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An investigation of the chemistry of cinnolines

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Earlier work which has resulted in the synthesis of
cinnolines is reviewed. The strictly historical approach
has been modified to accommodate a classification based
upon the type of cinnoline involved.

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A second route which utilises 4-chloro-2-nitrobenzoyl chloride
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phenone and thence to the amine.

Diazotisation of 4-chloro-2-aminoacetophenone and
subsequent ring closure produces 7-chloro-4-hydroxycinnoline.

Nitration of 4-chloro-2-acetamidoacetophenone has given
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Hydrolysis to the corresponding nitro-amines and diazotisation
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8-nitro-7-chloro-4-hydroxycinnoline. In hydrochloric acid,
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cyclisation to the cinnoline.

Attempts to prepare 4-chloro-2-aminopropiophenone are described and work on the projected synthesis of 7-methoxy-4-hydroxycinnoline is reported.

Widman's synthesis of 4-methylcinnoline-7-carboxylic acid has been repeated; in general, the original results are confirmed but the acid is best purified via the ethyl ester.

4-Methylcinnoline and the 6- and 7-chloro-compounds have been prepared by ring closure of the diazotised o-isopropenylanilines; these are formed by dehydration of the corresponding carbinols which arise from the o-amino-acetophenones or methyl anthranilates by a Grignard reaction. The 4-methylcinnolines are characterised by their green picrates and red ethiodides.

The application of a wide variety of reactions to estimate the reactivity of the methyl group in 4-methylcinnoline has had little success. Confirmation of enhanced reactivity and hence of the postulate that N_1 is the basic centre of the molecule is provided by the formation of 4-p-dimethylaminostyryl-1-ethylcinnolinium iodides.

Reduction of a number of cinnolines with sodium and alcohol has been carried out.

Qualitative examination has shown partial conversion to the corresponding indoles of 4-(4'-hydroxyphenyl)cinnoline, the

3-_methyl_ _compound_ and of 3-_methyl_-4-p-_anisylcinnoline;_
3-phenyl-4-p-anisylcinnoline and the demethylated compound
are virtually unchanged. 4-Methylcinnoline and its 6- and
7-chloro-derivatives all give 3-methylindole as the final
product but data on the intermediate stages is incomplete.

Estimation of the ammonia liberated in each case
confirms the above findings.

Attempts to repeat Stollé and Becker's synthesis of
3-phenylcinnoline-4-carboxylic acid are reported.

AN INVESTIGATION OF THE CHEMISTRY OF CINNOLINES.

-being a thesis presented in candidature for

the Degree of Doctor of Philosophy in the

University of Durham.

CHARLES M. ATKINSON.

The work described in this thesis was carried
out under the direction of J.C.E. Simpson, Ph.D.,
D.Sc., at the Science Laboratories of Durham
Colleges in the University of Durham (January 1944
to December 1944) and the Liverpool School of
Tropical Medicine (January 1945 to June 1946).

Summary.

Earlier work which has resulted in the synthesis of cinnolines is reviewed. The strictly historical approach has been modified to accommodate a classification based upon the type of cinnoline involved.

Preparative routes to 4-chloro-2-aminoacetophenone are described. Reaction between the acid chloride of 4-chloro-2-phthalimidobenzoic acid and diethyl sodiomalonate followed by hydrolysis gives the pure amine via the acetamido-compound. A second route which utilises 4-chloro-2-nitrobenzoyl chloride and ethyl sodioacetoacetate leads to 4-chloro-2-nitroacetophenone and thence to the amine.

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Attempts to repeat Stollé and Becker's synthesis of 3-phenylcinnoline-4-carboxylic acid are repeated.

CONTENTS

Introduction.

The relation of cinnoline to other isomeric compounds was stated first by Widman in 1888 (184) during an attempt to rationalise the nomenclature of existing nitrogen heterocycles. He proposed the general name "azine" for compounds consisting of a six membered ring formed from carbon and nitrogen atoms; according to the number of the latter, the substances were designated as monoazines, diazines, etc.

The diazine group clearly gave rise to three possibilities depending on the relative positions (o, m, or p) of the nitrogen atoms and Widman's nomenclature followed easily from this.

DIAZINE   MIAZINE   PIAZINE
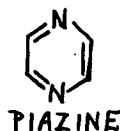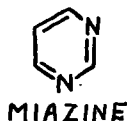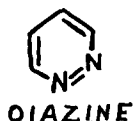
It is interesting to note that the 'accepted' names (for all were known) -pyridazine, pyrimidine and pyrazine - have survived Widman's bid for reform in spite of the fact that they have little claim to systematisation. In the benzodiazine series the same state of affairs prevailed and with the preparation of cinnoline in 1897 (34) all

four possibilities were known to exist (only hydro-
quinazolines were known).
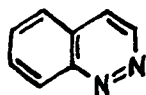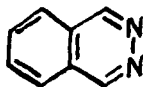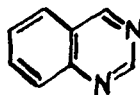
| α-PHENOIAZINE | β-PHENOIAZINE | PHENMIAZINE | PHENPIAZINE |
| CINNOLINE | PHTHALAZINE | QUINAZOLINE | QUINOXALINE |
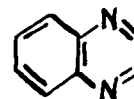
Again the 'traditional' names (cinnoline, etc.) have
survived but others have been assigned a fitting place in
obscurity (e.g., "dehydromethylenbenzylenamidin" for
quinazoline!). Although this relationship has been
repeatedly mentioned (34,140) it is unfortunate that no
157.
detailed comparison has been made of compounds of each
type.

The scarcity of early work on cinnolines has been
emphasised already (152,140) but it is evident that such
complaint is justified only when more favourable fields
of work are taken as standard. Thus Niementowski and
Sucharda (114) pointed out the almost complete lack of
information on compounds in which each of two fused rings
contained one N-atom in comparison to the attention given
to cinnolines and similar compounds. The inaccessibility
of intermediates for cinnoline syntheses has been decisive
in causing the slow development of cinnoline chemistry,

whilst the absence of cinnolines in any natural products
so far investigated has been recognised (/40) as a con-
tributory factor.   Even the more readily available
3:4-benzocinnoline (usually referred to as "phenazone" in
consequence of the undeveloped state of cinnoline chemistry)
has been little studied.

Cinnoline.

The earliest attempt to prepare cinnoline itself was
made by von Richter (130) using distillation of 4-hydroxy-
cinnoline[*] with zinc dust, a process which, it was claimed,
converted carbostyril to quinoline. An alkali-insoluble
oil which possessed the properties of oxindole (pine
shaving test) was isolated although after removal of this
component a yellow flocculent platinichloride was prepared;
this 'salt' resinified on attempted purification. Thus no
decision was reached and the conclusion of Richter's work
was necessitated by "the beginning of the vacation and
shortage of material". Busch and Klett (33) carried out
Richter's experiment in a stream of hydrogen but despite
many experiments using other reducing agents there was
obtained only an oil having an intense "nitrilartig" smell;
no crystalline platinichloride or hydrochloride could be
prepared. The detection of ammonia during the distillation
indicated disruption of the cinnoline molecule so this route
was abandoned in favour of the preparation of some derivatives
of 4-hydroxycinnoline. It was hoped that reduction of the
highly reactive chloro-derivative would yield cinnoline but
early experiments were not encouraging. However, Busch and
Rast (34) achieved rapid reduction using iron and sulphuric

[*] Obtained by decarboxylation of 4-hydroxycinnoline-3-carboxylic
acid.

acid, a method successfully employed by Königs (88) in
his researches on the cinchona alkaloids. Not only was
the chlorine atom removed but the hetero-ring was reduced
to give dihydrocinnoline; this was stable towards other
reducing agents but was readily oxidised by mercuric oxide
to cinnoline. The stability towards reduction and the easy
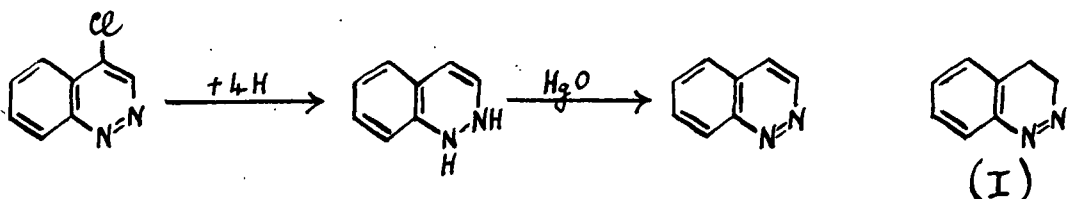
oxidation to cinnoline both provide evidence against
structure (I) for the dihydrocinnoline. A notable contrast
between cinnoline and its dihydro-derivative lies in the
basicity of each compound; the former is a strong base and
forms stable salts with mineral acids, the latter is weakly
basic, its salts being readily hydrolysed by water. Apart
from these observations and the preparation of a few simple
derivatives, e.g. hydrochloride, picrate and methiodide, the
chemistry of cinnoline was not investigated although mention
was made of its poisonous nature. The instability of the
methiodide towards alkali, as evidenced by the production of
a "magnificent deep blue colour" followed by separation of
blue flocculent material, is most interesting.

4-Hydroxycinnoline-3-carboxylic Acids.

The simplest member of this series was discovered accidentally by von Richter (130) during an attempt to prepare o-hydroxyacetophenone from o-nitrophenylpropiolic acid and hence to synthesise α-cumaric acid. Indeed, 4-hydroxycinnoline-3-carboxylic acid was the first known cinnoline derivative although von Richter recognised Fischer's (57) 'internal anhydride' of o-hydrazinobenzoic acid as a similarly constituted compound.

The cinnoline separated in glistening needles on heating to 70° an acid solution of diazotised o-amino-phenylpropiolic acid. The mechanism forwarded by von Richter

$$C_6H_4 \diagup \begin{array}{c} C \equiv C.CO_2H \\ N=N.Cl \end{array} \quad + H_2O \longrightarrow C_6H_4 \diagup \begin{array}{c} C(OH)=C.CO_2H \\ N=N \end{array} + HCl$$
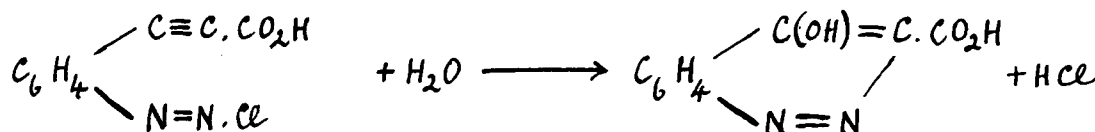
was associated with the contemporary work of Baeyer and Bloem (14), namely, the conversion of o-aminophenylpropiolic acid derivatives to γ-carbostyrils.

$$C_6H_4 \diagup \begin{array}{c} C \equiv C.CO_2H \\ NH_2 \end{array} \quad + HX \longrightarrow C_6H_4 \diagup \begin{array}{c} C(X) \geqslant CH \\ N = C(OH) \end{array} + H_2O$$
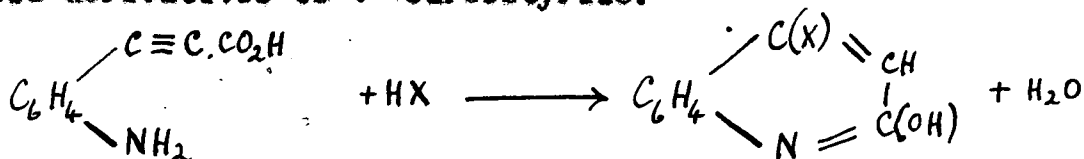
A lapse of sixty two years between the investigation of von Richter and the next contribution to compounds of this group was broken only by workers (33,34) whose ambitions in the cinnoline field were limited by, and often subsidiary to, other researches. The results of a study of the Richter

reaction have been published recently by Schofield and Simpson (141) whose original aims:

(i) "To establish reliable conditions for the preparation of 4-hydroxycinnoline-3-carboxylic acid.

(ii) To extend the scope of the synthesis to new examples" (140; p.35), were fully realised. Each of the following stages of Richter's synthesis was examined and much of the cursory detail given in the literature was found unsatisfactory for preparative purposes.
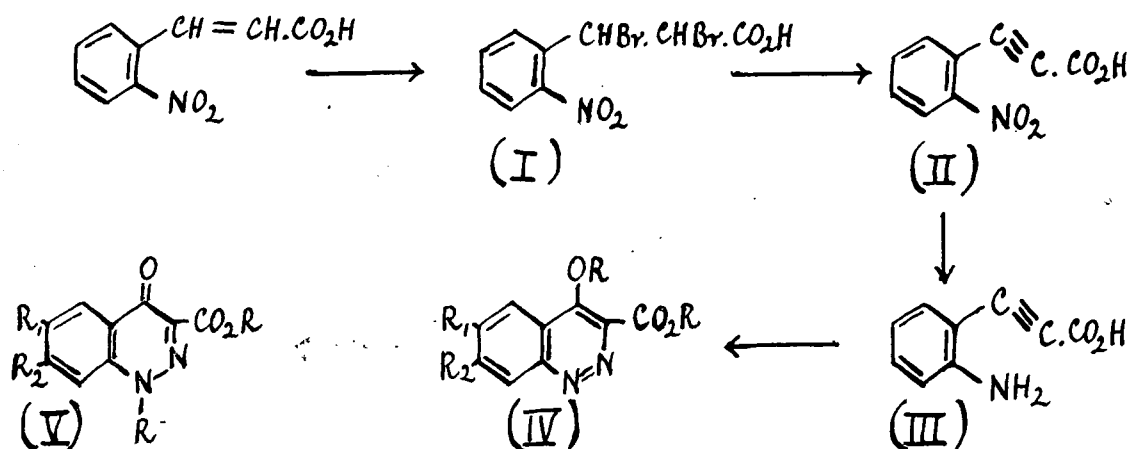
Schofield (140) has given a detailed account of these experiments: literature methods for the bromination of o-nitrocinnamic acid were never explicitly described and one had to presume that von Richter prepared o-nitrophenyl-propiolic acid via (I). Dehydrobromination of this substance according to Baeyer (13) again left much to the imagination although the number of undesirable products observed surely indicated the need for full instructions. Comparative

quantitative experiments, based on determination of the
bromine liberated, were used (140 ;-page 34) to establish
the optimum conditions for dehydrobromination.

$$\text{(structure) } CHBr.CHBr.CO_2H,\ NO_2 \quad + 2\ OH' \longrightarrow \text{(structure) } C\!\equiv\!C.CO_2H,\ NO_2 + 2\ H_2O + 2\ Br'$$
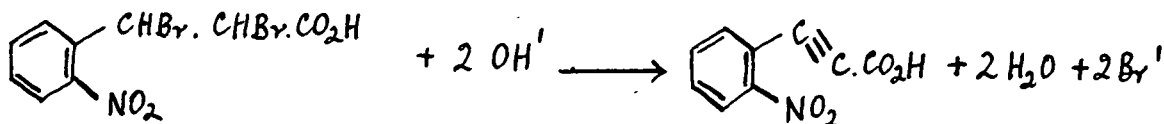
Although reduction to the amino-acid was at first carried
out using von Richter's method, itself a modification of
that of Baeyer and Bloem (14), a procedure was evolved
(141) by which the amino-acid was diazotised without being
isolated or even allowed to separate in acid solution. In
this way the formation of carbostyril derivatives, previously
observed both in the reduction (130) and in the attempted
dissolution of the amine prior to diazotisation (33), was
avoided.

Examination of the generality of the Richter reaction
(ii above) was restricted to those propiolic acids arising
from the more readily accessible o-nitrobenzaldehydes. The
cinnamic acids corresponding to 6-nitropiperonal, 2-nitro-5-
methoxybenzaldehyde, and to 6-nitroveratraldehyde were
already known. By the route established for the unsub-
stituted acid (above) there was obtained 4-hydroxy-6:7-
methylenedioxycinnoline-3-carboxylic acid (IV; R = H,
R_1R_2 = O_2CH_2) and 4-hydroxy-6-methoxycinnoline-3-carboxylic
acid (IV; R = R_2 = H, R_1 = OMe). Dehydrobromination of the

nitroveratrylcinnamic acid dibromide gave the corresponding
α- (or β-)-bromoacrylic acid, probably the α-derivative by
analogy with the dehydrobromination of cinnamic acid (163).

4-hydroxycinnoline-3-carboxylic acid was unchanged by
normal Fischer-Speier esterification conditions but the
use of diazomethane gave a small yield of an ester-ether
(IV or V; R = Me, R_1 = R_2 = H).

Titration of the Richter acid with sodium hydroxide
required more than one equivalent of the latter for
neutralisation; the indicator used was phenolphthalein
but this was not wholly satisfactory.

$(\underline{Va})$ $(\underline{Vb})$
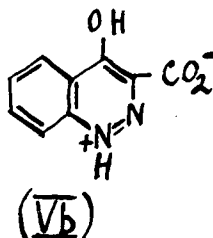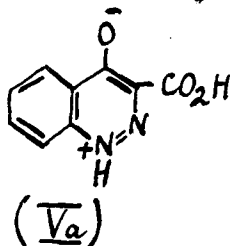
The "zwitterion" structures (Va and Vb) suggested were
in accord with the known properties of the Richter acid
(high m.p., insolubility in hydrocarbon solvents) though
a more strict representation involving a resonance hybrid
of the two canonical states was preferred.

Attempts to acetylate the Richter acid by Schofield and
Simpson (141) led to a series of unexpected reactions which
formed the basis of an investigation (143) noteworthy for its
practical elegance on the one hand and its ingenious

interpretations on the other. [References to the chart
and tables on page 19 of this thesis may prove helpful
throughout the following account].

The action of boiling acetic anhydride on 4-hydroxy-
cinnoline-3-carboxylic acid gave either unchanged material
or, by decarboxylation, 4-acetoxycinnoline. When a mixture
of the Richter acid, pyridine and acetic anhydride in the
proportions 2:9:13 respectively, was heated to 60° or
95°, there was produced a highly reactive compound,
$C_{16}H_{11}O_3N_3$ or $C_{21}H_{16}O_4N_4$ (mean of three analyses). Attempts
to recrystallise this substance from alcohols gave a series
of different products, which, like their common precursor,
showed distinct amphoteric properties in the cold but were
decomposed by hot acids or alkalis. The analysis figures
of these substances indicated two possible series depending
on which of the two formulae above was correct:

Compound	m.p.	Series A.	Series B.
Initial product	217°	$C_{16}H_{11}O_3N_3$	$C_{21}H_{16}O_4N_4$
Product from methanol on initial material	$143\text{-}4^o$	$C_{17}H_{15}O_4N_3$	$C_{22}H_{20}O_5N_4$
Product from methanol on initial material	$128\text{-}128.5^o$	$C_{18}H_{17}O_4N_3$	$C_{23}H_{22}O_5N_4$
Product from isopropanol on initial material	$130\text{-}131^o$	$C_{19}H_{19}O_4N_3$	$C_{24}H_{24}O_5N_4$

Series A could clearly arise thus:

$$C_5H_5N + (CH_3CO)_2O + C_9H_6O_3N_2 \longrightarrow C_{16}H_{11}O_3N_3 + H_2O + CH_3CO_2H,$$
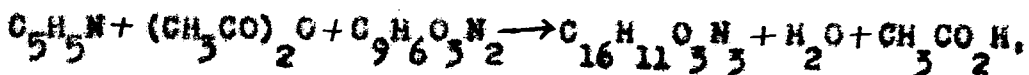
whereas series B might arise either by condensation of a
cinnolyl- with two pyridyl-groups or by fusion of two
cinnoline molecules. This question was settled by the
results of reaction "k" (page 19), but chiefly by substi-
tution of quinoline for pyridine (reaction "l") and treatment
of the reaction product with ethanol; the substance
(m.p. 170°) obtained was distinct from that, m.p. 128°,
tabulated above. The selection of series A was based
initially upon the analysis of this new derivative but the
support of later analyses was welcome in view of the fact
that only in one experiment could the substance, m.p. 170°, be
isolated. Indication of the position of attachment of the
pyridyl (quinolyl) group to the cinnoline ring was afforded
by the absence of reaction on substitution of α-picoline
(quinaldine) for pyridine.

It is convenient, before presenting an interpretation
of the facts so far revealed, to consider the evidence for-
warded by Schofield and Simpson for the belief that this
reaction using pyridine and acetic anhydride is highly
specific to 4-hydroxycinnoline-3-carboxylic acids. 4-Hydroxy-
cinnoline gave 4-acetoxycinnoline on treatment with pyridine
and acetic anhydride or with the latter alone. It was

apparent (page 19, experiment "b") that mere adjacency of
hydroxyl groups was an insufficient qualification for
reactivity, whilst this arrangement in a heterocyclic
system (experiment "c") conferred no property which would
challenge the above claim to specificity. Again, (experi-
ment "d"), ethyl 4-hydroxyquinoline-3-carboxylate with
pyridine and acetic anhydride gave the 4-acetoxy-derivative
(151). Repitition of the reaction using 4-hydroxy-6-
methoxycinnoline-3-carboxylic acid (experiment "e") provided
a striking contrast to the foregoing results. An obvious
reaction occurred and the crude product, on treatment with
methanol and also with boiling pyridine (cf. reaction "g"),
gave two compounds whose analyses agreed well with calculated
figures.

A working hypothesis to explain the above results was
gradually created on the basis of known analogies. The
chief of these was the formation of covalent compounds by
pyridinium or quinolinium kations and a weak anion, ample
illustration of this phenomenon being provided by the work
of Decker (48a) and Hantzsch and Kalb (70a). A closely
analogous reaction, first reported by Reissert (129a), was
eventually used as a model on which to build the following
mechanism of the 'pyridine-acetic anhydride' reaction.

Reissert observed that the reaction between quinoline, benzoyl chloride and alkali cyanide yielded N-benzoyl-2-cyano-1:2-dihydroquinoline; his finding that acids attacked the latter substances (as shown below) has been adopted as a general method for the preparation of aromatic aldehydes (32).
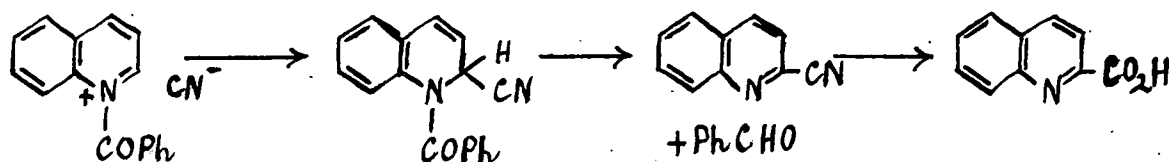
Schofield and Simpson represented the reaction between pyridine, acetic anhydride and the Richter acid as follows:
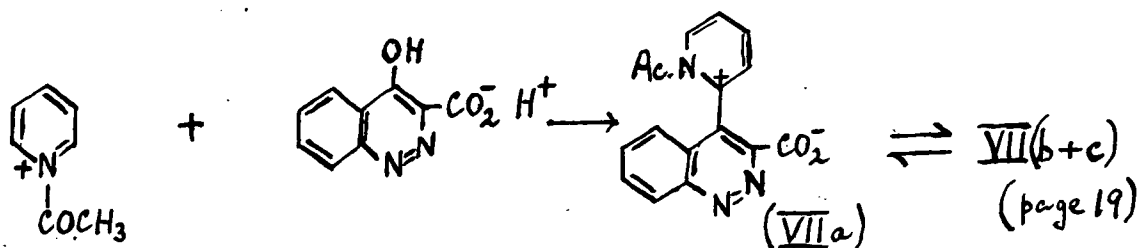
It was pointed out that the general properties (page 19) of the initial reaction product and its remarkable reactivity towards alcohols were in greater accord with its representation as either of the canonical states (VII; a - c) than as the lactone (VII d), although the latter structure was fully considered earlier (140). The alcohol addition products were represented as (VI or VIa) but on statistical grounds the former was selected as the dominating species; such representation as ether-acids was strengthened by the isolation of compound (X) on treatment of (VII) with aniline.

Further experimental work upheld the zwitterion
structures (VII; a - c) in preference to the lactone (VII d).
It was found that a base $C_{15}H_{13}O_2N_3$ was produced by reactions
("f, g, h", page 19) but that reactions ("i,j") gave no
definite substance. Using structure (VIII) for the new
base, formed, presumably, by direct hydroxylic attack on the
species (VII a), a discussion of the results of reactions
("f - j") was offered, such considerations as the relative
proportions of acetic anhydride and pyridine, etc., being
woven into a convincing argument in favour of the 'accepted'
structures.

The analogy with "Reissert compounds" (page 13), and
hence the representation of this series of new substances as
α-pyridinium (or α-dihydropyridyl) compounds,was more
firmly established by the loss of the N-acetyl group as
follows. The compound (VI; R = Me) on treatment with either
methanol or ethanol and sulphuric acid gave the same product
and the substance (VI; R = Et) behaved similarly. Clearly
esterification was not the case and the substances
(IX; R = Me or Et respectively) were recognised as the
simplest possibilities. Insolubility in alkalis (page 19)

was accounted for by the related structures -

IX(a)　　(b)　　(c)
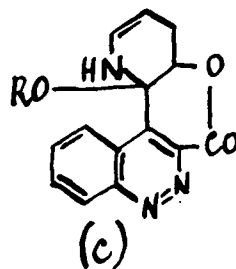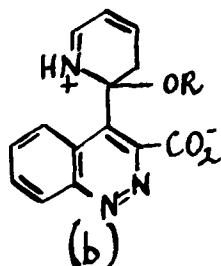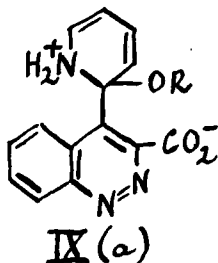
- and by the known insolubility of, for example, diphenyl-4-acrylic acid (73) in these reagents.

Treatment of the substance (IX; R = Me) with hot aqueous sodium hydroxide yielded a water soluble base to which only the structure (XIII) could be assigned, bearing in mind the constitution of earlier compounds and their degradation to this same base (see page 19). The substance (IX; R = Et) appeared to be more stable under these conditions. The formula (XIII. $2H_2O$) agreed well with analysis figures of the base, but the validity of such representation was questioned when it was discovered that the base was readily oxidised to a substance, m.p. 146°, by permanganate at room temperature. Indeed, were the formula of the base $C_{13}H_{13}O_2N_3$ instead of $C_{13}H_9N_3.2H_2O$, such a structure as (XIX or XIXa) would be possible. This possibility (XIX) has been discussed by

(XIX)　　XIX(a)
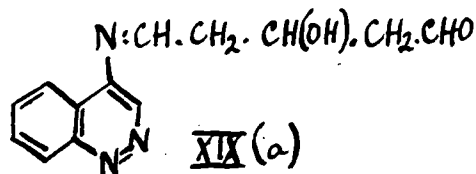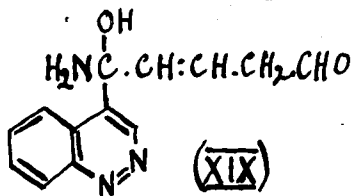
Schofield (140, page 184) and (XIXa) was put forward by members

of the research staff of I.C.I; in fact, the problem was
solved by the preparation of simple derivatives of the base,
it being found that the picrate was anhydrous, i.e.
$C_{13}H_9N_3 \cdot C_6H_3O_7N_3$.

The oxidation product, m.p. 146°, referred to above
showed marked amphoteric properties (page 19) considerations
of which, together with the analysis agreement with a formula
$C_{12}H_9O_2N_3$, led to its representation as (XII). Comparison of
the deep colour of (XII) with that of near carbocylic
analogues e.g. α-phenyl-δ(2-nitrophenyl)-pentadienoic acid
is yellow (12) and the observations of Cook et al (42) on
the bathochromic effect of certain accumulations of nitrogen
atoms afford general support for the structure (XII). This
oxidation product gave a mixture of two compounds on re-
fluxing with 6N hydrochloric acid; the first of these, m.p.
195°, analysed as $C_{12}H_9O_4N_3$ or $C_8H_5O_3N_2$, the former being
preferred because of the similarity in properties to (XII)
and the consequent representation as (XVII). Such an enolic
structure was more in keeping with the colour of the substance
and its apparent stability towards hot permanganate, than
would be the corresponding (di)ketonic form. The second com-
pound, m.p. 254°, had similar properties to the first though
to a lesser extent and it differed in its action on
permanganate. Agreement with analyses figures was not good

so the representation as (XVI) was regarded as "based
largely on speculation".

The preparation of the compound (XIII) in quantity by
the alkaline degradation of (VIII) indicated a number of
side reactions; thus from the alkaline mother liquor there
was obtained the sodium salt of a substance, m.p. 187°,
$C_{12}H_9O N_3$ or $C_{12}H_{10}O N_3$ and an acid, $C_{13}H_9O_2N_3$, which de-
carboxylated quantitatively to produce a weak base, $C_{12}H_9N_3$.
Taking $C_{12}H_9O N_3$ as the correct formula for the compound, m.p.
187°, a structure (XV) was provisionally suggested by the
investigators and the related acid was represented as (XIV),
arising from the hypothetical intermediates (XI a or b). The
weak base was thus the compound (XVIII), 1-methyl-3:9:10-
triazaphenanthrene. Support for such a mechanism was based
on the properties of the compounds and on the estimation of
acetic acid set free in the first stage (VIII→XI); this
loss of acetic acid, incidentally, provided a final analogy
with the "Reissert compounds" originally used as models.

The lack of close analogues of the compounds discussed in
this paper by Schofield and Simpson was emphasised by them
in the case of the compound (XIII). Oxidation results of this
substance were interpreted in a somewhat revolutionary manner
but no oxidation data are available for the closest analogues,
viz. the 2- and 4-lutidylquinolines (43). The reactions

described showed fully the variance which exists between cinnoline derivatives and their quinoline analogues and it was pointed out that this might well be due to "a considerable initial polarisation, resulting in a concentration of the attack of the oxidising agent solely on the pyridine ring".

The explanations offered throughout the paper and their qualification with reference to a wide variety of known phenomena are all the more commendable in view of the scarcity of analogies such as those detailed for the oxidation of (XIII).

Experiments which illustrate the specificity of the
reaction to 4-Hydroxycinnoline-3-carboxylic acids.

Expt.	Richter acid	Pyridine	Ac$_2$O	Expt. conditions	Result
a.	2 parts	9 parts	13 parts	Heat at 60° or 95°	VII
b.	2-Hydroxy-3-naphthoic acid	present	present		2-Acetoxy-3-naphthoic acid
c.	4-Hydroxy-quinoline-3-carboxylic acid	"	"		No reaction
d.	Ethyl ester of "c"	"	"		4-Acetoxy-derivative
e.	6-Methoxy-"Richter acid".1 part	7 parts	8 parts	Heat at 95° for 1½ hours	Reaction

Experiments (not charted) capable of explanation by
the structures (VII; a - d) shown.

f.	1 part	3 parts	1 part	Reflux for ½ hour	VIII C$_8$H$_{6(7)}$O$_5$N
g.	VII	present	absent	Reflux	VIII
h.	VII	absent	"	Reflux aq. suspension	Mod. yield VIII
i.	2	9	13	Reflux	No xalline product
j.	VII, 2 parts	9	13	"	"

Other relevant data.

k.	present	present	Propionic anhydride		No xalline product
l.	1 part	Quinoline 16 parts	12 parts		Reaction
m.	present	Quinaldine or -picoline	present		No reaction
n.	present	absent	present	Reflux	4-Acetoxy-cinnoline
o.	"	present	absent		Unchanged Richter acid.

RO H
Ac.N
CO₂H
(VIa)

Ac.N
O
CO
N
(VIId)

Ac.N⁺
CO₂⁻
N
N
(a)

"g", "h" → Ac.N
OH
N
N
(VIII)

VII
AcN⁺
CO₂⁻
N
N
(b)

AcN⁺
CO₂⁻
N
N
(c)

Ac.N
OR
CO₂H
N
N
(VI) R=Me   R=Et

ROH
R = Me, Et, Pr-β.

PhNH₂.

Ac.N
NHPh
CO₂H
N
N
(X)

Hot
Acid

HCl
or
NaOH

Hot
Dilute
Alkali

N
CH₂
CO₂H
OH
N
N
(a)
(XI)

N
CO CH₃
CO₂H
N
N
(b)

MeOH
OR
EtOH
+
H₂SO₄

Acid
then
Alkali

HN
OR
CO₂H
N
N
(IX)

R=Me. Hot NaOH OR HCl →

N
N
N
(XIII)

KMnO₄
R.T.

N CO₂H
N
N
N
(XII)

6N. HCl

CH₃CO₂H

HO₂C N
N
CH₃
N
N
(XIV)

HO N
N
CH₃
N
N
(XV)

HN CO₂H
CO
N
N
(XVI)

OH
CO₂H
N OH
N
N
(XVII)

N
N
CH₃
N
N
(XVIII)

Cpd.	Sol. in acids.	Sol. in alkalis.	Other properties.
VI	Sol. in dilute HCl	Sol. in dil. aq. Na$_2$CO$_3$. Sol. with R = Me R = Pr .	Insol. in water.
VII	E. sol. in mod. conc. HCl.	E. sol. in cold aq. Na$_2$CO$_3$.	Suspension in aq. dioxane conc. NH$_4$OH intense blue purple solution.
VIII	Readily sol. in 2N.HCl.	Insol. in aq. NaOH.	Insol. in cold water.
$C_8H_{4(7)}O_5N$	Sol. in conc. HCl	Insol. in 4N. NH$_4$OH, sp. sol. in 0.880 NH$_4$OH. Sol. in warm 10% aq. NaOH.	Sp. sol. in boiling water.
IX	Readily sol. in mod. conc. HCl.	Insol. in cold NaOH or Na$_2$CO$_3$.	Insol. in cold water, apprec. sol. in hot.
X	Sl. sol. in cold 2N.HCl.	-	V. e. e. in alcohol.
XII	Sol. in dil. HCl.	Sol. in aq. NaHCO$_3$.	Sp. sol. in cold, sol. in hot water.
XIII	Readily sol. in hot 2N.HCl HCl-ide in cold. V.e. hydrolysed by water.	-	Sol. in hot, sp. sol. in cold water.
XIV	Sp. sol. in 2N.HCl.	Readily sol. in cold aq. NaHCO$_3$.	Insol. in water.
XV	Readily sol. in warm 2N.HCl HCl-ide in cold.	Insol. in cold aq. NaHCO$_3$ dissolves on adding NH$_4$OH.	-
XVI	Sp. sol. in hot 2N.HCl. Fairly sol. in hot 6N.HCl.	Aq. NaHCO$_3$ sp. sol. Na salt. More e. sol. in Na$_2$CO$_3$ or NaOH (aq.).	Almost insol. in boiling water. Reduces aq. KMnO$_4$.
XVII	Sol. in HCl orange solution.	E. sol. in aq. NaHCO$_3$ and other aq. alkalis orange solutions.	V. sp. sol. in hot water. Stable to hot aq. KMnO$_4$.
XVIII	Sp. sol. in 2N.HCl (h. & c.). Fairly e.s. in warm 6N.HCl.	-	Almost insol. in hot water.

4-Hydroxycinnoline-3-acetic Acids.

During an unsuccessful attempt by Koelsch (95) to synthesise (by Dieckmann ring closure of III) a derivative of the unknown 1:3-dihydrobenz (c.d) indole (I), the first 4-hydroxycinnoline-3-acetic acid was prepared. The importance of (I) lay in its relation to lysergic acid (II) and in particular to the conversion of derivatives of the latter into those of iso-lysergic acid. Koelsch intended to establish the orientation of the Fischer-cyclisation products (III and IV) by degradation to the amino-esters (V and VI) and hence to obtain a simple derivative of phthalic and terephthalic acid. The amino-group of (V or VI), although capable of diazotisation, could not be replaced by hydrogen, methoxyl or iodine; treatment of the diazo-compound of (V) with alcohol furnished the ethoxy-derivative (VII) but in the case of (VI) "only the cinnoline" (VIII) was formed.
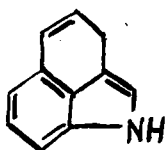
(I)
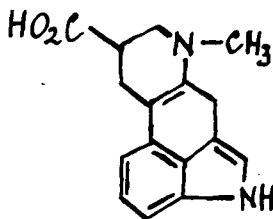
(II)

THE WORK OF KOELSCH

- - - - - - Indicates intended reactions.

CO_2H / $NH_2 \cdot HCl$ + (cyclopentanone with EtO_2C) $\longrightarrow$ CO_2H / $N=N$ / CO_2Et / O

CO_2H / $NH \cdot N = C$ / CO_2Et with $CH_2 \cdot CH_2 \cdot CH_2$ / CO_2Et $\longleftarrow$ CO_2H / $NH \cdot N = C$ / CO_2Et with $CH_2 \cdot CH_2 \cdot CH_2$ / CO_2H

EtO_2C / EtO_2C / CO_2Et / NH (III)

$CH_2 \cdot CH_2 \cdot CO_2Et$ / EtO_2C / NH / CO_2Et (IV)

EtO_2C / $COCH_2 \cdot CH_2 \cdot CO_2Et$ / NH_2 (V)

$COCH_2 \cdot CH_2 \cdot CO_2Et$ / EtO_2C / NH_2 (VI)

R_1 / $COCH_2 \cdot CH_2 \cdot CO_2Et$ / R_2 / R

$R = H, MeO, or I.$

(a) $R_1 = CO_2Et$ $R_2 = H$

(b) $R_1 = H$ $R_2 = CO_2Et$

EtO_2C / $COCH_2 \cdot CH_2 \cdot CO_2Et$ / OEt (VII)

CO_2H / CO_2H / R

CO_2H / HO_2C / R

OH / $CH_2 \cdot CO_2Et$ / EtO_2C / N / N (VIII)

The next compounds of this group were prepared by
Schofield and Simpson (142) as an extension of the preparation
of 4-hydroxycinnolines by "the diazotisation of o-aminoketones
of the general formula $NH_2.C_6H_4.COCH_2R$". Thus, 4-hydroxy-
6:7-dimethoxycinnoline-3-acetic acid (IX; R = R' = H) was
obtained by diazotisation of either a suspension of
β-(6-aminoveratdryl)propionic acid or a solution of its ethyl
ester in 2N hydrochloric acid; only a small amount of the
cinnoline-ester was formed by the latter method. Researches
into the methylation of this cinnoline acid were carried out
by Simpson (149); the main facts of the investigation are
as follows.

(a) The action of dimethyl sulphate and alkali on
4-hydroxy-6:7-dimethoxycinnoline-3-acetic acid gave a mixture
of two isomeric ether-acids (IX; R = H, R' = Me) which could
only be wholly resolved as the methyl esters (IX; R = R' = Me;
X; R = Me)although a pure specimen of one acid, m.p. 260°
(decomp.) - designated as the α-isomer - was obtainable by
fractionation of the crude reaction product.

(b) The 'β'-ether-acid was more basic than the α-isomer
since hydrolysis of the β-ester with hydrochloric acid gave a
"well defined hydrochloride", easily hydrolysed by hot water.
The α-ester gave the α-ether-acid directly using dilute hydro-
chloric acid.

(c) The α-acid decarboxylated at the melting point
to give a base (XI or XII) - called the α-ether. The
β-acid was stable above its melting point.

(d) 4-Hydroxy-6:7-dimethoxycinnoline-3-acetic acid
did not appear to decarboxylate when heated at the melting
point, alone or with quinoline and copper carbonate.

(e) The α-ether formed a hydrochloride and appeared to
quaternise slightly with ethyl iodide.

(IX) (X) (XI) (XII)
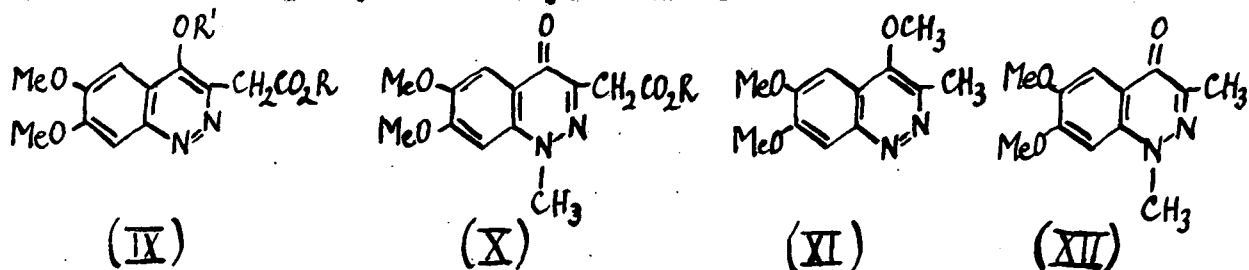
The non-basic nature (b) of the α-ether acid, when
related to the absence of basicity observed in the acid
(IX; R = R' = H), offered no evidence for an O-ether
structure for the former since "4-methoxycinnoline is
decidedly more basic than 4-hydroxycinnoline". Further the
observations of (c) and (d) gave support to the representation
of the α-series as N-ethers. The ease of dealkylation of
O-ethers compared with N-ethers suggested an attempt to
decide between the structures of the α and β series by Zeisel
determinations; however, the figures from a representative
compound of each series did not indicate the presence of even
two methoxyl groups. Such stability of an alkoxy group on
C_4 of the cinnoline nucleus was in agreement with the
stability shown during hydrolysis of the esters [a striking

contrast to the reactivity of like substituents in the
quinazoline ring $(25,72)$]. Experiments designed to detect
a reactive methyl group (arising from structure XII) were
indecisive since only "visible evidence of reaction" was
noted in the phthalonation of the α-ether in the presence
of zinc chloride, there being no isolable crystalline
product. Yet another line of attack based on the conversion
by a mixture of phosphorous pentachloride and oxychloride of
N-methyl- α-quinolones into α-chloroquinolines ($59,$ ^{168,169}) gave
but little evidence; decomposition of the reaction mixture
with alkali yielded water soluble products though the bright
colour of the latter was reminiscent of the alkaline decompo-
sition of certain 4-substituted- γ-cinnolinium salts ($151a$).
Thus, despite the distinct properties of the α- and β-compounds
no definite structure could be assigned to either series.

4-Hydroxycinnolines.

4-Hydroxycinnoline itself was first prepared by von Richter (130) by heating 4-hydroxycinnoline-3-carboxylic acid at its melting point; almost quantitative de-carboxylation occurred. Reference has already been made (page 4) to the use of this reaction during attempts to prepare cinnoline itself but generalisation of the method was explored much later by Schofield and Simpson (142). These workers discovered a novel decarboxylation procedure during "an attempt to determine the fine structure of the Richter acid", the theoretical bases for such an investigation being provided by Hammick and co-workers (9) who attributed the ready decarboxylation of acids containing the grouping -N = C' -CO$_2$H to the existence of a cyclic ion of the type $\left[N = C \right]^{-}$. Such an ion was usually identified by reaction with an aromatic aldehyde or ketone but the only product obtained on heating the Richter acid with benzophenone was 4-hydroxycinnoline "in yields more consistent than those obtainable by other means"; this claim was equally ap-plicable to the 6-methoxy- and 6:7-methylene-dioxy-acids (XV), R$_1$ = OMe, R$_2$ = H; R$_1$R$_2$ = CH$_2$O$_2$, respectively). The erratic nature of the decarboxylation when no benzophenone was used was particularly evident in the case of 4-hydroxy-6-

methoxycinnoline-3-carboxylic acid which yielded two products
besides the expected 4-hydroxy-6-methoxycinnoline.

Another route to 4-hydroxycinnolines arose from the same
study (/41) of the Richter reaction and was based on theo-
retical considerations to be discussed later (page 76). De-
carboxylation of the o-nitrophenyl propiolic acids (XIII;
$R_1 = R_2 = H$; $R_1 = OMe$, $R_2 = H$) in boiling aqueous solution
followed by reduction and diazotisation yielded the cor-
responding 4-hydroxycinnolines (XVI; $R_1 = R_2 = H$; $R_1 = OMe$,
$R_2 = H$); however, no crystalline product could be isolated
from an attempt to decarboxylate 2-nitro-4:5-methylenedioxy-
phenylpropiolic acid (XIII; $R_1 = R_2 = CH_2O_2$).
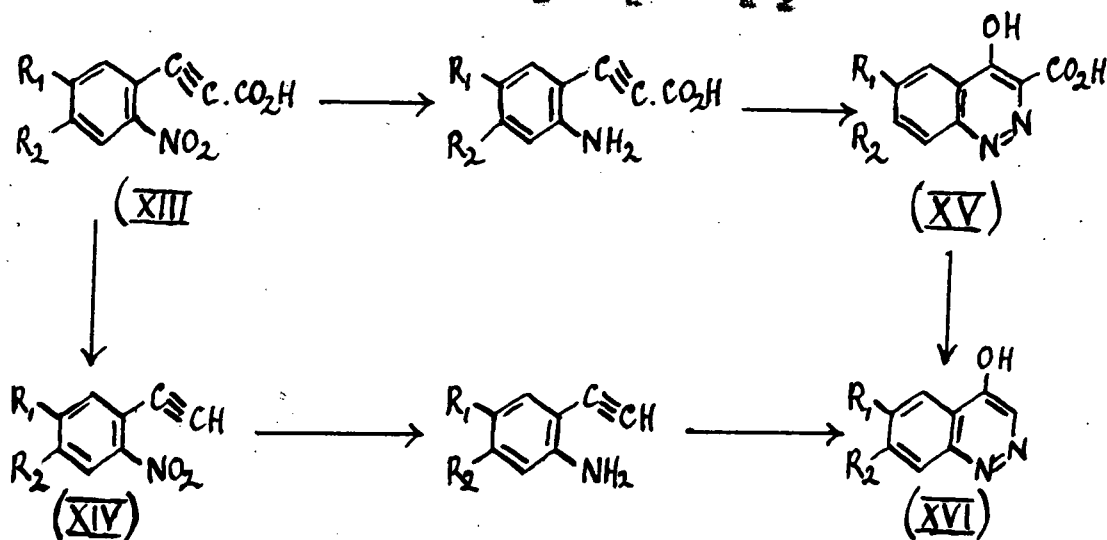
During researches on the use of 5-nitro-2-bromo-
acetophenone as a synthetic intermediate Borsche and Herbert
(27) prepared 6-nitro-4-hydroxycinnoline (XXII) by diazotisation

of 5-nitro-2-aminoacetophenone (XXI), the latter being
prepared from o-bromo-benzonitrile. A repitition of this
work (142) revealed some inconvenience in the method and
conversion of 5-nitro-2-bromoacetophenone into 5-nitro-2-
aminoacetophenone could not be achieved; however, the
constitution of Borsche's 5-nitro-2-bromoacetophenone
(XXVI) was proved as indicated in the diagram (page 29).

