Part I: "Nitrogenous analogues of polycyclic hydrocarbons."

Part II: "Syntheses in the naphthyridine series."

With an Appendix on

"The effect of diazomethane on 3-hydroxy-4-phenanthraldehyde".

T H E S I S

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PREFACE.

The author wishes to state his indebtedness to his supervisor, Professor J.W. Cook, F.R.S., for his constant encouragement and good advice so often given during the progress of these researches.

He also wishes to thank Imperial Chemical Industries Ltd. (Dyestuffs Division) for permission to publish an account of this work in his thesis, and acknowledges the award of a Research Scholarship from the Carnegie Trust.

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Part I: Nitrogenous analogues of polycyclic hydrocarbons.

CONTENTS.

Part I.

INTRODUCTION.

The proliferation of the constituent cells of animal tissue occurs usually in the normal growth of the body, in the repair of damaged tissues, in the hypertrophy of certain organs, such as the heart, and so on. In such cases, cell proliferation occurs with a definite end in view, namely, the maintenance of a healthy organism, and its progress is governed accordingly. When, however, excessive cell division occurs without apparent purpose, and when it proceeds wantonly, without regard to the requirements of the organism, the process results in the appearance of a tumour.

Tumours may arise from any tissue at any stage in its development, and are, therefore, represented by a great variety of types. On this basis a histological classification may be made, and this is useful in determining the nature and origin of a tumour. From a clinical point of view, however, tumours are divided into two classes - simple, or benign, and malignant. The former are composed chiefly of adult tissues, are well defined and often encapsulated, and do not infiltrate healthy tissue. The latter, with which this work is concerned, do not correspond to an adult tissue, being essentially cellular, are ill-defined at their margins, and invade and destroy healthy tissue both by direct invasion in the course of their growth, and by remote metastases or secondary deposits occurring via the blood stream or lymphatic vessels. Because of this

latter property, malignant tumours have received the closest attention since the earliest times, and, with the gradual accumulation of scientific knowledge, it was inevitable that an approach be made from the standpoint of the chemist.

Occupational cancers, because of the regularity of their occurrence, provided the starting point from which this approach was made. Percival Pott, in 1775, considered that the cause of chimney sweep's cancer was the effect of soot on the skin. A century later von Volkmann drew attention to the incidence of skin tumours among tar workers. In 1876 Bell described cases of cancer in workers in the Scottish shale-oil industry, and a year later the first case was reported of skin cancer among Lancashire cotton operatives, attributable to contamination with lubricating oil.

The accumulation of evidence encouraged investigators in attempts to simulate the effects of the suspected agencies, but it was not until 1915 that Yamagiwa and Ichikawa[1] induced cancers in the ears of rabbits by the repeated application of coal tar, a test three years later modified by Tsutsui, who produced analagous results by similarly painting the skin of mice.

Thereafter progress became rapid. At Zürich in 1921, Bloch[2] demonstrated that the active cancer-producing substance in coal tar was concentrated in the higher boiling fractions, and was a neutral compound, free from nitrogen, arsenic or

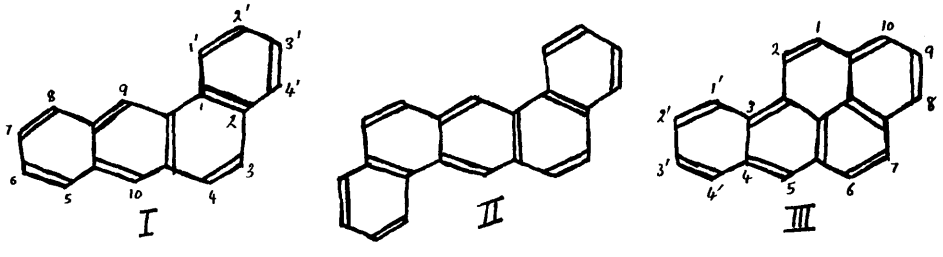
sulphur, and capable of forming a stable complex with picric acid. Kennaway, in 1924 [3] showed that potent carcinogenic agents existed in the highest boiling fractions of the complex mixture of hydrocarbons produced by Schroeter [4] by the action of aluminium chloride on tetrahydronaphthalene, and also in similar fractions from the products obtained by heating to a high temperature mixtures of acetylene and isoprene in presence of hydrogen.

The first definite clue was finally discovered by Mayneord in 1927 who noted that a factor common to all carcinogenic tars was the possession of a characteristic fluorescence spectrum with three bonds at low dispersions. This method of identification was developed by Hieger [5] who, after testing a number of hydrocarbons, found that 1,2-benzanthracene (I) gave a fluorescence spectrum similar to that of the known carcinogenic tars. 1,2-benzanthracene itself, however, was found to have little or no carcinogenic activity [6], and Cook [7] subsequently synthesised a large number of its homologues in the hope of finding a compound with the same spectrum as that of the carcinogenic tars. A number of these, especially those substituted in the 5,6,9, or 10 positions, have been found to be carcinogenic, although none of them is responsible for the cancer-producing property of the tars.

About this time Clar [8] succeeded in synthesising

1,2,5,6-dibenzanthracene (II) by a method which made it readily available, and Kennaway and Hieger in 1930 [6] found that it was able to induce epitheliomas in the skin of mice when repeatedly applied in dilute benzene solution. This was the first case of experimental carcinogenesis by a pure polynuclear hydrocarbon whose structure was accurately known.

Shortly afterwards, in 1932, the active constituent of coal tar was finally isolated by Cook, Hewett and Hieger [9], using fluorescent spectroscopy to direct the extraction of the potent material. It proved to be a hydrocarbon, whose constitution they later established, by synthetic methods, to be 3,4-benzpyrene (III).

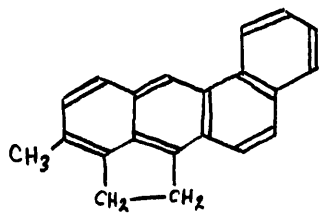


I II III

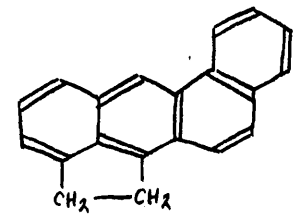
An interesting development occurred in 1933, when, by the dehydrogenation of dehydronorcholene, a simply-obtained derivative [10] of a naturally occurring constituent of bile, deoxycholic acid, there was obtained simultaneously by two groups of workers [11,12] the compound methylcholanthrene (IV), whose structure was established by Cook and Haslewood by

degradation [13] and by Fieser and Seligman by synthesis [14].

The discovery in 1935 that, with its parent hydrocarbon, cholanthrene (V) [15,16], it possessed the greatest carcinogenic potency of any compounds yet investigated [17] proved of great interest, as the precursor in its preparation had been a naturally occurring product.

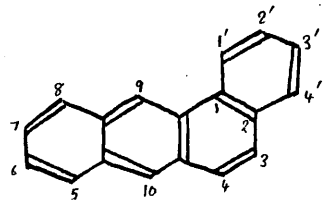


IV

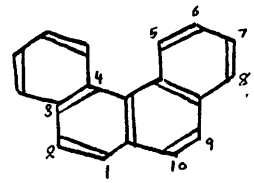


V

It became increasingly obvious that a structural relationship existed between many of the now numerous carcinogenic hydrocarbons that had by this time been prepared, and as a result of the large amount of data that had ultimately accumulated, it became possible to relate molecular features and biological activity. Many actively carcinogenic hydrocarbons were now perceived to fall into certain groups, notably those related to 1,2-benzanthracene (I), to 3,4-benzphenanthrene (VI), and to chrysene (VII).



I



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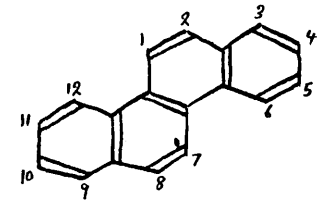


VII

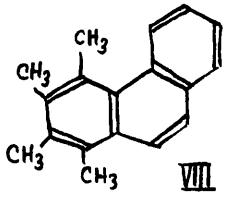
Brief mention may be made regarding the carcinogenic potency of these compounds, and of some of their simpler homologues, as this assumes a certain significance, which will become apparent, regarding the inhibitory power of some similar compounds to be discussed later.

In the 1,2-benzanthracene group, the parent compound itself (I) has little or no carcinogenic activity [6], but the substitution of alkyl groups in the positions 5,6,9 or 10 confers considerable potency [18] although this depends on an optimum complexity of structure.

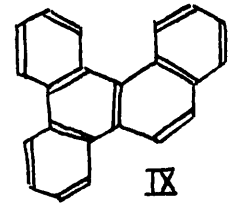
3,4-benzphenanthrene (VI), first synthesised by Cook [19], is itself carcinogenic [20], and this property is enhanced by the substitution of a methyl group in positions 1 or 2; for example, 2-methyl-3,4-benzphenanthrene, synthesised by Hewett [21] has been found to be a powerful carcinogen [22].

Specially purified synthetic chrysene (VII) has also been shown to cause epithelioma in mouse skin [22], and although its carcinogenic potency is of a very low order, substitution of methyl groups at positions 1 and 2 increases its activity, and 1,2-dimethyl chrysene [23] is weakly, but quite recognisably carcinogenic.

Working on the principle that a condensed benzene ring is equivalent to two o-methyl groups in its influence in promoting carcinogenic activity, Hewett linked these three classes of compounds by the synthesis of 1,2,3,4-tetramethylphenanthrene (VIII) [24] and 1,2,3,4-dibenzphenanthrene (IX) [25], both of which proved to be carcinogenic.

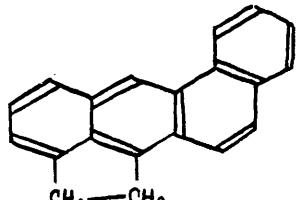


VIII

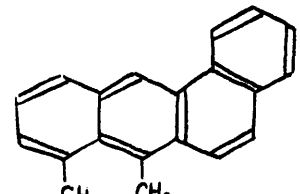


IX

Comparison of the structure of (VIII) with the formulation of methyl derivatives of 1,2-benzanthracene, 3,4-benzanthracene and chrysene, substituted in the positions indicated above to ensure enhanced carcinogenic activity, readily illustrates Hewett's correlation. This principle might also be extended to the cholanthrene molecule (V), where replacement of the pentacyclic system by a pair of methyl groups in corresponding positions would give 5,10-dimethyl-1,2-benzanthracene (X), which has been synthesised by Fieser and Newman [26], and itself possesses a carcinogenic activity comparable with that of cholanthrene [27].

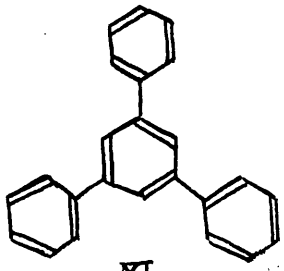


V

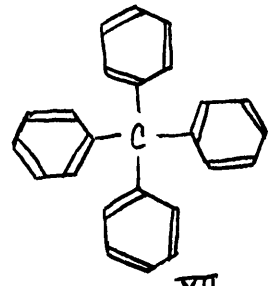


X

The power of causing cancer is, however, not limited entirely to the above classes of polycyclic hydrocarbons, and a few agents other than these may be mentioned. Triphenylbenzene (XI), and tetraphenylmethane (XII) both appear to possess the ability to produce malignant tumours in mice [28], although their activity is of a low order.

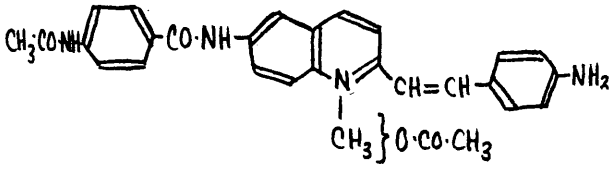


XI

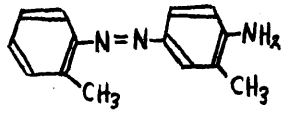


XII

Carcinogenic substances, however, need not even be hydrocarbons. Apart from certain polynuclear heterocyclic substances mentioned later, in this Introduction, it has been found that the compound 2-(p-aminostyryl)-6-(p-acetylaminobenzoylamino)-quinoline methoacetate (XIII), originally intended as a trypanocide, caused sarcomas in mice at the site of injection [29], while the production of liver and urinary bladder neoplasms by many azo-compounds such as o-aminoazotoluene (XIV) [30] has been recorded on many occasions by Japanese workers.



XIII



XIV

Since it had now become possible regularly to cause malignant tumours by the application of chemical compounds, attempts quickly followed to cause their regression and eventual disappearance by the same means, and this implied the use of agents capable of destroying the cells of the tumour without detriment to the adjacent healthy tissues. Such selective action is not easy to attain, since tumour cells, as was mentioned previously, are derived from those of the normal tissues and show a marked similarity to these in their general behaviour.

The earlier work on the inhibition of malignant tumours by chemical compounds was mainly of an empirical nature, since it aimed at a depression of the growth rate of tumours by the creation of an environment unfavourable to the malignant proliferation of cells, and by direct interference in the metabolism of the tumour.

The use of formaldehyde in cases of human uterine cancer has been reported as beneficial [31], but this appeared due to the subsidence of inflammation. Certain aldehydes have also been tested for inhibitory properties. Propionic aldehyde, injected into mice treated with benzpyrene, slightly reduced the incidence of tumours [32], and Strong [33] found that heptaldehyde caused the regression of spontaneous tumours in mice and dogs, although it had no effect on tumours

induced by methylcholanthrene, or in inoculated Crocker mouse sarcomas [34].

Attempts to interfere with the respiration of malignant tissues led to the use of hydrogen cyanide, and this appeared to cause regression of certain mouse carcinomas, although the dose had to be almost lethal to have any effect [35].

An interesting approach to the problem was made in attempts to stain cancerous tissue preferentially with suitable dyes, and thus achieve a selective attack on malignant cells themselves, leaving the healthy tissues unaffected. It was found that the cadmium salt of acridinium nitrate caused regression of some mouse tumours [36], and Isamine blue was claimed to have a beneficial effect on certain animal tumours [37] but did not fulfil this promise in respect to human neoplasms [38]. Methylene blue administered perorally, however, has been recorded as being beneficial in certain cases of human cancer [39]. Work along this line seems, however, to have been abandoned in its early stages in spite of its apparent promise.

The profound effect of many alkaloids on the animal organism led to a certain amount of investigation regarding their possible application to the inhibition of tumour growth, and one of them, colchicine, was especially notable because of its ability to arrest cell mitosis at a certain stage in its development. This alkaloid has been used in malignant

lymphoid tumours of mice with some success [40] but the dosage necessary was found to be almost lethal [41]. Improvements in the method of administration resulted in regression of some rat carcinomas [42], and certain human neoplasms showed a favourable response to colchicine [43], although in other cases no effect was observed [44]. A disadvantage in the use of colchicine lies in its high toxicity, and a search for less toxic derivatives might yield interesting results in this field.

Of recent years, one of the most fruitful approaches to the chemotherapy of cancer has been that of Haddow, who made the surprising observation that carcinogenic compounds themselves have a sustained inhibitory effect on the growth of tumours and of young animals [45].

It was found that, if a rat bearing a grafted tumour, be given an intraperitoneal injection of a carcinogenic hydrocarbon, such as 1,2,5,6-dibenzanthracene or 3,4-benzpyrene, either in colloidal suspension in water or dissolved in oil, the growth rate of the tumour was decreased appreciably, an effect which was not observed when non-carcinogenic hydrocarbons were used, such as anthracene, phenanthrene, pyrene, or fluoranthene. Compounds such as chrysene, which are only feebly carcinogenic, possessed a correspondingly lesser degree of inhibitory activity.

In the course of these experiments it was noted that animals injected with carcinogenic hydrocarbons grew more slowly than those which were not so treated, and the conclusion was reached that the reduction in the rate at which the tumours grew was the result of a general inhibition of growth of the whole organism, rather than an inhibitory effect specific to tumours. This observation led to more particular experiments along these lines, and it was found that in young rats, a single intraperitoneal injection of a carcinogenic hydrocarbon, as before, resulted in an immediate diminution in the rate of body growth, so prolonged in its effect that none of the rats so treated recovered, and it was further demonstrated that although the hydrocarbon eventually could not even be detected in the tissues by their fluorescent spectra, the inhibitory effect might still be maintained. Again, this phenomenon was not observed when non-carcinogenic compounds, such as pyrene, were used, while chrysene was only feebly effective, as might be expected for the same reasons as before.

These results have been independently confirmed by a number of other workers, notably by Lees [46] in respect of the prolonged growth ~~in~~ inhibitory powers of the carcinogenic hydrocarbons as opposed to the similar, but temporary, effect of certain systemic poisons such as thallium acetate, and

again by the same worker [47] in respect of the inhibitory effect of these hydrocarbons on the growth rate of malignant tumours in rats. An interesting corollary was furnished by the discovery of Morelli and Dansi [48] that the injection of carcinogenic compounds into rats bearing newly implanted tumour grafts resulted in the failure of the graft to "take". Once again it was found that non-carcinogenic compounds usually failed to cause this effect.

An interpretation of these important findings was given by Haddow, who considers that a carcinogenic compound acts primarily by interfering with the growth of normal cells, which therefore eventually undergo an irreversible change, enabling them to proliferate in an environment in which a normal cell would find growth difficult or even impossible. This new feature of the altered cells is permanent, and continues to operate even when they have been removed, by metastes or deliberate transplantation to other hosts, from the environment which produced them. A considerable volume of evidence has been collected in support of this theory [49].

A fuller examination of the effects on tumour growth of both carcinogenic and non-carcinogenic compounds was not long delayed, and it was found by Haddow that in animals bearing spontaneous or transplanted malignant tumours, 86.5% of 171 experiments using carcinogenic compounds showed

inhibition of tumour growth, while in 79 experiments using non-carcinogenic compounds, 79.7% indicated no inhibition [50].

Some carcinogenic compounds, however, do not show an inhibitory power, e.g., 2'-methyl-1,2,5,6-dibenzanthracene, 9-methyl-10-cyano-1,2-benzanthracene, and 10-acetoxymethyl-1,2-benzanthracene, while a few non-carcinogenic compounds do show this power, e.g., 2',3'-naphtha-3,4-pyrene, 4'-hydroxy- and 4'-methoxy-3,4-benzpyrene, and 1,2'-azonaphthalene. However, it has been found that the powerful growth inhibitors 3- and 7-methyl-1,2-benzanthracene, which had not hitherto been found carcinogenic to the skin of mice, are able to give rise to sarcomas, and this incidence of experimental error, with the individual variability of the animal used for testing, may account for many of these discrepancies. Haddow [51], in order to explain these anomalies, accounts for the lack of carcinogenic potency in certain growth-inhibitory substances by supposing that their effect upon cells is not to cause the discontinuous change in the growth rate necessary for the inception of malignant proliferation, but that the change produced may be in these cases continuous and gradual, or that such discontinuity may be difficult or impossible to produce for unknown reasons.

Nevertheless, a considerable, if not exact, degree of correlation between carcinogenic and inhibitory activity has been demonstrated to exist, and this theory may be illustrated by reference to the simple homologues of the main groups of carcinogenic hydrocarbons mentioned previously.

In the 1,2-benzanthracene series, the positions, 5, 6, 9 and 10 have been shown to be those most suitable for the introduction of alkyl groups to give carcinogenic compounds. Haddow[52] has shown that these compounds have an inhibitory effect, which, however, is decreased by an increase in the number of carbon atoms in the alkyl group.

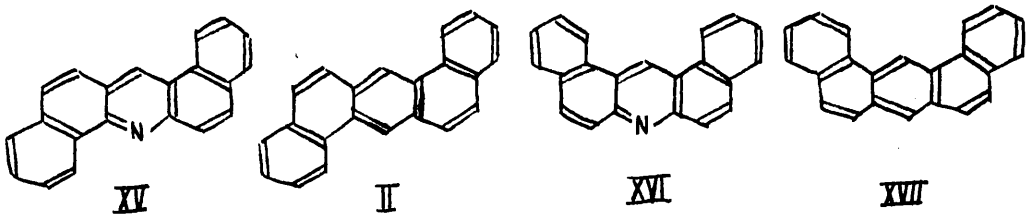
3,4-benzphenanthrene, a weak carcinogen, itself shows little or no inhibitory power, but, just as its carcinogenic activity is increased by substitution of a methyl group in position 2, so 2-methyl-3,4-benzphenanthrene shows an appreciable inhibitory power[53], and this is even greater in the case of 2-ethyl- and 2-isopropyl-3,4-benzphenanthrene[54].

In the chrysene series of compounds, 1,2-dimethylchrysene, which shows pronounced carcinogenic activity, has been proved to have marked growth-inhibitory properties[54].

In the case of the compounds Hewett had used to demonstrate the correlation between these three groups of carcinogens, the carcinogenic 1,2,3,4-dibenzphenanthrene exhibits pronounced growth-inhibitory power, but

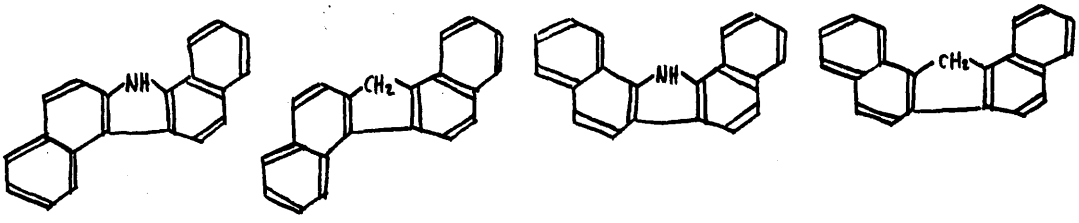
1,2,3,4-tetramethylphenanthrene is negative in this respect [54], being only a weakly carcinogenic substance.

As in the case of carcinogenic substances, compounds which inhibit tumour growth need not be hydrocarbons, but may exhibit this property if their structural relationship with a carcinogenic hydrocarbon is close enough, a circumstance which often confers carcinogenic potency itself. Thus 1,2,5,6-dibenzacridine (XV) and 3,4,5,6-dibenzacridine (XVI), which superficially resemble the carcinogenic hydrocarbons 1,2,5,6-dibenzanthracene (II) and 1,2,7,8-dibenzanthracene (XVII), are themselves carcinogenic [55], and 1,2,5,6-dibenzacridine has been found to possess considerable inhibitory properties [56].



XV II XVI XVII

In the same way, 1,2,5,6-dibenzcarbazole (XVIII) and 3,4,5,6-dibenzcarbazole (XIX), structurally related to the carcinogenic hydrocarbons 1,2,5,6-dibenzfluorene (XX) [57] and 1,2,7,8-dibenzfluorene (XXI) [58] are also carcinogenic [59] and both have marked growth-inhibitory powers [53,60].



XVIII XX XIX XXI

It was found, however, that, in these cases, the correlation between carcinogenic potency and growth-inhibitory activity was not always as closely followed as in the carcinogenic hydrocarbons with which we have dealt. In view of this, it was considered desirable that some nitrogenous analogues of chrysene, 3,4-benzphenanthrene, and pyrene be examined, in the hope that a potent growth-inhibitor might be obtained which would yet possess only the weak or non-existent carcinogenic power of the analogous hydrocarbon. The present work is concerned, therefore, with the synthesis of a number of these compounds with which the following section deals more fully.

Many compounds in these series have been already prepared, notably 3-aza-[61], 7-aza-[62] and 8-azachrysene [63], and also 3,4-benz-8-azaphenanthrene [64], 3,4-benz-10-azaphenanthrene [65], and 4-azapyrene [66].

Some of these have been tested for carcinogenic potency, e.g., Joseph [67] reports that 3,4-benz-8-azaphenanthrene lacks

carcinogenic activity, and Shear and Leiter [68] find 1-aza-chrysene and 3,4-benz-8-azaphenanthrene unable to cause tumours at the site of injection.

It is of interest to note that many other nitrogenous analogues of various carcinogenic hydrocarbons have been synthesised, for instance, certain aza-cholanthrenes [69,70], aza-benzanthracenes [64,69], and aza-3,4-benzpyrenes [71,72], but these are not immediately concerned with this work, and are mentioned only in passing.

The growing importance of nitrogenous growth-inhibitors is emphasised by the more recent work of Haddow [73], which deals with two main classes of these compounds; those with heterocyclic structures related to 1,2-benzanthracene, the benzfluorenes, and other polycyclic hydrocarbons, and certain triarylethylenes, some of which may be regarded as being structurally related to 1,2-benzanthracene or 3,4-benzphenanthrene. In the former group it is found that certain compounds, mainly phenazines and indoloquinoxalines containing one six-membered ring with two nitrogen atoms, and a five-membered ring with one nitrogen atom, show outstanding inhibitory properties greater than hitherto observed in any other class.

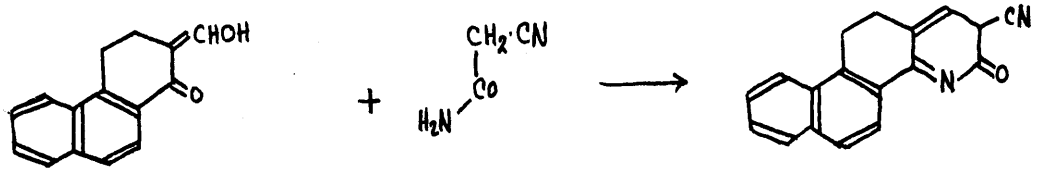
Although the more spectacular approaches to cancer therapy have been made recently using synthetic oestrogens

in combination with surgery and the use of X-rays, the treatment of the disease is still difficult and its origin obscure. The recent very active investigation of the mechanism of growth-inhibition and the compounds that cause it may, however, lead to a successful treatment by chemical means alone, and a steady prosecution of research along these lines is certainly indicated in view of the significant information we have discussed above.

INTRODUCTION TO EXPERIMENTAL.

In view of the observations made in the general Introduction regarding the effects on healthy and on malignant tissue, of some polycyclic compounds containing a heterocyclic nucleus, it was considered that a series of these compounds, structurally related to pyrene, chrysene, and 3,4-benzphenanthrene, should be prepared for biological testing. The object of this work was to accomplish the synthesis of some of these compounds.

It was decided first to extend the condensation of α-hydroxymethylene ketones with cyanacetamide [74] to the preparation of polycyclic compounds containing a fused pyridine nucleus, viz.:-



2-Hydroxymethylene-1-keto-1,2,3,4-tetrahydrophenanthrene | cyanacetamide | Derivative of azachrysene.

The available information concerning the products of this type of reaction has been largely conflicting for two main reasons.

The first of these is that, in the preparation of α-hydroxymethylene ketones by the action of ethyl formate on open chain ketones of the type

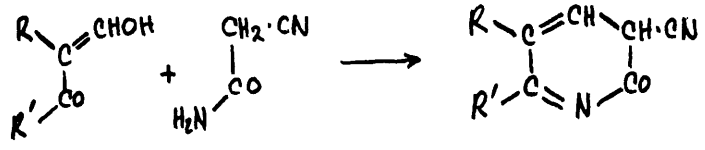
$R.CH_2.CO.CH_2.R'$

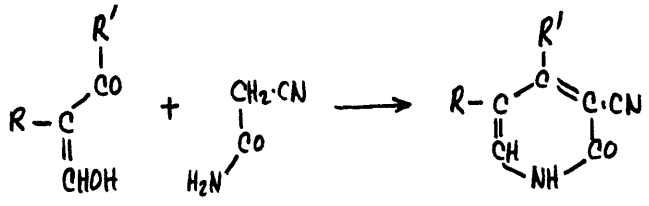
the hydroxymethylene group may be introduced on either of the two reactive methylene groups adjacent to the carbonyl group. This possibility renders doubtful the structure of the product, and hence that of the product of its condensation with cyanacetamide. In certain cases, nevertheless, the constitution of the hydroxymethylene ketone has been determined, e.g., the action of ethyl formate on methyl ethyl ketone has been proved to take place preferentially on the methylene group.[75)]
The ketone used in our synthesis, however, could give rise to one possible hydroxymethylene derivative only, as it contains only one suitable reactive methylene group adjacent to the carbonyl group, so that in this case the above problem does not arise.

