

**SIX-MEMBERED HETEROCYCLIC
NITROGEN COMPOUNDS
WITH THREE CONDENSED RINGS**

This is the twelfth volume published in the series

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

A SERIES OF MONOGRAPHS

ARNOLD WEISSBERGER, *Consulting Editor*



SIX-MEMBERED HETEROCYCLIC NITROGEN COMPOUNDS WITH THREE CONDENSED RINGS

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Eastman Kodak Company, Rochester, N. Y.

In collaboration with

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The Chemistry of Heterocyclic Compounds

The chemistry of heterocyclic compounds is one of the most complex branches of organic chemistry. It is equally interesting for its theoretical implications, for the diversity of its synthetic procedures, and for the physiological and industrial significance of heterocyclic compounds.

A field of such importance and intrinsic difficulty should be made as readily accessible as possible, and the lack of a modern detailed and comprehensive presentation of heterocyclic chemistry is therefore keenly felt. It is the intention of the present series to fill this gap by expert presentations of the various branches of heterocyclic chemistry. The subdivisions have been designed to cover the field in its entirety by monographs which reflect the importance and the interrelations of the various compounds, and accommodate the specific interests of the authors.

*Research Laboratories
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ARNOLD WEISSBERGER

Preface

The polynuclear heterocyclic compounds containing nitrogen and three fused six-membered rings are of great theoretical interest and of considerable practical importance to the drug industry. Applications to dyes and in analytical chemistry have been of only minor significance. It is hoped that the arrangement and the discussion of the various classes included in this volume will emphasize their similarities and significant differences. The literature has been covered through 1952.

Many students have acquired a distaste for heterocyclic chemistry, owing to "the presentation of an apparently endless series of syntheses of compounds having illogical names and systems of numbering, little mention being made of their properties."¹ In this volume the aim has been to simplify naming and numbering by use of the "a" system of nomenclature, and in an introductory chapter to collect the syntheses as far as possible by "name reactions," pointing out the similarities and nature of the products that result from different conditions of cyclization; a discussion of mechanisms to account for the latter is included.

The "a" system of nomenclature, which "is quite rightly preferred,"² has been used in this as in our earlier volume. All individual chemical substances are also named according to *Chemical Abstracts*, and the index includes all names. There have been too many inconsistencies in the past; for instance, acridine has been numbered like anthracene, but phenanthridine has not been numbered in conformity with phenanthrene (which, however, is an unfortunate exception to the rule for hydrocarbons). In this volume all the azaphenanthrenes are numbered and oriented as in *The Ring Index*. Phenanthridine is 5-azaphenanthrene; it is of interest to note that the latter is also the name used in the Dyson system. A complete description of the nomenclature is given in the individual chapters.

The first part of this volume was set up with the oxo radical placed close to the ring  instead of with the author's double bond . Since the former may cause confusion with a heterocyclic oxygen, the more common double-bonded designation is preferred and used in the remainder of the book.

A series of tables listing all of the compounds reported which belong to

¹ C. M. Atkinson, *J. Chem. Soc.*, 1953, 720.

² S. Coffey, *J. Soc. Dyers Colourists*, 68, 214 (1952).

the particular ring system under discussion are included in each chapter. Depending upon the numbers involved, the compounds are generally classified in tables or the tables arranged in the following order, with the substituent lowest on the list determining the location of a compound; for example, a substance containing both carboxyl and amino groups will be found only among the carboxyl derivatives.

1. Alkyl and Aryl Derivatives.
2. Reduction Products.
3. Halogen Derivatives.
4. Nitro Derivatives.
5. Sulfo Derivatives.
6. Amino Derivatives.
7. Hydroxy Derivatives.
8. Carboxy and Carbonyl Derivatives.
9. Miscellaneous.

Exceptions and additional tables occasionally are found primarily for the convenience of the reader.

The chapter on the relation between structure and ultraviolet absorption rounds out the picture of heterocyclic systems, especially since it includes other polynuclear systems than those referred to in the title of this volume.

The authors are very grateful to Dr. D. M. Burness, Mrs. Florence Otter, and Mrs. Esther Weaver for typing, proofreading, and general editorial assistance.

Eastman Kodak Company
Rochester, New York
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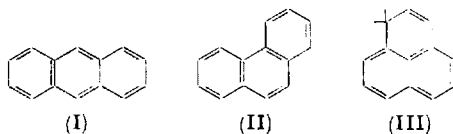
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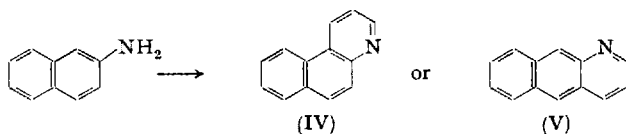
Introduction

By C. V. WILSON

The heterocyclic compounds described in this volume are azalogues of anthracene (I), phenanthrene (II) and benzonaphthene (III). Though



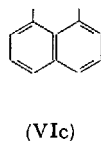
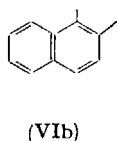
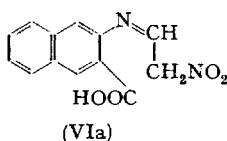
many of the derivatives of these ring systems can be prepared by the usual substitution or replacement reactions, the basic structures are the result of certain well-known cyclization procedures, including the Skraup, Doebner, Doebner-Miller, Combes, Conrad-Limpach, Pfitzinger, and Knorr carbostyryl syntheses. These ring closures may lead to either angular (IV) or linear (V) compounds. The Skraup, Doebner-



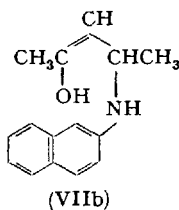
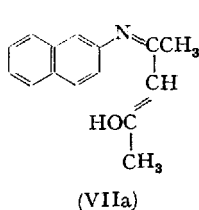
Miller, and Conrad-Limpach syntheses are commonly associated with angular cyclization. Generally, they must be modified to give the linear product, though occasionally both isomers result. Conversely, the Combes synthesis, which normally leads to the linear isomer, can be modified to produce the angular product.

The various cyclization procedures used in the syntheses of these heterocycles may be divided into two general classes; (1) those in which cyclization is effected by removal of HX (generally H₂O) from ortho-

disubstituted naphthalene derivatives containing a nitrogen atom in at least one of the substituent groups, as indicated in types VIa, b, and c;

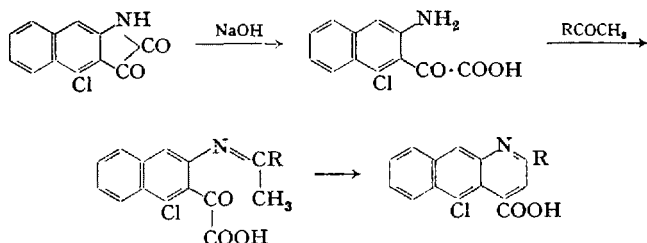


(2) those in which the naphthalene nucleus is only monosubstituted and cyclization involves the removal of a hydrogen atom from an ortho position, usually as water or hydrogen (VIIa and b). It is obvious that the former type of cyclization is unambiguous and that either



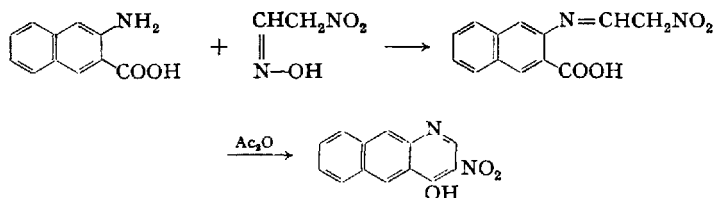
angular or linear heterocycles can be obtained by the proper choice of starting material. In the latter case, however, it is just as clear that the cyclization can proceed in two ways to give either a linear or an angular product.

The Pfitzinger reaction is an example of the first type (see p. 28);



obviously it can be used to produce the angular isomer by starting with the isomeric naphthisatin^{1,2} (see pp. 177 and 233). Another example involves the use of methazonic acid (see p. 30); this substance

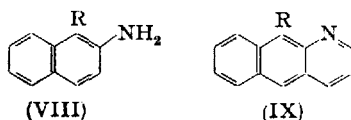
reacts with 2-amino-3-naphthoic acid, and the resulting product can be cyclized with sodium acetate and acetic anhydride. It should be



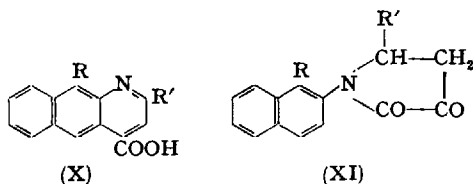
possible to obtain the angular isomer by the proper choice of starting material. In these examples the cyclization can proceed in one way only, and there can be little doubt as to the structure of the product.

The second type of reaction, including such syntheses as the Skraup, Doebner-Miller, Combes, Knorr, and Conrad-Limpach, can proceed in two different ways to give either an angular or a linear product. Thus, a problem of structure arises; while the nature of the product or products obtained has been established in many cases, instances are still recorded in which the structure is in doubt. The use of ultraviolet absorption spectra is a valuable aid in the study of such problems.^{3,4}

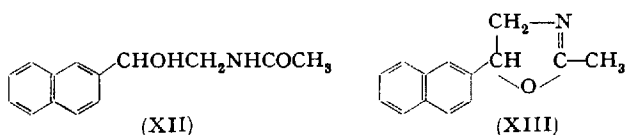
In general, the Skraup, Doebner-Miller, Knorr, and Conrad-Limpach syntheses, applied to 2-naphthylamine, lead predominantly to angular cyclization. A small amount of the linear product may be formed simultaneously. However, three of these syntheses (Skraup, p. 24; Knorr, p. 27; Conrad-Limpach, p. 26) will yield a linear product if the 1-position of the 2-naphthylamine ring is blocked by a chlorine or a methyl group (VIII). Some of the angular derivative may also be formed by the ejection of the blocking group.⁵⁻⁸ The 1-azaanthracene (IX) formed in these reactions is not isomeric with the normally formed 4-azaphenanthrene because it contains a substituent in the 9-position. Nevertheless, the syntheses that commonly produce angular derivatives lead in these cases to linear compounds.



The Doebner synthesis (an amine, aldehyde, and pyruvic acid) normally leads to an angular product, but when the 1-position is blocked in an attempt to effect linear cyclization, as X, a totally different type of reaction occurs, a pyrrolidine (XI) being formed.⁵



A reaction somewhat similar to this occurs when one attempts to cyclize 2-(2-acetamido-1-hydroxyethyl)naphthalene (XII). Neither an



azaphenanthrene nor an azaanthracene, but a 5- β -naphthyloxazoline (XIII) is formed.¹⁰

The Combes synthesis, which normally gives the linear isomer, can be modified to produce the angular product. The change is so marked that it bears little resemblance to the original Combes synthesis other than the use of 2-naphthylamine and an α,β -dicarbonyl compound. Concentrated sulfuric acid or hydrogen fluoride yield the abnormal, linear product,^{3,11,12} while hydrochloric acid, ethyl alcohol, and zinc chloride give the normal angular isomer.⁴ The blocking procedure, employed successfully in the Skraup synthesis, has not been useful in this case. The Schiff base from 2-amino-3-methylnaphthalene, for example, is hydrolyzed into its components under the conditions of the reaction before cyclization to the 4-azaphenanthrene derivative can be effected.^{9,13} It is possible that under nonhydrolytic conditions (*e.g.*, by heating in Dowtherm) this reaction may take place.

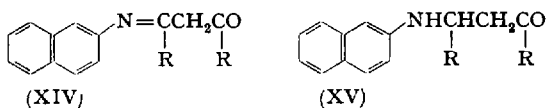
It is of interest that the Skraup reaction and each of the variations of the Doebner-Miller reaction has a Combes reaction as its counterpart. The former type proceeds by the primary addition of the amine to α,β -unsaturated ketones (or aldehydes), the latter by the formation of

a Schiff base from 1,3-diketones (or aldehydes). In the accompanying table the relationship of the two types of active groups that react with 2-naphthylamine is shown. All of these reactions, except that of

<i>Skraup or Doebner-Miller</i>		<i>Combes</i>
Starting product	Reactive intermediate	
$\text{CH}_2\text{OHCHOHCH}_2\text{OH}$	$\text{CH}_2=\text{CHCHO}$	OHCCH_2CHO
CH_3CHO	$\text{CH}_3\text{CH}=\text{CHCHO}$	$\text{CH}_3\text{COCH}_2\text{CHO}$
$\text{CH}_3\text{CHO} + (\text{CH}_3)_2\text{CO}$	$\text{CH}_3\text{CH}=\text{CHCOCH}_3$	$\text{CH}_3\text{COCH}_2\text{COCH}_3$
$\text{CH}_3\text{OCH}_2\text{CH}_2\text{COCH}_3$	$\text{CH}_2=\text{CHCOCH}_3$	$\text{OHCCH}_2\text{COCH}_3$

malonic dialdehyde with 2-naphthylamine, have been reported. It is possible that this aldehyde may produce 1-azaanthracene, which has been difficult to procure by other procedures.

A comparison of the primary product from 2-naphthylamine and an α,β -unsaturated ketone with that from the corresponding diketone points up the difference in structure that is presumably the cause for angular cyclization in one case and linear in the other. The Schiff base (XIV) gives the linear product while its reduced form (XV) gives the

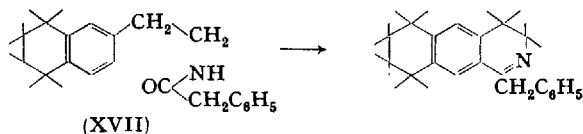


angular. A possible mechanism for the anomolous, linear ring closure is discussed on p. 10.

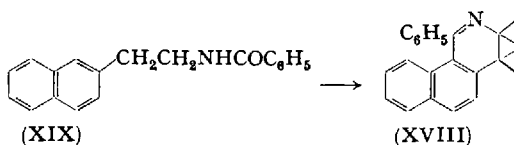
In addition to the blocking effect and the influence of substituents in the side chain in determining the course of the reaction, there is another feature that has an effect. This is concerned with the type of ring structure that is fused to the aromatic amine. In the case of 2-naphthylamine, of course, it is a benzene ring. If the latter is reduced, *i.e.*, as in 6-aminotetralin, application of the Skraup synthesis leads to a mixture of angular and linear products with the latter predominating.¹⁴ Since 2-naphthylamine gives only an angular product with the Skraup synthesis, it is apparent that the disposition of electrons is

modified in the reduced form in such a way that linear cyclization is favored.

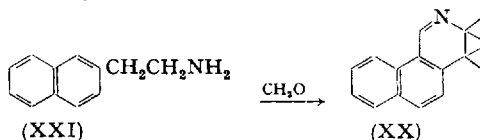
This effect is again demonstrated in the application of the Bischler-Napieralski reaction to *N*-(β -6-tetralylethyl)phenylacetamide (XVII).



Here, cyclization is exclusively linear.¹⁵ On the other hand, it is probable that only the angular product (XVIII) is formed from 2-(β -benzamidoethyl)naphthalene (XIX),¹⁵ analogous to the synthesis of 1,2,3,4-tetra-

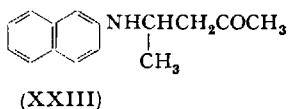
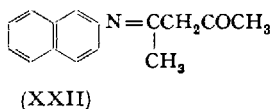


hydro-2-azaphenanthrene (XX) from 2-(β -aminoethyl)naphthalene (XXI) and formaldehyde.¹⁶



It is obvious, therefore, that the type of product obtained cannot be predicted solely from the type of reaction used to effect the cyclization. Consideration must be given to the atoms carried in the molecule, especially with respect to their activating or deactivating influence on the 1- or 3-position.

One other problem in connection with these two types of syntheses is worthy of attention. This arises from the fact that the cyclization of a Schiff base (XXII) to a substituted 1-azaanthracene requires no



oxidizing agent, while an oxidizing agent is required to procure an azaphenanthrene from the saturated compound (XXIII). Since the latter can be considered as a dihydro derivative of the Schiff base, it is obvious that cyclization must precede the oxidation, otherwise a linear and not an angular product would be expected. The use of an oxidizing agent is standard practice in the Skraup reaction, but, until recently, the use of an oxidizing agent in the Doebner-Miller reaction was rarely, if ever, reported. It has been established that the Doebner reaction yields a dihydro and a tetrahydro compound in addition to the fully aromaticized product. It is possible that the initially formed dihydro derivative disproportionates to give the aromatic compound and its tetrahydro derivative.¹⁷⁻²⁰ It seems more likely that the intermediate anil acts as the hydrogen acceptor, because increasing the proportion of anil increases the yield of the 4-azaphenanthrene derivative.^{21,22} There appears to be no instance recorded in which the addition of an oxidizing agent has been effective in increasing the yield in the Doebner reaction. On the other hand, investigations on oxidizing agents in the Doebner-Miller reaction have shown that some oxidizing agents, particularly ferric chloride and *m*-nitrobenzenesulfonic acid (Ludigol), raise the yield of product substantially.²³⁻²⁵

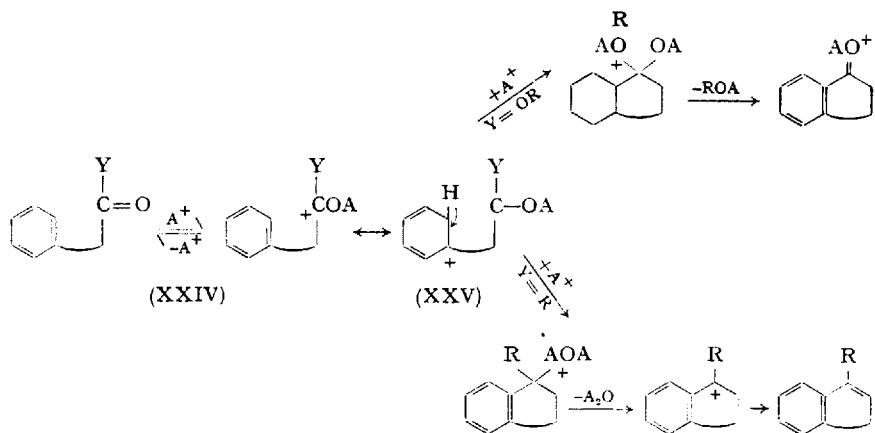
Mechanism of Ring Closure*

The most common syntheses of heterocyclic compounds involve ring closure. Frequently such syntheses or cyclizations which lead to heterocyclic substances are special cases of acylation. Such cyclization seldom occurs exclusively in only one of the two possible ways, but in most instances only one type of product can be isolated. A satisfactory mechanism must embrace all the facts concerning such acylations in both carbocyclic and heterocyclic series.

The cyclization of certain aromatic aldehydes, ketones, acids, and esters, by means of acidic reagents, to form polynuclear compounds can be considered as an intramolecular acid-catalyzed condensation in

* This section was written by G. A. Reynolds of the Kodak Research Laboratories.

which the aromatic nucleus acts as the electron donor and the carbonyl group as the acceptor. A general mechanism may be written as follows:



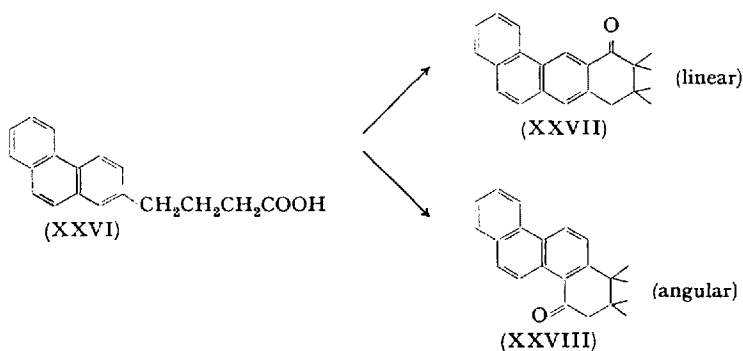
The acidic reagent greatly increases the electrophilic (+) character of the carbonyl group, as shown in XXIV. This positive center causes a polarization of the double bond in the aromatic nucleus, which results in the formation of the resonance contributor, XXV. The latter loses a proton to restore the aromatic system along with the elimination of ROA or A_2O . This scheme of representation is similar to the one that has been proposed for the Friedel-Crafts acylation²⁶ in that a carbonium ion is formed by an acidic reagent followed by the attack of this positively charged species upon the aromatic nucleus. Actually, acids and esters can often be cyclized without the use of acidic reagents simply by heating. A similar mechanism applies, but the positive center is furnished only by the carbonyl group, since there is no acid present to form the complex XXIV. As would be expected, the reaction takes place at a lower temperature and usually gives better yields in the presence of the acidic reagent; the latter is essential when aldehydes and ketones are employed, since its use facilitates elimination and avoids reversal of the reaction.

It is clear from the mechanism outlined that cyclization of carbonyl compounds must take place at one of the positions ortho to the side chain. Frequently but one substance results because (1) the two positions are equivalent, (2) one of the positions is blocked by a sub-

stituent in the aromatic part of the molecule, or (3) because one position is much more reactive than the other. In some instances a mixture results owing to ring closure at both positions; occasionally the cyclization can be controlled by a choice of the acidic reagents.

While no ambiguity arises with unsubstituted benzene, naphthalene may react at one of two positions giving rise to either a linear or an angular tricyclic system. A β -naphthylbutyric acid, for instance, might cyclize through the adjacent 3-position to give a linear structure, or through the adjacent 1-position to form an angular compound. The 1-position possesses a somewhat greater electron density, but it is, at the same time, subject to a slightly greater degree of hindrance due to the adjacent ring. Actually, β -naphthylbutyric acids always cyclize at the active 1-position to give angular products except in cases in which the 1-position is blocked or a substituent in the 8-position sterically hinders cyclization at the 1-position.³⁰

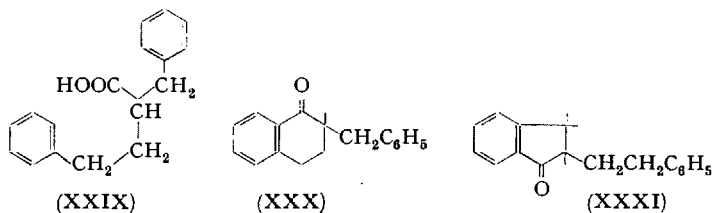
The cyclization of 4-(2-phenanthryl)butyric acid, XXVI, leads to a mixture of the linear XXVII and angular XXVIII products, the proportions depending on the method used for cyclization.²⁷ This is not



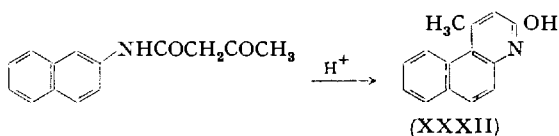
unexpected since acylation of phenanthrene by the Friedel-Crafts procedure gives mixtures of 1-, 2-, and 3-acylphenanthrenes. However, a completely satisfactory explanation for the relation between cyclization products and acidic reagents cannot be proposed at this time.

Other factors that are of importance in the cyclization of carbocyclics are the size of the ring formed and activation by substituents.²⁸ If the side chain can cyclize to form rings of different sizes, the tendency

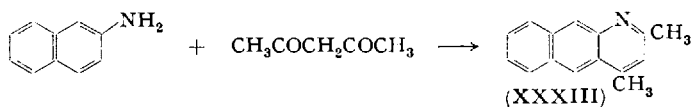
is to form rings of the following sizes: six > five > seven > others. This is illustrated by the cyclization of 1,4-diphenyl-2-carboxybutane, XXIX, to 2-benzyl-1-tetralone, XXX, rather than to the isomeric 2-(2-phenylethyl)-1-indanone, XXXI.



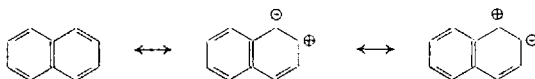
Cyclization of β -naphthylamine derivatives takes place almost exclusively in the 1-position to give angular products as shown by the formation of XXXII. This is similar to the result obtained with



4-(2-naphthyl)butyric acid, and is not surprising, since the greater reactivity of the 1-position of naphthalene with electrophilic reagents is well known. The Combes synthesis with β -naphthylamine presents an anomaly in that cyclization occurs at the normally inactive 3-position to give a linear product, XXXIII. However, a consideration of the

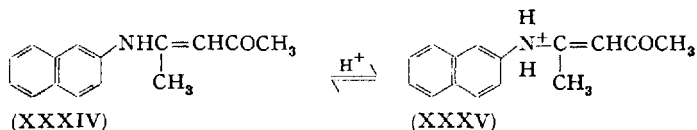


important resonance contributors of naphthalene shows that both the 1- and 2-positions are open to electrophilic attack. This being the case, it becomes necessary to explain why angular cyclization is usual and

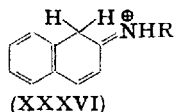


linear cyclization the exception. Johnson *et al.*⁴ suggest that the linear cyclization is due to the deactivating influence of the side chain in the

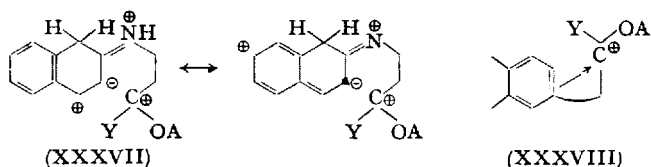
presence of acid, which would be expected to affect the more active 1-position to a greater extent. Huisgen¹³ goes a step further and states that this deactivating influence is caused by salt formation of the intermediate anil, XXXIV. The salt, XXXV, would be expected to exert a deactivating influence on the 1-position because a tautomer of



the type XXXVI would block reaction at the 1-position. Therefore the

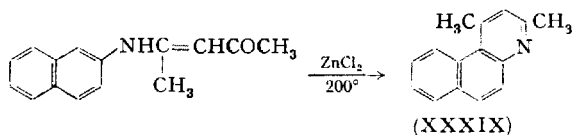


cyclization is forced to take place at the 3-position through a contributor such as XXXVII, formed through the polarization of the double bond



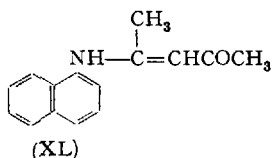
on the approach of the carbonyl-acid complex as shown in XXXVIII.

An interrelation between the salt formation and deactivation of the 1-position is shown by carrying out the cyclization with acidic reagents that do not form salts with the amino ketones. For example, the use of zinc chloride as the acidic reagent causes cyclization in the normal manner at the 1-position to give XXXIX without detectable



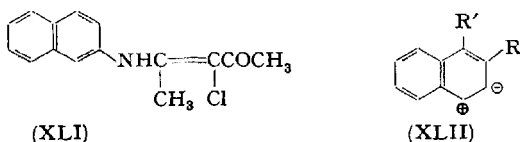
formation of any of the linear product (XXXIII). The importance of the salt in inhibiting the cyclization at the active center is em-

phasized by a consideration of the product from 1-naphthylamine, XL. This compound is recovered unchanged on treatment with hydrogen fluoride; the salt formation deactivates or blocks the cyclization



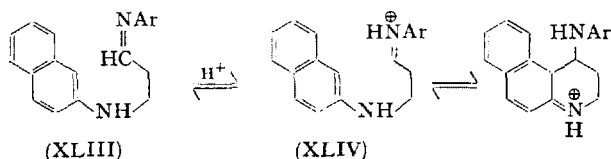
at the 2-position, and there is no alternative position for cyclization as there is in the case of the β -naphthylamine derivatives.

The basicity of the nitrogen atom at which the salt formation takes place seems to be quite important. The basicity of this nitrogen atom is small because it is conjugated with both an aromatic nucleus and a carbonyl group (see XXXIV). It might be expected that any further decrease in its basicity could cause it to lose the power to form salts, and the intermediates would then cyclize at the 1-position. If another electron-attracting group is added to the side chain, the basicity of the nitrogen atom should be decreased below the salt-forming level. This is found to be true in the case of XLI, and this intermediate is

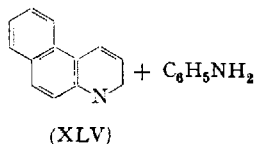


cyclized with sulfuric acid at the 1-position. Where the 1-position is blocked by a substituent, then, as is usually the case, the cyclization at the 3-position takes place through resonance contributors such as XLII.

The most familiar of all ring closures, the Skraup reaction, always gives the angular product. While superficially it appears to resemble some of the ring closures already considered, actually, it differs in that



the reaction proceeds by way of an intermediate anil (XLIII), which on ring closure and elimination of aniline gives XLV.



Anilino anils such as XLIV are also intermediates in the König quinoline synthesis,²⁹ and when the Combes reaction intermediates (XXXIV) are cyclized by heating with aromatic amines and zinc chloride in alcoholic solution⁴ angular cyclization always takes place because protonation of the active 1-position does not occur.

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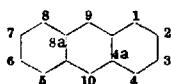
CHAPTER I

Azaanthracenes

By C. V. WILSON

1. Monoazaanthracenes

Azaanthracenes, as the name implies, are azalogs of anthracene. As such, they possess the linear skeleton of anthracene in which one or more —CH= is replaced by nitrogen. The orientation and numbering employed for this group of nitrogen heterocycles conform to anthracene. The aza system of nomenclature, being the simplest and most direct system available, is used throughout. It will be obvious that



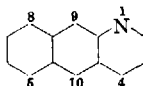
azaanthracenes containing from one to fourteen nitrogen atoms are possible, although many of them may be incapable of existence. Acridine (9-azaanthracene), phenazine (9,10-diazaanthracene), and alloxazine (1,3,9,10-tetrazaanthracene) will not be included in this survey because they will be considered in detail elsewhere.* Substances in which nitrogen is common to two rings will not be considered, since all such substances will be treated as a unit at some later date.*

Aside from the exceptions noted above, aza- and polyazaanthracenes of twenty-nine different parent compounds have been reported. These include the two monoazaanthracenes, nine diaza, seven triaza, seven tetraza, one pentaza, and three hexazaanthracenes. In cases in which the structure is in doubt, this is pointed out. If the

* The chemistry of these substances will be considered in forthcoming books of this series.

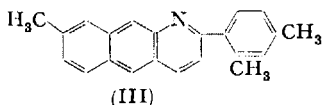
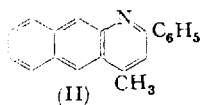
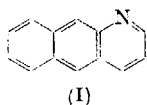
structure is definitely wrong, and angular cyclization is known to take place, reference is made to the proper section on angular azatricyclic systems.

- A. 1-Azaanthracene. 6,7-Benzo[g]quinoline, α -Azaanthracene. α -Anthrapyridine. 6,7-Benzoquinoline. Naphthazine. Naphtho-2',3',2,3-pyridine. R.I. 1971



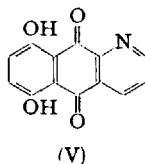
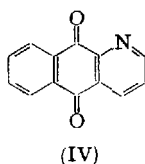
(I) Nomenclature

1-Azaanthracene (I) and its derivatives are described in the literature under a variety of names. The parent compound, originally called α -anthrapyridine¹ was subsequently named 6,7-benzoquinoline² and still later α -azaanthracene.³ The substance is listed in *Chemical Abstracts* as " α -anthrapyridine; see 6,7-benzoquinoline" up to 1936. Since then it has been listed as 6,7-benzo[g]quinoline. To confuse matters further, the substituted compounds, II⁴ and III,⁵ have been named 4-methyl-2-phenylnaphthoquinoline and 7-methyl-1-xylyl-benzoquinoline, respectively. While *The Ring Index* lists 6,7-benzo[g]-



quinoline as the preferred name, it also gives two other possible names; naphtho-2',3',2,3-pyridine and naphthazine.

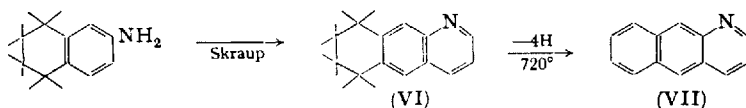
The quinone (IV) of 1-azaanthracene also has appeared under a variety of names, of which the oldest is α -anthrapyridinequinone.¹ It has been called pyranthraquinone and 2,3-phthaloylpyridine,⁶ while the dihydroxy derivative (V) has been given the name α -pyrquinizarin.⁷ *Chemical Abstracts* lists IV as 6,7-benzoquinoline-5,10-dione through



1936; since then it has been called 6,7-benzo[*g*]quinoline-5,10-dione, while V is 6,7-benzo[*g*]quinoline-6,9-dihydroxy-5,10-dione.

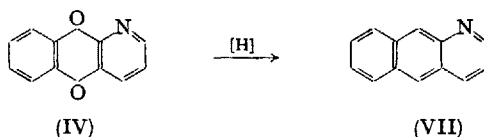
(2) *Synthesis of 1-Azaanthracene*

(a) From 6-Aminotetralin. 1-Azaanthracene (VII) probably is best prepared by subjecting 6-aminotetralin to a Skraup synthesis.² The mixture of two bases obtained is separated by fractional crystallization of the picrates. The linear base, 5,6,7,8-tetrahydro-1-azaanthracene (VI), is obtained in the greater amount (*ca.* 35 %). The angular



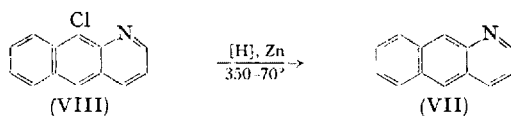
base is obtained in about 20% yield. By dehydrogenation over litharge in an electric oven at 720°, 1-azaanthracene (VII) is formed in 70% yield. Dehydrogenation with palladized charcoal in diphenyl ether gives a 15% yield; sulfur, iodine, and chloranil are not effective.³⁰

(b) From 1-Azaanthraquinone. The difficult separation of the mixture of linear and angular isomers can be avoided by first preparing 1-azaanthraquinone (IV) (see p. 43) and reducing it with zinc, zinc chloride, and sodium chloride^{8a} by Clar's procedure.⁹ The yield is said to be 53%. The value of the process depends upon the ease with which 1-azaanthraquinone can be obtained (see p. 45). It is limited by the size of the batch that can be handled conveniently. Reduction of the

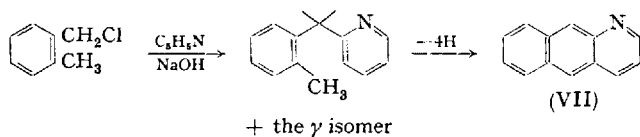


quinone with zinc was the method used in first isolating the compound,¹ but apparently the product was very impure and did not agree in properties with the compound prepared by other methods.^{2,3} Application of Clar's procedure to 9-chloro-1-azaanthracene (VIII) results in a 20% yield of the required product.^{8d}

(c) From 9-Chloro-1-azaanthracene. The simplest process is to dehalogenate 9-chloro-1-azaanthracene (VIII) (p. 24) by means of zinc and hydrogen. The process is carried out by passing a current of hydrogen through a tube containing an intimate mixture of 9-chloro-1-azaanthracene and zinc at a temperature of 350–70°; yields of 45–50 % are obtained.^{8b} Again the process is limited, for only 0.5–1 g. can be used without seriously diminishing the yield. 9-Chloro-1,2,3,4-tetrahydro-1-azaanthracene also can be converted to VII by this procedure.^{8c}



(d) From *o*-Xylyl Chloride and Pyridine. Another method consists of dehydrogenation of the mixture of bases obtained by the reaction of *o*-xylyl chloride with pyridine.³ The α - and β -azaanthracenes thus formed are separated through their picrates. The yield is poor; only 5 % of the cyclized mixture is the α -compound.^{8c} Since the cyclization takes place to an extent of only 30–40 %, the method is of little value.

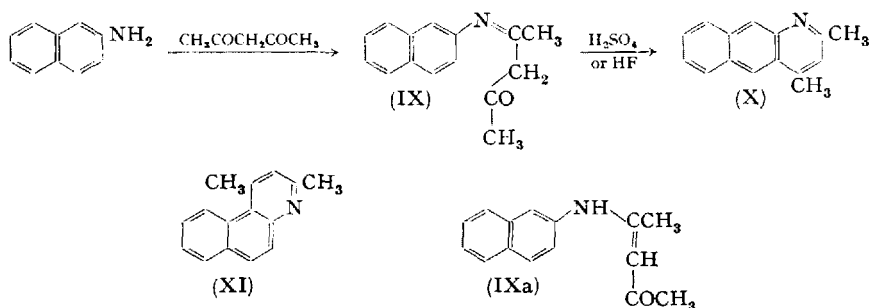


(e) From 2,4-Dicarboxy-1-azaanthracene. 1-Azaanthracene has been secured recently⁴⁸ by decarboxylation of 2,4-dicarboxy-1-azaanthracene, the preparation of which involves the use of the Pfitzinger reaction (see p. 28). Yields of substances produced by this decarboxylation procedure are said to vary between 45 and 60 %, but the specific yield of 1-azaanthracene is not recorded. If it is as high as indicated, this may be the best method for the preparation of the parent compound.

Proof of Structure. The proof that 1-azaanthracene possesses the linear configuration follows from the synthesis of 1-azaanthraquinone from quinolinic acid (section 6 following); the product thus formed is identical with that formed by oxidation of 1-azaanthracene.

(3) Substituted 1-Azaanthracenes

(a) By Ring Closure. *Combes Synthesis.* The Combes synthesis is the best procedure available for the preparation of substituted 1-azaanthracenes. In general, this synthesis involves the condensation of a 1,3-diketone with an arylamine followed by cyclization of the anil thus formed. When the anil (IX) from β -naphthylamine and acetylacetone is cyclized with sulfuric acid, the linear product, 2,4-dimethyl-1-azaanthracene (X), is formed in excellent yield.^{12,13,29,37} It is remarkable that in this synthesis cyclization is effected in the normally



unreactive β -position, though a small yield of the angular isomer (XI) is formed simultaneously. Theories to account for this anomalous behaviour have been advanced by Johnson and Mathews¹³ and by Huisgen³⁷ (see Introduction). The latter author prefers the structure IXa for the anil because oxidation with potassium permanganate in acetone solution results in the formation of 2-acetamidonaphthalene.

Originally,¹² 2,4-dimethyl-1-azaanthracene (X) was obtained in 91% yield as the monosulfonic acid by treating the Schiff base (IX) with concentrated sulfuric acid at 100° for 0.5 hour. Desulfonation with dilute sulfuric acid at 220° gave the base. The isomeric base (XI) was formed to the extent of only 4% (see p. 225). More recently¹³ it has been shown that a slight change in reaction conditions (sulfuric acid for two minutes below 60°) gives an 83% yield of the base directly, while cyclization with hydrogen fluoride raises the yield to 96%. Other changes in operating conditions^{29,37} have further simplified the process so that excellent yields are obtained by using 90% sulfuric

acid below 60° ²⁹ or concentrated sulfuric acid at 0° ³⁷. In the former case a 76% yield is recorded while the low-temperature procedure is said to produce a 90% yield.

When Combes¹² originally made this base, he gave it the *angular structure* (XI), in accordance with the Skraup and Doebner-Miller types of syntheses. However, the latter synthesis (paraldehyde, acetone, and β -naphthylamine) yielded a compound which, although quite different in properties, was given the same structure.¹⁴ Assignment of the linear configuration to the compound obtained by Combes is, therefore, contingent upon the following evidence:¹³

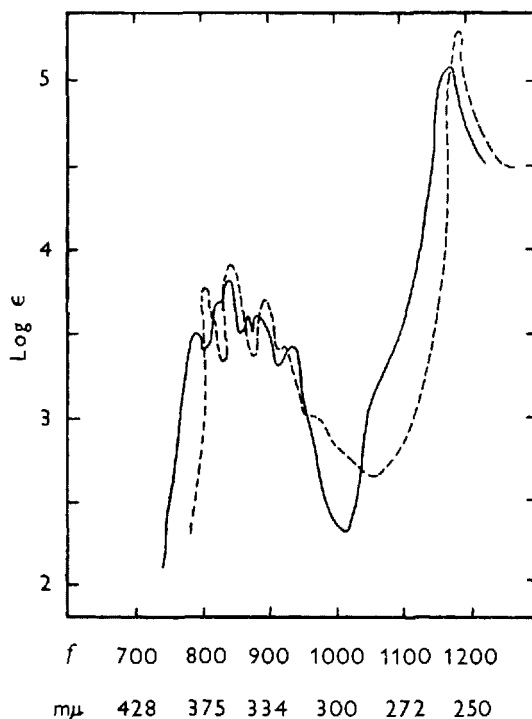


Fig. I-1. — 2,4-Dimethyl-1-azaanthracene (X); ---- anthracene.

1. Oxidation of the compound results in the formation of a quinone which gives a purple vat with alkaline hydrosulfite, and which, on further oxidation with acid permanganate, gives phthalic acid. 1-

Azaanthraquinone, the structure of which has been determined, reacts toward hydrosulfite and acid permanganate in the same manner.

2. A study of the absorption spectra shows that the substance **X** is similar to anthracene (Fig. I-1), while the higher melting isomer, **XI**,

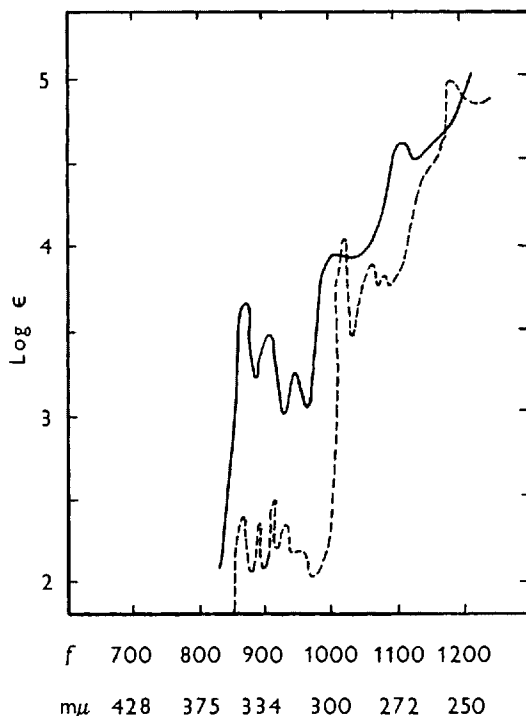


Fig. I-2. — 1,3-Dimethyl-4-azaphenanthrene (**XI**); ---- phenanthrene.

resembles phenanthrene (Fig. I-2). In addition, the absorption spectrum of **XI** has its principal maxima at wave lengths almost identical to those of 4-azaphenanthrene (benzo[*f*]quinoline) of known structure (Fig. I-3).

3. A homolog, 2,4,9-trimethyl-1-azaanthracene (**XIII**), prepared by the same general procedure (p. 21) is oxidized to the same quinone as **X**. Since only linear cyclization is possible in the preparation of the former (unless the α -methyl group is removed in the reaction; see p. 24), and since the same quinone is obtained on oxidation, the linear configuration of both compounds is established. Such an oxidation is normal for compounds substituted in the meso position with methyl or

chlorine (p. 46), and is similar to the oxidation of meso alkyl anthracenes to anthraquinone.

2,4,9-Trimethyl-1-azaanthracene, XIII, mentioned above in connection with 2,4-dimethyl-1-azaanthracene, is formed in 96 % yield by

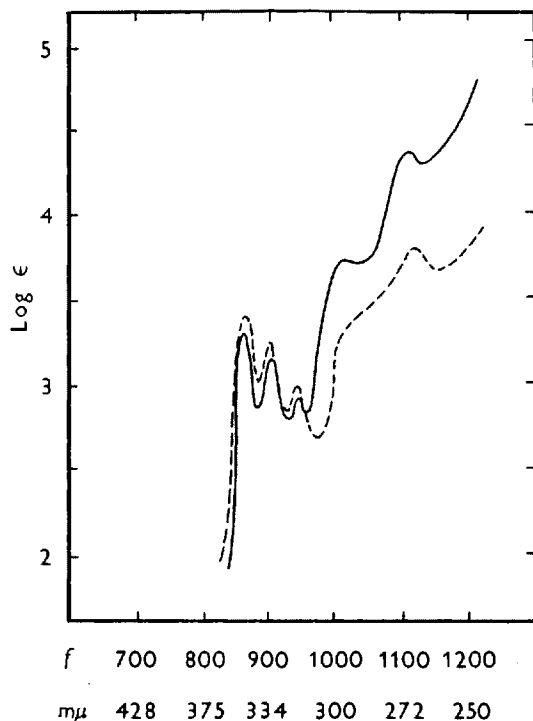
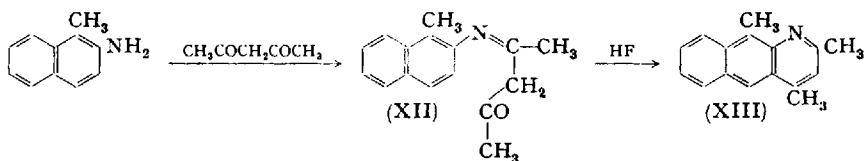


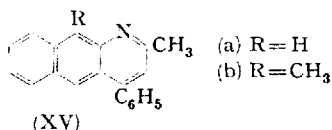
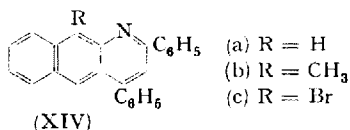
Fig. I-3. — 1,3-Dimethyl-4-azaphenanthrene (XI); --- 4-azaphenanthrene.

cyclization of the anil, XII, from 1-methyl-2-naphthylamine and acetylacetone by the hydrogen fluoride procedure,¹³ or in 90% yield by treatment with sulfuric acid at 0°C.³⁷ A sulfonic acid is formed when

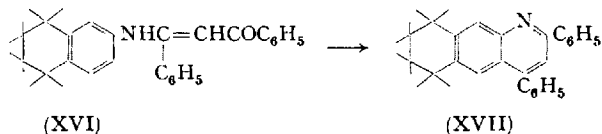


the original Combes procedure is applied. Proof of the structure of this compound has already been given above.

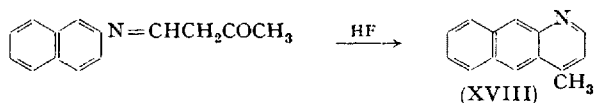
An extension of this reaction has been used³⁷ to produce 2,4-diphenyl-1-azaanthracene (XIVa) and its 9-methyl derivative (XIVb) as well as 2-methyl-4-phenyl-1-azaanthracene (XVa) and its 9-methyl



derivative (XVb). By a similar procedure,³⁷ the Schiff base (XVI) from 6-aminotetralin and dibenzoylmethane gives 2,4-diphenyl-5,6,7,8-tetrahydro-1-azaanthracene (XVII); this compound can be dehydrogenated to XIVa. Cyclization of the Schiff base from β -naphthylamine

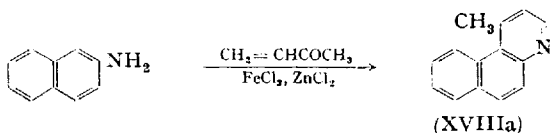


and formyl acetone with hydrogen fluoride (100° for six hours) is reported³² to give a 43% yield of 4-methyl-1-azaanthracene (XVIII). This product forms a yellow hydrochloride and has an absorption spectrum characteristic of the 1-azaanthracenes. Its isolation from the



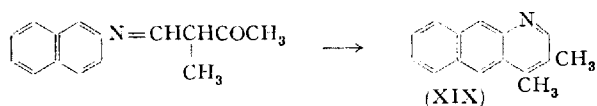
reaction mixture requires the use of the chromatographic absorption technique.

In this connection it is interesting to note that β -naphthylamine and methyl vinyl ketone (or its equivalent), when treated with ferric chloride and zinc chloride in alcohol, produce a benzolepidine⁴⁰ of melting point 95–98°. Though the substance is not further identified, this melting point indicates angular cyclization, for the recorded melting



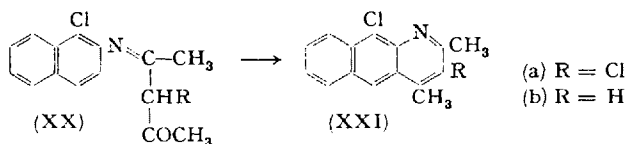
point of 1-methyl-4-azaphenanthrene (XVIIIa) is 100° (see p. 256), while the linear product melts at 84–85°. It has already been noted that the Schiff base (IX) from 2-naphthylamine and acetylacetone is cyclized to the linear product almost exclusively with hydrogen fluoride.¹³ Nevertheless, the angular product (XI) can be obtained, though in poor yield, by the use of zinc chloride in alcohol.³²

The anil from 2-naphthylamine and 2-methyl-1,3-butanedione is cyclized with hydrogen fluoride to 3,4-dimethyl-1-azaanthracene (XIX)



in 80% yield.³² (Compare p. 11.) The operating conditions are somewhat more drastic (higher temperature and under pressure) than for the isomeric 2,4-dimethyl compound.

A number of alkyl-1-azaanthracenes containing substituent halogen atoms have been prepared by this synthesis. Thus, the Schiff base (XX, R = Cl) from 1-chloro-2-naphthylamine and 3-chloro-acetylacetone is cyclized by 90% sulfuric acid to 3,9-dichloro-2,4-dimethyl-1-azaanthracene (XXIa), in substantially good yield.²⁹ By

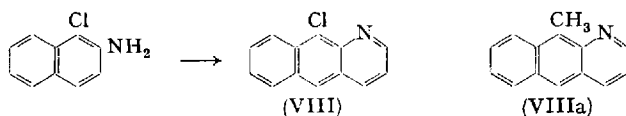


way of contrast, the corresponding anil from the nonchlorinated amine and the chlorodiketone gives an angular product²⁹ (see p. 226). Since the anil from the simple ketone (acetylacetone) gives a linear product almost exclusively, it is apparent that the chlorine atom in the aliphatic chain of the anil has a marked effect on the cyclization (see Introduction). 9-Chloro-2,4-dimethyl-1-azaanthracene (XXIb) is secured by cyclization of the anil from 1-chloro-2-naphthylamine and acetyl-



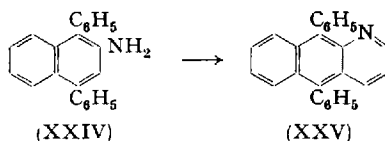
acetone, while 6-bromo-9-chloro-2,4-dimethyl-1-azaanthracene (XXII) results from the diketone and 6-bromo-1-chloro-2-naphthylamine.²⁹ Cyclization of the anils from 5-, 6-, and 8-chloro-2-naphthylamines and acetylacetone with 90% sulfuric acid also gives good yields of linear products (XXIII, R = 5-, 6-, or 8-Cl).²⁹

Skraup Synthesis. While an angular product is formed exclusively when the Skraup synthesis is applied to 2-naphthylamine, it is possible to secure linear cyclization by blocking the 1-position. Thus, 9-chloro-1-azaanthracene (VIII) is obtained in 25–44% yield from 1-chloro-2-naphthylamine.^{8f, 11, 21, 33} There is some loss of chlorine under the con-



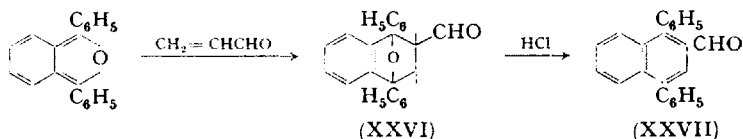
ditions of the reaction and a simultaneous formation of the angular compound. It has been shown that 1-bromo- and 1-nitro-2-naphthylamines give predominantly angular products when subjected to the Skraup reaction¹⁵; however, in line with the linear cyclization described above, 1-methyl-2-naphthylamine^{11, 34} gives a 30% yield of the linear compound (VIIIa). The reaction is said to proceed¹¹ in this manner when the 1-position is substituted with ethyl, benzyl, naphthyl, phenyl, or benzoyl. Marckwald³⁸ was apparently in error when he stated that a 1-substituent blocked the reaction.³⁹

Application of the Skraup synthesis to 1,4-diphenyl-2-naphthylamine (XXIV) results in a 40% yield of 9,10-diphenyl-1-azaanthracene (diphenylantrapyridine) (XXV).^{8g} The naphthylamine derivative,

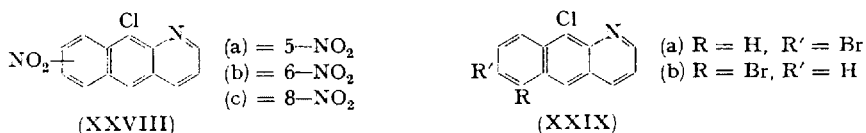


XXIV, is prepared as follows: The Diels-Alder adduct (XXVI) of acrolein and 1,3-diphenylisobenzofuran loses water when treated with cold hydrochloric acid to give 1,4-diphenyl-2-naphthaldehyde (XXVII); the latter is converted to the acid, and then by a Curtius degradation

to the required amine (XXIV).^{8b} Other syntheses of 9,10-diphenyl-1-azaanthracene are described on pp. 32-33.



Small yields of 5-, 6-, and 8-nitro-9-chloro-1-azaanthracenes (XXVIIIa, b, c) are obtained by application of the Skraup synthesis to the requisite nitro-1-chloro-2-naphthylamines.²¹ These syntheses, car-



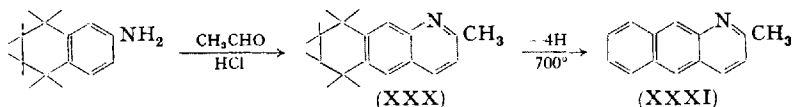
ried out by Gerhardt and Hamilton to establish the structure of the nitration products of 9-chloro-1-azaanthracene (p. 34), could not be confirmed by Clemo and Driver,³³ except in the case of the 6-nitro compound. In the other two cases angular cyclization resulted. In a similar manner^{11, 33} 5- and 6-bromo-1-chloro-2-naphthylamines give 5- and 6-bromo-9-chloro-1-azaanthracenes (XXIXa, b). No properties of the compounds are recorded other than their easy oxidation to 5- and 6-bromo-1-azaanthraquinone, respectively.

Skraup syntheses have been carried out also on 1,5- 1,6-, and 1,8-dichloro-2-naphthylamines,³¹ but the crude 1-azaanthracenes were oxidized directly to the 1-azaanthraquinones. In the case of the 1,8-dichloro compound no quinone was obtained and only the angular product could be isolated.

Doebner-Miller Synthesis. This synthesis, which essentially involves the use of α,β -unsaturated carbonyl compounds, or materials that can give rise to their formation, usually leads to angular cyclization. There are two instances recorded, however, in which the product formed is described as an azaanthracene.

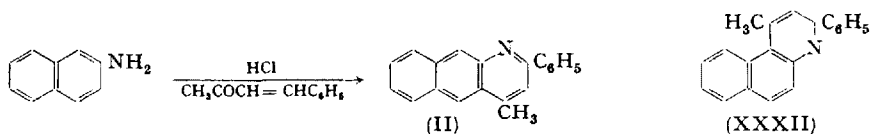
In one of these,¹⁰ 6-aminotetralin is treated with paraldehyde and hydrochloric acid to give a 35% yield of a mixture of two tetrahydro bases, which are separated through their picrates. The linear compound

(XXX) makes up only 35 % of the mixture; the remainder is the angular derivative (see p. 225). Dehydrogenation of the tetrahydro base yields 2-methyl-1-azaanthracene (XXXI), previously called α' -methyl- α -anthrapyridine or benzolo-6,7-quinaldine.¹⁰ Proof of the structure of



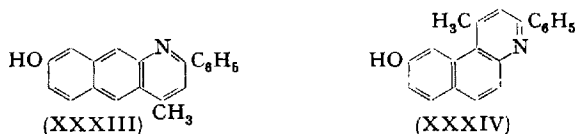
the linear compound is indirect; it follows from the fact that the dehydrogenated angular compound is identical with that obtained from 2-naphthylamine by a Doebner-Miller synthesis (see p. 224).

In the second instance, the product formed when benzalacetone reacts with β -naphthylamine hydrochloride is recorded as 2-phenyl-4-methyl-1-azaanthracene (2-phenyl-4-methylnaphthoquinoline) (II), though the angular structure (XXXII) is also mentioned as a possibility⁴; indeed, the latter seems more logical in view of the fact that



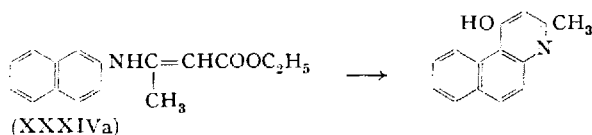
2-naphthylamine usually gives the angular derivative with the Skraup and Doebner-Miller syntheses (see pp. 217 and 223).

When applied to 2,7-aminonaphthol, this reaction gives a small yield (11 %) of a substance that is recorded⁴ as either the linear compound (XXXIII) or its angular isomer (XXXIV). Again the angular structure is preferred, but no proof has been given.



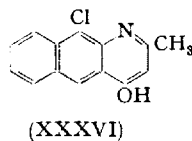
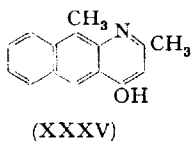
Conrad-Limpach Synthesis. Angular cyclization results when this synthesis is applied to 2-naphthylamine. The condensation product, XXXIVa, of the amine and ethyl acetoacetate is heated in liquid

paraffin or Dowtherm to bring about the ring closure (p. 230). The anil, XXXIVa, is formed from the amine and the ester at about 100°. At

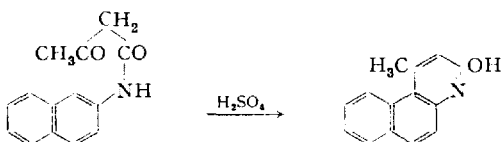


higher temperatures an amide is formed, which is the intermediate for the Knorr synthesis (see below).

Linear cyclization can be effected in this type of reaction if the 1-position of 2-naphthylamine is blocked. For example, the anil from 1-methyl-2-naphthylamine and ethyl acetoacetate is cyclized to 4-hydroxy-2,9-dimethyl-1-azaanthracene (XXXV) in good yield by heating in Dowtherm³⁴ to 280°. A similar reaction³⁰ with 1-chloro-2-naphthylamine yields 9-chloro-4-hydroxy-2-methyl-1-azaanthracene (XXXVI).

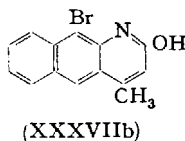
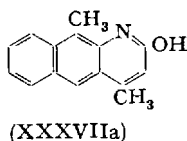


Knorr Synthesis. When 2-naphthylamine is heated to 160° in a five-fold amount of ethyl acetoacetate an amide, rather than the anil (XXXIVa) described above, is formed. Treatment of the amide with cold concentrated sulfuric acid results in the formation of 3-hydroxy-1-methyl-4-azaphenanthrene (see p. 229).

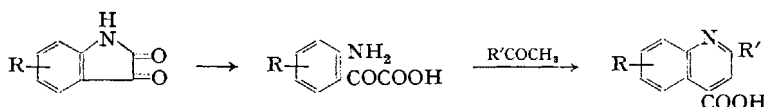


This synthesis is known as the Knorr carbostyryl synthesis. Normally an angular product is formed but linear cyclization can be effected if the 1-position of the amine is blocked. Good yields of 2-hydroxy-4,9-dimethyl-1-azaanthracene (XXXVIIa) and 9-bromo-2-hydroxy-4-methyl-1-azaanthracene (XXXVIIb) are obtained by

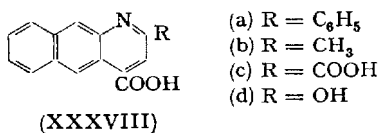
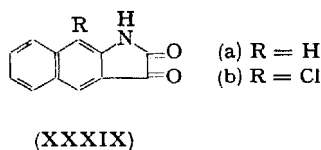
treatment of the properly substituted naphthylamine derivatives with cold sulfuric acid.³⁴



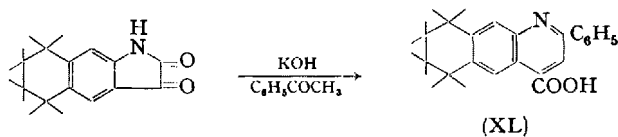
Pfitzinger Synthesis. The cyclization of isatin or substituted isatins with methyl ketones is known as the Pfitzinger reaction. Presumably the isatin ring opens and reacts in this form with the ketone, thus:



Application of this reaction to 5,6-benzisatin (XXXIXa), a substance which has been synthesized only recently,⁴⁷ leads to 4-carboxy-1-azaanthracenes in which the 2-position carries a substituent.⁴⁸ Thus,



acetophenone yields 4-carboxy-2-phenyl-1-azaanthracene (XXVIIIa). In a similar manner acetone and pyruvic acid give the corresponding 2-methyl and 2-carboxy derivatives (XXXVIIIb, c). 5,6,7,8-Tetrahydro-1-benz[*f*]indole-2,3-dione (5,6-cyclotetramethyleneisatin) and acetophenone in 33 % potassium hydroxide solution¹⁷ give the 5,6,7,8-tetrahydro derivative (XL). A variation (the Camps reaction) consists

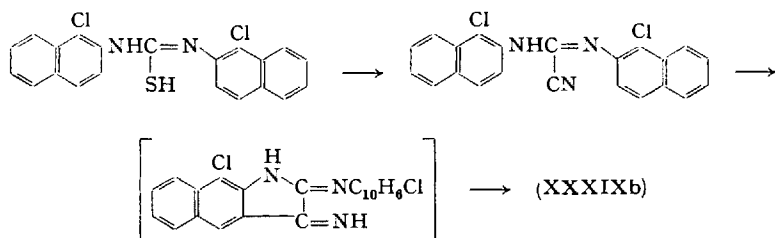


in treating 1-acetyl 5,6-benzisatin with alkali to produce the 2-hydroxy derivative (XXXVIIIId). These are yellow substances of high melting

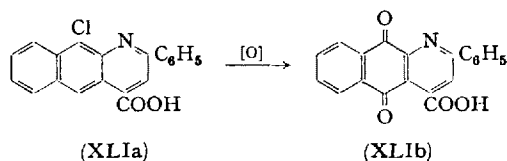
points; they are converted by oxidation to the corresponding 1-azaanthraquinones (p. 47).

This reaction has been used to prove the structure of 2-phenyl-1-azaanthracene, previously obtained by the action of phenylmagnesium bromide on 1-azaanthracene (p. 33). Although the Grignard reagent usually alkylates the 2-position of compounds of this type, it has been shown recently⁴³ that benzylmagnesium bromide and pyridine lead to 4-benzylpyridine. Hence, a proof of structure of 2-phenyl-1-azaanthracene was desirable.

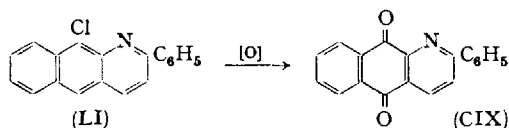
At the time this work was undertaken, the requisite intermediate, 5,6-benzisatin (XXXIXa), was unknown, but a suitable chlorine analog (XXXIXb) was available. This substance is formed by the following reactions:



The cyclization is effected with sodium aluminum chloride.^{42, 45} Treatment of the chlorobenzisatin (XXXIXb) with acetophenone under

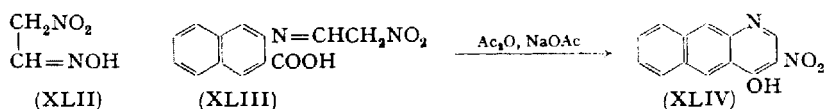


alkaline conditions gives 4-carboxy-9-chloro-2-phenyl-1-azaanthracene (XLIa). This substance is easily oxidized to the corresponding 1-aza-



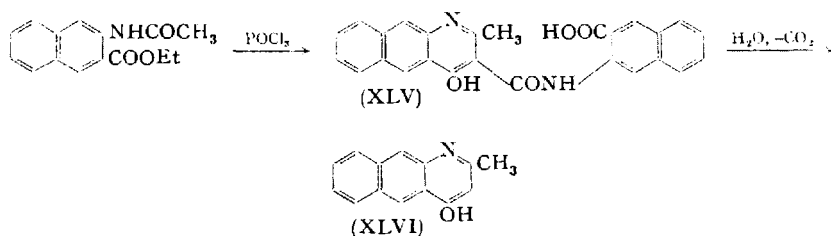
anthraquinone (XLIb). Decarboxylation of XLIa leads to 9-chloro-2-phenyl-1-azaanthracene (LI, p. 31), identical with the substance obtained by the reaction of phenylmagnesium bromide on 9-chloro-1-azaanthracene. The oxidation of 9-chloro-2-phenyl-1-azaanthracene (LI) from either source gives 2-phenyl-1-azaanthraquinone (CIX, see p. 47).

Miscellaneous Syntheses. There are a few syntheses that cannot be grouped under any of the foregoing procedures. The first of these involves the use of methazonic acid (XLII), a little known compound available from nitromethane. When this substance reacts with 2-amino-3-naphthoic acid, 2- β -nitroethylideneamino-3-naphthoic acid (XLIII) is formed. This material is cyclized by acetic anhydride and sodium



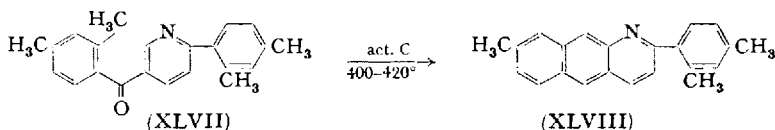
acetate to 4-hydroxy-3-nitro-1-azaanthracene (XLIV).^{22, 30} By a similar procedure 4-methyl-3-nitro-5,6,7,8-tetrahydro-1-azaanthracene can be synthesized.⁴¹ In this case, the ring closure is effected with dilute sodium hydroxide or activated alumina; the yield is excellent.

A second synthesis involves the cyclization of ethyl 3-acetamido-2-naphthoate by phosphoryl chloride. The intermediate cyclic compound (XLV) is simultaneously hydrolyzed and decarboxylated by heating to 210° with dilute sulfuric acid (1:1); 4-hydroxy-2-methyl-1-azaanthracene (XLVI) is formed in good yield.³⁰



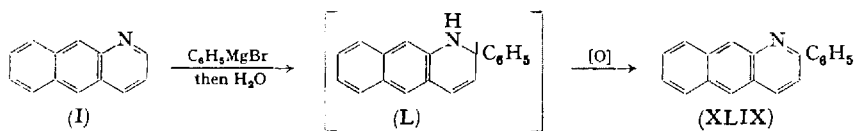
The vapor phase cyclization of 2-(2',4'-dimethylphenyl)-5-(2'',4''-dimethylbenzoyl)pyridine (2-*m*-xylyl-5-*m*-xyloylpyridine, XLVII) with

activated carbon as the catalyst to 2-(2',4'-dimethylphenyl)-7-methyl-1-azaanthracene (1-*m*-xylyl-7-methylbenzoquinoline, XLVIII) is recorded.⁵



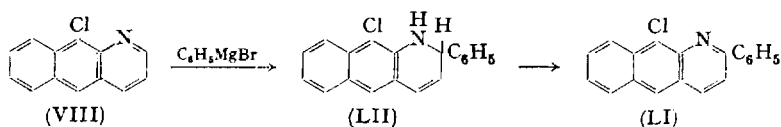
(b) By Direct Substitution. While the cyclization procedures just described are very useful reactions, products are also derived from the parent compound by substitution reactions such as alkylation, nitration, halogenation, and sulfonation, or by the alteration of other groups in the molecule.

(1) *Alkylation.* The action of phenylmagnesium bromide on 1-azaanthracene (I) gives 2-phenyl-1-azaanthracene (XLIX). No evidence of an intermediate dihydro compound (L) can be detected because dehydrogenation is so rapid. Nevertheless, the isolation of derivatives



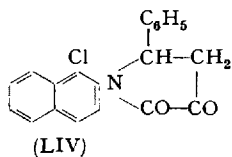
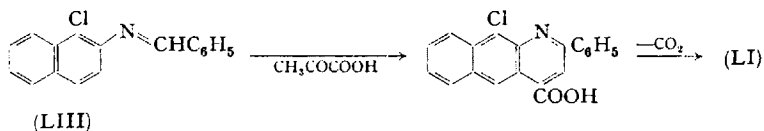
of a dihydro compound in a closely related case (see below) shows that the reaction proceeds through a preliminary 1,2-addition. Purified through its picrate, 2-phenyl-1-azaanthracene is obtained in a yield of 75%.⁸¹ Despite the good yield, the reaction is impractical because of the difficulty of obtaining 1-azaanthracene (I). Proof of the structure is derived from an unequivocal synthesis (see p. 29).

In a similar manner, treatment of 9-chloro-1-azaanthracene (VIII) with phenylmagnesium bromide in excess gives a mixture of 9-chloro-2-phenyl-1-azaanthracene (LI) and its dihydro derivative (LII). The

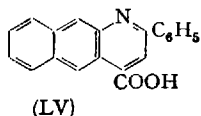


two compounds can be separated through fractional crystallization of the picrates. While the dihydro compound has not been obtained in a pure state, the secondary nature of the N-atom is clearly demonstrated by the formation of an acetyl derivative and a nitroso compound. By oxidation of the mixture obtained from the Grignard reaction with litharge, arsenic acid or quinone, respective yields of 60, 57, and 44 % of 9-chloro-2-phenyl-1-azaanthracene (LI) are obtained.^{8j}

An attempt to synthesize this substance by cyclization of 1-chloro-2-benzylidinenaphthylamine (LIII) with pyruvic acid followed by decarboxylation failed^{8k}; the original cyclization apparently follows a different course to give 1-(1-chloro-2-naphthyl)-2-phenyl-4,5-dioxo-pyrrolidine (LIV). Nevertheless, the tetrahydro derivative of the

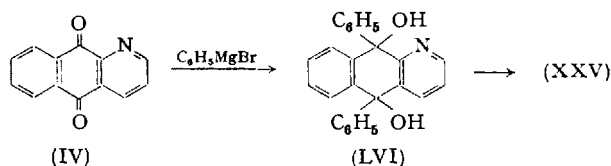


nonchlorinated homolog (XL) has been reported¹⁷ (see p. 28). The product from benzylidine- β -naphthylamine and oxalacetic ester originally formulated as LV,³⁵ is actually the angular compound.³⁶

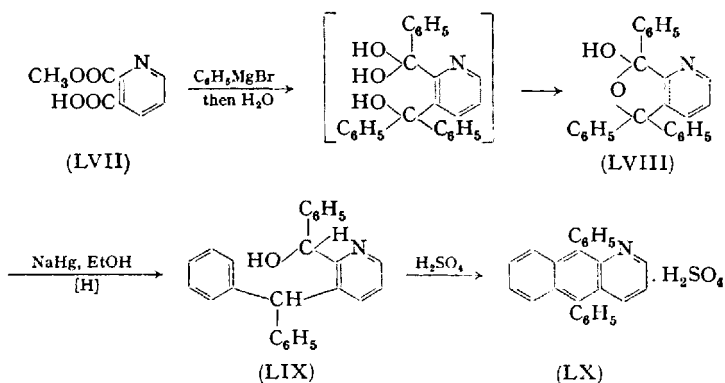


Meso-diphenyl-1-azaanthracene (XXV) obtained by a Skraup synthesis on 1,4-diphenyl-2-naphthylamine (see p. 24), can be obtained also by the action of six moles of phenylmagnesium bromide on 1-azaanthraquinone (IV) followed by reduction with potassium iodide and sodium hypophosphite. Here the yield is not good as two other

compounds are formed simultaneously. The intermediate quinol (LVI) is a well-defined compound.⁸¹



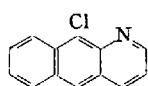
Another preparation of XXV that involves the use of the Grignard reagent is in need of confirmation. Phenylmagnesium bromide is allowed to react upon the half ester of quinolinic acid (LVII); decomposition of the Grignard complex results in the formation of triphenylhydroxypyridophthalane (LVIII). Treatment of the latter with sodium amalgam



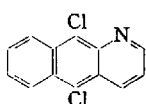
gives an impure product (LIX) which, when digested in benzene containing a little sulfuric acid, yields a small amount of 9,10-diphenyl-1-azaanthracene sulfate (LX).¹⁸ The free base, isolated by treatment with alkali, is purified by sublimation. However, this substance is not further characterized; no melting point is recorded, and no mention is made of the remarkable blue fluorescence of its solutions. A repetition of the experiment by Etienne^{8m} failed to produce any compound having the properties of 9,10-diphenyl-1-azaanthracene secured by other methods. As a consequence, this method of preparation must be viewed with reasonable doubt.

(2) *Halogenation.* Chlorination of 1-azaanthracene itself has not been described, but the 9-chloro compound (VIII) gives 9,10-dichloro-

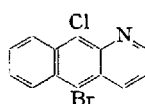
1-azaanthracene (LXI).^{8n, 11, 21, 33} The corresponding 10-bromo-9-chloro-1-azaanthracene (LXII) is formed by bromination in carbon tetrachloride.³³ Proof of the structure of these compounds lies in their ready oxidation to 1-azaanthraquinone. More vigorous bromination results in the formation of a dibromo derivative, the structure of which has not been established. Oxidation of this dibromo derivative gives a bromo-1-azaanthraquinone identical to the bromo derivative obtained by the direct bromination of 1-azaanthraquinone (p. 47).



(VIII)

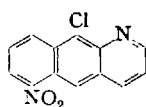


(LXI)

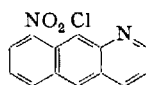


(LXII)

(3) *Nitration*. Nitration of the parent compound is not reported, no doubt because of its difficult accessibility. 9-Chloro-1-azaanthracene (VIII) yields a mixture of the 5-(LXIII) and 8-(LXIV) nitro derivatives (the former in the larger proportion²¹) when the nitration is carried out with concentrated nitric acid (sp.gr. 1.49) at -18° .

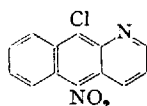


(LXIII)

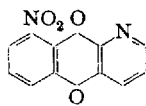


(LXIV)

Under entirely different nitrating conditions (in acetic acid at 100°), 9-chloro-10-nitro-1-azaanthracene (LXV) is formed in 70% yield³³; its orientation is established by its oxidation to 1-azaanthraquinone. The structures of the 5- and 8-nitro derivatives were established by



(LXV)



(LXVI)

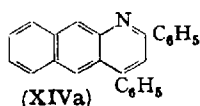
Skraup syntheses on the requisite chloronitronaphthylamines (see p. 49).

The nitration of 9-chloro-1-azaanthracene with boiling nitric acid

Azaanthracenes

gives a nitro-1-azaanthraquinone identical with the product obtained by nitrating 1-azaanthraquinone in sulfuric acid.³³ This is to be expected, as oxidation would probably precede nitration under these conditions. It has been shown³¹ that this product is 8-nitro-1-azaanthraquinone (LXVI, see reaction scheme I-1, p. 48).

(4) *Sulfonation*. The direct sulfonation of 1-azaanthracene has not been reported, but the 2,4-diphenyl derivative (XIVa) forms a mono-sulfonic acid³⁷; the position taken by the entering sulfonic acid group



has not been established. The only other sulfonation products of 1-azaanthracene that have been reported are those formed as intermediates^{12,13} in the Combes synthesis of 2,4-dimethyl- (X, p. 18) and 2,4,9-trimethyl-1-azaanthracene (XIII, p. 21). Here again, the orientation is unknown.

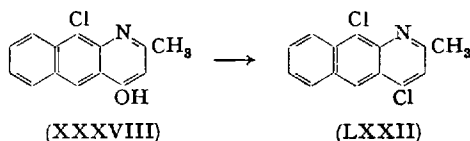
(c) **By Replacement or Alteration of Other Groups.** *OH* $\rightarrow$ *Cl*. In addition to the meso halogen derivatives obtained by other procedures, a number of chloro-substituted 1-azaanthracenes have been secured by treatment of the corresponding hydroxy compound with phosphoryl chloride (one hour at 125°). By this procedure 4-chloro-1-azaanthracene (LXVIII) is obtained from 4-hydroxy-1-azaanthracene (LXIX; see p. 38).³⁰ In a similar manner 4-chloro-2-methyl- and 4-chloro-3-nitro-1-azaanthracenes (LXX and LXXI) are secured from the corresponding



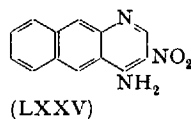
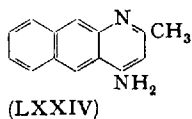
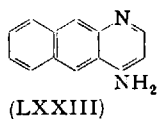
hydroxy derivatives.³⁰ The conversion of 9-chloro-4-hydroxy-2-methyl-1-azaanthracene (XXXVIII) to 4,9-dichloro-2-methyl-1-azaanthracene



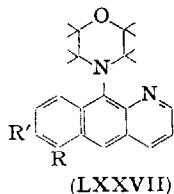
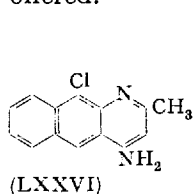
(LXXII) is also reported.³⁰ The replacement of a 2-hydroxyl group by chlorine has not been described, but probably it would replace as readily as the 4-hydroxyl group.



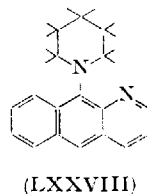
$Cl \rightarrow NH_2$ or NR_2 . Few amino derivatives have been obtained by reduction of the corresponding nitro compound (see below); but several amino derivatives have been prepared by replacement of halogen atoms.³⁰ Thus, 4-amino-1-azaanthracene (LXXIII) results when ammonia is bubbled through a solution of 4-chloro-1-azaanthracene (LXXVIII) in phenol at 180°. By a similar procedure, 4-chloro-2-methyl-



1-azaanthracene (LXX) yields 4-amino-2-methyl-1-azaanthracene (LXXIV), and 4-chloro-3-nitro-1-azaanthracene (LXXI) gives the corresponding amino derivative (LXXV).^{*} The amino derivative (LXXIII) is identical with that obtained by decarboxylation of 4-amino-2-carboxy-1-azaanthracene (LXXXVIII; see p. 38). The reaction of ammonia on a phenol solution of 4,9-dichloro-2-methyl-1-azaanthracene (LXXII) to give 4-amino-9-chloro-2-methyl-1-azaanthracene (LXXVI) has been reported, but no proof that the ammonia replaces the chlorine atom in the 4-rather than in the 9-position is offered.



- (a) $R = R' = H$
 (b) $R = NO_2, R' = H$
 (c) $R = H, R' = NO_2$



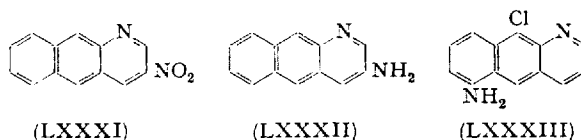
^{*} When this reaction is applied to 1-chloro-3-methyl-4-azaphenanthrene, the reaction is arrested at the phenyl ether stage, but, with a copper sulfate catalyst in diphenyl ether, amination is successful.

In addition to ammonia, some secondary amines have been used to replace the halogen atom.²¹ In this case the 9-halogen atom has been involved. Thus, 9-chloro-1-azaanthracene (VIII) reacts with morpholine or piperidine to give the corresponding tertiary amines (LXXVIIa and LXXVIII). The 5- and 6-nitro-9-chloro-1-azaanthracenes undergo a similar reaction with morpholine to give small yields of the corresponding tertiary amines (LXXVIIb, c). These latter compounds were prepared in connection with the antimalarial program during the war.

$\text{NO}_2 \rightarrow \text{NH}_2$. Some amino derivatives of 1-azaanthracene have been obtained by reduction of nitroazaanthracenes. Reduction of LXXV, for example, gives an excellent yield of 3,4-diamino-1-azaanthracene (LXXIX)³⁰; treatment of the latter with nitrous acid leads to 3,4-triazolo-1-azaanthracene (LXXX). In a similar manner 3-nitro-

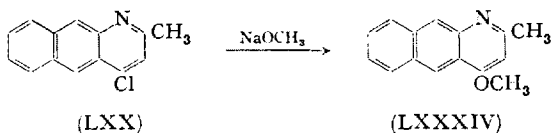


1-azaanthracene (LXXXI) is reduced to the 3-amino compound



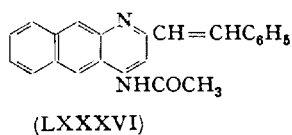
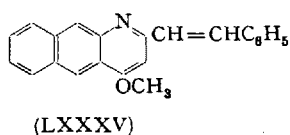
(LXXXII),³⁰ and 9-chloro-5-nitro-1-azaanthracene (XXVIIIa) to 5-amino-9-chloro-1-azaanthracene (LXXXIII).²¹

$\text{Cl} \rightarrow \text{OCH}_3$. In one instance the replacement of chlorine with OCH_3 by treatment with sodium methoxide is reported; 4-chloro-2-methyl-1-azaanthracene (LXX) leads to 4-methoxy-2-methyl-1-azaanthracene (LXXXIV).³⁰

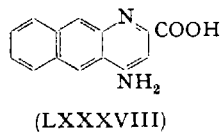
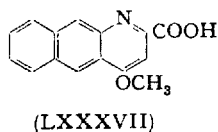


$2\text{-CH}_3 \rightarrow 2\text{-CH=CHR}$. The 2-methyl group in 2-methyl-1-azaanthracenes will undergo condensation with aldehydes, though acetic

anhydride or zinc chloride must be used to force the reaction. The methoxy derivative, LXXXIV, for example, reacts with benzaldehyde in the presence of zinc chloride (anhydrous) to give 4-methoxy-2-styryl-1-azaanthracene (LXXXV). Similarly, 4-amino-2-methyl-1-azaanthracene (LXXIV), benzaldehyde, and acetic anhydride react to produce 4-acetamido-2-styryl-1-azaanthracene (LXXXVI).³⁰

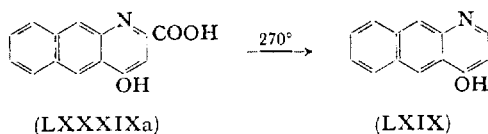


$2\text{-CH=CHR} \rightarrow 2\text{-COOH}$. Oxidation of the styryl derivatives, LXXXV and LXXXVI with potassium permanganate leads to the 1-azaanthracene-2-carboxylic acids, LXXXVII and LXXXVIII.³⁰



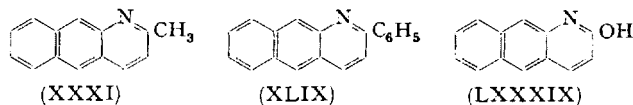
LXXXVII has been demethylated ($\text{OCH}_3 \rightarrow \text{OH}$) by heating it to 210° with sulfuric acid.³⁰

$\text{COOH} \rightarrow \text{H}$. The carboxy compound (LXXXIXa) loses carbon dioxide when heated to 270° in liquid paraffin to give 4-hydroxy-1-

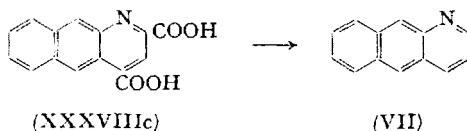


azaanthracene (LXIX). Azaanthracenes carrying carboxyl groups in the 4-position also are decarboxylated by heating the substance, alone or in admixture with copper chromite, to 270° in a vacuum. The formation of 2-methyl- (XXXI, p. 26), 2-phenyl- (XLIX, p. 31), and 2-hydroxy-1-azaanthracenes (LXXXIX) is accomplished by this proce-

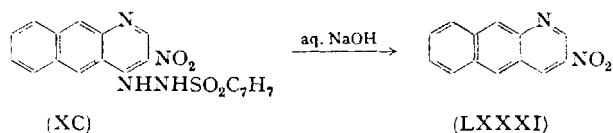
ture. The 2,4-dicarboxy derivative (XXXVIIIc, p. 28) yields a 2- or 4-carboxy compound when heated to 270–80° in a vacuum. Further



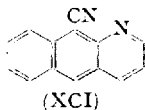
heating in admixture with copper chromite yields 1-azaanthracene (VII).⁴⁸



Cl → *H*. By treatment of 4-chloro-3-nitro-1-azaanthracene (LXXI) with *p*-toluenesulfonehydrazide in chloroform, 3-nitro-4-(β-*p*-toluenesulfonehydrazino)-1-azaanthracene (XC) is formed. The toluenesulfonehydrazino group is removed with loss of nitrogen to yield 3-nitro-1-azaanthracene (LXXXI) by boiling XC in 5 *N* sodium hydroxide solution.³⁰



Cl → *CN*. The conversion of 9-chloro-1-azaanthracene (VIII) to the 9-cyano derivative (XCI) is effected with cuprous cyanide in boiling quinoline.⁸ⁿ



(4) Properties of the 1-Azaanthracenes

(a) Physical Properties. In general, 1-azaanthracene and its derivatives are basic in nature. The simpler members are soluble in the usual organic solvents giving solutions that show a green, blue, or violet fluorescence. This fluorescence is affected by hydrogen ion, being less

intense in acid solution (salt formation). The ultraviolet absorption spectra of linear heterocycles of this type are similar to those of anthracene and differ markedly from those of the angular isomers which are similar to phenanthrene. These similarities and differences are shown in the absorption curves in Figures I-1 to I-3.

(b) Chemical Properties. (1) *Salt Formation.* 1-Azaanthracene, its alkyl and aryl derivatives, and the 9-chloro compound, are basic enough to form salts such as the hydrochloride, hydroiodide, picrate, and, in some cases, the methiodide.* In one instance, that of 9,10-diphenyl-1-azaanthracene, treatment with methyl iodide gives the hydroiodide.^{8p} Unless modified by some other group, such as the nitro group, the salts are all yellow and give deep yellow solutions. In this respect, 1-azaanthracene derivatives differ from those of the isomeric angular compound, 4-azaphenanthrene, derivatives of which usually give colorless salts. This serves as an indication of the structure of a product resulting from a ring closure reaction.

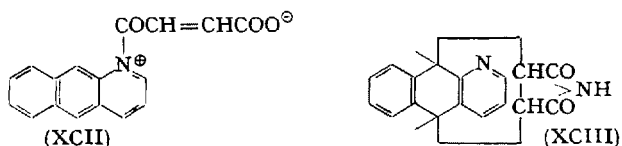
(2) *Reduction.* 1-Azaanthracene is reduced by tin and hydrochloric acid to the 1,2,3,4-tetrahydro derivative.² It is reasonable to assume that Raney nickel reacts similarly, for 9-chloro-1-azaanthracene gives the 9-chloro-1,2,3,4 compound with this reagent.^{8r} In this respect, 1-azaanthracene differs from anthracene and acridine, which are reduced in the meso (9,10) position. The alkyl-1-azaanthracenes would probably respond in the same manner to these reducing agents, but nothing has been recorded in this connection.

(3) *Oxidation.* 1-Azaanthracene and its alkyl and aryl derivatives are oxidized with chromic acid in acetic acid to the corresponding 1-azaanthraquinones (see section 6 following). Derivatives carrying a meso substituent (CH_3 , C_2H_5 , $\text{C}_6\text{H}_5\text{CH}_2$, $\text{C}_6\text{H}_5\text{CO}$, or Cl) lose the latter on oxidation and yield the corresponding 1-azaanthraquinone.¹¹ 2-Methyl-1-azaanthracene has been reported to lose the methyl group on oxidation to yield 1-azaanthraquinone,¹⁰ but under less drastic conditions the methyl group remains intact.⁶ Azaanthraquinones also result from azaanthracenes carrying substituents in both the 9 and 10-

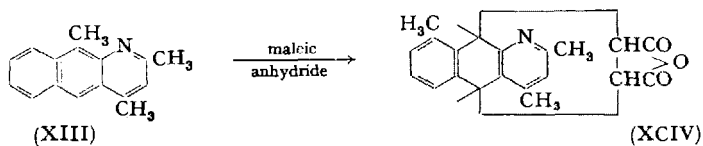
* There is considerable variation in the melting points of the salts prepared by different experimenters. The reader is referred to Etienne's article (reference 8) for details.

positions.^{21, 33} This oxidation to the quinones is useful in determining whether a linear or angular product is formed in certain cyclizations. The latter does not produce a quinone on oxidation. It should be noted, however, that certain highly substituted 1-azaanthracenes are not oxidized to the quinones. These include such compounds as 9-chloro-2,4-dimethyl- and 9-chloro-6-nitro-1-azaanthracenes (see p. 46).

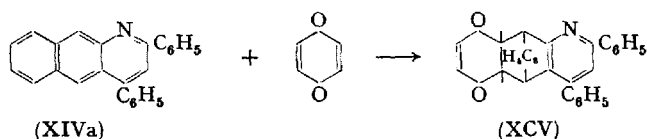
(4) *Diels-Alder Addition*. Certain of the alkyl-1-azaanthracenes are said to undergo a typical Diels-Alder reaction. A complicating factor is a tendency toward salt formation between the base and maleic anhydride. Thus, 1-azaanthracene reacts rapidly with maleic anhydride, but the yellowish-red insoluble product is apparently a salt of the structure XCII. With maleimide, on the other hand, a typical Diels-Alder addition yields XCIII.³⁸ 2,4,9-Trimethyl-1-azaanthracene



(XIII) adds maleic anhydride to form a substance that probably has the structure XCIV. 2,4-Dimethyl-1-azaanthracene (XI) also appears to add maleic anhydride, but the product is intractable.



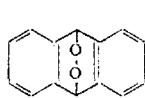
Quinone has been used as the dienophile with 2,4-diphenyl-1-azaanthracene (XIVa). The product obtained, XCV, melts at 240° and dissociates into its components above the melting point.³⁷ The formation of photooxides in some members of this series (p. 42) can be considered as a Diels-Alder addition of oxygen across the diene system. This diene



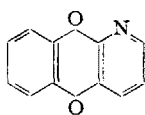
property exhibited by azaanthracenes is useful in distinguishing them from the isomeric azaphenanthrenes, which do not react as dienes.

(5) *Photochemistry of the 1-Azaanthracenes*⁸

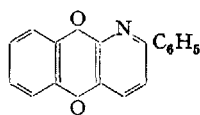
(a) **Photooxides and Photooxidation.** It has been shown that anthracene can be converted to a photooxide in certain solvents by exposure to light.¹⁹ The photooxide (XCVI) is the result of Diels-Alder addition of oxygen.



(XCVI)



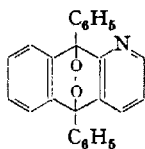
(IV)



(IVa)

With 1-azaanthracene in carbon disulfide solar irradiation results in the formation of 1-azaanthraquinone (IV). In a concentration of 0.1 g per liter the conversion is about 60% in one hour. In higher concentrations, much longer exposure is required to effect a comparable conversion. 9-Chloro-1-azaanthracene and 9-chloro-2-phenyl-1-azaanthracene undergo similar conversions to produce IV and IVa, respectively.

On the other hand, 9,10-diphenyl-1-azaanthracene (XXV) gives, on irradiation in carbon disulfide (1 g. per liter), a 90% yield of the photooxide (XCVII), which melts at 212-14° (Maquenne Block) and gives up its oxygen slowly at about 165°. It is possible to prepare the



(XCVII)

hydrochloride (m.p. 146-8°) and the picrate (m.p. 190-2°) of the photooxide. The hydrochloride hydrolyzes easily, losing hydrogen chloride at ordinary temperature; on heating, hydrogen chloride is lost first, the oxygen being liberated at a higher temperature. The picrate is hydrolyzed in alcohol or acetone. Heat liberates the oxygen and the

residue is a mixture of 9,10-diphenyl-1-azaanthracene, its picrate, and picric acid. 2-Phenyl-1-azaanthracene also forms a photooxide that can be isolated, but it is very unstable.

(b) Photodimerization. The dimerization of anthracene by light has been known for many years.²⁰ In the 1-azaanthracene series, 1-azaanthracene itself dimerizes by irradiation with light to the extent of 60–70 % in about five weeks in solvents such as acetone, alcohol, ether, and benzene. Some photooxidation occurs simultaneously. The dimer dissociates to the monomer at 260–90°. The dimer forms a hydrochloride that does not melt before dissociation at 200° to the hydrochloride of azaanthracene; the latter can be dimerized in water or alcohol. The methiodide of the monomer is dimerized in 4 % solution in alcohol to the extent of 40 % in six weeks. The product melts at 310° (Maquenne Block) and decomposes at 260–70° to 1-azaanthracene methiodide, 1-azaanthracene, and methyl iodide.

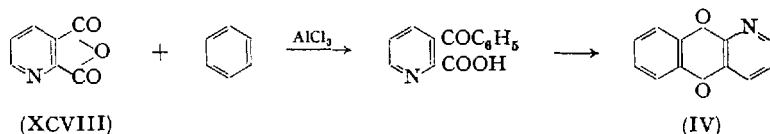
9-Chloro-1-azaanthracene (2 % in alcohol) dimerizes to the extent of 80 % in 20 days. The dimer dissociates when heated slowly. It forms a hydrochloride that can also be obtained by photodimerizing the hydrochloride of 9-chloro-1-azaanthracene. Photodimerization of 2,4-diphenyl-1-azaanthracene occurs in benzene solution in an atmosphere of nitrogen. The photodimer gives a bright yellow fluorescent melt and depolymerizes at the melting point (*ca.* 273°).³⁷ 9-Methyl-2,4-diphenyl-1-azaanthracene also forms a photodimer.³⁷

(6) *1-Azaanthraquinone and Its Derivatives*

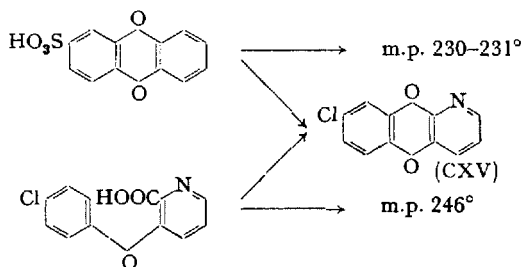
1-Azaanthraquinone and its derivatives are formed: (a) by ring closure reactions, (b) by oxidation of 1-azaanthracenes; (c) by direct substitution and (d) by replacement or alteration of other groups. Only two ring closure reactions are known; most derivatives reported are prepared by procedures (b) and (c). In many instances derivatives made by procedure (c) have not been oriented. Phomazarin, a natural product, appears to be a highly substituted 1-azaanthraquinone.

(a) By Ring Closure. Application of the benzoylbenzoic acid type of synthesis, with quinolinic anhydride (XCVIII) replacing

phthalic anhydride, gives a very small yield of 1-azaanthraquinone (IV), which is very difficult to isolate and purify. The structure of the inter-

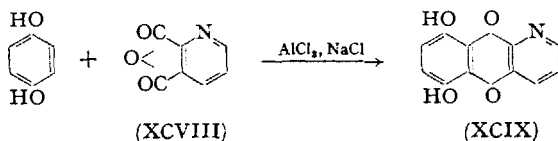


mediate follows from the fact that it decarboxylates to form a phenylpyridyl ketone, which can be oxidized to nicotinic acid.¹⁶ Philips¹ and Bernthsen and Mettegang²³ secured only traces of the quinone. Many years later Johnson and Mathews¹³ obtained the material in a 6% yield. Despite the poor yield, this is a useful synthesis, for it establishes the structure of the product. If chlorobenzene is used instead of benzene in this reaction, 3-*p*-chlorobenzoylpicolinic acid is formed as an intermediate. Treatment of this intermediate with sulfuric acid at 250° gives a 10% yield of 7-chloro-1-azaanthraquinone (CXV, see below).²⁸ Its recorded melting point of 246° is not in agreement with that of a substance assigned the same structure and obtained from 1-azaanthraquinone-7-sulfonic acid by treatment with chlorine (p. 50). The spread in melting point (about 15°) indicates one of two things: either there was a rearrangement during the cyclization of the chlorobenzoylpicolinic acid in the first instance or the 1-azaanthraquinone-7-sulfonic acid, the precursor of the 7-chloro derivative in the second instance, was still contaminated with one, or both, of the two isomeric sulfonic acids formed along with it by sulfonation of 1-azaanthraquinone.



When quinolinic anhydride (XCVIII) reacts with hydroquinone^{7, 8t, 24} or hydroquinone dimethyl ether²⁴ by the usual Friedel-

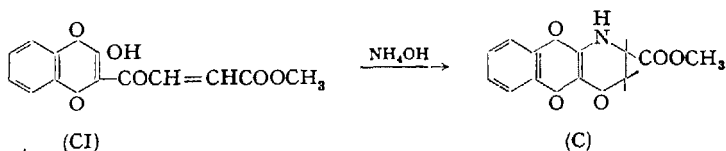
Crafts procedure, or by use of a sodium chloride-aluminum chloride melt, 5,8-dihydroxy-1-azaanthraquinone (XCIX) results. The use of the



ether appears to give a somewhat higher yield. Toluhydroquinone has been said to undergo a similar reaction, but the small amount of product obtained did not permit examination.²⁴

The isolation of 5,8-dihydroxy-1-azaanthraquinone (XCIX) is difficult. The aluminum lake formed in the reaction is decomposed with excess alkali, and the quinone obtained as the sodium salt. Since the hydrochloride of the required product is soluble, it is difficult to isolate it by the use of hydrochloric acid, as suggested by Raudnitz. According to Etienne,^{8t} the use of acetic acid avoids this difficulty.

The only other 1-azaanthraquinone formed by a cyclization reaction is 2-carbomethoxy-4-oxo-1,2,3,4-tetrahydro-1-azaanthraquinone (C). Its structure has not been established. It is obtained when

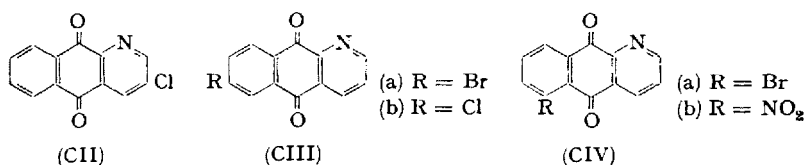


the substituted naphthoquinone (CI) is treated with concentrated aqueous ammonium hydroxide.²⁵ The naphthoquinone derivative is formed (as the free acid) by oxidation of quinizarin with potassium ferricyanide.

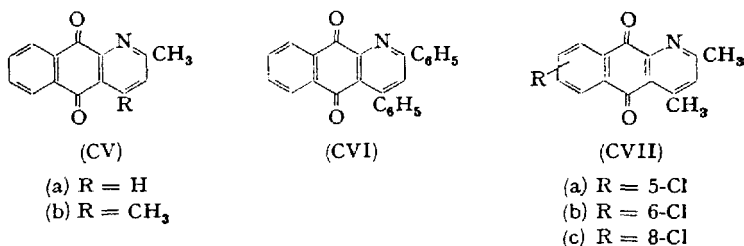
(b) By Oxidation of 1-Azaanthracene Derivatives. Oxidation of 1-azaanthracene by chromic acid in acetic acid solution leads directly to 1-azaanthraquinone.² However, the difficulty encountered in preparing the parent compound (see pp. 16 ff.) makes the method impractical. Probably the best way of obtaining 1-azaanthraquinone (IV) is by oxidation of 9-chloro-1-azaanthracene (VIII), a substance

that is formed in fair yield by a Skraup reaction on 1-chloro-2-naphthylamine (p. 24). Many 1-azaanthracenes substituted in either one or both meso positions undergo this reaction to give 1-azaanthraquinones. Thus, the quinone is obtained from azaanthracenes substituted in the 9-position by chlorine,^{8, 11, 12} methyl, ethyl, benzyl, benzoyl, naphthyl, or 9',1-azaanthracene,¹¹ and from 9,10-dichloro-1-azaanthracene,^{21, 33} and 9-chloro-10-nitro-1-azaanthracene.³³

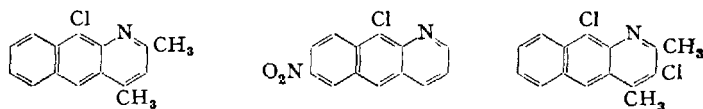
A number of substituted 1-azaanthraquinones are prepared by the same procedure. These are the 3-chloro (CII),³¹ the 6-bromo,^{11, 31} and 6-chloro derivatives³¹ (CIIIa, b), the 5-bromo-³³ and 5-nitro-²¹ derivatives (CIVa, b), and some alkyl substituted compounds, including



2-methyl- (CVa)⁶ and 2,4-dimethyl-1-azaanthraquinones (CVb),²⁹ the

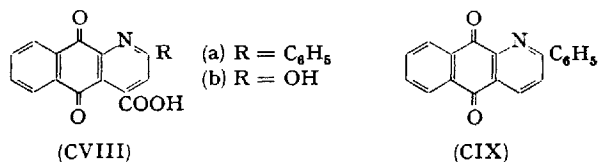


2,4-diphenyl analog (CVI)³⁷ and the halogen-substituted compounds of structure CVII.²⁹ It should be pointed out, however, that there are exceptions; for example, the following compounds could not be oxidized to the quinone:²⁹



While a substantially good yield of the quinone (CVb) results by oxidation of 2,4-dimethyl-1-azaanthracene, the 2,4,9-trimethyl deriva-

tive gives only a very low yield.²¹ On the other hand, 4-carboxy-9-chloro-2-phenyl-1-azaanthracene (XL1a) is oxidized to the quinone



(CVIIIa) in 70% yield.⁴² 4-Carboxy-2-phenyl-1-azaanthracene (XXXVIIIa) also yields CVIIIa on oxidation⁴⁸; the latter can be decarboxylated to 2-phenyl-1-azaanthraquinone (CIX). A similar oxidation of 4-carboxy-2-hydroxy-1-azaanthracene (XXXVIIId) gives the azaanthraquinone, CVIIIb, while a 2- or 4-carboxy-1-azaanthracene in which the position of the carboxyl group has not been established (p. 39) leads to a 2- or 4-carboxy-1-azaanthraquinone.⁴⁸

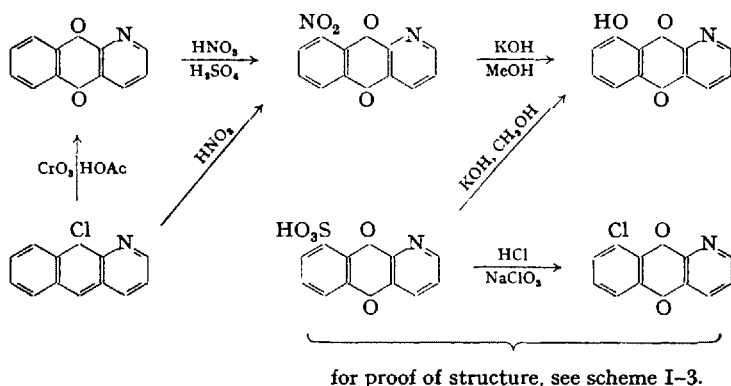
(c) By Direct Substitution in 1-Azaanthraquinone or its Derivatives. 1-Azaanthraquinone may be halogenated, sulfonated, or nitrated. While the sulfonic acids have been identified, and the chlorine compounds derived from them by replacement of the sulfonic groups with chlorine have been oriented, the positions occupied by halogen or nitro groups introduced by direct substitution have not been established in many cases.

(1) *Halogenation.* Direct bromination of 1-azaanthraquinone³³ gives a bromo-1-azaanthraquinone, which is identical with the product obtained by the oxidation of α ,10-dibromo-9-chloro-1-azaanthracene (p. 41). The position of the bromine atom is unknown. Bromination of 5,8-dihydroxy-1-azaanthraquinone (XCIX) is reported, but details are lacking.⁶ Direct chlorination is not recorded.

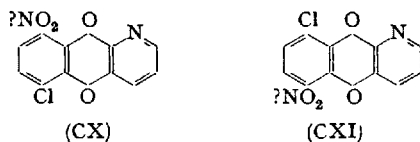
(2) *Nitration.* Nitration of 1-azaanthraquinone in concentrated sulfuric acid gives an 80% yield of the 8-nitro derivative (LXVI; see reaction scheme I-1 for proof of structure).^{31, 33} The same substance is obtained in 40% yield by heating 9-chloro-1-azaanthracene (VIII) with concentrated nitric acid. It is probable that the mononitro derivative reported in the patent literature⁶ has the same structure. By boiling 1-azaanthraquinone in a mixture of sulfuric acid, nitric acid, and potassium nitrate, Clemons and Driver³³ were able to isolate two mono-

nitro derivatives, neither of which is identical with the 8-nitro compound, despite the fact that one of them has the same melting point. This problem of nitro derivatives and the amino compounds derived therefrom is in need of clarification. Reaction scheme I-2 is designed to show the status of this problem.

Reaction Scheme I-1



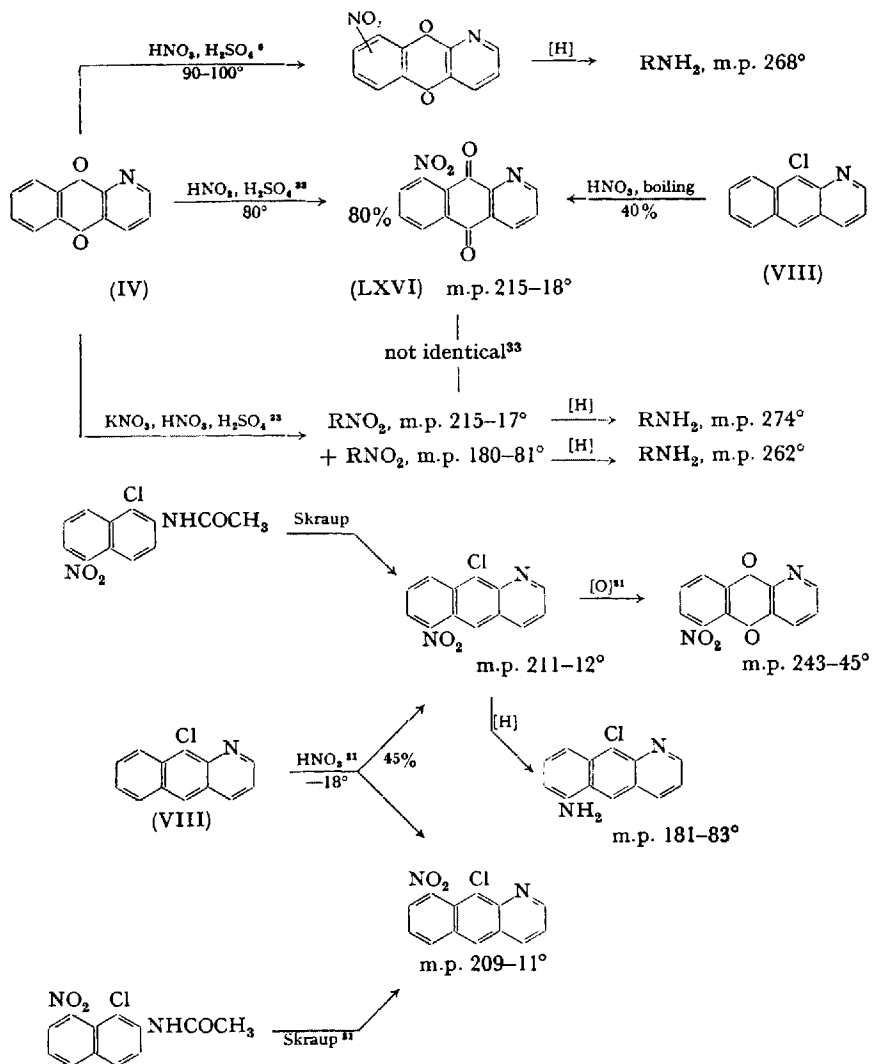
Nitration of 5-chloro- and 8-chloro-1-azaanthraquinones gives chloronitroazaanthraquinones (CX and CXI), which have not been oriented. By analogy with anthraquinone, the nitro group is probably para to the halogen atom in each instance.³¹ 6-Bromo- and 6-chloro-1-



azaanthraquinones (CIIIa, b) also give well-defined nitration products (two isomeric ones in the former case), but the position of the entering nitro group is unknown.³¹

(3) *Sulfonation*. Sulfonation of 1-azaanthraquinone with oleum, with or without a mercury catalyst, gives a mixture of monosulfonation products.³¹ There is no evidence of disulfonation, which is not unexpected because of the deactivating property of the ring nitrogen. It is comparable to the sulfonation of anthraquinonemonosulfonic acid; in

Reaction Scheme I-2

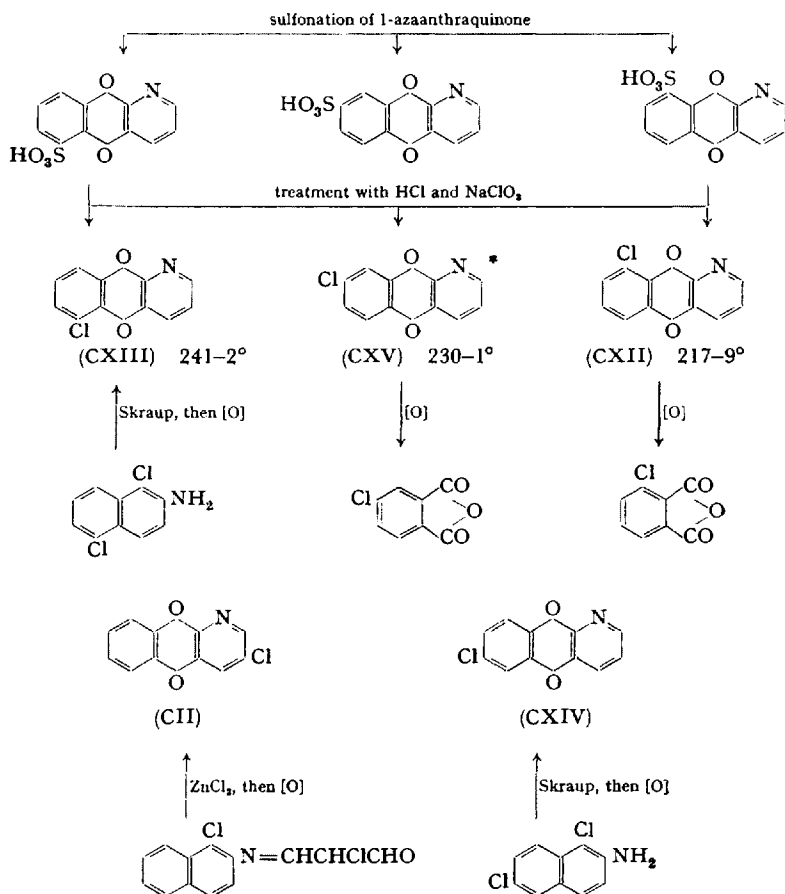


this instance the deactivating influence of the sulfonic acid groups prevents the formation of trisulfonic acids. While the mercury catalyst does not promote α -sulfonation exclusively, there is a higher yield of the α -isomers when it is present. The 5-, 7-, and 8-isomers are formed

(none of the 6-isomer has been isolated). The sulfonic acids are separated by fractionally crystallizing the barium salts; they are purified by recrystallization of the *p*-chlorobenzyl-*ψ*-thiuronium derivatives.

The structures of these sulfonic acids were established as follows (*cf.* reaction scheme I-3): They were converted to the corresponding chloroazaanthraquinones by treatment with sodium chlorate in hydrochloric acid, a common reaction in the anthraquinone field. The three halogen derivatives (5-, 7-, and 8-) had melting points of 241–2°,

Reaction Scheme I-3



• Compare p. 44.

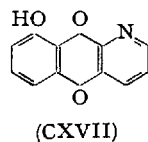
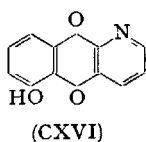
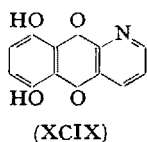
230–1° and 217–9°, respectively. Oxidation of the 217–9° product gave 3-chlorophthalic anhydride. This established it as 8-chloro-1-azaanthraquinone (CXII), because the 5-chloro compound (CXIII), the only other chloro derivative that could give 3-chlorophthalic anhydride on oxidation, was synthesized by a Skraup reaction on 1,5-dichloro-2-naphthylamine followed by oxidation; the product was identical with the isomer of melting point 241–2°. Similarly, oxidation of the 230–1° isomer gave 4-chlorophthalic anhydride. This could arise from either the 6-chloro or 7-chloro-1-azaanthraquinone. Since the 6-chloro derivative (CXIV) was synthesized from 1,6-dichloro-2-naphthylamine and was not identical with the 230–1° product, the latter must be the 7-chloro isomer (CXV). The orientation of the sulfonic acids follows from the structure of the chlorine compounds.

Sulfonation of 2-methyl-1-azaanthraquinone, with and without mercury present, is reported, but the sulfonation products are probably mixtures.⁶ In contrast, 2,4-dimethyl-1-azaanthraquinone cannot be sulfonated under the conditions used for azaanthraquinone itself³¹; however, it should be noted that the original synthesis of the former compound involved the desulfonation of an initially formed sulfonic acid (p. 18).^{12,13} Sulfonation of 2,4-diphenyl-1-azaanthraquinone with concentrated sulfuric acid at 80°C. is reported, but the position taken by the entering sulfonic acid group is unknown,³⁷ and may well be attached to a substituent phenyl group.

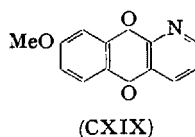
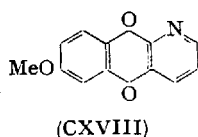
(d) By Replacement or Alteration of Other Groups. (1) *Halogen Derivatives.* Chlorine derivatives of 1-azaanthraquinone are obtained from the corresponding sulfonic acids by treatment of the latter in hydrochloric acid solution with sodium chlorate. They have been considered (pp. 49 ff.) in connection with the proof of structure of the sulfonic acids.

(2) *Hydroxy and Methoxy Derivatives.* The dihydroxy-1-azaanthraquinone, XCIX, is formed by a cyclization reaction (p. 45). The 5- and 8-monohydroxy derivatives (CXVI and CXVII) are prepared from the corresponding sulfonic acids or the chlorine derivatives by treatment with potassium hydroxide and methanol at 120–30°. The structure of 8-nitro-1-azaanthraquinone (p. 48) was established by converting it

to the 8-hydroxy derivative (CXVII) by a similar procedure.³¹ By way of contrast, the 6- and 7-chloro-1-azaanthraquinones (CXIV and CXV)

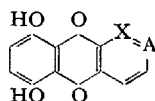


yield the 6- and 7-methoxy derivatives (CXVIII and CXIX) when treated in the same manner.³¹



The dihydroxy compound (XCIX) is interesting because of its relationship to quinizarin (1,4-dihydroxyanthraquinone), a valuable intermediate in the preparation of certain anthraquinone acid and acetate dyes. The absorption spectra of these two substances and of 5,8-dihydroxy-2-azaanthraquinone are compared in Table I-1.⁴⁹

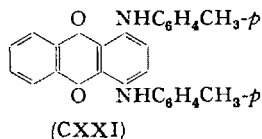
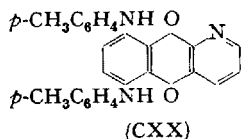
TABLE I-1. Absorption Spectra



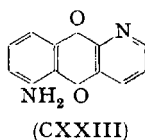
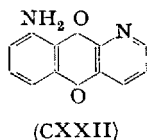
Formulae		Solution in KOH		H ₂ SO ₄		H ₂ SO ₄ + H ₂ BO ₃	
		Color	Abs. Max. mμ	Color	Abs. Max. mμ	Color.	Abs. Max. mμ
X = CH	A = CH	Violet	596, 553, 517	Red	548, 509, 476	Red	547, 508, 475
X = N	A = CH	Violet	600, 561	Carmine red	574, 532	Rose red	547, 506, 473
X = CH	A = N	Blue	618, 573	Violet	—	Red	559, 518, 483

It will be noted that there is a small progressive bathochromic shift in the order quinizarin → 5,8-dihydroxy-1-azaanthraquinone → 5,8-dihydroxy-2-azaanthraquinone. It is possible that dyes derived from 5,8-dihydroxy-1-azaanthraquinone might also have their absorption maxima at somewhat longer wave lengths than do the corresponding dyes from quinizarin. For example, 5,8-di-*p*-toluidino-1-azaanthraquinone (CXX) would be expected to be very similar to the base of quinizarin green (CXXI, *C.I.* 1078). A recent patent has been issued⁴⁶

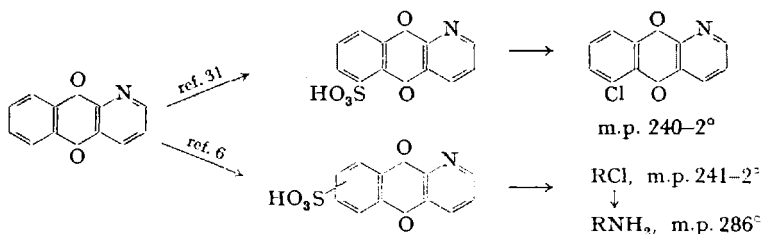
covering dyes of this type, prepared from leuco-5,8-dihydroxy-1-azaanthraquinone.



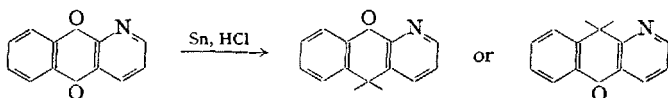
(3) *Amino Derivatives*. A few amino derivatives are known, but in most cases the position of the amino group has not been established. It seems reasonable to assume that the amino derivative of melting point 268° (see reaction scheme I-2) mentioned in the patent literature⁶ and derived from the nitro compound is the 8-amino derivative (CXXII). The 5-amino compound (CXXIII) has not been reported,



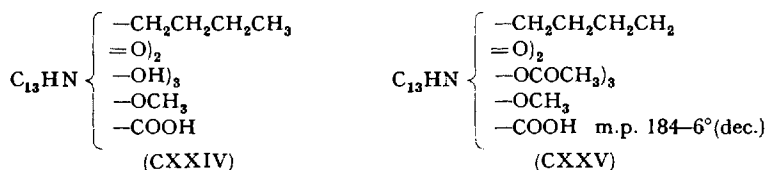
although the corresponding nitro derivative is known (see reaction scheme I-2). In view of the evidence illustrated by the reactions below, it appears that the nonoriented amino derivative of melting point 286°



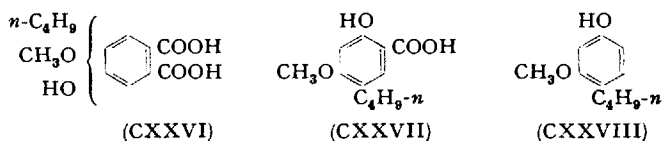
is the 5-isomer. Two other nonoriented amino derivatives are reported (see reaction scheme I-2).³³ This problem in conjunction with the nitro derivatives is in need of clarification. While nitro compounds are reduced to the amino-1-azaanthraquinones in alkaline solution, acid reduction ($\text{Sn} + \text{HCl}$) leads to amino-1-azaanthrones.³³ Reduction of 1-azaanthraquinone gives 1-azaanthrone.



(e) **Phomazarin.** Phomazarin is a dye extracted from *Phoma terrestris*, a fungus responsible for the "pink-root" disease of onions. It is obtained as orange crystals (m.p. 197°) from alcohol and has the empirical formula $C_{13}H_{17}NO_8$. As a result of Kögl's work^{26,27} it appears to be a derivative of 1-azaanthraquinone, although the structure was not established absolutely. Preliminary investigation showed that the substance contained three hydroxyl groups and one each of methoxyl, *n*-butyl, and carboxyl groups. In addition, it was easily reduced to a dihydro derivative, which was oxidized readily in the air. On the basis of these facts, Kögl represented the structure as shown in CXXIV.

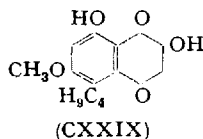


Oxidation (CrO_3) of the triacetyl derivative (CXXV), followed by methylation and saponification with sodium hydroxide, gave a phthalic acid carrying a butyl, hydroxyl, and methoxyl group (CXXVI).

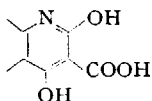


By heating the calcium salt of this phthalic acid derivative with soda-lime a yellow oil was obtained that was separated into an acid fraction and a neutral fraction. From the acid fraction 5-*n*-butyl-2-hydroxy-4-methoxybenzoic acid (CXXVII) of melting point 136° was obtained. Its structure was established by direct synthesis. The neutral fraction gave, by treatment with 3,5-dinitrobenzoyl chloride, the 3,5-dinitrobenzoate of 4-*n*-butyl-3-methoxyphenol (CXXVIII), established by comparison with an authentic specimen. In addition to the phthalic acid formed by the chromic acid oxidation, a deep yellow-colored substance of the formula $C_{15}H_{16}O_5$ was isolated. Because this substance contained no nitrogen, and because it has the properties of a quinone, it was assumed that it was an intermediate in the formation of the phthalic acid derivative, and had either the structure CXXIX

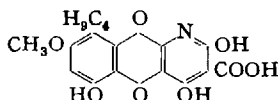
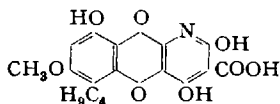
or that of an isomer in which the 2-OH group is in the other β -position. Since phomazarin has a tricyclic ring system, containing one —N=



group, it is evident that it must be a derivative of 1-azaanthracene, 2-azaanthracene, or 1-azaphenanthrene. The quinone of the azaphenanthrene system would be of the type found in phenanthraquinone, and this structure was ruled out. The basis for this is that phenanthraquinone, on heating in aqueous alkali, gave a fluorene derivative, and in alcoholic alkali a diphenic acid, while phomazarin was not affected under the same conditions. Further evidence derived from certain hydrolytic reactions has led to the prediction that the arrangement of atoms in the pyridine nucleus is as follows:

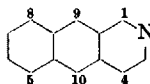


From this evidence the structure of phomazarin can be represented by one of the following formulae:



Conclusive evidence of the orientation of the atoms in the pyridine entity of the molecule has not been obtained. It would seem that the synthetic approach is the only way to establish which of the two structures actually represents phomazarin.

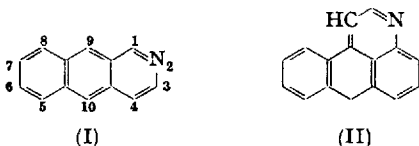
- B. 2-Azaanthracene. 6,7-Benz[*g*]isoquinoline.
 β -Azaanthracene. β -Anthrapyridine. 6,7-
 Benzisoquinoline. R.I. 1972**



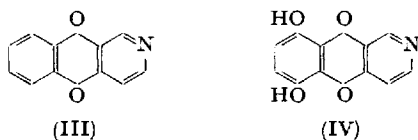
(1) Nomenclature

Like 1-azaanthracene this compound and its derivatives have been given a variety of names, and in all cases the names are analogous to

those of the 1-isomer. Thus, 2-azaanthracene (I) was first called β -anthrapyridine.¹ Later the name was changed to 6,7-benzisoquinoline



and eventually to β -azaanthracene.³ In *Chemical Abstracts* the compound is listed as 6,7-benzisoquinoline with a cross reference to β -anthrapyridine up to 1936. Since then it has appeared under benz[g]-isoquinoline. The term anthrapyridine appears in the 1937-1946 decennial index as a cross reference to naphthoquinoline and in the 1939 index as a cross reference to dibenz[f,ij]isoquinoline (II). This confusion is dispelled by adopting the name 2-azaanthracene. In a similar manner, the quinone (III) and the dihydroxy quinone (IV) become 2-azaanthraquinone and 5,8-dihydroxy-2-azaanthraquinone, respectively. The old names of these compounds were β -anthrapyridinequinone¹ and β -pyrquinizarin.²⁴

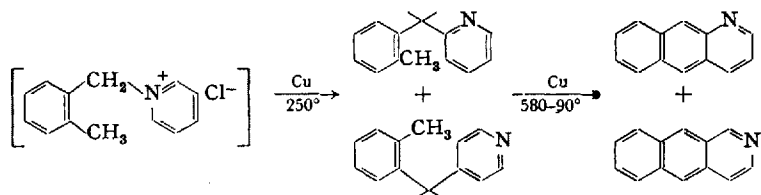


(2) Syntheses of 2-Azaanthracenes

Unlike the 1-azaanthracene series, little work has been done with 2-azaanthracene and its derivatives. The parent compound (I),^{1,3} its quinone (III),^{1,3} a dihydroxy derivative of the latter,^{24,49} and a few alkyl derivatives^{3,50,51} are all that are known. Only the quinones are obtained by the ring closure procedures used in the α -series.

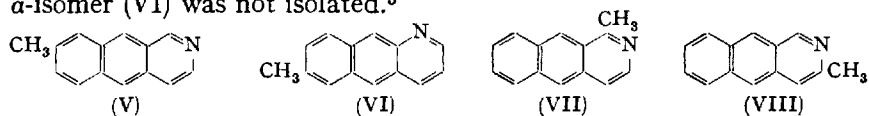
(a) **2-Azaanthracene** (I) is obtained by reducing 2-azaanthraquinone (III) with zinc dust and ammonia, or by distilling the material with zinc dust. The yield is poor, and, since the quinone (III) is not easily secured (see below), the method is impractical. It may also be prepared by cyclizing the mixture of bases resulting when *o*-xylylpyridinium chloride is heated with a trace of copper. The cyclization is

effected by passing the vapors of the mixed bases through a tube packed with copper turnings heated to a temperature of 580–90°. The mixture



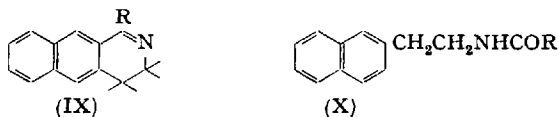
of azaanthracenes, obtained in a yield of about 25 %, is separated into its components by fractional crystallization; the β -isomer (I) makes up the greater portion of the mixture.^{3, 52}

(b) **7-Methyl-2-azaanthracene (V)** is prepared from 2,4-dimethylbenzylpyridinium chloride by a similar procedure. In this case, the α -isomer (VI) was not isolated.³

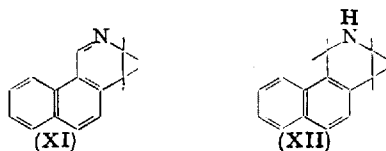


An attempt to prepare 1-methyl-2-azaanthracene (VII) and 3-methyl-2-azaanthracene (VIII) from *o*-xylylpicolinium chloride was not successful. The cyclization was effected but the mixture of bases obtained could not be separated.³

A number of alkyl and aryl derivatives of 3,4-dihydro-2-azaanthracene (IX, R = H) have been reported.⁵⁰ Presumably, they are secured by cyclizing the alkoyl or aroyl derivatives of β -2-aminoethylnaph-

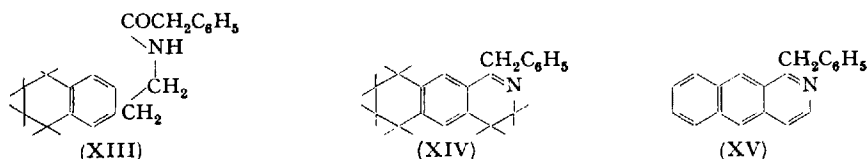


thalene (X) with phosphorus pentoxide in xylene. Compounds are described in which R = C₆H₅, CH₃-, *n*-C₃H₇-, C₆H₁₁-, and 3,4-(C₂H₅O)₂C₆H₃-. However, as has been pointed out by Schultz and Arnold,⁵¹ these products are probably derivatives of 7,8-benziso-



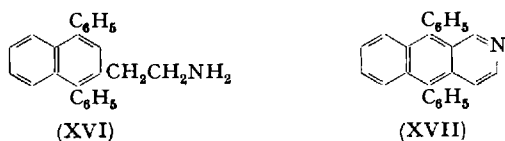
quinoline (2-azaphenanthrene) of the general structure XI. Evidence for this conclusion arises from the fact that cyclization of β -2-aminoethylnaphthalene with formaldehyde and hydrochloric acid gives 1,2,3,4-tetrahydro-2-azaphenanthrene (XII), the structure of which is proved by oxidation to benzene-1,2,3,4-tetracarboxylic acid. The 1,2,4,5-isomer would result if the cyclization were linear.

(c) **1-Benzyl-2-azaanthracene** (XV) is obtained, nevertheless, by a similar cyclization of *N*-[β -(6-tetralyl)ethyl]phenylacetamide (XIII) followed by dehydrogenation of the 3,4,5,6,7,8-hexahydro-2-azaanthracene (XIV) so formed.⁵¹ While XIV is an oil, it gives a solid picrate; XV is a well-defined solid. That linear cyclization occurs is



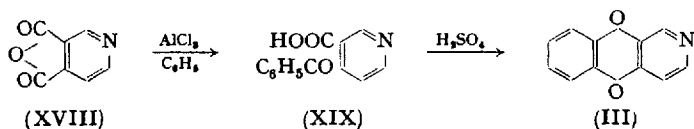
shown by oxidation of the hexahydro compound (XIV) to benzene-1,2,4,5-tetracarboxylic acid.

(d) **9,10-Diphenyl-2-azaanthracene** (XVII) is formed in 30% yield when 2- β -aminoethyl-1,4-diphenylnaphthalene (XVI) is treated with formaldehyde, and the product cyclized with phosphoryl bromide.⁵³



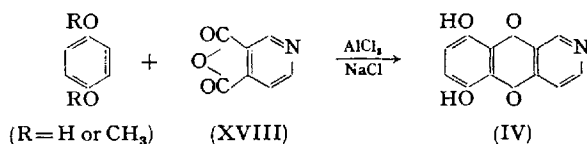
(3) Synthesis of 2-Azaanthraquinones

(a) **2-Azaanthraquinone** (III) is obtained in about 12% yield when 4-benzoylnicotinic acid (XIX), secured from benzene and cinchomeronic anhydride (XVIII) by a Friedel-Crafts reaction, is cyclized with sulfuric acid.¹ It is formed also by oxidation³ of 2-aza-



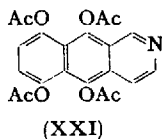
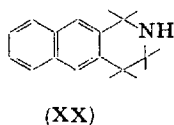
anthracene (I) with chromic acid. Solar irradiation of 2-azaanthracene in carbon disulfide is said to produce the quinone (III), but the melting point recorded for the product thus obtained is almost 100° higher than when the substance is secured as above.⁵³

(b) **5,8-Dihydroxy-2-azaanthraquinone (IV)** is obtained when hydroquinone⁴ or hydroquinone dimethyl ether^{5, 24} is condensed with XVIII in a sodium chloride-aluminum chloride melt, and the resulting aluminum lake decomposed with excess alkali.



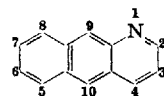
(4) Properties of 2-Azaanthracenes

2-Azaanthracenes are fairly strong bases, forming salts with hydrochloric, picric, and other acids. 2-Azaanthracene itself forms a methiodide. The solutions of the bases show a blue-green fluorescence while the salts fluoresce green in solution. Reduction of 2-azaanthracene with tin and hydrochloric acid yields the 1,2,3,4-tetrahydro derivative (XX).³ The unsubstituted base (I) has photochemical properties similar to 1-azaanthracene.⁵³



2-Azaanthraquinone (III) is a weak base, dissolving in dilute acids and being precipitated therefrom by alkali. The dihydroxy derivative (IV) shows color reactions corresponding to those of quinizarin and 5,8-dihydroxy-1-azaanthraquinone. The absorption spectra of these three substances in alkali, sulfuric acid, and sulfuric acid-boric acid are shown earlier in Table I-1.⁴⁹ The sodium salt of IV is not very soluble in the presence of sodium ions, but it can be dissolved in warm water from which the free base is precipitated by acidification. It forms a diacetate, and a tetraacetate (XXI) results when the acetylation is carried out in the presence of zinc.

TABLE I-2A. Alkyl and Hydrogenated 1-Azaanthracenes

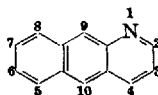


Position of substituent											
Formula	?	1	2	3	4	5	6	7	8	9	10
VII											
VI						H	H	H	H		
—		H	H	H	H						
XXXI			CH ₃								
XXX			CH ₃			H	H	H	H		
XVIII					CH ₃						
VIIIa										CH ₃	
X			CH ₃		CH ₃						
XIX				CH ₃	CH ₃						
XIII			CH ₃		CH ₃					CH ₃	
XLIX			C ₆ H ₅								
XVa			CH ₃		C ₆ H ₅						
II			C ₆ H ₅		CH ₃						
XLVIII			<i>m</i> -Xylyl					CH ₃			
XIVa			C ₆ H ₅		C ₆ H ₅						
XVII			C ₆ H ₅		C ₆ H ₅	H	H	H	H		
XXV										C ₆ H ₅	C ₆ H ₅
XVb			CH ₃		C ₆ H ₅					CH ₃	
XIVb			C ₆ H ₅		C ₆ H ₅					CH ₃	

^a Substance is dimorphous.

Method of synthesis	M.p., °C.	Yield, %	Properties	Salts, m.p., °C.	Ref.
Dehydrogenation	114; 117-8	70; 15	Cream colored	P 258;	2, 3, 8,
Decarboxylation				CH ₃ I 225	30, 48
Skraup	71-2	55	Colorless (dist.)	HCl 177;	2
				P 270	
Red.	149		Colorless	HCl 229	2
Dehydrogenation	129; 129-30		Colorless needles (sublimation)	HCl 200;	10, 48
				P 216	
Doebner-Miller	45	35		HCl 209-12; 10	
				P 206	
Combes	84-5	43	Yellow needles (pet. ether)	P 264-6	32
Skraup	53-4	30	Bright yellow solid (dist.)	P 212; HCl	11, 34
Combes	93; 71-72*	75; 96	Pale yellow needles (C ₆ H ₆)	P 271-3;	12, 13,
				HCl 325	29, 37
Combes	139-40	80	Yellow needles (ligroin)	P 270-1	32
Combes	127	96; 90	Colorless (C ₂ H ₅ OH)	P 253-5;	13, 37
				HCl 296	
Alkylation:	188; 192-3	75	Pale yellow prisms	P 188-90;	8, 42, 48
Pfitzinger			(sublimation)	HCl 168	
Combes	110		Pale yellow (pet. ether)		37
Doebner-Miller	152	24		Salts	4
Dehydrogenation	172		(CH ₃ OH) (pet. ether)		5
Combes	146*; 165	82	Yellow needles (C ₂ H ₅ OH; CHCl ₃)		37
Combes	129	92	Colorless needles (C ₂ H ₅ OH)	Colorless	37
LVI + KI + HOAc	289-90	40, 70	Yellow needles (C ₆ H ₆)	HCl 275-7; 8g	
				P 236	
Combes	105-6	70	Colorless prisms (C ₂ H ₅ OH)		37
Combes	138-9	96	Yellow (C ₂ H ₅ OH; CHCl ₃)		37

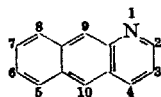
TABLE I-2B. Halogenated 1-Azaanthracenes



Formula	Position of substituent										
	?	1	2	3	4	5	6	7	8	9	10
LXVIII					Cl						
VIII										Cl	
—		H	H	H	H					Cl	
—				Cl						Cl	
—						Cl				Cl	
—							Cl			Cl	
—									Cl	Cl	
LXI										Cl	Cl
XXIXa							Br			Cl	
LXII										Cl	Br
—	Br									Cl	Br
LXX			CH ₃		Cl						
XXIII			CH ₃		CH ₃				Cl		
XXIa			CH ₃		CH ₃					Cl	
—			CH ₃		CH ₃					Br	
LXXII			CH ₃		Cl					Cl	
XXIb			CH ₃	Cl	CH ₃					Cl	
XXII			CH ₃		CH ₃		Br			Cl	
LI			C ₆ H ₅							Cl	
LI			C ₆ H ₅							Cl	
LII		H	H, C ₆ H ₅							Cl	
XXIII			CH ₃	CH ₃		Cl					
XXIII			CH ₃		CH ₃		Cl				

Method of synthesis	M.p., °C.	Yield, %	Properties	Ref.
POCl ₃ on LXIX	Not characterized			30
Skraup	138–40; 141	25–44	Colorless plates (ligroin); P 252	8, 11, 21, 33, 34
Reduction (Raney Ni)	63–4	80	Needles (ligroin)	8r
ZnCl ₂ fusion	Not purified			31
Skraup	Not purified			31
Skraup	Not purified			31
Skraup	Not purified			31
Cl ₂ on VIII	213–5; 208	46; 71	Yellow needles (C ₂ H ₅ OH)	8, 11, 21, 33
Skraup	178	5	Pale yellow plates (ligroin)	11, 33
Br ₂ on VIII	190	43	Yellow (C ₂ H ₅ OH)	33
Br ₂ on VIII	224–7	74	Yellow needles (C ₂ H ₅ OH)	33
POCl ₃ on XLVI	130 (dec.)	100	Pale yellow solid	30
		(crude)		
Combes	153	76	Colorless needles (C ₆ H ₆ ; pet. ether)	29
Combes	166–7	52	Colorless needles (C ₆ H ₆ ; pet. ether)	29
Combes	168–9	Good	Bright yellow (C ₂ H ₅ OH)	37
POCl ₃ on XXXVIII	159–61	100	Pale yellow solid (crude)	30
Combes	224–5	90	Colorless needles (C ₆ H ₆)	29
Combes	166–8		Colorless needles (C ₂ H ₅ OH)	29
Oxid. LII	157	44–60	HCl 125; P 147	8j
—CO ₂ from XLa	156	46	Yellow needles (acetone)	42
C ₆ H ₅ MgX on VIII	Oil		Forms acetyl deriv. and nitroso compds	8
Combes	145–6	82	Colorless needles (pet. ether)	29
Combes	130–1	84	Colorless needles (pet. ether)	29

TABLE I-2C. Nitro-1-azaanthracenes



Formula	Position of substituent									
	?	1	2	3	4	5	6	7	8	10
LXXX I				NO ₂						
LXXI				NO ₂	Cl					
LXIII						NO ₂				Cl
XXVIIIa						NO ₂				Cl
XXVIIIb							NO ₂			Cl
XXVIIIc									NO ₂	Cl
LXIV									NO ₂	Cl
LXV										Cl
—				NO ₂	CH ₃	H	H	H	H	NO ₂

TABLE I-2D. 1-Azaanthracene Sulfonic Acids

Formula	Position of substituent									
	?	1	2	3	4	5	6	7	8	10
—	SO ₃ H		CH ₃		CH ₃					
XIVa	SO ₃ H		C ₆ H ₅		C ₆ H ₅					
—	SO ₃ H		CH ₃		CH ₃					CH ₃

TABLE I-2E. Amino-1-azaanthracenes

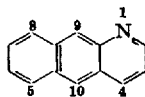
Formula	Position of substituent									
	?	1	2	3	4	5	6	7	8	10
LXXXII				NH ₂						
LXXIII					NH ₂					
LXXIX				NH ₂	NH ₂					
LXXIV			CH ₃		NH ₂					
LXXXIII						NH ₂				Cl
LXXVI			CH ₃		NH ₂					Cl
LXXV				NO ₂	NH ₂					
LXXVIIa										9-C ₄ H ₈ ON
LXXVIII										9-C ₅ H ₁₀ N
LXXVIIb						NO ₂				9-C ₄ H ₈ ON
LXXVIIc							NO ₂			9-C ₄ H ₈ ON
LXXXVI	2-C ₆ H ₅ CH=CH				NHR			{ R = —COCH ₃ }		
LXXXV	2-C ₆ H ₅ CH=CH				OCH ₃					
XC				NO ₂	NHR			{ R = —NHSO ₂ C ₇ H ₇ }		

Method of synthesis	M.p., °C.	Yield, %	Properties	Ref.
Hydrolysis of XC	206	60	Orange (C ₂ H ₅ OH or C ₆ H ₆)	30
POCl ₃ on XLII	237 (dec.)	90	Orange (C ₆ H ₆)	30
HNO ₃ on VIII	211-2	45	Yellow needles (C ₂ H ₅ OH)	21
Skraup	211-2			21
Skraup	243-5	4	Yellow needles (C ₂ H ₅ OH)	21, 33
Skraup	209-11		Yellow (C ₂ H ₅ OH)	21
HNO ₃ on VIII	209-11	12		21
HNO ₃ on VIII	201-3	70	Yellow solid (HOAc)	33
Methazonic acid	135-6	96	Cream leaflets (aq. C ₂ H ₅ OH)	41

Method of synthesis	M.p., °C.	Yield, %	Properties	Ref.
Combes (intermediate)		91	Yellow rods	12, 13
H ₂ SO ₄ on XIV	300		Orange-red needles	37
Combes (intermediate)	>	92	Orange-yellow rods	13

Method of synthesis	M.p., °C.	Yield, %	Properties	Ref.
Red. of LXXXI	240-1	85	Yellow-brown (toluene)	30
—CO ₂ from LXXXV	233	50	Bright yellow (toluene or acetone)	30
Red. of LXXV	212 (dec.)	90	Pale yellow; HCl 310 (dec.)	30
NH ₃ on LXX	180		Pale yellow (C ₆ H ₆)	30
Red. of XXVIIIa	181-3	30	Orange needles (C ₂ H ₅ OH)	21
NH ₃ on LXXII	179-80	65	Brownish-yellow (C ₂ H ₅ OH)	30
NH ₃ on LXXI	282-3	95	Orange (C ₂ H ₅ OH)	30
Morpholine and VIII	160-1	6	Bright yellow prisms (C ₂ H ₅ OH)	21
Piperidine and VIII	97-9	8	Bright yellow needles (C ₂ H ₅ OH)	21
Morpholine and LXXIII	156-8	5	Red needles (C ₂ H ₅ OH)	21
Morpholine and XXVIIIb	202-4	3	Tan platelets (C ₂ H ₅ OH)	21
C ₆ H ₅ CHO + Ac ₂ O on LXXIV	244	90	Yellow (hygr.) (CH ₃ OH)	30
C ₆ H ₅ CHO on LXXXIV	128	Good	Yellow (crude)	30
C ₇ H ₇ SO ₂ NHNH ₂ on LXXI	ca. 170		Crude	30

TABLE I-2F. Hydroxy-1-azaanthracenes



Formula	Position of substituent										
	?	1	2	3	4	5	6	7	8	9	10
LXXXIX			OH								
LXIX					OH						
XLVI			CH ₃		OH						
XLIV				NO ₂	OH						
LXXXIV			CH ₃		OCH ₃						
XXXVIIa			OH		CH ₃					CH ₃	
XXXV			CH ₃		OH					CH ₃	
XXXVI			CH ₃		OH					Cl	
XXXVIIb			OH		CH ₃					Br	
LVI										OH	OH
										C ₆ H ₅	C ₆ H ₅

TABLE I-2G. Carboxy-1-azaanthracenes

Formula	Position of substituent										
	?	1	2	3	4	5	6	7	8	9	10
—		COOH (2 or 4)									
XXXVIIIb			CH ₃		COOH						
XXXVIIIa			C ₆ H ₅		COOH						
XL			C ₆ H ₅		COOH	H	H	H	H		
XLia			C ₆ H ₅		COOH					Cl	
LXXXVIII			COOH		NH ₂						
LXXXIXa			COOH		OH						
XXXVIIId			OH		COOH						
LXXXVII			COOH		OCH ₃						
XLV			CH ₃	COR	OH			{ R = NHC ₁₀ H ₆ COOH- <i>o</i> }			
XCI										CN	
XXXVIIIc			COOH		COOH						

Method of synthesis	M.p., °C.	Yield, %	Properties	Ref.
—CO ₂ from XXXVIII d	272–3		Colorless needles (HOAc)	48
—CO ₂ from LXXXIX	272–3		Cream (aq. C ₂ H ₅ OH)	30
	296–8	60	Buff (aq. C ₂ H ₅ OH)	30
Methazonic acid	> 300	50	Yellow solid	22, 30
NaOCH ₃ on LXX	103–5	90	Yellow (aq. CH ₃ OH)	30
Knorr	253	70	Bright yellow needles (CH ₃ OH)	34
Conrad-Limpach	340 (dec.)	68	Yellow needles (C ₆ H ₅ NO ₂ ; then C ₂ H ₅ OH)	34
Conrad-Limpach	> 350	55	Colorless	30
Knorr	232–4	Good	Bright yellow needles (CH ₃ OH)	34
C ₆ H ₅ MgBr on IV	248–50	Poor	Colorless plates (C ₆ H ₆)	81

Method of synthesis	M.p., °C.	Yield, %	Properties	Ref.
—CO ₂ from XXXVIII c	321–3		Yellow needles (HOAc)	48
Pfitzinger	327–9		Yellow prisms (HOAc)	48
Pfitzinger	282–3		Yellow needles (dioxane)	48
Pfitzinger	237	53	Pale yellow leaves (xylene)	17
Pfitzinger	297–8 (dec.)	70	Yellow-orange crys.	42
Oxid. of LXXXVI		70	Yellow crys.	30
H ₂ SO ₄ on LXXXVII			(Not purified)	30
Camps	341–2		Yellow needles (HOAc)	48
Oxid. LXXXV	255 (dec.)		Yellow powder	30
		55	Yellow amorph. solid	30
Cu in quinoline on VIII	180	50	Yellow needles (C ₂ H ₅ OH)	8n
Pfitzinger	316–7		Orange-yellow needles (dioxane)	48

TABLE I-2H. Miscellaneous 1-Azaanthracenes

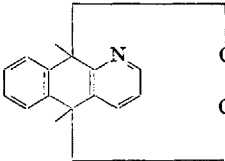
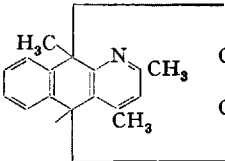
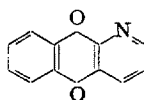
Formula	
XCIII	 $\begin{array}{l} \text{CH-CO} \\ \text{CH-CO} \end{array} \begin{array}{l} \diagup \\ \diagdown \end{array} \text{NH}$
XCIV	 $\begin{array}{l} \text{CH-CO} \\ \text{CH-CO} \end{array} \begin{array}{l} \diagup \\ \diagdown \end{array} \text{O}$
XCV	

TABLE I-3. 1-Azaanthraquinones



Position of substituent		1	2	3	4	5	6	7	8
Formula		?							
IV									
CVa			CH ₃						
CVb			CH ₃		CH ₃				
CIX			C ₆ H ₅						
CVI			C ₆ H ₅		C ₆ H ₅				
CII				Cl					
CXIII						Cl			
CIIIb or CXIV							Cl		
CXV								Cl	
CXII									Cl
—		Cl (probably same as CXIII)							
—		Cl							

Method of synthesis	M.p., °C.	Yield, %	Properties	Ref.
Diels-Alder	301	70		8s
Diels-Alder	204-5		Colorless (C ₂ H ₅) ₂ O	13
Diels-Alder	240		Colorless (C ₆ H ₈)	37

Method of preparation	M.p., °C.	Properties	Ref.
Oxid. of VIII	276; 280	Tan needles (C ₆ H ₈)	1, 2, 8, 11, 13, 21, 33
Oxid. of XXXI	173		6
Oxid. of X	214-6	Yellow needles (C ₆ H ₆ ; pet. ether)	13, 29
Decarboxylation of CVIIIa	166	Yellow	42
Oxid. of XIVa	250-1	Yellow needles (HOAc; C ₆ H ₆)	37
Oxid. of 3,9-dichloro-1-aza-anthracene	237-8	Yellow needles (C ₆ H ₆ ; pet. ether)	31
—SO ₃ H → Cl	243-4	Yellow needles (HOAc)	31
Oxid. of 6,9-diCl-1-azaanthracene	265-6	Yellow needles (HOAc)	31
—SO ₃ H → Cl	230-1; 246	Yellow needles (HOAc)	31
—SO ₃ H → Cl	217-9	Yellow needles (HOAc)	31
—SO ₃ H → Cl	241-2	Yellow plates (C ₆ H ₅ Cl)	6
—SO ₃ H → Cl	223-6	Yellow needles (CH ₃ OH)	6

(Table continued)

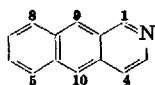
TABLE I-3 (continued)

Formula	Position of substituent							
	?	1	2	3	4	5	6	7
CIVa						Br		
CIIIa							Br	
—	Br							
CVIIa			CH ₃		CH ₃	Cl		
CVIIb			CH ₃		CH ₃		Cl	
CVIIc			CH ₃		CH ₃			Cl
CIVb						NO ₂		
LXVI								NO ₂
—	NO ₂							
—	NO ₂							
CXI						NO ₂ ?		Cl
CX						Cl		NO ₂ ?
—	NO ₂						Cl	
—	NO ₂						Br	
—	NO ₂						Br	
—						SO ₃ H		
—								SO ₃ H
—								SO ₃ H
	NH ₂							
	NH ₂							
CXXII	NH ₂ (probably the 8-deriv.)							
CXXIII	NH ₂ (probably the 5-deriv.)							
CXVI						OH		
CXVII								OH
CXVIII							OCH ₃	
CXIX								OCH ₃
XCIX						OH		OH
—	Br					OH		OH
—	COOH							
CVIIIa			C ₆ H ₅		COOH			
CVIIIb			OH		COOH			
C	{	H	H	H	O			
			COOMe					

1-Azaanthrone

Method of preparation	M.p., °C.	Properties	Ref.
Oxid. of 5-bromo-9-chloro-1-aza-anthracene	268	Yellow needles (sub.)	33
Oxid. of XXIXa	268; 259	Yellow needles	11, 33
Bromination of IV	242	Yellow needles (50 % HOAc; sub.)	33
Oxid. of XXIII; R = 5-Cl	210-11	Yellow plates (C ₆ H ₆ -pet. ether)	29
Oxid. of XXIII; R = 6-Cl	201-2	Yellow needles (C ₆ H ₆ -pet. ether)	29
Oxid. of XXIII; R = 7-Cl	228-9	Yellow needles (C ₆ H ₆ -pet. ether)	29
Oxid. of LXIII	243-5	Tan (C ₂ H ₅ OH)	21
Oxid. of LXIV	215-8	Red powder (C ₂ H ₅ OH; xylene)	31, 33, 6
Nitration of IV in H ₂ SO ₄ + KNO ₃	180-1	Red (xylene)	33
Nitration of IV in H ₂ SO ₄ + KNO ₃	215-7	Buff (xylene)	33
Nitration of CXII	222-3	Orange needles (aq. HOAc)	31
Nitration of CXIII	257-8	Yellow needles (aq. HOAc)	31
Nitration of CIIIa	283-4	Yellow needles (aq. HOAc)	31
Nitration of CIIIb	292-3	Yellow needles (HOAc)	31
Nitration of CIIIb	255-6	Yellow needles (HOAc)	31
Sulfonation of IV		<i>p</i> -Cl-benzyl- <i>ψ</i> -thiuronate; m.p. 227-8	31
Sulfonation of IV		<i>p</i> -Cl-benzyl- <i>ψ</i> -thiuronate; m.p. 215-6	31
Sulfonation of IV		<i>p</i> -Cl-benzyl- <i>ψ</i> -thiuronate; m.p. 265-6	31
Red. of 215-7° NO ₂ with Na ₂ S	274	Red (xylene)	33
Red. of 180-1° NO ₂ with Na ₂ S	262	Red (xylene)	33
NO ₂ → NH ₂ ; Na ₂ S	268	Needles (water)	6
Cl → NH ₂	286		6
KOH + CH ₃ OH on CXIII	214-5	Yellow needles (H ₂ O, sub.)	31
KOH + CH ₃ OH on CXII	199-200	Yellow needles (H ₂ O, sub.)	31
KOH + CH ₃ OH on CIIIa	259-61	Yellow needles (HOAc)	31
KOH + CH ₃ OH on CXV	205-7	Yellow needles (HOAc)	31
Cyclization	237; 230	Dark red needles (toluene)	7, 8, 24
Bromination of XCIX	—	Brownish red leaflets (C ₂ H ₅ OH)	6
Oxid.	356-7	Yellow needles (HOAc)	48
Oxid. of XXXVIIIa	270-1	Yellow prisms (C ₂ H ₅ OAc)	42, 48
Oxid. of XXXVIIId	349-51	Yellow needles (HOAc)	48
			} 25
Red. of IV, Sn + HCl	274	Red brown powder (C ₂ H ₅ OH)	33

TABLE I-4. 2-Azaanthracenes

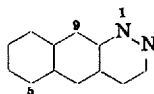


Formula	Name	M.p., °C.	Properties	Refs.
I	2-Azaanthracene	166; 169-171; 174	HCl 235; CH ₃ I 255; P 248-50	3,53
V	7-Methyl-	178-80	Yellow (ligroin); HCl 244-45	3
XV	1-Benzyl-	115-6	Yellow (hexane); P 211-12	51
XVII	9,10-Diphenyl-	240	Yellow needles	53
XX	1,2,3,4-Tetrahydro-	147	(Aq. CH ₃ OH)	3
XIV	1-Benzyl-3,4,5,6,7,8- hexahydro-	Oil	P 193-4	51
XXI	5,8,9,10- Tetraacetoxy-	283	Yellow	24
III	2-Azaanthraquinone	179; 189-90; 265-6		1,3,53
IV	5,8-Dihydroxy-2- azaanthraquinone	209; 211	Red plates (C ₂ H ₅ OH)	24,49
—	5,8-Diacetoxy-2- azaanthraquinone	187-9	Yellow	24
—	Photo dimer of I	265-70° (dec.)		8,53
—	Photooxide of XVII	212-13	Colorless prisms	8,53

2. Diazaanthracenes

Exclusive of phenazine (9,10-diazaanthracene), which will be considered elsewhere, there are only nine diazaanthracene types definitely known. These include derivatives in which the nitrogen atoms are in the 1,2-, 1,3-, 1,4-, 1,5-, 1,8-, 1,9-, 1,10-, 2,3-, and 2,10-positions. Efforts directed toward the synthesis of derivatives of 2,6- and 2,9-diazaanthracenes have been unsuccessful. These are considered along with the known derivatives as a matter of record.

