# THE CHEMISTRY OF PHENANTHRIDINE AND ITS DERIVATIVES

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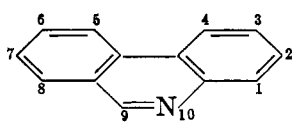
CONTENTS

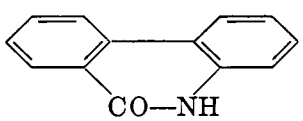


## I. HISTORICAL INTRODUCTION

Although three systems (7, 10, 61) of numbering the phenanthridine (benzo[*c*]-quinoline) nucleus have been advanced, the literature, until quite recently, adopted almost exclusively that of Beilstein's *Handbuch* (see formula I). The present review will therefore follow this method.




I

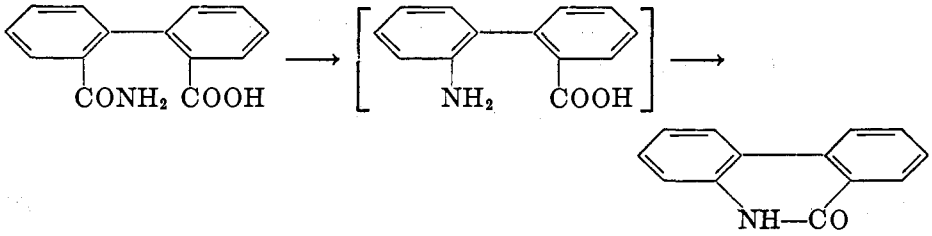



II

Both phenanthridine and 9(10)-phenanthridone (II) are products of the destructive distillation of coal, the former being isolated (59, 82) to the extent of 50 g. per 35 kg. of high-boiling anthracene oil bases, and the latter occurring (45) as 1 per cent of coal tar pitch. Neither source is of commercial importance. In addition, a small group of alkaloids, comprising chiefly chelidonine (15, 85), tazettin (84), and lycorin (38, 41, 42), have been shown to contain the phenanthridine skeleton. These natural products will not be considered in the present review.

The discovery of phenanthridine was reported in 1889 by Pictet and Ankersmit (66), who obtained it from the pyrolysis of benzylideneaniline at bright-red heat. It is possible, however, that the first specimen was prepared some five years earlier by Gräbe (29) in a similar experiment carried out at a slightly lower

temperature. Phenanthridone was first synthesized by Gräbe and Wander (31) in 1893 by a Hofmann reaction on 2,2′-amidobiphenylcarboxylic acid.




Distillation with zinc dust afforded the parent base.

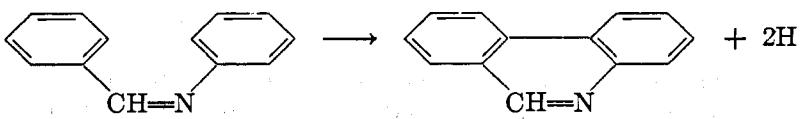
Over the next forty years several new syntheses of phenanthridine and phenanthridone were described, but the number of substituted derivatives remained surprisingly small. It was not until the potential therapeutic interest of the series was recognised in 1931 by Morgan and Walls (55) that systematic study resulted. The improved method of preparation of phenanthridines used by these workers proved to be of wide application, but a further seven years elapsed before the outstanding trypanocidal activity of some phenanthridinium compounds became apparent (14). Over the last decade the search for therapeutic agents of this type has commanded increasing attention.

## II. METHODS OF SYNTHESIS OF PHENANTHRIDINES

A variety of methods exists for the preparation of both substituted and unsubstituted phenanthridines, and of these five are worthy of some discussion.

### *A. Pyrolytic methods*

Firstly there may be considered together the several pyrolytic syntheses resorted to especially by earlier workers in the field. As already mentioned, phenanthridine itself is formed when the vapor of benzylideneaniline is passed through a pumice-filled tube at bright-red heat (66). Fractionation of the product




removes benzene, benzonitrile, aniline, and some biphenyl which also arise, and the phenanthridine is isolated as its crystalline mercurochloride (67). Meyer and Hofmann (50) subjected the Schiff base to the continuous action of an electrically heated platinum spiral. The increasing proportion of phenanthridine formed with rising temperature, with consequent decrease in the benzonitrile and benzene content, has been used (27) as an argument for the simultaneous *trans* → *cis* conversion of benzylideneaniline, and this theory receives some support from dipole moment evidence. Small amounts of phenanthridine may also be obtained from a similar decomposition of benzylaniline (69), though the reaction is a far more profitable source of acridine (50).

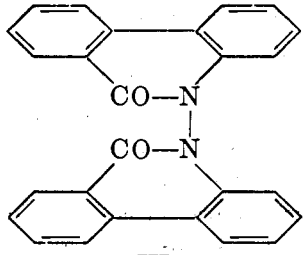
The highest recovery of phenanthridine in this type of synthesis undoubtedly results from the thermal rearrangement of *N*-methylcarbazole (65), and a technique recently described by de Diesbach and Aeschbach (23) gives 50 per cent of the desired product from a continuous process. When benzanilide vapor is passed over red-hot pumice a small proportion of phenanthridone results (69), and conversion is said to be very efficient on a platinum spiral (50).

Pyrolytic methods have had almost no application to the preparation of substituted derivatives, the sole recorded examples being 1- and-3-methylphenanthridines, obtained from the corresponding benzylidenetoluidines (68).

### *B. Dehydration of 2-aminobiphenyl-2'-carboxylic acid*

Several syntheses of phenanthridone, and hence of phenanthridine, can be imagined as involving the intermediate formation of 2-aminobiphenyl-2'-carboxylic acid, which undergoes spontaneous dehydration to the lactam structure. The amino acid may arise from reduction of the nitro compound, from a Hofmann or Curtius reaction on diphenic acid, or from the ring cleavage of 4-aminofluorenone.

