then treated with water. The white precipitate of the *tetrachloro*-compound obtained, after being twice crystallised from alcohol, formed slender needles, m. p. 150—152° (Found : Cl, 47·5. $C_{11}H_7NCl_4$ requires Cl, 48·1%).

6-*Chloro*-2 : 4-*dimethylquinoline.*—The Beyer reaction mixture from *p*-chloroaniline was poured into water, and the product was extracted with ether. The aqueous layer was evaporated to about one-third of its original volume; a crystalline precipitate of crude hydrochloride was slowly deposited. This was collected, extracted with boiling acetone to remove colouring matter, and then treated with warm aqueous ammonia. The almost pure base so obtained separated from light petroleum (b. p. 80—100°) in stout prisms, m. p. 98—99° (Found: Cl, 16·4%) (yield, 16%). The quinoline crystallises from aqueous alcohol as the *hydrate*, silky needles, m. p. 84—85·5° (Found: Cl, 17·0. $C_{11}H_{10}NCl,H_2O$ requires Cl, 16·9%). The mother-liquor from which the above crude hydrochloride separated was found to contain only *p*-chloroaniline hydrochloride.

The quinoline forms an orange-yellow *dichromate*, which may be crystallised from water.

Nitration of 6-*Chloro*-2 : 4-*dimethylquinoline*.—The nitration mixture, when poured on ice, afforded a crystalline precipitate of the *sulphate* of 6-*chloro*-5-*nitro*-2 : 4-*dimethylquinoline*, which was filtered off and decomposed with warm aqueous ammonia. The practically pure base was then crystallised from alcohol, and formed canary-yellow prisms, m. p. 132—133° (Found: Cl, 15·8%) (yield over 90%). The chloronitro-compound was unaffected when heated for 10 minutes at 100° with excess of piperidine.

6-*Chloro*-5-*amino*-2 : 4-*dimethylquinoline*.—The preceding nitro-compound was reduced with iron powder, aqueous alcohol, and ferric chloride. The reaction mixture was filtered while still hot, the residual iron well washed with alcohol, and the alcoholic extracts and filtrate were evaporated. The solid that separated on cooling crystallised from benzene in pale yellow, prismatic needles, m. p. 131—133° (Found: Cl, 17·2%) (yield, 52%).

Conversion of 6-*Chloro*-5-*amino*- *into* 5 : 6-*Dichloro*-2 : 4-*dimethylquinoline*.—The base (9·1 g.) was ground with 30 c.c of concentrated hydrochloric acid, and the resulting canary-yellow hydrochloride paste was treated at −5° with a solution of 3·1 g. of sodium nitrite in 5 c.c. of water. Diazotisation was rapid, and to the clear solution so obtained copper and hydrochloric acid were added as usual. The whole assumed a dirty green colour, and suddenly set to a stiff paste. Two volumes of water were then added, the whole was heated to boiling and filtered, and the filtrate was cooled. The resulting yellowish-brown hydrochloride (prisms) was collected and digested with aqueous ammonia. The base so obtained (6 g.), after being crystallised first from alcohol and then from light petroleum (b. p. 80—100°), formed stout, colourless prisms, m. p. 119—120° (Found: Cl, 30·9. $C_{11}H_9NCl_2$ requires Cl, 31·4%). A mixture of this quinoline (then of unknown constitution) with the 6 : 7-dichloro-isomeride (also then of unknown constitution) melted at about 90°.

Chlorination of 6-*Chloro*-2 : 4-*dimethylquinoline*.—A solution, heated at 60°, of 1 g. (1 mol.) of the chloro-compound in 20 c.c. of glacial acetic acid containing 2·2 g. (5 mols.) of fused sodium acetate was saturated with chlorine. No precipitate was formed, but on dilution an oily *tetrachloro*-compound was thrown down. This became solid on standing, and after being crystallised from aqueous alcohol, and then from light petroleum (b. p. 40—60°), formed slender needles, m. p. 75·5—81° (Found: Cl, 48·4. $C_{11}H_7NCl_4$ requires Cl, 48·1%).

Nitration of 5 : 6-*Dichloro*-2 : 4-*dimethylquinoline*.—When the nitration mixture was poured on ice, the free base was precipitated. It crystallised from alcohol, in which it was very sparingly soluble, in silky needles, m. p. 151—152·5° (Found: Cl, 26·2. $C_{11}H_8O_2N_2Cl_2$ requires Cl, 26·2%) (yield, over 90%).

