INTRODUCTION

PART I
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PART I

The synthesis of 4-hydroxy quinoline derivatives which are used in the preparation of antimalarial drugs involves two main steps:

(i) Condensation of a β-keto ester with aromatic amines to give the intermediate acrylates or crotonates, and

(ii) Cyclisation of the acrylates or the crotonates.

Ethyl acetoacetate reacts with aromatic amines in two different ways:

(1) At higher temperature, it yields the anilides with the elimination of a molecule of alcohol, thus,

\[ \text{CH}_3\text{COCH}_2\text{COOC}_2\text{H}_5 + \text{R-NH}_2 \rightarrow \text{CH}_3\text{COCH}_2\text{CONH-R} + \text{C}_2\text{H}_5\text{OH} \]

( Knorr, Annalen, 1888, 245, 358; Ber, 1884, 17, 540, 542 )

In a previous paper, Knorr ( Ber, 1882, 16, 2593 ) had suggested that by heating ethyl acetoacetate and aniline in a sealed tube at 120°C, anil of acetoacetic acid, subsequently called phenyl β-imidobutyric acid,
$\text{C}_6\text{H}_5-N=\text{C(CH}_3)\text{-CH}_2\text{COOH}$, was obtained. The same compound was also stated to be obtained later on (Knorr, Annalen, 1894, 236, 74) by simply heating the reactants at $150^\circ$-$60^\circ$ C. Knorr's conception was that at ordinary temperature, a molecule of water separates and an oil is obtained having the formula $\text{C}_6\text{H}_5-N=\text{C(CH}_3)\text{-CH}_2\text{COOC}_2\text{H}_5$, but the reaction becomes rapid if the reactants are heated to the boiling point till the whole mass becomes dark yellow. According to him, treatment with sulphuric acid converted it into hydroxy methyl quinoline, then incorrectly formulated by him as follows:

$$\text{C}_6\text{H}_5\text{NH}_2 + \text{CH}_3\text{COCH}_2\text{COOC}_2\text{H}_5 \quad \longrightarrow \quad \text{C}_6\text{H}_5\text{N}=\text{C(CH}_3)\text{-COOC}_2\text{H}_5 + \text{H}_2\text{O}$$

$$\text{C}_6\text{H}_5\text{N}=\text{C(CH}_3)\text{-CH}_2\text{COOH} + \text{C}_2\text{H}_5\text{OH} + \text{H}_2\text{SO}_4$$

The anilides have also been obtained by refluxing the reactants for one and a half minutes by Ewins and King (J. Chem. Soc., 1913, 104). Hauser and Reynolds (J. Am. Chem. Soc., 1948, 70, 2402) recommend three to four minutes' reflux.
Knorr's γ-hydroxy quinoline derivatives were in reality all 2-hydroxy 4-methyl quinoline derivatives. This he had already corrected in a later paper (loc.cit.). Knorr's original method of synthesising 2-hydroxy 4-methyl quinoline derivatives gave very unsatisfactory results as found by Ewins and King (loc.cit.), for 2-hydroxy 4:8 dimethyl quinoline which was reported to melt at 185 °C by Knorr, was actually found to melt at 217 °C although prepared by a slight modification of Knorr's method by Ewins and King.

The formation of a hydroxy quinoline by the above process depends upon the production of the toluidide of acetoacetic acid which then under the dehydrating action of sulphuric acid loses water as follows:

\[
\begin{align*}
\text{CH}_3 & \quad \text{CO} \quad \text{CH}_3 \\
\text{CH}_2 & \quad \text{NH} \\
\text{CO} & \\
\text{H}_2\text{SO}_4 & \rightarrow \\
\text{CH}_3 & \quad \text{N} \\
\text{CH}_2 & \quad \text{OH} \\
\end{align*}
\]

The intermediate toluidide was not isolated by Knorr. Pawlewski (Ber, 1889, 22, 2203), however, described a substance obtained from the product which he consi-
dered to be β-tolyl imino crotonic acid (isomeric with the toluidide) in accordance with Knorr's original view that condensation took place, not as indicated above, but according to the following scheme whereby 4-hydroxy 2-methyl quinoline derivatives were obtained.

Knorr, however, had already corrected his original interpretation of the reaction and Pawlewski's substance was in all probability, from its melting point and the analytical figures, the ortho-toluidide of acetoacetic acid.

Knorr also reported that the anilide from aniline and ethyl benzoylacetae upon cyclisation gave 4-hydroxy 2-phenyl quinoline. This was shown to be incorrect by Hau-ser and Reynolds (loc.cit.), as the product actually obtained was 2-hydroxy 4-phenyl quinoline, as it should be.

(2) At lower temperatures, mixing equimolecular proportions of ethyl acetoacetate and aromatic amines yields ethyl β-arylamino crotonates with the elimination of a molecule of
water, thus,

$$\text{CH}_3\text{COCH}_2\text{COOC}_2\text{H}_5 + R\text{-NH}_2 \rightarrow$$

$$\text{R-N} = \text{C(CH}_3)\text{-CH}_2\text{COOC}_2\text{H}_5 + \text{H}_2\text{O}$$

(I)

$$\downarrow$$

$$\text{R-NH- C(CH}_3) = \text{CHCOOC}_2\text{H}_5$$

(II)

Ethyl β-anilino crotonate was first prepared by Conrad and Limpach (Ber, 1887, 20, 944; Ber, 1888, 21, 521, 1649, 1965; Ber, 1887, 20, 523, 524) by simply heating the reactants at 100 °C for a few hours and then alternately by keeping the reactants in cold for a few days, the time period being varied from one to five days. With aniline, they obtained compound II above.

Later on, this method of preparing the crotonates was modified by Coffey, Thomson and Wilson (J. Chem. Soc., 1936, 856). With highly purified ethyl acetoacetate and aniline, the reaction takes several days to complete in cold. The modification consisted in using catalysts, in main, concentrated hydrochloric acid and powdered iodine. The proportion of the catalyst used was either one drop of concentrated hydrochloric acid released from a capillary
end or 0.05 g. of powdered iodine. With the catalyst, the main advantage is that the rate of the formation of the crotonate is hastened up and is proportional to the strength of the acid. The turbidity, indicating the separation of water and therefore the start of the reaction, which otherwise appears after some hours was noticed in a few minutes. The time period, however, was different with different amines. In certain cases, the turbidity appeared in half a minute. In other cases, as many as forty-two minutes elapsed before the first separation of water was marked. In a few cases, the hydrochloride of the amine was also used as a catalyst. In all these cases, the formation of the crotonate proceeds almost to completion in twenty-four hours, but the reactants can be conveniently kept over some dehydrating agent such, for instance, as concentrated sulphuric acid or phosphorous pentoxide with chances of improved yields.

Coffey, Thomson and Wilson (loc.cit.) condensed various amines with ethyl acetoacetate and it appears from their results that the time taken for the turbidity to
appear under identical experimental conditions varied in
the following order of the amines:
P-anisidine < aniline < p-chloroaniline < p-phenyl
amino aniline < p-phenetidine < 1:3:4-xylidine <
o-chloroaniline < m-chloroaniline < p-or 1:4:5-xylidine

Later, Hauser and Reynolds (loc.cit.) prepared
these crotonates by a number of methods, all of which were,
in chief, modifications of the original Conrad-Limpach
method, and studied the mechanism involved therein. The
following methods were adopted:
(A) To 0.1 mole of the reactants, one drop of concentrated
hydrochloric acid was added and the mixture allowed to
stand for five days at room temperature.
(B) To 0.1 mole of the reactants, absolute alcohol (30 c.c.),
drierite (35 g.) and three to four drops of glacial acetic
acid were added and the mixture refluxed at 100° C for
three to four hours.
(C) To 0.1 mole of the reactants, drierite (10 g.) was add-
ed and the mixture heated at 95°-100° C in an oil-bath for
three to four hours.
(D) A mixture of 0.1 mole of the reactants was heated at 130°-40°C for three to four hours in the case of esters of higher alcohols.

![Chemical Reaction]

(III)

Using esters of different alcohols i.e. by varying the group R', they compared the yields of the final 4-hydroxy quinolines and studied the effect of group R' upon cyclisation. It appears from their observations that the yield of 4-hydroxy quinoline varied in the following order according as R' is

- ethyl > 2-ethyl-butyl > n-amyl.

Keeping R' constant and varying R, it was found that the yield of the 4-hydroxy quinoline is greater when R is methyl than when it is phenyl. This means that yields obtained with ethyl benzoylacetate are much less than those obtained with ethyl acetoacetate.

Hauser and Reynolds' publication showed the
interconvertibility of the crotonate and the anilide with rather fair ease and brought to light the mechanism involved in their formations viz. that since the crotonate and the anilide are readily interconvertible, the temperature dependence of the course of the reaction is due to the displacement of equilibrium rather than to the existence of two competing reaction paths with sufficiently differing temperature coefficients of rate.

\[
\begin{align*}
\text{COOCH}_2\text{CH}_3 & \quad 130^\circ-40^\circ + \\
\text{H}_2\text{O} \cdot \text{H} & \quad \rightarrow \\
\text{C}_6\text{H}_5\text{OH} & \quad \text{anhyd. CaSO}_4
\end{align*}
\]

Whether the anilide or the crotonate is formed in the initial condensation appears to be determined by the relative volatility of water and alcohol. By substituting higher esters (e.g. amyl) of acetoacetic acid for the ethyl ester, it has been possible to shift the above equilibria so as to direct the reaction in any desired way merely by setting conditions so that the more volatile elimination product (water or an alcohol) is formed. Similar considerations apply to condensations.
involving benzoylacetic esters.

It has been reported that nitraniines fail to
give crotonates with ethyl acetoacetate (Coffey, Thomson,
and Wilson, loc. cit.) (Misani and Bogert, J. Org. Chem.,
1945, 10, 347). However, three years later, Kaslow and
Stayner (J. Am. Chem. Soc., 1948, 70, 3350) condensed p-
nitraniine with ethyl acetoacetate to form ethyl \( \beta \)-p-
nitraniilino crotonate by a special device using the
amine, ester and one drop of concentrated hydrochloric
acid in either methylene dichloride or chloroform. The
reactants were refluxed under a water-cooled condenser
attached to a water-separator for immiscible liquids
heavier than water until no more water is collected.

Backeberg (J. Chem. Soc., 1935, 1568) condensed
p-aminoacetanilide with ethyl acetoacetate by heating the
reactants at 100 °C for thirty minutes to obtain ethyl-\( \beta \)-
( p-acetamido anilino ) crotonate. He was however, unable
to cyclise it to a 4-hydroxy quinoline derivative.

A modification of the above method consists in
refluxing pure p-aminoacetanilide and ethyl acetoacetate
in methanol for five hours when excellent yields of the intermediate crotonate are obtained. This has been cyclised by Pratt and Archer (J.Am.Chem.Soc., 1948, 70, 4065).

N-aminoacetanilide has been similarly condensed with ethyl acetoacetate to obtain ethyl-β-(m-acetamido anilino) crotonate (Backsberg, loc.cit.; Kermack and Webster, J.Chem.Soc., 1942, 213).

The reaction between o-phenylenediamine and ethyl acetoacetate was first investigated by Hinsberg and Koller (Ber, 1896, 29, 1500). Later, Sexton (J.Chem.Soc., 1942, 308) who condensed o-phenylenediamine with excess ethyl acetoacetate reported that even in presence of excess ethyl acetoacetate, anil formation takes place only on one amino group and obtained ethyl-β-(o-amino anilino) crotonate. The latter has been reported to exist in two forms which are supposed to be the cis- and trans-isomers. The first form is a white one which slowly changes on exposure for eight days to a yellow variety, the melting points reported for the two products being different.
With m-phenylenediamine and two moles of ethyl acetoacetate, Backesberg (loc. cit.) obtained ethylm-phenyl-
ene-bis-β-amino crotonate.

P-phenylenediamine has been similarly condensed with two moles of ethyl acetoacetate (Backesberg, loc. cit.)
to obtain ethyl-p-phenylene-bis-β-amino crotonate. Knorr (Ber, 1884, 17, 545; 1886, 19, 3303) reported that p-
phenylenediamine reacted with ethyl acetoacetate to form the dianilide which could not be converted into a quinoline
derivative. Inspite of numerous attempts (Backesberg, loc. cit.) under widely different conditions, it was not
possible to prepare this compound. Only ethyl-p-phenylene-
bis-β-amino crotonate was obtained.

Ethyl acetoacetate has also been condensed with 1- and 2-naphthylamines to obtain ethyl-β-(1- and 2-
naphthylamino) crotonates (Conrad and Limpach, Ber, 1888, 21, 531; Limpach, Ber, 1931, 64, 969). The condensa-
sation has, however, not been found to be so smoother as that with other aromatic amines and heating for a length-
ier period is necessary.
Ethyl benzoylacetate can be similarly condensed with aromatic amines. Conrad and Limpach (Ber, 1888, 21, 521) condensed ethyl benzoylacetate with aniline and obtained ethyl-β-phenyl-β-anilino acrylate. Elderfield et al. (J. Am. Chem. Soc., 1946, 68, 1272) condensed this ester with m-chloroaniline and p-anisidine although the intermediate ethyl-β-phenyl-β-(m-chloroanilino) and ethyl-β-phenyl-β-(p-anisidino) acrylates were not isolated. Hauser and Reynolds (loc. cit.) condensed in a similar manner ethyl benzoylacetate with aniline and o-toluidine and Kaslow and Lawton (J. Am. Chem. Soc., 1950, 72, 1724) employed p-bromoaniline.

Shah, Thakor and Kulkarni (J. Indian Chem. Soc., 1951, 28, 688) condensed ethyl benzoylacetacetate with aromatic amines and obtained ethyl-α-acyl-β-phenyl-β-(arylamino) acrylates. The reactants were first heated on a water-bath for one hour and then kept in cold for twenty-four hours.

With ethyl ethoxalylacetate (Surrey and Hamm-er, J. Am. Chem. Soc., 1946, 68, 113) and ethyl ethoxalyl
propionate (Steck, Hallock and Holland, J. Am. Chem. Soc., 1946, 68, 129, 132, 380; Hauser et al, J. Am. Chem. Soc., 1946, 68, 1232), the formation of the acrylate was accomplished by heating the reactants with stirring in either glacial acetic acid or methylene dichloride at 40°-50° C for four to forty-eight hours.

The condensation of ethoxymethyleneemalonic ester with aromatic amines was first carried out by Claisen (Ber, 1903, 36, 2729; Claisen and Haase, Annalen, 1897, 297, 75) by heating the reactants on a water-bath (Gould and Jacobs, J. Am. Chem. Soc., 1939, 61, 2890). Price and Roberts (J. Am. Chem. Soc., 1946, 68, 1204) however, report that the method of Claisen was satisfactory on a small scale. But with larger quantities, the handling of the acrylate was tedious and could be conveniently circumvented by mixing the reactants in diphenyl ether at room temperature (the solution later to be heated directly to the cyclising temperature).

Gould and Jacobs (loc. cit.) also condensed acetylmalonic ester with aniline. In the case of aceto-
acetic ester and ethoxymethylenemalonic ester, to typify two extreme cases, the condensation to the intermediate alkylidene derivative proceeds smoothly and apparently in only one sense with all the amines used, but acetylmalonic ester was found to give poorer yields of the alkylidene derivatives because of competing side-reactions. With aniline, a yield of about 50% of acetanilide and of 70% of the normal anilido-methyl methylene malonic ester was obtained.


The acrylates have in all cases, except when solid, been purified by washing with a solution of 0.5 N hydrochloric acid, then with water and finally drying.
When solid, they have been purified by crystallisations from suitable solvents.

Cyclisation of the acrylates:

It was reported by Conrad and Limpach (loc.cit.; Ber, 1892, 25, 772) that ethyl-β-arylamino crotonates can be converted into 4-hydroxy 2-methyl quinoline derivatives by quickly heating them at 240°-260° C for a short period. It was also reported that when the above operation is carried out, the crotonate is converted into 4-hydroxy 2-methyl quinoline derivative and among various other volatile components not further investigated, chiefly alcohol passes over, whereas in the retort is left a viscous residue which gradually crystallises to a solid mass which is then extracted with a suitable solvent and purified. In the original attempt of Conrad and Limpach (loc. cit.), ethyl-β-anilino crotonate was rapidly heated at 240° C, giving

(i) a distillate- ethyl alcohol, acetone, carbamidine

(ii) a viscous residue- 4-hydroxy quinaldine and ethyl phenyl lutidone monocarboxylate in proportions depending
upon the temperature and the duration of heating.

A number of 4-hydroxy 2-methyl quinolines were prepared in this way, all of which were soluble in aqueous alcohol and were amphoteric in character. Further, in almost all cases, the simultaneous formation of sym-bis-phenyl-substituted ureas has always been reported. It is due to this reason and many other uninvestigated operating factors, it seems, that the yields reported by Conrad and Limpach in all cases were quite poor. Further, definite melting points of such compounds obtained from the naphthylamines were also not mentioned.

Forty-four years later, Limpach (loc. cit.) suggested the use of medicinal oil as an inert diluent for the cyclisation of the crotonates. This method, however, did not give quite satisfactory results. Criticisms have been advanced by various workers (Maurin, Ann. Chim., 1935, 3093) because of excessive decomposition in this method.

The original Limpach-cyclisation as utilized by Gould and Jacobs (loc. cit.) involved adding a β-arylamino crotonate to from two to ten times its weight of mineral
oil preheated to $250^\circ-30^\circ \text{C}$ and then heating the solution
at $240^\circ-50^\circ \text{C}$ for fifteen to twenty minutes even after the
dropping process is over.

It has, however, since then been found (Price
and Roberts, loc. cit.) that both diphenyl ether and
'Dowtherm A' (eutectic of diphenyl ether and diphenyl)
are far superior as cyclisation media. These solvents boil
at a temperature which is optimum for the cyclisation,
are much less viscous and more easily removed from the
product by filtration and in general, the product is
formed with much less darkening.

Modifications resulting in increased yields by
the use of a number of high boiling solvents have been
made by various investigators from time to time
Gillie, Lions and Ritchie, J. Proc. Roy. Soc. N.S.Wales,
1940, 72, 258- C.A. 1940, 34, 5896;
Hughes and Lions, J. Proc. Roy. Soc. N.S.Wales, 1938, 71,
458- C.A. 1939, 33, 611;
Riegel et al., ibid., 1946, 68, 1264;
Tarbell et al., ibid., 1946, 68, 1277;
Lauer et al., ibid., 1946, 68, 1268;
Synder et al., ibid., 1947, 69, 371;
Gouley, Hoersch and Hosher, ibid., 1947, 69, 303;
Price et al., ibid., 1947, 69, 373; etc.

4-hydroxy 2-methyl quinolines have thus been obtained by Conrad and Limpach (loc.cit.) by the cyclisation of ethyl-β-arylamino crotonates obtained from aniline, o-toluidine, p-toluidine, o-anisidine, p-anisidine and 1:3:4 xylidine. 1- and 2-naphthylamines have also been obtained employed giving benzoquinolines. Hauser and Reynolds (loc.cit.) obtained 4-hydroxy 2-methyl 6-chloroquinoline by the cyclisation of ethyl-β-(p-chloroanilino) crotonate and Kernack (J. Chem. Soc., 1939, 563) similarly obtained the corresponding 6-bromo derivative. Kaslow and Stayner (loc.cit.) have prepared 4-hydroxy 2-methyl 6-nitro quinoline by the cyclisation of ethyl-β-(p-nitranilino) crotonate. The same compound was also obtained
by Kermack (loc. cit.) by nitration of 4-hydroxy 2-methyl quinoline. Backeberg (loc. cit.) prepared ethyl-\(\beta\)-(p-acetamido anilino) crotonate, but he was unable to cyclise it. This has however, been cyclised by Kermack (loc. cit.) and later by Pratt and Archer (loc. cit.) to 4-hydroxy 2-methyl 6-acetamido quinoline which has also been obtained by the reduction of 4-hydroxy 2-methyl 6-nitro quinoline (Kermack, loc. cit.) followed by acetylation of the amino derivative. Backeberg (loc. cit.) was also unable to cyclise ethyl-\(\beta\)-(m-acetamido anilino) crotonate. This has, however, since then been cyclised (Kermack and Webster, loc. cit.) by the thermal method to give only 4-hydroxy 2-methyl 5-acetamido quinoline which has been hydrolysed to 4-hydroxy 2-methyl 5-amino quinoline. Ethyl-\(\beta\)-(o-amino anilino) crotonate obtained from o-phenylenediamine and ethyl acetoacetate (Sexton, loc. cit.) also does not seem to have been cyclised to a 4-hydroxy quinoline derivative.

Spivey and Curd (J. Chem. Soc., 1949, 2656) obtained 4-hydroxy 2:5 and 2:7 dimethyl quinolines by cyclising ethyl-\(\beta\)-(m-toluidino) crotonate. They also
effected the cyclisation of ethyl-\(\beta\)-(m-chloroanilino) crotonate and obtained a mixture of 5- and 7-isomers from which 4-hydroxy 2-methyl 7-chloro quinoline alone could be separated. 4-hydroxy 2-methyl 5-chloro quinoline, however, could not be isolated.

Until recently, not much attention was centred on the problem of isomerism existing between 4-hydroxy 2-methyl quinolines obtained from ethyl acetooacetate and \(m\)-substituted anilines except in the case of \(m\)-amino acetoanilide (Kermack, loc.cit.), and a complete separation of these isomers was not effected till 1949 in which year, Spivey and Curd (loc.cit.) prepared and separated 4-hydroxy 2:5 and 2:7 dimethyl quinolines and 4-hydroxy 2-methyl 7-chloro quinoline and who report that in the case of both \(m\)-toluidine and \(m\)-chloroaniline, a mixture of isomers is obtained which it is difficult to separate into individual isomers, although after many an unsuccessful attempt at separation, the isolation of 4-hydroxy 2:5 and 2:7 dimethyl quinolines has been successfully secured in the
form of their oxalates and in a ratio 56:44. But with m-chloroaniline, they succeeded in obtaining only one isomer viz. 4-hydroxy 2-methyl 7-chloro quinoline as its picrate. The isomeric 4-hydroxy 2-methyl 5-chloro quinoline, however, could not be isolated at all. It was also reported that in the case of ethyl-β-(m-chloroanilino) crotonate, the yield of 4-hydroxy quinoline varied with different ratios of the crotonate and diphenyl ether and was maximum (41 %) when this ratio was 1:16. In the case of ethyl-β-(m-toluidino) crotonate, the proportion of 4-hydroxy 2:5 and 2:7 dimethyl quinolines did not vary appreciably with the crotonate: diphenyl ether ratio, the nature of the solvent and the temperature at which cyclisation is carried out.

Conrad and Limpach (loc. cit.) first cyclised ethyl-β-phenyl-β-anilino acrylate by quickly heating it at 250° C and obtained 4-hydroxy 2-phenyl quinoline.
Later on, Hauser and Reynolds (loc.cit.) condensed ethyl benzoyleacetate with aniline and o-toluidine and obtained 4-hydroxy 2-phenyl and 4-hydroxy 2-phenyl 8-methyl quinolines by cyclisation of the intermediate acrylates using the modified method of Price and Roberts (loc.cit.). Kaslow and Lawton (loc.cit.) obtained 4-hydroxy 2-phenyl 6-bromo quinoline in a similar manner.

Elderfield et al (loc.cit.) condensed ethyl benzoyleacetate with m-chloroaniline and p-anisidine by mixing the reactants in diphenyl ether at room temperature and then directly heating the solution to the cyclising temperature. The products obtained were directly converted into 4:7 dichloro and 4-chloro 6-methoxy 2-phenyl quinolines by treatment with phosphorous oxychloride. The yields reported were however, poor- 3-5% for the former and 6-8% for
the latter. Application of the familiar Conrad-Limpach synthesis with its modifications has thus not been found satisfactory starting with ethyl benzoylacetae.

Just (Ber, 1885, 19, 2623, 2632; Ber, 1886, 19, 979, 1541) condensed benzanilide imidochloride with ethyl sodiomalonate in ether and obtained ethyl mono- and di-(phenyl imino benzyl) malonate, the former of which underwent ring closure on heating to give ethyl 4-hydroxy 2-phenyl quinoline-3-carboxylate, which in turn was hydrolysed to 4-hydroxy 2-phenyl quinoline-3-carboxylic acid (Seka and Fuchs, Monatsch, 1931, 57, 52).

\[
\begin{align*}
\text{Cl} & \quad \text{COOC}_2\text{H}_5 \\
\text{CH}_3 & \quad \text{CH} = \text{COOC}_2\text{H}_5 \\
\text{N} & \quad \overset{\text{Na}}{\text{CH} = \text{COOC}_2\text{H}_5} \\
\end{align*}
\]

(VIII)

\[
\begin{align*}
\text{OH} & \quad \text{C-cooc}_2\text{H}_5 \\
\text{N} & \quad \overset{\text{C-cooc}_2\text{H}_5}{\text{C-cooc}_2\text{H}_5} \\
\end{align*}
\]

(IX)

\[
\begin{align*}
\text{OH} & \quad \text{C-cooh} \\
\text{N} & \quad \overset{\text{C-cooh}}{\text{C-cooh}} \\
\end{align*}
\]

(X)
A substantial improvement in this method was made by using toluene as a solvent and employing ethyl malonate (1 mole) together with its sodio-derivative (1 mole), with the result that the formation of the di-condensation product was minimised (Shah and Heeramaneck, J.Chem.Soc., 1936, 428). Crystalline mono-condensation products were thus obtained from various anilide imidochlorides and cyclised to the corresponding 4-hydroxy quinoline derivatives in yields varying from 30-40%. It has also been reported that the condensation and the cyclisation were little influenced by the presence of substituents. The synthesis has been carried out with aniline, o-m-p-toluidines, and o-m-p-chloroanilines. In the case of both m-toluidine and m-chloroaniline, mixtures of isomeric 5- and 7-substituted esters were obtained. In the case of m-toluidine, isolation of the two isomeric esters has been effected by fractional crystallisation from ethyl acetate. In the case of m-chloroaniline, only one isomer could be isolated. In either case, however, the positions (5 or 7) of the substituents (methyl
or chloro) have not been ascertained.

Elderfield et al (loc.cit.) have thus obtained 4-hydroxy 2-phenyl 7-chloro, 4-hydroxy 2-phenyl 7-methoxy and 4-hydroxy 2-phenyl 6-methoxy quinolines by decarboxylation of the corresponding 3-carboxylic acids and have converted them into the corresponding 4-chloro 2-phenyl quinolines (Elderfield and Maggiolo, J.Am.Chem. Soc., 1949, 71, 1806).

The imidochloride method has also been extended (Shah and Desai, J.Indian Chem.Soc., 1949, 26, 121) for the preparation of 4-hydroxy 2-phenyl 3-acetyl quinolines from various anilide imidochlorides and ethyl sodioacetoacetate.

