

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

This is the second 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 FOUR CONDENSED RINGS

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Eastman Kodak Company, Rochester, N. Y.

In collaboration with

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INTRODUCTION TO THE SERIES

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.

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ARNOLD WEISSBERGER

Preface

The polynuclear heterocyclic compounds containing nitrogen and four fused six-membered rings are not only of considerable interest to the drug and dye industries, but are also of great theoretical interest and historical importance. In several instances the proof of structure was unexpectedly difficult, requiring many years, to which well-known chemists devoted much of their scientific lives. The similarities and significant differences shown by the various members of the larger heterocyclic condensed systems are lost in the usual treatment given them in the literature. It is hoped that the arrangement and discussion of the closely related classes included in this volume will arouse a greater interest in and impart a new viewpoint to the chemistry of the individual substance. The literature has been covered through 1950.

The varied nomenclature was most confusing, each group of investigators applying names that gave little clue as to structures. Even the indexing journals were not consistent. Both names and numbering differed markedly for strictly analogous types of compounds. In a monograph such as this, uniformity is essential, particularly for locating different series of compounds for comparison. For these reasons, the "a" system of nomenclature has been adopted, and every substance named accordingly. In the index, all individual chemical substances are listed under the names used in the text. The name of the parent ring system, as listed in the *Ring Index* and used in *Chemical Abstracts*, is also indexed. Thus, anyone unfamiliar with the "a" nomenclature can find the "a" name of the corresponding ring system by its *Chemical Abstracts* name, and then look up the individual substance under the "a" name of the parent ring system.

The publishers have cooperated in every way to make the volume of the greatest possible use and have been most liberal in the allowance of space for structural formulas and an extensive index. The authors are very grateful to Mrs. A. H. Talbot for typing, proofreading, and general editorial assistance.

Eastman Kodak Company
Rochester, New York
March 15, 1951

C. F. H. ALLEN

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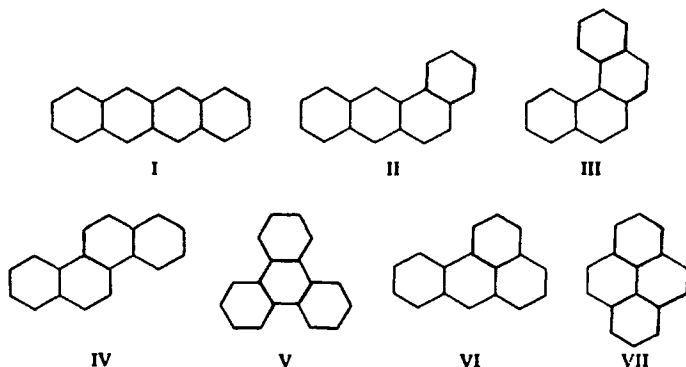
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Introduction

Heterocyclic nitrogen analogs of the seven different ring systems established by fusion of four benzene rings are described in this volume. The azalogs of naphthacene (I), benz[*a*]anthracene (II) (exclusive of those which are benzacridines or benzophenazines), benzo[*c*]phenanthrene (III), chrysene (IV), triphenylene (V), benzanthrenes (VI), and pyrene (VII) will be discussed in this order.



All systems in which there is a nitrogen atom common to two rings are omitted; it is anticipated that these types will be collected in a subsequent volume.

A structural formula, which is numbered according to the standard rules, is given at the beginning of each section. The aza names which are used in the chapter are indicated in boldface type beside each of the ring skeletons, and are followed in general by the preferred *Chemical Abstracts* systematic name. Some of the other names which have appeared in the literature for these same compounds are also included, along with the *Ring Index* number (if one has been assigned) to afford assistance in checking the literature.

A series of tables listing practically all of the compounds reported which belong to six of the basic systems is given at the end of the chapter. In the case of the patent literature, however, incompletely characterized compounds whose exact nature has not been determined have been omitted. The very numerous derivatives of the 3-azabenzanthrenes have

not been included in the tables.

It is readily apparent that the number of theoretically possible aza and polyaza isomers for the seven different ring systems containing ten or twelve replaceable carbon atoms not common to two or more rings is prodigious. However, a survey of the literature reveals that very few of these heterocycles have been synthesized. It is even more surprising to find that so little systematic investigation of the known systems has been carried out.

Although many substituted azalogs of these four-ring hydrocarbons have been reported, most of them have not been prepared from the parent heterocycles. Hence, there is very little information available regarding the reactivity of these ring systems. Furthermore, in cases where ring closure may take place in more than one direction, the exact structure of the product has not always been proved, thus introducing uncertainty.

In view of the fact that a number of the compounds belonging in this volume are derivatives suitable for the identification of amines and ketones, are biologically active, and are potentially useful in the dye industry, it is highly desirable that additional research be undertaken in neglected portions of the field.

CHAPTER I

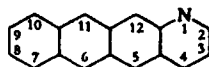
Azanaphthacenes

BY ELEANOR R. WEBSTER

1. Monoazanaphthacenes

Although derivatives of all three of the theoretically possible mono-azanaphthacenes, the 1-, 2-, and 5-aza compounds, have been synthesized, only the 1- and 5-isomers have been investigated extensively. Since the field as a whole has not been examined either systematically or comprehensively, it is probable that considerably more information on these three ring systems will be published in the future as a number of members of these series are potential dyes or dye intermediates. Table 2 of this chapter includes compounds belonging to these three systems.

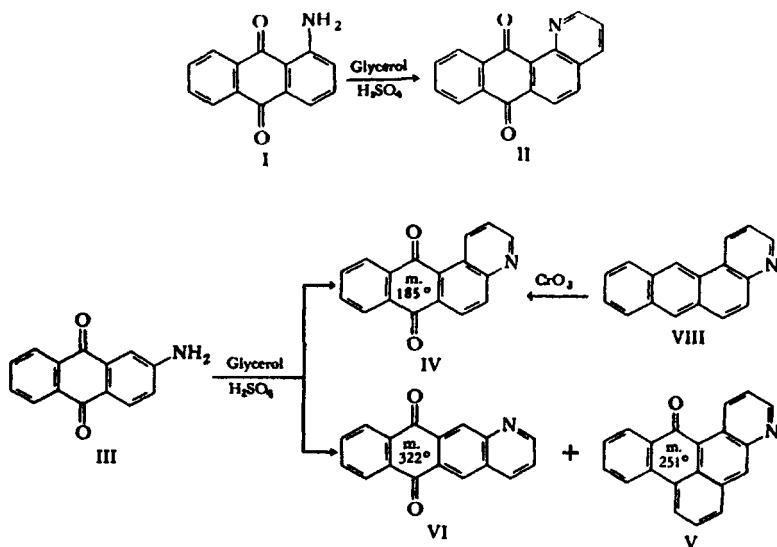
A. 1-Azanaphthacene, Naphtho[2,3-*g*]quinoline, 6,7- β -Naphthoquinoline, 2,3-Pyridinoanthracene. R.I. 2729



Inasmuch as naphthacene and dihydronaphthacene are readily obtained by zinc dust distillation of unsubstituted and hydroxyl-substituted naphthacenediones, it might be expected that 1-azanaphthacenediones would be similarly reduced to the corresponding 1-azanaphthacenes. Surprisingly, there is no report of any such reduction, and consequently all the 1-azanaphthacenes found in the literature are either 6,11- or 5,12-diketo derivatives.

The first member of the 1-azanaphthacene series to be synthesized was obtained as a by-product from the reaction of 2-aminoanthraquinone with glycerol and sulfuric acid,¹ but the substance which was found to have the empirical formula $C_{17}H_9NO_2$ was not characterized other than as an isomer of Graebe's " β -anthraquinonequinoline." Since 1-aminoanthraquinone (I) reacts normally in the Skraup synthesis to give " α -anthraquinonequinoline" (II),² it is logical to assume that 2-

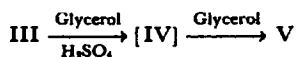
aminoanthraquinone (III) would be converted to " β -anthraquinone-quinoline" [or 4-azabenz[*a*]anthraquinone (IV)]. The main product of this reaction is, however, "benzanthronequinoline," a five-ring compound, shown by Bally³ to have the structure V. Although the principal



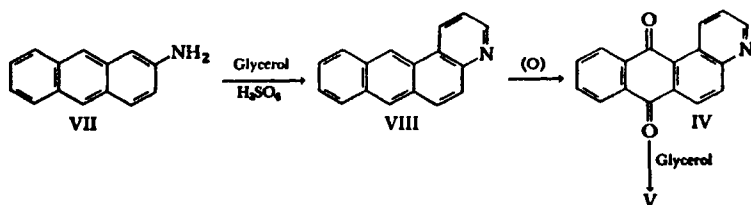
product of the reaction is V, both in the presence and absence of an oxidizing agent such as nitrobenzenesulfonic acid, repeated purification of the crude material gives two fractions. The one melting at 251° is pure V while the one melting at $232\text{--}234^\circ$, which at first appears to be a single substance, is in reality a mixture of VI ($\text{C}_{17}\text{H}_9\text{NO}_2$), melting at 322° , and V. Graebe's isomeric " β -anthraquinonequinoline" (IV) was prepared by the chromic acid oxidation of " β -anthraquinoline" $\text{C}_{17}\text{H}_{11}\text{N}$ (VIII) which he⁴ had obtained from the treatment of 2-aminoanthracene (VII) with glycerol and sulfuric acid, or from a zinc dust distillation of the dye, Alizarin Blue.⁵ Even though IV cannot be identified in the product from the Skraup reaction on 2-aminoanthraquinone,* Bally

* Investigations of the Skraup synthesis with β -naphthylamine and its derivatives have established that the normal angular product results even if the 1-position of the naphthalene nucleus is substituted by bromine or by a nitro group. On the other hand, when the 1-position contains chlorine, a methyl, or aryl group, the direction of ring closure is influenced so that a linear arrangement results.

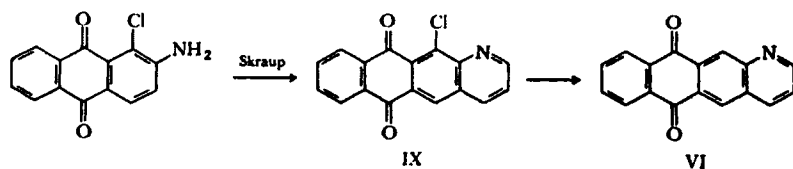
showed that it must be an intermediate in the preparation, since IV



reacts with a mole of glycerol to give V. Bally and Scholl⁶ therefore postulated this series of reactions to account for the course of this reaction: since the compound melting^{1,6} at 322° has properties similar to those of the two known azabenz[*a*]anthraquinones but is not identical with either of them, and since the nitrogen was originally in the β -position of the anthraquinone nucleus, Bally and Scholl⁶ proposed the structure VI, 1-azanaphthacene-6,11-dione.

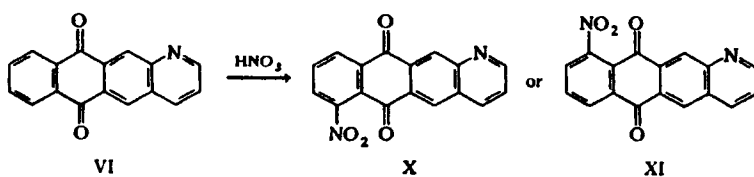


Although 2-aminoanthraquinone is not a suitable starting material for the preparation of 1-azanaphthacenediones through the Skraup reaction, certain 2-aminoanthraquinones substituted in the 1-position give 12-substituted-1-azanaphthacenediones. 12-Chloro-1-azanaphthacene-6,11-dione (IX) is described in the patent literature,⁷ along with a number of its derivatives. The best preparation of the halogen-free compound (VI) is through a dehalogenation of the 12-chloro compound.

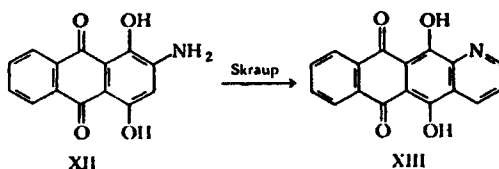


The nitration of 1-azanaphthacenedione (VI) has been reported,⁸ but the position of the entering nitro group was not established. It seems probable that the product is either 7-nitro- (X) or 10-nitro-1-azanaphthacene-6,11-dione (XI). No reference to the reduction of the nitro compound or to its reactivity toward other reagents has as yet appeared in the literature.

2-Aminoquinizarin (XII) prepared in an investigation of the ethylenic

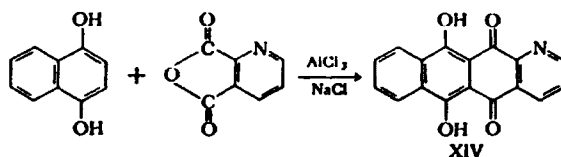


character of the 2,3 bond in quinizarin undergoes the Skraup reaction to give a linear isomer of Alizarin Blue. Marschalk⁹ noted that the product, 5,12-dihydroxy-1-azanaphthacene-6,11-dione (XIII), condenses with aromatic amines at one or both of the hydroxyl groups in the presence of boric acid to form a brown dye base. On sulfonation of the latter, the acids which are formed can be used to color wool brown. In Table 1, on page 8, XIII is compared with two isomeric azanaphthacenediones.



The only other method of preparation of a substituted 1-azanaphthacenedione recorded in the literature is analogous to the phthalic anhydride synthesis of anthraquinone derivatives.

Raudnitz¹⁰ was successful in condensing quinolinic anhydride with 1,4-dihydroxynaphthalene in an aluminum chloride-sodium chloride melt, obtaining 6,11-dihydroxy-1-azanaphthacene-5,12-dione (XIV) which is isomeric with Alizarin Blue.

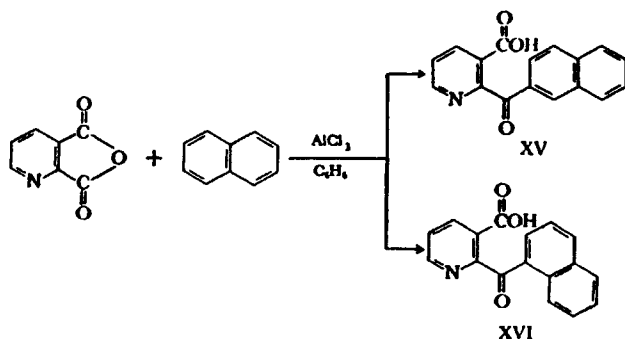


A summary of absorption data relating to three isomeric linear dihydroxyazanaphthacenediones is given in Table 1, Section B.

Jephcott¹¹ prepared the intermediate naphthoylpicolinic acids, (XV) and (XVI), by treating naphthalene with quinolinic anhydride in the presence of benzene and aluminum chloride, but the ring closure of XV to 1-azanaphthacene-5,12-dione was not accomplished.

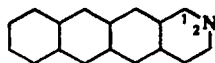
In view of the fact that two different methods of synthesis are avail-

able for the preparation of 1-azanaphthacenediones, it is surprising that so few compounds of this type have been investigated. None of the examples reported has been very fully characterized as to reactivity, basicity, or other properties, nor has the structure of all the reported

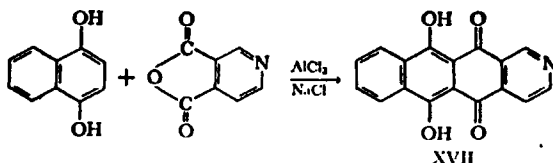


derivatives been definitely established. Research into the properties of the 1-azanaphthacenes (at present unknown), which presumably would result on reduction of the diketo derivatives, might be of interest. These heterocyclic diketones vary in color from light yellow through red to brown, and many of them give vats dyeing cotton yellow to brown.

B. 2-Azanaphthacene, Naphth[2,3-*g*]isoquinoline, 6,7-Benzo- β -anthrapyridine. R.I. 2739



The only recorded synthesis of a 2-azanaphthacene derivative is Raudnitz's¹² preparation of 6,11-dihydroxy-2-azanaphthacene-5,12-dione (XVII) by the condensation of cinchomeronic anhydride (the anhydride



of pyridine-3,4-dicarboxylic acid) with 1,4-dihydroxynaphthalene. The product may be purified through its water-soluble sodium salt from which red-brown needles of the base, melting at 343° after sublimation *in vacuo*, are obtained.

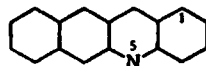
Raudnitz^{10,12} prepared a number of heterocyclic compounds for spectral examination to determine the influence of the pyridine ring in such substances as 1- and 2-azaanthraquinones and 1- and 2-azanaph-

TABLE 1

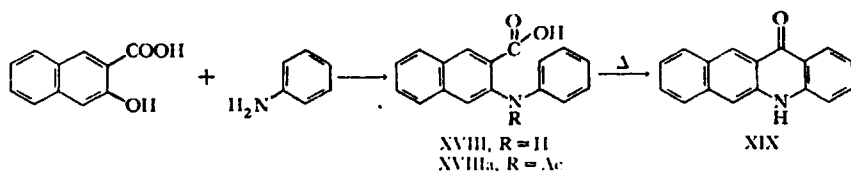
Solvent	Color	Absorption at λ maxima
6,11-Dihydroxy-1-azanaphthacene-5,12-dione ¹⁰		
KOH	Red-violet	586.5, 544
H ₂ SO ₄	Yellow-red	Partial absorption (590) at beginning of yellow
H ₂ SO ₄ -H ₃ BO ₃	Orange	541.5, 503, 467
5,12-Dihydroxy-1-azanaphthacene-6,11-dione ⁹		
NaOH	Violet	
H ₂ SO ₄	Orange	
H ₂ SO ₄ -H ₃ BO ₃	Red-orange with strong yellow-orange fluorescence	
6,11-Dihydroxy-2-azanaphthacene-5,12-dione ¹²		
KOH	Blue-violet	600.5, 555.5
H ₂ SO ₄	Wine-red	540, 500 (indistinct)
H ₂ SO ₄ -H ₃ BO ₃	Orange	552, 513, 576

thacene-5,12-diones. The spectrographic data for both 6,11-dihydroxy-2-azanaphthacene-5,12-dione and two 1-aza isomers are given in Table 1.

C. 5-Azanaphthacene, Benz[*b*]acridine, 2,3-Benzacridine, *lin*-Phenonaphthacridine.
R.I. 2731

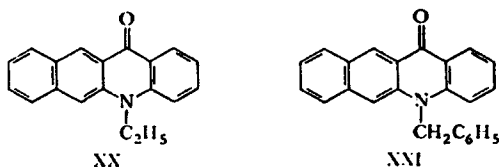


Although a number of investigators have reported the preparation of different 5-azanaphthacenes, the field as a whole has not been examined systematically nor have all the different compounds described been fully characterized. In 1892, Schöpf¹³ attempted the ring closure of 2-anilino-3-naphthoic acid (XVIII) to give 12-keto-5*H*,5-azanaphthacene (XIX). The reaction was not successful using sulfuric acid as the dehydrating agent, but in a later article¹⁴ he described the preparation of the ketone by substituting hydrochloric acid and using a sealed tube. Schöpf discovered that cyclization could also be effected by heating the intermediate acid (XVIII) (or aniline and 2-hydroxy-3-naphthoic acid without isolation of the intermediate) with zinc chloride, or more simply by merely heating it to 250°.

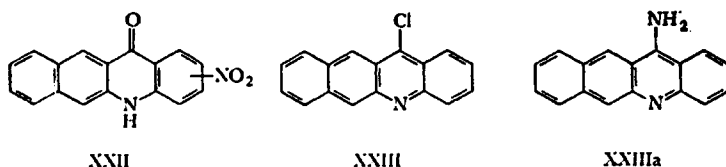


3-Anilino-2-naphthoic acid (XVIII) gave a 97% yield of 12-chloro-5-azanaphthacene (XXIII), which was easily hydrolyzable to 12-keto-5*H*,5-azanaphthacene (XIX) by an hour's refluxing with 3*N* hydrochloric acid.^{14a}

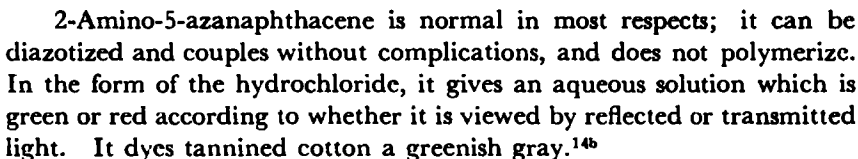
The golden-colored product (XIX), m.p. 304–305°, is difficultly soluble in most solvents, forming yellow solutions having a green fluorescence. Although the color of solutions of the base in acids and alcoholic alkalis indicates that salt formation does occur, none of the salts is sufficiently stable for isolation. Schöpf¹⁴ stated that 12-keto-5*H*,5-azanaphthacene is not very reactive, and cited as evidence its failure to form an acetyl or nitroso compound. No acetyl derivative can be obtained under vigorous conditions of acetylation, and XIX rather than *N*-acetyl-(XIX) is the product of ring closure of *N*-acetyl-2-anilino-3-naphthoic acid (XVIIIa). 5-Ethyl- (XX) and 5-benzyl-12-keto-5-azanaphthacene (XXI) may be prepared from XIX by treatment with ethyl and benzyl iodides.



A difficultly soluble red *o*-nitro-12-keto-5*H*,5-azanaphthacene (XXII) instead of the expected *N*-nitroso compound results from the treatment of the base with nitrous acid. Chlorination of XIX using phosphoryl chloride and phosphorus pentachloride¹⁴ gives 12-chloro-5-azanaphthacene (XXIII); long warming of the orange product in alcohol reconverts it to 12-keto-5*H*,5-azanaphthacene (XIX).



The English authors ¹⁴ also prepared 2-amino-5-azanaphthacene (XXIIIc) by sodium amalgam reduction of 2-nitro-12-keto-5*H*,5-azanaphthacene (XXIIIb); the latter was obtained by a phosphoryl chloride cyclization of 2-(4'-nitroanilino)-3-naphthoic acid with isolation of the intermediate chloro compound.

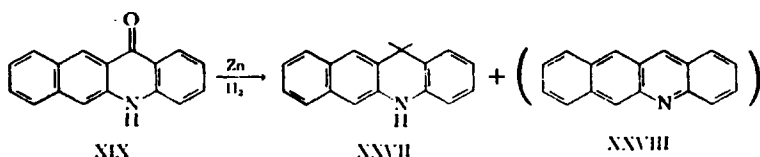




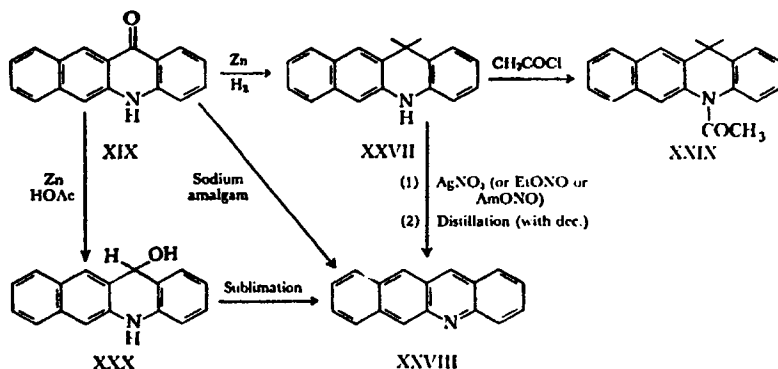
XXIV
 XXV, R = H
 XXVa, R = CH₃
 XXVI

from treatment of the 2-hydroxy compound with sodium methoxide, while the acetate (XXVI) resulted from treatment with acetic anhydride.

Schöpf¹⁴ first reported that the material melting at 289°, which he obtained from the distillation of 12-keto-5*H*,5-azanaphthacene (XIX) over zinc dust in a stream of hydrogen, was 5-azanaphthacene (XXVIII). He published a correction the following year, stating that although some XXVIII was obtained in this distillation, the principal product (which melts at 289°) was 5,12-dihydro-5-azanaphthacene (XXVII).¹⁷



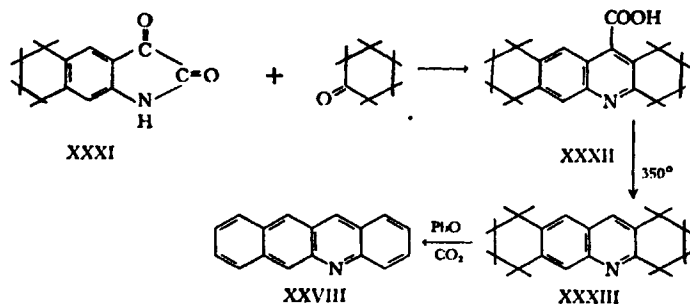
This dihydro base (XXVII) forms an *N*-acetyl derivative (XXIX), is oxidized to a base containing two fewer hydrogen atoms than XXVII, and is a weak base—as would be expected from a comparison with dihydroacridine. The aromatic base (XXVIII), on the other hand, is more strongly basic in its properties and forms crystalline salts with acids. 5-Azanaphthacene (XXVIII) is obtained from 12-keto-5*H*,5-azanaphthacene (XIX) directly on treatment of this compound with sodium amalgam, or from XXVII by the oxidizing action of silver nitrate. However, the main product of the reaction of XIX with zinc dust and acetic acid is 12-hydroxy-5,12-dihydro-5-azanaphthacene (XXX), which is apparently a very weak base, since no salts are reported. The various interrelationships among these 5-azanaphthacenes are summarized in the following flowsheet:



Since the attempted preparation of an *N*-acetyl derivative of XIX had been unsuccessful, both by direct acylation and by ring closure of the acetylated intermediate (XVIIIa), Schöpf¹⁷ tried to oxidize 5-acetyl-5,12-dihydro-5-azanaphthacene (XXIX) to 5-acetyl-12-keto-5-azanaphthacene. However, the dihydro compound (XXIX) was not affected by silver nitrate, and on chromic acid oxidation gave the free keto base (XIX), indicating that the acetyl derivative is too unstable to be obtained.

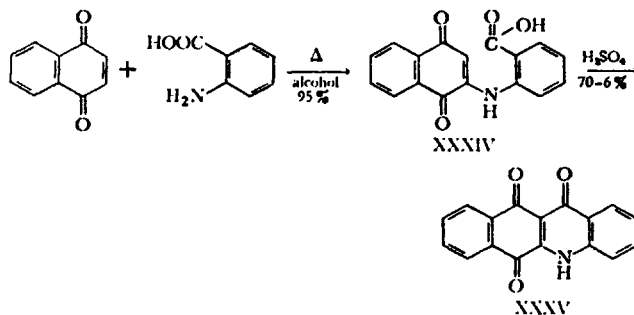
Whereas Schöpf^{14,17} and Wilke^{15,16} employed ring closure of the acid obtained from 2-hydroxy-3-naphthoic acid and aromatic amines for the preparation of 5-azanaphthacenes, later workers in the field have described several other syntheses. It is unfortunate that in most cases the products, expected to be 5-azanaphthacenes, which should be identical with those of Schöpf, are very incompletely characterized.

Von Braun¹⁸ obtained 5-azanaphthacene (XXVIII) from 2,3-diketo-5,6,7,8-tetrahydro-1-benz[*f*]indole (XXXI) by condensation with cyclohexanone, followed by decarboxylation of 1,2,3,4,7,8,9,10-octahydro-5-azanaphthacene-12-carboxylic acid (XXXII), and dehydrogenation of 1,2,3,4,7,8,9,10-octahydro-5-azanaphthacene (XXXIII). The melting point of the dehydrogenated base (XXVIII) agreed with that reported by Schöpf, and both investigators described a platinum double salt.



Leśnianski¹⁹ prepared several 5-azanaphthacenes in the course of research designed to discover whether acridonelike quinones are vat dyes. His method of synthesis, rather than that of Schöpf or von Braun, is the one which has been used most extensively for preparing 5-azanaphthacenes. The reaction involves the condensation of 1,4-naphthoquinones with anthranilic acids to form intermediate acids (XXXIV); on dehydration, the 4-ring heterocyclic trione (XXXV) is formed.

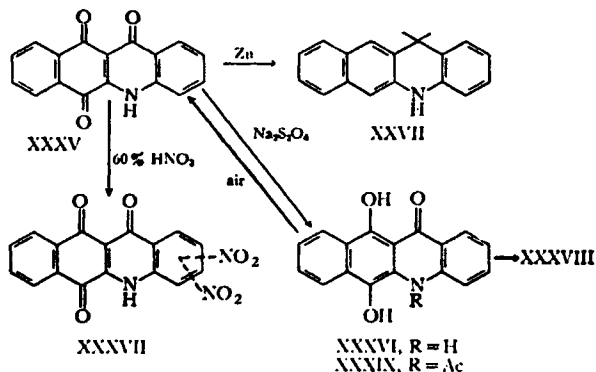
Although Hauschka²⁰ had reported this same preparation of 5-azanaphthacene-6,11,12-trione (XXXV) four years earlier, Leśniasński's failure to refer to it may be explained by the delay in publication of his manuscript. The melting points of the intermediate acids are reasonably close, but Hauschka described the acid melting at 265° as orange, while Leśniasński reported it to be red, melting at 271°. In any event, the



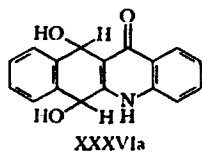
compound obtained by Hauschka on sulfuric acid dehydration melted at about 350° and was indifferent to acids and alkalis, whereas Leśniasński's trione melted at 384° and formed crystalline salts with both acids and alkalis. Since Hauschka reported no other details of properties or reactivity, this discussion is concerned with the base described by Leśniasński. The orange base is difficultly soluble and its solutions do not show fluorescence. In view of the weak basicity of Schöpf's 12-keto-5H,5-azanaphthacene (XIX) and of acridones in general, it is surprising that the trione (XXXV) should form a light yellow crystalline dinitrate and a crystalline yellow sulfate and hydrochloride. It also forms a crystalline hydrated potassium salt, stable to cold but not hot alkalis, but is unreactive toward picric acid, bisulfite, sulfur dioxide, phenylhydrazine, and *o*-phenylenediamine.

According to Leśniasński, zinc dust distillation of 5-azanaphthacene-6,11,12-trione gives a dihydro compound (XXVII) said to be identical with Schöpf's. Treatment of the trione with sodium hydrosulfite ($\text{Na}_2\text{S}_2\text{O}_4 \cdot 2\text{H}_2\text{O}$) yields 6,11-dihydroxy-12-keto-5-azanaphthacene [the dihydroquinone (XXXVI)] which is reconverted to XXXV on standing in the air. The leuco compound (XXXVI) dissolves in alkali with a blue color, but on standing, the alkali salt of XXXV separates. Although Leśniasński gives the empirical formula $\text{C}_{17}\text{H}_{11}\text{NO}_3$ for the compound obtained in this reduction, it is apparent from the analytical data that $\text{C}_{17}\text{H}_{13}\text{NO}_3$ (XXXVIa) is not ruled out. Leśniasński did not comment on this, but it seems that XXXVIa is perhaps a more likely structure for

the reduction product. The leuco base forms an orange acetyl derivative (XXXIX) which is soluble in cold alkali and does not change color; on warming, the blue color of the alkali salt of the reduction compound appears.

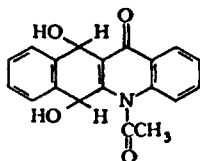


The difficultly soluble yellow dinitro compound obtained on direct nitration of the trione has lost the weakly basic properties of the unsubstituted compound, so that no nitrate is formed. In alkaline hydro-sulfite, the color changes from red to violet and finally to blue-green; a red-violet precipitate, probably of the diamino compound, separates on standing in the air. Both the diamine and the trione (XXXV) show vat characteristics, and the latter gives a blue vat which dyes cotton orange-yellow.



XXXVIa

	C ₁₇ H ₁₁ NO ₂	Found	C ₁₇ H ₁₁ NO ₂
C	73.64	73.22	73.10
H	4.00	4.21	4.69

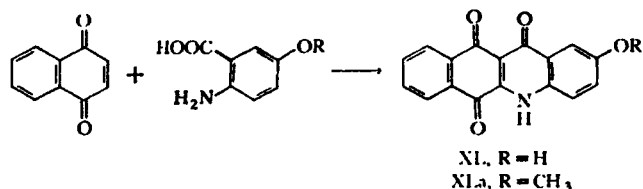


XXXIXa

	C ₁₈ H ₁₃ NO ₄	Found	C ₁₈ H ₁₃ NO ₄
C	71.47	71.08, 71.21	71.02
H	4.10	4.20, 4.27	4.71

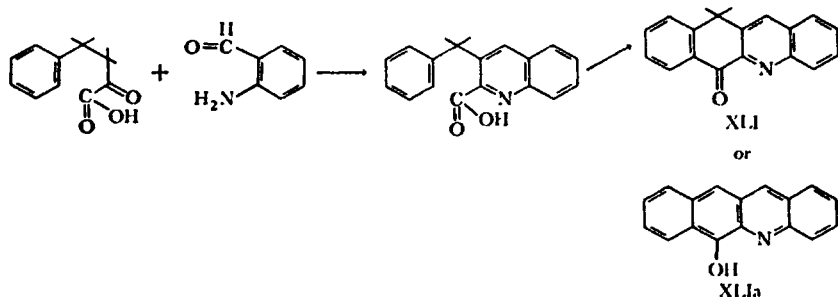
Yakushevskii²¹ prepared 5-azanaphthacene-6,11,12-trione (XXXV) by the same method, but (according to the abstract) did not characterize the product very completely. It forms colored precipitates with metallic salts and dyes cotton orange-yellow from sulfurous acid, and wool and silk

orange-yellow from alkaline hyposulfite. Lewicka,²² too, used the same synthesis to prepare 2-hydroxy- (XL) and 2-methoxy-5*H*,5-azanaphthacene-6,11,12-trione (XL*a*) from 1,4-naphthoquinone and 2-amino-5-



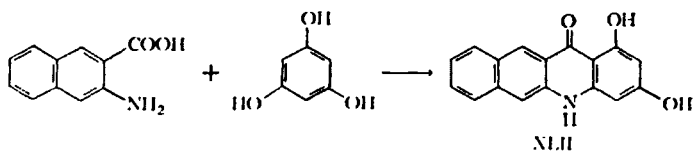
methoxybenzoic acid. No details of the work are included in the abstract beyond the statement that both compounds dye cotton and wool red.

Borsche and Noll²³ prepared a 5-azanaphthacene in the course of an investigation on forming 5- and 6-membered rings by intramolecular ring closure. Aluminum chloride cyclization of the acid chloride of 3-benzylquinaldinic acid (obtained from benzylpyruvic acid and *o*-aminobenzaldehyde) gives 6-keto-5-azanaphthacene (XLI) or its enol

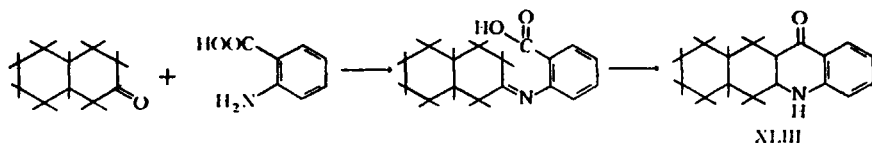


tautomer (XLI*a*). The product is obtained in poor yield as a stable aluminum salt, (C₁₇H₁₀NO)₂Al, which melts above 360°, and dissolves in both concentrated sulfuric acid and alcoholic sodium hydroxide, with a blue color. On standing in the air, the alkaline solution slowly turns brown. A similar stability of metal complexes formed from 8-hydroxyquinoline, of which XLI may be considered the dibenzolog, is noted.

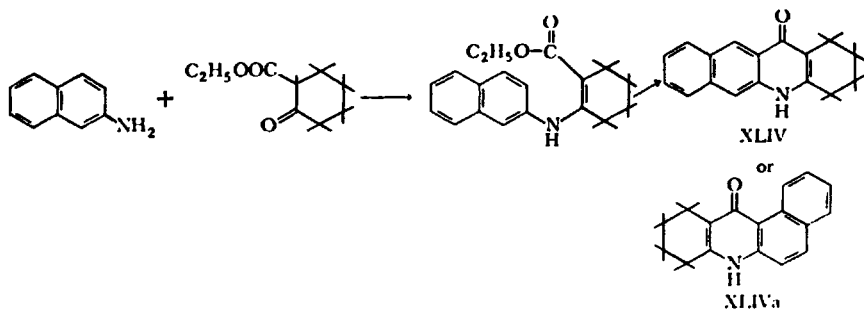
In a patent²⁴ there is described the synthesis of 1,3-dihydroxy-12-keto-5*H*,5-azanaphthacene (XLII) from the condensation of phloroglucinol with 2-amino-3-naphthoic acid. It is an orange-yellow solid, and is patented as a dye intermediate, but not described further. During an investigation relating to decalins, Bukhsh and Desai²⁵ treated *trans*-β-



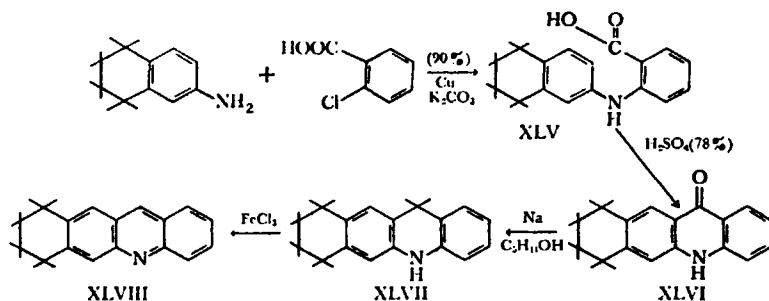
decalone with anthranilic acid. The resulting acid gives 12-keto-6,6a,7,8,9,10,10a,11-octahydro-5H,5-azanaphthalene (XLI.II) on de-



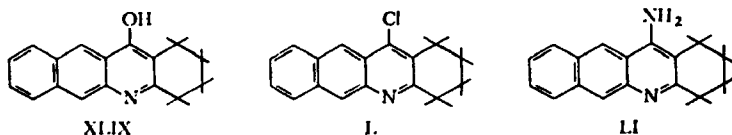
hydration; it does not melt below 350°. Hughes and Lions²⁶ cyclized the ethyl ester obtained from condensing ethyl cyclohexanone-2-carboxylate with β -naphthylamine; the pale yellow product melted above 300° and gave fair analytical results for $C_{17}H_{15}NO$. No attempt was made to determine whether the product is 12-keto-1,2,3,4-tetrahydro-5H,5-azanaphthalene (XLI.IV) or 12-keto-8,9,10,11-tetrahydro-7H,7-azabenz-[a]anthracene (XLI.IVa).



In the synthesis of new compounds to be tested for bactericidal activity, Kränzlein²⁷ prepared three 5-azanaphthalenes which are not reported elsewhere. Condensation of 6-amino-1,2,3,4-tetrahydronaphthalene and *o*-chlorobenzoic acid gives "3',4'-cyclotetramethylenediphenylamine-2-carboxylic acid" (XLV) from which 12-keto-7,8,9,10-tetrahydro-5H,5-azanaphthalene (XLVI) is obtained in good yield on sulfuric acid dehydration. Sodium and amyl alcohol reduction of the yellow ketone (XLVI) gives white flakes of the hexahydro compound (XLVII), and ferric chloride oxidation of 5,7,8,9,10,12-hexahydro-5-azanaphthalene (XLVII) gives 7,8,9,10-tetrahydro-5-azanaphthalene (XLVIII).



When 3-amino-2-naphthoic acid and cyclohexanone were heated together under certain specified conditions^{14a} yellow 12-hydroxy-1,2,3,4-tetrahydro-5-azanaphthacene (XLIX; enol of XLIV) resulted. Upon treatment with phosphoryl chloride, the 12-chloro analog (L) was obtained, and the latter on amination gave the 12-amino derivative (LI). As previously mentioned, this amine underwent photopolymerization.



EXPLANATION OF THE TABLES

Although Tables 2-4 are incomplete, an attempt has been made to include all compounds reported in the literature prior to January, 1947, which belong to the six basic heterocyclic ring systems discussed in this chapter. In view of the incompleteness of information in the patent literature, not all the reaction products claimed have been listed. References to most of the pertinent patents have been given, however, and a few articles published before July, 1947, have been reviewed.

Compounds whose configuration has not been established conclusively are listed in more than one portion of the tables, and question marks indicate cases where there is still some doubt as to the structure of the product obtained. The Roman numerals in the first column refer to the structural formulas given in the appropriate sections of the text.

SYMBOLS USED

Red S, green Fl, the compound gives a red solution in concentrated sulfuric acid and this solution shows green fluorescence.

S, sulfuric acid.

SB, a solution in concentrated sulfuric acid to which boric acid has been added.

O, organic solvents.

·MeI, methiodide.

·HCl, hydrochloride, etc.

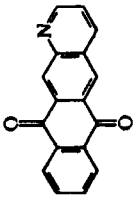
·P, picrate.

OH⁻ and H⁺, alkaline and acid solutions.

Ac, acetyl derivative.

Other abbreviations conform to the customary *Chemical Abstracts* usage.

TABLE 2. Monoazanaphthacenes (see page 17 for a description of symbols used).

Formula	Compound	Ref.	Appearance	Properties
 1-Azanaphthacene-6,11-dione:				
VI	Unsubstituted	1,6,7	Yellow needles	m. 322°
IX	12-Chloro-	7	Gray powder	—
	x-Bromo-	7	Yellow needles	Yellow-green S; yellow-green vat
	x-Bromo-12-chloro-	7	Light yellow needles	Yellow-green S; yellow-green vat
	12-Chloro-x-iodo-	7	—	—
X or XI	7- (or 10-) Nitro-	8	Yellow-white powder	m. 305°; strong yellow S, no Fl
	12-Amino-	27a,27c	Brown needles	m. 283-5°
	7- (or 10-) Amino-	27d	—	—
	12-Hydrazino-	27a,27c	Blue-green needles	On loss of water, undergoes ring closure to form a pyrazolone
	12-Methylamino-	27a,27c	Orange-red needles	Orange S; olive-green vat, dyes rayon raspberry tones
	7- (or 10-) Benzoylamino-	27d	Yellow	Yellow-red S; gray-green vat, dyes cotton clear yellow
	12-(1'-[and 2']Antraquinone-carbonylamino)-	27d	—	—
	12-(1'-Amino-2'-antraquinonecarbonylamino)-	27d	—	—
	7- (or 10-) 1'-Acetylamino-6'-antraquinonyl-	27b	—	—
XIII	5,12-Dihydroxy-	9	Orange needles	Brownish-olive S; vat dyes cotton violet-brown
XVI	6,11-Dihydroxy-5,12-dione	10	Red-brown needles	Orange S; red-orange, SB with strong yellow-orange Fl; violet, OH ⁻ ; yellow, Ac ⁻ ; see Table 1, this chapter
				m. 365°; dark violet Na salt; see Table 1, this chapter

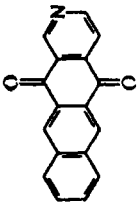
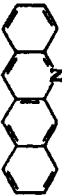
2-Azanaphthacene-5,12-diones:				
				
XVII	6,11-Dihydroxy-	12	Red-brown needles	m. 343°; Na salt; see Table 1, this chapter
5-Azanaphthacenes:				
				
XXVIII	Unsubstituted	17,18	Orange	m. 225-226°; .HCl, .HNO ₃ , .EtI; salts, red in alcohol with greenish-blue fl; salts, deep violet S; green Fl O
XXVII	5,12-Dihydro-	14,17,19	Fine white needles	m. 287°; orange-brown S; diff. sol. O, colorless with violet F; ins. dil. HCl
XLVIII	7,8,9,10-Tetrahydro-	27	Yellow flakes	m. 117°; green Fl S
XLVII	5,7,8,9,10,12-Hexahydro-	27	White flakes	m. 169-170°
XXXIII	1,2,3,4,7,8,9,10-Octahydro-	18	Colorless crystals	m. 146°; b. 380°/15 mm.; .P m. 208°; gold .MeI m. 231°
XXIII	12-Chloro-	14	Reddish-orange needles	m. 165°; green P; violet double salts
XXIIIa	12-Amino-	14a	Scarlet	m. 231-232°; orange Fl mono-HCl
	12-Acetyl-	14a	Orange	m. 230° dec.; green Fl
XLIIa	6-Hydroxy-	23	—	m. >360°; blue S and OH ⁻ ; Al salt
XIX	12-Keto-5H-	14,17	Gold crystals	m. 304-305°; diff. sol. O, green Fl; dark red S; weak base
XX	5-Ethyl-12-keto-	14	Yellow needles	m. 174-175°
XXI	5-Benzyl-12-keto-5H-	14	Yellow needles	m. 188-189°
XXII	12-Keto-2-nitro-5H-	14	Scarlet needles	m. 304°; diff. sol. O
XXIV	2-Amino-12-keto-5H-	15	Red	m. >380°; very diff. sol. O
XXV	2-Hydroxy-12-keto-5H-	16	Dark red	m. 275°; diff. sol. with green Fl; red-violet OH ⁻
XXVa	12-Keto-2-methoxy-5H-	16	—	m. 175°; ins. OH ⁻
XXVI	2-Acetoxy-12-keto-5H-	16	Yellow	m. 324°; diff. sol. O, green Fl; red S
XLII	1,3-Dihydroxy-12-keto-5H-	24	Orange-yellow	m. 232°
XXXVI	6,11-Dihydroxy-12-keto-5H-	19	Red-violet	m. 317°; sol. O, oxidizes in air; blue OH ⁻

Table continued

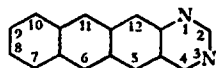
TABLE 2. Monoazanaphthacenes (*Continued*)

Formula	Compound	Ref.	Appearance	Properties
5-Azanaphthacenes (<i>continued</i>)				
XXXIX	5-Acetyl-6,11-dihydroxy-12-keto-	19	Orange needles	m. 292°; ins. OH ⁻ cold, sol. blue hot
XXV	6,11,12-Triketo-5H-	19-21	Orange needles	m. 384°; yellow .2HNO ⁺ ; red K salt; no FI O; blue vat dyes cotton orange-yellow
XXXXVII	6,11,12-Triketo-x,x-dinitro-5H-	19	Yellow	m. 299°; red OH ⁻ ; violet vat
XL	2-Methoxy-6,11,12-triketo-5H-	22	—	Dyes cotton and wool red
XLIV	12-Hydroxy-1,2,3,4-tetrahydro-?	26	Pale yellow plates	m. >300°
XLIX	12-Hydroxy-1,2,3,4-tetrahydro-	14a	Yellow	m. 315°
L	12-Chloro-1,2,3,4-tetrahydro-	14a	Cream	m. 141-142°
LI	12-Amino-1,2,3,4-tetrahydro-	14a	Orange-yellow	m. 236-238°; blue FI
XXX	12-Hydroxy-5,12-dihydro-	17	White crystals	m. 320-325°; violet FI O; yellow-brown S; ins. OH ⁻
XXIX	5-Acetyl-5,12-dihydro-	17	Colorless prisms	m. 181°; very sol. O
XLVI	12-Keto-7,8,9,10-tetrahydro-5H-	27	Long yellow needles	m. 309°
XLIII	12-Keto-6,6a,7,8,9,10,10a,11-octahydro-5H-	25	—	m. >350°
XXXII	12-Carboxy-1,2,3,4,7,8,9,10-octahydro-	18	Yellow crystals	m. >300°
	1,12-Dichloro-	27c	Pale orange	m. 231-232°
	2,12-Dichloro-	27c	Orange	m. 239-240°
	3,12-Dichloro-	27c	Red-orange	m. 180.5°
	4,12-Dichloro-	27c	Orange-red	m. 203°
	1,5,7-Trichloro-	27c	Dark red	m. 265-266°
	1,5,8-Trichloro-	27c	Long red rods	m. 262-263°
	x,x,x-Trichloro-	27c	Orange-pink	m. 238°
	Pentachloro-	27c	Pale pink	m. 183°
	6-Bromo-3-chloro-	27c	Pale pink	m. 205°
	6-Bromo-3,12-dichloro-	27c	Pale yellow	m. 212-213°
	1-Chloro-12-keto-5H-	27c	Pale pink	m. 241-242°
	2-Chloro-12-keto-5H-	27c	Yellow orange	m. >360°; green FI in alc.
	3-Chloro-12-keto-5H-	27c	Yellow orange	m. >360°; green FI in alc.
	4-Chloro-12-keto-5H-	27c	Orange	m. 360°
	3,6-Dichloro-12-keto-5H-	27c	Yellow	m. 271-272°
	6-Bromo-3-chloro-12-keto-5H-	27c	Yellow	m. 349-350°; green FI in alc.
		27c	Buff	m. >360°

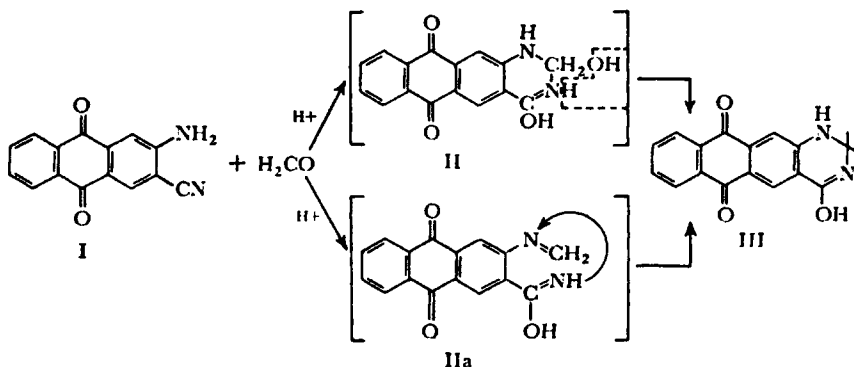
2. Diazanaphthacenes

Examples of only six of the twenty-one possible diazanaphthacenes (in which the nitrogens are not common to two rings) have been reported; in the case of the 1,11-diaza isomer, the probability is great that an angular four-ring system was obtained rather than the linear. Although the 5,6- and 5,12-diaza compounds have been more fully investigated than any of the others, the information available on these examples is surprisingly limited, both in scope and completeness. (The diazanaphthacenes reported are listed in Table 3 on pages 40-42.)

A. 1,3-Diazanaphthacene, Naphtho[2,3-*g*]quinazoline. R.I. 2663



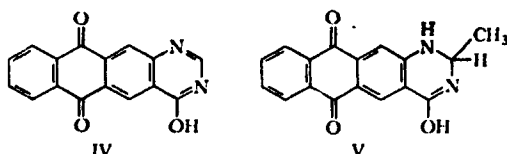
The only syntheses of the 1,3-diazanaphthacene ring system appear to be those described in two related I.G. Farbenindustrie patents.^{28,29} The more general of these²⁸ claims the formation of the heterocyclic ring by condensation of aldehydes with *o*-aminocyano or *o*-aminocarboxamido compounds in the presence of acids. Two possible interpretations of the reaction mechanism involved in the formation of 4-hydroxy-1,2-dihydro-1,3-diazanaphthacene-6,11-dione (III) are indicated by the two intermediates, (II) and (IIa). If the claim of this patent that *o*-



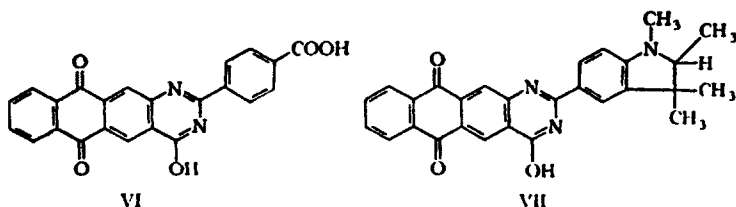
aminocarboxamido compounds also undergo the reaction is justified, the assumption that partial hydrolysis of the nitrile occurs seems reasonable.

A variety of agents, among them thionyl chloride, peroxide, and

permanganate, are said²⁸ to be suitable for dehydrogenating the 1,2-dihydro-4-hydroxypyrimidine derivatives or the 4-chloro-1,2-dihydro compounds prepared from them by means of phosphorus pentachloride. 4-Hydroxy-1,2-dihydro-1,3-diazanaphthacene-6,11-dione (III), a brilliant red base soluble in concentrated sulfuric acid with a red color, yellow-red in caustic, and giving a brilliant green vat, is obtained in quantitative yield. Dehydrogenation gives pale yellow crystals of 4-hydroxy-1,3-diazanaphthacene-6,11-dione (IV), which dye cotton yellow from a green vat. Diethylacetal behaves like acetaldehyde to give a good yield of

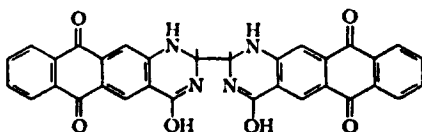


4-hydroxy-2-methyl-1,2-dihydro-1,3-diazanaphthacene-6,11-dione (V), which forms a green vat and dyes acetate-silk yellow-orange. Crotonaldehyde and oleylaldehyde are said to react in the same way, giving dyes with properties similar to those of V, and *p*-carboxybenzaldehyde reportedly gives directly the 4-hydroxy-2-(4'-carboxyphenyl)-1,3-diazanaphthacene-6,11-dione (VI) (a yellow vat dye for cotton).



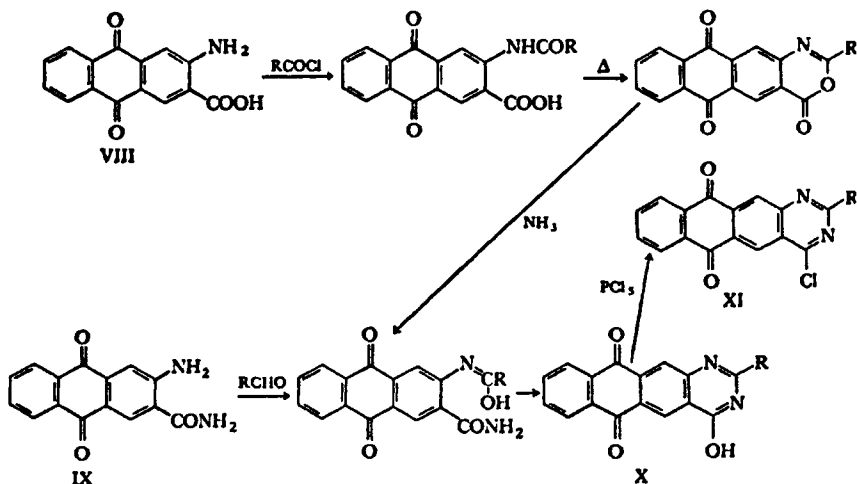
Although the patent does not explicitly give structures for all the compounds claimed, it is to be expected that aldehydes, RCHO, will give 2-R-4-hydroxy-1,2-dihydro-1,3-diazanaphthacene-6,11-diones. Presumably 2-furyl, 2-[2'-(1'-aminoanthraquinonyl)] derivatives and VII are obtained by the reactions described between 2-amino-3-cyanoanthraquinone (I) and the corresponding aldehydes. Dyes of varying shades of yellow are said to be prepared in good yield from such dialdehydes as glyoxal, and phthalic, terephthalic, and isophthalic dialdehydes. No structures are given for any of the products nor is there any indication of the determination of molecular weight or other physical

constants, but the dyes from glyoxal, for instance, might be represented by the following structure:

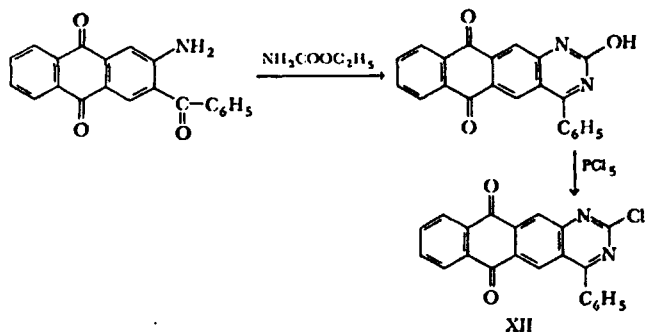


Although this reaction between 2-amino-3-cyanoanthraquinones and various aldehydes is reported to give excellent yields of 1,3-diazanaphthacene derivatives which are easily obtained in a pure state or are readily purified, no description of such synthesis other than the one in the patent²⁸ has appeared.

The other patent²⁹ describes the preparation of 4-hydroxy- (X) or 4-chloro-2-R-1,3-diazanaphthacene-6,11-diones (XI) from 2-amino-3-carboxy- (VIII) or 2-amino-3-carboxamidoanthraquinone (IX), but does not include any mention of intermediate dihydro compounds.

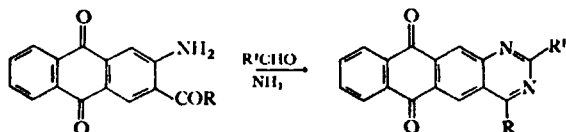


This patent reports 1,3-diazanaphthacenediones, where R is phenyl, tolyl, 2,5-dichlorophenyl, anisyl, and $-\text{C}_6\text{H}_4\text{COCl}$, evidently prepared as described above, and a 2-chloro-4-phenyl-1,3-diazanaphthacene-6,11-dione (XII), prepared by the reactions shown. A number of vat dyes ranging in color from yellow to green may be obtained by treating these halogen-containing 1,3-diazanaphthacenes with various amino com-



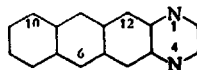
pounds, among them 1- and 2-aminoanthraquinone, and 1-amino-5-carboxamidoanthraquinone.

In a PB report^{29a} a slight variation in the two previous procedures consists in using an amino ketone in nitrobenzene solution, and leading in ammonia at 100–140°. While the products are mostly red or orange and form vats, they have no affinity for the fiber.

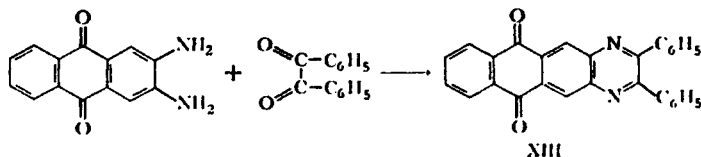


Since neither of the patents includes physical properties for many of the compounds described, Table 3 (on pages 40–42) lists only a few of the substituted 1,3-diazanaphthacenediones claimed in the patents.

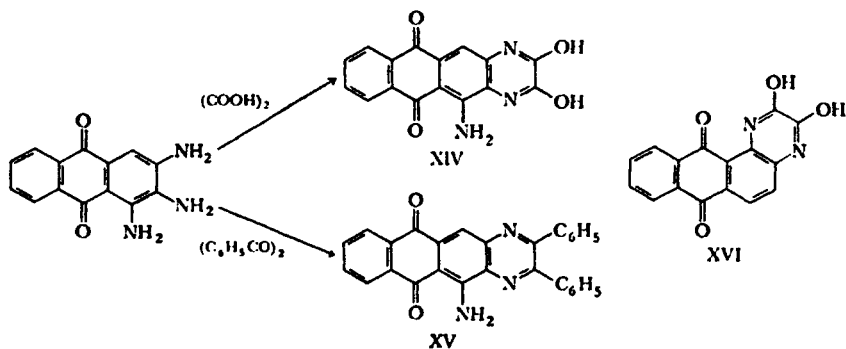
B. 1,4-Diazanaphthacene, Naphtho[2,3-*g*]-quinoxaline, Anthraceno-2',3',2,3-pyrazine, 2,3-Pyrazinoanthracene, 2,3-Anthraquinoxaline. R.I. 2664



All of the members of the 1,4-diazanaphthacene series which have been reported have been synthesized by the usual quinoxaline synthesis from a molecule containing *ortho*-amino groups and one with two adjacent carbonyl groups. Scholl and Kačer³⁰ refluxed 2,3-diaminoanthraquinone with benzil in acetic acid, and obtained a good yield of 2,3-diphenyl-1,4-diazanaphthacene-6,11-dione (XIII). By analogous reactions in the course of investigations into the chemistry of indanthrene these workers prepared a number of polycyclic azines containing more than four fused rings.



Scholl, Eberle, and Tritsch³¹ reported the preparation of 5-amino-2,3-dihydroxy-1,4-diazanaphthacene-6,11-dione (XIV) from 1,2,3-triaminoanthraquinone and anhydrous oxalic acid. On heating 1,2,3-triaminoanthraquinone with benzil, they obtained 5-amino-2,3-diphenyl-1,4-diazanaphthacene-6,11-dione (XV). In view of the fact that Scholl and Edlbacher³² described the synthesis of a four-ring angular quinoxaline (XVI) by the condensation of 1,2-diaminoanthraquinone with oxalic acid (see page 93, Ch. II), it seems surprising that the triamine



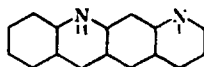
gives a product having a linear arrangement. Since the unaminated 2,3-diphenyl-1,4-diazanaphthacene-6,11-dione (XIII) fails to undergo vat formation while the azine (XVI) from 1,2-diaminoanthraquinone readily gives a blue vat characteristic of indanthrenes, Scholl, Eberle, and Tritsch³¹ cited the failure of their azines (XIV) and (XV) to exhibit this behavior as evidence of the linear arrangement of the rings. Neither 5-amino-2,3-dihydroxy- (XIV) nor 5-amino-2,3-diphenyl-1,4-diazanaphthacene-6,11-dione (XV) dissolves in alkaline hydrosulfite even on warming.

The dihydroxydiazanaphthacene (XIV) is a high-melting substance which sublimes (with simultaneous decomposition) as dark brown needles. Because it is insoluble in low-boiling solvents and difficultly soluble in nitrobenzene and quinoline, it is best purified by dissolving in alkali and reprecipitation with acid. A red sodium salt is formed on cooling a very dilute solution of the dihydroxydiazanaphthacene in

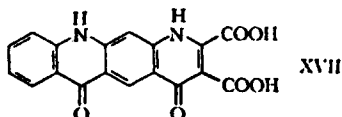
dilute sodium hydroxide. Although XIV dissolves in sulfuric acid to give a yellow solution, the free base is recovered on dilution with water.

The aminodiphenyl compound is more soluble than the dihydroxy analog, and may be recrystallized from methanol. It is difficultly soluble in ether, forming a yellow solution with green fluorescence. None of these three diazanaphthalenes has been very fully characterized, nor has any one been investigated with respect to its reactivity.

**C. 1,11-Diazanaphthalene, Quino[3,2-*g*]quino-
line**

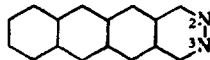


Only one synthesis of a compound which may contain the 1,11-diazanaphthalene ring system has ever been reported, and according to Baczyński and Niementowski³³ the four-ring heterocyclic compound

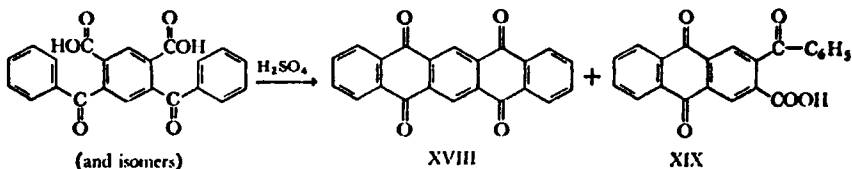


obtained is more likely to be a 1,7- or 4,12-diazabenz[*a*]anthracene than 2,3-dicarboxy-1,11-dihydro-1,11-diazanaphthalene-4,6-dione (XVII). A brief discussion of the work done by these investigators is found on page 96.

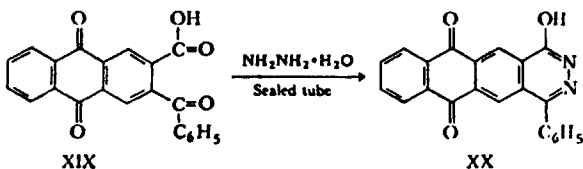
**D. 2,3-Diazanaphthalene, as is Naphtho[2,3-*g*]-
phthalazine. R.I. 2665**



The only synthesis of a 2,3-diazanaphthalene was reported by Seka, Sedlatschek, and Preissecker,³⁴ along with their work on derivatives of pyromellitic acid. Treatment of a mixture of isomeric 1,2,4,5-dibenzoyl-

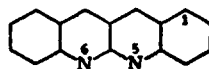


benzenedicarboxylic acids with sulfuric acid gives, in addition to 5,7,12,14-pentacenetetrone (XVIII), 2-benzoylanthraquinone-3-carboxylic acid (XIX). Treatment of the acid with hydrazine hydrate in a sealed tube

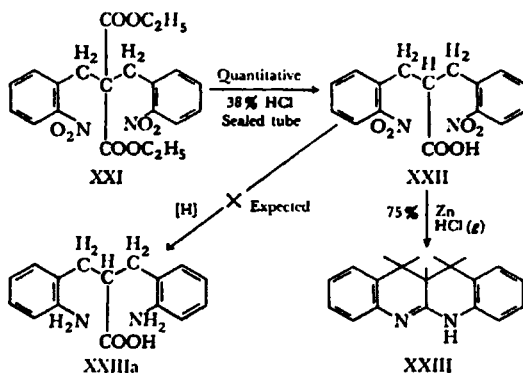


yields the phthalazine derivative, 1-hydroxy-4-phenyl-2,3-diazanaphthacene-6,11-dione (XX). The crude product, a gray powder, carbonizes and decomposes at 360°. It is very soluble in hot aniline, quinoline, pyridine, acetic anhydride, and nitrobenzene, and is crystallized from the latter to give a yellow powder melting at 374° with decomposition.

E. 5,6-Diazanaphthacene, Naphthinoine, Di-benzo[*b,g*][1,8]naphthyridine, α -Naphthinoine. R.I. 2695



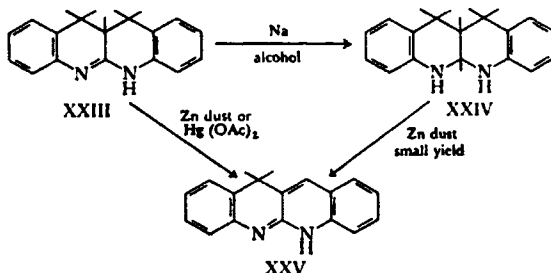
Reisert³⁵ first synthesized compounds of the 5,6-diazanaphthacene series as an extension of work with 1,8-naphthyridines,* and investigated a number of these tetracyclic compounds fairly extensively. He attempted the ring closure of di-*o*-nitrobenzylmalonic ester (XXI) with dilute hydrochloric acid in a sealed tube, but recovered the starting material unchanged. With more concentrated acid, the product obtained is di-(*o*-nitrobenzyl)acetic acid (XXII). Reduction of this dinitro acid or its ethyl ester is readily carried out with a variety of reducing agents, the best of which is zinc and hydrogen chloride; but the reaction gives not the expected diamino acid (XXIIIa), but a basic compound, C₁₆H₁₄N₂, i.e., 5,11,11a,12-tetrahydro-5,6-diazanaphthacene (XXIII).



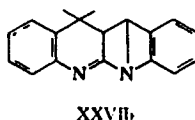
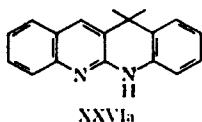
Reduction of the tetrahydro base (XXIII) with sodium and alcohol gives a hexahydro derivative, 5,5a,6,11,11a,12-hexahydro-5,6-diazanaphthacene (XXIV), while distillation of the tetrahydro derivative with zinc dust or treatment with mercuric acetate yields a dihydro compound, 5,11-dihydro-5,6-diazanaphthacene (XXV). On zinc dust

* See *Compounds with Pyridine Rings*, by Bambas and Klingsberg, *this series*, in preparation.

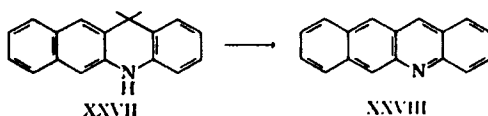
distillation, the hexahydro base undergoes carbonization, with the formation of a very small yield of the dihydro base (XXV).



These three heterocyclic compounds are formulated here as they were by Reissert³⁵ with respect to bond arrangement, but it is immediately apparent that other configurations are possible. Reissert suggested that the dihydro base, for instance, might be represented by XXVIa or

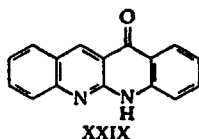


XXVIb instead of XXV. Since this compound forms an acetyl derivative indicating the presence of a secondary nitrogen atom, he eliminated XXVIb from consideration as it contains two tertiary nitrogen atoms. XXVIa is the formula corresponding to the most probable structure for Schopf's 5,12-dihydro-5-azanaphthacene (XXVII)¹⁴ (page 8), which readily loses a mole of hydrogen to form 5-azanaphthacene (XXVIII).



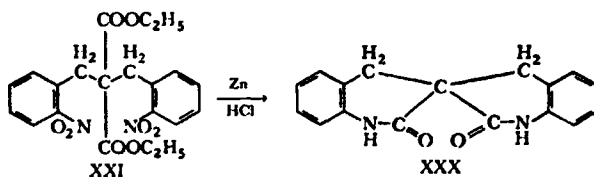
Since 5,11-dihydro-5,6-diazanaphthacene (XXV) is not oxidized to the expected 5,6-diazanaphthacene but gives instead an acridonelike product, a formula such as XXVIa, indicating the probability of dehydrogenation to the unsaturated base, is less likely than XXV, which accounts for the formation of an acetyl derivative as well as for the failure of dehydrogenation to give a compound analogous to XXVIII.

Various yellow monobasic salts are reported for the three diaza bases, XXIII, XXIV, and XXV, such as a picrate, monohydrochloride, and hemisulfate for the tetrahydro, a hydrochloride and picrate for the dihydro and hexahydro, and a number of noble metal double salts for the tetra and dihydro bases. Both XXIII and XXV, the tetra and dihydro compounds, give crystalline monoacetyl derivatives, and XXIII gives a mono-*N*-methyl compound. In one case,³⁵ acetylation of an impure sample of the dihydro base gave a nitrogen-containing compound, $C_{16}H_{10}N_2O$, which might possibly be 12-keto-5*H*,6-diazanaphthacene (XXIX).



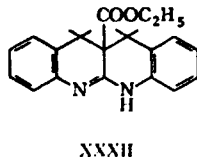
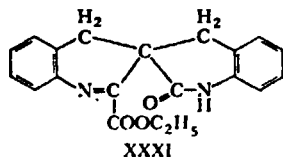
In the course of one of their investigations of spiro compounds, Leuchs and Katinsky³⁶ reported a diazanaphthacene said to be identical with Reissert's 5,11,11a,12-tetrahydro-5,6-diazanaphthacene (XXIII). Although they observed a slightly different melting point and a decomposition point well above it, the properties of their product are in accord with those given by Reissert, who had commented that variation in the rate of heating gave different decomposition points.

Lellmann and Schleicht³⁷ had concluded earlier that the product obtained on reduction of di-(*o*-nitrobenzyl)-malonic ester (XXI) was the spiran (XXX), even though the analysis for carbon was 2-3% too low.

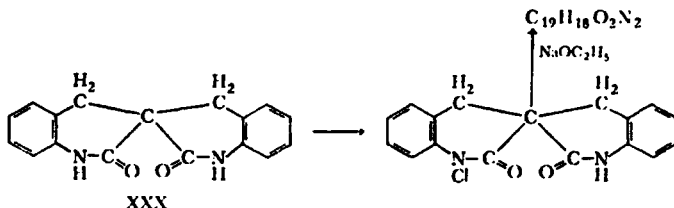


When Radulescu³⁸ reduced XXI with zinc and hydrochloric acid in boiling alcohol, he too obtained a compound whose analytical data were not completely in agreement with the figures calculated for the spiran. Since he concluded that incomplete combustion accounted for the discrepancy, he repeated the combustion according to the analytical method discussed by Scholl³⁹ and obtained a more consistent carbon

analysis. Leuchs and Katinsky³⁰ modified the reduction procedure used by these earlier workers, and prepared a pure product which analyzed correctly for XXX. In addition to a 65–80% yield of this spiro compound, they obtained 16–21% of a basic ether, $C_{19}H_{18}N_2O_3$, apparently identical with a substance which Radulescu had considered to be XXIIIa, a precursor of XXX.



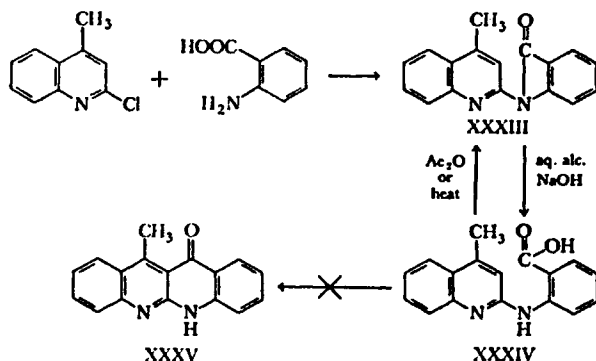
XXXI and XXXII were considered to be more probable structures for the basic substance because it was shown to contain one ethoxyl group, to give crystalline monobasic salts, and to give 5,11,11a,12-tetrahydro-5,6-diazanaphthalene (XXIII) on long boiling with hydrobromic or hydriodic acid. The same diazanaphthalene resulted also from treatment of the spiro compound (XXX) with boiling mineral acids. Two further facts led them to conclude that the so-called "basic ether" was actually XXXI: (1) the compound $C_{19}H_{18}N_2O_2$ did not give an acetyl derivative as would be expected of XXXII by analogy with XXIII; and (2) it could be obtained in 33% yield from the spiro compound (XXX) *via* the action of sodium ethoxide on its imide chloride.



Up to the present time, the only satisfactory synthesis of 5,6-diazanaphthalenes has been *via* di-(*o*-nitrobenzyl)acetic acid prepared from di-(*o*-nitrobenzyl)malonic ester, and these reactions have not been extended to substituted nitrobenzyl compounds. Therefore, all the 5,6-diazanaphthalenes so far reported are those which Reissert prepared from the tetrahydrodiazanaphthalene obtained by reduction of di-(*o*-nitrobenzyl)acetic acid, and the only compound other than those already mentioned is probably an *x,x*-dibromo-5,11,11a,12-tetrahydro-5,6-diazanaphthalene. It is obtained on direct bromination of the tetrahydro base, but the analytical data do not indicate whether or not oxida-

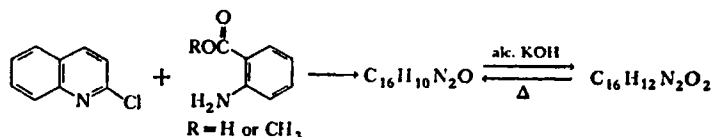
tion to the dihydro compound occurs simultaneously.

Backeberg⁴⁰ established the structure of the reaction product from the treatment of 2-chlorolepidine with anthranilic acid as the anthranil (XXXIII), which is readily hydrolyzed to 2-(2'-carboxyanilino)lepidine (XXXIV). It was expected, because of the analogous dehydration of 4-(2'-carboxyanilino)quinaldine to give 7-keto-6-methyl-7,12-dihydro-5,12-diazabenz[*a*]anthracene (page 114), that dehydration of the acid (XXXIV) would give rise to the formation of 12-keto-11-methyl-5,12-dihydro-5,6-diazanaphthacene (XXXV). However, heating the acid alone or in the presence of acetic anhydride yields the anthranil



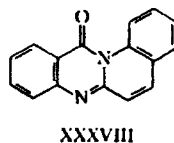
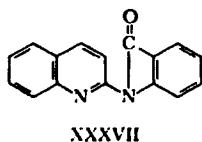
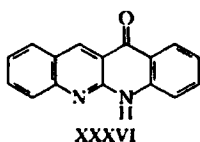
(XXXIII), while treatment with sulfuric acid gives a complex sulfur-containing substance of unknown structure. No conditions for effecting ring closure to the 5,6-diazanaphthacene have been discovered.

When Bose and Sen⁴¹ condensed 2-chloroquinoline with anthranilic acid (or methyl anthranilate), they obtained a substance melting at 170° which has the empirical formula $C_{16}H_{10}N_2O$. Hydrolysis of this basic

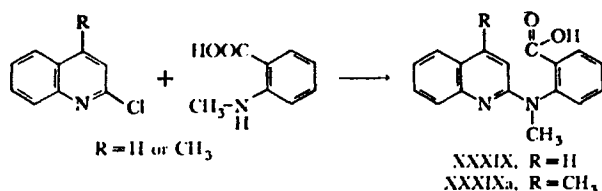


material with alcoholic potassium hydroxide gives a carboxylic acid, $C_{16}H_{12}N_2O_2$. There are three possible structural configurations for the condensation product: XXXVI, XXXVII, or XXXVIII.

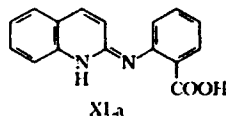
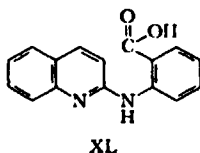
Bose and Sen concluded that their product was not 12-keto-5,12-dihydro-5,6-diazanaphthacene (XXXVI) because of the ease of hydrolysis to a carboxylic acid and the absence of fluorescence in acid solution. An



attempt to prepare XXXVI by the reaction of 2-chloroquinoline-3-carboxylic acid with aniline was unsuccessful, and condensation of 2-chloroquinoline or its 4-methyl derivative with *N*-methylantranilic acid gave compounds XXXIX and XXXIXa rather than 5,6-diazaanthracenes.

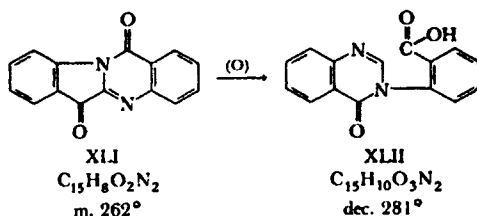


Although the anthranil structure accounts for the ease of hydrolysis, the reconversion of the carboxylic acid to the basic material in 90% yield does not correspond to the usual behavior of anthranils. Bose and Sen concluded that the condensation product is 12-keto-7,12a-diaza-benz[*a*]anthracene (XXXVIII) and that the acid obtained from it on hydrolysis is XL or its tautomer, XLa.

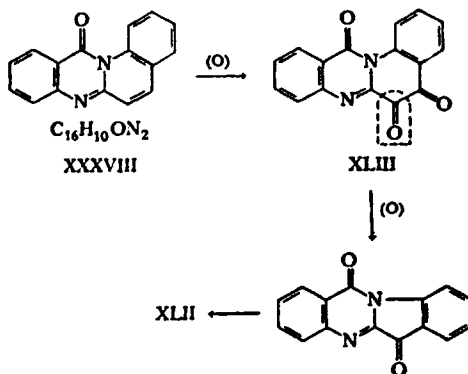


Seide and Chelintsev⁴² heated 2-chloroquinoline and anthranilic acid and obtained a substance having the same melting point as that of Bose and Sen. This compound, on hydrolysis with sodium ethoxide, gives an acid which melts with decomposition at 206–207°, while the acid obtained by the Indian workers melts at 198°. Treatment with phosphoryl chloride regenerates the basic condensation product from which two compounds result on oxidation with alkaline permanganate. Hence, it was concluded that the two compounds were indolo[2,1-*b*]-quinazoline-6,12-dione (XLI) and 4-keto-3-(*o*-carboxyphenyl)-3,4-dihydroquinazoline (XLII) which would be formed by the oxidation of a compound of structure XXXVIII but not from XXXVI or XXXVII.

Seide postulated an intermediate diketone, such as XLIII, to account for the oxidation products actually isolated.



Since both XLI and XLII had been synthesized previously (from the reaction of isatin chloride with anthranilic acid, and by heating *N*-formylanthranilic acid, respectively), it seems evident that Seide has demonstrated rather conclusively that the reaction of 2-chloroquinoline with anthranilic acid gives a compound whose structure is that shown in XXXVIII rather than the 5,6-diazanaphthacene (XXXVI). A more

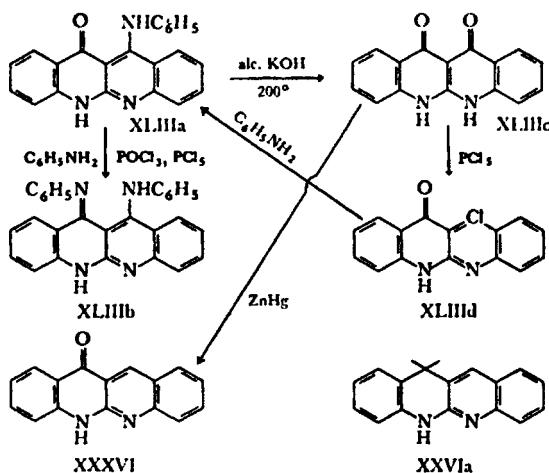


complete discussion of reactions which may lead to angular structures with a nitrogen atom common to two rings rather than the linear configuration may be found in Wilson's chapter in *Six Membered Heterocyclic Nitrogen Compounds with Three Condensed Rings, this series*, in preparation.

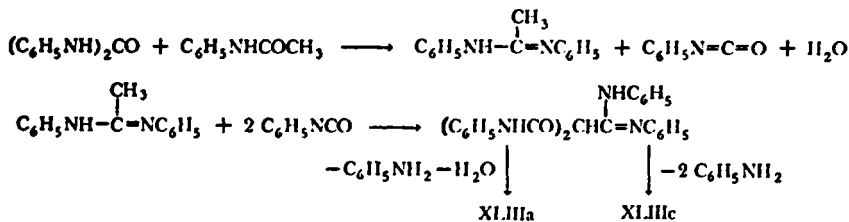
When a mixture of acetanilide and *sym*-diphenylurea is heated for three hours at 250 – 280° , an alcoholic extraction removes 2,4-dianilinoquinoline; a subsequent benzene extraction takes out 12-anilino-11-keto-6*H*,5,6-diazanaphthacene (XLIIIa), and leaves a residue of 11,12-diketo-5,6-dihydrodiazanaphthacene (XLIIIc, or an isomer). The 12-anilino derivative (XLIIIa) was synthesized independently by the action of aniline on the 12-chloro analog (XLIIId). Treatment of the

12-anilino derivative with a mixture of phosphorus pentachloride and phosphoryl chloride, followed by aniline, gives the di-anilino derivative (XLIIfb).

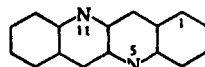
The diketo derivative (XLIIfc) is reduced by zinc amalgam to 12-keto-5*H*,5,6-diazanaphthalene (XXXVI), while all the substances on distillation with zinc dust give the long-known 5,12-dihydro-5,6-diazanaphthalene (XXVIa).³⁶ All the reactions are summarized herewith.



The authors^{42a} suggest the following mechanism:

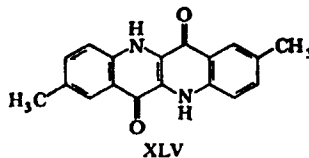
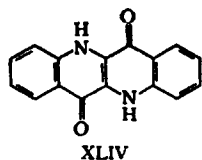


F. 5,11-Diazanaphthalene, Quino[3,2-*b*]quinoline, Epindoline. R.I. 2696

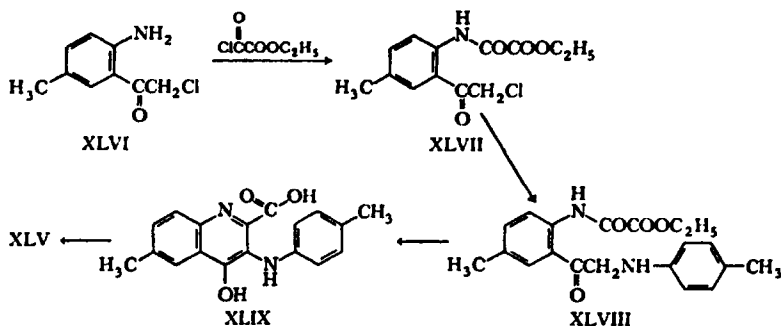


Only one unambiguous synthesis of a 5,11-diazanaphthalene has been reported, and this was achieved by Ainley and Robinson⁴³ only after a considerable amount of experimentation with different methods. The desired product was the unsubstituted 5*H*,11-diazanaphthalene-6,12-dione (XLIV) ("epindolidione"), which is isomeric with indigo. After a long series of experiments, 2,8-dimethyl-5,11-dihydro-5,11-diaza-

naphthacene-6,12-dione (XLV) was obtained, but the difficultly soluble compound bears no resemblance to indigo. The starting material for the synthesis is ω -chloro-2-amino-5-methylacetophenone (XLVI), which



is condensed with ethoxalyl chloride to give XLVII. After the chlorine has been replaced with iodine, *p*-toluidine is introduced, and ring closure of XLVIII is effected with boiling caustic to give XLIX. Ring closure of this acid is best carried out by boiling it (or its methyl ester or diacetyl

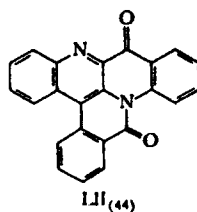
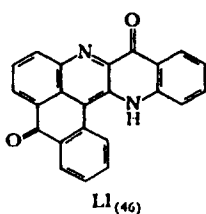
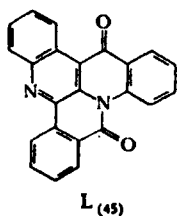


derivative) with 60% sulfuric acid; in this way 3,9-dimethyl-5,11-dihydro-5,11-diazanaphthacene-6,12-dione (XLV) is obtained. The compound is very slightly soluble in boiling pyridine and is insoluble in alcohol, acetic acid, nitrobenzene, and the like, but does dissolve in alcoholic potassium hydroxide with a yellow color and intense yellowish-green fluorescence. Although the compound is basic, as is shown by its increased solubility in acetic acid in the presence of sulfuric acid, the salt is unstable in the presence of water. The weak base is not reduced by alkaline hydrosulfite even in the presence of pyridine. Addition of zinc dust to a boiling suspension in pyridine-acetic acid decolorizes the solution, but the color is restored on oxidation with air. No other properties of the compound were reported by Ainley and Robinson⁴³ in 1934, and apparently the proposed extension of the work has not yet been published.