- A. 1,2-Diazaanthracene. Benzo[g]cinnoline.
R. I. not listed

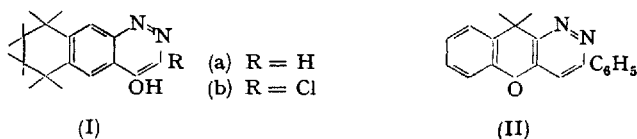


(1) Nomenclature

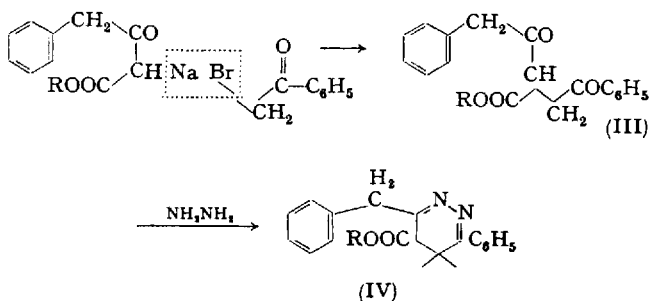
The first compound of this structural type to appear in the literature is named by the aza system used throughout this text.⁵⁴ *Chemical Abstracts*, however, lists it as benzo[g]cinnoline. Recent literature⁵⁵ refers to a tetrahydro derivative as a "cyclohexenocinnoline."

(2) Syntheses

Two substituted "cyclohexenocinnolines" (5,6,7,8-tetrahydro-1,2-diazaanthracenes) (Ia, Ib) and 10-oxo-3-phenyl-9,10-dihydro-1,2-diazaanthracene (II) are the only derivatives known. The synthesis of the latter, named 3-phenyl-1,2-diazaanthrone by its discoverers,⁵⁴



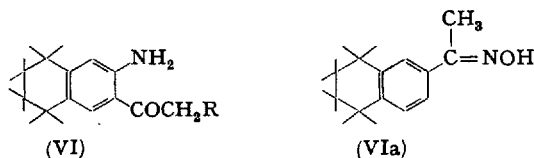
involves the following steps. Phenacyl bromide is condensed with the sodium salt of ethyl γ -phenylacetoacetate to give ethyl β -benzoyl- α -phenylacetylpropionate (III). Treatment of III with hydrazine yields the dihydrazone, which loses a mole of hydrazine in boiling alcohol and forms 6-benzyl-5-carbethoxy-3-phenyl-4,5-dihydropyridazine (IV).



Dehydrogenation with chromium trioxide gives the pyridazine as the free acid, which is converted to the acid chloride (V) and cyclized by treatment with aluminum chloride in nitrobenzene to 10-oxo-3-phenyl-9,10-dihydro-1,2-diazaanthracene (II). A dinitrophenylhydrazones of II is reported.

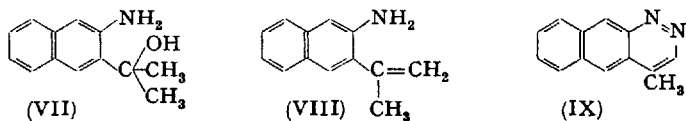


The "cyclohexenocinnolines" are formed when 7-acetyl-6-aminotetralin (VI, R = H) or 7-chloroacetyl-6-aminotetralin (VI, R = Cl) is treated with nitrous acid.⁵⁵ These intermediates are obtained from 6-acetyltetralin by subjecting the oxime (VIa) to a Beckmann rear-

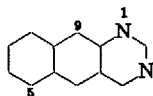


rangement and acylating the product with the requisite acid chloride by a Friedel and Crafts reaction.

A "more promising route" to a 1,2-diazaanthracene (IX) has been suggested⁵⁵ but no details are recorded. The suggested method consists of dehydrating 2-amino-3-naphthyldimethylcarbinol (VII) (obtained from ethyl 3-amino-2-naphthoate by the Grignard reaction), and treating the resulting ethylenic compound (VIII) with nitrous acid.



B. 1,3-Diazaanthracene. Benzo[g]quinazoline. 6,7-Benzoquinazoline. 2(N),3-Pyrimidinonaphthalene. R. I. 1902



No compound of this skeletal structure was reported in the literature until 1929. Since then several derivatives have been made, and two have been tested as antimalarials.

(1) *Nomenclature*

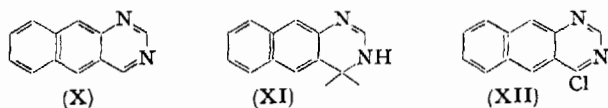
While compounds of this class have been listed in the indexes of *Chemical Abstracts* as benzo[g]quinazolines, in the actual abstracts the names "6,7-benzoquinazoline" and "2(*N*),3-pyrimidinonaphthalene" have been used. The corresponding quinones appear in the indexes as benzo[g]quinazoline-5,10-diones, and are cross-indexed as 1,3-diazaanthraquinones in some instances but not in others. In all the abstracts, however, these products are referred to as derivatives of 1,3-diazaanthraquinone. In this section the benzo[g]quinazolines are called 1,3-diazaanthracenes, and the corresponding quinones, 1,3-diazaanthra-



quinones. The meso positions are given the numbers "9,10," by analogy with anthraquinone.

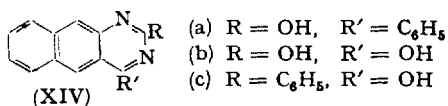
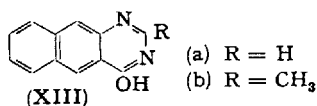
(2) *Syntheses*

(a) By Cyclization Procedures. 1,3-Diazaanthracene (X), the parent compound of the series, is obtained by oxidation of the dihydro derivative (XI), which in turn is secured from the 4-chloro derivative (XII) by reduction with palladium on calcium carbonate (see p. 78). The oxidation is carried out with potassium ferricyanide.⁵⁸

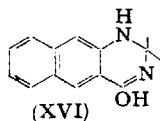
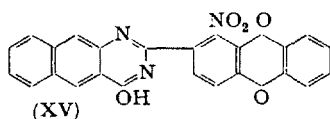


The formation of this ring structure involves cyclization of β -naphthylamines substituted in the 3-position with $-\text{COOH}$, $-\text{CONH}_2$, or $-\text{COC}_6\text{H}_5$ groups. The derivative formed depends upon the reagent used with the naphthylamine derivative. Thus, formamide reacts with

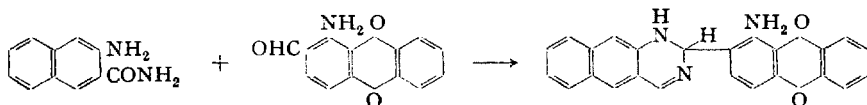
3-amino-2-naphthoic acid to give 4-hydroxy-1,3-diazaanthracene (XIIIa).⁵⁶ A similar reaction with acetamide yields 4-hydroxy-2-methyl-1,3-diazaanthracene (XIIIb). Benzamide does not react under the same conditions. Variations of this reaction to produce other 1,3-diazaanthracene derivatives have appeared in the patent literature.⁵⁷



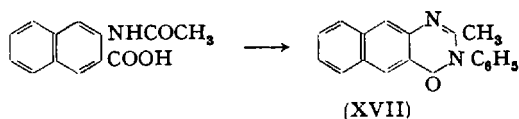
They include the following: 2-hydroxy-4-phenyl-1,3-diazaanthracene (XIVa) from 3-benzoyl-2-naphthylamine and urethan in the presence of zinc chloride; 2,4-dihydroxy-1,3-diazaanthracene (XIVb) from 3-amino-2-naphthoic acid and urea; 4-hydroxy-2-phenyl-1,3-diazaanthracene (XIVc) from 3-amino-2-naphthamide and benzoyl chloride; and 4-hydroxy-2-(1-nitro-2-anthraquinonyl)-1,3-diazaanthracene (XV) from 3-amino-2-naphthamide and 1-nitroanthraquinone-2-carbonyl chloride in the presence of alkali and pyridine. While no details are available in the patent literature, recent work⁶² indicates that the reactions proceed well in phenol.



A dihydro derivative, 4-hydroxy-1,2-dihydro-1,3-diazaanthracene [*py*-4-hydroxy-*py*-1,2-dihydro-2(*N*),2-pyrimidinonaphthalene] (XVI) results when 3-amino-2-naphthamide is treated with paraformaldehyde in acetic acid,⁵⁸ or by treatment of hydroxy-1,3-diazaanthracene (XIIIa) with lithium aluminum hydride.⁵⁶ It is described as a useful dye intermediate, but no definite application is indicated. Apparently, 1-amino-2-formylantraquinone undergoes a similar reaction.

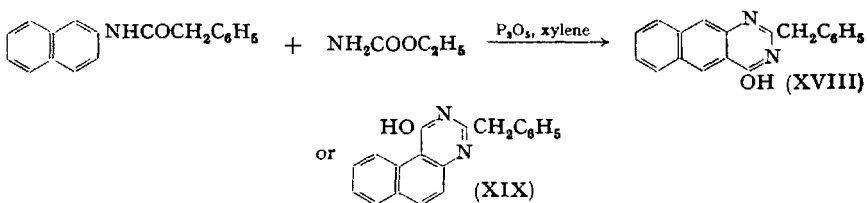


A modification of these reactions consists in the use of phosphazobenzene anilide.⁵⁹ This reagent is made by treating aniline in toluene with phosphorus trichloride, and evaporating to dryness to isolate the compound. It can, however, be used in the toluene solution. It is apparently dimeric, the formula being given as $(C_6H_5N=PNHC_6H_5)_2$. The interaction of this reagent with 3-acetamido-2-naphthoic acid gives



2-methyl-4-oxo-3-phenyl-1,3-dihydro-1,3-diazaanthracene XVII. The analog from *p*-chloroaniline is obtained by a similar procedure.⁶⁰

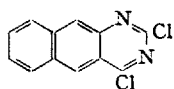
A somewhat different type of cyclization is involved in the synthesis of 2-benzyl-4-hydroxy-1,3-diazaanthracene (XVIII). Treatment of compounds of the type $RNHCOCH_2C_6H_5$ with urethan and phosphorus pentoxide in xylene results in 3–13 % yields of benzopyrimidines when R is phenyl or a substituted phenyl group. Application of this reaction⁶¹ to the β -naphthalide of phenylacetic acid gives 2-benzyl-4-hydroxy-1,3-diazaanthracene (2-benzyl-4-hydroxy-6,7-benzoquinazoline) (XVIII) or the isomeric derivative (XIX). In view of the fact that



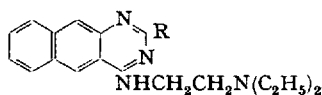
the Doebner-Miller and Skraup syntheses usually give angular products with β -naphthylamine, the angular structure (XIX) would be preferred (see p. 360). No proof as to which compound is obtained has been indicated, but, in view of the preparation of 4-hydroxy-2-phenyl-1,3-diazaanthracene (XIVc) by an unambiguous procedure, a method of proof as to whether linear or angular cyclization has occurred is obvious. By using phenylacetyl chloride instead of benzoyl chloride in a similar

synthesis, a compound identical with XVIII should result if the cyclization of phenylacetamidonaphthalene with phosphorus pentoxide in xylene is linear.

(b) By Replacement of Other Groups. It has already been mentioned that 4-chloro-1,3-diazaanthracene (XII) is the precursor of the parent compound. This substance is obtained from 4-hydroxy-1,3-diazaanthracene (XIIIa) by treatment with phosphoryl chloride in chlorobenzene.⁵⁶ The chlorine is quite active; it is hydrolyzed to the hydroxy derivative in either acid or alkaline solution. If phosphorus pentachloride is used instead of phosphoryl chloride, a dichloro-1,3-diazaanthracene is formed in which the position of the second chlorine atom is unknown.⁵⁶ However, 2,4-dihydroxy-1,3-diazaanthracene (XIVb) can be dichlorinated by using a mixture of phosphoryl chloride and phosphorus pentachloride, and this substance is presumably the 2,4-dichloro derivative (XX).^{62,63} The melting point of XX (184°) is somewhat lower than that reported for the dichloro derivative (192°) obtained by chlorination of the monohydroxy compound. They may or may not be identical. One piece of evidence that points to their



(XX)

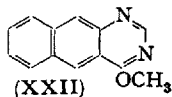
(a) $R = Cl$ (b) $R = p\text{-}ClC_6H_4NH$

(XXI)

nonidentity is a statement to the effect that the unknown dichloro compound is hydrolyzed easily to a hydroxychloro derivative, the structure of which is also unknown. Hydrolysis of XX would be expected to produce the dihydroxy derivative from which XX is prepared, but one chlorine atom may be somewhat more reactive than the other, and mild hydrolysis may replace one chlorine atom only. Evidence in support of this is derived from the fact that XX has been converted successively to 2-chloro-4-(β -diethylaminoethylamino)-1,3-diazaanthracene (XXIa) and 2-*p*-chloroanilino-4-(β -diethylamino-

ethylamino)-1,3-diazaanthracene (XXIb).^{62,63} These two derivatives have been tested as antimalarials.

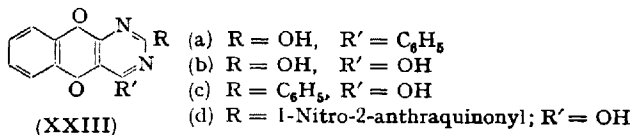
Dechlorination of XII to the dihydro compounds (XI) has already been mentioned. The methoxy derivative (XXII) results when the chloro derivative, XII, is treated with sodium methoxide. Treatment



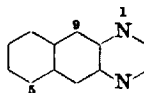
of the hydroxy derivative (XIIIa) with methyl iodide leads to two monomethyl derivatives⁵⁶; their structures have not been determined.

(3) 1,3-Diazaanthraquinones

According to the patent literature⁵⁷ 2-hydroxy-4-phenyl-, 2,4-dihydroxy-, 4-hydroxy-2-phenyl- (XIVa, b, c), and 2-(1-nitro-2-anthraquinonyl)-4-hydroxy-1,3-diazaanthracenes are oxidized to the corresponding 1,3-diazaanthraquinones (XXIII) with chromic acid in acetic acid. The substances are said to be useful in the preparation of vat, acid, and pigment dyes.



- C. 1,4-Diazaanthracene. 6,7-Benzo[g]quinoxaline. Naphtho-2',3',2,3-pyrazine. 2,3-Naphthoquinoxaline. R. I. 1903



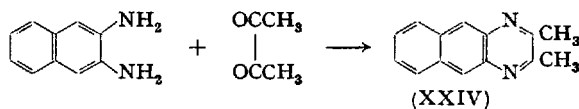
(1) Nomenclature

The parent substance, 1,4-diazaanthracene, is unknown, but several substitution products have been prepared. They are listed in the indexes of *Chemical Abstracts* as 6,7-benzo[g]quinoxalines. They

have been called 6,7-benzoquinoxalines, naphtho-2',3',2,3-pyrazines, 2,3-naphthoquinoxalines (Beilstein), and linear benzoquinoxalines.⁶⁴

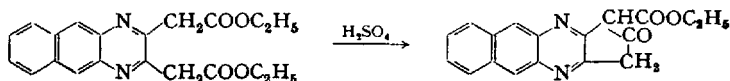
(2) Synthesis

The 1,4-diazaanthracenes are essentially quinoxalines, and, as such, are formed by the general reaction of an *o*-diamine with a 1,2-dicarbonyl compound. Thus, when 2,3-diaminonaphthalene dihydrochloride is treated with an α -dicarbonyl compound in an appropriate solvent, the 1,4-diazaanthracene derivative separates.⁶⁴ For example, diacetyl reacts with 2,3-diaminonaphthalene to give 2,3-dimethyl-1,4-diazaanthracene (XXIV). In the same manner benzil,^{64,65} pyruvic



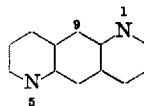
acid,⁶⁴ methyl oxalate,⁶⁴ and ethyl ketipate (ethyl β,γ -dioxoadipate)⁶⁵ react with 2,3-diaminonaphthalene to give 2,3-diphenyl-, 2-hydroxy-3-methyl-, 2,3-dihydroxy-, and 2,3-dicarbethoxymethyl-1,4-diazaanthracenes, respectively. The 2,3-dihydroxy derivative is also formed directly by melting the diamine with oxalic acid.⁶⁶ A slight variation in the general reaction, which specifies the use of α -dicarbonyl compounds, is evident in the reaction of dihydroxytartaric acid with the diamine. Four moles of water are lost in the reaction, which is carried out in acid solution, and 2,3-dicarboxy-1,4-diazaanthracene results.⁶⁶ The reaction is in line with the general statement if one assumes that two moles of water are lost from dihydroxytartaric acid prior to its reaction with the diamine. Similar compounds are obtained by treating more complex ortho diketones such as phenanthraquinone and perinaphthenequinone with the diamine.⁶⁴

2,3-Dicarbethoxymethyl-1,4-diazaanthracene undergoes a further cyclization when it is treated with sulfuric acid:



The product is isolated as the sulfate, and, like many members of the azaanthracene series, shows a green fluorescence in solution.

- D. 1,5-Diazaanthracene. Pyrido[2,3-*g*]quinoline. 1,5-Anthrazoline. lin-*p*-Benzodipyridine. R. I. 1947H**



(1) Nomenclature

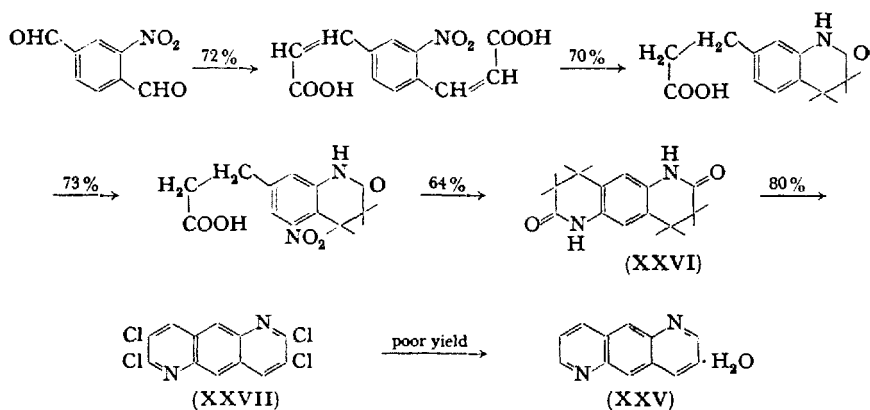
References to compounds of this type first appeared in the literature in 1939. In indexing them, *Chemical Abstracts* uses the name 1,5-anthrazoline but gives cross references to pyrido[2,3-*g*]quinoline except in the first reference to 1,5-anthrazoline. The latter name was suggested by Ruggli⁶⁷ for linear tricyclic systems containing nitrogen, but, as he points out, azaanthracene is equally appropriate.

(2) Syntheses

Preparative methods leading to 1,5-diazaanthracene and its 10-methyl, 2,6-dimethyl, and 2,6-diphenyl derivatives are known. Certain tetrahydro and octahydro derivatives are obtained as intermediates. These syntheses are outlined below; the properties of the derivatives are collected in Table I-5 at the end of this section.

(a) 1,5-Diazaanthracene (XXV).⁶⁷ The synthesis of 1,5-diazaanthracene (XXV) involves several steps: Nitroterephthalaldehyde is treated with malonic acid in pyridine to give nitro-*p*-phenylenediacrylic acid; this material is reduced with Raney nickel to dihydrocarbostyryl-7-propionic acid. The reduction is carried out by suspending the nitro compound in a mixture of water, methanol, ethanol, and ethyl acetate, and heating to 75° under normal hydrogenation conditions. At room temperature hydrogenation leads to the free amino compound unless a large amount of catalyst is used. The carbostyryl derivative is then nitrated (KNO₃ in H₂SO₄); the nitration is carried out at 15–20° and is complete in 2–3 minutes; a longer nitration time leads to the intro-

duction of a second nitro group. The 6-nitro-3,4-dihydrocarbostyryl-7-propionic acid thus formed is hydrogenated at room temperature with Raney nickel as the catalyst (10 hours). The resulting product, 2,6-dihydroxy-3,4,7,8-tetrahydro-1,5-diazaanthracene or the tautomeric oxo form (XXVI) is treated with a mixture of phosphoryl chloride and phosphorus pentachloride to give 2,3,6,7-tetrachloro-1,5-diazaanthracene (XXVII). Dechlorination with phosphorus and hydriodic acid in acetic acid (sealed tube) yields 1,5-diazaanthracene (XXV) as the monohydrate.



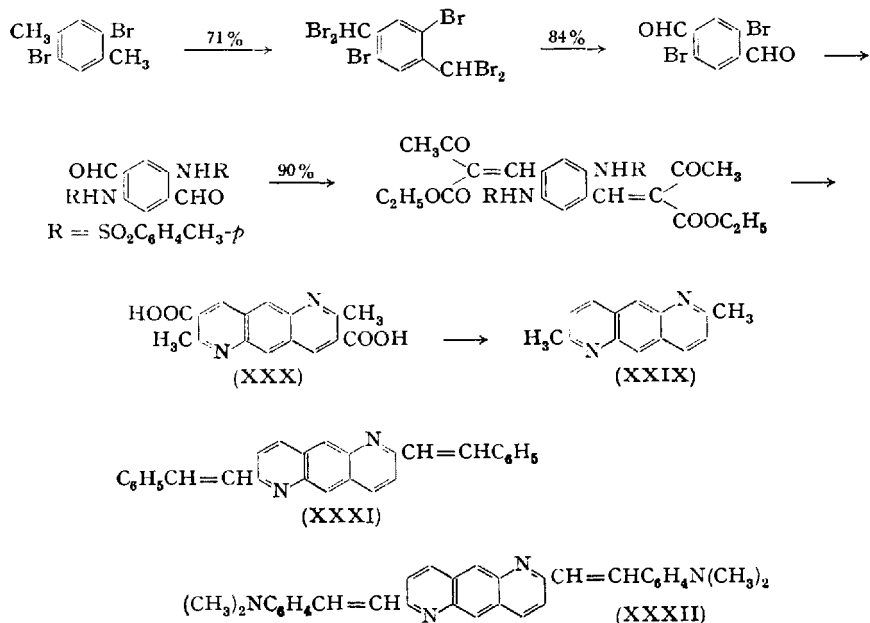
(b) **10-Methyl-1,5-diazaanthracene (XXVIII)** is formed in small yield when 6-acetamido-5-methylquinoline is subjected to a Skraup synthesis.⁷⁰ The product is isolated as the monohydrate and in this



respect is similar to the parent compound, 1,5-diazaanthracene (XXV). It shows the characteristic deep blue fluorescence of the azaanthracenes.

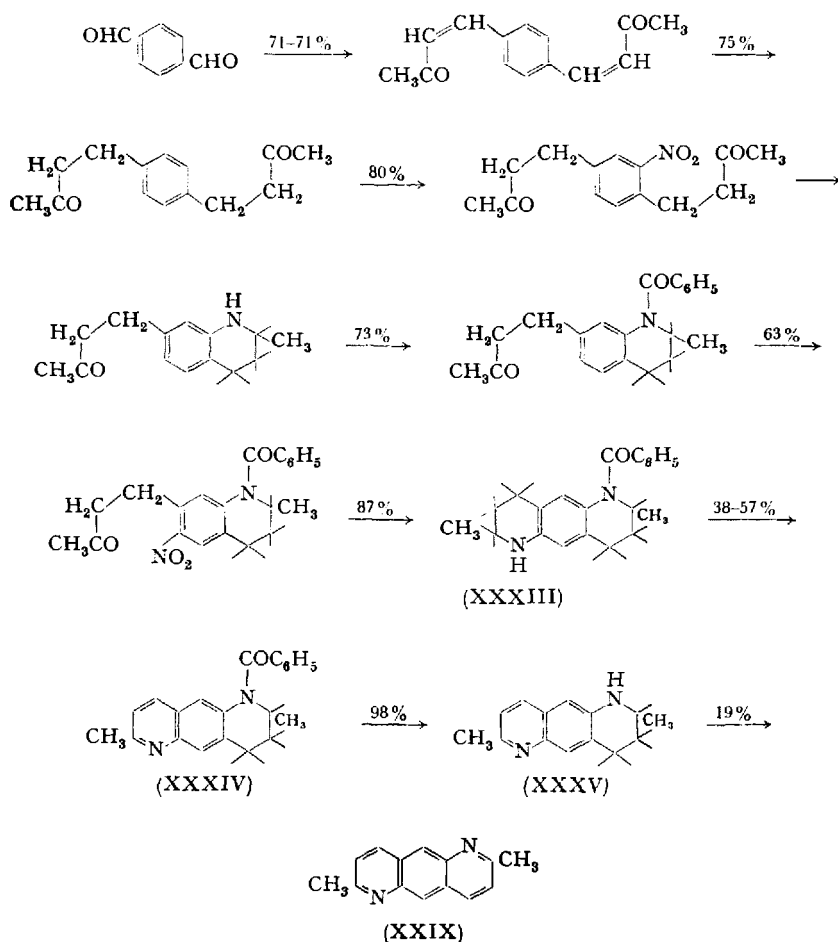
(c) **2,6-Dimethyl-1,5-diazaanthracene (XXIX).**⁶⁸ As with the parent compound, synthesis of the 2,6-dimethyl derivative requires several steps: 2,5-dibromo-*p*-xylene is brominated in ultraviolet light to

1',1',4',4',2,5-hexabromo-*p*-xylene, which is treated with sulfuric acid (monohydrate) at 130–40° under reduced pressure to give 2,5-dibromoterephthalaldehyde. The dibromo compound is converted by use of *p*-toluenesulfonamide (Ullmann synthesis) into 2,5-ditolylsulfonamido-terephthalaldehyde. The dialdehyde condenses readily with ethyl acetoacetate in alcohol solution in the presence of piperidine to give a diethyl acetoacetate derivative, which is hydrolyzed, and cyclized to 3,7-dicarboxy-2,6-dimethyl-1,5-diazaanthracene (XXX) by treatment with sulfuric acid at 35–40°. Decarboxylation is effected by boiling the acid in quinoline in the presence of copper. The 2,6-dimethyl-1,5-diazaanthracene (XXIX) thus formed gives a distyryl- (XXXI) and a bis(*p*-dimethylaminostyryl) derivative (XXXII).

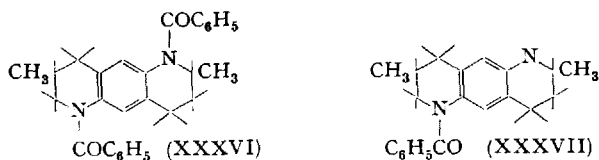


A second synthesis⁶⁹ of 2,6-dimethyl-1,5-diazaanthracene consists of the following steps: Terephthalaldehyde is condensed with acetone in the presence of alkali and the product reduced with Raney nickel to 1,4-bis(γ -oxobutyl)benzene. Nitration in sulfuric acid, followed by a Raney nickel catalyzed reduction, gives 7-(γ -oxobutyl)-1,2,3,4-tetra-

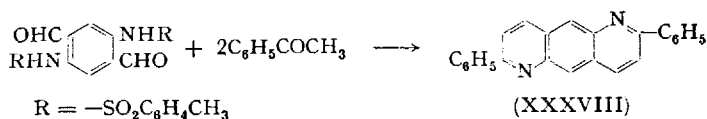
hydroquinoline. This is converted to the benzoyl derivative, and the latter is nitrated and then reduced (Raney nickel) to yield 1-benzoyl-2,6-dimethyl-1,2,3,4,5,6,7,8-octahydro-1,5-diazaanthracene (XXXIII). Dehydrogenation with sulfur or maleic acid and palladium-charcoal leads to the benzoyl derivative of 2,6-dimethyl-1,2,3,4-tetrahydro-1,5-diazaanthracene (XXXIV), which is debenzoylated by heating with hydrochloric acid at 125°. The resulting 2,6-dimethyl-1,2,3,4-tetrahydro-1,5-diazaanthracene (XXXV) is dehydrogenated by heating it with an aqueous suspension of arsenic acid and palladium-charcoal (sealed tube).



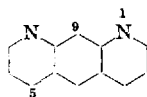
A number of derivatives of these 1,5-diazaanthracenes are reported; XXXIII gives a dibenzoyl derivative (XXXVI) and a nitroso compound (XXXVII); XXXV also forms a nitroso compound.



(d) **2,6-Diphenyl-1,5-diazaanthracene (XXXVIII)** results when di-*p*-toluenesulfonamidoterephthalaldehyde is heated with acetophenone to 190°, ⁶⁸



E. **1,8-Diazaanthracene. Pyrido[3,2-*g*]quinoline. 1,8-Anthrazoline. lin-*m*-Benzodipyridine. R.I. 1948**

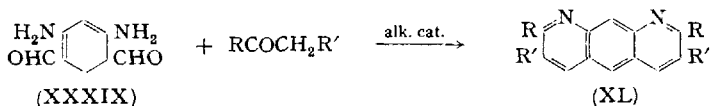


(1) Nomenclature

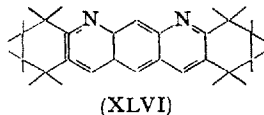
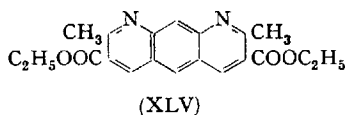
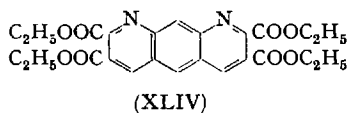
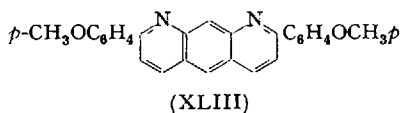
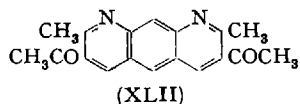
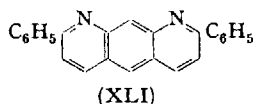
Compounds of this class are listed in *Chemical Abstracts* as pyrido[3,2-*g*]quinolines. While the name 1,5-anthrazoline was applied by Ruggli⁶⁷ to 1,5-diazaanthracene (linear *p*-benzodipyridine), 1,8-diazaanthracene (linear *m*-benzodipyridine) was prepared prior to the adoption of the name anthrazoline.

(2) Synthesis

Derivatives of 1,8-diazaanthracene are prepared by what appears to be quite a general reaction; 4,6-diaminoisophthalaldehyde (XXXIX) is treated with compounds containing a carbonyl and an adjacent active methylene group:

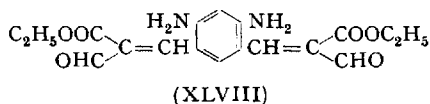
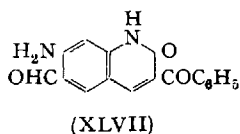


The reaction proceeds in the presence of an alkaline condensing agent (piperidine or alcoholic alkali). The use of acetophenone⁷¹ leads to 2,7-diphenyl-1,8-diazaanthracene (XLI). Acetylacetone⁷², *p*-methoxy-



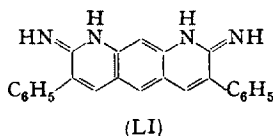
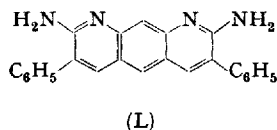
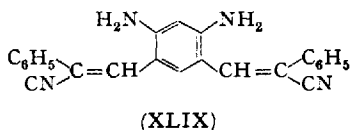
acetophenone,⁷² ethyl oxalacetate,⁷² and ethyl acetoacetate⁷¹⁻⁷³ react with XXXIX in a similar manner to give the substituted 1,8-diazaanthracenes (XLII, XLIII, XLIV, XLV), respectively. Cyclohexanone⁷³ also reacts to give compound XLVI, an octahydro diazapentacene.

Ethyl benzoylacetate,⁷² ethyl formylacetate,⁷³ and benzyl cyanide⁷³ also react with 4,6-diaminoisophthalaldehyde (XXXIX). Only one mole of ethyl benzoylacetate reacts with XXXIX and the product is a

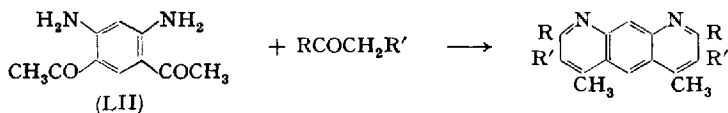


carbostyryl (XLVII). With ethyl formylacetate, a double condensation takes place, but the main product of the reaction is an open-chain compound (XLVIII). A small amount of 2,7-dicarboxy-1,8-diazaanthracene (LXIV) is formed simultaneously. The condensation product formed with benzyl cyanide and 4,6-diaminoisophthalaldehyde

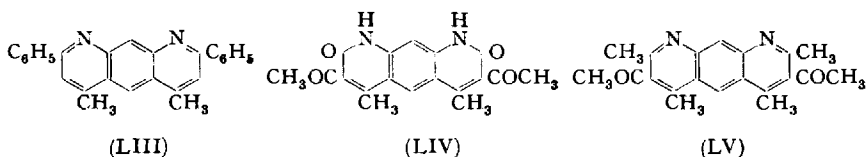
(XXXIX) may exist in one of three forms (XLIX, L, LI). The formation of a tetracycl derivative is best explained by structure LI.



An extension of this reaction makes use of 4,6-diacetyl-*m*-phenylenediamine (LII)⁷⁴; this diketone reacts toward carbonyl compounds having an active methylene group in the same manner as the



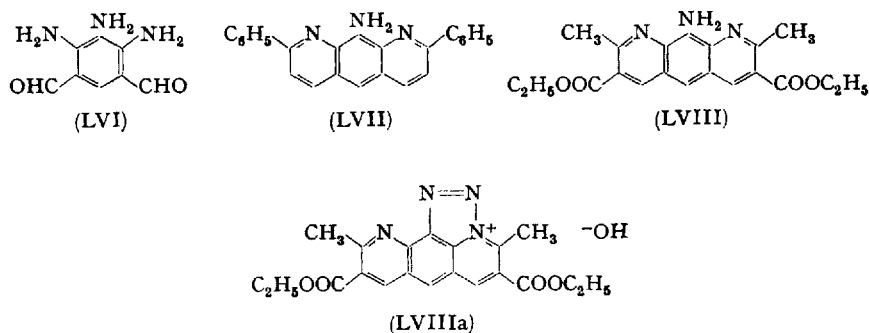
dialdehyde (XXXIX). Thus, acetophenone gives 4,5-dimethyl-2,7-diphenyl-1,8-diazaanthracene LIII; ethyl acetoacetate and acetyl-



acetone yield the 1,8-diazaanthracenes, LIV and LV, respectively.

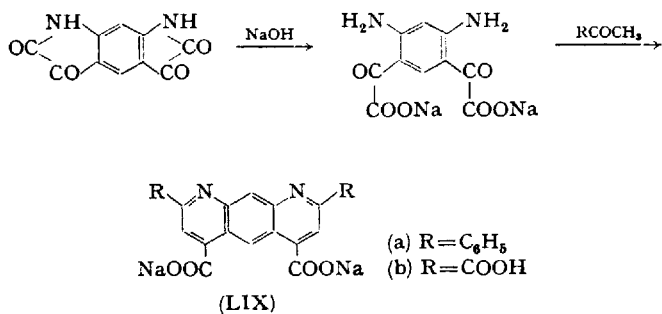
In an analogous manner, 4,5,6-triaminoisophthalaldehyde (LVI) (made by nitrosation of XXXIX followed by reduction with stannous chloride), reacts with acetophenone and ethyl acetoacetate to give 9-amino-2,7-diphenyl-1,8-diazaanthracene (LVII) and 9-amino-3,6-dicarboxy-2,7-dimethyl-1,8-diazaanthracene (LVIII), respectively.⁷⁵

The latter compound on treatment with nitrous acid gives a substance which fails to couple with resorcinol or R salt and which on treatment



with sodium acetate solution forms a substance, the analysis of which agrees with the structure LVIIIa.

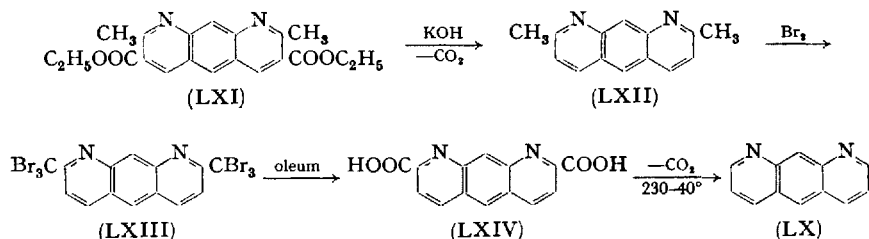
Substances of the general structure LIX are prepared by the application of the Pfitzinger reaction to bisdioxopyrrolino[2',3',1,2,2'',3'',5,4] benzene, the reaction proceeding as follows^{75a}:



With acetophenone, 4,5-dicarboxy-2,7-diphenyl-1,8-diazaanthracene (LIXa) is obtained, while pyruvic acid leads to 2,4,5,7-tetracarboxy-1,8-diazaanthracene (LIXb).

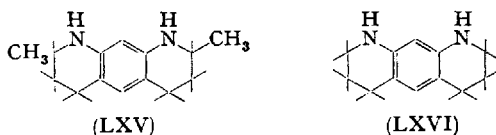
The parent base, 1,8-diazaanthracene (LX) is known; it is prepared as follows: 3,6-Dicarbethoxy-2,7-dimethyl-1,8-diazaanthracene (LXI) prepared from XXXIX and ethyl acetoacetate, is hydrolyzed to the free acid and decarboxylated;

The resulting product, LXII, is brominated in chloroform to give 2,7-di(tribromomethyl)-1,8-diazaanthracene (LXIII), which is converted

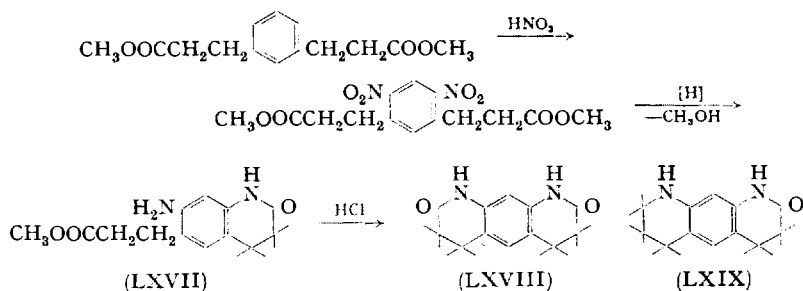


to the acid, LXIV, by treatment with oleum. Decarboxylation of the acid by heating at 230–40° results in the formation of 1,8-diazaanthracene (LX). More recently this base was obtained by decarboxylation of 2,4,5,7-tetracarboxy-1,8-diazaanthracene (LIXb).^{75a}

Hydrogenation of the bases (LXII and LX) with sodium and amyl alcohol results in the formation of the octahydro compounds, LXV and LXVI, respectively.⁷³ Being secondary bases, these compounds form diacetyl and dinitroso derivatives.⁷³ The octahydro compound (LXVI)

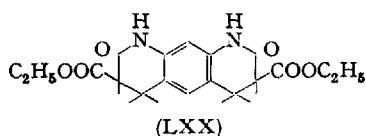


was one of the first 1,8-diazaanthracene derivatives to be prepared. The methylester of *m*-phenylene- β,β' -dipropionic acid is dinitrated and then reduced: simultaneously there is a loss of methanol and methyl 7-amino-3,4-dihydrocarbostyryl-6- β -propionate (LXVII) is formed. When the latter is boiled in concentrated hydrochloric acid, cyclization

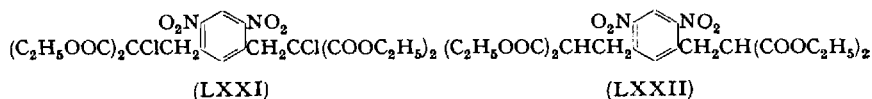


occurs with the elimination of the elements of methanol to give 2,7-dioxo-1,2,3,4,5,6,7,8-octahydro-1,8-diazaanthracene (LXVIII), which is reduced by phosphorus and hydriodic acid at 185° to the base⁷⁶ (LXVI). Under special conditions an intermediate, LXIX, can be obtained.⁷⁶

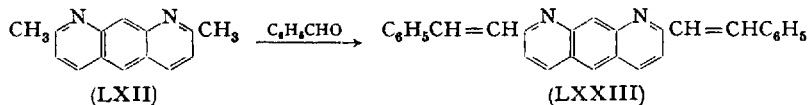
Other syntheses which lead to 2,7-dioxo-1,2,3,4,5,6,7,8-octahydro-1,8-diazaanthracene (LXVIII) and its 3,6-dicarbethoxy derivative (LXX) have been described. Thus, LXVIII is prepared by heating 4,6-



diamino-1,3-phenylenediacrylic acid in a sealed tube with concentrated hydrochloric acid for five hours at 160°, ⁷² and LXX results when 4,6-dinitro-1,3-xylylenedi(chloromalonic ester) (LXXI) or 4,6-dinitro-1,3-xylylenedimalonic ester (LXXII) is hydrogenated with Raney nickel as the catalyst.⁷⁷ The resulting ester (LXX) can be hydrolyzed to the free acid.

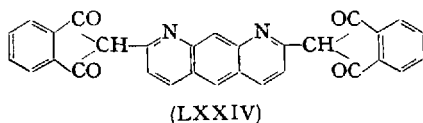


2,7-Dimethyl-1,8-diazaanthracene (LXII) reacts with aldehydes in the same manner as picoline; thus, benzaldehyde yields 2,7-di- β -styryl-1,8-diazaanthracene (LXXIII).⁷³ Furfural and *p*-dimethylaminobenzaldehyde⁷³ react similarly. The product resulting from the



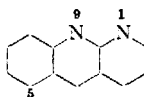
latter has four basic groups, which undergo salt formation with various concentrations of hydrochloric acid, giving rise to violet, blue, green, and yellow salts.

Some further possibilities of reactions of LXII are indicated by Ruggli and Frey.⁷³ By treatment with ethyl phthalate and sodium, for example, LXII gives a scarlet-red powder, the nitrogen content of which corresponds to the formula LXXIV. Sulfonation results in a water-soluble product that dyes wool and silk bluish-red shades from



an acid bath. Condensation of LXII with isoquinoline, benzotrichloride, and zinc chloride, which should lead to a quinoline red-like substance of high molecular weight, gives a violet-colored dye which colors silk violet. It desensitizes a photographic plate, whereas quinoline red causes sensitization.

- F. 1,9-Diazaanthracene. Pyrido[2,3-*b*]quinoline. α -Quinoquinoline. Pyracridine. 6,7-Benzo-1,8-naphthyridine. R. I. 1949**



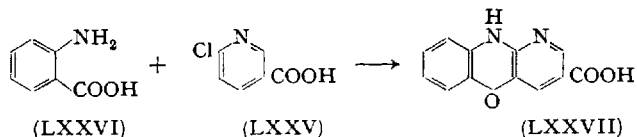
(1) *Nomenclature*

1,9-Diazaanthracene and its derivatives, described variously as pyrido[2,3*b*]quinoline (*Ring Index*), α -quinoquinoline,⁷⁸ pyracridine,⁷⁹ 6,7-benzo-1,8-naphthyridine,⁸⁰ etc., are of interest for comparison with acridine. Because of the seemingly contradictory evidence involved in various syntheses of 1,9-diazaanthracene derivatives, this section will be developed in more or less chronological order.

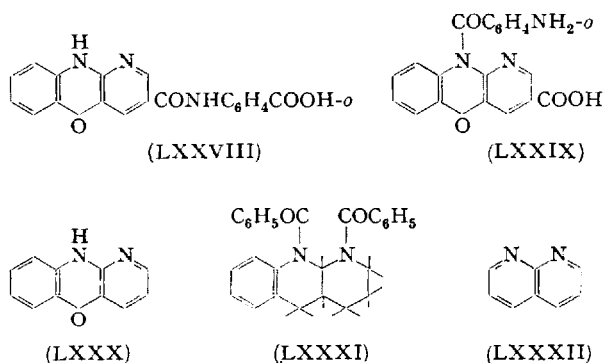
(2) *Historical*

In 1895, Reissert⁷⁸ heated equimolecular amounts of 5-carboxy-2-chloropyridine (LXXV) and anthranilic acid (LXXVI) and obtained

in good yield a substance he considered to be 3-carboxy-10-oxo-9,10-dihydro-1,9-diazaanthracene (LXXVII).

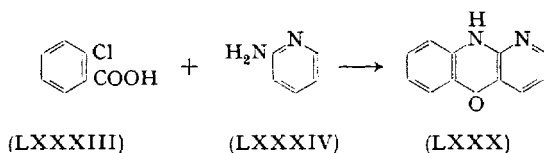


A by-product LXXVIII or LXXIX, formed in the same reaction, presumably by the action of LXXVII with LXXVI, was decomposed into LXXVII and LXXVI by treatment with alkali. Decarboxylation of LXXVII by heat resulted in the formation of 10-oxo-9,10-dihydro-

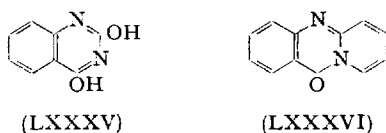


(9*H*)-1,9-diazaanthracene (α -quinoquinolone, LXXX). Reissert failed to prove the structure of LXXVII though he did prepare an octahydro compound which he isolated as the dibenzoyl derivative and represented by the structure LXXXI. He also obtained a small amount of a substance he thought might be 1,8-naphthyridine (LXXXII).

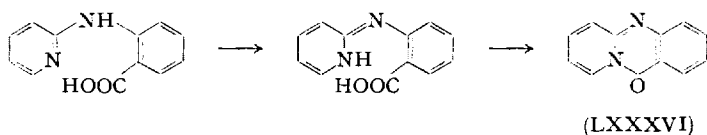
Some years later Seide,⁸¹ because of his interest in 1,8-naphthyridine, attempted to obtain the latter from " α -quinoquinolone" (LXXX). He prepared LXXX by heating *o*-chlorobenzoic acid (LXXXIII) and 2-aminopyridine (LXXXIV) to 190° with potassium carbonate and



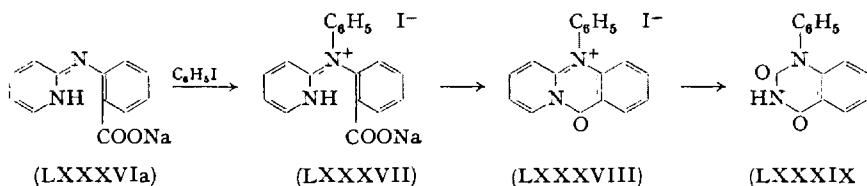
copper, a typical Ullmann acridone synthesis. This compound showed all the properties of Reissert's " α -quinoquinolone," having the same melting point and giving three salts that melted or decomposed as described by Reissert. Oxidation of the compound, however, led to 2,4-dihydroxyquinazoline (LXXXV) which, according to Seide, proved that



the structure is that represented by LXXXVI. Seide concluded that the cyclization proceeded as follows, Reissert's formulation being incorrect:

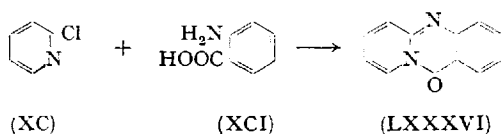


Further evidence in support of this mechanism arose from the fact that treatment of LXXXVI with alkali opened the ring and gave a sodium salt (LXXXVIa), which reacted with iodobenzene, producing an "iodophenylate" (LXXXVII); the latter on acidification gave a "phenylquinoquinolonium iodide" (LXXXVIII) that was oxidized to 1-phenyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline (LXXXIX).

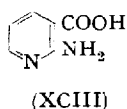
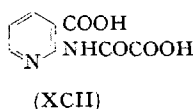


Despite the evidence indicating that the compounds prepared by Reissert and Seide were identical, Rath⁸² chose a different procedure for the synthesis. 2-Chloropyridine (XC) reacted with anthranilic acid (XCI) to give a substance melting at the same point as that prepared by Seide. Rath, however, pointed out that, while this substance

appeared to be identical with Seide's compound, it differed in two respects; it was insoluble in dilute alkali, and it gave a well-defined hydrazone (XCIV). Seide had failed to obtain a carbonyl reaction, and his product was alkali-soluble. Furthermore, oxidation of this product

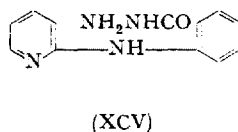
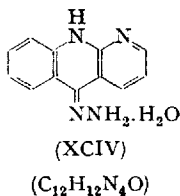


led to a good yield of 2-oxalylamino-3-carboxypyridine (XCII), which was converted to 2-aminonicotinic acid (XCIII). From these results



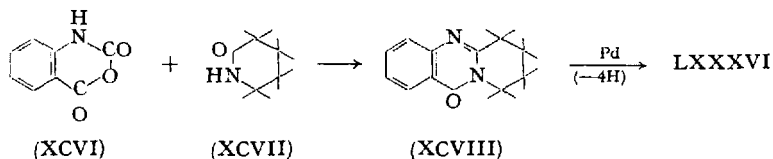
Rath concluded that the original compound was LXXX and not LXXXVI, and that Reissert's formulation, LXXX, was correct.

With Rath's evidence confronting him, Seide⁸³ reinvestigated the problem, using Rath's procedure for the preparation of the material. He pointed out that the so-called hydrazone of "pyracridone" (XCIV) which, according to Rath, separated with one mole of water of crystallization, is the hydrazone of α -pyridylanthranilic acid (XCV). In the case of the oxidation product, Seide maintains that the 2-amino-

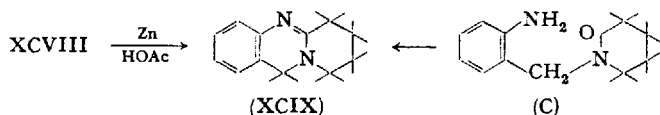


nicotinic acid (XCIII) reported by Rath is actually 4-hydroxyquinazoline. The fact that the melting point (217°) recorded by Rath is the same as that given in the literature for 4-hydroxyquinazoline, while 2-aminonicotinic acid melts at 310°, certainly bears out Seide's conclusion.

Furthermore, Späth⁸⁴ synthesized a tetrahydro derivative (XCVIII) of LXXXVI from isotoic anhydride (XCVI) and α -piperidone (XCVII) and showed that, on dehydrogenation with palladium black, a substance was obtained which was identical with LXXXVI. As



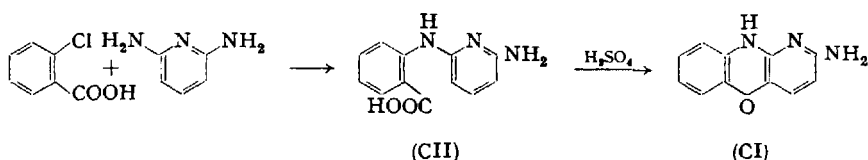
additional evidence, XCVIII was reduced with zinc and acetic acid to XCIX, and the latter also was synthesized from *N*-*o*-aminobenzyl-piperidone (C) by ring closure.



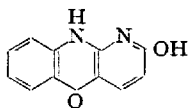
Rath has patents on the preparation of "pyracridone" and its nitration products,⁷⁹ but, since Seide and Späth have shown that Rath was in error, these substances must be considered as derivatives of 10-oxo-4a,9-diazaanthracene (LXXXVI).

(3) Syntheses

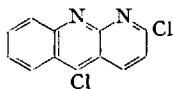
In contrast to 2-aminopyridine, 2,6-diaminopyridine leads to 2-amino-10-oxo-9,10-dihydro-1,9-diazaanthracene (CI) when it reacts with *o*-chlorobenzoic acid and the intermediate product, CII, is cyclized by means of sulfuric acid.⁸⁵ This is a typical acridone synthesis and presumably takes place because of the activation, by the additional amino group, of the position in which cyclization is effected. Treatment



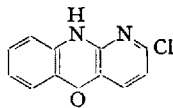
of CI with nitrous acid leads to the 2-hydroxy compound (CIII); the latter, when treated with phosphoryl chloride and poured on ice and ammonium hydroxide, gives 2,10-dichloro-1,9-diazaanthracene (CIV). (A compound of structure CIV, in which the two Cl atoms are replaced by $-\text{NHCH}_2\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2$, is reported in a survey on antimalarial drugs.⁸⁶) If warm ammonium hydroxide is used, the monochloro derivative, CV, is formed.



(CIII)

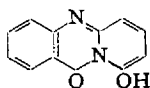


(CIV)



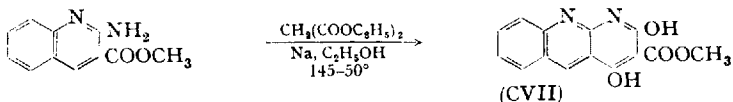
(CV)

It is well known that 2,6-diaminopyridine and 2-aminopyridine, in general, react quite differently in cyclization reactions; with the latter the ring is usually closed through the pyridine nitrogen, while with the former it is closed through a carbon atom (*cf.* naphthyridines).⁸⁷ By analogy, therefore, the formation of a 1,9-diazaanthracene derivative from 2,6-diaminopyridine is to be expected. Indeed, the preparation of a dichloro derivative from the corresponding dihydroxy compound (or a tautomer) can be explained only from a structure such as CIII; a compound of the type CVI would not give a *dichloro* derivative in which both oxygens are replaced by chlorine.



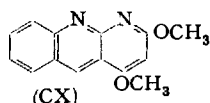
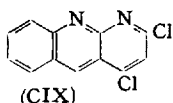
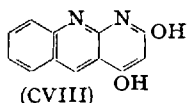
(CVI)

The only other 1,9-diazaanthracenes known are those prepared by Koller and Strang⁸⁰ and by Sucharda.⁸⁶ The former prepared 2,4-dihydroxy-3-carbomethoxy-1,9-diazaanthracene (CVII) by the action of ethyl malonate on the methyl ester of 2-aminoquinoline-3-carboxylic

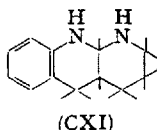


(CVII)

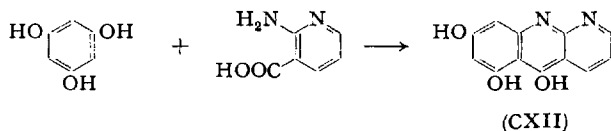
acid. Apparently, there is ester interchange during the reaction. The product is obtained as a brittle, yellow mass, which is hydrolyzed and decarboxylated, on treatment with alkali, to give 2,4-dihydroxy-1,9-diazaanthracene (CVIII). This substance yields 2,4-dichloro-1,9-diaza-



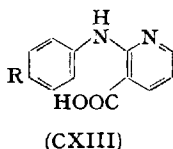
anthracene (CIX) when treated with phosphoryl chloride, and this, in turn, forms the dimethoxy derivative (CX) when heated with sodium methoxide. Treatment of CX with methyl iodide gives a methiodide. Reduction of CIX with sodium and ethyl alcohol yields 1,2,3,4,4a,9,9a,10-octahydro-1,9-diazaanthracene (CXI).



Sucharda⁸⁶ prepared 5,7,10-trihydroxy-1,9-diazaanthracene (CXII) by heating a mixture of 2-aminonicotinic acid and phloroglucinol. The compound forms a sodium derivative and an acetyl compound, and is oxidized by alkaline permanganate to 2,3-dicarboxy-4-hydroxy-1,8-naphthyridine.

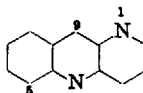


Unsuccessful attempts have been made to cyclize 2-phenylamino-nicotinic acid (CXIII, R = H) and its 4'-methoxy derivative (CXIII, R = OCH₃) by the same procedures used in preparing acridone.⁸⁹⁻⁹¹



While it has been shown that in certain cyclodehydration reactions a methoxyl group meta to the position in which cyclization is expected inhibits the reaction,^{92,93} it is apparent that in this case the pyridine nitrogen also has an inhibiting effect because the unsubstituted compound (CXIII, R = H) will not cyclize.

G. **1,10-Diazaanthracene. Pyrido[3,2-*b*]quinoline. Benzo-1,5-naphthyridine. 1-Aza-acridine. R.I. 1947**

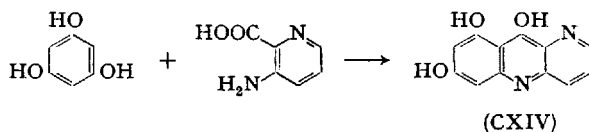


(1) Nomenclature

Listed in *Chemical Abstracts* as pyrido[3,2-*b*]quinolines or 1,5-pyridoquinolines, substances of this basic structure have also been called benzo-1,5-naphthyridines.⁹⁴ They are more conveniently named as derivatives of 1,10-diazaanthracene.

(2) Syntheses

When phloroglucinol and 3-aminopyridine are heated at 205° for one-half hour 6,8,9-trihydroxy-1,10-diazaanthracene (CXIV) is formed.⁹⁴ Oxidation of CXIV with nitric acid (d. 1.5) leads to 2,3-dicarboxy-4-hydroxy-1,5-naphthyridine (CXV), together with a small



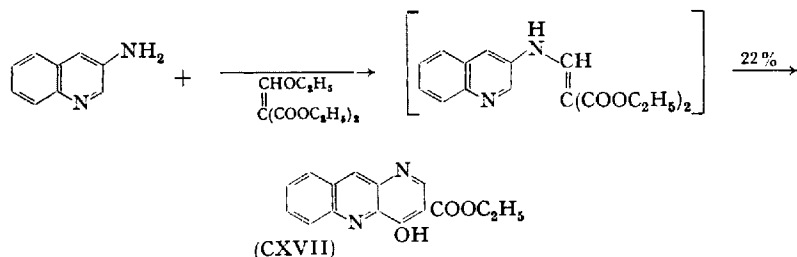
amount of 6,8,9-trihydroxy-5,7-dinitro-1,10-diazaanthracene (CXVI). This oxidation of CXIV to CXV proves the structure of the former, and,



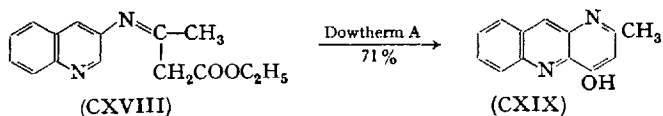
since CXVI is also oxidized to CXV, its structure is also established. The dinitro compound (CXVI) is obtained from CXIV by treatment

with nitric acid (d. 1.4). CXIV and CXVI are amphoteric in nature, forming well-defined sodium salts as well as hydrochlorides.

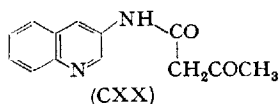
Other derivatives that have been assigned this basic structure have been prepared from 3-aminoquinoline.⁹⁵ When the latter is treated with ethyl ethoxymethylenemalonate, 3-carbethoxy-4-hydroxy-1,10-diazaanthracene (CXVII) is obtained. Application of the Conrad-Limpach



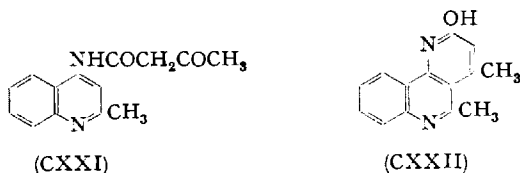
ring closure to the anil (CXVIII) from 3-aminoquinoline and ethyl acetoacetate gives 4-hydroxy-2-methyl-1,10-diazaanthracene (CXIX).



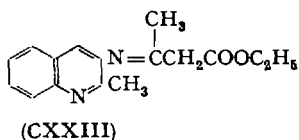
On the other hand, the amide, CXX, cannot be cyclized by the Knorr procedure.



While cyclization in the 4-position of the quinoline nucleus is also a possibility, the following evidence, though not conclusive, indicates that linear cyclization does result and that the structures CXVII and CXIX are correct. The amide (CXXI) from 4-aminoquinoline and ethyl acetoacetate cyclizes to 2-hydroxy-4,5-dimethyl-1,6-diazaphen-

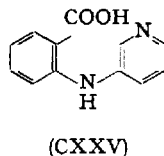
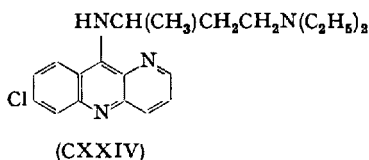


anthrene (CXXII) (see p. 357), while the anil (CXXIII) from 3-aminoquinaldine and ethyl acetoacetate cannot be cyclized.⁹⁶ Since cyclization is effected in the latter case if there is no methyl group in the

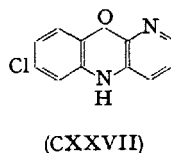
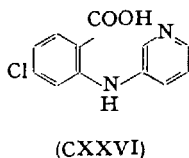


2-position, one is at least partially justified in assuming that the cyclization of CXVIII is in the 2-position as represented in CXVIII $\rightarrow$ CXIX.

Because of the success of atabrin in the treatment of malaria, the preparation of an analog (CXXIV) was of interest. While Kermack⁹⁰

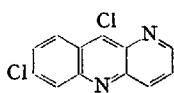


and Petrov⁹¹ were unable to cyclize *N*-(3-pyridyl)anthranilic acid (CXXV), Price and Roberts⁹⁷ have shown that the chlorine analog (CXXVI), prepared from 2,4-dichlorobenzoic acid and 3-aminopyridine, is cyclized with sulfuric acid. The free base (CXXVII), however, is not reported; the product is isolated as the sulfate or

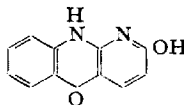


hydrochloride. While ring closure might also take place in the 4-position to give a 2,9-diazaanthracene derivative, the cyclization in the 2-position is more likely to occur because such syntheses as the Skraup, Doebner, and Doebner-Miller with 3-aminopyridine proceed in this manner. All attempts to obtain the dichloro compound, CXXVIII, by

treatment of CXXVII with phosphoryl chloride were unsuccessful, though there was a marked reaction with the reagent.⁹⁷ In view of the



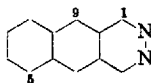
(CXXVIII)



(CXXIX)

fact that 2-hydroxy-10-oxo-9H,1,9-diazaanthracene (CXXIX) gives the dichloro derivative (see p. 95) a similar reaction with CXXVII would be expected.

H. 2,3-Diazaanthracene. Benzo[g]phthalazine. Naphthalene-2,3-diazine.

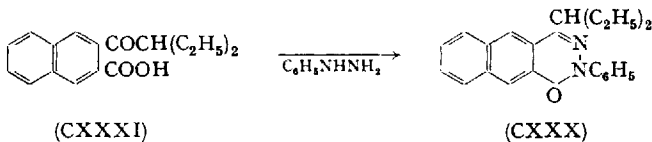


(1) *Nomenclature*

Substances of this general structure are named as benzo derivatives of phthalazine or as naphthalene 2,3-diazines. At present *Chemical Abstracts* uses the name benzo[g]phthalazine. The 1,4-dioxo derivatives (dihydroxy in the tautomeric form) are benzo[g]phthalazine-1,4-diones (*Chemical Abstracts*), but they are called β,β' -naphthalazdiones in the literature.^{99,100}

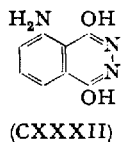
(2) *Syntheses*

Few derivatives are known; until 1939 only one derivative was recorded: 1-diethylmethyl-4-oxo-3-phenyl-3,4-dihydro-2,3-diazaanthracene (CXXX). This substance is prepared⁹⁸ by the action of phenylhydrazine on the oxo acid, CXXXI. Excess phenylhydrazine is

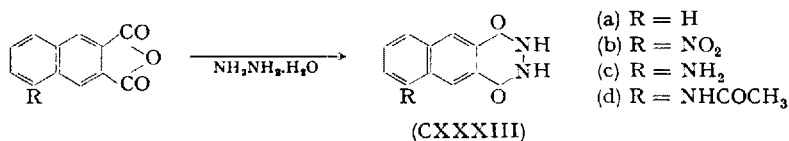


removed by treatment with acetic acid, and the product purified by recrystallization from alcohol.

In 1939 a number of other derivatives were prepared in order to compare their properties with certain chemiluminescent properties possessed by the phthalazine analogs, particularly Luminol (5-amino-1,4-dihydroxyphthalazine, CXXXII). The method used is a general one

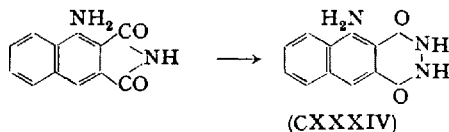


that consists in treating 2,3-naphthalic anhydride or its derivatives with hydrazine hydrate in acetic acid.⁹⁹ Thus, 2,3-naphthalic anhydride



gives 1,4-dioxo-1,2,3,4-tetrahydro-2,3-diazaanthracene (CXXXIIIa). By a similar procedure, 5-nitro-, 5-amino-, and 5-acetamido-1,4-dioxo-1,2,3,4-tetrahydro-2,3-diazaanthracenes (CXXXIIIb, c, d) are obtained. The luminescent power of the amino compound (CXXXIIIc) is greater than that of the unsubstituted derivative (CXXXIIIa) but not as great as that shown by Luminol (CXXXII).

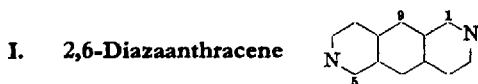
A substance bearing a closer relationship to Luminol (CXXXII), 9-amino-1,4-dioxo-1,2,3,4-tetrahydro-2,3-diazaanthracene (CXXXIV) is obtained by treating 1-amino-2,3-naphthalenedicarboximide with hydrazine hydrate.¹⁰⁰ The imide is obtained from 3-acetamido-2-



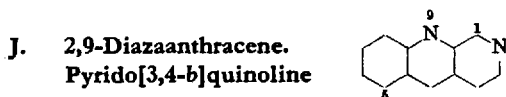
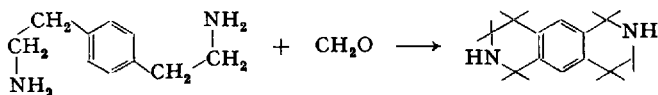
naphthoic acid as follows. The acid is nitrated in the 4-position, and the product is hydrolyzed to the free amino compound; the amino group is replaced by cyano (Sandmeyer) and the latter is hydrolyzed to 1-nitronaphthalene-2,3-dicarboxylic acid. This dibasic acid is con-

verted to the imide and reduced (Adam's catalyst) to the required amino derivative.

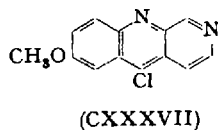
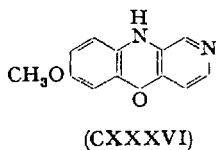
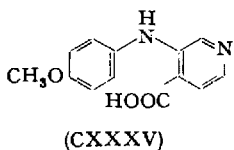
While the 9-amino-2,3-diazaanthracene derivative (CXXXIV) has strong luminescent properties, it is weaker than Luminol (CXXXII) under similar conditions.



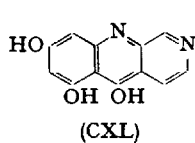
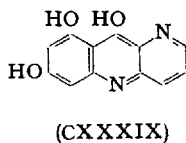
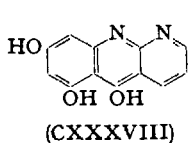
No derivatives of this ring structure are known. Attempts to prepare 1,2,3,4,5,6,7,8-octahydro-2,6-diazaanthracene by condensation of 1,4-di(β -aminoethyl)benzene with aldehydes, such as formaldehyde, have not been successful.¹⁰¹



Derivatives of this ring structure are unknown. Unsuccessful attempts were made to cyclize 3-*p*-methoxyphenylaminoisonicotinic acid (CXXXV) to either 10-oxo-6-methoxy-9,10-dihydro-2,9-diazaanthracene (CXXXVI) or 10-chloro-6-methoxy-2,9-diazaanthracene (CXXXVII) by the same procedures used to prepare acridone.⁸⁹

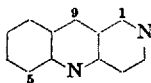


Since phloroglucinol condenses with 2-aminonicotinic acid to give 5,7,10-trihydroxy-1,9-diazaanthracene (CXXXVIII) (see p. 97), and



with 3-aminopicolinic acid to yield 6,8,9-trihydroxy-1,10-diazaanthracene (CXXXIX) (see p. 98), it might be expected to react with 3-aminoisonicotinic acid to give 5,7,10-trihydroxy-2,9-diazaanthracene (CXL); such a reaction has not been recorded.

K. 2,10-Diazaanthracene. Pyrido[4,3-*b*]quinoline. 2,3-Benzo-1,6-naphthyridine. Benzo-2,5-naphthyridine. 2,5-Naphthodiazine.
R.I. 1950

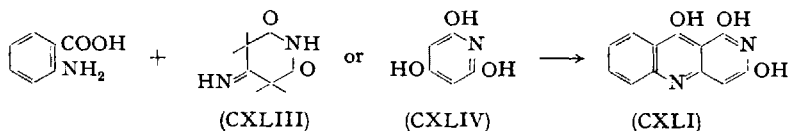


(1) Nomenclature

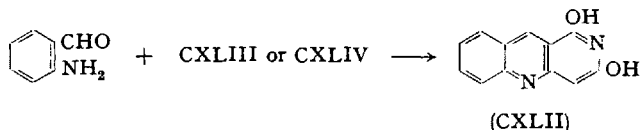
Derivatives of 2,10-diazaanthracene are listed in *The Ring Index* as pyrido[4,3-*b*]quinolines. They appear in the early literature as derivatives of benzo-2,5-naphthyridine or 2,5-naphthodiazine.¹⁰²

(2) Syntheses

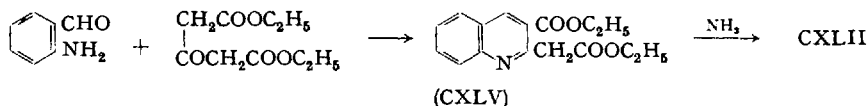
Several compounds of this general structure have been synthesized. These include 1,3,9-trihydroxy-(CXLI) and 1,3-dihydroxy-2,10-diazaanthracene (CXLII). The former is prepared from glutazine (CXLIH) or trihydroxypyridine (CXLIV) by heating with anthranilic acid¹⁰²;



the latter is formed in a similar reaction with *o*-aminobenzaldehyde.¹⁰³

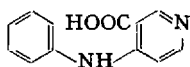


It also results when 3-carbethoxy-2-carbethoxymethylquinoline (CXLV)

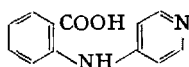


(obtained by condensing *o*-aminobenzaldehyde with diethyl- β -oxoglutarate) is treated with dry ammonia.¹⁰⁴

Both acidic and basic properties are shown by CXLI and CXLII in the formation of hydrochlorides and monometallic salts. Their phenolic character is indicated by the formation of azo dyes with *p*-nitrobenzenediazonium chloride. They form monoacetyl and benzoyl derivatives. They are both cleaved by hydrochloric acid at 200–50° to give 4-hydroxyquinaldine and quinaldine, respectively. Cleavage of CXLII with alkali gives 3-carboxy-2-carboxymethylquinoline, which is difficult to isolate because further loss of carbon dioxide results in the formation of 3-carboxy-2-methylquinoline. Both CXLI and CXLII are colored and are capable of existing in tautomeric forms. This is illustrated by the fact that they are reduced by zinc dust and acetic acid, the color returning by aerial oxidation as with anthraquinone. Substances of this general structure were investigated during World War II in connection with the antimalarial program.^{89–91} While 4-phenylaminonicotinic acid (CXLVI) and *N*-(4-pyridyl)anthranilic acid (CXLVII) could not be cyclized with phosphoryl chloride or sulfuric

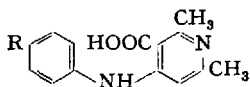


(CXLVI)

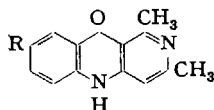


(CXLVII)

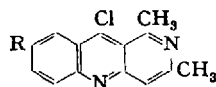
acid, the substituted derivatives CXLVIIa and b were cyclized readily with phosphoryl chloride to give 9-oxo-1,3-dimethyl-9,10-dihydro-2,10-diazaanthracene (CXLVIIIa), and its methoxy derivative (CXLVIIIb).



(CXLVII) (a) R = H
(b) R = OCH₃



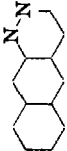
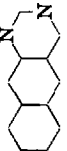
(CXLVIII) (a) R = H
(b) R = OCH₃



(CXLIX)

However, all efforts to convert these substances to the corresponding chlorides (CXLIX) failed.

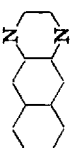
TABLE I-5. Diazaanthracenes

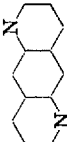
Formula	Diazaanthracene	M.p., °C.	Appearance	Recrystallized from	Refs.
	1,2-Diazaanthracene				
Ia	4-Hydroxy-5,6,7,8-tetrahydro-	262-3	Colorless	Methanol	55
Ib	3-Chloro-4-hydroxy-5,6,7,8-tetrahydro-	288-9	Colorless	Ethanol	55
II	Acetyl deriv. of Ib	148-9	Colorless needles	Ethanol	55
	10-Oxo-3-phenyl-	236	Brown	Methanol	54
	9,10-dihydro-Dinitrophenyl-hydrazone of II	244	Yellow needles	Ethyl acetate	54
	1,3-Diazaanthracene				
X	Unsubstituted	160	Yellow		56
XI	3,4-Dihydro-	196	Colorless		56
XII	4-Chloro-	179	Yellow		56
XX	2,4-Dichloro-	184	Orange	(Distillation)	62, 63
XX?	4,4-Dichloro-	192	Golden yellow	(Probably same as XX)	56
XXIa	2-Chloro-4-β-diethylaminoethylamino-	140-2	Yellow needles	Petroleum	62, 63

Formula	Diazaanthracene	M.p., °C.	Appearance	Recrystallized from	Refs.
XXIb	2-p-Chloroanilino-4- β -diethylamino-ethylamino-	—	a		62, 63
XIIIa	4-Hydroxy-	278	Colorless		56
XVI	4-Hydroxy-1,2-dihydro-	269-72	Yellow		56, 58
XIVb	2,4-Dihydroxy-	358-9	Colorless	Phenol	57, 62
XIIIb	4-Hydroxy-2-methyl-	320			56
XVIII (or XIX)	4-Hydroxy-2-benzyl-	278		Pyridine	61
XIVa	2-Hydroxy-4-phenyl-				57
XIVc	4-Hydroxy-2-phenyl-	—			57
XV	4-Hydroxy-2-(1-nitro-2-anthraquinonyl)-	—			57
XXII	4-Methoxy-	120	Yellow		56
XVII	2-Methyl-4-oxo-3-phenyl-3,4-dihydro-				59
—	2-Methyl-4-oxo-3- <i>p</i> -chlorophenyl-	—			60

(Table continued)

TABLE I-5 (continued)

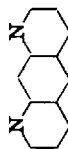
Formula	Diazaanthracene	M.p., °C.	Appearance	Recrystallized from	Refs.
XXIIIa	2-Hydroxy-4-phenyl-1,3-diazaanthraquinone	344		Nitrobenzene	57
XXIIIc	4-Hydroxy-2-phenyl-1,3-diazaanthraquinone			Nitrobenzene	57
XXIIIb	2,4-Dihydroxy-1,3-diazaanthraquinone		Yellow needles	Pyridine	57
	 1,4-Diazaanthracene				
—	2,3-Dimethyl-	211	Yellow needles	Ethanol	64
—	2,3-Diphenyl-	192; 190	Yellow needles	Aq. ethanol	64, 65
—	2-Hydroxy-3-methyl-	290 (dec.)	Yellow needles	Ethanol	64
—	2,3-Dihydroxy-	415 (dec.); > 350	Colorless platelets	Acetic acid	64, 66
—	2,3-Dicarboxy-	192	Yellow needles		66
—	2,3-Dicarbethoxymethyl-	139.5	Yellow	Ethanol	65

Formula	Diazaanthracene	M.p., °C.	Appearance	Recrystallized from	Refs.
	1,5-Diazaanthracene				
XXV ^{b,d}	Unsubstituted	240-2	Colorless needles	Aq. ethanol	67
XXVIII ^c	10-Methyl- (hydrate)	62	Colorless needles	Water	70
XXIX ^d	2,6-Dimethyl-	238-9; 240	Yellow needles	Aq. ethanol	68, 69
XXXV	2,6-Dimethyl-	170-1	Yellow leaves	Aq. ethanol	69
	1,2,3,4-tetrahydro-				
XXXVIII ^a	2,6-Diphenyl-	284-5	Yellow leaves	Acetic acid	68
XXXI ^c	2,6-Distyryl-	267	Yellow needles	Chloroform	68
XXVII ^c	2,3,6,7-Tetrachloro-	ca. 300 (dec.)	Yellow needles	Acetic acid	67
—	5-Nitroso-2,6-	121-2			69
	dimethyl-1,2,3,4-				
	tetrahydro-				
XXXII ^e	2,6-Di-(<i>p</i> -dimethyl-aminostyryl)-	340 (carb.)	Red	Anisole	68
XXVI	2,6-Dihydroxy-	360 (chars)	Colorless leaves	Acetic acid	67
	3,4,7,8-tetrahydro-				
XXX	2,6-Dimethyl-3,7-	320 (dec.)	Yellow	Aq. pyridine	68
	dicarboxy-				
XXXIV	1-Benzoyl-2,6-	152-4	Yellow leaves	Aq. ethanol	69
	dimethyl-1,2,3,4-				
	tetrahydro-				

(Table continued)

TABLE I-5 (continued)

Formula	Diazaanthracene	M.P., °C.	Appearance	Recrystallized from	Salts	Refs.
XXXIII ^a	1-Benzoyl-2,6-dimethyl- 1,2,3,4,5,6,7,8-octahydro-	144-5	Yellow needles	Aq. ethanol		69
XXXVI	1,5-Dibenzoyl-2,6-dimethyl- 1,2,3,4,5,6,7,8-octahydro-	269-70	Colorless			69
XXXVII	1-Benzoyl-5-nitroso-2,6-dimethyl- 1,2,3,4,5,6,7,8-octahydro-	164-7 (dec.)	Red prisms	Aq. ethanol		69
LX	1,8-Diazaanthracene					
	Unsubstituted	164-5; 166	Colorless needles	(Sublimation)	2P 262 (dec.); CH ₃ I 200	72, 73, 75a
LXVI	1,2,3,4,5,6,7,8-Octahydro-Diacetate of LXVI	111.5; 114	Yellow	Ethanol	2P 165-70; HI 307	73, 76
	Dibenzoate of LXVI	143 209	Colorless needles	Ethanol		73, 76
				Ethanol		73, 76



Formula	Diazaanthracene	M.p., °C.	Appearance	Recrystallized from	Salts	Refs.
LXII	2,7-Dimethyl-	196-7	Colorless	Aq. ethanol	2P 230 (dec.); CH ₃ I 244	72, 73
LXIII	2,7-Di-(tri-bromomethyl)-	190-2 (dec.)	Yellow			72
LXV	2,7-Dimethyl-1,2,3,4,5,6,7,8-octahydro-		(Isolated as perchlorate)		ClO ₄ 285-6 (dec.)	73
XLI	2,7-Diphenyl-	216-7	Greenish-yellow	Xylene-ethanol	2P 270 (dec.)	71
LIII	4,5-Dimethyl-2,7-diphenyl-	284-5 (dec.)	Yellow needles	Xylene	2P (dec.)	74
LVI	9-Amino-2,7-diphenyl-	224-5	Red needles	Dioxane-ethanol		75
LVIII	9-Amino-3,6-dicarboethoxy-2,7-dimethyl-Acetyl deriv. of LVIII	160	Red needles	Ethanol		75
—	9-Amino-3,6-dicarboxy-2,7-dimethyl-	234 (dec.)	Orange	Pyridine-alcohol		75
		318 (dec.)	Lilac powder		Yellow salts	75
I	2,7-Diamino-3,6-diphenyl-	294	Yellow needles	Anisole		73
	Tetracetate of I	239 (dec.)	Yellow needles	Ethanol		73

(Table continued)

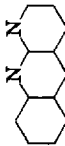
TABLE I-5 (continued)

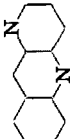
Formula	Diazaanthracene	M.p., °C.	Appearance	Recrystallized from	Salts	Refs.
XLIII	2,7-Di-(<i>p</i> -methoxy-phenyl)-	268-9	Yellow needles	Xylene	2P	72
LXIV	2,7-Dicarboxy- <i>g</i>	Impure	Yellow needles	(Acidification)		72, 73
—	2,7-Dicarbo-methoxy-	272 (dark.)	Yellow needles	Ethanol		72, 73
—	3,6-Dicarboxy-2,7-dimethyl- <i>g</i>	180-2 (dec.)	Yellow needles	(Acidification)		72, 73
XLV and LXI	3,6-Dicarbethoxy-2,7-dimethyl-	166-7	Colorless	Acetone	2P	71-73
LIX a	4,5-Dicarboxy-2,7-diphenyl-	> 325		Water		75a
XLIV	2,3,6,7-Tetra-carbethoxy-	212	Yellow	Ethanol		72
LIX b	2,4,5,7-Tetra-carbethoxy	311				75a
XLII	3,6-Diacetyl-2,7-dimethyl-	213-5	Yellow	Aq. ethanol	2P	72
—	Dioxime of XLII	255-7	Yellow needles	Ethanol		72
LV	3,6-Diacetyl-2,4,5,7-tetramethyl-	(246-8dec.)	Yellow	Xylene	2P 180 (dec.)	74
LXXIII	2,7-Di- β -styryl-	279	Yellow	Anisole	HCl; HNO ₃	72
—	2,7-Di(furalmethyl)-	271-2 (dec.)	Yellow	Ethanol		72
—	2,7-Di-(<i>p</i> -dimethyl-amino- β -styryl)-	340 (dark.)	Brown needles	Anisole		73

Formula	Diazaanthracene	M.p., °C.	Appearance	Recrystallized from	Salts	Refs.
LIV	3,6-Diacetyl-2,7-dioxo-4,5-dimethyl-1,2,7,8-tetrahydro-	415 (dec.)	Yellow	Aq. acetic acid		74
—	1,8-Dinitroso-1,2,3,4,5,6,7,8-octahydro-	179 (dec.); 187	Yellow needles	Ethanol		73, 76
—	1,8-Dinitroso-2,7-dimethyl-1,2,3,4,5,6,7,8-octahydro-	164; 152	Yellow	Ethanol	Two stereo-isomers	73
LXIX	2-Oxo-1,2,3,4,5,6,7,8-octahydro-	234-5		Ethanol		76
LXVIII	2,7-Dioxo-1,2,3,4,5,6,7,8-octahydro-	300 (subl.)	Needles	Acetic acid		72, 76
—	2,7-Dioxo-1,2,7,8-tetrahydro-	Sublimes	Yellow powder			72
—	2,7-Dioxo-3,6-dicarboxy-1,2,3,4,5,6,7,8-octahydro-	412 (dec.)	Needles	Water + HCl		77
LXX	2,7-Dioxo-3,6-dicarbethoxy-1,2,3,4,5,6,7,8-octahydro-	252	Colorless	Ethanol		77

(Table continued)

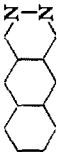
TABLE I-5 (continued)

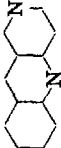
Formula	Diazaanthracene	M.p., °C.	Appearance	Recrystallized from	Salts	Refs.
LXXIV	2,7-Di-(2'-1,3-dioxindanyl)-	195 (dec.)	Yellow	Ethanol		75
XLVI	2,3,4,5,8,9,10,11-Octahydro-1,12-diazapentacene	251	Yellow needles	Ethyl acetate	2P 195 (dec.)	73
		1,9-Diazaanthracene				
CXI	1,2,3,4,4a,9,9a,10-Octahydro-	158-9	Colorless needles	Ethanol		80
CIX	2,4-Dichloro-	195-6	Yellow needles	Ethanol		80
CIV	2,10-Dichloro-	249-51				85
—	2,10-Di-(β -diethyl-aminoethylamino)-					88
CVIII	2,4-Dihydroxy-	343	Platelets	Ethanol		80
CXII	5,7,10-Trihydroxy-	348	Yellow			86
—	Monoacetate of CXII					86

Formula	Diazaanthracene	M.p., °C.	Appearance	Recrystallized from	Salts	Refs.
CX	2,4-Dimethoxy-	152-3	Colorless needles	Water		80
CV	2-Chloro-10-oxo- 9,10-dihydro-	357-8				85
CI	2-Amino-10-oxo- 9,10-dihydro-	362-3				85
CIII	2-Hydroxy-10-oxo- 9,10-dihydro-	373-4				85
CVII	3-Carbomethoxy- 2,4-dihydroxy-	240		Ethanol		80
	 1,10-Diazaanthracene					
CXIX	4-Hydroxy-2-methyl-	> 300		Ethanol-water		95
CXIV	6,8,9-Trihydroxy- Monoacetate of CXIV	378 338	Yellow		Na salt; HCl HCl	94 94
CXVI	6,8,9-Trihydroxy- 5,7-dinitro-	277 (dec.)	Yellow			94

(Table continued)

TABLE I-5 (continued)

Formula	Diazaanthracene	M.p., °C.	Appearance	Recrystallized from	Salts	Refs.
CXVII	3-Carbethoxy-4-hydroxy-	264-5		Aq. pyridine		95
CXXVII	6-Chloro-9-oxo-9,10-dihydro-	—	Yellow ^b		HCl 320	97
	 2,3-Diazaanthracene					
CXXX	1-Diethylmethyl-4-oxo-3-phenyl-3,4-dihydro-	175	Colorless needles	Ethanol	Yellow Na salt	98
CXXXIIIa	1,4-Dioxo-1,2,3,4-tetrahydro-	345	Colorless needles ^t		Red Na salt	99
CXXXIIIb	5-Nitro-1,4-dioxo-1,2,3,4-tetrahydro-	> 350	Yellow ^t			99
CXXXIIIc	5-Amino-1,4-dioxo-1,2,3,4-tetrahydro-	320 (dec.)	Brown ^t			99
CXXXIIId	5-Acetamido-1,4-dioxo-1,2,3,4-tetrahydro-					99
CXXXIV	9-Amino-1,4-dioxo-1,2,3,4-tetrahydro-	342-4 (dec.)	Cream ^t		Na salt	100

Formula	Diazaanthracene	M.p., °C.	Appearance	Recrystallized from	Salts	Refs.
 2,10-Diazaanthracene						
CXLII	1,3-Dihydroxy-	375 (dec.)	Red	Acetic acid		103, 104
—	Acetate of CXLII	ca. 350	Yellow plates	Acetic acid		103
—	Benzoate of CXLII	295 (dec.)	Yellow needles	Acetic acid		103
—	<i>p</i> -Nitrophenylazo deriv. of CXLII	360 (dec.)	Brown needles	Nitrobenzene		103
CXLI	1,3,9-Trihydroxy-	370	Yellow needles			102
—	Acetate of CXLI	373				
—	Dibenzoate of CXLI	235				
—	<i>p</i> -Nitrophenylazo deriv. of CXLI	336				
CXLVIIIa	9-Hydroxy-1,3- dimethyl-	319-20 (dec.)	Yellow	Ethanol	HCl 376-8 (dec.)	89-91
CXLVIIIb	9-Hydroxy-7- methoxy-1,3- dimethyl-	298-9 (dec.)	Yellow	Ethanol	HCl 319-20 (dec.)	89-91

^a Forms a yellow dihydrochloride, m.p. 286-7.

^b Bluish-red fluorescence in solution.

^c Shows blue fluorescence in solution.

^d Forms a picrate.

^e Solid fluoresces red in ultraviolet light.

^f A hydrochloride is known.

^g Precipitated by acidification.

^h As the sulfate.

ⁱ Precipitated on addition of acetic acid to alkaline solution.

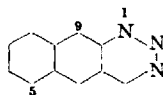
3. Triazaanthracenes

The six known triazaanthracene types include derivatives containing nitrogen atoms in the 1,2,3-, 1,3,9-, 1,8,9-, 1,9,10-, 2,3,9- and 2,3,10-positions. A derivative of 1,2,4-triazaanthracene is reported but this appears to be due to an error in indexing. There is some doubt about the 1,9,10-derivatives because the type of synthesis used in their production could also give rise to 2,9,10-triazaanthracenes, and proof is lacking.

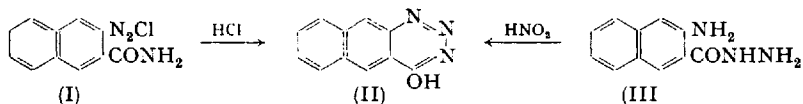
Nomenclature

Throughout this section the name recorded immediately after the triazaanthracene under discussion is the name used by *Chemical Abstracts* in indexing the substance. The other names are those given by the authors who investigated the compounds. *The Ring Index* number is also included.

- A. **1,2,3-Triazaanthracene.** Naphtho[2,3]-*v*-triazine. *lin*-1,2,3-Naphthotriazine.
R.I. 1818



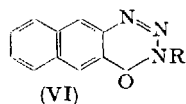
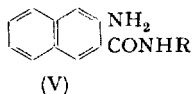
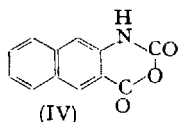
The only known substance of this basic structure is 4-hydroxy-1,2,3-triazaanthracene (II). It is formed when the diazonium salt of 3-amino-2-naphthamide (I) is heated with dilute hydrochloric acid,¹⁰⁵ and is isolated as colorless needles from alcohol (m.p. 250°, dec.) Treat-



ment of 2-amino-3-naphthydrazide (III) with nitrous acid also yields II. The diazonium salt (I) and the triazine (II) give the same red, azo dye when heated with resorcinol. This indicates that the triazine ring is easily cleaved in the 2,3-position.

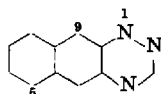
A more general reaction is indicated in the literature,¹⁰⁶ but details

are lacking. Naphthisatoic anhydride (IV) is treated with a primary amine to give a substituted 3-amino-2-naphthamide (V); the latter



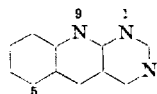
on treatment with nitrous acid should form a 3-alkyl(or aryl)-4-oxo-3,4-dihydro-1,2,3-triazaanthracene (VI).

- B. 1,2,4-Triazaanthracene. Naphtho[2,3]as-triazine. 1,2,4-Naphthotriazine. R.I. 1819**

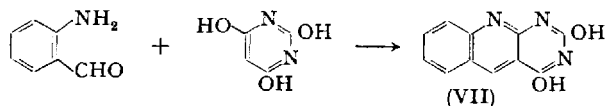


Derivatives of this basic structure are listed in *Chemical Abstracts Decennial Index* (1907–1916) and also in *The Ring Index*. However, the abstract concerned,¹⁰⁷ as well as the original patent, shows clearly that the substance in question does not possess this configuration. It does indicate that the structure of the product is that of a 1,2,4-triaza-phenanthrene, but it has since been shown that this also is incorrect and that the substance is actually a naphthimidazole derivative (see p. 458).

- C. 1,3,9-Triazaanthracene. Pyrimido[4,5-b]-quinoline. Quinopyrimidine. 1,3-Quinolinediazine. 1,3-Diazaacridine. R.I. 1887**

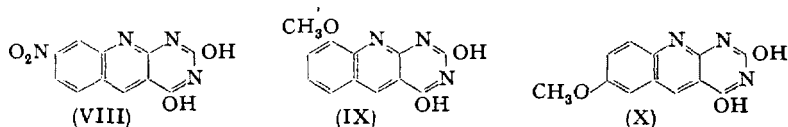


Substances of this general structure are prepared by treating *o*-aminobenzaldehydes with barbituric acid or certain other pyrimidine derivatives. Thus, *o*-aminobenzaldehyde and barbituric acid, heated together in water,¹⁰⁸ give 2,4-dihydroxy-1,3,9-triazaanthracene (VII).

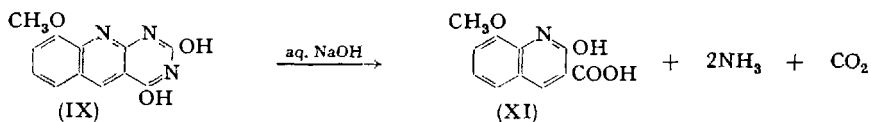


The substituted *o*-aminobenzaldehydes, 4-nitro-, 3-methoxy-, and 5-methoxy-, undergo a similar reaction to give the 7-nitro-,¹⁰⁹ 8-

methoxy-,¹⁰⁹ and 6-methoxy-2,4-dihydroxy-1,3,9-triazaanthracenes¹¹⁰ (VIII, IX, X), respectively. When the 8-methoxy derivative (IX) is

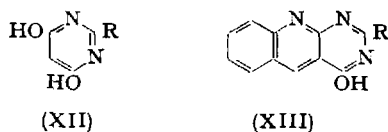


heated under pressure with aqueous sodium hydroxide solution, the pyrimidine ring is opened and 3-carboxy-2-hydroxy-8-methoxyquinoline (XI) is formed. Synthesis of the degradation product (XI)

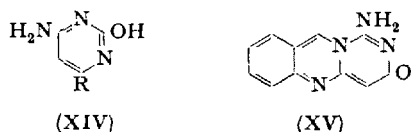


from 2-amino-3-methoxybenzaldehyde and malonic acid establishes the structure of (IX).

The use of substituted pyrimidines¹¹¹ of the type XII leads to substances of the general structure XIII in which R includes such groups as $-\text{NH}_2$, $-\text{NHCH}_3$, $-\text{NHC}(\text{NH})\text{NH}_2$, and $-\text{NH}(\text{CH}_2)_3\text{N}(\text{C}_2\text{H}_5)_2$. The



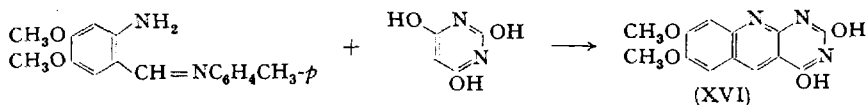
pyrimidine (XIV, $\text{R} = \text{OH}$), produces the 1,3,9-triazaanthracene, VII,



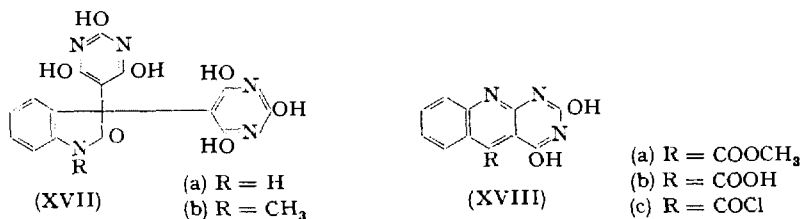
by loss of ammonia as well as water in the cyclization. On the other hand, if a diaminohydroxypyrimidine (XIV, $\text{R} = \text{NH}_2$) is employed, a substance believed to be XV results.¹¹¹

In a modification of this reaction a Schiff base is prepared from the aldehyde and allowed to react with barbituric acid in the presence

of piperidine, using glycerine as a solvent.¹¹² The 1,3,9-triazaanthracenes, VII and XVI, are prepared by this procedure.

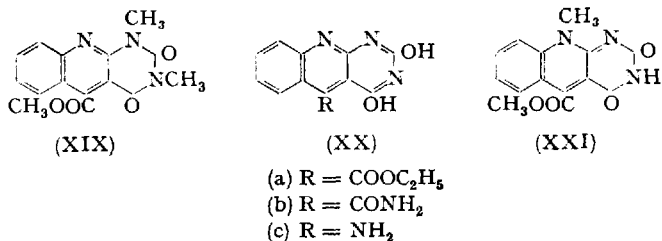


Because of the general inaccessibility of *o*-aminobenzaldehydes, King *et al.*¹¹³ investigated the possible use of isatin and its derivatives in this type of reaction. Isatin reacts with barbituric acid in the presence of hydrochloric acid to give 3,3-di-(5-barbituryl)oxindole (XVIIa).



If this compound is treated with methanol saturated with hydrogen chloride, 10-carbomethoxy-2,4-dihydroxy-1,3,9-triazaanthracene (XVIIIa) is formed. Hydrolysis of the ester gives the free acid (XVIIIb); the latter is also obtained directly from XVIIa by treatment with concentrated hydrochloric acid.

The acid is quite stable; it cannot be decarboxylated by copper chromite in boiling quinoline nor can it be esterified directly. Methylation of the acid (XVIIIb) or the ester (XVIIIa) with diazomethane gives 10-carbomethoxy-2,4-dioxo-1,3-dimethyl-1,2,3,4-tetrahydro-1,3,9-triazaanthracene (XIX). Treatment of the acid with thionyl chloride yields the acid chloride (XVIIIc); the latter is converted to the ethyl ester (XXa) and also to the amide (XXb) by the usual pro-

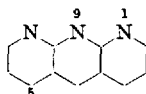


cedures. Treatment of the amide with sodium hypobromite gives the amine (XXc).

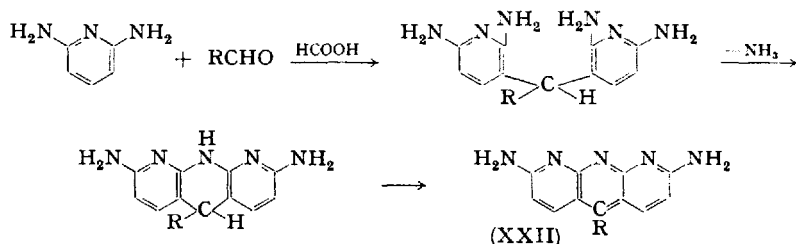
If 1-methylisatin is reacted with barbituric acid and the product (XVIIb) is treated with methyl alcohol and hydrogen chloride, 10-carbomethoxy-2,4-dioxo-9-methyl-2,3,4,9-tetrahydro-1,3,9-triazaanthracene (XXI), or a tautomer, results. This ester can be hydrolyzed to the free acid; the latter can also be formed directly from the oxindole, XVIIb, by treatment with concentrated hydrochloric acid.

In general, these substances are colorless, but those carrying a methyl group in the 10-position are brilliant yellow. They have high melting or decomposition points. They show both acidic and basic properties, forming hydrochlorides and sodium and silver salts. For the most part they show a strong blue to green fluorescence in solution, the color depending somewhat on the solvent. Their properties are collected in Table I-6.

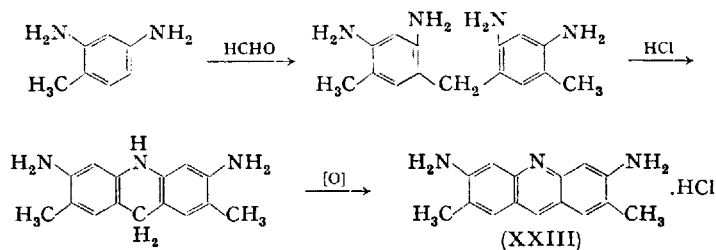
D. 1,8,9-Triazaanthracene. Pyrido[2,3-*b*][1,8]-naphthyridine. Anthyridine. 1,8-Diazaacridine. R.I. 1941



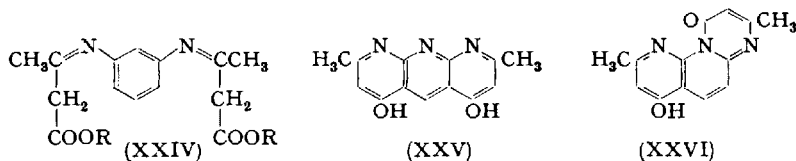
Derivatives of this general structure, which are said to be useful as bactericides, are described only in the patent literature.¹¹⁴ They are formed from 2,6-diaminopyridine or a monoacylated derivative by treatment with an aldehyde and formic acid. Thus, a mixture of 2,6-diaminopyridine, formic acid, and formaldehyde is refluxed for several hours; the excess formaldehyde is removed by steam distillation, and the residue concentrated and acidified; the solid obtained is recrystallized from alcohol to give 2,7-diamino-1,8,9-triazaanthracene (XXII) as a yellow powder that decomposes without melting. Its solutions in water or alcohol fluoresce brilliant green. The reaction is represented as follows:



This reaction is similar to one used in the production of acridine yellow (XXIII) from 4-methyl-*m*-phenylenediamine and formaldehyde¹¹⁵:

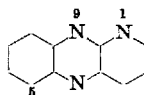


A compound of this type (XXV) may also result when the dianil (XXIV) from 2,6-diaminopyridine and ethyl acetoacetate is cyclized by heating in boiling Dowtherm A, a typical Conrad-Limpach reaction.¹¹⁶ However, the compound may be the isomeric angular derivative (XXVI); indeed, the relatively low melting point (230–1°) favors the

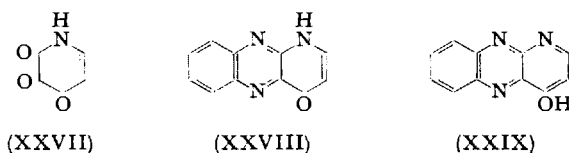


pyrimidine structure (XXVI) rather than the naphthyridine structure (XXV).

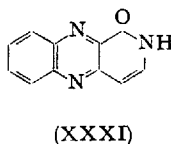
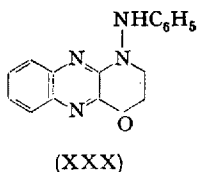
E. 1,9,10-Triazaanthracene. Pyrido[2,3-*b*]-quinoxaline. 1-Azaphenazine. R.I. 1888



When *o*-phenylenediamine dihydrochloride reacts with 2,3,4-trioxo-1,2,3,4-tetrahydropyridine (XXVII) in aqueous alcohol a substance is produced which is assigned the structure XXVIII.¹¹⁷ In its enolic form this substance is 4-hydroxy-1,9,10-triazaanthracene



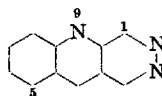
(XXIX). A similar reaction is said to take place when the anilino derivative of XXVII reacts with *o*-phenylenediamine. The product, XXX, is a derivative of the ketonic form, XXVIII. These two com-



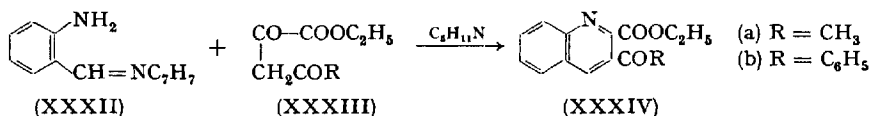
pounds, XXVIII and XXX, and an acetyl derivative of the former are the only compounds of this basic structure that have been reported.¹¹⁷

It will be noted that the formation of a 2,9,10-triazaanthracene derivative (XXXI) is also a possibility in this cyclization. However, it is pointed out that α -pyridones do not form acetyl derivatives while γ -pyridones do. This seems to be the only evidence for assigning structure XXVIII rather than XXXI to the substance.

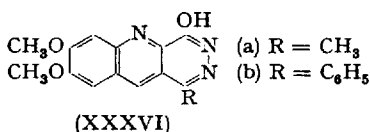
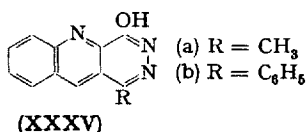
F. 2,3,9-Triazaanthracene. Pyridazo[4,5-*b*]-quinoline. 4,5-Quinolinopyridazine. R.I. 1889



All known derivatives of this basic structure are obtained by one typical reaction. When the Schiff base (XXXII) from *o*-aminobenzaldehyde and *p*-toluidine is treated with ethyl β -acetyl (or benzoyl)-pyruvate (XXXIII) in the presence of piperidine, ethyl 3-acetyl (or benzoyl)quinaldate (XXXIV) is formed. Treatment of the latter with hydrazine hydrate in alcohol solution results in the formation of

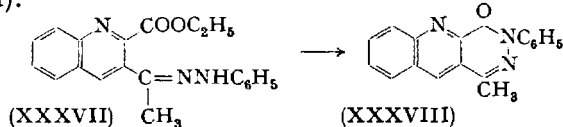


1-hydroxy-4-methyl(or phenyl)-2,3,9-triazaanthracene (XXXV). If 4,5-dimethoxy-2-aminobenzaldehyde is used, dimethoxy substituted

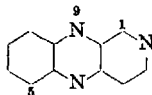


2,3,9-triazaanthracenes (XXXVI) are obtained¹¹⁹; 6-aminopiperonal undergoes a similar reaction. In the 1,3,9-triazaanthracene series, the free aldehyde, rather than the anil, is used in the same type of synthesis. There is nothing to indicate that such a reaction would not proceed equally well here.

This reaction was discovered by Koller and Ruppertsberg,¹²⁰ who used phenylhydrazine in place of hydrazine. Thus, the phenylhydrazone (XXXVII) of XXXIVa is cyclized by heating in a stream of carbon dioxide to 4-methyl-1-oxo-2-phenyl-1,2-dihydro-2,3,9-triazaanthracene (XXXVIII).

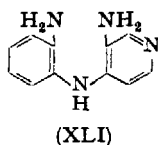
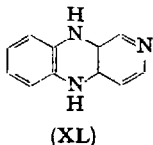
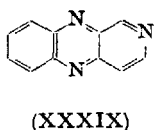


G. 2,9,10-Triazaanthracene. Pyrido[3,4-*b*]-quinoxaline. 2-Azaphenazine. R.I. not listed



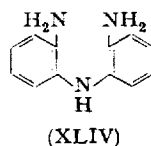
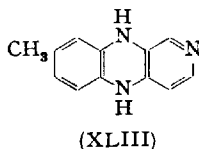
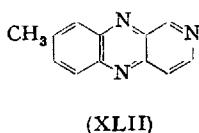
Compounds of this basic structure are described only in the recent literature.^{118,121} There is a possibility that some substances listed as pyrido[2,3-*b*]quinoxalines (1,9,10-triazaanthracenes) are in fact derivatives of 2,9,10-triazaanthracene (see p. 123).

The parent base XXXIX is obtained by oxidation (H_2O_2) of the dihydro base (XL), which in turn is secured from the hydrochloride of 3-amino-4-*o*-aminoanilinopyridine (XLI) by heating the latter for two

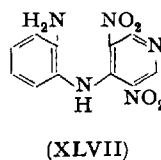
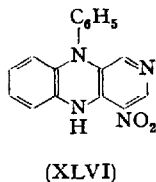
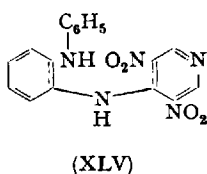


minutes at its decomposition point. The synthesis of XLI involves the condensation of 4-chloro-3-nitropyridine hydrochloride with *o*-nitroaniline, followed by reduction of the nitro groups with iron. By a similar procedure, 7-methyl-2,9,10-triazaanthracene (XLII) and its dihydro derivative (XLIII) are obtained. Cyclization of the diamine (XLI) directly to the base (XXXIX) by oxidation with ferric chloride or

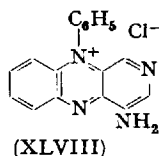
hydrogen peroxide, a reaction that proceeds with 2,2'-diaminodiphenylamine (XLIV)¹²² does not work in this case.



In a variation of this reaction, 3,5-dinitro-4-*o*-phenylamino-anilinopyridine (XLV) is cyclized by treatment with one mole of



sodium hydroxide. The reaction proceeds with the loss of one mole of nitrous acid to give 4-nitro-9-phenyl-9,10-dihydro-2,9,10-triazaanthracene (XLVI). Pyrolysis of XLV in boiling quinoline also leads to XLVI, but the yield is generally poorer than by the other procedure.¹²¹ The primary amino compound (XLVII) does not undergo this cyclization. The nitro group in XLVI is reduced with iron in aqueous methanol and in the presence of ferric chloride to the amino derivative, which is



isolated as the chloride (XLVIII). Acetylation with acetic anhydride gives the acetyl derivative. The reduction is similar to the formation of isophenosafranine (L) from 1,3-dinitro-10-phenyl-9,10-dihydrophenazine (XLIX).¹²³

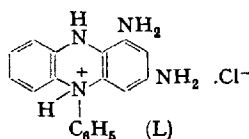
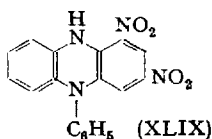
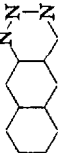
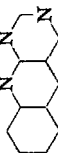
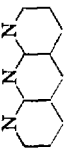
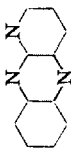


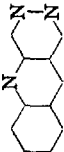
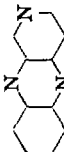
TABLE I-6. Triazaanthracenes

Formula	Triazaanthracene	M.p., °C.	Appearance	Recrystallized from	Refs.
	1,2,3-Triazaanthracene				
II	4-Hydroxy-	250 (dec.)	Colorless needles	Ethanol	105
	1,3,9-Triazaanthracene				
VII	2,4-Dihydroxy-	368	Yellow prisms	Acetic acid	108, 111, 112
X	2,4-Dihydroxy-6-methoxy-	273			110
IX	2,4-Dihydroxy-8-methoxy-	276-7		Acetic acid	109
XVI	2,4-Dihydroxy-6,7-dimethoxy-	358-60	Yellow prisms	Acetic acid	112
XIII, R = NH ₂	2-Amino-4-hydroxy-	> 310	As HCl	Dil. HCl	111
XXc	10-Amino-2,4-dihydroxy-		Colorless prisms	As HCl	113
XIII, R = NHCH ₃	4-Hydroxy-2-methylamino-	> 310	Yellow prisms		111
XIII, R = NH(CH ₂) ₃ N(C ₂ H ₅) ₂	2-γ-Diethylaminopropyl-amino-4-hydroxy- ^a				111
XIII, R = NHC(NH)NH ₂	2-Guanidino-4-hydroxy- ^b				111
VIII	2,4-Dihydroxy-7-nitro-	> 310	Cream-colored needles	Acetic acid	111
XVIIIb	10-Carboxy-2,4-dihydroxy-	> 325	Colorless prisms	Acetic acid	113
XVIIIa	10-Carbomethoxy-2,4-dihydroxy-	> 320	Colorless plates	Acetic acid	113

(Table continued)

TABLE I-6 (continued)

Formula	Triazaanthracene	M.p., °C.	Appearance	Recrystallized from	Refs.
XXa	10-Carbethoxy-2,4-dihydroxy-	> 320	Colorless	Dioxane	113
XVIIIc	10-Chlorocarbonyl-2,4-dihydroxy-	250 (dec.)	Yellow		113
XXb	10-Carbamido-2,4-dihydroxy-	> 310	Colorless needles	Formamide	113
—	10-Carboxy-9-methyl-2,4-dioxo-2,3,4,9-tetrahydro-	> 300	Yellow prisms		113
XXI	10-Carbomethoxy-9-methyl-2,4-dioxo-2,3,4,9-tetrahydro-	280-2	Yellow prisms	Water	113
XIX	10-Carbomethoxy-2,4-dioxo-1,3-dimethyl-2,3,4,9-tetrahydro-	220	Colorless needles	Methanol	113
	1,8,9-Triazaanthracene				
XXII	2,7-Diamino-	(Dec.)	Yellow	Ethanol	114
	1,9,10-Triazaanthracene				
XXIX	4-Hydroxy-				117
XXX	4-Oxo-1-phenylamino-1,4-dihydro-				117

Formula	Triazaanthracene	M.p., °C.	Appearance	Recrystallized from	Refs.
	2,3,9-Triazaanthracene				
XXXXVa	1-Hydroxy-4-methyl-	320 (dec.)	Colorless leaves	Acetic acid	119
XXXXVb	1-Hydroxy-4-phenyl-	308-10	Colorless needles	Acetic acid	119
XXXXVIa	1-Hydroxy-6,7-dimethoxy-4-methyl-	315	Yellow	Acetic acid	119
XXXXVIb	1-Hydroxy-6,7-dimethoxy-4-phenyl-	316-8	Colorless needles	Acetic acid	119
—	1-Hydroxy-6,7-methylene-dioxy-4-methyl-	355-7	Yellow needles	Acetic acid	119
XXXXVIII	4-Methyl-1-oxo-2-phenyl-1,2-dihydro-	244		Acetic acid	120
	2,9,10-Triazaanthracene				
XXXIX	Unsubstituted	181-2	Yellow needles	Pet. ether	118
XLII	7-Methyl-	148	Yellow needles	Aq. ethanol	118
XL	9,10-Dihydro- ^a	290	Red needles	Ethanol	118
XLIII	7-Methyl-9,10-dihydro-				118
XLVI	4-Nitro-9-phenyl-9,10-dihydro-	247-8	Violet prisms	Benzene	121
XLVIII	4-Amino-9-phenyl-2,9,10-triazaanthracenium chloride	> 310	Bronze plates	Methanol	121
	Acetyl deriv. of XLVIII	275 (dec.)	Red prisms	Ethanol	121

^a Isolated as the meconate.^b P 222 (dec.)^c Hydrochloride hydrate.

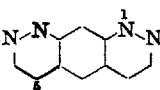
4. Tetrazaanthracenes

Of the sixty possible isomers of tetrazaanthracene (excluding those with nitrogen common to two rings) only eight have been reported. These are the 1,2,7,8-, 1,3,5,7-, 1,3,6,8-, 1,3,9,10-, 1,4,5,8-, 1,4,9,10-, 2,3,6,7-, and 2,7,9,10-tetrazaanthracenes. The 1,3,9,10-isomer is the parent compound of a number of biologically active materials, including alloxazine and isalloxazine, which will be considered elsewhere (see footnote, p. 14).

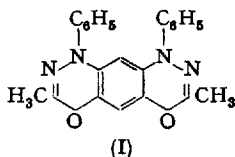
Nomenclature

In the sections to follow the azaanthracene nomenclature is used throughout. The second name given in the heading is the one preferred by *Chemical Abstracts*. Other names recorded are those used by the authors in their original reports on the subject. *The Ring Index* number is included.

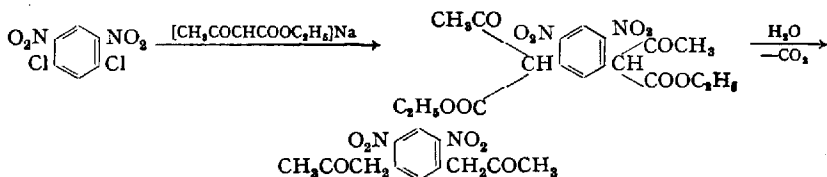
- A. **1,2,7,8-Tetrazaanthracene. Pyridazo[4,3-g]cinnoline. Benzodipyridazine. R.I. 1873**



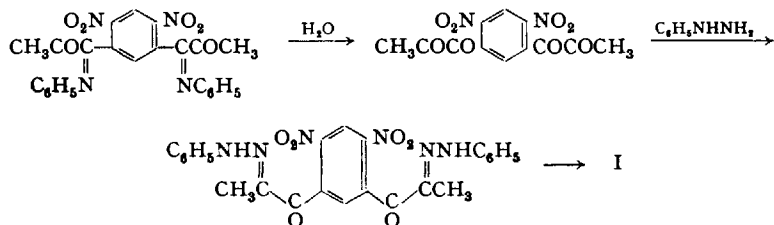
The only known derivative of this ring structure is 4,5-dioxo-3,6-dimethyl-1,8-diphenyl-1,4,5,8-tetrahydro-1,2,7,8-tetrazaanthracene (3,6-dimethyl-1,8-diphenylbenzodipyridazolone) (I). It is prepared as



follows:¹²⁴ 4,6-Dichloro-1,3-dinitrobenzene is condensed with the sodium salt of ethyl acetoacetate to give diethyl 4,6-dinitrophenylene-

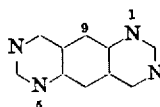


1,3-diacetoacetate, which is hydrolyzed and decarboxylated in sulfuric acid to 1,3-diacetyl-4,6-dinitrobenzene. This product is treated with nitrosobenzene to form a dianil, which is hydrolyzed to the tetraketone, 4,6-dinitro-1,3-dipyrrolylbenzene; the latter is converted to the

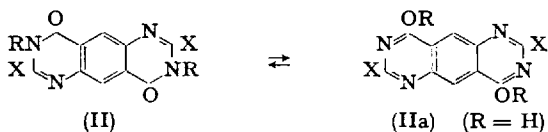


α,α' -diphenylhydrazone, which is cyclized with the loss of two moles of nitrous acid to the tetrazaanthracene (I). This cyclization is similar to that involved in the preparation of 4-nitro-9-phenyl-9,10-dihydro-2,9,10-triazaanthracene (XLVI) from 3,5-dinitro-4-*o*-phenylamino-anilinopyridine (XLV) (pp. 126 ff.).

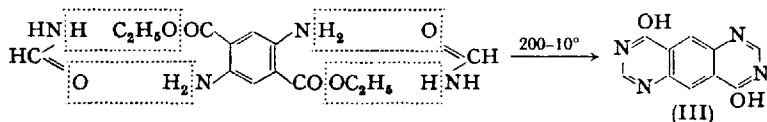
B. 1,3,5,7-Tetrazaanthracene. Pyrimido-[4,5-g]quinazoline. *as-p*-Benzodipyrimidine. Antetrazine. 1,3,5,7-Naphthotetrazine. 1,3,6,8-Naphthotetrazine. 5,4',4,5'-Dimethylenediacil. R.I. 1875



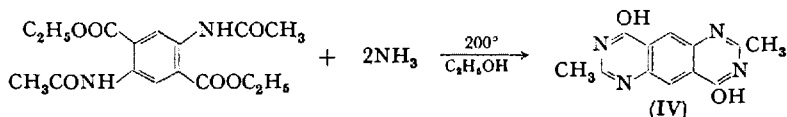
The parent base of this specific ring structure is unknown, but several derivatives have been prepared. Most of these have the general structure II; if a hydrogen atom is available, they may exist in the tautomeric form IIa. The simplest known compound, 4,8-dihydroxy-



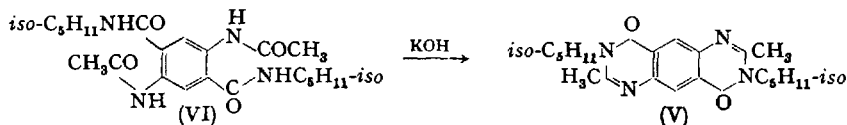
1,3,5,7-tetrazaanthracene (III), is obtained by the action of formamide on ethyl 2,5-diaminoterephthalate.¹²⁵



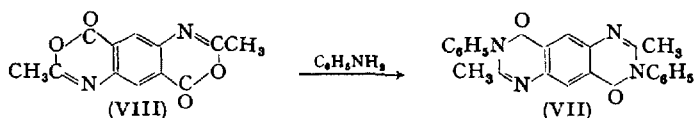
The 2,6-dimethyl analog (IV) results¹²⁵ when ethyl 2,5-diacetamidoterephthalate is treated with alcoholic ammonia at 200°:



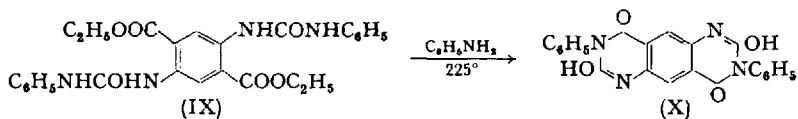
N-Alkyl derivatives such as 3,7-diisoamyl-2,6-dimethyl-4,8-dioxo-3,4,7,8-tetrahydro-1,3,5,7-tetrazaanthracene (V) are secured by cyclizing the intermediate amide (VI) with aqueous potassium hydroxide.¹²⁵



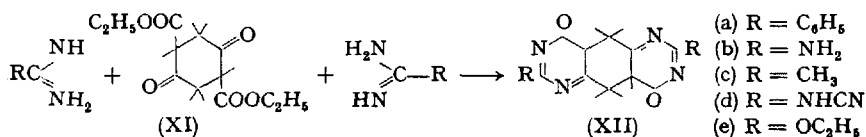
The corresponding diphenyl derivative (VII) is prepared by heating the "diacetanthranil" (4,8-dioxo-2,6-dimethyl-3,7-dioxo-1,5-diazaanthracene) (VIII) with aniline.¹²⁵



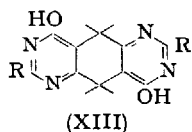
Ethyl 2,5-di(phenyluramino)terephthalate (IX) and aniline yield 2,5-dihydroxy-4,8-dioxo-3,7-diphenyl-3,4,7,8-tetrahydro-1,3,5,7-tetrazaanthracene (X).¹²⁵



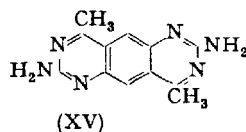
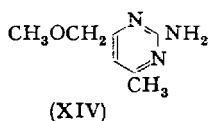
Similar heterocyclic compounds are formed by the action of benzamidine hydrochloride,¹²⁶ guanidine thiocyanate,¹²⁷ acetamidine hydrochloride,¹²⁸ dicyandiamide,¹²⁹ and ethylisourea¹³⁰ on ethyl succinosuccinate (XI). The products (XIIa-e, respectively) can be



written in a number of tautomeric forms of which the form XIII is the most convenient to name. The product from ethylisourea originally was



(a-e; R as in XII)

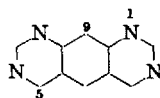


given the name 5,4',4,5'-dimethylenebis(ethoxyuracil). The others were named as derivatives of naphthotetrazine.

In an effort to cleave the ether group of 2-amino-6-methoxymethyl-4-methylpyrimidine (XIV) with hydrogen bromide, Price, Leonard, and Curtin¹³¹ obtained a high-melting, yellow solid to which they ascribed the structure XV. Assignment of this structure was based on a study of the ultraviolet absorption spectra of the pyrimidine (XIV) and the reaction product. The marked differences between the two suggested a modification of the pyrimidine nucleus, and the tetrazaanthracene structure, XV, represents such a change. No chemical proof was offered.

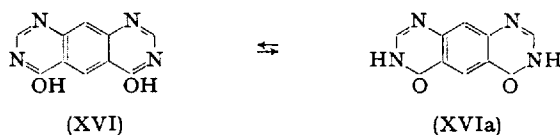
In general, these substances are very high-melting, crystalline solids, insoluble in the usual organic solvents; however, the diisoamyl derivative (V) melts at 179°. In instances in which hydrogen atoms are available, the substances may be written in various tautomeric forms. The solubility of such compounds in alkali is indicative of their phenolic nature. Those that cannot tautomerize to a phenolic form can be recrystallized from acetic anhydride. Alkaline solutions of a number of them show the characteristic blue fluorescence of the azaanthracenes.

C. 1,3,6,8-Tetrazaanthracene, Pyrimido-[5,4-g]quinazoline. 1,3,7,9-Naphthotetrazine. R.I. 1876

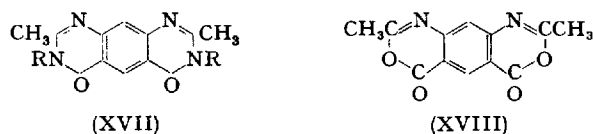


Syntheses of substances of this ring structure follow closely the methods used in preparing 1,3,5,7-tetrazaanthracenes. Thus, ethyl 4,6-diaminoisophthalate reacts with formamide¹³² to yield 4,5-dihydroxy-1,3,6,8-tetrazaanthracene (XVI or its tautomer XVIa). The

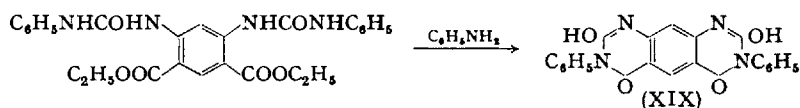
action of alcoholic ammonia on the diacetyl derivative of ethyl 4,6-diaminoisophthalate produces the dimethyl analog (XVII, R = H).



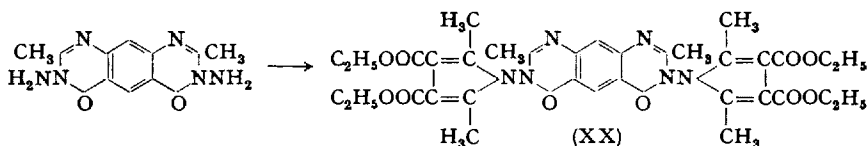
The above reactions are carried out under pressure and at a temperature



of 200–10°C.; XVII (R = H) is more conveniently prepared by boiling the "bisacetanthranil," XVIII, with aqueous ammonia. By the use of aqueous solutions of the requisite amines, analogs of XVII in which R = -CH₃, -C₃H₇, -C₆H₅, -β-C₁₀H₇, -NH₂, and NHC₆H₅ are obtained. Treatment of ethyl 4,6-diphenyluraminoisophthalate with aniline at 225° gives 2,7-dihydroxy-4,5-dioxo-3,6-diphenyl-3,4,5,6-tetrahydro-1,3,6,8-tetrazaanthracene (XIX).

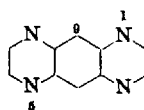


All these substances have high melting points. For those in which tautomerism is possible (XVI; and XVII, R = H) they are very high. Solubilities are slight when R = H, but, when R = CH₃, C₃H₇, C₆H₅, or β-C₁₀H₇, the substances can be recrystallized from alcohol. The diamino compound (XVII, R = NH₂) forms a hydrochloride, a diacetyl

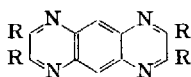


derivative, a dibenzal derivative, and condenses with ethyl diacetyl-succinate, to give 4,5-dioxo-2,7-dimethyl-3,6-di(2,5-dimethyl-3,4-dicarbethoxy-1-pyrryl)-3,4,5,6-tetrahydro-1,3,6,8-tetrazaanthracene (XX). With sodium nitrite in dilute hydrochloric acid the amino groups are replaced by hydrogen, but, if the diazonium solution is poured immediately after its formation into alkaline β -naphthol a deep red dye is formed.

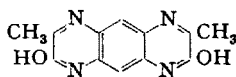
D. 1,4,5,8-Tetrazaanthracene. Pyrazino[g]-quinoxaline. Diquinoxaline. 1,4,6,9-Naphthotetrazine. R.I. 1878



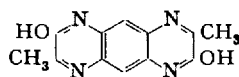
When 1,2,4,5-tetraminobenzene¹³³ is treated with two molecular equivalents of a 1,2-dicarbonyl compound, a 1,4,5,8-tetrazaanthracene results. Thus, 2,3,6,7-tetramethyl-1,4,5,8-tetrazaanthracene (XXI, $R = CH_3$) is formed when 1,2,4,5-tetraminobenzene is treated with diacetyl.¹³⁴ In a similar manner, pyruvic acid,¹³⁴ benzil,¹³⁴ and ethyl ketipate (ethyl β,γ -dioxoadipate)¹³⁵ yield 2,7-dimethyl-3,6-dihydroxy-,



(XXI)



(XXII)

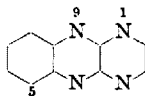


(XXIII)

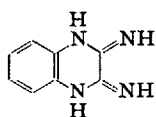
2,3,6,7-tetraphenyl-, and 2,3,6,7-tetracarboethoxymethyl-1,4,5,8-tetrazaanthracenes (XXII; XXI, $R = C_6H_5$; XXI, $R = CH_2COOC_2H_5$), respectively. No mention is made of the possibility of securing an isomeric compound, 2,6-dimethyl-3,7-dihydroxy-1,4,5,8-tetrazaanthracene (XXIII), with pyruvic acid nor is any proof of structure given. The reaction is usually carried out by treating the tetrahydrochloride of the base in alcohol with sodium acetate and the dicarbonyl compound, the alkali serving to liberate the base from its hydrochloride and to catalyze the condensation.

The products have high melting points and are insoluble in the usual solvents. They give blue solutions in sulfuric acid and show some fluorescence in dilute alkali.

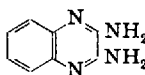
- E. 1,4,9,10-Tetrazaanthracene. Pyrazino-[2,3-*b*]quinoxaline. Pyrazinophenazine. 1,4,5,10-Naphthotetrazine. R.I. 1877



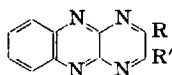
When *o*-phenylenediamine is treated with hydrogen cyanide a "dicyanphenylenediamine" which may exist in two forms (XXIV and XXV) is obtained.¹³⁶ Proof that the substance exists as XXV under certain conditions is derived from the formation of 1,4,9,10-tetrazaanthracene derivatives (XXVI) by treatment with dicarbonyl com-



(XXIV)



(XXV)

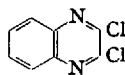


(XXVI)

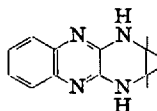
- (a) $R = R' = C_6H_5$
 (b) $R = CH_3, R' = OH$
 (c) $R = R' = OH$

pounds.¹³⁷ For example, benzil reacts with XXV to give 2,3-diphenyl-1,4,9,10-tetrazaanthracene (XXVIa). In a similar manner pyruvic acid and oxalic acid yield the 1,4,9,10-tetrazaanthracenes, XXVIb and XXVIc, respectively.

It will be apparent that a tetrazaanthracene (XXVIII) should result if 2,3-dichloroquinoxaline (XXVII) is treated with ethylenediamine, and this has been realized.¹³⁸

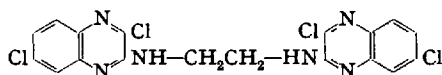


(XXVII)



(XXVIII)

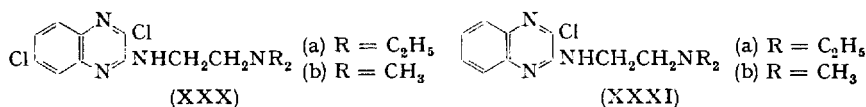
The investigators concerned called this product "*o*-phenyleneethylenexamidine." The same type of reaction with 2,3,6-trichloroquinoxaline, however, is said to yield only the bis compound, XXIX.¹⁴⁰



(XXIX)

The tetrahydro derivative, XXVIII, is the parent compound of a number of 1,4,9,10-tetrazaanthracenes prepared during a study of the

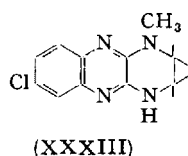
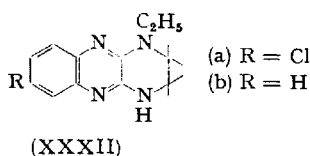
antimalarial activity of certain quinoxaline derivatives.^{139,140} The investigation was prompted by the fact that 2,6-dichloro-3- β -diethylaminoethylaminoquinoxaline (XXXa) shows marked activity against avian malaria. This derivative is formed by treating 2,3,6-trichloroquinoxaline with β -diethylaminoethylamine. 2,3-Dichloroquinoxaline gives 2-chloro-3- β -diethylaminoethylaminoquinoxaline (XXXIa). The



corresponding derivatives, XXXb and XXXIb, are formed with β -dimethylaminoethylamine.

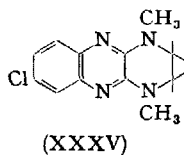
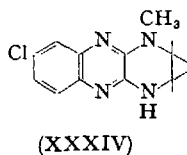
It is surprising that a homogeneous product and not a mixture of isomers is usually formed in the reaction of amines with 2,3,6-trichloroquinoxaline. Apparently, one chlorine atom is more reactive than the others and it has been assumed that the 3-chlorine atom is preferentially attacked while the 2-chlorine atom is stabilized by conjugation with the chlorine atom in position 6.¹³⁹ Evidence supporting this conclusion arises from the following facts: γ -piperidylpropylamine gives, with 2,3,6-trichloroquinoxaline, a mixture of two isomers, the structures of which have been established by unequivocal syntheses; these isomers are formed in a 3:1 ratio with the one involving the 3-chlorine atom predominating.¹⁴⁰

In the preparation of the above compounds it is necessary to operate in the cold; otherwise there is cyclization to tetrazaanthracene derivatives. As a result, these intermediates have been used in the synthesis of tetrazaanthracenes. When XXXa or XXXIa is heated to 190–200° for a few minutes, cyclization is effected with the loss of ethyl chloride, and a derivative of 1,2,3,4-tetrahydro-1,4,9,10-tetrazaanthracene (XXXIIa or b) is formed. When XXXb is heated to con-



stant weight at 135–45° and the residue extracted with petroleum ether, 6-chloro-1-methyl-1,2,3,4-tetrahydro-1,4,9,10-tetrazaanthracene (XXXIII) crystallizes from the extract. The insoluble portion, which is purified by recrystallization from alcohol, is apparently the dimethochloride of XXXIII.

If 2,3,6-trichloroquinoxaline is heated under reflux for twenty hours with the amine in alcohol solution, two isomeric tetrazaanthracenes are formed; β -dimethylaminoethylamine gives a mixture of the 6-chloro- and 7-chloro-1-methyl-1,2,3,4-tetrahydro-1,4,9,10-tetraza-

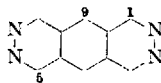


anthracenes (XXXIII and XXXIV). The latter, being the less soluble of the two, separates first. The other is more difficult to purify, but it is identical with the 6-isomer obtained by cyclization of 2,6-dichloro-3- β -dimethylaminoethylaminoquinoxaline (XXXb).

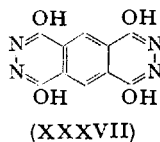
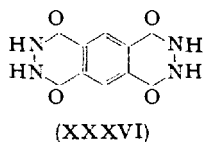
It has already been noted that 2,3-dichloroquinoxaline yields 1,2,3,4-tetrahydro-1,4,9,10-tetrazaanthracene (XXVIII) when treated with ethylenediamine, and that this amine and 2,3,6-trichloroquinoxaline give only the bis compound, XXIX. Symmetrical dimethylethylenediamine, however, reacts with 2,3,6-trichloroquinoxaline to give 6-chloro-1,4-dimethyl-1,2,3,4-tetrahydro-1,4,9,10-tetrazaanthracene (XXXV).

It will be noted from Table I-7 that the fully aromatic compounds of this basic structure are yellow in color and have very high melting points. The tetrahydro derivatives, on the other hand, have moderate melting points. The tetrahydro compounds, being secondary bases in several cases, form acetyl and benzoyl derivatives with ease; they also form salts such as picrates and hydrochlorides. While only monopicates are formed with picric acid, in other cases bis salts apparently are obtained. The dimethochloride of XXXIII undergoes a metathesis with picric acid or potassium iodide to give a methochloride picrate or a methochloride methiodide, respectively.

F. 2,3,6,7-Tetrazaanthracene. Pyridazo-[4,5-g]phthalazine. Benzodipyridazine. Pyromellitic dihydrazide. R.I. 1880

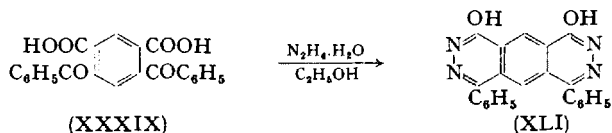
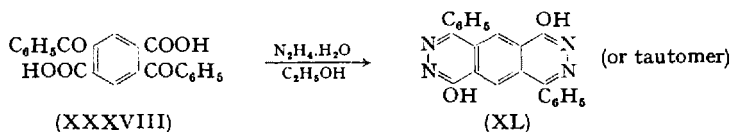


Interest in this type of compound is due to the chemiluminescent properties of phthalhydrazides of which the 2,3,6,7-tetrazaanthracenes are heterologs. In general, these substances are prepared by the action of hydrazine or phenylhydrazine on a benzene derivative carrying four symmetrically situated carbonyl substituents; the latter may be $-\text{COOH}$, $-\text{CHO}$, or COR . For example, pyromellitic anhydride reacts with hydrazine hydrate^{141,142} to give 1,4,5,8-tetroxo-1,2,3,4,5,6,7,8-octahydro-2,3,6,7-tetrazaanthracene (XXXVI) or its tautomer, 1,4,5,8-



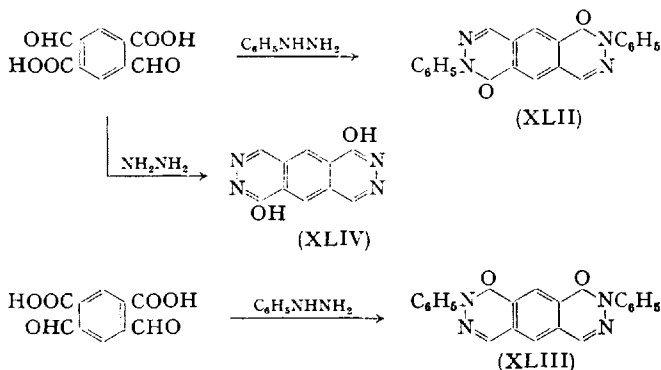
tetrahydroxy-2,3,6,7-tetrazaanthracene (XXXVII). The substance forms a tetraacetyl derivative.¹⁴¹

In the same manner, 2,5-dibenzoylterephthalic acid (XXXVIII) and 4,6-dibenzoylisophthalic acid (XXXIX) react with hydrazine in alcohol solution under pressure to give the isomeric substances, 1,5-dihydroxy-4,8-diphenyl-2,3,6,7-tetrazaanthracene (XL) and 1,8-dihydroxy-4,5-diphenyl-2,3,6,7-tetrazaanthracene (XLI), respectively.¹⁴¹

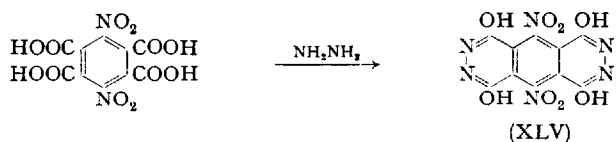


Two isomeric compounds, XLII and XLIII, which are also isomeric with XL and XLI, are secured by the action of phenylhydrazine on 2,5-dicarboxyterephthalaldehyde and 4,6-dicarboxyisophthalaldehyde,

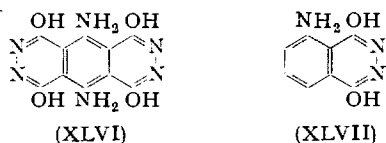
respectively.¹⁴³ The former aldehyde also yields 1,5-dihydroxy-2,3,6,7-tetrazaanthracene (XLIV) when treated with hydrazine.



When dinitropyromellitic acid is treated with hydrazine hydrate, 1,4,5,8-tetrahydroxy-9,10-dinitro-2,3,6,7-tetrazaanthracene (XLV) is formed.¹⁴⁴ This substance, in the presence of hydrogen peroxide, shows a pale chemiluminescence that becomes stronger on the addition of a

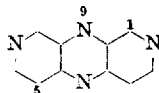


solution of chlorinated lime (bleaching powder). However, the diamino compound (XLVI) secured by reduction of XLV shows only a very feeble chemiluminescence as compared to 3-aminophthalhydrazide (XLVII, Luminol). In view of the low melting point (42°) recorded for

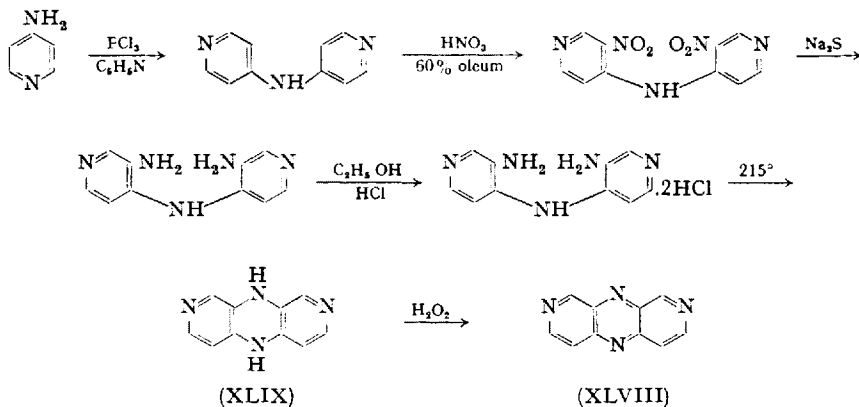


this substance, the fact that no analytical figures are reported, and that it changes into a higher melting compound when heated above its original melting point, the report on its chemiluminescent properties must be accepted with reserve until the structure of the product is more clearly established.

G. 2,7,9,10-Tetrazaanthracene. Dipyrido-[3,4-*b*, 4',3'-*e*]pyrazine. Di-3,4-pyridopyrazine. R.I. 1884



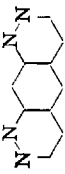
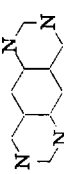
Only two tetrazaanthracenes of this general structure are known, 2,7,9,10-tetrazaanthracene (XLVIII) and its 9,10-dihydro derivative (XLIX). They are obtained as follows: 4-Aminopyridine is treated with phosphorus trichloride in pyridine to give 4,4'-dipyridylamine, which is nitrated in 60% oleum to 3,3'-dinitro-4,4'-dipyridylamine; the latter is reduced to 3,3'-diamino-4,4'-dipyridylamine with sodium sulfide and isolated as the dihydrochloride. 9,10-Dihydro-2,7,9,10-tetrazaanthracene (XLIX) is formed when the dihydrochloride is heated to 215°, and is oxidized with hydrogen peroxide to 2,7,9,10-tetrazaanthracene (XLVIII).¹⁴⁵ This synthesis is similar to the synthesis of 2,9,10-triazaanthracene and its dihydro derivative from 3-amino-4-*o*-aminopyridine (p. 125). Unlike 2,2'-diaminodiphenylamine, which is

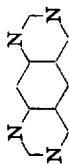


oxidized to phenazine with ferric chloride, the 3-amino-4-*o*-aminopyridine could not be oxidized directly to the triazaanthracene derivative; this is probably true of 3,3'-diamino-4,4'-dipyridylamine.

Substance XLVIII (m.p. 290–300°), surprisingly, is said to be a very weak base; it does not form stable salts. The dihydro compound (XLIX) is a stronger base, forming salts with oxalic, hydrochloric, nitric, and picric acids; the picrate decomposes at 300–1°; the other salts are unchanged at 310°.

TABLE I-7. Tetrazaanthracenes

Formula	Tetrazaanthracene	M.p., °C.	Appearance	Recrystallized from	Refs.
	1,2,7,8-Tetrazaanthracene				
I	3,6-Dimethyl-4,5-dioxo-1,8-diphenyl-1,4,5,8-tetrahydro-	353-4 (dec.)	Golden brown needles	Ethanol pyridine	124
	1,3,5,7-Tetrazaanthracene				
					
III	4,8-Dihydroxy-	> 310	Yellow	(Sol. NaOH)	125
IV	4,8-Dihydroxy-2,6-dimethyl-	> 325	Yellow		125
XIIIc	4,8-Dihydroxy-2,6-dimethyl-9,10-dihydro-	Chars	Colorless ^a		128
V	3,7-Diisooamyl-4,8-dioxo-2,6-dimethyl-3,4,7,8-tetrahydro-	179	Yellow needles	Ethanol	125
XIIIa	4,8-Dihydroxy-2,6-diphenyl-9,10-dihydro- ^a				126
VII	2,6-Dimethyl-4,8-dioxo-3,7-diphenyl-3,4,7,8-tetrahydro-	> 325	Greenish-yellow leaves	Acetic anhydride	125
X	2,6-Dihydroxy-4,8-dioxo-3,7-diphenyl-3,4,7,8-tetrahydro-	> 330	Yellow	(Sol. NaOH)	125
XV	2,6-Diamino-4,8-dimethyl-				
XIIIb	2,6-Diamino-4,8-dihydroxy-9,10-dihydro-	285-6 (dec.)	Yellow	Acetic acid	131
			Yellow		127

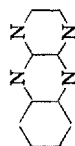
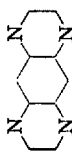
Formula	Tetrazaanthracene	M.p., °C.	Appearance	Recrystallized from	Refs.	
XIIIId	2,6-Dicyanamino-4,8-dihydroxy-9,10-dihydro-	Darkens ca. 320	Yellow		129	
XIIIe	2,6-Diethoxy-4,8-dihydroxy-9,10-dihydro-				130	
	1,3,6,8-Tetrazaanthracene					
	XVI	4,5-Dihydroxy-	> 310	Reddish-yellow powder	Sol. NaOH	132
	XVII, R = H	4,5-Dihydroxy-2,7-dimethyl-	> 310	Pale yellow powder		132
	XVII; R = CH ₃	2,3,6,7-Tetramethyl-4,5-dioxo-3,4,5,6-tetrahydro-	> 350	Colorless needles	Ethanol	132
	XVII, R = - <i>n</i> -C ₃ H ₇	2,7-Dimethyl-4,5-dioxo-3,6-di- <i>n</i> -propyl-3,4,5,6-tetrahydro-	220	Colorless needles	Aq. ethanol	132
	XVII, R = C ₆ H ₅	2,7-Dimethyl-4,5-dioxo-3,6-di-phenyl-3,4,5,6-tetrahydro-	315	Colorless needles	Ethanol	132
	XVII, R = -β-C ₁₀ H ₇	2,7-Dimethyl-4,5-dioxo-3,6-di-naphthyl-3,4,5,6-tetrahydro-	304	Fluorescent needles	Ethanol	132
	XIX	2,7-Dihydroxy-4,5-dioxo-3,6-di-phenyl-3,4,5,6-tetrahydro-	> 300	Colorless; amorph.		132
	XX	2,7-Dimethyl-3,6-di-(2,5-dimethyl-3,4-dicarbethoxy-1-pyrryl)-4,5-dioxo-3,4,5,6-tetrahydro-	268	Colorless prisms	Ethanol	132

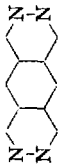
(Table continued)

(Table continued)

TABLE I-7 (continued)

Formula	Tetrazaanthracene	M.p., °C.	Appearance	Recrystallized from	Refs.
XVII, R = NH ₂	3,6-Diamino-2,7-dimethyl-4,5-dioxo-3,4,5,6-tetrahydro-		Yellow scales	HCl > 360	132
XVII, R = NHC ₆ H ₅	3,6-Dianilino-2,7-dimethyl-4,5-dioxo-3,4,5,6-tetrahydro-	> 320	Colorless solid		132
XVII, R = NHCOCH ₃	3,6-Diacetamido-2,7-dimethyl-4,5-dioxo-3,4,5,6-tetrahydro-	> 350	Colorless needles	Ethanol	132
XVII, R = N = CHC ₆ H ₅	3,6-Dibenzalamino-2,7-dimethyl-4,5-dioxo-3,4,5,6-tetrahydro-	> 350	Yellow solid	Benzaldehyde	132
	1,4,5,8-Tetrazaanthracene				
XXI, R = CH ₃	2,3,6,7-Tetramethyl-	> 300	Reddish leaves	Aniline	134
XXI, R = C ₆ H ₅	2,3,6,7-Tetraphenyl-		Yellow (K salt)		134
XXII or XXIII	3,6(or 7)-Dihydroxy-2,7(or 6)-dimethyl-	289	Needles	Acetic acid	134
XXI, R = CH ₂ COOC ₂ H ₅	2,3,6,7-Tetracarboethoxymethyl-		Orange	Ethanol	135
	1,4,9,10-Tetrazaanthracene				
XXVIII	1,2,3,4-Tetrahydro-	> 350	Colorless leaves	Ethanol	138
XXVIa	2,3-Diphenyl-	235	Yellowish-red	Methanol	137



Formula	Tetrazaanthracene	M.p., °C.	Appearance	Recrystallized from	Refs.
XXVIc	2,3-Dihydroxy-	> 300	Pale yellow	Pptd. with NaOH from HCl	137
XXVIIb	2-Hydroxy-3-methyl-	> 300	Yellow needles	Dil. acetic acid	137
XXXIIb	1-Ethyl-1,2,3,4-tetrahydro-	155-6	Colorless prisms	Methanol ^b	139
XXXIII	6-Chloro-1-methyl-1,2,3,4-tetrahydro-	169-70	Colorless prisms	Light petroleum ^c	139
XXXIV	7-Chloro-1-methyl-1,2,3,4-tetrahydro-	222-3	Colorless plates	Methanol ^d	140
XXXIIa	6-Chloro-1-ethyl-1,2,3,4-tetrahydro-	187-8	Prisms	Ethanol ^e	139, 140
XXXV	6-Chloro-1,4-dimethyl-1,2,3,4-tetrahydro-	83	Colorless	Methanol ^f	140
—	4-Acetyl-6-chloro-1-methyl-1,2,3,4-tetrahydro-	180-1	Colorless prisms	Ethanol	140
—	4-Acetyl-7-chloro-1-methyl-1,2,3,4-tetrahydro-	167-9	Colorless prisms	Ethanol	140
—	4-Benzoyl-6-chloro-1-methyl-1,2,3,4-tetrahydro-	239-40	Cream colored prisms	Ethanol	140
—	4-Benzoyl-7-chloro-1-methyl-1,2,3,4-tetrahydro-	207-8	Pale cream prisms	Ethanol	130
	2,3,6,7-Tetrazaanthracene				
	XLIV				
XLIV	1,5-Dihydroxy-	> 350	Colorless	(Impure)	143

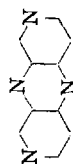
(Table continued)

TABLE I-7 (continued)

Formula	Tetrazaanthracene	M.p., °C.	Appearance	Recrystallized from	Refs.
XL	1,5-Dihydroxy-4,8-diphenyl-	Carbonizes 445	Colorless		141
XLI	1,8-Dihydroxy-4,5-diphenyl-	430 (dec.)		Nitrobenzene	141
—	1,8-Dihydroxy-4,5-dixylyl-	Carbonizes			141
XLII	1,5-Dioxo-2,6-diphenyl-1,2,5,6-tetrahydro-	362	Yellow plates	Nitrobenzene	143
XLIII	1,8-Dioxo-2,7-diphenyl-1,2,7,8-tetrahydro-	340	Colorless plates		143
XXXXVII	1,4,5,8-Tetrahydroxy-	ca. 450	White		141, 142
—	Tetraacetate of XXXVII	(dec.)	Yellow (Na salt)		141
XLV	1,4,5,8-Tetrahydroxy-9,10-dinitro-	235-8			144
XLVI	9,10-Diamino-1,4,5,8-tetrahydroxy-	ca. 260	Yellow	Ethanol	144
		42	Yellow crystals	Acetone	144
	2,7,9,10-Tetrazaanthracene				
XLVIII	Unsubstituted	290-300			145
XLIX	9,10-Dihydro- <i>g</i>				145

^a Isolated as a sodium salt.^b 2HCl 206 (dec.).^c P indef. m.p.; 2MeCl 244; MeClP

231-2; MeCl-MeI 239-40.

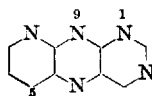
^d P ca. 258.^e P 257-8.^f P 197-8.^g P 300-1.

5. Pentazaanthracenes

Only one ring system containing five nitrogen atoms in a linear arrangement of three six-membered rings has been investigated, namely, the 1,3,8,9,10-pentazaanthracene system.

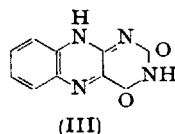
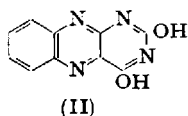
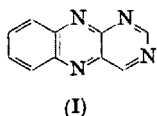
Interest in compounds of this type arises from the remarkable properties of flavine (III), to which they are similar in color, green fluorescence in neutral solution, absorption spectrum, reversible reduction, negative redox potential, etc. They may also have some biological significance as antagonists for folic acid, a vitamin that plays an important part in the growth of certain bacteria and normal and malignant tissue.¹⁴⁶

A. 1,3,8,9,10-Pentazaanthracene. Pyrido-[2,3-*b*]pyrimido[5,4-*e*]pyrazine. R.I. 1872

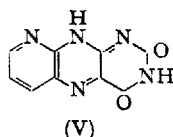
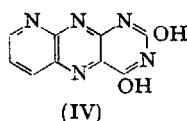


(I) Nomenclature

Substances of this type bear a very close resemblance to 1,3,9,10-tetrazaanthracene (I). Because of the large amount of research that has been carried out with the latter type, a special survey of the subject



is to appear elsewhere (see footnote, p. 14). However, the various names applied to the 2,4-dihydroxy derivatives (II) of I have been carried over in naming the 8-aza derivatives. The substance known as alloxazine (II), derived from *o*-phenylenediamine and alloxan, can exist in a number of tautomeric forms of which III has been called isoalloxazine or flavine. When this nomenclature is applied to the

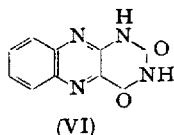


pentaza series, the aza analog (IV) of alloxazine becomes either 8- or 9-azaalloxazine depending upon the numbering system used. In the same way the tautomeric form (V) of IV becomes 8- or 9-azaisoalloxazine (8- or 9-azaflavine). By the "a" system of nomenclature, IV and V would be named 2,4-dihydroxy-1,3,8,9,10-pentazaanthracene and 2,4-dioxo-2,3,4,9-tetrahydro-1,3,8,9,10-pentazaanthracene, respectively.

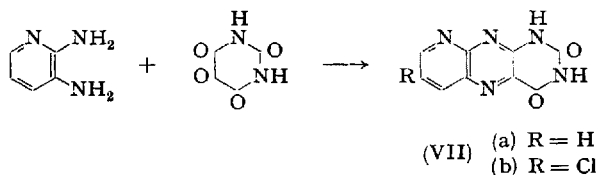
(2) Syntheses

The preparation of 1,3,8,9,10-pentazaanthracenes involves methods similar to those used in the tetrazaanthracene series. While analogous compounds are obtained, certain modifications in the syntheses are necessary because of the decreased activity of the 2-amino group in 2,3-diaminopyridine, one of the necessary reactants.

Alloxazine (VI) is formed by heating an aqueous solution of *o*-phenylenediamine hydrochloride and alloxan.¹⁴⁹ Under similar con-

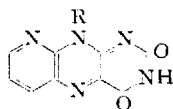


ditions, 2,3-diaminopyridine and alloxan do not give the expected pentazaanthracene derivative VIIa.¹⁴⁷ However, if boric acid, which



has been shown to be an effective condensing agent in reactions of this type,^{150, 152} is used in a glacial acetic acid solution of the reactants, 2,4-dioxo-1,2,3,4-tetrahydro-1,3,8,9,10-pentazaanthracene (VIIa) is formed in good yield.¹⁵¹ When 5-chloro-2,3-diaminopyridine reacts with alloxan under the same conditions (boric acid catalyst), azaflavine formation does not take place, but, if the boric acid is replaced by boron trifluoride etherate, the condensation proceeds to give 6-chloro-2,4-dioxo-1,2,3,4-tetrahydro-1,3,8,9,10-pentazaanthracene (VIIb).