Niementowski (Ber, 1894, 27, 1394) discovered that when anthranilic acid and acetophenone were heated to 120-30°C for three days, 4-hydroxy 2-phenyl quinoline was obtained in poor yields.

A very useful modification of the above method was suggested by Fuso and Burness (J.Am.Chem.Soc., 1946, 68, 1270) who discovered that when ethyl anthranilate
is heated in phenyl ether with slightly more than equimolar amount of diethyl acetal of acetophenone, 4-hydroxy 2-phenyl quinoline (XI) is obtained in an 84% yield.

\[
\begin{align*}
\text{Formation of the anil (XIII) by the elimination of ethanol appears to be the first step in the reaction. It seems probable too that the acetal, under the}
\end{align*}
\]
influence of heat loses a molecule of ethanol to yield 
α-ethoxy styrene (XII) and that this compound rather 
than the acetal combines with the amino ester to give 
the anil. This mechanism is further substantiated by the 
fact that the yield of 4-hydroxy 2-(p-chlorophenyl) 
quinoxline obtained from ethyl anthranilate and α-ethoxy 
styrene compared favourably with that obtained from the 
ketal. The final step in the synthesis, the ring closure 
to (XI), appears to be a condensation of the Claisen 
type via (XIV).

When anthranilic acid was substituted for its 
ester, the yield of (XI) was only 50 %, probably because 
of decarboxylation of anthranilic acid at high tempera­
ture required for ring closure. However, there seems to 
be no generalisation governing the use of the ester in 
preference to the acid, since with diethyl acetal of 
propiophenone, the higher yield of 4-hydroxy 2-phenyl 
3-acetyl quinoline was obtained from anthranilic acid 
rather than its ester. This method is very useful for 
the unequivocal synthesis of 5- and 7-substituted 2-
aryl 4-hydroxy quinolines. This was demonstrated by the preparation of 4-hydroxy 2-phenyl 7-chloro quinoline from 4-chloro anthranilic acid.

Shah, Thakor and Kulkarni (loc.cit.) have explored the Conrad-Limpach synthesis with ethyl benzoyl-acetoacetate-anile and have obtained 4-hydroxy 2-phenyl 3-acetyl and 4-hydroxy 2-methyl 3-benzoyl quinolines.

\[
\text{C}_6\text{H}_5\text{COCH} - \text{COO}_2\text{H}_5 \\
\text{COCH}_3
\]

\[
\begin{array}{c}
\text{NH}_2 \\
\text{C}_{\text{H}_2}\text{COOH}_5 \\
\text{C-\text{COCH}_3} \\
\text{C-\text{CH}_5} \\
\text{NH} \\
\text{H} \\
\text{C-COO}_2\text{H}_5 \\
\text{C-COCH}_3 \\
\text{C-\text{CH}_5} \\
\text{NH} \\
\text{H} \\
\text{C-COO}_2\text{H}_5 \\
\text{C-COCH}_3 \\
\end{array}
\]
The synthesis has been carried out using aniline, o-toluidine, p-toluidine and 2-naphthylamine.

From ethyl formylacetate, 4-hydroxy quinolines carrying no substituent in 2-position have been prepared in 40-50 % yield (Price, Leonard and Reitsma, loc. cit.). With m-chloroaniline, 7-chloro 4-hydroxy quinoline and 5-chloro 4-hydroxy quinoline were obtained in a ratio 4:1.

The key to successful ring closures of the anilines of the type (XIX) is found in high dilution (30:1) in the inert solvent in which cyclisation is carried
out. Otherwise, formation of diaryl ureas according to \((\text{XXII}) - (\text{XXIII})\) is found to be the predominating reaction (Jadhav, J. Indian Chem. Soc., 1931, 8, 681).

\[
\begin{align*}
&\begin{array}{c}
\text{COOC}_2\text{H}_5 \\
\text{CH} \\
\text{CH} \\
\text{NH}
\end{array} \\
+ \\
&\begin{array}{c}
\text{NH}_2
\end{array}
\end{align*}
\]

\((\text{XXII})\)

\[
\begin{align*}
&\begin{array}{c}
\text{NH} \\
\text{CH}_3\text{CO}\text{NH}
\end{array} \\
+ \\
&\begin{array}{c}
\text{CH}_3\text{CHO}
\end{array}
\end{align*}
\]

\((\text{XXIII})\)

This point was apparently overlooked by Reissert (Ber, 1887, 20, 3105; Ber, 1888, 21, 1362; Hurst and Thrope, J. Chem. Soc., 1935, 934), since the properties of the substance reported by him as 4-hydroxy quinoline agree with those of diphenyl urea.

When other \(\beta\)-formyl esters are employed, the products obtained are 3-substituted 4-hydroxy quinolines (Wieliczenus, Ann. 1917, 413, 206, 248). Elderfield and Wright (loc. cit.) employed ethyl \(\alpha,\alpha\)-formyl phenylacetate
and prepared 3-phenyl 4-chloro and 3-phenyl 4:7 dichloro quinolines with a view to test the antimalarial activity of the 4-amino quinoline derivatives obtained therefrom. Price, Leonard and Herbrandson (loc.cit.) prepared 4-hydroxy 7-chloro 3-cyano quinoline from ethyl ethoxy-methylene cyanoacetate and m-chloroaniline. A direct synthesis of the above compound has also been achieved from ethyl orthoformate, cyanacetic ester and m-chloroaniline (Synder and Jones, J. Am. Chem. Soc., 1946, 68, 1253).

When cyanacetic ester was replaced by acetoacetic ester, the product obtained was 3-acetyl 7-chloro 4-hydroxy quinoline (Elderfield, Heterocyclic compounds, Vol IV).

Employing ethyl ethoxalylacetate as the β-keto ester in the conrad-Limpach synthesis, Surrey and Hammer (loc.cit.) prepared 4-hydroxy 2-carboethoxy quinolines using m-chloroaniline, m-bromoaniline, m-iodoaniline and p-anisidine. 4-hydroxy quinolines have been obtained by hydrolysis of the esters followed by decarboxylation of the 2-carboxylic acids (Mueller and Hamilton, J. Am. Chem. Soc., 1943, 65, 1017).
An almost similar type of work was done by Steck, Hallock and Holland (loc.cit.) and Hauser et al (loc.cit.) using ethyl ethoxalylpropionate. They prepared a number of 4-hydroxy 3-methyl quinolines via the ester and the acid. The oxaloacetic ester synthesis is general in application and the yields obtained in general are high, but the cyclisation and the decarboxylation...
steps require conditions which are subject to variation depending upon the substituents present in the carbocyclic ring (Riegel et al., loc.cit.). In most of the cases, the decarboxylation of the acid is a simple operation which consists in heating the acid at 250-70°C in medicinal oil. But when negative groups such as nitro are present, the decarboxylation requires special conditions and is best effected in poorer yields by heating the silver salt of the acid (Baker et al., J. Am. Chem. Soc., 1946, 68, 1267).

When m-substituted anilines are employed, the oxaloacetic ester synthesis gives a mixture of 5- and 7-substituted quinolines. With m-chloroaniline, a mixture of 4-hydroxy 5- and 7-chloro 2-carboxylic esters is obtained. Lisk and Stacy (J. Am. Chem. Soc., 1946, 68, 2686) in an attempt to investigate conditions under which the formation of 5-isomer would be precluded, revealed that with the help of a melting point diagram that when limited amounts of diluent were employed, virtually all 5-isomer was obtained. With large amounts
of the diluent (30:1), about 40% of the 5-isomer resulted. It has also been reported that with m-iodoaniline, it is the 7-isomer which predominates. Obviously, steric effects are at work and have an influence on the proportion of the 5- and 7-isomers.

The most general method thus far developed for the synthesis of 4-hydroxy quinolines is the ethoxymethylene malonic ester synthesis. Ring closure of the anilino methylenemalonic ester was first employed by Gould and Jacobs (loc.cit.) to prepare 4-hydroxy quinoline 3-carboxylic acid.

\[
\text{(XXVIII)} \quad + \quad \text{C}_2\text{H}_5\text{OCH} = \text{C} (\text{COOC}_2\text{H}_5)_2 \quad \rightarrow \quad \text{(XXIX)}
\]
The reaction has been developed by Price and Roberts (loc.cit.). The volume of the solvent required for cyclisation of the various acrylates varied considerably. The m-chloroanilino compound could be cyclised in good yield by heating without any solvent, but 3-pyridylamino acrylates and others required dilution up to 40 volumes of 'Dowtherm'. The decarboxylation step is, in general, simple and nearly quantitative with most quinolines, although when nitro groups are present, special conditions are required for decarboxylation, to effect which silver salts of the acids have been employed (Baker et al, loc.cit.).

The m-chloroanilino acrylate has also been cyclised by various other workers (Breslow et al, loc.}
Synder et al (loc. cit.) prepared 4-hydroxy quinolines from m-fluoro and m-trifluoromethyl amines. The synthesis has also been carried out using anilines with substituents such as bromo and iodo (Conroy, Mosher and Whitmore, J. Am. Chem. Soc., 1949, 71, 3236), methoxy and phenoxy (Breslow et al, loc. cit.; Synder et al, loc. cit.; Lauer et al, loc. cit.; Ramsey and Cretcher, J. Am. Chem. Soc., 1947, 69, 1660), sulphide and disulphide (Price, Leonard and Stacy, J. Am. Chem. Soc., 1947, 69, 855), benzyl mercapto, amino and acetyl (Price and Roberts, J. Am. Chem. Soc., 1946, 68, 1255) and nitro (Gouley, Moersch and Mosher, loc. cit.; Price et al, loc. cit.). Price et al (loc. cit.) also prepared 4-hydroxy 7-cyano and 4-hydroxy 5-cyano quinolines by reduction of the corresponding quinolines obtained from m-nitramine and ethoxymethylenemalonic ester and converting the resulting amino quinolines into cyanoquinolines by Sandmeyer's reaction. In view of the difficulty of purification of the cyanoquinolines, these were directly
converted into the corresponding 4-chloro 7-cyano and 4-chloro 5-cyanoquinolines.

In contrast to the oxaloacetic ester method, this cyclisation proceeds to a remarkable degree in one direction (Price and Roberts, loc.cit.). In the early work involving the cyclisation of ethyl-α-carboethoxy-β-(m-substituted anilino) acrylates, there was no indication of the presence of isomers, when, however, the syntheses were carried out on a laboratory scale. Only one isomer was isolated from a Price-Robert's synthesis with m-nitraniline, m-chloroaniline, m-trifluoromethyl aniline, 3-chloro 5-methoxy aniline and 3-chloro 4-methoxy aniline. After the discovery that the cyclisation of ethyl-α-carboethoxy-β-(m-fluoroanilino) acrylate yielded a mixture of isomers (Synder et al, loc.cit.), it was found in large scale operations (Price et al, loc.cit.) that about 15% of the 5-isomer was formed even with m-chloroaniline. The factors governing the formation of the 5- and 7-isomers, however, have not been clearly understood, since m-cyanoaniline gave
Apparently exclusively the 5-isomer (Price et al, loc. cit.).

A variation of the above synthesis consists in using ethoxy methylenecyanoacetic ester for ethoxymethylenemalononic ester. Price, Leonard and Herbrandson (loc. cit.) obtained 7-chloro 3-cyano 4-hydroxy quinoline.

The cyclisation is sluggish and requires heating for a prolonged period and the yields in general are lower.

Synder and Jones (loc. cit.) prepared the same compound by cyclisation of the intermediate ethyl-β-(m-chloroanilino)-α-cyanoacetate obtained directly from ethyl orthoformate, cyanoacetic ester and m-chloroaniline. The synthesis was also extended to p-anisidine and m-trifluoromethyl aniline.

\[
\text{Cl} \quad \text{NH}_2
\]

\[
+ (C_2H_5O)_3CH + CH_2COOC_2H_5 \quad \rightarrow \quad (R = \text{CN, } C_6H_5, \text{CH}_3\text{CO, COOC}_2\text{H}_5)
\]

\[
\text{Cl} \quad \text{CH}
\]

\[
(\text{XXXII})
\]
A similar direct synthesis of ethyl-α-acetyl-β-(m-chloroanilino) acrylate from m-chloroaniline, ethyl orthoformate and acetoacetic ester was achieved. The latter has been cyclised to give 7-chloro 3-acetyl 4-hydroxy quinoline. The reaction with malonic ester also occurred but the product was not the expected di-carboxylic ester, but rather the corresponding mono-m-chloroanilide.

4-hydroxy 3-acetyl quinolines have been similarly obtained (Baker et al., loc.cit.), using ethoxymethyleneacetoacetic ester.

Price (J. Am. Chem. Soc., 1951, 73, 3577) prepared

(A) methyl-β-(m-chloroanilino) acrylate (XXXIII) from m-chloroaniline hydrochloride and methyl β-β-dimethoxy propionate, but attempts to cyclise it gave sym-bis-m-chlorophenyl urea.
(B) However, methyl β-(m-chloroanilino) acrylate prepared from m-chloroaniline and methyl propiolate could be cyclised to the expected 4-hydroxy 7-chloro quinoline (XXXIV). (A) is the cis-isomer in which the phenyl and the carbomethoxy groups are on the same side. (B) is the trans-isomer. They are the syn- and anti-forms of the anil.

Thiepape (Ber, 1922, 55, 127) has reported similar failure of the products of the condensation of formylacetone and acetoneoxallic ester with representative aromatic amines e.g. (XXXV) and (XXXVI) to undergo ring closure to quinolines.
This failure to undergo ring closure is attributed to the possible existence of (XXXV) and (XXXVI) almost exclusively in the trans-form. In support of such an interpretation, Thielpape obtained quantitative ring closure of the corresponding N-methyl compound (XXXVII) to (XXXVIII).

The resistance to ring closure seems strange since, in general, no difficulty is encountered in the cyclisation of very similar aniles to quinolines.

Finally, it is also possible to obtain 2,3-

Certain of these substances possess interest because of their high order of activity against avian malaria. Their value against human malaria is questionable.
Phenanthrolines;

Kermack and Weatherhead (J. Chem. Soc., 1940, 1164) have synthesised a number of p-phenanthroline derivatives carrying a basic group in 4-position. 6-amino quinoline (XXXIX, $R_1=R_2=H$) and 4-hydroxy 2-methyl 6-amino quinoline (XXXIX, $R_1=\text{CH}_3$, $R_2=\text{OH}$) were converted by Skraup reaction into 5:6:3':2'-pyrido quinoline (XL, $R_1=R_2=\text{H}$) and 4-hydroxy 2-methyl - 5:6:3':2'-pyrido quinoline (XL, $R_1=\text{CH}_3$, $R_2=\text{OH}$) respectively.

The angular structure was given to (XL) in accordance with the views of Skraup and Vortmann (Monatsch, 1883, 4, 571).
5-amino 4-hydroxy 2-methyl quinoline was similarly converted by Skraup reaction into 4-hydroxy 2-methyl 5:6:2':3'-pyridoquinoline (XLI) (Kermack and Webster, J. Chem. Soc., 1942, 213). The isomeric 4-hydroxy 2-methyl 7:8:2':3'-pyrido quinoline (XLII) was obtained by Hazlewood, Hughes and Lions (J. Proc. Roy. Soc. N.S. Wales, 1937-38, 71, 472) from 5-amino quinoline and ethyl acetoacetate.
Kermack and Halcrow (J. Chem. Soc., 1946, 155) subjected o-phenylenediamine to Skraup reaction and obtained o-phenanthroline (XLIII).

Later, Kermack and Douglas (J. Chem. Soc., 1949, 1017) condensed 6-amino quinoline with ethoxy methylene-malonic ester to give ethyl-β-(6′-quinolyl amino)-α-carbo-
ethoxy acrylate (XLIV) which when cyclised in medicinal oil afforded 4-hydroxy 3-carboethoxy p-phenanthroline (XLV) which could be converted into 4-chloro 3-carboethoxy p-phenanthroline.

![Diagram](image)

(XLIV)  
(XLV)

The possibility that the cyclised product might be the isomeric linear diazaanthracene derivative (XLVI) and not the angular p-phenanthroline was excluded by the fact that when the ester was hydrolysed to the acid and the latter decarboxylated, the product was 4-hydroxy p-phenanthroline already prepared by a different route (Kermack and Weatherhead, loc.cit.) and converted into p-phenanthroline.
4-hydroxy 9-chloro 3-carboethoxy p-phenanthroline was similarly obtained from 8-chloro 6-amino quinoline and ethoxymethylene malonic ester.

They also condensed p-phenylenediamine with ethoxymethylene malonic ester and obtained the intermediate \( NN' -\text{bis-}(2:2\text{-dicarboethoxy vinyl}) - p\)-phenylenediamine (XLVII) which could be cyclised only in diphenyl ether to give 4:5 dihydroxy 3:6 dicarboethoxy p-phenanthroline (XLVIII).
The latter has been converted through hydrolysis, decarboxylation and treatment with phosphorous oxychloride into 4,5 dichloro p-phenanthroline.

Kermack and Tebrich have also prepared 4-hydroxy m-phenanthroline by subjecting 8-amino 4-hydroxy quinoline to Skraup reaction (J. Chem. Soc., 1945, 375).

With m-phenylenediamine and two moles of ethyl acetoacetate, Backeberg (loc. cit.) obtained ethyl-m-phenylene-bis-p- amino crotonate (XLIX). Ethyl-p-phenylene-bis-p-amino crotonate (L) has been similarly obtained from p-phenylenediamine and two moles of ethyl acetoacetate (Backeberg, loc. cit.). Till now, no reference is available in the literature as regards the cyclisation of (XLIX) and (L).
(XLIX)  

(L)
4-hydroxy 2-methyl quinolines have been synthesised by cyclising ethyl-β-arylamino crotonates in medicinal oil at 250-90°C or in boiling diphenyl ether.

The thesis entitled "Reactions of aromatic amines with acetyl urethane and ethyl acetoacetate in presence of different condensing agents" - presented to the University of Bombay for which the degree of M.Sc. was awarded to the candidate - comprised of

(i) the condensation of ethyl acetoacetate with arylamines by the general method of Coffey, Thomson and Wilson (loc.cit.) to yield the intermediate ethyl-β-arylamino crotonates and

(ii) cyclisation of these crotonates to 4-hydroxy 2-methyl quinolines using acetic anhydride and sulphuric acid as cyclising agents.

The cyclisation was effected by dissolving the crotonate in acetic anhydride and adding sulphuric acid to it.

With ethyl-β-(m-toluidino) and (m-chloro-
anilino) crotonates, the thermal method has been reported to give a mixture of 5- and 7-substituted 4-hydroxy 2-methyl quinolines (Spivey and Curd, loc.cit.). Ethyl-\(\beta\)-(m-acetamido anilino) crotonate, however, is reported to give only the 5-isomer (Kermack and Webster, loc.cit.). Spivey and Curd (loc.cit.) could separate both the isomers as oxalates in case of ethyl-\(\beta\)-(m-toluidino) crotonate and only the 7-isomer in case of ethyl-\(\beta\)-(m-chloroanilino) crotonate.

Using acetic anhydride and sulphuric acid, ethyl \(\beta\)-(m-toluidino) and (m-chloroanilino) crotonates give only the 5-isomer (Bangdiwala and Desai, Curr. Sci., 1952, 21, 256). The synthesis was carried out with aniline, o-m-p-toluidines, m-p-chloroanilines, o-p-anisidines, p-phenetidine, 1:3:4 and 1:4:5 xyldines and 1-naphthylamine. (Bangdiwala and Desai, Synthesis of 4-hydroxy quinolines using acetic anhydride and sulphuric acid, Part I, J. Indian Chem. Soc., 1953, 30, ).

The yields of the 4-hydroxy quinolines varied from
38 % in the case of 1-naphthylamine to 73 % in the case
of m-toluidine. Out of the 4-hydroxy 2-methyl quinolines
prepared, 4-hydroxy 2,5,8 trimethyl quinoline is new.
Lockhart and Turner ( J.Chem.Soc., 1937, 420 ) prepared
4-hydroxy 2-methyl 6-ethoxy quinoline but the melting
point and the yield were not mentioned. 4-hydroxy 2-
methyl 5-chloro quinoline also was isolated for the
first time.

Oxalates and the 4-chloro derivatives of some
of these were also prepared.

Over and above this, acetyl urethane was con-
densed with aniline in presence of anhydrous zinc chlo-
ride and mercuric chloride at 100 °C giving the anil-
zinc chloride and anil-mercuric chloride complexes
analogous to those obtained with ethyl acetoacetate

By reaction of acetyl urethane with aromatic
amines in presence of anhydrous zinc chloride at 150 °C,
sym-bis-phenyl-substituted ureas were obtained from
aniline, o-m-p-toluidines, o-p-anisidines and o-p-phenetidines, out of which those from o-p-anisidines and o-p-phenetidines do not seem to have been prepared.

Using phosphorous trichloride in toluene, acetyl urethane and aniline gave a mixture of acetyl phenyl urea and sym-bis-phenyl urea.

Sym-bis-phenyl-substituted ureas could also be obtained in 91% yield by heating acetyl phenyl-substituted ureas with 40% sulphuric acid.

Concentrated sulphuric acid, however, gave phenyl urea.
The Present Investigation:

The Object:

The marked antimalarial activity of a number of quinoline derivatives having an alkylamino side-chain attached in 4-position has led to an investigation of new procedures for the preparation of 4-hydroxy quinolines which may be readily converted to the desired drugs.

It has been observed that quinine suffers attack in vitro in the presence of liver slices to yield the 2-hydroxy derivative (Mead and Koepfli, J. Biol. Chem. 1944, 154, 104). Therefore it was expected that if this position is blocked in other active groups of antimalarials, enhanced activity might result. A number of investigators have employed various 4-hydroxy quinoline derivatives in the synthesis of antimalarials, 4,7 dichloro and 6-methoxy 4-chloro 2-phenyl quinolines to-gether with such others find important use in the synthesis of several types of dialkylaminoalkylamino quinolines - used as antimalarials (Drake et al, J.Am.Chem.Soc.,
1943, 66, 1208). 4-hydroxy 2-phenyl quinolines required for this purpose have been obtained by a number of methods (Fuson and Burness, loc.cit.; Elderfield et al., loc.cit.), the earlier ones, however, suffering from limitations. Application of the familiar Conrad-Limpach synthesis with its modifications has not been found satisfactory, starting with ethyl benzoylacacetate. The yields reported by Elderfield et al (loc.cit.) for 4:7 dichloro and 6-methoxy 4-chloro 2-phenyl quinolines were 3-5% and 6-8% respectively.

The present work was undertaken to obtain these intermediates in good yields from ethyl benzoylacacetate and other β-keto esters, by cyclisation of the intermediate ethyl-β-phenyl-β-arylamino and ethyl-α-substituted-β-phenyl-β-arylamino acrylates, using acetic anhydride and sulphuric acid as cyclising agents (Bangdiwala and Desai, Curr. Sci. 1952, 21, 348). The use of acetic anhydride and sulphuric acid as cyclising agents has already met with success in the synthesis of
several 4-hydroxy 2-methyl quinolines from ethyl-β-aryl-amino crotonates (Bangdiwala and Desai, loc. cit.). With this method, ethyl-β-(m-substituted anilino) crotonates give only the 5-substituted 4-hydroxy 2-methyl quinolines.

The object of the present work was also to see whether the acrylates obtained from m-substituted anilines and other β-keto esters upon cyclisation using the present method give only one isomer or a mixture of isomers and in the latter case, the object was to separate the isomers if possible.

The synthesis has been explored with the following eight β-keto esters.

1. Ethyl benzoylacetate, \( \text{C}_6\text{H}_5\text{COCH}_2\text{COOC}_2\text{H}_5 \)

2. Ethyl benzoylethacetoacetate, \( \text{C}_6\text{H}_5\text{COCH} \cdot \text{COOC}_2\text{H}_5 \)

3. Ethyl benzoylmalonate, \( \text{C}_6\text{H}_5\text{CO.CH.}(\text{COOC}_2\text{H}_5)_2 \)

4. Ethyl benzoyleyanoacetate, \( \text{C}_6\text{H}_5\text{CO.CH.COOC}_2\text{H}_5 \)

5. Ethyl diacetoacetate, \( \text{CH}_3\text{CO.CH.COOC}_2\text{H}_5 \)
6. Ethyl dibenzoylacetate, \( \text{C}_6\text{H}_5\text{CO} \cdot \text{CH} \cdot \text{COOC}_2\text{H}_5 \)

7. Acetyl malonic ester, \( \text{CH}_3\text{CO} \cdot \text{CH} \cdot (\text{COOC}_2\text{H}_5)_2 \)

8. Ethyl acetoacetate, \( \text{CH}_3\text{CO} \cdot \text{CH}_2\cdot \text{COOC}_2\text{H}_5 \)

Out of these, condensations with ethyl benzoyl malonate, ethyl benzoylcyanoacetate, ethyl diacetoacetate and ethyl dibenzoylacetate have not been investigated so far.

**Preparation of acrylates:**

**General Method:**

The acrylates were in general all prepared by the general method of Coffey, Thomson and Wilson (loc. cit.), using a drop of concentrated sulphuric acid as catalyst. Equimolecular amounts of the \( \beta \)-keto ester and the proper amine were mixed and a drop of concentrated hydrochloric acid added. The mixture was kept in a vacuum desiccator for three days. In the case of ethyl benzoylacetooacetate - anilis, the reactants were heated on a water-bath for one hour and the mixture kept in cold for two days. \( \beta \)-aminoacetanilide and \( \alpha \)-aminoaceta-
nilide were condensed with ethyl acetoacetate by boiling in methanol for a period of five to six hours.

Except in the cases of acetyl malonic and benzoyl malonic esters, the condensation to the intermediate acrylate went smoothly and apparently in only one sense with all the amines used. With acetyl malonic ester, the acrylates were found to be formed in poor yields on account of competing side reactions, chiefly the formation of acetonilide and its derivatives, which proceeded to the extent of about 40%. The percentage of the formation of acetonilide and its derivatives is high compared to that reported by Gould and Jacobs (loc. cit.) (about 30%), perhaps due to the local high room temperature at which the condensations were carried out. (about 30-40°C).

With benzoyl malonic ester, the competing side reactions, chiefly the formation of benzanilide and its derivatives, were found to predominate largely, giving still poorer yields of the acrylates - about 30-40%.
The acrylates were in most cases liquids. The solid acrylates were purified by crystallisation from suitable solvents. In those cases where the acrylates were liquids, purification was effected by dissolving them in ether, and washing the ethereal solution with 0.5 N hydrochloric acid, then with water and finally drying with anhydrous magnesium sulphate and removing the ether. The purification step is absolutely essential and important in so far as the yield and the purity of the final cyclised product is concerned, for should the acrylate be not purified previously thoroughly, the yield of the final cyclised product, it is found, is considerably reduced and the purity suffers a great deal. The structures of the acrylates have been written from their conversion into 4-hydroxy quinolines which have been identified.