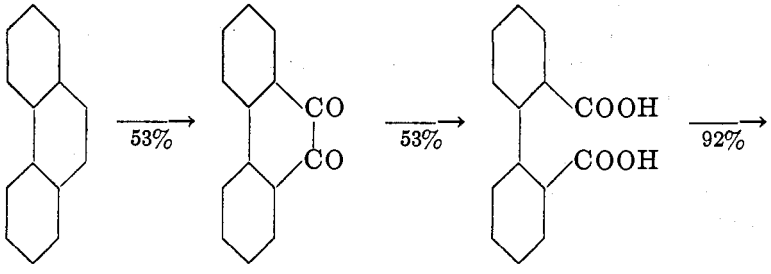
The first route is not satisfactory for phenanthridone itself (31), a large proportion of the product consisting of a substance, m.p. > 340°C., probably III. Pictet and Ankersmit (67) wrongly believed this compound to be phenanthridone, since distillation with zinc dust yielded the desired base. Reduction of

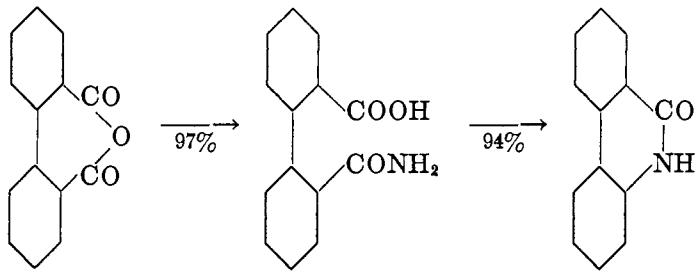



III

4,6,4'-trinitrodiphenic acid with tin and hydrochloric acid is reported (20) to lead successfully to 2,7-diaminophenanthridone-4-carboxylic acid.

A Hofmann reaction on diphenimide, or preferably the corresponding monoamide (31), thus avoiding one step, proceeds smoothly and is adaptable to the large-scale preparation of phenanthridone from phenanthrene (60).






This method has seen a limited application to substituted derivatives, 2,7-diacetamido- (2), 2- and 7-nitro- (51), and 8-methyl-2-isopropylphenanthridones (1) having been prepared.

The Curtius degradation of diphenic monoazide in ether–ethanol or in various alcohols saturated with hydrogen chloride leads to phenanthridone or its *N*-carbalkoxy derivatives, respectively (46, 47).

Phenanthridone (15a) is formed in 77 per cent yields by cyclization of *o*-biphenyl isocyanate with aluminum chloride in *o*-dichlorobenzene as the solvent.

An almost quantitative recovery of phenanthridone from the fusion of 4-aminofluorenone with potash at 260°C. is claimed (30), but 7-nitrophenanthridone cannot be secured in this way (51), owing to its sensitivity to the reagent. No other examples have been tried.

### *C. Beckmann and Schmidt rearrangements*

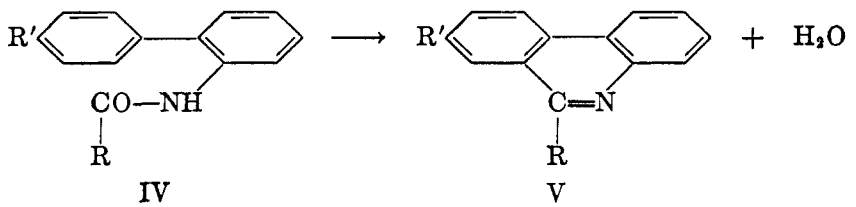
Ring enlargement of fluorenone by means of the Beckmann or Schmidt rearrangement leads to phenanthridone. Using a mixture of phosphorus pentachloride and oxychloride Beckmann and Wegerhoff (6) in 1889 obtained from fluorenone oxime a small amount of an uninvestigated yellow powder, m.p. 287°C., many years later identified (52) as phenanthridone. In the meantime Pictet (64, 69) had achieved more success in the rearrangement with zinc chloride at 260–280°C., but his yields of 30 per cent were not subsequently confirmed by Kerp (39). Sulfuric acid, or hydrogen chloride in acetic anhydride, is reported to be ineffective (6), causing sulfonation and acylation, reaspectively.

The product given by 2-nitrofluorenone oxime in a refluxing mixture of phosphorus pentachloride and oxychloride was considered by Moore and Huntress (52) to be an equilibrium mixture of the oxime chloride and 9-chloro-7-nitrophenanthridine. Subsequent hydrolysis with undried chlorobenzene, acetic acid, or 50 per cent sulfuric acid appeared to cause progressive conversion to 7-nitrophenanthridone, ultimately isolated in 90 per cent yield. Since it has been shown (86) that oxime chlorides do not figure as intermediates in the Beckmann rearrangement, it appears likely that the primary product is partially hydrolyzed 9-chloro-7-nitrophenanthridine. The stereochemically pure oxime of an unsymmetrically substituted fluorenone can rearrange to only one phenanthridone isomer, and this is borne out in the case of retenone oxime, where 7-isopropyl-1-methylphenanthridone arises (1, 9).

In an inert solvent, e.g., benzene, fluorenone reacts with hydrazoic acid in the presence of sulfuric acid to give phenanthridone (32, 35). When the sulfuric acid is used as both solvent and catalyst, recovery approaches the theoretical (83), and the method forms the most convenient laboratory preparation of phenanthridone. Under these latter conditions, 2-nitrofluorenone gives, as would be expected, a mixture of 2- and 7-nitrophenanthridones (89), contrasting with an earlier patent (35) which infers the production of only the 2-isomer. The appropriate fluorenones (89) also lead to mixtures of 2- and 7-amino-, hydroxy-, and methoxy-phenanthridones, and to 2,7-dinitrophenanthridone. Caronna (17), however, would seem to have isolated only 7-isopropyl-1-methylphenanthridone from a Schmidt reaction on retenone.

### *D. Morgan–Walls reaction*

The most generally applicable method for synthesizing substituted phenanthri-




dines involves the cyclodehydration of acyl-*o*-xenylamines (IV), and was due originally to Pictet and Hubert (70), who heated a mixture of the anilide with zinc chloride at 250–300°C. until evolution of hydrogen chloride ceased. Phenanthridine itself, in unstated yield, was thus secured from *o*-formamidobiphenyl, whilst phenanthridone resulted from the removal of the elements of ethanol from *o*-diphenylurethan.