In view of the observations of Borsche and Koelsch
(85) it was suggested (142) "that diazotisation of o-amino-
ketones . . . . . . might offer a simple and general route to
4-hydroxycinnolines"; although this was found to be the
case the yield of each cinnoline was found to depend signi-
ficantly (see page 78) on the nature of the substituent in
the aminoketone. Starting from acetophenone, Schofield and
Simpson (142) prepared by the routes shown not only 6-nitro-
-4-hydroxycinnoline but also 6- and 8-chloro-, 6- and
8-bromo-(XXIV and XXV; R = Cl and Br), and 6-cyano-4-hydroxy-
cinnoline (XXIII). These were obtained in good yield but
diazotisation of o-aminoacetophenone itself gave only a poor
yield of 4-hydroxycinnoline (XX). Further, no cinnoline
formation occurred on diazotisation of 6-aminoacetoveratrone
or of 2:3-diamino or 2-amino-3-methoxyacetophenone. 6-Bromo-
-4-hydroxycinnoline (XXV; R = Br) was probably prepared
earlier by Gibson and Levin (67) as the by-product of a

Bart reaction using diazotised 5-bromo-2-aminoacetophenone;
they formulated the arsenic-free compound (m.p. 278°) as
5-bromo-2-nitrosaminoacetophenone or as 5-bromo-2-amino-
oximinoacetophenone but there is little doubt that the
cinnoline (m.p. 277°) was obtained in spite of the poor
agreement with analytical data.

Further interest in the diazotisation of o-aminoaceto-
phenones was aroused by the work of de Diesbach and Klement
(49) who diazotised ω-anilino-o-aminoacetophenone and
obtained a substance, $C_{14}H_{11}O N_3$, m.p. 283°, which Simpson
and Schofield (142) regarded as 4-hydroxy-3-anilinocinnoline.
Preliminary results of an investigation into the extension
of this reaction to "other terminally substituted o-amino-
acetophenones" have been described by Schofield (140).
Attempts to repeat the work of de Diesbach and Klement were
discouraging; two substances, m.p. 95-103° and 120°
(according to the method of isolation employed) were produced,
but no compound melting at 283° was isolated. The diazo-
tisation of ω-bromo-o-aminoacetophenone (XIX) furnished a
crystalline product, m.p. 277-278°; which, in the absence of
analytical data, was represented as 3-bromo-4-hydroxycinnoline
(however, see page 120 of this thesis). Similar treatment of
ω-phthalimido-o-aminoacetophenone (XVII) gave a highly

Preparation of 4-Hydroxycinnolines from Acetophenone (140).
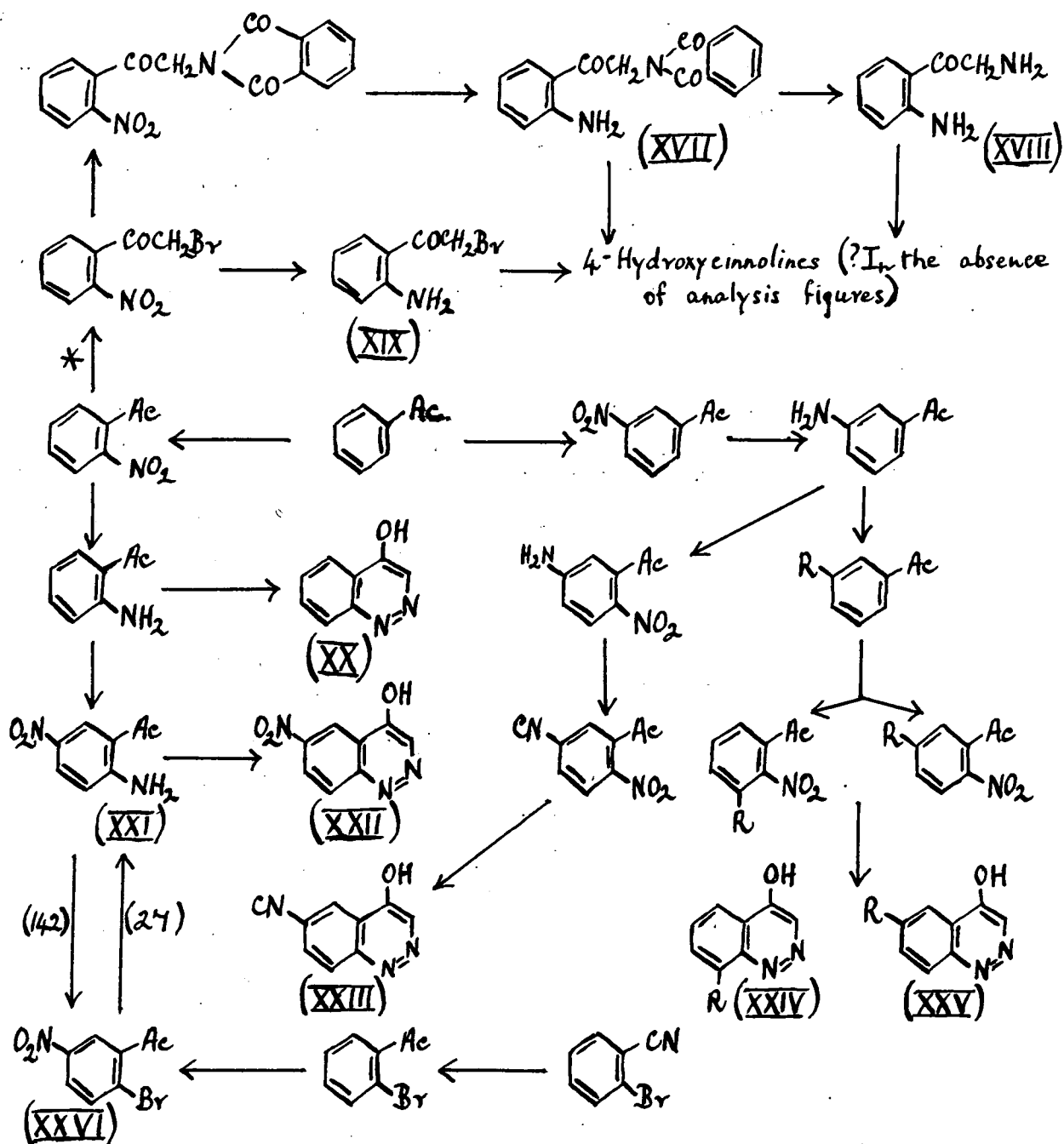
* o-Nitroacetophenone for this route prepared from
o-nitrobenzoic acid and acetoacetic ester (113).

crystalline solid, originally believed to be 3-phthalimide-
-4-hydroxycinnoline in spite of its insolubility in aqueous
sodium hydroxide; subsequent analysis did not support such
a representation. Hydrolysis of the supposed 3-phthalimide-
-4-hydroxycinnoline to the 3-amino-compound was tried without
success whilst a proposed route to 3-substituted 6-nitro-4-
hydroxycinnolines led to difficulties which were not resolved.
The diazotisation of o-ω-diaminoacetophenone (XVIII) gave no
useful product.

Another route to a 4-hydroxycinnoline was revealed by
Pfannstial and Janecke (120) when they prepared 5-chloro-3-
phenyl-4-hydroxycinnoline (XXVII) by boiling 5-chloro-2-
hydrazinobenzoic acid with benzaldehyde; the yield was low
because of the concomitant formation of 4-chloroindazolone
(XXVIII). It was stated that the unphenylated cinnoline was
"not yet purified" but no further details were given .
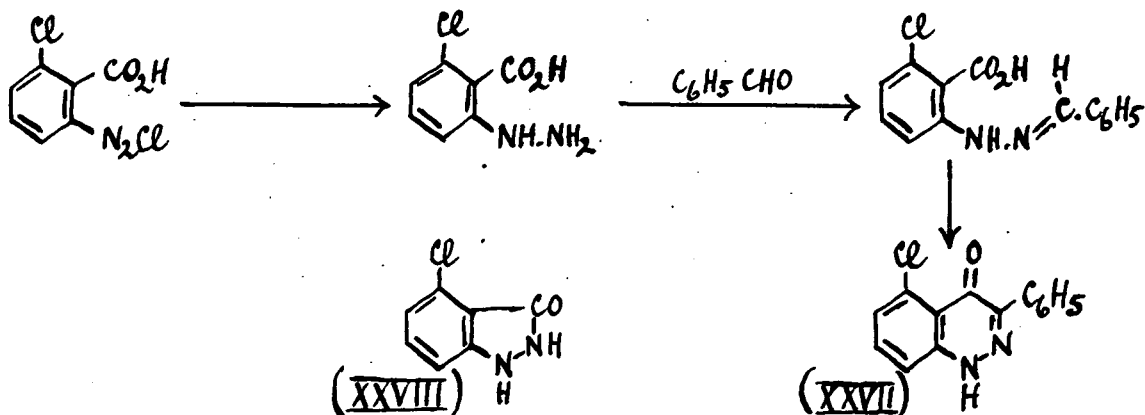
This discovery was incidental to the main work, namely, the

reduction of diazotised anthranilic acids to the corresponding
o-hydrazinobenzoic acids and conversion of the latter to
indazoles by boiling with very dilute hydrochloric acid. The
reaction with benzaldehyde was abnormal only in the case of
the 5-chloro-acid, other substituted o-hydrazinobenzoic acids
giving the expected benzalphenylhydrazones.

Some properties of 4-hydroxycinnolines.

Several properties are common to the great majority of
4-hydroxycinnolines although special effects are often
exerted by additional substituents, the nature of such effects
being often characteristic for substitution in a given position.
Thus,

(a) 4-Hydroxycinnolines generally have melting points
greater than 250° but the 8-chloro- and 8-nitro-derivatives
(for example) melt at 198° and 185° respectively.

(b) Solubility in aqueous alkalis is a general feature,
sometimes even aqueous ammonia or sodium carbonate being
effective. Sparingly soluble alkali-salts have been
encountered and 6-nitro-4-hydroxycinnoline is noteworthy for
the deep yellow colour of its alkaline solution. 3-Phenyl-5-
chloro-4-hydroxycinnoline is insoluble in aqueous sodium
hydroxide (120°).

(c) These compounds are often amphoteric; this property has been illustrated for 4-hydroxycinnoline itself by the titration of the Richter acid (above, page 9) and also by the isolation of 4-hydroxycinnoline hydrochloride. The latter is readily hydrolysed by water and is thus similar to the hydrochlorides (not purified, 140) of 6-methoxy- and 6:7-methylenedioxy-4-hydroxycinnolines.

Solubility in various solvents depends largely upon the nature of the substitution in the nucleus. In alcohol moderate solubility is the general rule; 6-chloro or 6-cyano groups have a solubilising effect whereas 6-nitro-4-hydroxy-cinnoline is only very sparingly soluble in alcohol; the 6-methoxy-derivative is more soluble whilst Pfannstiel and Janecke's compound (XXVII) is "insoluble in all the usual solvents". In every case the solubility in acetic acid is greater than that in alcohol.

The chief derivatives of 4-hydroxycinnolines, such as acetoxy- and chloro-compounds, are dealt with below.

Nitration of 4-hydroxycinnoline was carried out by Schofield and Simpson (141) and is of great theoretical interest. Three isomeric mononitro-derivatives were obtained, the pre-dominant one being 6-nitro-4-hydroxycinnoline, identical with that described by Borsche and Herbert (27). It was

observed that nitration of similar hydroxy-heterocycles, e.g. carbostyril (48, 64), 2-methyl and 2:3-dimethylquinazoline (23) and 2:4-diketotetrahydroquinazolone (24), gave mainly the 6-nitro-compounds. However, since no search for other isomers was evident in these studies no attempt was made to interpret the significance of the points of attack in the cinnoline ring. A second isomer was unchanged after boiling with acetic anhydride and, on steric grounds was represented as 5-nitro-4-hydroxycinnoline;* attack on the 3-position was excluded by analogy with 3-nitro-2:4-dihydroxyquinoline which exhibits no steric hindrance (8). The third isomer was provisionally regarded as 8-(or 7-) nitro-4-hydroxy-cinnoline.

Attempts to reduce 6-nitro-4-hydroxycinnoline and 6-nitro-4-acetoxycinnoline (detailed by Schofield, 140) have had little success, only a small amount of 6-amino-4-hydroxy-cinnoline being isolated.

Some experiments on the reduction of 4-hydroxycinnoline have already been dealt with (pages 4 and 5); further, tetrahydro-4-hydroxycinnoline has been prepared by Weber and co-workers (112) by means of phosphorus and hydriodic acid. Treatment of 3-<u>hydroxycinnoline</u> and its 1:2-dihydro-derivative with the same reducing agent gave oxindole, this

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*This compound has since been shown (155a) to be the 8-nitro-derivative.

result confirming the structure of the former compound prepared by Bossel (Inaug. Diss., Tubingen. May 1925).

4-Acetoxycinnolines.

In striking contrast to the complex reaction witnessed during attempts to acetylate the Richter acid (page 9) 4-hydroxycinnoline gives a highly crystalline acetoxy-derivative by treatment with acetic anhydride, alone or in the presence of pyridine (143); acid hydrolysis regenerates 4-hydroxycinnoline. 6-Nitro-4-acetoxycinnoline is similarly formed (141) whilst reference has already been made to the stability of the 8- (originally presumed 5-)nitro-4-hydroxy-cinnoline towards boiling acetic anhydride.

4-Chlorocinnolines.

These compounds are prepared by the action of a mixture of phosphorus oxychloride and phosphorus pentachloride on the relevant 4-hydroxycinnolines, a method first used in this series by Busch and Klett (33) for the preparation of 4-chlorocinnoline. This compound was at once recognised as "a very reactive substance, capable of giving rise to a great number of cinnoline derivatives", a statement based on the observed spontaneous decomposition to a black, water-soluble mass and on the reaction of the chlorocinnoline with aniline, p-toluidine and sodium ethoxide. The reduction of 4-chloro- cinnoline has already been dealt with (page 4). A more detailed study of 4-chlorocinnoline was reported by Schofield (140) who showed that the spontaneous decomposition of 4-chlorocinnoline (in a corked tube) gave rise to 4-hydroxy- cinnoline hydrochloride but that storage in a desiccator prevented decomposition. A series of general observations (tabulated) together with particular experiments on the ease of phenoxylation of some 4-chlorocinnolines led to their gradation in order of increasing reactivity as follows (140):
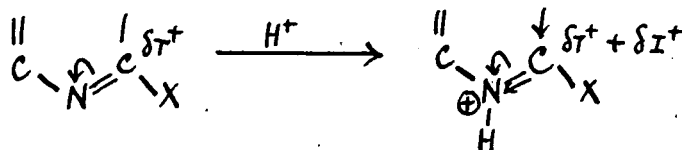
$$6 \text{ MeO} < 6 \text{Cl} < \text{unsubstituted} < 6 \text{ N O}_2.$$

GENERAL OBSERVATIONS.

CINNOLINE.	Spontaneous Decomposition	Decomposition in aqueous media
4-Chloro-6-methoxycinnoline	Impure specimen gave dark mass on standing.	Unaffected by short boiling or standing at R.T. for several hours (w. dil. mineral acid).
4:6-Dichloro-cinnoline	Stable to atmospheric moisture when pure.	Warm 2N-hydrochloric * acid caused hydrolysis.
4-Chloro-cinnoline	Decomposed in one or two days, more slowly if in corked tube. Stable in desiccator.	Gave 4-hydroxycinnoline on warming with water; accelerated by mineral * acids. The hydrochloride +AgNO₃ indicated more than salt forming halogen (33).
4-Chloro-6-nitrocinnoline	Very rapidly decomposed in atmosphere. Yellow xals. turned dull in a few hours. Decomp. to hydroxycinnoline complete in one month.	Similar to 4-chloro-cinnoline. Even recrystallisation from alcohol precipitated the 4-hydroxy-compound.

Reference was made to the theoretical suggestions of
Banks (16) who explained the reactivity of certain halogen
atoms in heterocyclic systems, e.g. by a tautomeric shift of
electrons towards the nitrogen atom. It was apparent that

the N atoms of the cinnoline ring showed enhanced reactivity
in this respect and the order of increasing reactivity was
also associated (140) with the same sequence obtained when
the 6-substituents were arranged in order of "decreasing
power of electron release", the 6-nitro group being, by
virtue of its electrophilic character, the best stimulant to
activity on C_4. The development of an integral positive
charge on the N atom was suggested by Banks (16) to explain
the enhanced reactivity of halogeno-heterocycles in acid
solution.

$$\underset{C}{\overset{||}{C}}\diagdown\underset{N}{\overset{\frown}{N}}=\overset{|}{C}\overset{\delta\tau^+}{\diagdown}_X \quad\xrightarrow{\quad H^+\quad}\quad \underset{C}{\overset{||}{C}}\diagdown\underset{\underset{H}{\overset{|}{\underset{\oplus}{N}}}}{\overset{\frown}{N}}\Leftarrow\overset{\downarrow}{C}\overset{\delta\tau^+ + \delta I^+}{\diagdown}_X$$

Such a mechanism explained well the reactions ($*$) tabulated
above. Comparisons were offered (140) with the reactivity of
comparable compounds in the quinoline and acridine series but
the lack of quantitative data was stressed throughout.

Other reactions (140) of 4-chlorocinnoline itself include
the action of acetic anhydride, giving the acetoxy-compound; an
attempt to prepare a Grignard reagent failed and 4-chloro-
cinnoline could not be reacted with benzene in the presence of
aluminium chloride. Treatment with potassium cyanide in
methanol gave only 4-methoxycinnoline.

4-Anilidocinnolines (and attempts to prepare 4-aminocinnoline).

As already mentioned (page 36), the reactivity of
4-chlorocinnoline was quickly exploited by Busch and Klett
(33) who prepared 4-anilinocinnoline and 4-p-toluidinocinnoline
by direct reaction of the chloro-compound with aniline and
p-toluidine respectively. This method of characterisation
was adopted later (140) and the anilido-derivatives of
6-methoxy- and 6-nitro-4-chloro-cinnoline were prepared, the
latter being notable for its bright orange colour, attributed
to the predominance of the form (XXIX). Preliminary attempts
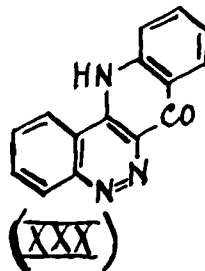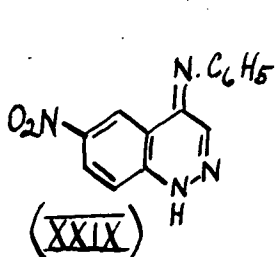
using anthranilic acid as the amine were begun with a view
to preparing (XXX) but little success was achieved (140).
A scheme (A) for the preparation of 4-aminocinnoline from
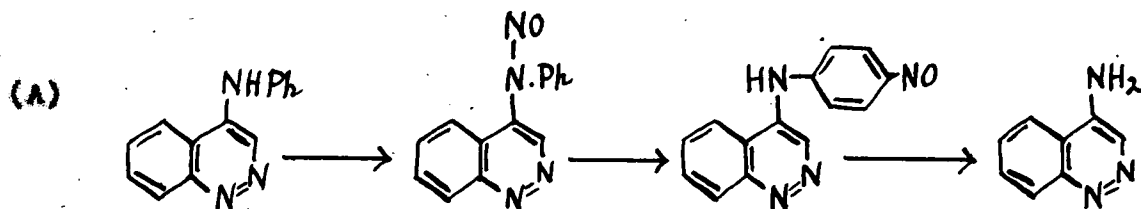
4-anilidocinnoline has been reported (140) but preliminary
attempts to carry out the first stage met with no success.

Other attempts to prepare 4-aminocinnoline also failed: thus 4-chlorocinnoline did not react with liquid ammonia or with potassium phthalimide in the presence of potassium carbonate; with aqueous alcoholic ammonia at temperatures greater than 100° 4-chlorocinnoline gave no useful product.

4-Alkoxycinnolines.

Reference has already been made (page 36) to the
preparation of 4-ethoxycinnoline by Busch and Klett but no
further examples of this type of compound were published
until recently. These examples, furnished by Schofield and
Simpson (141), arose during a study of the reduction of
6-nitro-4-hydroxycinnoline though the belief that the ampho-
teric nature of 6-amino-4-hydroxycinnoline was partly
responsible for the failure to isolate appreciable amounts of
the latter from any of numerous experiments. It was hoped
that methylation of 6-nitro-4-hydroxycinnoline would provide
material more amenable to reduction and isolation. Treatment
with dimethyl sulphate and alkali gave "extensive decomposition
and formation of a tar" unless the quantities were so arranged
as to ensure an acid medium. Under these conditions there was
obtained a high yield of methylated products from which two
isomeric compounds were isolated; the predominant orange-
coloured one, m.p. 229°, was originally regarded as 6-nitro-1-
methyl-4-cinnolóne (XXXI; R = NO$_2$) and the pale yellow con-
comitant substance, m.p. 183°, as 6-nitro-4-methoxycinnoline
(XXXII; R = NO$_2$).
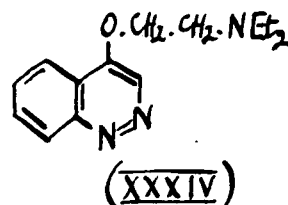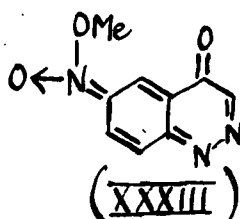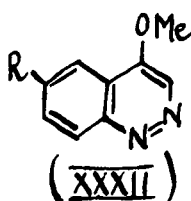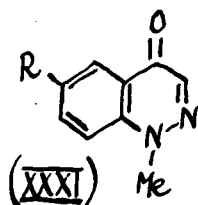
These structures were discounted by the facts that -

(a) Methylation of 4-hydroxycinnoline itself gave a colourless derivative which must have been 1-methyl-4-cinnolone (XXXI; R = H) since it was different from authentic 4-methoxy-cinnoline (XXXII; R = H), prepared from 4-chlorocinnoline and sodium methoxide.

(b) 4-Chloro-6-nitrocinnoline, on treatment with sodium methoxide, gave a third isomer, m.p. 194°, undoubtedly 6-nitro-4-methoxycinnoline. Adoption of the methyl nitronate structure (XXXIII) for the substance, m.p. 229°, and the cinnolone form (XXXI; R = NO_2) for the isomer, m.p. 183°, clearly solved this investigation.

An interesting attempt to prepare a compound (XXXIV) of this type by reaction of 4-chlorocinnoline with sodium β-diethylaminoethoxide has been reported (140) but "the product was an uncrystallisable oil".

Little is known of the properties of 4-alkoxycinnolines but Busch and Klett (33) observed that boiling alcohol converted 4-ethoxycinnoline into the hydroxy-compound.

4-Phenoxycinnolines.

The preparation of these compounds by the action of phenol on 4-chlorocinnolines in the presence of potassium hydroxide was not merely of value for synthetic purposes (see below) but yielded useful information on the reactivity of 4-chlorocinnolines (140). The latter estimation was only approximate since the yields of phenoxy-compounds were not accurately determined; e.g. the great reactivity of 4-chloro-6-nitrocinnoline exhibited itself by rapid decomposition to the hydroxycinnoline rather than by an enhanced yield of phenoxy-compound; again, the 6-methoxy-derivative was only obtained in poor yield under comparative conditions but longer heating of the components gave a 70% yield.

4-Phenoxycinnolines are generally easily soluble in alcohol, moderately soluble in ether, but only sparingly soluble in ligroin or water. Partial fission to 4-hydroxycinnoline on refluxing in alcohol has been observed (140), this behaviour being comparable to that of 4-ethoxycinnoline. Again, treatment of 4-phenoxycinnoline with boiling acetic anhydride gave the acetoxy-compound. 4-Phenoxycinnoline could be recovered unchanged from its solution in dilute hydrochloric acid and an attempt (140) to prepare the hydrochloride in dry ethereal solution gave an indeterminate result since the (supposed) hydrochloride decomposed to 4-hydroxycinnoline on moderate heating.

4-Dialkylaminoalkylaminocinnolines.

The most important application of 4-phenoxycinnolines has been to the preparation of compounds of the type (XXXV) which it was hoped might show antimalarial properties. Such a type provided cinnoline compounds related to the two most successful synthetic antimalarials known at that time[*], me-pacrine (XXXVI) and plasmoquine (XXXVII).

$(\underline{XXXV})$　　$(\underline{XXXVI})$　　$(\underline{XXXVII})$
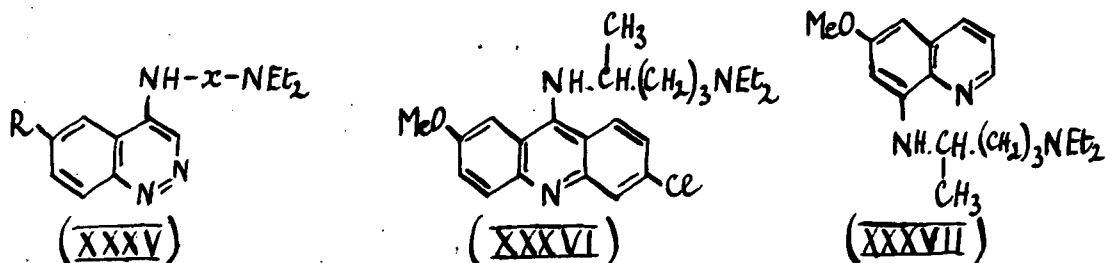
Attempts (140) to react 4-chlorocinnoline with 2-amino-5-diethylaminopentane were unsuccessful although direct condensation of β-diethylaminoethylamine with 4-chlorocinnoline gave a reasonable yield of 4-(β-diethylaminoethylamino)cinnoline (XXXV; R = H, x = $(CH_2)_2$). The formation of "tars and un-crystallisable oils" observed in the first example was reminiscent of the results of Kermack and Goodall (82) and Magidson and Grigorowsky (98) during similar experiments with certain 5-chloroacridines. The procedure adopted (140) was based on the findings of both groups of workers and consisted

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[*]Before the discovery of 'paludrine'.

in heating the amine with either the phenoxy-compound or with
a mixture of chloro-compound and phenol. In this way
4-(α-methyl-δ-diethylaminobutylamino)cinnoline and
4-(β-diethylaminoethylamino)cinnoline were prepared and
characterised as their dihydrochlorides.

It was expected that a 6-methoxy-group would enhance the
antimalarial activity of the 4-'basic side chain'-compounds
by analogy with the work of Ainley and King (3), who, during
a study of synthetic quinoline derivatives related to quinine,
observed that absence of a methoxyl group was invariably
associated with lack of antimalarial activity. However,
6-methoxy-4-(α-methyl-δ-diethylaminobutylamino)cinnoline,
prepared from the chloro-compound in the presence of phenol,
gave disappointing biological results (see table) (154).

| COMPOUND (XXXV)	DOSE (mgm./kgm.)	ACTIVITY
(a). $x = CH(Me)(CH_2)_3$, $R = H$.	250 120	Marked Slight
(b). $x = CH(Me)(CH_2)_3$, $R = OMe$.	60	None
(c). $x = (CH_2)_2$. $R = H$.	200 120	Doubtful None

4-Alkyl and Aryl Cinnolines.

Following closely on the work of Richter (130), an investigation by Widman (185,182) of the 3-nitro- (and amino-) derivatives of 4-hydroxy-propyl- and 4-*iso*-propenyl-benzoic acids led to the preparation of 4-methylcinnoline-7-carboxylic acid (III).[*] This discovery arose during the diazotisation of 3-amino-4-*iso*-propenylbenzoic acid (II) and was unexpected since similar treatment of 3-amino-4-hydroxypropylbenzoic acid (I) had given the usual phenolic product. Further, it was known that o-aminocinnamic acid, "a similarly constituted compound", behaved normally on diazotisation and furnished o-cumaric acid (58).

$$(I) \qquad (II) \qquad (III) \qquad (IV)$$
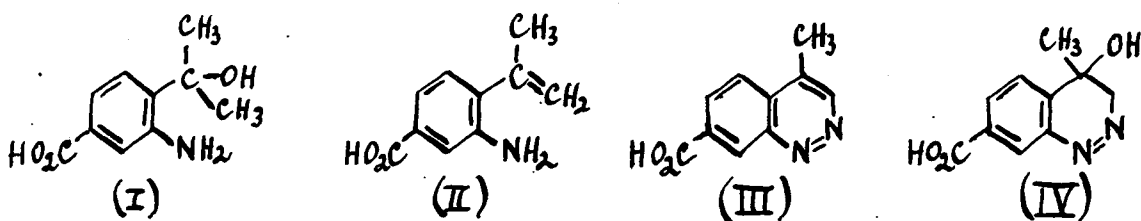
A distinction between the mode of formation of Richter's acid and that of his own compound was drawn by Widman; he pointed out that whereas Richter's compound could conceivably be formed by migration of the hydroxyl group of the diazotate – the

$$C_6H_4 \underset{N=N.OH}{\overset{C\equiv C.CO_2H}{\diagup}} \longrightarrow C_6H_4 \underset{N=N}{\overset{C(OH)=C.CO_2H}{\diagup}}$$
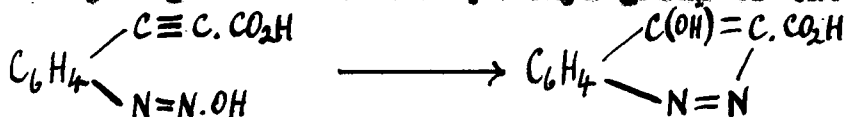
methylcinnoline could only be formed by loss of a molecule of

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water.

$$HO_2C \cdot C_6H_3 \overset{\overset{\displaystyle CH_3}{|}}{\underset{N=N-OH}{C=CH_2}} \quad \longrightarrow \quad HO_2C \cdot C_6H_3 \overset{\overset{\displaystyle CH_3}{|}}{\underset{N=N}{C=CH}}$$
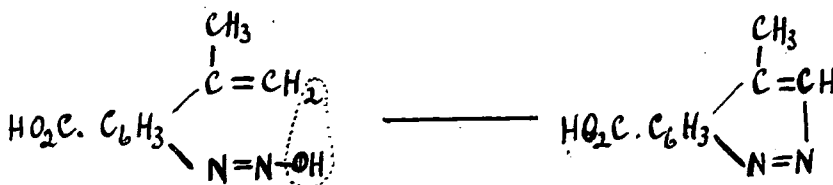
Widman could find no experimental support for his tentative suggestion that a compound (IV) might figure as an intermediate in the formation of the methylcinnoline.

Although Widman's acid is the only 4-alkylcinnoline available for review a considerable number of 4-arylcinnolines have been prepared; the discovery of the early members supports the generalisation that cinnoline chemistry began as a series of accidents. Thus 4-phenylcinnoline (VIII; $R_1 = R_3 =$ H) was obtained by Stoermer and Finoke[*] (158) "during an investigation of certain o-aminodiphenylethylenes concerned with the detection of stereoisomerism in the series". Instead of the expected o-hydroxy-compound the cinnoline was isolated on diazotisation of the compound (VII; $R_1 = R_3 =$ H) and by the same procedure 3-methyl-4-phenylcinnoline (VIII; $R_1 =$ H, $R_3 =$ Me) and 4-p-tolylcinnoline (VIII; $R_1 =$ Me, $R_3 =$ H) were

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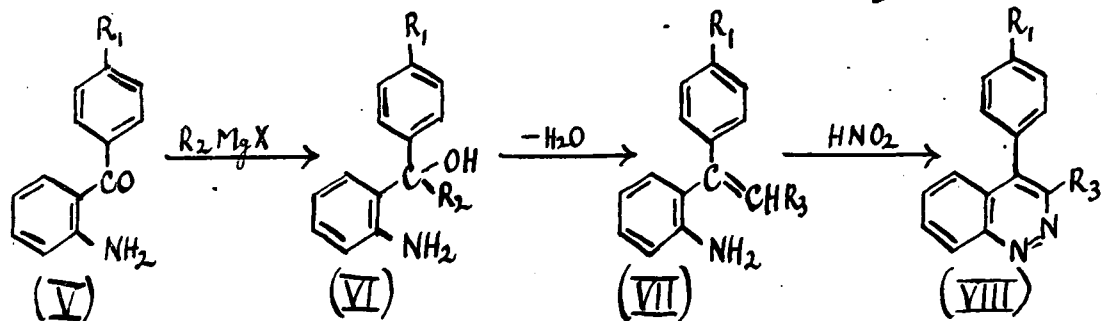
[*]These authors were unaware of Widman's work and when the latter pointed out their mistake (183) it was explained (159) that standard works (e.g. Anschutz-Schroter) omitted any reference to Widman.

prepared. The requisite ethylenes (VII) were made from the o-amino-ketones (V) as shown, the latter being produced according to the instructions of Ullmann and Bleier (174). Evidence in favour of the cinnoline structure for the two compounds (VIII; R_1 = H, R_3 = Me; and R_1 = R_3 = H) was their degradation to 3-methyl-4-phenylcinnolinic acid (IX; R = CH₃) and 4-phenyl-pyridazine (X) respectively.
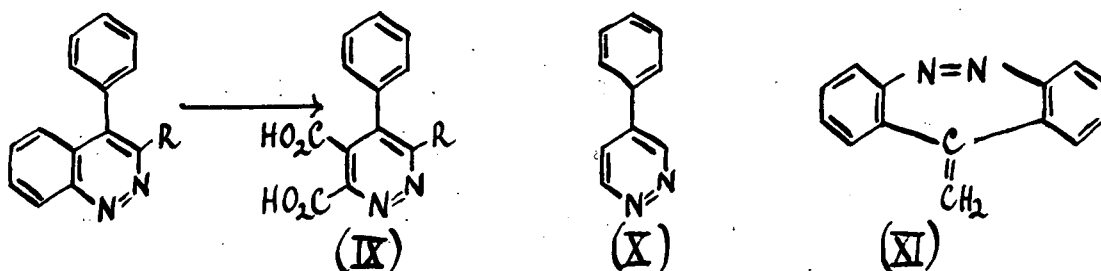
An alternative structure (XI) was rejected when its undoubted instability towards oxidation was considered; further, the fact that diazotisation of the bromo-ethylene (VII; R_1 = H, R_3 = Br) gave only a poor yield of 4-phenylcinnoline - accompanied by loss of bromine and much resinification - was inexplicable on the structure (XI).

The absence of cinnoline formation on diazotisation of the carbinol (VI; R_1 = H, R_2 = Me) indicated the essential nature of the ethylenic side chain for cinnoline synthesis and this was in accord with the known susceptibility of such a group to undergo addition reactions giving cyclic compounds (3.5).

119.

Apart from the preparation of several salts, Stoermer and Fineke did not develop the synthetic chemistry of their compounds. The colour of several salts was noteworthy; two hydriodides of 4-phenylcinnoline were prepared, a yellow variety $(C_{14}H_{10}N_2)_2.HI$ and a red one, $C_{14}H_{10}N_2.HI$, the latter being formed spontaneously from the former. The colours of solutions of the salts in various solvents varied widely, this behaviour being reminiscent of cinnoline methiodide.

The reduction of 4-phenylcinnoline was carried out by Neber in 1929 (112) and both the dihydro- and tetrahydro-compounds were prepared. Reduction of the cinnoline or its dihydro-derivative with zinc and acetic acid furnished 3-phenylindole in good yield.

4-(p-Anisyl)cinnoline was described in a later paper by Stoermer and Gaus (160) which was important for two reasons.

(1) For the first time a cinnoline derivative was degraded to a known compound (page 50), and

(2) Some attempt was made to account for the known limitations of the reaction.

The degradation proved the assumption, made earlier in connection with the degradation of 4-phenylcinnoline (page 48) that the 2-carboxyl-group of 4-phenylpyridazine-2:3-dicarboxylic acid is eliminated first during decarboxylation: this proof

Degradation of 4-p-Anisylcinnoline (160).
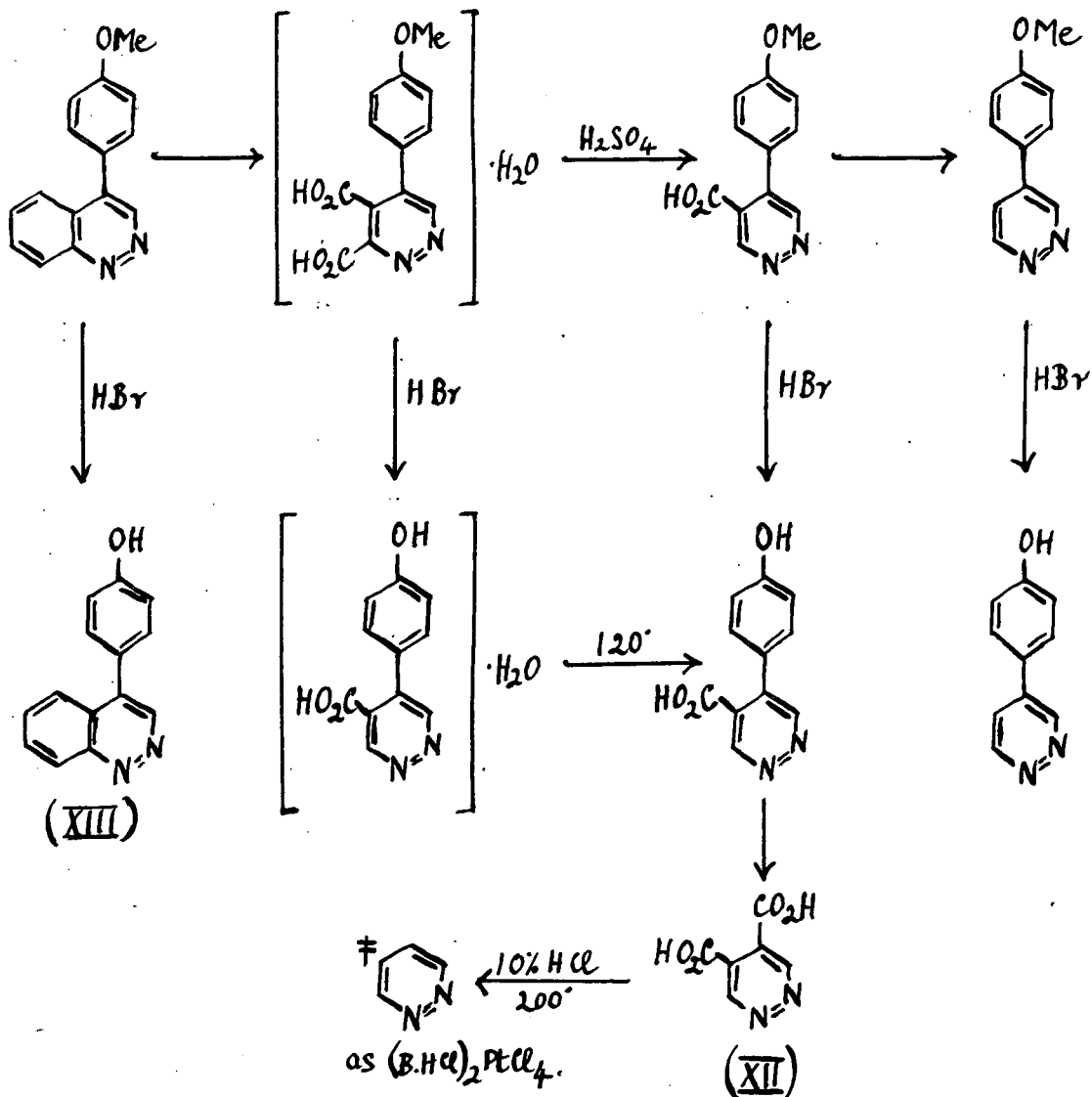
‡ Pyridazine was first prepared by Tauber (164) by oxidation degradation of phenazone (3:4-Benzocinnoline):-
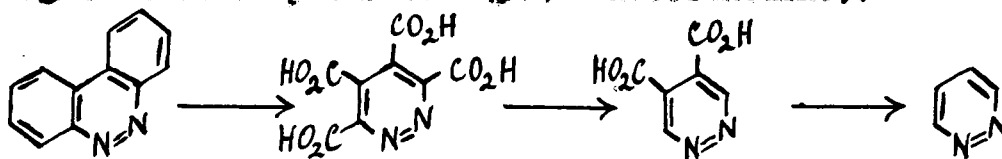
However, the constitution of the acid (XII) was really proved by Gabriel (65) who obtained it from phthalazines.

rested on the identity of the product (XII) with authentic pyridazine 4:5-dicarboxylic acid.

4-Anisylcinnoline formed brightly coloured salts similar to those of 4-phenylcinnoline, and like the latter gave two different gold double-salts, B.HCl. Au Cl_3 and $(B.HCl)_2$ Au Cl_3. The action of boiling concentrated hydrobromic acid on 4-(p-anisyl)cinnoline furnished 4-(p-hydroxyphenyl)cin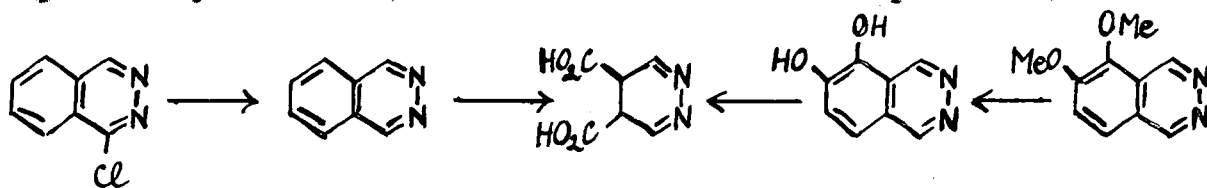noline (XIII); this also gave highly coloured salts and a deep yellow solution in aqueous sodium hydroxide. The confirmation of Fischer's (58) result on the diazotisation of o-aminocinnamic acid indicated the adverse effect of a negative group on the β-C-atom but the assertion of Stoermer and Gaus that the opposite 'group-effect' relationship operated in the case of the α-C-atom was without experimental support.

The possibility that the Widman-Stoermer reaction would prove to be of wide applicability was strengthened by Simpson and Stephenson's preparation of three new 4-arylcinnolines (152). The o-aminoethylenes required were prepared by the general method of Stoermer and co-workers; thus the substance (XIV) arose from 5-bromo-2-aminoacetophenone by a Grignard reaction and subsequent dehydration of the carbinol. Diazotisation of the ethylene-sulphate in dilute sulphuric acid furnished 6-bromo-4-phenylcinnoline (XV) in almost quantitative yield.

Synthesis of the o-aminoketones (XVI and XVII) was achieved using the method of Zincke and Siebert (191) although reduction of the anthroxans to the ketones with iron and acetic acid was more satisfactory than the original method using tin and hydrochloric acid. The action of methylmagnesium iodide on compound (XVI) gave a resin from which the o-aminoethylene (XVIII) was eventually obtained pure via the hydrochloride. Diazotisation of the latter yielded 6-chloro-4-(2'-hydroxy-5'-methylphenyl)cinnoline (XIX). The carbinol from the second aminoketone (XVII) was spontaneously dehydrated to the ethylene (XX), which, on diazotisation in hydrochloric acid, gave a 70% yield of 6-chloro-4-(4'-hydroxyphenyl)cinnoline (XXI); diazotisation in dilute sulphuric acid gave only a 50% yield of the cinnoline.

It was clear that proof of the structure of these cinnolines depended on the correctness of the orientation of the intermediates. Simpson and Stephenson followed up the deamination of (XVII), previously effected by Zincke and Siebert, by oxidation to m-chlorobenzoic acid. Since this result could have arisen from the 3-chloro-2-aminoketone, the substance (XVII) was converted by a Sandmeyer reaction and subsequent oxidation into 2:5-dichlorobenzoic acid: this result was also obtained using the ketone (XVI), thus fixing the positions of the amino- and

Routes to three new 4-Arylcinnolines (152).
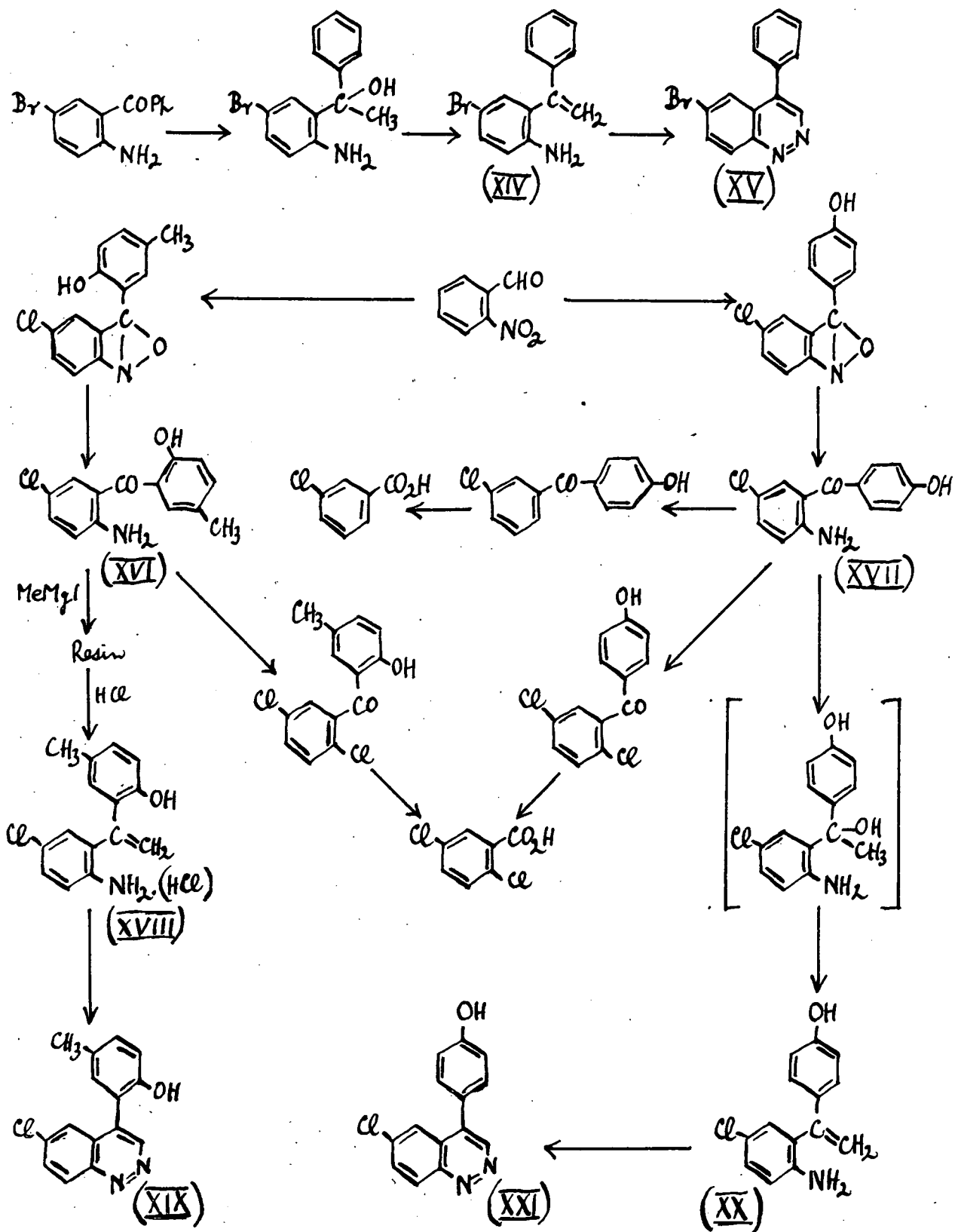
chloro-groups. An unsuccessful attempt to confirm the position
of the hydroxyl groups in each of the aminoketones was also
reported.