The following acrylates were thus prepared:
1. From ethyl benzylacetate:

(i) Ethyl-\(\beta\)-phenyl-\(\beta\)-anilino acrylate

(\(\text{LI}, R_1 = R_2 = R_3 = R_4 = H\))

(ii) Ethyl-\(\beta\)-phenyl-\(\beta\)-(o-toluidino) acrylate

(\(\text{LI}, R_1 = R_2 = R_3 = H; R_4 = CH_3\))

(iii) Ethyl-\(\beta\)-phenyl-\(\beta\)-(m-toluidino) acrylate

(\(\text{LI}, R_1 = R_2 = R_4 = H; R_3 = CH_3\))

(iv) Ethyl-\(\beta\)-phenyl-\(\beta\)-(p-toluidino) acrylate

(\(\text{LI}, R_1 = R_3 = R_4 = H; R_2 = CH_3\))

(v) Ethyl-\(\beta\)-phenyl-\(\beta\)-(m-chloroanilino) acrylate

(\(\text{LI}, R_1 = R_2 = R_4 = H; R_3 = Cl\))

(vi) Ethyl-\(\beta\)-phenyl-\(\beta\)-(p-chloroanilino) acrylate

(\(\text{LI}, R_1 = R_3 = R_4 = H; R_2 = Cl\))
(vii) Ethyl-\(\beta\)-phenyl-\(\beta\)-(o-anisidino) acrylate

\[
\text{Ll, } R_1 = R_2 = R_3 = H \land R_4 = \text{OCH}_3
\]

(viii) Ethyl-\(\beta\)-phenyl-\(\beta\)-(p-anisidino) acrylate

\[
\text{Ll, } R_1 = R_3 = R_4 = H \land R_2 = \text{OCH}_3
\]

(ix) Ethyl-\(\beta\)-phenyl-\(\beta\)-(p-phenetidino) acrylate

\[
\text{Ll, } R_1 = R_3 = R_4 = H \land R_2 = \text{OC}_2\text{H}_5
\]

(x) Ethyl-\(\beta\)-phenyl-\(\beta\)-(1:3:4 xylidino) acrylate

\[
\text{Ll, } R_1 = R_3 = H \land R_2 = R_4 = \text{CH}_3
\]

(xi) Ethyl-\(\beta\)-phenyl-\(\beta\)-(1:4:5 xylidino) acrylate

\[
\text{Ll, } R_2 = R_3 = H \land R_1 = R_4 = \text{CH}_3
\]

(xii) Ethyl-\(\beta\)-phenyl-\(\beta\)-(2-naphthylamino) acrylate

(LII)
Table I gives a comparative idea of the yields of the different acrylates mentioned above.

<table>
<thead>
<tr>
<th>Acrylate</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(i)</td>
<td>52.7</td>
</tr>
<tr>
<td>(ii)</td>
<td>42.6</td>
</tr>
<tr>
<td>(iii)</td>
<td>53.3</td>
</tr>
<tr>
<td>(iv)</td>
<td>49.7</td>
</tr>
<tr>
<td>(v)</td>
<td>54.0</td>
</tr>
<tr>
<td>(vi)</td>
<td>52.8</td>
</tr>
<tr>
<td>(vii)</td>
<td>46.5</td>
</tr>
<tr>
<td>(viii)</td>
<td>47.3</td>
</tr>
<tr>
<td>(ix)</td>
<td>57.1</td>
</tr>
<tr>
<td>(x)</td>
<td>54.4</td>
</tr>
<tr>
<td>(xi)</td>
<td>54.0</td>
</tr>
<tr>
<td>(xii)</td>
<td>40.5</td>
</tr>
</tbody>
</table>

The acrylates (iii), (iv), (vi), (vii), (ix), (x), (xi) and (xii) are new in view of the fact that their corresponding 4-hydroxy quinolines are new.
4-hydroxy 2-phenyl quinolines from ethyl benzoylaceta-
tate and m-chloroaniline and p-anisidine have been
prepared (Elderfield et al., loc.cit.). But their
 corresponding acrylates (v) and (viii) were not isola-
ted.

2. **From Ethyl benzoylacetoacetate**

![Chemical structures](LIII) (LIV)

(i) Ethyl-α-benzoyl-β-anilino crotonate

(LIII, \( R_1 = R_2 = R_3 = H \))

(ii) Ethyl-α-benzoyl-β-(o-toluidino) crotonate

(LIII, \( R_1 = R_2 = H; R_3 = CH_3 \))

(iii) Ethyl-α-acetyl-β-phenyl-β-(p-toluidine) acrylate

(LIV, \( R_1 = CH_3; R_2 = R_3 = H \))

(iv) Ethyl-α-benzoyl-β-(m-toluidino) crotonate

(LIII, \( R_1 = R_3 = H; R_2 = CH_3 \))
Ethyl-\(\alpha\)-acetyl-\(\beta\)-phenyl-\(\beta\)-(m-toluidino) acrylate

\((\text{LIV}, R_1 = R_3 = H; R_2 = \text{CH}_3)\)

(vi) Ethyl-\(\alpha\)-acetyl-\(\beta\)-phenyl-\(\beta\)-(m-chloroanilino) acrylate

\((\text{LIV}, R_1 = R_3 = H; R_2 = \text{Cl})\)

Table II gives a comparative idea of the yields of the different acrylates mentioned above.

<table>
<thead>
<tr>
<th>Acrylate or Crotonate</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(i)</td>
<td>58.9</td>
</tr>
<tr>
<td>(ii)</td>
<td>49.5</td>
</tr>
<tr>
<td>(iii)</td>
<td>55.7</td>
</tr>
<tr>
<td>(iv)</td>
<td>49.6</td>
</tr>
<tr>
<td>(v)</td>
<td>49.0</td>
</tr>
</tbody>
</table>

The m-toluidino acrylate (iv) could not be identified as the corresponding 4-hydroxy quinoline could not be identified.
5. From Ethyl benzoylmalonate:

(i) Ethyl-\(\alpha\)-carboethoxy-\(\beta\)-phenyl-\(\beta\)-anilino acrylate

\[(LV, R_1 = R_2 = H)\]

(ii) Ethyl-\(\alpha\)-carboethoxy-\(\beta\)-phenyl-\(\beta\)-(o-toluidino) acrylate

\[(LV, R_1 = H; R_2 = CH_3)\]

(iii) Ethyl-\(\alpha\)-carboethoxy-\(\beta\)-phenyl-\(\beta\)-(p-toluidino) acrylate

\[(LV, R_1 = CH_3; R_2 = H)\]

(iv) Ethyl-\(\alpha\)-carboethoxy-\(\beta\)-phenyl-\(\beta\)-(p-chloroanilino) acrylate

\[(LV, R_1 = Cl; R_2 = H)\]

All the four acrylates are known, but they have been prepared from the corresponding anilide imidochlorides and ethyl sodiomalonate (Shah and Heeramaneck, loc.
cit. ). They are crystalline solids of definite melting points.

Table III gives their melting points and a comparative idea of the yields of the acrylates obtained from ethyl benzoylmalonate and the imidochloride method.

Table III

<table>
<thead>
<tr>
<th>Acrylate</th>
<th>M.P.</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>From ethyl benzoyl</td>
</tr>
<tr>
<td></td>
<td></td>
<td>malonate</td>
</tr>
<tr>
<td>(i)</td>
<td>74-75 °</td>
<td>38.0</td>
</tr>
<tr>
<td>(ii)</td>
<td>95-96 °</td>
<td>31.0</td>
</tr>
<tr>
<td>(iii)</td>
<td>62-63 °</td>
<td>28.2</td>
</tr>
<tr>
<td>(iv)</td>
<td>74-75 °</td>
<td>33.0</td>
</tr>
</tbody>
</table>

4. *From ethyl benzoylvanacetae:*
(i) Ethyl-α-cyano-β-phenyl-β-anilino acrylate

\[ \text{LVI, } R_1 = R_2 = R_3 = H \]

(ii) Ethyl-α-cyano-β-phenyl-β-(o-toluidino) acrylate

\[ \text{LVI, } R_1 = R_2 = H; R_3 = CH_3 \]

(iii) Ethyl-α-cyano-β-phenyl-β-(p-toluidino) acrylate

\[ \text{LVI, } R_1 = CH_3; R_2 = R_3 = H \]

(iv) Ethyl-α-cyano-β-phenyl-β-(m-chloroanilino) acrylate

\[ \text{LVI, } R_1 = \text{CH}_3; R_2 = R_3 = \text{Cl} \]

All the four acrylates are new.

Table IV gives a comparative idea of the yields of the acrylates mentioned above.

**Table IV**

<table>
<thead>
<tr>
<th>Acrylate</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(i)</td>
<td>50.0</td>
</tr>
<tr>
<td>(ii)</td>
<td>49.0</td>
</tr>
<tr>
<td>(iii)</td>
<td>48.0</td>
</tr>
<tr>
<td>(iv)</td>
<td>36.7</td>
</tr>
</tbody>
</table>
5. From Ethyl diacetoneacetate:

Ethyl-α-acetyl-β-anilino crotonate (LVII) is new and was obtained in a 55% yield.

6. From Ethyl dibenzoylacetate:

Ethyl-α-benzoyl-β-phenyl-β-anilino acrylate (LVIII) is new and was obtained in a 56.7% yield.

7. From Acetyl Malonic Ester:

(LIX)
(i) Ethyl-α-carboethoxy-β-anilino crotonate

(\text{LIX}, \text{R}_1 = \text{R}_2 = \text{H})

(ii) Ethyl-α-carboethoxy-β-(m-toluidino) crotonate

(\text{LIX}, \text{R}_1 = \text{H}; \text{R}_2 = \text{CH}_3)

(iii) Ethyl-α-carboethoxy-β-(p-toluidino) crotonate

(\text{LIX}, \text{R}_1 = \text{CH}_3; \text{R}_2 = \text{H})

(iv) Ethyl-α-carboethoxy-β-(m-chloroanilino) crotonate

(\text{LIX}, \text{R}_1 = \text{H}; \text{R}_2 = \text{Cl})

The crotonates (ii), (iii), and (iv) are new.

Table V gives a comparative idea of the yields of the different crotonates mentioned above.

<table>
<thead>
<tr>
<th>Crotonate</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(i)</td>
<td>50.0</td>
</tr>
<tr>
<td>(ii)</td>
<td>48.1</td>
</tr>
<tr>
<td>(iii)</td>
<td>41.3</td>
</tr>
<tr>
<td>(iv)</td>
<td>51.4</td>
</tr>
</tbody>
</table>
8. From Ethyl acetoacetate:

![Chemical Structure](attachment:image.png)

\[(LX)\]

(i) Ethyl-\(\beta\)-(p-acetamido anilino) crotonate

\[(LX, R_1 = NHCOCH_3 ; R_2 = H)\]

(ii) Ethyl-\(\beta\)-(m-acetamido anilino) crotonate

\[(LX, R_1 = H ; R_2 = NHCOCH_3)\]

Table VI gives the melting points and the yields of the two crotonates mentioned above.

<table>
<thead>
<tr>
<th>Crotonate</th>
<th>M.P.</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(i)</td>
<td>182°</td>
<td>52.0</td>
</tr>
<tr>
<td>(ii)</td>
<td>92°</td>
<td>48.1</td>
</tr>
</tbody>
</table>
Cyclisation of the acrylates:

The acetic anhydride - sulphuric acid method:

Development, Action and Theory:

During the first attempts at cyclisation, the ring closure of ethyl-\( \beta \)-arylamino crotonates was effect-
ed with a mixture of acetic anhydride and sulphuric acid in the ratio 2:1 (by volume) by heating on an oil-bath at 130-40°C for two hours. The reaction mixture was then poured on ice and neutralised with sodium carbonate. An oil separated in each case which then quickly solidified to a precipitate. The yields of 4-hydroxy 2-methyl quino-
lines were, however, not quite satisfactory and varied between 29% to 40%. This was attributed to the charring that took place to some extent.

Repeating the reaction on a steam-bath for a lengthier period of three to four hours seemed to improve the yields and charring was minimised much.

An attempt to cyclise the crotonates to 4-
hydroxy 2-methyl quinolines with the anhydride and the acid in very small quantities yielded viscous products
restated crystallisation and hence were not further investigated. Also, an attempt to prepare these compounds directly from ethyl acetoacetate and amines was unsuccessful.

When an attempt was made to cyclise ethyl-β-(m-chloroanilino) crotonate with the anhydride and the acid in the then optimum proportion by heating at 130°C for two hours on an oil-bath, a compound was obtained which melted at 230°C. This was at the first glance mistaken to be 4-hydroxy 5- or 7-chloro 2-methyl quinoline. In reality, it was m-chloroaniline sulphonate. Hence a modification of the above method seemed inevitable. After a number of trials with ethyl-β-(m-toluidino) crotonate, it was discovered that it could be cyclised to 4-hydroxy 2,5 dimethyl quinoline in a 53% yield by adding to the crotonate a hot mixture of the anhydride and the acid immediately after mixing, whilst the proportion of the anhydride and the acid was maintained the same. This method also, however, did not give very satisfactory results.
Next the crotonate was dissolved in twice its volume of acetic anhydride and sulphuric acid equal to the volume of the crotonate was added to it. Considerable heat was developed and the mixture boiled vigourously. Experiments revealed that

(i) the crotonate cyclised almost immediately

(ii) the heat of the mixture of the anhydride and the acid was necessary and sufficient in effecting ring closure

(iii) a mixture of the anhydride and the acid after cooling was without much effect

(iv) keeping the reaction mixture for further twenty-four hours had little influence on the yield

(v) no tarry matter was obtained, should the crotonate be purified previously throughly

(vi) heating the reaction mixture further even on a steam-bath for varying periods had no effecting in improving the yield

(vii) exhaustive purification was necessary to secure a clean ring closure product in good yield.
But with ethyl-$\beta$-(m-chloroanilino) crotonate, however, using the above modified method, the expected 4-hydroxy 2-methyl 5-chloro quinoline was obtained in yields never exceeding 12 - 15%.

In a further modification of the method, the proportion of the anhydride and the acid was changed to 2:2\(\frac{1}{2}\) (by volume) and the 4-hydroxy 2-methyl 5-chloro quinoline was obtained in cold in a 40% yield in an almost pure form (Bangdivala and Desai, loc.cit.).

Thus with ethyl-$\beta$-(m-chloroanilino) crotonate it was noticed that when the anhydride : acid ratio was changed from 2:1 to 2:1\(\frac{1}{2}\), the yield of the cyclised product increased considerably. Should it be possible to increase the yield still further with increasing acid concentration, an attempt was made to study the effect of increased acid concentration upon the cyclisation and upon the yield of the cyclised product. Thus when the anhydride : acid ratio was changed to 2:2, it was found that the yield was only about 10%. When this ratio was 2:3, then also the yield was nearly the same.
With still greater amount of the acid provided in the anhydride : acid ratio 2:4, the yields went below 10%.

When however, concentrated sulphuric acid alone was employed in cold, the crotonate decomposed and m-chloro aniline was obtained.

In the case of ethyl-β-(p-acetamido anilino) crotonate, the anhydride : acid ratio used was 5:1, since the crotonate is a solid of high melting point and required considerable amount of acetic anhydride for dissolution purposes.

Whether sulphuric acid is added to the solution of the crotonate in acetic anhydride or vice versa, the yield of the cyclised product was little influenced.

Acetic anhydride alone was also quite ineffective as a cyclising agent. Thus, neither acetic anhydride nor sulphuric acid when employed alone could effect cyclisation, but the two when mixed in the above manner, ring closure could be secured.

The literature does not seem to record the use of these reagents for cyclisation purposes in the
manner described in this work.

However, Marrian and Russell (J.Chem.Soc., 1946, 753) condensed ortho-hydroxy aldehydes with \( \Delta \) -angelica lactone in presence of small quantities of a mixture of acetic anhydride and sulphuric acid.

It appears that one of the chief factors responsible in effecting ring closure is the heat developed when sulphuric acid is added to a solution of the crotonate in acetic anhydride. However, the heat developed thus alone cannot be solely responsible in effecting cyclisation, since considerable amount of heat is developed even when sulphuric acid alone is added to the crotonate as such. In the latter case, the crotonate on the other hand decomposes giving the amine. This establishes that there is some important factor other than the heat which governs the ring closure. It is also clear that this governing property is present neither in acetic anhydride nor in sulphuric acid alone but comes into play only when the two are mixed in the above manner.
Russell and Cameron (J. Am. Chem. Soc., 1938, 60, 1347) have suggested that when acetic anhydride and sulphuric acid are mixed, a mixed anhydride of the two is formed, which is monobasic and exhibits ultra-acidic behaviour. This is a fast reaction. The mixed anhydride on standing undergoes rearrangement to sulphoacetic acid which is also monobasic but which does not exhibit ultra-acidic behaviour. This produces a slow decrease in the pH of the mixture. The formation of sulphoacetic acid via the mixed anhydride has been formulated as follows:

\[
\begin{align*}
\text{CH}_3 - C &= O \\
\text{HO} &\quad + \\
\text{CH}_3 - C &= O \\
\text{HO} &\quad \rightarrow \text{CH}_3 \text{COOH} \\
\end{align*}
\]

Mixed anhydride
(Nonobasic, shows ultra-acidic behaviour)
rearrangement
\[ \text{O} \quad \rightarrow \quad \text{HO-S-CH}_2\text{COOH} \]
on standing

Sulphoacetic acid
( Monobasic, does not show ultra-acidic behaviour)

In view of the fact that cyclisation takes place to some extent only with a freshly prepared mixture of acetic anhydride and sulphuric acid to-gether with the observation that the extent of cyclisation is consider-ably improved when the acid is added to a solution of the crotonate in acetic anhydride, it seems reasonable that the instantaneous formation of the mixed anhydride may be an important governing factor in such a ring closure.

General method of cyclisation:

The acrylate or the crotonate was dissolved in acetic anhydride and sulphuric acid was added to it (anhydride : acid :: 2:1). Considerable heat was deve-lopèd. After the mixture had cooled to room temperature, it was poured on ice and neutralised with strong sodium hydroxide. In the case of ethyl 4-hydroxy quinoline 3-
carboxylates and 4-hydroxy 3-cyano quinolines, towards the end of neutralisation sodium carbonate was employed to prevent the hydrolysis of the ester and the cyano groups. In other cases, further purification could be done by dissolving the product in sodium hydroxide (a little decolourising carbon added), filtering and acidifying. The 4-hydroxy quinolines could be crystallised from alcohol or glacial acetic acid. Many of these compounds give colourations with neutral ferric chloride solution.
1. **Cyclisation of ethyl-β-phenyl-β-(arylamino) acrylates**

obtained from ethyl benzoyleacetate and arylamines:

4-hydroxy 2-phenyl quinolines were obtained by the general method of cyclisation described before. Unlike ethyl-β-(m-substituted anilino) crotonates which on cyclisation give only the 5-isomer, (Bangdiwala and Desai, loc.cit.), cyclisation of the intermediate acrylates obtained from ethyl benzoyleacetate and m-toluidine and m-chloroaniline gives a mixture of 5- and 7-isomers. In the case of m-toluidine, it was found that one of the two isomers was soluble in dilute sodium hydroxide, whilst the other was insoluble. The mixture was accordingly treated with sodium hydroxide, warmed and filtered.

(i) Residue was one isomer- 4-hydroxy 2-phenyl 7- or 5-methyl quinoline. It was purified by crystallisation from alcohol. Its alcoholic solution gives a red colour with a solution of ferric chloride. It gives a 4-chloro derivative on treatment with phosphorous oxychloride.
(ii) The filtrate on acidification gave another isomer: 4-hydroxy 2-phenyl 5- or 7-isomer methyl quinoline purified by crystallisation from alcohol. Its alcoholic solution gives red colour with ferric chloride. It gives a 4-chloro derivative on treatment with phosphorous oxychloride.

In the case of m-chloroaniline, too, separation of the two isomers was effected, advantage being taken of the sparing solubility of one of the isomers viz. 4-hydroxy 2-phenyl 7-chloro quinoline in alcohol. This isomer was crystallised from glacial acetic acid. The isomeric 4-hydroxy 2-phenyl 5-chloro quinoline was soluble in alcohol. Both the isomers gave 4-chloro derivatives.

The following 4-hydroxy 2-phenyl quinolines were obtained:

![Chemical Structure](LXI)
(i) 4-hydroxy 2-phenyl quinoline

\[(\text{LXI, } R_1 = R_2 = R_3 = R_4 = H)\]

(ii) 4-hydroxy 2-phenyl 8-methyl quinoline

\[(\text{LXI, } R_1 = R_2 = R_3 = H; R_4 = \text{CH}_3)\]

(iii) 4-hydroxy 2-phenyl 5-methyl quinoline

\[(\text{LXI, } R_1 = \text{CH}_3; R_2 = R_3 = R_4 = H)\]

(iv) 4-hydroxy 2-phenyl 7-methyl quinoline

\[(\text{LXI, } R_1 = R_2 = R_4 = H; R_3 = \text{CH}_3)\]

(v) 4-hydroxy 2-phenyl 6-methyl quinoline

\[(\text{LXI, } R_1 = R_3 = R_4 = H; R_2 = \text{CH}_3)\]

(vi) 4-hydroxy 2-phenyl 5-chloro quinoline

\[(\text{LXI, } R_1 = \text{Cl}; R_2 = R_3 = R_4 = H)\]

(vii) 4-hydroxy 2-phenyl 7-chloro quinoline

\[(\text{LXI, } R_1 = R_2 = R_4 = H; R_3 = \text{Cl})\]

(viii) 4-hydroxy 2-phenyl 6-chloro quinoline

\[(\text{LXI, } R_1 = R_3 = R_4 = H; R_2 = \text{Cl})\]

(ix) 4-hydroxy 2-phenyl 8-methoxy quinoline

\[(\text{LXI, } R_1 = R_2 = R_3 = H; R_4 = \text{OCH}_3)\]
(x) 4-hydroxy 2-phenyl 6-methoxy quinoline
(LXI, \( R_1 = R_3 = R_4 = H \); \( R_2 = \text{OCH}_3 \))

(xi) 4-hydroxy 2-phenyl 6-ethoxy quinoline
(LXI, \( R_1 = R_3 = R_4 = H \); \( R_2 = \text{OC}_2\text{H}_5 \))

(xii) 4-hydroxy 2-phenyl 6:8 dimethyl quinoline
(LXI, \( R_1 = R_3 = H \); \( R_2 = R_4 = \text{CH}_3 \))

(xiii) 4-hydroxy 2-phenyl 5:8 dimethyl quinoline
(LXI, \( R_2 = R_3 = H \); \( R_1 = R_4 = \text{CH}_3 \))

(xiv) 1-hydroxy 3-phenyl benzo 8:6 quinoline

(LXII)

As regards the structure (LXII), it is presumed that cyclisation of the intermediate acrylate takes place to give the angular compound in accordance with the views of Lellmann and Schmidt (Ber, 1887, 20, 3154) and Von
Braun and Gruber (ibid, 1922, 55,1710). In this case, the anil can undergo ring closure either in \(\gamma\)-position giving the linear compound, or else in \(\alpha\)-position giving the angular compound. But it has been reported that the tendency to undergo ring closure in \(\alpha\)-position giving the angular compound is so great that groups such as bromo or nitro which are present in \(\alpha\)-position before cyclisation are knocked out during cyclisation giving the angular compound.

With one exception, the usual quinoline syntheses with 2-naphthylamine give benzo (\(f\)) or 5:6 quinolines exclusively. The formation of the angular rather than the linear systems by building a third ring on \(\beta\)-derivatives of naphthalene is common experience and finds convenient explanation in modern theory. Naphthalene reactions take place at a double bond; if the predominant structure of naphthalene is (LXIII), angular cyclisation of \(\beta\)-naphthalenes would be expected.
Such an assumption is justified by the well-known greater reactivity of bond A over bond B. In naphthalene there are three structures (LXIII), (LXIV), and (LXV) which contribute almost equally to the resonance hybrid. Consequently, bond A is 2/3 of a double bond and B only 1/3, thus according with the greater reactivity of the former. (Elderfield, Heterocyclic compounds, Vol. IV).

Out of the fourteen hydroxy quinolines enumerated above, (iii), (iv), (v), (vi), (viii), (ix), (xi), (xii), (xiii) and (xiv) are new.

4-chloro 2-phenyl quinolines:

These were obtained by refluxing the corresponding 4-hydroxy 2-phenyl quinolines with phosphorous oxychloride for twenty minutes. The solution after cooling to 60°C was poured on crushed ice and neutralised with
strong ammonia, when a voluminous mass of the 4-chloro compound was obtained.

The following 4-chloro 2-phenyl quinolines were prepared:

![Chemical structure diagram]

(LXVI)

(i) 4-chloro 2-phenyl quinoline

(LXVI, \( R_1 = R_2 = R_3 = R_4 = H \))

(ii) 4-chloro 2-phenyl 8-methyl quinoline

(LXVI, \( R_1 = R_2 = R_3 = H \); \( R_4 = CH_3 \))

(iii) 4-chloro 2-phenyl 5-methyl quinoline

(LXVI, \( R_1 = CH_3 \); \( R_2 = R_3 = R_4 = H \))

(iv) 4-chloro 2-phenyl 7-methyl quinoline

(LXVI, \( R_1 = R_2 = R_4 = H \); \( R_3 = CH_3 \))

(v) 4-chloro 2-phenyl 6-methyl quinoline

(LXVI, \( R_1 = R_3 = R_4 = H \); \( R_2 = CH_3 \))
(vi) 4:5 dichloro 2-phenyl quinoline
\[ \text{(LXVI, } R_1 = \text{Cl; } R_2 = R_3 = R_4 = \text{H}) \]

(vii) 4:7 dichloro 2-phenyl quinoline
\[ \text{(LXVI, } R_1 = R_2 = R_4 = \text{H; } R_3 = \text{Cl}) \]

(viii) 4:6 dichloro 2-phenyl quinoline
\[ \text{(LXVI, } R_1 = R_3 = R_4 = \text{H; } R_2 = \text{Cl}) \]

(ix) 4-chloro 2-phenyl 8-methoxy quinoline
\[ \text{(LXVI, } R_1 = R_2 = R_3 = \text{H; } R_4 = \text{OCH}_3) \]

(x) 4-chloro 2-phenyl 6-methoxy quinoline
\[ \text{(LXVI, } R_1 = R_3 = R_4 = \text{H; } R_2 = \text{OCH}_3) \]

(xi) 4-chloro 2-phenyl 6-ethoxy quinoline
\[ \text{(LXVI, } R_1 = R_3 = R_4 = \text{H; } R_2 = \text{OC}_2\text{H}_5) \]

(xii) 4-chloro 2-phenyl 6:8 dimethyl quinoline
\[ \text{(LXVI, } R_1 = R_3 = \text{H; } R_2 = R_4 = \text{CH}_3) \]

(xiii) 4-chloro 2-phenyl 5:8 dimethyl quinoline
\[ \text{(LXVI, } R_2 = R_3 = \text{H; } R_1 = R_4 = \text{CH}_3) \]

(xiv) 1-chloro 3-phenyl benzo 5:6 quinoline (LXVII)
Out of the fourteen 4-chloro derivatives mentioned above, (i), (ii), (iii), (iv), (v), (vi), (vii), (ix), (xi), (xii), (xiii) and (xiv) are new.

