PART I

GENERAL

INTRODUCTION
PRESENT WORK

PART I

GENERAL INTRODUCTION

The first two \( \beta \)-keto esters investigated for the synthesis of hydroxyquinolines, were ethyl acetocacetate and ethyl benzoylacacetate. These hydroxyquinolines may carry a hydroxyl group in either 2- or 4-position or two hydroxyl groups in both the 2- and 4-positions.

Ethyl acetocacetate reacts with an aromatic amine, such as aniline, in two different ways:

(1) When equimolecular quantities of ethyl acetocacetate and aniline are mixed at room temperature, ethyl \( \beta \)-anilino-
acetonate is formed (Stark; Boc, 1907, 49, 3431; Limbach; Boc, 1931, 66, 969) with the elimination of a molecule of water thus:

\[
\begin{align*}
\text{H}_2\text{C} & \quad \text{CH}_2 \\
\text{NH}_2 & \quad \text{O} \cdot \text{C} \cdot \text{H}_3 \\
\text{COOCH}_2 & \\
\text{CH}_3 & \\
\end{align*}
\]

\[
\begin{align*}
\text{H}_2\text{C} & \quad \text{CH}_2 \\
\text{NH} & \quad \text{COOCH}_2 \text{H}_5 \\
\text{CH}_2 & \quad \text{C} \cdot \text{H}_3 \\
\end{align*}
\]

Ethyl \( \beta \)-anilinoacetonate was prepared for the first time by Conrad and Limbach (Boc, 1897, 20, 523, 944; Boc, 1898, 21, 521, 1649, 1935) by keeping the reactants...
in cold for a few days or alternatively by heating them on
a steam-bath for a few hours.

Coffey, Thompson and Wilson (J. Chem. Soc., 1936; 850) later on modified the method for the preparation of crotonates
of this type and studied in detail experimental conditions
for their formation using different aromatic amines. They
observed that the reaction between highly purified aniline
and pure crotonic ester took as many as twenty days
for its completion. When technical quality of aniline
was employed, the reaction was over in a few days. They
accelerated the rate of formation of the crotonates by using
various catalysts like concentrated hydrochloric acid, hydro-
chloride of the amine or powdered iodine. A very small amount
of the catalyst; that is, a drop of concentrated hydrochlo-
ric acid released from the end of a capillary tube or
0.05 gm. of hydrochloride of the corresponding amine or
powdered iodine was sufficient to bring about completion of
the reaction within a short time. It was also observed by
them that the rate of formation of a particular crotonate
was proportional to the strength of the acid. Using the above
catalysts, they condensed ethyl acetoacetate with various aromatic amines. The turbidity indicating the separation of water in the reaction, which without a catalyst appeared after hours, was noticed in a few minutes. This time period, however, was found to be different with different amines. It varied from half a minute in the case of p-anisidine to two hours with the xyldinca. The reaction proceeded almost to completion in twentyfour hours but the yields could be improved by keeping the reaction mixture in a desiccator over dehydrating agents such as concentrated sulphuric acid or phosphorus pentoxide.

Later on, Hauser and Reynolds (J. Am. Chem. Soc., 1943, 65, 2402) studied the factors governing the formation of crotonates and anilides from p-keto esters and aromatic amines. They employed a number of methods for the preparation of anilides from acetoacetic ester. These methods were more or less modifications over the original Conrad-Limpach method. They are summarized below:

(1) A drop of concentrated hydrochloric acid was added to a mixture of 0.1 mole of each of the reactants and the mixture
was allowed to remain in a vacuum desiccator over concentrated sulphuric acid for one to three days.

(ii) Drierite (10 gms.) was added to the mixture of 0.1 mole of each of the reactants and the mixture was subsequently heated at 95°-100°C in an oil-bath for three to four hours. Drierite was then filtered off.

(iii) To a mixture containing 0.1 mole of each of the reacting components, 35 gms. of drierite, 30 to 40 c.c. of absolute alcohol and 3 to 4 drops of glacial acetic acid were added and the reacting mixture was refluxed on a steam-bath for three to four hours.

(iv) In this method, which was applied to β-keto esters of higher alcohols, the mixture of the reactants (0.1 mole each) was heated at 130° - 140°C in an oil-bath for three to four hours.

(II) At higher temperatures, the condensation of ethyl acetocacetate and aromatic amines yields the anilides with the elimination of a molecule of alcohol thus:

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

Knorr (Bor., 1885, 16, 2598) reported that by heating
equimolecular quantities of ethyl acetacetate and aniline in a sealed tube at 120°C, anil of acetacetate acid (phenyl β-imidobutyric acid), \( C_6H_5 - H : C(CH_3) - CH_2COOH \), was obtained. Later on Knorr himself (Annalen, 1894, 256, 94) obtained the same compound by heating the reactants in equimolecular proportions in an oil-bath at 150°-160°C. According to him, this compound, on treatment with concentrated sulphuric acid, was converted into hydroxy-methyl-quinoline; the formation of which was then incorrectly explained by him according to the following reactions:

\[
C_6H_5\text{H}_2 + CH_3COCl_2COCCO_2H_5 \xrightarrow{H_2O} C_6H_5N \cdot C\{CH_3\} \cdot CH_2COOC_2H_5 \\
\xrightarrow{H_2O} C_6H_5N \cdot C\{CH_3\} \cdot CH_2COOH + C_2H_5OH
\]

\[
C_6H_5N \cdot C\{CH_3\} \cdot CH_2COOH \xrightarrow{(H_2SO_4)} C_2H_5\text{OH}
\]

Knorr's conception was that when ethyl acetacetate reacts with an aromatic amine at lower temperatures, the amide is formed with the elimination of a molecule of water, whereas the anilide is formed with the elimination of a molecule of ethyl alcohol when the condensation is carried out at
the boiling point of the reaction mixture.

Knorr's 4-hydroxy-2-methylquinoline derivatives were in fact all 2-hydroxy-4-methylquinoline derivatives. This was later on realized by Knorr and he, therefore, revised his view in his later publications (Knorr, Annalen, 1886, 233, 83; ibid., 1888, 245, 379; Ber., 1892, 25, 772).

The anilides have also been obtained by Ems and King (J. Chem. Soc., 1913, 104) by refluxing the reagents for one and half a minute. Hausser and Reynolds (loc. cit.) suggested that refluxing the mixture for three to four minutes was essential. Ems and King (loc. cit.)*, using a slightly modified method of Knorr, prepared 2-hydroxy-4:3-dimethylquinoline by cyclisation of the product obtained from o-toluidine and acetoacetic ester. This product was actually found to melt at 217°C whereas Knorr had reported it to melt at 185°C.

The formation of 4:3-dimethyl-2-hydroxyquinoline by the above process depends upon the production of the toluidide of acetoacetic acid; which on cyclisation with concentrated sulphuric acid, loses a molecule of water as formulated
The intermediate toluidide was not isolated by Knorr.

Paulczewski (Ber., 1900, 22, 2203), however, considered this intermediate product to be β-o-tolyl iminocrotonic acid (isomeric with the toluidide) in accordance with Knorr's original view that condensation took place according to the following scheme whereby 4-hydroxy-2-methylquinoline derivatives are obtained:

Paulczewski's intermediate product, therefore, in all probability, was the ortho-toluidide of acetoacetic acid.

Knorr also reported that condensation of ethyl benzoyleacetate with aniline yielded the enil even at high temperatures. Elderfield et al. (J. Am. Chem. Soc., 1945, 67, 1272), however, observed that this compound was obtained in very poor yield. Moreover, the enilide from aniline and
ethyl benzoylecetate was stated by Knorr to give an cyclization 4-hydroxy-2-phenylquinoline. The latter compound was proved to be 2-hydroxy-4-phenylquinoline by Hauser and Reynolds (loc. cit.).

Hauser and Reynolds suggested that the two reactions, namely, the formation of a crotonate and that of an anilide are reversible reactions and that the two are interconvertible. The crotonate can be converted into the anilide by heating the former with an equivalent of water and a trace of acid at 130°-140°C; whereas the reverse transformation takes place upon boiling the anilide with ethanol and drierite. Since the crotonate and the anilide are interconvertible, the temperature dependence of the course of the reaction is due to the displacement of the equilibrium rather than to the existence of two competing reaction paths with sufficiently differing temperature coefficients of rate.

\[
\text{COOC}_2\text{H}_5 
\xrightarrow{130°-140°C} 
\text{H}_2\text{O}^+ \cdot \text{II}^+ 
\xleftarrow{\text{C}_2\text{H}_5\text{OH} \& \text{anhyd. } \text{CaSO}_4}
\]
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 ester) of acetocetic acid for ethyl ester, it has been possible to shift the equilibrium so as to direct the reaction in any desired way merely by setting the conditions so that the more volatile elimination product (water or an alcohol) is formed. Similar considerations also apply to condensations involving benzoacetic esters.

It has been reported that substituted anilines, in which the basicity of the amino-group had been lowered by the introduction of negative groups, such as the nitro-group, could not form anils (Coffey, Thompson and Wilson, loc. cit.; Nicomi and Bagert, J. Org. Chem., 1945, 10, 347). But three years later, Nasclou and Staynor (J. Amer. Chem. Soc., 1948, 70, 3350) obtained ethyl 3-p-nitroanilinocrotonate in yield of about 90 per cent by refluxing ethyl acetocetate and p-nitroaniline dissolved in chloroform. The water formed during the condensation was removed by water separator which was attached to a reflux condenser.
1935; 1938) obtained \( \text{p-(p-acetamido anilino)} \) crotonate
by heating ethyl acetoxacetate and \( \text{p-amine-acetanilide} \) on
a steam-bath for half an hour. But he reported that the
crotonate thus obtained could not be cyclised to produce
a 4-hydroxyquinolino derivative. Pratt and Archer (J. Amer.
Chem. Soc., 1949, 70, 4065) modified the above method for
the formation of the crotonate and refluxed ethyl acetoxacetate
and \( \text{p-amine-acetanilide} \) in methanol for five hours. They
obtained very good yield of the intermediate crotonate which
could be readily cyclised. Ethyl \( \text{p-(m-acetamido anilino)} \)-
crotonate was similarly prepared and cyclised (Hakomori,

Ethyl \( \text{p-(1- and 2-naphthylamino)} \) crotonates have also
been prepared by the condensation of 1- and 2-naphthylamines
with ethyl acetoxacetate (Conrad and Limpach, Ber., 1888, 21,
531; Limpach, ibid., 1931, 64, 939). Compared to condensations
with other aromatic amines, in this case prolonged heating
of the reaction mixture is necessary.

Ethyl benzyloacetate resembles ethyl acetoxacetate and
can therefore be similarly condensed with various aromatic
amines. Conrad and Limbach (Ber., 1888, 21, 531) observed that when ethyl benzoylacetate was heated for several days with aniline, ethyl \( p \)-phenylamidophenyl acrylate was obtained as a thick oil. When the latter was quickly heated at 250°C for a short time, alcohol and some other volatile products distilled over, whilst 2-phenyl-4-hydroxyquinoline was isolated from the residue. This product was found to be identical with the compound described by Just (Ber., 1886, 19, 1492). The same ester was condensed by Elderfield et al. (loc. cit.) with \( m \)-chloroaniline. Hauser and Reynolds (loc. cit.) prepared the two amines from aniline and \( o \)-toluidine by condensing them with ethyl benzoylacetate. Kaelke and Lauten (J. Amer. Chem. Soc., 1950, 72, 1721) prepared ethyl \( p \)-phenyl(\( p \)-\( p \)-bromoanilino) acrylate by the condensation of \( p \)-bromoanilino with the same ester.

Ethyl benzoylacetacetacetate has been condensed by Shah, Thakor and Kulhari (J. Ind. Chem. Soc., 1951, 28, 688) with a number of aromatic amines. They obtained either ethyl \( \alpha \)-acetyl \( p \)-phenyl-\( p \)-(arylmino) acrylates or ethyl \( \alpha \)-benzoyl \( p \)-methyl-\( p \)-(arylmino) acrylates by heating the
ester and various aromatic amines on a water-bath at 100°C for one hour and allowing the mixture to remain at room-temperature for twenty-four hours for the completion of the reaction.

In the Conrad-Limpach synthesis (Conrad and Limpach, J. Chem. Soc., 1940, 1164), when ethyl ethoxymalylate is condensed with various aromatic amines, ethyl p-aminolino-β-carboxy benzylate are obtained thus:

\[
\begin{align*}
\text{X} & \quad + \quad \text{COOC}_2\text{H}_5 + \text{CH}_2 & \quad = \quad \text{COOC}_2\text{H}_5 + \text{CH}_2
\end{align*}
\]

Anils from ethyl ethoxymalylate and aromatic amines were prepared for the first time by Kowack and Weatherhead (J. Chem. Soc., 1940, 1164) by keeping the mixture of one mole of aniline or substituted aniline, 1.05 moles of ethyl ethoxymalylate and 2 c.c. of concentrated hydrochloric acid in a vacuum desiccator over concentrated sulphuric acid overnight or longer. They were also obtained by warming the components in glacial acetic acid (Cavallito and Haskell, J. Amer. Chem. Soc., 1942, 64, 1166). Surrey and Humor
(J. Am. Chem. Soc., 1940, 62, 113) prepared a number of
acylates by heating ethyl ethoxycyanacetate with m-chloro-
acetyl chloride, m-bromoacetyl chloride, m-iodoacetyl chloride,
and 3-chloro-4-methoxyacetyl chloride in either glacial acetic acid or
methylene dichloride at 40°-50° C for two to fortyeight hours.
Riegel and his coworkers (J. Am. Chem. Soc., 1946, 68, 2385)
have described an improved method which makes unnecessary
the isolation of acylacetic ester and which is more rapid
than the method used by Musajo (Gazz. chim. ital., 1937, 67,
222). Acidification of a benzene-water suspension of the
sodium salt of ethyl ethoxycyanacetate with sulphuric acid
liberated the free ester. The amine was obtained by refluxing
the mixture of the ester and an amine in benzene medium
for one hour.

Ethyl ethoxycyanopropionate has been similarly condensed
with a number of aromatic amines to produce ethyl \( \alpha \)-methyl-
\( \beta \)-amino-\( \beta \)-carbethoxy acrylates (Steck, Hallock and Holland,
J. Am. Chem. Soc., 1940, 62, 129, 132, 380; Bracou et al.,
ibid., 1946, 68, 1232).

The reaction of ethyl ethoxymethyleneamalonate with
aromatic amines to form ethyl \(\alpha\)-carboxy p-arylamino-acrylates, which take place readily even at room temperature.

Glisson and Hanco (Annalen, 1897, 297, 75; Ber., 1903, 36, 2729) carried out the reaction with aniline and ethyl ethoxymethylene malonate by heating the reactants for a short time on a water-bath. The modification of this method was employed by Gould and Jacobs (J. Am. Chem. Soc., 1939, 61, 2390) for the preparation of a large number of acrylates of this type. Using the same method, however, Schofield and Simpson (J. Chem. Soc., 1942, 1033) reported difficulties in the preparation of ethyl ethoxymethylene malonate and ethyl anilinomethylene malonate. Two years later, Duffin and Kendall (J. Chem. Soc., 1943, 893) used an analogous method and found that no difficulties were experienced by them in the preparation of either the ester or ethyl anilinomethylene malonate. They also prepared a number of ethyl arylaminomethylene malonates by heating the reactants on a steam-bath for periods varying from twenty minutes to sixteen hours.

Price and Roberts (J. Am. Chem. Soc., 1946, 68, 1204) found this method to be very satisfactory on a small scale.
but when large quantities were to be prepared, isolation
and handling of acrylates proved to be inconvenient and this
could be circumvented by mixing the reactants in diphenyl
other at room temperature and then heating this mixture
containing the reactants to the cyclisation temperature.

Price, Leonard and Harbrandon (J. Am. Chem. Soc.,
1946, 68, 1251) observed that one of the principal dis-
advantages of the synthesis of 4-hydroxyquinolines through
ethyl othoxymethylene malonate is the mediocre yield in the
preparation of the euter itself. They, therefore, employed
ethyl othoxymethylene cyanocacetate instead and prepared
ethyl α-cyano β-arylamino acrylates. They, however,
observed that the preparation of ethyl othoxymethylene-
cyanocacetate and hence the acrylates appeared to offer no
particular advantage over the preparation of othoxymethylene-
malonic euter and its acrylates.

The preceding two methods for the synthesis of acrylates
make use of ethyl orthoformate, a reactive methylene compound
and an aromatic amine as the raw materials. The first two
reagents are brought into reaction to give an othoxymethylene
compound which is isolated and it is subsequently allowed
to react with the amine, forming a derivative of \( p \) -arylamino-
acrylic ester. Snyder and Jones (J. Amer. Chem. Soc., 1946,
68, 1253) suggested that the first two steps in the process
might be combined, so that the acrylic ester derivative might
be obtained directly by heating a mixture of the active
methylene compound, ethyl orthoformate and the amine. For
this purpose they heated in a flask fitted for distillation
a mixture containing equimolecular quantities of ethyl ortho-
formate, the reactive methylene component and an aromatic
amine in an oil-bath at a temperature of \( 100^\circ \text{C} - 165^\circ \text{C} \), until
the calculated volume of alcohol had distilled over. The
time of the reaction varied from twenty minutes to several
hours depending upon the activity of the methylene group of
the active methylene reagent and also that of the aromatic
amine.

Moreover, Daines (Bor., 1902, 35, 2507; Univ. of Kansas
Sci. Bull., 1903, 19, 215) reported that disubstituted
formamidines, \( R_1 - \text{CH} = \text{NR}_2 R_2 \), might be condensed with active
methylene compounds, \( X \cdot \text{CH}_3 Y \), to form \( p \)-arylamino acrylates
as follows:-

\[ 
\text{KII} : \text{CH}_2\text{NH} + \text{XCH}_2\text{Y} \rightarrow \text{KII} \cdot \text{CH} : \text{CH} + \text{XCH}_2\text{Y} 
\]

where \( \text{X} \) represents \( \text{CH}_3\text{CO}, \text{Cl} \) or \( \text{COO}_2\text{H}_3 \) and \( \text{Y} \) is \( \text{COO}_2\text{H}_3 \) group. This reaction has been applied by Price, Leonard and Herbrandson (loc. cit.) to the condensation of bis-(m-chlorophenyl)-formamidine with malonic ester.