The detail of the above investigation, with particular
reference to the preparation of the intermediate o-aminobenzo-
phenones, has been reported by Stephenson (/57). A number of
unsuccessful attempts to prepare cinnolines by new routes was
also described:-
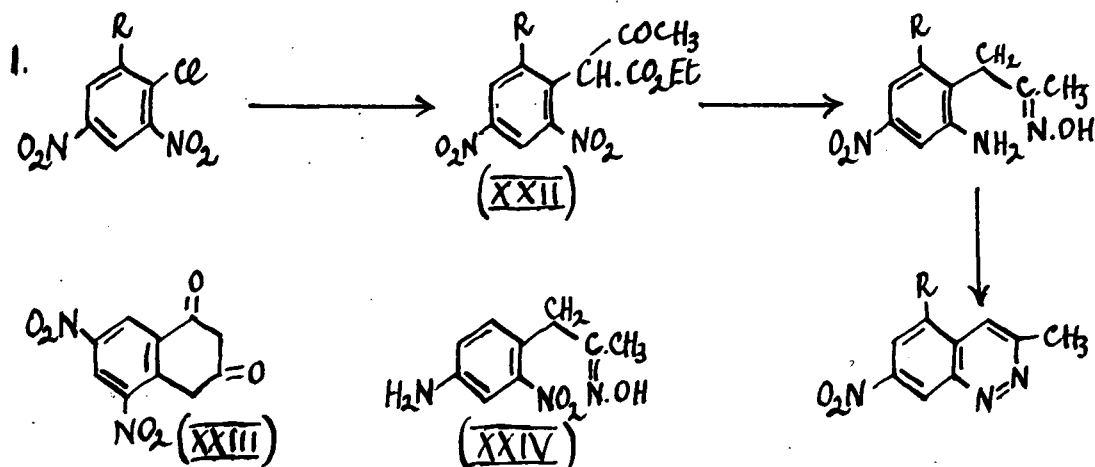
Hydrolysis of the ketone (XXII; R = H) could not be achieved
using boiling dilute sulphuric acid - ring closure appeared to
occur giving (XXIII).

2:4-dinitrophenylacetone was prepared by the hydrolysis
of (XXII; R = H), the method used by Borsche (26). After
reduction in acid solution had failed careful reduction of the
oxime of the phenylacetone gave a monoamine tentatively
represented as (XXIV). Diazotisation of (XXV) followed by

2.
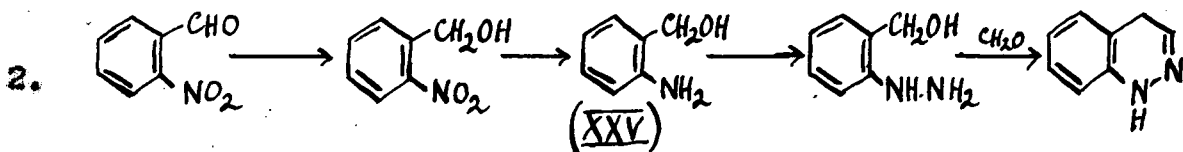
reduction gave a highly coloured amorphous product which
would not react with ketones; it was presumed to be the
indazole

3.
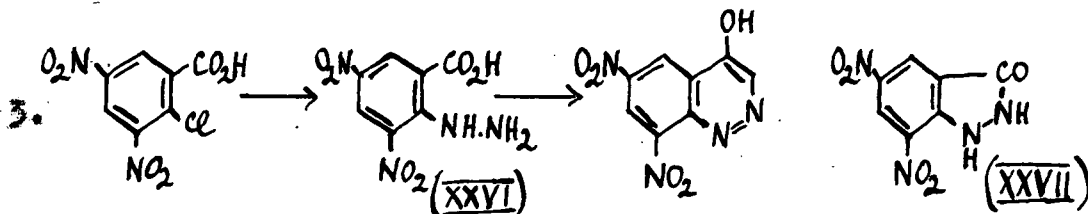
Again the hydrazine (XXVI) yielded only the indazole (XXVII).

4.
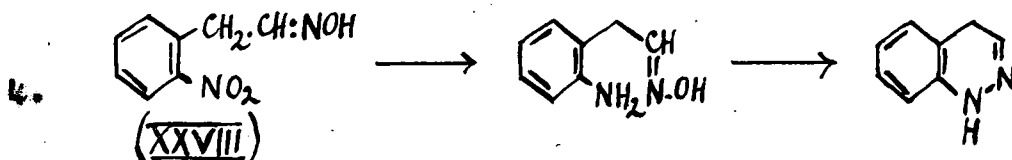
Attempted reduction of (XXVIII) gave only tarry material.

Although some attempt to explain the effect of side
chain substituents on the cyclisation of o-aminophenylethylenes
was made by Stoermer and Gaus (page 51) no serious study of
this aspect of cinnoline chemistry was reported until 1943. In
this year Simpson (150) presented a review of the diazotisation
of some o-amino-ethylenes together with some new examples of
4-arylcinnolines, the preparation of which was highly relevant
to the arguments proposed. Since the actual review is largely
of theoretical importance it will be dealt with later (page 74)
and the more factual contents are reported below.

$$(\overline{XXIX}) \qquad (\overline{XXX}) \qquad (\overline{XXXI}) \qquad (\overline{XXXII})$$
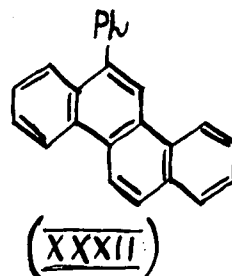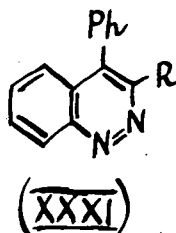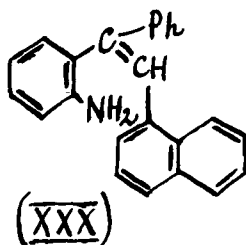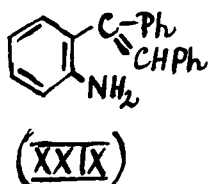
The ethylene (XXIX) was isolated in both geometrical forms and diazotisation of each of these gave 3:4-diphenylcinnoline (XXXI; R = Ph) in high yield. Both forms of the ethylene were stable to hot alcoholic hydrochloric acid.

Two stereoisomers of the compound (XXX), were isolated but owing to the stability of one of these towards both diazotisation and acetylation the extent to which cinnoline formation depends on spatial configuration could not be estimated in this case. The diazotisable ethylene gave 4-phenyl-3-(1'-naphthyl)cinnoline (XXXI; R = α-naphthyl) together with a hydrocarbon $C_{24}H_{16}$, believed to be 2-phenyl-chrysene (XXXII). In contrast to the diphenyl-ethylene (XXIX) the unreactive isomer could be converted to the diazotisable type, the 'cis' configuration of which was evident from its ability to give the Pschorr product (XXXII), (132, see page 75).

4-Phenyl-3-benzylcinnoline (XXXI; R = $CH_2C_6H_5$) was prepared by diazotisation of the corresponding ethylene; as in the two previous examples, the cyclisation was not spontaneous and the concentration of the acid medium was suspected as being responsible for this result.

Attempts to prepare the butadiene (XXXIII) were
unsuccessful since the requisite carbinol resinified when
treated with hot dilute sulphuric acid. The carbinol
yielded some normal acetamido-derivative on acetylation
but the chief product was a basic substance which underwent
rearrangement in hot dilute sulphuric acid;   these results
are represented as follows.
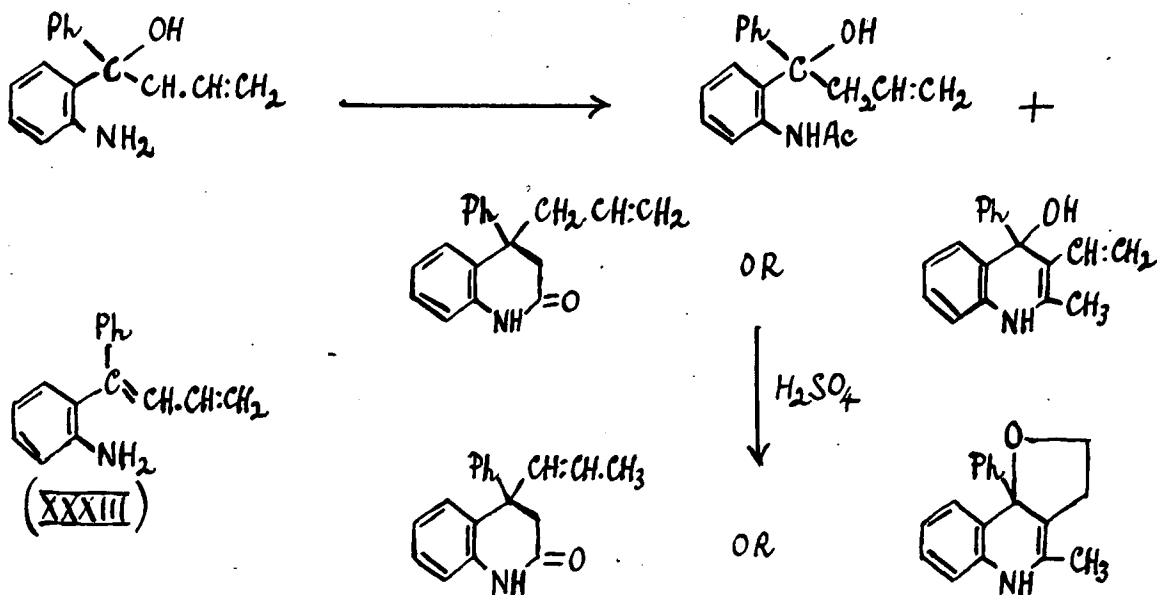
Synthesis of some 2-aminostilbenes with varying β-carbon-
atom substituents was also considered. Using the method which
was generalised by Pfeiffer (121) 2:4-dinitrotoluene was
condensed with furfural and the product reduced to yield the
isomeric amines:
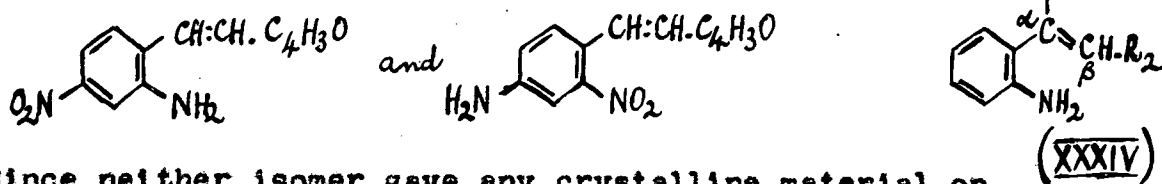
Since neither isomer gave any crystalline material on

diazotisation, other condensation products, prepared by the use of vanillin or piperonal instead of furfural, were not studied.

Although the literature survey, which was reported by Simpson along with this work, has been left over to a later section it is emphasised that both contributions are essential to the conclusion reached, "that the formation of cinnolines from ethylenes of the type (XXXIV) does not occur where R_2 is aryl or another negative group and R_1 is either hydrogen or carboxyl".

Mention may here be made of an investigation by Zerner (190) who, by boiling the phenylhydrazone of diphenylhydroxy-acetaldehyde (XXXV) with sulphuric acid, obtained a red crystalline solid which he represented as a dihydrocinnoline (XXXVI):
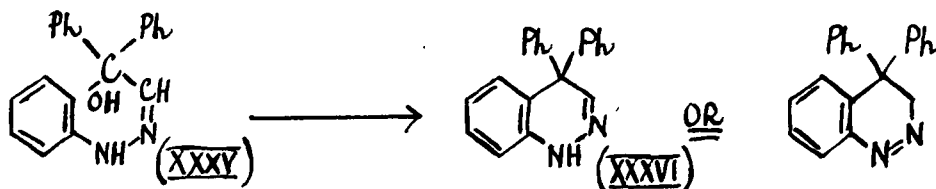
The deep colour of this compound and its lack of basicity, in contrast to the properties (page 5) of cinnoline and 1:2-dihydrocinnoline, were both attributed to the phenyl groups attached to the heterocyclic ring.

N-Substituted Cinnolines.

The earliest member in this series, prepared by Fischer and Kuzel (60), was referred to by Widman (182) as the only cinnoline derivative, other than the Richter acid, which was reported prior to 4-methylcinnoline-7-carboxylic acid. An attempt (58) to ring-close the β-nitrogen atom of o-hydrazinocinnamic acid with the carboxyl group arose from the earlier observation of Fischer (57) that reduction of the diazonium nitrate of o-aminocinnamic acid yielded N-amino-2-quinolone. Careful reduction of o-nitrosoethylamino-cinnamic acid with zinc and acetic acid gave an acid (instead of the expected hydrazine) which was readily decarboxylated to a base $C_{10}H_{12}N_2$.
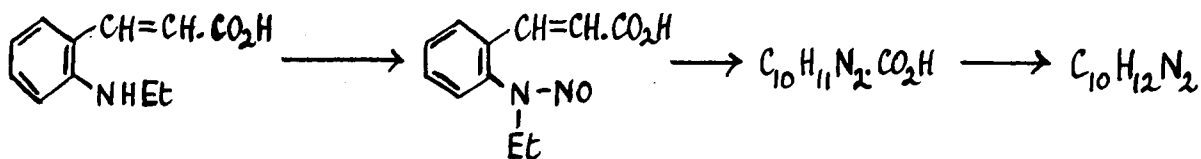
The following structures were suggested for the base, "ethyl-chinazole", but these cinnoline-type possibilities were later
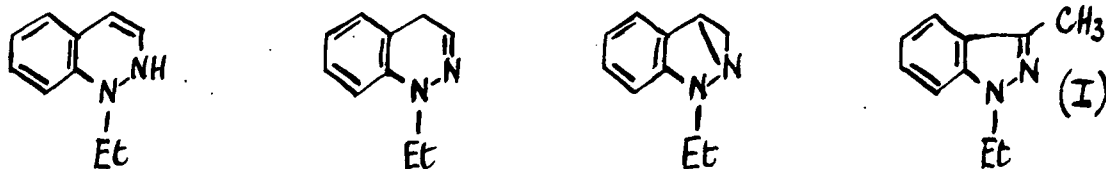
discarded (61) in favour of the "isindazole" structure (I).

The evidence for this decision was -

(a). The oxidation of monobromo-'ethylchinazole carboxylic acid' (II) to an aldehyde and thence to an acid which decarboxylated to a compound $C_9H_9N_2Br$.
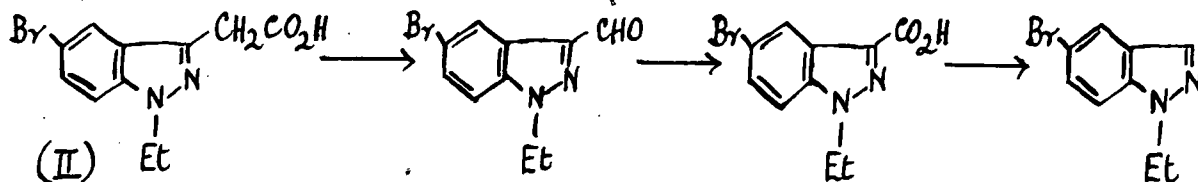
(b). The synthesis of 'ethylchinazole' (identical with the original preparation) by an unambiguous route from o-amino-acetophenone.
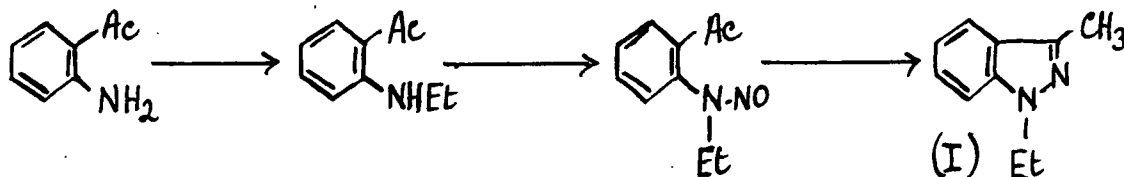
The preparation of another compound of this group was claimed by Tichwinski (170) during his study of the reaction between zinc diethyl and benzene diazonium chloride; he isolated from the liquid product mono- and di-ethylphenyl-hydrazine and a feebly basic sweet smelling oil, $C_{10}H_{14}N_2$. This compound was presumed to be N-ethyl-1:2-dihydrocinnoline (III) formed thus:-

$$C_6H_5N(Cl)\equiv N \longrightarrow C_6H_5N(C_2H_5)\equiv N$$
$$\downarrow C_2H_6 \text{ by } ZnEt_2 + H_2O$$
$$C_6H_5NC_2H_5NHC_2H_5$$
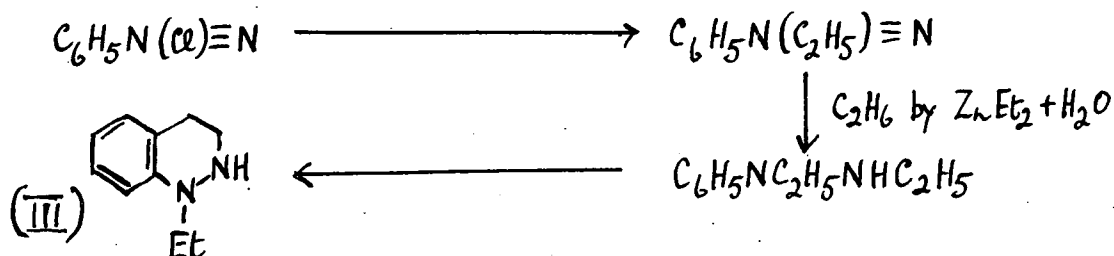
Later, Tichwinski (171) prepared the same substance by the

action of zinc diethyl on phenylazoethane.

In 1911, Ullmann and Schalk (178) used anthraquinone α-carboxylic acid to synthesise two new derivatives, "pyridazone-anthrones", which can be considered to be N-derivatives of dibenzo $\left[\text{de,h}\right]$cinnoline-3,7-dione (IV).
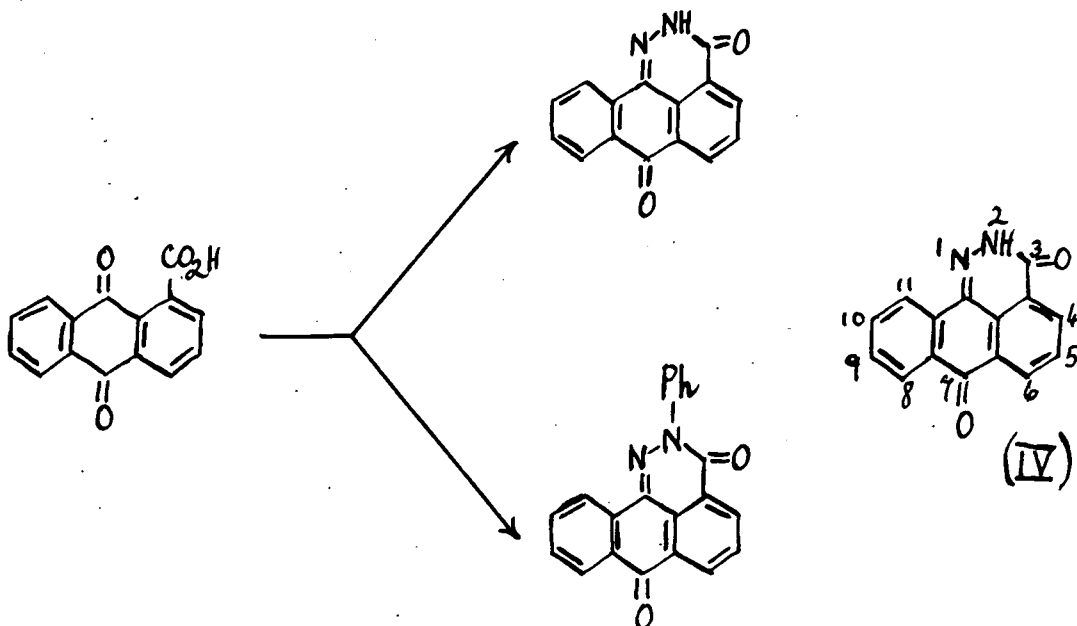
An attempt (54) to assign correct structural formulae to the three possible hydroxynaphthalene-1,8-dicarboxylic acids using the known directional tendencies of coupling in α- and β-naphthols led to the discovery of an anomalous coupling reaction. Whereas 3-hydroxynaphthalene-1,8-di-carboxylic acid gave the expected azo-compound the 2- and 4-isomers gave alkali soluble products which were converted to alkali insoluble substances on heating with acid or

merely an organic solvent, this result being reversed by
hot alkalis.
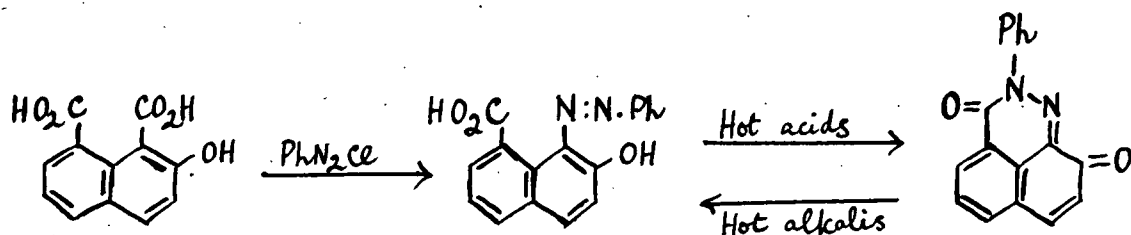
This cyclisation of the 2-naphthol probably takes place
through the quinonoid form (V); the 4-hydroxy-compound
gives rise to (VI).
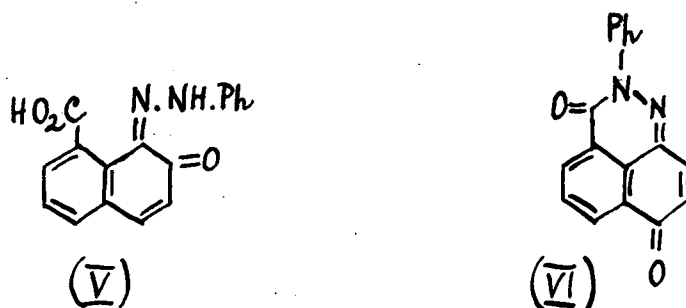
Particular interest attaches to the next N-substituted
cinnoline in view of the novel method of preparation. An
investigation into the course of the "azo-ester reaction"
led Diels and Alder (50) to the preparation of tetrahydro-
pyridazine derivatives from certain unsaturated hydrocarbons;
these syntheses strengthened their belief that too much stress
had been made previously on the role of substituents. The
latter had merely confused the fundamental requirements,
namely, an ethylenic system to which 1:4-addition might take
place. Styrene reacted with two molecules of the ester

(curiously only when R = Me and not when R = Et). The
substance (VII) was unattacked by bromine, ozonolysis was
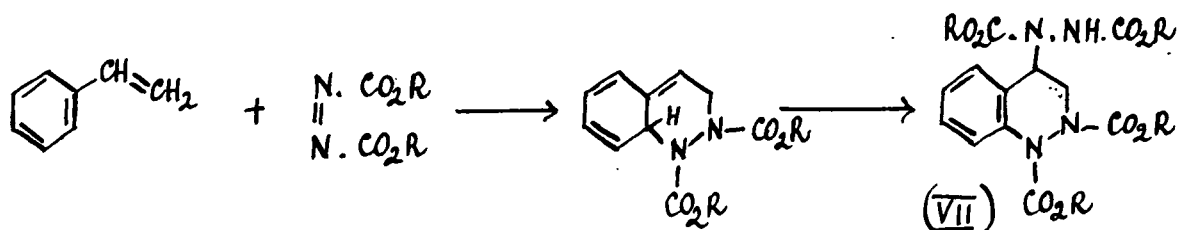
ineffective and hydrogenation produced no positive result.
Although stable to concentrated aqueous hydrochloric acid
and concentrated ammonia the substance (VII) on treatment
with 33% aqueous potassium hydroxide gave rise to (IX),
obtained via the potassium salt (VIII) by the action of 50%
aqueous acetic acid.
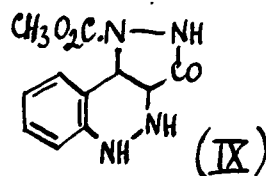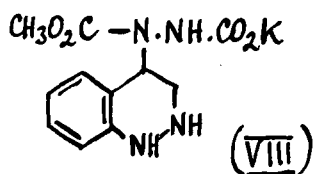
During researches on tetrahydroindazoles Auwers (10)
determined the structure of benzoylated hydroxymethylene
cyclohexanone by cyclisation of the phenylhydrazone

to the indazole and comparison of the spectrochemical constants
of the latter with those of authentic 1- and 2-phenyl-4:5:6:7-
tetrahydroindazoles (X and XI respectively).
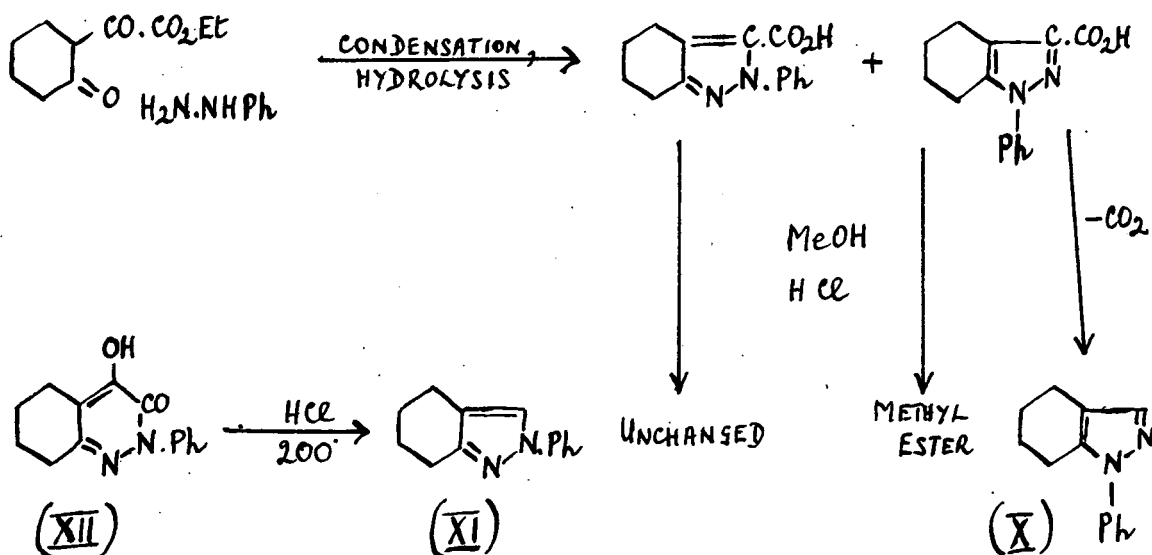
The mixed ethyl-esters formed by the original condensation were accompanied by the cinnoline-derivative (XII), which, like the phenyl-methyl-hydroxypyridazone of Ach (I), possessed both acidic and basic properties and gave a characteristic colour with ferric chloride. The isolation of (XI) from the cinnoline (XII) is analogous to the preparation by Ach of a pyrazole from his pyridazone.

Yet another example of the preparation of a cinnoline during researches on entirely different compounds is apparent in the preparation by Ebel, Huber and Brunner (55) of the cinnoline (XIV) from acetonylcyclohexanone (XIII), the latter being prepared during a study of Bz-tetrahydrocoumarones (XV).
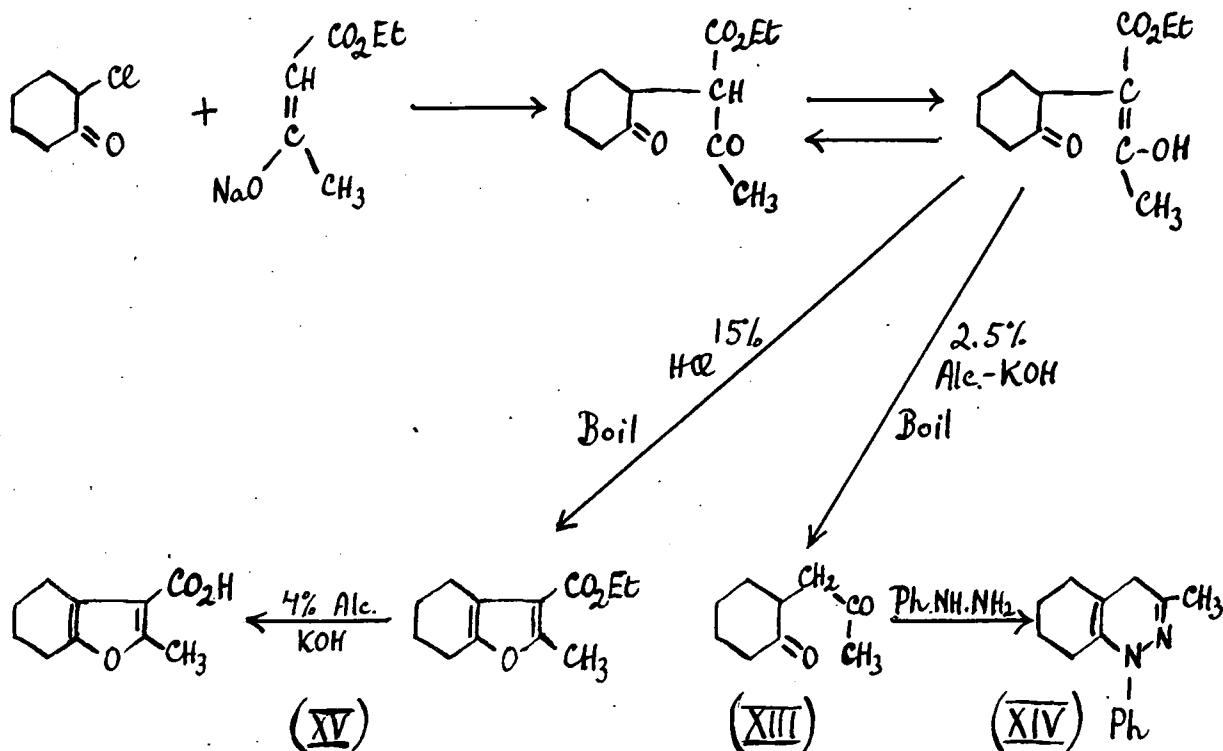
It is noteworthy that the same method has been applied
by Hale (70) to the preparation of several pyridazine derivatives
from 1:4-diketones.

Wittig and Stichnoth (188), during work on the con-
figurations of phenanthrenes and phenazones (page 89), found
that "4:5-dimethylphenazone" (XVI) formed addition products
with two atoms of lithium, sodium, or potassium [azobenzene
adds on only one atom/mol. (139)]. Treatment of the lithium
adduct with methyl sulphate gave "4:5:9:10-tetramethylphenazone"
(XVII). The structure of (XVII) was proved by reductive fission
followed by reaction with toluene-p-sulphochloride, the product
being identical with that obtained when "o:o'-diaminoditolyl" is
'tosylated' and then methylated.
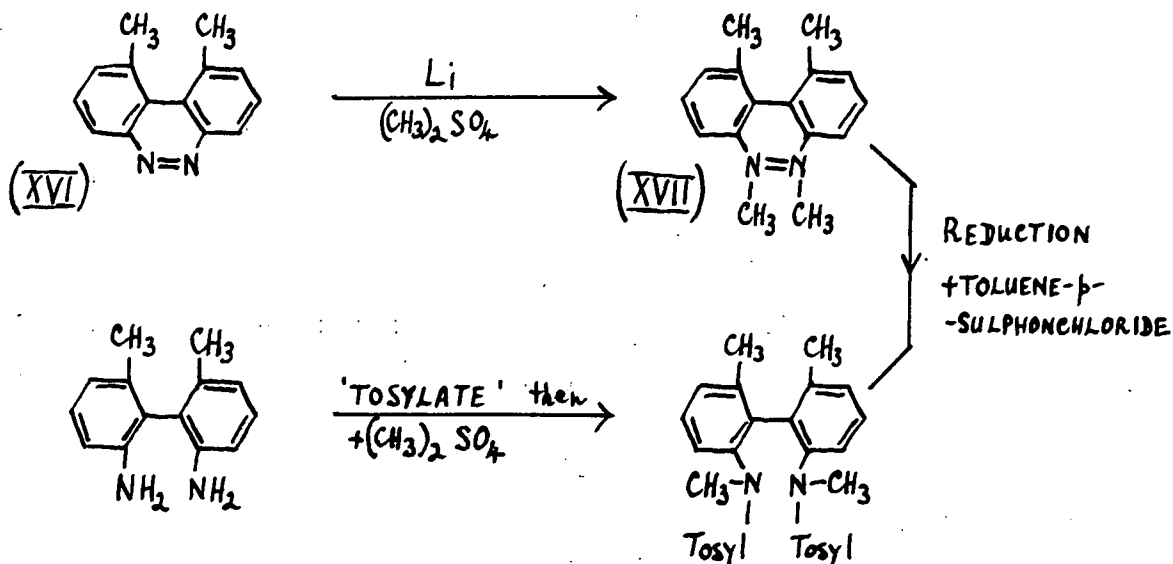
The cinnoline (XVII) (and its α-bromocamphor- π-sulphonate) were slowly decomposed to "4:5-dimethylphenazone" in acid solution with the development of a blue colour. That this decomposition was caused by atmospheric oxidation was evident when the same result was reached using mild oxidising agents and the following scheme was proposed:
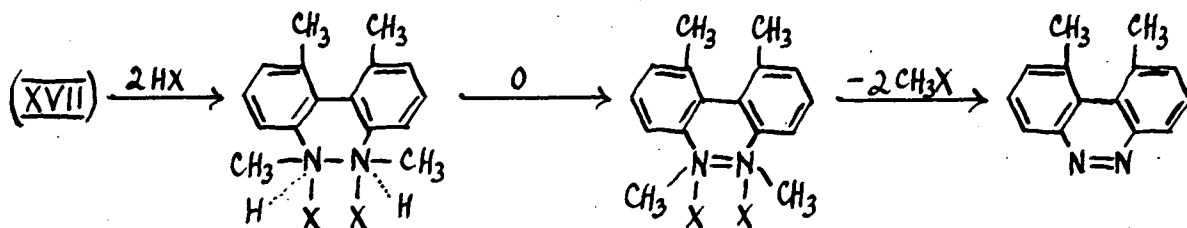
The '9,10'-dihydro-compound was prepared and isolated as the sulphate but attempts to regenerate the freebase gave only "4,5-dimethylphenazone". The difficulties encountered in the phenazone series in conjunction with the known futile attempts of Sako (see below), led to concentration of the research on the phenanthrene field.

Exploitation of 4:6-dinitro-1:3-dichlorobenzene as a source of benzodipyrroles by Ruggli and Straub (133) gave rise to the complicated cinnoline (XVIII). The following scheme, one of many carried out, indicates the route to the cinnoline derivative.
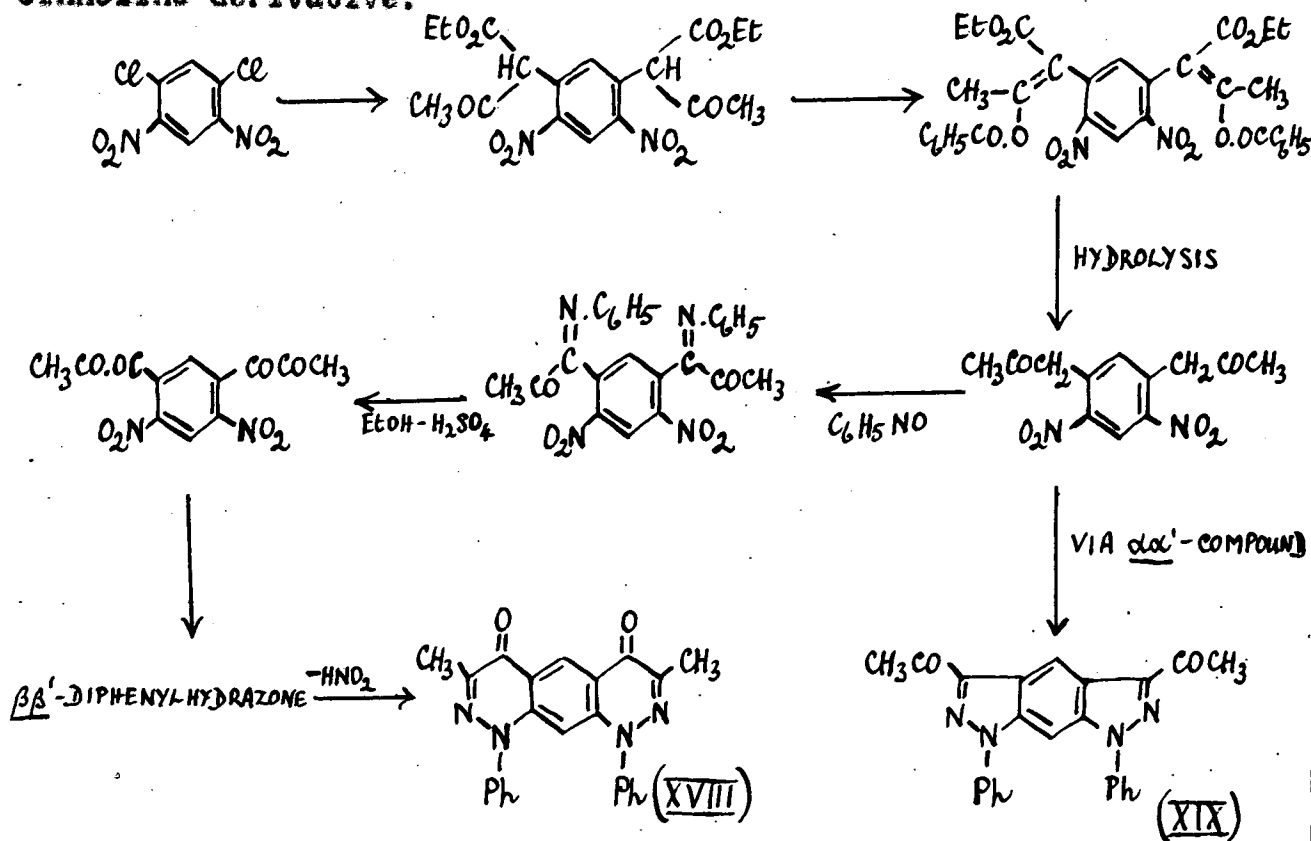
This was shown to be distinct from the substance (XIX) obtained by similar treatment of the $\alpha\alpha'$-diphenylhydrazone.

Various oxides of cinnoline derivatives can be considered in this group. The first cinnoline oxide was obtained by Tauber (165) as a concomitant of "diphenylenazon" - a compound consisting of "a new N-containing closed ring system". Moderate

treatment of o-dinitrodiphenyl with zinc and alcoholic
potassium hydroxide gave a monoxide (XX) and a dioxide
[possibly XXI (a), (b), or (c)].
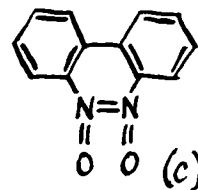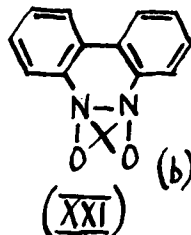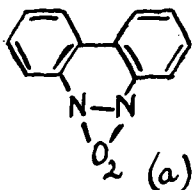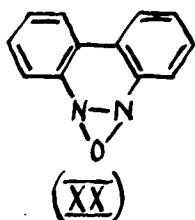
The monoxide alone was obtained when the calculated quantity
of sodium amalgam was used as the reducing agent. Both oxides
gave phenazone by further reduction with sodium amalgam and
the dioxide was reduced by zinc and hydrochloric acid to the
diphenyl-hydrazone. The monoxide showed weak basic properties
and the dioxide was even less powerful in this respect. Ullmann
and Dieterle (175) prepared the pure monoxide (they questioned
the purity of Tauber's oxide) from o-dinitrodiphenyl and sodium
sulphide and reduced it further to phenazone either with
stannous chloride and hydrochloric acid, a process later used
by Duval (53), or by an electrolytic method. Similar treat-
ment of the requisite dinitrodiphenyls with sodium sulphide
furnished the monoxides of 3:8-dimethyl- and 3:8-tetra-
methylamino-phenazone[(XXII) and (XXIII) respectively]and
the latter gave the corresponding phenazone on further
reduction; the oxides were recovered unchanged on dilution
of the solution in concentrated acids.
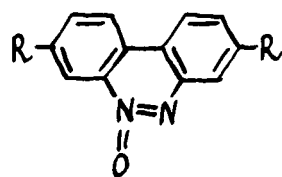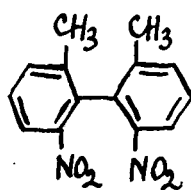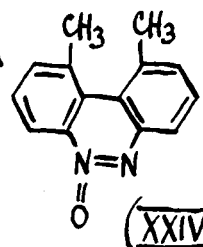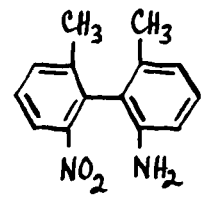
A mixture of the monoxide and dioxide of the isomeric
"tolazone" was obtained by treating "2,2'-dinitroditolyl"
with zinc and potassium hydroxide but only the dioxide was
isolated (107).
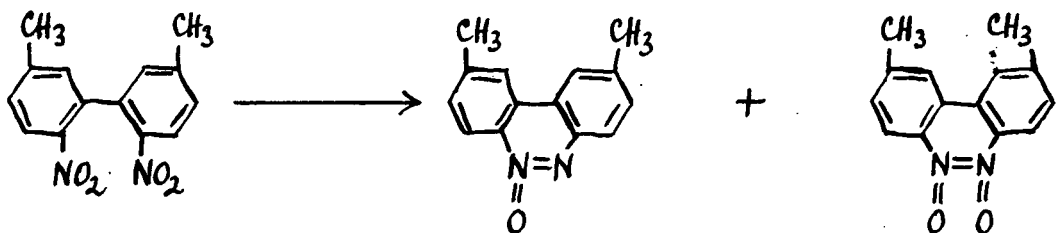
In connection with an unsuccessful attempt to resolve
6-nitro-6'-acetamido-diphenic acid, Sako (135) found that the
requisite intermediate was formed by reduction of 2:2'-di-
methyl-6:6'-dinitrodiphenyl with alcoholic sodium sulphide
at 50°; at 100°, however, there was formed "4:5-dimethyl-
phenazone oxide" (XXIV).

The Nitration of 3:4-Benzocinnoline-N-oxide (83).
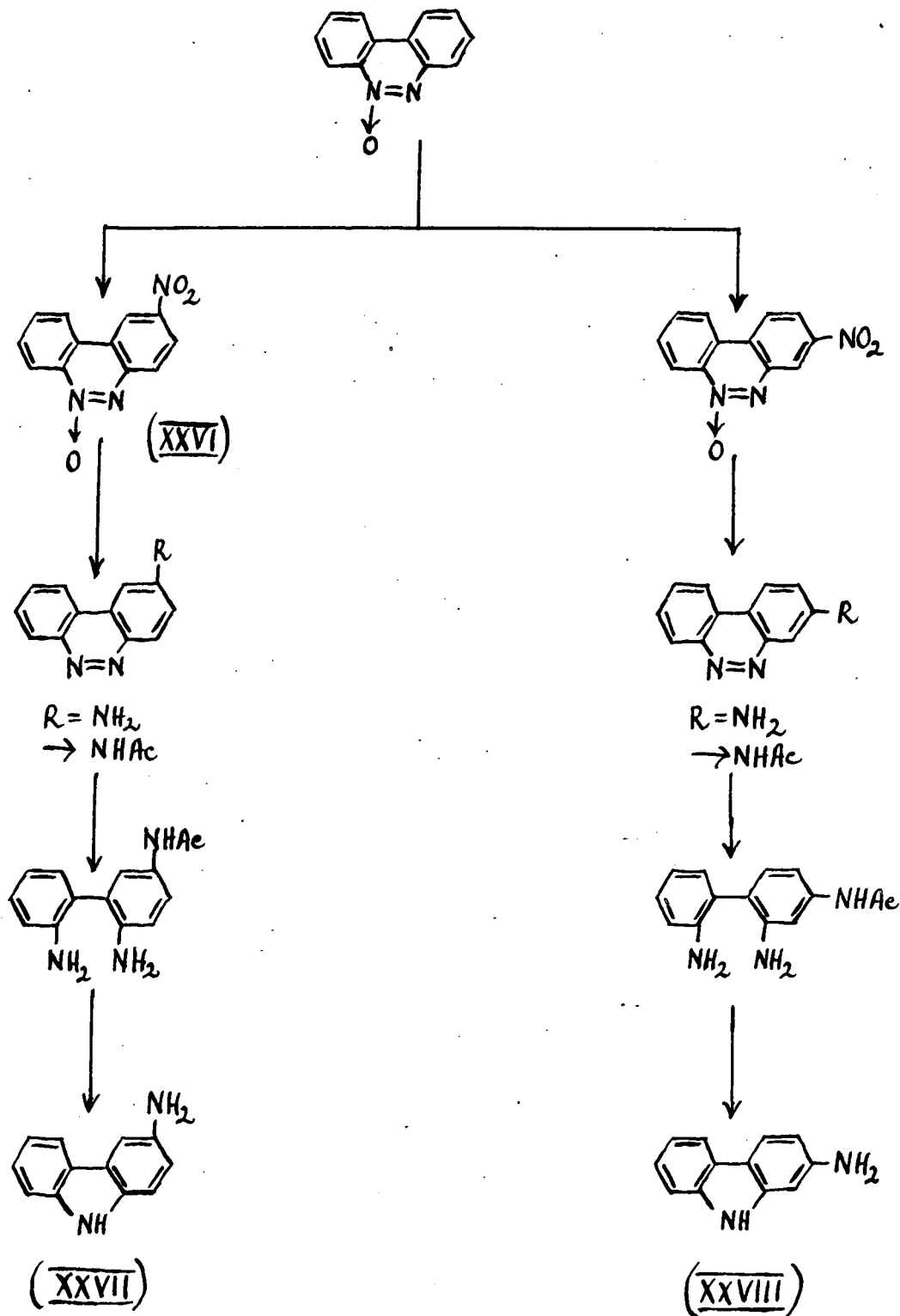
In 1935 Hata and co-workers (41) prepared "2,7-dimethoxyphenazone" monoxide (XXV) from the 2,2'-dianisidine and hence by the action of hydriodic acid the corresponding dihydroxy-compound; this was identical with that obtained from resorcinol.
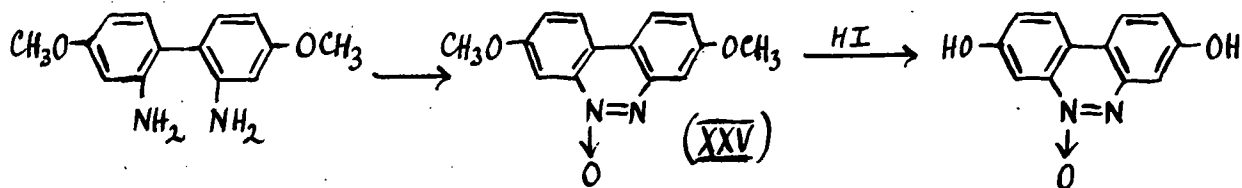
The absorption spectra of the oxides of "phenazone" were measured in 1936 (128) and the close similarity to the spectrum of benzo[c]cinnoline was noticed, this being in striking contrast to the effect of 'oxygenating' the nitrogen atoms of azobenzene.