It may be mentioned that the overall yields of 4:7 dichloro and 6-methoxy 2-phenyl 4-chloro 2-phenyl quinolines have been found to be much greater (6-8% and 60% respectively) in contrast to the yields reported by Elderfield et al (loc.cit.) (3-5% and 6-8% respectively). It may however be noted that the 5-isomer viz. 4:5 dichloro 2-phenyl quinoline is obtained in much greater proportion by this method only (25-30%).

(Bangdiwala and Desai, Science and Culture, 1953.)

Table VII gives the yields and m.p.s of 4-hydroxy 2-phenyl quinolines and their 4-chloro compounds.
<table>
<thead>
<tr>
<th>No.</th>
<th>Substituent</th>
<th>4-hydroxy 2-phenyl quinoline</th>
<th>4-chloro 2-phenyl quinoline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>yield(%)</td>
<td>M.P.</td>
</tr>
<tr>
<td>(i)</td>
<td>Unsubstituted</td>
<td>54.0</td>
<td>254°</td>
</tr>
<tr>
<td>(ii)</td>
<td>8-methyl</td>
<td>52.8</td>
<td>224°-25°</td>
</tr>
<tr>
<td>(iii)</td>
<td>5/7 methyl</td>
<td>total yield</td>
<td>56.0</td>
</tr>
<tr>
<td>(iv)</td>
<td>7/5 methyl</td>
<td>ratio</td>
<td>40:60</td>
</tr>
<tr>
<td>(v)</td>
<td>6-methyl</td>
<td>75.2</td>
<td>294°-95°</td>
</tr>
<tr>
<td>(vi)</td>
<td>5-chloro</td>
<td>total yield</td>
<td>45.7</td>
</tr>
<tr>
<td>(vii)</td>
<td>7-chloro</td>
<td>ratio</td>
<td>80:20</td>
</tr>
<tr>
<td>(viii)</td>
<td>6-chloro</td>
<td>33.8</td>
<td>356°-51° (decom)</td>
</tr>
<tr>
<td>(ix)</td>
<td>8-methoxy</td>
<td>35.7</td>
<td>262°-63°</td>
</tr>
<tr>
<td>(x)</td>
<td>6-methoxy</td>
<td>67.0</td>
<td>306°-7°</td>
</tr>
<tr>
<td>(xi)</td>
<td>6-ethoxy</td>
<td>57.3</td>
<td>285°</td>
</tr>
<tr>
<td>(xii)</td>
<td>6:8 dimethyl</td>
<td>46.3</td>
<td>231°-32°</td>
</tr>
<tr>
<td>(xiii)</td>
<td>6:8 dimethyl</td>
<td>35.8</td>
<td>187°</td>
</tr>
<tr>
<td>(xiv)</td>
<td>benzo 5:6</td>
<td>31.4</td>
<td>&gt;300° (decom)</td>
</tr>
</tbody>
</table>

1. Hauser and Reynolds (loc.cit.) give m.p. 253°-54°, yield 50%.
2. Hauser and Reynolds (loc.cit.) give m.p. 245°-46°, yield 38%.
2. Cyclisation of the acrylates obtained from Ethyl benzoylacetooacetate and arylamines:

Sheh et al. (loc. cit.) carried out the condensation between ethyl benzoylacetooacetate and aryl amines and obtained by the cyclisation of the intermediate acrylates, 4-hydroxy 2-methyl 3-benzoyl quinolines in some cases and 4-hydroxy 2-phenyl 3-acetyl quinolines in other cases. The first type of compounds can also be obtained by Friedel-Crafts benzoylation of 4-hydroxy 2-methyl quinolines. The latter type has also been obtained from various anilide imidochlorides and ethyl sodioacetooacetate (Desai and Shah, loc. cit.).

The present work was undertaken to see the mode of anil formation with ethyl benzoylacetooacetate since there are two competing keto groups. Anil formation can therefore take place with the acetyl group or with the benzoyl group or partly with both. The object was also to study the effect of acetic anhydride and sulphuric acid on the cyclisation of the anils and to see whether anils obtained from m-substituted anilines upon cyclisation
give a single product or a mixture of isomers (Bangdiwala and Desai, loc.cit.). It has been found that when anil formation takes place with the acetyl group, cyclisation gives 4-hydroxy 2-methyl 3-benzoyl quinolines. When however, anil formation takes place with the benzoyl group, the free acetyl group is knocked out during cyclisation inspite of the presence of a strong acetyating agent viz. acetic anhydride and simple 4-hydroxy 2-phenyl quinolines are obtained. This is one of the most interesting features of the method. That the acetyl group is in fact prior to cyclisation is further substantiated by the fact that the same anil when cyclised by the thermal method gave 4-hydroxy 2-phenyl 3-acetyl quinoline.

Preliminary experiments with aniline showed that only one product - 4-hydroxy 2-methyl 3-benzoyl quinoline was obtained on cyclisation of the anil, in contrast to the two products: 4-hydroxy 2-methyl 3-benzoyl and 4-hydroxy 2-phenyl 3-acetyl quinolines reported by Shah et al (loc.cit.). Hence, a systematic investigation was undertaken and the anils were cyclised using both the present
and the thermal methods (Price and Roberts, loc.cit.). In those cases where simple 4-hydroxy 2-phenyl quinolines are obtained by the present method, cyclisation by the thermal method has proved valuable in showing that the acetyl group is in fact prior to cyclisation and is knocked out only during cyclisation.

The following 4-hydroxy quinolines were thus obtained:

(i) **From aniline:**

4-hydroxy 2-methyl 3-benzoyl quinoline

(LXVIII, $R_1 = R_2 = H$)

The acrylate from ethyl benzoylacetooacetate on cyclisation by the anhydride-acid method gave only a single product: 4-hydroxy 2-methyl 3-benzoyl quinoline also obtained by Friedel-Crafts benzoylation of 4-hydroxy 2-
methyl quinoline. Hence, anil formation must have taken place solely with the acetyl group of the ester. Cyclisation by the thermal method also gave a single product: 4-hydroxy 2-methyl 3-benzoyl quinoline. The isomeric 4-hydroxy 2-phenyl 3-acetyl quinoline (LXIX, \( R_1 = R_2 = R_3 = H \)) could not be traced at all.

According to Shah et al (loc. cit.), in this case, anil formation takes place partly with the acetyl group and partly with the benzoyl group of the ester. Consequently, cyclisation is reported to give two products: 4-hydroxy 2-methyl 3-benzoyl and 4-hydroxy 2-phenyl 3-acetyl quinolines.

(ii) From o-toluidine:

4-hydroxy 2:8 dimethyl 3-benzoyl quinoline

(LXVIII, \( R_2 = CH_3 \); \( R_1 = H \))

The acrylate from ethyl benzoylacetoacetate and o-toluidine upon cyclisation by both the anhydride and the thermal methods gave the same compound: 4-hydroxy 2:8 dimethyl 3-benzoyl quinoline, also, obtained by Friedel-Crafts benzoylation of 4-hydroxy 2:8 dimethyl quinoline.
Shah et al. (loc. cit.) also report the same product.

(iii) From p-toluidine:

(a) anhydride-acid method:

\[
4\text{-hydroxy 2-phenyl 6-methyl quinoline}
\]

\[
(\text{LXI}, R_1 = R_3 = R_4 = H; R_2 = \text{CH}_3)
\]

(b) thermal method:

\[
4\text{-hydroxy 2-phenyl 3-acetyl 6-methyl quinoline}
\]

\[
(\text{LXIX}, R_1 = R_3 = H; R_2 = \text{CH}_3)
\]

Curiously enough, the acrylate from ethyl benzoylacetate and p-toluidine upon cyclisation by the present method gave 4-hydroxy 2-phenyl 6-methyl quinoline, also obtained from ethyl benzoylacetate and p-toluidine (loc. cit.). It appears, therefore, that anil-formation must have taken place with the benzoyl group of the ester and that the free acetyl group is knocked out during cyclisation, in spite of the presence of a strong acetylating agent vis. acetic anhydride. This is substantiated by the fact that when the same anil is cyclised by the thermal method, 4-hydroxy 2-phenyl 3-acetyl 6-methyl quinoline was obtained – indicating clearly that the acetyl group is in
tact prior to cyclisation. Shah et al (loc. cit.) however, report the formation of 4-hydroxy 2:6 dimethyl 3-benzoyl quinoline (LXVIII, \( R_1 = CH_3 \); \( R_2 = H \)) in this case.

(iv) From \( m \)-toluidine:

The acrylate from ethyl benzoylacetoacetate and \( m \)-toluidine upon cyclisation by the present method gave a mixture of products, out of which one product could be separated as its oxalate. The oxalate on decomposition with alkali gave a product (m.p.260°-61° C) which was soluble in dilute sodium hydroxide and gave no colouration with ferric chloride. Its constitution has not been definitely established, but the following light can be thrown:

1. Its mixed m.p. with 4-hydroxy 2-phenyl 5 or 7-methyl quinoline (m.p.261°-62° C) obtained from ethyl benzoyl acetate and \( m \)-toluidine (loc. cit.) was undepressed. The latter product however, is different in its properties — insoluble in sodium hydroxide and gives red colouration with ferric chloride. It also differs in its crystalline form. It is very likely that the present product may not be 4-hydroxy 2-phenyl 5 or 7-methyl quinoline in view of
the data reported in literature that mixed m.p.s are not always reliable with cinnoline types of compounds (Schofield and Swain, J.Chem.Soc. 1950, 385). Also, according to the work done in this laboratory (Desai and Desai, unpublished), the mixed m.p. of 4-hydroxy 2:5 dimethyl quinoline (m.p.274°C) and 4-hydroxy 2:6 dimethyl quinoline (m.p.278°C) was 274-75°C. The same behaviour was noticed in case of their bromo derivatives.

2. Its mixed m.p. with an authentic specimen of 4-hydroxy 2:5 dimethyl 3-benzyol quinoline was depressed.

It is probable therefore the present compound may be 4-hydroxy 2:7 dimethyl 5-benzyol quinoline.

The same acrylate on thermal cyclisation also gives a mixture of products, purifiable with difficulty, from which no pure product could be isolated. Shah et al (loc.cit.) could not obtain any solid product in this case.

(v) From m-chloroaniline:

(a) anhydride-acid method:

4-hydroxy 2-phenyl 7-chloro quinoline

\( (\text{LXI}, R_1 = R_2 = R_4 = H ; R_3 = \text{Cl} )\)
(b) thermal method:

4-hydroxy 2-phenyl 3-acetyl 5- or 7-chloro quinoline

(LXXIX, \( R_1 = \text{Cl} \); \( R_2 = R_3 = \text{H} \) or

LXXIX, \( R_3 = \text{Cl} \); \( R_1 = R_2 = \text{H} \)

The acrylate from ethyl benzoylacetooacetate and m-chloroaniline upon cyclisation by the present method gave only one product: 4-hydroxy 2-phenyl 7-chloro quinoline also obtained from ethyl benzoylacetate and m-chloroaniline (loc.cit.). The anil formation, therefore, must have taken place with the benzoyl group of the ester.

Cyclisation by the thermal method gives a single product (acrylate : diphenyl ether :: 1:10), obviously 4-hydroxy 2-phenyl 3-acetyl 5- or 7-chloro quinoline. This compound was not isolated by as such by Desai and Shah (loc.cit.).

2:4 dinitrophenyl hydrazones of compounds (i), (ii), (iii) b, and (v) b have been prepared. Oxime of compound (i) has been prepared. The following 4-chloro derivatives of compounds (iii) a, (v) a and (v) b were prepared.
(a) 4-chloro 2-phenyl 6-methyl quinoline

\[(\text{LXVI, } R_1 = R_3 = R_4 = H ; R_2 = \text{CH}_3)\]

(b) 4:7 dichloro 2-phenyl quinoline

\[(\text{LXVI, } R_1 = R_2 = R_4 = H ; R_3 = \text{Cl})\]

(c) 4:5 or 4:7 dichloro 2-phenyl 3-acetyl quinolines

\[(\text{LXX or LXXI})\]

\[\text{(LXX)} \quad \text{(LXXI)}\]

Out of these, compound (c) is new. Compound (a)
is also new but it has been referred to in the earlier part.

Table VIII gives a comparative idea of the yields and m.p.s of the various 4-hydroxy quinolines obtained by the present method and Table IX records the yields and m.p.s of the products obtained by the thermal method.
### Table VIII

<table>
<thead>
<tr>
<th>No.</th>
<th>Amine used</th>
<th>Compound obtained</th>
<th>Present Method</th>
<th>Yield (%)</th>
<th>M.P.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>aniline</td>
<td>(i)</td>
<td></td>
<td>48.1</td>
<td>284°</td>
</tr>
<tr>
<td>2.</td>
<td>o-toluidine</td>
<td>(ii)</td>
<td></td>
<td>30.1</td>
<td>297°-98°</td>
</tr>
<tr>
<td>3.</td>
<td>p-toluidine</td>
<td>(iii) a</td>
<td></td>
<td>54.4</td>
<td>294°-95°</td>
</tr>
<tr>
<td>4.</td>
<td>m-toluidine</td>
<td>?</td>
<td></td>
<td>21.6</td>
<td>220°-30°</td>
</tr>
<tr>
<td>5.</td>
<td>m-chloroaniline</td>
<td>(v) a</td>
<td></td>
<td>20.0</td>
<td>260°-61°</td>
</tr>
</tbody>
</table>

### Table IX

<table>
<thead>
<tr>
<th>No.</th>
<th>Amine used</th>
<th>Compound obtained</th>
<th>Thermal Method</th>
<th>Yield (%)</th>
<th>M.P.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>aniline</td>
<td>(i)</td>
<td></td>
<td>39.0¹</td>
<td>284°</td>
</tr>
<tr>
<td>2.</td>
<td>o-toluidine</td>
<td>(ii)</td>
<td></td>
<td>20.0</td>
<td>297°-98²</td>
</tr>
<tr>
<td>3.</td>
<td>p-toluidine</td>
<td>(iii) b³</td>
<td></td>
<td>40.0</td>
<td>263°</td>
</tr>
<tr>
<td>4.</td>
<td>m-toluidine</td>
<td>?</td>
<td></td>
<td>20.2</td>
<td>230°-41°</td>
</tr>
<tr>
<td>5.</td>
<td>m-chloroaniline</td>
<td>(v) b</td>
<td></td>
<td>44.0</td>
<td>312°-15°</td>
</tr>
</tbody>
</table>

1. Shah et al (loc.cit.) give yield 20.0%.
2. Shah et al (loc.cit.) give m.p. 289° C.
3. Shah et al (loc.cit.) report the formation of 4-hydroxy 2:6 dimethyl 3-benzoyl quinoline - m.p. >290° C.
3. Cyclisation of ethyl-α-carboxethoxy-β-phenyl-β-(aryl-amino) acrylates obtained from ethyl benzoylemalonate:

The acrylates were cyclised according to the general method described before, giving ethyl 4-hydroxy 2-phenyl quinoline 3-carboxylates.

The esters were hydrolysed by refluxing with a 5% solution of sodium hydroxide for two hours, giving the corresponding 4-hydroxy 2-phenyl quinoline 3-carboxylic acids which were precipitated by acidifying with 50% hydrochloric acid.

The acids were decarboxylated to the corresponding 4-hydroxy 2-phenyl quinolines which were identified by taking mixed melting points with authentic specimens prepared from ethyl benzoylacetate and aryl amines (loc. cit.). The decarboxylation step was simple and was carried out by adding the acid with stirring to mineral oil preheated to 275°C and maintaining the temperature at 270-275°C for five minutes. The product was precipitated by diluting the oil with petroleum ether and scratching.

4-chloro 2-phenyl quinolines were obtained by
refluxing the corresponding 4-hydroxy 2-phenyl quinolines with phosphorous oxychloride.

The synthesis has been carried out with aniline, o-toluidine, p-toluidine and p-chloroaniline.

The following ethyl 4-hydroxy 2-phenyl quinoline 3-carboxylates were prepared:

(LXXII)

(i) Ethyl 4-hydroxy 2-phenyl quinoline 3-carboxylate

(LXXII, \( R_1 = R_2 = H \))

(ii) Ethyl 4-hydroxy 2-phenyl 8-methyl quinoline 3-carboxylate

(LXXII, \( R_1 = H ; R_2 = CH_3 \))

(iii) Ethyl 4-hydroxy 2-phenyl 6-methyl quinoline 3-carboxylate

(LXXII, \( R_1 = CH_3 ; R_2 = H \))

(iv) Ethyl 4-hydroxy 2-phenyl 6-chloro quinoline 3-carboxylate

(LXXII, \( R_1 = Cl ; R_2 = H \))

Hydrolysis gave the following acids.
(i) 4-hydroxy 2-phenyl quinoline 3-carboxylic acid

( LXXIII, R₁ = R₂ = R₃ = R₄ = H )

(ii) 4-hydroxy 2-phenyl 8-methyl quinoline 3-carboxylic acid

( LXXIII, R₁ = R₂ = R₃ = H ; R₄ = CH₃ )

(iii) 4-hydroxy 2-phenyl 6-methyl quinoline 3-carboxylic acid

( LXXIII, R₁ = R₃ = R₄ = H ; R₂ = CH₃ )

(iv) 4-hydroxy 2-phenyl 6-chloro quinoline 3-carboxylic acid

( LXXIII, R₁ = R₃ = R₄ = H ; R₂ = Cl )

Decarboxylation of the above acids gave 4-hydroxy 2-phenyl, 4-hydroxy 2-phenyl 8-methyl, 4-hydroxy 2-phenyl 6-methyl and 4-hydroxy 2-phenyl 6-chloro quinolines respectively (See vide p. 83, compounds (i), (ii), (v) and (viii), formula LXI).

4-chloro 2-phenyl quinolines prepared were compounds (i), (ii), (v) and (viii) stated on p.87-88.
Ethyl 4-hydroxy 2-phenyl quinoline 3-carboxylic esters have already been obtained from various anilide imidochlorides (Shah and Heeramaneck, loc.cit.) and ethyl sodiomalonate. But in view of the easy preparation of ethyl benzoylmalonate and the ease of cyclisation in spite of low yields of the corresponding acrylates, this method constitutes a shorter route to the synthesis of this type of compounds. Shah and Heeramaneck (loc.cit.) prepared the esters and the acids, but did not decarboxylate the acids to the corresponding 4-hydroxy 2-phenyl quinolines.

Table X gives the yields and m.p.s of the various ethyl 4-hydroxy 2-phenyl quinoline 3-carboxylic esters obtained by the anhydride-acid and the imidochloride methods.

Table XI gives the yields and m.p.s of 4-hydroxy 2-phenyl quinoline 3-carboxylic acids obtained.

Table XII gives the yields and m.p.s of the corresponding 4-hydroxy 2-phenyl quinolines.
**Table X**

Ethyl 4-hydroxy 2-phenyl quinoline 3-carboxylate

<table>
<thead>
<tr>
<th>No. Substituent</th>
<th>Present Method</th>
<th>Imidochloride method</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>yield(%)</td>
<td>M.P.</td>
</tr>
<tr>
<td>1. unsubstituted</td>
<td>27.7</td>
<td>260°-61°</td>
</tr>
<tr>
<td>2. 8-methyl</td>
<td>26.0</td>
<td>243°-44°</td>
</tr>
<tr>
<td>3. 6-methyl</td>
<td>22.6</td>
<td>252°-53°</td>
</tr>
<tr>
<td>4. 6-chloro</td>
<td>29.0</td>
<td>250°-52°</td>
</tr>
</tbody>
</table>

**Table XI**

4-hydroxy 2-phenyl quinoline 3-carboxylic acid

<table>
<thead>
<tr>
<th>No. Substituent</th>
<th>Present Method</th>
<th>Imidochloride method</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>yield(%)</td>
<td>M.P.</td>
</tr>
<tr>
<td>1. unsubstituted</td>
<td>74.0</td>
<td>230°-32°</td>
</tr>
<tr>
<td>2. 8-methyl</td>
<td>84.0</td>
<td>202°-3° (decom)</td>
</tr>
<tr>
<td>3. 6-methyl</td>
<td>79.0</td>
<td>210°-11</td>
</tr>
<tr>
<td>4. 6-chloro</td>
<td>72.0</td>
<td>301°-2° (decom)</td>
</tr>
<tr>
<td>No.</td>
<td>Substituent</td>
<td>Yield (%)</td>
</tr>
<tr>
<td>-----</td>
<td>----------------</td>
<td>-----------</td>
</tr>
<tr>
<td>1.</td>
<td>unsubstituted</td>
<td>75.0</td>
</tr>
<tr>
<td>2.</td>
<td>8-methyl</td>
<td>81.0</td>
</tr>
<tr>
<td>3.</td>
<td>6-methyl</td>
<td>76.0</td>
</tr>
<tr>
<td>4.</td>
<td>6-chloro</td>
<td>66.6</td>
</tr>
</tbody>
</table>
4. **Cyclisation of the acrylates obtained from benzoyloyan-acetic ester and aryl amines.**

The acrylates were cyclised according to the general method described before. However, in no case 4-hydroxy 2-phenyl 3-cyano quinolines could be isolated. It appears therefore that the cyano group is hydrolysed during cyclisation giving the corresponding 3-carboxylic acids. The acids were decarboxylated to the corresponding 4-hydroxy 2-phenyl quinolines by adding in mineral oil preheated to 275°C and maintaining the temperature at 270-75°C for five minutes. The latter compounds were identified by taking mixed melting points with authentic specimens prepared from ethyl benzoylacetate and arylamines (loc. cit.).

4-chloro 2-phenyl quinolines were obtained as before.

The synthesis has been carried out with aniline, o-toluidine, p-toluidine and m-chloroaniline.

In the case of m-chloroaniline, a mixture of 5- and 7-chloro 4-hydroxy 2-phenyl quinoline 3-carboxylic acids is obtained. The individual isomers were separated by fra-
ctional crystallisation from glacial acetic acid in which
the 7-isomer is comparatively quite less soluble. That the
less soluble isomer is the 7-isomer was proved by its de-
carboxylation to the corresponding known 4-hydroxy 2-phenyl
7-chloro quinoline (loc.cit.).

The following 4-hydroxy 2-phenyl quinoline 3-
carboxylic acids were thus prepared.

(i) 4-hydroxy 2-phenyl quinoline 3-carboxylic acid
    \( \text{LXXIII, } R_1 = R_2 = R_3 = R_4 = H \)

(ii) 4-hydroxy 2-phenyl 8-methyl quinoline 3-carboxylic
     \( \text{acid LXXIII, } R_1 = R_2 = R_3 = H \quad R_4 = CH_3 \) 

(iii) 4-hydroxy 2-phenyl 6-methyl quinoline 3-carboxylic
     \( \text{acid LXXIII, } R_1 = R_3 = R_4 = H \quad R_2 = CH_3 \) 

(iv) 4-hydroxy 2-phenyl 5-chloro quinoline 3-carboxylic
     \( \text{acid LXXIII, } R_1 = Cl \quad R_2 = R_3 = R_4 = H \) 

(v) 4-hydroxy 2-phenyl 7-chloro quinoline 3-carboxylic
    \( \text{acid LXXIII, } R_1 = R_2 = R_4 = H \quad R_3 = Cl \) 

Decarboxylation of the acids gave the correspond-
ing 4-hydroxy 2-phenyl quinolines (vide p.83, compounds
(i), (ii), (v), (vi) and (vii), formula LXI).

4-chloro 2-phenyl quinolines were obtained from the corresponding 4-hydroxy 2-phenyl quinolines as before (vide p. 87-88, compounds (i), (ii), (v), (vi), and (vii), formula LXVI).

Although the yields obtained are low, the synthesis of 4-hydroxy quinoline 3-carboxylic acids from benzoylcyanoacetic ester constitutes comparatively a more direct route than the imidochloride method using malonic ester.

Table XIII gives the yields and the m.p.'s of the various 4-hydroxy quinolines obtained from benzoylcyanoacetic ester and arylamines.
<table>
<thead>
<tr>
<th>No.</th>
<th>Substituent</th>
<th>Yield(%)</th>
<th>M.P</th>
<th>Yield(%)</th>
<th>M.P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>unsubstituted</td>
<td>32.1</td>
<td>230°</td>
<td>75.0</td>
<td>254°</td>
</tr>
<tr>
<td>2</td>
<td>8-methyl</td>
<td>26.0</td>
<td>201-2°</td>
<td>80.0</td>
<td>224-25°</td>
</tr>
<tr>
<td>3</td>
<td>6-methyl</td>
<td>23.0</td>
<td>209-11°</td>
<td>76.0</td>
<td>294-95°</td>
</tr>
<tr>
<td>4</td>
<td>7-chloro</td>
<td>total</td>
<td>350-52°</td>
<td>73.2</td>
<td>355-57°</td>
</tr>
<tr>
<td>5</td>
<td>5-chloro</td>
<td>ratio</td>
<td>242-45°</td>
<td>82.0</td>
<td>280-82°</td>
</tr>
</tbody>
</table>

Table XIII

<table>
<thead>
<tr>
<th>4-hydroxy 2-phenyl quinoline 3-carboxylic acid</th>
<th>4-hydroxy 2-phenyl quinoline</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. Substituent</td>
<td>Yield(%)</td>
</tr>
<tr>
<td>1 unsubstituted</td>
<td>32.1</td>
</tr>
<tr>
<td>2. 8-methyl</td>
<td>26.0</td>
</tr>
<tr>
<td>3. 6-methyl</td>
<td>23.0</td>
</tr>
<tr>
<td>4. 7-chloro</td>
<td>total</td>
</tr>
<tr>
<td>5. 5-chloro</td>
<td>ratio</td>
</tr>
</tbody>
</table>
5. **Cyclisation of ethyl-α-acetyl-β-aniline crotonate**

obtained from ethyl diacetoacetate and aniline:

The cyclisation was carried out as usual. It was found that the free acetyl group is knocked out during cyclisation inspite of the presence of a strong acetylationing agent viz. acetic anhydride, and 4-hydroxy 2-methyl quinoline was obtained in a 47.1% yield. Further extension of the work was postponed, since such products could be readily obtained from ethyl acetoacetate.

