An investigation of the chemistry of cinnolines

Charles W. Atkinson

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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.

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.

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

Nitration of 4-chloro-2-acetamidoacetophenone has given the 5-nitro-derivative with some of the 3-nitro-isomer. Hydrolysis to the corresponding nitro-amines and diazotisation of these in sulphuric acid yields 6-nitro-7-chloro- and 8-nitro-7-chloro-4-hydroxycinnoline. In hydrochloric acid, however, the corresponding dichloro-4-hydroxycinnolines are formed, the replacement (nitro ⟶ chloro) taking place before 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-aminoacetophenones 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).

The author is deeply sensible of the opportunity afforded him to study under Dr. J. C. E. Simpson and wishes to express sincere thanks for his guidance and encouragement throughout the investigation.

Acknowledgement is due to I.C.I. (Dyestuffs Division) for material and financial support of the project.

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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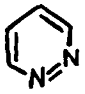
CONTENTS

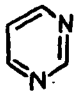
Historical

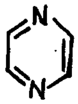
Introduction.

The relation of cinnoline to other isomeric compounds was stated first by Widman in 1888 (154) 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.

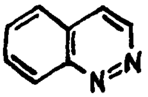
The diazine group clearly gave rise to three possibilities depending on the relative positions (o, m, or p) of the nitrogen atoms and Widman's nomenclature followed easily from this.


OIAZINE

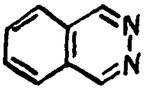

MIAZINE


PIAZINE

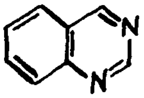
It is interesting to note that the 'accepted' names (for all were known) -pyridazine, pyrimidine and pyrazine - have survived Widman's bid for reform in spite of the fact that they have little claim to systematisation. In the benzodiazine series the same state of affairs prevailed and with the preparation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



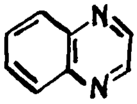
α-PHENOIAZINE
CINNOLINE



β-PHENOIAZINE
PHTHALAZINE



PHENMIAZINE
QUINAZOLINE



PHENPIAZINE
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, 154.) it is unfortunate that no 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 (140) as a contributory 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-hydroxycinnoline* 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

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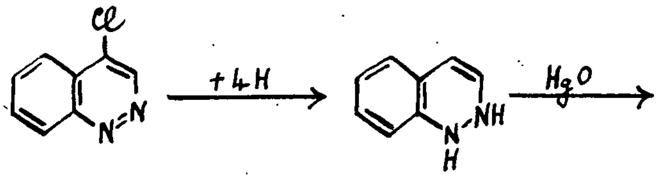
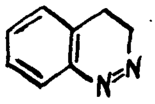
*Obtained by decarboxylation of 4-hydroxycinnoline-3-carboxylic acid.

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





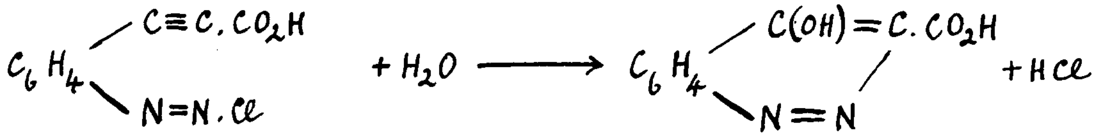
(I)

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.

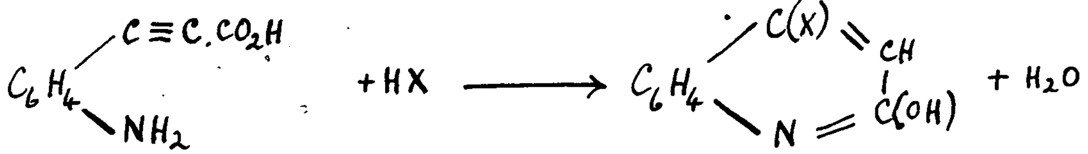
4-Hydroxycinnoline-3-carboxylic Acids.

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-aminophenylpropiolic acid. The mechanism forwarded by von Richter



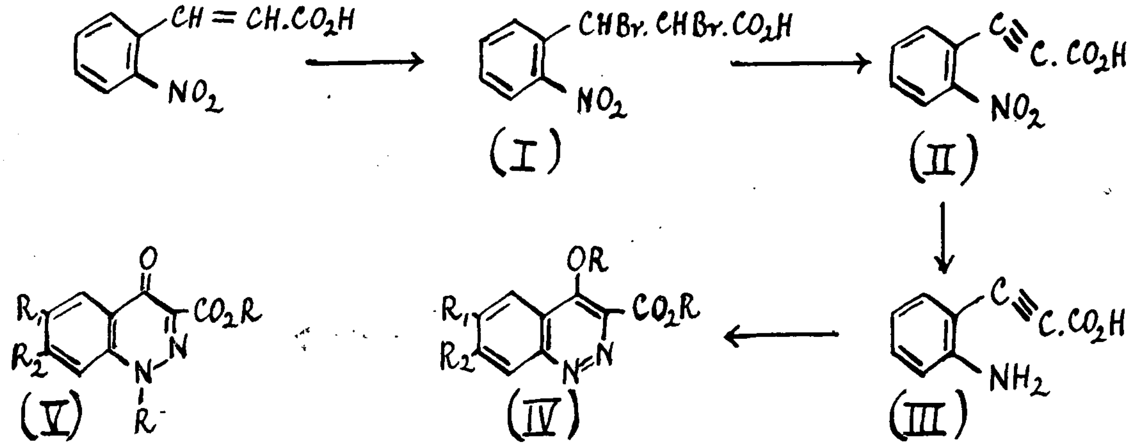
was associated with the contemporary work of Baeyer and Bloem (14), namely, the conversion of o-aminophenylpropiolic acid derivatives to γ-carbostyrils.



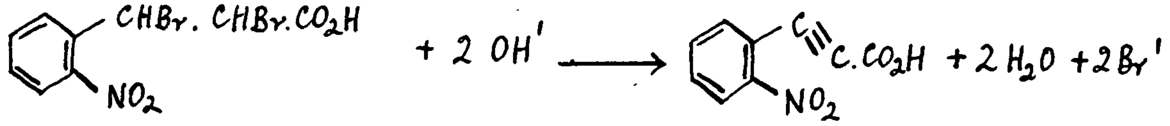
A lapse of sixty two years between the investigation of von Richter and the next contribution to compounds of this group was broken only by workers (33,34) whose ambitions in the cinnoline field were limited by, and often subsidiary to, other researches. The results of a study of the Richter reaction 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; page 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-nitrophenylpropiolic 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 37) to establish the optimum conditions for dehydrobromination.

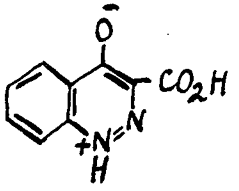


Although reduction to the amino-acid was at first carried out using von Richter's method, itself a modification of that of Baeyer and Bloem (14), a procedure was evolved (141) by which the amino-acid was diazotised without being isolated or even allowed to separate in acid solution. In this way the formation of carbostyril derivatives, previously observed both in the reduction (130) and in the attempted dissolution of the amine prior to diazotisation (33), was avoided.

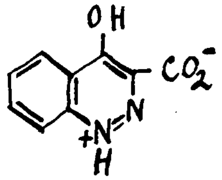
Examination of the generality of the Richter reaction (ii above) was restricted to those propiolic acids arising from the more readily accessible o-nitrobenzaldehydes. The cinnamic acids corresponding to 6-nitropiperonal, 2-nitro-5-methoxybenzaldehyde, and to 6-nitroveratraldehyde were already known. By the route established for the unsubstituted 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.



(Va)



(Vb)

The "switterion" 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. [Reference 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-hydroxycinnoline-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:

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

Series A could clearly arise thus:

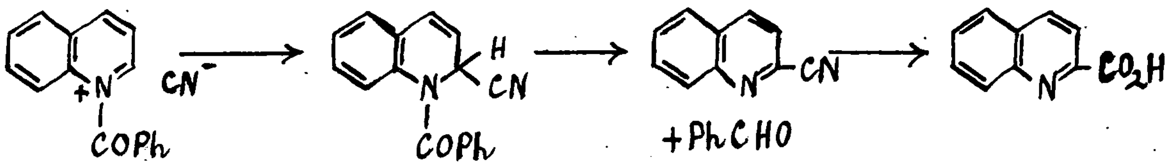
$$C_5H_5N + (CH_3CO)_2O + C_9H_6O_3N_2 \longrightarrow C_{16}H_{11}O_3N_3 + H_2O + CH_3CO_2H,$$

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 substitution 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.

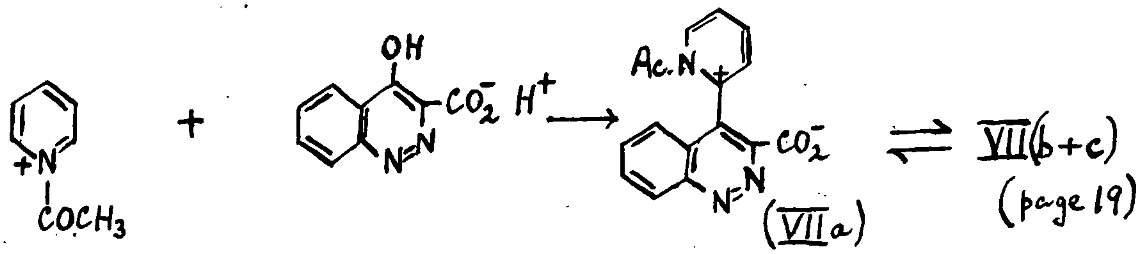
It is convenient, before presenting an interpretation of the facts so far revealed, to consider the evidence forwarded by Schofield and Simpson for the belief that this reaction using pyridine and acetic anhydride is highly specific to 4-hydroxycinnoline-3-carboxylic acids. 4-Hydroxycinnoline gave 4-acetoxycinnoline 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, (experiment "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 (40a). 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).



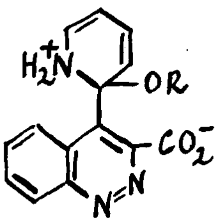
Schofield and Simpson represented the reaction between pyridine, acetic anhydride and the Richter acid as follows:



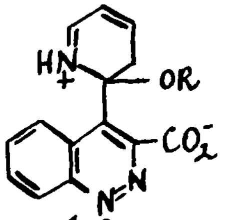
It was pointed out that the general properties (page 19) of the initial reaction product and its remarkable reactivity towards alcohols were in greater accord with its representation as either of the canonical states (VII; a - c) than as the lactone (VII d), although the latter structure was fully considered 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.

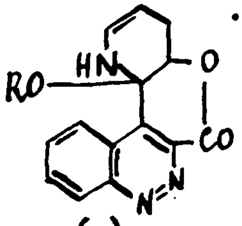
The analogy with "Reissert compounds" (page 13), and hence the representation of this series of new substances as α-pyridinium (or α-dihydropyridyl) compounds, was more firmly established by the loss of the N-acetyl group as follows. The compound (VI; R = Me) on treatment with <u>either</u> methanol 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)



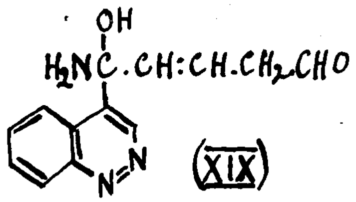
(b)



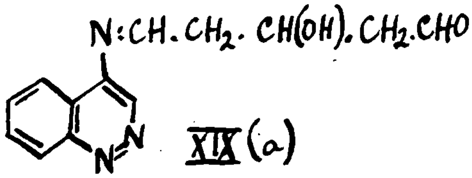
(c)

- 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. $C_{13}H_9N_3$. $C_6H_3O_7N_3$.

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 refluxing 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 compound, 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 liquer 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 decarboxylated 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 <u>or</u> 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.

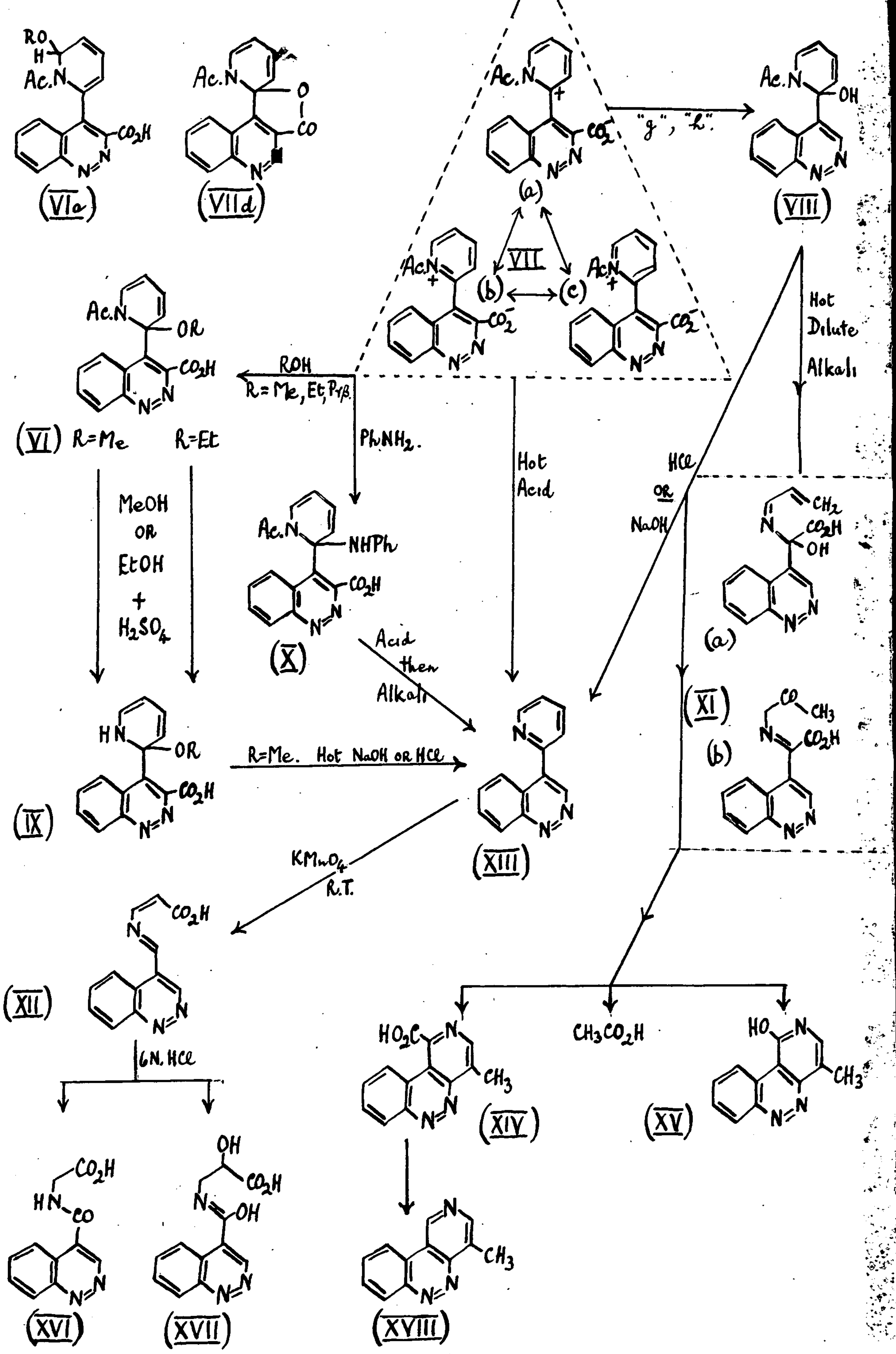
Expt.	Richter acid	Pyridine	Ac_2O	Expt. conditions	Result
a.	2 parts	9 parts	13 parts	Heat at 60° or 95°	VII
b.	2-Hydroxy-3-naphthoic acid	present	present		2-Acetoxy-3-naphthoic acid
c.	4-Hydroxyquinoline-3-carboxylic acid	"	"		No reaction
d.	Ethyl ester of "c"	"	"		4-Acetoxy-derivative
e.	6-Methoxy-"Richter 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.

Expt.	Richter acid	Pyridine	Ac_2O	Expt. conditions	Result
f.	1 part	3 parts	1 part	Reflux for ½ hour	VIII $C_8H_{6(7)}O_5N$
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.

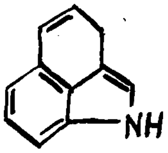
Expt.	Richter acid	Pyridine	Ac_2O	Expt. conditions	Result
k.	present	present	Propionic anhydride		No xalline product
l.	1 part	Quinoline 16 parts	12 parts		Reaction
m.	present	Quinaldine or -picoline	present		No reaction
n.	present	absent	present	Reflux	4-Acetoxy-cinnoline
o.	"	present	absent		Unchanged Richter acid.


RO
H
Ac.N
CO₂H
(VIa)
Ac.N
O
CO
(VIId)
Ac.N
+
CO₂⁻
(a)
VII
(b)
(c)
AcN
+
CO₂⁻
"g", "h".
Ac.N
OH
(VIII)
Ac.N
OR
CO₂H
(VI) R=Me
R=Et
ROH
R = Me, Et, Prβ.
PhNH₂.
Hot
Acid
HCl
OR
NaOH
Hot
Dilute
Alkali
MeOH
OR
EtOH
+
H₂SO₄
Ac.N
NHPh
CO₂H
(X)
Acid
then
Alkali
N
CH₂
CO₂H
OH
(a)
(XI)
CO
CH₃
N
CO₂H
(b)
HN
OR
CO₂H
(IX)
R=Me. Hot NaOH or HCl
N
(XIII)
KMnO₄
R.T.
CO₂H
N
(XII)
6N. HCl
HO₂C
N
CH₃
(XIV)
CH₃CO₂H
HO
N
CH₃
(XV)
CO₂H
HN
CO
(XVI)
OH
CO₂H
N
OH
(XVII)
N
CH₃
(XVIII)
N=N

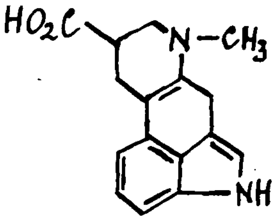
Cpd.	Sol. in acids.	Sol. in alkalis.	Other properties.
VI	Sol. in dilute HCl	Sol. in dil. aq. Na_2CO_3. Sol. with R = Me R = Pr .	Insol. in water.
VII	E. sol. in mod. conc. HCl.	E. sol. in cold aq. Na_2CO_3.	Suspension in aq. dioxane conc. NH_4OH intense blue purple solution.
VIII	Readily sol. in 2N.HCl.	Insol. in aq. NaOH.	Insol. in cold water.
$C_8H_{4(7)}O_5N$	Sol. in conc. HCl	Insol. in 4N. NH_4OH, sp. sol. in 0.880 NH_4OH. Sol. in warm 10% aq. NaOH.	Sp. sol. in boiling water.
IX	Readily sol. in mod. conc. HCl.	Insol. in cold NaOH or Na_2CO_3.	Insol. in cold water, apprec. sol. in hot.
X	Sl. sol. in cold 2N.HCl.	-	V. e. s. 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_4OH.	-
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_2CO_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.



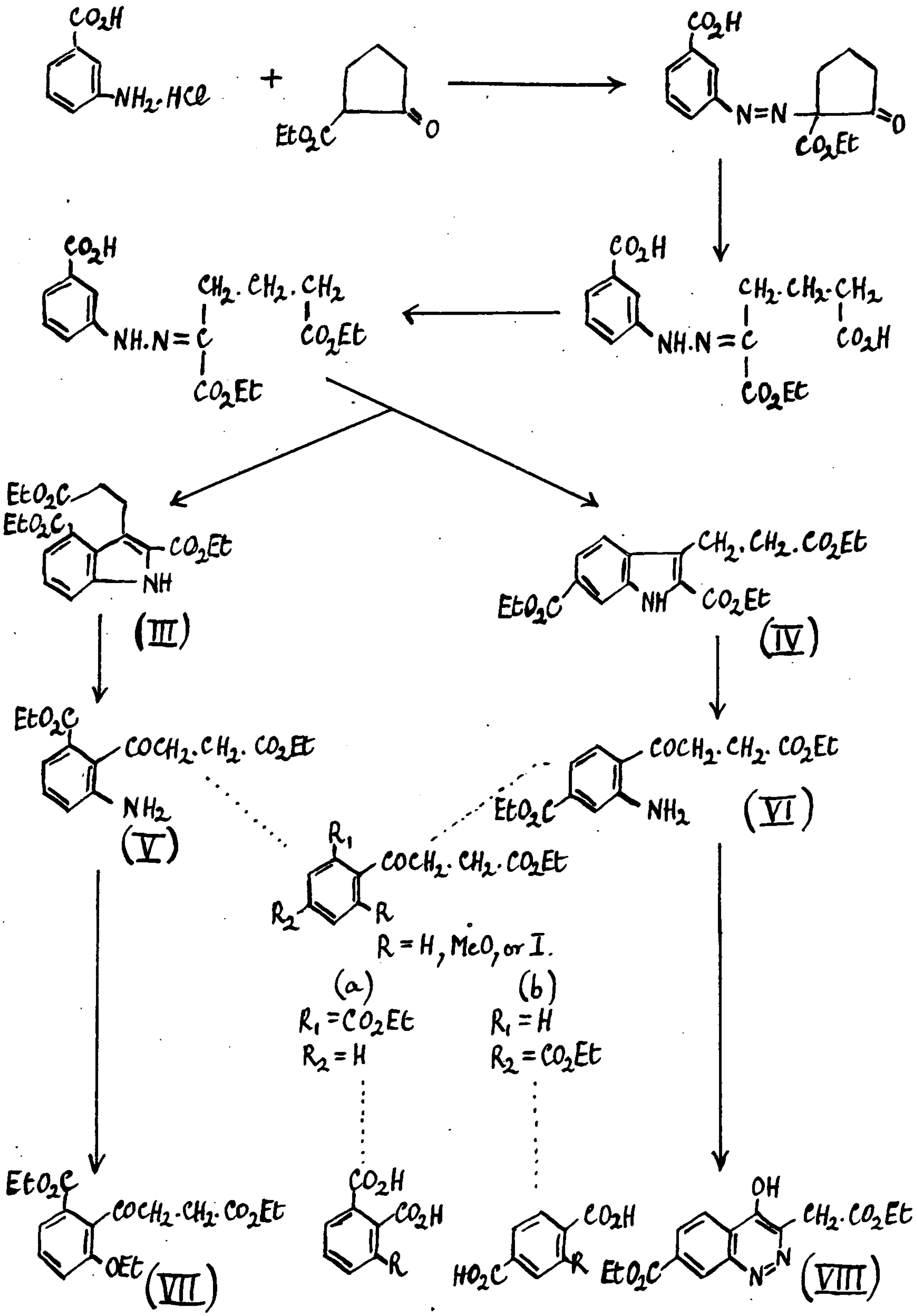
(I)



(II)

THE WORK OF KOELSCH

- - - - - - Indicates intended reactions.



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-aminoveratryl)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.