More recently the use of the phenazone (benzocinnoline) nucleus as a basis for potential chemotherapeutic agents has stimulated new interest in this series, and 3:4-benzocinnoline-N-oxide figures largely in this development. It has been found (83) that Ullmann and Dieterle's method for preparing the N-oxide presupposes the existence of free alkali in the sodium sulphide used but that under such conditions the yield of oxide is quantitative. Nitration of
(XXVI)
this oxide gave mainly 2-nitrobenzocinnoline-6-oxide/together with a small amount of the 3-nitro-compound, this selective

attack on the aromatic ring distant from the N→O group
being fully expected. Reduction of these nitro-compounds
with stannous chloride furnished the corresponding amino-
benzocinnolines, the orientations of these being proved by
reduction over Raney nickel and heating under pressure with
hydrochloric acid (see chart). The aminocarbazoles
(XXVII and XXVIII) compared favourably in m.p. etc., with
authentic specimens described in the literature.

The reduction of 2-nitronaphthalene with sodium
stannite yielded a curious cinnoline monoxide the structure
of which is given later (page 101).

Theoretical Considerations.

In spite of the small amount of experimental evidence available to early workers in the cinnoline field several attempts to explain the mechanism resulting in cinnoline formation were made and comparisons between cinnoline syntheses and those of other heterocyalic compounds were often stressed. Reference has already been made (page 6) to Richter's efforts in this direction, e.g. the formation of 4-hydroxycinnoline-3-carboxylic acid from diazotised o-aminophenylpropiolic acid by simultaneous addition of the elements of water and expulsion of hydrogen chloride, and
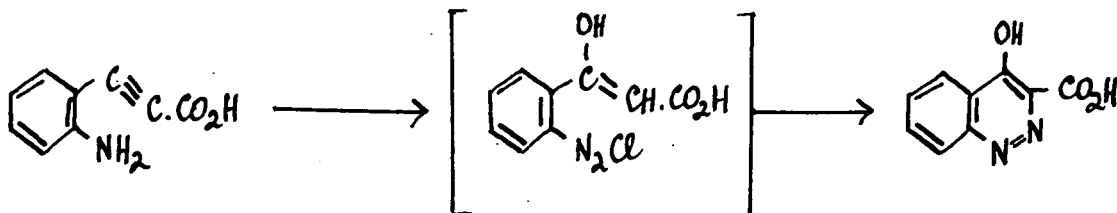
Widman's comparison of his synthesis with Richter's has also been dealt with (page 46). Stoermer and Fincke (158) recognised the essential role of the ethylenic rather than the acetylenic side chain, the successful preparation of 4-phenylcinnoline and later (160) 4-anisylcinnolinebeing carried out to support this belief. The latter communication (of Stoermer and Gaus) endeavoured to relate the ease of cinnoline formation to electrical character of the ethylenic

side chain; thus the hindering effect of a negative group

on the ω-C-atom was noted, Fischer's (58) preparation of

o-coumaric acid by diazotisation of o-aminocinnamic acid

being repeated by Stoermer and Fincke. However, no evidence

was produced in defence of the claim that a similar group

on the α-C-atom favoured cyclisation to the cinnoline.

A valuable classification of o-amino-ethylenes of the

type (IV) with particular reference to the results of

diazotisation was published by Simpson in 1943; the close

integration of original work with this review has already

been stressed (page 58). The following groups were

considered:

(a). Those ethylenes having no hydrogen atom on the

β-Carbon atom of the side chain and hence unable to undergo

cyclisation to a cinnoline, e.g.(41,100,181,124);
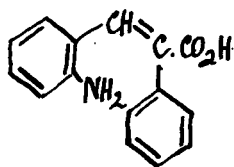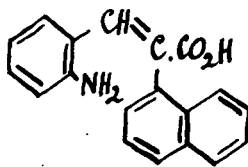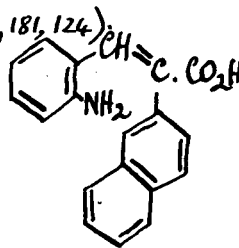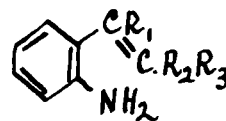
(I)   (II)   (III)   (IV)

(b). Compounds having the necessary hydrogen atom for

cinnoline formation to occur but which, in fact, gave the

Pschorr-cyclisation product on diazotisation, e.g. the

substances (V and VI) investigated by Mayer and Balle (101).
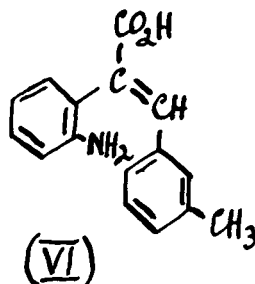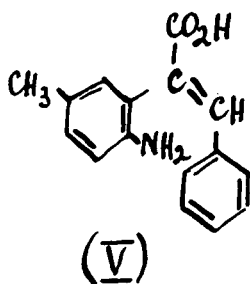
This behaviour was attributed to either one or both of the substituents on the α- and β-carbon atoms.

Cis and trans 2-aminostilbenes were included in this group since neither isomer gives rise to a cinnoline. The cis form generally gives some Pschorr cyclisation product but the trans isomer undergoes decomposition; thus Ruggli and Staub (132) showed that diazotised cis 2-aminostilbene gave a good yield of phenanthrene whilst the trans isomer gave either trans stilbene (62% yield) or trans 2-hydroxy-stilbene and a little benzaldehyde. This decomposition of trans-derivatives has also been noted in the case of 4-cyano- and 4-nitro-2-aminostilbene (176 and 134 respectively). In view of these results, so unfavourable from the standpoint of cinnoline syntheses, it is astonishing that in all but one of the diazotised ethylenes studied by Simpson (see page 56) cinnolines were the only isolable products. This contrast clearly indicates the powerful effect of a phenyl group on the α-carbon atom in promoting cinnoline formation, especially

since similar β-substituents have already been shown to eliminate cinnoline closure in diazotised stilbenes. In connection with the latter clause, the possible significance of the low yield of phenanthrene acid from (V) compared with the usual high yields of such processes was pointed out by Simpson, although Mayer and Balle (/0/) did not mention any cinnoline formation.

(c) o-Aminocinnamic acid and its derivatives; additional evidence (/6/) concerning the diazotisation of the former was presented as well as the successful preparation of o-cyano-cinnamic ester by a Sandmeyer reaction on diazotised o-amino-cinnamic ester by Linstead and Noble (96).

This correlation between the type of substituent on the α- and β-carbon atoms of the ethylenic side chain and cinnoline formation was extended to the Richter synthesis by Schofield and Simpson (/42). In the cyclisation of diazotised o-amino-phenylpropiolic acid there was suggested the following mechanism involving an intermediate chloro-compound (see, however, page 34).
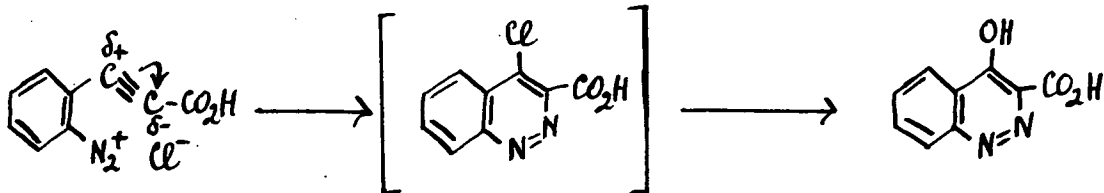
Since the preparation of 4-hydroxyquinoline-3-carboxylic acid from o-formamidophenylpropiolic acid might be explained by

by a similar initial polarisation it appeared that the
terminal carboxyl group was wholly responsible for the
electromeric shift;   on this basis the diazotisation of
o-aminophenylacetylene would yield indazole-3-aldehyde
(VII). However, the fact that phenyl- and o-aminophenyl-

acetylene yield the corresponding acetophenones on hydration
(63,75) together with the known behaviour (76) of acetylenes
of the type $CH_2.Ar.C:C.Ar'$ on hydration (giving $CH_2.Ar.CH_2.$
$CO.Ar'$) led Schofield and Simpson to predict the cyclisation
of diazotised o-aminophenylacetylene to the cinnoline:
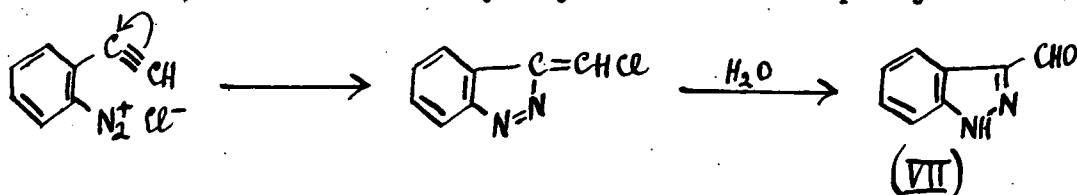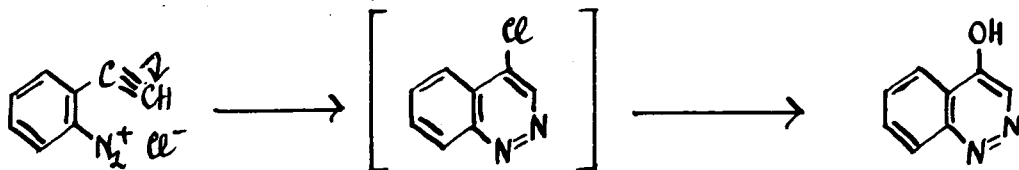
This anticipation was justified, 4-hydroxycinnoline and its
6-methoxy-analogue being prepared by this method in good yield
(page 26).

In a consecutive paper, the same authors described the
preparation of several cinnolines (142) and worked out a
comprehensive mechanism for cinnoline syntheses. From their
own wide experience in the preparation of hydroxycinnolines
it was evident that weakness in the basic strength of the

aminoketone favoured cyclisation (compare the ready solubility in acids of 2-amino-3-methoxyacetophenone and 6-aminoaceto-veratrone, neither of which form cinnolines (page 27), with the weak basicity of 5-nitro-2-aminoacetophehone). Ready enolisation of the ketonic side chain was recognised as another essential, although this would obviously be more important in a discussion involving p-substituents. Any mechanism involving the operation of such enolisation was considered desirable since the Borsche type of cyclisation could then be correlated with the syntheses of Richter and Stoermer.

Direct hydration of the acetylenic bond in the Richter reaction was dismissed when the usual conditions (76) of such hydrations were considered. Again, the idea of an intermediate chloro-compound was not consistent with the facts, (a) that o-aminophenylpropiolic acid could be successfully diazotised and cyclised in sulphuric acid, and (b) that the ready hydrolysis of such an intermediate is not feasible in view of the known stability of (e.g.) 4-chloro-6-methoxycinnoline (page 37). An acceptable solution to this problem was reached by proposing intramolecular coordination (of the anionoid carbon atom of the side chain with the diazonium kation) as the essential electronic requirement; subsequent hydroxyl-ion

attack occurring thus:
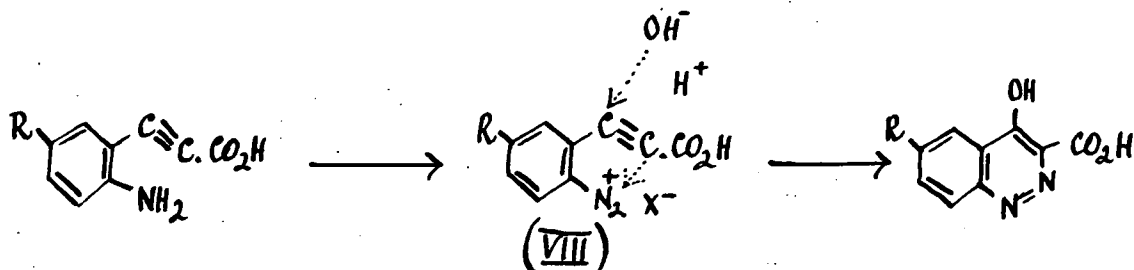
From this base was built the whole argument of the thesis - that the three chief cinnoline syntheses were "essentially manifestations of the same fundamental process" (142). Complete hydration (by coordination of a proton with anionoid carbon) was rejected as an intermediate in the above mechanism for two reasons:

(a) o-Aminobenzoylacetic acid, the intermediate of the hydration hypothesis, shows a marked tendency to form quinoline derivatives, none of which were observed by Schofield and Simpson; also (b) the process of hydration must outpace that of diazotisation (an unlikely probability), the alternative being the mechanism shown above via the electromer (VIII).

Moreover, on the hydration theory it was impossible to reconcile the facts that diazotisation of certain o-amino-phenylacetylenes gave good yields of cinnolines whilst related o-aminoacetophenones, which _ex hypothesi_ are intermediate in these cyclisations, gave little or no cinnoline on similar treatment.

In diazotised o-aminoacetophenones the increased kationoid activity produced by nuclear substituents (R = CN, NO_2, halogen) led to a general shift to the right terminating in the hydroxy-cinnoline. A similar polarisation explained the Widman-Stoermer
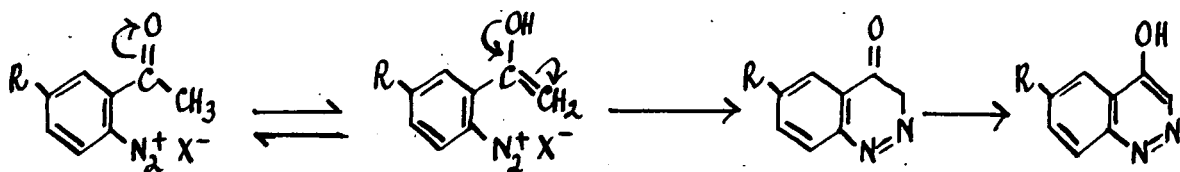
reaction, the anionoid nature of the terminal carbon atom being induced by an aryl α-substituent. The explanation of "ir-regularities" such as the formation of 2-phenylchrysene (IX)
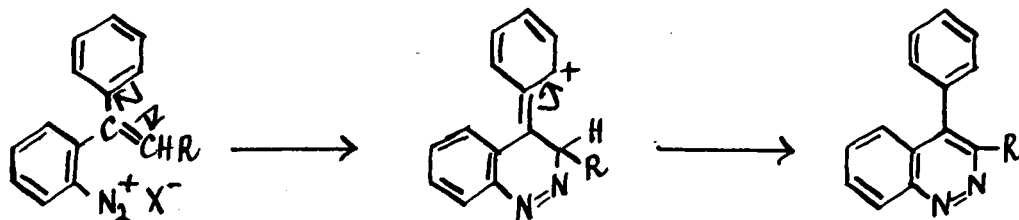
as well as 4-phenyl-3-(α-naphthyl)cinnoline (page 56) did not require any additional assumptions, the reason being the increased ability of the α-naphthyl nucleus to act as a "sink" for the electron drive from the α-phenyl group. This process

$$(IX)$$
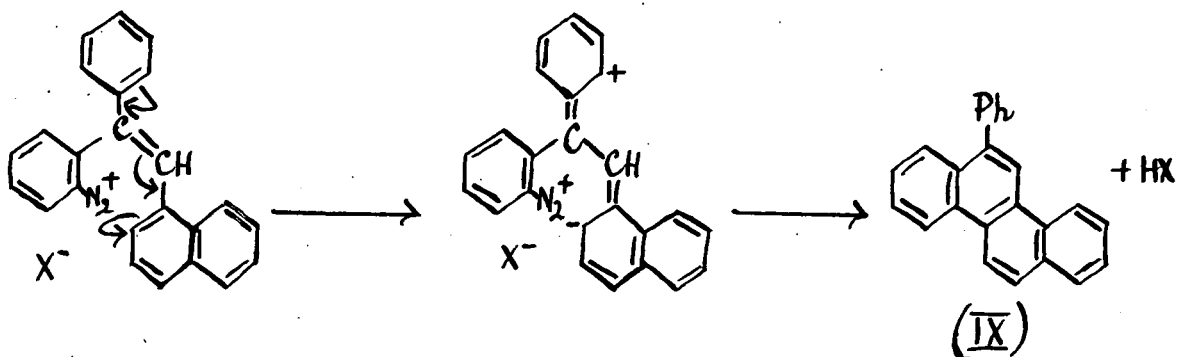
reduces the anionic charge on C_β with consequent reduction in

the yield of cinnoline. The absence of phenanthrene formation noted when the C_β substituent was phenyl (page 56) is not surprising in view of the smaller electron capacity of the single aromatic ring.

It was of interest to note the different sources of the proton which is eliminated as HX; in the Widman-Stoermer reaction it is eliminated from the C_β position, in diazotised o-aminoacetophenones the hydrogen atom of the C_α enolic group is clearly involved, whilst the Richter synthesis utilizes the solvent as a proton source.

A brief critical examination was given of an apparently formal analogy of cinnoline syntheses, namely, the preparation of benztriazoles by diazotisation of substituted amides of anthranilic acid (56). One point of possible significance was the production of methylanthranil (X) instead of the unknown oximâno-dihydro-cinnoline (XI) by diazotisation of o-aminoacetophenone oxime(11, 104).
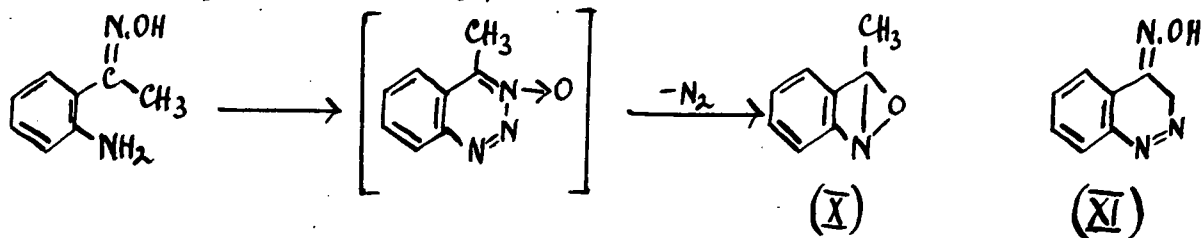
Benzocinnolines.

Compounds of this type are generally more accessible than simple cinnoline derivatives and for this reason have been studied more fully by early workers. Derivatives of benzocinnolines have been prepared by a variety of routes which are described by Leonard (93) as "special methods" in contrast to the three general ones involving diazotisation of o-amino-ketones, -ethylenes or acetylenes.

Considerable confusion exists over the nomenclature of substances of this group; thus 3,4-benzocinnoline or benzo[c]cinnoline (I) has been called phenazone and diphenylene-azone (both names are listed as "objectionable" by "The Ring Index") whilst other names not based on cinnoline are in common use, e.g. dibenzopyridazine and 2,2'-azodiphenyl. Further complications are introduced into such indiscriminate nomenclature by the adoption of different systems of numbering by different workers.

CINNOLINE   (I)   (II)
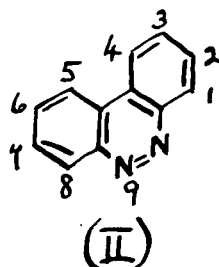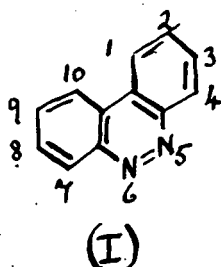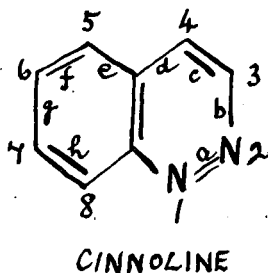
The order of numbering (I) is now generally accepted but system (II) has been frequently employed (71, 135, 188, 192). Even in

recent literature this trouble is perpetuated: King and

King (83) state "the 2-sulphonic acid[*] and the corresponding

phenol are the only monosubstituted benzocinnolines hitherto

prepared", but do not point out that the parent document (192)

of this work uses the system of numbering (II), this omission

being more serious in view of the fact that they use the

correct system (I) in reference to other benzocinnolines.

In the following account the 'historical' nomenclature

will usually be mentioned once and thereafter only the

recognised system employed.

Benzo[c]cinnoline was first prepared by Tauber (165) by

the reduction of 2,2'-dinitrodiphenyl, a compound which he

had prepared earlier and used in a synthesis of carbazole.

The new compound "Diphenylenazon", was formed by prolonged

boiling with zinc and alcoholic potassium hydroxide or by

treatment with excess 3% sodium amalgam, milder treatment

giving only the oxides (page 68). Application of the same

technique to "m-dinitrobenzidine" furnished 3,8-diaminobenzo

[c]cinnoline but in this case no oxides were isolated. Later

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[*] King and King also refer to a disulphonic acid and continue
"as in the analogous case of azobenzene mono- and di-substitution
would appear to occur simultaneously" - such comparison is hardly
warranted since the patent describes the introduction of the mono
and disulphonic acid groups **before** reduction of the dinitrodiphenyl
to the benzocinnoline.

(166) whilst investigating the possibility that formation of carbazole (from tetrazotised 2,2'-diaminodiphenyl and stannous chloride) proceeded via the dihydrazine, Tauber carried out a general study of the latter compound. The action of aqueous hydrochloric acid at 150° yielded 3,4-benzocinnoline which was also produced on merely heating to 240° the diacetyl derivative of the hydrazine.

The best method for the preparation of 3,4-benzocinnoline is due to Wohlfahrt(189) who subjected 2,2'-dinitrodiphenyl to electrolytic reduction thus securing a 95% yield of the cinnoline.

In 1904, Ullmann and Dieterle prepared several "phenazones" by a variety of methods; their preparation of benzo[c]cinnoline-6-oxide and the 3,8-dimethyl- and 3,8-tetramethyldiamino-derivatives (using sodium sulphide) has already been mentioned (page 68) together with the reduction of the first and last of these to the "phenazone". In addition, electrolytic reduction of the corresponding 2,2'-dinitrodiphenyl yielded 3,8-diamino-, 38-diamino-2,9-dimethoxy- and 3,8-tetramethyl (or ethyl) diamino-benzo[c]cinnoline, although it was pointed out that the success of this method depended upon the solubility of the nitro-compound in the cathode-solution (alcohol).

A novel method for preparing "phenazones", described in a German Patent (193), requires fusion of azobenzene and aluminium

chloride in the presence of a flux (e.g. sodium chloride) or a diluent (e.g. pyridine), the temperature being capable of wide variation. Thus "in a suitable melt 'phenazone' formation was observed at 60°" but fusion with salt at 120° gave the best yield, (60.) of 3,4-benzocinnoline; the 3,8-dimethyl- and 3,8-tetramethyldiamino-derivatives were prepared thus in yields of 25% and 40. respectively. The success of these syntheses was unexpected in view of the work of Pummerer and Binapfle (125) on the rearrangements of azobenzene in the presence of aluminium chloride and aromatic hydrocarbons.

During an attempt to prepare 2,2'-diarsonodiphenyl by a Bart reaction on tetrazotised 2,2'-diaminodiphenyl, Sandin and Cairns (136) isolated "considerable amounts of phenazone"; the authors believed that this was a general reaction, the arsenite functioning as a reducing agent. 3,8-Dimethylbenzo[c]cinnoline was prepared by the same procedure.

Since each of the above groups of workers prepared benzo c cinnoline itself it is convenient to correlate their impressions of its properties before proceeding with other derivatives. Although Tauber (165) stated benzo[c]cinnoline to be a strong base (in contrast to azobenzene) his contradictory observation of the stability of the salts ("only in solution") was uncorrected until a later date (167). The behaviour towards reducing agents was described by Tauber as irregular, acid reduction yielding the

dihydrazine whilst alkaline reduction left the nucleus
unaffected; the latter finding was later challenged by Duval
(53) who prepared the dihydrazine in an alkaline medium. Early
attempts (167) to oxidise 3,4-benzocinnoline were unsuccessful
but later (164) it was found that the finely powdered compound
was smoothly oxidised by permanganate to the labile pyridazine
tetracarboxylic acid (degradation of this to pyridazine has
already been described; page 50). In a comparison of
"phenazone" with phenazine (167) the difficulty in subliming
benzo[c]cinnoline was noted as well as its non-volatility in
steam; it resembled phenazine in its reaction with bromine,
giving a red crystalline precipitate which changed to yellow
on drying without loss of bromine. The action of dimethyl
sulphate on benzo[c]cinnoline yielded to Wohlfahrt (189) an
hygroscopic compound which was estimated as the platinum salt
and analysis indicated a formula

$$\left[\text{structure} \right]_2 Pt\,Cl_6$$
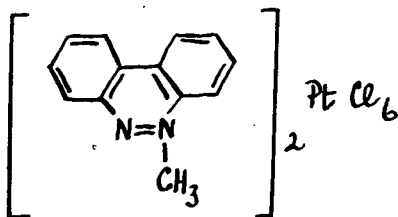
The methiodide was prepared from the methyl methosulphate and
potassium iodide but the ethiodide by direct reaction between
benzo[c]cinnoline and ethyl iodide. Ullmann and Dieterle's
(175) specimen of benzo[c]cinnoline had the properties described

by Tauber (e.g. the pure yellow solution in concentrated acids) and the decomposition of "phenazonium" salts by ammonia was noted, the only isolable product being "phenazone".

The absorption spectra of "phenazone" in the visible and ultra violet regions were measured by Ramart-Lucas and Biquard (128); comparison with those of azobenzene indicated that 'cyclisation' of the latter molecule to benzo[c]cinnoline was accompanied by a hypsochromic effect and diminished sensitivity (intensity of absorption). This result was in striking contrast to other 'cyclisations', thus the data for diphenylmethane and fluorene showed a bathochromic effect and increased sensitivity in the latter compound, these results being the same when only one N-atom separated the rings, i.e. for diphenylamine and carbazole.

Two years after Tauber's preparation of "phenazone", reduction of 2,2'-dinitroditolyl by L. Meyer (jun.) (107) furnished "tolazone" or a mixture of the monoxide and dioxide, depending on the conditions used. Oxidation of the 2,9-dimethylbenzo[c]cinnoline with chromic acid did not give the expected dicarboxylic acid but 9-methylbenzo[c]cinnoline-2-carboxylic acid. 3,8-Diamino-2,9-dimethylbenzo[c]cinnoline was also prepared and hence the 2,9-dibenzylidene-diamino-compound by reaction with benzaldehyde.

The next paper to mention benzo[c]cinnolines (other
than the parent compound) was published in 1932 by Schiemann
and Roselius (138). During a study of fluorinated diphenyl
compounds 4,4'-difluoro-3,3'ditolyl was nitrated to give a
mixture of two dinitro compounds, one of which furnished
3,8-difluoro-2,9-dimethylbenzo[c]cinnoline on reduction with
4% sodium amalgam.

In 1932 and the following year a commercial interest in
benzo[c]cinnolines asserted itself in the form of two patents.
The first (194) described the production of "valuable vat
dyes" by condensation of certain aminoanthraquinones with
acid chlorides having such nuclei as fluorene, phenanthrene,
carbazole, etc., ... "besides the known diphenylene
2,2'-azondicarboxylic acid", which, it was claimed, could
be prepared by "nitration of diphenyl-4,4'-dicarboxylic acid
and subsequent reduction of the nitro body with ammonia and
zinc dust or with the calculated quantity of hydrosulphite
and sodium hydroxide". It was claimed that "diphenylenoxide-
dicarboxylic acid" could be prepared by condensation of
"diphenylenoxide" with acetyl chloride and oxidation of the
acetyl group to the acid. The second patent (195) described
the preparation of "2-hydroxy- and 2,7-dihydroxy-phenazone"
(system II, page 82) by alkaline fusion of the corresponding
sulphonic acids, whilst milder conditions yielded 3-hydroxybenzo

[c]cinnoline-8-sulphonic acid (system I). These compounds were said to be useful as intermediates for dyestuffs and medicinals. It may be pointed out that Tauber (164) reported the failure of attempts to prepare "symmetrical dihydroxyphenazone" during his search for an easily oxidisable derivative of the parent compound.

A group of Japanese workers (71) isolated (in 1935) a sample of 3,8-dimethoxybenzo[c]cinnoline from the steam volatile material resulting from a synthesis which confirmed the constitution of the "hydroxydiphenylene oxide obtained from resorcinol" (page 71). Reference has already been made (page 65) to the preparation of "4,5-dimethylphenazone" in the same year by Wittig and Stichnoth, although a somewhat less pure form of the same 1,10-dimethylbenzo[c]cinnoline* was prepared in 1921 by Kenner and Stubbings (80).

The 2- and 3-aminobenzo[c]cinnolines, already referred to (page 70), were prepared by reduction of the corresponding nitrobenzo[c]cinnoline-6-oxides with stannous chloride (83). Further experiments were performed on the predominant 2-amino-derivative (III; R = H); it could not be condensed with β-chloroethyldiethylamine "under normal conditions" and heating

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*The earlier (1934) work of Sako (page 69) did not, as stated by Leonard (93), include the preparation of 1,10-dimethylbenzo[c]cinnoline.

with sodamide in boiling toluene was unsuccessful. The
N-acetyl derivative was no more reactive but the p-toluene-
sulphonamide (sodium salt) reacted with the amine and with
the higher homologue

The sulphonamides were hydrolysed by cold sulphuric acid to the
amines (III; R = $CH_2CH_2NEt_2$ and R = $CH_2CH_2CH_2NEt_2$ respectively)
which were characterised as the dihydrochlorides.

Two other benzocinnolines are worthy of note. The first of
these, "3-phenyl-1,2-diazaanthrone" (IV) was described by
Borsche and Klein (28) in a paper on the preparation of
pyridazine derivatives. Secondly, the following study of the
cyclisation of phenylbenzylpyrotartaric acid led Borsche and
Ginn (29) to the preparation of the benzo[h]cinnoline (V):-
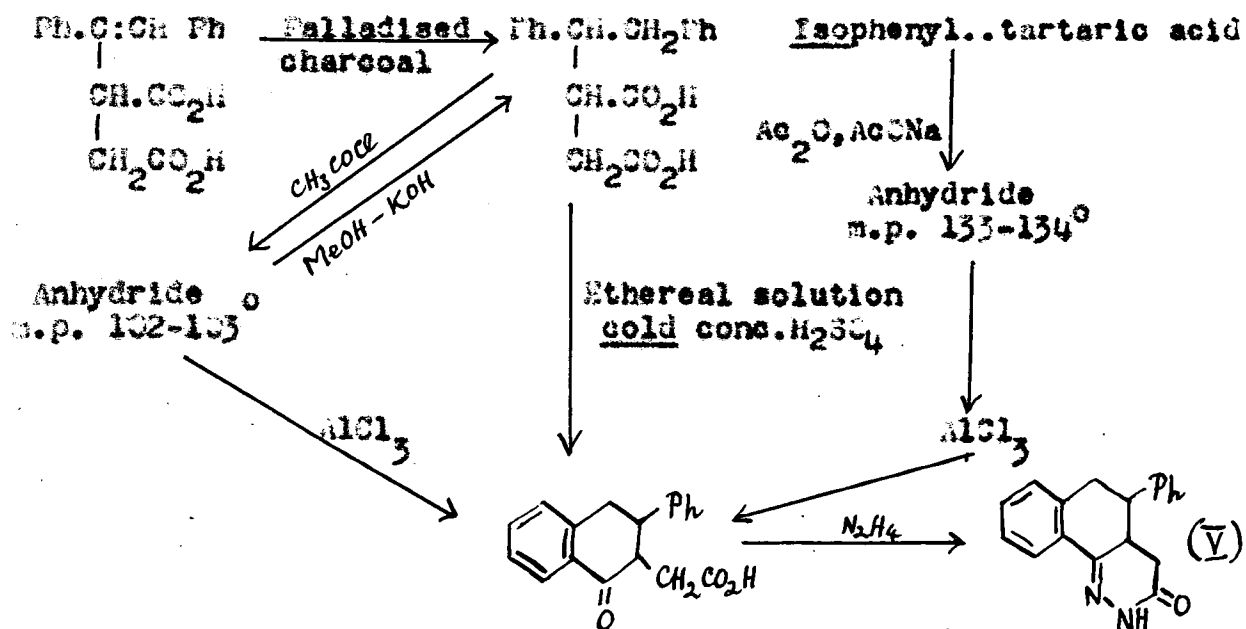
The properties of benzocinnolines, other than physical
constants and solubilities, have not been investigated; most
examples resemble the parent compound (benzo[c]cinnoline) in
giving yellow solutions in concentrated acids but the effects
of dilution are often striking, e.g. 3,8-tetramethyl(ethyl)
diaminobenzo[c]cinnoline give: a deep blue solution on dilution
with water (175).
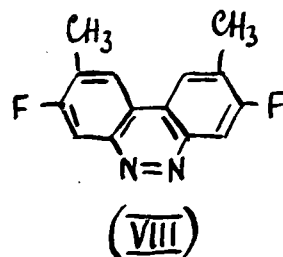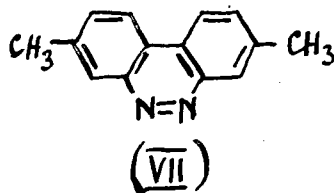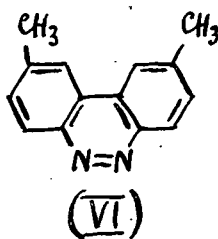
The "tolazone" prepared by Meyer (107) was represented as
(VI) although the melting point of this product differs only
by one degree from that of 3,8-dimethylbenzo[c]cinnoline (VII).
The latter was described by Ullmann and Dieterle (175) as being
"wholly identical in all its properties with the substance
prepared by L. Meyer". However, Schiemann and Roselius (138),
in reference to their synthesis of 3,8-difluoro-2,9-dimethylbenzo-
[c]cinnoline (VIII) say it "corresponds fully to the tolazone
from 6,6'-dinitro-3,3'-ditolyl prepared by L. Meyer; a position
isomer (not the same) as the compound of Ullmann and Dieterle".
Inspection of the descriptions given by L. Meyer and Ullmann
(and D.) to their respective products has revealed only one
important difference, the former is "very easily soluble" in
benzene whilst the latter is recrystallised from the same solvent.

Dibenzocinnolines.

The earliest dibenzocinnoline on record is that prepared by Heiduschka and Khudadad (71a) by condensation of "retoxylenacetoacetic ester [   ] with hydrazine.

Ethyl 3,5-dimethyl-
-11-isopropyldibenzo[f,h]
cinnoline-4-carboxylate
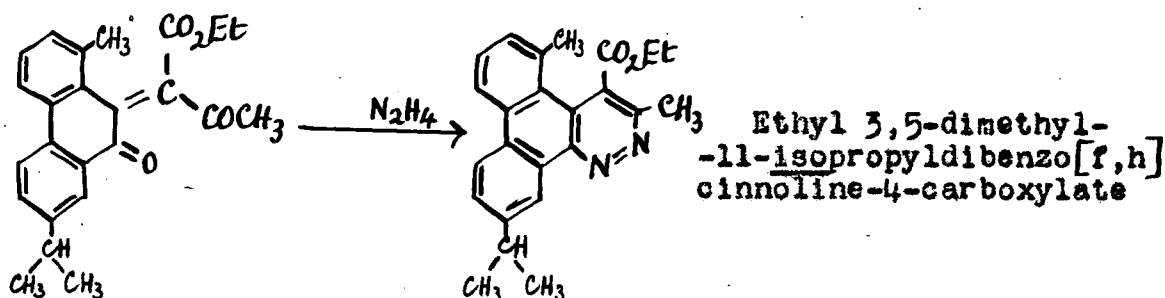
The synthesis of two cinnolines of this group, useful as dye intermediates, was described in Swiss patents (197, and 198 respectively); 8-chloro- and 8-amino-3-phenyldibenzo[de,h] cinnoline-7-one (IX; R = Cl and NH_2 respectively) were prepared by reaction between the corresponding benzoyl anthraquinone and hydrazine.

(IX)
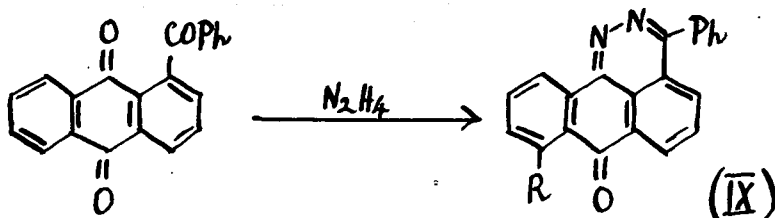
A similar type of compound (X) was prepared a few years later by Waldman and Oblath (180a) using the following route.

(X)
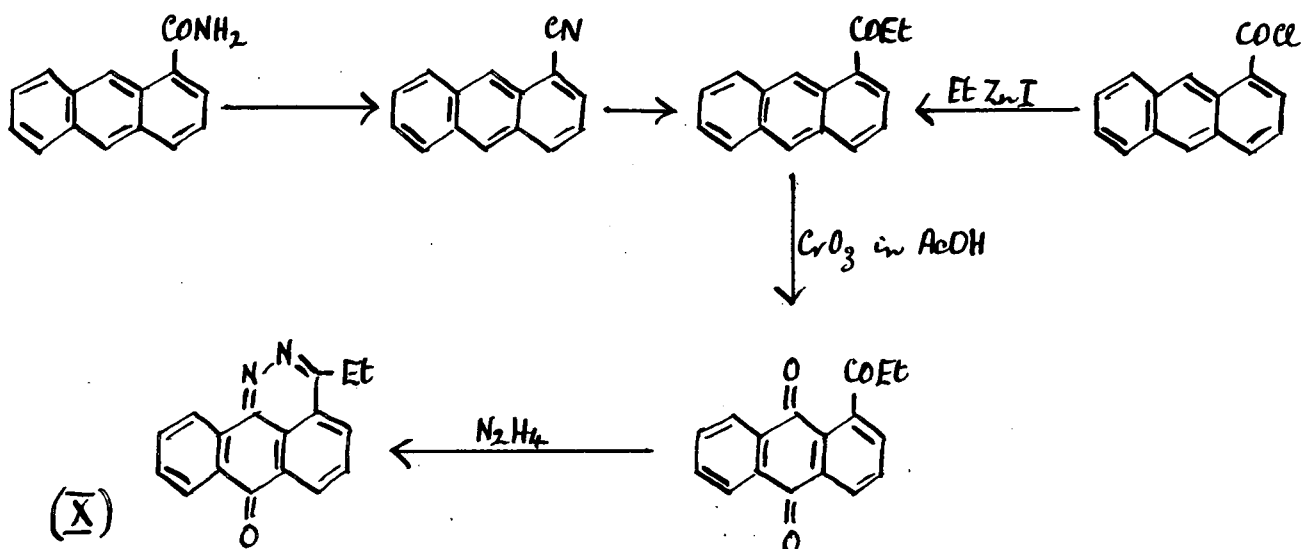
N-Substituted compounds having this type of structure have already been referred to on page 61 .

Polynuclear Cinnolines.

Many compounds of this type have already been reviewed
by Leonard (93) although one is led to believe, as elsewhere
in the same publication, that a large number of workers were
concerned wholly with the chemistry of cinnolines. The
majority of the following cinnolines were obtained by the action
of hydrazine on a 1,4-diketone and their isolation served only
to confirm the structure of some polycyclic aromatic system.
In order to illustrate this point, the work of each group
of investigators is more fully dealt with than their contri-
bution to cinnoline chemistry really deserves.