6. **Cyclisation of ethyl-α-benzoyl-β-phenyl-β-aniline**

acrylate obtained from ethyl dibenzoylacetaate and aniline:

Cyclisation was carried out as usual. The product obtained was 4-hydroxy 2-phenyl 3-benzoyl quinoline (LXXIV). Yield: 32.6%. The same product could also be obtained by Friedel-Crafts benzoylation of 4-hydroxy 2-phenyl quinoline. Further extention of the work was postponed, since these products could be easily obtained by Friedel-Crafts benzoylolation of 4-hydroxy 2-phenyl quinolines which in turn are easily obtained in good yields from ethyl benzoylacetaate.
and arylamines, using the anhydride - acid method (loc.cit.).

\[ \text{OH} \]
\[ \text{C-CO}_2\text{H}_5 \]
\[ \text{C-}_7\text{H}_5 \]
\[ \text{N} \]

(LXXIV)

2:4 dinitrophenyl hydrazone of compound (LXXIV) has been prepared.

7. Cyclisation of ethyl-\(\alpha\)-carboxethoxy-\(\beta\)-(arylamine) crotonates obtained from acetyl malonic ester and arylamines.

Cyclisation of the crotonates was carried out by the general method described before, giving ethyl 4-hydroxy 2-methyl quinoline 3-carboxylates. The synthesis has been carried out with aniline, p-toluidine, m-toluidine and m-chloroaniline. In the case of both m-toluidine and m-chloroaniline, a mixture of 5- and 7-substituted esters was obtained. A separation of the individual isomers could not be effected at this stage in both cases.

The esters were hydrolysed by boiling with a 5% solution of sodium hydroxide for two hours. In the case
of m-toluidine, the mixture of 4-hydroxy 2:5 and 2:7 dimethyl quinoline 3-carboxylic acids could not be resolved into individual isomers. In the case of m-chloroaniline, the mixture of isomeric 5- and 7-chloro 4-hydroxy 2-methyl quinoline 3-carboxylic acids obtained by hydrolysis, could be resolved into individual isomers by fractional crystallisation from glacial acetic acid, the 7-isomer being less soluble. That the less soluble component is 4-hydroxy 2-methyl 7-chloro quinoline 3-carboxylic acid was shown by subsequent decarboxylation to the corresponding known 4-hydroxy 2-methyl 7-chloro quinoline. The isomeric 4-hydroxy 2-methyl 5-chloro quinoline 3-carboxylic acid is more soluble by comparison and is precipitated from the acetic acid mother liquor by dilution with water and subsequently crystallised from alcohol.

The acids were decarboxylated as described in the earlier section. In the case of m-toluidine, the mixture of acids gave a mixture of 4-hydroxy 2:5 and 2:7 dimethyl quinolines which were separated as oxalates (Spivey and Curd, loc. cit.).
The following ethyl 4-hydroxy 2-methyl quinoline 5-carboxylates were thus obtained.

\begin{center}
\begin{tikzpicture}
\node[draw] (A) at (0,0) {
\scalebox{0.7}{
\begin{tikzpicture}
\node[draw] (N) at (0,0) {N};
\node[draw] (C1) at (1,1) {C};
\node[draw] (C2) at (1,-1) {C};
\node[draw] (C3) at (0,1) {C};
\node[draw] (C4) at (0,-1) {C};
\node[draw] (C5) at (2,0) {C};
\node[draw] (C6) at (-2,0) {C};
\node[draw] (H1) at (0.5,0.5) {H};
\node[draw] (H2) at (0.5,-0.5) {H};
\node[draw] (H3) at (1.5,0.5) {H};
\node[draw] (H4) at (1.5,-0.5) {H};
\node[draw] (H5) at (2.5,0.5) {H};
\node[draw] (H6) at (-1.5,0.5) {H};
\node[draw] (H7) at (-1.5,-0.5) {H};
\node[draw] (H8) at (0,1.5) {H};
\node[draw] (H9) at (0,-1.5) {H};
\node[draw] (O1) at (0.5,1.5) {O};
\node[draw] (O2) at (0.5,-1.5) {O};
\node[draw] (O3) at (1.5,1.5) {O};
\node[draw] (O4) at (1.5,-1.5) {O};
\node[draw] (O5) at (2.5,1.5) {O};
\node[draw] (O6) at (-1.5,1.5) {O};
\node[draw] (O7) at (-1.5,-1.5) {O};
\node[draw] (O8) at (0,2) {O};
\node[draw] (O9) at (0,-2) {O};
\node[draw] (O10) at (1.5,2) {O};
\node[draw] (O11) at (1.5,-2) {O};
\node[draw] (O12) at (2.5,2) {O};
\node[draw] (O13) at (-1.5,2) {O};
\node[draw] (O14) at (-1.5,-2) {O};
\node[draw] (O15) at (2.5,-2) {O};
\node[draw] (O16) at (-2.5,2) {O};
\node[draw] (O17) at (-2.5,-2) {O};
\node[draw] (O18) at (2.5,2) {O};
\node[draw] (O19) at (-2.5,2) {O};
\node[draw] (O20) at (2.5,-2) {O};
\node[draw] (O21) at (-2.5,-2) {O};
\node[draw] (O22) at (2.5,2) {O};
\node[draw] (O23) at (-2.5,2) {O};
\node[draw] (O24) at (2.5,-2) {O};
\node[draw] (O25) at (-2.5,-2) {O};
\node[draw] (O26) at (2.5,2) {O};
\node[draw] (O27) at (-2.5,2) {O};
\node[draw] (O28) at (2.5,-2) {O};
\node[draw] (O29) at (-2.5,-2) {O};
\node[draw] (O30) at (2.5,2) {O};
\node[draw] (O31) at (-2.5,2) {O};
\node[draw] (O32) at (2.5,-2) {O};
\node[draw] (O33) at (-2.5,-2) {O};
\node[draw] (O34) at (2.5,2) {O};
\node[draw] (O35) at (-2.5,2) {O};
\node[draw] (O36) at (2.5,-2) {O};
\node[draw] (O37) at (-2.5,-2) {O};
\node[draw] (O38) at (2.5,2) {O};
\node[draw] (O39) at (-2.5,2) {O};
\node[draw] (O40) at (2.5,-2) {O};
\node[draw] (O41) at (-2.5,-2) {O};
\node[draw] (O42) at (2.5,2) {O};
\node[draw] (O43) at (-2.5,2) {O};
\node[draw] (O44) at (2.5,-2) {O};
\node[draw] (O45) at (-2.5,-2) {O};
\node[draw] (O46) at (2.5,2) {O};
\node[draw] (O47) at (-2.5,2) {O};
\node[draw] (O48) at (2.5,-2) {O};
\node[draw] (O49) at (-2.5,-2) {O};
\node[draw] (O50) at (2.5,2) {O};
\node[draw] (O51) at (-2.5,2) {O};
\node[draw] (O52) at (2.5,-2) {O};
\node[draw] (O53) at (-2.5,-2) {O};
\node[draw] (O54) at (2.5,2) {O};
\node[draw] (O55) at (-2.5,2) {O};
\node[draw] (O56) at (2.5,-2) {O};
\node[draw] (O57) at (-2.5,-2) {O};
\node[draw] (O58) at (2.5,2) {O};
\node[draw] (O59) at (-2.5,2) {O};
\node[draw] (O60) at (2.5,-2) {O};
\node[draw] (O61) at (-2.5,-2) {O};
\node[draw] (O62) at (2.5,2) {O};
\node[draw] (O63) at (-2.5,2) {O};
\node[draw] (O64) at (2.5,-2) {O};
\node[draw] (O65) at (-2.5,-2) {O};
\node[draw] (O66) at (2.5,2) {O};
\node[draw] (O67) at (-2.5,2) {O};
\node[draw] (O68) at (2.5,-2) {O};
\node[draw] (O69) at (-2.5,-2) {O};
\node[draw] (O70) at (2.5,2) {O};
\node[draw] (O71) at (-2.5,2) {O};
\node[draw] (O72) at (2.5,-2) {O};
\node[draw] (O73) at (-2.5,-2) {O};
\node[draw] (O74) at (2.5,2) {O};
\node[draw] (O75) at (-2.5,2) {O};
\node[draw] (O76) at (2.5,-2) {O};
\node[draw] (O77) at (-2.5,-2) {O};
}\end{tikzpicture}}
\end{tikzpicture}
\end{center}

\textit{(LXXV)}

(i) ethyl 4-hydroxy 2-methyl quinoline 3-carboxylate

(\textit{LXXV, }R_1 = R_2 = R_3 = H)

(ii) ethyl 4-hydroxy 2:6 dimethyl quinoline 3-carboxylate

(\textit{LXXV, }R_1 = R_3 = H ; R_2 = \text{CH}_3)

(iii) ethyl 4-hydroxy 2:5 and 2:7 dimethyl quinoline 3-carboxylates

(\textit{LXXV, }R_1 = \text{CH}_3 ; R_2 = R_3 = H)

+ \hspace{2cm}

(\textit{LXXV, }R_1 = R_2 = H ; R_3 = \text{CH}_3)

(iv) A mixture of

ethyl 4-hydroxy 2-methyl 5-chloro quinoline 3-carboxylate

(\textit{LXXV, }R_1 = \text{Cl} ; R_2 = R_3 = H) and

ethyl 4-hydroxy 2-methyl 7-chloro quinoline 3-carboxylate

(\textit{LXXV, }R_1 = R_2 = H ; R_3 = \text{Cl})

Hydrolysis gave the following acids.
(i) 4-hydroxy 2-methyl quinoline 3-carboxylic acid

(LXXVI, $R_1 = R_2 = R_3 = H$

(ii) 4-hydroxy 2:6 dimethyl quinoline 3-carboxylic acid

(LXXVI, $R_1 = R_3 = H; R_2 = CH_3$

(iii) A mixture of
4-hydroxy 2:5 dimethyl quinoline 3-carboxylic acid

(LXXVI, $R_1 = CH_3; R_2 = R_3 = H$) and

4-hydroxy 2:7 dimethyl quinoline 3-carboxylic acid

(LXXVI, $R_1 = R_2 = H; R_3 = CH_3$

(iv) 4-hydroxy 2-methyl 5-chloro quinoline 3-carboxylic acid

(LXXVI, $R_1 = Cl; R_2 = R_3 = H$

(v) 4-hydroxy 2-methyl 7-chloro quinoline 3-carboxylic acid

(LXXVI, $R_1 = R_2 = H; R_3 = Cl$

Decarboxylation gave the following 4-hydroxy 2-methyl quinolines.
(i) 4-hydroxy 2-methyl quinoline

\[ X \]

( LXXVII, \( R_1 = R_2 = R_3 = H \) )

(ii) 4-hydroxy 2:6 dimethyl quinoline

( LXXVII, \( R_1 = R_3 = H ; R_2 = \text{CH}_3 \) )

(iii) 4-hydroxy 2:5 dimethyl quinoline

( LXXVII, \( R_1 = \text{CH}_3 ; R_2 = R_3 = H \) )

(iv) 4-hydroxy 2:7 dimethyl quinoline

( LXXVII, \( R_1 = R_2 = H ; R_3 = \text{CH}_3 \) )

(v) 4-hydroxy 2-methyl 5-chloro quinoline

( LXXVII, \( R_1 = \text{Cl} ; R_2 = R_3 = H \) )

(vi) 4-hydroxy 2-methyl 7-chloro quinoline

( LXXVII, \( R_1 = R_2 = H ; R_3 = \text{Cl} \) )

Table XIV gives the yields and m.p.s of the various ethyl 4-hydroxy 2-methyl quinoline 3-carboxylates.

Table XV gives the yields and m.p.s of the
various 4-hydroxy 2-methyl quinoline 3-carboxylic acids.

Table XVI gives the yields and m.p.s of the various 4-hydroxy 2-methyl quinolines.

<table>
<thead>
<tr>
<th>No.</th>
<th>Substituent</th>
<th>Yield (%)</th>
<th>M.P.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>unsubstituted</td>
<td>42.0</td>
<td>104.6°</td>
</tr>
<tr>
<td>2.</td>
<td>6-methyl</td>
<td>39.5</td>
<td>250.52°</td>
</tr>
<tr>
<td>3.</td>
<td>5-methyl</td>
<td>total</td>
<td>m.p. of mixture</td>
</tr>
<tr>
<td>4.</td>
<td>7-methyl</td>
<td>yield</td>
<td>256-65°</td>
</tr>
<tr>
<td>5.</td>
<td>5-chloro</td>
<td>total</td>
<td>m.p. of mixture</td>
</tr>
<tr>
<td>6.</td>
<td>7-chloro</td>
<td>37.8</td>
<td>246-59°</td>
</tr>
</tbody>
</table>
### Table XV
4-hydroxy 2-methyl quinoline 3-carboxylic acids

<table>
<thead>
<tr>
<th>No.</th>
<th>Substituent</th>
<th>Yield (%)</th>
<th>M.P.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>unsubstituted</td>
<td>86.0</td>
<td>245°-47°</td>
</tr>
<tr>
<td>2.</td>
<td>6-methyl</td>
<td>92.0</td>
<td>286°</td>
</tr>
<tr>
<td>3.</td>
<td>5-methyl</td>
<td>total yield</td>
<td>m.p. of mixture</td>
</tr>
<tr>
<td>4.</td>
<td>7-methyl</td>
<td>94.0</td>
<td>276°-83°</td>
</tr>
<tr>
<td>5.</td>
<td>5-chloro</td>
<td>total yield</td>
<td>245°-50°</td>
</tr>
<tr>
<td>6.</td>
<td>7-chloro</td>
<td>ratio</td>
<td>279°-80°</td>
</tr>
</tbody>
</table>

### Table XVI
4-hydroxy 2-methyl quinoline

<table>
<thead>
<tr>
<th>No.</th>
<th>Substituent</th>
<th>YIELD (%)</th>
<th>M.P.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>unsubstituted</td>
<td>85.7</td>
<td>230°</td>
</tr>
<tr>
<td>2.</td>
<td>6-methyl</td>
<td>87.0</td>
<td>278°-79°</td>
</tr>
<tr>
<td>3.</td>
<td>5-methyl</td>
<td>ratio</td>
<td>274°</td>
</tr>
<tr>
<td>4.</td>
<td>7-methyl</td>
<td>71:29</td>
<td>260°</td>
</tr>
<tr>
<td>5.</td>
<td>5-chloro</td>
<td>74.0</td>
<td>260°-62°</td>
</tr>
<tr>
<td>6.</td>
<td>7-chloro</td>
<td>75.0</td>
<td>312°</td>
</tr>
</tbody>
</table>
8. Cyclisation of ethyl-β-((p-acetamido anilino) and ethyl-β-((m-acetamido anilino) crotonates obtained from ethyl acetoacetate and p- and m-amino acetanilides:

Cyclisation was carried out as usual. Ethyl-β-(p-acetamido anilino) crotonate on cyclisation gives 4-hydroxy 2-methyl 6-acetamido quinoline (LXXVII, \( R_1 = R_3 = H \); \( R_2 = \text{NHCOCH}_3 \)) which when hydrolysed by boiling with 25% hydrochloric acid gives 4-hydroxy 2-methyl 6-amino quinoline (LXXVII, \( R_1 = R_3 = H \); \( R_2 = \text{NH}_2 \)) (Kermack, loc.cit.; Pratt and Archer, loc.cit.).

Ethyl-β-(m-acetamido anilino) crotonate on cyclisation gives only the 5-isomer viz. 4-hydroxy 2-methyl 5-acetamido quinoline (LXXVII, \( R_1 = \text{NHCOCH}_3 \); \( R_2 = R_3 = H \)). The thermal method is also reported to give only the 5-isomer (Kermack and Webster, loc.cit.). On hydrolysis, it gives 4-hydroxy 2-methyl 5-amino quinoline (LXXVII, \( R_1 = \text{NH}_2 \); \( R_2 = R_3 = H \)).

The following two 4-chloro quinolines were prepared:

(i) 4-chloro 2-methyl 6-acetamido quinoline

(LXXVIII, \( R = \text{NHCOCH}_3 \))
(ii) 4-chloro 2-methyl 6-amino quinoline

( LXXVIII, R = NH$_2$ )

Table XVII gives the yields and m.p.s of the 4-hydroxy quinolines and their 4-chloro derivatives.

<table>
<thead>
<tr>
<th>No.</th>
<th>Substituent</th>
<th>Yield (%)</th>
<th>M.P.</th>
<th>Yield (%)</th>
<th>M.P.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>6-acetamido</td>
<td>56.6</td>
<td>364$^\circ$</td>
<td>87.0</td>
<td>209-10$^\circ$</td>
</tr>
<tr>
<td>2.</td>
<td>6-amino</td>
<td>95.0</td>
<td>345$^\circ$</td>
<td>91.0</td>
<td>144-45$^\circ$</td>
</tr>
<tr>
<td>3.</td>
<td>5-acetamido</td>
<td>37.0</td>
<td>236$^\circ$</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4.</td>
<td>5-amino</td>
<td>86.5</td>
<td>200$^\circ$</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

1. Kermack and Webster (loc.cit.) give m.p. 210$^\circ$ C.
Phenanthrolines:

In continuation of the work on 4-hydroxy quinoline derivatives, it was thought of interest to prepare p-phenanthroline derivatives containing two hydroxyl groups, where there is a possibility of introducing two basic side-chains.

P-phenylenediamine can react with two moles of ethyl acetoacetate to give the intermediate ethyl-p-phenylene-bis-p-amino crotonate (L) (Backeberg, loc.cit.).

It was thought interesting to see whether p-phenanthroline derivatives could be obtained by means of a double cyclisation of the intermediate crotonate (L), which has not been cyclised so far.

Attempts to cyclise this compound with the use of acetic anhydride and sulphuric acid were not successful. It was therefore thought interesting to explore the Price-Roberts' synthesis as the Conrad-Limpach synthesis has been reported to fail in such cases where double cyclisation is involved (Kermack and Douglas, loc.cit.).

It was found that cyclisation proceeded smoothly to give a compound which melted at 345°C. The melting point
reported for 4-hydroxy 2-methyl 6-amino quinoline is also 345°C. The possibility that the latter compound might have been formed by rupture of one of the two crotonic ester-chains was eliminated by a synthesis of 4-hydroxy 2-methyl 6-amino quinoline, mixed melting point of which with the present compound was 290°C.

The product obtained was 4:5 dihydroxy 2:7 dimethyl p-phenanthroline (LXXIX), which yielded 4:5 dichloro 2:7 dimethyl p-phenanthroline (LXXX) on treatment with phosphorous oxychloride, the melting point of which was 184-85°C in contrast to the melting point 145°C of 4-chloro 2-methyl 6-amino quinoline

![Chemical structures](LXXIX) ![Chemical structures](LXXX)

The possibility that the new compound might be the isomeric linear diazaanthracene derivative (LXXXI) and
not the angular \( p \)-phenanthroline derivative (LXXXI) may be neglected in view of the large mass of evidence which shows that an angular structure is formed in preference to the linear one when both are possible products of a reaction (Hellmann and Schmidt, loc.cit.; Kermack et al, loc.cit.; Von Braun and Gruber, loc.cit.; Skraup and Vortmann, loc.cit.).

Further evidence about the structure of the compound (LXXXI) was provided by its synthesis from 4-hydroxy 2-methyl 6-amino quinoline and ethyl acetoacetate.

4-hydroxy 2-methyl 6-amino quinoline was condensed with ethyl acetoacetate giving ethyl-\( \beta \)-[6'--(4-hydroxy 2-methyl quinolyl) amino]-crotonate (LXXXII)
Cyclisation by the thermal method afforded 4:5 dihydroxy 2:7 dimethyl p-phenanthroline (LXXIX) identical with the one obtained from p-phenylenediamine and ethyl acetoacetate by double cyclisation of the intermediate crotonate.

Further work on similar lines with o- and m-phenylenediamines and ethyl acetoacetate as well as other \(\beta\)-keto esters is in progress with a view to prepare other phenanthroline derivatives.
The following comparative assessment is made:

(i) As compared to the thermal method, this method has proved more successful for the cyclisation of the acrylates obtained from ethyl acetoacetate, ethyl benzoylacetoacetate and ethyl benzoyletacetate, particularly the last one, starting with which 2-phenyl 4-hydroxy quinolines are obtained in better yields as compared to the thermal method. It may be added that 2-phenyl 4-chloro quinolines which are obtained in excellent yields (Bangdiwala and Desai, loc.cit.) from the corresponding 2-phenyl 4-hydroxy quinolines, find important use as intermediates for the synthesis of antimalarial drugs (Drake et al., loc.cit.).

(ii) With ethyl benzoyletacetate and m-chloroaniline, cyclisation of the intermediate acrylate gives only 4-hydroxy 2-phenyl 7-chloro quinoline, deacetylation having taken place during cyclisation.

(iii) The above 4-hydroxy 2-phenyl quinolines have also been obtained by Elderfield et al (loc.cit.) using the imido-chloride method devised by Just (loc.cit.) and used by Shah and Heeramaneck (loc.cit.), as also employing derivatives.
of anthranilic acid and diethyl acetal of acetophenone
(Fuson and Burness, loc. cit.). However, the synthesis of
4-hydroxy 2-phenyl quinolines from ethyl benzoylcyano-
acetate and aryl amines constitutes comparatively a more
direct route, giving improved yields. By the present method,
the cyano derivatives could not be isolated but by the
thermal method there is scope for the preparation of 3-
cyano derivatives.

Nevertheless, it appears that the synthesis of
4-hydroxy 2-phenyl quinolines starting with ethyl benzoyl-
acetate and arylamines and cyclising the intermediate acry-
lates obtained therefrom offers a general and convenient
method both as regards the ease of ring closure and the
yields of the products.
EXPERIMENTAL

PART I
EXPERIMENTAL

PART I

(1) Syntheses with Ethyl benzoylacetae:

Preparation of ethyl benzoylacetae:

(i) Preparation of ethyl benzoylaetosacetate:

For preparing this ester, the method given by Shriner, Schmidt and Roll (Org. Syn. Vol. XVIII, p. 33) was employed with some useful modifications. The method with the modifications is described below:

Pulverization of sodium:

Clean freshly cut sodium (13.8 g. = 0.6 gm. mol) was suspended in a litre round-bottom flask under pure dry xylene (400 c.c.). The flask was fitted with a reflux condenser and the contents heated to the boiling temperature of xylene on a sand-bath. When all the sodium had melted, the flask was removed, cooled slightly and then the contents were vigorously circularly stirred mechanically. By this process, all the sodium solidified on cooling in an extremely pulverized form. The xylene was decanted and the sodium washed with two fifty c.c. portions of dry benzene.
Preparation of the ester:

In a three litre three-necked flask, fitted with a liquid sealed mechanical stirrer, an efficient reflux condenser and a two hundred c.c. dropping funnel, the latter two being protected from moisture by calcium chloride-U-tubes, were placed pulverized sodium (13.8 g.), dry benzene (distilled over sodium) (1360 c.c.) and ethyl acetoacetate (78 g. = 0.6 mole). The reaction started immediately. The mixture was heated on a steam-bath with stirring and allowed to reflux gently for eight hours (by the use of pulverized sodium, the time of the formation of ethyl sodioacetoacetate is was reduced to one-third the period reported by Shriner et al (loc.cit.) ). After the suspension of ethyl sodioacetoacetate had cooled slightly, benzoyl chloride (66 c.c., slightly less than the theoretical quantity 0.6 mole i.e. 84.3 g. = 69.7 c.c. -density 1.209) was added from the dropping funnel over a period of two hours. The mixture was refluxed with stirring for an additional eight hours. It was then cooled to room temperature and filtered. The filtrate was dried with anhydrous magnesium sulphate and the benzene was dis-
tilled on an oil-bath (external temperature not exceeding 105°C). (Shriner et al., loc. cit. recommend washing the benzene containing ethyl benzoylacetoacetate with water and then with a 5% solution of sodium bicarbonate. The washing process has been avoided in the present method as it has been experienced that during such a washing, there are chances of the acetyl group of the ester being partially hydrolysed. For this reason only, a slightly less than the theoretical quantity of benzoyl chloride was employed). The residue was distilled in vacuo from a five hundred c.c. Claisen flask with a fifty cm. fractionating side-arm. The fraction boiling at 176–182°C at 20 mm. was collected. Yield: 77 g. (55.1%). The reaction is represented as follows:

\[
\text{CH}_3\text{COCH}_2\text{COOC}_2\text{H}_5 + \text{Na} \rightarrow \text{CH}_3\text{COCH}_(\text{Na}) \cdot \text{COOC}_2\text{H}_5 + \text{H}
\]

\[
\text{CH}_3\text{COCH}_(\text{Na}) \cdot \text{COOC}_2\text{H}_5 + \text{C}_6\text{H}_5\text{COCl} \rightarrow \text{CH}_3\text{CO} \cdot \text{CH} \cdot \text{COOC}_2\text{H}_5 + \text{NaCl}
\]

(ii) Hydrolysis of ethyl benzoylacetoacetate:

32 g. (0.3 mole) of ammonium chloride were dissolved in 75 c.c. (4.15 moles) of water in a 250 c.c. flask and 5 c.c. (0.075 mole) of ammonia (sp. gr. 0.9) were added to it.
After the solution was warmed to 42° C, 29.25 g. (0.125 mole) of ethyl benzoylacetoacetate at 20° C was quickly added to it and the mixture shaken. The flask was placed in a water-bath at 42° C for exactly ten minutes and then cooled rapidly by placing in an ice-bath. The solution was extracted twice with fifty c.c. portions of ether and the ether extracts dried with anhydrous magnesium sulphate. After distilling the ether on a water-bath, the residue was distilled in vacuo, and the fraction boiling at 165-170° C at 20 mm. was collected. Yield: 18.0 g. (75 %)

1. Condensation of ethyl benzoylacetoacetate with aniline:

(A) Preparation of ethyl-β-phenyl-β-anilino acrylate:

Ethyl benzoylacetoacetate (9.6 g., 0.15 mole) and aniline (4.6 g., 0.05 mole) were mixed together and a drop of concentrated hydrochloric acid added to it as catalyst. The mixture was kept in a desiccator over calcium chloride for five days. Next, it was taken up in ether (30 c.c.). The ethereal solution was washed twice with dilute hydrochloric acid (0.5 N, 75 c.c.), then with water till free from acid and finally dried with anhydrous magnesium sulphate. Ether was removed
giving an oil. Yield: 7.0 g. (52.7 %)

(B) **Cyclisation of the acrylate:**

(4-hydroxy 2-phenyl quinoline)

The acrylate (7.0 g.) was dissolved in acetic anhydride (20 c.c.) and concentrated sulphuric acid (10 c.c.) was added to it. Considerable heat was developed and the mixture boiled vigorously. After allowing the mixture to cool to room-temperature, it was poured on crushed ice and neutralised with strong sodium hydroxide (40 %). The product which precipitated was filtered, washed with little water and dried. Yield: 3.1 g. (54.0 %). (It can be further purified by dissolving in sodium hydroxide, charcoal, filtering and reprecipitating with acid). It was crystallised from 50 % alcohol in tan yellow needles, m.p. 254 ºC. Mixed m.p. with an authentic specimen of 4-hydroxy 2-phenyl quinoline prepared by the thermal method was undepressed. Hauser and Reynolds (loc. cit.) give m.p. 253-254 ºC, yield: 50 %. Its alcoholic solution gives red colouration with a solution of ferric chloride.