By a similar procedure 2-alkylamino-3-aminopyridines condense with alloxan to produce 9-alkyl-2,4-dioxo-2,3,4,9-tetrahydro-1,3,8,9,10-pentazaanthracenes (VIII). The *n*-propyl derivative (VIIIa) is formed



(a) $R = n\text{-C}_3\text{H}_7$

(b) $R = \text{C}_6\text{H}_{11}$

(c) $R = \text{C}_6\text{H}_5$

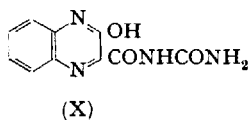
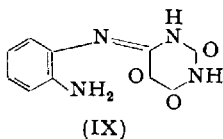
(VIII)

in glacial acetic acid in the presence of zinc chloride and boric acid.¹⁵² The cyclohexyl compound (VIIIb) requires neither the boric acid nor the zinc chloride,¹⁵³ while boric acid alone is sufficient to form the phenyl derivative (VIIIc).

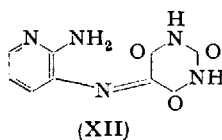
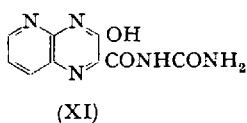
An explanation of these various reactions rests upon the activity of the 2-amino group in 2,3-diaminopyridine and its derivatives. This amino group is less reactive than the amino groups in *o*-phenylenediamine; as a result, a catalyst (boric acid) is necessary to cause formation of the dioxopentazaanthracene (VIIa). Further deactivation of the 2-amino group, brought about by a chlorine atom in the 5-position, is sufficient to overcome the catalytic effect of the boric acid and the formation of the tricycle (VIIb) does not take place. The use of a more active catalyst, boron trifluoride etherate, again makes formation of the tricycle possible. Activation of the 2-amino group results by substituting one of the hydrogens of the amine with a cyclohexyl group, and the pentazaanthracene derivative (VIIIb) forms easily without a catalyst. Phenyl and propyl groups are not as effective as the cyclohexyl group, and catalysts are required.

It is significant that an entirely different type of reaction takes place if the acid or catalyst employed is not sufficiently active to cause formation of the tricyclic compound. This is true of alloxan and *o*-phenylenediamine if the reaction is allowed to proceed in the absence of acid. Alloxazine formation does not take place but a substance is formed which, until recently, has been considered to be an alloxananil (IX).¹⁴⁸ It now appears that this interpretation is incorrect and that

the substance is actually a quinoxaline derivative, X,^{154, 155} the structure originally assigned to the product by Hinsberg.¹⁵⁶ On this



basis, the product derived from 2,3-diaminopyridine and alloxan in the absence of a catalyst should be the azaquinoxaline derivative (XI) and not the anil (XII). However, the initial yellow product formed in this reaction undergoes a change to a colorless isomer and this has been attributed to conversion of XII into XI.¹⁴⁷ In view of the work of King and Clark-Lewis¹⁵⁵ on the simpler analog, the structures assigned to



these substances and to related compounds containing substituent groups should be reinvestigated (see p. 153). As has been pointed out by these authors, there is little evidence to support the contention that other alloxananils obtained during the researches on riboflavine actually have this Schiff base structure.

TABLE I-8. Pentazaanthracene

Formula	Pentazaanthracene	M.p., °C.	Appearance	Recrystallized from	Refs.
	1,3,8,9,10-Pentazaanthracene				
VIIa	2,4-Dihydroxy-	> 300	Reddish-brown		151
VIIb	6-Chloro-2,4-dihydroxy-	> 380	Yellowish-brown		151
VIIIa	2,4-Dioxo-9 <i>n</i> -propyl-2,3,4,9-tetrahydro-	345-50 (dec.)	Orange-yellow needles	Dil. acetic acid	152
VIIIb	9-Cyclohexyl-2,4-dioxo-2,3,4,9-tetrahydro-	320-5 (dec.)	Yellow needles	Acetic acid	153
VIIIc	2,4-Dioxo-9-phenyl-2,3,4,9-tetrahydro-	335-40 (dec.)	Yellow	Acetic acid	153

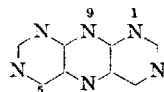
It is apparent that two competing reactions are involved in these syntheses, the formation of the tricycle, and the hydrolysis of the alloxan ring. If the 2-amino group is active enough, the former reaction takes place; if it is deactivated, the alloxan ring is opened and an aza-quinoxaline or similar product is formed.

6. Hexazaanthracenes

The only known substances containing six nitrogen atoms in a linear arrangement of three six-membered rings are derivatives of 1,3,5,7,9,10- and 1,3,6,8,9,10-hexazaanthracenes. The tetrahydroxy derivatives of both are of interest because of their close resemblance to flavine (2,4-dioxo-2,3,4,9-tetrahydro-1,3,9,10-tetrazanthracene), which has some biological significance as a folic acid antagonist.¹⁴⁶

A 1,2,4,5,7,8-hexazaanthracene derivative has been described but its structure is open to question.

- A. 1,3,6,8,9,10-Hexazaanthracene. Dipyrimido-[4,5-b,5',4'-e]pyrazine. Pyrimido[4,5-b]-pteridine. Pyrimido[5,4-g]pteridine

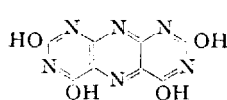


(1) Nomenclature

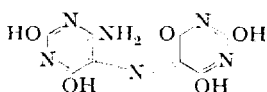
As with the other polyazaanthracenes, the "a" system of nomenclature is preferred. The second name recorded is that used by *Chemical Abstracts* in indexing the substance. The other names are those used by the various authors in describing their work. Because of its similarity to alloxazine, the 2,4,5,7-tetrahydroxy derivative of this hexazaanthracene has been called bisalloxazine.¹⁵⁷

(2) Synthesis and Proof of Structure

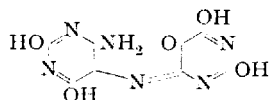
When 4,5-diamino-2,6-dihydroxypyrimidine is allowed to react with alloxan in cold aqueous suspension, a purple-bronze intermediate is formed; this intermediate, which was isolated and characterized, is transformed, under the influence of mild reagents, into the so-called



(I)

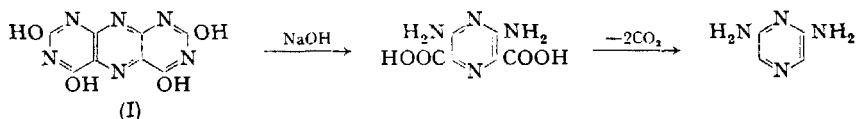


(II)

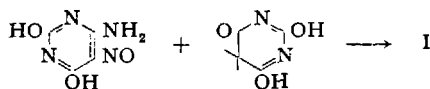


(III)

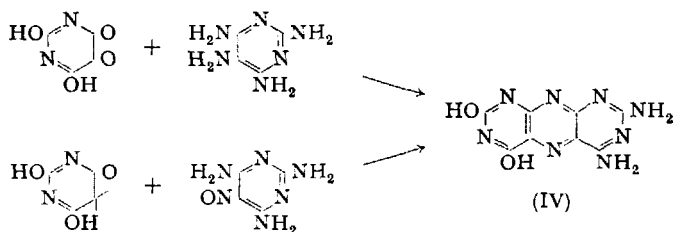
"bisalloxazine" (2,4,5,7-tetrahydroxy-1,3,6,8,9,10-hexazaanthracene, I). This method for formation was suggested by Wieland,¹⁵⁷ who recognized that the reaction might have proceeded by way of an intermediate involving III rather than II. The latter was preferred because of the known greater activity of the 5-amino group in 4,5-diaminopyrimidine and of the 5-carbonyl group in alloxan.¹⁵⁸ Proof that the reaction proceeded as suggested by Wieland was obtained by Taylor and co-workers.¹⁵⁹ They cleaved the "bisalloxazine" (I) with strong aqueous alkali to a diaminopyrazinedicarboxylic acid, which was decarboxylated to 2,6-diaminopyrazine. The isomeric 1,3,5,7,9,10-hexazaanthracene described in the next section should yield 2,5-diaminopyrazine by this procedure. It was this isomeric structure that was assigned to the compound originally by Hepner.¹⁶⁰



Further evidence for structure I evolves from a method of synthesis of compounds of this type, devised by Timmis,¹⁴⁶ which avoids the disadvantages of possible isomer formation; 4-amino-5-nitrosopyrimidines are condensed with compounds that contain adjacent active carbonyl and methylene groups. Using this method, Taylor¹⁵⁹ has shown that the compound formed from 4-amino-5-nitroso-2,6-dihydroxypyrimidine and barbituric acid is identical with Wieland's

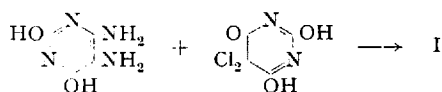


bisalloxazine (I). Identification was made through a comparison of the infrared spectra. The identity of the compound (IV) obtained from

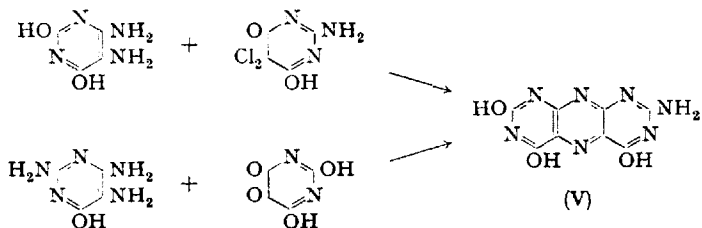


2,4,5,6-tetraminopyrimidine and alloxan with that formed from 2,4,6-triamino-5-nitrosopyrimidine and barbituric acid was similarly established.

The following observations constitute further evidence in favor of the 1,3,6,8,9,10-hexazaanthracene structure for the reaction product of 4,5-diaminopyrimidines with alloxan: (a) the condensation of 5,5-dibromo or 5,5-dichlorobarbituric acid with 4,5-diamino-2,6-dihydroxypyrimidine gives I; (b) the condensation of 2-amino-5,5-dichloro-4-



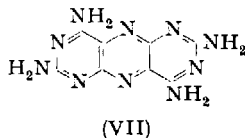
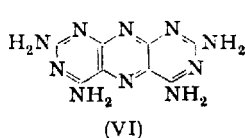
hydroxy-6-oxodihydropyrimidine with 4,5-diamino-2,6-dihydroxypyrimidine gives 2-amino-4,5,7-trihydroxy-1,3,6,8,9,10-hexazaanthracene (V), identical with the product obtained from 2,4,5-triamino-6-hydroxypyrimidine and alloxan. These reactions indicate that the



5-amino group of 4,5-diaminopyrimidines is the more reactive, a property substantiated by Wilson¹⁸⁵ disclosure that acid chlorides react exclusively with the 5-amino group of 4,5-diaminopyrimidine itself. This is in line with the reaction of acid chlorides with the 3-amino group of 2,3-diaminopyridine discussed in an earlier section (see p. 148).

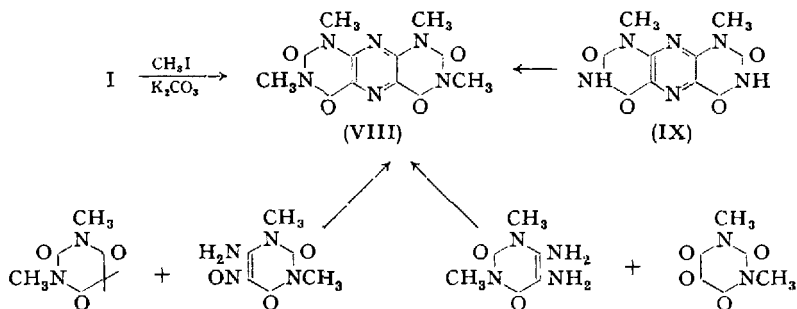
The mild conditions under which these reactions occur is further indicated by the discovery that the deeply colored by-products formed during the synthesis of pteridines and purines involving the use of diaminopyrimidines are actually oxidative self-condensation products of the latter.¹⁸¹ Air oxidation in aqueous solution of 2,4,5,6-tetraminopyrimidine, for example, leads to a mixture of two compounds, which can be separated through their acetates into the isomeric tetramino-1,3,6,8,9,10- and 1,3,5,7,9,10-hexazaanthracenes (VI) and (VII). The

structure of VI is confirmed by deamination to the 2,4,5,7-tetrahydroxy-1,3,6,8,9,10-hexazaanthracene (I) of Wieland. Controlled de-



amination to 2-amino-4,5,7-trihydroxy-1,3,6,8,9,10-hexazaanthracene (V), which had been previously synthesized, constitutes further evidence. The isomer, VII, is considered in the following section.

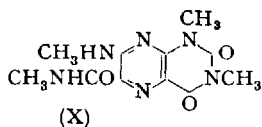
Methylation of the (I) gives 1,3,6,8-tetramethyl-2,4,5,7-tetroxo-1,2,3,4,5,6,7,8-octahydro-1,3,6,8,9,10-hexazaanthracene (VIII).^{159,161} It is identical with the substance obtained by Timmis¹⁶² from the interaction of 1,3-dimethylbarbituric acid with 1,3-dimethyl-



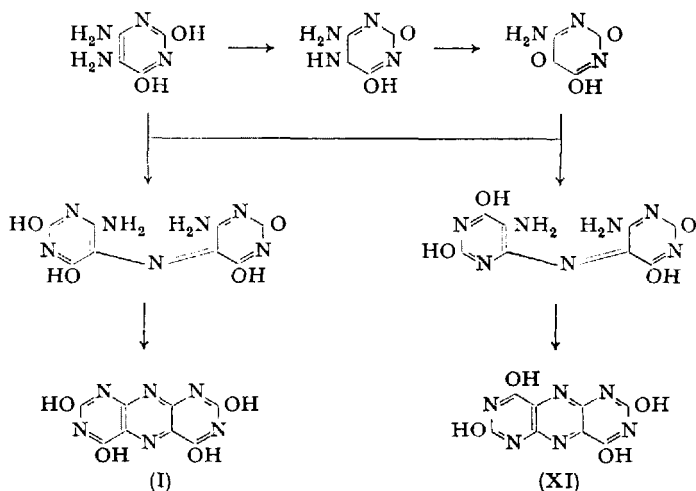
4-amino-5-nitroso-2,6(1*H*, 3*H*)-pyrimidinedione. Despite a discrepancy of about 10° in melting points of the product, which clouded the issue for a short time, VIII is also formed from 1,3-dimethyl-5,6-diamino-2,4(1*H*, 3*H*)-pyrimidinedione and dimethylalloxan,¹⁶³ as well as by treatment of the former with 2 *N* sulfuric acid¹⁶³ or dilute hydrochloric acid.¹⁶⁴ This was established¹⁶⁵ by comparison of the melting point, mixed melting point, and ultraviolet absorption spectrum of the product with the substance obtained by the Timmis unequivocal synthesis.¹⁶² VIII was also obtained by methylation of 1,8-dimethyl-2,4,5,7-tetroxo-1,2,3,4,5,6,7,8-octahydro-1,3,6,8,9,10-hexazaanthracene (IX), which in turn was secured from 3-methylalloxan.

The product melting at 206–7°, described by DeGarmo¹⁶⁶ as VIII,

has been shown to be 1,3-dimethyl-7-methylamino-2,4(1*H*,3*H*)-pteridinedione-6-*N*-methylcarboxamide (X).¹⁶⁵



Taylor and co-workers¹⁶¹ consider that the initial step in the self-condensation of 4,5-diaminopyrimidines is the oxidation of the diaminopyrimidine to the quinonimine. This is followed by hydrolysis to the quinone, which condenses with unchanged diaminopyrimidine to yield either or both of the anils, which undergo ring closure by loss of ammonia or preliminary hydrolysis and dehydration to give the isomeric hexazaanthracene derivatives (I and XI).



Such a mechanism is said to be consistent with the fact that oxidative self-condensation fails with diaminopyrimidines that lack an enolizable hydrogen in the 2-position, for with such substances oxidation to a quinonimine would be precluded. In addition, in all cases investigated the 1,3,6,8,9,10-hexaza isomer either predominates or is formed to the exclusion of the 1,3,5,7,9,10-hexaza isomer, which would be expected because the imino group of the quinonimine or the keto group of the quinone should react preferentially or exclusively with the more active 5-amino group of the 4,5-diaminopyrimidine. The

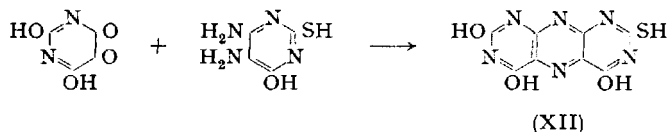
TABLE I-9

Substituent in pyrimidine						Hexazaanthracene deriv. obtained		
1	2	3	4	5	6	Conditions	1, 3, 6, 8, 9, 10	1, 3, 5, 7, 9, 10
OH		OH	NH ₂	NH ₂	NH ₂	Air + H ₂ O or 1 % NaOH	*	*
OH		OH	NH ₂	NH ₂	NH ₂	Air + NH ₄ OH	*	—
NH ₂		OH	NH ₂	NH ₂	NH ₂	Air + H ₂ O + 1 % NaOH	*	*
NH ₂		OH	NH ₂	NH ₂	NH ₂	Air + NH ₄ OH	*	*
SH		NH ₂	NH ₂	NH ₂	NH ₂	Air + H ₂ O	—	—
SH		NH ₂	NH ₂	NH ₂	NH ₂	Air + NaOH	*	—
SH		OH	NH ₂	NH ₂	NH ₂	Air + H ₂ O	—	—
SH		OH	NH ₂	NH ₂	NH ₂	Air + NaOH	* (probably)	
—		OH	NH ₂	NH ₂	NH ₂	Air + H ₂ O or NaOH	—	—
—		—	NH ₂	NH ₂	NH ₂	Air + H ₂ O or NaOH	—	—
OH		OH	NH ₂	—	—	Air + H ₂ O or NaOH	—	—
OH		OH	NH ₂	—	—	K ₃ Fe(CN) ₆	—	*
OH		NH ₂	—	—	—	Air or K ₃ Fe(CN) ₆	—	—

results obtained with compounds studied in this connection are collected in Table I-9. The hexazaanthracene derivatives present in the reaction product are indicated by a star (*).

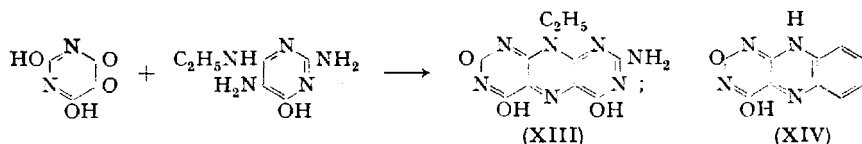
These results are based on an examination of the ultraviolet absorption spectra of the reaction products that had been freed of unreacted diaminopyrimidine. An absorption spectrum at about 380–90 m μ indicates the presence of the 1,3,6,8,9,10-isomer, while a well-defined shoulder at 430–50 m μ indicates the presence of the 1,3,5,7,9,10-derivative.

On the basis of the above results, the compound prepared by Robinson¹⁶⁷ from 5,6-diamino-4-hydroxy-2-mercaptopyrimidine and alloxan should be 4,5,7-trihydroxy-2-mercapto-1,3,6,8,9,10-hexazaanthracene (XII). This product, which was described without structural



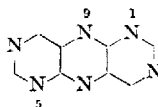
assignment, appears to be the first compound of this class recorded in the literature. A number of compounds of this type have also been prepared by Gal.¹⁶⁸

The only other product of this basic structure described in the literature is 2-amino-9-ethyl-4,5-dihydroxy-7-oxo-7,9-dihydro-1,3,6,8,9,10-hexazaanthracene (XIII).¹⁶⁹ It was obtained by condensing 2,5-diamino-6-ethylamino-4-hydroxypyrimidine with alloxan. It is



related to isoalloxazine (XIV) rather than alloxazine. The reaction is similar to the type described in the pentazaanthracene series (p. 148).

B. 1,3,5,7,9,10-Hexazaanthracene. Dipyrimido-[4,5-b,4',5'-e]pyrazine. Pyrimido[4,5-g]-pteridine



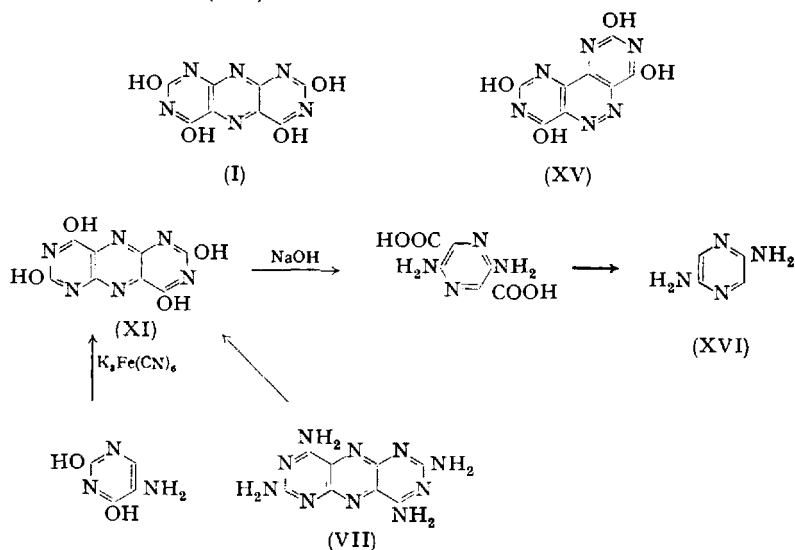
(1) Nomenclature

Derivatives of this hexazaanthracene have been called¹⁶¹ pyrimido-[4,5-g]pteridines. The tetrahydroxy derivative is isomeric with the so-called "bisalloxazine."

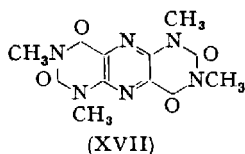
(2) Synthesis and Proof of Structure

As mentioned in the previous section, the oxidative self-condensation of 2,4,5,6-tetraminopyrimidine gives a mixture of two isomeric tetraminohexazaanthracenes that can be separated through their acetates.¹⁶¹ The least soluble of these is a red crystalline solid that fluoresces greenish-yellow in aqueous solution. Deamination of the red solid gives a tetrahydroxy derivative, which is isomeric with bisalloxazine (I), and which has been shown by comparison of infrared spectra to be identical with a product derived from 5-aminouracil by potassium ferricyanide oxidation. While this product has been described as "diuracilpyridazine" and assigned structure XV¹⁷⁰ by analogy with the oxidation of isobarbituric acid¹⁷¹ to 4,4'-diisobarbituric acid, it is actually 2,4,6,8-tetrahydroxy-1,3,5,7,9,10-hexazaanthracene (XI). The proof lies in the fact that alkaline cleavage followed by decarboxylation yields the known 2,5-diaminopyrazine

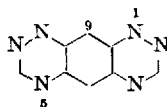
(XVI).¹⁶¹ It follows that the red solid is 2,4,6,8-tetramino-1,3,5,7,9,10-hexazaanthracene (VII).



Subsequent investigations have shown that oxidative self-condensation of some other 4,5-diaminopyrimidines yield analogous 1,3,5,7,9,10-hexazaanthracenes but always in combination with the isomeric 1,3,6,8,9,10-derivative (see Table I-9). Generally they have not been isolated, but their presence is indicated by the ultraviolet absorption spectra of the reaction products. The tetramethyl derivative (XVII) of XI has been described.¹⁶¹



C. 1,2,4,5,7,8-Hexazaanthracene. Benzo-[1,2-e,5,4-e']bis[1,2,4]triazine. R.I. 1817



When *m*-phenylenedicyanamide was treated with an excess of benzenediazonium chloride a complex mixture resulted from which three substances were isolated: 3,4-dicyanaminoazobenzene (XVIII);

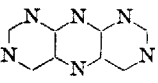
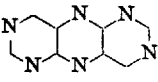
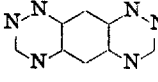
[illegible]

(XXIII) (XXIII a) (XXIV) (XXIV a)

$$\begin{array}{ccc} \text{C}_6\text{H}_5\text{N}^+=\text{N}^- & & \text{C}_6\text{H}_5\text{N}^+=\text{N}^- \\ \diagup & & \diagup \\ \text{O}^- & & \text{O}^- \\ \diagdown & & \diagdown \\ \text{N}^+ & & \text{N}^+ \\ \diagup & & \diagup \\ \text{N}^- & & \text{N}^- \\ \diagdown & & \diagdown \\ \text{O}^- & & \text{O}^- \\ \diagup & & \diagup \\ \text{N}^+ & & \text{N}^+ \\ \diagdown & & \diagdown \\ \text{O}^- & & \text{O}^- \\ \diagup & & \diagup \\ \text{C}_6\text{H}_5\text{N}^+=\text{N}^- & & \text{C}_6\text{H}_5\text{N}^+=\text{N}^- \end{array} \longleftrightarrow \begin{array}{ccc} \text{C}_6\text{H}_5\text{N}^+=\text{N}^- & & \text{C}_6\text{H}_5\text{N}^+=\text{N}^- \\ \diagup & & \diagup \\ \text{O}^- & & \text{O}^- \\ \diagdown & & \diagdown \\ \text{N}^+ & & \text{N}^+ \\ \diagup & & \diagup \\ \text{N}^- & & \text{N}^- \\ \diagdown & & \diagdown \\ \text{O}^- & & \text{O}^- \\ \diagup & & \diagup \\ \text{N}^+ & & \text{N}^+ \\ \diagdown & & \diagdown \\ \text{O}^- & & \text{O}^- \\ \diagup & & \diagup \\ \text{C}_6\text{H}_5\text{N}^+=\text{N}^- & & \text{C}_6\text{H}_5\text{N}^+=\text{N}^- \end{array}$$

(XXV)

TABLE I-10. Hexazaanthracenes^a

Formula	Hexazaanthracene	M.p., °C.	Appearance	Recrystallized or precipitated from	Refs.
	1,3,6,8,9,10-Hexazaanthracene				
I	2,4,5,7-Tetrahydroxy-	> 270	Yellow prisms		157, 159
V	2-Amino-4,5,7-trihydroxy-	> 360	Yellow	Dil. NaOH with HCl	159, 161
XIII	2-Amino-9-ethyl-4,5-dihydroxy-7-oxo-7,9-dihydro-		Yellow	Pyridine	168
XII	4,5,7-Trihydroxy-2-mercapto-		Yellow		167
IV	2,4-Diamino-5,7-dihydroxy-	> 360	Orange	Dil. NaOH with HCl	161
VI	2,4,5,7-Tetramino-	> 360	Bright yellow	Dil. HCl with NH ₄ OH	159, 161
IX	4,5-Dihydroxy-1,8-dimethyl-2,7-dioxo-1,2,7,8-tetrahydro-				163
VIII	1,3,6,8-Tetramethyl-2,4,5,7-tetroxo-1,2,3,4,5,6,7,8-octa-hydro-	403-4; 390	White	Sublimed	159, 162-5
	1,3,5,7,9,10-Hexazaanthracene				
XVI	2,4,6,8-Tetrahydroxy-	> 360	Orange-yellow	NH ₄ OH with HCl	161, 169
VII	2,4,6,8-Tetramino-	> 360	Dark red	HCl with NH ₄ OH	161
XVII	1,3,5,7-Tetramethyl-2,4,6,8-tetroxo-1,2,3,4,5,6,7,8-octa-hydro-	358-60	Yellow	Sublimed	161
	1,2,4,5,7,8-Hexazaanthracene				
XXV	3,6-Dioxo-2,7-diphenyl-	> 310	Yellow prisms	Acetic acid	171

^a A number of hexazaanthracenes are recorded in Table I-9. These were not isolated and characterized, but their presence was established by the use of ultra-violet absorption spectra.

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3. von Braun and Nelles, *Ber.*, 70, 1760 (1937).
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5. German Pat. 514,174; *Frdl.*, 17, 817 (1932).
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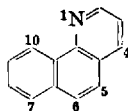
CHAPTER II

Azaphenanthrenes

BY JOHN R. THIRTLE

1. Monoazaphenanthrenes

- A. 1-Azaphenanthrene. Benzo[*h*]quinoline.
7,8-Benzoquinoline. Naphtho-1',2',2,3-
pyridine. α -Naphthoquinoline. R.I. 1974



(1) *Introduction*

The occurrence of 1-azaphenanthrene or its derivatives in natural materials was not discovered until recently. The unsubstituted base was found to be a minor ingredient of coal tar,¹¹⁸ and 2,4-dimethyl-1-azaphenanthrene and 2,3-dimethyl-1-azaphenanthrene were found in California petroleum fractions boiling at 355° and 365°, respectively. These materials were identified by comparison with authentic preparations.

The Skraup reaction alone has been used to prepare the unsubstituted base by ring closure. However, the base has been obtained by decarboxylation of the 2,4-dicarboxylic acid⁸ and 6,7-dicarboxylic acid,²⁸ as well as by heating the 10-sulfo compound in a bomb tube at 250° with hydrochloric acid.⁷³ A review of the important preparative methods and properties of benzoquinolines appeared recently.⁶⁹

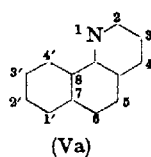
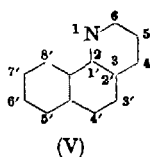
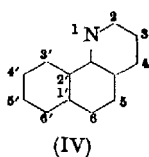
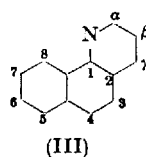
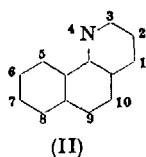
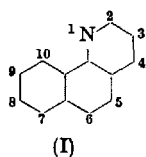
(2) *Nomenclature*

Because of its close similarity to quinoline in both structure and properties, 1-azaphenanthrene has been most generally called benzo[*h*]quinoline or 7,8-benzoquinoline. Early workers in this field frequently named the system α -naphthoquinoline because of its synthesis

from α -naphthylamine, or naphthopyridine because of its similarity to pyridine. The designation 7,8-benzoquinoline was used by *Chemical Abstracts* until 1937. From that time the system has been called benzo-[h]quinoline.

In accord with recent simplification of heterocyclic nomenclature, *i.e.*, naming the compounds as aza derivatives of the carbocyclic systems, this system will be named 1-azaphenanthrene. The naming of derivatives generally will follow *Chemical Abstracts* style; however, hydroxy derivatives will *not* usually be named azaphenanthrols or -ones, and carboxylic acids and their esters will be called carboxy- and carbalkoxyazaphenanthrenes. Sulfonic acids will be called sulfoazaphenanthrenes.

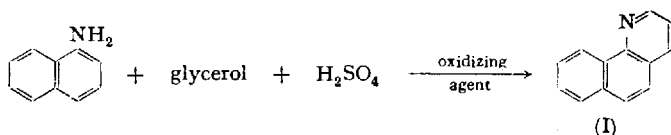
The numbering follows *The Ring Index* and is shown in I. European



journals frequently follow the numbering shown in II; such differences in names have been changed to agree with I. The numberings shown in III, IV, and V are no longer used. System Va was used as late as 1948.⁹⁹

(3) Preparation

(a) From Glycerol (Skraup). 1-Azaphenanthrene (I) was first synthesized in 25 % yield by Skraup¹ in 1881 by the now familiar reaction of an aromatic amine, glycerol, and sulfuric acid in the presence of an oxidizing agent:

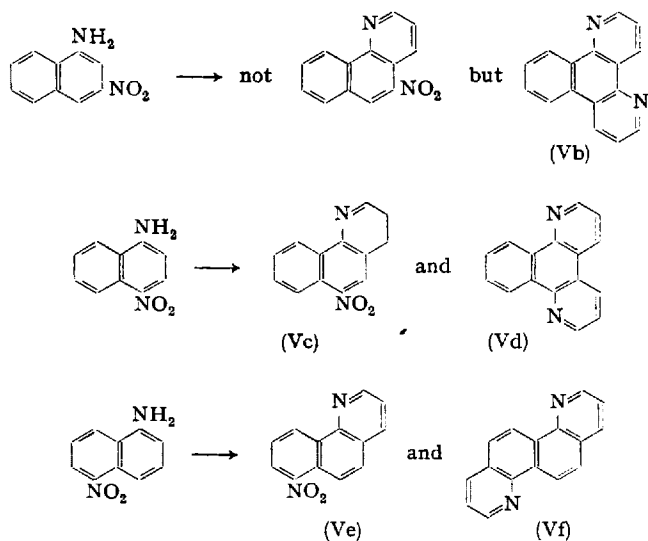


The mechanism of this reaction has been discussed extensively elsewhere^{83, 94, 97} and in this volume (pp. 1-13). The procedure was more difficult and the yields poorer than those encountered in the preparation of the corresponding 4-azaphenanthrene formed by using 2-naphthylamine. Skraup used 1-nitronaphthalene as his oxidizing agent. Subsequent workers^{2, 3} modified and, in some instances, improved the procedure. Claus and Imhoff⁴ used arsenic acid for the oxidation, giving a smoother and less violent reaction. Steele and Adams³⁴ synthesized the 10-chloro derivative by the method of Claus and Imhoff in 20 % yield, and recently 6-methyl-1-azaphenanthrene was synthesized in unreported yield from 4-methyl-1-naphthylamine by this method.¹⁸ Haid,⁷ however, reported that Skraup's original synthesis, with substitution of nitrobenzene for 1-nitronaphthalene and extension of the reaction time to 6-7 hours, was best. His yield equaled that of Skraup (25 %) and bettered that of Bamberger and Stettenheimer.³ Claus and Imhoff did not state their yield, but Haid reported their method to be inferior in that respect.

Derivatives of 1-azaphenanthrene can be synthesized by using a substituted naphthalene in this reaction; for example, 5,6,7,8-tetrahydro-1-naphthylamine gives a poor yield of 7,8,9,10-tetrahydro-1-azaphenanthrene.⁵⁹ Especially valuable in industry are the sulfonic acids,^{15, 41, 73, 75} obtained either by ring closure reactions or by direct introduction of the sulfo group into the 1-azaphenanthrene nucleus.^{4, 52} In this connection H. and M. Schenkel-Rudin⁷³ obtained a 61 % conversion of 8-sulfo-1-naphthylamine to 10-sulfo-1-azaphenanthrene using nitrobenzene and 84 % phosphoric acid at 140-150° for 24 hours.

Hamilton and co-workers have done considerable work in the field of the azaphenanthrenes. In one of their papers⁶⁴ they reported poor yields in the Skraup reaction with 4-, and 5-nitro-1-naphthylamines; the reaction was entirely unsuccessful with 8-nitro-1-naphthylamine. They attributed these results to inhibition by the nitro group since 8-chloro-1-naphthylamine gives a fair yield in the Skraup reaction.³⁴ Albert, Brown, and Duewell reported that the Skraup reaction led to the complete destruction of 4- and 5-nitro-1-naphthylamines.⁹⁹

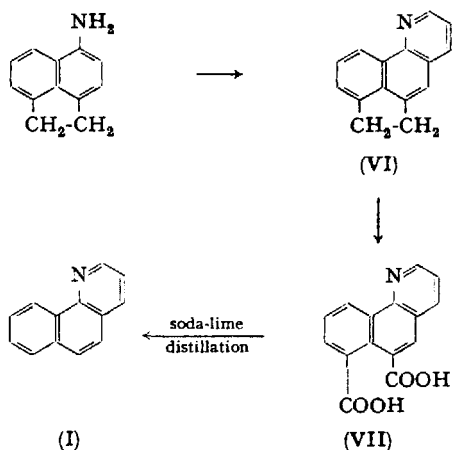
Recently, however, Barltrop and McPhee¹¹⁷ studied the Skraup reaction involving nitro-1-naphthylamines with more success: 6-, 7-, 8-, and 9-nitro-1-azaphenanthrenes were prepared in apparently low yields by the Skraup reaction on 4-, 5-, 6-, and 7-nitro-1-naphthylamines. The attempt to prepare 5-nitro-1-azaphenanthrene from 3-nitro-1-naphthylamine (Iwai and co-workers reported success in this preparation¹¹⁸) gave only the diazatetracyclic product 1,5-diazatriphenylene (Vb). Indeed, the chief products in the preparation of 6- and 7-nitro-1-azaphenanthrenes (Vc and Ve) appear to be 1,8-diazatriphenylene (Vd) and 1,7-diazachrysene (Vf). Barltrop and McPhee were also unsuccessful in repeated attempts to prepare 10-nitro-1-azaphenanthrene from 8-nitro-1-naphthylamine.



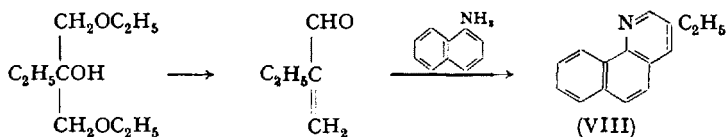
An interesting application of the Skraup reaction involves the conversion of 5-aminoacenaphthene to " α -acenaphthoquinoline" (VI) in good yield.²⁸ The latter is oxidized to 6,7-dicarboxy-1-azaphenanthrene (VII), which is then decarboxylated to 1-azaphenanthrene, giving proof of the direction of ring closure.

Another variation of the Skraup reaction was introduced by Warren.⁴³ The reaction is essentially between an aromatic amine and a substituted acrolein. The latter is generated *in situ*, and the ready

polymerization of α -substituted acroleins is avoided. For example, 1-naphthylamine reacts with 2-ethylglycerol 1,3-diethyl ether under

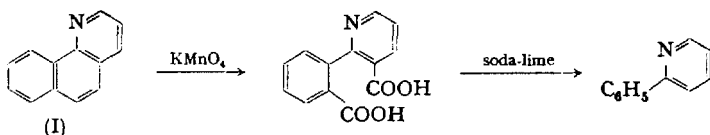


Skraup conditions, giving 3-ethyl-1-azaphenanthrene (VIII) in 12 % yield. In general, the Skraup reaction has given better yields in recent



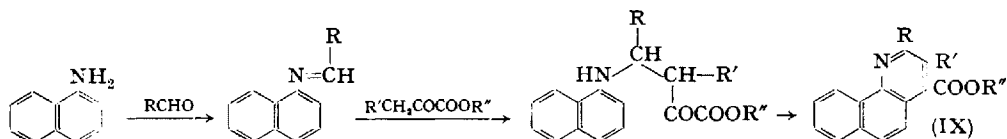
applications. This is primarily a result of superior techniques and especially the use of acids other than sulfuric. Notable in this respect is phosphoric acid. The use of arsenic pentoxide and sulfuric acid has given recently a 32 % yield of 1-azaphenanthrene.¹¹⁷

Proof that ring closure occurs in the 2-position of the naphthalene nucleus and not in the 8-position is supplied by oxidation to pyridine derivatives. For example, 1-azaphenanthrene is oxidized by neutral potassium permanganate to 2-(2-carboxyphenyl)pyridine-3-carboxylic acid, which is decarboxylated to 2-phenylpyridine:²



Other oxidation reactions will be discussed later (see p. 183).

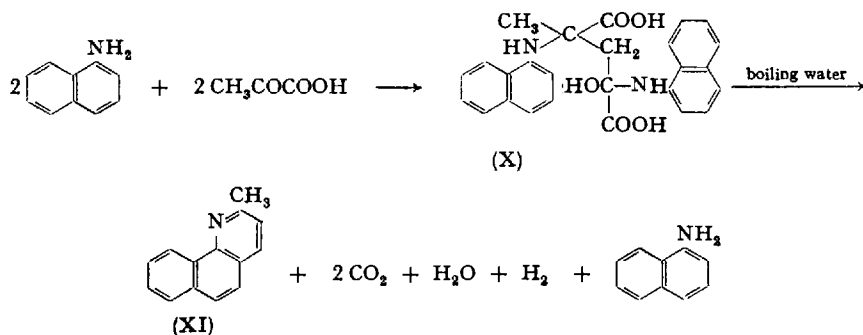
(b) **From α -Oxo Acids (Doebner).** Some substituted 1-azaphenanthrenes are synthesized in excellent yields by the Doebner reaction. This appears to involve the reaction of 1-naphthylamine with an aldehyde to form an anil, followed by reaction of the anil with pyruvic acid or ester, or a derivative thereof, and subsequent ring closure:



R can be aliphatic or aromatic; R' is usually H but can be aliphatic or aromatic; R'' is usually H . The reaction is generally effected by heating a mixture of all three ingredients.

This reaction was first applied to 1-azaphenanthrene derivatives by Doebner and Kuntze,¹² who used benzaldehyde and pyruvic acid in cold ether or boiling alcohol to form 4-carboxy-2-phenyl-1-azaphenanthrene (IX, $\text{R} = \text{C}_6\text{H}_5$, $\text{R'} = \text{H}$, $\text{R''} = \text{H}$). Cinnamaldehyde has been used in place of benzaldehyde, giving 4-carboxy-2-styryl-1-azaphenanthrene in about 90 % yield (based on pyruvic acid).⁸

The reaction has been effected in the absence of an aldehyde, in which case it was first assumed that acetaldehyde was formed by loss of CO_2 from a portion of the pyruvic acid and that the reaction then followed the normal course of the Doebner reaction. Simon,^{84,85} however, showed that the reaction occurs as follows:

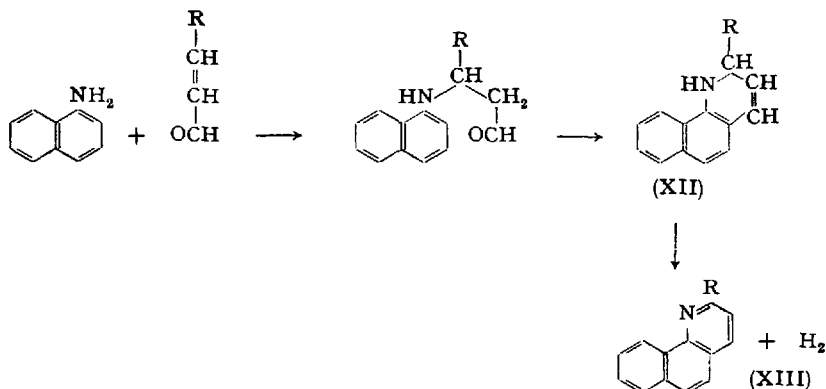


Compound X is a derivative of glutaric acid. Silberg⁵⁷ carried out this reaction in alcohol and obtained a good yield of 4-carboxy-2-

methyl-1-azaphenanthrene, which exists in two crystalline forms not separable by crystallization.

Other variations have been introduced into the Doebner synthesis. Borsche and Sinn,⁵⁸ using phenylpyruvic acid and *o*-nitrobenzaldehyde, obtained a 21 % crude yield of the azaphenanthrene (IX, R = *o*-nitrophenyl, R' = C₆H₅, R'' = H). Apparently the nitro group has an inhibiting effect since phenylpyruvic acid and benzaldehyde give a 47 % yield, and the same reaction using acetaldehyde gives a 46 % yield. However, with benzylpyruvic acid, benzaldehyde, and 1-naphthylamine the yield is only 24 %.⁶³ Formaldehyde has also been used in this reaction with phenylpyruvic acid, but the yield is poor (22 %). When *N*-formyl-1-naphthylamine is treated with phenylpyruvic acid the yield of the 1-azaphenanthrene derivative (IX, R = H, R' = C₆H₅, R'' = H) is 42 %.⁶³ The use of benzylpyruvic acid with formaldehyde and 1-naphthylamine has been unsuccessful, whereas ethyl pyruvate and benzaldehyde give good results even in cold chloroform or benzene.⁸⁵ 5,6,7,8-Tetrahydro-1-naphthylamine, benzaldehyde, and pyruvic acid give 4-carboxy-2-phenyl-7,8,9,10-tetrahydro-1-azaphenanthrene in 20 % yield.²⁸

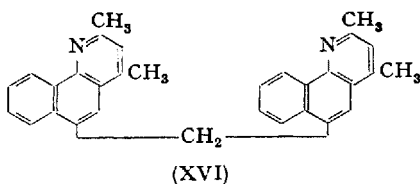
(c) **From α,β -Unsaturated Aldehydes (Doebner-Miller).** This reaction appears to take the course of addition of the 1-naphthylamine to an α,β -unsaturated aldehyde followed by ring closure and oxidation. The unsaturated aldehyde may be formed *in situ* by the reaction of two molecules of aldehyde with each other:



60 % yield. Johnson and Mathews⁶² refined the method still further, obtaining from acetylacetone a 99 % yield of the crude anil which could be cyclized in 80–90 % yield. An attempt to close the ring of the anil by means of hydrogen fluoride was unsuccessful; hydrolysis to 1-naphthylamine occurred. The Reed modification of the Doebner-Miller synthesis was reported to give only a 2 % yield of 2,4-dimethyl-1-azaphenanthrene,⁶² whereas Schenk and Bailey⁶⁵ obtained an 80 % over-all yield by the Combes method.

There has been considerable variation in the melting points reported for 2,4-dimethyl-1-azaphenanthrene. Vasserman⁶¹ reported a melting point of 44°, as did Combes¹¹ and Reed.¹⁰ Johnson and Mathews,⁶² reporting 51.5–53°, agreed with von Braun²⁷ at 52°, but Schenk and Bailey⁶⁵ gave the melting point as 55–6° (corr.).

Buu-Hoi and Guettier⁷⁸ used the Combes reaction to make several derivatives of 1-azaphenanthrene. Starting with 4-methyl-1-naphthylamine and acetylacetone, they synthesized 2,4,6-trimethyl-1-azaphenanthrene in 53 % yield. The same naphthylamine with 3-methylacetylacetone gave a 25 % yield of 2,3,4,6-tetramethyl-1-azaphenanthrene and with 3-ethylacetylacetone gave only a 10 % yield of 3-ethyl-2,4,6-trimethyl-1-azaphenanthrene. The reaction of acetylacetone with 4,4'-methylenebis-1-naphthylamine gave the compound, 6,6'-methylenebis(2,4-dimethyl-1-azaphenanthrene) (XVI).

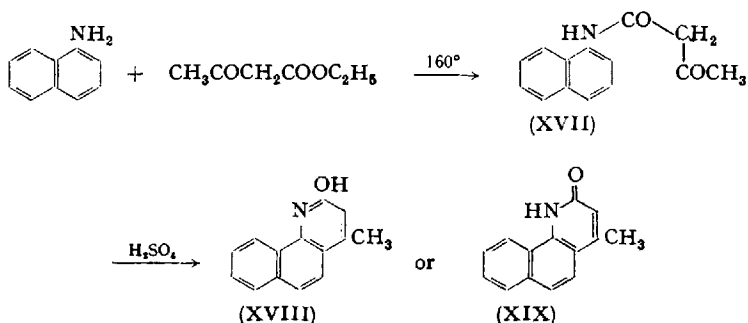


A short discussion of the Combes reaction has been published in *Chemical Reviews*,⁸⁰ and the mechanism has been elucidated in recent literature.¹¹⁶

Substitution in the naphthylamine nucleus by halogen or NO₂ in the ortho or para position is said to prevent the Combes reaction from occurring.⁶¹

A modification of the Combes reaction that involves the use of β -oxoaldehydes is described on p. 180.

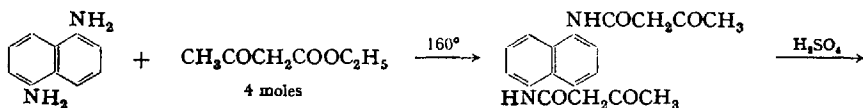
(e) **From Acetoacetonaphthylide (Knorr).** When a 1-naphthylamine is treated with ethyl acetoacetate under the influence of heat and a trace of acid, which is usually present in the ester,⁹⁶ 1-acetoacetonaphthylide (XVII) is formed. The latter is then cyclized by warming with sulfuric acid to give a 2-hydroxy-4-methyl-1-azaphenanthrene (XVIII). This reaction is frequently confused with the Conrad-Limpach

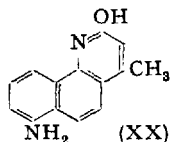


reaction, particularly since Conrad and Limpach studied and used the reaction quite extensively.

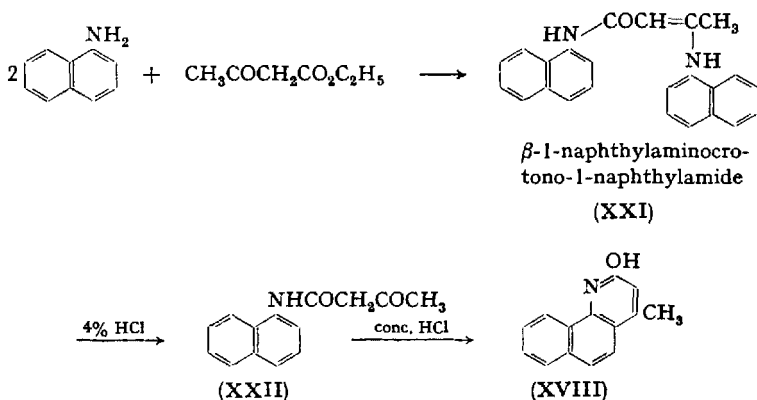
Knorr¹⁶ appears to have been the first to obtain a 1-azaphenanthrene by this method, which he had developed earlier for the synthesis of quinoline. He, however, mistakenly referred to the compound (m.p. 292°) as " α -naphtho- γ -oxychinaldin" (4-hydroxy-2-methyl-1-azaphenanthrene). Knorr gave no experimental details for the preparation of this compound, but had been describing reactions of the crotonates of 2-naphthylamines, which give quinaldines (Conrad-Limpach) rather than carbostyryls on cyclization. That this was a mistake in identity appears to be borne out by the experiments of later workers.^{30:77, 96:99}

In an interesting application of the Knorr reaction to 1-azaphenanthrene chemistry, Finger and Spitz²⁰ treated 1,5-naphthalenediamine with an excess of ethyl acetoacetate at 160° , then effected ring closure of one of the acetoacetamido groups while hydrolyzing the other, and obtained 7-amino-2-hydroxy-4-methyl-1-azaphenanthrene (XX).





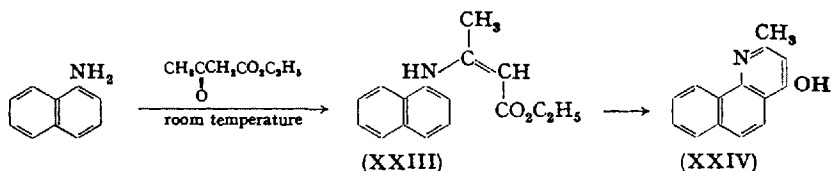
Gibson *et al.*³⁰ reported that their intermediate was not an arylide but a more complex compound (XXI), formed from one mole of ethyl acetoacetate and two moles of 1-naphthylamine:



They reported two isomorphous forms for XXI: one from alcohol melts at 167–8°, and the other from benzene melts at 144–5°. One of these forms may be the anil or Schiff base. The above reaction obviously is unsuited for optimum yields of the azaphenanthrene.

The preparation of arylides of the type XXII was improved by Kibler and Weissberger, who heated the ester and the amine in xylene and distilled off the alcohol through a steam-heated distilling head. Yields as high as 76% were reported.⁷⁴ Limpach⁸⁷ obtained yields of better than 90% (1-naphthylamine was not used in these studies) by adding the amine slowly to four moles of ethyl acetoacetate at 160° and maintaining this temperature for a short period thereafter. A recent article claims that pure 1-naphthylamine and ethyl acetoacetate do not react. A trace of cupric acetate causes reaction, giving a 70% yield of the arylide.⁹⁹ These authors used concentrated hydrochloric acid to effect cyclization in 85% yield. A modification of the Knorr reaction that involves the use of diketene gives a high yield of XVIII (see p. 180).

(f) **From Ethyl α -(2-Naphthylamino)crotonate (Conrad-Limpach).** The Conrad-Limpach reaction resembles the Knorr reaction except for the temperature used. By allowing 1-naphthylamine and ethyl acetoacetate to stand at room temperature, the crotonate (XXIII) is formed which, in turn, is cyclized to give 4-hydroxy-2-methyl-1-azaphenanthrene (XXIV). This reaction was first applied to

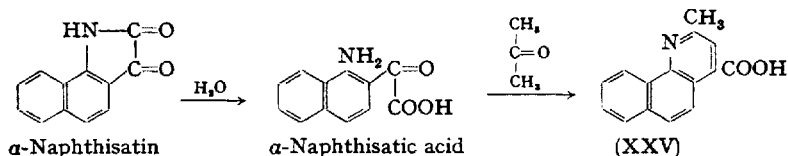


1-azaphenanthrene by Knorr,¹⁶ who, however, appears to have isolated not XXIV but XVIII, having a melting point of 292°. Conrad and Limpach¹⁷ prepared XXIV, patented a process, and reported the melting point to be over 300°.

Limpach⁸⁷ reported that the yields seldom exceeded 30 %, probably because insufficient reaction time was allowed for the preparation of the crotonate. Heating too soon after mixing gives a mixture of the crotonate and the arylide and the nature of the azaphenanthrene isolated is a matter of chance. However, by allowing the reactants to stand for 24 hours, separating the water, and then heating the crotonate in paraffin oil at 240–50° for 20–30 minutes, a yield of over 90 % of the 4-hydroxy-2-methyl-1-azaphenanthrene is obtained.⁸⁷ A few drops of 6 *N* hydrochloric acid have been used to catalyze the condensation.^{64, 118a} The yield of XXIV by this modification is not stated, but 4-bromo-1-naphthylamine gives 51 % of the crotonate which is converted to the azaphenanthrene in 60 % yield. The usual practice, however, is to neutralize traces of acid which might be present. The 6-methyl derivative of XXIV is formed in unstated yield by using a drop of piperidine to catalyze the formation of the crotonate⁷⁸; the use of diethylamine as a catalyst also has been reported.³⁰ The melting point of over 300° for 4-hydroxy-2-methyl-1-azaphenanthrene (XXIV) was confirmed.³⁰

(g) **Miscellaneous Methods.** (1). *Pfitzinger Reaction.* Although this reaction, involving a substituted isatin and a ketone, has been

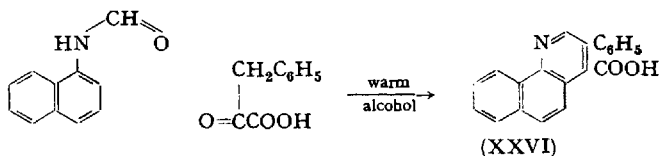
known for some time, it was not applied to 1-azaphenanthrene chemistry until 1940,⁶³ when Borsche and Wagner-Roemmich used it to synthesize 4-carboxy-2-methyl-1-azaphenanthrene (XXV). The



yield was 70%, whereas the yield by Doebner's method from 1-naphthylamine is only 20%.⁹⁰ The corresponding 2-phenyl derivative was made in 75% yield from acetophenone; this compares with a 30% yield by the Doebner and Kuntze method.⁶³

The Pfitzinger reaction failed with benzyl methyl ketone.⁶³ A similar failure was noted when an attempt was made to cause α -naphthisatin to react with 1-acetyl-2-methylnaphthalene. The presence of the ortho substituent was claimed to inhibit the reaction, since the reaction proceeds as usual with the analogous 4-methyl compound.⁹² The presence of a fused ring in the ortho position apparently has no steric effect since a number of bulky ketones, such as 3-acetylpyrene, 2-acetylchrysene, 2-acetylanthracene, 5-acetylacenaphthene, 2-acetylfluorene, and 4-acetylbiphenyl, reacted as expected.⁹² 3-(and 5)-Methyl-2-acetothienones have been used recently in this reaction.¹⁰⁰

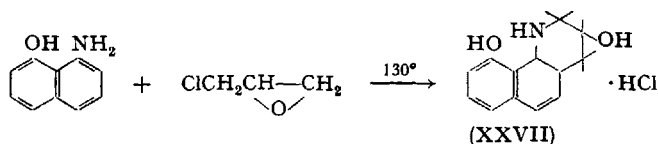
(2) *From N-Formyl-1-naphthylamine.* The preparation of 4-carboxy-3-phenyl-1-azaphenanthrene (XXVI) was effected in 42% yield by the reaction of *N*-formyl-1-naphthylamine with phenylpyruvic acid.⁶³ The same product was prepared in 22% yield from the amine,



phenylpyruvic acid, and formaldehyde.⁶³ Silberg⁹⁰ prepared 4-carboxy-2-methyl-1-azaphenanthrene (XXV) by reaction of *N*-formyl-1-naphthylamine with pyruvic acid.

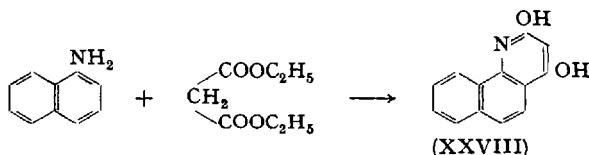
(3) *From Epichlorohydrin.* The reaction of hydroxy-1-naphthyl-

amines with epichlorohydrin is reported in the patent literature to give 1,2,3,4-tetrahydro-1-azaphenanthrenes.⁴² For example, 8-hydroxy-1-naphthylamine is heated at 130° with epichlorohydrin to give 3,10-dihydroxy-1,2,3,4-tetrahydro-1-azaphenanthrene hydrochloride (XXVII). The amine apparently first opens the 3-membered ring,



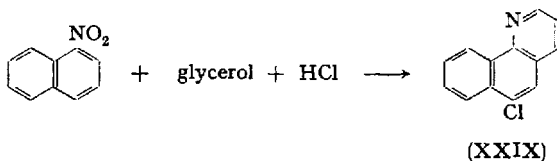
adding to the terminal carbon atom; the 6-membered ring is then formed by elimination of hydrogen chloride. These compounds are used as coupling components for azo dyes for acetate fabrics.

(4) *From Ethyl Malonate.* Ethyl malonate reacts with 1-naphthylamine to give 2,4-dihydroxy-1-azaphenanthrene (XXVIII) in 80 % yield.^{5, 31, 35} This reaction appears to have been first effected by



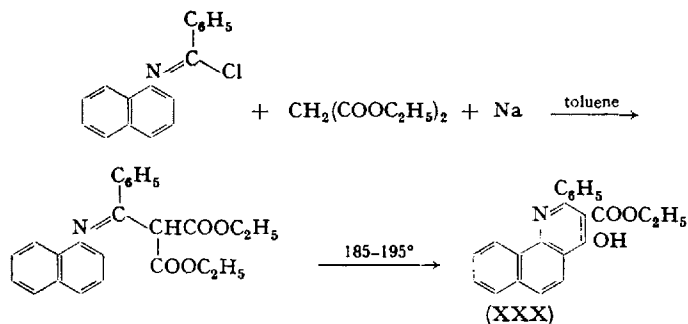
Meyer,⁴⁴ who ascribed a different structure to the product. King¹¹⁵ has established that the product obtained by Meyer was XXVIII. The 3-phenyl derivative is formed in quantitative yield by the use of phenylmalonic ester.³¹

(5) *From 1-Nitronaphthalene.* This is a rather unusual reaction in which 1-nitronaphthalene, heated in a sealed tube at 170° with glycerol and hydrochloric acid, gives 6-chloro-1-azaphenanthrene (XXIX).⁴⁶



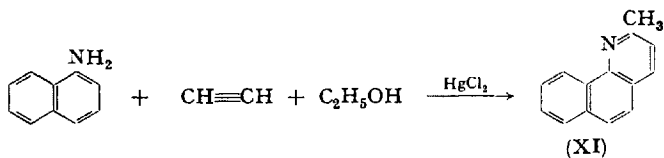
(6) *From N-1-Naphthylbenzimidyl Chloride.* When *N*-1-naphthylbenzimidyl chloride was heated with ethyl malonate and sodium in

toluene, a 17.5 % yield of ethyl 1-naphthyliminobenzylmalonate was obtained. The latter undergoes ring closure to give 3-carbethoxy-4-hydroxy-2-phenyl-1-azaphenanthrene (XXX).⁴⁹ Similarly, the imi-



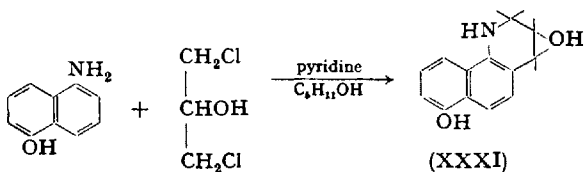
dochloride gave a 5.5 % yield of 3-acetyl-4-hydroxy-2-phenyl-1-azaphenanthrene when ethyl sodioacetoacetate was used.¹¹²

(7) *From Acetylene.* Acetylene, 1-naphthylamine, and ethanol in the presence of mercuric chloride are reported to give 2-methyl-1-azaphenanthrene (XI).⁵³ The picrate, however, is not identical with that reported in a later article.⁵⁷ When acetone is employed instead of



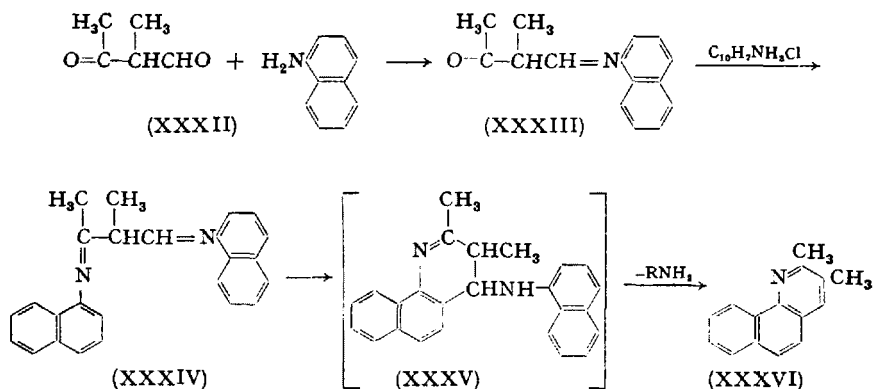
ethanol a 19 % yield of 2,4-dimethyl-1-azaphenanthrene (XV) is obtained (see Combes reaction, p. 172).

(8) *From 1,3-Glycerol Dichlorohydrin.* A single patent⁷⁰ reports that the reaction of 5-hydroxy-1-naphthylamine with 1,3-glycerol dichlorohydrin in the presence of pyridine and amyl alcohol gives 3,7-dihydroxy-1,2,3,4-tetrahydro-1-azaphenanthrene (XXXI). The in-

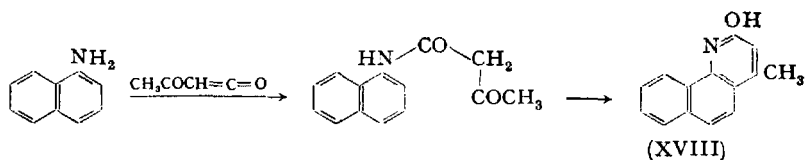


ventors claim that this method of ring closure avoids toxic materials and requires no special safeguards, contrary to former experience with this type of reaction. The product couples with diazotized amines to give dischargeable dyes.

(9) *From β -Oxoaldehydes.* An interesting synthesis⁶⁸ of 1-azaphenanthrenes makes use of β -oxoaldehydes in an extension of the Combes, Knorr, and Conrad-Limpach methods. 1-Naphthylamine reacts with 3-formyl-2-butanone (XXXII) to give a quantitative yield of the anil (XXXIII). The anil then reacts with a mole of 1-naphthylamine hydrochloride, either directly at 160–200° or in absolute alcohol solution, forming a dianil (XXXIV). Ring closure with elimination of a molecule of the amine gives a 50% over-all yield of 2,3-dimethyl-1-azaphenanthrene (XXXVI). The yield may be increased to 65% by using two moles of the amine hydrochloride and zinc chloride in the reaction with the anil.

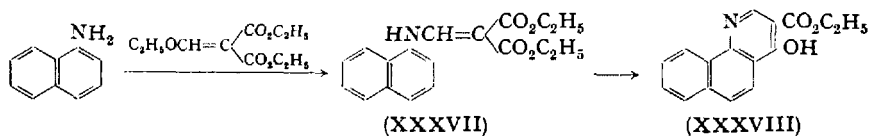


(10) *From Diketene.* A recent modification of the Knorr reaction (see p. 174) for 1-azaphenanthrene derivatives uses diketene, which reacts with 1-naphthylamine to give the arylyde in 86% yield. Ring closure is effected in 99% yield.⁷⁷ These workers report a melting

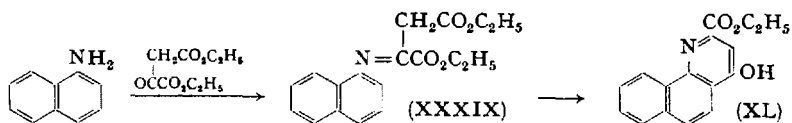


point of $291-2^\circ$ for XVIII, which agrees with that of Knorr¹⁶ for the "4-hydroxy-2-methyl" derivative. It appears from this and other evidence^{30,99} (see p. 174) that Knorr's compound, reported as the 4-hydroxy-2-methyl derivative, is actually the 2-hydroxy-4-methyl derivative.

(11) *From Ethyl Ethoxymethylenemalonate.* A recent publication by Hamilton and co-workers⁷⁹ utilizes a reaction developed by Price and Roberts⁸⁸ in preparing some 1-azaphenanthrenes of possible pharmaceutical value. For example, 1-naphthylamine reacts with ethyl ethoxymethylenemalonate (E.M.M.E.) to give a quantitative yield of ethyl 1-naphthylaminomethylenemalonate (XXXVII), which in boiling phenyl ether gives a 94 % yield of good quality 3-carbethoxy-4-hydroxy-1-azaphenanthrene (XXXVIII) (see also reference 82).

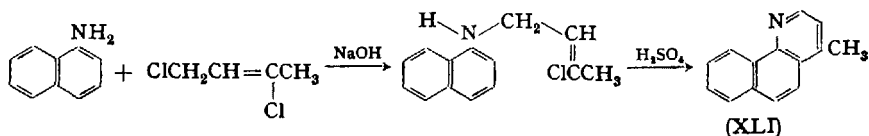


(12) *From Ethyl Ethoxalylacetate.* By using ethyl ethoxalylacetate,⁷⁹ in condensation with 1-naphthylamine, the intermediate (XXXIX) is obtained in 77 % yield and the cyclized product, 2-carbethoxy-4-hydroxy-1-azaphenanthrene (XL), in 89 % yield. The

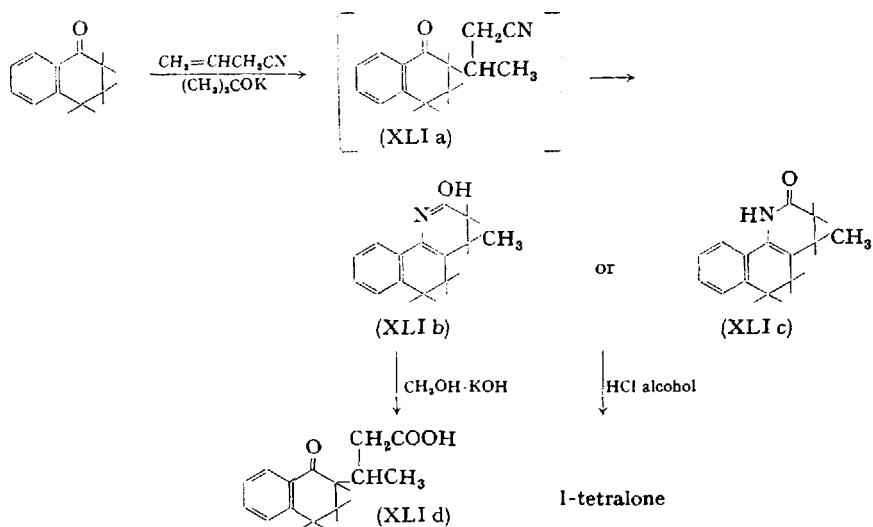


latter, as well as XXXVIII, on saponification, decarboxylation,^{79,82} and treatment with $\text{PCl}_5\text{-POCl}_3$ gives 4-chloro-1-azaphenanthrene in good over-all yield.⁷⁹

(13) *From N-(3-Chloro-2-butenyl)-1-naphthylamine.* A recent paper describes the preparation of 4-methyl-1-azaphenanthrene (XLI) as follows.¹¹¹



(14) *From 1-Tetralone and Allyl Cyanide.* The reaction of 1-tetralone with allyl cyanide in the presence of potassium *tert*-butoxide was recently reported to give a 40 % yield of 2-hydroxy-4-methyl-3,4,5,6-tetrahydro-1-azaphenanthrene (XLIb) or its tautomer (XLIc).⁹¹ Apparently the reaction involves isomerization of the allyl cyanide to crotononitrile, which forms the adduct (XLIa), followed by cyclization. Some of the adduct is found among the reaction products. Treatment of XLIb or c with alcoholic hydrochloric acid gives a quantitative yield of 1-tetralone while methanolic potassium hydroxide gives 2-(2-carboxyisopropyl)-1-tetralone (XLI d).



(4) Substitution Reactions

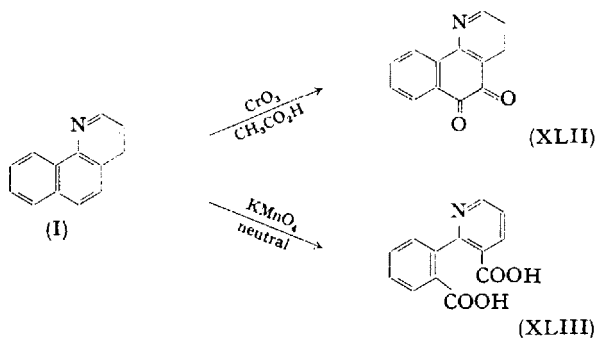
(a) Reduction. 1-Azaphenanthrene is reduced by tin and hydrochloric acid to the 1,2,3,4-tetrahydro derivative melting at 46.5° .³ Reduction of the parent substance with sodium and amyl alcohol gives the 1,2,3,4,7,8,9,10-octahydro derivative,³ melting at $47-8^\circ$. These compounds are differentiated by their *N*-nitroso derivatives; that of the former melts at 59.5° and the latter at 77.5° . Sodium and ethanol have been used to reduce 4-chloro-2-methyl- and 2-chloro-4-methyl-1-azaphenanthrenes to their respective methyl-1,2,3,4-tetrahydro-1-azaphenanthrenes, with loss of the chlorine atoms.³⁰

The hydrogenation of 2,4-dimethyl-1-azaphenanthrene has been studied using a nickel catalyst at temperatures above 200°. ¹⁷ It was found that reduction at the 7-, 8-, 9-, and 10-positions occurs first under these conditions, followed by reduction at the 1-, 2-, 3-, and 4-positions. No 2,4-dimethyl-1,2,3,4-tetrahydro-1-azaphenanthrene could be isolated, indicating the sequence of reactions. When 2,4-dimethyl-7,8,9,10-tetrahydro-1-azaphenanthrene was hydrogenated the product was 2,4-dimethyl-1,2,3,4,7,8,9,10-octahydro-1-azaphenanthrene in 20 % yield. There was no attack at the 5,6-positions. Another use of nickel for reduction of the azaphenanthrene ring has been patented. ⁴⁷ It is claimed that such compounds as the 5-acetoxy- and 7-alkoxy derivatives are reduced by a nickel-chromium catalyst at 80° and 150 atm. of hydrogen to the 1,2,3,4-tetrahydro derivatives.

Other hydrogenated 1-azaphenanthrenes are obtained by ring closure reactions. For example, 7,8,9,10-tetrahydro derivatives are obtained from 5,6,7,8-tetrahydro-1-naphthylamine, ^{28,59,118f} and 1,2,3,4-tetrahydro derivatives from 1-naphthylamine in reactions with compounds such as epichlorohydrin, as was shown earlier (p. 177). Methods for the dehydrogenation of these compounds have been patented. ¹⁰⁸

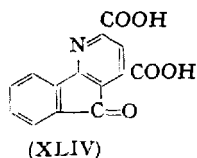
Zinc dust distillation of 2,4-dihydroxy-1-azaphenanthrene gives 1-azaphenanthrene. ³¹

(b) Oxidation. 1-Azaphenanthrene, in contrast with 4-azaphenanthrene, is readily oxidized. In hot acetic acid with the calculated amount of chromium trioxide the oxidation product is the 5,6-quinone



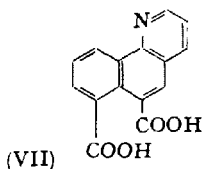
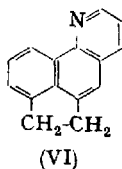
(XLII). ² This quinone forms dark orange-red needles. It is decolorized by sulfite and regenerated by ferric chloride.

Oxidation with neutral permanganate at 40–50° is much more destructive, and the product (70% yield), constituting a proof of the structure of I, is 2-(2-carboxyphenyl)pyridine-3-carboxylic acid (XLIH).^{2,37,95} The 10-chloro derivative is reported to have required more vigorous conditions.³⁴ Oxidations with permanganate seem anomalous. For example, 2-phenyl-1-azaphenanthrene is scarcely attacked by alkaline permanganate but easily by acid permanganate.¹² On the other hand, 4-carboxy-2-styryl-1-azaphenanthrene is oxidized in the cold by alkaline permanganate to the 2,4-dicarboxylic acid and at higher temperatures to 3'-oxo-(indeno-1',2',2,3-pyridine)-4,6-dicarboxylic acid or 1,3-dicarboxy-4-azafluorenone (XLIV).⁸ 10-Chloro-1-



azaphenanthrene is oxidized by neutral permanganate to the 2-(2-carboxy-6-chlorophenyl) compound analogous with (XLIH),³⁴ and alkaline permanganate is strong enough to oxidize 4-carboxy-1-azaphenanthrene to pyridine-2,3,4-tricarboxylic acid.⁴⁰

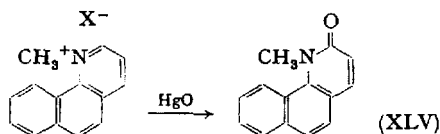
When the 5- or 6-position is substituted, potassium dichromate in acetic acid is suitable for the oxidation of side chains without affecting the nucleus. For example, 6,7-ethylene-1-azaphenanthrene (acenaphthopyridine) (VI) is oxidized thus to 6,7-dicarboxy-1-azaphenanthrene (VII) in excellent yield.²⁸ On the other hand, potassium dichromate in



sulfuric acid has been reported to oxidize 1,2,3,4,7,8,9,10-octahydro-1-azaphenanthrene to an undefined product, $C_{26}H_{26}N_2$.³ The same octahydro-1-azaphenanthrene gives a violet-red dye with chromic acid.³

Selenium dioxide has been used for the selective oxidation of 2,3-dimethyl-1-azaphenanthrene to 2-carboxy-3-methyl-1-azaphenan-

threne.⁶⁵ Oxidation of quaternary salts with mercuric oxide gives the alkyl pyridone (XLV).⁴ The same product is obtained by electrolytic



reduction of the methyl sulfuric acid salt of 1-azaphenanthrene methohydroxide in the presence of potassium ferricyanide in dilute alkali.¹⁸ Reaction of 1-azaphenanthrene with hydrogen peroxide gives the 1-oxide. The base can be regenerated by reduction of the oxide using sulfur dioxide.^{118g}

(c) Nitration. Although the nitration of 1-azaphenanthrene was first reported in 1898, the nature of all of the products obtained then was not established until lately.¹¹⁷ The nitration of 1-azaphenanthrene was reported by Claus and Imhoff⁴ to give two nitro derivatives, m.p. 151° and 138°. The presumption that these were the 5- and 6-nitro-1-azaphenanthrenes, respectively, is not borne out by subsequent reports. Haid,⁷ using one equivalent of fuming nitric acid (d. 1.52) in concentrated sulfuric acid in a freezing mixture, obtained by a laborious fractionation four isomeric mononitro derivatives (total yield 54%), melting at 230°, 175°, 166°, and 155°. The first two were the chief products (90%). The probable location of the nitro groups was determined by the relative ease of hydrolysis of the salts by water or alcohol, suggesting that the 230° and 175° isomers were substituted in the ring farthest from the hetero atom, while the other two isomers were substituted in the hetero ring or in the 5- or 6-positions. The location of the nitro groups of the 230° and 175° isomers in the "benz" ring was further proved by reduction to the corresponding amines, which gave, on oxidation, quinoline-7,8-dicarboxylic acid.

None of the four isomers prepared by Haid was identical with either of the nitro derivatives prepared by Claus and Imhoff. Untermohlen and Hamilton,⁶⁴ however, prepared 6-nitro- and 7-nitro-1-azaphenanthrenes, m.p. 149° and 175°, respectively, by the Skraup reaction on 4- and 5-nitro-1-naphthylamines. They suggested then that Haid's 175° compound was 7-nitro-1-azaphenanthrene.

Barltrop and McPhee¹¹⁷ recently reinvestigated the nitration of 1-azaphenanthrene by Haid's directions, separating the isomers by chromatography on alumina in ultraviolet light; the total yield of mononitro-1-azaphenanthrenes was thus raised to 92 %. The melting points, in good agreement with those of Haid, were 225°, 174°, 166°, and 155°.

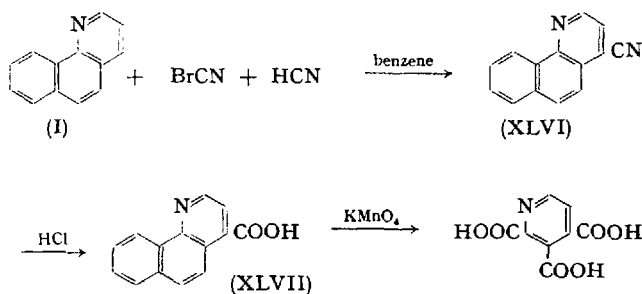
The structures of three of these nitro derivatives were proved by comparative ultraviolet absorption curves and by mixed melting points with authentic samples prepared by the Skraup reaction on appropriate nitronaphthylamines (see p. 168). Thus, the 225° isomer (Haid, 230°) is 9-nitro-1-azaphenanthrene; the 174° isomer (Haid, Untermohlen, and Hamilton, 175°) is 7-nitro-1-azaphenanthrene as suggested earlier; the 155° isomer (Haid, 155°; Untermohlen and Hamilton, 149°) is 6-nitro-1-azaphenanthrene. Barltrop and McPhee prepared in addition 8-nitro-1-azaphenanthrene, m.p. 200–1°, in relatively low yield by the Skraup reaction. This material is different from any nitration product. The Skraup reaction with 3-nitro-1-naphthylamine and with 8-nitro-1-naphthylamine failed to give the corresponding 5-nitro- and 10-nitro-1-azaphenanthrenes for comparison with the 166° isomer. However, reduction of the 166° isomer gives an amine melting at 140°. The corresponding 5-amino-1-azaphenanthrene and 10-amino-1-azaphenanthrene prepared by other methods melt at 146° and 85–6°, respectively. From this and other collateral evidence, Barltrop and McPhee conclude that the 166° isomer is 5-nitro-1-azaphenanthrene and that no nitration occurs in the hetero nucleus of 1-azaphenanthrene.

Iwai and co-workers have prepared a number of dinitro derivatives by nitration of nitro-1-azaphenanthrenes and by the Skraup reaction on 4,8-dinitro-1-naphthylamine.^{118i,j} Nitration of the 1-oxide of 1-azaphenanthrene gives the 7-, 9-, and 10-nitro derivatives and an unknown dinitro compound. The failure to obtain a 4-nitro derivative indicates that the polar effects of the oxides of pyridine and quinoline do not apply here.^{118b}

(d) Sulfonation. Sulfonation of 1-azaphenanthrene with 10 % fuming sulfuric acid is believed⁴ to give the 5-sulfo derivative. The recent patent literature⁴¹ reports the same compound by ring closure;

in fact, ring closure reactions constitute almost the entire source of the sulfo derivatives, which are so suitable for the preparation of the amino and hydroxy compounds. One report concerns the reaction of 4-chloro-2-methyl-1-azaphenanthrene with sodium sulfite to give the 4-sulfo derivative⁵²; this reaction was used also to prepare 4-sulfo-1-azaphenanthrene.^{118e}

(e) Miscellaneous. Cyanogen bromide and hydrogen cyanide reacted with 1-azaphenanthrene in benzene to give the 4-cyano derivative (XLVI),⁴⁰ the structure of which was proved by hydrolysis to the acid (XLVII) (see also reference 72), which in turn was oxidized with alkaline permanganate to α -carboxycinchomeric acid (pyridine-2,3,4-tricarboxylic acid).



Only one example of amination has been recorded. With potassium amide an 83 % yield of 2(?) -amino-1-azaphenanthrene is obtained.⁵⁴

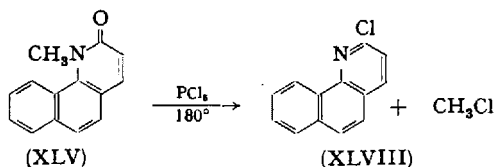
Alkali fusion of 1-azaphenanthrene with potassium hydroxide gives 2-hydroxy-1-azaphenanthrene.³⁶

Halogenation has not been utilized, except indirectly, on this ring system (see below).

(5) Replacement Reactions

2-Chloro-1-azaphenanthrene has not been prepared by direct halogenation but is formed by a replacement reaction; for example, 1-methyl-2-oxo-1-azaphenanthrene (XLV) reacts with phosphorus pentachloride to give 2-chloro-1-azaphenanthrene (XLVIII) in almost quantitative yield.¹⁹ Other reactions by which hydroxy-, amino-, and

sulfo-1-azaphenanthrenes, etc., are prepared are well known and will be ascertained by consulting the original literature.



(6) *Physical Properties*

1-Azaphenanthrene is a fairly strong base, existing as white monoclinic prisms or needles melting at 52° and boiling at $338^\circ/719$ mm. or $223^\circ/47$ mm.³ It decomposes above 345° ⁴ and is volatile with superheated steam. It is almost tasteless and has an extremely weak odor which is unlike that of quinoline.

1-Azaphenanthrene and its derivatives exhibit the properties of quinoline and pyridine in forming salts with acids (HCl, m.p. 213°). It forms a crystalline compound with 1,3,5-trinitrobenzene, which melts sharply at 133.5° and constitutes a good method of identification.²³ It quaternarizes readily with alkyl halides and sulfates (CH_3I , m.p. 179°),^{4,18,67} and reacts with hydrogen peroxide to form the 1-oxide (m.p. 123°).^{118g}

1-Azaphenanthrene derivatives have been reported to fluoresce. 2-Phenyl-1-azaphenanthrene gives a weak green fluorescence in ethanol or ether, and also fluoresces in amyl alcohol.¹² The hydrogenated derivatives fluoresce more strongly; 1,2,3,4-tetrahydro-1-azaphenanthrene and its derivatives in inert solvents are an intense blue.^{3,30} Probably many of the amines fluoresce, but few have been reported to do so. 2-(4-Diethylaminobutylamino)-4-methyl-1-azaphenanthrene is a brown fluorescent oil,⁶⁴ and 10-acetamido-1-azaphenanthrene gives a yellow fluorescence under ultraviolet light.⁷⁵

The following other physical properties of 1-azaphenanthrene have been studied:

- (1) Density and dispersion of solutions in benzene.⁹
- (2) Absorption spectra,^{22,33} reduction,²² antiseptic activity.²²

(3) Solubility of the base in acid of known concentration.³⁹

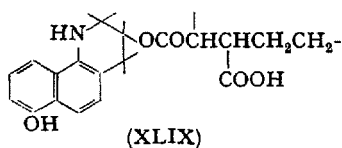
(4) The rate of exchange of hydrogen in 2-methyl-1-azaphenanthrene with C_2H_5OD .⁵⁰

(5) The rate of reaction with ethyl iodide.¹⁰⁴

1-Azaphenanthrene strongly hinders the solution of zinc in hydrochloric or sulfuric acid. This and other properties of metals in the presence of 1-azaphenanthrene have been studied.^{105,106}

(7) Uses

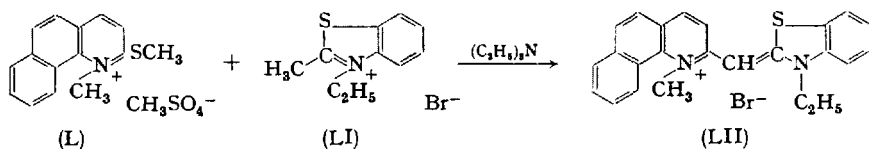
(a) **Azo Dyes.** Hydrogenated 1-azaphenanthrenes couple readily with diazonium salts to give red dyes for wool.^{3,98} Other compounds such as the 3,7-, 3,8-, 3,9-, and 3,10-dihydroxy-1,2,3,4-tetrahydro-1-azaphenanthrenes are suitable coupling components for azo dyes for acetate fabrics.^{42,44,70,98,118b} 3,7-Dihydroxy-1,2,3,4-tetrahydro-1-azaphenanthrene has been esterified with ethylene-maleic anhydride copolymer to give an ester (XLIX) of the type:



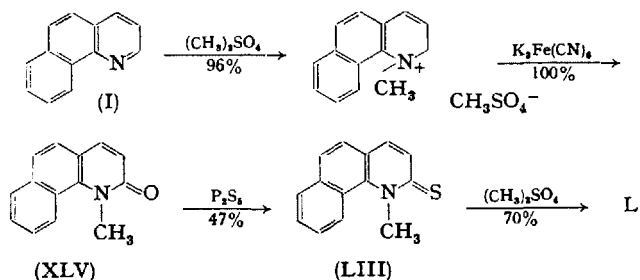
which is claimed to be of value in photographic emulsions.⁷⁶ Azo coupling is stated to take place at the 6-position in acid solution. Green to blue dyes are obtained on coupling with oxidized developer; such coupling generally occurs para to a hydroxyl group.

The nonhydrogenated 1-azaphenanthrenes also are capable of coupling. A 7, α -dihydroxy-1-azaphenanthrene is reported to give basic, green azo dyes with 4-nitrosomethylaniline, 4-nitrosodimethylaniline, and the analogous ethyl derivatives.¹⁵ With diazotized naphthionic acid a brownish-red azo dye is obtained in alkaline solution; acidification gives a pure blue color.¹⁵ 4-Carboxy-2-phenyl-1-azaphenanthrene has been reported to give a 6-phenylazo derivative.³² Other 1-azaphenanthrenes, such as the 9-carboxy-8-hydroxy- and the 8-carboxy-9-hydroxy derivatives have been proposed as dye intermediates.³⁸

(b) **Cyanine Dyes.** An interesting series of cyanine dyes involving the 1-azaphenanthrene nucleus has been described.⁶⁷ As an example of the reaction, 2-methylmercapto-1-azaphenanthrene methosulfate (L) reacts with 2-methylbenzothiazole ethobromide (LI), giving "1-methyl-1'-ethyl-2,2'-naphthoquinone-thiocyanine bromide" (LII) in 26.5 % yield.



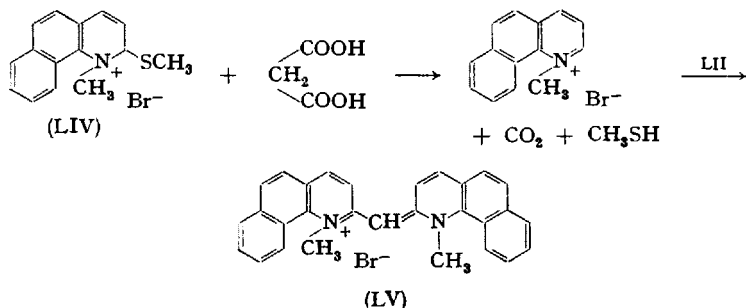
The synthesis of L is effected as follows:



The dyes involving the 1-azaphenanthrene system, which were prepared using these reactions, and variations thereof, are listed in Table II-12.

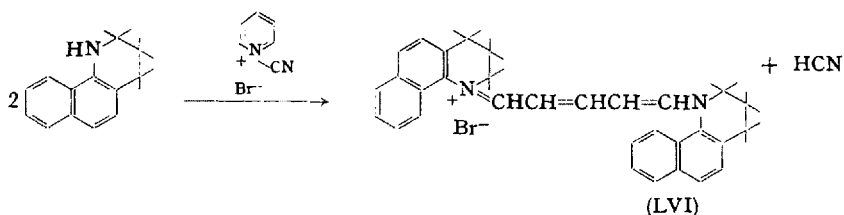
From the absorption curves it is evident that the 1-azaphenanthrene nucleus shifts the absorption strongly to longer wave lengths relative to those of the corresponding benzothiazolyl and quinolyl nuclei.

Compound g in Table II-12 is synthesized as follows:



1-Methyl-2-dithiocarboxymethylene-1,2-dihydro-1-azaphenanthrene has been described as an intermediate for carbocyanine dyes,¹⁰⁹ and other cyanine dye studies have involved the 1-azaphenanthrene system.^{118c,d}

(c) Other Dyes. An unusual type of dye is obtained from the reaction of 1,2,3,4-tetrahydro-1-azaphenanthrene with bromocyanopyridine.¹³ Presumably the reaction is as follows:



Although the compound melts sharply at 151° and is a member of a series of well-defined dyes, no precise analysis could be obtained. High instability made isolation difficult.

(d) Other Uses. 1-Azaphenanthrenes have been studied as carcinogens with uncertain or negative results.^{78,81} Vague⁵² or negative⁵ therapeutic value has been reported for certain amino derivatives, and at least one patent deals with compounds that were obviously part of a pharmaceutical research program.⁵⁶ Among the pure research programs in the pharmaceutical field is that of Hamilton and co-workers,^{64,72,79} the World War II antimalarial program,^{93,110} and others.^{99,101,118e} The antibacterial action of 1-azaphenanthrene has been investigated.¹¹³

Some photographic applications have been reported,^{78,103} and numerous claims have been made for 1-azaphenanthrenes as dye intermediates.^{3, 13, 15, 38,41, 42,44,47,70,76,98, 103}

The effect of inhibition of acid attack on mild steel has been studied,¹⁰² and its use in bismuth analysis⁵⁸ and complex formation with other metals have been reported.¹⁰⁷

1-Azaphenanthrene is one of a number of organic bases studied as condensation catalysts.¹¹⁴

(8) Tables

In Tables II-1 and 2 alkyl and aryl derivatives of 1-azaphenanthrene are listed. Several of the methods of synthesis by ring closure result in these compounds; they are also formed by decarboxylation of the corresponding acids. The hydroxyalkyl derivatives may be converted to alkyl derivatives *via* the corresponding chloroalkyl derivatives by reduction.⁷²

Footnotes *a* and *b* to Table II-1 give further information on symbols and sequence.

TABLE II-1. 1-Azaphenanthrenes. Alkyl Derivatives

Formula	Compound	M.p. or b.p., °C. ^a	Refs.
XI, XIII	2-Methyl- ^c	b 324-6; P 226, 186-7	14, 53, 84, 85; 53, 57
XLI	4-Methyl-	77-8, 71-2, b _{0.2} 152-6; P 218-219; oxalate 94-96	72, 77, 111; 77; 111
	6-Methyl-	57; P 206	78
VIII	3-Ethyl-	75.5; P. MeOH 188	43
XXXVI	2,3-Dimethyl-	83-4, 86-7; P 228-9, 233.5	65, 68
XV	2,4-Dimethyl-	43-4, 44; 51.5-53, 52, 55-6; P 230-1	10, 11, 61; 62, 27, 65; 65
	2,3,4-Trimethyl-	—	81
	2,4,6-Trimethyl-	134; P 188	78
	2,3,4,6-Tetramethyl-	184; P 209	78
	3-Ethyl-2,4,6-tri- methyl-	117; P 175	78
XVI	6,6'-Methylenebis(2,4- dimethyl-)	271	78

^a The following symbols are used: b, boiling point; P, picrate; HCl, hydrochloride; MeI, methiodide; N → O, N-oxide, etc.

^b The tables of derivatives are arranged as follows: 1. alkyl; 2. aryl; 3. hydrogenated; 4. halogen; 5. nitro; 6. sulfo; 7. amino; 8. hydroxy (including ethers); 9. carboxy and carbonyl; 10. miscellaneous; 11. azo dyes; 12. cyanine dyes. The position of a compound in the tables will be determined by the substituent having the highest order of preference as listed above. For example, 2-carboxy-3-methyl-1-azaphenanthrene is listed in Table II-9, not in Table II-1.

^c See section on cyanine dyes, p. 190.

TABLE II-2. 1-Azaphenanthrenes. Aryl Derivatives

Compound	M.p., °C.	Refs.
2-Phenyl- ^a	68	12
3-Phenyl-	106-8	63
2-Styryl-	104	8
4-Styryl- ^b	139-40	72, 93
2-(2-Naphthyl)-	117; P 172-3	92
2-(1-Methyl-4-naphthyl)-	119; P 201-2	92
2-(<i>p</i> -Biphenyl)-	195; P 189-90	92
2-(5-Acenaphthyl)-	144; P 187-8	92
2-(2-Fluorenyl)-	226	92
2-(2-Anthryl)-	202; P 197	92
2-(3-Pyrenyl)-	200; P 223-4	92
2,3-Diphenyl-	144	63
3-Benzyl-2-phenyl-	132-4	63

^a Weak green fluorescence in ether and ethyl and amyl alcohols.

^b Survey Number 5871 of ref. 93. In following tables "Survey Number" will be designated as "SN".

In Table II-3 the hydro derivatives of 1-azaphenanthrene and its alkyl and aryl derivatives are listed. The hydro-1-azaphenanthrenes are prepared by hydrogenation, by cyclization involving a tetralin, or by cyclization involving 1-naphthylamine and a reactant such as epichlorohydrin (see p. 177).

TABLE II-3. 1-Azaphenanthrenes. Hydrogenated Derivatives^a

Compound	M.p. or b.p., °C.	Refs.
1,2,3,4-Tetrahydro- ^b	46.5; 1,3,5-trinitrobenzene 129-30	3, 98; 34
2-Methyl-1,2,3,4-tetrahydro- ^c	b ₂₀ 202-3	30
4-Methyl-1,2,3,4-tetrahydro- ^d	b ₁₀ 186-8	30
2-Phenyl-1,2,3,4-tetrahydro-	—	12
7,8,9,10-Tetrahydro-	26; P 186	59
2-Methyl-7,8,9,10-tetrahydro-	55	29
2,4-Dimethyl-7,8,9,10-tetrahydro-	49 (b ₁₅ 196-200)	27
1,2,3,4,7,8,9,10-Octahydro- ^e	47-8 (b _{37.5} 216)	3
1-Methyl-1,2,3,4,7,8,9,10-octahydro-	37-8	3
2,4-Dimethyl-1,2,3,4,7,8,9,10-octahydro-	b ₁₈ 190	27

^a See also Tables II-7, 8, 9, and 10.

^b Solutions in inert solvents fluoresce intense blue.³ Oxidizing agents in acid solution give crimson colors.³ For the refractive power in benzene, see reference 9. Couples with diazotized amines.^{9a} See Table II-11.

^c Blue fluorescence. ^d Blue-green fluorescence.

^e Gives red color on warming with acid FeCl₃. Color disappears on cooling. Gives violet-red dye with chromic acid. See also Table II-11.

Table II-4 lists the halogen derivatives of 1-azaphenanthrene and its alkyl and aryl derivatives. These halogen derivatives are prepared by several methods, such as the Skraup reaction on a halogenated 1-naphthylamine, the Sandmeyer reaction on the 10-amino derivatives, and the reaction of phosphorus pentachloride on oxo and hydroxy derivatives of 1-azaphenanthrene.

TABLE II-4. 1-Azaphenanthrenes. Halogen Derivatives

Compound (formula)	M.p., °C.	Refs.
2-Chloro- (XLVIII)	105 (111)	19, 118g
4-Chloro-	95	52, 56
	88-89	79
6-Chloro- (XXIX)	101 (dec.)	46
10-Chloro- ^a	81.5-82	34
	84.5	73, 93
2,4-Dichloro-	133, 134-5	5, 99
2-Chloro-4-methyl-	134-5	30, 77
	134-6	72
	136-7	99
4-Chloro-2-methyl-	92-3	30, 64
5-Bromo-	102-3	118i
6-Bromo-	115.5-116	64
10-Bromo-	99	75
6-Bromo-2-methyl-	99-100	30
6-Bromo-4-chloro-2-methyl-	146.5-147	64
4-Chloro-2-methyl-7,8,9,10-tetrahydro-	170	118f

^a SN 662 of ref. 93.

The preparation of the nitro derivatives of 1-azaphenanthrene has been discussed at length (p. 185). The Skraup reaction and the Doebner-Miller reaction on nitro-1-naphthylamines as well as direct nitration of the 1-azaphenanthrene nucleus have been involved. Table II-5 lists the nitro derivatives.

TABLE II-5. 1-Azaphenanthrenes. Nitro Derivatives

Compound	M.p., °C.	Refs.
5-Nitro-	116 ^a (150)	7, 117, 118j
6-Nitro-	155 (149)	7, 64, 117, 118i
7-Nitro-	175	7, 64, 117, 118i, j
	N → O 220	118h
8-Nitro-	200-1	117
9-Nitro-	225 (230)	7, 117, 118i
	N → O 242	118h
10-Nitro-	N → O dec. 238	118h
5,7-Dinitro-	181-2	118j
6,7-Dinitro-	205	118j
6,10-Dinitro-	243	118j
9, <i>x</i> -Dinitro-	206-7	118j
<i>x,x</i> -Dinitro-	274	118i
	N → O dec. 255	118h
6-Nitro-2-methyl-	141-2	30, 99
7-Nitro-2-methyl-	153	99
6-Nitro-2-styryl-	142-3	99
7-Nitro-2-chloro-	206	118g

^a Amine melts at 140° (Table II-7).

The preparation of sulfo-1-azaphenanthrenes by the Skraup reaction has been indicated above (p. 167). Other methods for preparing sulfo derivatives were described on p. 186. Table II-6 lists the sulfo derivatives of 1-azaphenanthrene.

TABLE II-6. 1-Azaphenanthrenes. Sulfo Derivatives

Compound	M.p., °C.	Refs.
4-Sulfo-	390 (dec.)	118e
5-Sulfo-	> 300	4, 41
	(methyl ester) 127	4
	(acid chloride) <i>ca.</i> 116	4
	(amide) <i>ca.</i> 225	4
6-Sulfo-		21, 41
7-Sulfo-		15
10-Sulfo-		73, 75
7, <i>x</i> -Disulfo-		15
4-Sulfo-2-methyl		52

Amino-1-azaphenanthrenes have been prepared by the amination of 1-azaphenanthrene,⁵⁴ of 4-chloro-1-azaphenanthrene,^{79,99} and of 10-sulfo-1-azaphenanthrene.^{73,75} A number of alkylamino and arylamino derivatives have been prepared by similar reactions. Aminoalkyl and aminoaryl derivatives, which were studied intensively as possible antimalarial drugs, are included in the table of amino derivatives, Table II-7.

TABLE II-7. 1-Azaphenanthrenes. Amino Derivatives

Compound	M.p. or b.p., °C.	Refs.
2(?) -Amino-	104-5; P 259-62 (dec.)	54
4-Amino- ^a	173-5 173-4	79, 93 99
5-Amino-	146, 140	41, 115, 117, 118i
6-Amino-	b ₄ 228 118	55, 115 41, 117
7-Amino-	167-8, 175, 192	7, 41, 115, 117, 118i, j
8-Amino-		41, 115
9-Amino-	146-7, 151	7, 117, 118i
10-Amino-	85-6 99	73, 118j 75
5,10-Diamino-		41
2,5,10-Triamino-		41
2,5,6,10-Tetramino-		41
2-Amino-4-methyl-	133-4	99
4-Amino-2-methyl-	149-50	99
4-Amino-3-methyl-		52
6-Amino-2-methyl- ^b	128-9	99
7-Amino-2-methyl- ^c	141.5	99
4-Amino-2-phenyl-	162.5-163	69
6-Amino-1,2,3,4,7,8,9,10-octahydro-	97	3
4-Amino-7-bromo-		52
5-Methylamino-	b ₃ 190-4	60
6-Methylamino-	b ₇ 215-20	60
7-Methylamino-	b ₄ 204-6	60
6-Butylamino-		55
2-Vinylamino-4-methyl- ^d		93
6-Cyclohexylamino-		41
4-(1-Piperidyl)- ^e	85-6	79, 93

(Table continued)

TABLE II-7 (*continued*)

Compound	M.p. or b.p., °C.	Refs.
2-(1-Piperidyl)-4-methyl- ^f	79-80	64, 93
4-(4-Morpholinyl)- ^g	98-100	97, 93
2-(4-Morpholinyl)-4-methyl- ^h	101.5	64, 93
4-(4-Morpholinyl)-2-methyl- ⁱ	127.5	64, 93
4-Benzylamino-	154.5-155.5	79
6-Benzylamino-		41
5-Anilino-	146-7	41
7-(8-Quinolinylamino)-		41
4-(2-Chloroethylamino)-		52
4-(2-Chloroethylamino)-2-methyl-	153; (MeOH) 83-4	64
4-(2-Diethylaminoethylamino)-2-methyl-		52
4-(2-Diethylaminoethylamino)-2-chloro-	112	118e
4-(3-Diethylaminopropylamino)-	(H ₂ O?) 60.5-62.5	79
2-(3-Diethylaminopropylamino)-4-methyl- ^j	b ₃ 275-80	64, 93
4-(3-Diethylaminopropylamino)-2-methyl- ^k	84-5	64, 93
4-(3-Diethylaminopropylamino)-2-chloro-	112	118e
4-(4-Diethylaminobutylamino)-	(H ₂ O?) 73-5	79
2-(4-Diethylaminobutylamino)-4-methyl- ^l	b ₂ 240-5	64, 93
4-(4-Diethylaminobutylamino)-2-methyl- ^m	98-100	64, 93
4-(4-Diethylamino-1-methylbutylamino)- ⁿ	b ₂ 235-45	52, 79, 93
4-(4-Diethylamino-1-methylbutylamino)-3-methyl-	b _{0,2} 240-2	52
4-(4-Diethylamino-1-methylbutylamino)-7-bromo-	b _{0,2} 235-40	52
4-(2-Amino-5-diethylaminoamyl)-	b ₂ 235-45	52
4-(2-Amino-5-diethylaminoamyl)-3-methyl-		52
4-(2-Amino-5-diethylaminoamyl)-6-chloro-		52
4-(2-Amino-5-diethylaminoamyl)-6-bromo-7,8,9,10-tetrahydro-		52
2-(4-Chloroanilino)-4-chloro-	160-2	5
2-(4-Chloroanilino)-4-(3-diethylaminopropylamino)- 2 HCl.3H ₂ O	108-10	5
2-(4-Dimethylaminophenyl)- ^o		93
4-(4-Dimethylaminostyryl)- ^p	183.5-184	72, 93
4-[2-(1-Piperidyl)ethylamino]-		52
4-[3-(4-Morpholinyl)propylamino]- ^q	122-3	79, 93
2-[3-(4-Morpholinyl)propylamino]-4-methyl- ^r	83-4	64, 93
4-[4-(4-Morpholinyl)butylamino]-2-methyl- ^s	110-12	64, 93
2-[4-(4-Morpholinyl)butylamino]-4-methyl- ^t	b ₄ 285-90	64, 93
5-Acetamido-	194-5	117
7-Acetamido-	205	117
9-Acetamido-	183	117

(Table continued)

TABLE II-7 (*continued*)

Compound	M.p. or b.p., °C.	Refs.
10-Acetamido-	110	75
7-(α -Acetylacetamido)-	170	45 ^a
6-(α -Benzoylacetamido)-	191-2	45
7-(α -Benzoylacetamido)-	193	45

^a SN 1725. ^b Weak blue fluorescence in alcohol; monosalts intense yellow, disalts colorless; salts diazotize and couple readily. ^c Properties of salts resemble those described in *b*. ^d SN 1721. ^e SN 8173. ^f SN 1717. ^g SN 3332. ^h SN 1718. ⁱ SN 1726. ^j SN 7414. ^k SN 1725. ^l SN 7415. ^m SN 1734. ⁿ SN 11021. ^o SN 10654. ^p SN 7413. ^q SN 3335, slightly active. ^r SN 1719. ^s SN 1722. ^t SN 7416. ^u Many other acylacetamides with undefined properties are listed in reference 45.

Most of the hydroxy derivatives (Table II-8) were prepared by the Skraup, Knorr, and the Conrad-Limpach methods as well as from sulfonic acids. Hydroxyalkylamino derivatives have been prepared by the reactions for amino derivatives. The preparation of other types of hydroxy derivatives listed is adequately described in the literature references.

TABLE II-8. 1-Azaphenanthrenes. Hydroxy Derivatives

Compound (formula)	M.p., °C.	Refs.
2-Hydroxy-	252-3	36, 118g
4-Hydroxy-	$\frac{1}{2}$ H ₂ SO ₄ (?) 242-3	79, 82
5-Hydroxy- ^a	ca. 270 (dec.)	4, 41, 98
6-Hydroxy- ^a		41, 55, 98
7-Hydroxy- ^a		41, 98
8-Hydroxy-	188 (dec.)	38, 41
9-Hydroxy-	268 (dec.)	38
10-Hydroxy-	104-5	73, 75
2,4-Dihydroxy- (XXVIII)	ca. 320 (dec.)	5, 31, 99
		35, 41
5,10-Dihydroxy- ^a		41, 98
7, α -Dihydroxy-	ca. 290-5	15
2,5,10-Trihydroxy-		41
2,5,6,10-Tetrahydroxy-		41
2-Hydroxy-4-methyl- (XVIII)	292	16, 30
	294-5	77, 99

(Table continued)

TABLE II-8 (*continued*)

Compound (formula)	M.p., °C.	Refs.
4-Hydroxy-2-methyl- ^b (XXIV)	300	17, 30, 87 64, 93
5-Hydroxy-2-methyl- ^a		98
6-Hydroxy-2-methyl- ^a		98
8-Hydroxy-2-methyl- ^a		98
2-Hydroxy-4-(2-furyl)-	262	118a
4-Hydroxy-2-(2-furyl)-	> 320	118a
4-Hydroxy-2,6-dimethyl-	293	78
4-Hydroxy-2-(5-methyl-2-thienyl)-	280-2	100
4-Hydroxy-1,2-dihydro-	158-9	48
3-Hydroxy-1,2,3,4-tetrahydro- ^c		93
2-Hydroxy-4-methyl-3,4,5,6-tetrahydro-	178	91
4-Hydroxy-2-methyl-7,8,9,10-tetrahydro-	298; HCl 310 (dec.); H ₂ SO ₄ 245 (dec.)	118f
10-Hydroxy-7,9-dibromo-	243	73
2-Hydroxy-7-nitro-	> 300	118g
2-Hydroxy-4-amino-	324	41
6-Hydroxy-7-amino- ^a		98
2-Hydroxy-7-amino-4-methyl-	> 300	20
2-Hydroxy-4-(2-diethylaminoethylamino)-	228	118e
2-Hydroxy-4-(3-diethylaminopropylamino)-	242	118e
5-Hydroxy-4-(2-amino-5-diethylaminoamyl)-		56
9-Hydroxy-4-amino-2-methyl-		103
9-Hydroxy-4-laurylamino-2-methyl-		103
9-Hydroxy-4-anilino-2-methyl-		103
9-Hydroxy-4-(4-sulfoanilino)-2-methyl-		103
9-Hydroxy-4-(4-sulfoacetamidoanilino)-2-methyl-		103
9-Hydroxy-4-(4- <i>N</i> -tetradecylsulfoacetamidoanilino)- 2-methyl-		103
9-Hydroxy-4-(4-arsonoanilino)-2-methyl-		103
10-Hydroxy-5-acetoxy-1,2,3,4-tetrahydro-	78	47
4-Ethoxy-	119-20	79
6-Acetoxy-		55
2-Methoxy-4-methyl-	68.5-69.2	77
7-Methoxy-1,2,3,4-tetrahydro-	92-3	47
7-Ethoxy-1,2,3,4-tetrahydro-	67-8	47
5-Acetoxy-1,2,3,4-tetrahydro-	96-8	47
2,9-Dihydroxy-4-methyl-		103
4,8-Dihydroxy-2-methyl-		103
4,9-Dihydroxy-2-methyl-		103

(*Table continued*)

TABLE II-8 (*continued*)

Compound (formula)	M.p., °C.	Refs.
2,4-Dihydroxy-3-phenyl-	322	31
3,7-Dihydroxy-1,2,3,4-tetrahydro- ^d (XXXI)	186-7	42, 70, 98, 118b
3,8-Dihydroxy-1,2,3,4-tetrahydro- ^d	206-7	42
3,9-Dihydroxy-1,2,3,4-tetrahydro- ^d	176-7	42
3,10-Dihydroxy-1,2,3,4-tetrahydro- ^d (XXVII)	185	42
3,7-Dihydroxy-1,2,3,4,7,8,9,10-octahydro-		76
4-(2-Hydroxyethylamino)-		52
6-(2-Hydroxyethylamino)-		55
2-(2-Hydroxyethylamino)-4-methyl- ^e	108	64, 93
4-(2-Hydroxyethylamino)2-methyl- ^f	181-181.5	64, 93
4-[1-Hydroxy-2-(1-piperidyl)ethyl]-	2 HCl 230-2	72
4-[1-Hydroxy-1-(2-piperidyl)methyl]-2-phenyl- ^g	227	93, 110
4-[1-Hydroxy-1-(2-piperidyl)methyl]-2-(<i>p</i> -chlorophenyl)- ^h	225	93, 110
4-(3-Diethylaminoethyl-4-hydroxy)anilino- ⁱ		93
4-[2-(2-Diethylaminoethoxy)ethylamino-		52
6-(2-Hydroxy-3-naphthamido)-		51

^a See Azo Dyes, Table II-11. ^b SN 670. ^c SN 13545. ^d Coupling component for azo dyes for acetate fabrics. ^e SN 1720. ^f SN 1724. ^g SN 10534. ^h SN 12895. ⁱ SN 11613.

Table II-9 lists the carboxy and carbonyl derivatives of 1-azaphenanthrene. The former have been prepared by the Doebner and the Skraup reactions and by the hydrolysis of nitriles. The Doebner reaction with glyoxylic acid and oxidation of alkyl carboxylic acids have been used for the synthesis of dicarboxylic acids. The carbonyl derivatives have been prepared by the usual reactions from the 4-carboxylic acids,⁷² from the corresponding ester,¹¹⁰ by cyclization involving ethyl sodioacetoacetate and naphthalide imidochloride,¹¹² and by oxidation of 4-methyl-1-azaphenanthrene with selenium dioxide.⁷²

TABLE II-9. 1-Azaphenanthrenes. Carboxy and Carbonyl Derivatives

Formula	Compound	M.p., °C.	Refs.
XLVII	2-Carboxy-	182-3	118g
	4-Carboxy-	278, 281-2	40, 72
		(acid chloride)	72
		(amide) 226-227.5	72
		(methyl ester) 99-100	72

(Table continued)

TABLE II-9. (continued)

Formula	Compound	M.p., °C.	Refs.
VII	2,4-Dicarboxy-	278 (dec.), 262-3	8, 57, 65
		(diethyl ester) 100-2	57
	6,7-Dicarboxy-	^a	28
		(anhydride) 317	25
XXV	2-Carboxy-3-methyl-	162-3	65
	4-Carboxy-2-methyl-	(mixture) 228-35	57, 63
		(pure) 245	90
	4-Carboxy-2-trichloromethyl-	240	57
		(ethyl ester) 145	57
		(acid chloride) 162-4	57
		(amide) 202	57
	4-Carboxy-2-methyl-3-phenyl-	292	63
IX	4-Carboxy-2-phenyl- ^b	300 (dec.), 288	12, 32, 63, 69
		(ethyl ester) 103, 96	12, 85, 110
		(amide) 268-9	69
		(acid chloride)	69
XXVI	4-Carboxy-3-phenyl-	282	63
	4-Carboxy-2-styryl-	305	8
	4-Carboxy-2-(3-methyl-2-thienyl)-	245-7 (dec.)	100
	4-Carboxy-2-(5-methyl-2-thienyl)-	284	100
	4-Carboxy-2-(2-naphthyl)-	227-8	92
	4-Carboxy-2-(2-fluorenyl)-	280	92
	4-Carboxy-2-(5-acenaphthyl)-	210 (dec.)	92
	4-Carboxy-2-(1-methyl-4-naphthyl)-	255	92
	4-Carboxy-2-(3-pyrenyl)-	280-5 (dec.)	92
	4-Carboxy-2-biphenyl-	274	92
	4-Carboxy-2-(2-anthryl)-	305 (dec.)	92
	4-Carboxy-3-benzyl-2-phenyl-	268 (dec.)	63
	4-Carboxy-2,3-diphenyl-	271	63
	4-Carboxy-2-phenyl-7,8,9,10-tetrahydro-	260	26
	4-Carboxy-2-(4-chlorophenyl)-	308-9	110
		(ethyl ester) 127.4-127.8	110
	4-Carboxy-2-(2-nitrophenyl)-3-phenyl-	294 (dec.)	58
XXX	3-Carboxy-4-hydroxy-2-phenyl-	(ethyl ester) 228-30	49
	2-Carboxy-4-hydroxy-	280	79
XL		(ethyl ester) 126-7	79
	3-Carboxy-4-hydroxy-	291-2, 278	79, 82

(Table continued)

TABLE II-9. (*continued*)

Formula	Compound	M.p., °C.	Refs.
XXXVIII		(ethyl ester) 261-2, 256	79, 82
	9-Carboxy-8-hydroxy-	295	38
	8-Carboxy-9-hydroxy-		38
	2-Carboxymethyl-1,2-dihydro- ^c	Me ₂ SO ₄	67
	4-Formyl-	126-7	72
	1-Benzoyl-2-methyl-1,2,3,4-tetrahydro-	102-3	30
	1-Acetyl-1,2,3,4,7,8,9,10-octahydro-	68-9	3
	1-Benzoyl-2,4-dimethyl-1,2,3,4,7,8,9,10-octahydro-	130-1	27
	4-Chloroacetyl-	171-2	72
	4-Bromoacetyl-	154.5-155	72
	4-(4-Morpholinylacetyl)-	209-10	72
	4-(1-Piperidylacetyl)-	183-5	72
	4-Diazoacetyl-	110.5-112	72
	3-Acetyl-4-hydroxy-2-phenyl-	263-5	112
		(methyl ether) 139-40	112
	4-(ϵ -Aminovaleryl)-2-phenyl-	69-72	110
		HBr 206-7	110
	4-(ϵ -Amino- α -bromovaleryl)-2-phenyl-	HBr.2H ₂ O 196; HBr.H ₂ O 191.8-192.2	110
	4-(ϵ -Aminovaleryl)-2-(4-chlorophenyl)-	Variable	110
	4-(ϵ -Amino- α -bromovaleryl)-2-(4-chlorophenyl)-	2HBr.H ₂ O 189	110

^a Goes to anhydride at 150°. ^b See Azo Dyes, Table II-11. ^c See Cyanine Dyes, Table II-12.

TABLE II-10. 1-Azaphenanthrenes, Miscellaneous Derivatives

Formula	Compound	M.p., °C.	Refs.
	1-Oxide	123	118g
XLV	1-Methyl-2-oxo- ^a	178	4, 18, 67
LIH	1-Methyl-2-thiono- ^a	109-10	67
XLII	5,6-Dioxo-	205-7	2
	2,4-Dioxo-1,2,3,4-tetrahydro- ^b	(nitroso) dec. ca. 330	31
	1-Methyl-2-methylene-		109
	2-Ethylidene-4-methyl-	184.5-186.5	64
	1-Nitroso-1,2,3,4-tetrahydro- ^c	59.5	3
	1-Nitroso-1,2,3,4,7,8,9,10-octahydro-	77.5	3

(Table continued)

TABLE II-10 (*continued*)

Formula	Compound	M.p., °C.	Refs.
	1-Nitroso-2,4-dimethyl- 1,2,3,4,7,8,9,10-octahydro-	62	27
	1-Methyl-2-dithiocarboxymethylene-	200	109
	2-Cyano-	161-2	118g
XLVI	4-Cyano-	154-6	40
	5-, 6-, and 7-Hydrazino-		41
	5-Hydroxylamino-		41
L	2-Methylmercapto-	Me ₂ SO, 169-71 MeBr	67 67
	4-(3-Arsonoanilino)-	> 250	71
	4-(4-Arsonoanilino)-		71
	4,4'-[3-(4-Morpholinyl)- propylimino]bis(2-methyl)- ^d	151-152.5	64, 93
	2-, 5-, 6-, 7-, 8-, 9-, and 10-Acetamido- (α,α' -terephthaloylbis-) derivs.		45
XLVII	Copolymer of 3,7-dihydroxy- 1,2,3,4-tetrahydro- with ethylenemaleic anhydride		76

^a See Cyanine Dyes, Table II-12. ^b Wine red color; solution in NaOH deep red and in Na₂CO₃ and NH₄OH, green. ^c Yellow solution in H₂SO₄ becomes violet-red on dilution with water. ^d SN 1723.

TABLE II-11. 1-Azaphenanthrenes. Azo Dyes

Substituent on 1-azaphenanthrene	Diazo component ^a	Color	Refs.
5-Hydroxy-	A. <i>o</i> -Chloroaniline	Yellow	98
	B. Monobenzoyl-4,6-diamino-1,3-dimethylbenzene	Bright scarlet	98
	C. 4-Amino-4'-methoxydiphenylamine	Blue-violet	98
	D. 1,5-Dimethoxy-2-amino-4-benzoylaminobenzene	Red-violet	98
	E. 3,3'-Dimethyl-4-aminoazobenzene	Bluish-red	98
	F. 1-Methyl-2-amino-5-nitrobenzene	Bright brick-red	98
	G. 1-Amino-3-chlorobenzene-6-sulfonic acid	Orange	98
	H. 1-Methyl-4-aminobenzene-3-sulfonic acid	Yellow-red	98
6-Hydroxy-	I. 1-Amino-2-nitro-4-chlorobenzene	Gold-orange	98
	B	Yellowish-red	98
	J. 5-Amino-2-benzoylamino-1,4-dimethoxybenzene	Red-violet	98

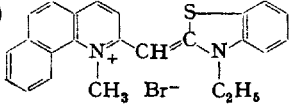
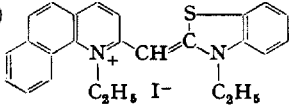
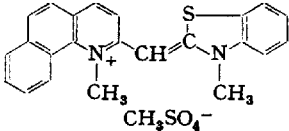
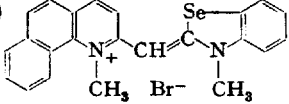
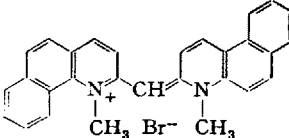
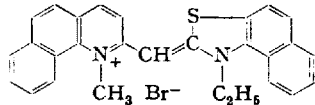
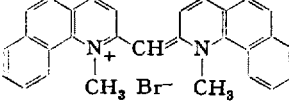
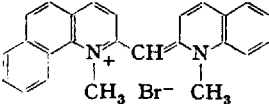
(Table continued)

TABLE II-11 (*continued*)

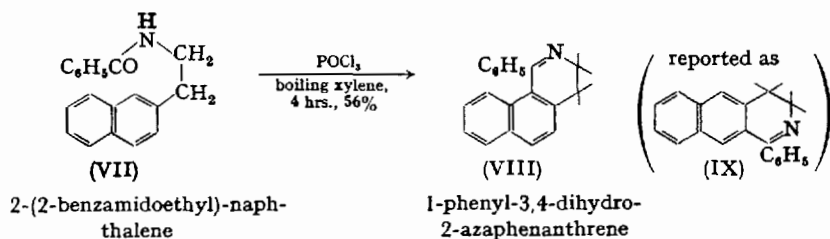
Substituent on 1-azaphenanthrene	Diazo component ^a	Color	Refs.
6-Hydroxy-	C	Violet	98
	D	Bordeaux	98
	K. <i>o</i> -Toluidine	Bluish-red	98
	L. 1-Aminobenzene-4-sulfonic acid	Orange	98
	M. 1-Methoxy-2-aminobenzene-4-sulfonic acid	Yellow-red	98
	N. 1-Aminonaphthalene-4-sulfonic acid	Blue-red	98
	H	Red-orange	98
	O. 1-Methyl-2-aminobenzene-4-sulfonic acid	Red-orange	98
	P. 1-Methyl-2-chloro-4-amino-benzene-5-sulfonic acid	Red-orange	98
7-Hydroxy-	A	Reddish-brown	98
	I	Brown	98
	Q. 4,4'-Diamino-3,3'-dimethoxy-biphenyl	Corinth	98
5-Hydroxy-2-methyl-	J	Brownish-violet	98
	A	Golden yellow	98
	F	Yellowish-scarlet	98
	R. 5-Amino-4'-methoxy-diphenylamine	Violet	98
	Q	Reddish-violet	98
6-Hydroxy-7-amino-	A	Corinth	98
	Q	Blue-violet	98
6-Hydroxy-7-benzamido-	A	Scarlet	98
	Q	Blue	98
6-Hydroxy-2-methyl-	F	Brick-red	98
	J	Red-violet	98
	A	Orange-yellow	98
	Q	Violet	98
8-Hydroxy-2-methyl-	A	Orange	98
	L	Yellow-red	98
	S. 1-Methyl-3-amino-4-methoxy-benzene-6-sulfonic acid	Brownish-red	98
5,10-Dihydroxy-	A	Red-brown	98
	I	Bordeaux	98
	Q	Blue	98
4-Carboxy-2-phenyl-	Aniline	—	32
1,2,3,4-Tetrahydro-	Aniline	Cherry-red	3
	Sulfanilic acid	Violet-red	3
1,2,3,4,7,8,9,10-Octahydro-	Sulfanilic acid	Bright red	3

^a In order to identify the diazo components properly with those in the original patent, the names have *not* been changed to agree with modern usage.

TABLE II-12. 1-Azaphenanthrenes. Cyanine Dyes

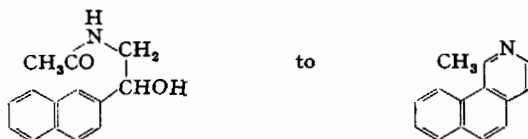
Formula	M.p. (°C.) and yield	$\lambda_{\text{max.}}$ (m μ)	Sensitization range to AgBr emulsion (m μ)	Refs.
(a) 	178–80 26.5 %	510–15	380–590	67
(b) 		510–15	380–570	67
(c) 	248–50 30 %	510–15	380–590	67
(d) 	193 8 %	520	380–590	67
(e) 	178 10 %	565 (sharp)	380–640	67
(f) 		530		67
(g) 	Yield low	575 (sharp)		67
(h) 		550 (sharp)		67

The postulation of V (the "enol" form of the amide) as an intermediate suggests that the laboriously obtained IV was not necessary to the reaction. This conclusion is substantiated by the reaction below, where the benzamidoethyl derivative of naphthalene is used (Bischler-Napieralski reaction)¹²⁸; the acetamidoethyl compound appears not to have been tried. This synthesis of 2-azaphenanthrenes was effected by Kindler *et al.*,¹²¹ although they reported the compounds as azaanthracenes (IX). Much better yields were obtained than in the reactions described above.



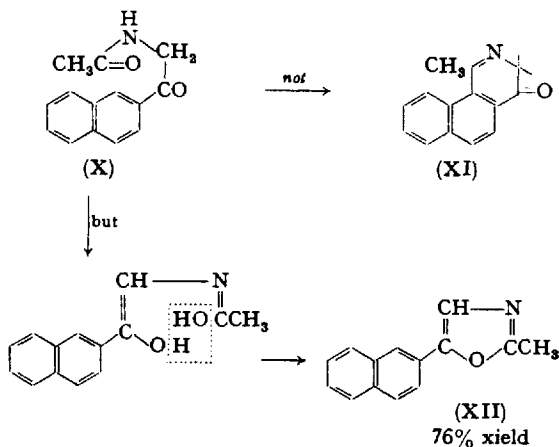
In another reaction of this type, 2-[2-(3,4-diethoxybenzamido)-ethyl]naphthalene gave an 83 % yield of the 3',4'-diethoxy derivative of VIII. Here also a linear configuration was postulated, although the authors indicated the azaphenanthrene structure as a possibility. The evidence available seems to indicate that these products have the angular configuration, *i.e.*, are 1-azaphenanthrenes^{119,126} (see also p. 6).

Kindler *et al.*¹²¹ could not effect ring closure of the compound



nor of the same compound with the chain at the 1-position of the naphthalene nucleus, which was reported by Pictet and Manevitch¹²³ to give 4-methyl-3-azaphenanthrene (see p. 209). However, a similar reaction was reported by Dey and Rajagopalan.¹²⁴ The physical and chemical properties of the product, postulated as XI, indicate that the product is not a 2-azaphenanthrene. It is a very weak base, not easily

soluble in acids. It could not be reduced to the tetrahydro derivative; the keto group is not reactive, and the ordinary derivatives are not obtained. These facts seem to indicate that the reaction occurs as follows:



The properties of the product obtained, and presumed to be XI, are more like those expected of XII [2-methyl-5-(2-naphthyl)oxazole]. The authors later corrected this work, and reported structure XII to be correct for the substance isolated.¹²⁵

(2) Reactions

The reactions of 2-azaphenanthrenes have not been studied extensively. 1,2,3,4-Tetrahydro-2-azaphenanthrene (III) exhibits the normal reactions of a strong secondary aliphatic amine; it absorbs carbon dioxide from the air. Oxidation of III has been described above. Reduction of the dihydro derivatives is effected with palladium on barium sulfate; VIII, for example, gives the 1,2,3,4-tetrahydro- derivative and a by-product melting at 229–30°¹²¹ (see also p. 211).

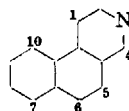
Uses. No practical uses for 2-azaphenanthrenes have been claimed. In a continuation of their studies on toxicity to protozoa of compounds such as 2-aminomethylnaphthalene and 2-(2-naphthyl)ethylamine, Kindler *et al.* studied azaphenanthrenes of analogous structure. The results are included in Table II-13.

TABLE II-13. 2-Azaphenanthrenes

Compound	M.p. or b.p., °C.	Refs.
1,2,3,4-Tetrahydro-	40 (b ₂₀ 200–5); P 225–6; HCl 275–6	119
1-Methyl-3,4-dihydro-	36–7; P 207–8	120; 120, 122
1-Propyl-3,4-dihydro-	P 168–9	122
1-Cyclohexyl-3,4-dihydro-	P 218–9	122
1-Phenyl-3,4-dihydro- ^a	127–8	121, 122
1-(3,4-Diethoxyphenyl)-3,4-dihydro- ^b	148–9	121, 122
1-Phenyl-1,2,3,4-tetrahydro- ^c	124–5	121
1-Nitroso-1,2,3,4-tetrahydro-	105	119
1- <i>o</i> -Nitrobenzoyl-1,2,3,4-tetrahydro-	240	119

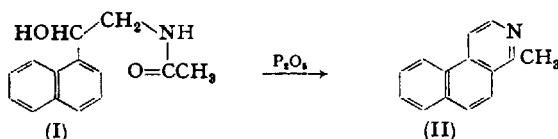
^{a-c} Toxicity to paramecia *re* quinine = 1000: (a) 2400; (b) 1600; (c) 11,000.¹²¹

- C. 3-Azaphenanthrene. Benz[f]isoquinoline.
5,6-Benzisoquinoline. Naphthisoquinoline. R.I. 1976



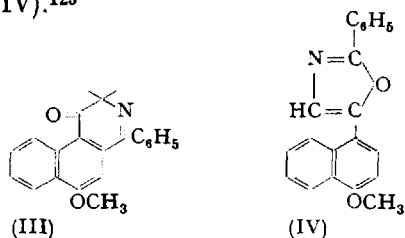
(I) Preparation

3-Azaphenanthrene itself has never been obtained, but the preparation of the 3-azaphenanthrene system was first reported in 1913 by what is known now as the Pictet-Gams modification of the Bischler-Napieralski reaction¹²⁸; 1-(2-acetamido-1-hydroxyethyl)naphthalene (I) is cyclized, giving 4-methyl-3-azaphenanthrene (II) in 24 % yield.¹²³

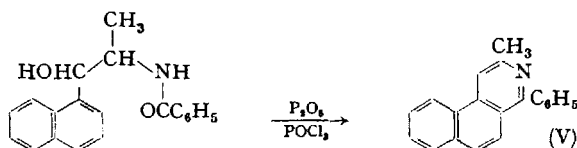


Other investigators^{124, 129} were unsuccessful in repeating this preparation, nor could they apply the method to the preparation of the 2-azaphenanthrene analog (p. 207). They were able, however, to prepare what they assumed to be 6-methoxy-4-phenyl-1-oxo-1,2-dihydro-3-azaphenanthrene (III) by a similar method, but they concluded sub-

sequently that the compound was probably 2-phenyl-5-(4-methoxy-1-naphthyl)oxazole (IV).¹²⁵

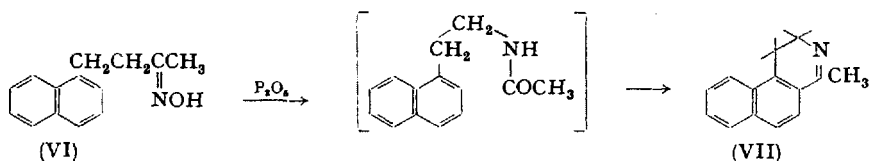


Recently the Pictet-Gams reaction was applied successfully, giving 2-methyl-4-phenyl-3-azaphenanthrene (V) in 12 % yield.¹³¹ The low

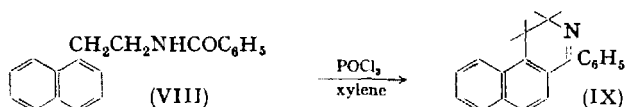


yields in these reactions are indicative of the difficulties encountered; most of the products probably consist of the corresponding oxazoles.

Another preparation of a 3-azaphenanthrene is due to Gibson and co-workers.¹²⁰ In a manner similar to the preparation of the 2-azaphenanthrene system, 1- γ -oximinobutylnaphthalene (VI) is cyclized, after a Beckmann rearrangement, to 4-methyl-1,2-dihydro-3-azaphenanthrene (VII) in a very low yield.



A similar reaction^{121, 122} (Bischler-Napieralski) involves 1-(2-benzamidoethyl)naphthalene (VIII), giving 4-phenyl-1,2-dihydro-3-azaphenanthrene (IX). The latter investigators explored a number



of other routes to synthesize the 3-azaphenanthrene system without success.

(2) Reactions

Few reactions of 3-azaphenanthrenes have been reported. 4-Phenyl-1,2-dihydro-3-azaphenanthrene is reduced over palladium-barium sulfate at two atmospheres of hydrogen in one hour giving the 1,2,3,4-tetrahydro derivative.¹²¹ A by-product of undisclosed nature, which may be a bis compound, was also obtained (see also p. 208).

Sulfonation of 3-azaphenanthrene has been claimed in a patent,¹³⁰ even though there is no report of the base in the literature. The sulfo group is claimed to have been replaced, giving successively α -hydroxy- and α -amino-3-azaphenanthrenes. The latter reportedly was condensed with bis esters. There have been no uses reported for 3-azaphenanthrenes. Their toxicity has been studied¹²¹ and their reactivities calculated from molecular diagrams.¹³²

TABLE II-14. 3-Azaphenanthrenes

Compound	M.p., °C.	Refs.
4-Methyl-	95-6	123
2-Methyl-4-phenyl-	HCl 235 (dec.)	131
4-Methyl-1,2-dihydro-	101-2	120
	P 221 (dec.)	120
4-Phenyl-1,2-dihydro- ^a	78-80	121, 122
	P 200-2	121
4-Phenyl-1,2,3,4-tetrahydro- ^b	103-4	121

^{a,b} Toxicity to paramcia *re* quinine = 1000: (a) 2000; (b) 7500.¹²¹

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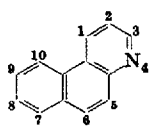
CHAPTER III

4-Azaphenanthrenes

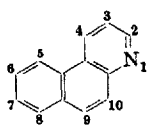
BY J. A. VAN ALLAN

A. Nomenclature

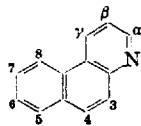
The ring system of 4-azaphenanthrene bears the same relation to quinoline that phenanthrene does to naphthalene. 4-Azaphenanthrene contains the benzene ring fused to the quinoline ring in the 5,6-position. It has therefore acquired various names, such as β -naphthoquinoline, 5,6-benzoquinoline, and benzo[*f*]quinoline. The various methods of numbering the positions of substituents in the 4-azaphenanthrene ring system are shown below.



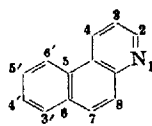
(I)



(II)



(III)



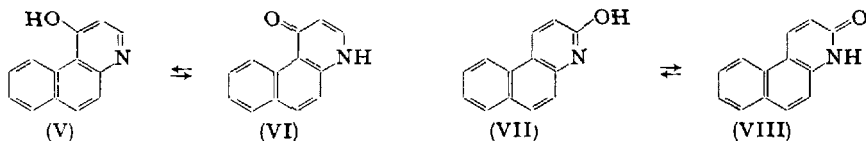
(IV)

System I is now widely used. *Chemical Abstracts* has followed it consistently, but has changed the manner of indicating the point of fusion. Previous to 1937 the base was named benzo-5,6-quinoline; in that year the name was changed to benzo[*f*]quinoline to conform with the quinoline nomenclature. System II has found extensive use in the past, and is used by Beilstein. Systems III and IV are variations of II^{3,71,127}

According to another nomenclature, 4-azaphenanthrene is considered a derivative of pyridine, and it receives the name naphtho-2',1',2,3-pyridine. In conformity with the system outlined in the preface, the parent base is considered a derivative of phenanthrene and the numbering used in this monograph follows that shown in I. The term

" β -benzocinchoninic acid" is reserved for the 4-azaphenanthrenes that have a carboxyl group in the 1-position.

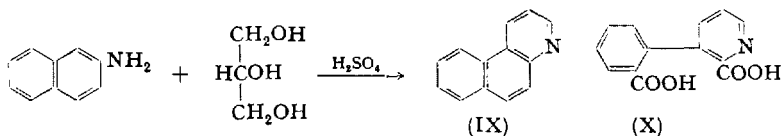
The 1- and 3-hydroxy derivatives of 4-azaphenanthrene are capable of existing in tautomeric forms (V, VI, VII, VIII). If 1-hydroxy-



4-azaphenanthrene is written as the tautomer V, names that have been used are represented by 4-hydroxy-5,6-benzoquinoline or 4-hydroxy- β -naphthoquinoline; if written as the tautomer VI, the corresponding names, *e.g.*, 4-oxo-1,4-dihydro-5,6-benzoquinoline or 4-oxo-1,4-dihydro- β -naphthoquinoline have been given. 3-Hydroxy-4-azaphenanthrene (VII), which may also exist in the tautomeric form VIII, has been named 5,6-benzocarbostyryl because of its relation to carbostyryl. *Chemical Abstracts* classes all the hydroxy-4-azaphenanthrenes as benzoquinolinols.

B. Synthesis of the 4-Azaphenanthrene System

(a) From Glycerol (Skraup). The first synthesis of 4-azaphenanthrene was reported in 1883. In investigating the scope of the Skraup reaction, 2-naphthylamine was caused to react with glycerin in the presence of concentrated sulfuric acid. A base having the melting point 90° and the empirical formula $C_{13}H_9N$ was isolated in 40% yield.^{4,5} On oxidation, it yielded 3-*o*-carboxyphenyl-2-carboxypyridine (X), which indicated that ring closure had taken place through the 1-position of the naphthalene nucleus. This synthesis has been repeated under a

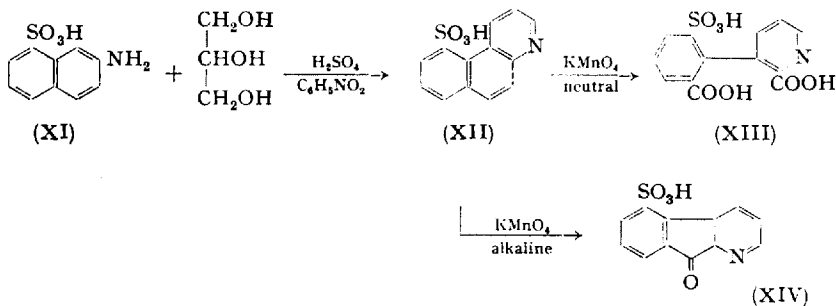


variety of conditions by different investigators. Arsenious acid has been used in place of nitrobenzene as an oxidant with excellent results.^{6,59,148} These later investigators all obtained about the same yield (93–96 %,

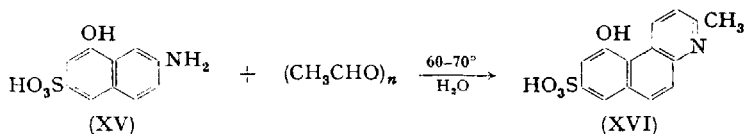
based on the 2-naphthylamine used). The ferric salt of *m*-nitrobenzene-sulfonic acid has been used also, but the yield was not reported.¹⁴⁷ The Skraup synthesis is the best method of making the parent 4-azaphenanthrene.

The tendency toward ring closure through the 1-position of the naphthalene nucleus is so strong that certain groups, such as bromo and nitro, are eliminated in the Skraup reaction.^{7,69} However, it is reported^{116,187} that a chloro or hydrocarbon substituent in the 1-position directs the ring closure to give a 1-azaanthracene. (Compare 1,8-dichloro-2-naphthylamine, which gives only 10-chloro-4-azaphenanthrene when employed in the Skraup synthesis.^{166,187}) This linear cyclization also occurs in the case of 2-aminotetralin which gives 30% of the hydrogenated 4-azaphenanthrene and 55% of the hydrogenated 1-azaanthracene (p. 225) both of which may be smoothly dehydrogenated to the aromatic bases.²⁵ The Skraup reaction may be modified by the use of crotonaldehyde, aldol, or substances that yield crotonaldehyde, in place of glycerin. In such event, a 3-methyl-4-azaphenanthrene is obtained.⁵²

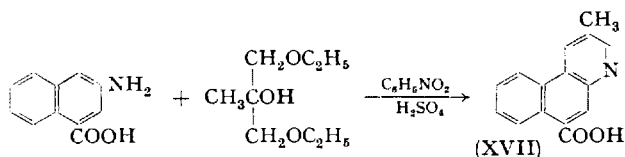
A few dye intermediates have been made by means of the Skraup reaction with derivatives of 2-naphthylamine. For example, 2-naphthylamine-8-sulfonic acid (XI), when treated with glycerin in the presence of concentrated sulfuric acid and nitrobenzene, is converted smoothly to 10-sulfo-4-azaphenanthrene (XII).⁸¹ Oxidation of XII in neutral permanganate results in the formation of the picolinic acid derivative, XIII. If the oxidation is carried out in alkaline solution, the aza-fluorenone, XIV, is obtained. This type of oxidative cleavage is characteristic of 4-azaphenanthrenes¹³⁵ (p. 246).



German patents^{82,83} cover the conversion of 2-aminonaphthol-sulfonic acids into hydroxy-4-azaphenanthrenesulfonic acids by means of a Skraup reaction. 2-Amino-8-hydroxynaphthalene-6-sulfonic acid (γ acid) (XV) is converted to the 4-azaphenanthrene, XVI, by treating it with paraldehyde, either alone or in the presence of hydrochloric acid.



Another variation of the Skraup reaction is employed for the synthesis of 2-methyl-4-azaphenanthrenes. In place of glycerol, the 1,3-diethyl ether of 2-methylglycerol is used to give XVII.¹²⁷

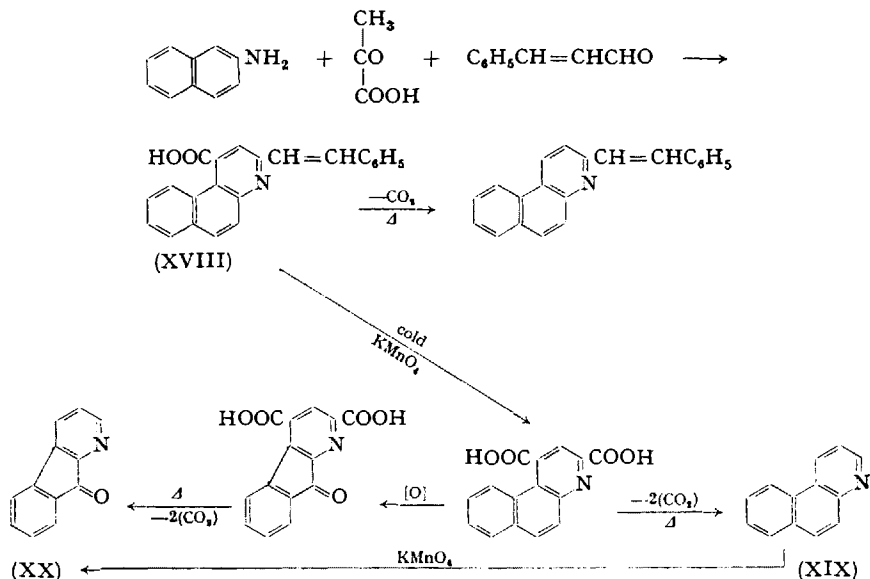


Further examples of the latter reaction are known;^{1,63,121,126} it is the most convenient process for making 4-azaphenanthrene derivatives substituted in the 2-position. Compounds substituted in this position cannot be obtained directly by any other synthesis.

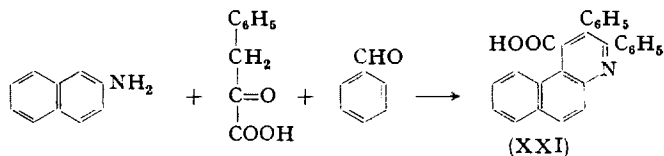
(b) From α -Oxo Acids. In 1890, Doebner⁹ found that equimolecular amounts of cinnamaldehyde, pyruvic acid, and 2-naphthylamine in ether resulted in a compound, XVIII, which could be degraded to the known 4-azaphenanthrene (XIX) of Skraup.⁴ Further confirmation of the 4-azaphenanthrene structure was obtained by oxidative degradation to 1-azafluorenone (XX).

Substituted pyruvic acids (easily obtained by hydrolysis of the reaction products from oxalic ester and acetonitriles) may be used in place of pyruvic acid.¹⁸ Thus, phenylpyruvic acid with benzaldehyde and 2-naphthylamine gives XXI in 40% yield. It is possible, however, that ring closure may occur in a different manner⁴⁴ when these substituted pyruvic acids are employed, to give dioxopyrrolidines (XXII) rather than 4-azaphenanthrenes (XXIII). It is only in exceptional

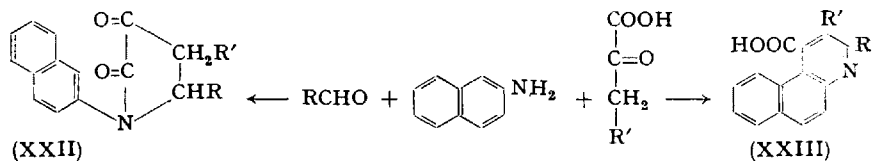
cases, however, that the reaction between an aromatic aldehyde, 2-naphthylamine, and a substituted pyruvic acid takes this course. An



example is the formation of 1-naphthyl-2-phenyl-3-(2'-nitrophenyl)-4,5-dioxopyrrolidine when *o*-nitrophenylpyruvic acid reacts with 2-naphthylamine and benzaldehyde.^{18,98}

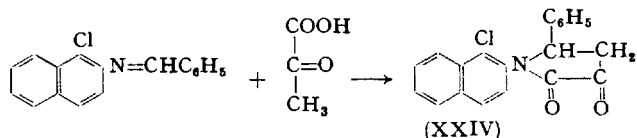


Etienne¹⁵⁶ has found that a chlorine atom in the α -position of 2-naphthylamine inhibits the formation of either 1-azaanthracene or

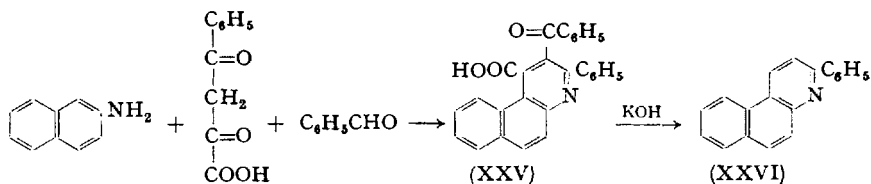


4-azaphenanthrene by a Doebner reaction, a dioxopyrrolidine (XXIV) being formed instead. In contrast, the Skraup reaction, as already

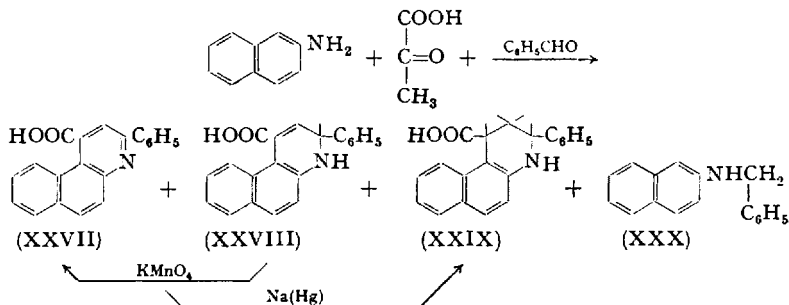
mentioned, takes place with α -substituted 2-naphthylamines, either with the elimination of the substituent to give 4-azaphenanthrenes, or with occurrence of cyclization through the 3-position (p. 218).



Benzoylpyruvic acid yields a derivative with a benzoyl group in the 2-position of the 4-azaphenanthrene ring,^{18,28} that may be easily decarboxylated and debenzoylated.²⁸ For example, molecular equivalents of benzoylpyruvic acid, benzaldehyde, and 2-naphthylamine in alcohol react to form 2-benzoyl-1-carboxy-3-phenyl-4-azaphenanthrene (XXV). The carboxyl group is eliminated by heating the compound above its melting point, and fusion with potassium hydroxide results in cleavage of the benzoyl group to give XXVI.

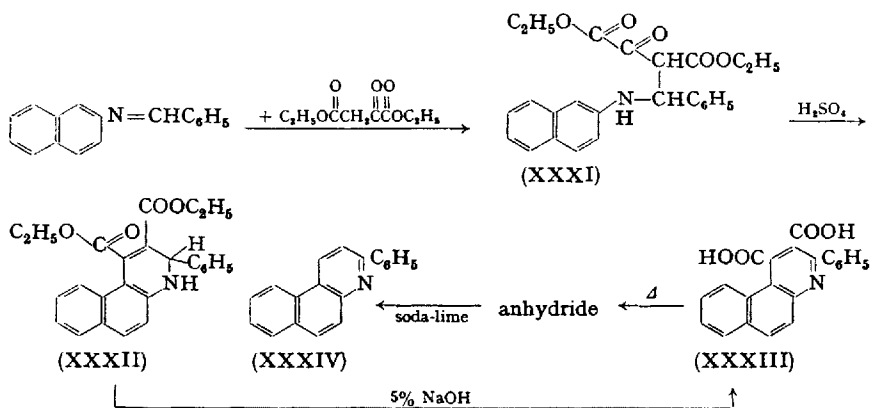


During an investigation of the mechanism of the Doebner reaction between pyruvic acid, benzaldehyde, and 2-naphthylamine, a dihydro (XXVIII) and a tetrahydro derivative (XXIX) of 1-carboxy-3-phenyl-4-azaphenanthrene (XXVII) were obtained as by-products.^{47,86,87,139} In a later paper²⁸ the structures of these two acids were proved. 2-Benzyl-naphthylamine (XXX)^{97,139} and a dimer of the Schiff base, α,β -di-



(2-naphthylamino)bibenzyl,⁴⁷ were found in the mother liquors. In interpreting these results, Ciusa⁴⁷ concluded that the benzal-2-naphthylamine reacted with the pyruvic acid to give the dihydro acid, which disproportionated to the completely aromatic and the tetrahydro acids.²⁸

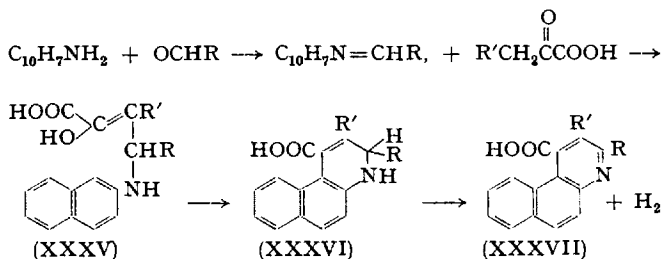
In a series of four papers by Simon and co-workers (1904–1908), the reaction between oxalacetic ester and benzal-2-naphthylamine was thoroughly investigated.^{19, 114, 115, 117} Since the intermediate products and the by-products of the reaction were identified, it is possible to form a reasonably accurate picture of the course of the reaction. Benzal-2-naphthylamine and oxalacetic ester give the addition product, XXXI, which can be isolated. Treatment of XXXI with sulfuric acid gives the dihydro compound, XXXII, which with dilute sodium hydroxide undergoes simultaneous dehydrogenation and saponification to XXXIII. The latter is converted to the anhydride by heat, and the carboxy groups are removed by fusion with soda lime, yielding 3-phenyl-4-azaphenanthrene (XXXIV). This work was repeated by



Ciusa in 1922.²⁴ On following Simon's directions, with a few alterations, slightly different results were obtained. A dimer of the Schiff's base was isolated in addition to the compounds reported previously. The dimer was identified as α,β -di-(2-naphthylamino)bibenzyl.

In general, it may be stated that the products formed in a Doebner synthesis vary not only with the initial starting materials but also with the solvent, temperature, and duration of the reaction. The

benzocinchoninic acids are among the products. The mechanism of the reaction has been the topic of many papers and is still under discussion. It has been suggested²⁸ that the following scheme represents the probable course of the reaction (*cf.* reference 41):



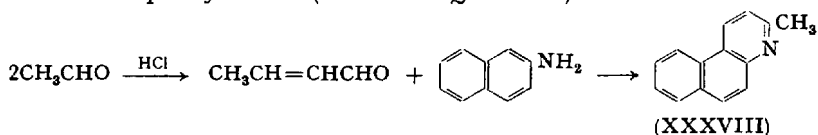
The oxidation of the hypothetical intermediate, XXXVI, to XXXVII appears to be at the expense of the anil. Increasing the proportion of anil increases the yield of the cinchoninic acid. This is in agreement with the findings of Ciusa and Masajo.¹⁴⁰

A large variety of aldehydes have been condensed with pyruvic acid and 2-naphthylamine^{29,29b} to give 3-substituted 4-azaphenanthrenes. The reaction is so general that it has been suggested as a method for characterizing aldehydes. The exceptions are the aldehydes that have a hydroxyl group in the α -position (glucose, galactose). If the hydroxyl group is in a position other than the alpha (*e.g.*, aldol), the reaction proceeds normally. Protocatechualdehyde, β -resorcyraldehyde, and gentisaldehyde do not react.¹⁰⁶ Sulfonated derivatives of benzocinchoninic acid may be obtained by the reaction of naphthylamine sulfonic acids with pyruvic acid and an aromatic aldehyde.¹⁹⁰

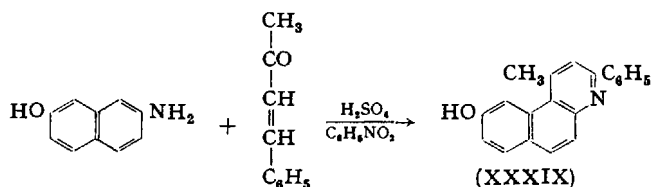
If two moles of pyruvic acid and one mole of 2-naphthylamine are used, 3-methylbenzo[h]cinchoninic acid is formed. One mole of the pyruvic acid is first converted to acetaldehyde, which then condenses in the usual manner.^{29b} The loss of carbon dioxide on pyrolysis to yield aromatic bases is characteristic of the cinchoninic acids. The yields in the Doebner reaction are usually between 60 and 80 %.

(c) From α,β -Unsaturated Aldehydes (Doebner-Miller). If two equivalents of acetaldehyde react with one of 2-naphthylamine, 3-methyl-4-azaphenanthrene (XXXVIII) is obtained. This type of re-

action is termed a Doebner-Miller synthesis.^{8,74,171} It is postulated that the acetaldehyde is converted to crotonaldehyde, which then condenses with the 2-naphthylamine (see under Quinoline).