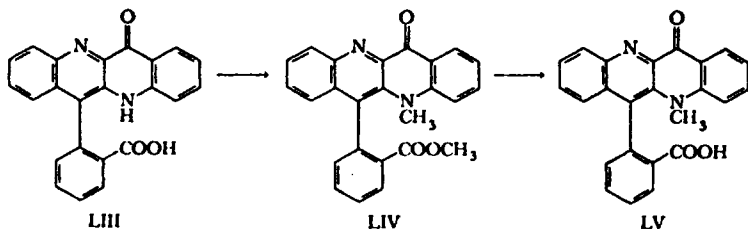
Subsequently the unmethylated diketone (XLIV) was prepared⁴⁴ by essentially the same procedure, from the anilino derivative, but using phosphoric acid for the ring closure. It is, likewise, a high-melting yellow substance, insoluble in most solvents; it was purified by sublima-

tion. No way of benzoylating or methylating was found.

Another preparation of a 5,11-diazanaphthacene is reported by Hope and Richter,⁴⁴ but the method of synthesis does not establish the structure nor do the reactions of the compound determine its configuration conclusively. Ciba Yellow 3G (*Colour Index No. 1195*), $C_{23}H_{12}N_2O_2$, is prepared by the prolonged action of benzoyl chloride on indigo at 150° in the presence of copper powder. Various structures have been postulated for the dye, such as L, LI, and LII, of which the last two are fused ring derivatives of 5,11-diazanaphthacene.



One of the characteristic reactions of Ciba Yellow 3G is its reversible hydrolysis to a monocarboxylic acid on heating with 15% sodium hydroxide; the dye is regenerated on heating the acid in neutral solution. If the dye has the structure, LI or LII, the acid obtained is 2'-carboxy-12-keto-6-phenyl-5,12-dihydro-5,11-diazanaphthacene (LIII). Methylation of the acid (LIII) gives a dimethyl derivative, thought by Hope and Richter to be LIV, from which a monomethyl carboxylic acid, LV, can be obtained. This methyl group was assumed to be attached to the nitrogen since it is not removed by treatment with hydriodic acid. Hope and Richter concluded LII to be the most likely structure for Ciba

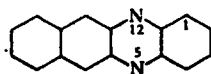


Yellow 3G because ring closure of LV to an *N*-methyl compound of structure LI cannot be effected under the same conditions which reconverted LIII to the dye and because the reversible hydrolysis of the dye suggests an amino acid – lactam relationship. The physical proper-

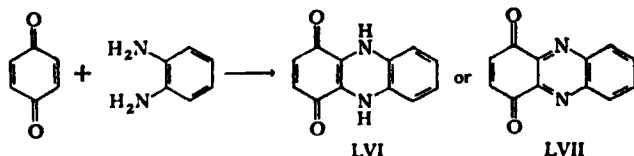
ties reported for LIII, LIV, and LV are included with those of XLV in Table 3 on the assumption that they are all 5,11-diazanaphthacenes.

Although more recent work on the structure of Ciba Yellow 3G has cast doubt on Hope and Richter's formulation of the dye, the problem has not yet been solved satisfactorily. A discussion of a number of investigations of three related dyes obtained from indigo may be found on page 101.

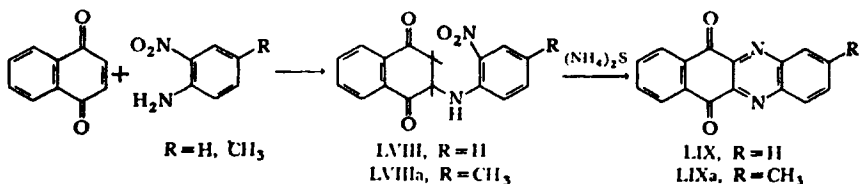
G. 5,12-Diazanaphthacene, Benzo[*b*]phenazine, *lin*-Naphthophenazine. R. I. 2666



The first synthesis of a 5,12-diazanaphthacene appears to have been carried out by Leicester⁴⁷ in 1890. Since the action of aniline on quinone is known to give quinone anilides, it might be expected that *o*-diamines would give quinone aminoanilides such as LVI or "quinone phenazines" such as LVII. Unfortunately, such reactions resulted in the formation

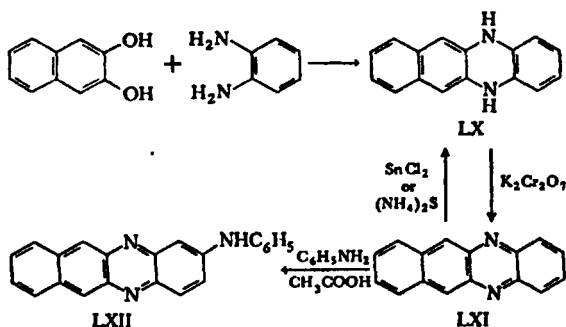


of difficultly separable mixtures, but Leicester found that quinone *o*-nitroanilines such as LVIII, readily prepared from nitroanilines and quinone, give heterocyclic fused ring systems on reduction. He obtained 5,12-diazanaphthacene-6,11-dione (LIX) and the 2-methyl homolog (LIXa) on reduction of the intermediate nitro compounds from the appropriate *o*-nitroanilines and 1,4-naphthoquinone.



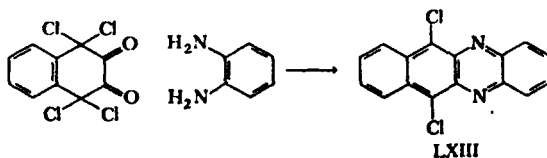
In 1901 Hinsberg⁴⁸ prepared 5,12-dihydro-5,12-diazanaphthacene (LX) in good yield by a condensation reaction between an *ortho*-diamine and an *ortho*-dihydroxy compound. The dihydro compound is stable in

the air and on heating to 180° , but yields 5,12-diazanaphthalene (LXI) on chromic acid oxidation. The unsaturated base is reconverted to the dihydro compound on treatment with stannous chloride or ammonium sulfide. The color of acid solutions of LXI indicates that salt formation



occurs, but, because of the weak basicity of the compound, dilution with water precipitates the free base. Blue-black crystals of 2-anilino-5,12-diazanaphthalene (LXII), which gives a crystalline hydrochloride and sulfate, are isolated from the crude green product obtained from heating the unsaturated base (LXI) with aniline and acetic acid. Treatment of 5,12-diazanaphthalene with benzenesulfinic acid is said to give a yellow sulfone whose structure is not established.

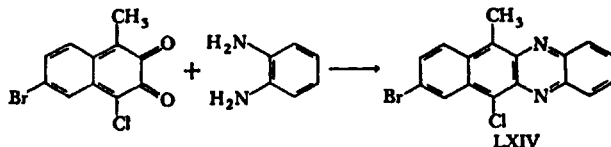
The synthesis which has been used most frequently for making compounds of the 5,12-diazanaphthalene series involves a condensation between an *ortho*-diketone and an *ortho*-diamine. The general reaction has found considerable use with lower molecular weight diketones, since the preparation of quinoxalines not only proves the existence of *ortho*-ketonic groups but also provides solid derivatives. Zincke and Fries⁴⁹ were the first to employ this method to make the aromatic base, 6,11-dichloro-5,12-diazanaphthalene (LXIII) from 1,1,4,4-tetrachloro-



1,2,3,4-tetrahydro-2,3-naphthoquinone. The dark red needles with bluish luster are stable to alkali and are so weakly basic that dilution of the dark brown sulfuric acid solution precipitates the free base.

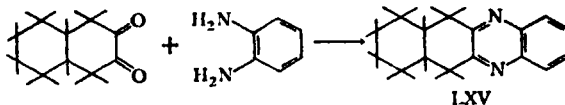
Fries and Empson⁵⁰ obtained red needles of 8-bromo-6-chloro-11-methyl-5,12-diazanaphthalene (LXIV) from the smooth reaction be-

tween *o*-phenylenediamine and 6-bromo-4-chloro-1-methyl-2,3-naphthoquinone. This product is identical with one prepared by Fries and Hempelmann⁵¹ from 6-bromo-1,4,4-trichloro-1-methyl-1,2,3,4-tetrahydro-2,3-naphthoquinone. In this case, as in that reported by Zincke and Fries,⁴⁹ condensation is accompanied by the splitting out of chlorine,



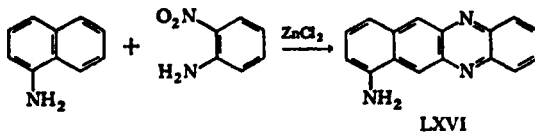
thereby forming the aromatic base, LXIV. The carmine needles of the substituted diazanaphthacene turn gray on rapid heating to 230° and carbonize at about 270°. The green salt precipitated from a red solution of the base in sulfuric acid on the addition of water is reconverted to the base on treatment with alkali.

Ganapathi⁵² employed the same kind of reaction to prepare 6,6a,7,8,9,10,10a,11-octahydro-5,12-diazanaphthacene (LXV) from 2,3-diketeto-*trans*-decalin. Since his interest was primarily in the diketone



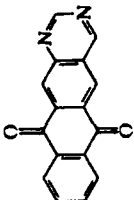
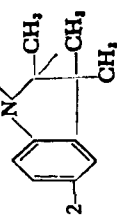
itself rather than in the quinoxaline derivative, he did not describe the product whose analysis corresponds to that for LXV other than as colorless rhombs, melting at 177–178°.

Wohl and Lange⁵³ prepared several phenazines by treating various substituted anilines with *o*-nitroaniline in the presence of zinc chloride. They extended the synthesis to one member of the 5,12-diazanaphthacene series, the 7-amino derivative (LXVI).



In view of the smoothness of the reactions involved and the potential interest in such benzophenazines as the 5,12-diazanaphthacenes, it is somewhat surprising that other syntheses of these somewhat weakly basic compounds have not been carried out and that the reactivity of the substances has not been investigated.

TABLE 3. Diazanaphthacenes (see page 17 for a description of symbols used).

Formula	Compound	Ref.	Appearance	Properties
 1,3-Diazanaphthacene-6,11-diones:				
XI R = H	4-Chloro-	29	—	Condensation products with various amino-anthraquinones give vats dyeing cotton yellow to green As above
XI R = C ₆ H ₅ XII	4-Chloro-2-phenyl-	29	—	As above
	2-Chloro-4-phenyl-	29	—	As above
	4-Chloro-2-tolyl-	29	—	As above
	4-Chloro-2-(2',5'-dichlorophenyl)-	29	—	As above
	4-Chloro-2-(4'-chlorocarbonylphenyl)-	29	—	As above
IV	4-Chloro-2-(4'-methoxyphenyl)- 4-Hydroxy-	29 28	— Pale yellow crystals	As above Yellow-red S; yellow OH ⁻ ; green vat dyes cotton yellow
X R = C ₆ H ₅	4-Hydroxy-2-phenyl-	29	—	Aminoanthraquinone vats —
	2-Hydroxy-4-phenyl-	29	—	—
III	4-Hydroxy-2-tolyl-	29	—	—
V	4-Hydroxy-1,2-dihydro-	28	Brilliant red	m. 318–320°; red S; yellow-red OH ⁻ ; green vat
VII	4-Hydroxy-2-methyl-1,2-dihydro-	28	Red-brown	Red S; green vat dyes rayon yellow-orange m. 286°; green vat dyes cotton brownish-yellow
				
VI	2-Furyl-4-hydroxy-1,2-dihydro-	28	Yellow	Olive-green S; green vat dyes cotton yellow
	4-Hydroxy-2-(4'-carboxyphenyl)-	28	Red-brown	m. 328–333°; red S; yellow-red OH ⁻ ; green vat dyes cotton yellow
	Di-2-(4-hydroxy-1,3-diaza-1,2-dihydro-6,11-dione)	28	—	Green vat dyes cotton brownish-yellow

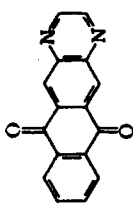
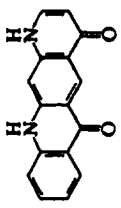
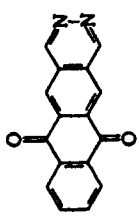
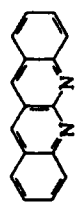
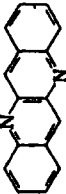
1,4-Diazanaphthacene-6,11-diones:			
XIII	2,3-Diphenyl-	30	Brown needles
XV	5-Amino-2,3-diphenyl-	31	Red needles
XIV	5-Amino-2,3-dihydroxy-	31	Brown needles
			m. 271°; no vat m. 241°; diff. sol.; green Fl ether; no vat m. >400°; diff. sol.; yellow S; red Na salt; no vat
1,11-Diazanaphthacene-4,6-dione (?):			
XVII	2,3-Dicarboxy-	33	Yellow
			m. 283° dec.; diff. sol. O; yellow H ⁺ and OH ⁻
2,3-Diazanaphthacene-6,11-dione:			
XXII	1-Hydroxy-4-phenyl-	34	Yellow powder
			m. 374° dec.
5,6-Diazanaphthacenes:			
XXV	5,11-Dihydro-	35	Leaflets
			m. 201°; solutions of XXV and salts show green Fl; double salts; orange-yellow .HCl m. 230°; ins. yellow .P m. 241° dec.
XXIII	5-Acetyl-5,11-dihydro- 5,11,11a,12-Tetrahydro-	35 35,36	White crystals Colorless leaflets
			m. 217-8°; very sol. O; yellow .HCl m. 270°; yellow 1/2 H ₂ SO ₄ m. 222°; yellow .P m. 208° dec.

Table continued

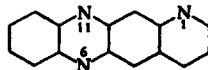
TABLE 3. Diazanaphthacenes (Continued)

Formula	Compound	Ref.	Appearance	Properties
XXIII (contd.)				
	5-Methyl-5,11,11a,12-tetrahydro- x,x-Dibromo-5,11,11a,12-tetra- hydro-	35	Plates	m. 114°
		35	Brownish-yellow needles	m. 244°; sol O
XXIV	5-Acetyl-5,11,11a,12-tetrahydro- 5,5a,6,11,11a,12-Hexahydro- 12-Keto-5,12-dihydro- (?)	35	Needles	m. 240°; sol O
XXIX		35	Needles	m. 128°; very sol O; .P m. 180° m. >300°
				
5,11-Diazanaphthacenes:				
XLV	2,8-Dimethyl-5,11-dihydro-6,12-diketo-	43	Yellow needles	No vat; yellow OH ⁻ with yellow-green Fl; diff. sol O; crimson K salt; salmon red S; green Fl
LIII	6-(2'-Carboxyphenyl)-5,12-dihydro-12-keto-	44	—	—
LIV	Dimethyl derivative of LIII	44	—	—
LV	5-N-Methyl-6-(2'-carboxyphenyl)-5,12-dihydro-12-keto-	44	—	—
				
5,12-Diazanaphthacenes:				
LXI	Unsubstituted	48	Red plates	m. 233°; yellow S
LX	5,12-Dihydro-	48	Yellow crystals	m. >300°; yellow S
LXV	6,6a,7,8,9,10,10a,11-Octahydro-	52	Glistening rhombs	m. 177-8°
LXIII	6,11-Dichloro-	49	Red, bluish luster	m. 265°; diff. sol. O; dark brown S; green with water
LXVI	α-Phenylsulfonyl-	48	Yellow	—
LXVII	7-Amino-	53	Yellow-brown prisms	m. 294° dec.
LXII	2-Anilino-	48	Blue-black crystals	m. 155°; brown .HCl; yellow-brown S
LIX	6,11-Diketo-	47	Green crystals	Brown O with weak green Fl
LIXa	2-Methyl-	47	Steel blue, green luster	Yellow-green O with moss-green Fl; green S
LXIV	8-Bromo-6-chloro-11-methyl-	50, 51	Carminc crystals	Diff. sol O; red S; green .H ₂ SO ₄

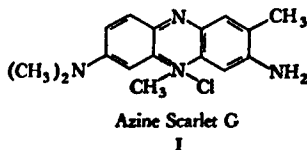
3. Triazanaphthacenes

Of the fifty-six theoretically possible triazanaphthacenes only two systems, the 1,6,11- and the 5,6,11-, are represented in the literature. Only one example of a member of the latter series has as yet appeared. (Table 4 on pages 52 and 53 lists the polyazanaphthacenes.)

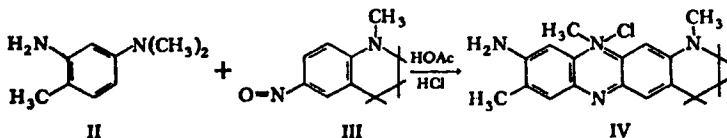
A. 1,6,11-Triazanaphthacene, Pyrido[2,3-*b*]-phenazine, Quinolinophenazine. R.I. 2654



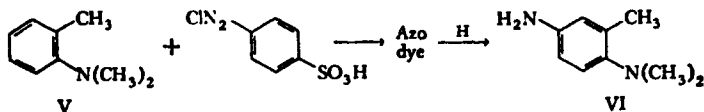
Cohen and Crabtree⁶⁴ first synthesized a triazanaphthacene during their work on the structure and color of the Azine Scarlets, which are phenazine derivatives such as I. They prepared a number of phenazine compounds of this type to determine the effect of ring and amino group



substituents on the color of the dyes formed. Among them was a triazanaphthacene derivative, the methochloride of 9-amino-1,8-dimethyl-1,2,3,4-tetrahydro-1,6,11-triazanaphthacene (IV). This was prepared from 6-nitroso-*N*-methyltetrahydroquinoline (III) and "*p*-dimethylamino-*o*-toluidine" (II). The green iridescent solid dissolves in water with a magenta color and has the empirical formula $C_{18}H_{21}ClN_4 \cdot HCl$.

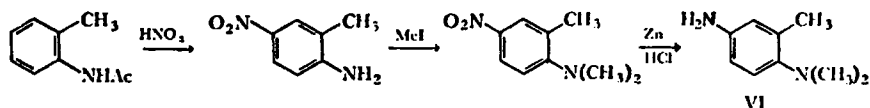


Cohen and Crabtree attempted to prepare analogous compounds from the nitroso compound, using *m*-phenylenediamine and tolylenediamine, but were unsuccessful because of the violence of the reactions.

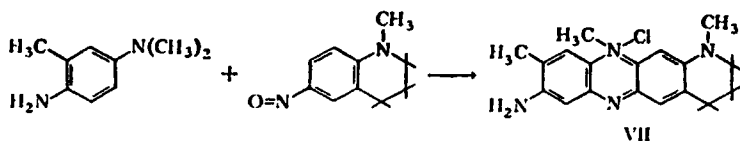


Cohen and Crabtree formulated their product as shown in IV; in order to synthesize this compound, the diamine used must be that shown by II. However, they prepared "*p*-dimethylamino-*o*-toluidine" by

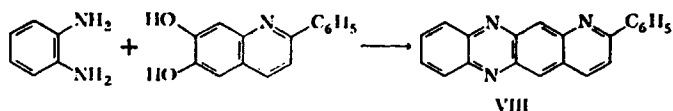
coupling dimethyl-*o*-toluidine (which must be V) with diazotized sulfanilic acid and reducing the azo dye. It is certainly to be expected that the product would be VI, and in any case it is very unlikely to be II. They stated that the same compound was prepared by Bernthsen,⁵⁵ who nitrated acetyl-*o*-toluidine, methylated the nitroamine, and reduced the nitro compound to obtain 2-dimethylamino-5-aminotoluene (VI),



b.p. 253–254°; m.p. 47°. Bernthsen pointed out that the formation of a quinonoid bond arrangement in 2,5-diaminotoluene on ferric chloride oxidation is additional evidence of the *para* arrangement of the two amino groups. It seems more likely that the triazanaphthacene which would result from a reaction between the nitrosoquinoline derivative, III, and the dimethylaminotoluidine prepared by the coupling reaction above would be VII, the methochloride of 8-amino-1,9-dimethyl-1,2,3,4-tetrahydro-1,6,11-triazanaphthacene rather than IV, as formulated by Cohen and Crabtree.

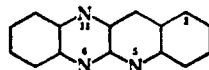


Borsche and Barthenheier⁵⁶ prepared a triazanaphthacene by the reaction of 2-phenyl-6,7-dihydroxyquinoline with *o*-phenylenediamine. On repeated vacuum sublimation of the crude product, they obtained brown leaflets of 2-phenyl-1,6,11-triazanaphthacene (VIII) which melt

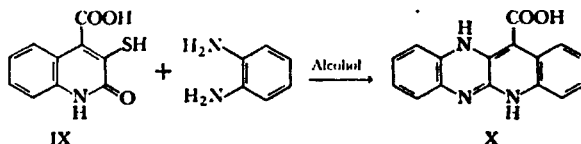


at 212–213°. They did not describe the compound further, nor did they prepare any analogous 4-ring compounds by the same type of synthesis.

B. 5,6,11-Triazanaphthacene, Quino[2,3-*b*]-quinoxaline. R.I. 2655



During an investigation of the relative stability of different ring types, Aeschlimann⁶⁷ synthesized the only 5,6,11-triazanaphthacene derivative so far reported in the literature. Condensation of 3-mercapto-2-quinolone-4-carboxylic acid (IX) with *o*-phenylenediamine gave a quinoxaline derivative, $C_{16}H_{11}N_3O_2$, which is probably 5,11-dihydro-5,6,11-triazanaphthacene-12-carboxylic acid (X). The product was first obtained as an amorphous brown material which is purified by continuous alcoholic extraction. The residue is insoluble in cold alkalis but dissolves in boiling sodium hydroxide, and gives a satisfactory carbon-hydrogen analysis for

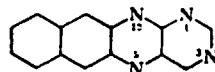


$C_{16}H_{11}N_3O_2 \cdot C_2H_5OH$. It is surprising, in view of the free carboxyl group, that the product is not soluble in cold alkali, but Aeschlimann postulated internal salt formation to account for the fact. Apparently, he did not investigate the product further, nor has any other synthesis of a 5,6,11-triazanaphthacene been reported.

4. Tetrazanaphthacenes

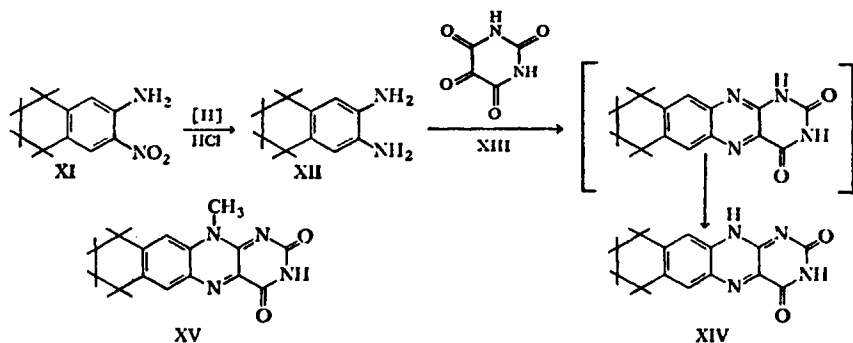
Three of the one hundred and forty-three possible tetrazanaphthacenes have been synthesized. The 1,3,5,12- series was investigated because its members are benzologs of the fused ring portion of such flavins as riboflavin. However, despite their relationship to biologically important naturally occurring substances, very few 1,3,5,12-tetrazanaphthacenes have been reported. Neither is the published work on members of the 1,4,6,11- or 5,6,11,12- series at all extensive. (Compounds belonging to these series are included in Table 4 at the end of this chapter.)

A. 1,3,5,12-Tetrazanaphthacene, Benzo[*g*]pyrimido[4,5-*b*]quinoxaline. R.I. 2641

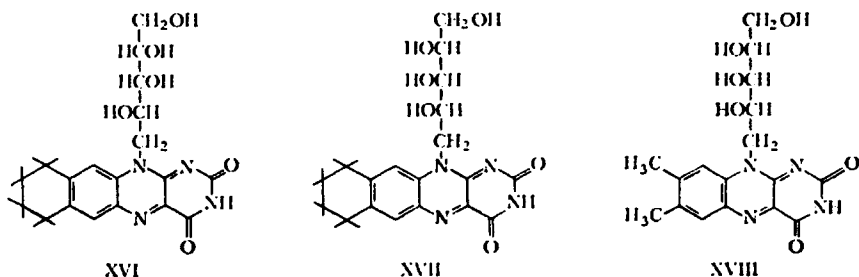


Kuhn, Vetter, and Rzeppa⁶⁸ synthesized a number of 12-substituted 1,3,5,12-tetrazanaphthacenes in a study relating to the specificity of lactoflavins. The parent compound, 3,7,8,9,10,12-hexahydro-1,3,5,12-

tetrazanaphthacene-2,4-dione (XIV), results from condensation between 2,3-diamino-5,6,7,8-tetrahydronaphthalene (XII) and alloxan (XIII). The 12-methyl homolog (XV) is prepared in the same fashion from *N*-methyldiaminotetrahydronaphthalene obtained by methylation of the aminonitro compound (XI) prior to reduction. The 12-L-



arabityl- (XVI) and 12-D-ribityl- (XVII) compounds are formed by the reaction of 2,3-dinitro-5,6,7,8-tetrahydronaphthalene with arabinamine and ribamine (prepared from the corresponding oximes), followed by reduction and treatment with alloxan tetrahydrate. XVI is also

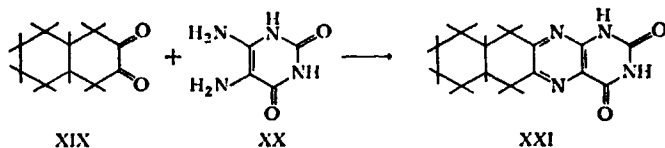


obtained as the tetracetyl derivative from reactions analogous to those used in the preparation of XV; in this case, L-arabinose itself is used to alkylate the nitroamino compound, XI. Kuhn does not discuss why the condensations between alloxan and *N*-substituted aminotetrahydronaphthalenes should give the 1,3-diaza rather than the theoretically possible 2,4-diaza derivatives. It may be that experimental evidence showing the great similarity between these compounds and riboflavin led him to that conclusion.

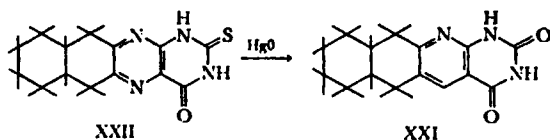
It may be seen by comparison of the structures that substitution of the two methyl groups of riboflavin (XVIII) by a tetramethylene ring gives 12-D-ribityl-3,7,8,9,10,12-hexahydro-1,3,5,12-tetrazanaphthacene-

2,4-dione (XVII). Replacement of the two alkyl groups by an additional ring results in slightly diminished coenzyme action, but the effect does not appear to be greatly dependent on the nature of the substituent group in position 12, since the activity of XV and XVI was shown to be almost the same. Absorption curves for XIV, XVI, and XVII given in the original article show that the wave lengths of maximum absorption are practically the same for all three, and that the variations in intensity are only slightly different. The similarity among these three ribo-flavinlike compounds is shown also by their olive-green fluorescence. Included in the article are the results of investigations of the effects of administration of these compounds on the increase in weight of previously starved rats.

Ganapathi⁵² also prepared two 1,3,5,12-tetrazanaphthacenes as an extension of his work with diketo-*trans*-decalins. Condensation of the 2,3-diketo compound (XIX) with 4,5-diaminouracil sulfate (XX) gives colorless needles of 1,3,6,7,8,9,10,10a,11-decahydro-1,3,5,12-tetrazanaphthacene-2,4-dione (XXI). The corresponding sulfur-containing com-

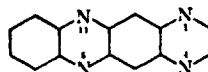


pound, 4-keto-2-thio-1,3,6,7,8,9,10,10a,11-decahydro-1,3,5,12-tetrazanaphthacene (XXII), prepared in the same way from 4,5-diaminothiouracil, gives XXI on treatment with yellow mercuric oxide. The dione (XXI) is moderately soluble in alcohol, and dissolves gradually in alkali,



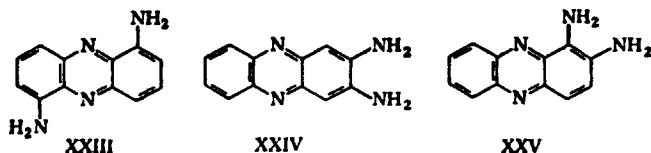
forming a solution which exhibits blue fluorescence under a quartz lamp. The sulfur analog is readily soluble in aqueous sodium hydroxide with a faint green fluorescence.

B. 1,4,6,11-Tetrazanaphthacene, Pyrazino[*b*]-phenazine. R.I. 2642

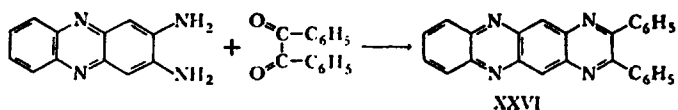


The first synthesis of a member of the 1,4,6,11-tetrazanaphthacene series was carried out by Fischer and Hepp⁵³ in the course of their investi-

gation of the oxidation of *o*-phenylenediamine with ferric chloride. They had previously concluded⁶⁰ that the diaminophenazine obtained was either XXIII or XXIV, but did not specifically eliminate the possibility of its having the structure XXV. The formation of a quinoxaline

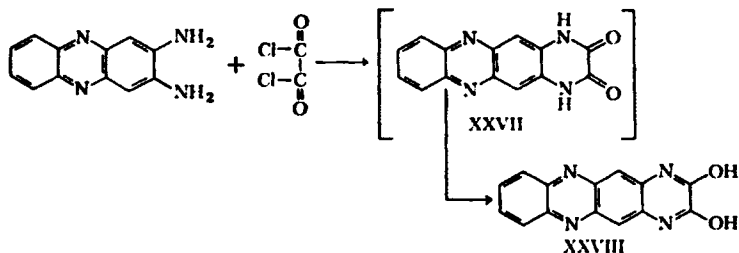


derivative (XXVI) on treatment of the diaminophenazine with benzil established that both amino groups were in the same ring and in the *ortho* position to one another, thus excluding XXIII. The 2,3-diphenyl-



1,4,6,11-tetrazanaphthacene (XXVI) that resulted was not fully characterized, since its preparation was not the primary aim of the research. The red-brown leaflets which decompose on heating dissolve in concentrated sulfuric acid with a deep blue color which fades on dilution with water.

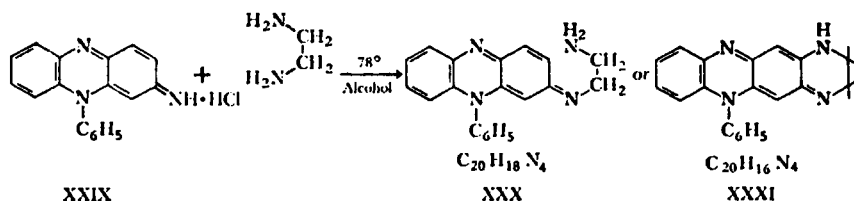
Sircar and De⁶¹ used the same diaminophenazine to synthesize 2,3-dihydroxy-1,4,6,11-tetrazanaphthacene (XXVIII). They had hoped



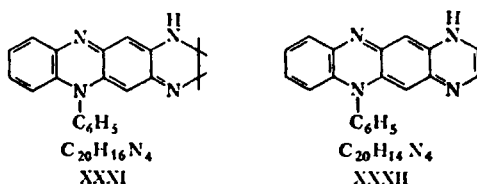
to obtain the *ortho*-diketone (XXVII) into which further heterocyclic rings might be introduced, but the immediate tautomerism to the dihydroxynaphthacene derivative (XXVIII) made the product useless for their purposes. Although the compound is isolated as a brown precipitate which cannot be crystallized, it can be purified by solution in

dilute aqueous ammonia and reprecipitation by dilute hydrochloric acid. It is a high-melting substance, insoluble in the usual organic solvents, soluble in alkali, and soluble in sulfuric acid, with blood-red color.

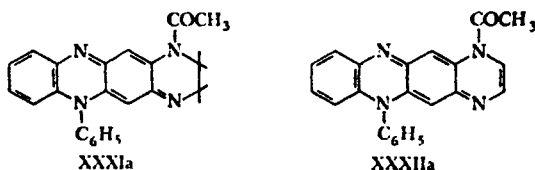
The structures of the only other 1,4,6,11-tetrazanaphthacenes synthesized are not definitely established. Fischer and Giesen⁶² refluxed aposafranin hydrochloride (XXIX) with ethylenediamine and ethylenediamine hydrochloride in alcohol and obtained bluish-green lustrous crystals of material with the empirical formula, $C_{20}H_{18}N_4$ (XXX) or $C_{20}H_{16}N_4$ (XXXI). The base, which may be 6-phenyl-1,2,3,6-tetra-



hydro-1,4,5,6-tetrazanaphthacene (XXXI), is somewhat soluble in organic solvents and is soluble in acids without fluorescence, but decomposes on heating into fluorescent materials. On oxidation, either by long heating in alcohol or by mercuric oxide, the base is converted into a different basic substance, $C_{20}H_{16}N_4$ (XXXI) or $C_{20}H_{14}N_4$ (XXXII),

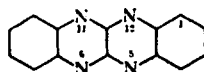


identical with the material obtained when aposafranin hydrochloride, and ethylenediamine and its hydrochloride are heated at $150-160^\circ$. The high-melting lustrous greenish crystals are difficultly soluble in organic solvents with a yellow color and greenish-yellow fluorescence. The base forms a difficultly soluble monoacetyl derivative, (XXXIa) or

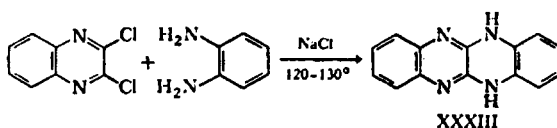


(XXXIIa), the analysis of which does not indicate conclusively which of the two structures is correct, but which does prove that a secondary amino group is present. No very complete investigation of any of the 1,4,6,11-tetrazanaphthacenes has been carried out, even though Fischer and Giesen⁶² remarked upon the tinctorial strength of the reduced base, (XXX) or (XXXI).

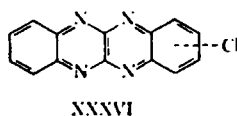
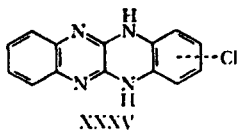
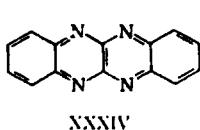
C. 5,6,11,12-Tetrazanaphthacene, Quinoxalo-[2,3-*b*]quinoxaline, Quinoxalophenazine.
R.I. 2643



The first synthesis of a 5,6,11,12-tetrazanaphthacene seems to be the preparation of fluoflavin, that is, 5,12-dihydro-5,6,11,12-tetrazanaphthacene (XXXIII), by Hinsberg and Pollak⁶³ from 2,3-dichloroquinoxaline



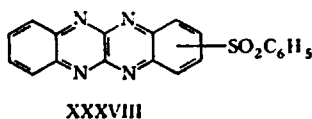
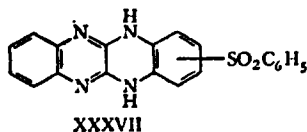
and *o*-phenylenediamine. The high-melting difficultly soluble yellow dihydro compound forms yellow solutions with intense yellow-green fluorescence; it is this latter property which suggested the name "fluo-flavin." The compound is stable to such reducing agents as stannous chloride, and is unaffected by warm acetic anhydride, probably because of its almost complete insolubility in the reagent. Although alcoholic alkali dissolves the base with a green color indicative of salt formation, the compound is sufficiently strongly basic to form a stable dihydrochloride. The dihydro base may also be prepared from 2,3-hydroxyquinoxaline or from two moles of the diamine and one of the oxalic acid, but in both cases the yield is not as good.⁶³ During the search for compounds with antimalarial activity, fluoflavin was subjected to testing as compound SN 2364, but it showed less than 0.6 of the activity of quinine against *P. lophurae*.⁶⁴



Oxidation of the dihydro base with dichromate gives the somewhat more soluble unsaturated 5,6,11,12-tetrazanaphthacene (XXXIV) which is very readily reduced to the parent dihydro compound (XXXIII) with

hydrogen sulfide, stannous chloride, or hydroquinone. The aromatic base (XXXIV) goes into solution with a blue color (indicating salt formation) on long heating with alcoholic alkali; it also dissolves in sulfuric acid with a yellowish-brown color. The weakly basic character is shown by the fact that addition of water precipitates the free base from acid solution. Treatment of the base with concentrated hydrochloric acid produces a high-melting yellow monochloro derivative (XXXV) of the dihydro base. In its solubility and in the color and fluorescence of its solutions this halogenated compound shows great similarity to the parent dihydro base (XXXIII). Because of its great stability, the halogen atom was assumed to be in one of the two benzene rings; for example, on oxidation of the chlorodihydro product, *x*-chloro-5,6,11,12-tetrazanaphthacene (XXXVI) was obtained.

Benzenesulfonic acid acted on the base (XXXIV) to give "phenyl fluoflavyl sulfone" (XXXVII), a high-melting yellow substance closely resembling fluoflavin in its behavior and color reactions. As in the case of the halogenated fluoflavin, *x*-phenylsulfonyl-5,12-dihydro-5,6,11,12-tetrazanaphthacene (XXXVII) is converted by oxidation into an *x*-

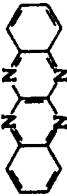


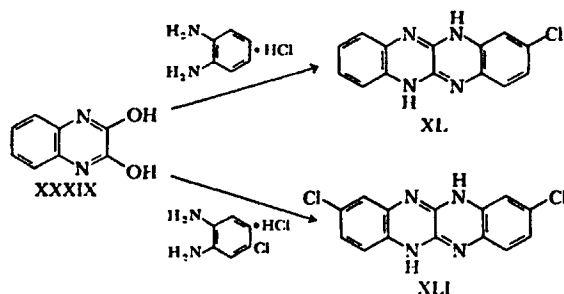
phenylsulfonyl derivative (XXXVIII) of the base (XXXIV). This rather surprising addition of hydrogen chloride and benzenesulfonic acid to 5,6,11,12-tetrazanaphthacene is significant in indicating the relationship of the heterocyclic compound to the parent naphthacene, which has a marked tendency to form a dihydro compound. The unsaturated base gives anilino derivatives which form blue-green salts, but no other properties are reported.⁴⁸

Kehrmann and his students synthesized a great many heterocyclic compounds containing four or more fused six-membered rings, among them two halogen and one phenyl derivative of fluoflavin as well as a number of oxygen isologs of fluoflavin and of benzofluoflavins. Kehrmann and Bener⁴⁵ obtained poor yields of 2-chloro- (XI) and 2,9-dichloro-6,12-dihydro-5,6,11,12-tetrazanaphthacene (XLI) from the reaction of 6-chloro-2,3-dihydroxyquinoxaline (XXXIX) with *o*-phenylenediamine hydrochloride and with 4-chloro-1,2-phenylenediamine hydrochloride, respectively.

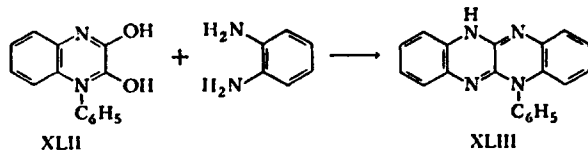
TABLE 4. Polyzanaphthalenes (see page 17 for a description of symbols used).

Formula	Compound	Ref.	Appearance	Properties
1,6,11-Triazanaphthalenes:				
VIII VII (?)	2-Phenyl-			
	Methochloride of 8-amino-1,9-di- methyl-1,2,3,4-tetrahydro-	56 54	Brown leaflets Green iridescent crystals	m. 212-3° Magenta in water
5,6,11-Triazanaphthalenes:				
X	12-Carboxy-5,11-dihydro-	57	Brown	Ins. cold OH ⁻
1,3,5,12-Tetrazanaphthalenes:				
XIV	2,4-Diketo-3,7,8,9,10,12-hexahydro-	58	Yellow crystals	m. > 360°
XV	2,4-Diketo-12-methyl-3,7,8,9,10,12- hexahydro-	58	Yellow needles	m. > 360°
XVII	2,4-Diketo-12-D-ribityl-3,7,8,9,10, 12-hexahydro-	58	—	Not readily crystallized
XVI	2,4-Diketo-12-L-arabityl-3,7,8,9, 10,12-hexahydro-	58	Yellow needles	m. 285-6°; orange tetra Ac ⁻ m. 243°
XXI	2,4-Diketo-1,3,6,6a,7,8,9,10,10a,11- decahydro-	52	Colorless needles	m. 315°; sol. OH ⁻ with blue Fl in quartz lamp
XXII	4-Keto-2-thio-1,3,6,6a,7,8,9,10,10a, 11-decahydro-	52	Light yellow needles	m. 295°; weak green Fl OH ⁻

Formula	Compound	Ref.	Appearance	Properties
1,4,6,11-Tetrazanaphthacene:				
XXVI	2,3-Diphenyl-	59	Brown-red plates	Dec. on heating; blue S
XXVII	2,3-Dihydroxy-	61	Brown	m. > 280°; ins. O; blood-red S; sol. OH ⁻
XXXIII	6-Phenyl-1,6-dihydro-	62	Greenish luster	Yellow C ₆ H ₆ with greenish-yellow Fl; blue S
XXXI	6-Phenyl-1,2,3,6-tetrahydro-	62	Bluish-green	Yellow-red ·HCl; violet H ⁺ without Fl; orange-red OH ⁻ without Fl; blue S, with H ₂ O red
XXXIa	Acetyl-6-phenyl-di-	62	Brown	Very diff. sol.
XXXIIa	or tetrahydro-			
5,6,11,12-Tetrazanaphthacenes:				
				
XXXIV	Unsubstituted	48,63	Red-brown needles	m. > 370°; yellow-brown S; blue OH ⁻
XXXIII	5,12-Dihydro-	48,63	Yellow needles	m. > 360°; prac. ins. O, yellow-green Fl; ·dihCl; green OH ⁻ ; yellow S
XXXVI	x-Chloro-	48,63	—	From XXXV on oxidation
XXXVIII	2-Phenylsulfonyl-	63	—	From XXXVII on oxidation
	2-(?) -Anilino-	48	Blue-black crystals	m. 155°; blue-green salts; blue O; yellow-brown S
XLIII	5-Phenyl-5,11-dihydro-	65	Yellow crystals	Diff. sol.; yellow with green Fl; yellow S green Fl
XXXVII	x-Chloro-5,12-dihydro-	48,63	Yellow crystals	m. > 360°; as in XXXIII
XL	2-Chloro-6,12-dihydro-	65	Gold needles	m. > 350°
XXI	2,9-Dichloro-6,12-dihydro-	65	Long yellow needles	m. > 350°; diff. sol.; orange-yellow S
XXXVII	2-Phenylsulfonyl-5,12-dihydro-	48,63	Yellow crystals	m. > 340°; intense Fl; yellow-green OH ⁻



N-Phenyl-2,3-dihydroxyquinoxaline (XLII) and *o*-phenylenediamine give a poor yield of 5-phenyl-5,11-dihydro-5,6,11,12-tetrazanaphthacene (XLIII). The properties of these three derivatives show great simi-



larities to those of fluoflavin (XXXIII) itself, and the reported characteristics of the monochloro derivative (XL) indicate that it is probably identical with Hinsberg's⁸³ chloro compound (XXXV). The phenyl compound (XLIII) does not give an addition product with dimethyl sulfate, and neither of the halogen-containing bases reacts with aniline.

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CHAPTER II

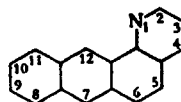
Azabenz[*a*]anthracenes

BY JEAN V. CRAWFORD AND ELEANOR R. WEBSTER

1. Monoazabenz[*a*]anthracenes

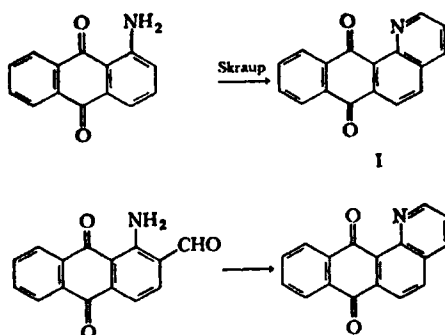
Although only eight of the twelve theoretically possible monoazabenz[*a*]anthracenes have been synthesized, these eight classes have been much more thoroughly investigated than any of the other four fused six-membered ring systems containing only nitrogen as the heterocyclic atom. This is particularly true in the case of the 1- and 4-azabenz[*a*]anthraquinones, which have been extensively used in the dye industry, and the 7- and 12-azabenz[*a*]anthracenes, both of which are acridine derivatives. Because of the very large number of compounds in these last two classes, they will not be discussed in this chapter. Four monoazabenz[*a*]anthracenes, the 2-, 3-, 6-, and 9-aza compounds have not been reported in the literature.

- A. 1-Azabenz[*a*]anthracene, Naphtho[2,3-*h*]-quinoline, 7,8- β -Naphthoquinoline, 1,2-Anthrapyridine, Anthraquinoline. R.I. 2732

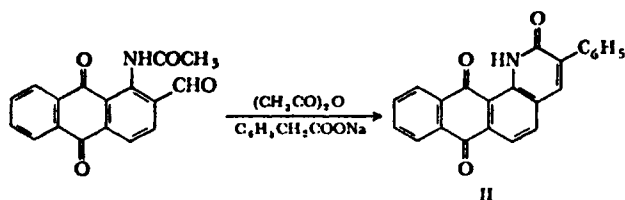


Most of the compounds in the 1-azabenz[*a*]anthracene series which have been prepared are anthraquinone derivatives and have been used commercially as dyes or dye intermediates. There are two general methods used in the preparation of these compounds: the Skraup reaction with 1-aminoanthraquinones, and the reaction of 1-aminoanthraquinone-2-carboxaldehydes (or ketones) with compounds containing a methylene group adjacent to a carbonyl group.* The former method yields compounds substituted on the anthraquinone nucleus, while the latter method gives products which are substituted in the pyridine ring as well.

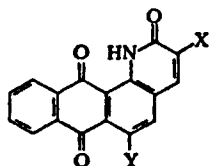
* A number of patents specify the use of this type of reaction for the preparation of dyes or dye intermediates, but the specific compounds often are not characterized as to physical or chemical properties.¹



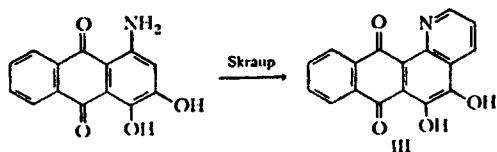
A substituted aminoanthraquinone may also be used in the latter type of reaction. For example, when 1-acetaminoanthraquinone-2-carboxaldehyde is heated with sodium phenylacetate in the presence of acetic anhydride, 2-keto-3-phenyl-1*H*,1-azabenz[a]anthraquinone (II) is formed.²



is formed.² Similar series of dyes are mentioned, with no clue as to the method of preparation, in which X = NH₂, NHCOAr, CONH₂, CONHR; Y = H, Br. The substances are yellow to orange vat dyes, fast to light but not to soda.³



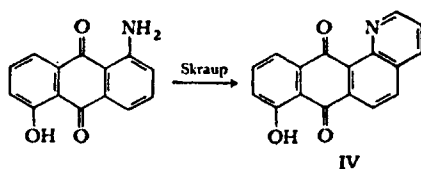
Although 1-azabenz[a]anthraquinone (I) is brownish yellow, it has no dyeing characteristics.⁴ However, when 4-amino- or 4-nitroalizarin is subjected to the Skraup reaction, using either arsenic acid^{5,6} or other



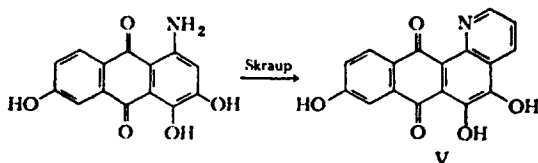
oxidizing agents,⁷ 5,6-dihydroxy-1-azabenz[a]anthraquinone (III), the dye known as Alizarin Green, is formed.

Reducing agents, such as zinc and sodium hydroxide, convert the dye into a leuco compound, which dissolves in alkali with a yellow-brown color and is oxidized to the quinone by air. With chromium mordants, a beautiful pure green color is produced on cotton and wool. The dye is readily transformed into the soluble bisulfite compound (Alizarin Green S, *Colour Index No. 1181*) which yields vivid shades of green with good stability to light.

The hydroxy derivatives of Alizarin Green are prepared from the corresponding hydroxyanthraquinones. For example, either 1,5- or 1,8-aminoanthraquinonesulfonic acid is transformed into the corresponding aminohydroxyanthraquinone, which is then subjected to a Skraup

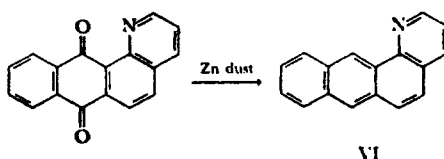


reaction, forming 8- or 11-hydroxy-1-azabenz[a]anthraquinone.⁸ This hydroxy derivative (IV) is a gray-yellow powder and forms a water-soluble sodium salt; it dissolves to an orange solution in concentrated sulfuric acid which, on warming with boric acid, becomes bluish-red. A sulfonic acid may be prepared by heating with 20% oleum at 100°, and the sulfonic acid group is replaced by hydroxyl by fusing with calcium hydroxide. The polyhydroxy-1-azabenz[a]anthraquinone is a dark brown powder which dyes a vivid bluish-black shade on chromium mordants. Similarly, 5,6,9-trihydroxy-1-azabenz[a]anthraquinone ("anthrapurpurin- α -quinoline") (V) may be prepared by the Skraup reaction



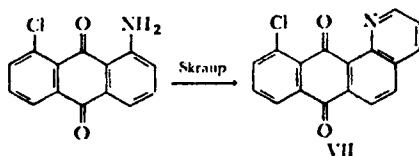
with 1-nitro- or 1-aminoanthrapurpurin.⁹ The soluble bisulfite compound produces shades similar to those from Alizarin Green (III).

The parent heterocycle, 1-azabenz[a]anthracene (VI), may be pre-



pared by zinc dust distillation of the corresponding anthraquinone (I).¹⁰

Although the 1-azabenz[*a*]anthraquinones have not been widely investigated from the standpoint of substitution reactions, it has been reported that only a mononitro compound results from 1-azabenz[*a*]anthraquinone, even when the nitration mixture is warmed, and that the nitro group is introduced on the anthraquinone nucleus.¹¹ The resulting nitro derivative was not characterized other than by solubility tests: it is insoluble in dilute alkali but soluble in dilute acid and most organic solvents, with a yellow color, and without fluorescence. 1-Azabenz[*a*]anthraquinone resists the action of fuming sulfuric acid.¹² Halogen derivatives of this heterocyclic system may be synthesized by treating the 1-azabenz[*a*]anthraquinone with halogenating agents or halogens, preferably in the presence of carriers,¹³ but the position of the entering group has not been established. Halogen derivatives in which the location of the halogen is certain, for example, 11-chloro-1-azabenz[*a*]anthraquinone (VII), are prepared from the corresponding haloanthraquinone *via* the Skraup reaction.¹³



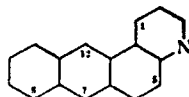
Compounds useful as dye intermediates are prepared by the reaction of 1-azabenz[*a*]anthraquinone in the presence of an alkaline condensing agent with compounds containing a reactive methyl or methylene group, such as phenylacetonitrile or malonic ester.¹⁴ Dyes producing red shades on cotton are produced by the interaction of 1-azabenz[*a*]anthracene and primary aromatic amines in the presence of an organic solvent and strong alkali.¹⁵

1-Azabenz[*a*]anthracene is a weak base whose salts are yellow¹⁰ and show an intensive green fluorescence in alcohol. The corresponding anthraquinone derivative is also very soluble in dilute acid, forming yellow salts.⁴ The hydroxy derivatives form two series of salts: in excess

sodium hydroxide, greenish-blue salts which are difficultly soluble in water; in solutions of strong acids, easily hydrolyzable red salts are formed.⁹ Alizarin Green is insoluble in ammonia but forms a green sodium salt.⁶

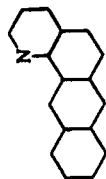
Although 1-azabenz[a]anthraquinone and its 2- and 3-substituted derivatives are yellow,⁴ introduction of an amino group in the anthraquinone nucleus yields a red-brown product, and the presence of several hydroxyl groups on the anthraquinone nucleus gives a greenish- or bluish-black compound (see Table 5). The 1-azabenz[a]anthraquinones are readily converted to the easily soluble bisulfite compounds.^{7,9}

B. 4-Azabenz[a]anthracene, Naphtho[2,3-f]-quinoline, 5,6- β -Naphthoquinoline, β -Anthraquinoline. R.I. 2733



Of all the nitrogen heterocycles containing four fused six-membered rings, this particular ring system, 4-azabenz[a]anthracene, has been most exhaustively investigated, principally because one compound of this series early became available commercially as a dye. Because the method of preparation of this dye, the proof of its structure, and the discovery of the identity of its sulfonation products were all important milestones in early organic chemistry, an attempt will be made to present these discoveries in chronological order. Since the 4-azabenz[a]anthraquinones have been more thoroughly investigated than the parent heterocycle, their methods of preparation, proof of structure, and derivatives will be discussed prior to those of the 4-azabenz[a]anthracenes.

Prud'homme¹⁶ in 1877 reported the isolation of two dyes from the reaction of nitroalizarin (Alizarin Orange), glycerin, and concentrated sulfuric acid—the first reaction of the type which was later studied extensively by Skraup. In 1878 at a meeting of the German chemical society, Graebe¹⁷ reported that Brunck at the Badische Anilin und Sodafabrik had been successful in preparing and isolating the blue dye and that Alizarin Blue (*Colour Index No. 1178*), as it was called, was on the market at that time. Although similar to alizarin in use, it was somewhat more difficult to dye and print than alizarin because of its slight solubility and tendency to form an insoluble calcium salt. With calcium, barium, and iron salts, Alizarin Blue formed greenish-blue lakes, while aluminum salts gave a reddish-blue, tin a red-violet, and chromium a blue-violet lake. The colors, Graebe said, were noteworthy because of their extraordinary stability and their resistance to change by soap. The

TABLE 5. 1-Azabenz[*a*]anthracenes (see page 17 for a description of symbols used).

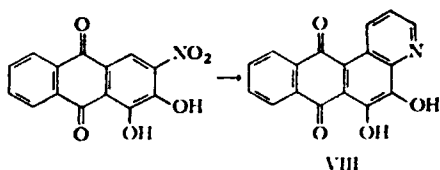
Formula	Compound	Ref.	M.p., °C.	Color	Properties
VI	1-Azabenz[<i>a</i>]anthracene	10	126.5-128	Y	Blue fluorescence in alc.
I	1-Azabenz[<i>a</i>]AQ ^a	4	169	Br-Y	No dyeing characteristics
	9-Methyl-1-azabenz[<i>a</i>]AQ	94	—	Gr-Y	—
	2-Phenyl-1-azabenz[<i>a</i>]AQ	95	215-217	—	Sol. S. with Y color. Gives red vat
	2-(2'-Naphthyl)- and 2-(1'-naphthyl)-1-azabenz[<i>a</i>]AQ	95	—	Y	—
	2-(2'-Anthranlyl)-1-azabenz[<i>a</i>]AQ	95	289-290	Br-Y	—
VII	2-(2'-Anthraquinonyl)-1-azabenz[<i>a</i>]AQ	95	324-326	—	May be vatted with wine-red color
	6-Chloro-1-azabenz[<i>a</i>]AQ	13	207	—	—
	8-Chloro-1-azabenz[<i>a</i>]AQ	13	257-258	—	—
	11-Chloro-1-azabenz[<i>a</i>]AQ	13	197	Y-Br	Sol. S. with Y-R color. Sol. dil. acid
	<i>x</i> -Chloro-1-azabenz[<i>a</i>]AQ	13	—	Y	Sol. S. with Y color. Gives orange vat
	<i>x</i> -Bromo-11-chloro-1-azabenz[<i>a</i>]AQ	13	—	R-Br	When treated with NaHSO ₃ yields a sulfonic acid which dyes wool Y-R from acid

Formula	Compound	Ref.	M.p., °C.	Color	Properties
	<i>x</i> -Bromo-8-amino-9-methyl-1-azabenz- [a]AQ	94	—	R-Br	—
	<i>x</i> -Chloro-6-methoxy-1-azabenz[a]AQ	13	—	O	—
	<i>x</i> -Nitro-1-azabenz[a]AQ	11	284	Gray	Sol. S. without fluorescence; sol. dil. acid
	8-Amino-9-methyl-1-azabenz[a]AQ	94	206-207	R-Br	Sol. S. with Br-Y color; sol. HOAc and dil. min. acids with B color
	11-Amino-10-methyl-1-azabenz[a]AQ	94	100	R-Br	Sol. min. acids with V color
IV	8-Hydroxy-1-azabenz[a]AQ	8	—	Gray-Y	Sol. in S. with O color
III	5,6-Dihydroxy-1-azabenz[a]AQ (Alizarin Green)	6,7	—	—	Dyes chromium-mordanted cotton and wool green; bisulfite cpd. (C.I. 1787) dyes G
V	5,6,9-Trihydroxy-1-azabenz[a]AQ	9	—	B-Black	Bisulfite cpd. gives shades similar to those of Alizarin Green
IV	5,6,10-Trihydroxy-1-azabenz[a]AQ	9	—	Gray-Black	Bisulfite cpd. gives clearer shades than Alizarin Green
	2-Hydroxy-3-carboxy-1-azabenz[a]AQ	1d,95	365-366 355-357	—	Also Refs. 1a, 1b, 1c, and 1c
	2-Hydroxy-3-cyano-1-azabenz[a]AQ	95	—	Y	Also Refs. 1a, 1b, and 1c
	6-Methoxy-1-azabenz[a]AQ	13	—	—	—
II	2-Keto-3-phenyl-1-azabenz[a]AQ	2	278	YO	Sol. S. with O color. Forms purple-red K salt with conc. MeOH-KOH

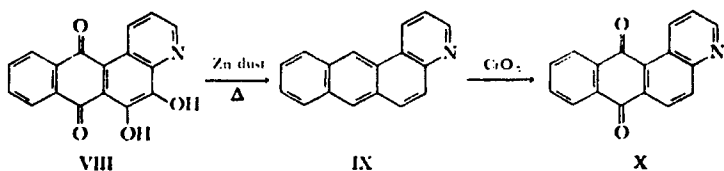
• AQ = anthraquinone.

new dye was capable of being vatted in alkaline solution and produced a blue color. At this time, Graebe also reported that after crystallization from benzene the dye was obtained as brown-violet needles, m.p. 270°, difficultly soluble in the usual organic solvents.

The following year, Graebe¹⁸ published his conclusions as to the structure of Alizarin Blue, $C_{17}H_9NO_4$, and showed that the two hydroxyl groups from alizarin were still present, as well as the two ketonic groups. He further proved that the starting material, a nitro-1,2-dihydroxyanthraquinone, was 3-nitroalizarin, and therefore postulated the structure



VIII. Additional experimental evidence¹⁹ confirmed this conclusion: the oxidation of Alizarin Blue with either potassium permanganate or nitric acid gave phthalic acid, showing that the glycerin had reacted with the ring containing the hydroxyl groups; the dye was reduced by zinc and sodium hydroxide in a manner analogous to the reduction of anthraquinone; distillation with zinc dust gave a tertiary base, $C_{17}H_{11}N$ (IX), which on oxidation formed a quinone, $C_{17}H_9NO_2$ (X). Since the



type of reaction used in the preparation of the dye and König's²⁰ synthesis of quinoline from allylaniline are similar, formation of such a heterocyclic system as VIII is probable.

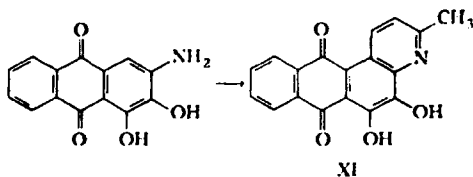
In 1879 Auerbach²¹ noted that the expectations for the success of Alizarin Blue had not been realized, partly because of its high price and partly because the dye was not fast to sunlight. Other modifications for its preparation were advanced: the use of arsenic acid as an oxidizing agent^{22,23} or the substitution of formaldehyde²⁴ or acrolein²⁵ for glycerol. Although Prud'homme had obtained only traces of the dye, better yields were obtained when dry 3-nitroalizarin was used and the proportions of reactants varied slightly.

Alizarin Blue forms two series of salts with alkali, the monopotassium or sodium salt being blue whereas the disodium or dipotassium salt is green.¹⁹ The barium, calcium, etc. salts are bluish-green. An indigo blue solution is formed when the dye is treated with ammonia. On the other hand, the dye is soluble in concentrated sulfuric acid, forming a red solution, from which the sulfate separates on dilution; the hydrochloride likewise is red, and both salts are easily decomposed by cold water. Vogel²⁶ first reported the characteristics of the spectra of the dye in aqueous and alcoholic ammonia as well as in hydrochloric and nitric acids.

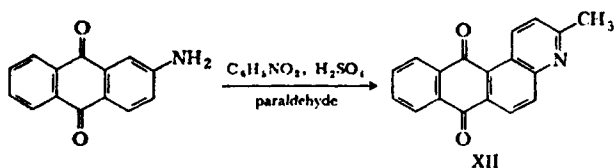
Because of its insolubility, Alizarin Blue could be fixed on the fiber only with difficulty, and therefore was little used until the discovery that it could be made water soluble by the action of alkali acid sulfate.²⁷⁻³⁰ The so-called Alizarin Blue S (*Colour Index No. 1179*) (Alizarin Blue plus two moles of acid sodium sulfite), prepared by allowing a mixture of Alizarin Blue paste and concentrated acid sodium sulfite to stand eight to fourteen days, is a red-brown powder which is stable when dry but whose aqueous solution decomposes into Alizarin Blue at 60°.³¹ Recent improvements in the method of preparing the water-soluble salt have shortened the reaction time to sixteen to eighteen hours.³² The blue color is reported to be especially resistant to light, soap, and chlorine³¹ and the dye is useful for printing cotton.

(1) Alkyl Derivatives

The only alkyl derivative of Alizarin Blue reported is the so-called Methyl Alizarin Blue (XI) prepared by the Doebner-Miller reaction using 3-aminoalizarin with acetaldehyde²⁸ in alcohol in the presence

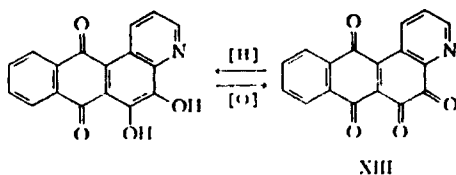


of sulfuric acid or oxalic acid. Both physical and chemical properties of this dye are analogous to those of Alizarin Blue itself. 3-Methyl-4-azabenz[a]anthraquinone (XII) is prepared similarly from 2-aminoanthraquinone and paraldehyde in the presence of nitrobenzene and sulfuric acid.³³

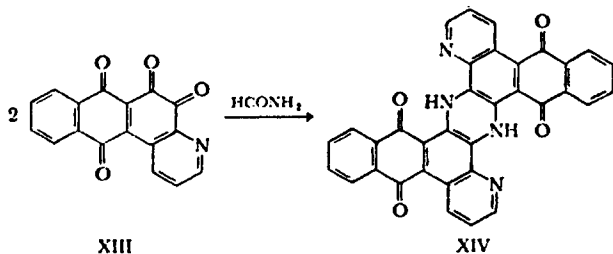


(2) Oxidation Products

Alizarin Blue is readily oxidized in acid solution by various oxidizing agents (*e.g.*, sodium hypochlorite, bromine, aqueous or acetic acid solutions of nitric acid, or manganese dioxide) to form the corresponding quinone (XIII).^{34,35} "Alizarin Blue Quinone," which separates from



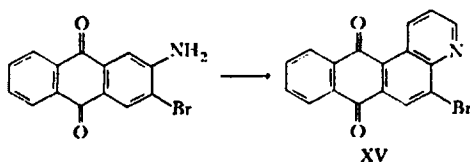
the mixture as bright yellow crystals, dissolves in concentrated hydrochloric acid with a pure yellow color and in concentrated sulfuric acid with a yellow-brown color. The quinone is easily transformed into Alizarin Blue by reducing agents. Mono- and dihydroxy-Alizarin Blue are similarly oxidized^{36,37} All of these quinones react with *ortho*-diamines to produce products useful as dyes. For example, Alizarin Blue Quinone reacts with 2,3-diaminoanthraquinone to give a yellow condensation product which is reported to dye cotton from a vat a beautiful shade of green,³⁵ and reacts in the presence of formamide to give a product which is postulated as the dipyridinoindanthrene (XIV).³⁸



Blue-green chromium-mordanted dyes are obtained by the condensation of dihydroxy-Alizarin Blue Quinone with phenolic carboxylic acids.³⁶

(3) *Halogen Derivatives*

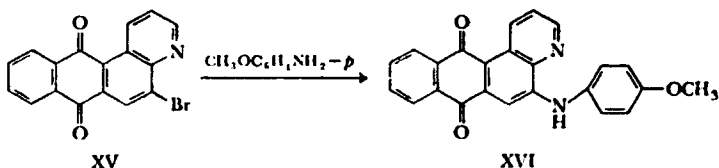
4-Azabenz[a]anthraquinones containing halogen in the anthraquinone nucleus have been prepared by four methods: (1) the direct halogenation of the 4-azabenz[a]anthraquinone; (2) the replacement of a hydroxyl group by halogen; (3) replacement of an amino group; or (4) the Skraup reaction with a halo-2-aminoanthraquinone. In 1879 Auerbach³⁹ reported that although chlorine reacted with Alizarin Blue dissolved in nitrobenzene to give a white product, m.p. 174°, no bromination product could be isolated when an acetic acid solution of Alizarin Blue was treated with bromine. When chlorine is passed into a boiling trichlorobenzene solution of 4-azabenz[a]anthraquinone, a monochloro derivative, giving a violet vat, is obtained.⁴⁰ This same reaction is used to prepare chloro-4-azabenz[a]anthraquinones which contain a substituent in the 5-position. 5-Hydroxy-4-azabenz[a]anthraquinone, when dissolved in dilute sodium hydroxide and treated with bromine, gives an excellent yield of a product which forms a reddish-brown vat with alkaline hydrosulfite.⁴⁰ Diazotization of amino-4-azabenz[a]anthraquinone (see Section 7, p. 75) with nitrosylsulfuric acid, followed by treatment with potassium iodide, produces the corresponding monoiodo compound.⁴⁰ 2-Amino-3-bromoanthraquinone, when subjected to the Skraup reaction, gives 5-bromo-4-azabenz[a]anthraquinone (XV).⁴⁰ The halogen-sub-



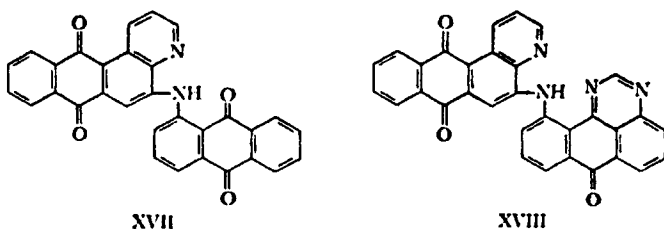
stituted 4-azabenz[a]anthraquinones are almost colorless or pale yellow compounds which are soluble in concentrated sulfuric acid, producing yellow to orange-red solutions, and give vat solutions whose colors vary from orange to blue.

The halogen may be replaced by various groups. For example, 5-bromo-4-azabenz[a]anthraquinone (XV) may be converted to the corresponding 5-mercapto or 5-cyano derivatives and the latter saponified to the carboxylic acid. These compounds may then be directly halogenated again to use as dye intermediates. Various dyes may be obtained by the reaction of the halogenated 4-azabenz[a]anthraquinones with amines; *e.g.*, *p*-anisidine and 5-bromo-4-azabenz[a]anthraquinone give

a product, XVI, which is soluble in concentrated sulfuric acid with a blue-green color.^{41,42} These vat dyes produce violet shades of good fastness



on cotton (see also page 75). An analogous series of metallizable 5-amino derivatives (see XVII) was examined in Germany; they were metallized on the fiber with copper salts, and gave dull greens, blues, violets, and browns with excellent light fastness. The most attractive product was obtained by after-coppering the dye (XVIII).



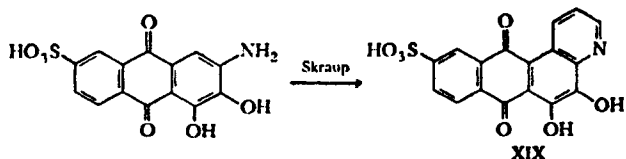
(4) Nitro Derivatives

Only a mononitro derivative is obtained when 4-azabenz[*a*]anthraquinone is nitrated in concentrated sulfuric acid, and it is assumed that the nitration occurs on the anthraquinone nucleus rather than on the pyridine ring⁴³ just as in the case of 1-azabenz[*a*]anthraquinone.

Alizarin Blue (VIII) may be nitrated by concentrated nitric acid in the presence of 20% oleum at 0°, but the product is not characterized other than as a dark greenish-blue powder which forms green salts with calcium, aluminum, chromium, and iron, and readily hydrolyzable salts with strong acids.⁴⁴

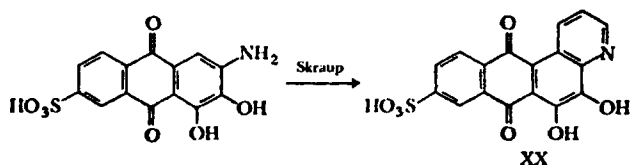
(5) Sulfonated and Hydroxylated Derivatives

In 1888 several monosulfonic acids of Alizarin Blue were reported

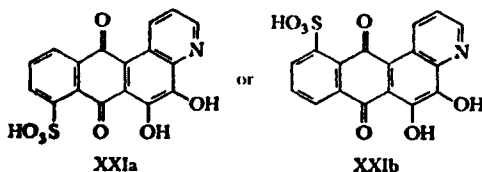


to have been synthesized *via* the Skraup reaction. One such acid (XIX) is prepared from 3-aminoalizarin-6-sulfonic acid with either the corresponding nitro compound or some other nitro compound as the oxidizing agent.⁴⁵

The free acid is obtained as a blood-red precipitate which dissolves with a yellow-green color in alkali and which separates from a large excess of alkali as the deep blue neutral sodium salt. Like the other sulfonic acids of Alizarin Blue when converted to the bisulfite compound, it prints cotton greener than does Alizarin Blue itself. Alizarin Blue-9-sulfonic acid (XX) was synthesized that same year from 3-aminoalizarin-7-sulfonic acid and its corresponding nitro compound.⁴⁶ The shades produced by this acid are redder than those with the 10-sulfonic acid.



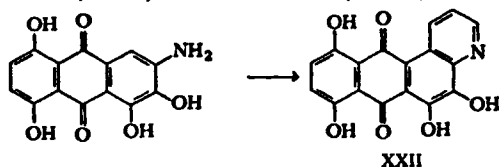
The first sulfonations of the 4-azabenz[a]anthraquinone series are reported in a German patent⁴⁷ on the sulfonation of Alizarin Blue and are interesting from a historical point of view. Although the structures were not elucidated, a number of derivatives of Alizarin Blue were prepared using varying concentrations of sulfuric acid and different temperatures and reaction times. The so-called "Alizarin Blue-sulfuric acid," prepared by treating Alizarin Blue (VIII) with one to two parts of 23% fuming sulfuric acid at a temperature not exceeding 50°, was available commercially as the sodium salt. Since this compound is easily decomposed by acid into Alizarin Blue, it is not a true sulfonic acid. When Alizarin Blue (VIII) is heated with about five parts of 23% fuming sulfuric acid at 100–200°, Alizarin Blue-sulfonic acid is formed, which



dyes chromium-mordanted wool somewhat greener shades than the unsulfonated product. This product is assumed to be either the 8- or 11-sulfonic acid (XXIa or XXIb).

An unstable "intermediate," obtained by treating Alizarin Blue (VIII) with ten parts of 70% oleum at 50°, is used in the preparation of two other dyes, Alizarin Bluegreen and Alizarin Green (not to be confused with the unsulfonated 5,6-dihydroxy-1-azabenz[a]anthraquinone, Alizarin Green, page 59). The acid solution of this intermediate, when diluted with concentrated sulfuric acid and allowed to stand for a short time, is poured into water. Purification of the dye is achieved in the usual manner by transforming it into the soluble alkali sulfite compound and decomposing the salt with acid. Alizarin Bluegreen produces greener lakes on fibers than does Alizarin Blue; the bisulfite compound is used for printing cotton. By warming Alizarin Bluegreen with sulfuric acid monohydrate at 120°, Alizarin Green (*Colour Index No. 1184*), which dyes chromium-mordanted wool green, is formed. When Alizarin Green is warmed with 10% oleum at 130°, a product which is similar to Alizarin Bluegreen is formed.⁴⁶ However, the new compound, Alizarin Green-sulfonic acid, is more water soluble than Alizarin Bluegreen, dissolves in 100% sulfuric acid with a muddy brown color, and in 23% oleum with a gray-green color, while Alizarin Bluegreen is violet and blue-green in the same solvents. Both dyes produce similar shades with chromium-mordanted wool. Alizarin Green, when heated to 200° with concentrated sulfuric acid, produces Alizarin Indigoblue, which dyes chromium-mordanted wool in indigo tones.

Graebe⁴⁹ undertook an investigation of the sulfonation products of Alizarin Blue which had been reported by Bohn⁴⁷ and discovered in 1890 that Alizarin Bluegreen is a mixture of mono- and dihydroxy-Alizarin Blue, and that by heating it with hydrochloric acid the main product is a tetrahydroxy-4-azabenz[a]anthraquinone. It is interesting from a historical point of view that after thorough investigation this hitherto unknown method of introducing hydroxy groups into an anthraquinone nucleus led to an easier and cheaper method of preparing highly hydroxylated anthraquinones than had been available previously. At this time Graebe established the fact that quinalizarin (Alizarin Bordeaux or 1,2,5,8-tetrahydroxyanthraquinone) and a trihydroxyanthraquinone were formed by heating alizarin with concentrated sulfuric acid. The preparation of a dihydroxy-Alizarin Blue (XXII) from amino-1,2,5,8-



tetrahydroxyanthraquinone is described in a German patent⁶⁰ and by Schmidt.⁶¹ Schmidt and Gattermann⁶² attempted the preparation of this dihydroxy-Alizarin Blue in a manner analogous to the synthesis of 1,2,5,8-tetrahydroxyalizarin from alizarin but the product obtained by the reaction of Alizarin Blue with 80% oleum at 30–40° gave analytical results corresponding to a trihydroxy-Alizarin Blue.

With a view to identifying the products formed, these investigators repeated the sulfonations of Alizarin Blue previously described. After purification, Alizarin Bluegreen was shown to be a monohydroxy-Alizarin Blue-monosulfonic acid. By heating Alizarin Bluegreen with concentrated sulfuric acid at 160–170°, the sulfonic acid group is removed and monohydroxy-Alizarin Blue is formed. Furthermore, it was shown that Alizarin Green is also a monohydroxy-Alizarin Blue-monosulfonic acid⁶³ which, when heated with hydrochloric acid, yields the same monohydroxy-Alizarin Blue previously described. When Alizarin Bluegreen is heated with concentrated sulfuric acid at 200°, the acid solution shows the same spectral characteristics as 8,11-dihydroxy-Alizarin Blue (XXII). At a higher temperature, however, a trihydroxy-Alizarin Blue is formed which is isomeric with that obtained by the reaction of 80% oleum on Alizarin Blue at 30–40°, and which is the principal component of Alizarin Indigoblue. When Alizarin Green is heated with sulfuric acid at 200° a sulfonic acid is obtained which on heating with hydrochloric acid gives a compound having a spectrum identical with that of 8,11-dihydroxy-Alizarin Blue (XXII).

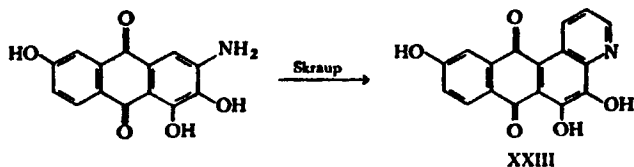
In 1893 Graebe and Phillips attempted to explain the formation of these polyhydroxy-Alizarin Blue derivatives. Schmidt⁶¹ had reported the isolation of an intermediate product, which was regarded as a sulfuric acid ester, from the sulfonation of alizarin. Graebe and Phillips⁶⁴ postulated that after the introduction of the sulfonic acid group spontaneous loss of sulfur dioxide occurred, thus forming the hydroxy compound directly. For example, Alizarin Green, which consists primarily of a trihydroxy-4-azabenz[a]anthraquinonesulfonic acid, when heated with sulfuric acid, yields a mixture of tetrahydroxy- and pentahydroxy-4-azabenz[a]anthraquinones. It appears that Alizarin Green first forms a tetrahydroxy derivative, which is then converted into a sulfonic acid; and this compound is transformed into a pentahydroxy derivative by loss of sulfur dioxide.

In 1891 Graebe and Phillips⁶⁵ obtained a monohydroxy-Alizarin Blue by two different methods: from the nitrobenzene-insoluble main component of Alizarin Green, and from the crude dye. Although a small

quantity of a tetrahydroxy-4-azabenz[*a*]anthraquinone was isolated from Alizarin Green by extraction with nitrobenzene, its structure was not established. The principal component of Alizarin Indigoblue was found to be a pentahydroxy-4-azabenz[*a*]anthraquinone.

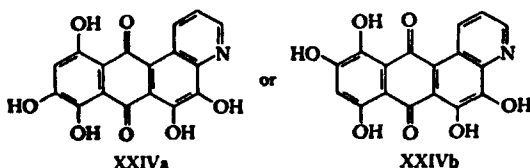
In only one case, that of Schmidt's⁵¹ 8,11-dihydroxy-Alizarin Blue (XXII), was the position of the hydroxy groups known. Graebe and Phillips⁵⁶ therefore oxidized Alizarin Green and Alizarin Indigoblue, and obtained from both the same acid, pyridine-2,3-dicarboxylic acid, which also results from oxidation of quinoline. Consequently, no one of the hydroxy groups could have been located on the pyridine ring.

After the preliminary work on identification of the products formed by sulfonating Alizarin Blue, Graebe and Phillips made a thorough investigation of the hydroxy-4-azabenz[*a*]anthraquinones and summarized the methods of preparing them. 5- (or 6-) Hydroxy-4-azabenz[*a*]anthraquinone may be prepared by diazotization of the so-called Alizarin Blue amide (page 82), followed by replacement of the diazonium group with hydrogen. A trihydroxy compound (*x*,5,6-trihydroxy-4-azabenz[*a*]anthraquinone) had been prepared by Schmidt and Gattermann⁵² by heating Alizarin Bluegreen—a monohydroxy-Alizarin Blue-sulfonic acid—with hydrochloric or sulfuric acid, while Graebe and Phillips⁵⁴ prepared the same trihydroxy derivative from the nitrobenzene-insoluble component of crude Alizarin Green by heating with hydrochloric acid at 180° or by sublimation. The former method is preferable. Since the sulfonic acid of this trihydroxy derivative forms a tetrahydroxy derivative or its sulfonic acid, it was suggested that the third hydroxy group might be in either position 8- or 11-. Another trihydroxy-4-azabenz[*a*]anthraquinone had been prepared by subjecting either 3-amino- or 3-nitroflavopurpurin to a Skraup reaction.⁵⁶ The product, 10-hydroxy-Alizarin Blue (XXIII) (Alizarin Black P, *Colour Index No. 1182*), is transformed into the bisulfite compound (*Colour Index No. 1183*) which produces gray to black shades on cotton.



A tetrahydroxy-4-azabenz[*a*]anthraquinone (dihydroxy-Alizarin Blue) was isolated in small quantities from technical Alizarin Green and

from Alizarin Indigoblue by extraction with nitrobenzene.⁵⁴ It was also obtained by sublimation of Alizarin Indigoblue. By this procedure separation from the pentahydroxy compound, which does not sublime, is achieved. This tetrahydroxy-4-azabenz[*a*]anthraquinone is identical with the compound which Schmidt and Gattermann⁵² prepared by the Skraup reaction with 3-amino-1,2,5,8-tetrahydroxyanthraquinone and therefore must be 5,6,8,11-tetrahydroxy-4-azabenz[*a*]anthraquinone (XXII). A pentahydroxy compound (trihydroxy-Alizarin Blue) forms the nitrobenzene-soluble portion of Alizarin Indigoblue. Since the pentahydroxy derivative yields 2,3-pyridinedicarboxylic acid on oxidation, thus excluding a hydroxyl group on the pyridine ring, and since 5,6,8,11-tetrahydroxy-4-azabenz[*a*]anthraquinone is found as an intermediate in its preparation, the most reasonable structures appear to be either 5,6,8,9,11- or 5,6,8,10,11-pentahydroxy-4-azabenz[*a*]anthraquinone (XXIVa or XXIVb).



As a result of this work, it can be stated definitely that Alizarin Bluegreen is a hydroxy-Alizarin Blue-monosulfonic acid and that Alizarin Indigoblue is a mixture of a pentahydroxy-4-azabenz[*a*]anthraquinone, a small amount of a tetrahydroxy-4-azabenz[*a*]anthraquinone, and a sulfonic acid derived from the latter.

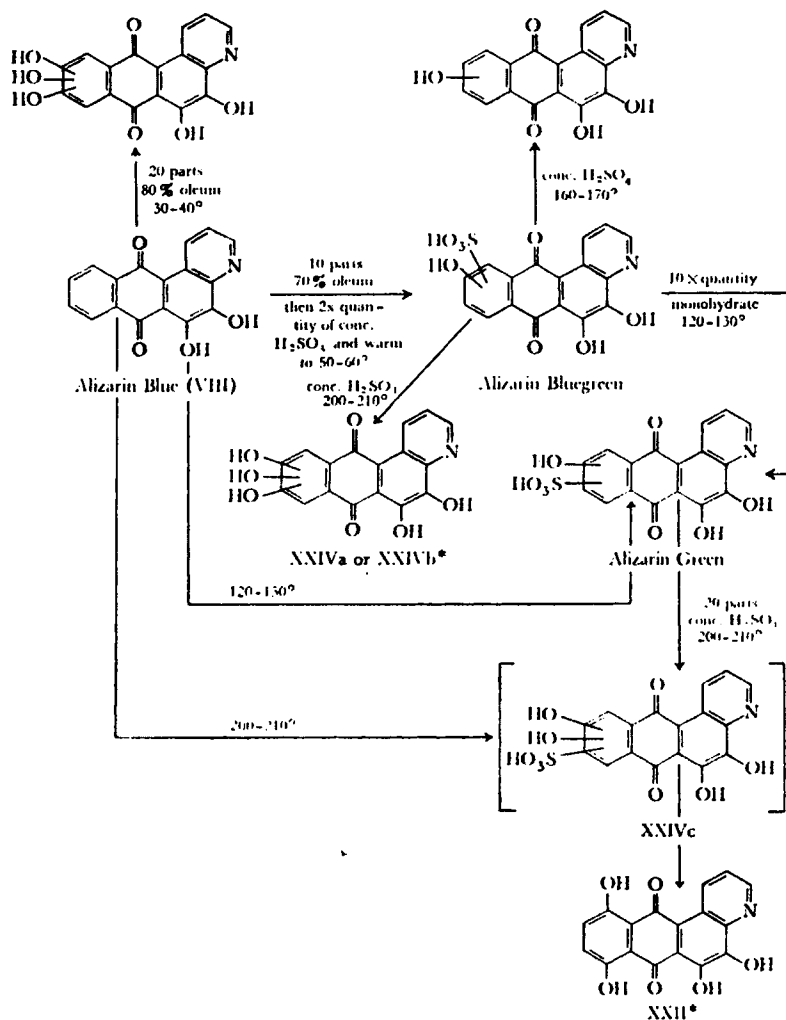
In 1894, a German patent⁵⁷ described a quicker, simpler, and cheaper method of preparing di- and trihydroxy-Alizarin Blue than that involving a large excess of fuming sulfuric acid. The use of boric acid with concentrated sulfuric acid—a reaction which had been discovered in the preparation of hydroxylated anthraquinones—produced a mixture of di- and trihydroxy-Alizarin Blue.