Ethyl arylaminomethylencacetoneacetates can be prepared by three methods. In the first method originally developed by Claisen (Annalen, 1897, 237, 33), ethyl ethoxymethyleneacetoneacetate is prepared by prior reaction of ethyl acetooacetate and ethyl orthoformate. The anil is then obtained by heating equimolecular quantities of the \( \beta \)-keto ester thus formed and an aromatic amine. The method used by Dains and his collaborators involves the reaction of ethyl orthoformate and an aromatic amine to give the corresponding substituted diphenylformamidine which in turn reacts with ethyl acetooacetate to produce ethyl arylaminomethylencacetoneacetates (Dains, loc. cit.; Dains and Brown, J. Amer. Chem. Soc., 1909, 31, 1151; Dains and Griffin, ibid., 1913, 35, 939; Dains and Harper, ibid., 1919, 40, 535). Snyder
and Jones (loc. cit.) combined the two steps of the first process and they obtained ethyl aroylanilinomethylacetoacetates directly by heating a mixture of equimolecular quantities of ethyl orthoformate, ethyl acetoacetate and an aromatic amine. Two plausible paths of this direct synthesis, one(I) through the substituted diphenylformamidine and the other(II) through the ethoxymethylene derivative are shown below:

(I)

(a) \[ 2 \text{RNM}_2 + \text{HC}(\text{OC}_2\text{H}_5)_3 \longrightarrow \text{RNM} \cdot \text{CH} \cdot \text{NHR} \rightarrow 3 \text{C}_2\text{H}_5\text{OH} \]

(b) \[ \text{RNM} \cdot \text{CH} \cdot \text{NHR} \rightarrow \text{CH}_3\text{COCH}_2\text{COOC}_2\text{H}_5 \rightarrow \text{RNM} \cdot \text{CH} \cdot \text{C} \cdot \text{COOC}_2\text{H}_5 \]

\[ \text{COCl}_3 \rightarrow \text{RNM}_2 \]

(II)

(a) \[ \text{CH}_3\text{COCH}_2\text{COOC}_2\text{H}_5 \rightarrow \text{HC}(\text{OC}_2\text{H}_5)_3 \rightarrow \text{C}_2\text{H}_5\text{O} \cdot \text{CH} \cdot \text{C} \cdot \text{COOC}_2\text{H}_5 \]

\[ \text{COCH}_3 \rightarrow 2\text{C}_2\text{H}_5\text{OH} \]

(b) \[ \text{C}_2\text{H}_5\text{O} \cdot \text{CH} \cdot \text{C} \cdot \text{COOC}_2\text{H}_5 \rightarrow \text{RNM}_2 \rightarrow \text{RNM} \cdot \text{CH} \cdot \text{C} \cdot \text{COOC}_2\text{H}_5 \]

\[ \text{COCH}_3 \rightarrow \text{C}_2\text{H}_5\text{OH} \]

The two reactions of scheme (I) are well-known as separate processes (Glaisher, Annalen, 1895, 297, 366; Dains, loc. cit.). Their combination into a single process has the advantage
that the amine liberated in the second step is formed in the presence of ethyl orthoformate and hence is reconverted into the amidine, with the result that one mole of the amine used would give one mole of the acrylate. The individual processes of scheme (II) 

have been described by Price, Leonard and Herbrandoon (loc. cit.) for the synthesis of acrylates from cyanoacetic ester. It was found that this direct synthesis of the acryllic acid derivatives proceeded smoothly and gave excellent yields with cyanoacetic ester and mediocre yields with acetoacetic ester. The yield of the acrylate has been found to be low in the latter case because the anilide of the corresponding ethyl arylaminomethyleneacetoacetate is also produced along with it. With malonic ester, however, the acrylate could not be produced at all by this method.

When, for instance, equimolecular quantities of malonic ester, ethyl orthoformate and m-chloroaniline were condensed together, the product was not the following dicarboxylic ester

![Dicarboxylic Ester](attachment:image.png)
but rather the corresponding mono-n-chloroanilide:

\[
\text{CONHCH}_2\text{Cl}
\]

The latter was produced in yield of about 80% when two moles of the amine were employed. The replacement of the ethoxyl group by the amine residue might have occurred before, during or after the other reactions.

It has, however, been reported by Baker and his coworkers \(\text{(J. Amer. Chem. Soc., 1949, 71, 3060)}\) that the direct combination of an aromatic amine, orthoformic ester and ethyl acetoacetate is simpler but gives poorer yields than the reaction of the amine with ethoxymethylacetoacetic ester.

Ethyl anilinomethyleneacyanoacetic ester was prepared for the first time by de Boilemont \(\text{(Bull. soc. chim., 1901, (iii), 25, 20; Chem. Centr. Hl., 1901, I, 374)}\) from ethyl ethoxymethyleneacyanoacetic ester and aniline. By using one or the other of the three methods described above, various other ethyl arylaminomethyleneacyanoacetates were prepared.
by a number of workers ( Beins, loc. cit., 1922, 35, 2510 ; Beins and Brown, loc. cit.; Price, Leonard and Hartmannson, loc. cit.; Synder and Jenco, loc. cit.).

Condensations have also been effected using ethyl formylacetate and ethyl formylpropionate (Price, Leonard and Hartmannson, J. Am. Chem. Soc., 1926, 48, 1950), ethyl \( \beta \)-formylphenylacetate (Roderfield and Wright, ibid., 1926, 48, 1976).}

**CYCLIZATIONS LEADING TO HYDROXYQUINOLINES**

6-Hydroxyquinolines, which have become of great importance with the recognition of the therapeutic value of the 6-aminquinolines prepared from them, have been synthesized by a number of chemists from time to time by the cyclization of several \( \beta \)-amino \( \beta \)-unsaturated esters. The ethoxy group of the unsaturated ester condenses with a free position ortho to the amino nitrogen to yield a hydroxyquinoline derivative. For example, the ethyl \( \beta \)-aminoacetone ester in cyclized, 3-methyl-6-hydroxyquinoline results as shown below:

\[
\begin{align*}
\text{COO}_2\text{H}_5 & \quad \rightarrow \quad \text{CO} & \quad \leftarrow \quad \text{OH} \\
\text{CH} & \quad \text{CH} & \quad \text{C} & \quad \text{C-CH}_3 \\
\text{NH} & \quad \text{NH} & \quad \text{C-CH}_3 & \quad \text{C-CH}_3
\end{align*}
\]
The above reaction was investigated for the first time by Conrad and Limpach (loc. cit.) who reported that ethyl 
β-aminocrotonate, in general, can be converted into 
4-hydroxy-2-methylquinoline derivatives by rapidly heating 
the crotonates at 240° - 250°C for a few minutes. Then the 
product, which they obtained by mixing equimolecular quan-
tities of ethyl acetoacetate and quinoline and allowing the 
mixture to remain at room temperature for some days or heat-
ing the mixture on a steam-bath for some hours, was quickly 
heated at 240°C for a short period, a distillate amounting 
to about 40% of the crotonate was obtained. This distillate 
consisted chiefly of ethyl alcohol, acetone and carbanilide. 
A thick viscous mass was left in the retort as a residue, 
by extracting which with water, γ-hydroxyquinoline could 
be obtained to the extent of 23%. From the aqueous mother-
liquor, they also isolated ethyl phenylbutyrate monocarbo-
xylate. The relative proportions of the two non-volatile 
products depend upon the duration of heating and the temp-
erature. Since then a number of 2-methyl-4-hydroxyquinolines 
have been prepared in this way (Conrad and Limpach, Ber.,
1888, 21; 521; 1949; 1965; ibid., 1892, 25, 772). These 4-hydroxyquinolines were found to be sparingly soluble in cold water and more soluble in hot water. They were highly soluble in alcohol. They were, therefore, crystallised from aqueous-alcohol. Their aqueous solutions produced intense reddish-yellow colorations with ferric chloride. They were amphoteric in character. Besides the formation of ethyl alcohol during cyclisation, there was simultaneous formation of sym-disubstituted phenyl carbamides in almost all the cases. It was due to the formation of the latter products and several other products not then investigated, that the yields of the cyclised products as reported by Conrad and Limbach were on the average about 30 per cent.

After a lapse of about four decades, Limbach (Ber., 1931, 54, 969) made use of a mineral oil as the cyclisation medium and cyclisation of the crotonates was effected by heating them in this mineral oil at 240° - 250° C for a few minutes. The yield of the crude hydroxyquinolines thereby increased from 30% to 90%. Because of considerable decomposition taking place during cyclisation in the mineral
oil, several criticisms were also advanced against this
method of cyclisation (Maurin, Ann. Chim., 1935, 3095). In
view of these criticisms, Lions and his collaborators as
well as some others suggested several modifications and
improvements on the original Conrad-Limpach procedure of
cyclisation whereby the yields have been made to increase
by using a number of high boiling solvents (Hughes and Lions,
J. Proc. Roy. Soc. N. S. Wales, 1938, 72, 453; Gillis, Lions,
and Ritchie, ibid., 1940, 74, 253; Stephen, Tonkin and Walker,

Following the above method, Conrad and Limpach (loc.
cit.) obtained a number of derivatives of 4-hydroxyquinoline
by the cyclisation of the corresponding ethyl \( \beta \)-arlylamino-
crotonates using aniline, \( o \)- and \( p \)-toluidines, 1:3:4-xylidines,
and \( o \)- and \( p \)-anilidines. Using \( o \)- and \( p \)-naphthylamines,
the corresponding benzoquinolines were also synthesised
by them. Kernack (J. Chem. Soc., 1939, 563) obtained
4-hydroxy-2-methyl-6-bromoquinoline by the cyclisation of
ethyl \( \beta \)-(p-bromoanilino) crotonate and Hauser and Reynolds
(loc. cit.) obtained the corresponding 6-chloro-derivative.
Kaletich and Stayner (loc. cit.) synthesised 4-hydroxy-2-methyl-6-nitroquinoline by the cyclisation of ethyl p-(p-nitroanilino) crotonate. This compound had previously been obtained by Kemnack (loc. cit.) by the nitration of 4-hydroxy-2-methylquinoline. Pratt and Archer (loc. cit.) synthesised 4-hydroxy-2-methyl-6-acetamido quinoline by the cyclisation of ethyl p-(p-acetamido anilino) crotonate which could not be cyclised by Backeberg (loc. cit.). The former was identical with the acetyl derivative of the product obtained by the reduction of 4-hydroxy-2-methyl-6-nitroquinoline (Kemnack, loc. cit.). Similarly, ethyl p-(m-acetamido anilino) crotonate, which could not be cyclised by Backeberg, has been cyclised by Kemnack and Webster (loc. cit.) by the thermal method to give only 4-hydroxy-2-methyl-5-acetamido quinoline a which has been hydrolysed to 4-hydroxy-2-methyl-5-aminoquinoline.

The above method of Limpach to synthesise 4-hydroxyquinolines was found to be sufficiently general to be applicable not only to a very large number of substituted anilines and naphthylamines but it has also been extended to the synthesis of all types of 4-hydroxyquinoline deri-
vatives. Gould and Jacobs (loc. cit.) employed this method
for the preparation of 4-hydroxyquinolines carrying a carboxyl
group in the 3-position of the pyridine ring. Using three
different \(\beta\)-keto esters, namely, ethyl acetoacetate, ethyl
ethoxymethyleneacetoacetate and acetylmalonate ester and condensing
then with various aromatic amines, they obtained various
alkylidene derivatives. In the case of acetoacetic ester and
ethyl ethoxymethyleneacetoacetate, the condensation to the inter-
mediate alkylidene derivatives went smoothly in one sense
only with all the amines used, but poorer yields of the
alkylidene derivatives were obtained in the case of acetyl-
malonic ester\(^1\), because of certain side-reactions. The
cyclisations of the alkylidene derivatives thus obtained
were carried out in 10 - 30 parts of mineral oil at 250\(^0\) -
265\(^0\)C, in an atmosphere of dry nitrogen and with good
mechanical stirring. The alkylidene derivative was added
in small portions to the mineral oil preheated to 250\(^0\)-270\(^0\)C
and after the addition was over, heating of the resulting
solution was continued for a further period of about fifteen
minutes. The alkylidene derivatives, which resulted from the
normal condensation of the three esters mentioned above with aromatic amines, cyclised smoothly and produced in each case the corresponding quinoline derivative. With acetoacetic ester, it was a 4-hydroxyquinoline derivative which had previously been described by Conrad and Limpach (loc. cit.) or a benzoquinolina derivative, whereas in the case of othoxymethylcinnamalonic ester, the product was a derivative of 4-hydroxyquinoline-3-carboxylic acid or benzoquinoline-3-carboxylic acid (Campos, Ber., 1901, 34, 2714) and with acetylmalonic ester, it was a derivative of 4-hydroxyquinolinone-3-carboxylic acid (Conrad and Limpach, Ber., 1888, 21, 1775).

Seven years later, Price and Roberts (J. Amer. Chem. Soc., 1946, 68, 1204) observed that both diphenyl ether and "Dowtherm A" (a cutectic mixture of diphenyl ether and diphenyl) were far superior to the mineral oil as the cyclisation media. These solvents boil at a temperature which is optimum for cyclisation purposes. Moreover, they are much less viscous and can therefore be more easily removed from the cyclised product than the medicinal oil. The volume
of the solvent required for cyclisation of different acrylates varies considerably. During cyclisation, comparatively smaller decomposition has been reported to take place due to the maintenance of constant temperature and hence the product was formed with much less darkening. With highly purified ethyl ethoxymethylene malonate and properly established conditions, the yields of the cyclised products were found to be on the average 80 to 85 per cent and when some large-scale experiments were performed, the yield exceeded even 95 per cent. The use of impure water led to deep coloration and low yield of the final cyclised product. Price and Roberts (loc. cit.) later on experienced that handling of very large quantities of the acrylates was inconvenient and tedious and that the separate preparation of the acrylates was unnecessary. Hence they simplified the procedure in which the reactive methylene compound and the amine were dissolved in a requisite quantity of dipheneol ether and the solution was directly heated to the cyclisation temperature. In order that complete cyclisation might take place, the mixture was boiled for about thirty minutes in an open flask.
The application of quinoline synthesis to meta-substituted aromatic amines, in which both positions, ortho to the amino-group are free, may give rise to both 5- and 7-substituted quinolines or either of them. Although it was expected that the application of the Conrad-Limpach procedure to \( \text{n-chloroanilino} \) and ethyl acetoneacetate would lead to both 5- and 7-chlorohydroxyquinaldines, such was not the case. Despite careful study, only one discrete compound could be isolated. Oxidation of the cyclised product with alkaline potassium permanganate led to 4-chloroanthranilic acid. Hence the product was proved to be the 7-chloro-isomer.

In this connection, Bradford, Elliot and Rowe (J. Chem. Soc., 1947, 457) investigated the Skraup reaction with several meta-substituted aromatic amines and found that the proportion of 5- to 7-substituted quinolines was dependent on the nature of the meta-substituent. Strongly \( \text{o-p} \)-directing groups, such as methyl, produced only the 7-substituted derivative, whilst weakly \( \text{o-p} \)-directing substituents, such as chlorine, produced a mixture in which the 7-substituted derivative was predominant and \( \text{m} \)-directing substituents,
such as nitro-group, gave a mixture in which the 5-substituted derivative predominated. The ratio of isomers was also influenced by the concentration of sulphuric acid in the case of m-chloroaniline.

Since then attempts have been made to study the effect of the meta-substituent in other quinoline synthesis and the effect of groups ultimately appearing in the heterocyclic ring on the direction of ring-closure.

Spivck and Curd (J. Chem. Soc., 1949, 2653) effected the cyclizations of ethyl $\beta$-(m-toluidino)-crotonate and ethyl $\beta$-(m-chloroanilino)-crotonate to produce 4-hydroxy-2:5- and 2:7-dimethylquinolines and 4-hydroxy-2-methyl-5- and 7-chloroquinolines respectively. They also studied the effect of the nature of the cyclizing medium and cyclisation temperature on the yield and the proportion of isomers. Their experiments indicated that the yield and proportion of isomers were practically independent of the nature of the cyclising solvent and of the temperature within the range of $250^\circ\text{C} - 300^\circ\text{C}$.

After many trials at separation of the mixture of the isomeric 4-hydroxy-5- and 7-methylquinolines by the fractional
crystallisation of the free bases or their salts from a number
of solvents; they were successful in resolving the mixture
by fractional crystallisation of the oxalates of the bases
from ethyl alcohol. The composition of the mixture of oxalates
was found to be 50% of the 5-methyl isomer and 44% of the
7-isomer. Moreover, separation of 5- and 7-chloroquinaldines
was also accomplished after many unsuccessful preliminary
attempts at fractional crystallisation of the salts of the
bases from various solvents. Although a complete separation
of both the isomers could not be achieved, the picrate of
4-hydroxy-7-chloroquinaldine could be isolated by crystalli-
sing the mixture of picrates from ethanol. The amount of
the product indicated that the 7-isomer predominated in
the product.

Price, Nelson and Baitnora (J. Amer. Chem. Soc., 1946,
68, 1253) observed that when ethyl 4(p-m-chloroanilino
acrylate was cyclised in boiling diphenyl ether at high
dilution, three crystalline products were isolated of which
two were identified as 5- and 7-chloro-4-hydroxyquinolines.
That isomer which was formed in greater yield was identical
with the 7-chloro-4-hydroxyquinoline obtained in the synthesis through ethyl ethoxymethyleneacrylate (Price and Roberts, loc. cit.). Its structure was also established by conversion to 7-chloro-8-nitroquinoline (Price and Guthrie, J. Amer. Chem. Soc., 1945, 68, 1532). They, however, presumed the other isomer to be 5-chloro-4-hydroxyquinoline.

Price and Roberts (loc. cit.) obtained ethyl \(\alpha\)-carboxy 6-m-chloroanilino acrylate by the condensation of n-chloroaniline and ethoxymethyleneacrylic ester. They reported that the cyclisation of this acrylate proceeded to a remarkable degree in one direction forming 5-carboxy-7-chloro-4-hydroxyquinoline in yields of over 90 per cent. Only minor amounts of the isomeric 5-carboxy-5-chloro-4-hydroxyquinoline were found.

It was expected by Synder et al. (J. Amer. Chem. Soc., 1947, 69, 371) that the cyclisation of any anilino acrylic ester derived by the condensation of a meta-substituted anilino with ethoxymethyleneacrylic ester would yield ultimately the 7-substituted-4-hydroxyquinoline as the major product, in analogy to the cyclisation of the intermediate
obtained from m-chloroaniline (Price and Roberts, loc. cit.).