(C) **4-chloro 2-phenyl quinoline:**
4-hydroxy 2-phenyl quinoline (1.0 g.) was refluxed with phosphorous oxychloride (10 c.c.) for twenty minutes. After cooling to 60°C, the mixture was poured on crushed ice (250 g.) and neutralised with strong ammonia. The product separating was collected, washed with water and dried. Yield: 89%. It was crystallised from alcohol, m.p. 60-62°C. (Found: Cl, 14.9%; C_{10}H_{10}NCl requires: Cl, 14.8%)

2. Condensation of ethyl benzoylacetate with o-toluidine:

(A) Ethyl-β-phenyl-β-(o-toluidino) acrylate:

Ethyl benzoylacetate (9.6 g., 0.05 mole) and o-toluidine (5.3 g., 0.05 mole) were condensed together as before and the acrylate purified as before. Yield: 6.0 g. (42.6%).

(B) 4-hydroxy 2-phenyl 8-methyl quinoline:

The acrylate (6.0 g.) was dissolved in acetic anhydride (20 c.c.) and sulphuric acid (10 c.c.) was added to it. The product was worked up as before. Yield: 3.1 g. (52.8%).

It was crystallised from alcohol in white needles, m.p. 224-25°C. Hauser and Reynolds (loc. cit.) give m.p. 245-46°C, yield: 38.0% (Found: N, 5.8%; C_{16}H_{13}NO requires: N,
It was prepared by refluxing the above quinoline with phosphorous oxychloride. Yield: 89.0%. It was crystallised from alcohol, m.p. 82-83°C. (Found: Cl, 14.2%)

C₁₆H₁₂Cl requires: Cl, 14.0%

3. Condensation of ethyl benzoylacetate with m-toluidine:

(A) Ethyl-B-phenyl-B-(m-toluidine) acrylate:

Ethyl benzoylacetate (19.2 g., 0.1 mole) and m-toluidine (10.7 g., 0.1 mole) were condensed together as before. Yield: 15.0 g. (53.3%).

(B) 4-hydroxy 2-phenyl 5- and 7-methyl quinolines:

The acrylate (15.0 g.) was dissolved in acetic anhydride (30 c.c.) and sulphuric acid (15 c.c.) was added to it. The product was worked up as before. Yield: 7.0 g. (56.0%). It was crystallised from alcohol, m.p. 220-40°C. Further crystallisation failed to raise the melting point. It was therefore presumed to be a mixture of isomers. Surprisingly enough, the whole product did not dissolve in dilute sodium hydroxide. It appeared therefore, that one
isomer was soluble in dilute sodium hydroxide, while the
other one was insoluble. Separation was therefore, effected
by using dilute sodium hydroxide.

Separation of the isomers:

The mixture of isomers (7.0 g.) was treated with
dilute sodium hydroxide (10 %, 300 c.c.), warmed and the
solution was filtered.

(1) Residue (4-hydroxy 2-phenyl 7- or 5-methyl quinoline):

It was washed with water and dried (2.8 g., 40 %). It
was crystallised from alcohol in needles, m.p. 261-61 C.
Further crystallisation did not raise the melting point. It
was therefore presumed to be a pure product. (Found: N,
5.9 %; C₁₆H₁₃NO requires: N, 6.0 %). An alcoholic solution
of the substance gave red colouration with a solution of
ferric chloride.

4-chloro 2-phenyl 7- or 5-methyl quinoline:

It was prepared by refluxing the above quinoline
with phosphorous oxychloride. Yield: 84 %. It was crystalli-
from alcohol in white needles, m.p. 80-82 C. (Found: Cl,
13.8 %; C₁₆H₁₂Cl requires: Cl, 14.0 %)
(ii) **Filtrate: (4-hydroxy 2-phenyl 5- or 7-methyl quinoline)**

The filtrate was acidified with concentrated hydrochloric acid. The product separating was collected, washed with water and dried. (4.0 g., 87%). It was crystallised from alcohol in white fluffy needles, m.p. 278° C. Further crystallisation did not raise the melting point. It was therefore presumed to be a pure product. (Found: N, 5.9%; C₁₆H₁₅NO requires: N, 6.0%). Its alcoholic solution gave red colouration with a solution of ferric chloride.

**4-chloro 2-phenyl 5- or 7-methyl quinoline:**

It was prepared by refluxing the above quinoline with phosphorous oxychloride. Yield: 86%. It was crystallised from alcohol, m.p. 66°-67° C. (Found: Cl, 13.8%; C₁₆H₁₂NCl requires: Cl, 14.0%).

4. **Condensation of ethyl benzoylecetate with p-toluidine:**

(A) **Ethyl-β-phenyl-β-(p-toluidino) acrylate:**

Ethyl benzoylecetate (9.3 g., 0.05 mole) and p-toluidine (5.3 g., 0.05 mole) were condensed together as before. Yield: 7.0 g. (49.7%).

(B) **4-hydroxy 2-phenyl 6-methyl quinoline:**
The acrylate (7.0 g.) was dissolved in acetic anhydride (20 c.c.) and sulphuric acid (10 c.c.) was added to it. The product was worked up as before. Yield: 4.74 g. (75.2 %). It was crystallised from alcohol (80 %), m.p. 294-96 °C. (Found: N, 5.8 %. C₁₆H₁₃NO requires: N, 6.0 %)

Its alcoholic solution gave red colouration with a solution of ferric chloride.

(C) 4-chloro 2-phenyl 6-methyl quinoline:

It was prepared by refluxing the above quinoline with phosphorous oxychloride. Yield: 94 %. It was crystallised from alcohol, m.p. 95-97 °C. (Found: Cl, 14.1 %.

C₁₆H₁₂NCl requires: Cl, 14.0 %)

5. Condensation of ethyl benzoyletacetate with m-chloroaniline:

(A) Ethyl-3-phenyl-3-(m-chloroanilino) acrylate:

Ethyl benzoyletacetate (19.2 g., 0.1 mole) and m-chloroaniline (12.7 g., 0.1 mole) were condensed together as before. Yield: 17.0 g. (54.0 %).

(B) 4-hydroxy 2-phenyl 7- and 5-chloro quinolines:

The acrylate (17.0 g.) was dissolved in acetic anhydride (30 c.c.) and sulphuric acid (15 c.c.) was added
to it. The product was worked-up as before. Yield: 5.1 g. (45.7 %). m.p. 250°-60° C. It was therefore presumed to be a mixture of isomers.

Separation of the isomers:

The mixture of isomers (5.0 g.) was treated with alcohol (100 c.c.) and boiled. The solution was filtered hot.

(1) Residue: (4-hydroxy 2-phenyl 7-chloro quinoline)

It is insoluble in alcohol. It was washed with alcohol and dried (0.95 g., 19 %). It was crystallised from glacial acetic acid, m.p. 357°-55° C. Further crystallisation did not raise the melting point. Mixed with an authentic sample of 4-hydroxy 2-phenyl 7-chloro quinoline prepared by the method of Elderfield et al (loc. cit.) using benz-m-chloroanilide imidochloride, the m.p. was 357°-58° C. Elderfield et al (loc. cit.) give m.p. 361°-62° and 355° C. (Found: N, 5.7 %; Cl, 14.1 %; C₁₅H₁₀NOCl requires: N, 5.9 %; Cl, 13.9 %)

4:7 dichloro 2-phenyl quinoline:

It was prepared by refluxing the above quinoline
with phosphorous oxychloride. Yield: 89%. It was crystallised from alcohol, m.p. 99-100° C. Elderfield et al (loc.cit.) give m.p. 99-100.5° C and 101-101.5° C for the compound.

(ii) Filtrate: (4-hydroxy 2-phenyl 5-chloro quinoline)

The filtrate on concentration and cooling gave 4-hydroxy 2-phenyl 5-chloro quinoline (3.9 g., 78%), m.p. 279-280° C. A second crystallisation raised the melting point to 282° C. Further crystallisation failed to raise the melting point. (Found: N, 5.8%; Cl, 14.1%; C₁₅H₁₀NCl₂ requires: N, 5.9%; Cl, 13.9%). Its alcoholic solution gave red colouration with a solution of ferric chloride.

4,6-dichloro 2-phenyl quinoline:

It was prepared by refluxing the above quinoline with phosphorous oxychloride. Yield: 86%. It was crystallised from alcohol, m.p. 102-3° C. (Found: Cl, 26.0%; C₁₅H₁₀NCl₂ requires: Cl, 26.0%). Mixed m.p. with 4,7 dichloro 2-phenyl quinoline was 75-90° C.

6. Condensation of ethyl benzoylacetaete with p-chloroaniline:

(A) Ethyl-p-phenyl-B-(p-chloroanilino) acrylate:

Ethyl benzoylacetaete (9.6 g., 0.05 mole) and p-
chloroaniline (6.3 g., 0.05 mole) were condensed together as before. Yield: 8.0 g. (52.8%).

(B) 4-hydroxy 2-phenyl 6-chloro quinoline:

The acrylate (8.0 g.) was dissolved in acetic anhydride (20 c.c.) and sulphuric acid (10 c.c.) was added to it. The product was worked up as before. Yield: 2.3 g. (33.8%). It was crystallised from glacial acetic acid, m.p. 350-51° C (decom). (Found: N, 5.9%; Cl, 13.8%)

C₁₅H₁₀NOCl requires: N, 5.9%; Cl, 13.9%). Its alcoholic solution gave red colouration with a solution of ferric chloride.

(C) 4,6-dichloro 2-phenyl quinoline:

It was prepared by refluxing the above quinoline with phosphorous oxychloride. Yield: 80%. It was crystallised from alcohol, m.p. 118-20° C. (Found: Cl, 26.2%)

C₁₅H₉NCl₂ requires: Cl, 26.0%)

7. Condensation of ethyl benzoylacetate with o-anisidine:

(A) Ethyl-β-phenyl-β-(o-anisidino) acrylate:

Ethyl benzoylacetate (9.6 g., 0.05 mole) and β-o-anisidine (6.1 g., 0.05 mole) were condensed together as
before. Yield: 6.9 g. (46.5 %)

(B) 4-hydroxy 2-phenyl 8-methoxy quinoline:

The acrylate (6.9 g.) was dissolved in acetic anhydride (20 c.c.) and sulphuric acid (10 c.c.) was added to it. The product was worked up as before. Yield: 2.1 g. (35.7 %). It was crystallised from alcohol, m.p. 262-63 °C.

(Found: N, 5.5 %; C₁₆H₁₅NO₂ requires: N, 5.6 %). Its alcoholic solution gave red colouration with a solution of ferric chloride.

(C) 4-chloro 2-phenyl 8-methoxy quinoline:

It was prepared by refluxing the above quinoline with phosphorous oxychloride. Yield: 84 %. It was crystallised from alcohol, m.p. 179 °C. (Found: Cl, 13.0 %)

C₁₆H₁₅NOCl requires: Cl, 13.1 %)

8. Condensation of ethyl benzoylacetate with p-anisidine:

(A) Ethyl-3-phenyl-3-(p-anisidino) acrylate:

Ethyl benzoylacetate (9.6 g., 0.05 mole) and p-anisidine (6.1 g., 0.05 mole) were condensed together as before. Yield: 7.0 g. (47.3 %).

(B) 4-hydroxy 2-phenyl 6-methoxy quinoline:
The acrylate (7.0 g.) was dissolved in acetic anhydride (20 c.c.) and sulphuric acid (10 c.c.) was added to it. The product was worked up as before. Yield: 4.0 g. (67.0 %). It was crystallised from alcohol, m.p. 306°-7°C. Elderfield et al. (loc.cit.) give m.p. 287°-90°C. (Found: N, 5.6 %; C₁₈H₁₅NO₂ requires: N, 5.6 %). Its alcoholic solution gave red colouration with a solution of ferric chloride.

(C) 4-chloro 2-phenyl 6-methoxy quinoline:

It was prepared by refluxing the above quinoline with phosphorous oxychloride. Yield: 90 %. It was crystallised from alcohol, m.p. 109°-10°C. Elderfield et al. (loc.cit.) also give m.p. 109°-10°C. (Found: Cl, 13.0 %; C₁₆H₁₂ClNO requires: Cl, 13.1 %).

9. Condensation of ethyl benzoylacetae with p-phenetidine:

(A) Ethyl-β-phenyl-β-(p-phenetidino) acrylate:

Ethyl benzoylacetae (9.6 g., 0.05 mole) and p-phenetidine (6.8 g., 0.05 mole) were condensed together as before. Yield: 8.7 g. (57.1 %).

(B) 4-hydroxy 2-phenyl 6-ethoxy quinoline:
The acrylate (8.7 g.) was dissolved in acetic anhydride (20 c.c.) and sulphuric acid (10 c.c.) was added to it. The product was worked up as before. Yield: 4.2 g. (57.3%). It was crystallised from alcohol, m.p. 285°C.

(Found: N, 5.1%; C_{17}H_{15}NO_{2} requires: N, 5.3%). Its alcoholic solution gave red colouration with a solution of ferric chloride.

(C) 4-chloro 2-phenyl 6-ethoxy quinoline:

It was prepared by refluxing the above quinoline with phosphorous oxychloride. Yield: 86%. It was crystallised from alcohol, m.p. 130°C.

10. Condensation of ethyl benzoylacetaete with 1:3:4-xyldine:

(A) Ethyl-2-phenyl-2-(1:3:4-xyldino) acrylate:

Ethyl benzoylacetaete (9.6 g., 0.05 mole) and 1:3:4-xyldine (6.05 g., 0.05 mole) were condensed together as before. Yield: 8.0 g. (54.4%)

(B) 4-hydroxy 2-phenyl 6:8 dimethyl quinoline:

The acrylate (8.0 g.) was dissolved in acetic anhydride (20 c.c.) and sulphuric acid (10 c.c.) was added to it. The product was worked up as before. Yield: 3.1 g.
(46.3 %). It was crystallised from alcohol, m.p. 231-32° C.

(Found: N, 5.5 %; C₁₇H₁₅NO requires: N, 5.6 %). Its alcoholic solution gave red colouration with a solution of ferric chloride.

(C) 4-chloro 2-phenyl 6:8 dimethyl quinoline:

It was prepared by refluxing the above quinoline with phosphorous oxychloride. Yield: 79 %. It was crystallised from alcohol, m.p. 81° C. (Found: Cl, 13.3 %; C₁₇H₁₄NCl requires: Cl, 13.2 %)

11. Condensation of ethyl benzoylacetate with 1:4:5-xylidine:

(A) Ethyl-β-phenyl-β-(1:4:5-xylidine) acrylate:

Ethyl benzoylacetate (9.6 g., 0.05 mole) and 1:4:5-xylidine (6.05 g., 0.05 mole) were condensed together as before. Yield: 7.9 g. (54.0 %)

(B) 4-hydroxy 2-phenyl 5:8 dimethyl quinoline:

The acrylate (7.9 g.) was dissolved in acetic anhydride (20 c.c.) and sulphuric acid (10 c.c.) was added to it. The product was worked up as before. Yield: 2.4 g. (35.8 %). It was crystallised from alcohol, m.p. 187° C.

(Found: N, 5.4 %; C₁₇H₁₅NO requires: N, 5.6 %). Its alco-
holic solution gave red colouration with a solution of ferric chloride.

(C) 4-chloro 2-phenyl 5:8 dimethyl quinoline:

It was prepared by refluxing the above quinoline with phosphorous oxychloride. Yield: 81 %. It was crystallised from alcohol, m.p. 89 °C. (Found: Cl, 13.0 %)

C_{17}H_{14}Cl requires: Cl, 13.2 %)

12. Condensation of ethyl benzoylacete with 2-naphthylamine:

(A) Ethyl-β-phenyl-2-(2-naphthylamino) acrylate:

Ethyl benzoylacetate (9.6 g., 0.05 mole) and 2-naphthylamine (7.15 g., 0.05 mole) were condensed to-gether as before. Yield: 6.4 g. (40.5 %)

(B) 4-hydroxy 3-phenyl benzo 5:6 quinoline:

The acrylate (6.4 g.) was dissolved in acetic anhydride (20 c.c.) and sulphuric acid (10 c.c.) was added to it. The product was worked up as before. Yield: 1.7 g. (51.4 %). It was crystallised from alcohol, m.p.>300° C(dec)

(Found: N, 5.3 %; C_{19}H_{14}NO requires: N, 5.4 %) Its alcoholic solution gave red colouration with a solution of ferric chloride.
(C) 1-chloro 3-phenyl benzo 5:6 quinoline

It was prepared by refluxing the above quinoline with phosphorous oxychloride. Yield: 92 %. It was crystallised from alcohol, m.p. 114-15 °C. (Found: Cl, 13.0 %; C_{19}H_{13}Cl requires: Cl, 12.8 %)
(II) Syntheses with Ethyl benzoylacetoacetate:

Preparation of ethyl benzoylacetoacetate:

Please refer to p.126, this vol.

1. Condensation with aniline:

(A) Ethyl-α-benzoyl-β-anilino crotonate:

Ethyl benzoylacetoacetate (23.4 g., 0.1 mole) and redistilled aniline (9.3 g., 0.1 mole) were mixed together and a drop of concentrated hydrochloric acid added to it as catalyst. The mixture was heated on a steam-bath for one hour with an air-condenser, cooled and left in a desiccator over calcium chloride for forty-eight hours. The turbidity, indicating the separation of water, which appeared some time after the reactants were mixed disappeared completely. The crude crotonate was dissolved in ether (100 c.c.) and the ethereal solution was washed with two fifty c.c. portions of 0.5 N hydrochloric acid, then with five fifty c.c. portions of water till it was free from acid and finally dried with anhydrous magnesium sulphate. Ether was removed, giving an oil. Yield: 18.0 g. (58.9%)

(B) Cyclisation of the crotonate:
The crotonate (8.7 g.) was dissolved in acetic anhydride (20 c.c.) and sulphuric acid (10 c.c.) was added to it. Considerable heat was developed and the mixture boiled vigourously. The mixture was shaken continually for five minutes. After it had cooled to room temperature, it was poured on crushed ice (300 g.) and neutralised with strong sodium hydroxide (40 %), when precipitates were obtained. The solution was allowed to stand for two hours at room temperature and the product was filtered, washed with water and dried. Yield: 2.6 g. (48.1 %). m.p. 279-80 °C. It was crystallised from 60 % alcohol in yellow needles, m.p. 284 °C. Mixed with an authentic specimen of 4-hydroxy 2-methyl 3-benzoyl quinoline prepared by Friedel-Crafts benzoylation of 4-hydroxy 2-methyl quinoline, the melting point was 284 °C.

Friedel-Crafts benzoylation of 4-hydroxy 2-methyl quinoline:

4-hydroxy 2-methyl quinoline (1.2 g.) and anhydrous aluminium chloride (3.0 g., 2 moles) were thoroughly mixed
and benzoyl chloride (1.2 c.c.) was added to it. The mixture was heated on an oil-bath at 155–60° C, with an air-condenser and a calcium chloride U-tube for three hours. It was then cooled. Ice (60 g.) and concentrated hydrochloric acid (3 c.c.) were added to it and the mixture left overnight. Next day, the solid separating was collected, washed with water (100 c.c.), a 5% solution of sodium carbonate (25 c.c.) and finally with boiling water (300 c.c.) and dried (0.99 g.– 60%). It was crystallised from alcohol (60%) in yellow needles, m.p. 284° C. (Found: N, 5.2%; C_{17}H_{13}NO_2 requires: N, 5.3%)

Preparation of Oxime:

Hydroxylamine hydrochloride (0.5 g.) and crystallised sodium acetate (1 g.) were dissolved in water (5 c.c.). To this a warm solution of 4-hydroxy 2-methyl 3-benzoyl quinoline (0.263 g.) in alcohol (18 c.c.) was added and the mixture gently heated on a water-bath for one hour. After cooling, water (100 c.c.) was added to it and the precipitates of the oxime were collected, washed with water and dried (0.2 g.). It was crystallised from alcohol in white needles,
m.p. 253°-54° C. (Found: N, 10.0 %; C\textsubscript{17}H\textsubscript{14}O\textsubscript{2}N\textsubscript{2} requires: N, 10.1 %)

Preparation of 2:4 dinitrophenyl hydrazone:

4-hydroxy 2-methyl 3-benzoyl quinoline (0.26 g.) in 50 % acetic acid (10 c.c.) was boiled with a solution of 2:4 dinitrophenyl hydrazone (0.15 g.) in 50 % acetic acid (15 c.c.) for ten minutes. The mixture was cooled and diluted with water. The hydrazone was collected, washed with water (250 c.c.) and dried. It was crystallised from glacial acetic acid, m.p. >310° C. (Found: N, 15.6 %; C\textsubscript{23}H\textsubscript{17}O\textsubscript{5}N\textsubscript{5} requires: N, 15.8 %)

(ii) The thermal method:

(4-hydroxy 2-methyl 3-benzoyl quinoline)

The crotonate (8.7 g.) was added to boiling diphenyl ether (87 c.c.) over a period of ten minutes. The mixture was boiled for an additional fifteen minutes and left overnight. Next day, the mixture was diluted with petroleum ether (250 c.c.) and the product was filtered. Yield: 2.1 g. (39.0 %). It was crystallised from 60 % alcohol, m.p. 284° C, undepressed by an authentic specimen of
4-hydroxy 2-methyl 3-benzoyl quinoline prepared by Friedel-Crafts benzoylation of 4-hydroxy 2-methyl quinoline. The isomeric 4-hydroxy 2-phenyl 3-acetyl quinoline could not be isolated as reported by Shah et al (loc. cit.).

2. Condensation with o-toluidine:

(A) Ethyl-α-benzoyl-β-(o-toluidino) crotonate:

Ethyl benzoylacetoacetate (11.7 g., 0.05 mole) and o-toluidine-freshly distilled (5.3 g., 0.05 mole) were condensed together as before. Yield: 3.0 g. (49.5%).

(B) Cyclisation of the crotonate:

(i) The present method:

(4-hydroxy 2:8 dimethyl 3-benzoyl quinoline)

(8.0 g.)
The crotonate was dissolved in acetic anhydride (20 c.c.) and sulphuric acid (10 c.c.) was added to it. The product was worked up as before. Yield: 2.0 g. (30.1%). It was crystallised from glacial acetic acid, m.p. 297°-98° C.

Mixed m.p. with an authentic specimen of 4-hydroxy 2:8 dimethyl 3-benzoyl quinoline prepared by Friedel-Crafts benzoylation of 4-hydroxy 2:8 dimethyl quinoline was undepressed.
**Friedel-Crafts benzoylation of 4-hydroxy 2:8 dimethyl quinoline.**

4-hydroxy 2:8 dimethyl quinoline (1.2 g.) and anhydrous aluminium chloride (3.0 g., 2 moles) were mixed thoroughly and benzoyl chloride (1.1 c.c.) was added to it. The mixture was heated on an oil-bath at 155–60°C for three hours. The product was worked up as before. Yield: 1.0 g.

It was crystallised from glacial acetic acid, m.p. 297–98°C. Shah et al. (loc. cit.) give m.p. 289°C for the product.

(Found: N, 5.0%; C_{18}H_{15}NO. requires: N, 5.1%)

2:4 dinitrophenyl hydrazone was prepared as before. It was crystallised from glacial acetic acid, m.p. >320°C.

(ii) **The thermal method:**

The crotonate (8.0 g.) was cyclised by adding in boiling diphenyl ether (80 c.c.) and the product worked up as before. Yield: 1.3 g. (20.0%). It was crystallised from glacial acetic acid in yellow needles, m.p. 297–98°C, unde-pressed by an authentic specimen of 4-hydroxy 2:8 dimethyl 3-benzoyl quinoline prepared by Friedel-Crafts benzoylation of 4-hydroxy 2:8 dimethyl quinoline.

3. **Condensation with p-toluidine:**
(A) Ethyl-α-acetyls-β-phenyl-β-(p-toluidine) acrylate:

Ethyl benzoylacetoacetate (11.7 g., 0.05 mole) and p-toluidine (5.3 g., 0.05 mole) were condensed together as before. Yield: 9.0 g. (55.7 %)

(B) Cyclisation of the acrylate:

(i) The present method:

(4-hydroxy 2-phenyl 6-methyl quinoline)

The acrylate (9.0 g.) was dissolved in acetic anhydride (20 c.c.) and sulphuric acid (10 v.c.) was added to it. The product was worked up as before. Yield: 3.7 g. (54.4 %). It was crystallised from 80 % alcohol, m.p. 294-95 °C, undepressed by an authentic specimen of 4-hydroxy 2-phenyl 6-methyl quinoline prepared from ethyl benzoylacetoacetate and p-toluidine (loc.cit.)

4-chloro 2-phenyl 6-methyl quinoline prepared from the above compound melted at 95-97 °C (loc.cit.)

(ii) The thermal method:

(4-hydroxy 2-phenyl 3-acetyl 6-methyl quinoline)

The acrylate (9.0 g.) was cyclised by adding in boiling diphenyl ether (90 c.c.) and the product worked up
as before. Yield: 2.9 g. (40.0 %). It was crystallised from alcohol in white fluffy needles, m.p. 263 °C. Mixed m.p.

with an authentic specimen of 4-hydroxy 2-phenyl 3-acetyl 6-methyl quinoline prepared from benz-p-toluidide and ethyl sodioacetoacetate (Desai and Shah, loc.cit.) was undepressed.

2:4 dinitrophenyl hydrazone was prepared as before. It was crystallised from glacial acetic acid, m.p. >320 °C.

Shah et al (loc.cit.), however, have reported the formation of 4-hydroxy 2:6 dimethyl 3-benzoyl quinoline (m.p. >290 °C) in this case.

4. Condensation with m-toluidine:

(A) Ethyl benzoylacetoacetate (23.4 g., 0.1 mole) and m-toluidine (10.7 g., 0.1 mole) were condensed together as before. Yield: 16.0 g. (49.6 %)

(B) Cyclisation of the acrylate:

(i) The present method:

The acrylate (16.0 g.) was dissolved in acetic anhydride (30 c.c.) and sulphuric acid (15 c.c.) was added
to it. The product was worked up as before. Yield: 3.0 g. (21.6 %). It was crystallised from alcohol, m.p. 220°-30° C.

On two crystallisations from alcohol, the melting point was not raised. It was therefore presumed to be a mixture of isomers.