The work of Scholl and collaborators provides several
examples of this type of compound: the earliest paper (144)
describes the azine (II), prepared to confirm the angular
structure of (I):-

$$\text{(I)} \qquad\qquad \text{(II)}$$
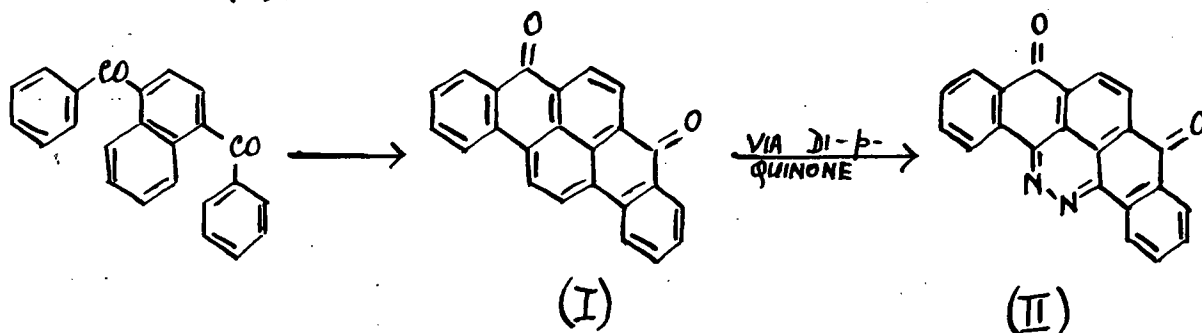
- such confirmation was necessary in view of the fact that
the following analogous cyclisation did not occur as shown.
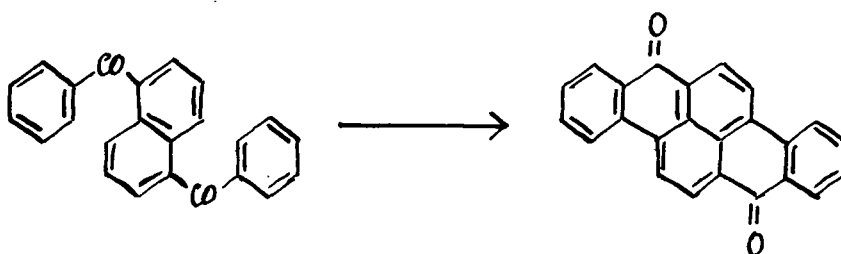
In 1928, Scholl and Meyer (*145*) found that isoviol-
anthrone was oxidised to the compound (III), which, because
of the two 1,4-diketo groups, "was considered well adapted
for synthetic purposes". The formation of a hydro-derivative
of the azine (IV) was quoted as an example of such synthetic
possibilities.
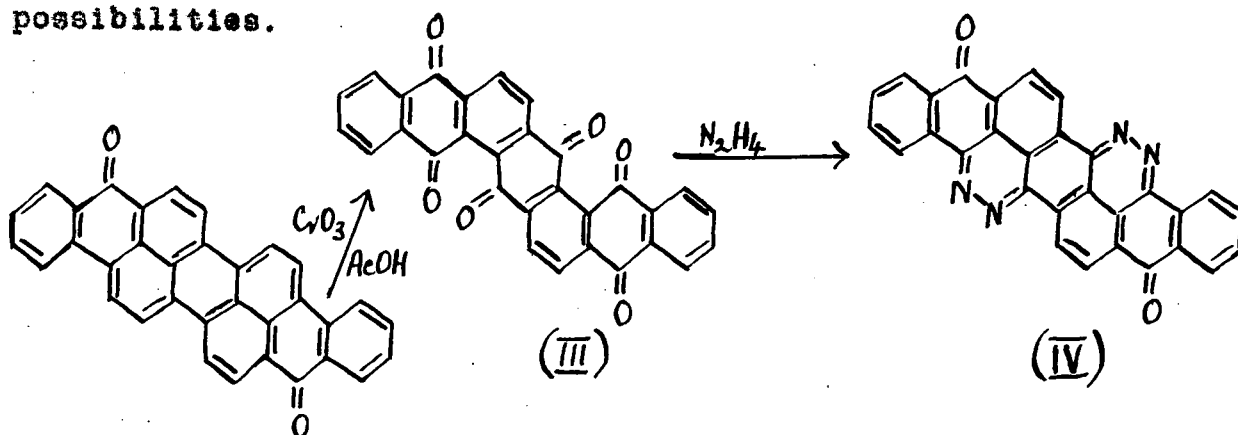
A similar series of reactions was carried out on
3,9-dibenzoylperylene (V) by Benndorf and Sorns (*18*) and
isolation of the dicinnoline type of compound (VI) was
claimed in spite of the failure to prepare an analytically
pure sample.

$$(\underline{V}) \qquad\qquad (\underline{VI})$$
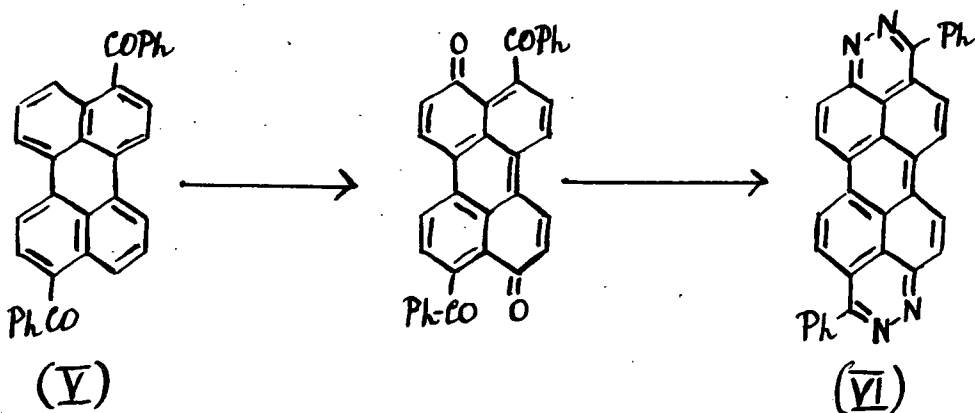
Confirmation of the synthesis of _angul._ 1,2-phthaloyl-
anthraquinone-6-carboxylic acid (VII) by Scholl, Hornuff
and Meyer (146) was assured by the formation of the azine
(VIII).

$$(\underline{VII}) \qquad\qquad (\underline{VIII})$$
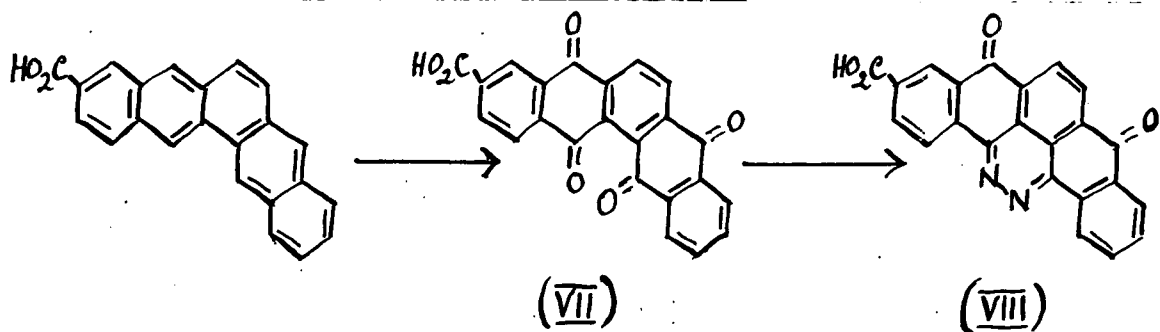
Five examples of this kind are due to Clar and
collaborators: in 1929 the azine (XI) was described in a
paper on naphthophenanthrenes and their quinones (35).
Formation of the cinnoline proved the structure of the
compound (X) and hence of (IX). This tendency of aromatic
ketones having a methyl group ortho to the carbonyl group to
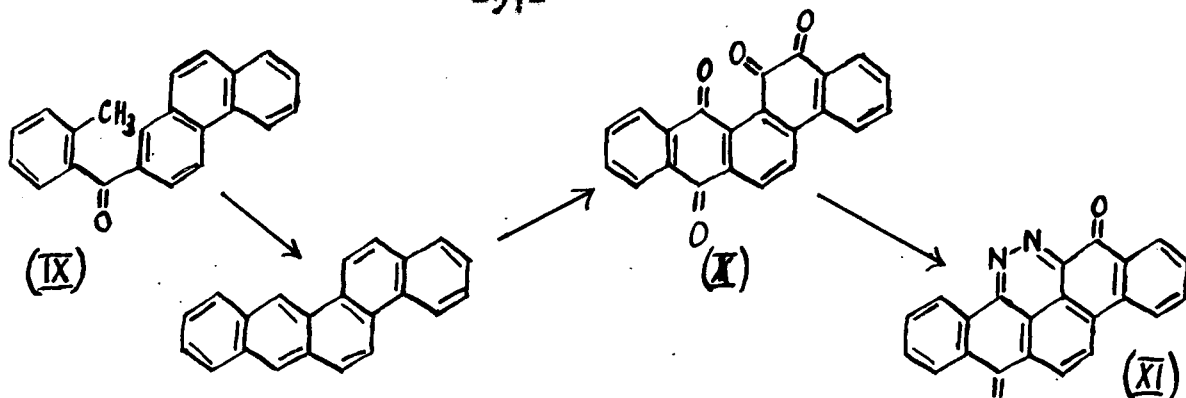
lose water and give polynuclear hydrocarbons was exploited
(37) using di-o-tolyl benzenes. The angular structure of
the resulting naphthoanthracene was proved by isolation of
the same cyclisation product (different from lin. dibenz-
anthracene) from (XII) and the pure isomer (XIII).
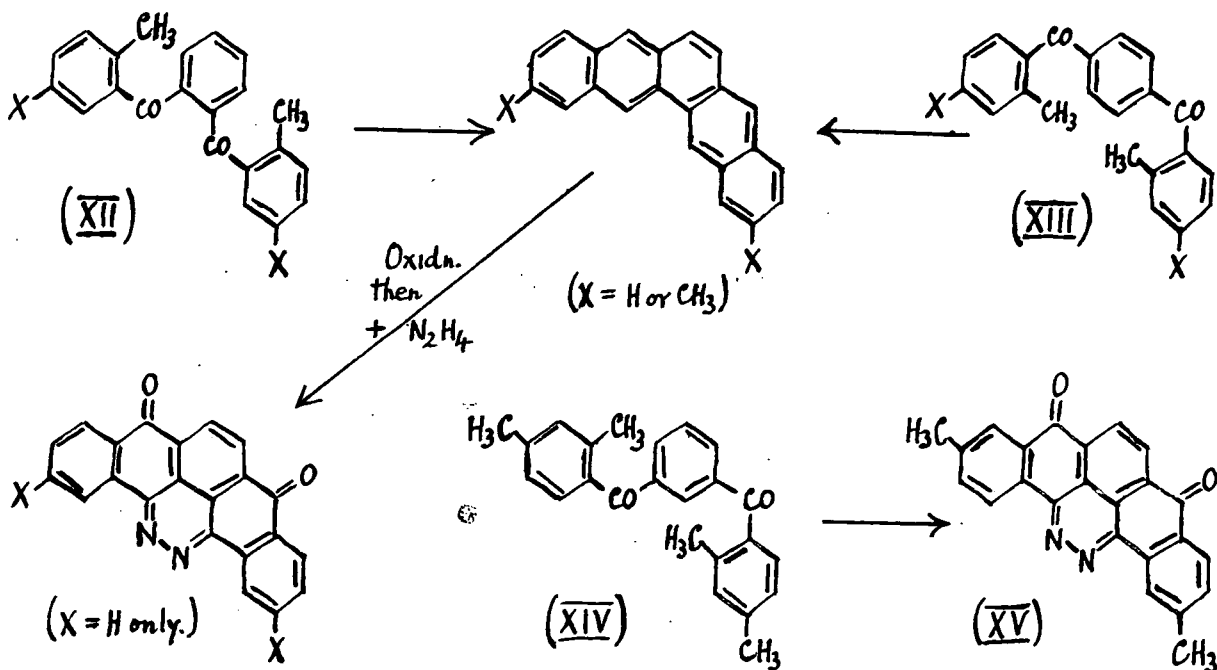
Further, the 2',4'-isomer (XIV) gave rise to the azine
(XV), again a clear indication of the angular structure of
the initial cyclisation product.

Clar, John and Avenarius (36) obtained four hydro-
carbons by pyrolysis of the ketones (XVI) and (XVII); two
of these (yellow) were shown to be identical and on oxidation
and then treatment with hydrazine gave the cinnoline
derivative (XVIII). The other pair (red) were also considered
to be the same substance (XIX).
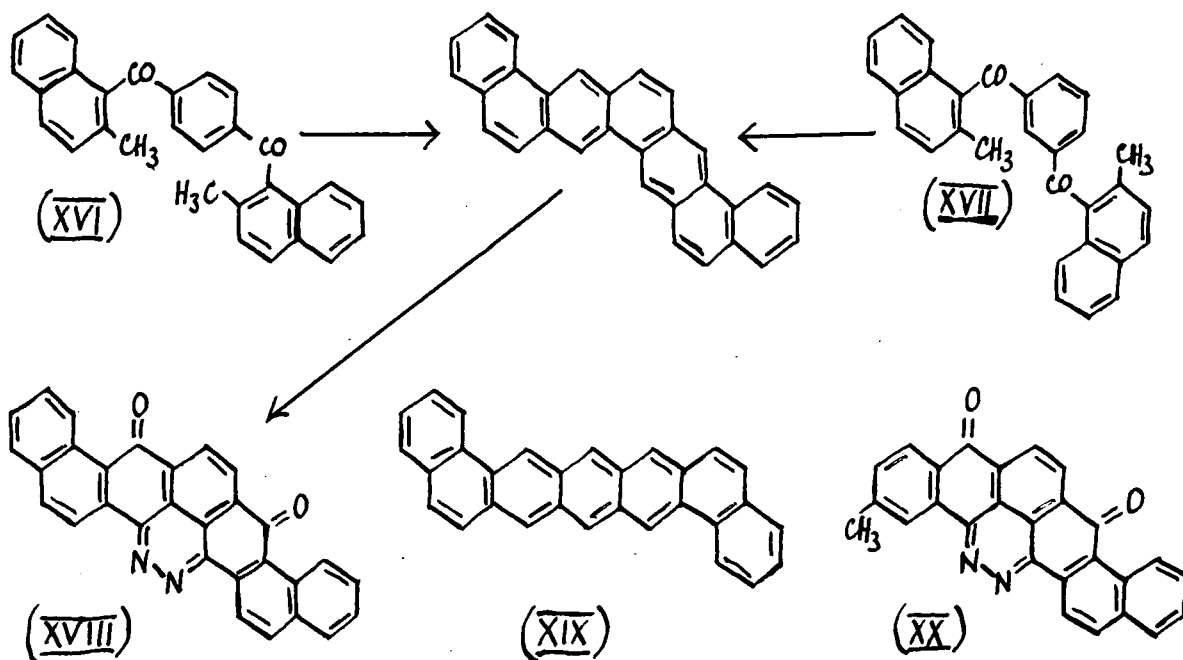
The derivative (XX) arose from a synthesis carried out
to assess the effect of a single fused benzene ring on the
absorption spectrum of the "pentaphene" nucleus (this name
was proposed in the adjacent paper of the 'Berichte').

Mention may here be made of two similar compounds
prepared by Ullmann (179 and 173). The first (XXI) was
derived from an anthraquinone-acridone (prepared for testing
as a dyestuff) and served to confirm the angular structure

of the product (⟶) as against the linear possibility (⋯⟶).

The sulphur analogue (XXII) was prepared by a similar route
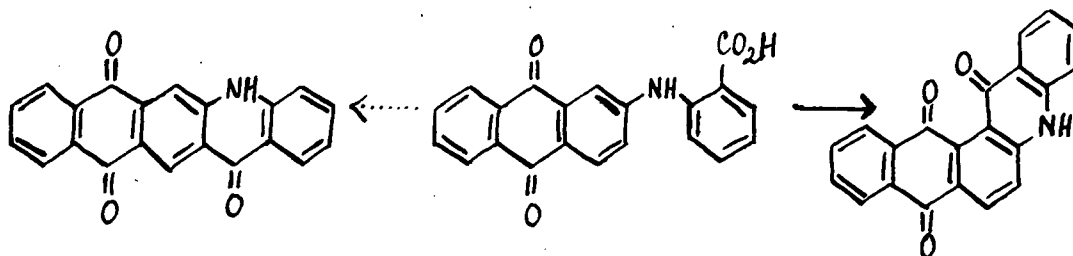
from β-chloroanthraquinone and salicylic acid.

$(\underline{XXI})$ $(\underline{XXII})$
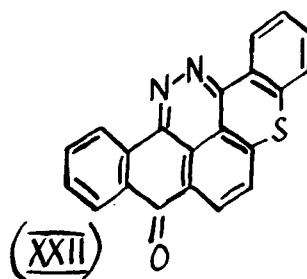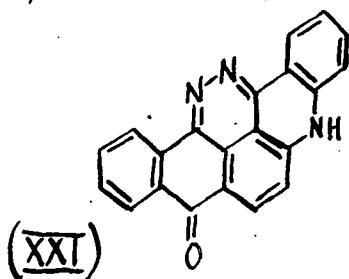
The polymerisation of 1,4-naphthaquinone to triphthaloyl-benzene (XXIII) was studied in 1939 (126) and the polymer was characterised as the bis-azine (XXIV).

$(\underline{XXIII})$ $(\underline{XXIV})$
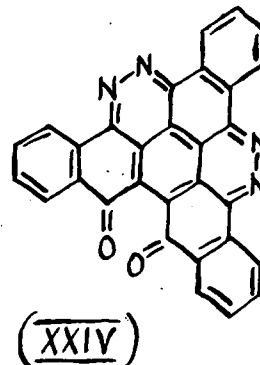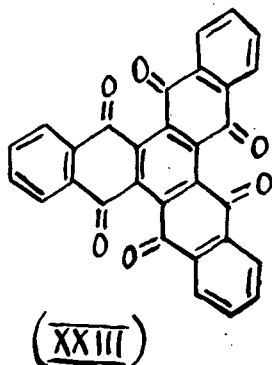
Schonberg and Rosenthal (147) proposed a cinnoline-like structure (XXVII) for phenanthraquinone imide anhydride, a compound prepared by Zincke (1902) by treating the imide (XXV)

with acid anhydrides. The oxygen-free compound obtained by
heating the anhydride to a high temperature was different
from the known diphenanthrylenazotide (XXVI) and was
represented as (XXVIII). Additive reactions of the imide
anhydride were clearly in accord with the proposed structure:
the elements of one molecule of water, methanol, ethanol,
propanol, hydrochloric acid or acetic acid were readily
accommodated by the general structure (XXIX). The possibility
that such addition occurred at a double bond was eliminated by
the negative action of bromine in chloroform. Regeneration of
the imide anhydride from such derivatives was readily effected
by warm acetic anhydride or merely by melting. The resistance

(XXV) (XXVI) (XXVII) (XXVIII)

(XXIX) (XXX) (XXXI)
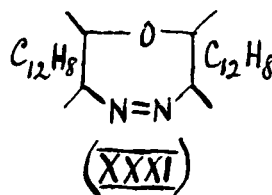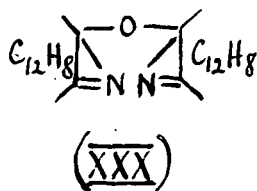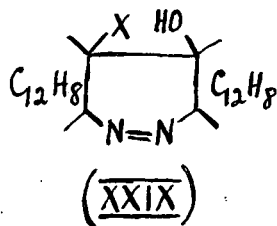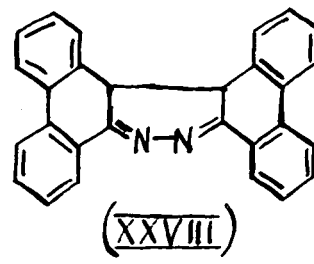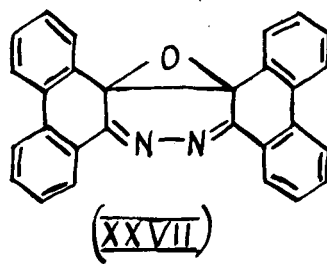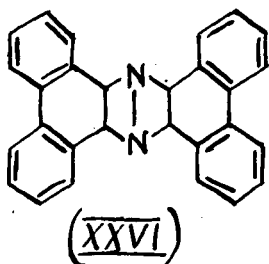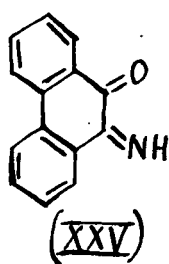
of the imide anhydride to reduction indicated the impossibility
of an azoxy-link whilst the structures(XXX and XXXI), advanced
by Graebe and Oehme respectively, did not explain satisfactorily

the properties of the addition compounds.

Another example of a polynuclear cinnoline formed without the use of hydrazine is "1,1'-dinaphthyl-2,2'-o-diazine" (XXXII) formed as one component of a mixture by reduction of 2-nitronaphthalene with sodium hydroxide and zinc dust(103).
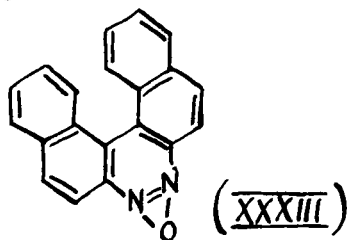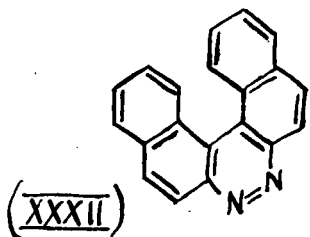
The cinnoline was not further reduced by zinc and alkali or by stannous chloride but long boiling with zinc and acetic acid gave 2,2'-diamino-1,1'-dinaphthyl. Reference has already been made (page 72) to the cinnoline oxide (XXXIII) prepared by the action of sodium stannite on 2-nitronaphthalene.

Other Cinnolines.

Substances of this group do not fall into any of the previous categories. An interesting series of compounds arose from the researches of Angelico on diazopyrroles. It was found (4) that the diazotriphenylpyrrole (II) was converted by long boiling with dilute sulphuric acid into an isomeric compound, tentatively represented as (III). Evidence for this structure was the oxidation to a diketone (VI) which could be reduced to a "furane-like" compound (VII). The conversion (5,6) of the latter into the original substance (III) by means of alcoholic ammonia further strengthened the earlier choice between this and the possibility (I).
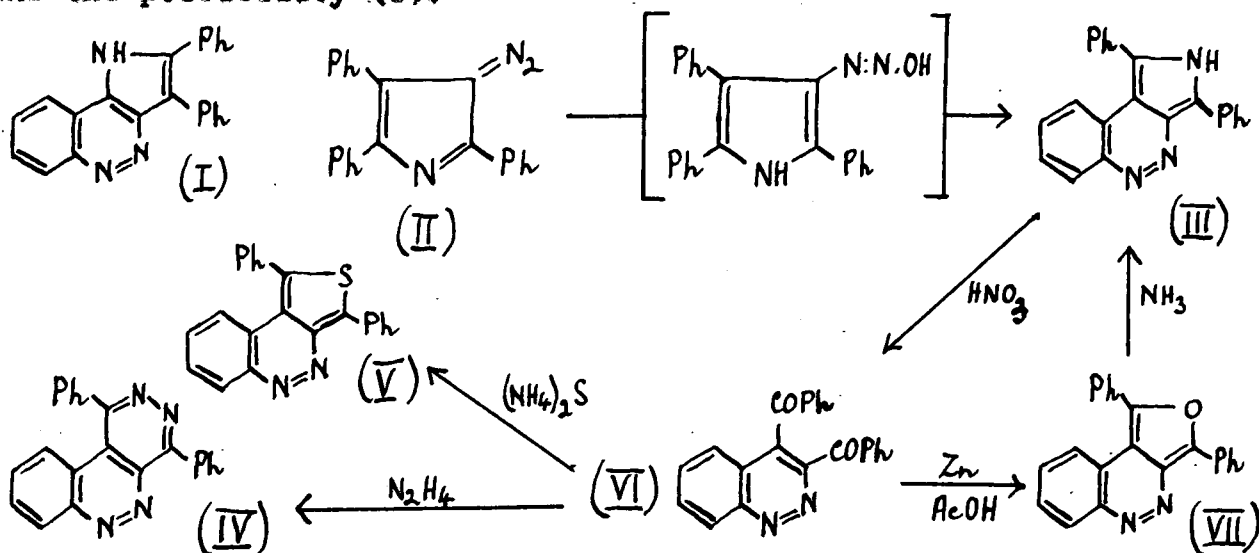
The diketone (VI) readily yielded the cinnoline (IV) on treatment with hydrazine (4) whilst the action of sodium sulphide gave a small amount of the thiophene derivative (V).

In 1924, 3-phenylcinnoline-4-carboxylic acid (IX) was prepared from 3-benzylideneamino-isatin (VIII) during an unsuccessful attempt to prepare N-aminoisatin. Stolle and Becker (162) noted the similar ease of decarboxylation between their compound and Richter's acid (page 25) although no
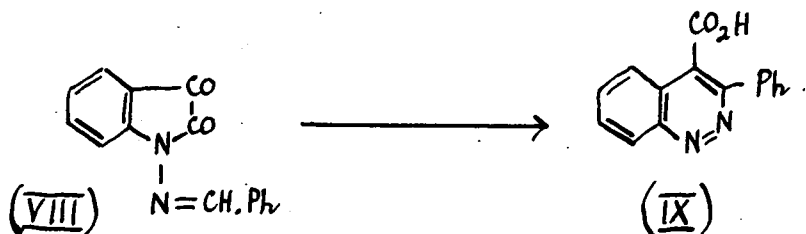
attempt was made to isolate the decarboxylation product. An attempt to repeat this work is described later, page 207.

During an attempt to increase the basicity of compounds destined for antimalarial testing Krahler and Burger (89) investigated the nitration and subsequent reduction of 2-chloro-lepidine. The first process gave a mixture of 6-nitro-2-chloro-lepidine and a new mononitro-derivative, which, on the basis of simple replacement reactions and comparison with known compounds, was represented as 5-nitro-2-chlorolepidine (X). Diazotisation of 5-amino-2-hydroxylepidine yielded a substance whose data agreed with the structure (XI).
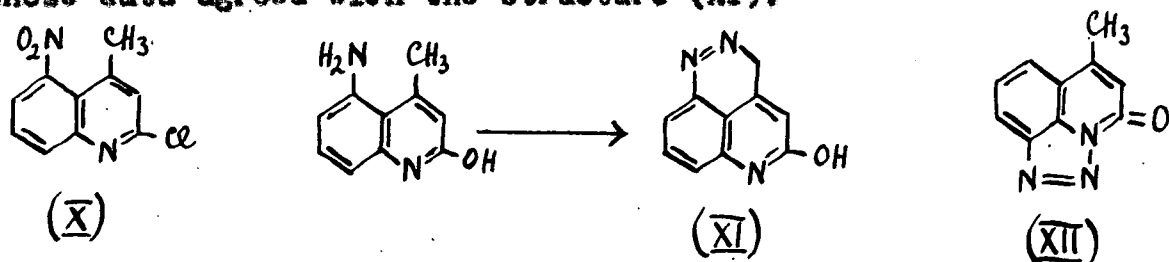
In the following year (90) new evidence revealed that the

structures of certain "known compounds" was incorrect and
it was proved that the 8-nitro-derivative had been obtained;
the cinnoline structure (XI) was thus amended to the diazo-
imide (XII).

The Preparation of 4-Hydroxycinnolines from 4-Chloro-2-amino-acetophenones.

In its preliminary stages this investigation was concerned with the broader question of 4-substituted-2-aminoacetophenones and the corresponding 7-substituted-4-hydroxycinnolines. Theoretical and practical interest in this problem arose from the following considerations.

(a). No information regarding the ease of formation of 7-substituted cinnolines was available apart from the single examples of Koelsch (85) and Widman (182). The synthesis of 6- and 8-substituted-4-hydroxycinnolines from diazotised 5- and 3-substituted-2-aminoacetophenones, respectively, has been shown (142) to be dependent on the kationic activity of the diazonium group, this being determined by the nature of the substituents. It was expected that the formation of 7-substituted-4-hydroxycinnolines from the corresponding diazotised o-aminoacetophenones would be almost wholly[*] dependent on electromeric shifts affecting the kationic side chain.

(b). The evaluation of some cinnoline derivatives as antimalarial agents has already been mentioned (page 45),the effect of a 6-methoxy group on the activity of a cinnoline

[*] The weak inductive effect (±I) exerted by the 4-substituent on the 2-diazonium group can probably be neglected here although examples of such an effect between "m-substituents" are known (51).

derivative being in striking contrast to the effect produced
in the quinoline series (3). It is evident from a
consideration of the structure of atebrin (I)that antimalarial
activity might be correlated with each "half" (II and III) of
the molecule. Until very recently*the only published evidence
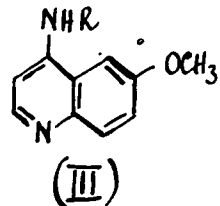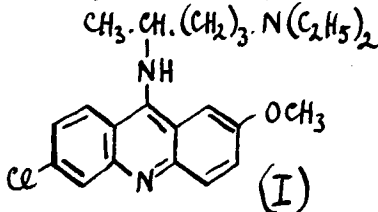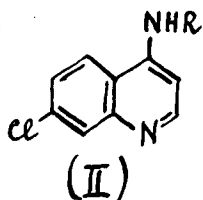
to strengthen this hypothesis was contained in a patent
(196) in which 7-chloro-3-methylquinolines having a basic
side chain on C_4 were described as "effective against blood
parasites, particularly plasmodia". It was of interest to
discover whether the above contrast between cinnoline and
quinoline analogues was reflected in the 7-substituted
derivatives.

(c). The possibility of synthesising 4-methylcinnoline-7-
carboxylic acid (Widman's acid) by a method independent of
cuminal (see page 156) was attractive in view of the inacces-
sibility of the latter material. The preparation of 7-cyano-4-
methylcinnoline either directly or via the 7-halogeno-compound

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* Contributions to current (1946) issues of the J.A.C.S. have
exploited fully the possibility that 7-substituted-quinolines
(122), -quinazolines (123) and -phthalazines (52) might show
antimalarial activity. Some duplication of the present work
has occurred (94,95) and will be dealt with later.

offered such an alternative route to Widman's acid.

Possible routes to 4-substituted-2-aminoacetophenones which appeared to be most direct gave discouraging results.
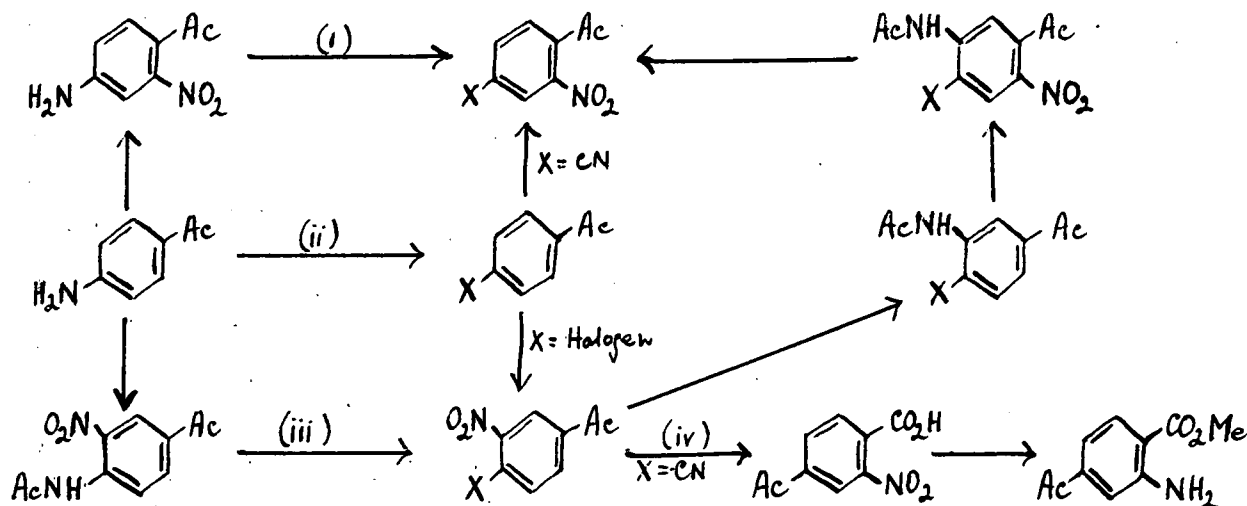
Thus (route i) nitration of p-aminoacetophenone in the presence of a large excess of sulphuric acid gave a resinous product, completely soluble in alkali. A preliminary attempt (route ii) to nitrate p-cyanoacetophenone, obtained from the amine by a Sandmeyer reaction, was unsuccessful. The substance did not appear to undergo nitration at -10° and on standing at room temperature a vigorous reaction developed; the only isolable product was a low melting solid which was not purified. The third route (iii) was more attractive since p-acetamidoacetophenone had been described by Raadsveld (127) and the subsequent nitration by Gibson and Levin (67). Further, 4-chloro-3-nitroacetophenone and 4-bromo-3-amino-acetophenone were known (102 and 67 respectively) whilst reference to other relevant work (route iv) was available (102).

Dn practice, Raadeveld's conditions for the acetylation of
p-aminoacetophenone proved unsatisfactory and the use of
pyridine as catalyst instead of sulphuric acid was adopted.
Nitration of the acetamido-compound by the published method
(67) revealed the critical nature of the reaction temperature;
a 63% yield of pure 3-nitro-4-acetamidoacetophenone was
obtained from an experiment at 0° but at -5° both yield and
purity were inferior. Hydrolysis to the amine was effected by
the method of either Raadeveld (124) or Gibson and Levin (67).
A temporary shortage of material led to the development of
alternative routes and the success of these resulted in the
conclusion of the above lines of attack.

The first alternative route to a 4-substituted-2-amino-
acetophenone arose from the findings of Gabriel and Lowenberg
(66). These workers prepared o-aminoacetophenone by
condensation of o-phthalimido-benzoyl chloride with dimethyl
sodiomalonate and subsequent hydrolysis with hydriodic acid.
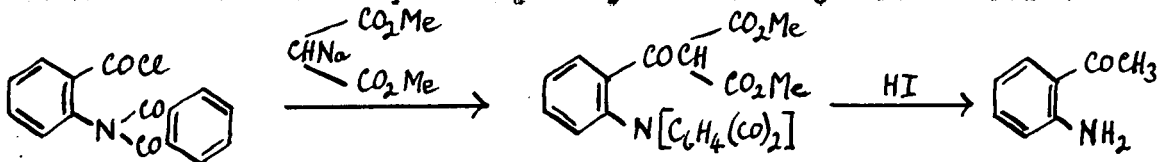
4-Chloroanthranilic acid, the essential starting material
for the synthesis of 4-chloro-2-aminoacetophenone, was
initially prepared from p-toluidine as follows:
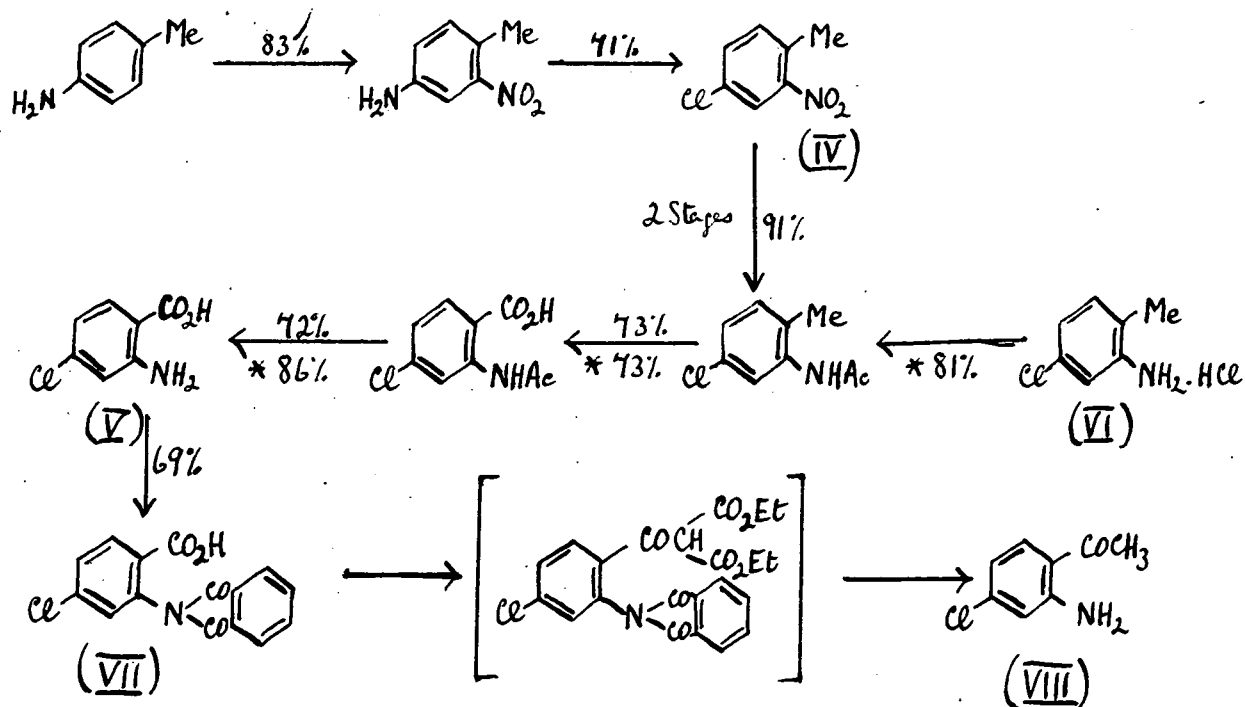
(* Indicates yields using the technique of I.C.I.)

4-Chloro-2-nitrotoluene (IV) was reduced with stannous
chloride, the resulting amine acetylated and the acetamido-
derivative oxidised with neutral potassium permanganate to
yield 4-chloro-2-acetamidobenzoic acid (40); hydrolysis
with sulphuric acid yielded 4-chloroanthranilic acid (V).
This was later obtained from 4-chloro-2-toluidine hydro-
chloride (VI), which, together with details of the process,
was supplied by I.C.I. (Dyestuffs Division). Phthalonation
of 4-chloroanthranilic acid by fusion of the dry components
(the method of Gabriel and Lowenberg) gave variable yields
of 4-chloro-2-phthalimidobenzoic acid (VII) and the use of
∝-chloronaphthalene as a diluent was only successful on the

small scale. Refluxing the components in acetic acid, a procedure which has been successfully employed with a wide variety of amines (180), was eventually chosen for preparative purposes; although the reaction proceeded slowly, this method gave practically pure 4-chloro-2-phthalimidobenzoic acid in 69. yield. Condensation of the acid chloride (of the latter compound) with diethyl sodiomalonate and hydrolysis of the oily product yielded crude 4-chloro-2-aminoacetophenone (VIII), best isolated as the acetamido-derivative. A study of various conditions of condensation and hydrolysis furnished data which are detailed in the table below.

The chief differences between the condensation conditions "A" and "B" were three in number; no mechanical stirring was employed in "A", rigorous care in the preparation of diethyl sodiomalonate (186) was only adopted in "B" and lastly the protection of the acid chloride from moisture was only developed in the latter experiments. Although no wide variations, ether than those tabulated, were allowed, the yields varied considerably. This state of affairs makes any attempt at generalisation hazardous but some conclusions are noteworthy. On the small scale (at least) the hydrolytic conditions appear to be fairly reproducible (note the difference of only 1.4 between "4a" and "4c") and the treatment selected for preparative purposes is undoubtedly the most efficient. The

Expt. No.	Scale * (grms.)	Conden- sation ‡ conditions	Hydrolysis conditions (gentle refluxing)	% Yield ∮
1	6	"A"	HI (D = 1.7) for 45 mins.	15.9
a	7	"	HI (1.7) " 30 "	17.3
2b	7	"	H Br (1.45) " 40 "	18.3
c	7	"	HI (1.5) " 30 "	13.3
a	7	"	H_2SO_4 (1:1, v/v) for 2 hrs.	21.4
3b	7	"	H Br (1.45) " 9 hrs.	24.4
c	7	"	H Br (1.45) " 40 mins.	14.3
a	7	"B"	H Br (1.45) " 9 hrs.	38.3
4b	7	"	H Br, AcOH (1:1) " 9 hrs.	24.4
c	7	"	H Br (1.45) " 9 hrs.	36.9
5	21	"	"	27.2
6	21	"	"	40.0
7	42	"	"	26.6
8	42	"	"	32.4
9	42	"	"	33.4
10	84	"	"	35.6
11	84	"	"	41.2

* Weight of 4-chloro-2-phthalimidobenzoic acid taken.

‡ "A" and "B" are fully described on page 135.

∮ Yield of 4-chloro-2-acetamidoacetophenone.

behaviour of the condensation was more capricious, a 4
difference in yield being noted in experiments ("2b" and "3c")
in which 'identical' conditions were used; on the larger
scale (expts. 5-11) the fluctuations were even greater. The
preparative yield of 30-40 of 4-chloro-2-acetamidoacetophenone
(based on 4-chloro-2-phthalimidobenzoic acid) represents an
average yield of 74-80 for each of the four stages involved.

Mention may here be made of an attempt to condense
4-chloro-2-phthalimidobenzoyl chloride with ethyl sodio-
acetoacetate. Treatment of the highly crystalline intermediate
compound, ethyl(4-chloro-2-phthalimidobenzoyl)acetoacetate, with
hydriodic acid did not give the desired result, 4-chloro-
anthranilic acid being the only isolable product. The use of
alcoholic sulphuric acid in the hydrolysis (8/) yielded no
useful result.

Another synthesis of 4-chloro-2-aminoacetophenone was
based on the preparation of o-aminoacetophenone from ethyl
o-nitrobenzoylacetoacetate (X; R = H) by Needham and Perkin
(113). The following schemes were examined:
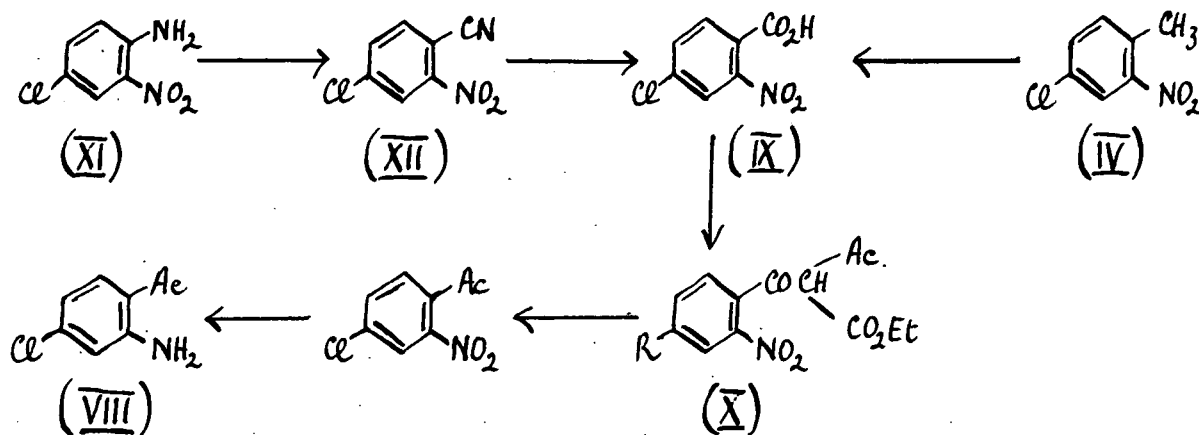
Preliminary attempts to prepare the requisite o-nitrobenzoic acid (IX) by oxidation of 4-chloro-2-nitrotoluene (IV, page 109) indicated the unsuitability of the method for preparative purposes. A poor yield of the acid together with some unchanged material resulted from treatment with alkaline potassium permanganate. The use of aqueous pyridine with this reagent, whilst effecting homogeneity and hence more rapid reaction, gave as the sole isolable crystalline product a substance which yielded unsatisfactory analytical data. Preliminary bromination of the methyl group, a measure used successfully in the oxidation of 2,6-dichlorotoluene (115), was ineffective; the consumption of permanganate by the crude bromination product was most rapid but only unchanged 4-chloro- -2-nitrotoluene was isolated and this in moderate yield. The nitrotoluene was also wholly unchanged after refluxing for one day with equal parts of concentrated and dilute nitric acid(cf. 69)

In view of these results, effort was concentrated on the route from 4-chloro-2-nitraniline (XI), initially prepared by literature methods (177, 21) but later made available by I.C.I. Preparation of the nitrile (XII) was never wholly satisfactory. Application of the procedure of Heller (72) invariably led to incomplete diazotisation in spite of the use of a well stirred, finely divided suspension of the amine hydrochloride. Further, reduction of the acidity of the diazotised solution, as

recommended by Meller, gave a highly coloured impurity, possibly a diazoamino-compound.

A second technique (forwarded by I.C.I.) was reported to give a 50% yield of 2-nitro-4-methoxybenzonitrile from the nitro-anisidine. This procedure effected only slight improvement in the case under consideration, diazotisation being still incomplete and the product discoloured.

At this stage attention became focussed on a statement by Hunn (74) claiming the preparation of (XII) in 75% yield. An attempt to reproduce Hunn's result was unsuccessful but the use of his method with modification in the isolation stage gave consistent yields (55) of the pure nitrile.

Several methods were tested in the purification of the crude nitrile which was always highly coloured and of low melting point. Meller's method (extraction with hot water) did not appear adaptable for preparative purposes; distillation in vacuo gave a clean product of somewhat low melting point. Material obtained by the "I.C.I. technique" was readily purified by steam distillation but an attempt to isolate (by this means) clean material direct from the reaction mixture failed. The most effective method of purification was found to consist of chromatographic adsorption on activated alumina.

The yield and purity of 4-chloro-2-nitrobenzoic acid (IX), obtained by hydrolysis of the nitrile, appeared to be greatly

affected by slight changes in the concentration of the
sulphuric acid used. Heller's method gave excellent results
initially but later the use of sulphuric acid from a different
source led to inferiority in both yield and purity. Re-
producible conditions were eventually established using a
slight variation of those of Heller.

4-Chloro-2-nitrobenzoic acid reacted spontaneously with
phosphorus pentachloride and the acid chloride so formed was
treated with ethyl sodioacetoacetate according to the method
of Needham and Perkin (113). Hydrolysis of the crude 4-chloro-
-2-nitrobenzoylacetoacetate (X) with alcoholic sulphuric acid
furnished 4-chloro-2-nitroacetophenone in good yield and
reduction to the amine (VIII) was equally successful.

The only reference to the latter compound in the literature
is a note by Roberts and Turner (131) on unsuccessful attempts
to prepare 4-chloro-2-aminoacetophenone for use in the synthesis
of 7-chloro-2,4-dimethylquinoline. The following routes were
examined by these workers:

(a) treatment of 2,4-dichloroacetophenone with
alcoholic ammonia at 180° for 6 hours

(b) interaction between p-chloroacetophenone and
acetic anhydride in the presence of zinc chloride.

(c) conversion of 2,4-dinitroethylebenzene to the
acetophenone oxime by amyl nitrite and piperidine.

The failure of these methods was unexpected since substitution of aniline for the p-chloro-derivative in (b) afforded p-aminoacetophenone (84) and the use of sodium ethoxide instead of piperidine in (c) was known to give a small yield of the desired oxime (129).

It is apparent that some duplication of the work of the present investigation has been effected by Leonard and Boyd whose papers (94 , 95) appeared after the completion of the historical introduction of this thesis. Since the American work consists largely of a belated presentation of results which have already been dealt with in the introduction, only material relevent to this chapter will be discussed.

The earlier work of Roberts and Turner (131) was overlooked by Leonard and Boyd in spite of the fact that they had occasion to refer to the publication of the former workers in connection with the nitration of 3,4-dichloroacetophenone. 4-Chloro-2-aminoacetophenone was prepared in low yield by the ammonolysis of 2,4-dichloroacetophenone using a modification of the method described (195) for the corresponding benzoic acid. A more satisfactory procedure was based on 4-chloro-2-nitrobenzoic acid (prepared by permanganate oxidation of 4-chloro-2-nitrotoluene in aqueous pyridine, cf. page 113),the method being essentially that described above (page 112), except for the reduction in which the Americans employed catalytic hydrogenation.

Leonard and Boyd (95) carried out the diazotisation of
4-chloro-2-aminoacetophenone in glacial acetic acid using
nitrosylsulphuric acid and cyclisation to 7-chloro-4-hydroxy-
cinnoline was allowed to proceed during 28 days*; even after
this time it was necessary to heat to 70-80° to complete the
reaction.

In the present investigation a preliminary small scale
diazotisation of a suspension of 4-chloro-2-aminoacetophenone
in hydrochloric acid (6N) yielded a trace of solid together
with a relatively large amount of a sweet smelling oil. A
larger experiment gave a better yield, superior to that of
4-hydroxycinnolineitself but less than the corresponding
6-substituted derivatives, this correlation between yield and
substituent being fully expected on the theory of Schofield
and Simpson (page 78). The following table shows the yields
obtained in the synthesis of 7-chloro-4-hydroxycinnoline.

(Table over)

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* The yield in this experiment was 81, but a cyclisation
effected overnight at room temperature and then at 60-70° for
5 hours gave an 80% yield of pure material; the concentration
of the acid in the latter cyclisation was not clearly specified.

Starting Material	4-Chloro-2-nitro-			4-Chloro-2-amino-aceto-phenone	Cinnoline
	benzo-nitrile	benzoic acid	aceto-phenone		
4-Chloro-2-nitro-aniline	50-55	80	74	85	39.5 ⌀
4-Chloro-2-nitro-toluene	⟶	41 ‡			
"	Leonard et al. ⟶	72 *	61	64.2	81

Figures represent ⁒ yield based on the preceding intermediate.
‡ Based on unrecovered starting material; 22⁒ based on total
starting material.
✳ "   "   "   "   "   ; 48⁒ "   "   "
⌀ This yield has since been raised to 95⁒ (155).

In view of the dubious yield of 7-chloro-4-hydroxycinnoline
from the small scale experiment, an attempt was made to increase
the extent of cinnoline formation by introducing a nitro-group
(cf. p.29) into the nucleus. Nitration of 4-chloro-2-acetamido-
acetophenone was carried out in the belief that the powerful
p-directive effect of the acetamido-group would assert itself.
In fact, 4-chloro-5-nitro-2-acetamidoacetophenone (XIII) was
formed in 77⁒ yield whilst the aqueous nitration mother liquor
yielded 4⁒ of a more basic isomer. Each of these compounds

yielded the corresponding nitro-amine on hydrolysis. Evidence proving the structure of the major product is presented later; the identity of the second isomer as the 3-nitro-derivative (XIV) rests on its conversion to 4-chloro-2,3-diaminoacetophenone and hence to a phenazine identical with an authentic sample previously prepared in this laboratory by Mr. J. R. Keneford.