A mixture of acetone and acetaldehyde under the same conditions gives 1,3-dimethyl-4-azaphenanthrene,⁷⁹ the active intermediate being ethylideneacetone. In one instance, the use of an oxidizing agent in the presence of sulfuric acid, conditions which are similar to the Skraup reaction,¹¹⁸ gave a yield of only 11.8 %. The reactants in this case were 7-hydroxy-2-naphthylamine and benzalacetone, which in the presence of nitrobenzene and sulfuric acid gave XXXIX. This



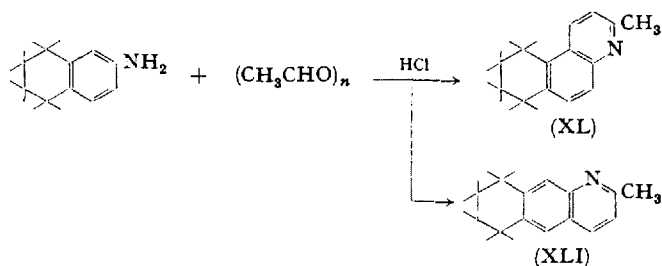
method was improved and patented by I.G. Farbenindustrie A.-G. in 1931. Crotonaldehyde was used in place of the benzalacetone, and an oxidation catalyst, ammonium vanadate, was added to the reaction mixture.⁵² The product in this case is 1-methyl-4-azaphenanthrene. The method has been greatly improved by Campbell.¹⁶⁹

Acetylenic compounds have been used in place of the α,β -unsaturated carbonyl compounds. Phenylpropargyl aldehyde in acetic acid at 80° reacts with 2-naphthylamine to give a small yield of 1-phenyl-4-azaphenanthrene,⁵⁵ a method that is of theoretical interest only.

The Doebner-Miller synthesis was applied to 3-aminonaphthalene-1-carboxylic acid as one step in the synthesis of lysergic acid. Paraldehyde was simply refluxed with the amine *without a condensing agent*. The product was 6-carboxy-3-methyl-4-azaphenanthrene¹²⁵ (*cf.* reference 83).

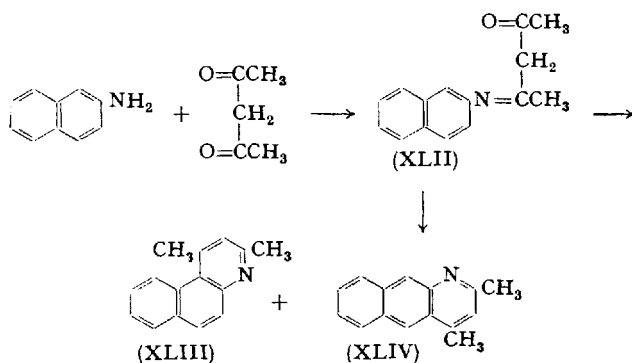
Campbell and Schaffner⁷³ have investigated the Doebner-Miller reaction intensively and have found that good yields can be obtained by the use of mild conditions, an oxidizing agent, and a condensing agent. An innovation is the use of 1,3,3-trimethoxybutane in place of the unstable methyl vinyl ketone. 4-Methoxy-2-butanone, which can be obtained by acid hydrolysis of the trimethoxybutane, can also be used in the reaction.¹⁷⁰

On reaction with paraldehyde in the presence of hydrochloric acid, 6-aminotetralin gives a 35 % yield of mixed bases; of these, 65 % is the angular 3-methyl-7,8,9,10-tetrahydro-4-azaphenanthrene (XL) and 35 % is the linear 2-methyl-5,6,7,8-tetrahydro-1-azaanthracene (XLI)¹³⁷ (pp. 26 and 60). These tetrahydro compounds are



smoothly dehydrogenated to the parent bases, through which their structures are confirmed.

(d) From β -Diketones. It has been shown⁷⁹ that the Doebner-Miller type of reaction with paraldehyde, acetone, and 2-naphthylamine gives a benzoquinoline derivative, C₁₃H₁₅N, m.p. 126–7°. Combes⁸⁰ reported a benzoquinoline derivative of the same empirical formula, but of m.p. 66–7°, by reaction of acetylacetone and 2-naphthylamine in the presence of concentrated sulfuric acid. Both authors assumed their compound to be 1,3-dimethyl-4-azaphenanthrene. This discrepancy was resolved in 1944 by Johnson and Mathews⁶⁹, who showed that when the Combes method is used only a 4 % yield of the angular base, XLIII, is obtained from the intermediate, XLII. The greater portion of the product is isolated as a sulfonic acid of the linear base, XLIV (91 % yield), which could be hydrolyzed to the 1-azaanthracene, the structure of which was proved (pp. 18 ff.).

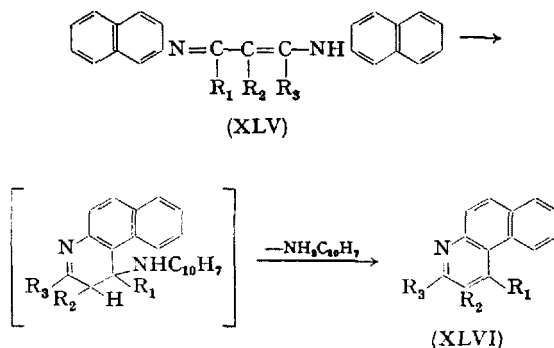


The synthesis was improved by Clemo and Legg,¹⁶⁵ who used 90 % sulfuric acid as a condensing agent and thus obtained cyclization without sulfonation. Furthermore, it was found that 3-chloroacetylacetone gives only the 4-azaphenanthrene derivative.¹⁶⁶ Wasserman states that a halogen or a nitro group in the 1-position of 2-naphthylamine prevents the Combes reaction from taking place.⁶¹ (See Chapter I for a survey of this reaction.) However, 2,4,9-trimethyl-1-azaanthracene is prepared in excellent yield by the condensation of 1-methyl-2-naphthylamine with acetylacetone in the presence of hydrogen fluoride,⁶⁹ and under the same conditions as are used with the unsubstituted 2-naphthylamine.

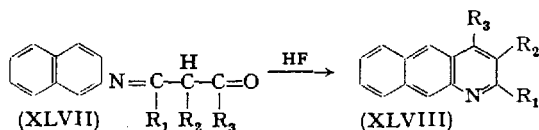
In a later paper by Mathews and Johnson,¹⁶⁸ angular cyclization of XLII was accomplished to give a 70 % yield of XLIII. The method of ring closure involved heating the anil in alcoholic solution with 2-naphthylamine hydrochloride and zinc chloride, according to Petrow⁶⁶ (Section Be following). This angular cyclization of XLII suggests that the ring closure of 3-(2-naphthyliminomethyl)-2-butanone by this method gave, as presumed by Petrow, 2,3-dimethyl-4-azaphenanthrene (see next section). Confirmatory evidence for this structure was furnished by the ultraviolet absorption spectrum characteristic of 4-azaphenanthrenes.

In view of these facts, it has been suggested¹⁶⁸ that the Skraup synthesis proceeds through the formation of an intermediate anilino anil, XLV. As suggested by Sidgwick,¹⁶⁴ this affords an opportunity for cyclization either into a nucleus substituted by an imino group or into one substituted by an amino group. Since the latter may have an

activating influence, the ring closes not into the original nucleus but into the activated 1-position of the second nucleus to give XLVI. This explains the apparent reversal of the positions of the substituents on the side chain of the intermediate anil. Compare XLVI and XLVIII.



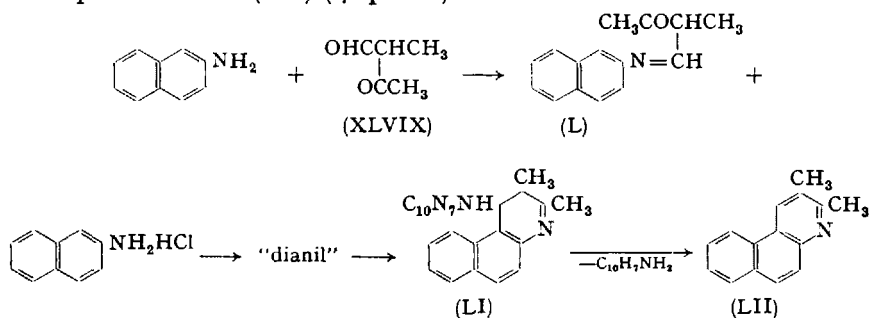
In contrast, the closure of XLVII with hydrogen fluoride does not involve an intermediate anilino anil, and the 1-position of the naphthalene nucleus is deactivated by the anil group in the 2-position, so that ring closure occurs through the 3-position to give XLVIII.



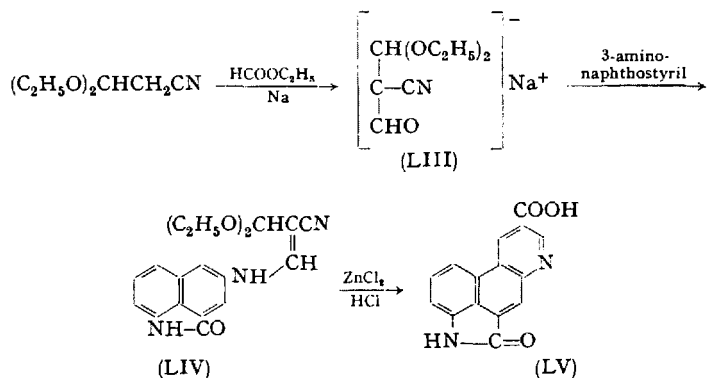
(e) From Formyl Ketones. A method which is allied to the Combes reaction, but which produces angular bases of the 4-azaphenanthrene type, consists in making the formyl derivative of an aliphatic ketone of the type, RCOCH_2R^1 (where R and R^1 are alkyl groups), and condensing it with a primary aromatic amine (quantitative yield). The "anil" is then heated with the amine hydrochloride, either directly at $160\text{--}200^\circ$ or in alcoholic solution. The yields are of the order of 50–65 %, and the reaction appears to be very general.⁸⁶

For example, 2-naphthylamine and 3-formyl-2-butanone (XLVIX) condense readily to give the anil, L, which, on treatment with 2-naphthylamine hydrochloride, forms the intermediate compound, LI; the

latter at once loses a molecule of 2-naphthylamine to give 2,3-dimethyl-4-azaphenanthrene (LII) (*cf.* p. 226).



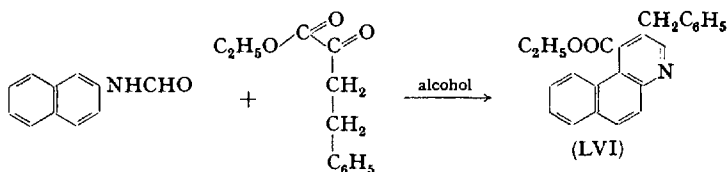
(f) From a Dialdehyde. A variation of the preceding synthesis was developed by Uhle and Jacobs⁷¹ during their investigation of lysergic acid. By this procedure, it is possible to synthesize, directly, azaphenanthrenes in which the hetero ring is substituted in the 2-position only. 2-Cyanoacetal is allowed to react with ethyl formate and sodium in ether solution. The resulting sodiocyanomalondialdehyde acetal (LIII) is condensed with 3-aminonaphthostyryl in acid solution, and the resulting acetal of 2-cyano-2-formylethylidene-3-aminonaphthostyryl (LIV) is converted to 7-amino-4-azaphenanthrene-2,6-dicarboxylic acid lactam (LV) by fusion with zinc chloride and hydrolysis of the mixture of basic products with hydrochloric acid.



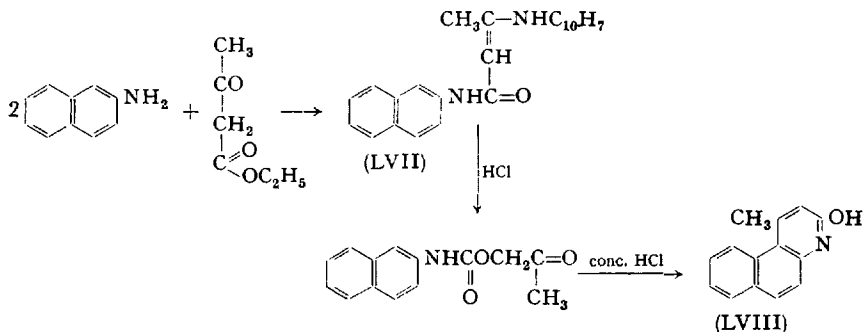
In a similar manner, 2-naphthylamine is condensed with sodionitromalonodialdehyde to give the difficultly accessible 2-nitro-4-aza-

phenanthrene.⁷¹ Zinc chloride is the only condensing agent that appeared to effect ring closure to the azaphenanthrene compound. Acetic anhydride, concentrated sulfuric acid, potassium acid sulfate, sodium ethoxide in absolute alcohol, and hot mineral oil, when allowed to react with the anil, led to no basic products.

(g) From a Formylamine. In the two foregoing synthetic methods, a formyl group is introduced into an aliphatic ketone or aliphatic aldehyde to yield compounds capable of reacting with 2-naphthylamine to give 4-azaphenanthrene-type compounds. A third method achieves the same result by substituting one of the amino hydrogens of 2-naphthylamine by a formyl group.⁹⁹ Excellent yields of 2-benzyl-1-carboxy-4-azaphenanthrene (LVI) are obtained by simply refluxing equimolecular proportions of *N*-formyl-2-naphthylamine with ethyl benzylpyruvate in alcohol solution for a few hours.



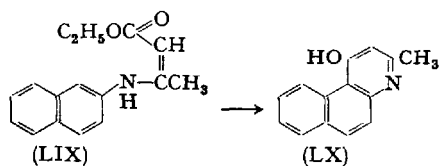
(h) From Acetoacetic Ester Type Compounds. (1) *From Acetoacetonaphthylide (Knorr).* In 1884 a synthesis of 3-hydroxy-4-azaphenanthrenes was described.^{76, 171} Ethyl acetoacetate is condensed with 2-naphthylamine under specific conditions to yield β -(2-naphthyl-amino)crotono-2-naphthamide (LVII) which, on hydrolysis with dilute acid, gave 2-acetoacetonaphthalide. This latter compound, on



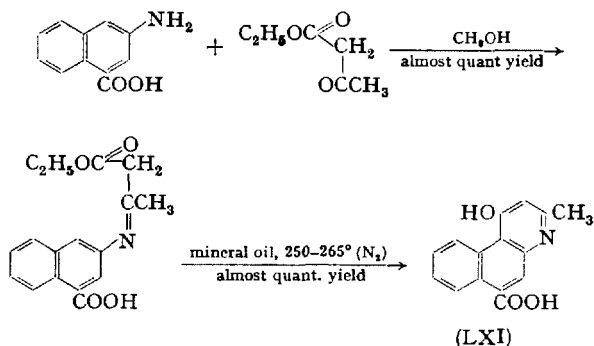
heating with concentrated hydrochloric acid, gave 3-hydroxy-1-methyl-4-azaphenanthrene (LVIII).

This reaction was reinvestigated in 1926 by Gibson. The procedures for the preparations of the intermediates were improved, and the previous results confirmed.⁴⁹ Considerable 2-naphthylamine is obtained in the final cyclization, and the yields are low. Benson and Hamilton¹³⁶ could not duplicate the yields of Gibson for the condensation of 2-naphthylamine and ethyl acetoacetate. (See *Organic Syntheses*, Vol. 25, Wiley, New York, p. 7, for an improved procedure for the synthesis of this type of compound.) The cyclization of the anilide was accomplished by means of concentrated sulfuric acid; the base was obtained in a yield of 75 %. This reaction merits further study.

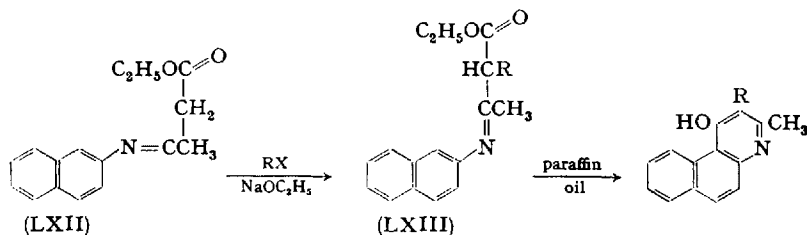
(2) *From Ethyl β-(2-Naphthylamino)crotonate (Conrad-Limpach).* If 2-naphthylamine is treated with ethyl acetoacetate at room temperature, ethyl β-(2-naphthylamino)crotonate (LIX) is formed. This "anil," on being heated to 240°, gives 1-hydroxy-3-methyl-4-azaphenanthrene (LX) in 30 % yield.^{77,141} The use of mineral oil as a diluent for the cyclization step increases the yield to 90–95 %.¹²⁸ This synthesis has



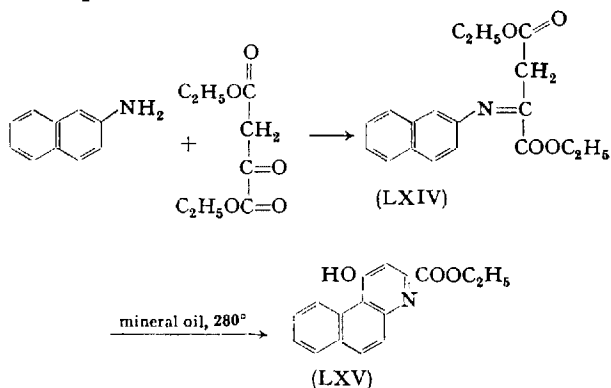
been used with excellent results in the preparation of 6-carboxy-1-hydroxy-3-methyl-4-azaphenanthrene (LXI).¹²⁸



A modification of this Conrad-Limpach reaction was worked out by Gillis and co-workers. The intermediate anil (LXII) is treated with an alkyl halide in the presence of sodium ethoxide in alcohol. The alkylated anil (LXIII) is then cyclized in paraffin oil at 250° to give a 4-azaphenanthrene substituted in the 1-, 2-, and 3-positions.¹³² The yields are of the order of 50–90%.

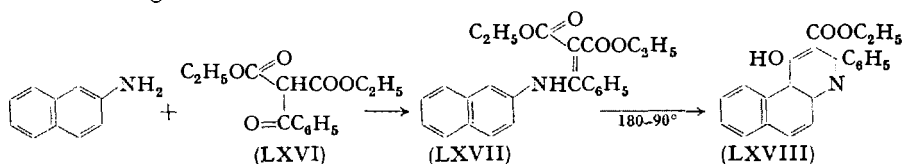


(3) *From Ethyl Oxalacetate.* When ethyl oxalacetate is treated with 2-naphthylamine, an intermediate product (LXIV) can be isolated which is similar to that obtained in the reaction just mentioned. The final product, 3-carbethoxy-1-hydroxy-4-azaphenanthrene (LXV), contains the carbethoxy group in place of the 3-methyl group; the carbethoxy group is easily saponified and decarboxylated to give 1-hydroxy-4-azaphenanthrene.^{65, 68}

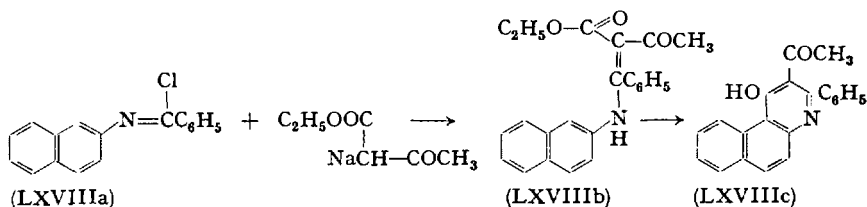


(4) *From Ethyl Benzoylmalonate.* Heeramanick and Shah succeeded in developing a synthesis for the formation of 2-carboxy-4-azaphenanthrenes. They used as starting materials ethyl benzoylmalonate (LXVI) and 2-naphthylamine. The carbonyl group of the ethyl ben-

zoylmalonate forms an anil (LXVII), which is cyclized in mineral oil 185–90° to give LXVIII.¹³¹

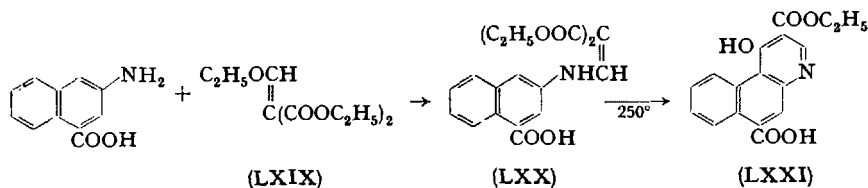


(5) *From N-2-Naphthylbenzimidyl Chloride.* Desai and Shah effected the condensation of *N*-2-naphthylbenzimidyl chloride (LXVIIIa) with ethyl sodioacetoacetate to give the intermediate oxo ester (LXVIIIb), which was cyclized by heating. The product was 2-acetyl-1-hydroxy-3-phenyl-4-azaphenanthrene (LXVIIIc).¹⁷⁹ If the



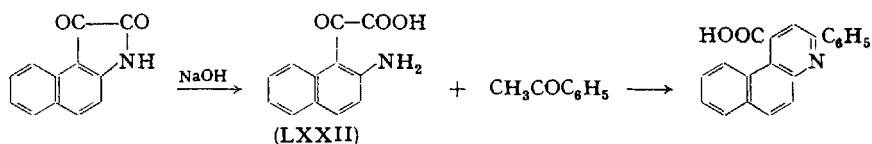
ethyl sodioacetoacetate in the above synthesis is replaced by ethyl sodiomalonate, the product is 2-carbethoxy-1-hydroxy-3-phenyl-4-azaphenanthrene.¹³¹

(6) *From Ethoxymethylenemalonic Ester.* The foregoing synthesis may be modified in a novel manner by replacing the benzoyl group in benzoylmalonic ester by an ethoxymethylene group, which is, in effect, a formyl group. In this case the product has a hydrogen atom in the 3-position in place of the phenyl group in LXVIII. For example, 3-aminonaphthalene-1-carboxylic acid is condensed with ethoxymethylenemalonic ester (LXIX) to give the anil, LXX. Cyclization in mineral oil at 250° gives 2-carbethoxy-6-carboxy-1-hydroxy-4-azaphenanthrene (LXXI). It is worthy of note that the use of mineral

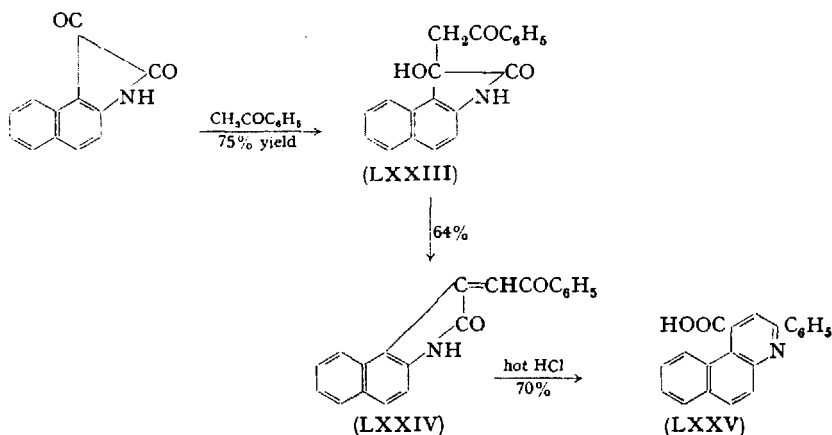


oil in the cyclization step improves the yield greatly in all the acetoacetic ester types of synthesis (probably by preventing local overheating).¹²⁸

(i) From 2-Naphthisatin. The Pfitzinger reaction has been used in a few instances to obtain derivatives of the 4-azaphenanthrene type.^{172, 174} The active intermediate in this reaction is 2-amino-1-naphthylglyoxylic acid (LXXII), which is obtained from 2-naphthisatin by alkaline hydrolysis. The glyoxylic acid derivative reacts with acetophenone in the presence of an alkaline catalyst to give a benzocinchoninic acid.²⁸ The yields are good. A variation of this synthesis

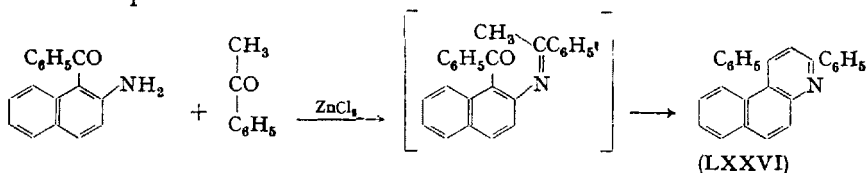


has been developed in which the 2-naphthisatin is not saponified to the glyoxylic acid derivative, but is condensed directly with the acetophenone. The initial product is an aldol-like condensation product, LXXIII, which readily loses water to give the unsaturated isatinal-acetophenone, LXXIV; the latter is then rearranged by strong mineral acid to a benzocinchoninic acid, LXXV⁹⁶ (*cf.* Cross and Henze^{128a}).

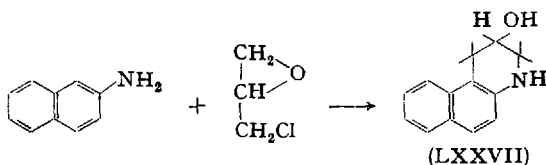


(j) From 1-Benzoyl-2-aminonaphthalene. A direct synthesis of 1,3-diaryl-4-azaphenanthrenes, which is capable of many variations,

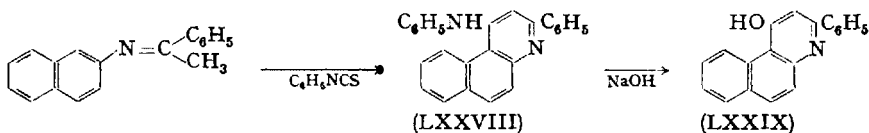
has been developed by Dziewoński and co-workers. It has the disadvantage that one of the intermediates, 1-benzoyl-2-aminonaphthalene, is not readily available. The method consists in condensing the latter compound with acetophenone in the presence of zinc chloride.⁵¹ The product, 1,3-diphenyl-4-azaphenanthrene (LXXVI), is obtained in one step.



(k) From Epichlorohydrin. The method developed for the preparation of 3-hydroxy-1,2,3,4-tetrahydro-1-azaphenanthrene¹⁶³ has been applied successfully to 2-naphthylamine. Epichlorohydrin, on condensation with the latter compound, gave 2-hydroxy-1,2,3,4-tetrahydro-4-azaphenanthrene (LXXVII). The yield was not given.¹²⁸

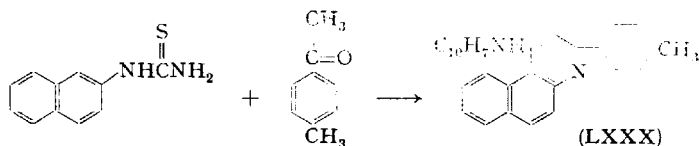


(l) From Phenyl Isothiocyanate. It is claimed that the Schiff base from acetophenone and 2-naphthylamine, on reaction with phenyl isothiocyanate at 200° for one hour, then at 280° for 30 minutes, gives 1-anilino-3-phenyl-4-azaphenanthrene (LXXVIII) in unstated yield.²⁷ The anil condenses with the isothiocyanate, with the elimination of hydrogen sulfide, to give an azaphenanthrene. The anilino group may be replaced by a hydroxyl group by hydrolysis with sodium hydroxide to give LXXIX.



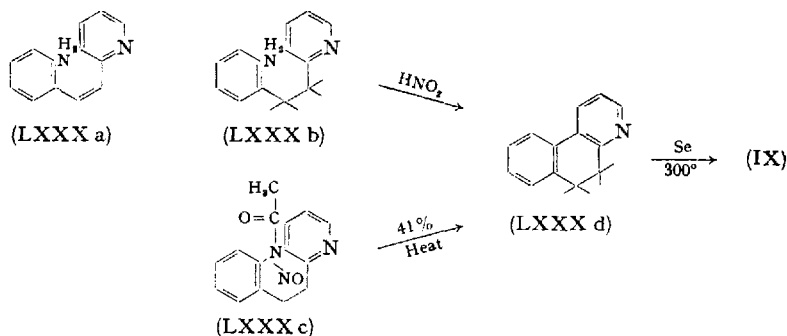
(m) From Naphthylthiourea. Dziewoński, Gisler, and Moszew,⁵⁴ in a variation of the latter method, report that 1-(2-naphthylamino)-

3-phenyl-4-azaphenanthrene is obtained by treating 34.8 grams of 2-naphthylthiourea and 15 grams of acetophenone at 180° for 4 hours, then at 280° for 0.5 hour. The 1-(2-naphthylamino)-3-*p*-tolyl derivative (LXXX) is prepared in a similar manner from 2-naphthylthiourea and *p*-tolyl methyl ketone. In this modification the thiocarbanilide is de-

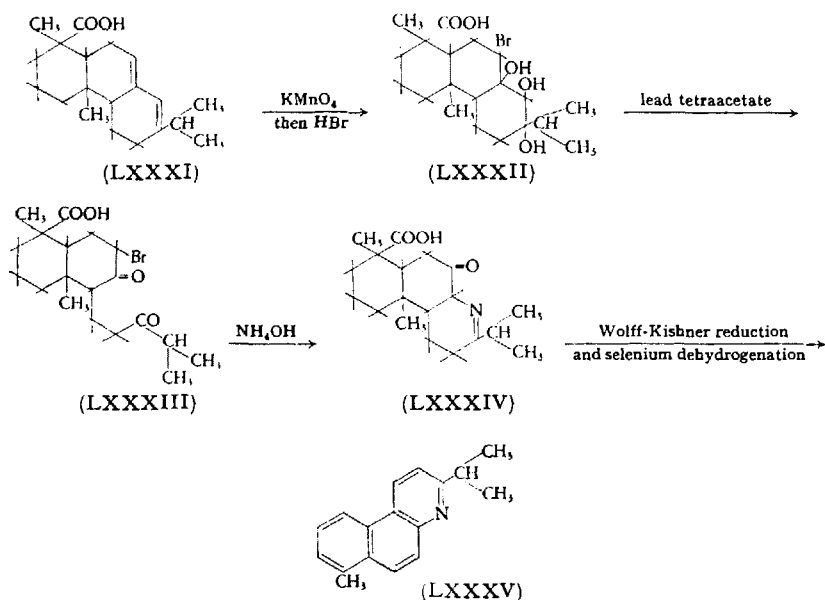


composed *in situ* to the required isothiocyanate. The yields are generally low; however, the method makes available compounds not otherwise obtainable.

(n) **From Nitrosoacetamidophenylethylpyridine.** An attempt was made to bring about a ring closure of 2-(2-aminostyryl)pyridine (LXXXa) to 4-azaphenanthrene, but this failed, owing to the *trans*-configuration of the molecule. In order to overcome this difficulty, arising from the geometric isomerism of the styrylpyridine, 2-(2-*o*-aminophenylethyl)pyridine (LXXXb) was prepared. When this base was subjected to the normal Pschorr procedure, a small yield of 4-azaphenanthrene was obtained. The intermediate 5,6-dihydro-4-azaphenanthrene (LXXXd) presumably was oxidized by the excess nitrous acid present. 2-(2-*o*-Nitrosoacetamidophenylethyl)pyridine (LXXXc) decomposes in benzene solution to give 5,6-dihydro-4-azaphenanthrene in 41 % yield. By heating this dihydro compound with selenium at 300°, 4-azaphenanthrene is obtained.¹⁷⁶

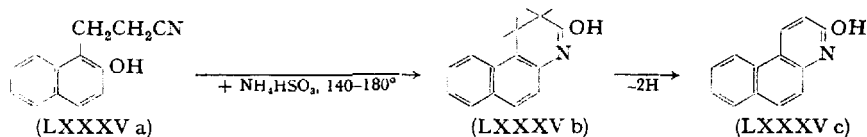


(o) **From 1,5-Diketones.** Ruzicka, Steinbach, and Jeger have presented evidence that appears to establish conclusively the positions of the double bonds in abietic acid (LXXXI). This involved a stepwise conversion of the latter to a 4-azaphenanthrene derivative.⁶² The acid, LXXXI, was oxidized with potassium permanganate, and the crude product treated with hydrogen bromide to give bromotrihydroxyabietic acid (LXXXII). This acid, on treatment with lead tetraacetate, was converted to a bromo-1,5-dioxo acid, LXXXIII, from which the 4-azaphenanthrene, LXXXIV, was formed by treatment with concentrated aqueous ammonia. Dehydrogenation by means of selenium gave 3-isopropyl-7-methyl-4-azaphenanthrene (LXXXV) (Ruzicka called this 8-azaretene). The structure of LXXXV was proved by a Doebner synthesis.⁶⁷



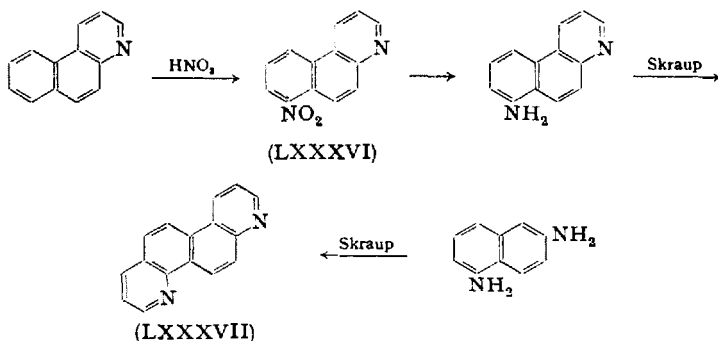
(p) **From 1-Cyanoethyl-2-naphthol.** 3-Hydroxy-1,2-dihydro-4-azaphenanthrene (LXXXVb) may be prepared in good yield by heating 1-cyanoethyl-2-naphthol (LXXXVa) with aqueous ammonium bisulfite to a temperature of about $140\text{--}180^\circ$ under pressure. 1-Cyanoethyl-2-naphthol is obtained by refluxing 2-naphthol with acrylonitrile in benzene solution in the presence of a strong alkali. The dihydro com-

pound, LXXXVb, may be dehydrogenated by heating with palladium on charcoal to give LXXXVc.¹⁸⁸



C. Derivatives

(a) Nitro- and Sulfo-4-azaphenanthrenes. The nitration of 4-azaphenanthrene was studied by Claus and Bessler,¹⁰ but the constitution of the mononitro compound obtained by them was not determined. This nitro compound, LXXXVI, was identified¹⁵ by its conversion into 4,7-diazachrysene (LXXXVII), which was obtained from 1,6-diaminonaphthalene by the Skraup reaction. Thus, LXXXVI is 7-nitro-4-azaphenanthrene.



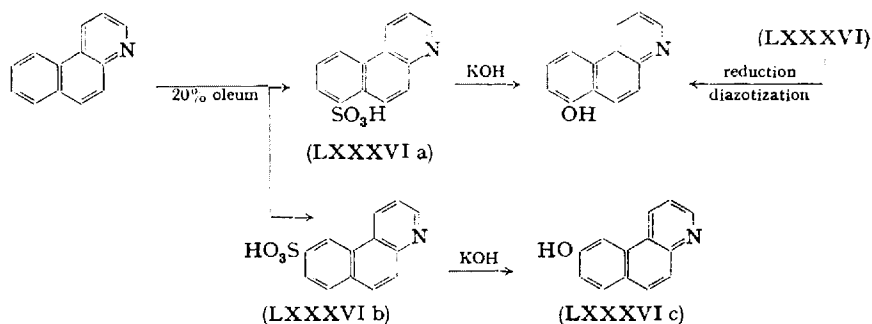
A dinitro compound was obtained by Hepner,¹¹ and reduced to the corresponding diamine. Since oxidation of this latter compound produces quinoline-5,6-dicarboxylic acid, the nitro groups must be in the benzo ring furthest removed from the heterocyclic ring. 7-Nitro 4-azaphenanthrene was nitrated to give a dinitro compound⁵⁹ identical with that described by Hepner¹¹ and, since Hepner¹⁴³ showed that the nitro groups are situated in a position meta to one another, the dinitro compound must be 7,9-dinitro-4-azaphenanthrene. The nitration of the 3-methyl derivative has also been investigated.⁸

The 8- and 10-nitro-4-azaphenanthrenes were prepared by the

Skraup synthesis.⁵⁹ The isomeric 2-nitro-4-azaphenanthrene has been synthesized from 2-nitromalonic aldehyde⁷¹ (see p. 228). Its structure was established by reduction of the nitro group to the amine, which was replaced by hydrogen through the diazo reaction.⁷¹

Nitration of 6-carboxy-4-azaphenanthrene¹²⁴ and 3,6-dicarboxy-4-azaphenanthrene¹²⁵ results in the introduction of a nitro group in the 7-position. This tendency of substituents to enter the benzo ring farthest removed from the ring containing nitrogen, as shown in the examples of nitration just given, is again encountered in several other reactions, as will be shown.

Sulfonation of 4-azaphenanthrene with 20 % oleum at 100° gives three isomers, the principal product (55.3 % yield) is 7-sulfo-4-azaphenanthrene (LXXXVIa). The secondary products are the 9-sulfo (LXXXVIb) (10 % yield) and, presumably, the 5- or 6-sulfo derivative (trace). The 7- and 9-sulfo-4-azaphenanthrenes were identified by their conversion into the corresponding phenols and their benzoates.⁶⁰

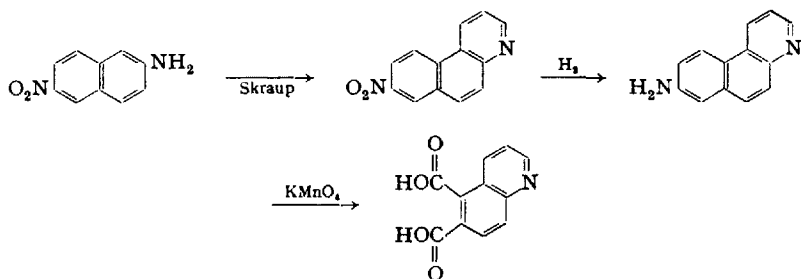


The 7-, 8-, 9-, and 10-monosulfonic acids of 4-azaphenanthrene are prepared from the appropriate aminonaphthalenesulfonic acids by means of the Skraup synthesis. By fusion with potassium hydroxide the corresponding phenols are obtained. The structure of LXXXVIc was thus established.¹²⁶

Thus, direct nitration and sulfonation give substituents in the 7- and 9-positions, with the 7-isomer predominating.

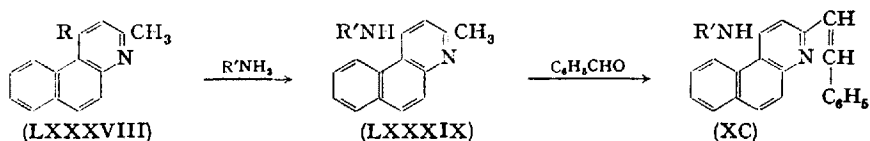
(b) Amino-4-azaphenanthrenes. The 3-amino-,⁷¹ 7-amino-,¹⁵ and 7,9-diamino-4-azaphenanthrenes^{11,59} are prepared by reduction

of the corresponding nitro compounds, the structures of which are known. (See preceding section.) The 8- and 10-amino-4-azaphenanthrenes are synthesized by an application of the Skraup reaction to 6-nitro-2-naphthylamine and 8-nitro-2-naphthylamine, respectively, with subsequent reduction. Oxidation of the 8- and 10-amino-4-azaphenanthrenes to 5,6-quinolinedicarboxylic acid proves that ring closure takes place through the 1-position of the naphthalene ring. The positions of the amino groups are thus established.⁵⁹



1-Amino-3-styryl-4-azaphenanthrene and its derivatives are prepared from 3-methyl-4-azaphenanthrenes substituted in the 1-position by a halogen, alkoxy, hydrazino, carbamido, or carbazido group, by exchanging these substituents for the amino group, and converting the 3-methyl group into a styryl residue.¹

For example, if LXXXVIII (R = halogen or alkoxy) is heated with a primary amine (R' = alkyl or aryl), a substituted 1-amino-3-methyl-4-azaphenanthrene (LXXXIX) is obtained, which is readily converted to the corresponding styryl derivative, XC. If R = NHNH_2 ,

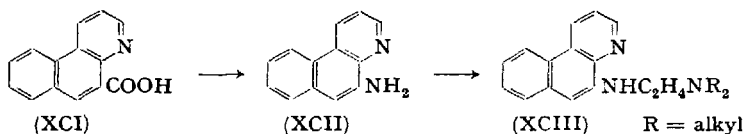


the corresponding primary amine can be obtained by reduction. Again, if R = carbamido or carbazido, the Hofmann or Curtius degradation results in formation of the 1-amino compound. The styryl residue can again be introduced into the molecule in the usual way by condensation with benzaldehyde.¹ 1-Chloro-4-azaphenanthrene is the most

commonly used intermediate, and is produced by the action of phosphoryl chloride on 1-hydroxy-4-azaphenanthrene.⁶⁵

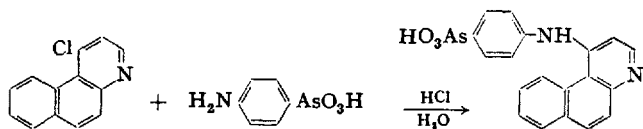
A variation of one of these methods is covered in a British patent,³ e.g., 1-chloro-4-azaphenanthrene is condensed with ethanolamine and the resulting 2-hydroxyethylamine is treated with phosphoryl chloride to give the chloride. The latter reacts smoothly with 2-hydroxyethyldiethylamine to give 2-diethylaminoethoxyethylamino-4-azaphenanthrene. A large number of compounds of this type have been tested as antimalarial agents.

A series of substituted 5-amino-4-azaphenanthrene derivatives has been synthesized for study in connection with the antimalarial program.² 5-Carboxy-4-azaphenanthrene (XCI) is made by a Skraup reaction, and the carboxy group is converted into an amino group by a Curtius reaction. The resulting 5-amino-4-azaphenanthrene (XCII), in contrast to the 1- and 3-amino isomers, can be diazotized and coupled with 2-naphthol. The amine, XCII, has been condensed with various dialkylaminoethyl bromides to produce 5-(2-dialkylaminoethylamino)-4-azaphenanthrenes (XCIII). It is interesting to note that the 7-, 8-, and 10-amino-4-azaphenanthrenes cannot be alkylated.²



A few *N*-aryl-1-amino-4-azaphenanthrenes have been reported by Dziewoński and co-workers.^{27,54} The methods of preparation have been described in Sections B1 and Bm.

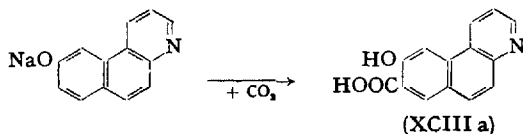
Arsenicals containing the 4-azaphenanthrene nucleus are obtained by treating the appropriate anilinoarsonic acid with 1-chloro-4-azaphenanthrene in aqueous solution.⁷²



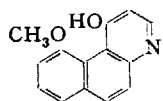
No report has been made as to the action of sodium amide on the parent base, but 1-amino-3-phenyl-4-azaphenanthrene was obtained

in fair yield by the interaction of potassium amide (and potassium nitrate) on 1-carboxamido-3-phenyl-4-azaphenanthrene.¹⁰¹

(c) Hydroxy-4-azaphenanthrenes. Of the nine possible isomeric hydroxy-4-azaphenanthrenes, seven are known, the exceptions being the 2- (*cf.* reference 128a for a method of synthesis for the 2-isomer) and the 6-isomers. 1-Hydroxy-4-azaphenanthrene is made indirectly, by decarboxylation of 3-carboxy-1-hydroxy-4-azaphenanthrene.⁶⁵ Fusion of the parent base with potassium hydroxide at 250–60° produces 3-hydroxy-4-azaphenanthrene in about 50 % yield.¹³⁰ The 5-, 7-, 8-, and 9-isomers are produced by application of the Skraup synthesis.^{2,60,121,122,126} Their use as azo-dye components has been described.¹⁷⁵ The 7- and 9-isomers have been found to react with carbon dioxide in the presence of sodium hydroxide under pressure (Kolbe synthesis) to produce hydroxy-4-azaphenanthrenecarboxylic acids (XCIIIa).^{121,144}

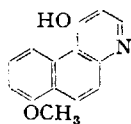


The 1- and 3-hydroxy-4-azaphenanthrenes and their derivatives are converted smoothly to the corresponding chlorides by the action of phosphoryl chloride. However, a methoxyl substituent in the 10-position prevents the formation of the chloride. Thus, 1-hydroxy-10-methoxy-4-azaphenanthrene (XCIIIb) fails to form a chloride under these conditions. The authors believe that a group in the 10-position exerts a blocking effect upon the 1-position of the nucleus. Furthermore, XCIIIb differs widely from XCIIIc and XCIIId in other properties, namely, melting point, color, and solubility in alkali.⁶⁸



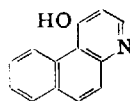
(XCIII b)

m.p. 188°,
yellow,
insol. in OH⁻



(XCIII c)

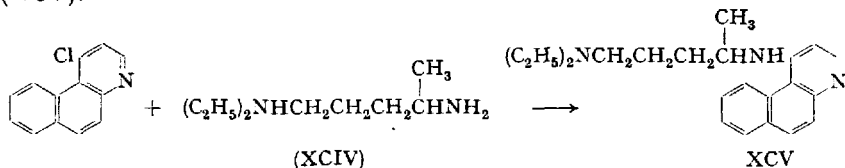
m.p. 309°,
white,
sol. in OH⁻



(XCIII d)

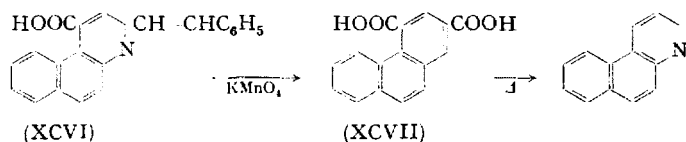
m.p. 288°,
white
sol in OH⁻

The chlorides recently have attained significance as intermediates in the synthesis of therapeutically valuable compounds.^{1,3,4,14,49,59,72,78} For example: 5-diethylamino-2-aminopentane (XCIV) was condensed with 1-chloro-4-azaphenanthrene, according to directions in a British patent,³ to give 1-(5-diethylamino-2-pentylamino)-4-azaphenanthrene (XCV).



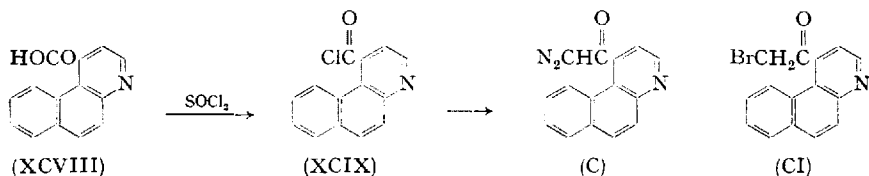
(d) Carboxy-4-azaphenanthrenes. The carboxylic acids of the 4-azaphenanthrene series having no other substituents in the ring have not been as thoroughly investigated as the hydroxy compounds. Only four of the monocarboxylic acids and two of the dicarboxylic acids are known. 1-Carboxy-4-azaphenanthrene was obtained by a Doebner synthesis from 2-naphthylamine, pyruvic acid, and formaldehyde; the yield was 35%.²⁸ 3-Carboxy-4-azaphenanthrene initially was obtained by oxidation of the corresponding benzoquinaldine⁸ and later by hydrolysis of 3-cyano-4-azaphenanthrene.¹²⁰

The 5- and 6-carboxy-4-azaphenanthrenes are made by application of the Skraup reaction to 3-amino-2-naphthoic acid and 3-amino-1-naphthoic acid, respectively. Doubtless, the remaining isomers, with the exception of the 2, could be made in a similar manner. The 1,3-dicarboxylic acid is synthesized in the following manner: The reaction product, XCVI, of cinnamaldehyde, pyruvic acid, and 2-naphthylamine is oxidized in the cold with potassium permanganate to give the dicarboxylic acid, XCVII. Since this acid gives 4-azaphenanthrene on decarboxylation, the initial condensation product must have the 4-azaphenanthrene ring structure.⁹ The structure of XCVII has been confirmed by an independent synthesis.¹⁰³



The isomeric 3,6-dicarboxy-4-azaphenanthrene is obtained by an application of the Doebner-Miller reaction, using acetaldehyde and 3-amino-1-naphthoic acid. The 3-methyl-6-carboxy-4-azaphenanthrene that results is oxidized smoothly with selenium dioxide to the corresponding dicarboxylic acid.¹²⁵

An interesting series of reactions was carried out by Benson and Hamilton¹³⁶ on 1-carboxy-4-azaphenanthrene. The acid, XCVIII, was converted to the chloride, XCIX, by treatment with thionyl chloride. The addition of XCIX to an ethereal solution of diazomethane yielded 1-diazoacetyl-4-azaphenanthrene (C), which on treatment with 48 % hydrobromic acid resulted in the formation of 1-bromoacetyl-4-azaphenanthrene (CI).



D. Reactions of the Ring

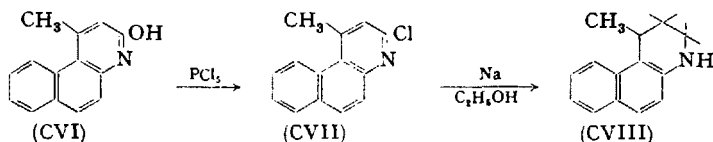
(I) Reduction

4-Azaphenanthrene (CII) is reduced to the 1,2,3,4-tetrahydro derivative, CIII, by the action of tin and hydrochloric acid.⁵ It behaves chemically like a 1-substituted 2-naphthylamine; for example, it will not form an azo dye under any conditions. When it is brought into reaction with a diazonium salt, a diazoamino compound is formed. In contrast, 1,2,3,4-tetrahydro-1-azaphenanthrene readily forms azo dyes. The tetrahydro base, CIII, is readily nitrosated and acetylated. 3-Methyl-4-azaphenanthrene, under the same reducing conditions, gives 3-methyl-1,2,3,4-tetrahydro-4-azaphenanthrene.

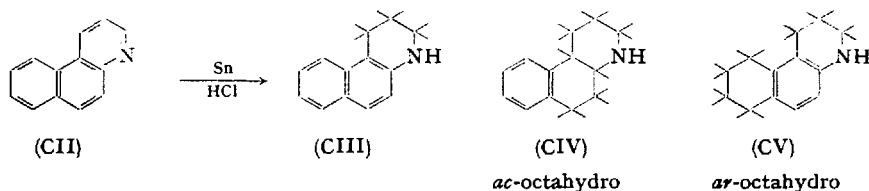
3-Methyl-1,2,3,4-tetrahydro-4-azaphenanthrene has been resolved into its optically active components by means of α -bromocamphor- π -sulfonic acid.²²

The isomeric 1-methyl-1,2,3,4-tetrahydro-4-azaphenanthrene has been obtained by converting 3-hydroxy-1-methyl-4-azaphenanthrene

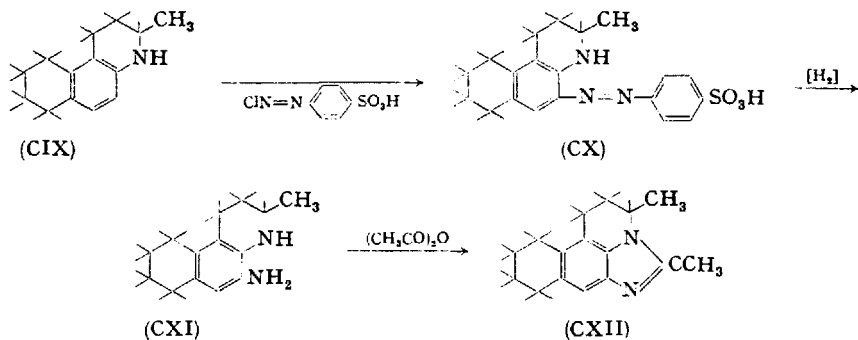
(CVI) into the chloro compound, CVII, which can be reduced smoothly to the tetrahydro compound, CVIII,⁴⁹ with sodium and ethanol.



If sodium and amyl alcohol are used as the reducing agent on 4-azaphenanthrene, a mixture of *ac*-octahydro (CIV) and *ar*-octahydro-4-azaphenanthrene (CV) is produced. The isomers are separated by precipitation of the *ac*-octahydro derivative from ligroin with moist carbon dioxide. The *ar*-octahydro compound is always formed in greater amount than the *ac*-octahydro compound.¹⁵³



3-Methyl-4-azaphenanthrene behaves toward sodium and amyl alcohol in a similar manner. The resulting 3-methyl-*ar*-octahydro-4-azaphenanthrene has been investigated intensively.¹⁵⁴ If benzenediazonium chloride is added to an aqueous solution of the base in the presence of sodium acetate, a diazoamino compound is formed. If the



sodium acetate is omitted, phenylazo-*ar*-octahydro-4-azaphenanthrene results. The position of the azo group was shown by coupling the *ar*-

octahydro base (CIX) with diazotized sulfanilic acid. The azo dye (CX) thus formed was reduced with zinc dust, and the resulting solution of amine (CXI) was treated directly with acetic anhydride. An imidazole (CXII) was formed, a reaction characteristic of orthodiamines. Hence, the azo group must be linked through the 5-position of the azaphenanthrene nucleus.

Shimomura and Cohen¹⁵² examined the ultraviolet absorption spectra of 1,2,3,4-tetrahydro and 1,2,3,4,7,8,9,10-octahydro-4-azaphenanthrene in the hope of finding a relation between the hydrogenated derivatives and the completely aromatic base. As a result of their work it has been shown that: (a) the hydrogenated compounds show quite a different absorption spectrum from the original; (b) the absorption curve shown by tetrahydro-4-azaphenanthrene is very similar in its general form to that of the corresponding alkylated 2-naphthylamine; (c) as the degree of unsaturation increases, the tendency to exhibit distinct absorption bands decreases; and (d) although 1- and 4-azaphenanthrenes show rather similar absorptions, those of their tetrahydro derivatives are entirely different. They concluded that a compound having the structure of an α -alkyl-2-alkylaminonaphthalene will have ultraviolet absorption spectra similar to 1,2,3,4-tetrahydro-4-azaphenanthrene.

The reduction of 4-azaphenanthrene at the dropping mercury electrode has been studied.¹⁷³

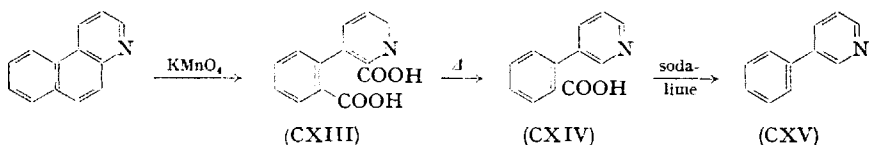
Gould and Jacobs¹²⁸ have found that a hydroxyl group in the heterocyclic ring prevents reduction of that ring, both catalytic and chemical, under normal conditions. In contrast, a carboxyl group in the heterocyclic ring has no effect on the reduction. 1-Carboxy-3-phenyl-4-azaphenanthrene is readily reduced by sodium amalgam to 1-carboxy-3-phenyl-1,2,3,4-tetrahydro-4-azaphenanthrene.²⁶

1-Methyl-4-azaphenanthrene was prepared from 3-chloro-1-methyl-4-azaphenanthrene by reduction with tin and hydrochloric acid and also by hydrogenation over a palladium-on-barium sulfate catalyst. The products by the two methods were identical and melted at 98–9°. ¹³⁶ Reed⁷⁹ obtained the same base by the condensation of 2-naphthylamine, methylal, and acetone, and reported a melting point of 112°, while Knorr⁷⁸ and Gibson *et al.*,⁴⁹ who prepared the methyl

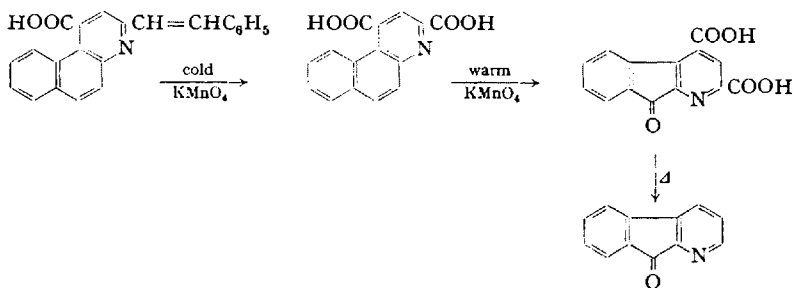
compound by distillation of 3-hydroxy-1-methyl-4-azaphenanthrene with zinc dust, report a melting point of $91-2^{\circ}$.

(2) Oxidation

In 1883, 4-azaphenanthrene itself was synthesized and subjected to the action of potassium permanganate in an attempt to elucidate its structure.⁴ The initial product was 3-(2-carboxyphenyl)-2-carboxypyridine (CXIII). This dicarboxylic acid was pyrolyzed to give 3-(2-carboxyphenyl)pyridine (CXIV). The last carboxyl group was eliminated with soda-lime, giving 3-phenylpyridine (CXV). Hence, the synthesis must have involved cyclization through the 1-position of the 2-naphthylamine nucleus.

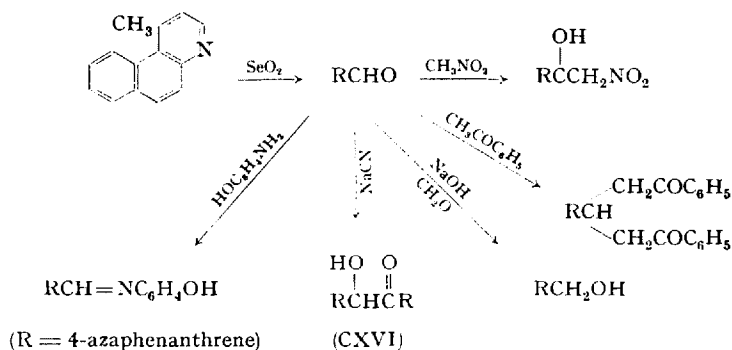


In a somewhat similar series of reactions, Doebner demonstrated the structure of 3-styrylbenzocinchoninic acid.⁹

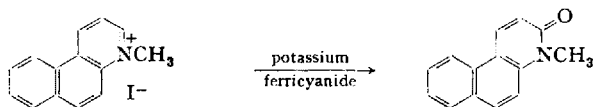


Cleavage of the central ring in the 5,6-positions by potassium permanganate is characteristic of the 4-azaphenanthrene ring system. 4-Azaphenanthrene-10-sulfonic acid,⁸¹ 3-phenyl-4-azaphenanthrene,⁸⁸ and 3-(2-nitrophenyl)-5,6-benzocinchoninic acid⁸⁷ have been oxidized to the corresponding 3-(2-carboxyphenyl)-2-carboxypyridines. In all three instances the bond at the 5,6-positions was cleaved by the action of potassium permanganate as in phenanthrene.

1-Formyl-4-azaphenanthrene is obtained in 63 % yield by the oxidation of the corresponding methyl compound with selenium dioxide.¹³⁶ A small amount of acid is also formed. The formyl derivative can be condensed with nitromethane, quinaldine, or acetophenone to give the expected products. A benzoin-type reaction gives 1,1'-(4-azaphenanthroin) (CXVI), while a crossed Cannizzaro reaction gives 1-methylol-4-azaphenanthrene. Several amines have been condensed with the formyl compound to give anils, which can be reduced to the amines with zinc dust and sodium hydroxide or with palladium-on-barium sulfate.



Oxidation of the quaternary salts of 4-azaphenanthrene with potassium ferricyanide gives products similar to those obtained from other related heterocyclic bases. Thus the methiodide salt of 4-azaphenanthrene with potassium ferricyanide gives 3-oxo-4-methyl-4-azaphenanthrene.^{2, 10, 48}

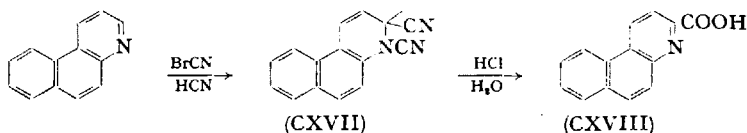


(3) Halogenation

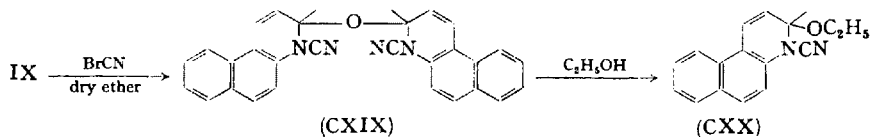
Bromination of 4-azaphenanthrene in the presence of hydrobromic acid results in the formation of the 3-bromo derivative. The structure has been proved by oxidation to 2-bromo-5-carboxypyridine.¹⁰

The action of chlorine upon the *N*-oxides of 4-azaphenanthrenes has been utilized for the preparation of 1- and 3-chloro-4-azaphenanthrenes. A mixture of these two chloro compounds has been prepared by the action of phosphoryl chloride on the *N*-oxide of 4-azaphenanthrene.⁷⁰

The action of a mixture of cyanogen bromide and hydrogen cyanide on 4-azaphenanthrene in benzene gives a mixture of products,¹⁶ which are considered to be the *cis* and *trans* isomers of 3,4-dicyano-3,4-dihydro-4-azaphenanthrene (CXVII),¹²⁹ hydrolysis of which produces 3-carboxy-4-azaphenanthrene (CXVIII).



ether alone, however, gives an entirely different result. A bimolecular product, CXIX, is formed which, on solution in ethanol, gives 4-cyano-3-ethoxy-3,4-dihydro-4-azaphenanthrene (CXX).¹²⁹

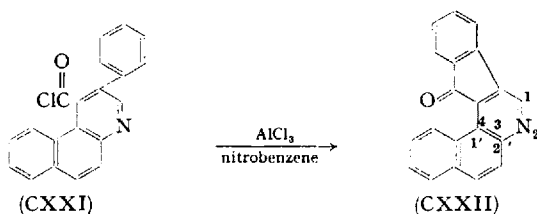


(4) Friedel-Crafts

Substituted benzocinchoninic acids have been utilized by Borsche and Sinn⁵⁷ as intermediates in the synthesis of polynuclear hetero-

cycles. 1-Carboxy-3-phenyl-4-azaphenanthrene is unchanged by aluminum chloride in nitrobenzene at 50° for 8 hours or by concentrated sulfuric acid at 100° for 2 hours. However, the same acid, when converted to the chloride and treated with benzene in the presence of aluminium chloride, readily gives 1-benzoyl-3-phenyl-4-azaphenanthrene.

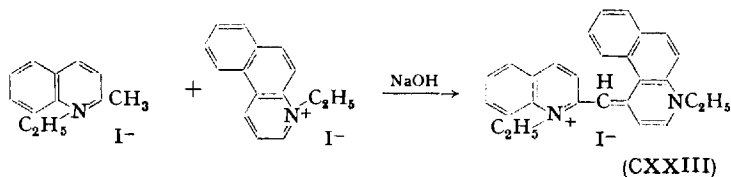
In contrast, the acid chloride of 1-carboxy-2-phenyl-4-azaphenanthrene (CXXI), in the presence of aluminum chloride and nitrobenzene, gives 3,4(1',2')-naphtho-2-aza-9-oxofluorene (CXXII) very smoothly.



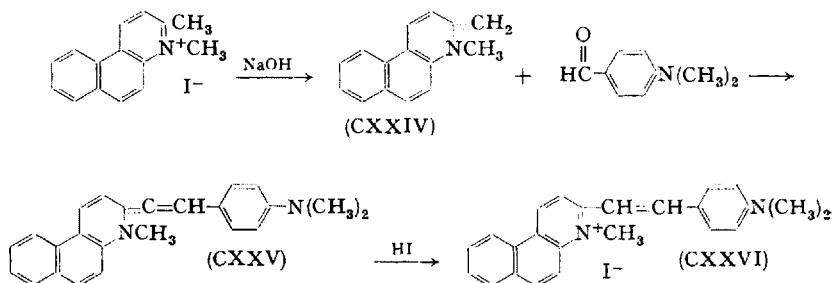
1-Carboxy-3-isopropyl-2-phenyl-4-azaphenanthrene gives similar results.

(5) Cyanine Dyes

In a German patent¹² it is reported that 3-methyl-1-azaphenanthrene quaternary salts are not capable of cyanine dye formation, nor do they give dyes with 4-azaphenanthrene quaternary salts. In contrast, the latter yield cyanine dyes with the alkyl halide salts of quinoline and 6- and 7-methylquinolines, but not with 8-methylquinoline. However, both the 1- and 4-azaphenanthrene alkyl halide salts form dyes of this type with quaternary salts of quinaldine and of 6- and 7-methylquinaldine. The new dyes are said to be excellent photographic sensitizers. For example, quinaldine ethiodide and 4-azaphenanthrene ethiodide condense in the presence of alkali to yield 1,1'-diethyl-5',6'-benzo-2,4'-cyanine iodide (CXXIII).



In investigating the mechanism of cyanine dye formation, it was found¹¹⁹ that 3-methyl-4-azaphenanthrene methiodide with cold aqueous alkali gives a crystalline methylene base, CXXIV. When an alcoholic solution of this methylene base is heated with 4-dimethylaminobenzaldehyde, condensation to CXXV takes place readily without the need of a catalyst. It is immediately converted by hydriodic acid into the purple styryl dye, CXXVI, which can also be formed by treating 3-methyl-4-azaphenanthrene methiodide with 4-dimethylaminobenzaldehyde and piperidine.



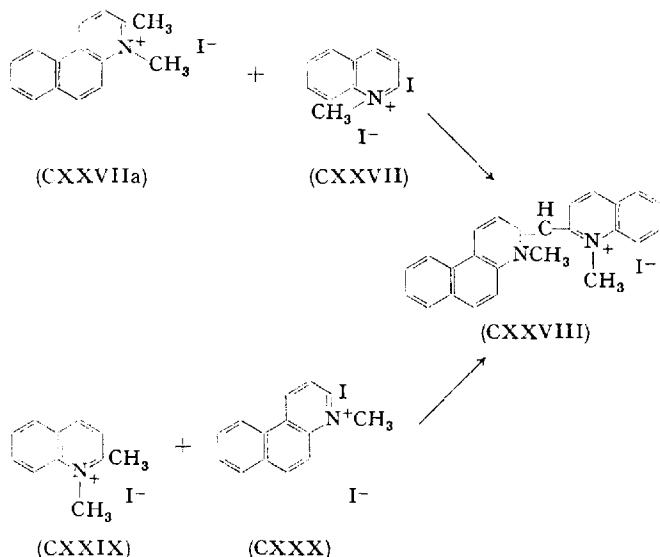
In a similar manner, 3-methyl-4-azaphenanthrene ethobromide, formaldehyde, and the methylene base from quinaldine ethiodide give an unsymmetrical carbocyanine.

Three symmetrical cyanines containing two 4-azaphenanthrene nuclei have been prepared by condensing an alkiodide of 3-iodo-4-azaphenanthrene with a 3-methyl-4-azaphenanthrene alkiodide.⁴⁸ The condensation proceeds normally. As compared with the corresponding cyanines with two quinoline nuclei, their absorption bands are usually shifted somewhat toward the red end of the spectrum. These dyes are said to be powerful photographic sensitizers.

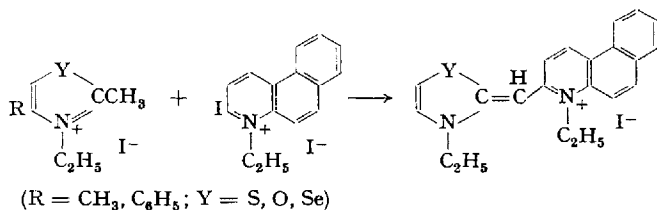
Cyanines containing one quinoline nucleus and one 4-azaphenanthrene nucleus (*e.g.*, CXXVIII) are obtainable by: (a) condensation of a 2-iodoquinoline alkiodide (CXXVII) with a 3-methyl-4-azaphenanthrene alkiodide (CXXVIIa) (two members of this series have been prepared),¹⁵¹ or (b) condensation of a quinaldine alkiodide (CXXIX) with a 3-iodo-4-azaphenanthrene alkiodide (CXXX).⁴⁸

Brooker, Keyes, and White¹⁵⁹ have investigated the formation of 2'-cyanine dyes further and have found that triethylamine is an

excellent condensing agent for this reaction. They have succeeded in condensing with 3-iodo-4-azaphenanthrene ethiodide the quaternary

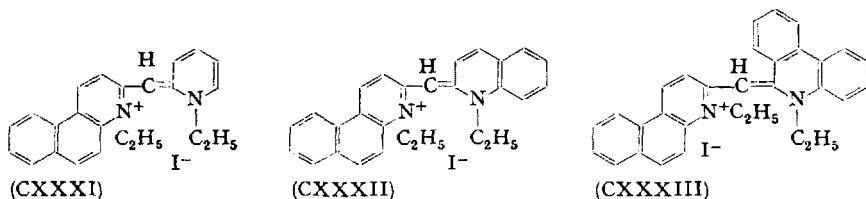


salts of several compounds containing five-membered rings: 2-methyl, 2,4-dimethyl, and 2-methyl-4-phenylthiazole; 2-methyl-4-phenyloxazole; and 2,4-dimethylselenazole. These new dyes are all photographic sensitizers. 3-Iodo-4-azaphenanthrene¹⁶⁰ ethiodide was con-



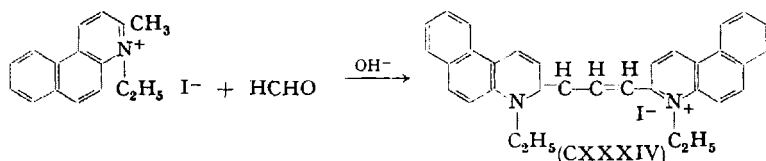
densed with α -picoline ethiodide and 6-methylphenanthridine to yield the dyes, CXXXI and CXXXIII, respectively, while 3-methyl-4-azaphenanthrene ethiodide and 2-iodoquinoline ethiodide gave CXXXII. These may be considered as derived from the simpler dyes, 1,1'-diethyl-2-pyrido-2'-cyanine iodide, 1,1'-diethyl-2,2'-cyanine iodide, and 1,1'-diethyl-3,4-benzo-2,2'-cyanine iodide by the attachment of an additional benzene residue, and the effect on the absorption spectra of

introducing the latter can be observed. In all three cases, replacement of a quinoline ring by a 4-azaphenanthrene ring is accompanied by a



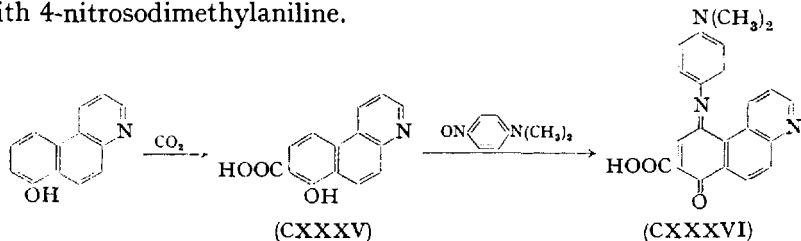
shift in the position of maximum absorption toward the red.

A carbocyanine of the 4-azaphenanthrene series that is a powerful photographic sensitizer has been reported by Mees and Gutekunst.^{182, 183} 3-Methyl-4-azaphenanthrene ethiodide and formaldehyde are mixed in the presence of potassium hydroxide, and the resulting 1,1'-diethyl-di- β -naphthcarbocyanine iodide (CXXXIV) precipitates immediately. It is a sensitizer for the deep red. The absorption spectra for a few

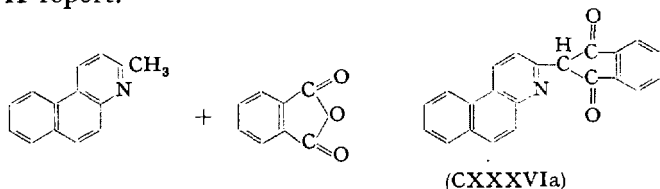


cyanine dyes of the 4-azaphenanthrene series, which act as reversible polymers in solutions of high dye concentration, have also been reported.¹⁶¹

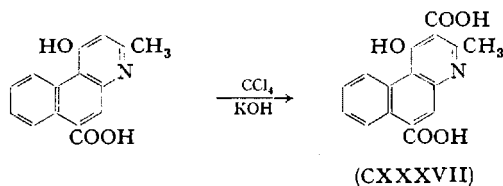
A patent covers the use of certain azaphenanthrenes as azomethine dye intermediates.¹⁴⁴ For example, 7-hydroxy-4-azaphenanthrene is converted to the carboxy acid, CXXXV, by means of carbon dioxide and sodium hydroxide (*cf.* p. 232). (A long-chain, aliphatic radical may be introduced into the molecule by means of the carboxyl group in order to confer nondiffusibility to the molecule.) The resulting compound gives blue dye images of the type CXXXVI when treated with 4-nitrosodimethylaniline.



A dye (CXXXVIa) of the quinoline yellow type has been reported in a FIAT report.¹⁸⁹

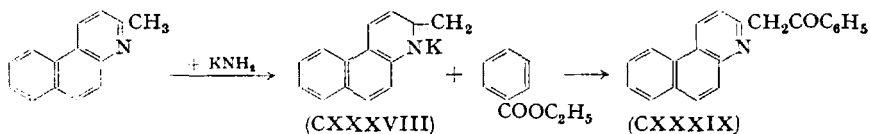


In an application of the Tiemann-Reimer reaction to 6-carboxy-1-hydroxy-3-methyl-4-azaphenanthrene, the dicarboxylic acid, CXXXVII, was obtained in about 50 % yield.¹²⁸



(6) With Alkali Metals

During the investigation of the action of potassium amide on certain heterocyclic nitrogen compounds, it was found that 3-methyl-4-azaphenanthrene was converted smoothly to the potassium salt, CXXXVIII.¹⁴⁶ Bergstrom and Moffat made use of this reaction to synthesize 3-phenacyl-4-azaphenanthrene (CXXXIX) by allowing



ethyl benzoate to react with the alkali-metal salt.⁵⁶ This reaction should be capable of many variations and merits further investigation.

4-Dimethylaminophenyllithium adds to the azomethine linkage of 4-azaphenanthrene to give a 62 % yield of 3-(4-dimethylaminophenyl)-3,4-dihydro-4-azaphenanthrene. This latter product is readily dehydrogenated to the completely aromatic compound in boiling nitrobenzene.¹⁸²

E. Properties

(1) *Physical*

4-Azaphenanthrene is a weak base that crystallizes from water or petroleum ether in leaflets, m.p. 94° ,^{9, 10, 28, 59, 71, 176} and boils at 340° ¹⁰ [349.5–350° corr. at 721 mm.].⁵ It is not very volatile with steam.⁴ It is only sparingly soluble in water, but is very soluble in alcohol, ether, benzene, and dilute acids.⁴ Its density and the dispersion of a solution in benzene have been reported.¹⁵⁵ On storage, it becomes yellow-brown. Its alcoholic solution with copper acetate gives a green color and a precipitate of green prism-like crystals.⁴ Ferric chloride colors an alcoholic solution brown.⁴ The ultraviolet absorption spectrum of 4-azaphenanthrene has five maxima as shown in the table.^{69, 145, 168}

$\lambda_{\text{max.}}, \text{\AA}^{\circ}$	log <i>E</i>
2335	4.58
2670	4.30
3150	3.17
3290	3.43
3440	3.53

It is also worthy of note that 3-methyl-1,2,3,4-tetrahydro-4-azaphenanthrene exhibits a remarkable blue fluorescence, which is best observed in benzene or alcohol solution.²²

(2) *Chemical*

4-Azaphenanthrene readily forms quaternary ammonium salts that may be converted to the chromates and sulfates: $[(\text{C}_{13}\text{H}_9\text{NCH}_3)\text{Cl}]$, m.p. 236° ; $(\text{C}_{13}\text{H}_9\text{NCH}_3)\text{I} \cdot 2\text{H}_2\text{O}$, m.p. 186° ; $(\text{C}_{13}\text{H}_9\text{NCH}_3)_2 \cdot \text{Cr}_2\text{O}_7 \cdot 2\text{H}_2\text{O}$ m.p. 232° ; $(\text{C}_{13}\text{H}_9\text{NC}_7\text{H}_7)_2 \cdot \text{C}_2\text{H}_7 \cdot 2\text{H}_2\text{O}$, m.p. 200° .¹⁰ Silver oxide reacts with the methochloride to give the ether-insoluble quaternary ammonium base, which is rearranged by alkali to the ether-soluble pseudo base. This behavior is in contrast to the corresponding derivative of quinoline, which gives the pseudo base immediately on treatment with silver oxide. The pseudo base on treatment with bromine gives 3-bromo-4-azaphenanthrene.¹⁰

4-Azaphenanthrene forms a 1:1 molecular complex with *sym*-trinitrobenzene,¹⁷ as does its 1,2,3,4-tetrahydro derivative.²⁰ Several simple salts have been described: the hydrochloride,^{4,7} the sulfate,^{10, 158} and the chromate,^{4,10} as well as the complex salts, $C_{13}H_9.NHCl.ClI$ ¹⁵⁷ and $2C_{13}H_9.NH.2HCl.PtCl_4.XH_2O$.^{7,8} The picrate melts at $251-2^\circ$.^{4,176}

Molecular diagrams have been utilized in studies of the reactivity of 4-azaphenanthrene.¹⁸⁶

(3) *Physiological*

The 1-amino-3-styryl-4-azaphenanthrenes possess bactericidal properties.¹ The 2-diethylaminoethylamino group and various closely related groups have been introduced into the 4-azaphenanthrene nucleus during the course of antimalarial work, but none of this series has been especially active.^{1, 3, 4, 49, 72, 78}

The physiological properties of the 7-nitro and 7,9-dinitro-4-azaphenanthrenes have also been investigated.⁵⁰ Effects produced by all these compounds are central paralysis and a marked drop in temperature. The heart is stopped in systole.

The cationic ionization of 4-azaphenanthrene derivatives has been correlated with antibacterial activity. It has been found that a high degree of cationic ionization markedly increases the antibacterial action in the isomeric azaphenanthrenes. At least 50% ionization at 20° is required for full activity.¹⁸⁵

The antiseptic properties of 4-azaphenanthrene and some of its hydrogenated derivatives were examined by Shimomura and Cohen.¹⁵²

F. Uses

4-Azaphenanthrene derivatives have been used in the synthesis of cyanine and azomethine dyes (Section D5) and have also been of some value as medicinals, for example, Diapurin, the trade name applied to 1-carboxy-3-phenyl-4-azaphenanthrene. The 3-methyl derivative has been used for the separation of sulfonic acids from sulfite waste liquors.⁶⁴

Tellurium chloride has been found to react with 1-carboxy-3-phenyl-4-azaphenanthrene in carbon tetrachloride solution to form 4-(1-carboxy-4-azaphenanthrene-3)phenyltellurium trichloride. It is

quantitatively converted to the corresponding oxychloride by treatment with water.¹⁰²

Intermediates for azomethine dyes that are of use in photography have been made by condensing amines of the 4-azaphenanthrene series with compounds containing an active methylene group such as ethyl acetoacetate.¹⁶⁵

4-Azaphenanthrene is used as an analytical reagent for the determination of cadmium.¹⁸¹

TABLE III-1. Alkyl and Aryl 4-Azaphenanthrenes

Substituent and position	M.p., °C.	Refs.
(a) Alkyl-4-azaphenanthrenes		
1-CH ₃ -	100	49, 53, 76, 77, 79, 136, 169, 171, 183
2-CH ₃ -	81	52, 58, 64, 74, 75, 171
3-CH ₃ -	133	8, 28, 74, 171
3-C ₂ H ₅ -	63	75
3-CH ₂ =CHCH ₂ -	78	75
3-(CH ₃) ₂ -CH-	77	75
3-CH ₃ CH=C(CH ₃)-		75
3-(CH ₃) ₂ CH-7-CH ₃ -	115	62, 67
3-CH ₃ CH ₂ CH(CH ₃)-	55	75
3-CH ₃ (CH ₂) ₅ -	83	75
1,3-CH ₃) ₂ -	127	58, 61, 69, 79, 80
2,3-(CH ₃) ₂ -	125	66
(b) Aryl-4-azaphenanthrenes		
1-C ₆ H ₅ -	187	55
2-C ₆ H ₅ -	111	18, 44, 99
2-C ₆ H ₅ -3-CH ₃ -	101	8, 18, 44
2-C ₆ H ₅ -3-(CH ₃) ₂ CH-	124	57
2-C ₆ H ₅ CH ₂ -3-C ₆ H ₅ -	152	18
3-C ₆ H ₅ -	188	87, 114, 115
3-C ₆ H ₅ -1-CH ₃ -	152	23
3-C ₆ H ₅ CH=CH ₂ -	175	9
3-(CH ₃) ₂ CHC ₆ H ₄ -	150	75
1,3-(C ₆ H ₅) ₂ -	146	51, 184
2,3-(C ₆ H ₅) ₂ -	180	18, 44
3-(2-CH ₃ -5-C ₄ H ₂ S)-	177	172
3-(2-C ₄ H ₃ O)-	94	75

TABLE III-2. Hydrogenated 4-Azaphenanthrenes

Substituent and position	M.p., °C.	Refs.
(a) Dihydro-4-azaphenanthrenes		
3-HO-1,2-dihydro-	245	188
1-COOH-3-[4-(CH ₃) ₂ NC ₆ H ₄]-3,4-dihydro-	275	86
3-C ₆ H ₅ -1,2-dihydro-	226	87, 88
3-[4-(CH ₃) ₂ NC ₆ H ₄]-1,2-dihydro-	275	87
3-(CH ₂ =)-4-CH ₃ -3,4-dihydro-	80	119
1-COOH-3-[4-(CH ₃) ₂ NC ₆ H ₄]-3,4-dihydro-	275	86
3-[4-(CH ₃) ₂ NC ₆ H ₄]-3,4-dihydro-	139	82
3-HO-4-CN-3,4-dihydro-	200	129
3-CH ₃ O-4-CN-3,4-dihydro-	159	129
3-C ₂ H ₅ O-4-CN-3,4-dihydro-	128	129
3-C ₃ H ₇ O-4-CN-3,4-dihydro-	72	129
5,6-dihydro-	P 206	176
5-COOCH ₃ -5,6-Cl ₂ -5,6-dihydro-	135	63
(b) 1,2,3,4-Tetrahydro-4-azaphenanthrenes		
1-H-	93.5	5
1-CH ₃ -		49
1-COOH-3-(2-C ₄ H ₃ O)-	200	94
1-COOH-3-C ₆ H ₅ -	224	26, 47
1-COOH-3-(4-CH ₃ OC ₆ H ₄)-	234	47
1-COOCH ₃ -3-(4-CH ₃ OC ₆ H ₄)-	144	47
1-COOH-3-(3,4-CH ₂ O ₂ -C ₆ H ₃)-	233	47
1-COOCH ₃ -3-C ₆ H ₅ -	134	86
1-COOH-3-C ₆ H ₅ -4-C ₆ H ₅ CO-	221	86
1-COOCH ₃ -3-C ₆ H ₅ -4-C ₆ H ₅ CO-	211	86
2,6-(COOH) ₂ -4-CH ₃ -7-NH ₂ -	230-5	71
3-CH ₃ -	52	22, 5
3-C ₆ H ₅ -	234	26
3-CH ₃ -4-NO-	69	5
3-CH ₃ -4-CH ₃ O-	86	5
3-COOCH ₃ -6-COOH-7-NH ₂ -	234-6	125
3-COOC ₂ H ₅ -6-COOH-7-NH ₂ -	240-2	125
3,6-(COOH) ₂ -7-NH ₂ -	237-9	125
4-NO-	105.5	5
4-CH ₃ CO-	77	5
4-C ₆ H ₅ N=N-	97	5
4-CH ₃ -6-COOH-7-NH ₂ -	221	125
4-CH ₃ -		
6-COOH-7-NH ₂ -	249	45
7,8,9,10-Tetrahydro-	158	25

(Table continued)

TABLE III-2 (*continued*)

Substituent and position	M.p., °C.	Refs.
(c) Octahydro-4-azaphenanthrenes		
1,2,3,4,4a,5,6,10b-octahydro-	91	153
3-CH ₃ -1,2,3,4,4a,5,6,10b-octahydro-	Not given	154
4-NO-octahydro-	122	153
4-CH ₃ CO-octahydro-	110	153
4-C ₆ H ₅ N=N-	95	153
6-HOCH ₂ -7-NH ₂ -		45
1,2,3,4,7,8,9,10-octahydro-	60	153
3-CH ₃ -1,2,3,4,7,8,9,10-octahydro-	75	154
4-NO-1,2,3,4,7,8,9,10-octahydro-	106	153
4-CH ₃ CO-octahydro-	69	153
4-NO-3-CH ₃ -octahydro-	86	154
4-CH ₃ CO-3-CH ₃	92	154
4-(C ₆ H ₅ N=N)-3-CH ₃ -octahydro-	98	154
5-(C ₆ H ₅ N=N)-3-CH ₃ -octahydro-		154
3,6-(COOH) ₂ -7-NH ₂ -1,2,3,4,5,6,6a,10a-octahydro-	232-6	125
6-HOCH ₂ -7-NH ₂ -1,2,3,4,5,6,6a,10a-octahydro-	248-9	45
7-COOH-5-HO-3-(CH ₃) ₂ CH-7,10a-(CH ₃) ₂ - 5,6,6a,7,8,9,10,10a-octahydro-		62
3-(CH ₃) ₂ CH-7,10a-(CH ₃) ₂ -5,6,6a,7,8,9,10,10a- octahydro-		62
3-(CH ₃) ₂ CH-7,10a-(CH ₃) ₂ -5-oxo-5,6,6a,7,8,9,10,10a- octahydro-		62

TABLE III-3. Halogenated Derivatives

Substituent and position	M.p., °C.	Refs.
1-Cl-	67	65, 70
1-Cl-3-CH ₃ -	100	171
1-Cl-2-C ₂ H ₅ -	42	3
1-Cl-9-Br-	143	3
2-Cl-1,3-(CH ₃) ₂ -	144	166
3-Cl-	112	14, 48, 70
3-Cl-1-CH ₃ -	158	76, 77, 136, 171
3-Br-	117	10
3-(2-ClC ₆ H ₄)-1-(6-C ₁₃ H ₉ N)-	260	180
5-Br-1,3-(C ₆ H ₅) ₂ -	153	184
7-Br-	122	187
10-Br-	165	187

TABLE III-4. Nitro Derivatives

Substituent and position	M.p., °C.	Refs.
1-NO ₂ CH ₂ CH(OH)-	170	136
2-NO ₂ -	156	71
7-NO ₂ -	173	10, 11, 15, 50, 59, 60
8-NO ₂ -	240	59
10-NO ₂ -	145	59
7,9-(NO ₂) ₂ -	250	11, 50, 59

TABLE III-5. Sulfo Derivatives

Substituent and position	M.p., °C.	Refs.
7-SO ₃ H-	375-6	60, 126
8-SO ₃ H-	440	126
9-SO ₃ H-	420	60, 126
10-SO ₃ H-	355-6	81, 126
α -SO ₃ H-1,3-(CH ₃) ₂ -		79
α,α' -(SO ₃ H) ₂ -1,3-(CH ₃) ₂ -		79
1-Carboxy-3-(2-HOC ₆ H ₄ -)-8-SO ₃ H		190

TABLE III-6. Amino-4-azaphenanthrenes

Substituent and position	M.p., °C.	Refs.
1-NH ₂ -	150	63, 71, 177
1-NH ₂ -3-CH ₃ -	164	1, 177
1-CH ₃ CONH-	192	63
1-C ₆ H ₅ CH=N-	202-5	136
1-(4-HOC ₆ H ₄ CH=N-)-	241-2	136
1-C ₆ H ₅ NH-3-C ₆ H ₅ -	194	27
1-O(CH ₂ CH ₂) ₂ N-	146-8	65
1-C ₅ H ₁₁ N-	138-40	65
1-(C ₂ H ₅) ₂ NCH ₂ CH ₂ CH ₂ CH(CH ₃)NH-	P 214	3
1-(C ₂ H ₅) ₂ NCH ₂ CH ₂ CH ₂ CH(CH ₃)NH-8-Br-	b245-55/0.1 mm.	3
1-(C ₂ H ₅) ₂ NCH ₂ CH ₂ CH ₂ CH(CH ₃)NH-2-C ₂ H ₅ -	b220-5/1.0 mm.	3
1-O(CH ₂ CH ₂) ₂ NCH ₂ CH ₂ NH-	75-6	65
1-(C ₂ H ₅) ₂ NCH ₂ CH ₂ NH-	57	3
1-(C ₂ H ₅) ₂ NC ₆ H ₄ CH=N-	136-8	2

(Table continued)

TABLE III-6 (*continued*)

Substituent and position	M.p., °C.	Refs.
1-(CH ₃) ₂ NC ₆ H ₄ CH=N-	216-8	2
1-C ₆ H ₅ N(CH ₃)-3-C ₆ H ₅ -	191	27
1-[2-C ₁₀ H ₇ N(NO)-]-3-C ₆ H ₅ -	250	54
1-(2-C ₁₀ H ₇ NH-)-3-(4-CH ₃ C ₆ H ₄)-	226	54
1-[2-C ₁₀ H ₇ N(CH ₃ CO)-]-3-C ₆ H ₅ -	173	54
1-(2-C ₁₀ H ₇ NH-)-3-C ₆ H ₅ -	203	54
1-[2-C ₁₀ H ₇ N(NO)-]-3-(4-CH ₃ C ₆ H ₄)-	195	54
1-[6-CH ₃ O-8-(CH=N)-C ₆ H ₄ N]-	209	136
2-NH ₂ -	136	71
3-[4-(CH ₃) ₂ N-C ₆ H ₄ -CH=CH]-	227-35	119
	(CH ₃ I)	
3-[4-(CH ₃) ₂ NC ₆ H ₄]-	249	84, 182
3-CH ₂ =CHNH-1-CH ₃ -	164	59
3-(2-NH ₂ C ₆ H ₄)-2-C ₆ H ₅ -	201	98
5-NH ₂ -	138	63
5-CH ₃ CONH-	127	63
5-(CH ₃) ₂ NC ₂ H ₄ NH-	85	2, 3
5-(2-C ₅ H ₄ N-NH)-	142-4	2
6-CH ₃ COCH ₂ CONH-	185	165
7-NH ₂ -	176	10, 15, 59, 60
7-CH ₃ CONH-	235	59, 60
7-CH ₃ COCH ₂ CONH-	202	165
7-C ₆ H ₅ CH=N-	101	59
7-C ₆ H ₅ CH ₂ NH-	152-4	59
7-(3-NO ₂ C ₆ H ₄ CH=N)-	183	59
7-(3-NH ₂ C ₆ H ₄ CH ₂ -NH)-	141-4	59
8-NH ₂ -	222-4	59
8-CH ₃ CONH-	213	59
8-C ₆ H ₅ CH=N-	148-51	59
10-NH ₂ -	157	59
10-CH ₃ CONH-	152-4	59
10-CH ₃ COCH ₂ CONH-	192	165
7,9-(NH ₂) ₂ -	246	11, 59

TABLE III-7. Hydroxy- and Alkoxy-4-azaphenanthrenes

Substituent and position	M.p., °C.	Refs.
1-HO-	286-8	65, 68
1-HO-7-CH ₃ O-	309	68
1-HO-10-CH ₃ O-	183	68
1-HO-2,3-(CH ₃) ₂ -	> 300	132

(*Table continued*)

TABLE III-7 (continued)

Substituent and position	M.p., °C.	Refs.
1-HO-2-C ₂ H ₅ -3-CH ₃ -	> 300	132
1-HO-2-(CH ₃) ₂ CH-3-CH ₃ -	> 300	132
1-HO-2-CH ₃ CH ₂ CH ₂ -3-CH ₃ -	> 300	132
1-HO-3-C ₆ H ₅ -	280	27, 54
1-HO-4-CH ₃ C ₆ H ₄ -	315	54
1-HO-2-C ₆ H ₅ CH ₂ -3-CH ₃ -	> 300	132
1-HO-2-CH ₃ (CH ₂) ₃ -3-CH ₃ -	> 300	132
1-HO-2-C ₆ H ₅ CH ₂ CH ₂ -3-CH ₃ -	> 300	132
1-HO-3-CH ₃ -	350	171
1-HOCH ₂ -	171-5	136
1-(4-CH ₃ C ₆ H ₄ O)-3-CH ₃ -	137	177
3-HO-	280	188
3-HO-1-CH ₃ -	286	136
3-HO-1-C ₆ H ₅ -	305	51
3-(2-HOC ₆ H ₄)-	217	75
3-(2-CH ₃ OC ₆ H ₄)-	184	75
3-(3,4-CH ₂ O ₂ C ₆ H ₃)-	178	28, 75
3-(3,4-CH ₂ O ₂ C ₆ H ₃)-2-C ₆ H ₅ CO-	211	28
3-(4-CH ₃ OC ₆ H ₄)-2-C ₆ H ₅ CO-	186	28
3-(4-CH ₃ OC ₆ H ₄)-	190	28
3-(4-CH ₃ OC ₆ H ₄)-C ₆ H ₄ COCH ₂ -	155	56
3-(4-CH ₃ OC ₆ H ₄ CH ₂)-	158	56
5-HO-	104-6	2, 63
7-HO-6-NH ₂ -		175
7-HO-	245-7	60, 126, 144, 175
7-CH ₃ O-1-Cl-	119	3, 38
7-HO-6-CH ₃ CONH-		175
7-C ₆ H ₅ COO-	156	60
7-CH ₃ O-1-(C ₂ H ₅) ₂ NCH ₂ CH ₂ CH ₂ CH(CH ₃)NH-	b 220-30 0.2 mm.	3
7-CH ₃ O-1-O(CH ₂ CH ₂) ₂ N-	137	68
7-CH ₃ O-1-CH ₂ (CH ₂ CH ₂) ₂ N-	117	68
8-HO-	289-92	121, 122, 126
8-C ₆ H ₅ COO-	164	126
9-HO-	270-2	121, 122, 126, 175
9-HO-1-CH ₃ -3-C ₆ H ₅ -	108	118
9-HO-2,4-(CH ₃) ₂ -	268-70	164
9-C ₆ H ₅ COO-	145	60, 126
9-CH ₃ O-1-Cl-	98	3
9-CH ₃ O-1-Cl-2-CH ₃ -	125	3

(Table continued)

TABLE III-7 (*continued*)

Substituent and position	M.p., °C.	Refs.
9-CH ₃ O-1-(C ₂ H ₅) ₂ NCH ₂ CH ₂ CH ₂ CH(CH ₃)NH-	b. 240-50/ 0.2 mm.	3
9-CH ₃ O-1-(C ₂ H ₅) ₂ NCH ₂ CH ₂ CH ₂ CH(CH ₃)NH- 2-CH ₃ -	b. 210-20/ 0.05 mm.	3
10-HO-8-SO ₃ H-		82
10-HO-	281-5	126
10-C ₆ H ₅ COO-	114-5	126
6,10-(HO ₂)-		175
5,9-(HO) ₂ -		175
α -HO-1,3-(CH ₃) ₂ - α' -SO ₃ H-		79

TABLE III-8. Carboxy and Carbonyl Derivatives

Substituent and position	M.p., °C.	Refs.
1-COOH-3-[CH ₃ (CH ₂) ₉]-		33, 36, 110
1-COOH	302	28, 136, 152
1-COOH-3-CH ₃ -	310	28-31, 75
1-COOH-3-HOCH ₂ -	255	43, 113
1-COOH-3-C ₂ H ₅ -	283	29b, 75, 92, 174
1-COOH-3-(4-C ₃ H ₃ N ₂)-	300	95
1-COOH-3-CH ₃ CH=CH ₂ -	289	29b, 75
2-COOH-3-HOOCCH ₂ CH ₂ -	> 250	104
1-COOH-3-(CH ₃) ₂ CH-	266	29b, 75, 92
1-COOH-3-CH ₃ CH ₂ CH ₂ -	248	32, 92
1-COOH-3-CH ₃ CH(OH)CH ₂ -	234	29b
1-COOH-3-(2-C ₄ H ₄ O)-	275	94
1-COOH-3-CH ₃ CH=C(CH ₃)-	226	75
1-COOH-3-CH ₃ COCH ₂ CH ₂ -	291	85
1-COOH-3-CH ₃ CH ₂ CH(CH ₃)-	251	75, 92
1-COOH-3-(iso-C ₅ H ₇)-	241-3	91
1-COOH-3-CH ₃ (CH ₂) ₇ -	238-40	33, 108, 109
1-COOH-3-C ₉ H ₁₇ -	255	75
1-COOH-3-C ₉ H ₁₅ -	197	75, 100
1-COOH-3-iso-C ₉ H ₁₅ -	150	100
1-COOH-3-C ₉ H ₁₁ -	255-60	33
1-COOH-3-C ₁₀ H ₂₁ -		121
1-COOH-3-CH ₃ (CH ₂) ₈ -	239-42	33, 36, 109
1-COOH-3-CH ₃ (CH ₂) ₅ -	291	75
1-COOH-3-CH ₃ (CH ₂) ₅ CH(C ₂ H ₅)-	190-5	33, 110
1-COOH-3-C ₁₀ H ₁₇ -	294	38

(*Table continued*)

TABLE III-8 (*continued*)

Substituent and position	M.p., °C.	Refs.
1-COOH-3-(2'-CH ₃ -5-C ₄ H ₂ S-)-	172	226
1-COOH-3-(CH ₃) ₂ CH-7-CH ₃ -		67
1-COOH-3-CH ₃ (CH ₂) ₆ -	240	34, 92, 109
1-COOH-2-C ₆ H ₅ -	293	18, 44, 57, 99
1-COOH-3-C ₆ H ₅ -	296	28, 40, 41, 73, 86, 87, 102
1-COOH-2,3-(C ₆ H ₅) ₂ -		39, 44, 57
1-COOH-2-C ₆ H ₅ CH ₂ -3-C ₆ H ₅ -		44
1-COOH-3-C ₆ H ₅ CH=CH-	305	9, 75
1-COOH-3-(4-C ₃ H ₇ C ₆ H ₄)-	255	37, 75
1-COOH-2-C ₆ H ₅ CO-3-C ₆ H ₅ -	249	28, 44
1-COOH-2-C ₆ H ₅ CO-	247	28, 44
1-COOH-2-C ₆ H ₅ CH ₂ -	256	99
1-COOH-2-C ₆ H ₅ -3-CH ₃ -	101	18, 44
1-COOH-3-(4-CH ₃ OC ₆ H ₄)-	283	28, 47, 75
1-COOH-2-C ₂ H ₅ -3-C ₆ H ₅ -		39
1-COOH-3-[4-HO-3,5-(CH ₃ O) ₂ C ₆ H ₂]-	275	89
1-COOH-2-C ₆ H ₅ CO-3-CH ₃ -	271	28
1-COOH-3-[2,3,3,3-(CH ₃) ₃ C ₆ H ₃]-		111
1-COOH-3-[3,4,5-(CH ₃ O) ₃ C ₆ H ₂]-	263	90
1-COOH-3-[2,4,5-(CH ₃ O) ₃ C ₆ H ₂]-	258	107
1-COOH-2-C ₆ H ₅ -3-(CH ₃) ₂ CH ₂ -	277	35, 57
1-COOH-3-(2-C ₄ H ₄ O-)-	278	94
1-COOH-3-(2-NO ₂ C ₆ H ₄)-	266	43, 97, 113
1-COOH-3-(3-NO ₂ C ₆ H ₄)-	282	97
1-COOH-3-(4-NO ₂ C ₆ H ₄)-	262	97
1-COOH-2-(2-NO ₂ C ₆ H ₄)-3-C ₆ H ₅ -		44
1-COOH-2-C ₆ H ₅ -3-(2-NO ₂ C ₆ H ₄)-	278	98
1-COOH-2-(2-NH ₂ C ₆ H ₄)-3-C ₆ H ₅ -	206-10	98
1-COOH-2-C ₆ H ₅ -3-(2-NH ₂ C ₆ H ₄)-	284	9
1-COOH-3-[4-(CH ₃) ₂ N-C ₆ H ₄]-	305	84, 87
1-COOH-3-[4-(CH ₃) ₂ N-C ₆ H ₄]- <i>x,x'</i> -(NO ₂) ₂	260-3	84
1-COOH-3-(2-C ₄ H ₄ N)-	300	43
1-COOH-3-(2-HOC ₆ H ₄)-	226	75, 87
1-COOH-3-(4-HOC ₆ H ₄)-	325.5	106
1-COOH-3-(3-HOC ₆ H ₄)-	284.5	106
1-COOH-3-(4-HO-3-CH ₃ OC ₆ H ₃)-	288	75
1-COOH-2-C ₆ H ₅ CO-3-(3,4-CH ₂ O ₂ C ₆ H ₃)-	259	28
1-COOH-2-C ₆ H ₅ CO-3-(4-CH ₃ C ₆ H ₄)-	237	28
1-COOH-3-(3,4-CH ₂ O ₂ C ₆ H ₃)-	292	47
1-COOH ₃ -3-(3,4-CH ₂ O ₂ C ₆ H ₃)-	170	47
1-COOH-3-(3-HO-4-CH ₃ OC ₆ H ₃)-	295	106

(*Table continued*)

TABLE III-8 (*continued*)

Substituent and position	M.p., °C.	Refs.
1-COOH-3-(2-HO-3-CH ₃ OC ₆ H ₃)-	251	106
1-COOH-3-[2,4-(HO) ₂ C ₆ H ₃]-	317	106
1-COOH-3-[3,4-(CH ₃ O) ₂ C ₆ H ₃]-	142-3	93
1-CONH ₂	253-5	63
1-COOCH ₃	104-5	63
1-COOC ₂ H ₅	56	63
1-CONHNH ₂	225	63
1-CONHN=CHC ₆ H ₄ N(C ₂ H ₅) ₂	216-8	63
1-COCl-2-C ₆ H ₅ CO-	197-9	28
1-COCl-2-C ₆ H ₅ CO-3-C ₆ H ₅ -	206	28
1-COCl-2-C ₆ H ₅ CO-3-(4-CH ₃ OC ₆ H ₄)-	181-3	28
1-COCl-2-C ₆ H ₅ CO-3-(3,4-CH ₂ O ₂ C ₆ H ₃)-	189	28
1-COOC ₂ H ₅ -2-C ₆ H ₅ CO-	147	28
1-COOC ₂ H ₅ -2-C ₆ H ₅ CO-3-C ₆ H ₅ -	144	28
1-COOC ₂ H ₅ -2-C ₆ H ₅ CO-3-(4-CH ₃ OC ₆ H ₄)-	161	28
1-COOC ₂ H ₅ -2-C ₆ H ₅ CO-3-(3,4-CH ₂ O ₂ C ₆ H ₃)-	159	28
1-CONH ₂ -3-C ₆ H ₅ -	240	101
1-COOCH ₃ -3-(4-CH ₃ OC ₆ H ₄)-	145	47
1-COOC ₂ H ₅ -3-C ₆ H ₅ -	84	178
1-COOCH ₃ -3-C ₆ H ₅ -	126	178
1-COOC ₂ H ₅ -3-(4-CH ₃ OC ₆ H ₄)-		
2-COOH-1-HO-3-C ₆ H ₅ -	248-50	131
2-COOC ₂ H ₅ -1-HO-3-C ₆ H ₅ -	280-2	131
3-COOH-	187	8, 103, 120, 129
3-COOH-1-HO-	302	65
3-COOH-1-HO-7-CH ₃ O-	292-5	68
3-COOH-1-HO-10-CH ₃ O-	250-3	68
3-HOOCCH ₂ CH ₂ -	> 250	104
3-COOC ₂ H ₅ -1-HO-	215-9	65
3-COOC ₂ H ₅ -1-HO-7-CH ₃ O-	256-8	68
3-COOC ₂ H ₅ -1-HO-10-CH ₃ O-	181-3	68
5-COOH	205	63
5-COOH-6-Cl-	187-9	63
5-COOCH ₃	86	63
5-CONHNH ₂	204	63
5-CON ₃	65-7	63
5-CONH ₂	206	63
6-COOH	298-300	45, 125
6-COOH-1-HO-3-CH ₃ -	> 360	128
6-COOH-2-CH ₃ -7-NO ₂ -	320-4	127
6-COOCH ₃ -1-HO-3-CH ₃ -	296	128
6-COOC ₂ H ₅ -1-HO-3-CH ₃ -	297	128

(*Table continued*)

TABLE III-8 (*continued*)

Substituent and position	M.p., °C.	Refs.
6-COOH-7-NO ₂ -	310	45, 124, 127
6-COOH-3-CH ₃ -	313-5	125
6-COOH-7-NH ₂ -	280	45, 124
6-COOH-2-CH ₃ -	320-4	127
6-COOH-2-CH ₃ -7-NH ₂ -	288-9	127
6-COOC ₂ H ₅ -	104-5	45
6-COOCH ₃ -3-CH ₃ -	114-6	125
6-COOC ₂ H ₅ -3-CH ₃ -	104	125
8-COOH-9-HO-	315	121-123
9-COOH-8-HO-	340-2	121-123
1,2-(COOH) ₂ -3-C ₆ H ₅ -	218	24, 114, 115, 133
1,3-(COOH) ₂ -	288	9
2,6-(COOH) ₂ -1-HO-	> 360	128
2,6-(COOH) ₂ -1-HO-3-CH ₃ -	> 360	128
2,6-(COOH) ₂ -1-HO-3-CH ₃ - <i>x</i> -NH ₂ -	> 360	128
1-COOH-3-CH ₃ -6-COOCH ₃ -	266	128
2,3-(COOH) ₂ -1-C ₆ H ₅ -	152	24
2,6-(COOCH ₃) ₂ -1-HO-3-CH ₃ -	240	128
2,6-(COOCH ₃) ₂ -1-CH ₃ O-3-CH ₃ -	142-4	128
2,6-(COOH) ₂ -7-NH ₂ -	> 360	71
2-COOCH ₃ -6-COOH-7-NH ₂ -	300	71
3-COOCH ₃ -6-COOH-7-NH ₂ -	305-7	125
3-COOC ₂ H ₅ -6-COOH-7-NH ₂ -	275	125
3,6-(COOH) ₂ -	258	125
3,6-(COOH) ₂ -7-NO ₂ -		125
3,6-(COOH) ₂ -7-NH ₂ -	271	125
1-COOH-2-COOC ₂ H ₅ -3-C ₆ H ₅ -	218	115
1,3-(COOH) ₂ -6-COOCH ₃ -	200	128
1-BrCH ₂ CO-	133	136
1-N ₃ CH ₂ CO-	145	136
1-(C ₆ H ₅ COCH ₂) ₂ CH-	147	136
2-C ₆ H ₅ CO-	109	18, 28
2-C ₆ H ₅ CO-3-C ₆ H ₅ -	185	18, 28
3-C ₆ H ₅ COCH ₂ -	208	56
2-CH ₃ CO-3-C ₆ H ₅ -1-HO-	262-4	179
2-CH ₃ CO-3-C ₆ H ₅ -1-CH ₃ O-	220	179
3-(4-CH ₃ OC ₆ H ₄ COCH ₂)-	158	56
1-CH=NOH	224	136
4-Oxo-		70
3-CH ₃ -4-oxo-	129	180
4-CH ₃ -3-oxo-	183	10
1,2-Bis(1-HO-3-CH ₃ -4-azaphenanthrene-3)-ethane-	> 300	132

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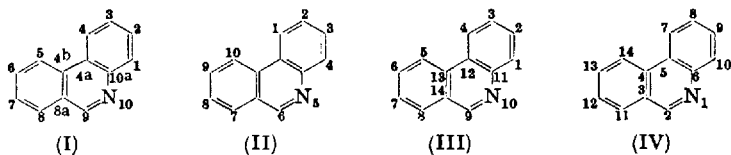
CHAPTER IV

5-Azaphenanthrenes

By J. A. VAN ALLAN

A. Nomenclature

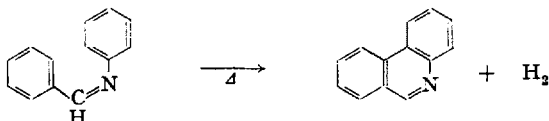
In 1889 only two of the five isomeric substances obtainable by replacement of a "CH" group in phenanthrene by nitrogen were known. They were the 1- and 4-azaphenanthrenes. In both of these compounds the nitrogen is in a terminal ring of the phenanthrene molecule. Pictet and Ankersmit succeeded in synthesizing a third isomer in which the nitrogen atom is in the central ring.¹ Since it was considered as the "acridine" of the phenanthrene series, it was named *phenanthridine*, as suggested by Étard and Bernthensen. Because this name has been used consistently from the time of its inception, it will be used in this section in place of the systematic 5-azaphenanthrene. Several systems of numbering have been used to locate substituents in the phenanthridine nucleus, as indicated below:



Prior to 1937 *Chemical Abstracts* used the sequence illustrated in I. This system is used exclusively by the English co-workers. This numbering was superseded by II in 1937, the angular positions being designated by (a, b, ...) following the lowest adjacent number. Systems III⁴⁴ and IV¹¹ have found very little use. In conformity with *Chemical Abstracts* and with the system adopted for this series of azaphenanthrenes, the numbering shown in II will be followed.

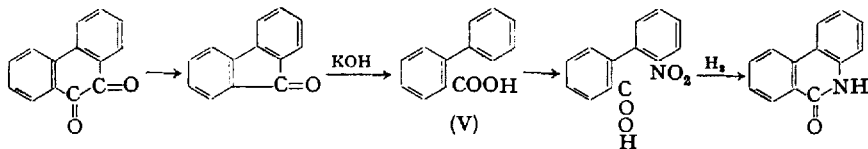
B. Methods of Synthesis

(a) **From Benzalaniline.** Phenanthridine was first synthesized by Pictet and Ankersmit by passing benzalaniline through a red-hot iron tube filled with pumice; the base was purified through its mercuric chloride salt. This pyrogenic method has been investigated intensively.¹⁴



At the optimum temperature of 800° only a 3 % yield of the base is obtained. This low yield is ascribed to the unfavorable spatial configuration of the benzalaniline; it has been shown that the most probable configuration of benzalaniline is linear.^{45, 50} Various catalysts have been tried in an attempt to improve the yield but no effect whatever has been noticed. Since the yield is extremely low, this method is not of preparative interest.¹ It is interesting to note that benzylaniline under the same conditions yields only acridine.¹⁶

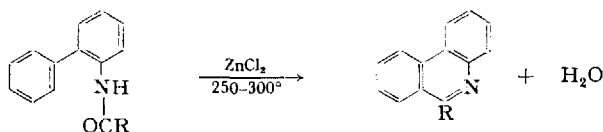
(b) **From Phenanthraquinone.** In searching for a proof of structure of their newly synthesized base, Pictet and Ankersmit² devised an unambiguous synthesis starting from phenanthraquinone. The latter compound is oxidized with lead dioxide to fluorenone, which, on cleavage with potassium hydroxide, gives *o*-phenylbenzoic acid (V); nitration of the latter gives chiefly 2-nitro-2'-carboxybiphenyl. On reducing the nitro group, phenanthridone is formed immediately; it can be converted to phenanthridine by zinc dust distillation. This synthesis constitutes a satisfactory structural proof for phenanthridine. A



variation of this synthesis, which gives excellent results,¹⁷ is reported in the section on phenanthridone (p. 286).

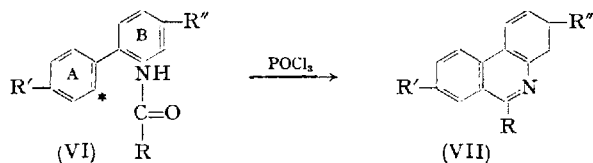
(c) **From Acyl-*o*-xenylamines (Morgan-Walls).** In 1896 it was found that acyl-*o*-xenylamines could be converted into derivatives of

phenanthridine by fusion with zinc chloride at 250–300°. The yield is very poor with the formyl derivative but the acetyl and benzoyl derivatives give moderately good yields of the respective 6-methyl and 6-phenylphenanthridines.^{15, 21}



Since there are several disadvantages in this method, Morgan and Walls²⁰ improved it by substituting phosphoryl chloride for zinc chloride as a condensing agent. The reaction is fairly general and has been applied successfully to the preparation of alkyl, chloroalkyl, phenyl, and nitrophenyl derivatives of phenanthridine. It fails, however, in the case of formyl-*o*-xenylamine. This synthesis has been applied successfully to nuclear-substituted acetyl-*o*-xenylamines, as, for example, 4'-nitro and 5-nitro-2-acetylaminobiphenyl.²¹ The phenanthridine from the 4'-nitro- compound is formed in very poor yield. Although the reaction proceeds smoothly when $\text{R} = \text{CH}_2\text{Cl}$, it fails completely when $\text{R} = \text{CHCl}_2$ or CCl_3 , which suggests that, as the negative character of R increases, enolization—a probable preliminary to ring closure—is inhibited. The electronic character of R has, however, no consistent influence, for $\text{R} = \text{CH}_2\text{Cl}$ gives a better result than $\text{R} = \text{CH}_3$; when $\text{R} = \text{COOC}_2\text{H}_5$ the yield is very poor. The yield from the *ortho* exceeds that from the *meta* and *para* nitrobenzoylxenylamides.

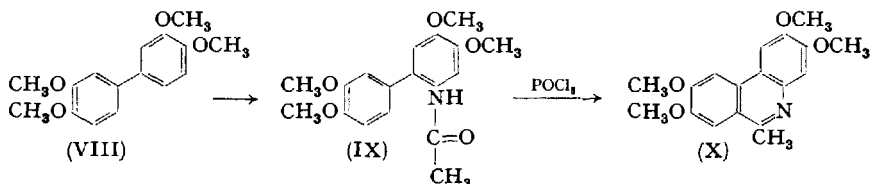
It is stated in a patent⁴⁸ that the conversion of acylated nitro-*o*-xenylamines into the corresponding phenanthridines by means of phosphoryl chloride is greatly facilitated by diluting the reaction



mixture with a high-boiling solvent, such as nitrobenzene.⁵⁸ If $\text{R}' = \text{nitro}$ ($\text{R} = \text{phenyl}$, $\text{R}'' = \text{H}$) in VI, ring closure is inhibited owing to

the electromeric effect of the nitro group on the strategic hydrogen atom at position 2'. Such a group in ring A of VI would depress the mobility of H*, whereas in ring B it would have only a slight effect. In order to obtain phenanthridines substituted in the 8-position by an amino group, it is necessary to devise an alternate route. The desired result is obtained by replacing the nitro group (R') by a carbethoxy-amino group, which has a powerful electromeric effect opposite to that of the nitro group. It directs ortho and para, is quite stable, and is readily converted to the amine. It has the further advantage of conferring on the compound a conveniently low melting point and high solubility in organic solvents. That this new method is strikingly successful is exemplified by the case in which VI (R = phenyl, R', R'' = carbethoxyamino) is converted into the corresponding phenanthridine; a yield greater than 50 % is obtained by a 15-minutes heating with phosphoryl chloride alone. In contrast, the corresponding nitro compound (VI; R = phenyl, R', R'' = nitro) requires over 12 hours' heating with phosphoryl chloride in nitrobenzene at 180° to obtain the same degree of ring closure.^{43, 57, 59}

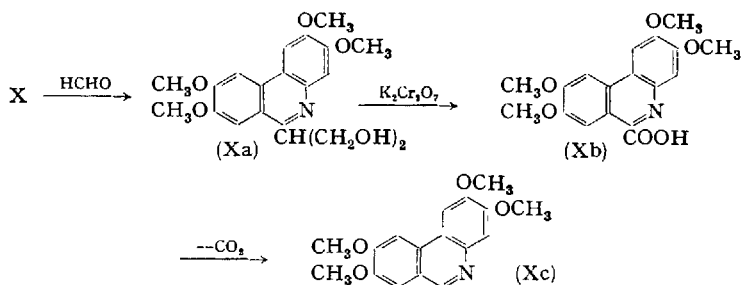
In a comprehensive investigation of this reaction,^{71a} Ritchie has synthesized a tetramethoxy derivative (X) of phenanthridine, as follows: 4-Iodoveratrole is treated with copper powder, giving the biphenyl derivative, VIII. On nitration, reduction, and acetylation, the latter compound furnishes the requisite acyl-*o*-xenylamine, IX, which, on cyclization with phosphoryl chloride, gives 2,3,8,9-tetramethoxy-6-methylphenanthridine (X) in 85 % yield. The propionyl



and benzoyl derivatives of IX likewise give high yields of the corresponding phenanthridines.

Condensation of X with formaldehyde gives the dimethylol derivative, Xa, which is smoothly oxidized to the 6-carboxylic acid, Xb, with potassium dichromate. Decarboxylation of the latter compound

proceeds readily to a tetramethoxyphenanthridine (Xc), which can also be synthesized in small yield from the formyl derivative (IX; CHO for CH₃CO). All of these phenanthridine derivatives show a



marked blue fluorescence in neutral solution which is stronger in acetic acid. The methiodides are strongly fluorescent in aqueous ethanol.

2-Acetamido-4,4'-dibromobiphenyl is readily cyclized by means of phosphoryl chloride, whereas 2-acetamido-4,4'-tetramethyldiaminobiphenyl has not yet been cyclized under any conditions.^{71b}

6-*p*-Aminophenyl-1,10-dimethylphenanthridine,^{71d} 3-methylphenanthridine, and 3,6-dimethylphenanthridine^{71f} also have been synthesized by the Morgan-Walls reaction.

The influence of the acyl group in the Morgan-Walls reaction has been thoroughly investigated. Various substituents (indicated by R in Table IV-1) have been introduced in the amino group of 2-aminobiphenyl, and the effect on the yield has been determined. Positive reactions give 6-substituted phenanthridines. The results are listed in Table IV-1.

In the case of R = COCH₂COCH₃ (No. 13) cyclization can be

TABLE IV-1

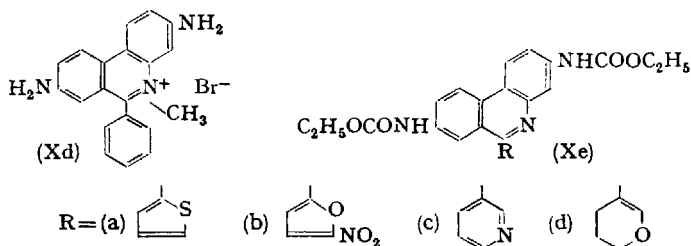
R	Yield	R	Yield
1. -COCH ₂ COOC ₂ H ₅	Tar	9. -COCH ₂ OC ₆ H ₅	65 %
2. -COCH ₂ CH ₂ COOCH ₃	Tar	10. -COCH=CHCH ₃	Tar
3. -COCH ₂ CH ₂ COOH	Tar	11. -COCH=CHC ₆ H ₅	12 %
4. -CO(CH ₂) ₃ COOH	Tar	12. -COCH=CHCOOH	Tar
5. -CO(CH ₂) ₃ COOCH ₃	50 %	13. -COCH ₂ COCH ₃	Tar
6. -CO(CH ₂) ₄ COOC ₂ H ₅	50 %	14. - <i>o</i> -COC ₁₀ H ₇	Good
7. -COCH ₂ C ₆ H ₅	20 %	15. -mesityl	Good
8. -CO(CH ₂) ₂ C ₆ H ₅	70 %		

effected with concentrated sulfuric acid, but the product is 8-(*p*-sulfophenyl)-4-methylcarbostyryl. When R = α -naphthoyl (No. 14) or mesitoyl (No. 15), ring closure is not inhibited, indicating that the size of the acyl group is not an important factor in the Morgan-Walls reaction. A mechanism has been proposed for this reaction.^{71c}

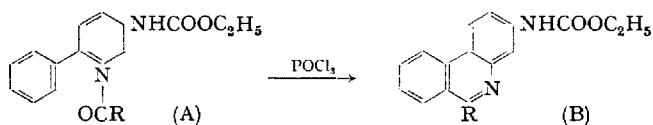
Petrow states that 6-(3-pyridyl)-, 2-nitro-6-(3-pyridyl)-, and 8-nitro-6-(3'-pyridyl)-phenanthridines have been prepared by ring closure of the appropriate nicotinamidobiphenyls. It is also reported that the quaternary methiodide salt of 2-nicotinamidobiphenyl has been cyclized to give a methiodide of 6-(3-pyridyl)phenanthridine in which the methyl iodide is presumably on the pyridine nitrogen.⁸⁰

This reaction has been extended to the preparation of some 3,8-disubstituted 6-(3-pyridyl)phenanthridine quaternary salts. In particular the preparation of a 6-(3-pyridyl)-analog of the potent trypanocide, Dimidium bromide (3,8-diamino-5-methyl-6-phenylphenanthridinium bromide), is described.¹²¹ Walls and Whittaker⁹⁵ have been able to cyclize 4,4'-bis(carbethoxyamino)-2-nicotinamidobiphenyl with phosphoryl chloride in nitrobenzene; however, the yield is rather low. A superior route to 3,8-dicarbethoxyamino-6-(3-pyridyl)phenanthridine is by cyclization of 2-nicotinamido-4,4'-dinitrobiphenyl with phosphoryl chloride and stannic chloride in nitrobenzene. Reduction of this dinitrophenanthridine with stannous chloride gives 3,8-diamino-6-(3-pyridyl)phenanthridine, which is readily converted into the dicarbethoxyamino compound by treatment with ethyl chloroformate.¹²¹

Several other analogs of Dimidium bromide (Xd) in which the 6-phenyl group is replaced by a cyclohexyl, benzyl, or heterocyclic nucleus have been synthesized by the Morgan-Walls reaction with a view to correlating structure with trypanocidal activity. All of the phenanthridines, Xe, were readily obtained.⁹⁵



The powerful trypanocidal properties of aminophenanthridinium salts suggested that further isomerides should be prepared. Those with 3-, 9-, and 7-amino substituents are of particular interest because of the possibility of ionic resonance. For the preparation of the 3-amino isomerides, 2-nitro-3-aminobiphenyl is converted by a number of stages into the 2-acylamido-4-carbethoxyaminobiphenyls (A) ($R = \text{CH}_3$ and $4\text{-C}_6\text{H}_4\text{NO}_2$), which are cyclized to the corresponding 3-amino-phenanthridine derivatives (B) ($R = \text{CH}_3$ and $4\text{-C}_6\text{H}_4\text{NO}_2$).

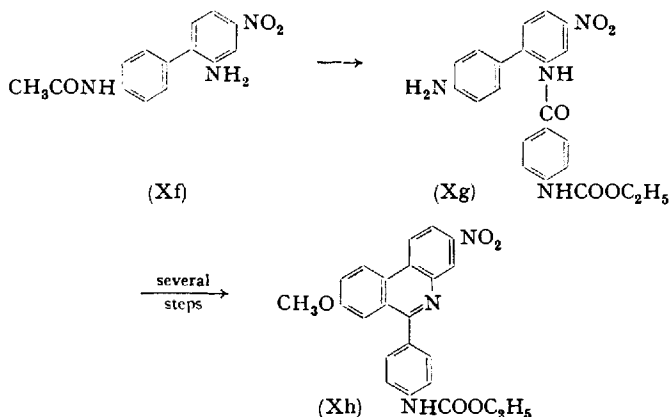


For the 9- and 7-amino compounds acyl derivatives of 2-amino-3'-carbethoxyaminobiphenyl are cyclized. The yields are quantitative, illustrating the favorable influence of the urethane grouping on this type of ring closure. The acetamido compound gives a high yield of the 9-isomeride, with some 7-isomeride, but the 4'-nitrobenzamide compound gives a higher yield of 7-isomeride. An explanation is offered for this phenomenon.¹⁰³ Compounds of similar structure with a 6-(4'-aminobenzyl) substituent also have been synthesized.¹⁰³

The fact that the acetamido group is much more readily hydrolyzed than is the carbethoxyamino group has been used advantageously in the preparation of intermediates, and also in the synthesis of quaternary salts containing an amino group in the phenanthridine part of the molecule and a carbethoxyamino group attached to the 6-substituent.¹⁰³

In the treatment of *Trypanosoma cruzi* infections, two compounds have been found markedly active: 2-carbethoxyamino- and 3-amino-6-(4'-carbethoxyaminophenyl)-5-methylphenanthridinium bromide. In a search for a convenient route to the 3-amino compound and analogous substances 2,4'-diamino-4-nitrobiphenyl has been monoacetylated to give 4'-acetamido-2-amino-4-nitrobiphenyl (Xf). This product is condensed with 4-carbethoxyaminobenzoyl chloride and selectively hydrolyzed to give Xg. Since this latter cannot be cyclized, the free amino group is converted to a methoxyl group by the Sandmeyer reaction and subsequent methylation. The methoxy compound is cyclized under

mild conditions to 6-(4'-carbethoxyaminophenyl)-8-methoxy-3-nitrophenanthridine (Xh).



If the acetamido group in Xf is replaced by the carbethoxyamino, followed by successive stages of condensation with benzoyl chloride, ring closure, quaternary salt formation, and reduction, 3-amino-8-carbethoxyamino-5-methyl-6-phenylphenanthridinium chloride is obtained. This compound is active in the incubation period of *T. cruzi* infection.¹²⁰

The observation that 6-phenylphenanthridinium salts with only a methoxyl group as a substituent possess significant trypanocidal properties suggested the examination of a series of such compounds. A large group of these, including some with a free hydroxyl group, have been synthesized using the Morgan-Walls reaction.¹⁰³

In the course of process development for Dimidium bromide, a study has been made of the Morgan-Walls phosphoryl chloride cyclization of 2-benzamido-4,4'-dinitrobiphenyl to the corresponding phenanthridine. The reaction involves an intermediate imido chloride, which is readily isolated and which undergoes facile cyclization only in the presence of certain ionorganic halide catalysts.

The fact that the imido chloride has been shown to be an intermediate in the reaction necessitates a reconsideration of the mechanism by which phenanthridines are formed in the Morgan-Walls reaction. It has now been found that the essential reaction is the catalyzed loss of hydrogen chloride from the imido chloride formed by the action of

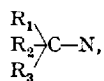
$$\begin{array}{c}
 \text{Ph}-\text{CH}_2-\text{Ph} + \text{MCl}_n \longrightarrow \text{Ph}-\text{CH}=\text{C}^+\text{R} + \text{MCl}_{n+1}^- \\
 \text{N}=\text{CCl} \\
 | \\
 \text{R}
 \end{array}$$

$$\begin{array}{c}
 \text{Ph}-\text{CH}=\text{C}^+\text{R} \longrightarrow \text{Ph}-\text{CH}=\text{C}(\text{R})-\text{Ph} + \text{H}^+ \\
 \text{N}=\text{C}^+ \\
 | \\
 \text{R}
 \end{array}$$

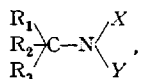
$$\text{H}^+ + \text{MCl}_{n+1}^- = \text{MCl}_n + \text{HCl}$$
CN1c2ccccc2c3ccccc13>>N1=Cc2ccccc2c3ccccc13

recorded by Diesbach and Aeschbuch,⁵⁶ who have raised the yield to 50 %.

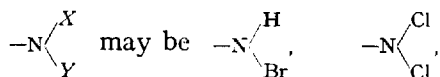
(e) **From Fluorylamines.** The rearrangements of hypothetical intermediates such as



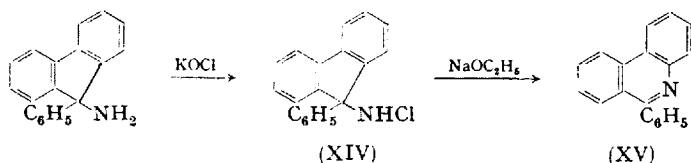
resulting from appropriate treatment of tertiary methyl nitrogen substituted compounds of the type



where R_1 , R_2 , and R_3 usually are aromatic groups and where



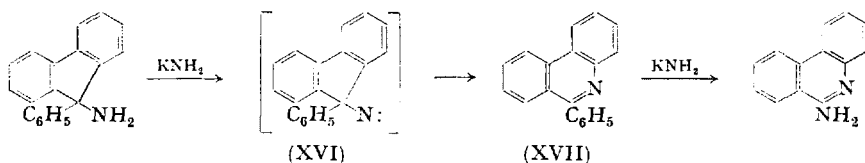
or $\text{N}(\text{N}_2)$, have been studied extensively by Stieglitz and coworkers. This rearrangement has been applied to 9-alkyl or aryl-9-amino-fluorenes. Theoretically, a 9-substituted fluoryl nitrogen can be stabilized by undergoing two possible types of rearrangements: (1) opening of the ring with subsequent cyclization to give a phenanthridine derivative, or (2) migration of the 9-alkyl or 9-aryl group to the nitrogen to give an imide. The former prevails. For example, when 9-phenyl-9-fluorylamine is converted to the corresponding chloroamine, XIV, by means of potassium hypochlorite, and the product is treated with sodium ethoxide in dry pyridine, 6-phenylphenanthridine (XV) is formed. No imide can be detected. Thus, the primary factor in



directing the course of the rearrangement of the intermediate free radical seems to be the highly strained condition of the five-membered ring in fluorene rather than the electronegativity of the radicals attached to the tertiary carbon atom. In every case the yield is ex-

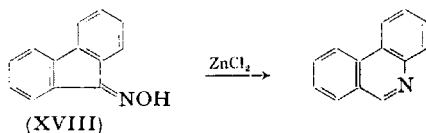
cellent. However, the method is indirect and the intermediates are not readily available.²⁹

9-Phenyl-9-fluorylamine reacts with potassium amide in liquid ammonia in the presence of potassium nitrate to give 6-aminophenanthridine.⁵¹ The mechanism of this reaction bears a formal similarity to that of the Stieglitz rearrangement in that the initial step is the formation of the unstable intermediate, XVI, which immediately rearranges to XVII. Since potassium amide reacts with 6-phenyl-



phenanthridine to form 6-aminophenanthridine,⁶³ the latter product is the only one isolated in the liquid ammonia reaction.

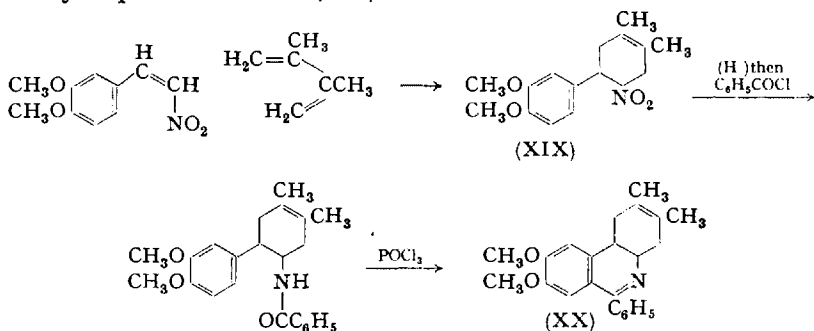
(f) From Fluorenone Oxime. When fluorenone oxime (XVIII) is fused with zinc chloride it undergoes the Beckmann rearrangement to give phenanthridine in 30 % yield.³ The conditions are quite critical,



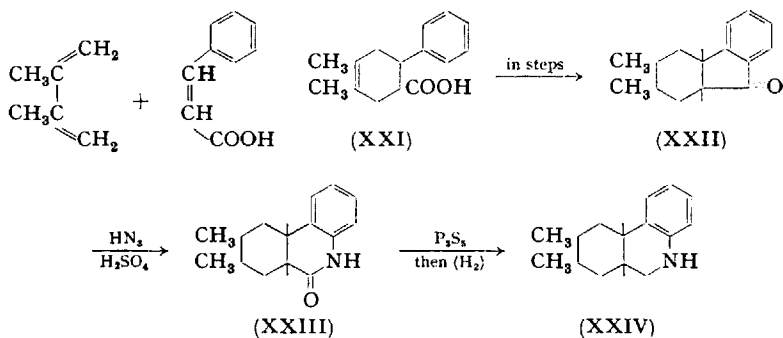
making the yields unpredictable, and the method has not been used extensively. The oxime of 2-formylbiphenyl (the aldehyde is made from calcium *o*-phenylbenzoate and calcium formate) has also been converted to phenanthridine under the same conditions.³

(g) From Butadiene Derivatives. In a search for antimalarial compounds, a series of partially hydrogenated phenanthridines has been synthesized by a novel procedure.³⁶ A diene synthesis is carried out using β -nitrostyrene as a dienophile. The resulting nitrocyclohexene is reduced, benzoylated, and cyclized by phosphoryl chloride to give a partially hydrogenated phenanthridine. For example, 3,4-dimethoxy- β -nitrostyrene reacts with 2,3-dimethylbutadiene in xylene at 180° to

give 4-(3',4-dimethoxyphenyl)-1,2-dimethyl-5-nitrocyclohexene (XIX), which is reduced electrolytically to the corresponding amine. The latter compound is benzoylated and treated with phosphoryl chloride in boiling xylene to give 8,9-dimethoxy-2,3-dimethyl-6-phenyl-1,4,4a,10b-tetrahydrophenanthridine (XX).³⁶



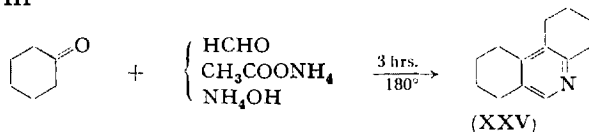
The diene synthesis also has been used to make octahydro derivatives of phenanthridine.⁴⁴ Hydrogenated biphenylcarboxylic acid derivatives are made by hydrogenating the reaction product of butadiene and a cinnamic acid. A fluorenone is obtained by ring closure of the corresponding acid chloride with aluminum chloride. Conversion to the phenanthridone is accomplished by treating the fluorenone with hydrazoic acid in sulfuric acid (Schmidt reaction). The former compound is converted to the 6-thione by fusion with phosphorus pentasulfide, and the thione on electrolytic reduction gives an octahydrophenanthridine. For example, cinnamic acid and 2,3-dimethylbutadiene react to



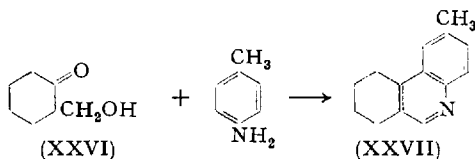
give 5-carboxy-1,2-dimethyl-4-phenylcyclohexene (XXI), which is reduced catalytically to the corresponding cyclohexane. The carboxyl

group is converted to the acid chloride by means of thionyl chloride and ring closure is effected by aluminum chloride. The resulting 2,3-dimethyl-1,2,3,4,4a,9a-hexahydrofluorenone (XXII) is treated with hydrazoic acid in sulfuric acid to give the hexahydrophenanthridone (XXIII). The latter is converted smoothly to 8,9-dimethyl-5,6,6a,7,8,9,10,10a-octahydrophenanthridine (XXIV) by treatment with phosphorus pentasulfide followed by electrolytic reduction.

(h) From Cyclohexanone. When formaldehyde, cyclohexanone, and ammonium acetate are heated together for 3 hours at 180°, a mixture of basic products is obtained that can be separated into its components by means of the picrates. Among the products 1,2,3,4,7,8,9,10-octahydrophenanthridine (XXV) is obtained in 28% yield. It can be oxidized to 2,3,4,5-tetracarboxypyridine by potassium permanganate. When paraldehyde is used in place of formaldehyde, 6-methyloctahydrophenanthridine is formed. Its structure has been determined by dehydrogenation with palladium to 6-methylphenanthridine.^{42,111}



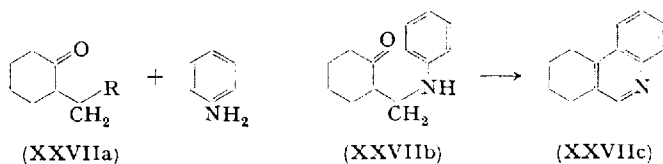
In a somewhat similar synthesis, a mixture of 2-hydroxymethylcyclohexanone (from cyclohexanone and formaldehyde), an aromatic amine, and its hydrochloride, stannic chloride hydrate, and alcohol is heated at 100° for 7 hours to give a 40% yield of a 7,8,9,10-tetrahydrophenanthridine, the basic structure of which is determined by selenium dehydrogenation.³⁰ For example, *p*-toluidine and 2-hydroxymethylcyclohexanone (XXVI), under the conditions just described, give 2-methyl-7,8,9,10-tetrahydrophenanthridine (XXVII)



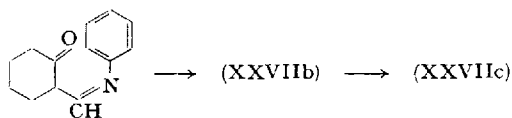
which, on selenium dehydrogenation, forms 2-methylphenanthridine. Systematic study has shown that this new reaction is applicable with

varying yields to alkyl, halogenated, and alkoxy derivatives of aniline; however, halogen and alkoxy substituents do not survive the dehydrogenation process. Moreover, the presence of stannic chloride is not essential to the success of this synthesis. The method is extremely flexible because the phenanthridine ring system is built up from separate benzene nuclei or their equivalents.

Petrow⁸⁹ has modified the above procedure with improved results. Several tetrahydrophenanthridines have been prepared by: (a) reaction of 2-diethylaminomethylcyclohexanone hydrochloride (XXVIIa, $R = N(C_2H_5)_2.HCl$), aniline hydrochloride, and stannic chloride in boiling cyclohexanone; (b) condensation of 2-chloromethylcyclohexanone



(XXVIIa, $R = Cl$), aniline, and aniline hydrochloride in boiling alcohol; and (c) reduction and ring closure of certain aryliminomethylcyclohexanones by heating them with anhydrous formic acid:

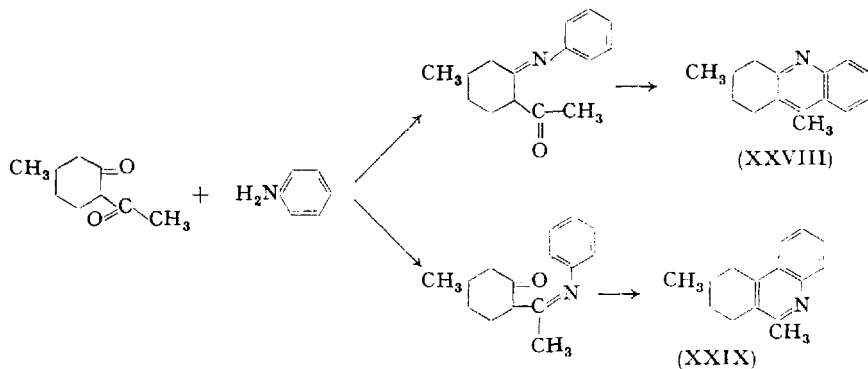


The formic acid, a reagent enjoying wide usage in the reduction of azomethines, not only reduces the anil linkage but also achieves ring closure to give tetrahydrophenanthridines.

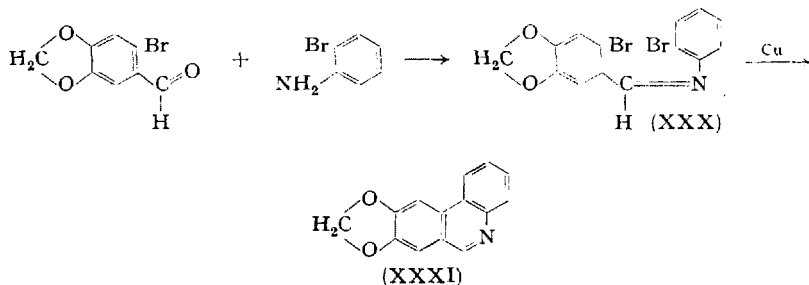
In contrast to the above, Borsche^{11,64} has found that 2-acylated cyclohexanones, when condensed with an aromatic amine at 150° , give only small yields of hydrogenated phenanthridines. When condensed at 150° , 2-acetyl-5-methylcyclohexanone and aniline give predominately a dimethyltetrahydroacridine (XXVIII); 6,9-dimethyl-7,8,9,10-tetrahydrophenanthridine (XXIX) is also formed in small yield.

In this case, the Schiff base is formed preferentially with the carbonyl group of the cyclohexanone ring; this results in linear ring

closure, whereas in hydroxymethylcyclohexanone (XXVI) the azo-methine linkage is formed through the hydroxymethylene group.



(i) **From *o*-Halobenzaldehydes.** While investigating the structure of lycorine, Kondo and Uyeo²⁷ developed a novel method for the synthesis of phenanthridine derivatives from an ortho halobenzaldehyde and an ortho haloaromatic amine. For example, when 2,6'-dibromopiperonylideneaniline (XXX) (easily obtained by warming equivalent quantities of *o*-bromoaniline and 6-bromopiperonal for a short time) is heated at 180–200° with Naturkupfer C, ring closure takes place to give 8,9-methylenedioxyphenanthridine (XXXI) in



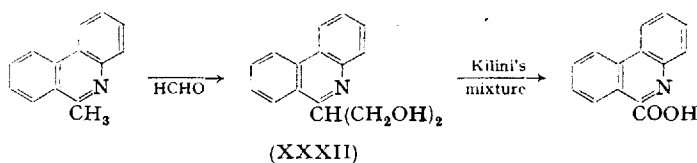
small yield. This synthesis has been extended to other derivatives, but the yields are all very low.²⁸

In view of the antiseptic effect of 3,6-diaminoacridine, the preparation of its phenanthridine analog, 3,8-diaminophenanthridine, and related compounds has been attempted. The Schiff base formed from 2-chloro-5-nitrobenzaldehyde and 2-chloro-5-nitroaniline cannot be

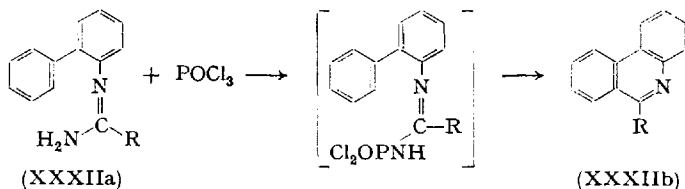
cyclized by copper powder. (Section Bi). Ritchie explains this by the assumption that this Schiff base has a *trans*-configuration and therefore the bromine atoms do not approach each other closely enough for the formation of a bond between the two benzene rings.^{71g}

(j) From Phenanthridones. Distillation of phenanthridones with zinc dust leads to the corresponding phenanthridine; but it is not a good preparative method because the yields are low. It has frequently been used, however, as a method of structure proof.^{2,7,27}

Walls¹⁸ gives an interesting and useful method for the synthesis of phenanthridine itself. Although the procedure involves several steps, each gives a good yield. The reaction conditions are moderate so that the procedure may be applied to more complex compounds. For example, 6-methylphenanthridine condenses with formaldehyde to yield 6-dimethylolmethylphenanthridine (XXXII). Oxidation with "Kilini's mixture" furnishes 6-carboxyphenanthridine and a small amount of phenanthridine. Decarboxylation of this acid proceeds quantitatively to phenanthridine.¹⁸

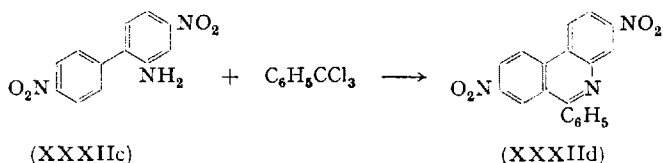


(k) From Amidines. 6-Substituted phenanthridines (XXXIIb) are produced in good yield by heating *N*-2-biphenylamidines (XXXIIa) and phosphoryl chloride in nitrobenzene solution.

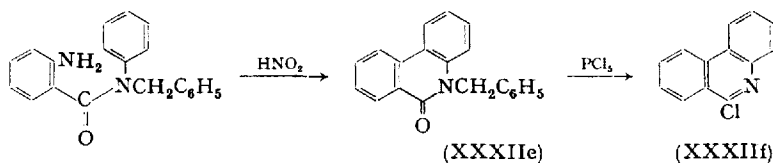


The yield by this method of the important intermediate, 3,8-dinitro-6-phenylphenanthridine, is 20–30 % higher than that obtained by Wall's method, and the intermediate amidine is easily prepared.^{83, 108}

(l) **From 2-Aminobiphenyls and Benzotrichloride.** Phenanthridine compounds are obtained by condensing benzotrichloride with nitro-substituted 2-aminobiphenyls at 200–20° in the presence of an inorganic halide catalyst. Thus, 2-amino-4,4'-dinitrobiphenyl (XXXIIc) gives a 93.5 % yield of 3,8 dinitro-6-phenylphenanthridine (XXXIIId). With AlCl_3 , ZnCl_2 , and BiCl_3 respective yields of 84, 85, and 77 % are obtained. The nitro compounds are intermediates in the preparation of the corresponding amino compounds.^{102, 116} This method is among the best for the preparation of phenanthridines and has been investigated as a commercial process.¹²³



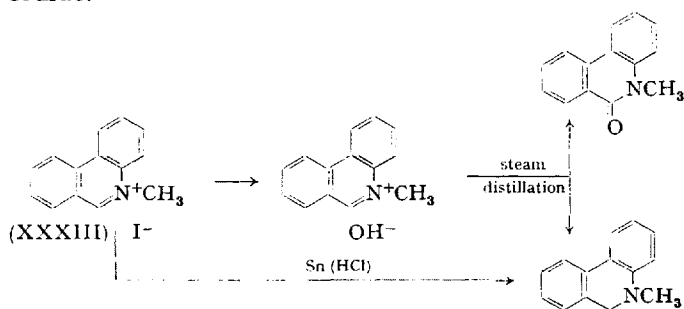
(m) **From *o*-Aminobenzanilides.** Diazotization of *o*-aminobenzanilides results in triazole formation instead of Pschorr cyclization. However, if the imido hydrogen of an anilide is first substituted by radicals of great mobility, such as benzyl, and then diazotized, Pschorr cyclization occurs giving an *N*-benzylphenanthridone. Phosphorus pentachloride converts the latter to a chlorophenanthridine with elimination of the benzyl radical. Thus, benzylaniline reacts by the Schotten-Baumann method with *o*-nitrobenzoyl chloride to give 81.6 % of *N*-benzyl-2-nitrobenzanilide. This on reduction and diazotization gives 6-benzylphenanthridone (XXXIIe), which with phosphorus pentachloride yields 6-chlorophenanthridine (XXXIIIf).¹²⁵



C. Phenanthridinium Salts

Phenanthridine, like pyridine and quinoline, forms quaternary ammonium salts with alkyl halides. These salts are converted to the quaternary ammonium bases on treatment with sodium hydroxide.

Steam distillation of the base gives an alkyl phenanthridone and an alkyl dihydrophenanthridine. For example, phenanthridine and methyl iodide react readily to form 5-methylphenanthridinium iodide (XXXIII), which with sodium hydroxide gives 5-methylphenanthridinium hydroxide.² Steam distillation of this quaternary base gives the steam volatile 5-methyldihydrophenanthridine (compare reference 114) and the nonvolatile 5-methylphenanthridone.⁸ The former compound also has been obtained by the action of tin and hydrochloric acid on phenanthridine methiodide, and also from dihydrophenanthridine and methyl chloride at 100°. The 5-methylphenanthridone has been obtained also by oxidizing the quaternary base with potassium ferricyanide,⁶ or by treating the potassium salt of phenanthridone with methyl iodide.⁷



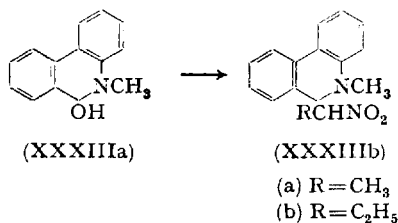
It has been found¹⁰ that XXXIII reacts with potassium cyanide to give a pseudo nitrile, which on the basis of absorption spectra is considered to be 6-cyano-5-methyl-5,6-dihydrophenanthridine.

Phenanthridinium salts are obtained in a novel manner by reduction of *N*-alkyl phenanthridones in ether solution with lithium aluminum hydride.¹²⁶

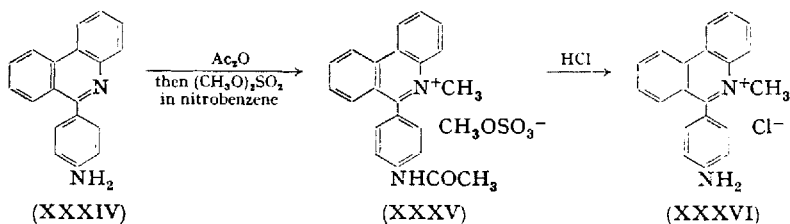
5-Methylphenanthridinium iodide in an ethanolic solution of potassium hydroxide (essentially, the pseudo base, 6-hydroxy-5-methyl-5,6-dihydrophenanthridine (XXXIIIa) condenses with nitroethane and nitropropane to give, respectively, 5-methyl-6-(α -nitroethyl) and 6-(α -nitropropyl)-5,6-dihydrophenanthridine (XXXIIIba and bb).¹²⁴

In a search for active pharmaceutical compounds, the salts of various phenanthridines have been investigated intensively. Syntheses

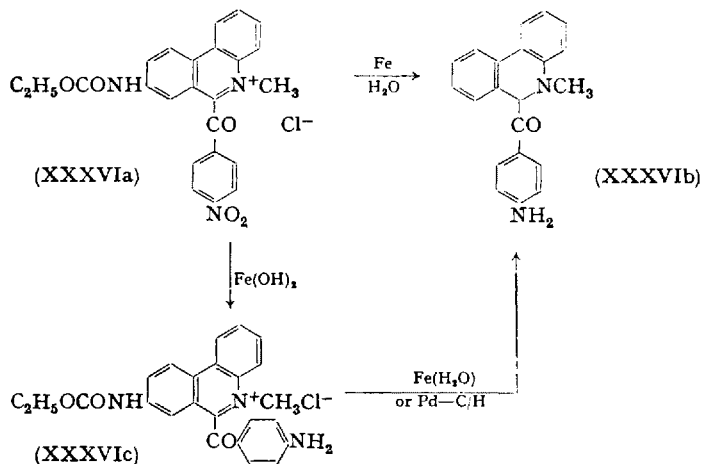
of phenanthridinium salts containing a free amino group have been described.²⁰ For example, 6-*p*-aminophenylphenanthridine (XXXIV)



is acetylated and treated with methyl sulfate in nitrobenzene to give the methosulfate of 6-*p*-acetamidophenylphenanthridine (XXXV). When XXXV is dissolved in hydrochloric acid, it loses the acetyl group and is converted into 6-*p*-aminophenyl-5-methylphenanthridinium chloride (XXXVI).

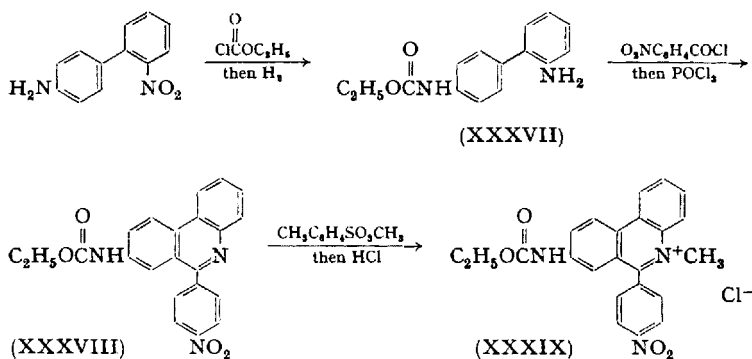


An alternate route, which is superior to that described, consists of treating a nitrophenanthridine with methyl *p*-toluenesulfonate in nitrobenzene to give a salt that is readily reduced to the free amine



by iron and acidified water. This procedure reduces the number of operations necessary to obtain the amine by eliminating the acylation and deacylation.⁵⁸ The iron-water method of reduction, however, when applied to 8-carbethoxyamino-5-methyl-6-(4-nitrobenzoyl)phenanthridinium chloride (XXXVIa), unexpectedly causes simultaneous reduction in the ring to give 6-(4-aminobenzoyl)-8-carbethoxyamino-5-methyl-5,6-dihydrophenanthridine (XXXVIb). Ferrous hydroxide gives the normal phenanthridinium salt (XXXVIc). This anomalous reduction also occurs with 6-benzoyl-3,8-bis(carbethoxyamino)-5-methylphenanthridinium chloride.¹¹⁸

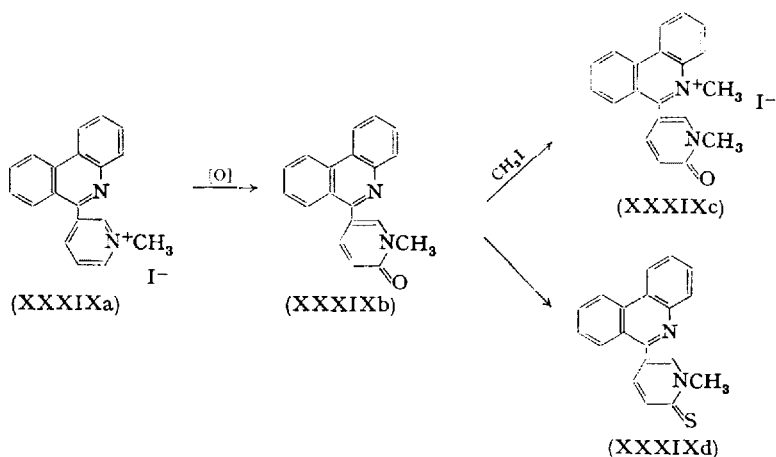
To obtain amino groups in the 8-position of the phenanthridine nucleus, it has been necessary to devise a modification of the acyl-*o*-xenylamine procedure (see Section Bc). For instance, 4'-amino-2-nitrobiphenyl is carbethoxylated and the nitro group reduced to give 2-amino-4'-carbethoxyaminobiphenyl (XXXVII). Condensation of this amine with *p*-nitrobenzoyl chloride yields the acyl derivative, which is smoothly and rapidly converted into 8-carbethoxyamino-6-(4-nitrophenyl)phenanthridine (XXXVIII). The latter is converted quantitatively into the quaternary salt, XXXIX.⁵⁹ This facile synthesis of carbethoxyaminophenanthridines provides a method of synthesizing phenanthridinium salts with various substituents.⁵⁹



As a result of intensive investigation it has been determined that quaternary phenanthridinium compounds containing two primary amino groups, at least one of which is situated in the phenanthridine nucleus, constitute the most powerful chemotherapeutic agents known

against trypanosomiasis (African sleeping sickness). Reduction of trypanocidal action is produced by substitution in the amino group or groups of the phenanthridine part of the molecule. If the amino groups are restricted to a 6-phenyl ring, trypanocidal action is weak.^{33, 34, 57, 59, 60}

It was mentioned in Section Bc that ring closure of nicotinamido-biphenyls yields the 6-(3'-pyridyl)-phenanthridines. Conversion of the latter compounds into monoquaternary salts may involve either the pyridyl or the phenanthridyl basic centers, but the following transformations prove conclusively that it is the pyridyl nitrogen which is involved (compare reference 121). Oxidation of 6-(3-pyridyl)phenanthridine methiodide (XXXIXa) with alkaline ferrocyanide gives 6-(6-oxo-1-methyl-3-pyridyl)phenanthridine (XXXIXb), the constitution of which follows from its conversion into the thiopyridone derivative (XXXIXd). Quaternization of XXXIXb gives the corresponding



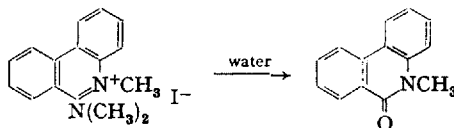
5-methiodide, XXXIXc, which exhibits the typical reactions of a 5-methyl-6-arylphenanthridinium salt in giving a pseudo base with one equivalent of alkali which is unaltered by treatment with hot alkaline ferricyanide.