Morgan and Walls (55) in 1931 avoided the disadvantages attending the use of zinc chloride, such as long heating, wasteful purification, and inapplicability to reactive substituents, by employing phosphorus oxychloride as the dehydrating agent. In the case of *o*-formamidobiphenyl itself this modification was unsuccessful, but the original procedure, combined with a new purification technique (56), realized a 42 per cent yield of phenanthridine. Where ring closure with phosphorus oxychloride alone proceeds with difficulty, the inclusion of a high-boiling solvent has often marked beneficial effect (57, 90). The especial suitability of nitrobenzene in this connection is probably associated also with its known ionizing properties (92).

The use of aluminum chloride as condensing agent has been recorded (24) only for the very stable *o*-phthalimidobiphenyl, the conversion of which to 9-(*o*-carboxyphenyl)phenanthridine has also been carried out with zinc chloride (40). The examples of this general phenanthridine synthesis which have appeared to date (May, 1949) are listed in table 1.

The efficiency of cyclization shows some dependence both on nuclear substituents and on the nature of the acyl grouping. In a recent discussion (75) of

TABLE 1

*Phenanthridines from acyl o-xenylamines*

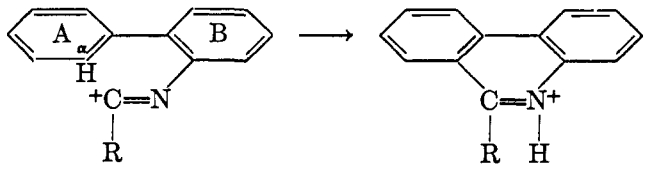
| PHENANTHRIDINE | REAGENT* AND TIME | YIELD | MELTING POINT | REFERENCE |
|---|---|---|---|---|
| | | *per cent* | °C. | |
| 9-Methyl- | a, 1 hr. | 70 | 84 | (55) |
| | b, — | | 85 | (70) |
| 9-ω-Chloromethyl- | a, — | 80 | 134 | (55) |
| 9-Ethyl- | a, 1 hr. | 80 | 56.5 | (55) |
| | b, — | | 54 | (70) |
| 9-Phenyl | a, 1 hr. | 75 | 105 | (55) |
| | b, — | | 109 | (70) |
| 9-*o*-Nitrophenyl- | a, 2 hr. | 74 | 122.5 | (55) |
| 9-*m*-Nitrophenyl- | a, 2 hr. | 61 | 172 | (55) |
| 9-*p*-Nitrophenyl- | a, 3 hr. | [65] | 192 | (55) |
| 9-(3′,5′-Dinitrophenyl)- | c, 12 hr. | | 294 | (90) |
| 9-Benzyl- | a, 1 hr. | 20 | 112 | (75) |
| 9-*p*-Nitrobenzyl- | a, — | 65 | 168 | (16) |
| 9-Carbethoxy- | a, — | Small | 58 | (88) |
| 9-(Methyl butyrate) | a, 1 hr. | 65 | 71 | (75) |
| 9-(Ethyl valerate) | a, 1 hr. | 45 | 54 | (75) |
| 9-Phenylethyl- | a, 1 hr. | 70 | 93 | (75) |
| 9-Phenoxymethyl- | a, 1 hr. | 65 | 142 | (75) |
| 9-*o*-Carboxyphenyl- | b, 1 min. | 80 | 268 | (40) |
| | d, — | | 266 | (24, 25, 37) |
| 9-(2,4,6-Trimethylphenyl)- | a, 5 min. | 90 | 157 | (75) |
| 9-α-Naphthyl- | a, 5 min. | 70 | 125 | (75) |
| 9-Styryl- | a, 1 hr. | 12 | 133 | (75) |
| 9-(3′-Pyridyl)- | c, 20 hr. | 72 | 125 | (63) |
| 2,9-Dimethyl- | a, 1 hr. | 75 | 104 | (62, 78) |
| 2-Methyl-9-phenyl- | a, 1 hr. | 90 | 120 | (78) |
| 2-Carbethoxyamino-9-methyl- | a, ½ hr. | 70 | 197 | (16) |
| 2-Carbethoxyamino-9-*p*-nitrophenyl- | a, ¾ hr. | 40 | 258 | (16) |
| 3-Nitro-9-methyl- | a, — | 80 | 201 | (56) |
| 3-Nitro-9-*o*-nitrophenyl- | a, — | Small | 227 | (56) |
| 3-Nitro-9-*m*-nitrophenyl- | c, — | | 269 | (90) |
| 3-Nitro-9-*p*-nitrophenyl- | a, 30 hr. | 60 | 294 | (58) |
| 3-Nitro-9-(3′-pyridyl)- | c, 20 hr. | 94 | 250 | (63) |
| 3-Bromo-9-methyl- | a, ½ hr. | 85 | 130 | (5, 89) |
| 3-Bromo-9-*p*-bromophenyl- | c, 2 hr. | 100 | 234 | (5) |
| 3-Cyano-9-methyl- | a, ½ hr. | 31 | 202 | (5) |

* a, $POCl_3$ alone; b, fused $ZnCl_2$; c, $POCl_3/C_6H_5NO_2$; d, fused $AlCl_3$; e, $P_2O_5$ in xylene.