Of the meta-substituted esters studied by then, only the one derived from m-fluoroaniline gave a detectable amount of the 5-substituted quinoline; the pure 7-fluoro-4-hydroxyquinoline was obtained by recrystallisation from water. This structure, rather than that of 5-fluoro-4-hydroxyquinoline, was therefore assumed by then for the isomer formed in large quantity; the relationships of relative abundance in the cyclisation mixture, of solubility of the 4-hydroxyquinolines and of the activity of the final drugs in the 5- and 7-fluoro series were assumed to be the same as in the 5- and 7-chloro series.

In the early work involving the cyclisation of ethyl 2-carboxy-1-(meta-substituted)-aniline acrylates, there was no definite indication of the presence of isomers when the syntheses were carried out on a laboratory scale. Only one isomer was isolated from a Price-Roberts synthesis with m-chloroaniline (Price and Roberts, loc. cit.), m-nitroaniline, m-trifluoromethylaniline, 3-chloro-5-methoxyaniline and 3-chloro-4-methoxyaniline (Synder et al., loc. cit.). After the discovery that the cyclisation of
ethyl α-carboxylic p-(m-chloroanilino)-acrylate yielded a mixture of isomers (Syder et al., loc. cit.), it was found in large scale operations that about 15% of ethyl 5-chloro-1-hydroxyquinoline-3-carboxylate was formed in the cyclisation of ethyl α-carboxylic p-(m-chloroanilino)-acrylate (Price et al., loc. cit.). On the other hand, during the same observation, it was found that only 4-chloro-5-cyano-quinoline could be isolated from the Price-Roberts synthesis with m-cyanoaniline.

When cyclisation of acrylates prepared from meta-substituted anilines and ethyl ethoxymethyl acrylate was attempted (Link and Stacy, J. Amer. Chem. Soc., 1945, 68, 2696), a mixture of 5- and 7-substituted quinolines resulted. Thus cyclisation of ethyl p-carboxylic p-(m-chloroanilino)-acrylate yielded both possible isomeric quinoline derivatives in about equal amounts. Since only the 7-isomer was useful in the preparation of "Chloroquine", they fully investigated the synthesis to establish the proper conditions under which the tendency towards the formation of the 5-isomer would be minimised. They could achieve this by
varying the amounts of diluent used in cyclisation. The results of their experiments revealed that when limited amounts of diluent were employed, practically the whole of the 5-isomer was obtained. The proportion of the 5- and 7-chloro-4-hydroxyquinoline-2-carboxylic α esters obtained from n-chloroaniline varied from a ratio of about 12:1 when the ratio of the inert solvent to acrylate in the cyclisation mixture was 1:1 to a ratio of about 4:10 when a dilution of 20:1 was used in the cyclisation. Moreover, steric effects also exert an influence on the proportion of the isomers formed, since it has been reported that from n-iodoaniline, the proportion of the 7-iodo-quinoline derivative has been found to be much greater than that obtained from n-chloroaniline.

Elderfield et al. (loc. cit.) observed that the application of the familiar Conrad-Limpach synthesis to the anil obtained from ethyl benzoate and n-chloroaniline resulted in the formation of but a small amount of 2-phenyl-7-chloro-4-hydroxyquinoline. Hence the latter was prepared by refluxing equimolecular quantities of ethyl benzoate...
and m-chloroaniline in 'Dowtherm A' for ten hours. However, ring-closure in this way led to a difficultly separable mixture of the 5- and 7-chloro-isomers in good yield from which only a small amount of the 7-isomer could be converted into pure 2-phenyl-4,7-dichloroquinoline on treatment of the mixture with phosphorus oxychloride. A number of modifications were tried to improve the yield, but they were not successful. Later on, cyclisations of the acylates prepared by the condensation of ethyl benzoylacetoacetate with aniline, o-toluidine, and p-bromoaniline were effected by other chemists (Rauscher and Reynolds, loc. cit.; Kanou and Lenton, loc. cit.) to produce 2-phenyl-4-hydroxyquinoline, 2-phenyl-6-methyl-4-hydroxyquinoline and 2-phenyl-6-bromo-4-hydroxyquinoline using the modified method of Price and Roberts.

Several other methods have also been reported for the synthesis of 2-aryl-4-hydroxyquinolines. Nierentowski (Ber., 1894, 27, 1336) discovered that when anthranilic acid and acetophenone were heated at 120°-130° C for two days, 2-phenyl-4-hydroxyquinoline was obtained, the yield being
5 to 5 per cent only. Fuson and Dunning (J. Am. Chem. Soc.,
1946, 68, 1270) suggested a modification over Dimentowski's
process. They observed that 2-aryl-4-hydroxyquinolines
could be conveniently prepared in comparatively better
yields by heating either anthranilic acid or ethyl anthra-
nilate with the acetal of an alkyl aryl ketone. Thus 2-phenyl-
4-hydroxyquinoline was produced in a yield of 64%, when
ethyl anthranilate was heated with slightly more than an
equimolecular amount of the diethyl acetal of acetophenone
in diphenyl ether at temperatures changing from 120° to
200°C and finally the mixture was boiled for ten hours.

\[
\begin{align*}
\text{COOC}_{2}H_{5} & \quad \text{CH}_{3} \\
\text{NH}_{2} & \quad \text{C(OOC}_{2}H_{5})_{2}
\end{align*}
\]

\[
\quad \rightarrow \quad \begin{align*}
\text{OH} & \\
\text{N} & \quad \text{C}_{6}H_{5}
\end{align*}
\]

\[
+ 3\text{C}_{6}H_{5}OH
\]

Formation of the enol with the accompanying evolution of
ethyl alcohol, which occurred below 120°C, appears to be the
first step in the reaction. It also appears probable that
the acetal, under the influence of heat, may be losing a
molecule of ethanol to yield \(\alpha\)-ethoxy-styrene and that the
latter rather than the acetal may be combining with the
amine ester to give the amil as shown below:

\[
\begin{align*}
\text{COOC}_2\text{H}_5 + \text{C}_6\text{H}_5\text{COCH}_3 & \rightarrow \text{COOC}_2\text{H}_5 + \text{C}_6\text{H}_5\text{CH}_2\text{OH} \\
\text{NH}_2 & \quad \text{N} = \text{C} \quad \text{C} \quad \text{N} \\
\text{C}_6\text{H}_5 & \quad \text{C}_6\text{H}_5
\end{align*}
\]

In the final step of the synthesis, ring closure must be taking place with the formation of an intermediate product which loses the third molecule of ethanol to produce 2-phenyl-4-hydroxyquinoline thus:

\[
\begin{align*}
\text{COOC}_2\text{H}_5 & \rightarrow \text{HO} \quad \text{OC}_2\text{H}_5 \\
\text{N} = \text{C} \quad \text{C} \quad \text{N} & \quad \text{N} \\
\text{C}_6\text{H}_5 & \quad \text{C}_6\text{H}_5
\end{align*}
\]

Then, in the above condensation, the acetal was condensed with anthranilic acid instead of its ethyl ester, the yield of the cyclised product reduced to 30% only. This might possibly be due to decarboxylation of anthranilic acid at the high temperature required for the ring closure.

Just (Ber., 1885, 18, 2023, 2032; 1886, 19, 979; 1887, 1541) had for the first time employed benzylamide imidochloride for the cyclisation of 2-phenyl-4-hydroxy-quinoline derivatives. Then he condensed benzylamide imido-
chloride with ethyl sodiomalonate in ether, a mixture of
mono- and di-(phenylimino benzy1) malonate was produced.
On heating the former, cyclization occurred with the formation
of ethyl 2-phenyl-4-hydroxyquinoline-3-carboxylate, which
was hydrolysed to the previously known 2-phenyl-4-hydroxy-
quinoline-3-carboxylic acid ( Sehn and Buchs, Honatsch,
1931, 57, 52).

\[
\text{In order to minimize as much as possible the formation of the discondensation product, the above method was modified by Shah and Necamraev (J. Chem. Soc., 1933, 423), who employed a mixture of diethyl malonate (1 mole) and its sodium derivative (1 mole) and toluene was used as a solvent instead of ether. Crystalline mono-condensation products were obtained thereby from various amidine imidechlorides.}
\]
using aniline, o-n-p-toluidine and o-m-p-chloroaniline.

These mono-condensation products on cyclisation produced

the corresponding 2-phenyl-4-hydroxyquinoline-3-carboxylates,

the yields of which were 30 to 40% calculated on the imido-

carboxylic chloride employed. It has been reported that the presence

of substituents in the benzene ring did not appear to

influence appreciably the condensation or cyclisation. The

cyclisation of the mono mono-condensation product had also

been effected by phosphoryl chloride, which gave ethyl

2-phenyl-4-hydroxyquinoline-3-carboxylates whereas cyclisation

with concentrated sulphuric acid produced the corresponding

4-hydroxyquinoline-3-carboxylic acid. In the case of m-tolu-

uidine, a mixture of 5-methyl and 7-methyl isomers was

obtained; the separation of which was effected by fractional

crystallisation from ethyl acetate. m-Chloroaniline likewise

produced both the isomers out of which only one isomer could

be isolated by fractional crystallisation from the same

solvent. However, in the case of both m-toluidine and

m-chloroaniline, they have not ascertained the positions

(5 or 7) of the substituents.
Following the two methods described above, and effecting the subsequent action of the mixture of phosphorus oxychloride and phosphorus pentachloride on the 4-hydroxyquinolines obtained, Elderfield et al. (loc. cit.) described the synthesis of 2-phenyl-4-chloro-6-methoxyquinoline and 2-phenyl-4,7-dichloroquinoline.

The anilide imidechloride method has been extended by Shah and Decai (J. Ind. Chem. Soc., 1949, 26, 131) who have described the synthesis of 2-phenyl-3-acetyl-4-hydroxyquinolines from the condensation products obtained by the interaction of ethyl sodioacetacetoacetate and various anilide imidechlorides. When the condensation of benzamidic anilide imidechloride with ethyl sodioacetacetoacetate was carried out in toluene, an uncrystallizable condensation product, namely, ethyl α-(phenyl iminophenyl)-acetacetoacetate, was produced. Ring closure of this crude condensation product took place by heating it at 190°-200°C under reduced pressure (30 mm.) to produce 2-phenyl-3-acetyl-4-hydroxyquinoline:
From various other substituted imidochlorides derived from benzyl derivatives of o-m-p-toluidines, o-m-p-chloroanilines, p-anisidine and p-phenetidine, the corresponding 2-phenyl-3-acetyl-4-hydroxyquinolines were synthesised in about 10\% yield, calculated on the weight of the imidochloride employed.

The condensation of benz-m-toluidide imidochloride afforded a mixture of 4-hydroxy-2-phenyl-3-acetyl-5-methyl- and 4-hydroxy-2-phenyl-3-acetyl-7-methylquinolines from which only one isomer (5 or 7) could be isolated in the pure state by fractional crystallisation from acetic acid. In the case of p-chloroaniline, a similar mixture was obtained, but the two isomers could not be separated. Their methyl ethers, however, were separated by fractional crystallisation from ethyl alcohol. The synthesis was also extended to naphthalene series and the corresponding benzoquinolines were synthesised from imidochlorides derived from the benzyl derivatives of α- and β-naphthylamines.
Shah, Thakor and Kulkarni (J. Ind. Chem. Soc., 1951, 28, 688) applied the Conrad-Limpach synthesis to the cyclisation of anils obtained from ethyl benzoylacetoacetate and aniline, o- and p-toluidines and p-naphthylanine.

Depending upon whether the anil-formation took place at the carbonyl benzoyl group or the acetyl carbonyl group, 2-phenyl-3-acetyl-4-hydroxyquinolines and 2-methyl-3-benzoyl-4-hydroxyquinolines were produced as shown below:

The anil from aniline and ethyl benzoylacetoacetate on ring closure in boiling diphenyl ether afforded a mixture of
4-hydroxy-2-phenyl-3-acetylquinoline and 4-hydroxy-2-methyl-3-benzoylquinoline. Ortho- and para-toluidines on similar condensations and cyclizations furnished 4-hydroxy-2:8-dimethyl-3-benzoylquinoline and 4-hydroxy-2:6-dimethyl-3-benzoylquinoline respectively, showing that the anil formation in these cases took place solely at the acetyl group.

p-Toluidine, however, did not give any solid product on cyclisation. p-Naphthylamine, on the other hand, yielded 4-hydroxy-2-phenyl-3-acetyl-benzoquinoline (Shah and Demin, loc. cit.), the condensation being taken place with the benzoyl group.

Violoneus (Annalen, 1917, 415, 248) reported the synthesis of 3-phenyl-4-hydroxyquinoline by the cyclisation of the anil obtained from methyl α,α′-diphenylacetate and aniline. Elderfield and Wright (J. Amer. Chem. Soc., 1946, 68, 1276) described the synthesis of the same compound by cyclising the same anil in a mixture of diphenyl and diphenyl ether.
3-Phenyl-7-chloro-4-hydroxyquinoline was prepared in the same manner using m-chloroaniline. Ring closure of the anil led to the formation of a mixture of the 5-chloro and 7-chloro isomers of which the latter predominated and it could be separated from the mixture by crystallisation from ethyl alcohol.

The recently developed synthesis of 3-substituted 4-hydroxyquinolines makes use of ethyl orthoformate, an active methylene compound and an aromatic amine as the raw materials. The reactive methylene compounds which have been investigated are ethyl ethoxymethyleneamalonate, ethyl ethoxymethyleneacrylate and ethyl ethoxymethyleneacetoacetate.

The most general method for the preparation of 4-hydroxyquinolines carrying a carboxy group in the position-3 is that originally suggested by Gould and Jacobs (loc. cit.). They condensed ethyl ethoxymethyleneamalonate with aromatic amines and cyclised the resulting p-aminooxy-α-carboxy-
acetylates by heating them in a mineral oil between 250° - 265°C. This reaction was subsequently developed by Price and Roberts (loc. cit.) who used diphenyl ether and "Dowtherm A" as the cyclization media. The resulting ethyl 4-hydroxyquinoline-3-carboxylates gave, on hydrolysis and subsequent decarboxylation, the corresponding 4-hydroxyquinolines as shown below:

\[
\begin{align*}
\text{C}_{2}H_{5}.O.CH: C(COO_{2}C_{6}H_{5})_{2} & \rightarrow \\
\end{align*}
\]

Most of the 3-carboxylic acids yielded on decarboxylation nearly quantitative yields of the corresponding 4-hydroxyquinolines. When, however, a nitro-group is present in the benzene nucleus, the usual decarboxylation methods are not satisfactory. Baker et al. (J. Amer. Chem. Soc., 1946, 68, 1237) described an improved method of decarboxylation of such nitro-substituted 4-hydroxyquinoline-3-carboxylic acids.
through the pyrolysis of the silver salts in refluxing
'Dowtherm A'.

The volume of the solvent medium required for cyclisation
of the various acrylates varied considerably. Ethyl\(\alpha\)-carboc-
thoxy-\(\beta\)-\(\alpha\)-chloroanilino acrylate could be cyclised in good
yield by heating without any solvent, but 3-pyridyl-amino
acrylate and some other acrylates required dilution with up
to forty volumes of 'Dowtherm'.

Schofield and Simpson (loc. cit.), using the same method,
however, reported the formation of by-products in the
cyclisation of ethyl anilinomethylendomalonate. The difficulties
experienced by them were mostly due to impurities in their
starting materials, particularly the ester. This would
account for the formation, in the ring closure of their
impure anilinomethylendomalonate, of by-products derived from
more than one mole of aniline. Later on, Duffin and Kendall
(loc. cit.) experienced no difficulties in the preparation
of either the ester or the acrylate. The cyclisation was not
effected easily by heating the aniline esters in liquid
paraffin at 260°-290°C for periods varying from 15 minutes
to one hour, but without the formation of the by-products. The acids were decarboxylated by heating them with liquid paraffin at 270°-310° C for 5 to 30 minutes.

Riegel et al. (J. Am. Chem. Soc., 1946, 68, 1254) cyclised a very large number of substituted-anilinomethylene-malononitrile esters to prepare substituted-3-carboxy-4-hydroxyquinolines. The carboxy group in all these compounds was then removed by hydrolysis and decarboxylation and the resulting 4-hydroxyquinolines were converted into the corresponding 4-chloroquinolines. 4,6- and 4,8-Dichloroquinolines were similarly prepared by Tarboll (J. Am. Chem. Soc., 1945, 68, 1277) from p-chloroaniline and o-chloroaniline respectively making use of ethyl ethoxymethylenemalonate. Syndor et al. (loc. cit.) prepared 4-hydroxyquinolines from m-fluoro- and m-trifluoromethyl anilines. Syntheses have also been effected using substituted-anilines with substituents such as bromo and iodo (Conroy, Hashor and Whitesmore, J. Am. Chem. Soc., 1949, 71, 3233), methoxy and phenoxo (Riegel et al., loc. cit. Syndor et al., J. Am. Chem. Soc., 1947, 69, 3715; Lauver et al., ibid., 1946, 68, 1258; Rumney and Crotcher, ibid.,
1947, 69, 1560); sulphide and disulphide (Price, Leonard and Stacy, ibid., 1957, 69, 855) and nitro (Goulo, Hoersch and Kocher, ibid., 1947, 69, 303; Price et al., ibid., 1947, 69, 373, 375).

On account of ordinary yields of the acylates and hence also those of the 3-hydroxyquinolines through othoxymethylene-malonic ester, Price, Leonard and Herbrandson (loc. cit.) prepared 7-chloro-5-cyano-4-hydroxyquinoline by the cyclization of ethyl \( \beta \)-m-chloroaniline-\( \alpha \)-cyano acylate produced by the condensation of ethyl othoxymethyleneacrylanacetate and \( m \)-chloroaniline. The hydrolysis of the cyclized product was readily accomplished by refluxing it with 50\% sulphuric acid to yield 7-chloro-4-hydroxyquinoline-3-carboxylic acid.

A number of other \( \beta \)-substituted 3-cyano-4-hydroxyquinolines were later on prepared by Snyder and Jones (loc. cit.) from various ethyl \( \alpha \)-cyano-\( \beta \)-(arylamino) acylates using other aromatic amines. It was, however, noticed that these acylates were found to require much higher dilution for cyclization than that in the case of ethyl \( \alpha \)-carboxy-\( \beta \)-(arylamino) acylates. Moreover, the rate of cyclization to the 3-cyano-
4-hydroxyquinolines was slower and the yields in general were
lower.