The second difficulty arises in the condensation of cyanacetamide with α-hydroxymethylene ketones of the type

$$R.\underset{\underset{CHOH}{\|}}{C}.CO.R'$$

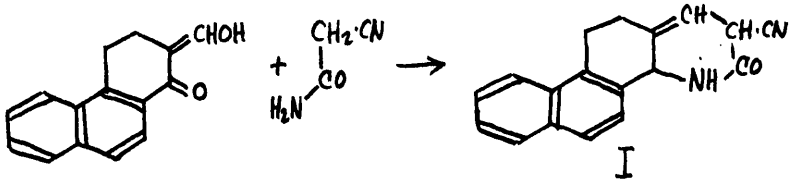
when two reaction mechanisms are possible :-

(i) 

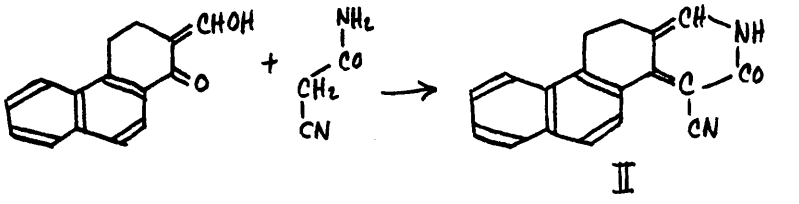
or (ii) 

The first of these is a Michael addition of the cyanacetamide to the double bond on the hydroxymethylene group, while the second is a Knoevenagel condensation of the active methylene group of the cyanacetamide with the carbonyl group of the α-hydroxymethylene ketone; and in both, ring closure is brought about by means of the amino group.

The product of our reaction might thus be a quinoline (I) or an isoquinoline (II) derivative, depending on the reaction mechanism, i.e.,

either  (Michael Addition)

I

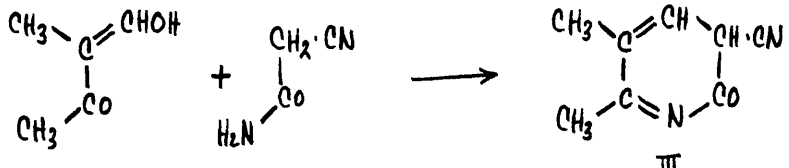
or  (Knoevenagel Condensation)

II

It is not proposed to enter here upon a general review of the considerable literature, mainly by Indian workers, as to the exact nature of the condensation, as much of it is conflicting, e.g., Sen Gupta (loc.cit.) states that the condensation of cyanacetamide and hydroxymethylene cyclohexanone in presence of piperidine gives a quinoline derivative, and that the same substance results from the condensation of cyanacetic

ester and aminomethylene cyclohexanone under the same conditions, while Basu and Banerjee [77] maintain on the other hand, that the latter condensation gives an isoquinoline derivative. A few references, however, are sufficiently pertinent regarding the synthesis undertaken.

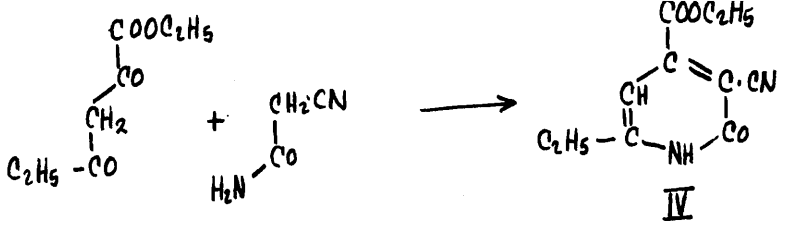
Barat [78] and Sen Gupta (loc.cit.) believe that the reaction takes place by means of a Michael addition; their opinion is supported by the more rigid experimental evidence offered by Tracy and Elderfield [79] who condensed cyanacetamide with the hydroxymethylene derivative of methyl ethyl ketone to obtain 3-cyano-5,6-dimethyl-2-piperidone (III) as the only product of the reaction:-



III

These workers had previously proved that the hydroxymethylene ketone had the structure shown above, and gave a satisfactory proof of the structure of the pyridone.

The same workers further supported this view [80] by condensing ethyl propionyl pyruvate, the structure of which they had established previously, with cyanacetamide in presence of piperidine to obtain 3-cyano-4-carbethoxy-6-ethyl-2- pyridone (IV) with no trace of an isomeric product:-

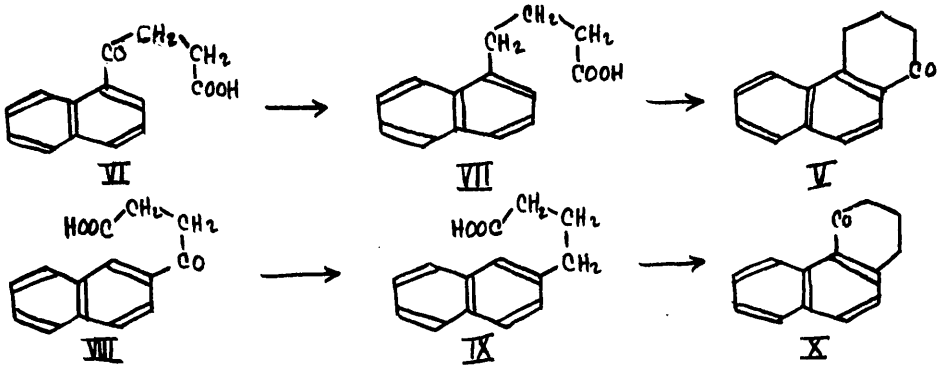


IV

As before, they gave a convincing proof of the structure of this product by a series of degradative experiments.

However, although there was thus sufficient reason for supposing that our condensation would thus yield a quinoline and not an isoquinoline derivative, the constitution of the final product was ultimately established, as being a quinoline, by an alternative synthetic method to be discussed later.

The starting material for the synthesis was 1-keto-1,2,3,4-tetrahydrophenanthrene (V), and this was prepared by the method of Haworth:-



VI VII V

VIII IX X

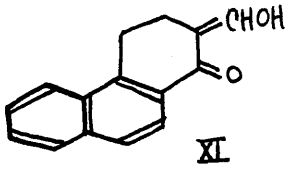
Succinic anhydride was reacted with naphthalene in presence of anhydrous aluminium chloride, using dry nitrobenzene as a solvent, to give β-1-naphthoylpropionic acid (VI)[81]; this was then converted to γ-1-naphthylbutyric acid (VII) by a modified Clemmensen reduction[82], which proved more convenient than that recommended by Haworth. The product was finally cyclised to 1-keto-1,2,3,4-tetrahydrophenanthrene (V) by

heating with 75% H_2SO_4 .

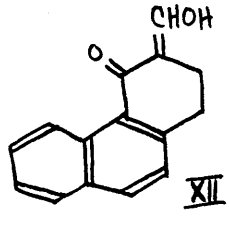
A slightly smaller yield of β-2-naphthoyl propionic acid (VIII) was simultaneously obtained from the synthesis; this was converted in a similar manner first to γ-2-naphthyl-butyric acid (IX) and thence to 4-keto-1,2,3,4-tetrahydro-phenanthrene (X) as before. This product was used for syntheses described later in the experimental section.

The preparation of 2-hydroxymethylene-1-keto-1,2,3,4-tetrahydrophenanthrene (XI) was then carried out by the method of Claisen[83] by acting on 1-keto-1,2,3,4-tetrahydrophenanthrene (V) in toluene solution with ethyl formate in the presence of atomised sodium. The substance was characterised as its methyl ether, prepared by reacting some of it with ethereal diazomethane, and also as the aminomethylene compound, prepared by the action of gaseous ammonia on its solution in chloroform.

At the same time, 3-hydroxymethylene-4-keto-1,2,3,4-tetrahydrophenanthrene (XII) was prepared for future use by the same method from 4-keto-1,2,3,4-tetrahydrophenanthrene (X); it was similarly characterised by means of its methyl ether as before.



XI



XII

Details of the preparation and properties of the above substances were published by Meyer and Reichstein[84] some time

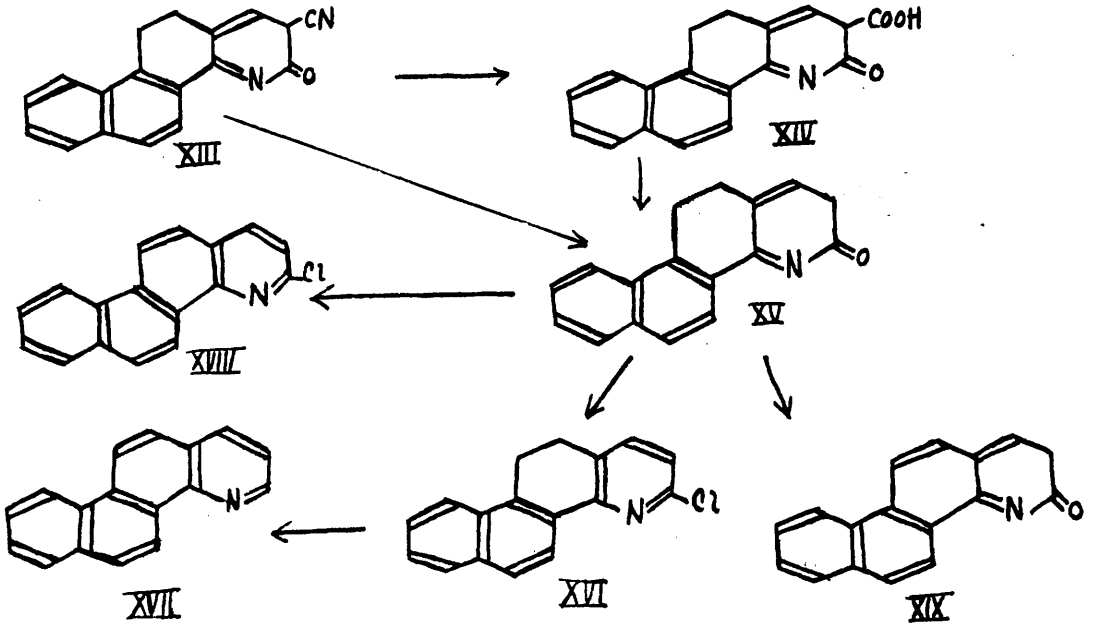
after the substances had been prepared by us, and, as this publication has now been made available, it might be of interest to note that the preparations were carried out by similar methods and conditions, and that the melting points are in good agreement with ours, viz:-

	Meyer & Reichstein	Ourselves
M.pt. of 2-hydroxymethylene-1-keto-1,2,3,4-tetrahydrophenanthrene (XI)	86°C	84-85°C
" of 2-methoxymethylene-1-keto-1,2,3,4-tetrahydrophenanthrene cf. (XI)	97°C	96-97°C
" of 3-hydroxymethylene-4-keto-1,2,3,4-tetrahydrophenanthrene (XII)	41°C	39-41°C
" of 3-methoxymethylene-4-keto-1,2,3,4-tetrahydrophenanthrene cf. (XII)	114°C	110-112°C.

It may also be mentioned here that, as a bye-product of the oxidation by periodic acid of 2-hydroxymethylene-1-keto-1,2,3,4-tetrahydrophenanthrene (XI), the same workers obtained 1-phenanthrol-2-aldehyde (XXXV), which we ourselves had previously obtained, as will be shown later, by the auto-oxidation of the same substance. Meyer and Reichstein give the m.pt. of this substance as 128-129°C; the substance from our preparation melted at 127°C. Whereas these workers characterised this product as a methyl derivative prepared by the action of ethereal diazomethane, we instead prepared its oxime for the same purpose.

The condensation of 2-hydroxymethylene-1-keto-1,2,3,4-tetrahydrophenanthrene (XI) with cyanacetamide was carried out in aqueous alcoholic solution in presence of piperidine; the yield of the product, 5-hydroxy-4-cyano-1,2-dihydro-6-aza-chrysene (XIII), which crystallised from glacial acetic acid with two molecules of solvent of crystallisation, was disappointing, although sufficient material was obtained for the completion of the synthesis. A similar attempt was made to condense 3-hydroxymethylene-4-keto-1,2,3,4-tetrahydrophenanthrene (XII) with cyanacetamide, but this merely resulted in tars which could not be purified.

The remainder of the synthesis resolved itself into the conversion of this condensation product to the fully aromatic azachrysene, and this was accomplished by the following scheme:-



The hydrolysis of the nitrile (XIII) to the carboxylic acid (XIV) was accomplished by heating it with fuming hydrochloric acid in a sealed tube. By using a slightly higher temperature, decarboxylation was also brought about, and the pyridone (XV) resulted. This pyridone could also be prepared by decarboxylating the acid (XIV) by simple fusion, but attempted decarboxylation of the acid by boiling in quinoline solution with copper bronze resulted not only in decarboxylation, but in dehydrogenation to the fully aromatic pyridone (XIX) together with the production of much carbonaceous matter. The method finally adopted for the preparation of the pyridone (XV) was that of heating at the higher temperature with fuming hydrochloric acid.

The acid (XIV) was characterised by reacting it with ethereal diazomethane, resulting in a derivative methylated not only in the carboxylic acid grouping, but also in the tautomeric form of the carbonyl group in position 5.

The pyridone (XV) was characterised by preparing its acetyl and benzoyl derivatives on the tautomerised carbonyl group in position 5. The substance could not be methylated by ethereal diazomethane, and methyl sulphate acted on its sodium salt to give a compound containing sulphur, for which no satisfactory formula could be found.

An attempt to convert the pyridone (XV) directly to the azachrysene (XVII) by fusing it with a mixture of zinc dust, zinc chloride, and sodium chloride [85] resulted merely in dehydrogenation to the fully aromatic pyridone (XIX), identified by taking mixed melting points with an authentic sample of (XIX) prepared as described later.

Two lines of approach were now open. The pyridone (XV) could be dehydrogenated at positions 1 and 2 to the fully aromatic pyridone (XIX), and the product chlorinated to give the compound (XVIII); or the pyridone (XV) could be chlorinated to give the compound (XVI), the chlorine removed catalytically to give an unsubstituted pyridine ring, and the product dehydrogenated at positions 1 and 2 to give the fully aromatic azachrysene (XVII).

Accordingly, following the first method, the pyridone (XV) was dehydrogenated by direct fusion with palladium-black in an atmosphere of carbon dioxide to give the fully aromatic pyridone (XIX), the volume of hydrogen evolved corresponding to the loss of two atoms of hydrogen. The product was characterised by preparing the acetyl derivative of its tautomeric hydroxy form. The dehydrogenation was, however, tedious, as it could only be performed conveniently on small quantities of material.

The second method was therefore adopted, and the pyridone (XV) was reacted with phosphorus pentachloride.

Unfortunately, the product of the reaction was a mixture of the fully aromatic pyridone (XIX), which was identified by analysis, and by taking mixed melting points with an authentic sample prepared as above, together with a rather smaller quantity of a compound found, on fusion with sodium, to contain chlorine.

The main stock of the pyridone (XV) was ultimately converted, in good yield, to the chloro compound (XVI) by heating it with phosphorus oxychloride at a high temperature in a sealed tube, a method which has been applied in similar cases[86]; the resulting product was successfully converted directly to the azachrysene (XVII) by prolonged heating with palladium-black in boiling tetralin, which removed not only the chlorine as hydrogen chloride, but also two hydrogen atoms from positions 1 and 2, thus giving a fully aromatic product. The picrate of the azachrysene (XVII) was prepared in order to characterise it.

At the same time, the chloro compound obtained above by reacting the pyridone (XV) with phosphorus pentachloride was examined more closely. It was obtained, unfortunately, in proportions too small to warrant the further preparation of an analytical sample. Its melting point was different from that of the chloro compound (XVI) obtained by the action of phosphorus oxychloride on the pyridone (XV), and, on admixture, the melting points of both were depressed, showing that the two substances were different. On prolonged heating with

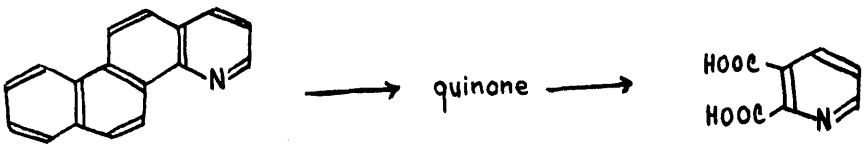
palladium-black in boiling tetralin, however, it yielded the same product as did the chloro compound (XVI), namely the azachrysene (XVII), which was identified by taking mixed melting points with the base itself, and of the picrate prepared from it. The substance was therefore presumed to have been 5-chloro-6-azachrysene (XVIII), resulting from combined chlorination and dehydrogenation of the pyridone (XV) by the action of phosphorus pentachloride.

It remained only to prove first, that the aza chrysene (XVII) prepared from the dihydro-chloro compound (XVI) was fully aromatic, as it could not be assumed that the palladium-black in boiling tetralin had necessarily removed the two hydrogen atoms in positions 1 and 2, as well as the chlorine atom in position 5; and secondly that the azachrysene was the quinoline, 6-azachrysene, and not the isoquinoline, 5-aza-chrysene, a possibility which has been discussed previously.

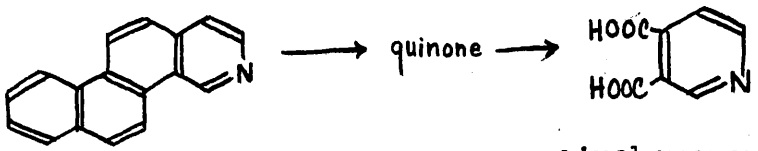
That the substance was fully aromatic was first formally proved by its failure to evolve any hydrogen whatsoever on prolonged heating at a high temperature with palladium-black in an atmosphere of carbon dioxide. Had positions 1 and 2 been hydrogenated, this treatment should have sufficed to remove the hydrogen, as unsaturated chrysene derivatives of this nature are themselves susceptible under these conditions.

In order to determine the position of the nitrogen atom

in the substance, it was proposed to prepare the quinone from the azachrysene (XVII) by oxidation with chromic acid [87] and, by subsequent complete oxidation of the quinone to a known pyridine dicarboxylic acid, to determine whether the original substance was 6-azachrysene or 5-azachrysene:-



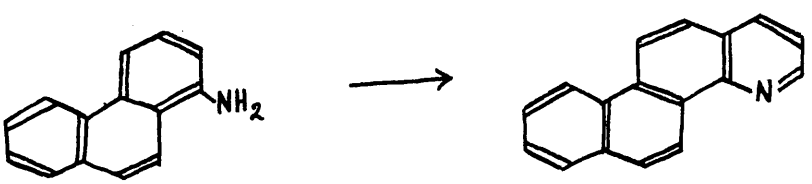
quinolic acid.



cinchomeronic acid.

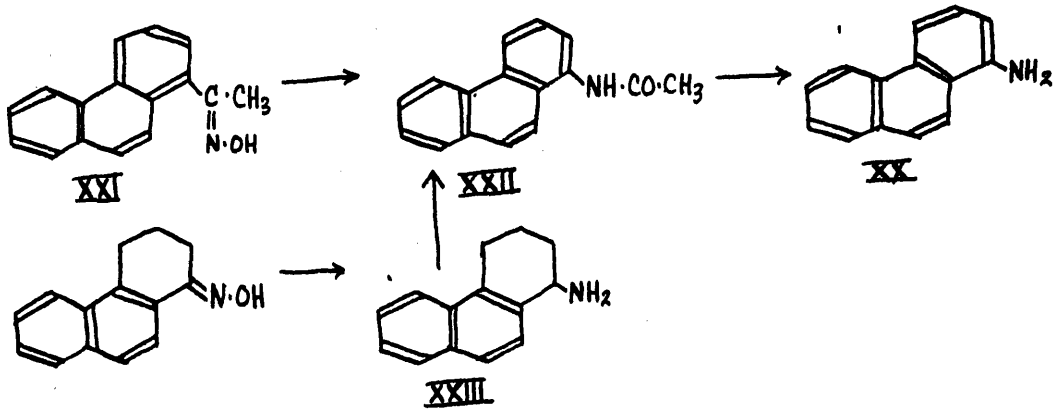
Unfortunately, the quinone could not be prepared because of charring during the reaction, and the method was abandoned.

It was therefore resolved to perform a Skraup reaction on 1-aminophenanthrene (XX), since, owing to the position of the amino group on the compound, this reaction could give one product only, namely, 6-azachrysene (XVII):-



XX XVII

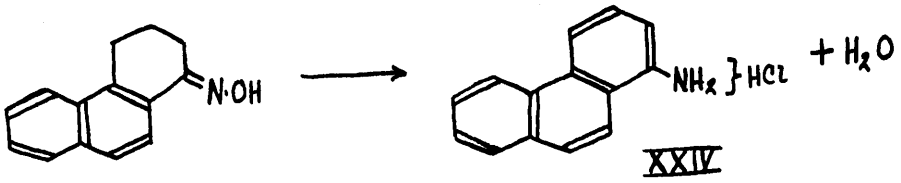
Two methods available for the preparation of 1-aminophenanthrene (XX) are due to Bachmann; they are the Beckmann rearrangement of the oxime of 1-acetylphenanthrene (XXI), and subsequent hydrolysis with alcoholic hydrochloric acid of the resulting 1-acetamidophenanthrene (XXII) to give a 72% yield of 1-aminophenanthrene (XX) [88]; and also the reduction of the oxime of 1-keto-1,2,3,4-tetrahydrophenanthrene (V) with sodium amalgam and alcohol to the alicyclic amine (XXIII), which is then acetylated and dehydrogenated with palladium-black to the fully aromatic 1-acetamidophenanthrene (XXII) which in turn is hydrolysed as before to 1-aminophenanthrene (XX) [89].



XXI XXII XX XXIII

The method eventually chosen, however, because of its simplicity, was a modification of that due to Langenbeck and Weissenborn [90], and is an application of Schroeter's method [91]. The oxime of 1-keto-1,2,3,4-tetrahydrophenanthrene (V) [89,92] is rearranged by passing dry hydrogen chloride through its solution in glacial acetic acid containing a trace of acetic

anhydride, when the amine (XX) is thrown down as its hydrochloride (XXIV):-



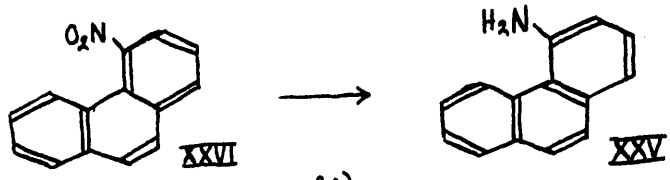
XXIV

A satisfactory yield of 1-aminophenanthrene (XX) was obtained, and the Skraup reaction performed on it in the usual manner using the technique of Mosettig [64] who carried out similar reactions on 2- and 3-aminophenanthrenes. The pure 6-azachrysene (XVII) obtained from the reaction, and its picrate, were respectively proved, by analysis and by the method of mixed melting points, to be identical with the azachrysene and its picrate obtained from the previous synthesis; this compound was thus formally established beyond doubt to be 6-azachrysene.

In the rearrangement of the oxime of 1-keto-1,2,3,4-tetrahydrophenanthrene (V), a very small quantity of a substance isomeric with, but different from a prepared sample of pure 1-acetamidophenanthrene (XXII), was isolated; an attempted hydrolysis of this substance using boiling alcoholic sulphuric acid resulted merely in the formation of tars, and the quantity of material available was too small to permit further investigation. It is thought that it may have resulted from the migration of the acetyl group of 1-acetamidophenanthrene (XXII) which might have been formed during the reaction by the action

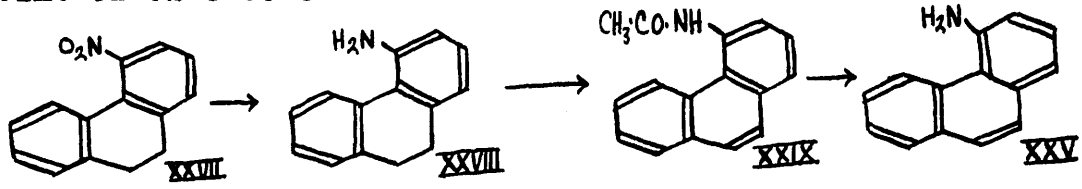
of the acetic acid solvent on the 1-aminophenanthrene (XX).

4-Aminophenanthrene (XXV) has been described on at least two occasions; Schmidt and Heinle [93] reduced 4-nitrophenanthrene (XXVI) (obtained in 20% yield by fractionally crystallising the nitration products of phenanthrene) by means of stannous chloride and glacial acetic acid, and obtained an amine melting at 105°C, which gave a benzoyl and an acetyl derivative.



XXVI XXV

Krueger and Mosettig [94] nitrated 9,10-dihydrophenanthrene and obtained 3-4% of 4-nitro-9,10-dihydrophenanthrene (XXVII), which they reduced to 4-amino-9,10-dihydrophenanthrene (XXVIII), diacetylated this, dehydrogenated it to give 4-acetamidophenanthrene (XXIX) and hydrolysed this to the free 4-aminophenanthrene (XXV); this they found to have a melting point of 62.5-63.5°C.

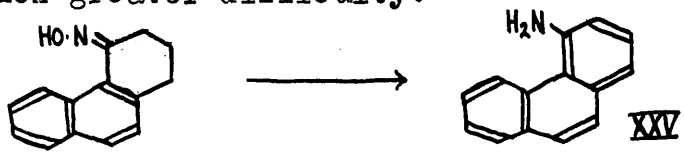


XXVII XXVIII XXIX XXV

The discrepancy between this melting point and that of Schmidt and Heinle's 4-aminophenanthrene is believed to be due to the existence of two different forms of the base.

However, the oxime of 4-keto-1,2,3,4-tetrahydrophenanthrene (X) [92] was rearranged by the method described above

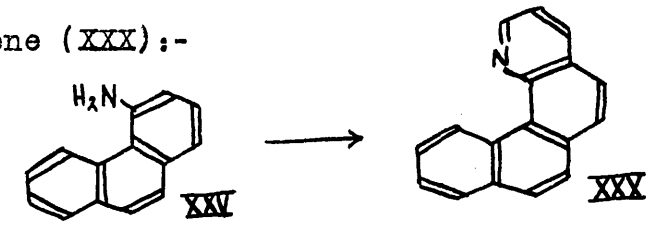
to give a much smaller yield of 4-aminophenanthrene (XXV), and with much greater difficulty.



XXV

The amine we obtained by using this modified method of Langenbeck and Weissenborn was found to melt at 63-64°C in agreement with that of Krueger and Mosettig, although the compound prepared by Langenbeck and Weissenborn themselves was stated by them to melt at 55°C. The melting points of both the benzoyl and acetyl derivatives of both Krueger and Mosettig's and our 4-aminophenanthrene (XXV) were, however, in agreement with those of the corresponding derivatives of the amine prepared by Schmidt and Heinle. The base was prepared for use in the following series of syntheses.

It was decided to carry out the Skraup reaction on 4-aminophenanthrene (XXV) in order to prepare 3,4-benz-5-azaphenanthrene (XXX):-



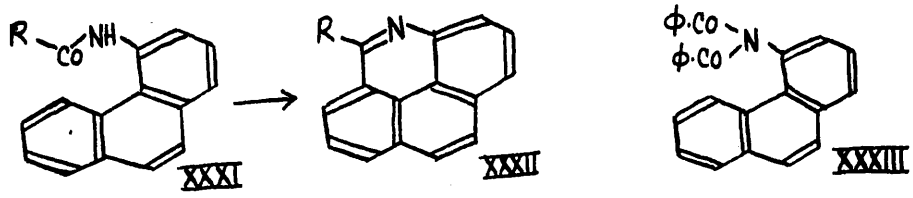
XXV XXX

However, when the reaction was carried out as in the case of 1-aminophenanthrene (XX), complete charring occurred, and nothing could be isolated but carbonaceous material. After several such attempts, it was decided to use sodium m-nitrobenzene sulphonate as the oxidising agent, together with

water as a diluent, thus rendering unnecessary the use of ferrous sulphate as a moderating agent. The method had been used successfully in several other cases [95], and proved useful in this one, the base 3,4-benz-5-azaphenanthrene (XXX) being isolated from the reaction mixture, albeit in small yield and in a very impure state. It was purified through its hydrochloride and characterised by means of its picrate.

.....

It was considered possible that, owing to the position of the amino group in 4-aminophenanthrene (XXV), its acyl and aroyl derivatives (XXXI) might be cyclised to give 2-substituted 1-azapyrenes (XXXII), a method analagous to that used by Morgan and Walls [96] to obtain phenanthridines:-



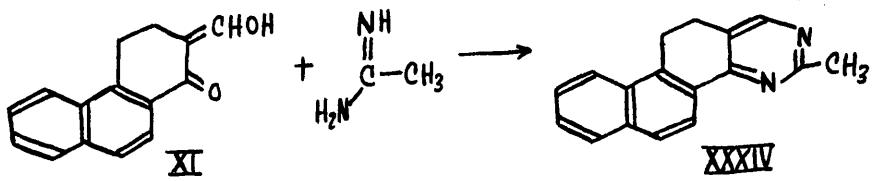
The formyl derivative of 4-aminophenanthrene [(XXXI); R = H] prepared by heating the amine with 98% formic acid, was thus cyclised to give 1-azapyrene [(XXXII); R = H] by boiling its solution in xylene with phosphoric oxide. The base obtained was purified through its picrate, which also served to characterise it, and was found to melt at 157-159°C. It is interesting to note that "thebenidine", which Vongerichten [97] obtained by distillation of the alkaloid thebenine with zinc dust, is thought to have the same structure, and,

although its melting point is given as 144-148°C, this does not exclude its identity with our compound, especially as the range over which it appears to have melted indicates that it was probably slightly impure.