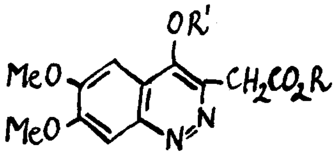
(a) The action of dimethyl sulphate and alkali on 4-hydroxy-6:7-dimethoxycinnoline-3-acetic acid gave a mixture of two isomeric ether-acids (IX; R = H, R' = Me) which could only be wholly resolved as the methyl esters (IX; R = R' = Me; X; R = Me) although a pure specimen of one acid, m.p. 260° (decomp.)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

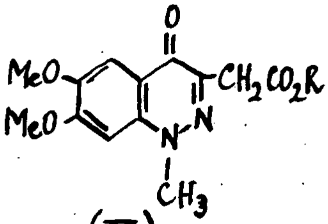
(c) The α-acid decarboxylated at the melting point to give a base (XI or XII) - called the α-ether. The β-acid was stable above its melting point.

(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.

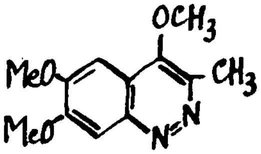
(e) The α-ether formed a hydrochloride and appeared to quaternise slightly with ethyl iodide.



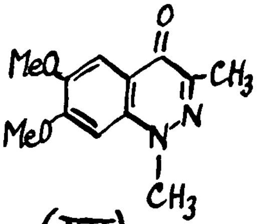
(IX)



(X)



(XI)



(XII)

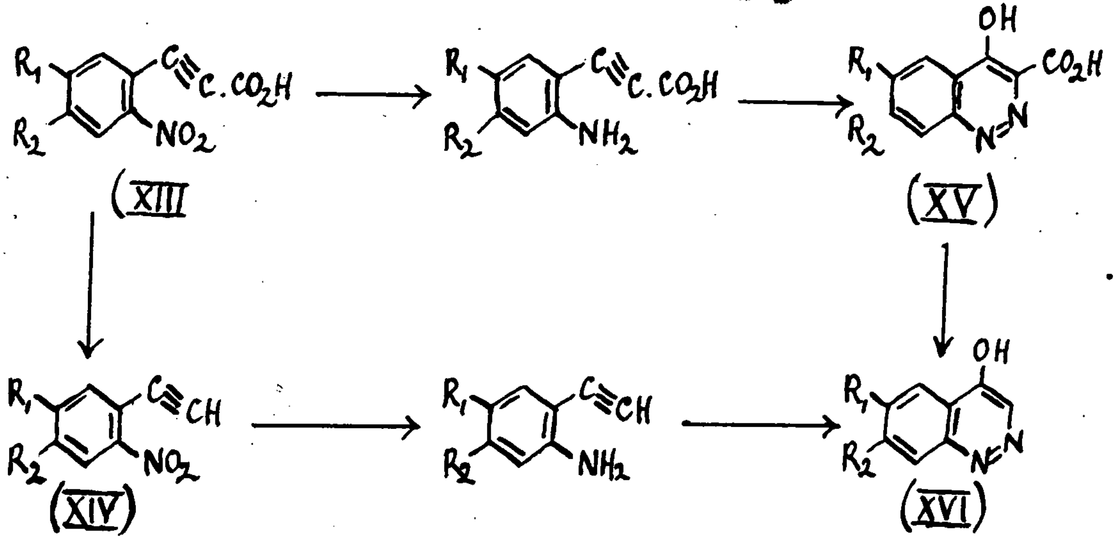
The non-basic nature (b) of the α-ether acid, when related to the absence of basicity observed in the acid (IX; R = R' = H), offered no evidence for an O-ether structure for the former since "4-methoxycinnoline is decidedly more basic than 4-hydroxycinnoline". Further the observations of (c) and (d) 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 (25,91)]. 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 decomposition 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 decarboxylation 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 $-N = C' - CO_2H$ to the existence of a cyclic ion of the type $[N = C]^-$. 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 applicable to the 6-methoxy- and 6:7-methylene-dioxy-acids (XV), $R_1 = OMe$, $R_2 = H$; $R_1R_2 = CH_2O_2$, 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 (141) of the Richter reaction and was based on theoretical considerations to be discussed later (page 76). Decarboxylation 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 corresponding 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-methylenedioxyphenylpropiolic acid (XIII; $R_1 = R_2 = CH_2O_2$).



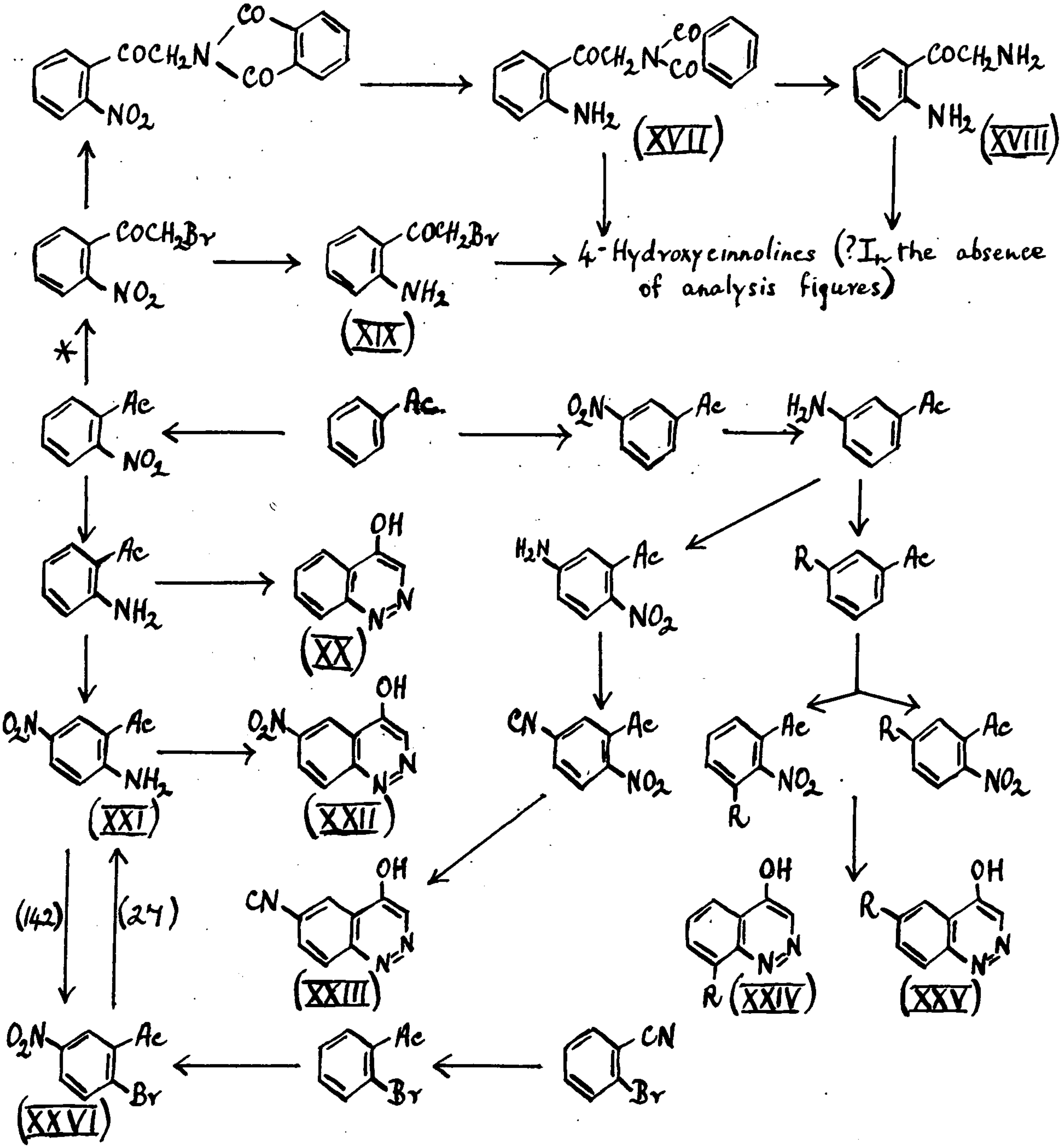
During researches on the use of 5-nitro-2-bromoacetophenone as a synthetic intermediate Borsche and Herbert (27) prepared 6-nitro-4-hydroxycinnoline (XXII) by diazotisation of 5-nitro-2-aminoacetophenone (XXI), the latter being prepared from o-bromo-benzonitrile. A repitition of this work (142) revealed 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-aminoketones . . . . . 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 significantly (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-hydroxycinnoline (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-aminoacetophenones was aroused by the work of de Diesbach and Klement (49) who diazotised ω-anilino-o-aminoacetophenone and obtained a substance, $C_{14}H_{11}ON_3$, m.p. 285°, 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-aminoacetophenones" have been described by Schofield (140). Attempts to repeat the work of de Diesbach and Klement were discouraging; two substances, m.p. 95-105° and 120° (according to the method of isolation employed) were produced, but no compound melting at 285° was isolated. The diazotisation 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

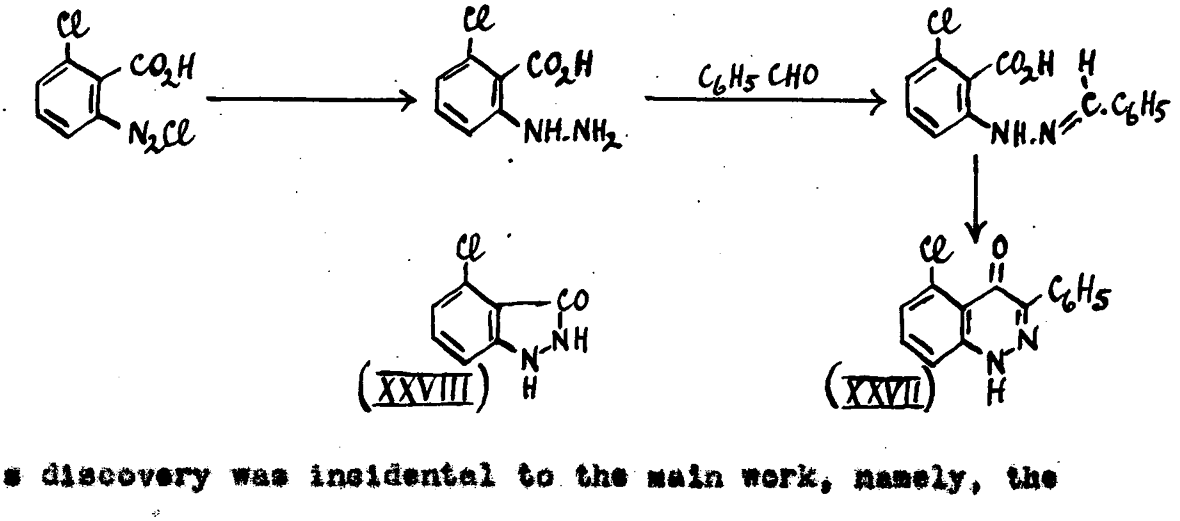
Preparation of 4-Hydroxycinnolines from Acetophenone (140).



*o-Nitroacetophenone for this route prepared from o-nitrobenzoic acid and acetoacetic ester (113).

crystalline solid, originally believed to be 3-phthalimido-4-hydroxycinnoline in spite of its insolubility in aqueous sodium hydroxide; subsequent analysis did not support such a representation. Hydrolysis of the supposed 3-phthalimido-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-hydroxycinnolineis noteworthy for the deep yellow colour of its alkaline solution. 3-Phenyl-5-chloro-4-hydroxycinnolineis 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-hydroxycinnoline is only very sparingly soluble in alcohol; the 6-methoxy-derivative is more soluble whilst Pfannstial 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-hydroxycinnoline.

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-hydroxycinnoline 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 Neber and co-workers (112) by means of phosphorus and hydriodic acid. Treatment of 3-hydroxycinnoline 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-hydroxycinnoline towards boiling acetic anhydride.

4-Chlorocinnolines.

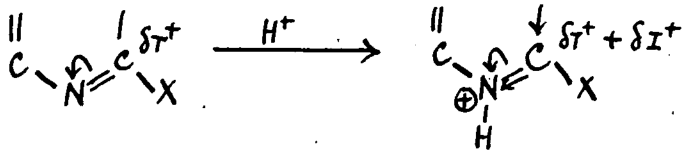
These compounds are prepared by the action of a mixture of phosphorus oxychloride and phosphorus pentachloride on the relevant 4-hydroxycinnolines, a method first used in this series by Busch and Klett (33) for the preparation of 4-chlorocinnoline. This compound was at once recognised as "a very reactive 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-chlorocinnoline 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-hydroxycinnoline 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):

$$6\ \mathrm{MeO} < 6\mathrm{Cl} < \text{unsubstituted} < 6\ \mathrm{NO_2}.$$

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-Dichlorocinnoline	Stable to atmospheric moisture when pure.	Warm 2N-hydrochloric* acid caused hydrolysis.
4-Chlorocinnoline	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 + $AgNO_3$ 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-chlorocinnoline. 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-heterocyclics in acid solution.

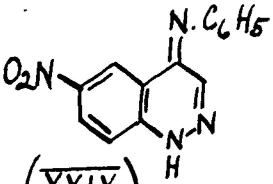


Such a mechanism explained well the reactions (✳) tabulated above. Comparisons were offered (140) with the reactivity of comparable compounds in the quinoline and acridine series but the lack of quantatative data was stressed throughout.

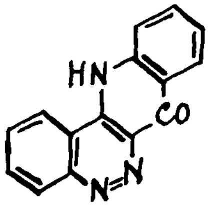
Other reactions (140) of 4-chlorocinnoline itself include the action of acetic anhydride, giving the acetoxy-compound; an attempt to prepare a Grignard reagent failed and 4-chlorocinnoline could not be reacted with benzene in the presence of aluminium chloride. Treatment with potassium cyanide in methanol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



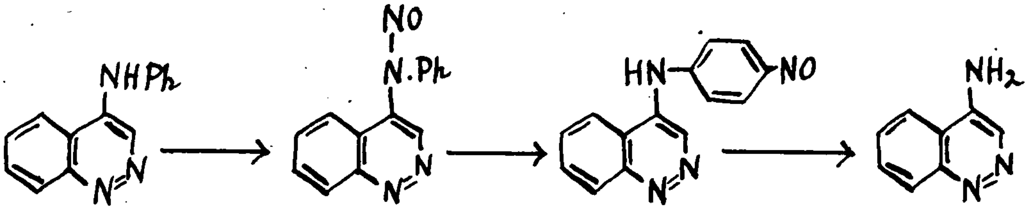
(XXIX)



(XXX)

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

(A)

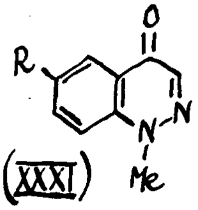


4-anilidocinnoline has been reported (140) but preliminary attempts to carry out the first stage met with no success.

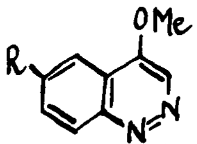
Other attempts to prepare 4-aminocinnoline also failed: thus 4-chlorocinnoline did not react with liquid ammonia or with potassium phthalimide in the presence of potassium carbonate; with aqueous alcoholic ammonia at temperatures greater than 100° 4-chlorocinnoline gave no useful product.

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 amphoteric 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-cinnolone (XXXI; $R = NO_2$) and the pale yellow concomitant substance, m.p. 183°, as 6-nitro-4-methoxycinnoline (XXXII; $R = NO_2$).



(XXXI)



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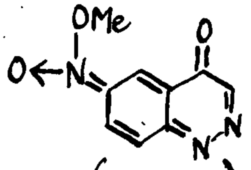

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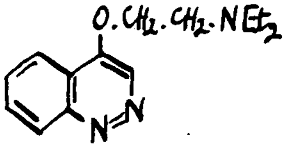


(XXXIV)

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-methoxycinnoline (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.

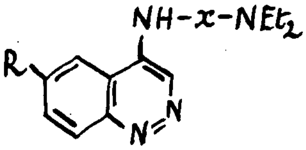
4-Phenoxycinnolines.

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[*], mepacrine (XXXVI) and plasmoquine (XXXVII).



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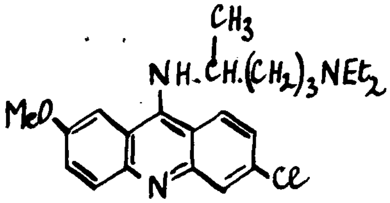

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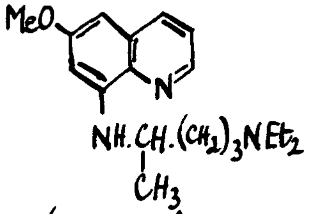

(XXXVII)

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 uncrystallisable 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'.

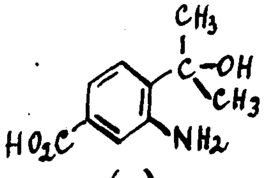
in heating the amine with either the phenoxy-compound or with a mixture of chloro-compound and phenol. In this way 4-(α-methyl-δ-diethylaminobutylamino)cinnoline and 4-(β-diethylaminoethylamino)cinnoline were prepared and characterised as their dihydrochlorides.

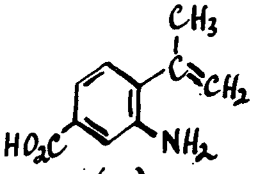
It was expected that a 6-methoxy-group would enhance the antimalarial activity of the 4-'basic side chain'-compounds by analogy with the work of Ainley and King (3), who, during a study of synthetic quinoline derivatives related to quinine, observed that absence of a methoxyl group was invariably associated 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-isopropenyl-benzoic acids led to the preparation of 4-methylcinnoline-7-carboxylic acid (III).* This discovery arose during the diazotisation of 3-amino-4-isopropenylbenzoic 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)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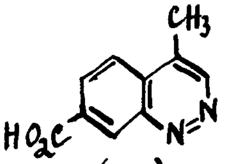
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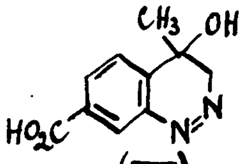
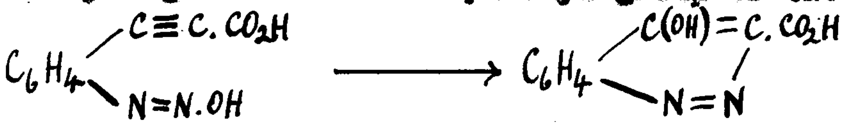

(IV)

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 methylcinnoline could only be formed by loss of a molecule of



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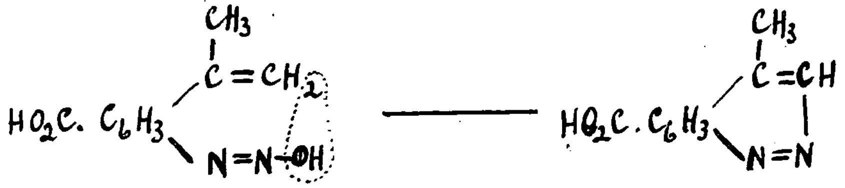
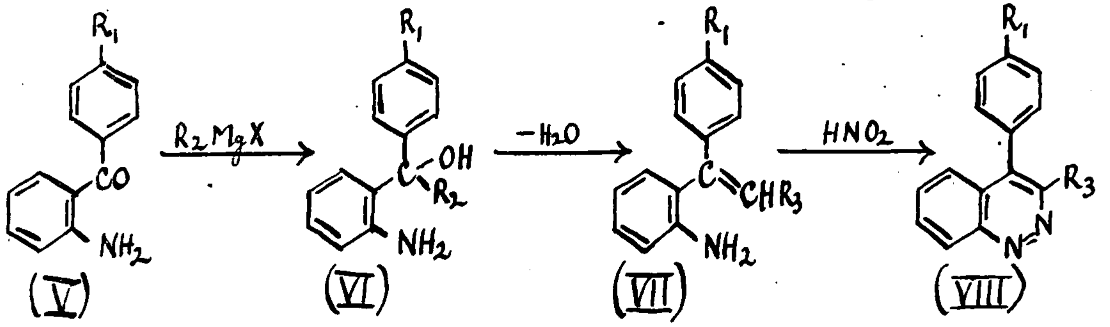
*The preparation of this compound and a study of some of its reactions are detailed later (page 156).

water.



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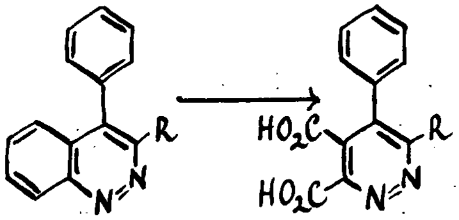
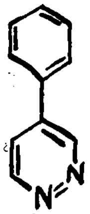
*These authors were unaware of Widman's work and when the latter pointed out their mistake (183) it was explained (159) that standard works (e.g. Anschutz-Schroter) omitted any reference to Widman.

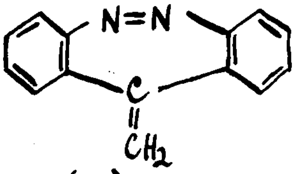
prepared. The requisite ethylenes (VII) were made from the o-amino-ketones (V) as shown, the latter being produced according to the instructions of Ullmann and Bleier (174). Evidence in favour of the cinnoline structure for the two compounds (VIII; $R_1 = H$, $R_3 = Me$; and $R_1 = R_3 = H$) was their degradation to 3-methyl-4-phenylcinnolinic acid (IX; R = CH_3) and 4-phenylpyridazine (X) respectively.



(IX)



(X)



(XI)

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 (31, 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.