Conversion of the corresponding chloro-nitro-aminoaceto-phenones to hydroxycinnolines developed into a most interesting problem. Both the 5- and 3-nitro-derivatives appeared to behave normally on diazotisation in hydrochloric acid since these separated from the clear diazonium solution on heating to 70° a solid which possessed properties typical of a 4-hydroxy-cinnoline. Thus the 5-nitro-derivative yielded a substance soluble in dilute alkalis (reprecipitated by acids), the sodium salt being precipitated from more concentrated solutions which, however, were not so deeply coloured (yellow) as was expected by analogy with 6-nitro-4-hydroxycinnoline (142). Analytical data indicated that the product was not the expected 7-chloro-6--nitro-4-hydroxycinnoline and a similar conclusion was reached regarding the product from diazotised 4-chloro-3-nitro-2-amino-acetophenone; in this case the usual properties were again evident (the sodium salt was much more soluble). In order to provide extra analytical data the 4-chloro- and 4-phenoxy-derivatives of both 'cinnolines' were prepared; it was noted at

this stage that the melting point of the substance obtained
from 4-chloro-5-nitro-2-aminoacetophenone was identical with
that of 6,7-dichloro-4-hydroxycinnoline*(XV, page 125) and this
relationship extended to other derivatives. This identity of
the two series of compounds was confirmed by mixed melting point
determinations and fully supported by analytical data; preparation
of the 4-acetoxy-derivative†of the cinnoline from each source did
not reverse the above decision. It was clear from the analysis
figures that the cyclisation product of diazotised 4-chloro-X-
-nitro-2-aminoacetophenone was isomeric with 6,7-dichloro-4-
-hydroxycinnoline and it was regarded as 7,8-dichloro-4-hydroxy-
cinnoline (XVI); the 4-chloro- and 4-phenoxy-derivatives yielded
confirmatory analytical data.

It was believed that the replacement of the nitro- by the
chloro-group took place directly although it was not known whether
such replacement occurred before or after cyclisation to the
cinnoline. This point was settled by deamination of the 4-chloro-
-'x'-nitro-2-aminoacetophenone; diazotisation of the 5-nitro

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*This compound and its 4-chloro- and 4-phenoxy-derivatives were
prepared earlier in this laboratory (Liverpool) by Mr.J.R. Keneford
and such identity confirms the orientation of the nitro-group in
the major nitration product of 4-chloro-2-acetamidoacetophenone
(page 117).

†By treatment with boiling acetic anhydride; treatment with the
hot reagent and a five-fold amount of pyridine was ineffective
whilst a four-fold quantity of acetic anhydride (relative to
pyridine) gave almost total acetylation - this behaviour is
similar to that observed (151) with ethyl 6-methoxy-4-hydroxy-
quinoline-3-carboxylate.

isomer in hydrochloric acid and addition of the cold diazonium
solution to cold hypophosphorous acid yielded a mixture from
which pure 4-chloro-3-nitroacetophenone was isolated. However,
when the diazotised solution was warmed until a faint turbidity
appeared and then added to cold hypophosphorous acid, the
product was practically pure 3,4-dichloroacetophenone. Similar
manipulation of 4-chloro-3-nitro-2-aminoacetophenone yielded
3,4-dichloroacetophenone and identification of the alkali-soluble
cinnoline (responsible for the turbidity in the warm solution)
as the 7,8-dichloro-derivative suggested that replacement of
the nitro-group occurred wholly before cyclisation to the
cinnoline.

Although the cause of the curious results obtained on
diazotisation was unexpected a literature survey disclosed a
number of similar examples which were equally explicable by
the direct replacement hypothesis mentioned above. Thus
Meldola (105) observed the same replacement reaction in certain
dinitroanisidines, the stage at which replacement occurred being
decided by isolation of an azo-dye, e.g.
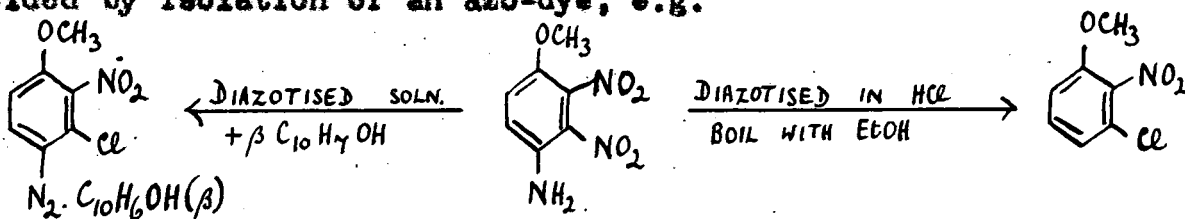
More recently, Keilen and Cass (79) obtained 8-chloroisoquinoline
by diazotisation of 8-nitro-5-aminoisoquinoline and subsequent

deamination.   Both groups of workers noticed the presence of
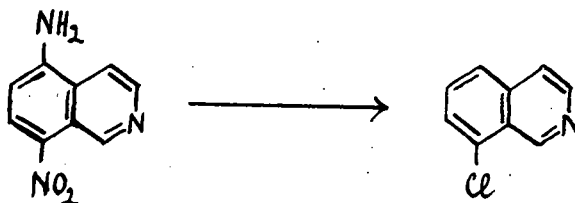
excess nitrous acid, even when a theoretically insufficient

amount of nitrite was used. Similar replacements are more

common in the naphthalene series; Clemo and coworkers (39)

found that diazotisation of α-nitro-β-naphthylamine in

hydrochloric acid and treatment with cuprous chloride gave

the compound (XIX; R = R' = Cl) instead of (XIX; R = Cl,

R' = NO_2).   Diazotisation in sulphuric acid followed by the

appropriate Sandmeyer reaction gave 1,2-dibromo- (XIX; R = R'

= Br) and 1,2-diiodo-naphthalene (XIX; R = R' = I).
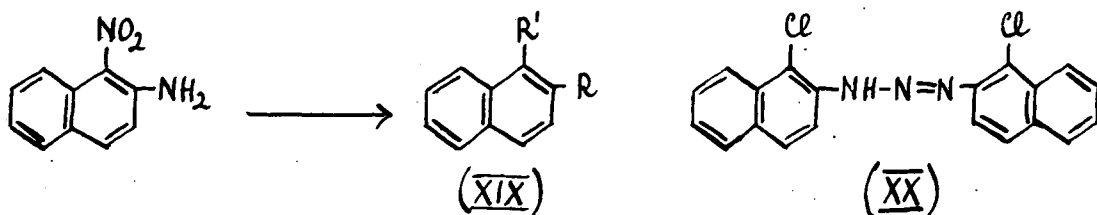
An anomalous result was obtained on diazotising in hydrochloric

acid and adding the diazotised solution to cuprous bromide

(in hydrochloric acid) the product being 2-chloro-1-bromo-

naphthalene (XIX; R = Cl, R' = Br). During work on the

influence of substituents on the formation of diazoamines and

amino-azo compounds, Morgan (///) found that reaction of

diazotised (in hydrochloric acid) α-nitro-β-naphthylamine with

a solution of 1-chloro-2-naphthylamine gave 2-diazoamino-1-

chloronaphthalene (XX) instead of the expected 'mixed'

diazoamino compound. The yield of the product excluded its derivation wholly from the added chloro-base and this clearly constitutes added proof to one of the above examples. Morgan's study is of added interest since he noted that the replacement reaction was not instantaneous, a point which is evident from the isolation of 4-chloro-3-nitroacetophenone from the 'cold deamination experiment (page 125).

In 1934, Willstaedt and Scheiber (187) failed to reduce 2-fluoro-1-nitronaphthalene, prepared by borofluoride treatment of diazotised α-nitro-β-naphthylamine (in hydrochloric acid); repetition of this work by Schiemann and Ley (137) was prompted by their success in reducing 2-fluoro-1-nitronaphthalene from a different source and it was proved that the product from the borofluoride route was actually 1-chloro-2-fluoronaphthalene:-

NO₂ / NH₂ ⟶ Cl / N₂Cl ⟶ Cl / N₂BF₄ ⟶ Cl / F
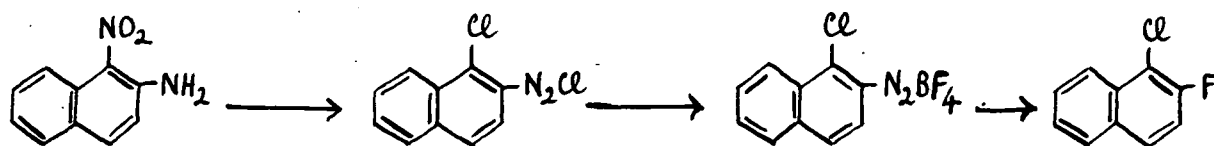
A similar diazotisation of α-nitro-β-naphthylamine and subsequent treatment with potassium iodide yielded to Italian workers (99) a substance presumed to be 1-chloro-2-iodo-naphthalene. Formation of this compound was explained by the

NO₂ / NH₂ — DIAZOTISATION IN HCl + H₂SO₄ / INSOL. SULPHATE + KI ⟶ Cl / I + Cl / N₂Cl·ICl
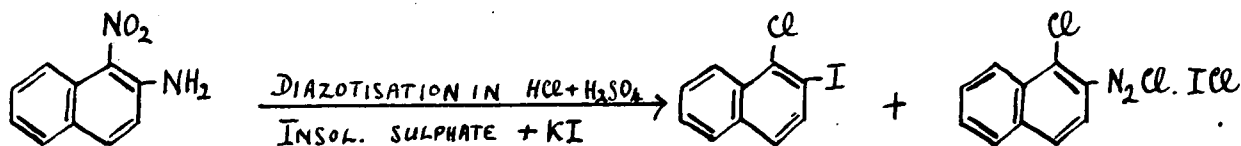
attack of "nascent chlorine" (from iodine monochloride) on the nitro-group, especially susceptible in view of the "mobility"

of substituents in the naphthalene series as compared with
the benzene series. In the latter it is evident that the
"mobility" depends upon substitution although some anomalies
appear when the type of substituent is considered. Meldola
and Hay (106) summarised the conditions for elimination
(replacement) of a group (nitro, methoxyl):

(a) the group must be ortho or para to a diazo-group, and

(b) the group must have a nitro-group in an ortho position
to act as an 'inactivator', for example;
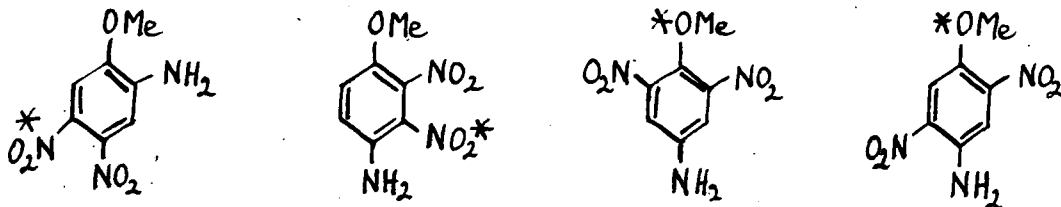
(*Indicates the group replaced on diazotisation).

In contrast to these examples, in which activation is produced
by a powerfully electrophilic group, the reactivity of nitro-
groups (ortho or para to a diazonium cation) in the present
investigation appears to be enhanced by a substituent (Cl)
whose normal tautomeric ($+T$) effect is reinforced by a
p-carbonyl group.

Diazotisation of 4-chloro-5-nitro- and 4-chloro-3-nitro-2-
-aminoacetophenones in sulphuric acid yielded 7-chloro-6-nitro-
and 7-chloro-8-nitro-4-hydroxycinnolines (XVII and XVIII)
respectively.

Since this investigation was not concerned with the
actual preparation of compounds for antimalarial testing it
was decided to extend the scope of the present study to the
synthesis of 7-chloro-3-methyl-4-hydroxycinnolines. Interest
in such compounds lay in their function as intermediates for
potential antimalarials whilst a study of the reactivity of
the 3-methyl group appeared particularly attractive in view of
the parallel work on 4-methylcinnolines (page 167).

Each of the routes developed for the preparation of 4-chloro-
-2-aminoacetophenone was utilised in attempts to prepare the
corresponding propiophenone:
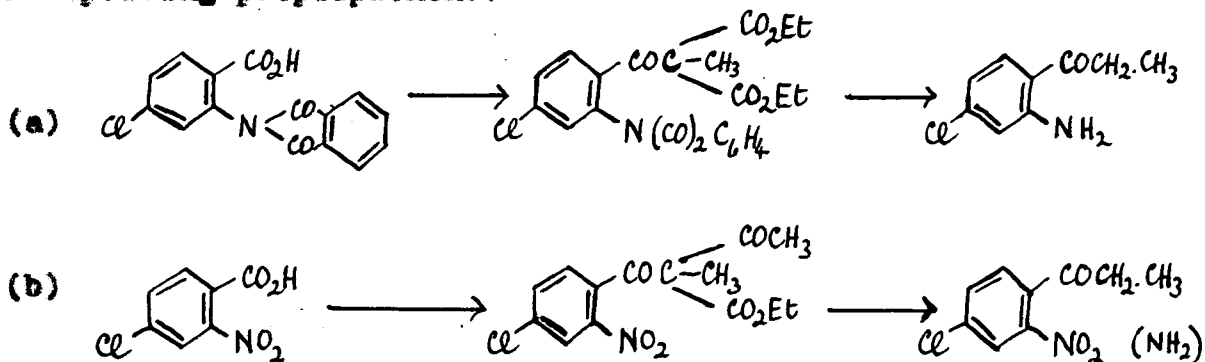
Methylmalonic ester, required for method (a), was prepared
by a method (117) which is essentially that of Lucas and Young
(97). Condensation with the acid chloride was carried out

4-Hydroxycinnolines from 4-Chloro-2-aminoacetophenones.

[DIAMINE]

Ac / NHAc (Cl)

Ac / NH₂ (Cl) (VIII)

OH ... Cl ... N=N (cinnoline)

Ac / NHAc / NO₂ (Cl) (XIV)

O₂N / Ac / NHAc (Cl) (XIII)

Ac / NH₂ / NO₂ (Cl)

O₂N / Ac / NH₂ (Cl)

DIAZOTISATION ETC. IN HCl

DIAZOTISATIONS AND CYCLISATIONS IN H₂SO₄ + AcOH

DIAZOTISATION ETC. IN HCl

OH ... Cl ... Cl ... N=N (XVI)

OH ... Cl ... NO₂ ... N=N (XVIII)

OH ... O₂N ... Cl ... N=N (XVII)

OH ... Cl ... Cl ... N=N (XV)

DEAMINATION (WARM)

DEAMINATIONS (WARM) (COLD)

OH ... Cl ... Cl ... N=N

+ Ac / Cl / Cl

Cl / Cl / Ac

O₂N / Cl / Ac
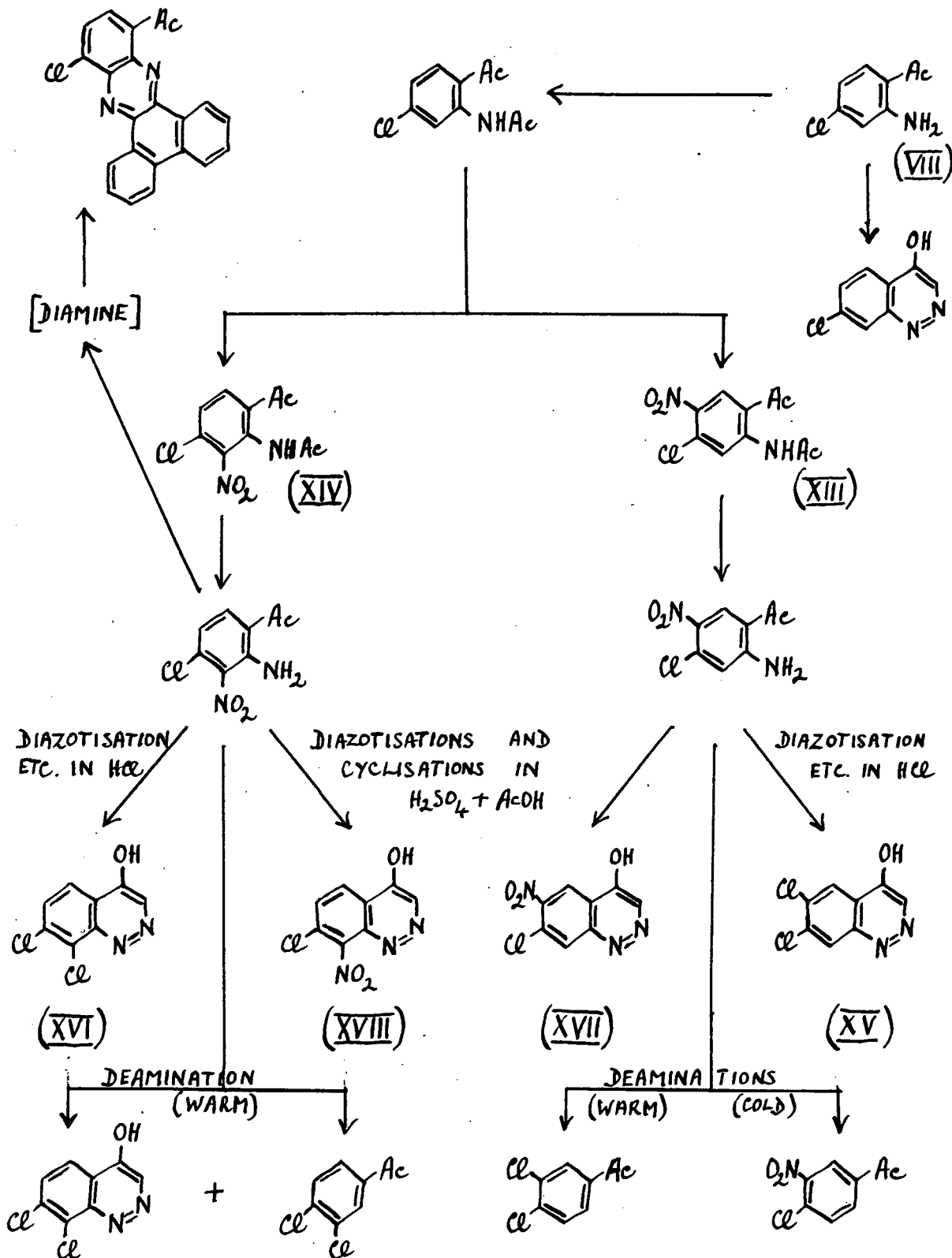
using these conditions (page *III*) which gave an optimum yield
of 4-chloro-2-aminoacetophenone (as the N-acetyl derivative),
but the product after hydrolysis and acetylation contained
appreciable quantities of 4-chloro-2-acetamidoacetophenone.
A repetition of this experiment using methylmalonic ester,
purified by a method kindly supplied by Dr. F. H. S. Curd, gave
the following results. The initial oily condensation product
was accompanied by a small amount of a crystalline compound,
m.p. 270° (decomp.), distinct from 4-chloro-2-phthalimidobenzoic
acid (m.p. 270°). Treatment of the oil with boiling hydrobromic
acid furnished a second crystalline substance, m.p. 123.5-125°,
again accompanied by much oily material. In two experiments
the small amount of the substance, m.p. 270°, was not isolated
and after treatment with hydrobromic acid the oily product was
combined with material from other runs. None of the compound,
m.p. 123.5-125°, was isolated but a third substance, m.p. 152-
153°, was obtained. The bulk of the final material, however,
was still a dark oil and an attempt to prepare a crystalline
acetyl derivative was unsuccessful. On the basis of melting
points only the substance, m.p. 123.5-125°, could be the
desired aminopropiophenone but this was excluded by the
following results. The compound resisted the treatment of
acetic anhydride at 90° and was sparingly soluble in hot dilute
or concentrated hydrochloric acid; the suspension obtained on

cooling a boiling solution in mixed hydrochloric and acetic acids could not be diazotised. Further examination of the substance showed no nitrosation and no picrate formation. Structures consistent with analytical data and experimental conditions could not be assigned to any of these products. The substance, m.p.270°, is _tentatively_ represented as (XXII) since the latter can only arise from unmethylated malonic ester and the operation of a remarkable series of reactions under the conditions of the experiment;
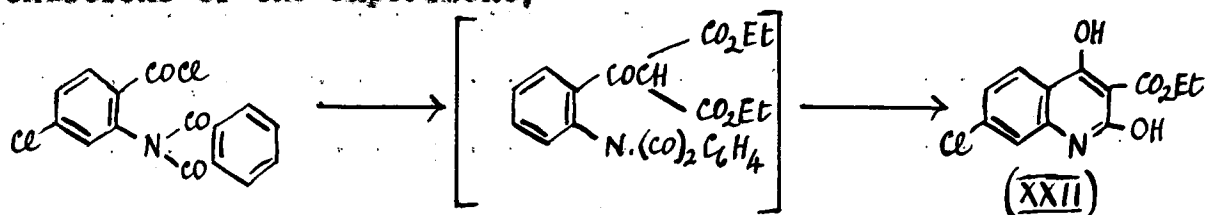
Substance	Analytical Data Found	Required
m.p. 125°	C,62.15; H,3.7; N,5.1; Cl,10.5%.	-
m.p. 153°	C,59.85; H,4.65; N,3.5; Cl,8.35%.	-
$C_{12}H_{10}O_4N\,Cl$ (XXII)	C,53.4; H,3.7; N,5.75; Cl,13.3%.	C,53.8; H,3.8; N,5.2; Cl,13.3%.

For route (b), ethyl methylacetoacetate was prepared by methylation of acetoacetic ester with methyl iodide. Since this method gives mainly the monomethyl derivative and only about 4% of the dimethyl compound (7) the procedure of Michael (108) was adopted, purification involving only the removal of unchanged acetoacetic ester. Condensation with 4-chloro-2-nitro-benzoyl chloride and subsequent hydrolysis with alcoholic

sulphuric acid (cf. page //4a) yielded a pale yellow oil, b.p.
167-170°/14 mm.   Reduction of the latter gave an oily amine,
the crystalline acetyl-derivative of which was identified
(analysis) as ethyl 4-chloro-2-acetamidobenzoate.   An attempt
to condense the material, b.p. 167-170°/14 mm., with benzaldehyde
in the presence of potassium hydroxide furnished only a specimen
of potassium 4-chloro-2-nitrobenzoate.

The probability that the establishment of conditions for
the synthesis of 4-chloro-2-aminopropiophenone would require
as much effort as that expended on the corresponding aceto-
phenone, combined with priority of other schemes, led to the
conclusion of this work.

Mention may here be made of a related project on which
only preliminary work was carried out, namely, the investigation
of possible routes to 7-methoxy-4-hydroxycinnolines.   The effect
of the methoxyl group on the extent of cinnoline formation was
of obvious interest whilst the possibility of similar replace-
ment reactions to those observed above (page /25) was an added
stimulus.   Antimalarials derived from this compound would not
only provide further comparative data on the relation between
substitution and activity in cinnolines but would offer another
means of comparing the contribution of various heterocyclic
nuclei to antimalarial activity.

The following scheme to intermediates was envisaged.
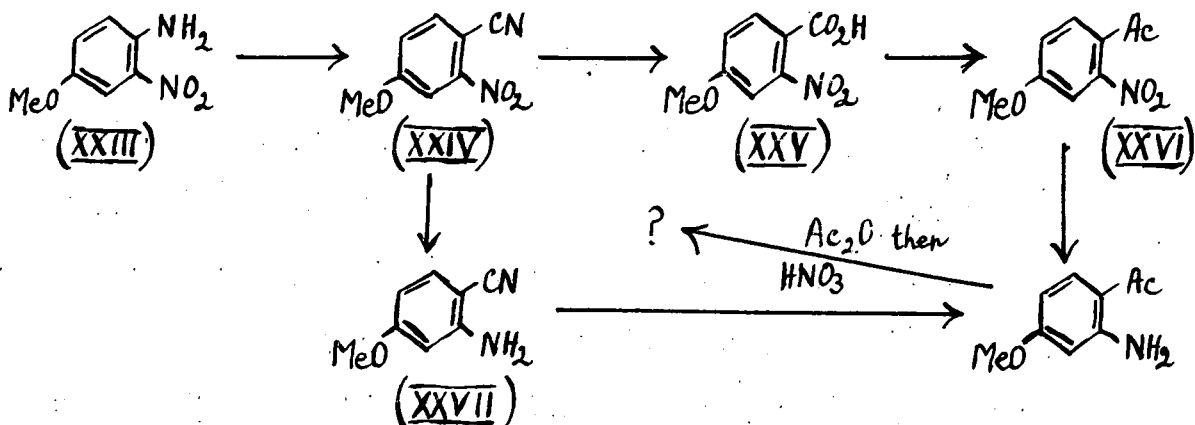
The compound (XXVI) has been obtained (8) in satisfactory

yield from (XXV) (prepared by nitration of p-tolyl carbonate

or from 2-nitro-p-tolyl-methyl ether). Since (XXIII) and a

preparative route to (XXIV) were supplied by I.C.I. the above

routes were investigated. Hydrolysis of (XXIV) to (XXV) was

not effected on any useful scale; the use of sulphuric acid

(18N, 24N, or 85. v/v) at 90° gave only low melting material

whilst boiling 18N-acid resulted in a poor yield of the

desired acid (XXV), much decarboxylation being observed as soon

as the acid was formed. Treatment of the nitrile with alkaline

hydrogen peroxide (cf.46) also gave only low melting material.

Attempts to proceed via the amine (XXVII), prepared according to

Cook et al.(44), were equally disappointing. The subsequent

Grignard reaction on (XXVII) gave no useful product; refluxing

in diethyl ether gave only unchanged material (as the acetyl-deriv.

m.p. 158-159°) whilst the use of isoamyl ether at 100° furnished

a small amount of unchanged material together with much oil
which resisted acetylation.

EXPERIMENTAL.

(Melting points are uncorrected).

4-Chloroanthranilic acid.- Route (1).

(a) 2-Nitro-4-toluidine.

A well stirred solution of p-toluidine (100 g.) in concentrated sulphuric acid (2000 g.) at -10° was treated with a mixture of nitric acid (D = 1.48, 75 g.) and concentrated sulphuric acid (300 g.), the temperature being kept below 5° throughout the addition. The cooling mixture was removed, stirring maintained for another hour (final temperature 10°) and the reaction mixture poured into iced water (ca. 6 l.). 2-Nitro-4-toluidine sulphate thus formed was drained well and the free amine liberated with aqueous alcoholic ammonia and recrystallised in one operation; the pure compound, m.p. 77-79°, formed orange coloured leaflets. A further quantity of product was obtained by basification of the original mother liquors (diluted to 15 l.) and recrystallisation of the second crop using the alcoholic mother liquors from the main crop. The total yield was 118 g. (83%).

(b) 4-Chloro-2-nitrotoluene.

A boiling solution of 2-nitro-4-toluidine (50 g.) in hydrochloric acid (500 c.c. of 2N and 50 c.c. of 12N) was cooled and the suspended hydrochloride diazotised at $0-5^{\circ}$ with

sodium nitrite (115 c.c. of 20% solution). The clear
diazotised solution was added during 15 minutes to one of
cuprous chloride in concentrated hydrochloric acid (200 c.c.)
prepared from copper sulphate (105 g.), sodium chloride (27 g.)
in water (320 c.c.) and sodium bisulphite (22 g.), sodium
hydroxide (14.5 g.) in water (150 c.c.). During the addition
the temperature was kept below 20° and after standing for one
hour the mixture was heated to 60° for $\frac{1}{4}$ hour. Two batches
carried out as above were combined, extracted with ether, and
the extract washed with successively less concentrated hydro-
chloric acid solutions then with sodium hydroxide and water.
Evaporation of the ethereal extract yielded a rapidly
crystallising oil (92 g.) which gave pale yellow material
(80 g., 71), b.p. $122^\circ/14$ mm.

(e) 4-Chloro-2-acetamidotoluene.

A solution of 4-chloro-2-nitrotoluene (30 g.) in acetic
acid (50 c.c.) was added to one of stannous chloride (157 g.)
in hydrochloric acid (200 c.c. concentrated and 30 c.c. fuming)
and shaken well. When the reaction was essentially complete
the mixture (including separated stannichloride) was heated on
a steam bath for $\frac{1}{2}$ hour, cooled and basified with potassium
hydroxide solution. Two batches prepared as above were
combined, extracted with ether and the extract washed and dried.

Evaporation to dryness yielded a pale yellow oil (47.4 g.) which was acetylated with acetic anhydride (100 c.c.) and the crystalline derivative isolated by dilution with water. The total yield, m.p. ca. 126°, was 58.3 g. (91 based on 4-chloro- -2-nitrotoluene). Beilstein, XII, 835 gives m.p. 130-131°.

(d) 4-Chloro-2-acetamidobenzoic acid.

4-Chloro-2-acetamidotoluene (50 g.) and crystalline magnesium sulphate (40 g.) were stirred with water (1½ l.) and treated at 65-70° with a mixture of potassium permanganate (120 g.) and magnesium sulphate (40 g.) added during 5 hours. Excess permanganate was destroyed, the hot reaction mixture filtered and the sludge of manganese dioxide washed once with hot water. The combined filtrate was acidified (congo red) and the white needle mass filtered cold and oven-dried, (42.5 g., 73%), m.p. 208-210° Beilstein, XIV, 365 gives m.p. 214°.

(e) 4-Chloroanthranilic acid.

The above acetamido-derivative (32 g.) was refluxed for one hour with sulphuric acid (18N, 50c.c.), cooled and the suspended amine sulphate carefully neutralised with ammonia (D = 0.880). The mixture was definitely acid to congo red when maximum precipitation of the anthranilic acid was noted. It was filtered and dried (18.6 g., 72) and melted at 218° (Lit. m.p. 235-236°).

4-Chloroanthranilic acid (Method supplied by I.C.I.):

4-Chloro-2-toluidine hydrochloride (178 g.) and fused sodium acetate (164 g.) were mixed in a flask fitted with an air condenser, stirrer, tap-funnel and thermometer. Acetic anhydride (204 g.) was added and stirring begun. An equal amount was added during 1 hour so that the temperature did not rise above 70° and the reaction completed by heating on the steam bath for 1 hour. The reaction mixture was poured into water (3 l.), the flask washed with water (1 l.) and the liquors allowed to stand overnight. The product was filtered, ground with water (1 l.) at $50-60^{\circ}$ and again filtered and washed with water (1 l.); after drying at $60-65^{\circ}$ it had m.p. 136° (133 g., 72.5).

A 5 l. flask was charged with hot water (3 l.), the acetamido-compound (183.5 g.) and magnesium sulphate (360 g.) and stirring begun. The temperature was raised to 80° and potassium permanganate (360 g.) added over a period of 3 hours at $90-95^{\circ}$. Stirring was maintained for another 2 hours and the mixture made alkaline to brilliant yellow with sodium carbonate and filtered hot. The residue was washed thrice with hot water (900 c.c. in all) and the combined filtrate acidified with hydrochloric acid, allowed to cool and filtered. The crude acid was washed with a little cold water and purified by reprecipitation from a

a solution of sodium carbonate (60 g. in 1 l. of water) at 60°.
After washing and drying 4-chloro-2-acetamidobenzoic acid (154 g.,
72%) had m.p. 212°.

This acid (107 g.) was warmed with concentrated hydro-
chloric acid (400 c.c.) in a 2 l. flask until frothing moderated.
Hydrochloric acid (100 c.c.) was added and the mixture refluxed
gently for 3 hours, cooled and the white solid filtered cold.
After thorough washing with water, 4-chloroanthranilic acid was
dried and melted at 224° (74 g., 86.5%).

4-Chloro-2-phthalimidobenzoic acid.- 4-Chloroanthranilic acid
and phthalic anhydride (100 g. of each) were ground together
and the mixture refluxed in acetic acid (500 c.c.) for 7 hours.
(Slight fuming at this stage was due to the presence of a little
hydrochloric acid in the anthranilic acid; no advantage attended
the use of wholly purified 4-chloroanthranilic acid). Small
colourless prisms separated from the boiling solution which was
allowed to cool overnight and the pure phthalimido-acid, m.p.
269-270°, filtered off (122 g., 69%) (Found: C,59.65; H,2.55.
$C_{15}H_8O_4N$ Cl requires C,59.7; H,2.65%).

4-Chloro-2-acetamidoacetophenone.- Procedure "A".

The above phthalimido-acid (6 g.) was refluxed with
phosphorus pentachloride (4.5 g.) in dry benzene (50 c.c.) for
one hour and the clear solution evaporated to dryness under
reduced pressure to remove phosphorus oxychloride. The solid

residue was redissolved in benzene (40 c.c.) and added in one
portion to a suspension of ethyl sodiomalonate prepared the
previous day from powdered sodium (0.92 g.), diethyl malonate
(7.6 c.c.) and benzene (40 c.c.). After standing overnight
at room temperature the mixture was decomposed by shaking with
dilute hydrochloric acid (20 c.c.) and the benzene layer
separated. This was combined with an ethereal extract of the
aqueous layer, washed, dried and concentrated. The residual oil
was hydrolysed by gentle refluxing with the reagent (50 c.c., see
page ///) and crude 4-chloro-2-aminoacetophenone isolated by ether
extraction of the cold reaction mixture after basification with
sodium carbonate. Acetylation of the amine was effected by heating
on a steam bath for 1½ hours with acetic anhydride (2 parts).
Crystals of the acetamido-derivative separated from the cold reaction
mixture and were filtered and washed with ether. Pure 4-chloro-2-
acetamidoacetophenone crystallised from ethanol in fine colourless
needles, m.p. 148-149° (Found: C,56.55; H,4.8. $C_{10}H_{10}O_2$ N Cl
requires C,56.7; H,4.7%).

Procedure "B".

A solution of diethyl malonate (108 c.c.) in dry benzene
(160 c.c.) was added with high speed stirring to a suspension of
powdered sodium (12.8 g.) in benzene (500 c.c.) and the mixture
refluxed for 5 hours then allowed to stand overnight. The well

stirred sludge of the sodio-derivative was treated with a
solution of the acid chloride in benzene (500 c.e.) prepared
as in "A" from 4-chloro-2-phthalimidobenzoic acid (84 g.),.
phosphorus pentachloride (64 g.) and benzene (250 c.c.).

In concentrating to dryness under reduced pressure to remove
phosphorus oxychloride the entering stream of air was dried
by phosphorus pentachloride; further evaporation of an added
volume of benzene (100 c.c.) ensured complete removal of
oxychloride . The reaction mixture was stirred for a further
7 hours, allowed to stand overnight and decomposed with
hydrochloric acid (300 c.c.) as above. Hydrolysis of the
condensation product was achieved by refluxing with hydrobromic
acid (D = 1.5, 600 c.c.) for 9 hours; the cold reaction
mixture was basified with ammonia (1 part of concentrated to
3 parts of water) and worked up as in "A".

4-Chloro-2-aminoacetophenone.- The above acetamido-compound
(1.5 g.) was refluxed for 15 minutes with hydrochloric acid
(6N, 24 c.c.), cooled and basified with ammonia. The free
amine, m.p. 91-93°(1.15 g.),formed a mixture of solidified oil
drops and colourless needles; pure 4-chloro-2-aminoacetophenone,
m.p. 92-94°, crystallised from aqueous alcohol in colourless
needles (Found: C,56.2; H,4.65. $C_8H_8O\,N\,Cl$ requires C,56.6;
H,4.7.).

<u>4-Chloro-2-phthalimidobenzoylacetoacetate</u>.- A mixture of ethyl acetoacetate (3 g.) and sodium ethoxide, prepared from sodium (1 g.) and ethanol (absolute, 18 c.c.), was cooled to 5° and treated with a solution of 4-chloro-2-phthalimidobenzoyl chloride prepared from the acid (6 g.) and phosphorus pentachloride (4.5 g.) as above. The pale yellow solution was allowed to stand overnight, shaken with hydrochloric acid and the benzene layer removed; this was combined with an ethereal extract of the aqueous layer, washed and dried. Concentration yielded glistening needles (3.6 g.), m.p. $102-104^o$, which yielded colourless leaflets of the pure condensation product, m.p. 104°. (Found: C,60.6; H,4.5; N,4.0. $C_{21}H_{16}O_6N$ Cl requires C,60.9; H,3.9; N,3.4).

A portion (1.5 g.) of this product was refluxed with hydriodic acid (4.5 c.c.) for $\frac{3}{4}$ hour and worked up as usual (page 136). A dark coloured crystallising oil (0.14 g.) which did not melt on the steam bath and had no characteristic smell was isolated. The alkaline mother liquor was acidified and yielded by ether extraction a white solid (0.84 g.) which after several recrystallisations from alcohol had m.p. 237° (decomp.) (4-chloroanthranilic acid has m.p. 236°) (Found: C,48.85; H,3.3; Cl, 20.5. Calc. for $C_7H_6O_2N$ Cl: C,48.9; H,3.5; Cl,20.7).

<u>4-Chloro-2-nitrobenzonitrile</u>.- In the following experiments the crude nitrile was always isolated by extraction of the reaction mixture with ether; the extract was washed with water, sodium

hydroxide solution and again with water, dried and evaporated.

(a) An experiment (using 0.2 gm. mol., 34.5 g. of amine) employing Heller's (72) conditions indicated his use of an exceptionally large excess of sodium acetate over that required to buffer the diazotised solution (with respect to congo red); a second experiment required roughly 1/3 the quantity of sodium acetate. The yields were combined and furnished on distillation a pale yellow product (22.6 g.), b.p. 228-240°/12 mm., which on recrystallisation from ether gave pure 4-chloro-2-nitrobenzo-nitrile (18 g., 25%), m.p. 98-99°.

(b) Method of I.C.I.

4-Chloro-2-nitraniline (34.5 g., 0.2 mol.) was converted into hydrochloride with the minimum of boiling concentrated hydrochloric acid and the dark red prismatic needles filtered cold and drained. The hydrochloride was added during 2 hours at -5° to 0° to a well stirred mixture of sodium nitrite (16 g. in 40 c.c. of water), concentrated hydrochloric acid (40 c.c.) and ice (200 g.). Unchanged hydrochloride (13.4 g., m.p. and mixed m.p. 113-116°) was filtered off and excess nitrite in the filtrate was destroyed with urea. The clear solution was added to the Sandmeyer solution prepared from copper sulphate (56 g.) and "double salt" (60 g.) in water (280 c.c.), the temperature being kept below 20° and the mixture was heated to 60° the next day. The yield of crude nitrile, m.p. 75-92°, was 13.3 g. (36%).

A portion (5 g.) was partially purified by steam distillation to yield pale yellow material (4 g.), m.p. 80-90°.

An attempt to steam distil the basified reaction mixture yielded no nitrile; some crystalline material, m.p. 172° and at 230° (decomp.), probably impure amide, was formed in the distillation flask but this did not yield any acid on further hydrolysis with 50% v/v sulphuric acid.

(c) Procedure according to Hunn (74):- 4-Chloro-2-nitraniline (34.5 g.) yielded only 10 g. (28%) of the nitrile, m.p. 94-96°.

(d) 4-Chloro-2-nitraniline (138 g., 0.8 mol.) was diazotised according to the directions of Hunn and the clear solution halved. One half was made neutral to congo red with sodium acetate solution and this solution again halved; each portion was added to an aliquot of the Sandmeyer solution at 70° (a) and at room temperature (b). The other part of the untreated diazotised solution was similarly divided and added to the Sandmeyer solution at 70° (c) and at room temperature (d). The Sandmeyer solution was prepared exactly as in (b) . The yields of crude nitrile obtained from (a), (b), (c) and (d) were 31.5 g., 31.4 g., 30.1 g., and 29.55 g. respectively. (a) and (c) were combined, dissolved in benzene (1 l.) and allowed to percolate through a column of "Merck's" alumina (65 x 2 cm.); elution with benzene, evaporation of the eluates

and digestion with ether (150 c.c.) furnished pure 4-chloro-2-nitrobenzonitrile (40.5 g., 55.5%), m.p. 97-98°, as reddish yellow needles. Similarly, (b) and (d) yielded 36.65g., 50%, m.p. 99-101°.

4-Chloro-2-nitrobenzoic acid.-

(a) By hydrolysis of the above nitrile.

The nitrile (10 g.) was heated on a steam bath for $1\frac{1}{2}$ hours with sulphuric acid (80 c.c. of 80 v/v). Water (48 c.c.) was added with cooling and the mixture (50 sulphuric acid now present) refluxed gently for $1\frac{1}{2}$ hours, cooled and diluted with water (138 c.c.). The dark coloured crystalline material was filtered and purified by reprecipitation by acid from its solution in aqueous sodium carbonate, yield (8.8 g., 80%), m.p. 141-145°.

(b) By oxidation of 4-chloro-2-nitrotoluene.

(1) The nitrotoluene (10 g.) was refluxed with water (250 c.c.) and potassium permanganate (20 g.) added during 24 hours, volatile material being occasionally melted from the condenser. The cold reaction mixture was filtered and the filtrate acidified to give 4-chloro-2-nitrobenzoic acid (2.6 g.), m.p. 140-141°. The dried sludge from the oxidation yielded 4-chloro-2-nitrotoluene (4.6 g.) by ether extraction. (The yield of acid was thus only 22 unless based on the nitrotoluene consumed when it was 41%).

(2). A solution of 4-chloro-2-nitrotoluene (10 g.) in pyridine and water (60 c.c. of each) was refluxed and treated portionwise with permanganate (30 g.). Pyridine was removed by steam distillation, the manganese dioxide filtered off and the solution acidified; colourless leaflets, m.p. 125° (decomp.) were obtained and after recrystallisation from 95% ethanol melted at 185-200°. Analysis of this material gave unsatisfactory results, viz.-

(3). Bromine (9.4 g.) was added dropwise during one hour to 4-chloro-2-nitrotoluene (10 g.),maihtained at 160-170° in a bath of liquid paraffin,and illuminated by a 200 watt lamp. Some crystalline material separated after ½ hour and at the end of the reaction the mixture was completely solid at 80°. This product was oxidised in sodium hydroxide solution (3 g. in 250 c.c. of water) and permanganate (20 g.) added to the boiling solution. The usual method of working up yielded a yellow powder (0.9 g.), m.p. 133-136°, and some of the nitrotoluene (4.1 g.).

4-Chloro-2-nitroacetophenone.- 4-Chloro-2-nitrobenzoic acid (24 g.) and phosphorus pentachloride (27 g.) were mixed together and the vigorous spontaneous reaction was completed by heating on a steam bath for 1½ hours. Phosphorus oxychloride was removed under reduced pressure, this process being completed by two additions of dry benzene and subsequent evaporation under reduced pressure. The oily product was dissolved in dry

benzene (50 c.c.).

A solution of sodium (6.15 g.) in ethanol (80 g., purified via diethyl phthalate) was prepared and halved. One half was treated with acetoacetic ester (17.05 g.) in the cold and to this stirred mixture was added at 0° the rest of the sodium ethoxide and the acid chloride solution, these additions being made simultaneously at approximately equal rates. The temperature tended to rise but was kept below 5° throughout the reaction, towards the end of which some separation of solid occurred. The mixture was stirred for 3 hours, allowed to stand overnight, decomposed with iced hydrochloric acid and extracted with ether. The extract was washed with sodium bicarbonate solution and then with water, dried and evaporated to yield a red mobile oil (35 g.). This was hydrolysed in two equal parts with alcoholic sulphuric acid (15 parts, 10% w/w of concentrated sulphuric acid) by the method of Kermack and Smith ( ) and yielded a rapidly crystallising oil; this separated from its solution in ether-ligroin as long soft needles (17.6 g., 74% based on the acid). A pure sample, m.p. 55-56°, crystallised from ligroin (b.p. 60-80°) in long, colourless brittle needles. (Found: C,48.25; H,3.05. $C_8H_6O_3N$ Cl requires C,48.1; H,3.0).

4-Chloro-2-aminoacetophenone.- The above nitro-compound (6.5 g.) was dissolved in acetic acid (50 c.c.) and treated on a steam bath with iron filings (13 g.) added during $\frac{1}{2}$ hour. Water

(25 c.c.) was added after 15 minutes and again when all the
iron had been added. The mixture was heated for another
½ hour, cooled, extracted with ether and the extract washed
with aqueous sodium carbonate and then with water. The extract
was dried and yielded on evaporation a readily crystallising
oil; pure 4-chloro-2-aminoacetophenone (4.7 g., 85%), m.p.
and mixed m.p. 91-93°, was obtained by recrystallisation from
ligroin (b.p. 60-80°).

7-Chloro-4-hydroxycinnoline.- 4-Chloro-2-aminoacetophenone
(3 g.) was boiled with hydrochloric acid (60 c.c., 6N) and the
finely divided suspension cooled to ca.5°. This was diazotised
with sodium nitrite (1.3 g. in 10 c.c. of water), mechanical
stirring being maintained throughout the diazotisation (1 hour)
and then left for a further hour at room temperature. The clear
solution was heated on a steam bath until all coupling had
disappeared (1 hour at 70°) and the precipitate filtered cold.
Purification was effected by reprecipitation with acid from a
solution of the cinnoline in sodium hydroxide (the sodium salt
of the cinnoline appeared to be sparingly soluble) and the
filtered product was freed from some sweet smelling oil by
washing with ether. Recrystallisation from absolute alcohol
furnished pure 7-chloro-4-hydroxycinnoline (1.1 g., 34%), m.p.
274-275°, as soft bronze coloured needles (Found: C,52.9; H,2.75;
N,15.25. $C_8H_5O N_2Cl$ requires C,52.2; H,2.8; N,15.5%).

<u>Nitration of 4-chloro-2-acetamidoacetophenone.</u>- The acetamido-compound (10 g.) was added with stirring, during 35 minutes, to a mixture of nitric acid ($D = 1.48$) and concentrated sulphuric acid (60 c.c. of 5:2 by volume) the temperature being kept below -10° throughout the reaction. The added solid soon dissolved with slight evolution of heat. After stirring for 20 minutes the solution was poured on to crushed ice (ca. 250 c.c.) and the solid filtered and washed well with water. Recrystallisation from ethanol yielded slender yellow blades of 4-<u>chloro</u>-5-<u>nitro</u>-2-<u>acetamidoacetophenone</u>, m.p. $166-168^\circ$ (9.37 g., 77%) (Found: C,46.5; H,3.5. $C_{10}H_9O_4N_2Cl$ requires C,46.8; H,3.5%).