5 : 6-*Dichloro*-8(?)-*amino*-2 : 4-*dimethylquinoline*.—The preceding nitro-compound readily underwent reduction when heated with iron powder, aqueous alcohol, and a little hydrochloric acid. The mixture was finally filtered, the residue well washed with alcohol, and the alcoholic filtrates diluted with water. The precipitated amino-compound (yield, 83%) was dried, and then melted at 118—120° (Found: Cl, 27·6. $C_{11}H_{10}Cl_2N_2$ requires Cl, 29·5%). The crude base was used for the succeeding experiment.

Attempted Conversion of 5 : 6-*Dichloro*-8(?)-*amino*-2 : 4-*dimethylquinoline into* 5 : 6 : 8(?)-*Trichloro*-2 : 4-*dimethylquinoline*.—A suspension of the amino-compound in concentrated hydrochloric acid did not appear to undergo diazotisation when treated with sodium nitrite. Subsequent addition of copper caused no evolution of nitrogen.

Chlorination of 5 : 6-*Dichloro*-2 : 4-*dimethylquinoline*.—When chlorine was passed into a solution of 1·1 g. of the quinoline (1 mol.) in 30 c.c. of glacial acetic acid containing 1·23 g. (3 mols.) of fused sodium acetate, a precipitate of a *tetrachloro*-compound was formed. This separated from alcohol, in which it was very sparingly soluble, in slender needles, m. p. 157—158° (Found: Cl, 48·3. $C_{11}H_7NCl_4$ requires Cl, 48·1%). A mixture of the tetrachloro-compound with the tetrachloro-compound (m. p. 150—152°) obtained from 8-chloro-2 : 4-dimethylquinoline melted below 130°.

Preparation of 7-*Chloro*-2 : 4-*dimethylquinoline by the Beyer Method*.—The reaction mixture obtained from *m*-chloroaniline was poured into water, and the resulting mixture extracted several times with ether. The aqueous layer was basified, and extracted with ether, and the ethereal extract was washed with brine and dried. Distillation of the contained basic mixture under diminished pressure afforded 55% of unchanged *m*-chloroaniline as a first fraction, and then a 36% yield of crude chloroquinoline, b. p. about 174°/10 mm. The latter partly crystallised on prolonged standing, and the crystalline portion, isolated on porous porcelain, separated from light petroleum (b. p. 40—60°) in prismatic needles, m. p. 42—45°, either alone or when mixed with the product from *m*-chloroaniline and acetylacetone (above). A little of the 5-isomeride was presumably present in the crude basic mixture, but in insufficient quantity for isolation.

7-Chloro-2 : 4-dimethylquinoline was unaffected by piperidine after 1 hour's heating at 100°.

Nitration of 7-*Chloro*-2 : 4-*dimethylquinoline*.—For this purpose, the chloro-compound obtained by the more convenient acetylacetone method was used. Nitration, followed by pouring on ice, gave a precipitate of the almost pure 7-*chloro*-8-*nitro*-2 : 4-*dimethylquinoline* (yield over 95%). Nitration with warm mixed acid gave a similar result, either product separating from alcohol in slender, white needles, m. p. 189—189·5° (Found : N, 12·0. $C_{11}H_9O_2N_2Cl$ requires N, 11·8%).

When the nitro-compound was heated for 0·5 hour at 100° with an excess of piperidine, piperidine hydrochloride separated, and on extensive dilution with water a yellow powder was obtained. This separated from alcohol, in which it was sparingly soluble even when hot, in prisms; a second crystallisation from light petroleum (b. p. 80—100°)–benzene afforded 8-*nitro*-7-*piperidino*-2 : 4-*dimethylquinoline* in rectangular plates, m. p. 168—170°. When mixed with the original chloronitro-compound, the substance melted at about 140°.

7-*Chloro*-8-*amino*-2 : 4-*dimethylquinoline*.—This substance, which was practically insoluble in hot aqueous alcohol, rapidly dissolved at 90—100° in that solvent in presence of iron powder and a little ferric chloride. Filtration, extraction of the iron powder with alcohol, and evaporation gave a black oil which solidified on cooling, and then crystallised from light petroleum (b. p. 40—60°) in slender, pale yellow needles, m. p. 51—53° (yield 83%) (Found : Cl, 17·4%).