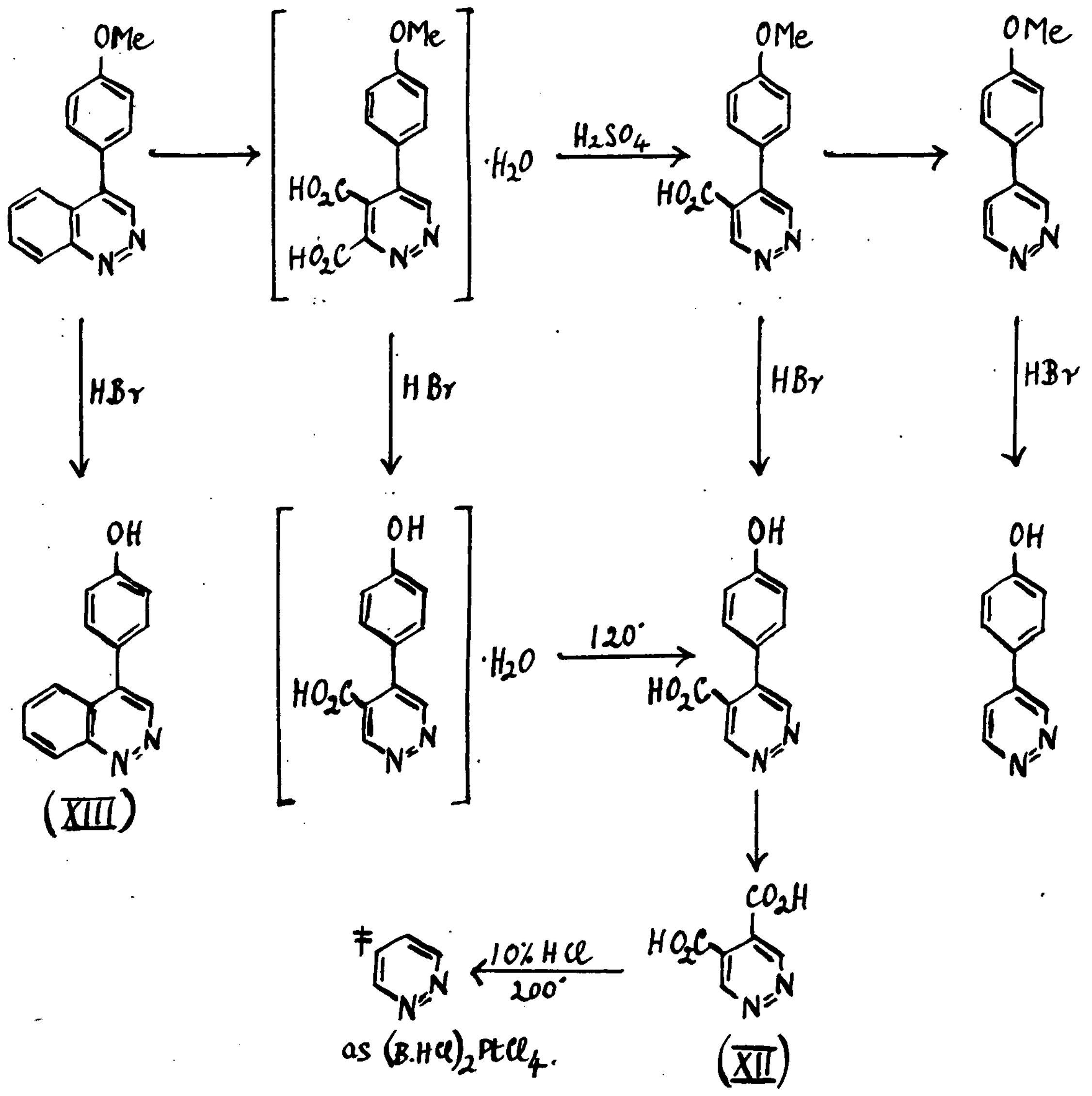
4-(p-Anisyl)cinnoline was described in a later paper by Stoermer and Gaus (160) which was important for two reasons.

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

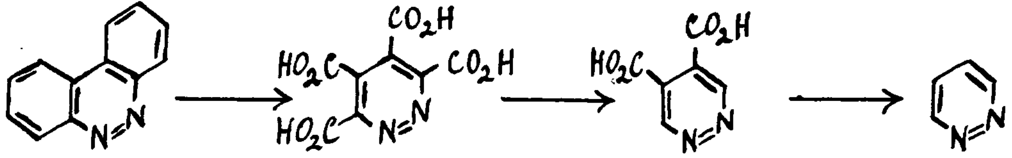
(2) Some attempt was made to account for the known limitations of the reaction.

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

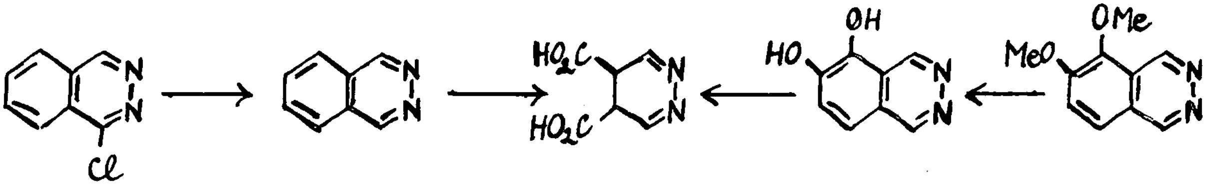
Degradation of 4-p-Anisylcinnoline (160).



‡ Pyridazine was first prepared by Tauber (164) by oxidation degradation of phenazone (5:4-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.

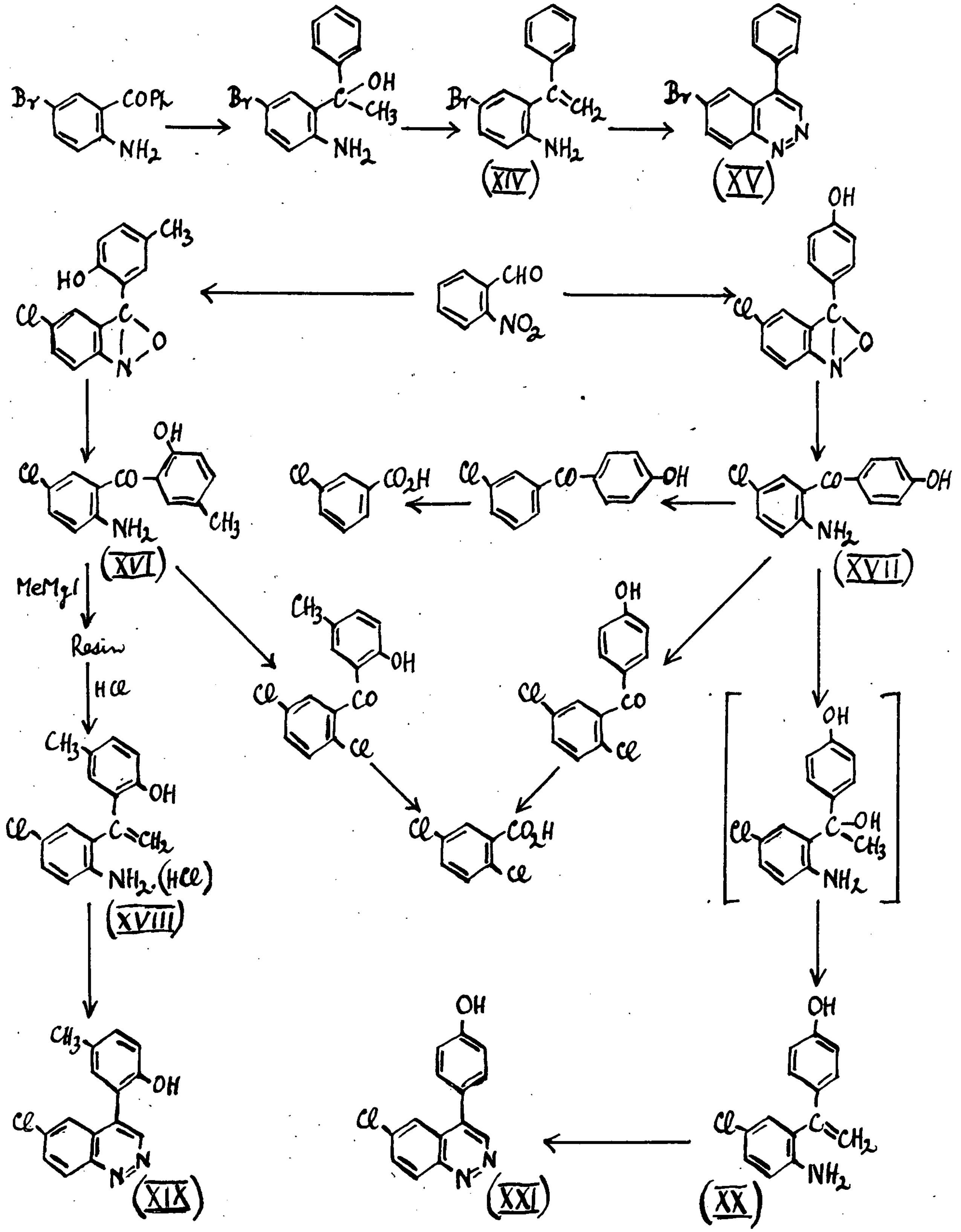
4-Anisylcinnoline formed brightly coloured salts similar to those of 4-phenylcinnoline, and like the latter gave two different gold double-salts, B.HCl. Au Cl_3 and $(B.HCl)_2$ Au Cl_3. The action of boiling concentrated hydrobromic acid on 4-(p-anisyl)cinnoline furnished 4-(p-hydroxyphenyl)cinnoline (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

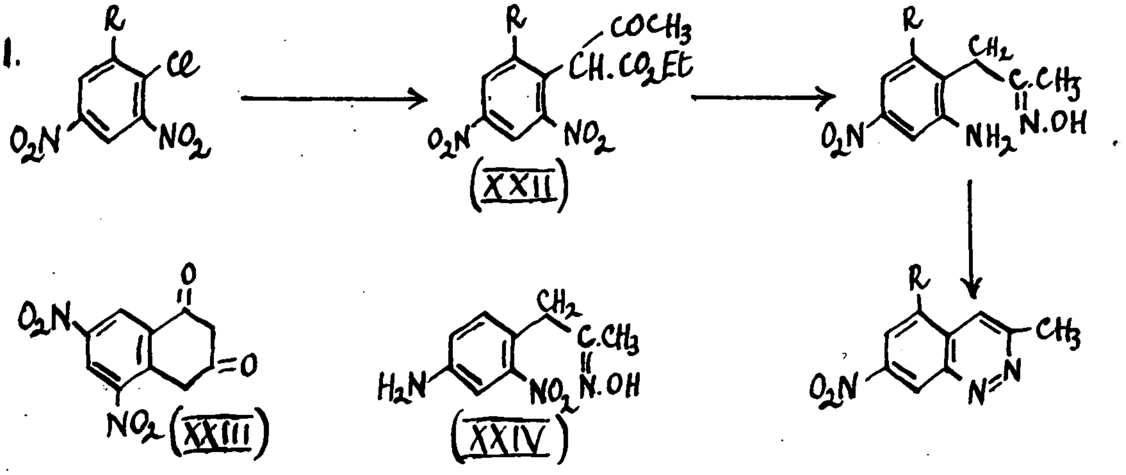
Routes to three new 4-Arylcinnolines (152).



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-aminobenzophenones, has been reported by Stephenson (157). A number of unsuccessful attempts to prepare cinnolines by new routes was also described;-

1.



(XXII)

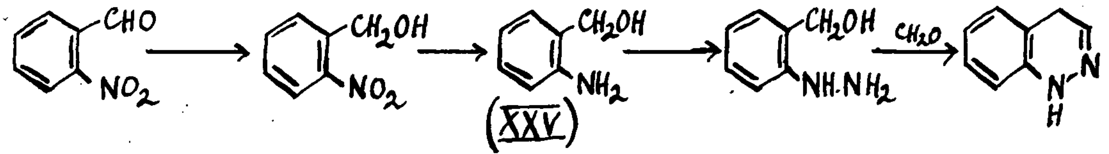
(XXIII)

(XXIV)

Hydrolysis of the ketone (XXII; R = H) could not be achieved using boiling dilute sulphuric acid - ring closure appeared to occur giving (XXIII).

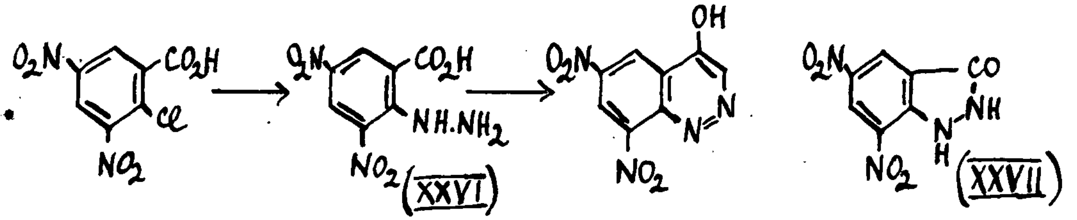
2:4-dinitrophenylacetone was prepared by the hydrolysis of (XXII; R = H), the method used by Borsche (26). After reduction in acid solution had failed careful reduction of the oxime of the phenylacetone gave a monoamine tentatively represented as (XXIV). Diazotisation of (XXV) followed by

2.



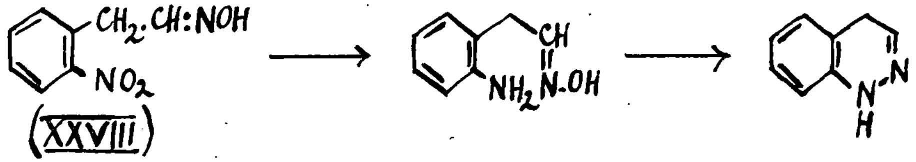
reduction gave a highly coloured amorphous product which would not react with ketones; it was presumed to be the indazole

3.



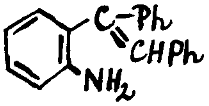
Again the hydrazine (XXVI) yielded only the indazole (XXVII).

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.



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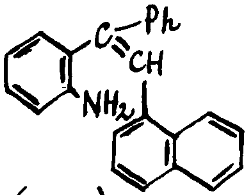
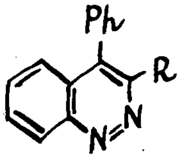
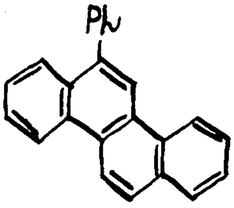


(XXX)



(XXXI)



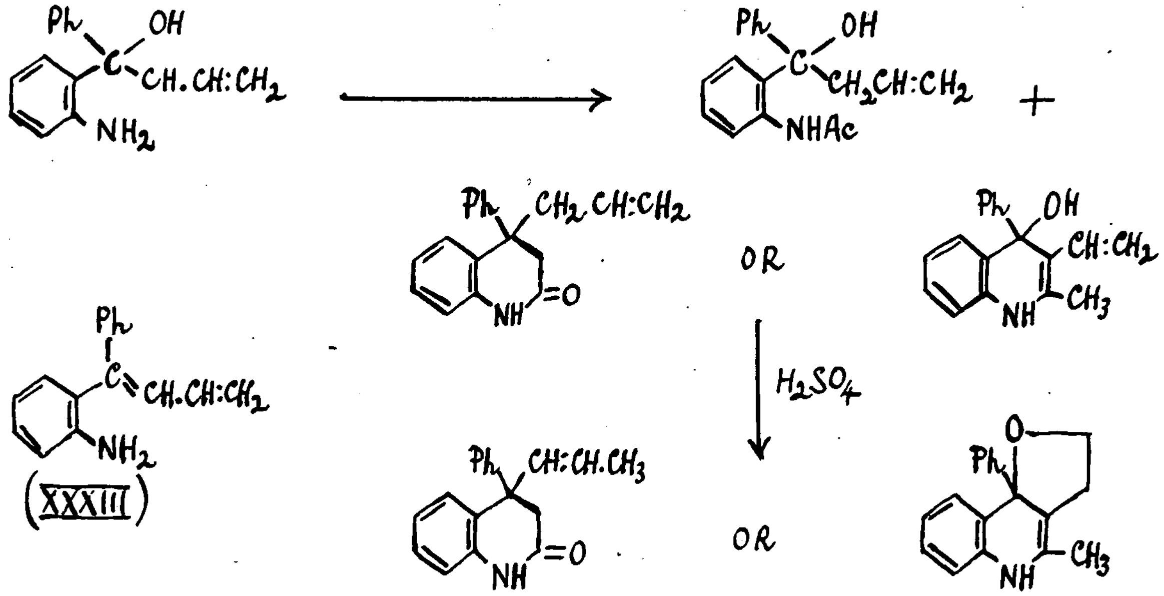
(XXXII)

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-phenylchrysene (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).

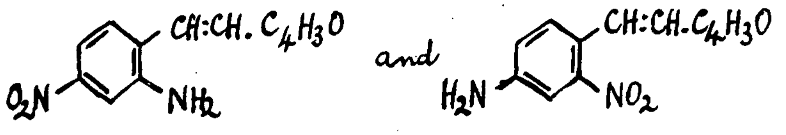
4-Phenyl-3-benzylcinnoline (XXXI; R = $CH_2C_6H_5$) was prepared by diazotisation of the corresponding ethylene; as in the two previous examples, the cyclisation was not spontaneous and the concentration of the acid medium was suspected as being responsible for this result.

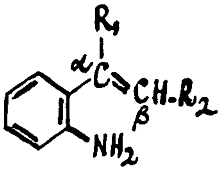
Attempts to prepare the butadiene (XXXIII) were unsuccessful since the requisite carbinol resinified when treated with hot dilute sulphuric acid. The carbinol yielded some normal acetamido-derivative on acetylation but the chief product was a basic substance which underwent rearrangement in hot dilute sulphuric acid; these results are represented as follows.



(XXXIII)

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:



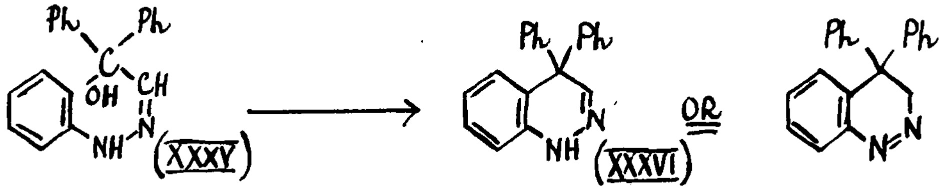


(XXXIV)

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".

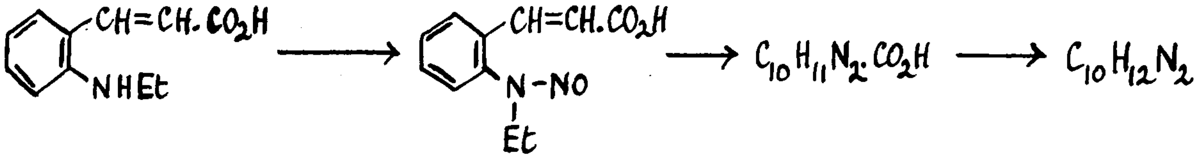
Mention may here be made of an investigation by Zerner (190) who, by boiling the phenylhydrazone of diphenylhydroxyacetaldehyde (XXXV) with sulphuric acid, obtained a red crystalline solid which he represented as a dihydrocinnoline (XXXVI):



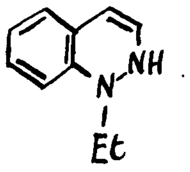
The deep colour of this compound and its lack of basicity, in contrast to the properties (page 5) of cinnoline and 1:2-dihydrocinnoline, were both attributed to the phenyl groups attached to the heterocyclic ring.

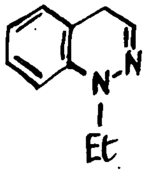
N-Substituted Cinnolines.

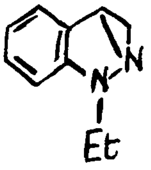
The earliest member in this series, prepared by Fischer and Kuzel (60), was referred to by Widman (182) as the only cinnoline derivative, other than the Richter acid, which was reported prior to 4-methylcinnoline-7-carboxylic acid. An attempt (58) to ring-close the β-nitrogen atom of o-hydrazinocinnamic 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 $C_{10}H_{12}N_2$.

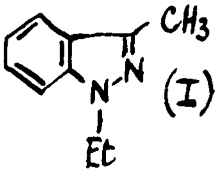


The following structures were suggested for the base, "ethyl-chinazole", but these cinnoline-type possibilities were later







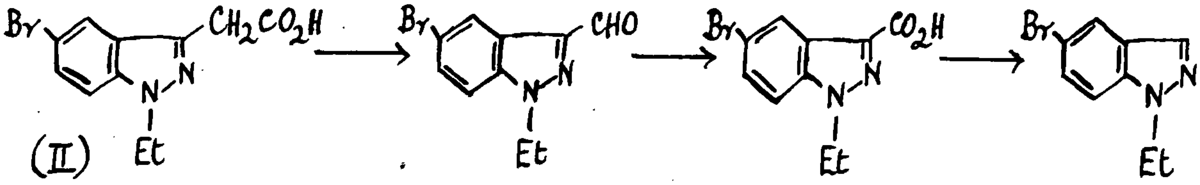


(I)

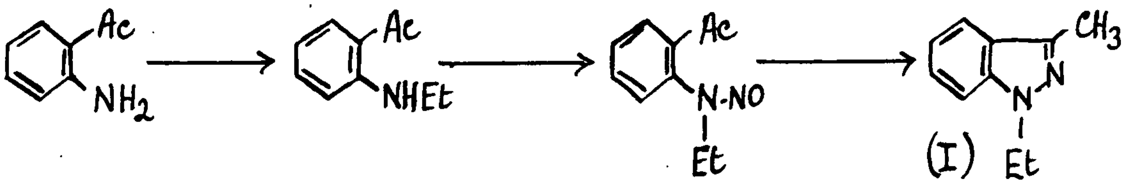
discarded (61) in favour of the "isindazole" structure (I).

The evidence for this decision was -

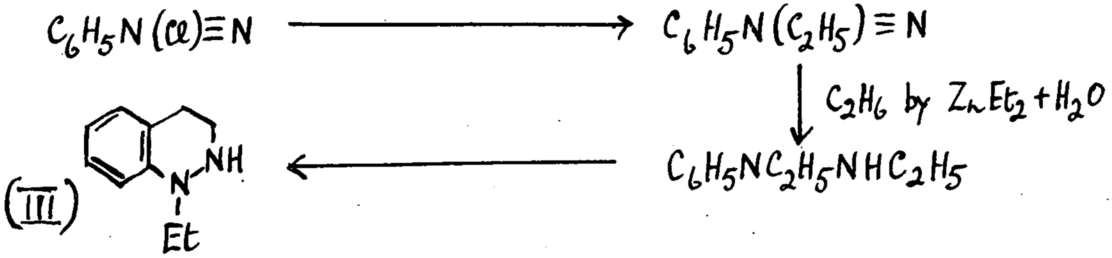
(a). The oxidation of monobromo-'ethylchinazole carboxylic acid' (II) to an aldehyde and thence to an acid which decarboxylated to a compound $C_9H_9N_2Br$.



(b). The synthesis of 'ethylchinazole' (identical with the oréginal preparation) by an unambiguous route from o-amino-acetophenone.

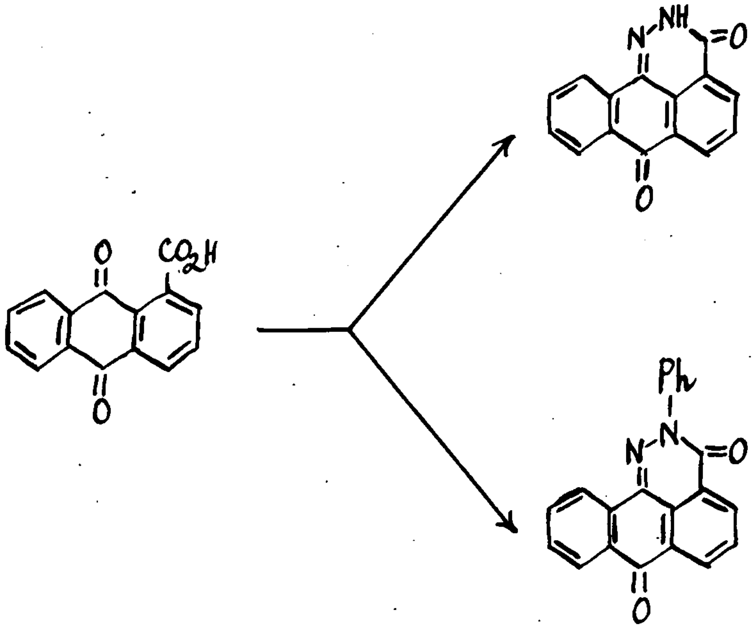


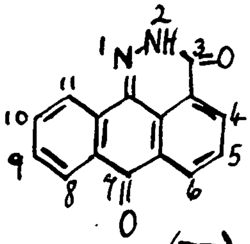
The preparation of another compound of this group was claimed by Tichwinski (170) during his study of the reaction between zinc diethyl and benzene diazonium chloride; he isolated from the liquid product mono- and di-ethylphenylhydrazine and a feebly basic sweet smelling oil, $C_{10}H_{14}N_2$. This compound was presumed to be N-ethyl-1:2-dihydrocinnoline (III) formed thus:-



Later, Tichwinski (171) prepared the same substance by the action of zinc diethyl on phenylazoethane.