Ethyl acetacetate can be substituted for either malonic
ceter or cyanacetacetic ceter in the above reactions to produce
a variety of 3-acetyl-4-hydroxyquinolines. Syndor and Jansz
(loc. cit.) prepared 7-chloro-3-acetyl-4-hydroxyquinolines
by the ring closure of ethyl α-acetyl-β-(n-chloroaniline)-
acrylate. The preparation of 3-acetyl-6-methoxy-8-nitro-
4-hydroxyquinolines was accomplished by Baker et al. (loc.
cit.) by cyclization of the anil obtained by heating equi-
molecular quantities of n-nitroanisidine and ethyl ethoxy-
methylenecacetacetate at 150°C for fifteen minutes.

By substituting ethyl ethoxymalacetate as the β-keto
ceter in the Conrad-Limpach synthesis, a number of ethyl
4-hydroxyquinoline-2-carboxylates have been obtained.

Andresen, Bredin and Jung (U. S. Patent, 2, 233, 970; C. A.,
1941, 36, 5771; German Patent, 683, 692; C. A., 1942, 36,
4073) prepared a number of 2-carboxethoxy-4-hydroxyquinoline
derivatives by thermal cyclization of β-carboxethoxy-β'-anilino-
acrylates. Since then several other workers have elaborated
this synthesis and prepared a number of such substituted quinolines. Mueller and Hamilton (J. Am. Chem. Soc., 1943, 65, 1017) synthesised 1-hydroxybenzo(\(f\))quinoline in which \(\beta\)-naphthylamine was condensed with exalactonic ester to give \(\beta\)-naphthylmethylene-succinic ester (I). When the latter was cyclised in mineral oil, preheated to 250°C, 1-hydroxy-3-carboxybenzo(\(f\))quinoline (II) resulted and the latter upon hydrolysis and decarboxylation yielded 1-hydroxybenzo(\(f\))quinoline (III) as shown below:

\[ \text{I} \quad \text{CH}_2\text{COOC}_2\text{H}_5 \quad \text{II} \quad \text{III} \]

Using \(n\)-substituted anilines, Sutro and Harper (loc. cit.)

prepared the corresponding ethyl 4-hydroxyquinoline-2-carboxylates. Somewhat at a later date, ethyl 4-hydroxyquinoline-2-carboxylate and ethyl 6-naphthoxy-4-hydroxyquinoline-2-carbo-
xylate were obtained (Hagedorn et al., J. Amer. Chem. Soc., 1946, 68, 3385). These chemists used mineral oil to cyclise the xylate from p-anisidine because the product was more soluble in diphenyl ether. Some 7-chloro-4-hydroxyquinoline derivatives employing ethyl ethoxymethylacetate have also been reported (Lisk and Stacy, loc. cit.). With meta-substituted amines, a mixture of both the possible isomers was obtained of which the 7-isomer appeared to be higher-melting and more soluble than the 5-isomer. The quantities of solvents needed in the separation of the isomers depended on the amounts and kinds of solvents employed in the washing of the crude mixtures of isomers.

Substituting ethyl ethoxymethylpropionate for ethyl ethoxymethylacetate, Steck, Hallock and Holland, loc. cit.; Brenlow et al., loc. cit.), certain ethyl 3-methyl-4-hydroxyquinoline-2-carboxylates have also been synthesised. An important observation, made by these authors, was that the condensation of o-substituted anilines to the oxoanthrones gave considerably poorer yields of product, and correspondingly larger amounts of the anilines were recovered. It might
De just possible that the lesser degree of reactivity of the o-substituted anilines was due to either the lesser basicity of the amines (Danner and Warth, J. Chem. Soc., 1904, 85, 1715; Hall and Sprinkle, J. Am. Chem. Soc., 1932, 54, 3269) or to steric effects.

Since criticisms have also been advanced by some workers for the decomposition occurring during Price-Roberts synthesis Decai and Bongadiva (Curr. Sci., 1952, 21, 256, 356; Science and Culture, 1953, 19, 308; J. Ind. Chem. Soc., 1953, 30, 655; ibid., 1954, 31, 43; Parts V--VI in course of publication) employed in this laboratory acetic anhydride and concentrated sulphuric acid to cyclise anilines of different p-keto esters, such as ethyl acetoacetate, ethyl benzoyleacetae, ethyl acetyl malonate, ethyl acetylcyanoacetate and obtained different 4-hydroxyquinolines. The cyclisation was effected by dissolving the amine in acetic anhydride and rapidly adding concentrated sulphuric acid to the mixture. When ethyl p-(m-toluidino) and p-(m-chloroanilino) crotonates were cyclised by the thermal method, a mixture of 5- and 7-substituted 4-hydroxy-2-methylquinolines was produced. When,
however, the same crotonates were cyclised using acetic anhydride and sulphuric acid, only the 5-isomer was obtained in each case (Devi and DuggadiWal, Curr. Sci., 1952, 21, 253; J. Ind. Chem. Soc., 1953, 30, 655). They also prepared a number of 2-phenyl-4-hydroxy- and 4-chloroquinolines cyclising ethyl 2-phenyl-4-aminocetol acetates (J. Ind. Chem. Soc., 1952, 31, 43).

The method was further extended to the cyclisation of anils of ethyl benzoylacetoacetate, benzaldehyde, benzoyl-4-cyanacetate, diaacetate and dibenzoylacetae (Ph. D. Thesis, B. P. Duggadivala). This work is in course of publication.

Prior to 1942, little attention had been given to quinoline derivatives bearing dialkylamino-alkylamino groups in the 4-position. The marked antimalarial activity and efficacy of a number of such quinoline derivatives having an alkylamino side-chain attached to the 4-position in the pyridine ring has led to investigation of new procedures for the preparation of 4-4-hydroxyquinolines, which may be readily converted into 4-chloroquinolines. When the latter
are condensed with properly substituted dialkylaminoalkylamines, they are readily converted into a variety of drugs. It has been found that the conditions necessary for such condensations vary widely as a function of substitution. 4-Chloroquinolines bearing a substituent in the 2 or 3-position require longer times and higher temperatures for complete reaction than do 4-chloroquinolines bearing their other substituents only in the benzene ring.

Derivatives of 4-aminoquinolines containing a methyl group in the 3-position are characterised by relatively high antimalarial activity and in some cases at least, by favourable toxicity ("Antimalarial Drugs 1941-1945", published by the Survey of Antimalarial Drugs). Since the effect of other substituents in the 3-position in this series has not been widely investigated, it was of interest to prepare 4-hydroxyquinolines with various substituents in the 3-position.

* * * * * * *
PARTICULAR

INTRODUCTION
PARTicular INTRODUCTION

The reaction reported by Gould and Jacobs (loc. cit.), namely, the thermal cyclisation of ethyl β-cyanino-α-carbathoxy acrylate to yield ethyl 4-hydroxyquinolino-3-carboxylate in capable of very general application. Furthermore, the 4-hydroxyquinolino-3-carboxylic acids obtained by the saponification of the esters may be readily decarboxylated, producing 4-hydroxyquinolines containing no other substituent in the pyridine ring.

Following the procedure adopted by Synder and Jones (loc. cit.), when equimolecular quantities of cyanacetic ester, ethyl orthoformate and m-chloroaniline were heated in an oil-bath between 150°-160° C in an apparatus fitted for distillation, an amount of ethanol corresponding to complete reaction distilled over and the residue consisted of ethyl m-chloroanilinonmethylenecyanacacetate in nearly pure state and excellent yield. Very good yields of the acrylates were also produced when p-anisidine and m-toluidine were employed.

Synder and Jones (loc. cit.) have also stated that the direct synthesis of ethyl m-chloroanilinonmethylenecyanacacetate from acetoacetic ester, ethyl orthoformate and m-chloroaniline
proceeded smoothly as in the above manner and produced excellent yields. But it was actually observed by the candidate that along with the acrylate, a white product (m. p. 150°-152°) was also obtained in fairly good quantity. This product could not be bin-(m-chlorophenyl)formamidine (m. p. 117°) (Price and Roberts, loc. cit.). The formamidine must have been first formed and that reacted with acetoacetic ester to produce the m-chlorogalilide of ethyl m-chloroanilino-methyleneacetoacetate.

It was also confirmed by us that this direct reaction with malonic ester occurred readily, but the product was not the expected dicarboxylic ester, \( \text{H}_{2}\text{H} \cdot \text{CH} \cdot \text{C} \cdot \text{OOC}_{2}\text{H}_{5} \cdot \text{C} \cdot \text{OOC}_{2}\text{H}_{5} \cdot \text{C} \cdot \text{OOC}_{2}\text{H}_{5} \) but rather the corresponding mono-anilide having the formula:

\[
\text{H}_{2}\text{H} \cdot \text{CH} \cdot \text{C} \cdot \text{OOC}_{2}\text{H}_{5} \\
\text{CONHR}
\]

where \( R \) represents any aryl radical.

The above observations have been indirectly supported by the fact that when a diaryl-substituted formamidine reacts with ethyl cyanacetate, only the acrylate is formed without anilide being produced. With ethyl acetoacetate, 50 to 80%
of the amine reacts with the carboxylic group to produce the
anilide whereas with diethyl malonate, a quantitative yield
of the anilide is produced (Dains and Brown, loc. cit.).

A number of 4-hydroxyquinolines has been prepared in
this laboratory, using acetic anhydride and concentrated
sulphuric acid as cyclising agents (Desai and Bagnadivala,
loc. cit.). The present work was undertaken to study the
applicability of this method of cyclisation to a number of
B-arylamino acrylates, obtained from the following esters:

(1) Ethyl ethoxymethylacetoacetoacetate, \( C_2H_5O\cdot CH:O-\text{COOC}_2H_5 \)
\[
\text{COCH}_3
\]

(2) Ethyl ethoxymethylmalonate, \( C_2H_5O\cdot CH:O-\text{COOC}_2H_5 \)
\[
\text{COOC}_2H_5
\]

(3) Ethyl ethoxylacetate, \( C_2H_5\text{OOC}.CO.CH_2\cdot\text{COOC}_2H_5 \)

(4) Ethyl ethoxymethylacryloyacetate, \( C_2H_5O\cdot CH:O-\text{COOC}_2H_5 \)
\[
\text{CH}
\]

Another object of the present work has also been to
investigate whether the acrylates prepared from \( n \)-substituted
aromatic amines and the above esters, on being cyclised with
acetic anhydride and sulphuric acid would give only one isomer
or a mixture of 5- and 7-substituted isomers.

Preparation of Acylates

General methods

Ethyl arylaminomethylenebenzaldehydes, employed during the present investigation, were prepared according to the method of Duffin and Kendall (loc. cit.) by heating equimolecular quantities of ethyl othoxymethylenebenzaldehyde and substituted anilines on a steam-bath for periods varying from 20 minutes for aniline and o-toluidine to 16 hours for p-nitroaniline.

The aniles thus obtained were either viscous oily liquids or low-melting solids. The aniles from m-toluidine, m-xyldine, p-phenetidine and p-bromoaniline do not seem to have been prepared before.

Similar method has been used for the preparation of ethyl arylaminomethyleneacetacetates from ethyl othoxymethyleneacetacetate and aromatic amines in which the periods of heating the appropriate intermediates on the steam-bath varied from 45 minutes in the case of aniline to 15 hours for p-nitroaniline. All the aniles of this series have been obtained as solids. Those from m- and p-toluidines, o- and
p-chloroanilines, p-anisidines, p-phenetidines and n- and p-nitroanilines are now.

Ethyl p-aminophenyl p-carboxy acrylates were obtained according to the procedure adopted by Suryoy and Hammer (loc. cit.) by heating the mixture of ethyl ethoxymethacrylate slightly (1 mole) and excess of the appropriate amino (1.5 moles) dissolved in glacial acetic acid for four to six hours on a water-bath at 45°-50° C. The acrylates obtained with this ester were oily liquids.

Ethyl arylaminocarboxyacrylates were directly prepared by the method described by Sandler and Jones (loc. cit.) by heating together equimolecular quantities of ethyl orthoformate, acrylates ester and the requisite aromatic amine in an oil-bath at a temperature of 160°-165° C until the calculated quantity of alcohol had distilled over.

All the solid acrylates were purified by first pouring the hot liquid reaction mixture in dilute hydrochloric acid (1 H) in which dissolved unreacted amine. After shaking the solid particles four times with dilute hydrochloric acid and thoroughly washing with water, the acrylates were further
purified by crystallisation from suitable solvents. When the
acrylates were in the liquid condition, they were dissolved
in ether, their ethereal solutions were shaken four times
with dilute hydrochloric acid (1 N), then twice with sodium
bicarbonate solution (10%) and finally with water. The drying
of the ethereal solution was effected by keeping it in contact
with anhydrous potassium carbonate overnight. Ether was
removed by evaporation on the next day. They were then
desiccated over calcium chloride to remove the last traces
of water.

The purification step is absolutely essential in so far
as the yield and purity of the final cyclised product are
concerned. Practically the whole of the unreacted amine should
be removed in the isolation of the amine in as much as even
small amounts of the amine have been found to interfere with
the expected reaction in the cyclisation stage.

The B-arylamino acrylates having the general formula

![Chemical Structure]
(where R is any substituent in ortho-, meta-, or para-position to the amino-group in the benzene ring) obtained from ethyl ethoxymethyleneacetoneacetate have been mentioned below:

(1) Ethyl anilinoethylenemethacetoacetate
(2) Ethyl o-toluidinomethylenemethacetoacetate
(3) Ethyl n-toluidinomethylenemethacetoacetate
(4) Ethyl p-toluidinomethylenemethacetoacetate
(5) Ethyl 1:3:4-xyldinomethylenemethacetoacetate
(6) Ethyl o-chloroanilinomethylenemethacetoacetate
(7) Ethyl n-chloroanilinomethylenemethacetoacetate
(8) Ethyl p-chloroanilinomethylenemethacetoacetate
(9) Ethyl o-anisidinomethylenemethacetoacetate
(10) Ethyl p-anisidinomethylenemethacetoacetate
(11) Ethyl o-phenetidinomethylenemethacetoacetate
(12) Ethyl p-phenetidinomethylenemethacetoacetate
(13) Ethyl n-nitroanilinomethylenemethacetoacetate
(14) Ethyl p-nitroanilinomethylenemethacetoacetate

The acylates (3), (4), (6), (8), (10), (12), (13) and (14) do not seem to have been prepared before.

Compared to ethyl ethoxymethyleneacetoneacetate, ethyl
Ethoxymethylene malonate has been well investigated. A number of esterates have been prepared by various chemists (Gould and Jacobs, loc. cit.; Price and Roberts, loc. cit.; Riegel et al., loc. cit.; Turbell et al., loc. cit.; Synder et al., loc. cit.; Inner et al., loc. cit.; Price, Leonard and Stacy, loc. cit.; Goulay, Hoensch and Nashor, loc. cit.; Price et al., loc. cit.). The following esterates, having the structure

were prepared from ethyl ethoxymethylene malonate:

1. Ethyl anilinomethylene malonate
2. Ethyl n-toluidinomethylene malonate
3. Ethyl n-chloroanilinomethylene malonate
4. Ethyl p-chloroanilinomethylene malonate
5. Ethyl 1:3:4-xylidinomethylene malonate
6. Ethyl p-anilidinomethylene malonate
7. Ethyl o-phenetidinomethylene malonate
8. Ethyl p-phenetidinomethylene malonate
9. Ethyl p-triacetylomethylene malonate
(10) Ethyl $\beta$-nitroanilinomethylenacetonate

The acylates numbered (2'), (3'), (4) and (6) mentioned in the above list are new.

Owing to the similarity of the structures of the acylates (I) obtained from ethyl o-toluidinomethylenacetonate with those (II) from ethyl o-toluidylacetate,

the following acylates were also prepared from the latter ester:-

(1) Ethyl $\beta$-aniline $\beta$-carbethoxy acylate
(2) Ethyl $\beta$-o-toluidine $\beta$-carbethoxy acylate
(3) Ethyl $\beta$-p-toluidine $\beta$-carbethoxy acylate
(4) Ethyl $\beta$-p-anisidine $\beta$-carbethoxy acylate
(5) Ethyl $\beta$-o-phenetidino $\beta$-carbethoxy acylate
(6) Ethyl $\beta$-p-chloroanilino $\beta$-carbethoxy acylate

Out of the acylates mentioned in the above list,

(2)', (3)', (5) and (6) are new.

In order to see whether the acetic anhydride-sulphuric
acid method can be applied to cyclize the acrylates (III)

obtained from ethyl ethoxymethylenecyanacetate and in
addition, to ascertain whether one isomer or both the isomers
are produced in the case of the acrylates prepared from
n-substituted anilines, the following acrylates were prepared:

1. Ethyl n-chloroanilinomethylenecyanacetate
2. Ethyl n-toluidinomethylenecyanacetate
3. Ethyl p-anilinomethylenecyanacetate

Acrylate No. (2) has been prepared for the first time.

Cyclisation of the Acrylates: Acetic anhydride Sulphuric acid

method:

The use of acetic anhydride and concentrated sulphuric
acid for the purposes of cyclisation in the manner in which
they have been used in this laboratory does not seem to be
recorded as in literature.

Thiele, Tischboim and Lemsoo (Annalen, 1901, 312, 185)
condensed $\Delta^2\gamma$-angelicalactone with benzaldehyde and anisaldehyde in presence of diethylamine and showed that under these conditions benzaldehyde yielded $\alpha$-benzylidene-laconulinic acid. The latter was then cyclised by heating with acetic anhydride and a little concentrated sulphuric acid to $\gamma$-methyl-$\alpha$-benzylidene-$\Delta^2$-butenalide. Anisaldehyde likewise yielded the corresponding $\alpha$-anisylidene lactone.

Using the same method, von Outingen (J. Am. Chem. Soc., 1930, 52, 2024) condensed a series of aldehydes including salicyl aldehyde and $\beta$-resorcy1 aldehyde with $\Delta^2\gamma$-angelicalactone and obtained similar type of products.

Harriss and Buncel (J. Am. Chem. Soc., 1946, 755) condensed ortho-hydroxy aldehydes with $\Delta^2\gamma$-angelica lactone in presence of small quantities of a mixture of acetic anhydride and sulphuric acid.