Conversion of 7-*Chloro*-8-*amino*-2 : 4-*dimethylquinoline into* 7 : 8-*Dichloro*-2 : 4-*dimethylquinoline*.—The amino-compound was ground with concentrated hydrochloric acid, and the bright yellow hydrochloride paste diazotised at −10° with aqueous sodium nitrite. The clear red diazo-solution tended to undergo spontaneous decomposition, producing a coppery-brown, amorphous solid, but when it was added to a solution of cuprous chloride in hydrochloric acid normal decomposition appeared to occur. The product was treated with excess of ammonia, and the precipitated solid was collected, dried, and extracted with light petroleum (b. p. 40—60°). 7 : 8-

Dichloro-2 : 4-*dimethylquinoline* was then obtained in slender, prismatic needles, m. p. 104—104·5° (yield under 20%) (Found : Cl, 30·7%).

Chlorination of 7-*Chloro*-2 : 4-*dimethylquinoline*.—Chlorination of this base by the usual method in the cold afforded a *trichloro*-2 : 4-*dimethylquinoline*, which separated from alcohol in colourless needles, m. p. 195° (Found : Cl, 41·0. $C_{11}H_8NCl_3$ requires Cl, 40·9%).

6 : 8-*Dichloro*-2 : 4-*dimethylquinoline*.—The condensation mixture obtained by applying the Beyer reaction to 2 : 4-dichloroaniline was poured into water, and the resulting mixture repeatedly extracted with ether. The aqueous layer was boiled until free from ether, and then basified. The solid precipitated, after being collected and dried, was extracted with hot light petroleum (b. p. 80—100°), from which solvent 6 : 8-dichloro-2 : 4-dimethylquinoline separated in slender needles, m. p. 148—148·5° (yield 20%) (Found : Cl, 31·4%). The base separated anhydrous from aqueous alcohol.

Nitration of 6 : 8-*Dichloro*-2 : 4-*dimethylquinoline*.—The nitration solution when poured into a large bulk of water gave a precipitate of crude 6 : 8-*dichloro*-5(?)-*nitro*-2 : 4-*dimethylquinoline*, which separated from alcohol in pale yellow prisms, m. p. 120—122°. A further crystallisation from light petroleum (b. p. 40—100°) raised the m. p. to 122—123° (yield, 80%) (Found : Cl, 26·7%).

6 : 8-*Dichloro*-5(?)-*amino*-2 : 4-*dimethylquinoline*.—Reduction of the corresponding nitro-compound was effected by the usual method, using aqueous alcohol. The iron residue was extracted with hot acetone, and the extracts were evaporated. Crystallisation of the residue from alcohol afforded white, rectangular plates, m. p. 194—195° (yield, 81%) (Found : Cl, 29·6%). The amino-compound was converted by concentrated hydrochloric acid into a stiff, orange hydrochloride paste, which diazotised very slowly. Addition of copper powder caused some nitrogen evolution, but only unchanged base was isolated when the product was worked up.

Chlorination of 6 : 8-*Dichloro*-2 : 4-*dimethylquinoline*.—A solution of 1 g. of the quinoline (1 mol.) in 20 c.c. of glacial acetic acid containing 0·36 g. (1 mol.) of fused sodium acetate was heated at 60°, and saturated with chlorine. The precipitated solid separated from alcohol in needles, m. p. 124—125°, and was a *pentachloro*-quinoline. A mixture with the product obtained by the chlorination of 5 : 8-dichloro-2 : 4-dimethylquinoline (m. p. 127—128°) melted at 125—127°.

5 : 8-*Dichloro*-2 : 4-*dimethylquinoline*.—The product of the Beyer condensation using 2 : 5-dichloroaniline was poured into a large bulk of water, and the black, oily layer separated. The aqueous

layer was treated in the usual manner, and finally gave the dichloroquinoline as a solid, which separated from alcohol or from light petroleum (b. p. 80—100°) in prismatic needles, m.p. 117—118·5° (yield, 29%) (Found : Cl, 31·5%).