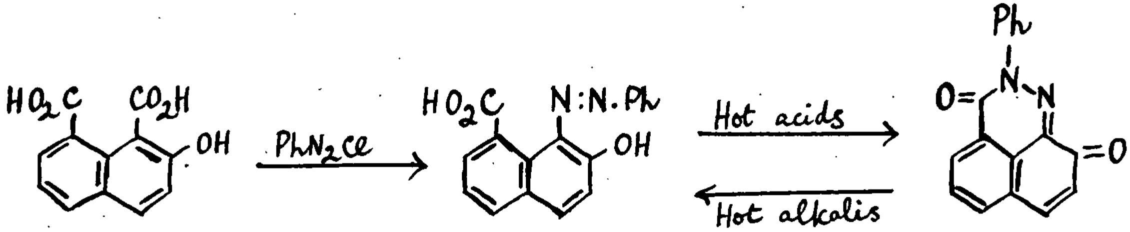
In 1911, Ullmann and Schalk (178) used anthraquinone α-carboxylic acid to synthesise two new derivatives, "pyridazone-anthrones", which can be considered to be N-derivatives of dibenzo [de,h]cinnoline-3,7-dione (IV).



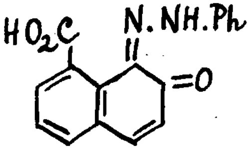


(IV)

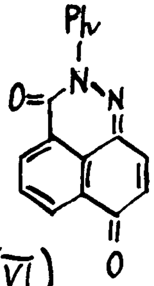
An attempt (54) to assign correct structural formulae to the three possible hydroxynaphthalene-1,8-dicarboxylic acids using the known directional tendencies of coupling in α- and β-naphthols led to the discovery of an anomalous coupling reaction. Whereas 3-hydroxynaphthalene-1,8-dicarboxylic acid gave 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).

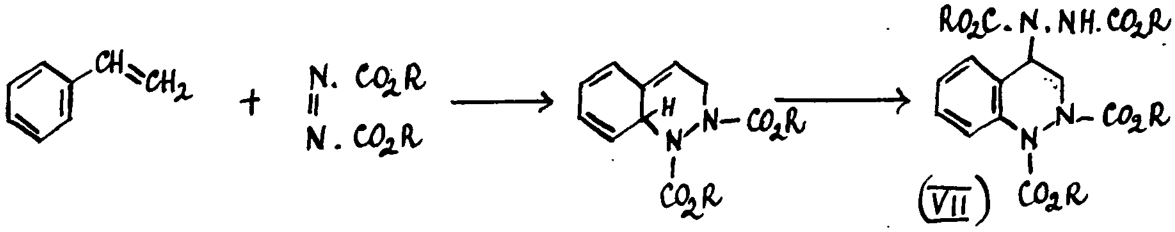


(V)

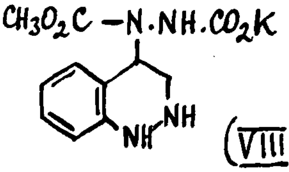


(VI)

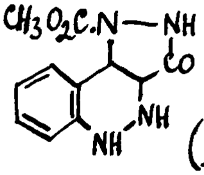
Particular interest attaches to the next N-substituted cinnoline in view of the novel method of preparation. An investigation into the course of the "azo-ester reaction" led Diels and Alder (50) to the preparation of tetrahydropyridazine derivatives from certain unsaturated hydrocarbons; these syntheses 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.



(VII)

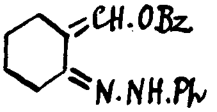


(VIII)

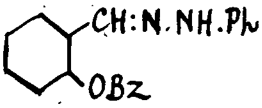


(IX)

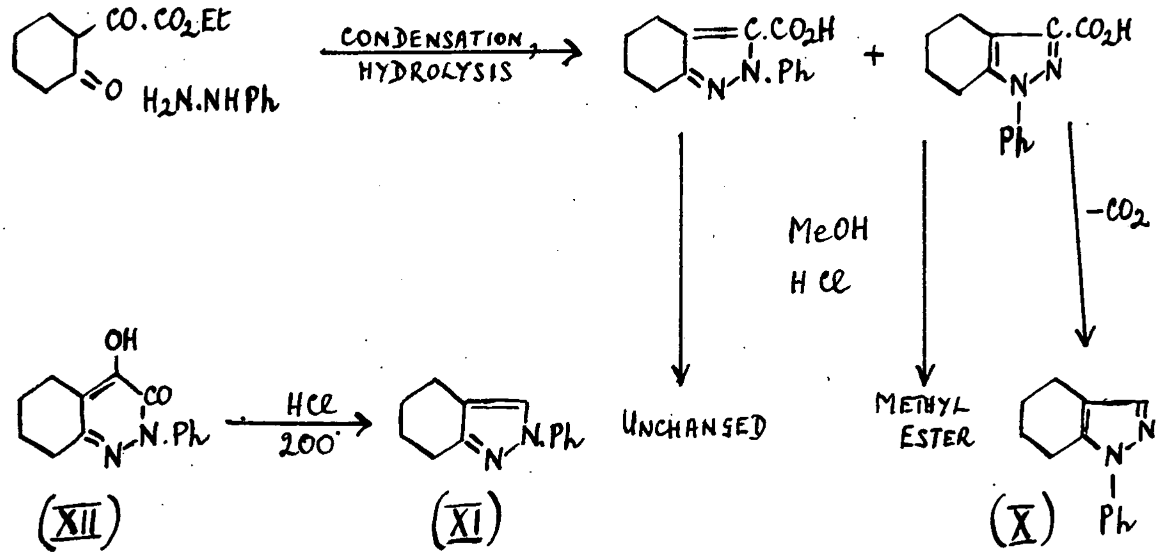
During researches on tetrahydroindazoles Auwers (10) determined the structure of benzoylated hydroxymethylene cyclohexanone by cyclisation of the phenylhydrazone



OR

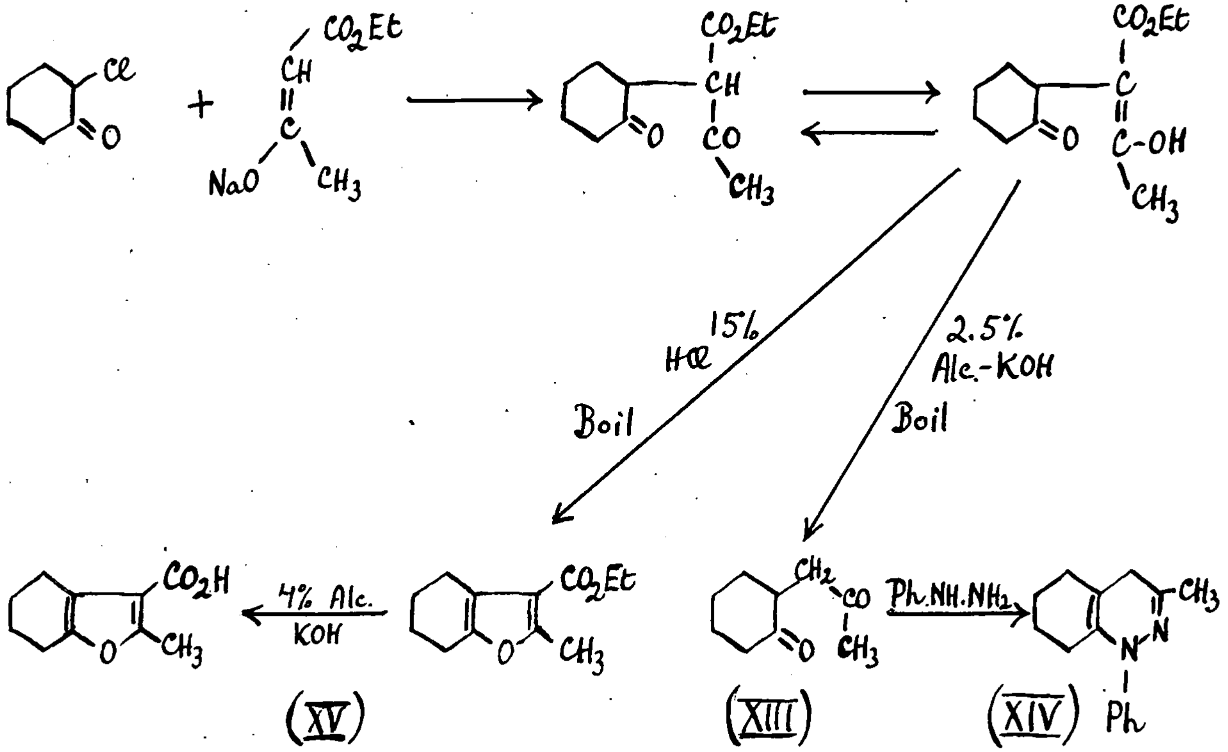


to the indazole and comparison of the spectrochemical constants of the latter with those of authentic 1- and 2-phenyl-4:5:6:7-tetrahydroindazoles (X and XI respectively).



The mixed ethyl-esters formed by the original condensation were accompanied by the cinnoline-derivative (XII), which, like the phenyl-methyl-hydroxypyridazone of Ach (1), 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.

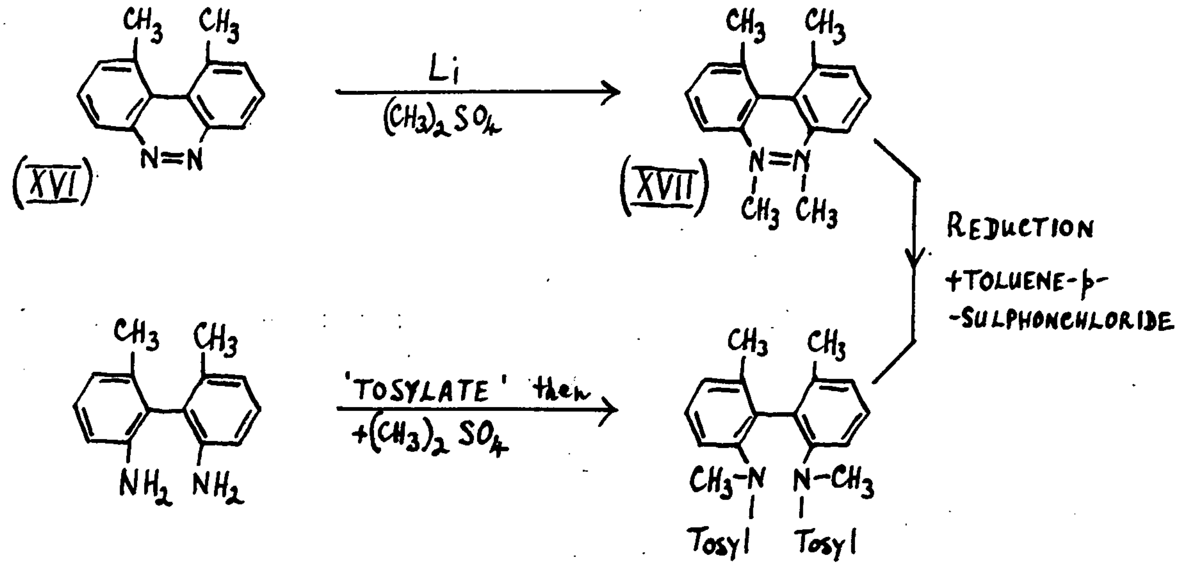
Yet another example of the preparation of a cinnoline during researches on entirely different compounds is apparent in the preparation by Ebel, Huber and Brunner (55) of the cinnoline (XIV) from acetonylcyclohexanone (XIII), the latter being prepared during a study of Bz-tetrahydrocoumarones (XV).



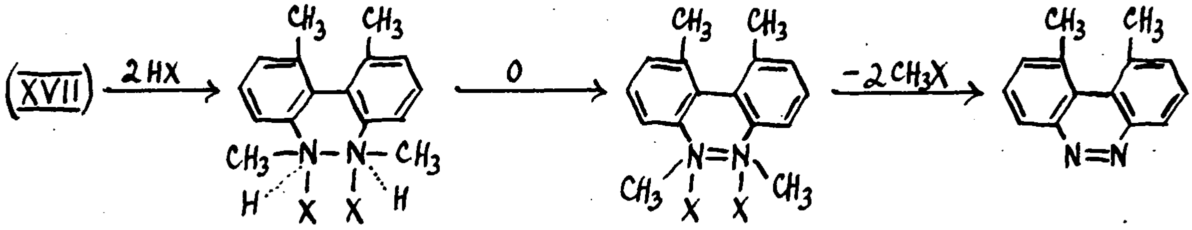
(XV) (XIII) (XIV)

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 configurations 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.

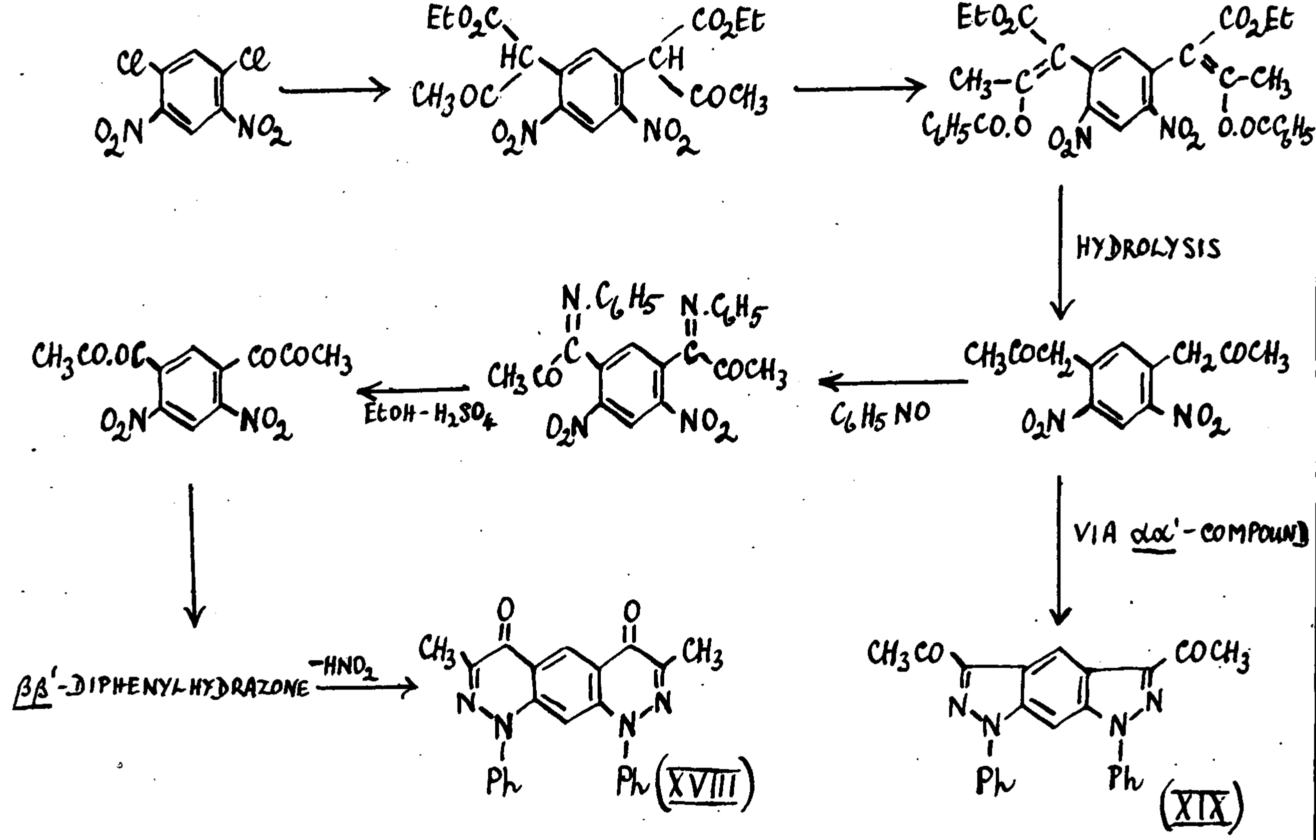


The cinnoline (XVII) (and its α-bromocamphor-π-sulphonate) were slowly decomposed to "4:5-dimethylphenazone" in acid solution with the development of a blue colour. That this decomposition was caused by atmospheric oxidation was evidant when the same result was reached using mild oxidising agents and the following scheme was proposed:



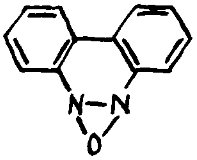
The '9,10'-dihydro-compound was prepared and isolated as the sulphate but attempts to regenerate the freebase gave only "4,5-dimethylphenazone". The difficulties encountered in the phenazone series in conjunction with the known futile attempts of Sako (see below), led to concentration of the research 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.

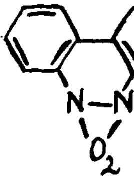


This was shown to be distinct from the substance (XIX) obtained by similar treatment of the αα'-diphenylhydrazone.

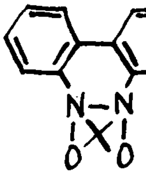
Various oxides of cinnoline derigatives can be considered in this group. The first cinnoline oxide was obtained by Tauber (165) as a concomitant of "diphenylenazon" - a compound consisting of "a new N-containing closed ring system". Moderate treatment of o-dinitrodiphenyl with zinc and alcoholic potassium hydroxide gave a monoxide (XX) and a dioxide [possibly XXI (a), (b), or (c)].



(XX)

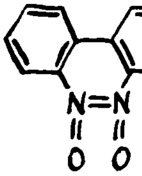


(a)



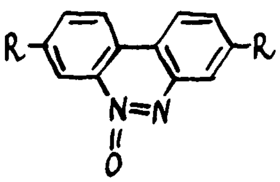
(b)

(XXI)

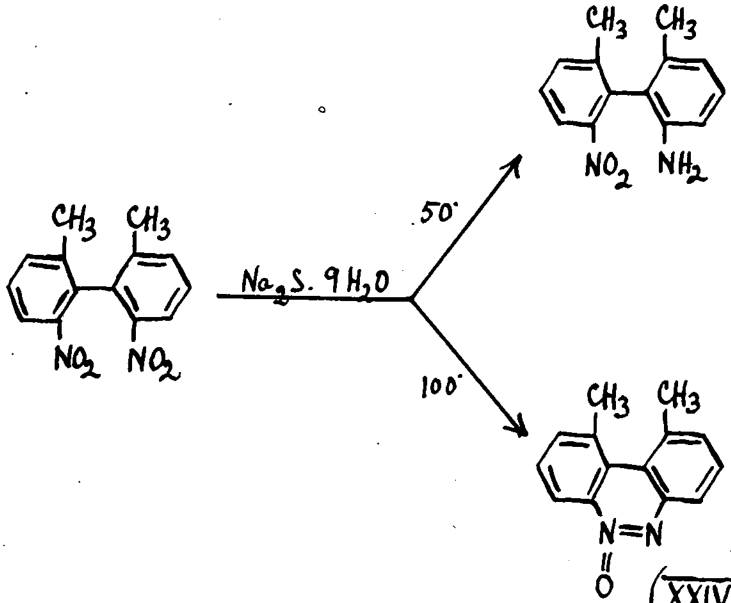


(c)

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 treatment of the requisite dinitrodiphenyls with sodium sulphide furnished the monoxides of 3:8-dimethyl- and 3:8-tetramethylamino-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.

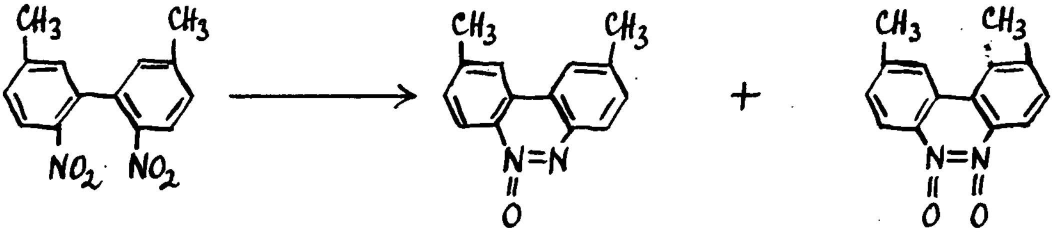


(XXII; R=CH$_3$)
[XXIII; R= N(CH$_3$)$_2$]



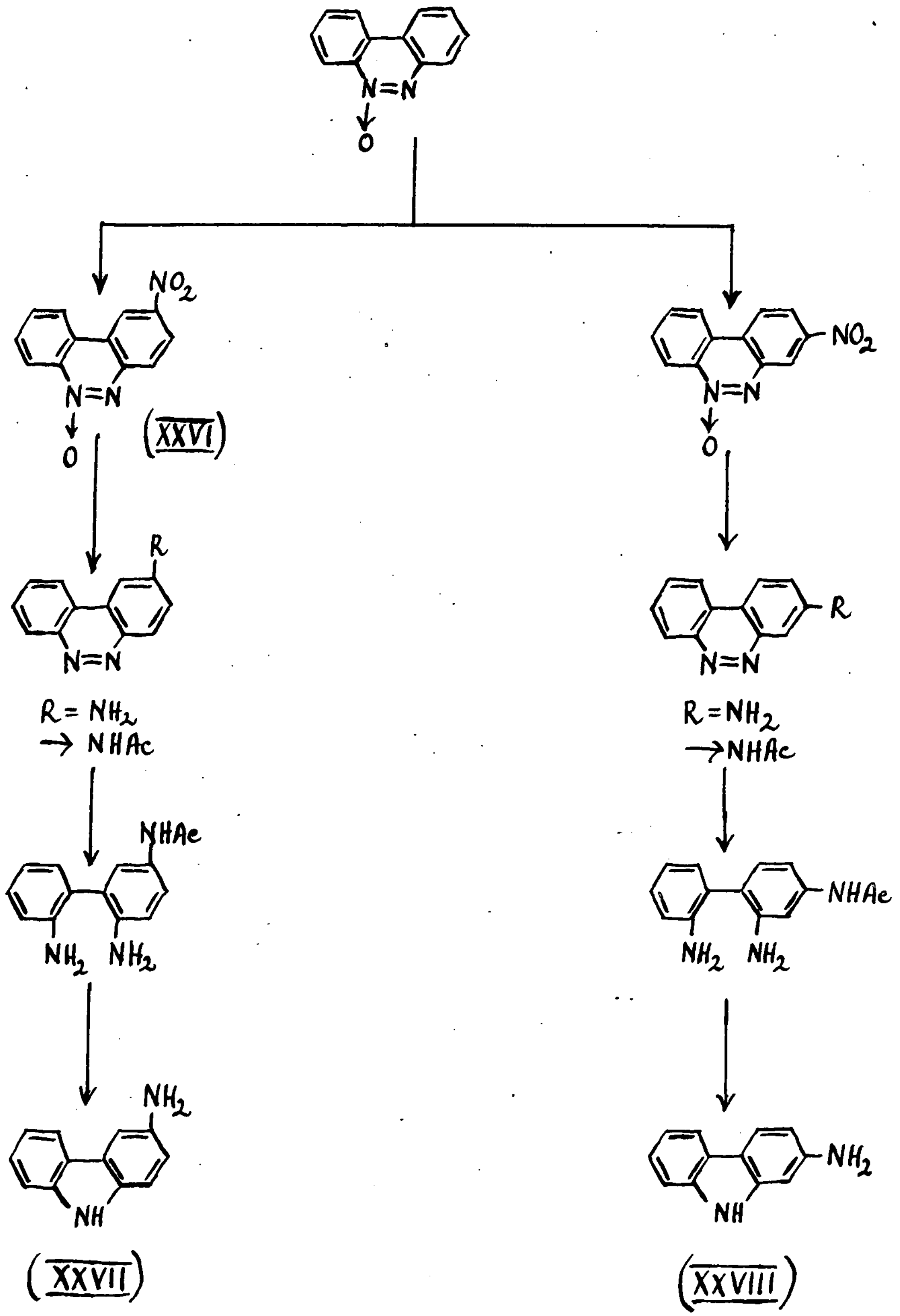
(XXIV)

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).