Separation of one product (m.p. 261° C) as oxalate:

The above mixture of products (3.0 g.) was dissolved in alcohol (20 c.c.). To this was added a boiling solution of oxalic acid (1.0 g.) in alcohol (10 c.c.). The solution was allowed to cool. On standing, the product which separated was filtered (0.8 g.). m.p. 194°-95° C (decom). It was crystallised from alcohol, m.p. 201° C (decom).

The oxalate (0.6 g.) was decomposed by boiling with a 25 % solution of sodium hydroxide (10 c.c.) and the product precipitated with 50 % hydrochloric acid. It was crystallised from alcohol, m.p. 260°-61° C. It was soluble in sodium hydroxide. Its alcoholic solution did not give colouration with a solution of ferric chloride. Its mixed m.p. with a specimen of 4-hydroxy 2-phenyl 7-
or 5-methyl quinoline (m.p. 261-62° C) prepared from ethyl benzoylacetaete and m-toluidine (loc.cit.) was undepressed. But the latter compound in contrast to the present product is insoluble in sodium hydroxide and its alcoholic solution gives red colouration with a solution of ferric chloride. Also, its mixed m.p. with an authentic specimen of 4-hydroxy 2:5 dimethyl 3-benzoyl quinoline prepared by Friedel-Crafts benzoylation of 4-hydroxy 2:5 dimethyl quinoline was depressed. It may be therefore, 4-hydroxy 2:7 dimethyl 3-benzoyl quinoline, though this has not yet been definitely established. (Found: N, 5.4%; C<sub>18</sub>H<sub>15</sub>NO requires: N, 5.1%)

(ii) The thermal method:

The acrylate (8.0 g.) was cyclised by adding in boiling diphenyl ether (80 c.c.). The product was worked up as before. It could be purified with difficulty. Yield: 1.4 g. (20.2%). It was crystallised from alcohol, m.p. 235-42° C. Repeated crystallisations failed to raise the m.p. It was therefore presumed to be a mixture of isomers. Attempts to separate the isomers by fractional crystallisations from alcohol, acetic acid etc., as also by oxalate formation.
were unsuccessful. No pure product could be isolated in any case.

5. Condensation with \( m \)-chloroaniline:

(A) Ethyl-\( \alpha \)-acetyl-\( \beta \)-phenyl-\( \beta \)-(\( m \)-chloroanilino) acrylate:

Ethyl benzoylacetoacetate (23.4 g., 0.1 mole) and \( m \)-chloroaniline (12.7 g., 0.1 mole) were condensed as before. Yield: 17.0 g. (49.0 %).

(B) Cyclisation of the acrylate:

(I) The present method:

(4-hydroxy 2-phenyl \( 7 \)-chloro quinoline)

The acrylate (17.0 g.) was dissolved in acetic anhydride (30 c.c.) and sulphuric acid (15 c.c.) was added to it. The product was worked up as before. Yield: 2.6 g. (20.0 %). It was crystallised from glacial acetic acid, m.p. 357°-358° C. Mixed m.p. with an authentic specimen of 4-hydroxy 2-phenyl \( 7 \)-chloro quinoline prepared from ethyl benzoylacetoacetate and \( m \)-chloroaniline (loc.cit.) was undepressed.

4:7 dichloro 2-phenyl quinoline prepared from the above compound melted at 99°-100° C.
(ii) The thermal method:

(4-hydroxy 2-phenyl 3-acetyl 5- or 7-chloro quinoline)

The acrylate (8.0 g.) was cyclised by adding in boiling diphenyl ether (80 c.c.). The product was worked up as before. Yield: 2.6 g., (44.0 %). It was crystallised from alcohol, m.p. 312°-13° C. The m.p. was sharp and was not raised by further crystallisation from alcohol or acetic acid. It was therefore presumed to be one isomer only.

(Found: N, 4.5 %; Cl, 11.6 %; C$_{17}$H$_{12}$NO$_2$Cl requires: N, 4.7 %; Cl, 11.7 %). Since by the present method 4-hydroxy 2-phenyl 7-chloro quinoline is obtained, deacetylation of the anil must have taken place and hence anil formation must have taken place with the benzoyl group of the ester. This product may be therefore 4-hydroxy 2-phenyl 3-acetyl 5- or 7-chloro quinoline.

4:5 or 4:7 dichloro 2-phenyl 3-acetyl quinoline:

It was prepared by refluxing the above quinoline with phosphorous oxychloride. Yield: 66.0 %. It was crystallised from alcohol, m.p. 125° C. (Found: Cl, 22.2 %; C$_{17}$H$_{11}$NOCl$_2$ requires: Cl, 22.5 %).
2:4 dinitrophenyl hydrazone was prepared as before. It was crystallised from glacial acetic acid, m.p. 

> 320°C.
(III) Syntheses with Ethyl benzoylemalonate:

Preparation of ethyl benzoylemalonate:

It was prepared essentially according to the method described for the preparation of ethyl benzoylacetoacetate (p. 126, this vol.) except in that ethyl acetoacetate was replaced by diethyl malonate. The yield of ethyl benzoyle malonate was 90 g. (56.8%) starting with 96 g., i.e., 0.6 mole of diethyl malonate. The reactions involved are:

\[ \text{CH}_2(\text{COOC}_2\text{H}_5)_2 + \text{Na} \rightarrow \text{CH} - (\text{COOC}_2\text{H}_5)_2 + \text{H} \]

\[ \text{Na} \]

\[ \text{CH} - (\text{COOC}_2\text{H}_5)_2 + \text{C}_6\text{H}_5\text{COCl} \rightarrow \text{C}_6\text{H}_5\text{CO.CH} (\text{COOC}_2\text{H}_5)_2 \]

\[ \text{Na} \]

\[ + \text{NaCl} \]

1. Condensation with aniline:

(A) Ethyl-\(\alpha\)-carboxethoxy-\(\beta\)-phenyl-\(\beta\)-anilino acrylate:

Ethyl benzoylemalonate (26.4 g., 0.1 mole) and freshly distilled aniline (9.3 g., 0.1 mole) were mixed together and a drop of concentrated hydrochloric acid was added to it as catalyst. The mixture was allowed to stand at room temperature for three days. Crystals of benzanilide
which had separated were filtered off and the oil was
taken up in ether (100 c.c.). The ethereal solution was
washed with two fifty c.c. portions of 0.5 N hydrochloric
acid, then with five fifty c.c. portions of water till free
from acid and finally dried with anhydrous magnesium sulph-
ate. Ether was removed and the residual oil on keeping for
twenty-four hours in a dessicator, crystallised. Yield:
13.0 g. (38.0 %). M.P. 74°-75° C. Shah and Heeramaneck (loc.
cit.) give m.p. 75° C. (Found: N, 4.0 %; C_{20}H_{21}O_{4}N requires: N, 4.1 %).

(B) Ethyl 4-hydroxy 2-phenyl quinoline 3-carboxylate:

The acrylate (13.0 g.) was dissolved in acetic
anhydride (25 c.c.) and sulphuric acid (12 c.c.) was added
to it. Considerable heat was developed. The mixture was allo-
wed to cool to room temperature. It was then poured on ice
and then just neutralised with sodium hydroxide, employing
sodium carbonate towards the end-point. The solution was
scratched and the product separating was collected, washed
with water and dried. Yield: 3.1 g. (27.7 %). It was crys-
tallised from alcohol in needles, m.p. 260°-61° C. Shah and
Heeramanek (loc.cit.) give m.p. 260°C. (Found: N, 4.6%)

C_{18}H_{15}O_{3}N requires: N, 4.8%.

(C) 4-hydroxy 2-phenyl 3-carboxylic acid:

The above ester (3.0 g.) was refluxed with 5% sodium hydroxide (40 c.c.) for two hours. The mixture was cooled and acidified with 50% hydrochloric acid. The product was filtered, washed with water and dried. Yield: 2.0 g. (74.0%). It was crystallised from 60% alcohol, m.p. 230°-32°C. Shah and Heeramanek (loc.cit.) give m.p. 230°-32°C. (Found: N, 5.1%; C_{16}H_{11}O_{3}N requires: N, 5.3%).

(D) 4-hydroxy 2-phenyl quinoline:

The above acid (2.0 g.) was added with stirring to mineral oil (20 c.c.) preheated to 275°C, and the temperature was maintained at 270-75°C for five minutes. The oil containing the product was cooled, diluted with petroleum ether and scratched. The product was collected and dried. Yield: 1.2 g. (75.0%). It was crystallised from 60% alcohol in tan yellow needles, m.p. 254°C. Mixed m.p. with an authentic specimen of 4-hydroxy 2-phenyl quinoline prepared from ethyl benzoylacacetate and aniline (loc.cit.) was unde-
pressed.

(E) 4-chloro 2-phenyl quinoline:

It was prepared by refluxing 4-hydroxy 2-phenyl quinoline with phosphorous oxychloride. (loc.cit.). m.p. 60°-62° C

2. Condensation with o-toluidine:

(A) Ethyl-t-carboxethoxy-3-phenyl-3-(o-toluidino) acrylate:

Ethyl benzoylmalonate (26.4 g., 0.1 mole) and freshly distilled o-toluidine (10.7 g., 0.1 mole) were condensed together as before and crystals of benz-o-toluidide were filtered off. The acrylate was purified as before. The pure acrylate crystallised on standing, m.p. 95°-96° C. (reported m.p. 95° C). Yield: 11.0 g. (31.0 %) (Found: N, 4.0 %; C_{21}H_{23}O_{4}N requires: N, 4.0 %).

(B) Ethyl 4-hydroxy 2-phenyl 8-methyl quinoline 3-carboxylate:

The above acrylate (11.0 g.) was dissolved in acetic anhydride (20 c.c. ) and sulphuric acid (10 c.c.) was added to it. The product was worked up as before. Yield: 2.5 g. (26.0 %). It was crystallised from alcohol, m.p. 245°-44° C (reported 242° C). (Found: N, 4.5 %; C_{19}H_{17}O_{3}N)
requires: N, 4.6 %).

(C) 4-hydroxy 2-phenyl 8-methyl quinoline 3-carboxylic acid:

The above ester (2.5 g.) was refluxed with 5 % sodium hydroxide (35 c.c.) for two hours. The product was worked up as before. Yield: 1.9 g. (84.0 %). It was crystallised from aqueous alcohol, m.p. 205-5° C (decom) (reported m.p. 201-3° C). (Found: N, 4.8 %; C₁₇H₁₅O₃N requires: N, 5.0 %).

(D) 4-hydroxy 2-phenyl 8-methyl quinoline:

The above acid (1.9 g.) was added with stirring to mineral oil preheated to 275° C and the temperature was maintained at 270-75° for five minutes. The product was worked up as before. Yield: 1.3 g. (81.0 %). It was crystallised from alcohol in yellowish needles, m.p. 224-25° C. Mixed m.p. with an authentic specimen of 4-hydroxy 2-phenyl 8-methyl quinoline prepared from ethyl benzoylacetate and o-toluidine (loc.cit.) was undepressed.

(E) 4-chloro 2-phenyl 8-methyl quinoline:

It was prepared by refluxing 4-hydroxy 2-phenyl 8-methyl quinoline with phosphorous oxychloride. Yield
3. Condensation with p-toluidine:

(A) Ethyl-α-α-β-phenyl-β-(p-toluidine) acrylate:

Ethyl benzoylmalonate (26.4 g., 0.1 mole) and p-toluidine (10.7 g., 0.1 mole) were condensed together as before, and crystals of benz-p-toluidide were filtered off. The acrylate was purified as before. The pure acrylate crystallised on standing, Yield: 10.0 g. (28.2 %), m.p. 62°-63° C. (reported m.p. 62°-63° C). (Found: N, 4.2 %)

C21H23O4N requires: N, 4.0 %)

(B) Ethyl 4-hydroxy 2-phenyl 6-methyl quinoline 3-carboxylate:

The above acrylate (10.0 g.) was dissolved in acetic anhydride (20 c.c.) and sulphuric acid (10 c.c.) was added to it. The product was worked up as before, Yield: 2.0 g. (22.6 %). It was crystallised from alcohol, m.p. 253°-55° C (reported m.p. 253°-55° C) (Found: N, 4.4 %)

C19H17O3N requires: N, 4.6 %)

(C) 4-hydroxy 2-phenyl 6-methyl quinoline 3-carboxylic acid:

The above ester (2.0 g.) was refluxed with 5 % sodium hydroxide (30 c.c.) for two hours. The product was
worked up as before. Yield: 1.4 g. (79.0 %). It was crystallised from aqueous alcohol, m.p. 210-11° C (reported m.p. 209-11° C). (Found: N, 4.9 %; C17H15O2N requires: N, 5.0 %).

(D) 4-hydroxy 2-phenyl 6-methyl quinoline:

The above acid (1.4 g.) was added with stirring to mineral oil 15 c.c. preheated to 275° C and the temperature was maintained at 270-75° C for five minutes. The product was worked up as before. Yield: 0.9 g. (76.0 %).

It was crystallised from alcohol (90 %) in shining crystals with a slightly greenish tinge, m.p. 294-95° C. Mixed with an authentic specimen of 4-hydroxy 2-phenyl 6-methyl quinoline prepared from ethyl benzoylacetate and p-toluidine (loc.cit.), the melting point was 294-95° C.

(E) 4-chloro 2-phenyl 6-methyl quinoline:

It was prepared by refluxing the above 4-hydroxy 6-methyl 2-phenyl quinoline with phosphorous oxychloride (loc. cit.), m.p. 95-97° C.

4. Condensation with p-chloroaniline:

(A) Ethyl-α-carboethoxy-β-phenyl-β-(p-chloroanilino) acrylate:

Ethyl benzoylmalonate (26.4 g., 0.1 mole) and
p-chloroaniline (12.7 g., 0.1 mole) were condensed together as before and crystals of benz-p-chloroanilide were filtered off. The acrylate was purified as before. The pure acrylate crystallised on standing. Yield: 12.5 g. (33.0 %), m.p. 74-75 °C. (reported m.p. 75 °C). (Found: Cl, 9.3 %; C₂₀H₂₀O₄NCl requires: Cl, 9.5 %)

(B) Ethyl 4-hydroxy 2-phenyl 6-chloro quinoline 3-carboxylate:

The above acrylate (12.5 g.) was dissolved in acetic anhydride (25 c.c.) and sulphuric acid (12 c.c.) was added to it. The product was worked up as before. Yield: 3.2 g. (39.0 %). It was crystallised from alcohol, m.p. 250-52 °C (reported m.p. 251-52 °C). (Found: Cl, 11.0 %; C₁₆H₁₄O₅NCl requires: Cl, 11.1 %)

(C) 4-hydroxy 2-phenyl 6-chloro quinoline 3-carboxylic acid:

The above ester (3.2 g.) was refluxed with 5 % sodium hydroxide (50 c.c.) for two hours. The product was worked up as before. Yield: 2.1 g. (72.0 %). It was crystallised from alcohol, m.p. 301-2 °C (decom) (reported m.p. 300 °C (decom)). (Found: Cl, 11.8 %; C₁₆H₁₀O₅NCl requires: Cl, 11.9 %)
(D) 4-hydroxy 2-phenyl 6-chloro quinoline:

The above acid (2.1 g.) was added with stirring to mineral oil (22 c.c.) preheated to 275 °C and the temperature was maintained at 270-75 °C for five minutes. The product was worked up as before. Yield: 1.2 g. (66.6 %). It was crystallized from glacial acetic acid, m.p. 350-51 °C (decom). Mixed m.p. with an authentic specimen of 4-hydroxy 2-phenyl 6-chloro quinoline prepared from ethyl benzoyl acetate and p-chloroaniline, (loc. cit.), was undepressed.

(E) 4,6-dichloro 2-phenyl quinoline:

It was prepared by refluxing 4-hydroxy 2-phenyl 6-chloro quinoline with phosphorous oxychloride (loc. cit.), m.p. 118-20 °C.
(IV) Syntheses with Ethyl benzoylcyanoacetate:

Preparation of ethyl benzoylcyanoacetate:

It was prepared essentially according to the method described for the preparation of ethyl benzoyl-
(P. 126, This vol.)
acetoacetate except in that ethyl acetoacetate was re-
placed by cyanoacetic ester. The yield of ethyl benzoyl
cyanoacetate was 78 g. (60 %) starting with 67.8 g. i.e.
0.6 mole of cyanoacetic ester. The reactions involved are:

\[ \text{CH}_2\text{.COOC}_2\text{H}_5 + \text{Na} \rightarrow \text{CH}_3\text{(Na)}\text{.COOC}_2\text{H}_5 + \text{H} \]

\[ \begin{array}{c}
\text{CH}_3\text{(Na)}\text{.COOC}_2\text{H}_5 + \text{C}_6\text{H}_5\text{COCl} \rightarrow \text{C}_6\text{H}_5\text{CO.CH.COOC}_2\text{H}_5 + \text{NaCl}
\end{array} \]
Condensation with aniline:

(A) Ethyl benzoyloyanooacetate (16.3 g, 0.075 mole) and freshly distilled aniline (7.0 g, 0.075 mole) were mixed together and a drop of concentrated hydrochloric acid added to it as catalyst. The mixture was allowed to stand over calcium chloride for three days. The oil was then taken up in ether (60 c.c.). The ethereal solution was dried and the ether removed, giving an oil. Yield: 11.1 g. (50.0 %).

(B) 4-hydroxy 2-phenyl quinoline 3-carboxylic acid:

The above acrylate (11.1 g.) was dissolved in acetic anhydride (20 c.c.) and sulphuric acid (10 c.c.) was added to it. Considerable heat was developed. The mixture was allowed to cool to room temperature. It was then poured on crushed ice (300 g.) and neutralised with strong sodium hydroxide. Excess sodium hydroxide was added to it and the solution was boiled, charcoaled and filtered. The filtrate was acidified with 50 % hydrochloric acid and the product separating was collected, washed with water and dried. Yield: 3.2 g. (32.1 %). It
was crystallised from alcohol, m.p. 230°C. Mixed m.p.
with a specimen of 4-hydroxy 2-phenyl quinoline 3-carboxylic acid, prepared from ethyl benzoylmalonate and aniline (loc. cit.), was undepressed.

(c) 4-hydroxy 2-phenyl quinoline:

The above acid (3.0 g.) was added with stirring to mineral oil (30 c.c.) preheated to 275°C and the temperature was maintained at 270-275°C for five minutes. The oil containing the product was cooled, diluted with petroleum ether and scratched. The product was collected and dried. Yield: 1.8 g. (75.0%). It was crystallised from 60% alcohol in tan yellow needles, m.p. 254°C. Mixed m.p.

with an authentic specimen of 4-hydroxy 2-phenyl quinoline prepared from ethyl benzoylacetate and aniline (loc. cit.), was undepressed.

(d) 4-chloro 2-phenyl quinoline:

It was prepared by refluxing the above 4-hydroxy 2-phenyl quinoline with phosphorous oxychloride (loc. cit.).

m.p. 60-62°C.
2. Condensation with o-toluidine:

(A) Ethyl benzoylcyanoacetate (16.3 g., 0.075 mole) and o-toluidine (7.9 g., 0.075 mole) were condensed together as before. Yield: 11.1 g. (49.0%).

(B) 4-hydroxy 2-phenyl 8-methyl quinoline 3-carboxylic acid:

The above acrylate (11.1 g.) was dissolved in acetic anhydride (20 c.c.) and sulphuric acid (10 c.c.) was added to it. The product was worked up as before. Yield: 2.6 g. (26.0%). It was crystallised from aqueous alcohol, m.p. 201-2° C. Mixed m.p. with an authentic specimen of 4-hydroxy 2-phenyl 8-methyl quinoline 3-carboxylic acid prepared from ethyl benzoylmalonate and o-toluidine (loc. cit.), was undepressed.

(C) 4-hydroxy 2-phenyl 8-methyl quinoline:

The above acid (2.0 g.) was added with stirring to mineral oil (20 c.c.) preheated to 275° C and the temperature was maintained at 270-75° C for five minutes. The product was worked up as before. Yield: 1.3 g. (80.0%). It was crystallised from aqueous alcohol, m.p. 224-25° C. Mixed with an authentic specimen of 4-hydroxy 2-phenyl
8-methyl quinoline prepared from ethyl benzoylacetate and o-toluidine (loc.cit.), the melting point was 224°-25 C.

(D) 4-chloro 2-phenyl 8-methyl quinoline:

It was prepared by refluxing the above quinoline with phosphorous oxychloride (loc.cit.). m.p. 82°-83 C.

3. Condensation with p-toluidine:

(A) Ethyl benzoylcyanacetate (16.3 g., 0.075 mole) and p-toluidine (7.9 g., 0.076 mole) were condensed together as before. Yield: 10.9 g. (48.0 %).

(B) 4-hydroxy 2-phenyl 6-methyl quinoline 3-carboxylic acid:

The above acrylate (10.9 g.) was dissolved in acetic anhydride (20 c.c.) and sulphuric acid (10 c.c.) was added to it. The product was worked up as before. Yield: 2.3 g. (23.0 %). It was crystallised from aqueous alcohol, m.p. 209°-11 C. Mixed m.p. with an authentic specimen of 4-hydroxy 2-phenyl 6-methyl quinoline 3-carboxylic acid prepared from ethyl benzoylmalonate and p-toluidine (loc.cit.), was undepressed.

(C) 4-hydroxy 2-phenyl 6-methyl quinoline:

The above acid (2.0 g.) was added with stirring
to mineral oil (20 c.c.) preheated to 275° C and the temperature was maintained at 270°-75° C for five minutes.

The product was worked up as before. Yield: 1.3 g. (76.0 %). It was crystallised from aqueous alcohol, m.p. 294-95° C. Mixed with an authentic specimen of 4-hydroxy 2-phenyl 6-methyl quinoline prepared from ethyl benzoyl acetate and p-toluidine (loc.cit.), the melting point was 294-95° C.

(D) 4-chloro 2-phenyl 6-methyl quinoline:

It was prepared by refluxing the above quinoline with phosphorous oxychloride (loc.cit.). m.p. 95-97° C.

4. Condensation with m-chloroaniline:

(A) Ethyl benzoylecyanoacetate (32.5 g., 0.15 mole) and m-chloroaniline (19.0 g., 0.15 mole) were condensed together as before. Yield: 18.2 g. (36.7 %).

(B) 4-hydroxy 2-phenyl 5- and 7-chloro quinoline 3-carboxylic acids:

The above acrylate (18.2 g.) was dissolved in acetic anhydride (30 c.c.) and sulphuric acid (15 c.c.) was added to it. The product was worked up as before.
Yield: 4.8 g. (27.5 %). m.p. 230°-61° C. It was therefore
presumed to be a mixture of isomers.

**Separation of the isomers:**

The mixture of isomers (4.8 g.) was dissolved
in hot glacial acetic acid (28 c.c.) and the solution
was allowed to cool. The product separating was filtered.

(i) **Residue:**

(4-hydroxy 2-phenyl 7-chloro quinoline 3-carboxylic acid)

It was crystallised again from glacial acetic
acid, m.p. 35°-52° C. Yield: 1.6 g. (Found: Cl, 10.9 %;
C₁₆H₁₀O₃NCl requires: Cl, 11.1 %). Its identity was
proved by its decarboxylation to the corresponding known
4-hydroxy 2-phenyl 7-chloro quinoline.

(ii) **Filtrate or mother liquor:**

(4-hydroxy 2-phenyl 5-chloro quinoline 3-carboxylic acid)

The acetic acid mother liquor was diluted with
water. The product was collected, washed with water and
dried. Yield: 2.4 g. It was crystallised twice from alco-
hol, m.p. 242°-45° C. (Found: Cl, 11.2 %; C₁₆H₁₀O₃NCl
requires: Cl, 11.1 %). Its identity was proved by its
decarboxylation to the corresponding known 4-hydroxy 2-phenyl 5-chloro quinoline. From the weights of the products, the ratio of 4-hydroxy 2-phenyl 7-chloro to 4-hydroxy 2-phenyl 5-chloro quinoline 3-carboxylic acids was approximated at 40:60.

(C) (1) Decarboxylation of 4-hydroxy 2-phenyl 7-chloro quinoline 3-carboxylic acid:

( 4-hydroxy 2-phenyl 7-chloro quinoline )

The above acid (1.6 g.) was added with stirring to mineral oil (16 c.c.) preheated to 275°C and the temperature was maintained at 270-75°C for five minutes. The product was worked up as before. Yield: 1.0 g. (73.2%). It was crystallised from glacial acetic acid, m.p. 358-57°C, undepressed by an authentic specimen of 4-hydroxy 2-phenyl 7-chloro quinoline prepared from ethyl benzoyl acetate and m-chloroaniline (loc.cit.)

(ii) Decarboxylation of 4-hydroxy 2-phenyl 5-chloro quinoline 3-carboxylic acid.

( 4-hydroxy 2-phenyl 5-chloro quinoline )

The above acid (2.0 g.) was added with stirring
to mineral oil (20 c.c.) preheated to 275°C and the temperature was maintained at 270–75°C for five minutes.

The product was worked up as before. Yield: 1.3 g. (82.0%)

It was crystallised from alcohol, m.p. 280–282°C, undepressed by an authentic specimen of 4-hydroxy 2-phenyl 5-chloro quinoline, prepared from ethyl benzoylacetae and m-chloroaniline (loc.cit.)

(D) (i) 4:7 dichloro 2-phenyl quinoline:

It was prepared by refluxing the above 4-hydroxy 2-phenyl 7-chloro quinoline with phosphorous oxychloride (loc.cit.). m.p. 99–100°C.

(ii) 4:5 dichloro 2-phenyl quinoline:

It was prepared by refluxing the above 4-hydroxy 2-phenyl 5-chloro quinoline with phosphorous oxychloride (loc.cit.), m.p. 102–3°C.
(V) **Synthesis with Ethyl diacetoacetate:**

**Preparation of ethyl diacetoacetate:**

It was prepared essentially according to the method described for the preparation of ethyl benzoyl acetoacetate (p. 126, this vol.). Benzoyl chloride was replaced by acetyl chloride. Using 39 g. of ethyl acetoacetate (0.3 mole) and 23 g. (19.1 c.c.) of acetyl chloride, the yield of ethyl diacetoacetate was 26.8 g. (52.0%). The reactions involved can be represented as:

\[
\text{CH}_3\text{COCH}_2\text{COOC}_2\text{H}_5 + \text{Na} \rightarrow \text{CH}_3\text{CO CH} \cdot \text{COOC}_2\text{H}_5 + \text{H} \quad \text{Na}
\]

\[
\text{CH}_3\text{CO CH} \cdot \text{COOC}_2\text{H}_5 + \text{CH}_3\text{COCl} \rightarrow (\text{CH}_3\text{CO})_2\text{CH} \cdot \text{COOC}_2\text{H}_5 + \text{NaCl} \quad \text{Na}
\]

**Condensation of ethyl diacetoacetate with aniline:**

(A) Ethyl diacetoacetate (17.2 g., 0.1 mole) and freshly distilled aniline (9.3 g., 0.1 mole) were mixed together with a drop of concentrated hydrochloric acid as catalyst, and the mixture was allowed to stand for three days. Next, the oil was taken up in ether and the ethereal solution was washed with 0.5 N hydrochloric acid, then with
water and finally dried. Ether was removed giving an oil.