5 : 8-*Dichloro*-6-*nitro*-2 : 4-*dimethylquinoline*.—Nitration of the preceding quinoline, followed by dilution, afforded a precipitate which, after treatment with ammonia, separated from alcohol, in which it was very sparingly soluble, in white, slender needles, m. p. 155—157°. It separated from benzene in prisms (yield, over 90%) (Found : Cl, 26·3%).

5 : 8-*Dichloro*-6-*amino*-2 : 4-*dimethylquinoline*.—The nitro-compound underwent reduction with the usual reagents, in presence of aqueous alcohol. The iron residue was extracted for several hours with boiling benzene, the latter then evaporated, and the residue crystallised from benzene; the amino-compound was then obtained in brown octahedra, m. p. 192—193° (yield, 40%) (Found : Cl, 29·5%).

Conversion of 5 : 8-*Dichloro*-6-*amino*- *into* 5 : 6 : 8-*Trichloro*-2 : 4-*dimethylquinoline*.—The base was converted by concentrated hydrochloric acid into a paste consisting of yellow leaflets, which underwent diazotisation with difficulty. Addition of copper caused nitrogen evolution. Dilute hydrochloric acid was added, and then benzene, the latter to remove a black, tarry by-product. The acid solution, after being basified, gave a small quantity of a dark solid, which was boiled in alcoholic solution with charcoal, and after this treatment separated from alcohol, and later from light petroleum (b. p. 80—100°), in needles, m. p. 111—112·5°. A mixture of this compound with 5 : 6 : 8-trichloro-2 : 4-dimethylquinoline (see below) melted at 112—113·5°.

Chlorination of 5 : 8-*Dichloro*-2 : 4-*dimethylquinoline*.—Chlorination of this base at 60° in glacial acetic acid in presence of sodium acetate (1 mol.) afforded a pentachloroquinoline derivative as a precipitate, which separated, after two crystallisations from alcohol, in slender needles, m. p. 127—128° (Found : Cl, 54·0. $C_{11}H_6NCl_5$ requires Cl, 53·9%).

Preparation of 6 : 7-*Dichloro*-2 : 4-*dimethylquinoline by Beyer's Process*.—The reaction product obtained from 3 : 4-dichloroaniline when worked up in the usual manner gave about 55% of unchanged dichloroaniline, and a fraction, b. p. 180—190°/15 mm., which was evidently a mixture of 5 : 6- and 6 : 7-dichloro-2 : 4-dimethylquinoline. Separation by crystallisation of the dichromates gave a product, m. p. 80—105°, which was converted into a mixture of hydrochlorides. The latter was crystallised from dilute hydrochloric acid, and the hydrochloride of the 6 : 7-base so obtained was treated with alkali. Crystallisation of the product from light petroleum (b. p. 80—100°) afforded a substance, m. p. 119—120°, which did not depress the m. p. of the quinoline obtained from acetylacetone (Found : Cl, 31·5%).

5 : 7-*Dichloro*-2 : 4-*dimethylquinoline.*—The reaction mixture from the Beyer condensation, using 3 : 5-dichloroaniline, was treated in the usual manner. Basification of the final acid solution gave a solid which was purified only with difficulty, but after being crystallised from light petroleum (b. p. 80—100°) and then from light petroleum (b. p. 60—80°) formed small prisms, m. p. 84—86° (yield, 20%) (Found : Cl, 31·5%).

On the first occasion of attempting this preparation, the paraldehyde–acetone–hydrogen chloride mixture used had been prepared 2 months previously. Condensation, followed by pouring into a large bulk of water, gave a black oil containing suspended solid. This was filtered and pressed, and then thoroughly extracted with a mixture of equal volumes of benzene and light petroleum (b. p. 80—100°). After decantation of the cooled extract, a yellowish-brown solid separated (31 g. from 50 g. of the dichloroaniline). It crystallised from alcohol in yellow leaflets, m. p. 168—169° (Found : Cl, 41·9, 42·0%). This *substance*, which will be examined later, was converted by aqueous ammonia into a second *substance*, which separated from light petroleum (b. p. 40—100°) in bunches of colourless needles, m. p. 69—70° (Found : Cl, 36·5, 36·6%). The second substance readily dissolved in hot dilute mineral acids, the solutions depositing crystalline precipitates on cooling.