Similarly 4-acetamidophenanthrene and 4-benzamidophenanthrene [(XXXI); R = CH_3,C_6H_5] were cyclised to give 2-methyl- and 2-phenyl-1-azapyrene respectively [(XXXII); R = CH_3,C_6H_5], both bases being characterised by their picrates. In the preparation of 4-benzamidophenanthrene, a small quantity of 4-dibenzoylaminophenanthrene (XXXIII) was isolated.

.....

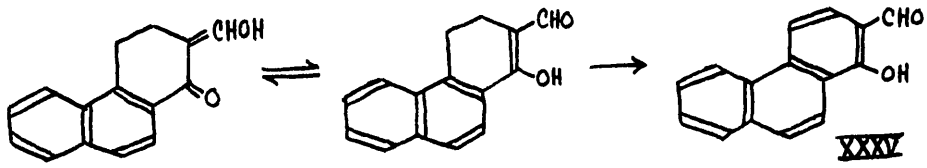
The physiological importance of the pyrimidine nucleus made it desirable that some polycyclic compounds be synthesised containing a fused pyrimidine ring. Accordingly, the following synthesis of a derivative of 4,6-diazachrysene (XXXIV) was attempted by the condensation of acetamidine with 2-keto-1-hydroxymethylene-1,2,3,4-tetrahydrophenanthrene (XI):-



XI XXXIV

The condensation was attempted in anhydrous ethanol, using sodium ethoxide as the condensing agent, a method which has been found to have been successful in other cases [98].

Unfortunately, condensation could not be induced even after numerous attempts. Under mild conditions the hydroxymethylene ketone underwent auto-oxidation to 1-phenanthrol-2-aldehyde (XXXV), which was characterised by the preparation of its oxime.



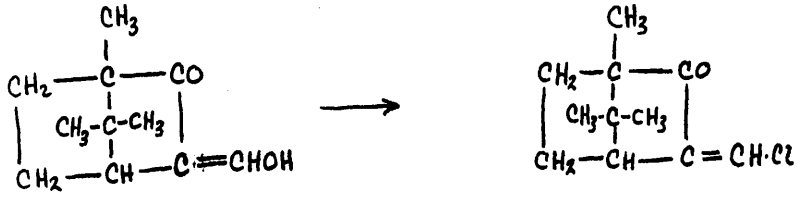
XXXV

More vigorous conditions, which involved heating on the steam bath, resulted in removal of the hydroxymethylene group from the starting material to give 1-keto-1,2,3,4-tetrahydrophenanthrene (V).

It was thought, however, that a suitable derivative of the hydroxymethylene ketone might prove successful, and it was resolved to prepare the chloromethylene derivative of the ketone with this end in view.

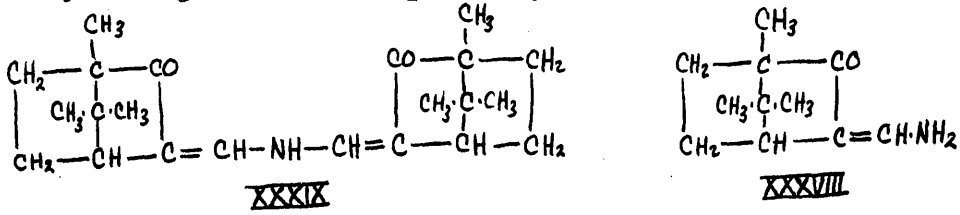
Chloromethylene ketones of this type have been recorded on only two occasions, and have not yet been employed for broad synthetic purposes, although a thorough investigation of their potentialities in this direction would almost certainly prove fruitful.

Claisen, Bishop and Sinclair [99] acted on α-hydroxymethylene camphor (XXXVI) with phosphorus trichloride and obtained a stable α-chloromethylene camphor (XXXVII):-



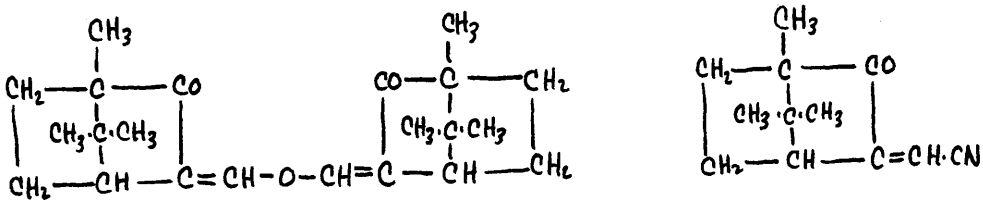
XXXVI XXXVII

This substance was unaffected by boiling water, and was only hydrolysed to its parent hydroxymethylene ketone by warm alcoholic caustic potash. Methyl alcoholic ammonia at 100°C yielded α-aminomethylene camphor (XXXVIII), and under certain conditions the imido-bis-methylene camphor (XXXIX) could be formed by using a reduced quantity of ammonia:-



XXXIX XXXVIII

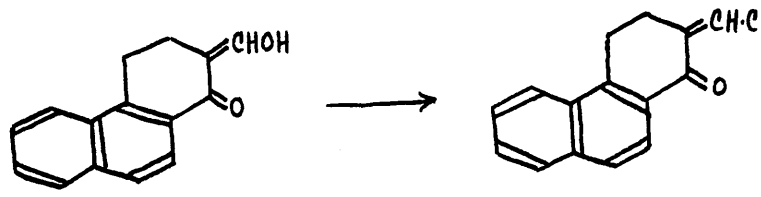
Similarly with aniline at 160°C the anilide could be prepared, and under similar conditions, the p-toluidide, while the action of potassium cyanide on the chloromethylene ketone produced the cyanomethylene ketone (XL) with elimination of potassium chloride. By heating with the sodium salt of the hydroxymethylene ketone an anhydride (XLI) could be formed with elimination of sodium chloride:-



XLI XL

The corresponding ∝-bromomethylene camphor could similarly be prepared by the action of phosphorus tribromide on ∝-hydroxymethylene camphor (XXXVI).

Thus, because of the stability and high reactivity of chloromethylene ketones, and because the sodium chloride produced in their possible condensation with acetamidine in presence of alcoholic sodium ethoxide, would be insoluble and incapable of back-reacting (unlike the sodium hydroxide that would have been produced in the previous attempt using the free hydroxy methylene ketone), the preparation of 2-chloromethylene-1-keto-1,2,3,4-tetrahydrophenanthrene (XLII) was accordingly attempted. It was successfully carried out by acting on 2-hydroxymethylene-1-keto-1,2,3,4-tetrahydrophenanthrene (XI) with excess thionyl chloride in the cold; the reaction proceeded to completion in a very short time, and the yield of the resulting chloromethylene ketone was found to be almost quantitative:-



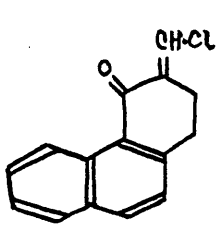
XI XLII

The product was easily purified by crystallisation from ligroin as massive aggregates of colourless plates.

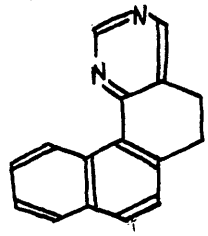
In the same way a quantitative yield of 3-chloromethylene-4-keto-1,2,3,4-tetrahydrophenanthrene (XLIII) was obtained by a similar reaction carried out on 3-hydroxymethylene-4-keto-1,2,3,4-tetrahydrophenanthrene (XII).

Both of these chloromethylene ketones were found to condense immediately in the cold with alcoholic solutions of amidine hydrochlorides, using sodium ethoxide as the condensing agent, to give almost quantitative yields of the corresponding pyrimidines.

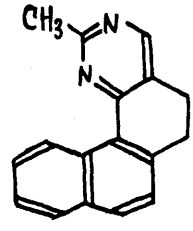
By this means, 3-chloromethylene-4-keto-1,2,3,4-tetrahydrophenanthrene (XLIII) was condensed with formamidine - prepared by the method of Pinner[100] - and with acetamidine to give 9,10-dihydro-3,4-benz-5,7-diazaphenanthrene (XLIV) and 6-methyl-9,10-dihydro-3,4-benz-5,7-diazaphenanthrene (XLV) respectively; and 2-chloromethylene-1-keto-1,2,3,4-tetrahydrophenanthrene (XLII) was similarly condensed with acetamidine to give 5-methyl-1,2-dihydro-4,6-diazachrysene (XLVI). Each of these bases was characterised by the preparation of its picrate.



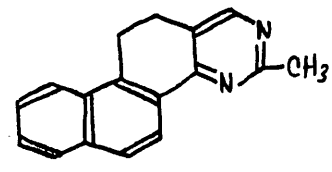
XLIII



XLIV

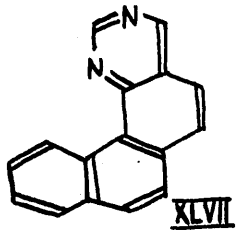


XLV

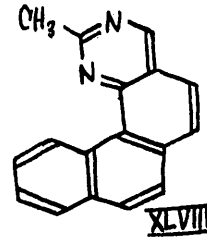


XLVI

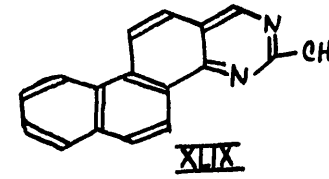
These compounds were then dehydrogenated by fusion at a high temperature with palladium-black in an atmosphere of carbon dioxide to give the fully aromatic polycyclic compounds 3,4-benz-5,7-diazaphenanthrene (XLVII), 6-methyl-3,4-benz-5,7-diazaphenanthrene (XLVIII) and 5-methyl-4,6-diazachrysene (XLIX) respectively. Each of these bases was characterised, as before, by the preparation of its picrate.



XLVII



XLVIII



XLIX

The full text of these experiments, together with the relevant analytical figures, is given in the Experimental section.

EXPERIMENTAL

(A) Synthesis of 6-Azachrysene, with a Proof of its Structure by an Alternative Synthesis.

(1) 2-Hydroxymethylene-1-keto-1,2,3,4-tetrahydrophenanthrene.

Sodium wire (7.5 g.) followed by ethyl formate (27 ccs.) was added to a cold solution of 1-keto-1,2,3,4-tetrahydrophenanthrene (60 g.) in dry toluene (300 ccs.) previously dried over sodium wire. A reaction began after a time with evolution of hydrogen, and a brown solid slowly separated. After being kept overnight, the resulting paste was treated first with concentrated caustic soda solution, and then more cautiously with cold water.

The aqueous solution was separated from the toluene layer, thoroughly washed by shaking several times with ether, and acidified with dilute sulphuric acid. The product at once separated as an oil which soon became a sandy brown solid; this was filtered off, dried in a desiccator, and recrystallised from methanol (charcoal) as straw-coloured crystals, m.pt. 84-85°C. The yield was 45 g. The substance gave an intense green colour with ferric chloride in methanol.

Found: C, 80.2%; H, 5.4%. $C_{15}H_{12}O_2$ requires C, 80.3%; H, 5.4%.

2-Methoxymethylene-1-keto-1,2,3,4-tetrahydrophenanthrene was prepared by mixing an ethereal solution of the hydroxymethylene ketone with excess of an ethereal solution of diazomethane. After keeping for some days, the ether was allowed to evaporate, the gum left redissolved in ether, and the solution shaken first with dilute caustic soda solution to remove unchanged hydroxymethylene ketone, and then with water. After drying over anhydrous sodium sulphate the ether was removed by evaporation, and the reaction product, remaining behind as a sticky solid, was crystallised several times from methanol as colourless plates, m.pt. 96-97°C.

Found: C, 80.5%; H, 6.0%. $C_{16}H_{14}O_2$ requires C, 80.6%; H, 5.9%.

2-Aminomethylene-1-keto-1,2,3,4-tetrahydrophenanthrene was prepared by passing dry gaseous ammonia into a solution of 2-hydroxymethylene-1-keto-1,2,3,4-tetrahydrophenanthrene (5 g.) in dry chloroform (50 ccs.). The solution became a thin paste as a yellow solid began to separate almost at once, and small amounts of chloroform were added from time to time to offset evaporation due to the current of ammonia, the evaporation also serving to keep the mixture cool.

After four hours, passage of ammonia was stopped, the precipitate collected, dried, and boiled up with charcoal in

chloroform, and the solution filtered and concentrated to a small bulk. The red powder that deposited on cooling was collected, and recrystallised several times from benzene as tufts of carmine needles, m.pt. 147-149°C.

Found: C, 80.9%; H, 5.6%. $C_{15}H_{13}ON$ requires C, 80.7%; H, 5.8%.

(2) 5-Hydroxy-4-cyano-1,2-dihydro-6-azachrysene.

A solution of cyanacetamide (Org.Synthesis, Vol.IX, p.36) (3.4 g.) in water (25 ccs.) was added to a solution of 2-hydroxymethylene-1-keto-1,2,3,4-tetrahydrophenanthrene (9 g.) dissolved in just enough ethanol to effect solution of the final mixture at room temperature.

Frequent alternate additions of water and ethanol were necessary to secure these conditions, but it was found that the final bulk might be anything between 250 ccs. and 500 ccs. without materially affecting the final result.

Piperidine (1.5 ccs.) was then added, and the whole maintained at 40°C for 100 hours. The brown powder which had separated from the now deep red reaction liquor was filtered off and washed with ethanol. More piperidine (1.5 ccs.) was added to the filtrate, after it had been concentrated under reduced pressure, and this was heated at 40°C for a further 100 hours. The second crop of product that had then

precipitated was collected, and the combined crops crystallised several times from glacial acetic acid (charcoal) as fine, bright yellow, microscopic needles, m.pt. 364-366°C. The yield was 3 g.

Found: C, 67.6%; H, 5.0%. $C_{18}H_{12}ON_2,2C_2H_4O_2$ requires C, 67.4%; H, 5.1%.

(3) 5-Hydroxy-1,2-dihydro-6-azachrysene-4-carboxylic acid.

5-Hydroxy-4-cyano-1,2-dihydro-6-azachrysene (0.5 g.) was heated for 3 hours at 150°C in a sealed tube with fuming hydrochloric acid (d. 1.19; 10 ccs.). On cooling and opening the tube, the brown needles which filled the solution were filtered off, washed with water, and boiled up with excess dilute sodium carbonate solution for some time. The solution was filtered while hot, cooled, and the aqueous suspension of the sodium salt of the product, which had now crystallised out, being only sparingly soluble, was acidified with dilute hydrochloric acid solution.

The precipitated product was filtered off, dried, and recrystallised several times from ethylene glycol monomethyl ether as fine, fluffy yellow needles, m.pt. 324-325°C, with much frothing (probably owing to carbon dioxide evolved by decarboxylation at the high temperature of fusion).

Found: C, 74.5%; H, 4.5%; N, 5.55%. $C_{18}H_{13}O_3N$ requires C, 74.2%; H, 4.5%; N, 4.8%.

Methyl 5-methoxy-1,2-dihydro-6-azachrysene-4-carboxylate was prepared by adding 5-hydroxy-1,2-dihydro-6-azachrysene-4-carboxylic acid (0.25 g.) to a cold saturated ethereal solution of diazomethane (25 ccs.), when a slow effervescence at once began. After being kept for a week, the solution was filtered free from undissolved material and the ether removed from the filtrate by evaporation. The lemon-yellow crystals remaining were crystallised several times from ethanol as tufts of colourless needles, m.pt. 118-120°C.

Found: C, 75.5%; H, 5.25%; N, 4.5%. $C_{20}H_{17}O_3N$ requires C, 75.2%; H, 5.3%; N, 4.45%.

That this substance was neither phenolic nor acidic was confirmed by its complete insolubility in hot dilute caustic soda solution.

(4) 5-Hydroxy-1,2-dihydro-6-azachrysene.

(a) By simultaneous hydrolysis and decarboxylation of 5-hydroxy--4-cyano-1,2-dihydro-6-azachrysene.

5-Hydroxy-4-cyano-1,2-dihydro-6-azachrysene (0.5 g.) was heated for 4 hours at 170-180°C in a sealed tube with fuming HCl (d. 1.19; 10 ccs.). On cooling and opening the tube, the mass of thick brown plates that filled the solution was filtered off, washed with water, dried, and dissolved in hot glacial acetic acid (25 ccs.). The solution was then

clarified by boiling with charcoal and subsequent filtration, and concentrated to a small bulk, by distillation, in order to drive off any hydrogen chloride present. The concentrated solution, on pouring into cold water (500 ccs.), gave a bulky, light yellow precipitate; this was collected, dried, and crystallised from a large volume of methanol as thick, yellow, elongated prisms m.pt. 275-276°C. The yield was 90% of the theoretical quantity.

Found: C, 82.4%; H, 5.0%; N, 5.8%. $C_{17}H_{13}ON$ requires C, 82.6%; H, 5.3%; N, 5.7%.

The compound dissolved in hot concentrated caustic soda solution, but not in hot sodium carbonate solution, and the solution on cooling deposited colourless leaflets of the sodium salt, m.pt. 526-528°C, which readily hydrolysed in warm water to its parent compound.

The methyl ether of 5-hydroxy-4-cyano-1,2-dihydro-6-azachrysene could not be obtained either by refluxing its sodium salt with dry methyl iodide in ethanol, or by treating the free hydroxy-compound in ether/dioxan solution with ethereal diazomethane, as from both attempts the starting material was recovered unchanged.

A compound was obtained when the sodium salt (0.25 g.) was heated for 90 minutes on the water bath, with pure dry methyl sulphate (5 ccs.). The clear solution obtained was filtered

while hot and allowed to stand overnight; the silky needles deposited were filtered off and a further crop obtained by concentration of the filtrate under reduced pressure. The combined crops after several crystallisations from acetone were obtained as greenish-yellow rhombs, m.pt. 211-212°C.

Found: C, 60.3%; H, 4.4%; N, 4.4%.

This compound was very soluble in ethanol, was insoluble in, and unaffected by water, and was found, by the method of sodium fusion, to contain sulphur. As no acceptable formula could be found to satisfy this data, the nature of the compound was not investigated further.

5-Benzoyloxy-1,2-dihydro-6-azachrysene was prepared by dissolving 5-hydroxy-1,2-dihydro-6-azachrysene (0.1 g.) in hot dilute caustic soda solution (125 ccs.), and by shaking this while still warm with excess benzoyl chloride. The product separated as a white clotted precipitate, which was collected, washed with dilute caustic soda solution, then water, dried, and recrystallised several times from ethanol as short, colourless needles, m.pt. 209-210°C.

Found: C, 81.95%; H, 4.7%; N, 4.2%. $C_{24}H_{17}O_2N$ requires C, 82.1%; H, 4.8%; N, 4.0%.

5-Acetoxy-1,2-dihydro-6-azachrysene was prepared by dissolving 5-hydroxy-1,2-dihydro-6-azachrysene (0.25 g.) together with

acetic anhydride (0.2 g.) in pure dry pyridine (5 ccs.); the whole was then heated on the water bath, and left overnight. On pouring the solution into cold water (150 ccs.), the product was thrown down as a flocculent white precipitate, which was collected, washed with water, dried, and crystallised several times from ethanol as long, colourless needles, m.pt. 145-147°C, having a violet or blue fluorescence.

Found: C, 78.8%; H, 5.2%; N, 5.0%. $C_{19}H_{15}O_2N$ requires C, 78.9%; H, 5.2%; N, 5.2%.

(b) By decarboxylation of 5-hydroxy-1,2-dihydro-6-azachrysene-4-carboxylic acid.

(i) 5-Hydroxy-1,2-dihydro-6-azachrysene-4-carboxylic acid (0.3 g.) was heated in a test-tube for 10 minutes at 340-350°C on a metal bath. A considerable effervescence was observed, and the evolved gas produced a turbidity in lime water through which it was conducted, thus indicating it to be carbon dioxide.

The dark residue left in the test-tube, after effervescence had ceased, was scraped out and found to weigh 0.225 g.; it was then sublimed at 200°C and at 0.15-0.2 mm. pressure. The sublimate was crystallised from methanol as long yellow prisms, 275-277°C, which did not depress the melting point of the product obtained in (a) by combined hydrolysis and decarboxylation of 5-hydroxy-4-cyano-1,2-dihydro-6-azachrysene.

An exceedingly small quantity of sparingly soluble material crystallised out, prior to the crystallisation of the main yield, as light yellow shining laminae, m.pt. 345-355°C; this was probably 5-hydroxy-6-azachrysene (see below).

The identity of the products obtained by methods (a) and (b) was further established by the preparation, as before, of the acetyl derivative of the substance obtained by method (b); this was found, by mixed melting points, to be identical with the acetyl derivative of the product obtained by method (a).

(ii) 5-Hydroxy-1,2-dihydro-6-azachrysene (0.2 g.) was refluxed for 1 hour in pure dry quinoline (25 ccs.) with a trace of copper bronze. The solution darkened, and on cooling, the copper was filtered off, and the quinoline removed from the filtrate by steam distillation, leaving behind a brown powdery residue. This was collected, dried, and crystallised from methanol (charcoal) as orange-yellow needles, m.pt. 330-350°C. This was probably 5-hydroxy-6-azachrysene resulting from combined decarboxylation and dehydrogenation by the copper bronze at the high temperature used.

No 5-hydroxy-1,2-dihydro-6-azachrysene could be obtained by this method.

(5) 5-Hydroxy-6-azachrysene.

(a) By direct fusion of 5-hydroxy-1,2-dihydro-6-azachrysene with palladium-black.

5-Hydroxy-1,2-dihydro-6-azachrysene (0.22 g.) was fused in a hard glass tube with palladium-black (0.02 g.) at 290-300°C on a metal bath, any evolved hydrogen being swept out by a constant current of carbon dioxide into a modified inverted measuring cylinder containing concentrated caustic potash solution. The carbon dioxide was thus absorbed, leaving the hydrogen behind to be measured.

In 1 hour, 8 ccs. of hydrogen were evolved; the temperature was then raised to 350°C for a further 75 minutes, and a further 11 ccs. of hydrogen were evolved. As the theoretical amount of hydrogen that would be evolved by removal of two atoms of hydrogen from the compound was almost 20 ccs. at N.T.P., the apparatus was disconnected and the reaction mixture allowed to cool.

The colourless crystalline mass in the tube was scraped out and recrystallised from a large volume of ethanol as colourless, highly refractive prisms, m.pt. 355-365°C.

The substance was soluble in hot dilute caustic soda solution, but not in hot sodium carbonate solution, indicating its phenolic nature; it was reprecipitated by acidification of its solution in dilute caustic soda with dilute hydrochloric acid solution.

(b) By refluxing 5-hydroxy-1,2-dihydro-6-azachrysene with palladium-black in xylene.

5-Hydroxy-1,2-dihydro-6-azachrysene (0.25 g.) was boiled in pure sulphur-free xylene (25 ccs.) until solution was achieved. Palladium-black (0.025 g.) was then added to the solution, and the whole refluxed for 24 hours. At the end of this time a yellow solid was observed to have been deposited; this was collected and crystallised from ethanol as colourless, highly refractive prisms, m.pt. 355-365°C, which did not depress the melting point of the product obtained by method (a), the two substances being thus identical.

Found: C, 84.0%; H, 4.4%; N, 5.5%. $C_{17}H_{11}ON$ requires C, 83.3%; H, 4.5%; N, 5.7%.

(c) By fusing 5-hydroxy-1,2-dihydro-6-azachrysene with a mixture of sodium chloride, zinc chloride, and zinc dust.

5-Hydroxy-1,2-dihydro-6-azachrysene (0.25 g.), sodium chloride (0.25 g.), moist zinc chloride (1.25 g.) and zinc dust (0.25 g.) were well mixed together and heated in a test tube at 290-300°C for four hours. On cooling, the dark mass was repeatedly extracted with boiling water, dried, and fractionally sublimed at 280°C in an oil-pump vacuum.

The first fraction, which deposited as yellow flakes near the top of the tube in the subliming apparatus, was crystallised from methanol and proved by mixed melting points to be unchanged starting material.

The second fraction, which deposited further down the tube as a colourless solid, was recrystallised from methanol as colourless shining needles, melting between 320°C and 350°C; these did not depress the melting point of an authentic sample of 5-hydroxy-6-azachrysene prepared as in method (a), with which they were thus identical. The yield was excessively small.

(d) By fusing 5-hydroxy-1,2-dihydro-6-azachrysene with phosphorus pentachloride.

See page 57. The sample of 5-hydroxy-6-azachrysene obtained by this method as a bye-product melted sharply at 362-364°C and gave a very good analysis.

5-Acetoxy-6-azachrysene.

5-Hydroxy-6-azachrysene (0.1 g.) was dissolved in hot pyridine (8 ccs.), and excess acetic anhydride added. After heating on the water bath for an hour, the clear solution was left overnight and poured into water (250 ccs.). A white, flocculent precipitate of the acetyl derivative was thrown down; it was collected, dried after washing, and crystallised repeatedly from ethanol as colourless silky needles, m.pt.149-151°C. These depressed the melting point of an authentic sample of 5-acetoxy-1,2-dihydro-6-azachrysene (m.pt. 145-147°C) to 132°C.

Found: C, 79.4%; H, 4.3%. $C_{19}H_{13}O_2N$ requires C, 79.4%; H, 4.5%.

(VI) 5-Chloro-1,2-dihydro-6-azachrysene.

5-Hydroxy-1,2-dihydro-6-azachrysene (2.7 g.) was heated with phosphorus oxychloride (11 ccs.) in a sealed tube at 175°C for 7 hours. After cooling and opening the tube, the dark solution obtained was poured on ice, and the solid thrown down was collected, repeatedly washed with water, dried, and recrystallised several times from glacial acetic acid as large colourless plates, m.pt. 115-116°C. The yield was 2.1 g.

Found: C, 77.0%; H, 4.4%; N, 5.1%. $C_{17}H_{12}NCl$ requires C, 76.85%; H, 4.5%; N, 5.3%.

(VII) 5 Chloro-6-azachrysene.

(a) 5-Hydroxy-1,2-dihydro-6-azachrysene (1 g.) was refluxed with phosphorus pentachloride (1 g.) in chlorobenzene (60 ccs.) for 3½ hours on an oil bath at 150°C. The solvent and phosphorus oxychloride were then removed under reduced pressure on the water bath, the last traces being removed by a second evaporation after addition of benzene. The yellow oil left quickly solidified on cooling.

The solid was dissolved in boiling glacial acetic acid (20 ccs.), clarified with charcoal, and filtered hot. A mass of colourless platelets deposited on cooling; these were filtered off, and the filtrate concentrated to a small bulk and poured into water. A small quantity of a yellow precipitate was thrown down; it was collected, dried, and crystallised

from methanol as yellow prisms which did not depress the melting point of an authentic sample of 5-hydroxy-1,2-dihydro-6-azachrysene. This substance was thus unchanged starting material.

The colourless platelets first obtained were recrystallised from glacial acetic acid as rosettes of colourless blades, m.pt. 176-178°C; these were found by the sodium fusion test to contain chlorine. The yield was 0.2 g. This compound was believed to be 5-chloro-6-azachrysene, and, as it was all used for the preparation of 6-azachrysene, none was available for analysis, and no more was prepared.

The acetic acid mother liquors from the above recrystallisation of the colourless platelets were concentrated to a small volume, and on cooling, a quantity of colourless needles (0.2 g.) deposited. These were repeatedly recrystallised from glacial acetic acid, and finally melted sharply at 362-364°C with decomposition. Several sodium fusion tests on this compound failed to reveal the presence of chlorine. Its melting point was not depressed by admixture with a sample of 5-hydroxy-6-azachrysene prepared as before by the dehydrogenation of 5-hydroxy-1,2-dihydro-6-azachrysene with palladium black. The identity of this compound with 5-hydroxy-6-azachrysene was confirmed by its analysis as follows:-

Found: C, 83.6%; H, 4.5%; N, 5.6%. $C_{17}H_{11}ON$ requires C, 83.3%; H, 4.5%; N, 5.7%.