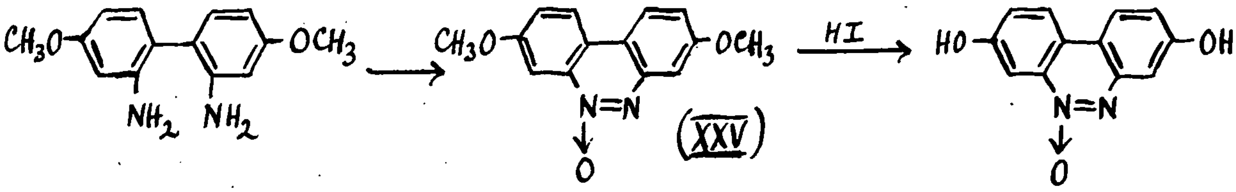


In connection with an unsuccessful attempt to resolve 6-nitro-6'-acetamido-diphenic acid,$ako (135) found that the requisite intermediate was formed by reduction of 2:2'-dimethyl-6:6'-dinitrodiphenyl with alcoholic sodium sulphide at 50°; at 100°, however, there was formed "4:5-dimethylphenazone oxide" (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.



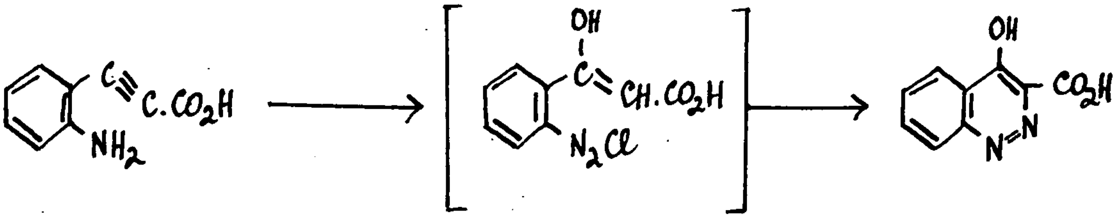
The absorption spectra of the oxides of "phenazone" were measured in 1936 (128) and the close similarity to the spectrum of benzo[c]cinnoline was noticed, this being in striking contrast to the effect of 'oxygenating' the nitrogen atoms of azobenzene.

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 this oxide gave mainly 2-nitrobenzocinnoline-6-oxide (XXVI) 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 aminobenzocinnolines, 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.

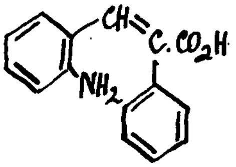
In spite of the small amount of experimental evidence available to early workers in the cinnoline field several attempts to explain the mechanism resulting in cinnoline formation were made and comparisons between cinnoline syntheses and those of other heterocyclic compounds were often stressed. Reference 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



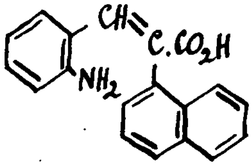
Widman's comparison of his synthesis with Richter's has also been dealt with (page 46). Stoermer and Fincke (158) recognised the essential role of the ethylenic rather than the acetylenic side chain, the successful preparation of 4-phenylcinnoline and later (160) 4-anisylcinnoline being carried out to 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:

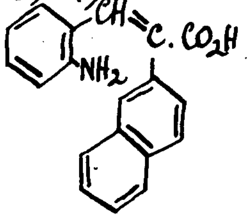
(a). Those ethylenes having no hydrogen atom on the β-Carbon atom of the side chain and hence unable to undergo cyclisation to a cinnoline, e.g.(41,100,181,124);



(I)



(II)



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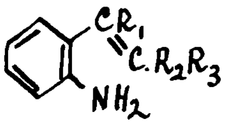
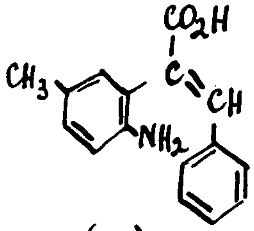


(IV)

(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).



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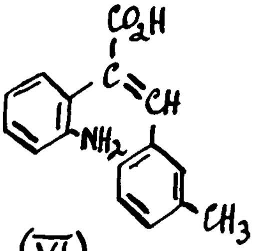


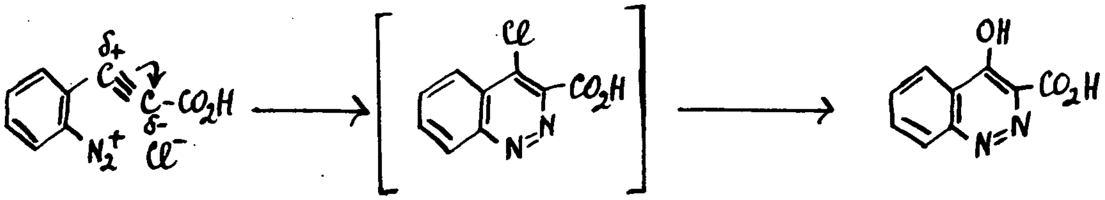
(VI)

This behaviour was attributed to either one or both of the substituents on the α- and β-carbon atoms.

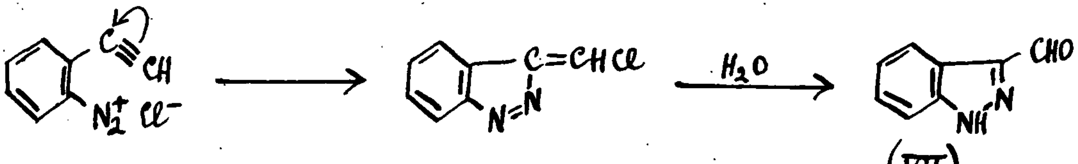
Cis and trans 2-aminostilbenes were included in this group since neither isomer gives rise to a cinnoline. The cis form generally gives some Pschorr cyclisation product but the trans isomer undergoes decomposition; thus Ruggli and Staub (132) showed that diazotised cis 2-aminostilbene gave a good yield of phenanthrene whilst the trans isomer gave either trans stilbene (62% yield) or trans 2-hydroxystilbene 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 (101) did not mention any cinnoline formation.

(c) o-Aminocinnamic acid and its derivatives; additional evidence (161) concerning the diazotisation of the former was presented as well as the successful preparation of o-cyanocinnamic ester by a Sandmeyer reaction on diazotised o-aminocinnamic 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 (142). In the cyclisation of diazotised o-aminophenylpropiolic acid there was suggested the following mechanism involving an intermediate chloro-compound (see, however, page 37).



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-aminophenylacetylene yield the corresponding acetophenones on hydration (63,15)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:



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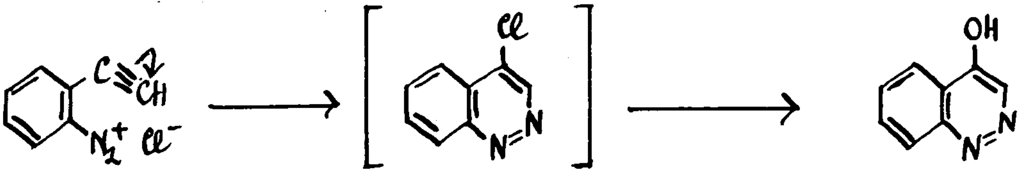
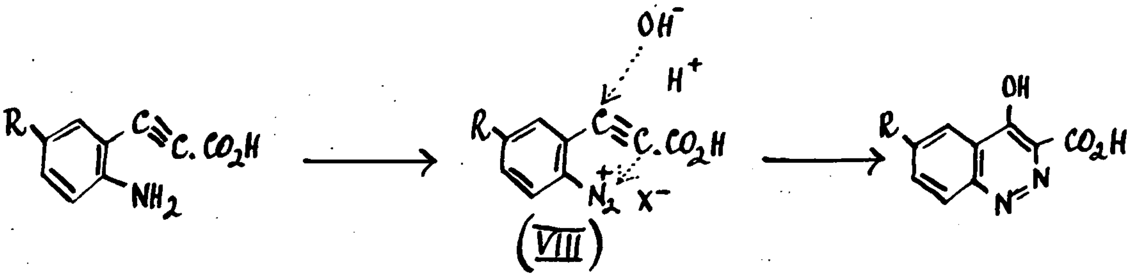


This anticipation was justified, 4-hydroxycinnoline and its 6-methoxy-analogue being prepared by this method in good yield (page 26).

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-aminoacetoveratrone, neither of which form cinnolines (page 27), with the weak basicity of 5-nitro-2-aminoacetophenone). 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:

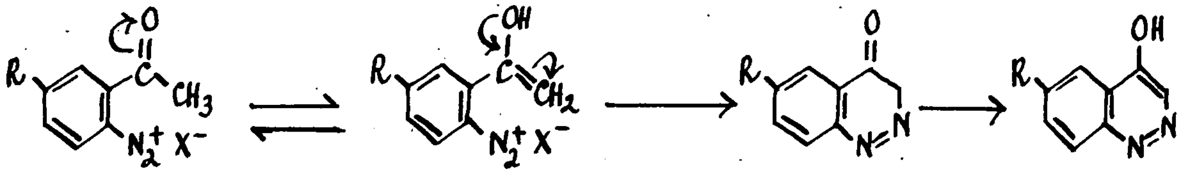


From this base was built the whole argument of the thesis - that the three chief cinnoline syntheses were "essentially manifestations of the same fundamental process" (142). Complete hydration (by coordination of a proton with anionoid carbon) was rejected as an intermediate in the above mechanism for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

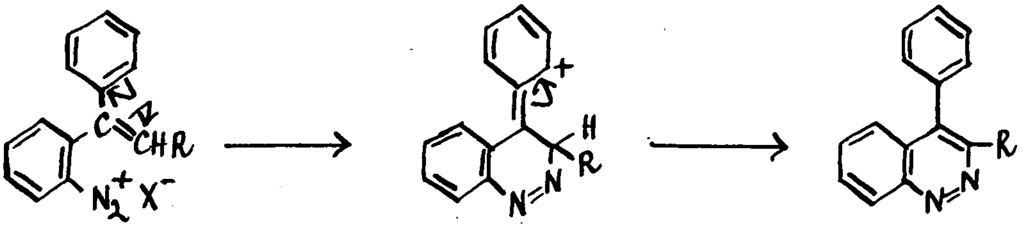
(a) o-Aminobenzoylacetic acid, the intermediate of the hydration hypothesis, shows a marked tendency to form quinoline derivatives, none of which were observed by Schofield and Simpson; also (b) the process of hydration must outpace that of diazotisation (an unlikely probability), the alternative being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

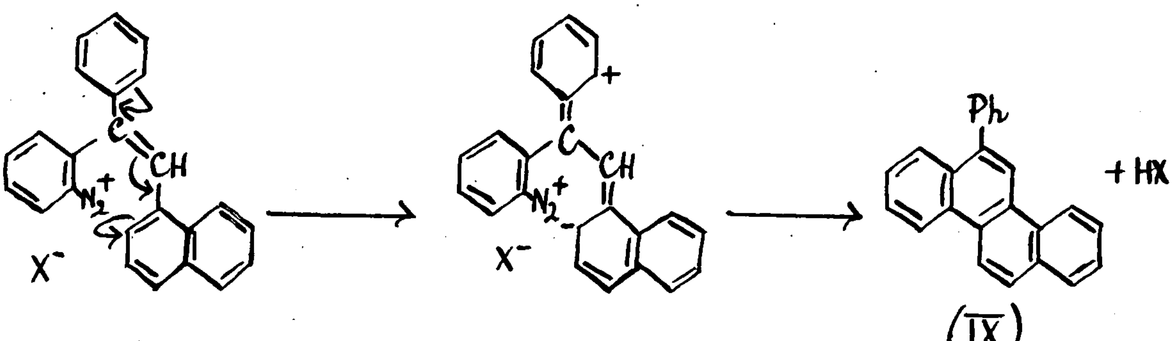
In diazotised o-aminoacetophenones the increased kationoid activity produced by nuclear substituents (R = CN, NO_2, halogen) led to a general shift to the right terminating in the hydroxycinnoline. A similar polarisation explained the Widman-Stoermer



reaction, the anionoid nature of the terminal carbon atom being induced by an aryl α-substituent. The explanation of "irregularities" 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

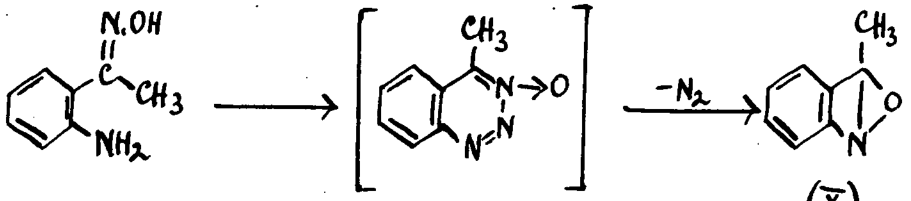


(IX)

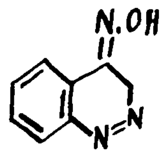
reduces the anionic charge on Cβ with consequent reduction in the yield of cinnoline. The absence of phenanthrene formation noted when the C_β substituent was phenyl (page 56) is not surprising in view of the smaller electron capacity of the single aromatic ring.

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 oximino-dihydro-cinnoline (XI) by diazotisation of o-aminoacetophenone oxime(11, 104).



(X)

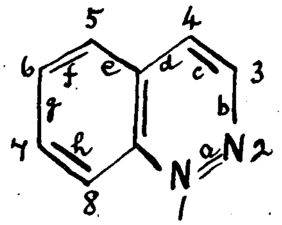


(XI)

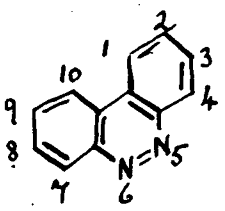
Benzocinnolines.

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.

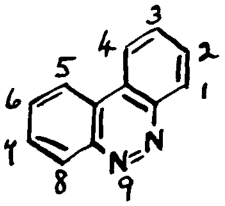
Considerable confusion exists over the nomenclature of substances of this group; thus 3,4-benzocinnoline or benzo[c]cinnoline (I) has been called phenazone and diphenyleneazone (both names are listed as "objectionable" by "The Ring Index") whilst other names not based on cinnoline are in common use, 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.

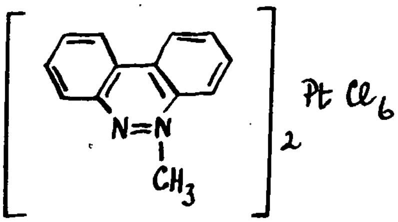
The best method for the preparation of 3,4-benzocinnoline is due to Wohlfahrt(189) who subjected 2,2'-dinitrodiphenyl to electrolytic reduction thus securing a 95% yield of the cinnoline.

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 thd 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



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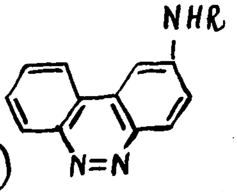
*The earlier (1934) work of Sako (page 69) did not, as stated by Leonard (93), include the preparation of 1,10-dimethylbenzo[c]cinnoline.

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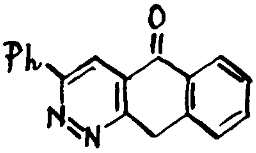
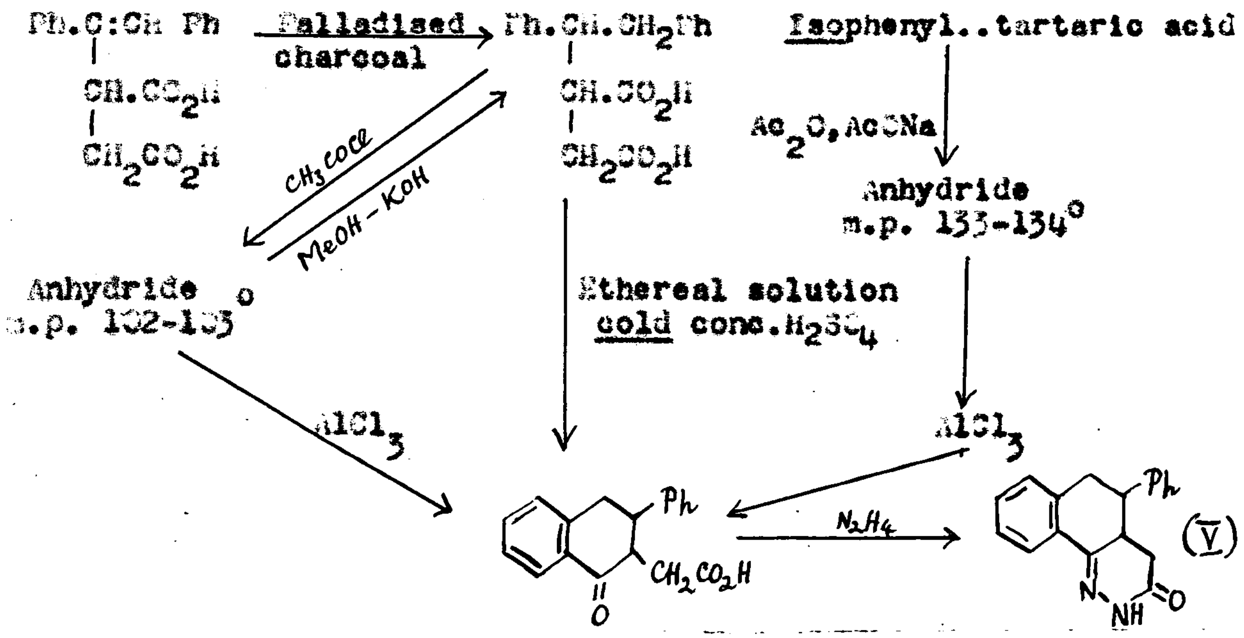
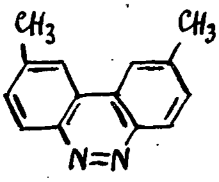

(IV)

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 Sinn (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 (145).



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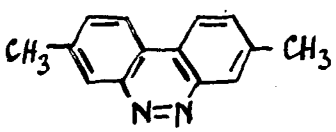

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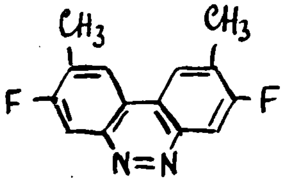
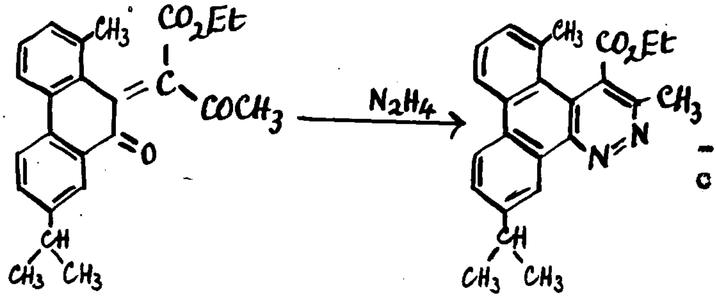


(VIII)

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). Thelatter was described by Ullmann and Dieterle (145) 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.

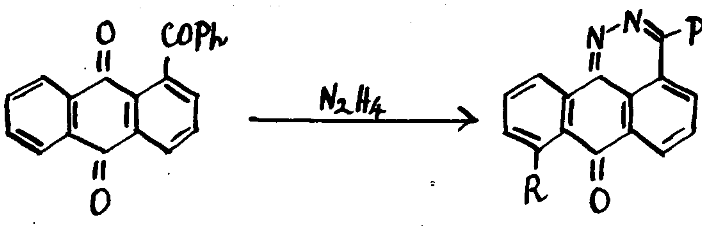
Dibenzocinnolines.

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



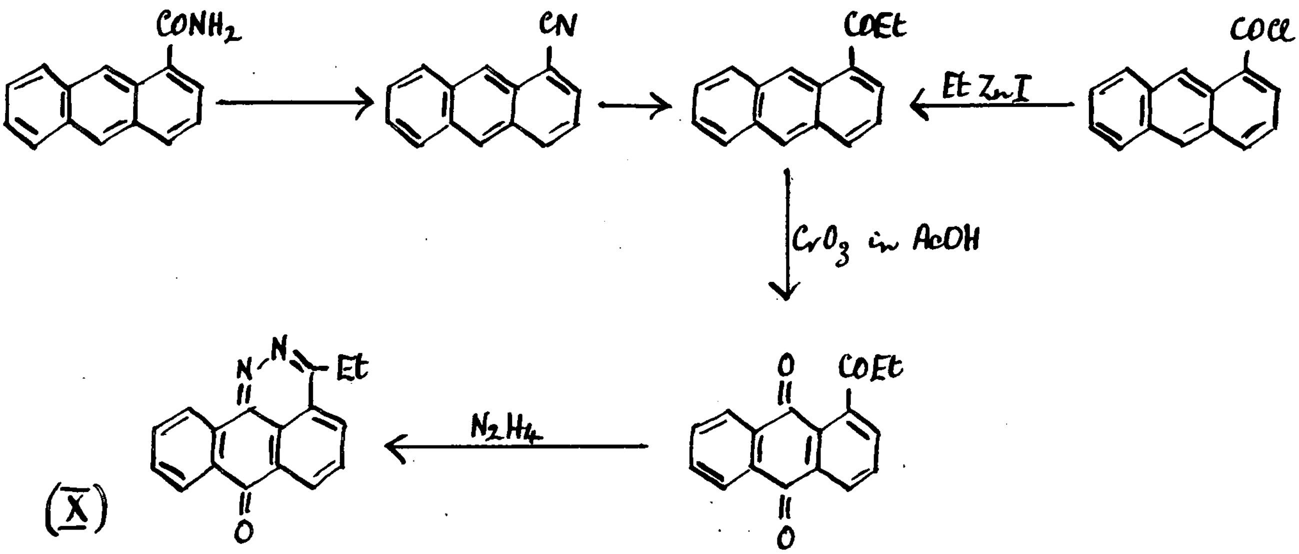
Ethyl 3,5-dimethyl-11-isopropyldibenzo[f,h]cinnoline-4-carboxylate

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.