(6) *Physical Properties*

Table 6 gives the color of the various hydroxy-4-azabenz[*a*]anthraquinones, their alkali salts, sulfates, and the color of the solution in concentrated sulfuric acid.⁵⁴

One characteristic difference between Alizarin Blue and its mono- and dihydroxy derivatives is the ready solubility of the former in cold

aqueous ammonia in contrast to the insolubility of the latter in the same reagent. The trihydroxy derivative is also soluble in ammonia.⁵⁴ All these compounds form soluble bisulfite compounds which are used for dyeing and printing. With chromium mordants, greener shades are



obtained with the hydroxy-Alizarin Blue derivatives than with Alizarin Blue itself. The sulfonic acids of Alizarin Blue, without being converted

* Alizarin Indigoblue is a mixture of XXII, XXIVa or XXIVb, and XXIVc.

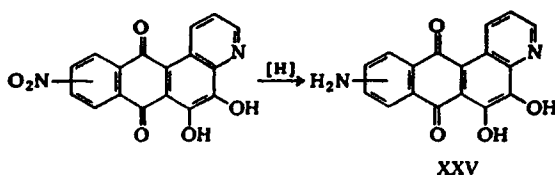
TABLE 6. Hydroxy-4-azabenz[a]anthraquinones

Compound	Free base	Alkali salts	Sulfate	Conc. H ₂ SO ₄ Solu.
5- (or 6-) Hydroxy-	Brick-red	Violet	Yellow-brown	Yellow-brown
5,6-Dihydroxy-(Alizarin Blue)	Brownish-violet	Blue or green	Red	Red
Hydroxy-Alizarin Blue	Blue-violet	Blue or green	Red	Red
5,6,8,11-Tetrahydroxy-(dihydroxy-Alizarin Blue)	Blue	Blue	Dark red	Blue
Trihydroxy-Alizarin Blue	Blue	Blue	Violet-red	Blue

to the bisulfite compounds, also print greener colors than does Alizarin Blue. Alizarin Blue and its hydroxy derivatives react with aldehydes to give products which, when converted to the bisulfite compounds, are chromium-mordant dyes which print cotton blue-green to green-blue shades with good fastness.⁵⁸ Alizarin Gray SD (*Colour Index No. 1180*), formed from Alizarin Blue, formaldehyde, and sodium bisulfite, is an example.

(7) Amino Compounds

Amino derivatives of 4-azabenz[a]anthraquinone have been synthesized by the usual methods: reduction of the corresponding nitro compound, replacement of a halogen atom or hydroxyl group, or amination of a keto group. Nitroalizarin Blue (page 68) is reduced by dextrose to the corresponding dark-red amino compound (XXV), which



dissolves in ammonia with a pure blue color and forms difficultly soluble alkali salts and easily hydrolyzable salts with strong acids. Aminoalizarin Blue may be used to dye and print cotton directly, as well as in the form of a soluble bisulfite compound.⁵⁹

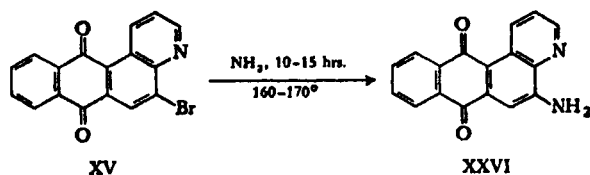
5-Amino-4-azabenz[a]anthraquinone (XXVI) is prepared by heating the corresponding 5-bromo compound with 20% ammonia for ten to fifteen hours, but this amino compound has no affinity for fibers.⁶⁰ When

TABLE 7. Alizarin Blue and Its Derivatives (see page 17 for a description of symbols used).

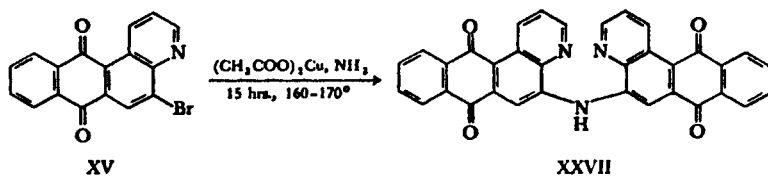
Formula	Compound	Ref.	Preparation	Color	Properties
VIII	Alizarin Blue	17,19,21, 23	Skraup on β -NO ₂ or β -NH ₂ alizarin	Br-V	M.p. 270°; sol. cold NH ₃ ; diBz, m.p. 244°; diAc, m.p. 196°; P, m.p. 245°
XII	Methyl-AB ^a	25	2-NH ₂ AQ ^b , CH ₃ CHO, and S.	B	—
	<i>x</i> -Chloro-AB	21	AB + Cl ₂ in C ₆ H ₅ NO ₂	C	M.p. 174°
	<i>x</i> -Nitro-AB	44	AB, conc. HNO ₃ and 20% oleum at 0°	Gr-B	—
	AB-sulfuric acid	47	AB and 2 parts 23% oleum at 50°	—	—
XX	AB-9-sulfonic acid	46	Skraup on 3-aminoalizarin-7-sulfonic acid	V-Br	—
XIX	AB-10-sulfonic acid	45	Skraup on 3-aminoalizarin-6-sulfonic acid	R	Difficultly sol. H ₂ O; dissolves with Y-Gr color and separates as the B neutral salt from excess alkali
XXIa or XXIb	AB-sulfonic acid (8- or 11-SO ₃ H)	47	AB and 5 parts 23% oleum at 120°	V-R	Sol. in HCl with R color; gives B-Gr alkali salts
	Alizarin Bluegreen (8-OH-11-SO ₃ H or 11-OH-8-SO ₃ H)	47,53	AB and 10 parts 70% oleum at 50° and diluted with S.	—	Fuschin-R soln. in S., B-Gr in 23% oleum, B in alkali carbonates, Gr in NaOH and KOH; alkali salts sol. in excess base
	Alizarin Green (hydroxy-sulfonic acid isomeric with above)	47,48,52, 53	Alizarin Bluegreen and 10 parts of monohydrate at 120°	Gray-V; B-Gr	R in S., Gr in caustic alkalis B in alkali carbonates, muddy V in cold monohydrate; alkali salts insol. in excess base
	Alizarin Green-sulfonic acid	48	Alizarin Green and 20 parts 10% oleum at 130°	—	Sol. H ₂ O with B-Gr, alkali carbonates with B, and caustic alkali with Gr color; completely sol. in excess alkali

Formula	Compound	Ref.	Preparation	Color	Properties
	8- (or 11-) Hydroxy-AB	54	Alizarin Bluegreen heated with S., or from C ₆ H ₄ NO ₂ , insoluble component of crude Alizarin Green by sublimation or heating with HCl at 180°	B-V	Ins. hot and cold NH ₃ ; sol. in S. with B-V color, in alkali with B color; excess alkali ppts. salt
XXXIII	10-Hydroxy-AB	56	Skraup on 2-aminoflavopurpurin	R-Br	Sol. in NaOH with V-R color; bisulfite cpd. dyes cotton gray to black
XXII	8,11-Dihydroxy-AB	50,51,54	Skraup on 3-aminoquinizarin and in small quantity from tech. Alizarin Green and Alizarin Indigoblue	B	Ins. hot and cold NH ₃ ; sol. in NaOH and KOH with B color; B salts separate on addn. of excess alkali; S. soln. is R; sublimes
	Alizarin Indigoblue	48	Alizarin Green and 20 parts S. at 200° or Alizarin Green-sulfonic acid and 20 parts S. at 200°	V	Ins. boiling H ₂ O; alkalis and alkali carbonates give B salts, ins. in excess alkali; B color in S. and cold monohydrate
XXIVa or XXIVb	8,9,11- or 8,10,11-Trihydroxy-AB	54	From CaH ₄ NO ₂ -soluble portion of Alizarin Indigoblue	B	Does not sublime; sol. in NH ₃ and S. with B color; penta-Bz, m.p. 175°
XXV	<i>x</i> -Amino-AB	44	<i>x</i> -NO ₂ -AB and dextrose or alkaline reducing agents	B-R	Sol. in NH ₃ with B color; forms B difficultly sol. salts with alkalis, and salts with dil. acid
XIII	AB-Quinone	34,35 37	Oxidation of AB Product obtained by oxidation of diOH-AB	Y	—
		36	Product obtained by oxidation of Alizarin Indigoblue	R-Br	—

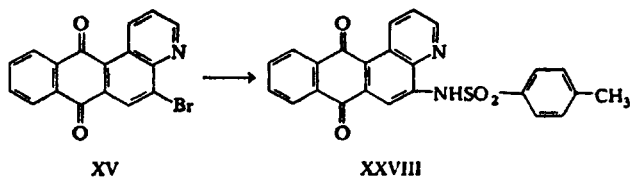
^a AB = Alizarin Blue.^b AQ = Anthraquinone.



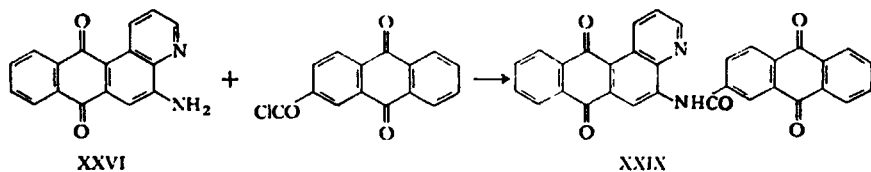
this reaction is carried out with the same quantities of material and the same temperature but for fifteen hours and in the presence of copper acetate, a violet-brown powder is obtained, the analysis of which corresponds to an anthrimide structure XXVII. The product is soluble in sulfuric acid with a red color and vat dyes cotton in violet shades.



Various substituted 5-amino-4-azabenz[*a*]anthraquinones are prepared by treating 5-bromo-4-azabenz[*a*]anthraquinone with *p*-toluenesulfonamide (XXVIII), benzamide, or *m*-methoxybenzamide.⁶¹



5-Amino-4-azabenz[*a*]anthraquinone (XXVI) reacts with acid chlorides, for example, 2-anthraquinonecarbonyl chloride, to produce

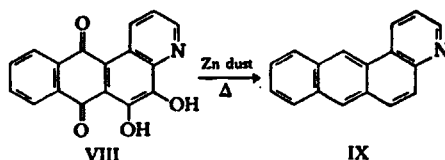


vat dyes which yield yellowish shades on plant fibers.⁶¹ (See also page 67.)

When Alizarin Blue is heated with concentrated ammonia at 160°,

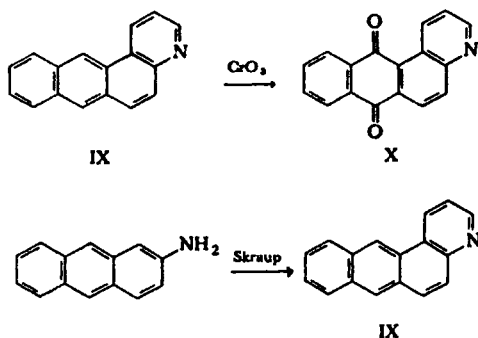
VIII **XXX**

The parent heterocycle in this series, 4-azabenz[*a*]anthracene (IX), was first prepared by Graebe⁶⁸ by zinc dust distillation of Alizarin Blue.



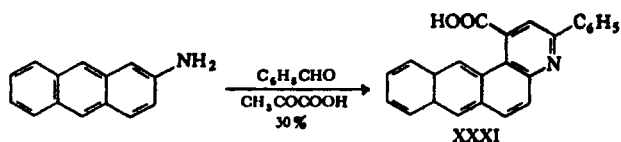
When 4-azabenz[*a*]anthracene is oxidized with chromic acid, a compound, $C_{17}H_9NO_3$, is obtained, which shows the characteristic reactions of an anthraquinone.⁸⁸ After Skraup had shown that β -naphthylamine reacted with glycerin and sulfuric acid in the presence of

nitrobenzene to give 4-azaphenanthrene, Graebe undertook the preparation of 4-azabenz[a]anthracene (IX) from β -anthramine and the same

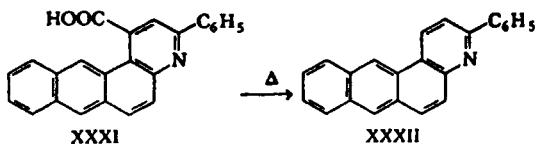


reagents. The product obtained was identical with that from the zinc dust distillations of Alizarin Blue.⁷⁰ The use of arsenic acid is reported to give better yields than those obtained with nitrobenzene.^{71,72}

In addition to the Skraup reaction, the Doebner pyruvic acid synthesis has also been employed with β -anthramine. For example, 3-phenyl-4-azabenz[a]anthracene-1-carboxylic acid (XXXI) is prepared by the reaction of β -anthramine, benzaldehyde, and pyruvic acid.⁷³



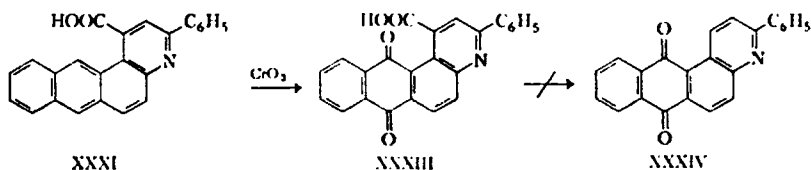
This acid, when heated above its melting point, is converted to the corresponding 3-phenyl compound (XXXII).⁷³



The substituted 4-azabenz[a]anthracenes discussed are yellow and the 3-phenyl derivative produces a pale violet fluorescence in neutral solutions, while in acidic solvents a greenish-yellow fluorescence is observed.⁷³ The corresponding anthraquinones are yellow. 3-Phenyl-4-azabenz[a]anthraquinone-1-carboxylic acid forms a yellow salt with two moles of

nitric acid⁷⁴; a trace of the free acid in sulfuric acid gives an intense red color. The 3-phenyl compound, however, gives no color in sulfuric acid.

Even though the Doebner synthesis is successful with β -anthramine, conditions could not be found for effecting the same reaction with 2-aminoanthraquinone. The 7,12-diketo derivatives are prepared by oxidizing the substituted 4-azabenz[a]anthracene with chromic oxide.⁷⁵ Although 3-phenyl-4-azabenz[a]anthraquinone (XXXIV) cannot be prepared from 3-phenyl-4-azabenz[a]anthraquinone-1-carboxylic acid (XXXIII), oxidation of 3-phenyl-4-azabenz[a]anthracene (XXXI) gives the desired compound.⁷⁵



The difference in behavior between β -anthramine and 2-aminoanthraquinone is also observed in the Skraup reaction, in which the former yields 4-azabenz[a]anthracene⁷⁰ and the latter yields not 4-azabenz[a]anthraquinone, but a compound containing an additional three carbon atoms. Bally⁷⁶ found that 4-azabenz[a]anthraquinone could not be detected in the product from a Skraup reaction on β -anthramine, but that the product isolated had the empirical formula $\text{C}_{20}\text{H}_{11}\text{NO}$. This same compound results when 4-azabenz[a]anthraquinone condenses with glycerin. Bally proposed the structure XXXV for the product; this has since been confirmed.

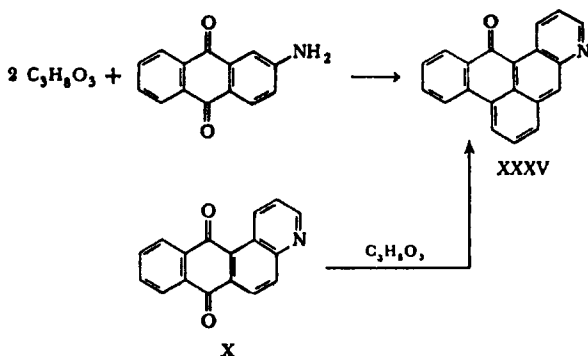
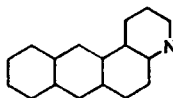


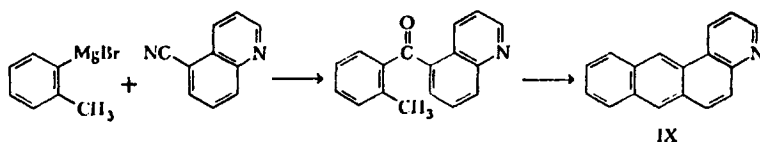
TABLE 8. 4-Azabenz[a]anthracenes*



Formula	Compound	Ref.	M.p., °C.	Color	Properties
IX	4-Azabenz[a]anthracene	18,19,23, 70,77, 78	170	C	Solns. show intense B fluorescence; salts Y, and their solns. have green fluorescence; MeI, m.p. 221°
XXXII	3-Phenyl-4-azabenz[a]anthracene	73	236	—	Pale V fluorescence in neutral solvents; intense G-Y fluorescence in acid soln.
XXXI	3-Phenyl-1-carboxy-4-azabenz[a]anthracene	73	285	Y	Me ester, m.p. 204°
X	4-Azabenz[a]anthraquinone	19	185	Y	Unstable salts
XII	3-Methyl-4-azabenz[a]AQ	33	—	—	—
XXXIV	3-Phenyl-4-azabenz[a]AQ	75	284	Y	Solns. not fluorescent. No color in S
XV	5-Bromo-4-azabenz[a]AQ	40	230	Y	S. soln. is Y; gives a V vat
	x-Chloro-4-azabenz[a]AQ	40	—	Y	S. soln. is O; gives a V vat
	x-Iodo-4-azabenz[a]AQ	40	213	—	—
	x-Nitro-4-azabenz[a]AQ	43	258	—	S. soln. is Y
XXVI	5-Amino-4-azabenz[a]AQ	42	277	—	No affinity for fibers
	5-Hydrazino-4-azabenz[a]AQ	42	237 238	—	Sol. in S. with O color; gives a V vat
XV	5-(4'-Anisidino)-4-azabenz[a]AQ	41,42	—	—	Sol. in S. with B-Gr color
XXVII	Di-(4-azabenz[a]-anthraquinonyl)-amine	42	—	V-Br	S. soln. is red; dyes cotton V-gray from a red vat
XXX	5- (or 6-) Amino-6- (or 5-) hydroxy-4-azabenz[a]AQ "AB-amide"	54	255	B	—
XXVIII	5-(p-Toluenesulfamido)-4-azabenz[a]AQ	61	225	—	K salt is red
	5- (or 6-) Hydroxy-4-azabenz[a]AQ	54	208	R	S. soln. is Y-Br; sol. in NH ₃ with cherry-red color; alkaline solns. and salts are V; Bz, m.p. 175°
XXXIII	1-Carboxy-3-phenyl-4-azabenz[a]AQ	75	—	Y	S. soln. red

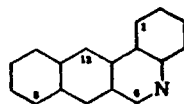
* For the 5,6-dihydroxy-4-azabenz[a]anthracenes, see Table 6. See page 17 for a description of the symbols used.

One further method has been utilized in the synthesis of the 4-azabenz[*a*]anthracenes. When attempting the synthesis of several heterocyclic nitrogen-containing compounds which might have carcinogenic activity, Fieser and Hershberg⁷⁷ extended the applicability of the Elbs synthesis. 5-Cyanoquinoline was condensed with *o*-tolylmagnesium bromide and the ketone pyrolyzed to give 4-azabenz[*a*]anthracene (IX), which was purified by chromatographic adsorption.

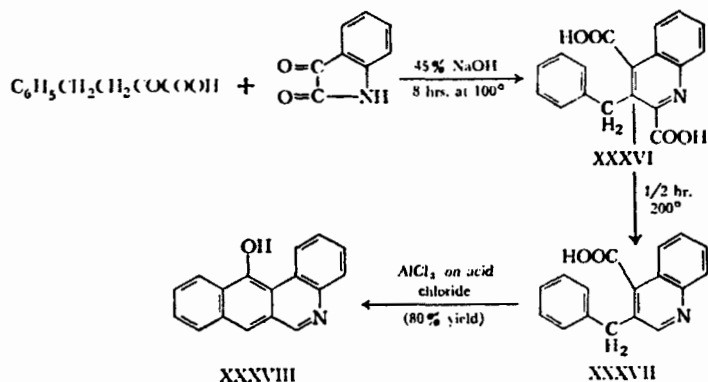


A number of physiological effects produced by 4-azabenz[*a*]anthracene have been investigated. Although both Joseph⁷⁸ and Shear and Leiter⁷⁹ reported that carcinoma did not occur with either skin paintings or subcutaneous implantations of 4-azabenz[*a*]anthracene in mice, Sempronj and Morelli^{80,81} reported that kidney tumors or cystic nephritis were produced after subcutaneous injections of the same compound in rats over a period of eleven months. Jahn,⁸² however, found that no carcinogenic action was exerted on the kidneys of rats, and suggested that the results of Sempronj and Morelli may have been caused by the hereditary disposition of the animals employed. 3-Phenyl-4-azabenz[*a*]anthracene (XXXII) is reported to have a marked action in increasing uric acid elimination.⁸³

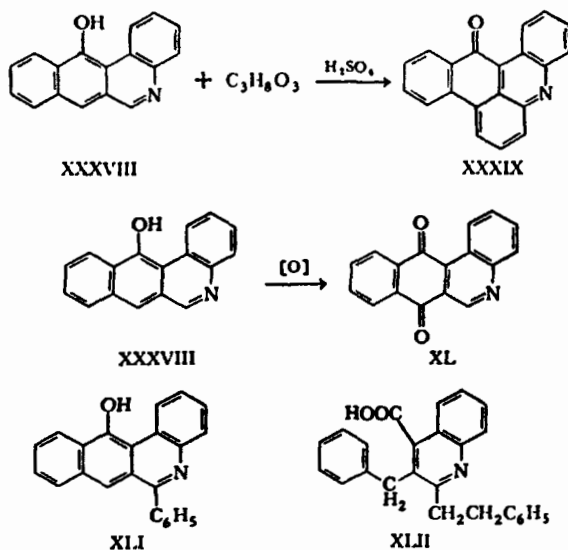
C. 5-Azabenz[*a*]anthracene, Benzo[*j*]phenanthridine, 1,2-Benzo-3-azaanthracene. R.I. 2734



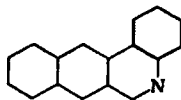
The 5-azabenz[*a*]anthracenes which have been prepared are mainly the 12-hydroxy derivatives. 12-Hydroxy-5-azabenz[*a*]anthracene (XXXVIII) is synthesized by the following series of reactions⁸⁴: benzylpyruvic acid is condensed with isatin in the presence of alkali to form 3-benzylquinoline-2,4-dicarboxylic acid (XXXVI) which, on heating, loses the carboxyl group adjacent to the nitrogen, yielding 3-benzylcinchoninic acid (XXXVII); the acid chloride of the latter is cyclized by aluminum chloride to 12-hydroxy-5-azabenz[*a*]anthracene (see XXXVIII) in 80% yield. Only a 27% yield was obtained when sulfuric acid was used as the cyclizing agent. The product (XXXVIII)

II. Azabenz[*a*]anthracenes

is a brownish-yellow, high-melting powder, which forms both an acetyl derivative and an oxime. When treated with glycerin and sulfuric acid, a benzanthrone (XXXIX) is formed. Although reduction of XXXVIII with hydrazine hydrate gave no definite products, acidified sodium dichromate oxidizes the anthrol to the corresponding anthraquinone (XL) which may be reductively acetylated to the 7,12-diacetyl derivative.



12-Hydroxy-6-phenyl-5-azabenz[*a*]anthracene (XLI) is prepared by a series of reactions entirely analogous to those used in the synthesis of XXXVIII with ω -benzylacetophenone as the starting material.⁵⁸ The product is a red-brown powder, which forms an acetyl derivative but does not react with 2,4-dinitrophenylhydrazine. Sulfonation of the anthrol

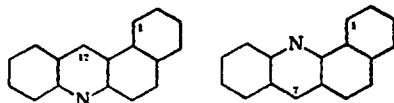
TABLE 9. 5-Azabenz[*a*]anthracenes

Formula	Compound	Ref.	M.p., °C.	Color	Properties
XXXVIII	12-Hydroxy-5-azabenz[<i>a</i>]anthracene	84	"high melting"	Br-Y	O-Ac, m.p. 177–178°; oxime, m.p. 277–278°; P, m.p. 248–249°
XLI	12-Hydroxy-6-phenyl-5-azabenz[<i>a</i>]anthracene	85	265	R-Br	Ac, m.p. 197°; P, m.p. 234°
	12-Hydroxy-6-phenyl-5-azabenz[<i>a</i>]anthracene- <i>x</i> -sulfonic acid	85	>360	R	—
XL	5-Azabenz[<i>a</i>]anthraquinone	84	186	Y	7,12-di-O-Ac, m.p. 267°

with concentrated sulfuric acid produces a red powder whose analysis indicates that it is a monosulfonic acid.

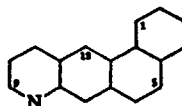
When an attempt was made to cyclize 3-benzyl-2-phenylethyl-cinchoninic acid (XLII) with phosphoryl chloride, a chlorine-containing product was obtained. Cyclization with aluminum chloride gave only an amorphous product, ring closure with sulfuric acid produced sulfonation, and phosphorus pentoxide was unreactive toward this compound.

The 7-azabenz[*a*]anthracenes and 12-azabenz[*a*]anthracenes:



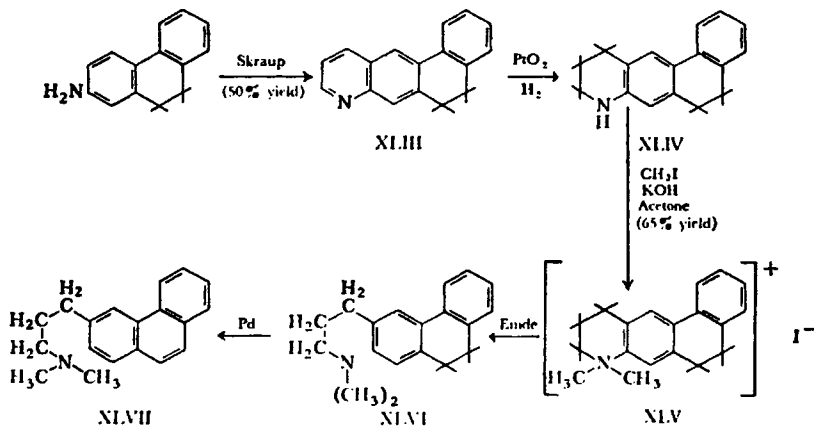
are not described here, but are left for the volume on *Acridine*.

D. 8-Azabenz[*a*]anthracene, Naphtho[1,2-*g*]-quinoline. R.I. 2736

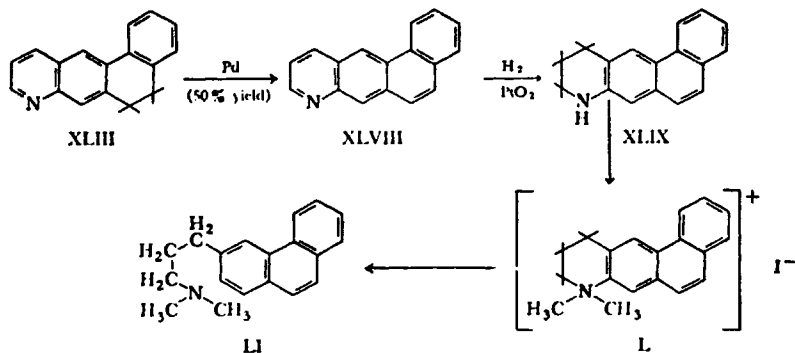


Mosettig and Krueger⁸⁶ synthesized the first 8-azabenz[*a*]anthracene derivatives. When the Skraup reaction is applied to 2-amino-9,10-dihydrophenanthrene, a dihydronaphthoquinoline (XLIH) is obtained in 50% yield. Hydrogenation of this compound, using Adams' platinum catalyst, gives a hexahydro derivative (XLIV) which is converted to the methiodide of the *N*-methyl derivative (XLV). The latter compound, after Emde⁸⁷ degradation, gives a 3-[3'-(dimethylamino)-*n*-propyl]-9,10-dihydrophenanthrene (XLVI). This amine may be dehydro-

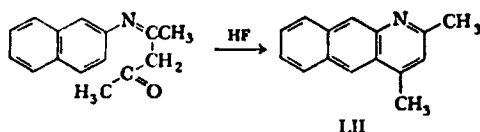
genated to a compound identical with a synthetic sample of 3-[3'-(dimethylamino)-*n*-propyl]-phenanthrene (XLVII), thus establishing the structure of XLIII as 5,6-dihydro-8-azabenz[*a*]anthracene. This direction of ring closure is in contrast to that observed when 2-aminophenanthrene undergoes the Skraup reaction to form 1-azachrysene (page 51).



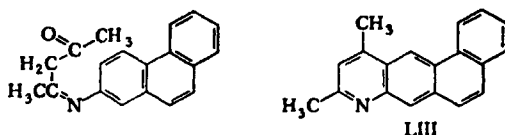
5,6-Dihydro-8-azabenz[*a*]anthracene (XLIII) can be dehydrogenated by palladium, and the resulting 8-azabenz[*a*]anthracene (XLVIII) hydrogenated with platinum oxide catalyst to a tetrahydro derivative (XLIX). The methiodide (L) of the *N*-methyltetrahydro derivative also gives a compound identical with a synthetic sample of 3-[3'-(dimethylamino)-*n*-propyl]phenanthrene (LI).



After it had been shown⁸⁸ that 4-(2-naphthylimino)-pentan-2-one is cyclized by hydrogen fluoride in almost quantitative yield to the linear compound 2,4-dimethyl-1-azaanthracene (LII), Johnson, Woroch, and Mathews⁸⁹ prepared the corresponding anil from 2-aminophenanthrene and cyclized it with hydrogen fluoride. Since the absorption spectrum



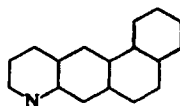
of the product closely resembles that of benz[a]anthracene and is quite different from that of 1-azachrysene, and since the hydrochloride of the base has the intense yellow color characteristic of linear azaanthracenes, the product is assumed to be 9,11-dimethyl-8-azabenz[a]anthracene (LIII).



It has been suggested⁸⁹ that this abnormal cyclization of the anil into the 3-position may be caused by the deactivating influence of the anil side chain in the presence of the acid catalyst. Since hydrogen fluoride apparently effects linear cyclization almost exclusively, it is probable that other substituted 8-azabenz[a]anthracenes will be synthesized by this method.

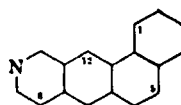
8-Azabenz[a]anthracene and its 5,6-dihydro and 5,6,8,9,10,11-hexahydro derivatives are white, while the 8,9,10,11-tetrahydro and 9,11-dimethyl compounds are pale yellow. All the 8-azabenz[a]anthracenes form bright yellow hydrochlorides and the 9,11-dimethyl derivative exhibits a blue fluorescence in dilute alcohol.

TABLE 10. 8-Azabenz[a]anthracenes

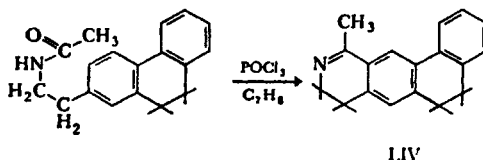


Formula	Compound	Ref.	M.p., °C.	Color	Properties
XLVIII	8-Azabenz[a]anthracene	86	159–160	W	HCl, m.p. 280–295°
XLIII	5,6-Dihydro-8-azabenz- [a]anthracene	86	72–74	W	HCl, m.p. 258–262°
XLIX	8,9,10,11-Tetrahydro-8- azabenz[a]anthracene	86	Oil	W	MeI of N-Me deriv., m.p. 203–205°
XLIV	5,6,8,9,10,11-Hexahydro- 8-azabenz[a]anthra- cene	86	72–73	C	HCl, m.p. 240–244°; MeI of N-Me deriv., m.p. 196–200° (dec.)
LIII	9,11-Dimethyl-8-azabenz- [a]anthracene	89	211–212	Y	P, m.p. 288–289°; max. and (log <i>E</i>) for abs.: 2220 (4.58), 2505 (4.59), 2790 (4.81), 2890 (4.88), 3325 (3.80), 3455 (3.81), 3625 (3.76), 3820 (3.56)

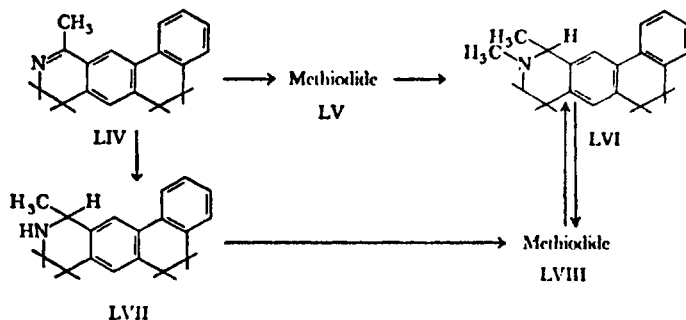
E. 10-Azabenz[*a*]anthracene, Naphtho[2,1-*g*]-isoquinoline



Stuart and Mosettig⁹⁰ tried various ways of cyclizing 2-(2'-aminoethyl)-9,10-dihydrophenanthrene: the Decker and Becker method of cyclizing the formaldehyde condensation product was unsuccessful, as was the Bischler and Napieralski ring closure of the formyl derivative with phosphorus pentoxide. However, phosphoryl chloride in boiling toluene proved to be effective in cyclization of the *N*-acetyl derivative. As only a limited quantity of the final product was available, its structure was not determined; by analogy with the product obtained from 2-amino-9,10-dihydrophenanthrene *via* the Skraup reaction it was assumed to be 11-methyl-5,6,8,9-tetrahydro-10-azabenz[*a*]anthracene (LIV).

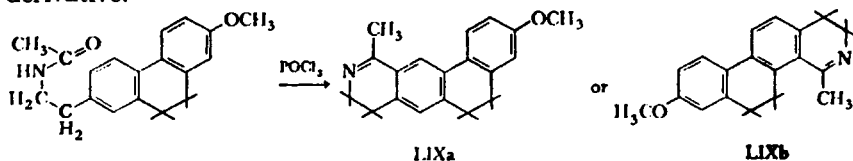
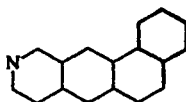


The tetrahydro base (LIV) was converted to its methiodide and then to the 10,11-dimethyl-5,6,8,9,10,11-hexahydro base (LVI); or to the monomethylhexahydro base (LVII), and to its methiodide; and finally to the same 10,11-dimethyl-5,6,8,9,10,11-hexahydro base (LVI).



Since no other substituted 9,10-dihydrophenanthrenes have been subjected to ring closure under similar conditions, it is impossible to predict the course of such a reaction. However, the product prepared from the acetyl derivative of 2-(2'-aminoethyl)-7-methoxy-9,10-dihydrophenanthrene is assumed to have a configuration (LIXa), analogous to that of the unsubstituted derivative, although the structure LIXb cannot

be discounted. Insufficient material was obtained to prove the structure. The base may be converted to the corresponding hexahydro derivative.

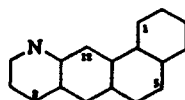
TABLE 11. 10-Azabenz[*a*]anthracenes

Formula	Compound	Ref.	M.p., °C.	Color	Properties
LIV	11-Methyl-5,6,8,9-tetrahydro-10-azabenz[<i>a</i>]anthracene	90	Oil	—	HCl, m.p. 230–232°; MeI, m.p. 267–268°
LVII	11-Methyl-5,6,8,9,10,11-hexahydro-10-azabenz[<i>a</i>]anthracene	90	—	—	HCl, m.p. 239–241°; *MeI, m.p. 231°
LVI	10,11-Dimethyl-5,6,8,9,10,11-hexahydro-10-azabenz[<i>a</i>]anthracene	90	Oil	—	HCl, m.p. 234–236°; *MeI, m.p. 231°
LIXa	3-Methoxy-11-methyl-5,6,8,9-tetrahydro-10-azabenz[<i>a</i>]anthracene	90	—	—	HCl, m.p. 249–250°; MeI, m.p. 287–288°
	3-Methoxy-11-methyl-5,6,8,9,10,11-hexahydro-10-azabenz[<i>a</i>]anthracene	90	—	—	HCl, m.p. 261–263°; **MeI, m.p. 256–258°
	3-Methoxy-10,11-dimethyl-5,6,8,9,10,11-hexahydro-10-azabenz[<i>a</i>]anthracene	90	97–98	—	HCl, m.p. 200–202°; HI, m.p. 236–238°; **MeI, m.p. 256–258°

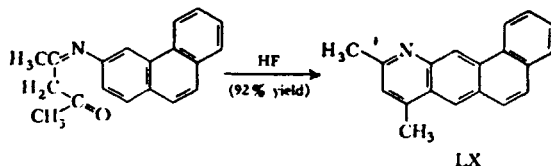
* Identical.

** Identical.

F. 11-Azabenz[*a*]anthracene, Naphtho[2,1-*g*]-quinoline

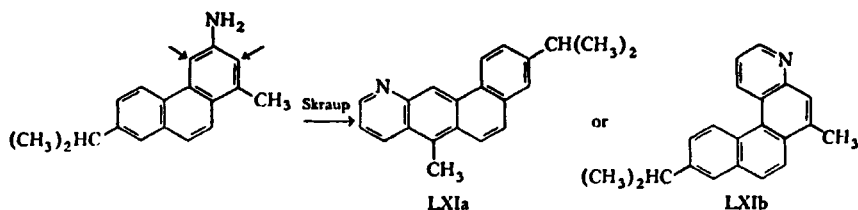


The only 11-azabenz[*a*]anthracene reported was synthesized by Johnson, Woroch, and Mathews⁸⁹ from the anil of 3-aminophenanthrene and acetylacetone by cyclization with hydrogen fluoride. The reasons for assuming a linear rather than an angular cyclization have already been discussed (Sect. 1, D). The product, 8,10-dimethyl-11-azabenz[*a*]-an-



thracene (see LX), is obtained as yellow needles which exhibit a blue fluorescence in dilute alcoholic solution and produce an intense yellow color with dilute hydrochloric acid.

A compound which may have the basic structure of either an 11-azabenz[*a*]anthracene or a 4-azabenz[*c*]phenanthrene was prepared by Cassaday and Bogert⁹¹ by the Skraup reaction on 3-aminoretene. Although it has been shown⁹² that 3-retolylpropionic acid cyclizes through



the 2- rather than the 4-position (thus producing a benz[*a*]anthracene), a closer analogy with the reaction above is a Skraup synthesis with 3-aminophenanthrene which has been proved to give 4-azabenz[*c*]phenanthrene.⁹³ The structure of the product obtained by Cassaday and Bogert⁹¹ was not definitely established, although they favored the 10-

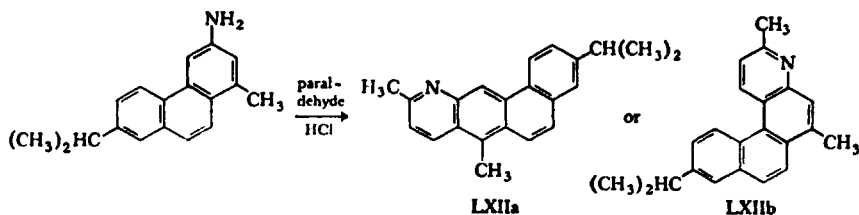
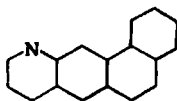


TABLE 12. 11-Azabenz[*a*]anthracenes*



Formula	Compound	Ref.	M. p., °C.	Color	Properties
LX	8,10-Dimethyl-11-azabenz[<i>a</i>]anthracene	89	135-136	Y	P, m. p. 305-307°; B fluorescence in dil. EtOH; max. and (log <i>E</i>) for abs.: 2195 (4.68), 2775 (4.91), 2885 (4.98), 3330 (3.82), 3480 (3.78), 3660 (3.72), 3845 (3.63)

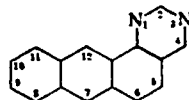
* See also the Table 25 of 4-azabenz[*c*]phenanthrene derivatives; the 10-isopropyl-6-methyl-4-azabenz[*c*]phenanthrene and 10-isopropyl-3,6-dimethyl-4-azabenz[*c*]phenanthrene listed there may possibly have the structure of 3-isopropyl-7-methyl-11-azabenz[*a*]anthracene and 3-isopropyl-7,10-dimethyl-11-azabenz[*a*]anthracene, respectively.

isopropyl-6-methyl-4-azabenz[o]phenanthrene configuration (LXIb), nor was the fundamental ring system of the compound obtained from 3-aminoretene and paraldehyde by the Doebner-Miller reaction identified, although again the 4-azabenz[o]phenanthrene (LXIIb) seemed more probable to these investigators (see also Ch. III, Sect. 1, C.).

2. Diazabenz[a]anthracenes

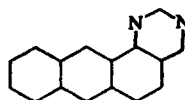
Eleven of the sixty-six possible diazabenz[a]anthracene systems have been synthesized. The 7,12-diazabenz[a]anthracenes are benzophenazines; since the number of derivatives is so great, this ring system is not being discussed in this chapter.

A. 1,3-Diazabenz[a]anthracene, Naphtho[2,3-*h*]quinazoline, 1(*N*),2-Pyrimidinoanthracene. R.I. 2667



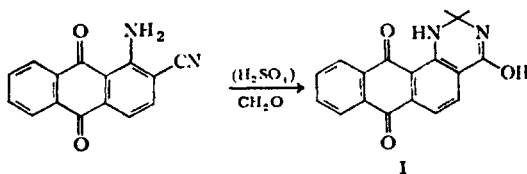
Various substituted 1,3-diazabenz[a]anthraquinones may be prepared by the reaction of aldehydes with 1-amino-2-cyanoanthraquinone⁹⁶; the resulting dihydropyrimidines may be dehydrogenated to the corresponding pyrimidines. For example, 4-hydroxy-1,2-dihydro-1,3-diazabenz[a]anthraquinone (I) is synthesized from 1-amino-2-cyanoanthra-

TABLE 13. Substituted 1,3-Diazabenz[a]anthracenes



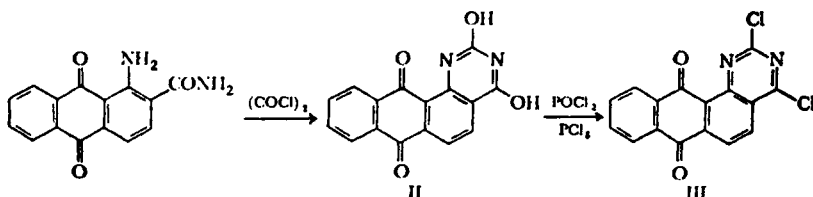
Formula	Position and substituent	Ref.	M.p., °C.	Properties
III	2,4-Dichloro-1,3-diazabenz[a]AQ	96	—	Reacts with 1-aminoanthraquinone to give an orange dye for cotton
IV	4-Chloro-2-phenyl-	96	—	Reacts with 1-amino AQ to give an orange dye for plant fibers
I	4-Hydroxy-1,2-dihydro-	96	300-302	Dyes artificial silk rose
	4-Hydroxy-1-methyl-1,2-dihydro-	96	—	Dyes artificial silk red
	2-Anthraquinonyl-4-hydroxy-	96	—	Dyes artificial silk yellow-brown
II	2-Carboxy-4-hydroxy-1,2-dihydro-	96	216-217	Dyes artificial silk orange-yellow
	4-Keto-3-methyl-1,2-dihydro-	96	—	—
	4-Keto-2,3-diphenyl-	97	288	—
V	6-Nitro-4-keto-2,3-diphenyl-	97	325-327	—
	4-Keto-2-(4'-chlorophenyl)-3-phenyl-	97	—	—

quinone and formaldehyde in the presence of sulfuric acid. The red-brown product is soluble in concentrated sulfuric acid, with a blue color,

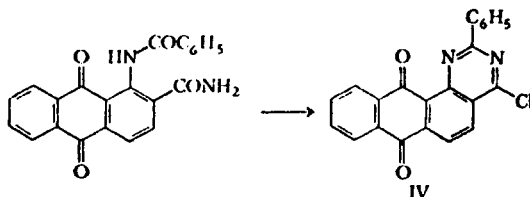


and in caustic soda, with a red-brown color. Artificial silk is dyed rose from a red vat.

When 1-aminoanthraquinone-2-carboxamide is treated with oxalyl chloride, 2,4-dihydroxy-1,3-diazabenz[*a*]anthraquinone (II) is produced; the latter may be converted to the 2,4-dichloro compound (III) by phos-

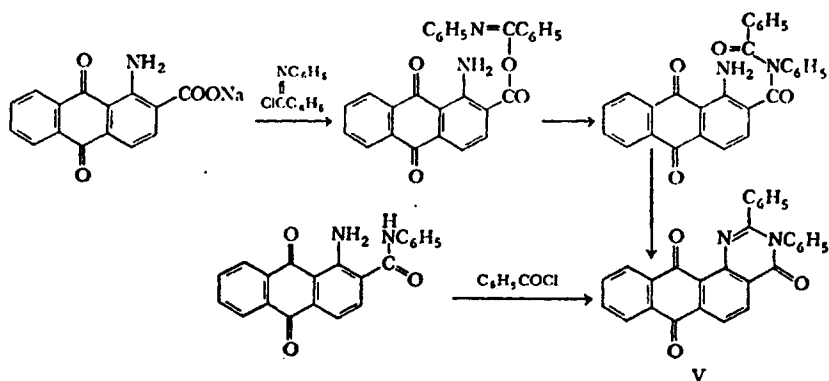


phoryl chloride and phosphorus pentachloride. Analogously, 1-benzoylaminoanthraquinone-2-carboxamide, when treated with thionyl chloride, gives 2-phenyl-4-chloro-1,3-diazabenz[*a*]anthraquinone (IV), which yields an orange dye with 1-amino-5-benzoylaminoanthraquinone.

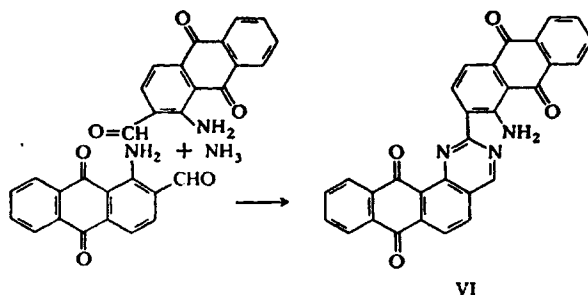


The properties of some other dyes of this series are summarized in Table 13 (page 91).

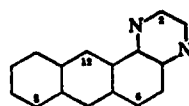
2,3-Diarylated derivatives (V) have been prepared by the action of benzanilide imide chloride on an ether suspension of sodium 1-aminoanthraquinone-2-carboxylate.⁹⁷ The mechanism suggested involves a rearrangement. Proof of structure was afforded by the independent synthesis shown.



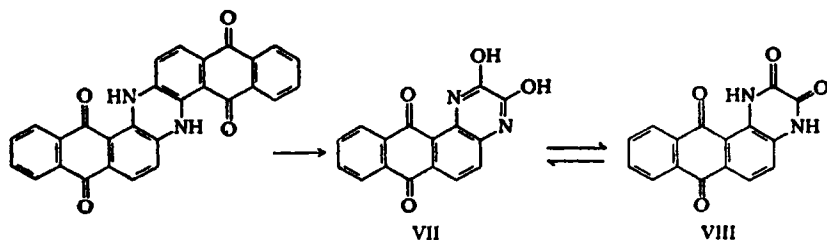
Finally, a 2-anthraquinonyl derivative (VI) was obtained by the interaction of two moles of 1-amino-2-formylantraquinone and ammonia.⁹⁷



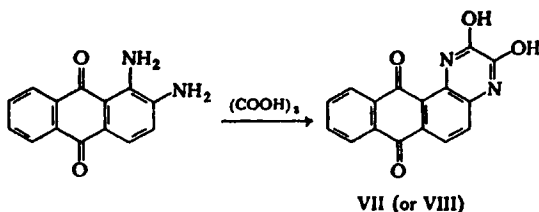
B. 1,4-Diazabenz[*a*]anthracene, Naphtho[2,3-*f*]quinoxaline, 1,2-Pyrazinoanthracene, α,β -Anthraquinoxaline. R.I. 2668



The first compound of this series to be prepared was reported by Scholl and Edlbacher,⁹⁸ who obtained it by chromic acid oxidation of indanthrene. After the removal of insoluble material, a product to



which structure VII was assigned was obtained from the acid solution on cooling. In order to confirm their conclusions as to the structure of the degradation product, 2,3-dihydroxy-1,4-diazabenz[*a*]anthraquinone (VII) was synthesized from 1,2-diaminoanthraquinone and anhydrous oxalic acid. This compound was found to be identical in all respects with that obtained from indanthrene on oxidation. The dihydroxy derivative was subsequently prepared on a commercial scale using oxalyl chloride.⁹⁹



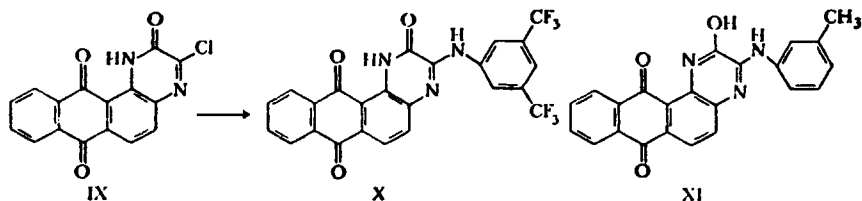
The product obtained by the reaction of 1,2-diaminoanthraquinone and ethyl oxalate was first reported to be 2,3-diethoxy-1,4-diazabenz[*a*]anthraquinone¹⁰⁰; however, when this work was repeated by Ertl,¹⁰¹ the product was proved to be the 2,3-dihydroxy compound previously described by Scholl and Edlbacher.⁹⁸

2,3-Dihydroxy-1,4-diazabenz[*a*]anthraquinone is a high-melting, yellow, very weakly basic compound which is insoluble in concentrated hydrochloric acid but soluble in concentrated sulfuric acid, forming a red solution. A brick-red, difficultly soluble disodium salt is produced with either sodium hydroxide or sodium ethoxide. Although the dihydroxy compound gives a red-brown vat with alkaline sodium hydrosulfite, the dye shows little affinity for unmordanted plant fibers. Zinc dust distillation of VII gave a brown product, whose benzene solution showed a strong blue fluorescence and which was assumed to be 1,4-diazabenz[*a*]anthracene, although too small a yield was obtained for positive identification.

Although 2,3-dihydroxy-1,4-diazabenz[*a*]anthraquinone is not affected by boiling sulfuric acid or by heating with excess bromine, a yellow mononitro derivative is formed when it is treated with concentrated nitric acid at room temperature. This compound also yields a red, difficultly soluble sodium salt. Reduction of the nitro compound with ammonium sulfide produces a violet amino compound which is difficultly soluble in sodium hydroxide but which gives a yellow solution in sulfuric acid.

One or both of the hydroxy groups of VII are readily replaceable by chlorine by means of phosphorus pentachloride, and the chlorine atoms

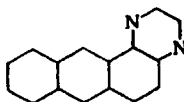
are then available for reactions of double decomposition. Various dyes have been described in which primary or secondary aromatic amines have been introduced into the molecule. For instance, the use of 3,5-ditrifluoromethylaniline on the monochloro derivative (IX) is said to give a greenish-yellow vat dye (X) of excellent fastness to light and chlorine; no proof of structures or properties are given.⁹⁸



The replacement of one of the hydroxy groups of 2,3-dihydroxy-1,4-diazabenz[a]anthraquinone by an aromatic amino group is described in a British patent.¹⁰² For example, when VII is heated with *m*-toluidine in the presence of nitrobenzene and boric acid, 2- (or 3-) hydroxy-3- (or 2-) *m*-toluidino-1,4-diazabenz[a]anthraquinone is formed. This dye is probably Indanthrene Brilliant Scarlet RK (XI).¹⁰³

A French patent¹⁰⁴ describes the synthesis of various dyes from 2,3-dichloro-1,4-diazabenz[a]anthraquinone; these are prepared by first heating the corresponding dihydroxy compound (VII) with phosphorus pentachloride, followed by treatment with primary or secondary aromatic amines. The 2,3-dianilino derivative, for example, is reported to dye cotton fast bluish-red shades.

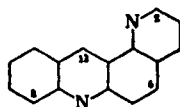
TABLE 14. 1,4-Diazabenz[a]anthraquinones



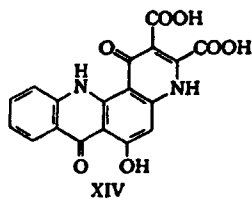
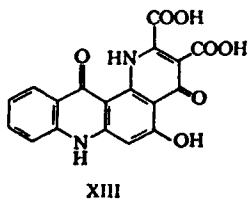
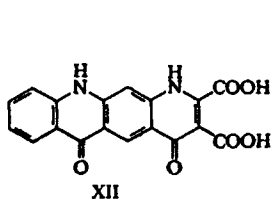
Position and substituent	Ref.	M.p., °C.	Color
1,4-Diazabenz[a]AQ	98	—	Brown
2,3-Diphenyl-	100	282–283	Yellow
2,3-Dianilino-	104	—	—
*2,3-Dihydroxy-	98,101	subl. 300 chars 370	Yellow
2,3-Dihydroxy- <i>x</i> -nitro-	98	—	Yellow
<i>x</i> -Amino-2,3-dihydroxy-	98	ca. 365	Violet

* First reported¹⁰⁰ erroneously as 2,3-diethoxy-.

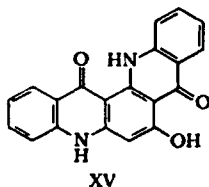
C. 1,7-Diazabenz[*a*]anthracene, Pyrid[2,3-*a*]acridine, Benzo-*m*-phenanthroline. R.I. 2698



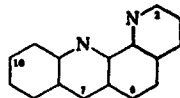
Only one compound which may have the basic structure of a 1,7-diazabenz[*a*]anthracene has been reported in the literature; although the actual configuration of this compound is uncertain, it is included for the sake of completeness. The product prepared from phloroglucinol and *o*-aminobenzaldehyde—the so-called “hydroxyquinacridone”—when oxidized with dilute nitric acid, gives a very small yield of a compound which shows reactions characteristic of an *o*-dicarboxylic acid.¹⁰⁵ This acid may have any one of formulas XII–XIV. Since these



investigators suggest that the “hydroxyquinacridone” is most probably represented by XV, structure XII is ruled out for the acid. The yellow acid melts with decomposition at 283°, is difficultly soluble in neutral organic solvents, but readily forms a yellow solution with ammonia, alkalis, and dilute mineral acids.



D. 1,12-Diazabenz[*a*]anthracene, Benzo[*b*]1,10-phenanthroline, 1,2,2',3'-Pyridinoacridine, Pyrid[3,2-*c*]acridine



Nearly all the known derivatives of this ring system were prepared in connection with the antimalarial program. The same general synthesis^{106–108} was employed, which consisted of cyclization of the appropriately substituted quinolyanthranilic acid. With phosphoryl chloride, a 7-chloro-1,12-diazabenz[*a*]anthracene (XVI) resulted, whereas the use of concentrated sulfuric acid gave a less useful acridone type (XVII and XVIII). The acridone can be converted to the 7-chloro derivative by phosphoryl chloride.¹⁰⁷

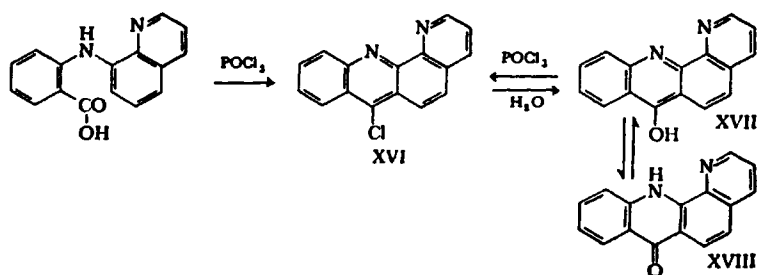
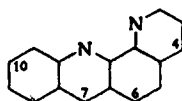


TABLE 15. 1,12-Diazabenz[a]anthracenes

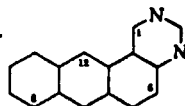


Position and substituent*			Ref.	M.p. or b.p., °C.	Properties of derivatives
6	7	10			
—	Cl	—	106,108	164;165	—
—	Cl	—	106,107	238;222–225	—
OCH ₃	Cl	—	106,108	169	—
OCH ₃	Cl	Cl	106	196–197	—
—	R	—	106	196	—
—	R'	—	106	Oil	Picrate, m.p. 196°
—	R'	Cl	106	118	—
—	R	Cl	106	131	—
OCH ₃	R	—	106	Oil	Picrate, m.p. 118°
OCH ₃	R'	—	106	Oil	Picrate, m.p. 201°
OCH ₃	R	Cl	106	152	—
OCH ₃	R''	Cl	106	Oil	Picrate, m.p. 158–159°
F	Cl	—	108	207–208	—
F	OCH ₃	—	108	184	—
F	NH ₂	—	108	297–298	Diacetyl deriv., m.p. 227–228°
—	OCH ₃	—	108	167–168	—
—	NH ₂	—	108	252	Diacetyl deriv., m.p. 191–192°
OCH ₃	OCH ₃	—	108	205	—
OCH ₃	NH ₂	—	108	220	Diacetyl deriv., m.p. 255–256°
—	OH	Cl	107	—	—
—	R*	Cl	107	Oil	Dipicrate, m.p. 213–216°
—	OH	—	106	275–276	—
—	OH	Cl	106,107	311;315–320	—
OCH ₃	OH	—	106	245.5	—
OCH ₃	OH	Cl	106	257–258	—

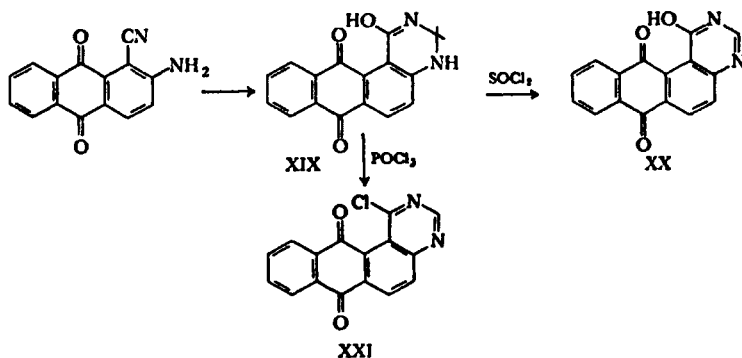
* R = 2-Diethylaminoethylamino; —NH(CH₂)₂N(C₂H₅)₂.R' = 1-Methyl-4-diethylaminobutylamino; —NHCHCH₂(CH₂)₃N(C₂H₅)₂.R'' = 3-Diethylaminopropylamino; —NH(CH₂)₃N(C₂H₅)₂.

The chlorine in position 7 can be readily replaced by OH (hydrolysis in neutral or acid solution); OCH_3 (sodium methoxide); alkyl-NH (the appropriate amine in boiling phenol). The monohydrochloride of the 7-amine results when the 7-methoxy derivative is heated with ammonium chloride in alcohol; the free base is liberated by sodium hydroxide. The properties of the 1,12-diazabenz[a]anthracenes are collected in Table 15. They are all yellowish in color, and many exhibit fluorescence in solution. They form monohydrochlorides in most instances; there is one unstable dihydrochloride described.¹⁰⁸ None of the bases in this series, when tested biologically, showed any antimalarial activity.

E. 2,4-Diazabenz[a]anthracene, Naphtho[2,3-*f*]quinazoline, 2(*N*),1-Pyrimidinoanthracene. R.I. 2669

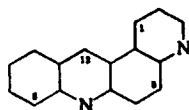


2,4-Diazabenz[a]anthraquinones may be prepared in a manner analogous to that employed in the synthesis of 1,3-diazabenz[a]anthraquinones: the condensation of 1-cyano-2-aminoanthraquinone with an aldehyde.¹⁰⁹ The resulting dihydro compound is dehydrogenated by warming with thionyl chloride. For example, when formaldehyde is used, 1-hydroxy-3,4-dihydro-2,4-diazabenz[a]anthraquinone (XIX) is formed and may be dehydrogenated to 1-hydroxy-2,4-diazabenz[a]anthraquinone (XX). 1-Chloro-2,4-diazabenz[a]anthraquinone (XXI) is prepared by heating 1-hydroxy-3,4-dihydro-2,4-diazabenz[a]anthraquinone with phosphoryl chloride.

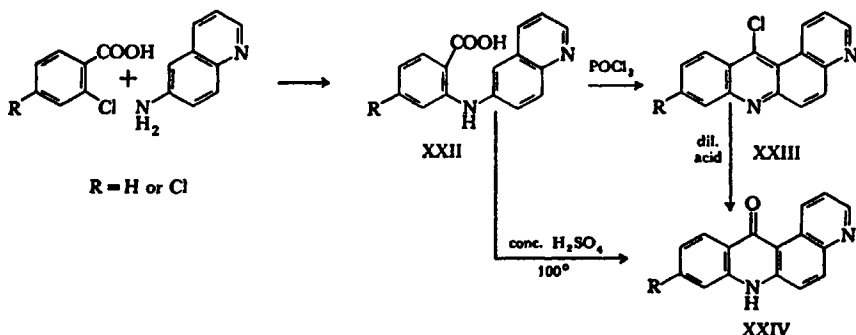


These compounds are not characterized other than as forming red-brown vats. 1-Hydroxy-3,4-dihydro-2,4-diazabenz[a]anthraquinone (XIX) dyes artificial silk a vivid yellow.

F. 4,7-Diazabenz[*a*]anthracene, Benzo[*b*]4,7-phenanthroline, 3,4,2',3'-Pyridoacridine



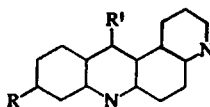
Several 4,7-diazabenz[*a*]anthracenes were synthesized by a method similar to that used for the preparation of 1,12-diazabenz[*a*]anthracenes. The condensation of a 6-aminoquinoline with an *o*-chlorobenzoic acid, followed by treatment of the resulting 6-(2'-carboxyphenylamino)-quinoline (XXII) with phosphoryl chloride, produces a 12-chloro-4,7-diazabenz[*a*]anthracene (XXIII), which may be converted to the corresponding 12-keto compound (XXIV) by heating with dilute mineral acid.



The same 12-keto compound is formed when XXII is heated with concentrated sulfuric acid at 100° .¹⁰⁶

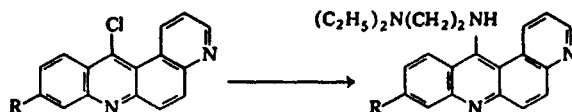
These substances resemble the corresponding 1,12-diazabenz[*a*]anthracenes; the 12-chloro derivatives (XXIII) are yellow solids soluble in dilute acid and insoluble in dilute alkali. 9,12-Dichloro-4,7-diazabenz[*a*]anthracene shows a green fluorescence in alcohol and benzene solutions. These compounds are unchanged after heating with dilute sodium hydroxide, although they are very readily hydrolyzed to the 12-keto compounds on treatment with hot dilute acid, or even on boiling with neutral solvents which contain a trace of water. The 12-keto-4,7-diazabenz[*a*]anthracenes (XXIV; $R = H \text{ or } Cl$) are high-melting light-brown solids, which are very soluble in concentrated sulfuric acid, in which the 9-chloro derivative exhibits a green fluorescence. The latter is only very slightly soluble in dilute acid and is insoluble in dilute alkali. The properties of the 4,7-diazabenz[*a*]anthracenes are collected in Table 16.

The 12-(diethylaminoalkylamino)-4,7-diazabenz[*a*]anthracenes, which are prepared by heating the diethylaminoalkylamine with the 12-chloro compound in phenol solution, are yellow. These amino-

TABLE 16. 4,7-Diazabenz[*a*]anthracenes¹⁰⁶

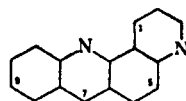
Position and substituent		M.p., °C.	Properties of derivatives
9 (R)	12 (R')		
—	Cl	181.5–182	—
Cl	Cl	219	—
—	OH	360	HCl, m.p. >360°
Cl	OH	298	HCl, m.p. 386–387°
Cl	OC ₄ H ₉	218	—
—	2'-diethylaminoethylamino-	92	—
—	4'-diethylamino-1'-methyl-butylamino-	Oil	Picrate, m.p. 120°
Cl	2'-diethylaminoethylamino-	127	—
Cl	3'-diethylaminopropyl-amino-	119.5–120	—
Cl	4'-diethylamino-1'-methyl-butylamino-	Oil	Acetate, m.p. 76–78°; tripicrate, m.p. 216°
Cl	3'-dimethylaminopropyl-amino-	127	—
Cl	3'-Butylaminopropylamino-	78	—
Cl	3'-diethylaminobutylamino-	Oil	Picrate, m.p. 168°; 3,5-dinitrobenzoate, m.p. 233°

4,7-diazabenz[*a*]anthracenes all showed a definite antimalarial activity when tested on *P. gallinaceum* infections of chicks, the action being par-

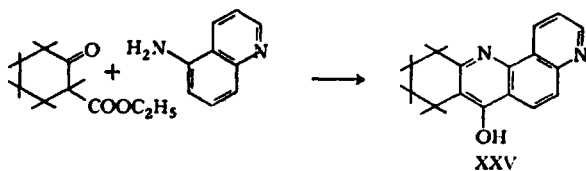


ticularly pronounced in the case of the 9-chloro compounds. This is interesting in view of the inactivity of the corresponding 1,12-diazabenz[*a*]anthracenes (see page 98).

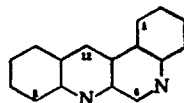
G. 4,12-Diazabenz[*a*]anthracene, Benzo[*b*][1,7]-phenanthroline, 8,9-Benzo-4,10-phenanthroline. R.I. 2699



The only compound of this group which has been synthesized is prepared by heating 5-aminoquinoline and ethyl 2-cyclohexanonecarboxylate and pouring the resulting mixture into paraffin oil preheated to 280°. ¹¹⁰ The purified product, isolated as colorless rhombs decomposing at 250° but not completely melted below 300°, is apparently 7-hydroxy-8,9,10,11-tetrahydro-4,12-diazabenz[*a*]anthracene (XXV). It was impossible to isolate any similar product from 8-aminoquinoline and ethyl 2-cyclohexanonecarboxylate.



H. 5,7-Diazabenz[*a*]anthracene, Quino[3,4-*b*]-quinoline. R.I. 2700

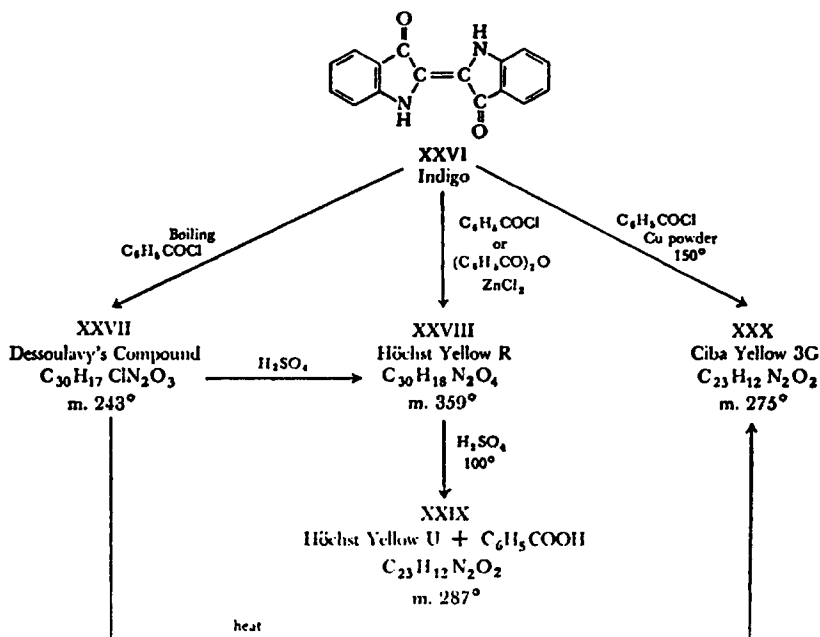


The structures of three related dyes, Ciba Yellow 3G (*Colour Index No. 1195*), Höchst Yellow R, and Höchst Yellow U, prepared by benzylation of indigo, have not been conclusively determined as yet in spite of considerable experimental work on the problem.¹¹¹ Although hydrolysis of these dyes gives products which may fall into any one of four basic four ring systems (the 5,12-diazanaphthacene,* the 5,12-diazabenz[*a*]anthracene, the 5,7-diazabenz[*a*]anthracene, and the 6,12-diazabenz[*a*]anthracene) the different possibilities will be discussed together in a single section. (No attempt has been made to review the extensive literature pertaining to these dyes since only the hydrolysis products fall within the scope of this volume. Reference has been made, however, to most of the important and comprehensive articles on the subject.)

The treatment of indigo with benzoyl chloride under different reaction conditions gives a number of different products. Some of these are included in the flow-sheet on page 102.

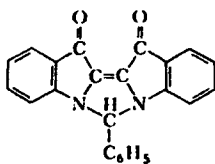
De Diesbach, Jacobi, and Teddei¹¹² arranged the benzylation products in four principal groups. The first and second contain compounds in which the indigo structure is unchanged, but the second includes those products in which a new fused ring has been introduced. Group A comprises dibenzoyl-¹¹³ and tetrabenzoylindigo¹¹⁴ and their derivatives. Dessoulavy's compound (XXVII) and its derivatives, as formulated by these workers,¹¹² are placed in group B. Those compounds in which a nucleus different from that of indigo has been established are found in groups C and D and are differentiated according to the nature of their alkaline fusion products. Höchst Yellow R (XXVIII) and U (XXIX), which yield anthranilic acid and 2-(2'-carboxyphenyl)-quinoline, are in C, and Ciba Yellow 3G, which gives phthalic acid and an indoloquinoline, is in D. Although not all of the experimental evidence reported by other investigators supports this classification, it is useful in organizing the material available. Since the most extensive work has been done with Ciba Yellow 3G, it will be discussed first.

* A brief discussion of this ring system may be found in Chapter I, Section 2, G.

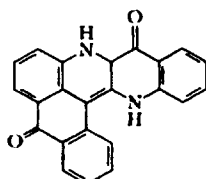
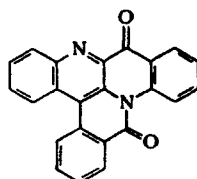


(1) Ciba Yellow 3G

Ciba Yellow 3G was thought to analyze for $\text{C}_{23}\text{H}_{14}\text{N}_2\text{O}_2$, and was assigned the structure shown in XXXa by Engi.¹¹⁵ This conclusion was revised by Posner and Hofmeister,¹¹⁸ who suggested XXXb as the correct structure the empirical formula, $\text{C}_{23}\text{H}_{12}\text{N}_2\text{O}_2$, having two fewer atoms of hydrogen. They postulated direct substitution of a benzoyl group, followed by ring closure and rearrangement of the molecule to an anthraquinone derivative to explain the formation of XXXb. The structure XXXb has been excluded by its recent synthesis.¹¹⁶ The properties of the synthetic product are entirely different from those of Ciba Yellow 3G. Hope and Richter¹¹⁷ concluded that the structure of the dye was that shown in XXXc.

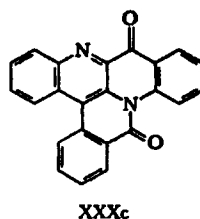
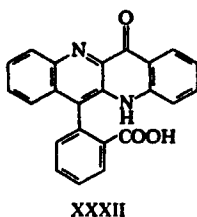
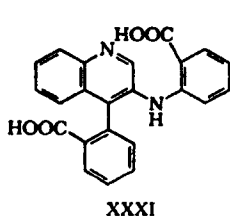


XXXa

XXXb
Ciba Yellow 3G

XXXc

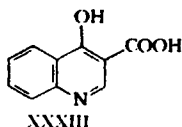
When heated with 15% sodium hydroxide, Ciba Yellow 3G is hydrolyzed to the sodium salt of a carboxylic acid from which the dye can be regenerated by warming in neutral solution. Because Posner and Hofmeister¹¹³ had succeeded in preparing a diethyl derivative of this acid, they assumed that the latter was a dicarboxylic acid, probably XXXI. However, Hope and Richter showed by electrometric titration that the compound contained only one carboxyl group. The reversible hydrolysis of Ciba Yellow suggested to them an amino acid-lactam relationship, such as would exist between XXXII and XXXc. Addi-



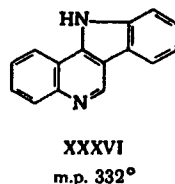
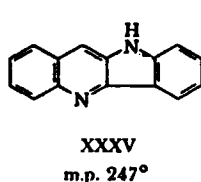
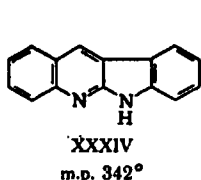
tional evidence for such a structure was obtained by preparing a dimethyl derivative of the acid; on hydrolysis, a monomethylcarboxylic acid, $C_{22}H_{12}NO(NCH_3)COOH$, resulted. Since the second methyl group was not removed by treatment with hydriodic acid, it was assumed to be attached to a nitrogen atom. The fact that ring closure was not effected by heating the monomethyl acid supported the lactam structure for Ciba Yellow. Decarboxylation of this same acid gave a product melting at 168° , which Hope and Richter believed to be 6-phenyl-12-keto-5,11-diazanaphthacene.

De Diesbach and Lempen¹¹⁸ accounted for differences between their alkaline fusion products and those of Hope and Richter's¹¹⁷ alkaline degradation by saying that the latter method did not give homogeneous products. Despite the excellent correspondence between analytical results and proposed formulas reported by de Diesbach and Lempen,¹¹⁸ de Diesbach, de Bie, and Rubli¹¹⁹ reinvestigated the fusion of Ciba Yellow and obtained compounds with significantly different empirical formulas. The two principal nitrogen-containing products were bases, $C_{14}H_{10}N_2O_2$ and $C_{14}H_{10}N_2$; the formula of the latter suggested that it might be an indoloquinoline. On oxidation, decarboxylation, and further oxidation of the base $C_{14}H_{10}N_2$, a 4-hydroxyquinoline-3-carboxylic acid (XXXIII) was obtained. Although no details of its properties were reported its identification apparently was made by mixed melting points "with other

hydroxyquinolinecarboxylic acids." De Diesbach¹¹⁹ concluded that his indoloquinoline was XXXVI rather than XXXIV or XXXV for

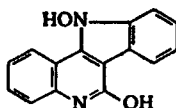


two reasons: neither XXXIV nor XXXV would give XXXIII on degradation, and a mixed melting point of XXXVI and XXXIV, the indoloquinoline whose melting point was nearest that of the product, was 300°. De Diesbach, however, did not consider any indoloquinolines

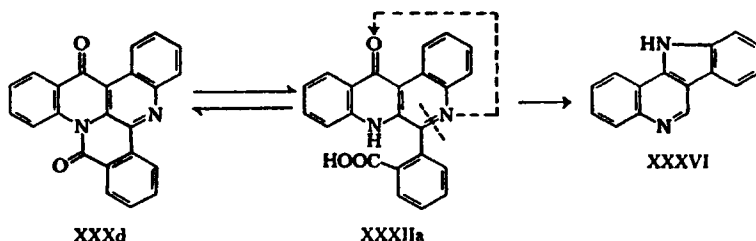


other than XXXIV, XXXV, and XXXVI. If the hydroxyquinoline acid obtained is XXXIII, the only indoloquinoline listed in the *Ring Index* from which it could be derived is XXXVI. Since a straightforward synthesis of XXXVI was reported by Clemo and Perkin¹²⁰ in 1924, ten years earlier, it is surprising that de Diesbach made no reference to it. Unfortunately, neither article gives sufficient information on the properties of the compound to warrant any conclusions as to the identity of the two indoloquinolines.

The base $C_{18}H_{10}N_2O_2$ gave oxalylanthranilic acid (which excluded the possibility of having a hydroxy group substituted in the benzene ring of the quinoline portion of the molecule) on permanganate oxidation, and apparently for this reason the base was concluded to be the dihydroxy-indoloquinoline (XXXVII):

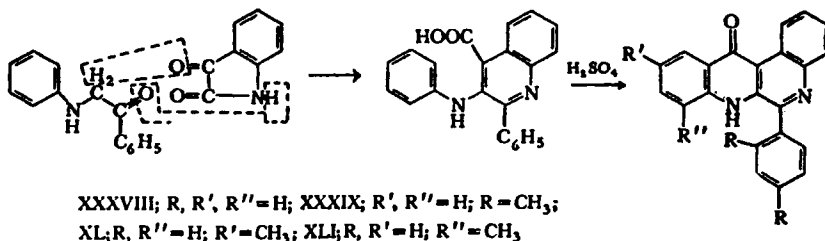


Since phthalic acid was obtained in a quantity equivalent to the indoloquinoline, de Diesbach¹¹⁹ explained the formation of these two compounds from Ciba Yellow by postulating the following series of reactions:

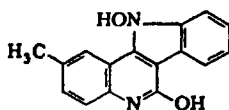


Both acids, XXXIIa, 6-(2'-carboxyphenyl)-12-keto-7*H*,5,7-diazabenz[*a*]anthracene, and XXXII, 6-(2'-carboxyphenyl)-12-keto-5*H*,5,11-diazanaphthacene (Ch. I, Sect. 2, F), account satisfactorily for the reversible hydrolysis of Ciba Yellow, if it has one of the lactam structures, XXXc or XXXd. De Diesbach and Dobbelman¹²¹ proposed a mechanism to account for the rearrangement, cyclization, and oxidation of *N*-benzoyl-indigo to Ciba Yellow 3G.

De Diesbach and Moser¹²² next reported the synthesis of four homologous 5,7-diazabenz[*a*]anthracenes by the following reactions: condensation of isatin with an ω -anilinoacetophenone gives a 2-phenyl-3-anilinoquinoline-4-carboxylic acid, which is cyclized by sulfuric acid to the 12-keto-7*H*,5,7-diazabenz[*a*]anthracene (XXXVIII). On alkaline

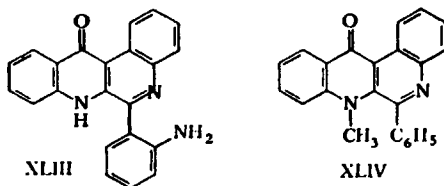


degradation, XXXVIII, 6-phenyl-12-keto-7*H*,5,7-diazabenz[*a*]anthracene, and XXXIX, 6-(2',4'-dimethylphenyl)-12-keto-7*H*,5,7-diazabenz[*a*]anthracene, gave the same dihydroxyindoloquinoline (XXXVII) as did Ciba Yellow, in addition to benzoic acid and 2,4-dimethylbenzoic acid, respectively. XL gave a methylindoloquinoline (XLII):



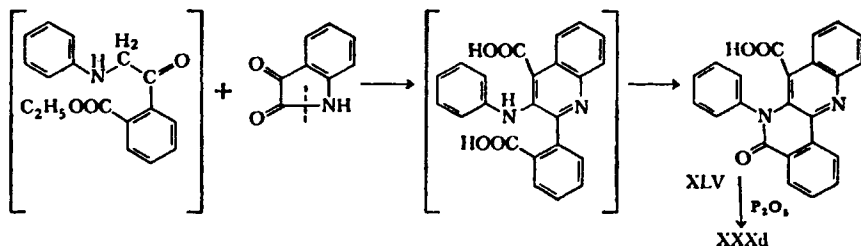
De Diesbach and Klement¹²³ extended this same type of synthesis to compounds more closely related to Ciba Yellow. Although 6-(2'-

aminophenyl)-12-keto-7*H*,5,7-diazabenz[*a*]anthracene (XLIII) may be prepared from *o*-amino- ω -anilinoacetophenone by the sequence of reactions mentioned above (cyclization being effected by phosphorus pentoxide but not by sulfuric acid), attempts to replace the amino group by halogens or a cyano group have been unsatisfactory. The diazonium salt apparently undergoes a ring closure with the imino group. 7-Methyl-12-keto-6-phenyl-5,7-diazabenz[*a*]anthracene (XLIV) is similarly prepared from ω -(*N*-methylanilino)-acetophenone and isatin *via* 2-phenyl-3-(*N*-methylanilino)-quinolinc-4-carboxylic acid. When 70% sulfuric acid is used as the cyclizing agent, sulfonation results; the desired product (XLIV), however, is obtained with phosphorus pentoxide.



If Ciba Yellow 3G contains the 5,7-diazabenz[*a*]anthracene ring system as in XXXd, methylation and decarboxylation of the acid obtained by alkaline hydrolysis would be expected to give XLIV. However, since the melting point (168°) of the compound, $C_{16}H_8NO(NCH_3)C_6H_5$, obtained in this way from Ciba Yellow by Hope and Richter¹¹⁷ does not correspond with that of the synthetic sample (249°), it appears that XXXd cannot be the correct formulation of the structure of the dye.

Even more conclusive evidence that Ciba Yellow is not XXXd was obtained by the synthesis of XXXd, whose properties are very different from those of the dye.¹²³ The lactam of 6-(2'-carboxyphenyl)-12-keto-7*H*,5,7-diazabenz[*a*]anthracene was prepared by condensation of isatin with the product obtained by treating ethyl ω -bromoacetophenone-*o*-carboxylate with aniline, followed by cyclization of the intermediate acid, 12-carboxy-5-keto-6-phenyl-6,12-diazabenz[*a*]anthracene (XLV). Since the synthetic XXXd melts at 297° in contrast to Ciba Yellow,



which melts at 275°, and since XXXd does not give a vat, Ciba Yellow is not XXXd.

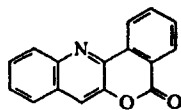
In the course of attempting to elucidate the structure of Ciba Yellow 3G, Höchst Yellow R and Yellow U, various alkaline degradation products, which may belong to the 5,11-diazanaphthacene, 5,7-, 5,12-, or 6,12-diazabenz[*a*]anthracene ring systems have been obtained. Table 17 includes some of the properties of these compounds.

TABLE 17. Degradation Products of Ciba Yellow 3G Which Contain Four Fused Six-Membered Rings¹¹⁷

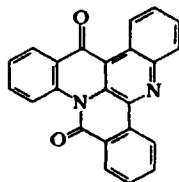
Formula	Preparation	M.p., °C.	Properties
$C_{22}H_{12}ON(NMe)(COOMe)$	Methylation of carboxylic acid obtained by heating Ciba Yellow 3G with 15% caustic soda	—	Insol. in dil. alkali
$C_{22}H_{12}ON(NMe)(COOH)$	Hydrolysis of ester	232	Slightly basic; HCl soln. is R; sol. in dil. Na_2CO_3 and dil. NaOH
$C_{22}H_{12}ON(NMe)$	Heating acid at 280°	168	Yellow needles

(2) Höchst Yellow U

Although the empirical formulas for Ciba Yellow 3G and Höchst Yellow U are identical, their melting points are somewhat different and their reactions significantly different. De Diesbach, de Bie, and Rubli¹¹⁰ carried out an alkaline fusion of Yellow U and obtained one equivalent of anthranilic acid and one of a base, $C_{16}H_8NO_2$, which was considered to be the lactone (XLVI), and which was also obtained on degradation of Höchst Yellow R. Oxidation of the lactone gave anthranilic and phthalic acids. They proposed XLVII as a possible structure for the



XLVI



XLVII

dye, even though it differs from the one suggested for Ciba Yellow only in the arrangement of double bonds. This formulation of Ciba Yellow 3G, in which a $-N=C-$ is *para* to a carbonyl group, might account for the difference in degradation products obtained from the dye (Group D) and the two Höchst Yellows (Group C) (see page 101).