5 : 6 : 8-*Trichloro*-2 : 4-*dimethylquinoline.*—Beyer condensation with 2 : 4 : 5-trichloroaniline gave a product, which, on pouring into water, afforded tarry material containing a solid in suspension. The aqueous portion, when basified, deposited tarry material only. The above solid was extracted with boiling hydrochloric acid (concentrated acid : water, 1 : 1), and tar removed. On cooling, 2 : 4 : 5-trichloroaniline hydrochloride separated, and this was removed. The mother-liquor, on basification, afforded the crude trichloroquinoline, which then separated from alcohol and later from light petroleum (b. p. 80—100°) in small, prismatic needles, m. p. 113—114° (Found : Cl, 41·5. $C_{11}H_8NCl_3$ requires Cl, 40·9%). The quinoline does not form a hydrate, and when dissolved in the usual manner in a mixture of nitric and sulphuric acids remained unchanged.

Beyer Condensation with o-*Nitroaniline.*—The condensation product was treated in the usual manner. At the basification stage, a brown, tarry solid was obtained. This readily dissolved in hot alcohol to give a solution, which on cooling deposited crystals.

These dissolved only with difficulty in fresh hot alcohol, from which solvent a *substance* separated in prismatic needles, m. p. 145—147° (12 g. from 35 g. of *o*-nitroaniline).

Beyer Condensation with p-*Nitroaniline.*—The condensation product, when poured into water, deposited a black tar, which was rejected. The aqueous layer was repeatedly extracted with benzene, the latter removed, and alkali added. The *substance* so obtained then separated from alcohol in brownish leaflets, m. p. 159—162° (31 g. from 50 g. of *p*-nitroaniline). This compound and that obtained from *o*-nitroaniline are under investigation.

When *m*-nitroaniline was submitted to the Beyer condensation, only unchanged base was isolated. 3-Chloro-6-nitroaniline and 3 : 4-dichloro-6-nitroaniline, on the other hand, were converted into unworkable tarry products.

3 : 4-*Dichloroacetophenone.*—A mixture of 251 g. of *o*-dichlorobenzene and 229 g. of anhydrous aluminium chloride was slowly treated with 133 g. of acetyl chloride and then heated at 100° for 3 hours. The product was poured on ice, hydrochloric acid added, and the oily material extracted with carbon tetrachloride. Vacuum distillation afforded 130 g. of pure 3 : 4-*dichloroacetophenone*, b. p. 135°/12 mm. (yield, 40%). This became solid on cooling, and then separated from light petroleum (b. p. 80—100°) in bunches of white needles, m. p. 76° (Found : Cl, 37·6. $C_8H_6OCl_2$ requires Cl, 37·5%).

When 2 : 4 : 5-trichlorobenzene was treated in a similar manner, it was unaffected.

Nitration of 3 : 4-*Dichloroacetophenone.*—When the ketone was dissolved either in nitric acid (*d* 1·5) kept at 10—15°, or in a mixture of glacial acetic and fuming nitric acids, it was unaffected. When it was heated with the fuming acid at 50—55°, it was extensively oxidised. Addition of fuming nitric acid to a solution of the ketone in acetic anhydride at 60—70° effected no change. A mixture of fuming nitric and concentrated sulphuric acids at −10° did not affect the ketone, but at 15° caused resinification. A large number of variations of these experiments gave similar results. Finally, nitration was effected by the following method : The ketone was added in small portions to seven times its weight of nitric acid (*d* 1·5), the temperature being allowed to rise to 35—38°, but not above 40°. The solution was kept for 5 minutes, the temperature being maintained between 35° and 38°, and was then poured into a large bulk of water. 3 : 4-*Dichloro*-2-*nitroacetophenone* separated as a pale yellow solid, which was collected, washed, and crystallised from alcohol. It formed irregular plates, m. p. 100—102° (Found : Cl, 30·4. $C_8H_5O_3NCl_2$ requires Cl, 30·4%).

3 : 4-*Dichloro-2-aminoacetophenone*.—The nitro-compound underwent rapid and almost quantitative reduction when heated with iron powder, water, and a little ferric chloride. The cooled mixture was filtered, and the solid residue repeatedly extracted with benzene. After concentration of the extract, the amino-compound separated on cooling in yellow prisms, the m. p., 154—156°, of which was not affected by a further crystallisation from acetone (Found : Cl, 34·8. $C_8H_7ONCl_2$ requires Cl, 34·9%).