In the present work, acetic anhydride alone was found to be quite ineffective as an agent for cyclisation. This was also the case with concentrated sulphuric acid alone. With the latter reagent, too much charring took place with the formation of dark tarry products. Thus neither acetic
anhydride nor sulphuric acid, when employed alone, could affect cyclisation, but successful ring closure could be assured when sulphuric acid was added to the homogeneous solution of the acrylate in acetic anhydride. Whether sulphuric acid is added to the solution of the acrylate in acetic anhydride or vice versa, the yield of the cyclised product is very little affected.

During the preliminary stages, when an attempt was made to cyclise the acrylates with acetic anhydride and very small quantities of sulphuric acid, large portions of the acrylates remained uncyclised and viscous products were obtained. It has been observed that in the case of those acrylates which are easily soluble in acetic anhydride, ring closure could be successfully affected with the mixture of acetic anhydride and sulphuric acid in the ratio of 2:1 (by volume); the weight of the acrylate being the same as the volume of sulphuric acid. Those acrylates which could not dissolve in two volumes of cold acetic anhydride, were cyclised by adding one volume of sulphuric acid to the solution of the acrylate in three volumes of the anhydride.
If the mixture of acetic anhydride and sulphuric acid was previously prepared and the cold mixture was added to the acrylate, cyclisation did not take place at all. When, however, this resulting mixture was heated on an oil-bath at 125°-150° C for one to two hours, partial cyclisation together with some charring took place and the remaining acrylate was recovered from the viscous mass thus obtained.

In order to minimise charring, the reaction was carried out by heating the mixture on a steam-bath for a period of three to four hours. There seemed to be only a slight improvement in the yield.

Ring closure was, therefore, effected by first dissolving an acrylate in cold acetic anhydride. A little warming was found to be necessary for preparing homogeneous solutions of a few solid acrylates of comparatively high M. P. Concentrated sulphuric acid was then added to the solution within two to three minutes. The mixture became very much hotter as a result of which vigorous effervescence was noticed. The vapours, issuing from the boiling mixture, consisted of a mixture of ethyl alcohol, ethyl acetate and acetic anhydride.
After trying a variety of conditions to effect cyclisation with the anhydride and the acid, the following facts have been established:

(i) The anil should be completely purified prior to cyclisation, otherwise tarry mass would be obtained and it would be very difficult to get rid of colour of the final product even after a number of purifications.

(ii) The cyclisation of the anil could be effected within a very short time.

(iii) The previously prepared cold mixture of the anhydride and the acid was not effective.

(iv) Once the cyclisation took place, keeping the reaction mixture for any further period or heating the reaction mixture later on at 100°C had very little influence on the improvement of the yield.

It appears that one of the chief factors responsible for affecting cyclisation is the heat developed when sulphuric acid is added to the solution of the acrylate in acetic anhydride, because this heat was found to be sufficient in effecting ring closure. However, the heat thus developed
cannot be solely responsible for affecting cyclisation since

(1) considerable amount of heat in also developed when

sulphuric acid is mixed with the acrylate as such and

(2) the maximum temperature of the reaction mixture after

the addition of sulphuric acid did not exceed 140°C in any

case. It has been reported that cyclisation by the thermal

method does not take place even when the temperature of the

cyclisation medium is below 240°C. When sulphuric acid alone

was mixed with the acrylate, the latter was found to be

decomposed producing the amine. There must, therefore, be

some important factor, other than the development of heat,

which is responsible for ring closure by this method. As

already pointed out, since neither the anhydride nor the

acid alone could bring about cyclisation, the factor

governing cyclisation must be coming into operation when the

two are mixed with the acrylate in the manner described above.

It has been suggested by Russell and Cameron (J. Amor.

Chem. Soc., 1939, 60, 1547) that when acetic anhydride and

conc. sulphuric acid are mixed together, a mixed anhydride

of the two is formed as shown by the chemical reaction
mentioned below:

\[
\begin{align*}
\text{CH}_3 - C = O & \quad \text{HO} \quad 0 \\
\text{HO} & \quad \text{=} \quad 0 \\
\text{CH}_3 - C = O & \quad \text{HO} \quad 0 \\
\text{HO} - S = 0 & \quad \text{CH}_3\text{COOH}
\end{align*}
\]

Mixed anhydride

The mixed anhydride thus formed is monobasic and exhibits ultra-acidic behaviour. Furthermore, the above reaction is a very rapid one and the mixed anhydride on keeping suffers an intramolecular rearrangement to sulphoacetic acid, which is also monobasic, but does not exhibit ultra-acidic behaviour.

A new decrease in the \( p_{\text{H}} \) is also produced as a result of the rearrangement. The mixed anhydride is converted into sulphoacetic acid according to the following formulation:

\[
\begin{align*}
\text{CH}_3 - C = O & \quad \text{Rearrangement} \quad 0 \\
\text{HO} & \quad \text{=} \quad 0 \\
\text{HO} - S = 0 & \quad \text{CH}_3\text{COOH}
\end{align*}
\]

It is, therefore, reasonable to conclude that the transient formation of the mixed anhydride is the important factor governing cyclization in view of the fact that ring closure takes place only when the acid is added to the solution of
an acrylate in acetic anhydride.

**Method of Cyclisation**

The acrylates have been cyclised by the thermal method of Price and Roberts as well as by the acetic anhydride-sulphuric acid method. For affecting cyclisation by the second method, the acrylate (1 part by weight) was dissolved in acetic anhydride (2 or 3 parts by volume) and concentrated sulphuric acid (1 part by volume) was added to the solution. There was considerable evolution of heat accompanied by copious effervescence. On cooling down to room temperature, the mixture became rather viscous. It was then poured on ice and neutralised with 33% caustic soda solution. In the case of ethyl 4-hydroxyquinoline-5-carboxylates, ethyl 4-hydroxyquinoline-2-carboxylates and 5-cyano-4-hydroxyquinolines, after the mixture had been almost neutralised, the final complete neutralisation was effected by employing sodium carbonate to prevent hydrolysis of the carboxy or the cyano group. In many cases the cyclised products readily separated out as a result of this neutralisation. In a few cases, the solid separated after some hours. Those cyclised
products which did not contain either the carboxylic group
or the cyano group were purified by dissolving the crude
products in hot sodium hydroxide; their solutions were
decolourised by using animal charcoal and filtered. Acidifi-
cation of the filtrate with hydrochloric acid liberated
purified cyclised products which were then further purified
by recrystallisation from suitable solvents.
I. Cyclisation of ethyl aminomethylmethyleneacetocacteates.

3-Acetyl-4-hydroxyquinolines were obtained by the cyclisation of the acylates using both the thermal method and acetic anhydride-sulphuric acid method. In some cases, the yields obtained by both the methods have been compared. The salient distinguishing feature of the two methods of cyclisation exists in the production of one or the other of two possible isomers obtained from ethyl n-substituted aminomethylmethyleneacetocacteates. Cyclisation of the acylate obtained from ethyl ethoxymethyleneacetocacteate and n-toluindine by the thermal method yields mainly the 7-methyl isomer. When, however, the same acylate is cyclised by the acetic anhydride-sulphuric acid method, only the 5-isomer is obtained. Snyder and Jones (loc. cit.) obtained 7-chloro-3-acetyl-4-hydroxyquinoline by the cyclisation of ethyl n-chloroanilinomethyleneacetocacteate in boiling diphenyl ether. The same isomer was obtained by the candidate with the thermal method. But the 5-chloro-isomer was obtained with the acetic anhydride-sulphuric acid method. Using these two methods, 3-acetyl-4-hydroxyquinolines mentioned on the next page were
obtained:

(1) 3-Acetyl-4-hydroxyquinoline:

(2) 3-Methyl-3-acetyl-4-hydroxyquinoline:

(3) 6-Methyl-3-acetyl-4-hydroxyquinoline:

(4) 7-Methyl-3-acetyl-4-hydroxyquinoline:

(5) 5-Methyl-3-acetyl-4-hydroxyquinoline:
(6) 8-Chloro-3-acetyl-4-hydroxyquinoline:

(7) 6-Chloro-3-acetyl-4-hydroxyquinoline:

(8) 7-Chloro-3-acetyl-4-hydroxyquinoline:

(9) 5-Chloro-3-acetyl-4-hydroxyquinoline:

(10) 6,8-Dimethyl-3-acetyl-4-hydroxyquinoline:
(11) 8-Hydroxy-3-acetyl-6-hydroxyquinoline:

(12) 6-Hydroxy-3-acetyl-4-hydroxyquinoline:

(13) 8-Hydroxy-3-acetyl-4-hydroxyquinoline:

(14) 6-Hydroxy-3-acetyl-4-hydroxyquinoline:

(15) 7-Nitro-3-acetyl-4-hydroxyquinoline:
(16) 6-Nitro-3-acetyl-4-hydroxyquinoline:

Out of the sixteen 3-acetyl-4-hydroxyquinolines mentioned above, only (8) has been previously prepared (Synder and Jones, loc. cit.). All others have been prepared for the first time.

The presence of the carbonyl group of the acetyl group in 3-position has been confirmed by preparing phenyl hydrazones of some of them, namely, (1), (3), (10) and (11).

II. Cyclisation of ethyl arylaminomethylcinnamaldehyde:

Cyclisation of an ethyl arylaminomethylcinnamaldehyde produces ethyl 4-hydroxyquinoline-3-carboxylate and its derivatives. Using the thermal method, cyclisation of a number of acrylates belonging to this group has been already carried out by some of the previous investigators (Price and Roberts, loc. cit.; Hiegel et al., loc. cit.; Duffin and Kendall, loc. cit.). Some of these acrylates were cyclised by the acetic anhydride-sulphuric acid method to study its
applicability. It was observed that the acylates did undergo cyclisation with these reagents. Some additional acylates were also cyclised by thermal method to 4-hydroxyquinoline derivatives hitherto unknown.

Ethyl m-toluidinomethylene malonate, which was not cyclised before, has been cyclised by both the methods. Cyclisation by the Price-Roberts synthesis produces the 7-methyl isomer, whereas anhydride-sulphuric acid method yields the 5-methyl isomer exclusively. Price and Roberts (loc. cit.) obtained the 7-chloro isomer when ethyl m-chloroanilinomethylene malonate was cyclised in diphenyl ether.

When, however, its cyclisation was effected with acetic anhydride and sulphuric acid, the 5-chloro isomer was formed.

During the present investigation, the following ethyl 4-hydroxyquinoline-5-carboxylates were prepared:

(1) Ethyl 4-hydroxyquinoline-3-carboxylate:

![Chemical Structure](image)
(2) Ethyl 7-methyl-4-hydroxyquinoline-3-carboxylate:

(3) Ethyl 5-methyl-4-hydroxyquinoline-3-carboxylate:

(4) Ethyl 6-chloro-4-hydroxyquinoline-3-carboxylate:

(5) Ethyl 7-chloro-4-hydroxyquinoline-3-carboxylate:

(6) Ethyl 5-chloro-4-hydroxyquinoline-3-carboxylate:
(7) Ethyl 8-ethoxy-4-hydroxyquinoline-3-carboxylate:

(8) Ethyl 6-bromo-4-hydroxyquinoline-3-carboxylate:

Of the compounds enumerated above, (2), (3), (6), (7) and (8) are new. Hydrolysis of the above esters give the corresponding 4-hydroxyquinoline-3-carboxylic acids which are mentioned below:

(1) 4-Hydroxyquinoline-3-carboxylic acid.

(2) 7-Methyl-4-hydroxyquinoline-3-carboxylic acid.

(3) 5-Methyl-4-hydroxyquinoline-3-carboxylic acid.

(4) 8-Chloro-4-hydroxyquinoline-3-carboxylic acid.

(5) 7-Chloro-4-hydroxyquinoline-3-carboxylic acid.

(6) 5-Chloro-4-hydroxyquinoline-3-carboxylic acid.

(7) 8-Ethoxy-4-hydroxyquinoline-3-carboxylic acid.

(8) 6-Bromo-4-hydroxyquinoline-3-carboxylic acid.
Out of the acids mentioned on the preceding page, (2), (3), (5), (6), (7), and (8) have been prepared for the first time. Moreover, the acid produced by the hydrolysis of the 5-isomer has been found to be quite different from that obtained from the 7-isomer in the case of both m-toluidine and m-chloroaniline.

III. Cyclisation of ethyl β-oxylamine-2-carboxy acylates:

The acylates obtained by the condensation of ethyl ethoxalylacetate and some aromatic amines have been cyclised by the oxhydride-sulphuric acid method only to see whether the method is applicable in their case or not. They have been found to undergo cyclisation readily by this method producing ethyl 4-hydroxyquinoline-2-carboxylates. The following three esters have been synthesised:

(1) Ethyl 4-hydroxyquinoline-2-carboxylate
(2) Ethyl 6-methyl-4-hydroxyquinoline-2-carboxylate

(3) Ethyl 6-methoxy-4-hydroxyquinoline-2-carboxylate

Of the above esters, (2) does not seem to have been prepared before. Hydrolysis of the above esters yielded the following 4-hydroxyquinoline-2-carboxylic acids:

(1) 4-Hydroxyquinoline-2-carboxylic acid

(2) 6-Methyl-4-hydroxyquinoline-2-carboxylic acid

(3) 6-Methoxy-4-hydroxyquinoline-2-carboxylic acid.

Out of these acids, (2) appears to be new.

IV. Cyclisation of ethyl acylaminomethyleneacetoacetates:

To study the efficacy of the anhydride-sulphuric acid method to cyclise the acylates prepared from ethyl ethoxy-methyleneacetoacetate and aromatic amines, a few of them
were subjected to the action of these reagents to produce
3-cyano-4-hydroxyquinolines. As a result of this cyclisation,
the expected products were not obtained but 4-hydroxyquinoline
-3-carboxylic acids were produced instead, the cyano group
being hydrolysed to the carboxyl group due to the presence
of concentrated sulphuric acid.

When ethyl m-chloroanilinomethylenecyanocetate was
cyclised in boiling diphenyl ether, 7-chloro-3-cyano-
4-hydroxyquinoline was the main product (Prigo, Leonard and
Hofmannson, loc. cit.; Snyder and Jones, loc. cit.). The
hydrolysis of the cyanoquinoline was readily accomplished
by refluxing it with 50 per cent sulphuric acid to yield
the corresponding acid. When, however, the same acylate
was cyclised with acetic anhydride and sulphuric acid,
5-chloro-4-hydroxyquinoline-3-carboxylic acid was obtained,
the cyano group in 3-position being hydrolysed to the
carboxyl group. This acid was found to be different from
the acid obtained by the hydrolysis of the 7-chloro isomer,
but it was identical with the acid obtained by the hydrolysis
of ethyl 5-chloro-4-hydroxyquinoline-3-carboxylate. The same
acid was however different from the acid produced by the hydrolysis of ethyl 7-chloro-4-hydroxyquinoline-5-carboxylate. Using ethyl ethoxymethylencyanocacetate, the following two 3-cyano-4-hydroxyquinolines were prepared for the first time by cyclisation of the respective anils in diphenyl ether:

(1) 7-Methyl-3-cyano-4-hydroxyquinoline:

![Chemical Structure of 7-Methyl-3-cyano-4-hydroxyquinoline]

(2) 6-Methoxy-3-cyano-4-hydroxyquinoline:

![Chemical Structure of 6-Methoxy-3-cyano-4-hydroxyquinoline]

Hydrolysis of the above 3-cyano-4-hydroxyquinolines as well as cyclisation of the acylates from m-chloroaniline and p-anisidine with acetic anhydride and sulphuric acid yielded the following 4-hydroxyquinoline-3-carboxylic acids:

(1) 7-Methyl-4-hydroxyquinoline-3-carboxylic acid

(2) 6-Methoxy-4-hydroxyquinoline-3-carboxylic acid

(3) 5-Chloro-4-hydroxyquinoline-3-carboxylic acid.* * * * * * *
EXPERIMENTAL
EXPERIMENTAL

PART I

Synthesis with ethyl ethoxymethylenecacetate:

Preparation of Ethyl ethoxymethylenecacetate:

This ester was prepared according to the procedure described by Claissen (Ber., 1895, 28, 2751; Annalen, 1897, 287, 16). A mixture of pure ethyl acetocetate (66 gms., 0.5 mole), ethyl orthoformate (74 gms., 0.5 mole) and acetic anhydride (102 gms., 1 mole) was placed in a one-litre round-bottom flask fitted with a reflux condenser. The flask was gently heated for the first fifteen minutes and then refluxed for 35 to 40 minutes. The contents of the flask were then immediately transferred to a flask fitted for distillation and the mixture was distilled as rapidly as possible within half an hour till the temperature in the boiling liquid was below 195° C. A dark-red thick liquid was left in the flask. It was then purified by distillation in vacuum. A colourless thick liquid (yield, 74.4 gms., 80%; B.P. 234° - 236° C) was obtained. The liquid did not solidify in the freezing mixture and it became coloured on keeping.
(1) Condensation of ethyl ethoxymethyleneacetocetate with

(4) Preparation of ethyl anilinemethylenecetoneacetate:

This aniline was prepared by modifying the method originally
used by Claisen (Annalen, 1897, 292, 33). Freshly distilled
aniline (10.2 gms.) was added in portions to ethyl ethoxymes-
methyleneacetoneacetate (20 gms.). The mixture became warm
because of the heat of the reaction that had commenced.
The mixture was then heated on a steam-bath for 45 minutes
and then it was left overnight at room temperature.

The thick brown liquid acrylate was taken up in ether
(100 c.c.) in a separating funnel and the ethereal solution
was shaken four times with 75 c.c. of dilute hydrochloric
acid (1 N) to remove excess of the unreacted aniline. It was
then shaken twice with 50 c.c. of sodium bicarbonate solution
(10 %) and finally washed with water several times. The
ethereal solution of the acrylate was left in contact with
anhydrous potassium carbonate for twentyfour hours for
dehydration. After removing potassium carbonate by filtration,
the ethereal solution was evaporated and the thick liquid
Acrylate obtained was kept in a desiccator over calcium chloride for three days. The oil solidified to a yellowish white mass (yield, 12.5 gms., 20%). On crystallising this solid mass from petroleum ether, yellowish white needles (m.p. 45-46°C) were obtained (Claisen, loc. cit.; Daims, loc. cit.).