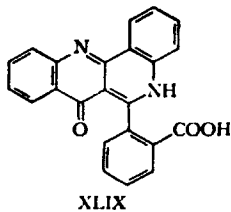
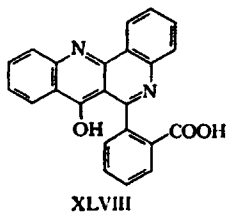
TABLE 18. Höchst Yellow U Degradation Products Which Contain Four Fused Six-Membered Rings¹²⁴

Formula	Preparation	M.p., °C.	Properties
1. $C_{22}H_{13}ON_2(COOH)$	Höchst Yellow U, digested with excess EtOH-NaOEt	—	R; sol. in 3% NaOH with R-Br color and G fluorescence; forms HCl; acid is also sl. sol. in 8% Na_2CO_3 and forms sl. sol. Na salt
2. $C_{22}H_{16}O_2N_2$ (dimethyl cpd.)	Methylation of 1	168	Scarlet. "This is apparently the compound described by Posner ¹²⁵ as the monomethyl derivative of the monohydrate of U." Fairly strong base sol. in HCl with indigo-blue color
3. $C_{24}H_{16}O_2N_2$ (monomethyl cpd.)	Methylation of 1	238-240	R., stable to dil. alkali, fairly strong base sol. in HCl with indigo-blue color
4. $C_{22}H_{13}ON_2(COOH)$ (isomeric with 1)	Höchst Yellow U, heated at 210-215° with 15% NaOH	182 ^a 232 ^b 198 ^c	Sparingly sol. Na and NH_4 salts; sol. 4% HCl; forms lactone. Benzoyl deriv., m.p. 265-267° (+ 1 H_2O); 212-213° (anhyd.). Acetyl deriv., m.p. 272°
5. $C_{24}H_{16}O_2N_2$ (dimethyl cpd.)	Methylation of 4	238-239	Sol. 3% HCl; insol. in alkali
6. $C_{22}H_{13}ON_2(COOH)(OMe)$	Hydrolysis of 5	308-310 dec.	Does not form acetyl deriv.
7. $C_{23}H_{14}O_2N_2 \cdot H_2O$ (isomeric with 4)	Höchst Yellow U, heated at 210-215° with 15% NaOH	222-227 ^d 206-208 ^e	— —
8. $C_{22}H_{16}O_2N_2$	Methylation of 7	247-249	Only 1 methyl group removed by HI

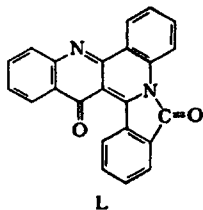
^a Dried over phosphorus pentoxide.^b Crystallized from ethyl acetate.^c Crystallized from 90% methanol.^d Acid precipitated from the sodium salt.^e Crystallized from nitrobenzene.

On alkaline hydrolysis of the dye, Hope and Anderson¹²⁴ obtained a carboxylic acid (XLVIII), isomeric with the amino acid (XLIX), designated as "Höchst Yellow U monohydrate,"¹²⁵ which resulted from treatment with alcoholic sodium ethoxide. As was the case with Ciba Yellow, the acid (XLIX) could be reconverted to Höchst Yellow U.¹²⁶

This acid gave a monomethylcarboxylic acid and a dimethyl derivative in which one methyl occurred as an ester linkage, but the analyses for these derivatives were not entirely satisfactory. The tautomeric hydroxy



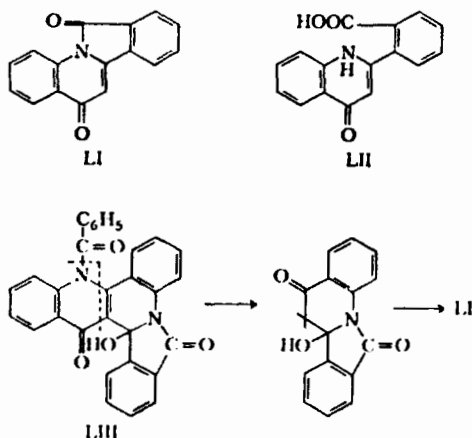
acid (XLVIII) exhibited various melting points, depending primarily upon the solvent used for crystallization. Methylation gave a dimethyl derivative which is also an ester, but hydrolysis of the ester linkage gave an acid containing one methyl group. The parent acid (XLVIII) gave an acetylcarboxylic acid and a benzoylcarboxylic acid, as well as sparingly soluble ammonium and sodium salts. One of the most significant properties of this acid is its ready lactonization in diphenyl ether. The acid obtained by hydrolysis of the lactam linkage in de Diesbach's Höchst Yellow U (XLVII) can account for other reactions, but cannot undergo lactone formation. Therefore, Hope and Anderson suggest L as the structure for this dye.



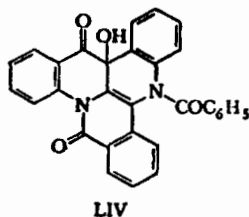
(3) Höchst Yellow R

Benzoylation of indigo in the presence of zinc chloride gives Höchst Yellow R, $C_{30}H_{18}N_2O_4$, which is converted to Höchst Yellow U, with the loss of one molecule of benzoic acid on treatment with hot sulfuric acid. Hope, Kersey, and Richter¹²⁶ reported that Yellow R is easily attacked by boiling aqueous 10% potassium hydroxide, forming approximately equimolar amounts of benzoic acid, anthranilic acid, and a compound, $C_{16}H_9NO_2$, to which structure LI was assigned. Further hydrolysis gives an acid, presumably LII (which is also obtained from the dye itself with 15% potassium hydroxide); the quinolone

structure, with its potential tautomerism, may account for the difficulty of preparing an *N*-acyl derivative. Because of the nature of its degradation products, Höchst Yellow R falls in group C along with Höchst Yellow U. The only reasonable formula for Yellow U, which would account for the formation of equivalent amounts of benzoic acid, anthranilic acid, and LI, is LIII.



De Diesbach, de Bie, and Rubli¹¹⁹ remarked that Höchst Yellow R exists in at least two different forms, one of which gives a vat and is changed in the air to the higher melting nonvattable form. It is this latter compound, obtained from Dessoulavy's substance, with which their investigation was concerned. Alkaline fusion gave one equivalent of benzoic acid and one of anthranilic acid, as well as the lactone (XLVI) of 3-hydroxy-2-phenylquinoline-2'-carboxylic acid identical with the base obtained from Yellow U. They concluded that the probable structure of Yellow R is LIV.

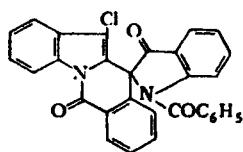


After their investigation of Höchst Yellow U, from which they had concluded it to be L, Hope and Anderson¹²⁴ preferred the similar formula-

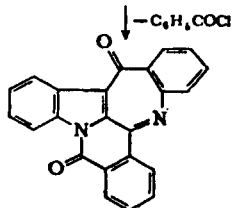
tion LIII rather than LIV for Höchst Yellow R. LIII also accounts for the formation of equivalent amounts of benzoic and anthranilic acids and a lactam, $C_{16}H_9NO_2$, without necessitating preliminary cleavage of the lactam linkage. Since two different methods of synthesis¹²⁷ of LI gave identical products which did not correspond in any way with the degradation product obtained by Hope and Anderson, which had been assigned this formula, it appears that LIII is probably not the correct structure for Höchst Yellow R.

Until recently, Dessoulavy's compound was regarded as identical with Höchst Yellow R, except that the hydroxy group in the latter was replaced by chlorine, but de Diesbach, Jacobi, and Taddei¹²⁸ have proposed a structure in which the indigo linkages are still present.

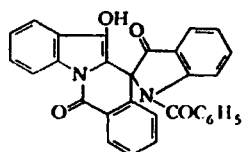
In 1949, de Diesbach proposed new ring structures, which showed clearly the interrelations between Ciba Yellow 3G, the two Höchst Yellows, and the Dessoulavy substance. Since the compounds in question are not diazabenzanthracenes, a further discussion of the chemistry is out of place, and the original literature^{129,130} should be consulted. However, it will be appropriate to include the structures and complete the account of these puzzling substances. The proposals go back to the observation that a five-membered ring appeared to persist in reactions of degradation,¹²⁹ and a parallel was noted in the case of the di-anil of indigo. The currently proposed structures contain 5- and 7-membered rings. The stability and ease of formation of rings having seven members no longer seems too unusual in view of Thiele's reaction products of



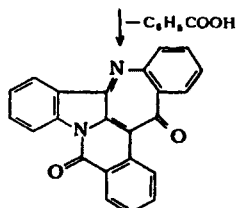
Dessoulavy substance



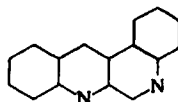
Ciba Yellow 3G



Höchst Yellow R



Höchst Yellow U

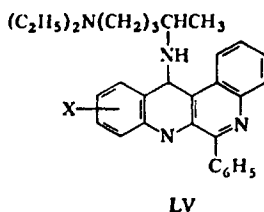
TABLE 19.^a 5,7-Diazabenz[a]anthracenes;

Formula	Position and substituent	Ref.	M.p., °C
XXXVIII	12-Keto-6-phenyl- ^b	122	266
XLIV	12-Keto-7-methyl-6-phenyl-	123	249–250
XL I	12-Keto-8-methyl-6-phenyl-	122	317–320
XL	12-Keto-10-methyl-6-phenyl-	122	256
XXXIX	12-Keto-6-(2',4'-dimethylphenyl)- ^c	122	250
XLIII	12-Keto-6-(2'-aminophenyl)- ^d	123	262
	12-Chloro-6-phenyl-	130	216 ^e
	10,12-Dichloro-6-phenyl-	130	243 ^e
	11,12-Dichloro-6-phenyl-	130	251 ^f
	9,12-Dichloro-6-phenyl-	130	320 ^e
	12-Chloro-10-methoxy-6-phenyl-	130	199 ^e
	12-Chloro-8-methoxy-6-phenyl-	130	215 ^e
	12-Chloro-10-methyl-6-phenyl-	130	216 ^e
	12-Chloro-8-methyl-6-phenyl-	130	186 ^e
	12-(1'-Methyl-4'-diethylaminobutyl- amino)-10-methyl-6-phenyl-	130	101–102 ^g
	6-Phenyl-12-phenoxy-	131	206
	8-Methyl-6-phenyl-12-phenoxy-	131	198
	10-Methyl-6-phenyl-12-phenoxy-	131	209
	6-Phenyl-8-methoxy-12-phenoxy-	131	—
	6-Phenyl-10-methoxy-12-phenoxy-	131	171
	6-Phenyl-10-ethoxy-12-phenoxy-	131	178
	6-Phenyl-10-chloro-12-phenoxy-	131	232
	6-Phenyl-12-hydroxy-	131	266
	8-Methyl-6-phenyl-12-hydroxy-	131	318
	10-Methyl-6-phenyl-12-hydroxy-	131	256
	6-Phenyl-8-methoxy-12-hydroxy-	131	298
	6-Phenyl-10-methoxy-12-hydroxy-	131	233–234
	6-Phenyl-10-ethoxy-12-hydroxy-	131	262
	6-Phenyl-10-chloro-12-hydroxy-	131	284
	6-Phenyl-12-amino-10-ethoxy-	131a	177
	6-Phenyl-12-chloro-10-ethoxy-	131a	—
	12-(4'-Methoxyphenylimino)-	131a	250–252
	10-Methoxy-12-phenylimino-	131a	212–213
	10-Methoxy-12- <i>p</i> -tolylimino-	131a	213–214
	10-Methoxy-12- <i>p</i> -methoxyphenylimino-	131a	178
	10-Methoxy-12- <i>p</i> -ethoxyphenylimino-	131a	234–235
	10-Ethoxy-12- <i>p</i> -methoxyphenylimino-	131a	205
	8-Methyl-12-phenylimino-	131a	204–205
	8-Methyl-12- <i>p</i> -methoxyphenylimino-	131a	203
	8-Methyl-12- <i>p</i> -ethoxyphenylimino-	131a	181

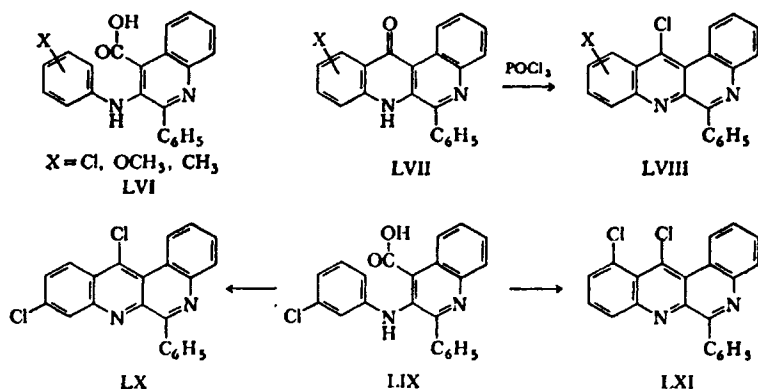
^aAll substances are yellow. ^b Imino group cannot be acylated or alkylated. ^c Cannot cyclize with methyl and imino groups. ^d Diazonium salt appears to cyclize through imino group; cannot replace NH₂ by halogens or CN. ^e From chlorobenzene. ^f From dioxane. ^g From alcohol.

ortho-diamines and 1,3-diketones, and the azulenes, which, like two of these yellow dyes have adjacent 5- and 7-membered rings. In Höchst Yellow R the chlorine atom of the Dessoulavy substance is replaced by a hydroxyl group; Ciba Yellow 3G is formed by loss of benzoyl chloride, and Höchst Yellow G by loss of benzoic acid, with concurrent formation of a 7-membered ring.^{129a}

Colonna¹³⁰ attempted, without success, to synthesize antimalarials of the type LV in the 5,7-diazabenz[*a*]anthracene series. The ring system L.VII is formed by cyclization of appropriate carboxylic acids (LVI)



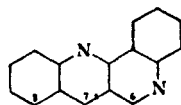
using sulfuric acid, aluminum chloride, or phosphorus halides. With the latter, the intermediate acridone (LVII) is not isolated, but is at once chlorinated to give LVIII. When a *meta*-substituted acid (LIX) is employed, isomers (LX, LXI) result. Colonna was unable to isolate



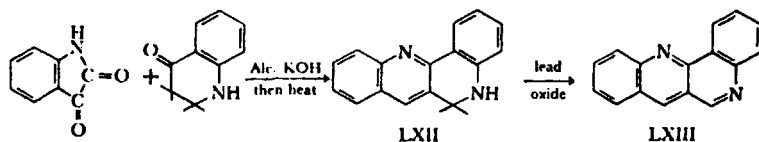
crystalline amines of the type LV from the resins formed when either chloro derivative was used, except where X = CH₃.

The 12-keto-5,7-diazabenz[*a*]anthracenes are listed in Table 19 on page 112 facing.

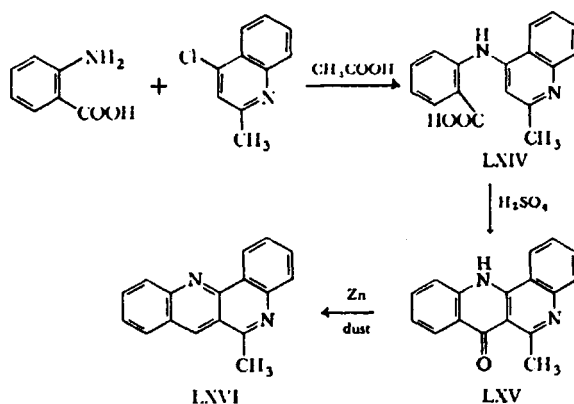
I. 5,12-Diazabenz[*a*]anthracene, Quino[4,3-*b*]-quinoline, 2,3-Quinoquinoline, 8,9-Benzo-quinoquinoline. R.I. 2701



5,12-Diazabenz[*a*]anthracenes have been prepared by several investigators using various methods. The synthesis of the parent compound, 5,12-diazabenz[*a*]anthracene (LXIII), is achieved through the condensation of isatin and tetrahydroquinolone in alcoholic potassium hydroxide to an intermediate compound, which is decarboxylated by heating under reduced pressure at 210° to 5,6-dihydro-5,12-diazabenz[*a*]anthracene (LXII), and the latter compound is dehydrogenated to the desired product by distillation over lead oxide.¹³²

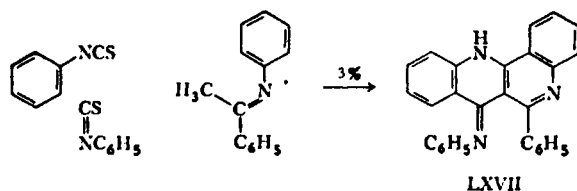


Backeberg¹³³ reported the synthesis of a 6-substituted 5,12-diazabenz[*a*]anthracene by the following series of reactions: the condensation of 4-chloroquinaldine with anthranilic acid in the presence of acetic acid yields 4-(2'-carboxyphenylamino)-quinaldine (LXIV), which is cyclized by concentrated sulfuric acid to 7-keto-6-methyl-12*H*,5,12-diazabenz[*a*]anthracene (LXV), and the latter compound, after zinc dust dis-

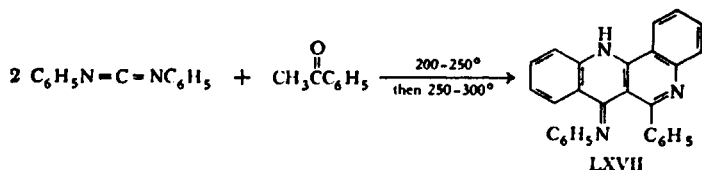


tillation, gives 6-methyl-5,12-diazabenz[*a*]anthracene (LXVI). Another 6-substituted 5,12-diazabenz[*a*]anthracene is found as a side product in the preparation of 2-phenyl-4-anilinoquinoline from acetophenone and

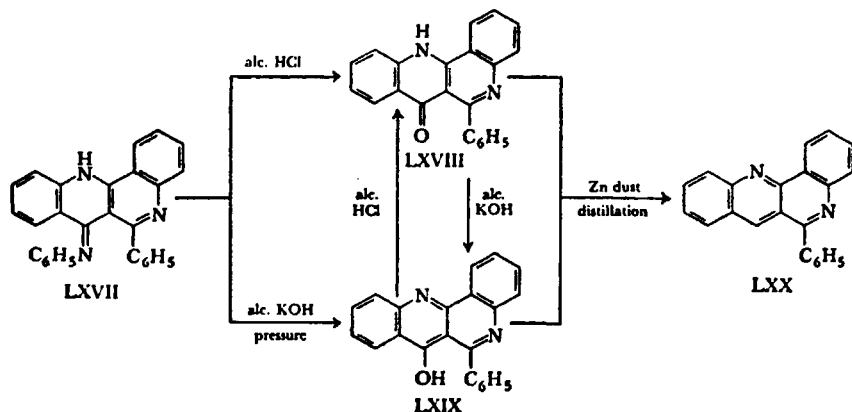
thiocarbanilide. According to Moszew,¹³⁴ the main reaction of acetophenone with thiocarbanilide apparently goes in three phases: decomposi-



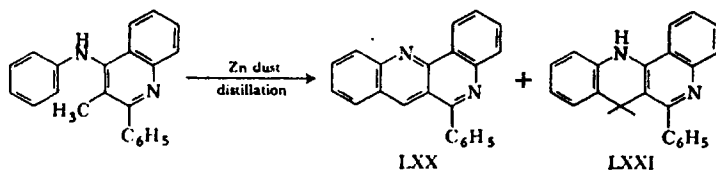
tion of thiocarbanilide into phenylisothiocyanate and aniline; then formation of acetophenoneanil; and finally the condensation of this compound with phenylisothiocyanate. However, the condensation of acetophenoneanil with two moles of phenylisothiocyanate yields 6-phenyl-12*H*,5,12-diazabenz[*a*]anthracene-7-anil (LXVII). The same product has been prepared in a 21% yield by heating carbodiphenylimide with acetophenone and the corresponding 6-*p*-tolyl derivative by substituting *p*-methylacetophenone for acetophenone.¹³⁵



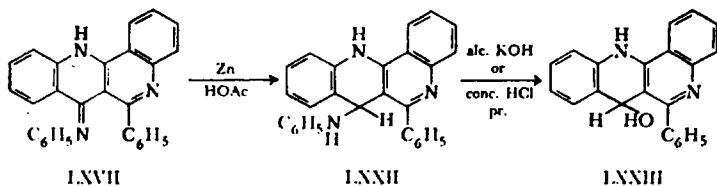
When the anil (LXVII) is refluxed with alcoholic hydrochloric acid, the 7-keto compound (LXVIII) is formed; when the anil is heated under pressure with alcoholic potassium hydroxide, the 7-hydroxy compound (LXIX) is formed.¹³⁴ The 7-keto and 7-hydroxy derivatives are interconvertible. 6-Phenyl-5,12-diazabenz[*a*]anthracene (LXX) may be



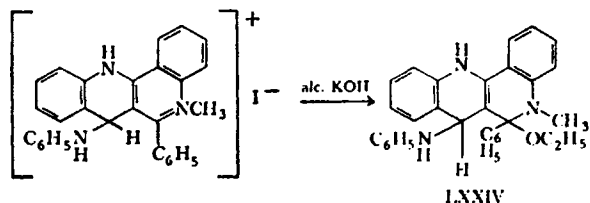
prepared by zinc dust distillation of either the keto or enol form. This same compound may be obtained, along with the 7,12-dihydro derivative (LXXI), by zinc dust distillation of 2-phenyl-3-methyl-4-anilinoquinoline.



Reduction of the anil (LXVII) with zinc and acetic acid gives 7-anilino-6-phenyl-7,12-dihydro-5,12-diazabenz[a]anthracene (LXXII) and hydrolysis of the latter with either alcoholic potassium hydroxide or con-



centrated hydrochloric acid under pressure yields 7-hydroxy-6-phenyl-7,12-dihydro-5,12-diazabenz[a]anthracene (LXXIII). The methiodide of the base (LXXII), when treated with alcoholic potassium hydroxide, forms 7-anilino-6-ethoxy-5-methyl-6-phenyl-7,12-dihydro-5,12-diazabenz-



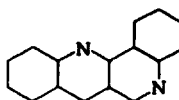
[a]anthracene (LXXIV). Reduction of either 7-keto- or 7-hydroxy-5,12-diazabenz[a]anthracene with sodium and amyl alcohol gives 7-keto-5,6,6a,12a-tetrahydro-5,12-diazabenz[a]anthracene.

Most of the 5,12-diazabenz[a]anthracenes prepared are yellow solids, and most of them exhibit fluorescence in acid solution as well as in organic solvents. Although 5,12-diazabenz[a]anthracene itself is described as a strong base and its 5,6-dihydro derivative as a fairly strong base,¹³² Moszew¹³⁴ reports that the dihydro derivatives he prepared appear to be stronger bases than the corresponding unsaturated compounds.

Several compounds which are obtained by alkaline degradation of the dye Höchst Yellow U have been tentatively assigned structures of 5,12-diazabenz[a]anthracenes.¹³⁶ However, since the degradation products of this dye are discussed in detail elsewhere (page 107), these compounds are not included in this section.

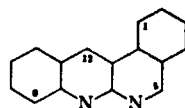
Properties of 5,12-diazabenz[a]anthracenes are collected in Table 20.

TABLE 20. 5,12-Diazabenz[a]anthracenes



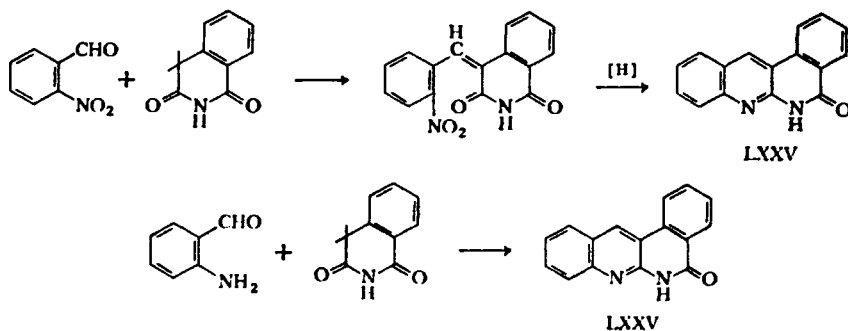
Formula	Position and substituent	Ref.	M.p., °C.	Picrates
LXIII	5,12-Diazabenz[a]anthracene	132	186-187	—
LXII	5,6-Dihydro-5,12-diazabenz[a]anthracene	132	235-237	—
LXVI	6-Methyl-5,12-diazabenz[a]anthracene	133	137	m.p. 234°
LXX	6-Phenyl-5,12-diazabenz[a]anthracene	134	300-301	m.p. 200-201°
LXXI	6-Phenyl-7,12-dihydro-5,12-diazabenz[a]anthracene	134	202	m.p. 265-266°
LXV	7-Keto-6-methyl-5,12-diazabenz[a]anthracene	133	295-296	Chars 270-280
LXVIII	7-Keto-6-phenyl-5,12-diazabenz[a]anthracene	134	365	—
	7-Keto-6-(<i>p</i> -tolyl)-5,12-diazabenz[a]anthracene	135	364	—
	7-Keto-5,6,6a,12a-tetrahydro-5,12-diazabenz[a]anthracene	134	308-309	m.p. 224°
LXIX	7-Hydroxy-6-phenyl-5,12-diazabenz[a]anthracene	134	324-325	m.p. 240°
	7-Hydroxy-6-(<i>p</i> -tolyl)-5,12-diazabenz[a]anthracene	135	331-333	—
LXXIII	7-Hydroxy-6-phenyl-7,12-dihydro-5,12-diazabenz[a]anthracene	134	250-260	—
LXVII	6-Phenyl-5,12-diazabenz[a]anthracene-7-anil	134	247-248	m.p. 243°
	7-(<i>p</i> -Tolyl)-5,12-diazabenz[a]anthracene-7-anil	135	222-223	m.p. 238-239°
LXXII	7-Anilino-6-phenyl-7,12-dihydro-5,12-diazabenz[a]anthracene	134	210	m.p. 257°
LXXIV	7-Anilino-6-ethoxy-5-methyl-6-phenyl-7,12-dihydro-5,12-diazabenz[a]anthracene	134	105-106	m.p. 278-279°

J. 6,7-Diazabenz[a]anthracene, Dibenzo[b,f]-naphthyridine, 2,3,5,6-Dibenzo-1,8-naphthyridine. R.I. 2702

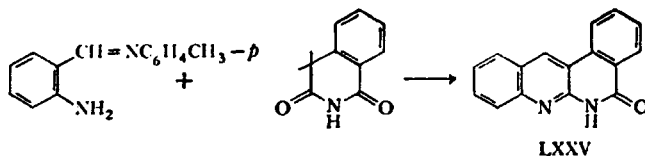


Several different representatives of this series have been prepared by different investigators. 5-Keto-6*H*,6,7-diazabenz[a]anthracene (LXXV) was first reported by Haworth and Pink,¹³⁷ who synthesized it by con-

densing homophthalimide and *o*-nitrobenzaldehyde in pyridine solution containing a trace of piperidine, followed by reducing the *o*-nitrobenzylidenehomophthalimide. Meyer¹³⁸ obtained the same product from homophthalimide and *o*-aminobenzaldehyde, by a method similar to the



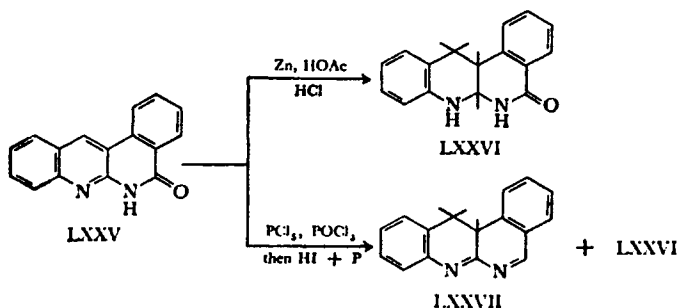
Friedländer synthesis of quinoline, while Borsche and his co-workers¹³⁹ prepared it from homophthalimide by condensation with 2-aminobenzal-



4-toluidine. Substituted *o*-aminobenzaldehydes give 5-keto-6H,6,7-diazabenz[*a*]anthracenes with substituents in the 8-, 9-, 10-, or 11-positions¹³⁹ and *N*-substituted homophthalimides yield the corresponding 5-substituted compounds.^{137,139}

Reduction of the keto compound (LXXV) with zinc dust in acetic acid saturated with hydrogen chloride, gives 5-keto-6a,7,12,12a-tetrahydro-6H,6,7-diazabenz[*a*]anthracene (LXXVI). When the keto compound (LXXV) is heated with phosphorus pentachloride and phosphoryl chloride, followed by reduction of the unstable chloro compound by hydrogen iodide and red phosphorus, a yellow base, C₁₆H₁₂N₂, probably 12,12a-dihydro-6H,6,7-diazabenz[*a*]anthracene (LXXVII) is obtained. The reduction product (LXXVI) forms an amorphous nitroso compound, while LXXVII gives neither a nitroso compound nor an acetyl derivative, nor can it be reduced further by zinc dust and acid.¹³⁷ An attempted reduction of the keto compound (LXXV) to the base, C₁₆H₁₂N₂, with hydrazine hydrate was unsuccessful; the product isolated analyzed best for (C₁₆H₁₂N₂)_x.¹³⁹

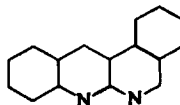
The 6,7-diazabenz[a]anthracenes prepared are colorless or yellow solids. An alcoholic solution of 12,12a-dihydro-6,7-diazabenz[a]anthracene (LXXVII) shows an intense violet fluorescence. Both this substance (LXXVII) and 5-keto-6a,7,12,12a-tetrahydro-6,7-diazabenz[a]-



anthracene (LXXVI) form monohydrochlorides. 5-Keto-6,7-diazabenz[a]anthracene (LXXV), however, shows more marked acidic properties: (1) it dissolves in concentrated hydrochloric acid, but is precipitated from solution on dilution with water; and (2) it forms sparingly soluble sodium and potassium salts.

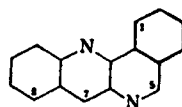
Properties of 6,7-diazabenz[a]anthracenes are collected in Table 21 below.

TABLE 21. 6,7-Diazabenz[a]anthracenes

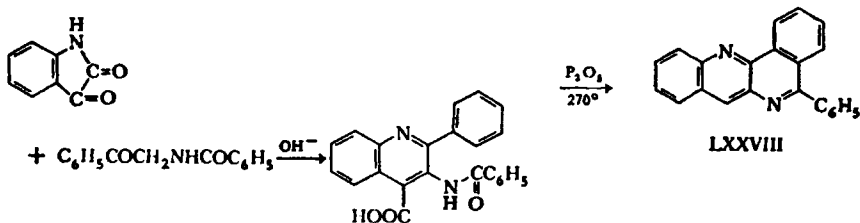


Position and substituent	Ref.	M.p., °C.	Picrates
12,12a-Dihydro- (LXXVII)	137	232	—
5-Keto- (LXXV)	137	246–247	—
	139	262	m.p. 276–278°
5-Keto-6a,7,12,12a-tetrahydro- (LXXVI)	137	250	m.p. 270°
5-Keto-6-methyl-	139	244–245	—
5-Keto-6-(2'-phenylethyl)-	137	220	—
5-Keto-6-(2'-piperonylethyl)-	137	217	—
5-Keto-6a,7,12,12a-tetrahydro-6-(2'-phenyl-ethyl)-	137	217	—
5-Keto-6a,7,12,12a-tetrahydro-6-(2'-piperonyl-ethyl)-	137	211	—
5-Keto-9,10-dimethoxy-	139	330–332	m.p. 286–288°
5-Keto-9,10-methylenedioxy-	139	340–342	—

K. 6,12-Diazabenz[*a*]anthracene, Dibenzo[*b,h*][1,5]naphthyridine, 3,4,6,7-Dibenzo-1,5-naphthyridine

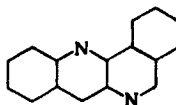


Only a few compounds with this heterocyclic structure have been synthesized, among them 5-phenyl-6,12-diazabenz[*a*]anthracene (LXXVIII), which was prepared to test for possible trypanocidal activity.¹⁴⁰ The condensation of ω -benzamidoacetophenone with isatin produces 3-benzamido-2-phenylquinoline-4-carboxylic acid (90% yield), which is cyclized and decarboxylated (60% yield) by heating with phos-



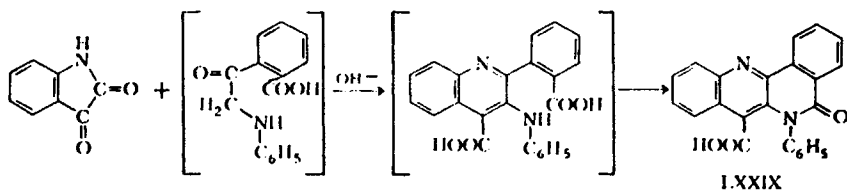
phorus pentoxide at 270°. Attempts to cyclize the acetyl instead of the benzoyl derivative were unsuccessful.

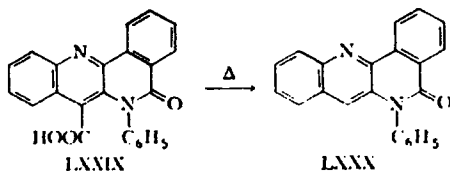
TABLE 22. 6,12-Diazabenz[*a*]anthracenes



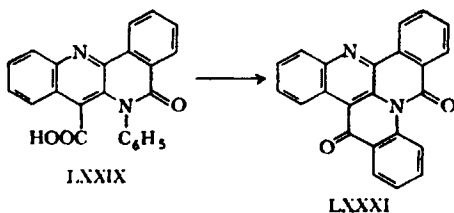
Formula	Position and substituent	Ref.	M.p., °C.	Properties
LXXVIII	5-Phenyl-	140	197–198	Picrate, m.p. 240–241°
LXXX	5-Keto-6-phenyl-	141	276	—
LXXIX	7-Carboxy-5-keto-6-phenyl-	141	273	Sol. in Na ₂ CO ₃ ; can be cyclized by P ₂ O ₅

5-Keto-6-phenyl-6,12-diazabenz[*a*]anthracene-7-carboxylic acid (see LXXIX) is prepared from isatin and the reaction product of aniline and





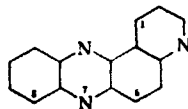
ethyl 2-carboxy- ω -bromoacetophenone.¹⁴¹ When heated below its melting point, LXXIX loses carbon dioxide to form 5-keto-6-phenyl-6,12-diazabenz[*a*]anthracene (LXXX). LXXIX can be converted to the ketone (LXXXI) by treatment with either phosphorus pentoxide or thionyl chloride, followed by heat (see page 106).



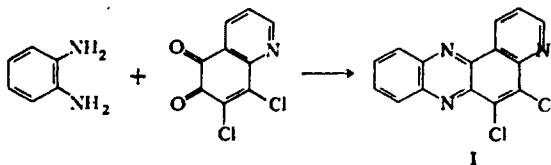
3. Triazabenz[*a*]anthracenes

Of the two hundred twenty triazabenz[*a*]anthracenes theoretically possible, members of only two series—4,7,12- and 6,7,12-triazabenz[*a*]anthracene—have been synthesized.

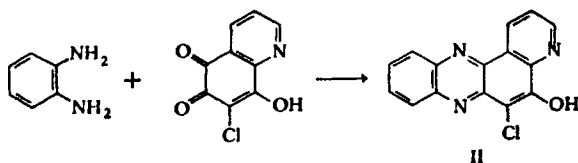
A. 4,7,12-Triazabenz[*a*]anthracene, Pyrido[3,2-*a*]phenazine, Quinalinophenazine. R.I. 2656



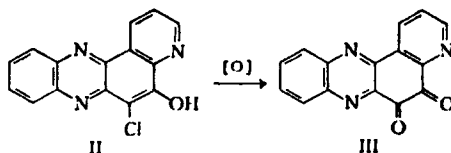
Inasmuch as 4,7,12-triazabenz[*a*]anthracene is a phenazine derivative, it is surprising that only three compounds of this group have been prepared. Zincke and Wiederhold¹⁴² have synthesized 5,6-dichloro-4,7,12-



triazabenz[*a*]anthracene (I) merely by mixing solutions of *o*-phenylenediamine and dichloroquinolinequinone. Similarly, an acetic acid solution of *o*-phenylenediamine and 7-chloro-8-hydroxyquinolinequinone,

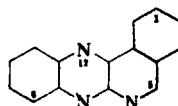


when heated, yields 6-chloro-5-hydroxy-4,7,12-triazabenz[*a*]anthracene (II). When an acetic acid suspension of the latter compound is treated with concentrated nitric acid, a yellow, chlorine-free compound (III) separates. The product, 5,6-diketo-4,7,12-triazabenz[*a*]anthracene (III), becomes white in sodium acetate solution but regains its yellow color when warmed in water or acetic acid.

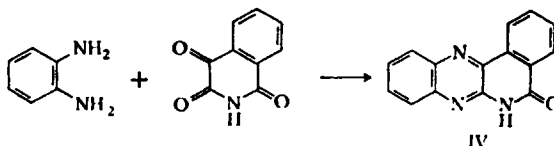


Both the dichloro compound (I) and the chlorohydroxy compound (II) are yellow and both are weakly basic. The chlorohydroxy compound forms red salts with mineral acids as well as a red, slightly soluble sodium salt with sodium hydroxide.

B. 6,7,12-Triazabenz[*a*]anthracene, Isoquino-[3,4-*b*]quinoxaline. R.I. 2657

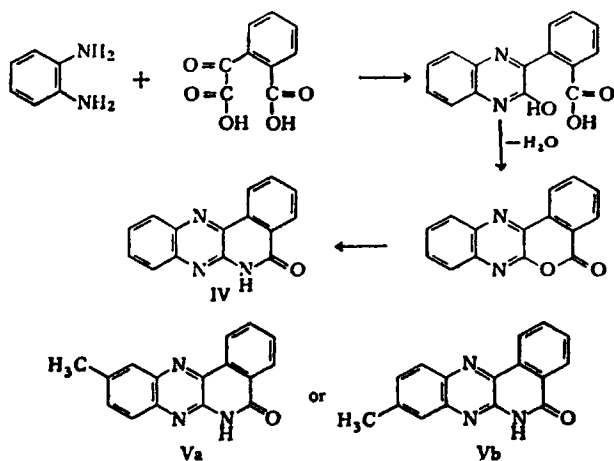


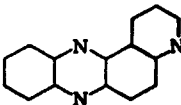
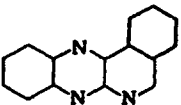
Only two compounds of this general structure have been reported. 5-Keto-6*H*,6,7,12-triazabenz[*a*]anthracene (IV) is easily prepared by mixing aqueous solutions of phthalonimide and *o*-phenylenediamine.¹⁴³



The same compound is also obtained in a similar way by condensing *o*-phenylenediamine with phthalonic acid, and converting the intermediate product to the lactone, which, when heated in a sealed tube at 100° with alcoholic ammonia, gives IV.¹⁴⁴ 5-Keto-9- (or 10-) methyl-6*H*,6,-

7,12-triazabenz[*a*]anthracene (Vb or a) is prepared by a similar series of reactions from 1,2-diamino-4-methylbenzene.¹⁴⁵ Both compounds are yellow.

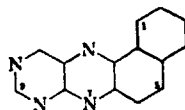
TABLE 23. Triazabenz[*a*]anthracenes

Formula	Position and substituent	Ref.	M.p., °C.	Remarks
(a) 4,7,12-Triazabenz[<i>a</i>]anthracenes:				
				
I	5,6-Dichloro-	142	239-240	A weak base The hydrochloride is carmine-red; forms a red Na salt Reacts with <i>o</i> -phenylenediamine
II	6-Chloro-5-hydroxy-	142	dec. >200	
III	5,6-Diketo-	142	dec. >270	
(b) 6,7,12-Triazabenz[<i>a</i>]anthracenes:				
				
IV	5-Keto-	143,144	267-268	— Does not form HCl
Vb or a	5-Keto-9- (or 10-) methyl-	145	303	

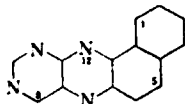
4. Tetrazabenz[*a*]anthracenes

There are four hundred ninety-five possible arrangements for the tetrazabenz[*a*]anthracenes but only two have been prepared.

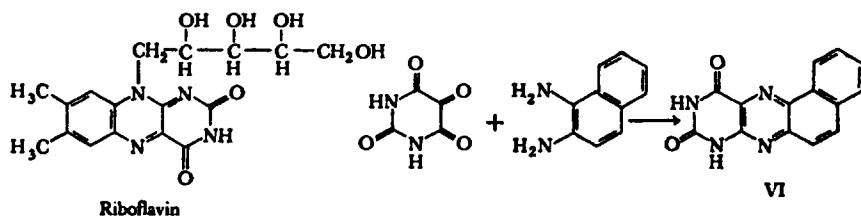
A. 7,8,10,12-Tetrazabenz[*a*]anthracene, Benzo[*f*]pyrimido[4,5-*b*]quinoxaline, 5,6-Benzo-flavin. R.I. 2646



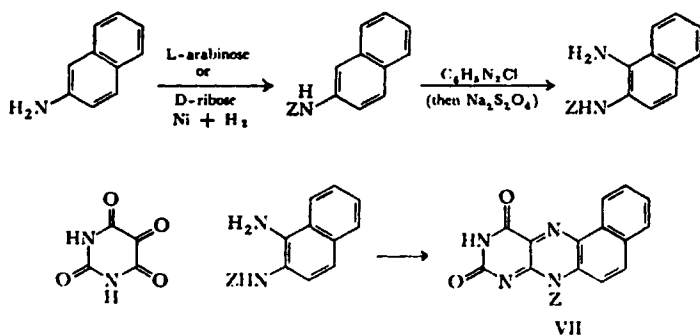
B. 7,9,11,12-Tetrazabenz[*a*]anthracene, Benzo[*f*]pyrimido[5,4-*b*]quinoxaline, 7,8-Benzo-flavin. R.I. 2647



Since all the tetrazabenz[*a*]anthracenes prepared could possess either the 7,8,10,12- or the 7,9,11,12-tetraza structure and since in no case has the specific heterocyclic structure for a given compound been established, these two ring systems will be discussed together and the individual investigator's choice of ring system will be used. There has been considerable interest in these compounds because of their close relationship to riboflavin. Kühling,¹⁴⁶ in 1891, prepared the so-called "naphthoalloxazine" (VI) from 1,2-diaminonaphthalene hydrochloride and

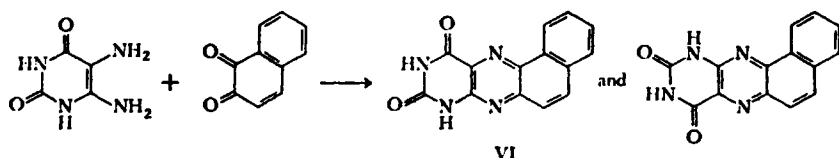


alloxan. By the following series of reactions, Karrer and Quibell¹⁴⁷ synthesized two derivatives (VII) of this same compound containing sugar radicals in the 7-position (where Z = L-arabityl or D-ribityl).

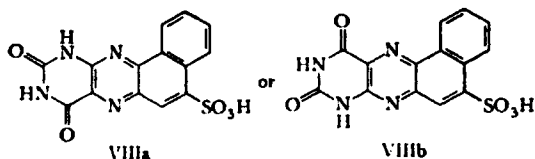


Lettré and Fernholz¹⁴⁸ prepared a series of 7-alkyl and aryl compounds by the same method, and by using methylalloxan they obtained the corresponding 10-methyl derivatives.

Since the "naphtholumazine" described by Kühling¹⁴⁶ decomposes above 300° without a definite melting point, Kuhn and Cook¹⁴⁹ prepared the 8,10-dimethyl derivative. A single "naphtholumazine" was obtained using Kühling's procedure, and it was converted to a dimethyl derivative, m.p. 260°, by treatment with diazomethane.¹⁴⁹ However, when β -naphthoquinone was condensed with 4,5-diaminouracil, both theoretically possible isomers were obtained in addition to a red compound which was not investigated.¹⁴⁹ After separation of the isomers, a second dimethyl derivative, m.p. 304°, was obtained.



The only other substituted tetrazabenz[a]anthracene reported, a sulfonic acid, is prepared by condensation of 1,2-diaminonaphthalene-4-sulfonic acid and alloxan and is probably VIIIa or b, or a mixture of both.¹⁵⁰ However, β -naphthoquinone-4-sulfonic acid did not react



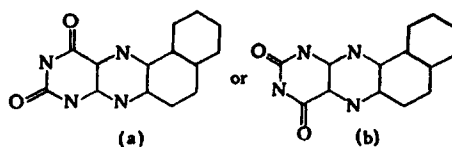
with 4,5-diaminouracil sulfate to yield either VIIIa or b, perhaps because the sulfonic acid group in β -naphthoquinone has a great tendency to react first with the amino group.

Little work has been done to illustrate the chemical properties of the tetrazabenz[a]anthracenes because most of them have been prepared specifically for pharmacological testing. Since a characteristic of carcinogenic hydrocarbons is their lack of solubility in water and their one-sided lipoid-solubility, the series of compounds prepared by Lettré and Fernholz¹⁴⁸ was designed to have one-sided lipoid-solubility. The homologous 7-alkyl-7,8,10,12- (or 7,9,11,12-) tetrazabenz[a]anthracenes—from methyl to cetyl—are all easily soluble in alkali, while the cetyl compound forms a difficultly soluble sodium salt. When an aqueous solution of these compounds is shaken with chloroform, the solubility in this solvent increases with the length of the side chain. The cetyl derivative dissolves completely in chloroform. The cetyl tetrazabenz-

[a]anthracene or its 10-methyl derivative in aqueous suspension or in tributyrin or olive oil solution, injected into mice, form deposits that are still detectable after ten weeks, while flavins which are easily soluble in water, or form easily soluble salts, appear in the urine within an hour after subcutaneous injection and disappear from the organism in a few days and are not carcinogenic. Injection of the 7-phenyl derivative in albino rats produced an orange-yellow pigmentation of the hair.¹⁶¹ 7-Alkyl compounds produced less color. The 7-(1'-D-ribityl) compound shows detectable activity in promoting the growth and acid production of *Lactobacillus casei* and *Bacillus lactis* only when small quantities of ribo-flavin are present,¹⁶² while it was inactive in promoting the growth of animals fed vitamin B₂-free diets.¹⁴⁷

The tetrazabenz[a]anthracenediones are collected in Table 24.

TABLE 24. Tetrazabenz[a]anthracenediones*



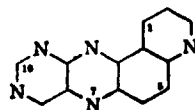
Position and substituent	Ref.	M.p., °C.	Color
Unsubstituted (VIa or b)	146	(1) dec. >300	Yellow
	149	(2) >330	Yellow
7-Methyl-	148	>365	Yellow
7-Ethyl-	148	326	Orange-yellow
7-n-Propyl-	148	319-320	Yellow
7-n-Butyl-	148	297-298	Yellow
7-Isoamyl-	148	273	Orange-yellow
7-n-Hexyl-	148	274	Orange-yellow
7-n-Octyl-	148	248-249	Orange-yellow
7-n-Decyl-	148	230	Orange-yellow
7-n-Dodecyl-	148	236	Orange-yellow
7-Cetyl-	148	221-222	Orange-yellow
7-Phenyl-	148	>365	Orange-red
7-(2'-Naphthyl)-	148	ca. 357 (dec.)	Orange
7-(L-1'-Arabityl)- (VII)	147	275	Yellow
7-(D-1'-Ribityl)- (VII)	147	dec. 290	—
7-Cetyl-10-methyl-	148	187-188	Orange
10-Methyl-7-phenyl-	148	>365 dec.	Orange
8,10-(?)Dimethyl- [from (1)]	149	258-260	Yellow
8,10(?)Dimethyl- [from (2)]	149	304	Orange-yellow
-5-sulfonic acid (VIIIa or b)	150	—	Orange-yellow

* These compounds may be either a or b, but for convenience in tabulation all are assigned structure a.

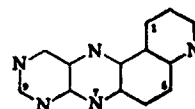
5. Pentazabenz[*a*]anthracenes

Although there are seven hundred ninety-two theoretically possible isomers of the pentazabenz[*a*]anthracene series, only two of these ring systems have been reported in the literature. In these two examples, the specific ring structure was not established.

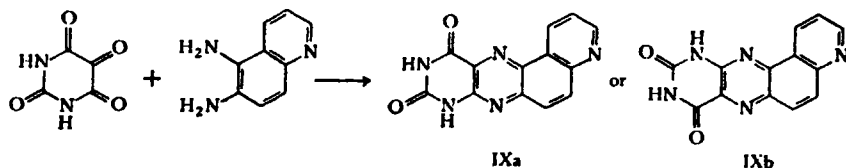
A. 4,7,9,11,12-Pentazabenz[*a*]anthracene, Pyridino-2'.3':7.8-alloxazine



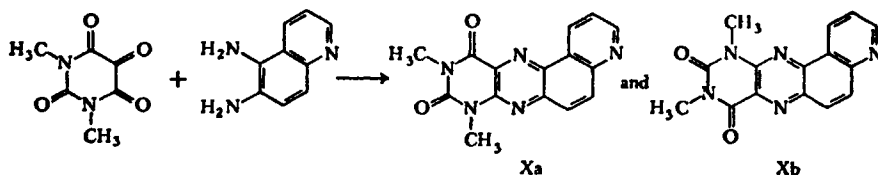
B. 4,7,8,10,12-Pentazabenz[*a*]anthracene, Pyridino-3'.2':5.6-alloxazine



Rudy¹⁵³ reports the condensation of 5,6-diaminoquinoline with alloxan, which could yield either of the two possible isomers (IXa or b). No attempt was made to fractionate the product, which decomposes at



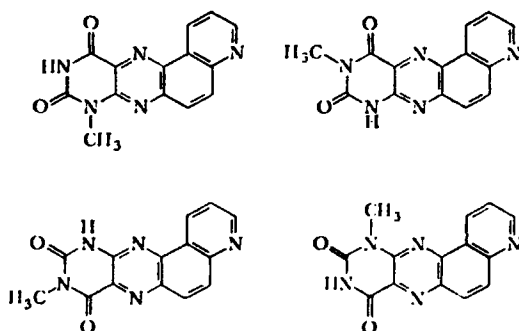
410°, to determine whether it was a single compound or a mixture, but since 1,3-dimethylalloxazines appear, in general, to melt sharply at lower temperatures than the nonmethyl compounds, 5,6-diaminoquinoline was condensed with dimethylalloxan, and both isomers, Xa and Xb, were isolated. Dimethylalloxan in acid solution or with zinc chloride-acetic



acid as the condensing agent gives a small amount of material, m.p. 264°, and a larger proportion of the isomer, m.p. 375°. Only the higher melting isomer is obtained when dimethylalloxan-sodium bisulfite is used in neutral solution. The two isomers differ in appearance and solubility. The high-melting, difficultly soluble one crystallizes in short, lemon-

yellow prisms, the lower melting more soluble compound in long, light yellow needles.

No attempt was made to separate the four possible monomethylpyridinoalloxazines which theoretically could result from the reaction of 5,6-diaminoquinoline with methylalloxan, although two fractions were obtained, one with a m.p. 380°, and the other decomposing slowly from 370° to 450° without melting.



The pyridinoalloxazines resemble the known alloxazines with respect to their light yellow color, sparing solubility, and high melting point. They are soluble in concentrated hydrochloric and sulfuric acids with a pale yellow color. Those which possess at least one free imino group in the alloxazine nucleus yield, with alkali, deep yellow salts showing an intense yellow-green fluorescence with a quartz lamp and a green fluorescence in daylight. The 1,3-dimethyl derivatives are insoluble in alkali. No fluorescence is observed when the pyridinoalloxazines are dissolved in mineral acids.

On reduction with zinc and hydrochloric acid, the pentazabenz[a]anthracenes go through an intermediate red stage; they are reversibly reduced in neutral solution by hydrosulfite. The pyridinoalloxazines also resemble the alloxazines in their stability to hot alkali.

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CHAPTER III

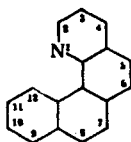
Azabenzo[*c*]phenanthrenes

BY ELEANOR R. WEBSTER

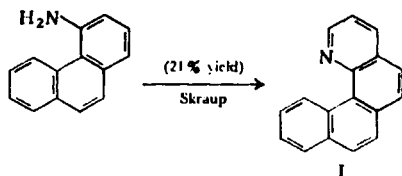
1. Monoazabenzo[*c*]phenanthrenes

Only three of the six different monoazabenzo[*c*]phenanthrenes have been synthesized successfully, and the appropriate intermediate for the synthesis of a fourth, the 2-aza isomer, has been reported. In a number of cases where ring closure can occur in two directions, giving rise to two different ring systems, the identity of the product having the azabenzo[*c*]phenanthrene nucleus has not been established conclusively. The total number of preparations of members of all three systems is very small. (The azabenzo[*c*]phenanthrenes and their derivatives which appear in the literature are listed in Table 25.)

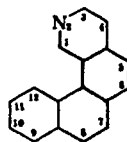
A. 1-Azabenzo[*c*]phenanthrene, Naphtho[2,1-*b*]quinoline



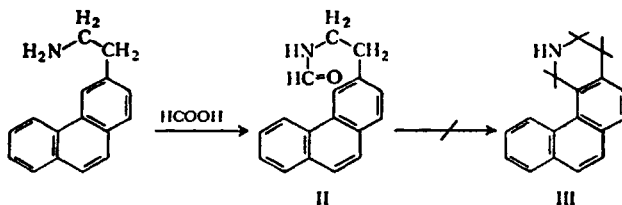
1-Azabenzo[*c*]phenanthrene (I), the only member of this series which is reported in the literature, was prepared by Cook and Thomson¹ by a Skraup reaction on 4-aminophenanthrene, using *m*-nitrobenzenesulfonic acid as the oxidizing agent. The base is recrystallized from aqueous methyl alcohol, and it forms a water-soluble hydrochloride and a picrate. It was synthesized for biological testing as an inhibitor of tumor growth.



B. 2-Azabenzoc[*c*]phenanthrene, Naphth[2,1-*h*]-isoquinoline

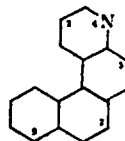


As yet no synthesis of any 2-azabenzoc[*c*]phenanthrenes has been reported, but Mosettig and May² synthesized the formyl derivative (II) of the phenanthrylethylamine which would be expected to give 2-aza-1,2,3,4-tetrahydrobenzo[*c*]phenanthrene (III) on loss of water. Although cyclization of the formyl derivatives of 2-(2'-aminoethyl)-phenanthrene and 9-(2'-aminoethyl)-phenanthrene yields the expected, tetrahydro derivatives of azachrysene and azatriphenylene (pages 154 and 185), cyclization of *N*-formyl-3-(2-aminoethylphenanthrene) (II) to 2-aza-1,2,3,4-tetrahydrobenzo[*c*]phenanthrene (III) could not be



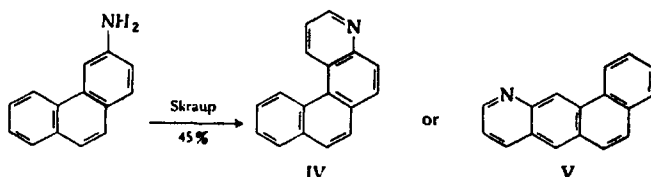
accomplished. The Decker and Becker⁸ method of cyclization was the most satisfactory for the 2- and 9-isomers, but this method and any of the others attempted resulted either in hydrolysis of the formyl group and recovery of the amine or in the formation of amorphous hydrochlorides which could not be purified.

C. 4-Azabenzoc[*c*]phenanthrene, Naphtho[1,2-*f*]-quinoline. R.I. 2742

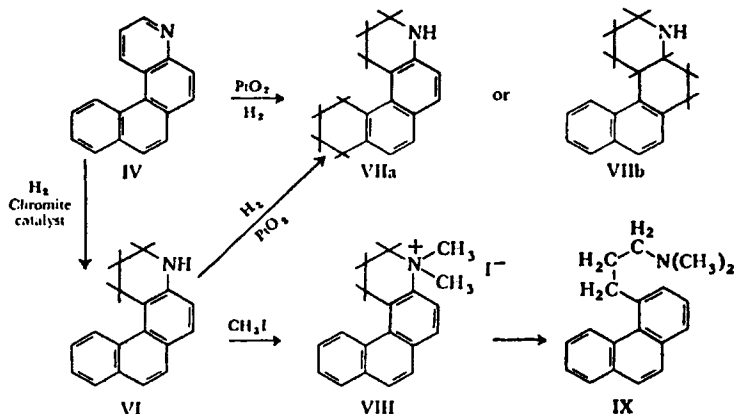


In the course of research related to the problem of drug addiction, Mosettig and Krueger⁴ prepared compounds containing a condensed phenanthrene and pyridine ring in order to simulate the properties of morphine, which at that time was the only known product, natural or synthetic, containing such a ring system. The product of the Skraup reaction of 3-aminophenanthrene appeared to be a single compound,

either 4-azabenzoc[*c*]phenanthrene (IV) or 11-azabenz[*a*]anthracene (V) rather than a mixture of the two isomers. Apparently ring closure had taken place exclusively in one of the two possible directions. Tetra and octahydro derivatives were prepared, and the Emde degradation,⁶ which involves boiling aqueous solutions of quaternary bases with sodium amalgam, was carried out on the methochloride of the *N*-methyltetrahydro derivative. However, the results of the degradation were not sufficiently clearcut for a final conclusion to be made as to whether the reaction product was IV or V.

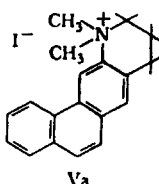
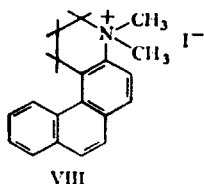


In a later paper, Mosettig and Krueger⁶ proved that the compound obtained is IV, 4-azabenzoc[*c*]phenanthrene. Some of the reactions carried out are shown in the flow sheet below.

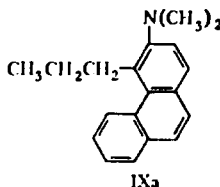
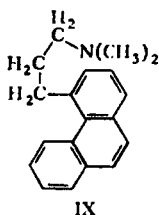


Although electrolytic reduction and reduction with tin and hydrochloric acid or sodium and alcohol are not satisfactory, high-pressure hydrogenation of IV with Adams' chromite catalyst readily yields VI,

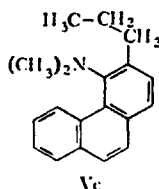
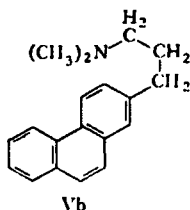
the tetrahydro derivative.^{4,6} The octahydro compound, (VIIa) or (VIIb), is best obtained by the platinum oxide hydrogenation of the pure tetrahydro compound, rather than of the aromatic base, since platinum oxide-catalyzed reduction of IV to VI takes place very slowly.



Because the product of the Skraup reaction on 3-aminophenanthrene is either IV or V, and because hydrogenation of quinolines occurs first in the pyridine ring, Mosettig and Krueger concluded by analogy that the methiodide of the tetrahydro derivative obtained must probably be either VIII or Va. The Emde degradation of the methiodide, $C_{19}H_{20}IN$, yields a base whose empirical formula, $C_{19}H_{21}N$ or $C_{19}H_{23}N$, fits any of these four compounds or their 9,10-dihydro derivatives.



or



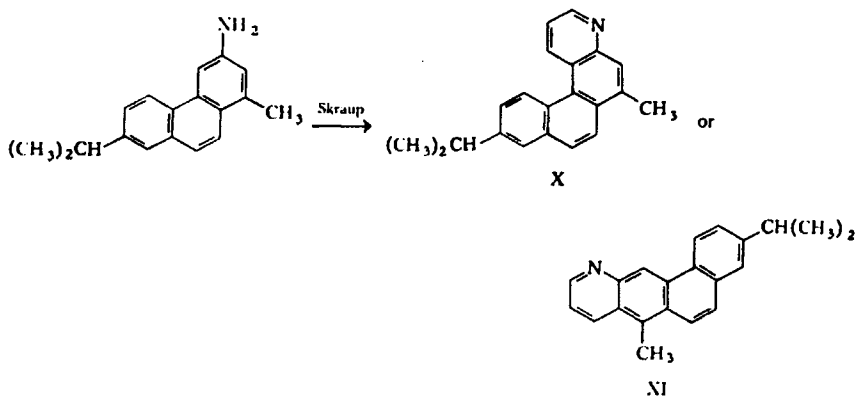
or

Since the degradation product and its hydrochloride are not identical with a synthetic sample of Vb or its 9,10-dihydro derivative and the corresponding hydrochlorides, it was concluded that the amine obtained was 4-[3-(dimethylamino)-*n*-propyl]-phenanthrene (IX). However, this compound was not synthesized to prove the identity of structures because

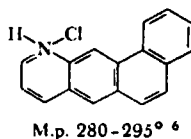
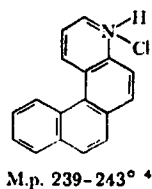
of the difficulties in preparation. The other two possible products (IXa) and (Vc) were eliminated as possibilities because such compounds are known to form methiodides with difficulty and to form readily hydrolyzable salts, while the compound obtained from the degradation forms a methiodide readily, and its hydrochloride does not hydrolyze.⁶

N-Methyl-4-aza-1,2,3,4-tetrahydrobenzo[*c*]phenanthrene shows very slight analgesic activity,⁶ and 4-azabenzoc[*c*]phenanthrene^{7,8} and its methiodide⁷ are noncarcinogenic in mice, when tested by painting the skin or by subcutaneous implantation.

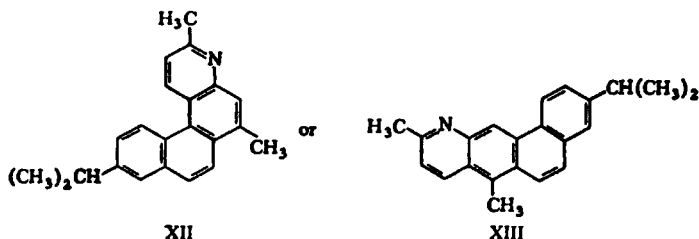
In the course of an investigation of the physiological activity of nitrogen-containing polycyclic compounds, Cassaday and Bogert⁹ obtained a single heterocyclic product, either X or XI, from a Skraup reaction on 3-aminoretene (3-amino-1-methyl-7-isopropylphenanthrene).



Since attempted hydrogenations of the base under varying conditions were uniformly unsuccessful, no degradation to determine the correct structure could be carried out. These authors commented on the unusually low melting point (96–101°) of the hydrochloride of the base obtained as compared with those of such hydrochlorides as:



The treatment of 3-aminoretene and paraldehyde in hydrochloric acid in the Doebner-Miller reaction yields either 10-isopropyl-3,6-dimethyl-4-azabenzoc[*c*]phenanthrene (XII) or 3-isopropyl-7,10-dimethyl-11-azabenz[*a*]anthracene (XIII).⁹ Cassaday and Bogert came to no conclusion as to which was the correct structure for the reaction product. They referred to the discussion of Mosettig and Krueger⁶ regarding various factors which may be involved, and commented that X is a more likely structure than XI by analogy with the behavior of 3-aminophenanthrene in the Skraup synthesis. On the other hand, they pointed out that the possible influence of the methyl group must be considered. Regardless of its actual structure, they predicted interesting uses of XII (or XIII) in the fields of new dyes, sensitizers, and drugs.



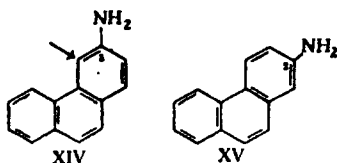
A more recent investigation¹⁰ of cyclizations involving the formation of four-ring heterocyclic systems has added further evidence to justify Mosettig and Krueger's conclusions. Ultraviolet absorption spectra show characteristic spectral differences between the ring systems benzo[*c*]phenanthrene and benz[*a*]anthracene. The absorption curve of 4-azabenzoc[*c*]phenanthrene (IV) follows very closely that of the parent hydrocarbon, while it differs markedly from the curve of 8,10-dimethyl-11-azabenz[*a*]anthracene, a homolog of V. (For further discussion and specific absorption data, see Table 12, page 90).

In the light of this recent work, it is probable that the structure of the two heterocycles obtained by Cassaday and Bogert⁹ may be determined by comparison of their absorption curves with those of the two possible heterocyclic ring systems.

Although Mosettig and Krueger⁶ did not attempt to justify or correct conclusions made by other workers as to the configurations of polycyclic compounds, they pointed out certain similarities and analogies. According to Marckwald's rule¹¹ (formulated from experimental evidence which indicates that a β -amino or β -hydroxy group, for instance, stabilizes

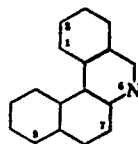
the symmetrical bond arrangement in naphthalene and hence in quino-line) ring closure, which forms a fused heterocyclic ring, takes place so that a double bond in the original ring is the common bond between the two (or more) rings of the new system.

If aminophenanthrene is considered by analogy to contain a fixed bond system, and if the rule holds, it would be expected that a Skraup reaction on 3-aminophenanthrene (XIV) would yield 4-azabenzoc[*c*]phenanthrene (IV) and 2-aminophenanthrene (XV), 1-azachrysene. Mosettig and Krueger prove the correctness of these assumptions. Although most ring closures involving side chains of —C—C—C— and —N—C—C—C— in the phenanthrene series do cyclize following Marckwald's rule, there are certain exceptions. A side chain, —C—C—C—C— , in the 3-position joins at the 2- rather than at the expected 4-position; and when side chains which will produce five- or six-membered

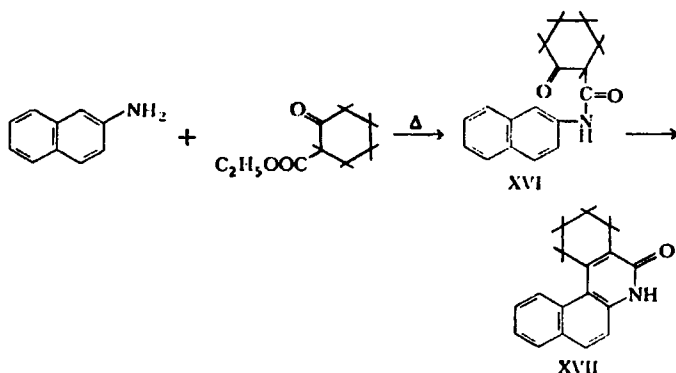


rings are attached in the 2-position of partially hydrogenated phenanthrenes, ring closure occurs in the 3-position. Mosettig attributed these apparent exceptions to steric effects. It is likely that the recent work of Johnson and his associates,¹⁰ in which both directions of ring closure are achieved by varying the conditions of cyclization, may elucidate this question.

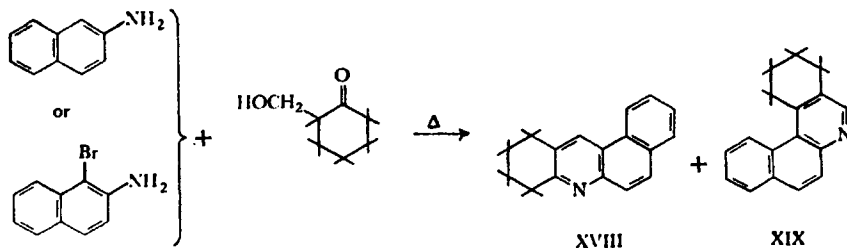
D. 6-Azabenzoc[*c*]phenanthrene, Benzo[*a*]-phenanthridine, β -Chrysidine. R.I. 2743



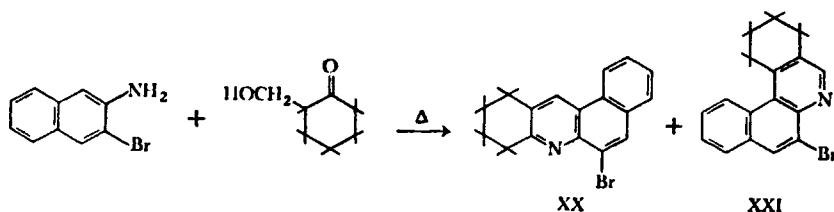
The first preparation of a 6-azabenzoc[*c*]phenanthrene was reported by Sen and Basu.¹² They assumed that the reaction product obtained by condensing β -naphthylamine with ethyl cyclohexanone-2-carboxylate was 5-keto-6-aza-1,2,3,4-tetrahydrobenzo[*c*]phenanthrene (XVII). Although the product apparently was not a mixture of isomers, neither proof of structure nor properties were reported.



While the condensation of 2-methylolcyclohexanone and aniline (as well as of various alkyl, nitro, or halo derivatives of aniline and α -naphthylamine) results only in the formation of phenanthridines (angular ring closure),¹³ two isomeric tetrahydro bases (XVIII) and (XIX) are unexpectedly obtained by the condensation of this hydroxy ketone with



β -naphthylamine.^{13,11} Since the same two bases (XVIII) and (XIX) are obtained from a condensation using 1-bromo-2-naphthylamine, it is evident that ring closure has taken place through the 1-position. As



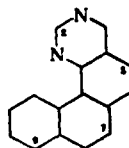
further evidence, 3-bromo-2-naphthylamine was condensed with the methylol compound; in this case, two isomeric bromine-containing compounds, $C_{17}H_{14}NBr$, (XX) and (XXI), were obtained. The authors did

not specify which product was the 7-bromo-6-aza-1,2,3,4-tetrahydrobenzo[*c*]phenanthrene (XXI) because too little material was available for further investigation of the isomers. Their conclusions regarding the unsubstituted heterocycles (XVIII) and (XIX), were based on the fluorescence of solutions of the bases in sulfuric acid, but nothing was reported of the properties of such solutions of the two bromine-containing bases. The higher melting unsubstituted base was assigned the structure (IV) because it showed the blue fluorescence characteristic of phenanthridines instead of the green fluorescence shown by acridines.

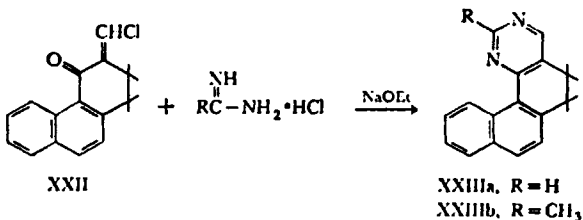
2. Diazabenzoc[*c*]phenanthrenes

Of the thirty-six theoretically possible isomeric diazabenzoc[*c*]phenanthrenes, only two systems are reported in the literature. The information available on members of the 1,3-series is very limited, but a comparatively large number of 5,8-diazabenzoc[*c*]phenanthrenes have been prepared.

A. 1,3-Diazabenzoc[*c*]phenanthrene, Naphtho-[2,1-*h*]quinazoline

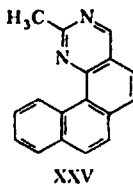
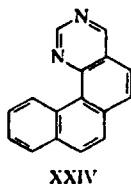


The only compounds of the series 1,3-diazabenzoc[*c*]phenanthrene reported so far were synthesized by Cook and Thomson¹ for biological testing. The reaction of 3-chloromethylene-4-keto-1,2,3,4-tetrahydrophenanthrene (XXII) with formamidine or acetamidine hydrochlorides

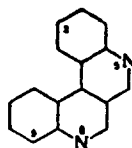


yields 1,3-diaza-5,6-dihydrobenzo[*c*]phenanthrene (XXIIIa) or 2-methyl-1,3-diaza-5,6-dihydrobenzo[*c*]phenanthrene (XXIIIb), respectively. De-

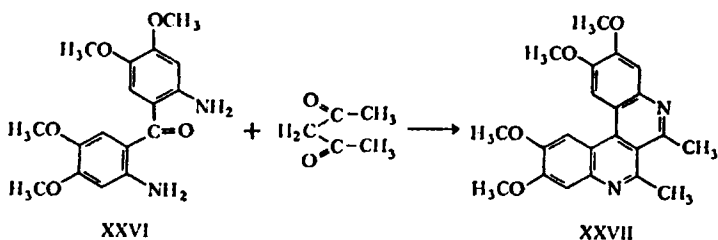
hydrogenation of both dihydro bases over palladium black produces 1,3-diaza- (XXIV) and 2-methyl-1,3-diazabenzoc[*c*]phenanthrene (XXV). The picrates of all four compounds were prepared but no further characterization of these heterocyclic products was reported.



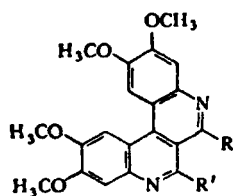
**B. 5,8-Diazabenzoc[*c*]phenanthrene, Dibenzo-
[*c,f*]copyrine. R.I. 2710**



A number of substituted 5,8-dibenzo[*c*]phenanthrenes such as XXVII have been reported in the course of a series of investigations relating to the synthesis of heterocyclic systems analogous to that found in harmine.¹⁶ The general reaction, the so-called double Friedländer synthesis, depends upon the reactivity of 2,2'-diaminobenzophenones and a β -diketone. For example, 2,3,10,11-tetramethoxy-6,7-dimethyl-5,8-diazabenzoc[*c*]phenanthrene (XXVII) is prepared by heating diaminoveratrone (XXVI)



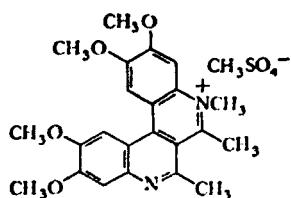
with an equivalent of acetylacetone in acetic acid solution. The reaction time is short and the yield of product good. These 5,8-diazabenzoc[*c*]phenanthrenes serve as useful derivatives for the identification of dibenzoylmethanes,¹⁶ and a number of qualitative characteristics of these derivatives have been reported.



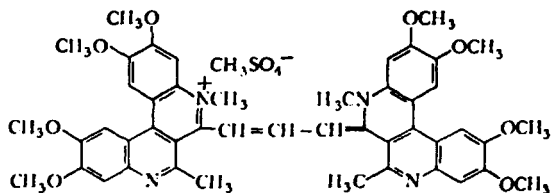
$R = R'$ and $R \neq R'$

R and $R' = \text{CH}_3-$, C_6H_5- ,
 $-\text{OH}$, $-\text{NH}_2$, $\text{ClC}_6\text{H}_4 =$
 $\text{CH}_2\text{OC}_6\text{H}_4-$, etc. (see
 Table 25, pages 144–148)

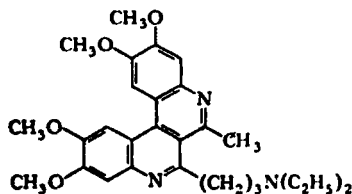
Three other compounds containing the 5,8-diazabenzoc[*c*]phenanthrene nucleus were prepared for testing as antimalarials.¹⁷ The methosulfate (XXVIII) of XXVII is first prepared; on treatment with ethyl orthoformate, the cyanine (XXIX) is obtained. The third compound (XXX) is prepared in good yield by condensing 7-diethylaminoheptane-2,4-dione with the diaminoveratrone (XXVI).



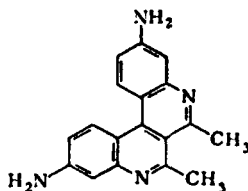
XXVIII



XXIX



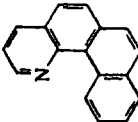
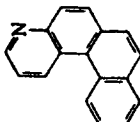
XXX

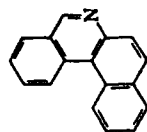


XXXI

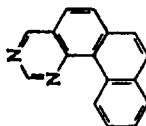
By treating 2,4,2',4'-tetraminobenzophenone with acetylacetone, Gulland and Robinson¹⁸ prepared 3,10-diamino-6,7-dimethyl-5,8-diazabenzoc[*c*]phenanthrene (XXXI) in almost quantitative yield. Since 2,2'-diaminobenzophenone would probably give good yields of easily purified, crystalline compounds with most β -diketones, both alkyl and aralkyl, it is surprising that no work with these simpler unsubstituted diaminobenzophenones has as yet been reported.

TABLE 25. Azabenzoc[*c*]phenanthrenes

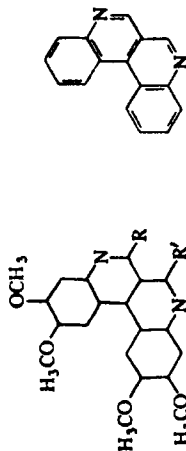
Formula	Compound	Rcd.	Appearance	Properties
 1-Azabenzoc[<i>c</i>]phenanthrene:				
I	Unsubstituted	1	Colorless plates	m. 95–96°; ·P m. 200–201°, small yellow plates
 4-Azabenzoc[<i>c</i>]phenanthrenes:				
IV	Unsubstituted	4	Nearly colorless needles	m. 106–107°; lemon yellow ·HCl m. 239–243°
X	10-Isopropyl-6-methyl-(?)	9	White plates	m. 87.5–88.5°; pale yellow ·HCl m. 96–101°; yellow ·P m. 277–279° dec.
XII	10-Isopropyl-3,6-dimethyl-(?)	9	White plates	m. 110–111°; yellow ·HCl m. 258–261°; yellow ·P m. 221–226°
III	1,2,3,4-Tetrahydro- <i>N</i> -Methyl-1,2,3,4-tetrahydro-	4,6 6	Flat rods	m. 74–76°; white leaflets ·HCl m. 255–260° m. 77–78.5°; colorless ·HCl m. 215–217° dec.; ·MeI m. 185–187°; ·MeCl m. 174–176°
VIIa	1,2,3,4,9,10,11,12-(?)-Octahydro-	4,6		m. 111–112°; ·HCl m. 305–307°; white ·MeI m. 275–280° dec.

6-Azabenzoc[*c*]phenanthrenes:

	Unsubstituted	13,14	m. 127°; ·P m. 266-267° dec.
XIX	1,2,3,4-Tetrahydro-	13,14	m. 114-115°; ·P m. 218-219° dec.
XXI	7-Bromo-1,2,3,4-tetrahydro-	14	m. 133° or 145°; ·P m. 206° or 156-157°
XVII	5-Keto-1,2,3,4-tetrahydro-	12	m. 291-292°

1,3-Diazabenzoc[*c*]phenanthrenes:

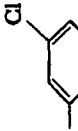
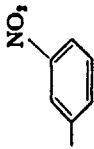
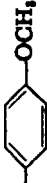
XXIV	Unsubstituted	1	Colorless rhombs	m. 155-156°; fine yellow needles ·P m. 255-258° dec.
XXV	2-Methyl-	1	White silky needles	m. 133-134°; yellow ·P m. 217-219° dec.
XXIIIa	5,6-Dihydro-	1	Colorless prisms	m. 70-71°; deep yellow ·P m. 238-239° dec.
XXIIIb	2-Methyl-5,6-dihydro-	1	Thick colorless prisms	m. 102-103°; fine yellow needles ·P m. 216-217° dec.

5,8-Diazabenzoc[*c*]phenanthrenes:

	R	R'		
1	—CH ₃	—CH ₃	Colorless needles	m. 230-231°; reddish-violet Fl; yellow Strong
XXVII			15	·HNO ₃ and ·P dec. 245°; salts with bluish-green Fl

Table continued

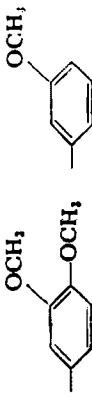
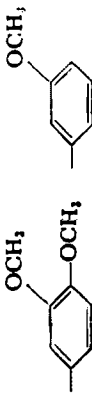
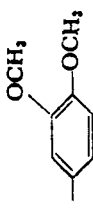
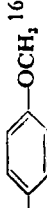
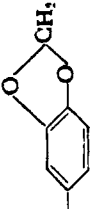
TABLE 25. Azabenzoc[*c*]phenanthrenes (Continued)

Formula	R	R'	Ref	Appearance	Properties	Basicity
5,8-Diazabenzoc[<i>c</i>]phenanthrenes (continued)						
2	$-\text{C}_6\text{H}_5$	$-\text{CH}_3$	15	Colorless needles	m. 270°; no Fl; yellow salts with green Fl	Moderately strong
3	$-\text{C}_6\text{H}_5$	$-\text{C}_6\text{H}_5$	15	Faintly yellow needles	m. 362°; no Fl; yellow salts with green Fl	Weak
4		$-\text{C}_6\text{H}_5$	16	Plates	m. >355°; yellow salts	—
5		$-\text{C}_6\text{H}_5$	16	Plates	m. >370°	—
6		$-\text{C}_6\text{H}_5$	16	Pale yellow needles	m. 324°; bright yellow salts	—
7		$-\text{C}_6\text{H}_5$	16		m. >355°; orange salts	Fairly weak
8	$-\text{NH}_2$	$-\text{OH}$	15	Terra cotta needles	280–290° dec.; pale yellow salts with bluish-violet Fl	Phenolic character
9	$-\text{CH}_3$	$-\text{OH}$	15	Pale yellow needles	Soft 310°, m. 320–330°; bluish-violet Fl; yellow salts with yellowish-green Fl	Weak
10	$-\text{OH}$	$-\text{OH}$	15	Yellow needles	Soft 285°, 300° dec.; yellow salts with bright bluish-green Fl	10 > 3
11		$-\text{C}_6\text{H}_5$	16	Almost colorless needles	Dec. 352°; yellow salts	11 > 3

Formula	R	R'	Ref.	Appearance	Properties	Basicity
12		-C ₆ H ₅	16	Faintly yellow needles	m. 315°	12 > 11
13		-C ₆ H ₅	16	Micro needles	m. 308°; orange-yellow salts	13 > 12 > 11
14		-C ₆ H ₅	16	Pale yellow needles	m. 355°; orange salts	—
15		-C ₆ H ₅	16	Needles	m. 296°	Strong 15 = 13
16		-C ₆ H ₅	16	Pale yellow needles	m. 323°; yellow salts	15 > 16
17			16	Almost colorless needles	m. 290-293°	15 > 17
18		-C ₆ H ₅	16	Pale yellow needles	m. 289°; orange salts	15 > 18

Table continued

TABLE 25. Azabenzoc[*c*]phenanthrenes (Continued)

Formula	R	R'	Ref.	Appearance	Properties	Basicity
5,8-Diazabenzoc[<i>c</i>]phenanthrenes (continued)						
19			16	Almost colorless needles	m. 301–305°; orange salts	13 > 19 > 3
20			16		m. 300°	Moderately strong
21		—C ₆ H ₅	16	Pale yellow needles	m. 328°	—
XXVIII	<i>N</i> -Methyl methosulfate XXVII		17	Greenish-yellow needles	Dec. 250°; red solns. with intense green fl	—
XXIX	Cyanine from 2 moles XXVIII		17	Mauve-black needles with green luster	m. 205°; absorption 5600 Å, 6100 Å, log ϵ 3.45, 3.55; dichroic soln. crimson and blue-green	—
XXX	—CH ₃ —(CH ₂) ₂ N(C ₆ H ₅) ₂		17	Cream-colored needles	m. 148–149°; saffron micro needles, ·HCl, without definite m.p.	—
XXXI	3,10-Diamino-6,7-dimethyl-5,8-diazabenzoc[<i>c</i>]phenanthrene		18	Pale brown cubes	Partial dec. 305°, not melted by 340°; weak green fl, orange-red, ·3HCl dec. 310° without melting	—

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14. Kenner, Ritchie, and Wain, *J. Chem. Soc.*, **1937**, 1526.
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16. Bradley and Robinson, *J. Chem. Soc.*, **1926**, 2356.
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CHAPTER IV

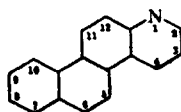
Azachrysenes*

BY JEAN V. CRAWFORD

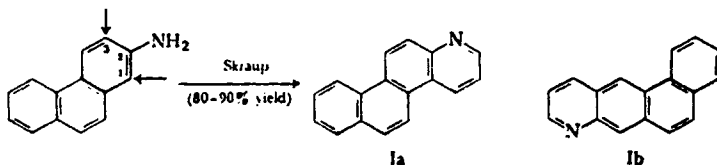
1. Monoazachrysenes

A representative of each of the six theoretically possible monoazachrysenes, 1-, 2-, 3-, 4-, 5-, and 6-, has been prepared. However, in most cases only a few derivatives of the parent heterocycle have been made, and no systematic study of the chemical properties of any of these ring systems has been carried out.

A. 1-Azachrysene, Naphtho[2,1-*f*]quinoline.
R.I. 2738



Although an impure product was obtained when 2-aminophenanthrene was first used in a Skraup reaction, Herschmann¹ suggested that 1-azachrysene (Ia) might have been formed. Using the same reactants, Mosettig and Krueger² prepared in excellent yield a single compound (I) to which they also assigned the structure Ia. Since ring closure may



take place through either the 1- or the 3-position of phenanthrene, the product formed from the Skraup reaction might have structure Ia or Ib. Furthermore, compound I is not identical with the product I' obtained by dehydrogenation of the dihydronaphthoquinoline formed from the Skraup reaction on 2-amino-9,10-dihydrophenanthrene, and thus it was necessary to decide between structures Ia and Ib, the only probable configurations for compound I (see page 85). According to an extension of Marckwald's rule, cyclization would be expected to take place through the 1-position, thus preserving a double bond between the two rings and producing Ia.

Mosettig and Krueger based their conclusion as to the structure of the reaction product on the following evidence: a tetrahydro compound is readily prepared by catalytic hydrogenation at 140° and high pressure, using as a catalyst either platinum oxide or copper chromite. At higher temperatures, a hexahydro derivative is obtained. The Emde³ degradation of the methiodide of the *N*-methyltetrahydro derivative of I gives a product whose analysis does not distinguish between its being an α -(dimethylamino-*n*-propyl)phenanthrene or a 9,10-dihydro-3-(dimethylamino-*n*-propyl)phenanthrene, which could be formed by reduction during the Emde degradation. Thus, the compounds IIa and IIa' (which would be formed from Ia) and IIb and IIb' (which would be the degradation products of Ib) were considered as possible structures for the Emde degradation product.