(b) 5-Hydroxy-1,2-dihydro-6-azachrysene (0.25 g.) was heated on an oil bath at 150°C together with phosphorus pentachloride (0.25g.) and a few drops of phosphorus oxychloride. The mass liquefied with evolution of much hydrogen chloride, which ceased after 15 minutes. The heating was continued for a further 15 minutes, then discontinued, and the phosphorus oxychloride removed on the water bath under reduced pressure.

The solid residue remaining was fractionally crystallised from acetic acid as in the experiment previously described in (a). The products obtained, and the proportions in which they were obtained, were found to be similar.

VIII) 6-Azachrysene.

(a) From 5-chloro-6-azachrysene.

A solution of 5-chloro-6-azachrysene (0.2 g.) in boiling tetralin (25 ccs.) was boiled under reflux for 19 hours with palladium-black (0.02 g.). Hydrogen chloride was evolved throughout.

The filtered solution was evaporated under reduced pressure on the water bath, the residue re-evaporated after addition of benzene, and the light brown oil remaining triturated with light petroleum, when it formed a few clusters of thick, clear prisms. Attempts to crystallise the oil from light petroleum resulted merely in the deposition of gums and oils.

Accordingly the brown oil was dissolved in hot ethanol (50 ccs.), and to this was added excess picric acid in hot ethanol (50 ccs.). A yellow crystalline precipitate of the picrate of 6-azachrysene began to deposit instantly, and its formation was hastened by boiling the solution under reflux for 15 minutes. On cooling, the picrate was filtered off, and a second smaller crop obtained by concentration and cooling of the ethanol mother liquors. The yield of the dry picrate was 0.23 g. A small quantity of the picrate, recrystallised several times from ethanol, was obtained for analysis as fine yellow needles, m.pt. 256-258°C with decomposition.

Found: C, 60.4%; H, 2.9%; N, 12.2%. $C_{17}H_{11}N, C_6H_3O_7N_3$ requires C, 60.3%; H, 3.1%; N, 12.2%.

The free base was obtained from the picrate by boiling it for 10 minutes with dilute ammonium hydroxide solution (150 ccs.) and subsequently allowing to cool overnight. The white insoluble powder remaining was filtered from the yellow solution, washed with water, dried, and recrystallised twice from aqueous acetone, and then n-hexane, as small, colourless, saw-toothed laminae, m.pt. 137-138°C.

Found: C, 89.3%; H, 4.6%; N, 6.1%. $C_{17}H_{11}N$ requires C, 89.1%; H, 4.8%; N, 6.1%.

(b) From 5-chloro-1,2-dihydro-6-azachrysene.

A solution of 5-chloro-1,2-dihydro-6-azachrysene (2.1g.)

in boiling tetralin (150 ccs.) was boiled under reflux for 20 hours with palladium-black (0.23 g.). Hydrogen chloride was evolved throughout.

The filtered solution was evaporated repeatedly under reduced pressure with benzene as in (a), and the picrate of the resulting oil prepared satisfactorily in ethanol as before. After drying it was found to weigh 3 g. A small sample of this picrate was recrystallised repeatedly from ethanol, being obtained finally as fine yellow needles, m.pt. 256-258°C, which on admixture did not depress the m.pt. of the pure picrate of 6-azachrysene obtained as in (a), with which it was therefore identical.

The free base was similarly obtained by treatment of the picrate with hot dilute aqueous ammonia, and was also crystallised first from acetone, then twice from n-hexane as large, colourless prisms, m.pt. 137-138°C. This substance on admixture with the pure base obtained in (a) did not depress its melting point; the two substances were therefore identical.

The structure of the supposed 6-azachrysene obtained by the foregoing synthesis.

(i) Attempted dehydrogenation with palladium-black.

6-Azachrysene (0.08 g.) obtained by the foregoing synthesis was heated with palladium-black (0.01 g.) at 300°C in a stream of carbon dioxide, any hydrogen evolved being

swept out by the carbon dioxide and collected in a modified inverted measuring cylinder filled with concentrated caustic potash solution. Here the carbon dioxide was absorbed, leaving the hydrogen undissolved so that its volume could be measured.

During continuous heating for 90 minutes under these conditions, the fused mass was at no time observed to effervesce, and no hydrogen was collected in the measuring apparatus.

After cooling, the fused mass was extracted with boiling acetone, the palladium-black filtered off, and the filtrate diluted with a few drops of hot water. Aggregates of colourless crystals deposited on cooling; these were collected and found to melt at 136-137°C. On admixture with a sample of the original 6-azachrysene the melting point was unchanged; the two substances were thus identical, the product being unchanged starting material.

(ii) Attempted oxidation to the quinone.

6-Azachrysene (0.1 g.) from the previous synthesis was dissolved in glacial acetic acid (2 ccs.) which had been purified by refluxing and distilling over chromic anhydride. To this solution was added a slight excess of the theoretical quantity of sodium dichromate (0.15 g.) dissolved in a similar quantity of pure glacial acetic acid.

The yellow, sparingly soluble chromate of the base separated immediately, but redissolved quickly on warming the solution, which was then boiled under reflux.

Ten minutes after boiling had begun, the solution assumed a greenish colour which deepened until 40 minutes later it was practically black. After boiling under reflux for a total of 23 hours, the solution was poured into cold water (250 ccs.), when a dark, colloidal suspension was formed which was coagulated by refrigeration and addition of sodium chloride.

The carbonaceous precipitate was collected, dried, and extracted with boiling benzene (100 ccs.); the cooled extract was then passed by gravity through a column of anhydrous alumina, and the segregation of the adsorbed fractions was observed under ultraviolet light.

The benzene solution that passed through the column without adsorption of its content was evaporated to dryness. The colourless crystalline solid left (0.5 g.) had a melting point of 132-134°C, which was not depressed on admixture with a pure sample of the original 6-azachrysene; the two substances were therefore identical, and this part of the product was hence unchanged starting material.

In the alumina column itself, the main band was at the lower end and was eluted easily with benzene, leaving adsorbed a band of tarry, carbonaceous material at the top of the

column, with an excessively narrow red band about an inch below it too inconsiderable to merit further investigation. The benzene solution of the eluted main band on evaporation left only an exceedingly small trace of a bright red powder, which was much too small to be manipulated.

(iii) Alternative synthesis of 6-azachrysene from 1-aminophenanthrene.

The oxime of 1-keto-1,2,3,4-tetrahydrophenanthrene was obtained by heating on the water bath a solution in ethanol of 1-keto-1,2,3,4-tetrahydrophenanthrene, hydroxylamine hydrochloride, and pyridine; on evaporation of the solvent in vacuo the residue was washed with water and the product, obtained in quantitative yield, collected and crystallised from ethanol as aggregates of colourless prisms, m.pt. 168-170°C.[89]

(a) 1-Aminophenanthrene, cf.[90]

1-Keto-1,2,3,4-tetrahydrophenanthrene oxime (10.4 g.) dissolved in a mixture of hot glacial acetic acid (100 ccs.) and acetic anhydride (6 ccs.) was heated under reflux on the steam bath with continuous passage of dry hydrogen chloride gas through the solution.

The solution became almost black, and, after 20 minutes, a colourless precipitate began to separate rapidly. Heating and passage of hydrogen chloride was continued for a further 100 minutes, when the solution was allowed to cool. The

passage of hydrogen chloride was then discontinued, and the precipitate was rapidly filtered off and washed several times with anhydrous ether. It was then dissolved in 1 litre of hot acidulated (HCl) water, the solution clarified by shaking with charcoal and filtering, cooled, and made alkaline with ammonium hydroxide solution. A white, clotted precipitate of 1-aminophenanthrene was thrown down immediately, and was collected, washed, and dried.

A second crop of 1-aminophenanthrene was obtained by pouring the original acetic acid reaction liquors into a large volume of anhydrous ether and collecting the brown precipitate that at once deposited; this was extracted with hot acidulated (HCl) water, clarified (charcoal), and made alkaline with ammonium hydroxide solution. The white precipitate thrown was collected, dried, and added to the main yield of 1-aminophenanthrene.

The combined crops of 1-aminophenanthrene were crystallised from benzene/ligroin as colourless plates, m.pt. 146°C. The yield of the pure base was 4.5 g.

In the working up of the second crop of 1-aminophenanthrene, a small part of the brown precipitate remained insoluble in hot acidulated water. This byeproduct was recrystallised several times from methanol as colourless needles, m.pt. 153-155°C.

Found: C, 81.95%; H, 5.5%; N, 5.8%. $C_{16}H_{13}NO$ requires C, 81.7%; H, 5.5%; N, 6.0%.

A small sample of authentic 1-acetamidophenanthrene was prepared by dissolving a little 1-aminophenanthrene in a few ccs. of dry pyridine; a slight theoretical excess of acetic anhydride was then added, the whole warmed on the water bath for 30 minutes, kept at room temperature overnight, and poured into a large volume of water. The white precipitate of 1-acetamidophenanthrene was collected, washed, and dried, and was recrystallised several times from ethanol as large, colourless plates, m.pt. 221-223°C.

The melting point of a pure sample of the above byeproduct was depressed considerably on admixture with this 1-acetamidophenanthrene, the two compounds being therefore different in constitution.

Found: C, 81.2%; H, 5.7%; N, 5.6%. $C_{16}H_{13}NO$ requires C, 81.7%; H, 5.5%; N, 6.0%.

(b) 6-Azachrysene.

Concentrated sulphuric acid (1 c.c.) was added, with stirring, to a mixture of 1-aminophenanthrene (1 g.), powdered crystalline ferrous sulphate (0.2 g.), dry glycerol (2 g.), and dry nitrobenzene (1 c.c.) and the whole heated first at 145°C in an oil bath for one hour, then for two hours over a free

flame sufficient to ensure gentle boiling. The dark reaction mixture was then cooled, freed from nitrobenzene by steam distillation, filtered free from carbonaceous material, boiled with a trace of charcoal, filtered, and cooled.

The dark aqueous solution obtained (about 150 ccs.) was poured into cold saturated brine (500 ccs.), when the hydrochloride of the base was thrown down as a brown precipitate; this was filtered off and boiled up for a short time with dilute aqueous ammonia. The free base obtained was filtered off on cooling, dried, and dissolved in hot ethanol (150 ccs.); to this solution was added a hot solution of picric acid (1 g.) in ethanol (25 ccs.) and the formation of the yellow crystalline picrate that immediately deposited was hastened by boiling the solution for a few minutes.

On cooling, the picrate was filtered off, and a small portion recrystallised several times from ethanol as fine yellow needles. These melted at 258-260°C, and did not on admixture depress the melting point of the pure picrate of the supposed 6-azachrysene obtained by the previous synthesis. The two substances were therefore identical.

The main bulk of the picrate was decomposed by boiling for a short time with dilute aqueous ammonia, the free base being filtered off as a white powder, which was washed, dried, and crystallised several times from n-hexane as stout colourless

prisms, m.pt. 137-139°C. These on admixture did not depress the melting point of a pure sample of the supposed 6-aza-chrysene obtained by the previous synthesis. The two substances were thus identical, and this was confirmed by analysis:-

Found: C, 89.2%; H, 4.7%; N, 6.1%. $C_{17}H_{11}N$ requires C, 89.1%; H, 4.8%; N, 6.1%.

B) Synthesis of 3,4-benz-5-azaphenanthrene.

The oxime of 4-keto-1,2,3,4-tetrahydrophenanthrene was obtained in a similar manner, using similar conditions and technique, as that of 1-keto-1,2,3,4-tetrahydrophenanthrene (see page 63). The yield was quantitative, and was recrystallised from ethanol as clumps of colourless, diamond-shaped plates, m.pt. 171-173°C.

(i) 4-Aminophenanthrene, cf.[90]

4-Keto-1,2,3,4-tetrahydrophenanthrene oxime (5.2 g.) dissolved in a mixture of glacial acetic acid (25 ccs.) and acetic anhydride (3 ccs.) was heated under reflux on the steam bath with continuous passage of dry gaseous hydrogen chloride through the solution. After 1 hour, the solution became almost black in colour, and after much scratching of the walls of the flask with a glass rod, a solid began to separate. Heating and passage of hydrogen chloride was continued for a further two hours, and the mixture was allowed to cool. Passage of hydrogen chloride was then discontinued and the precipitate was

rapidly filtered off and washed several times with anhydrous ether. It was then dissolved in hot acidulated (HCl) water (400 ccs.), the solution clarified with charcoal, filtered, cooled, and made alkaline with aqueous ammonia. The solution became milky and deposited slowly a clotted precipitate of 4-aminophenanthrene, which was collected and dried as a faintly pink powder, m.pt. 63-64°C. The yield was 0.7 g.

Owing to its excessive solubility in all the solvents tried, the base was not recrystallised, but was used as prepared.

No further crops of the base could be obtained by further heating and passage of dry hydrogen chloride through the original acetic acid reaction liquors, and only oils and tars, insoluble in dilute acid, were obtained when these liquors were poured into a large volume of dilute hydrochloric acid and the clarified (charcoal) and filtered solution made alkaline with dilute ammonium hydroxide.

(ii) 3,4-Benz-5-azaphenanthrene.

(a) Several attempts to perform a Skraup reaction on 4-aminophenanthrene using similar quantities, conditions and methods as used in the case of 1-aminophenanthrene (see page 65) resulted in complete decomposition and the production of carbonaceous material only.

(b) A mixture of 4-aminophenanthrene (1 g.), sodium

m-nitro-benzene sulphonate (2 g.), concentrated sulphuric acid (2.5 ccs.), water (2.5 ccs.), and glycerol (1.5 ccs.) was boiled under reflux for 2¾ hours. At the end of this time, slight charring had begun, and the now deep red solution was poured into water (100 ccs.), clarified by boiling with charcoal and filtering, and the cooled filtrate just neutralised with dilute ammonium hydroxide, when a dark precipitate was thrown down. This was collected, dried, and extracted with light petroleum, which on evaporation left a yellow oil that soon solidified; attempts to purify this through its picrate failed, as the picrate itself could not be purified by crystallisation.

Accordingly, the solidified oil was dissolved in dry benzene through which was passed dry gaseous hydrogen chloride. The white, clotted precipitate of the hydrochloride thrown down was filtered off, washed with dry benzene, dried, and dissolved in a small volume of dilute aqueous hydrochloric acid. Neutralisation of the resulting colourless solution with dilute ammonium hydroxide solution precipitated the free base which was collected, dried, and recrystallised several times from methanol as colourless, rectangular plates, m.pt. 95-96°C. The yield of the pure base was small.

Found: C, 89.0%; H, 5.0%; N, 6.1%. $C_{17}H_{11}N$ requires C, 89.1%; H, 4.8%; N, 6.1%.

A small quantity of the pure base was dissolved in a

few ccs. of hot methanol, and to this was added excess picric acid, also dissolved in a small volume of hot methanol. On boiling for a few minutes and allowing the solution to cool, the picrate of the base crystallised out; this was collected, and after several crystallisations from methanol was obtained as small, thick, saw-toothed yellow plates, m.pt. 200-201°C with decomposition.

Found: C, 60.1%; H, 3.3%;. $C_{17}H_{11}N, C_6H_3O_7N_3$ requires C, 60.3%; H, 3.1%.

C) Synthesis of some Nitrogenous Analogues of Pyrene.

(i) 1-Azapyrene.

(a) 4-Formamidophenanthrene.

4-Aminophenanthrene (1.9 g.) and formic acid (98-100%; 0.5 g.) were together heated on the water bath. At the end of ten minutes, the liquid had solidified to a white crystalline mass, and, after heating for a further 100 minutes, this was cooled, ground up under cold acidulated (HCl) water, filtered off, washed with water and dried. It was then crystallised several times from ethanol as long, colourless, silky needles, m.pt. 208-210°C. The yield of the pure formyl derivative was 2.2 g.

Found: C, 81.4%; H, 4.9%; N, 6.2%. $C_{15}H_{11}ON$ requires C, 81.45%; H, 5.0%; N, 6.3%.

(b) 1-Azapyrene.

4-Formamidophenanthrene (1.8 g.) dissolved in dry purified xylene (250 ccs.) was heated for 30 minutes in an oil bath at 160°C with phosphoric oxide (6 g.). The yellow solid residue which remained after decantation of the xylene solution was washed several times by decantation with pure xylene and dissolved in cold water (250 ccs.).

Traces of xylene were removed from the aqueous solution by boiling, and the green solution left was filtered, cooled, and made alkaline with dilute ammonium hydroxide solution, when the free base was thrown down as a white precipitate. Further yields of the base were obtained in the same way by successively concentrating the original xylene reaction liquors and by again heating them with further quantities of phosphoric oxide.

The combined yields of the base were collected, washed with water, dried, and dissolved in hot ethanol (25 ccs.). This solution was then filtered and added to a solution of picric acid (1 g.) in hot ethanol (25 ccs.), and the precipitation of the yellow crystalline picrate, which commenced immediately, was completed by boiling the solution for a few minutes and by allowing it to cool. The picrate of the base was then collected and recrystallised once from glacial acetic acid; a small sample was crystallised repeatedly from this

solvent, being obtained as a mixture of fine, yellow fronded needles and deep orange prisms, m.pt. 250-253°C after softening.

Found: C, 58.5%; H, 2.7%; N, 13.0%. $C_{15}H_9N, C_6H_3O_7N_3$ requires C, 58.3%; H, 2.8%; N, 13.0%.

The main bulk of the picrate was decomposed by boiling for a short time with dilute aqueous ammonia, and the regenerated base was filtered off as a white insoluble powder, washed with water, and dried. It was crystallised several times from n-hexane as colourless needles, m.pt. 157-159°C. The yield of the pure base was 0.55 g.

Found: C, 88.6%; H, 4.5%; N, 6.8%. $C_{15}H_9N$ requires C, 88.7%; H, 4.4%; N, 6.9%.

(ii) 2-Methyl-1-azapyrene.

(a) 4-Acetamidophenanthrene.

4-Aminophenanthrene (1.5 g.) was dissolved in pure dry pyridine (25 ccs.), and acetic anhydride (1.5 g.) added to the solution; the whole was heated for 30 minutes on the water bath, cooled overnight, and poured into a large volume of water, when the acetyl derivative was thrown down as a white precipitate. This was filtered off, washed with water, dried, and crystallised several times from benzene/ligroin as balls of long, colourless needles, m.pt. 198-200°C. The yield of the pure product was 1.5 g.

(b) 2-Methyl-1-azapyrene.

The cyclisation of 4-acetamidophenanthrene (1.5 g.) was carried out in a similar manner to that of 4-formamidophenanthrene, using similar quantities, conditions and methods of isolation. The picrate of the free base was prepared in ethanol in a similar manner; after several crystallisations from ethanol, in which it was sparingly soluble, it was obtained as a mixture of long, fronded orange-yellow needles and short, stout yellow prisms, m.pt. 239-240°C with decomposition.

Found: C, 59.3%; H, 3.2%; N, 12.7%. $C_{16}H_{11}N, C_6H_3O_7N_3$ requires C, 59.2%; H, 3.1%; N, 12.6%.

The free base was regenerated from the pure picrate by treatment with hot aqueous ammonia as before; after collecting, washing, and drying, it was crystallised several times from n-hexane as large, colourless rhombic tablets, m.pt. 139-141°C. The yield of the pure base was 0.65 g.

Found: C, 88.7%; H, 5.0%; N, 6.4%. $C_{16}H_{11}N$ requires C, 88.5%; H, 5.1%; N, 6.45%.

(iii) 2-Phenyl-1-azapyrene.

(a) 4-Benzamidophenanthrene.

4-Aminophenanthrene (0.5 g.) was dissolved in pure dry pyridine (8 ccs.) and a slight excess of benzoyl chloride added to the solution; the whole was heated for 30 minutes

on the water bath, cooled overnight, and poured into a large volume of water. The white precipitate thrown down was collected, washed with water, dried and crystallised from benzene/ligroin as tufts of colourless needles, m.pt. 216-218°C. The yield of 4-benzamidophenanthrene was 0.2 g.

4-Dibenzoylaminophenanthrene was obtained by concentrating and cooling the benzene/ligroin mother liquors of the (first) crystallisation of 4-benzamidophenanthrene prepared as above. After several crystallisations from n-hexane this product was obtained as hemispheres of close-packed, colourless thick plates, m.pt. 190-192°C, and on admixture depressing the m.pt. of a pure sample of 4-benzamidophenanthrene to 175-177°C.

Found: C, 83.9%; H, 4.9%; N, 3.6%. $C_{28}H_{19}O_2N$ requires C, 83.8%; H, 4.7%; N, 3.5%.

(b) 2-Phenyl-1-azapyrene.

4-Benzamidophenanthrene (0.2 g.) was cyclised as in the previous two experiments, using similar quantities, conditions, and methods of isolation. The free base, after collecting, washing, and drying, was crystallised directly several times from ethanol as tufts of colourless, silky needles, m.pt. 143-144°C.

Found: C, 90.5%; H, 4.7%; N, 5.0%. $C_{21}H_{13}N$ requires C, 90.3%; H, 4.7%; N, 5.0%.

The picrate of the base was prepared by concentrating the ethanol liquors from its crystallisation, and by adding to them a hot solution of excess picric acid in ethanol. The precipitation of the yellow crystalline picrate that instantly appeared was completed by boiling for a short time and subsequently allowing the solution to cool. The picrate was then collected and crystallised several times from ethanol as golden-yellow blades, m.pt. 256-258°C with decomposition.

Found: N, 10.9%. $C_{21}H_{13}N, C_6H_3O_7N_3$ requires N, 11.0%.

(D) Synthesis of Pyrimidines related to Chrysene and 3,4-Benzphenanthrene.

(i) Attempted condensation of 2-hydroxymethylene-1-keto-1,2,3,4-tetrahydrophenanthrene with acetamidine.

(a) 2-Hydroxymethylene-1-keto-1,2,3,4-tetrahydrophenanthrene (2.5 g.) (see page 44) in ethanol (30 ccs.) was added to a solution of sodium (0.255 g.) in ethanol (5 ccs.) and to this was added a solution of acetamidine hydrochloride (1.05 g.) in ethanol (20 ccs.). These were all molecular quantities of reagents.

The solution, after keeping for 5 days, turned dark brown, and a white precipitate of sodium chloride separated; it was then poured into cold water (1000 ccs.), giving a dark red solution with a green fluorescence. A smell of acetamide was observed.

After keeping for a month in a covered beaker, a red-brown solid had deposited from the now turbid, brown colloidal solution. This was filtered off with considerable difficulty owing to the colloidal nature of the solution, dried, and continuously extracted in a Soxhlet apparatus with light petroleum, leaving a trace of a dark red residue and giving a yellow solution; this solution on concentration and cooling deposited a mass of dark-red needles, m.pt. 125-126°C. The yield of this substance was about 1 g.

On repeated crystallisation from light petroleum, these needles were transformed into yellow plates, m.pt. 125-127°C; admixture of needles and plates did not depress the melting points, proving them to be isomorphous forms of the same substance, namely, 1-hydroxy-2-phenanthraldehyde.

Found: C, 80.9%; H, 4.4%. $C_{15}H_{10}O_2$ requires C, 81.0%; H, 4.5%.

Nitrogen was found to be absent in the compound on testing by fusion with sodium. The substance was soluble in dilute caustic soda solution.

1-Hydroxy-2-phenanthraldehyde oxime.

1-Hydroxy-2-phenanthraldehyde (0.2 g.) and hydroxylamine hydrochloride (.07 g.) were dissolved in pure dry pyridine (2-3 ccs.), the whole heated on the water bath for 2 hours and left overnight at room temperature. The resulting solution

was poured into a large volume of water, and the light brown precipitate thrown down was collected, washed, dried, and crystallised twice from aqueous methanol and twice from light petroleum as fawn needles, m.pt. 188-189°C.

Found: C, 76.6%; H, 4.6%; N, 6.0%. $C_{15}H_{11}O_2N$ requires C, 76.0%; H, 4.6%; N, 5.9%.

(b) To acetamidine hydrochloride (0.95 g.) dissolved in a cold solution of sodium (0.23 g.) in ethanol (5 ccs.) was added 2-hydroxymethylene-1-keto-1,2,3,4-tetrahydrophenanthrene (2.25 g.) in ethanol (25 ccs.); the whole was then tightly corked up to exclude air.

After keeping at room temperature for 1 hour, the solution had become yellow-brown, with a greenish-yellow fluorescence, and a precipitate of sodium chloride had deposited. The solution was then refluxed for 2 hours on the water bath, when it became blood-red in colour; it was then corked up tightly, kept for a week, and poured into a warm aqueous solution of caustic soda (10%; 300 ccs.) to remove unchanged hydroxymethylene ketone, and the cold solution extracted with four lots of chloroform (250 ccs. each).

The crimson chloroform extracts were then washed with dilute aqueous caustic soda, then water, and finally dried over anhydrous sodium sulphate. On removal of the chloroform by distillation, a dark brown, semi-crystalline solid remained.

This was continuously extracted in a Soxhlet apparatus with light petroleum, giving a solution which on evaporation left a red, crystalline mass, and this was recrystallised after decantation from the traces of oil which separated first, once from n-hexane, as light orange hemispheres. After several crystallisations from ethanol (charcoal), the substance was obtained as colourless leaflets, m.pt. 94-96°C, which on admixture did not depress the similar melting point of a pure sample of 1-keto-1,2,3,4-tetrahydrophenanthrene. The two substances were thus identical.

The same product was later isolated in the previous experiment (a) by the extraction with light petroleum of the brown powder precipitated by the addition of sodium chloride solution to the aqueous colloidal filtrate of the water-diluted reaction mixture of (a).

(ii) 2-Chloromethylene-1-keto-1,2,3,4-tetrahydrophenanthrene.

To finely powdered 2-hydroxymethylene-1-keto-1,2,3,4-tetrahydrophenanthrene (6.7 g.) (see page 44) was added thionyl chloride (6 g.). Vigorous effervescence ensued, and the solution was kept for an hour at room temperature. The deep red solution was then poured into ice-cold 2N caustic soda solution (500 ccs.), and after two hours, the pink solid that had instantly deposited was collected, washed with water, and dried in a vacuum over solid KOH.

The crude chloro compound was then continuously

extracted in a Soxhlet apparatus with light petroleum, leaving a trace of a dark red powder, and giving a colourless solution, which on evaporation left a crystalline, almost colourless solid; this was crystallised several times from n-hexane as agglomerates of thick, colourless plates, m.pt. 106-107°C. The yield of the pure substance was 5.5 g.

Found: C, 74.3%; H, 4.5%. $C_{15}H_{11}OCl$ requires C, 74.2%; H, 4.5%.

(iii) 3-Chloromethylene-4-keto-1,2,3,4-tetrahydrophenanthrene.

(a) 3-Hydroxymethylene-4-keto-1,2,3,4-tetrahydrophenanthrene.

4-Keto-1,2,3,4-tetrahydrophenanthrene was converted to its hydroxymethylene derivative in exactly the same manner as in the case of 1-keto-1,2,3,4-tetrahydrophenanthrene using similar quantities, conditions, and methods of isolation (see page 44). The product, precipitated by acidifying with dilute sulphuric acid the aqueous solution obtained from the reaction, was, however, an oil. This was extracted with ether, the ethereal extracts washed with water, dried over anhydrous sodium sulphate, and evaporated to a dark yellow oil; this was twice distilled at 160°C under 3 m.m. pressure to give a clear, light yellow oil which was analysed directly, although found to crystallise from light petroleum as lemon-yellow tablets, m.pt. 39-41°C.

Found: C, 80.25%; H, 5.5%. $C_{15}H_{12}O_2$ requires C, 80.3%; H, 5.4%.

3-Methoxymethylene-4-keto-1,2,3,4-tetrahydrophenanthrene was prepared from the hydroxymethylene compound by acting on its ethereal solution for 2 days at room temperature with excess of an ethereal solution of diazomethane. On evaporation of the ether, the sticky yellow solid left was dissolved in fresh ether, and the solution shaken first with dilute caustic soda solution to remove unchanged starting material, then with water. The ether solution was then dried over solid sodium sulphate, the ether removed by distillation, and the gum left crystallised several times from acetone as thick, straw-coloured rods of the product, m.pt. 110-112°C.

Found: C, 80.7%; H, 5.8%. $C_{16}H_{14}O_2$ requires C, 80.7%; H, 5.9%.

(b) 3-Chloromethylene-4-keto-1,2,3,4-tetrahydrophenanthrene.

3-Chloromethylene-4-keto-1,2,3,4-tetrahydrophenanthrene was obtained from the hydroxymethylene compound in exactly the same manner as in the case of 2-chloro-1-keto-1,2,3,4-tetrahydrophenanthrene, except that the reaction mixture had to be warmed for 30 minutes on the water bath to complete the reaction and to prevent the product from crystallising out. Otherwise the quantities, conditions, and mode of isolation were all similar.