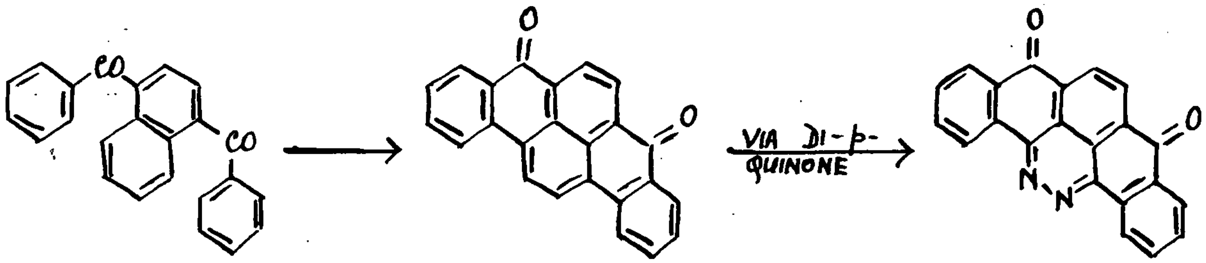
(X)

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

Polynuclear Cinnolines.

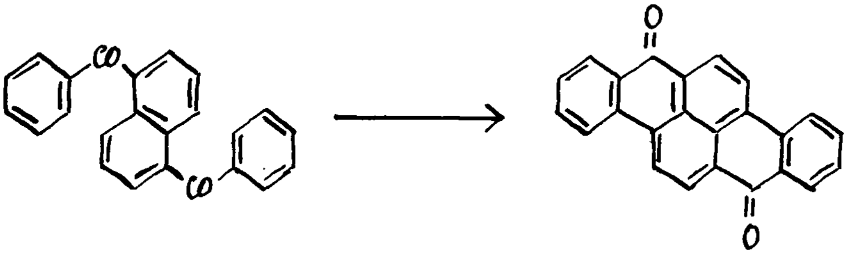
Many compounds of this type have already been reviewed by Leonard (93) although one is led to believe, as elsewhere in the same publication, that a large number of workers were concerned wholly with the chemistry of cinnolines. The majority of the following cinnolines were obtained by the action of hydrazine 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 contribution 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):-

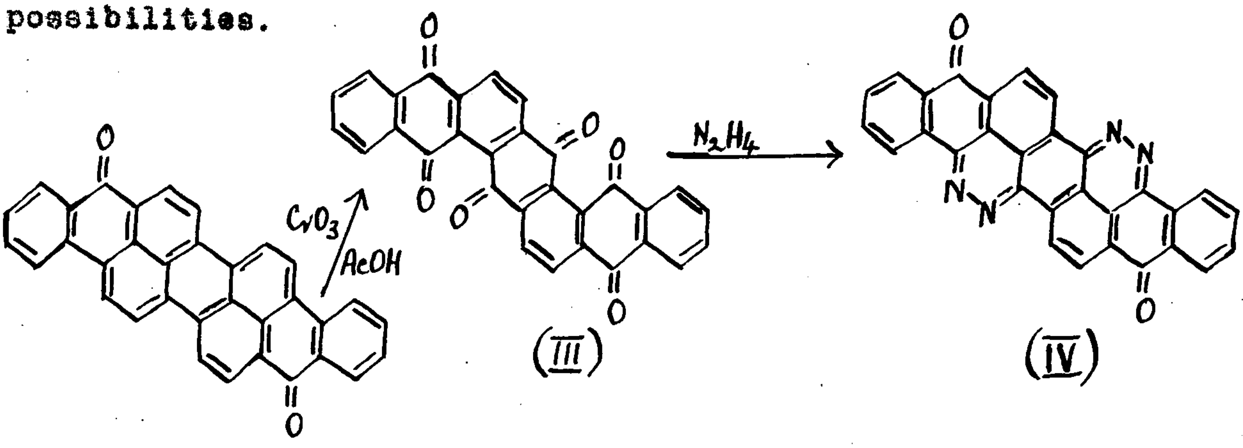


(I) (II)

- such confirmation was necessary in view of the fact that the following analogous cyclisation did <u>not</u> occur as shown.

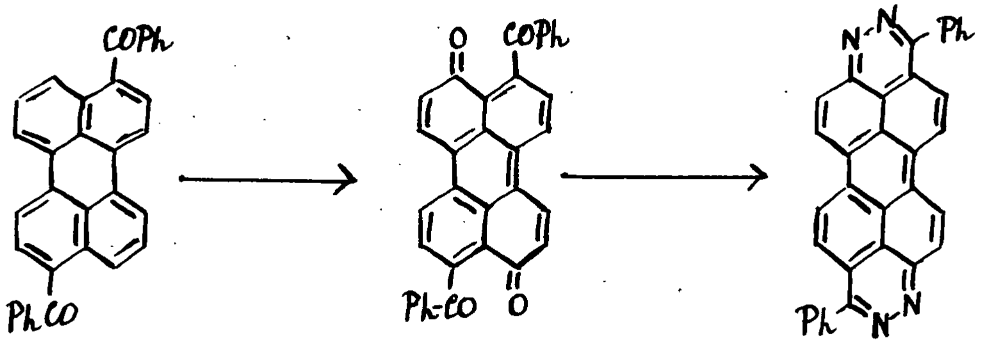


In 1928, Scholl and Meyer (145) found that isoviolanthrone was oxidised to the compound (III), which, because of the two 1,4-diketo groups, "was considered well adapted for synthetic purposes". The formation of a hydro-derivative of the azine (IV) was quoted as an example of such synthetic possibilities.



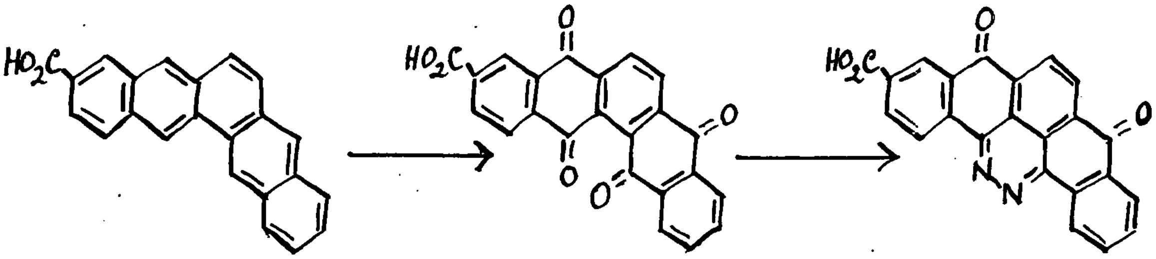
(III) (IV)

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.



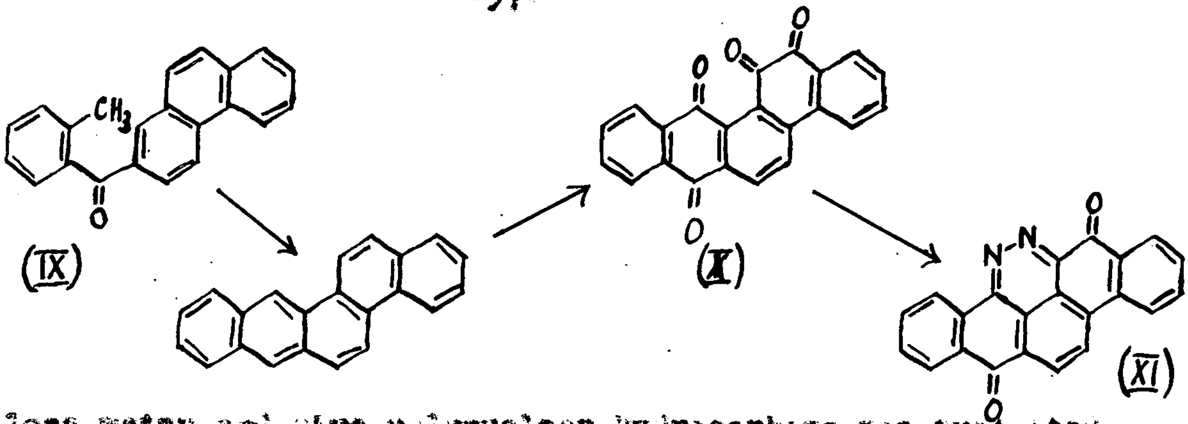
(V) (VI)

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).

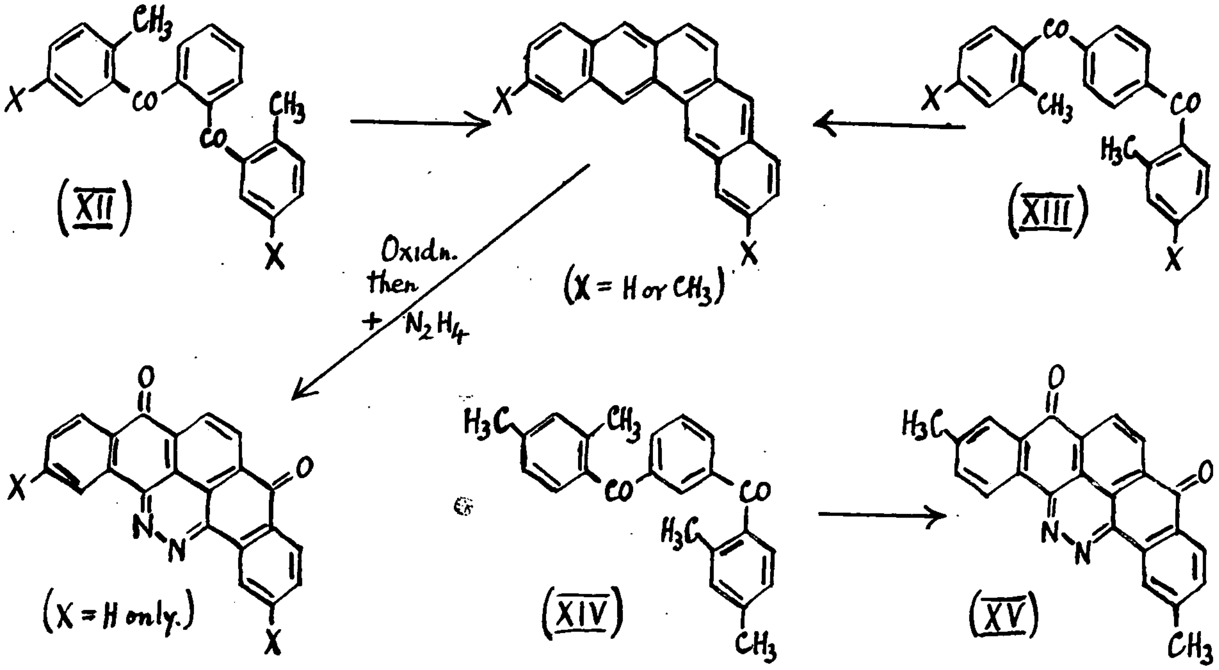


(VII) (VIII)

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

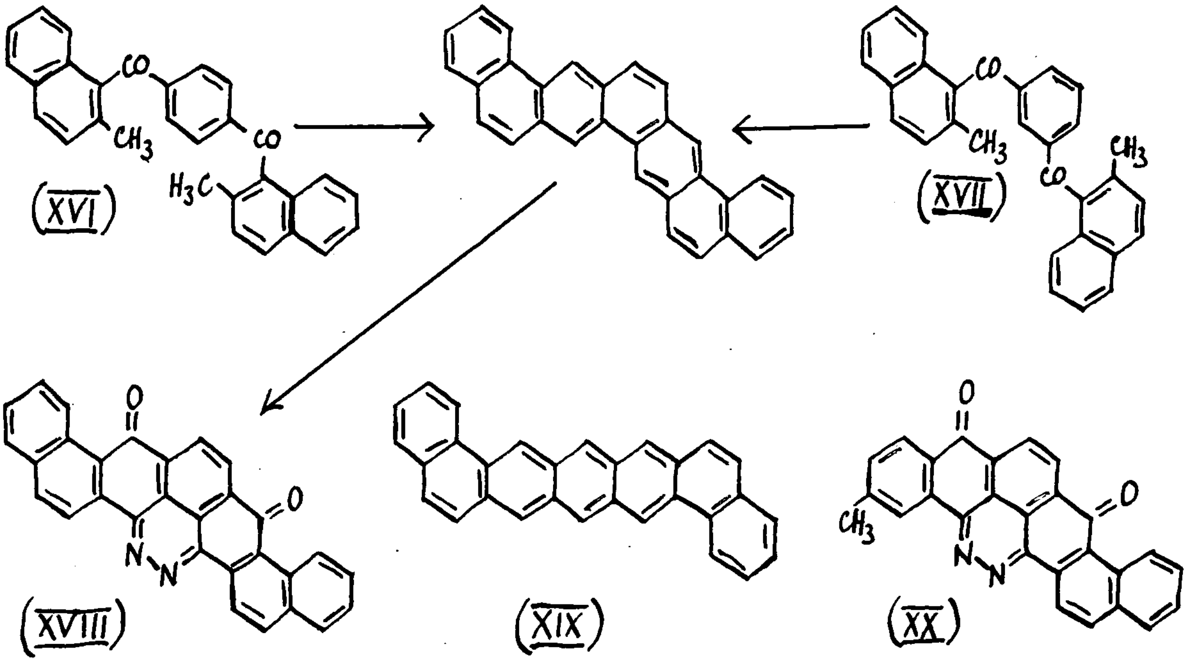


lose water and give polynuclear hydrocarbons was exploited (37) using di-o-tolyl benzenes. The angular structure of the resulting naphthoanthracene was proved by isolation of the same cyclisation product (different from lin. dibenzanthracene) from (XII) and the para isomer (XIII).



Further, the [illegible],4'-isomer (XIV) gave rise to the azine (XV), again a clear indication of the angular structure of the initial cyclisation product.

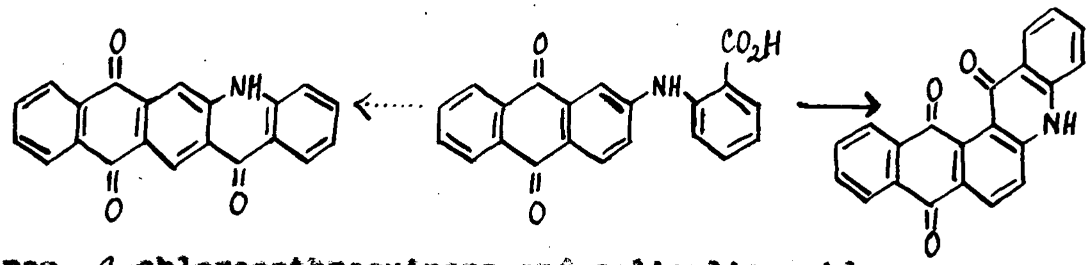
Clar, John and Avenarius (36) obtained four hydrocarbons by pyrolysis of the ketones (XVI) and (XVII); two of these (yellow) were shown to be identical and on oxidation and then treatment with hydrazine gave the cinnoline derivative (XVIII). The other pair (red) were also considered to be the same substance (XIX).



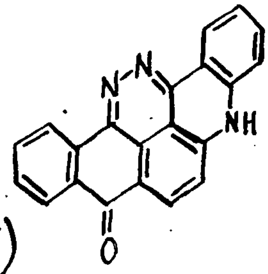
(XVI) (XVII) (XVIII) (XIX) (XX)

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').

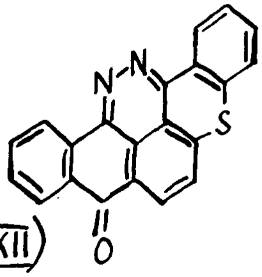
Mention may here be made of two similar compounds prepared by Ullmann (179 and 173). The first (XXI) was derived from an anthraquinone-acridone (prepared for testing as a dyestuff) and served to confirm the angular structure of the product (⟶) as against the linear possibility (⇢). The sulphur analogue (XXII) was prepared by a similar route



from β-chloroanthraquinone and salicylic acid.

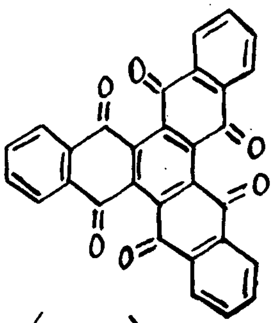


(XXI)

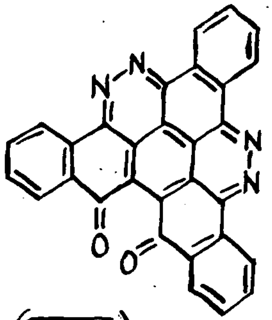


(XXII)

The polymerisation of 1,4-naphthaquinone to triphthaloylbenzene (XXIII) was studied in 1939 (126) and the polymer was characterised as the bis-azine (XXIV).

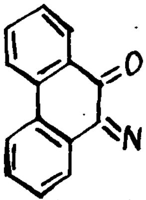


(XXIII)

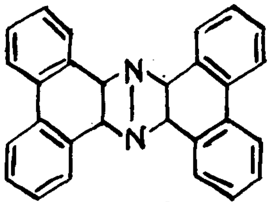


(XXIV)

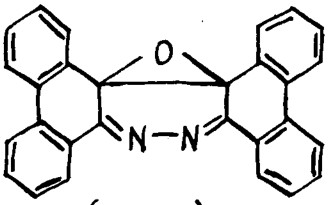
Schonberg and Rosenthal (147) proposed a cinnoline-like structure (XXVII) for phenanthraquinone imide anhydride, a compound prepared by Zincke (190) by treating the imide (XXV) with acid anhydrides. The oxygen-free compound obtained by heating the anhydride to a high temperature was different from the 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 of the imide anhydride to reduction indicated the impossibility of an azoxy-link whilst the structures(XXX and XXXI), advanced by Graebe and Cehme respectively, did not explain satisfactorily



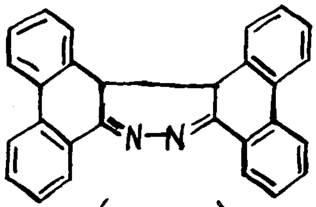
(XXV)



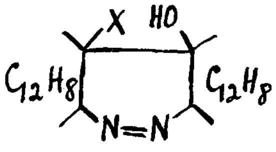
(XXVI)



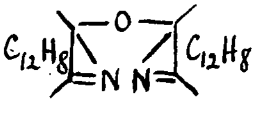
(XXVII)



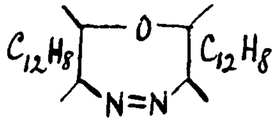
(XXVIII)



(XXIX)



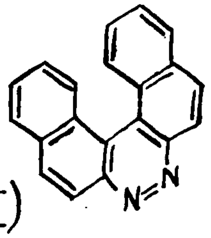
(XXX)



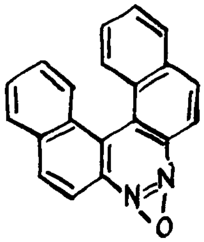
(XXXI)

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).



(XXXII)

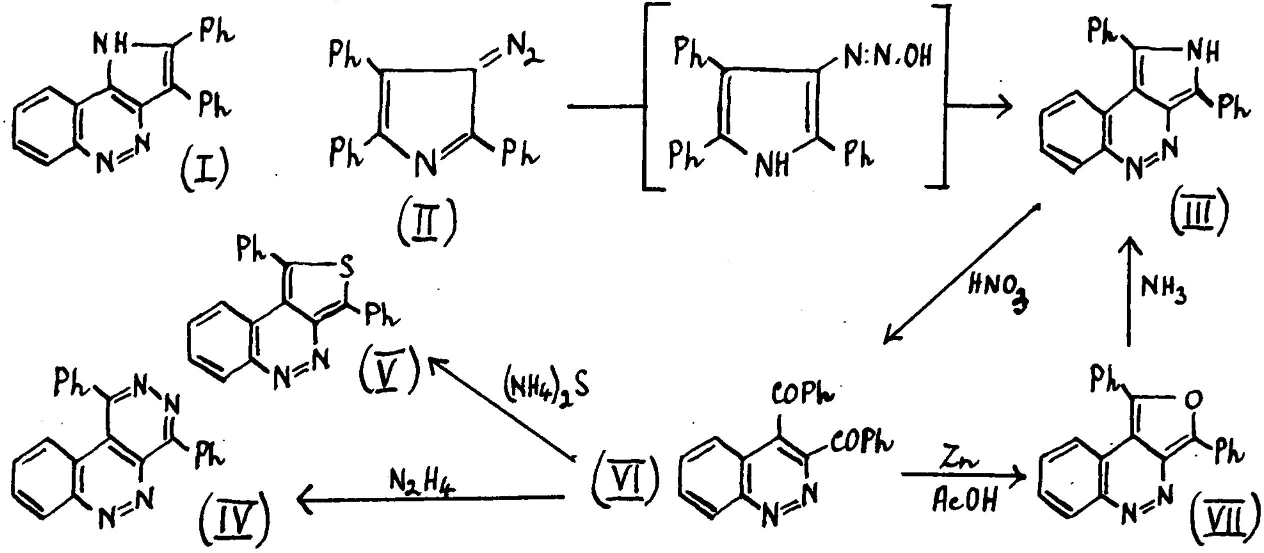


(XXXIII)

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.

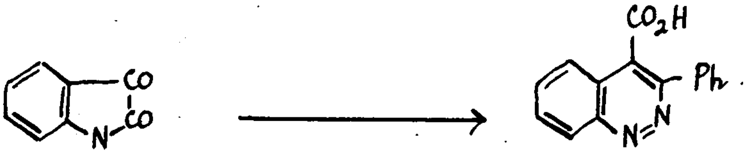
Other Cinnolines.

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).

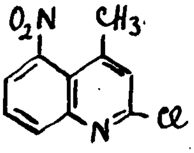
In 1924, 3-phenylcinnoline-4-carboxylic acid (IX) was prepared from N-benzylideneamino-isatin (VIII) during an unsuccessful attempt to prepare N-aminoisatin. Stolle and Becker (162) noted the similar ease of decarboxylation between their compound and Richter's acid (page 25) although no



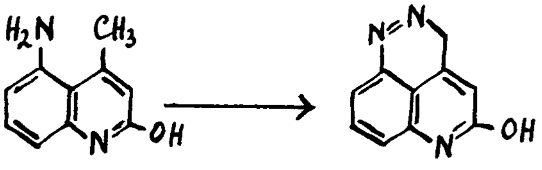
(VIII) (IX)

attempt was made to isolate the decarboxylation product. An attempt to repeat this work is described later, page 207.