TABLE 1—*Concluded*

| PHENANTHRIDINE | REAGENT* AND TIME | YIELD | MELTING POINT | REFERENCE |
|---|---|---|---|---|
| | | *per cent* | °C. | |
| 6-Carbethoxyamino-9-methyl- | a, ½ hr. | 84 | 163 | (16) |
| 6-Carbethoxyamino-9-*p*-nitrophenyl- | a, 1 hr. | 35 | 248 | (16) |
| 7-Nitro-9-methyl- | a, — | 4 | 243 | (56, 62) |
| 7-Nitro-9-phenyl- | c, 12 hr. | 90 | 237 | (90) |
| 7-Nitro-9-*m*-nitrophenyl- | c, 12 hr. | 85 | 269 | (90) |
| 7-Nitro-9-*p*-nitrophenyl- | a, 30 hr. | 30 | 327 | (58) |
| 7-Nitro-9-(3′-pyridyl)- | c, 24 hr. | 37 | 292 | (63) |
| 7-Benzamido-9-methyl- | a, — | 62 | 214 | (62) |
| 7-Carbethoxyamino-9-methyl | a, 1 hr. | 90 | 205 | (91) |
| 7-Carbethoxyamino-9-*o*-nitrophenyl- | a, 1 hr. | 60 | 199 | (91) |
| 7-Carbethoxyamino-9-*p*-nitrophenyl- | a, — | | 253 | (91) |
| 7-Carbethoxyamino-9-*p*-nitrobenzyl- | a, 1 hr. | 99 | 186 | (16) |
| 8-Carbethoxyamino-9-methyl- | a, ½ hr. | 12 | 160 | (16) |
| 8-Carbethoxyamino-9-*p*-nitrophenyl- | a, 1 hr. | 45 | 194 | (16) |
| 2,7-Dinitro-9-phenyl- | c, 20 hr. | 65 | 261 | (79, 90) |
| 2,7-Dibromo-9-methyl- | a, 3 hr. | 7 | 186 | (74) |
| 2,7-Dibromo-9-phenyl- | c, 6 hr. | 95 | 201 | (74) |
| 2,7-Biscarbethoxyamino-9-methyl- | a, 1 hr. | 70 | 252 | (91) |
| 2,7-Biscarbethoxyamino-9-phenyl- | a, ¼ hr. | 50 | 222 | (93, 91) |
| 3,7-Dinitro-9-methyl- | — — | | | (19) |
| 3,7-Dinitro-9-phenyl- | c, 18 hr. | 50 | 277 | (58, 90) |
| 3-Bromo-7-nitro-9-*p*-nitrophenyl- | c, 12 hr. | High | 348 | (90) |
| 4,5-Dimethyl-9-*p*-nitrophenyl- | c, 5 hr. | 70 | 163 | (76) |
| 4,5-Dimethyl-9-phenyl- | c, 5 hr. | 70 | Gum | (76) |
| 2,3,6,7-Tetramethoxy- | e, 3 hr. | 5 | 185 | (73) |
| 2,3,6,7-Tetramethoxy-9-methyl- | a, 1 hr. | 85 | 212 | (73) |
| 2,3,6,7-Tetramethoxy-9-ethyl- | a, 1 hr. | 85 | 202 | (73) |
| 2,3,6,7-Tetramethoxy-9-phenyl- | a, 1 hr. | 90 | 207 | (73) |

the mechanism of the reaction, Ritchie envisages the initial step as the formation of a carbonium ion (VI) under the influence of the strong acid, phosphorus oxychloride.



VI

Electrophilic addition of the positively charged carbon atom to the $\alpha$-carbon atom of the heteronucleus (A), and capture of the released proton by the lone pair of the nitrogen atom then complete the synthesis. The ease of formation and stability of the carbonium ion, together with the electron density at the anticipated position of attack, therefore control the cyclization process.

The first two of these factors are governed mainly by the nature of R, ion-formation being faciliated by an increase in its electron-donating properties. Thus benzamidobiphenyls (R = $C_6H_5$) usually cyclize readily, whereas di- and tri-chloroacetamidobiphenyls (R = $CHCl_2$,$CCl_3$) are recovered unchanged from treatment with phosphorus oxychloride (88). The actual size of the acyl grouping appears to exert no important effect upon cyclization (75).

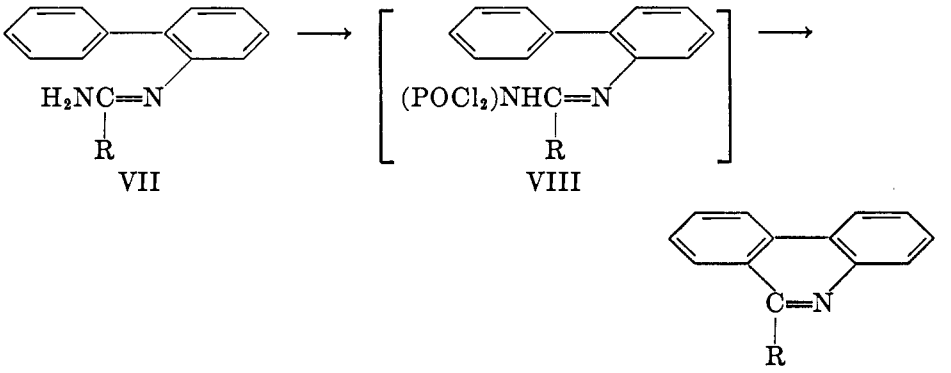
The rate of ring closure is chiefly dependent on the availability of electrons at the ortho positions of nucleus A, and where this nucleus is strongly deactivated the carbonium ion must be highly stable in order to escape decomposition until the process is complete. This is seen in the fact that 7-nitro-9-phenylphenanthridine (V: R = $C_6H_5$, R′ = $NO_2$) be obtained in 90 per cent yield (90), whereas 2-acetamido-4′-nitrobiphenyl (IV: R = $CH_3$, R′ = $NO_2$) is cylized to the extent of only 4 per cent, owing to the greater instability of the acetamido radical (56). In consequence, 7-amino-9-methylphenanthridine is conveniently synthesized by taking advantage of the favorable electron-donating properties of the carbethoxyamino group (91).

When a heteronuclear substituent is placed meta to the biphenyl linkage ring closure in two directions becomes possible, and in the case of electron-releasing groups the ortho:para ratio is, as would be expected, usually less than unity. An interesting exception is 3′-carbethoxyamino-2-*p*-nitrobenzamidobiphenyl, where electrostatic attraction between the carbonium ion and the carbonyl oxygen of the urethan group is believed to be responsible for enhanced ortho condensation (16).

Deactivating substituents in ring B of VI exert little influence, and, provided ion formation is possible, ring closure is a rapid process, e.g., 9-methyl-3-nitrophenanthridine (80 per cent).

