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FRANCIS H. CASE

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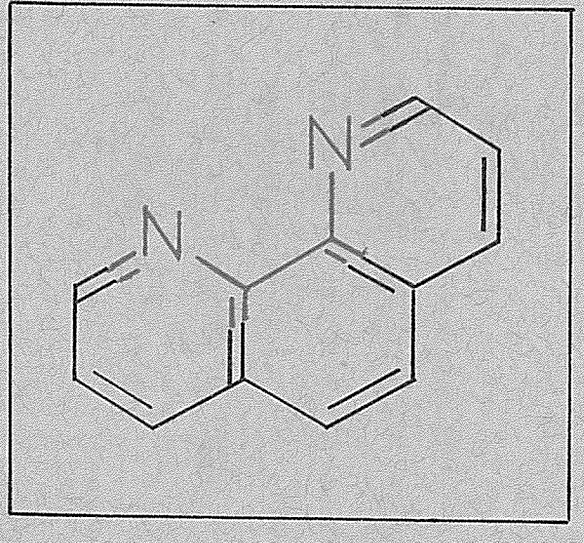

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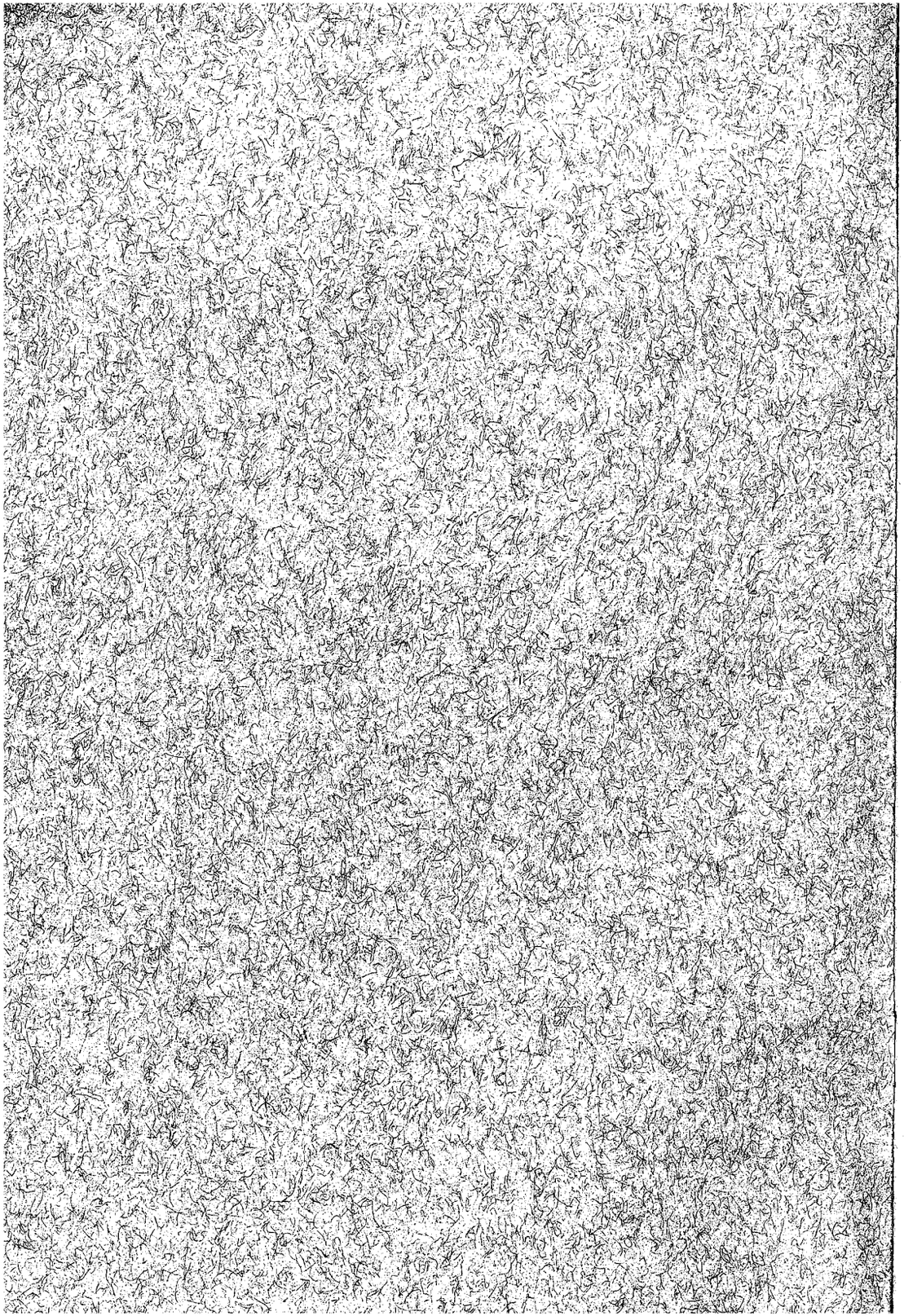
COLUMBUS, OHIO