The dimethiodide salt of 6-(3-pyridyl)phenanthridine on oxidation with ferricyanide gives 5-methylphenanthridone, the quaternary pyridyl group being removed; however, treatment of the dimethiodide with alkali followed by ferricyanide at room temperature results in loss of the 5-methiodide and the formation of XXXIXb. Further work

shows that 5-methylphenanthridone can also be obtained from the dimethiodide salt by simply heating with alcoholic sodium hydroxide. The conversion presumably takes place by a direct transfer of hydrogen from the C₈ hydroxyl group of the intermediate pseudo base to the quaternary pyridyl grouping.⁹⁸

The pseudo base derived from 3,8-diamino-5-methyl-6-phenylphenanthridinium bromide (Dimidium bromide) reacts readily with alcohols (especially easily with butanol) to give practically colorless alkoxy derivatives from which the colored salts are regenerated with acids with liberation of the alcohols. This behavior may be used as diagnostic of quaternization of the phenanthridine nitrogen atom.

The ease with which 5-methylphenanthridinium salts give 5-methylphenanthridones is perhaps demonstrated most convincingly by the smooth conversion of 6-dimethylamino-5-methylphenanthridinium iodide into 5-methylphenanthridone even in warm water.

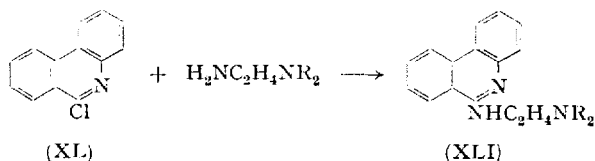


Comparisons have been made between stilbamidines and phenanthridinium compounds in *Trypanosoma congolense* infections. The most active compounds of each series have been compared, namely, dimethylstilbamidine, or 4,4'-diamidino- α,β -dimethylstilbene, and 8-amino-6-*p*-aminophenyl-5-methylphenanthridinium chloride. The latter was found to be twice as toxic but also twice as active against acute strains of *T. congolense*; however against one chronic strain the phenanthridinium compound was the less active of the two compounds.

D. Aminoalkylphenanthridines

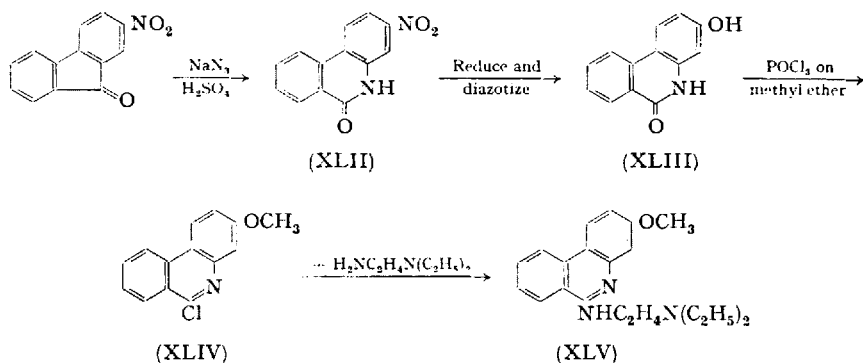
As with 2-chloropyridine, the chlorine atom in the position adjacent to the N atom is reactive; for example, when 6-chlorophenanthridine (XL) is heated with an excess of a diamine at 120°, substances of the type XLI are formed. They are colorless, oily bases stronger than quinine, for only dihydrochlorides can be prepared.¹⁸

Several of these compounds have been tested in avian malaria and trypanosomiasis and found to possess no curative properties. Attempts to obtain the same type of compound by alkylation of 6-amino-



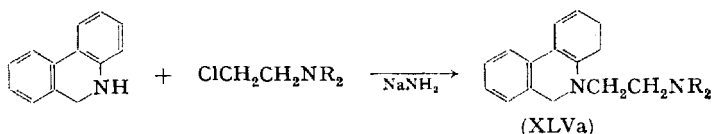
phenanthridine have been unsuccessful; only intractable gums are formed in all cases.

Several β -dialkylaminoalkylaminophenanthridines that are substituted in the nucleus by methoxyl groups also have been prepared.¹⁹ These compounds are close approximations to the antimalarials, Plasmochin and Atabrine, and may be obtained from phenanthridones. For example, when 2-nitrofluorenone is dissolved in concentrated sulfuric acid and treated with sodium azide it gives 3-nitrophenanthridone (XLII), which can be reduced, diazotized, and converted to 2-hydroxyphenanthridone (XLIII). The latter compound is then converted to the methyl ether which, in turn, is smoothly converted to 6-chloro-3-methoxyphenanthridine (XLIV) by reaction with phosphoryl chloride. This chloro compound reacts with β -aminotriethylamine to give 3-methoxy-6-(2-diethylaminoethylamino)phenanthridine, (XLV).



These compounds lack therapeutic value and are more toxic than the well-known antimalarials.

Several 5,6-dihydrophenanthridines¹⁰⁹ were condensed with various substituted aminoethyl halides in the presence of sodamide, using toluene as the solvent, to give compounds of type XLVa.



Condensation of 4-amino-6-methylphenanthridine with β -chloroethyl-diethylamine hydrochloride proceeds smoothly to give 4-(β -diethylaminoethylamino)-6-methylphenanthridine.⁸⁴ The same type of *N*-alkylation has been achieved by simply heating the reactants together at 100° without the use of sodamide.¹¹⁴

When 6-chloromethylphenanthridine reacts with isopropylamine, benzylamine, benzyloisopropylamine, dimethylamine, piperidine, or morpholine, the corresponding secondary or tertiary amine is obtained. It has also been found that tertiary benzylamines of this type can be obtained by benzylation of the secondary amines.¹¹⁹

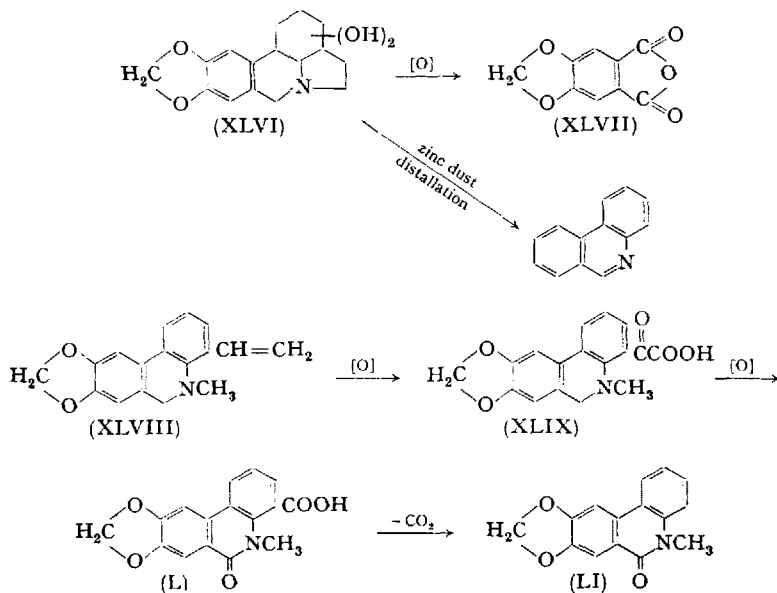
When *N*-benzyl-*p*-toluenesulfonamide is treated with 6-chloromethylphenanthridine the expected alkylation reaction takes place with the formation of *N*-benzyl-*N*-(6-phenanthridylmethyl)-*p*-toluenesulfonamide. Other products resulting from the replacement of the chlorine atom in 6-chloromethylphenanthridine include 6-(β -diethylaminoethoxymethyl)phenanthridine and 6-phenanthridylacetone-trile.¹¹⁹

E. Plant Alkaloids of the Phenanthridine Group

From the plant, *Lycoris radiata*, nine alkaloids have been isolated, of which lycorine, lycoramine, and tazettine have been investigated most intensively.⁶⁹

On oxidation with alkaline permanganate, lycorine (XLVI) furnished hydrastic anhydride (XLVII) (4,5-methylenedioxy-*o*-phthalic anhydride).⁶⁷ Kondo and Uyeo^{27, 28, 68} later found that, on distillation with zinc dust, lycorine yielded phenanthridine. They also found that the lycorine-anhydromethine base (XLVIII) (obtainable by degradation of the quaternary methylammonium base of lycorine), on oxida-

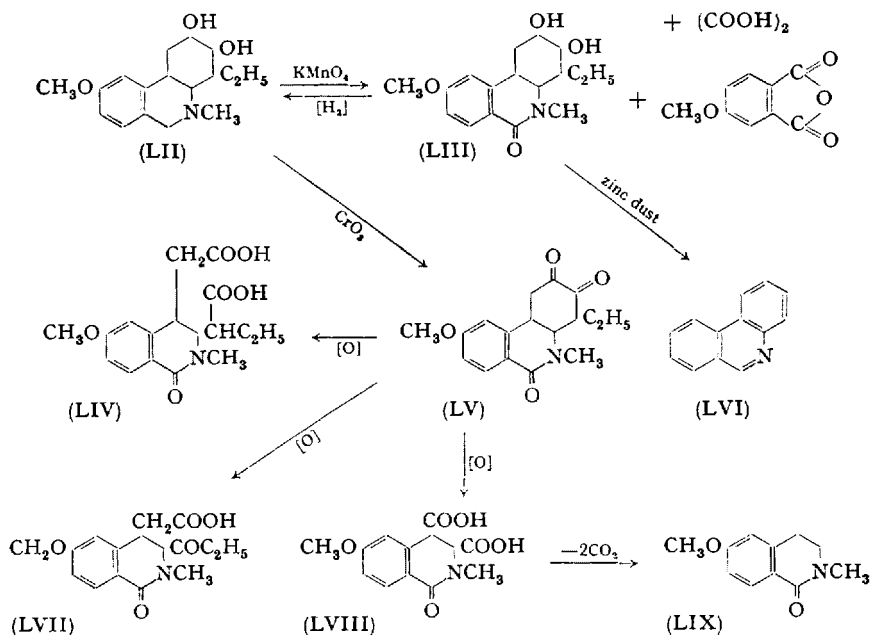
tion with permanganate, yielded two acids tentatively assigned the structures, XLIX and L. Conversion of XLIX to L was effected by further oxidation with hydrogen peroxide; therefore, it must be a 2-oxocarboxylic acid. The acid, L, was decarboxylated to give 5-methyl-8,9-methylenedioxyphenanthridone (LI), whose structure was confirmed by synthesis²⁷ (see Section Bi).



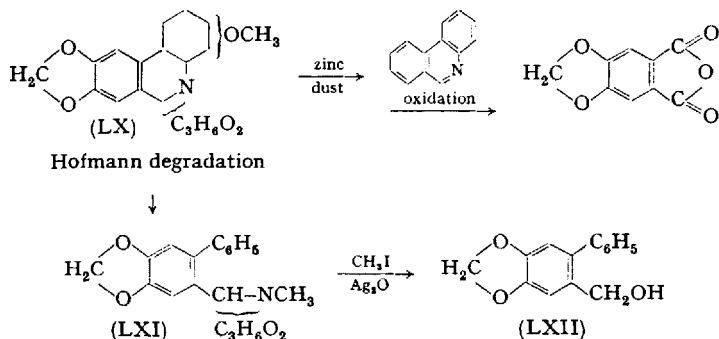
The base, lycoramine (LII), contains one methylamino group, one methoxyl group, and two nonphenolic hydroxyl groups. On oxidation with permanganate, it yields oxalic acid, *m*-methoxyphthalic anhydride, and a neutral substance, LIII, from which the parent base is regenerated on electrolytic reduction. Zinc dust distillation of LIII gives 4-methylphenanthridine (LVI). The base, LII, on oxidation with chromic acid, gives the diketone, LV, which on further oxidation with permanganate yields three acids: LIV, LVII, and LVIII. On decarboxylation, the acid, LVIII, yields 6-methoxy-2-methyldihydroisocarbostyryl (LIX). On the basis of these and other results, structure LII is assigned to lycoramine.³⁶

Tazettine (LX) has been isolated by Späth and Kahover⁷⁰ from the bulbs of *Narcissus tazetta* L. Distillation of tazettine with zinc dust

yields phenanthridine, and oxidation with permanganate furnishes hydrazic acid. The methiodide of tazettine gives the oily methine base (LXI) by a Hofmann degradation. On treatment with methyl iodide



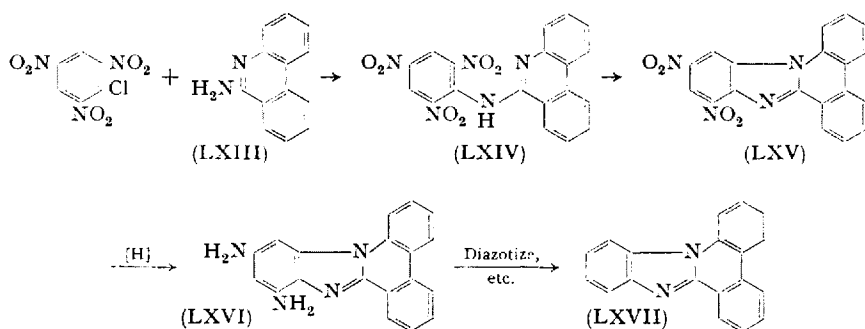
and silver oxide, this latter compound yields 6-phenylpiperonyl alcohol (LXII), which has been synthesized by heating 6-bromopiperonal and iodobenzene in the presence of Naturkupper C and subjecting the resulting aldehyde to a Cannizzaro reaction.



To account for these and other reactions, the partial formula (LX) has been assigned to tazettine. Several other alkaloids of the phenanthridine group, and the pharmacology of these compounds, are discussed by Henry.⁶⁹

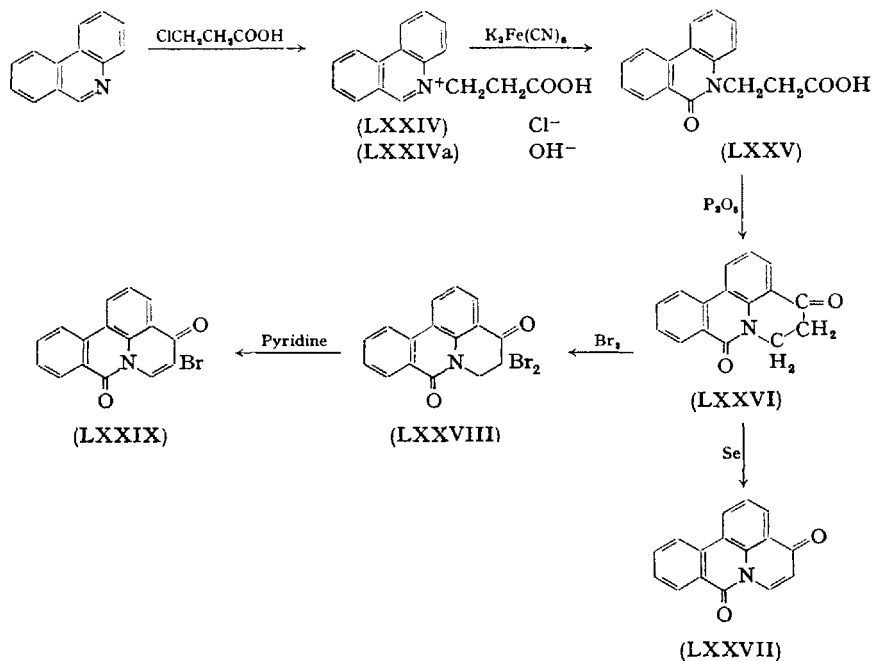
F. Reactions of Phenanthridine Derivatives¹⁰⁸

In an attempt to prepare therapeutically active compounds, Morgan and Stewart⁹⁹ have prepared a series of 1,3-diazolines by condensation of 6-aminophenanthridine with picryl chloride; the initial addition compound readily loses the elements of nitrous acid to form a diazoline. For example, 6-aminophenanthridine (LXIII) is condensed with picryl chloride in xylene to give 6-picrylaminophenanthridine (LXIV). If the solution is heated under reflux, oxides of nitrogen are spontaneously evolved, and a mixture of LXIV and LXV is formed. If this mixture is treated further with boiling dimethylaniline, the reaction goes smoothly to completion yielding 10,12-dinitrobenzimidazo[1,2-*f*]phenanthridine (LXV). The latter compound can be reduced to the diamino compound (LXVI) and the 10,12-diaminobenzimidazo[1,2-*f*]phenanthridine (LXVI) converted to the parent base, benzimidazo[1,2-*f*]phenanthridine (1,2,3,4-dibenzo-4a,9-diazafluorene) (LXVII) by elimination of the amino groups through diazotization.



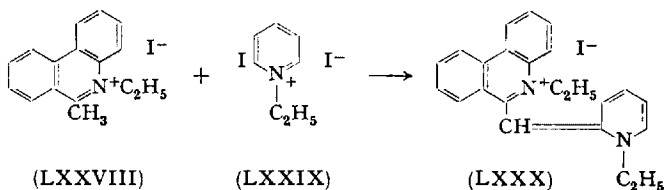
Phenanthridine reacts with two equivalents of methyl acetylenedicarboxylate in benzene solution, forming a labile adduct (LXVIII).⁴⁷ If ether or acetonitrile is used as a solvent, a yellow by-product is also obtained; this yellow substance has been shown to be the trimethyl

derivatives, and examined their behavior. Phenanthridine and β -chloropropionic acid react at $205-10^\circ$ to give 5- β -carboxyethylphenanthridinium chloride (LXXIV). Sodium hydroxide converts the latter compound into the quaternary ammonium base (LXXIVa), which is oxidized in the usual manner to give the phenanthridone derivative (LXXV). This is cyclized by means of phosphorus pentoxide in xylene to give the diketone (LXXVI). Treatment of LXXVI with selenium gives the dehydrogenated product, 4-oxo-6a-azabenzanthrone (LXXVII). It is not possible to obtain LXXVII by bromination and subsequent removal of hydrogen bromide with pyridine, for two bromine atoms enter the position alpha to the 4-oxo group to give LXXVIII, and pyridine removes only one molecule of hydrogen bromide, resulting in LXXIX.



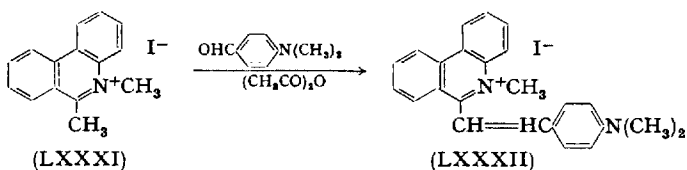
Several cyanine dyes containing the phenanthridine nucleus have been synthesized.²⁶ The method used consists in condensing a quaternary salt of 6-methylphenanthridine with a quaternary salt of 2-iodopyridine. For example, 6-methylphenanthridine is heated first with

ethyl *p*-toluenesulfonate at 100° for 3 days and then with potassium iodide in water, to give LXXVIII. The salt thus formed is heated with 2-iodopyridine ethiodide (LXXIX) and triethylamine in *n*-propyl alcohol at 100° for 40 minutes to give the dye, LXXX. This dye and



others of the same type show no signs of photographic sensitizing action (*cf.* p. 249 in Chapter III).

In examining a series of styryl compounds as possible bactericides, Petrow⁶¹ has developed a new method for preparing styryl derivatives of the phenanthridine series. For instance, 6-methylphenanthridine methiodide (LXXXI) and *p*-dimethylaminobenzaldehyde react in the presence of acetic anhydride to give 6-*p*-dimethylaminostyrylphenanthridine methiodide (LXXXII) in excellent yield.

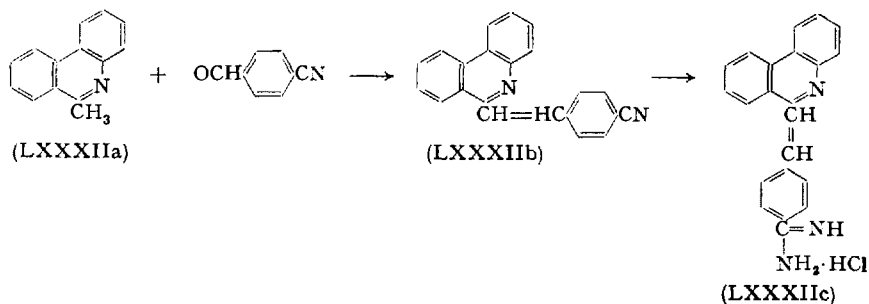


It has been suggested that the condensation proceeds through the intermediate formation of alkine bases, which, as has been shown, can undergo dehydration under these conditions. Several more highly substituted styryl derivatives of the same type have been synthesized.

6-Methylphenanthridine (LXXXIIa) has been condensed with *p*-cyanobenzaldehyde⁹⁰ to give the *p*-cyanostyryl derivative (LXXXIIb), which is converted to the *cis*- and *trans*-6-(*p*-amidinstyryl)phenanthridine (LXXXIIc).

6-Methylphenanthridine also has been condensed with para-formaldehyde and dimethylamine hydrochloride to give 6-(2'-dimethyl-aminoethyl)phenanthridine. Other secondary amines react in a similar

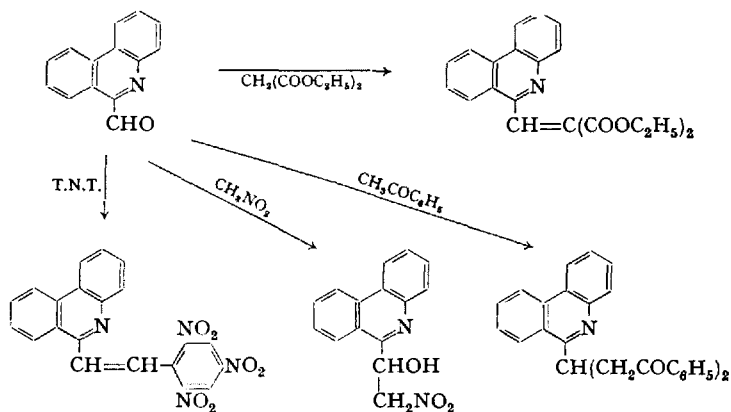
manner.¹¹⁹ The hydrogen of the methyl group of 6-methylphenanthridine is sufficiently reactive to be replaced by chlorine with *N*-chlorosuccinimide.



G. Oxidation

Ritchie^{71e} describes the preparation of 6-formylphenanthridine from 6-methylphenanthridine by oxidation with selenium dioxide.

Potassium dichromate converts the aldehyde quantitatively to phenanthridone. Potassium permanganate in acid solution at 60° likewise gives phenanthridone, but at 40° it produces chiefly the 6-carboxylic acid. The aldehyde does not undergo the benzoin condensation, nor is it reducible with formaldehyde in alkaline solution; it has been condensed with ethyl malonate, acetophenone, nitromethane, and trinitrotoluene to give the condensation products expected.^{71e} An



important reaction which the aldehyde undergoes is the reductive aldehyde-amine condensation. With either β -diethylaminoethylamine

or β -aminoethylmorpholine, the expected secondary amine is obtained with hydrogen and Raney nickel.¹¹⁹

6-Benzylphenanthridines also are oxidized readily with selenium dioxide to 6-benzoylphenanthridines.^{71b, 118}

H. Direct Substitution

Quite surprisingly, very little work has been done on the introduction of substituents directly into the phenanthridine nucleus. Walls²¹ reports that the nitration of phenanthridine gives rise to three mononitro compounds whose orientations have not been determined. His method consists in dissolving the phenanthridine in concentrated sulfuric acid and adding solid sodium nitrate. Phenanthridine is not nitrated by hot nitric acid.

Because of the failure of the halobenzaldehyde synthesis for preparing 3,8-diaminophenanthridine (see Section Bi), Ritchie^{71a} has investigated the nitration of 5,6-dihydrophenanthridine. The latter compound is obtained by the tin and hydrochloric acid reduction of phenanthridine. The reduced compound is acetylated and treated with fuming nitric acid, thereby forming 2-nitro-5-acetyl-5,6-dihydrophenanthridine, which, upon hydrolysis, gives 2-nitrophenanthridine; this is probably identical with one of the products of unknown constitution obtained by Walls²¹ in the direct nitration of phenanthridine. 6-Methylphenanthridine has been carried through the same series of reactions.

6-Phenylphenanthridine adds phenyllithium to the azomethine linkage giving 6,6-diphenyl-5,6-dihydrophenanthridine. The course of the reaction has been demonstrated by showing that 6-phenyl-6-(*p*-tolyl)-5,6-dihydrophenanthridine is formed from 6-(*p*-tolyl)-phenanthridine and phenyllithium as well as from 6-phenylphenanthridine and *p*-tolyllithium. In the latter case there is also formed a *N,N'*-bis-6-phenylphenanthridine; particularly good yields are obtained when mesityllithium is used.⁸⁵

N-Oxides of Phenanthridine

Conversion of phenanthridine itself and its 6-methyl and 6-ethyl derivatives into the corresponding *N*-oxides is smoothly achieved by

employing perphthalic acid. Peracetic acid, however, has proved to be the reagent of choice for the preparation of the 6-arylphenanthridine *N*-oxides,⁹⁶ which generally differ from their 6-alkyl analogs in failing to liberate iodine from potassium iodide.

Reduction of the nitro-6-phenylphenanthridines with stannous chloride in hydrochloric acid furnishes the corresponding amino-6-phenylphenanthridine *N*-oxides.⁹⁶

By the action of phosphoryl chloride on 6-phenylphenanthridine *N*-oxide, 2-chloro-6-phenylphenanthridine has been obtained. 6-Methylphenanthridine *N*-oxide, however, gives 6-chloromethylphenanthridine together with what is probably 2-chloro-6-methylphenanthridine.⁹⁶

Attempts to obtain the *N*-oxide analog of Dimidium bromide have proved unsuccessful.⁹⁶

I. Properties

Phenanthridine, in a recent review,¹²⁸ is compared with acridine and other aza-aromatics in both physical and chemical properties. It crystallizes from dilute alcohol in long hair-like white needles which melt at 104° (106°) and it boils without decomposition at 349° (769 mm).⁶⁶ It is soluble with difficulty in cold water (1:35000) to give solutions with a weak blue fluorescence.¹ This fluorescence is very marked with some methoxy derivatives^{19,71a} and is increased by reduction of the pyridine ring,² and it is diminished in the 7,8,9,10-tetrahydrophenanthridine system.¹¹ Its vapors are irritating and cause sneezing.

In comparing phenanthridine with acridine, its behavior toward reducing agents is significant. With acridine, tin and hydrochloric acid give a substance with no basic properties while, with phenanthridine, a basic 5,6-dihydro derivative⁶⁵ is produced; the latter gives a nitroso compound with nitrous acid. This difference is attributed to the dissimilar linking of the nitrogen atoms, for in hydroacridine, as in carbazole, the nitrogen is connected to phenyl groups, whereas in dihydrophenanthridine it is joined to a phenyl and a methylene group.¹

Substituted 5,6-dihydrophenanthridines are obtained from phenanthridinium salts by hydrogenation with palladium on charcoal in aqueous solution at 1 to 20 atmospheres or in alcohol in the presence

of sodium carbonate or sodium acetate.^{87, 114} Phenanthridine itself is quantitatively reduced to the dihydro derivative by hydrogen with Raney nickel.¹⁰⁹ 6-Methylphenanthridine is readily reduced to 6-methyl-5,6-dihydrophenanthridine in the presence of platinum at room temperature; at 100° and 1000 p.s.i. 6-methyloctahydrophenanthridine is obtained.^{114, 118} 6-Bromophenanthridine is readily transformed by hydrogenation with Raney nickel into phenanthridine; the yield is 95%. Hydrogenation usually ceases abruptly when two atoms of hydrogen have been taken up.⁸²

Phenanthridine is stable toward chromic acid in acetic acid and toward dilute nitric acid. Alkaline potassium permanganate attacks it very slowly.⁴

The salts which phenanthridine forms with colorless acids are colorless¹⁵ and are easily hydrolyzed upon dilution with water. Besides forming salts with mineral acids, it yields a picrate, an insoluble nitrite, and well-defined crystalline derivatives with platinic, auric, and mercuric chlorides.¹ Morgan and Davis¹¹² have prepared coordination compounds with rhenium oxycyanide during valency studies on the latter metal.

The recent calculations of Torguet, Higgins, and Coulson¹¹³ of the relative net charges at external positions of the phenanthridine nucleus have provided theoretical confirmation of the known activity of C_6 toward nucleophilic reagents. The dipole moment of phenanthridine has been found to be 1.5, *vs.* a calculated value of 1.6,⁴⁵ and its melting-point diagram with benzalaniline has been determined.⁵⁰

The basic strengths of several phenanthridines have been measured.¹⁰⁰ Phenanthridine itself is a weak base ($pK_a = 3.30$ in 50 % alcohol at 20°),¹⁰⁰ and its salts with mineral acids, which are largely dissociated in solution, are generally more soluble and less fluorescent than those of acridine.¹ An excellent review of the chemistry of phenanthridine has been published.¹²⁷

J. Tables

In accordance with the general plan, the derivatives of phenanthridine are grouped into nine tables:

1. Alkyl and aryl phenanthridines.	6. Hydroxy- and Alkoxyphenanthridines.
2. Hydrogenated phenanthridines.	7. Carboxyphenanthridines.
3. Halogenated phenanthridines.	8. Phenanthridine oxides.
4. Nitrophenanthridines.	9. Miscellaneous.
5. Aminophenanthridines.	

In exception to the general plan, hydrogenated phenanthridines are all collected in Table IV-3 regardless of any other functional groups. Also in exception to the general plan, in each table the compounds are arranged so that the substituted phenanthridine with the lowest numbered substituent occurs first; the others are in numerical order. The nitro, amino, and hydroxy derivatives, where the main functional derivative is not attached directly to the nucleus, are collected in the latter part of their respective tables.

TABLE IV-2. Alkyl and Aryl Phenanthridines

Substituent and position	M.p., °C.	Refs.
Unsubstituted base	104	21, 30, 71, 82
1-C ₂ H ₅ -	P 223	28
1,3-(CH ₃) ₂ -	76.5	30
1,10-(CH ₃) ₂ -6-C ₆ H ₅ -	Gum	71
2-CH ₃ -	89	30
2-C ₂ H ₅ -	62	28
2,4-(CH ₃) ₂ -	84.5	30
3-CH ₃ -	81	71
3-C ₂ H ₅ -	P 216	28
3-CH ₃ -6-C ₆ H ₅ -	120	71
3,6-(CH ₃) ₂ -	104	61, 71
4-CH ₃ -	95.5	30, 35, 89
4-C ₂ H ₅ -	P 231	28
6-CH ₃ -	84	15, 20, 29, 42, 71, 119
6-C ₂ H ₅ -	56.5	20
6-C ₆ H ₅ -	109	15, 20, 29, 36, 83, 85, 108
6-C ₆ H ₅ CH ₂ -	112	71, 103
6-(1'-C ₁₀ H ₇)-	125	29, 71

(Table continued)

TABLE IV-2 (*continued*)

Substituent and position	M.p., °C.	Refs.
6-(2',4',6'-(CH ₃) ₃ C ₆ H ₂)-	157	71
6-C ₆ H ₅ CH ₂ CH ₂ -	93	71
6-C ₆ H ₅ CH=CH-	133	71
6-(4'-CH ₃ C ₆ H ₄)-	108	85, 96
6-(3'-CH ₃ C ₆ H ₄)-	99	96
6-C ₆ H ₁₁ -	205 (dec.)	108
6-C ₆ H ₉ -	48	108
6- <i>n</i> -C ₇ H ₁₅ -	50	83
6,6'-(-CH ₂) ₄ -	214	71
6,9-(CH ₃) ₂ -	P 214	11
6-(4'-CH ₃ C ₆ H ₄ CH=CH)-	87	71
8-CH ₃ -	88	30
π,π' -(CH ₃) ₂ -	P 241	25

TABLE IV-3. Hydrogenated Phenanthridines

5,6-Dihydrophenanthridines	M.p., °C.	Refs.
Unsubstituted base	90	2, 91, 71, 109
2-NO ₂ -5-CH ₃ CO-6-CH ₃ -	204	71
3,8-(CH ₃ CONH-) ₂ -5-CH ₃ -6-C ₆ H ₅ -	181	87
3,8-(CH ₃ CONH-) ₂ -5-CH ₃ -6-C ₆ H ₅ CO-	193-5	118
5-C ₂ H ₅ -6-OH-	95	6
5-CH ₃ -6-OH-	109	8, 10
5-CH ₃ -6-C ₆ H ₅ CH ₂ -	175-7	87, 118
5-CH ₃ -6-(4'-CH ₃ OC ₆ H ₄ CH ₂)-	HCl 168	87, 118
5-CH ₃ -6-(4'-CH ₃ OC ₆ H ₄ CH ₂)-8-CH ₃ O-	93-4	87, 118
5-CH ₃ -6-C ₆ H ₅ -	102	87, 118
5,6-(CH ₃) ₂ -8-OH-	182	87, 118
5,6-(CH ₃) ₂ -8-C ₂ H ₅ OCO-	90	87, 118
5-CH ₃ -	108	8, 115
5,6-(CH ₃) ₂ -8-CH ₃ CONH-	173	87, 118
5-CH ₃ -6-(4'-CH ₃ CONHC ₆ H ₄ CO)-8-C ₂ H ₅ OCONH-	175	118
5-CH ₃ -6-(4'-CH ₃ CONHC ₆ H ₄ CO)-8-C ₂ H ₅ OCONH-10-CH ₃ CO-	205-10	118
5-CH ₃ -3,8-(C ₂ H ₅ OCONH-) ₂ -6-C ₆ H ₅ CO-	193-5	118
5,6-(CH ₃) ₂ -8-CH ₃ CO-	110-11	118
5,6-(CH ₃) ₂ -8-NH ₂ -	"Glass"	118
5-CH ₃ -6-CN-	120	10
5-(1'-C ₁₀ H ₇ NHCO)-6-CH ₃ -	133	91
5-(1'-C ₁₀ H ₇ NHCO)-	174	91

(*Table continued*)

TABLE IV-3 (*continued*)

5,6-Dihydrophenanthridines	M.p., °C.	Refs.
5-C ₆ H ₅ NHCO-6-CH ₃ -	150	91
5-C ₆ H ₅ NHCO-	141	91
5-(4'-CH ₃ C ₆ H ₄ SO ₂ -)-6-CH ₃ -	166-8	114
5-(C ₂ H ₅) ₂ NCH ₂ CH ₂ NH-6-CH ₃ -	187	114
5-C ₂ H ₅ -6-CH ₃ -	HCl 149	114
5-CH ₃ CO-	108	2, 71
5-CH ₃ CO-6-CH ₃ -	102	71
5-CH ₃ CO-8-NO ₂ -	176	71
5-(CH ₃) ₂ NC ₂ H ₄ -	P 184	109
5-(C ₂ H ₅) ₂ NC ₂ H ₄ -	P 159	109
5-C ₅ H ₁₀ NC ₂ H ₄ -	HCl 236-8	109
5-C ₄ H ₈ ONC ₂ H ₄ -	HCl 189-91	109
5-HO ₂ CCH ₂ CH ₂ -	163	56
5-[CH ₃ O ₂ CC(OCH ₃)=C(CO ₂ CH ₃)-]-	108	47
5-CH ₃ O ₂ CC=CHCOOH-	181	47
6-CH ₃ -	88.5	71, 91
6-C ₆ H ₅ -	148	85
6,6-(C ₆ H ₅) ₂ -	275-7	85
6-C ₆ H ₅ -6-(4'-CH ₃ C ₆ H ₄)-	144	85
6-CH ₃ -8-OH-	300	87
π,π' -(NO ₂) ₂ -	209	71
π,π' -(NO ₂) ₂ - π'' -CH ₃ CO-	218	71
7,8,9,10-Tetrahydrophenanthridines	M.p., °C.	Refs.
	63	30, 84, 89
1,4-(CH ₃ O) ₂ -	86.5	30
1,4-(CH ₃) ₂ -	63.0	30, 89
1(or 3)-CH ₃ -	Oil	89
2-CH ₃ -	73.5	30
2-Br-	110	30
2-Cl-	90	30, 89
2,4-(CH ₃) ₂ -	49.5	30, 89
2-CH ₃ O-	110	89
2-NO ₂ -	172	89
2-C ₆ H ₅ -	122	89
2-CH ₃ -6-NH ₂ -	170	89
2,4-(CH ₃) ₂ -6-NH ₂ -	137	89
4-CH ₃ -	80.5	30, 89
4-NO ₂ -	Oil	30
4-CH ₃ -6-NH ₂ -	122	89
4-CH ₃ O-	106	89
6,9-(CH ₃) ₂ -	78	11
6-NH ₂ -	165	89
8-CH ₃ -	45	30, 89

(Table continued)

TABLE IV-3 (*continued*)

Other Tetrahydrophenanthridines	M.p., °C.	Refs.
2,3-(CH ₃) ₂ -8,9-(CH ₃ O) ₂ -6-C ₆ H ₅ -1,4-4a,10b-	178-80	36
2,3-(CH ₃) ₂ -8,9-(CH ₃ O) ₂ -1,4,4a,10b-	158.5	36
Hexahydrophenanthridines	M.p., °C.	Refs.
2,3-(CH ₃ O) ₂ -8,9-(CH ₃) ₂ -5,6,6a,7,10,10a-	HCl 240	44
2,3-(CH ₃ O) ₂ -8,9-(CH ₃) ₂ -5-NO-5,6,6a,7,10,10a-	186	44
Octahydrophenanthridines	M.p., °C.	Refs.
1,2,3,4,7,8,9,10-	38	42
6-CH ₃ -1,2,3,4,7,8,9,10-	68	42
6-CH ₃ -octahydro-	57-8	114
8,9-(CH ₃) ₂ -5,6,6a,7,8,9,10,10a-	HCl 181	44

TABLE IV-4. Halogenated Phenanthridines

Phenanthridine	M.p., °C.	Refs.
2-Br-6-(4'-BrC ₆ H ₄)-	234	62
2-Br-6-CH ₃ -	129	19, 62
2-Cl-6-(4'-ClC ₆ H ₄)-8-NO ₂ -	318	108
4-Cl-6-CH ₃ -	113-4	84
6-Cl-	117-8	18, 71, 125
6-ClCH ₂ -	134	20, 119
6-(2'-ClC ₆ H ₄)-	125	96
6-(3'-ClC ₆ H ₄)-	138	96
6-(4'-ClC ₆ H ₄)-	157.5	96
6-Br-		7, 18, 82
8-Cl-6-C ₆ H ₅ -	120	96
2,6-(Br) ₂ -	170-1	19
3,8-(Br) ₂ -6-CH ₃ -	186	62, 71
3,8-(Br) ₂ -6-C ₆ H ₅ -	201	71

TABLE IV-5. Nitrophenanthridines

Phenanthridine	M.p., °C.	Refs.
2-NO ₂ -	263	71
2-NO ₂ -3-CH ₃ -	201	21, 71
2-NO ₂ -6-(3'-NO ₂ C ₆ H ₄)-	269	58, 77
2-NO ₂ -6-(2'-NO ₂ C ₆ H ₄)-	227	21
2-NO ₂ -6-(4'-NO ₂ C ₆ H ₄)-	294	33, 43, 58
2-NO ₂ -6-C ₆ H ₅ -	229	96

(*Table continued*)

TABLE IV-5 (*continued*)

Phenanthridine	M.p., °C.	Refs.
2-NO ₂ -6-CH ₃ CO-	181	71
2-Br-6-(4'-NO ₂ C ₆ H ₄)-8-NO ₂ -	348	58
2,8-(NO ₂) ₂ -6-CH ₃ -		46
2,8-(NO ₂) ₂ -6-C ₆ H ₅ -	227	33, 58
3,8-(NO ₂) ₂ -6-C ₆ H ₅ -	274	58, 71, 83, 102, 108, 110, 116, 123
3,8-(NO ₂) ₂ -6-(4'-NO ₂ C ₆ H ₄)-	356-8	95
4-NO ₂ -6-CH ₃ -	167	84
4-NO ₂ -6-COOH-	248	84
6-CH ₃ -8-NO ₂ -	243	21
6-(3'-NO ₂ C ₆ H ₄)-8-NO ₂ -	269	58, 77
6-(4'-NO ₂ C ₆ H ₄)-8-NO ₂ -	327	33, 58, 83, 108
6-(4'-ClC ₆ H ₄)-8-NO ₂ -	291	83, 108
6-C ₆ H ₅ -8-NO ₂ -	327	58, 33
6-(4'-CH ₃ OSO ₂ C ₆ H ₄)-8-NO ₂ -	292	108
6-(4'-NO ₂ C ₆ H ₄)-	192	20, 83, 108
8-NO ₂ -	178	71
Nitro Group Not Attached Directly to Nucleus		
6-(4'-NO ₂ C ₆ H ₄)-1,10-(CH ₃) ₂ -	163	71
6-(4'-NO ₂ C ₆ H ₄)-	191	83, 108
6-(2',4',6'-(NO ₂) ₃ C ₆ H ₂ CH=CH)-	180	71
6-(3',5'-(NO ₂) ₂ C ₆ H ₃)-	294	58
6-(2'-NO ₂ C ₆ H ₄)-	122.5	20
6-(3'-NO ₂ C ₆ H ₄)-	172	20
6-(4'-NO ₂ C ₆ H ₄ CH ₂)-	168	103

TABLE IV-6. Aminophenanthridines

Phenanthridine	M.p., °C.	Refs.
1,10-(CH ₃) ₂ -6-CH ₃ CONH-	199	71
2-NH ₂ -6-CH ₃ -	152	21, 33, 79
2-(CH ₃) ₂ N-6-CH ₃ -	146	33
2-CH ₃ CONH-6-CH ₃ -	240-2	21, 33, 61
2-C ₂ H ₅ OCONH-6-CH ₃ -	180	57, 79
2-CH ₃ -6-NH ₂ -	170-1	89
2,4-(CH ₃) ₂ -6-NH ₂ -	142-3	89
2,8-(NH ₂) ₂ -	198	71
2,8-(NH ₂) ₂ -6-CH ₃ -		46
2,8-(CH ₃ CONH-) ₂ -6-CH ₃ -		46

(*Table continued*)

TABLE IV-6 (*continued*)

Phenanthridine	M.p., °C.	Refs.
2-NH ₂ -6-(4'-NH ₂ C ₆ H ₄)-	233	33, 43
2-NH ₂ -6-(3'-NH ₂ C ₆ H ₄)-		77
2-Br-6-(C ₂ H ₅) ₂ NC ₃ H ₄ NH-	P 156	19
2-Br-6-(4'-NH ₂ C ₆ H ₄)-8-NH ₂ -	265	58
2-CH ₃ CONH-6-(4'-CH ₃ CONHC ₆ H ₄)-	328	33
2-CH ₃ CONH-6-(3'-CH ₃ CONHC ₆ H ₄)-	HCl 215-7	77
2-Br-6-(C ₂ H ₅) ₂ NCH(CH ₃)CH ₂ CH ₂ CH ₂ NH-	P 218	19
2-CH ₃ CONH-6-(4'-(CH ₃) ₂ NC ₆ H ₄ CH=CH)-	CH ₃ I 268	61
2,8-C ₂ H ₅ OCONH-6-C ₆ H ₅ -	CH ₃ Cl 261	79, 110
2,8-(NH ₂) ₂ -6-C ₆ H ₅ -	194	57-59
2-C ₂ H ₅ OCONH-6-(4'-C ₂ H ₅ OCONHC ₆ H ₄)-	CH ₃ Cl 261	57, 79
2-NH ₂ -6-(3'-C ₅ H ₄ N)-	128	98
2-CH ₃ CONH-6-(3'-C ₅ H ₄ N)-	253	98
2-Br-6-(4'-CH ₃ CONHC ₆ H ₄)-8-CH ₃ CONH-	301	58
2,8-(CH ₃ CONH-) ₂ -6-C ₆ H ₅ -	266	58
2-NH ₂ -6-(4'-(CH ₃) ₂ NC ₆ H ₄ CH=CH)-		61
2-[NH=C(NH ₂)]-6-[4'-NH=C(NH ₂)C ₆ H ₄]-		62
2-[NH=C(NH ₂)]-6-CH ₃ -		62
2-NO ₂ -6-(4'-C ₂ H ₅ OCONHC ₆ H ₄)-	245-50	120
2-NO ₂ -6-(4'-NH ₂ C ₆ H ₄)-	297	120
2-NO ₂ -6-(4'-CH ₃ OCONHC ₆ H ₄)-	269	120
2-NO ₂ -6-(4'-n-C ₃ H ₇ OCONHC ₆ H ₄)-	265	120
2-NO ₂ -6-(4'-i-C ₃ H ₇ OCONHC ₆ H ₄)-	272	120
2-NO ₂ -6-(4'-n-C ₄ H ₉ OCONHC ₆ H ₄)-	251	120
2-NO ₂ -6-(3'-C ₂ H ₅ OCONHC ₆ H ₄)-	232	120
2-NO ₂ -6-(4'-CH ₃ SO ₂ NHC ₆ H ₄)-	259-62	120
2-NO ₂ -6-(4'-C ₂ H ₅ SO ₂ NHC ₆ H ₄)-	223-4	120
2-NO ₂ -6-(4'-CH ₃ SO ₂ N(CH ₃)C ₆ H ₄)-	274-5	120
3-C ₂ H ₅ OCONH-6-(4'-NO ₂ C ₆ H ₄)-	258	103
3-NH ₂ -6-CH ₃ -	174-5	103
3-C ₂ H ₅ OCONH-6-CH ₃ -	197	103
3,8-(NH ₂) ₂ -6-(3'-C ₅ H ₄ N)-	262-4	121
3,8-(CH ₃ CONH-) ₂ -	296	71
3,8-(NH ₂) ₂ -6-CH ₃ -	265	59, 72
3-NO ₂ -6-C ₆ H ₅ -8-NH ₂ -	281-3	71
3,8-(NH ₂) ₂ -6-C ₆ H ₅ -	198	58, 59, 71
3-CH ₃ O-6-(C ₂ H ₅) ₂ NC ₃ H ₄ NH-	P 207	19
3,8-(CH ₃ CONH) ₂ -6-CH ₃ -	252	59, 72, 79
3-CH ₃ O-6-[(C ₂ H ₅) ₂ NCH(CH ₃)CH ₂ CH ₂ CH ₂ NH]-	192-3	19
3,8-(C ₂ H ₅ OCONH) ₂ -6-C ₆ H ₅ -	222	57, 59, 72, 79, 95
3,8-(C ₂ H ₅ OCONH) ₂ -6-C ₆ H ₅ CH ₂ -	255	95
3,8-(C ₂ H ₅ OCONH) ₂ -6-(2'-C ₄ H ₃ S)-	227-9	95

(Table continued)

TABLE IV-6 (continued)

Phenanthridine	M.p., °C.	Refs.
3,8-(C ₂ H ₅ OCONH) ₂ -6-(5'-NO ₂ -2'-C ₆ H ₄ O)-	286-8	95
3,8-(C ₂ H ₅ OCONH) ₂ -6-(3'-C ₅ H ₄ N)-	196-8	95, 121
3,8-(C ₂ H ₅ OCONH) ₂ -6-(5',6'-dihydro-3'-pyranyl)-	215-6	95
3,8-(C ₂ H ₅ OCONH) ₂ -6-(4'-NO ₂ C ₆ H ₄)-	247	95
3,8-(C ₂ H ₅ OCONH) ₂ -6-(4'-CH ₃ OC ₆ H ₄)-	190-2	95
3,8-(C ₆ H ₅ CONH) ₂ -6-C ₆ H ₅ -	321-2	96
3,8-(C ₂ H ₅ OCONH) ₂ -6-C ₆ H ₅ CO-	244	118
3,8-(C ₂ H ₅ OCONH) ₂ -6-CH ₃ -	169-71	118
3,8-(C ₂ H ₅ OCONH) ₂ -6-C ₆ H ₁₁ -	234	95
3-NO ₂ -6-(4'-C ₂ H ₅ OCONHC ₆ H ₄)-8-CH ₃ O-	221-3	120
3-NO ₂ -6-C ₆ H ₅ -8-C ₂ H ₅ OCONH-	247-9	120
3-NO ₂ -6-C ₆ H ₅ -8-NH ₂ -	227	120
4-CH ₃ -6-NH ₂ -	116-7	89
4-CH ₃ CONH-6-CH ₃ -	142-3	84
4-NH ₂ -6-CH ₃ -	111-2	84
4-(C ₂ H ₅) ₂ NCH ₂ CH ₂ NH-	56-7	84
5-CH ₃ -6-(4'-NH ₂ C ₆ H ₄)-8-NH ₂ -		49
6-[(CH ₃) ₂ CHCH ₂] ₂ NC ₂ H ₄ NH-	HCl 142-4	18
6-(4'-CH ₃ CONHC ₆ H ₄)-8-CH ₃ CONH-	172-3	33, 79
6-(2'-CH ₃ CONHC ₆ H ₄)-8-CH ₃ CONH-	CH ₃ Cl 240.5	59
6-(4'-CH ₃ CONHC ₆ H ₄)-8-C ₂ H ₅ OCONH-	CH ₃ Cl 213	59
6-(2'-CH ₃ CONHC ₆ H ₄)-8-C ₂ H ₅ OCONH-	CH ₃ Cl 203-5	59
6-(4'-C ₂ H ₅ OCONHC ₆ H ₄)-8-CH ₃ CONH-	CH ₃ Cl 200-6	59
6-(4'-(CH ₃) ₂ NC ₆ H ₄ CH=CH)-8-CH ₃ CONH-	CH ₃ Cl 270-1	61
6-(4'-C ₆ H ₅ OCONHC ₆ H ₄)-8-C ₂ H ₅ OCONH-	CH ₃ Cl 239	57, 79
6-(3'-C ₂ H ₅ OCONHC ₆ H ₄)-8-C ₂ H ₅ OCONH-	CH ₃ Cl 219	79
6-(4'-NO ₂ C ₆ H ₄ CO)-8-C ₂ H ₅ OCONH-	244	118
6-(4'-NO ₂ C ₆ H ₄ CO)-8-NH ₂ -	280	118
6-(4'-NH ₂ C ₆ H ₄ CH ₂)-8-C ₂ H ₅ OCONH-	208	118
6-(4'-C ₂ H ₅ OCONHC ₆ H ₄ CH ₂)-8-C ₂ H ₅ OCONH-	212	118
6-(4'-C ₂ H ₅ OCONHC ₆ H ₄ CO)-8-C ₂ H ₅ OCONH-	242-5	118
6-(3'-C ₅ H ₄ N)-8-NH ₂ -	227-9	98
6-(3'-C ₅ H ₄ N)-8-CH ₃ CONH-	296-8	98
6-CH ₃ -9-C ₂ H ₅ OCONH-	163	103
6-CH ₃ -7-C ₂ H ₅ OCONH-	160	103
6-(4'-NO ₂ C ₆ H ₄)-9-C ₂ H ₅ OCONH-	248	103
6-(4'-NO ₂ C ₆ H ₄)-7-C ₂ H ₅ OCONH-	194	103
6-(4'-NO ₂ C ₆ H ₄)-7-NH ₂ -	180	103
6-(4'-NO ₂ C ₆ H ₄)-8-C ₂ H ₅ OCONH-	CH ₃ Cl 221	103
6-(4'-NO ₂ C ₆ H ₄ CH ₂)-7-NH ₂ -	CH ₃ Cl 245	103
6-(4'-NO ₂ C ₆ H ₄ CH ₂)-	169	103
6-(4'-NO ₂ C ₆ H ₄ CH ₂)-8-C ₂ H ₅ OCONH-	186	103

(Table continued)

TABLE IV-6 (*continued*)

Phenanthridine	M.p., °C.	Refs.
6-(4'-OC ₄ H ₉ NCH ₂ CH ₂ NH)-	HCl 251-4	119
6-(CH ₃) ₂ NCH ₂ CH ₂ NHCH ₂ C ₆ H ₅ -	350-6 (dec.)	119
6-CH ₃ -8-C ₂ H ₅ OCONH-	HCl 199	118
6-[4'-(CH ₃) ₂ NC ₆ H ₄ CH=CH]-8-NH ₂ -		61
6-(4'-HN=C(NH ₂)C ₆ H ₄ -)-8-HN=C(NH ₂)-	HCl 295	62
6-NH ₂ -	195	21, 51, 73, 89
6-CH ₃ NH-	187	33
6-CH ₃ -8-NH ₂ -	232	59, 61, 72, 77, 78
6-(CH ₃) ₂ N-	61.5	33
6-CH ₃ CONH-	193.5	21
6-CH ₃ -8-CH ₃ CONH-	248-9	59, 72, 77, 78
6-CH ₃ -8-C ₂ H ₅ OCONH-	210	59, 72, 79
6-CH ₃ CON(CH ₃)-	155	33
6-(3'-NH ₂ C ₆ H ₄)-8-NH ₂ -	77	
6-(4'-NH ₂ C ₆ H ₄)-8-NH ₂ -	212	33, 62
6-(2'-NH ₂ C ₆ H ₄)-8-NH ₂ -	158	59
6-(C ₂ H ₅) ₂ NC ₂ H ₄ NH-	HCl 238-43	18
6-(4'-NO ₂ C ₆ H ₄)-8-NH ₂ -	279	59, 72
6-(2'-NO ₂ C ₆ H ₄)-8-NH ₂ -	230	59, 72
6-C ₅ H ₁₀ NC ₂ H ₄ NH-	HCl 265-70	18
6-(C ₆ H ₅) ₂ NCH(CH ₃)CH ₂ CH ₂ CH ₂ NH-	P 196-7	19
6-CH ₃ -8-C ₆ H ₅ CONH-	214	61
6-(4'-NH ₂ C ₆ H ₄)-8-CH ₃ CONH-	(CH ₃) ₂ SO ₄ 258	59
6-(2'-NH ₂ C ₆ H ₄)-8-CH ₃ CONH-	HCl 271.5	59
6-(2'-NO ₂ C ₆ H ₄)-8-CH ₃ CONH-	287.5	59, 72
6-(4'-NO ₂ C ₆ H ₄)-8-CH ₃ CONH-	282	59, 72
6-(4'-NH ₂ C ₆ H ₄)-8-C ₂ H ₅ OCONH-	CH ₃ Cl	59
	297-300	
6-(2'-NH ₂ C ₆ H ₄)-8-C ₂ H ₅ OCONH-	CH ₃ Cl 272	59
6-(2'-NO ₂ C ₆ H ₄)-8-C ₂ H ₅ OCONH-	199	59
6-(4'-NO ₂ C ₆ H ₄)-8-C ₂ H ₅ OCONH-	253	59
Amino Group Not Attached Directly to Nucleus		
6-(3'-C ₆ H ₄ N)-	125	83, 98, 108
6-(2'-C ₆ H ₄ N)-	133	83, 108
6-(2'-C ₄ H ₃ S)-	P 215	92
6-(4'-C ₆ H ₄ N)-	160	96
6-(2'-C ₄ H ₃ O)-	P 225-7	92
6-(2'-C ₆ H ₄ -4'-C ₆ H ₆ N)-	183-4	96
6-(2'-NH ₂ C ₆ H ₄)-	168.5	20
6-(3'-NH ₂ C ₆ H ₄)-	159-61	20
6-(4'-NH ₂ C ₆ H ₄)-	197-9	20, 33

(*Table continued*)

TABLE IV-6 (*continued*)

Phenanthridine	M.p., °C.	Refs.
6-C ₅ H ₁₀ NCH ₂ -	90-3	33
6-(4'-CH ₃ C ₆ H ₄ NHCH ₂)-	182	71
6-(4'-NH ₂ C ₆ H ₄)-1,10-(CH ₃) ₂ -	134	71
6-(4'-CH ₃ CONHC ₆ H ₄)-1,10-(CH ₃) ₂ -	199	71
6-(2'-CH ₃ CONHC ₆ H ₄)-	185	20
6-(4'-CH ₃ CONHC ₆ H ₄)-	219	20, 33
6-(4'-(CH ₃) ₂ NC ₆ H ₄)-	179-81	33
6-(CH ₃) ₂ NC ₂ H ₄ OCH ₂ -	HCl 158-66	119
6-(4'-(CH ₃) ₂ NC ₆ H ₄ CH=CH)-	CH ₃ I 237	61
6-(3'-C ₂ H ₅ OCONHC ₆ H ₄)-	CH ₃ Cl 261	79
6-(4'-CH ₃ CONHC ₆ H ₄)-8-(4'-CH ₃ CONHC ₆ H ₄)-	312	95
6-(C ₆ H ₁₁ NHCH ₂)-	90-3	33
6-(3'-CH ₃ CONHC ₆ H ₄)-	237.5	20
6-(C ₂ H ₅) ₂ NCH ₂ CH ₂ -	HCl 152-4	119
6-C ₅ H ₁₀ NCH ₂ CH ₂ -	HCl 173-6	119
6-O(CH ₂) ₄ NCH ₂ CH ₂ NHCH ₂ -	HCl 180-5	119
6-(CH ₃) ₂ NCH ₂ CH ₂ NHCH ₂ -	HCl 240	119
6-(CH ₃) ₂ NCH ₂ CH ₂ -	HCl 198-200	119
6-(CH ₃) ₂ CHNHCH ₂ -	HCl 209-10	119
6-C ₅ H ₁₀ NCH ₂ -	HCl 191-3	119
6-O(CH ₂) ₄ NCH ₂ -	HCl 211-6	119
6-C ₆ H ₅ CH ₂ NHCH ₂ -	HCl 201-3	119
6-[3'-(4''-NH ₂ C ₆ H ₄ SO ₂ NH)C ₆ H ₄]-	251-3	52
6-(3'-C ₆ H ₄ N-)-2-NO ₂ -	250	98
6-(3'-C ₆ H ₄ N-)-8-NO ₂ -	292	98
6-(2'-C ₆ H ₅ -4'-C ₆ H ₄ N-)-2-NO ₂ -	> 295	96
6-(2'-C ₆ H ₅ -4'-C ₆ H ₄ N-)-8-NO-	282	96
6-(3'-C ₆ H ₄ N-)-3,8-(NO ₂) ₂ -	293-4	121

TABLE IV-7. Hydroxy- and Alkoxyphenanthridines

Phenanthridine	M.p., °C.	Refs.
2-C ₂ H ₅ O-	95-7	125
2-C ₂ H ₅ O-6-Cl-	160-2	125
2,3,8,9-(CH ₃ O) ₄ -	185	71
2,3,8,9-(CH ₃ O) ₄ -6-COOH-	240	71
2,3,8,9-(CH ₃ O) ₄ -6-CH ₃ -	212	71
2,3,8,9-(CH ₃ O) ₄ -6-C ₆ H ₅ -	207	71
2,3,8,9-(CH ₃ O) ₄ -6-C ₂ H ₅ -	212	71
2,3,8,9-(CH ₃ O) ₄ -6-(HOCH ₂) ₂ CH-	214	71

(*Table continued*)

TABLE IV-7 (*continued*)

Phenanthridine	M.p., °C.	Refs.
3-CH ₃ O-6-Cl-	137.5	19
3-CH ₃ O-6-(4'-NO ₂ C ₆ H ₄)-	199	97
4-C ₂ H ₅ -8,9-CH ₂ O ₂ -	142	32
6-(HOCH ₂) ₂ CH-	129.5	18
6-O ₂ NCH ₂ CHOH-	132	71
6-Cl-8-CH ₃ O-	107	19
6-CH ₃ -8-CH ₃ O-	57	97
6-CH ₃ -8-C ₂ H ₅ OCO-	98-9	97
6-CH ₃ -8-C ₆ H ₅ OCO-	P 270	87, 97
6-C ₆ H ₅ -8-CH ₃ O-	Gum	97
6-(4'-CH ₃ OC ₆ H ₄)-8-CH ₃ O-	94	97
6-(4'-ClC ₆ H ₄)-8-CH ₃ O-	158	97
6-(4'-NO ₂ C ₆ H ₄)-8-CH ₃ O-	233-4	97
6-(3'-NO ₂ C ₆ H ₄)-8-CH ₃ O-	184	97
6-(4'-C ₂ H ₅ OCONHC ₆ H ₄)-8-CH ₃ O-	132-6	97
6-[3',5'-(NO ₂) ₂ C ₆ H ₃]-8-CH ₃ O-	252-3	97
6-(4'-NO ₂ C ₆ H ₄)-8-CH ₃ O-	233	97
6-(4'-NO ₂ C ₆ H ₄)-8-C ₃ H ₇ O-	169	97
6-(3'-NO ₂ C ₆ H ₄)-8-C ₃ H ₇ O-	146	97
6-(4'-NO ₂ C ₆ H ₄)-8-(CH ₃) ₂ CHO-	159-60	97
6-(4'-NO ₂ C ₆ H ₄)-8-CH ₃ (CH ₂) ₃ O-	173	97
6-(4'-NO ₂ C ₆ H ₄)-8-C ₆ H ₅ CH ₂ O-	180	97
6-(4'-NO ₂ C ₆ H ₄ CH ₂)-8-CH ₃ O-	142	97
6-CH ₃ -8-HO-	298-300	87, ^a 97
6-(4'-NO ₂ C ₆ H ₄)-8-HO-	275	97
6-(3'-NO ₂ C ₆ H ₄)-8-HO-	250	97
6-CH ₃ -8-HO-	HCl 300	103
6-(4'-NO ₂ C ₆ H ₄)-7-HO-	263	103
6-(4'-NO ₂ C ₆ H ₄)-9-HO-	280-2	103
6-(4'-CH ₃ OC ₆ H ₄)-8-CH ₃ O-	94	87
6-(2'-CH ₃ OC ₆ H ₄)-	127	96
6-(3'-CH ₃ OC ₆ H ₄)-	129	96
6-(4'-CH ₃ OC ₆ H ₄)-	146	96, 108
6-(2'-CH ₃ O-5'-BrC ₆ H ₃)-	148	96
6-(4'-C ₂ H ₅ OC ₆ H ₄)-	150	96
6-[2',5'-(CH ₃ O) ₂ C ₆ H ₃]-	163	96
6-[3',4'-(CH ₃ O) ₂ C ₆ H ₃]-	169	96
6-[3',4'-(CH ₂ O) ₂ C ₆ H ₃]-	113	96
6-[4'- <i>n</i> -C ₃ H ₇ OC ₆ H ₄]-	117	96
6-[4'-Iso-C ₃ H ₇ OC ₆ H ₄]-	119	96
6-[3'-CH ₃ O-4'-C ₂ H ₅ OC ₆ H ₃]-	118-20	96
6-[3'-CH ₃ O-4'- <i>i</i> -C ₃ H ₇ OC ₆ H ₃]-	137-9	96

(*Table continued*)

TABLE IV-7 (*continued*)

Phenanthridine	M.p., °C.	Refs.
6-[3'-CH ₃ O-4'-i-C ₃ H ₇ OC ₆ H ₅]-	128-9	96
6-[4'-CH ₃ OC ₆ H ₄ CH ₂]-	127	87, 97
6-C ₆ H ₅ OCH ₂ -	142	71
6-NO ₂ CH ₂ CHOH-	132	71
6-[4'-CH ₃ OC ₆ H ₄]-8-NO ₂ -	233	108

TABLE IV-8. Carboxyphenanthridines

Phenanthridine	M.p., °C.	Refs.
4-CH ₃ OCO-8,9-CH ₂ O ₂ -	149-51	22
6-HO ₂ C(CH ₂) ₄ -	108-15	71
6-HO ₂ C(CH ₂) ₃ -	158	71
6-(2'-HO ₂ CC ₆ H ₄)-	268	23, 24, 31
6-CH ₃ OCO(CH ₂) ₃ -	71	71
6-C ₂ H ₅ OCO(CH ₂) ₄ -	54	71
6-(CH ₃ OCOCH ₂) ₂ CH-	93	18
6-COOH-	155	71
6-C ₆ H ₅ OCO-	58	18
6-C ₂ H ₅ OCO-	58	18

TABLE IV-9. Phenanthridine 5-Oxides

Phenanthridine 5-oxide	M.p., °C.	Refs.
6-(4'-CH ₃ C ₆ H ₄)-	196	96
6-(2'-ClC ₆ H ₄)-	200	96
6-(4'-ClC ₆ H ₄)-	252 (dec.)	96
6-C ₆ H ₅ -2-Cl-	175	96
6-C ₆ H ₅ -8-Cl-	218	96
6-(3'-NO ₂ C ₆ H ₄)-	181	96
6-(4'-NO ₂ C ₆ H ₄)-	242-5	96
6-C ₆ H ₅ -8-NO ₂ -	269-71	96
6-(3'-NO ₂ C ₆ H ₄)-2-NO ₂ -	286	96
6-CH ₃ -2-NO ₂ -	265	96
6-(4'-CH ₃ OC ₆ H ₄)-	232-4	96
6-C ₆ H ₅ -2-NO ₂ -	231	96

TABLE IV-10. Miscellaneous

Phenanthridine	M. p., °C.	Refs.
6-(4'-CH ₃ SO ₂ C ₆ H ₄)-	238	83, 108
6-(4'-CNC ₆ H ₄ CH=CH)-	201	90
6-(4'-HN=C(OCH ₃)C ₆ H ₄)-		90
6-(4'-HN=C(NH ₂ ·HCl)C ₆ H ₄)-	175	90
6-[C ₂ H ₅ OCOCH=C(COOC ₂ H ₅)]-	91	71
6-[4'-CH ₃ C ₆ H ₄ SO ₂ N(CH ₂ C ₆ H ₅)CH ₂]-	148	119
6-CNCH ₂ -	95-108	119
6-C ₆ H ₅ CO-	152	71
6-(4'-CNC ₆ H ₄)-2-CN-	340	62
6-CH ₃ -2-CN-	202	62
6-OCH-	139	71
6-(4'-CNC ₆ H ₄)-8-CN-	323	62

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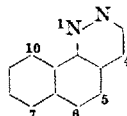
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CHAPTER V

Diazaphenanthrenes (except Phenanthrolines)

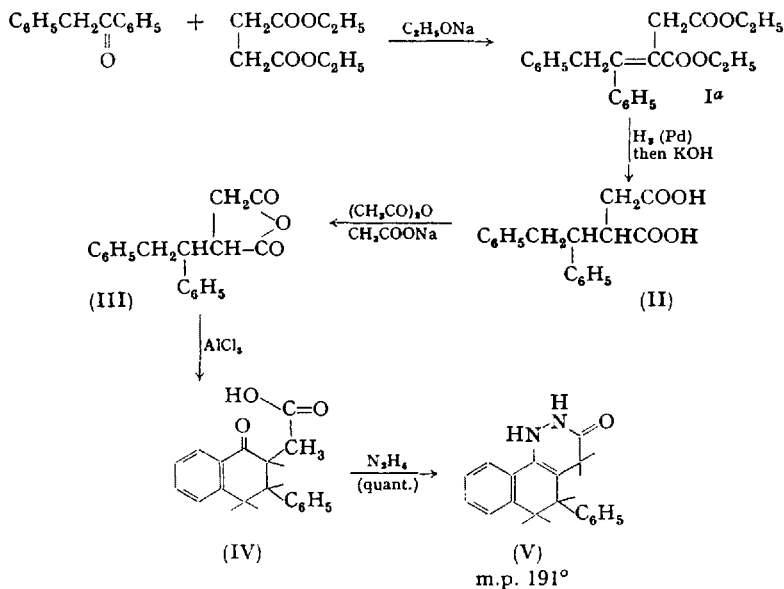
BY JOHN R. THIRTLE

**A. 1,2-Diazaphenanthrene. Benzo[h]cinno-
line. 7,8-Benzocinnoline.**



(1) Preparation and Properties

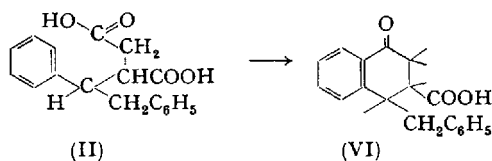
Although there has been a great deal of activity in the preparation and study of cinnoline (1,2-diazanaphthalene), few reports have been



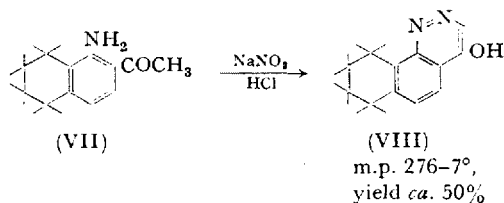
^a Russwurm² first synthesized this compound but indicated the double bond in the β,γ -position with respect to the nearest carbonyl group. We believe the bond should be in the α,β -position, as shown here.

made of the corresponding 1,2-diazaphenanthrene. The chemistry involved in the first preparation, that of 5-phenyl-3-oxo-1,2,3,4,5,6-hexahydro-1,2-diazaphenanthrene (V) from desoxybenzoin and ethyl succinate, is interesting.¹

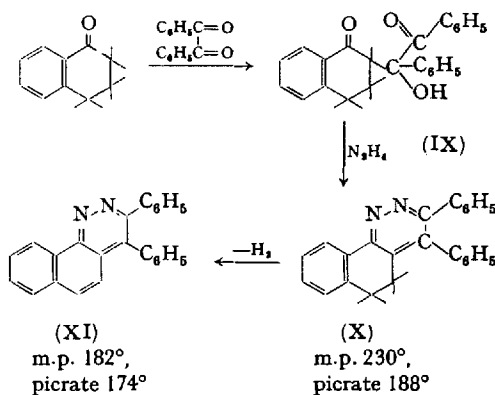
The authors stated that for preparative purposes the crude acid (II) can be converted to the diacid chloride by thionyl chloride. The acid chloride with aluminum chloride gives IV. It is interesting that cyclization of III or its acid chloride could give 4-benzyl-3-carboxy-1-tetralone (1-benzyl-4-oxotetralin-2-carboxylic acid) (VI) by ring closure in another direction. Under certain conditions some VI is formed, but it cannot react with hydrazine to give elimination of two molecules of water.



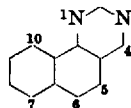
Recently, as part of a lengthy study of cinnolines by Schofield and co-workers, 4-hydroxy-7,8,9,10-tetrahydro-1,2-diazaphenanthrene (VIII) was prepared³ by a method for 4-hydroxycinnolines developed by Borsche and Herbert⁴. Compound VII was obtained in poor yield.



The only method reported by which the completely aromatic, 1,2-diazaphenanthrene system has been prepared is that of Allen and Van Allan.⁵ Benzils react with α -tetralone, giving products of the type IX in 70-90% yield. The latter react with hydrazine, giving for benzil itself 3,4-diphenyl-5,6-dihydro-1,2-diazaphenanthrene (X) in 80-90% yield. Dehydrogenation to 3,4-diphenyl-1,2-diazaphenanthrene (XI) is easily accomplished with chromic oxide or with palladium on charcoal.

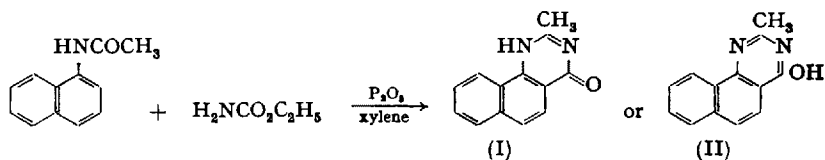


B. 1,3-Diazaphenanthrene. Benzo[h]quinazoline. 7,8-Benzoquinazoline. 1,3-Naphth-
isodiazine. R.I. 1906



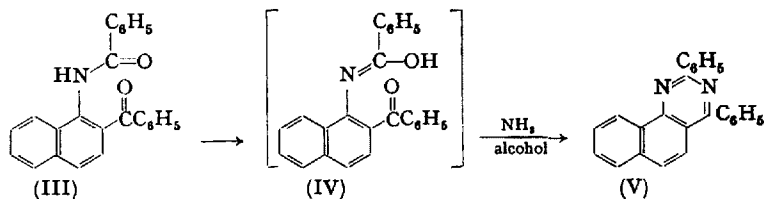
(I) Preparation

The 1,3-diazaphenanthrene system was first synthesized in 1929, using a newly discovered reaction for the preparation of 4-quinazolones; amines are caused to react with acyl urethans, or acylamines with urethans, using phosphorus pentoxide as a condensing agent.^{6,7} 2-Methyl-4-oxo-1,4-dihydro-1,3-diazaphenanthrene (I) was prepared by this method.⁶ The authors favored structure II, 4-hydroxy-2-



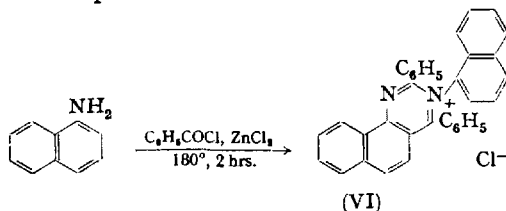
methyl-1,3-diazaphenanthrene, in subsequent work.⁷ This reaction has been used also for the synthesis of 2,4-diazaphenanthrene (p 360).

Another synthesis of this system involves the interaction of *N*-(2-acyl-1-naphthyl)benzamide and ammonia or an amine.⁸

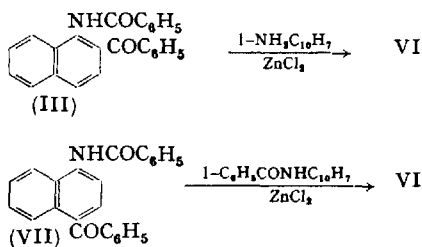


It is postulated that the enolic form (IV) of *N*-(2-benzoyl-1-naphthyl)benzamide (III) is involved in the reaction.

When 1-naphthylamine is heated with benzoyl chloride and zinc chloride for two hours, the reaction does not stop at III, but gives 2,4-diphenyl-3-(1-naphthyl)-1,3-diazaphenanthrenium chloride (VI) as the zinc chloride complex.

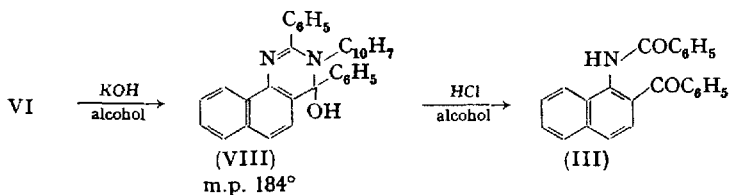


Compound VI, which can be converted to III or IV by the reactions which follow, can be obtained from III or from *N*-(4-benzoyl-1-naphthyl)benzamide (VII).

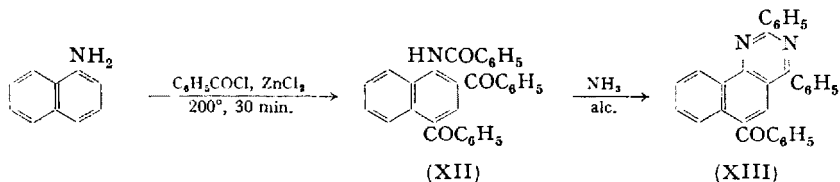


Compound VII was obtained by the reaction of benzoyl chloride with 1-naphthylamine and zinc chloride under less vigorous conditions, and it is probably then an intermediate, along with III, in the synthesis of VI by the over-all method.

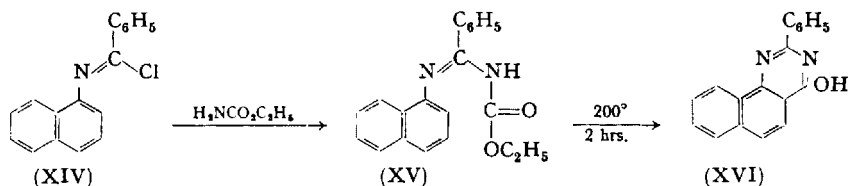
The transformations of VI are interesting and lead to other 1,3-diazaphenanthrenes. In the first place, VI was the source for *N*-(2-benzoyl-1-naphthyl)benzamide (III). When treated with excess con-



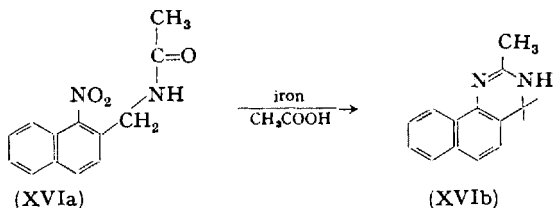
centrated ammonium hydroxide, VI is converted to V, which may also



Another synthesis of the 1,3-diazaphenanthrene system is somewhat similar to the imidochloride preparation of 1-azaphenanthrenes (see p. 178). *N*-(1-Naphthyl)benzimidyl chloride (XIV) reacts with the sodium derivative of urethan in ether, giving (1-naphthylimino-benzyl)urethan (XV), which cyclizes to 4-hydroxy-2-phenyl-1,3-diazaphenanthrene (XVI).¹⁰

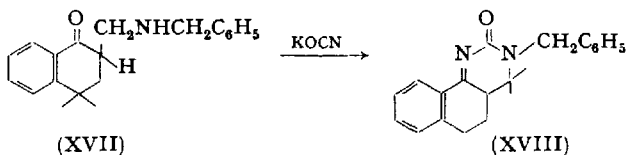


Finally, the 1,3-diazaphenanthrene system has been prepared by cyclization involving substituents already present on the naphthalene ring. In the first of these, β -acetamidomethyl-1-nitronaphthalene (XVIa) is cyclized on reduction with iron in acetic acid, giving 2-methyl-3,4-dihydro-1,3-diazaphenanthrene (XVIb) in 87% yield by isolation as the hydrochloride.^{13a} Compound XVIa has also been used in the preparation of 1,2,3-triazaphenanthrene (p. 457).



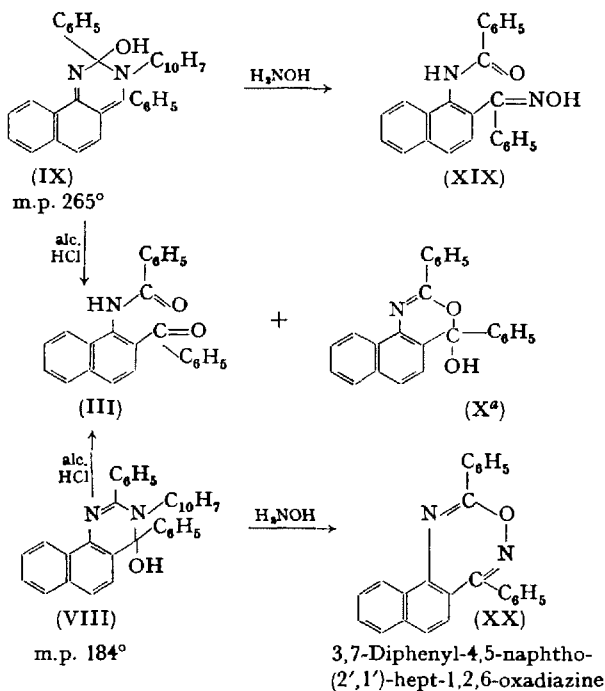
A last synthesis of this system involves the cyclization of an aminomethyltetralone.¹¹ For example, 1-tetralone reacts with benzylamine and formaldehyde to give a 55% yield of 2-benzylaminomethyl-1-tetralone (XVII). Reaction of XVII with potassium cyanate gives 3-benzyl-2-oxo-2,3,4,4a,5,6-hexahydro-1,3-diazaphenanthrene (XVIII)

in undisclosed yield. Piperonylamine may be used in place of benzylamine, giving the corresponding 3-piperonyl-2-oxo-2,3,4,4a,5,6-hexahydro-1,3-diazaphenanthrene.



(2) Reactions

The hetero ring in 1,3-diazaphenanthrene is easily cleaved. For example, 2,4-diphenyl-2-hydroxy-3-(1-naphthyl)-2,3-dihydro-1,3-diazaphenanthrene (IX) and 3-(1-naphthyl)-4-hydroxy-2,4-diphenyl-3,4-dihydro-1,3-diazaphenanthrene (VIII), when heated with alcoholic hydrochloric acid, give *N*-(2-benzoyl-1-naphthyl)benzamide (III);



^a Reported to be formed from the reaction of IX with alcoholic hydrochloric acid. X was probably also formed from VIII, although not isolated in that case.

under the same conditions the metoxazine (X) is also formed from IX. There seems little reason to doubt that the metoxazine could also be formed from VIII, though such was not reported. When IX is treated with hydroxylamine, the oxime of III (XIX) is formed.⁹ On the other hand, the corresponding 4-hydroxy-compound (VIII) gives a quantitative yield of 3,7-diphenyl-4,5-naphtho-(2',1')-hept-1,2,6-oxadiazine (XX).⁹ The latter reaction constitutes a structure proof for the 1,3-diaza system. Recrystallization of VIII from methanol or ethanol gives the corresponding methyl or ethyl ethers.⁸

(3) Uses

One patent¹² mentioning 1,3- and 2,4-diazaphenanthrene derivatives claims the reaction of the dihalo derivatives with ammonia, amines, and alkoxides. The products are claimed to be useful as intermediates for dyes. A second patent¹³ claims 7(or 10)-hydroxy-1,2,3,4-tetrahydro-1,3-diazaphenanthrene as an azo coupling component or as a coupler for color photographic processes.

TABLE V-1. 1,3-Diazaphenanthrenes

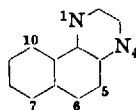
Formula	Compound	M.p., °C.	Refs.
IX	2-Methyl-3,4-dihydro-	62	13a
		HCl 252 (dec.)	13a
		P 235 (dec.)	13a
	2,4-Diphenyl-2-hydroxy-3-(1-naphthyl)- 2,3-dihydro-	265	8, 9
VIII	2,4-Diphenyl-4-hydroxy-3-(1-naphthyl)- 3,4-dihydro-	184	8
XVIII		HCl 209	8
		P 260-1	8
	2,4-Diphenyl-4-methoxy-3-(1-naphthyl)- 3,4-dihydro-	193	8
	2,4-Diphenyl-4-ethoxy-3-(1-naphthyl)- 3,4-dihydro-	224	8
		HCl 292	8
	3-Benzyl-2-oxo-2,3,4,4a,5,6-hexahydro-	208	11
	3-Piperonyl-2-oxo-2,3,4,4a,5,6-hexahydro-	228	11

(Table continued)

TABLE V-1 (*continued*)

Formula	Compound	M.p., °C.	Refs.
V	2,4-Diphenyl-	160 HgCl ₂ 212-5 (dec.) P 168-70	8, 9
VI	2,4-Diphenyl-3-(1-naphthyl)-chloride	ZnCl ₂ 310	8
II or I	4-Hydroxy-2-methyl-	332	6
	2-Benzyl-4-hydroxy-	265	7
XVI	4-Hydroxy-2-phenyl-	300	10
XIII	6-Benzoyl-2,4-diphenyl-	190	9
	3-Benzenesulfonyl-2-methyl-3,4-dihydro-	149	13a

C. 1,4-Diazaphenanthrene. Benzo[*f*]quinoxaline. 5,6-Benzoquinoxaline. 1,4-Naphth-isodiazine. Naphtho-1',2'; 2,3-pyrazine, α,β -Naphthoquinoxaline. R.I. 1907

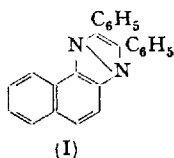


(1) Introduction

In general, 1,4-diazaphenanthrenes are prepared by the usual methods for quinoxalines and, therefore, there is little ambiguity in their synthesis. Interest in them, both from a theoretical as well as a practical viewpoint, has not waned since they were first prepared.

(2) Nomenclature

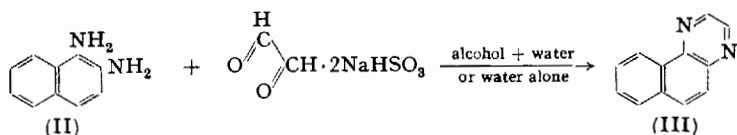
While the 1,4-diazaphenanthrene system is generally now designated as benzo[*f*]quinoxaline, early workers named it α,β -naphthoquinoxaline, which is a misnomer by modern rules. The 2,3-diphenyl derivatives were called "stilbazines" on account of an apparent analogy with stilbene, which is noted as part of the structure as portrayed by Witt (I).²³ The quaternary salts and their bases were called "stil-



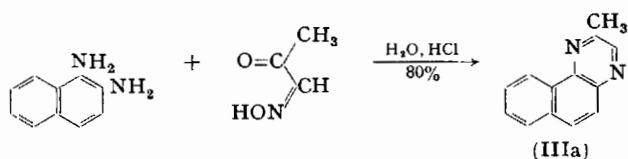
bazonium" compounds. This designation was not permanent, most workers preferring "phenazonium." These salts and bases have been referred to recently as benzoquinoxalinium compounds.

(3) Preparation

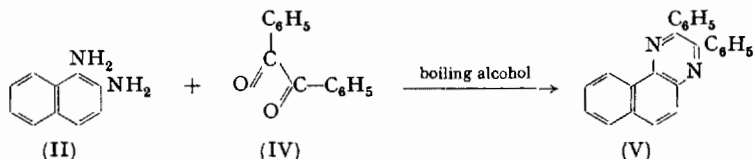
(a) From 1,2-Dicarbonyl Compounds with 1,2-Naphthalenediamine. 1,4-Diazaphenanthrene (III) was first prepared in 1890¹⁸ by the reaction of 1,2-naphthalenediamine (II) with glyoxal-bisulfite, a reaction that has also been utilized more recently.⁶⁴ The yield appears to be good.



Phenylglyoxal gives a quantitative yield of 2- or 3-phenyl-1,4-diazaphenanthrene.⁶⁶ Probably a mixture of both is obtained since the melting point (136–8°) disagrees with that of either isomer (153°, 163°), obtained in other ways (see pp. 345 and 346). Methylglyoxal gives 2-methyl-1,4-diazaphenanthrene (IIIa), whose structure has more recently been confirmed^{79,80} (see p. 339). The monoxime of methylglyoxal also gives a high yield of IIIa.⁸⁰



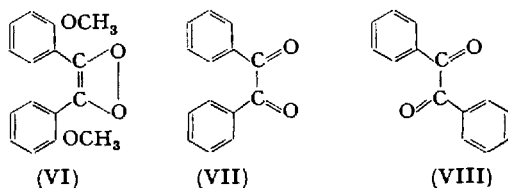
The preparation of the 1,4-diazaphenanthrene system was first effected by Lawson in 1885.¹⁵ The reaction takes place readily and nearly quantitatively as follows:



The hydrochloride of II may also be used, and some workers also added extra hydrochloric acid with undefined effect. Apparently 2,3-diphenyl-1,4-diazaphenanthrene (V) is too weak a base to form the hydrochloride under these conditions.

A modification of this reaction involves the use of the dihydrochloride of II in boiling acetic acid, giving quantitative yields of the 1,4-diazaphenanthrene but in a somewhat long reaction time.⁴² Another modification⁴⁴ uses as a solvent dimethylaniline, the effect of which will be discussed below. Dilute acetic acid seems to have great merit; for example, benzil and 4-acetamido-1,2-naphthalenediamine were simply heated with 50 % acetic acid to the boiling point, and the reaction mixture was allowed to cool, depositing 6-acetamido-2,3-diphenyl-1,4-diazaphenanthrene.^{48,62}

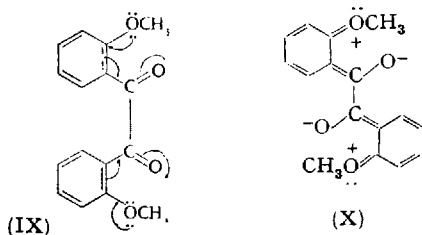
Schönberg and Kraemer⁴² used the reaction of 1,2-naphthalenediamine with 1,2-diketones to study the nature of variously substituted benzils. While *p*-alkoxybenzils react with 1,2-naphthalenediamine in boiling acetic acid in excellent yields, 2,2'-dimethoxy- and 2,2'-dimethoxy-5,5'-dimethylbenzil would not react; it was believed that the latter existed in a pseudo form,^{42, 44, 45} a so-called superoxide (VI), which was inactive. The pseudo form, however, was presumed to be in equilibrium with the keto form and the equilibrium could be shifted to the latter by the use of dimethylaniline,⁴⁴ the normal reaction then being complete in two hours.



Some doubt has been cast on this mechanism. Burawoy⁶⁸ states that the pseudo or superoxide hypothesis is superfluous and that the existence of two forms of 4,4'-dibenzoyloxy-, 4,4'-dihydroxy-, and 2,2'-dimethoxybenzil can be explained by an isomerism between the ketonic and peroxide forms; he notes that this hypothesis is arbitrary, however. Caldwell and Le Fèvre⁷⁵ suggest, from dipole measurements, that benzil itself exists in a "skew" structure that is between the

extremes, VII and VIII, *i.e.*, the angles $\text{Ph}-\text{C}=\text{O}$ and $\text{Ph}-\text{C}-\text{C}$ are 120° and that the two PhCO groups lie in planes that make an angle of $90-100^\circ$ with each other. These angular dimensions would seem to make a structure like VI unlikely.

It is evident that structure VII must be present to obtain reaction with *o*-diamines. The presence of methoxyl groups in the 2,2'-positions (IX) (or even in the 4,4'-positions) may induce negative charges on the carbonyl oxygen thereby causing a repulsion and consequent assumption of the *trans* form (X). In this *trans* configuration there appears also the possibility of electrical attraction between the CH_3O^+

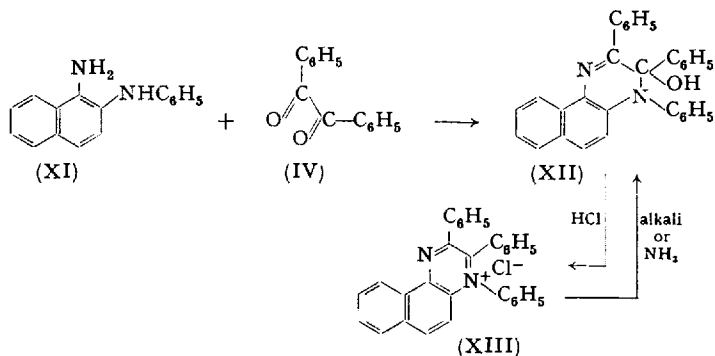


group and the O^- . This latter attraction would not exist in the case of the 4,4'-dialkoxybenzils, which apparently react readily with *o*-diamines, even though the repulsion between the negative oxygen atoms should exist as in X. However, the isolation of two forms of some of these benzils indicates that some structural or electronic isomerization exists, although the possibility that the two forms may be only polymorphs should not be disregarded.

The fact that strong electron-donating groups in the 4,4'-positions of benzil either prevent entirely or greatly inhibit its reactions with other substances lends further weight to the supposition that electronic factors are of major importance.^{5, 76-78}

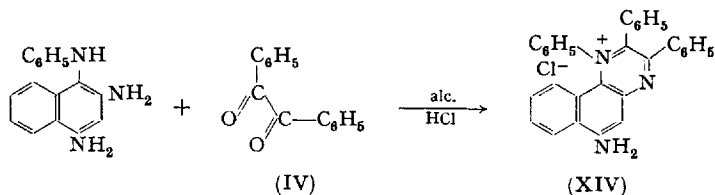
When an *N*-substituted 1,2-naphthalenediamine is used it seems necessary to employ hydrochloric acid to force the reaction.²⁰

The hydroxy compound (XII), a pseudo base first named a "stilbazonium" hydroxide,²¹ is usually not isolated at first but is converted to the chloride (XIII) for purification. In fact, the requisite hydrochloric acid is usually present in the reaction mixture, and the chloride

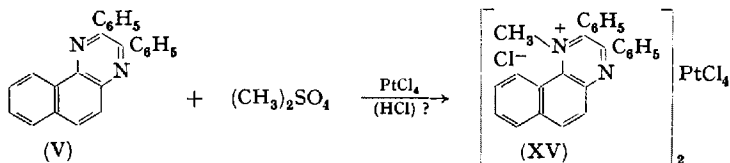


is formed with unusual ease.²⁸ The latter can be converted to the hydroxide by treatment with alkali. These hydroxides are identical with those prepared by reaction of XI and its analogs with benzoin, followed by oxidation (see p. 347). The location of the hydroxyl groups as shown has been established.^{70,71}

When 1-anilino-2-naphthylamine is used, the compounds analogous to XII and XIII are formed in which the ring is inverted, giving the

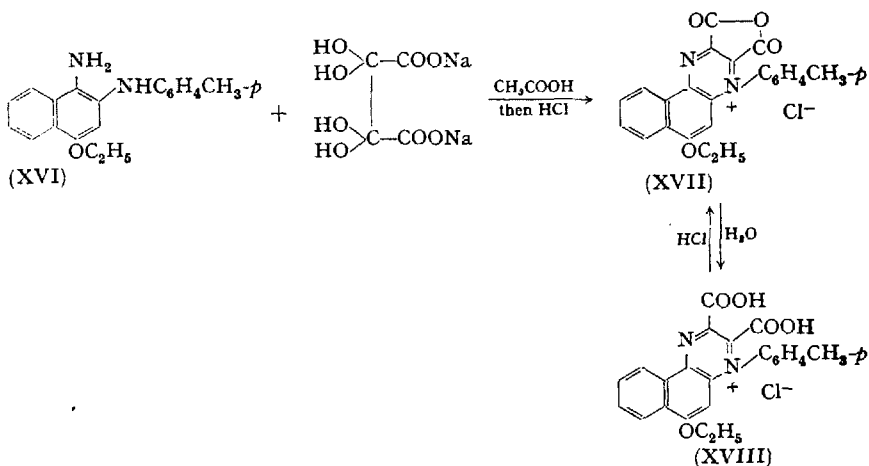


chloride (XIV).⁵⁰ Similar compounds presumably can be obtained by direct alkylation of 2,3-diphenyl-1,4-diazaphenanthrene.^{48,62} The possibility of quaternarization in the 4-position was disregarded.

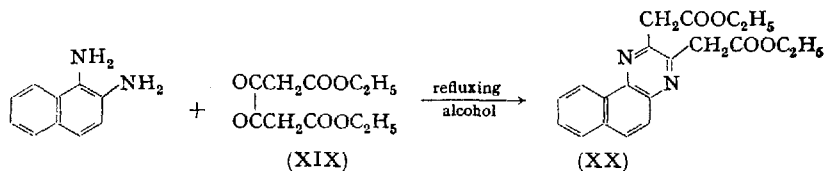


The reaction of diketones other than benzil and its derivatives has been demonstrated. For example, Witt and Helmolt²⁷ treated 4-ethoxy-2-(*N*-*p*-tolyl)-1,2-naphthalenediamine (XVI) with the sodium

salt of dihydroxytartaric acid, obtaining the anhydride (XVII), which is easily converted to 2,3-dicarboxy-6-ethoxy-4-*p*-tolyl-1,4-diazaphenanthrenium 4-chloride (XVIII) by crystallization from water. Treatment of XVIII with hydrochloric acid reconverts it to the anhydride (XVII). This was an application of a reaction discovered by Hinsberg⁷² in 1887, and utilized further by Hinsberg and König⁷³ and by Chattaway and Humphrey.⁷⁴

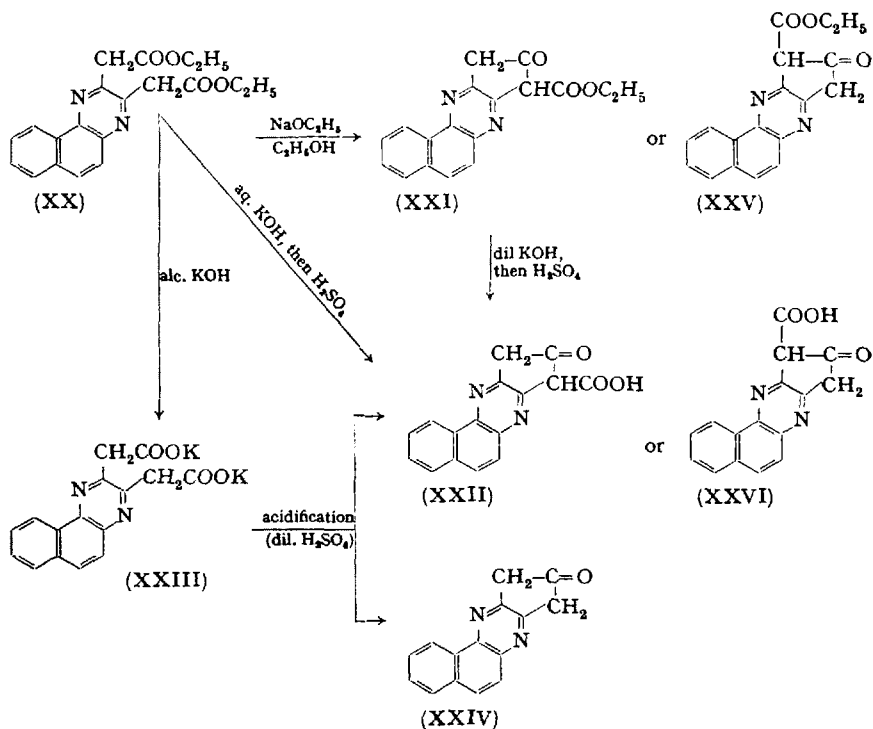


An interesting variation of this reaction involves the diethyl ester of ketipinic acid (XIX).³² The diethyl ester of 2,3-bis(carboxymethyl)-1,4-diazaphenanthrene (XX) is obtained in good yield. However, it is



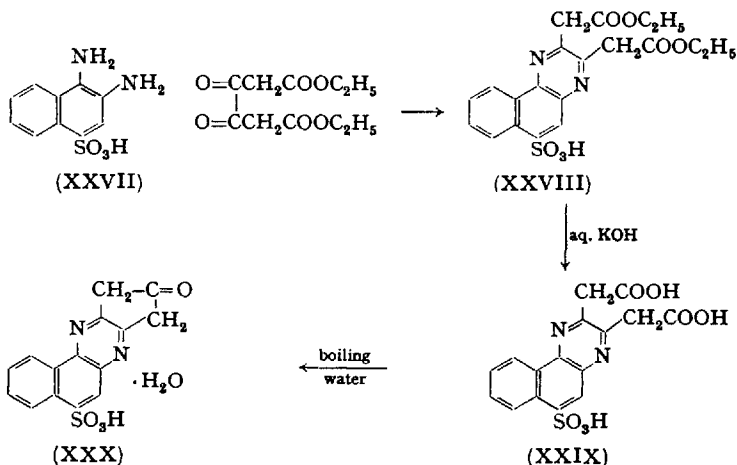
essential to work with only 5- to 10-gram amounts of the diamine since larger runs give resins almost exclusively. The reactions of this ester are quite interesting. With sodium ethoxide a Dieckmann condensation occurs, giving XXI which can be saponified to XXII. The latter is also obtained by the action of aqueous or alcoholic potassium hydroxide on the diethyl ester. The reaction of alcoholic potassium hydroxide on the diethyl ester (XX) gives the dipotassium salt of the 2,3-diacetic

acid (XXIII), which on acidification with dilute sulfuric acid gives an acid-insoluble product (XXII) and an acid-soluble product (XXIV). The acid-insoluble product loses carbon dioxide by boiling with water giving XXIV and, indeed, the crude saponification mixture when thus treated yields only XXIV. It should be understood that XXI and XXII may exist in their isomeric forms, XXV or XXVI, and that all of these structures as well as XXIV may be enolized.

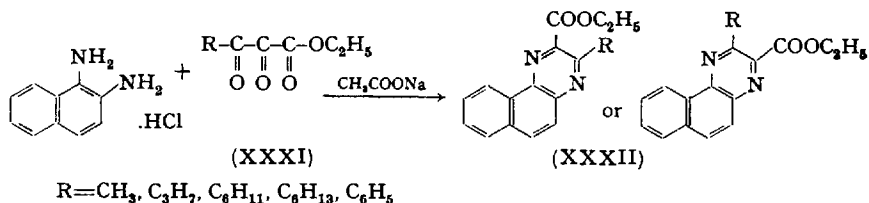


When 4-sulfo-1,2-naphthalenediamine (XXVII) is used in the same type of reaction, the diethyl ester (XXVIII) obtained is saponified normally by standing with cold aqueous potassium hydroxide for one hour, giving, after acidification, 2,3-biscarboxymethyl-6-sulfo-1,4-diazaphenanthrene (XXIX). The latter loses carbon dioxide and water on boiling with water for three hours, to give the hydrated ketone (XXX).

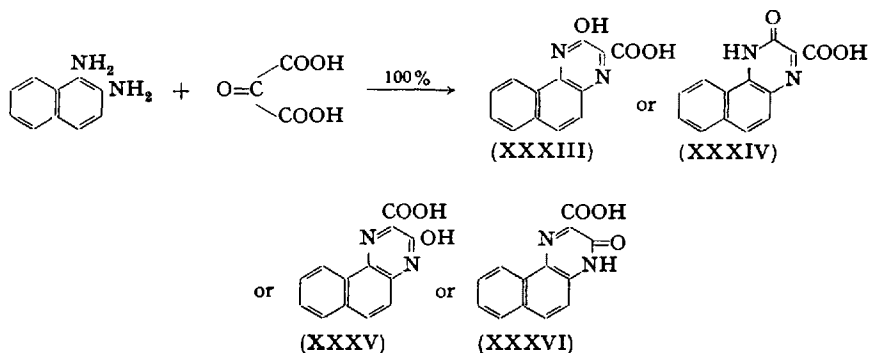
A similar reaction of 1,2-naphthalenediamine with 1,2-diketones



involves ethyl acylglyoxylates (XXXI).³⁸ The perfectly crystalline products (XXXII) obtained are suitable for characterization.

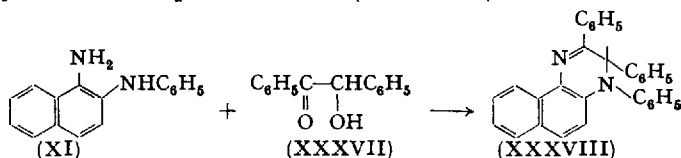


A final illustration in this series is the reaction of mesoxalic acid with 1,2-naphthalenediamine, giving a quantitative yield of product that may consist of one or more of four isomeric forms, 3-carboxy-2-hydroxy-1,4-diazaphenanthrene (XXXIII), its oxo form XXXIV, 2-carboxy-3-hydroxy-1,4-diazaphenanthrene (XXXV), or its oxo form XXXVI.

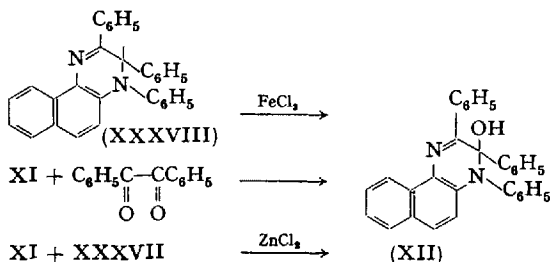


Several other 1,2-dicarbonyl compounds react abnormally with 1,2-naphthalenediamine, and will be discussed in another section (p. 343).

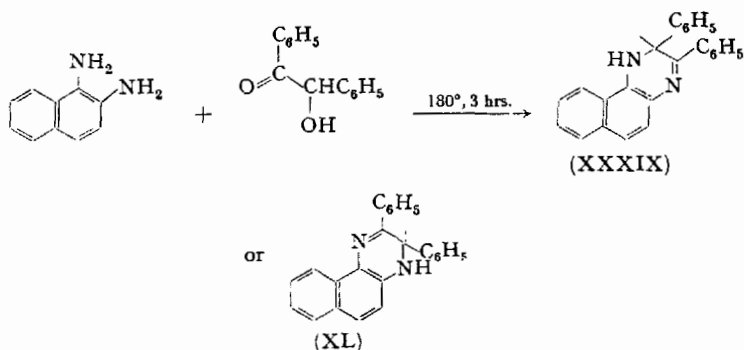
(b) From α -Keto Alcohols with 1,2-Naphthalenediamine. The reaction of benzoin with 1,2-naphthalenediamine is similar to that of benzil, especially if one of the amino groups is substituted with an alkyl or aryl residue. For example, 2-anilino-1-naphthylamine, heated with benzoin (XXXVII) for two hours at 200°, gives 2,3,4-triphenyl-3,4-dihydro-1,4-diazaphenanthrene (XXXVIII).¹⁷



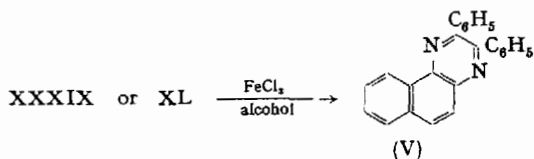
A bitter controversy arose over this type of reaction. Witt¹⁴ claimed to have discovered a "new class of fluorescing quinoxalines" in 1887²¹ by the reaction of *o*-diketones with *N*-aryl-*o*-diamines. He claimed that Fischer,¹⁷ and also Kehrman and Messinger,⁵⁷ had invaded a field he had reserved for himself. Fischer retorted that Witt had not properly identified his compounds with those of Fischer. The fact was that Witt's and Kehrman and Messinger's compounds contained oxygen (*cf.* XII, p. 332), while Fischer, by avoiding acids, certain salts (ZnCl_2), and air, was able to obtain oxygen-free compounds. The situation arose because of the close similarity in melting points between the oxygen-containing compound (XII), m.p. 167°, and the oxygen-free compound (XXXVIII), m.p. 163–4°. Compound XXXVIII can be oxidized with ferric chloride to the 3-hydroxy compound (XII), which can be obtained also from XI and benzil (see p. 332) or from XI and XXXVII in the presence of zinc chloride.¹⁸



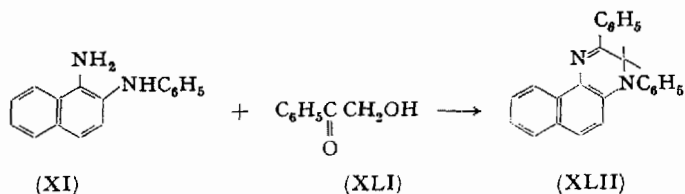
Benzoin also reacts with unsubstituted 1,2-naphthalenediamine to give 2,3-diphenyl-1,2(or 3,4)-dihydro-1,4-diazaphenanthrene (XXXIX or XL).²⁶ The compound obtained (m.p. 172°) is oxidized by ferric



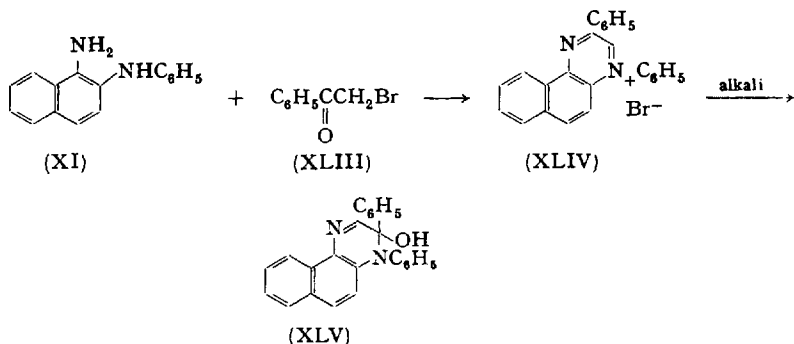
chloride to 2,3-diphenyl-1,4-diazaphenanthrene (V).^{15, 26} This is contrary to the course followed when one of the nitrogen atoms is substituted.



α -Hydroxyacetophenone (XLI) is reported to react similarly with XI, except that only one product is to be expected, 2,4-diphenyl-3,4-dihydro-1,4-diazaphenanthrene (XLII).²⁰



(c) From α -Halo Ketones with 1,2-Naphthalenediamine. α -Bromoacetophenone (XLIII) reacts rapidly with 2-anilino-1-naphthylamine (XI) in boiling alcohol, giving the 4-phenobromide of 2-phenyl-1,4-diazaphenanthrene (XLIV). Cold, dilute sodium hydroxide converts the product to 2,4-diphenyl-3-hydroxy-3,4-dihydro-1,4-

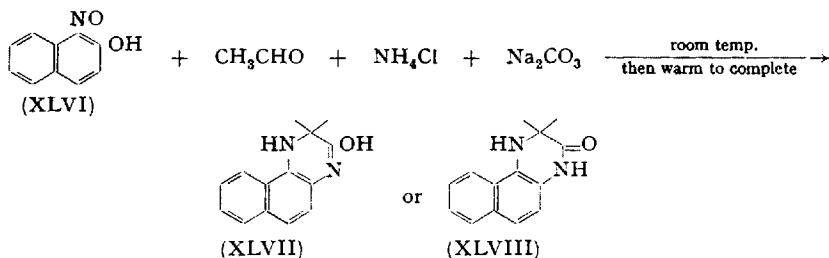


diazaphenanthrene (XLV). The structures XLIV and XLV are written to conform with other studies (see references 20, 70, 71).

The reaction of 1,2-naphthalenediamine with *m*(and *p*)-nitro-derivatives of XLIII gives high yields of α -[*m*(and *p*)-nitrophenyl]-1,4-diazaphenanthrenes.^{80a} Although two isomers are possible (*i.e.*, nitrophenyl at 2- or 3-position), only one was isolated. No attempt was made to define the product further.

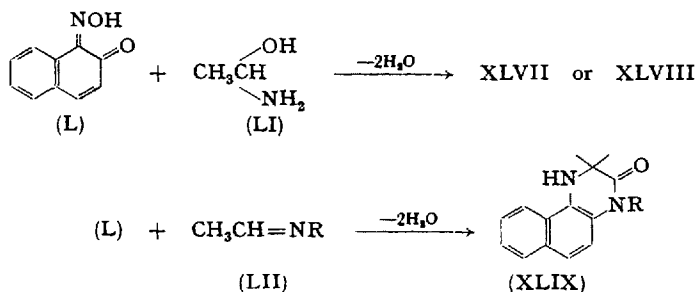
(d) From 1-Nitroso-2-naphthol with Aldehydes and Amines.

The reaction of 1-nitroso-2-naphthol (XLVI) with acetaldehyde, ammonium chloride, and sodium carbonate (essentially acetaldehyde-ammonia) gives a quantitative yield of 3-hydroxy-1,2-dihydro-1,4-diazaphenanthrene (XLVII) or its tautomer 3-oxo-1,2,3,4-tetrahydro-1,4-diazaphenanthrene (XLVIII).^{36, 37} One may start with β -naphthol, and need not isolate the nitroso compound.



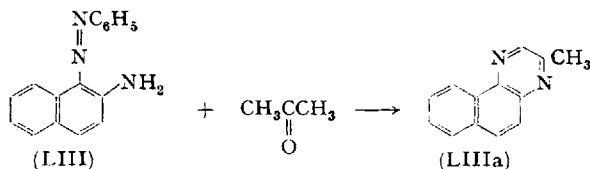
Instead of ammonium chloride an alkylamine or its salt may be used. In this case only the oxo form (XLVIII) is produced, with the alkyl group found in place of hydrogen in the 4-position (XLIX). It has been suggested that the nitrosonaphthol reacts in the form of the iso-

nitrosonaphthone (L) with acetaldehyde-ammonia (LI) or with the condensation product of acetaldehyde and the amine (*i.e.*, Schiff base) (LII).



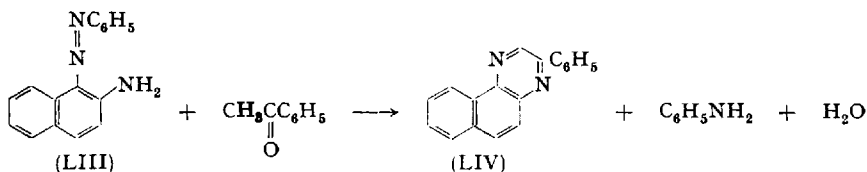
The reaction has been applied³⁷ to 2-nitroso-1-naphthol and its derivatives, giving the analogous compounds in which the hydroxyl or oxo group is in the 2-position. It is reported that only compounds of the type XLVII, XLVIII and XLIX which have the hydroxyl group at position 9 couple with diazotized anilines.

(e) From Azonaphthylamines and Ketones. The interesting reactions of 1-arylazo-2-naphthylamines with a number of carbonyl compounds have given a considerable number of 1,4-diazaphenanthrene derivatives. For example, acetone reacts with 1-phenylazo-2-naphthylamine to give, after much manipulation, a low yield of 3-methyl-1,4-diazaphenanthrene (LIIIIa).⁸⁰ This compound was shown to differ

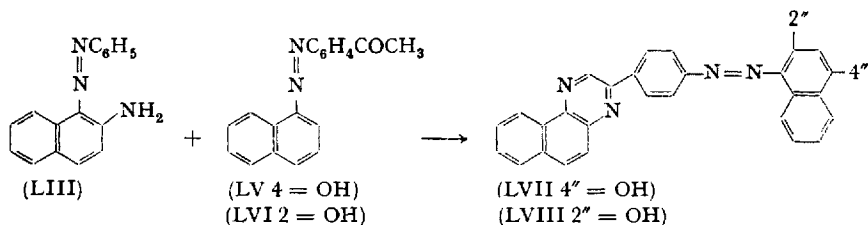


from that (2-methyl-1,4-diazaphenanthrene) prepared from 1,2-naphthalenediamine and methylglyoxal⁷⁹ or its monoxime.⁸⁰ 1-Phenylazo-2-naphthylamine (LIII) reacts with acetophenone in the presence of a few drops of hydrochloric acid to give 3-phenyl-1,4-diazaphenanthrene (LIV).⁵² If propiophenone is used, LIV is substituted by a methyl group at the 2-position.⁵⁶ The phenyl group of the ketone may be variously substituted.^{53, 57}

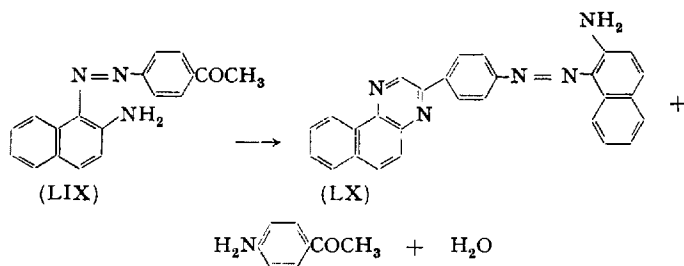
Some competitive reactions of this type have been described.⁵³ For example, 1-phenylazo-2-naphthylamine reacts easily with 4-(*p*-



acetylphenylazo)-1-naphthol (LV) or with 1-(*p*-acetylphenylazo)-2-naphthol (LVI), giving the correspondingly substituted 1,4-diaza-phenanthrene (LVII and LVIII).

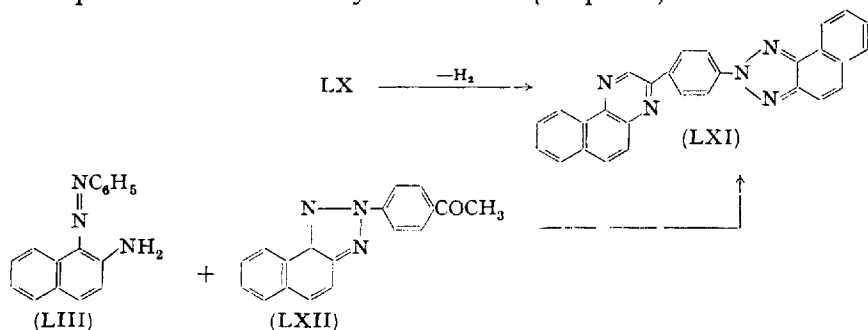


When the naphthylamine corresponding to LV is used, the reaction is normal, giving the *p*-amino compound corresponding to LVII. When the amino analog (LIX) of LVI is used, most of the product is the expected one (LX). However, some *p*-aminoacetophenone was isolated from the reaction mixture, which seemed to indicate that some of LIX had reacted with itself in the following manner:

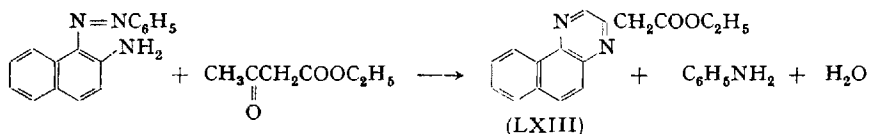


It is interesting that LX can be catalytically dehydrogenated to a naphtho[1,2]triazole (LXI); the latter can be synthesized from LIII and 2-(*p*-acetylphenyl)naphtho[1,2]triazole (LXII). Since the structure of LXII was known, the structures of LX and LXI were

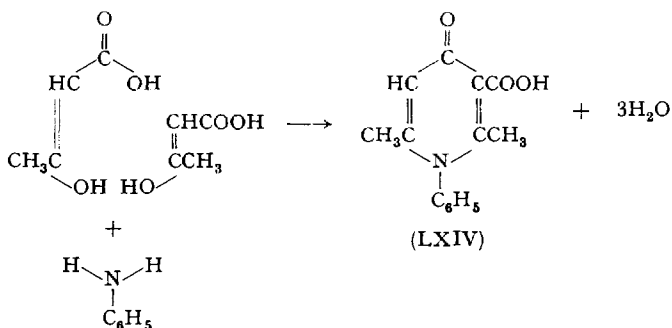
proved, contingent upon the general proof of structure of the 1,4-diazaphenanthrenes made by this method (see p. 347).



(f) **From Azonaphthylamines and β -Oxoesters.** The reaction of 1-phenylazo-2-naphthylamine with β -oxoesters can take two courses: that characteristic of the ketones just discussed, and that in which the methylene group may be involved. The first course is believed to occur when the azo compound reacts with acetoacetic ester.⁵⁵ The product,



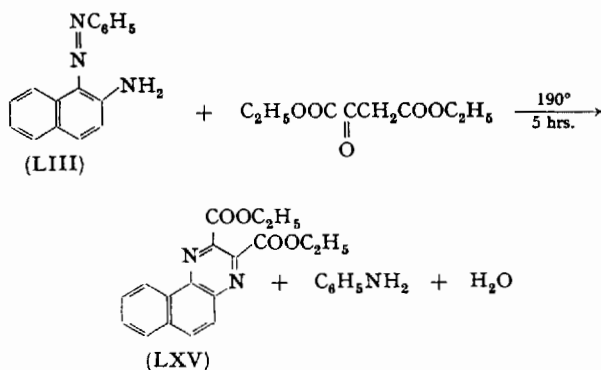
3-carbethoxymethyl-1,4-diazaphenanthrene (LXIII), is formed in undisclosed yield. The by-product was 3-carboxy-2,6-dimethyl-1-phenyl-4-pyridone (LXIV), which apparently was formed from the aniline and 2 moles of excess acetoacetic ester.



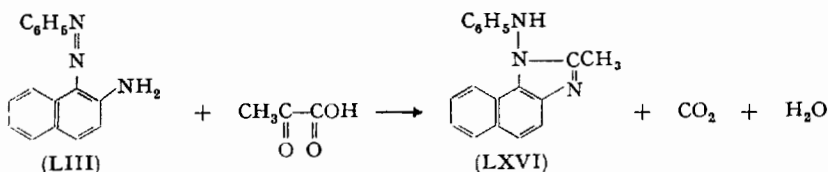
Saponification of LXIII gives the acid, which can be oxidized to a pyrazinetricarboxylic acid. This rules out the possibility that the

product (LXIII) was 2-carbethoxy-3-methyl-1,4-diazaphenanthrene, which would have involved reaction of the methylene group, and which would give a pyrazinetetracarboxylic acid on oxidation.

In the case in which no group of the oxoester except the methylene is available, the reaction can be forced to take place in the second manner. 1-Phenylazo-2-naphthylamine reacts with oxalacetic ester to give 2,3-dicarbethoxy-1,4-diazaphenanthrene (LXV).⁶¹

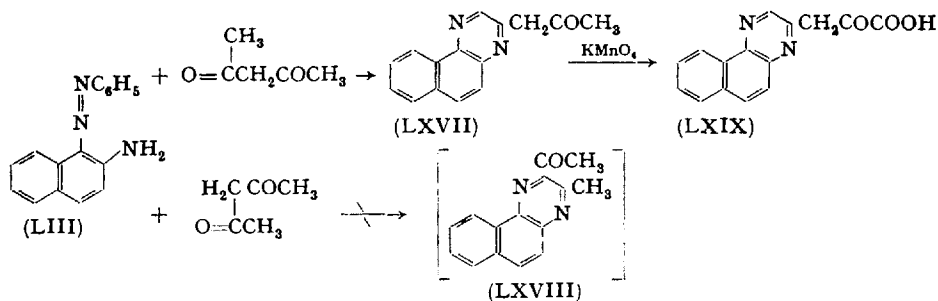


It is interesting to note that the reaction of LIII with pyruvic acid gives, not 3-carboxy-1,4-diazaphenanthrene, but a quantitative yield of 1-anilino-2-methylnaphth[1,2]imidazole (LXVI).⁵⁶

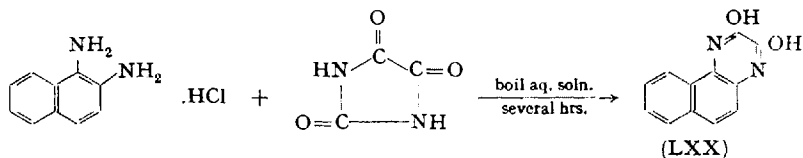


(g) From Azonaphthylamines and β -Diketones. The preceding reactions of oxomethyl compounds with 1-phenylazo-2-naphthylamine prompted further study to see if the active methylene group in acetylacetone would be more reactive than the methyl group.⁵⁹ This reaction could give 3-acetyl-1,4-diazaphenanthrene (LXVII) or 2-acetyl-3-methyl-1,4-diazaphenanthrene (LXVIII). Oxidation of the product gave a monocarboxylic acid, stated to be 1,4-diazaphenanthrene-3-pyruvic acid (3-carboxycarbonylmethyl-1,4-diazaphenanthrene) (LXIX). Oxidation of LXVIII would give a dicarboxylic acid. These experi-

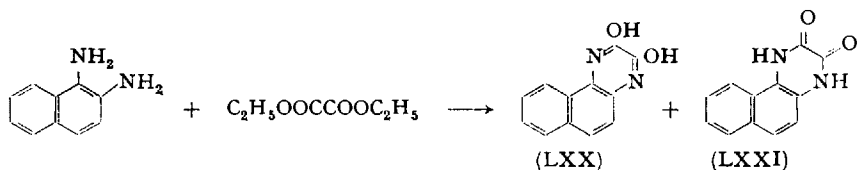
ments show that the methyl group is much more reactive than the methylene group in these reactions.



(h) Miscellaneous Methods. (1) *From 1,2-Naphthalenediamine and Parabanic Acid.* Although parabanic acid (oxalylurea) is a 1,2-dioxo compound, and might be expected to undergo the normal reaction, a different course is followed, 2,3-dihydroxy-1,4-diazaphenanthrene (LXX) being formed.²² This product is obtained also by



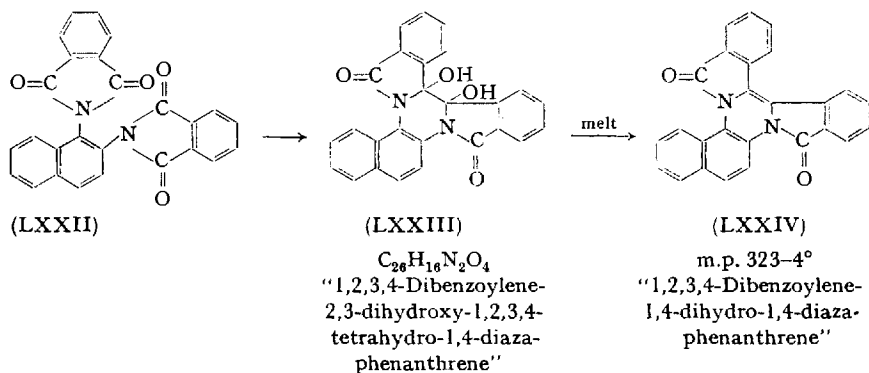
treatment of 1,2-naphthalenediamine with ethyl oxalate, although in this case the main product is said to be the dioxo form, 2,3-dioxo-1,2,3,4-tetrahydro-1,4-diazaphenanthrene (LXXI).³⁰ Moreover, by



heating 1,2-naphthalenediamine with oxalic acid at $140\text{--}60^\circ$ the same reaction is effected.³³ The dihydroxy compound is reported to have weakly acid characteristics and melts above 300° .

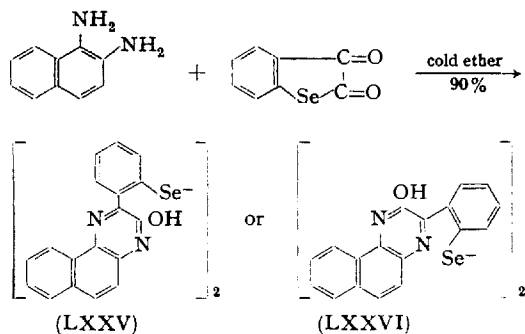
(2) *From 1,2-Naphthalenediamine and Phthalic Anhydride.* This reaction is not entirely substantiated but an interesting course is postulated.⁴¹ 1,2-Naphthalenediamine reacts with two moles of

phthalic anhydride giving the diphthalyl derivative (LXXII) in 45% yield. The latter, when reduced by zinc and acetic acid, gives a compound, $C_{26}H_{16}N_2O_4$, melting at $280-4^\circ$ with evolution of gas and the formation of a red mass and a compound in the form of red needles melting at $323-4^\circ$. These transformations are represented as follows:



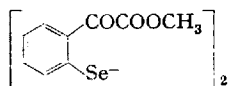
These compounds may be considered as acyl derivatives of the dihydro- and tetrahydro-1,4-diazaphenanthrene systems.

(3) *From 1,2-Naphthalenediamine and Selenonaphthenequinone.* The reaction of 1,2-naphthalenediamine and selenonaphthenequinone has been reported to give a 90% yield of a product designated as 2-(*o,o'*-diselenobisphenyl)-3-hydroxy-1,4-diazaphenanthrene (LXXV) or 3-(*o,o'*-diselenobisphenyl)-2-hydroxy-1,4-diazaphenanthrene (LXXVI)³⁹.



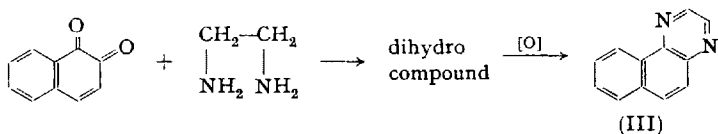
The compound is an orange-colored, crystalline powder, melting at $352-5^\circ$, soluble in cold alcoholic potassium hydroxide but resinifying

when treated with hot aqueous potassium hydroxide. The same compound is formed if:

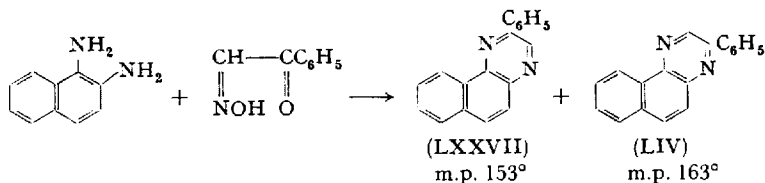


is used instead of selenonaphthenequinone.

(4) *From 1,2-Naphthoquinone and Ethylenediamine.* An early paper²⁹ reported that 1,2-naphthoquinone reacted with phenylethylenediamine to give a phenyl-1,4-diazaphenanthrene melting at 187°. Later work³⁵ has shown that neither of the two possible structures has that melting point (see below). However, the reaction of the quinone with the unsubstituted ethylenediamine is unambiguous, giving 1,4-diazaphenanthrene identical in its properties but in poorer yield than that formerly reported¹⁶ (see p. 329).



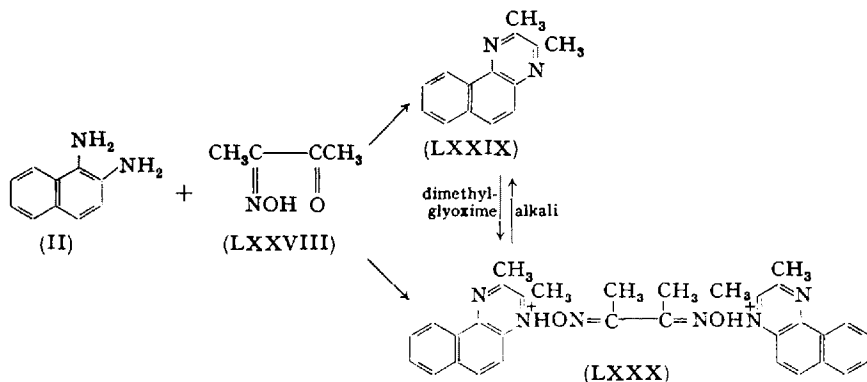
(5) *From 1,2-Naphthalenediamine and Isonitrosoacetophenone.* This reaction³⁵ was investigated for the preparation of the 2- and 3-phenyl derivatives (LXXVII and LIV) of 1,4-diazaphenanthrene, since isonitrosoacetophenone is more readily available than the bromoacetophenone used previously (see p. 337). The diamine is treated with the isonitroso compound in methanol, giving a mixture of the two phenyl derivatives, which are separated by means of the different solubilities



of their hydrochlorides in alcohol. These compounds were identical with the same author's previous preparations³⁴ (p. 346) but unlike that prepared by Feist and Arnstein²⁹ and reported to melt at 187°.

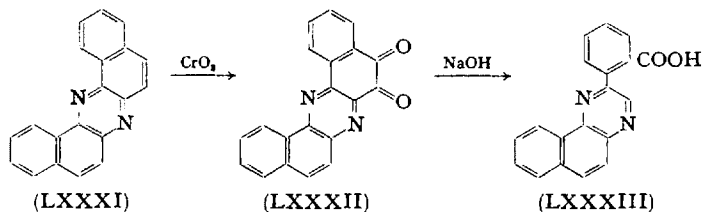
(6) *From 1,2-Naphthalenediamine and Biacetylmonoxime.* In a reaction similar to (5), 2,3-dimethyl-1,4-diazaphenanthrene (LXXIX)

is formed.⁵¹ It is believed⁵¹ that II reacts with LXXVIII to give LXXIX, hydroxylamine, and water. The hydroxylamine reacts with



LXXVIII to give dimethylglyoxime, which then combines with LXXIX, giving a "salt" (LXXX) isolated as the product of the reaction. The desired compound (LXXIX) is then obtained by treatment of LXXX with alkali.

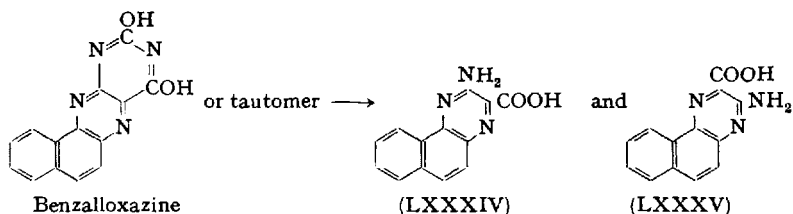
(7) *From Dibenzo[*a,j*]phenazine.* The 2- and 3-*o*-carboxyphenyl derivatives of 1,4-diazaphenanthrene were prepared by an interesting method.³⁴ Dibenzo[*a,j*]phenazine (LXXXI) is oxidized to the 5,6-quinone (LXXXII). The latter on digestion with sodium hydroxide



gives 2-*o*-carboxyphenyl-1,4-diazaphenanthrene (LXXXIII). The asymmetric form of LXXXI gives the corresponding 3-*o*-carboxyphenyl derivative in an over-all yield of about 50%. Decarboxylation of these acids gives authentic 2- and 3-phenyl-1,4-diazaphenanthrene (see pp. 329 and 345).

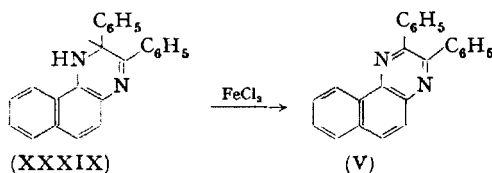
(8) *From "Benzalloxazine"* (8,10-Dihydroxy-7,9,11,12-tetrazabenz[*a*]anthracene).⁵ This degradative reaction gives a mixture of 2(and 3)-amino-3(and 2)-carboxy-1,4-diazaphenanthrenes (LXXXIV and

LXXXV).⁶⁸ These acids have been decarboxylated and the amines applied in antibacterial research.

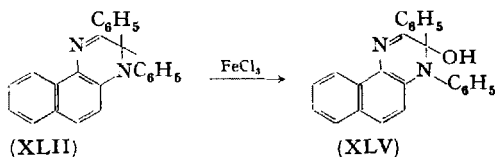


(4) Substitution Reactions

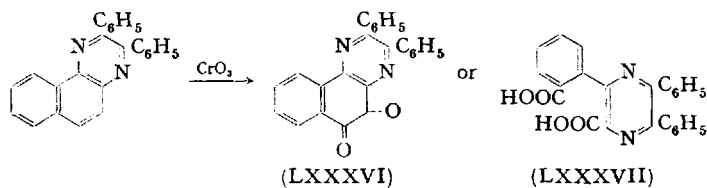
(a) Oxidation. Mild oxidation²⁶ of 2,3-diphenyl-1,2(or 3,4)-dihydro-1,4-diazaphenanthrene (XXXIX or XL) with ferric chloride gives 2,3-diphenyl-1,4-diazaphenanthrene (V). However, the oxidation



of similar compounds having an aryl group in the 4-position introduces an oxygen atom on the ring.^{18, 21, 25} More vigorous oxidation of V with



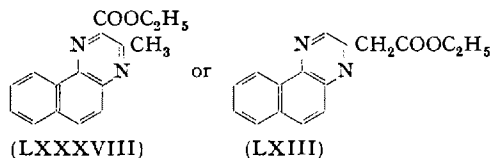
chromic acid leads to the formation of the 5,6-quinone (LXXXVI),^{52-54, 68} but the reaction may go further to yield a pyrazine (LXXXVII).⁵⁸ The



latter can also be prepared by oxidation of the quinone by potassium permanganate.^{54, 58} Decarboxylation of the pyrazine gives 2,3,5-tri-

phenylpyrazine, proving the orientation of 2,3-diphenyl-1,4-diazaphenanthrene (V). A phenazine has been prepared from LXXXVI by reaction with *o*-phenylenediamine.⁵⁸

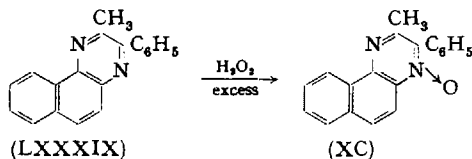
The proof of structure of 3-carbethoxymethyl-1,4-diazaphenanthrene (LXIII) was effected by this oxidative method.⁵⁵ By the



method of synthesis either of the two structures (LXXXVIII or LXIII) could have been obtained. Oxidation of LXXXVIII would give a tetrabasic acid and oxidation of LXIII would give a tribasic acid; since the latter was found the structure LXIII was assigned to the product of the reaction of 1-phenylazo-2-naphthylamine with ethyl acetoacetate.

By the action of hydrogen peroxide the *N*-oxides of 1,4-diazaphenanthrenes are obtained. According to Crippa,⁵⁸ there have been no other cases of direct introduction of oxygen to form such compounds, although the analogous benzotriazole type may be made by ring closure of *o*-aminoazo derivatives in the presence of hydrogen peroxide. The oxygen may be removed by reduction, but is retained on oxidation to the 5,6-quinone.

In an interesting study of the reaction of hydrogen peroxide with quinoxalines, Maffei⁶⁷ found that 2,3-diphenylquinoxaline would form an *N,N'*-dioxide whereas 2,3-dimethylquinoxaline would not. Since 2-methyl-3-phenyl-1,4-diazaphenanthrene (LXXXIX) would not form a dioxide, he concluded the oxygen had attached to the 4-position to give XC.

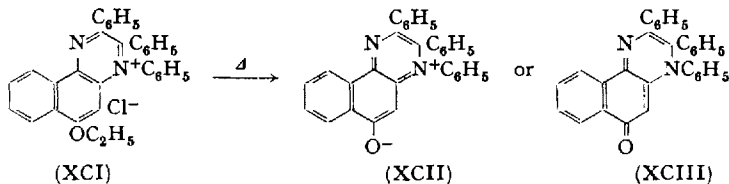


Alkaline potassium permanganate has been used for oxidation of a side chain without affecting the nucleus,⁵⁹ but the oxidation of the

N-methiodide of 1,4-diazaphenanthrene (III) with potassium ferricyanide gives 1(or 4)-methyl-2(or 3)-oxo-1,2(or 3,4)-dihydro-1,4-diazaphenanthrene.³⁴

(5) Replacement Reactions

Some interesting reactions of substituent groups occur in the 1,4-diazaphenanthrene system. For example, the 6-ethoxy group is replaced readily by an amino or anilino group.^{23, 24, 27, 28} Both hydroxy groups of 2,3-dihydroxy-1,4-diazaphenanthrene are replaced readily by chlorine atoms using phosphorus pentachloride,³³ and one of the chlorine atoms is replaced by an amino group in alcoholic ammonia.³³ An interesting reaction of the 6-ethoxy group consists in its elimination as ethyl chloride from the quaternary salt (XCI) of 2,3-diphenyl-6-ethoxy-1,4-diazaphenanthrene, resulting in the "inner anhydride" (XCII) or its tautomer (XCIII) of the pseudo base of 2,3-diphenyl-6-hydroxy-1,4-diazaphenanthrene.^{23, 24} This pair of tautomers has been



called "phenylnaphthostilborosindon." The compound exists as deep garnet needles melting above 300° but distilling undecomposed at a high temperature. The vapors are deep red. In concentrated sulfuric acid the compound forms a beautiful violet solution, which becomes yellow on dilution. The free base (rose-red) is deposited in cloth by boiling a water-diluted yellow solution of one of its salts in alcohol.²⁴

The reaction of 2,3-dimethyl-1,4-diazaphenanthrene with dimethylglyoxime has been described above (p. 346), and the interesting reactions of 2,3-bis(carbethoxymethyl)-1,4-diazaphenanthrene were discussed earlier (pp. 333-5). 2,3-Dicarbethoxy-1,4-diazaphenanthrene is saponified in the usual way to the dibasic acid, which forms the cyclic anhydride on heating.⁶¹

Also of interest is the fact that a methyl group adjacent to the hetero atom behaves like that in picoline, etc.; *i.e.*, it reacts with aromatic aldehydes to form styryl derivatives.⁵⁶

(6) *Physical Properties*

1,4-Diazaphenanthrene melts at 62° and is volatile with steam.¹⁶ Its salts give yellow solutions, and are not dissociated by water. It forms a difficultly soluble chloroplatinate and a nicely crystalline sulfate. Its picrate melts at 171°. Solutions in concentrated sulfuric acid are deep red, but become yellow on dilution with water. This latter behavior is exhibited also by the polyarylated dihydro derivatives; however, the ferric chloride oxidation products of the latter, *i.e.*, the pseudo bases, form stable salts.^{18,20} The hydroxides (pseudo bases) show in neutral aqueous solution strong, yellow-green fluorescence which disappears on addition of mineral acids. These properties are indicated in Table V-2.

1,4-Diazaphenanthrene is readily quaternized once with methyl iodide³⁴ or sulfate.^{48,50,52} However, most of the quaternary salts have been formed in the synthesis of the ring system (see pp. 332 and 338). The salts are readily converted into hydroxypseudo bases as shown on p. 338.

(7) *Uses*

Few applications of 1,4-diazaphenanthrenes have been mentioned. The quaternary salts of the 6-amino-, 6-*p*-toluidino-, and 6-hydroxy-derivatives of 2,3-diphenyl-1,4-diazaphenanthrene are reported to dye wool, cotton, and silk rose-red to red-violet.^{24,27,28} This behavior is similar to that of the phenylphenazonium salts (rosindone, safranin types).

2,3-Bis(α -cyanobenzyl)-1,4-diazaphenanthrene is reported to dye wool in orange-yellow shades; its 7-sulfo derivatives dyes wool intense yellow; the 8-sulfo-10-hydroxy derivative dyes wool chocolate; and the quaternary salt with chlorobenzene dyes wool in orange shades.⁴³

Certain derivatives of the 1,4-diazaphenanthrene system were synthesized in medical^{38,49,64,68} and dye³⁷ research programs.

TABLE V-2. 1,4-Diazaphenanthrenes.^a Alkyl, Aryl, and Hydrogenated Derivatives

Formula	Compound	M.p., °C.	Refs.
	2-Methyl-	95	79, 80
LIH ^a	3-Methyl-	81	80
LXXIX	2,3-Dimethyl-	101-2	51

(Table continued)

TABLE V-2 (continued)

Formula	Compound	M.p., °C.	Refs.
LXXX	(compound with di-methylglyoxime)	123–200	51
LXXVII	2-Phenyl- ^b	153	34, 35, 66 (?)
XLIV		N ⁴ -C ₆ H ₅ Br	67
XLV		N ⁴ -C ₆ H ₅ OH ^c 148	20, 67
LIV	3-Phenyl- ^b	163	34, 35, 52, 66(?)
		N → O 236	58
	<i>π</i> -Phenyl- ^d	187	29
	3-(1-Naphthyl)-	161.5	56
	3-(2-Naphthyl)-	162	56
LXXXIX	2-Methyl-3-phenyl-	121	56, 57
XC		N ⁴ → O 212	67
V	2,3-Diphenyl-	147	15, 26
		N ⁴ → O 252	58
XIII		N ⁴ -C ₆ H ₅ Cl	18, 20
XII		N ⁴ -C ₆ H ₅ OH ^e 167	18, 20
		N ⁴ - <i>p</i> -CH ₃ C ₆ H ₄ Cl	25
		N ⁴ - <i>p</i> -CH ₃ C ₆ H ₄ OH ^e 194	25
XV		N ⁴ -CH ₃ Cl.H ₂ PtCl ₆	49, 62
	2,3-Di-4'-tolyl- ^f	183	42
	3-Phenyl-2-styryl-	166	56
	2-(4-Methylstyryl)-3-phenyl-	178	56
XXXIX or XL	2,3-Diphenyl-3,4(or 1,2)-dihydro- ^e	172	26
XLII	2,4-Diphenyl-3,4-dihydro-	164–5	20
XXXVIII	2,3,4-Triphenyl-3,4-dihydro- ^e	163–4	17
	2,3-Diphenyl-4-(<i>p</i> -tolyl)-3,4-dihydro- ^e	173	25

^a Oxo compounds are listed under the tautomeric hydroxy derivatives when possible. Abbreviations used conform to those previously employed; in addition pseudo bases will be listed for convenience as N—ArOH; quaternary salts as N—ArX; N-oxides as N → O. The position of substitution, *i.e.*, N¹ or N⁴, will be indicated where certain.

^b Dark red color in sulfuric acid.

^c Beautiful yellow-green fluorescence in alcohol, and especially in acetic acid.

^d The product should be 2(or 3)-phenyl-1,4-diazaphenanthrene, but the melting point is in disagreement with both.

^e Yellow-green fluorescence in organic solvents; deep red in mineral acid solutions.

^f Blue-violet with sulfuric acid.

TABLE V-3. 1,4-Diazaphenanthrenes. Halogen, Nitro-, and Amino Derivatives

Compound (or formula)	M.p., °C.	Refs.
2,3-Dichloro- ^a	142	33
5-Bromo-2,3-diphenyl-	195-9	60
7-Bromo-2,3-diphenyl- ^b	214	46
2,3-Bis-bromomethyl-	196-8	65
2,3-Bis- α -bromoethyl-	173-4	65
2(or 3)-(<i>m</i> -Nitrophenyl)-	196	80a
2(or 3)-(<i>p</i> -Nitrophenyl)-	237	80a
2,3-Di-(3-nitro-4-phenetyl)- ^c	178	42
2-Amino-	215-7	68
3-Amino-	150-2	68
6-Amino-2,3-diphenyl- ^d	245	48, 62
	N ¹ -C ₆ H ₅ Cl.H ₂ O ^e loses H ₂ O at 150°	24
XIV ^f	N ¹ -C ₆ H ₅ Cl	50
	N ⁴ - <i>p</i> -CH ₃ C ₆ H ₄ Cl ^g	27
	N ⁴ - <i>p</i> -C ₂ H ₅ OC ₆ H ₄ Cl.H ₂ O ^h loses H ₂ O at 150°	28
7-Amino-2,3-diphenyl- ⁱ	208	47
9-Amino-2,3-diphenyl-	215	63
2(or 3)-Amino-3(or 2)-chloro- ^j	222	33
6- <i>p</i> -Toluidino-2,3-diphenyl-	N ⁴ -C ₆ H ₅ Cl ^k	24
6-Acetamido-	252-3	64
6-[N-(2-Diethylaminoethyl)acetamido]-	P 195-7 (dec.)	64
2- and 3-Sulfanilamido- ^l	205-8	68
2- and 3-(4-Acetylsulfanilamido)-	155-205	68
6-Acetamido-2,3-diphenyl- ^m	245	48, 62
	N ¹ -C ₆ H ₅ Cl ⁿ	50
2(or 3)-(<i>m</i> -Aminophenyl)-	174	80a
2(or 3)-(<i>p</i> -Aminophenyl)-	186	80a
3-(4-Acetamidophenyl)- ^o	235	53
3-(4-Benzamidophenyl)-	246	53
2(or 3)-(<i>m</i> -Sulfanilamidophenyl)-	193	80a
2(or 3)-(<i>p</i> -Sulfanilamidophenyl)-	249	80a
2(or 3)-[<i>m</i> -(N ⁴ -Acetylsulfanilamido)phenyl]-	245	80a
2(or 3)-[<i>p</i> -(N ⁴ -Acetylsulfanilamido)phenyl]-	287	80a

^a Yellow with sulfuric acid.^b Violet with sulfuric acid.^c Red-violet with sulfuric acid.^d Organic solutions fluoresce blue-green. Fuchsin-red in sulfuric acid; gives olive-green, then eosin-red on dilution.^e Fluoresces in alcohol; dyes wool, cotton, and silk a rose color.

TABLE V-3 (*continued*)

^f Violet crystals. Ponceau red solutions in water, alcohol. Intense reddish-violet with sulfuric acid; dilution with little water gives bluish-green; more water gives ponceau red (crimson).

^g Red plates. Green-yellow fluorescence in alcohol.

^h Red needles.

ⁱ Bright red with sulfuric acid.

^j Weak yellow hydrochloride, difficultly soluble in excess hydrochloric acid. Dark red with sulfuric acid.

^k Bronze plates. Fuchsin red in alcohol. Slate-blue color in sulfuric acid; gives pure blue, then red-violet on dilution. Dyes cotton red-violet.

^l Survey Number 11,857 of ref. 49.

^m Feeble blue-violet fluorescence in organic solvents. Fuchsin-red in sulfuric acid.

ⁿ Red-violet in sulfuric acid; gives yellow on dilution.

^o Solutions fluoresce violet.

TABLE V-4. 1,4-Diazaphenanthrenes. Hydroxy Derivatives

Formula	Compound	M.p., °C.	Refs.
LXX	2,3-Dihydroxy- ^a	> 300	24, 30, 33
XCII or XCIII	6-Hydroxy-2,3-diphenyl-	N ⁴ -C ₆ H ₅ Cl ^b dec. at 100	24
XCI	6-Ethoxy-2,3-diphenyl-	N ⁴ -C ₆ H ₅ OH ^c (inner anhydride) > 300	23, 24
		N ⁴ -C ₆ H ₅ Cl ^d	23
		N ⁴ -C ₆ H ₅ OH 175-8	23, 31
		N ⁴ - <i>p</i> -CH ₃ C ₆ H ₄ Cl	27
		N ⁴ - <i>p</i> -C ₂ H ₅ OC ₆ H ₄ Cl ^e	28
	6-Ethoxy-2,3-diphenyl-7,8,9,10- tetrahydro-	N ⁴ -C ₆ H ₅ OH 151.5	31
		N ⁴ -C ₆ H ₅ Cl	31
	9-Methoxy-2,3-diphenyl- ^f	168	40
	2-Hydroxy-3,4-dihydro-	255	37
XLVII	3-Hydroxy-1,2-dihydro-	240	36, 37
	3,9-Dihydroxy-1,2-dihydro- ^g	(dec.)	37
	3-Hydroxy-5,8-disulfo-1,2-dihydro-		37
	2,3-Di- <i>o</i> -anisyl- ^h	180	44
	2,3-Di- <i>p</i> -anisyl- ⁱ	161	42
	2,3-Di- <i>o</i> -phenetyl- ^h	180	44
	2,3-Di- <i>p</i> -phenetyl- ⁱ	155	42
	2,3-Di-(3,4-methylenedioxy- phenyl)- ⁱ	205	42
	2,3-Di-(<i>p</i> -benzyloxyphenyl)-	156	45
	2,3-Di-(<i>p</i> -phenoxyphenyl)-	157	42

^a Shows weakly acid characteristics.

^b Orange-yellow. Colors silk rose-red. Decomposes at 100°, giving hydrogen chloride and the anhydride, a rosindone dye (XCII or XCIII).

TABLE V-4 (*continued*)

^c Deep garnet needles. Distills undecomposed at high temperature. The vapors are deep red. Violet in sulfuric acid; gives yellow on dilution.

^d Gives a rosindone (XCII or XCIII) on heating.

^e Green-yellow fluorescence in water, increased by excess hydrochloric acid.

^f Pale yellow crystals become red when wet with hydrochloric or sulfuric acid.

^g Couples to form azo dyes.

^h Blue-violet with sulfuric acid.

ⁱ Blue with sulfuric acid.

TABLE V-5. 1,4-Diazaphenanthrenes. Carboxy and Carbonyl Derivatives

Formula	Compound	M.p., °C.	Refs.
	2,3-Dicarboxy-	195	61
	(anhydride)	235	61
LXV	(diethyl ester)	119	61
XXXIII	2(or 3)-Carboxy-3(or 2)-hydroxy-		19
XXXII	2(or 3)-Carboxy-3(or 2)-methyl-	113-4	38
	(ethyl ester)		
XXXII	2(or 3)-Carboxy-3(or 2)-propyl-	83-4	38
	(ethyl ester)		
XXXII	2(or 3)-Carboxy-3(or 2)-cyclohexyl-	64-5	38
	(ethyl ester)		
XXXII	2(or 3)-Carboxy-3(or 2)-phenyl-	146	38
	(ethyl ester)		
LXXXIV and LXXXV	2-Carboxy-3-amino- } mixture 3-Carboxy-2-amino- }	212-5	68
	2,3-Dicarboxy-6-ethoxy-	N ⁴ -C ₆ H ₅ Cl	27
XVIII	2,3-Dicarboxy-6-ethoxy-	N ⁴ - <i>p</i> -CH ₃ C ₆ H ₄ Cl	27
XVII	2,3-Dicarboxy-6-ethoxy- (anhydride)	N ⁴ - <i>p</i> -CH ₃ C ₆ H ₄ Cl	27
	5-Carboxy-3-hydroxy-1,2-dihydro-	(dec.)	37
	3-Carboxymethyl-	206	55
LXIII	(ethyl ester)	96	55
LXIX	3-Carboxycarbonylmethyl-	204	59
	i.e. (1,4-diazaphenanthrene-3-pyruvic acid) ^a		
XXIII	2,3-Bis(carboxymethyl)-		32
	(potassium salt)		
XX	(diethyl ester)	98	32
LXXXIII	2-(<i>o</i> -Carboxyphenyl)-	> 300	34
	3-(<i>o</i> -Carboxyphenyl)- ^b	246	34
XXIX	6-Sulfo-2,3-bis(carboxymethyl)-	> 275	32
XXVIII	(diethyl ester)	> 285	32
LXVII	3-Acetyl-	152	59

^a Bordeaux red color on concentrated sulfuric acid.

^b Weak acid.

TABLE V-6. 1,4-Diazaphenanthrenes. Oxo Derivatives

Formula	Compound	M.p., °C.	Refs.
XLIX ^a	3-Oxo-4-methyl-1,2-dihydro-	155.5	37
	(2or 3)-Oxo-1(or 4)-methyl-3,4(or 1,2)-dihydro- ^b	214	34
	3-Oxo-4-ethyl-1,2-dihydro-	164	37
	3-Oxo-4-methyl-8-sulfo-1,2-dihydro-		37
	3-Oxo-5-carboxy-4-methyl-1,2-dihydro-		37
	2,3-Dioxo-1,4-dihydro-	> 300	30
	5,6-Dioxo-3-phenyl-	211	52, 54
		N → O > 300	58
	3-(<i>p</i> -Acetamidophenyl)-5,6-dioxo-	270	53
	3-(<i>p</i> -Benzamidophenyl)-5,6-dioxo-	286	53
LXXXVI	5,6-Dioxo-2,3-diphenyl-		58

^a Couples to form azo dyes.^b Probably 2-oxo-1-methyl-3,4-dihydro- since the m.p. disagrees with that of XLIX.