The pale orange crystalline mass left after evaporation of the light petroleum extract was crystallised several times

from n-hexane as long, greenish-white plates, m.pt. 94-96°C. The yield of the pure product from 17.7 g. of the hydroxymethylene ketone was almost 15 g.

Found: C, 74.3%; H, 4.5%. $C_{15}H_{11}OCl$ requires C, 74.2%; H, 4.5%.

(iv) 9,10-Dihydro-3,4-benz-5,7-diazaphenanthrene.

3-Chloromethylene-4-keto-1,2,3,4-tetrahydrophenanthrene (4.85 g.) and formamidine hydrochloride (Pinner, Ber., 1883, 16, 352, 1647) (1.6 g.) were dissolved in ethanol (80 ccs.). To this solution was added a solution of sodium (1.4 g.) in ethanol (40 ccs.), when a precipitate of sodium chloride was instantly thrown down and the solution at once became carmine in colour. The reaction mixture was then heated under reflux on the water bath for 90 minutes, kept at room temperature overnight, evaporated to half its volume under reduced pressure on the water bath, and poured into hot acidulated (HCl) water (2500 ccs.).

This solution was then shaken while hot with charcoal, filtered, cooled, and made alkaline with aqueous ammonia; the free base appeared as a dark turbidity, and was extracted with ether, the extracts washed, dried over anhydrous sodium sulphate, and evaporated, leaving a dark green oil.

The oil was extracted with boiling light petroleum, leaving a small insoluble, carbonaceous residue; the extract

on evaporation yielded an oil, which was purified by being filtered in dry benzene solution through a column of dry alumina. On evaporation of the benzene, the oil obtained, which had begun to crystallise on scratching, was crystallised several times from n-hexane as colourless, thick plates, m.pt. 70-71°C. The yield of the pure base was 2.8 g.

Found: C, 82.9%; H, 5.4%; N, 12.2%. $C_{16}H_{12}N_2$ requires C, 82.75%; H, 5.2%; N, 12.1%.

A small quantity of the base was dissolved in hot ethanol, and to it was added excess picric acid, also dissolved in a minimal quantity of hot ethanol. The combined solutions were boiled for a few minutes and allowed to cool, when the crystalline picrate that had deposited was filtered off and crystallised several times from ethanol as deep yellow prisms, m.pt. 238-239°C, with decomposition.

Found: C, 57.4%; H, 3.1%. $C_{16}H_{12}N_2, C_6H_3O_7N_3$ requires C, 57.3%; H, 3.25%.

(v) 3,4-Benz-5,7-diazaphenanthrene.

9,10-Dihydro-3,4-benz-5,7-diazaphenanthrene (1.8 g.) was fused at 200°C with palladium-black (0.2 g.) in an atmosphere of carbon dioxide. Vigorous effervescence was observed, and after 4 hours the apparatus was disconnected and cooled, and the red solid left was ground up, dissolved in dry benzene and filtered through a column of dry alumina to remove

coloured impurities. The purified benzene solution was then evaporated to dryness and the solid residue sublimed at 140°C under 0.3 m.m. pressure; the sublimate was recrystallised once from ethanol and then several times from n-hexane as small colourless rhombs, m.pt. 155-156°C.

Found: C, 83.3%; H, 4.5%; N, 12.2%. $C_{16}H_{10}N_2$ requires C, 83.5%; H, 4.35%; N, 12.2%.

A small quantity of the pure base was dissolved in a little hot ethanol, and excess picric acid, dissolved also in a small quantity of hot ethanol, was added; the precipitation of the yellow, crystalline picrate, which appeared at once, was completed by boiling the solution for a few minutes and then allowing it to cool. The picrate of the base was then collected and crystallised several times from ethanol as balls of fine, yellow needles, m.pt. 255-258°C, with decomposition.

Found: C, 57.5%; H, 2.9%. $C_{16}H_{10}N_2, C_6H_3O_7N_3$ requires C, 57.5%; H, 2.8%.

(vi) 6-Methyl-9,10-dihydro-3,4-benz-5,7-diazaphenanthrene.

3-Chloromethylene-4-keto-1,2,3,4-tetrahydrophenanthrene (4.85 g.) and acetamidine hydrochloride (1.9 g.) were dissolved in ethanol (80 ccs.). To this solution was added a solution of sodium (1.4 g.) in ethanol (40 ccs.), when a precipitate of sodium chloride was instantly thrown down and the solution at once became carmine in colour. The reaction

mixture was then heated under reflux on the water bath for 90 minutes, kept overnight at room temperature, evaporated to half its volume under reduced pressure on the water bath and poured into hot acidulated (HCl) water (2,500 ccs.). The solution was shaken with charcoal, filtered, cooled, and made alkaline with aqueous ammonia; the free base appeared as a white turbidity that became a grey precipitate overnight, and was filtered off, dried, and crystallised several times from n-hexane as thick colourless prisms, m.pt. 102-103°C. The yield of the pure base was almost 4 g.

Found: C, 83.0%; H, 5.6%; N, 11.35%. $C_{17}H_{14}N_2$ requires C, 82.9%; H, 5.7%; N, 11.4%.

The picrate of the base was prepared in ethanol as in previous instances, and after several recrystallisations from ethanol was obtained as fine, yellow needles, m.pt. 216-217°C, with decomposition.

Found: C, 58.3%; H, 3.6%; N, 14.8%. $C_{17}H_{14}N_2,C_6H_3O_7N_3$ requires C, 58.1%; H, 3.6%; N, 14.7%.

(vii) 6-Methyl-3,4-benz-5,7-diazaphenanthrene.

6-Methyl-9,10-dihydro-3,4-benz-5,7-diazaphenanthrene (1.94 g.) was dehydrogenated as before by heating with palladium black (0.2 g.) at 200°C for 4 hours in an atmosphere of carbon dioxide. After cooling, the orange crystalline solid left in the apparatus was dissolved in hot ethanol (40 ccs.), filtered

free from palladium-black, boiled up with charcoal, refiltered and evaporated to dryness; the light-coloured residue was crystallised several times from n-hexane as long, white, silky needles, m.pt. 133-134°C.

Found: C, 83.5%; H, 5.0%; N, 11.5%. $C_{17}H_{12}N_2$ requires C, 83.6%; H, 4.9%; N, 11.4%.

The picrate of the base was prepared in ethanol as in previous instances, and after several crystallisations from ethanol was obtained as fine, yellow needles, m.pt. 217-219°C, with decomposition.

Found: C, 58.3%; H, 3.4%; N, 14.8%. $C_{17}H_{12}N_2, C_6H_3O_7N_3$ requires C, 58.3%; H, 3.2%; N, 14.8%.

(viii) 5-Methyl-1,2-dihydro-4,6-diazachrysene.

3-Chloromethylene-4-keto-1,2,3,4-tetrahydrophenanthrene (4.85 g.) was reacted with acetamidine hydrochloride (1.9 g.) in exactly the same manner as in the preparation of 6-methyl-9,10-dihydro-3,4-benz-5,7-diazaphenanthrene (see page 83), using similar quantities, conditions, and methods of isolation. The colourless precipitate of the free base was filtered off, dried, and recrystallised several times from n-hexane as thin, colourless blades, m.pt. 142-143°C. The yield of the pure base was almost 3 g.

Found: C, 83.0%; H, 5.7%; N, 11.2%. $C_{17}H_{14}N_2$ requires C, 82.9%; H, 5.7%; N, 11.4%.

The picrate of the base was prepared in ethanol as in previous instances, and after several recrystallisations from ethanol was obtained as hemispherical clumps of yellow, microcrystalline fronds, m.pt. 225-227°C, with decomposition.

Found: C, 58.2%; H, 3.8%; N, 14.9%. $C_{17}H_{14}N_2,C_6H_3O_7N_3$ requires C, 58.1%; H, 3.6%; N, 14.7%.

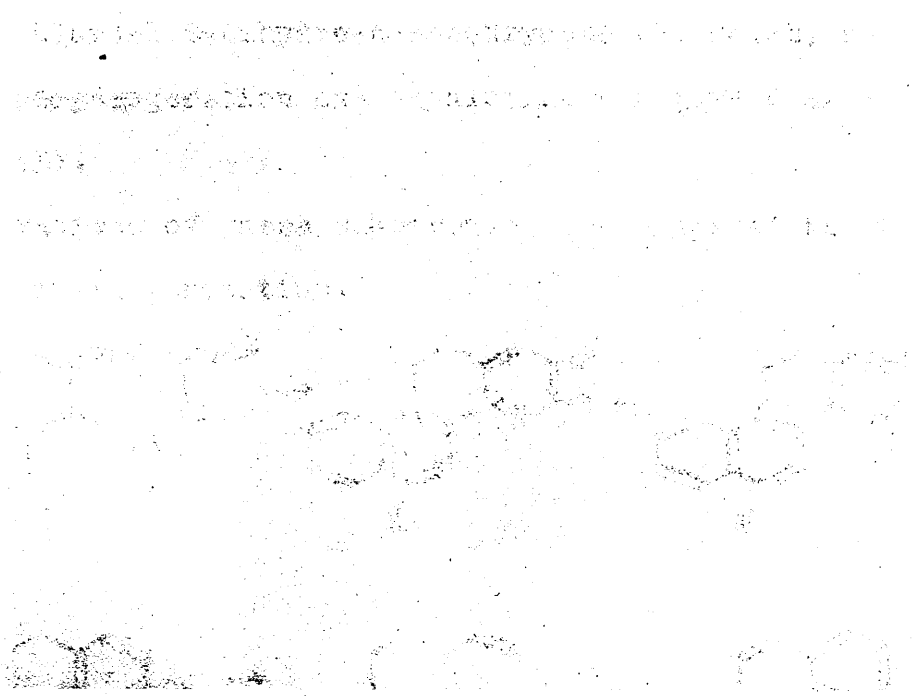
(ix) 5-Methyl-4,6-diazachrysene.

5-Methyl-1,2-dihydro-4,6-diazachrysene (0.5 g.) was dehydrogenated as before by heating with palladium-black (0.05 g.) at 200-250°C for 15 minutes in an atmosphere of carbon dioxide. The red solid left after cooling was dissolved in hot benzene (50 ccs.) and filtered free from palladium-black. The filtrate on cooling deposited a small quantity of a sparingly soluble red powder, which was filtered off; the filtrate was boiled up with charcoal, filtered, and concentrated to 10 ccs. A quantity of yellow plates (0.25 g.) crystallised out; these were collected, and a further crop obtained by further concentration and cooling of the mother liquors of the crystallisation. This product was then recrystallised several times from ethanol as pale, greenish-yellow leaflets, m.pt. 196-197°C, which were found to be soluble in cold dilute HCl, being reprecipitated by dilute aqueous ammonia.

Found: C, 83.4%; H, 4.8%; N, 11.5%. $C_{17}H_{12}N_2$ requires C, 83.6%; H, 4.9%; N, 11.5%.

The picrate of the base was prepared in ethanol as in previous instances, and after several recrystallisations from ethanol was obtained as a mixture of orange spheres and clumps of deep orange prisms, m.pt. 230-231°C, with decomposition.

Found: C, 58.3%; H, 3.1%; N, 14.9%. $C_{17}H_{12}N_2,C_6H_3O_7N_3$ requires C, 58.3%; H, 3.2%; N, 14.8%.

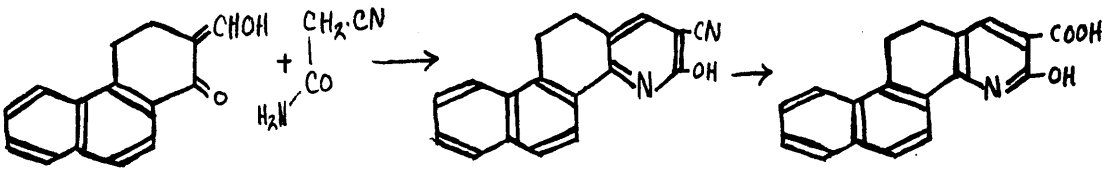


Summary of Part I.

The syntheses of certain nitrogenous analogues of chrysene, pyrene, and 3,4-benzphenanthrene have been accomplished.

6-azachrysene (VI) was prepared by condensing 2-hydroxymethylene-1-keto-1,2,3,4-tetrahydrophenanthrene (I) with cyanacetamide to give 5-hydroxy-6-cyano-1,2-dihydro-6-azachrysene (II), which was hydrolysed to 5-hydroxy-1,2-dihydro-6-azachrysene-4-carboxylic acid (III), decarboxylated to give 5-hydroxy-1,2-dihydro-6-azachrysene (IV), and chlorinated to give 5-chloro-1,2-dihydro-6-azachrysene (V) which, by catalytic dehydrogenation and dechlorination gave 6-azachrysene (VI).

Derivatives of these substances were prepared for the purpose of characterisation.



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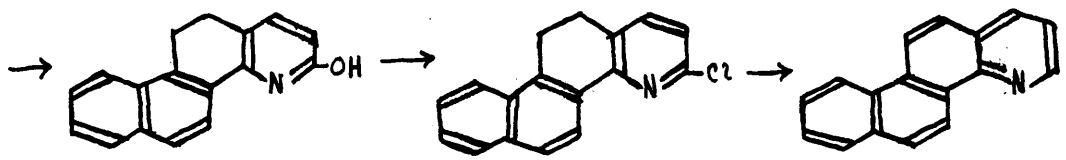
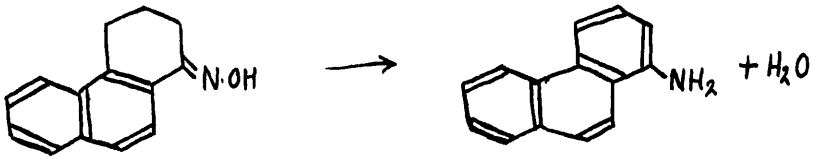


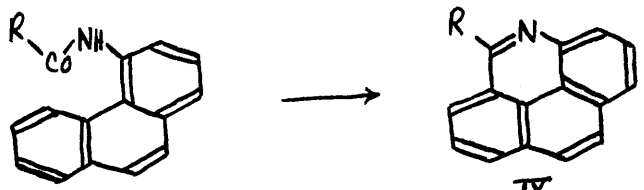
IV V VI

The structure of the 6-azachrysene, which was open to doubt, was confirmed by its alternative synthesis from 1-aminophenanthrene (VII) by a Skraup reaction. The 1-aminophenanthrene was obtained by rearranging the oxime of 1-keto-1,2,3,4-tetrahydrophenanthrene (VIII) by the action of dry hydrogen chloride on its hot solution in glacial acetic acid.



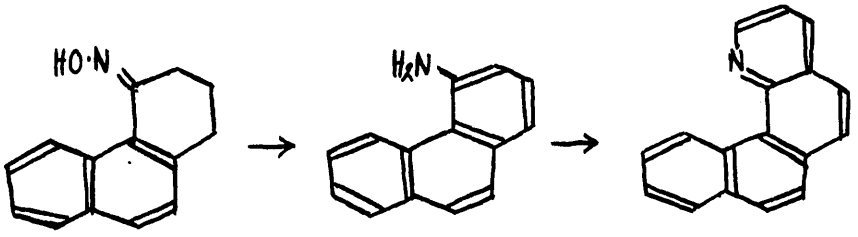
VIII VII

1-azapyrene, 2-methyl-1-azapyrene and 2-phenyl-1-azapyrene ((IX); R = H, CH_3, C_6H_5) were synthesised by the action of phosphoric oxide on the hot xylene solution of 4-formamido-, 4-acetamido-, and 4-benzamidophenanthrene ((X); R = H, CH_3, C_6H_5).



X IX

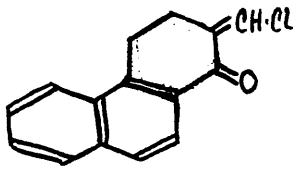
3,4-benz-5-azaphenanthrene (XI) was synthesised by means of a Skraup reaction on 4-aminophenanthrene (XII) prepared by rearranging the oxime of 4-keto-1,2,3,4-tetrahydrophenanthrene (XIII) by the action of dry hydrogen chloride on its hot solution in glacial acetic acid.



XIII XII XI

Attempts to condense amidines with hydroxymethylene-keto-tetrahydrophenanthrenes failed, but excellent yields of pyrimidines were obtained on using chloromethylene ketones instead, prepared in quantitative yields by the action of thionyl chloride on the corresponding hydroxymethylene ketones.

Hence, by the condensation, in presence of sodium ethoxide, of formamidine and acetamidine with 2-chloromethylene-1-keto-1,2,3,4-tetrahydrophenanthrene (XIV) and 3-chloromethylene-4-keto-1,2,3,4-tetrahydrophenanthrene (XV) were obtained 9,10-dihydro-3,4-benz-5,7-diazaphenanthrene (XVI), 6-methyl-9,10-dihydro-3,4-benz-5,7-diazaphenanthrene (XVII), and 5-methyl-1,2-dihydro-4,6-diazachrysene (XVIII), which, by fusion with palladium-black, were dehydrogenated to the fully aromatic pyrimidines.



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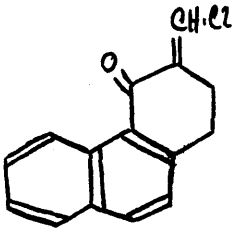

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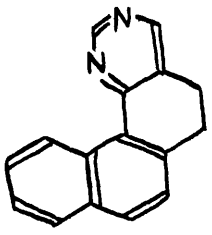
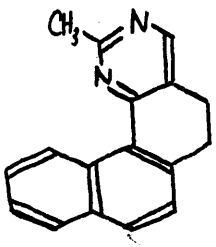
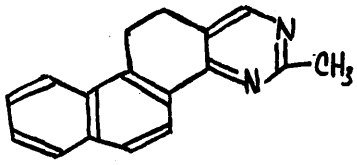


XVI



XVII



XVIII

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Part II: Syntheses in the naphthyridine series.

With an appendix on

the effect of diazomethane on 3-hydroxy-

4-phenanthraldehyde.

CONTENTS.

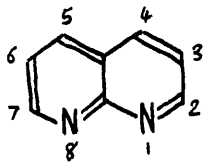
Part II.

x x x

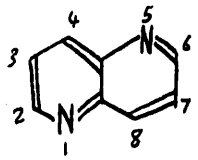
Appendix.

INTRODUCTION.

The primary purpose of this work was to investigate and improve synthetic methods for the preparation of 1,8- and 1,5-naphthyridines, and it was therefore considered desirable that a brief survey be made of the main existing methods of synthesis in these series.



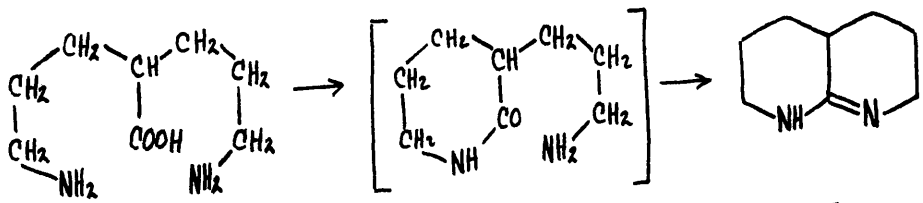
1,8-naphthyridine



1,5-naphthyridine

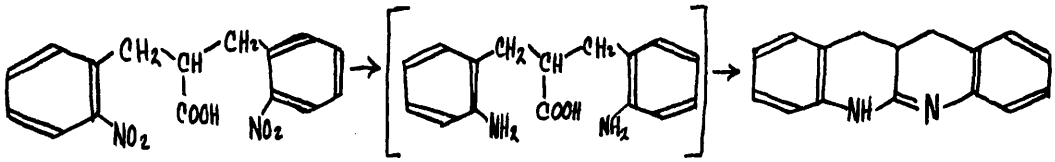
We shall deal in the first instance with the 1,8-naphthyridine series.

Reissert [1] prepared an octahydro-1,8-naphthyridine (I) by direct distillation of di-(γ-aminopropyl) acetic acid (II), and extended this method [2] to the preparation of a dibenz-tetrahydro-1,8-naphthyridine (III), the formation of which was brought about by reducing di-(o-nitrobenzyl) acetic acid (IV) with zinc and alcoholic hydrochloric acid, and by cyclising the product without its intermediate isolation.



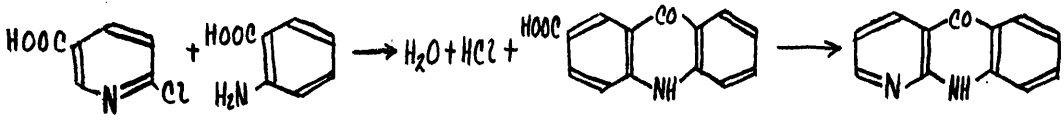
II

I



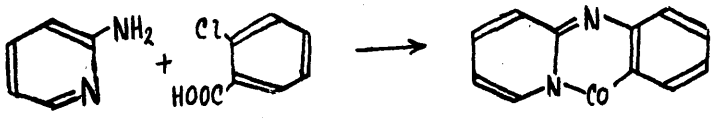
IV III

Reissert later claimed [3] to have prepared the 2,3-benz-1,8-naphthyridone (V) by condensing α'-chloronicotinic acid with anthranilic acid, giving the acid (VI), which on decarboxylation yielded (V).



VI V

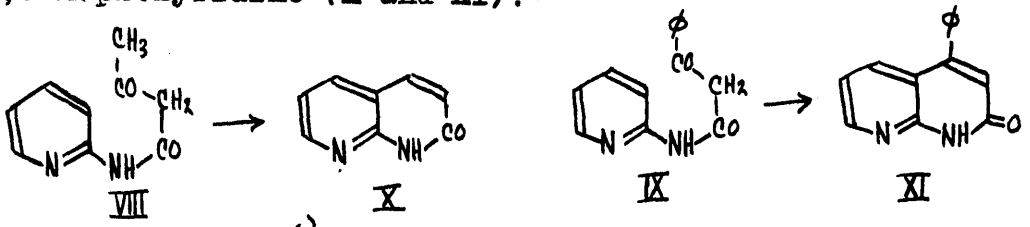
Seide, however, obtained the same compound [4] by condensing o-chlorobenzoic acid with 2-aminopyridine. Finding that it possessed little or no carbonyl activity, he oxidised it to a known quinazoline derivative, thus indicating that it had the structure (VII), and disproving the 1,8-naphthyridine structure alloted to it by Reissert.



VII

Palazzo and Tamburini [5] state that acetoacet-2-pyridylamide (VIII), obtained from acetoacetic ester and 2-aminopyridine, and benzoylacet-2-pyridylamide (IX), obtained in similar fashion, may be cyclised to the respective derivatives of

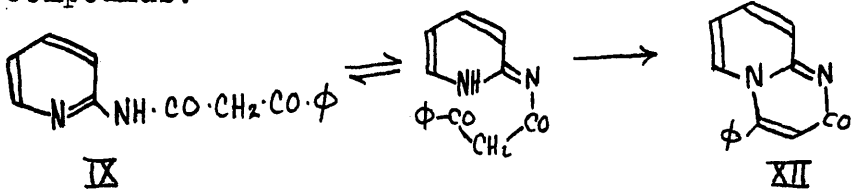
1,8-naphthyridine (X and XI):-



VIII X IX XI

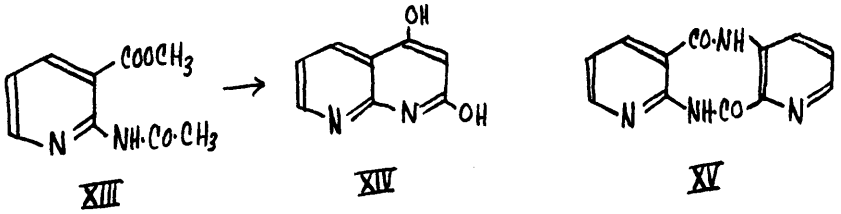
Khitrik [6], however, finds that the cyclisation of aceto-acet-2-pyridylamide (VIII) does not result in the formation of a derivative of 1,8-naphthyridine, and the work of Sokov [7] on the reaction between benzil and 2-aminopyridine, to give derivatives of pyrimidazole, casts further doubt on the assumption of Palazzo and Tamburini.

Seide [8] further maintains that the cyclisation of benzoylacet-2-pyridylamide (IX) takes place in the tautomeric α-pyridone-imine form, resulting in the pyrimidine derivative (XII), the structure of which he then proved by degradation to known compounds:-



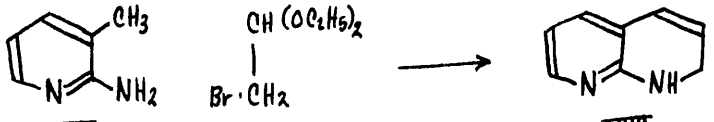
IX XII

Seide [4], however, failed to cyclise methyl α-acetylaminonicotinate (XIII) in the presence of sodium ethoxide to give 2,4-dihydroxy-1,8-naphthyridine (XIV), obtaining instead the anhydride of α-aminonicotinic acid (XV):-



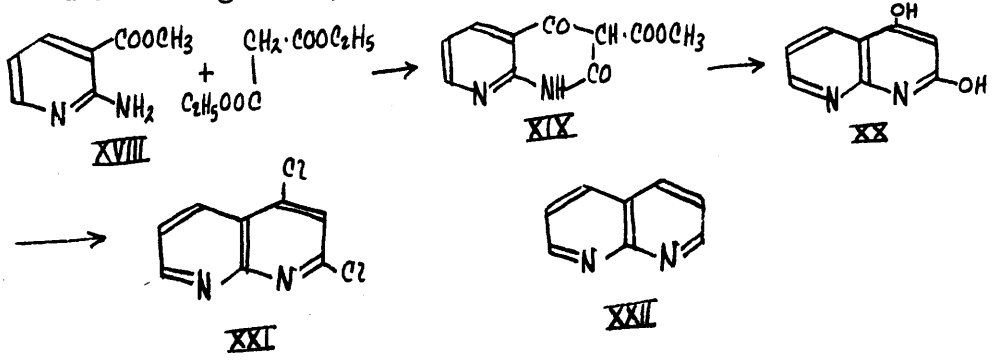
XIII XIV XV

A successful synthesis using a 3-substituted 2-amino-pyridine was later developed by Räth [9], who condensed the acetal of brom-acetaldehyde with 2-amino-3-methylpyridine (XVI), prepared by the action of sodamide on β-picoline, and obtained 1,2-dihydro-1,8-naphthyridine (XVII):-



XVI XVII

Koller [10], by using a modification of Seide's attempted synthesis, obtained methyl 2,4-dihydroxy-1,8-naphthyridine-3-carboxylate (XIX) by condensing methyl α-aminonicotinate (XVIII) with malonic ester in presence of alcoholic sodium ethoxide. The methyl ester grouping of the product was believed due to alcoholysis by the methyl alcohol set free during the reaction. Hydrolysis and decarboxylation of the product with dilute potassium hydroxide resulted in 2,4-dihydroxy-1,8-naphthyridine (XX), which could then be treated with phosphorus pentachloride to give 2,4-dichloro-1,8-naphthyridine (XXI):-

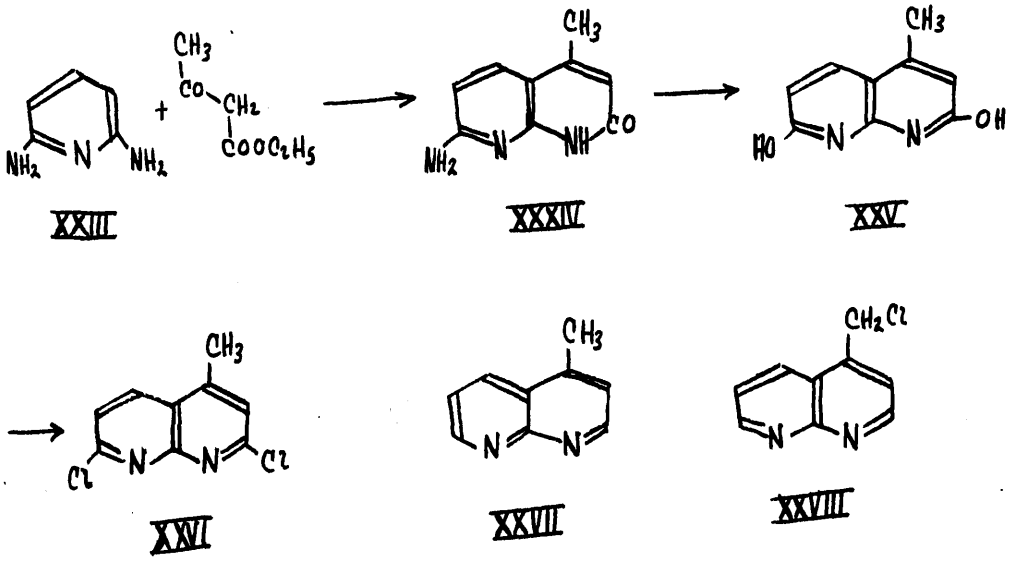


XVIII XIX XX

XXI XXII

In a later paper [11], the same author reports the failure of a number of reducing agents to remove the chlorine atoms from 2,4-dichloro-1,8-naphthyridine (XXI), but states that, by using lead and hydrogen, the compound reduces to a dihydro-1,8-naphthyridine with great difficulty; however, he finally succeeded [12] in a catalytic reduction of the compound to a mixture of bases from which, with difficulty, he isolated 1,8-naphthyridine itself (XXII).