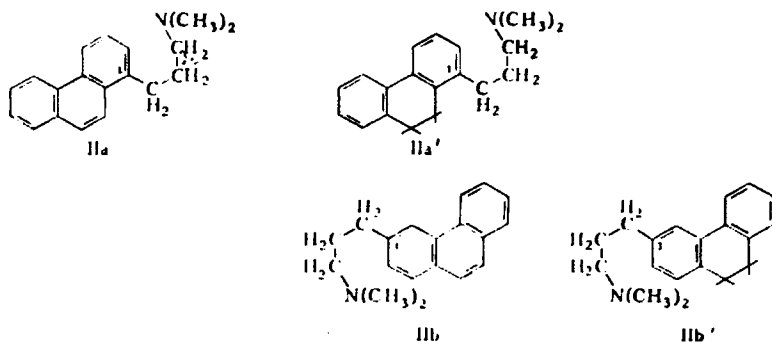


TABLE 26. Melting Points of Derivatives of α -(Dimethylamino-*n*-propyl)phenanthrenes

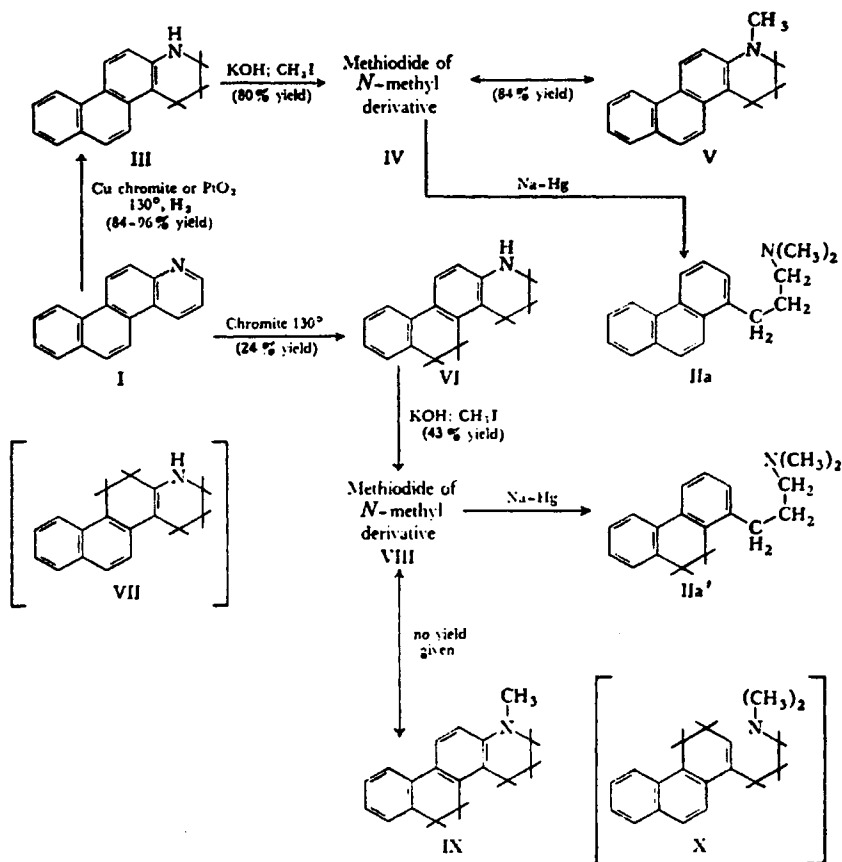
Derivative	Product	Hydrochloride, $^\circ\text{C}$.	Picrate, $^\circ\text{C}$.
Emde degradation product of the methiodide of <i>N</i> -methyltetrahydro I	—	206–207 (210–213)	164.5–166.5
Emde degradation product of the methiodide of <i>N</i> -methylhexahydro I	IIa'	207–209	145.5–146.5
Emde degradation product of the methiodide of <i>N</i> -methylhexahydro I'	IIb'	150–151	101.5–103
Synthetic 3-[3-(dimethylamino)- <i>n</i> -propyl]-phenanthrene	IIb	160.5–162	150.5–151.5

As a comparison of the corresponding hydrochlorides and picrates shows, the degradation product of I is different from a synthetic sample of IIb, and from IIb', prepared by degradation of the methiodide of an *N*-methylhexahydro derivative of a compound proved to have structure Ib. Therefore, the degradation product must be either IIa or IIa'. Since the Emde degradation product of hexahydro I must be a dihydro derivative, it is IIa'. The degradation product from I is obviously different

from IIa' and must then be IIa. Therefore, the product of the Skraup reaction on 2-aminophenanthrene is 1-azachrysene (Ia).

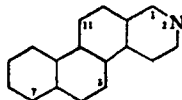
Recently, Johnson and Woroch¹ have shown the similarity between the absorption spectra of chrysene and those of the naphthoquinoline prepared by Mosettig and Krueger's procedure, thus further confirming the 1-azachrysene structure for I.

The structure of the most saturated compound, apparently a hexahydro derivative, is probably 1,2,3,4,5,6-hexahydro-1-azachrysene (VI), although the possibility of a 1,2,3,4,11,12-hexahydro derivative (VII) may be considered.² Emde degradation of the methiodide of the *N*-methyl derivative of VII, however, should yield a 1-[3-(dimethylamino)-*n*-propyl]-3,4-dihydrophenanthrene (X) which might be further reducible to a tetrahydrophenanthrene during the degradation. This additional reduction was not observed.

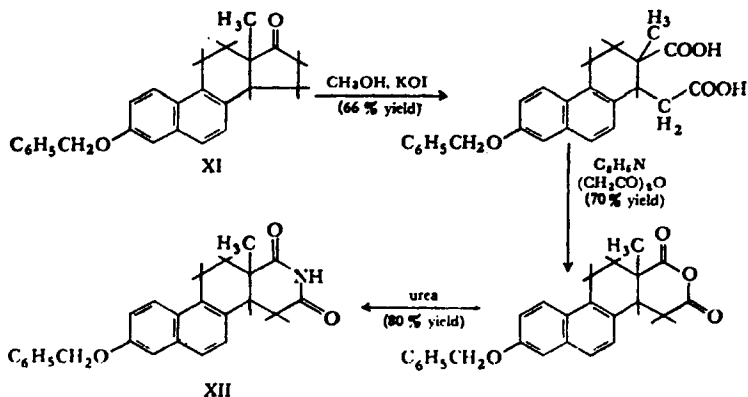


This series of compounds was prepared to test for possible pharmacological activity. 1-Methyl-1,2,3,4-tetrahydro-1-azachrysene shows no analgesic action (200 mg./kg.) in cats but causes slight depression in doses of 200 mg. 1-Azachrysene is reported to have no carcinogenic action in mice.⁵

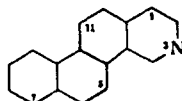
B. 2-Azachrysene, Naphtho[2,1-*f*]isoquinoline



The only representative of this heterocyclic system reported in the literature is synthesized from equilenin benzyl ether (XI) by the following series of reactions.⁶ The product, 8-benzyloxy-12 α -methyl-2,4,4a,11,12,12a-hexahydro-2-aza-1,3-chrysenedione (XII), is only slightly soluble in methanol, ethyl alcohol, acetone, and ethyl acetate but dissolves readily in acetic acid.

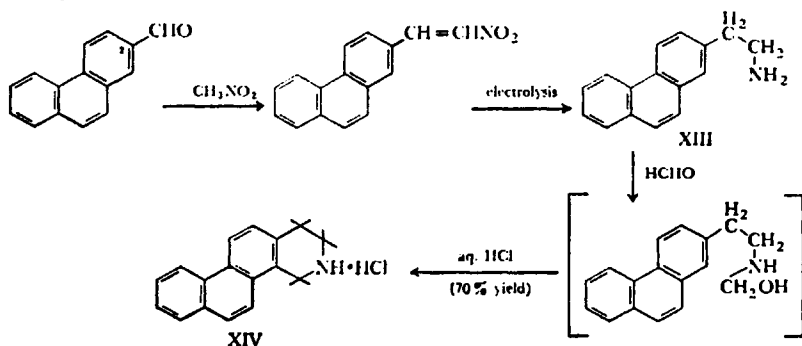


**C. 3-Azachrysene, Naphtho[1,2-*h*]isoquinoline.
R.I. 2739**



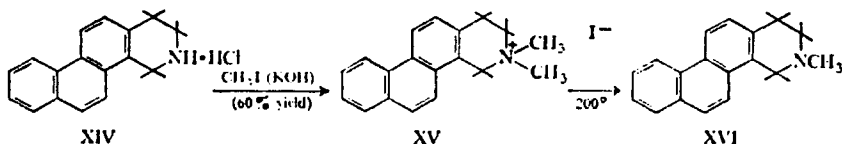
A tetrahydro-3-azachrysene was synthesized by Mosettig and May,⁷ who prepared several isoquinoline derivatives which, it was thought, might prove valuable pharmacologically because of their structural relationship to morphine. The series of reactions employed with 2-(2'-aminoethyl)-phenanthrene are the same as those described (page 185) for the formation of 2-azatriphenylene from 9-(2'-aminoethyl)phenanthrene.

The requisite 2-(2'-aminoethyl)-phenanthrene (XIII) is prepared from 2-phenanthrenecarboxaldehyde in the following way:



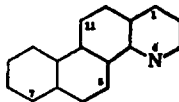
Successful cyclization of the formaldehyde product of pure XIII to the tetrahydroisoquinoline derivative is effected by Decker and Becker's method employing aqueous hydrochloric acid. Structure XIV is assumed to represent the product because cyclizations of side chains, $-\text{C}-\text{C}-\text{C}$, $-\text{C}-\text{C}-\text{C}-\text{C}$, and $-\text{N}-\text{C}-\text{C}-\text{C}$, attached to the 2-position of phenanthrene, are believed to take place preferentially through position 1.

Since the hydrochloride (XIV) is likely to be contaminated with small quantities of 2-(2'-aminoethyl)-phenanthrene hydrochloride from which it is separable only with difficulty, purification is achieved by conversion of the crude hydrochloride by way of the quaternary methiodide (XV), to the *N*-methyl compound (XVI). The latter is readily purified.



A compound whose hydrochloride is identical with the hydrochloride of XVI was obtained by complete methylation of 2-(2'-aminoethyl)-phenanthrene, followed by decomposition of the resulting methiodide with heat.

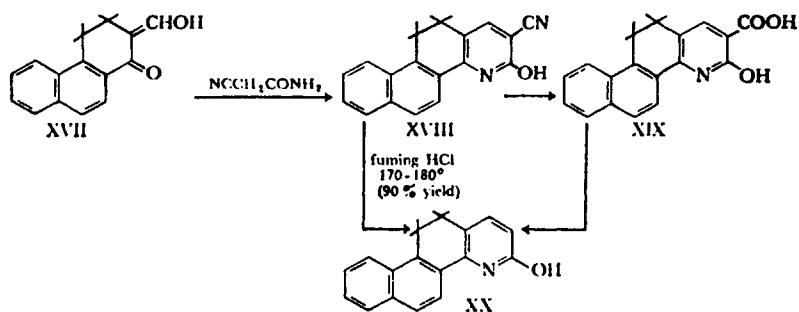
D. 4-Azachrysene, Naphtho[1,2-*h*]quinoline



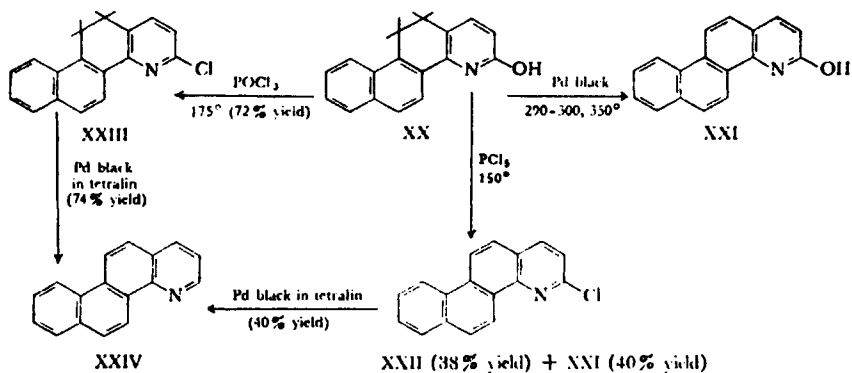
4-Azachrysene and certain of its derivatives have been prepared as compounds which, it was thought, might have an inhibitory action on tumor growth without having the carcinogenic characteristics of the benz[*a*]anthracenes.⁸

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

condenses with cyanoacetamide to form 2-cyano-3-hydroxy-11,12-dihydro-4-azachrysenes (XVIII); this nitrile is hydrolyzed to the acid, which is then decarboxylated. The product, 3-hydroxy-11,12-dihydro-4-azachrysenes (XX), is prepared in better yield directly by treatment of the nitrile with fuming hydrochloric acid at 170–180°. 3-Hydroxy-11,12-dihydro-4-azachrysenes forms a sodium salt in concentrated sodium hydroxide; this salt, however, does not react with methyl iodide or diazomethane. When the salt is treated with dimethyl sulfate at 100° for several hours, a sulfur-containing product is formed, but this has not been characterized further. 3-Hydroxy-11,12-dihydro-4-azachrysenes is dehydrogenated by palladium black, is converted to a mixture of 3-

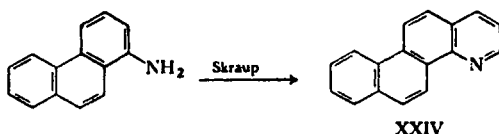


hydroxy-4-azachrysenes (XXI) and 3-chloro-4-azachrysenes (XXII) by treatment with phosphorus pentachloride, and yields 3-chloro-11,12-dihydro-4-azachrysenes (XXIII) with phosphoryl chloride.



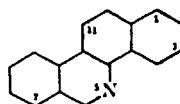
4-Azachrysenes (XXIV) may be prepared from either 3-chloro-4-azachrysenes (XXII) or its 11,12-dihydro derivative (XXIII) *via* pal-

ladium black in tetralin, or it may be synthesized from 1-aminophenanthrene by the Skraup reaction. As XXIV is the only probable product

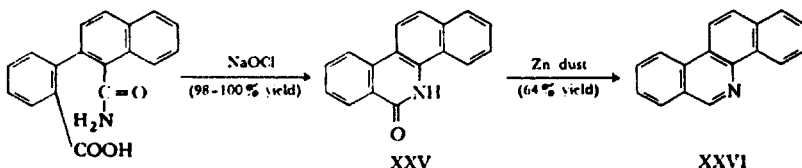


of the Skraup reaction, and since samples of the base prepared by either method are identical, the reaction of 2-hydroxymethylene-1-keto-1,2,3,4-tetrahydrophenanthrene with cyanoacetamide is shown to give exclusively the quinoline derivative (XVIII) rather than the possible isoquinoline.

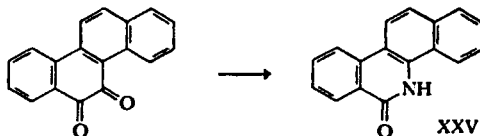
E. 5-Azachrysene, Benzo[c]phenanthridine, 1,2-Benzophenanthridine, α -Naphthophenanthridine, α -Chrysidine. R.I. 2740



Although there are a number of compounds containing the fundamental ring structure of 5-azachrysene, most of them are compounds of the chelidonium alkaloid group obtained from naturally occurring products. Graebe⁹ reported the first synthesis of the parent heterocycle (XXVI) by zinc dust distillation of 5-aza-6-chrysenone, which had been

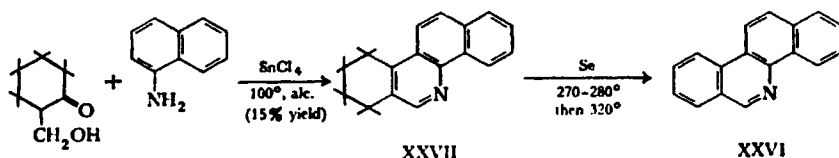


prepared by the reaction of sodium hypochlorite on 2-(2'-carboxyphenyl)-1-naphthamide. The intermediate ketone (XXV) may also be prepared from chrysenequinone and hydrazoic acid.¹⁰ An alternative route for the formation of 5-azachrysene involves the use of 1-naphthylamine with

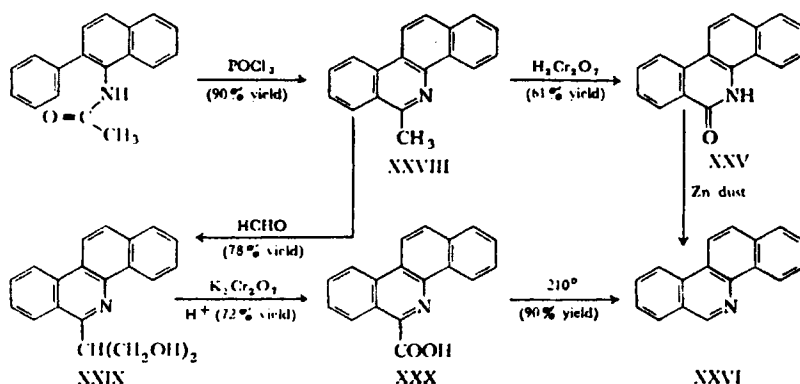


2-hydroxymethyl-1-cyclohexanone in the presence of stannic chloride, followed by dehydrogenation of the resulting tetrahydro derivative.¹¹

These authors found that stannic chloride was not essential and that the methylol solution, formed by the interaction of aqueous formaldehyde



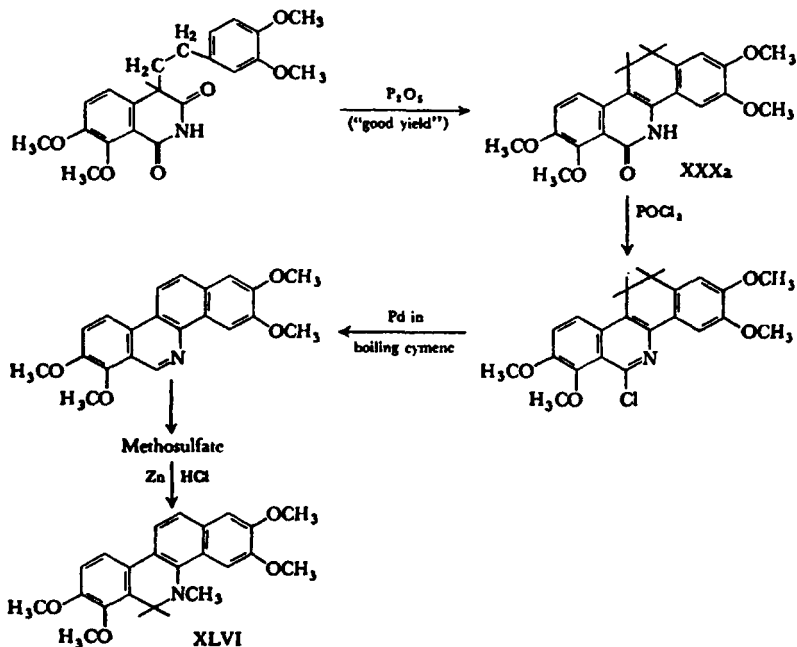
and cyclohexanone, could be used without purification; hence, convenience of this reaction with readily available materials may compensate for the low yield of the tetrahydro derivative. Ritchie¹² cyclized 1-acetamido-2-phenylnaphthalene to 6-methyl-5-azachrysene (XXVIII) by phosphoryl chloride. Various transformations carried out in this work are indicated below.



A new ring closure of a substituted β -arylethylhomophthalimide, which opens up a way to syntheses in the chelerythrine and sanguinarine series has recently been announced.^{12, 13a} The reference compound, 5,6-dihydro-2,3,7,8-tetramethoxy-5-methyl-5-azachrysene (XLVI)²⁶ has recently been synthesized by this procedure; substance XXXa has likewise been synthesized.^{13b}

A small amount of 5-azachrysene (XXVI) dissolves in concentrated sulfuric acid to give a colorless solution with blue fluorescence; in more concentrated solutions, however, the acid becomes yellow.⁹ The 6-dimethylolmethyl derivative behaves in the same way in hot mineral acids.¹² The yellow hydrochloride of XXVI, on the other hand, forms almost colorless solutions.⁹ 5-Azachrysene reacts with dimethyl sulfate in boiling toluene to form the methosulfate in good yield. Whereas

the methosulfate, whose aqueous and alcoholic solutions show a greenish-blue fluorescence, may be converted into the methiodide by aqueous potassium iodide, direct action of methyl iodide on 5-azachrysenone produces only a small yield of the salt. This resistance of 5-azachrysenone



to methylation with methyl iodide has been attributed to the hindrance due to the closeness of the ring at position 4.¹² Such an explanation seems inconsistent with the relative ease of formation of the methosulfate.

Four alkaloids of the isoquinoline group, chelidonine, sanguinarine, α -homochelidonine, and chelerythrine may be isolated from *Chelidonium majus* (the yellow poppy), and from some other members of the family *Papaveraceae*.^{*} Since these alkaloids are difficultly separable, both from other alkaloids occurring with them and from one another, many of the early observations reported in this particular field were made with impure material. Consequently, characterization and identification of the individual compounds have progressed slowly.

In 1829, Dana¹⁴ obtained sanguinarine from *Sanguinaria canadensis*.¹⁵

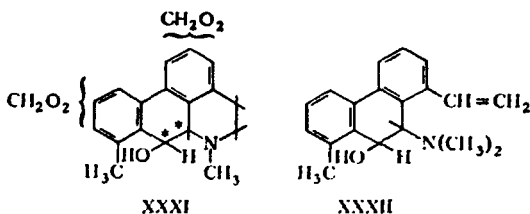
^{*}This section does not represent a complete survey of the literature, inasmuch as a separate volume in this series will deal with alkaloids. For this reason also, no details for the isolation of the separate compounds will be given.

In 1839, Probst¹⁶ reported the isolation from *Chelidonium majus* of chelidonine as well as a base which was called chelerythrine (*chel* + *erythros* = red + ine) because of the intense red color of its salts. Sanguinarine gave colorless acid salts, while the latter gave neutral salts. In the same year Reuling¹⁷ reported that chelidonine was volatile with steam, easily soluble in the usual organic solvents, and that an alcoholic solution was alkaline to litmus. α -Homochelidonine was obtained from *Chelidonium majus* and various of its characteristic color reactions were discussed by Selle¹⁸ in 1890.

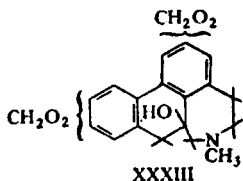
(1) Chelidonine

Since chelidonine is isolated in larger quantity than any of the other three alkaloids, a more thorough investigation of its properties has been made. Chelidonine forms salts with acids; it reacts with ethyl iodide, but the product is not acted upon by potassium hydroxide; it is oxidized by alkaline potassium permanganate to methylamine and oxalic acid¹⁹ but is unchanged by barium permanganate; and it is not reduced by either sodium amalgam or sodium in alcohol.²⁰ These reactions indicate that chelidonine is a tertiary base which possesses a methylimino group. A carefully purified sample was found to have the empirical formula $C_{20}H_{19}NO_5 \cdot H_2O$,²⁰ and to contain a hydroxy and two methylenedioxy groups. The base is optically active.

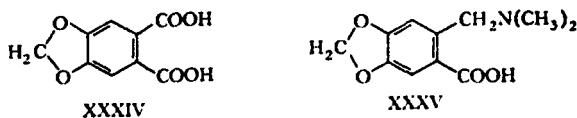
When this alkaloid is oxidized with mercuric acetate, a yellowish-red salt of a dehydro quaternary base is formed, which is readily transformed into the colorless carbinol, even by ammonia. The fact that the optical activity of the oxidized product is greater than that of the unoxidized form led Gadamer²¹ to assume that the double bond introduced is adjacent to an asymmetrical carbon atom. Acetylation of chelidonine with acetic anhydride at ordinary temperature produces an *O*-acetyl derivative which is optically active, while acetylation at the boiling point gives an *N*-acetyl compound which is optically inactive. Exhaustive methylation of chelidonine with methyl iodide yields chelidonine methine, $C_{21}H_{21}NO_5$; exhaustive methylation with methyl sulfate, however, gives a base, $C_{21}H_{19}NO_4$, methylanhydrochelidonine, identical with that resulting from the action of methyl sulfate on *O*-acetylchelidonine. Chelidonine methochloride or methosulfate, when boiled with sodium hydroxide, forms a strongly levorotatory methine base and a small proportion of an apparently inactive methine base. On the basis of these observations, Gadamer²¹ first proposed XXXI as the structure for chelidonine and XXXII as the corresponding methine.



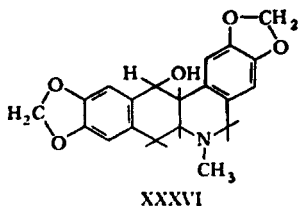
He later suggested the following structure:



In 1930, von Bruchhausen and Bersch²² showed that neither of these structures was justified in view of the work of Schwartz²³ and Kling.²⁴ Schwartz reported that oxidation of chelidonine-methine gave hydrastic acid (XXXIV) and 6-dimethylaminomethylpiperonylic acid (XXXV). The latter would not be a degradation product of XXXIII. Schwartz



assumed that the two acids were derived from different portions of the molecule, even though XXXV could be oxidized to XXXIV, and therefore proposed XXXVI as the formula for chelidonine.



Von Bruchhausen and Bersch,²² however, found that certain reactions of chelidonine, namely, the Hofmann degradation, its behavior toward ethyl chlorocarbonate, and its oxidative transformation into ψ -chelerythrine, were not adequately explained by this formula. Hofmann degradation should yield two optically active methine bases, but only one is known and that easily loses a mole of water in the presence of acid.

TABLE 27. Chelidonine*

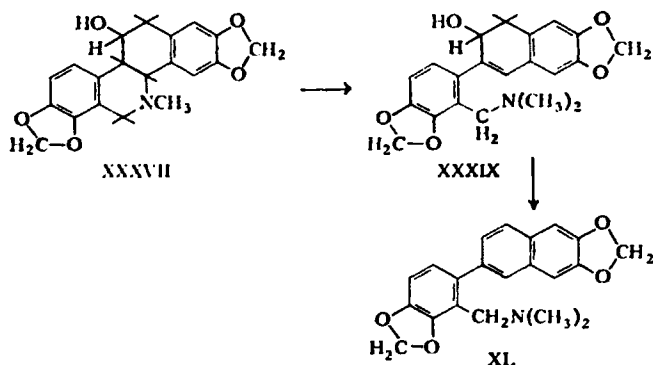
M.p., °C.	Other physical properties	Salts	Color reactions	M.p. of derivatives
135-136 (CHCl ₃ -EtOH) ³⁰ 134-135 ^{28a}	[α] _D 115°24' (2% in alc.) [α] _D 150°59' (1% alc.) [α] _D 117°02' (2% in CHCl ₃) ³⁰ [α] _D 122°55' ²⁸ Absorption spectra: Band between 3059.2 and 2666.7 A. with maximum in ex- treme ultraviolet and mini- mum at 2599.5-2598.5 ^{28a} Yellow fluorescence in alcohol or water ^{28b}	Sulfate [α] _D 90°56' (2% aq.) ³⁰	Conc. H ₂ SO ₄ : coffee-brown ³⁷ yellow, brownish, then violet ²⁸ Conc. HNO ₃ : orange-yel- low ³⁷ ; red-violet ²⁸ F.R.: violet, turning green ³⁷ ; yellow, then green, fin- ally blue-green ²⁸ E.R.: green ²⁸ M.R.: bright green, dark green, blue-green ²⁸ Reagent prepared by dissolv- ing 0.05 g. KReO ₄ in 5 ml. water and making up to 100 ml. with conc. sulfuric acid: grayish green and finally violet ²⁸ Acetyl derivative in sulfuric acid: practically color- less but gradually be- comes weak yellow F.R. colorless E.R. colorless M.R. yellow-green chang- ing to blue-green	Acetyl m.p. 161° ³⁰ m.p. 165-166° ^{28d} Dimorpha 184-186) ²⁸ [α] _D 110° ^{28d} Acetyl-aurichloride m.p. 155° ³⁰ —platinic chloride m.p. 204° ³⁰ Benzoyl m.p. 210-211° ³⁰ Compound with ethyl chloroformate m.p. 97-98° ²⁸ N-Acetyl m.p. 149-152° ²⁸

* F.R. = Froehde's reagent. E.R. = Erdmann's reagent. M.R. = Mandelin's reagent.

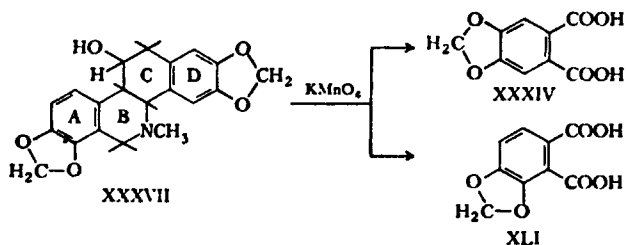
TABLE 28. Chelidonine Derivatives

Derivative and m.p., °C.	Empirical formula	Ref.	Preparation	Derivatives	Physical properties
Chelidonine perbromide	$C_{29}H_{19}BrNO_2$	20	Bromine water with chelidonine sulfate		
Bromocheilidonine 225–30 ¹⁰ 230–231 ¹²	$C_{29}H_{19}BrNO_2$		Sodium amalgam or zinc and sulfuric acid on the perbromide ¹⁰	Platinichloride m.p. 231 ¹⁰ Aurichloride m.p. 137 ¹⁰ O-Acetyl m.p. 150–152 ¹² N-Acetyl m.p. 170–172 ¹²	$[\alpha]_D^{25} 134.7'$ (CHCl ₃) $135.4'$ (CHCl ₃) (32)
Chelidonine peroxide >250	$C_{29}H_{19}NO_4 \cdot H_2O$	20	Hydrogen peroxide and sulfuric acid on cheilidonine		
Oxycheilidonine >285	$C_{29}H_{17}NO_4$	28	Naturally occurring; oxidation of cheilidonine with mercuric acetate	—	$[\alpha]_D^{25} 102.5'$ (natural) $100.4'$ (synthetic)
Methoxycheilidonine 221	$C_{31}H_{21}NO_4$		Naturally occurring	Aurichloride m.p. 237–238° O-Acetyl m.p. 137° (147°) aurichloride m.p. 136–137° Compound with ethyl chloroformate m.p. 107°	$[\alpha] 115.48'$ Conc. H ₂ SO ₄ : yellow, later ochre yellow Conc. HNO ₃ : yellow F.R.: green, dirty green, then dark green E.R.: yellow-red M.R.: red-brown

When Späth and Kuffner²⁸ oxidized *N*-acetylanhydrochelidonine with nitric acid to determine which of the proposed structures was correct they obtained trimellitic acid (benzene-1,2,4-tricarboxylic acid) instead



As was mentioned previously, chelidonine may be transformed into ψ -chelerythrine (sanguinarine) by mild oxidation. Sanguinarine is converted by zinc dust distillation into a compound, $C_{17}H_{11}N$, which is identical with a synthetic sample of 5-azachrysene,²⁸ thus establishing the fundamental ring structure for these compounds. Späth and Kuffner²⁸ also found that permanganate oxidation of chelidonine gives hydrastic acid (XXXIV) and 3,4-methylenedioxyphthalic acid (XLI), proving conclusively that the two methylenedioxy groups must be located on rings



A and D. In view of these oxidation products, which show that the hydroxy group is not in either of the rings containing methylenedioxy groups, together with the results of the Hofmann degradation of cheli-

donine, it seems reasonable to assume that the hydroxy group is located on ring C. It is thought to be at C₁₁ because of the characteristic behavior of the nitrogen-free compound derived from the Hofmann degradation of the base obtained by the Emde degradation of chelidonine.²⁴

Although the physiological action of chelidonine has been investigated thoroughly, it must be remembered that in many cases the compound tested was not pure and consequently some of the reactions observed are not caused by chelidonine.

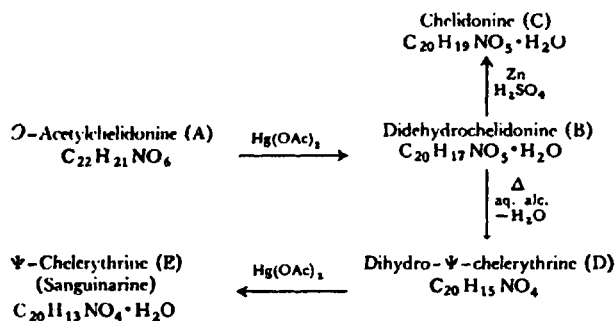
Gadamer and his collaborators have isolated two other alkaloids, apparently possessing the same fundamental structure as chelidonine, from the residues of chelidonine extracts. Gadamer and Theissen²⁵ demonstrated that the crystalline compound obtained by the oxidation of chelidonine with mercuric acetate is identical with a compound of similar structure occurring naturally and separated from the secondary products remaining after the commercial extraction of chelidonine. This so-called oxychelidonine, C₂₀H₁₇NO₆, differs from the one prepared by oxidizing chelidonine with hydrogen peroxide as described by Wintgen.²⁰ Oxychelidonine forms no acetyl derivative with acetic anhydride, no oxime, and no reduction product by reaction with zinc amalgam and hydrochloric acid. The second alkaloid, methoxychelidonine, C₂₁H₂₁NO₆, was shown by Gadamer and Winterfeld²⁶ to contain a methoxy, methylimino, two methylenedioxy, and a hydroxy group, and thus to be closely related to chelidonine. Von Bruchhausen and Bersch²² suggested that the methoxy group might be located at C₄, by analogy with narcotine, an alkaloid containing a similar arrangement of substituents.

(2) *Sanguinarine*

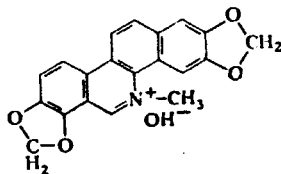
Sanguinarine, which occurs with chelerythrine and protopine and is difficultly separable from them, remained inadequately characterized for a number of years.²⁹ The naturally occurring alkaloid was reported to melt at 213°,³⁰ to crystallize with one-half mole of alcohol,³¹ and to form blood-red salts.

As previously mentioned, when *O*-acetylchelidonine (A) is oxidized by mercuric acetate, didehydrochelidonine (B) is formed which loses water when heated with alcohol to give dihydro- ψ -chelerythrine (D). Dihydro- ψ -chelerythrine (D) is oxidized by mercuric acetate to an intense red salt of a dehydro quaternary base, which is readily converted to the corresponding colorless carbinol base, ψ -chelerythrine (E).^{21,32}

It was shown by Gadamer and his co-workers³² that the so-called pseudochelerythrine formed by oxidation of chelidonine is identical

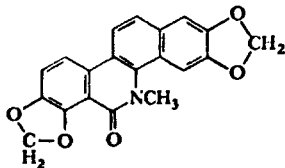


with sanguinarine, whose empirical formula was established as $\text{C}_{20}\text{H}_{14}\text{NO}_4 \cdot \text{OH}$. On zinc dust distillation of pure sanguinarine, Späth and Kuffner²⁶ obtained a base melting at 136° which Gadamer and co-workers²² had reported previously. However, Späth and Kuffner established its identity with Graebe's 5-azachrysene (page 157), and thus left no doubt as to the basic ring structure of both sanguinarine (XLII) and chelidonine.



XLII

In the course of isolating different alkaloids from the root of *Sanguinaria canadensis* (bloodroot), Späth and co-workers²³ separated a nitrogenous compound, which, because of its empirical formula, $\text{C}_{20}\text{H}_{13}\text{NO}_5$, appears to be closely related to the other *Sanguinaria* alkaloids (see also ref. 34). The new compound is difficultly soluble in the usual organic solvents and in dilute alkali and acid, contains no methoxy group, shows



XLIII

no optical activity, and melts at $360\text{--}361^\circ$ (vac. corr.). The investigators proposed the structure of "oxysanguinarine" (XLIII) and noted its analogy to oxychelidonine reported by Gadamer and Theissen²⁸ to

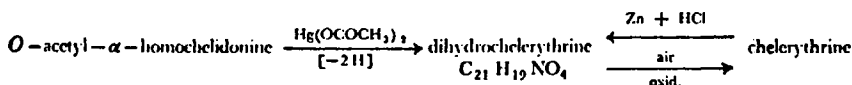
be found with chelidonine in celandine. Gadamer and Theissen²⁸ had also described oxysanguinarine as a nonbasic compound, melting above 285°, which is obtained in small yield by the action of hot alkali on sanguinarine. Oxidation of pure sanguinarine with alkaline potassium ferricyanide gives a product identical with the natural product.³³

TABLE 29. Sanguinarine (ψ -Chelerythrine) and Related Compounds

Compound	M.p., °C.	Physical properties	Color reactions	M.p. of derivatives
Sanguinarine	211 (1/2 EtOH) ³¹ 212, 213 ^{30, 36} 266–267 ²⁸	Bluish-violet ³⁰ Fluorescence	Conc. H ₂ SO ₄ : blue F.R.: brownish-green; gradually streaked with blue ²⁷	ψ -cyanide m.p. 235.5–237° ³³
Compound	Empirical formula	Preparation	M.p., °C.	
Dihydrosanguinarine	—	Sanguinarine nitrate and zinc and hydrochloric ³⁸	188–189 (vac.) ³⁸	
Oxysanguinarine	C ₂₀ H ₁₂ NO ₅	Naturally occurring; sanguinarine + potassium ferricyanide ³³ ; sanguinarine + hot alkali ²⁸	360–361 (vac., corr.) 360–361 (vac., corr.) ³³ >285 ²⁸ 205 ³⁶	
Sanguinarine periodide	C ₂₀ H ₁₅ I ₂ NO ₄ ·HI	—		

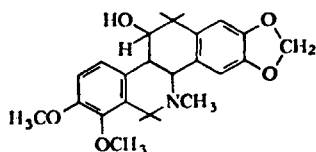
(3) α -Homochelidonine

Gadamer²¹ showed that α -homochelidonine contains two methoxy groups, a methylenedioxy, a methylimino, and an alcoholic hydroxy group; that its optical activity is of the same direction and order of magnitude as that of chelidonine; and that it resembles chelidonine in many of its reactions. For example, acetylation with acetic anhydride at moderate temperature gives an *O*-acetyl derivative, whereas on acetylation at the boiling point the heterocyclic ring is cleaved, water is lost, and *N*-acetylanhydrohomochelidone is formed. In addition, when the *O*-acetyl compound was oxidized with mercuric acetate, Gadamer²⁵ showed that the product formed is identical with the dihydrochelerythrine obtained from chelerythrine by Karrer,³⁹ and that on oxidation in air the dihydro compound gives chelerythrine. This series



of reactions is analogous to the conversion of chelidonine into sanguinarine described on page 166.

Gadamer's²¹ conclusion that α -homochelidonine (XLIV) is analogous to chelidonine—one methylenedioxy group being replaced by two methoxy groups—is now accepted as correct.



XLIV

TABLE 30. Properties of α -Homochelidonine*

M.p., °C.	Physical properties	Ref.	Color reactions
182 (from acetic acid)		18	Conc. H ₂ SO ₄ : gradual formation of yellow streaks Conc. HNO ₃ : yellow, sulfomolybdic acid, dirty brownish-green and then brownish-yellow Erdmann's reagent + H ₂ SO ₄ → reddish-yellow
169–70 (from ethanol)	Monoclinic $\leq x_8$ a:b:c = 0.9883:1:1.4035 [β —76°8']	20	
		37	Conc. H ₂ SO ₄ : coffee-brown sulfomolybdic acid, violet then green Conc. HNO ₃ : orange-yellow
	[α] _D = +118°25' M = 437.3	28	F.R.: smutty brown-green then yellow-brown E.R.: reddish-yellow M.R.: reddish-yellow Conc. HNO ₃ : yellow

* F.R. = Froehde's reagent. E.R. = Erdmann's reagent. M.R. = Mandelin's reagent.

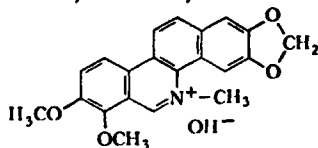
(4) Chelerythrine

Chelerythrine crystallizes from alcohol as colorless leaflets, m.p. 203° containing one mole of alcohol,³⁰ or from toluene with one-half mole of toluene, m.p. 257°.³¹ Alcoholic solutions of the pure alkaloid are colorless and show no fluorescence, although a few pure preparations⁴⁰ show a blue-violet fluorescence. Its salts are yellow.³⁰

On the basis of the reaction with phenylhydrazine, Karrer³⁹ reported that this alkaloid contained a ketonic group. When the carbonyl group

was altered, the basic properties of the compound were destroyed. According to Karrer,^{39,41} when chelerythrine is treated with Grignard reagents, nonbasic alkyl dihydro derivatives are formed. Reduction of chelerythrine with tin and hydrochloric acid produces dihydrochelerythrine, a white, nonbasic compound which is insoluble in and gives no color with hydrochloric acid.³⁹ Catalytic hydrogenation with colloidal palladium causes two atoms of hydrogen to be absorbed but no pure product could be isolated.⁴⁰ Gadamer³⁵ demonstrated that since chelerythrine contains two methoxy groups in addition to one methylenedioxy group, no ketonic group is present, and that the reactions which were ascribed to the ketonic group have been noted with other alkaloids (cotarnine and berberine), which are assumed to exist in different tautomeric forms, one of which is an iminoaldehyde. Chelerythrine behaves toward acids as a quaternary ammonium base whose basic properties are due to nitrogen, not oxygen as postulated by Karrer. The free ammonium base apparently does not exist, but a colorless carbinol base is formed when the salts are treated with alkali. Gadamer³⁵ proved Karrer's dihydrochelerythrine to be identical with the product obtained by mercuric acetate oxidation of *O*-acetylhomochelidonine, thus showing the fundamental relationship between α -homochelidonine and chelerythrine.

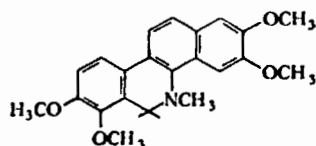
In an attempt to determine the structure of chelerythrine, Späth and Kuffner⁴² isolated the pure compound from a commercial mixture of sanguinarine and chelerythrine by crystallizing the nitrates and finally converted chelerythrine into the pseudocyanide. Chelerythrine chloride was prepared from this by boiling with concentrated hydrochloric acid and methanol. After oxidation of the chloride with potassium permanganate at room temperature, hemipinic methylimide (*N*-methyl-3,4-dimethoxyphthalimide) and hydrastic acid (XXXIV) were isolated. Since the oxygen atoms in chelidonine and α -homochelidonine, and in chelerythrine, are assumed to occupy the same positions, and since zinc dust distillation of chelerythrine chloride gave 5-azachrysenes, Späth and Kuffner⁴² represented chelerythrine by XLV.



XLV

In order to prove with certainty that the substituents in chelerythrine and sanguinarine occupy the same positions, Späth and Kuffner³⁸ first

transformed each base into the corresponding dihydro derivatives (to facilitate saponification of the methylenedioxy group in chelerythrine), then saponified the dihydro derivatives with phloroglucinol and boiling sulfuric acid, and finally methylated the resulting dihydrophenols. The



XLVI

product in each case was *N*-methyl-2,3,7,8-tetramethoxy-5-aza-5,6-dihydrochrysen-3-one (XLVI), thus demonstrating the similarity in structure of these four alkaloids.

In an attempt to synthesize compounds of the chelerythrine-sangui-

INTERRELATIONSHIPS OF CHELIDONIUM ALKALOIDS

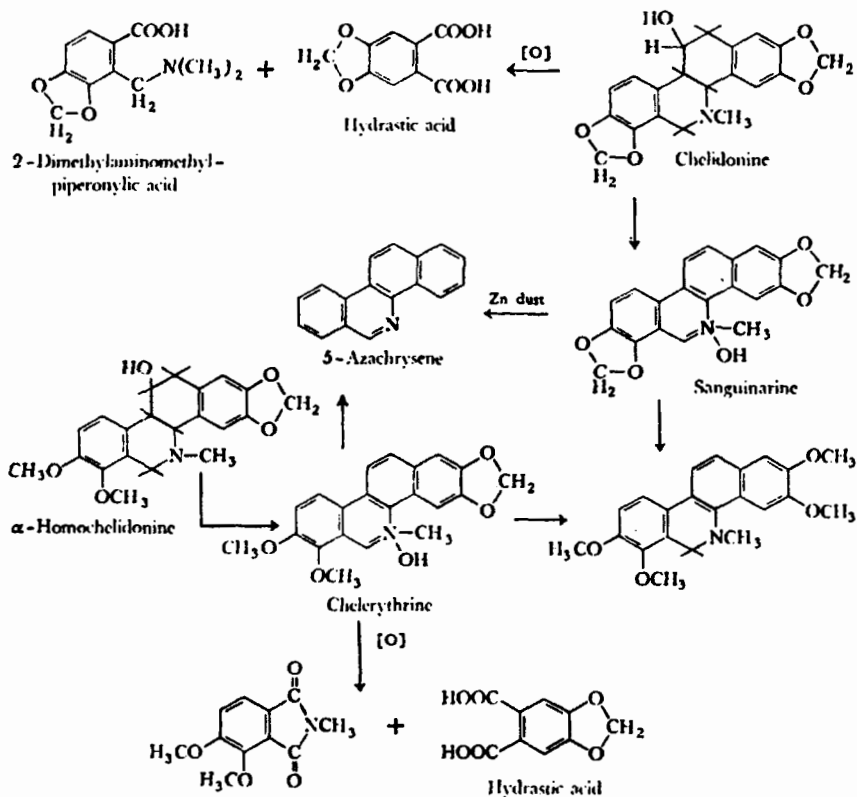
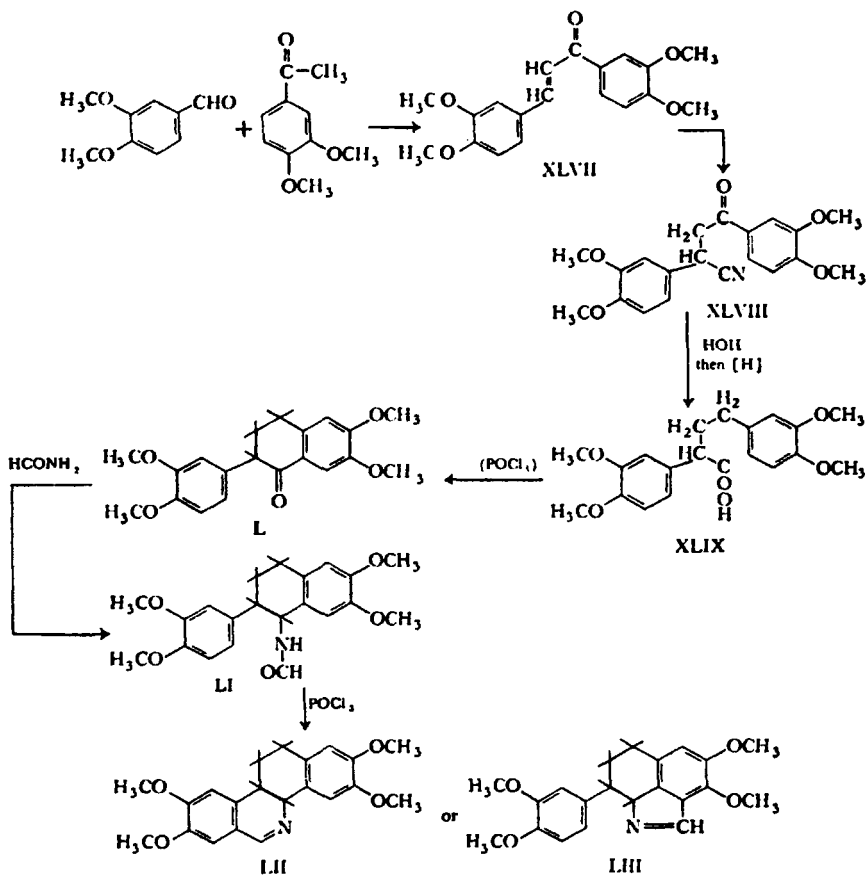


TABLE 31. Chelerythrine and Related Compounds

Compound and m.p., °C.	Salts	Color reactions	M.p. derivatives	Pharmacological action
Chelerythrine m.p. 199 (C ₂₁ H ₁₉ OH) ²⁰ 203-204 (C ₂₁ H ₁₉ OH) ^{20, 21} 207 (C ₂₁ H ₁₉ OH) ^{9, 13} 250 (+ ¹ / ₂ H ₂ O) ²⁰ 257 (toluene) ²¹	Aurichloride m.p. 233 ²⁰	Conc. H ₂ SO ₄ : orange-yellow, then brown with a tinge of green Conc. HNO ₃ : reddish-yellow E.R.: red-brown then rose Mayer's reagent: rose-colored precipitate ⁴⁰	ψ-Cyanide 260-261 ^{9, 13} 258 ²⁰	Toxic; poisonous to gram-positive bacteria ²²
Compound and m.p., °C.	Empirical formula	Preparation	Properties	
Dihydrochelerythrine m.p. 160-162 ²⁴ ; 166-167 ²⁸	C ₂₁ H ₁₉ NO ₄	Chelerythrine and Sn and HCl ²⁰ or Zn and HCl ¹³ ; O-acetylhomochelidonine + mercuric acetate ²³	Nonbasic, gradually turning yellow in air	
Methyl dihydrochelerythrine, 206 ²²	C ₂₁ H ₁₉ NO ₄ ·CH ₃	Methyl magnesium iodide + chelerythrine chloride ²²	Stable to Beyer's reagent ²²	
Phenyl dihydrochelerythrine, 236 ²²	C ₂₁ H ₁₉ NO ₄ ·C ₆ H ₅	Phenylmagnesium bromide and chelery- thrine chloride ²²	Dissolves in acetic acid with rose, then yellow color ²²	
Chelerythrine periodide 225 ²⁴	C ₂₁ H ₁₇ I ₂ NO ₄ ·HI	Chelerythrine + iodine dissolved in car- bon disulfide ²⁴	Ruby-red ²⁴	

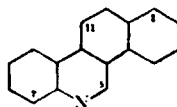
narine type, Richardson, Robinson, and Seijo⁴⁴ tried several different methods of preparation. The phenylnaphthalenediamine synthesis of Atkinson and Thorp was unsuccessful when applied to the piperonyl and veratryl series, as was an extension of the Pschorr phenanthrene synthesis; reduction of the Schiff base from 6-nitropiperonal (or *o*-nitrobenzaldehyde) and α -naphthylamine, followed by diazotization, gave only a tar. Although piperonyl- (or veratroyl-) acetonitrile was dimerized by alcoholic sodium ethoxide and the resulting imine hydrolyzed to the ketone, neither the imine nor the ketonitrile could be cyclized.



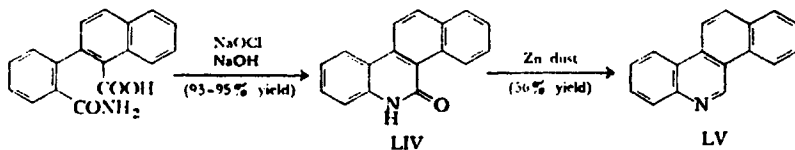
Noller and co-workers⁴⁵ also attempted to use a modification of the Bischler-Napieralski synthesis of isoquinolines. Although the *N*-piperonylamides of γ -piperonylisocrotonic acid and γ -piperonylpropionic acid were prepared, ring closure could not be achieved. However, synthesis of a substituted 5-azachrysene was achieved by means of the

series of reactions⁴⁴ on page 173: condensation of veratraldehyde and acetoveratrone gives 3,4,3',4'-tetramethoxychalcone (XLVII) to which hydrogen cyanide can be added to form XLVIII. Hydrolysis of the nitrile and Clemmensen reduction of the resulting keto acid formed the substituted butyric acid (XLIX) which was cyclized with phosphoryl chloride to the tetralone (L). Treatment of L with formamide gives LI, which was dehydrated by phosphoryl chloride to a base, more likely LII than LIII.

F. 6-Azachrysene, Benzo[*i*]phenanthridine, 7,8-Benzophenanthridine, β -Naphthophen-acridine. R.I. 2741



Graebe⁹ synthesized 6-azachrysene (LV) in a manner analogous to his preparation of 5-azachrysene (XXVI), by the Hofmann degradation of 2-(2'-carboxamidophenyl)-1-naphthoic acid, followed by zinc dust distillation of the resulting 6-aza-5-chrysenone (LIV).

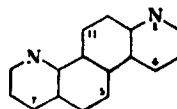


Both the product (LV) and its 5-keto derivative are colorless. Although 6-azachrysene is very sparingly soluble in cold dilute hydrochloric acid, it is very soluble in hot acid and the hydrochloride is bright yellow. A small amount of the free base dissolves in concentrated sulfuric acid to form a colorless solution with a blue fluorescence.

2. Diazachrysenes

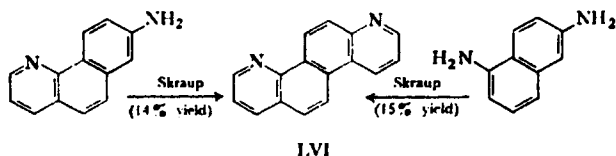
Thirty-six diazachrysenes are possible, but only three of these, the 1,10-, 2,4-, and 4,10-, are reported in the literature.

A. 1,10-Diazachrysene, Quino[7,8-*f*]quinoline, 1,6-Naphthadiquinoline. R.I. 2705

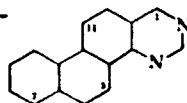


Since 1,10-diazachrysene (LVI) may be prepared by the Skraup reaction on both "amino- β -naphthoquinoline" and 1,6-diaminonaphthalene, Armit and Robinson⁴⁶ concluded that the "nitro- β -naphthoquinoline" must be 7-nitro-4-azaphenanthrene. The colorless product (LVI)

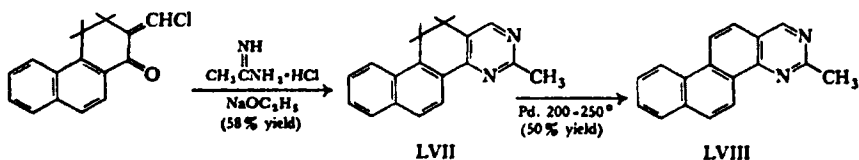
is only slightly soluble in alcohol, ether, and benzene, but dissolves in dilute sulfuric acid, giving a colorless solution exhibiting a bright blue fluorescence.



B. 2,4-Diazachrysene, Naphtho[1,2-*b*]quinazoline

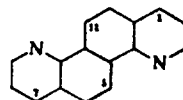


The substituted quinazoline, 3-methyl-2,4-diazachrysene (LVIII), was among the compounds prepared by Cook and Thomson⁸ to be tested for possible inhibitory action on tumor growth. Although condensation of 2-hydroxymethylene-1-keto-1,2,3,4-tetrahydrophenanthrene with acetamidine to give the desired pyrimidine could not be effected, the corresponding chloromethylene ketone readily gives 3-methyl-11,12-dihydro-2,4-diazachrysene (LVII), which may be dehydrogenated with palladium.

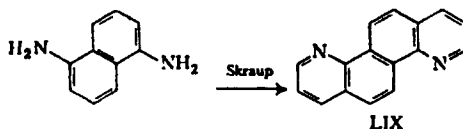


The dihydro compound is colorless whereas the unsaturated product is greenish-yellow and soluble in cold dilute hydrochloric acid.

C. 4,10-Diazachrysene, Quino[8,7-*b*]quinoline, 1,7- $\alpha\gamma'$ -Naphthodipyridine. R.I. 2706

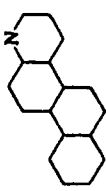
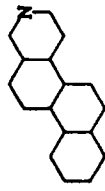
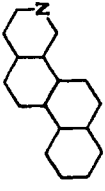


Four of the classical methods for the preparation of quinoline and its derivatives have been used in this series. 4,10-Diazachrysene (LIX)



itself is prepared by the Skraup reaction of 1,5-diaminonaphthalene.¹⁷ When 1,5-diaminonaphthalene is subjected to the Doebner-Miller

TABLE 32. Azachrysenes

Formula	Compound	Ref.	M.p., °C.	Color	Properties
	 1-Azachrysenes:				
I	1-Azachrysene	2	226-227	C	.HCl, m.p. 296-300°
		4	229-230		Max. and (log E) for abs.: 2620 (4.86), 2975 (4.27), 3590 (3.29)
III	1,2,3,4-Tetrahydro-1-azachrysene	2	157-159	Yellow	.HCl, m.p. 310-313° (dec.)
VI	1,2,3,4,5,6-Hexahydro-1-azachrysene	2	115-116	W	.HCl, m.p. 274-285°
V	1-Methyl-1,2,3,4-tetrahydro-1-azachrysene	2	170-171	—	.HCl, m.p. 240-260° (dec.)
IX	1-Methyl-1,2,3,4,5,6-hexahydro-1-azachrysene	2	129-131	—	.MeI, m.p. 204-205° .MeI, m.p. 193-195°
	 2-Azachrysenes:				
XII	8-Benzoyloxy-12a-methyl-2,4,4a,11,12,12a-hexahydro-2-aza-1,3-chrysenedione	6	247	—	—
	 3-Azachrysenes:				
XIV	1,2,3,4-Tetrahydro-3-azachrysene	7	—	—	.HCl, m.p. 313-315°
XVI	3-Methyl-1,2,3,4-tetrahydro-3-azachrysene	7	Oil	—	.MeI, (XV) m.p. 244.5-246° (dec.) .HCl, m.p. 257-259°

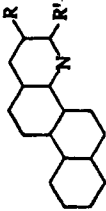
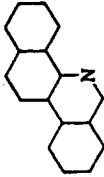
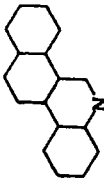
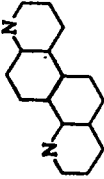
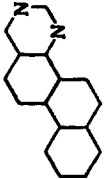
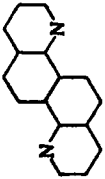
Formula	Compound	Ref.	M.p., °C.	Color	Properties
4-Azachrysenes: 					
XXIV	R H	8	137-138	C	.P, m.p. 256-258°
XXII	R H	8	179-180	C	—
XXIII	R Cl	8	115-116	C	—
XXI	R OH	8	362-364	C	Acetate, m.p. 149-151°
XX	R OH	8	275-276	Yellow	Acetate, m.p. 145-147°
XIX	R COOH	8	324-325	Yellow	Benzoate, m.p. 209-210°
XVIII	R CN	8	364-366	Yellow	Methyl ester, m.p. 118-120°
5-Azachrysenes: 					
XXVI	5-Azachrysenes	9	135.5	C	.HCl, m.p. 235° .P, m.p. 256° (dec.) .MeI, m.p. 195°
XXVIII	6-Methyl-5-azachrysenes	26	117	C	.P, m.p. 233° (dec.)
XXVII	7,8,9,10-Tetrahydro-5-azachrysenes	11	118	C	.P, m.p. 215-216° (dec.)
XXIX	6-(Dimethylolmethyl)-5-azachrysenes	12	169	C	—
LII	2,3,8,9-Tetramethoxy-11,12-dihydro-5-azachrysenes	44	230-231	C	—
XLVI	5-Methyl-2,3,7,8-tetramethoxy-5,6-dihydro-5-azachrysenes	13a, 38	182-183	—	—

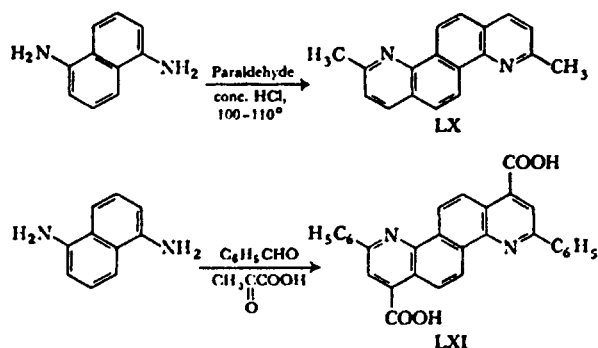
Table continued

TABLE 32. Azachrysenes (Continued)

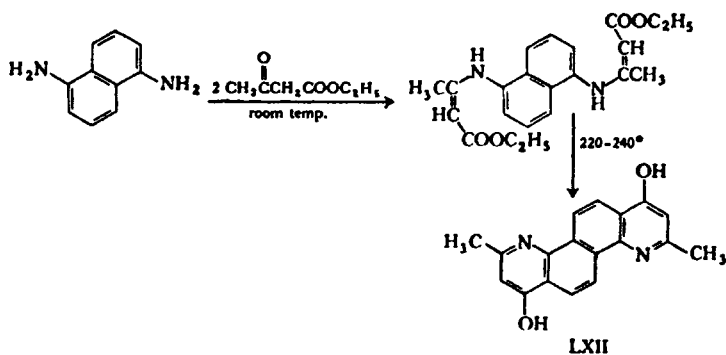
Formula	Compound	Ref.	M.p., °C.	Color	Properties
5-Azachrysenes (continued)					
XXV	6-Keto-5-azachrysene	9	332-335	C	—
		10	331	—	—
XXX	6-Carboxy-5-azachrysene	12	329	Brown	—
	2,3,7,8-Tetramethoxy-5-azachrysene	12	198 (dec.)	Yellow	—
		13a	218-219	C	—
	2,3,8,9-Tetramethoxy-5-azachrysene	13a	230-231	C	Blue-violet Fl ·HCl, m.p. 265-7° (dec.) ·Me ₂ SO ₄ , O·Y, m.p. 255-7° (dec.) ·MeCl, m.p. 207-10° (dec.)
	11,12-Dihydro-2,3,7,8-tetramethoxy-5-azachrysenic	13a	162-163	C	·Me ₂ SO ₄ , Y, m.p. 305-8° (dec.) ·MeCl, Y, m.p. 293-5° (dec.) Sol. dil. mineral acids, Y
	6-Chloro-11,12-dihydro-2,3,7,8-tetramethoxy-5-azachrysene	13a	176-178	Cream	Sol. 6 <i>N</i> HCl
	6-Anilino-11,12-dihydro-2,3,7,8-tetramethoxy-5-azachrysene	13a	143-144	C	Blue Fl org. solvents. Sol. dil. mineral acid
	6-Cyano-5,6-dihydro-2,3,7,8-tetramethoxy-5-methyl-5-azachrysene	13a	178-180	C	—
6-Azachrysenes:					
					
LV	6-Azachrysene	9	182	C	Soln. in S. is colorless with blue fluorescence ·HCl, m.p. 257-259
LIV	5-Keto-6-azachrysene	9	338	C	—

Formula	Compound	Ref.	M.p., °C.	Color	Properties
	1,10-Diazachrysenes:				
					
LVI	1,10-Diazachrysene	46	183.5–184.5	C	Soln. in S. is colorless with blue fluorescence
	2,4-Diazachrysenes:				
					
LVIII	3-Methyl-2,4-diazachrysene	8	196–197	Greenish-yellow	.P, m.p. 230–231° (dec.)
LVII	3-Methyl-1,1,12-dihydro-2,4-diazachrysene	8	142–143	C	.P, m.p. 225–227° (dec.)
	4,10-Diazachrysenes:				
					
LIX	4,10-Diazachrysene	47	217–217.5	Yellow	Gives pyridine-2,3-dicarboxylic acid on permanganate oxidn.
LX	3,9-Dimethyl-4,10-diazachrysene	47	238–240	—	—
LXIII	5,11-Dichloro-4,10-diazachrysene	48	269–271	Yellow	—
LXII	1,7-Dihydroxy-3,9-dimethyl-4,10-diazachrysene	47	—	Yellow	Diacetate, m.p. 258°
LXI	3,9-Diphenyl-4,10-diazachrysene-1,7-dicarboxylic acid	47	—	Yellow	—

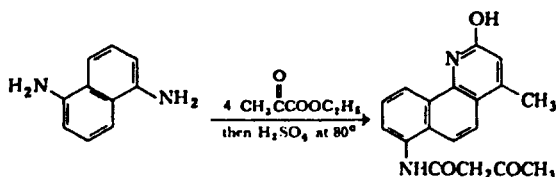
reaction using paraldehyde, the corresponding 3,9-dimethyl-4,10-diazachrysenes (LX) is formed.⁴⁷ Doebner's pyruvic acid synthesis applied to 1,5-diaminonaphthalene with benzaldehyde gives 3,9-diphenyl-4,10-diazachrysenes-1,7-dicarboxylic acid (LXI).⁴⁷



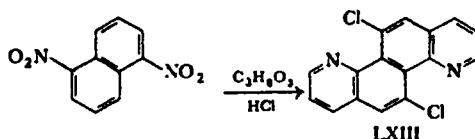
The Conrad-Limpach reaction using 1,5-diaminonaphthalene and ethyl acetoacetate first forms ethyl naphthalene-1,5-bis-(3-aminocrotonate), which is then transformed into 1,7-dihydroxy-3,9-dimethyl-4,10-diazachrysenes (LXII). However, when 1,5-diaminonaphthalene is heated



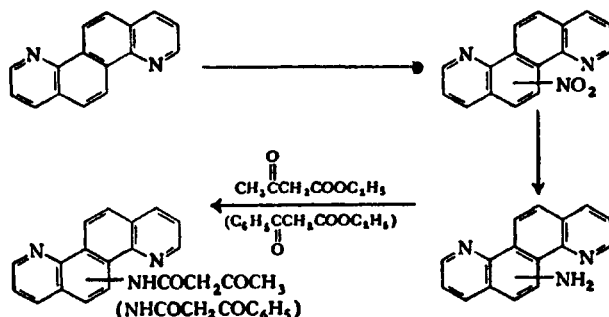
with four moles of ethyl acetoacetate and the resulting product is cyclized with concentrated sulfuric acid at 80°, not the diazachrysenes, but 2-hydroxy-4-methyl-7-acetoacetamido-1-azaphenanthrene is formed.⁴⁷ It is also reported that 1,5-dinitronaphthalene, when heated with glycerol



and concentrated hydrochloric acid in a sealed tube, gives 5,11-dichloro-4,10-diazachrysene (LXIII).⁴⁸



Oxidation of 4,10-diazachrysene (LIX) with potassium permanganate gives pyridine-2,3-dicarboxylic acid.⁴⁷ Nitration of this parent heterocycle forms a mononitro derivative which can be reduced to the corresponding amino compound.⁴⁹ By heating the amine with either ethyl



acetoacetate or benzoylacetic acid, yellow amides are obtained which are soluble in both dilute acid and a dilute alcoholic solution of potassium hydroxide. It has been suggested that these compounds may be used as dyes and medicinals.⁴⁹

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CHAPTER V

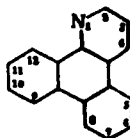
Azatriphenylenes

BY JEAN V. CRAWFORD

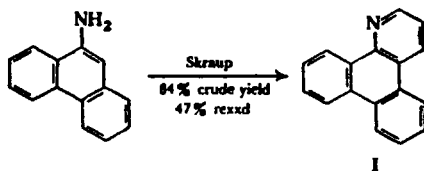
1. Monoazatriphenylenes

Although compounds representative of the 1-aza- and 2-azatriphenylene systems—the only two monoazatriphenylenes—have been prepared, neither type has been investigated extensively.

A. 1-Azatriphenylene, Dibenzo[*f,h*]quinoline, 5,6,7,8-Dibenzoquinoline, 9,10-Phenanthroquinoline. R.I. 2744

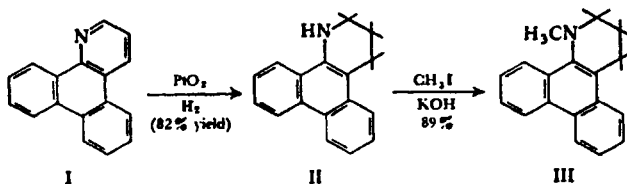


The earliest reference to the use of the Skraup synthesis with a phenanthrylamine is in the preparation of 1-azatriphenylene (I) from



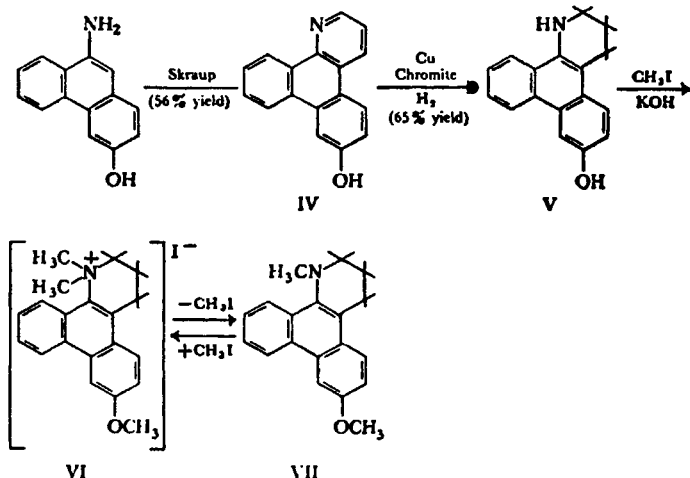
9-aminophenanthrene.¹ Although Herschmann¹ described the product as white needles, m.p. 174°, Krueger and Mosettig² obtained a yellow base, m.p. 167–169°.

The base (I) can be reduced catalytically to the corresponding tetrahydro derivative (II) and the latter is easily converted to 1-methyl-1,2,3,4-tetrahydro-1-azatriphenylene (III).² Since addition of methyl iodide to the *N*-methyltetrahydro derivative could not be achieved under



the conditions employed, the authors suggested that steric hindrance, caused by the nearness of C₁₂ to the *N*-methyl group, was responsible.

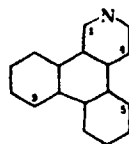
Similarly, the Skraup reaction on 9-amino-3-hydroxyphenanthrene yields 7-hydroxy-1-azatriphenylene (IV), which can be reduced cata-



lytically to the tetrahydro base (V). In contrast to the unsubstituted tetrahydro-1-azatriphenylene (II), 7-hydroxy-1,2,3,4-tetrahydro-1-azatriphenylene (V) does form a methiodide (VI), although with difficulty. The salt (VI) is easily converted into the corresponding tertiary base (VII). Because these observations were qualitative, the authors did not speculate on the influence of a 7-hydroxy or 7-methoxy group on quaternary salt formation.

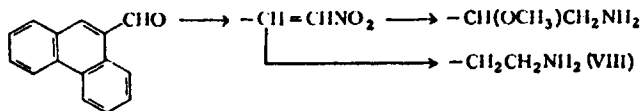
The 1-azatriphenylenes reported are yellow, with the exception of the white *N*-methyl derivatives, and are soluble in organic solvents except for 7-hydroxy-1-azatriphenylene, which is sparingly soluble in alcohol, ether, etc. They form white hydrochlorides, which hydrolyze readily in the case of the methoxy and hydroxy derivatives.

B. 2-Azatriphenylene, Dibenz[*f,h*]isoquinoline.
R.I. 2745

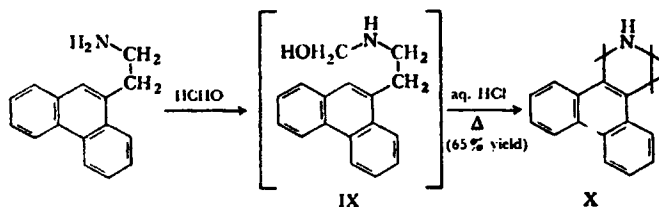


A partially saturated 2-azatriphenylene was prepared as a possible analgesic because of its similarity to morphine, which also contains an isoquinoline nucleus.³

The most successful synthesis of 9-(2-aminoethyl)-phenanthrene, used as the starting material, is found to be the following:

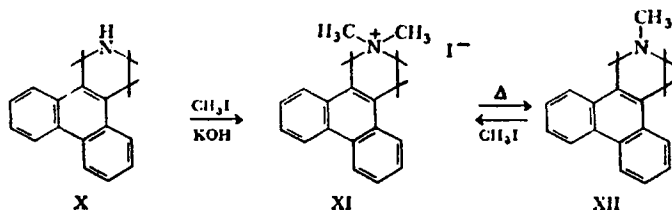


Attempts to cyclize the formyl or benzoyl derivatives of 9-(1'-methoxy-2'-aminoethyl)-phenanthrene in order to obtain the desired isoquinoline were unsuccessful, as were attempts to cyclize the formyl derivative of 9-(2'-aminoethyl)-phenanthrene *via* the Bischler-Napieralski method. However, when the formaldehyde condensation product of 9-(2'-aminoethyl)-phenanthrene (IX) is treated with dilute aqueous hydrochloric acid according to the method of Decker and Becker, the expected tetrahydroisoquinoline derivative is obtained in satisfactory yield. There is little doubt concerning the structure of the base (X), as



ring closure from position 9 to position 8 of phenanthrene would result in a seven-membered nitrogen-containing ring.

The free base (X) forms an *N*-methyl methiodide (XI) which can be converted almost quantitatively to the *N*-methyl base (XII).

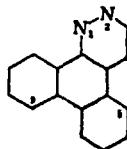


When tested pharmacologically, 2-methyl-1,2,3,4-tetrahydro-2-azatriphenylene showed great hypnotic effect (M.E.D. 5 mg./kg. in the cat) in addition to its analgesic effect (M.E.D. 20 mg./kg. in the cat), but unfortunately an equally marked emetic effect was observed when the substance was administered orally.

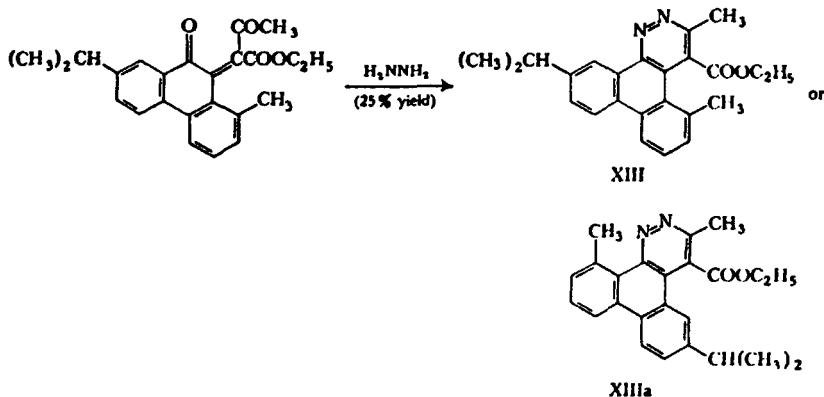
2. Diazatriphenylenes

Of the fifteen possible diazatriphenylenes, only the 1,2-, 1,4-, 1,8-, and 2,3-systems have been reported in the literature.

A. 1,2-Diazatriphenylene, Dibenzo[*f,h*]cinno- line. R.I. 2671

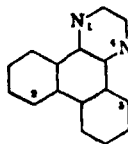


The only 1,2-diazatriphenylene derivative reported, ethyl 11-iso-propyl-3,5-dimethyl-1,2-diazatriphenylene-4-carboxylate (XIII) or its isomer (XIIIa) is obtained by treating retoxyleneacetoacetic ester with

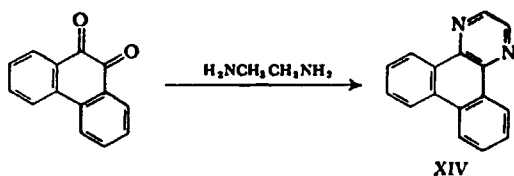


hydrazine hydrate.⁴ The deep red product was not characterized other than by listing its various solubilities in organic solvents.

B. 1,4-Diazatriphenylene, Dibenzo[*f,h*]quin- oxaline, Phenanthrapyrazine, Xenylene- pyrazine. R.I. 2672

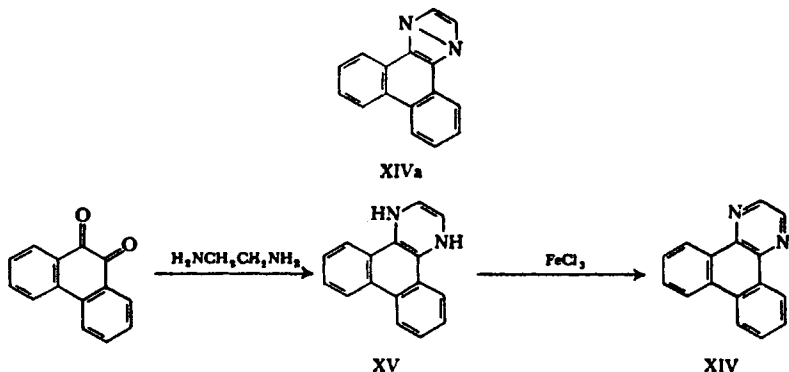


The 1,4-diazatriphenylenes, which are at the same time quinoxalines, are easily prepared crystalline compounds suitable for the identification of substituted 1,2-ethylenediamines and substituted phenanthrene-quinones. For this reason, the number of derivatives of this ring system reported is larger than that for the other diazatriphenylenes. In all cases, they may be prepared by refluxing a solution of the quinone and diamine in a suitable solvent, such as alcohol, acetic acid, or benzene.



For example, ethylenediamine and phenanthrenequinone in warm aqueous acetic acid yield 1,4-diazatriphenylene (XIV).⁵⁻⁷

Mason first reported the product as the dihydro derivative of XIV,^{5,7} but on the basis of new analytical data he assumed that two atoms of hydrogen are lost and that a stable base, to which he assigned the structure XIVa, is formed.⁶ In later work, Mason described the isolation of the intermediate dihydro product, when pure starting materials and a reaction time of only fifteen minutes are employed.⁸ When a warm alcoholic solution of the yellow dihydro derivative is treated with ferric chloride, the solution changes to red, then green, and finally the yellow 1,4-diazatriphenylene separates.



The freshly prepared dihydro compound is easily soluble in cold alcohol whereas the unsaturated compound is very sparingly soluble. Although the dihydro-1,4-diazatriphenylene is only partially soluble in dilute hydrochloric acid, it dissolves in hot concentrated acid. Surprisingly it is the dehydrogenated product which separates from this green solution or from the dark brown solution of the dihydro product in hot acetic anhydride. These same reactions and color changes in hydrochloric acid and acetic anhydride are reported for the corresponding 6-isopropyl-12-methyl- and the 2- (or 3-) methyl-6-isopropyl-12-methyl-1,4-diazatriphenylenes.

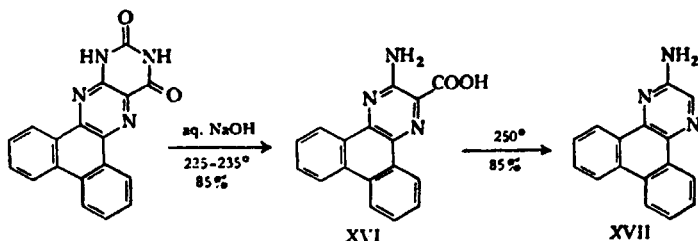
No dihydro derivatives of this series have been reported by other workers, but in most of the preparations described the mixtures of quinone

and amine were refluxed for at least an hour, and usually for six to twelve hours. This may account for complete conversion to the unsaturated product.

An interesting example of the usefulness of 1,4-diazatriphenylenes as derivatives of ethylenediamines is found in recent work with biotin.^{9,10} In deciding among several possible structures for biotin, it was necessary to determine whether the diaminocarboxylic acid obtained from it by degradation was a 1,2- or a 1,3-diamine. A condensation did occur with phenanthrenequinone, indicating that the acid has amino groups on two adjacent carbon atoms. The condensation product was not the expected dihydro derivative, but the oxidized form, as was shown by analysis and by comparison of its absorption spectrum with those of authentic dihydro and oxidized derivatives obtained from the reaction of 3,4-diaminotetrahydrothiophene and phenanthrenequinone.

When it was necessary to compare the diamino acid, isolated by degradation of biotin, with a synthetic sample ($\text{CH}_2\text{CH}(\text{NH}_2)\text{CH}(\text{NH}_2)\text{CH}_2\text{CH}_2\text{CH}_2\text{COOH}$), a derivative with no optical isomers was desired to avoid the necessity of resolving the synthetic diamino acid. The preparation of the 1,4-diazatriphenylene containing no asymmetric carbon atoms was a simple solution to the problem.

One synthesis of a 1,4-diazatriphenylene involving the degradation of a pentacyclic system is reported.¹¹ 11,13-Diketo-9,10,11,12-tetrahydridibenzo[*a,c*]9,10,12,14-tetrazaanthracene (phenanthrolumazine) undergoes degradation with sodium hydroxide to give 2-amino-1,4-diazatriphenylene-3-carboxylic acid (XVI), which may be decarboxylated to the 2-amino compound (XVII).



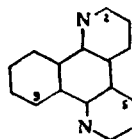
Most of the 1,4-diazatriphenylenes are yellow. They have been observed to give either a red,^{10,12} or an olive green⁸ color with concentrated sulfuric acid, but in only one case is the blue fluorescence characteristic of solutions of triphenylene in organic solvents reported.⁹

The 1,4-diazatriphenylenes are all weak bases. The hydrochloride of 1,4-diazatriphenylene itself is decomposed by heat, hot water,⁷ or by standing in a desiccator,⁵ while the hydrochloride of the 2-methyl com-

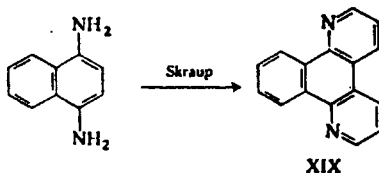
pound, formed only with hot concentrated acid, decomposes on standing in the air.¹² The 6-isopropyl-12-methyl compound is not attacked even by concentrated hydrochloric acid.¹²

The 1,4-diazatriphenylenes are stable toward most reagents. For example, the 2-methyl compound is recovered unchanged from a hot concentrated nitric acid solution. It is not reduced by sodium in boiling alcohol,¹² although 1,4-diazanaphthalene yields the tetrahydro derivative under the same conditions. 6-Isopropyl-12-methyl-1,4-diazatriphenylene is reported to give a water-soluble compound after boiling with concentrated sulfuric acid.⁸ Only 1,4-diazatriphenylene and its 2-methyl derivative have been treated with methyl iodide, and both are unreactive.

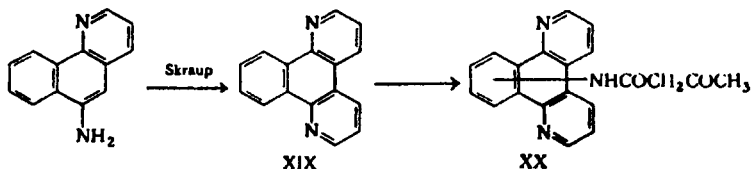
C. 1,8-Diazatriphenylene, Benzo[*f*][4,7]phenanthroline, Benzo-*p*-phenanthroline. R.I. 2711



The unsubstituted base, 1,8-diazatriphenylene (XIX), may be synthesized from 1,4-diaminonaphthalene by the Skraup reaction.¹³

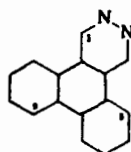


Another preparation of this heterocycle involves the use of 9-amino-4-azaphenanthrene, which is subjected to the Skraup reaction.¹⁴

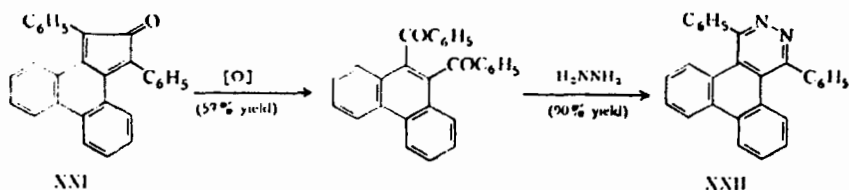


Nitration of the product (XIX) with nitric acid and concentrated sulfuric acid forms a mononitro compound which may be reduced to the corresponding amino derivative. When the latter is treated with ethyl acetoacetate, a yellow amide (XX), which dissolves in acid to give a yellow solution, is formed. The pale yellow product forms easily hydrolyzable colored salts with one equivalent of acid, varying in color from the yellow hydrochloride through the yellowish-brown sulfate to the brownish nitrate.