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Printed in U.S.A. by
THE WATKINS PRINTING CO.
Columbus, Ohio

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PREFACE

"Organic Compounds Containing the Ferroïn Group," $=N-\overset{|}{C}-\overset{|}{C}-N=$, which forms colored complexes with Fe(II) and Cu(I) have been known for over seventy years. The first representative, 2,2′-bipyridine was described by Fritz Blau [Ber., **21,** 1077 (1888)]. An exhaustive study of this first outstanding example of ferroïn-reacting compound was published by him [Monatsh., **19,** 666 (1889)] as well as the synthesis of the second example, 1,10-phenanthroline.

Gerdeissen [Ber., **22,** 244 (1889)] described the preparation of the first substituted product, 2-methyl-1,10-phenanthroline. Alfred Werner [Ber., **45,** 433 (1912)] disclosed the true structural configuration of the Fe(II) complex of 2,2′-bipyridine. Morgan and associates in England investigated the polypyridines during the period 1930 to 1938. Smirnoff studied 2,2′-biquinoline in 1921.

Although 1,10-phenanthroline was first synthesized in Germany, as already mentioned, its first manufacture and distribution in the United States was provided by the publisher of the present book (1933).

The first important analytical applications of the 1,10-phenanthrolines were made by Walden, Hammett, and Chapman at Columbia University [J. Am. Chem. Soc., **53,** 3908 (1931) and **55,** 2644 (1933)]. The redox system, 1,10-phenanthroline ferrous complex in conversion to the corresponding ferric complex, was described. The corresponding 5-nitro-1,10-phenanthroline redox indicator system was introduced.

The ferroïn type chelation reagents were then continuously improvised and studied from 1933 to the present, first through the research developments at the University of Illinois. A wide extension of the original synthetic studies with particular reference to 1,10-phenanthrolines and polypyridines has been carried out at Temple University, although other new ferroïn type compounds have appeared from a large number of other laboratories. Studies of the analytical applications of these newly developed species have come mainly from the departments of chemistry at the University of Illinois and at Iowa State University. The documentation and review publication of research papers involving the utility of the various types the synthesis of which is herein described, is left to companion publications in this series now supplied by the present publishers.

The name ferroïn as a generic designation for these "phenolphthaleins of oxidimetry" was coined by Gleu [Z. anal, Chem., **95,** 305 (1933)]. Perhaps a more suitable generic term is that of J. C. Bailar, "the methine chromophore" reagents. This designation includes reference to the spectrophotometric trace metal determinations as well as those of redox indicator utility. The term ferroïn is employed here because of literature priority.

The organic reagents of the present summary are noted for the large number of possible substitution products. They represent a system of derivatives amenable to definite property prognosis. Their applicability in improved analytical techniques is second to no other known system of organic compounds in analysis. Future developments in this field promise other important advances.