(B) Cyclisation of ethyl anilinomethylencacetoacetate:

Preparation of 3-Acetyl-1-hydroxyquinoline:

The acrylate (12.5 gms.) described above was dissolved in acetic anhydride (25 c.c.) and concentrated sulphuric acid (12.5 c.c.) was added to the solution by portions within two minutes. There was considerable evolution of heat as a result of which the mixture began to boil vigorously. The mixture, which assumed red-brown colour, was allowed to cool down to the room temperature. It was then poured on powdered ice (50 gms.) and left for a further period of one hour so that excess of acetic anhydride might decompose. The acidic mixture was then neutralised with strong sodium hydroxide solution (33%). reddish white precipitates were obtained on complete neutralisation of the acid. The mixture was left overnight for complete separation of the solid.
On the next day the precipitates were filtered and the residue was washed with water and dried. (Yield, 6.2 gms; i.e. 62%). For purification, the crude cyclized product was dissolved in hot aqueous alcohol (50%) and treated with animal charcoal and filtered. White woolly needles (m.p. 233°-245° C) appeared on cooling. On recrystallisation from the same solvent-mixture, a white crystalline product (m.p. 244° C) was obtained.

The aqueous-alcoholic solution of the product gave red coloration with the solution of ferric chloride.

(Found: N, 7.6%; C<sub>11</sub>H<sub>9</sub>O<sub>2</sub>N requires N, 7.5%)

Preparation of Phenyl hydrazone of (II):-

Purified 3-acetyl-4-hydroxyquinoline (0.5 gms.) was heated for 2 to 3 minutes with phenyl hydrazine (0.5 c.c.) on a gentle flame and 2 c.c. of alcohol were added to dissolve the mixture. Water was then added drop by drop to this solution till the phenyl hydrazone began to crystallise out. On twice recrystallising it from the mixture of water and alcohol, white needles (m.p. 225°-226° C) were obtained.

(Found: N, 15.0%; C<sub>17</sub>H<sub>15</sub>N<sub>2</sub>O requires N, 15.2%).
(2) Condensation of ethyl o-tolydromethyleneacetacetate with

\( \text{o-toluidine} \)

(a) Preparation of ethyl o-toluidinomethyleneacetacetate:

11.5 gms. of purified o-toluidine was mixed with ethyl

o-tolydromethyleneacetacetate (20 gms.). The mixture became

warm due to the commencement of the reaction. It was then

heated on a steam-bath for one hour and was kept overnight

at room temperature. The impure semi-solid acrylate was

purified in the same manner as that from aniline. (Yield,

14.5 gms.; m.p. 71°C).

(Bains, Kiev, 1902, 35, 2500, prepared the same compound

by heating di-o-tolyldromuidine with acetoacetic ester

at 150°C.)

(b) Cyclisation of ethyl o-toluidinomethyleneacetacetate:

Preparation of 6-Methyl-5-acetyl-4-hydroxyquinoline:

Ethyl o-toluidinomethyleneacetacetate (13 gms.) was

mixed with 25 c.c. of pure acetic anhydride which dissolved

the acrylate. Concentrated sulphuric acid (15 c.c.) was

added to the solution within three minutes. Considerable

heat developed and the mixture began to boil with effervesc
nccne. It was then allowed to assume room temperature,
poured on crushed ice and kept for an additional hour. The
acidic mixture was almost completely neutralised with caustic
soda solution(33%). The cyclised hydroxyquinoline derivative
separated as a reddish white solid.

On the next day, it was filtered, washed with water and
dried.(Yield, 3.2 gms.; 59.5 %). After treatment with
charcoal and twice recrystallising the crude product from
alcohol, white needle-shaped product(M.P. 273°-274°) was
obtained.

(Found: N, 6.8 %; C_{12}H_{11}O_{2} requires N, 7.0 %)

(3) Condensation of ethyl ethoxymethyleneacetocetate with
m-toluidine:

(A) Preparation of ethyl m-toluidinemethylacetoacetate:-

The warm mixture of ethyl ethoxymethyleneacetocetate
(59 gms.) and m-toluidine(23.5 gms.) was heated on a steam-
bath for one hour. The alcoholic solution of the viscous
product was shaken with four portions of dilute hydrochloric
acid(1 N), then with sodium bicarbonate solution(10%) and
finally with water. The product obtained on evaporation
and desiccation for two days was crystallised from petroleum ether. White needles (m.p. 55°C).

(Found: N, 5.5%; C_{16}H_{17}O_{4} requires N, 5.7%).

(B) Formation of 5-Methyl-3-acetyl-4-hydroxyquinoline:

(Cyclisation with acetic anhydride and sulphuric acid)

Ethyl m-toluidinomethylcinnamate (II gms.) was cyclised by means of acetic anhydride (22 c.c.) and concentrated sulphuric acid (11 c.c.). The reaction mixture, which became very much hot, was allowed to cool down to room temperature and was treated with powdered ice. As a result of the complete neutralisation of the mixture, semi-solid tarry mass separated, which was kept overnight for further solidification. The crude product was dissolved in hot 2 N sodium hydroxide solution (100 c.c.), treated with animal charcoal and then the solution was filtered. The filtrate, when acidified with concentrated hydrochloric acid, gave white solid (yield 1 gms., 12%); which was recrystallised from alcohol melted at 222°C.

(Found: N, 6.9%; C_{18}H_{11}O_{2} requires N, 7.0%).

(C) Formation of 7-Methyl-3-acetyl-4-hydroxyquinoline:
(c) 7-ethyl-5-acetyl-4-hydroxyquinoline:

Eudication by thermal method:

The solution of ethyl n-toluidinoethylacetocetate (5.5 gms.) in diphenyl ether (50 c.c.) was added within fifteen minutes to boiling diphenyl ether (60 c.c.) and the boiling of the mixture was continued for an additional half an hour. The solid obtained on cooling was filtered and was treated three times with boiling petrolatum ether to disolve the unsolubilized acrylate. The crude cyclized product was then dissolved in 2 N sodium hydroxide, the hot solution was charcoalized and filtered. Acidification of the filtrate with hydrochloric acid yielded yellowish white precipitates (yield: 2.7 gms.) which were repeatedly crystallized from nitrobenzene gave white needles (M.P. 270°C). The mixed melting point of this product with that obtained by the acetic anhydride-sulphuric acid method was considerably depressed.

(Found: N 7.3%; C_{15}H_{11}O_{2}N requires N 7.0%).
(4) Condensation with p-toluidine:

(A) Preparation of ethyl p-toluidinomethylcinnamatoacetate:

p-Toluidine (11.1 gms.) was mixed with ethyl o-hydroxymethylcinnamatoacetate (19.4 gms.). There was little rise in the temperature of the mixture. It was then heated on a steam-bath for one hour and allowed to cool. The amil was obtained as a red-brown viscous liquid which was purified in the same way as the amil from aniline, using ether. (Yield, 15.5 gms.; 60 %). Crystallization from petroleum ether yielded white prismatic needles melting at 65^oC.

(B) 6-Methyl-3-acetyl-4-hydroxyquinoline:

(i) Acetic anhydride-sulphuric acid method:

15.5 gms. of the esterate described above was dissolved in acetic anhydride (31 c.c.). To this solution, concentrated sulphuric acid (15.5 c.c.) was added in two minutes. Vigorous effervescence was produced due to heat of the reaction. After cooling the mixture, chopped ice (50 gms.) was added to decompose the anhydride. On being neutralised with caustic soda solution (33 %), red-brown solid began to separate out.
The solid was filtered on the next day, washed with water and dried. (Yield, 4.5 gms.; 33 %). Repeated crystallisations from nitrobenzene yielded white needles (m.p. 253°C).

(Found: N, 6.7 %; C_{12}H_{11}O_{2}N requires N, 7.0 %).

(ii) Cyclisation by thermal method:

The same acrylate (10 gms.) was mixed with diphenyl ether (20 c.c.) and the mixture was added in portions to boiling diphenyl ether (100 c.c.). The boiling was continued for an hour. On cooling, brown solid separated out. It was filtered and the residue was treated several times with boiling petroleum ether to extract the unreacted anil. (Yield, 6.2 gms., 77 %). Crystals from nitrobenzene (m.p. 257°-258°C). Its mixed melting point with the sample obtained by the first method was not depressed.

(5) Condensation with o-chloroaniline:

(A) Ethyl o-chloroanilinomethyleneacetooacetate:

Ethyl ethoxymethyleneacetooacetate (20 gms.) was mixed with 13.7 gms. of o-chloroaniline; the resulting was mixture was heated on a steam-bath for one and half hours and left overnight. The acrylate solidified to a brownish-white mass.
on the next day. The powdered solid was shaken several times
with dilute hydrochloric acid (1 N), filtered and washed with
water. (Yield: 25.4 gms.; 81 %). On being twice recrystallised
from petroleum ether, white prisms (m.p. 64.0°C) were obtained.

(Found: N, 5.0 %; Cl, 12.9 %; C_{15}H_{14}O_{3}N requires
N, 5.2 %; Cl, 15.3 %)

(ii) 2-Chloro-5-acetyl-4-hydroxyquinoline

(i) Cyclisation with acetic anhydride and sulphuric acid:

Ethyl 2-chloroquinolin-4-methylacetacetate (10 gms.) was
dissolved in acetic anhydride (30 c.c.) by little warming.
Concentrated sulphuric acid (10 c.c.) was poured into the
solution within three minutes. There was considerable
evolution of heat. The acidic mixture, to which powdered
ice was previously added, was just neutralised with strong
sodium hydroxide solution. The brown solid, which separated,
was removed by filtration and dissolved in hot ordinary
caustic soda solution, charcoalred and filtered. On acidifi-
fication of the filtrate with HCl, slightly coloured white
product was precipitated. This cyclised product (yield 1 gms.)
in very slightly soluble in alcohol. Its alcoholic solution
given orange coloration with ferric chloride. It was crystallised from nitrobenzene; white plates (m.p. 294°C).

(Found: N, 6.5% ; Cl, 16.3% ; C_{11}H_{9}O_{2}Cl requires:
N, 6.3% ; Cl, 16.0%).

(ii) Cyclisation by the thermal method:

2.53 gms. of the above acylate was cyclised in boiling diphenyl ether (60 c.c.). Heating was continued for fifteen minutes. On cooling, yellowish-brown solid (2.6 gms., yield 60%); which separated, was washed with petrolatum ether and crystallised from nitrobenzene. The white crystalline solid melted at 233°-234°C. Its mixed melting point with the specimen prepared by the first method was not depressed.

Its phenyl hydrazine, prepared by heating the compound (0.2 gms.) with a slight excess of phenyl hydrazine on a small flame for 5 minutes, the resulting hot liquid mass mixed with alcohol (5 c.c.), precipitated by adding water and recrystallised from aqueous-alcohol, melted at 235°C.

(c) Synthesis with m-chloroaniline:

(A) Ethyl m-chloroanilinomethylcnenacetacetate:

A mixture of ethyl ethoxymethylcnenacetacetate (30 gms.)
and freshly distilled m-chloroaniline (21.6 gms.) was heated on a steam-bath for one hour and fifteen minutes and was left overnight. Reddish-white solid (yield, 60 gms.) obtained was purified in the same manner as the oil from o-chloroaniline. Yellowish-white crystals from petroleum ether melted at 80° C (Synder and Jones, loc. cit.).

(b) Cyclisation of the acrylate:

(1) Acetic anhydride-sulphuric acid method: Formation of 5-Chloro-5-acetyl-2-hydroxyquinoline:

Concentrated sulphuric acid (8 c.c.) was added within two minutes to the solution of ethyl m-chloroaniline-nitroethylene-acetoacetate (8 gms.) dissolved in warm acetic anhydride (21 c.c.). The reaction was accompanied by heat and effervescence. On almost completely neutralising the mixture containing chopped ice, a brownish-white solid separated. On crystallising the crude product from nitrobenzene, white prismatic crystals (m.p. 218°C) were obtained.

(Found: N, 6.1% ; Cl, 15.7% ; C_{11}H_{8}O_{2}NCl requires: N, 6.3% ; Cl, 16.0%)
(11) Thermal method: Formation of 7-Chloro-5-acetyl-
4-hydroxyquinoline:

This compound was produced when the cyclisation of
ethyl m-chloroanilinomethyleneacetocetate (10 gms.) was
carried out in boiling diphenyl ether (125 c.c.). After two
crystallisations of the crude product (yield: 7 gms., 81%) from
nitrobenzene, white crystals (m.p. 313°-315°C) were
obtained (Synder and Jones, loc. cit.). The mixed melting
point of this substance with the sample obtained by the
first method was considerably depressed.

(7) Synthesis with m-chloroaniline:

(a) Preparation of ethyl m-chloroanilinomethyleneacetocetate

Purified m-chloroaniline (14 gms.) was mixed with ethyl
methoxynmethylenacetocetate (20 gms.). The mixture dissolved
in the coto with development of heat. On shaking, the
mixture solidified, indicating that considerable reaction
took place. For completion of the reaction, the mixture
was heated on a steam-bath for one and half hours. The
brownish-white solid, obtained on cooling the reaction-mass,
was shaken several times with dilute hydrochloric acid.
filtered, washed with water and dried (yield 21.6 gms., 76%).

On being crystallised from petroleum ether, white prisms (m.p. 97°C) were obtained.

(Found: N, 5.3%; Ca, 13.0%; C13H12O3JIC requires:

N, 5.2%; Ca, 15.5%).

(2) 6-Chloro-3-acetyl-1-hydroxyquinoline

(1) Cyclisation with anhydride sulphuric acid:

Concentrated sulphuric acid (8 a.c.) was added to the solution of 8 gms. of the above acrylate dissolved in acetic anhydride (25 a.c.) within one minute. Evolution of heat was noticed as usual. After adding powdered ice, the mixture was neutralised with concentrated NaOH solution. The red-brown solid, which precipitated, was purified by dissolving in hot 2 N NaOH, charcoalising and reprecipitating from the filtrate with concentrated HCl (yield 2 gms., 50%).

Further purification was effected by crystallisation from nitrobenzene. White prisms, which began to blacken above 205°C, but they did not melt up to 330°C.

(ii) Cyclisation by thermal method:

The same acryl (3.5 gms.) was cyclised by dropping it into
boiling diphenyl ether (40°C) within ten minutes. Boiling
was continued for additional fifteen minutes. Brown solid
(yield, 1.5 gms.), which separated on cooling, on being
crystallized from nitrobenzene, yielded white prism which
began to blacken above 235°C but did not melt up to 300°C.

(Found: N, 6.0% ; C, 16.4% ; C_{11}H_{8}O_2.0 requires:
N, 6.3% ; C, 16.0% )

8) Condenation with 1:3:4-xylidine:

A) Ethyl m-xyldinomethylacetoacetate:

When a mixture of ethyl ethoxymethyleneacetoacetate
(20 gms.) and 1:3:4-xylidine (13 gms.) was heated on a steam-
bath for one hour, brownish-white solid amil (21.6 gms.,
yield 77%) was produced, which on being crystallized as
white prism, melted at 122°C.

(Day and Griffin, J. Amer. Chem. Soc., 1913, 35, 999)
prepared this compound by heating di-m-xylyliminodimine with
acetoacetic ester at 120°C).

B) 6:8-Dimethyl-3-acetyl-4-hydroxyquinoline:

I) Cyclization with acetic anhydride and sulphuric acid:

Ethyl m-xyldinomethylacetoacetate (10 gms.) was
cylised by dissolving it in vacuo acetic anhydride (30 c.c.) and adding 10 c.c. of concentrated sulphuric acid in two minutes. Brown solid (yield 2 gms.; 24 %) which separated on neutralisation with strong NaOH when crystallised from alcohol, yielded yellowish-white needles (m.p. 250°-251°).  

(Found: N, 6.3 %; C₁₅H₁₅O₂ requires N, 6.5 %).  

(ii) Cyclisation by thermal method:-  

The same hydroxyquinoline derivative was produced on dropping ethyl m-xylidinemethylbenzacetate (6 gms.) into boiling diphenyl ether (75 c.c.) and continual boiling for further period of fifteen minutes. Brownish-white needles; which separated on cooling, were filtered after being shaken thrice with boiling petroleum ether. (Yield 5.2 gms.; 65 %). The mixed melting point of this product, after it was crystallised from alcohol, with the pure specimen prepared by the previous method, did not show any depression.

Its phenyl hydrazone, after being recrystallised from alcohol, melted at 230° C.
(9) Synthesis with o-quinidine:

(A) Preparation of ethyl o-quinidinomethylacetacetaete:

On heating o-quinidine (15.5 gms.) with ethyl ethoxy-

methylacetacetate (23.5 gms.) on a steam-bath, 23.4 gms.

(yield, 86 %) of the acrylate was obtained. White needles

from petroleum ether (M.P. 113° C).

(Doams and Brown, J. Am. Chem. Soc., 1909, 31, 1151;

it was prepared it by the action of the corresponding diaroylforma-

midine on acetacetic ester.)

(B) 2-Nethoxy-5-acetyl-4-hydroxyquinoline:

(1) Cyclisation with anhydride-sulphuric acid:

On adding sulphuric acid (10 c.c.) to the solution of

the acrylate (10 gms.) in acetic anhydride (50 c.c.),

and neutralising the resulting iceq mixture with strong NaOH,

brownish-white solid (yield 1 gms., 12 %) separated. Crystals

from rectified spirit, after treatment with animal charcoal,

melted at 225°- 230° C.

(II) Cyclisation by thermal method:

Ethyl o-quinidinomethylacetacetate (10 gms.) was

cyclised in boiling diphenyl ether (100 c.c.) to yellowish-
brown mass (yield: 3.2 gms.; 39 %). White wooly needles
(H.P. 235°C) were obtained; when a portion of the crude
product was crystallized from rectified spirit after treatment
with charcoal.

(Found: N, 6.2 %; C_{18}H_{11}O_3N requires N, 6.5 %)

Its phenyl hydrazone, after crystallization from recti-
ified spirit, melted at 253°C.

(10) Condensation with p-anisidine:

(A) Preparation of ethyl p-anisidinomethyleneacetoacetate:

After mixing purified p-anisidine (15 gms.) with ethyl
ethoxymethyleneacetoacetate (22.6 gms.) and heating the
resulting warm mixture on a steam-bath for one hour, the
acylato was produced as a greyish-white solid (yield, 23.3 gms.
I.e. 75 %). Purification of the acylato in the usual manner
and its recrystallization from petroleum ether yielded white
needles (H.P. 83°C).

(Found: N, 5.1 %; C_{14}H_{17}O_4N requires N, 5.3 %).