The aqueous nitration liquor was basified with sodium carbonate, extracted with ether and the extract washed and dried. Concentration of the ethereal solution to small volume yielded almost colourless needles (0.5 g.) which furnished on recrystallisation from ligroin (b.p. $60-80^\circ$) pure 4-<u>chloro</u>-3-<u>nitro</u>-2-<u>acetamidoacetophenone</u>, m.p. $143-144^\circ$ (Found: C,47.15; H,3.45. $C_{10}H_9O_4N_2Cl$ requires C,46.8; H,3.5%). Melting point depressions were obtained on admixture with the starting material, m.p. $148-150^\circ$ and with the main product, m.p. $166-168^\circ$.

In experiments where the latter isomer was contaminated with the former, purification was best effected by recrystallisation from benzene in which the 3-nitro-derivative is very easily soluble.

4-<u>Chloro</u>-5-<u>nitro</u>-2-<u>aminoacetophenone</u>.- The above acetamido-derivative (4 g., m.p. 166-168°) was refluxed with a mixture of equal volumes of alcohol, concentrated hydrochloric acid and water (120 c.c. in all). The free amine, which separated from the boiling solution after about 5 minutes, was re-dissolved by addition of more ethanol and refluxing continued for another 10 minutes. The alcohol was boiled off, the mixture cooled and basified, and the amine (3.2 g.), m.p. 176-177°, filtered off and dried; the m.p. was unchanged after recrystallisation from alcohol (Found: C,45.2; H,3.2; N,13.05. $C_8H_7O_3N_2Cl$ requires C,44.8; H,3.3; N,13.05).

4-<u>Chloro</u>-3-<u>nitro</u>-2-<u>aminoacetophenone</u>.- A mixture of the acetamido-derivative (2.4 g., m.p. 142-143°) and hydrochloric acid (10 c.c., 2N) was refluxed for a short time (after one minute the free amine separated from the clear solution), cooled and then basified. The crude product (2.3 g.), m.p. 148-150°, was unchanged by recrystallisation from alcohol from which the amine separated in characteristic golden yellow plates (Found: C,44.5; H,3.2. $C_8H_7O_3N_2Cl$ requires C,44.8; H,3.3).

This compound (0.2 g.) was reduced to the diamine by iron filings and acetic acid and was then condensed with phenanthra-quinone to yield an azine, m.p. 287-288°, identical with material prepared by Mr. J. R. Keneford.

Diazotisation of 4-chloro-5-nitro-2-aminoacetophenone in hydrochloric acid.

A suspension of the amine (5 g.) in 6N hydrochloric acid (60 c.c.) was cooled to 5° and treated with 10% aqueous sodium nitrite (20 c.c.). After standing overnight in a refrigerator some solid remained but this gradually dissolved at room temperature. The clear solution was heated on a water bath until a sample gave no further coupling (with an alkaline solution of β-naphthol) and the solid which separated was filtered cold. The moist product was dissolved in warm dilute sodium hydroxide, filtered and the filtrate acidified with hydrochloric acid. The precipitated cinnoline (4.6 g., m.p. 320°, decomp.) was dried and on recrystallisation from boiling acetic acid yielded pure 6,7-dichloro-4-hydroxycinnoline (3 g., 57%), m.p. 327° (decomp.), as small brown crystals (Found: C, 44.8; H, 2.4; N, 13.35; Cl, 32.5. Calc. for $C_8H_4O N_2Cl_2$: C, 44.7; H, 1.9; N, 13.0; Cl, 33.0%).

This method was identical with an authentic sample prepared by Mr. J. R. Keneford and the following derivatives were prepared.

6,7-Dichloro-4-acetoxycinnoline.- The above cinnoline (0.3 g.) was refluxed with acetic anhydride (0.5 c.c.) for 1 hour and cooled; there separated from the red solution almost colourless needles (0.25 g.), m.p. $147-149^{\circ}$, alone and when

mixed with a sample (m.p. 148-150°) similarly prepared from authentic 6,7-dichloro-4-hydroxycinnoline (Found: N,11.15; Cl,27.5. $C_{10}H_6O_2N_2Cl_2$ requires C,10.9; H,27.6.).

4,6,7-Trichlorocinnoline.- An intimate mixture of the hydroxycinnoline (0.5 g.) with phosphorus pentachloride (0.5 g.) and phosphorus oxychloride (1.6 c.c.) was heated on a steam bath for 1 hour. Excess oxychloride was removed under reduced pressure and the dry solid digested repeatedly with ligroin (60-80°); the ligroin solution (charcoal) yielded on concentration 4,6,7-trichlorocinnoline (0.35 g.), m.p. 141.5-142.5°, alone and when mixed with an authentic sample (Found: C,41.5; H,1.8; N,12.65; Cl,44.7. Calc. for $C_8H_3N_2Cl_3$: C,41.1; H,1.3; N,12.0; Cl,45.6.).

6,7-Dichloro-4-phenoxycinnoline.- The foregoing chloro-compound (0.2 g.) was heated in a solution of potassium hydroxide (0.05 g.) with phenol (0.6 g.) for one hour. The mixture was cooled, basified with dilute sodium hydroxide and extracted with ether. After washing with water, evaporation furnished tiny colourless needles, m.p. 162-163° (after recrystallisation from absolute alcohol). Admixture with authentic material produced no depression in melting point (Found: C,57.6; H,2.75; N,9.8; Cl,24.7. Calc. for $C_{14}H_8ON_2Cl_2$: C,57.7; H,2.8; N,9.6; Cl,24.4.).

Diazotisation of 4-chloro-3-nitro-2-aminoacetophenone in
hydrochloric acid.

A suspension of the amine (0.67 g.) in 6N hydrochloric acid
(30 c.c.) was diazotised at room temperature with solid sodium
nitrite (0.25 g.). The amine only reacted slowly and after
several hours the last traces of solid dissolved on warming.
Prolonged heating on a steam bath caused separation of colourless
needles, m.p. 220-225°. After reprecipitation from alkali as
above the cinnoline was recrystallised from alcohol, from which it
separated in colourless needles, m.p. 242-245° (slow decomp.).
Pure 7,8-dichloro-4-hydroxycinnoline had m.p. 253-254° (Found:
C,45.1; H,2.2; N,13.2; Cl,33.1. $C_8H_4ON_2Cl_2$ requires C,44.7; H,1.9;
N,13.0; Cl,33.0).

The following derivatives were prepared exactly as above.

4,7,8-Trichlorocinnoline.- From petroleum ether (60-80°) in
colourless needles, m.p. 217-218° (Found: C,41.1; H,1.5; N,12.65;
Cl,45.5. $C_8H_3N_2Cl_3$ requires C,41.1; H,1.3; N,12.0; Cl,45.6).

7,8-Dichloro-4-phenoxycinnoline.- This compound was much
less soluble in ether and alcohol than the other isomer (above)
and separated from ethyl acetate in colourless blades, m.p. 214.5°.
(Found: C,57.6; H,2.75; Cl,24.6. $C_{14}H_8ON_2Cl_2$ requires C,57.7;
H,2.8; N,9.6; Cl,24.4).

Mixed melting points of these compounds with authentic
7,8-dichloro-derivatives (prepared later by Mr. J. R. Keneford)
showed no depressions.

Deamination of 4-chloro-5-nitro-2-aminoacetophenone.

(a) A well stirred suspension of the amine (0.5 g.) in hydrochloric acid (6 c.c., 6N) was diazotised with 10. aqueous sodium nitrite (2 c.c.). Some unchanged amine (0.2 g.) was filtered off and the filtrate added at 0° to stirred hypophosphorous acid (10 c.c., 30.). After 4 hours at 0°, there separated a small amount of solid, m.p. (82) 84-87°, depressed by 3,4-dichloroacetophenone in spite of the similarity in smell. Recrystallisation from absolute alcohol yielded almost pure 4-chloro-3-nitroacetophenone, m.p. and mixed m.p. 97.5-99°.

(b) The amine (3 g.) was diazotised as above and the filtrate (unchanged material, 1.5 g.) heated on a steam bath until a slight turbidity was noted, cooled and added at 0° to hypophosphorous acid (60 c.c.). An obvious reaction occurred and the solid was digested with dilute sodium hydroxide and filtered, washed and dried (0.66 g., m.p. 71-73°). Sublimation at 50-60°/0.05 mm. yielded pure 3,4-dichloroacetophenone, m.p. 76-77°, as tiny colourless needles.

Deamination of 4-chloro-3-nitro-2-aminoacetophenone.

The amine (1 g.) was suspended in 6N hydrochloric acid (44 c.c.) and diazotised with solid sodium nitrite (0.4 g.). After standing overnight at room temperature, unchanged material (0.5 g.) was filtered off and the filtrate treated as in (b) with hypophosphorous acid (20 c.c.). The crude

3,4-dichloroacetophenone (0.25 g.), m.p. 75-76°, was best
purified as in (b); from the alkaline digestion there was
isolated 7,8-dichloro-4-hydroxycinnoline, m.p. and mixed m.p.
253-254°.

7-Chloro-6-nitro-4-hydroxycinnoline.- A solution of
4-chloro-5-nitro-2-aminoacetophenone (0.5 g.) in a mixture of
acetic acid (7.5 c.c.), concentrated sulphuric acid (2 c.c.)
and water (ca. 0.5 c.c.) was treated at 0-5° with solid sodium
nitrite (0.18 g.), added during 15 minutes with hand stirring.
The somewhat turbid solution was heated on a steam bath to 85°
until no further diminution was apparent in the coupling power
of the clear red solution (ca. 1 hour). Addition of water
(100 c.c.) to the cold solution gave a dark red solid which was
purified by precipitation from its solution in N/4 sodium
hydroxide; this solid (0.3 g.), m.p. 246-248°, crystallised
from acetic acid and furnished the pure cinnoline, m.p. 252-254°
(slow decomp.), in clusters of stout bronze needles (Found:
C,42.7; H,2.05; N,18.55. $C_8H_4O_3N_3Cl$ requires C,42.6; H,1.8;
N,18.6%). The cinnoline was soluble in dilute alkalis and
moderately easily soluble in sodium bicarbonate; from its
warm solution in 2N sodium hydroxide slender yellow needles of
the sodium salt separated on cooling.

7-Chloro-8-nitro-4-hydroxycinnoline.- This was prepared
exactly as for the 6-nitro-isomer from 4-chloro-3-nitro-2-amino-
acetophenone (0.5 g.). Final purification of the product (0.3 g.),
m.p. 254-255° (decomp.), was achieved by recrystallisation from
alcohol from which the pure cinnoline, m.p. 262-264° (decomp.),
separated in yellow jagged needles (Found: C,42.8; H,2.1; N,15.9;
Cl,16.0. $C_8H_4O_3N_3Cl$ requires C,42.6; H,1.8; N,18.6; Cl,15.7.).

Reaction between 4-chloro-2-phthalimidobenzoic acid and methyl-
malonic ester.

Diethyl methylmalonate, prepared according to Organic
Syntheses (117), was shaken in ethereal solution with three
portions of ammonium hydroxide (d = 0.880), washed with 5%
sulphuric acid and then with water. The ester had b.p. 90°/12mm.
A well stirred solution of diethyl methylsodiomalonate prepared
from powdered sodium (1.6 g.), ester (14.5 c.c.) and benzene
(140 c.c.) was treated during 20 minutes with a solution of
4-chloro-2-phthalimidobenzoyl chloride from the acid (10 g.)
and phosphorous pentachloride (8 g.) . After stirring for
3 hours at room temperature the mixture was allowed to stand
overnight, decomposed with dilute hydrochloric acid and extracted
with ether-benzene. The extract was dried and on evaporation
yielded, from large volume, fine yellow needles (0.6 g.) which
crystallised from acetic acid in soft, colourless needles, m.p.
270° (decomp.with turbid orange melt); mixed m.p. with

4-chloro-2-phthalimidobenzoic acid, 235-245° (decomp.)
(Found: C,53.4; H,3.7; N,5.75; Cl,13.3. $C_{12}H_{10}O_4N$ Cl requires
C,53.8; H,3.8; N,5.2; Cl,13.3.). Further concentration yielded
an oil (23 g.) which was refluxed with hydrobromic acid
(70 c.c., d = 1.45) for 8 hours. The cold solution was basified
with ammonia and yielded by ether extraction 5.1 g. of an oil
together with crystalline material (1.15 g.), m.p. 108-117°.
After two recrystallisations from alcohol (6 c.c.) small colour-
less needles, m.p. 123.5-125°, were obtained. From other runs
(40 g. of acid) no isolation of the substance, m.p. 270°, was
undertaken and treatment with hydrobromic acid gave 18.5 g. of
an oil from which there separated crystalline material (1.5 g.).
Recrystallisation from alcohol furnished brittle colourless
needles, m.p. 152-153° (this gave a positive Beilstein test). The
remaining oil (17 g.) was heated with acetic anhydride (34 c.c.)
on a steam bath but no crystalline product was obtained.

Attempted condensation of 4-chloro-2-nitrobenzoic acid with ethyl methylacetoacetate.

The conditions were as for the acetophenone preparation
(page 43) using 13.4 g. of the benzoic acid with roughly
proportionate quantities of other reagents. Hydrolysis of the
oily product (18 g.) was effected with 15 parts (w/w) of alcoholic
sulphuric acid as before, ethyl acetate being detected in the
distillate along with methylethyl ketone (2,4-dinitrophenyl-
hydrazone, m.p. 111-113°). Distillation of the oil from the

hydrolysis gave 8.65 g. of a mobile yellow oil, b.p. 167-170°/14mm.
This material (0.3 g.) was refluxed for 1½ hours with benzaldehyde
(0.3 g.) in 2 c.c. of alcohol containing 3 drops of 30% aqueous
potassium hydroxide; the derivative (70 mg.), presumed to be a
chalkone, crystallised from alcohol in fine colourless needles,
m.p. 292°, analysis indicated this to be potassium 4-chloro-2-
nitrobenzoate (Found: C,35.0; H,1.5; Cl,14.5; Ash,28%.
$C_7H_3O_4N$ Cl K requires C,35.1; H,1.25; Cl,14.8; K_2CO_3, 28.8%).

Reduction of the presumed nitropropiophenone (167-170°/14mm.)
(6.6 g.) in acetic acid (50 c.c.) was effected on a steam bath
using iron filings (12 g.), added during 45 minutes. Water
(30 c.c.) was added during the reaction and the oily amine
(5.8 g.) isolated by ether extraction.

The amino-compound (0.5 g.) was heated with acetic anhy-
dride (1 c.c.) on a steam bath for 30 minutes and,on cooling,
colourless crystals (0.27 g.), m.p. 77-79°, separated. Recrystal-
lisation from ligroin (b.p. 40-60°) furnished tiny jagged
needles, m.p. 80-81°, which analysis indicated as ethyl 4-chloro-
-2-acetamidobenzoate (Found: C,54.7; H,5.25; N,6.3; Cl,14.4.
$C_{11}H_{12}O_3N$ Cl requires C,54.6; H,5.0; N,5.8; Cl,14.7%).

The preparation and properties of some 4-Methylcinnolines.

The aims of this section of the investigation were twofold;

(1) to confirm Widman's synthesis of 4-methylcinnoline-7-carboxylic acid, and

(2) to extend his method to the preparation of other 4-methylcinnolines. Each of these aims was realised.

Reference has been made earlier (page 46) to the historical aspects of Widman's discovery. In the present study his clear expression of practical conditions together with some assessment of alternative methods was of value in the selection of a preparative route to the cinnoline; a chart of Widman's work appears on page 157. Nitration of cuminal (I) gave consistent yields (96%) of the pure nitro-compound (II) although later runs (using cuminal and acids from different sources) provided variable (average 56.) yields of pure nitrocuminal together with an oil which resisted nitration under the standard conditions. Oxidation of nitrocuminal with warm permanganate yielded mainly nitrocuminic acid (III) which, as noted by Widman (185), was comparatively resistant to further oxidation; the hydroxylpropylbenzoic acid (IV) was obtained only by refluxing nitrocuminal with a large excess of permanganate for 10-12 hours. Dehydration to (V) with concentrated sulphuric acid at room temperature was satisfactory but Widman's procedure for the reduction to (VI) gave variable results. Reversal of the order

The routes to 4-methylcinnoline-7-carboxylic acid (Gldman).
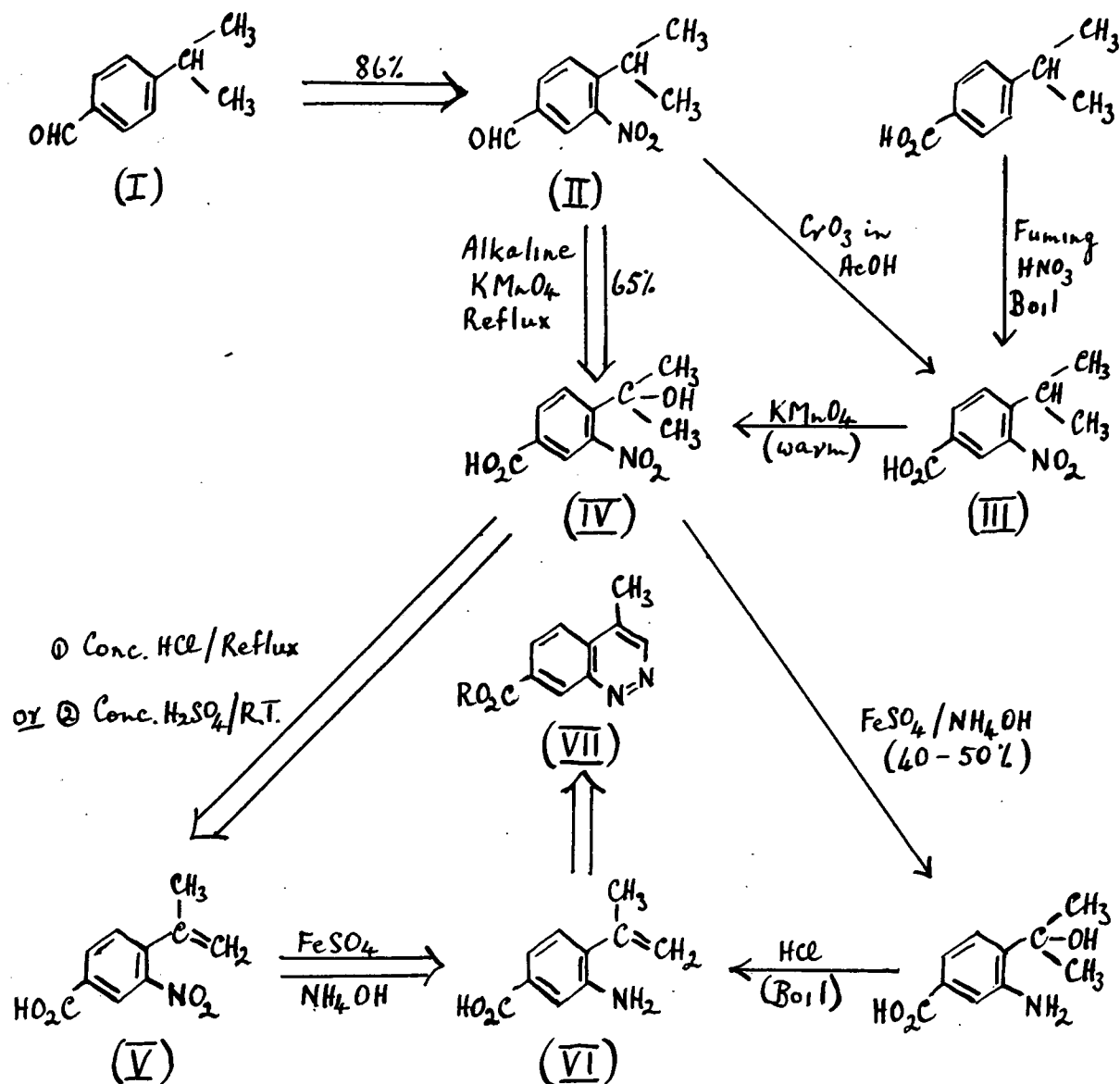
$\Rightarrow$ Indicates the route chosen for preparative purposes in the present investigation.

Numbers indicate the yields obtained by Gldman, where these were stated.

of addition (thus addition of an ammoniacal solution of the nitro-
acid to ferrous hydroxide) and isolation of the amine hydrochloride
(instead of Widman's tedious extraction of the base) gave
consistently good yields. The original method of diazotisation
using an aqueous solution of the hydrochloride proved wholly
successful, although preliminary experiments were carried out using
excess hydrochloric acid; in the latter procedure isolation was
effected by addition of excess sodium phosphate. Purification
of the crude cinnoline via the ethyl ester (VII, R = Et) was found
to be most adaptable to preparative work.

   The first successful extension of Widman's synthesis("2" above)
was reached in the preparation of 6-chloro-4-methylcinnoline.
5-Chloro-2-aminoacetophenone (VIII), prepared by the method already

$$(\underline{VIII}) \qquad (\underline{IX}) \qquad (\underline{X}) \qquad (\underline{XI})$$
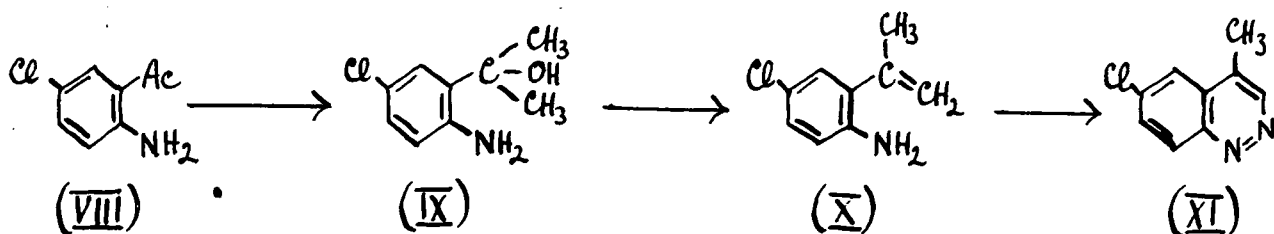
described (153), was converted by a Grignard reaction into a solid
which was recovered from treatment with hot 5N sulphuric acid.
Analysis indicated that this compound was the carbinol (IX) although
the unusual stability towards sulphuric acid caused it to be
regarded initially as the ethylene[*], produced by spontaneous
dehydration of the Grignard product. This stability towards

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[*] Diazotisation of the "ethylene" was carried out before the receipt
of analysis figures but the non-phenolic fraction was only subjected to
preliminary tests.

sulphuric acid is interesting in view of the ease of dehydration
of carbinols to give other o-aminoethylenes (e.g. XII; $R_1 = R_2 = Ph$;
$R_1 = Ph$, $R_2 = CH_2Ph$) using even less drastic conditions (150, 152).
Moreover, the compound (XIII) has been obtained (17) simply by

$(\underline{XII})$ $(\underline{XIII})$ $(\underline{XIV})$
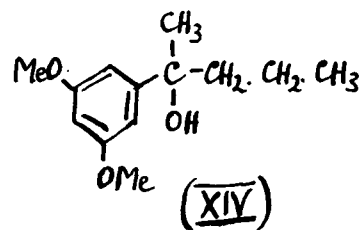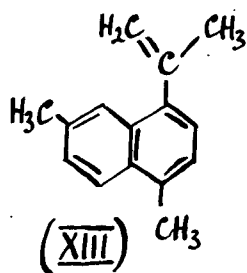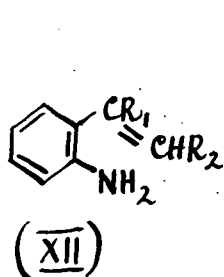
boiling the corresponding carbinol with alcoholic picric acid, whilst
dehydration of (XIV) to the ethylene was accomplished (2) by
distillation under reduced pressure with "a few drops of 20% sulphuric
acid". An attempt to dehydrate dimethyl (5-chloro-2-aminophenyl)
carbinol (IX) using concentrated sulphuric acid at room temperature
resulted in pronounced sulphonation but dehydration with only slight
sulphonation was achieved using hot 18N sulphuric acid; preparation
of N-benzoyl derivatives confirmed the success of this dehydration.
Diazotisation of the ethylene (X) in hydrochloric acid (actually a
suspension of the hydrochloride) and subsequent warming of the
diazotised solution yielded 6-chloro-4-methylcinnoline (XI) together
with purple tarry material. The latter, best removed by chromato-
graphic adsorption on alumina, was not further examined.

The route to 4-methylcinnoline (XVIII; R = H) is exactly
analogous to that used for the 6-chloro-derivative. The carbinol
(XVI; R = H) was prepared initially from o-aminoacetophenone, itself

obtained from acetophenone (153), but the same result could be more easily reached using methyl anthranilate (XV; R = H). The early work on this synthesis was conducted alongside that on 6-chloro-4-

R—C₆H₃(CO₂Me)(NH₂) (XV) → R—C₆H₃(C(CH₃)₂OH)(NH₂) (XVI) → R—C₆H₃(C(CH₃)=CH₂)(NH₂) (XVII) → R—[4-methylcinnoline] (XVIII)

(XV)   (XVI)   (XVII)   (XVIII)
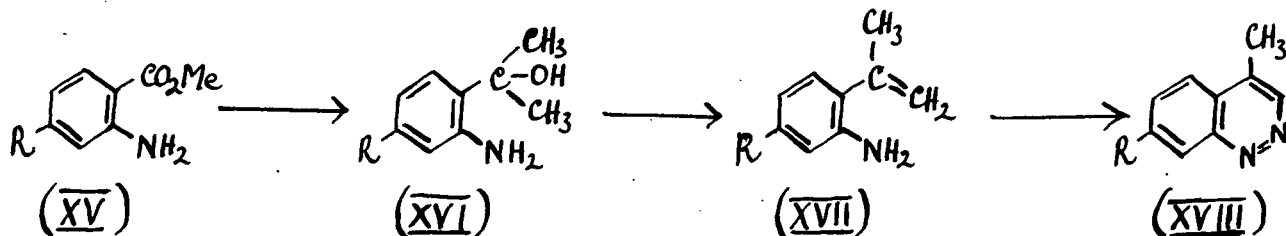
methylcinnoline and the same mistaken assumption was made regarding the ease of dehydration of the carbinol (XVI; R = H) using hot 5% sulphuric acid. Moreover, this carbinol was unchanged by hot 18N sulphuric acid (cf. page 159) and pronounced sulphonation attended the use either of concentrated acid at room temperature or of 27N acid at 90°. In the search for alternative methods of dehydration various high temperature techniques (45) were rejected in view of the possibility of polymerisation (cf., 17). Treatment with phosphorus pentoxide in boiling benzene, a modification of the well known method of ring closure (at 140°) involving loss of water, furnished the required ethylene (XVII; R = H). After removal of a small amount of acid-insoluble oil from the crude ethylene it was diazotised; on warming the diazotised solution some bright green oily material and a small phenolic fraction as well as a moderate yield of 4-methylcinnoline was produced. Chromatography on alumina did not improve the colour of the product whilst distillation under reduced pressure did not appear applicable to preparative work.

While dehydration conditions for the carbinol (XVI; R = H) were being sought, an attempt was made to facilitate dehydration by rendering the nucleus less susceptible to sulphonation. Nitration of dimethyl-(o-acetamidophenyl)carbinol gave as sole isolable product a mono-nitro-derivative of the corresponding ethylene but attempts to reproduce this result on a larger scale were unsuccessful.

Since the completion of this work on 4-methylcinnoline publication of an interesting study of 4-substituted-cinnolines by American workers (75) has been noted. This investigation, based upon biochemical observations, is summarised by reproduction of a chart (page 162). Dehydration of the carbinol was effected by refluxing in toluene with a trace of iodine and the ethylene was purified by distillation. After diazotising in sulphuric acid cyclisation (at room temperature) to the cinnoline was carried out at great dilution and in the dark. The crude cinnoline was obtained in 89-90% yield (based on the ethylene) by continuous extraction of the basified solution with benzene.

The use of the methyl anthranilate as starting material instead of the o-aminoacetophenone was extended to the 4-chloro-derivative in the preparation of 7-chloro-4-methylcinnoline. Methyl 4-chloro-anthranilate (XV; R = Cl) was prepared from the acid by an improved modification of Munn's method (74) and was thus much more accessible than the o-aminoacetophenone (page 110). The carbinol (XVI; R = Cl), obtained by a Grignard reaction, was smoothly dehydrated by phosphorus

4-Substituted Cinnoline Derivatives (Jacobs et al.).

---> Indicates attempted reactions.

pentoxide and the success of this process was confirmed by the preparation of distinct N-acetyl derivatives of the carbinol and ethylene. 5-Chloro-2-_isopropenylaniline_ (XVII; R = Cl) formed a crystalline hydrochloride with dilute hydrochloric acid and diazotisation furnished 7-chloro-4-methylcinnoline (XVIII; R = Cl) in good yield; a small amount of a green impurity was also formed.

The synthesis of 4-methyl-3-phenylcinnoline, interesting on account of possible steric effects on the reactivity of the methyl group and also as a route (by oxidation) to 3-phenyl-cinnoline-4-carboxylic acid (see page 207), was not completed. The carbinol from the reaction between benzylmagnesium chloride and o-aminoacetophenone was unchanged by 5% sulphuric acid.

In the foregoing routes to 4-methylcinnolines reference to yields has been omitted since the latter were complicated by variations which depended upon the scale of each stage. This is illustrated by the following typical runs.

(Table overleaf).

Methyl anthra- nilate	Carbinol		Ethylene		4-Methyl- cinnoline	Yield % of cinnoline based on ester.
25 g.	28 g. *	12.3 g.	12 g.		6 g.	58
50 g.	53 g.	26.5 g.	26 g.	13 g.	3.5 g.	23
4-Chloro- deriv.					7-Chloro- deriv.	
12 g.	14.7g.	10 g.	9.1 g.		5.4 g.	72
30 g.	30 g.		26.5 g.	20 g.	11.7 g.	54

* where two figures are entered in one column the first refers to the yield from the preceding column and the second indicates the quantity subjected to the next stage.

This irregularity in the extent of cinnoline formation is only apparent since it must be remembered that neither the carbinols or the corresponding ethylenes were purified. Thus the presence of undesirable by-products from the Grignard reaction as well as incomplete dehydration (due to the heterogeneous character of the procedure) were both intensified on the large scale and only discernable at the cinnoline stage in the form of a lower yield. A consideration of the solubilities of the methylcinnolines in water and ether respectively (see later) combined with the tendency to use proportionately less ether for large scale extractions is another factor which probably contributed to the reduced yields. It is not surprising that wide divergencies in yield were absent in the case of

6-chloro-4-methylcinnoline since the carbinol was purified and the dehydration mixture was completely homogeneous. The high yield of 4-methylcinnoline obtained by American workers (page 162) is clearly explicable in view of the contributory factors mentioned above; no estimate can be made of the effect exerted by their method of cyclisation.

The relation between nuclear substituents and the ease of cyclisation of o-isopropenylanilines cannot be defined on the basis of the above results but formation of 4-methylcinnolines is definitely much more rapid than that of 4-hydroxycinnolines. This constitutes striking evidence of the powerful hyper-conjugation (47) exerted by the methyl group of the diazotised ethylenes since it is this effect which creates an essential for cinnoline formation, viz., anionoid character in the terminal carbon atom of the diazotised aniline.

The expected similarities in the properties of 4-methyl-cinnolines are fully realised only if the earliest example (Widman's acid) is considered separately; indeed, the wide variation of some properties is surprising. 4-Methylcinnoline-7-carboxylic acid is practically insoluble in water but can be recrystallised from alcohol in which it is somewhat less soluble than in acetic acid. In contrast, 4-methylcinnoline is very easily soluble in cold water or alcohol and the 6- and 7-chloro-derivatives are progressively (though only slightly)

less soluble; these 4-methylcinnolines can all be recrystallised from ligroin (b.p. 60-80°) and are only moderately soluble in ether. Although insoluble in water, Widman's acid dissolves easily in dilute hydrochloric acid but a parallel test using 4-methylcinnoline is less instructive in view of the great water-solubility of this compound. The chloromethylcinnolines appear to dissolve only in distinctly acid solutions (pH ca. 3). Both 4-methylcinnoline and the chloroisomers gave characteristic bright green picrates whilst red (or orange-red) ethiodides were formed by these cinnolines as well as by the ethyl ester of Widman's acid. Even under the mild conditions of refluxing alcohol conversion to the ethiodide appeared to be complete since (in the case of 4-methylcinnoline) no unchanged material could be detected. These ethiodides suffered irreversible decomposition by even the smallest amounts of alkali; this change was accompanied by striking colour changes when piperidine or diethylamine was used (see page 5).

Reactions of 4-Methylcinnolines.

Although the predominance of 4-substituted cinnolines
arises mainly from the essential requirements for cinnoline
formation (page 73) the great reactivity of many of these
substances (e.g., page 56) can only be considered as a
property of the cinnoline nucleus. It is believed that this
property arises from the fact that N_1 is the basic centre of
the molecule and other results are suggestive of the same
state of affairs. Thus 4-aryl and -alkyl cinnolines are
easily quaternised with boiling alcoholic ethyl iodide
whilst 4-hydroxycinnolines existing, presumably, as the
1:4-dihydrocinnolones, are unaffected by this treatment.
Further, various 3:4-disubstituted cinnolines yield monoxides
(page 194) whilst 3:4-benzocinnolines can form dioxides
(page 68); clearly, in the latter examples both nitrogen
atoms lose the individuality which they possess in the former.

The exceptional reactivity of 4-chlorocinnolines (above)
is undoubtedly the most powerful argument for N_1 basicity and
some realisation of C_4-reactivity in other groups appeared to
offer the most direct support for this hypothesis. The choice
of 4-methylcinnolines for this purpose was considered appropriate
because of the wide variety of reactions by which possible
reactivity might be tested whilst the practical value of any
products formed would not be inconsiderable. It was also of

interest to confirm for cinnolines the general relationship
between the reactivity of chloro- and methyl-substituents first
mentioned by Mills (109).

One type of reaction which has been used widely with
reactive methyl groups in heterocyclic molecules is the
condensation of the reactive compound with an aromatic aldehyde.
In connection with "conventional procedures" applied to the
preparation of styrylpyrimidines and quinolines Gilman and
Karmas (68) referred to Kaplan and Lindwall (78) and to
Shaw and Wagstaff (148). The latter workers brought about
condensation between 2-picoline and aromatic aldehydes by
refluxing in acetic anhydride, a technique used earlier by
Bennett and Pratt (19); purer products in higher yield were
claimed by Shaw and Wagstaff but application of this method
to the preparation of 2(p-dialkylaminostyryl)quinolines by
Tipson (172) gave inferior yields. In the present investigation
4-methylcinnoline-7-carboxylic acid was reacted with o-nitro-
benzaldehyde in acetic acid at 120° with anhydrous zinc
chloride as 'catalyst', a modification of the method of
Kaplan and Lindwall. The product gave analysis figures in
reasonable agreement with those calculated for 4-(o-nitrostyryl)
cinnoline-7-carboxylic acid, although it was insoluble in
sodium carbonate or hydroxide solutions; no agreement could be

reached using any figures based upon a decarboxylated molecule.
A preliminary run yielded a trace of alkali-soluble material
which was not further investigated. Treatment of 4-methyl-
cinnoline with p-dimethylaminobenzaldehyde at 160° in acetic
anhydride furnished a small amount of a solid, m.p. 130-156°,
which was not purified; no reaction occurred on merely fusing
the two components at 100° in the presence of a trace of
piperidine. That no striking evidence[*] of reactivity was noted
was not surprising in view of the variety of techniques which
might be tried and the possibilities of mixtures being formed.

The generalisation that the reactivity of a methyl group
situated α or γ with respect to a cyclic nitrogen atom is
enhanced by quaternisation of the latter was fully upheld in
the present study. It was demonstrated for α-picoline and
quinaldine (109) by the action of p-nitrosodimethylaniline
which reacted only with the quaternary salts of these compounds;
the finding that this enhancement of activity was not bestowed
upon a methyl group originally devoid of activity was used to
support the theory that reactivity depends on the possible
formation of a reactive methylene base by migration of an
hydrogen atom from methyl to nitrogen. This hypothesis was
extended later (110) to quaternised derivatives and the mechanism
of catalysis by bases, a device used by Königs (87), was

[*] Such evidence was obtained by American workers (see page 162)
by the preparation of 4-styrylcinnoline in theoretical yield.

discussed. This use of a trace of pyridine, piperidine, di-
methylamine or trimethylamine either in aqueous alcohol or
acetic anhydride has been shown to be wholly detrimental in
the case of cinnoline ethiodides in view of the decomposition
which they undergo in the presence of alkalis (page 185).
However, reaction of the ethiodides of 4-methylcinnoline and
its 6-chloro-, 7-chloro-, and 7-carbethoxy-derivatives with
p-dimethylaminobenzaldehyde took place in boiling acetic
anhydride in the absence of any added catalyst. The yields
of styryl cinnolinium compounds were low but attempts (with
4-methylcinnoline ethiodide) to improve the yield using basic
catalysts gave low melting material. The most striking results
were obtained using absolute alcohol as solvent and no added
catalyst; an intense blue colour developed on warming for a
few minutes and on heating for some time the styryl-derivative
(identical with that from acetic anhydride and in good yield)
separated in lustrous green-blue needles. The fact that such
a simple procedure yielded the evidence necessary to pronounce
the methyl group on C_4 as definitely reactive is striking, since
the vast literature of cyanine dyes and simpler coloured
compounds of the type under investigation contains many examples
of the use of curious empirical methods to achieve a certain
reaction. The synthesis of a series of cyanine dyes from

4-methylcinnoline ethiodides and subsequent study of their spectra would provide interesting comparative data; for example, the relative basicities of cinnoline and related heterocycles might be determined (cf. 30 and 20).

The preparation of phthalones from other heterocyclic compounds having a reactive methyl group is well known, quinoline-yellow dyes being prepared from quinaldines and phthalic anhydride by heating with or without a condensing agent. Bogert and Heidelberger (22) describe a similar reaction with 2-methyl-4-quinazolone and refer to parallel examples in the pyridine, benzimidazole and phthalazine fields. Distinct signs of a reaction were noted between Widman's acid and phthalic anhydride in the presence of anhydrous zinc chloride but no product could be isolated. Using 4-methylcinnoline, with or without zinc chloride, only unchanged material (in 5% and 10% yield respectively) could be isolated. This failure to recover unchanged material in substantial yield constitutes evidence, although negative in character, of the reactivity of the methyl group. The use of a diluent in such reactions has already had success (19b) and is an obvious choice for further work in this direction.

An attempt to oxidise the methyl group of Widman's acid by means of freshly prepared (77) selenium dioxide in aqueous dioxane gave no crystalline material although this was not

surprising in view of the capricious nature of this reagent
(e.g. 38 , 91). 4-Methylcinnoline was rapidly oxidised at
25° by aqueous permanganate but the only isolable product,
other than unchanged starting material, was obtained as the
picrate, m.p. 342° (decomp.); this decomposed violently on
combustion and gave no useful analytical data. The reduction
of 4-methylcinnolines is dealt with later (page 191).

A single condensation of 4-methylcinnoline with diazotised
aniline (cf. 86) gave a low melting purple solid which could
not be purified; attempts to prepare a crystalline hydrochloride
were unsuccessful.

A preliminary attempt to carry out a Mannich reaction (118)
between ethyl 4-methylcinnoline-7-carboxylate, diethylamine and
formaldehyde gave a trace of a crystalline picrate, m.p. 127-150°;
other conditions were not investigated.

A more general study of 4-methylcinnolines was envisaged;
reaction with a mixture of nitric and sulphuric acids led to
a poor yield of a substance, m.p. 131-133° (decomp.), from the
basified nitration mother liquor. When nitric acid alone was
used there was obtained a curious product, m.p. 124-128°, which
dissolved in sodium carbonate solution with transient formation
of a violet coloured oil; it appeared to form a hygroscopic
hydrate, m.p. 131-135°, on recrystallisation from alcohol but
mixed melting point determinations with the former product

(insoluble in sodium carbonate) were inconclusive. A complete study of the nitration of 4-methylcinnoline would be most interesting, the problem of orientation being attacked by synthesis (from nitro-acetamido-ethylenes,cf. page 161), by conversion to available methylcinnolines and by degradation (e.g. to indoles).

A survey of the literature associated with the above selection of reactions has indicated a distinct lack of reliable comparative data between related benzodiazines. It is believed that emphasis on comparative experiments will (for a given reaction) contribute more to the chemistry of each group of diazines than will be the case if development follows its present course.

4-METHYLCINNOLINES.

Compound	Melting point	Solvent for recrystallisation,colour and form.
4-Methyl-cinnoline	76-77°	Ligroin (b.p. 60-80°). Slender golden needles.
6-Chloro-	157°	Ligroin. Fine colourless needles.
7-Chloro-	119-120°	Ligroin. Pale yellow needles or leaflets.
7-Carb-ethoxy-	117°	Ether. Pale yellow plates.
-7-carb-oxylic acid	248-250°	Acetic acid. Small colourless needles.

Derivatives of 4-methylcinnolines (e.g.picrate, ethiodide, 4-dimethylaminostyryl) are not listed here since they are presented in compact form in the experimental section (page 184-5).

EXPERIMENTAL.

(Melting points are uncorrected).

4-Methylcinnoline-7-carboxylic acid.- Cuminal (50 g.) was added dropwise during 40 minutes to a well stirred mixture of nitric acid (250 c.c., $d = 1.525$) and concentrated sulphuric acid (260 c.c.). The reaction temperature was maintained at -5° but was allowed to rise to 10° after the addition of cuminal. The clear solution was poured on ice and the yellow granular solid filtered, washed with sodium carbonate solution and finally with water. The yields of pure material, m.p. 54°, were variable (average 56%).

Nitrocuminal (20 g.) was refluxed with 5% potassium permanganate solution (2.2 l) until an excess of the latter persisted (10 hours). Excess permanganate was destroyed and the hot mixture filtered; acidification of the filtrate furnished colourless needles, m.p. $185-187^\circ$, of 3-nitro-4-hydroxypropylbenzoic acid (11.6 g., 50%). The pure compound, m.p. $191-192^\circ$, was obtained by recrystallisation from benzene (Found: C,53.5; H,5.0. Calc. for $C_{10}H_{11}O_5N$: C,53.3; H,4.9%). Dehydration of this hydroxypropylbenzoic acid (20 g.) was achieved by dissolving in concentrated sulphuric acid (100 c.c.) at room temperature and allowing to stand for 1 hour. The clear red solution was poured into iced water and the precipitated solid filtered and purified by reprecipitation from its solution in

sodium hydroxide. The crude material (17.2 g.) was recrystallised from aqueous alcohol and had m.p. 153-154° (15.2 g., 82.5%). For reduction 3-nitro-4-isopropenylbenzoic acid (5 g.) was dissolved in aqueous ammonia (2 c.c., D = 0.880; 14 c.c. water) and added, with shaking, during 10 minutes, to a suspension of ferrous hydroxide prepared from ferrous sulphate (50 g.) in water (100 c.c.) and concentrated ammonia (25 c.e.). A distinct rise in temperature was noted and the reaction was completed by heating on a steam bath for 30 minutes. The hot sludge was filtered, washed well with water and the combined filtrate concentrated under reduced pressure to ca. 250 c.c. Addition of hydrochloric acid (12N, 150 c.c.) precipitated the hydrochloride of 3-amino-4-isopropenylbenzoic acid, m.p. 230-240° (decomp.), as colourless needles (3.5 g., 68%).

For diazotisation, the crude hydrochloride (5 g.) was dissolved in water (50 c.c.) and treated at 0° with 10% aqueous sodium nitrite (18 c.e.); an immediate precipitate was formed and the coupling power quickly faded, being negligible after several hours at room temperature. The crude methylcinnoline (4.2 g.), m.p. 238-241° (decomp.) was purified either (a) by repeated digestion with boiling water and recrystallisation of the insoluble portion from alcohol, (b) by direct recrystallisation from acetic acid, or preferably (c) via the ethyl ester.

Widman's acid (9.1 g.) was suspended in 10 parts of absolute alcohol and the mixture saturated at 0° with dry hydrogen chloride.

After refluxing for ½ hour, the mixture was again saturated, concentrated somewhat, cooled and poured into an excess of sodium carbonate solution. Extraction with ether yielded ethyl 4-methylcinnoline-7-carboxylate (7 g.), m.p. 116-117°; a pure specimen crystallised from ether in pale yellow plates, m.p. 117° (Found: C,66.5; H,5.4; N,13.15. $C_{12}H_{12}O_2N_2$ requires C,66.7; H,5.6; N,13.0%). The ester (5 g.) was hydrolysed by refluxing for 3 hours with 10% aqueous potassium hydroxide (60 c.c.) and the free acid (4.2 g.), m.p. 245-250° (decomp.), isolated by pouring into 50% aqueous acetic acid (40 c.c.). Pure 4-methylcinnoline-7-carboxylic acid, m.p. 248-250°, was obtained by recrystallisation from acetic acid (Found: C,63.5; H,4.4; N,15.25. Calc. for $C_{10}H_8O_2N_2$: C,63.8; H,4.3; N,14.9%).

The preparation of 4-methylcinnoline.

Dimethyl-o-aminophenyl carbinol.- (a) From o-aminoaceto-phenone: A solution of o-aminoacetophenone (5 g.) in ether (50 c.c.) was added during 15 minutes to a Grignard solution prepared from magnesium (5 g.), methyl iodide (27 g.) and ether (100 c.c.). The green solution, formed after temporary separation of a red solid, was refluxed for 1½ hours and then decomposed with an ice-ammonia-ammonium chloride mixture. Ether extraction and subsequent evaporation of the washed and dried extract yielded a red oil (6.3 g.).

(b) From methyl anthranilate: A solution of methyl anthranilate (50 g. in 50 c.c. of dry ether) was added dropwise to a well stirred Grignard solution prepared from magnesium (40 g.), methyl iodide (240 g.) and ether (750 c.c.). A yellow solid appeared and redissolved to give a green solution which was refluxed for ca. ½ hour. The dark coloured complex was added to ice (etc.) and the ethereal extract was washed, dried and evaporated to give 55.4 g. of an oil.

Acetylation of a portion with cold acetic anhydride (2 parts) and recrystallisation of the solid product from benzene gave the pure N-acetyl derivative, m.p. 145-146°, identical with authentic material prepared from (a) (Found: C,68.0; H,7.65; N,7.2. $C_{11}H_{15}O_2N$ requires C,68.4; H,7.8; N,7.25%).

o-Isopropenylaniline.- A solution of the above carbinol (30 g.) in benzene (300 c.c.) was refluxed with phosphorus pentoxide (60 g.) for 3 hours. The cold mixture was treated with successive quantities of iced ammonium hydroxide and the alkaline solution extracted with ether. Evaporation of the washed and dried extract yielded ca. 30 g. of a mobile oil; this was distinct from the carbinol since treatment with cold acetic anhydride gave no sign of a reaction and no crystalline product was obtained.