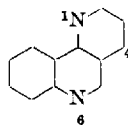
TABLE V-7. 1,4-Diazaphenanthrenes. Miscellaneous

Formula	Compound	M.p., °C.	Refs.
	2,3-Bis(α -cyanobenzyl)- ^a	230	43
		N ⁴ -C ₈ H ₈ Cl ^b	43
	2,3-Bis(α -cyanobenzyl)-7-sulfo- ^c	> 270 (dec.)	43
	2,3-Bis(α -cyanobenzyl)-10-hydroxy-8-sulfo- ^d		43
LX	3-[4-(2-Amino-1-naphthylazo)phenyl]- ^e	258	53
	3-[4-(4-Amino-1-naphthylazo)phenyl]-		53
LVIII	3-[4-(2-Hydroxy-1-naphthylazo)-phenyl]- ^f	294	53
LVII	3-[4-(4-Hydroxy-1-naphthylazo)-phenyl]- ^g	> 310	53
LXI	3-[4-(2- α , β -Naphthotriazolyl)-phenyl]-	299	53
LXXIV	1,2,3,4-Dibenzoylene-1,4-dihydro-	323-4	41
LXXIII	1,2,3,4-Dibenzoylene-2,3-dihydroxy-1,2,3,4-tetrahydro-	280-4	41
LXXV or LXXVI	<i>o,o'</i> -Diselenobis[3(or 2)-phenyl-2(or 3)-hydroxy]- ^h	352.5	39

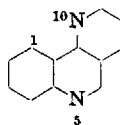
^a Dyes wool in orange-yellow shades; violet color with sulfuric acid.^b Dyes wool in orange shades; orange-red color in sulfuric acid.^c Violet with sulfuric acid. Dyes wool in intense yellow shades.^d Dyes wool in chocolate shades.

TABLE V-7 (*continued*)^e Red.^f Dark red.^g Brown-red.^h Orange colored. Soluble in cold alcoholic potassium hydroxide, but resinifies when heated with concentrated aqueous potassium hydroxide.

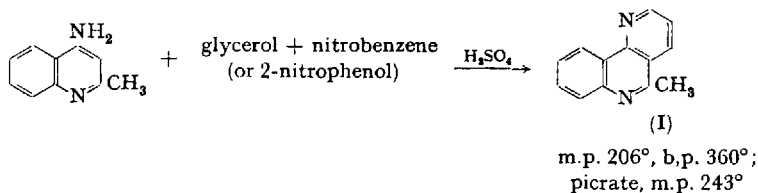
D. 1,6-Diazaphenanthrene. Pyrido[3,2-c]quinoline. 7,8-Benzo-1,6-naphthyridine. Pyridino-3',2',3,4-quinoline. γ -Quinoquinoline. 1,6-Phenanthroline. 5,10-Phenanthroline. R.I. 1952



other numbering:

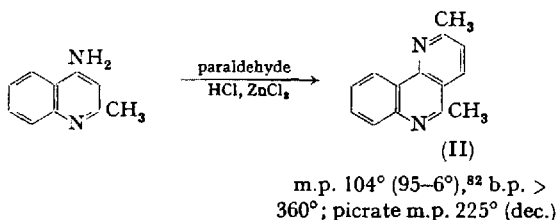
*(1) Preparation and Properties*

The first representative of the 1,6-diazaphenanthrene system was synthesized about 60 years ago, and there have been but two subsequent reports. The methods involved are those used in quinoline



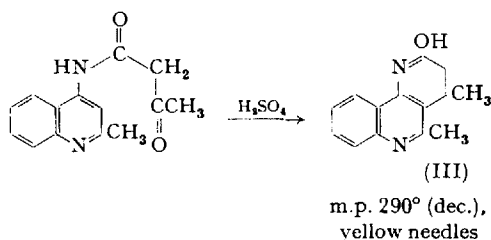
synthesis, *i.e.*, Skraup, Doebner-Miller, Knorr, Conrad-Limpach, and ethoxymethylenemalonic ester (E.M.M.E.) methods.

5-Methyl-1,6-diazaphenanthrene (I) was prepared in "poor" yield by Marckwald⁸¹ using the Skraup reaction. Lions and Ritchie⁸² con-

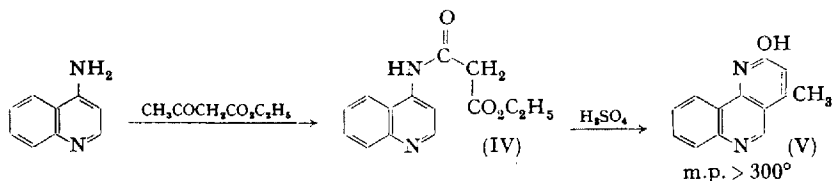


firmed this synthesis, using arsenic acid as the oxidant, and obtained a yield of about 5%.

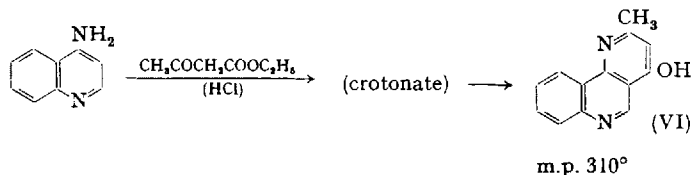
2,5-Dimethyl-1,6-diazaphenanthrene (II) was prepared by the Doebner-Miller reaction in undisclosed yield by Marckwald⁸¹ and in less than 1% yield by Lions and Ritchie.⁸² The latter authors⁸² also reported the preparation of 4,5-dimethyl-2-hydroxy-1,6-diazaphenanthrene (III) in approximately 60% yield by the Knorr reaction.



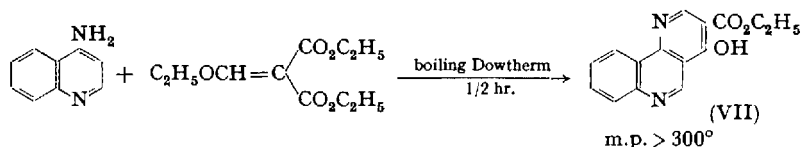
More recently Hauser and Reynolds studied the reactions of 3- and 4-aminopyridines and quinolines in Knorr, Conrad-Limpach, and E.M.M.E. (ethoxymethylenemalonic ester) reactions.⁸³ Whereas the Knorr reaction with *N*-(3-quinolyl)acetoacetamide failed completely, a 58% yield of 2-hydroxy-4-methyl-1,6-diazaphenanthrene (V) was obtained from the corresponding *N*-(4-quinolyl)acetoacetamide (IV).



The Conrad-Limpach reaction gave a 70% yield of the corresponding 4-hydroxy-2-methyl-1,6-diazaphenanthrene (VI), while only a 40% yield of the isomeric diazaanthracene was obtained from 3-aminoquinoline. Likewise, the E.M.M.E. method gave a 22% yield



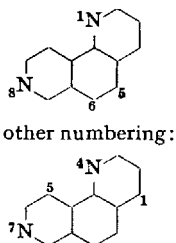
with 3-aminoquinoline, but a 93 % yield of 3-carbethoxy-4-hydroxy-1,6-diazaphenanthrene (VII) with 4-aminoquinoline as the starting



material. The differences in reactivity of 3- and 4-aminoquinoline are explained by the low electron densities at the 2- and 4-positions at which cyclization of substituted 3-aminoquinolines would have to occur.⁸³

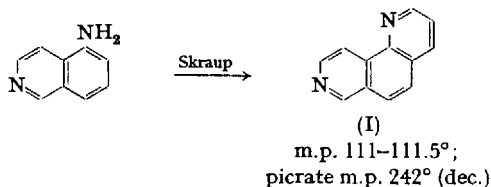
The 1,6-diazaphenanthrenes, excepting III, appear to be stable to heat, boiling undecomposed at high temperatures. They exhibit the usual basicity associated with quinolines, and are highly soluble in the ordinary organic solvents. Their chemical reactivity has not been investigated.

E. 1,8-Diazaphenanthrene. 1,8-Phenanthroline. Pyrido[3,4-*h*]quinoline. Pyrido[2,3-*f*]isoquinoline



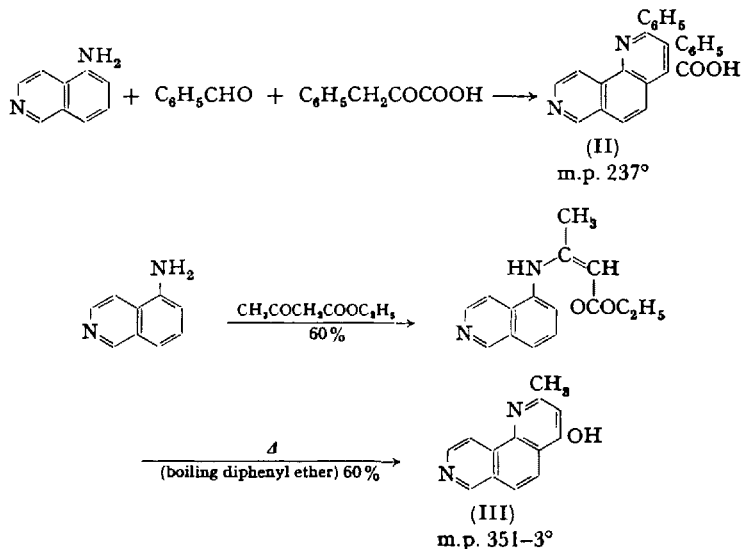
(1) Preparation and Properties

The 1,8-diazaphenanthrene system is of rather recent origin. 1,8-Diazaphenanthrene (I) was prepared in about 5 % yield by the Skraup reaction on 5-aminoisoquinoline.⁸⁴ Earlier, the Doebner re-



action with 5-aminoisoquinoline was used to obtain 4-carboxy-2,3-diphenyl-1,8-diazaphenanthrene (II) in fairly good yield.⁸⁵

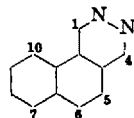
Finally, the Conrad-Limpach reaction gives an over-all yield of 36 % of 4-hydroxy-2-methyl-1,8-diazaphenanthrene (III).⁸⁴



(2) Reactions

Some reactions of these 1,8-diazaphenanthrenes have been studied. For example, decarboxylation of II gives a small yield of 2,3-diphenyl-1,8-diazaphenanthrene which melts surprisingly higher than the acid at $263-4^\circ$.⁸⁵ The hydroxyl group of III has been replaced in 75 % yield giving 4-chloro-2-methyl-1,8-diazaphenanthrene, m.p. $191-191.5^\circ$.⁸⁴ The latter, on treatment with hydrogen and palladium on charcoal, gives 2-methyl-1,8-diazaphenanthrene, m.p. $97-9^\circ$.

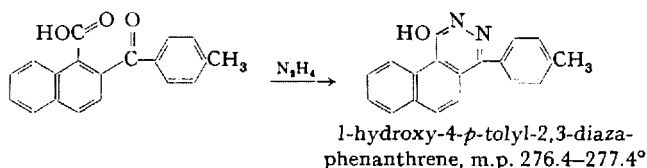
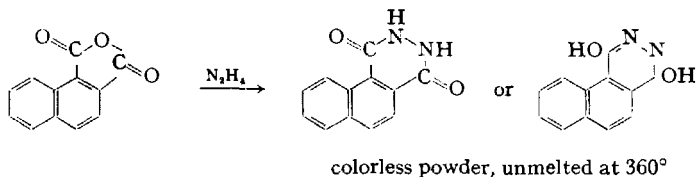
F. 2,3-Diazaphenanthrene. Benzo[f]phthalazine. 7,8-Benzophthalazine



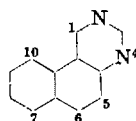
(1) Preparation and Properties

Only two reports of 2,3-diazaphenanthrenes have appeared. 1,4-Dihydroxy-2,3-diazaphenanthrene or its diketonic tautomer was prepared in studies on chemiluminescent organic compounds.¹⁵³

The 2,3-diazaphenanthrene system is believed to have been formed also in an unsuccessful Wolff-Kishner reduction.¹⁵⁴

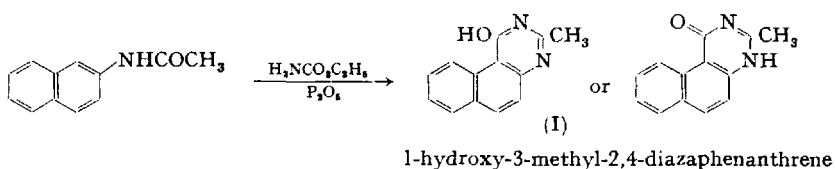


G. **2,4-Diazaphenanthrene. Benzo[f]quinazoline. 5,6-Benzoquinazoline. 2,4-Naphth-
isodiazine. R.I. 1908**



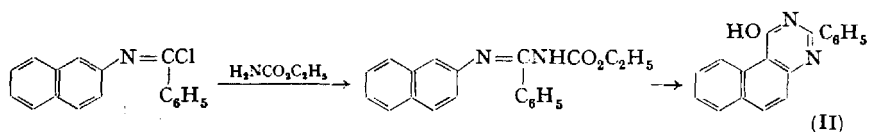
(I) Preparation

The 2,4-diazaphenanthrene system was first synthesized by a method used also for 1,3-diazaphenanthrene; the reaction of an acyl-naphthylamine with urethan.^{6,7} The yields are about 30 %. Although



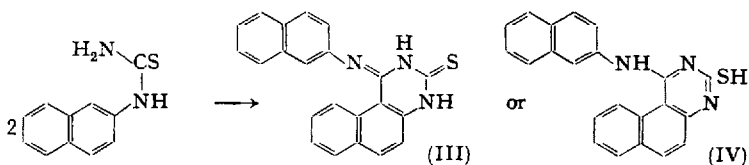
indicating I as a possibility, the authors postulated the linear anthracene derivative. Such a structure controverts the evidence, ring closure generally occurring in the 1-position of naphthalene where possible (see Introduction).

Another method, also used in the synthesis of 1,3-diaza compounds,

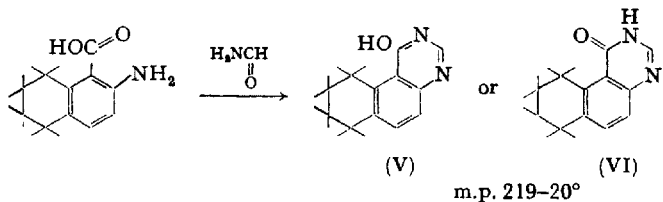


involves *N*-2-naphthylbenzimidyl chloride, giving II, the 3-phenyl analog of I.¹⁰

An interesting preparation of this ring system involves heating 2-naphthylthiourea (or 2-naphthylamine and thiourea).⁸⁶ The product is 1-(2-naphthylimino)-3-thiono-2,4-dihydro-2,4-diazaphenanthrene (III) or a tautomer, 3-mercapto-1-(2-naphthylamino)-2,4-diazaphenanthrene (IV). Finally, the reaction of 2-amino-5,6,7,8-tetrahydro-1-

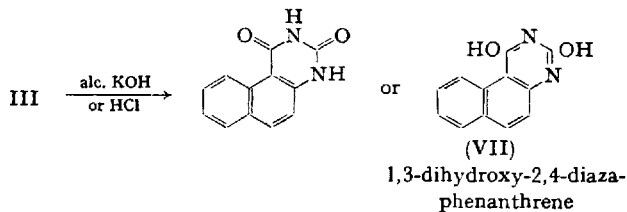


naphthoic acid with formamide gives 1-hydroxy-7,8,9,10-tetrahydro-2,4-diazaphenanthrene (V) or its tautomer, 1-oxo-1,2,7,8,9,10-hexahydro-2,4-diazaphenanthrene (VI).⁸⁷



(2) Reactions

Compound III may be converted to the dione by reaction with alcoholic potassium hydroxide or hydrochloric acid. VI has been used

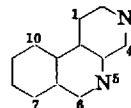


for the preparation of compounds involved in studies on the effect of substituents in the benzene ring on the antimalarial activity and the chemotherapeutic index of the DL-form of the hydrangea alkaloid.⁸⁷

TABLE V-8. 2,4-Diazaphenanthrenes

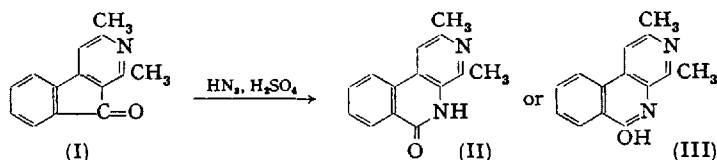
Formula	Compound	M.p., °C.	Refs.
V	1-Hydroxy-7,8,9,10-tetrahydro-	219-20	87
I	1-Hydroxy-3-methyl-	295	6
	1-Hydroxy-3-benzyl-	278	7
II	1-Hydroxy-3-phenyl-	295-8	10
VII	1,3-Dihydroxy-	341	86
IV	3-Mercapto-1-(2-naphthylamino)-	318	86
	2-[3-(3-Hydroxy-2-piperidyl)acetyl]-	1½H ₂ O.2HCl 207	87
	1-oxo-1,2,7,8,9,10-hexahydro-		
	2-[3-(3-Methoxy-2-piperidyl)acetyl]-	2H ₂ O.2HCl 226	87
	1-oxo-1,2,7,8,9,10-hexahydro-		

H. 3,5-Diazaphenanthrene. Pyrido[3,4-c]isoquinoline. 3,4-Benzo-1,7-naphthyridine



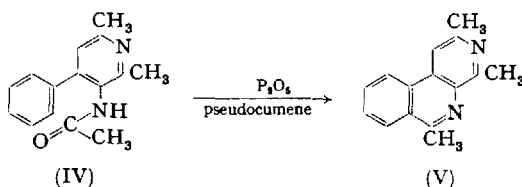
(1) *Preparation*

The 3,5-diazaphenanthrene system is of rather recent origin. The Schmidt reaction, having shown its value in the preparation of phenanthridones, or 5-azaphenanthrenes (Chapter 4), was applied to azafluorenones, from which the 3,5-diazaphenanthrene system evolved. When 1,3-dimethyl-2-azafluorenone (I) is submitted to the Schmidt reaction,⁹⁴ 2,4-dimethyl-6-oxo-5,6-dihydro-3,5-diazaphenanthrene (II), or its tautomer, 2,4-dimethyl-6-hydroxy-3,5-diazaphenanthrene (III), is obtained in about 90% yield.^{90, 92} This reaction, is, however, of



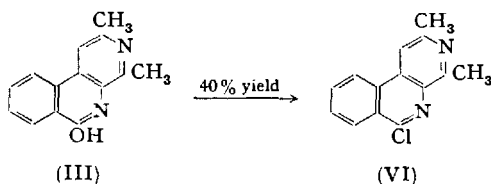
limited value in the preparation of 3,5-diazaphenanthrenes having substituents in the 1-position. The yield of 1-carbethoxy-2,4-dimethyl-6-hydroxy-3,5-diazaphenanthrene from the correspondingly substituted fluorenone was 35%,^{91, 92} but when I was substituted by NH₂, NHC₆H₅, or COOH in the 4-position or by NO₂, NH₂, NHCOC₆H₅, or OCH₃ in the 7-position, the reaction failed entirely.⁹¹

A second method for preparing 3,5-diazaphenanthrene is also due to Petrow.⁹⁰ When 3-acetamido-4-phenyl-2,6-dimethylpyridine (IV) is heated with phosphorus pentoxide in pseudocumene, 2,4,6-trimethyl-3,5-diazaphenanthrene (V) is obtained in 30% yield. The corresponding benzamidopyridine gives 2,4-dimethyl-6-phenyl-3,5-diazaphenanthrene.

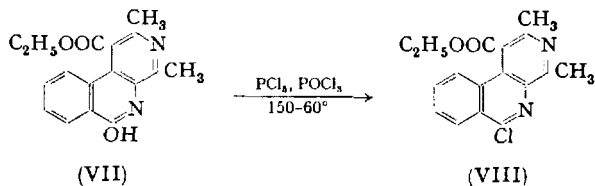


(2) Reactions

Oxidation of V with chromic acid gave a mixture of products from which II (or III) was isolated and identified by mixed melting point. This constituted a proof of structure of II (or III) and proved the direction of the rearrangement. If the rearrangement had taken place in the other possible manner, a 3,6-diazaphenanthrene would have resulted. The hydroxyl group of III can be replaced by chlorine, using phosphorus pentachloride and phosphoryl chloride at 180°. The



chlorine atom in 6-chloro-2,4-dimethyl-3,5-diazaphenanthrene (VI) is then readily replaceable by other groups. In the customary manner the analogous 6-phenoxy-, 6-piperidino-, and 6-amino-derivatives can be prepared.⁹⁰ Replacement of the chlorine atom by hydrogen (P + H₂) was unsuccessful, the 6-hydroxy compound (III) being regenerated.



When the 1-carbethoxy derivative (VII) of III is treated similarly, a 55 % yield of the 6-chloro derivative (VIII) is obtained.⁹¹ Treatment of VIII with alcoholic ammonia gives a 40 % yield of the 6-amino derivative. The latter is converted back to VII by nitrous acid.

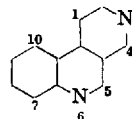
(3) Uses

It is stated that some of these 3,5-diazaphenanthrenes have shown interesting therapeutic properties.^{90,92} Recent studies reveal that certain of the 3,5-diazaphenanthrenes as well as 3,6-diazaphenanthrenes show marked analeptic properties.^{95,96}

TABLE V-9. 3,5-Diazaphenanthrenes

Formula	Compound	M.p., °C.	Refs.
V	2,4,6-Trimethyl-	132.5-133	90
		HCl > 310	90
	2,4-Dimethyl-6-phenyl-	131-2	90
		HCl > 300	90
		P 206-7	90
VI	6-Chloro-2,4-dimethyl-	153-4	90, 92
	6-Amino-2,4-dimethyl-	189.5-190.5	90, 92, 93
		2HCl > 310	90, 92, 93
		P 261-2 (dec.)	90, 93
	6-Piperidino-2,4-dimethyl-	113.5-114.5	90, 92
		2HCl 165-6	90, 92
III	6-Hydroxy-2,4-dimethyl-	P 228-9	90, 92
		320-1	90, 92
	6-Phenoxy-2,4-dimethyl-	112-3	90, 92
		P 203-203.5	90, 92
VIII	1-Carbethoxy-6-chloro-2,4-dimethyl-	186-7	91, 92
	1-Carbethoxy-6-amino-2,4-dimethyl-	200-1	91, 92
VII	1-Carbethoxy-2,4-dimethyl-6-hydroxy-	255-6	91, 92

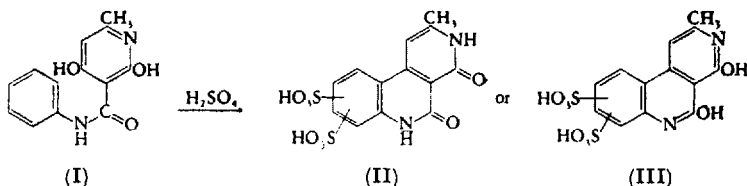
I. 3,6-Diazaphenanthrene. Pyrido[3,4-c]quinoline



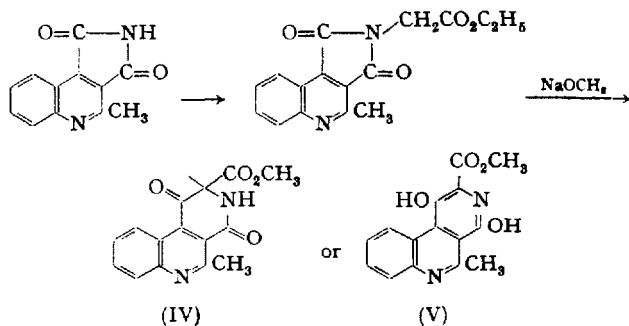
(1) Preparation

The 3,6-diazaphenanthrene system is of relatively recent origin and was reported almost simultaneously by different investigators.^{97,98}

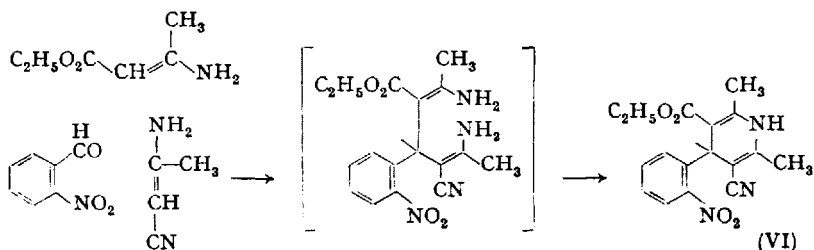
One method⁹⁷ of synthesis employed the cyclization of 2,4-dihydroxy-6-methyl-3-(phenylcarbonyl)pyridine (I) with sulfuric acid, giving 4,5-dioxo- α,α' -disulfo-2-methyl-3,4,5,6-tetrahydro-3,6-diazaphenanthrene (II) or its tautomer, 4,5-dihydroxy- α,α' -disulfo-2-methyl-3,6-diazaphenanthrene (III). Attempts to make the acetyl derivative of III were unsuccessful.



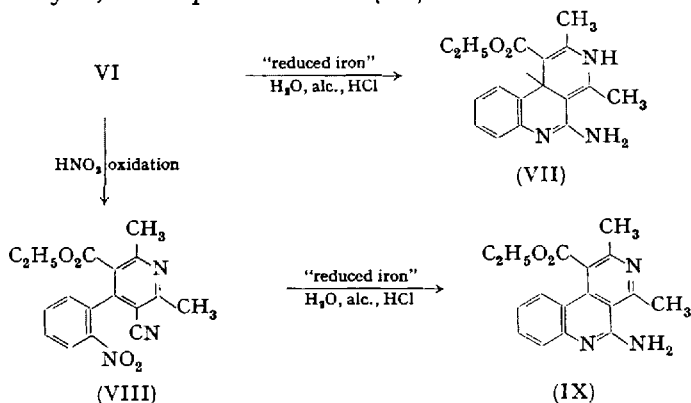
The second method,⁹⁸ utilizing the Gabriel phthalimide-glycine ester isoquinoline synthesis, gave a product postulated as 2-carbomethoxy-1,4-dioxo-5-methyl-1,2,3,4-tetrahydro-3,6-diazaphenanthrene (IV) or its tautomer, 2-carbomethoxy-5-methyl-1,4-dihydroxy-3,6-diazaphenanthrene (V).



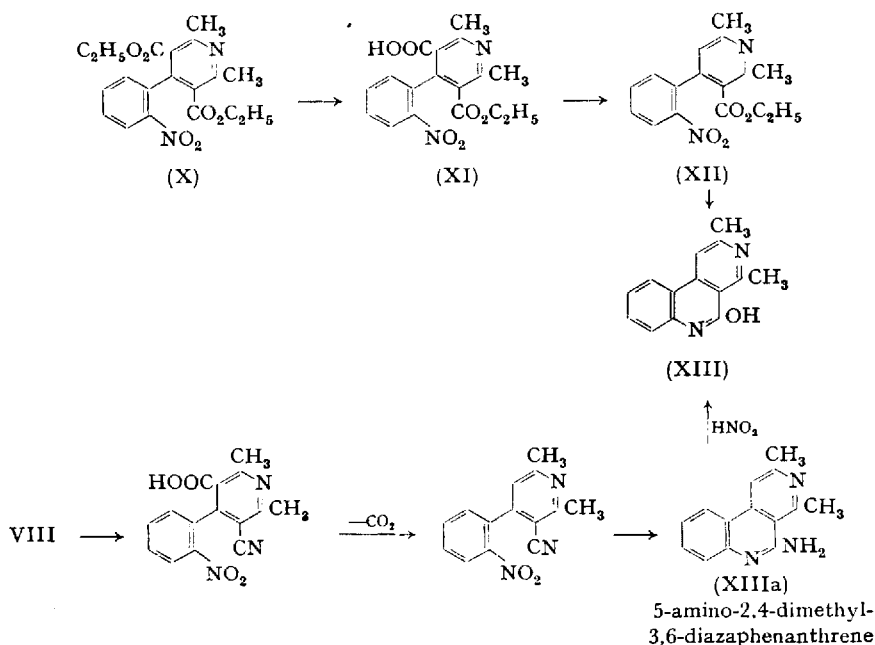
A third method⁹⁹ involves a mixed Hantzsch-Knoevenagel reaction, giving the intermediate, ethyl 3-cyano-2,6-dimethyl-4-*o*-nitrophenyl-1,4-dihydropyridine-5-carboxylate (VI). Compound VI can then



be reduced to 5-amino-1-carbethoxy-2,4-dimethyl-3,10b-dihydro-3,6-diazaphenanthrene (VII), or first oxidized to ethyl 3-cyano-2,6-dimethyl-4-*o*-nitrophenylpyridine-5-carboxylate (VIII), which then may be transformed by reduction and cyclization to 5-amino-1-carbethoxy-2,4-dimethyl-3,6-diazaphenanthrene (IX).

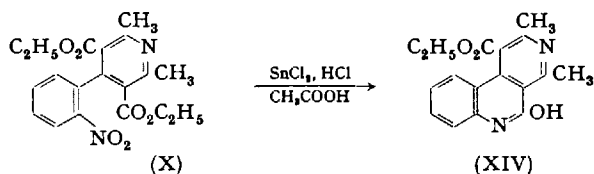


A fourth method for formation of the 3,6-diazaphenanthrene system is also due to Petrow. Ethyl 2,6-dimethyl-4-*o*-nitrophenyl-



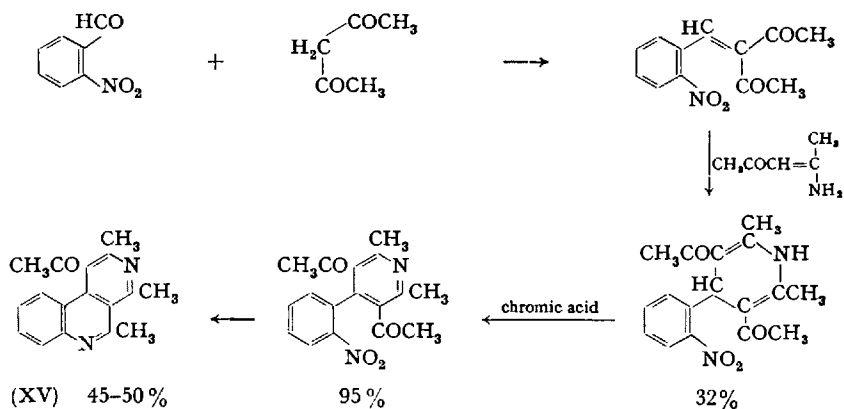
pyridine 3,5-dicarboxylate (X) was partially hydrolyzed to 3-carbethoxy-4-*o*-nitrophenyl-2,6-dimethylpyridine-5-carboxylic acid (XI). Decarboxylation of this acid-ester gave 3-carbethoxy-2,6-dimethyl-4-*o*-nitrophenylpyridine (XII), which on reduction and lactamization gave 2,4-dimethyl-5-hydroxy-3,6-diazaphenanthrene (XIII). The same compound was formed by the accompanying reactions starting with VIII, thus proving the formulation of IX.

Another interesting synthesis of 3,6-diazaphenanthrenes starts with compound X, and gives 1-carbethoxy-2,4-dimethyl-5-hydroxy-3,6-diazaphenanthrene (XIV) in one step.⁹¹ This compound was shown to



be unlike the product of the Schmidt reaction and is further proof that the Schmidt reaction gave 3,5-diazaphenanthrenes (p. 362).

These methods have recently been extended by Courts and Petrow to include 5-amino-1-cyano- and 1-acetyl-5-methyl-derivatives of 3,6-diazaphenanthrene.⁹⁵ In addition, a new route for the preparation of derivatives of 5-methyl-3,6-diazaphenanthrene was found. When the



4-acetoxy-3-methoxy-2-nitrobenzaldehyde was used, the yield in the cyclization was better than 90%.

The corresponding 5-amino derivatives were prepared by reductive cyclization of 4-(*o*-nitrophenyl) derivatives of 3,5-dicyanopyridines.



When R was methyl, the reduction was effected in 47% yield with hot hydrosulfite. The corresponding phenyl analog was prepared in unstated yield, using stannous chloride. The agents and conditions for each cyclization had to be worked out independently.

Marked analeptic properties have been found for certain 3,6(as well as 3,5)-diazaphenanthrenes.^{95,96}

(2) Reactions

Compound II or III, being only feebly basic, forms a picrate but not a hydrochloride. Attempts to form the oxime or acetyl derivative were unsuccessful.⁹⁷ Most of the customary reactions of other substituents have been observed; however, the 5-amino derivatives could not be diazotized.

TABLE V-10. 3,6-Diazaphenanthrenes

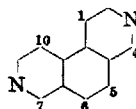
Formula	Compound	M. p., °C.	Refs.
XIIIa	5-Amino-2,4-dimethyl-	197-8	99
	5-Benzamido-2,4-dimethyl-	P 254-5	99
	5-Hydroxy-2,4-dimethyl-	230-230.5	99
XIII	5-Hydroxy-7,8-dimethoxy-2,4-dimethyl-	310-1	99
	5-Hydroxy-7,8-dimethoxy-2,4-dimethyl-	242.5-243.5	99
	7,8-Dimethoxy-5-amino-2,4-dimethyl-	183-4	99
III	4,5-Dihydroxy- α,α' -disulfo-2-methyl-		97
VII	1-Carbethoxy-5-amino-2,4-dimethyl-3,10b-dihydro-	164-165.5	99
	1-Carbethoxy-5-amino-2,4-dimethyl-	191.5-192.5	99
	1-Carbethoxy-5-amino-2,4-dimethyl-8,9-methylenedioxy-	239-40	99
XIV	1-Carbethoxy-2,4-dimethyl-5-hydroxy-	184-5	91
V	2-Carbomethoxy-1,4-dihydroxy-5-methyl-	> 300	98
	1-Carbethoxy-5-acetoxy-2,4-dimethyl-	171	91

(Table continued)

TABLE V-10 (*continued*)

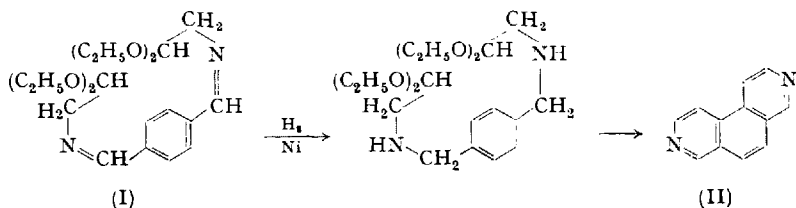
Formula	Compound	M.p., °C.	Refs.
XV	1-Acetyl-2,4,5-trimethyl-	166-7	95
	1-Acetyl-7,8-dihydroxy-2,4,5-trimethyl-	202-3	95
	1-Acetyl-7,8-dimethoxy-2,4,5-trimethyl-	136-7	95
	5-Acetoxy-1-acetyl-2,4-dimethyl-	134	95
	8-Acetoxy-1-acetyl-7-methoxy-2,4,5-trimethyl-	153.5-154.5	95
	5-Amino-1-cyano-2,4-dimethyl-	273	95
XVI	5-Amino-1-cyano-2,4-diphenyl-	276-7	95
	1-Cyano-5,8-diamino-2,4-dimethyl-	288-9	95
	8-Acetoxy-5-amino-1-cyano-2,4-dimethyl-7-methoxy-	239	95
	8-Acetoxy-5-amino-1-cyano-2,4-diphenyl-7-methoxy-	253	95
	1-Cyano-7,8-dimethoxy-2,4-dimethyl-5-hydroxy-	301-2	99

J. **3,8-Diazaphenanthrene. 3,8-Phenanthroline**



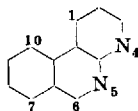
(1) *Preparation and Properties*

Only one report of a 3,8-diazaphenanthrene has appeared in the literature.¹⁰⁸ In attempts to prepare isoquinoline-type phenanthrolines, the isoquinoline synthesis of Pomeranz¹⁰⁹ was extended to the condensation of dialdehydes with aminoacetal. A 90% yield of the Schiff base (I) was obtained from terephthalaldehyde and aminoacetal. Attempts to cyclize I by hot concentrated sulfuric acid failed, due to the ease of hydrolysis of the C=N bonds. However, protection of these bonds by reduction permitted ring closures, with the loss of four moles of ethanol and simultaneous dehydrogenation, giving 3,8-diazaphenanthrene (II).



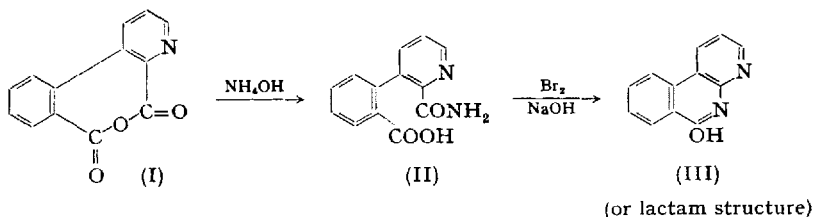
3,8-Diazaphenanthrene becomes colored on exposure to light and air. It melts at 225° , and forms a hydrochloride with m.p. 225° , a picrate with m.p. 235° , and a dimethiodide with m.p. 258° .

K. 4,5-Diazaphenanthrene. Pyrido[2,3-c]isoquinoline. 3,4-Benzo-1,8-naphthyridine. Pyridino-2',3',3,4-isoquinoline. Isoquino- β -pyridine. R.I. 1955



(1) Preparation

The synthesis of the 4,5-diazaphenanthrene system was reported in 1902,¹¹⁰ but no further work has been published. The anhydride of 3-(2-carboxyphenyl)pyridine-2-carboxylic acid (I), when treated with concentrated ammonium hydroxide, gave 2-carbamyl-3-(2-carboxyphenyl)pyridine (II), which was freed of a small amount of the isomeric substance by crystallization. Cyclization of II to give 6-hydroxy-4,5-diazaphenanthrene (III) occurred in hypobromite solution.



Proof that II is as represented and not the corresponding 3-(2-carbamylphenyl)-pyridine-2-carboxylic acid is furnished by the fact that the latter would not be expected to react with hypobromite solution. If it did, however, and cyclization *via* the lactam did occur, the product would be a 4,6-diazaphenanthrene. Oxidation of the latter by alkaline permanganate would give quinolinic acid. Oxidation of the product, 6-hydroxy-4,5-diazaphenanthrene (III), gave *o*-phthalic acid, which was to be expected.

(2) Reactions

Compound III underwent the usual reactions of the pyridols and pyridones. It was converted to the 6-chloro derivative by phosphorus

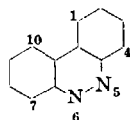
pentachloride and phosphoryl chloride. The chloro compound was converted to the model structure, 4,5-diazaphenanthrene, by heating with red phosphorus and hydrogen iodide. Attempted reduction of the chloro compound by zinc dust and acetic acid, or by hydriodic acid ($d. = 1.7$), regenerated the 6-hydroxy derivative.

(3) Properties

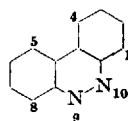
The anhydrous hydrochloride of 4,5-diazaphenanthrene is phototropic,¹¹¹ the salt taking on an intense green color in light in the absence of air. The original color returns after one day in the dark at about 90° . Dilute aqueous solutions of the hydrochloride show a strong green fluorescence.

4,5-Diazaphenanthrene melts at $113-4^\circ$, and boils above 360° . It forms a hydrochloride, m.p. 207° ; a hydrochloride dihydrate, m.p. 99° ; a picrate, m.p. 240° ; and a chromate, m.p. 170° (dec.). 6-Chloro-2,4-diazaphenanthrene melts at $182-3^\circ$, and forms a picrate, m.p. 240° (dec.). 6-Hydroxy-4,5-diazaphenanthrene, m.p. $274-6^\circ$, forms a picrate, m.p. 260° .

- L. 5,6-Diazaphenanthrene. Benzo-**
[c]cinnoline. 3,4-Benzocinnoline.
Dibenzopyridazine. 2,2'-Azodiphenyl.
Phenazone. 5,6-Naphthisodiazine.
Diphenylenazone. R.I. 1909



other
numbering:



(1) Nomenclature

Of the names listed above, the most frequently used have been benzo[c]cinnoline¹¹² and phenazone. The numbering of the positions has most generally followed that shown in the first structure above and will be used here.

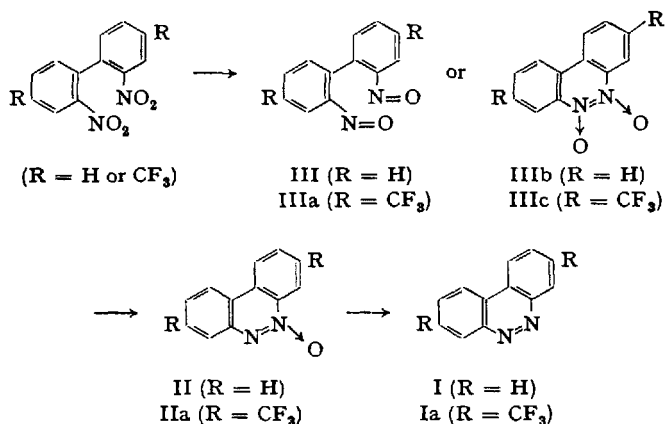
(2) Preparation

(a) Reduction of 2,2'-Dinitrobiphenyl. The most frequently used method of preparation for 5,6-diazaphenanthrenes has been the reduction of 2,2'-dinitrobiphenyl and its derivatives. The preparation was first

effected by Tauber in 1891.¹¹⁶ Numerous reducing agents have been used, giving a variety of products.



Recent studies by Ross and Kuntz¹⁵⁰ appear to establish the course of the reduction reactions involving *o,o'*-dinitrobiphenyl. Using the 4,4'-bis(trifluoromethyl) derivative, they found that the sodium sulfide reduction involved first the production of the 2,2'-dinitroso derivative (IIIa), followed by the 5,6-diazaphenanthrene 5-oxide (IIa), and finally by 3,8-bis(trifluoromethyl)-5,6-diazaphenanthrene (Ia). They assign structure IIIa to the compound which would have been described previously as the 5,6-dioxide (IIIc).



The extent to which these reactions occur, and therefore the products obtained, depends on the type of reducing agent. Table V-11 lists the reducing agents used and the data available concerning the yields of the various products.

The amine oxides can be reduced further by sodium amalgam, stannous chloride, or electrolytically to 5,6-diazaphenanthrenes.^{114, 116}

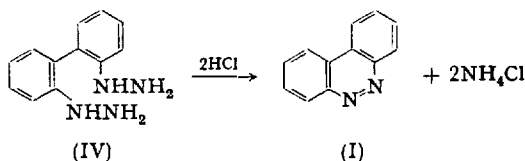
(b) From 2,2'-Dihydrazinobiphenyl. Historically, the next synthesis of 5,6-diazaphenanthrene was due also to Tauber,¹²⁶ who obtained

TABLE V-11. Reduction of *o,o'*-Dinitrobiphenyl

Reducing agent	Products	Refs.
Electrolysis	I (95 %)	113-115
Sodium amalgam	I (<i>ca.</i> 40-62 %)	115-117, 119
"Reduced iron"	I (17 %) and III ^a or III ^b	120, 121
Hydrogen (Raney nickel)	I (yield not indicated)	122
Hydrogen (Adams' catalyst)	I (low yield)	148
Zinc dust (alc. KOH)	(I), II, and III (25 %)	116, 117, 123
Sodium sulfide (dil. alc.)	II (91 %)	114
Sodium sulfide 9H ₂ O (100°)	II (95 %) (+ III)	114, 124, 125
Sodium sulfide (0.25 mole)	III ^a or c (43.6 %); II ^a (31.1 %)	150
Sodium sulfide (1.0 mole)	II ^a (21 %); I ^a (68 %)	150
Sodium sulfide (3.0 moles)	I ^a (95 %; 2.4 % unreacted)	150

^a Slack and Slack¹²⁰ appear to have isolated III or IIIb, m.p. 241–3°, not I, m.p. 157°.

a quantitative yield by heating 2,2'-dihydrazinobiphenyl (IV) with hydrochloric acid at 150° under pressure. The diacetyl derivative of IV also gives I under these conditions.

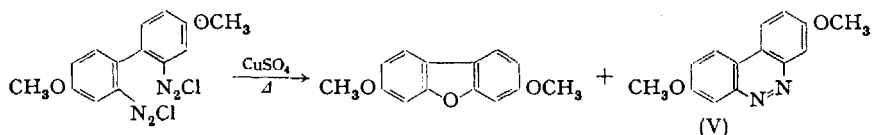


(c) From 2,2'-Diaminobiphenyl. Many of the attempts to remove or replace amino groups of 2,2'-diaminobiphenyls have lead to 5,6-diazaphenanthrenes among other products.^{127-129,133,150} By treating tetrazotized 2,2'-diaminobiphenyl with cuprous bromide, 5,6-diazaphenanthrene (I) is formed together with some carbazole and 2,2'-dibromobiphenyl.¹²⁷ Other reagents have been used with varying

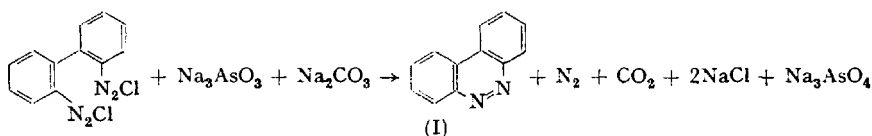


results. For instance, by heating tetrazotized 2,2'-diamino-4,4'-dimethoxybiphenyl in copper sulfate solution, the main product is 3,7-

dimethoxydibenzofuran with 3,8-dimethoxy-5,6-diazaphenanthrene (V) as a by-product.¹²⁸ The use of sodium arsenite in sodium carbonate

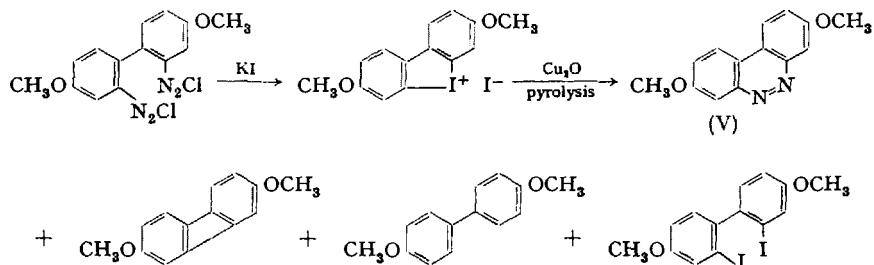


solution has been reported to give a 45 % yield of 5,6-diazaphenanthrene by the following reaction:¹²⁹

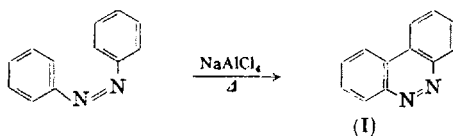


The 3,8-dimethyl derivative of I was made likewise, but in unreported yield.¹²⁹ The mechanism of this type of reaction has been the subject of some discussion.¹³⁰⁻¹³²

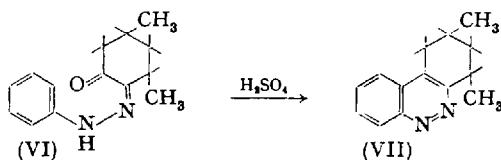
Another reaction starting with 2,2'-diamino-4,4'-dimethoxybiphenyl gave an unreported but evidently small yield of 3,8-dimethoxy-5,6-diazaphenanthrene (V). This reaction involved the use of potassium iodide, giving first an iodonium iodide, which then was pyrolyzed with cuprous oxide.¹³³



(d) From Azobenzene. A rather interesting synthesis of 5,6-diazaphenanthrene involves the action of sodium aluminum chloride on azobenzene at 120° .¹³⁴ 5,6-Diazaphenanthrene itself was made in 60 % yield. The corresponding 3,8-dimethyl (yield 25 %) and 3,8-bis(dimethylamino) (yield 40 %) derivatives were prepared likewise, but at 100° .



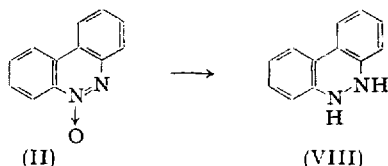
(e) From Phenylhydrazones of *o*-Quinones. In an elaboration of a synthesis of 1-ketotetrahydrocarbazole,¹³⁵ Moore¹³⁶ found a way to an interesting synthesis of benzocinnoline derivatives. 3,5-Dimethyl-1,2-cyclohexanedione-2-phenylhydrazone (VI) is cyclized by dissolving in concentrated sulfuric acid, giving 2,4-dimethyl-1,2,3,4-tetrahydro-5,6-diazaphenanthrene (VII) in 85% yield. In a similar way 1,2,3,4-



tetrahydro-5,6-diazaphenanthrene was prepared, but in only 15% yield, from the monophenylhydrazone of cyclohexanedione.

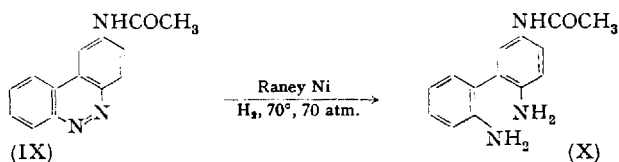
(3) Reactions

(a) Reduction. Reduction of the oxides of 5,6-diazaphenanthrene to the base has been described on p. 372. Reduction by zinc dust^{114, 116, 137} or by Raney nickel¹²⁵ at 40° gives 5,6-dihydro-5,6-diazaphenanthrene (VIII).



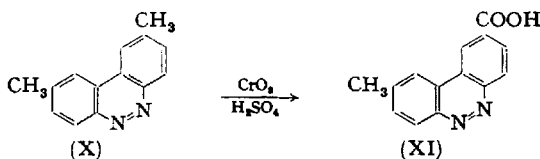
The 5,6-dihydro derivative (VIII) is produced in high yield by treatment of the dilithium adduct of 5,6-diazaphenanthrene with benzoic acid or with the theoretical amount of hydrogen chloride in ether.¹⁵² Wittig and Stichnoth found that VIII is readily autoxidizable in acid solution, regenerating 5,6-diazaphenanthrene.¹¹⁵

Under more vigorous conditions further reduction may occur. For example, 2-acetamido-5,6-diazaphenanthrene (IX) is reduced with Raney nickel and hydrogen at 70° to 5-acetamido-2,2'-diaminobiphenyl

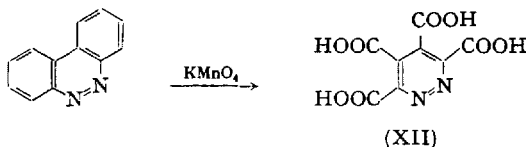


(X).¹²⁵ In certain reactions involving the 5,6-dilithium adduct, reduction to 2,2'-diaminobiphenyl may occur.¹⁵²

(b) Oxidation. The 5,6-diazaphenanthrene ring structure is fairly stable to oxidizing agents.¹⁴⁷ Tauber¹¹⁶ found no reaction with chromic acid in dilute sulfuric acid, but 2,9-dimethyl-5,6-diazaphenanthrene is oxidized by chromic acid-sulfuric acid to 2-carboxy-9-methyl-5,6-diazaphenanthrene (XI). Oxidation of 3,8-bis(trifluoromethyl)-5,6-

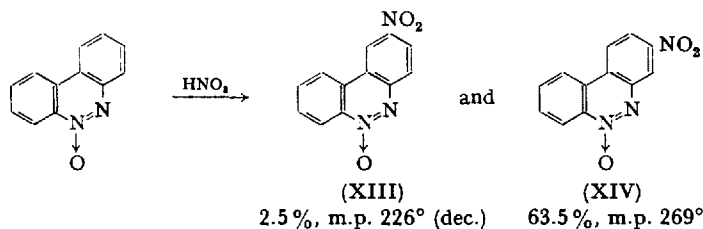


diazaphenanthrene with peracetic acid gives the *N*⁵-oxide in almost quantitative yield.¹⁵⁰ However, potassium permanganate in dilute alkaline solution reacts with 5,6-diazaphenanthrene to give pyridazine-3,4,5,6-tetracarboxylic acid (XII).¹³⁸

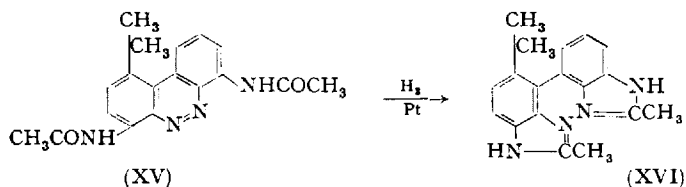


(c) Nitration. The mononitration of 5,6-diazaphenanthrene itself has not been reported, but that of the 6-oxide has. (Designated as the 6-oxide to permit the location of the nitro group in the 1,2,3,4-ring. The properties of azoxy compounds in general are discussed by

Bigelow.¹³⁹) King and King¹²⁵ reported a 63.5% yield of one nitro derivative (m.p. 269°) together with a 2.5% yield of an isomer (m.p. 226° dec.). On the basis of conversion by reduction to triamino-biphenyls and cyclization to known aminocarbazoles, they assigned the structure 2-nitro-5,6-diazaphenanthrene-6-oxide (XIII) to the material obtained in the higher yield, and 3-nitro-5,6-diazaphenanthrene-6-oxide (XIV) to the material obtained in 2.5% yield. The comparison of their materials with authentic samples was not rigid, however, and recently Calderbank and Le Fèvre¹⁴⁹ determined from the dipole moments of a number of 5,6-diazaphenanthrene-6-oxides that the major product is the 3-nitro derivative. King and King conceded that their own conclusions regarding the orientation could not be maintained on the basis of chemical evidence. While the other isomer was not examined by Calderbank and Le Fèvre, it is most likely 2-nitro-5,6-diazaphenanthrene-6-oxide.



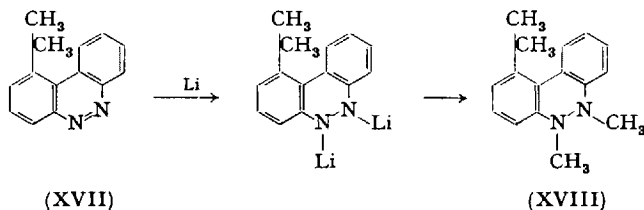
Theilacker and Baxmann¹⁵⁶ recently dinitrated 1,10-dimethyl-5,6-diazaphenanthrene and showed that one of the products was 1,10-dimethyl-4,7-dinitro-5,6-diazaphenanthrene. The structure was proved by reduction of the corresponding diacetamido compound to 2,2',5,5'-tetramethyl-4,4'-bisbenzimidazolyl (XVI).



(d) Sulfonation. There has been no report of the sulfonation of 5,6-diazaphenanthrene, although the 3-monosulfonate and the 3,8-

disulfonate reportedly have been used.¹⁴⁰ It is highly probable that these sulfonic acids were prepared by ring closure reactions involving the appropriately substituted 2,2'-dinitrobiphenyl derivatives.

(e) Metalation. In an investigation of the possibility of optical activity of the biphenyl type, Wittig and Stichnoth reacted 1,10-dimethyl-5,6-diazaphenanthrene (XVII) with lithium and converted the adduct to 1,5,6,10-tetramethyl-5,6-dihydro-5,6-diazaphenanthrene (XVIII) by reaction with methyl sulfate.¹¹⁵ The structure of XVIII was proved by reduction with zinc and hydrochloric acid to 2,2'-dimethyl-6,6'-bis-(methylamino)biphenyl. Salts of XVIII, like VIII, showed a ready tendency to oxidize, and no optical activity was observed (see below).



(4) Properties

5,6-Diazaphenanthrene has been reported to form yellow needles from dilute alcohol or prisms from absolute alcohol or benzene. The crystalline structure has been described as monoclinic prisms.¹⁴¹ The melting point is 157°, ¹³⁴ and the material boils without decomposition above 360°. ¹¹⁶ It is soluble in acetic acid, chloroform, ether, alcohol, and benzene, with difficulty in ligroin, and with very great difficulty in water. Its solutions in acids are an intense sulfur yellow. ¹¹⁸ Two oxides have been described; the monoxide melts at 139° (152°) ^{114, 116, 125} and the dioxide at 240° (241-3°). ^{116, 120} Doubt concerning the cyclic nature of the latter has been expressed. ¹⁵⁰

5,6-Diazaphenanthrene is monobasic toward mineral acids and quaternizes readily with methyl sulfate, methyl and ethyl iodides, ¹¹³ chloroplatinic acid, ¹⁴⁷ etc. The picrate melts at 194°. ^{129, 147} The base-strengthening effect of an amino group in the 2-position has been studied. ¹⁴² The α -bromocamphor- π -sulfonate is a nicely crystalline salt

but there was no indication of diastereoisomers on fractionation.¹¹⁵

Thielacker and Baxmann¹⁵⁶ reasoned that the failure to resolve optical isomers of 1,10-dimethyl-5,6-diazaphenanthrene¹¹⁵ was due to the inability of the compound to form a stable salt. They found, however, that 4,7-diamino-1,10-dimethyl-5,6-diazaphenanthrene could be resolved as the bromocamphorsulfonate into two antipodes. This proved the contention of Wittig and Stichnoth that the deformation that must exist in 1,10-dimethyl derivatives of 5,6-diazaphenanthrenes would give rise to optical isomers.

A study of the absorption spectra of 5,6-diazaphenanthrene and related compounds indicates that a considerable deformation of the valency angles of azobenzene must occur in the cyclization to 5,6-diazaphenanthrene, since a strong shift toward the ultraviolet is observed.^{143, 155} On the other hand, comparison of the absorption curves of azoxybenzene, 5,6-diazaphenanthrene-*N*-oxide, and *N,N'*-dioxide shows that cyclization does not involve a strong shift toward the red end of the spectrum. (See reference 150, however, and p. 372 for recent conclusions regarding the structure of the "dioxide".) From the analogy of the variation of absorption between diphenylamine and carbazole (*i.e.*, shift toward the visible wave lengths, change in the form of the curve, and increase in the intensity of absorption), the structures of the oxide and dioxide of 5,6-diazaphenanthrene must be *N*- and *N,N'*-dioxide.¹⁴³ (See note in parentheses above.) Molecular diagrams have been presented to show the relative charges on each atom,¹⁴⁴ and the dipole moments of 5,6-diazaphenanthrene and its oxide have been used to furnish additional proof that azo- and azoxybenzenes of m.p. 71° and 84°, respectively, are *cis* isomers.¹⁴⁵

(5) Uses

Uses claimed for derivatives of 5,6-diazaphenanthrene include possible medicinal^{125, 140} and dye applications.^{114, 123, 140, 146} 3,8-Diamino-5,6-diazaphenanthrene dyes cotton a green-grey¹¹⁴ and, when tetrazotized and coupled with naphthionic acid, a red dye is obtained.¹⁴⁶ Condensation of the 3,8-dicarbonyl chloride with two moles of aminoanthraquinone gives yellow to orange dyes.¹³³

TABLE V-12. 5,6-Diazaphenanthrenes. Alkyl, Hydrogenated, Halogen, Nitro, and Sulfo Derivatives

Formula	Compound	M.p., °C.	Refs.
X	2,9-Dimethyl-	187 (b > 360)	117
		?N ⁶ → O N ⁶ → O 128	117
	3,8-Dimethyl-	188	114, 129, 134
		N ⁶ → O 209	114
		CH ₃ Cl. $\frac{1}{2}$ ZnCl ₂ 231	114
XVII	1,10-Dimethyl-	113-4 (96-7) (135-6)	114, 118, 149
		N ⁶ → O 153	124, 125, 149
VIII	5,6-Dihydro-		115, 116, 137, 162
	1,10-Dimethyl-5,6-dihydro- ^a	$\frac{1}{2}$ H ₂ SO ₄ 134	115
XVIII	1,5,6,10-Tetramethyl-5,6-dihydro- ^b	84-5	115
	1,2,3,4-Tetrahydro-	98	136
VII	2,4-Dimethyl-1,2,3,4-tetrahydro-	111	136
	3-Bromo-	N ⁶ → O 194.5	151
	3,8-Dichloro-	259-60	149
		N ⁶ → O 244-5	149
	3,8-Difluoro-2,9-dimethyl-	228	119
Ia	3,8-Bis(trifluoromethyl)-	192.5-193	150
IIa		N ⁶ → O 210.5-212	150
XIII	2-Nitro-	N ⁶ → O 226	125, 149
XIV	3-Nitro-	N ⁶ → O 269	125, 149
	4,7-Dinitro-1,10-dimethyl-	254	156
	α,α -Dinitro-3,8-dichloro-	N → O 294-5	149
	3-Sulfo-		140
	3,8-Disulfo-		140

^a Autoxidizable to 1,10-dimethyl-5,6-diazaphenanthrene.^b Ferric chloride gives a blue color, changing through green to yellow, and finally 1,10-dimethyl-5,6-diazaphenanthrene results.

TABLE V-13. 5,6-Diazaphenanthrenes. Amino Derivatives

Compound	M.p., °C.	Refs.
2-Amino- ^a	243 (dec.)	125
3-Amino- ^b	$\frac{1}{2}$ H ₂ O 194-5 (dec.)	125
3,8-Diamino- ^c	267	114, 116
3,8-Diamino-1,10-dimethyl-		156
·bromo(+)camphorsulfonic acid	192-3	156

(Table continued)

TABLE V-13 (*continued*)

Compound (and formula)	M.p., °C.	Refs.
3,8-Diamino-2,9-dimethyl-	276	117
4,7-Diamino-1,10-dimethyl-	178-9	156
3,8-Bis(dimethylamino)-	276, 285	114, 134
	HCl 236	114
	N ^s → O ^d 242	114
3,8-Bis(diethylamino)-	184	114
2-(2-Diethylaminoethylamino)-	2HCl 224-5	125
	2P 178-9 (dec.)	125
2-(3-Diethylaminopropylamino)-	2HCl 222	125
3,8-Bis(furfurylideneamino)-	207	146
3,8-Bis(benzylideneamino)-	210	146
3,8-Bis(benzylideneamino)-2,9-dimethyl-	239 (dec.)	117
2-Acetamido- ^e (IX)	233	125
3-Acetamido-	$\frac{1}{2}$ H ₂ O 171-2	125
4,7-Diacetamido-1,10-dimethyl- (XV)	221	156
4,7-Dibenzamido-1,10-dimethyl-	269	156
2- <i>p</i> -Tolylsulfonamido-	230 (dec.)	125
2-[N-(2-Diethylaminoethyl)- <i>p</i> -tolylsulfon- amido]-	122-3	125
2-[N-(3-Diethylaminopropyl)- <i>p</i> -tolylsulfon- amido]-	108-9	125
5-Acetyl-4,7-diacetamido-1,9-dimethyl-5,6- dihydro-	275	156

^a Intense green fluorescence in alcohol and ether; see also reference 142.

^b Weaker fluorescence than 2-amino.

^c Dyes cotton "green grey"; red dye by diazotization and coupling with naphthionic acid.¹⁴⁶

^d Carmine-red needles.

^e Solutions do not fluoresce.

TABLE V-14. 5,6-Diazaphenanthrenes. Miscellaneous Derivatives

Compound (and formula)	M.p., °C.	Refs.
3-Hydroxy-	275	140
3,8-Dihydroxy-	300	140
3,8-Diacetoxy-	239	140
3,8-Dimethoxy- (V)	202-3	128, 133
	P 231-3	133
2,9-Dimethoxy-3,8-diamino-	244	114

(Table continued)

TABLE V-14 (*continued*)

Compound (and formula)	M.p., °C.	Refs.
8-Hydroxy-3-sulfo-		140
2-Carboxy-9-methyl-(XI)	290	117
2,9-Dicarbomethoxy-	224-5	148
3,8-Bis(chlorocarbonyl)- ^a	208	123
5-Benzoyl-5,6-dihydro-	131.5-132.5	152
5-Cinnamoyl-5,6-dihydro-	163-4	152
5,6-Dibenzoyl-5,6-dihydro-	157.5-158.5	152

^a Condenses with two moles of aminoanthraquinone to give yellow to orange dyes.

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1. Borsche and Sinn, *Ann.*, 555, 70 (1943).
2. Russwurm, *Ann.*, 308, 156 (1899).
3. Schofield and Swain, *J. Chem. Soc.*, 1949, 2399.
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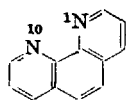
CHAPTER VI

1,10-, 1,7-, and 4,7-Diazaphenanthrenes

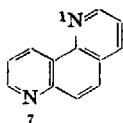
BY BRUCE GRAHAM

Introduction

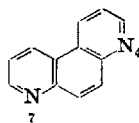
These three diazaphenanthrenes are grouped in one section because they are generally called the *phenanthrolines*. (The name phenanthroline occasionally has been applied to other diazaphenanthrenes,¹² *R.I.* 1953. However, the name generally refers to the three isomers described below.) They are the isomers that can be derived from the phenylenediamines. Therefore, 1,10-diazaphenanthrene is commonly known as *ortho*-phenanthroline, the 1,7-isomer as *meta*-phenanthroline, etc.



1,10-diazaphenanthrene
(*ortho*-phenanthroline
from *o*-phenylenediamine)



1,7-diazaphenanthrene
(*meta*-phenanthroline
from *m*-phenylenediamine)



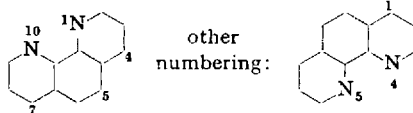
4,7-diazaphenanthrene
(*para*-phenanthroline
from *p*-phenylenediamine)

Skraup and Vortmann¹ prepared the first member (1,7-) of the series in 1883, and named it phenanthroline because they proved that it corresponds to the angular structure of phenanthrene rather than to the linear structure of anthracene (see Section B1).

The novel *ortho*, *meta*, and *para* nomenclature for the phenanthrolines, suggested by Kaufmann and Radosevic² in 1909, has proved so useful that it has been adopted generally. However, since the numbering of phenanthrolines is very confused, this system is inadequate. Even though the structure of the ring is obvious from the name *ortho*-phenanthroline, the positions of the substituents are not fixed unless the numbering system is stipulated (*i.e.*, 1,10- or 4,5- for *ortho*-

phenanthroline). Therefore, in this chapter, the *ortho*-, *meta*-, and *para*-phenanthroline nomenclature will be used only occasionally to designate the parent ring systems. Specific compounds will be named by the diaza system.

- A. 1,10-Diazaphenanthrene or *ortho*-Phenanthroline. 1,10-Phenanthroline. 4,5-Phenanthroline. α -Phenanthroline. α -Phenanthroline. α -Phenanthroline. 7,8:3',2'-Pyridoquinoline. Dipyridino-3',2':1,2;2'',3'':3,4-benzene.**
R.I. 1954



(1) History and Nomenclature

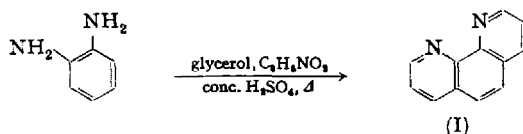
The first *o*-phenanthroline (2-methyl-1,10-diazaphenanthrene) was prepared by Gerdeissen³ in 1889. Blau⁴ synthesized the parent compound nine years later. He called it α -phenanthroline, and recorded the fact that it formed complexes with metal salts. However, it was not until thirty-three years later that Walden, Hammett, and Chapman⁵ made use of this coordination phenomenon in analytical chemistry (see Section Aba). The 1,10-numbering has been used for *o*-phenanthrolines by *Chemical Abstracts* since the compounds first appeared there in 1930. This system has been adopted in some foreign journals such as *Helvetica Chimica Acta*, but the British and German journals use the 4,5-designation. Beilstein (XXIII-227) employs the old 4,5-numbering as well as the 1,10-. Since *o*-phenanthroline is a symmetrical molecule, the translation from one numbering system to the other is a simple process.

The base is a white solid melting at 117° in the anhydrous form. The monohydrate melts at: 99–100°,⁷ 91–5°,⁶ 102°,⁴ and 103°.⁹ 1,10-Diazaphenanthrene distills undecomposed above 300°. It is soluble in most organic solvents.

(2) Preparation (Ring Closures)

(a) Skraup-Type Reactions. (1) *Glycerol on o-Phenylenediamines.* Blau⁴ originally synthesized *o*-phenanthroline (I) in a 30% yield by a double Skraup reaction on *o*-phenylenediamine.

The feasibility of the reaction has ever since been a controversial subject. C. R. Smith⁶ in 1930 stated that *o*-phenanthroline could not be prepared by this method; however, he made no reference to Blau's



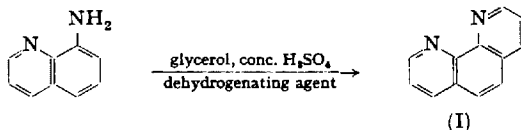
synthesis in 1898⁴ or to that of Hieber and Mühlbauer in 1928.⁸ Apparently he was unaware that *o*-phenanthroline had been reported in the literature thirty-two years previously. G. F. Smith⁷ in 1944 referred to the method as being of no preparative value, but later acknowledged that there was no longer any necessity to avoid it.¹⁰³ However, other workers report yields of 18%,⁸ 20%,⁹ and 45% crude.¹⁰ A recent patent¹¹ reviews the literature pertaining to the synthesis, and claims an improved procedure whereby a yield of 30% is obtained. The cyclization is run in the presence of copper salts, using *m*-nitrobenzenesulfonic acid as a dehydrogenating agent. The product is isolated from the reaction mixture as a copper salt, from which it is freed by means of hydrogen sulfide. It is interesting that addition of the copper salts after the cyclization is not as effective as addition before the Skraup reaction. The reduction products of the *m*-nitrobenzenesulfonic acid are more easily separated from the *o*-phenanthroline than are those of nitrobenzene.

Misani and Bogert¹² report that syntheses of substituted 1,10-diazaphenanthrenes from *o*-phenylenediamines are unsatisfactory. Specifically, they failed to prepare 5,6-dimethoxy-1,10-diazaphenanthrene from 4,5-diaminoveratrole. A double Skraup reaction on 5-bromo-*o*-phenylenediamine,¹³ which was reported to be successful, later was proved to have yielded an unknown product (see Section A2a2 following).

The two-step Skraup synthesis is much more useful.

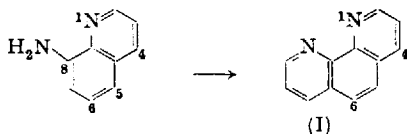
(2) *Glycerol on 8-Aminoquinolines.* 2-Methyl-1,10-diazaphenanthrene, the first *o*-phenanthroline, was synthesized by this method.³ The unsubstituted 1,10-diazaphenanthrene (I) has been synthesized in

this way by many different investigators, employing varied reagents and conditions.^{4,6,7,11,14,15} Yields above 50% are possible, with the



best yield (60–5% of the hydrate) again being obtained by cyclization in the presence of copper salts.^{11,16} Generally, *o*-phenanthroline is isolated by extraction from the reaction mixture with solvents such as chloroform or benzene. After removal of the solvent the residue is purified by distillation *in vacuo* and/or crystallization from water, water-ethanol, moist benzene, etc.

1,10-Diazaphenanthrenes substituted in positions 1 to 6 can be prepared by the Skraup synthesis from the corresponding 8-aminoquinolines.^{3,7,10,17–23} The relationship between positions in the quinoline used and in the product therefrom is:

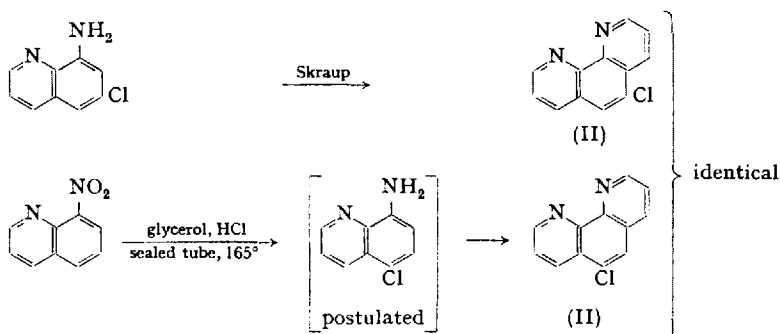


It is convenient that identical positions have the same numbering in both ring systems.

The following substituted 1,10-diazaphenanthrenes have been synthesized from the corresponding 8-aminoquinolines: 2-methyl-^{3,22} 4-methyl-¹⁸ 5-methyl-^{7,17} 3,4-dimethyl-²⁰ 3,6-dimethyl-¹⁹ 4,5-dimethyl-¹⁹ 4,6-dimethyl-¹⁹ 5,6-dimethyl-¹⁸ 3,4,8-trimethyl-²⁰ 5-chloro-^{7,17,21} 5-bromo-^{7,10,17} 5-nitro-¹⁰ and 2-hydroxy-4-methyl-²³ General procedures for the application of the Skraup reaction to the particular syntheses of substituted 1,10-diazaphenanthrenes have been carefully developed.^{7,17,18}

Since the 5- and 6-positions of otherwise unsubstituted 1,10-diazaphenanthrenes are equivalent, the same product is obtained by the Skraup reaction on 5- or 6-substituted 8-aminoquinolines. Richter and Smith offer a sensible proof for the equivalence of the 5- and 6-positions.¹⁴ They synthesized 5-chloro-1,10-diazaphenanthrene by a Skraup

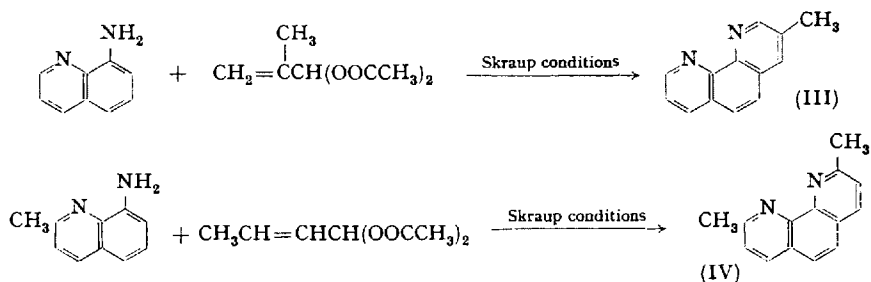
reaction on 8-amino-6-chloroquinoline. It was identical with the product obtained²⁴ by heating a mixture of 8-nitroquinoline, glycerol, and hydrochloric acid, in which they postulate 8-amino-5-chloroquinoline as an intermediate.



An absolute proof could easily be made by Skraup reactions on 8-amino-5-chloroquinoline and on 8-amino-6-chloroquinoline. The 5-bromo compound has been made from 8-amino-5-bromoquinoline¹⁰ and from 8-amino-6-bromoquinoline,^{7,17} but unfortunately the products differed in melting point due to varying degrees of hydration (see Table VI-1). A third source¹³ has reported the compound, but was proved to be in error (see Section A3f).

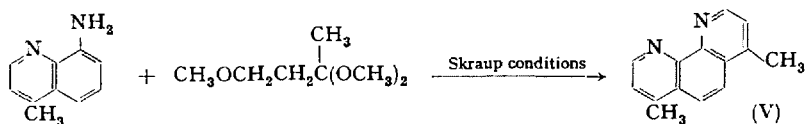
The attempted synthesis of 5-methoxy-1,10-diazaphenanthrene from 8-amino-6-methoxyquinoline was unsatisfactory even though the authors¹² tried several variations in the reaction conditions.

(3) *From α,β -Unsaturated Aldehyde Diacetates.* In a study concerning the oxidation potentials of the ferrous complexes of substituted 1,10-diazaphenanthrenes, Case¹⁸⁻²⁰ prepared many methyl and polymethyl derivatives by treatment of various 8-aminoquinolines with α,β -unsaturated aldehyde diacetates under Skraup conditions:

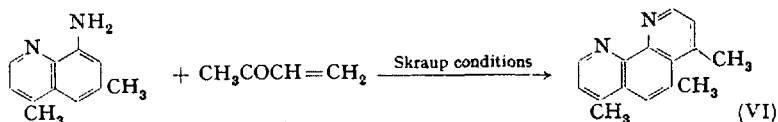


These two syntheses serve as methods for introducing methyl groups into the β - and α -positions of the rings so formed.

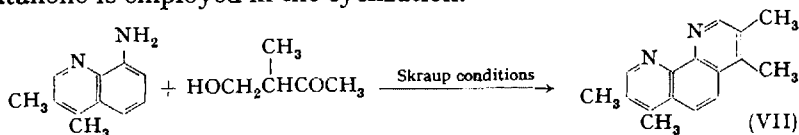
(4) *From Ketals*. Case¹⁸ used 1,3,3-trimethoxybutane in order to procure a phenanthroline with a methyl group in the γ -position of the ring formed in the synthesis.



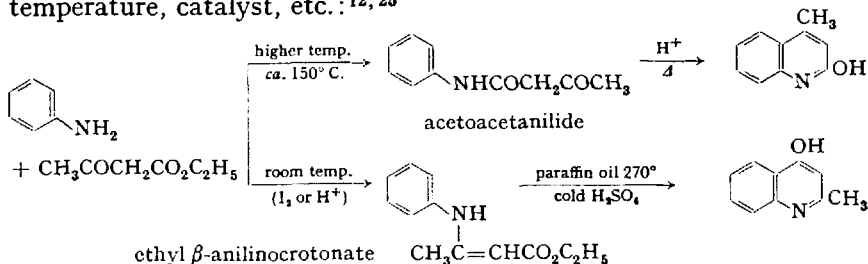
(5) *From α,β -Unsaturated Ketones*. Later Case^{19,20} was able to accomplish the formation of 1,10-diazaphenanthrenes with a methyl group in the γ -position by means of the commercially available methyl vinyl ketone.



(6) *From Oxo Alcohols*. Two methyl groups (β and γ) can be introduced during the formation of the ring¹⁹ if 4-hydroxy-3-methyl-2-butanone is employed in the cyclization.



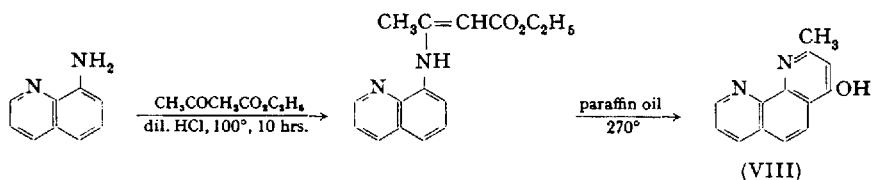
(b) **Conrad-Limpach and Knorr Reactions.** Primary aromatic amines can react with acetoacetic esters in two ways, depending upon temperature, catalyst, etc.:^{12, 25}



Misani and Bogert¹² combine these reactions under the name Conrad, Limpach, and Knorr (CLK), while Morton²⁵ calls the first reaction Knorr's quinoline synthesis. The latter reaction is generally known as the Conrad-Limpach synthesis.

When applied to the synthesis of phenanthrolines, the first reaction is generally unsuccessful¹² (however see Section C2c), while the second reaction (Conrad-Limpach) is quite useful except when applied to *o*-phenylenediamine. Only one amino group of this base reacts¹² with ethyl acetoacetate, producing both the acetoacetanilide and ethyl β -anilinocrotonate. The former cyclizes to form 2-hydroxybenzimidazole while the latter forms 2-methylbenzimidazole.

Hazelwood, Hughes, and Lions²⁶ failed in an attempt to cyclize 8-acetoacetamidoquinoline with sulfuric acid; however, they obtained 4-hydroxy-2-methyl-1,10-diazaphenanthrene (VIII) according to the following equation (see reference 43):



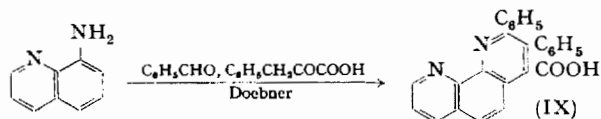
Misani and Bogert¹² produced the 5-methoxy derivative of VIII by a similar reaction on 8-amino-6-methoxyquinoline. They raised the yield from 20 to 30% by substituting boiling diphenyl ether for the hot paraffin oil. An attempted cyclization of 8-acetoacetamido-6-methoxyquinoline with cold sulfuric acid or with hot paraffin oil failed to yield the desired product.¹²

Burger, Bass, and Frederickson²³ attempted to cyclize 8-acetoacetamido-5-nitroquinoline to form 2-hydroxy-4-methyl-6-nitro-1,10-diazaphenanthrene under a variety of conditions, *i.e.*, heating in sulfuric acid at 60° and 100°, in paraffin oil at 220°, in paraffin oil plus phosphorus pentoxide at 220°, in syrupy phosphoric acid, or in boiling xylene containing either phosphorus pentoxide or pentachloride. All the attempts gave negative results. The cyclization also failed on 8-amino-6-methoxy-5-nitroquinoline.¹² Such cyclizations involving a ring substituted with a nitro group are known to be difficult.

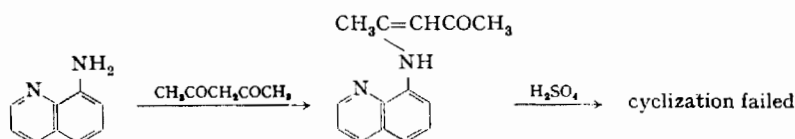
(c) Doebner's Pyruvic Acid Synthesis (From α -Oxo Acids).

This famous quinoline synthesis has been used only once in this field,

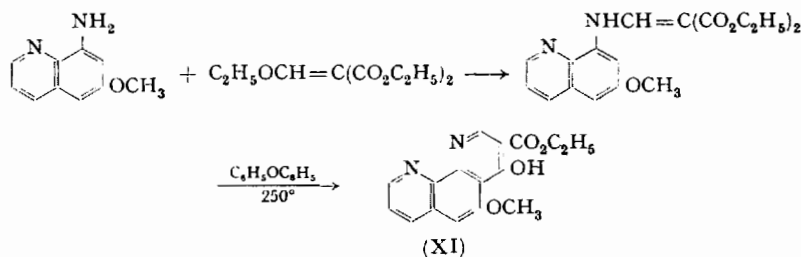
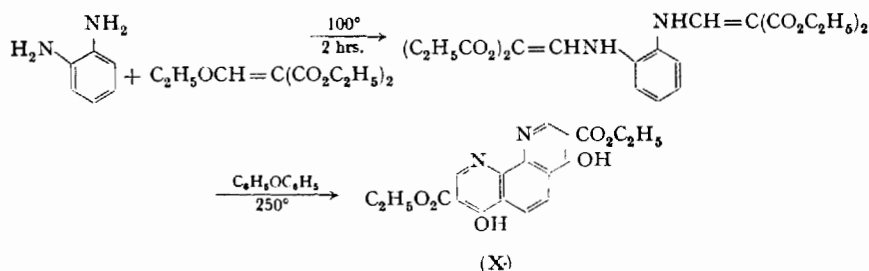
i.e., in the preparation of 4-carboxy-2,3-diphenyl-1,10-diazaphenanthrene (IX).²⁷



(d) From β -Diketones. The only attempt to prepare a 1,10-diazaphenanthrene from a β -diketone failed.²⁶

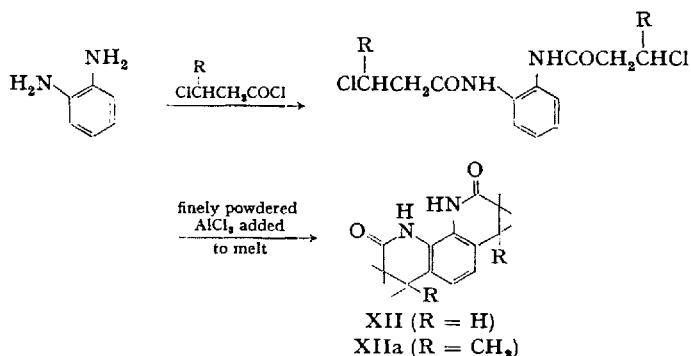


(e) From Ethoxymethylenemalonic Ester. This reactant produces 1,10-diazaphenanthrenes that bear a carbethoxy group beta to the nitrogen and a hydroxyl group gamma to the nitrogen. The reaction (Price-Roberts) affords excellent yields with *o*-phenylenediamine and with 8-aminoquinolines:²⁸

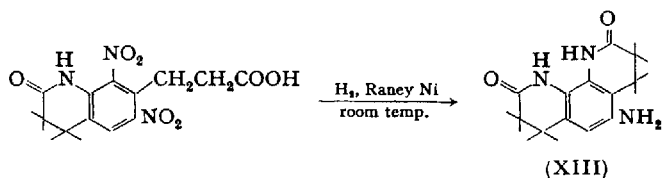


(f) From β -Chloroacid Chlorides. These reactants with *o*-phenylenediamine yield 2,9-dioxo-1,2,3,4,7,8,9,10-octahydro-1,10-diazaphen-

anthrenes (XII) corresponding to the dihydro-2-carbostyrils.²⁹ This synthesis can be used with facility to form α -oxohydrophenanthrolines having various groups in the 3,4- and/or 7,8-positions.



(g) Other Methods. A method that produces compounds similar to those above, but by the opposite approach, is described by Ruggli and Preiswerk³⁰ for the synthesis of 5-amino-2,9-dioxo-1,2,3,4,7,8,9,10-octahydro-1,10-diazaphenanthrene (XIII).



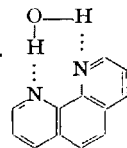
(3) Reactions of 1,10-Diazaphenanthrene

(a) Salt Formation. 1,10-Diazaphenanthrene is a monoacid base. Lee, Kolthoff, and Leussing³¹ have found the dissociation constant of the phenanthroline ion to be 1.1×10^{-5} at 25°; therefore, the ionization constant of the base, phenanthroline, is about 9×10^{-10} at 25°. They explain the fact that the compound is not dibasic by the proximity (2.5 Å) of the two nitrogens. Steric and/or electrostatic effects could prevent the addition of a second proton. Allen³² offers an explanation for the similar behavior of 1,8-naphthyridine based on electrostatic effects.

Smith and Richter⁷ state that the basicity of the nitrogen atoms is greatly affected by substitution in the 5- and 6-positions. As might be

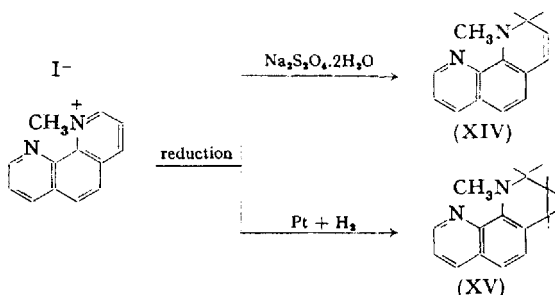
expected, electron-releasing groups, such as methyl groups, increase the electron density and therefore the basicity at the nitrogen atoms, while electron-attracting groups, such as halogens and nitro groups, lower the basicity. 5-Bromo-6-nitro-1,10-diazaphenanthrene is insoluble in strong acids.

(b) Hydration. 1,10-Diazaphenanthrene and many of its derivatives form stable monohydrates. These hydrates lose water when heated, but the reaction is reversible. The decomposition pressures of the base hydrate and of its 5-methyl- and its 5-bromo- derivatives have been determined at various temperatures. From these data it has been possible to calculate the strength of the hydrogen bonds in the hydrate.³³ Infrared data⁷ indicate that the water is attached to the base by means of two hydrogen bonds to the nitrogens. The bond energy of the hydrogen bond in 1,10-diazaphenanthrene monohydrate was found to be 7.15 cal./g. mole.³³

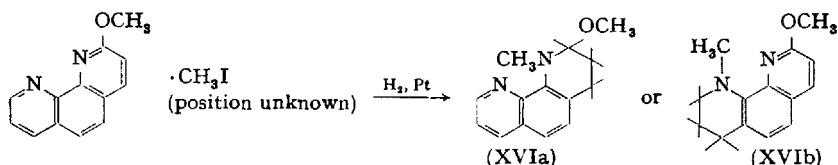


The hydrates are quite stable, exhibiting sharp melting points (see Table VI-1). 5,6-Dimethyl-1,10-diazaphenanthrene does not seem to form a hydrate. Fritz *et al.*³³ correlated this with the relatively high melting point of the compound (272°) compared with that of the 5-methyl- derivative (114°) and that of 1,10-diazaphenanthrene itself (117°). Anyone interested in the correlation of constitution and physical properties should take cognizance of the great variations in the melting points of the polymethyl-1,10-diazaphenanthrenes prepared by Case.¹⁸⁻²⁰ These are listed in Table VI-1. For instance, the melting point of the 3,6-dimethyl- isomer is 117-8°, while that of the 5,6-dimethyl- compound is 272°. In general, the symmetrical compounds melt at much higher temperatures than the unsymmetrical compounds; however, the very unsymmetrical 3,4-isomer also has a high melting point (234-5°) as compared to the average melting point (176°) of the dimethyl compounds.

(c) Reduction. Reduction of the unsubstituted 1,10-diazaphenanthrene has not been reported; however, Karrer, Pletscher, and Manz³⁴ investigated the reduction of the methiodide. Sodium hydrosulfite below 0°C. gives a very poor yield of 1-methyl-1,2-dihydro-1,10-diazaphenanthrene (XIV), while 1-methyl-1,2,3,4-tetrahydro-1,10-diazaphenanthrene (XV) is produced by catalytic reduction over platinum.



Reduction of 2-methoxy-1,10-diazaphenanthrene methiodide³⁵ over platinum produced a 2-methoxy-*N*-methyltetrahydro-1,10-diazaphenanthrene of structure XVIa or XVIb.

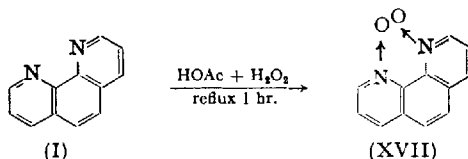


A possible explanation for the selective reduction of the heterocycle containing the quaternary nitrogen is based on the presence of the open positive charge. The resulting electron impoverishment of that ring produces decreased aromaticity and, therefore, increased susceptibility to addition reactions. Structure XVIb seems more feasible than XVIa since the 10-nitrogen of 2-methoxy-1,10-diazaphenanthrene is probably more basic than the 1-nitrogen, which is adjacent to the electron-attracting and bulky methoxyl group.

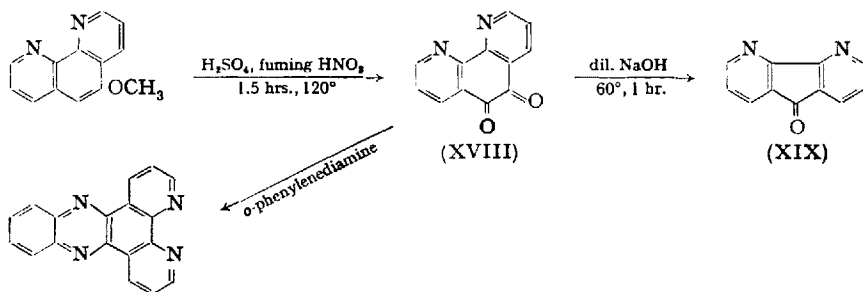
(d) Oxidation. Compared to phenanthrene, 1,10-diazaphenanthrene is surprisingly resistant to oxidation. However, Smith⁶ oxidized the base with alkaline permanganate to 2,2'-bipyridine-3,3'-dicar-

boxylic acid, which he decarboxylated by heat to give 2,2'-bipyridine. This oxidation was used as a structure proof. (For a detailed description of the reaction, see page 20 of reference 7.)

Linsker and Evans,³⁶ by boiling the base in 100 volumes of a solution of glacial acetic acid and hydrogen peroxide (2:1), were able to prepare the di-*N*-oxide (1,10-diazaphenanthrene-1,10-dioxide, XVII). This reaction is general for the phenanthrolines, and is preferred to the older perbenzoic acid method.³⁶

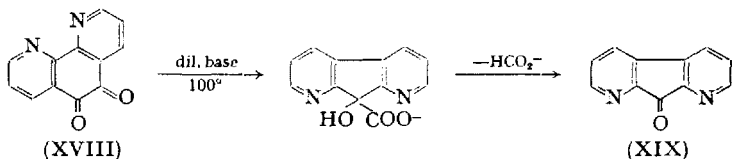


Smith and Cagle³⁷ obtained 5,6-dioxo-1,10-diazaphenanthrene (XVIII) (1,10-phenanthroline-5,6-quinone) as a by-product (1%) in the nitration of the base (see Section A3e). Druey and Schmidt²¹ prepared XVIII in a good yield by a similar reaction on the 5-methoxy-1,10-diazaphenanthrene, and proved its structure by converting it to 4,5,9,14-tetraza-(1,2,3,4)-dibenzanthracene.



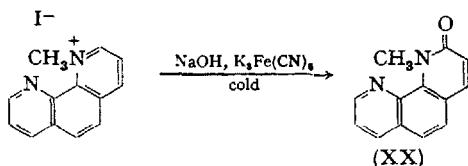
At about the same time Inglett and Smith³⁸ in the United States and Druey and Schmidt²¹ in Switzerland discovered that XVIII forms 9-oxo-4,5-diazafluorene (XIX), upon treatment with dilute alkali. Inglett and Smith suggested that the reaction mechanism involved a loss of carbon monoxide. Druey and Schmidt soon published their more comprehensive study involving other phenanthrolines (see Sections B3h1 and C3f), and compared the reaction to the similar behavior of phenanthrene-5,6-quinone (benzilic acid rearrangement).

Gore and Hughes³⁹ also suggested the well-known benzilic acid rearrangement as the probable mechanism, and pointed out the improba-



bility of direct loss of carbon monoxide from such a molecule at 100°.

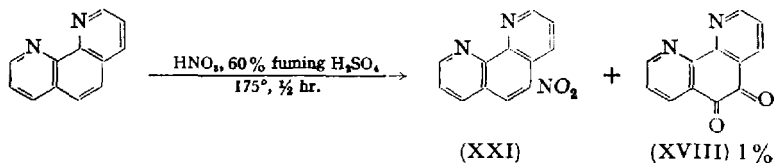
An oxidation involving the 2-position has been used by Halcrow and Kermack,¹⁰ and by Karrer and Pletscher.³⁵ 2-Oxo-1-methyl-1,10-



diazaphenanthrene (XX) is a useful intermediate for the preparation of 2-substituted 1,10-diazaphenanthrenes (see Section A4).

Richter and Smith¹⁷ attempted to prepare 5-carboxy-1,10-diazaphenanthrene by oxidation of the 5-methyl homolog. This failed, however, even under mild conditions, presumably because of cleavage of the 5,6-double bond. The presence of the electron-releasing methyl group at the 5-position no doubt promotes the oxidation of the 5,6-double bond.

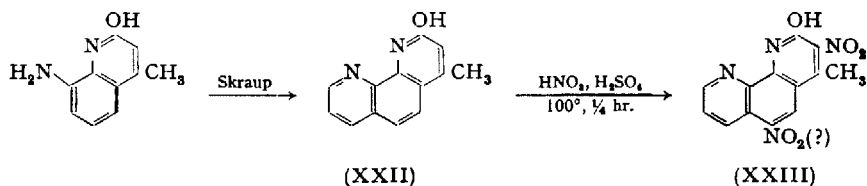
(e) Nitration. Hammet, Walden, and Edmonds⁴⁰ obtained a mononitro-1,10-diazaphenanthrene of unknown structure in 1934, and published claims for its advantages in oxidimetry. This later was shown to be 5-nitro-1,10-diazaphenanthrene (XXI).¹⁰ This nitration of 1,10-diazaphenanthrene has been investigated extensively by Smith and co-workers,^{7, 37} who developed and improved the synthesis until a yield of 90% was obtained in the preparation of XXI.



Halcrow and Kermack¹⁰ nitrated 1,10-diazaphenanthrene under slightly different conditions and obtained XXI. They proved its structure by an unequivocal synthesis involving a Skraup reaction on 8-amino-5-nitroquinoline. A dinitro derivative has never been prepared; the mononitro derivative decomposes when subjected to drastic nitrating conditions.⁷

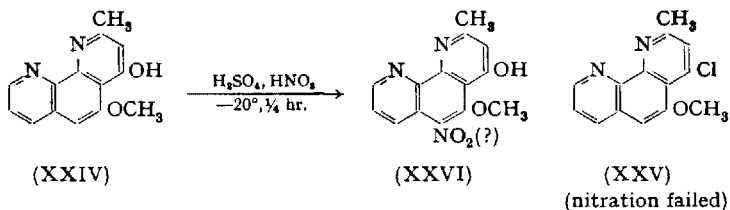
The 5-methyl homolog^{7,13} easily nitrates (120°) in 80% yield to produce 5-methyl-6-nitro-1,10-diazaphenanthrene. No fuming acids are necessary in this nitration because of the hyperconjugative activation provided by the methyl group.

Burger, Bass, and Frederickson²³ nitrated 2-hydroxy-4-methyl-1,10-diazaphenanthrene (XXII), which they produced by a Skraup reaction on the appropriate aminoquinoline. They formulated a dinitro derivative obtained as 2-hydroxy-4-methyl-(3,6?)-dinitro-1,10-diazaphenanthrene (XXIII). This formulation seems entirely reasonable,



since the 2-hydroxyl and 4-methyl positions are both conjugated with the 6-position but not with the 5-position.

Misani and Bogert¹² succeeded in nitrating 4-hydroxy-5-methoxy-2-methyl-1,10-diazaphenanthrene (XXIV) but failed in the attempted nitration of the 4-chloro analog, XXV.



(f) Other Reactions of the Ring. Linsker and Evans³⁶ made the statement that "phenanthrenes can be nitrated, sulfonated, and chlorinated under comparatively mild conditions, but the phenanthro-

lines resist all such attempts." This statement is probably generally true, with the exception of nitration, which is a practical reaction with 1,10-diazaphenanthrene and a possible reaction with the 1,7-isomer (see Section B3f).

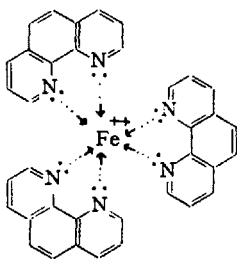
Brandt and Smith⁴¹ state that 5-bromo-1,10-diazaphenanthrene can be prepared by direct bromination of the parent base, and refer to the pamphlet of Smith and Richter.⁷ However, this source has only the following to say on the subject (on page 4): "The formation of a tribromo derivative of undetermined structure by heating the parent compound with aqueous bromine under pressure has been claimed,¹³ but the authenticity of this source is questionable. Little has been reported about the direct halogenation of 1,10-phenanthrolines." The patent referred to also claims to have made 5-bromo-1,10-diazaphenanthrene by direct bromination. The authors obtained a compound melting at 215°, whereas the actual melting point is 118°. ^{7,10,17} Smith and Richter⁷ state that sulfonation does not take place under any known conditions.

(g) Quaternization. When 1,10-diazaphenanthrene was treated¹⁰ with more than a 2 molar excess of methyl iodide in nitrobenzene for 24 hours, only monomethiodide resulted. 1,10-Diazaphenanthrene methiodide is a useful intermediate since it contains a ring susceptible to oxidation and reduction (see Sections A3c and d). The methiodide does not form a ferrous complex¹⁰ since the octet of electrons on the 1-nitrogen is saturated by the quaternization (see Section A3a).

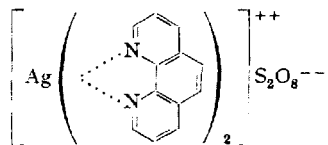
(h) Complex Formation. Blau⁴ originally synthesized 1,10-phenanthroline to compare its behavior in the formation of metal complexes with that of 2,2'-bipyridine. He reported that, when treated with ferrous sulfate, it formed triphenanthroline ferrous sulfate which could be oxidized to "pseudoferric compounds." Blau also mentioned complex formation with nickel bromide and with salts of cobalt, copper, zinc, and cadmium. Several decades later Walden, Hammet and Chapman⁵ announced the application of the ferrous complex to oxidimetric titrations.

In the last twenty years the 1,10-diazaphenanthrenes have be-

come some of the most useful organic reagents in analytical chemistry (see Section A3a). The metal complexes can be illustrated by the tri-(1,10-diazaphenanthrene)ferrous ion.

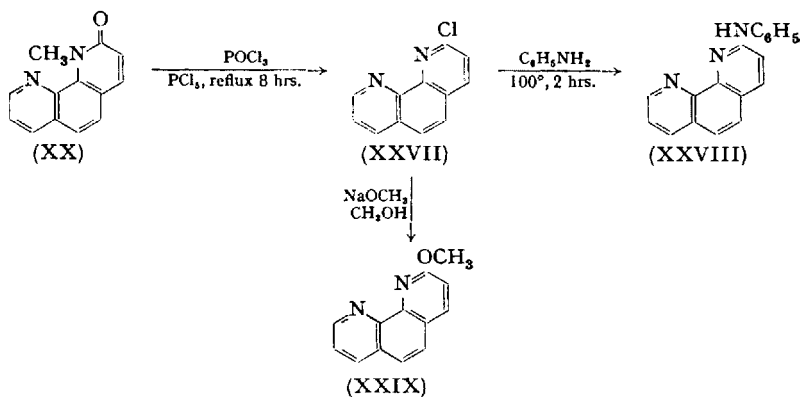


Smith and Richter⁷ point out that the formation of these Werner complexes proves that 1,10-diazaphenanthrene is planar. The non-planar 3,3'-dicarboxy-2,2'-bipyridine fails to give the complex while the planar 2,2'-bipyridine does form the complex. The $\text{N}\text{---}\text{N}$ angular structure is necessary for ferroin formation. The ferric 1,10-diazaphenanthrene ion cannot be prepared from ferric salts but only by oxidation of the ferrous complexes.⁴² 1,10-Diazaphenanthrene complexes are formed with several other ions;^{42a} namely, Cu^{++} , Cd^{++} , Zn^{++} , Ru^{++} , Cr^{++} , Ni^{++} , Co^{++} , and some ions of the noble metals.^{42b,c} Hieber and Muhlbauer⁸ state that *o*-phenanthroline forms complexes with bivalent silver ions such as that illustrated with bivalent silver persulfate:

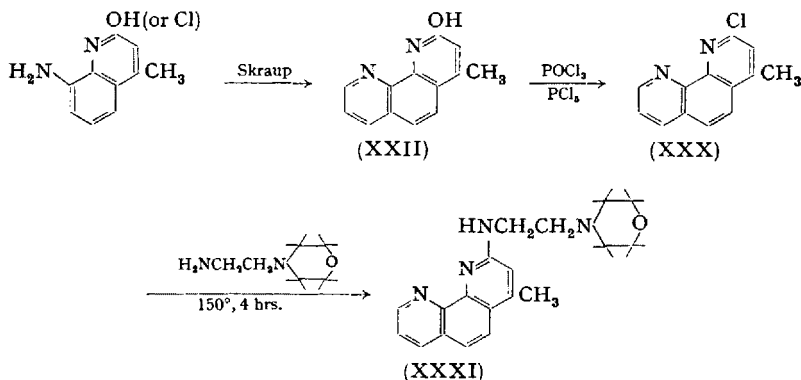


(4) Reactions of Substituted 1,10-Diazaphenanthrenes

Halcrow and Kermack¹⁰ developed a useful route to 1,10-diazaphenanthrenes basically substituted in the 2-position, yet unsubstituted in the 4-position. This is illustrated by the formation of 2-anilino-1,10-diazaphenanthrene (XXVIII) from XX through the intermediate 2-chloro-1,10-diazaphenanthrene (XXVII), which was obtained by the standard procedure using phosphoryl chloride.

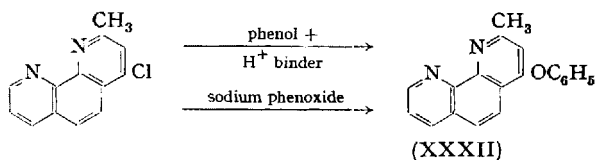


In a similar manner Burger and co-workers²³ synthesized 4-methyl-2-[2-(4-morpholinyl)ethylamino]-1,10-diazaphenanthrene (XXXI), starting from either 2-hydroxy- or 2-chloro-4-methyl-8-aminoquinoline. An attempt to replace a 5-bromo substituent with a 5-amino group, by

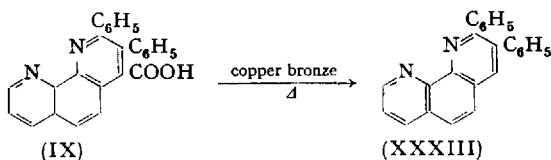


heating compounds containing the former with ammonia at 190° for three days, gave none of the desired product.¹⁰

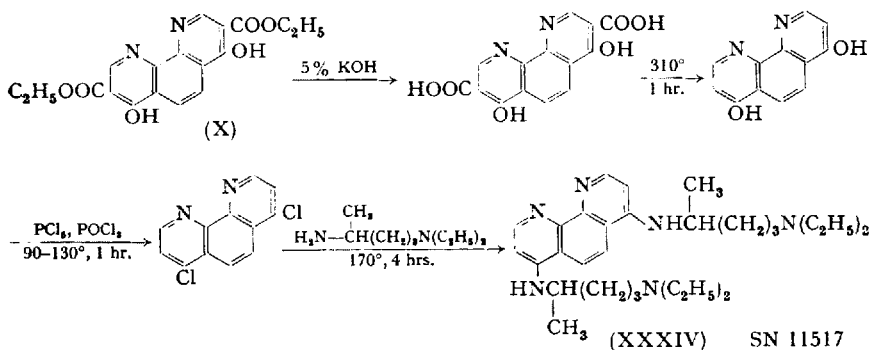
Halogen atoms in the positions α or γ to the ring nitrogens can be replaced by ether linkages, as in the preparation of XXIX or of 2-methyl-4-phenoxy-1,10-diazaphenanthrene (XXXII).⁴³



Carboxyl groups can be removed from the molecule by the usual methods; thus, IX is easily decarboxylated to form 2,3-diphenyl-1,10-diazaphenanthrene (XXXIII).²⁷



Snyder and Freier²⁸ produced a series of compounds for anti-malarial testing by combining several of these procedures:



The Survey Number (SN), assigned to 4,7-bis(4-diethylamino-1-methylbutylamino)-1,10-phenanthroline (XXXIV) is the designation used by the Survey of Antimalarial Drugs.¹²⁶

(5) Uses

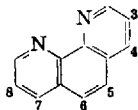
(a) Analytical Reagents. The principal use of 1,10-diazaphenanthrene and its simple derivatives is in the production of oxidation and reduction indicators. The tri-(1,10-diazaphenanthrene) ferrous complex ion is red while the ferric complex is a faint blue. The complex is stable in acid³¹ (this is especially marked in the 5-nitro isomer), and is of sufficient color intensity to be observed in otherwise colored solutions. The oxidation and reduction of the 1,10-diazaphenanthrene complex ions is reversible, and covers a wide range of redox potentials. There are numerous articles in the literature describing the phenan-

throline indicators. However, only a few outstanding ones will be listed.

Hammett, Walden, and co-workers gave the first detailed descriptions of the method.^{5, 40, 44} A study of the ferrous complex of 2-methyl-1,10-diazaphenanthrene was made by Pfeiffer and Christeleit²² in 1938. G. F. Smith and co-workers have published a pamphlet⁷ and several papers^{14, 41} on the subject. The last reference is a recent comprehensive review of 1,10-diazaphenanthrenes in analytical chemistry. In this paper Brandt and Smith studied the ferrous complexes derived from twenty-four of the monomethyl-, dimethyl-, trimethyl-, and tetramethyl-1,10-diazaphenanthrenes that can be formed by substituting methyl groups into the parent base in positions 3 to 8 inclusive. They also studied seven bromo or polybromo derivatives. Most of these compounds have been described by Case,¹⁸⁻²⁰ but some of the preparations had not been published at the time of this writing. The redox potentials, the molecular extinction coefficients, and absorption maxima of the ferrous complexes have been recorded. Methyl groups lower the redox potentials of the resulting ferroins by varying amounts, depending upon their location:

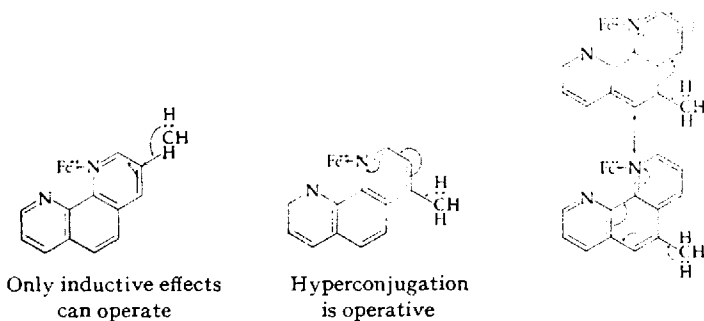
Substituent	Potential compared to parent base
3,8-Dimethyl	—0.07 volt
5,6-Dimethyl	—0.10 volt
4,7-Dimethyl	—0.22 volt

It is seen that the mechanism for transferring the electron release of the methyl group to the nitrogens is most effective in the 4- and 7-positions, less effective in the 5- and 6-positions, and least effective in the 3- and 8-positions. Consideration of the structure of 1,10-diazaphenanthrene will show that this is an entirely reasonable series:



The 3-position is not conjugated with the 1-position (an even number of bonds separate them), so the hyperconjugative electron release of the methyl group can be relayed to the 1-position only by an

inductive mechanism. The 4- and 7-positions are conjugated with the 1-position, so the hyperconjugative electron release of the methyl group can be transferred by a tautomeric mechanism to the nitrogen:



A methyl group in the 5-position is conjugated with the 1-nitrogen but only by long routes involving the bonds of some of the less stable of the five possible resonance hybrids. Electron-attracting substituents (such as bromo) increase the redox potential. The same effects are observed in the molecular extinction coefficients, indicating that electrons are more abundant at the nitrogens when electron-releasing groups are in the 4- and 7-positions.

The 1,10-diazaphenanthrenes are useful in the detection and determination of ferrous iron^{41, 42, 45, 46} and of copper.^{41, 47, 48} These reagents are also employed in the spectrophotometric determination of iron, being useful even in solutions as dilute as 1 mg. of iron per cubic yard of water.⁴¹ The analyses are widely applied to commercial beverages such as beer, wine, and fruit juices. 2,8-Dimethyl-1,10-diazaphenanthrene has been mentioned as a possible replacement for diquinoline as a specific reagent for determination of cuprous copper in the presence of iron.^{48a} It is commercially available under the name "neo-cuproine."

A third analytical application of the 1,10-diazaphenanthrenes⁴¹ makes use of them as organic precipitants for anions. Reactions of two types are involved. In the first, the free bases are used to form salts with acids by means of the spare pair of electrons on one of the nitrogens. In the second type, the tri-(1,10-diazaphenanthrene) ferrous ion is used as a precipitant for dibasic anions. Such anions as per-

TABLE VI-1. 1,10-Diazaphenanthrenes

Formula	1,10-Diazaphenanthrenes	M.p., °C.	Refs.
I	1,10-Diazaphenanthrene	117	4, 6-11, 14, 15, 33, 52
		HICl ₂ 167	116
		H ₂ O 99-100, 102, 103	4, 7, 9, 33
		MeI 210-13	10
	2-Methyl-	75-6	3, 22
		b. 243/12 mm.	
		2H ₂ O 50-3, 53	3
III	3-Methyl-	HClO ₄ 205-20 (dec.)	22
		158-9	18
		4-Methyl-	18
		144-5	18
	5-Methyl-	114	7, 17, 33, 45
		b. 280-2/13 mm.	17
		H ₂ O 67	33
IV	2,9-Dimethyl-	P 203-4	17
		159-60	18
		3,4-Dimethyl-	20
		234-5	20
		3,5-Dimethyl-	19
		169-70	19
		3,6-Dimethyl-	19
V	4,7-Dimethyl-	117-8	19
		136-7	18
		4,5-Dimethyl-	19
		151-2	19
		4,6-Dimethyl-	19
		161-2	19
		194-5	18
VI	4,5,7-Trimethyl-	265-6, 272	18, 33
		217-8	20
		3,4,6-Trimethyl-	20
		221-2	20
		3,4,8-Trimethyl-	20
		211-12	20
		3,5,6-Trimethyl-	18
VII	3,5,7-Trimethyl-	196-7	18
		201-2	19
		3,5,8-Trimethyl-	19
		185-6	19
		3,6,7-Trimethyl-	19
		177-8	19
		184-5	19
XXXIII	2,3-Diphenyl-	3,4,6,7-Tetramethyl-	41
		189-90	20
		3,4,7,8-Tetramethyl-	20
		275-6	20
XIV	1-Methyl-1,2-dihydro-	3,5,6,7-Tetramethyl-	41
		260-1	18
XV	1-Methyl-1,2,3,4-tetrahydro-	3,5,6,8-Tetramethyl-	18
		b. 120-5/0.05 mm.	34
XXVII	2-Chloro-	HI 184	34
		129	39
		4-Chloro-	28
		180-230	28

(Table continued)

TABLE VI-1 (*continued*)

Formula	1,10-Diazaphenanthrenes	M.p., °C.	Refs.
		H ₂ O 80	28
		P 203-6	28
II	5-Chloro-	123	7, 17, 21, 24, 45
	4,7-Dichloro-	249-50	28
XXX	2-Chloro-4-methyl-	210-12	23
	4-Chloro-2-methyl-	136-7	43
	7-Chloro-3-methyl-	178-9	18
	5-Bromo-	118, 119	7, 10, 17, 33, 45
		$\frac{1}{2}$ H ₂ O 113-5	10
		H ₂ O 84, 86	17, 33
		P 228	17
		(incorrectly reported) 215	13
	3,5-Dibromo-		41
	3,6-Dibromo-		41
	5,6-Dibromo-		41
	3,4,5-Tribromo-		41
	3,5,6-Tribromo-		41
	3,5,6,8-Tetrabromo-		41
XXI	5-Nitro-	197-8	7, 10, 37, 38, 40, 45
		199-201, 202	
	5-Nitro-6-methyl-	268-70	7, 17, 45
	5-Amino- (unsuccessful)		10
XXVIII	2-Anilino-	231-3	10
XXXIV	4,7-Bis(4-diethylamino-1-methylbutylamino)-SN 11517	152-5	28
	2-(2-Diethylaminoethylamino)-	Oil	10
		3,5-DNB 190-2	10
	2-(4-Diethylamino-1-methylbutylamino)-	Oil	10
		3,5-DNB 157-8	10
	4-(4-Diethylamino-1-methylbutylamino)-5-methoxy-SN 12535	196-200	28
	2-(3-Diethylaminopropylamino)-	Oil	10
		3,5-DNB 150-2	10
	4-(3-Diethylaminopropylamino)-	166-8	28
		P 172-4	28
XXXI	4-Methyl-2-[2-(4-morpholinyl)ethylamino]-		23
		2HCl 261-3	23
	2-(1-Piperidino)-	213-17	10
	3-Hydroxy-		46

(Table continued)

TABLE VI-1 (*continued*)

Formula	1,10-Diazaphenanthrenes	M.p., °C.	Refs.
XXIX	4-Hydroxy-	214-15	28
	4,7-Dihydroxy-	475 (dec.)	28
	2-Methoxy-	88-9	35
		MeI 234-5 (dec.)	35
	5-Methoxy-	104-5	21
XXII	4-Hydroxy-5-methoxy-	165-85	28
		P 215-21	28
	2-Hydroxy-4-methyl-	177-9	23
VIII	4-Hydroxy-2-methyl-	196, 210-11	26, 43
XXIV	4-Hydroxy-5-methoxy-2-methyl-	234-5	12
XXXII	4-Phenoxy-2-methyl-	126-7	43
XXIa or b	2-Methoxy-N ^x -methyl- <i>x,x,x,x</i> -tetrahydro-	190	35
XXV		P 157-8	
	5-Methoxy-4-chloro-	164-7	28
		P 218-20	
XXV	5-Methoxy-4-chloro-2-methyl-	175-7	12
XXIII	2-Hydroxy-3,6(?)-dinitro-4-methyl-	255-60	23
XXVI	4-Hydroxy-5-methoxy-2-methyl-6(?)-nitro-	290	12
IX		Darkens > 230	
		> 270 (dec.)	
	4-Carboxy-2,3-diphenyl-	260-2	27
	3-Carboxy-4-hydroxy-	300-5 (dec.)	28
	3-Carbethoxy-4-hydroxy-	237-41	28, 46
XI	3-Carboxy-4-hydroxy-5-methoxy-	278-84 (dec.)	28
	3-Carbethoxy-4-hydroxy-5-methoxy-	217-20	28
	3,8-Dicarboxy-4,7-dihydroxy-	300-10 (dec.)	28
X	3,8-Dicarbethoxy-4,7-dihydroxy-	264-5	28
XVIII	5,6-Dioxo-	250, 255	21, 37, 38
XII		256-7	
		2,4-DNPH > 300	
		dioxime 189	
XII	2,9-Dioxo-1,2,3,4,7,8,9,10-octahydro-	365	29
XX	2-Oxo-1-methyl-	123-4	10, 35
XIIa	2,9-Dioxo-4,7-dimethyl-1,2,3,4,7,8,9,10-octahydro-	242	29
XIII	2,9-Dioxo-1,2,3,4,7,8,9,10-octahydro-5-amino-		30
XVII	2,9-Dioxo-1,2,3,4,7,8,9,10-octahydro-5-acetamido-	310	30
	1,10-Diazaphenanthrene-1,10-dioxide		36
		P 191-2	36

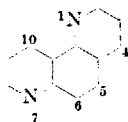
chlorate, persulfate, and thiocyanate can be determined by using these reagents.

The 5-nitro-1,10-diazaphenanthrenes are employed as indicators in the determination of calcium in biological specimens.⁴⁹ *o*-Phenanthrolines are also useful in the qualitative determination of molybdenum.⁴⁵

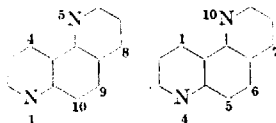
(b) Drying Agents. Cobalt and manganese complexes, such as cobaltous-1,10-diazaphenanthrene oleate, have been used in linseed oil paints as agents to decrease the drying time of the paints.⁵⁰ Wheeler found that the free bases of 1,10-diazaphenanthrene and other tertiary nitrogen heterocycles serve to increase the drying rates of certain oleoresinous paints.⁵¹ The effect of the base as an additive to prevent loss on drying of inks has recently been studied.¹²⁵

(c) Physiological Uses. The 1,10-diazaphenanthrenes, suitably substituted with alkylamino groups, have been investigated in the general search for antimalarials both in the United States and in England.^{10, 23, 28} The synthesis of compounds of this nature are described elsewhere in this chapter (Section A4). Baldwin⁵² reported in 1948 that 1,10-diazaphenanthrene possesses a high order of activity as an anthelmintic. Karrer, Pletscher, and Manz³⁴ have investigated the antibiotic activity of salts of 1-methyl-1,2,3,4-tetrahydro-1,10-diazaphenanthrene (XV) and found the HI salt to be active. 2-Methyl-4-phenoxy-1,10-diazaphenanthrene (XXXII) is listed in a patent⁴³ describing useful analgesics.

B. 1,7-Diazaphenanthrene or meta-Phenanthroline. 1,7-Phenanthroline. 1,5-Phenanthroline. 4,10-Phenanthroline. Dipyridino-2',3':1,2;2'',3'':3,4-benzene.5,6:2',3'-Pyridoquinoline. 7,8:2',3'-Pyridoquinoline. 4,10-Naphthisodiazine. R.I. 1953



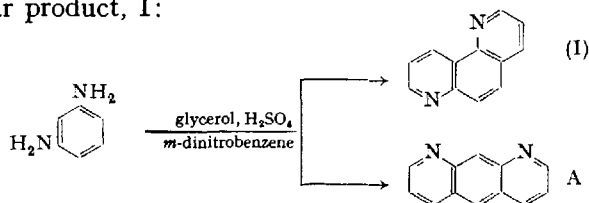
other numberings:



(1) History and Nomenclature

The first 1,7-diazaphenanthrene was prepared by Skraup and Vortmann^{1, 1a} in 1882 by the action of sulfuric acid, glycerol, and

m-dinitrobenzene on the tin salts of *m*-phenylenediamine. They realized that the cyclization could have formed either the linear product, A, or the angular product, I:



Since oxidation (Section B3e) produced 3,2'-dicarboxy-2,3'-dipyridine, the angular cyclization was confirmed and the name, phenanthroline, was suggested. About ten years later, Marckwald⁵³ proved that the Skraup cyclization proceeds in such a way as to include the double bond adjacent to the amino group. It is now realized that this empirical rule assumes partial bond fixation in heterocycles, a phenomenon which is generally accepted.

The early German literature, Beilstein, and the British abstracts refer to 1,7-diazaphenanthrene as 1,5-phenanthroline. *Chemical Abstracts* called it 4,10-phenanthroline until the 1937 Index appeared, at which time they adopted the present 1,7-phenanthroline terminology.

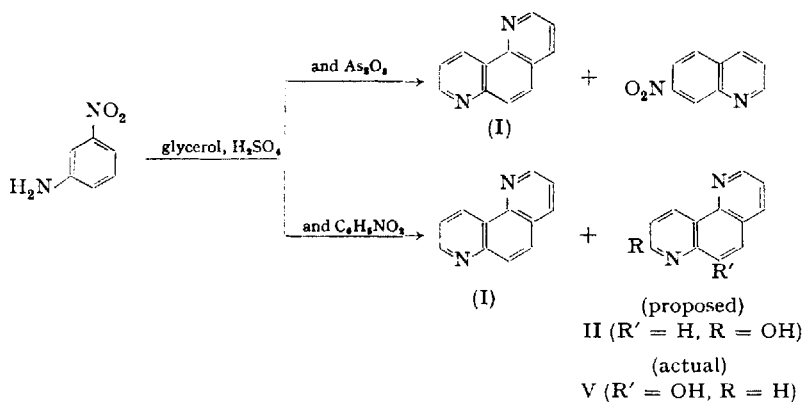
In translating from one numbering system to another, it is important to consider the dissymmetry of 1,7-diazaphenanthrene (I). The 5- and 6-positions are not equivalent, since the 6-position is *peri* to the 7-nitrogen while the 5-position is not adjacent to either nitrogen. The nitrogen atom in the 1-position is somewhat hindered, so reactions that involve only one of the two nitrogens probably occur at the 7-position. The relation between the numbers of identical positions in the various numbering systems is shown by the following table:

1,7	1,5	4,10
1	5	10
2	6	9
3	7	8
4	8	7
5	9	6
6	10	5
7	1	4
8	2	3
9	3	2
10	4	1

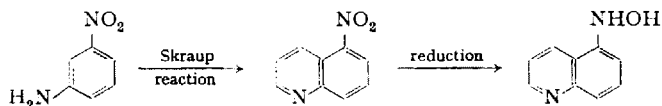
(2) Preparation (Ring Closures)

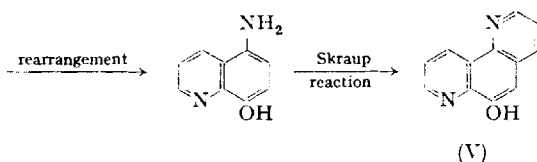
(a) Skraup-Type Reactions. (1) Glycerol on *m*-Phenylenediamines.

The original synthesis of Skraup (Section B1), with minor variations, has proved to be one of the most useful methods of preparation of 1,7-diazaphenanthrene^{1,1a,6,54} and its derivatives. Druce⁸³ repeated the exact preparation of Skraup and Vortmann, but obtained low yields. His minor innovations did not improve the yield perceptibly. However, C. R. Smith⁶ was able to obtain 40–5% yields in the synthesis, which certainly shows it to be an economical reaction. It is interesting that addition of acrolein during the reaction reduced the yield. Kneuppl⁵⁵ treated *m*-nitroaniline with arsenic acid, glycerol, and sulfuric acid, and obtained a mixture of “*m*-nitroquinoline” (7-nitro) and “phenanthroline.” LaCoste,⁵⁶ using nitrobenzene as the oxidizing agent in a similar reaction, obtained 1,7-diazaphenanthrene and a hydroxyphenanthroline as a by-product. He assumed that the latter was 8-hydroxy-1,7-diazaphenanthrene (II). Later this was proved to be 6-hydroxy-1,7-diazaphenanthrene (V)^{71,84} (see Section B2a4).

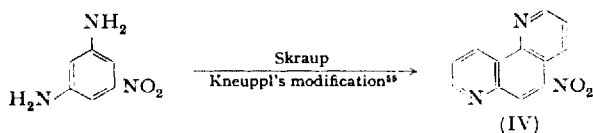
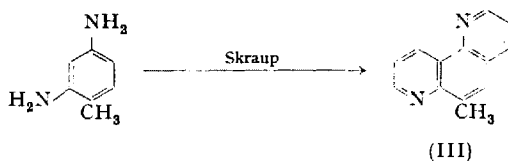


Sucharda and Mazonski⁹³ proposed the following mechanism for the formation of V as a by-product in a Skraup reaction on *m*-nitroaniline:





Substituted *m*-phenylenediamines are useful in preparing 5- or 6-substituted 1,10-diazaphenanthrenes. Skraup and Fischer⁵⁷ prepared 6-methyl-1,7-diazaphenanthrene (III) from 4-methyl-*m*-phenylenediamine. 6-Methoxy-1,7-diazaphenanthrene has been made by a similar reaction.²¹ Symmetrically substituted *m*-phenylenediamines yield 5-substituted products, as is illustrated by the synthesis of 5-nitro-1,7-diazaphenanthrene (IV).^{58-60,66} Haworth and Sykes⁸² failed in an

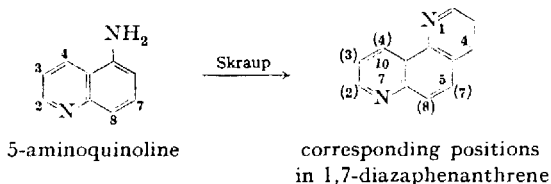


attempt to make 6-nitro-1,7-diazaphenanthrene by a double Skraup reaction on 4-nitro-*m*-phenylenediamine.

6-Hydroxy-1,7-diazaphenanthrene (V) was produced in rather poor yields by a Skraup reaction on 2,4-diaminophenol,^{21,61} and by a synthesis involving the action of stannic chloride on the dihydrochloride salt of 2,4-diaminophenol.⁶² Several patents offer the application of the Skraup synthesis to 4-halo-*m*-phenylenediamines, or their corresponding azo derivatives, as a possible preparation for the 6-halo-1,7-diazaphenanthrenes.^{13,63,64} However, Haworth and Sykes⁸² were able to obtain yields no better than 10 to 30 % in the synthesis of 6-bromo-1,7-diazaphenanthrene. The 6-alkylamino compounds can be prepared by a similar reaction,⁶⁵⁻⁶⁷ as can 6-methoxy-1,7-diazaphenanthrene.²¹

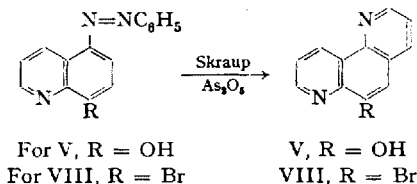
(2) *Glycerol on 5-Aminoquinolines.* The following 1,7-diazaphenanthrenes, which are substituted in the 5-, 6-, 8-, 9-, and/or 10-

positions, have been prepared by the Skraup reaction on corresponding substituted 5-aminoquinolines: 8-hydroxy- (II),⁷¹ 6-methyl- (III),⁶⁸ 6-hydroxy- (V),⁸² 10-hydroxy- (VI),⁶⁹ 6-chloro- (VII),^{13, 64, 66a, 82} 6-bromo- (VIII),^{13, 64, 66a} 8-methyl- (IX),⁷⁰ 10-hydroxy-8-methyl- (X),⁷¹ and 6- β -diethylaminoethylamino- (XI).⁶⁵ The relationship between substituents in the 5-aminoquinoline and the product is:

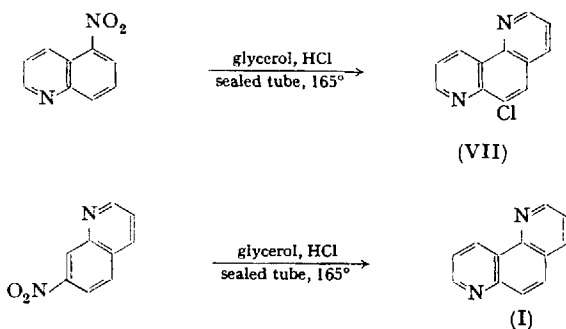


(3) *Glycerol on 7-Aminoquinolines.* Skraup⁷² prepared 1,7-diazaphenanthrene from 7-aminoquinoline (β -aminoquinoline). 1,7-Diazaphenanthrenes substituted in any of the positions 2 to 6 inclusive can be prepared from the 7-aminoquinolines substituted in the same positions. This synthesis has been used to prepare the following: 2-hydroxy- (XII),⁷¹ 2-hydroxy-4-methyl- (XIII),⁷¹ 2-methyl- (XIV),³ and 2,4-dimethyl- (XV)⁷³ (see references 13, 60, 63, 65, 66a, and 67).

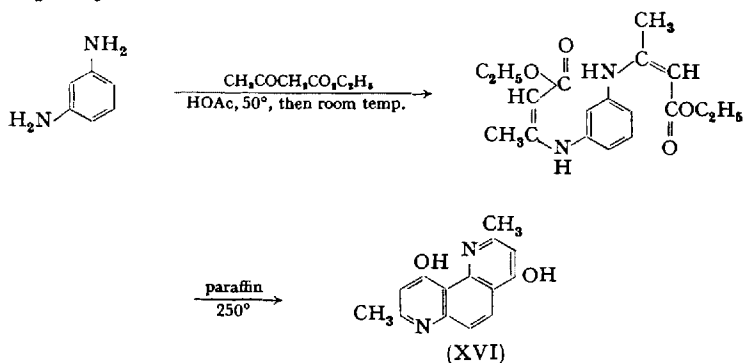
(4) *Glycerol on 5-Arylazoquinolines.* The Skraup reaction has been applied to azo derivatives and acyl derivatives^{66a} of the aromatic amines. For instance, Matsumura⁸⁴ obtained 6-hydroxy-1,7-diazaphenanthrene (V) by a Skraup reaction on 8-hydroxy-5-phenylazoquinoline. The yield in this reaction was poor. Matsumura suggested that the supposed 8-hydroxy-1,7-diazaphenanthrene (II) obtained by LaCoste⁵⁶ in a Skraup reaction on *m*-nitroaniline (Section B2a1) was actually the 6-hydroxy isomer, V. The compound obtained by LaCoste melted at 159–160°, which agrees with the 157–8° range of the known compound. The 8-isomer melts at 302–4°.^{35, 71} 6-Bromo-1,7-diazaphenanthrene (VIII) has been synthesized by a Skraup reaction on 8-bromo-5-phenylazoquinoline.



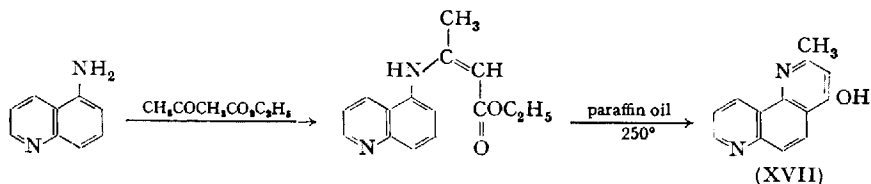
(5) *Glycerol and Hydrochloric Acid on Nitroquinolines.* Glycerol and hydrochloric acid react²⁴ with 5-nitroquinoline to produce 6-chloro-1,7-diazaphenanthrene (VII), and with 7-nitroquinoline to produce 1,7-diazaphenanthrene (I).



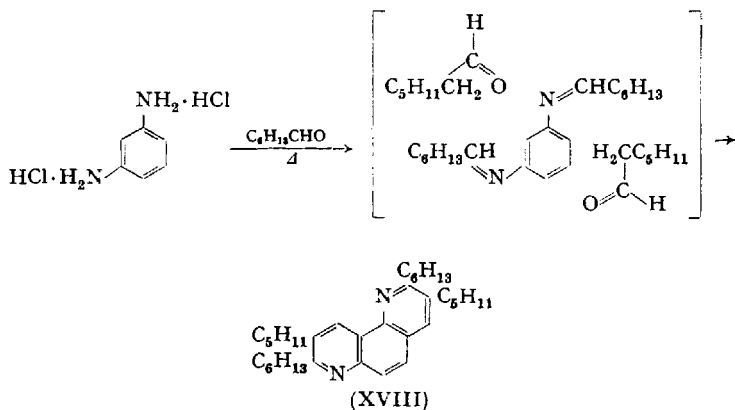
(b) **Conrad-Limpach Reaction.** Jacini⁷⁴ obtained 4,10-dihydroxy-2,8-dimethyl-1,7-diazaphenanthrene (XVI) from ethyl acetoacetate and *m*-phenylenediamine.



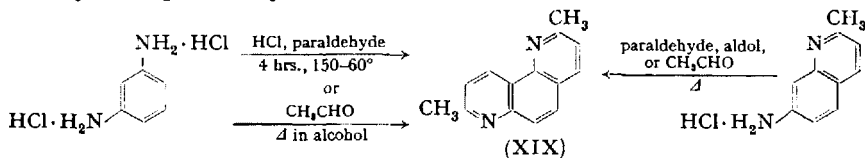
The Conrad-Limpach reaction also has been used to produce 4-hydroxy-2-methyl-1,7-diazaphenanthrene (XVII) from 5-aminoquinoline.^{26,71}



(c) **Doebner-Miller Synthesis.** Schiff and Vanni⁷⁵ prepared Schiff bases from *m*-phenylenediamine and three aldehydes, *i.e.*, heptaldehyde, acetaldehyde, and cinnamaldehyde. They proposed, erroneously, several phenanthrolines as possible cyclic structures derived from these (see Section B6). However, two years later von Miller and Gerdeissen⁷⁶ published a paper containing similar reactions, and pointed out that Schiff and Vanni were in error. Von Miller and Gerdeissen formulated their reactions as being of the same type as the Doebner and Miller quinoline synthesis discovered ten years previously.⁷⁷ Thus, *m*-phenylenediamine dihydrochloride and heptaldehyde, when heated in alcohol, yield 3,9-di-*n*-amyl-2,8-di-*n*-hexyl-1,7-diazaphenanthrene (XVIII).

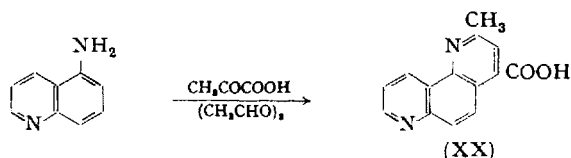


The same product was obtained from the reaction of heptaldehyde on 5- or 7-amino-3-*n*-amyl-2-*n*-hexylquinoline.⁷⁶ 2,8-Dimethyl-1,7-diazaphenanthrene (XIX) was produced by similar reactions using acetaldehyde or paraldehyde.^{76, 78}



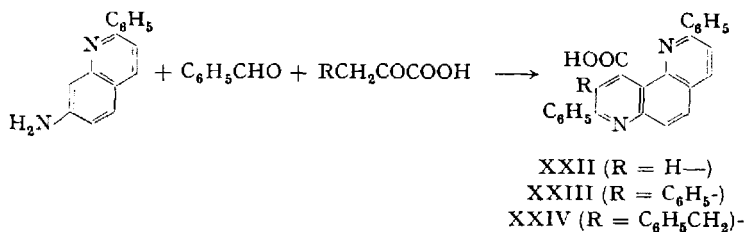
(d) **Doebner's Pyruvic Acid Synthesis.** Willgerodt and von Neander first applied Doebner's pyruvic acid synthesis to the preparation of 1,7-diazaphenanthrenes. They treated 5-aminoquinoline with pyruvic acid and paraldehyde to form 4-carboxy-2-methyl-1,7-diaza-

phenanthrene (XX).⁷⁹ A similar reaction using benzaldehyde produced 4-carboxy-2-phenyl-1,7-diazaphenanthrene (XXI).

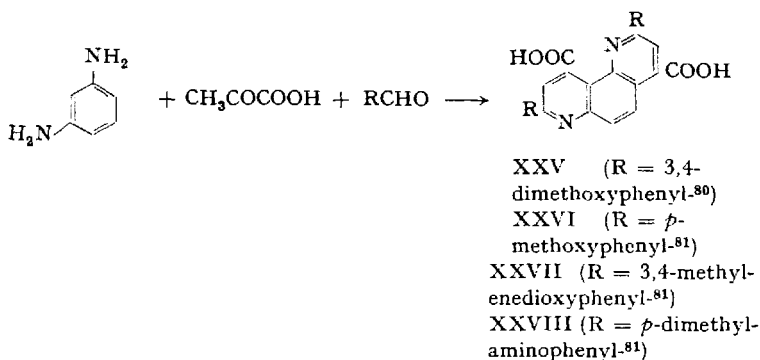


XXI = 2-phenyl

Borsche and Wagner-Roemmick²⁷ synthesized several 1,7-diazaphenanthrenes by applying Doebner's pyruvic acid synthesis to 7-amino-2-phenylquinolines.

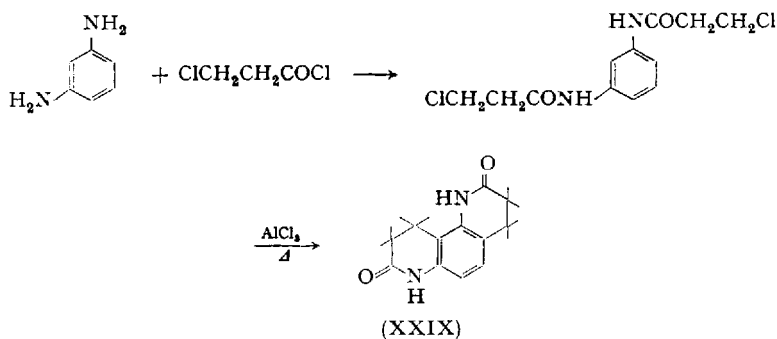


A double ring closure was used by Holdsworth and Lions^{80,81} to form 2,8-diaryl-4,10-dicarboxy-1,7-diazaphenanthrenes.

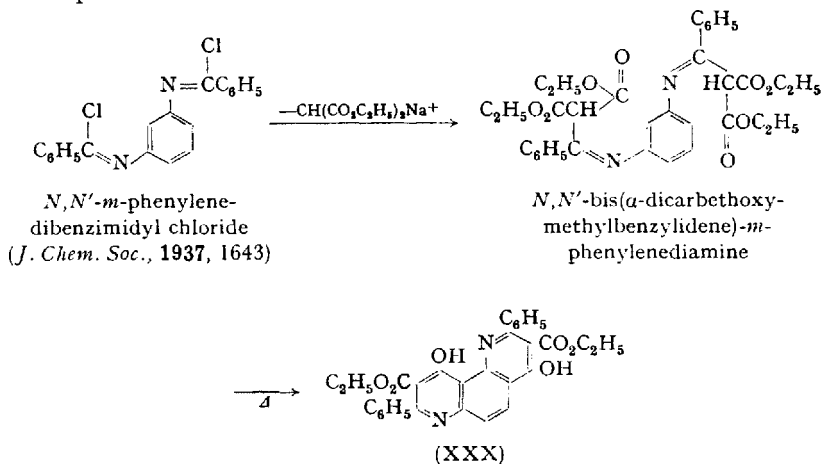


(e) From β -Chloropropionyl Chloride. Mayer and co-workers²⁹ condensed β -chloropropionyl chloride with *m*-phenylenediamine to

form 2,8-dioxo-1,2,3,4,7,8,9,10-octahydro-1,7-diazaphenanthrene (XXIX).



(f) **Other Methods.** Rao and Wheeler⁶⁵ prepared 3,9-dicarbethoxy-4,10-dihydroxy-2,8-diphenyl-1,7-diazaphenanthrene (XXX) by the novel procedure:



(3) Reactions of 1,7-Diazaphenanthrene

(a) **Salt Formation.** 1,7-Diazaphenanthrene functions as a diacid base. Since the 1-nitrogen is somewhat hindered, it might be predicted that salt formation would occur less easily there than at the 7-position. The phenomenon of salt formation has never been studied as such, but various salts have been used in the precipita-

tion and purification of the base. Skraup and Vortmann¹, and later, others^{82,83} isolated the compounds from the reaction mixtures as the chromate salts. The nitrates, picrates, sulfates, hydrochlorides, and hydrobromides also have been used in purification and identification procedures.^{1, 3, 35, 57, 61, 69, 71, 82, 84, 86}

Kermack and Webster⁷¹ found that 1,7-diazaphenanthrene, when placed in refluxing methyl alcohol-dimethyl sulfate solution for one hour, forms a monomethyl hydrogen sulfate salt rather than the expected quaternary compound.

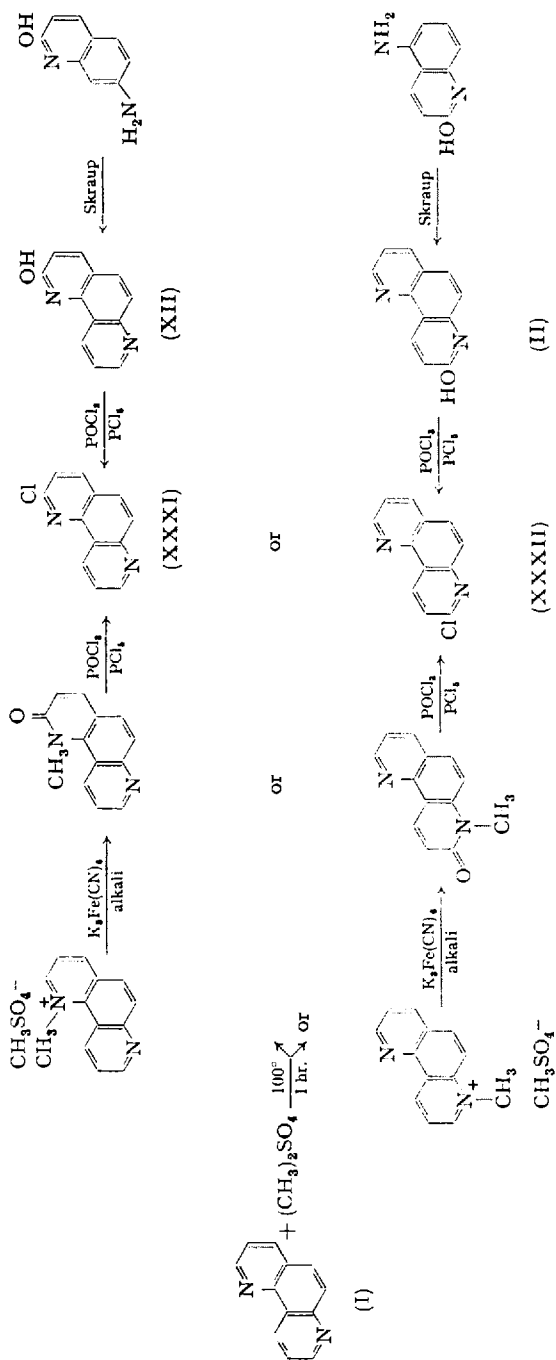
(b) Hydration. The formation of monohydrates,^{69,76,82} dihydrates,^{1, 3, 78} and polyhydrates^{3,68} has been reported.

(c) Quaternization. The relatively unreactive 1,7-diazaphenanthrene nucleus can be made more susceptible to oxidation and reduction reactions by quaternization (see Sections A3c and d). Likewise, a methyl group alpha to one of the nitrogens is further activated by quaternization of that nitrogen (see Section B4e). These phenomena are explained by the polarization of the C=N bond and by the electron impoverishment of the ring resulting from the open charge on the nitrogen produced by the quaternization.

Kermack and Webster⁷¹ studied the relative reactivities of the 1-nitrogen and the 7-nitrogen in the formation of a monoquaternary compound. They prepared a monomethosulfate of 1,7-diazaphenanthrene, oxidized it, and converted the product to either 2-chloro- or 8-chloro-1,7-diazaphenanthrene according to reaction scheme VI-1. 2-Chloro-1,7-diazaphenanthrene (XXXI) and 8-chloro-1,7-diazaphenanthrene (XXXII) were prepared from 2-hydroxy-1,7-diazaphenanthrene (XII) and 8-hydroxy-1,7-diazaphenanthrene (II), which, in turn, had been synthesized unequivocally by Skraup reactions on the corresponding amino-2-hydroxyquinolines. The unknown chloro compound derived by means of the quaternization was identical with XXXII, proving that the easily available 7-nitrogen was quaternized in preference to the crowded 1-nitrogen.

Haworth and Sykes⁸² observed that 6-acetamido-1,7-diazaphenanthrene did not react with methyl iodide or methyl sulfate, but it did react with excess methyl *p*-toluenesulfonate at 120–30°. A 6-amino-

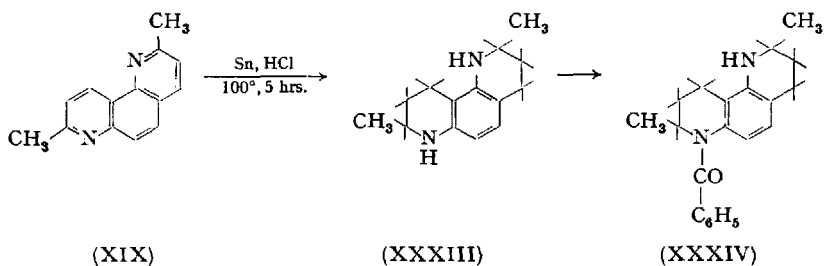
Reaction Scheme VI-1



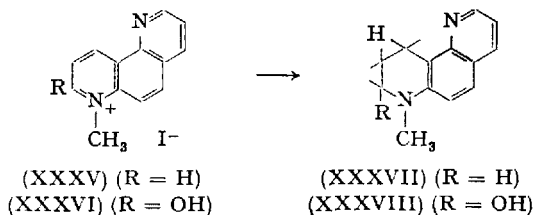
1,7-diazaphenanthrene methochloride hydrochloride monohydrate was obtained by hydrolysis of the above compound with hot 20% hydrochloric acid. These authors⁸² believe the quaternization involved the 1-nitrogen.

Many other examples of quaternized 1,7-diazaphenanthrenes are mentioned in the literature.^{1, 3, 34, 35, 69, 87, 89}

(d) Reduction. The reduction of 1,7-diazaphenanthrene itself has not been reported; however, 2,8-dimethyl-1,7-diazaphenanthrene (XIX) was reduced by von Miller *et al.*^{76, 78} to 2,8-dimethyl-1,2,3,4,7,8,9,10-octahydro-1,7-diazaphenanthrene (XXXIII). The latter was isolated as the mono (7-?) benzoyl derivative, XXXIV.

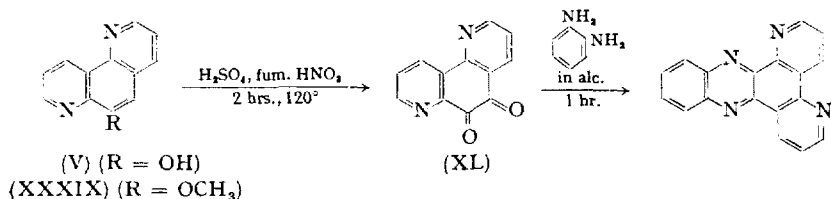


Karrer and co-workers reduced 7-methyl-1,7-diazaphenanthrenium iodide (XXXV)³⁴ and its 8-hydroxy derivative XXXVI³⁵ to 7-methyl-7,8,9,10-tetrahydro-1,7-diazaphenanthrene (XXXVII) and 8-hydroxy-7-methyl-7,8,9,10-tetrahydro-1,7-diazaphenanthrene (XXXVIII), respectively.

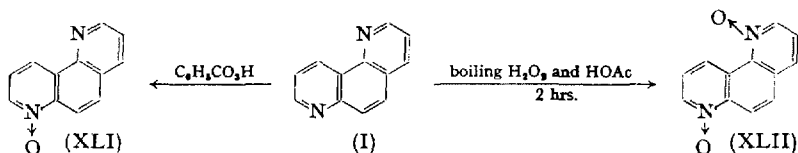


(e) Oxidation. The stability of the 5- and 6-positions of 1,7-diazaphenanthrene is demonstrated by the fact that no *ortho*-quinone is formed by treatment with selenium dioxide, vanadium pentoxide, iodic acid, or periodic acid.³⁶ Such quinone formation proceeds easily

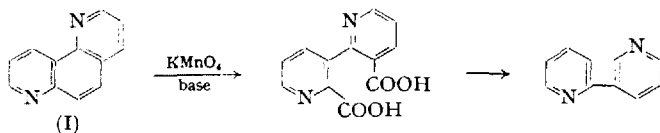
with phenanthrene and 1-azaanthracene. 5,6-Dioxo-1,7-diazaphenanthrene (XL) is formed, however, by oxidation of 6-methoxy- (XXXIX) or 6-hydroxy-1,7-diazaphenanthrene (V) with hot, mixed acids.²¹ This oxidation does not proceed with potassium permanganate or with hydrogen peroxide. Druey and Schmidt²¹ converted XL to 1,5,9,14-tetraza-(1,2,3,4)-dibenzanthracene by heating with *o*-phenylenediamine. This confirmed the 5,6-dioxo structure.



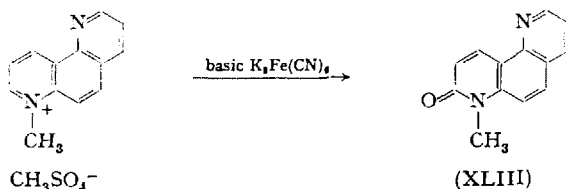
The 7-*N*-oxide, XLI, can be made from *m*-phenanthroline by oxidation with perbenzoic acid,⁶⁹ while 1,7-diazaphenanthrene-1,7-dioxide (XLII) is formed by the action of hydrogen peroxide.^{36, 90}



Alkaline permanganate oxidizes I to 3,2'-dicarboxy-2,3'-bipyridine, which can be decarboxylated stepwise to 2,3'-bipyridine in a preparative procedure.^{1, 6, 54}

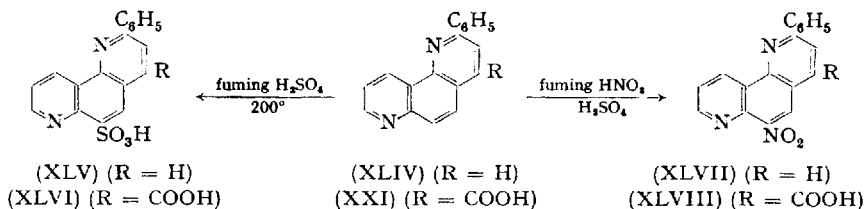


7-Methyl-1,7-diazaphenanthrenium methosulfate is oxidized to 8-oxo-7-methyl-1,7-diazaphenanthrene (XLIII) by basic potassium ferricyanide (below 5°)^{35, 43, 87} (see Section B3c).

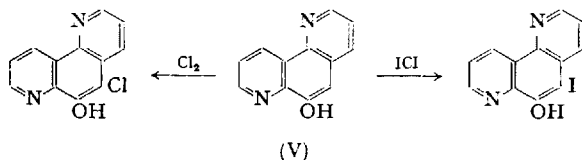


(f) Nitration and Sulfonation. The statement has been made in two papers by different authors^{36,82} that 1,7-diazaphenanthrene cannot be nitrated. However, Druey and Schmidt²¹ obtained an 8% yield of a mononitro derivative by treating 1,7-diazaphenanthrene with fuming nitric acid and sulfuric acid at 120° for two hours. Since 85% of the starting material was recovered, the reaction is certainly of little value. The mononitro derivative is probably the 6-nitro since it melts at 155°, while the 5-nitro derivative prepared from 5-nitro-*m*-phenylenediamine melts at 68°.⁵⁸ The hetero rings would not be substituted in acid solution because they would be deactivated toward electrophilic substitution by salt formation.

Linsker and Evans³⁶ state that 1,7-diazaphenanthrene cannot be sulfonated. Willgerodt and von Neander⁷⁹ were able to sulfonate and nitrate 2-phenyl-1,7-diazaphenanthrene (XLIV) and its 4-carboxy derivative (XXI). They proved the structure of these compounds by the same method used in similar work with the *p*-phenanthrolines (see Section C3c).



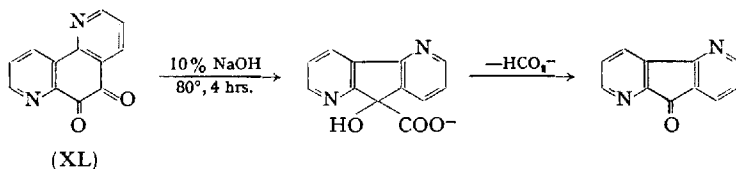
(g) Halogenation. Linsker and Evans report that 1,7-diazaphenanthrene cannot be halogenated.³⁶ No direct halogenation of the unsubstituted base has been reported, but Kermack and Tebrich⁶⁹ obtained a dichloro derivative of unknown structure in the treatment of the dihydrochloride of 1,7-diazaphenanthrene-7-oxide (XLI) with sulfonyl chloride at 100°. They assumed that one of the chlorine atoms was attached at the 8-position while the other was at the 5- or 6-



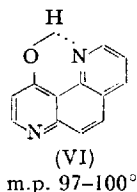
position. The 5-position in 6-hydroxy-1,7-diazaphenanthrene (V) is sufficiently activated that it can be halogenated⁶¹ to form 5-chloro-6-hydroxy-1,7-diazaphenanthrene and 6-hydroxy-5-iodo-1,7-diazaphenanthrene.