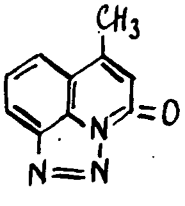
During an attempt to increase the basicity of compounds destined for antimalarial testing Krahler and Burger (89) investigated the nitration and subsequent reduction of 2-chlorolepidine. The first process gave a mixture of 6-nitro-2-chlorolepidine and a new mononitro-derivative, which, on the basis of 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).



(X)



(XI)



(XII)

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-aminoacetophenones.

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

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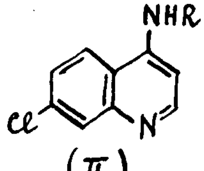
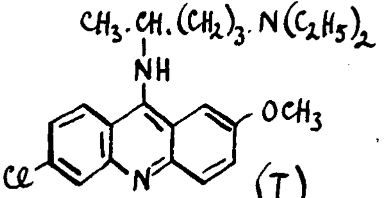
* The weak inductive effect (±I) exerted by the 4-substituent on the 2-diazonium group can probably be neglected here although examples of such an effect between "m-substituents" are known (51).

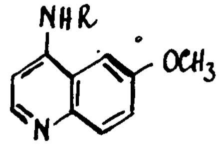
derivative being in striking contrast to the effect produced in the quinoline series (3). It is evident from a consideration of the structure of atebrin (I)that antimalarial activity might be correlated with each "half" (II and III) of the molecule. Until very recently* the only published evidence to 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.



(II)



(I)



(III)

(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 inaccessibility of the latter material. The preparation of 7-cyano-4-methylcinnoline either directly or via the 7-halogeno-compound

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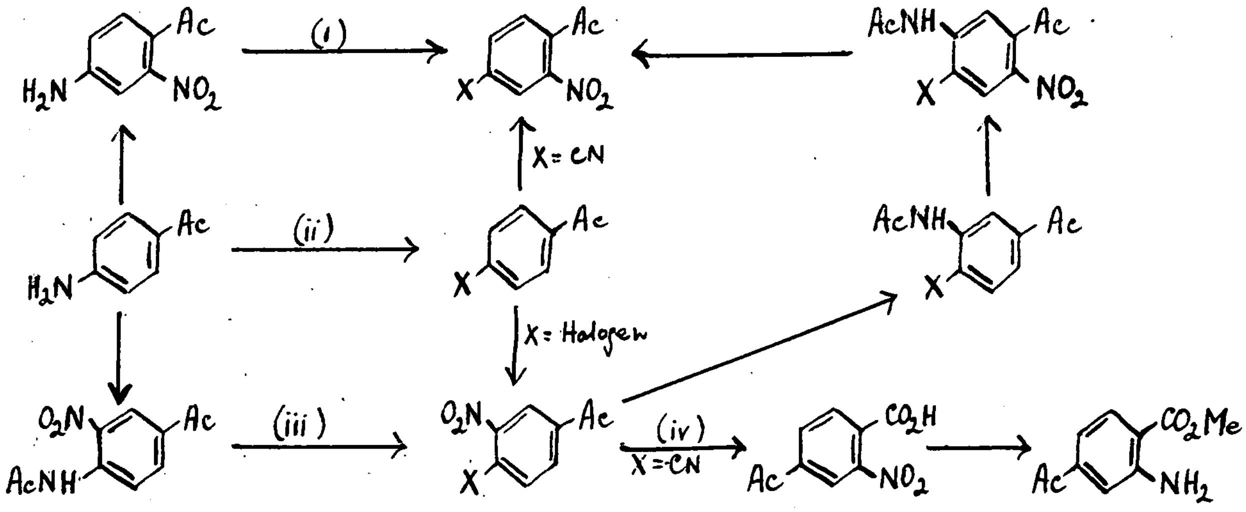
* Contributions to current (1946) issues of the J.A.C.S. have exploited fully the possibility that 7-substituted-quinolines (122), -quinazolines (123) and -phthalazines (52) might show antimalarial activity. Some duplication of the present work has occurred (94 , 95) and will be dealt with later.

offered such an alternative route to Widman's acid.

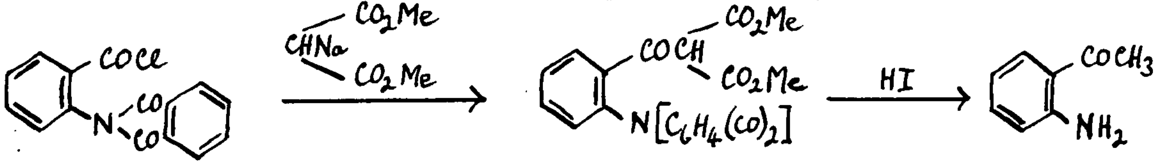
Possible routes to 4-substituted-2-aminoacetophenones which appeared to be most direct gave discouraging results.



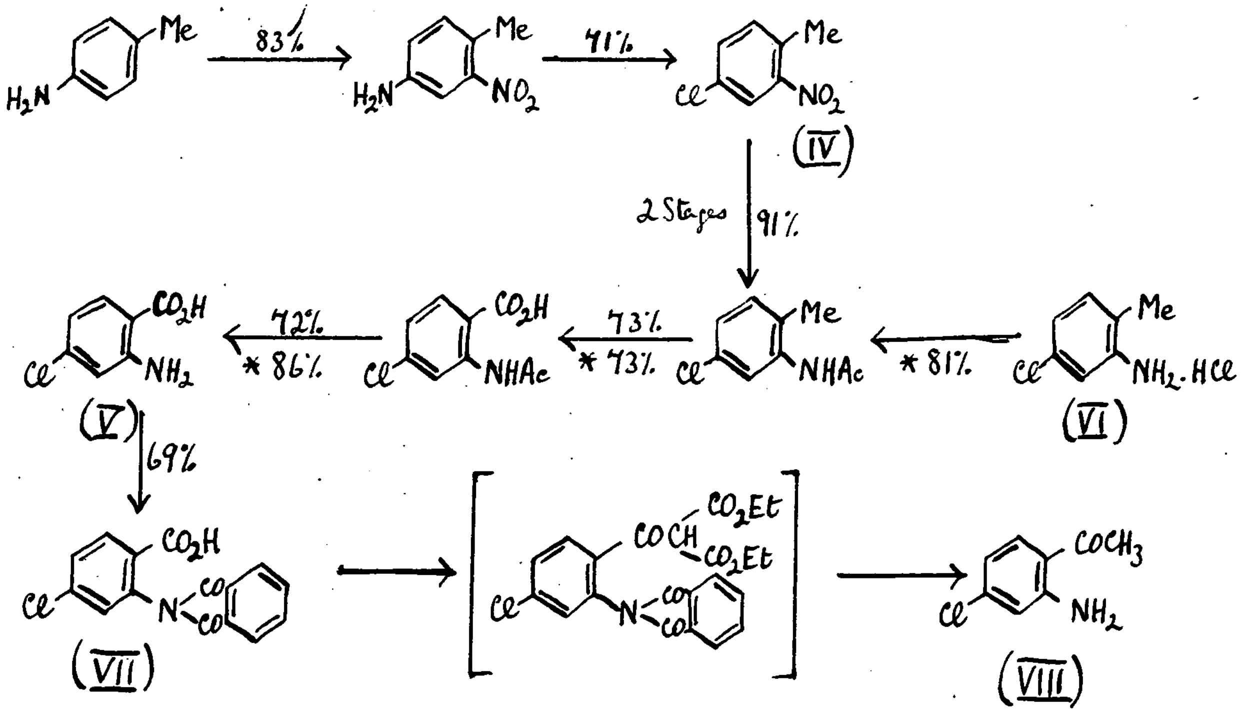
Thus (route i) nitration of p-aminoacetophenone in the presence of a large excess of sulphuric acid gave a resinous product, completely soluble in alkali. A preliminary attempt (route ii) to nitrate p-cyanoacetophenone, obtained from the amine by a Sandmeyer reaction, was unsuccessful. The substance 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 Raadeveld (127) and the subsequent nitration by Gibson and Levin (67). Further, 4-chloro-3-nitroacetophenone and 4-bromo-3-aminoacetophenone were known (102 and 67 respectively) whilst reference to other relevant work (route iv) was available (102).

In 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 affected by the method of either Raadeveld (127) 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-aminoacetophenone 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 hydrochloride (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 α-chloronaphthalene as a diluent was only successful on the small scale. Refluxing the components in acetic acid, a prodedure 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, other 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.)	Condensation ǂ 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.

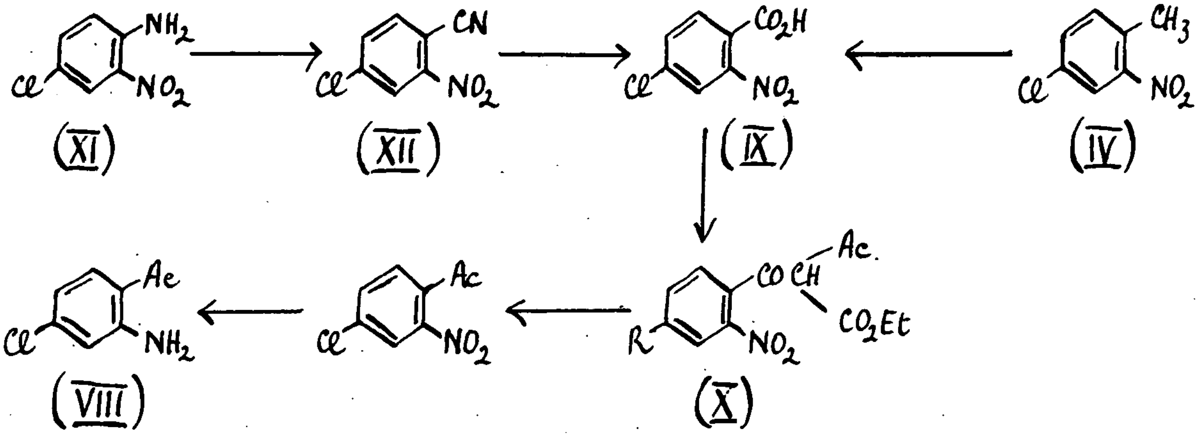
ǂ "A" and "B" are fully described on page 135.

§ 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 sodioacetoacetate. Treatment of the highly crystalline intermediate compound, ethyl(4-chloro-2-phthalimidobenzoyl)acetoacetate, with hydriodic acid did not give the desired result, 4-chloroanthranilic acid being the only isolable product. The use of alcoholic sulphuric acid in the hydrolysis (81) 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 Heller, 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 (53) 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. Heller'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. Reproducible 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-hydroxycinnoline 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- benzonitrile	 benzoic acid	 acetophenone	4-Chloro-2-amino-acetophenone	Cinnoline
4-Chloro-2-nitro-aniline	50-55	80	74	85	39.5ϕ
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% " " "
ϕ 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-aminoacetophenones 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-hydroxycinnoline. 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-aminoacetophenone; 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-5-nitro-2-aminoacetophenone was isomeric with 6,7-dichloro-4-hydroxycinnoline and it was regarded as 7,8-dichloro-4-hydroxycinnoline (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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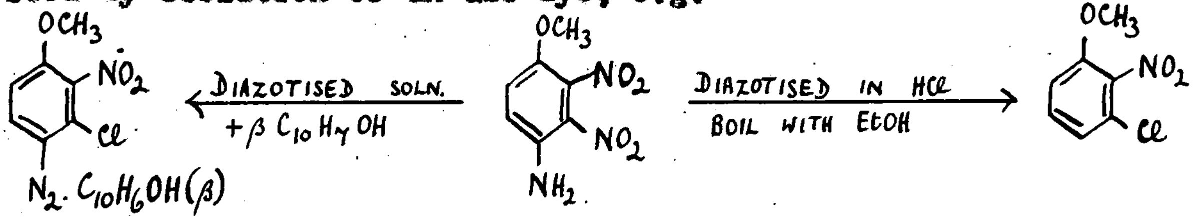
[*] This compound and its 4-chloro- and 4-phenoxy-derivatives were prepared earlier in this laboratory (Liverpool) by Mr.J.R. Keneford and such identity confirms the orientation of the nitro-group in the major nitration product of 4-chloro-2-acetamidoacetophenone (page 117).

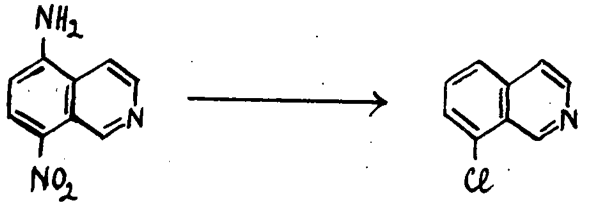
[†] By treatment with boiling acetic anhydride; treatment with the hot reagent and a five-fold amount of pyridine was ineffective whilst a four-fold quantity of acetic anhydride (relative to pyridine) gave almost total acetylation - this behaviour is similar to that observed (151) with ethyl 6-methoxy-4-hydroxyquinoline-3-carboxylate.

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.

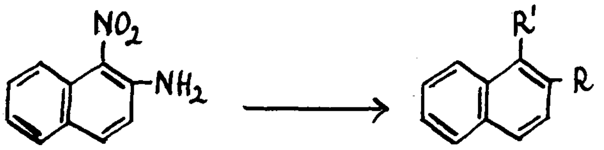
Although the cause of the curious results obtained on diazotisation was unexpected a literature survey disclosed a number of similar examples which were equally explicable by the direct replacement hypothesis mentioned above. Thus Meldola (105) observed the same replacement reaction in certain dinitroanisidines,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



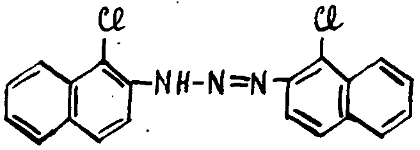
More recently, Keilen and Cass (79) obtained 8-chloro*iso*quinoline by diazotisation of 8-nitro-5-amino*iso*quinoline and subsequent deamination. Both groups of workers noticed the presence of



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).



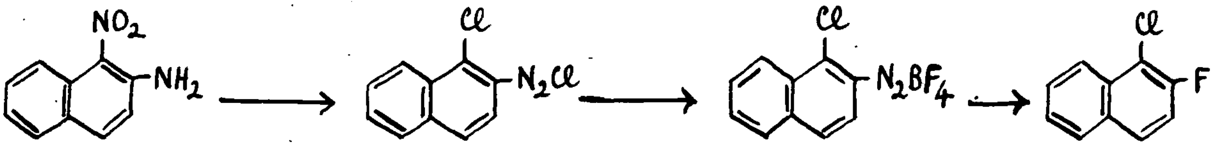
(XIX)



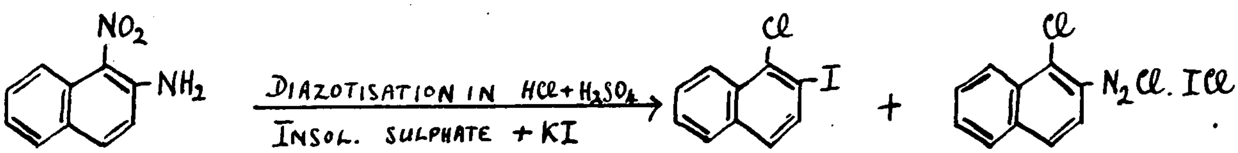
(XX)

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-bromonaphthalene (XIX; R = Cl, R' = Br). During work on the influence of substituents on the formation of diazoamines and amino-azo compounds, Morgan (111) 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:-



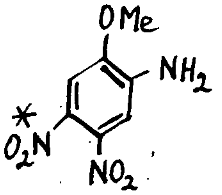
A similar diazotisation of α-nitro-β-naphthylamine and subsequent treatment with potassium iodide yielded to Italian workers (99) a substance presumed to be 1-chloro-2-iodonaphthalene. Formation of this compound was explained by the

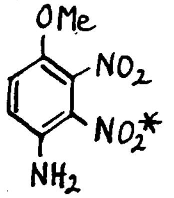


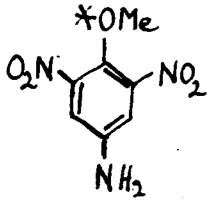
attack of "nascent chlorine" (from iodine monochloride) on the nitro-group, especially susceptible in view of the "mobility" of substituents in the naphthalene series as compared with the benzene series. In the latter it is evident that the "mobility" depends upon substitution although some anomalies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

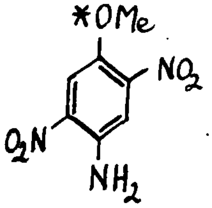
(a) the group must be <u>ortho</u> or <u>para</u> to a diazo-group, and

(b) the group must have a nitro-group in an <u>ortho</u> position to act as an 'activator', for example;









(*Indicates the group replaced on diazotisation).

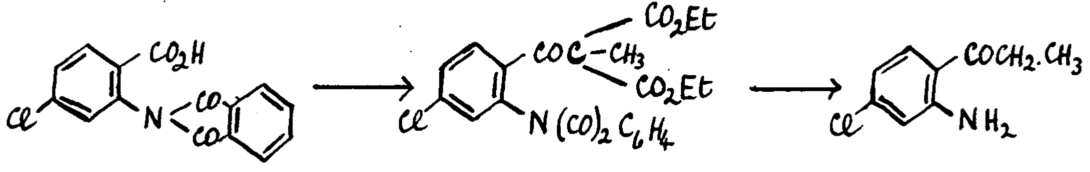
In contrast to these examples, in which activation is produced by a powerfully electrophilic group, the reactivity of nitro-groups (ortho or para to a diazonium cation) in the present investigation appears to be enhanced by a substituent (Cl) whose normal tautomeric (+T) effect is reinforced by a p-carbonyl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

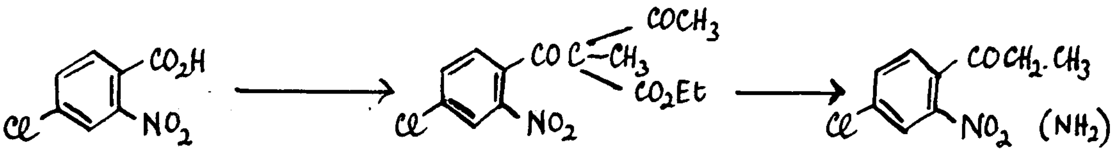
Since this investigation was not concerned with the actual preparation of compounds for antimalarial testing it was decided to extend the scope of the present study to the synthesis of 7-chloro-3-methyl-4-hydroxycinnolines. Interest in such compounds lay in their function as intermediates for potential 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:

(a)

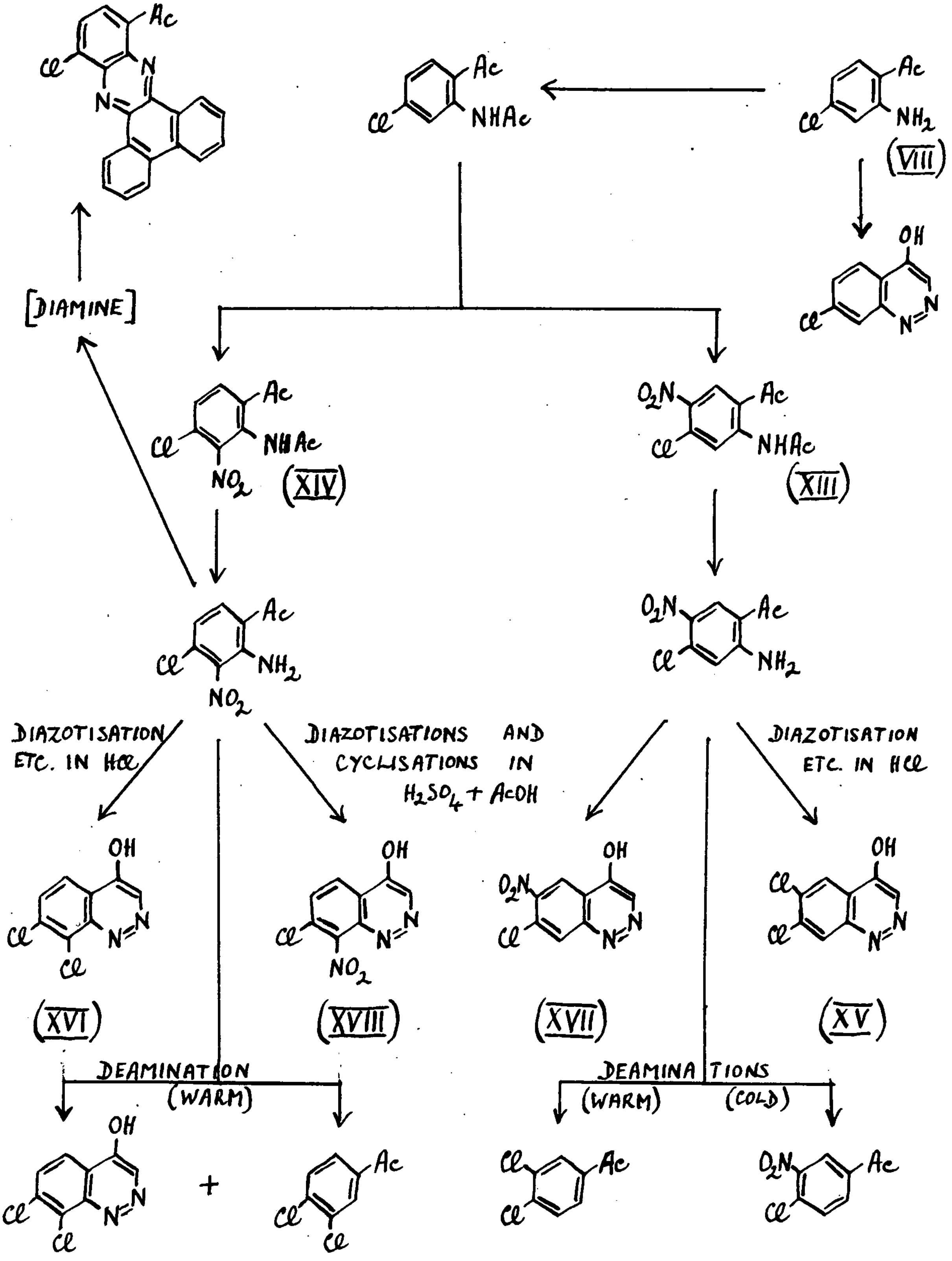


(b)

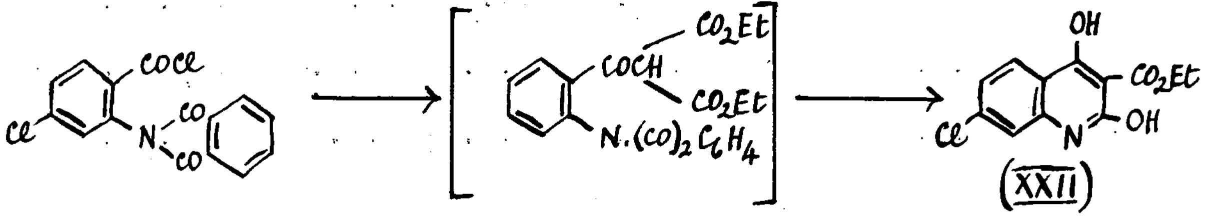


Methylmalonic ester, required for method (a), was prepared by a method (117) which is essentially that of Lucas and Young (97). Condensation with the acid chloride was carried out

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



using these conditions (page ///) 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;



(XXII)

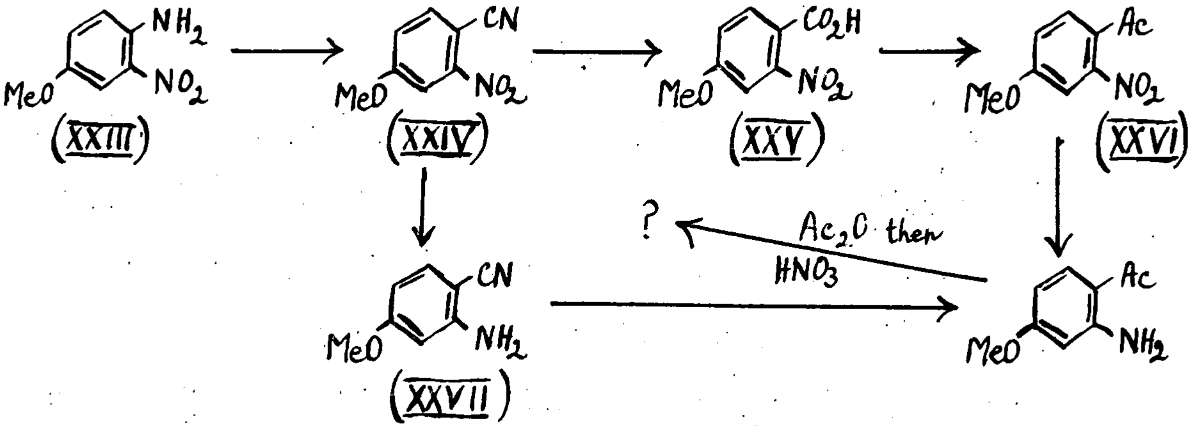
Substance	Analytical Data Found	Required
m.p. 125°	C,62.15; H,3.7; N,5.1; Cl,10.5%.	-
m.p. 153°	C,59.85; H,4.65; N,3.5; Cl,8.35%.	-
$C_{12}H_{10}O_4NCl$ (XXII)	C,53.4; H,3.7; N,5.75; Cl,13.3%.	C,53.8; H,3.8; N,5.2; Cl,13.3%.