Yield: 13.6 g. (55.0%).

(B) 4-hydroxy 2-methyl quinoline:

The en crotonate (13.6 g.) was dissolved in acetic anhydride (25 c.c.) and sulphuric acid (12 c.c.) was added to it. Considerable heat was developed. The mixture was allowed to cool to room temperature. It was then poured on crushed ice and neutralised with strong sodium hydroxide. The product separating was collected, washed with little water and then dried. Yield: 4.1 g. (47.1%).

It was crystallised from water, m.p. 230 °C, undepressed by an authentic specimen of 4-hydroxy 2-methyl quinoline.
(VI) **Synthesis with Ethyl dibenzoylacetate:**

**Preparation of ethyl dibenzoylacetate:**

It was prepared essentially according to the method described for the preparation of ethyl benzoylacetoacetate (p. 126, this vol.), except that ethyl acetoacetate was replaced by ethyl benzoylacacetate. Using 19.2 g. of ethyl benzoylacacetate, the yield of ethyl dibenzoylacacetate was 17.8 g. (60.0%). The reactions involved can be represented as:

\[
\text{C}_6\text{H}_5\text{COCH}_2\text{COOC}_2\text{H}_5 + \text{Na} \rightarrow \text{C}_6\text{H}_5\text{CO} \cdot \text{CH} \cdot \text{COOC}_2\text{H}_5 + \text{H} \quad \text{(Na)}
\]

\[
\text{C}_6\text{H}_5\text{CO} \cdot \text{CH} \cdot \text{COOC}_2\text{H}_5 + \text{C}_6\text{H}_5\text{COCl} \rightarrow (\text{C}_6\text{H}_5\text{CO})_2 \cdot \text{CH} \cdot \text{COOC}_2\text{H}_5 + \text{NaCl}
\]

**Condensation with aniline:**

(A) **Ethyl-α-benzoyl-β-phenyl-β-aniline acrylate:**

Ethyl dibenzoylacacetate (14.8 g., 0.05 mole) and freshly distilled aniline (4.7 g., 0.05 mole) were mixed together with a drop of concentrated hydrochloric acid as catalyst and the mixture was allowed to stand for three days. Next, the oil was taken up in ether and
the ethereal solution was washed with 0.5 N hydrochloric acid, then with water till free from acid and finally dried with anhydrous magnesium sulphate. Ether was removed giving an oil. Yield: 10.5 g. (56.7%).

(B) 4-hydroxy 2-phenyl 3-benzoyl quinoline:

The above acrylate (10.5 g.) was dissolved in acetic anhydride (20 c.c.) and sulphuric acid (10 c.c.) was added to it. Considerable heat was developed. The mixture was allowed to cool to room temperature. It was then poured on crushed ice and then neutralised with strong sodium hydroxide. The product was collected, washed with water and dried. Yield: 3.0 g. (32.6%).

It was crystallised from alcohol, m.p. 276-78° C. Mixed m.p. with an authentic specimen of 4-hydroxy 2-phenyl 3-benzoyl quinoline prepared by Friedel-Crafts benzylation of 4-hydroxy 2-phenyl quinoline, was undepressed.

(Found: N, 4.2%; C_{22}H_{15}NO_{2} requires: N, 4.3%)

Friedel-Crafts benzylation of 4-hydroxy 2-phenyl quinoline:

4-hydroxy 2-phenyl quinoline (1.8 g.) and
anhydrous aluminium chloride (3.0 g., 2 moles) were thoroughly mixed and benzoyl chloride (1.2 c.c.) was added to it. The mixture was heated on an oil-bath at 155-60°C for three hours. The mixture was cooled. Ice (50 g.) and concentrated hydrochloric acid (3 c.c.) were added and the mixture kept overnight. Next day, the solid separating was collected, washed with water (30 c.c.), 5% solution of sodium bicarbonate (25 c.c.), boiling water (300 c.c.) and dried. Yield: 1.0 g. It was crystallised from alcohol in faint yellowish needles, m.p. 276-78°C.

(Found: N, 4.1%; C_{22}H_{15}NO_2 requires: N, 4.3%).
(VII) Syntheses with acetyl malonic ester:

Preparation of acetyl malonic ester:

It was prepared essentially according to the method described for the preparation of ethyl benzoyl acetoacetate (p.126, this vol.), except that ethyl acetoacetate was replaced by malonic ester and benzoyl chloride by acetyl chloride. Using 96 g. (0.6 mole) of malonic ester and 46 g. (38.3 c.c., density 1.12)—slightly less than the theoretical quantity — of acetyl chloride, the yield of acetyl malonic ester was 64 g. (52.8%). The reactions involved can be represented as:

\[ \text{CH}_2\cdot(\text{COOC}_2\text{H}_5)_2 + \text{Na} \rightarrow \text{CH} \cdot (\text{Na}) \cdot (\text{COOC}_2\text{H}_5)_2 + \text{H} \]

\[ \text{CH} \cdot (\text{Na}) \cdot (\text{COOC}_2\text{H}_5)_2 + \text{C}_3\text{H}_5\text{COCl} \rightarrow \text{CH}_3\text{CO} \cdot \text{CH} \cdot (\text{COOC}_2\text{H}_5)_2 + \text{NaCl} \]

1. Condensation with aniline:

(A) Ethyl-\( \alpha \)-carboxethoxy-\( \beta \)-anilino crotonate:

Acetyl malonic ester (10.1 g., 0.05 mole) and freshly distilled aniline (4.7 g., 0.05 mole) were mixed together and a drop of concentrated hydrochloric acid added to it as catalyst. The mixture was allowed to stand
for three days at room temperature. Crystals of acetonilide which had separated during this period were filtered off and the oil was taken up in ether (50 c.c.). The ethereal solution was washed with two thirty c.c. portions of 0.5 N hydrochloric acid, then with water till free from acid and finally dried with anhydrous magnesium sulphate. Ether was removed, giving an oil. Yield: 7.0 g. (50.0 %).

(B) Ethyl 4-hydroxy 2-methyl quinoline 3-carboxylate:

The above crotonate (7.0 g.) was dissolved in acetic anhydride (20 c.c.) and sulphuric acid (10 c.c.) was added to it. Considerable heat was developed. The mixture was allowed to cool to room temperature. It was then poured on ice and just neutralised with sodium hydroxide. The solution was stirred and the product was collected, washed with water and dried. Yield: 2.4 g. (42.0 %). It was crystallised from alcohol, m.p. 104-6° C (Gould and Jacobs, loc. cit., give m.p. 104-7° C)

(Found: N, 6.0 %; C_{13}H_{15}O_{3}N requires: N, 6.1 %)

(C) 4-hydroxy 2-methyl quinoline 3-carboxylic acid:
The above ester (2.4 g.) was refluxed with 5% sodium hydroxide (34 c.c.) for two hours. The mixture was cooled and acidified with 50% hydrochloric acid. The product was collected, washed with water and dried. Yield: 1.8 g. (86.0%). It was crystallised from alcohol, m.p. 245-47°C (reported m.p. 245-47°C). (Found: N, 6.7%; C_{11}H_{9}O_{3}N requires: N, 6.9%)

(D) 4-hydroxy 2-methyl quinoline:

The above acid (1.8 g.) was added with stirring to mineral oil (18 c.c.) preheated to 275°C and the temperature was maintained at 270-75°C for five minutes. The oil containing the product was diluted with petroleum ether and scratched. The product was collected and dried. Yield: 1.2 g. (85.7%). It was crystallised from hot water, m.p. 236°C, undepressed by an authentic specimen of 4-hydroxy 2-methyl quinoline.

2. Condensation with p-toluidine:

(A) Ethyl-α-carbethoxy-β-(p-toluidino) crotonate:

Acetyl malonic ester (10.1 g., 0.05 mole) and p-toluidine (5.3 g., 0.05 mole) were condensed together
as before and crystals of aceto-p-toluidide were filtered off. The crotonate was purified as before. Yield: 6.0 g. (41.3%).

(B) Ethyl 4-hydroxy 2:6 dimethyl quinoline 3-carboxylate:

The above crotonate (6.0 g.) was dissolved in acetic anhydride (20 c.c.) and sulphuric acid (10 c.c.) was added to it. The product was worked up as before. Yield: 2.0 g. (39.5%). It was crystallised from alcohol, m.p. 250-52 C. (Found: N, 5.5%; C_{14}H_{15}NO_3 requires: N, 5.7%)

(C) 4-hydroxy 2:6 dimethyl quinoline 3-carboxylic acid:

The above ester (2.0 g.) was refluxed with 5% sodium hydroxide (30 c.c.) for two hours and the product was worked up as before. Yield: 1.6 g. (92.0%). It was crystallised from alcohol, m.p. 286 C. (Found: N, 6.3%; C_{12}H_{11}NO_3 requires: N, 6.4%). Neutral equivalent: 215.

(D) 4-hydroxy 2:6 dimethyl quinoline:

The above acid (1.6 g.) was added with stirring to mineral oil (16 c.c.) preheated to 275 C and the temperature was maintained at 270-75 C for five minutes. The
product was worked up as before. Yield: 1.1 g. (87.0%).

It was crystallised from aqueous alcohol, m.p. 278–79°C, undepressed by an authentic specimen of 4-hydroxy 2:6 dimethyl quinoline.

3. Condensation with m-toluidine:

(A) Ethyl-α-carboethoxy-β-(m-toluidino) crotonate:

Acetyl malonic ester (30.3 g., 0.15 mole) and m-toluidine (16.0 g., 0.15 moles) were condensed together as before and crystals of aceto-m-toluidide were filtered off. The crotonate was purified as before. Yield: 21.0 g. (48.1%).

(B) Ethyl 4-hydroxy 2:5 and 2:7 dimethyl quinoline 3-carboxylates:

The above crotonate (21.0 g.) was dissolved in acetic anhydride (30 c.c.) and sulphuric acid (15 c.c.) was added to it. The product was worked up as before.

Yield: 5.6 g. (31.7%), m.p. 251–62°C. It was crystallised from alcohol, m.p. 256–65°C. Further crystallisation failed to raise the melting point. It was therefore presumed to be a mixture of isomers. A number of attempts to sepa-
rate the isomeric esters by fractional crystallisations from various solvents were unsuccessful. (Found: N, 5.3%; C$_{14}$H$_{15}$NO$_3$ requires: N, 5.7%).

(C) 4-hydroxy 2:5 and 2:7 dimethyl quinoline 3-carboxylic acids:

The above mixture of esters (5.0 g.) was refluxed with 5% sodium hydroxide (60 c.c.) for two hours. The product was worked up as before. Yield: 4.1 g. (94.0%). It was crystallised from alcohol, m.p. 276-83°C. Repeated attempts to separate the isomeric acids were unsuccessful. (Found: N, 6.1%; C$_{12}$H$_{11}$NO$_3$ requires: N, 6.4%)

(D) 4-hydroxy 2:5 and 2:7 dimethyl quinolines:

The above mixture of acids (3.0 g.) was added with stirring to mineral oil (30 c.c.) preheated to 275°C and the temperature was maintained at 275-75°C for five minutes. The product was worked up as before. Yield: 1.9 g. (79.5%), m.p. 256-65°C.

Separation of the isomers:

A boiling solution of oxalic acid (0.7 g.) in alcohol (6 c.c.) was added to a solution of the mixture
of isomers (1.9 g.) in alcohol (12 c.c.). The solution was allowed to cool to 60°C and maintained at that temperature for ten minutes, during which period the oxalate of 4-hydroxy 2:5 dimethyl quinoline separated. This was collected and dried. Yield: 1.0 g. m.p. 207-10°C.

It was crystallised from alcohol, m.p. 212-15°C. On cooling the filtrate to room temperature, the oxalate of 4-hydroxy 2:7 dimethyl quinoline separated. Yield: 0.4 g. m.p. 172-74°C. From the weights of the oxalates, the proportion of 4-hydroxy 2:5 dimethyl and 4-hydroxy 2:7 dimethyl quinolines was approximated at 71.29.

(Spivey and Curd, loc.cit.)

4-hydroxy 2:5 dimethyl quinoline:

The oxalate (0.8 g.) was decomposed by boiling with 25% sodium hydroxide (5 c.c.). The solution was acidified and the product was crystallised from alcohol, m.p. 274°C, undepressed by an authentic specimen of 4-hydroxy 2:5 dimethyl quinoline.

4-hydroxy 2:7 dimethyl quinoline:

It was obtained by boiling its oxalate with sodium hydroxide. m.p. 260°C. (Spivey and Curd, loc.cit.)
give m.p. 261° C)

4. Condensation with m-chloroaniline:

(A) Ethyl-\alpha-carboxethoxy-\beta-(m-chloroanilino) crotonate:

Acetyl malonic ester (30.3 g., 0.15 mole) and m-chloroaniline (19 g., 0.15 mole) were condensed together as before and crystals of m-chloroacetoanilide were filtered off. The crotonate was purified as before. Yield: 24.0 g. (51.4%).

(B) Ethyl 4-hydroxy 2-methyl 5- and 7-chloro quinoline-3-carboxylates:

The above crotonate (12.0 g.) was dissolved in acetic anhydride (20 c.c.) and sulphuric acid (10 c.c.) was added to it. The product was worked up as before. A second experiment with another 12 g. of the crotonate was carried out. Total yield: 7.7 g. (37.8%). It was crystallised from alcohol, m.p. 246°-59° C. Further crystallisation failed to raise the m.p. It was therefore presumed to be a mixture of isomers. Attempts to separate the isomers were unsuccessful. (Found: Cl, 13.2%; C_{13}H_{12}NO_{3}Cl requires: Cl, 13.4%).
(C) 4-hydroxy 2-methyl 5- and 7-chloro quinoline 3-carboxylic acids:

The above mixture of esters (7.7 g.) was re fluxed with 5% sodium hydroxide (80 c.c.) and the product was worked up as before. Yield: 5.7 g. (92.0%), m.p. 244-53°C.

Separation of the isomeric acids:

The mixture of acids (5.7 g.) was dissolved in 30 c.c. of hot glacial acetic acid. The solution was cooled and the product, 4-hydroxy 2-methyl 7-chloro quinoline 3-carboxylic acid, was filtered off. Yield: 2.5 g. m.p. 276-78°C. A second crystallisation from acetic acid raised the m.p. to 279-80°C. (Found: Cl, 14.8%; C_{11}H_{8}NO_{3}Cl requires: Cl, 15.0%). The mother liquor was diluted with water and the product, 4-hydroxy 2-methyl 5-chloro quinoline 3-carboxylic acid, was filtered. m.p. 244-46°C. It was crystallised from alcohol, m.p. 248-50°C. Yield: 3.1 g. (Found: Cl, 15.1%; C_{11}H_{8}NO_{3}Cl requires: Cl, 15.0%). The proportion of 4-hydroxy 2-methyl 5-chloro to 4-hydroxy 2-methyl 7-chloro quinoline 3-carboxylic acids was thus
found to be 56:42. The constitutions of these acids were proved by their decarboxylation to the corresponding known 4-hydroxy 2-methyl 7- and 5-chloro quinolines.

(D) (i) 4-hydroxy 2-methyl 7-chloro quinoline:

4-hydroxy 2-methyl 7-chloro quinoline 3-carboxylic acid (2.5 g.) was added with stirring to mineral oil (25 c.c.) preheated to 275°C and the temperature was maintained at 270-75°C for five minutes. The product was worked up as before. Yield: 1.5 g. (75.0%). It was crystallised from alcohol, m.p. 312°C, undepressed by an authentic specimen of 4-hydroxy 2-methyl 7-chloro quinoline.

(ii) 4-hydroxy 2-methyl 5-chloro quinoline:

4-hydroxy 2-methyl 5-chloro quinoline 3-carboxylic acid (3.1 g.) was added with stirring to mineral oil (31 c.c.) preheated to 275°C and the temperature was maintained at 270-75°C for five minutes. The product was worked up as before. Yield: 1.8 g. (74.0%). It was crystallised from alcohol, m.p. 260-62°C, undepressed by an authentic specimen of 4-hydroxy 2-methyl 5-chloro quino-
(E) (i) 4:7 dichloro 2-methyl quinoline:

It was prepared by refluxing 4-hydroxy 2-methyl 7-chloro quinoline with phosphorous oxychloride. Yield: 82.0 %.

It was crystallised from alcohol, m.p. 96-8° 103°C.

(ii) 4:5 dichloro quinoline:

It was prepared by refluxing 4-hydroxy 2-methyl 5-chloro quinoline with phosphorous oxychloride. Yield: 80.0 %. It was crystallised from alcohol, m.p. 76°C.
(VIII) Syntheses with Ethyl acetoacetate:

Preparation of p-aminoacetanilide:

Pure p-phenylenediamine (54 g.) was refluxed with pure glacial acetic acid (30 g., 1 mole) for three hours on a sand-bath. The mixture was poured in water (600 c.c.). After cooling, the product was filtered and washed with water. It was crystallised from methanol, m.p. 162° C. Yield: 30 g.

Preparation of m-aminoacetanilide:

Pure m-phenylenediamine (21.6 g.) was refluxed with pure glacial acetic acid (12 g., 1 mole) for three hours on a sand-bath. The mixture was poured in water (300 c.c.). After cooling, the product was extracted with ethyl acetate, which when evaporated gave a syrupy mass of m-aminoacetanilide. Yield: 12 g.

1. Condensation with p-aminoacetanilide:

(A) Pure p-aminoacetanilide (20 g.) was mixed with ethyl acetoacetate (20 c.c.) and methanol (80 c.c.) was added to it. The mixture was refluxed for five hours on a water-bath. It was then cooled thoroughly and the
product which had crystallised was filtered, washed with methyl alcohol and dried. m.p. 182°C. (Pratt and Archer, loc.cit., give m.p. 180°-82°C; Backeberg, loc.cit. gives m.p. 186°C.) Total yield: 18 g. (52%);

(Found: N, 5.2% \( \text{C}_4\text{H}_2\text{O}_3\text{N}_2 \) requires: N, 5.3%)

(ii) Cyclisation of ethyl-β-(p-acetamido aniline)

Crotonate:

(4-hydroxy 2-methyl 6-acetamido quinoline)

The above crotonate (13.1 g.) was dissolved in acetic anhydride (50 c.c.) and sulphuric acid (12 c.c.) was added to it. Considerable heat was developed and the mixture boiled vigorously. It was allowed to cool to room temperature. It was then poured on crushed ice and neutralized with strong sodium hydroxide. The product separating was collected, washed with water and dried. Yield: 6.1 g. (56.5%). It was crystallised from alcohol, m.p. 364°C (Kermack, loc.cit. gives m.p. 365°C). Mixed m.p. with an authentic specimen prepared by the thermal method was undepressed.

4-chloro 2-methyl 6-acetamido quinoline:
It was obtained by boiling the above hydroxy quinoline with phosphorous oxychloride for thirty minutes. After cooling to room temperature, the mixture was poured on crushed ice and neutralised with strong ammonia. The product separating was collected, washed with water and dried. Yield: 87 %. It was crystallised from alcohol, m.p. 209°-10 °C. (Found: Cl, 15.0 %; 
\( \text{C}_{12}\text{H}_{11}\text{O} \text{N}_2\text{Cl} \) requires: Cl, 15.1 %).

(C) Hydrolysis of 4-hydroxy 2-methyl 6-acetamido quinoline

(4-hydroxy 2-methyl 6-amino quinoline)

4-hydroxy 2-methyl 6-acetamido quinoline (5 g.) was hydrolysed by boiling with 33 % hydrochloric acid (400 c.c.) for one hour. The mixture was cooled and neutralised with sodium hydroxide. The product precipitating was collected, washed with water and dried. Yield: 3.8 g. (95.0 %). It was crystallised from aqueous alcohol, m.p. 345 °C (Karmack, loc. cit., gives m.p. 345 °C).

(weighted)

(Found: N, 16.0 %; \( \text{C}_{10}\text{H}_{10}\text{N}_2\text{O} \) requires: N, 16.1 %)

Its alcoholic solution gave red colouration with a solu-
tion of ferric chloride. When diazotised, it coupled with 
$\beta$-naphthol to give an orange dye.

(2) 4-chloro 2-methyl 6-amino quinoline:

It was obtained by refluxing the above hydro-
xy quinoline with phosphorous oxychloride as before.

Yield: 91 %. It was crystallised from alcohol, m.p.
144-45 °C. (Found: Cl, 18.2 %; $C_{10}H_8N_2Cl$ requires:
Cl, 18.4 %).

2. Condensation with m-aminocetanilide:

(A) Ethyl-$\beta$-(m-acetamido anilino) crotonate:

m-aminocetanilide (12 g.) was mixed with
ethyl acetoacetate (12 c.c.) and methyl alcohol (50 c.c.)
was added to it. The mixture was refluxed on a water-
bath for six hours. It was then cooled cooled and left
overnight. Next day, the product which had crystallised
was filtered, washed with little ether and dried. Yield:
10 g. (48.1 %). m.p. 92 °C. (Found: N, 5.1 %;
$C_{14}H_{18}O_3N_2$ requires: N, 5.3 %). (Kermack and Webster, loc.
cit. give m.p. 92 °C).

(B) Cyclisation of the crotonate:

(4-hydroxy 2-methyl 5-acetamido quinoline)

The above crotonate (10 g.) was dissolved in
acetic anhydride (30 c.c.) and sulphuric acid (10 c.c.) was added to it. Considerable heat was developed. The mixture was allowed to cool to room temperature. It was then poured on crushed ice and neutralised with strong sodium hydroxide. The product was collected and dried. Yield: 3 g. (37%). It was crystallised from alcohol, m.p. 236° C, undepressed by an authentic specimen of 4-hydroxy 2-methyl 5-acetamido quinoline prepared by the thermal method (Kermack and Webster, loc. cit.).

(C) Hydrolysis of 4-hydroxy 2-methyl 5-acetamido quinoline

(4-hydroxy 2-methyl 5-amino quinoline)

4-hydroxy 2-methyl 5-acetamido quinoline (1.3 g.) was hydrolysed by boiling with 33% hydrochloric acid (100 c.c.). The mixture was cooled and neutralised with sodium hydroxide, when 4-hydroxy 2-methyl 5-amino quinoline precipitated. The product was filtered and dried. Yield: 0.9 g. (86.5%). It was crystallised from hot water in slender needles with a slightly greenish tinge.
m.p. 200° C. (Kermack and Webster, loc. cit., give m.p.
210° C.). (Found: N, 16.1 %; C_{10}H_{10}N_{2}O requires: N,
16.1 %)
Synthesis of 4:5 dihydroxy 2:7 dimethyl -p-phenanthroline and of 4:5 dichloro 2:7 dimethyl -p-phenanthroline:

(A) Ethyl-p-phenylene-bis-p-amino crotonate:

Pure p-phenylenediamine (32.4 g.) and ethyl acetoacetate (78 g., 2 moles) were heated on a water-bath for one hour. Methyl alcohol (160 c.c.) was added to it and the mixture heated at 100° C on a steam-bath for four hours more. The mixture was allowed to cool and left overnight. The crystals which had separated were filtered off. The mother liquor gave a further amount of the same product. Total yield: 90 g. (90.3 %). It was crystallised from ethyl acetate, m.p. 135° C.

(Backeberg, loc.cit., reports m.p. 135° C)

(Found: N, 8.5 %; C₁₈H₂₄N₂O₄ requires: N, 8.4 %).

(B) 4:5 dihydroxy 2:7 dimethyl -p-phenanthroline:

Pure ethyl-p-phenylene-bis-p-amino crotonate (16.6 g.) was added to boiling diphenyl ether (166 c.c.), over a period of ten minutes and heating was continued.
After heating for seven minutes, solid began to deposit.

The mixture was heated for fifteen minutes more. It was then cooled and left overnight. Next day, most of the product had crystallized. The whole mixture was diluted with light petroleum (boiling range 35°C to 75°C) (260 c.c.) and the solution was scratched. The product was collected, washed with little light petroleum and then with a little ether, and dried. Yield: 11.6 g. (96.6%). It was crystallized from 70% alcohol, m.p. 346°C (Found: N, 11.5% ; C₁₄H₁₂N₂O₂ requires: N, 11.7%). Mixed with an authentic specimen of 4-hydroxy 2-methyl 6-amino quinoline (m.p. 346°C) was 290°C. It is soluble in dilute sodium hydroxide and acids. Its alcoholic solution gave a red colouration with a neutral alcoholic solution of ferric chloride.

(C) 4:5 dichloro 2:7 dimethyl p-phenanthroline:

It was prepared by refluxing the above 4:5 dihydroxy 2:7 dimethyl p-phenanthroline with (5 g.)
with phosphorous oxychloride (75 c.c.) for two hours. The mixture was cooled and excess of phosphorous oxychloride was removed in vacuum. The residue in the flask was poured on chilled ice (400 g.) and neutralised with strong ammonia. The product precipitating was collected, washed with water and dried. Yield: 5.6 g. (97.6 %). It was crystallised from alcohol, m.p. 184-85 °C. (Found: Cl, 25.5 %; C<sub>14</sub>H<sub>10</sub>N<sub>2</sub>Cl<sub>2</sub> requires: Cl, 25.6 %).
Synthesis of 4:5 dihydroxy 2:7 dimethyl p-phenanthroline

from 4-hydroxy 2-methyl 6-amino quinoline:

(A) Ethyl-β-(6'-(4-hydroxy 2-methyl quinolyl) amino)-
crotonate:

4-hydroxy 2-methyl 6-amino quinoline (1.74 g.)
was mixed with ethyl acetoacetate (1.6 c.c.) and a drop
of concentrated hydrochloric acid added to it. Methanol
(30 c.c.) was added to it and the mixture refluxed on a
water-bath for ten hours and then kept in cold for two
days. The product which had crystallised was collected.
Yield: 2.1 g. (73.4 %). It was crystallised from ethyl ace-
tate, m.p. 194 °C. (Found: N, 9.6 %; C16H18N2O5 requires:
N, 9.8 %).

(B) 4:5 dihydroxy 2:7 dimethyl p-phenanthroline:

The above crotonate (2.1 g.) was added to boiling
diphenyl ether (21 c.c.) over a period of five minutes and
the solution was heated for fifteen minutes. It was cooled
and diluted with petroleum ether. The product was collected
and dried. Yield: 1.6 g. (90.9 %). It was crystallised from
aqueous alcohol, m.p. 345 °C. Mixed m.p. with an authentic
specimen of 4:5 dihydroxy 2:7 dimethyl p-phenanthroline
prepared from p-phenylenediamine and ethyl acetoacetate,
was undepressed (loc. cit.).

4:5 dichloro 2:7 dimethyl p-phenanthroline was
prepared as described before.