Skraup and Vortmann¹ in the original "phenanthroline" paper described a dibromide addition product, m.p. 149°, and an octabromide addition product, m.p. 176–8°, of 1,7-diazaphenanthrene.

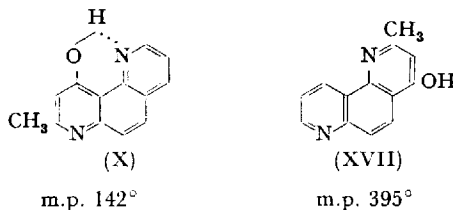
(h) Other Reactions. (1) *Benzilic Acid Rearrangement.* When 5,6-dioxo-1,7-diazaphenanthrene (XL) is treated with warm, dilute base, it undergoes a benzilic acid type of rearrangement and then loses the elements of a formate ion to form 9-oxo-1,5-diazafluorene.²¹



(2) *Chelation.* Kermack and Tebrich⁶⁹ attribute the low melting point of the monohydrate of 10-hydroxy-1,7-diazaphenanthrene (VI) to hydrogen bonding. Inspection of VI shows that this would require



partial bond fixation in one of the less stable of the five possible (Kekule) structures that contribute to the resonance hybrid. However, the melting points of the two isomeric compounds, 10-hydroxy-8-



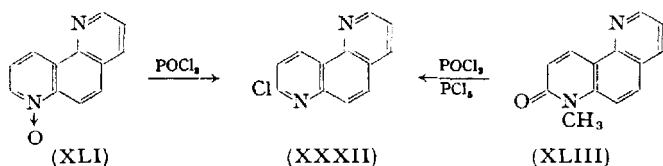
methyl-1,7-diazaphenanthrene (X) and 4-hydroxy-2-methyl-1,7-diazaphenanthrene (XVII), lend credence to the hydrogen bond structure.

(4) Reactions of Substituted 1,7-Diazaphenanthrenes

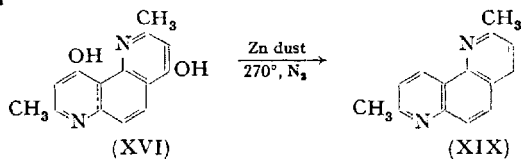
(a) Reactions of Oxo- and Hydroxy-1,7-diazaphenanthrenes.

(1) *Replacement of Oxo or Hydroxyl Groups by Halogen.* Hydroxyl groups in the 2-, 4-, 8-, and 10-positions can be replaced with chloro groups by the action of phosphorus pentachloride and phosphorus oxychloride at 120°. The following chloro-1,7-diazaphenanthrenes have been made by this useful reaction: 10-chloro-8-methyl-,⁷¹ 4-chloro-2-methyl-,⁷¹ 2-chloro-4-methyl-,⁷¹ 2-chloro-(XXXI),⁷¹ 8-chloro-(XXXII),⁷¹ and 4,10-dichloro-2,8-dimethyl-.⁷⁴

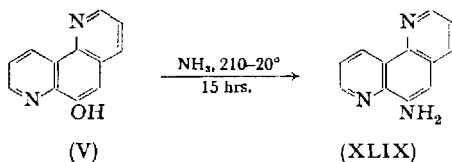
8-Chloro-1,7-diazaphenanthrene (XXXII) can be formed by the action of phosphorus oxychloride on either 1,7-diazaphenanthrene-7-oxide (XLI)⁶⁹ or 8-oxo-7-methyl-1,7-diazaphenanthrene (XLIII).^{35, 43, 71}



(2) *Replacement of Hydroxyl Groups by Hydrogen.* Hydroxyl groups can be reduced by heating with or distillation from zinc dust in an inert atmosphere.⁷⁴



(3) *Replacement of Hydroxyl Groups by Amino Groups.* 6-Amino-1,7-diazaphenanthrene (XLIX) was produced in 90% yield from the



6-hydroxy compound, V, but in only one-half that yield from the 6-bromo compound, VIII,⁸² by heating with ammonia.

(4) *Etherification*. Karrer and Pletscher³⁵ converted 8-hydroxy-1,7-diazaphenanthrene to its methyl ether with diazomethane, while a patent source⁴³ describes a method for the preparation of alkoxy and aryloxy diazaphenanthrenes based on treatment of the metaloxy derivatives with esters of alcohols and phenols.

(5) *Cleavage of Ethers*. Treatment of 8-methoxy-1,7-diazaphenanthrene with methyl iodide in an attempted quaternization resulted in cleavage to the hydroxy compound.³⁵

(b) Reactions of Carboxy-1,7-diazaphenanthrenes. (1) *Decarboxylation*. This is a useful procedure for the preparation of alkyl and aryl phenanthrolines from the products of Doebner, etc., cyclizations. The carboxy compounds can be decarboxylated by heat or by melting them with copper-bronze. See Table VI-2.

TABLE VI-2. Examples of Decarboxylation

Carboxy-1,7-diazaphenanthrene	Resulting 1,7-diazaphenanthrene
10-Carboxy-2,8-diphenyl- (XXII)	2,8-Diphenyl- ²⁷
10-Carboxy-9-benzyl-2,8-diphenyl- (XXIV)	9-Benzyl-2,8-diphenyl- ²⁷
8-Carboxy-	Parent base (I) ⁹¹
3,9-Dicarboxy-4,10-dihydroxy-2,8-diphenyl- (XXX)	4,10-Dihydroxy-2,8-diphenyl- ⁸⁸
4-Carboxy-2-phenyl- (XXI)	2-Phenyl- (XLIV) ⁷⁹

(2) *Esterification*. Willgerodt and von Neander⁷⁹ formed the methyl and ethyl esters of 4-carboxy-2-phenyl-1,7-diazaphenanthrene by treatment of the silver salt of the acid with the corresponding alkyl iodides.

(3) *Hofmann Degradation*. 6-Carboxy-1,7-diazaphenanthrene has been converted to 6-amino-1,7-diazaphenanthrene (XLIX) by means of amide formation followed by the Hofmann degradation.⁶⁶

(c) Reactions of Halo-1,7-diazaphenanthrenes. (1) *Replacement of Halogen by Amino or Substituted Amino Groups*. Compounds with halogen in the 2-, 4-, 6-, 8-, or 10-positions of 1,7-diazaphenanthrenes

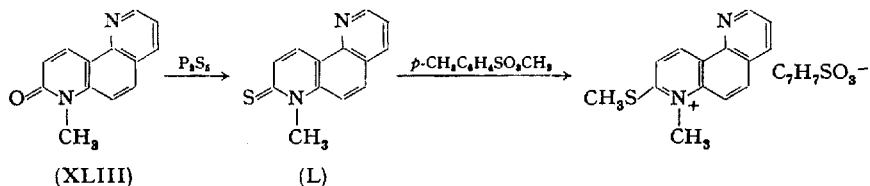
have been converted to the corresponding substituted amino derivatives by exchange reactions.^{66, 67, 71, 82} Such compounds have been made primarily for pharmaceutical testing.

(2) *Replacement of Halogen by Alkoxy or Aryloxy Groups.* Certain halo-1,7-diazaphenanthrenes are readily converted to ethers by treatment with metal alkoxides^{35, 43} or phenoxides,⁴³ or by reaction with alcohols or phenols in the presence of an acid binder.⁴³

(3) *Halogen Exchange.* 8-Iodo-1,7-diazaphenanthrene ethiodide has been prepared from 8-chloro-1,7-diazaphenanthrene by heating the latter with ethyl iodide in a sealed tube at 160°.⁸⁷

(d) **Reactions of Amino-1,7-diazaphenanthrenes.** 6-Amino-1,7-diazaphenanthrenes appear to have all the properties of normal aromatic primary amines. They can be acylated with acid chlorides and anhydrides^{66, 82} or with esters.⁹² Willgerodt and von Neander⁷⁹ prepared 6-amino-1,7-diazaphenanthrenes by reduction of the corresponding 6-nitro compounds with stannous chloride. They then diazotized the amines, and converted the diazonium compounds to the chloro, bromo, and hydroxy derivatives.

(e) **Other Reactions.** When 8-oxo-7-methyl-1,7-diazaphenanthrene (XLIII) is treated with phosphorus pentasulfide, 7-methyl-8-thiono-1,7-diazaphenanthrene (L) is formed. This in turn is converted to 8-methylmercapto-1,7-diazaphenanthrene metho-*p*-toluenesulfonate by the action of methyl *p*-toluenesulfonate.^{87, 88} These compounds and



several others of a very specialized nature have been described sketchily in patent literature.⁸⁷⁻⁸⁹ Reaction scheme VI-2 illustrates the procedures (pp. 428-429).

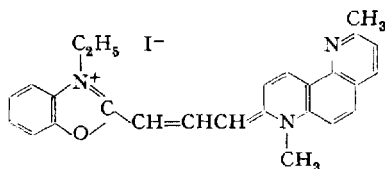
(5) Uses

(a) **Therapeutic.** The 1,7-diazaphenanthrenes have been widely tested as chemotherapeutic agents, and have been so effective that several patents have been granted in the field.

The 6-dialkylaminoalkylamino derivatives have been tested as antimalarials.⁶⁵ The 5- and 6-amino and acylamino compounds are patented for their anodyne, bactericidal, and therapeutic value,^{63a,66} and have been tested as trypanocidal agents.⁸² The salts of the partially reduced 1,7-diazaphenanthrenes, XXXVI and XXXVII, show activity as antibiotics and cause somnolence in mice.^{34,35} Salts of the aryl-1,7-diazaphenanthrene-4,10-dicarboxylic acids, XXV to XXVIII, are useful as atophans.⁸¹ The 5-halo-6-hydroxy compounds have been tested as amebicides.⁶¹

1,7-Diazaphenanthrene-1,7-dioxide (XLII) has been patented as a therapeutic agent.⁹⁰

(b) Photosensitization. Three patents⁸⁷⁻⁸⁹ have been issued covering the use of the compounds in Section B4a as intermediates in the preparation of useful cyanine dyes. For instance, the methiodide of 2,8-dimethyl-1,7-diazaphenanthrene is boiled in alcohol with triethylamine until all is in solution. Then 2- β -acetylanilinovinylbenzoxazole ethiodide is added and refluxing is continued. The cooled solution yields (2,7-dimethyl-1,7-phenanthroline-8)-(3-ethylbenzoxazole-2)-trimethine cyanine iodide:

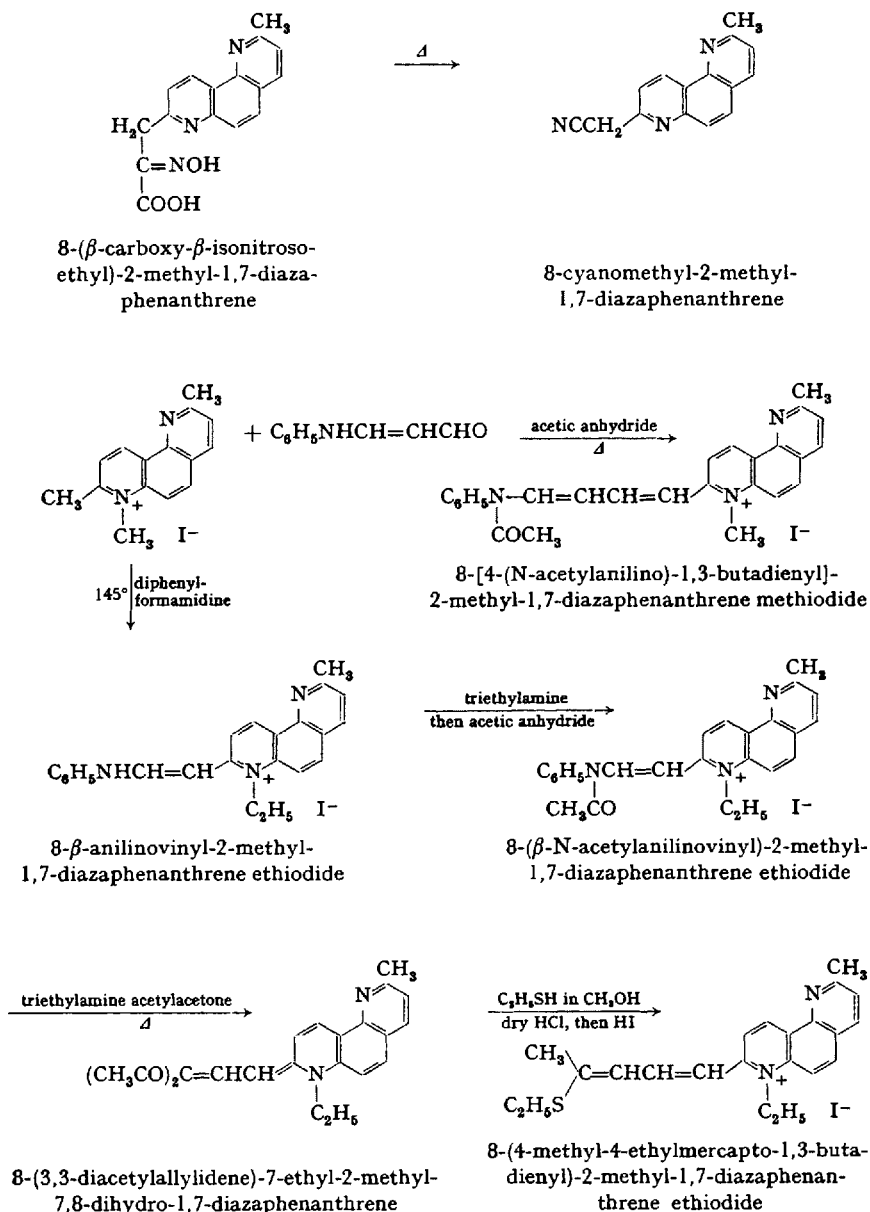


(6) Compounds Incorrectly Formulated as 1,7-Diazaphenanthrenes

Doebner and Ferber¹²³ obtained a red product (melting at 235°) by the reaction of *m*-phenylenediamine, benzaldehyde, and pyruvic acid in boiling alcohol. They formulated this product as 4,10-dicarboxy-2,8-diphenyl-1,7-diazaphenanthrene (LI). Bodforss,¹²⁴ by treating cinnamoylformic acid with *m*-phenylenediamine, proved that the structure is really LII, since the product (melting at 230–5°) is cleaved by phenylhydrazine to give the phenylhydrazone of cinnamoylformic acid.

Schiff and Vanni⁷⁵ formulated the reaction product of heptaldehyde and *m*-phenylenediamine as being a Schiff base that isomerized to

Reaction Scheme VI-2



(continued)

Reaction Scheme VI-2 (continued)

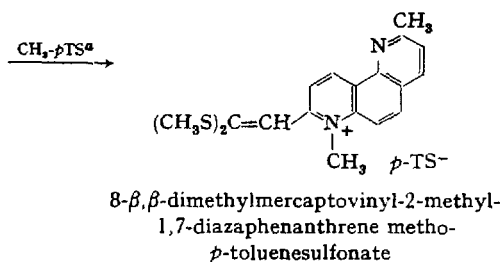
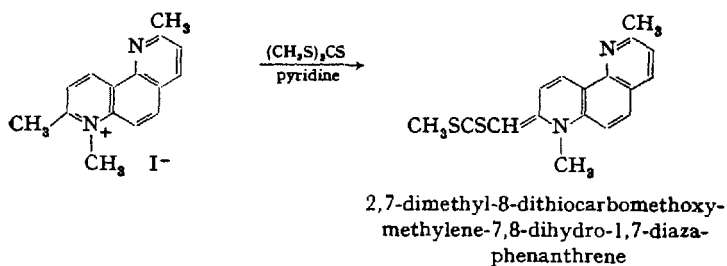
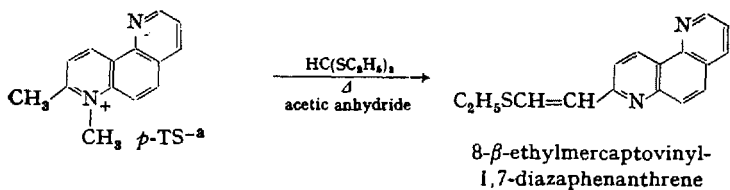
^a*p*-Toluenesulfonate radical.

TABLE VI-3. 1,7-Diazaphenanthrenes

Formula	1,7-Diazaphenanthrenes	M.p., °C.	Refs.
I	1,7-Diazaphenanthrene	79	1, 6, 11, 24, 54, 55, 72, 83, 86, 87
XXXV		2H ₂ O 66 ^c 7-MeI ^a HNO ₃ 243-5 P 238-40	1, 11 1 86 1
XIV	2-Methyl-	64-5 3 H ₂ O P 216-17 ^a MeI · 2H ₂ O 100-10	3 3 3 3
III	6-Methyl-	95-6 P 253	57, 68 57
IX	8(?) -Methyl-		70
XV	2,4-Dimethyl-	106-7	73
XIX	2,8-Dimethyl-	97-8, 98, 100 2H ₂ O 76 MeI 248 EtI 238-9	74, 76, 78, 87 78, 83 87, 89 87, 89
XVIII	3,9-Di- <i>n</i> -amyl-2,8-di- <i>n</i> -hexyl-	50-1	76
XLIV	2-Phenyl-	129	79
	8-Methyl-2-phenyl-		87
		EtI	87
	2,8-Diphenyl-	164 ^a	27
	9-Benzyl-2,8-diphenyl-	177	27
XXXVII	7-Methyl-7,8,9,10-tetrahydro-	b. 135/0.05 mm.	34
XXXIII	2,8-Dimethyl-1,2,3,4,7,8,9,10-octahydro-		76, 78
XXXIV	7-Benzoyl-2,8-dimethyl-1,2,3,4,7,8,9,10-octahydro-	167-8	76, 78
XXXI	2-Chloro-	160	71
VII	6-Chloro-	121, 124.5, 125	13, 24, 63, 64, 66a
XXXII	8-Chloro-	147-8, 148-9, 150, 151, 151-2	35, 43, 69, 71, 87
VIII	6-Bromo-	109-10, 110, 113	13, 63, 64, 66, 66a, 82
		HCl 268-74	82
	8-Iodo-	EtI	87, 88
	6,8(?) -Dichloro-	174-8	69
	4,10-Dichloro-	168	74

(Table continued)

TABLE VI-3 (*continued*)

Formula	1,7-Diazaphenanthrenes	M.p., °C.	Refs.
IV	2-Chloro-4-methyl-	161	71
	4-Chloro-2-methyl-	190	71
	10-Chloro-8-methyl-	140	71
	?-Tribromo-	270	13
	5-Nitro-	168	58, 59, 66
XLVII	(6?)-Nitro-	155 ^a	21
	6-Nitro-2-phenyl-		79
XLV	6-Sulfo-2-phenyl-	250 (dec.)	79
	5-Amino-	200, 201	60, 63a, 66, 67, 67a
XLIX	6-Amino-	143	60, 63a, 66, 67, 67a, 82, 92
		HCl 295	82
		P 235	82
	6-Amino-2-phenyl-	232	79
XI	6-Methylamino-	74	63a
	6-Ethylamino-	79	63a, 67
	6-Diethylamino-	64	63a, 65, 67
	6-(2-Diethylaminoethylamino)-	oil	63a, 65, 67
	8-(2-Diethylaminoethylamino)-	2P 223-4	71
	2-(2-Diethylaminoethylamino)-4-methyl-	2HBr 281-3	71
	4-(2-Diethylaminoethylamino)-2-methyl-	3HBr 284-5	71
	10-(2-Diethylaminoethylamino)-8-methyl-	2P 237	71
	8-(4-Diethylamino-1-methylbutylamino)-	2P 195	71
	2-(4-Diethylamino-1-methylbutylamino)-4-methyl-	P 260	71
	4-(4-Diethylamino-1-methylbutylamino)-2-methyl-	3P 130	71
	10-(4-Diethylamino-1-methylbutylamino)-8-methyl-	2P 195	71
	6-(3-Diethylaminopropylamino)-	oil	63a, 67
	6-Acetamido-	197-8, 201	63, 63a, 66, 82
		P 237	82
		MeCl · HCl · H ₂ O	82
		280 (dec.)	
	6-Acetylacetamido-	148	92
	6-Benzamido-	170	63a, 67

(*Table continued*)

TABLE VI-3 (continued)

Formula	1,7-Diazaphenanthrenes	M.p., °C.	Refs.
	6-Benzoylacetamido-	129	92
	8- β -Anilino vinyl-2-methyl	EtI	87
	8- β -N-Acetylanilino vinyl-	EtI	87
	8- β -N-Acetylanilino vinyl-2-methyl-	EtI 225-7	87
	8-[4-(N-Acetylanilino)-1,3-buta- dienyl]-2-methyl-	MeI	87
		EtI	87
XII	2-Hydroxy-	292-3	71
	6-Hydroxy-	157, 157-8, ^b 158-9, 160-1	21, 61, 62, 82, 84
		P 237 ^{a, b}	61, 84
		H ₂ SO ₄ 273 ^{a, b}	61, 84
		2 HCl 315 (dec.)	82
V	6-Hydroxy- (assumed to be 8-hydr- oxy in original article)	159-60 ^b	56
II	8-Hydroxy-	302-4, 315 290 after sublimation	35, 71
XXXVI		7-MeI	35
VI	10-Hydroxy-	97-100 H ₂ O 107-8	69 69
XIII	2-Hydroxy-4-methyl-	318	71
XVII	4-Hydroxy-2-methyl-	> 345, 395 darkens, 300 sub.	26, 71
X	10-Hydroxy-8-methyl-	142	71
XVI	4,10-Dihydroxy-2,8-dimethyl-	330 (dec.)	74
	4,10-Dihydroxy-2,8-diphenyl-	> 300	85
XXXVIII	8-Hydroxy-7-methyl-1,2,3,4-tetra- hydro-	305-8 ^a	35
XXXIX	6-Methoxy-	99 ^c	21
	8-Methoxy-	98-9 MeI 225-33	35 35
	8-Phenoxy-	121	43
	6-Hydroxy-5-chloro-	253-5 HCl 147-9	61 61
	6-Hydroxy-5-iodo-	217-19	61
	6-Carboxy-	277	57, 66
	8-Carboxy-		91
		H ₂ O 208-9	71
	6-Carbamyl-		66

(Table continued)

TABLE VI-3 (*continued*)

Formula	1,7-Diazaphenanthrenes	M.p., °C.	Refs.
XX	4-Carboxy-2-methyl-	309-10	79
	4-Carboxy-2-phenyl-	353-5	79
XXI	4-Carbethoxy-2-phenyl-	116	79
	4-Carbomethoxy-2-phenyl-	158	79
		MeI 262	79
	4-Carboxy-8-methyl-2-phenyl-	EtHSO ₄	87
XXII	10-Carboxy-2,8-diphenyl-	268	27
XXIV	10-Carboxy-9-benzyl-2,8-diphenyl-	273 (dec.)	27
XXIII	10-Carboxy-2,8,9-triphenyl-	275 (dec.)	27
	4-Carboxy-6-chloro-2-phenyl-	278	79
	4-Carboxy-6-bromo-2-phenyl-	286-9	79
XLVIII	4-Carboxy-6-nitro-2-phenyl-	285	79
XLVI	4-Carboxy-2-phenyl-6-sulfo-	310 (dec.)	79
	6-Carboxymethylamino-	244	63a, 65, 66
	4-Carboxy-6-amino-2-phenyl-	302-3	79
XXVIII	4,10-Dicarboxy-2,8-bis(<i>p</i> -dimethyl-aminophenyl)-	234	81
	4-Carboxy-6-hydroxy-2-phenyl-	293	79
	3,9-Dicarboxy-4,10-dihydroxy-2,8-diphenyl-		85
XXX	3,9-Dicarbethoxy-4,10-dihydroxy-2,8-diphenyl-	264	85
XXVI	4,10-Dicarboxy-2,8-di- <i>p</i> -anisyl-	205-6	81
XXV	4,10-Dicarboxy-2,8-bis(3,4-dimethoxy-phenyl)-	191	80
XXVII	4,10-Dicarboxy-2,8-bis(3,4-methylene-dioxyphenyl)-	210	81
XL	5,6-Dioxo-	255	21
		= NOH 255 (dec.)	21
XLIII	8-Oxo-7-methyl-	194, 195, 198-9 ^a	35,43, 71, 87
	8-Oxo-7-ethyl-		87
XXIX	2,8-Dioxo-1,2,3,4,7,8,9,10-octahydro->	365	29
	8-(3,3-Diacetylallylidene)-7-ethyl-2-methyl-7,8-dihydro-	222-3	87
	8-Methylmercapto-	Me- <i>p</i> -TS	87, 88
	8-Cyanomethyl-2-methyl-		87
	8-(β -Isonitroso- β -carboxyethyl)-2-methyl-		87
	7-Methyl-8-thiono-	204	87
	7-Ethyl-8-thiono-	268	87
	8- β -Ethylmercaptovinyl-	MeI 228	87

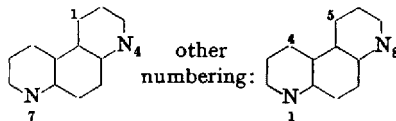
(*Table continued*)

TABLE VI-3 (*continued*)

Formula	1,7-Diazaphenanthrenes	M.p., °C.	Refs.
	8- β , β -Dimethylmercaptovinyl-2-methyl-	Me- <i>p</i> -TS	89
	8- β -Ethylmercapto- β -methylmercaptovinyl-	Me- <i>p</i> -TS	89
	8-(4-methyl-4-ethylmercapto-1,3-butadienyl)-2-methyl-	EtI 240	87
	2,7-Dimethyl-8-dithiocarbomethoxy-methylene-7,8-dihydro-	220-1	89
	7-Methyl-8-dithiocarbomethoxy-methylene-7,8-dihydro-	207	89
	7-Ethyl-8-dithiocarbomethoxy-methylene-7,8-dihydro-	193	89
XLI	1,7-Diazaphenanthrene-7-oxide	188 2 HCl 229	69
XLII	1,7-Diazaphenanthrene-1,7-dioxide	192 ^a	36, 69, 90

^a Yellow. ^b Needles from alcohol. ^c Plates.

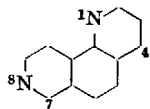
- C. 4,7-Diazaphenanthrene^a or *para*-Phenanthroline. 4,7-Phenanthroline. 1,8-Phenanthroline. Pseudophenanthroline. Dipyrindino-2',3': 1,2; 3'',-2'': 3,4-benzene. 5,6: 3',2'-Pyridoquinoline. 6,5: 2',3'-Pyridoquinoline. Quino-*p*- α -quinoline. 4,7-Naphth-isodiazine. R.I. 1956



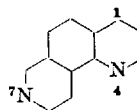
(I) History and Nomenclature

4,7-Diazaphenanthrene was first synthesized in 1883 by Skraup and Vortmann,⁹⁴ who called it "pseudophenanthroline". It was not

^a "1,8-Phenanthroline"¹² and "4,7-diazaphenanthrene"²⁷ have both been used to designate ring systems other than *para*-phenanthroline:



"1,8-phenanthroline"



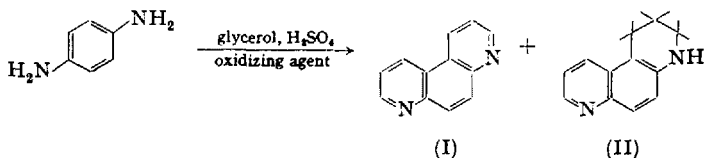
"4,7-diazaphenanthrene"

The reader is cautioned not to confuse these compounds with the 4,7-diazaphenanthrenes described herein. In this series the compounds illustrated in this footnote will be called 1,8-diazaphenanthrene and 3,10-diazaphenanthrene, respectively.

called *para*-phenanthroline until 1909,² but that name is still used generally to designate the parent base. *Chemical Abstracts* has always used the 4,7-phenanthroline nomenclature; the 1,8-numbering is widely used in most foreign journals and in Beilstein.

(2) Preparation (Ring Closures)

(a) Skraup-Type Reactions. (1) *Glycerol on *p*-Phenylenediamine (or Its Nitro Analogs)*. Skraup and Vortmann⁹⁴ first prepared 4,7-diazaphenanthrene from the tin double salts of *p*-phenylenediamine, which they obtained by the reduction of *p*-nitroaniline, while three years later Bornemann⁹⁵ used *p*-phenylenediamine itself in a successful preparation. Both methods are still used.

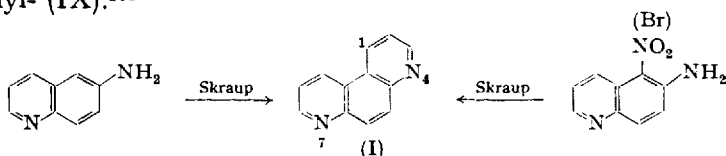


Even though Kaufmann and Radosevic² stated that only low yields are obtainable from *p*-phenylenediamine, Smith⁶ was able to increase the yield to 60%. Haskelberg⁹⁶ improved the yield from *p*-nitroaniline to 46%. Patents cover the synthesis, both for unsubstituted⁹⁷ and substituted 4,7-diazaphenanthrenes.¹³

Wibaut and co-workers⁹⁸ found 1,2,3,4-tetrahydro-4,7-diazaphenanthrene (II) as a by-product in the synthesis utilizing *p*-phenylenediamine. If the *p*-phenylenediamine bears strongly electronegative substituents, such as nitro or sulfo groups, the cyclization fails.⁹² However, 2-bromo-*p*-phenylenediamine yields 5-bromo-4,7-diazaphenanthrene.¹³

(2) *Glycerol on 6-Aminoquinolines*. Kaufmann and Radosevic² first applied the Skraup synthesis to 6-aminoquinolines to form 4,7-diazaphenanthrene. They claimed a quantitative yield. The reaction has been patented,^{13,97} and has been used to synthesize the following 4,7-diazaphenanthrenes: 1-hydroxy- (III),^{99,101} 3-hydroxy- (IV),¹⁰⁰ 3-hydroxy-1-methyl- (V),^{101,102} 1-hydroxy-3-methyl- (VI),¹⁰¹ 5-bromo- (VII),^{13,92}

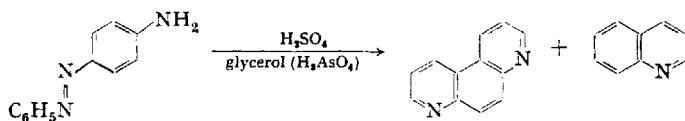
3-oxo-4-methyl- (VIII),¹⁰⁰ and 1-(2-diethylaminoethylamino)-3-methyl- (IX).¹⁰³



Huisgen¹⁰² observed that a nitro group or a bromine atom in the 5-position of 6-aminoquinoline does not prevent a Skraup cyclization at that position. Thus, he obtained 1,7-diazaphenanthrene in 65 % yield from 6-amino-5-bromoquinoline.

(3) *Glycerol on 6-Nitroquinoline.* Kuczynski and Sucharda²⁴ obtained 4,7-diazaphenanthrene (I) by heating 6-nitroquinoline, glycerol, and hydrochloric acid in a sealed tube at 165° (see Section A2a).

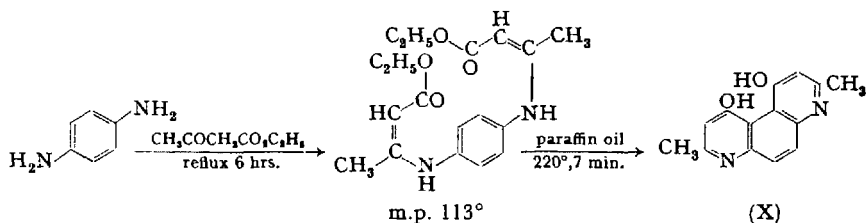
(4) *Glycerol on Azo Compounds or Aminophenols.* Lellman and Lippert¹⁰⁴ obtained 4,7-diazaphenanthrene by treating 4-aminoazobenzene with glycerol and sulfuric acid. This was later repeated by



Matsumura⁸⁴ using arsenic acid. From 10 grams of 4-aminoazobenzene he obtained 7.7 grams of I and 2.5 grams of quinoline. This encouraging yield led him to suggest the use of azo compounds in Skraup reactions in place of unstable amino analogs. 4,7-Diazaphenanthrene was also obtained by Skraup reactions on 4-phenylazoresorcinol and its dimethyl ether, on 4-aminoresorcinol dimethyl ether,¹⁰⁵ and on 4-*p*-nitrophenylazo-1-naphthol. The mechanisms involved in these surprising reactions have not been elucidated, but Matsumura⁸⁴ has suggested some possibilities.

(b) Conrad-Limpach Reactions. Jacini and co-workers^{106, 107} first applied the Conrad-Limpach reaction to phenylenediamines to obtain diazaphenanthrenes. A German patent¹⁰⁸ on the reaction appeared at about the same time (see reference 121). The yield of purified (extracted with base, isolated as dihydrochloride, and reconverted to free base)

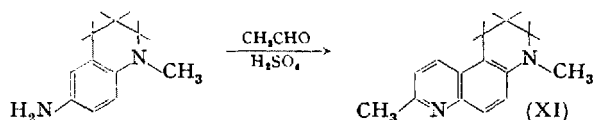
1,10-dihydroxy-3,8-dimethyl-4,7-diazaphenanthrene (X) is 37%. The second paper¹⁰⁷ reported a sodium carbonate extraction that increased the yield to 50–5%. Jacini¹⁰⁸ also synthesized X by a stepwise reaction



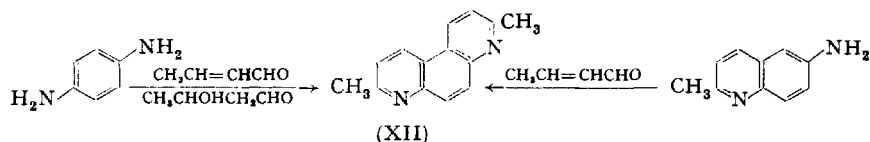
starting with *p*-aminoacetanilide, and isolated all the intermediates to confirm the reaction mechanism. Patents⁴³ cover the application of the reaction to the preparation of hydroxydiazaphenanthrenes such as 10-hydroxy-4,8-dimethyl-1,2,3,4-tetrahydro-4,7-diazaphenanthrene from 6-amino-1-methyl-1,2,3,4-tetrahydroquinoline, and 1-hydroxy-6-methyl-4,7-diazaphenanthrene (VI) from 6-aminoquinoline.

(c) **Knorr Synthesis** (see Section A2b). Kermack and Weatherhead¹⁰¹ obtained 3-hydroxy-1-methyl-4,7-diazaphenanthrene (V) by heating 6-aminoquinoline and ethyl acetoacetate. It was identical with the product obtained by the Skraup reaction on 6-amino-2-hydroxy-4-methylquinoline. Haskellberg¹⁰⁹ also prepared V by the Knorr synthesis.

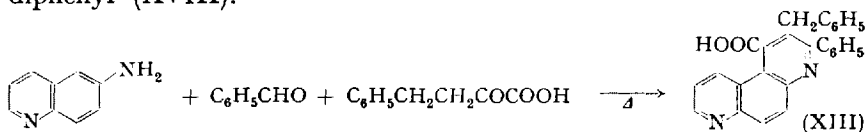
(d) **Doebner-Miller Synthesis.** Linder¹¹⁰ first applied the Doebner-Miller synthesis to the 1,7-diazaphenanthrenes. He treated 6-amino-kairolin with acetaldehyde and sulfuric acid to obtain 4,8-dimethyl-1,2,3,4-tetrahydro-4,7-diazaphenanthrene (XI).



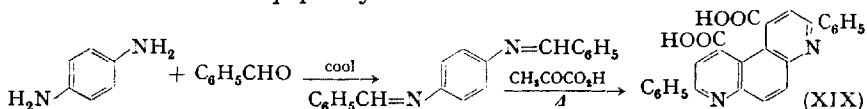
3,8-Dimethyl-4,7-diazaphenanthrene (XII) was prepared from both *p*-phenylenediamine¹¹¹ and 6-aminoquinoline.¹¹²



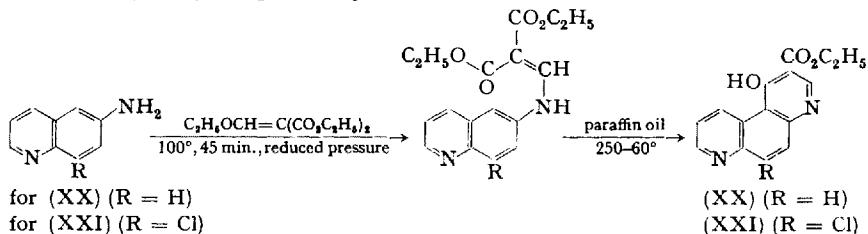
(e) **Doebner's Pyruvic Acid Synthesis.** Willgerodt and Jablonski¹¹³ pioneered the use of Doebner's pyruvic acid synthesis in the 4,7-diazaphenanthrene field. Forty years later Borsche and Wagner-Roemmick²⁷ again used the reaction on 6-aminoquinolines to produce other monocarboxy-4,7-diazaphenanthrenes, such as 2-benzyl-1-carboxy-3-phenyl-4,7-diazaphenanthrene (XIII). Other carboxy-4,7-diazaphenanthrenes prepared by this method are: 1-carboxy-3-phenyl- (XIV),¹¹³ 1-carboxy-3-methyl- (XV),¹¹³ 6-bromo-1-carboxy-3-phenyl- (XVI),¹¹³ 1-carboxy-3-methyl-2-phenyl- (XVII),²⁷ and 1-carboxy-2,3-diphenyl- (XVIII).²⁷



Woodruff and Adams¹¹⁴ made 1,10-dicarboxy-3,8-diphenyl-4,7-diazaphenanthrene (XIX) by the reaction of pyruvic acid with the double Schiff base of *p*-phenylenediamine.

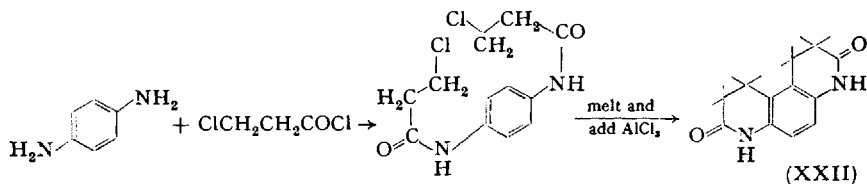


(f) **Price-Roberts Reaction.** Douglas and Kermack¹¹⁵ treated 6-aminoquinoline and 6-amino-8-chloroquinoline with ethoxymethyl-enamalononic ester to obtain 2-carbethoxy-1-hydroxy-4,7-diazaphenanthrene (XX) and 2-carbethoxy-6-chloro-1-hydroxy-4,7-diazaphenanthrene (XXI), respectively.



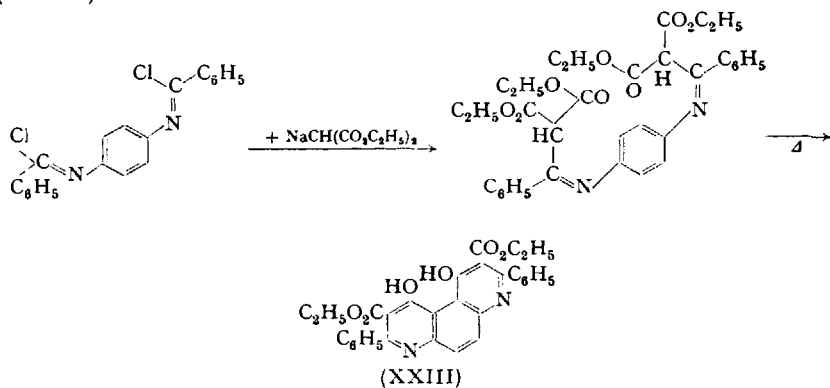
By a double Price-Roberts reaction on *p*-phenylenediamine, the same authors were able to synthesize 2,9-dicarbethoxy-1,10-dihydroxy-4,7-diazaphenanthrene.

(g) **From β -Chloropropionyl Chloride.** By the cyclization of 1,4-bis(β -chloropropionamido)benzene Mayer, van Zütphen, and Philipps²⁹ were able to prepare a hydrocarbostyryl analog of *p*-phenanthroline, *i.e.*, 3,8-dioxo-1,2,3,4,7,8,9,10-octahydro-4,7-diazaphenanthrene (XXII). XXII was converted to 1,2,3,4,7,8,9,10-octahydro-4,7-diaza-



phenanthrene in 90% yield by reduction with lithium aluminum hydride.^{115a}

(h) **Other Methods.** Rao and Wheeler⁸⁵ cyclized *N,N'*-bis(α -dicarbethoxymethylbenzylidene)-*p*-phenylenediamine to form 2,9-dicarbethoxy-1,10-dihydroxy-3,8-diphenyl-4,7-diazaphenanthrene (XXIII).



1-Hydroxy-4,7-diazaphenanthrene (III) has been prepared⁸⁹ from 6-aminoquinoline and ethyl oxalacetate.

(3) Reactions of 4,7-Diazaphenanthrenes

(a) **Salt Formation and Hydration.** The 4,7-diazaphenanthrenes generally behave as diacid bases.^{2, 94, 105, 116} However, Skraup and Vortmann in the original "pseudophenanthroline" article⁹⁴ formed the

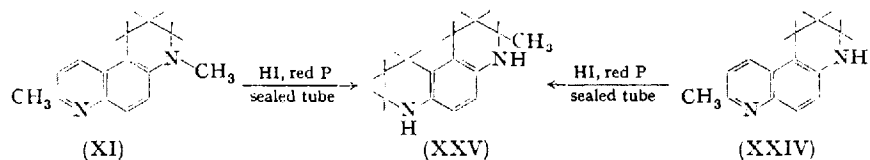
monohydrochloride of the parent base by using only one equivalent of acid. Both mono- and dipicrates have been formed.² Both the bases and the salts tend to form hydrates (see Table VI-4). The parent base crystallizes from water with three or four molecules of water of hydration,^{2,94} but tends to lose them easily.

(b) Quaternization. According to Skraup and Vortmann⁹⁴ 4,7-diazaphenanthrene forms a mixture of the monomethiodide and the dimethiodide when refluxed with three equivalents of methyl iodide in alcohol. Later, Kaufmann and Radosevic² stated that the monomethiodide can be prepared in pure form by mixing equimolar amounts of the reactants in dilute alcohol and letting the mixture stand for a long time, while the dimethiodide is prepared by heating the base in methyl sulfate at 140° and converting the product to the iodide with potassium iodide. A more modern reference¹⁰⁰ offers a better preparation of the monomethiodide: refluxing the base in a large excess of methyl iodide and nitrobenzene on a water bath for two hours; the monomethiodide precipitates from the hot reaction mixture.

The bifunctional nature of 4,7-diazaphenanthrene indicates that the two nitrogens are relatively free from steric hindrance and that they function independently of one another to an appreciable degree. The quaternization reaction is very useful in that it renders the 4,7-diazaphenanthrene nucleus vulnerable to oxidation, reduction, and even nitration (see Sections A3c and d).

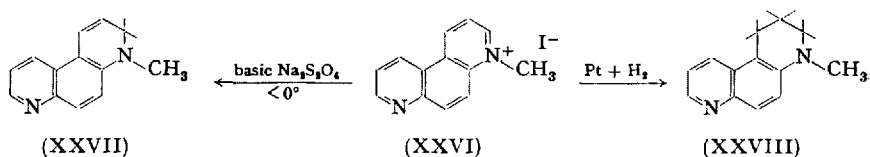
(c) Reduction. Matsumura¹¹⁷ attempted to reduce 4,7-diazaphenanthrene (I) to the octahydro derivative by means of sodium in boiling amyl alcohol, and with tin and hydrochloric acid. He isolated only 1,2,3,4-tetrahydro-4,7-diazaphenanthrene (II) in both reactions.

Using hydrogen iodide and red phosphorus in a sealed tube, Linder¹¹⁰ was able to reduce both 4,8-dimethyl-1,2,3,4-tetrahydro-4,7-diazaphenanthrene (XI) and 8-methyl-1,2,3,4-tetrahydro-4,7-diaza-



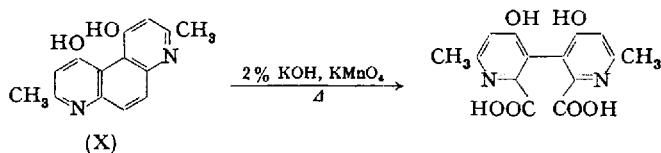
phenanthrene (XXIV) to 3-methyl-1,2,3,4,7,8,9,10-octahydro-4,7-diazaphenanthrene (XXV).

Karrer and co-workers^{34, 35} studied the reduction of the quaternized bases. 4,7-Diazaphenanthrene methiodide (XXVI) was reduced to 4-methyl-3,4-dihydro-4,7-diazaphenanthrene (XXVII) and to the tetrahydro derivative, XXVIII, as shown. The methiodide of XXVIII



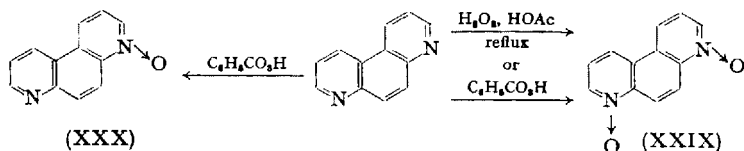
was not reduced further by sodium hydrosulfite, while the dimethiodide of the parent base (I) gave a semiquinoid compound or mixture. 3-Methoxy-4,7-diazaphenanthrene methiodide, when reduced catalytically over platinum, produced a mixture of compounds as a result of hydrolysis of the ether linkage.³⁵

(d) Oxidation. Skraup and Vortmann⁹⁴ first oxidized “pseudo-phenanthroline” to 2,2′-dicarboxy-3,3′-bipyridine by means of alkaline permanganate. Later the reaction was repeated by Smith,⁶ Kaufmann,² and Matsumura,¹⁰⁵ while others applied the oxidation to substituted 4,7-diazaphenanthrenes. Thus, 1,10-dihydroxy-3,8-dimethyl-4,7-diazaphenanthrene (X) is oxidized to 2,2′-dicarboxy-4,4′-dihydroxy-6,6′-dimethyl-3,3′-bipyridine, a compound useful in the study of restricted rotation of bipyridines.

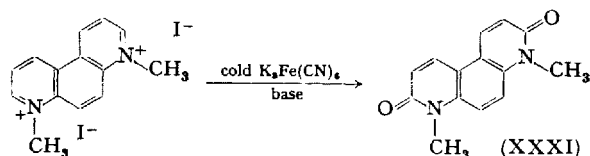


The parent base is not oxidized by selenium dioxide, vanadium pentoxide, or the iodic acids.³⁶ However, hydrogen peroxide in boiling acetic acid serves to oxidize the “phenanthrolines” to *N*-oxides^{36, 90, 100}; in this case 4,7-diazaphenanthrene-4,7-dioxide (XXIX) is formed.

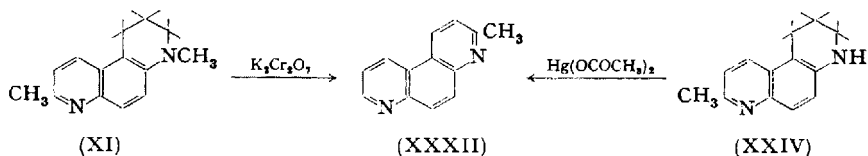
Douglas,¹⁰⁰ using perbenzoic acid as the oxidizing agent, could produce either the di-(XXIX) or the mono-*N*-oxide (XXX).



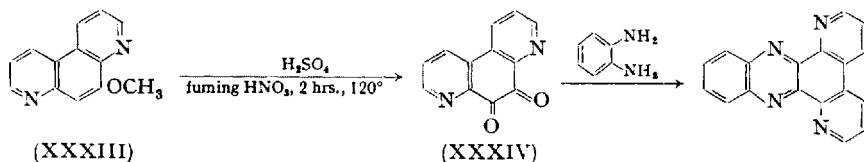
The very useful method of obtaining compounds with chlorine substituents in the 3- or 8-positions (see Section C4a1) was made possible by the discovery of Kaufmann and Radosevic² that the methiodide of 4,7-diazaphenanthrene, XXVI, can be oxidized to 3-oxo-4-methyl-4,7-diazaphenanthrene (VIII); or, if the dimethiodide is used, it in turn can be oxidized to 3,8-dioxo-4,7-dimethyl-4,7-diazaphenanthrene (XXXI) (see references 35, 43, and 100).



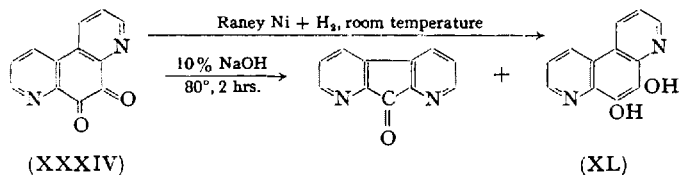
Linder¹¹⁰ was able to aromatize completely the tetrahydro-4,7-diazaphenanthrenes (XI and XXIV) by using powerful oxidizing agents, and thus to obtain in small yield 3-methyl-4,7-diazaphenanthrene (XXXII).



5-Methoxy-4,7-diazaphenanthrene (XXXIII) can be oxidized to 5,6-dioxo-4,7-diazaphenanthrene (XXXIV),²¹ but the parent base has never been oxidized to the quinone. The structure XXXIV,³⁴ was proved by conversion to 1,8,9,14-tetraza-(1,2,3,4)-dibenzanthracene.



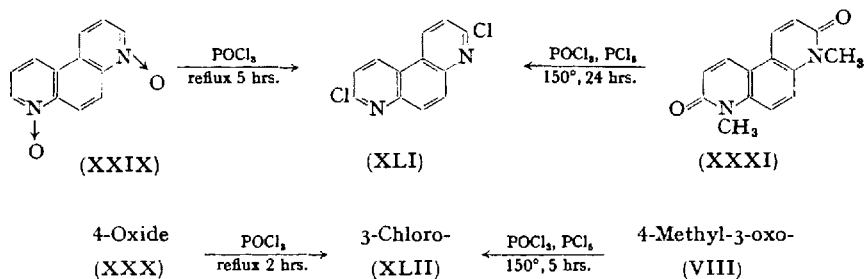
(f) **Benzilic Acid Rearrangement.** When XXXIV is treated with base, it rearranges to 9-oxo-1,8-diazafluorene and forms 5,6-dihydroxy-4,7-diazaphenanthrene (XL) as a by-product. The latter can also be formed by catalytic reduction of XXXIV.



(4) Reactions of Substituted 4,7-Diazaphenanthrenes

(a) Reactions of Oxo- and Hydroxy-4,7-diazaphenanthrenes.

(1) *Replacement of Oxo or Hydroxyl by Halogen.* Compounds bearing chlorine atoms in the 3- and/or 8-positions can be obtained from the *N*-oxides¹⁰⁰ or from the *N*-methyl- α -oxo^{43, 100} derivatives.



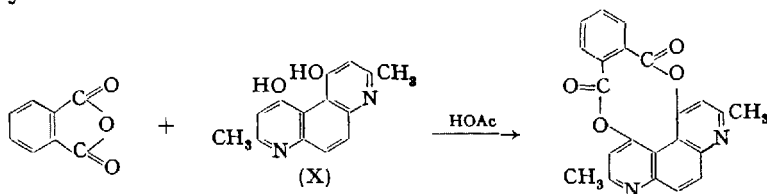
The following chloro-4,7-diazaphenanthrenes have been prepared from the corresponding hydroxy compounds by the action of refluxing phosphorus oxychloride and pentachloride: 3-chloro- (XLII),¹⁰⁰ 1-chloro- (XLIII),¹¹⁵ 1,6-dichloro- (XLIV),¹¹⁵ 1,10-dichloro-3,8-dimethyl- (XLV),^{43, 118} and 1,10-dichloro- (XLVI).¹¹⁵

(2) *Replacement of Hydroxyl Groups by Hydrogen.* Kermack and Weatherhead¹⁰¹ obtained 4,7-diazaphenanthrene by a zinc dust distillation of 1-hydroxy-4,7-diazaphenanthrene (III).



(3) *Etherification.* 1,10-Dihydroxy-4,7-diazaphenanthrenes are converted by methyl sulfate to the 10-hydroxy-1-methoxy derivatives,⁴³ or to the 1,10-dimethoxy derivatives if sodium hydroxide is added.¹⁰⁶ Active alkyl halides, such as benzyl chloride and allyl chloride, in the presence of bases also form the mono ethers of 1,10-dihydroxy-4,7-diazaphenanthrenes.

(4) *Esterification.* 1,10-Dihydroxy-3,8-dimethyl-4,7-diazaphenanthrene forms an interesting cyclic ester when treated with phthalic anhydride in acetic acid.¹⁰⁶

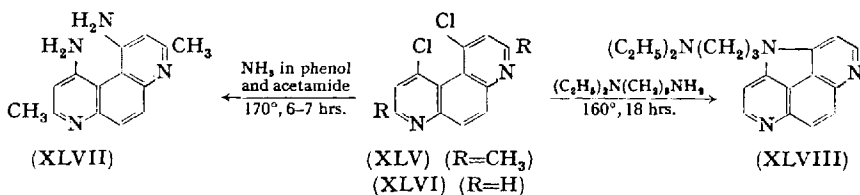


(b) **Reactions of Carboxy-4,7-diazaphenanthrenes.** (1) *Decarboxylation.* Several of the common types of decarboxylations have been applied to *p*-phenanthrolines. In the older literature¹¹³ distillation from soda-lime was used, while the more recent syntheses have employed high temperatures with copper-bronze²⁷ or with quinoline and copper-barium chromite.¹¹⁵ The following carboxy-4,7-diazaphenanthrenes have been decarboxylated: 1-carboxy-3-phenyl- (XIV),¹¹³ 1-carboxy-3-methyl- (XV),¹¹³ 1-carboxy-3-methyl-2-phenyl- (XVII),²⁷ 1-carboxy-2,3-diphenyl- (XVIII),²⁷ 2-benzyl-1-carboxy-3-phenyl- (XIII),²⁷ 1,10-dicarboxy-3,8-diphenyl- (XIX),⁸⁶ 2-carboxy-1-hydroxy-,¹¹⁵ 2-carboxy-6-chloro-1-hydroxy-,¹¹⁵ and 2,9-dicarboxy-1,10-dihydroxy-.¹¹⁵

(2) *Esterification.* Willgerodt and Jablonski¹¹³ were able to esterify 1-carboxy-3-phenyl-4,7-diazaphenanthrene (XIV) by refluxing its silver salt in solutions of alkyl iodides.

(c) **Reactions of Halo-4,7-diazaphenanthrenes.** (1) *Replacement of Halogen by Amino or Substituted Amino Groups.* Halogens in the 1-, 3-, 8-, or 10-positions are readily replaced by amino groups at temperatures of 140° or above.^{99, 100, 115, 118, 119} 1,10-Dichloro-*p*-phenanthrolines have given products of two types. Jacini¹¹⁸ prepared 1,10-diamino-3,8-dimethyl-4,7-diazaphenanthrene (XLVII) from XLV, while Douglas

and Kermack obtained 1,10-(3'-diethylaminopropylimino)-4,7-diazaphenanthrene (XLVIII) by a similar reaction on XLVI.¹¹⁵



Halogens in the 5- and 6-positions are less reactive than those on the heterocyclic rings. Thus, with 1,6-dichloro-4,7-diazaphenanthrene (XLIV) the 1-chloro atom can be selectively replaced by an alkyl-amino group to form a 1-alkylamino-6-chloro-4,7-diazaphenanthrene.¹¹⁵ Jacomb and Kermack¹²⁰ were unable to synthesize 5-alkylamino-*p*-phenanthrolines from the 5-bromo base, (VII), but Haworth and Sykes replaced the 5-bromo atom with an amino group by employing a catalyst at prolonged high temperatures.⁸²

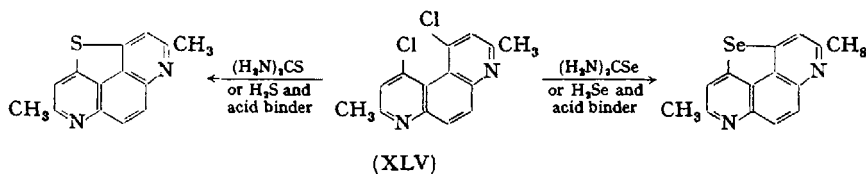
(2) *Replacement of Halogen by Alkoxy or Aryloxy Groups.* 4,7-Diazaphenanthrenes bearing halogens in α - or γ -positions of the heterocyclic rings are readily converted to ethers by treatment with metal alcoholates^{35, 43} or phenolates,^{43, 118} or by reaction with alcohols and phenols in the presence of an acid binder.⁴³

(d) **Reactions of Amino-4,7-diazaphenanthrenes.** Amino-*p*-phenanthrolines behave quite normally toward alkylation¹²⁰ and acylation.⁸² Amino groups in the 5- or 6-positions can be diazotized and then replaced by halogen atoms or hydroxyl groups.¹¹³ However, 1-amino-4,7-diazaphenanthrene cannot be diazotized in aqueous solution under normal conditions.⁹⁹

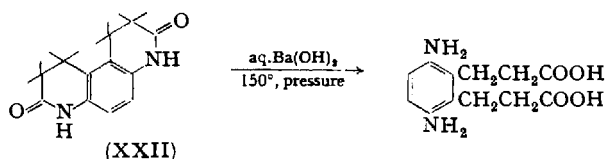
(e) **Reduction of Nitro-4,7-diazaphenanthrenes.** Several nitro-*p*-phenanthrolines have been reduced to the corresponding amino compounds by the action of stannous chloride¹¹³ or ammonium sulfide.²

(f) **Oxidation of Side Chains.** Willgerodt and Jablonski¹¹³ converted 1-carboxy-3-phenyl-4,7-diazaphenanthrene (XIV) to 1,3-dicarboxy-4,7-diazaphenanthrene by a permanganate oxidation.

(g) **Other Reactions.** 1,10-Dichloro-3,8-dimethyl-4,7-diazaphenanthrene (XLV) is converted to a cyclic sulfide or selenide by the action of thiourea or selenourea, respectively.¹²¹



Analogs of hydrocarbostyryl among the phenanthrolines have been subjected to cleavage conditions.¹²² The only well-defined reaction was that of 3,8-dioxo-1,2,3,4,7,8,9,10-octahydro-4,7-diazaphenanthrene (XXII), which formed 3,6-diaminobenzene-1,2- β,β -dipropionic acid.



(5) Uses

Practical uses of the *p*-phenanthrolines are confined to the field of therapeutics. Kermack and co-workers^{100,101,115,120} have prepared many dialkylaminoalkylamino-4,7-diazaphenanthrenes as possible antimalarials, and several other workers have been active in the field.^{103,106,119} Compounds bearing basic side chains in the 1-position,^{103,119,115} the 3-position,^{100,101} the 5-position,¹²⁰ and in the 3,8-positions¹⁰⁰ have been tested. Several of these, as well as 1,10-(3'-diethylaminopropylimino)-4,7-diazaphenanthrene (XLVIII), showed considerable activity toward *Plasmodium gallinaceum* in chicks.

p-Phenanthrolines bearing ether linkages,⁴³ or sulfide linkages¹²¹ at the 1,10-positions are patented as analgesics.

Other 4,7-diazaphenanthrenes have been described as trypanocides,^{82,106} as bactericides,^{34,35} and as useful therapeutic agents.⁹⁰

TABLE VI-4. 4,7-Diazaphenanthrenes

Formula	4,7-Diazaphenanthrenes	M.p., °C.	Refs.
I	4,7-Diazaphenanthrene	171, 173, 174, 177	2, 24, 84, 95-7, 101, 104, 105
		$3\frac{1}{2}$ H ₂ O 100 sub.	2
		P 255-6 ^a	105
		2P 189-90	2
XXVI		4-MeI · H ₂ O 268-9 ^a	2, 34, 39, 100
		270-1	94, 105
		2MeI · H ₂ O 265, 271 ^e	2, 94, 105
		HCl > 315	105
		2HCl ₂ · 2H ₂ O 197 ^c	116
XXXII	3-Methyl-	88 uncorr. ^d	113
		115 anhyd.	110
		2MeI 257 ^b	113
		2EtI 239 ^b	113
XII	3,8-Dimethyl-	175-6	111, 112
		b. 230-1/19 mm.	
XXXV	3-Phenyl-	183	113, 113a
		2MeI 242 ^a	
	2,3-Diphenyl-	242-3	27
	3-Methyl-2-phenyl-	144	27
	2-Benzyl-3-phenyl-	98	27
II	1,2,3,4-Tetrahydro-	152-152.5	117
		HCl 241	117
		2HCl 241	117
	1-Acetyl-1,2,3,4-tetrahydro-	121	98
	1-Benzoyl-1,2,3,4-tetrahydro-	180.7-181, 183.5	98, 117
		P 220-5	
	1,2,3,4,7,8,9,10-Octahydro-	161-2	115a
XXVII	4-Methyl-3,4-dihydro-	117-18	34
XXVIII	4-Methyl-1,2,3,4-tetrahydro-	98-9	34
		HCl 258 (dec.)	
XXIV	8-Methyl-1,2,3,4-tetrahydro-	$2\frac{1}{2}$ H ₂ O ca. 70	110
XXV	3-Methyl-1,2,3,4,7,8,9,10-octahydro-	HCl hygro., sub.	110
	3-Methylperhydro-		110
XI	4,8-Dimethyl-1,2,3,4-tetrahydro-	52	110
		H ₂ O 69	110
XLIII	1-Chloro-	146-7	99, 101, 115
XLII	3-Chloro-	188-9, 189-90	35, 100
	1-Chloro-3-methyl-	149, 195	101, 119
	3-Chloro-1-methyl-	204	101
	10-Chloro-4,8-dimethyl-1,2,3,4-tetrahydro-	89	43

(Table continued)

TABLE VI-4 (*continued*)

Formula	4,7-Diazaphenanthrenes	M.p., °C.	Refs.
XLIV	1,6-Dichloro-	237-8 ^f	115
XLVI	1,10-Dichloro-	247-8	115
XLI	3,8-Dichloro-		43
		H ₂ O 315-16	100
XLV	1,10-Dichloro-3,8-dimethyl-	173	43, 118
VII	5-Bromo-	147-9, 150	13, 82, 120
		HCl > 325	82
		MeI 305 (dec.)	82
XXXVIII	6-Nitro-3-phenyl-	281 ^a	113
XXXVI	3-Phenyl-6-sulfo-	> 350 ^a	113
	1-Amino-	204	99
		HCl ^a	99
	5-Amino-	213-5	82, 120
		MeCl·H ₂ O 272 (dec.)	82
	6-Amino-3-phenyl-	222 ^a	113
XLVII	1,10-Diamino-3,8-dimethyl-	333	118
	1-(2-Diethylaminoethylamino)-	235	101
	3-(2-Diethylaminoethylamino)-	3HBr·H ₂ O 284-285 ^f	100
	5-(2-Diethylaminoethylamino)-	Oil	120
		3,5-DNB ⁴ 172	120
IX	1-(2-Diethylaminoethylamino)-3-methyl		103
		H ₂ O 68	101
	3-(2-Diethylaminoethylamino)-1-methyl-	123	101
		3HBr 229	101
	1-(3-Diethylaminopropylamino)-	Oil	101
		P 231	101
	3-(3-Diethylaminopropylamino)-	3HBr·H ₂ O 268-70 ^a	100
	5-(3-Diethylaminopropylamino)-	Oil	120
		3,5-DNB 173	120
	3-(3-Diethylaminopropylamino)-1-methyl-	Oil	101
		2H ₂ O 265	101
	1-(4-Diethylamino-1-methylbutylamino)-	Oil ^b	115
		tri-3,5-DNB·EtOH	115
		160-1	
	3-(4-Diethylamino-1-methylbutylamino)-	tri-3,5-DNB 93-4	100
	1-(5-Diethylaminopentyl-2-amino)-3-methyl-	b. 235-45/1 mm.	119

(Table continued)

TABLE VI-4 (*continued*)

Formula	4,7-Diazaphenanthrenes	M.p., °C.	Refs.
	3-(1-Piperazyl)-1-methyl-	127	101
		2H ₂ O 110	101
	3-(1-Piperidyl)-1-methyl-	104	101
		2HBr > 400	101
	1-(1-Piperidyl)-3-methyl-	163	101
		P 225	101
	1-[N-Ethyl-N-(2-diethylamino-ethyl)amino]-3-methyl-	b. 210-15/1 mm.	119
	1-(3-Diethylaminopropylamino)-6-chloro-	Oil	
		di-3,5-DNB 193-4 ^a	115
XLVIII	1,10-(3-Diethylaminopropylimino)- ^b	Oil	
		di-3,5-DNB 194-5 ^f	115
	5-Acetamido-	188	82
		MeI · H ₂ O 283 (dec.)	82
III	1-Hydroxy-	298, 300-1 ^a	99, 101, 115
IV	3-Hydroxy-	202-3 ^a	100
	1,10-Dihydroxy-	365-70 ^a	115
XL	5,6-Dihydroxy-	240	21
VI	1-Hydroxy-3-methyl-	358	101
V	3-Hydroxy-1-methyl-	312 (dec.)	101, 102, 109
		330, 353 (dec.)	
	6-Hydroxy-3-phenyl-	168 ^a	113
X	1,10-Dihydroxy-3,8-dimethyl-	332 ^a	43, 106-108, 118
		P 290 ^a	106
	1,10-Dihydroxy-3,8-diphenyl-	> 300	85
	3-Hydroxy-4-methyl-1,2,3,4-tetrahydro-	290-2	35
	10-Hydroxy-4,8-dimethyl-1,2,3,4-tetrahydro-	248	43
	1-Hydroxy-6-chloro-	338-40 ^a	115
	1,10-Phthaloxy-3,8-dimethyl-	> 338	106
	1,10-Bis(β-naphthyloxy)-3,8-dimethyl-	202	43
	1,10-Bis(6-quinolyloxy)-3,8-dimethyl-	221	43
	3-Methoxy-	117	35
		CH ₃ I 243-5	35
XXXIII	5-Methoxy-	105	21
	1,10-Diphenoxy-	190	43
	3,8-Diphenoxy-	188	43

(Table continued)

TABLE VI-4 (continued)

Formula	4,7-Diazaphenanthrenes	M.p., °C.	Refs.
	1-Phenoxy-3-methyl-	255	43
	1-Hydroxy-10-methoxy-3,8-dimethyl-	246-7 ^a	43
		213-14	43
	1-Hydroxy-10-benzyloxy-3,8-dimethyl-	> 280	43
	1,10-Dimethoxy-3,8-dimethyl-	234-5	106
	1-Allyloxy-10-hydroxy-3,8-dimethyl-	> 290 ^a	43
	1,10-Bis(benzyloxy)-3,8-dimethyl-	143	43
	1,10-Bis(cyclohexyloxy)-3,8-dimethyl-	141	43
	1,10-Diphenoxy-3,8-dimethyl-	181, 182-3	43, 118
	1,10-Bis(3-methylphenoxy)-3,8-dimethyl-	140	43
	1,10-Bis(4-methylphenoxy)-3,8-dimethyl-	122	43
	1,10-Bis(3,5-dimethylphenoxy)-3,8-dimethyl-	123-4	43
	3-Methoxy-4-methyl-1,2,3,4-tetrahydro-	78-9	35
	10-Phenoxy-4,8-dimethyl-1,2,3,4-tetrahydro-	86	43
	1,10-Bis(4-chlorophenoxy)-3,8-dimethyl-	205	43
	1-Hydroxy-10-(2-nitrophenoxy)-3,8-dimethyl-	280 ^b	43
	1,10-Bis(3-nitrophenoxy)-3,8-dimethyl-	240 ^a	43
	1,10-Bis(4-nitrophenoxy)-3,8-dimethyl-	273-5 ^a	43, 118
	1,10-Bis(3-acetamidophenoxy)-3,8-dimethyl-	153	43
	1,10-Bis(4-acetamidophenoxy)-3,8-dimethyl-	202	43
	1,10-Bis(4-hydroxyphenoxy)-3,8-dimethyl-	280	43
	1,10-Bis(4-methoxyphenoxy)-3,8-dimethyl-	181	43
	1,10-Bis(2-methoxyphenoxy)-3,8-dimethyl-	265	43
	1,10-Bis(4-ethoxyphenoxy)-3,8-dimethyl-	167	43
	1,10-Bis(3-methoxyacetamidophenoxy)-3,8-dimethyl-	72	43
	1,10-Bis(4-methoxyacetamidophenoxy)-3,8-dimethyl-	171	43
	1,10-Bis(2-dibenzofuranoxy)-3,8-dimethyl-	236	43
	1,3-Dicarboxy-	248	113
XV	1-Carboxy-3-methyl-	205	113
XIV	1-Carboxy-3-phenyl-	290 ^a	113
XVII	1-Carboxy-3-methyl-2-phenyl-	288	27
XVIII	1-Carboxy-2,3-diphenyl-	278	27

(Table continued)

TABLE VI-4 (continued)

Formula	4,7-Diazaphenanthrenes	M.p., °C.	Refs.
XIII	1-Carboxy-2-benzyl-3-phenyl-	272	27
XIX	1,10-Dicarboxy-3,8-diphenyl-	250.5–251.5 ^g (dec.)	114
	1-Carboxy-6-chloro-3-phenyl-	289	113
XVI	1-Carboxy-6-bromo-3-phenyl-	285	113
	1-Carboxy-6-iodo-3-phenyl-	272	113
XXXVII	1-Carboxy-6-nitro-3-phenyl-	310 ^a	113
	1-Carboxy-6-amino-3-phenyl-	293 ^a	113
	2-Carboxy-6-chloro-1-hydroxy-	319–20	115
	3-Carboxy-1-hydroxy-	307–8 ^f	115
	1-Carboxy-6-hydroxy-3-phenyl-		113
	1-Carbomethoxy-3-phenyl-	158	113
	1-Carbethoxy-3-phenyl-	146	113
		EtI 225 ^a , ^d	113
XX	2-Carbethoxy-1-hydroxy-	285–6	115
	2,9-Dicarbethoxy-1,10-dihydroxy-	283–4	115
	1,10-Bis(4-carbethoxyphenoxy)-3,8-dimethyl-	133	43
XXIII	2,9-Dicarbethoxy-1,10-dihydroxy-3,8-diphenyl-	218	85
XXI	2-Carbethoxy-6-chloro-1-hydroxy-	311–12 ^f	115
	1,10-Bis(4-acetylphenoxy)-3,8-dimethyl-	196	43
XXXIV	5,6-Dioxo-	295 (dec.)	21
		= NOH 250 ^a (dec.)	21
VIII	3-Oxo-4-methyl-	239–40, 242 ^a	2, 35, 100
		MeI 290–1 ^a	100
		HCl·2H ₂ O 297–8	2
		HNO ₃ 229–30	2
XXXI	3,8-Dioxo-4,7-dimethyl-	363–4 ^a	2, 100
XXII	3,8-Dioxo-1,2,3,4,7,8,9,10-octahydro-	365	29, 122
XXXIX	3-Oxo-4-methyl-5-nitro-	$\frac{1}{2}$ H ₂ O 301–3	2
	3-Oxo-5-amino-4-methyl-	2H ₂ O 250	2
		Ac 280	2
	1,10-Thio- ^h	186–7	121
	3,8-Dimethyl-1,10-thio- ^h	229–31	121
	3,8-Dimethyl-1,10-seleno- ^h	232	121
XXX	4,7-Diazaphenanthrene-4-oxide	233–4	100
XXIX	4,7-Diazaphenanthrene-4,7-dioxide	308 ^a	36, 90
		324–5	100

^a Yellow. ^b Brown. ^c Orange. ^d Greenish. ^e Garnet-colored. ^f Cream colored. ^g Red.

^h These compounds are mistakenly called phenanthrolines in the literature, and since they are indexed as such, they are included in this table.

ⁱ DNB = dinitrobenzoate.

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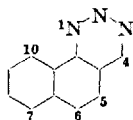
CHAPTER VII

Other Polyazaphenanthrenes

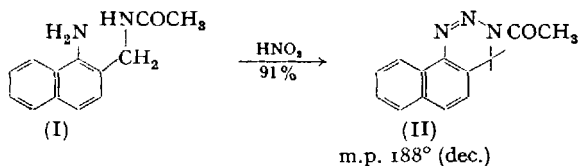
BY JOHN R. THIRTLE

There has been and still is to some extent uncertainty regarding authenticity of certain polyazaphenanthrenes, especially when three or more nitrogen atoms are present in the same ring. Insofar as possible, errors that have occurred in the literature have been corrected in this chapter. Some of the work which is presented, however, has not been rigorously proved; a careful perusal of the references is recommended if a proof of structure is not indicated in this chapter.

**A. 1,2,3-Triazaphenanthrene.
1,2,3-Naphthotriazine**



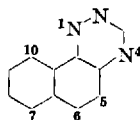
3-Acetyl-3,4-dihydro-1,2,3-triazaphenanthrene (II) has been reported by reduction of 2-acetamidomethyl-1-nitronaphthalene (see XVIa) to the amine (I) and reaction of the latter with nitrous acid.¹



The product is soluble in dilute acids. The structure of I was ascribed by virtue of its reaction with picryl chloride and with 2,4-dinitrochlorobenzene. 2,6-Disubstituted amines such as I and 2,6-dimethylaniline react with these reagents to give addition products without liberation of hydrogen chloride, whereas the 3-amino-derivative corresponding to I, a possible product in the sequence of reactions used, would be expected to give the secondary amine and hydrogen chloride.

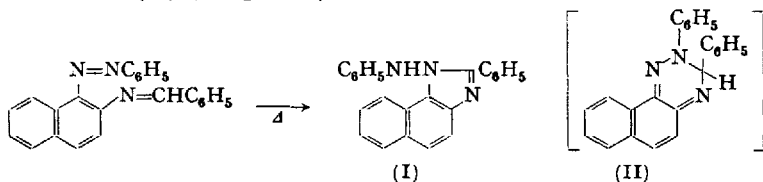
The cyclization reaction, giving 1,2,3-benzotriazines, had been described earlier.²

B. 1,2,4-Triazaphenanthrene. Naphtho-[2,1]-*as*-triazine. 1,2,4-Isonaphthotriazine. β -Naphthotriazine. R.I. 1820



(1) Introduction

Compounds containing the 1,2,4-triazaphenanthrene system were believed to have been first synthesized in 1890 almost simultaneously by Goldschmidt and Rosell³ and Meldola.⁴ The method involved the reaction of 1-arylaazo-2-naphthylamines with aromatic aldehydes. Fischer,⁵ however, proved that this reaction gives 1-anilino-2-aryl-naphthimidazole (I) and not a 2,3-diaryl-2,3-dihydro-1,2,4-triazaphenanthrene (II) (see p. 462):



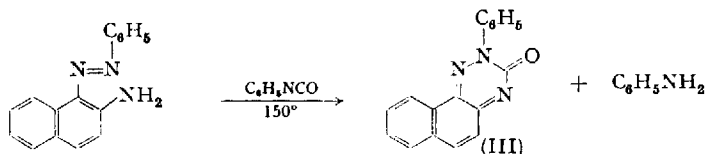
Likewise, the reaction of 1-arylaazo-2-naphthylamine with mandelonitrile leads to the naphthimidazole (I), although the original authors⁶ believed II to have been formed. (A list of all of the diaryl compounds proved by Fischer to be naphthimidazoles is found in Beilstein, 4th Ed., Vol. 26, p. 95.) A considerable volume of work involving what was believed to have been the 1,2,4-triazaphenanthrene ring system has been in error.^{7-13, 19} It appears that Neri and co-workers¹¹⁻¹³ as late as 1941 did not appear to be cognizant of the work of Fischer.

(2) Preparation

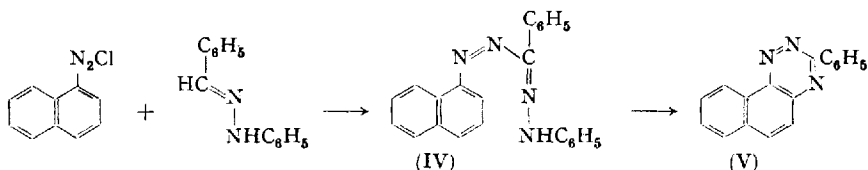
(a) From 1-Phenylazo-2-naphthylamine and Phenyl Isocyanate.

The earliest authentic preparation of a 1,2,4-triazaphenanthrene appears to have been that of Goldschmidt and Rosell.³ The reaction of 1-phenylazo-2-naphthylamine with phenyl isocyanate gives 2-phenyl-3-oxo-2,3-

dihydro-1,2,4-triazaphenanthrene (III). Compound III is better prepared by cyclization of 1-phenylazo-2-naphthylamine using phosgene (see below).

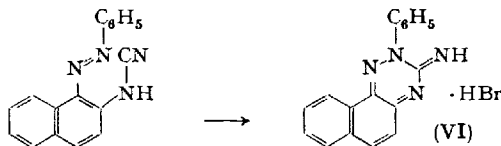


(b) From "Naphthylphenylformazylbenzene." Another synthesis of the 1,2,4-triazaphenanthrene system involves azo coupling of diazotized 1-naphthylamine with benzylidenephénylhydrazine. The product (IV) forms 3-phenyl-1,2,4-triazaphenanthrene (V) by the loss of aniline.¹⁴ Compound V may also be prepared, but in much poorer



yield, by cyclization of the intermediate obtained on reaction of benzylidene- α -naphthylhydrazine and benzenediazonium chloride.¹⁴

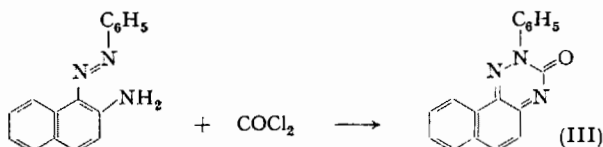
(c) From 1-Phenylazo-2-naphthylcyanamide. Cyclization of 1-phenylazo-2-naphthylcyanamide at 100° gives 2-phenyl-3-imino-2,3-dihydro-1,2,4-triazaphenanthrene (VI) as the hydrobromide.¹⁵ This



preparation can also be effected directly from 1-phenylazo-2-naphthylamine and cyanogen bromide.¹⁵

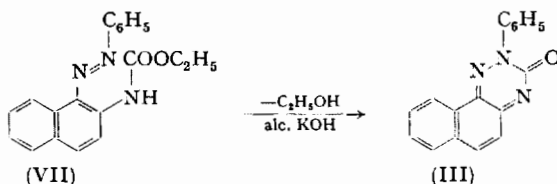
(d) From 1-Phenylazo-2-naphthylamine and Phosgene. One preparation, that of 2-phenyl-3-oxo-2,3-dihydro-1,2,4-triazaphenanthrene (III), by this reaction has been described.¹⁶ This method is re-

ported to be simpler than that of Goldschmidt and Rosell.³ Compound III initially precipitates as the bright red hydrochloride. When spread

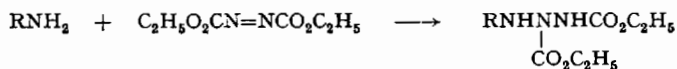


out to dry on a porous plate, the weakly basic compound loses hydrogen chloride and forms the yellow base.

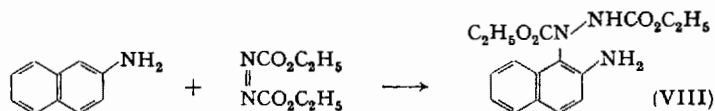
(e) From the Urethan of 1-Phenylazo-2-naphthylamine. An intramolecular ring closure of the urethan (VII) of 1-phenylazo-2-naphthylamine has also been reported to give III; the yield was not reported.¹⁶



(f) From 2-Naphthylamine and Ethyl Azodiformate. The reaction of amines with ethyl azodiformate usually has resulted in addition of the amino hydrogen to the N=N linkage and formation of a new nitrogen bond:

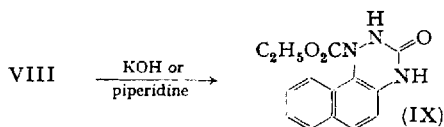


However, when the amine is 2-naphthylamine (or 1-naphthylamine, see p. 466) the reaction appears to take a different course and the amino group is unaffected, giving VIII.¹⁷ The latter readily cyclizes to give

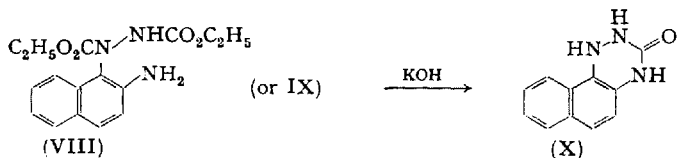


1-carbethoxy-3-oxo-1,2,3,4-tetrahydro-1,2,4-triazaphenanthrene (IX) when treated for two to three minutes with boiling aqueous potassium

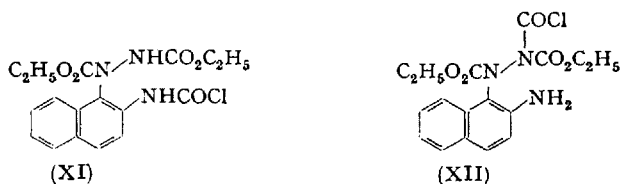
hydroxide (yield *ca.* 90%) or by boiling for six hours with piperidine (yield *ca.* 60%). Longer boiling (two hours) with aqueous alcoholic



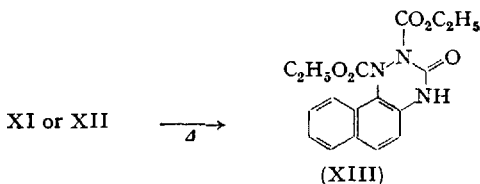
potassium hydroxide results in saponification of the ester and decarboxylation to 3-oxo-1,2,3,4-tetrahydro-1,2,4-triazaphenanthrene (X). The yield is approximately 50% based on compound VIII.¹⁷



The presence of a free amino group in VIII was demonstrated by the reaction with phosgene, whereby the compound designated as XI is formed. The alternate structure, XII, is not excluded. Compound XI

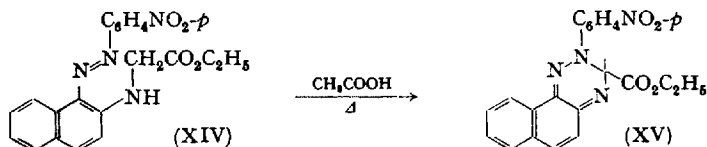


(or XII) goes smoothly to 1,2-dicarbethoxy-3-oxo-1,2,3,4-tetrahydro-1,2,4-triazaphenanthrene (XIII) or its phenolic tautomer.

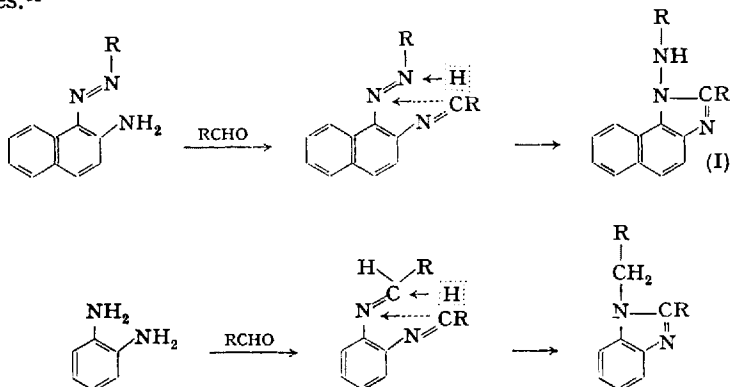


(g) From Ethyl 1-Arylazo-2-naphthylaminoacetate. In a reaction similar to those described above, ethyl 1-(*p*-nitrophenylazo)-2-naphthylaminoacetate (XIV) was reported to give 2-(*p*-nitrophenyl)-3-

carbethoxy-2,3-dihydro-1,2,4-triazaphenanthrene (XV) when heated briefly in boiling acetic acid.¹⁸ The yield was about 50%; some 2-carbethoxynaphth[1,2]imidazole and *p*-nitroaniline also were isolated.



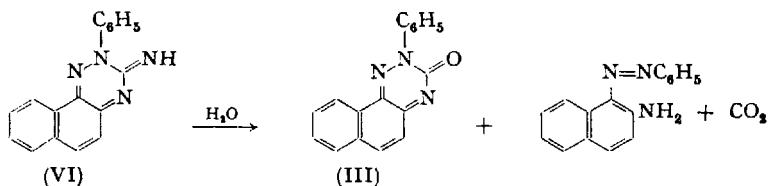
Considerable controversy concerning the mechanism of the reaction between 1-aryldiazo-2-naphthylamines and aromatic aldehydes and over the structure of the products prevailed until O. Fischer⁵ reported his work. He stressed the Schiff bases as the primary intermediates (see also reference 4), and showed that they cyclized to the so-called "naphthotriazines" on heating with acetic acid, formic acid, alcoholic hydrogen chloride, and pyridine. The products contain one secondary nitrogen and two tertiary nitrogen atoms since they give nitrosamines and acetyl derivatives and can be methylated. The "naphthotriazines" can be cleaved by hydriodic acid into naphthimidazoles and anilines. The "naphthotriazines" can also be synthesized from naphthimidazoles and aniline, provided the naphthimidazole is first converted into the chlorimide by treatment with a hypochlorite. On the basis of these experiments, Fischer concluded that the structure of the "naphthotriazines" prepared by the reaction in question was that of anilino-naphthimidazoles (I) as indicated below. An analogous reaction is the cyclization of *o*-phenylenediamines by aldehydes to aralkylbenzimidazoles.



Structural proof for some of the other 1,2,4-triazaphenanthrenes is still rather dubious or lacking.

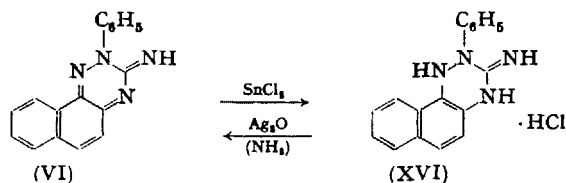
(3) Reactions

2-Phenyl-3-imino-2,3-dihydro-1,2,4-triazaphenanthrene (VI), has been fairly well characterized. Analytical data on it and several salts confirm the presence of four nitrogen atoms. The imino group is readily replaced by the oxo group using 5% potassium hydroxide. Some 1-phenylazo-2-naphthylamine is formed as a by-product, apparently by hydrolysis of III.¹⁵ It should be noted that III can be hydrolyzed



by hot hydrochloric acid or by alcoholic potassium hydroxide, giving carbon dioxide and 1-phenylazo-2-naphthylamine.^{3,16}

Although remarkably resistant to oxidation, compound VI is reduced easily by stannous chloride to 2-phenyl-3-imino-1,2,3,4-tetrahydro-1,2,4-triazaphenanthrene (XVI), from which it is regenerated by ammoniacal silver oxide.¹⁵



The fact that a benzamide of VI could not be formed indicates that an anilino group is not present. The imido nitrogen is apparently not basic enough for amide formation.

In two patents it is stated that 1,2,4-triazaphenanthrenes are intermediates for dyes.^{9,22} Neri and co-workers¹¹⁻¹³ have made a study of the relation between taste and chemical constitution of compounds they believed to be 1,2,4-triazaphenanthrenes. Pope and Taylor²⁰ re-

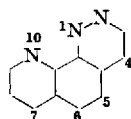
solved the *d*- α -bromocamphor- π -sulfonate of the compound which at that time was thought to be 2,3-diphenyl-2,3-dihydro-1,2,4-triazaphenanthrene; optical inversion occurred on attempts to isolate optically active bases. However, it is believed that all of this work is in error and that anilidonaphthimidazoles were being studied.

The authentic 1,2,4-triazaphenanthrenes are medium-to-high melting solids and are listed in Table VII-1.

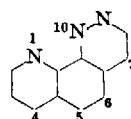
TABLE VII-1. 1,2,4-Triazaphenanthrenes

Formula	Compound	M.p., °C.	Refs.
V	3-Phenyl-	145	14
X	3-Oxo-1,2,3,4-tetrahydro-	315-20	17
III	3-Oxo-2-phenyl-2,3-dihydro-	255	3,15, 16
VI	3-Imino-2-phenyl-2,3-dihydro-	ca. 160	15
		HCl ca. 230	15
XVI	3-Imino-2-phenyl-1,2,3,4-tetrahydro-	HCl 242-5	15
IX	1-Carbethoxy-3-oxo-1,2,3,4-tetrahydro-	265 (dec. violently)	17
XV	3-Carbethoxy-2-(<i>p</i> -nitrophenyl)-2,3-dihydro-	210	18
XIII	1,2-Dicarbethoxy-3-oxo-1,2,3,4-tetrahydro-	180-1	17
		CH ₃ COOH 127-8	17

C. 1,2,10-Triazaphenanthrene.
Pyrido-[3,2-*h*]cinnoline.



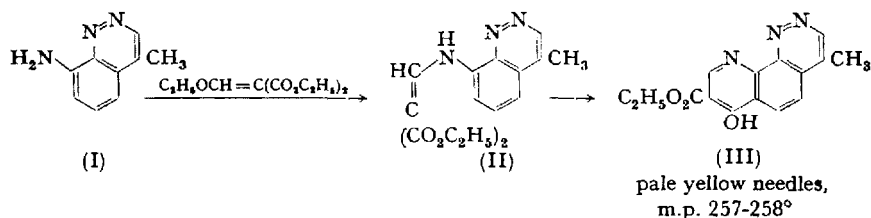
other
numbering:



The synthesis of 1,2,10-triazaphenanthrenes was accomplished rather recently²³ by one of the methods for producing an *N*-heterocyclic ring, which consists of the reaction of a primary amine with ethoxy-methylenemalonic ester followed by ring closure (see p. 181).

From 8-amino-4-methylcinnoline (I), 8-(2,2-dicarbethoxyvinyl-amino)-4-methylcinnoline (II) is formed in 78% yield. The latter is cyclized at 245° in diphenyl ether, giving a 31% yield of 8-carbethoxy-7-hydroxy-4-methyl-1,2,10-triazaphenanthrene (III). Saponification of the ester (III) gives 8-carboxy-7-hydroxy-4-methyl-1,2,10-triazaphen-

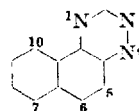
anthrene, white, m.p. 313–14° (dec.), in quantitative yield. Decarboxylation of the acid gives a 93% yield of 7-hydroxy-4-methyl-1,2,10-tri-



azaphenanthrene, a light tan amorphous powder, m.p. 325–6°.

8-Carbethoxy-7-hydroxy-4-methyl-1,2,10-triazaphenanthrene (III) has ultraviolet absorption maxima at 347 and at 276 μ .

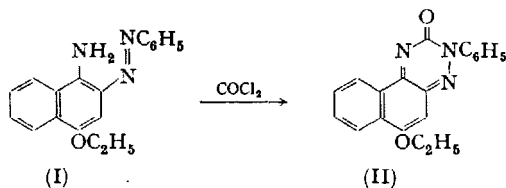
D. 1,3,4-Triazaphenanthrene. Naphtho-[1,2-*e*]-*as*-triazine. 1,3,4-Isonaphthotriazine. 1,3,4-Naphthoisotriazine. 5,6-Naphthotriazine. R.I. 1821



(I) Preparation

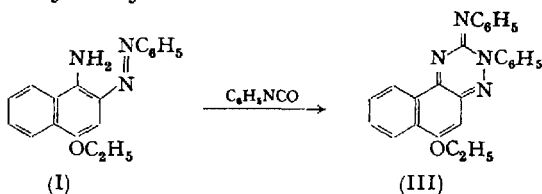
1,3,4-Triazaphenanthrenes have been prepared by some of the methods described in the section concerned with 1,2,4-triazaphenanthrenes; they will be considered only briefly here.

(a) **From 2-Arylazo-1-naphthylamine and Phosgene.** The preparation of 6-ethoxy-2-oxo-3-phenyl-2,3-dihydro-1,3,4-triazaphenanthrene (II) by the reaction of 4-ethoxy-2-phenylazo-1-naphthylamine (I) with phosgene was reported in 1905.²⁴

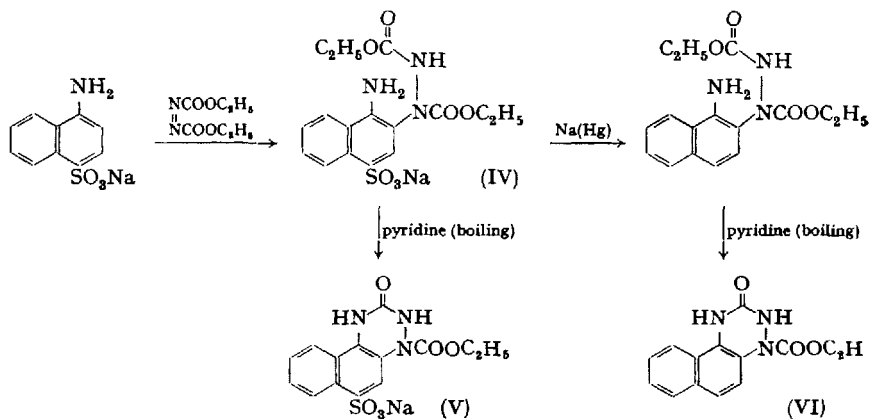


(b) **From 2-Arylazo-1-naphthylamine and Phenyl Isocyanate.** Contrary to the earlier experience (p. 458) whereby the reaction of the unsubstituted 1-arylazo-2-naphthylamine gave an oxo-1,2,4-triazaphen-

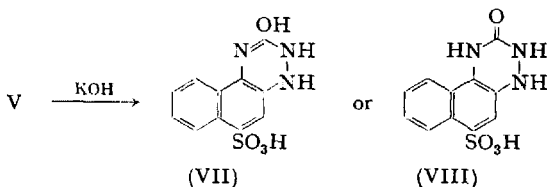
anthrene,³ Busch and Bergmann²⁴ reported the preparation of 6-ethoxy-3-phenyl-2-phenylimino-2,3-dihydro-1,3,4-triazaphenanthrene (III) from I and phenyl isocyanate.



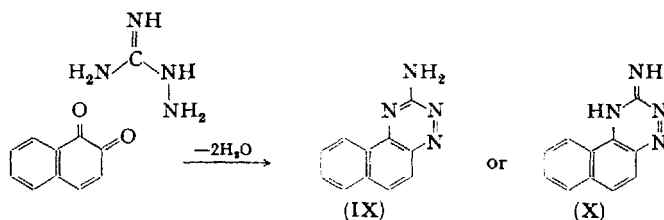
(c) **From 1-Naphthylamine and Ethyl Azodiformate.** As indicated in a preceding section (p. 460) the reaction of the naphthylamines with ethyl azodiformate gives anomalous substitution. For example, naphthionic acid gives the following sequence of reactions leading to 1,3,4-triazaphenanthrenes, V and VI, or their enolic tautomers.²⁵



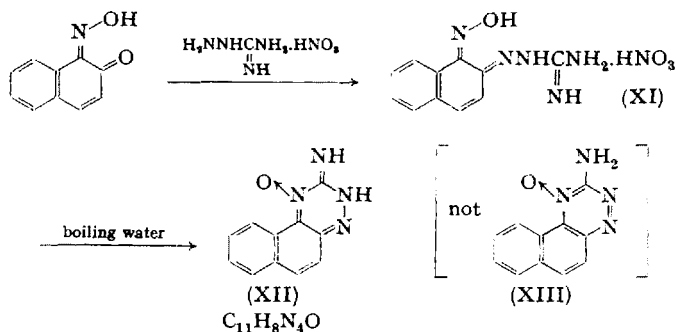
Compound V is converted to 2-hydroxy-6-sulfo-3,4-dihydro-1,3,4-triazaphenanthrene (VII) or 2-oxo-6-sulfo-1,2,3,4-tetrahydro-1,3,4-triazaphenanthrene (VIII) by heating with alcoholic potassium hydroxide. The nonsulfonated analog, VI, reacts likewise.



(d) **From 1,2-Naphthoquinone and Aminoguanidine.** In a further study of the reaction between aromatic diketones and aminoguanidine, ²⁶ De²⁷ heated 1,2-naphthoquinone with aminoguanidine hydrochloride in acetic acid. He reported the product to be "5,6-naphtho-3-aminotriazine" [2-amino-1,3,4-triazaphenanthrene (IX) or 2-imino-1,2-dihydro-1,3,4-triazaphenanthrene (X)], a result that had been anticipated by Thiele and Barlow.³⁰ The latter, however, appear to have obtained the corresponding 2-hydroxy-1,3,4-triazaphenanthrene (see XVI below).



(e) **From 1-Nitroso-2-naphthol and Aminoguanidine.** Thiele and Dralle³¹ in 1898 treated 1-nitroso-2-naphthol with aminoguanidine nitrate, obtaining the product postulated as XI. The latter lost the elements of ammonium nitrate in boiling water, giving a product having the composition $\text{C}_{11}\text{H}_8\text{N}_4\text{O}$. Scott and Reilly³² recently showed that this product is probably 2-imino-2,3-dihydro-1,3,4-triazaphenanthrene-1-oxide (XII). The absence of an amino group, as in 2-amino-1,3,4-triazaphenanthrene 1-oxide (XIII), was demonstrated. The fact



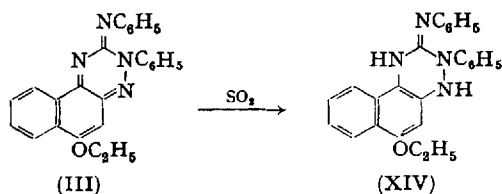
that cyclization involving the oximino group of XI had occurred was demonstrated by the stability of the methyl ether of XI to boiling

water. Reduction of the oxide (XII) to the tetrahydro derivative followed by dehydrogenation gives compound IX or X as further proof that cyclization involved the 1- and 2-positions of the naphthalene nucleus.

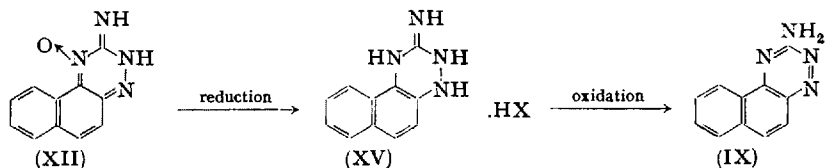
(f) From 2-Phenylazo-1-naphthylamine and Aldehydes. A considerable volume of work has been published by Neri and co-workers^{11-13,28,29} under the assumption that 1,3,4-triazaphenanthrenes were obtained by the reaction of 2-phenylazo-1-naphthylamine and aldehydes. However, as indicated in Section B (p. 462), this reaction has been demonstrated to yield anilidonaphthimidazoles.⁵

(2) Reactions

Few reactions of 1,3,4-triazaphenanthrenes have been reported. Reduction of 6-ethoxy-3-phenyl-2-phenylimino-2,3-dihydro-1,3,4-triazaphenanthrene (III) by sulfur dioxide is said to give the corresponding 1,2,3,4-tetrahydro derivative (XIV).²⁴ Likewise, reduction of the



1-oxide (XII) to the 2-iminotetrahydro-1,3,4-triazaphenanthrene (XV) followed by oxidation is reported to give 2-amino-1,3,4-triazaphenanthrene (IX), which was identified³² by comparison with a sample prepared by another method.²⁷



Acetylation of XII to the extent of 54% was reported, but the properties of the product were not described.³² The reaction of XII with phenyl isocyanate is also mentioned as proof of the presence of

TABLE VII-2. 1,3,4-Triazaphenanthrene Derivatives

Formula	Compound	M.p., °C.	Properties	Refs.
IX	2-Amino-	240, 201	Reddish yellow	27, 32, 33
	2-Acetamido-	208	"Dirty white"	27
XVI	2-Hydroxy-	?	Yellow	27, 30
	2-Oxo-1,2,3,4-tetrahydro-	299		25
VIII	2-Oxo-6-sulfo-1,2,3,4-tetrahydro-	ca. 330		25
VI	2-Oxo-4-carbethoxy-1,2,3,4-tetrahydro-	272-3		25
V	2-Oxo-4-carbethoxy-6-sulfo-1,2,3,4-tetrahydro-	> 135 (dec.)		25
II	2-Oxo-6-ethoxy-3-phenyl-2,3-dihydro-	236	Yellow	24
XII	2-Imino-2,3-dihydro-	1-oxide?		31, 32
XV	2-Imino-1,2,3,4-tetrahydro-	HX		32
III	2-Phenylimino-6-ethoxy-3-phenyl-2,3-dihydro-	230		24
		1½ HCl 237		24
		P 195		24
XIV	2-Phenylimino-6-ethoxy-3-phenyl-1,2,3,4-tetrahydro-	207		24
	2-Phenylimino-6-ethoxy-3-(α -4-ethoxynaphthyl)-2,3-dihydro-	275	Violet	24

the imino group. Compound IX (or X) on acetylation gives the 2-acetamido derivative of 1,3,4-triazaphenanthrene, while with potassium hydroxide 2-hydroxy-1,3,4-triazaphenanthrene (XVI) is obtained.



The reaction of XII with bromine gives a compound, $\text{C}_{11}\text{H}_5\text{Br}_3\text{N}_4\text{O}$, which is not a perbromide but whose nature has not been determined further.³²

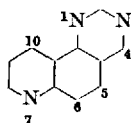
(3) Properties

All of the 1,3,4-triazaphenanthrenes reported have been relatively high melting solids (above 200°), with little or no range in melting point.

They range in color from white (2-acetamido) to yellow, reddish-yellow, and violet (6-ethoxy-3-(α -4-ethoxynaphthyl)-2-phenylimino-2,3-dihydro). 2-Hydroxy-1,3,4-triazaphenanthrene (XVI, yellow) is said to dissolve in ethanol to give a red solution with green fluorescence.²⁷ This compound, having a phenolic hydroxyl group, is stated to be distinctly acidic in character.

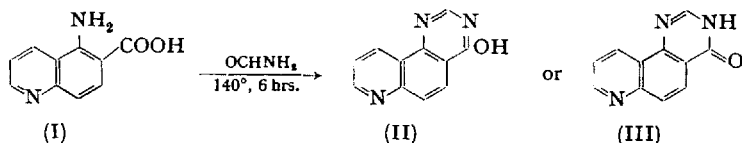
The fact that compound XII exists to some extent as the imino tautomer is shown by the amphoteric nature of the substance. It forms salts with metals, and also forms picrates, chloroplatinates, and other salts characteristic of amines. Both acidic and basic properties are, however, very weak.

E. 1,3,7-Triazaphenanthrene. Pyrido-[2,3-h]-quinazoline. 1,3,7-Naphthisotriazine.
R.I. 1891



(I) Preparation and Properties

The 1,3,7-Triazaphenanthrene system has been described only once.³⁴ In a continuation of studies on the quinazolines, Bogert prepared compounds of this new heterocyclic system by three different methods. 5-Aminoquinoline-6-carboxylic acid (I), when heated with formamide, gives about 10% of 4-hydroxy-1,3,7-triazaphenanthrene (II) or its tautomer (III).



A second method involves the fusion of equal weights of I and urea, giving 2,4-dihydroxy-1,3,7-triazaphenanthrene (IV) or its tautomer (V).

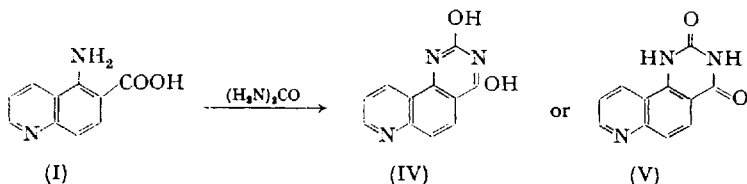
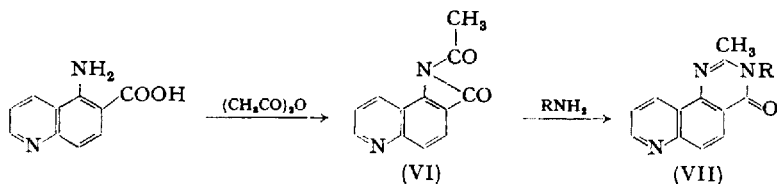


TABLE VII-3. 1,3,7-Triazaphenanthrenes³⁴

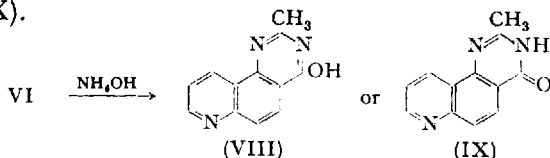
Formula	Compound ^a	M.p., °C.	Properties
II	4-Hydroxy-	298.7	Pink prisms, turn brown on standing
IV	2,4-Dihydroxy-	> 300	Yellow or brown, gives red sol. with diazotized benzidine or sulfanilic acid
VIII	4-Hydroxy-2-methyl-	> 300 (dec.)	Triboelectric, brown ppt. with diazotized benzidine
	4-Hydroxy-2-styryl-	> 300	Yellow powder
	4-Oxo-2,3-dimethyl-3,4-dihydro-	178	Yellow, triboelectric
	4-Oxo-3-ethyl-2-methyl-3,4-dihydro-	152.3	Yellow needles
	4-Oxo-2-methyl-3-propyl-3,4-dihydro-	121-122	Yellow needles
	4-Oxo-2-methyl-3-phenyl-3,4-dihydro-	263-263.5	Greyish needles
	4-Oxo-3-anisyl-2-methyl-3,4-dihydro-	246.9-247.9	Yellow plates
	4-Oxo-3-amino-2-methyl-3,4-dihydro-	256.7	Colorless, flocculent, triboelectric
	4-Oxo-3-acetamido-2-methyl-3,4-dihydro-	268.5-269.5	Colorless
	4-Oxo-3-anilino-2-methyl-3,4-dihydro-	249.5-250.5	Brownish needles
	4-Oxo-3-benzylideneamino-2-methyl-3,4-dihydro-	222.6	Resolidifies at 250-60°, then darkens at 300°

^a All oxo tautomers have been named as hydroxy derivatives where possible.

Finally, the lactam (VI) of 5-acetamidoquinoline-6-carboxylic acid can be heated with a number of substances having free amino groups such as ammonia, aniline, alkylamines, hydrazines, etc., giving 1,3,7-triazaphenanthrenes in apparently good yields. With ammonia, the



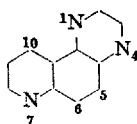
product is 4-hydroxy-2-methyl-1,3,7-triazaphenanthrene (VIII) or its tautomer (IX).



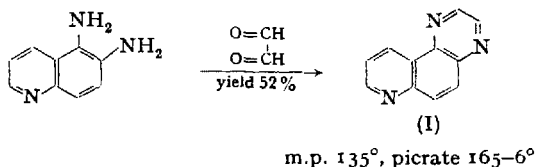
The chemistry of the 1,3,7-triazaphenanthrenes has been investigated only incidentally. Acetylation of the 3-amino group in VII ($R = NH_2$) gives the colorless acetamido derivative. The Schiff base of the same amine was prepared with benzaldehyde. The reactivity of the 2-methyl group in VIII (or IX) was demonstrated by the formation of the analogous 2-styryl derivative on treatment with benzaldehyde.

The 1,3,7-triazaphenanthrenes are mostly high melting solids having some color—yellow to brown. Those capable of existing in the phenolic state are soluble in dilute alkali. Some couple with diazotized amines, although a complete examination of this characteristic appears not to have been made.

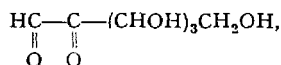
F. 1,4,7-Triazaphenanthrene. Pyrido-[3,2-f]-quinoxaline. Pyridino-3',2',5,6-quinoxaline. R.I. 1892



1,4,7-Triazaphenanthrene (I) has been prepared by methods used for the preparation of 1,4-diazaphenanthrene. The base was prepared in 1946 by the reaction of 5,6-diaminoquinoline with the bisulfite addition product of glyoxal.³⁵

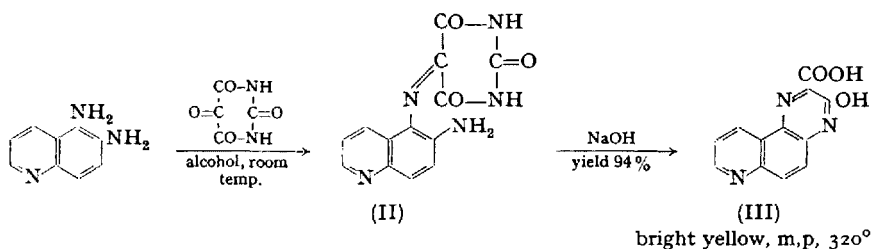


The analogous reaction involving biacetyl gives an 89% yield of the corresponding 2,3-dimethyl-1,4,7-triazaphenanthrene, m.p. 142-4°, and benzil gives 33 to 40% yields of the corresponding 2,3-diphenyl derivative, m.p. 205-6°. ^{36,37} In this same connection glucosone:

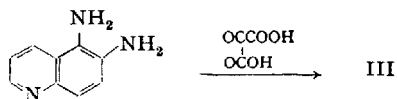


gave, presumably, 2(or 3)-(1,2,3,4-tetrahydroxybutyl)-1,4,7-triazaphenanthrene, m.p. 222-5°, but the material could not be purified and definitely characterised.³⁶

The first preparation of a 1,4,7-triazaphenanthrene was accomplished by Rudy in 1938.³⁸ In a study of the reaction between 5,6-diaminoquinoline and alloxan, he found that under proper conditions only one of the amino groups could be substituted. The imide so formed could then be cyclized by boiling for only five minutes with sodium hydroxide, giving 2-carboxy-3-hydroxy-1,4,7-triazaphenanthrene (III).



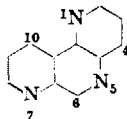
The structure of II is not unambiguous, for the 6-amino group could have formed the imide linkage. Since there was no mixture obtained and since the cyclized product was also a single material, Rudy attributed the formulation II to the greater reactivity of the 5-amino group. Compound III was also prepared in 90% crude yield by the reaction of 5,6-diaminoquinoline with mesoxalic acid.³⁸



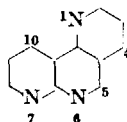
1,4,7-Triazaphenanthrene reacts with an acetic acid solution of hydrogen peroxide to give a tri-*N*-oxide, m.p. > 400°. On the other hand, the 2,3-dimethyl derivative forms only a di-*N*-oxide, m.p. 225–7°. This behavior is similar to that experienced with 2-methyl-3-phenyl-1,4-diazaphenanthrene, which forms a mono-*N*-oxide (p. 348). No other chemical properties have been described.

1,4,7-Triazaphenanthrene forms colorless leaflets melting at 135°; picrate, yellow, m.p. 165–6°. The 1,4,7-triazaphenanthrene system was investigated as a possible source of antimalarial compounds^{35,36} and other pharmaceutical agents.³⁵ 2,3-Diphenyl-1,4,7-triazaphenanthrene was reported to be devoid of antimalarial activity.³⁶

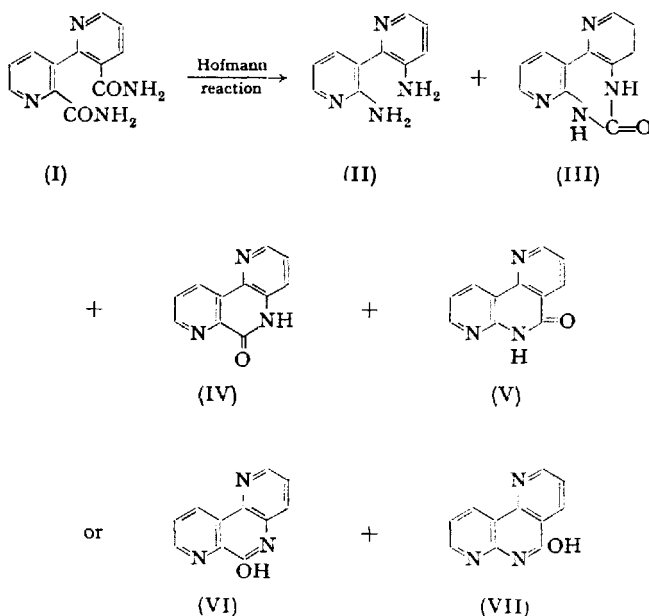
- G. 1,5,7-Triazaphenanthrene. Pyrido[2,3-*c*]-[1,5]naphthyridine. Dipyrdo[3,2-*b*,3',2'-*d*]-pyridine. R.I. 1942



- H. 1,6,7-Triazaphenanthrene. Pyrido[3,2-*c*]-[1,8]naphthyridine. R.I. 1943



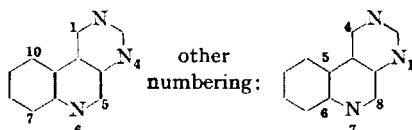
In the preparation of 2',3-diamino-2,3'-bipyridine (II) from 2',3-dicarbamyl-2,3'-bipyridine (I) by the Hofmann reaction, three by-products are formed.³⁹ One by-product is 2',3-carbamido-2,3'-bipyridine (III). The others, both with formula $C_{11}H_7N_3O$, are believed to be 6-oxo-5,6-dihydro-1,5,7-triazaphenanthrene (IV) and 5-oxo-5,6-dihydro-1,6,7-triazaphenanthrene (V) or their tautomers, 6-hydroxy-1,5,7-triazaphenanthrene (VI) and 5-hydroxy-1,6,7-triazaphenanthrene (VII).



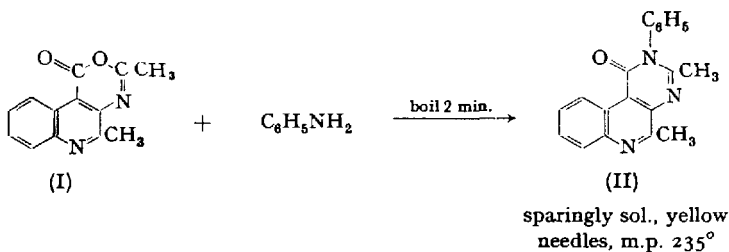
One, melting at 283–5°, is formed in greater quantity than the other, melting at 318–20°. Both isomers show great stability toward alkali and

acids as well as toward oxidation by chromic acid in sulfuric acid. These facts and the strong evolution of ammonia during the reaction lead to the conclusion that a cyclic structure results. Neither compound reacts with hydroxylamine or phenylhydrazine. The higher melting compound is less soluble in water; both dissolve in aqueous alcoholic sodium hydroxide, but are reprecipitated by the addition of 50% sodium hydroxide. The lower melting isomer gives a water-soluble potassium salt on melting with potassium hydroxide. Reaction of this salt with methyl iodide at 150–60° gives a derivative (claimed to be *N*-methyl), melting at 177–8°.

I. 2,4,6-Triazaphenanthrene. Pyrimido[4,5-*c*]quinoline. 2,4,6-Naphthisotriazine. 5,6-Benzocopazoline. R.I. 1893



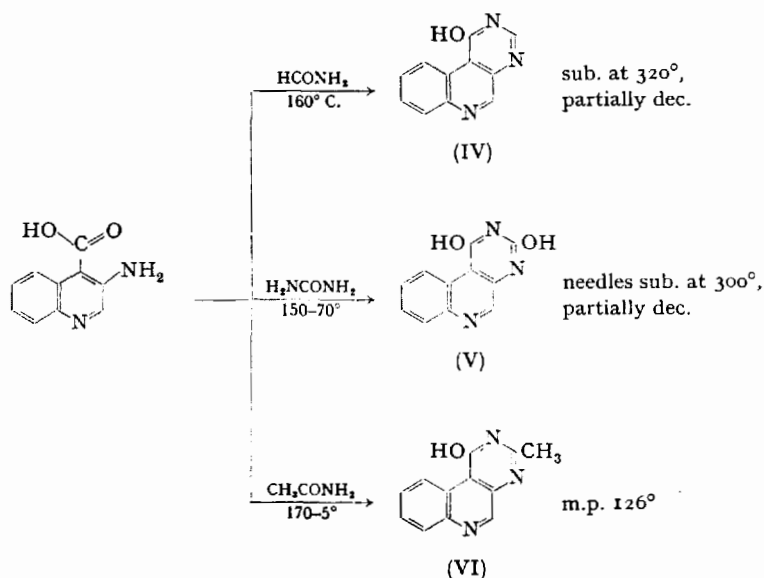
Only two instances of the 2,4,6-triazaphenanthrene system have been noted. In the first, 1-oxo-3,5-dimethyl-2-phenyl-1,2-dihydro-2,4,6-triazaphenanthrene (II) was reported as a by-product in studies of naphthyridine syntheses.⁴⁰ This preparation involves the reaction of anhydro-3-acetamido-2-methylcinchoninic acid (I) and aniline. The



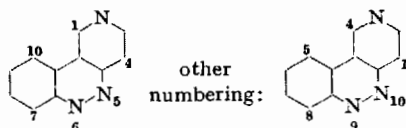
second instance involves the reaction of 3-aminocinchoninic acid (III) with amides, including formamide, urea, and acetamide. From such reactions are obtained 1-hydroxy-2,4,6-triazaphenanthrene (IV), 1,3-dihydroxy-2,4,6-triazaphenanthrene (V), and 1-hydroxy-3-methyl-2,4,6-triazaphenanthrene (VI), respectively.⁴¹ Compounds IV, V, and VI were named as derivatives of 4-hydroxy-5,6-benzocopazoline.⁴¹

In addition to the high melting points, it should be noted that

compound II is a weak base which dissolves in concentrated hydrochloric acid but which reprecipitates on dilution with water.

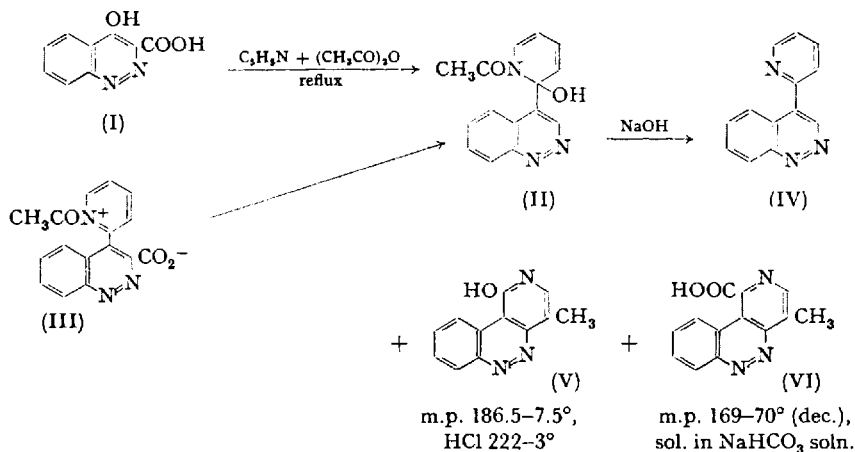


J. 2,5,6-Triazaphenanthrene. Pyrido-[4,3-c]-cinnoline



Only one record of a 2,5,6-triazaphenanthrene has been found. The authors proposed this ring system for substances that were obtained during some cinnoline studies; the empirical formulae were determined by analysis, but the structures were regarded as provisional pending further synthetic work.⁴² The reaction of 4-hydroxycinnoline-3-carboxylic acid (I) with pyridine and acetic anhydride gives 4-[2-(1-acetyl-2-hydroxy-1,2-dihydropyridyl)] cinnoline (II) in 52% yield. The same product can be obtained from the intermediate zwitterion represented as III. Treatment of II with sodium hydroxide gives 4-(2-pyridyl)cinnoline (IV) and, from the mother liquor, the sodium salt of 1-hydroxy-4-methyl-2,5,6-triazaphenanthrene (V). From 10 grams of compound II only 0.78 g. of compound V was obtained. In addition,

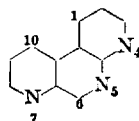
from the mother liquor of compound V, 0.45 g. of 1-carboxy-4-methyl-2,5,6-triazaphenanthrene (VI) was obtained. Compound VI can be



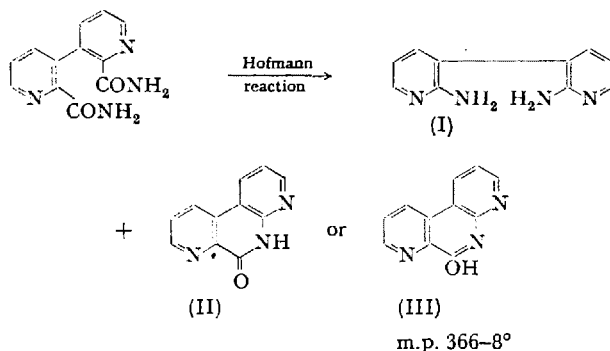
decarboxylated by heating at 180–5°, giving 4-methyl-2,5,6-triazaphenanthrene, m.p. 113–114°.

The only other physical data reported is the weak basicity of compound VI, which separates unchanged on cooling a hot solution in 2 *N* hydrochloric acid.

K. 4,5,7-Triazaphenanthrene. Pyrido[2,3-*c*]-[1,8]naphthyridine. 3,3'-Bipyridine-2,2'-pyridine. R.I. 1944

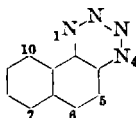


A compound of the 4,5,7-triazaphenanthrene system has been reported as a by-product of the Hofmann reaction involving 2,2'-

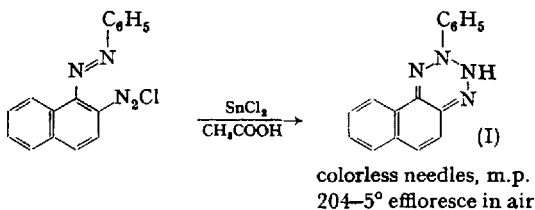


dicarbamyl-3,3'-bipyridine (I).⁴³ 6-Oxo-5,6-dihydro-4,5,7-triazaphenanthrene (II), or 6-hydroxy-4,5,7-triazaphenanthrene (III), is formed together with the desired 2,2'-diamino-3,3'-bipyridine (see also p. 474).

L. 1,2,3,4-Tetrazaphenanthrene. Naphtho-[1,2]-*v*-tetrazine. Naphtho-1',2',5,6-tetrazine. Isonaphthotetrazine. 1,2,3,4-Naphth-isotetrazine. R.I. 1801

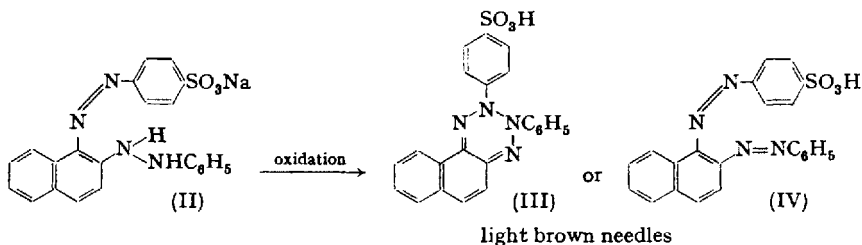


The preparation of 2-phenyl-2,3-dihydro-1,2,3,4-tetrazaphenanthrene (I) was reported in 1887 by Zinke and Lawson.⁴⁴ Similarly, the



corresponding 1-(2-naphthylazo)-2-naphthyl diazonium chloride gives 2-(2-naphthyl)-2,3-dihydro-1,2,3,4-tetrazaphenanthrene, white needles, m.p. 202-4°. The yields appear to be good.

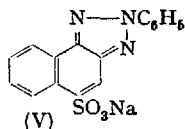
A second method of preparation of 1,2,3,4-tetrazaphenanthrenes was reported as a *possibility* by Bucherer and Stickel.⁴⁵ This method would involve the cyclization of a hydrazino-azo compound (II) by oxidation. The product was indicated to be either 3-phenyl-2-(*p*-sulfo-phenyl)-2,3-dihydro-1,2,3,4-tetrazaphenanthrene (III) or 2-phenylazo-1-(*p*-sulfo-phenylazo)naphthalene (IV). Bucherer and Stickel chose the



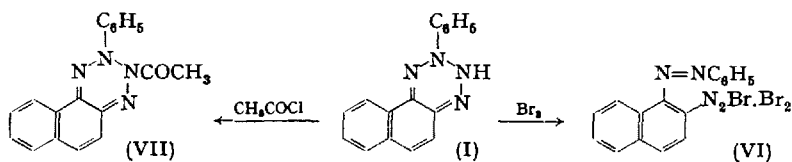
disazo dye structure, IV, as the more plausible, and this choice is substantiated by other studies.

When IV is warmed with sodium bisulfite solution it is decomposed, giving sulfanilic acid and a compound, $C_{16}H_{10}N_3O_3SNa$, which is probably

the naphthotriazole-5-sulfonic acid (V).⁴⁵ Moreover, heating the disazo dyes, or treatment with sodium nitrite and acid at ordinary



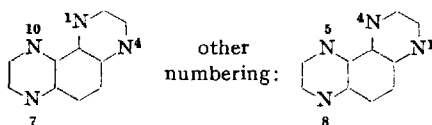
temperatures, gives elimination of an aromatic amine and the formation of the triazole ring.⁴⁵ These reactions appear to be characteristic of the *o*-disazo dyes that are formed by oxidation of hydrazino-azo compounds, but does not seem to occur with the cyclic compounds prepared from azo-diazonium compounds. Moreover, the *o*-disazo dyes are readily reduced by phenylhydrazine, for example, to the osazones. The cyclic compounds formed from azo-diazonium compounds are stable to reducing agents. They are, however, reactive to oxidizing agents such as bromine, chlorine, and nitric acid, reforming the azo-diazonium salt. For example, 2-phenyl-2,3-dihydro-1,2,3,4-tetrazaphenanthrene (I) gives 1-phenylazo-2-naphthyldiazonium perbromide (VI) on reaction with bromine.⁴⁴ The corresponding 2-(2-naphthyl) analog of I behaves



colorless needles, m.p. 137–9°

similarly. Reaction of compound I with acetyl chloride at 100° gives 3-acetyl-2-phenyl-2,3-dihydro-1,2,3,4-tetrazaphenanthrene (VII).

M. 1,4,7,10-Tetrazaphenanthrene. Pyrazino[f]quinoxaline. Diquinoxaline. 1,4,7,10-Naphthotetrazine. Dipyrazino-2',3',1,2-, 2'',3'',3,4-benzol. R.I. 1818



As would be expected, compounds of the 1,4,7,10-tetrazaphenanthrene system have been synthesized by the reaction of the 1,2,3,4-benzenetetramines with 1,2-diketones. The first preparation, giving

(I) (R = H) (II) (R = H) (III) (R = H)
 84%, m.p. 216° (dec.)

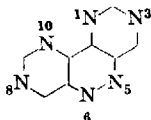
$$\text{III} \longrightarrow \text{R} \begin{array}{c} \text{CHO} \\ | \\ \text{N}_3 \end{array} \xrightarrow[\text{--N}_2]{\Delta} \text{R} \begin{array}{c} \text{CH-O} \\ | \\ \text{N}^{\pm} \end{array}$$

**O. 2,3,5,6-Tetrazaphenan-
threne. Pyridazo-[4,5-*c*]-
cinnoline. R.I. 1882**

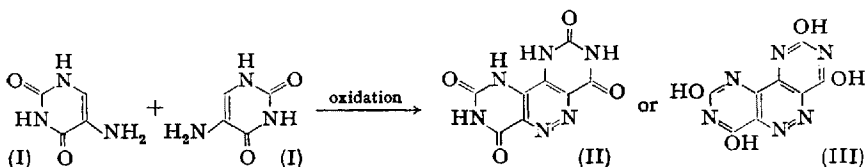
CC(=O)c1c(C(=O)c2ccccc2)c3ccccc3n1
 $\xrightarrow{\text{NH}_2\text{NH}_2, \text{H}_2\text{SO}_4}$
CC(=O)c1c2c(c3ccccc3n1n2)c4ccccc4

 (I)

P. 1,3,5,6,8,10-Hexazaphenanthrene.
Dipyrimido[5,4-c,4',5'-e]pyridazine.
R.I. 1869



The reaction of 5-aminouracil (I) with potassium ferricyanide has been reported to give 2,4,7,9-tetraoxo-1,2,3,4,7,8,9,10-octahydro-1,3,5,6,8,10-hexazaphenanthrene (II) [*Chemical Abstracts*, 1,10-dihydro-2,4,7,9(3,8)-dipyrimidopyridazinetetrone] or its tautomer, 2,4,7,9-tetrahydroxy-1,3,5,6,8,10-hexazaphenanthrene (III).⁵¹



The product, unattacked by concentrated nitric acid or bromine water, is in the form of orange-yellow platelets that do not melt below 300°. It forms an insoluble, red sodium salt, which is soluble in excess sodium hydroxide, giving a yellow solution with orange fluorescence.

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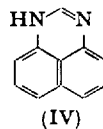
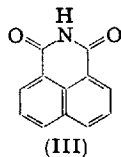
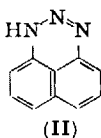
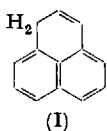
CHAPTER VIII

Azabenzonaphthenes

BY JAMES H. RICHMOND*

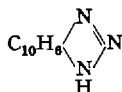
1. Historical

The azabenzonaphthenes include those compounds that possess a nucleus of three condensed six-membered rings arranged in the *peri*-benzonaphthalene structure (I), and which contain one or more nitrogen atoms in place of one or more of the carbon atoms. All the azabenzonaphthenes, except those in which a nitrogen atom is common to two rings, are described in this chapter.



No azabenzonaphthene has yet been found occurring in nature. They have nearly all been synthesized from *peri*-substituted naphthalenes by ring closure, using appropriate reagents. Once the nucleus has been formed, substitution products have been obtained, in a few instances, by replacement reactions.

In 1874¹ the Portuguese chemist, d'Aguiar, described the results of his investigation of 1,8-diaminonaphthalene and its behavior with oxalic acid, ethyl oxalate, and nitrous acid (pp. 519 and 543). Although he isolated and established the correct empirical formulas for his reaction products, he did not assign to them the now accepted structures. He wrote:



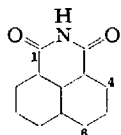
* Deceased July 6, 1951. Written from his notes by C. F. H. Allen.

for the substance obtained by the action of nitrous acid, which is essentially that of 1*H*,1,2,3-triazabenzonaphthene (II), as now in use (see p. 543).

At the turn of the century, when there was great interest in the newly discovered vat and sulfur dyes, there was considerable industrial activity in the azabenzonaphthene group, in particular those based upon naphthalimide (III) (pp. 493–517), and perimidine (IV) (pp. 518–543). Subsequent investigations have dealt with the analogs of indigo (p. 486), *peri*-naphthisatin (p. 486), dyes for resins and synthetic fibers, and efforts to prepare useful drugs.

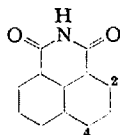
2. Nomenclature

The names and numberings that have been applied to the azabenzonaphthenes are very diverse and confusing. Since many of the substituted naphthalimides were obtained from acenaphthene derivatives, the numbering used in that hydrocarbon series was frequently retained; this gave rise to ambiguity. In this chapter, the well-established names, naphthalimide and perimidine, are retained; the latter and all other series are named according to the “a” system of nomenclature, and numbered in the approved fashion, by which the atom at the left side of the top ring is number 1.

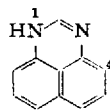


(III)

Current numbering



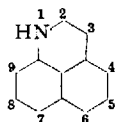
Numbering based on acenaphthene



(IV)

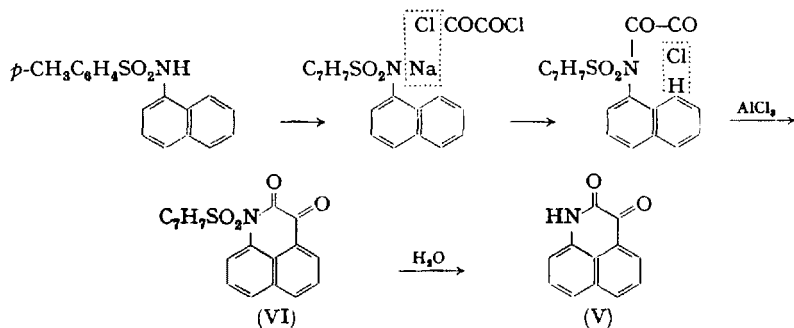
3. Monoazabenzonaphthenes

- A. 1*H*,1-Azabenzonaphthene,
1*H*-Benzo[*de*]quinoline.
4,5-Benzoquinoline. R.I.
1979.



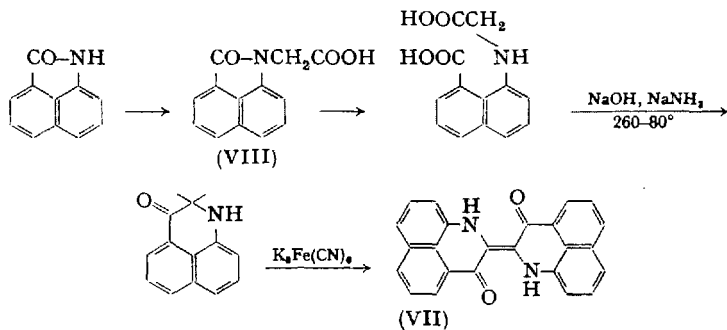
The only representatives in the 1-aza series are 1,8-naphthisatin, a prospective dye intermediate, and “*peri*-naphthindigo,” a polynuclear analog of indigo.

1,8-Naphthisatin; *1H,2,3-dioxo-1-azabenzonaphthene* (V). This substance, which is to be found under 4,5-benzoquinoline-2,3-dione in the 1936 Decennial Index of *Chemical Abstracts*, is obtained by ring closure of *N*-substituted α -naphthyloxamic chloride.²⁻⁵ The sodium derivative of α -*p*-toluenesulfonamidonaphthalene is acylated by means of oxalyl chloride, and the ring is closed by treatment with anhydrous aluminum chloride. The 2,3-dioxo-1-*p*-toluenesulfo-1-aza-



benzonaphthene (or *N*-*p*-toluenesulfo-1,8-naphthisatin) (VI) so formed is then hydrolyzed without isolation to 1,8-naphthisatin (V). The latter forms olive needles that melt above 300°. It dissolves in alkali to give a stable red solution. Its solution in concentrated sulfuric acid is reddish yellow.

peri-Naphthindigo (VII). Although the analogous thioindigo was synthesized as early as 1907,⁶ *peri*-naphthindigo was not known until 1923 when Dutt obtained it from naphthostyryl, employing a modified

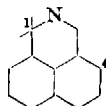


Heumann process.⁷ Naphthostyryl was treated for five minutes with potassium chloroacetate and potassium hydroxide, which mixture, after

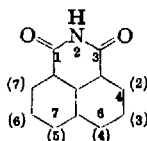
acidifying, gave naphthostyrlacetic acid (VIII). The ring was opened by sodium hydroxide; the disodium salt of α -naphthylglycine-8-carboxylic acid was isolated and fused with a mixture of sodium amide and sodium hydroxide. An aqueous solution of the melt gave the indigo (VII), in a yield of 7%, upon oxidation with potassium ferricyanide.

The indigo has no definite crystalline form, but appears as deep blue aggregates. It is very sparingly soluble in nitrobenzene, aniline, and quinoline. It gives a bluish-green solution in concentrated sulfuric acid. It forms a reddish-brown vat with sodium hyposulfite from which cotton is dyed a light green, not fast to light. The dye has no technical value.

- B. 1H,2-Azabenzonaphthene. 1H-Benz[de]-isoquinoline. 2,1-*peri*-Benzisoquinoline. *peri*-Naphthazole. R.I. 1980**



There has been more work in the 2-aza series than in any other of the azabenzonaphthenes, because of the relative accessibility of the 1,3-dioxo form, naphthalimide (III), and its convertibility into dyes. Substituted naphthalimides are known in great variety. When the substances are named as derivatives of naphthalimide, the numbering



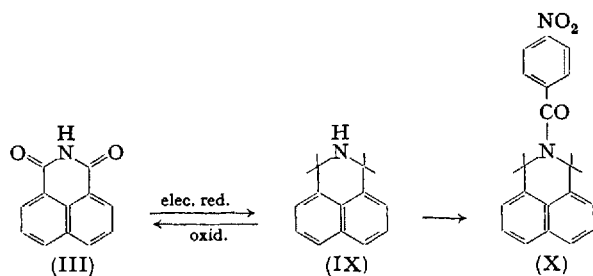
in parentheses is sometimes used which is different from that when the "a" names are used.

Subsequently, Beschke⁹ and somewhat later Späth¹⁰⁻¹³ obtained compounds in the 2-aza series that did not contain the carbonyl group. Naphthalimide can be chemically reduced only with lithium aluminium hydride, but the oxygen-free systems also can be obtained by electrolytic reduction.^{10, 15} A few phthalimidines (XIV) are also known, being formed from naphthalides and ammonia,^{16, 17} or by electrolytic reduction¹⁵ of naphthalimides.

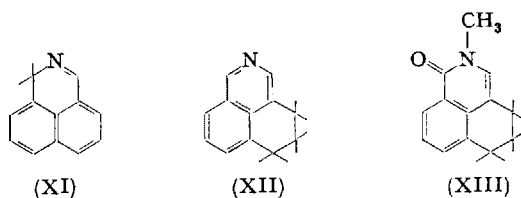
(1) Preparation

(a) Electrolytic Reduction. The simplest 2-azabenzonaphthene was obtained by Späth¹⁰ by electrolytic reduction of naphthalimide,

using a sulfuric acid solution in a cell having a lead cathode. The product was a mixture, the components of which were finally separated ten years later.¹³ The pure substance, 2,3-dihydro-1*H*-2-azabenzonaphthene (2,3-dihydro-2,1-*peri*-benzisoquinoline, naphthaleno-1',9',8',3,4,5-pyridine-1,2,3,6-tetrahydride¹⁴) (IX), was a liquid base, which formed a picrate. The re-formation of naphthalimide by acid permanganate oxidation showed that the condensed three-ring system was still intact. The hydrogen atom attached to the nitrogen atom was detected by preparation of a pale yellow-*p*-nitrobenzoyl derivative (X). Dehydro-



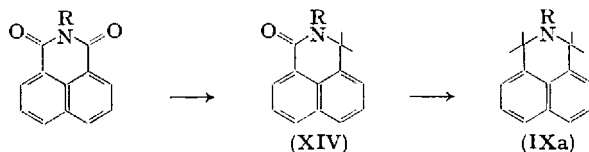
genation over palladium sponge was expected to give the still unknown 1*H*,2-azabenzonaphthene (XI), but instead all three extra hydrogen atoms were rearranged to one of the other rings, resulting in 5,6-dihydro-4*H*,2-azabenzonaphthene (4,5-trimethyleneisoquinoline) (XII). Späth called attention to this anomalous result, and cautioned against erroneous interpretations of structure that might arise when palladium sponge is used for dehydrogenation of unknown bases isolated from natural sources. The new base formed a picrate and a yellow methiodide.



Upon treatment with potassium ferricyanide, the latter was oxidized to 2-methyl-1-oxo-5,6-dihydro-4*H*,2-azabenzonaphthene (XIII).

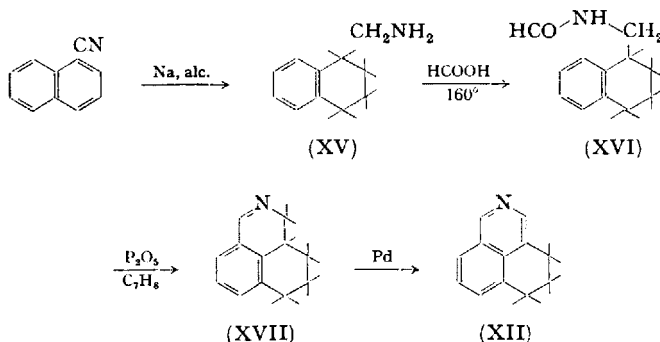
Sakurai¹⁵ was unable to duplicate the reduction as described in Späth's first paper, but did obtain an 8% yield using a zinc-amalgam

cathode. He also reduced *N*-methyl- and *N*-ethylnaphthalimides; in both instances the use of a lead cathode resulted in reduction of but one of the carbonyl groups, giving a "naphthalimidine" (XIV) whereas an "*N*-alkylhydrobenzisoquinoline" (IXa) was obtained with zinc amalgam. As the carbonyl groups disappear the nitrogen becomes progressively more basic. This work was done on a very small scale (1 g. amounts)



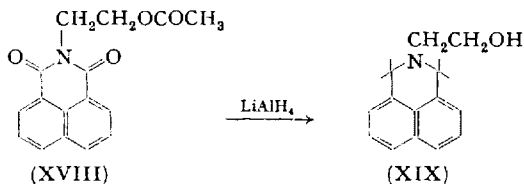
with considerable unchanged naphthalimide being recovered. Identifications were based on analyses of platinum double salts. 2-Methyl-2,3-dihydro-1*H*,2-azabenzonaphthene has also been obtained from naphthalene-1,8-dialdehyde and methyl amine;²² the free base was not isolated.

(b) Ring Closure. The location of the three hydrogen atoms in 4,5-trimethyleneisoquinoline (XII) was established by an independent synthesis¹² involving ring closure and partial dehydrogenation. α -Naphthonitrile was reduced by sodium and alcohol to tetrahydro- α -naphthylmethylamine (XV), which, with formic acid, gave the amide (XVI). This was then cyclized by phosphorus pentoxide in toluene to a tetrahydro-3*H*,2-azabenzonaphthene (XVII); the latter was dehydrogenated with palladium sponge to the same 5,6-dihydro-4*H*,2-azabenzonaphthene (XII) as had been obtained by rearrangement of the product from electrolytic reduction.



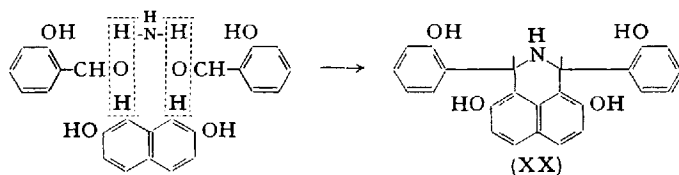
By using homologous acids in a similar series of reactions, there can be prepared 1-substituted derivatives in both the di- and tetrahydro series (Table VIII-1). The bases are distilled in a high vacuum; the boiling point given is the temperature of the air bath during the distillation.

(c) Chemical Reduction. 2- β -Hydroxyethyl-2,3-dihydro-1*H*,2-azabenzonaphthene (2,3-dihydro-1-benz[*de*]isoquinoline-2-ethanol) (XIX) was formed when the acetate (XVIII) of the corresponding imide was reduced by lithium aluminium hydride in ether.²³ This is the first



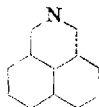
recorded instance of the chemical reduction of the $>\text{C}=\text{O}$ group in a naphthalimide. The hydrochloride of the 2- β -chloroethyl derivative, 2- β -chloroethyl-2,3-dihydro-1*H*,2-azabenzonaphthene (*N*- β -chloroethyl-2,3-dihydro-1-benz[*de*]isoquinoline), resulted when the alcohol was treated with thionyl chloride in benzene. The chloride was examined for adrenolytic activity, but none was found.

(d) Beschke Bases. An entirely different way of obtaining 2-azabenzonaphthenes was announced by Beschke.⁹ The products formed



always have two hydroxyl groups that are in the 4- and 9-positions. The interaction of 2,7-dihydroxynaphthalene, an aromatic aldehyde, and alcoholic ammonia results in the formation of the new bases; salicylaldehyde, for instance, gives 2',2'',4,9-tetrahydroxy-1,3-diphenyl-2,3-dihydro-2-azabenzonaphthene (XX). Beschke showed that, under slightly different conditions, a complex intermediate is formed, which

TABLE VIII-1. Partially Reduced 2-Azabenzonaphthenes



Formula	Substituent	M.p., °C.	B.p., range 0.01 mm.	Salts; m.p., °C.	Refs.
IX	2,3-Dihydro-1 <i>H</i> -	102-3	110-11	P 200 (dec.)	10, 11, 13-15
XII	5,6-Dihydro-4 <i>H</i> -			H ₂ PtCl ₆ 198 (dec.) P 230-1*	10, 12, 13
			80-100	CH ₃ I 204-5 (yellow)	
	1-Methyl-5,6-dihydro-4 <i>H</i> -		80-100	P 203-4 (dec.)*	12
	2-Methyl-2,3-dihydro-1 <i>H</i> -			H ₂ PtCl ₆ 212 (dec.)	15, 22
	1-Ethyl-2,3-dihydro-1 <i>H</i> -				14
	2-Ethyl-2,3-dihydro-1 <i>H</i> -			H ₂ PtCl ₆ 197 (dec.)	15
	1-Ethyl-5,6-dihydro-4 <i>H</i> -			P 191 (dec.)*	12
	1-Phenyl-5,6-dihydro-4 <i>H</i> -		120-30	P 179-80 (dec.)*	12
	1-Benzyl-5,6-dihydro-4 <i>H</i> -			P 194-6 (yellow)	12
XVII	3,3a,5,6-Tetrahydro-4 <i>H</i> -	32-3	80-100	P 211-12 (dec.)*	12
	1-Methyl-3,3a,5,6-tetrahydro-4 <i>H</i> -		110-20	P 221 (dec.)*	12
	1-Ethyl-3,3a,5,6-tetrahydro-4 <i>H</i> -		100	P 165-6	12
	1-Phenyl-3,3a,5,6-tetrahydro-4 <i>H</i> -	93-4	120-30	P 190-1 (dec.)	12
	1-Benzyl-3,3a,5,6-tetrahydro-4 <i>H</i> -		140-50		12
X	2-(4-Nitrobenzoyl)-2,3-dihydro-1 <i>H</i> -	171.5			13
XIII	2-Methyl-1-oxo-5,6-dihydro-4 <i>H</i> -	105-6			13
XIX	2-β-Hydroxyethyl-2,3-dihydro-1 <i>H</i> -	56		HCl 199-200 (yellow)	23
	2-β-Chloroethyl-2,3-dihydro-1 <i>H</i> -			HCl > 300 (yellow)	23
	2-Methyl-1-oxo-2,3-dihydro-1 <i>H</i> - (<i>N</i> -Methylnaphthalimidine)			Chloroplatinate 172 (dec.)	15
	2-Ethyl-1-oxo-2,3-dihydro-4 <i>H</i> -			Chloroplatinate 165 (dec.)	15
XXV	3-Acetonyl-1-oxo-2,3-dihydro-1 <i>H</i> -	142			16
XXVI	Oxime of XXV	208			16

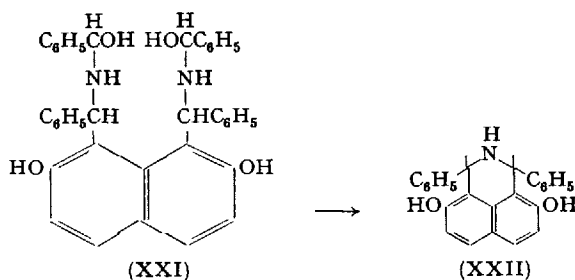
* *In vacuo*.

(Table continued)

TABLE VIII-1 (continued)

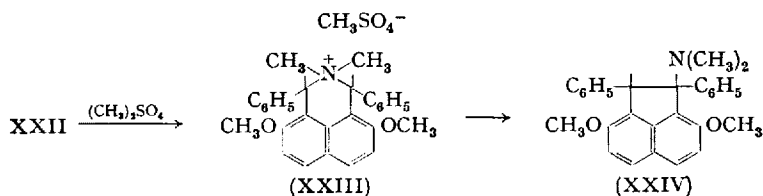
Formula	Substituent	M.p., °C.	B.p., range 0.01 mm.	Salts; m.p., °C.	Refs.
XXVII	3-Phenacylo-1-oxo-2,3-dihydro-1 <i>H</i> -	163			16
XXIX	3-Phenacylo-1-oxo-2-methyl-2,3-dihydro-1 <i>H</i> -	95-100			17
	3-(3-Methylphenacylo)-1-oxo-2,3-dihydro-1 <i>H</i> -	152-4			19
XXVIII	2-Acetyl-3-phenacylo-1-oxo-2,3-dihydro-1 <i>H</i> -	145			17
XXXI	Jaubert's oxime	220			18
XLVII	2-Anilino-1-hydroxy-3-oxo-				20

by loss of aldehyde and ammonia gives the 2-aza compound. Thus, with benzaldehyde the primarily formed 2,7-dihydroxynaphthalene-1,8-bis(α -benzyl- α' -hydroxybenzylamine) (XXI) gave 4,9-dihydroxy-1,3-diphenyl-2,3-dihydro-2-azabenzonaphthene (2,3-dihydro-1,3-diphenyl-2,1-*peri*-benzisoquinoline-4,9-diol) (XXII) upon short heating or warming with dilute alkali.



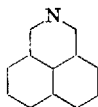
The new Beschke bases readily form salts. The hydroxyl groups and nitrogen atom in the new bases are readily alkylated and acylated, while the nitrogen atom is quaternarized by methyl sulfate.

When the methosulfates (XXIII) are heated at the boiling point



with 40% aqueous sodium hydroxide, a rearrangement takes place, resulting in the formation of a substituted acenaphthene (XXIV). The properties of Beschke bases and some of the salts are summarized in Table VIII-2.

TABLE VIII-2. 2,3-Dihydro-1*H*,2-azabenzonaphthenes. Beschke bases^a



Substituent (formula)	M.p., °C.	Properties ^d
4,9-Dihydroxy-1,3-diphenyl- (XXII) "2,7-Dioxynaphthylene-1,8-dibenzalimine"	152-3	Base 1H ₂ O m.p. 102-3 Base 1½C ₂ H ₅ OH m.p. 126-7 Red-brown or yellow 2,2-Dimethyl methosulfate m.p. 234-5
4,9-Dihydroxy-2',2''-dimethoxy-1,3-diphenyl-	266-7	
4,9-Dihydroxy-4',4''-dimethoxy-1,3-diphenyl-	206-7	Greyish
4,9-Dihydroxy-1,3-di-(2-furyl)-	198	2,2-Dimethyl methosulfate m.p. 215 2,2-Dimethyl chloride ^b m.p. 205-6
2',2'',4,9-Tetrahydroxy-1,3-diphenyl-	265-6	Violet salts
3',3'',4,9-Tetrahydroxy-1,3-diphenyl-	195-8	Grey
2-Acetyl-4,9-diacetoxy-1,3-diphenyl-	241-2	
2-Benzoyl-4,9-diacetoxy-1,3-diphenyl-	213	
2-Acetyl-2',2'',4,9-tetraacetoxy-1,3-diphenyl-	219-20	
2-Acetyl-4,9-diacetoxy-4'',4'-dimethoxy-1,3-diphenyl-	213-4	
2-Acetyl-4,9-diacetoxy-2',2''-dimethoxy-1,3-diphenyl-	167	
2-Acetyl-4,9-diacetoxy-1,3-di-(2-furyl)-	228	
2-Benzoyl-4,9-dibenzoyloxy-1,3-di-(2-furyl)-	211	
4,9-Dimethoxy-2,2-dimethyl-1,3-diphenyl-		Methosulfate m.p. 234-5
4,4',4'',9-Tetramethoxy-2,2-dimethyl-1,3-diphenyl-		Methosulfate m.p. 232 Methochloride ^b m.p. 214-15
2',2'',4,9-Tetramethoxy-2,2-dimethyl-1,3-diphenyl-		Methosulfate m.p. 268-9

^a Simple salts are yellow; methyl methosulfates are colorless.

^b By two recrystallizations of the methosulfate from hydrochloric acid.

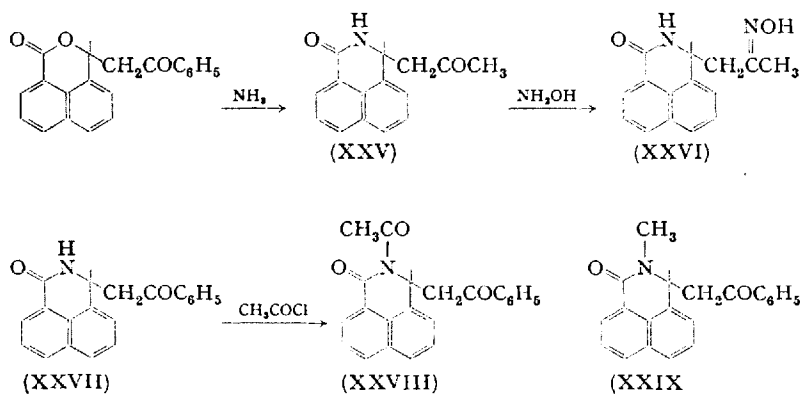
^c Beschke's name: 2,3-dihydro-1,3-bis(*o*-hydroxyphenyl)-2,1-*peri*-benzisoquinoline-4,9-diol.

(2) Naphthalimidines

Naphthalimidines are 1-oxo-2-azabenzonaphthenes (XIV). They have been obtained in three ways; by electrolytic reduction¹⁵ as already

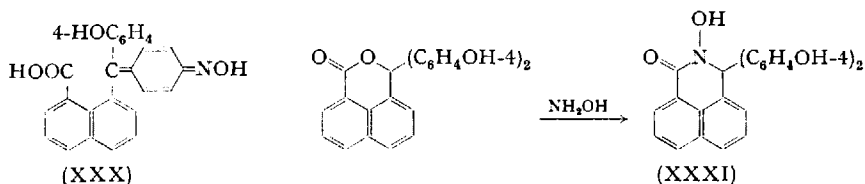
mentioned; by heating naphthalides with ammonia or amines;^{16,17} and in a single instance by interaction of phenolnaphthalein and hydroxylamine.¹⁸ The second method appears to be of general utility.