(B) Synthesis of 6-Methoxy-5-acetyl-4-hydroxyquinoline:-

The above acylato (6.8 gms.) was dropped into boiling
diphenyl ether (75 c.c.) within three minutes. Boiling was
continued for additional 15 minutes. Brown product (1.6 gms.) which separated on cooling, was purified by crystallisation from rectified spirit. White needles (M.P. 230°C).

(Found: N, 5.1%; C₁₂H₁₁O₂N requires N, 6.5%).

(11) Condensation with o-phenetidine:-

(A) Preparation of ethyl o-phenetidinomethylencacetacacetate:-

This ester had already been prepared by Daines and Hunger (J. Am. Chem. Soc., 1919, 41, 565) using di-o-phenetidylformamide and acetanilide ester. During the present work, it was prepared by heating ethyl o-nitrophenylencacetacacetate (25 gms.) with o-phenetidine (18.5 gms.) at 100°C.

(Yield, 25.8 gms.; 67%). M.P. 111°C.

(B) Synthesis of 3-Ethoxy-3-acetyl-4-hydroxyquinoline:-

Ethyl o-phenetidinomethylencacetacacetate (10 gms.) was added in portions to boiling diphenyl ether (120 c.c.) and the boiling was continued for additional 15 minutes. On cooling, yellowish-brown solid separated. After treating this crude product three times with boiling petrolatum ether, it (yield, 6.8 gms.; 82%) was crystallised from dilute acetic acid (2 N). Pale yellow plates (M.P. 278°C).
(Found: N, 5.8 %; C_{19}H_{16}O_{6}N requires N, 6.1 %).

(12) Condensation with p-phenetidine:–

(A) Ethyl p-phenetidinomethylcycloacetate:–

The warm mixture of p-phenetidine (11 gms.) and ethyl ethoxymethylcycloacetate (15 gms.) was heated for one and a quarter hours on a steam-bath. Brownish-yellow solid (yield, 14.5 gms.; 65 %); after being purified with dilute hydrochloric acid and washing with water, was crystallised from petroleum ether from which white needles (m.p. 87°–88°C) separated.

(Found: N, 5.3 %; C_{15}H_{19}O_{4}N requires N, 5.05 %).

(B) 6-Ethoxy-5-acetyl-6-hydroxyquinoline:–

7 gms. of the above acrylate were cyclised by dropping in boiling diphenyl ether (75 c.c.). Yield of the product; after being treated with hot petroleum ether was 5.3 gms. (85 %). Repeated crystallisations from dilute acetic acid yielded pale yellow plates melting at 265°–267°C.

(Found: N, 6.3 %; C_{13}H_{15}O_{3}N requires N, 6.1 %).
(13) **Synthesis with n-nitrosoiline:**

(A) **Preparation of ethyl n-nitrosoilineacoxymethylenacetoacetato:-**

n-nitrosoiline (15.5 gms.) was heated with ethyl ethoxymethylenacetoacetato (25 gms.) on a steam-bath for twelve hours. The yellow solid acrylate was shaken with dilute (1 N) hydrochloric acid to dissolve excess of the amine, filtered, washed and dried. (Yield: 31 gms.; 83 %). On twice recrystallising from ethyl acetate, yellow needles (m.p. 113°C) were obtained.

*Found: N, 5.8 %; C₁₅H₂₀O₃N₂ requires N, 10.1 %.*

(B) **Cyclisation of the acrylate: Formation of 7-nitro-5-acetyl-4-hydroxyquinoline:-**

The acrylate (8 gms.) mentioned in (A) was cyclised in boiling diphenyl ether (100 c.c.). The product, which separated on cooling, was washed several times with hot ethyl acetate to get rid of the uncyclised amine. (Yield: 6.2 gms.; 93 %). It was twice recrystallised from nitrobenzene giving yellow needles which began to blacken above 275°C but did not melt up to 300°C.

*Found: N, 12.4 %; C₁₁H₆O₄N₂ requires N, 12.1 %.*
(14) Synthesis with p-nitroaniline:

(A) Ethyl p-nitroaniline-methyleneacetoacate:

This oil was prepared and purified in the same manner as that from m-nitroaniline by heating the mixture of p-nitroaniline (18.5 gms.) and ethyl ethoxymethyleneacetoacate (25 gms.). The yellow solid acrylate (35.5 gms.; 95 %), on being crystallised from alcohol, yielded yellow needles (m.p. 140°-143° C).

(Found: N, 10.3 %; C_{13}H_{14}O_{2}F requires N, 10.1 %).

(B) 6-Nitro-3-acetyl-4-hydroxyquinoline:

Ring closure of the above acrylate (10 gms.) was effected in diphenyl ether (100 c.c.) as usual. The cyclised product, which separated on cooling, as a yellowish-brown mass, after being crystallised from nitrobenzene, yielded deep yellow needles. These crystals blackened above 235°C but did not melt up to 300°C. Yield: 5.5 gms. (66%).

(Found: N, 12.0 %; C_{11}H_{8}O_{2}N_{2} requires N, 12.1 %).
(II). Synthesis with Ethyl ethoxymethylmalonate:

Preparation of Ethyl ethoxymethylmalonate:

This ester was prepared according to the procedure described by Chaise (Annalen, 1897, 297, 73) with a few modifications. A mixture of freshly distilled diethyl malonate (80 gms., 0.5 mole); ethyl orthoformate (74 gms., 0.5 mole); acetic anhydride (102 gms., 1 mole) and anhydrous zinc chloride (1.5 gms.) was heated gently in the beginning for ten to fifteen minutes and then boiled under a reflux condenser for 45 minutes. Zinc chloride dissolved in the hot mixture in the beginning. A small amount of a white solid, which separated during the reaction, was removed by filtering the hot resulting mixture as rapidly as possible.

The filtrate was then immediately distilled at ordinary pressure until the temperature in the boiling liquid was below 100°C. When the residual liquid was distilled under reduced pressure, the fraction which collected between 140°C-160°C (10-15 mm.) was pure ethyl ethoxymethylmalonate. It was a colourless oily liquid.
(1) Condensation of Ethyl ethoxymethylenecaramate with aniline

(A) Preparation of Ethyl anilinoethylenecaramate:

This anil was prepared essentially according to the
same method as that employed by Duffin and Kendall (loc. cit.).
Freshly distilled aniline (8.6 gm.) was gradually mixed with
ethyl ethoxymethylenecaramate (20 gm.). There was appreciable
development of heat due to the commencement of the reaction
in cold. The mixture was then heated on a steam-bath for
half an hour. After cooling, the resulting thick oily anil
was taken up in ether (100 c.c.) and the ethereal solution
was shaken with four 75 c.c. portions of dilute (1 N) hydro-
chloric acid, then twice with 50 c.c. of sodium bicarbonate
solution (10 %) and finally washed with water. The ethereal
solution was then dehydrated by placing it in contact with
anhydrous potassium carbonate for one day. On evaporating
the ethereal solution, a red thick oil was left as the
residue which solidified to a transparent mass (yield: 18.8 gm.,
i.e. 77 %) on desiccation for two days. Colourless
crystals from petroleum ether melted at 49°-50°C (Duffin
and Kendall, loc. cit.).
(b) Cyclisation of the acrylate: Formation of Ethyl 4-hydroxyquinoline-3-carboxylate:

Ethyl amiloramide acrylate (14 gms.) was dissolved in acetic anhydride (23 c.c.) and concentrated sulphuric acid (14 c.c.) was added in portions within two minutes. The reaction mixture began to boil due to considerable development of heat. After cooling the resulting thick brown oily liquid, it was poured on crushed ice (50 gms.) and left for an hour. On neutralising the acidic solution with 33% sodium hydroxide solution on the acidic side, yellowish-white precipitates were obtained. To prevent the hydrolysis of the carboxylic group, final neutralisation was effected with sodium carbonate solution. It was then filtered, washed several times with water and dried. (Yield: 4.3 gms.; 42%). (Duffin and Kendall prepared the same compound using the thermal method—yield: 30%). On being recrystallised from acetic acid, white needles (m.p. 250°-270°) were obtained.

(c) Hydrolysis of Ethyl 4-hydroxyquinoline-3-carboxylate:

Formation of 4-Hydroxyquinoline-3-carboxylic acid:

Crude ethyl 4-hydroxyquinoline-3-carboxylate (2 gms.) was
hydrolysed by refluxing with 2 N sodium hydroxide solution (50 c.c.) for one and half hours. The hot alkaline solution was treated with animal charcoal and filtered. On adding concentrated hydrochloric acid to the cooled filtrate, the acid separated as a white flocculent solid in almost quantitative yield. The acid on being crystallised from nitrobenzene, melted at 239°-270° with decomposition (Duffin and Kendall, loc. cit.).

(A) Condensation with m-toluidine:

(A) Preparation of Ethyl m-toluidinomethylenemalonate:

Purified m-toluidine (9 gms.) was heated with ethyl othoxy methylenemalonate (17.7 gms.) for half an hour on a steam-bath. It was subjected to purification in the same manner as the amyl from anilino and then destilled. But the red-brown oil (yield: 13 gms.) did not solidify even on prolonged destillation, so it was used for cyclisation without further purification.

(Found: H, 4.8 %; C_15H_21O_5 requires H, 5.05 %).
(B) Cyclisation of the carboxylate:

1. With acetic anhydride and sulphuric acid:

   a. Formation of ethyl 5-methyl-4-hydroxyquinoline-3-carboxylate:

   Concentrated sulphuric acid (15 c.c.) was added within five minutes to ethyl m-toluidinomethylcamphorate (15 gm.) dissolved in acetic anhydride (25 c.c.). Vigorous reaction took place with the evolution of heat and effervescence. On first neutralising the resulting mixture, in which powdered ice was previously added, with caustic soda solution (33%) and finally with sodium carbonate solution, yellowish-white solid separated (yield: 8 gm., 74%). It was then twice recrystallised from rectified spirit (M.P. 246° C).

   (Found: N, 5.8% ; C₁₃H₁₂O₃ requires N, 6.1%).

b. 5-Methyl-4-hydroxyquinoline-3-carboxylic acid:

   On being refluxed with 2 N NaOH solution (25 c.c.) for two hours, the above cyclised ester (1 gm.) was hydrolysed. After treating the hot alkaline solution with charcoal, it was filtered and the filtrate was acidified with dilute hydrochloric acid. The acid was liberated in the form of...
flocculent white precipitates which on crystallisation from nitrobenzene melted at 255°C with decomposition.

(found: N, 7.1 %; C_{11}H_{12}O requires N, 6.9 %; Neutral equivalent: 202).

(11) Cyclisation by thermal method:

(a) Ethyl 7-methyl-4-hydroxyquinoline-3-carboxylate:

Ethyl m-toluidinocarboxylate (10 g m.) was cyclised by dropping it into boiling diphenyl ether (125 c.c.) within ten minutes and boiling the mixture for additional thirty minutes. Yellowish-white solid that was separated on cooling was filtered and washed repeatedly with hot petroleum ether. White needles (H.P. 272°-275°C) were obtained on crystallisation from nitrobenzene. The mixed melting point of this product with that obtained by the preceding method was considerably depressed.

(found: N, 5.7 %; C_{15}H_{13}O requires N, 6.1 %).

(b) 7-Methyl-4-hydroxyquinoline-3-carboxylic acid:

The above ester (1 g m.) on being hydrolysed with 2 N HCl in the same way as the previous ester and subsequently acidifying the alkaline filtrate with HCl produced 7-methyl-
4-hydroxyquinoline-3-carboxylic acid, which on being crystallised from nitrobenzene separated as white needles (m.p. 263° dec.). This acid was found to be different from the acid (10) (a) as noted by the mixed melting point method.

(Found: H, 6.6%  C_{11}H_{9}O_2 requires H, 6.9%).

(Neutral equivalent: 202.5).

(3) Condensation with o-chloroaniline:

(a) Preparation of Ethyl o-chloroanilinoethylmalonate:

The mixture of ethyl ethoxymethylmalonate (21.6 gms., 0.1 mole) and purified o-chloroaniline (13.3 gms.), on being heated on a steam-bath for one and a quarter hours produced a pinkish-white solid acrylate (22.5 gms.). White prismatic needles from petroleum ether melted at 92°C. (Tarbell, J. Am. Chem. Soc., 1946, 68, 1278).

(b) Ethyl o-chloro-4-hydroxyquinoline-3-carboxylate:

Concentrated sulphuric acid (10 c.c.) was rapidly added to the solution of ethyl o-chloroanilinoethylmalonate (10 gms.) in acetic anhydride (30 c.c.). Vigorous reaction occurred due to which there was effusion. From solid (yield: 4.6 gms., 53%) separated on neutralisation of the
acidic mixture. Repeated crystallisations from ethanol yielded white needles (m.p. 254°C) (Tarrall, loc. cit.).

(c) 3-Chloro-4-hydroxyquinoline-3-carboxylic acid:

This acid was liberated when hydrochloric acid was added to the alkaline solution obtained after refluxing one g. of the ester (b) with 2 N NaOH (25 c.c.), charcoal and filtering. When crystallised from nitrobenzene, the acid melted at 231°-233°C. (Tarrall, loc. cit.) has reported the same acid to melt at 215°-250°C).

(d) Synthesis with m-chloroaniline:

(d) Preparation of Ethyl m-chloroanilinomethylenemalonate:

This ester had already been prepared before by Price and Roberts (loc. cit.) as well as by Baffin and Kendall (loc. cit.). For cyclisations during the present work, the ester was similarly prepared by heating together ethyl ethoxy-methylenemalonate (43 gms.) and pure m-chloroaniline (25.5 gms.) on a steam-bath for one hour. Yield: 35 gms (63%). White needles from petroleum ether (m.p. 56°-57°C).

(b) Cyclisation of the esterate:

(1) Using acetic anhydride and sulphuric acid:
(a) Ethyl 4-chloro-4-hydroxyquinoline-3-carboxylate:

Concentrated sulphuric acid (20 c.c.) was added within 2 minutes to a mixture of ethyl m-chloroquinolinomethylcarbonate (20 gms.) and acetic anhydride (40 c.c.). The reaction mixture, after being cooled and mixed with chopped ice, was just neutralised with strong sodium hydroxide and carbonate, reddish-white solid (3 gms., yield 18%), after being filtered, washed and dried, melted between 230°-235° C. Repeated crystallisations from nitrobenzene gave white prismatic crystals, m.p. 271° C.

(Found: N, 5.3%; Cl, 13.7%; C_{12}H_{10}Cl_{2}N requires:
N, 5.6%; Cl, 14.1%).

(b) 4-Chloro-4-hydroxyquinoline-3-carboxylic acid:

The above ester (2 gms.) was hydrolysed by refluxing it for an hour with 50 c.c. of 2 N NaOH, then treated with charcoal, filtered and the filtrate was acidified with HCl. The white precipitate, when crystallised from alcohol, gave needles (m.p. 241°-243° C dec.),

(Found: N, 6.0%; Cl, 15.5%; C_{10}H_{8}Cl_{2}NO requires:
N, 6.3%; Cl, 15.9%; Neutral equivalent: 222.0).
(11) Cyclisation by thermal method:

(a) Ethyl 7-chloro-4-hydroxyquinoline-3-carboxylate:

This compound was prepared by cyclising ethyl m-chloro-anilino-4-methylene maleate (5 gms.) in boiling diphenyl ether. The greyish-white solid, which separated on cooling, after being treated with boiling petroleum ether and subsequently crystallised from nitrobenzene melted at 290° C. (Price and Roberts, loc. cit.; Duffin and Kendall, loc. cit.). A considerable depression in the mixed melting point was observed when this product was mixed with the sample of the previous method.

(b) 7-Chloro-4-hydroxyquinoline-3-carboxylic acid:

The above ester (1 gm.) on being refluxed with 25 c.c. of dilute NaOH for one hour and subsequent acidification with HCl and crystallisation from nitrobenzene yielded white needles of the corresponding acid melting at 299° C., docs. (Duffin and Kendall, loc. cit.; Price and Roberts have reported it to be 275°-276° C. docs.).
(5) Condensation with o-phenetidine:

(A) Ethyl o-phenetidinomethyleneacetylacetate:

The warm mixture formed on adding purified o-phenetidine (12.5 gms.) to a flask containing ethyl ethoxymethyleneacetoacetate (20 gms.) was heated on a steam-bath for one hour. The crude solid unil that was formed was purified as usual and then crystallised from petroleum ether (b.p. 65°-80° C).

Yield: 8.5 gms. (80 %).

This unil had been prepared by heating di-o-phenetidyl-formamidine with diethyl malonate (Baines, O’Brian and Johnson, J. Am. Chem. Soc., 1916, 38, 1517).

(B) Ethyl 8-ethoxy-4-hydroxyquinoline-3-carboxylate:

8 gms. of the above acrylate were cyclised with acetic anhydride (16 c.c.) and sulphuric acid (3 c.c.). The resulting mixture was worked up in the usual manner for the isolation of the cyclised product (Yield: 1 gms. 15 %). White crystals from rectified spirit melted at 243° C.

(Found: N 5.7 %; C₁₄H₁₉O₅ requires N 5.4 %).

(C) 8-Ethoxy-4-hydroxyquinoline-3-carboxylic acid:

The above cyclised product, after being refluxed with
dilute HCl, and acidification liberated the corresponding acid, which when crystallized from ethanol, melted at 239°-270° C with decomposition.

(Found: N, 5.8%; C₁₂H₁₁O₄N requires N, 6.0%)

(6) Preparation of Ethyl p-xylidineethoxymethylmalonate:

After mixing 1:3:4-xylidine (15 gms.) with ethyl ethoxyethoxymethylmalonate (21.6 gms.), the warm mixture was heated on a steam-bath for one hour. Brownish-white solid, thus obtained, was purified in the usual way. (Yield: 19 gms.; 65%). White needles (m.p. 84° C) were obtained on crystallization from petroleum ether.

(Found: N, 5.9%; C₁₅H₂₄O₄N requires N, 4.8%)

Note: Several attempts, made to cyclise this amide with pure acetic anhydride and sulphuric acid, produced the acetyl derivative (m.p. 153° C) of the amine.

(7) Ethyl p-phenetidinemethylmalonate:

This amide was prepared in an analogous manner from ethyl ethoxymethylmalonate (21.6 gms.) and purified p-phenetidine (13.7 gms.). Since the amide was obtained in the oily liquid form, its purification was effected by dissolving it in ether
and then treating the ethereal solution in the usual manner. Evaporation of the ethereal solution and desiccation of the residual oil for a couple of days yielded solid anil (yield: 14.2 gms.), which when crystallized from petroleum ether melted at 55°C.