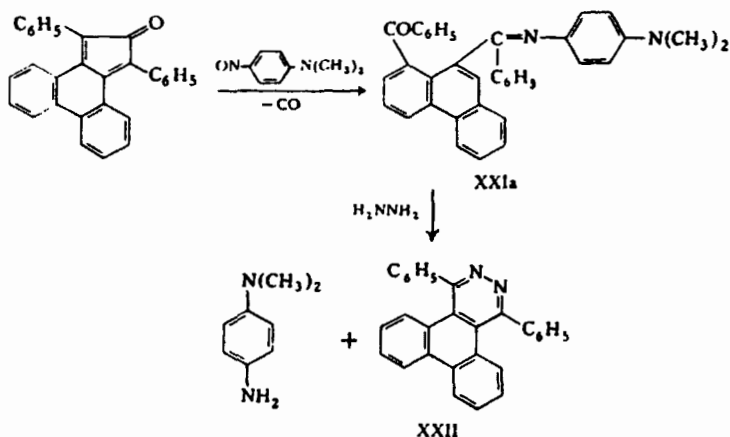
D. 2,3-Diazatriphenylene, Dibenzo[*f,h*]phthalazine, 3,4-(*o,o'*-Biphenylene)-pyridazine. R.I. 2673



1,4-Diphenyl-2,3-diazatriphenylene (XXII), the only 2,3-diazatriphenylene reported, may be synthesized from phencyclone (XXI) by several methods. Air oxidizes the latter compound to 9,10-dibenzoylphenanthrene, which is smoothly transformed by hydrazine hydrate into 1,4-diphenyl-2,3-diazatriphenylene (XXII), a white crystalline compound.¹⁶ If phencyclone is treated with an aryl nitroso compound then the resulting monoketimine, with aqueous hydrazine hydrate,



yields a compound identical with XXII.^{16,17} The reaction with hydrazine hydrate was used to demonstrate the presence of a keto group



in the intermediate condensation product (XXIa) whose structural configuration was in question.

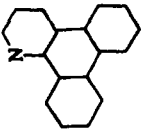
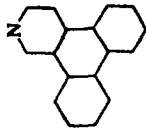
3. Triazatriphenylenes

Of the thirty-nine possible isomeric triazatriphenylenes, 1,2,4- and 1,5,9-triazatriphenylene are the only members of this group which have been synthesized.




Labile red Stable yellow

TABLE 33. Azatriphenylenes

Formula	Compound	Ref.	M.p., °C.	Color	Properties
	 1-Azatriphenylene:				
I	1-Azatriphenylene	1	174	C	·HCl, m.p. 248°
II	1,2,3,4-Tetrahydro-1-azatriphenylene	2	167-169	Y	·HNO ₃ , m.p. 240°
III	1-Methyl-1,2,3,4-tetrahydro-1-azatriphenylene	2	117-118	Y	·HCl, m.p. 245-247°
		2	81-83	C	·HCl, dec. 230-275°; does not form MeI
IV	7-Hydroxy-1-azatriphenylene	2	270-273	Y	·HCl, indefinite m.p.
V	7-Hydroxy-1,2,3,4-tetrahydro-1-azatriphenylene	2	230-232	G	·HCl, m.p. 279-286°
VII	7-Methoxy-1-methyl-1,2,3,4-tetrahydro-1-azatriphenylene	2	131.5-133	C	·HCl, m.p. 204-206°
	 2-Azatriphenylenes:				
X	1,2,3,4-Tetrahydro-2-azatriphenylene	3	223-225	W	·HCl, m.p. 304-306°
XII	2-Methyl-1,2,3,4-tetrahydro-2-azatriphenylene	3	113.5-114	C	·MeI, m.p. 268-270° (dec.)

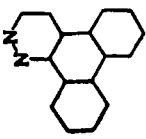
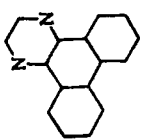
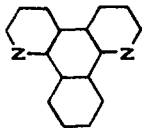
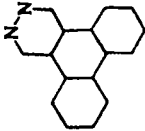
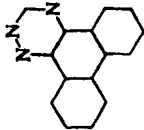
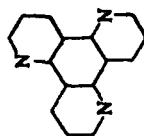
Formula	Compound	Ref.	M.p., °C.	Color	Properties
1,2-Diazatriphenylenes: 					
XIII	Ethyl 11-isopropyl-3,5-dimethyl-1,2-diazatriphenylene-4-carboxylate	4	200-205	R	—
XIIIa	Ethyl 6-isopropyl-3,12-dimethyl-1,2-diazatriphenylene-4-carboxylate or Ethyl 6-isopropyl-3,12-dimethyl-1,4-diazatriphenylene-4-carboxylate				
1,4-Diazatriphenylenes: 					
XIV	1,4-Diazatriphenylene	5, 7	180.5	Y	—
XV	1,4-Dihydro-1,4-diazatriphenylene	8	97-99	Y	Y in alc.
	2-Methyl-1,4-diazatriphenylene	12	—	Y	Soln. in S. is R
	6-Isopropyl-12-methyl-1,4-diazatriphenylene	8	110-111	Y	Olive-G in S.
	6-Isopropyl-12-methyl-1,4-diazatriphenylene	23	126-126.5	C	G in conc. acid
	6-Isopropyl-12-methyl-1,4-dihydro-1,4-diazatriphenylene	8	77-79	Y	—
	2, (or 3,) 12-Dimethyl-6-isopropyl-1,4-diazatriphenylene	8	143-144	C	Dil. HCl soln. is R with G
	2, (or 3,) 12-Dimethyl-6-isopropyl-1,4-dihydro-1,4-diazatriphenylene	8	83-85	Y	tinge
	2-Methyl-1,4-diazatriphenylene-3-caproic acid	10	186-187	—	—
	Ethyl 2-methyl-1,4-diazatriphenylene-3-caproate	10	78-79	—	Soln. in S. is R
	2-Phenyl-1,4-diazatriphenylene	24	190	Y	—
	2,3-Diphenyl-1,4-diazatriphenylene	24	265	Br	—
XVII	2-Amino-1,4-diazatriphenylene	11	249	—	—
XVI	2-Amino-1,4-diazatriphenylene-3-carboxylic acid	11	220-222	Y	—
	2-Sulfanilamido-1,4-diazatriphenylene	11	258-260	—	Acetyl deriv. m.p. 265-267°
	2,3-Dicyano-1,4-diazatriphenylene	25	320	Y	—

Table continued

TABLE 33. Azatriphenylenes (Continued)

Formula	Compound	Ref.	M.p., °C.	Color	Properties
	1,8-Diazatriphenylenes: 				
XIX	1,8-Diazatriphenylene	13,14	160	C	P, m.p. 256°
XX	α -Acetoacetamido-1,8-diazatriphenylene	14	182	Y	Sol. in acid and alc. with Y color
	2,3-Diazatriphenylenes: 				
XXII	1,4-Diphenyl-2,3-diazatriphenylene	15,16,17	340	W	—
	1,2,4-Triazatriphenylenes: 				
XXIII	R NH₂ NH₂ NH₂ Others 6- (or 11-) Bromo-1,2,4-triazatriphenylene 6,11-Dibromo-1,2,4-triazatriphenylene	18 19 19 20 — — —	262 235 288 333	Y R-Y O R-Y	— AC, * m.p. 278° — AC, m.p. 309°

Formula	Compound	Ref.	M.p., °C.	Color	Properties
1,2,4-Triazatriphenylenes (continued)					
R	Other				
NH ₂	8,9-Dibromo-1,2,4-triazatriphenylene	19	> 310°	G-Y	AC, m.p. > 310°
NH ₂	6- (or 11-) Nitro-1,2,4-triazatriphenylene	19	280	Y	AC, m.p. 298°
NH ₂	8- (or 9-) Nitro-1,2,4-triazatriphenylene	19	215	Y	AC, m.p. 298°
NH ₂	6,11-Dinitro-1,2,4-triazatriphenylene	19	> 310°	Br	AC, m.p. > 310°
NH ₂	8,9-Dinitro-1,2,4-triazatriphenylene	19	265	G-Y	AC, m.p. 275°
OH	—	26	287	Y	—
OH	7- (or 10-) Bromo-1,2,4-triazatriphenylene	27	285 dec.	—	—
OH	6- (or 11-) Chloro-1,2,4-triazatriphenylene	27	304	Y	—
OH	7- (or 10-) Nitro-1,2,4-triazatriphenylene	28	288	Y	—
OH	8- (or 9-) Nitro-1,2,4-triazatriphenylene	27	273-274	Y	—
OH	6,11-Dinitro-1,2,4-triazatriphenylene	26	285	Y	—
OH	6,11-Dibromo-1,2,4-triazatriphenylene	27	286	—	—
SH	—	20	295	Y	—
SH	6- (or 11-) Nitro-1,2,4-triazatriphenylene	26	198	—	—
SH	8- (or 9-) Nitro-1,2,4-triazatriphenylene	26	> 300	—	—
SH	6,11-Dinitro-1,2,4-triazatriphenylene	26	230	—	—
SH	—	26	220	—	—



1,5,9-Triazatriphenylenes:

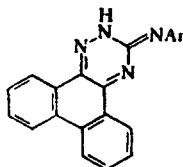
XXXVI	1,5,9-Triazatriphenylene	22	236	C	B-V fluorescence in org. solvents

• AC = acetyl deriv.

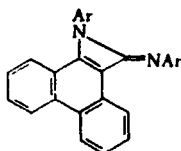
3-Hydroxy- and 3-thiol-1,2,4-triazatriphenylenes are made by substituting semicarbazide hydrochloride and thiosemicarbazide hydrochloride, respectively, for aminoguanidine hydrochloride and by using either phenanthrenequinones or phenanthrenequinone monoximes.

Aminoguanidine forms triazines more readily than either semicarbazide or thiosemicarbazide. De¹⁹ has interpreted this as being caused

by a relatively greater basicity of the —NH_2 group in $\text{—}\overset{\text{NH}}{\underset{\parallel}{\text{C}}}\text{NH}_2$ than in $\text{—}\overset{\text{O}}{\underset{\parallel}{\text{C}}}\text{NH}_2$. After the hydrazine residue has combined with a keto group, the amino group becomes more acidic, and hence reaction with the second keto group is less likely. In attempting to determine whether the basicity of aminoguanidine was diminished by aryl substituents, De and Dutt²¹ found that the reaction between phenanthrenequinones and arylaminoguanidines gives not the triazine (XXIV), but a compound to which they assigned the structure (XXV).

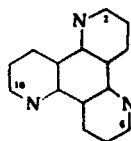


XXIV

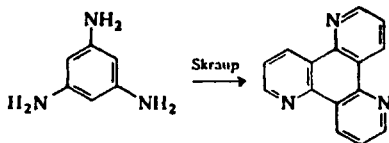


XXV

B. 1,5,9-Triazatriphenylene, Pyrido[2,3-*f*][1,7]-phenanthroline, Benzotripyridine, Phenotripyridine. R.I. 2692



1,5,9-Triazatriphenylene (XXVI) is prepared by the Skraup reaction with 1,3,5-trinitrobenzene, 1,3,5-triaminobenzene (as the chlorostannate), glycerol, and sulfuric acid.²² The white product is very soluble in benzene and in chloroform, and in these solutions exhibits a light bluish-violet fluorescence.



XXVI

The substance is a weak base, whose salts form only with strong acids and decompose in water. Two series of salts may be obtained, diacidic yellow and monoacidic white, but no salt has been prepared which contains three equivalents of acid.

The base does not undergo nitration, as would be expected from its relation to pyridine, and is resistant to oxidation with either chromic acid or potassium permanganate.

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CHAPTER VI

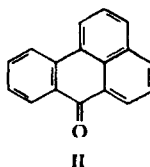
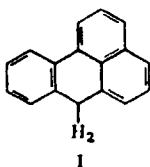
Azabenzanthrenes

By C. F. H. ALLEN, D. M. BURNES, AND F. W. SPANGLER

Introduction

A. Historical

The azabenzanthrenes include those compounds which possess a nucleus of four condensed six-membered rings arranged in the *peri*-benzanthracene structure (I), and which contain one or more nitrogen atoms in place of any one of the carbon atoms. These substances derive their name from their carbocyclic precursor, benzanthrone (benzanthren-7-one) (II), the parent compound of an important class of intermediates used in the preparation of anthraquinone vat dyes. In this section all the azabenzanthrenes, except those in which a nitrogen atom is common to more than one ring will be described.



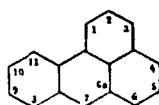
The first dye to be discovered in the azabenzanthrone series was Alizarin Rubinol R¹ (page 223). The earliest known azabenzanthrenes were alkaloids in the aporphine group (page 229). Nearly all the chemistry of azabenzanthrenes deals with dyes and alkaloids of these two groups. Dyes of commercial importance are found in the 3-aza- (page 209) and 1,3-diazabenzanthrone series (page 267). During the period 1933-1938 many patents describing dyes or intermediates in both series were issued to the I. G. Farbenindustrie; however, the German work was largely stopped by World War II. Relatively little has appeared from any other source. Isomers and homologs of these two series

were described in the earlier literature, and included in patents as a matter of policy, but they do not appear to have been of commercial value. There are no compounds definitely known to possess the structure of a 4-, 7-, 9-, or 10-azabenzanthrene.

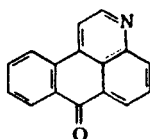
B. Nomenclature

(1) Numbering

The names that have been applied to intermediates and dyes are very diverse and confusing. In this chapter they will be called *aza-benzanthrenes*, *azabenzanthrones*, and *diazabenzanthrones*. The numbering starts in the top ring, at the left, and proceeds clockwise (III); angular positions are lettered by "a" and the lowest adjacent number. The extra hydrogen (indicated in the names by an italicized *H*) is nearly always in the 7-position, as is the carbonyl oxygen in benzanthrone (II).



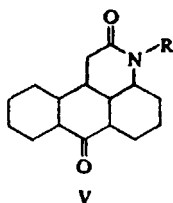
III



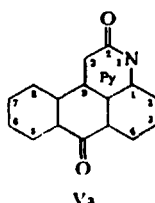
IV

(2) 3-Azabenzanthrones (*Anthrapyridines*, *Anthrapyridones*)

These substances were listed in *Chemical Abstracts* up to 1916 as *anthrapyridones* (V), since only the 2-keto derivatives were known at that time. This was changed to *naphthoquinolines* in the 1917-1926 Decennial Index; e.g., anthrapyridone (V, R = H) became 3,7-*peri*-naphthoquino-



V



Va

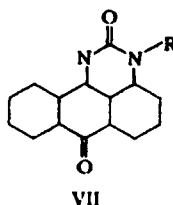
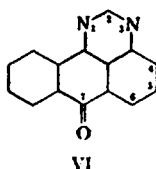
line-2(3),7-dione. Since 1937, it is to be found under *dibenz*[*f,i*]*isoquinoline*, R.I. 2750²; e.g., *anthrapyridone* is 7-dibenz[*f,i*]isoquinoline-2,7(3)-dione.

However, the individual abstractor often uses the term *anthrapyridone* and numbering as shown in Va. In the foreign literature, anthrapyridones may be found under that name, as well as pyridonanthrone, pyridanthrone, and *Py- α -oxy-1,9-pyridinoanthrone*. They should not be confused with α -anthrapyridines, which are 1-azaanthracenes. Beilstein³ lists anthrapyridones as *benzoylenechinolines*, and gives some alternative names used in the literature, e.g., 2-Oxy-4,5(CO)-benzoylenechinoline, 2-Oxo-4,5(CO)-benzoylene-1,2-dihydrochinoline, 4,5(CO)-benzoylene-chinolon-(2), 4,5(CO)-benzoylenecarbostyrin, "anthrapyridone," and "pyridanthrone." If the substances are named as derivatives of quinoline, they are numbered accordingly. As outlined at the beginning of this monograph, the prefix, *aza*, and appropriate number are to be added to the name of the ring system; the old anthrapyridine (IV) is, thus, 3-azabenzanthrone. (The abstractor may name this as *Bz-3-azabenzanthrone*; and use *Bz* interchangeably with *Py*.)

The abstracts of patents on anthrapyridones in *Chemical Abstracts*, especially in the early issues, are very poor.

(3) 1,3-Diazabenzanthrones (*Anthrapyrimidines*)

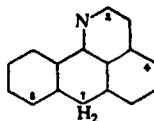
Anthrapyrimidine was the name used in the early patents for analogs of benzanthrone having two nitrogen atoms in nonadjacent positions in the top (*Py*) ring (VI). When there was a carbonyl group in the 2-position (VII) the name anthrapyrimidone was used. Substances belonging in this class are indexed under this name in the first Decennial Index of *Chemical Abstracts*. None of these compounds were described



in the decade covered by the second Decennial Index, but in the third they are listed under *naphthoquinazolines*. The *Ring Index*² gives three names that have been used: 3-dibenzo[*de,h*]quinazoline, 3-naphtho[1,2,3-*de*]quinazoline, and anthrapyrimidine. The latter name is used in patents and in most of the abstracts.

1. Monoazabenzanthrenes

A. * 7*H*,1-Azabenzanthrene, 7-Dibenzo[*de,h*]-quinoline, Bz-3-Azabenzanthrene. R.I. 2746

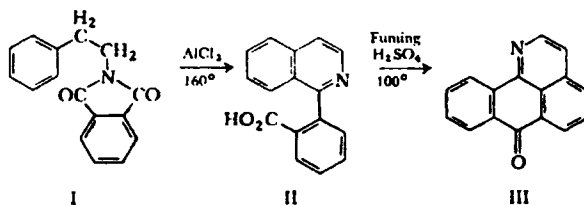


The few known compounds which possess the 7*H*,1-azabenzanthrene nucleus are, in fact, 1-azabenzanthrones (III). In the German patent literature these compounds were named Bz-3-azabenzanthrones; for, in the German system of numbering, the linear portion of the molecule was numbered as in anthracene, with the *peri* ring numbered separately and designated by the letters, Bz. Houben uses the term pyridinoanthrones for the 1-, 2-, and 3-azabenzanthrones.

The only available source of information on these compounds is in a series of patents granted the I.G. Farbenindustrie to cover their use as dyes or dye intermediates. In view of this, many of the structures are unknown, or not definitely established; on the whole, descriptions of the compounds are sketchy.

(1) Preparation

The parent compound, 1-azabenzanthrone (III), is prepared from *N*-β-phenylethylphthalimide (I). Treatment with anhydrous aluminum chloride at 160° gives 1-(2'-carboxyphenyl)-isoquinoline (II), which undergoes a second ring closure in the presence of fuming sulfuric acid to form 1-azabenzanthrone (III).⁴



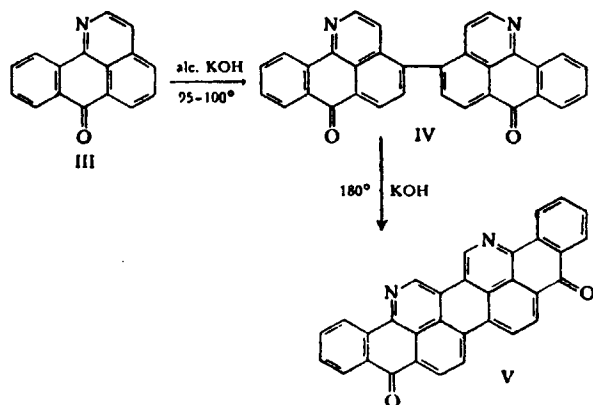
In a similar manner, 9- (or 10-) chloro-1-azabenzanthrone can be prepared from the imide derived from 4-chlorophthalic anhydride, while 6-chloro-1-azabenzanthrone is formed when β-4-chlorophenylethylamine is substituted for β-phenylethylamine. Final ring closure also can be effected with cold chlorosulfonic acid.

* D. M. Burness.

Other derivatives of 1-azabenzanthrone, in which the positions of the entering substituents are unknown, have been prepared by nitration and bromination of the parent compound.⁵ The amine formed by reduction of the nitro compound has been condensed with β -keto esters to form amides.⁶ Methyl-substituted derivatives have been prepared from 1-azabenzanthrone by treatment with formaldehyde in alkaline thiosulfate solution.⁷

(2) Reactions

A number of vat dyes of the indanthrene-type have been prepared by the condensation of two molecules of 1-azabenzanthrone, its bromo or amino derivatives, or substituted amino derivatives, by fusion with alkali.⁵ The 1-azabenzanthrones can be heated with alkali to form the dyes directly; or under milder conditions the intermediate products can be isolated. For example, when 1-azabenzanthrone is heated with



alcoholic potassium hydroxide, followed by air oxidation in hot aqueous solution, coupling of two molecules occurs to give 4,4'-di-1-azabenzanthronyl (IV). Fusion of this compound with alkali gives the vat dye (V), a diazaviolanthrone.

This substance dyes cotton violet from a blue vat.

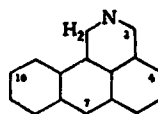
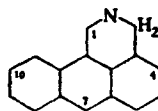
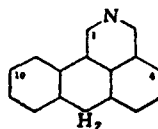
(3) Properties

1-Azabenzanthrone⁴ is a yellow crystalline solid melting at 182–183°. It dissolves in 10% sulfuric acid with a yellow color and crystallizes from solution on cooling. It can be reduced to give a brown vat. The properties of all the known 1-azabenzanthrones are collected in Table 34 following.

TABLE 34. 1-Azabenzanthrones

Substance	Ref.	M.p., °C.	Crystalline form and color	Vat dye obtained by alkaline fusion
1-Azabenzanthrone ^a	4,5	182-183	Yellow (from acetic acid)	Blue vat, dyes cotton violet
<i>x</i> -Methyl ^b	7	208-209	Pale yellow needles	—
<i>x,x</i> -Dimethyl-	7	245-246	Yellow needles (from acetic acid)	—
6-Chloro-	4	168-170	Needle- to star-shaped crystals (from butanol)	—
9- (or 10-) Chloro-	4	178-186	Yellow	—
3-Bromo-	5	255-256	Yellow	Blue vat, dyes cotton violet
<i>x</i> -Nitro-	5,6	273-274	—	—
<i>x</i> -Amino-	5,6	266-267	—	Blue-green vat, dyes cotton gray to black
<i>x</i> -Anilino-	5	—	—	Violet
<i>x</i> -Acetoacetylamino-	6	—	Brownish yellow	—
<i>x</i> -1'-Anthraquinonyl-	5	—	—	Brown vat, dyes cotton gray
4,4'-Di-1-azabenzanthronyl ^c	5	> 360	Yellow needles	Same as 1-azabenzanthrone
<i>x,x'</i> -Dinitro-4,4'-di-1-azabenzanthronyl	5	> 360	Yellow	Gray
3,3'-Di-1-azabenzanthronyl sulfide	5	> 360	Yellow	Sulfur-free violet dye

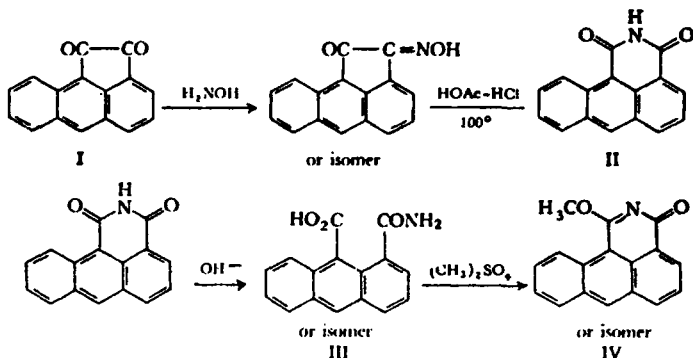
^a Forms a brown vat.^b Gives yellow color in concentrated sulfuric acid.^c Dyes cotton a weak yellow.

B.* 2-Azabenzanthrenes**1*H*,2-Azabenzanthrene,** **1-Dibenz[*de,h*]iso-**
quinoline. R.I. 2747**3*H*,2-Azabenzanthrene,** **3-Dibenz[*de,h*]iso-**
quinoline, 2,3-*peri*-Naphthisoquinoline.
R.I. 2748**7*H*,2-Azabenzanthrene,** **7-Dibenz[*de,h*]iso-**
quinoline, Bz-2-Azabenzanthrene, 2,7-
***peri*-Naphthisoquinoline, 7-Naphth[1,2,3-**
***de*]isoquinoline. R.I. 2749**

Few substances based upon this ring structure are known, and of these several are merely derivatives of 1,3-diketo-2-azabenzanthrene (II), commonly known as anthracene-1,9-dicarboximide.

(1) Preparation

1,3-Diketo-2-azabenzanthrene (II) is prepared from the monoxime of accanthrenequinone (I) by means of the Beckmann rearrangement with hydrogen chloride.⁸ Better yields have been reported using con-



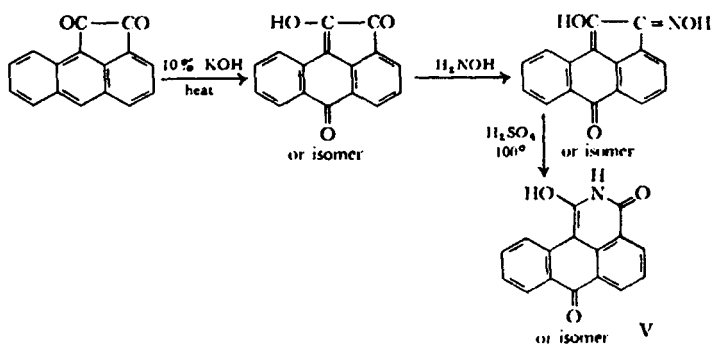
centrated sulfuric acid.⁹ Partial alkaline hydrolysis of the imide to the monoamide (III) and treatment of the latter in alkaline solution with methyl sulfate gives the methyl ether (IV) of an enolic form of the imide.⁸

A number of *N*-substituted derivatives of 1,3-diketo-2-azabenzanthrene also have been prepared by heating the anhydride of anthracene-

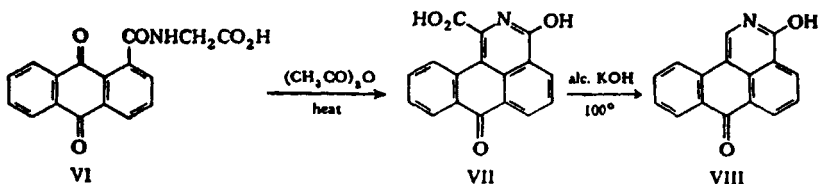
* D. M. Burness.

1,9-dicarboxylic acid with the appropriate primary amine.⁹ A few chloro derivatives from chlorine-substituted aceanthrenequinone also are known.¹⁰

By a slight change in the procedure aceanthrenequinone can be converted into an azabenzanthrone, namely, 1-hydroxy-3-keto-2*H*,2-azabenzanthrone (V).¹¹



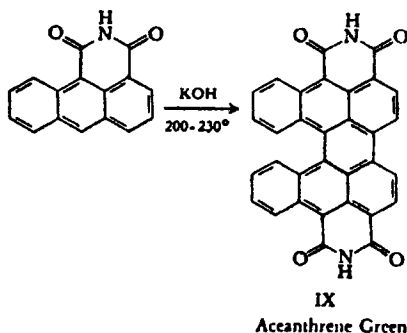
Ebel and Bayer¹² used an entirely different method for the preparation of 2-azabenzanthrones. When *N*-1-anthraquinonoylglycine (VI) was heated in the presence of any one of a variety of condensing agents,



ring closure took place to form 1-carboxy-3-hydroxy-2-azabenzanthrone (VII); this was readily decarboxylated to 3-hydroxy-2-azabenzanthrone (VIII).

(2) Reactions

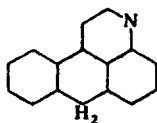
Just as was noted in the case of the 1-azabenzanthrones, compounds of the 2-azabenzanthrone series undergo bimolecular condensation under the influence of alkali to form indanthrene-type dyes^{8,9,11,13}; however, none is of any known commercial importance. The best known of these dyes is Aceanthrene Green (IX).¹⁴



(3) Properties

The 2-azabenzanthrones are, for the most part, high-melting crystalline compounds, yellow to red in color, and soluble in concentrated sulfuric acid in which some are fluorescent. They usually can be crystallized from glacial acetic acid in the form of needles. The properties of the known 2-azabenzanthrones are collected in Table 35 (page 210).

C. * 3-Azabenzanthrenes.
R.I. 2750



7H,3-Azabenzanthrene is unknown. As stated in the introduction the 7-keto derivatives have been important commercial products.

(1) Monoketo Derivatives: 3-Azabenzanthrones (Anthrapyridines)

The first member of the series, 3-azabenzanthrone itself, is unknown, but derivatives are readily obtained by a general method, in which substituted methyl ketones are heated with 1-aminoanthraquinones in the presence of an alkaline condensing agent.¹⁶ Thus, acetone and α -aminoanthraquinone give 2-methyl-3-azabenzanthrone (I). In the original patent it was claimed that acetoacetic ester gave the corresponding carboxylic acid (II); the error was later corrected.¹⁷ Other derivatives have been obtained, starting with various aminoanthraquinonesulfonic acids and other ketones; acetophenone can be used.¹⁸

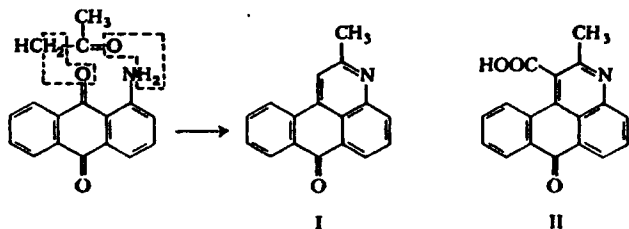
* C. F. H. Allen.

TABLE 35. 2-Azabenzanthrenes

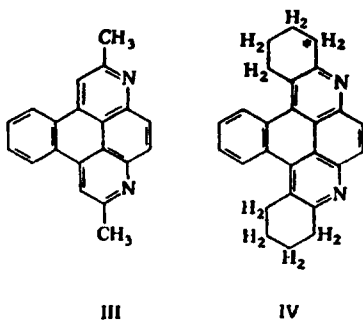
Substance	Ref.	M.p., °C.	Color of crystals	Color in H ₂ SO ₄	Vat dye obtained by alkaline fusion
1,3-Diketo- ^a	8,10,13,14	293-294	Yellow (from acetic acid)	Cherry-red with slight fluorescence	"Aceanthrene green"; dyes cotton deep emerald-green from cherry-red vat
2-Methyl-1,3-diketo-	9	230-231	Yellow	Carminc-red	Dyes cotton red-violet from red-violet vat, and becomes blue-green on air oxidation
2-Phenyl-1,3-diketo-4- (or 5-, 9-, or 10-) Chloro-1,3-diketo-	9 10	267-268 340	Yellow Orange-yellow (from acetic acid)	Red Yellow-red	—
6,8-Dichloro-1,3-diketo-	10	310	Orange-yellow (from acetic acid)	Bordeaux-red	—
2-Hydroxy-1,3-diketo-1-Methoxy-3-keto- (or isomer)	9 8	260-262 170-171	Brown-yellow —	Carminc-red	—
3-Hydroxy-7-keto- ^b	12,15	334	Green-yellow	Yellow fluorescence	Dyes cotton a fast blue-green from blue-red vat
1-Carboxy-3-hydroxy-7-keto-1,3-Dihydroxy-7-keto- (or isomer)	12 11	Loses CO ₂ >300	Yellow Red (from alc.)	— Cherry-red	"Isoacanthrene green"; dyes cotton dull green from cherry-red vat

^a Gives a yellow vat; dyes cotton in clear yellow shades.^b Gives a red vat.

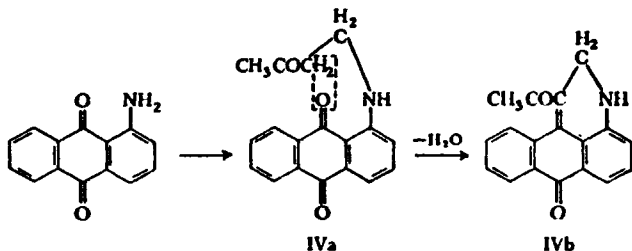
Diaminoanthraquinones are assumed to react twice to give "dianthrapyridines," e.g., 1,4-diaminoanthraquinone and acetone give



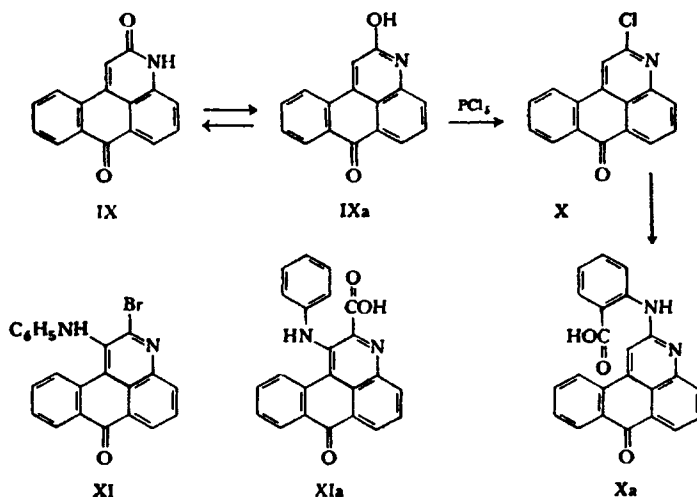
2,7-dimethyl-3,6-diazabenz[*e*]pyrene, ["2,7-dimethyl-4,5-*o*-phenylene-1,8-phenanthroline"], (III).¹⁶ A more complex "dianthrapyridine," 1,2,3,4,9,10,11,12-octahydro-5,8-diazadibenzo[*ghi,s*]picene, (IV) has been prepared from cyclohexanone and 1,4-diaminoanthraquinone. The monometho salt resembles picolinium salts and condenses with aldehydes (at $^{\circ}\text{C}$).¹⁸



A general method for preparing 2,3-dihydro-3-azabenzanthrones (IVb) consists of adding aminoanthraquinones to α,β -unsaturated aldehydes or ketones, or their equivalent,¹⁹ under conditions sufficiently drastic to close the ring of the open chain compound first formed. In illustration, 1-aminoanthraquinone adds to methyl vinyl ketone to give the alkyl derivative (IVa) which is then dehydrated at an elevated

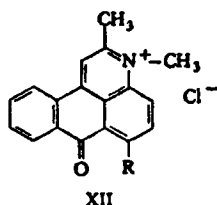


2-Halo-3-azabenzanthrones are obtained from 2-keto-3-azabenzanthrones (IX), in which the nitrogen atom is unsubstituted, by the action of phosphorus pentahalides.^{22,23} The reaction possibly proceeds through the 2-hydroxy tautomer (IXa). The halogen atom is replaceable by arylamino groups.^{22,23} The reactions may be illustrated by 2-(2'-carbethoxyanilino)-3-azabenzanthrone and the corresponding acid (Xa), which were prepared from 2-chloro-3-azabenzanthrone (X) during the investigation of the structure of the dye Ciba Yellow 3G.²³



In connection with the same problem, 1-anilino-2-bromo- (XI) and 1-anilino-2-carboxy-3-azabenzanthrone (XIa) were also prepared. The properties of the intermediate nitrile, obtained in a very low yield by a Rosenmund synthesis, were not determined.

3-Azabenzanthrones form quaternary salts,^{18,24} such as 2-methyl-3-azabenzanthrone methochloride ($R = H$) (XII), which is obtained by addition of methyl sulfate to the base, followed by replacement of SO_4



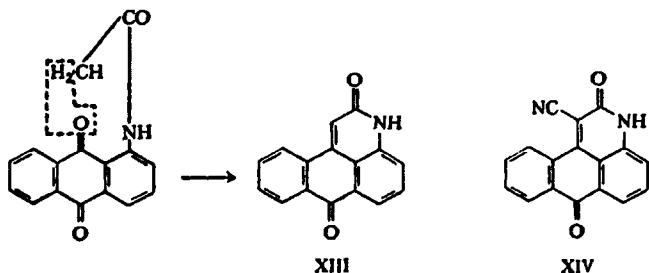
by Cl . This substance resembles many heterocyclic salts in that it undergoes condensation with *p*-dimethylaminobenzaldehyde or *m*-nitrobenzaldehyde (in alcohol, using piperidine as a catalyst) through the 2-methyl group.²⁵

(2) *Diketo Derivatives: 2-Keto-3-azabenzanthrones* (formerly "Anthrapyridones")

These are known in considerable number and variety, being largely in commercial use as intermediates or dyes. They can be obtained in

three general ways: (a) by ring closure from 1-aminoanthraquinones; (b) by ring closure starting from unsaturated compounds; and (c) from compounds in which the ring system is already formed. The first is the most important and is, in principle, the same as for the 3-azabenzanthrones, but it has several variations. It should be pointed out that many reactions which are useful with 2-keto-3-methyl-3-azabenzanthrones give very poor yields or none at all with 3-azabenzanthrone itself.

(a) **Ring Closure, from 1-Aminoanthraquinone.** (1) Acetyl derivatives of 1-aminoanthraquinones are readily cyclized to 2-keto-3-azabenzanthrones (XIII) by being heated alone^{24,27,28} or in the presence of alkali²⁹⁻³⁵; alkali salts such as the acetates or formates may be used.^{36,37} Copper is not necessary.³⁸ It is not even necessary to isolate the acetyl

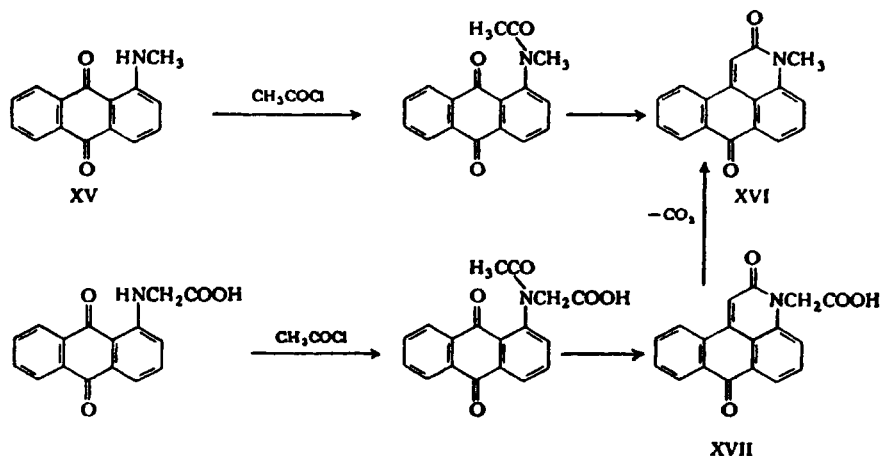


derivative though it may be advisable. Diacetyl derivatives lose an acetyl group during the reaction.²⁷

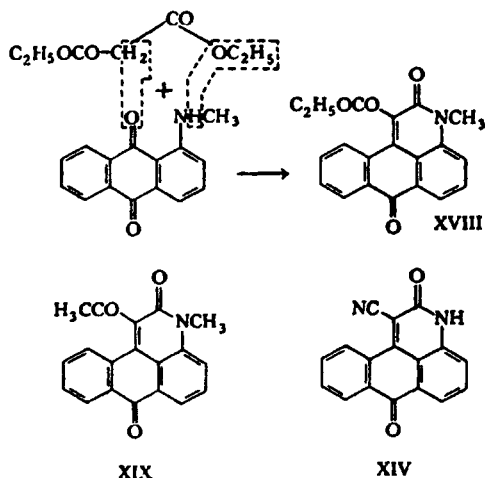
(2) Acetic anhydride or an acyl halide may be used—the acid halide is preferable when it is desired to isolate the acetyl derivative. Substituted acetyl halides can be employed; among those that have been specified are phenylacetyl,^{39,40} α -naphthylacetyl, and tetral- β -acetyl chlorides.⁴¹ The acylated 1-aminoanthraquinones so obtained are then cyclized, in the usual manner, to 1-substituted 2-keto-3-azabenzanthrones. Simple alkyl homologs of acetyl chloride form acylaminoanthraquinones, but the latter do not appear to undergo ring closure. Propionyl and ω -carbethoxyalkylacetyl chlorides have been used.⁴² However, 1-*p*-toluidinoanthraquinone can be acetylated and cyclized in a similar manner. If an alkali cyanide (as a concentrated aqueous solution) is used with the bromoacetyl derivative, 1-cyano-2-keto-3-azabenzanthrone (XIV) results.⁴³ The use of solvents such as the mono ethers and esters of ethylene glycol often results in an increased yield.^{43,44}

The more valuable commercial products are *N*-methyl derivatives, such as "*N*-methylantrapyridone" (XVI) obtained from 1-methyl-

aminoanthraquinone (XV). If aminoanthraquinones are used as starting material, the remaining amino hydrogen can be readily methylated by means of methyl *p*-toluenesulfonate.⁴⁵ In a variation, 1-anthraquinonylglycine gives the *N*-acetic acid (XVII), which can be decarboxylated readily to the same 3-methyl-2-keto-3-azabenzanthrone (XVI) as is obtained from acetylmethylaminoanthraquinone.³⁴



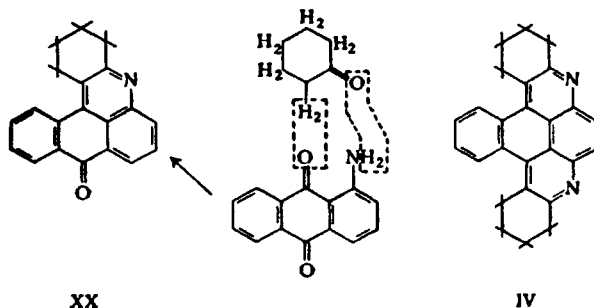
(3) 1-Aminoanthraquinones also condense with esters, and form 1-substituted 2-keto-3-azabenzanthrones.^{17, 45, 46, 47, 47a, 47b} Malonic ester and 1-methylaminoanthraquinone give the 1-carbethoxy derivative (XVIII),^{17, 36, 46, 47a, 48} whereas with acetoacetic ester the 1-acetyl derivative



(XIX) results, while cyanoacetic ester and 1-aminoanthraquinone give the 1-nitrile (XIV).^{45,46} Cyanoacetyl chloride can replace the ester in this reaction.⁴⁵ 1-Laurylaminoanthraquinone and malonic ester do not appear to react.⁴² The ester group may sometimes be hydrolyzed by the alkaline condensing agent; the resulting carboxylic acid so formed is readily decarboxylated to give XVI.^{17,47} Malonamide gives 1-carbox-amido derivatives.⁴⁵

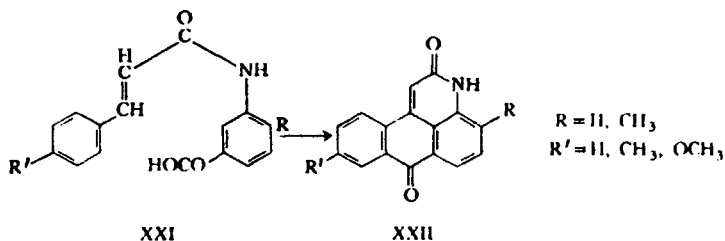
Generally the condensing agent does not hydrolyze the carbalkoxy group. It is necessary to use fairly strong alcoholic sodium hydroxide to hydrolyze 1-carbethoxy-2-keto-3-azabenzanthrone; the acid can be isolated. On the other hand, when the 3-methyl homolog is treated in the same manner, it is hydrolyzed and decarboxylated in the solution to give 2-keto-3-methyl-3-azabenzanthrone (XVI). No intermediate was isolated.⁴²

The action of cyclohexanone upon 1-amino- (or 1,4-diamino-) anthraquinone in the presence of an alkaline catalyst is said to give the highly condensed ring systems shown in XX and IV. The first is 1,2,3,4-tetrahydro-5-azaceranthren-9-one, while IV is 1,2,3,4,9,10,11,12-octa-



hydro-5,8-diazadibenzo[ghi,s]picene. By using sulfonated aminoanthraquinones, water-soluble products can be obtained.⁵¹

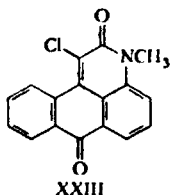
(b) **Ring Closure. Seka's Method.** *m*-Cinnamoylaminobenzoic acids (XXI) can be cyclized to 2-keto-3-azabenzanthrones (XXII) by



means of concentrated sulfuric acid, in yields up to 30%.^{52,53} Acetylenic compounds did not give an increased yield. Seka showed that the products so obtained were identical with those prepared by the patented procedures already described.

(c) **Formation of Substituted 2-Keto-3-azabenzanthrones.** For convenience in consideration, substituted 2-keto-3-azabenzanthrones can be grouped into two classes: (1) those in which the substituent is on the heterocyclic ring; and (2) those in which it is on the anthraquinone residue. Replacement of a group already present often takes place with unexpected ease. However, little is known about the behavior of substituents in other than the 1-, 4-, and 6-positions.

(1) *In the 1-Position.* The hydrogen atom on the carbon in position 1 is readily replaceable by chlorine by direct chlorination⁶⁰ or by the use of sulfonyl chloride.⁴⁴ In the patent it is stated that the product XXIII is

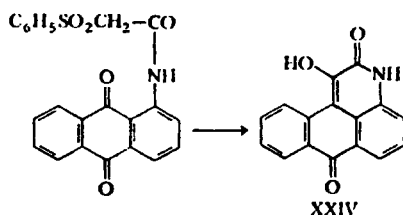


the same as that formed by ring closure of 1-chloroacetylmethylaminoanthraquinone in the presence of an alkaline condensing agent, but no experimental details are given.

The chlorine is available for reactions of double decomposition, thus making possible the formation of many other 1-substituted 2-keto-3-azabenzanthrones; it is much more active than the same halogen atom in 1-chloroanthraquinone.⁵⁶ The aromatic amines give arylamino compounds.^{23,50} *p*-Toluidine, for example, gives a yellow product which can be solubilized by sulfonation. *m*-Toluidine, *p*- and *m*-chloroaniline, *m*-trifluoromethylaniline, *p*-anisidine, and 2,5-dichloroaniline react in a similar manner. These products are wool dyes of excellent color but poor light stability, darkening on exposure. Alkylamines, such as ethanolamine, also react to give yellow dyes. These show a marked fluorescence, and dye cellulose acetate but have poor stability to light.³⁰⁸

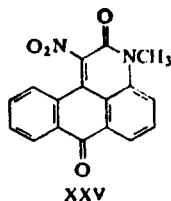
1-Cyano derivatives can be secured from the 1-chloro compounds by use of an alkali cyanide,⁴³ though the ring closure procedure already outlined may be preferable. 1-Hydroxy derivatives result from the interaction of the 1-chloro- or 1-nitro-2-keto-3-azabenzanthrones with alcoholic alkaline solutions⁴²; these are also formed by a modification of

the cyclization procedure, which employs 1-arylsulfonacetylaminanthraquinones.⁵⁶ The arylsulfonyl group is split off during the process,



e.g., 1-hydroxyanthrapyridone (XXIV) is obtained from benzenesulfonacetylaminanthraquinone. The use of alcoholic alkali sulfides gives rise to 1-mercapto-2-keto-3-azabenzanthrones.⁵⁰ 1-Aryl-2-keto-3-azabenzanthrones result from the ring closure procedure, using phenacetyl chlorides.^{39, 40}

1-Nitro-2-keto-3-methyl-3-azabenzanthrones (XXV) are secured by a novel ring closing reaction from 1-haloacetyl-amino-*N*-methylantraquinones and sodium nitrite.^{42, 57} The halogen is first replaced by a



nitro group, after which the ring is closed, for (a) 1-chloro-2-keto-3-methyl-3-azabenzanthrone is unaffected by sodium nitrite, and (b) a by-product is the open chain 1-hydroxyacetyl-1-methylaminoanthraquinone. The nitro group resembles the Cl atom in its easy replaceability. Other 1-substituted 2-keto-3-azabenzanthrones, containing ketone, acid, ester, and amide groups, have already been considered.

1-Nitro- and 1-chloro-2-keto-3-azabenzanthrones add to pyridine and α -picoline (probably to other heterocyclic bases), forming salts⁵⁸; this could not be confirmed in one instance.²³ According to Dupont these are photographic "dispensers" that cause fog. These pyridinium salts are the first anthraquinone *basic dyes* to be described. 1-Hydroxy- and 1-sulfo-2-keto-3-azabenzanthrones are said to be weak desensitizers when used in photographic processes.⁵⁴

1-Acetyl-3-methyl-6-arylamino-3-azabenzanthrones furnish valuable dyes.^{17, 47a} The *x*-sulfo-6-*o*-toluidino derivative is unique in coloring acetate silk, whereas the *meta* and *para* isomers are without effect on this fiber.⁵⁹

The sulfonated dye bases are soluble in water and have an absorption near 540 m μ .⁶⁰

(2) *In the 3-Position.* Since the nitrogen atom of the heterocyclic ring occupies this position, the variety of substituents is limited to alkyl and aryl groups (which, of course, may be modified). Many are formed by ring closure reactions as already outlined (e.g., β -hydroxyethyl,⁶¹ aryl,^{29,44} and the carboxymethyl ($-\text{CH}_2\text{COOH}$)³⁴ groups). As already mentioned the hydrogen on nitrogen may be alkylated by means of methyl *p*-toluenesulfonate.⁴⁵

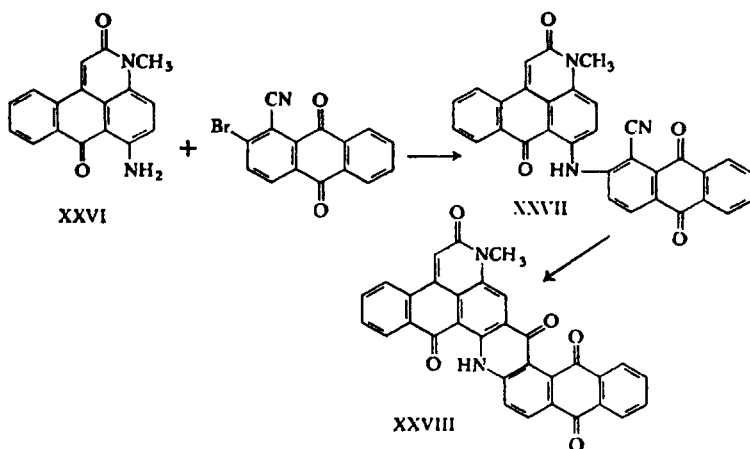
(3) *In the 4-Position.* 2-Keto-3-azabenzanthrones have been described having Br, Cl, CH₃, OR (R = alkyl and aryl), COOH, and SO₃H in this position. All have been secured by ring closure of suitably constituted compounds,^{17,26,29,36,38,43,45} except the aryloxy, which were prepared from 2-keto-3-azabenzanthrone and the alkali salt of the phenolic component.⁶¹ The sulfonic acid group has also been introduced by replacement of bromine, using sodium sulfite under pressure.^{62,63}

(4) *In the 6-Position.* This appears to be the most important location for substituents, since many of the products are either valuable commercial dyes or become so upon sulfonation. The groups reported comprise Br, Cl, NO₂, OR, OH, NH₂, NHR, NR₂, and SO₃H. Most of these are already in the molecule prior to ring closure, but where halogen atoms or a nitro group are present, they can be replaced readily by amino or aryloxy groups. This exchange is probably the most important of all the reactions.

Nitration of 2-keto-3-azabenzanthrone⁵³ probably gives the 6-nitro derivative, for it has been shown that the 3-methyl homolog is nitrated in this position.⁴²

The 6-amino derivatives can be obtained from the 6-bromo, 6-nitro, or 6-methoxy derivatives, although the former is generally employed. They include all variations—simple NH₂ (XXVI), mono- and dialkylated, and arylated. Alkyl groups include methyl, *n*-butyl, and cyclohexyl. Arylation takes place with aromatic amines in general from anilines to aminoanthraquinones and aminoazabenzanthrones.^{31,38,59,64-67,67a} If dihalides such as 2,8-dichlorochrysene are employed, two molecules of 6-amino-2-keto-3-azabenzanthrone react, one with each of the chloro groups.⁶⁸ Identical substances are secured (a) from a halo-2-keto-3-azabenzanthrone and an aromatic amine, and (b) from an amino-2-keto-3-azabenzanthrone and an aromatic halide.³¹ The arylamino-2-keto-3-azabenzanthrones are usually sulfonated to form acid dyes, while the more complex molecules are commonly employed as vat dyes.

If a 2-halo-1-cyanoanthraquinone is used, the product XXVII is a type useful for preparing vat dyes of the acridone series such as 6,10-, 15,18-tetraketo-7-methyl-7,18-diazadinaphth-*o*-[2,3*a*,3',2',1'-*i*]naphthacene (XXVIII).^{69, 69a}



The position taken by the SO_3H group upon sulfonation of many 6-substituted 2-keto-3-azabenzanthrones has only recently been determined. It has, indeed, been stated³⁸ that the dye formed by sulfonation of 6-*p*-toluidino-2-keto-3-methyl-3-azabenzanthrone is the same as that obtained by heating 6-bromo-2-keto-3-methyl-3-azabenzanthrone with the sodium salt of "*p*-toluidinesulfonic acid" under pressure and in the presence of a copper catalyst, but the experimental evidence of this identity is not given.

When Alizarin Rubinol R and Brilliant Alizarin Light Red B are treated with dilute nitric acid, the sulfonic acid residue is replaced by a nitro group.⁴² Assuming that the latter actually enters the position occupied by the former, this reaction affords a method of locating the sulfonic acid group. In the first instance cited, the substance containing the nitro group was synthesized, as will be described in a subsequent reaction (page 224); the nitro group is *ortho* to the NH of the amine residue, hence the sulfo group in Alizarin Rubinol R (and, by inference, in its homologs) appears to be adjacent to the —NH which connects the azabenzanthrone nucleus and the benzene ring of the aromatic amine used.

(5) *In the 8- and 11-Positions.* 2-Keto-3-azabenzanthrones with substituents in these positions have always been secured by appropriate ring

closures.^{16, 17, 32, 45, 49, 70} The groups used include Cl, OH, NH₂, RCONH, and SO₃H. The acylamides may likewise be obtained by acylation of the 8-amines. The amines react with polynuclear halides, in exactly the same fashion as the 6-amines.

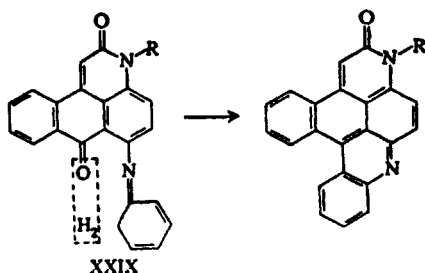
(6) *Miscellaneous.* When amino-2-keto-3-azabenzanthrones having a primary amino group are treated with alkali aldehyde bisulfite compounds, under acid conditions, *N*-alkylsulfonic acids are formed.⁷¹

Bromination of 2-keto-3-azabenzanthrones is not a cleancut reaction. From one to two atoms of bromine can be introduced, but nearly all is eliminated by warming to 150°. ⁵⁴

It has been claimed that nitric acid ($d = 1.52$) forms a mononitro-2-keto-3-azabenzanthrone,⁵³ but the work has not been repeated.⁴² The exact location of the nitro group was not determined, but it was suggested that it was in the heterocyclic ring because of its easy replaceability by aromatic amines. This reaction is not of diagnostic value, however, for 6-nitro-2-keto-3-azabenzanthrones exhibit a similar behavior.⁴² The nitro group can be reduced, using sodium hydrosulfite, to a primary amine; the latter forms a benzal derivative.

2-Keto-3-azabenzanthrones can be solubilized by treatment with sulfur trioxide in the presence of a basic solvent (pyridine) and copper catalyst.⁷² These new substances are presumably esters of leuco azabenzanthrones containing the group —OSO₃Na, resembling the Soledon group of dyes. (These may be used for dyeing wool and acetate silk. Certain of them are unstable, their aqueous solutions dec. on boiling.)

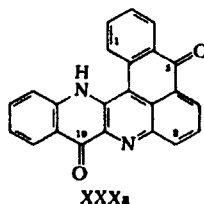
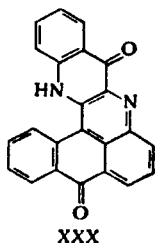
In sulfonating 2-keto-3-azabenzanthrones, care must be taken to avoid dehydration, which results in the production of commercially valueless "acridines" such as 5-carbethoxy-6-keto-7,13-dimethyl-7,10-diaza-



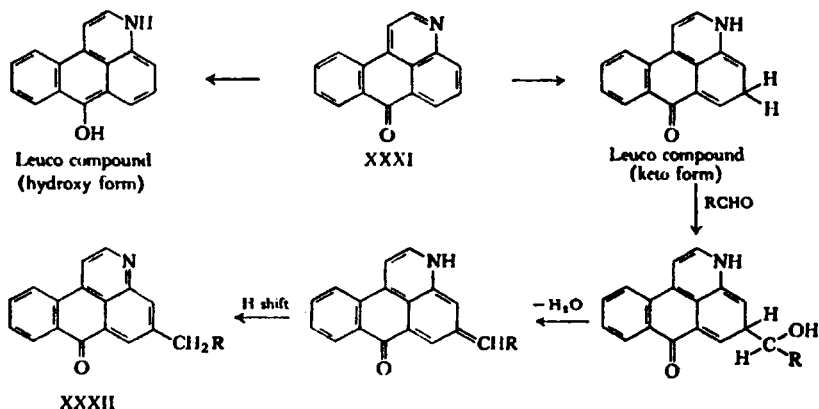
dibenzo[*a*,1]pyrene.⁷³ The amine (XXIX) can be represented as reacting in a tautomeric form.

The dye, Ciba Yellow 3G, is an acridone type of a 3-azabenzanthrone. The structure is usually written as shown in XXX²⁰ but should be oriented

as in XXXa. The chemical name is 15*H*,9,15-diazanaphtho[3,2,1-*q,r*]-naphthacene-5,10-dione.



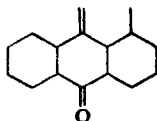
(d) **Products of Uncertain Structures.** Leuco compounds of 3-azabenzanthrone, when treated in an alkaline medium with aldehydes, give substances which are believed to be, in part, substitution products,⁷⁴ *e.g.*, formaldehyde gives a methyl, while benzaldehyde gives a benzyl derivative. Since the products are vat dyes, the carbonyl group must still be present, so the aldehyde probably did not react at that point. However, in view of the work of Zahn and Ochwat⁷⁵ on leuco quinones, which seems to indicate that in leuco compounds the extra hydrogen is on the β -carbon atom, it seems very likely that the aldehyde has reacted at this point. If this is so, then the new products XXXII are alkylated in the 5-position. A possible mechanism that accounts for the formation of 5-alkyl derivatives is shown in the outline. The reaction has an



analogy in Marschalk's discovery that many anthraquinones can be alkylated in the *beta* position by essentially the same procedure.^{76,77}

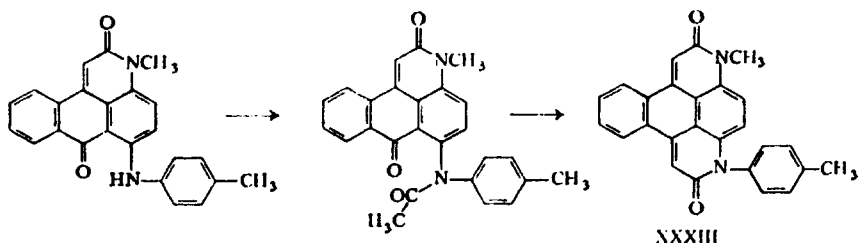
2-Keto-3-methyl-3-azabenzanthrone is said to react with 1-aminoanthraquinone in nitrobenzene in the presence of anhydrous aluminum chloride, or chlorosulfonic acid, to give a polycyclic dye.⁷⁸

Dyes and dye intermediates, the structures of which have not been disclosed, are obtained when primary amines of ring systems which can be reduced to vats are allowed to react in the presence of alkaline condensing agents with anthrone derivatives of the adjacent formula.⁷⁹ These anthrone derivatives may have substituents and/or rings condensed to them, but the total number of rings should not exceed 7.



3-Azabenzanthrones "negatively substituted" but not containing arylamino groups capable of sulfonation can be sulfonated^{25,80} without loss of the substituent. The examples of substituents used in the illustrations are bromine and methoxy.

(c) "**Dianthrpyridones.**" 6-Amino-3-azabenzanthrones can be acylated (*e.g.*, by acetic anhydride in presence of anhydrous zinc chloride) and cyclized in the usual way, to give "dianthrpyridones" (XXXIII).^{64,61} They may also be formed from 1,4- or 1,5-diaminoanthraquinones.⁴⁷



(3) Color

Simple 2-keto-3-azabenzanthrones are yellow to orange; the yellow color of the acylaminoanthraquinones appears to be only slightly deepened by the ring closure. 1-Arylamino derivatives are also yellow, but the introduction of amino groups in the 6-position deepens the color to red; many of these amines are bluish-red; when the 6-arylamino group contains an amino or alkoxy group the color is deepened to violet.^{62,63} Their sulfonic acids^{62,63} are valuable commercial acid dyes, while the unsulfonated bases, if properly dispersed, can be used to color cellulose acetate.

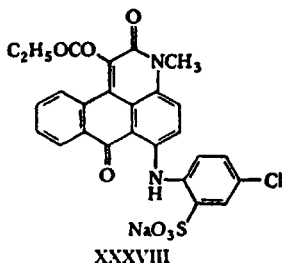
The longest known of these dyes is Alizarin Rubinol R (XXXIV), Anthralan Red 3B, which is a monosulfonated 2-keto-3-methyl-6-*p*-toluidino-3-azabenzanthrone. The position of the sulfonic acid group

Chemical reaction scheme showing the conversion of compound XXXIV to compound XXXV. Compound XXXIV is a triphenylmethane derivative with a 4-methylphenyl group and a sodium sulfonate group. Compound XXXV is the corresponding nitro-substituted product.

XXXIV XXXVI XXXVII

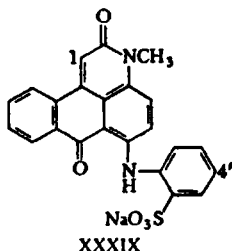
Brilliant Alizarin Light Red B appears to be a sulfonated 1-carboethoxy - 2 - keto - 3 - methyl - 6 - (4' - chloroanilino)-3-azabenzanthrone (XXXVIII). The sulfonic acid group is probably in the chloroanilino

ring, for it is easily replaced by a nitro group under the conditions just described.⁴²



4-Aryloxy-6-arylamino-3-(alkyl, oxyalkyl or alkoxyalkyl)-2-keto-3-azabenzanthrones have been obtained by treatment of the corresponding 4-bromo compounds with the sodium salts of various phenols and naphthols.⁶¹ These products may be used to color cellulose acetate red shades if the dye bath is properly prepared, using a dispersing agent. The sulfonated products dye wool; the position of the sulfonic acid group was not determined, but assumed to be in the aryloxy ring.

The absorption curves of Alizarin Rubinol B and of a number of analogs (XXXIX) are shown on page 226.⁶⁰



It will be noted that the introduction of unsaturated substituents in position "1" greatly increases the blue absorption. Substituents in the arylamino residue have a moderate effect.

Algol Red B(XL) (*Colour Index No. 1155*) has a 2-aminoanthraquinone residue in the 6-position; it can be prepared either from 2-aminoanthraquinone and 6-bromo-2-keto-3-methyl-3-azabenzanthrone, or from 2-bromoanthraquinone and 6-amino-2-keto-3-methyl-3-azabenzanthrone.³¹

Certain of the acid anthraquinone dyes form only moderately soluble salts, and in some instances the calcium salts are almost insoluble; thus, the dye may be precipitated by the calcium in the water supply used.

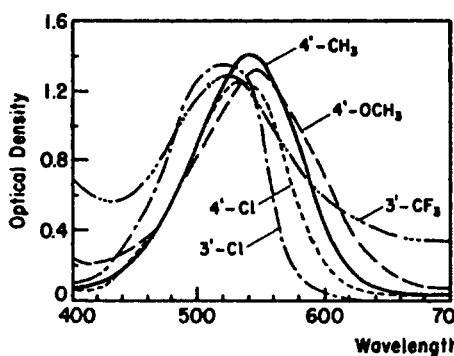
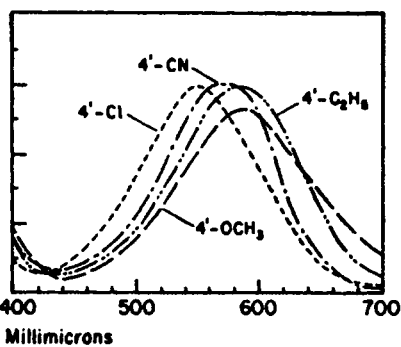
Fig. 1. 1-C₂H₅OOC series.

Fig. 2. 1-Cyano series.

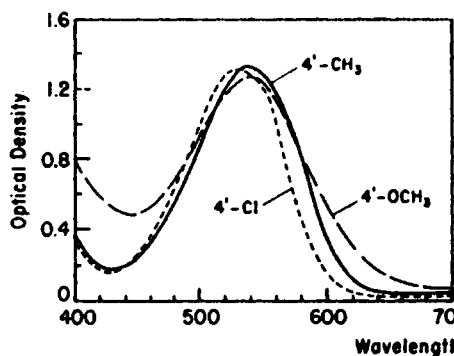


Fig. 3. 1-Phenyl series.

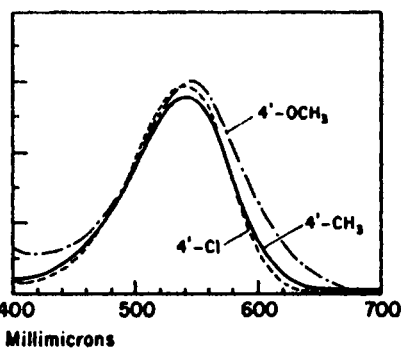
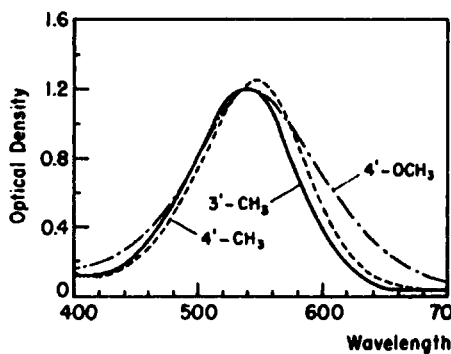
Fig. 4. 1-C₆H₅CO series.

Fig. 5. 1-Acetyl series.

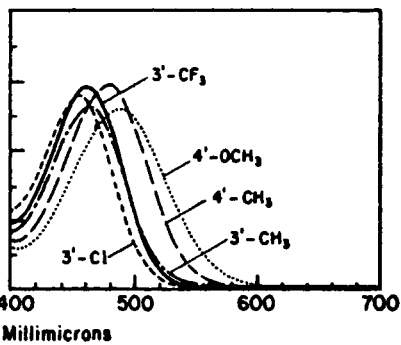
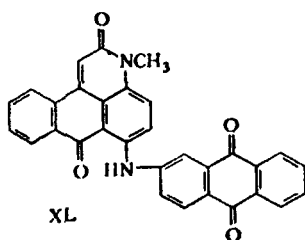
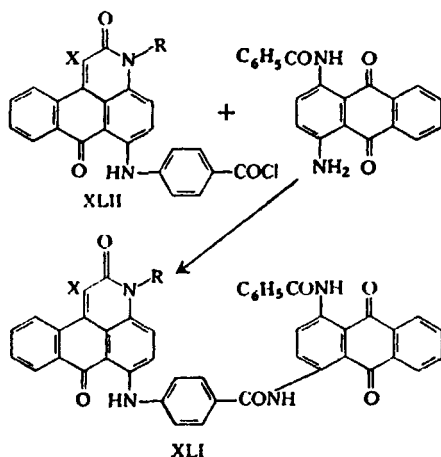


Fig. 6. 1-Anilino series.

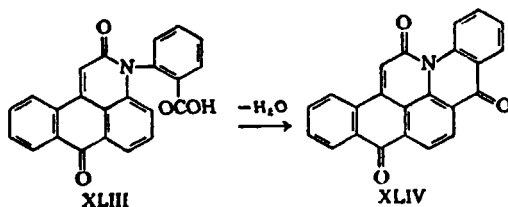


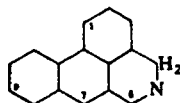
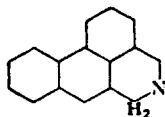
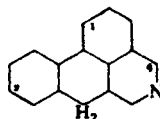
The lithium salt is claimed⁸⁴ to be useful on account of its greater solubility. The ammonium and ethanolanmonium salts are even more soluble than the sodium salt.

Other complex vat dyes (XLI) are obtained by condensing chlorides of 2-keto-6-arylamino-3-azabenzanthrone-3'- (or 4'-) carboxylic acids (XLII) with vatiable aminoanthraquinones.⁸⁵ The patent gives a large variety of aminoanthraquinones that have been used. A yellow vat dye.

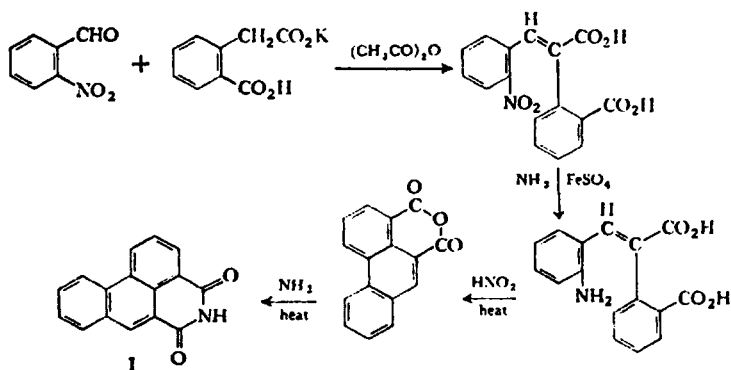


5,8,14-triketo-14a-azadibenzo[*a,i*]pyrene (XLIV), is reported, formed by cyclization of the acid (XLIII).²⁹

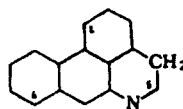


D.* 5-Azabenzanthrenes**4*H*,5-Azabenzanthrene,**
quinoline. R.I. 2751**4-Dibenz[*de,g*]iso-****6*H*,5-Azabenzanthrene****7*H*,5-Azabenzanthrene,**
quinoline, 7-Naphth[3,2,1-*de*]isoquinoline,
3-Azabenzanthrene (German). R.I. 2752

The only compound reported in the literature which has the basic structure of a 5-azabenzanthrene is the imide of phenanthrene-1,10-dicarboxylic acid (I).⁸⁶ This substance is prepared by the series of reactions shown below.

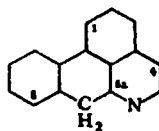


4,6-Diketo-5*H*,5-azabenzanthrene (phenanthrene-1,10-dicarboximide) sublimes in the form of long needles melting at 308–309°.

E.* 6-Azabenzanthrenes**4*H*,6-Azabenzanthrene,** 4-Dibenzo[*de,g*]quinoline,
6,4-*peri*-Naphthisoquinoline. R.I. 2753

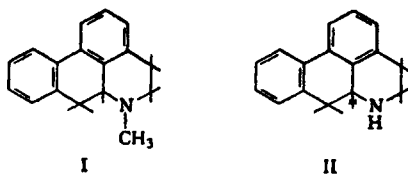
* D. M. Burness.

7H,6-Azabenzanthrene, 7-Dibenzo[de,g]quinoline, 4-Azabenzanthrene (German). R.I. 2754



(1) Introduction

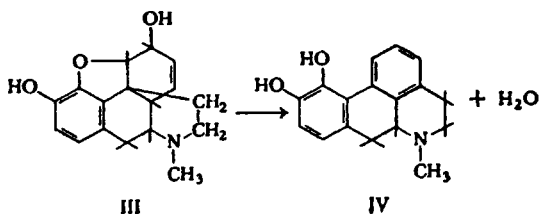
The only known compounds which possess the basic 6-azabenzanthrene nucleus are the partially hydrogenated derivatives which comprise the aporphine alkaloids and related synthetic products. These alkaloids may all be classified as phenolic (or phenolic ether) derivatives of aporphine (6-methyl-4,5,6,6a-tetrahydro-7H,6-azabenzanthrene) (I) or the unmethylated compound, noraporphine (II), neither of which occurs in nature. The name, aporphine, was coined by Gadamer for the parent base of this group of alkaloids.



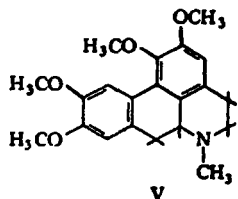
There are approximately twenty naturally occurring alkaloids of this class, the structures of most of which have been determined either by degradation or by total synthesis. In addition to the natural alkaloids, a considerable number of analogs are known. These have been derived largely by alkylation, dealkylation, etc. of the natural products, and to a lesser extent by synthesis from simpler compounds. A few are acid-degradation products of certain morphine alkaloids.

(2) Historical

Strangely enough, the first and best known member of the series, apomorphine (IV), does not occur in nature, but is obtained, as the name implies, from morphine (III). The conversion of morphine to apomorphine involves an extensive change in structure, and is accomplished by the action of hydrochloric or sulfuric acid on the parent compound.⁶⁷



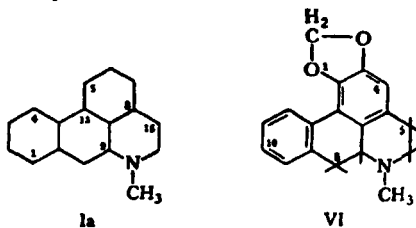
The structure for apomorphine was first proposed in 1902 by Pschorr,⁸⁸ and later confirmed by degradation studies.⁸⁹ Further proof of this structure was obtained in 1929 by syntheses of *dl*-apomorphine dimethyl ether; this was accomplished independently by Avenarius and Pschorr⁹⁰ and by Späth and Hromatka.⁹¹



Glaucine (V) was the first member of the aporphine series of alkaloids to be prepared synthetically. Gadamer⁹² performed the synthesis in 1911 from papaverine, using a process which Pschorr had carried nearly to completion seven years earlier. Gadamer also synthesized aporphine (I), the parent compound of the group.⁹³

(3) Nomenclature

The aporphine alkaloids, sometimes referred to as phenanthripyridines, although possessing the basic skeleton of a 6-azabenzanthrene, almost invariably have been named as derivatives of aporphine (I). Also, the system of numbering of the nucleus is different from that used throughout this monograph. Beilstein's handbook and most of the German and British investigators in the field have used the system of numbering indicated in formula Ia, in which the phenanthrene nucleus is numbered first. Other variations, which have seen limited use, are those of Stelzner and Kuh^{94,95} and Barger and Girardet.⁹⁶ *Chemical Abstracts* indexes the methylenedioxy derivative, roemerine (VI) as 7-methyl-5-benzo[g][1,3]-benzodioxolo[6,5,4-*de*]quinoline.



As an aid to workers in this field, the widely used aporphine name and numbering (based on formula Ia) is given in Table 36 (page 247) along with other essential data on these compounds.

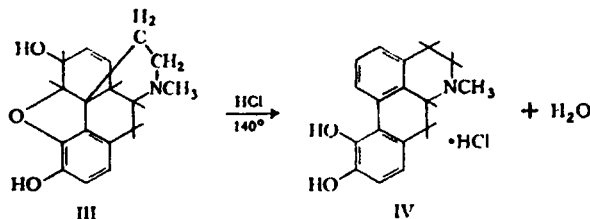
(4) Stereochemistry

It will be noted that there is an asymmetric carbon atom in the 6a-position (*) of the 4,5,6,6a-tetrahydro-7*H*,6-azabenzanthrene nucleus (II); thus all of the naturally occurring aporphines are optically active compounds. For purposes of comparison with the natural alkaloids, many of the synthetic products have been resolved by means of their hydrogen tartrates. In other cases, the center of symmetry has been destroyed by degradation methods which involve cleavage of the pyridine ring at the point of attachment to the asymmetric carbon atom (see page 236).

(5) Preparation

The naturally occurring members of this group, the aporphine alkaloids, have been prepared successfully in a pure state by extraction from the leaves, stems, or roots of various plants. These sources will be mentioned briefly in a later section where the natural alkaloids are discussed separately.

Three of the so-called aporphine alkaloids, apomorphine, apocodeine, and morphothebaine, although not occurring in nature, are obtained from plant alkaloids of the morphine group by treatment with acidic reagents.^{87,97} For example, when morphine (III) or its hydrochloride is heated in a sealed tube with hydrochloric acid at 140°, a molecule of water is lost and apomorphine (10,11-dihydroxy-6-methyl-4,5,6,6a-tetrahydro-7*H*,6-azabenzanthrene) hydrochloride (IV) is formed.⁸⁷



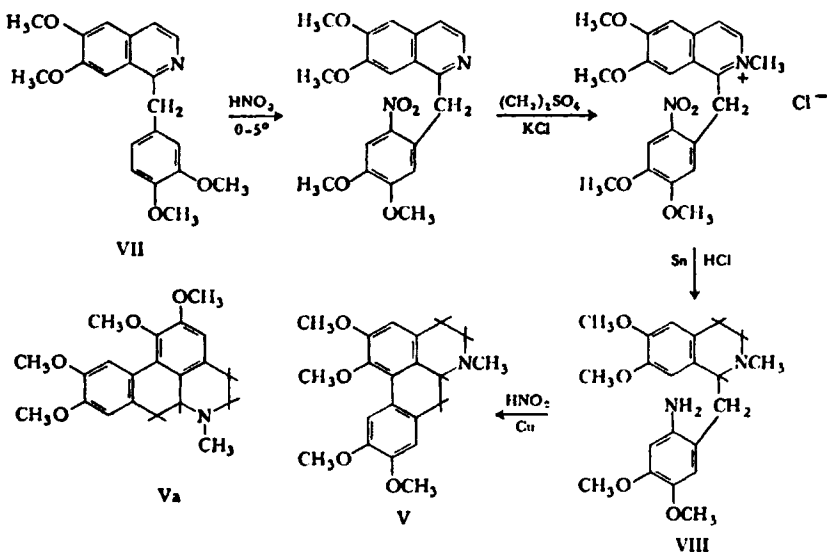
In a similar manner, apocodeine, the 10-methyl ether of compound IV, is formed when codeine or pseudocodeine is heated with anhydrous oxalic acid.⁹⁸ Morphothebaine (2,11-dihydroxy-10-methoxy-6-methyl-4,5,6,6a-tetrahydro-7*H*,6-azabenzanthrene) is produced by the action of hydrochloric acid on thebaine at 80–90°.⁹⁹

The methods which have been employed for the synthesis of the aporphine alkaloids vary but little from one another; all are based on

Pschorr's excellent method of ring closure¹⁰⁰ in which two aromatic nuclei are coupled by decomposition of a diazonium salt. The only essential difference between the various recorded syntheses is the method of preparing the requisite 1-*o*-aminobenzyl-1,2,3,4-tetrahydroisoquinolines.

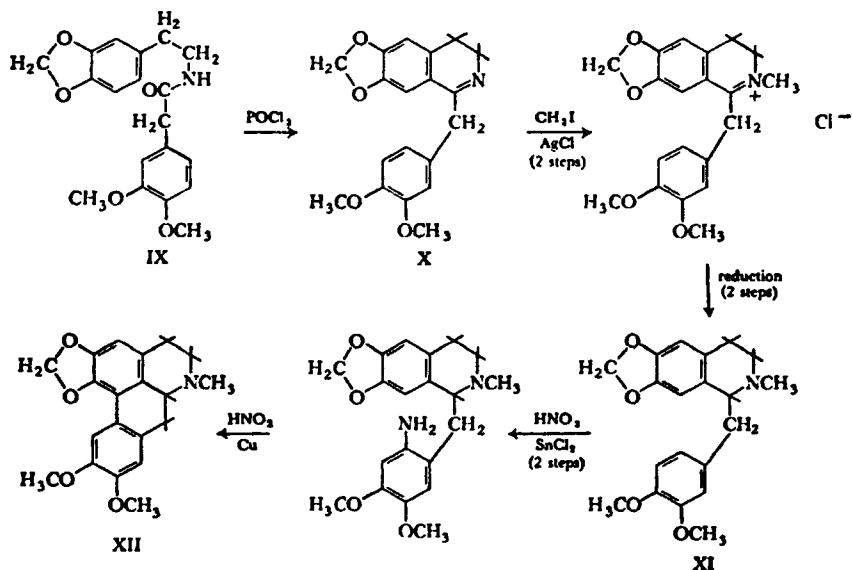
In the case of glaucine (1,2,9,10-tetramethoxy-6-methyl-4,5,6,6a-tetrahydro-7*H*,6-azabenzanthrene) (V), the first aporphine to be synthesized, this problem had been partially solved by the prior synthesis of papaverine (VII).¹⁰¹ Gadamer⁹² then (in 1911) succeeded in converting papaverine to glaucine by a method which earlier had been carried nearly to completion by Pschorr, Stählin, and Silberbach.¹⁰²

In this process, papaverine (VII) was nitrated, converted to the methochloride, and reduced with tin and hydrochloric acid. The resulting *N*-methyltetrahydroaminopapaverine (VIII) was diazotized and converted to *dl*-glaucine (V) by treatment with copper powder. The optically inactive product was resolved by recrystallization of the *d*- and *l*-hydrogen tartrates; the *d*-glaucine (m.p. 119–120°) thus produced was identical with the natural alkaloid. (The orientation in Va shows its relation to the other azabenzanthrenes.)

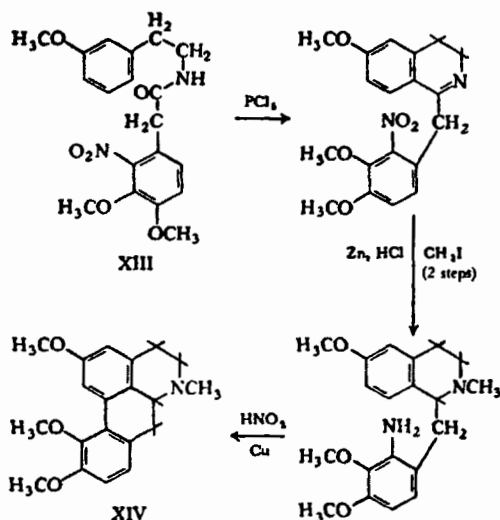


Fourteen years later (1925), the second synthesis of an aporphine alkaloid was recorded. Haworth, Perkin, and Rankin¹⁰³ prepared *dl*-dicentrine (9,10-dimethoxy-1,2-methylenedioxy-6-methyl-4,5,6,6a-tetrahydro-7*H*,6-azabenzanthrene) (XII), and subsequently resolved it into

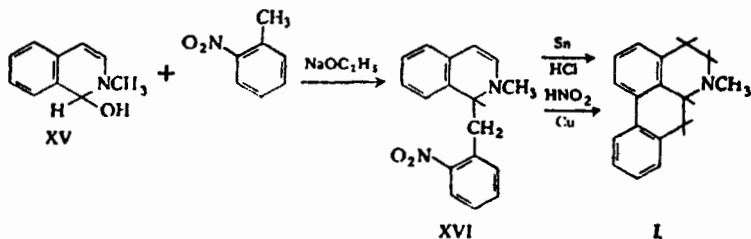
the naturally occurring *dextro* form and its optical isomer.¹⁰⁴ The amide (IX) was prepared by standard procedures (from veratraldehyde and piperonal), and converted by boiling with phosphoryl chloride into 1 - (3,4 - dimethoxybenzyl) - 6,7 - methylenedioxy - 3,4 - dihydroisoquinoline (X). Insertion of an amino group by nitration and reduction, followed by the Pschorr reaction, led to the formation of *dl*-dicentrine (XII).



Both glaucine and dicentrine conveniently contain methoxyl groups in the 9- and 10-positions of the azabenzanthrene nucleus, so that the necessary nitroisoquinoline bases are readily prepared by direct nitration of the appropriate 1-benzylisoquinoline derivative. Many alkaloids of the aporphine group contain phenolic or ethereal oxygen in the 10- and 11-positions of 6-azabenzanthrene. In order to prepare bases of this constitution by direct nitration, it would be necessary to introduce the nitro group into the 2'-position of a base of the papaverine type (VII) a feat which has yet to be accomplished. For this reason, Gulland and Haworth¹⁰⁶ found it necessary to modify the process of Haworth, Perkin, and Rankin, and to prepare amides (XIII) which already contained the necessary nitro group. This method has seen wider use than any other; it is illustrated below by the synthesis of morphothebaine dimethyl ether (2,10,11 - trimethoxy - 6 - methyl - 4,5,6,6a - tetrahydro - 7H,6 - azabenzanthrene) (XIV).

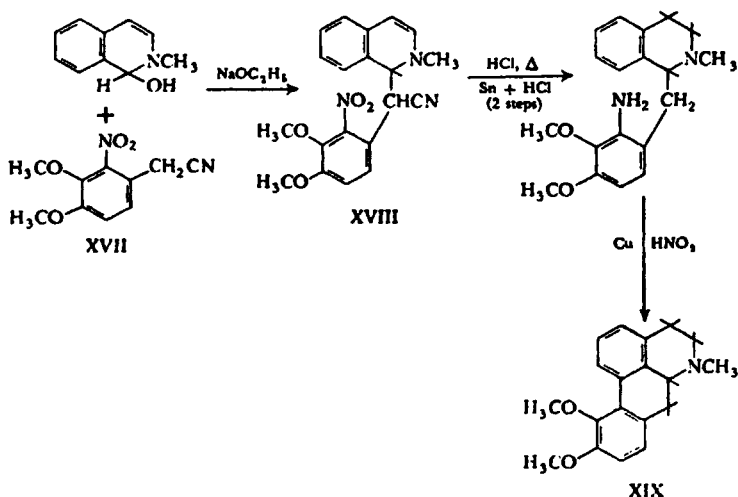


The discovery by Hope and Robinson¹⁰⁶ that pseudo bases such as 1-hydroxy-2-methyl-1,2-dihydroisoquinoline (XV) condense with derivatives of *o*-nitrotoluene provided another method for the preparation of the necessary *o*-nitrobenzylisoquinolines. Gadamer, Oberlin, and Schoeler¹⁰⁷ used this method for the synthesis of aporphine (I) itself, the parent compound of the group. The process is shown below.