After considerable investigation, Seide [13] concluded that derivatives of 1,8-naphthyridine could not be prepared by the usual quinoline syntheses applied to 2-aminopyridine, and took advantage of the reactivity of the hydrogen atom in the β-position of $\alpha\alpha'$-diamino pyridine [14] to execute a synthesis of 1,8-naphthyridine. $\alpha\alpha'$-diaminopyridine (XXIII) was condensed with acetoacetic ester by heating together, and the resulting 2-keto-4-methyl-7-amino [1,8-naphthyridine-1,2-dihydride] (XXIV) was converted to its hydroxy derivative (XXV) by means of nitrous acid; this was acted upon with phosphorus pentachloride to give 2,7-dichloro-4-methyl-1,8-naphthyridine (XXVI), which was then reduced with hydriodic acid to give a compound with all the properties of a tetrahydronaphthyridine.

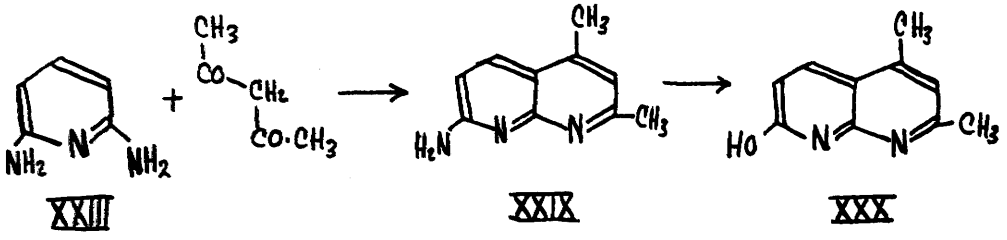


XXIII XXXIV XXV

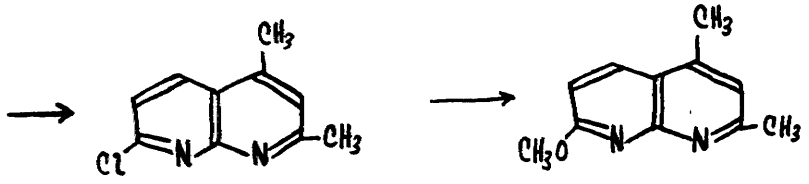
XXVI XXVII XXVIII

Koller and Kandler [15] give a fuller account of the reduction of 2,7-dichloro-4-methyl-1,8-naphthyridine (XXVI) using sodium and alcohol. Kataoka [16] reduced the compound catalytically and obtained a mixture of 4-methyl-1,8-naphthyridine (XXVII) and 4-chloromethyl-1,8-naphthyridine (XXVIII).

Mangini [17] extended the above synthesis by condensing $\alpha\alpha'$-diaminopyridine (XXIII) with acetyl acetone in presence of zinc chloride, and obtained 2,4-dimethyl-7-amino-1,8-naphthyridine (XXIX); this compound was later converted by Ochiai and Miyaki [18] to the hydroxy compound (XXX) by diazotisation, and thence, by heating with phosphorus oxychloride, to its chloro-derivative (XXXI), which was then converted to 2,4-dimethyl-7-methoxy-1,8-naphthyridine (XXXII) by means of sodium methoxide:-

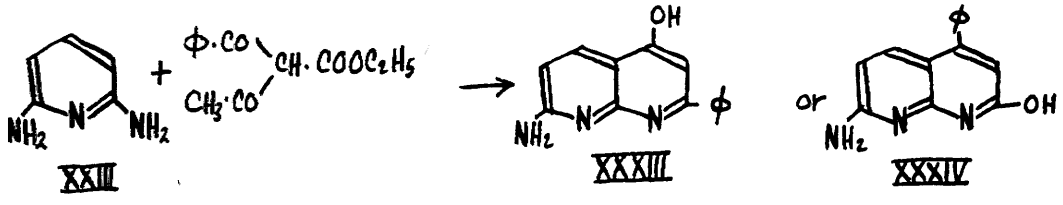


XXIII XXIX XXX



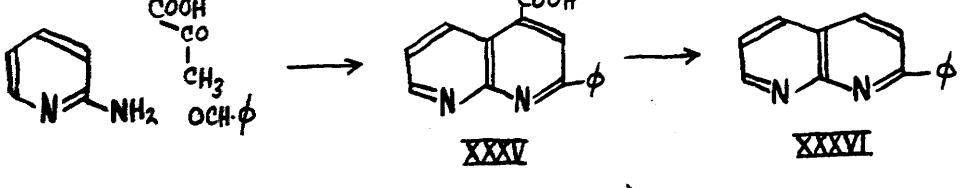
XXXI XXXII

Mangini and Colonna [19] more recently report the condensation of αα'-diaminopyridine (XXIII) with benzoylacetoacetic ester to give 7-amino-4-hydroxy-2-phenyl-1,8-naphthyridine (XXXIII) or 7-amino-2-hydroxy-4-phenyl-1,8-naphthyridine (XXXIV):-



XXIII XXXIII XXXIV

Two other methods of synthesis are worthy of note. Mazza and Migliardi [20] condensed 2-aminopyridine, pyruvic acid, and benzaldehyde by prolonged boiling in alcohol, to give 2-phenyl-1,8-naphthyridine-4-carboxylic acid (XXXV) which was decarboxylated by heat to give 2-phenyl-1,8-naphthyridine (XXXVI):-

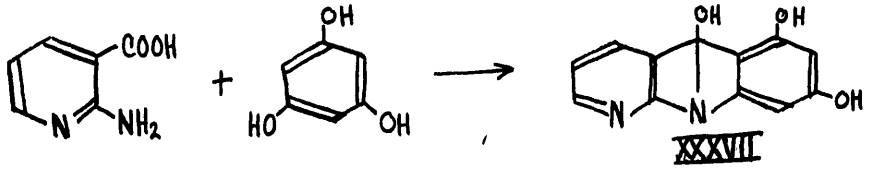


XXXV XXXVI

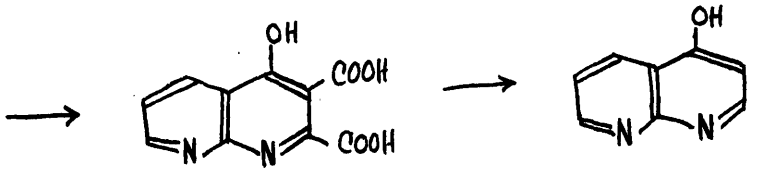
In a later paper, Migliardi [21] extended this synthesis

to the preparation of various 2-substituted-1,8-naphthyridines by the use of different aldehydes.

Sucharda [22], by fusion of α-amino-nicotinic acid with phloroglucinol, obtained 5,6,8-trihydroxybenzo-1,10-naphthyridine (XXXVII), which was then oxidised to 5-hydroxy-1,8-naphthyridine-6,7-dicarboxylic acid (XXXVIII) and decarboxylated to 5-hydroxy-1,8-naphthyridine (XXXIX); the very small yield of this product did not permit of its conversion into 1,8-naphthyridine itself.



XXXVII



XXXVIII XXXIX

.....

Much of the previous work on the 1,5-naphthyridine series has been patented, and details are accordingly difficult of access However, these syntheses are mainly elaborations of the Skraup reaction on 3-aminopyridine, a reaction which could not successfully be applied to the preparation of 1,8-naphthyridines [13,23] owing to the aliphatic nature of 2- (and 4-) aminopyridines, as they tend to react in the tautomeric pyridone-imine form.

Räth [24] describes a Skraup reaction on 2-chloro-3-aminopyridine (XL) by treating it with glycerol and sulphuric acid, in the presence of oxidising agents, to give 1,5-naphthyridine (XLI); in a later patent [25] the same author extends this synthesis to the preparation of certain hydroxy, alkyl, and aryl derivatives of 1,5-naphthyridine.

XL XLI

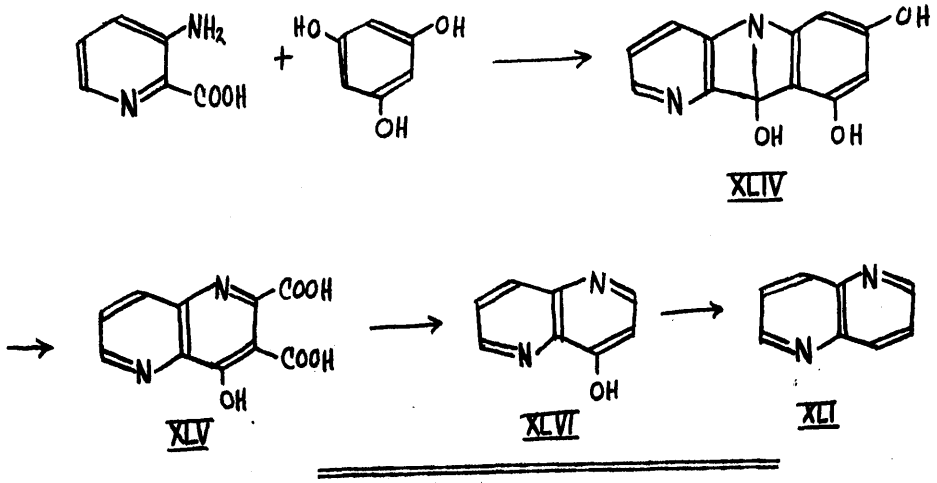
By subjecting 3-aminopyridine itself to a Skraup reaction, and to similar reactions commonly used for the preparation of quinolines, yet another patent [26] describes the synthesis of 1,5-naphthyridine; the same patent describes the synthesis, by similar methods of other hydroxy and aryl 1,5-naphthyridines.

Bobranski and Sucharda [27] also describe the preparation of 1,5-naphthyridine by means of a Skraup reaction on 3-aminopyridine by boiling it with glycerol, arsenic pentoxide, and sulphuric acid.

Binz and von Schickh [28] describe the catalytic dehydrogenation of 2-chloro-3-nitro-1,5-naphthyridine (XLII) to give 3-amino-1,5-naphthyridine (XLIII), but give no details of how their starting materials were obtained.

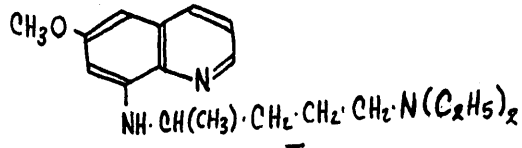
XLII XLIII

Following up their previous work on the 1,8-naphthyridine series, Klisiecki and Sucharda [29] achieve a synthesis of 1,5-naphthyridine by fusing β-aminopicolinic acid with phloroglucinol to give 7,9,10-trihydroxybenzo-1,5-naphthyridine (XLIV), which was oxidised with fuming nitric acid to 8-hydroxy-1,5-naphthyridine-6,7-dicarboxylic acid (XLV) and decarboxylated by heat to give 4-hydroxy-1,5-naphthyridine (XLVI); distillation of this compound with zinc dust gave an exceedingly small yield of 1,5-naphthyridine (XLI):-



INTRODUCTION TO EXPERIMENTAL.

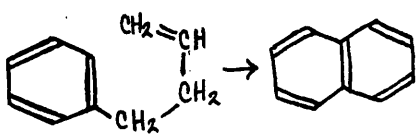
In the previous section, a general review was given of the principal methods available for the synthesis of 1,8- and 1,5-naphthyridines. The particular compounds in these series with which this work is concerned are those which might best lend themselves to the preparation of possible plasmodicides, i.e., those into which a basic aliphatic side chain might be introduced in a suitable position to give them a structural relationship to known plasmodicides such as plasmoquine (I).



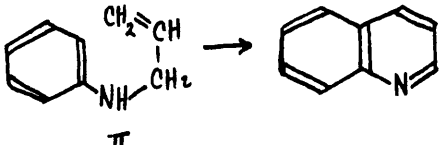
I

Accordingly an investigation was carried out on possible new synthetic methods, and improvements were made in the methods already existing for synthesis in these series.

It was decided first to extend to the preparation of 1,8-naphthyridines a synthesis of quinoline carried out by Koenigs [30] by passing the vapour of allylaniline (II) over red hot lead oxide. This synthesis was developed from that of Aronheim [31], who synthesised naphthalene by similar treatment of phenyl-butylene (III).

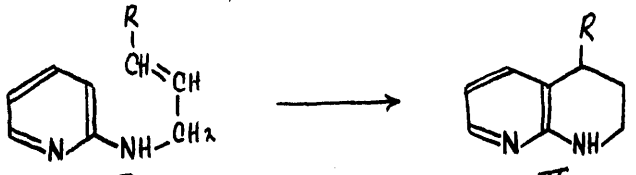


III



II

It was thought that, by a modified procedure, an analagous cyclisation* of allyl-2-aminopyridine (IV; R = H) could be brought about to give 1,2,3,4-tetrahydro-1,8-naphthyridine (V; R = H), and that, should this prove successful, the method could be extended to the preparation of suitably substituted derivatives of 1,8-naphthyridine (V) by similarly cyclising various alkyl-2-aminopyridines (IV).



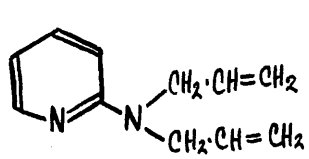
IV V

The synthesis of allyl-2-aminopyridine was accomplished by a modification of a method outlined in an industrial patent.[32] The sodium salt of 2-aminopyridine was prepared by reacting it with sodamide in dry toluene, and the theoretical quantity of pure allyl bromide was added to the reaction mixture to give the desired allyl-2-aminopyridine. After removal of the sodium bromide by filtration, and of the toluene by a preliminary distillation, attempts were made to distil the product fractionally under reduced pressure, as indicated by the patent. Apart from removing from the reaction product a quantity of lower-boiling, unchanged 2-aminopyridine, no separation into fractions could be achieved, and the remainder had to be distilled over a large range of temperature.

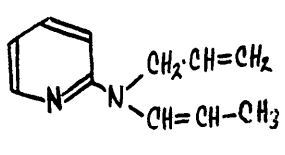
*Using, however, the more modern non-pyrolytic methods of cyclisation involving a double bond and aromatic nucleus, e.g., by sulphuric acid (c.f., Roblin, Davidson and Bogert, J.A.C.S., 57/

The crude distillate was eventually purified by conversion in ethanol into a mixture of picrates which were then fractionally recrystallised from a large volume of hot ethanol. On cooling, the pure picrate of allyl-2-aminopyridine separated first and was collected and converted to the free base (IV) by decomposing it with a large volume of dilute ammonia. It was found to distil under reduced pressure at a constant temperature, unlike the product described in the patent, which distilled over a range of several degrees.

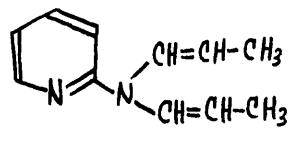
The ethanol liquors from which the picrate had been recrystallised deposited, on concentration and cooling, a much smaller quantity of crystals of another picrate different from that of allyl-2-aminopyridine. These, after one recrystallisation from ethanol, were converted, by decomposition with dilute aqueous ammonia, into the free base, which was also found to distil at a constant temperature under reduced pressure. No mention is made in the patent of the isolation of this product. Analysis both of the base and of its picrate showed it to be a diallyl derivative of 2-aminopyridine, whose formula might be one of the following (VI to IX):-



VI

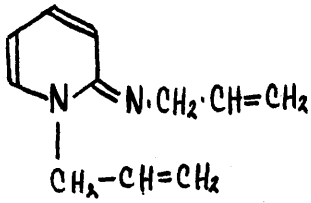


VII

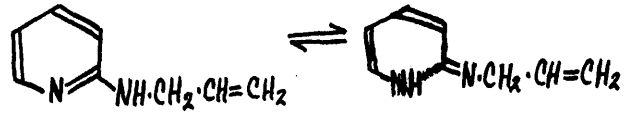


VIII

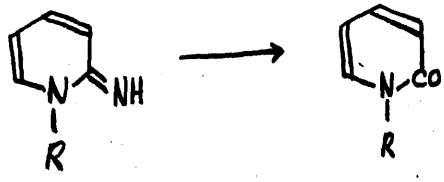
57, 151, (1935)) or aluminium chloride (cf., Cook and Hewett, J.C.S., 1933, 1098 and 1934, 365); compare also Linstead, Ann.Rep., 33, 318, (1936)).



IX



IV X



XI XII

The first three formulae (VI, VII, VIII) are possible tautomeric forms of 2-aminopyridine diallylated on the amino group. Formula IX, which admits of similar tautomerism although this has not been indicated above, is a diallyl derivative of 2-aminopyridine resulting from the further allylation of allyl-2-aminopyridine (IV) reacting in the tautomeric pyridone-imine form (X).

It has been found, however [33], that compounds of the latter type, notably 1-alkyl-2-pyridoneimines (XI), are readily hydrolysed to the 1-alkyl-2-piperidone (XII) by

boiling with alcoholic caustic potash. The diallylated product obtained here as a byeproduct was, on boiling for a prolonged period with alcoholic potash, recovered unchanged in its entirety, being identified, both qualitatively and quantitatively, as its picrate. The evidence is thus in favour of its having one of the formulae VI, VII, or VIII; but which particular one of these it did possess was not investigated further.

A similar alkylation of 2-aminopyridine to give mono- and dialkyl-2-aminopyridines is also recorded by Magidson and Menschikov [34]. Using substantially the same technique, these workers, by acting on 2-aminopyridine in toluene with sodamide, and by subsequent addition of excess isoamyl iodide to the reaction mixture, obtained both mono- and di-isoamyl-2-aminopyridine in proportions dependent on the temperature of the reaction mixture at the time of the addition. As in this case, they separated these substances by the fractional crystallisation of their picrates. Slotta and Francke [35], by acting on the sodium salt of 2-aminopyridine, not with alkyl halides, but with alkyl esters of p-toluenesulphonic acid, also obtained both mono- and di-alkyl-2-aminopyridines.

It may be noted that, in a small preliminary experiment on the preparation of allyl-2-aminopyridine using the same method as before, it was found that a picrate, which was not that of the diallyl-2-aminopyridine obtained as described

previously but which analysed as if it were, was isolated from the ethanol liquors in which the picrate of the reaction product had been prepared. The substance was not obtained in sufficient quantity to permit its conversion into the free base.

It is thought that it may have been the picrate of a diallylated 2-pyridone-imine with the structure (IX), formed, as mentioned previously, by the further allylation of allyl-2-aminopyridine (IV) reacting in the tautomeric pyridone-imine form (X). The sodamide used in this preparation was of a very inferior, unreactive quality, and it is known that in the absence, and possibly by using an insufficient amount, of sodamide, 2-aminopyridine in toluene solution does react in the tautomeric form to give 1-alkyl-2-pyridoneimines with the structure (XI)[14,33,36].

Nevertheless, in the absence of experimental proof, the possibility of the substance having one of the structures (VI), (VII), or (VIII) cannot be excluded, although it must have a structure different from that of the diallyl-2-amino-pyridine described previously, as the picrates were quite different from one another.

The cyclisation of the allyl-2-aminopyridine (XIII) to give 1,2,3,4-tetrahydro-1,8-naphthyridine (XIV) was then attempted using several well-known methods.

XIII XIV

Cyclisation was first attempted using strong sulphuric acid in the cold, but nothing but starting material could be isolated from the product; as progressively more vigorous conditions were imposed, involving heating on the water bath, it was found that a smell of sulphur dioxide developed, and the tarry product, when examined, was found to contain 2-amino-pyridine, the allyl grouping evidently having been removed either by hydrolysis or by oxidation. Heating allyl-2-amino-pyridine on the water bath for a prolonged period with a mixture of glacial acetic acid and sulphuric acid gave no better results, as, once again, the starting material alone was recovered unchanged. No matter how the procedure was varied, the results were negative in each case.

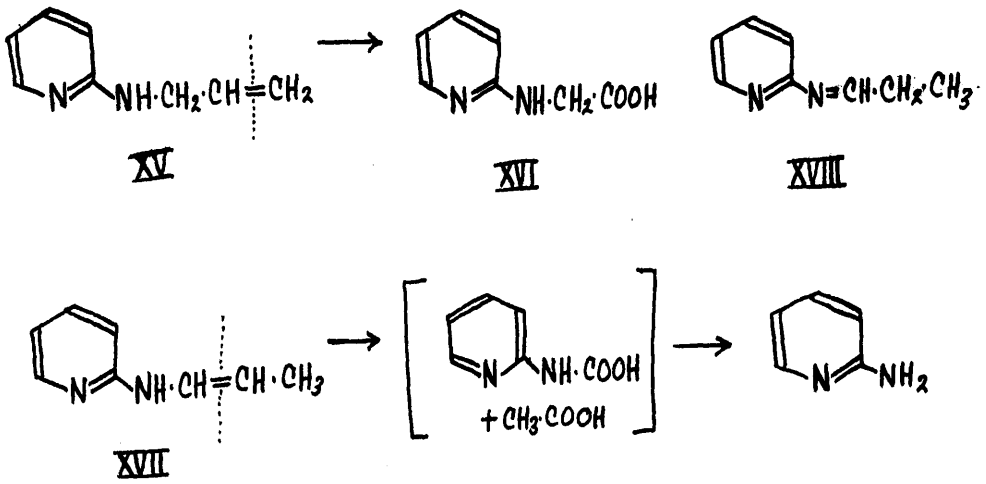
Accordingly, attempts were made to induce cyclisation to take place in the presence of anhydrous aluminium chloride. The solvent first used was dry nitrobenzene, but on working up the product, the starting material was recovered unchanged. Dry carbon disulphide was then used as the solvent, and the reaction was encouraged by prolonged boiling on the water bath. Apart from a minute trace of a waxy polymer, all that could be isolated from the reaction mixture was unchanged

allyl-2-aminopyridine.

It was decided, therefore, to use more drastic methods of cyclisation, but in view of the decomposition produced, without ring closure, by using hot, strong sulphuric acid, it was resolved to protect the secondary amino group by acetylation. However, neither prolonged boiling with acetic anhydride nor acetyl chloride had any effect on allyl-2-aminopyridine, the substance being recovered unchanged in each case.

In view of the singular unreactivity of the compound, it was therefore decided to investigate its structure by oxidative degradation of the allyl-amino side chain. This was quantitatively carried out using dilute aqueous potassium permanganate in alkaline conditions.

If the double bond of the allyl group were in the normal position, as in formula (XV), the product would have been 2-pyridylglycine (XVI), but if the double bond were in the position indicated in formula (XVII), the result of the oxidation would have been 2-aminopyridine. The possibility of the substance being an anil, as in formula (XVIII), was excluded because it was recovered unchanged in its entirety after prolonged boiling with dilute hydrochloric acid, while an anil would have hydrolysed readily under these conditions.



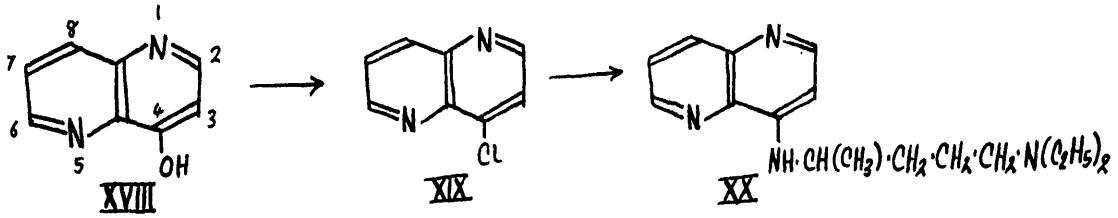
XV XVI XVIII XVII

The product of the oxidation was actually 2-aminopyridine, and the evidence is thus in favour of formula (XVII). Attempts were also made to isolate from the oxidation products the acetic acid that should have been produced. These, however, proved fruitless owing to the failure to remove completely all organic matter from the alkaline aqueous liquors, and to the subsequent extensive decomposition that attended the distillation with strong sulphuric acid of the partly organic residue obtained on evaporation of these liquors to dryness. Although many attempts were made, and several oxidations carried out, the results were the same in each case.

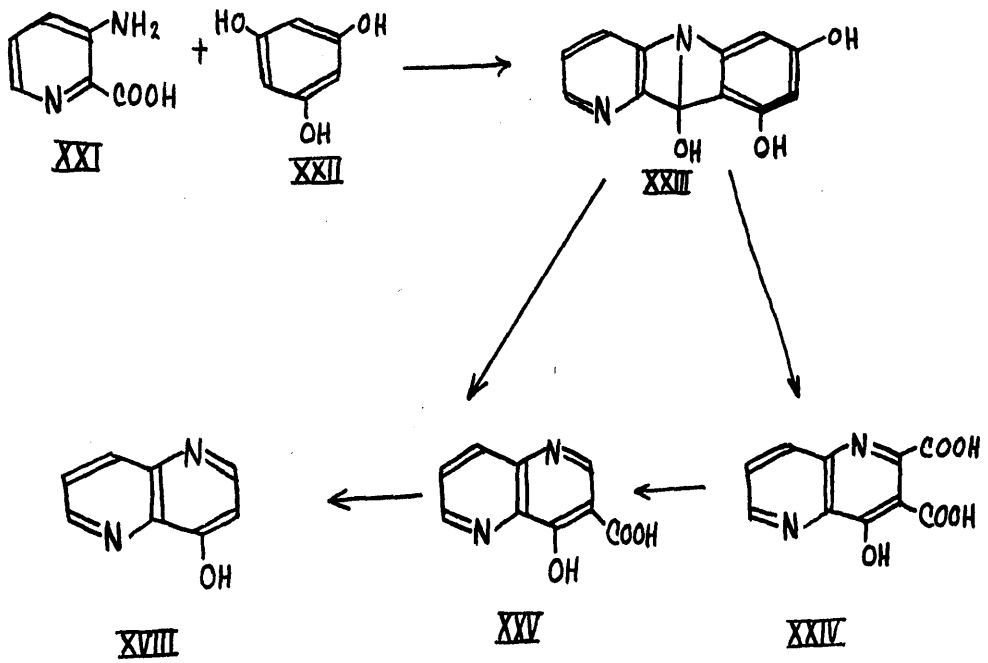
Nevertheless, it has thus been demonstrated that the position of unsaturation in the alkyl group of allyl-2-aminopyridine is represented by formula (XVII), which rendered cyclisation impossible in the manner desired.

.....

A synthesis of 8-hydroxy-1,5-naphthyridine (XVIII), carried out by Klisiecki and Sucharda [29] has been described in the Introduction (p.10). This was considered a suitable compound for our purposes, as conversion into 8-chloro-1,5-naphthyridine (XIX) and subsequent replacement of the chlorine atom by reacting this with, say, δ-diethylamino-α-methylbutylamine would give a compound (XX) bearing a structural relationship to known plasmodicides.

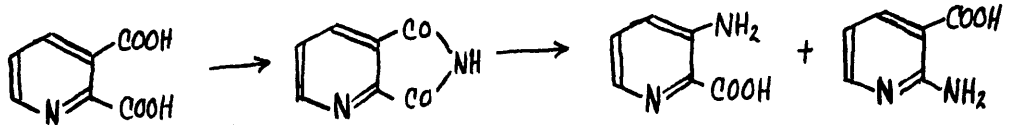


It was resolved, therefore, to investigate the synthesis of Klisiecki and Sucharda, and to improve the methods and yields obtained. Briefly, the synthesis consists of the fusion of β-aminopicolinic acid (XXI) with phloroglucinol (XXII) to give 7,9,10-trihydroxybenzo-1,5-naphthyridine (XXIII), which is then oxidised with fuming nitric acid to a mixture of 8-hydroxy-1,5-naphthyridine-6,7-dicarboxylic acid (XXIV) and 8-hydroxy-1,5-naphthyridine-7-carboxylic acid (XXV). These are then separately decarboxylated to 8-hydroxy-1,5-naphthyridine (XVIII) by heating at 340°C.