(Found: N, 4.4%; C16H14O2 requires N, 4.6%)

(a) Condensation with p-bromaniline:

(A) Ethyl p-bromanilinomethylenecapronate:

A mixture of 8 gms. of ethyl ethoxyethylenemalonate and 6.5 gms. of p-bromaniline was heated on a steam-bath for two hours. On cooling, the anil that was obtained in the solid state was purified in the usual way. Yield: 9.6 gms. (76%). Double recrystallization from alcohol yielded white prisms (mp 103°C).

(Found: N, 3.9%; Br, 22.9%; C16H14O2Br requires:

N, 4.1%; Br, 23.4%).

(b) Ethyl 6-bromo-6-hydroxyquinoline-5-carboxylate:

Ethyl p-bromanilinomethylenecapronate (3 gms.) was dissolved in diphenyl ether (20 c.c.) and this solution was added in portions to boiling diphenyl ether (30 c.c.) in
fifteen minutes. The boiling was continued for an additional hour and the solution was cooled. Grayish-white solid, which separated, was shaken several times with hot alcohol, filtered and dried (yield: 2.2 gms.). White crystals from nitrobenzene (b.p. 305°C).

(Found: H, 4.5 %; Br, 27.3 %; C_{18}H_{10}O_{3}Br requires: H, 4.7 %; Br, 27.0 %).

(c) 6-Fluoro-4-hydroxyquinoline-3-carboxylic acid:

The above cyclised ester (1 gm.) was hydrolysed in the usual manner by refluxing with 3 N HCl (50 c.c.), charcoal, filtered and the filtrate was acidified with HCl. The corresponding acid, that almost quantitatively precipitated, on being crystallised from nitrobenzene, yielded pure crystalline acid (b.p. 270°-277° C dec.).

(Found: H, 5.5 %; Br, 29.4 %; C_{18}H_{10}O_{3}Br requires: H, 5.2 %; Br, 29.9 %; Neutral equivalent: 257).
(III) Syntheses with Ethyl ethoxylate-

Preparation of Ethyl ethoxylate:

For preparing this ester, the method described by

Vinciguerra (Ber., 1886, 19, 2225; 1887, 20, 3393) was employed

with some necessary modifications.

Clean freshly cut metallic sodium (11.5 gms., 0.5 gms. atom) was placed in a one litre round-bottom flask containing pure dry xylene (300 c.c.). The flask was fitted to a reflux condenser and the contents were heated to the boiling temperature of xylene on a sand-bath. As sodium melted, it began to settle at the bottom as a shining silvery liquid. After all the sodium had melted, the flask was removed, tightly corked and vigorously shaken mechanically till sodium solidified on cooling to very fine particles. Xylene was then decanted off and the pulverised sodium was washed three times with 50 c.c. of dry benzene to remove traces of xylene.

Metallie sodium, thus powdered, was then transferred to a two litre three-necked flask containing 300 c.c. of dry benzene and fitted with a mercury-sealed mechanical stirrer, an efficient double-walled reflux condenser and a dropping
funnel. To protect the apparatus from being affected by atmospheric moisture, a calcium chloride U-tube was attached to the condenser. Freshly distilled neutral diethyl malate (73 gms., 0.5 mole) was added into the flask. Extra-pure ethyl acetate (50 gms.) was placed in the dropping funnel. The flask was surrounded by ice-cold water to control the reaction. Ethyl acetate was gradually added into the flask, the contents of which were being constantly stirred. In the beginning the reaction was rather slow. Addition of ethyl acetate was completed within one and a half hours. Precautions were taken to keep the reacting mixture at an ice temperature as possible because ethyl ethoxymalate decomposes at higher temperatures. The reaction was vigorous after about two and half hours, when the whole of the sodium had disappeared, the mixture assumed yellowish-brown colour. After about twelve hours, the sodium derivative of ethyl ethoxymalate separated as a pasty yellow solid mass. The latter was decomposed with 100 cc. of acetic acid (33 %). The decomposition was complete in four hours. The benzene layer was separated from the aqueous layer. The aqueous layer was
twice extracted with ether; the benzene layer and the two
other extracts were mixed and the mixture was dried by
keeping in contact with anhydrous sodium sulphate for one
day. The solvents were then removed by careful distillation
and the residual yellowish liquid, on being distilled at
130°-132° C under reduced pressure (25 mm.), yielded pure
colourless ethyl ethoxallylacolate (yield: 78 gms., 78.5 %).
The formation of ethyl ethoxallylacolate from the reactants
can be represented as follows:-

\[
\begin{align*}
\text{COOC}_2\text{H}_5 & \quad \text{COOC}_2\text{H}_5 & \quad \text{COOC}_2\text{H}_5 \\
\text{CH}_2\text{COCH}_3 & \quad \text{CH}_2\text{COCH}_3 & \quad \text{CH}_2\text{COCH}_3 \\
\text{C}_6\text{H}_5 & \quad \text{C}_6\text{H}_5 & \quad \text{C}_6\text{H}_5 \\
\end{align*}
\]

Hypothetical

(1) Condensation of Ethyl ethoxallylacolate with aniline;

(A) Preparation of Ethyl \( \beta \)-carboxathoxy \( \beta \)-anilino acrylate:-

Ethyl ethoxallylacolate (12.8 gms., 0.1 mole) was mixed
with pure aniline (10.3 gms., i.e., slightly more than 0.1 mole)
\( 8^1 \) and 75 g., c\( \) of glacial acetic acid in a conical flask
and the flask was heated on a water-bath at 60° - 50°C for
two hours and the cooled flask was then kept at room temper-
ature for 18 hours for the completion of the reaction. The
solution, which assumed brown colour, was poured on crushed
ice (50 gms.) and stirred vigorously. It was then almost
completely neutralized with sodium hydroxide solution (33%).
Final complete neutralization was effected with sodium
carbonate solution. Brown oil, which floated on the surface,
was twice extracted with ether and the etheral extract was
shaken with 300 c.c. (in four portions) of dilute (0.5 N)
hydrochloric acid to remove excess of the amine. It was
then shaken with sodium bicarbonate solution (10%) and
finally washed with water. The etheral layer was then
placed in contact with anhydrous potassium carbonate and
left overnight for drying. On evaporating the etheral
solution, the acrylate was left as a reddish-brown oil which
did not solidify even when kept in a desiccator for several
days. (Yield: 13.6 gms.; 51%).
(Riegel et al., loc. cit., prepared this acrylate by a
slightly different method).
(B) Cyclisation of the acrylate:

Preparation of Ethyl 4-hydroxyquinoline-2-carboxylate:-

The above acrylate (15.4 g.m.) was mixed with acetic anhydride (27 c.c.) and concentrated sulphuric acid (15.5 c.c.) was added to the solution within two minutes. Due to considerable development of heat, the mixture began to boil and assumed dark-brown colour. After cooling and pouring it over powdered ice, it was almost neutralised with strong sodium hydroxide solution (55%). Brownish-white precipitates were filtered, washed with water and dried. (Yield: 5.5 g.m., 48%). For purification, the cyclised product was dissolved in aqueous-alcohol (50%), treated with charcoal and filtered while hot. White leaflets (m.p. 212°-213°) separated on cooling. (Biegel et al., loc. cit.).

(C) 4-Hydroxyquinoline-2-carboxylic acid:-

The above ester (1 g.m.) was refluxed with 10% sodium hydroxide solution (40 c.c.) for two hours, charcoal and filtered. After the filtrate had cooled, it was acidified with dilute HCl. The acid, that separated as a white solid, was washed with water and crystallised from dilute acetic
acid (m.p. 275°-277°C dec.). (Riegel et al., loc. cit.).

(2) Condensation with p-aminodine:

(A) Preparation of Ethyl \( B \)-carboxylyl p-aminodine acrylate:

This acrylate had been prepared by Surroy and Harmer (loc. cit.). During the present investigation, the same procedure was adopted. A mixture of ethyl ethoxylacetate (18.3 gms.), purified p-aminodine \( \text{HCl} \) (19 gms.) and glacial acetic acid (75 c.c.) was heated on a water-bath between 40°-50°C for two hours. The acrylate was isolated as a brown oil from this mixture in the manner previously described in detail. Yield: 8.3 gms. (20%).

(B) Ethyl \( 6 \)-methoxy-4-hydroxyquinoline-2-carboxylate:

Concentrated sulphuric acid (8.3 c.c.) was added in a minute to the mixture of the above acrylate (8.3 gms.) and acetic anhydride (17 c.c.). The acidic mass, after cyclization was treated with ice, neutralized with 33% NaOH, brown solid that separated was filtered, washed and dried (yield: 5.5 gms.; 50%). White needles (m.p. 218°C) were obtained when subjected to crystallization from rectified spirit.

(Surroy and Harmer, loc. cit.; Riegel et al., loc. cit.).
(6) 6-Methoxy-4-hydroxyquinoline-2-carboxylic acid:

The crude ester (1 gm.) obtained above was hydrolysed in the usual manner and acidified with HCl with the result that white solid acid separated, which on being crystallised from dilute acetic acid melted at 235°C.

(Surrey and Hamon, loc. cit.).

(3) Condensation with p-toluidine:

(a) Preparation of Ethyl 6-carbethoxy p-toluidino acrylate:

This acrylate was prepared in the same manner as the preceding two esters by heating a mixture of ethyl ethoxymylacetate (20 gm.), p-toluidino (12 gm.) and glacial acetic acid (30 ml.) at 40°C-50°C for two hours. Further treatment for the isolation and purification of the acrylate was the same. Yield: 12 gm. (61%).

(b) Ethyl 6-methyl-4-hydroxyquinoline-2-carboxylate:

Concentrated sulphuric acid (12 c.c.) was added to the mixture of the above acrylate (12 gm.) dissolved in acetic anhydride (24 c.c.). The resulting cyclised mass was treated in an analogous way for the isolation of the crude cyclised product (yield: 5.2 gm., 52%). On being twice crystallised
from alcohol, white needles (m. p. 211°-212° C) were obtained.

(Found: N, 5.7 %; C_{13}H_{15}O_{3} requires N, 6.1 %).

(c) 6-Methyl-4-hydroxyquinoline-2-carboxylic acid:

Hydrolysis of the above ester (1 gm.), brought about by refluxing with dilute NaOH (25 c.c.) for one and half hours and subsequently acidification yielded the acid, which when crystallised from acetic acid melted at 275°-275° C (dec.).

(Found: N, 6.6 %; C_{11}H_{9}O_{3} requires N, 6.9 %)

(Neutral equivalent: 202.5)
(IV) Syntheses with Ethyl ethoxymethyleneacyanocacetate:

Preparation of Ethyl arylaminomethyleneacyanocacetates:

Ethyl arylaminomethyleneacyanocacetates can be prepared either (i) by heating together ethyl ethoxymethyleneacyanocacetate (de Bollmont, Bull. soc. chim., 1901(3), 25: 20) and the corresponding aromatic amines in an oil-bath at 120°-130° C (Price, Leonard and Herbrandson, loc. cit.) or (ii) by heating a mixture of equimolecular quantities of ethyl cyanocacetate, ethyl orthoformate and the aromatic amines in an oil-bath at a temperature of 160°-165° C until the calculated volume of alcohol distilled over (Synder and Jones, loc. cit.). Since the latter method is simpler and more convenient, it was employed for the preparation of acylates during the present work.

(1) (a) Preparation of Ethyl p-anisidinomethyleneacyanocacetate:

Purified p-anisidine (24.6 gms., 0.2 mole) was mixed with cyanacetic ester (22.6 gms., 0.2 mole) and ethyl orthoformate (29.6 gms., 0.2 mole) in a flask fitted for distillation. The mixture was heated in an oil-bath at 160°-165° C until the calculated volume (35 c.c.) of alcohol distilled
over. Actually alcohol began to pass over from above 110°C.

The reaction took about an hour. When the hot liquid mass
was poured into dilute (1 N) hydrochloric acid (200 c.c.),
greyish-white solid snail was obtained. Purification of the
snail was effected by shaking the powdered snail thrice with
dilute HCl and washing with water. Yield: 39 gms. (79.2%).

On being crystallised from alcohol, white needle-like
H.P. 105°-106°C) separated (Synder and Jones; loc. cit.).

B) Cyclisation of the acrylate:

(1) Thermal method:

Formation of 3-Cyano-6-methoxy-4-hydroxyquinoline:

Pure crystalline ethyl p-anisidinoethylenecyanacetate
(10 gms.) was dissolved in diphenyl ether (40 c.c.) by slight
warming. This solution was then added in portions to boiling
diphenyl ether (100 c.c.) within 15 minutes. The boiling was
prolonged for half an hour more. Brown solid, which separated
on cooling, was filtered and the residue was treated thrice
with hot alcohol. (Yield: 2.5 gms.; 31%). It was dissolved
in hot nitrobenzene, the hot solution was treated with
charcoal for 10 minutes and filtered. The crystals, which
appeared in the filtrate on cooling, were recrystallised from the same solvent. White needles \( (\text{m.p. } 315^\circ\text{C}-317^\circ\text{C}) \) with slight previous blackening.

\( \text{Found: } N, 13.7\% ; \text{C}_{11}\text{H}_{6}\text{O}_{2}\text{N}_{2} \text{ requires } N, 14.0\% . \)

(ii) Acetic anhydride and sulphuric acid method:

**Formation of 6-Methoxy-4-hydroxyquinoline-3-carboxylic acid:**

Ethyl \( p \)-anisidinomethyleneacetoacetate (10 gms.) was cyclised with acetic anhydride (20 c.c.) and concentrated sulphuric acid (10 c.c.) within two minutes. After pouring the cooled mixture on ice and neutralising the resulting solution with caustic soda (53%), dark semi-solid mass separated. It was then dissolved in dilute \( \text{NaOH} \), treated with charcoal, the alkaline solution was filtered and the filtrate was acidified with dilute \( \text{HCl} \). Yellowish-white acid (2.4 gms.) precipitated. Two crystallisations from dilute acetic acid yielded pure white acid \( (\text{m.p. } 271^\circ\text{C} \text{ dec.}) \). Its mixed melting point with the acid obtained on hydrolysing ethyl 6-methoxy-4-hydroxyquinoline-3-carboxylate \( (\text{Price and Roberts, loc. cit.}) \) was not found to be depressed.
(2) (A) Ethyl m-chloroanilinoacetylencycanoacetate:

This anil was prepared according to the method of Synder and Jones (loc. cit.) by heating a mixture of ethyl orthoformate (57 gms.), cyanoacetic ester (23.2 gms.) and m-chloroaniline (32 gms.) in an oil-bath at 160°-165° C till the calculated quantity (64 c.c.) of alcohol distilled over. On cooling, the anil was obtained in the form of a grey solid, which when crystallised from alcohol, melted at 123°-127° C (Price, Leonard and Herbrandson, loc. cit.; Synder and Jones, loc. cit.). Yield: 55.5 gms. (88 %).

(B) Cyclisation of the acetate:

 Acetic anhydride-sulphuric acid method:— Formation of 5-Chloro-4-hydroxyquinoline-3-carboxylic acid:

Concentrated sulphuric acid (20 c.c.) was added within 3 minutes to the mixture of ethyl m-chloroanilinoacetylencyanonoacetate (20 gms.) and acetic anhydride (60 c.c.). The reaction was accompanied with vigorous effervescence and evolution of heat. The mixture was then treated with ice, then just neutralised with strong NaOH and left overnight. The brownish-white solid was filtered off and dissolved in
100 c.c. of hot dilute NaOH, charcoaled and filtered. On
acidifying the cooled filtrate with HCl, white precipitates
were obtained. Recrystallisation from alcohol yielded white
needles (M.P. 241°-243° C dec.). The mixed melting point of
this substance with the acid, obtained by the hydrolysis of
the ester produced on cyclising ethyl m-chlorosaminomethylene-
monoclanate with acetic anhydride and sulphuric acid (page 121),
was undepressed. On the other hand, the mixed melting point
of the same acid with the acid obtained by the hydrolysis of
the cyclised product from the same acrylate by the thermal
method, was considerably depressed.

(3) (A) Preparation of Ethyl m-toluidinomethyleneacyonacetate:

This acrylate was prepared by heating together cyanocaco-
tic ester (22.6 gms.); ethyl orthoxymato (29.6 gms.) and
freshly distilled m-toluidine (21.4 gms.) in an oil-bath at
160°-165° C till the calculated volume (35 c.c.) of ethanol
distilled over. On pouring the hot mass into dilute HCl (200 c.c.)
and stirring vigorously, pale yellow solid was
obtained. Further purification was accomplished in the
usual manner. Yield: 45 gms. (94 %). Two crystallisations
from ethanol yielded white needles (M.P. 111° C).

(Found: H, 11.9 %; C_{15}H_{14}O_{2}N_{2} requires H, 12.2 %).

(2) Cyclisation of the acrylate: Formation of 7-Methyl-3-cyano-4-hydroxyquinoline:

The solution of the above acrylate (3 gms.) in diphenyl ether (50 c.c.) was poured in portions into boiling diphenyl ether (100 c.c.) within 15 minutes. The mixture was maintained at its boiling point for additional 20 minutes and then cooled. Deep yellow solid (2.2 gms.; yield 54 %), which twice crystallised from nitrobenzene, yielded white needles (M.P. 310°-315° C).

(Found: H, 15.0 %; C_{11}H_{8}O_{2} requires H, 15.2 %).

(3) 7-Methyl-4-hydroxyquinoline-3-carboxylic acid:

The above cyclised product (1 gm.) was refluxed with sulphuric acid (50 %) for one and half hours to hydrolyse the cyano group. The contents were cooled, filtered and the residue was dissolved in hot dilute NaOH. After treatment with charcoal, the alkaline solution was filtered. On acidifying the filtrate, flocculent white precipitates of the acid were obtained. Crystals from alcohol (M.P. 233° C)
dec.). Mixed melting point of this compound with the acid, produced by the hydrolysis of the ester obtained on cyclizing ethyl m-toluidinomethylenediaminate by the thermal method (pages 122-123) was undepressed.

(Found: N, 6.6 %; \( \text{C}_4\text{H}_8\text{O}_2\text{N} \) requires 6.9 %).

(Neutral equivalent: 202).