In a slight modification of this last method, Pschorr and Avenarius¹⁰⁸ replaced *o*-nitrotoluene with 3,4-dimethoxy-2-nitrophenylacetonitrile (XVII) to obtain the nitrile (XVIII). This was hydrolyzed and decarboxylated, the nitro group and dihydro ring reduced, and the resulting amine converted to apomorphine dimethyl ether (XIX) by the Pschorr reaction.

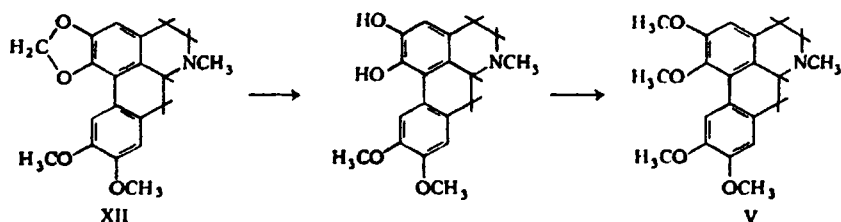
Whereas the preparation of the completely etherified derivatives has been rather successful and of great value in elucidating the structure of the alkaloids, the direct synthesis of the phenolic aporphines has been



realized in rare instances. It was accomplished by both Japanese¹⁰⁹ and English workers¹¹⁰ by protecting a hydroxy group with the benzyl group, which later was removed merely by treatment with concentrated hydrochloric acid at moderate temperatures. In a similar attempt by Gulland, Ross, and Virden¹¹¹ to protect the hydroxy group with the carbethoxy radical, the process met with failure. In the step involving reduction of the nitro group, the desired amine could not be obtained.

(6) Reactions

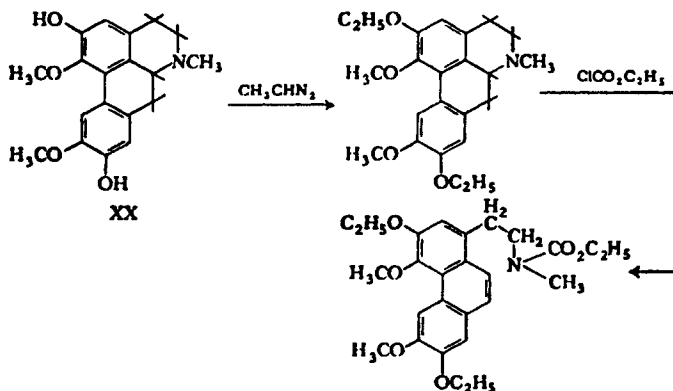
Those aporphine alkaloids which contain a methylenedioxy group undergo cleavage of this group by warming the compound with dilute sulfuric acid and phloroglucinol.¹¹² This is accomplished without disturbing any methoxy groups which may be present in the molecule.



The resulting dihydroxy compound then may be methylated with methyl sulfate or diazomethane to form new derivatives. In this manner, dicentrine (XII) was converted to glaucine (V) by Osada.¹¹²

A reaction which has proved useful in comparing two compounds whose structure might differ only in configuration at the asymmetric carbon atom is the one with acid chlorides, *e.g.*, ethyl chloroformate or benzoyl chloride. In this reaction, the nitrogenous ring is cleaved, and the center of symmetry destroyed; thus, it is possible to compare the racemic mixture obtained by synthetic means with the optically active natural alkaloid without recourse to the tedious procedure of resolution.

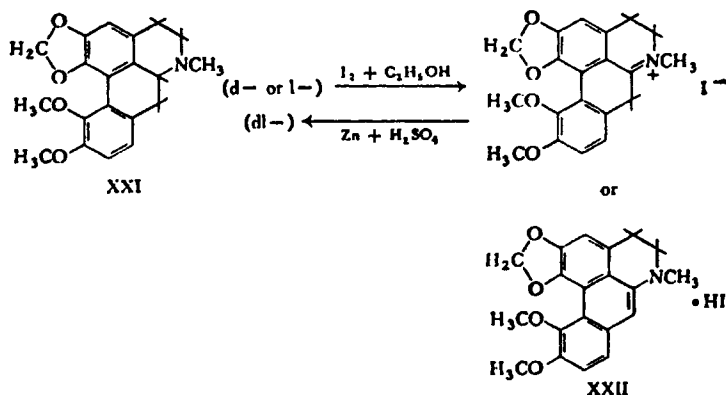
This method was used by Schlitter¹¹⁴ in his proof of structure of boldine (2,9-dihydroxy-1,10-dimethoxy-6-methyl-4,5,6,6a-tetrahydro-7*H*,6-azabenzanthrene) (XX), and is illustrated below.



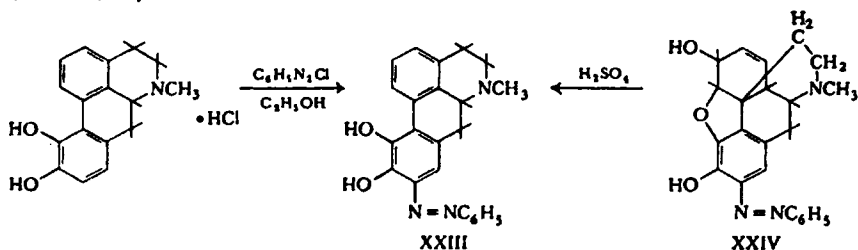
In a similar manner, Marion¹¹⁵ recently proved the structure of anolobine (9-hydroxy-1,2-methylenedioxy-4,5,6,6a-tetrahydro-7*H*,6-azabenzanthrene) by use of the Hofmann degradation on the synthetic and natural products; the subsequent dimethylaminoethylphenanthrene derivatives were identical. In a number of instances, the structure of these alkaloids has been determined by complete degradation of the molecule, by the Hofmann method, to the polyalkoxyphenanthrene.¹¹⁶

A reaction which effects racemization of the optically active alkaloids has been discovered by Gadamer¹¹⁷; for example, *d*-bulbocapnine methyl ether (10,11-dimethoxy-1,2-methylenedioxy-6-methyl-4,5,6,6a-tetrahydro-7*H*,6-azabenzanthrene) (XXI), when treated with alcoholic iodine, undergoes limited oxidation to an inactive didehydro derivative (XXII). This oxidation product reverts to the inactive *dl*-bulbocapnine methyl ether upon treatment with zinc and sulfuric acid.

In at least a few instances, the aporphines undergo substitution reactions typical of simpler aromatic compounds. For example, Goto and Kitasato¹¹⁸ have prepared a sulfonic acid of apomorphine by direct sulfonation; the product forms an inner salt of limited solubility in water.



The phenolic character of apomorphine is demonstrated by its ability to couple with diazonium salts; for example, with benzenediazonium chloride the product is 10,11-dihydroxy-6-methyl-9-phenylazo-4,5,6,6a-tetrahydro-7H,6-azabenzanthrene (XXIII). The latter was shown by Neri¹¹⁹ to be identical with the product obtained from phenylazomorphine (XXIV) by the action of sulfuric acid.



(7) Properties

The aporphines are, for the most part, colorless crystalline solids melting at 100° to 250°; a few have not yet been obtained in a crystalline state. They are capable of existing in two optically active forms; thus, the natural alkaloids exhibit optical activity, and are predominantly *dextro*-rotatory. They readily form salts with strong mineral acids and with alkyl halides and sulfates.

The bases dissolve in concentrated sulfuric acid to give colorless solutions; however, with certain other reagents (Erdmann's, Mandelin's, Froehde's, etc.) they give characteristic colors which may help to identify individual members of the group. Callow, Gulland, and Haworth¹²⁰ have recorded these properties for a number of the aporphines. Girar-

det¹²¹ has published absorption characteristics of a few of the better known aporphine alkaloids.

The aporphines which contain free hydroxy groups are susceptible to attack by atmospheric oxygen to varying degrees. In alkaline solution apomorphine absorbs oxygen in a manner similar to pyrogallol, while 6-hydroxyapomorphine has still greater activity than apomorphine.¹²²

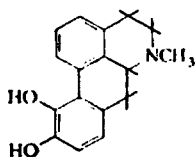
The properties of all the known 6-azabenzanthrenes are given in Table 36 on pages 247–253.

(8) *Source, Properties, and Physiological Action of the Natural Alkaloids**

The aporphine alkaloids occur for the most part in various species of the genera *Corydalis* and *Dicentra* (family, *Fumariaceae*), herbaceous plants native to Asia, South Africa, and North America. These alkaloids have some practical as well as historical and theoretical interest, as they are used to a limited degree in medicine.

The following brief survey is intended to present some of the more pertinent facts and references concerning each of the natural alkaloids. Data on natural sources, characterization, physical properties, and physiological action are included. An excellent treatise and thorough coverage of the literature on this subject, up to the year 1938, is given by Henry.¹²³

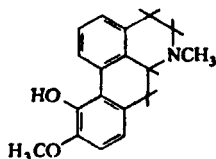
(a) **Apomorphine**, $C_{17}H_{17}NO_2$, is obtained from morphine by acidic



degradation, as has been described previously (page 231). The structure assigned to this alkaloid was suggested by Pschorr, Jaeckel, and Fecht¹²⁴ in 1902, and later proved correct by Pschorr *et al.*¹²⁵ *dl*-Apomorphine dimethyl ether was synthesized in 1929 by Avenarius and Pschorr¹²⁶ and by Späth and Hromatka.¹²⁷ Apomorphine melts at 195° with decomposition,¹²⁸ and decomposes on exposure to air; its salts, however, are quite stable, the methiodide melting at 180° (dec.).¹²⁹ Apomorphine is used in medicine, generally in the form of its hydrochloride hemihydrate, as an emetic, and to a certain extent as a sedative in delirium tremens.

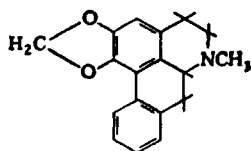
* The well-known alkaloids, apomorphine, apocodeine, and morphothebaine, although not found in nature, are derived from natural morphine alkaloids, and are of such importance that they are included in this survey.

(b) **Apocodeine**, $C_{18}H_{19}NO_2$, obtained from codeine or pseudocodeine by degradation with acidic reagents,¹²⁰ has been shown to be the 10-methyl ether of apomorphine, and may be obtained from the



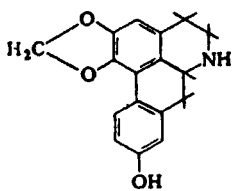
latter along with the dimethyl ether by methylation.¹²⁴ It has the m.p. $104.5\text{--}106.5^\circ$ with one molecule of ethanol, and $122.5\text{--}124.5^\circ$ when dry; $[\alpha]_D^{25} -90^\circ$ (alcohol).¹²¹ Apocodeine hydrochloride melts at $260\text{--}263^\circ$ (dec.),¹²¹ and the methiodide at $229\text{--}230^\circ$.¹²⁴ Apocodeine has a definite narcotic effect on dogs, and stimulates the intestine. It also has an emetic effect similar to that of apomorphine.¹²²

(c) **Roemerine** (remerine), $C_{18}H_{17}NO_2$, was discovered in *Roemeria*



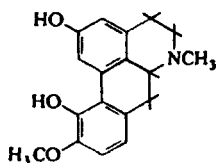
refracta, by Konowalowa, Yunussov, and Orekov,¹²³ who determined its structure with the aid of degradative experiments. This was confirmed by synthesis of the alkaloid by Marion and Grassie.¹²⁴ It has the m.p. 102° , $[\alpha]_D -79.9^\circ$ (alcohol), and forms a methiodide, m.p. 224.5° .¹²⁴

(d) **Anolobine**, $C_{17}H_{17}NO_3$, was isolated by Manske¹²⁵ from the



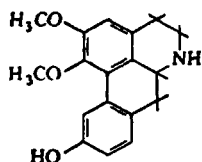
bark of *Asimina triloba*; its structure was proved by Marion.¹²⁶ It has the m.p. 262° (corr. dec.) and $[\alpha]_D^{25} -22.5^\circ$ (CH_3OH and $CHCl_3$).

(e) **Morphothebaine**, $C_{18}H_{19}NO_3$, does not occur in nature, but is obtained from the natural alkaloid, thebaine, by the action of concentrated hydrochloric acid at $80\text{--}90^\circ$.^{127,128} The correct structure for morphothebaine was proposed by Pschorr and Halle¹²⁹ in 1907, and later confirmed by degradation.¹⁴⁰ A final proof of structure was secured by the synthesis of morphothebaine dimethyl ether by Gulland and Haworth¹⁴¹



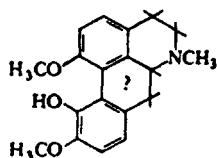
in 1928. Morphothebaine melts at 197–198° (dec.) and $[\alpha]_D^{15} -130^\circ$ (alcohol)¹³⁸; it forms acidic (m.p. 254–255°) and neutral (m.p. 256–260°) hydrochlorides,^{142,143} and a methiodide (m.p. 221–222°).¹⁴³ Morphothebaine has an emetic action on dogs, but it is weaker than that of apomorphine.¹⁴⁴

(f) **Tuduranine**, $C_{18}H_{19}NO_3$, was obtained by Goto¹⁴⁵ from *Sino-*



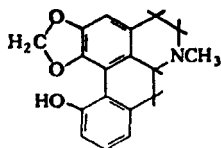
menium acutum; its structure was determined by Goto and Shishido¹⁴⁶ by the synthesis of *O,N*-diethyltuduranine. Tuduranine melts at 125° and forms a hydrochloride, m.p. 286° (dec.), and an *N*-methyl methiodide, m.p. 224°.¹⁴⁵

(g) **Isothebaine**, $C_{19}H_{21}NO_3$, occurs in the roots of *Papaver*



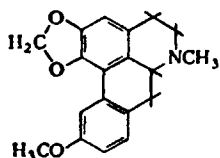
orientale.^{138,147} The structure shown was proposed by Klee¹³⁸ on the basis of degradation experiments on isothebaine methyl ether; however it cannot be considered definite, particularly in regard to the position of the free hydroxyl group. It has the m.p. 203–204°, $[\alpha]_D^{18} +285.1^\circ$ (alcohol), and forms a crystalline sulfate, m.p. 120–121° (dec.).¹³⁸

(h) **Pukateine**, $C_{18}H_{17}NO_3$, was isolated by Aston¹⁴⁸ along with



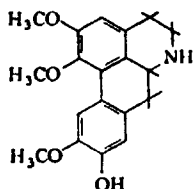
laureline from *Laurelia Novae-Zelandae*. The structure of the alkaloid was advanced by Barger and Girardet¹⁴⁹ on the basis of degradation experiments, and confirmed by the synthesis of pukateine methyl ether by Barger and Schlitter.¹⁵⁰ Pukateine melts at 200° and $[\alpha]_D^{15} -220^\circ$ (alcohol)¹⁴⁸; it forms a crystalline hydrochloride. The hydrochloride produces convulsions comparable to those of strychnine. On intravenous injection it causes a decline in blood pressure and pulse, and death results from respiratory failure.¹⁵¹

(i) **Laureline**, $C_{19}H_{19}NO_3$, was isolated by Aston¹⁴⁸ from the bark of



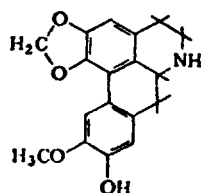
Laurelia Novae-Zelandae. The correct structure was assigned on the basis of degradation experiments,¹⁴⁹ and confirmed by synthesis of the alkaloid by Schlitter.¹⁵² Laureline is unstable in air and melts at 114°, $[\alpha]_D -97.4^\circ$. It forms a hydrochloride, m.p. 280°, and a methiodide, m.p. 223°.¹⁴⁹

(j) **Laurotetanine**, $C_{19}H_{21}NO_4 \cdot H_2O$, first discovered by Greshoff¹⁵³



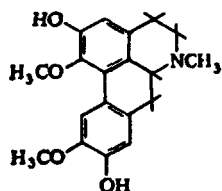
in various *Lauraceae*, has been obtained in 0.3–0.4% yield from *Litsea citrata*.^{154,155} Its structure has been established by the synthetic work of Barger, Eisenbrand, Eisenbrand, and Schlitter,¹⁵⁶ and the degradative experiments of Späth and Tharrer.¹⁵⁷ Laurotetanine has the m.p. 125° and $[\alpha]_D^{25} +98.5^\circ$; it forms salts readily, the picrate sesquihydrate melting at 148° (dec.).¹⁵⁴ It is said to produce tetanic convulsions upon subcutaneous injection.

(k) **Actinodaphnine**, $C_{18}H_{17}NO_4$, was isolated by Krishna and Ghose¹⁵⁸ from the bark of *Actinodaphne Hookeri*. Its structure has been elucidated by Ghose, Krishna, and Schlitter.¹⁵⁹ It has the m.p. 210–211°, $[\alpha]_D^{20} +32.77^\circ$ (abs. alcohol), and forms crystalline salts, among



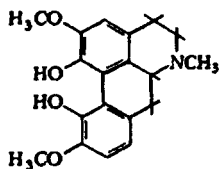
which are the hydrochloride, m.p. 280–281°, and the methiodide, m.p. 243–244°.

(l) **Boldine**, $C_{19}H_{21}NO_4$, was isolated by Bourgoïn and Verne¹⁶⁰



from the plant, *Boldea fragrans*, which grows in Peru and Chile. Its structure was determined by Späth and Tharrer¹⁶¹ by degradation, and almost simultaneously by Schlitter,¹⁶² who prepared *dl*-boldine diethyl ether. Boldine melts at 162–163°, and $[\alpha]_D^{20} +72.7^\circ$ (B·CHCl₃ in alcohol). It does not form crystalline salts. Boldine is similar in its physiological properties to bulbocapnine¹⁶³; it lowers blood pressure and in large doses causes violent clonic convulsions. It antagonizes, but does not reverse, the action of adrenaline in raising blood pressure.

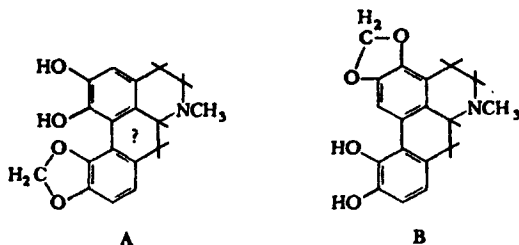
(m) **Corytuberine**, $C_{19}H_{21}NO_4 \cdot 5H_2O$, was isolated by Dobbie and



Lauder¹⁶⁴; it occurs in the root nodules of *Corydalis tuberosa* along with numerous other alkaloids. Its constitution was definitely established by Späth and Berger,¹⁶⁵ and confirmed by the synthesis of corytuberine dimethyl ether by Gulland and Haworth¹⁶⁶ and by Späth and Hromatka.¹⁶⁷ Corytuberine melts at 240° (dec.), $[\alpha]_D^{20} +282.7^\circ$ (alcohol); it forms a crystalline hydrochloride and a methiodide which melt above 250°. In warm-blooded animals the alkaloid causes tonic

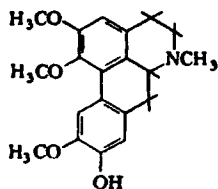
convulsions and a small increase in reflex irritability. There is an increase in blood pressure, and the pulse is slowed. It also causes emesis, and stimulates the secretion of saliva and tears.¹⁶⁹

(n) **Laurepukine**, $C_{18}H_{17}NO_4$, was obtained from *Laurelia Novae-*



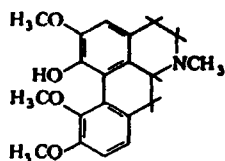
Zelandae by Barger and Girardet.¹⁷⁰ The name originally was coined by Aston for another substance, which later proved to be a mixture of laureline and pukateine. The structure A was assigned by Girardet¹⁷¹ merely by a comparison of the absorption spectra and color reactions of laurepukine dimethyl ether with those of the isomeric bulbocapnine methyl ether, dicentrine, and epidicentrine. Although the work of Girardet did not exclude completely an alternative structure B, it is considered unlikely, since none of the alkaloids known has a substituent in the 3-position of the azabenzanthrene nucleus. Laurepukine melts at 230–231°, $[\alpha]_D -222^\circ$ (chloroform) or -252° (alcohol), and forms a sulfate hexahydrate, m.p. 99–100°.¹⁷¹

(o) **N-Methylaurotetanine**, $C_{20}H_{23}NO_4$, was isolated by Späth and



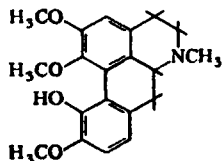
Suominen¹⁷² from *Litsea citrata*. Its identity was established by the formation of glaucine upon methylation, and by degradation of its ethyl ether. It distills at 205–215° (0.01 mm.) (bath temperature), and is dextrorotatory.

(p) **d-Corydine**, $C_{20}H_{23}NO_4$, was first obtained by Merck¹⁷³ from the root nodules of *Corydalis tuberosa*. The correct structure of corydine was assigned by Späth and Berger¹⁶⁵ who prepared it from bulbocapnine methyl ether; it has also been prepared by partial methylation of corytuberine.¹⁷⁴ It melts at 129–130°, with one-half molecule of ethanol,



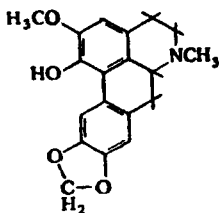
and 149° when dry; $[\alpha]_D^{20} +204.3^\circ$ (chloroform).¹⁷⁵ The hydrochloride has the m.p. 258° (dec.), and the methiodide m.p. $228\text{--}230^\circ$ (dec.). Corydine produces slight narcosis in warm-blooded animals, causes emesis, and stimulates the secretion of tears and saliva. It also causes an increase in blood pressure, but slows the heart.¹⁶⁹

(q) **Isocorydine**, $C_{20}H_{23}NO_4$, has been isolated from various species



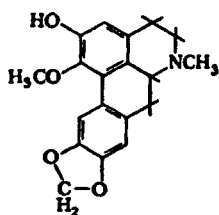
of *Corydalis*, *Dicentra*, and *Glaucium* by Manske.¹⁷⁶ Its structure was clarified by Späth and Berger,¹⁶⁵ and it has been prepared from corytuberine by partial methylation.¹⁷⁴ Isocorydine melts at 185° , and has $[\alpha]_D^{20} +195.3^\circ$ (chloroform). It forms a methiodide, m.p. $213\text{--}214^\circ$ (dec.).¹⁷⁴ Isocorydine is similar to bulbocapnine in its pharmacological action, having a strong tendency to produce catalepsy.¹⁷⁷

(r) **Domesticine**, $C_{19}H_{19}NO_4$, was obtained from *Nandina domestica*



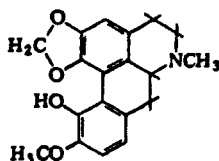
by Kitasato.¹⁷⁸ Its structure was established by Shishido¹⁷⁹ by the synthesis of domesticine ethyl ether. Domesticine has the m.p. $115\text{--}117^\circ$, and $[\alpha]_D +60.51^\circ$.¹⁷⁸ The pharmacological action of domesticine is similar to that of bulbocapnine; however, domesticine has a stronger paralyzing action.¹⁸⁰

(s) **Isodomesticine**, $C_{19}H_{19}NO_4$, was isolated by Kitasato¹⁷⁸ from *Nandina domestica*. Its methyl ether is identical with that of domesticine;



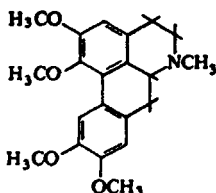
thus, proof of the structure of that alkaloid established the identity of isodomeesticine. It has the m.p. 82° .

(t) **Bulbocapnine**, $C_{19}H_{19}NO_4$, was first isolated by Freund and



Joseph¹⁸¹ from the root nodules of *Corydalis tuberosa*. Its structure was determined by degradation studies,^{182,183} and later confirmed by Gulland and Haworth's synthesis of bulbocapnine methyl ether.¹⁸⁴ Bulbocapnine has the m.p. 199° , $[\alpha]_D +237.1^{\circ}$ (chloroform), and forms a hydrochloride, m.p. 270° (dec.), and a methiodide, m.p. 257° .¹⁸¹ Bulbocapnine has a strong tendency to induce catalepsy; consequently, it has been used in medicine for the treatment of diseases involving involuntary muscular movement as in St. Vitus' dance and *Paralysis agitans*. It is also said to stimulate the secretion of tears and saliva.

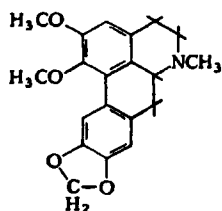
(u) **Glaucine**, $C_{21}H_{25}NO_4$, occurs in a number of different species



of *Corydalis* and *Dicentra*. It was isolated from *Glaucium flavum* by Probst,¹⁸⁵ and later prepared in a pure state by Fischer.¹⁸⁶ Its structure was determined by Gadamer's^{186a} synthesis from papaverine. Glaucine has the m.p. $119-120^{\circ}$, and $[\alpha] +115.4^{\circ}$ (alcohol); it forms a hydrochloride, m.p. 232° , and a methiodide, m.p. 216° . Glaucine "causes

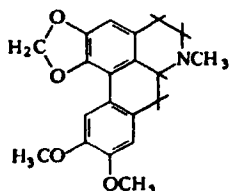
slight narcosis in animals interrupted by epileptiform convulsions. It is also a depressant of the heart and blood vessels and damages striated muscle."¹⁸⁷

(v) **Epidicentrine** (domestine, nantenine), $C_{20}H_{21}NO_4$, has been



isolated from *Nandina domestica* by Maniwa, Sakae, and Kan,¹⁸⁸ and by Takase.¹⁸⁹ Kitasato and Shishido^{178, 190} synthesized the compound, and showed it to be identical with domesticine methyl ether. The alkaloid melts at 139° , and has $[\alpha]_D^{18} +102.27$ (chloroform). It is said to act on the central nervous system producing increased reflex action; it also causes bradycardia and weakening of the heart action, leading to a fall in blood pressure.¹⁹¹

(w) **Dicentrine**, $C_{20}H_{21}NO_4$, occurs in a number of various species



of *Dicentra*; for example, *D. eximia*, *D. formosa*, *D. oregana*, and *D. pusilla*.¹⁹² The structure first proposed by Gadamer^{186a} was confirmed by the synthesis of the alkaloid by Haworth, Perkin, and Rankin.¹⁹³ Dicentrine has the m.p. $168-169^\circ$, $[\alpha]_D +62.7^\circ$ (chloroform), and readily forms salts; the methiodide melts at 224° .¹⁹⁴ Dicentrine, in small doses, acts as a narcotic on frogs and mammals; larger doses cause convulsions, and eventually paralysis of the respiratory center in mammals.¹⁹⁵

(x) **Glaucidine**, the composition of which is unknown, was isolated by Gadamer¹⁸⁶ in very small amounts from *Papaver orientale*. The compound is phenolic and gives color reactions similar to those of glaucine; thus, it is believed to be closely related to the latter. Glaucidine melts at $209-210^\circ$, and has $[\alpha]_D +47-54^\circ$.

TABLE 36. 6-Azabenzanthrenes

Noraporphines						
4,5,6,6a-Tetrahydro-7H,6a-benzanthrene	Noraporphine synonym ^a	Common name	M.p., °C. <i>d</i> - or <i>l</i> -	[α] _D of <i>d</i> - or <i>l</i> -	Methiodide, m.p., °C.	Key references ^b
1,2-Dimethoxy-10-hydroxy- ^c	5,6-Dimethoxy-3-hydroxy-	Tuduranine	125	·HCl, -148° (14.5°C. in H ₂ O + MeOH)	<i>N</i> -Me methiodide, 224° ·HCl, 265°	145,146 109
10,11-Dimethoxy-2-hydroxy- ^d	3,4-Dimethoxy-6-hydroxy-	—	<i>dl</i> -, 125	—	—	115,135
9-Hydroxy-1,2-methylenedioxy- ^e	2-Hydroxy-5,6-methylenedioxy-	Anobine	262	-22.5° (27°C. in MeOH + CHCl ₃)	—	116,154,155 156
9-Hydroxy-1,2,10-trimethoxy- ^f	2-Hydroxy-3,5,6-trimethoxy-	Laurotetanine	125	+98.5° (25°C.)	Picrate, 148° (dec.)	158,159
9-Hydroxy-10-methoxy-1,2-methylene- ^g	2-Hydroxy-3-methoxy-5,6-methylenedioxy-	Actinodaphnine	210-211	+32.77° (20°C. in alc.)	243-244°	154
1,2,9,10-Tetramethoxy- ^h	2,3,5,6-Tetramethoxy-	Laurotetanine	—	—	Oxalate, 233°	159
9,10-Dimethoxy-1,2-methylenedioxy-	2,3-Dimethoxy-5,6-methylenedioxy-	methyl ether	—	—	214°	154
Aporphines						
6-Methyl-4,5,6a-tetrahydro-7H,6a-benzanthrene	Aporphine synonym ^a	Common name	M.p., °C. <i>d</i> - or <i>l</i> -	[α] _D of <i>d</i> - or <i>l</i> -	Methiodide, m.p., °C.	Key references ^b
Unsubstituted base ^d	Aporphine	Aporphine	<i>dl</i> -, oil	—	Hydroiodide, 260° (dec.)	107
1,2-Dihydroxy-	5,6-Dihydroxy-	Epiapomorphine, norremine	—	162-164	—	133
10,11-Dihydroxy-	3,4-Dihydroxy-	Apomorphine	195 (dec.)	·HCl, -30.5° (16° in H ₂ O)	180° (dec.)	87,89,90,127
11-Hydroxy-10-methoxy-	4-Hydroxy-3-methoxy-	Apocodine, pseudoapocodine, apomorphine methyl ether	122.5-124.5	-90° (23° in alc.)	229-230°	98,124

Table continued

TABLE 36. 6-Azabenzanthrenes (continued)

6-Methyl-4,5,6a-tetrahydro-7H-6-azabenzanthrene	Aporphine synonym ^a	Common name	M.p., °C. <i>d</i> , or <i>l</i> .	[α] _D of <i>d</i> - or <i>l</i> -	Methiodide, m.p., °C.	Key references ^b
<i>Aporphines (continued)</i>						
1,2-Dimethoxy- ^d	5,6-Dimethoxy-	—	165–166 <i>dl</i> , 137	–145.2°	223° (<i>dl</i> -)	133,197
9,10-Dimethoxy- ^d	2,3-Dimethoxy-	—	—	—	Methosulfate, 246°	198
10,11-Dimethoxy- ^d	3,4-Dimethoxy-	Apomorphine dimethyl ether	—	–148° (15° in abs. alc.)	195° (<i>l</i> -)	98,126,127, 199
1,2-Methylenedioxy- ^{c,d}	5,6-Methylenedioxy-	Rosmerine, reserpine	102	–79.9° (alc.)	214° (<i>dl</i> -)	133,134
11-Acetoxy-10-methoxy-	4-Acetoxy-3-methoxy-	<i>O</i> -Acetyl apomorphine	—	Methiodide, –41° (15° in H ₂ O)	224.5°	88,98
11-Benzoyloxy-10-methoxy-	4-Benzoyloxy-3-methoxy-	<i>O</i> -Benzoyl apomorphine	85–90	—	241–242°	88
10,11-Diacetoxy-	3,4-Diacetoxy-	<i>O</i> , <i>O</i> -Diacetyl apomorphine	129	–67.26° (in dil. HCl)	233°	128
10,11-Dibenzoyloxy-	3,4-Dibenzoyloxy-	<i>O</i> , <i>O</i> -Dibenzoyl apomorphine	156–158	43.44° (17° in CHCl ₃)	229–230°	88
2,10,11-Trihydroxy-	3,4,6-Trihydroxy-	6-Hydroxy apomorphine	—	—	HBr, 261–262°	122
2,11-Dihydroxy-10-methoxy-	4,6-Dihydroxy-3-methoxy-	Morphothebaine	197–198 (dec.)	–130° (15°C. in alc.)	221–222°	99,138,140, 141
10-Hydroxy-1,2-dimethoxy-	3-Hydroxy-5,6-dimethoxy-	<i>N</i> -Methyl tudaurine	—	—	224°	145
11-Hydroxy-1,10-dimethoxy- ^c	4-Hydroxy-3,5-dimethoxy-	Isothebaine	203–204	+285.1° (18°C. in alc.)	Sulfate, 120–121° (dec.)	138,147
11-Hydroxy-1,2-methylenedioxy-	4-Hydroxy-5,6-methylenedioxy-	Pukateine	200	–220° (15°C. in alc.)	—	148,149,150
1,2,10-Trimethoxy- ^d	3,5,6-Trimethoxy-	Dimethyl tudaurine	108	–136.94° (12°C. in MeOH)	219° (<i>l</i> -)	145,146,200
1,10,11-Trimethoxy-	3,4,5-Trimethoxy-	Isothebaine	—	+234.5° (15°C. in CHCl ₃)	217° (<i>dl</i> -)	150
2,10,11-Trimethoxy- ^d	3,4,6-Trimethoxy-	Morphothebaine dimethyl ether	—	–184.8° (15°C. in CHCl ₃)	Methosulfate, 237–238°	138,141,199

6-Methyl-4,5,6,6a-tetrahydro-7H,6a-benzanthrene	Aporphine synonym ^a	Common name	M.p., °C. <i>d.</i> or <i>l.</i>	[α] _D of <i>l.</i> or <i>l.</i>	Methiodide, m.p., °C.	Key references ^b
9-Methoxy-1,2-methylenedioxy-4	2-Methoxy-5,6-methylenedioxy-	<i>O,N</i> -Dimethyl-anobine	—	—	241° (<i>dl.</i>)	115
10-Methoxy-1,2-methylenedioxy-4	3-Methoxy-5,6-methylenedioxy-	1-aureline	114	-97.4° (alc.)	223°	148,149,152
11-Methoxy-1,2-methylenedioxy-4	4-Methoxy-5,6-methylenedioxy-	Pukateine methyl ether	137	+256.4° -252°	—	150
10,11-Dihydroxy-8-sulfo-	3,4-Dihydroxy-1-sulfo-	Apomorphine	>300	—	—	118
9-Amino-10,11-dihydroxy-	2-Amino-3,4-dihydroxy-	2-Aminoapomorphine	—	—	HCl, 260-265°	201
10,11-Dihydroxy-9-nitroso-	3,4-Dihydroxy-2-nitroso-	2-Nitrosoapomorphine	>300	—	—	201
10,11-Dihydroxy-9-phenylazo-	3,4-Dihydroxy-2-phenylazo-	2-Phenylazoapomorphine	>310	—	—	119
10,11-Dihydroxy-9- <i>p</i> -chlorophenylazo-	3,4-Dihydroxy-2- <i>p</i> -chlorophenylazo-	2- <i>p</i> -Chlorophenylazoapomorphine	>300	—	—	119
1,2,9,10-Tetrahydroxy-	2,3,5,6-Tetrahydroxy-	—	—	—	Hydroiodide, 225-235° (dec.), 249-250°	186,202
1,2-Dihydroxy-9,10-dimethoxy-	5,6-Dihydroxy-2,3-dimethoxy-	—	175 (dec.)	—	—	113
2,9-Dihydroxy-1,10-dimethoxy- ^c	2,6-Dihydroxy-3,5-dimethoxy-	Boldine	162-163	+72.7° (alc.)	—	160,161,162
9,10-Dihydroxy-1,2-dimethoxy-	2,3-Dihydroxy-5,6-dimethoxy-	—	170-171	+127.63° (20°C.)	Hydrobromide, 113-253°	113
1,2-Dihydroxy-10,11-dimethoxy-	5,6-Dihydroxy-3,4-dimethoxy-	Epicorytuberine	129-130	137.5° (20°C.)	Picrate, 215° (dec.)	165,203
1,11-Dihydroxy-2,10-dimethoxy- ^c	4,5-Dihydroxy-3,6-dimethoxy-	Corytuberine	240 (dec.)	+282.7° (20°C. in alc.)	>250°	164,165,166,167
1,2-Dihydroxy-9-ethoxy-10-methoxy-	5,6-Dihydroxy-2-ethoxy-3-methoxy-	—	160 (dec.)	—	—	159

Table continued

TABLE 36. 6-Azabenzanthrenes, (continued)

6-Methyl-4,5,6,6a-tetrahydro-7H,6a-benzanthrene	Aporphine synonym ^a	Common name	M.P., °C. d- or l-	[α] _D of d- or l-	Methiodide, m.p., °C.	Key references ^b
Aporphines (continued)						
1,2-Dihydroxy-10,11-methylenedioxy- ^c	5,6-Dihydroxy-3,4-methylenedioxy-	Laurepukine	230-231	-222° (CHCl ₃) -252° (alc.)	—	149,171
9-Hydroxy-1,2,10-trimethoxy- ^c	2-Hydroxy-3,5,6-trimethoxy-	N-Methylaurotettanine	—	—	—	172
10-Hydroxy-1,2,9-trimethoxy- ^a	3-Hydroxy-2,5,6-trimethoxy-	—	—	—	—	110
1-Hydroxy-2,10,11-trimethoxy- ^c	5-Hydroxy-3,4,6-trimethoxy-	Corydine	149 dl-, 165-167 139-140	+204.3° (20°C. in CHCl ₃)	228-230° (dec.)	165,173,174
2-Hydroxy-1,10,11-trimethoxy- ^c (?)	6-Hydroxy-3,4,5-trimethoxy- ^c (?)	Epicorytuberine methyl ether	185	+195.3° (20°C. in CHCl ₃)	213-214° (dec.)	165,174,176
11-Hydroxy-1,2,10-trimethoxy- ^c	4-Hydroxy-3,5,6-trimethoxy-	Isocorydine	115-117	+60.51°	—	178,179
1-Hydroxy-2-methoxy-9,10-methylene-dioxy- ^c	5-Hydroxy-6-methoxy-2,3-methylenedioxy-	Domesticine	85	—	—	178
2-Hydroxy-1-methoxy-9,10-methylene-dioxy- ^c	6-Hydroxy-5-methoxy-2,3-methylenedioxy-	Isodomesticine	199 dl-, 209- 210	+237.1° (CHCl ₃)	257°	181,182,183, 184
11-Hydroxy-10-methoxy-1,2-methylenedioxy- ^c	4-Hydroxy-3-methoxy-5,6-methylenedioxy-	Bulbocarpine	211-214	+151.5° (20°C. in CHCl ₃)	—	168
1-Benzoyloxy-11-hydroxy-2,10-dimethoxy-	5-Benzoyloxy-4-hydroxy-3,6-dimethoxy-	O-Monobenzoylcorytuberine	119-120 dl-, 137-139	+115.4° (alc.)	216°, 221° (d-) 224-226° (dl-) 238° (dec.) 248° (dec.) 204-208°	102,185,186, 186a, 202 166,167,168 120
1,2,9,10-Tetramethoxy- ^c	2,3,5,6-Tetramethoxy-	Glauicine	125-125.5 dl-, 131-132	+168° (20°C. in CHCl ₃)	208-210° (l-)	120
1,2,10,11-Tetramethoxy- ^d	3,4,5,6-Tetramethoxy-	Corytuberine dimethyl ether	139 dl-, 142	+102.27° (18°C. in CHCl ₃)	Methosulfate of dl-, 238°	178,188,189, 190
2,3,9,10-Tetramethoxy- ^d	2,3,6,7-Tetramethoxy-	—	—	—	—	—
2,3,10,11-Tetramethoxy- ^d	3,4,6,7-Tetramethoxy-	—	—	—	—	—
1,2-Dimethoxy-9,10-methylenedioxy- ^d	5,6-Dimethoxy-2,3-methylenedioxy-	Epidicentrine, domesticine methyl ether	—	—	—	—

6-Methyl-4,5,6,6a-tetrahydro-7H,6-azabenzanthracene	Aporphine synonym ^a	Common name	M.p., °C. <i>d</i> - or <i>l</i> -	[α] _D of <i>d</i> - or <i>l</i> -	Meridiolide, m.p., °C.	Key references ^b
9,10-Dimethoxy-1,2-methylenedioxy- ^d	2,3-Dimethoxy-5,6-methylenedioxy-	Dicentrine	168-169 <i>dl</i> -, 178-179	+62.7° (CHCl ₃)	224°	159,186a, 192,193
1,2-Dimethoxy-10,11-methylenedioxy-	5,6-Dimethoxy-3,4-methylenedioxy-	Dimethylaurepukine	134	-314° (CHCl ₃) -211° (alc.)	249-250°	171
10,11-Dimethoxy-1,2-methylenedioxy- ^d	3,4-Dimethoxy-5,6-methylenedioxy-	Bulbocapnine	130-131 <i>dl</i> -, 135	+247.2° (20°C. in CHCl ₃)	245-247° (<i>d</i> -)	182,184,204
11-Benzoyloxy-10-methoxy-1,2-methylenedioxy-	4-Benzoyloxy-3-methoxy-5,6-methylenedioxy-	<i>O</i> -Benzoylbulbocapnine	202-203 <i>dl</i> -, 201-202	+92.7° (20°C. in CHCl ₃)	243 (<i>dl</i> -) 228-230° (dec.) (<i>d</i> -)	182
9-Ethoxy-1,2,10-trimethoxy-	2-Ethoxy-3,5,6-trimethoxy-	—	Oil	—	225-226° (<i>d</i> -)	157,159
10-Benzoyloxy-1,2,9-trimethoxy- ^d	3-Benzoyloxy-2,5,6-trimethoxy-	—	<i>dl</i> -, oil	—	—	110
2-Ethoxy-1-methoxy-9,10-methylenedioxy- ^d	6-Ethoxy-5-methoxy-2,3-methylenedioxy-	—	142-144 <i>dl</i> -, 136	±90° (28°C. in alc.)	Hydrobromide, 205 250-252° (dec.) (<i>dl</i> -) 260-261° (dec.) (<i>d</i> -)	205
1-Ethoxy-2-methoxy-9,10-methylenedioxy- ^d	5-Ethoxy-6-methoxy-2,3-methylenedioxy-	Domesticine ethyl ether	131 <i>dl</i> -, 132	110.8° (14°C. in MeOH)	·HCl, 275-277° (dec.) (<i>dl</i> -)	179
9-Ethoxy-10-methoxy-1,2-methylenedioxy- ^d	2-Ethoxy-3-methoxy-5,6-methylenedioxy-	<i>O</i> -Ethyl- <i>N</i> -methyl-actinodaphnine	198-199	—	—	159
2,9-Diethoxy-1,10-dimethoxy- ^d	2,6-Diethoxy-3,5-dimethoxy-	Boldine diethyl ether	Oil <i>dl</i> -, oil <i>dl</i> -, oil	—	—	161,162
1,9-Diethoxy-2,10-dimethoxy- ^d	2,5-Diethoxy-3,6-dimethoxy-	—	—	—	—	162
1,11-Diacetoxy-2,10-dimethoxy-	4,5-Diacetoxy-3,6-dimethoxy-	Diacetylorytuberine	72	—	—	168
1,11-Dibenzoyloxy-2,10-dimethoxy-	4,5-Dibenzoyloxy-3,6-dimethoxy-	Dibenzoylorytuberine	135-140	+133° (20°C. in CHCl ₃)	—	168
10-Acetamido-1,2,11-trimethoxy- ^d	3-Acetamido-4,5,6-trimethoxy-	—	—	—	210° (dec.)	198

Table continued

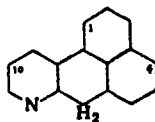
TABLE 36. 6-Azabenzanthrenes (continued)

6-Azabenzanthrene	Aporphine synonym ^a	Common name	M.p., °C. d ^b or l. ^c	[α] _D of d ^b or l. ^c	Derivative, m.p., °C.	References
Miscellaneous						
2-Benzoyloxy-10,11-dimethoxy-4,5-dihydro-7H ^d	6-Benzoyloxy-3,4-dimethoxy-9,17-didehydronoraporphine	—	(Not isolated)	—	—	109
1-Hydroxy-6-methyl-2,10,11-trimethoxy-4,5-dihydro-6H ^e (?)	—	Didehydrocorydine	—	—	Iodide, 248° (dec.)	206
10,11-Dimethoxy-6-methyl-1,2-methylenedioxy-4,5-dihydro-6H ^e (?)	—	Didehydrobulbocarpine methyl ether	—	—	Iodide, 228°	182
11-Benzoyloxy-10-methoxy-6-methyl-1,2-methylenedioxy-4,5-dihydro-6H ^e (?)	—	O-Benzoyldehydrobulbocarpine	—	—	Iodide, 219° (dec.)	182
10-Ethoxy-6-ethyl-1,2-dimethoxy-4,5,6,6a-tetrahydro-7H ^e	5,6-Dimethoxy-3-ethoxy-17-ethynoraporphine	N-Ethyltuduranine ethyl ether	—	Ethiodide, -112.47° (15°C. in CHCl ₃)	Ethiodide, 186-187° (dl-) Ethiodide, 238° (l-) Hydroiodide, 212°	145,146 207
6-Ethyl-9-hydroxy-1,2,10-trimethoxy-4,5,6,6a-tetrahydro-7H ^e	17-Ethyl-2-hydroxy-3,5,6-trimethoxynoraporphine	N-Ethyllaurotanine	127-130	—	Hydroiodide, 210° (dec.)	156
10-Ethoxy-6-ethyl-1,2,9-trimethoxy-4,5,6,6a-tetrahydro-7H ^e	3-Ethoxy-17-ethyl-2,5,6-trimethoxynoraporphine	—	—	—	—	—
9-Ethoxy-6-ethyl-1,2,10-trimethoxy-4,5,6,6a-tetrahydro-7H ^e	2-Ethoxy-17-ethyl-3,5,6-trimethoxynoraporphine	O,N-Diethylaurotetanine	—	—	Hydroiodide, 210° (dec.)	156
9-Ethoxy-6-ethyl-10-methoxy-1,2-methylenedioxy-4,5,6,6a-tetrahydro-7H ^e	2-Ethoxy-17-ethyl-3-methoxy-5,6-methylenedioxynoraporphine	O,N-Diethylacotinodaphnine	213-214	—	—	159

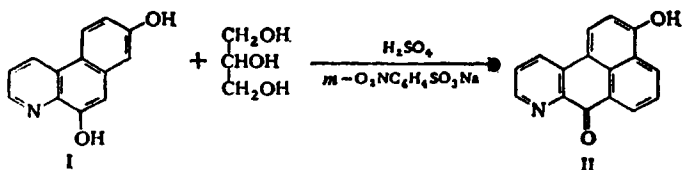
6-Azabenzanthrene	Aporphine synonym ^a	Common name	M.P., °C. d- or l-	[α] _D of d- or l	Derivative, m.p., °C.	References
6-Acetyl-10-hydroxy-1,2-dimethoxy-4,5,6,6a-tetrahydro-7H-	17-Acetyl-3-hydroxy-5,6-dimethoxynoraporphine	N-Acetyltudaurine	277	-395.24° (18°C. CHCl ₃ + MeOH)	—	145
6-Acetyl-1,2,10-trimethoxy-4,5,6,6a-tetrahydro-7H-	17-Acetyl-3,5,6-trimethoxynoraporphine	N-Acetyltudaurine ether	189	-400.17° (18°C. in CHCl ₃)	—	145
10-Acetoxy-6-acetyl-1,2-dimethoxy-4,5,6,6a-tetrahydro-7H-	3-Acetoxy-17-acetyl-5,6-dimethoxynoraporphine	Diacetyltudaurine	170	-321.71° (14°C. in MeOH)	—	145
6-Benzoyl-9-hydroxy-1,2,10-trimethoxy-4,5,6,6a-tetrahydro-7H-	17-Benzoyl-2-hydroxy-3,5,6-trimethoxynoraporphine	N-Benzoyllaurotetanine	194	—	—	207
6-Acetyl-9,10-dimethoxy-1,2-methylene-dioxy-4,5,6,6a-tetrahydro-7H-	17-Acetyl-2,3-dimethoxy-5,6-methylene-dioxynoraporphine	—	222-224	—	—	159
6-Benzoyl-9-benzoyl-oxyl-1,2,10-trimethoxy-4,5,6,6a-tetrahydro-7H-	17-Benzoyl-2-benzoyl-oxyl-3,5,6-trimethoxynoraporphine	Dibenzoyllaurotetanine	169-170	—	—	154
6-Anilinothioformyl-9-hydroxy-1,2,10-trimethoxy-4,5,6,6a-tetrahydro-7H-	17-Anilinothioformyl-2-hydroxy-3,5,6-trimethoxynoraporphine	N-Anilinothioformyllaurotetanine	211-212	—	—	154,207
6-Anilinothioformyl-9-hydroxy-10-methoxy-1,2-methylene-dioxy-4,5,6,6a-tetrahydro-7H-	17-Anilinothioformyl-2-hydroxy-3-methoxy-5,6-methylene-dioxynoraporphine	—	181	—	—	159
6-Anilinothioformyl-1,2,9,10-tetramethoxy-4,5,6,6a-tetrahydro-7H-	17-Anilinothioformyl-2,3,5,6-tetramethoxynoraporphine	—	154-155	—	—	154

^a See formula Ia on page 230. ^b Attempt has been made to include some (not all) references to natural sources, and to syntheses wherever possible. ^c Occurs in nature. ^d Product of total synthesis.

F.* 7*H*,8-Azabenzanthrene, 7-Naphtho[1,8-*fg*]-quinoline, 8,7-*peri*-Naphthoquinoline, 5-Azabenzanthrene (German). R.I. 2755

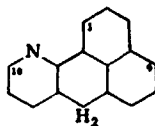


Only one substance in this group is mentioned in the literature,²⁰⁸ and its structure has not been definitely established. The compound in question, 3-hydroxy-8-azabenzanthrone (II), was prepared according to Bally's method²⁰⁹ for the synthesis of benzanthrone. When 7,10-dihydroxy-1-azaphenanthrene (I) was heated with glycerine and sulfuric acid, condensation took place, apparently in the following manner:



The compound is blue in aqueous alkaline solution, and red in concentrated sulfuric acid.

G.* 7*H*,11-Azabenzanthrene, 7-Naphtho[1,8-*gh*]quinoline, 11,7-*peri*-Naphthoquinoline, 8(*N*)-1,9-Pyrobenzanthrene, 8-Azabenzanthrene (German). R.I. 2758



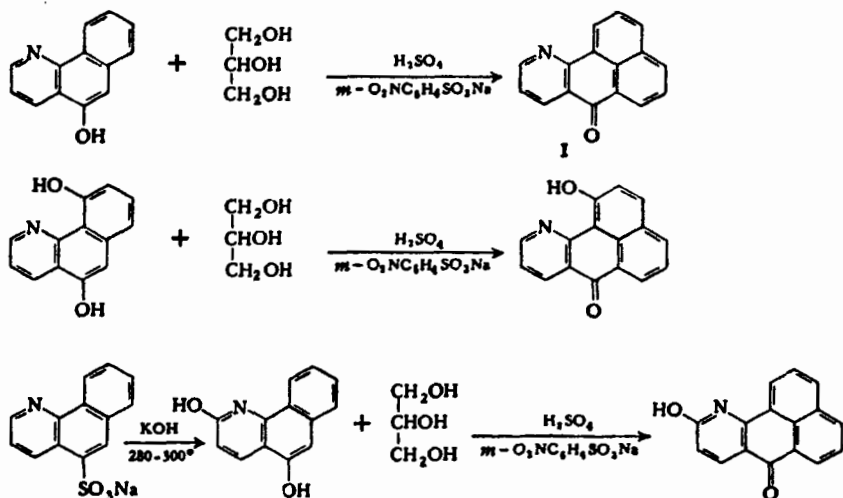
The 11-azabenzanthrones, which are designated in the German patent literature as 8-azabenzanthrones, are somewhat better known than other members of this series (with the obvious exception of the 3-azabenzanthrones). Their use as dyes and dye intermediates has been described in a number of German patents issued within the past fifteen years.^{210,211,212}

(1) Preparation

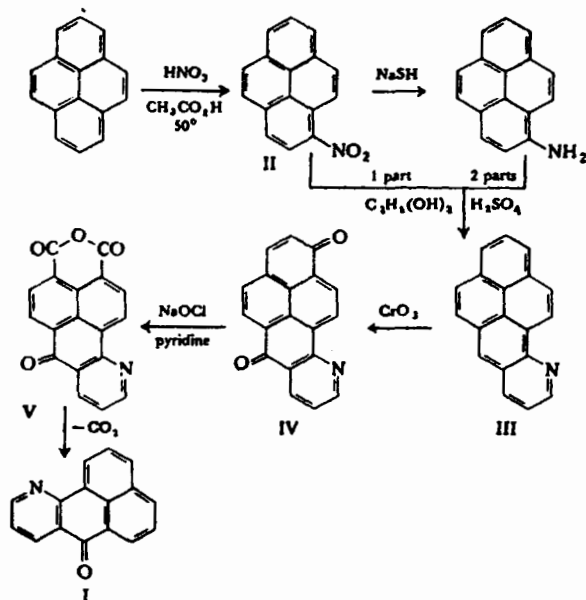
For the most part, the synthesis of the 11-azabenzanthrone nucleus is carried out according to Bally's method²¹³ for the preparation of benzanthrone. In this modification, anthraquinone is replaced by a 4-azaphenanthrene which has at least one phenolic or ketonic oxygen atom attached to the central ring. When such a compound is heated with glycerine or acrolein in the presence of sulfuric acid, a new ring is formed across two free *peri* positions of the carbocyclic rings to give an 11-azabenzanthrone. Good yields are obtained when the reaction is carried

* D. M. Burness.

out in the presence of an oxidizing agent (when the azaphenanthrene contains a hydroxy group) or a reducing agent (when a keto group is present). The method is illustrated by the following typical examples.¹¹²



The only other synthesis of the 11-azabenzanthrone nucleus recorded in the literature is that of Vollmann, Becker, Corell, and Streeck¹¹⁴ by a circuitous method starting with pyrene. This hydrocarbon was



nitrated to give 3-nitropyrene (II), which in turn was reduced and subjected to a Skraup synthesis leading to the formation of the base (III). The latter was oxidized readily to the quinone (IV) by chromic oxide. Further oxidation by means of sodium hypochlorite in pyridine or by chromic acid^{214a} yielded the anhydride of 3,4-dicarboxy-11-azabenzanthrone (V).

Dry distillation of the barium salt of the acid resulted in the formation of the parent compound, 11-azabenzanthrone (I), which was identical with the compound obtained above by Bally's method.

(2) Reactions

11-Azabenzanthrone undergoes the ordinary substitution reactions of halogenation, nitration, and sulfonation with moderate ease.²¹⁰

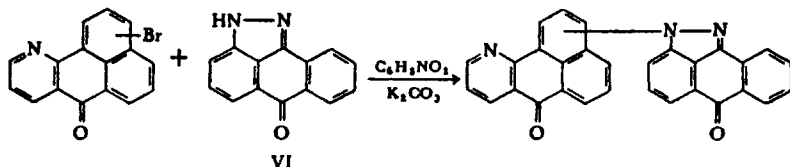
A monobromo compound is formed when bromination is carried out in nitrobenzene at 70–75° in the presence of catalytic amounts of iron and iodine. At 170–180° a dibromo compound is the chief product. Likewise, chlorination in trichlorobenzene at 170–180° gives dichloro and trichloro derivatives. A cyano derivative was prepared from the monobromo-11-azabenzanthrone by the action of cuprous cyanide in pyridine^{210,215}; acid hydrolysis of this nitrile yielded an 11-azabenzanthronecarboxylic acid.²¹⁰ Methoxy, phenoxy, and mercapto derivatives have also been prepared from the bromo compound.²¹⁰

Nitration of 11-azabenzanthrone has been effected by treatment with 98% nitric acid in nitrobenzene at 90°. From the mononitro (2-nitro?) compound so prepared, the corresponding amino and hydroxy compounds can be obtained.

Sulfonation with 23% oleum at 90–100° yields a monosulfonic acid.

An *x*-carboxy-11-azabenzanthrone is said to be formed in a 90% yield by a general type of reaction, in which the ketonic compound is treated with phosgene in a sodium-aluminum chloride melt.²¹⁶

A number of vat dyes have been prepared by the condensation of the *x*-bromo-11-azabenzanthrones with various aminoanthraquinones e.g., with pyrazoleanthrone (VI).²¹⁰



When 11-azabenzanthrone is heated with alcoholic potassium hydroxide at 90°, coupling of two molecules takes place to form a diaza-

benzanthronyl.²¹¹ At higher temperatures (150–155°) further condensation leads to the formation of a vat dye (a diazaviolanthrone), as was observed in the case of the 1-azabenzanthrones. The dye from 11-azabenzanthrone itself imparts to plant fibers a red-violet color; this may be deepened by nitration, chlorination, or bromination of the parent diazaviolanthrone.²¹¹

(3) Properties

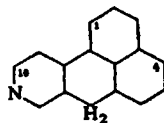
11-Azabenzanthrone is a yellow crystalline solid melting at 159–160°. It is soluble in dilute mineral acids and dissolves in concentrated sulfuric acid with a yellow-green fluorescence. A considerable number of the 11-azabenzanthrones show a strong tendency to fluoresce in solution. This property is not limited to concentrated sulfuric acid solutions, for certain hydroxyazabenzanthrones and azabenzanthronecarboxylic acids have been reported to fluoresce in aqueous alkaline solution.

The 11-azabenzanthrones, themselves, appear to be of no value as dyes except when coupled with the anthraquinone molecule; in this case, they impart a violet to brown color to vegetable fibers. The indanthrene-type dyes, formed by fusion of two 11-azabenzanthrone nuclei with alkali, dye cotton in shades varying from red-violet to green.

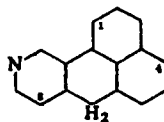
In Table 37 (see page 258) are listed the properties of all the known 11-azabenzanthrones.

H. * *x*-Azabenzanthrenes

**7H,9-Azabenzanthrene, 7-Naphth[1,8-*fg*]isoquinoline, 6-Azabenzanthrene (German).
R.I. 2756**



**7H,10-Azabenzanthrene, 7-Naphth[1,8-*gh*]isoquinoline, 7-Azabenzanthrene (German).
R.I. 2757**



The patent literature²¹⁷ contains reference to a few azabenzanthrones to which even a basic ring structure cannot be assigned. For the most, they are believed to be ketones of the above two ring systems and are termed “ β -azabenzanthrones”; they are prepared by the action of glycerine and sulfuric acid on a β -azaanthraquinone. With 2-azaanthraquinone (I) itself, the possible products are the 4-, 5-, 9-, and 10-azabenzanthrones.

* D. M. Burness.

TABLE 37. 11-Azabenzanthrenes

Substance	Ref.	M _p , °C.	Color and solvent	Color in conc. H ₂ SO ₄	Vat dye from alkaline fusion
11-Azabenzanthrone ^a	211,212, 214	157, 159-160	Yellow needles (aqueous acetic acid)	Yellow-green rescence	Dyes cotton red-violet from violet-blue vat ^b
10-Methyl-1(?) -Bromo-	212 210	159 214-215	Acetic acid	Yellow with yellow-green fluorescence	—
<i>x,x</i> -Dibromo-2(?) -Nitro-	210 210	>300 285-286	Yellow needles Orange-yellow needles (dichlorobenzene)	Yellow	—
<i>x</i> -Sulfo-	210,211	>300	—	—	Dyes cotton blue from violet-blue vat
1(?) -Amino	210	—	—	—	—
2(?) -Amino-	210,211	267-268	Scarlet red	—	Dyes plant fibers dark green from blue vat
1-Hydroxy-	212	—	Orange-yellow (65% acetic acid)	—	—
10-Hydroxy-	212	—	Yellow needles	—	—
1(?) -Methoxy-	210	—	—	—	—
2(?) -Methoxy-	210	—	Yellow plates (acetic acid)	—	—
1(?) -Phenoxy-1-Carboxy-	210 212	— —	— Yellow flakes (trichlorobenzene)	Green-blue fluorescence	—
3,4-Anhydridicarboxy- ^c	214	349	Yellow needles (nitrobenzene)	Yellow	Loss of CO ₂ H groups and formation of red-violet vat dyeing a violet-blue color
1(?) -Cyano-	210,215	305-307	Pale yellow needles (dichlorobenzene)	Yellow with green fluorescence	—
1(?) -Mercapto-	210,211	—	Yellow	Violet	Dyes cotton dark blue from wine-red vat
<i>S</i> -Thioglycolyl-	210	—	—	—	—

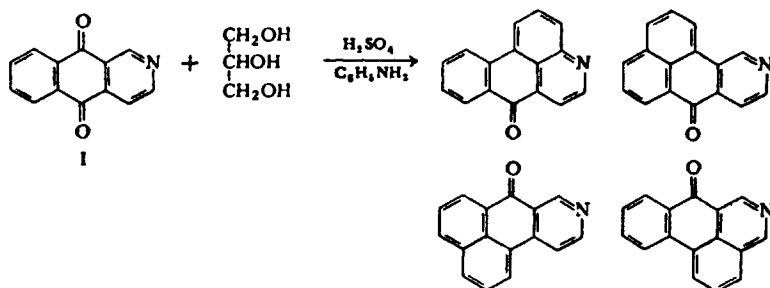
Substance	Ref.	M.p., °C.	Color and solvent	Color in conc. H ₂ SO ₄	Vat dye from alkaline fusion
<i>x,x'</i> -Diazabenzanthronyl	211	320	Orange-brown (tri-chlorobenzene)	—	Does not form vat
Bis(1(?) -azabenzanthronyl) sulfide	210	—	Yellow	—	—
1(?) - <i>α</i> -Anthraquinonylamino- ^a	210	—	—	Green	—
1-(1(?) -Azabenzanthronyl)-amino-5-aminoanthraquinone	210	—	Dark violet	—	—
1-(1(?) -Azabenzanthronyl)-amino-4-benzoylaminoanthraquinone	210	—	Violet	—	—
1-(1(?) -Azabenzanthronyl)-amino-5-benzoylaminoanthraquinone	210	—	Brown	—	—
<i>x,x</i> -Di-(1-anthraquinonyl-amino)-	210	—	Dark violet	—	—
Bis(1(?) -azabenzanthronyl)-1,5-diaminoanthraquinone	210	—	Violet-brown	Green	—
λ-(1(?) -Azabenzanthronyl)-1,9-pyrazoloanthrone	210	—	Yellow	Orange	—
λ-(<i>x</i> -Bromo- <i>x</i> -azabenzanthronyl)-1,9-pyrazoloanthrone	210	—	Straw-yellow	—	—
λ-[<i>x</i> -(1-Anthraquinonylamino)- <i>x</i> -azabenzanthronyl]-1,9-pyrazoloanthrone	210	—	Brown	Green	—

^a Gives a violet-blue vat.

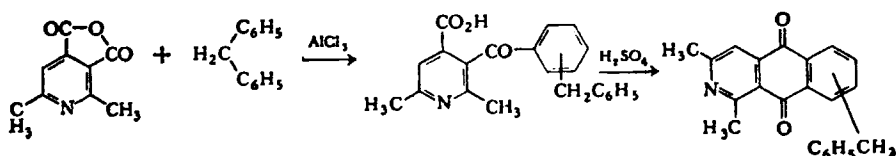
^b Nitration of this dye in nitrobenzene at low temperatures alters its color on cotton to gray-blue; the vat is red-blue. Nitration at 70–80° with 65% nitric acid gives a green dye (blue vat) of good fastness which by treatment with chlorine is converted toward gray or black. Chlorination of the original dye gives a very fast violet-blue (green-blue vat). Bromination gives clear violet colors from a blue-violet vat.

^c The free acid gives a yellow-green vat; the sodium salt a brown-red one.

^d Gives a brown vat, dyeing a weak violet-red.



In addition to 2-azaanthraquinone, the 1,3-dimethyl, 1-methyl-3-phenyl, a bromo-1,3-dimethyl, and a benzyl-1,3-dimethyl derivatives were used in the above reaction. The last-named intermediate was prepared as follows:

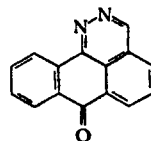


A single unknown azabenzanthrone has been prepared in a similar manner from 1-azaanthraquinone.²¹⁸

2. Diazabenzanthrenes

The parent substances in the diaza group are unknown. Keto derivatives of the 1,2- and 1,3-diazabenzanthrenes have been described. Current activity in the 1,3-series is very great, especially with substances that may be vat dyes.

A. * 1,2-Diazabenzanthrones (Pyridazinoanthrones)

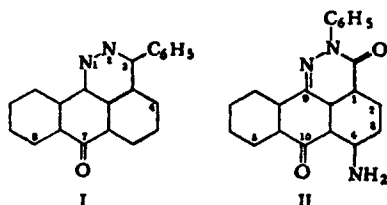


It does not appear that members of this class have ever become commercial products; hence, no short convenient name has been widely adopted. In the German literature, by analogy with pyridoanthrones, they were sometimes called pyridazinoanthrones.

In the *Ring Index*² and in *Chemical Abstracts*, representatives of this class are to be found under 7-naphtho[1,2,3-*de*]phthalazine or 7-dibenzo-

* F. W. Spangler.

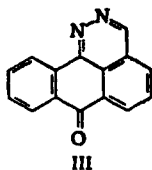
[*de,h*]cinnoline. Thus I is 3-phenyl-7-naphtho[1,2,3-*de*]phthalazin-7-one, while II is 6-amino-2-phenyl-7-naphtho[1,2,3-*de*]phthalazine-3,7-dione. In Beilstein this class is listed under pyridazinoanthrone (with a different numbering, shown in II) and benzoylenephthalazine, so that the substance having the structure shown in I becomes either *C*-phenyl-1,9(*N*)-



pyridazinoanthrone or 1-phenyl-4,5(*CO*)-benzoylenephthalazine, while II is 4-amino-*N*-phenyl-1,9(*N*)-pyridazonanthrone or 7-amino-3-phenyl-1,8(*CO*)-benzoylene-4-phthalazone. The name “anthrapyridazine” appears in two Swiss patents,^{219,220} and “anthrapyridazones” are described in a British patent.²²¹

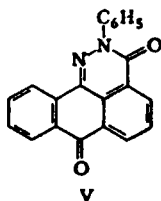
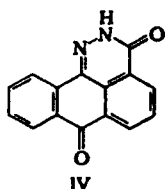
The advantages of the “aza” system used in this volume are very obvious. When this nomenclature is employed, I becomes 3-phenyl-1,2-diazabenzanthrone, whereas II is 6-amino-3-keto-2-phenyl-1,2-diazabenzanthrone. (Strictly speaking, this substance is a 2,3-dihydro derivative, but omission of this term does not lead to ambiguity, while its inclusion unnecessarily complicates the name.)

The parent compound, 1,2-diazabenzanthrene, is unknown. All of the known compounds of this class are 1,2-diazabenzanthrones (III) and have a carbonyl group in the 7-position.



(1) Historical

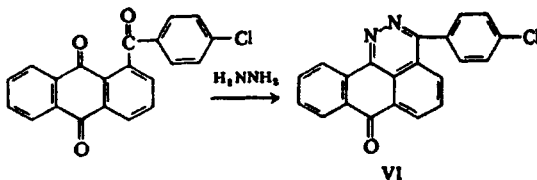
The first compounds of this type were prepared by Ullmann²²² in 1911 who showed that anthraquinone-1-carboxylic acid was a valuable starting material for the synthesis of new cyclic derivatives of anthraquinone. It was shown, for example, that anthraquinone-1-carboxylic acid chloride reacted with hydrazine (hydrate) and with phenylhydrazine to give 3-keto-1,2-diazabenzanthrone (IV) and 3-keto-2-phenyl-1,2-diazabenzanthrone (V), respectively.



An extension of this work to the use of substituted anthraquinone-1-carboxylic acids and their derivatives and of substituted phenylhydrazines, as well as subsequent reactions with other agents, has resulted in the preparation of numerous 1,2-diazabenzanthrones which may have found some use as dyes or dye intermediates.^{223,224} Several German patents²²⁵⁻²²⁷ have been issued in this field. Since this early period of investigation, only occasional references to these compounds have been observed.²²⁸⁻²³¹ It is interesting to note, however, that several patents^{219,220,221} have been issued recently for the preparation and use of these compounds as dyes and dye intermediates.

(2) 3-Substituted 1,2-Diazabenzanthrones

(a) *Preparation.* Schaarschmidt²²⁹ has shown that aromatic 1-anthraquinonylketones, reacting as 1,4-diketones, are readily converted to *ortho*-diazines by the action of hydrazine. Thus, from 1-*p*-chlorobenzoyl-anthraquinone there is obtained 3-*p*-chlorophenyl-1,2-diazabenzanthrone



(VI). The reaction is usually carried out in a refluxing solvent, the time of reaction is short, and the yields are practically quantitative. The reaction is general for the aromatic 1-anthraquinonyl ketones and has been extended to the aliphatic 1-anthraquinonyl ketones.²³¹

(b) *Properties.* The 1,2-diazabenzanthrones are moderately soluble in organic solvents, have rather high melting points, and all are colored. When unsubstituted in the anthraquinone portion of the molecule, they are mostly yellow in color and may exhibit fluorescence in solution. The introduction of substituents, especially auxochromic groups, in the

anthraquinone portion shifts the spectral absorption toward the longer wave lengths.

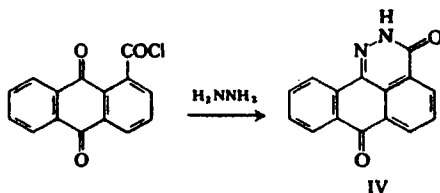
(c) *Uses.* The only reported application of the 1,2-diazabenzanthrones is their use as dye intermediates.^{219,220} In Table 38 are listed the known compounds of this group with data and references.

TABLE 38. 3-Substituted 1,2-Diazabenzanthrones

Compound	Ref.	M.p., °C.	Appearance
3-Ethyl-1,2-diazabenzanthrone	231	204	Yellow needles
3- <i>p</i> -Chlorophenyl-1,2-diazabenzanthrone (VI)	229	> 300	Yellow needles
8-Chloro-3-phenyl-1,2-diazabenzanthrone	219	> 300	Yellow powder
8-Amino-3-phenyl-1,2-diazabenzanthrone	220	257-259	Red needles

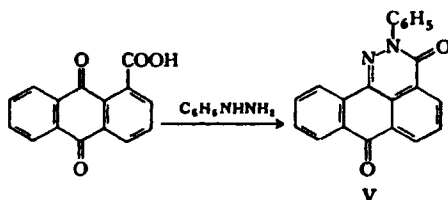
(3) 3-Keto-1,2-diazabenzanthrones

(a) *Preparation.* The action of hydrazine on the chloride or esters of anthraquinone-1-carboxylic acid has been shown by Ullmann^{222,223,225} to result in the formation of 3-keto-1,2-diazabenzanthrone (IV). The



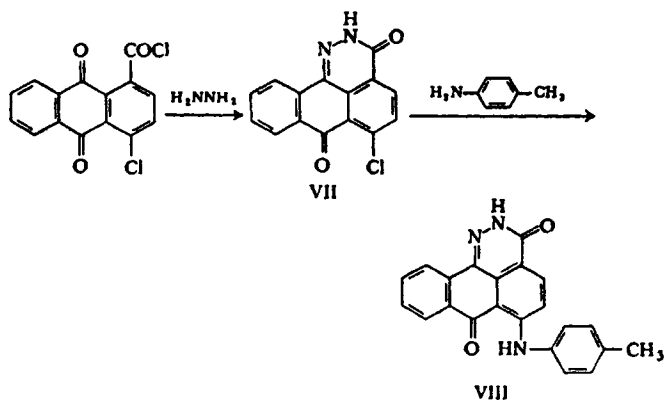
reaction proceeds readily in a solvent and the yield is practically quantitative.

Monosubstituted hydrazines react with anthraquinone-1-carboxylic acid, as well as with the acid chloride or esters, to give 3-keto-1,2-diazabenzanthrones which are substituted in the 2-position. Thus, the action of phenylhydrazine on anthraquinone-1-carboxylic acid in the presence of potassium acetate gives 3-keto-2-phenyl-1,2-diazabenzanthrone (V)

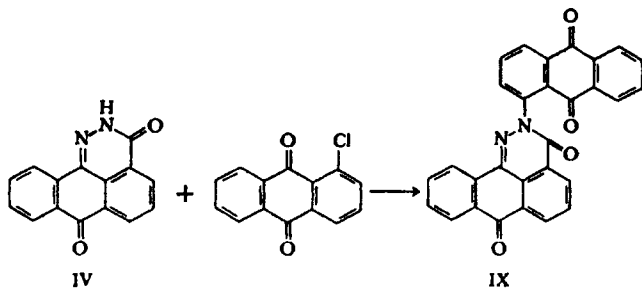


in 74% yield.^{223,225} Sulfonation of 3-keto-2-phenyl-1,2-diazabenzanthrone introduces a sulfonic acid group in the *para*-position of the phenyl group. The sulfonated product also can be obtained directly by the condensation of anthraquinone-1-carboxylic acid with phenylhydrazine-*p*-sulfonic acid.^{223,225}

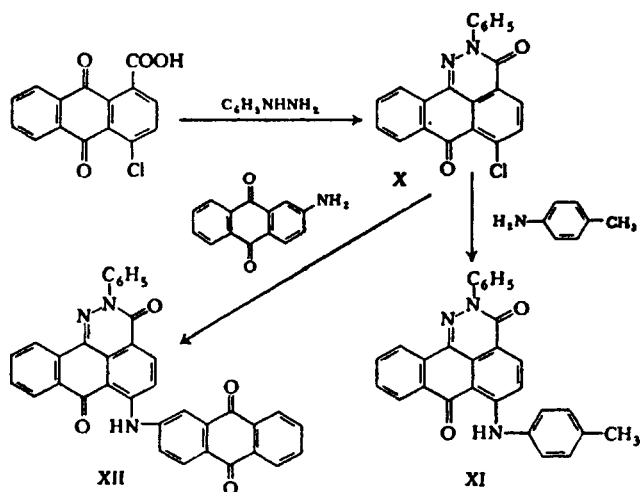
When substituted anthraquinone-1-carboxylic acid derivatives are employed, the reaction products can be converted to dyes. For instance, 4-chloroanthraquinone-1-carboxylic acid chloride is treated with hydrazine; the reaction product (VII) is subsequently condensed with *p*-toluidine to give 3-keto-6-*p*-toluidino-1,2-diazabenzanthrone (VIII). Sulfonation of the latter results in the formation of a yellow wool dye.²²⁴



The introduction of substituents into the 2-position is possible by condensing 3-keto-1,2-diazabenzanthrone with substances having a sufficiently active halogen. For example, the reaction with 1-chloroanthraquinone in the presence of potassium acetate and copper acetate gives a 93% yield of 2-(1'-anthraquinonyl)-3-keto-1,2-diazabenzanthrone (IX).²²³



3-Keto-1,2-diazabenzanthrones which are substituted in both the heterocyclic ring and the anthraquinone portion of the molecule can be prepared by employing appropriately constituted anthraquinone-1-carboxylic acids and hydrazines. The condensation products thus obtained can be subjected to further reactions to give useful dyes. In this manner, 3-keto-2-phenyl-6-*p*-toluidino-1,2-diazabenzanthrone (XI)^{224,226} and 6-(2'-anthraquinonylamino)-3-keto-2-phenyl-1,2-diazabenzanthrone (XII)²²⁴ are obtained from 6-chloro-3-keto-2-phenyl-1,2-diazabenzanthrone (X).²²⁴ Subsequent treatment of 3-keto-2-phenyl-6-*p*-toluidino-



1,2-diazabenzanthrone with oleum gives a sulfonated product which dyes wool orange.^{224,226} 6-(2'-Anthraquinonylamino)-3-keto-2-phenyl-1,2-diazabenzanthrone, when treated with sodium hydrosulfite, yields a vat which dyes cotton yellow-brown.²²⁴

(b) *Properties.* The 3-keto-1,2-diazabenzanthrones are only slightly soluble in organic solvents and have high melting points.

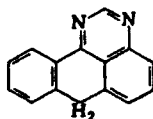
(c) *Uses.* The only reported use of the 3-keto-1,2-diazabenzanthrones is in the dye industry. When sulfonated, they give water-soluble dyes which color wool in yellow to orange shades of excellent fastness to light and washing. The increased substitution of auxochromic groups in the anthraquinone portion of the molecule deepens the color. A few of the 3-keto-1,2-diazabenzanthrones having anthraquinonyl substituents form vats which dye cotton weakly. In Table 39 are collected the known compounds of this group, with data and references.

TABLE 39. 3-Keto-1,2-diazabenzanthrones

Compound	Ref.	M.p., °C.	Appearance	Remarks
3-Keto-1,2-diazabenzanthrone (IV)	222,223,225	430	Yellow needles	—
3-Keto-4-methyl-1,2-diazabenzanthrone	230	332	Yellow needles	—
6-Chloro-3-keto-1,2-diazabenzanthrone (VII)	224	319	Yellow needles	—
6-Anilino-3-keto-1,2-diazabenzanthrone	226	—	Orange-red needles	—
6-Anilino-3-keto-1,2-diazabenzanthrone (sulfonated, potassium salt)	226	—	—	Dyes wool yellow in acid bath
3-Keto-6- <i>p</i> -toluidino-1,2-diazabenzanthrone (VIII)	224	352	Orange-red needles	—
3-Keto-6- <i>p</i> -toluidino-1,2-diazabenzanthrone (sulfonated)	224	—	Yellow	Dyes wool yellow with greenish shades
3-Keto-2-phenyl-1,2-diazabenzanthrone (V)	222,223,225	292	Yellow needles	—
2- <i>p</i> -Bromophenyl-3-keto-1,2-diazabenzanthrone	223	308	Yellow needles	—
3-Keto-2- <i>p</i> -sulphophenyl-1,2-diazabenzanthrone	223	—	Yellow needles	—
3-Keto-2- <i>p</i> -sulphophenyl-1,2-diazabenzanthrone (sodium salt)	223,225	—	Yellow needles	Dyes wool yellow
2-(1'-Anthraquinonyl)-3-keto-1,2-diazabenzanthrone (IX)	223	339	Yellow needles	Dyes cotton weakly from a brown-red vat
2-[<i>p</i> -(1'-Anthraquinonylamino)-phenyl]-3-keto-1,2-diazabenzanthrone	223	—	Brownish-red needles	Dyes cotton weak red from a red vat
6-Chloro-3-keto-2-phenyl-1,2-diazabenzanthrone (X)	224	285	Yellow needles	—
6-Amino-3-keto-2-phenyl-1,2-diazabenzanthrone (II)	224,227	340	Yellow needles	—
6-Amino-3-keto-2-phenyl-1,2-diazabenzanthrone (sulfonated)	227	—	—	Dyes wool green-yellow from acid bath
8-Amino-3-keto-2-phenyl-1,2-diazabenzanthrone	223	320	Carmine-red leaves	—
3-Keto-2-phenyl-6- <i>p</i> -toluidino-1,2-diazabenzanthrone (XI)	224,226	303	Orange-red needles	—
3-Keto-2-phenyl-6- <i>p</i> -toluidino-1,2-diazabenzanthrone (sulfonated, potassium salt)	226	—	Reddish crystals	Dyes wool orange
6-(1'-Anthraquinonylamino)-3-keto-2-phenyl-1,2-diazabenzanthrone	224	405	Red crystals	—
6-(2'-Anthraquinonylamino)-3-keto-2-phenyl-1,2-diazabenzanthrone (XII)	224	430	Brown needles	Dyes cotton yellow-brown from vat
3-Keto-2-phenyl-6-(<i>p</i> -toluenesulfonamido)-1,2-diazabenzanthrone	224,227	—	—	—

B.* 1,3-Diazabenzanthrones

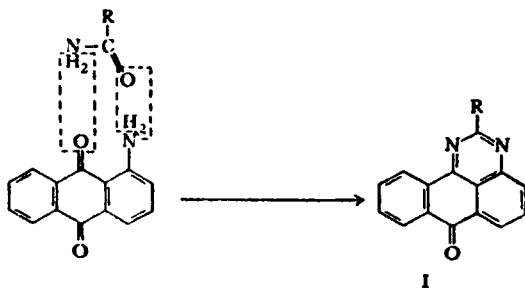
7H,1,3-Diazabenzanthrene. R. I. 2676



The basic reactions employed for the synthesis of 1,3-diazabenzanthrones were nearly all covered in the original patents.²³²⁻²³⁶ As specified in these and their subsequent modifications, anthraquinone derivatives, in which there is a reactive substituent in the *alpha* position, are treated with an amide,^{234,236-245} urea,^{232,234,246} nitrile,^{245,247,248,249} urethan,^{232,241,246} or their equivalent at an elevated temperature. The operation may be carried out with or without a condensing or acid-binding agent, or metal or metallic salt catalyst, and in a neutral solvent.^{232,233,238,243-257} An entirely different type of reaction involves the treatment of an anthraquinone-oxazole with ammonia.^{236,238,242,258,259} The oxazole ring is opened, but subsequent ring closure takes place in a different way so that a diazabenzanthrone results; this will be described in detail in the next section.

(1) Monoketo-1,3-diazabenzanthrenes (Anthrapyrimidines)

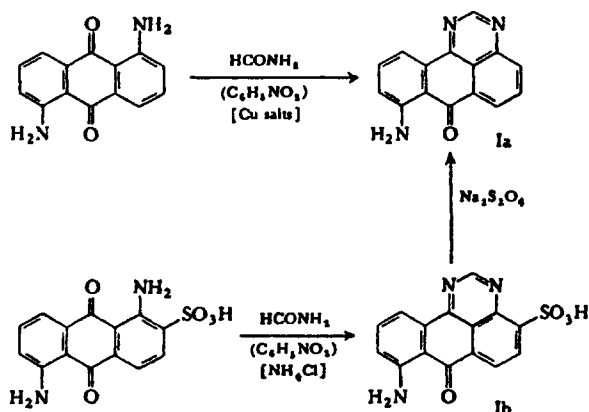
(a) Ring Closure. (1) Amides and 1-amino- or 1-nitroanthraquinones interact with elimination of water to give 1,3-diazabenzanthrones (I). Except with formamide, the products always have a substituent group in the 2-position; these are called *anthrapyrimidines* in most of the literature. Formamide (R = H) gives 1,3-diazabenz-



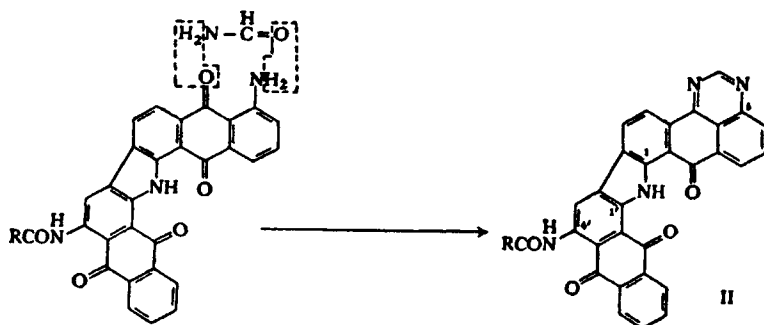
anthrone, the parent member of the series. 1,5-Diaminoanthraquinone, in nitrobenzene solution and in the presence of copper or copper salts, gives 8-amino-1,3-diazabenzanthrone (Ia) (cf. page 270); the yield is 50-60%. By substituting 1,5-diaminoanthraquinone-2-sulfonic acid,

* C. F. H. Allen.

and carrying out the reaction in the presence of ammonium chloride, however, the ring closure becomes quantitative.^{260a,c} The sulfonic acid group can be eliminated by the use of sodium hydrosulfite.



Very large condensed ring systems have been built up by this method. For example, 4'-aroylamino-5,10-pyrimidino-1,1'-anthrimidecarbazoles (II) result from the interaction of formamide and 5-amino-4'-aroylamino-1,1'-anthrimidecarbazoles.^{238,242}



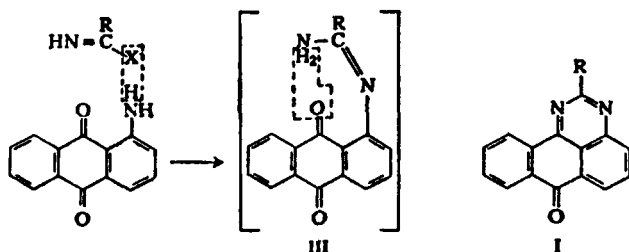
This formamide procedure, operating in nitrobenzene as a solvent and using ammonium metavanadate as a catalyst, was the most suitable for obtaining 6-amino-1,3-diazabenzanthrone until the relatively recent method was publicized; this involved the use of ammonia, formaldehyde, and sodium *m*-nitrobenzenesulfonate^{260a} ("Ludigol") (p. 271).