Very recently (21) a synthesis closely related to the Morgan–Walls reaction has been discovered. Elimination of the elements of ammonia from *N*-2-biphenylamidines (VII) by phosphorus oxychloride in boiling nitrobenzene provides the corresponding phenanthridines in yields which are in several cases higher than

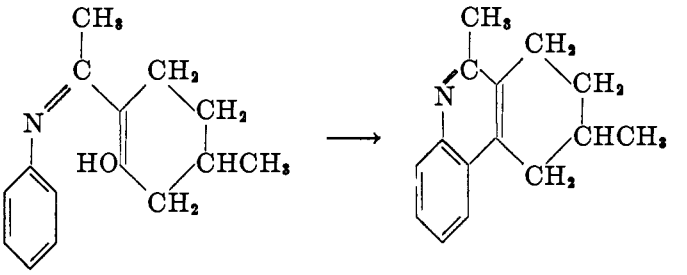
those given by the *o*-acylaminobiphenyls. Omission of nitrobenzene enables the labile intermediates




(VIII) to be isolated, but in the higher-boiling solvent these are converted to phenanthridines. The effect of deactivating substituents in the heteronucleus is somewhat less pronounced, recovery of 2,7-dinitro-9-phenylphenanthridine reaching 80 per cent, as compared with the 65 per cent yield of the earlier method (90). As far as can be judged from this preliminary investigation, the main disadvantage of the synthesis lies in the greater difficulty of obtaining the necessary starting materials.

*E. Methods for producing hydrogenated phenanthridines*

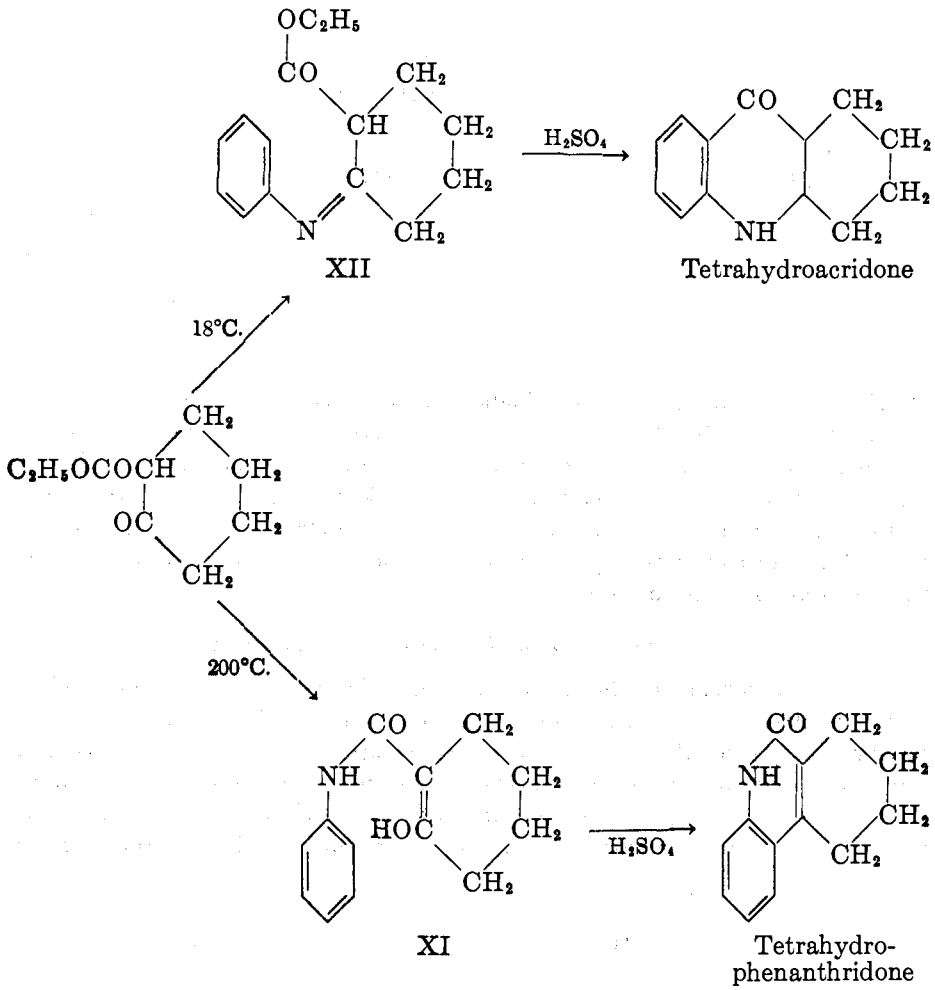
Various hydrogenated phenanthridines have been synthesized from anilines and derivatives of cyclohexanone, two modifications (33, 38) of this reaction having a fairly general application. The first example, reported in 1910 by Borsche (10), consisted in condensing 4-acetyl-1-methylcyclohexan-3-one with aniline at 150°C., and cyclizing the resultant anil (IX) with sulfuric acid to 6,9-dimethyl-5,6,7,8-tetrahydrophenanthridine (X) in 15 per cent overall yield. Simultaneous




IX X

condensation at the ring carbonyl group gave the isomeric anil, cyclizing to an acridine derivative, this being the only product isolated when the initial stage was carried out at room temperatures. An even closer analogy with the well-known aniline and acetoacetic ester condensation is provided by the reaction between aniline and ethyl cyclohexanone-2-carboxylate, which was investigated

in 1929 by two groups of workers (8, 80). The degree of anilide (XI) as opposed to anil (XII) formation increases with temperature as shown.




3-Methyl and 1,3-dimethyl-5,6,7,8-tetrahydrophenanthridones were also obtained (80) from the corresponding anilines.

By heating a mixture of 2-hydroxymethylcyclohexan-1-one, aniline, and aniline hydrochloride to 100°C., Kenner, Ritchie, and Statham (38) were able to carry out condensation and ring closure in one operation, two molecules of water and one molecule of hydrogen being eliminated to give tetrahydrophenanthridine. The addition of stannic chloride as an oxidizing agent was without effect on the yield, and the method was shown to be applicable to alkyl, halogeno, and alkoxy derivatives of aniline. More recently, Hollingsworth and Petrow (33) have utilized 2-diethylaminomethylcyclohexan-1-one, from a Mannich reaction on cyclohexanone, in a similar way. The synthesis involves the intermediate forma-

tion of 2-methylenecyclohexanone, and the authors find omission of stannic chloride to result in poor recovery of product. The examples investigated are given in table 2. As a route to phenanthridines themselves this mode of synthesis suffers from the disadvantage that halogen and alkoxy groups are unable to survive dehydrogenation processes with zinc or selenium.