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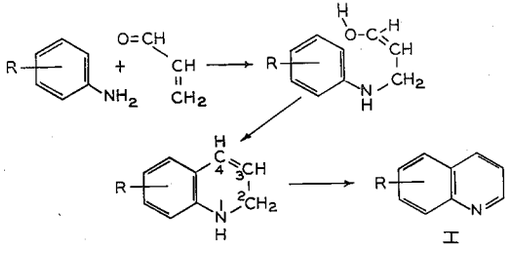
Philadelphia, Pennsylvania, 1960

A REVIEW OF SYNTHESES OF ORGANIC COMPOUNDS CONTAINING THE FERROÏN GROUP

The synthesis of a substituted quinoline (I) by the method of Skraup originally involved the condensation of a substituted aniline with glycerol in hot concentrated sulfuric acid in the presence of an oxidizing agent such as arsenic acid. Under these conditions the glycerol is dehydrated to acrolein, $H_2C=CHCHO$, to which the aniline is believed to add in the 1,4 manner with subsequent ring closure by elimination of water. Finally, removal of two hydrogen atoms, (in the 1 and 2 positions), by the oxidizing



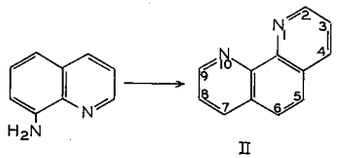
I

agent, affords a quinoline substituted in the homocyclic ring in a position depending on which substituted aniline was used.

In order to introduce substituents in the heterocyclic ring, one may use a compound in which any of the hydrogens in the original acrolein are substituted by various groups. As examples may be cited crotonaldehyde, $CH_3CH=CHCHO$, which would yield 2-methylquinoline; α-methyl acrolein, $H_2C=C(CH_3)CHO$, which would yield 3-methyloquinoline; methylvinyl ketone, $CH_3COCH=CH_2$, affording 4-methylquinoline; etc. In many cases instead of an unsaturated aldehyde or ketone, a compound is used which on dehydration or dehydrohalogenation in the reaction medium, yields the requisite unsaturated aldehyde or ketone. Thus, beta-chloropropiophenone, $ClCH_2CH_2COC_6H_5$, is used to make 4-phenylquinoline; and 4-hydroxy-3-methyl-2-butanone, $CH_3COCH(CH_3)CH_2OH$, to form 3,4-dimethylquinoline.

In the synthesis of quinolines the modification of the Skraup reaction due to Yale and Bernstein[1] frequently produces higher yields. In this procedure the sulfuric acid is replaced by phosphoric, and the temperature is kept much lower (about 100°). As oxidizing agent arsenic acid is used. In this modified technique acrolein must be used in place of glycerol. The method is particularly desirable where the substituted acroleins previously mentioned, or compounds capable of producing them in the reaction mixture, are used.

If o-nitroaniline is used in a Skraup reaction with glycerol the resulting product is 8-nitro-quinoline. Reduction of this substance yields 8-amino-quinoline and this compound in a second Skraup reaction with glycerol yields 1,10-phenanthroline (II). By starting with substituted o-nitroanilines



II

various substituents may be placed on the 5- and 6-positions of 1,10-phenanthroline. Thus 2-nitro-4-methylaniline would yield successively: 6-methyl-8-nitroquinoline, 6-methyl-8-aminoquinoline, and 5-methyl-1,10-phenanthroline. Use of substituted acroleins instead of acrolein or glycerol results in substitution in the nitrogen-containing rings of 1,10-phenanthroline. Thus, o-nitroaniline with methylvinyl ketone yields 4-methyl-8-nitroquinoline. This on reduction and further treatment with the same reagent affords 4-7-dimethyl-1,10-phenanthroline. If, however, in the second step, glycerol were used, then 4-methyl-1,10-phenanthroline would be the result. Thus, a wide variety of substituted phenanthrolines is possible depending on the choice of substituted nitroaniline and substituted acrolein.

In the case of symmetrically substituted, (not in the 5,6 position), 1,10-phenanthrolines, it would seem to be a much simpler procedure to perform a double Skraup reaction on o-phenylenediamine. Thus, from this compound and methylvinyl ketone one might hope to obtain 4,7-dimethyl-1,10-phenanthroline in one step. Unfortunately these double Skraup reactions are nearly always unsuccessful, the notable exceptions being the preparation of 1,10-phenanthroline itself from o-phenylenediamine and glycerol, and that of 2,9-dimethyl-1,10-phenanthroline from o-phenylenediamine and crotonaldehyde.