XXI XXII XXIII XVIII XXV XXIV

The starting material, β-aminopicolinic acid (XXI), was obtained by conversion of quinolinic acid to quinolinimide (XXVI), and by subjecting this to a Hofmann reaction to give β-aminopicolinic acid (XXI) and α-aminonicotinic acid (XXVII)



XXVI XXI XXVII

The quinolinic acid was prepared by the oxidation of 8-hydroxyquinoline by fuming nitric acid [37]. Linstead [38] recommends this method, and states that the orthodox oxidation of quinoline itself is much inferior; a method, however, claiming a 70% yield of quinolinic acid by oxidising quinoline with hydrogen peroxide in presence of sulphuric acid and

copper sulphate, has been recorded by Stiks and Bulgach [39].

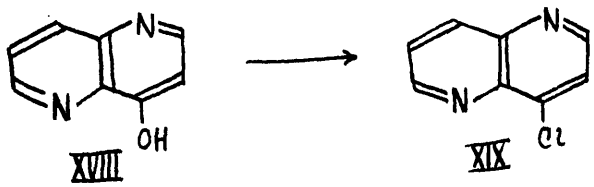
Conversion of the quinolinic acid to quinolinimide was achieved by a modification of the method of Sucharda [37]; the acid is first converted to its anhydride by the action of hot acetic anhydride, and thence to the imide by heating the quinolinic anhydride with acetamide, using acetic anhydride as the solvent. Sucharda's original method was first attempted, but gave very poor yields. Much better yields were obtained by using dry reagents freshly distilled, and by intermediate isolation of the quinolinic anhydride and addition of fresh acetic anhydride for the conversion to quinolinimide. The quinolinimide was recrystallised from glacial acetic acid, instead of hot water as Sucharda recommended, as this caused very considerable hydrolysis and loss of the product.

After the preparation of the β-aminopicolinic acid (XXI) in good yield by the action on quinolinimide of cold alkaline sodium hypochlorite solution [37], its fusion with phloroglucinol (XXII) was attempted [29], and much improved yields, though these were never good, were obtained by allowing the temperature to rise slowly over a considerable period, instead of quickly raising it to the required temperature. In other respects the preparation followed the lines suggested by

Klisiecki and Sucharda.

The oxidation of the 7,9,10-trihydroxybenzo-1,5-naphthyridine with fuming nitric acid was also carried out by the original method[29]. The individual acids (XXV) and (XXIV) were, however, not isolated from the acidic product left after evaporation of the nitric acid; this was instead sublimed directly at 350°C at atmospheric pressure to give an excellent yield of 8-hydroxy-1,5-naphthyridine (XVIII).

The conversion of 8-hydroxy-1,5-naphthyridine (XVIII) to the desired 8-chloro-1,5-naphthyridine (XIX) was then attempted, and was found to present considerable difficulty.



XVIII XIX

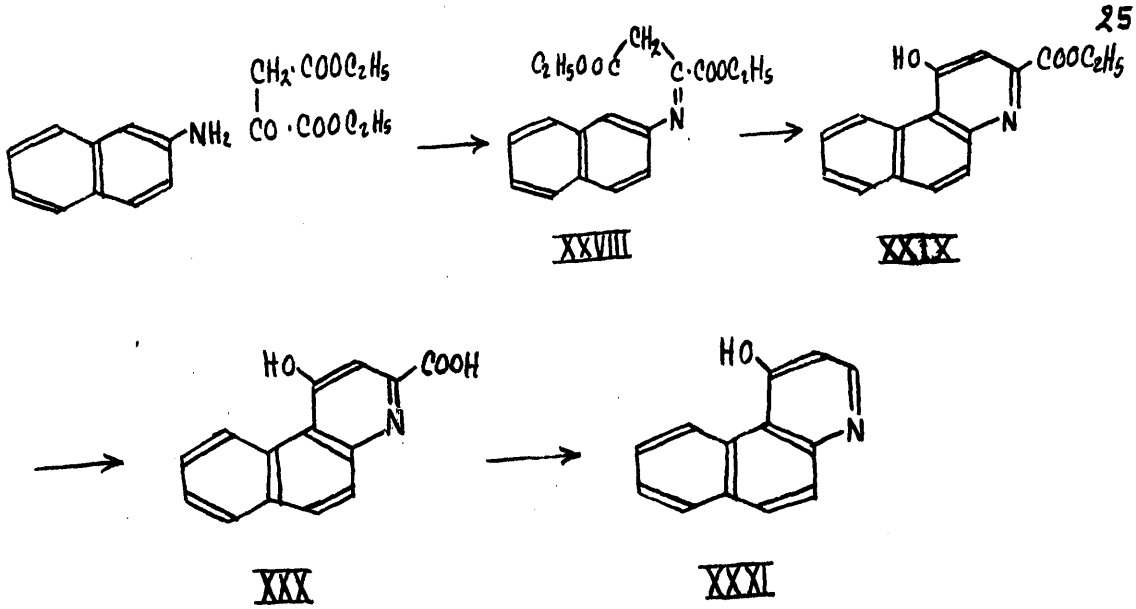
Heating with phosphorus oxychloride in a sealed tube produced merely a carbonaceous mass. Total charring also occurred on heating with phosphorus pentachloride on the water bath, and no matter how the technique was varied, the result was always carbon. Heating with thionyl chloride in a sealed tube at 120°C had no effect whatsoever on the substance, but, after several attempts, it was found that chlorination finally occurred at 180-200°C, and a small quantity of a chlorinated product was isolated from the experiment in a pure condition.

The rest of the reaction product was an uncrystallisable, gummy mass.

This chlorinated product could be crystallised from benzene for analysis, and the figures obtained indicated an approximate empirical formula $C_8H_3N_2Cl_4$. As the substance was soluble in benzene, insoluble in water, and unaffected by cold, dilute aqueous ammonia, it was probably not a hydrochloride, but a tetrachloro-1,5-naphthyridine with four hydrogen atoms replaced by chlorine. The gummy remainder of the reaction product, which was found to contain chlorine, was probably a mixture of 1,5-naphthyridines chlorinated in various positions and to various extents.

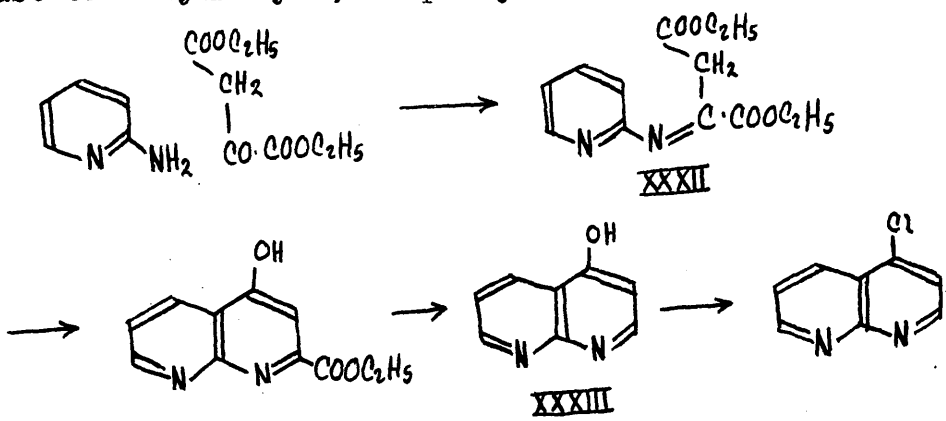
Before the nature of the substance was appreciated, an attempt was made to condense it with δ-diethylamino-α-methylbutylamine, but a basic oil was obtained which could neither be crystallised nor purified through either its picrate or hydrochloride, as these were both oils at room temperature.

Mueller and Hamilton [40] record the condensation of oxaloacetic ester with β-naphthylamine to give diethyl-2-naphthyliminosuccinate (XXVIII) which they subsequently cyclised, by heating in mineral oil, to 1-hydroxy-3-carbethoxy-4-azaphenanthrene (XXIX). This was readily hydrolysed by dilute alkali to the free carboxylic acid (XXX), which, on fusion, was decarboxylated to 1-hydroxy-4-azaphenanthrene (XXXI).



XXVIII XXIX XXX XXXI

It was proposed to extend this synthesis by condensing 2-aminopyridine with oxaloacetic ester to give diethyl-2-pyridyliminosuccinate (XXXII), by cyclising this to 4-hydroxy-2-carbethoxy-1,8-naphthyridine, and by a similar hydrolysis and decarboxylation to obtain 4-hydroxy-1,8-naphthyridine (XXXIII). This would then be chlorinated and condensed with a suitable base as proposed in the previous case of 8-hydroxy-1,5-naphthyridine.



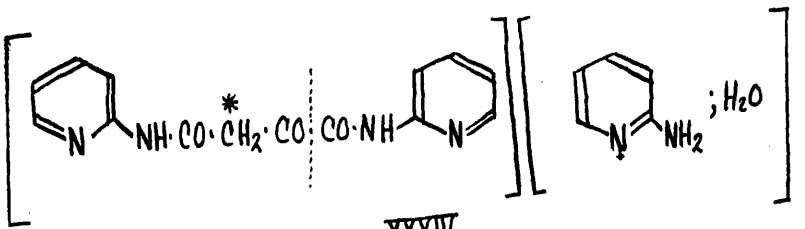
XXXII XXXIII

Following the methods used by Mueller and Hamilton, with slight modifications, 2-aminopyridine was heated on the water bath with a molecular quantity of oxaloacetic ester, prepared previously by a condensation of ethyl acetate and oxalic ester in presence of metallic sodium [41]. The product, isolated by its insolubility in benzene, was obtained as a homogeneous, crystalline, high melting solid, which was found to give, in ethanol solution, the picrate of 2-aminopyridine.

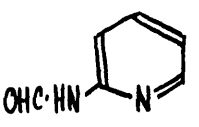
On heating at a few degrees above its melting point, a quantity of 2-aminopyridine distilled from it with much effervescence, leaving behind a tar. Heating below 100°C in a high vacuum, it again gave a distillate of 2-aminopyridine, and left a crystalline residue, which, after purification by crystallisation from ethanol, proved to be different from the starting material, and gave a picrate different from that of 2-aminopyridine.

The analyses of both the original condensation product and the substance obtained by heating it did not correspond to the compounds whose synthesis had been desired. The high nitrogen content of the condensation product implied the existence in its molecule of at least three residues of 2-aminopyridine to one of oxaloacetic ester, and at least one of these residues would have to be loosely associated with the molecule to account for the evolution of 2-aminopyridine on heating.

Although a large number of possible structures were considered, only one approached the analysis figures for the substance. This was oxaloacetic di-(2-pyridyl)-amide (XXXIV), associated by virtue of its acidic methylene group marked in the diagram below, with one molecule of 2-amino-pyridine, and crystallising with one molecule of water, originating probably from the hygroscopic 2-aminopyridine used in the reaction.



XXXIV



XXXV

The analysis figures are as follows:-

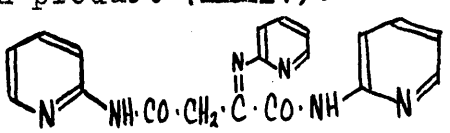
Found: C, 55.9%; H, 5.0%; N, 21.7%. $C_{19}H_{18}O_3N_6,H_2O$ requires C, 57.5%; H, 5.1%; N, 21.2%.

The partial hydrolysis of the substance by its molecule of water of crystallisation on heating, together with the dissociation of the attached 2-aminopyridine, would account for its behaviour.

When the condensation product had been heated and the 2-aminopyridine driven off, the substance remaining behind as a residue was at first thought to be 2-formamidopyridine (XXXV) formed by hydrolysis of the condensation product, as indicated by the dotted line in the diagram, by the water of crystallisation. However, although the amount of nitrogen

in 2-formamidopyridine approaches the analysis figure of the compound, it is excluded as a possibility because it melts at 71°C [42], whereas the melting point of the compound is 160-162°C.

It is now thought that, after some of the original condensation product (XXXIV) had hydrolysed, and after the water of crystallisation had been removed thus and by the high vacuum, the substance remaining may have condensed with part of the 2-aminopyridine not yet removed by distillation to give the anil of the diamide (XXXVI). It is possible that this compound could be formed only at this stage because of the presence of water previously, as anils are as a rule very easily hydrolysed. The nitrogen content of (XXXVI) closely approaches that of the substance obtained by heating the condensation product (XXXIV).



XXXVI

The analysis figures are as follows:-

Found: N, 23.5%. $C_{19}H_{16}O_2N_6$ requires N, 23.3%.

Although the above structures for these substances are the results largely of conjecture, no definite formulation being possible without sufficient data, it nevertheless became apparent that the above synthesis in its present form could not be applied successfully to the preparation of derivatives of 1,8-naphthyridine, and further investigation was therefore abandoned.

EXPERIMENTAL.

(A) Preparation, attempted cyclisation, and structure of allyl-2-aminopyridine.

(i) Allyl-2-aminopyridine.

2-Aminopyridine (100 g.) was dissolved in dry toluene (200 ccs.), and finely crushed sodamide (41.5 g.) was carefully added to the solution. A vigorous reaction ensued, and much ammonia was evolved, while the solution became purple in colour and thickened to a paste, owing to the separation of the sodium salt of 2-aminopyridine. When the reaction had subsided, the whole was heated on the water bath for two hours.

After cooling, dry redistilled allyl bromide (130 g.) was added drop-wise to the purple paste with constant cooling and shaking; much heat was evolved, and from the now brown mixture a large quantity of solid (sodium bromide) separated. The mixture was then heated on the water bath for two hours, cooled, and kept overnight.

The solid was then separated from the brown solution by filtration, washed with toluene, and discarded, and the filtrate fractionally distilled under reduced pressure. The yellow, oily liquid that distilled between 108-130°C under 12 mm. pressure was collected and found to weigh 130.5 g.

The crude liquid fraction was dissolved in hot ethanol (150 ccs.) and a solution of picric acid (250 g.) in hot

ethanol (600 ccs.) was added to it. The solution, which had instantly become a thick, yellow paste owing to separation of the picrate of the product, was heated on the water bath for 15 minutes, allowed to cool, and kept overnight. The crude cake of picrate which was thus obtained was crushed, filtered, washed with a little ethanol, and recrystallised once from rectified spirits (10,000 ccs.) as long yellow needles of the picrate of allyl-2-aminopyridine.

A small quantity of this picrate was crystallised several times from ethanol as long, silky yellow needles, m.pt. 146-148°C.

Found: C, 46.3%; H, 3.6%; N, 19.3%. $C_8H_{10}N_2,C_6H_3N_3O_7$ requires C, 46.3%; H, 3.6%; N, 19.3%.

The main bulk of the picrate was decomposed by heating with dilute aqueous ammonia (5,000 ccs.). The free base, although somewhat soluble in water, separated as a yellow oil as the picrate decomposed; it was extracted from the aqueous liquors by shaking with successive portions of a large volume of ether (3,000 ccs.). The ethereal extracts were combined and washed with several successive portions of very dilute aqueous ammonia (1,500 ccs.) until these remained colourless; after drying over anhydrous sodium sulphate the ether was removed by evaporation, and the brown oil remaining distilled at the constant temperature of 114°C under 12 mm. pressure. The pure allyl-2-aminopyridine thus obtained as a clear, colourless oil weighed 68 g. The

substance obtained by previous workers boiled at 124-129°C under 18 mm. pressure, which is in approximate agreement with the above findings.

A small portion of the pure product was subjected to analysis:-

Found: C, 71.4%; H, 7.4%; N, 20.7%. $C_8H_{10}N_2$ requires C, 71.6%; H, 7.5%; N, 20.9%.

Diallyl-2-aminopyridine was obtained as a byeproduct in the above preparation. The ethanol liquors from both the preparation and recrystallisation of the picrate of allyl-2-aminopyridine were concentrated and allowed to cool, when a mass of yellow plates crystallised out. Further crops of these were obtained by successive concentrations and coolings of the ethanol liquors. The combined crops were then crystallised once from rectified spirits as clumps of yellow plates, m.pt. 95-97°C.

This picrate was then ground up and decomposed in the cold by a large volume of dilute aqueous ammonia; the liberated base was extracted with ether, the extracts washed with very dilute ammonia solution, dried over anhydrous sodium sulphate, and the ether removed by evaporation. The yellow oil left was distilled at the constant temperature of 117°C under a pressure of 10 mm., and after distillation weighed 18.3 g.

A small quantity of the substance was redistilled at 113°C under a pressure of 8 mm. and subjected to analysis:-

Found: N, 16.4%. $C_{11}H_{14}N_2$ requires N, 16.1%.

The picrate of the substance was prepared by dissolving a small quantity of it (0.35 g.) in hot ethanol (15 ccs.) and adding to it a molecular quantity of picric acid (0.46 g.); the whole was boiled for a few minutes and allowed to cool, when a mass of light yellow plates crystallised out (0.64 g.). These were collected and crystallised repeatedly from ethanol as broad, lemon-yellow laminae, m.pt. 95-97°C.

Found: C, 51.1%; H, 4.2%; N, 17.2%. $C_{11}H_{14}N_2, C_6H_3N_3O_7$ requires C, 50.6%; H, 4.2%; N, 17.4%.

Note:- In a preliminary preparation of allyl-2-aminopyridine on a much smaller scale, the crude oil obtained by distillation of the filtered reaction liquors was converted to its picrate, mainly that of allyl-2-aminopyridine, as described previously. The ethanol liquors of this preparation, on concentration and cooling, deposited a crystalline substance which was collected and crystallised repeatedly from ethanol as stout orange rods, m.pt. 118-120°C.

Found: C, 50.9%; H, 4.3%; N, 17.2%. $C_{11}H_{14}N_2, C_6H_3N_3O_7$ requires C, 50.6%; H, 4.2%; N, 17.4%.

This substance appeared to be different from the picrate of diallyl-2-aminopyridine described above, as, on admixture, it depressed its melting point to 83°C.

(ii) Attempted cyclisation of Allyl-2-aminopyridine.

(a) Using sulphuric acid.

(i) With cooling.

To allyl-2-aminopyridine (5 g.) cooled in melting ice was slowly added, with stirring, concentrated sulphuric acid (10 g.) during the space of 15 minutes. The mixture became

orange yellow, and after a further 15 minutes was removed from the ice; stirring was continued, however, for yet a further 15 minutes, and the whole was removed to the ice-box and kept there for 45 hours.

The clear orange mixture was then poured into cold water (250 ccs.), and made alkaline with aqueous ammonia. The aqueous solution was extracted with ether, the extracts washed with water, dried with anhydrous sodium sulphate, and the ether removed by evaporation, leaving behind a yellow oil.

A portion of this oil (0.5 g.) was boiled up with picric acid (1 g.) in a small volume of ethanol; on cooling, yellow silky needles crystallised out (1.5 g.), m.pt. 151-152°C, which, on admixture, did not depress the melting point of an authentic sample of the pure picrate of allyl-2-aminopyridine, with which it was thus identical.

The quantity of the picrate (1.5 g.) obtained from the portion of oil (0.5 g.) indicated that the oil consisted almost entirely of unchanged allyl-2-aminopyridine.

(ii) Without cooling.

The previous experiment (i) was repeated on allyl-2-aminopyridine (1.25 g.) using concentrated sulphuric acid (2.5 g.), but without cooling in melting ice; the mixture was instead allowed to heat up to 100°C, when it had become quite dark in colour. On cooling, it was subjected to the same

process of working up by pouring into cold water, rendering alkaline with aqueous ammonia, and extracting with ether; the product was, as in (i), entirely unchanged allyl-2-aminopyridine which was identified in character and quantity as its picrate, as before.

(iii) With heating on the water bath.

The previous experiment (ii) was repeated, except that the reaction mixture was not allowed to cool, but was then heated for 4 hours on the water bath, when it became dark and a little sulphur dioxide was evolved. The whole was then poured into water (250 ccs.), and the trace of brown precipitate was filtered off and discarded; the filtrate was then made alkaline with aqueous ammonia and a further very small trace of a brown precipitate filtered off and also discarded.

The filtrate was extracted repeatedly with ether, the extracts dried over anhydrous sodium sulphate, and the ether removed by evaporation, leaving a small quantity of a clear, brown oil.

The oil was dissolved in a small volume of hot ethanol, and to the solution was added excess picric acid, also dissolved in a little hot ethanol. The copious yellow crystalline precipitate thrown down after boiling for a few minutes was collected and found to melt at 211-213°C. On admixture with an authentic sample of the picrate of 2-aminopyridine (m.pt. 215-218°C) prepared in ethanol as before from pure

2-aminopyridine, this melting point was not depressed.

The two substances were therefore identical, and the reaction product was thus identified as 2-aminopyridine.

(iv) Using glacial acetic acid with sulphuric acid.

Allyl-2-aminopyridine (1.5 g.) was dissolved in a mixture of glacial acetic acid (25 ccs.) and concentrated sulphuric acid (3 g.) and the whole heated on the water bath for 5 hours; on cooling, the solution was poured into excess dilute aqueous caustic soda, and the solution repeatedly extracted with ether. The extracts were washed with dilute caustic soda solution, then water, dried over anhydrous sodium sulphate, and the ether removed by evaporation.

A yellow oil (1.25 g.) remained which was dissolved in hot ethanol (50 ccs.) and added to a solution of picric acid (2.5 g.) also dissolved in hot ethanol (50 ccs.). On boiling for a short time and allowing to cool, yellow, silky needles crystallised out (2 g.), m.pt. 152-153°C, which did not depress the melting point of an authentic sample of the pure picrate of allyl-2-aminopyridine, with which it was therefore identical.

The product was thus mainly unchanged allyl-2-aminopyridine.

(b) Using anhydrous aluminium chloride.

(i) With dry nitrobenzene as solvent.

Allyl-2-aminopyridine (1 g.) was added to a cold solution of anhydrous aluminium chloride (2 g.) in dry, redistilled nitrobenzene (15 ccs.). The mixture instantly became dark red and grew slightly warmer. After keeping overnight at room temperature in anhydrous conditions, the solution was poured into a mixture of ice, with a slight excess of hydrochloric acid added, and steam distilled until free from nitrobenzene. The resulting solution was then made strongly alkaline with strong aqueous caustic soda, in order to redissolve the precipitated aluminium hydroxide; a minute dark precipitate was filtered off and discarded.

The clear alkaline filtrate was extracted repeatedly with ether, the combined extracts washed with water, dried over anhydrous sodium sulphate, and the ether removed by evaporation, leaving a small quantity of brown oil (0.7 g.) which was identified, by means of its picrate, as before, as being mainly unchanged allyl-2-aminopyridine.

(ii) With dry carbon disulphide as solvent.

Allyl-2-aminopyridine (1 g.) was dissolved in dry carbon disulphide (25 ccs.) and refluxed for 4½ hours with powdered anhydrous aluminium chloride (2 g.). After a few minutes, a brown oil precipitated and remained undissolved, slowly darkening as the heating continued.

The whole was then poured into cold dilute aqueous hydrochloric acid (300 ccs.) and the carbon disulphide was removed by a short distillation; the solution was then clarified with charcoal, filtered, cooled, and made strongly alkaline with strong aqueous caustic soda to redissolve the aluminium hydroxide. A very small trace of a dark precipitate was filtered off and discarded.

The filtrate was repeatedly extracted with ether, the extracts washed with water, dried over anhydrous sodium sulphate, and evaporated to a brown oil (0.6 g.), mixed with an excessively small trace of a waxy solid, probably a polymer, that was insoluble in alcohol. The oil was diluted with ethanol, filtered from the trace of wax, and converted to its picrate, as before. By this means the oil was identified as in previous instances as being almost entirely unchanged allyl-2-aminopyridine.

(iii) Attempted acetylation of allyl-2-aminopyridine

(a) Using acetic anhydride.

Allyl-2-aminopyridine (1 g.) was boiled under reflux for one hour with acetic anhydride (3.6 g.) and the dark solution on cooling was poured into a slight excess of ice-cold dilute caustic soda solution (400 ccs.). No precipitate was observed.

The clear, alkaline solution was rapidly extracted several times with ether, the combined extracts washed with water, dried over anhydrous sodium sulphate, and evaporated to

a small quantity of a light yellow oil. By conversion to its picrate in ethanol, the oil was identified, as in previous instances, as being almost entirely unchanged allyl-2-amino-pyridine.

(b) Using acetyl chloride.

Allyl-2-aminopyridine (0.5 g.) was boiled under reflux on the water bath for 3¼ hours with pure acetyl chloride (5 g.); excess acetyl chloride was then removed by a short distillation.

The small quantity of brown oil remaining was converted to its picrate in ethanol and thus identified, as in previous instances, as being almost entirely unchanged allyl-2-amino-pyridine.

(iv) Oxidation of allyl-2-aminopyridine with alkaline potassium permanganate.

(a) Detection of 2-aminopyridine.

To a mechanically stirred and ice-cooled suspension of allyl-2-aminopyridine (2 g.) in water (150 ccs.) was added dropwise, in the space of 45 minutes, a solution of potassium permanganate (8 g.) in cold water (150 ccs.).

The basicity of the allyl-2-aminopyridine provided sufficiently alkaline conditions to start the reaction, which proceeded smoothly to its conclusion with formation of gelatinous masses of manganese dioxide.

After keeping overnight, the precipitated manganese dioxide was filtered off and the filtrate made just acid to

litmus. The water was then removed from the filtrate by evaporation in vacuo on a luke-warm water bath, leaving behind a yellow, sticky solid.

This residue was boiled up with ethanol (250 ccs.), the hot extract filtered and concentrated to about 75 ccs., and added to a hot solution of excess picric acid in ethanol (75ccs.) After boiling for a few minutes, and allowing to cool, a copious yellow solid deposited, which was collected and recrystallised from ethanol as a matte of fine yellow needles, m.pt. 218-220°C. These on admixture did not depress the melting point of an authentic sample of the picrate of 2-aminopyridine (m.pt. 219-221°C) prepared in ethanol in the same way. The two substances were thus identical, and the product of the oxidation was therefore 2-aminopyridine.

(b) Detection of the aliphatic acid.

A suitable quantity of allyl-2-aminopyridine (10 g.) was suspended in cold water (500 ccs.) and to it was added dropwise, with mechanical stirring and cooling in ice-water, a cold solution of potassium permanganate (31.6 g.) in water (750 ccs.) exactly sufficient for the complete oxidation of the allyl-2-aminopyridine to 2-aminopyridine. The reaction proceeded smoothly to its conclusion as before, and the precipitated manganese dioxide was removed from the solution by filtration. The filtrate was then taken completely to dryness on the steam

bath and attempts made to remove the brown, oily organic material from the gummy residue by boiling it with suitable inert non polar organic solvents such as benzene, toluene, &c.; these, however, proved ineffectual, and it was decided to treat the substance as it stood.

Accordingly it was acidified with 50% sulphuric acid and steam distilled, the slightly acid aqueous distillate neutralised with a little dilute sodium carbonate solution, evaporated to dryness, and the residue once more steam distilled with strong sulphuric acid.

Attempts to isolate an aliphatic acid from the distillate as its p-phenylphenacyl ester in the usual manner failed entirely, and, although the experiment was repeated no less than seven times with widely varying conditions and methods of manipulation, no trace of an aliphatic acid could be discovered.

The problem is more fully discussed in the previous section.

(B) Preparation of 8-hydroxy-1,5-naphthyridine, and its chlorination.

A suitable quantity of quinolinic acid was prepared by the method of Sucharda[37]; 8-hydroxyquinoline was oxidised, with external cooling, by the dropwise addition of successive lots of cold nitric acid (d. 1.5), and the reaction was completed, between additions, by cautious heating on the water bath. The reaction mixture was then evaporated to small bulk on the water

bath, when the crude product crystallised out and was filtered off, further crops being obtained by successive concentration and cooling of the filtrate. The combined crops, after washing with 30% aqueous nitric acid, and then water, were recrystallised from 40% aqueous acetic acid to give a 70% yield of pure quinolinic acid.

(i) Quinolinimide.

Pure, dry, finely ground quinolinic acid (70 g.) was heated on the water bath with pure, freshly distilled acetic anhydride (78 g.) until solution was accomplished, care being taken to exclude moisture. The solution was then evaporated to dryness under reduced pressure on the water bath, and to the colourless, crystalline residue was added freshly distilled acetic anhydride (37.3 g.) followed by pure dry acetamide (43.6 g.), also freshly distilled.