### *F. Miscellaneous methods of synthesis*

Phenanthridine derivatives have resulted from various other reactions, among which the following may be mentioned. The diazotization of 2-amino-*N*-methylbenzanilide provides *N*-methylphenanthridone (69), whilst the Ulmann reaction has been applied to the synthesis of various lycorin degradation products (42, 43)

TABLE 2

*Preparation of tetrahydrophenanthridines*

| TETRAHYDROPHENANTHRIDINE | YIELD | | MELTING POINT |
|---|---|---|---|
| | Kenner, Ritchie, and Statham (38) | Hollingsworth and Petrow (33) | |
| | *per cent* | *per cent* | °C. |
| 1-Methyl- | 21 | 40 | 80.5 |
| 2(or 4)-Methyl- | | 15† | Oil |
| 3-Methyl- | 27† | 50 | 73.5 |
| 1,3-Dimethyl- | 23† | 20 | 49.5 |
| 1,4-Dimethyl | 6.5 | | 63 |
| 7-Methyl-* | 21† | 12 | 45 |
| 3-Chloro- | 26† | 30 | 90 |
| 3-Bromo- | 23.5 | | 110 |
| 1-Nitro- | Very poor | | Oil |
| 3-Nitro- | | 50 | 172 |
| 1-Methoxy- | | 25 | 106 |
| 3-Methoxy- | 34† | 50 | 110 |
| 1,4-Dimethoxy- | 5.3† | | 86.5 |
| 3-Phenyl- | | 70 | 122 |

* From corresponding 4-methylcyclohexanone derivative.

† As picrate.

and of four monoethylphenanthridines (44) from the appropriate 2,2′-dibromobenzylideneanilines. The condensation of cyclohexanone, formalin, and ammonia under pressure at 200°C. gives 34 per cent of octahydrophenanthridine with 6 per cent of the acridine analog (18). The Stieglitz rearrangement of 9-fluorylchloroamines in the presence of sodium methoxide (72) or of 9-fluorylamines in liquid ammonia by potassium amide (94) leads to phenanthridines.

## III. PROPERTIES AND REACTIONS OF PHENANTHRIDINE DERIVATIVES

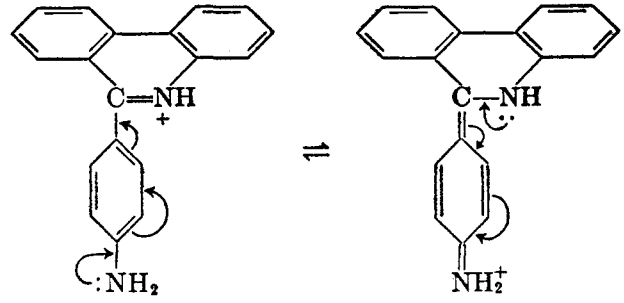
### *A. Properties and reactions of phenanthridines*

Phenanthridine itself separates from dilute ethanol in colorless needles, melting at 104°C., and dissolving with difficulty (1:3500) in cold water to give solutions

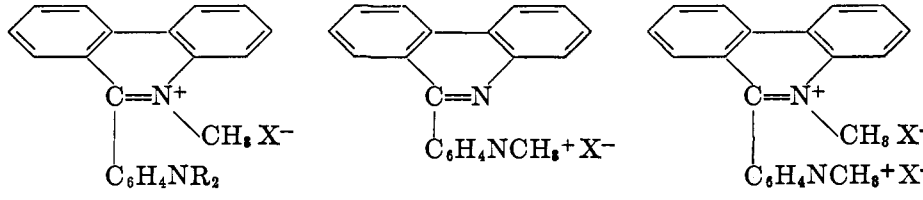
with a weak blue fluorescence (66). It is a weak base ($pK_a$ = 3.30 in 50 per cent alcohol at 20°C. (4)), forming with mineral acids colorless crystalline salts, which are largely dissociated in solution and in general are more soluble and less fluorescent than those of acridine (66).

Very similar physical properties are exhibited by simple monosubstituted phenanthridines, many possessing even lower melting points than the parent heterocycle. Disubstituted compounds are usually higher melting, particularly if a nitro group is present. Fluorescence is very marked in some methoxy derivatives (73, 89), and is increased by reduction of the pyridine ring (67), but is diminished in the 5,6,7,8-tetrahydrophenanthridine system (10, 38).

As in the dyestuffs of the acridine, cyanine, and triphenylmethane series, the appearance of deep color is largely associated with the possibility of resonance in the molecule. For instance, 9-*o*- and 9-*p*-aminophenylphenanthridines give orange solutions in dilute acids, whereas that of the *m*-compound is almost colorless (55).



The color is destroyed by concentrated acids, owing to protonization of the amino group. 3-Amino-9-methylphenanthridine is colored, in contrast to the 7-amino compound (56). Morgan and Walls have studied the relationship between constitution and color in the various quaternary salts of 9-*p*-aminophenylphenanthridine shown below (58). Only XIII is deeply colored (red), the other two salts



being colorless. When the terminal amino group is quaternized no resonance can occur, whilst in the corresponding *p*-acetamidophenylphenanthridinium salt it is largely suppressed. The color possessed by 7-amino-10-methyl-9-phenylphenanthridinium salts cannot be satisfactorily explained by the resonance theory (90), but with the 2,7-diamino derivative a benzidine resonance structure is possible, and the color deepens to almost black.

No cases of optical activity in the phenanthridine series have so far been reported. Thus, neither 5-nitrophenanthridone-4-carboxylic acid (81) nor 9-(*p*-

aminophenyl)-4,5-dimethylphenanthridine (76) shows evidence of a nonplanar configuration due to mutual obstruction of the 4,5-substituents. Phenanthridine possesses a dipole moment of 1.5 units in benzene, agreeing well with the calculated value of 1.6 (27).

Chemically, phenanthridine shows very similar properties to the closely related acridine. Besides forming salts with mineral acids, it yields a picrate, an insoluble nitrite, and well-defined crystalline derivatives with platinic, auric, and mercuric chlorides (66). Morgan and Davies (54) prepared coördination compounds with rhenium oxocyanide during valency studies on the latter metal. The tertiary nitrogen atom of phenanthridine may be quaternized with methyl iodide at 100°C., the resultant methiodide, m.p. 202°C., yielding an insoluble psuedo-base, m.p. 109°C., with caustic soda (67). This undergoes oxidation by ferricyanide to *N*-methylphenanthridone (71), also obtainable by direct alkylation of phenanthridone.