(2) Nitriles may be used instead of amides; in this event, the presence of a halogen acid is essential. This fact suggests that an imide

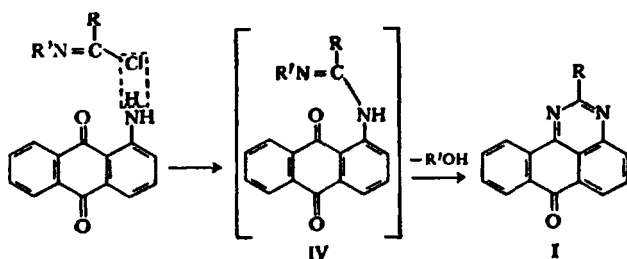
chloride is formed as an intermediate step, $\text{RC}\equiv\text{N} + \text{HX} = \text{RC}=\text{NH}$,



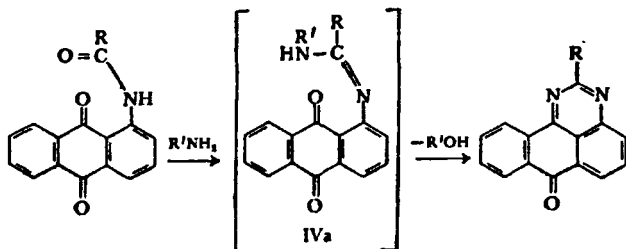
and that subsequent ring formation proceeds stepwise. The hypothetical amidine (III) may be an intermediate product. Hydrogen cyanide (or one of its salts) may be used, in which case, $\text{R} = \text{H}$.



(3) Since alkyl imide chlorides likewise give 1,3-diazabenzanthrones,^{237,241,245,261} the suggested mechanism receives convincing confirmation. It is not necessary to isolate the imide chloride; it may be formed *in situ* from the alkyl amide and a phosphorus halide. The alkyl group attached to nitrogen is eliminated during the cyclization.²³⁷

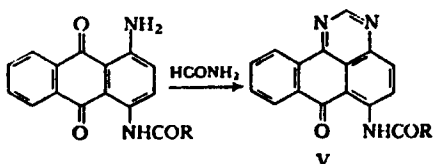


(4) 1-Acylaminoanthraquinones also give 1,3-diazabenzanthrones when heated under pressure with ammonia, amines, and

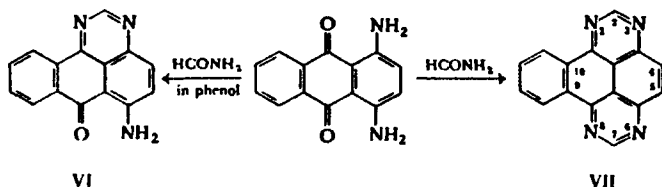


amides.^{235, 242, 245, 252, 253, 255, 262} In this reaction it appears probable that an amidine (IVa) is an intermediate product.

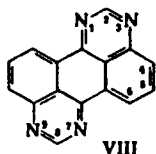
(5) Monoacyldiaminoanthraquinones give acylaminodiazabenzanthrones (V).^{234, 242, 243, 255} For example, 1-amino-4-acylaminoanthraquinone and formamide react to form 6-acylamino-1,3-diazabenzanthrone (V). Hydrolysis of the acyl group yields 6-amino-1,3-diaza-



benzanthrone (VI), which can also be obtained by the action of formamide on 1,4-diaminoanthraquinone in phenol as a solvent. In the absence of the solvent, ring closure involves both amino groups, and a pentacyclic compound (VII) results.^{232, 234, 236, 237, 242, 243, 245, 247-253, 255, 259, 263} This new type, containing four nitrogen atoms, is known in the literature as *Dianthrapyrimidine*. It is obvious that there can be two isomeric series,

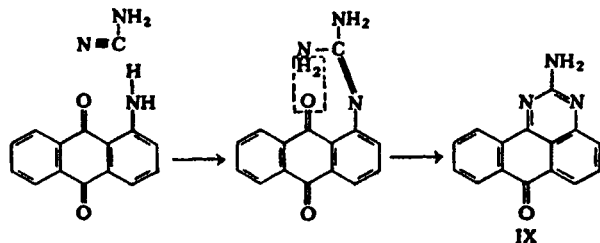


according to the nature of the diamine employed; 1,5-diaminoanthraquinone would give rise to 1,3,7,9-tetrazaperylene (VIII), while the

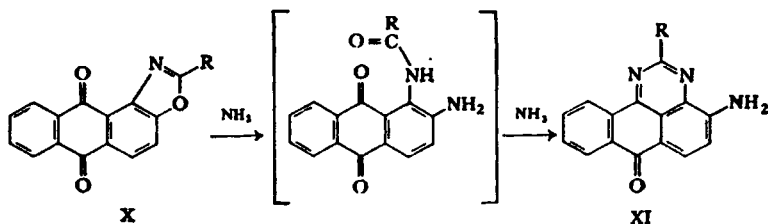


1,4-isomer results in 1,3,6,8-tetrazabenzopyrene (VII). Beyond noting that this condition may appear when diaminoanthraquinones are employed without suitable precautions, we shall not consider these polynuclear heterocyclic systems any further in this section.

(6) 2-Amino-1,3-diazabenzanthrones (IX) can be obtained by ring closure of anthraquinone-1-guanidines.²⁶⁴⁻²⁶⁷ The latter are not usually isolated, but the reaction of a 1-aminoanthraquinone and cyanamide hydrochloride is carried out at 70–180° in a current of hydrogen chloride.

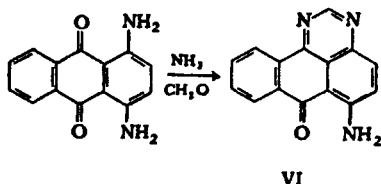


(7) Anthraquinone-oxazoles (X) and ammonia, under pressure, give rise to 4-amino-1,3-diazabenzanthrones (XI) which have a substituent in the 2-position. Presumably the oxazole ring is opened to



give an acylaminoanthraquinone, which, with ammonia, then cyclizes, as already shown on page 269.

(8) 6-Amino-1,3-diazabenzanthrone is now^{260a,268} prepared from 1,4-diaminoanthraquinone, aqueous formaldehyde, sodium *m*-nitrobenzenesulfonate, and ammonia by heating under pressure. It is purified by recrystallization of its sulfate and regeneration with ammonia. In the

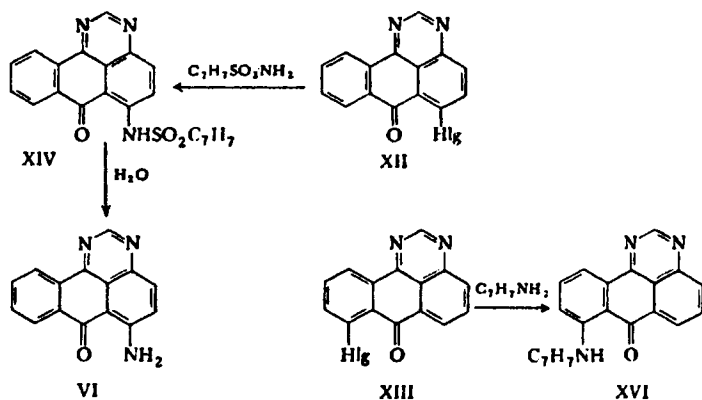


absence of the oxidizing agent the formaldehyde methylates the amino group. This methylation is possible because of the reducing action of the aldehyde, which leads to the formation of a dihydro derivative of the diaminoanthraquinone.^{268c}

This appears to be a very general reaction that has been particularly fruitful with the aminoanthraquinonecarboxylic acids.^{268a} By employing aldehydes other than paraformaldehyde, 2-substituted 1,3-diazabenzanthrones can be prepared. Diaminoanthraquinones can also give tetrazaperylenes or -benzopyrenes (see page 270).

(b) Replacement Reactions. A number of diazabenzanthrones are not obtained directly, but rather by substitution of the compounds whose synthesis has been described in the preceding section. Thereafter, the ordinary replacement and substitution reactions of organic chemistry serve to make available a great variety of derivatives. Since it is more convenient to summarize these reactions according to the type of compound produced, the derivatives will be arranged by groups.

(1) *Amines.* Diazabenzanthrones containing the amino (or substituted amino) group have the greatest technical importance as dyes. While the amino group can be introduced into the molecule by the familiar reactions of nitration and reduction,^{236, 238, 242, 259, 269} replacement of some other group already present is more commonly employed. Halogen,^{236, 250, 259, 262, 270} sulfonic acid,^{271, 272, 273} hydroxy,^{200c, 274-277} and methoxy²⁷⁸ are readily replaceable, using ammonia or amines. The action of *p*-toluenesulfonamide on halogenated nuclei,^{236, 238, 242, 260-253, 259} followed by hydrolysis, is of value in the preparation of aminodiazabenzanthrones. In illustration there are shown the reactions of *p*-toluidine²³⁸ and *p*-toluenesulfonamide with a 6-halo- (XII) and 8-halo-diazabenzanthrone (XIII). The 8-*p*-toluidino-1,3-diazabenzanthrone is unknown.



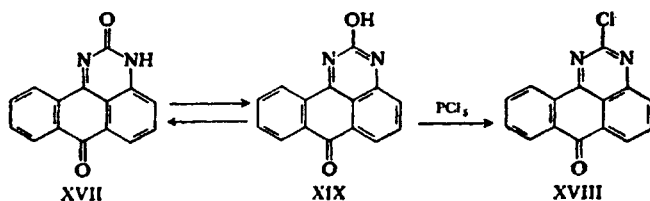
Alkylamino and arylamino derivatives are important; the first class are usually obtained by ring closure of alkylaminoanthra-

quinones,^{236,242,244,261,262,263,269,279} those having long alkyl groups being of recent interest.^{260f,263,290} The arylamino derivatives are obtained almost entirely by the replacement reaction.

(2) *Halogenated Derivatives.* These are of the greatest importance as intermediates for the preparation of other compounds. They are obtained by direct halogenation and by replacement of other groups.^{236,238,242,269,262} Amines and their acyl derivatives are easily halogenated.^{236,238,242,243,254,269,260e,280-284} Chlorine has been introduced by the action of the element,^{234,254,269,283} sulfonyl chloride,^{238,242,245,264,281,283} and chlorosulfonic acid.^{239,269}

More than one atom of halogen may be introduced; the position in which the halogen enters has not been determined in most instances. For this reason, replacement reactions are often more valuable; application of the Sandmeyer reaction results in a conversion of the primary amines to chloro^{236,238,242,269} and bromo²⁶² derivatives.

A special case is the formation of 2-chloro-1,3-diazabenzanthrones (XVIII); these result when 2-keto-1,3-diazabenzanthrones are treated with phosphorus pentachloride.^{236,242,269,262,285} The 2-keto derivative (XVII) is essentially a cyclic amide, the enolic form (XIX) of which corresponds to the chloro compound.



(3) *Sulfonic Acids.* The diazabenzanthrone ring system does not appear to be readily sulfonated. Chlorosulfonic acid can be used as a solvent in bromination.^{236,269} The use of fuming sulfuric acid results in oxidation, hydroxydiazabenzanthrones being formed.^{254,281,286} Arylamino groups, present as substituents, can be readily sulfonated, as in the preparation of the dye, Alizarin Geranol B.^{234,235,260e,287,288,288a}

Sulfonic acids can be obtained by the cyclization procedures.*^{245,246,260e} (One instance has been described²⁵⁹ in which the —SO₃H group was replaced by —NH₂ during the reaction. This replacement is the result of carrying out the cyclization without an oxidizing

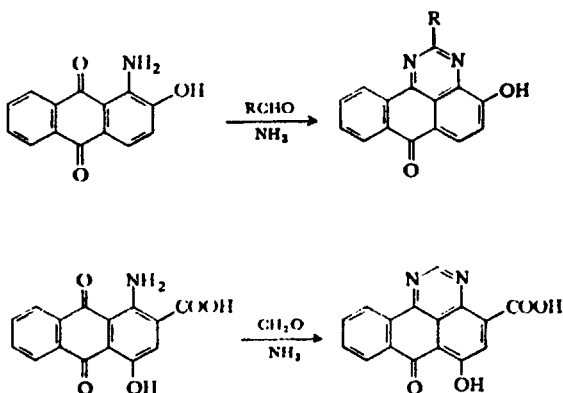
* Although no examples are given, the original patent²²³ claims "... the corresponding sulfonic acids."

agent. In the presence of the latter, the sulfonic acid group is retained.^{248c} They can also be obtained from halogenated or nitrated diazabenzanthrones by heating these with sodium bisulfite under pressure.²⁴⁵ In one instance²⁴⁵ it has been claimed that sodium chlorosulfonate in carbon tetrachloride is a sulfonating agent, but no details are given.

The presence of an amino group in the molecule appears to facilitate sulfonation of the nucleus for the amino-2-phenyl-1,3-diazabenzanthrones can be monosulfonated by the use of oleum.²⁴⁵

(4) *Hydroxy Derivatives.* As stated above, these result from the oxidizing action of fuming sulfuric acid on diazabenzanthrones. While it is believed that the hydroxy group appears in the 6-, 8-, or 11-position,²⁸⁶ this has been determined in only one instance, that of 6-hydroxy-1,3-diazabenzanthrone.

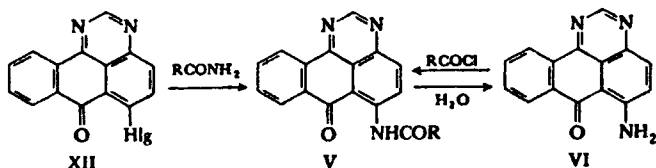
Hydroxy derivatives are also formed by ring closure of suitable intermediates, when the new aldehyde-ammonia procedure is followed^{268a,c} (cf. page 271).



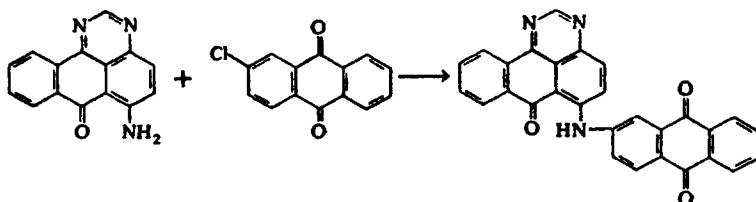
(5) *Miscellaneous Derivatives.* These can be considered most conveniently as resulting from the chemical properties of the four previous classes. The amines have been investigated to the greatest extent, since the products of these reactions appeared most likely to have commercial importance as dyes.

(a) *Acylamino-1,3-diazabenzanthrones.* These may be obtained by cyclization reactions, as already mentioned, by replacement of halogen atoms using aroylamides^{236,242,259} and by acylation of the amines.^{236,238,242,243,259,260,289,290} The replacement reaction is an extension of the long-known *p*-toluenesulfonamide process; the only complicating factor is the occasional loss of the acyl radical through hydrolysis if proper

precautions are not observed. Acylation is carried out at 130–150°, using an aroyl chloride in *o*-dichlorobenzene or nitrobenzene.^{260a,d} The acyl radical in the acylamino derivatives (V) is readily hydrolyzable.



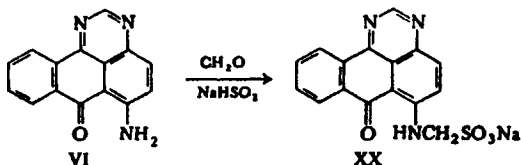
(b) Arylamino-1,3-diazabenzanthrones. In addition to the production of this class of compounds from halogenated diazabenzanthrones, the amines can be arylated by aryl halides, an application of the Ullmann reaction.^{238,260e,262,270,291} This is particularly valuable for the preparation of dyes containing large polynuclear groups. A simple case is



illustrated by the use of β -chloroanthraquinone. The position of the amino group to be arylated is not restricted.

(c) Haloamino-1,3-diazabenzanthrones are readily obtained by the action of halogenating agents. There is nothing unusual about the reactions.

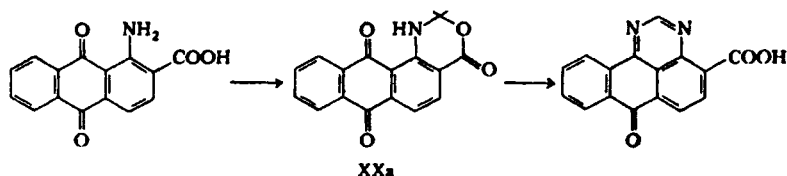
(d) *N*-Alkylsulfonic Acids. Amines, aldehydes, and sodium bisulfite are said to form *N*-alkylsulfonic acids (XX)²⁹² by analogy with the behavior of simpler amines.



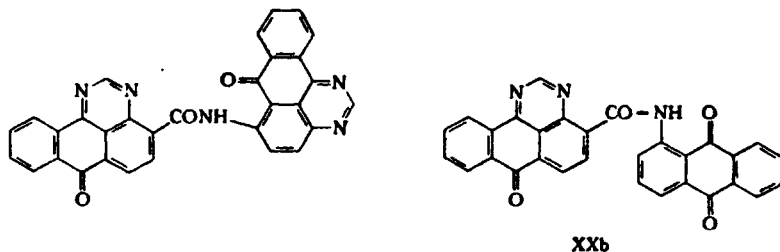
(e) Nitriles. Amino-1,3-diazabenzanthrones can be diazotized. Application of the Sandmeyer synthesis gives rise to cyano-²⁶⁴ and halo-diazabenzanthrones (Cl^{236,239,242,269}; Br²⁶²). The diazotized amine can

be reduced by alcohol, thus effectively replacing the NH_2 group by hydrogen; 1,3-diazabenzanthrone itself (page 267) has been so obtained.

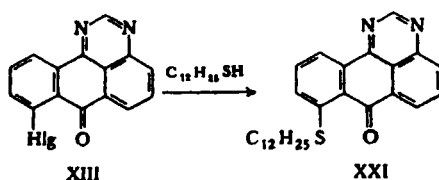
(f) Carboxylic Acids. While this class of substances could, doubtless, be obtained by hydrolysis of the nitriles, they have been prepared up to now by the aldehyde-ammonia process (page 271)^{268a} using aminoanthraquinone carboxylic acids, an aldehyde, and ammonia. In the specific case in which 2-carboxy-1-aminoanthraquinone is the starting material, a cyclic intermediate (XXa) has been postulated; obviously this type of substance is impossible with the isomeric acids.



1,3-Diazabenzanthronecarboxylic acids are known, having the carboxyl group in the 4-, 5-, 9- and 10-positions, and bearing as substituents, in the positions indicated, NO_2 ; 6,11: NH_2 ; 4,6,11: OH ; 6: alkyl and aryl; 2.^{268a} These carboxylic acids form acid chlorides readily, and the latter have been used to acylate various polynuclear amines (*e.g.*, 6-amino-1,3-diazabenzanthrone) to give vat dyes.²⁶⁰ A new yellow vat dye (XXb) said to have excellent light fastness has been reported.²⁹³

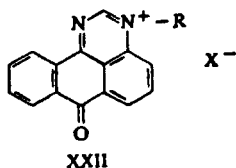


(g) Oxy, Thio, and Seleno Derivatives. 1,3-Diazabenzanthrones containing alkyl or aryloxy, -thio, and -seleno groups have been prepared by treatment of halogenated compounds with phenols, thiophenols, and selenophenols under suitable conditions.^{262, 263, 270, 280} The reaction is carried out in a high-boiling solvent and in the presence of a catalyst (such as copper or its compounds) and an acceptor for the halogen acid produced.²⁷⁰



Reaction products from aminodiazabenzanthrones and phosgene, thiophosgene, and perchloromethyl mercaptan have been mentioned²⁴² but without any indication as to their precise structure.

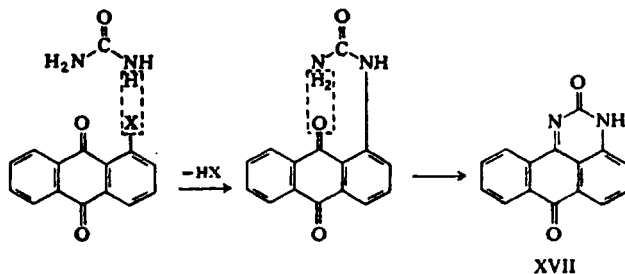
1,3-Diazabenzanthrones form monobasic salts (XXII) when treated with alkyl halides and esters.^{260e, 294, 295, 296} The dyes, which are yellow to blue, are not in use^{260e}; they color animal fibers.²⁶⁷



(2) Diketo-1,3-diazabenzanthrenes (Formerly Anthrapyrimidones)

Representatives of this class were the first of the diazabenzanthrone series to be discovered. The methods of preparation are logical extensions of those already outlined, taking into account that a carbonyl group in both components must be retained in the cyclization. Substitution products are readily obtained by replacement reactions of the types already described.

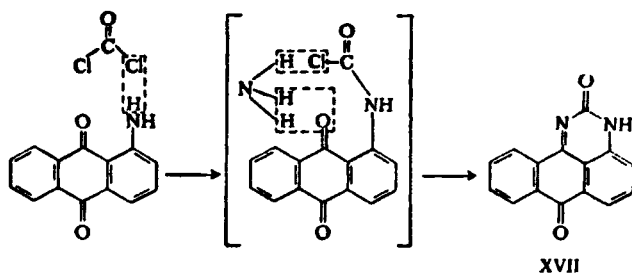
Urea and 1-amino- or 1-chloroanthraquinone^{233, 234, 246} give the parent member (XVII) of the series, with elimination of hydrogen chloride or ammonia. It should be noted that in the 2-keto derivatives the nitrogen



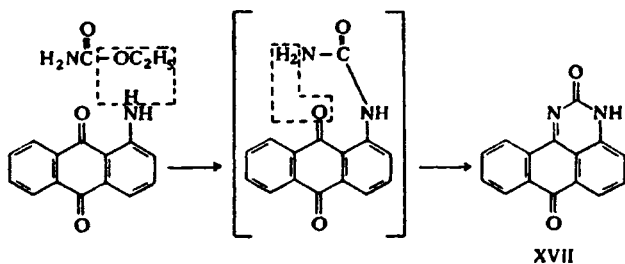
atom in the 3-position still bears one hydrogen atom; that is, only one hydrogen of the amino group has been eliminated. This feature makes it possible to utilize monoalkylaminoanthraquinones, the alkyl group

appearing in the product as a substituent in position 3. The commercially important dye, Alizarin Geranol B (page 281),^{287,297} contains a 3-methyl group.

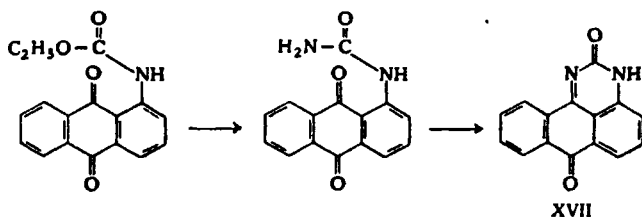
Phosgene may be used to introduce the 2-carbon atom; a subsequent treatment with ammonia both supplies the nitrogen atom in position 1 and brings about the cyclization.²³⁵



1-Aminoanthraquinones and urethan likewise furnish 2-keto-1,3-diazabenzanthrones, with elimination of alcohol.^{232,246,279}

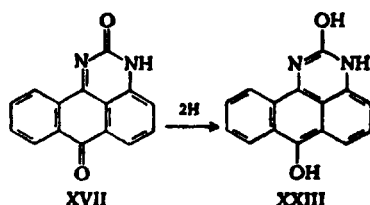


An anthraquinoneurethan and ammonia, heated under pressure, likewise result in the same product; presumably the ethoxy group is first replaced by —NH_2 .

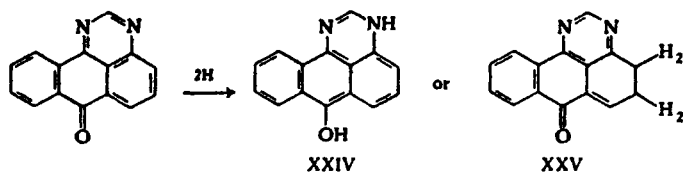


(3) *Products of Uncertain Structure*

As a whole, 1,3-diazabenzanthrones and their 2-keto derivatives are reducible by sodium hydrosulfite²⁷⁶ to leuco derivatives. By analogy with the commonly accepted method of representation used with the reduction products of other quinones, the leuco-2-keto-1,3-diazabenzanthrones are written as dihydroxy derivatives (XXIII). However, the



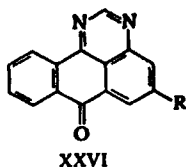
diazabenzanthrones themselves are also reducible to leuco derivatives; in this case, the location of the hydrogen has not been established. Several possible bond structures, of which two are shown, can be written for a leuco derivative involving one of the nitrogen atoms. One of the possible products of the 1,6-addition of hydrogen is shown in XXIV, whereas a rearrangement product of the latter that conforms to Zahn and Ochwat's ideas²⁹⁸ is shown in XXV (cf. page 222).



The leuco compounds are used for certain transformations. Many which have a substituent in the 6-position can be converted to the amine by heating them with methanol and ammonia or an aliphatic amine.^{276,278} The products are useful as dyes.

When treated under alkaline conditions with aldehydes, the leuco compounds give substances which are believed to be, in part, substitution products^{283c, 288, 299, 300}; the use of formaldehyde results in the formation of a methyl derivative, while a benzylated substance is obtained from benzaldehyde. Since the products are vat dyes, indicating the presence

of a carbonyl group, it must be concluded that the new group is not located at that point. It is possible that the entering radical is to be found on position 5, as shown herewith (XXVI) (compare page 222).



Esters of leuco derivatives are obtainable in the usual way, *i.e.*, the bases are treated with sulfur trioxide in a basic diluent and in the presence of a metal such as copper.²⁰¹

(4) Physical Properties

The physical properties of 1,3-diazabenzanthrones are not generally recorded in the literature. As would be expected of polynuclear compounds, their melting points, if revealed, are high, and their solubilities slight in most of the common laboratory solvents. It would be expected that they would dissolve in such reagents as pyridine and similar bases, in the high-boiling halogenated solvents, and to some extent in nitrobenzene. It is possible that the Cellosolve and Carbitol ethers and esters may prove to be useful solvents. Many of their solutions exhibit a greenish fluorescence.

2-Keto-1,3-diazabenzanthrone itself crystallizes from nitrobenzene in golden yellow needles that do not melt up to 280°. It is also soluble in pyridine. It dissolves in dilute sodium hydroxide, giving an orange-red solution, from which it is precipitated unchanged upon acidification. It is soluble in concentrated hydrochloric and sulfuric acids, forming orange-yellow solutions with a weak fluorescence; upon dilution, the base is precipitated. This property of salt formation with sulfuric acid is frequently employed as a step in purification.^{244 261, 262, 263}

Simple 1,3-diazabenzanthrones are yellow to orange. The introduction of amino groups deepens the color to red and violet; this shift is most noticeable if the amino groups are in the 6-, 8-, and 11-positions, arylamino groups being the most effective in this respect. The presence of polynuclear substituents leads to blues, grays, blacks, and browns.²⁶²

The absorption spectrum of the anthrapyrimidone dye, Alizarin Geranol B, is shown in Figure 7. The similarity to the 1-cyano-3-azabenzanthrone analogs should be noted.

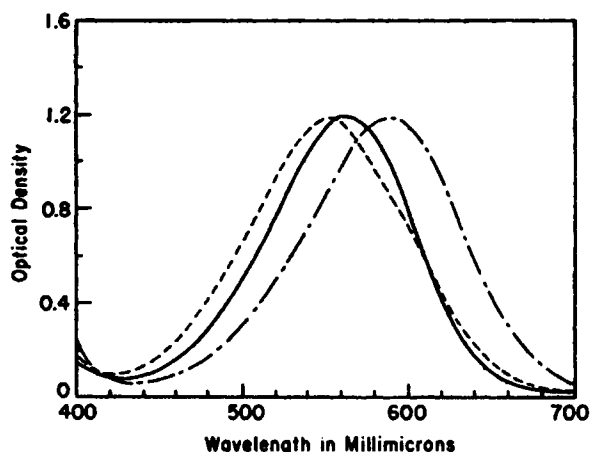
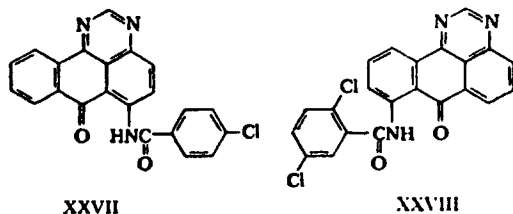


Fig. 7. (—) Alizarin Geranol B, 6-(2'-Sulfo-4'-methylanilino)-2-keto-3-methyl-1,3-diazabenzanthrone. (---) 1-Cyano-6-(2'-sulfo-4'-chloroanilino)-2-keto-3-methyl-3-azabenzanthrone. (- · - ·) 1-Cyano-6-(2'-sulfo-4'-sec.-amylanilino)-2-keto-3-methyl-3-azabenzanthrone.

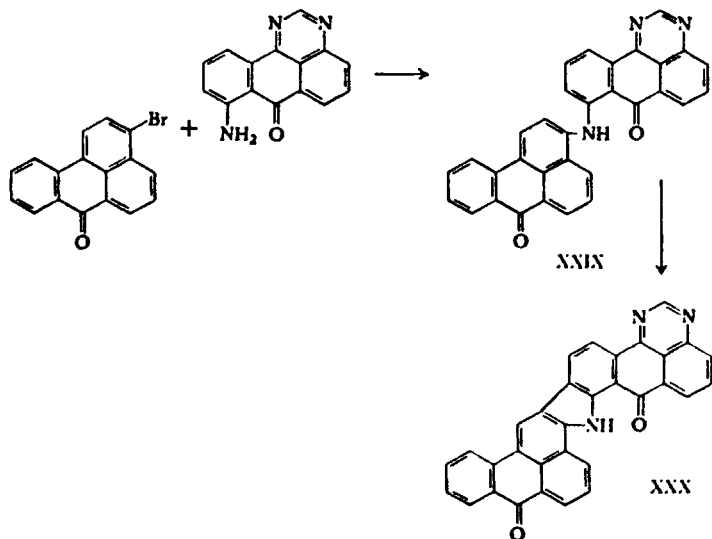
(5) Uses

The industrial application of the 1,3-diazabenzanthrones is in the field of dyes. Many can be used as vat dyes if their leuco compounds have an affinity for the fiber.^{234, 235, 238, 240, 242, 243, 244, 259, 260a, 262, 269, 302} Although the group had been known for a long time, it was neglected by the dye chemists until the 1930's, when a comprehensive program was inaugurated and carried out at Ludwigshafen.^{260a} It was expected that vat dyes containing the diazabenzanthrone nucleus would show less "tendering"; this expectation was realized. Two representatives of the class, Indanthrene Yellow 7GK (XXVII) and Indanthrene Yellow 4GK (XXVIII), were placed in production; these dyes were prepared by acylation of the appropriate amino-1,3-diazabenzanthrones.^{260a, b, d, e}



Imide dyes can be obtained by the usual type of synthesis, *viz.*, from halo-1,3-diazabenzanthrones and aminodiazabenzanthrones, with themselves or with other halo- and aminopolynuclear compounds (cf. page 273); it should be noted that 6-aminodiazabenzanthrone condenses with halogen compounds only with great difficulty. The most valuable dyes are derived from 8-amino-1,3-diazabenzanthrone; they are said to be very fast to light and useful for printing. The hues are violet, blue, and black. The imides can be cyclized by alkali to carbazoles, which dye gray or brown. A few examples follow.

An imide (XXIX) is formed from 3-bromobenzanthrone and 8-amino-1,3-diazabenzanthrone. The corresponding carbazole is shown in formula XXX; it is stated to be a very valuable gray dye.^{260a} The

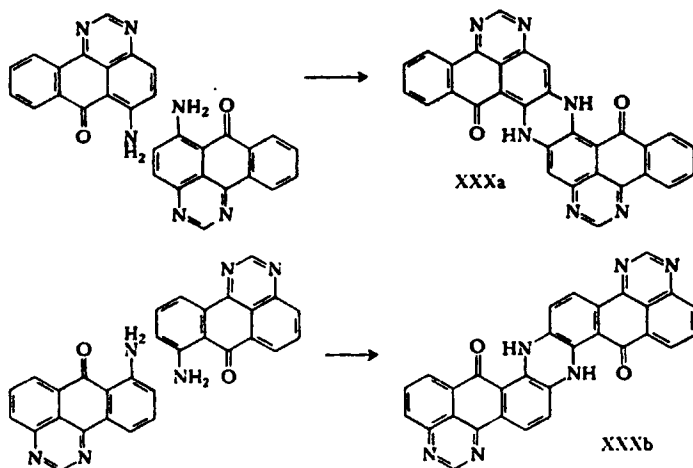


product from dibromoanthrone and two moles of 8-amino-1,3-diazabenzanthrone is a bluish gray; by substituting 1-phenyl-8-amino-1,3-diazabenzanthrone, a very level-dyeing product which is fast to chlorine is obtained.

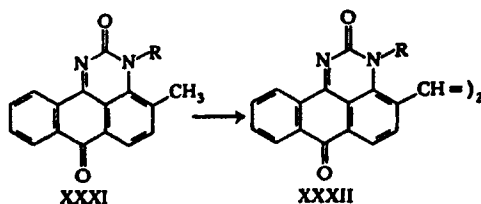
The products from 8-amino-1,3-diazabenzanthrone and other polynuclear compounds are as follows. Two moles of the amine and dibromobenzanthronepyrazoleanthrone gives a gray, while dibromoisodibenzanthrone gives a dark blue. Blacks or grays are "mixed imides," and prepared from (a) tetrabromopyranthron and two moles each of 8-amino-1,3-diazabenzanthrone and aminobenzanthrone, and (b) dibromo-

dibenzpyrenequinone and one mole each of 8-amino-1,3-diazabenzanthrone and aminodibenzanthrone.^{260c} A product that dyes cotton reddish-violet shades is formed from 8-amino-9-cyano-1,3-diazabenzanthrone and 1-aminoanthraquinone-2-aldehyde.²⁶¹

Azine types (indanthrenes) (XXXa and XXXb) have been prepared from 6- and 8-amino-1,3-diazabenzanthrones by aerating a pyridine solution containing potassium hydroxide at 50–55°. ^{262b} The 6-methylamino derivative failed to react under similar conditions. C-Aryl and C-alkyl derivatives are also mentioned. The dyes are of no practical value.



The stilbene type (XXXII) is obtained from 4-methyldiazabenzanthrones (XXXI) and alkali.^{264, 265} With the recent discovery that

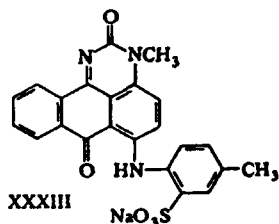


suitably constituted water-insoluble compounds can be dispersed, certain aminodiazabenzanthrones have been employed to color cellulose acetate.^{228, 244, 262, 269, 272, 266, 267}

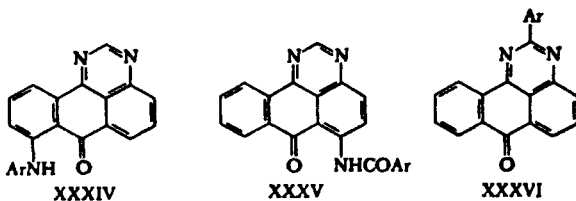
The acid dye in the diazabenzanthrone group in longest general use is known as Alizarin Geranol B.^{234, 257, 258, 297} This was used on wool, to which it gave a reddish-violet shade; if the dyeing operation is properly

done, in the presence of acetic acid, silk and cotton are not dyed. The dye on the wool is blued somewhat and made faster to milling by after-chroming.

It appears that this dye was discovered about the same time independently by Meister, Lucius, and Brünig^{282,283} at Höchst, and by Bayer^{284,285} at Elberfeld; the Meister, Lucius, and Brünig patent is dated November 3, 1907, and the Bayer patent, March 24, 1908. There is a slight disagreement in the literature as to the exact detailed structure, but the preponderance of opinion appears to favor the one having a methyl group on the nitrogen atom in the 3-position.^{287,297} Schultz²⁸⁸ gives the structure as having a hydrogen atom instead of a methyl group; in view of the fact that, as far as revealed, all commercial azabenzanthrone acid dyes are methylated, and also because Schultz gives the dates of the patents incorrectly as 1912, the nonmethylated structure seems less likely to represent the dye. Alizarin Geranol B (XXXIII) is, therefore, a salt of 2-keto-3-methyl-6-*p*-toluidino-2'-sulfo-1,3-diazabenzanthrone.



Other acid dyes without the keto group are known,^{245,260e,295} prepared by the sulfonation of the three type structures (XXXIV-XXXVI).

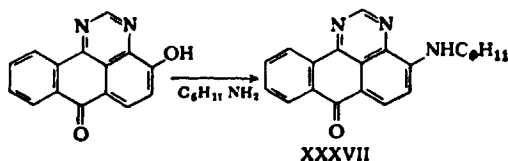


However, their fastness to light is poor and the hues are not outstanding. On the contrary, the sulfonated luminescent dyes, which are orange to red, are nearly all fast to light, and dyeings are very bright. The three preferred are:

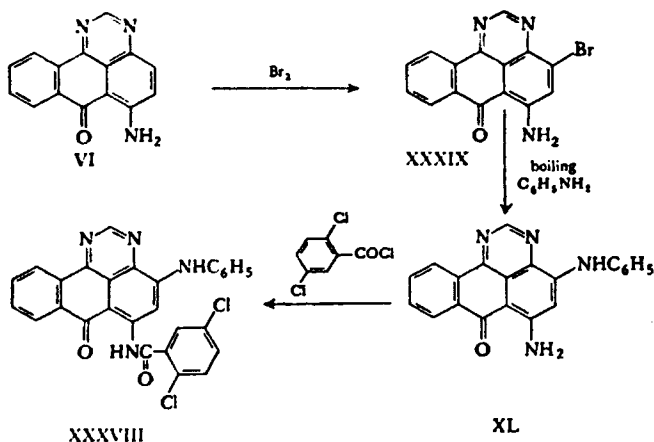
- (a) 4-Anilino-6-(3'-toluylamido)-1,3-diazabenzanthrone, sulfonated.
- (b) 4-*p*-Toluidino-6-(3'-toluylamido)-1,3-diazabenzanthrone, sulfonated.
- (c) 4-*p*-Toluidino-6-(4'-toluylamido)-1,3-diazabenzanthrone, sulfonated.

Sulfonation is accomplished by the use of weak oleum to avoid hydrolysis of the aroyl group. The technique of isolation appears to be difficult.^{200e}

Certain amino-1,3-diazabenzanthrones fluoresce brightly enough to be useful in solutions of organic solvents. Others, which are required to glow while in the solid state when illuminated with light of short wave length, are called "luminescent." Two of the latter variety are Luminescent Product 70 (XXXVII) and Lumogen L Red Orange (XXXVIII). Luminescent Product 70 is prepared by heating 4-hydroxy-1,3-diazabenzanthrone with cyclohexylamine. (The hydroxyl groups in the 4- and 6-positions of azabenzanthrones are easily replaced by amino groups, page 272.)

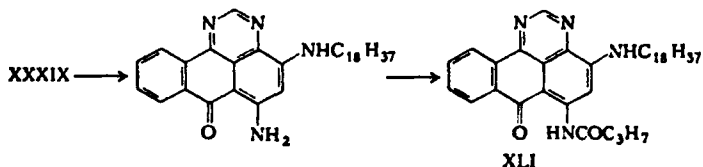


Lumogen L Red Orange is obtained by heating 4-bromo-6-amino-1,3-diazabenzanthrone (XXXIX) with aniline, and acylating the 4-anilino derivative (XL) with 2,5-dichlorobenzoyl chloride. The bromo compound is obtained by bromination of 6-amino-1,3-diazabenzanthrone (VI) in 90% sulfuric acid at 50–60°.



The only fluorescent material reported to be in use was Fluorol 242 (XLI); this oil-soluble substance has good fastness to light.^{200f} It is prepared by heating the 4-bromo compound (XXXIX) with octadecyl-

amine, and acylating the product with *n*-butyryl chloride in nitrobenzene, containing pyridine, at 120–150°. *o*-Dichlorobenzene is also a suitable solvent for acylation.



In marked contrast to the acid 3-azabenzanthrone dyes (anthrapyridones, page 223), the few 1,3-diazabenzanthrone dyes examined are not degraded by nitric acid; instead, a salt is formed, from which the dye is liberated by an excess of a base.²⁰⁸

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CHAPTER VII

Azapyrenes

BY ELEANOR R. WEBSTER

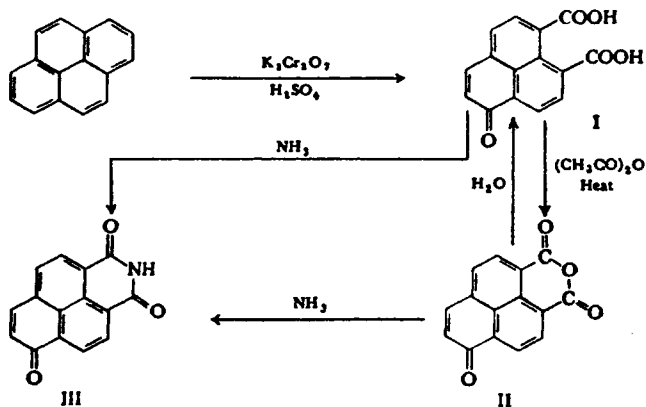
1. Monoazapyrenes

Three different monoazapyrenes could exist and members of two of these systems have been synthesized. Only one investigation of the 2-azapyrene series appears in the literature, and very little information is available concerning any 4-azapyrene compounds.

A. 2-Azapyrene, Naphth[2,1,8-*def*]isoquinoline. R.I. 2759



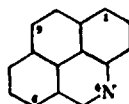
The only preparation of a 2-azapyrene that has been described is that by Bamberger and Philip,¹ who obtained pyrenequinone and pyrenic acid (I) from a dichromate oxidation of pyrene.



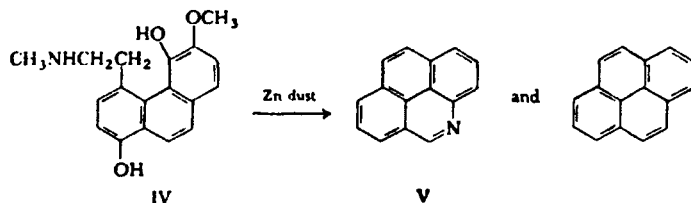
1,3,6-Triketo-2H,2-azapyrene (III), the imide of the dicarboxylic acid (I), results from the slow interaction of ammonia and the anhydride (II), but is very readily prepared by the action of ammonia on the acid

(I). The yellow plates of the 2-azapyrenetrione are insoluble in cold sodium hydroxide, but dissolve on warming. The color changes from yellow-brown to red, and on the addition of acid a flocculent precipitate whose properties are different from those of either the acid or the imide separates. Neither this product nor the imide itself has been characterized further.

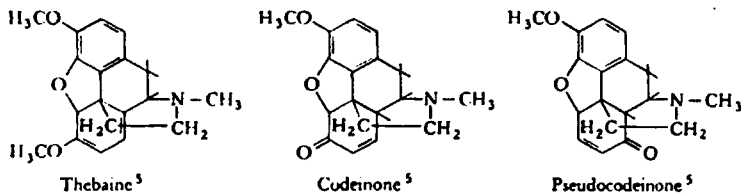
B. 4-Azapyrene, Thebenidine, Pyrenidine.
R.I. 2760



Although 4-azapyrene (V) itself has been known for many years very few members of the series have been reported in the literature. The base was first obtained by Vongerichten² on zinc dust distillation of the alkaloid thebenine (IV) in the course of research to elucidate its structure. Thebaine is one of the morphine group of plant alkaloids; on treatment with dilute hydrochloric acid it yields thebenine,³ whose structure has



now been established as that shown in IV.⁴ Interestingly enough thebenine is also obtained by hydrolysis of codeinone or pseudocodeinone.⁴

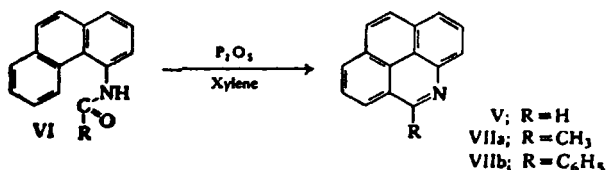


4-Azapyrene is very slightly attacked by chromic acid, is reduced by tin and hydrochloric acid, and apparently has not been investigated with respect to its behavior on halogenation, nitration, or the like. It forms a picrate, a methiodide which does not react further with methyl iodide, an ether-soluble crystalline hydroxide, and stable double salts with hydrochloric acid and mercuric chloride or platinic chloride. Solutions of the base in organic solvents such as ether, benzene, and alcohol (it is

insoluble in water) show a blue fluorescence, while those in dilute hydrochloric acid have a strong bluish-green fluorescence.

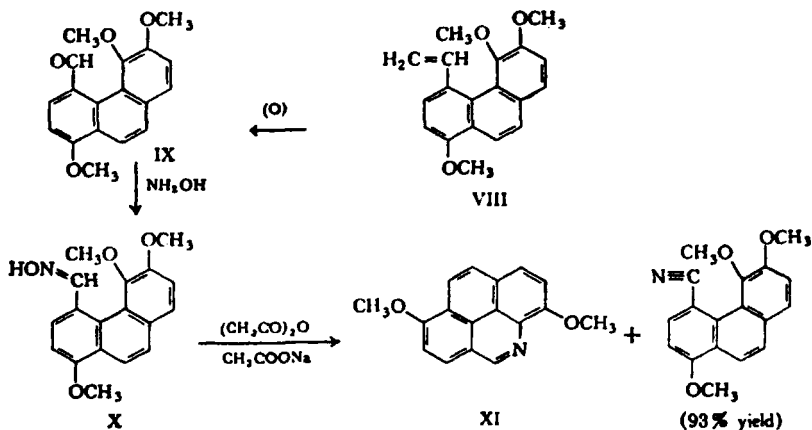
The only synthesis⁶ of 4-azapyrene resulted in the formation of a base which is probably identical with that obtained by Vongerichten, although its melting point is somewhat higher. However, no properties of this base are reported beyond its appearance, melting point, melting point of the picrate, and analytical data.

Cook and Thomson's⁶ synthesis of a 4-azapyrene (VII) is an extension of a phenanthridine synthesis,⁷ and depends upon the dehydration of 4-formamido- and substituted 4-formamidophenanthrenes (VI).

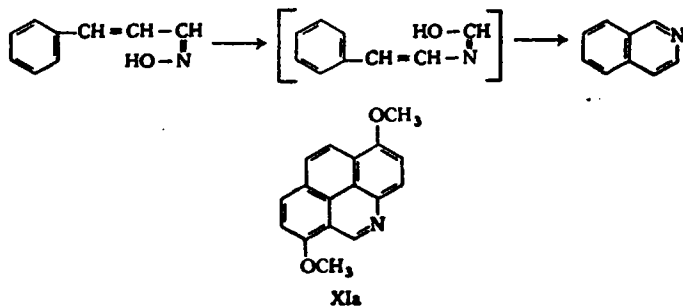


By this treatment of 4-formamido-, 4-acetamido-, and 4-benzamido-phenanthrene, 4-azapyrene (V) and its 5-methyl- (VIIa), and 5-phenyl- (VIIb) derivatives were obtained in moderate yield. These compounds and a number of other nitrogenous analogs of polycyclic aromatic hydrocarbons were prepared for biological testing. Since certain cyclic hydrocarbons, such as benz[*a*]anthracene, for instance, are strongly carcinogenic but possess a marked inhibitory action on tumor growth, it was hoped that similar heterocyclic systems might show the same inhibitory action accompanied by diminished carcinogenic properties.

In an investigation which conclusively established the structure of



thebenine, Gulland and Virden⁴ prepared a polycyclic nitrogen-containing compound which they considered to be 3,8-dimethoxy-4-azapyrene (XI). They obtained a small quantity of a base, $C_{17}H_{13}NO_2$, as a by-product in the dehydration of the oxime (X) of the aldehyde (IX) formed by the oxidation of 3,4,8-trimethoxy-5-vinylphenanthrene (VIII). They concluded that their by-product was a 4-azapyrene because of the similarity of its properties to those of thebenidine as reported by Vongerichten. Since the oxime of cinnamic aldehyde undergoes rearrangement to form isoquinoline rather than quinoline on dehydration,⁸ the possibility that the base is the 1,6-dimethoxy- (XIa) rather than 3,8-dimethoxy-4-azapyrene (XI) must not be overlooked.

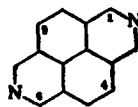


The basic orange compound obtained by Gulland and Virden⁴ is apparently stable toward nitrous acid, is soluble in hydrochloric acid, and is reprecipitated on the addition of alkali. The yellow-orange color of acid solutions of the base is discharged by tin, and solutions of the base show strong fluorescence.

2. Diazapyrenes

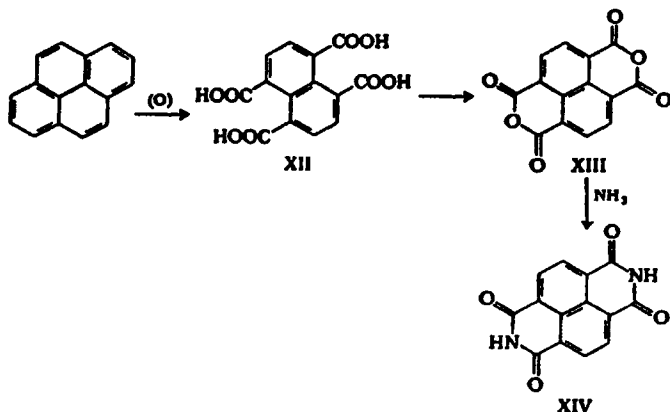
Since the pyrene molecule is symmetrical along two axes and has only ten carbon atoms not common to two or more rings which might be replaced by nitrogen atoms, there are only fifteen theoretically possible diazapyrenes. Of these, two systems appear in the literature, the 2,7- and the 4,9-

A. 2,7-Diazapyrene, Benzo[*lmn*][3,8]phenanthroline. R.I. 2713



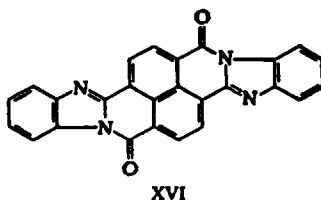
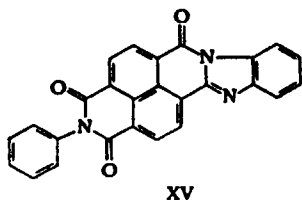
Although a number of different compounds of the 2,7-diazapyrene series have been prepared, only one method of synthesis, that from

1,4,5,8-naphthalenetetracarboxylic acid (XII), has been used; all compounds of the series are tetraketo derivatives. Bamberger and Philip¹ first prepared the diimide of the acid (XII) which had been obtained by



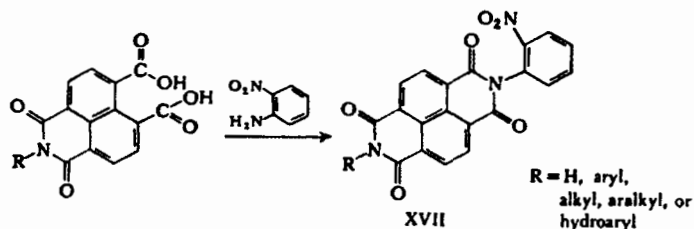
vigorous oxidation of pyrene. The yellow needles of 1,3,6,8-tetraketo-1,2,3,6,7,8-hexahydro-2,7-diazapyrene (XIV), which crystallize from the yellow solution of the anhydride (XIII) in warm ammonia solution, do not melt on heating to 270° and sublime above that temperature. The base, which is difficultly soluble in alcohol, ether, benzene, and acetic acid, forms a crystalline yellow sodium salt; on treatment with acid, hot water, or on standing in moist air, this is converted again to the diimide.

A number of patents⁸⁻¹¹ describe other methods of preparation of the naphthalenetetracarboxylic acid and include the preparation of the diimide (XIV) from it. The acid and diimide are patented as intermediates for dyes, such as the polycyclic vat dyes (XV and XVI), formed by the reaction of the acid with various *o*-phenylenediamines. Another

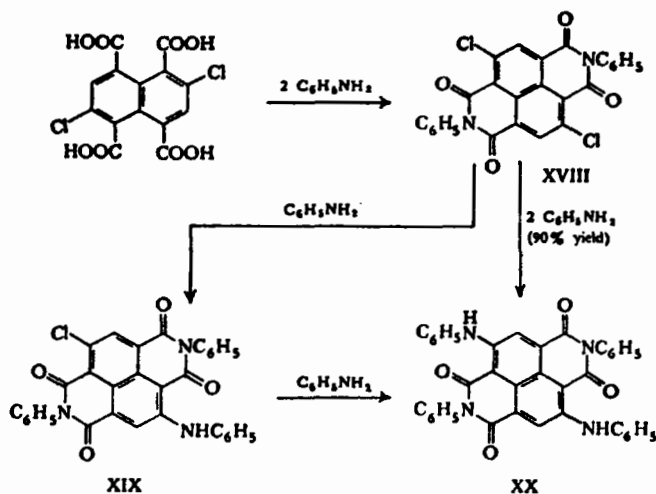


patent¹⁰ mentions certain derivatives of 1,3,6,8-tetraketo-1,2,3,6,7,8-hexahydro-2,7-diazapyrene (for example XVII) which will give similar vat dyes on reduction of the nitro group followed by ring closure. No

details of physical properties are included in any of these patent specifications.



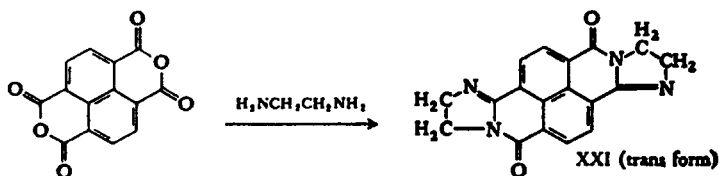
In a review article on pyrene and its derivatives, Vollmann, Becker, Corell, and Streeck¹² described the preparation of halogenated pyrenes which yield halogenated 1,4,5,8-naphthalenetetracarboxylic acids on oxidation. Although they reported the preparation of 2,6- and 2,7-dichloro- and 2,3,6,7-tetrachloronaphthalene-1,4,5,8-tetracarboxylic acid, only two diimides are described, 4,9-dichloro-2,7-diphenyl-1,3,6,8-tetraketo-1,2,3,6,7,8-hexahydro-2,7-diazapyrene (XVIII) and the corresponding 4,9-dianilino derivative (XX). The almost colorless dichloro base (XVIII) may be contaminated by a trace of the monoanilino compound (XIX). The latter compound can be isolated as red needles from the reaction mixture containing XVIII and a considerable excess of aniline,



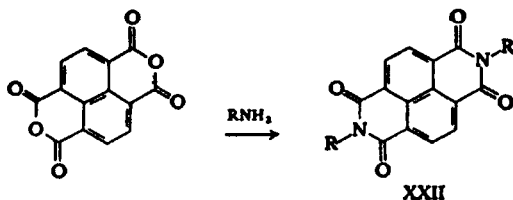
prior to the change of the solution from red to blue, which indicates complete conversion to XX.

Fierz-David and Rossi¹³ prepared a considerable number of nitrogen-substituted diimides, that is, 2,7-diR-1,3,6,8-tetraketo-1,2,3,6,7,8-hexahydro-2,7-diazapyrenes, in the course of research relating to the synthesis of "naphthoylene-diimidazolines," that is, XXI and its *cis* isomer.

The commercial dye, Indanthrene Scarlet 2G, is a mixture of the dull magenta *cis* and the vivid orange *trans* isomers of the condensation product between *o*-phenylenediamine and 1,4,5,8-naphthalenetetracarboxylic acid. The isomers have been separated and marketed; the *cis* form is known as Indanthrene Bordeaux RR, while the *trans* isomer is Indanthrene Brilliant Orange GR.¹⁴ Because of the commercial interest in these dyes, Fierz-David and Rossi undertook the synthesis of the parent structure, "naphthoylene-diimidazoline" (XXI), to determine its properties. Although the reaction of the dianhydride of 1,4,5,8-naphthalenetetracarboxylic acid and a diamine such as ethylenediamine gives the



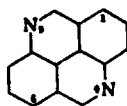
diimidazoline (XXI) directly, the dianhydride also reacts with compounds containing a single primary amino group to give 2,7-diR-1,3,6,8-tetraketo-1,2,3,6,7,8-hexahydro-2,7-diazapyrenes (XXII). In their in-



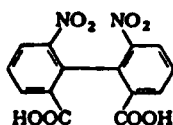
vestigation of several different routes to the preparation of XXI, they treated the dianhydride with such primary amines as β -aminopropionamide, ethyl β -aminopropionate, α -aminoacetamide, aminoethanol, and so on.

The diimidazoline (XXI) is not of technical interest, nor are the various 2,7-diazapyrene derivatives (XXII) of commercial value. Most of these compounds, which are obtained in fairly good yield, are high-melting, difficultly soluble, almost colorless substances whose other properties are not reported.

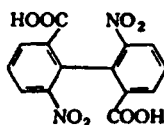
B. 4,9-Diazapyrene, Pyrido[2,3,4-*lmn*]phenanthridine. R.I. 2714



The first synthesis of the 4,9-diazapyrene ring system occurred somewhat unexpectedly in the reduction of a 6,6'-dinitrodiphenic acid.¹⁵ Schulze¹⁶ reported the preparation of 6,6'-dinitrodiphenic acid as one of the products of the nitration of diphenic acid, and he designated it as β -dinitrodiphenic acid. The properties of Schulze's acid are not in accord with those of the acid obtained by Kenner and Stubbings.¹⁵ To distinguish between the two, the latter investigators referred to Schulze's dinitro compound as the β -6,6'- and to their own as γ -6,6'-dinitrodiphenic acid. The two 6,6'-dinitrodiphenic acids are stereoisomers, owing to restricted rotation. Kenner and Stubbings assigned the two structures as shown herewith.

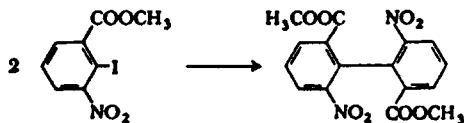


Schulze's β



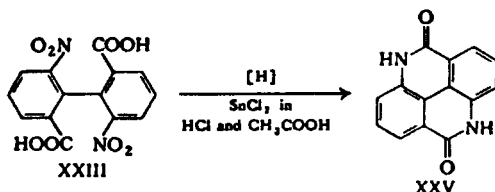
XXIII

The methyl ester of the *gamma* isomer (XXIV) is prepared from methyl 2-iodo-3-nitrobenzoate:



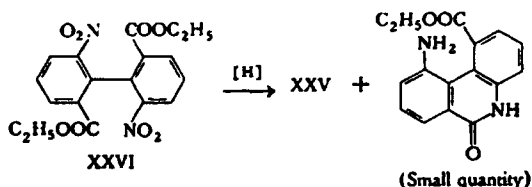
XXIV

Although the melting point of the methyl ester (XXIV) agrees fairly well with that reported by Schulze, hydrolysis to the acid gives a product which melts at 263° without decomposition rather than at 297° with decomposition. Whereas Schulze's acid gives the expected diamino acid on reduction, the acid obtained by Kenner and Stubbings gives an internal anhydride (XXV).

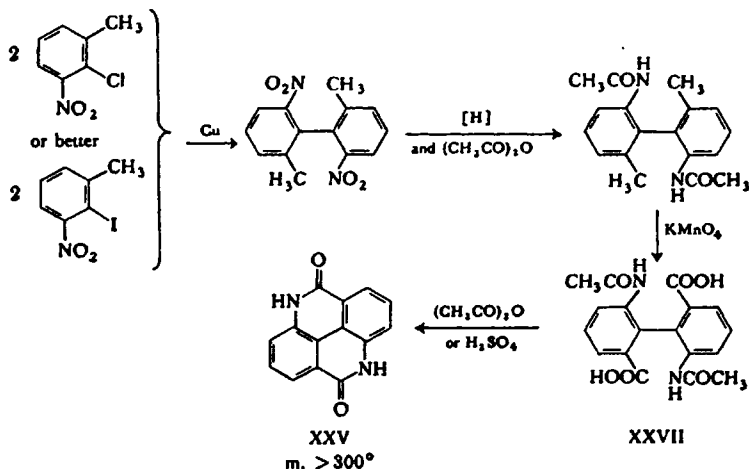


Analytical data,* and the strong resemblance of the reduction products obtained supported acceptance of XXV as the correct structure. 5,10-Diketo-4,5,9,10-tetrahydro-4,9-diazapyrene (XXV) sublimes as pale yellow needles, is sparingly soluble in the usual solvents, is soluble in concentrated H_2SO_4 with a blue fluorescence, and dissolves in concentrated KOH from which the base is precipitated on dilution with water.

The tendency toward formation of the 4,9-diazapyrene system is so strong that the same diketo derivative (XXV) is obtained even on careful reduction of ethyl γ -6,6'-dinitrodiphenate (XXVI).



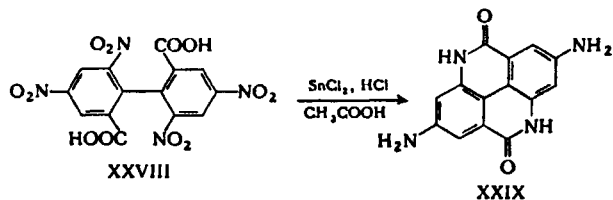
The best method of preparing 5,10-diketo-4,5,9,10-tetrahydro-4,9-diazapyrene (XXV) is by hydrolysis of γ -6,6'-diacetylaminodiphenic acid (XXVII) prepared by the following series of reactions:



In an investigation of nitration products from 2,7- and 4,5-dinitrophenanthraquinone, Christie and Kenner¹⁷ prepared 4,6,4',6'-tetranitrodiphenic acid (XXVIII), which gives 2,7-diamino-5,10-diketo-

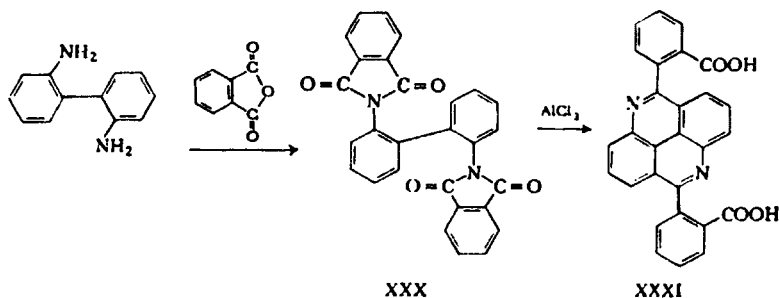
* Probably difficulties in obtaining complete combustion account for the low analytical values for carbon, but the agreement in the case of hydrogen and nitrogen is satisfactory. In any case, the value obtained for carbon is not sufficiently low to permit any other structural interpretation.

4,5,9,10-tetrahydro-4,9-diazapyrene (XXIX) on reduction. This 4,9-diazapyrene derivative forms a green basic sulfate and a yellow neutral

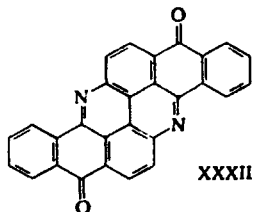


sulfate; the latter turns green on exposure to air and light and blackens but does not melt on heating to 300° . No properties of the free base or of any other derivatives are reported.

It is very probable that a compound which is obtained by aluminum chloride treatment of 2,2'-diphthalimidobiphenyl (XXX) is 5,10-di-(2'-carboxyphenyl)-4,9-diazapyrene (XXXI). The patent¹⁸ in which



the preparation is first recorded suggests the diazapyrene as the probable structure. This compound is converted into flavanthrene (XXXII) by heating it in the presence of sodium-aluminum chloride.



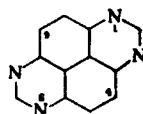
According to the patent, the intermediate phthalimido compound (XXX) may be transformed directly into flavanthrene with sodium-aluminum chloride, but Křepelka and Štefer¹⁸ obtained a dicarboxylic acid as a by-product in the formation of flavanthrene from XXX in such a melt. The crude yield of XXXII is 54% (recrystallized 21%), and

the other product to which they tentatively assigned the structure XXXI is obtained in 25% yield. Like the compound described in the patent, XXXI gives XXXII on treatment with concentrated sulfuric acid or aluminum chloride. XXXI, which melts at 380° , is soluble in alkaline solution with a yellow color, and with a faint yellow or orange color and blue-violet fluorescence in sulfuric acid. A molecular-weight determination by sodium hydroxide titration gave a value in excellent agreement with that calculated for the 4,9-diazapyrene compound (XXXI).

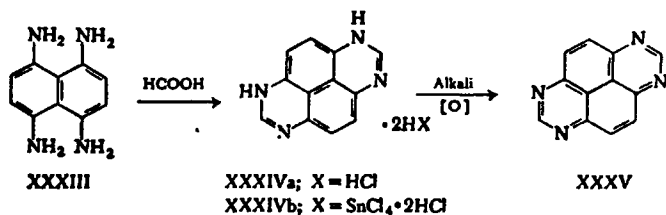
3. Tetrazapyrenes

The only tetrazapyrenes which have been reported in the literature are members of the 1,3,6,8-tetrazapyrene series, although sixty different tetrazapyrenes could exist. The first synthesis of a compound of this type occurred during the determination of the structure of naphthazarin.

1,3,6,8-Tetrazapyrene, Quinazo[6,5,4-*def*]quinazoline. R.I. 2649

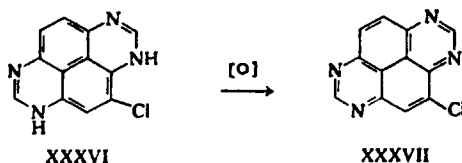


Inasmuch as Will²⁰ obtained naphthazarin (a dihydroxynaphthoquinone) *via* the reduction product from " δ -tetranitronaphthalene," which he had concluded was the 1,2,5,8-isomer,²¹ it was assumed for a good many years that naphthazarin was 1,2-dihydroxy-5,8-naphthoquinone, as had been postulated earlier. When Dimroth and Ruck²² observed that naphthazarin gave a diester rather than the expected monoester with pyroboracetate, they concluded that naphthazarin must be 1,4-dihydroxy-5,8-naphthoquinone, and that " δ -tetranitronaphthalene" must be the 1,4,5,8-isomer. The formation of 1,3,6,8-tetrazapyrene (XXXV) from the δ -tetranitro compound confirmed this conclusion.²³ Since perimidine is formed by the reaction of formic acid and 1,8-diaminonaphthalene,²⁴ the preparation of a double perimidine compound by Dimroth and Roos²⁵ established the structure of the tetranitro starting material as the 1,4,5,8-isomer.



Formic acid treatment of the tin double salt of the tetramine (XXXIII) obtained on reduction of 1,4,5,8-tetranitronaphthalene yields the tin double salt of "diperimidine" (XXXIVb), but a better yield of the brownish-red dihydrochloride of 1,8-dihydro-1,3,6,8-tetrazapyrene (XXXIVa) is obtained directly by reducing the tetranitro compound with stannous chloride in formic acid. The free base obtained on neutralizing XXXIVa oxidizes immediately in the air to the "imine," 1,3,6,8-tetrazapyrene (XXXV). This yellow compound is weakly basic and is reduced to a dihydro derivative by zinc but not by sulfur dioxide in acid solution. Very dilute solutions of XXXV in 13% hydrochloric acid are colorless, and the imine base is precipitated on the addition of water. The oxidized form of the base is best obtained, however, by ferric chloride oxidation of solutions of salts of the dihydro compound.

A monochloro derivative is obtained when fuming hydrochloric acid is added to the reddish-brown solution of XXXV in 20% hydrochloric acid; Dimroth and Roos²³ assigned to this product the structure XXXVI. On oxidation with ferric chloride, the reddish-brown needles of XXXVI are converted into the yellow imine form (XXXVII). On



heating the monochloro derivative with hydrochloric acid, a brown solution is obtained which turns yellow on addition of ferric chloride; the formation of a dichloro-1,3,6,8-tetrazapyrene probably takes place.

*

A summary of the data on azapyrenes follows in Table 40.

TABLE 40. Azapyrenes

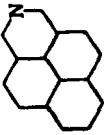
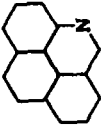
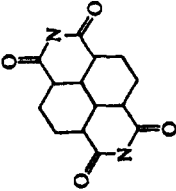
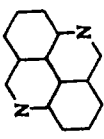
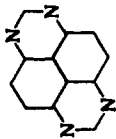
Formula	Compound	Ref.	Appearance	Properties
2-Azapyrenes:				
III	 1,3,6-Triketo-2-azapyrene	1	Yellow plates	Ins. cold OH^- ; sol. on warming—yellow-brown
4-Azapyrenes:				
V	 4-Azapyrene	2,6	Colorless needles	m. 157–159°; blue Fl O; double salts; yellow solution $\cdot \text{HCl}$ blue-green Fl; yellow solution $\cdot \text{MeI}$ (m. 240°) with blue Fl; $\cdot \text{P}$ m. 250–253°
VIIa	5-Methyl-4-azapyrene	6	Colorless thick rhombs	m. 139–141°; orange-yellow $\cdot \text{P}$ m. 240–241°
VIIb	5-Phenyl-4-azapyrene	6	Colorless silky needles	m. 143–144°; golden-yellow $\cdot \text{P}$ m. 256–258°
XI or XIa	3,8- (or 1,6-) Dimethoxy-4-azapyrene	4	Orange leaflets	m. 229–230°; blue Fl O; orange $\cdot \text{P}$, green Fl dec. 255°; orange in HCl green Fl; green Fl S

Table continued

VII. Azapyrenes

TABLE 40. Azapyrenes (Continued)

Formula	Compound	Ref.	Appearance	Properties
1,3,6,8-Tetraketo-1,2,3,6,7,8-hexahydro-2,7-diazapyrenes: 				
XIV	Unsubstituted	1,9	Yellow needles	Sublimes $>270^\circ$ diff. sol. O; yellow Na salt m. 400° ; yellow S; blue-green V with red fl
XVIII	4,9-Dichloro-2,7-diphenyl-	12	Almost colorless needles	
	2,7-Di($-\text{CH}_2\text{CH}_2\text{Br}-$)-	13	White micro needles	m. $250-251^\circ$; diff. sol. O
	2,7-Di($-\text{CH}_2\text{CH}_2\text{Cl}-$)-	13	White needles	m. $288-289^\circ$; diff. sol. O
	2,7-Di($-\text{CH}_2\text{CH}_2\text{I}-$)-	13	White needles	m. $293-294^\circ$; diff. sol. O
XIX	4-Anilino-9-chloro-2,7-diphenyl-	12	Red needles	
XX	4,9-Dianilino-2,7-diphenyl-	12	Dark blue metallic needles	m. 400° ; reddish-blue S; gives $x\text{-SO}_3\text{H}$ dyeing wool blue
	2,7-Di($-\text{CH}_2\text{CH}_2\text{NHSO}_2\text{C}_6\text{H}_4\text{CH}_2\text{-p-}$)-	13	Red powder	Sinters 215° ; m. 260°
	2,7-Di($-\text{CH}_2\text{CH}_2\text{N} \begin{array}{c} \diagup \text{CO} \diagdown \\ \diagdown \text{CO} \diagup \end{array} \text{C}_6\text{H}_4 \text{-}$)-	13	—	Very diff. sol. O
	2,7-Di($-\text{CH}_2\text{CH}_2\text{N} \begin{array}{c} \diagup \text{CO} \diagdown \\ \diagdown \text{CO} \diagup \end{array} \text{C}_6\text{H}_4\text{NO}_2 \text{-}$)-	13	—	—

Formula	Compound	Ref.	Appearance	Properties
	2,7-Di(-CH ₂ CH ₂ OH)-	13	Fairly yellow needles	m. > 360°
	2,7-Di(-CH ₂ COOH)-	13	Beige leaflets	Darken 389°
	2,7-Di(-CH ₂ COCl)-	13	—	—
	2,7-Di(-CH ₂ CONH ₂)-	13	Gray powder	Diff. sol. O
	2,7-Di(-CH ₂ CH ₂ CONH ₂)-	13	White powder	Diff. sol. O
	2,7-Di(-CH ₂ COOC ₂ H ₅)-	13	White crystals	m. 304-305°
	2,7-Di(-CH ₂ CH ₂ COOC ₂ H ₅)-	13	White crystals	—
	 4,9-Diazapyrenes:			
XXV	5,10-Diketo-4,9-diazapyrene	15	Pale yellow needles	Sublimes, m. > 300°; diff. sol. O; blue Fl S
XXIX	2,7-Diamino-5,10-diketo-4,9-diazapyrene·H ₂ SO ₄	17	Yellow plates turn green in air	Charring by 300°; also green hemisulfate
XXXI	5,10-Di-(2'-carboxyphenyl)-4,9-diazapyrene	18, 19	—	m. 380°; yellow OH ⁻ ; yellow S with blue-violet Fl
	 1,3,6,8-Tetrazapyrenes:			
XXXV	Unsubstituted	23	Yellowish needles	Diff. sol. O; sol. H ⁺ , weakly basic
XXXIV	3,6-Dihydro-1,3,6,8-tetrazapyrene·2HCl	23	Red-brown needles	Sol. H ₂ O—red-brown
XXXVII	4-Chloro-1,3,6,8-tetrazapyrene	23	Yellow crystals	—
XXXVI	4-Chloro-3,6-dihydro-1,3,6,8-tetrazapyrene·2HCl	23	Red-brown needles	Probably gives diCl derivative

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Azabenzanthrenes: Addendum

BY C. V. WILSON

1. 2-Keto-3-methyl-3-azabenzanthrones¹

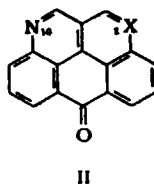
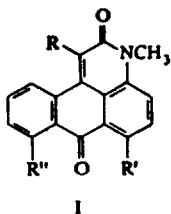
Since the original manuscript was prepared several new dyes in this series have become known; furthermore, others were shown in the text (page 226) only in a set of curves. It seems advisable to make this survey as complete as possible, and to include all of them as an addendum in this volume.

They were all prepared by the same general reaction (page 219), treatment of a halogen compound with the appropriate amine to give a "dye base," with a subsequent sulfonation. Two properties, the melting points of the dye bases (I, $R'' = H$) and the absorption maxima of the dyes, are recorded in Table 41. In a few instances the absorption maxima of the dye bases are also recorded. Although the amine used was usually aromatic, there were a few in the aliphatic series.

While most of the substances have the amino residue in the 6-position (I, $R'' = H$), there are a very few representatives in which the 8-position is so occupied (I, $R' = H$). In these instances the closing of the nitrogenous ring proceeded successfully with chloroacetylaminanthraquinones, but not when ethyl malonate and 1-methylamino-5-chloroanthraquinone were used (cf. pages 214-215).

When 1-methylamino-8-chloroanthraquinone was allowed to react with ethyl malonate, with the expectation of obtaining an 11-chloro-3-azabenzanthrone as an intermediate, the chlorine was lost. An abnormal product likewise resulted with 1,8-bis(methylamino)anthraquinone. It is tentatively suggested that these two substances contain the pentacyclic 2-oxa-10-aza- or 2,10-diazabenzoc[*c,d*]pyrene system (II).

The properties of the dye bases and dyes are collected in Tables 41-43.

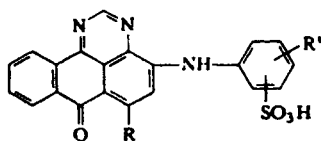


In a recent patent² 1-acetyl-6-(*o*-alkylaryl-amino)-2-keto-4-sulfo-3-azabenzanthrones are described as dyes for cellulose acetate (cf. p. 218).

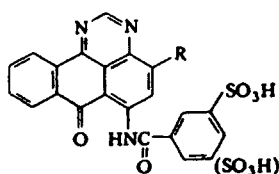
2. 1,3-Diazabenzanthrones

A. Aryl Group in the 4-Position

A number of these were made by the general procedure (page 275).¹ The absorption curves of the 6-amino derivatives showed two maxima. Their properties are collected in Table 44.



III



IV

B. Sulfobenzoylation³⁻⁵

The difficulty of isolation of dyes formed by the sulfonation of 6-acylamido-1,3-diazabenzanthrones was mentioned on page 285. A complicating factor is the ease of hydrolysis of the aroylamido link, which leads to regeneration of the amine initially used. It has been found¹ that if the amine is sulfobenzoylated, using 3- or 3,5-di-(chlorosulfonyl)-benzoic acid, the dyes formed are easily isolated, and there is no hydrolysis. The properties of several of these dyes are given in Table 45.

Usually, when a polynuclear amine is acylated, the absorption is moved to a shorter wave length (*e.g.*, a red amine gives a yellow acyl-amide). In the 4-aryl-amino-6-amino-1,3-diazabenzanthrone series the shift is in the opposite direction.

TABLE 41. 2-Keto-3-methyl-3-azabenzanthrones (I, R' = H)

R	R'	M.p., °C. of base	Max. absorption, mμ		Ref.
			of base	of dye	
CH ₃ CO	4-CH ₃ C ₆ H ₄ NH	210-212	548	547 ^a	6
CH ₃ CO	3-CH ₃ C ₆ H ₄ NH	186-188	546	540	6
CH ₃ CO	4-CH ₂ OC ₆ H ₄ NH	145-148	541	543	6
CH ₃ CO	4- <i>t</i> -C ₆ H ₁₁ C ₆ H ₄ NH	270-272	540	534	6
CH ₃ CO	4-ClC ₆ H ₄ NH	243-245	534	—	6
CH ₃ CO	4- <i>s</i> -C ₆ H ₁₁ C ₆ H ₄ NH	95-97 ^b	548	548	1
CH ₃ CO	3-CF ₃ C ₆ H ₄ NH	159-161	536	—	1
CH ₃ CO	2,4-(CH ₃) ₂ C ₆ H ₃ NH	208-210	543	—	1
CH ₃ CO	2,5-(CH ₃) ₂ C ₆ H ₃ NH	203-204	543	544	1
CH ₃ CO	2,6-(CH ₃) ₂ C ₆ H ₃ NH	277-279	—	—	1

TABLE 41. (Continued)

R	R'	M.p., °C. of base	Maximum absorption, m μ		Ref.
			of base	of dye	
CH ₃ CO	3,5-(CH ₃) ₂ C ₆ H ₃ NH	210–212	542	—	1
3-CH ₃ C ₆ H ₄ NH	H	244–245	—	456	6
4-CH ₃ C ₆ H ₄ NH	H	239–240	—	463	6
4-CH ₃ OC ₆ H ₄ NH	H	189–190	—	467	6
3-ClC ₆ H ₄ NH	H	252–253	—	450	6
4-ClC ₆ H ₄ NH	H	238–239	—	455	6
2,5-Cl ₂ C ₆ H ₃ NH	H	194–195	—	440	6
3-CF ₃ C ₆ H ₄ NH	H	244–245	—	447	6
HOCH ₂ CH ₂ NH	H	204–206	—	440	6
4-CH ₃ C ₆ H ₄ NH	4-CH ₃ C ₆ H ₄ NH	246	535	—	7
COOC ₂ H ₅	HOCH ₂ CH ₂ NH	240–242	—	521, 551	6
COOC ₂ H ₅	(CH ₃) ₂ N(CH ₃) ₂ NH	177–180	—	519, 550	1
COOC ₂ H ₅	4-CH ₃ C ₆ H ₄ NH	202–204	—	542	6
COOC ₂ H ₅	4-C ₂ H ₅ C ₆ H ₄ NH	174–176	—	540	6
COOC ₂ H ₅	4- <i>i</i> -C ₃ H ₇ C ₆ H ₄ NH	195–197	—	543	6
COOC ₂ H ₅	4- <i>r</i> -C ₃ H ₇ C ₆ H ₄ NH	148–150	—	546	6
COOC ₂ H ₅	4- <i>t</i> -C ₃ H ₇ C ₆ H ₄ NH	198–200	—	542	6
COOC ₂ H ₅	4-CH ₃ OC ₆ H ₄ NH	183–184	—	546	6
COOC ₂ H ₅	3-CF ₃ C ₆ H ₄ NH	—	—	525	6
COOC ₂ H ₅	2,4-(CH ₃) ₂ C ₆ H ₃ NH	199–201	—	548	6
COOC ₂ H ₅	3-ClC ₆ H ₄ NH	—	—	520	6
COOC ₂ H ₅	4-ClC ₆ H ₄ NH	215–217	—	532	6
COOC ₂ H ₅	4-BrC ₆ H ₄ NH	—	—	532	6
CN	4-CH ₃ C ₆ H ₄ NH	> 300	—	580	6
CN	4-C ₂ H ₅ C ₆ H ₄ NH	310–314	—	584	6
CN	4- <i>r</i> -C ₃ H ₇ C ₆ H ₄ NH	Indef.	—	590	6
CN	4- <i>t</i> -C ₃ H ₇ C ₆ H ₄ NH	Indef.	—	590	6
CN	2,4-(CH ₃) ₂ C ₆ H ₃ NH	343–350	—	587	6
CN	4-CH ₃ OC ₆ H ₄ NH	> 350	—	588	6
CN	4-CH ₃ COC ₆ H ₄ NH	> 360	—	568	6
CN	3-ClC ₆ H ₄ NH	332–334	—	564	6
CN	4-ClC ₆ H ₄ NH	368–372	—	554	6
CN	4-CNC ₆ H ₄ NH	> 360	—	570	6
C ₆ H ₅	4-CH ₃ C ₆ H ₄ NH	248–250	—	535	6
C ₆ H ₅	4- <i>r</i> -C ₃ H ₇ C ₆ H ₄ NH	232–234	—	536	6
C ₆ H ₅	4- <i>t</i> -C ₃ H ₇ C ₆ H ₄ NH	281–282	—	536	6
C ₆ H ₅	2,4-(CH ₃) ₂ C ₆ H ₃ NH	199–200	—	546	6
C ₆ H ₅	4-CH ₃ OC ₆ H ₄ NH	245–246	—	538	6
C ₆ H ₅	4-ClC ₆ H ₄ NH	283	—	525	6
C ₆ H ₅	(CH ₃) ₂ N(CH ₃) ₂ NH	240–242	—	526, 552	1
C ₆ H ₅ CO	4-CH ₃ C ₆ H ₄ NH	276–277	—	544	6
C ₆ H ₅ CO	4-CH ₃ OC ₆ H ₄ NH	255–257	—	545	6
C ₆ H ₅ CO	4-ClC ₆ H ₄ NH	302–304	—	538	6

* The 4-sulfo isomeric dye has a peak at 550.

* This dye base contains solvent of crystallization.

TABLE 42. 2-Keto-3,4-dimethyl-3-azabenzanthrones (I, R' = H)

R	R'	M.p., ° C. of base	Max. absorption, m μ		Ref.
			of base	of dye	
4-CH ₃ C ₆ H ₄ NH	H	231-233	—	464	6
COOC ₂ H ₅	4-CH ₃ C ₆ H ₄ NH	190-192	—	545	6

TABLE 43. 2-Keto-3-methyl-3-azabenzanthrones (I, R' = H)

R	R'	M.p., ° C. of base	Maximum absorption, m μ		Ref.
			of base	of dye	
H	4-CH ₃ C ₆ H ₄ NH	217-219	400, 503	527	1
H	3-ClC ₆ H ₄ NH	232-234	430, 490	508	1
CN	4-CH ₃ C ₆ H ₄ NH	332-334	430, 540	—	1

TABLE 44. 4-Arylamino-1,3-diazabenzanthrones (III)

R	R'	M.p., ° C. of base	Maximum absorption, m μ		Ref.
			of base	of dye (x'-sulfo)	
H	4-CH ₃	195	495	513	1
NH ₂	4-CH ₃	300-302	450, 480	467	1
NH ₂	4-OCH ₃	284	455, 480	474	1
NH ₂	3-Cl	288	456, 483	461	1
NH ₂	4-(CH ₃) ₂ N	275	483	—	1

TABLE 45. 6- (or 8-) [3'-Sulfo- (or 3',5'-disulfo-) aroylamido] -1,3-diazabenzanthrones (IV)

R	6 or 8	Mono- or disulfo	Maximum absorption, m μ	Ref.
4-CH ₃ C ₆ H ₄ NH ^a	6	di	525 (422)	1
H ^b	6	mono	434	1
H	8	mono	437	1
4-CH ₃ C ₆ H ₄ NH	6	mono	504	1
3-ClC ₆ H ₄ NH	6	di	506	1
4-CH ₃ OC ₆ H ₄ NH	6	di	520	1
4-C ₆ H ₄ C ₆ H ₄ NH	6	di	520	1

^a Good light stability.^b Poor light stability.

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