Condensation of 3 : 4-*Dichloro-2-aminoacetophenone with Acetone*.—(*a*) When the amino-compound was heated under reflux in acetone solution, together with a little piperidine, for 6 hours, it was unaffected. (*b*) A mixture of the amino-compound (1 g.), acetone (3 c.c.), and 50% aqueous sodium hydroxide (0·2 c.c.) was heated in a closed tube for 6 hours at 185°. When cold, the tube contained a mass of brown crystals. The contents of the tube were extracted with boiling acetone, the extract was filtered, and the acetone evaporated. The solid residue then crystallised from light petroleum (b. p. 80—100°) in slightly brown needles, m. p. 119—120°. The substance produced no depression of the m. p. of the products obtained by the acetylacetone and Beyer methods (from 3 : 4-dichloroaniline) and was 6 : 7-dichloro-2 : 4-dimethylquinoline. A mixture with 5 : 6-dichloro-2 : 4-dimethylquinoline melted below 90°.

Nitration of 2 : 4-*Dimethylquinoline*.—A solution of the quinoline (102 g.) in 510 g. of concentrated sulphuric acid was slowly treated at 5° with 290 g. of the usual mixture of nitric and sulphuric acids (*i.e.*, an excess for mononitration. Addition of the last half of the mixed acid caused no temperature rise). The solution was poured on ice, and the resulting clear solution basified with ammonia. The precipitated 8-*nitro*-2 : 4-*dimethylquinoline* crystallised from alcohol in brown needles, m. p. 118—119° (yield 93%) (Found : N, 13·7. $C_{11}H_{10}O_2N_2$ requires N, 13·8%).

8-*Amino*-2 : 4-*dimethylquinoline*.—Reduction of the preceding nitro-compound by means of iron powder, water, and ferric chloride proceeded vigorously, but the product was difficult to purify. Repeated extraction with light petroleum (b. p. 80—100°) gave a solution from which tarry matter separated on cooling. When no more tar separated, light petroleum (b. p. 40—60°) was added, whereupon the amino-compound separated in brownish-yellow plates, m. p. 89—92° (yield, 26 g.) (Found : N, 15·9. $C_{11}H_{12}N_2$ requires N, 16·3%). The *picrate* separates from alcohol in bunches of yellow prisms. The sulphate is bright yellow, and sparingly soluble in water. A dilute sulphuric acid suspension diazotised readily, but on heating, the resulting solution gave a product other than the expected hydroxy-compound.

Conversion of 8-Amino- into 8-Chloro-2 : 4-dimethylquinoline.—(*a*) The base was diazotised in hydrochloric acid suspension. Addition of cuprous chloride–hydrochloric acid solution gave an indefinite product. (*b*) The amino-compound (17 g.) was ground with 50 c.c. of concentrated hydrochloric acid, and the resulting orange-red paste treated slowly at −5° with a solution of 6·6 g. of sodium nitrite in 10 c.c. of water. Diazotisation proceeded rapidly, with the formation of a clear solution, to which a suspension of copper powder in hydrochloric acid was added. Nitrogen was at once evolved, and the mixture was diluted with water and filtered. Addition of excess of ammonia gave a gummy precipitate, which was dissolved in a hot mixture of 25 c.c. of concentrated sulphuric acid and 125 c.c. of water. On cooling, the sulphate of 8-chloro-2 : 4-dimethylquinoline separated in pale yellow needles, which were collected, and decomposed with ammonia. The base so obtained, after crystallisation from aqueous alcohol and then from light petroleum (b. p. 40—60°), melted at 74°. A mixture with the base obtained by the Beyer method using *o*-chloroaniline melted at the same temperature.

Condensation of Dibenzoylmethane with Aniline.—A mixture of dibenzoylmethane (1 mol.) and *freshly distilled* aniline (1·25 mols.) was boiled under reflux for 9 hours. On cooling, the whole became solid, and was fractionally crystallised from alcohol. Colourless plates, m. p. 161°, separated first, and these did not depress the m. p. of benzanilide (Found: N, 7·6. Calc.: N, 7·1%). The mother-liquor finally yielded a solid, which separated from benzene–light petroleum in bright yellow prisms, m. p. 102—103° (Found: N, 4·1; *M*, cryoscopic in benzene, 288. Calc.: N, 4·7%; *M*, 299). This substance is evidently identical with that described by Watson (*loc. cit.*).

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