Phenanthridine, like acridine, possesses a very stable ring system, which is resistant to oxidation by chromic or dilute nitric acids, and is only slowly attacked by alkaline permanganate (67). Pictet and Patry (71) succeeded in oxidizing it with bleaching powder and cobalt nitrate to a 30 per cent yield of phenanthridone, but this claim has been questioned by Sielisch and Sandke (82), who obtained only chlorine-containing products, possibly owing to the quality of the bleaching powder.

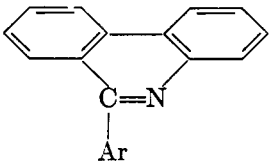
9-Methylphenanthridines exhibit the methyl group reactivity of quinaldine and similar compounds, and may be oxidized with sodium dichromate in acetic acid to the corresponding phenanthridones (89). Selenium dioxide effects the conversion of 9-methylphenanthridine itself to 70 per cent of phenanthridine-9-aldehyde (77), a pale yellow substance, melting at 139°C. and failing to quaternize owing to lowered electron availability at the nitrogen atom. The condensation of 9-methylphenanthridines with formaldehyde occurs readily, and the resultant 9-$\beta,\beta'$-dihydroxyisopropylphenanthridines are oxidized by dichromate to the 9-carboxylic acids (73, 88). Subsequent decarboxylation provides a simple route to derivatives which are unobtainable by the cyclization of *o*-formamidobiphenyls.

The different bonding of the imide groupings in phenanthridine and acridine results in a variation in their behavior towards reducing agents, acridine giving with tin and hydrochloric acid a compound with no basic properties, and phenanthridine yielding the basic 9,10-dihydro derivative, m.p. 123°C., slowly reoxidized by air. This undergoes the Liebermann nitrosamine reaction (67), is strongly fluorescent in alcoholic or ethereal solution, and its acetyl derivative (formed under pressure) nitrates predominantly at the 3-position in acetic acid (79). Nitrophenanthridines may be reduced to the corresponding amines, without affecting the azomethine linkage, by the agency of iron and acidified water (55), whilst stannous chloride has sometimes been used when the 9-position is substituted (5, 62).

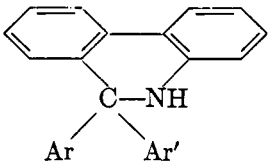
The mononitration (56) of phenanthridine leads to three uninvestigated isomers, having melting points of 260°, 160°, and 156°C., the first one being, how-

ever, probably the 3-nitro derivative (79). A patent (36) describes the only example of a Friedel–Crafts reaction on the heterocycle, and an isolated case of a diene synthesis is also known (22).

The recent calculations by Longuet-Higgins and Coulson (49) of the relative net charges at external positions of the phenanthridine nucleus have provided theoretical confirmation of the known activity of $C_9$ towards nucleophilic reagents. Thus, either one or two aryl groups may be introduced into this position by aryllithium compounds (28), giving XVI and XVII, respectively. Direct amination of phenanthridine with sodium amide (56) produces the 9-amino

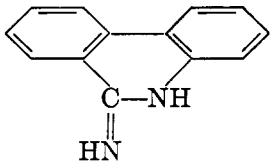



XVI




XVII

derivative, which also results from the 9-chloro compound and zinc chloride diammine (3), or by treating 9-fluoryl-9-phenylamine in liquid ammonia with potassium amide and potassium nitrate (94). It is not diazotizable (nitrous acid yielding phenanthridone), the monoacetyl derivative is easily hydrolyzed, and no quaternary salts are formed under normal conditions. An internal amidine structure (XVIII) has therefore been suggested (56).




XVIII

*B. Properties and reactions of phenanthridones*

Phenanthridone is a colorless high-melting (293°C.) compound which is insoluble in water and nonfluorescent (*cf.* acridone). It also fails to dissolve in acids and alkalis in the cold, and exhibits properties which would be expected of a lactam structure; thus it is resistant to acetylation, and methylation involves the nitrogen atom (31). Like acridone it will not form a hydrazone. Phenanthridone is unaffected by fused potash at 300°C. and by most oxidizing agents, although alkaline permanganate can bring about fission to phthalic acid, a degradation which has been utilized in the orientation of substituted derivatives (1, 51, 53). Reduction cannot be effected by sodium amalgam, by zinc and acetic or hydrochloric acid, or by phosphorus and hydriodic acid, but phenanthridine is secured by distillation with zinc dust (31). The most satisfactory route from the phenanthridone to the phenanthridine series lies in the catalytic reduction of 9-bromophenanthridine (3), which, like the 9-chloro analog, results from the direct action of phosphorus halides on phenanthridone. Sodium and boiling ethanol produce

octahydrophenanthridine from phenanthridone, and subsequent dehydrogenation with selenium furnishes the parent base (45). The nitration of phenanthridone has been described by only one pair of workers (51), and the products, melting at 251–253°C. (yellow) and 368–370°C. (white), remain unidentified, although 2- and 7-orientations were eliminated. Tables 3 and 4 list the known phenanthridones and 9-halogenophenanthridines, respectively.

TABLE 3

*The known phenanthridones*

| PHENANTHRIDONE | MELTING POINT | REFERENCE | PHENANTHRIDONE | MELTING-POINT | REFERENCE |
|---|---|---|---|---|---|
| | °C. | | | °C. | |
| 2-Nitro- | 349 | (51, 89) | 2-Acetoxy- | 273 | (89) |
| 3-Nitro- | >350 | (89) | 7-Acetoxy- | 261 | (89) |
| 7-Nitro- | 285 | (51, 52) | 2-Methoxy- | 251 | (89) |
| | 290 | (47) | 7-Methoxy- | 271 | (89) |
| 2,7-Dinitro | >340 | (89) | | | |
| 5-Nitro-4-carboxy- | >330 | (81) | 2-Methyl- | 251 | (78) |
| 2(or 7)-Chloro-7(or 2)-nitro- | 340 | (89) | 1-Methyl-7-isopropyl- | 220.5 | (1, 9) |
| | | | 8-Methyl-2-isopropyl- | 230 | (1) |
| 3-Bromo- | 302 | (89) | *N*-Methyl- | 108.5 | (31) |
| 2,7-Diacetamido- | >350 | (2) | *N*-Ethyl- | 89 | (31) |
| 2,7-Diamino-4-carboxy- | | (19) | *N*-Benzyl- | 112.5 | (31) |
| 2-Hydroxy- | 341 | (89) | *N*-Carbomethoxy- | 127 | (46)* |
| 7-Hydroxy- | 320 | (89) | *N*-Carbethoxy- | 143 | (46)* |

* Other *N*-carbalkoxyphenanthridones are listed in this paper.