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-nitrobenzoyl chloride and subsequent hydrolysis with alcoholic sulphuric acid (cf. page 114a) 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 acetophenone, 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 replacement reactions to those observed above (page 125) 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 <u>et</u> <u>al.</u>(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 <u>iso</u>amyl 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° 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 ¼ hour. Two batches carried out as above were combined, extracted with ether, and the extract washed with successively less concentrated hydrochloric 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°/14 mm.

(c) 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 ½ 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. <u>ca</u>. 126°, was 58.3 g. (91% based on 4-chloro-2-nitrotoluene). Beilstein, XII, 835 gives m.p. 130-131°.

(d) 4-<u>Chloro</u>-2-<u>acetamidobenzoic acid</u>.

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-<u>Chloroanthranilic acid</u>.

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° and again filtered and washed with water (1 l.); after drying at 60-65° 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°. 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 hydrochloric 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. $C_{15}H_8O_4NCl$ 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 111) 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. $C_{10}H_{10}O_2NCl$ 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.c.) 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 volumeof 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.).

4-Chloro-2-phthalimidobenzoylacetoacetate.- 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°, 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 ¾ 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%).

4-Chloro-2-nitrobenzonitrile.- 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-nitrobenzonitrile (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 1½ 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 1½ 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. 141-143°.

(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.), maintained 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 (17.85 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 ([illegible]) 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-<u>Chloro</u>-2-<u>aminoacetophenone</u>.- 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 ½ 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-<u>Chloro</u>-4-<u>hydroxycinnoline</u>.- 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).

Nitration of 4-chloro-2-acetamidoacetophenone.- 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-*chloro*-5-*nitro*-2-*acetamidoacetophenone*, m.p. 166-168° (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°) pure 4-*chloro*-3-*nitro*-2-*acetamidoacetophenone*, m.p. 143-144° (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° and with the main product, m.p. 166-168°.

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-*Chloro*-5-*nitro*-2-*aminoacetophenone*.- 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 redissolved 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-*Chloro*-3-*nitro*-2-*aminoacetophenone*.- 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 phenanthraquinone 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°, 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-aminoacetophenone (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 methylmalonic 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. $C_{12}H_{10}O_4NCl$ 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 colourless 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 143) 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-dinitrophenylhydrazone, 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 <u>potassium 4-chloro-2-nitrobenzoate</u> (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 anhydride (1 c.c.) on a steam bath for 30 minutes and, on cooling, colourless crystals (0.27 g.), m.p. 77-79°, separated. Recrystallisation from ligroin (b.p. 40-60°) furnished tiny jagged needles, m.p. 80-81°, which analysis indicated as <u>ethyl 4-chloro-2-acetamidobenzoate</u> (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.

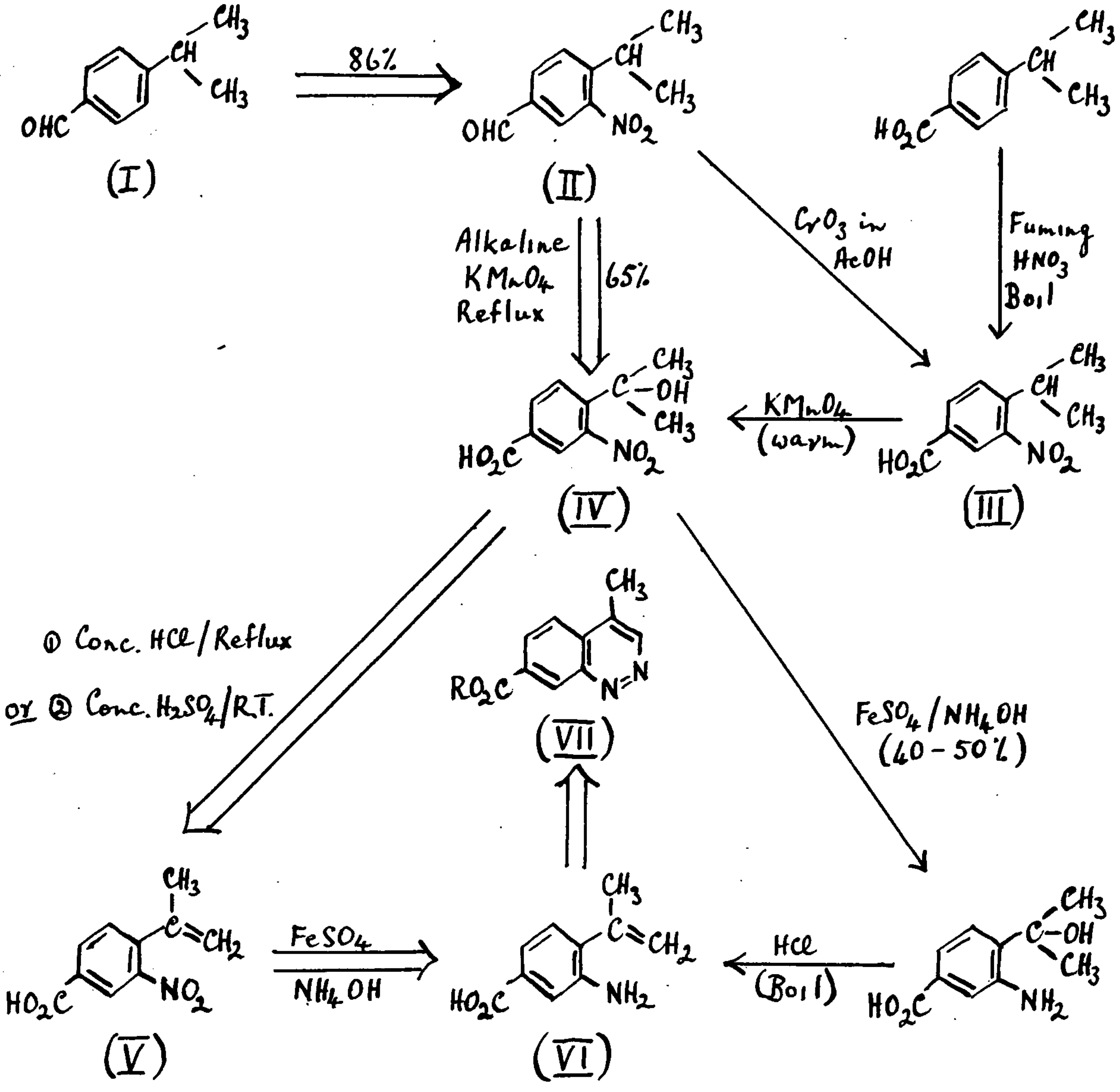
The aims of this section of the investigation were twofold;

(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 (Widman).

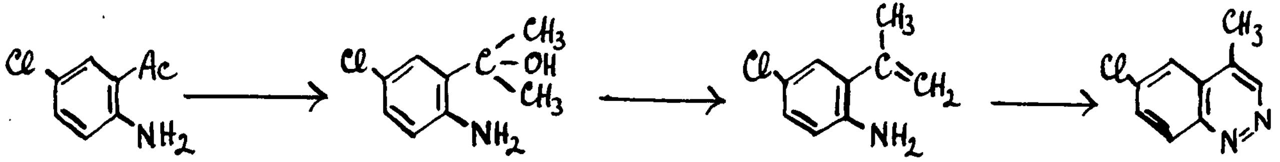


⟹ Indicates the route chosen for preparative purposes in the present investigation.

Numbers indicate the yields obtained by Widman, 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 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



(VIII) (IX) (X) (XI)

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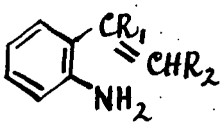
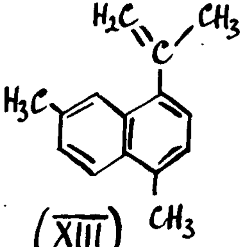
* Diazotisation of the "ethylene" was carried out before the receipt of analysis figures but the non-phenolic fraction was only subjected to preliminary tests.

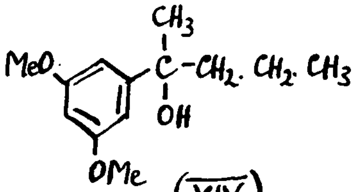
sulphuric acid is interesting in view of the ease of dehydration of carbinols to give other o-aminoethylenes (e.g. XII; $R_1 = R_2 =$ Ph; R_1 = Ph, R_2 = CH_2Ph) using even less drastic conditions (150,152). Moreover, the compound (XIII) has been obtained (17) simply by



(XII)



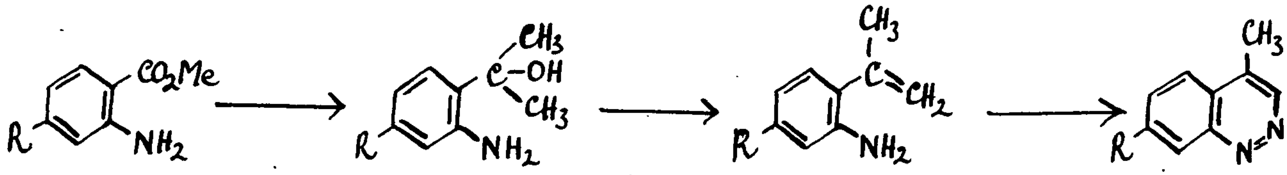
(XIII)



(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 chromatographic 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-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.



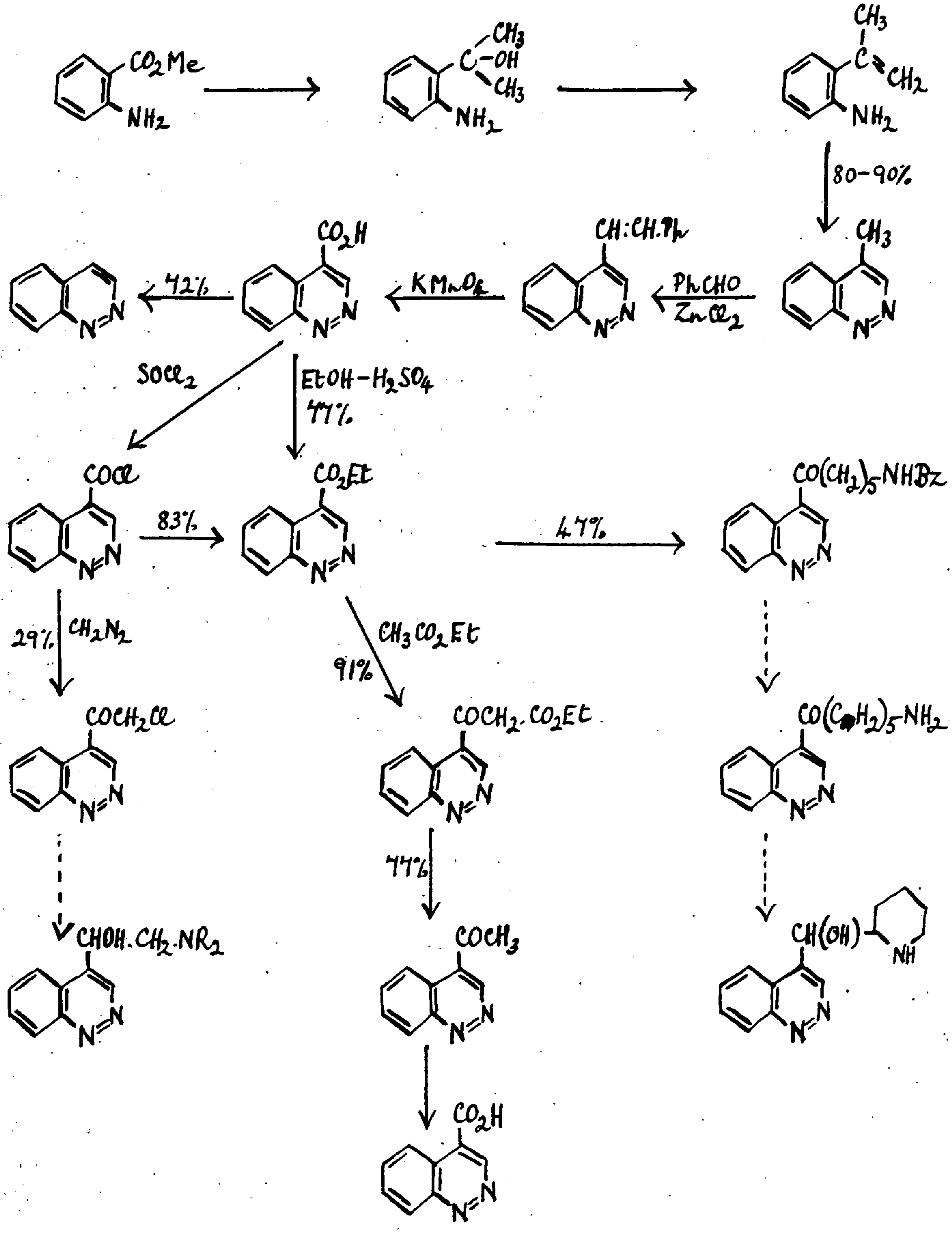
(XV) (XVI) (XVII) (XVIII)

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-chloroanthranilate (XV; R = Cl) was prepared from the acid by an improved modification of Hunn'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-*iso*propenylaniline (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-5-phenylcinnoline, interesting on account of possible steric effects on the reactivity of the methyl group and also as a route (by oxidation) to 5-phenylcinnoline-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 anthranilate	Carbinol	Ethylene	4-Methylcinnoline	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.	29
4-Chloro-deriv.			7-Chloro-deriv.	
12 g.	14.7g. 10 g.	9.1 g.	5.4 g.	70
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-*iso*propenylanilines 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 hyperconjugation (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-methylcinnolines 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. 5). 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 36) 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 styrylpyridines 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-nitrobenzaldehyde 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-methylcinnoline with p-dimethylaminobenzaldehyde at 160° in acetic anhydride furnished a small amount of a solid, m.p. 150-156°, 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

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* 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, dimethylamine 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 (196) 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 28° 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. 127-130°; 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°, of 3-nitro-4-hydroxypropylbenzoic acid (11.6 g., 50%). The pure compound, m.p. 191-192°, 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.c.). 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.c.); 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-aminoacetophenone: 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 (500 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°) and concentration of the solution so formed furnished the cinnoline (6 g., 46%), m.p. 74-75°. Pure 4-methylcinnoline, m.p. 76-77°, 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 seperated 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°, seperated 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-*iso*propenylaniline) 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-chloroanthranilic 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 (73 g., 69%), m.p. 69° (Munn, *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,58.15; H,6.1. $C_{11}H_{14}O_2NCl$ requires C,58.0; H,6.2%).

5-*Chloro*-2-*isopropenylanaline*.- 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,45.8; 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.

Reaction between Widman's acid and o-nitrobenzaldehyde.

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. 265-285° (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. $C_{17}H_{11}O_4N_3\cdot\frac{1}{2}H_2O$ requires C,61.8; H,3.7; N,12.7%). This substance was insoluble in hot or cold sodium carbonate or hydroxide solutions.

Reaction between diethylamine, formaldehyde and 4-methylcinnoline-7-carboxylic acid.

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. 151-153° (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 (0.15 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.

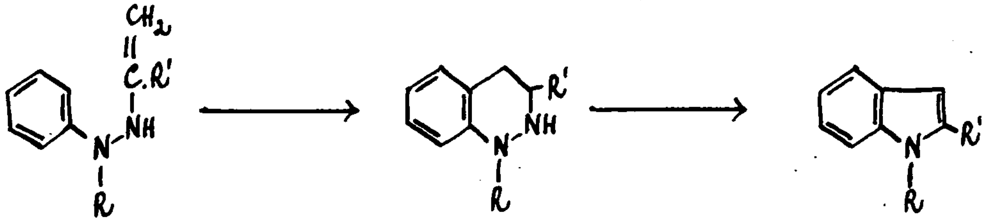
Condensation of 4-methylcinnoline ethiodide with p-dimethylaminobenzaldehyde.

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%).

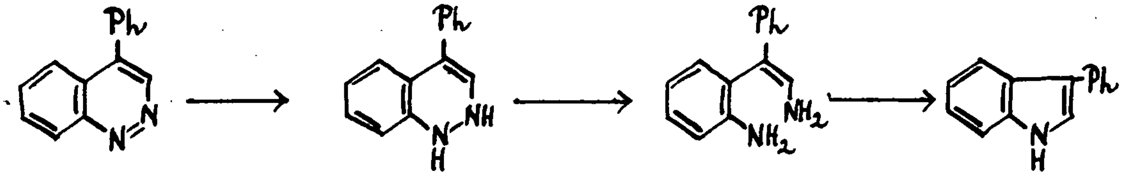
The Reduction of Some Cinnoline Derivatives.

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 Trissler (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 53). However, the mild conditions (above) employed by Neber 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-phenylcinnoline 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-disubstituted-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 unsubstituted 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.

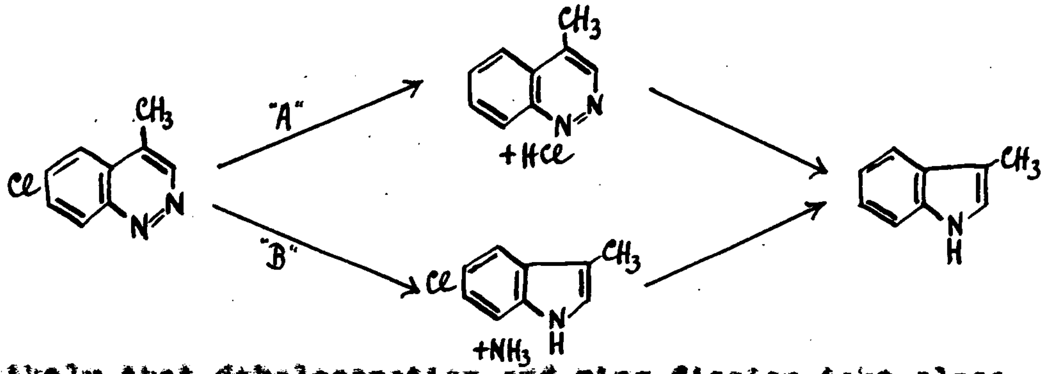
That these results are in general agreement with the estimations based upon ammonia evolved is shown by the following table. No simple relationship is apparent between the nature of a substitment and its effect upon the extent of indole formation; thus the distinct increase in the indole figure on passing 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

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

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 chloromethylcinnolines. 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 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).

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



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 193) 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 (*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,5.30).

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 ½ 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. 179-180°).

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-methylcinnoline 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 (0.8 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).

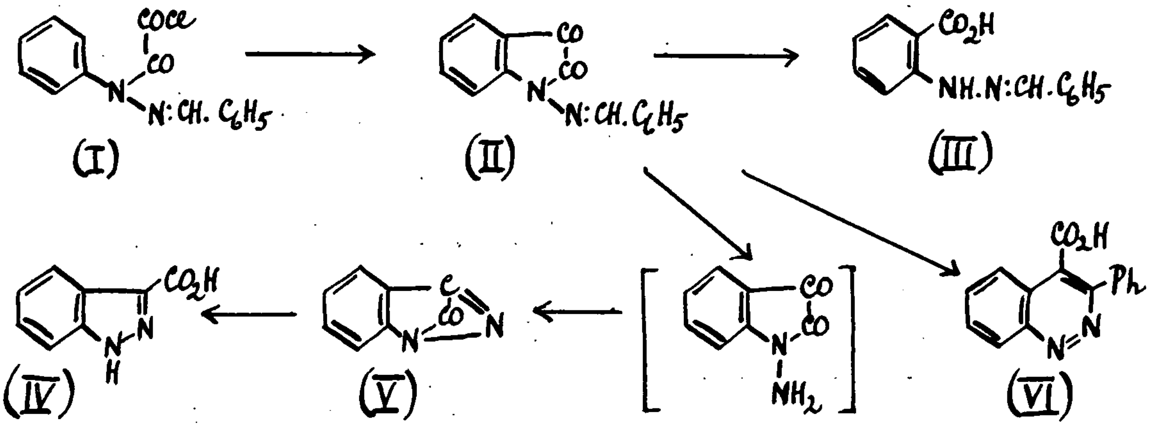
The pH 8 fraction (ca. 4 g.), consisting of a mixture of oil and crystalline material, the latter being the unchanged cinnoline, m.p. and mixed m.p. 234-235°.

3-Methyl-4-phenylcinnoline picrate.- This was prepared from an alcoholic solution of the cinnoline (0.5 g. in 10 c.c.) and a 5% 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 preceded 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 Standinger (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-benzilideneamino-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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