4-**Methylcinnoline**.- The above ethylene (12 g.) was dissolved in hydrochloric acid (80 c.c. of 2N and 20 c.c. of 12N) and a trace of insoluble oil removed with ether. The aqueous layer was freed from ether and the clear yellow solution cooled to 5° when fine leaflets of the amine hydrochloride separated. This suspension was diazotised with sodium nitrite (5.1 g.) to yield a clear green solution (positive coupling) which changed to red on heating to 60° (no coupling). Basification with sodium acetate solution gave an oily product which was extracted with ether and the extract washed with sodium hydroxide solution then with water, dried, and evaporated. The resultant green oil (8.8 g.) which crystallised readily on standing was digested with boiling ligroin (b.p. $60-80^\circ$) and concentration of the solution so formed furnished the cinnoline (6 g., 46%), m.p. $74-75^\circ$. Pure 4-**methylcinnoline**, m.p. $76-77^\circ$, separated from the same solvent in slender golden needles (Found: C, 74.9; H, 5.35; N, 20.0. $C_9H_8N_2$ requires C, 75.0; H, 5.6; N, 19.45%). The cinnoline was moderately soluble in ether but very easily soluble in water; the solution in hydrochloric acid was red in colour.

Nitration of dimethyl-2-acetamidophenyl carbinol.- The acetamido-derivative (0.5 g.) was added during 15 minutes to a mixture (5:2, 3 c.c.) of nitric acid ($d = 1.487$) and sulphuric acid ($d = 1.84$) at 15°. The mixture was allowed to stand at

the same temperature for another 15 minutes, added to ice and the clear solution basified with ammonia. After one crystallisation from aqueous alcohol, the product (0.34 g.), m.p. 87-88°, was recrystallised from ligroin from which it separated either in small yellow plates or as heavy colourless prisms, m.p. 88-89° (Found: C,60.2; H,5.6; N,13.05. $C_{11}H_{12}O_3N_2$ requires C,60.0; H,5.5; N,12.7%), i.e. dehydration and mono-nitration have occurred.

The preparation of 6-chloro-4-methylcinnoline.

Dimethyl-(5-chloro-2-aminophenyl)carbinol.- A solution of 5-chloro-2-aminoacetophenone (30 g.) (153) in dry ether (400 c.c.) was added during ca. 1 hour to a well stirred solution prepared from magnesium (20 g.), methyl iodide (120 g.) and ether (900 c.c.). A temporary red precipitate dissolved on stirring and the mixture was refluxed for a further 30 minutes then poured on to a mixture of ice and ammoniacal ammonium chloride. The washed and dried ethereal extract was evaporated to small volume and ligroin (b.p. 40-60°) added to give the carbinol (29.3 g.), m.p. 80-84°. The pure carbinol, m.p. 83-84°, separated from ether-ligroin in almost colourless needles (Found: C,58.3; H,6.35; N,8.65. $C_9H_{12}ONCl$ requires C,58.2; H,6.5; N,7.5%). Treatment of a portion with cold acetic anhydride (3 parts) and recrystallisation of the product from benzene-ligroin (b.p. 40-60°) furnished the N-acetyl-derivative, m.p. 136-137° (Found: C,58.65; H,6.2.

$C_{11}H_{14}O_2NCl$ requires C,58.0; H,6.15%). The N-benzoyl-derivative, prepared in pyridine using benzoyl chloride at ca. 90°, formed tiny glistening prisms, m.p. 148-153°, from aqueous alcohol (Found: C,66.3; H,5.5; N,5.2. $C_{16}H_{16}O_2NCl$ requires C,66.3; H,5.6; N,4.8%).

4-Chloro-2-isopropenylaniline.- Dehydration of the above carbinol (12 g.) was effected by treatment with sulphuric acid (160 c.c. of 50%, v/v) for one hour at 98° (steam bath), the carbinol being added gradually to the acid at first. The solution was cooled, diluted somewhat, basified with ammonia and extracted with ether; the extract yielded an oil which crystallised partly on standing. A portion was converted to the N-benzoyl-derivative (of 4-chloro-2-isopropenylaniline) as above, this compound separating from aqueous alcohol in clusters of fine needles, m.p. 126-127° depressed to 106-109° by the N-benzoylated carbinol. (Found: C,71.4; H,5.4; N,5.65. $C_{16}H_{14}ONCl$ requires C,70.7; H,5.2; N,5.15%).

6-Chloro-4-methylcinnoline.- A solution of the foregoing ethylene (12 g.) in hydrochloric acid (50 c.c.6N) was cooled to 0-5° and the suspended hydrochloride treated with 10% sodium nitrite solution (48 c.c.). The clear solution (strong coupling) was heated to 70° on a steam bath (when a deep purple colour was noted after a transient turbidity) and after 10 minutes at this temperature the coupling reaction was practically negative. Some tarry material which separated was filtered off (more was

deposited in the filtrate if allowed to stand overnight), washed
with a little hydrochloric acid and the combined filtrate
basified with sodium acetate solution. The mixture was extracted
with ether and the extract washed successively with sodium
hydroxide solution and water; the dried extract furnished 5.7 g.
of a solid, m.p. 123-128°. This material (10.2 g.) was dissolved
in benzene and allowed to percolate through a column of activated
alumina (50 g. "Merck"); evaporation of the eluates yielded
fractions of m.p. 128° to 136° which were purified (6.5 g., m.p.
135-136°) by reprecipitation from hydrochloric acid (with sodium
acetate), extraction with ether, and final crystallisation from
ligroin (b.p. 60-80°). Pure 6-chloro-4-methylcinnoline, m.p.
137°, crystallised from ligroin in fine, almost colourless
needles (Found: C,60.0; H,3.85; N,16.4; Cl,19.65. $C_9H_7N_2Cl$
requires C,60.5; H,3.9; N,15.7; Cl, 19.9%). The cinnoline was
only moderately soluble in cold water but more soluble in hot
water; it dissolved in hydrochloric acid (at pH about 3) and was
precipitated by sodium hydroxide solution.

The preparation of 7-chloro-4-methylcinnoline.

Methyl 4-chloroanthranilate.- A suspension of 4-chloro-
anthranilic acid (100 g.) in methanol (1 l., 98%) was saturated
at 0° with dry hydrogen chloride, the mixture refluxed for an
hour and the saturation repeated. The solution was concentrated
until almost wholly solid, added with stirring to iced water

and the resultant suspension of solid basified with ammonia and filtered. The well drained solid was best dried by dissolving in ether and adding anhydrous sodium sulphate; recrystallisation of the dry ester from ligroin (b.p. 60-80°) furnished soft colourless needles (75 g., 69%), m.p. 69° (Mann, loc. cit. gives 68.5°).

Dimethyl-(4-chloro-2-aminophenyl)carbinol.- A solution of the above ester (30 g.) in dry ether (300 c.c.) was added during ½ hour to a well stirred Grignard solution prepared from magnesium (20 g.), methyl iodide (115 g.) and ether (500 c.c.). A dark oil separated from the green solution (formed after a transient yellow precipitate) and the mixture was refluxed for 15 minutes; the crude carbinol (30 g. of an oil) was isolated as in the preparation of 4-methylcinnoline (page 179). The N-acetyl-derivative, m.p. 151-153°, obtained using cold acetic anhydride (3 parts), crystallised from benzene in short colourless prisms (Found: C,58.1%; H,6.1. $C_{11}H_{14}O_2NCl$ requires C,58.0; H,6.2%).

5-Chloro-2-isopropenylaniline.- This was prepared as above (page 177) using the foregoing carbinol (28 g.) and yielded an oily ethylene (26 g.). The N-acetyl-derivative, m.p. 68-70°, could not be prepared using cold acetic anhydride (2 parts) but was isolated as a readily crystallising oil from a reaction on the steam bath; the pure compound separated from ligroin

(b.p. 40-60°) in tiny colourless polyhedra (Found: C,63.0; H,5.35. $C_{11}H_{12}ONCl$ requires C,63.0; H,5.8%).

7-Chloro-4-methylcinnoline.- The foregoing ethylene (20 g.) formed a sparingly soluble crystalline hydrochloride with hydrochloric acid (160 c.c., 2N). Diazotisation of this suspension with sodium nitrite (6.2 g.) gave a clear solution (strong coupling) from which a solid (presumably the cinnoline hydrochloride) separated towards the end of nitrite addition (coupling faded at this stage and disappeared entirely on warming). The pure cinnoline was isolated as for the unsubstituted compound (page 178) and separated from ligroin (b.p. 60-80°) in pale-yellow needles or leaflets, m.p. 119-120°, (11.7 g., 55% based on methyl 4-chloroanthranilate) (Found: C,60.1; H,4.0; N,15.35. $C_9H_7N_2Cl$ requires C,60.5; H,3.9; N,15.7%). The cinnoline was moderately sparingly soluble in cold water and could be recrystallised from this solvent; a cold suspension in water only dissolved when the solution was made distinctly acid with hydrochloric acid and addition of sodium hydroxide solution precipitated the cinnoline.

Reaction between o-aminoacetophenone and benzylmagnesium chloride.

A solution of o-aminoacetophenone (5 g.) in dry ether (40 c.c.) was added dropwise to a Grignard solution prepared from magnesium (2.8 g.), benzyl chloride (24 c.c.) and ether (40 c.c.). A suspension of an amorphous solid soon dissolved to give a clear solution from which a crystalline complex

separated. The mixture was refluxed for one hour, decomposed in the usual way, and the product isolated by ether extraction; after concentration of the extract to ca. 100° it was washed with portions of N hydrochloric acid (90 c.c. in all) and these washings basified and again extracted. The crude carbinol was isolated as an oil (8.15 g.). Treatment of the carbinol (2 g.) with 5% sulphuric acid at ca. 90° for an hour effected no dehydration, the resultant oily product yielding a crystalline substance on treatment with cold acetic anhydride; methyl-(o-acetamidophenyl)-benzylcarbinol, m.p. 126-127°, crystallised from benzene-ligroin (b.p. 40-60°) in colourless leaflets (Found: C,75.5; H,7.1. $C_{17}H_{19}O_2N$ requires C,75.8; H,7.1%).

Picrates of 4-methylcinnolines.

The following picrates were prepared in alcohol and were recrystallised from the same solvent to give beautiful green needles. 4-Methylcinnoline picrate, m.p. 179-180° (Found: C,48.05; H,2.85. $C_{15}H_{11}O_7N_5$ requires C,48.25; H,3.0%) (see page 15). 6-Chloro-4-methylcinnoline picrate, m.p. 154-156° (decomp.) (Found: N, 17.5. $C_{15}H_{10}O_7N_5Cl$ requires N,17.2%). 7-Chloro-4-methylcinnoline picrate, m.p. 187-190° (decomp.). (No analysis).

Ethiodides of 4-methylcinnolines.

These were prepared by refluxing an alcoholic solution of the cinnoline with excess ethyl iodide for 2 hours and all formed soft red (or orange-red) needles from an alcohol-ether mixture.

4-Methyl-7-carbethoxycinnoline ethiodide, m.p. 207-208° (decomp.) (Found: C,45.3; H,4.5. $C_{14}H_{17}O_2N_2I$ requires C,45.15; H,4.6%).

6-Chloro-4-methylcinnoline ethiodide, m.p. 200-202° (decomp.) (Found: C,40.25; H,3.9; Cl I, 43.0. $C_{11}H_{12}N_2Cl$ I requires C,39.5; H,3.6; Cl I, 48.6%).

7-Chloro-4-methylcinnoline ethiodide, m.p. 185° (Found: C,39.45; H,3.65. $C_{11}H_{12}N_2Cl$ I requires C,39.5; H,3.6%).

4-Methylcinnoline ethiodide, m.p. 152-154° (Found: C,43.8; H,4.5. $C_{11}H_{13}N_2I$ requires C,44.0; H,4.4%). Evaporation of the alcoholic mother liquors to dryness and digestion of the residue with ligroin (b.p. 60-80°) yielded no unchanged 4-methylcinnoline. An aqueous solution of the ethiodide was decomposed by sodium hydroxide with the immediate formation of a flocculent precipitate. Treatment of the solution with piperidine or diethylamine led to a series of striking colour changes which varied with the quantity of base present and which were not reversed on acidifying.

<u>Reaction between Widman's acid and o-nitrobenzaldehyde.</u>

A mixture of o-nitrobenzaldehyde (1.5 g.), Widman's acid
(1.5 g.), anhydrous zinc chloride (1.5 g., crushed) and acetic
acid (6 c.c.) was heated in a flask fitted with an air condenser
and calcium chloride tube. The temperature (bath) was gradually
raised to 120° (15 minutes) and maintained there for one hour
(a dark brown semi-solid mass was formed - at no time was
complete solution observed). The mixture was allowed to cool
overnight and was then heated with hydrochloric acid (25 c.c.,2N),
cooled and filtered; the green precipitate (1.15 g.), m.p. 283-
285° (decomp.) was digested repeatedly with portions of boiling
acetic acid and the clear solution yielded almost colourless
needles on cooling. Recrystallisation from acetic acid furnished
4-(2'-nitrostyryl)cinnoline-7-carboxylic acid, m.p. 285° (decomp.)
(Found: C,61.5; H,3.9; N,12.85. $C_{17}H_{11}O_4N_3.\frac{1}{2}H_2O$ requires C,61.8;
H,3.7; N,12.7%). This substance was insoluble in hot or cold
sodium carbonate or hydroxide solutions.

<u>Reaction between diethylamine, formaldehyde and 4-methylcinnoline-
7-carboxylic acid.</u>

Widman's acid (0.3 g.) was suspended in dilute hydrochloric
acid (1 drop of 2N in 2 c.c. of water), diethylamine (0.3 c.c.)
added, and the warm solution (not acid to congo-red) treated
with formaldehyde (0.1 g.; 0.25 c.c. of 40% aqueous solution).

The mixture was warmed on the water bath for 2 hours and was frequently shaken; a drop of oil appeared towards the end of the reaction and this was extracted with ether (25 c.c.), the ethereal solution being washed with water and then dried. The residual oil, obtained on evaporation, showed no tendency to crystallise and on treatment with picric acid yielded an oil, insoluble in benzene and alcohol, thus making removal of excess picric acid possible. The residue dissolved in hot acetic acid and addition of water gave black needles(0.03 g.), m.p. 127-130°.

Attempted nitration of 4-methylcinnoline.

(1) A solution of the cinnoline (1 g.) in cold concentrated sulphuric acid (1.5 c.c.) was treated at -5° during 30 minutes with a mixture of sulphuric acid and nitric acid, d 1.49 (2 c.c. of 1:1, v/v). The brilliant green colour in sulphuric acid was immediately discharged and the temperature of the solution was allowed to rise slowly (2 hours) to 14°. The red solution was poured on to ice, basified and the tarry product recrystallised from alcohol (charcoal) to give only 0.2 g. of dark coloured crystals, m.p. 131-133° (decomp.).

(2) 4-Methylcinnoline (0.5 g.) was added during 20 minutes to nitric acid (2 c.c., d 1.49) at -17°, a transient red colour being noted on each addition. After standing for 10 minutes (-13°) the mixture was poured on to ice and the yellow solid (0.28 g.) filtered, washed and oven dried; this material dissolved

completely in aqueous sodium carbonate with transient formation of a violet coloured oil. Recrystallisation of the bulk furnished a microcrystalline solid (0.13 g.), which after oven drying had m.p. 131-135° (decomp.).

Reaction of 4-methylcinnoline with potassium permanganate.

A well stirred solution of the cinnoline (1 g.) in water (20 c.c., easily soluble in 1.5 c.c.) was treated at 28° with 4% permanganate. Consumption of the latter was rapid until 80 c.c. were added (during 40 minutes); a further 5 c.c. of permanganate were added and the mixture stirred for a short time. Excess permanganate was destroyed, the mixture filtered and the filtrate extracted with ether to yield a rapidly crystalline green oil (0.37 g.); digestion with ligroin (b.p. 60-80°) furnished pure 4-methylcinnoline (0.2 g.), m.p. and mixed m.p. 74-75°.

The aqueous alkaline layer gave no precipitate on acidification, even after concentration to small volume. A small portion, on evaporation to dryness, gave a strong positive qualitative N test. The bulk was made neutral with sodium acetate and treated at 90° with excess picric acid, allowed to cool overnight, filtered and the precipitate recrystallised (charcoal) from hot water to give slender yellow needles, m.p. 342° (decomp.), mixed m.p. with sodium picrate was 235-260° (Found: C,27.3; H,1.6; N,15.8; a preliminary combustion exploded violently.).

The recovered 4-methylcinnoline gave a colourless solution in hydrochloric acid but analysis figures showed no improvement over those of the original material; a sample of recovered material was used to prepare the picrate (page 184).

Reaction of 4-methylcinnoline with diazotised aniline.

4-Methylcinnoline (1 g.) was added to dimethyl sulphate (0.9 g.) and the purple solid, formed with great evolution of heat, was dissolved in water (8 c.c.). This solution was added to one of benzene diazonium chloride prepared from aniline (0.65 g.) in hydrochloric acid (1.7 c.c., 12N and 10 c.c. of water) with sodium nitrite (0.5 g.). The mixed solution was added a little at a time, with stirring and ice cooling, to water (5 c.c.), the reaction being kept just alkaline by frequent addition of sodium hydroxide solution (6 c.c., ca. 2.5 N). After the addition (½ hour) the dark coloured solid (1.2 g., m.p. ca. 110°) was filtered, washed with water and dried in an evacuated desiccator. This product could not be purified by recrystallisation from methanol and no crystalline hydrochloride was formed in acetic acid solution with dilute hydrochloric acid.

Condensation of 4-methylcinnoline ethiodide with p-dimethylamino-benzaldehyde.

The cinnoline ethiodide (0.5 g.) was mixed with the aldehyde (0.22 g.) and refluxed in ethanol (5 c.c.) for 2 hours. In all

the following examples an intense blue solution was formed from which (boiling) the product separated in beautiful blue needles having a green lustre when dry. The following 1-ethyl-4-(4'-dimethylaminostyryl)cinnolinium iodides were prepared: 7-carbethoxy-derivative (0.4 g.), m.p. 252° (decomp.). (Found: C,55.0; H,5.35; N,8.4. $C_{23}H_{26}O_2N_3I$ requires C,54.9; H,5.2; N,8.35); 6-chloro-(0.15 g.), m.p. 248-250° (decomp.). (Found: C,50.1; H,4.7; N,8.0. $C_{20}H_{21}N_3I$ Cl requires C,51.5; H,4.55; N,9.0%); 7-chloro- (0.2 g.), m.p. 246° (decomp.) (Found: C,51.6; H,4.8; N,8.6. $C_{20}H_{21}N_3I$ Cl requires C,51.5; H,4.55; N,9.0); 1-ethyl-4-(4'-dimethylaminostyryl) cinnolinium iodide, m.p. ca. 245° (Found: C,55.95; H,5.1; N,9.8. $C_{20}H_{22}N_3I$: C,55.65; H,5.15; N,9.7).

The Reduction of Some Cinnoline Derivatives.

Little attention has been given to the reduction of simple cinnolines. Reference has been made earlier (page 4) to the attempted synthesis of cinnoline by reduction of the 4-hydroxy derivative and to the successful reduction of 4-chlorocinnoline to the parent compound. The reduction of benzocinnoline has been dealt with (page 85) whilst the synthesis of other members of this series from the corresponding 2:2'-dinitrodiphenyls (page 83) provides implicit evidence of the stability of the products towards reducing agents; in particular the behaviour of benzocinnoline N-oxides towards further reduction is contained in an earlier section (page 67).

Brief reference has been made (page 49) to the work of Neber, Knöller, Herbst and Triesler (112) who found that certain oximino-phenylhydrazones cyclised "at room temperature in acetic acid solution" to give indoles instead of the expected triazoles. The authors advanced the following mechanism of indole synthesis in place of that which postulates a selective o-benzidene change. Support for this theory was afforded by results which have been reported earlier; thus 4-phenylcinnoline and its
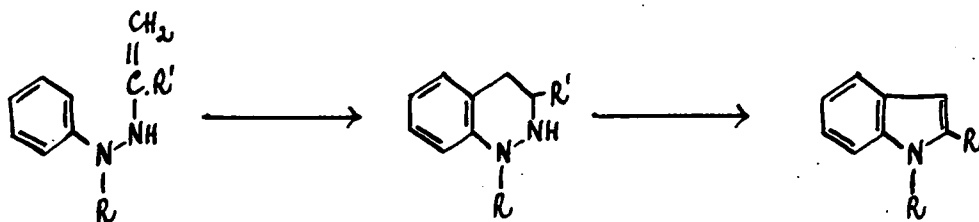
1:2-dihydro-derivative were both reduced in acid solution
to 3-phenylindole and 3-hydroxycinnoline (and the 1:2-
dihydro-compound) gave oxindole on reduction (page 33).
However, the mild conditions (above) employed by Meber
and the stability of tetrahydro-4-hydroxycinnoline, formed
by reduction with phosphorus and boiling hydriodic acid,
did not promote confidence in the new proposal; similarly,
tetrahydro-4-phenylcinnoline (obtained by catalytic
hydrogenation of the dihydro-compound) was unchanged by
boiling hydrochloric acid. Several attempts to obtain
decisive data for the choice between this hypothesis and
the earlier theory were inconclusive and the authors were
obliged to explain the production of 3-phenylindole from
4-phenylcinnoline by a simple ring fission in which a
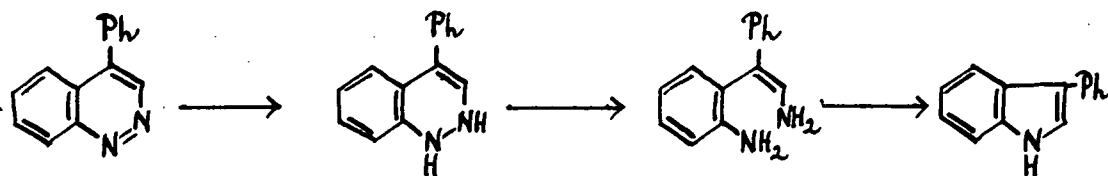
tetrahydro-derivative plays no part.

The present investigation arose from the observation
of Dr. J. C. E. Simpson that reduction of 3-methyl-4-phenyl-
cinnoline with sodium and alcohol yielded a mixture of

2-methyl-3-phenylindole and another compound which was
presumed to be the dihydrocinnoline. It appeared of interest
to carry out a series of reductions on simple 3:4-di-
substituted-cinnolines, to examine the products and to
estimate quantitatively the extent of indole formation by
measurement of the ammonia evolved; this plan was extended
to include 4-methylcinnolines.

Preparative work for this project utilised existing
stocks of intermediates as far as possible. The synthesis
of 4-p-anisylcinnoline by Stoermer and Gaus has been reported
earlier (page 49) but these workers gave no yield and the
poor properties of the crude substance were not mentioned.
The available crude material was purified by chromatography
in benzene on activated alumina and thence through the
crystalline hydrochloride. 4-(4'-Hydroxyphenyl)cinnoline,
prepared by treatment of the methoxy-compound with boiling
hydrobromic acid, was purified through the crystalline
acetoxy-derivative. The syntheses of 3-methyl- and 3-phenyl[*]
4-p-anisylcinnolines were achieved using standard procedures
based upon 2-amino-4'-methoxybenzophenone[*]; dehydration
of the carbinols to oily ethylenes was effected with dilute
sulphuric acid and diazotisation was carried out in

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[*] Prepared earlier by Dr. J. C. E. Simpson.

hydrochloric acid. The corresponding hydroxy-compound
(3-methyl and 3-phenyl[*]) were obtained as for the unsub-
stituted anisylcinnoline but purification via the acetoxy-
derivative was unnecessary in these cases. Reference has
been made already to the reduction of cinnoline N-oxides
and the preparation of the monoxides of 3-methyl and 3-phenyl-
4-p-anisylcinnolines was carried out with a view to their
use in the present study; this project could not be
further pursued. The stabilising effect (towards reduction)
of methyl groups on the nitrogen atoms of the cinnoline ring
was of particular interest in view of Neber's attempt (112)
to synthesise a similar derivative. It was hoped to utilise
a reaction between methylmagnesium iodide and the methiodide
of the heterocyclic base (which is known to apply to
quinolines, 62) but only 7-chloro-4-methylcinnoline methiodide
was prepared before this investigation was discontinued.

In the present study the cinnolines were reduced under
standard conditions using sodium and alcohol. 3-Methyl-4-p-
anisylcinnoline gave the corresponding indole which was
isolated and characterised as its picrate. The 3-phenyl
derivative yielded a resinous mixture which was only
imperfectly resolved whilst 4-p-anisylcinnoline furnished
only oily material which could not be converted to a
crystalline hydrochloride or picrate. In the demethylated

compound 4-(4'-hydroxyphenyl)cinnoline furnished the corresponding indole together with unchanged material and a similar result was obtained from the 3-methyl derivative; only unchanged material was identified from experiments using 3-phenyl-4-(4'-hydroxyphenyl)cinnoline the minute indole fraction being held, presumably, in the residual oily portion.

That these results are in general agreement with the estimations based upon ammonia evolved is shown by the following table. No simple relationship is apparent between

4-p-Anisyl- -cinnoline	% Conversion to Indole derivative		4-p-Hydroxyphenyl- -cinnoline	% Conversion to Indole derivative	
	Run 1.	Run 2.		Run 1.	Run 2.
Unsub- stituted	14.5	14.5	Unsubstituted	53	53
3-Methyl-	60	56	3-Methyl-	52	58
3-Phenyl-	3	3	3-Phenyl-	1	1

the nature of a substituent and its effect upon the extent of indole formation; thus the distinct increase in the indole figure on passing from 4-p-anisylcinnoline to the demethylated compound is not reflected in either the 3-methyl- or 3-phenyl-analogues. In the case of the latter compounds a steric factor appears to be decisive, the conversion of the

3-phenyl derivatives to indoles being expectedly less than for the corresponding methyl compounds.

Reduction of some 4-methylcinnolines gave most interesting results. The identification of unchanged material as well as the expected 3-methylindole from reduction of 4-methylcinnoline was surprising in view of the absence of steric hindrance. Even more remarkable results were provided by the chloro-methylcinnolines. The 7-chloro-derivative not only suffered reductive fission but the chloro-group was also eliminated thus giving 3-methylindole; this formed a red picrate, m.p. 177-178°, which gradually changed colour on standing and after three days the yellow product had m.p. 225-230°. A suspension of 4-methylcinnoline picrate was isolated from the crude reaction mixture. 6-Chloro-4-methylcinnoline gave a similar result to that using the 7-chloro-isomer, both skatole and its red picrate (turning yellow on standing) being isolated. However, a second picrate, m.p. 187-190°, was obtained which was different from that of 4-methylcinnoline (mixed melting point); the proximity of the melting point to that of 7-chloro-4-methylcinnoline picrate was not significant and the possibility of the product being derived from unchanged starting material was precluded by the widely different melting point of 6-chloro-4-methylcinnoline picrate. The indole conversion figures for 4-methylcinnolines (below) are significant only in their identity, within the limits of

experimental error. The qualitative results outlined below suggest that the reduction of 7-chloro-4-methylcinnoline

	% Conversion to Indole derivative	
	Run 1.	Run 2.
4-Methylcinnoline	65	-
7-Chloro-derivative	59	60
6-Chloro-derivative	55	59

takes place via 4-methylcinnoline ("A") whilst, in the absence of analytical data, the 6-chloro-derivative appears to proceed via the chloro-indole ("B"). In either case it is
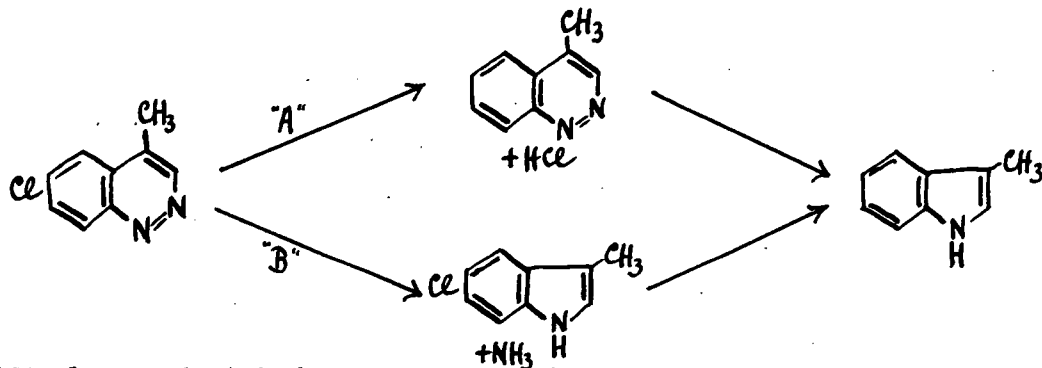
unlikely that dehalogenation and ring fission take place side by side since this would lead to the simultaneous production of hydrogen chloride and ammonia with consequent wide variation in the estimated conversion to indole; in fact the variations noted were no greater than for consecutive runs of 3-methyl-4-substituted-cinnolines (page 195).

In view of the frequent recovery of unchanged material from the above experiments the presumed 3-methyl-4-phenyl-1:2-dihydrocinnoline picrate (see page 173) was examined and shown to be identical with 3-methyl-4-phenylcinnoline picrate. The interest aroused by this single experiment was fully justified by the above results although the investigation had to be terminated in an obviously incomplete state.

EXPERIMENTAL.

Melting points are uncorrected.

Preparative work.

3-Methyl-4-p-anisylcinnoline.- A solution of
4-methoxy-2-aminobenzophenone (5 g.) in ether (80 c.c.) was
added dropwise during 15 minutes to a Grignard reagent
prepared from magnesium (3.2 g.), ethyl iodide (20.6 g.) and
ether (100 c.c.). A transient red precipitate was formed
and after refluxing for one hour the complex was decomposed
with ice-ammonia-ammonium chloride. Extraction with ether
yielded a yellow oil (5.5 g.). This crude carbinol was
dehydrated with sulphuric acid (1 part of concentrated acid
to 6 parts of water; 100 c.c.) on the steam bath and the
oily ethylene isolated by ether extraction of the basified
(ammonia) reaction mixture. A solution of the ethylene in
dilute hydrochloric acid (170 c.c. containing a little acetic
acid) was diazotised at 5-10° with 10% aqueous sodium nitrite;
cyclisation was rapid and basification (ammonia) furnished
small flakes (5.5 g.), m.p. ca. 125°. The pure cinnoline
crystallised from aqueous alcohol in yellow leaflets, m.p.
133-134° (Found: C,77.15; H,5.45; N,11.95. $C_{16}H_{14}ON_2$ requires
C,76.8; H,5.6; N,11.2%).

3-Methyl-4(4'-hydroxyphenyl)cinnoline.- The foregoing
anisylcinnoline (5 g.) was refluxed with hydrobromic acid
($\underline{d}$ = 1.5; 37 c.c.) for one hour and the crystalline
suspension obtained on cooling was basified with ammonia
(diluted with an equal volume of water). The granular solid
was separated from the supernatant liquid by decantation
and was dissolved by repeated treatment with sodium hydroxide
(N), the alkaline liquors being subsequently acidified with
acetic acid. Recrystallisation of the crude product from
alcohol (twice) furnished tiny yellow prisms of the pure
compound, m.p. 241-242° (Found: C,75.1; H,5.2; N,12.2.
$C_{15}H_{12}ON_2$ requires C,76.25; H,5.1; N,11.9.). The pure
substance dissolved in warm 2N sodium hydroxide and on
cooling gave pale yellow silky needles of the sodium salt.

3-Methyl-4-p-anisylcinnoline-N-oxide.- The cinnoline
(200 mg.) was dissolved in acetic acid (2 c.c.) and the
dark red solution heated with hydrogen peroxide (1.6 c.c.,
100 vols.) for 2 hours on a steam bath. The reaction mixture
was poured into water (10 c.c.) and the yellow solid obtained
on rubbing was recrystallised several times from very dilute
acetic acid. The pure derivative, m.p. 161°, separated from
this solvent in colourless jagged blades (Found: C,71.9;
H,5.0. $C_{16}H_{14}O_2N_2$ requires C,72.1; H,5.3).

3-Phenyl-4-p-anisylcinnoline-N-oxide.- This was prepared as above but slight reduction of the acidity of the aqueous mixture (with sodium hydroxide) was necessary to precipitate the solid derivative. The pure compound, m.p. 176-177°, formed light brown blades from aqueous alcohol (Found: C,77.1; H,4.85. $C_{21}H_{16}O_2N_2$ requires C,76.8; H,4.9%).

7-Chloro-4-methylcinnoline methiodide.- This was prepared as for the ethiodide (page 185) from the cinnoline (0.2 g.) and methyl iodide (3 c.c.); the pure compound, m.p. 202° (decomp.), crystallised from ethereal methanol in red needles. (No analysis carried out.)

Reduction of cinnoline derivatives with sodium and alcohol.

Apparatus. This consisted of a 500 c.c. R.B. bolt-necked flask fitted with a rubber bung carrying a vertical condenser and a trap for admitting sodium without loss of the gases being evolved; the latter were led to the hydrochloric acid traps (two 175 c.c. conical flasks) via the reflux condenser. Using this improvised apparatus 90% of the ammonia contained in a test solution of ammonium hydroxide was accounted for on boiling.

Procedure. A solution of the cinnoline (1/100 mol.) in absolute alcohol (150 c.c.) was refluxed and treated with sodium (10 g., ca. 20 pieces) added during ¾ hour. The gases evolved were passed through two portions of hydrochloric acid (each 75 c.c. approx. N/5) and when all the sodium had dissolved the flask was swept out during ¼ hour with a stream of nitrogen.

The hydrochloric acid used was standardised via
potassium hydroxide solution and succinic acid (standard).
Excess hydrochloric acid (after absorption of ammonia) was
estimated by back-titration with potassium hydroxide using
methyl red as indicator.

Isolation.   This was effected by cooling the reaction mixture,
pouring into water (400 c.c.), and extracting with ether; the
washed and dried ethereal extract was then evaporated to
dryness.   In reactions with cinnolines containing a hydroxyl
group the aqueous layer from such extraction was acidified to
pH 8 with acetic acid and extracted again; the product from
this is referred to the "pH 8 fraction". The products from
the following cinnolines were isolated as detailed below.

3-Methyl-4-(4'-methoxyphenyl)cinnoline.- The ethereal
extract yielded a readily crystallising oil (2.6 g. m.p. 110-
112°) which after recrystallisation from benzene-ligroin
(b.p. 40-60°) and then from aqueous alcohol had constant
m.p. 127-128° (Found: C,80.8; H,6.25. $C_{16}H_{15}ON$ requires
C,81.0; H,6.3%). The picrate, m.p. 128-130°, crystallised
from benzene in shining black needles (Found: C,56.65; H,3.95;
N,12.3. $C_{22}H_{18}O_8N_4$ requires C,56.65; H,3.86; N,12.0%).

3-Phenyl-4-(4'-methoxyphenyl)cinnoline.- The product,
after removal of a trace of alcohol in vacuo, consisted of
small brittle crystals (6.5 g. from two runs), m.p. 47-70°.

Digestion with ether yielded a less soluble fraction (1.95 g.), m.p. 132-145°, which melted at 135-145° after recrystallisation from alcohol; it was not further purified.

4-(4'-methoxyphenyl)cinnoline.- The sole product was a glassy oil (5.1 g.) which could not be induced to crystallise from aqueous alcohol, benzene-ligroin (b.p. 40-60°) or from ligroin (60-80°) alone. No crystalline picrate was formed in alcoholic solution and dilute hydrochloric acid (hot or cold) yielded no crystalline hydrochloride.

7-Chloro-4-methylcinnoline.- Colourless leaflets (0.6 g.), m.p. 92-94°, separated from the alkaline solution (from one run) obtained on pouring the reaction mixture into water. Recrystallisation of this product twice from ligroin gave colourless silky needles, m.p. 98.5°, of 3-methylindole (Found: C,82.0; H,7.5; N,10.6. Calc. for C_9H_9N: C,82.4; H,6.9; N,10.7%). Evaporation of the first mother-liquor gave a solid (0.35 g.) which was dissolved in benzene (2 c.c.) and warmed with a similar solution of picric acid (6 c.c. of a 5% solution). On cooling, soft red needles of skatole picrate (0.4 g.), m.p. 177-178° (unchanged by crystallisation from alcohol), were obtained (Found: C,50.0; H,3.4; N,14.3. Calc. for $C_{15}H_{12}O_7N_4$: C,50.0; H,3.4; N,15.55%). This specimen turned yellow on standing in the air and after 3 days melted at 225-230°.

In a second run, ether-extraction of the filtrate from the precipitated 3-methylindole yielded an oily product which was treated with picric acid as above and gave material (0.3 g.), m.p. 155-158°. This was digested with hot alcohol (15 c.c.) and gave small green crystals (0.1 g.), m.p. 170-173° - not depressed on admixture with 4-methylcinnoline picrate (m.p. 173-185°).

6-Chloro-4-methylcinnoline.- No separation of solid from the alkaline solution was noted and the general procedure yielded 3.2 g. (from two runs) of oily crystals. By digestion with boiling ligroin the dark oil was largely eliminated and a specimen of 3-methylindole, m.p. 96-97° was isolated. Evaporation of the colourless ligroin mother liquors and picration in benzene as above yielded red needles of skatole picrate, m.p. 172-174° - not depressed on admixture with the specimen already described.

The oil from the ligroin digestion was treated with picric acid as usual and the crude derivative digested with absolute alcohol and filtered hot; a green crystalline solid (0.2 g.), m.p. 185-187°, was obtained but distinct m.p. depressions were obtained with skatole picrate, and 4-methylcinnoline picrate. The picrate of 6-chloro-4-methylcinnoline has m.p. 154-156° (decomp.) . The product was not purified for analysis.

4-**Methylcinnoline**.- The crude product from one run, a mixture of oil and crystals, was recrystallised 3 times from ligroin (b.p. 40-60°) and gave pure 3-methylindole, m.p. 96.5-97.5°. Evaporation of the ligroin mother liquors gave 0.6 g. of an oil which was warmed with an equal weight of picric acid in benzene and on cooling gave red crystals (0.7 g.), m.p. 137-140°. Repeated recrystallisation from alcohol gave dark green prismatic needles of 4-methyl-cinnoline picrate, m.p. and mixed m.p. 177-178°.

3-**Methyl**-4-(4'-**hydroxyphenyl**)**cinnoline**.- The aqueous alkaline solution (after ether extraction) deposited fine golden needles(0.7 g.) which did not melt below 350° (presumably a sodium salt). The combined ethereal extracts (0.8 g. oily material) yielded on repeated recrystallisation from benzene almost colourless prisms, m.p. 155-156°, of 2-methyl-3-(4'-hydroxyphenyl)indole. (Found: C,80.2; H,5.8; N,7.0. $C_{15}H_{13}ON$ requires C,80.7; H,5.9; N,6.3%). This compound was soluble in 2N sodium hydroxide solution but not in sodium carbonate or ammonia.

The pH 8 fraction (3 g.) consisted of unchanged material and some oil, a pure specimen of the former, m.p. and mixed m.p. 238-241°, being obtained by recrystallisation from alcohol.

3-Phenyl-4-(4'-hydroxyphenyl)cinnoline.- Extraction of
the alkaline solution with ether yielded ca. 1 g. of oil
and crystals and the pH 8 fraction consisted of a solid
(2.5 g.), m.p. ca. 250° with some decomposition at 140°.
Each of the fractions, after recrystallisation from alcohol,
gave unchanged material, m.p. and mixed m.p. 283-286°, as
the only crystalline product.

4-(4'-Hydroxyphenyl)cinnoline.- The alkali-insoluble
fraction (0.6 g. from 2 runs) was a readily crystallising
oil; several recrystallisations from benzene gave pure
3-(4'-hydroxyphenyl)indole, m.p. 152-154°, as small golden
prismatic needles. The solubility of this compound in
alkalis was comparable with that of the 2-methyl analogue
(above).

The pH 8 fraction (ca. 4 g.), consisting of a mixture
of oil and crystalline material, the latter being the
unchanged cinnoline, m.p. and mixed m.p. 234-235°.

3-Methyl-4-phenylcinnoline picrate.- This was prepared
from an alcoholic solution of the cinnoline (0.5 g. in
10 c.c.) and a/solution of picric acid in alcohol (10.4 c.c.).
It separated from benzene in yellow prismatic needles, m.p.
180-181° alone and when mixed with the substance, m.p. 179-181°,
previously obtained (by Dr. J. C. E. Simpson) by treatment of
the cinnoline with sodium and alcohol.

Attempts to repeat the Stolle-Becker Reaction.

The researches already described were proceeded by a project which aimed at the preparation of 3-phenylcinnoline-4-carboxylic acid by the route of Stolle and Becker (162) and the subsequent generalisation of the method. Neither of these aims was realised and in view of the development of more successful lines of work the scheme was abandoned.

Brief reference has been made earlier (page 103) to the discovery of Stolle and Becker which arose from attempts to prepare N-amino-isatin from benzilidenamino-isatin (II). The latter compound was obtained "merely by heating" N_β-benzal-N_α-phenylhydrazine-N_α-oxalyl chloride (I), and was readily oxidised to the corresponding hydrazinebenzoic acid derivative(III); treatment with hydrochloric or acetic acids furnished indazole-3-carboxylic acid (IV), presumably via the labile N-amino-isatin. Stolle and Becker
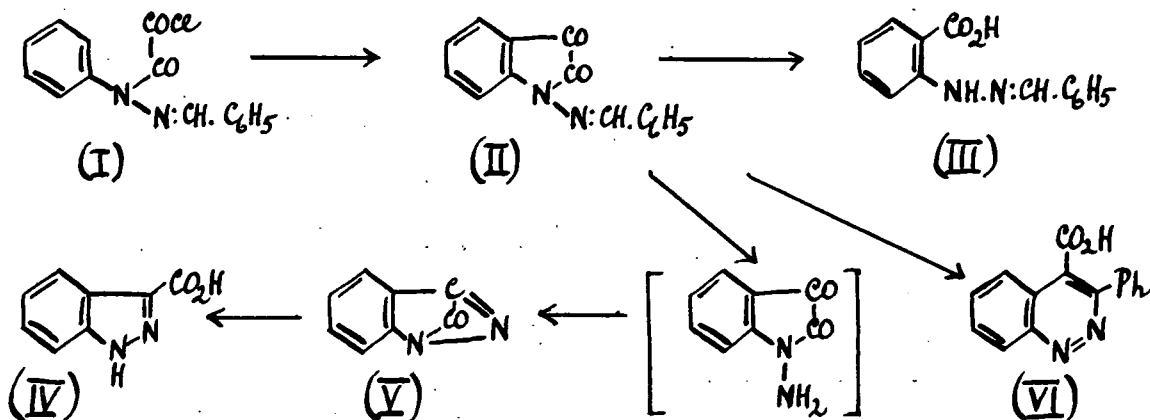
claimed that hot alkalis reacted with the benzylidenamino-isatin (II) to give 3-phenylcinnoline-4-carboxylic acid (VI).

In the present investigation the oxalyl chloride required for the first stage was prepared according to the directions of Staudinger (156) from anhydrous oxalic acid (116) and phosphorus pentachloride. The presence of the compound (I) in the reaction mixture was proven by the preparation of the crystalline anilide and the ethyl ester. A single experiment yielded a trace of red material which was presumed to be the compound (II) but no further progress attended variations on the literature method. Although the derivatives prepared by Stolle and Becker were amply described there was an unfortunate lack of detail in the experimental conditions; this, combined with the inexperience of the author at that time, was decisive in the adoption of a problem based upon more reliable original work.

EXPERIMENTAL.

Melting points are uncorrected.

Attempts to prepare N-benzilidenamino-isatin.

(1) A solution of oxalyl chloride (6.3 g. in 25 c.c.
of dry ether) was added dropwise to a refluxing solution
of benzaldehyde-phenylhydrazone (10 g.) in ether (260 c.c.)
and the mixture maintained thus for 3 hours. Evaporation
of the solvent yielded a red viscous oil which was heated
in an oil bath until hydrochloric acid gas was evolved
(150°). After 2 hours at this temperature a sample
of the product could not be obtained in crystalline form
and only 10% was soluble in aqueous sodium hydroxide.
Heating (in a stream of dry nitrogen) was continued for
6 hours (150-160°) and the mass digested with benzene and
filtered; free evaporation of the benzene gave only a
trace of red needles - presumably the desired product.

(2) A solution of oxalyl chloride in ether (6.3 g. in
25 c.c.) was added to one of benzaldehyde-phenylhydrazone
(10 g. in 250 c.c.) and the mixture refluxed in a current
of dry nitrogen until evolution of hydrochloric acid ceased.
Refluxing a portion (10 c.c.) of this mixture with an
ethereal solution of aniline (0.2 g.) for 10 minutes
furnished the anilide; recrystallisation from aqueous

alcohol gave the pure derivative, m.p. 192-193° (Literature m.p. 200°) (Found: C,73.3; H,4.6. Calc. for $C_{21}H_{17}O_2N_3$: C,73.5; H,5.0%). The remainder of the ethereal solution was concentrated to dryness and the resinous product treated in refluxing carbon disulphide (100 c.c.) with aluminium chloride (6.7 g.), added with stirring during 15 minutes. When a decrease in the evolution of hydrogen chloride was observed the reaction mixture was decomposed with an ice-hydrochloric acid mixture, filtered, and the carbon disulphide layer dried and evaporated; an oil, which did not crystallise on standing, was obtained.

(3) A solution of benzaldehyde-phenylhydrazone in carbon disulphide (5 g. in 200 c.c.) was added with stirring during 20 minutes to one of oxalyl chloride (3.2 g. in 25 c.c.). The red solution was refluxed for 1½ hours and allowed to cool; aluminium chloride (3.3 g.) was added portionwise and refluxing resumed for 1 hour. The product was isolated as in (2) and after four recrystallisations from alcohol the _ethyl ester_ was obtained as white flakes, m.p. 123-124° (Found: C,68.7; H,5.6. $C_{17}H_{16}O_3N_2$ requires C,68.9; H,5.4%).

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