The naphthalimidines prepared from naphthalides have all been of the same type, and have a ketonic side chain in the 3-position. The naphthalides used were obtained from naphthaldehydic acid and a methyl ketone; 3-acetonynaphthalide, upon heating with ammonia, gives 3-acetonynaphthalimidine (XXV), which forms the oxime (XXVI).¹⁶ The 3-phenacyl derivative, XXVII, is obtained from the corresponding naphthalide; it can be acylated (XXVIII). The substitution of methylamine for ammonia in the reaction gives the 2-methyl derivative (XXIX).¹⁷



In his study of phenolnaphthalein, Jaubert¹⁸ treated its sodium salt with hydroxylamine, expecting to prove the presence of a ketonic carbonyl group. The reaction took place, and gave a product, $\text{C}_{24}\text{H}_{17}\text{O}_4\text{N}$, to which Jaubert assigned the structure of the expected phenolnaphthaleinoxime, XXX. In view of his own earlier work²⁰ on the behavior of naphthalic anhydride with hydroxylamine, the product of which reaction was written as *N*-hydroxynaphthalimide, it seems strange that he suggested the structure XXX just mentioned. By analogy, the hydroxynaphthalimidine XXXI would be expected; this structure is indeed assigned to Jaubert's oxime in Beilstein,²¹ in which it is named 2-oxy-3,3-bis-(4-oxyphenyl)-naphthalimidine. By the "a" system, XXXI is 2-hydroxy-3,3-bis-(4-hydroxyphenyl)-1-oxo-2,3-dihydro-2-

azabenzonaphthene. Reissert¹⁵² attempted to prepare 3-hydroxy-2-naphthalimidine by the action of ammonia on the corresponding



hydroxynaphthalic anhydride, but did not obtain a homogeneous product.

(3) Naphthalimides

The name, naphthalimide, was assigned to the cyclic imide resulting from the interaction of naphthalic acid or its anhydride with ammonia, by analogy with phthalimide. Other names are 1,3-dioxo-2-azabenzonaphthene, 1*H*-benz[*de*]isoquinoline-1,3(2*H*)-dione, and 2,1*H*-*peri*-benzisoquinoline-1,3(2*H*)-dione. A considerable variety of substituted naphthalimides is known; many of these were prepared at the turn of the century, when the interest in vat and sulfur dyes was at its height. A large number have also resulted from their use as reference compounds; whenever a substituted naphthalic acid was made for any purpose (*e.g.*, a study of substitution products of acenaphthene), it was characterized as its anhydride and imide. The properties of all naphthalimides, except the 2-amino derivatives are collected in Table VIII-3. They are colorless or yellow, depending on the substituent group.

(a) Preparation. Naphthalimides result when naphthalic acids, chlorides,¹⁷⁷ or anhydrides are heated with ammonia or substituted ammonias at temperatures varying from 100 to 180°. ^{24-26, 186, 183, 184, 189} It is sometimes necessary to conduct the reaction under pressure with low-boiling amines and ammonia. Naphthalimides having a substituent group on the nitrogen (XXXII) can be obtained by the use of substituted ammonias, or by alkylation of the sodium derivative of naphthalimide, or by acylation. According to a recent patent,¹⁷⁴ 2- β -acetoxy-ethylnaphthalimide results when naphthalic anhydride and 2-methyl-2-oxazoline are heated in an autoclave at 225°. Of minor importance are: the formation of naphthalimide itself (III) from the monoxime of

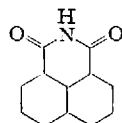


TABLE VIII-3. Naphthalimides

Substituent (formula)	M.p., °C. (color)	Refs.
None; Naphthalimide (III)	300	20, 24, 26-30, 176, 183, 184
2-Methyl- (IIIa)	205	20, 80, 181
2-Ethyl-	148	20
5-Ethyl-	217-218.5	172
6-Ethyl-	195-6	172
5-Ethyl-2-methyl-	113-4	172
6-Ethyl-2-methyl-	140	172
4- <i>tert</i> -Butyl-	201-2	164
5- <i>tert</i> -Butyl-	256	48, 165
6- <i>tert</i> -Butyl-	208.5-210.5	164
2- <i>n</i> -Amyl-	84-85	163
4- <i>tert</i> -Butyl-2-methyl-	132-3	164
5- <i>tert</i> -Butyl-2-methyl-	173	48, 165
6- <i>tert</i> -Butyl-2-methyl-	132-3	164
2- <i>n</i> -Hexyl-	74-5	163
2- <i>n</i> -Dodecyl-	57-8	163
5,8-Di- <i>tert</i> -butyl-	240	48, 165
5,8-Di- <i>tert</i> -butyl-2-methyl- ^a	231-2	48, 165
2-Benzyl-	196.5-197.5	20, 25, 31
6-Benzyl-	227 (yellow)	37, 38
2-Cyclohexyl-	224-5	163
2-Phenyl- (naphthalanil)	202	20
2- <i>o</i> -Tolyl-	217-8 (yellow)	20, 31
2- <i>m</i> -Tolyl-	175-6 (yellow)	31
2- <i>p</i> -Tolyl-	304-5 (yellow)	31
Biphenyl-4,4'-bis(2-naphthalimide) (dinaphthalylbenzidine)	ca. 500	60, 64
2- α -Naphthyl-	214-5	31
2- β -Naphthyl-	291-2	31
2- β -Naphthalimidoethyl-	372	46
2-Chloro- (XXXV)	233 (yellow)	32
4-Chloro-	332-3	41
5-Chloro-	315	41
6-Chloro-	301-2	41, 52
5-Chloro-2-methyl-	182-3	76
6-Chloro-5,8-di- <i>tert</i> -butyl-	294	165
6-Chloro-5,8-di- <i>tert</i> -butyl-2-methyl-	265	165

(Table continued)

TABLE VIII-3 (*continued*)

Substituent (formula)	M.p., °C. (color)	Refs.
6-Chloro-1-phenyl-	239-40	180
6-Chloro-1-(4-ethoxyphenyl)-	209-10	180
2- β -Chloroethyl-	306-7	46
5,8-Dichloro-	327-8	75
$\alpha,\alpha,\alpha,\alpha$ -Tetrachloro-	302-3 (yellow)	33
Hexachloro-	260-1 (yellow)	33
2-Bromo- (XXXIV)	200 (dec.) (yellow)	32
4-Bromo-	318	41
6-Bromo- (XXXVI)	294, 298 (yellow) (284)	33-35, 40, 78, 181
α -Bromo-	> 265	78
6-Bromo-2-methyl-	185-6 (yellow)	181
2- β -Bromoethyl-	222-3	46
6-Bromo-2- <i>n</i> -butyl-	104-5 (yellow)	53, 62
6-Bromo-2- <i>n</i> -amyl-	73-5 (yellow)	53, 62
6-Bromo-2- <i>n</i> -dodecyl-	55-8	62
5-Bromo-6,7-di- <i>tert</i> -butyl-	314-5	55
5-Bromo-6,7-di- <i>tert</i> -butyl-2-methyl-	218-20	55
6-Bromo-2-cyclohexyl-	223-5	53
α -Bromo-5- <i>tert</i> -butyl- α -methylamino-	301-2 (yellow)	165
α,α -Dibromo-5- <i>tert</i> -butyl-	294-5	165
α,α,α -Triiodo-	325 (dec.) (yellow)	33
2- β -Iodoethyl-	226-7	46
5-Nitro-	308 (yellow)	76
6-Nitro- (XXXVII)	284	36, 39
5-Nitro-2-methyl-	226-8	76
5-Nitro-6,7-di- <i>tert</i> -butyl-	288-9	55
5-Nitro-6,7-di- <i>tert</i> -butyl-2-methyl-	260	55
2',4',5-Trinitro-6,7-di- <i>tert</i> -butyl-2-phenyl-	308-9	55
2-(4'-Nitrophenyl)-	> 500	64
5,8-Dinitro-2-methyl-	280 (yellow)	76
2-Amino-(see Table VIII-4)		
5-Amino-	355	66
6-Amino-	> 325	70, 71
5-Amino-2-methyl-	278-80 (yellow)	76
2-(4-Aminophenyl)-	288	178
2- β -Aminoethyl- (LIX)	137-9 ^b	46
6-Amino-2- <i>n</i> -butyl-	184-5 (orange)	63
6-Amino-2-isobutyl-	206.5-207.5 (yellow)	63
6-Amino-2-amyl-	167-73 (yellow)	63
6-Amino-2-(2,4-dimethylphenyl)- ^g		166

(Table continued)

TABLE VIII-3 (*continued*)

Substituent (formula)	M.p., °C. (color)	Refs.
5-Methylamino-2-methyl-	235	66
6-Methylamino-2-methyl-	256-8	70, 71
6- <i>n</i> -Dodecylamino-2- <i>n</i> -amyl- ^d	90-2 (greenish-yellow)	62
6-Amylamino-2- <i>n</i> -dodecyl- ^d	Oil	62
6- <i>n</i> -Undecylamino-2- <i>n</i> -undecyl- ^d	84-6	70, 71
2- β -Naphthalimidoethyl-	372	46
6- β -Sulfoethylamino-2- β -sulfoethyl- (di-Na salt)		70, 71, 156
6-Cyclohexylamino-2-cyclohexyl-		70, 71
6-Anilino- (XXXXVIII)	237 (yellow)	72
6- <i>p</i> -Toluidino-	263 (yellow)	72
6-Anilino-2-methyl-	178, 256-8 (yellow-orange)	72, 181
2-Anilino-6- <i>tert</i> -butyl-	187-8	48
2-Anilino-6,7-di- <i>tert</i> -butyl-	246	48
2-(2-Aminophenyl)- (<i>o</i> -Aminonaphthalanil) (LXI)	245	74
2-(2-Amino-4(or 5)-methylphenyl)- ^d	196	74
2-(2-Ethylaminophenyl)-	235-7	74
2-(2-Aminobenzyl)-	233.5-235 (yellow)	182
2-(4'-Aminobiphenyl)- (Naphthalylbenzidine)	> 300, 318 (yellow)	60, 64
2-(4'-Benzalaminobiphenyl)-	297 (yellow)	60
2-[4'-(3-Nitrobenzalamino)biphenyl]-	299 (yellow)	60
2-(4-Salicylaminobiphenyl)-	283 (greenish-yellow)	60
2-(1-Amino- β -naphthyl)-	> 300	74
2-(2-Acetamidophenyl)-	224	74
2-(2-Benzamidophenyl)-	209	74
5-(1-Anthraquinonyl)-2-methyl-	286-7 (brown)	76
5-(4-Benzamido-1-anthraquinonyl)-2-methyl- (LXVI)	330-1 (mauve)	76
5-(5-Benzamido-1-anthraquinonyl)-2-methyl-	338-9 (red)	76
5,8-Diamino-	406 (dec.)	75
5,8-Diamino-2-methyl-	> 400 (yellow)	76
5-Amino-8-(4-benzamido-1-anthraquinonyl)- 2-methyl-	293-7 (blue)	76
5-Acetamido-2-methyl-	329-30	76
6-Acetamido-2- <i>n</i> -butyl- ^h	231-2	170, 173
6-Acetamido-2-octyl- ^h	186-7	170, 173
6-Acetamido-2-tetradecyl- ^h	165-6	170, 173
6-Acetamido-2-octadecyl- ^h	154-5	170, 173
2- β -Acetamidoethyl-	201-2	46
6-Benzamido-2- <i>n</i> -butyl- ^h	226	170, 173

(*Table continued*)

TABLE VIII-3 (*continued*)

Substituent (formula)	M.p., °C. (color)	Refs.
5,8-Diacetamido-	> 400 (dec.)	75
5,8-Diacetamido-2-methyl-	383-4 (yellow)	76
6-Amino-2- <i>n</i> -butyl- <i>x,x</i> -disulfo-	`	45
6-Amino-2-cyclohexyl- <i>x,x</i> -disulfo-		45
6-Amino-2-benzyl- <i>x,x</i> -disulfo-		45
6-Amino-2- β -hydroxyethyl- <i>x,x</i> -disulfo-		45
6-Amino-2-carboxymethyl- <i>x,x</i> -disulfo- (LXVII)		45
6-Amino-2- β -tolyl- <i>x,x</i> -disulfo-		45
6-Amino-2- β -naphthyl- <i>x,x</i> -disulfo-		45
2-Hydroxy- (XLVIII)	276-7 (yellow)	20, 33, 182
2-Hydroxy-5,8-di- <i>tert</i> -butyl-	180	48, 165
4-Hydroxy-	303-4	41
5-Hydroxy-		39
6-Hydroxy-	> 350, 249, 251	39, 51, 181
5-Hydroxy-2-methyl-	272-3 (yellow)	39, 76
5-Hydroxy-2-phenyl-	> 300	39
2,5-Dihydroxy-		39
5,8-Dihydroxy-	395 (dec.)	75
2,5,6-Trihydroxy- ^e		67
5-Hydroxy-6-bromo-	237-8	67
5-Hydroxy- <i>x</i> -bromo-	339	41
2,5-Dihydroxy-6-bromo-	247-8 (yellow)	67
5-Hydroxy-6-nitro-	310	67
5-Hydroxy-6-amino-	> 360 (red)	67
2-Methoxy- (L)	211	20
5-Methoxy-2-methyl-		39
2,5-Dimethoxy-	191	39
2-Ethoxy-	160	20
2- β -Hydroxyethyl-	175-6	23, 46
2- β -Hydroxyethyl-5- <i>tert</i> -butyl-	167-8	165
2- β -Hydroxyethyl-6- <i>tert</i> -butyl-	127-8	164
2- β -Hydroxyethyl-5,8-di- <i>tert</i> -butyl-	248	165
2- γ -Methoxypropyl-	95-6	163
2-Cyanomethyl- (LIV)	248 (dec.) (yellow)	69
6-Carboxy-		42
2-Carboxymethyl- (LV)	259-60	69
2-Carbomethoxymethyl-	175-6	46
2-Chloroformylmethyl-	232 (yellow)	69
2-Carboxamidomethyl- (LVI)	{ 319 (dec) (yellow) 323-4 (dec.)	{ 69 46
5-Sulfonamido- (LVII)	348	41

(Table continued)

TABLE VIII-3 (*continued*)

Substituent (formula)	M.p., °C. (color)	Refs.
2- β -Acetoxyethyl-	139.5-140.5, 130-2	23, 174
5-Acetoxy-2-phenyl-	212	39
5-Acetoxy-2-acetyl- (LI)	194	39
2,5-Diacetoxy-	194	39
5-Benzoxyl- α -bromo-	252-3	41
6,7-Diacetyl-	284	77
6-Propionyl-	221-2 (yellow)	49, 50
6-Benzoyl-	252	37
6-Benzoyl-2-methyl- <i>f</i>	190-1	76
6-Benzoyl-7-nitro-	302-4 (yellow)	38
6-(2-Carboxybenzoyl)-	> 300	36
6-(2-Carboxybenzoyl)-2-methyl- (LXIII)	238-9	44
2-Phenylmercuri- (LVIII)	181-2	43
5-(2-Hydroxy-1-naphthaleneazo)-2-methyl-	315-7 (red)	76
6- <i>n</i> -Octadecylamino-2- <i>n</i> -butyl- ^a		62
6- <i>n</i> -Octadecylamino-2- <i>n</i> -amyl- ^a	Wax (bright yellow)	62
6- <i>n</i> -Heptadecylamino-2- <i>n</i> -heptadecyl-		70, 71
6- β -Hydroxyethylamino-2- <i>n</i> -butyl-	168-9	53
6- β -Hydroxyethylamino-2- <i>n</i> -amyl-		53
6- β -Hydroxyethylamino-2-cyclohexyl-		53
6- β -Hydroxypropylamino-2- <i>n</i> -amyl-		53
6- β -Hydroxyethylamino-2- β -hydroxyethyl-	214	70, 71
2- β -Dimethylaminoethyl-	261 (dec.)	54
2- β -Diethylaminoethyl-	155-6 (dec.)	54
2- γ -Diethylaminopropyl-	226-7 ^c	54
2- β -4-Morpholinoethyl-	144 (dec.)	54
2- β -Phthalimidoethyl-	237-8	46
3-Hydroxy-6,2'-hydroxynaphthalene-1'-azo-naphthalimide	333-5 (dec.) (red)	75
6'-Naphthalimido- <i>N</i> -pyrazoloanthrones	> 300	

^a Violet fluorescence in alcohol.

^b Picrate m.p. 280° (dec.).

^c The melting points are those of the hydrochlorides.

^d Green fluorescence.

^e Blue-violet in alkali, purple aluminum lake; brown chromium lake.

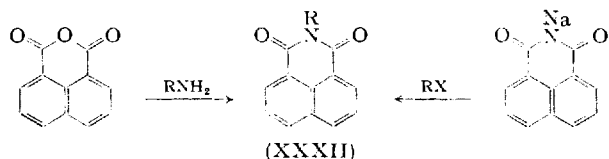
^f Red solution in Na₂S₂O₄.

^g Celliton Brilliant Yellow FF.¹⁶⁶

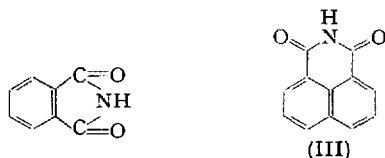
^h Blue fluorescence.

acenaphthenequinone and various acidic reagents,^{26-29,73,79} or by the action of sodium hypobromite or nitrous acid upon 2-aminonaphthalimide;³⁰ from naphthalyl benzalhydrazone and hydrogen peroxide in

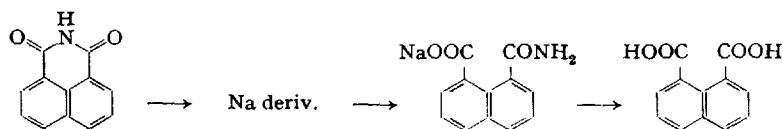
acetic acid¹⁶⁰ (see p. 510); and the formation of 2-alkyl or arylphthalimides by ring closure of *N*-alkyl or arylphthalamic acids.⁶¹



Since naphthalimide is the analog of phthalimide, it would be expected to show resemblances in chemical behavior, with some differences due to the nature of the ring system. Thus, both are insoluble in



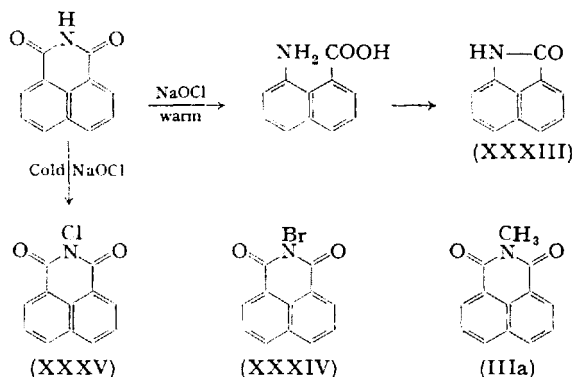
sodium carbonate solution, and react with dilute alkali hydroxides, to give sodium or potassium salts; if the reaction time is prolonged or concentrated solutions are used, ammonia is evolved, and the ring is cleaved, with formation of the corresponding dibasic acid. This behavior serves to show whether an introduced group has entered the hetero or



one of the homonuclear rings, so is useful in structure studies. A silver derivative of naphthalimide is also known; it is formed by mixing alcoholic solutions of the imide, silver nitrate, and ammonia.²⁴

Both phthalimide and naphthalimide give *N*-bromo or *N*-chloro substitution products when treated with cold (0–5°) hypohalous solutions,³² but at higher temperatures the hetero ring is opened and a Hofmann rearrangement takes place. Phthalimide gives anthranilic acid, but naphthalimide gives rise to naphthostyryl (XXXIII), the dehydration product of the expected 8-carboxy-1-naphthylamine.⁸⁹

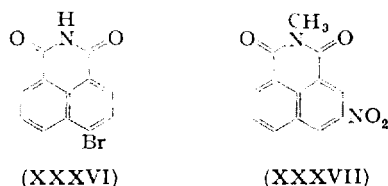
The 2-bromo derivative (XXXIV) is yellow. Both it and the chloro analog (XXXV) are reconverted to naphthalimide by treatment with ammonia.



The sodium derivatives of both cyclic imides are easily alkylated, pressure being needed when low-boiling alkyl halides are used; methyl iodide gives 2-methylnaphthalimide (IIa). Many other analogous reactions are known, but only those of naphthalimide will be described in the remainder of this section.

Naphthalimide itself is a white solid, m.p. 300° , that can be sublimed unchanged. It is insoluble in water and the common low-boiling organic solvents; it is soluble in acetic acid. It can be recrystallized unchanged from concentrated nitric acid (no nitration), from which it separates in long needles.²⁰ Its sulfuric acid solution shows a violet fluorescence.

(b) Halonaphthalimides. Most of the halogenated naphthalimides having halogen in the nucleus are obtained from the corresponding naphthalic anhydride and ammonia.⁵² Two melting points have been given for the 6-bromo derivative (XXXVI); Blumenthal,³⁴ Francesconi and Bargellini,³³ and Dzięwoński³⁵ give 284° , which value appears in



Beilstein,^{21a} while a later publication by Dziewoński⁴⁰ gives 294°. Some of the earlier investigators³³ had mixtures rather than a homogeneous product.

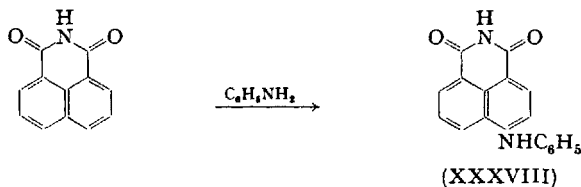
(c) Aminonaphthalimides. 6-Amino-2-alkylnaphthalimides can be prepared: (a) by treating 6-bromonaphthalic anhydride with an excess of the amine, with or without a copper catalyst and in a high boiling solvent,⁵³ or (b) by first making the 6-bromo-2-alkyl naphthalimide using but one equivalent of amine, followed by additional amine under the above conditions.⁵³ This second alternative is possible because of the great difference in reactivity of the anhydride group and bromine atom, and it allows the preparation of 2-alkyl-6-amines with unlike groups. The halogen replacement is essentially an Ullmann-type synthesis.^{72,76,137,164}

While naphthalimide can be crystallized unchanged from concentrated nitric acid, the 2-methyl homolog can be nitrated by a mixture of nitric acid and acetic acids; the nitro group enters the 5-position (XXXVII).

Aminonaphthalimides can be obtained by the usual type of ring closures,^{45,60,66,74} by reduction of nitro compounds,⁷⁶ by replacement of groups already present (*e.g.*, sulfonic acid,^{70,71} hydroxyl,^{66,75} Ullmann synthesis^{62,66}) and, in a side chain, by replacement of halogen⁶⁴ or by hydrolysis of a phthalimido derivative.⁴⁶ The special cases of the 6-anilino derivative⁷² and the 2-amino series will be considered separately.

A discrepancy in the literature may be mentioned at this point. There are two accounts describing the preparation and properties of 2-(4'-aminobiphenyl)naphthalimide. Sircar⁶⁰ obtained it as yellow needles, melting above 300°, by refluxing an aqueous suspension of naphthalic anhydride and benzidine in pyridine; he stated that it could be diazotized and coupled with phenols. Poray-Koshits⁶⁴ fused the anhydride and benzidine at 175–80° for five minutes, or heated them in a sealed tube (190–200°), and stated that this product melted at 318° and could not be diazotized. The bis-compound, dinaphthalylbenzidine, was made by heating the components for a long time, and melted above 500°.

6-Anilidonaphthalimide (XXXVIII) is prepared by an unusual type of reaction.⁷² Two equivalents of sodium are dissolved in aniline, traces of copper powder and nickel oxide are added as catalysts, followed by naphthalimide, and the mixture is heated; this has been confirmed.^{163a} This is an example of a rather rare nucleophilic substitu-

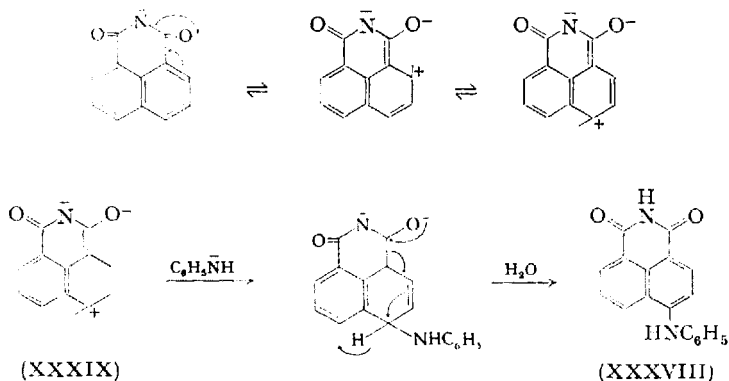


tion. Most of the other known examples are in the pyridine and quinoline series, *e.g.*, sodium amide and pyridine give 2-aminopyridine. The following mechanism has been suggested for the reaction; it should be noted that a hydride ion is displaced:⁸⁷ As might be expected, halo,

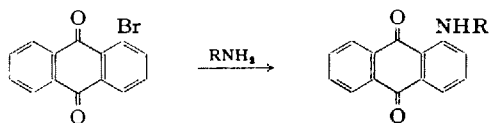


methoxy, or sulfo groups may also be displaced, more readily than the hydride ion. The presence of oxidizing agents may facilitate the displacement of the hydride ion.

Applied to naphthalimide, the mechanism may be represented as follows, using sodium derivatives of both the imide (XXXIX) and aniline:



The most familiar examples of this type of reaction are those involving the displacement of a bromide ion, *e.g.*, the Ullmann synthesis.

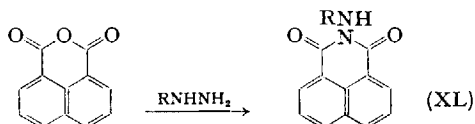


The reaction is facilitated by the elimination of the much more stable bromide ion.

Chemical. Properties. The amino groups on the aromatic rings have the expected properties; they can be diazotized and either replaced by other groups (*e.g.*, halogen,⁷⁶ hydroxyl⁷⁶) or coupled to form azo dyes.^{75,76} They are readily acylated^{30,74-76} and give Schiff bases.^{30,81,82}

Uses. Most of the amines are yellow; the solutions of many have a strong fluorescence. In addition to their use in synthesis, suitably substituted amines are used as dyes (see pp. 567 ff.).

(d) 2-Aminonaphthalimides. When naphthalic acids or their anhydrides are treated with hydrazines, 2-aminonaphthalimides (XL) result. The properties of the known 2-amino derivatives are collected in Table VIII-4.



The structure of the products arising from the reaction of a hydrazine and naphthalic acid or anhydride has been the subject of some speculation. The synthesis is ambiguous in that the product could

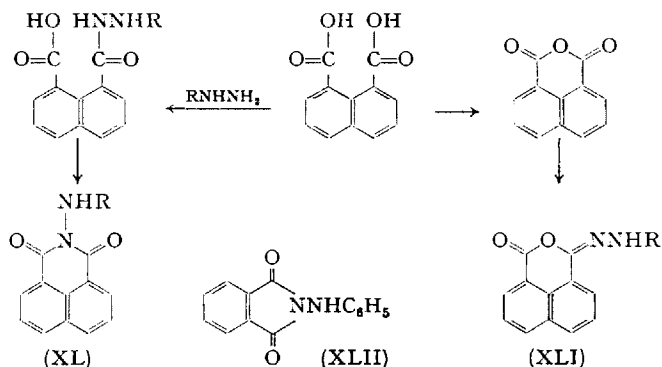


TABLE VIII-4. 2-Aminonaphthalimides

Substituent (formula)	M.p., °C. (color)	Refs.
None; 2-Aminonaphthalimide (XLIII)	262 (yellow)	30, 56, 82
2-Amino-5,8-di- <i>tert</i> -butyl-	246 (yellow)	48, 165
2-Formamido-	245-6 ^b	30
2-Succinylamido-	213 (dec.)	30
2-Maleoylamido-	205 (dec.)	30
2-Citraconoylamido-		30
2- <i>N</i> -Hydroxybenzylamino-		85
2-Anilino-	218-218.5 108-9	20, 33, 57
2-Anilino-6- <i>tert</i> -butyl-	187-8 (yellow)	48
2- <i>o</i> -Toluidino-	248-9	58
2- <i>m</i> -Toluidino-	209-10	58
α -Naphthylamino-	277-8 (dec.)	58
β -Naphthylamino-	268	58
<i>N</i> -Methylanilino-	210, 214-15	58, 68
<i>N</i> -Ethylanilino-	151-2	58
<i>N-n</i> -Propylanilino-	154-5	58
<i>N</i> -Cetylanilino-	97-9	58
2-Anilino-4-bromo- (really the 6-bromo)		41
2-Anilino-5-bromo-	316	59
2-Anilino-6-bromo-	223-4	33, 41
2-Anilino- <i>x,x,x,x</i> -tetrachloro-	269-70 (yellow)	33
2-Anilino- <i>x,x,x</i> -triiodo-	305-10 (dec. yellow)	33
2- <i>o</i> -Nitroanilino-	281-2	58
2- <i>p</i> -Nitroanilino-	> 300	58
2',4',5-Trinitro-2-anilino-6,7-di- <i>tert</i> -butyl-	308-9	55
4-Hydroxy-2-anilino-	238-9	41
5-Hydroxy-2-anilino-	265	39
5,6-Dihydroxy-2-anilino-	317-8 (yellow; purple in alk.)	67
2-(α -Hydroxybenzyl)amino- (XLVI)	180°	85, 169
2-(α -Hydroxycumyl)amino-	190°	169
5-Hydroxy-2-anilino-6-bromo-	283-4 (yellow)	67
2-Acetamido-	260-1	30
2-Benzamido-	290-1	30
2- <i>N</i> -Acetylanilino-	230	20
2- <i>N</i> -Benzoylanilino-	235	20
2,5-Dioxo-1-(2-naphthalimido)-pyrrolidine ^d	272-3	30
2,5-Dioxo-1-(2-naphthalimido)-3-pyrroline ^d	240	30
2,5-Dioxo-3-methyl-1-(2-naphthalimido)-3-pyrroline ^d	254-5	30

(Table continued)

TABLE VIII-4 (*continued*)

Substituent (formula)	M.p., °C. (color)	Refs.
2-Phthalimido-	<i>ca.</i> 320	30
2-Amino-6-hydrazino-	> 300	71
2-(α ,4-Dihydroxybenzylamino)-	(dec.)	30
2-(α ,3',4'-Trihydroxybenzylamino)-	(dec.)	30
2-(α ,4'-Dihydroxy-3'-methoxybenzylamino)-	(dec.)	30

^a Phosphate yellow, m.p. 192; blue fluorescence in sulfuric acid.

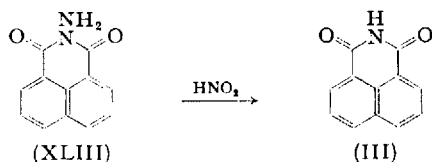
^b Violet fluorescence in sulfuric acid.

^c shr. 160–170°; resolidifies after melting and is still solid at 380–400°.

^d Complete name.

be either the 2-aminonaphthalimide (XL) or the hydrazone (XLI). Both possibilities are given in Beilstein.

A similar situation is encountered with *o*-phthalic acid; in this instance, the cyclic *N*-anilinophthalimide structure (XLII) has been generally accepted.⁸⁸ Because of this analogy, and because simple anhydrides never form hydrazones, the 2-aminonaphthalimide (XLIII) structure is favored. Furthermore, it seems to be reasonably well



established by its chemical behavior with nitrous acid; with this reagent the amino group is removed, and naphthalimide is formed.³⁰

A large number of Schiff bases of 2-aminonaphthalimide have been described; they are summarized in Table VIII-5.

Two reactions of 2-aminonaphthalimides merit mention: (*a*) When 2-aminonaphthalimide itself is heated with acetic or phthalic anhydride,⁸⁶ two moles condense with elimination of hydrazine, and binaphthalimyl (2-naphthalimylnaphthalimide, *N*-naphthalimylnaphthalimide, naphthalyl-*N*-aminonaphthalimide) (XLIV) results. A sub-

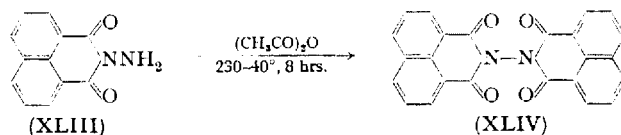
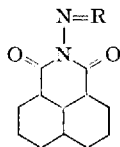


TABLE VIII-5. Schiff Bases of 2-Amino-naphthalimide



R	M.p., °C.	Refs.
$\text{CH}_3\text{CH}=\text{}$	172	30
$\text{C}_6\text{H}_5\text{CH}=\text{ (XLV)}$	206-7	30
$\text{C}_6\text{H}_5\text{CH}=\text{CHCH}=\text{}$	195-6	30
	230-1	30
	(dec.) ^a	30
	283-4 (dec.)	30
	216-7	30, 82
	288-9 (dec.) ^b	30
	c, d	30
	231-2 ^c	30
	229-30	30
	256-7	30
	118-20	30

(Table continued)

TABEL VIII-5 (continued)

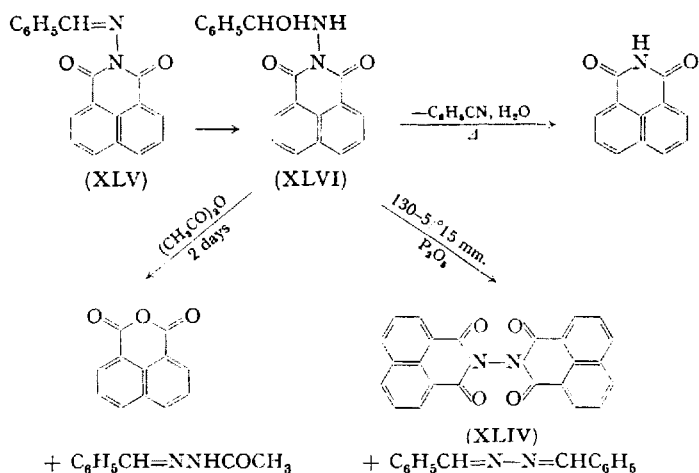
R	M.p., °C.	Refs.
$\text{CH}_3\text{-}\langle\text{C}_6\text{H}_4\rangle\text{-CH=}$	204-6	82
<i>iso</i> - $\text{C}_3\text{H}_7\text{-}\langle\text{C}_6\text{H}_4\rangle\text{-CH=}$	182	82, 162
$\text{C}_6\text{H}_5\text{COC=}$ CH_3 	170-1	81
Ozazones ⁸¹		
=CHCH=	327-8 (dec.)	81
CH_3 =C-CH=	238-40 (dec.)	81
$\text{CH}_3 \quad \text{CH}_3$ =C-C=	329-30 (dec.)	81
C_6H_5 =C-CH=	185-6 (dec.)	81
Unknown substance: 3 amino- naphthalimide: 1 glyoxal	244-6	81

^a Yellow-brown; red-violet in sulfuric acid.^b Turns red about 180°.^c Yellow.^d Turns brown *ca.* 260°, black at 280°, without melting.

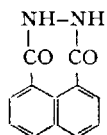
stance to which this structure had been assigned previously⁸⁰ proved to be unchanged 2-aminonaphthalimide.⁸⁶ Although the latter gives Schiff bases with aldehydes, an analogous reaction does not occur with ketones; instead, binaphthalimyl is formed. (b) When the Schiff base from 2-aminonaphthalimide and benzaldehyde ("naphthalylbenzalhydrazone," XLV) is treated with alcoholic alkalis, a disodium derivative results.¹⁶⁹ Upon acidification a new substance is obtained that gives analytical results that correspond to the addition of one molecule

of water. The new substance is now represented as shown in XLVI, although in the first report⁸² the positions of the H and OH were reversed, the OH being attached to the nitrogen atom. This behavior differs from that of the simple phenylhydrazone of benzaldehyde, which, under similar conditions, gives the α -osazone of benzil.¹⁶¹

When this addition product (the hydrate) is heated, it decomposes to benzonitrile, naphthalimide, and water. If it is heated with phosphorus pentoxide for eight hours, binaphthalimyl (XLIV) and benzaldazine result, whereas, with acetic anhydride, naphthalic anhydride and benzalacetylhydrazine are obtained. Naphthalylbenzalhydrazone is unaffected by acetic anhydride, hence does not appear to be an intermediate.

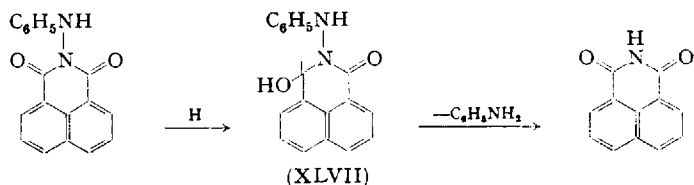


Bistrzyski and Risi⁵⁶ reported that when naphthalic anhydride was treated with hydrazine acetate they obtained a new, pale yellow substance that would neither react further with the anhydride nor form a benzal derivative. Accordingly, they assigned to it a structure having a seven-membered ring (*cf.* p. 519). However, they were unable to



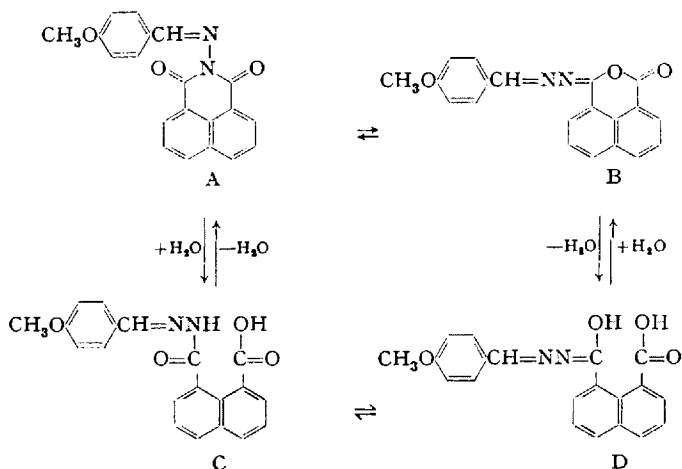
repeat the preparation after the first few times; all subsequent attempts gave 2-aminonaphthalimide (XLIII).

Jaubert²⁰ reported that reduction of 2-anilinonaphthalimide gave the hydrazone of oxynaphthalide; in modern terminology, this substance would be 2-anilino-1-hydroxynaphthalimidine (XLVII). While



this is presumably a general reaction, it has not been utilized to any extent. The hydroxynaphthalimidine dissociates to aniline and naphthalimide upon dry distillation.

A rearrangement of one of the Schiff bases of 2-aminonaphthalimide has been reported.⁸² A disodium hydroxide addition product was first prepared by allowing a mixture of the base, A, and alcoholic sodium hydroxide to stand for three days. The dry substance was then stirred with acetic anhydride, the initially white color changing to yellow. The purified product was said to be the isoimide, B. With alkali it reverted to the Schiff base. Probably the course of the "rearrangement" proceeds by ring opening (addition of water) to give the carboxy-



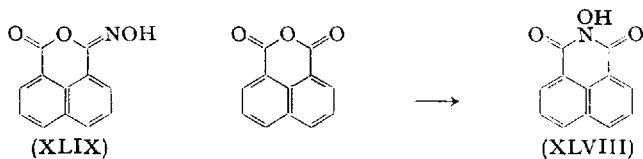
hydrazide, C; subsequent ring closure can proceed by loss of water either with the amino hydrogen, which reforms the Schiff base, or through the enolic form, D, which gives the isoimide.

Nomenclature. Owing to the uncertainty in structure, the names of the products arising from the interaction of hydrazine and naphthalic acid derivatives have been confusing. In spite of the evidence favoring the 2-aminonaphthalimide structure, they are often listed as hydrazones, *e.g.*, phenylhydrazone of naphthalic acid. This practice must be taken into account when a literature survey is being made. 2-Aminonaphthalimide (XLIH) has also been called *N*-aminonaphthalimide, *N,N*-naphthalylhydrazine, and β,β -naphthalylhydrazine.

(e) **Hydroxynaphthalimides.** (1) *Phenols.* Naphthalimides having a phenolic group are obtainable by the replacement of sulfo groups in an alkaline medium,^{41,47,76} by the diazo reaction,⁷⁶ and by the usual cyclization reaction using ammonia on naphthalic acids or anhydrides.^{39,51,67,75} Bromo, nitro, and amino hydroxynaphthalimides are obtainable by the usual reaction of ammonia on the cyclic anhydride.^{41,67} The 2-hydroxynaphthalimides will be discussed separately.

(2) *Alcohols.* 2- β -Hydroxyethylnaphthalimides result when ethanolamine reacts with the anhydrides,^{23,45,46} or when the β -aminoethyl analog is treated with nitrous acid.⁴⁶

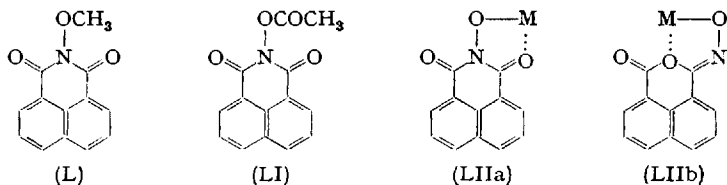
(f) **2-Hydroxynaphthalimides.** When naphthalic acids or their anhydrides are treated with hydroxylamine,²⁵ the products that result can be written in two possible ways. One is a 2-hydroxynaphthalimide (XLVIII) while the other is the monoxime of the anhydride (XLIX). The situation parallels that of the hydrazines (p. 505), as well as that of phthalic acid or anhydride and hydroxylamine. If hydroxylamine is



regarded as a substituted ammonia, the first alternative would be expected by analogy, and this structure is the one commonly accepted.

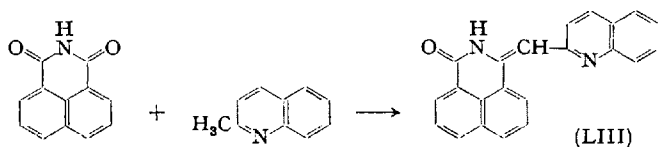
Both possibilities, however, are given in Beilstein. Other names that have been given to 2-hydroxynaphthalimide (XLVIII) are *N*-oxynaphthalimide, *N,N*-naphthalylhydroxylamine, naphthaldoxime, naphthalhydroxamic acid,¹⁷¹ and 3-oximinonaphthalide.

Reactions that might be used to distinguish between the two possible structures are inconclusive. The substances form red sodium salts, which, when heated with methyl iodide in a sealed tube, are converted to methyl ethers²⁵ (L). Acetylation is accomplished with acetic anhydride³⁹ (LI). At first sight it would seem that the best evidence for the 2-hydroxy structure is the formation of colored metallic salts, the production of color being associated with the presence

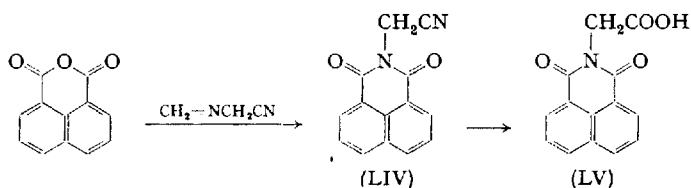


of a chelate ring. Unfortunately, this behavior is of no use, for such a ring can be written with both structures (LIIa, b).

The only substance that definitely contains the type structure of the oxime form is 3-quinaldylidenenaphthalimide (LIII), which results when naphthalimide is treated with quinaldine in the presence of zinc chloride.⁸⁴ 2-Hydroxynaphthalimide has been used in oxidimetry.¹⁷¹

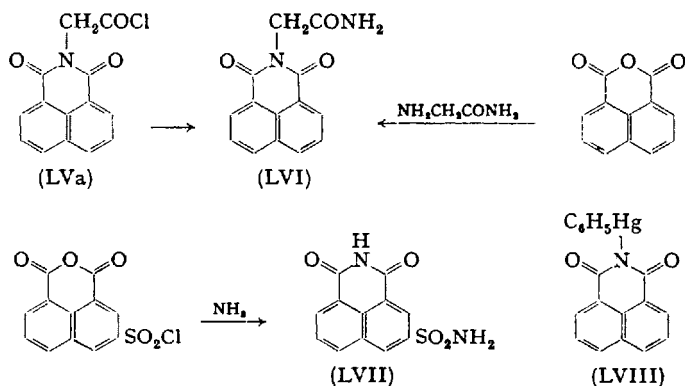


2-Cyanomethylnaphthalimide (LIV) can be obtained by the action of methyleneaminoacetonitrile upon the anhydride in boiling toluene.⁶⁹



This appears to be a novel application of the nitrile; the same type of reaction is observed with phthalimide. The cyano derivative (LIV) can be hydrolyzed to the acid (LV) without opening the hetero ring. The acid (LV) has also been obtained by chromic acid oxidation of 2- β -hydroxyethylnaphthalimide.⁴⁶

(g) Amides. The carboxamide (LVI) can be obtained either from the acid chloride⁶⁹ (LVa) with ammonia, or from naphthalic anhydride and glycine.⁴⁶ The only known sulfonamide (LVII) is formed by the action of ammonia on the 5-sulfonyl chloride of naphthalic anhydride.⁴¹



(h) Mercury Derivatives. Only one mercurated compound, 2-phenylmercurinaphthalimide (LVIII) is known; it is formed by treatment of naphthalimide with phenylmercuriacetate.⁴³

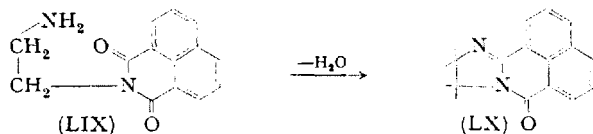
(4) Reactions of Naphthalimides

The characteristic reactions of naphthalimides, in addition to those of preparative value that have already been mentioned (pp. 501 and 502) may be grouped under (a) cleavage of the hetero ring, (b) dehydration of derivatives resulting in formation of an additional ring, and (c) dehydrogenation.

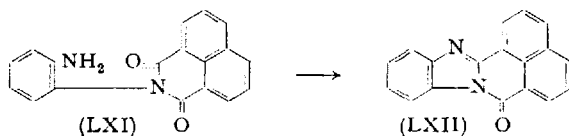
(a) Ring Cleavage. Cleavage of the hetero ring by alkali and by hypochlorite has already been discussed (pp. 501 and 502). In one in-

stance⁷⁵ it has been stated that 60% sulfuric acid transforms 5,8-diaminonaphthalimide to the corresponding diaminonaphthalic anhydride; this is presumably a ring opening with subsequent closing.

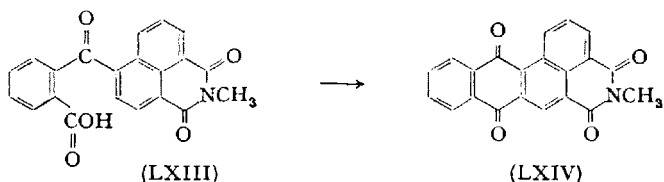
(b) Dehydration. Suitably constituted naphthalimides are, in general, easily dehydrated, with concomitant ring formation. 2- β -Aminoethylnaphthalimide (LIX) loses water on simple heating⁴⁶ to form the imidazoline, 7-oxo-8,9-dihydrobenz[*de*]imidazo[2,1-*a*]isoquinoline (7-oxo-8,9-dihydro-7a,10-diazacyclopent[*a*]benzonaphthene) (LX). *o*-Aminonaphthalanils are easily dehydrated to pseudoindoles;^{48,74}



thus, 2-(*o*-aminophenyl)naphthalimide (LXI) gives 9'-oxo-8'-azaphenaino-(7,8',2,3)- γ -indole (1,2-(1',8')-naphthylene-1,3-benzdiazole; 7-oxo-7a,12-diazanaphtho[1,8-*a*,*b*]fluorene) (LXII). 6-(2-Carboxybenzoyl)-2-

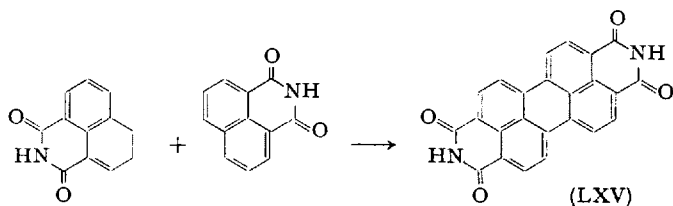


methylnaphthalimide (LXIII) can be cyclized⁴⁴ to 4,6,8,13-tetraoxo-5-methyl-5-azanaphth[1,8-*a*,*b*]anthracene (LXIV). The yellow quinone gives a greenish-brown vat with sodium hyposulfite.



(c) Dehydrogenation. The most important dehydrogenation of naphthalimides is the alkali melt with subsequent oxidation by air; two molecules of imide combine to form a perylene ring system.^{47,65,72,76,80,90,176} Naphthalimide gives the diimide of 3,4,9,10-

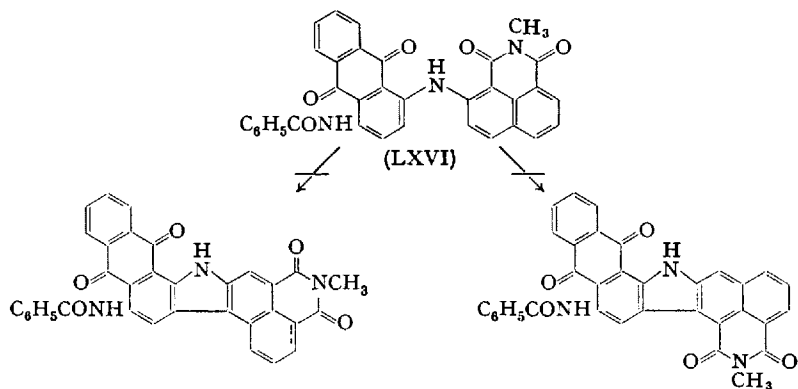
perylene-tetracarboxylic acid (1,3,8,10-tetraoxo-2*H*,9*H*,2,9-diazadibenzo[*cd,lm*]perylene; 1,3,8,10-tetraoxo-2*H*,9*H*-anthra[2,1,9-*def*, 6,5,10-*d'e'f'*]diisoquinoline) LXV. It appears obvious that the 6- and 7-positions must not be occupied by groups that cannot be eliminated



during the fusion; 2-alkylimides are commonly employed.^{76,80} In the preparation of 6-anilino-2-methylnaphthalimide (*cf.* p. 504) the dimethylated diimide is a by-product.⁷³

These seven-ring compounds are vat dyes; the dialkylated derivatives are a pure red,^{60,178} while the unmethylated is a bordeaux;⁹⁰ chlorination brightens the shade, while the introduction of amino or phenoxy groups gives blue or bluish-violet dyes.⁹¹

A dehydrogenation that could *not* be effected should be mentioned. The anthrimide (LXVI) could not be dehydrogenated to the desired carbazole.⁷⁶



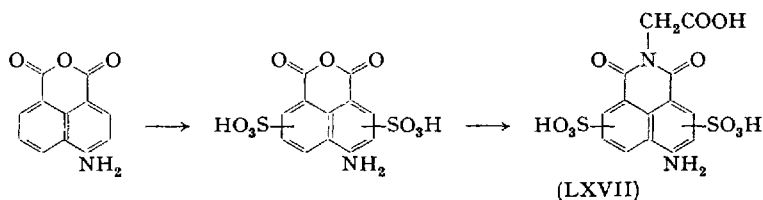
(5) Uses of Naphthalimides

Naphthalimides have found applications as intermediates for the preparation of vat dyes (p. 516), as dyes for animal fibers,^{45,70,72}

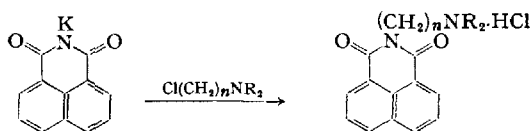
nylon,⁵³ cellulose acetate,^{53,63} oils,⁶² plastics,⁵³ and resins.⁶³ Certain substituted naphthalimides have also been examined for their physiological activity.

The 6-aminonaphthalimides are yellow and color the various materials yellow. Many are strongly fluorescent,^{45,53,62,63} even at a dilution of 1:30,000.⁶² Water solubility, needed to dye animal fibers, is imparted by the introduction of sulfonic acid groups^{70,72} (pp. 567 ff.).

An example of the preparation of one type of acid wool dye is as follows:⁴⁵ 6-Aminonaphthalic anhydride is disulfonated by treatment with fuming sulfuric acid, and the sodium salt then is heated with glycine in alkaline solution. The resulting yellow fluorescent dye is 6-amino-2-carboxymethyl-*x,x*-disulfonaphthalimide (LXVII). 2- β -Dialkylaminoalkylnaphthalimides were found to have some physiological

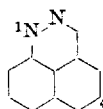


activity when tested as local anesthetics. They were prepared by the standard method, by refluxing the appropriate β -dialkylaminoalkyl halide with potassium naphthalimide. The products, obtained in yields of 28–90%, were isolated as hydrochlorides.



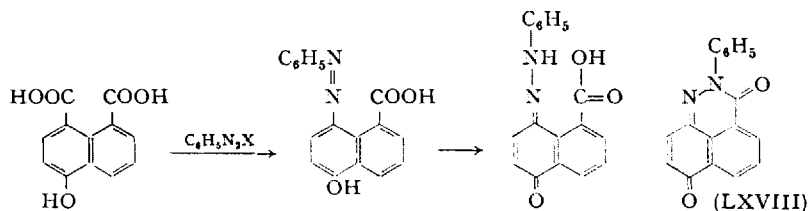
4. Polyazabenzonaphthenes

- A. 3H,1,2-Diazabenzonaphthene. 3H-Benzo-[de]phthalazine. 3-*peri*-Benzophthalazine. 3H-Benzo[de]cinnoline. 1,8-Pyridazine-naphthalene. 1,2-*peri*-Naphthdiazine.
R.I. 1910



Only one type of this series is known; there are few representatives, all of which have two carbonyl groups. They are prepared by the

coupling of a diazonium salt with a hydroxynaphthalic acid or anhydride.⁸⁴ The carboxyl group ortho or para to the hydroxyl group is eliminated in the coupling. Presumably rearrangement to the tautomeric hydrazone form next occurs, followed by elimination of water to close the ring, forming, for example, 3,7-dioxo-2-phenyl-1,2-diazabenzonaphthene (LXVIII); this was called the α -isomer by the discoverer.



The β -isomer, 3,9-dioxo-2-phenyl-1,2-diazabenzonaphthene, is also known, as are a few others (Table VIII-6).

These dioxo-1,2-diazabenzonaphthenes are cleaved when treated with strong alkaline reagents, giving red azo dyes.

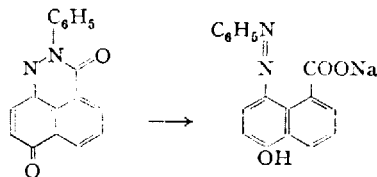
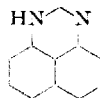


TABLE VIII-6. 2-Aryl-1,2-diazabenzonaphthenes⁸⁴

Substituent (formula)	M.p., °C.
3,7-Dioxo-2-phenyl- (LXVIII)	238-40
2,9-Dioxo-2-phenyl-	201-2
3,7-Dioxo-2-(4-nitrophenyl)-	305-7
3,7-Dioxo-2- α -naphthyl-	

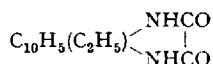
B. Perimidine. 1H,1,3-Diazabenzonaphthene. 1H-Benzo[de]quinazoline. 1,3-*peri*-Naphthodiazine. *peri*-Naphthimidazole. Ethenyl-1,8-diaminonaphthalene. *N,N'*-Methylnaphthylenediamine(1,8). R.I. 1911



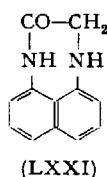
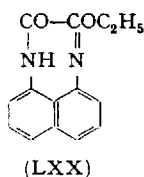
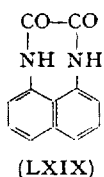
Our knowledge of the chemistry of perimidines is largely due to the excellent and extensive work of Franz Sachs.⁹⁴⁻⁹⁸ He established the

true structures and corrected the misconceptions of his predecessors. Although his name does not appear on any patents, it seems obvious that they are closely related to his work; statements are made about certain perimidines in his published papers, but the substances themselves appear only in the patents. The original purpose of his research was to find out whether seven-membered rings, involving the *peri* (1,8) positions of naphthalene, could exist. Such a substance had been reported by the Portuguese chemist, d'Aguiar.¹

In studying two isomeric diaminonaphthalenes, d'Aguiar¹ treated the 1,8-isomer with oxalic acid and with ethyl oxalate. The former gave an oxalate salt, but a mixture resulted when the ester was employed. He suggested that one of the components isolated was a seven-membered ring compound:



This work was repeated and confirmed by Meyer and Miller,⁹⁹ who wrote the seven-membered ring structures, LXIX–LXXI, for these

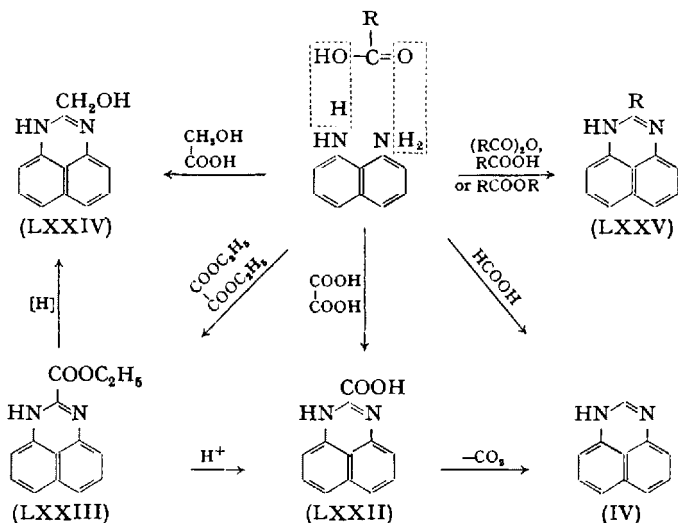


substances; the first two were from d'Aguiar's work, while LXXI was a reduction product of LXX.

In a very lengthy paper which established all classes of perimidines, Sachs⁹⁵ showed that d'Aguiar's difficulties were due to mixtures; d'Aguiar actually had the 1,8-naphthalenediamine neutral (1:1) oxalate [both hydrated (2H₂O) and anhydrous]; the basic (2:1) oxalate; 2-carboxyperimidine (LXXII); and perimidine (IV). The acid (LXXII) results from long boiling of aqueous solutions of the oxalate; it can also be formed by melting the components.

Sachs further showed that the ethoxy compound was, in reality, the ethyl ester (LXXIII) of the acid, and that the reduction product was

the 2-methylol derivative (LXXIV), which he then synthesized from the 1,8-diamine and both glycolic and chloroacetic acids.

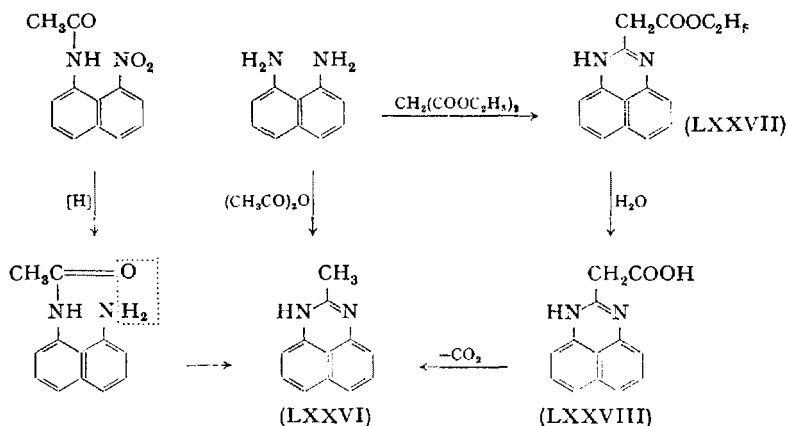


Sachs established the generality of the reaction—formation of the perimidine ring system by interaction of any carboxylic acid or ester and 1,8-diaminonaphthalene. He named the base perimidine, because it was an imide formed across the *peri* positions of naphthalene.

(1) Preparation

The parent substance, perimidine itself (IV), is best obtained from 1,8-diaminonaphthalene and formic acid. The use of homologous acids or esters, and of anhydrides, gives rise to 2-alkyl derivatives (LXXV).^{95,188} For instance, acetic anhydride, acetic acid, or ethyl acetate gives 2-methylperimidine (LXXVI). The latter also results along with the ester (LXXVII) when ethyl malonate is used; a part of the ester is hydrolyzed and decarboxylated during the reaction. 2-Methylperimidine is also formed on reduction of 1-acetamido-8-nitronaphthalene.^{94,113} 4,6-Dibromo-2-methylperimidine was said to be produced by a stannous chloride reduction of 1-acetamido-2,4-dibromo-8-nitronaphthalene,¹⁰² but the work could not be repeated.¹⁵⁹ An

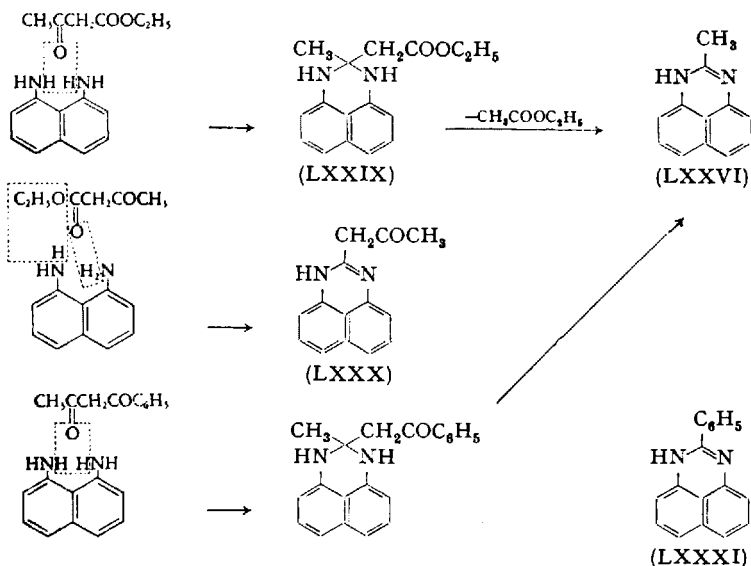
α,α -dibromo-2-methyl derivative was prepared by bromination of 2-methylperimidine and a 4,6,9-tribromo-2-methyl derivative from 1,8-diaminonaphthalene.



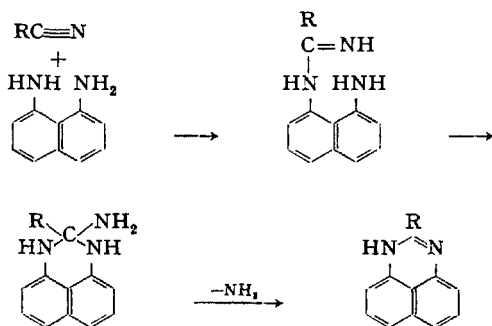
The behavior of ethyl acetoacetate and 1,8-diaminonaphthalene is complex, the products depending on the experimental conditions. (a) If the components are allowed to stand at room temperature, the ester acts like a ketone (see p. 522) and forms the colorless dihydropyrimidine (LXXIX). Upon being heated alone or in the presence of acid, ethyl acetate is lost from the latter, and 2-methylperimidine (LXXVI) results. (b) If the components are heated by themselves, water and alcohol are eliminated, and 2-acetonylperimidine (LXXX) is formed. (c) If the components are heated in hydrochloric acid solution, the only product is the hydrochloride of 2-methylperimidine. Even substituted acetoacetic esters give the same product; Sachs explained this as hydrolysis of the ethyl acetoacetate in a new way, to acetic acid and a substituted ethyl acetate. The latter was actually isolated in some instances. Benzoylacetone exhibited a similar behavior, giving 2-methylperimidine hydrochloride; in this instance, acetophenone could be isolated, but there was no other evidence for the intermediate. Dibenzoylmethane, with the diamine and alcoholic hydrochloric acid, gave 2-phenylperimidine (LXXXI) as though it had been likewise cleaved; even benzil gave the same 2-phenyl derivative.¹⁰¹

Since Sachs' publication, two syntheses that are essentially variants

have been reported. Wagner showed that a nitrile could be employed, instead of the usual acidic derivative, with the diamine hydrochloride



in a sealed tube.¹⁰³ The product, obtained in moderate yields, is a 2-substituted perimidine; to obtain perimidine itself, it is necessary to use diphenylformamidine.¹⁰⁴ A plausible mechanism may be written:

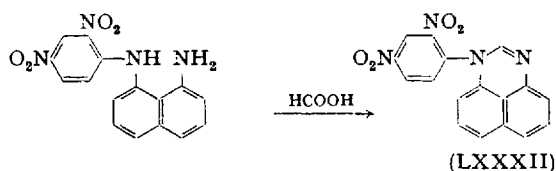


The function of the hydrochloric acid is probably to remove the ammonia as ammonium chloride, rather than to form an imide chloride with the nitrile.

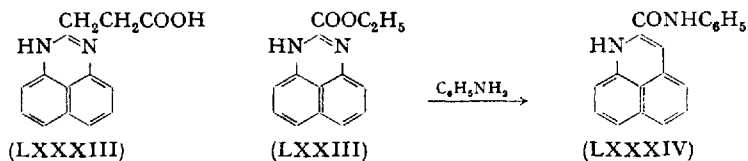
The second variation is the use of an acid chloride¹⁰⁵ with the

diamine and anhydrous aluminium chloride in carbon bisulfide; the yield is of the order of 40%.

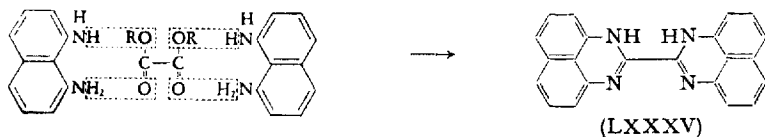
Most substituted perimidines are obtained by the ring closure method, using substituted, 1,8-diaminonaphthalenes with appropriate acidic derivatives to introduce substituents in the 2-position. A few examples will serve to illustrate their formation. 1-(2,4-Dinitrophenyl)-perimidine (LXXXII) results from heating together 8-amino-1-(2,4-dinitrophenylamino)naphthalene and formic acid.⁹⁷ The use of an-



hydrides of aliphatic dibasic acids gives rise to 2-carboxyalkyl derivatives, which can be cyclized (p. 527); 2- β -carboxyethylperimidine (LXXXIII) is so formed from succinic anhydride. The 2-anilides

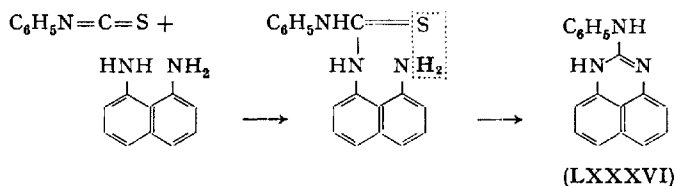


(LXXXIV) are obtained by the usual method of anilide formation: action of the base on the ester. A variant is the formation of 2,2'-di-perimidyl (LXXXV) by heating the ester with another mole of 1,8-diaminonaphthalene.⁹⁵



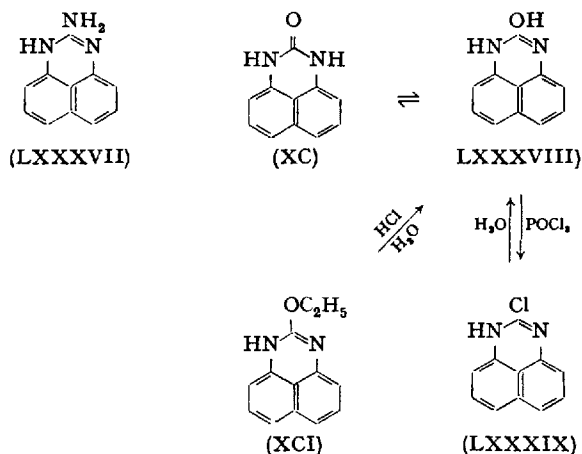
2-Anilinoperimidine (LXXXVI) is formed by refluxing 1,8-diaminonaphthalene with phenyl isothiocyanate in benzene for 12 hours; hydrogen sulfide is eliminated from the intermediate thiourea.⁹⁵ The use of ammonium thiocyanate with the 1,8-diamine gives 2-amino-

perimidine (LXXXVII). This substance is characterized by the formation of difficultly soluble salts (except the acetate); the sulfate is soluble



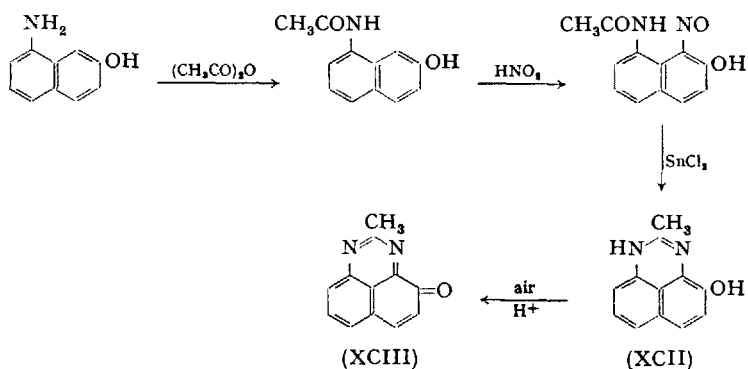
only to the extent of 1 part in 2000. The base itself dissolves in water, alcohol, and acetone.⁹⁵

2-Chloroperimidine (LXXXIX) is obtainable by treatment of the cyclic urea, XC, with phosphoryl chloride in a sealed tube;⁹⁵ presumably, the reaction proceeds through the enolic form LXXXVIII. The urea (XC) (p. 534) is easily formed by hydrolysis of 2-ethoxyperimidine (XCI), which, in turn, is obtained from 1,8-diaminonaphthalene and ethyl orthoformate.⁹⁵

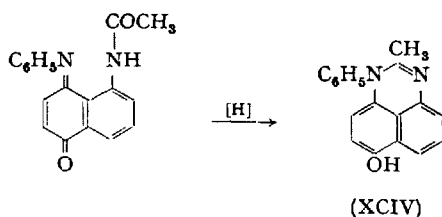


An unusual reaction that resulted in the formation of 4-hydroxy-2-methylperimidine (XCII) was discovered by Kehrmann and Engelke¹⁰⁰ while trying to make 8-acetamido- β -naphthoquinone. Monoacetylated 1-amino-7-naphthol was nitrosated and reduced, the ring spontaneously closing; they called the product "9-oxo-2-methylperimidine." Its

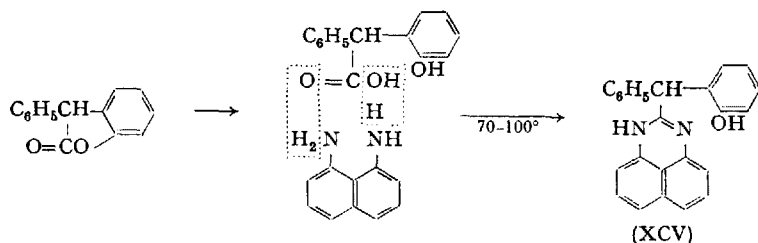
solutions in all solvents were very easily oxidized to "9-chino-2-methylperimidine," 4-oxo-2-methylperimidine (XCIII).



Another hydroxyperimidine (XCIV) has been described¹¹²; its hydrochloride is obtained by a stannous chloride reduction of the corresponding quinoneanil, the free base then being liberated in the



usual manner. An unusual formation of a perimidine, 2-(2-hydroxybenzhydryl)perimidine (XCV), arises from the use of a lactone.¹⁰⁶ Presumably, the lactone ring first is opened with a molecule of water; the acid then cyclizes with the diamine in the customary manner.



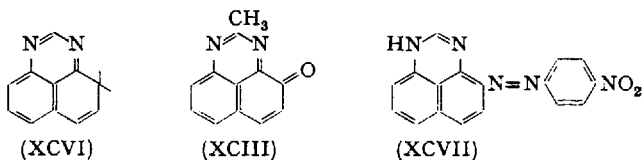
(2) *Properties and Reactions*

Perimidines are solids with medium-to-high melting points; they are generally yellow in color, but this deepens to red in several instances. They dissolve in the usual organic solvents to some extent, depending on the nature of the substituent groups, but are insoluble in water.

Chemically, perimidines are monobasic, forming colored salts with one equivalent of acid. Many of the salts are only sparingly soluble in water; for example, 2-methylperimidine nitrate is difficultly soluble. The sodium salts of the sulfonated perimidines are soluble in water.

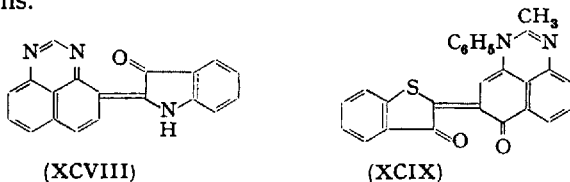
The 1- and 3-positions in perimidines are equivalent, the hydrogen atom being tautomeric, but if there is a substituent at position 1, isomers are possible when there is a substituent atom or group in the naphthalene residue.

Little is known about substitution reactions of perimidines, derivatives usually being formed from substituted 1,8-diaminonaphthalenes. Perimidine itself gives an α,α -dinitro derivative when treated with nitric acid in acetic acid.⁹⁵ From the available evidence, it appears that perimidines react as though they were α -naphthylamines. They couple (XCVII) with diazotized aromatic amines,^{95,107} and give condensation products with α -isatin chloride and quinone chloroimides. The entering radical is usually shown in the 4- or 6-position, without supporting evidence. These positions correspond to the 2- and 4-positions in α -naphthylamine. The only derivative known for certainty to be a derivative of the 4*H*-tautomer (XCVI) is Kehrman's ketone (XCIII) (p. 525).

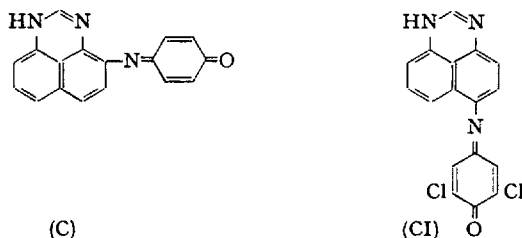


The complex reaction product of α -isatin chloride and perimidine is assigned the structure XCVIII by analogy with similar reactions of naphthosultam and certain naphthoquinones.¹¹¹ The complex 8-(2-methyl-1-phenylperimidine)-2'-(thionaphthene)indigo (XCIX) is ob-

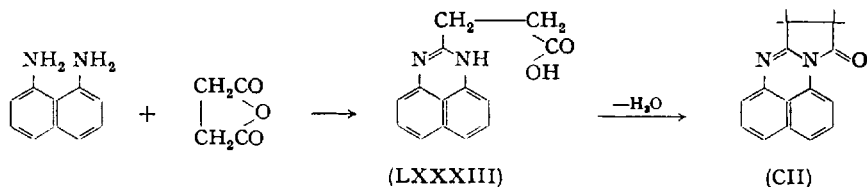
tained by ring closure of the already substituted 1,8-diamine, so there is no doubt about its structure.¹¹² It is a dark violet solid that dissolves in hot acetic acid and anhydride, or in high-boiling solvents, forming blue solutions.



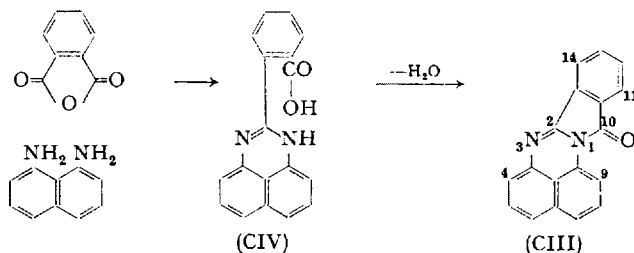
Indophenols are formed by the customary procedure using quinone chloroimides or aminophenols and an oxidizing agent.¹⁰⁹ The point of attachment is unknown, but is assumed to be at either position 4 (C) or 6 (CI). By analogy with the reaction of 1,8-diaminonaphthalene with *p*-aminophenol, which gives an indophenol para to one of the amino groups,¹¹⁵ the 6-position (CI) should be favored in the perimidine series. The indophenols are patented as intermediates for sulfur dyes.^{110, 114}



(a) Dehydration. Many carboxylic acids in the perimidine series are readily dehydrated, and precautions must be taken to avoid this complication. For instance, when 1,8-diaminonaphthalene is fused with succinic anhydride, "succinicoperinone," the lactam of β -(2-perimidyl)-propionic acid (CII)⁹⁵ is formed; the latter can be obtained also by heating the acid (LXXXIII) at its melting point. Similarly, "maleino-



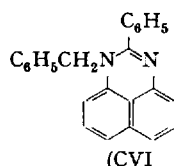
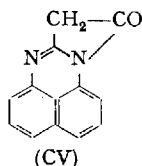
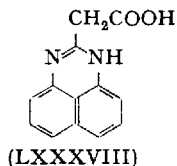
perinone" and "phthaloperinone" are so formed,^{95,125,154} The latter also has been called the lactam of 2[perimidy1-(2)]benzoic acid or (1-CO)-2-benzoyleneperimidine) and numbered as shown in CIII.⁹⁵ Naphthalic anhydride and saccharin act in the same way;^{95,107} a consideration of



these fused ring systems, and their substitution products is beyond the scope of this chapter. They are of interest as possible dyes or dye intermediates. Phthaloperinone was used by the Germans during the late war to form orange-colored smokes.¹⁶¹

(3) Products of Indeterminate Structure

When malonic acid and 1,8-diaminonaphthalene reacted, the main product was the malonate (salt) of 2-methylperimidine, the latter resulting from decarboxylation of the expected acid (LXXXVIII).⁹⁵ A by-product was a substance which, upon analysis, gave figures that agreed with those calculated for the acid minus a molecule of water. Sachs wrote a four-membered ring structure (CV) for this substance; it gave no salts, was insensitive to hydrochloric acid, and gave a red solution in concentrated sulfuric acid.



In their work on the behavior of *ortho* diamines with aldehydes, the authors^{153,167} included 1,8-diaminonaphthalene. The products from *o*-diamines were called "aldehydines." They are now known to be

1-benzyl-2-phenylbenzimidazoles.¹⁷⁵ If the analogy can be carried over from the 1,2-diamines, the product from 1,8-diaminonaphthalene would be 1-benzyl-2-phenylperimidine (CVI); such a structure was suggested by Sachs.⁹⁵

(4) Uses

Like the naphthalimides, the perimidines were evaluated as dyes or intermediates for dyes. It was stated that the 2-methyl and 2-phenyl derivatives would dye tanned cotton yellow.¹¹³ It was also noted that, when 2-methylperimidine was treated with phthalic anhydride in the presence of zinc chloride, a yellow dye was formed.¹¹³ This was presumably the quinone (CVII) formed by acylation and ring closure of the aroylbenzoic acid (CVIII), although no structures were given. Azo^{95,107}



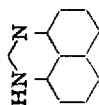
and sulfur dyes^{95, 109, 110, 114, 117, 119, 124, 125, 138} and indigoids^{108, 112} have already been mentioned. The sulfur dyes are brown unless copper is present in the melt, in which case the color is olive. A number of cyanine dyes have been described.¹⁸⁶

The only known instance of any physiological effect is that of perimidine itself, which has been reported to act as a muscle relaxant.¹³⁶

The properties of perimidines are shown in Table VIII-7.

(5) Reduced Perimidines; 2,3-Dihydro-1H,1,3-diazabenzonaphthenes

There are three classes of reduced perimidines in which the top ring only is reduced. The first includes those derivatives in which there are two substituent groups in the 2-position (CIX); the second, the 2-oxo derivatives (XC); and the third, the 2-thione analogs (CX). The oxo derivatives are the tautomeric forms of 2-hydroxyperimidines (LXXXVIII), while those of the thione series are tautomers of the

TABLE VIII-7. Perimidines (1*H*,1,3-Diazabenzonaphthenes)

Formula	Substituent	M.p., °C.	Color	Notes	Refs.
IV	None; Perimidine	220 (dec.)		P m.p. 245–50° (dec.)	95, 104, 188
LXXVI	2-Methyl-	216 (dec.)		HCl m.p. 360° (dec.), forms a difficultly sol. nitrate ^a	78, 94, 95, 105, 113, 159, 188
	2-Ethyl-	161	Yellow	P 238 (dec.) (orange-red)	95
	2- <i>n</i> -Propyl-	157	Yellow		95, 103
	2-Isopropyl-	87	Yellow-green		96
	2- <i>n</i> -Butyl-	165		HCl 245° (dec.), m.p. 252–3° (yellow-green)	96
	2,6-Dimethyl-	210–20			116
	2-Benzyl-	194	Yellow		95
LXXI	2-Phenyl-	187	Orange-yellow	HCl (orange-red)	95, 101, 113, 159, 188
	2-Styryl-	136	Dark red	HCl (dec.) (dark red) 230°	96
	6,7-Ethano-	285	Greenish-brown		98
LXXXIX	2-Chloro-	194	Gray-green		95
	6-Chloro-	200	Blue		107
	6-Chloro-2-methyl-	127	Green		107
	6-Chloro-2,7-dimethyl-	223			116
	6-Bromo-	220			107
	6-Bromo-2-methyl-	130	Dark green		107
	<i>x</i> -Bromo-2-methyl-	181	Pale green		159
	4,6-Dibromo-2-methyl-	176–7	Green		102
	<i>x,x</i> -Dibromo-2-methyl-	218–19 (dec.)	Green-yellow		159

(Table continued)

TABLE VIII-7 (continued)

Formula	Substituent	M.p., °C.	Color	Notes	Refs.
LXXXII	4,6,9-Tribromo-2-methyl- $\alpha,\alpha,\alpha,\alpha$ -Tetrabromo-2-phenyl-	217-18	Yellow	Isolated as mustard-yellow dibromide, m.p. 235-40° (dec.)	159
	α -Nitro-				117
	α,α -Dinitro- ^{b1}	Puffs		Red-violet in alkali	95, 117
	α,α -Dinitro-	238-40	Orange-yellow		159
	2-(2-Nitrophenyl)-	177	Red		96
	2-(3-Nitrophenyl)-	184 (dec.)	Red		96
LXXXVII	2-(4-Nitrophenyl)-	180 (dec.)	Copper		96
	1-(2,4-Dinitrophenyl)-	175, dec. 265	Red-brown	P m.p. 232° (orange-red)	97
	α -Sulfo-				117
	6-Sulfo-				110
	2-Cetyl- α -sulfo-				118
	5,8-Disulfo-		Yellow		110-119
LXXXVIII	2-Methyl-6, α -dichlorosulfonyl-	200-4	Yellow		120, 121
	2-Amino-	239		P (red)	95
	2-Anilino-	245		P (red)	95
	2- <i>o</i> -Toluidino-	240-1			95
	2- <i>p</i> -Toluidino-	259			95
	2-(2-Aminophenyl)-	148-50	Yellow		96
LXXXVIII	2-(3-Aminophenyl)-	175-80	Red-yellow		96
	2-(4-Aminophenyl)-	205	Yellow		96
	2-Hydroxy- (see p. 524)	304-5	White	Nitrate, sp. sol.	95
	4-Hydroxy-2-methyl- ^{b1}	None			100
	6-Hydroxy-2-methyl- (2-methyl-6-perimidino)	None	Yellow	Salts (bright yellow)	122

(Table continued)

TABLE VIII-7 (continued)

Formula	Substituent	M.p., °C.	Color	Notes	Refs.
XCIV	7-Hydroxy-2-methyl-1-phenyl-	> 300			112
XCV	2-(2-Hydroxybenzhydryl)-	295-7 (dec.)			106
	2-Hydroxy-5,8-dichlorosulfonyl-	250 (dec.)	Yellow		120, 121
LXXIV	2-Hydroxymethyl-	221-2	Green-yellow	P m.p. 230-40° (dec.) (yellow)	95
XCI	2-Ethoxy-	125	White		95
	2-Mercapto- (see p. 541)	Sub.		Very diff. sol. in usual solvents	95
	1-β-Cyanoethyl-	136-9			123, 155
	2-(4-Acetamidophenyl)-	dec. > 200	Yellow		96
	2-Carboxy-	dec. > 250			95
LXXXIII	2-β-Carboxyethyl-	253	Yellow-gray		95
	2-β-Acrylyl- ^{b2}	210 (dec.)	Red-brown		95
CIV	2-(2-Carboxyphenyl)-	dec.	Yellow		95
	2-(8-Carboxy-1-naphthyl)-	180 (dec.)			95
	2-(2-Carboxy-3,6-dichlorophenyl)-	180 (dec.)			95
	2-(2-Carboxy-4(or 5)-nitrophenyl)-	205 (dec.)	Yellow-brown		95
	2-Carboxy-1-(2,4-dinitrophenyl)- ^{b3}	170	Red		97
	2-(β-Carboxyethyl)-1-(2,4-dinitrophenyl)- ^{b4}	227	Red		97
	2-(2-Carboxyphenyl)-5,8-disulfo ^{b5}		Orange-yellow		124
	2-(2-Carboxyphenyl)-x,x-disulfo-				124
	2-Carbomethoxy-	197	Red		95

(Table continued)

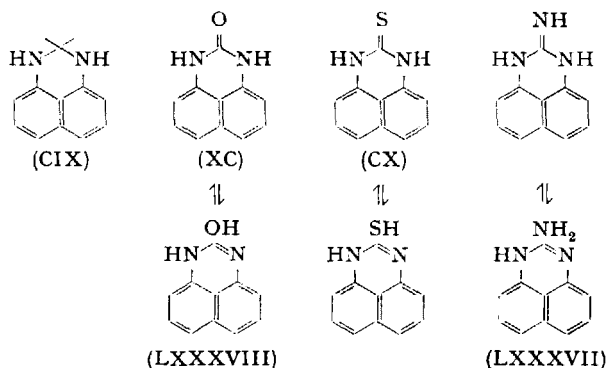
TABLE VIII-7 (continued)

Formula	Substituent	M.p., °C.	Color	Notes	Refs.
LXXIII	2-Carbethoxy-			P 200° (dec.) (dark violet)	95
LXXVII	2-Carbomethoxymethyl-	184			
LXXXIV	2-Carbethoxymethyl-	152	Yellow		95
LXXXIV	Phenylcarbamylo ⁶⁶	278	Red		95
LXXX	2-Acetyl-	267	Yellow		95
	Phenyldiazone of 2-acetyl-	195	Yellow		95
XCIH	4-Oxo-2-methyl- ⁶⁷	175 (dec.)	Orange-yellow	Red-violet with aniline; sol. all solvents except water	100
	6-Phenylazo- ⁶⁸	dec. > 180	Scarlet		157
XCVII	4-(or 6)- <i>p</i> -Nitrophenylazo-	None			95
	4-(<i>p</i> -Nitrophenylazo)-6-chloro-2-methyl-	125	Purple		107
LXXXV	2,2'-Diprimidyl ⁶⁹	> 300	Dark red		95
C	Indophenol of perimidinc				109
	Indophenol of 2-phenylperimidine				109
CI	3',5'-Dichloroindophenol of 2-methylperimidine				109
XCVIII	Indigoid				108
XCIX	Thioindigoid				112
	1,4-Bis(2-permidyl)benzene	300			188
	1,5-Bis(2-permidyl)naphthalene	300			188

^a The green acetate, m.p. 144°, is very soluble in all solvents except acetic acid.¹⁵⁹

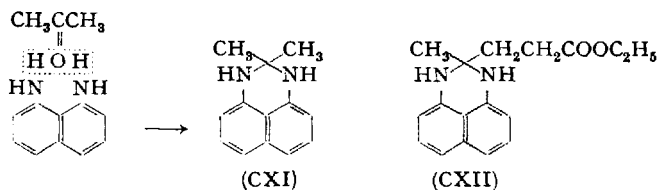
^b Color in concentrated sulfuric acid: 1, yellow-brown; 2, red-brown; 3, brown; 4, green-yellow; 5, orange-red; 6, dark red; 7, Bordeaux; 8, blue-green; 9, violet.

2-mercaptans. Representatives of all classes are described in Sach's general paper.⁹⁵ The last two are sometimes known as cyclic ureas or



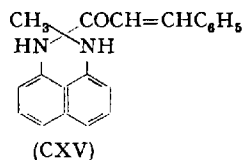
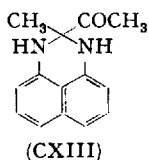
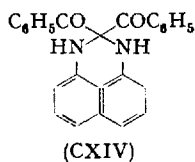
thioureas. Attempts to prepare cyclic imides, however, result in 2-aminoperimidines (LXXXVII).

(a) 2,2-Disubstituted 2,3-dihydroperimidines (CIX). The general method of preparation for this class of substances consists of mixing dilute alcoholic solutions of a ketone and a 1,8-diaminonaphthalene, with or without mineral acid, and, usually, allowing the mixture to stand at room temperature for a day. Acetone gives 2,2-dimethyl-2,3-dihydro-1*H*,1,3-diazabenzonaphthalene (CXI),^{95,128,168} while acetophenone gives the 2-methyl-2-phenyl analog.⁹⁵ Oxo esters, such as

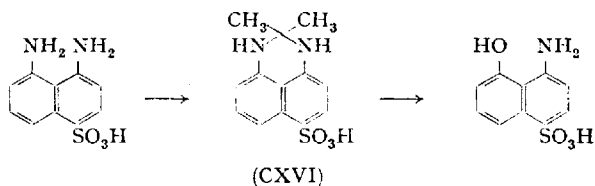


ethyl levulinate, give rise to esters of the type of 2- β -carbethoxyethyl-2-methyl-2,3-dihydro-1*H*,1,3-diazabenzonaphthalene (CXII). The special case of ethyl acetoacetate has already been considered (p. 522); it will be recalled that, on warming, the product from that ester lost ethyl acetate, thereby forming 2-methylperimidine. The ester, CXII, does not lose ethyl propionate under any conditions.⁹⁵

An aliphatic 1,2-diketone, such as diacetyl, gives the 2-acetyl-2-methyl derivative (CXIII), whereas the aromatic benzil forms 2-phenylperimidine (p. 522).¹⁰¹ 1,3-Diketones are first cleaved to an acid and a simple ketone; the acid gives rise to a 2-substituted perimidine (p. 522), but, when an excess of diamine is employed, in some instances the ketone also reacts to give a 2,2-disubstituted dihydroperimidine.⁹⁵ The only 1,2,3-triketone used behaved in normal fashion, reaction occurring on the central carbonyl group, to give 2,2-dibenzoyl-1,2-dihydroperimidine (CXIV).¹⁰¹ An α,β -unsaturated ketonic side chain (CXV) can be formed by an aldol-type condensation from the 2-acetyl derivative and an aldehyde.⁹⁵

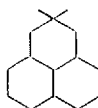


A special case was reported by Bucherer in his classic work on the replacement of amino groups by hydroxyl groups, employing sodium bisulfite.¹³⁵ When 1,8-diaminonaphthalene-4-sulfonic acid was treated with acetone bisulfite, 6-sulfo-2,2-dimethyldihydroperimidine (CXVI) resulted. Upon long standing (50–60 hrs.) this substance was hydrolyzed to 1-amino-8-hydroxynaphthalene-4-sulfonic acid, whereas in all the other instances, in which no cyclic compound was possible, two to three hours sufficed for the conversion.



Sachs also prepared two spiro compounds (CXVII, CXVIII) from 1,8-diaminonaphthalene, using isatin and alloxan, respectively. The known 2,2-disubstituted dihydroperimidines are listed in Table VIII-8.

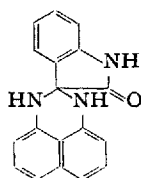
Properties. The known 2,2-disubstituted dihydroperimidines are

TABLE VIII-8. Reduced Perimidines (2,3-Dihydro-1*H*,1,3-diazabenzonaphthenes)

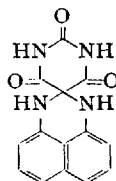
Substituent (formula)	M.p., °C.	Refs.
2,2-Dimethyl-	117	95
2-Methyl-2-phenyl-	213	95
2,2-Dimethyl-4-chloro-	110	134
2,2-Dimethyl-6-chloro-		128
2,2-Dimethyl-5,8-dinitro- ^d	241 (dec.)	133
2,2-Dimethyl-4,6,7,9-tetranitro- ^b	280 (dec.)	132
2,2-Dimethyl-6-bromo-4,7,9-trinitro-	264	157
2,2-Dimethyl-6-sulfo- (CXVI)		128, 135
2,2-Dimethyl-5,8-disulfo-		128
2-Carbomethoxymethyl-2-methyl-	97	95
2-Carbethoxymethyl-2-methyl-	145	95
2- β -Carbethoxyethyl-2-methyl- (CXII)	102	95
2-Acetyl-2-methyl- (CXIII)	181-3	95
Oxime of	dec. <i>ca.</i> 300	
Semicarbazone of	224-6	
Phenylhydrazone of	147-9	
Azine of ^c	229	
2-Cinnamoyl-2-methyl- ^a (CXV)		95
2,2-Dibenzoyl- ^a (CXIV)	215	101
Spiro-2- β -isatyl- ^b (CXVII)	181 and 254	95
"Spiro-2-(5-barbituryl)-" ^f (CXVIII)		95
Azo dyes (CXIX-CXXI)		129-131

^a Orange-yellow. ^b Yellow, ^c Rose. ^d Scarlet. ^e Brown-red. ^f Barbituryl = 2,4,6-trihydroxy-5-pyrimidyl.

all white unless they contain groups such as nitro or azo. The spiro compound, CXVII, has two melting points.⁹⁵

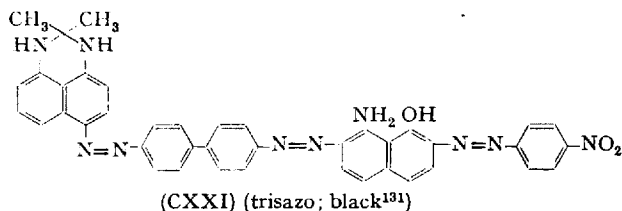
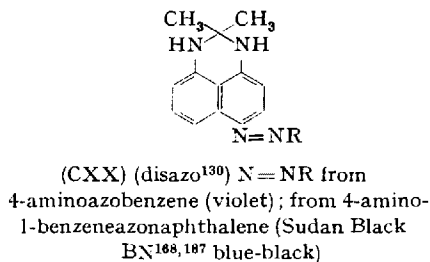
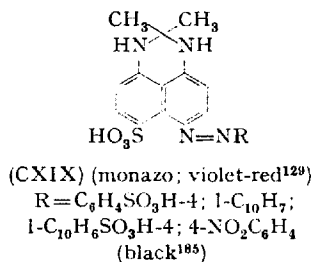


(CXVII)



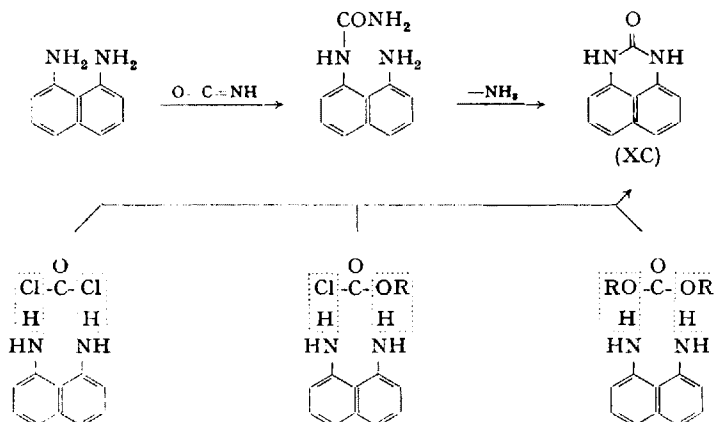
(CXVIII)

The dihydroperimidines resemble the perimidines and 1-naphthylamine in their coupling reactions to form azo dyes. The position taken by the entering group has not been determined, but the most probable structures are shown in formulae CXIX-CXXI.



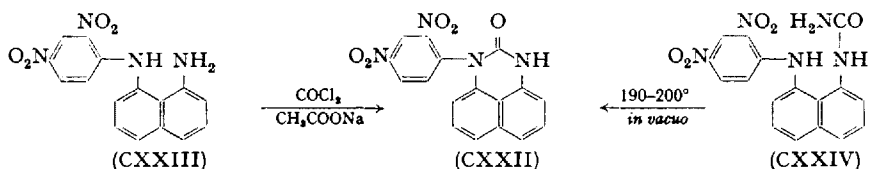
(b) Perimidones. Perimidone may also be named 2-oxo-2,3-dihydroperimidine, 2-oxo-2,3-dihydro-1*H*,1,3-diazabenzonaphthene, or *N,N'*-naphthyleneurea (XC).

Perimidones are obtainable from 1,8-diaminonaphthalene by several routes. Sachs states⁹⁵ that the use of potassium cyanate and

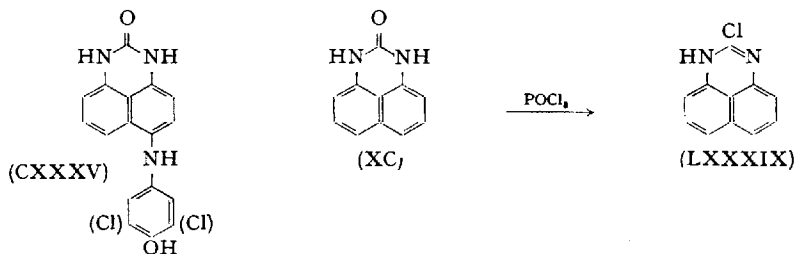


hydrochloric acid is preferred. The carbonyl group can be introduced also by means of phosgene in the cold, carbonates under pressure, and chlorocarbonates. Of minor interest only is the formation of perimidone from 2-chloroperimidine (p. 524).

In the above synthesis employing potassium cyanate the intermediate urea is not isolated; however, the 1-(2,4-dinitrophenyl) derivative (CXXII) can be obtained from either the appropriate diamine (CXXIII) or the urea CXXIV).



6-(4-Hydroxyanilino)perimidone (CXXXV) can be obtained also by the phosgene procedure. This and the dichloro derivative have been patented as intermediate products for making sulfur dyes.¹¹⁵

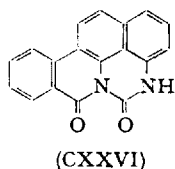


Properties. The few known perimidones are high-melting substances, very sparingly soluble in the usual solvents.

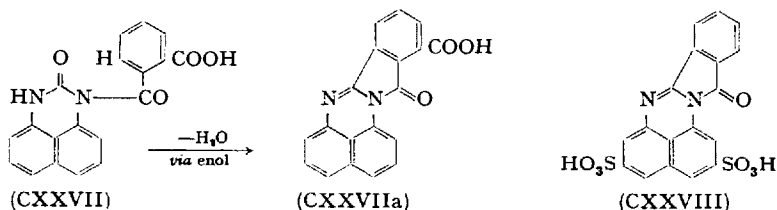
Chemically they resemble pyridones; thus, by means of phosphoryl chloride, a chlorine atom can be introduced into the 2-position. 2-Chloroperimidine (LXXXIX) is so obtained from perimidone (XC).

The perimidones can be acylated; benzoyl, *m*-nitrobenzoyl, and 1-naphthoyl chlorides have been used.^{126, 127} Isomers result, depending on the solvent used. In a sodium-aluminum chloride melt, the isomers can be cyclized to the same substance, which contains five six-membered rings. The product from benzoyl chloride, for instance, gives yellow 5,6-dioxo-4*H*,4,5*a*-diazabenzoc[*c*]pyrene (CXXXVI). Solutions of these

pyrene derivatives have an intense greenish fluorescence that is visible at a dilution of 1 part in 10,000,000.

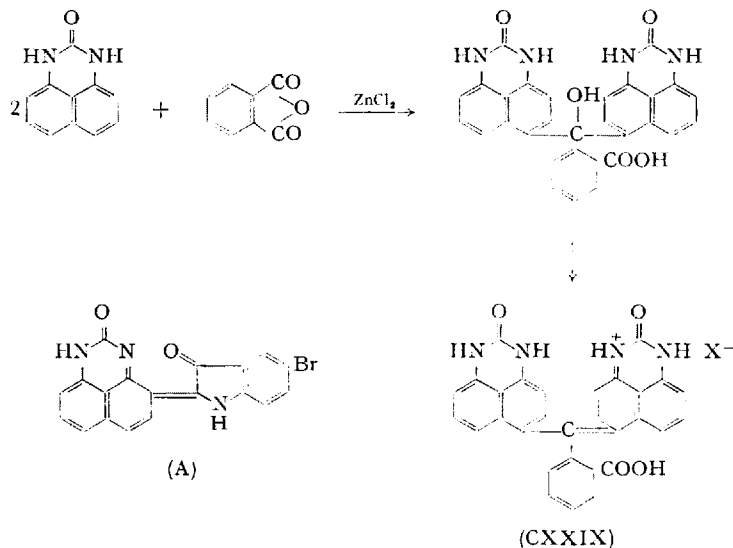


When phthalic anhydride, zinc chloride, and perimidone are fused together, a mixture of a yellow and a blue substance is formed; the blue one is insoluble in most organic solvents.⁹⁵ Both dissolve in sodium hydroxide, the blue forming a red solution, while the other remains yellow. In concentrated sulfuric acid the yellow substance gives a red solution that soon turns a deep blue, while the blue substance gives a deeper blue. Wool is dyed a weak yellow, but cotton is unattacked by the yellow substance, whereas an alkaline solution of the blue compound dyes cotton a violet-red, which is turned green by acids. Although Sachs did not assign structures to these two dyes, it



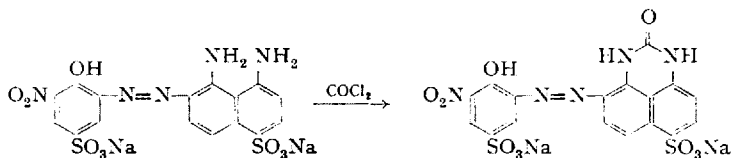
appears obvious that the blue is a dehydration product of the yellow substance. If the reaction takes the same course as that with acyl halides, the imide (CXXVII) would be formed first. This, especially if written as an enol, would be expected to be yellow by analogy with other perimides (p. 526), but so would the dehydration product (CXXVIIa), which would be a carboxyphthaloperinone (p. 528). 7,10-Disulphophthaloperinone (CXXVIII) is a yellow wool dye.¹⁴⁰

Alternatively, the anhydride might attack the 6-position, as was suggested for perimides (p. 529), perhaps reacting with two moles, to give a triphenylmethane dye (CXXIX); this might well be Sachs' blue product, the yellow being the carbinol.



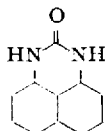
Uses. The indophenols (CXXV) are used as intermediates for bluish-green sulfur dyes; if copper is present, the color is yellowish-green.¹³⁹ Perimidone gives a condensation product with 5-bromo- α -chloroisatin; this is a violet-blue vat dye (A),¹⁴³ that is converted to a greenish-yellow bisulfite compound (*cf.* p. 542).

A complex azo dye containing the perimidone nucleus is prepared by ring closure of an azodiamine. Diazotized 2-amino-6-nitro-4-sulfo-phenol is coupled with 1,8-diamino-4-sulfonaphthalene, and the resulting compound cyclized by means of phosgene. The dye is metallized by chromium on the fiber.¹⁶² The properties of the perimidones are collected in Table VIII-9.



(c) 2-Imidoperimidine, N,N' -[Naphthylene-(1,8)]-guanidine, 2-Aminoperimidine (LXXXVII). This is obtained, along with the thione (CX) when 1,8-diaminonaphthalene is treated with ammonium thiocyanate (*cf.* p. 524). 2-Anilinoperimidine, phenyl-1,8-naphthylene-

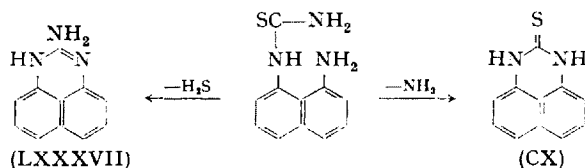
TABLE VIII-9. Perimidones



Formula	Substituent	M.p., °C.	Color in conc. H ₂ SO ₄	Refs.
XC	None; Perimidine	304-5		95
CXXII	1-(2,4-Dinitrophenyl)-	267-8	Bright yellow	97
	<i>x,x,x</i> -Triiodo-			33
CXXV	6-(4-Hydroxyanilino)-		Brown	115
CXXV	6-(3,5-Dichloro-4-hydroxyanilino)- ^a		Gray	115

^a Blue-black.

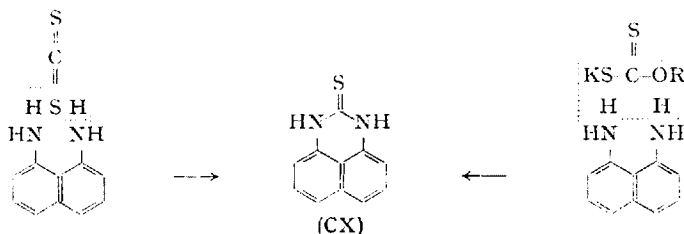
guanidine (LXXXVI), and the toluidino analogs are obtainable from the corresponding thiureas (which are formed from 1,8-diamino-



naphthalene and a mustard oil) (Table VIII-7). Their salts are all soluble with difficulty in water.⁹⁵

(d) Thioperimidones; 2-Thioperimidines. Thioperimidone (CX) may also be named 2-thione-2,3-dihydroperimidine, 2-thiono-2,3-dihydro-1*H*,1,3-diazabenzonaphthene, or *peri*-naphthylenethiourea.

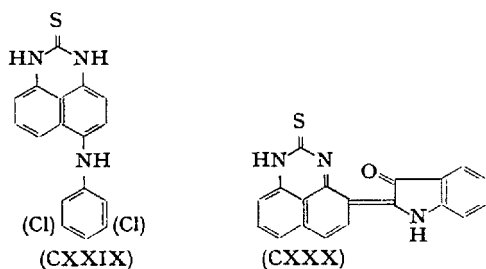
Thioperimidones may be prepared by several methods; the preferred is from 1,8-diaminonaphthalene and cold carbon disulfide.^{95,141} An alkali xanthate in acetic acid is likewise suitable, but requires long



heating. Less useful are procedures that employ ammonium thiocyanate (p. 523), or an alkyl mustard oil. The behavior of carbon disulfide is noteworthy, since there is no similar reaction with carbon dioxide or carbon oxysulfide. The use of thiophosgene has not been reported.

Properties. In general, the properties and reactions of thioperimidone are like those of the sulfur-free analog. It is a white solid that has no melting point; small amounts can be sublimed. It is very slightly soluble in the usual solvents. The sulfonic acids are not very soluble, even in hot water.

Thioperimidone has been nitrated using a mixture of nitric and acetic acids, to give mono and dinitro substitution products.¹⁴¹ While it is hinted in the patent that a monoamine could be made by reduction, there is no evidence of its preparation. The sulfonic acids¹⁴¹ and substituted aminophenols (CXXIX)¹¹⁵ were obtained by the ring closure method, using carbon disulfide. Since the aminophenol was obtained by cyclizing a substance in which the position of the substituent was known, its location is certain (*cf.* p. 540). The brown



alkaline solutions of the aminophenol turn blue in the air, owing to oxidation to an indophenol. This is probably the same product as is formed by the condensation of thioperimidone and quinoneimides.¹⁴²

Thioperimidone also condenses with α -chloroisatins to give products (CXXX) that are blue vat dyes.^{108,111,143} The latter form soluble yellowish bisulfite compounds, in which form they can be halogenated in aqueous solution.¹⁴⁴

Uses. The only applications of thioperimidones have been as intermediates for sulfur dyes,^{139,141} or for the vat dyes just mentioned.

The parent thioperimidone (CX) has a slight physiological action, being mildly goitrogenic.¹⁵¹

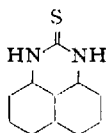
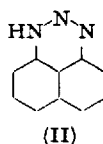


TABLE VIII-10. 2-Thionoperimidines

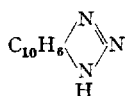
Substituent (formula)	Color	Refs.
None; 2-Thionoperimidine- ^a (CX)	White	95, 141
6,7-Ethano- ^b		98
<i>x</i> -Nitro-	Gray-brown	141
<i>x,x</i> -Dinitro-	Yellow-brown	141
6-Sulfo-	Gray	141
5,8-Disulfo-	Yellow	141
6-(4-Hydroxyanilino)- ^{c,d}	Gray	115
6-(3,5-Dichloro-4-hydroxyanilino)- ^{d,e}	Dark gray	115
4- α -Isatoyl-	Blue	108, 111

^a Sublimes. ^b Recrystallized from acetic acid or nitrobenzene. ^c Gray in concentrated sulfuric acid. ^d Brown in NaOH, turning blue in air. ^e Brown in concentrated sulfuric acid.

C. 1*H*,1,2,3-Triazabenzonaphthene, *peri*-Naphthotriazole. 1,2,3-Triazaperinaphthindene. 1,8-Aziminonaphthalene. 1-Naphtho[1,8]triazine. α -*peri*-Naphthotriazole. Naphthylenediazomide. R.I. 1822

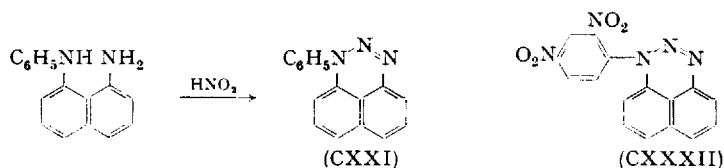


1*H*,1,2,3-Triazabenzonaphthene (II) has been known ever since d'Aguiar's first work¹ with 1,8-diaminonaphthalene. He treated the diamine with nitrous acid and obtained a red diazo compound having no melting point, which he wrote as:



and which Erdmann¹⁶⁰ expanded to II. Only a few derivatives are known; since they were prepared in a similar way, by the use of nitrous acid on a 1,8-diamine,¹⁴⁴⁻¹⁴⁷ this reaction may be assumed to be of a general nature.

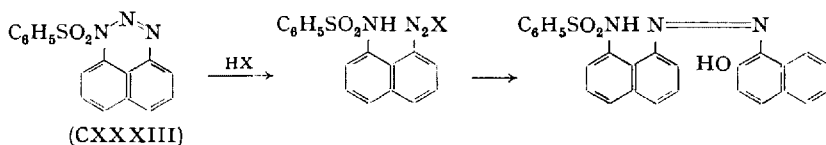
A second possible method is based on the similarity of the triazole (II) to benzotriazole; the substance is acidic and forms a sodium salt that can be alkylated. Thus, Sachs stated that the 1-methyl derivative



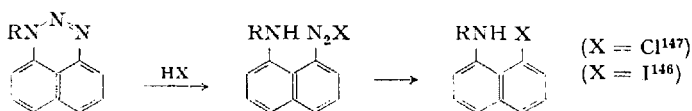
was prepared by the action of methyl sulfate or methyl iodide on II, but gave no experimental data other than that in solution its oxidation product was blue, whereas a red color resulted from the nonmethylated base (II).

Properties. The few known triaza compounds are deeply colored and dissolve in concentrated sulfuric acid, forming highly colored solutions. They are insoluble in water, and decompose on being heated. D'Aguiar stated that the parent compound decomposed when heated. Waldmann and Bach¹⁴⁵ were of the opinion that d'Aguiar had a mixture rather than the pure substance, and stated that *peri*-naphthotriazole melted at $236-7^\circ$ if heated rapidly; they were also able to recrystallize small amounts from nitrobenzene. The 1-benzenesulfonyl derivative (CXXXIII) puffs on being heated.¹⁴⁷ Since the substance is, in reality, an internal diazoamino compound, such instability to heat is to be expected.

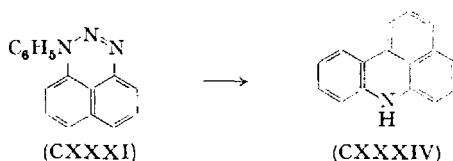
The chemical properties of the 1,2,3-triazabenzonaphthenes are also in agreement with their diazoamino structure. Thus, they are cleaved by acids, more or less readily, and give products that would be expected from diazonium salts. 1-Benzenesulfonyl-1,2,3-triazabenzonaphthalene (CXXXIII) dissolves in warm acetic acid, giving a diazonium salt which then couples to form an azo dye with β -naphthol. The cleavage can even be brought about by β -naphthol itself, if a solution in pyridine is heated for several hours.¹⁴⁷ The halogen acids also bring



about cleavage; the addition of copper may be beneficial. In these instances, the products are halonaphthylamines; *i.e.*, a Gattermann reaction takes place.

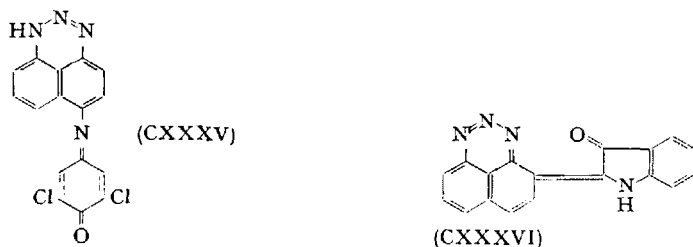


When 1-phenyl-1,2,3-triazabenzonaphthene (CXXXI) is heated in a naphthalene solution for some time, nitrogen is evolved and "meso-benzacridane," 7*H*,7-azabenzanthrene (CXXXIV), results.¹⁴⁵ The



1-(2,4-dinitrophenyl) derivative shows a similar behavior, and forms "8, 10-dinitro-*meso*-benzacridane," 8, 10-dinitro-7*H*, 7-azabenzanthrene.¹⁴⁵ These 7-azabenzanthrenes were omitted in the previously published volume in this series.⁹³

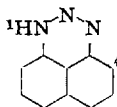
The triazine, like the perimidine, also condenses with quinone-imides¹⁴²; again no structures are written for the product (*cf.* p. 527). Because of the similarity to 1-naphthylamine, a probable structure (CXXXV) can be written. It has been suggested¹¹¹ that the triazine



should react with α -chloroisatin to give a product (CXXXVI) analogous with others known (p. 526).

The known triazabenzonaphthenes are collected in Table VIII-11.

No other triazabenzonaphthenes are known. In one instance¹⁴⁸ it was thought that a substance was a 1,2,6-triazabenzonaphthene

TABLE VIII-11. 1*H*,1,2,3-Triazabenzonaphthenes

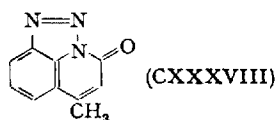
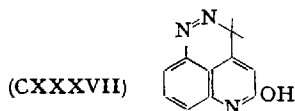
Formula	Substituent	M.p., °C.	Color	Refs.
II	None	(80-4?) 236-7	Red	1, 144, 145
	1-Methyl-			95
CXXXI	1-Phenyl- ^a	134	Red-brown	145
CXXXII	1-(2,4-Dinitrophenyl)- ^b		Red-brown	145
CXXXIII	1-Benzenesulfonyl- ^c	Puffs	Yellow	147
CXXXV	The indophenol		Brown-violet	142
	12 azo dyes			149

^a Red-brown, with a violet tinge, in concentrated sulfuric acid.

^b Yellow in concentrated sulfuric acid.

^c Forms a chloroplatinate.

(CXXXVII), but it was subsequently found to have an entirely different structure (CXXXVIII).¹⁵⁰



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CHAPTER IX

The Ultraviolet Absorption Spectra of Polycyclic Heterocyclic Aromatic Compounds

BY G. M. BADGER

1. Aromatic Hydrocarbons and Azahydrocarbons

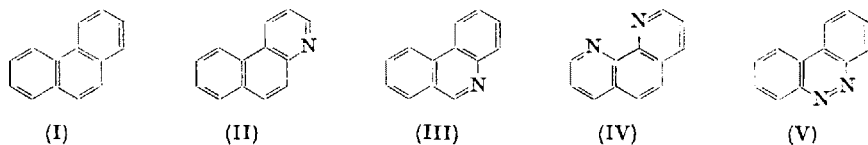
All aromatic compounds absorb in the ultraviolet or visible region of the spectrum. The aromatic hydrocarbons usually have relatively complex spectra with several absorption bands, the position of the bands depending on the number and arrangement of the aromatic rings.¹ Each hydrocarbon has its own characteristic absorption spectrum and this fact has been of great value in the identification of unknown products. Indeed, empirical rules have been devised that enable the absorption spectrum of a hydrocarbon to be predicted with considerable accuracy even before it has been prepared.¹ It is not so generally known that the azahydrocarbons also have characteristic absorption spectra, and that these spectra are very closely related to those of the corresponding aromatic hydrocarbons.

The aromatic hydrocarbons generally show three main regions of absorption (groups I, II, III) in the ultraviolet or visible region.² Benzene has a very strong absorption band (group I) in the far ultraviolet, with a maximum at 1790 Å.³ There is a second region (group II) of relatively intense absorption around 2000 Å, and a third region (group III) of low intensity absorption between 2300–2600 Å.⁴ Pyridine has a very similar absorption spectrum. It has an intense region of absorption in the far ultraviolet with a maximum at 1700 Å,³ a second region of absorption at about 2000 Å, and a third region of relatively

low intensity absorption around 2500 Å.^{5,6} Some of the absorption bands are shifted to slightly shorter wave lengths compared with benzene, but the general similarity is striking. One of the most important differences is to be found in the long wave length region, where the absorption is ten times as great for pyridine as for benzene. Moreover, the absorption spectrum of pyridine extends as far as 2900 Å, but benzene does not absorb beyond *ca.* 2750 Å. As a matter of fact this difference seems to be characteristic of the heterocyclic compounds, being particularly marked with diazines, and greatest when the nitrogen atoms are adjacent. It is discussed in greater detail in Section 3.

Similar comparisons may be made between the spectra of other aromatic hydrocarbons and their corresponding heterocyclic analogs. Many absorption curves have already been published in the literature, and the problem has been discussed in some detail.⁷ In most cases the absorption curves have been determined with a photoelectric spectrophotometer, and ethanol has generally been used as a solvent.

The absorption curves for quinoline, isoquinoline, and quinazoline all show the same three main regions of absorption as naphthalene.^{8,9} With the heterocyclic compounds, some of the maxima are shifted to slightly shorter wave lengths, but the most marked difference is again in the group III region. In every case the intensity of absorption in this region is much greater for the aromatic azahydrocarbon than for naphthalene.



Phenanthrene (I) shows three main regions of absorption, at about 2500 Å, at 2930-2750 Å and at 3140-3450 Å (Fig. IX-1).¹⁰ The related azaphenanthrenes, 4-azaphenanthrene (benzo[*f*]quinoline), (5,6-benzoquinoline) (II), 5-azaphenanthrene (phenanthridine) (III), 1,10-diazaphenanthrene (*o*-phenanthroline) (IV), and 5,6-diazaphenanthrene (3,4-benzocinnoline) (V), also show three main regions of absorption, and the spectra are all very similar to that of phenanthrene.^{7,11} For

4-azaphenanthrene, 5-azaphenanthrene and 1,10-diazaphenanthrene, the absorption bands are shifted to slightly shorter wave lengths. The maximum of the group I region for phenanthrene, for example, is at 2507 Å, but that for 4-azaphenanthrene is at 2350 Å, and that for 1,10-diazaphenanthrene at 2310 Å. For 5,6-diazaphenanthrene, there seems to be very little if any shift in the position of the group I region to shorter wave lengths. With all the azaphenanthrenes, however, the group III absorption is very much more intense than with phenanthrene itself, and it extends to longer wave lengths. This latter difference is most marked with 5,6-diazaphenanthrene, where the two nitrogen atoms are adjacent.

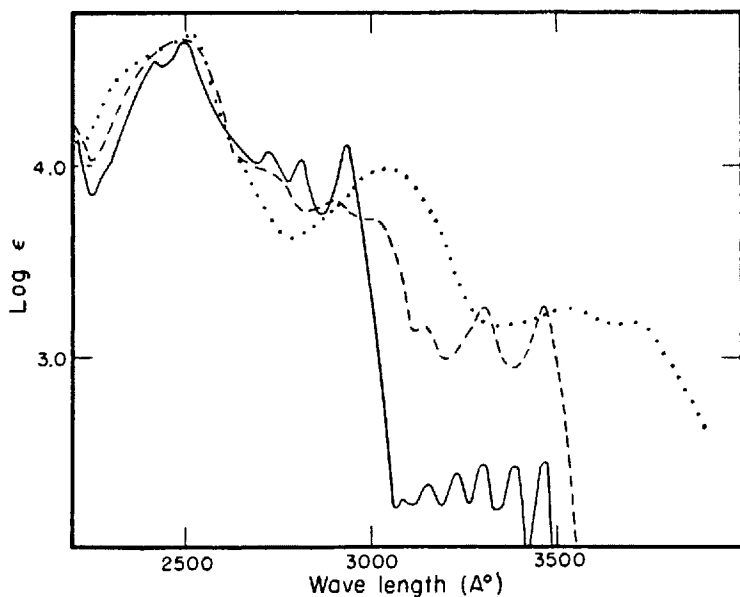
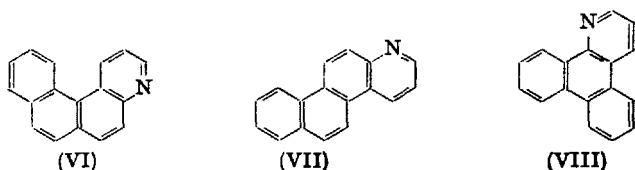


Fig. XI-1. Absorption curves of phenanthrene (—), 5-azaphenanthrene (---), and 5,6-diazaphenanthrene (····).

Many such comparisons of the spectra of polycyclic aromatic hydrocarbons with their heterocyclic analogues can be made. The spectrum of 4-azabenz[*c*]phenanthrene (1'-aza-3,4-benzophenanthrene) (VI) is very similar to that of benzo[*c*]phenanthrene itself (Fig. IX-2).⁷ The absorption bands are at almost the same wave lengths,

but the intensity of the group III region given by the azahydrocarbon is about ten times that with benzo[*c*]phenanthrene. Similarly, the spectrum of 1-azachrysene (VII) resembles that of chrysene, except that



the group III region is more intense;⁷ and the same difference may be noted between the spectra of triphenylene and of 1-azatriphenylene (VIII) (Fig. IX-3).⁷

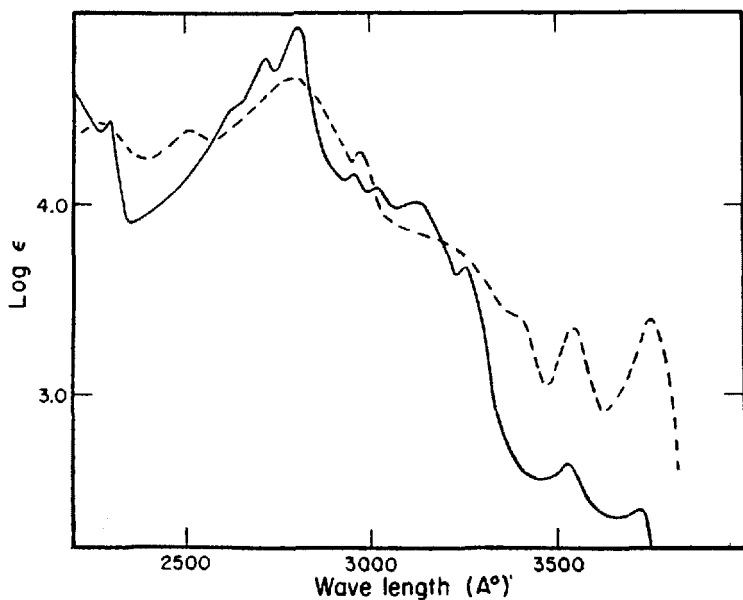


Fig. IX-2. Absorption curves of benzo[*c*]phenanthrene (—) and 4-azabenzo[*c*]phenanthrene (----).

Benz[*a*]anthracene has a complicated absorption spectrum with twelve peaks in all; but, as before, these may be divided into three groups.¹² Of the many possible heterocyclic analogs, the spectra of 7-azabenz[*a*]anthracene (3,4-benzacridine) (IX), 8-azabenz[*a*]anthra-

cene (5-aza-1,2-benzanthracene) (X) and of 7,12-diazabenz[*a*]anthracene (1,2-benzophenazine) (XI) have been determined.⁷ There is a considerable loss of fine structure with the azahydrocarbons, but the same

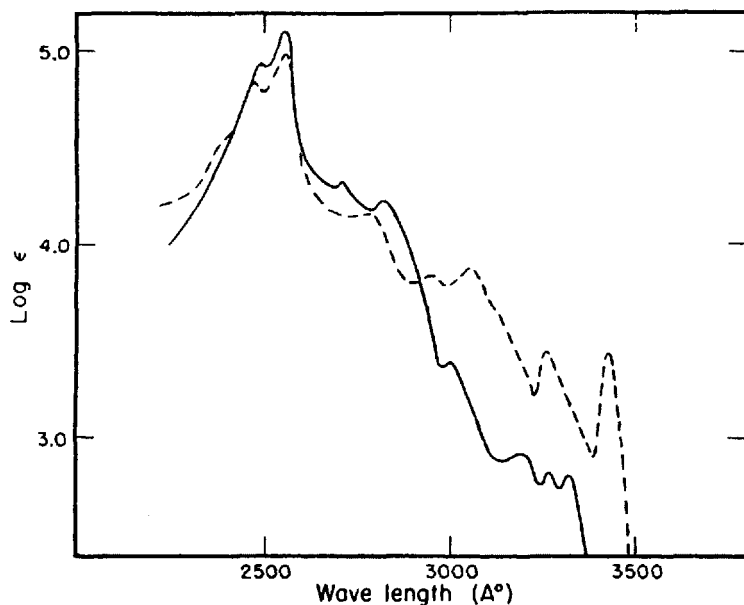
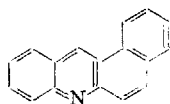
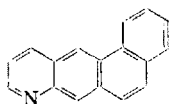


Fig. IX-3. Absorption curves of triphenylene (—) and 1-azatriphenylene (---).

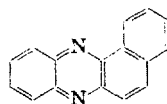
three regions of absorption can be identified without difficulty, for there is a strong over-all similarity between the curves (Fig. IX-4). The chief difference is again that the group III region is more intense with the azahydrocarbons, and extends to somewhat longer wave lengths. This effect is most marked with 7,12-diazabenz[*a*]anthracene, the absorption spectrum of which extends beyond 4200 Å. The absorption spectrum of benz[*a*]anthracene, on the other hand, extends only to *ca.* 3900 Å, and this hydrocarbon is colorless, whereas 7,12-diazabenz[*a*]anthracene is yellow.



(IX)



(X)



(XI)

Among more complex compounds, it has been shown that 5,8-diazapentaphene (XIII) has an absorption spectrum very similar to

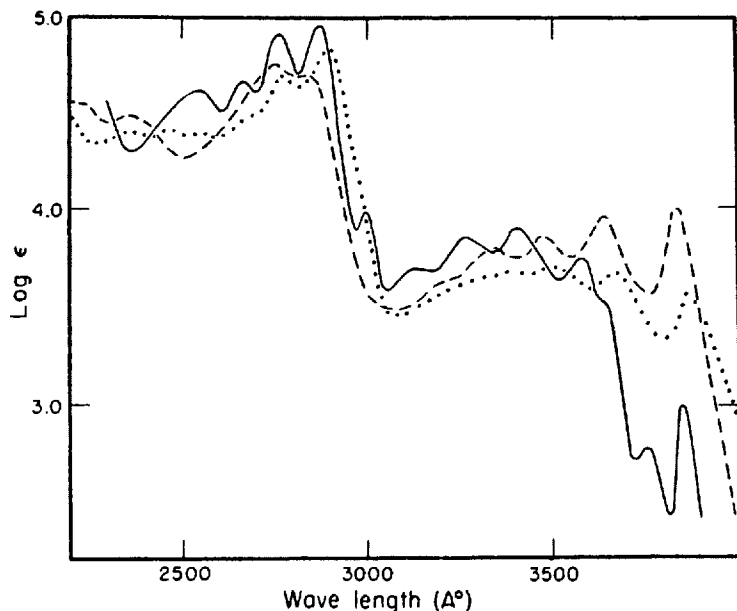
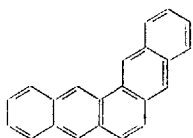
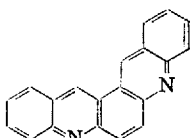


Fig. IX-4. Absorption curves of benz[*a*]anthracene (—), 7-azabenz[*a*]anthracene (---), and 8-azabenz[*a*]anthracene (····).

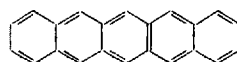
that of the analogous hydrocarbon pentaphene (XII), but very different from that of the linear pentacyclic hydrocarbon, pentacene¹³ (XIIa).



(XII)



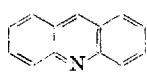
(XIII)



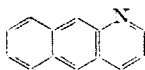
(XIIa)

Anthracene shows only two main regions of absorption. It has a strong absorption band (group I) at 2515 Å, corresponding to the benzene absorption at 1790 Å. It has a second region of absorption (group II) around 3000–3750 Å, corresponding to the benzene absorption at about 2000 Å; but no group III absorption bands can be observed, as these are hidden by the group II absorption.¹ As Clar has shown, each

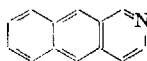
additional linear benzene ring shifts the group II absorption bands much further to longer wave lengths than the group III bands. Hence in the polyacenes (anthracene, naphthacene, pentacene, hexacene) the group III absorption is never evident. Group III absorption bands can only be observed with polycyclic aromatic hydrocarbons having an *angular* arrangement of benzene rings.



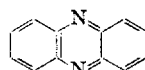
(XIV)



(XV)



(XVI)



(XVII)

The azahydrocarbons corresponding to anthracene likewise exhibit only two regions of absorption, the group III region being similarly masked, or hidden, under the group II bands. Acridine (XIV), 1-aza-anthracene (XV), 2-azaanthracene (XVI), and phenazine (XVII) all show spectra which are very similar to that of anthracene (Fig. IX-5), except that the absorption of the azahydrocarbons extends to slightly longer wave lengths.^{7,14} For example, the absorption of anthracene

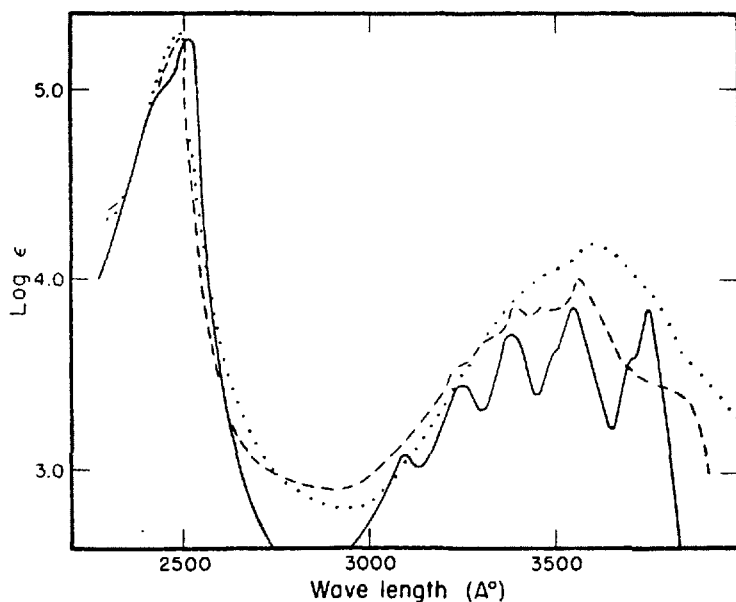


Fig. IX-5. Absorption curves of anthracene (—), acridine (---), and phenazine (····).

extends only to *ca.* 3900 Å, but that for phenazine extends beyond 4100 Å. As this absorption is in the visible region, phenazine is yellow, while anthracene (which absorbs only in the ultraviolet) is colorless. It may be noted further that the group II absorption with acridine and phenazine is considerably more intense than with the aromatic hydrocarbon.

It may be concluded therefore that the absorption spectra of aromatic azahydrocarbons resemble those of their carbocyclic analogs very closely indeed. The chief differences are: (1) that the group III absorption bands are much more intense (often ten times) than those of the corresponding aromatic hydrocarbons; (2) that, in compounds which do not exhibit group III absorption (anthracene, etc.), the group II bands are sometimes more intense than those for the hydrocarbon; (3) that there is considerable loss of fine structure in replacing a methine group by an annular nitrogen atom, at least in ethanol solution; and (4) that the absorption spectra of the azahydrocarbons generally extend to longer wave lengths than those of the corresponding hydrocarbons.⁷ This latter effect is most marked in diazacomounds, and especially with those compounds in which the two nitrogen atoms are adjacent.

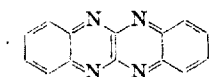
2. The Color of Aromatic Azahydrocarbons

The color of an organic substance is determined by the position of its absorption bands. Compounds that absorb in the violet region of the visible spectrum (4000–4350 Å) are yellow-green or yellow; those that absorb in the green region (5000–5600 Å) are purple; and those that absorb in the red region (6050–7500 Å) are blue-green; and so on.

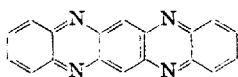
With the hydrocarbon polyacenes, the absorption bands shift progressively to longer and longer wave lengths with each additional benzene ring.¹ For benzene the absorption band of longest wave length has its maximum at 2607 Å, and this substance is colorless. Naphthalene has an absorption band at 3100 Å, and anthracene at 3745 Å, so that both these substances are also colorless. Naphthacene, however, has an absorption band at 4735 Å, in the visible region, and is therefore orange; while pentacene, which absorbs at 5800 Å, is deep blue.¹

All the evidence quoted in Section 1 supports the view that the

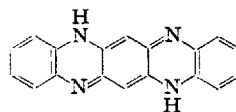
spectra of the aromatic azahydrocarbons are very similar to those of their carbocyclic analogs. It is therefore reasonable to expect the color of the linear heterocyclic compounds (or azapolyacenes) to deepen as the number of benzene rings increases, in the same manner as with the hydrocarbon polyacenes. This has been found to be the case. Pyridine, quinoline, and acridine are colorless, for they absorb only in the ultra-violet; but 5-azanaphthacene (2,3-benzacridine), an azahydrocarbon corresponding to naphthacene, is orange-red. Similarly, pyrazine and quinoxaline are colorless; but phenazine (the absorption spectrum of which extends beyond 4100 Å) is yellow; and 5,12-diazanaphthacene (2,3-benzophenazine) is red.¹⁵ Additional annular nitrogen atoms shift the absorption to slightly longer wave lengths, and 5,6,11,12-tetraazanaphthacene (XVIII) is red-brown.



(XVIII)



(XIX)



(XX)

It is difficult to extend the comparison to higher members of the series. Dutt¹⁶ obtained a *yellow* substance he described as 5,7,12,14-tetrazapentacene (XIX), but it is unlikely that his material had this structure, for the analogous hydrocarbon (pentacene) is *deep blue*. Moreover, recent attempts to prepare this substance have failed, or have given only the blue dihydride, apparently having the quinonoid structure (XX).¹⁵ Similarly, Dutt¹⁶ claimed to have prepared 5,7,9,14,16,18-hexazaheptacene, but the yellow substance he obtained cannot have this structure, as the analogous hydrocarbon, heptacene, would be deep green, almost black.

3. Absorption Spectra of Diazines and Related Compounds

Ethanol seems to be a suitable solvent when it is desired to emphasize the similarity between the spectra of the aromatic azahydrocarbons and their carbocyclic analogs; but it does not seem to be the most satisfactory solvent when it is desired to emphasize the differences. There is a considerable solvent effect with the azahydrocarbons.¹⁷ In

cyclohexane solution, more fine structure can be resolved, and with simple azahydrocarbons it is possible to detect an additional absorption region at long wave lengths that is not evident in ethanol solution. The absorption spectrum of pyridine in cyclohexane solution, for example, shows an additional "shoulder" in the long wave length region, which is not present in either ethanol or water solution.¹⁷



(XX)



(XXII)



(XXIII)

This additional absorption region is even more apparent with diazines such as pyridazine (XXI), pyrimidine (XXII), and pyrazine (XXIII). With these compounds a distinct absorption band (at about 3100–3300 Å) can be resolved even in aqueous solution. In cyclohexane solution, however, this additional absorption band is shifted to longer wave lengths, and shows some fine structure.¹⁷

The polyazines also give this additional absorption band, its position being shifted progressively to longer and longer wave lengths with every increase in the number of annular nitrogen atoms.¹⁸

In order to explain this additional absorption band it is necessary to consider the structures of these compounds. Electronically the aromatic azahydrocarbons closely resemble their carbocyclic analogs. Each annular nitrogen atom and each annular carbon atom contribute one π -electron to the "aromatic sextet," and it is not surprising that the ultraviolet absorption spectra of the heterocyclic systems so closely resemble those of the corresponding hydrocarbons. The two sets of compounds are isoelectronic.

On the other hand, there are some important structural differences. Nitrogen is somewhat heavier than carbon, and it is more electronegative; moreover, each annular nitrogen atom has two electrons (the lone pair) not involved in binding. This latter difference is significant, and evidence has recently been presented¹⁷ that indicates that the long wave length absorption band (which is most strongly observed with azahydrocarbons containing more than one annular nitrogen atom) is due to a nonbonding nitrogen electron transition.

Unfortunately, little or no attempt has so far been made to detect

this long wave length absorption band in the spectra of polycyclic azahydrocarbons, nearly all the experimental work having been carried out in ethanol solution.

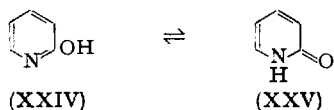
4. The Effect of Substituents

Substituents in aromatic hydrocarbons of the benzenoid type always produce a shift in the position of the absorption bands to longer wave lengths (bathochromic shift). The magnitude of the shift depends on the nature and position of the substituent, and seems to depend largely on the degree of conjugation with the ring system.^{2,19} On the other hand, substituents in nonbenzenoid aromatic hydrocarbons sometimes give rise to bathochromic shifts, and sometimes produce shifts to shorter wave lengths (hypsochromic shifts). For example, in two of the five possible substitution positions in azulene, a methyl group produces a bathochromic shift in the visible region of the spectrum, and in the remaining substitution positions a methyl group causes a hypsochromic shift.²⁰

The aromatic azahydrocarbons are similar to the nonbenzenoid aromatic hydrocarbons; that is, a given substituent can produce either a bathochromic or a hypsochromic shift depending on its position in the ring system. Both effects have, for example, been observed with alkoxy-*N*-methylacridones,²¹ and with fluoroquinolines.²² The problem has not yet been extensively investigated, but it has been suggested that such alternating effects can be correlated with the π -electron densities at the annular carbon atoms. In benzenoid aromatic hydrocarbons this density is always unity; but in nonbenzenoid aromatic hydrocarbons, and in azahydrocarbons, the π -electron density is sometimes less and sometimes greater than unity.

With hydroxyl substituents a further complication arises. A ketonol type of tautomerism is often encountered with the carboxylic phenols, the best example being that of 9-anthrol $\rightleftharpoons$ anthrone, for both forms can be isolated without difficulty. In certain heterocyclic phenols, however, an additional type of tautomerism can occur. This is a lactam-lactim tautomerism, as exemplified by 2-hydroxypyridine (XXIV, XXV). A similar tautomerism occurs with 4-hydroxypyridine; but no

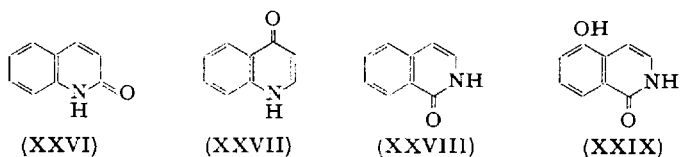
lactam structure can be written for 3-hydroxypyridine, and this compound has a phenolic structure.



The same argument holds in the case of the hydroxyquinolines and isoquinolines. There is now considerable spectrographic evidence that all hydroxyquinolines and isoquinolines having the substituent in the α - or γ -position relative to the ring nitrogen, exist predominantly in the lactam form, but that all other hydroxy derivatives have an essentially phenolic structure.⁸

With 1-naphthol there is a considerable bathochromic shift in passing from neutral to basic solution, and a similar shift is observed with all the hydroxyquinolines and isoquinolines that have a phenolic structure. Furthermore, quinoline gives a bathochromic shift in passing from neutral to acid solution, and a similar shift is obtained with all the hydroxy derivatives having a phenolic structure.

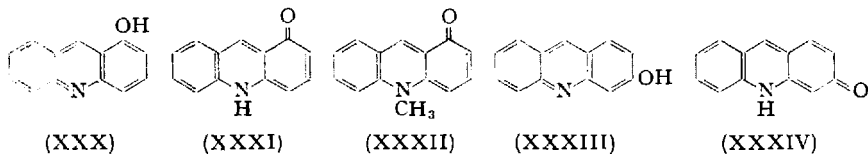
With 2- and 4-hydroxyquinoline, and with 1-hydroxyisoquinoline, however, the spectra are essentially identical in ethanol, in dilute acid, and in dilute alkali. The fact that no bathochromic shift occurs in basic solution indicates that no phenolic hydroxyl group is present, and the absence of a similar shift in acid solution indicates that the nitrogen is saturated and cannot make a greater contribution to resonance after taking up a proton. It may be concluded therefore that these compounds exist in solution essentially as XXVI, XXVII, and XXVIII.⁸



In order to test this conclusion the spectrum of 1,5-dihydroxyisoquinoline was examined. This compound gave a bathochromic shift in alkali due to the phenolic group in position 5, but it gave no shift in acid solution in agreement with the assignment of structure XXIX.⁸

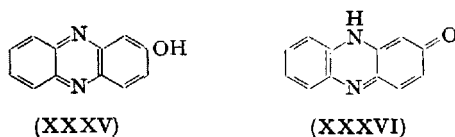
Lactam-lactim tautomerism occurs also in certain hydroxy-

acridines and phenazines, and in these cases it is possible to alter the position of the equilibrium by suitable change of solvent. A solution of 1-hydroxyacridine (XXX) in absolute ethanol, for example, is yellow, and its spectrum is that of an orthodox phenol, as it differs little from that of acridine itself. A solution of the same substance in 20% aqueous ethanol, however, is blue, and the altered spectrum is due to the lactam form (XXXI)—the characteristic blue color being identical with that of the nonenolizing ketone (XXXII). Aqueous ethanol of intermediate composition gives solutions having intermediate spectra, and the lactam form (XXXI) seems to be favored by a solvent of high dielectric constant.²⁴



3-Hydroxyacridine (XXXIII) behaves similarly. Its spectrum in ether-alcohol solution is of the ordinary acridine type; but in 20% aqueous ethanol a spectrum consistent with the lactam structure (XXXIV) is obtained.²⁴ No tautomeric pairs can be written for 2- and 4-hydroxyacridine, so that these compounds occur entirely as "phenols." There is no significant alteration in the spectra of these compounds with change in the dielectric constant of the solvent.²⁴

A tautomeric pair can be written for 2-phenazolin (XXXV, XXXVI), and this substance does show lactam-lactim tautomerism.²⁵ Its solution in absolute ethanol is yellow, and its absorption spectrum (Fig. IX-6) in this solvent closely resembles that of 2-methoxyphenazine in the same solvent. In absolute ethanol, therefore, 2-phenazolin must exist predominantly in the lactim form (XXXV). In aqueous ethanol solution, however, a deeper color is observed, indicating increased absorption at longer wave lengths. In pure water, 2-phenazolin gives an orange solution and the absorption spectrum extends as far as 5400 Å. This spectrum must be associated with the lactam form (XXXVI).



A tautomeric pair can also be written for 1-phenazinol (XXXVII, XXXVIII), but no evidence of lactam-lactim tautomerism could be found with this compound.²⁵ It gives a pale yellow solution in absolute

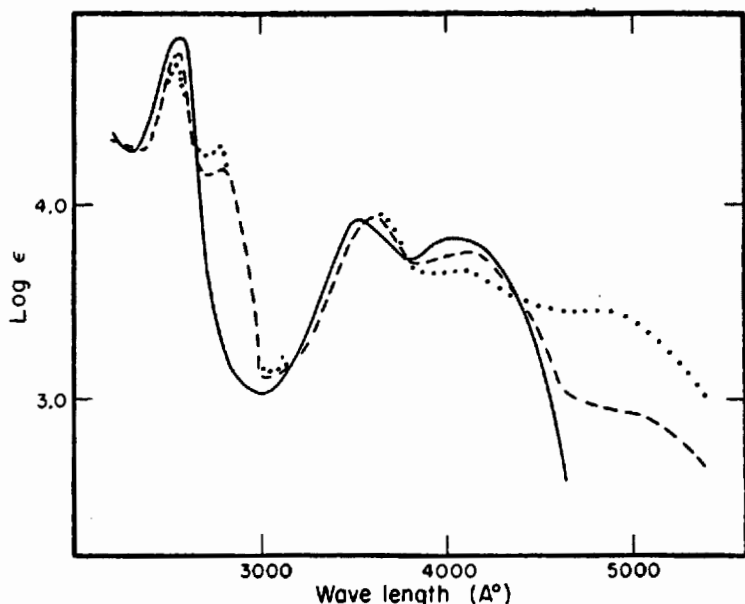
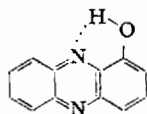
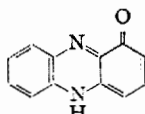


Fig. IX-6. Absorption curves of 2-phenazinol in absolute ethanol (—), 50% ethanol (----), and water (····).

ethanol, and its color is unchanged by dilution with water. The absorption spectra are almost identical in the two solvents, and it seems that the lactam form (XXXVIII) must be unimportant in this case. It is likely that the lactim form (XXXVII) is stabilized by hydrogen bonding between the hydroxyl group and the adjacent annular nitrogen atom.



(XXXVII)



(XXXVIII)

Lactam-lactim tautomerism has also been confirmed with 5,6-dihydroxy-7,12-diazabenz[*a*]anthracene (3,4-dihydroxy-1,2-benzophen-

azine) (XXXIX).²⁵ It gives a light brown solution in absolute ethanol, and on dilution with water this becomes dark blue, indicating the formation of an increased quantity of the lactam form (XL). Both

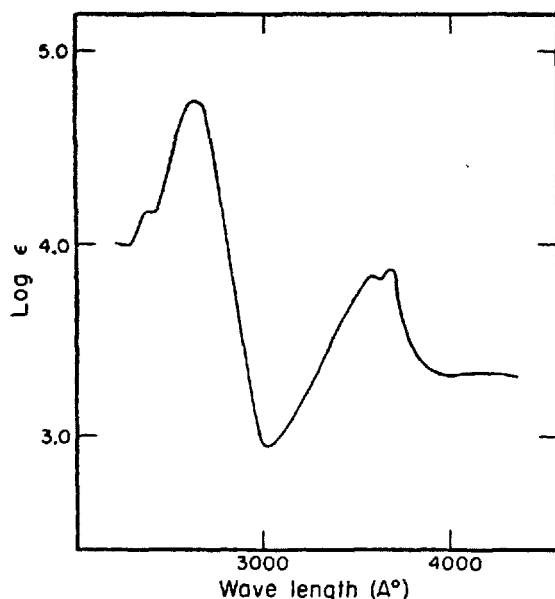
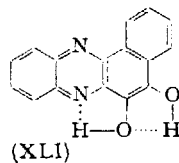
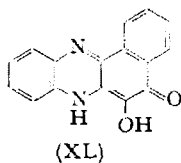
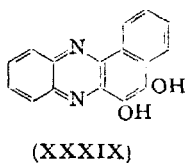


Fig. IX-7. Absorption curve of 1-phenazinol in absolute ethanol, unchanged in water.

solutions are rapidly oxidized by air, and it was not possible to obtain satisfactory solutions for accurate spectrographic use. Solutions in dioxane and in aqueous dioxane were therefore used, a little hydrazine being added to prevent oxidation. Under these conditions the expected change in the absorption spectra with increasing dielectric constant of the solvent was observed.



It is of some interest that 5,6-dihydroxy-7,12-diazabenz[*a*]anthracene has a blue color even in the solid state, so it must exist essentially

in the lactam form (XL). Weak hydrogen bonding would be expected between the two hydroxyl groups, and between the 6-hydroxyl group and the annular nitrogen atom (as in XLI). Unlike the case of 1-phenazinol, this hydrogen bonding would facilitate the formation of the lactam (XL).

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Naphthalimides: Addendum

BY C. F. H. ALLEN

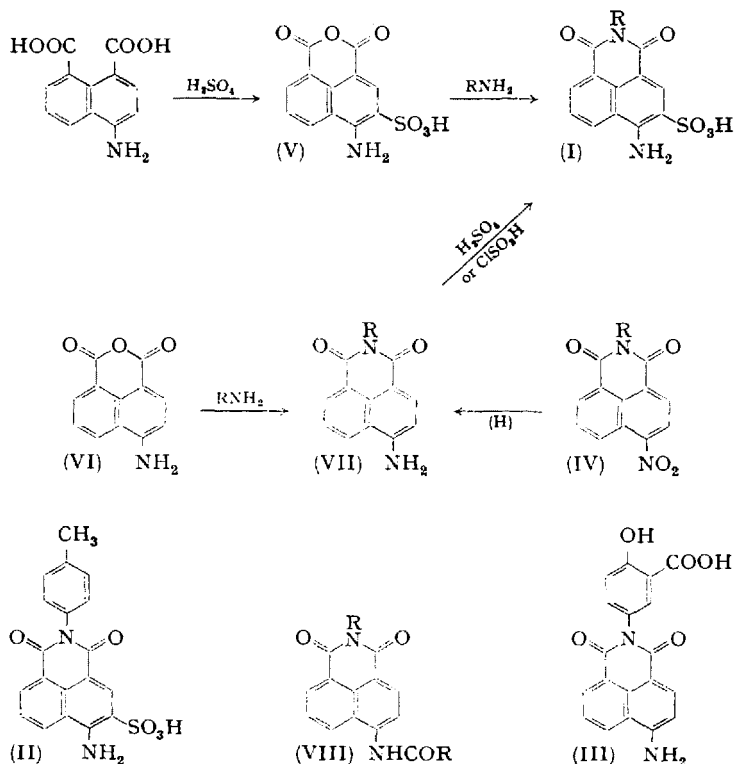
Brilliant Sulfo Flavine^{1,2} FF,^{3,4,6} Brilliant Acid Yellow 8G.⁵

A relatively new type of acid yellow dye^{6,15} first appeared on the market in 1930. The almost dazzling, pure yellow color of dyed materials, which exhibit a strong greenish-yellow fluorescence in ultra-violet light, cannot be matched by any previously known dye.

These dyes are sulfonated 6-amino-2-substituted naphthalimides (I, II). In most instances the sulfonic acid group is presumably in the 5-position, for the same product appears to result whatever the method of synthesis. For instance, sulfonated 4-aminonaphthalic acid derivatives (taken through the usual subsequent steps to the naphthalimides^{2,7,8}), simultaneous reduction and sulfonation of 6-nitronaphthalimides by sodium bisulfite or hyposulfite,^{9,10} and sulfonation of 6-aminonaphthalimides by the use of monohydrate⁷ or 20% oleum² and by chlorosulfonic acid^{7,11} all give essentially identical dyes. The observation that on sulfonation the sulfonic acid group enters the 5-position, *ortho* to the amino group, in II instead of the toluidine residue is worth mentioning.¹¹

There are three possible routes to these dyes, all of which are usual for preparation of naphthalimides (p. 495). The most general is from 4-amino-3-sulfonaphthalic anhydride and an amine (V → I). A second employs the unsulfonated amino anhydride (VI → VII → I), while the third involves a simultaneous reduction and sulfonation of a nitronaphthalimide (IV → I). These reactions are summarized in the chart. When a sulfonated halonaphthalic acid or anhydride is used as a source of the aminonaphthalic acid, the dyes are said to be redder;⁸ this

difference suggests that in these dyes the sulfo group is not in the same ring as the amino group. Acylation of the amino group (of VII) gives dyes (VIII) that have a bluish fluorescence.¹⁷ If 5-aminosalicylic acid

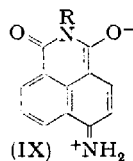


is the amino compound that reacts with the unsulfonated anhydride (VI), the product^{12,13,14} is a chelating dye (III), Chrome Fast Yellow 8GL (5GD).⁴ The unsulfonated 6-aminonaphthalimides dye cellulose acetate.¹⁹

The melting points of four intermediates (not in Table VIII-3) are as follows: 2-(2,5-dimethoxyphenyl)-, 237–239.5°;¹⁸ 2-(2,5-dihydroxyphenyl)-, 365–370° dec.;¹⁸ 6-amino-2-cyclohexyl-, about 242°;² 6-nitro-2-*p*-tolyl-, 243–244° (254–256°, corr.).¹⁶

The nature of R (*e.g.*, in II) can be shown by a treatment with hydrazine; the amine which is liberated can be steam-distilled out and identified in the usual way.¹⁶

The yellow color of these dyes is much greater than would be expected of a simple naphthalimide. It can probably be attributed¹⁶ to a quinoid form (IX) (*cf.* p. 504).



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