The mixture was then boiled gently under reflux for 8 hours on an oil bath at 120-125°C, again using anhydrous conditions, and the crystalline mass that resulted on allowing to cool overnight was crushed up, filtered off, and washed with glacial acetic acid. Further crops were obtained by concentration in vacuo, and cooling of the combined filtrate and washings, and the combined crops were crystallised from glacial acetic acid (charcoal) as colourless crystals of quinolinimide, m.pt. 235°C. The yield of the pure product was 47.5 g.

The experiment was successfully repeated using the same quantities and a similar yield was obtained in the same state of purity.

(ii) β-aminopicolinic acid and α-aminonicotinic acid[37].

Quinolinimide was dissolved in 10% aqueous caustic soda and reacted with an alkaline solution of sodium hypochlorite; the solution was then heated for some time on the steam bath, cooled, and acidified with 50% H_2SO_4. The precipitated α-aminonicotinic acid was filtered off, washed with water, and recrystallised from hot water as fawn needles, m.pt. 308-309°C, with decomposition.

To the filtrate was added excess of an aqueous solution of copper acetate, and the precipitated copper salt was filtered off, washed with water, and decomposed by passing hydrogen sulphide through its hot aqueous suspension; after removal of the precipitated copper sulphide, the solution was evaporated to small bulk on the water bath, when, on cooling, thick brown tablets of β-aminopicolinic acid crystallised out, m.pt. 210°C with decomposition.

From 41.5 g. of quinolinimide was obtained 20 g. of pure β-aminopicolinic acid and 8 g. of pure α-aminonicotinic acid.

(iii) 8-Hydroxy-1,5-naphthyridine.

(a) 7,9,10-trihydroxybenzo-1,5-naphthyridine[29].

β-aminopicolinic acid (18.25 g.) was finely ground with phloroglucinol (20.25 g.) and heated on a metal bath in an open

flask. The temperature was gradually raised, during the space of 30 minutes, to 205°C at which temperature it was maintained, with constant stirring, for a further 30 minutes. During this time the fused mixture evolved much steam, slowly darkening in colour and becoming steadily more viscous in consistency.

On cooling, the dark glass was finely ground in a mortar and dissolved in hot 10% aqueous caustic soda (75 ccs.). The solution, on being allowed to cool, deposited the sodium salt of the product as a mass of golden leaflets; these were recrystallised once from a minimal volume of hot water, re-dissolved in warm water, and acidified with acetic acid, when the product was thrown down as a gelatinous precipitate. This was filtered off and recrystallised from aqueous ethanol as light brown needles, m.pt. over 360°C. The yield of the pure product was 5.8 g.

(b) Oxidation of 7,9,10-trihydroxybenzo-1,5-naphthyridine[29].

To ice cold nitric acid (d. 1.5; 47 g.) was added 7,9,10-trihydroxybenzo-1,5-naphthyridine (5.8 g.) in small portions, and with constant mechanical stirring and external cooling in ice-water. The mixture became almost black in colour, and much nitrous fumes were evolved.

The reaction mixture was then heated on the water bath until the evolution of nitrous fumes had ceased, then diluted with hot water (174 g.), and the trace of precipitated nitro-

compound was filtered off from the hot solution.

The filtrate was repeatedly evaporated to dryness on the water bath with successive small volumes of water, and the resulting colourless solid was ground up and dried in a vacuum over solid caustic potash.

The weight of the dry solid was 4.5 g.

(c) Decarboxylation of the mixed acidic product of (b) to give 8-hydroxy-1,5-naphthyridine.

(i) Using copper bronze in boiling quinoline.

Quinoline was purified by steam distillation, drying over solid caustic potash, redistillation, refluxing over copper bronze, and subsequent redistillation.

The mixed acidic product of (b) (0.5 g.) was dissolved in pure quinoline (10 ccs.) and the solution was boiled under reflux with copper bronze (0.5 g.) on the metal bath for 30 minutes. The black, carbonaceous solution was then cooled and filtered, and the filtrate steam distilled, after addition of a little water, until free from quinoline. After clarification by boiling with a trace of charcoal, the aqueous residue was evaporated to dryness on the water bath; but nothing remained after removal of the water.

The steam distillate was made alkaline with caustic potash solution to retain any 8-hydroxy-1,5-naphthyridine present, once more steam distilled to remove the quinoline, and the aqueous residue evaporated to a small bulk on the water

bath and, on cooling, acidified with hydrochloric acid solution.

The small colourless precipitate that was thrown down proved merely to be silica dissolved by the caustic potash from the glassware. The attempt was abandoned.

(ii) By direct sublimation.

The mixed acidic product of (b) (4 g.) was sublimed at 350°C under atmospheric pressure to give an almost colourless, powdery sublimate, and leaving behind a granular carbonaceous residue (0.6 g.) due to decomposition.

The sublimate was recrystallised (charcoal) from hot water (150 ccs.) as woolly balls of fine, colourless needles, m.pt. 325-327°C. The yield of the pure 8-hydroxy-1,5-naphthyridine was 2 g.

(iv) Effect of chlorinating agents on 8-hydroxy-1,5-naphthyridine.

(a) Heating with phosphorus oxychloride in a sealed tube.

8-Hydroxy-1,5-naphthyridine (0.25 g.) was heated with phosphorus (1.5 ccs.) in a sealed tube at 170°C for 7 hours.

On cooling and opening, a black, essentially carbonaceous mass was observed in the tube under a colourless supernatant layer of phosphorus oxychloride; the whole was treated with cold water (75 ccs.), and clarified by boiling for a short time with charcoal.

The dark filtrate, on cooling, gave, on rendering just alkaline with aqueous ammonia, only a faint dark flocculence.

As nothing but carbonaceous material could be isolated, the attempt was abandoned.

(b) Heating with phosphorus pentachloride.

8-Hydroxynaphthyridine (0.1 g.) was heated, with phosphorus pentachloride (0.1 g.) and a few drops of phosphorus oxychloride, on the oil bath at 140-150°C for 3½ hours.

The carbonaceous mass left in the flask was treated precisely as in (a), and with the same negative results.

(c) Heating with thionyl chloride at 120°C.

8-Hydroxynaphthyridine (0.1 g.) and thionyl chloride (1.5 ccs.) were heated at 120°C in a sealed tube for 4 hours. On cooling, the starting material was found to be undissolved and unchanged.

(d) Heating with thionyl chloride at 180-200°C.

8-Hydroxynaphthyridine (2.35 g.) and thionyl chloride (37.5 ccs.) were heated in sealed tubes at 175°C, rising to 185°C, over a period of 3 hours, and then at 190-200°C for 2½ hours. The interval taken for the temperature to rise from 185° to 190°C was one hour.

On cooling and opening, a high pressure of gas was found to have developed in the tubes, and the clear yellow liquid resulting was distilled on the water bath to remove excess unreacted thionyl chloride.

The yellow oil left soon solidified, and was rapidly ground up under very dilute aqueous ammonia to remove the

last traces of thionyl chloride, then washed with water and dried in a vacuum over solid caustic potash.

The light yellow powder obtained was dissolved in hot glacial acetic acid, clarified with charcoal, and allowed to cool after filtration. Tufts of greenish yellow needles deposited; these were collected and crystallised repeatedly from benzene as fine, greenish-white, silky needles, m.pt. 276-278°C, with decomposition. Fusion with sodium in the usual manner revealed the presence of chlorine in the compound, but the presence of sulphur could not be detected. The yield of the substance was 0.7 g. Its possible structure is discussed in the previous section.

Found: C, 36.7%; H, 1.3%; N, 10.6%; Cl, 51.3%.

The acetic acid crystallisation mother liquors were concentrated and allowed to cool, when a quantity of amorphous material deposited; accordingly they were poured into a large volume of cold water and the gummy precipitate was filtered off. On drying in a vacuum over solid caustic potash, many attempts were made to purify the sticky mass, but it was found that it could not be crystallised. It was probably a complex mixture of 1,5-naphthyridines chlorinated in various positions and to various extents, as the method of fusion with sodium revealed the presence of chlorine in the impure residues.

(v) Condensation of the chlorinated product with δ-diethylamino-α-methyl butylamine.

δ-diethylamino-α-methyl butylamine (0.5 g.) and the chlorinated product of (iv)(d) (m.pt. 276-278°C; 0.4 g.) were together heated on an oil bath at 140°C for 2½ hours, and then at 160°C for 5 hours.

The dark red gum that resulted was dissolved in dilute aqueous hydrochloric acid, the solution was clarified with charcoal and made alkaline with aqueous ammonia. The milky precipitate that was thrown down was extracted with chloroform, the extracts washed with water, and then shaken with several lots of 5% aqueous acetic acid (200 ccs. each).

The acetic acid extracts were made alkaline with aqueous ammonia and the milky precipitate extracted with chloroform. The combined extracts were washed with dilute aqueous ammonia, then water, and dried over anhydrous sodium sulphate. On removal of the chloroform by evaporation on the water bath, the product was left behind as a deep red gum; this was repeatedly extracted with boiling light petroleum and the combined extracts evaporated to a very small trace of a yellow oil that did not solidify on freezing and scratching.

As the picrate formed by the substance in ethanol proved to be an oil at ordinary temperature, it was decided to purify it through the hydrochloride; accordingly it was

dissolved in dry benzene (20 ccs.) and the solution saturated with dry hydrogen chloride. The hydrochloride of the base immediately precipitated, but this proved to be an oil also; the supernatant benzene was then decanted, the hydrochloride washed with dry benzene by decantation, and dissolved in cold acidulated (HCl) water. After removal of excess benzene by a short distillation, the solution was cooled as far as possible without freezing occurring, and made alkaline with cold aqueous ammonia. A small quantity of a colourless waxy precipitate was thrown down and filtered off, but not enough was obtained to permit a possible purification by crystallisation. Owing to its sticky waxy nature it was found impossible to take the melting point of the substance.

(C) The condensation of 2-aminopyridine with oxaloacetic ester.

A suitable quantity of oxaloacetic ester was prepared by the method of Claisen [41]; to a solution of pure oxalic ester in anhydrous ether, covering the appropriate quantity of sodium wire, was added dry ethyl acetate at a rate that kept the reaction proceeding briskly without allowing the ether to boil. The sodium salt of the product that separated on standing overnight was collected, washed with ether, and dissolved in cold water. The aqueous solution was then acidified with hydrochloric acid solution, and the liberated product extracted

with ether and purified by distillation at 122°C under a pressure of 15 mm.

(i) Reaction of 2-aminopyridine with oxaloacetic ester.

To oxaloacetic ester (46 g.) was added dry, finely powdered 2-aminopyridine (25 g.), which rapidly passed into solution with the evolution of heat, so that the temperature of the solution rose to about 80°C.

On cooling somewhat, the now dark syrup was kept overnight in a vacuum over concentrated sulphuric acid, and in the morning was heated on the steam bath under reduced pressure in order to remove any water produced in the reaction. After ten minutes, the mixture suddenly solidified to a semicrystalline mass; heating was continued for two hours and the mixture then allowed to cool.

The solid obtained was finely ground under benzene and filtered off as a colourless crystalline product. A further small crop was obtained by evaporating the benzene from the dark filtrate, heating for a further period the black oil that remained, and again diluting this with benzene; further similar attempts to obtain other crops of the material failed, as the reaction liquors finally became a black, intractable tar.

The combined crops of the product were recrystallised once from ethanol as colourless leaflets. The yield of the

pure product was almost 25 g.

A small quantity of the substance was repeatedly crystallised for analysis from ethanol as colourless, shining leaflets, m.pt. 200-201°C, with effervescence. Its possible constitution is discussed in the previous section.

Found: C, 55.9%; H, 5.0%; N, 21.7%.

A small quantity of the pure substance was dissolved in a small volume of hot ethanol, and to the solution was added a solution of excess picric acid, also in a little hot ethanol. The formation of the yellow precipitate that commenced to deposit immediately was completed by boiling the solution for a short time and by allowing it to cool. The precipitate was collected and crystallised several times from ethanol as fine yellow needles, m.pt. 219-221°C. Admixture with an authentic sample of the picrate of 2-aminopyridine (m.pt. 219-221°C) did not depress its melting point, and the two substances were thus identical.

(ii) Effect of heat on the product of (i).

The product of (i) (1 g.) was heated at 200°C in a small distilling flask on the metal bath. Effervescence began as the substance melted, and when the temperature was allowed to rise to 220°C, a colourless oil began to distil, which soon solidified to a mass of colourless crystals, which were proved, by the method of mixed melting points, to be identical with an authentic sample of 2-aminopyridine (m.pt. 56°C).

The picrate of the distillate was prepared in ethanol, as in previous instances, and, after several recrystallisations from that solvent, was proved, by the method of mixed melting points, to be identical with an authentic sample of the picrate of 2-aminopyridine.

The substance remaining in the distilling flask was about half the bulk of the original material, but could not be dealt with as it consisted of a mass of black tar.

(iii) Effect of heating the product of (i) in a high vacuum at a low temperature.

The product of (i) (1 g.) was heated, by means of an air bath, in a small Claisen distilling flask at 80°C under a pressure of 0.1 mm. The substance darkened, but did not melt, and the temperature was allowed to rise to 100°C without further apparent alteration in its appearance; at this temperature, however, a colourless oil began to distil, which later became solid, and was identified, as before, as 2-aminopyridine (m.pt. 56°C).

To exclude the possibility of the distillate containing any oxaloacetic ester, it was dissolved in ether and shaken with very dilute hydrochloric acid solution, then with water, and the ether solution dried over anhydrous sodium sulphate and evaporated, when nothing remained. The oil was thus entirely basic or exceptionally soluble in water.

When the oil had ceased to distil, the apparatus was

disconnected and allowed to cool, and the dark, crystalline residue in the flask was scraped out and found to weigh 0.5 g. It was repeatedly crystallised (charcoal) from ethanol as colourless platelets, m.pt. 160-162°C, which on admixture consistently depressed the melting point of the starting material (the product of (1), m.pt. 200-201°C) to 157°C. The possible constitution of this substance is discussed in the previous section.

Found: N, 23.45%.

The picrate of this material was prepared in ethanol as before, and after repeated crystallisations from that solvent was obtained as fine, yellow needles, m.pt. 222°C, which on admixture depressed the melting point of an authentic sample of the picrate of 2-aminopyridine (m.pt. 219-221°C), prepared in a similar manner, to 204-206°C. The two substances were thus different.

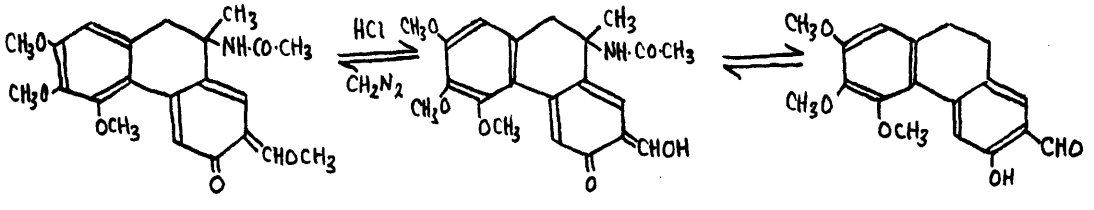
A P P E N D I X:

The effect of diazomethane on 3-hydroxy-4-phenanthraldehyde.

INTRODUCTION.

The structure (I) assigned to colchicine by Windaus [1] is not entirely satisfactory for a number of reasons. One of the difficulties is concerned with the behaviour of colchiceine (II), which is easily obtained by the saponification of colchicine, and from which colchicine may be regenerated by the action of diazomethane.

Although it might be expected that the tautomeric aromatic o-hydroxy-aldehyde (III) would be its more stable form, colchiceine does not react with ketonic or aldehydic reagents, and behaves as if it were the hydroxymethylene ketone (II).



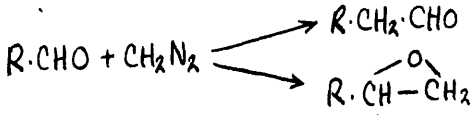
I II III

Since simpler hydroxy-aldehydes, of the salicylaldehyde type, do not exhibit this behaviour, it seemed of interest to examine an o-hydroxy-aldehyde of the phenanthrene series.

Accordingly, an attempt was made to methylate 3-hydroxy-4-phenanthraldehyde (IV) with diazomethane in order to ascertain whether the resulting ether arose from the hydroxy-aldehyde or the hydroxy-methylene ketone form. The substance obtained from this reaction, however, although it

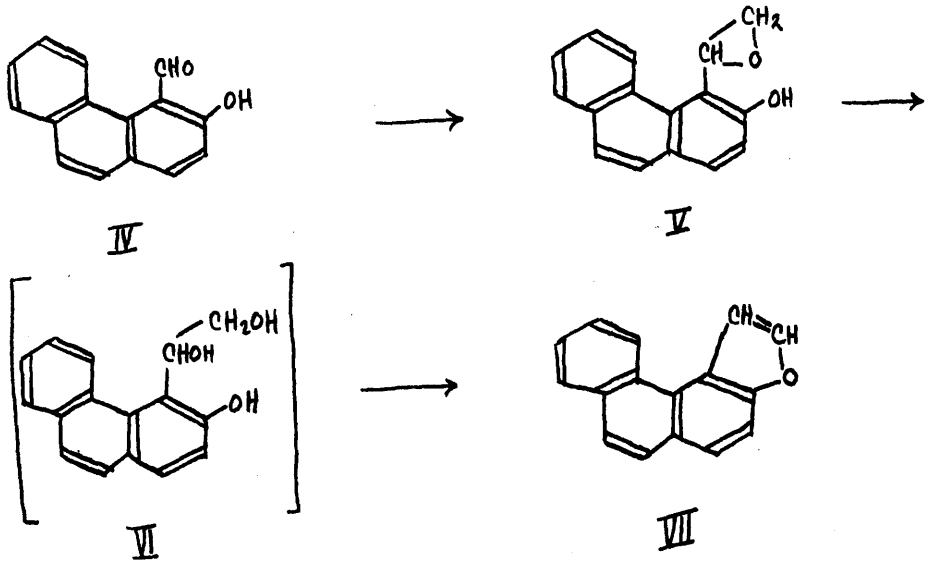
seemed still to contain a phenolic hydroxyl group, did not react with 2,4-dinitrophenylhydrazine. It is regarded as being 3-hydroxy-4-phenanthrylethylene oxide (V), which structure accounts fully for the behaviour of the compound towards various reagents described in the Experimental Section, and with which the analytical figures are in good agreement.

Further support for this opinion is given by the work of Arndt and Eistert [2], who, extending the work of Schlotterbeck [3] on the effect on aldehydes of ethereal diazomethane, found that such a reaction proceeds mainly in two directions, resulting chiefly in the formation of an aldehyde and a substituted ethylene oxide, the latter tending to be formed in greater yield.



On heating with alcoholic hydrochloric acid, 3-hydroxy-4-phenanthrylethylene oxide (V) passed into an alkali-insoluble compound which did not react with 2,4-dinitrophenylhydrazine; this is believed to be 4,5-(1',2'-naphtha)coumarone (VII), with which structure the analytical figures agree.

These reactions may thus be expressed as follows, the formation of the coumarone occurring probably by dehydration of the possible intermediate (VI):-



IV V VI VII

Although this work fails, therefore, to be significant regarding the possible structure of colchicine, it is not without interest on account of the unusual course taken by the reactions we have described above.

Experimental.

A suitable quantity of 3-hydroxy-4-phenanthraldehyde was prepared by the method of Smith [4]; 3-phenanthrol in cold, dry benzene solution, through which was passed a current of dry hydrogen chloride, was reacted with anhydrous liquid hydrogen cyanide in the presence of anhydrous aluminium chloride. The product was then obtained by evaporating the dried ethereal extract of the reaction mixture after it had been boiled with water, and was purified by distillation in an oil-pump vacuum.

Attempts to avoid the use of liquid hydrogen cyanide by reacting anhydrous zinc cyanide and dry hydrogen chloride in the presence of 3-phenanthrol dissolved in dry benzene [5] proved unsuccessful, although the method was tried and found to give good yields of the simpler hydroxy aldehydes, such as β-naphthol-α-aldehyde.

(i) 3-Hydroxy-4-phenanthrylethylene oxide.

To a solution of 3-hydroxy-4-phenanthraldehyde (1.6 g.) in dry ether (25 ccs.) was added a solution of diazomethane (from 4 g. of nitrosomethylurea) in dry ether (50 ccs.), and the mixture kept at room temperature for 3 days and then allowed to evaporate. The deep orange oil left, which slowly became semi-solid, was dissolved in ether, and the solution shaken several times with cold dilute caustic soda solution to remove

unchanged hydroxy-aldehyde, then washed with water, dried over anhydrous sodium sulphate, and evaporated; the light yellow gum left was boiled for several hours with light petroleum, which was then decanted, leaving a dark, granular solid. This was rapidly washed with a little cold benzene in which the dark impurities dissolved almost immediately; the almost colourless solid left was then dissolved in hot benzene, boiled with charcoal, filtered, and the hot filtrate diluted with hot ligroin. On cooling, the colourless crystals that deposited were collected and crystallised several times from benzene/ligroin as snow-white shining aggregates of narrow blades, m.pt. 152-153°C.

This substance was found to be soluble in cold dilute caustic soda solution, being reprecipitated unchanged by dilute aqueous hydrochloric acid; it was insoluble in hot dilute sodium carbonate solution, and resinified on prolonged boiling with dilute aqueous caustic soda. Nitrogen was not found to be present in the compound after testing by fusion with sodium.

Found: C, 81.6%; H, 4.95%. $C_{16}H_{12}O_2$ requires C, 81.4%; H, 5.1%.

(ii) 4,5-(1',2'-Naphtha)coumarone.

3-Hydroxy-4-phenanthrylethylene oxide (0.05 g.) was dissolved in ethanol (3.5 ccs.), and to the solution was added a solution of concentrated aqueous hydrochloric acid (1 cc.) in water (2 ccs.). The cold, faintly turbid solution

was then boiled under reflux for two hours; the solution was then left overnight to cool, and the colourless leaflets that had crystallised out were collected, dried, and, owing to their ready solubility in all solvents used, were purified by sublimation at 95°C under 3 m.m. pressure to give a micro-crystalline powder, m.pt. 114-115°C, which on admixture depressed the melting point of a pure sample of 3-hydroxy-4-phenanthrylethylene oxide. This substance was found to be insoluble in hot aqueous caustic soda, and did not give a 2,4-dinitrophenylhydrazone in the usual way.

Found: C, 87.7%; H, 4.4%. $C_{16}H_{10}O$ requires C, 88.0%; H, 4.6%.

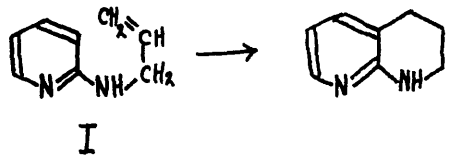
Summary of Part II

In an investigation of possible plasmodicides, the synthesis of derivatives of 1,8-naphthyridine was undertaken by attempting to cyclise allyl-2-aminopyridine (I), which was itself obtained by the action of allyl bromide on the sodium salt of 2-aminopyridine, in turn obtained by the action of sodamide on the toluene solution of the base.

The reaction product was purified by the fractional crystallisation of its picrate, and by this means a quantity of diallyl-2-aminopyridine (II) was isolated simultaneously.

The cyclisation of allyl-2-aminopyridine, although attempted by a variety of methods, was, however, unsuccessful because the position of the double bond in the unsaturated alkylamino side-chain had been altered by tautomerism to a position (III) which rendered the desired cyclisation impossible.

The unfavourable incidence of the double bond was demonstrated by the oxidation of allyl-2-aminopyridine by alkaline potassium permanganate to give 2-aminopyridine (IV).



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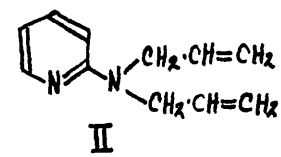
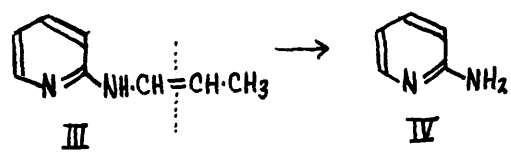
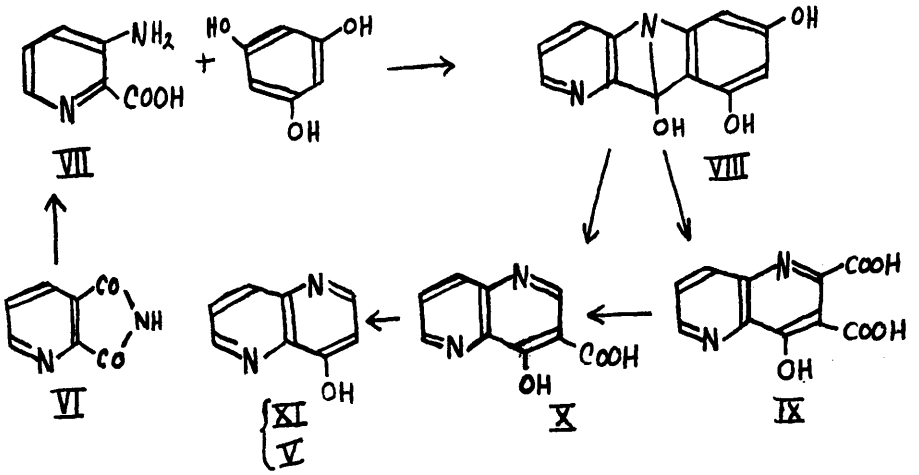


II

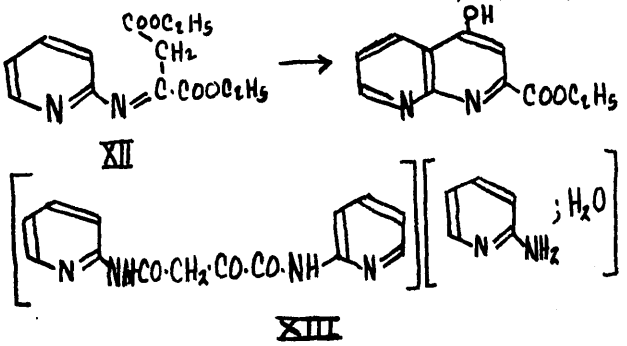


III IV

The synthesis of 8-hydroxy-1,5-naphthyridine (V) by the method of Klisiecki and Sucharda[29] was investigated and improved. The yield of the starting material, quinolinimide (VI), was considerably increased; after its conversion to β-aminopicolinic acid (VII) by means of a Hofmann reaction, the preparation of 7,9,10-trihydroxybenzo-1,5-naphthyridine (VIII) by fusion of this compound with phloroglucinol was accomplished in improved yield. Oxidation with fuming nitric acid to the mixture of acids (IX) and (X) was carried out as recommended, but instead of isolating these individually, the mixture was converted directly by sublimation into 8-hydroxy-1,5-naphthyridine (XI). Attempts to convert this to 8-chloro-1,5-naphthyridine failed using phosphorus pentachloride or oxychloride, and thionyl chloride at 180°C gave a tetrachloro-1,5-naphthyridine, which on condensation with δ-diethylamino-α-methylbutylamine yielded a basic wax not amenable to to the usual methods of purification.

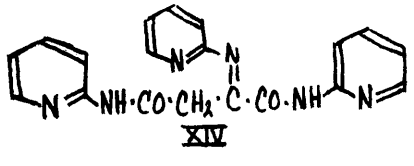


An attempt to condense 2-aminopyridine with oxaloacetic ester to give diethyl-2-pyridylimino-succinate (XII), which was then to be cyclised to 4-hydroxy-2-carbethoxy-1,8-naphthyridine, proved unsuccessful. The compound obtained was believed to be the di-(2-pyridyl)--amide of oxaloacetic acid , associated with one molecule of 2-aminopyridine and one molecule of water (XIII). At 100°C, this substance decomposed into 2-aminopyridine and a compound thought to be an anil formed by the condensation of 2-aminopyridine with the di-(2-pyridyl)--amide of oxaloacetic acid , (XIV).

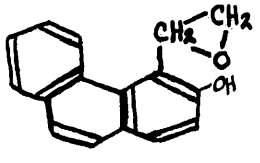


XII

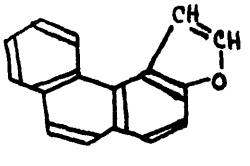
XIII



XIV



XV



XVI

The action of ethereal diazomethane on 3-hydroxy--4-phenanthraldehyde was examined in its relationship to the reactions of the colchicine molecule. It was found that the product was 3-hydroxy-4-phenanthrylethylene oxide (XV), which on boiling with alcoholic hydrochloric acid was cyclised to 4,5-(1',2'-naphtha)-coumarone (XVI).

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