TABLE 4

*The known 9-halogenophenanthridines*

| PHENANTHRIDINE | MELTING-POINT | REFERENCE |
|---|---|---|
| | °C. | |
| 9-Chloro- | 116.5 | (31) |
| 9-Chloro-2-methoxy- | 137 | (89) |
| 9-Chloro-2,7-dinitro- | 225 | (3) |
| 9-Bromo- | 124 | (88) |
| 3,9-Dibromo- | 170 | (89) |

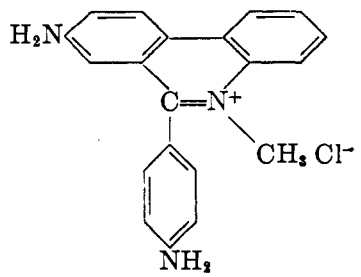
### *C. Practical applications*

Phenanthridine derivatives have found their greatest commercial application as therapeutic agents, mostly as trypanocides, but to a lesser extent as antiseptics. It is of interest to note that the phenanthridine analogs of atebrin and plasmoquin, prepared by Walls (88, 89) from 9-halogenophenanthridines and the appropriate diamines, are devoid of therapeutic value.

The greatest activity against trypanosomes has been found to reside in certain amino-9-phenylphenanthridinium salts, and systematic study over the last

decade has afforded considerable data on the relationship between structure and trypanocidal value in compounds of this type. It will be convenient therefore to consider an active compound, 7-amino-9-*p*-aminophenyl-10-methylphenanthridinium chloride (XIX), known also as S.897, and examine the effect of certain structural modifications on its activity against *T. congolense*.

1. The compound lacking an amino group in the phenanthridine nucleus is inactive (90), but if the group is transferred to positions 2, 3, or 6, high activity is retained (16, 92).
2. The position of the amino group in the phenyl nucleus is relatively unimportant (90), and its replacement by nitro causes but a slight reduction in activity (93).
3. The placing of both amino groups in the phenanthridine nucleus, so as to occupy the 2,7-positions, gives a benzidine-like structure of enhanced activity (90) (S.1553, quaternary bromide).
4. Acetylation (14, 90) or carbethoxylation (93) of the amino substituents, particularly of that in the phenanthridine system, has a markedly dystherapeutic effect.
5. Unquaternized derivatives are inactive (14).




XIX

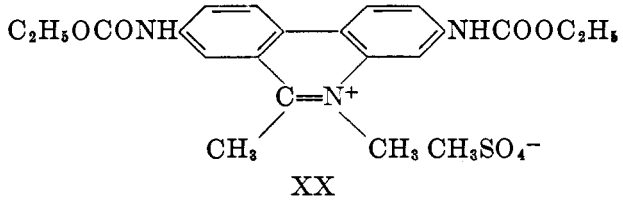
6. Replacement of the primary amino by amidino groups gives inactive compounds (5, 95).
7. Replacement of the 9-*p*-aminophenyl by a methyl (93) or 3′-pyridyl (95) group leads to reduced activity.
8. Introduction of an unsaturated linkage between the 9-phenyl group and the phenanthridine skeleton also decreases the activity of the product (95).

S.897 is prepared (58, 90), in 40 per cent yield based on *o*-xenylamine, by the methylation and subsequent reduction of 7-nitro-9-*p*-nitrophenylphenanthridine. Administered to infected mice it shows twice the activity of 4,4′-diamidino-$\alpha,\beta$-dimethylstilbene (95) against *T. congolense*. Browning and coworkers (14) claim a cure for *T. brucei* infections in mice by doses approaching the maximum tolerated (1 mg. per 20 g. mouse), but recently Launoy and Prieur (48) found the compound to be without action under these conditions.

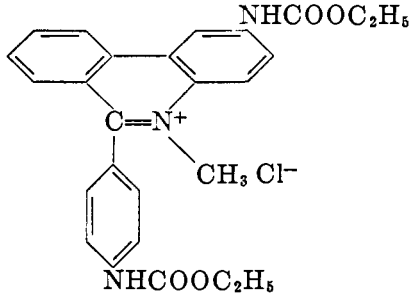
S.1553 ("Dimidium bromide"), which forms purple-black prisms, m.p. 241°C., is an even more powerful trypanocide, possessing the additional advantage of higher solubility, but in high doses it shows toxic effects (95). Its phenanthri-

dinium radical may be accurately estimated as an insoluble ferricyanide, formed in buffered solution (26).

The structural requirements for activity against *T. cruzi* are somewhat different from those listed above. S.1582 (XX), a 9-methylphenanthridine bearing acylated amino groups, shows significant action against this trypanosome in mice but will cure *T. brucei* or *T. congolense* infections only in high doses (13). The 3-substituted derivative (XXI), S.1544, is also capable of sterilizing *T. cruzi*, which is refractory to other classes of drugs (13).




XX




XXI

Many of the above compounds are of value as antiseptics, but the most active example yet found possesses no amino group in the phenanthridine ring system. It is 9-*p*-dimethylaminophenyl-10-methylphenanthridinium chloride, and it will inhibit *B. coli* at a concentration of 1:200,000 (53).

In 1924 Hollins (34) stated that no phenanthridine products of interest as dyestuffs had been discovered, and this observation remains largely true at the present day. A few complex structures with dyeing properties exist, but invariably owe these characteristics more to the rest of the molecule (usually an anthraquinone system) than to the phenanthridine skeleton itself. Brooker and Keyes (12) have investigated the photographic sensitizing properties of cyanine dyes derived from 9-methylphenanthridine, but find no results of value.

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