In the preparation of the quinolines and phenanthrolines described on the succeeding pages, usually, but not always, either the Skraup reaction, designated in the table by (S), or the Yale modification, designated by (Y), are used. The Doebner-Miller reaction is used occasionally for the preparation of quinolines or phenanthrolines. General directions are presented below for the use of each. The 8-nitroquinolines are usually reduced to the corresponding amino compounds by catalytic hydrogenation, (Adams' catalyst), or by stannous chloride in ethanol or concentrated hydrochloric acid.

A. **Skraup Reaction.** A stirred mixture of one mole of the appropriate aromatic amine, one mole of arsenic acid hemihydrate, four moles of sulfuric acid, in 96.8% solution, and a volume of water equal to one-third of the volume of sulfuric acid used is heated to 100° and treated with 3.5 moles of glycerol, or usually 1.5 moles of potential unsaturated aldehyde or ketone at such a rate that the temperature does not exceed 140°. Heating is continued at this temperature for two hours. The mixture is then poured into water, made alkaline, and the precipitate removed by filtration. Both filtrate and precipitate are extracted with hot benzene. After removal of the solvent the substituted phenanthrolines are crystallized, usually from hot benzene or benzene-petroleum ether.

B. **Yale Modification.** A stirred mixture of one mole of aromatic amine, two moles of arsenic acid hemihydrate and 85% phosphoric acid, (1000 ml per mole of amine), is heated to 100° and usually 1.5 moles of potential unsaturated aldehyde or ketone added dropwise at such a rate that the temperature does not exceed 105°. This temperature is maintained for an additional 0.5 hours. The reaction mixture is then poured on ice and neutralized with concentrated ammonium hydroxide. The resulting precipitate and filtrate are extracted with hot benzene and the combined extracts evaporated to dryness. The substituted quinolines or phenanthrolines are then crystallized, usually from benzene or benzene-petroleum ether.

C. **Doebner-Miller Reaction.** In this type of reaction, occasionally used for the preparation of quinolines or phenanthrolines, the aromatic amine, dissolved in concentrated hydrochloric acid containing arsenic acid and zinc chloride, is treated with the second component at 100°, followed by two-hour's refluxing at this temperature. The mixture is then made alkaline and extracted with hot benzene.

In the table below, G stands for glycerol. MAD stands for α-methyl-acrolein diacetate, and CAD for crotonaldehyde diacetate, which were prepared by the action of acetic anhydride on the aldehyde in the presence of a drop of sulfuric acid. MVK stands for methyl vinyl ketone, commercially available. MB stands for 4-hydroxy-3-methyl-2-butanone, $CH_3COCH(CH_3)CH_2OH$, prepared by the reaction of formaldehyde on butanone.[9] HP stands for 4-hydroxy-2-pentanone, $CH_3CH(OH)CH_2COCH_3$, formed by the action of acetaldehyde on acetone[10] and TA for tiglic aldehyde, $CH_3CH=C(CH_3)CHO$, commercially available.

Methyl-1,10-Phenanthrolines Prepared by the Skraup Reaction

Substituted 1,10-Phenanthroline	1st Component 8-Aminoquinoline	2nd Component	Method	Yield %	Literature Reference
2-methyl	2-methyl	G	S		2
3-methyl	unsubstituted	MAD	S	6.1	3
4-methyl	4-methyl	G	S	14.9	3
5-methyl	6-methyl	G	S	66	4
2-4-dimethyl	2,4-dimethyl	G	S	42.5	8
2,9-dimethyl	2-methyl	CAD	S	7.6	3
3,4-dimethyl	3,4-dimethyl	G	S	22.3	5
3,5-dimethyl	6-methyl	MAD	S	4.2	6
3,6-dimethyl	3,6-dimethyl	G	S	2.6	6
3,7-dimethyl	4-methyl	MAD	S	2.3	3
3,8-dimethyl	3-methyl	MAD	S	8.8	3
4,5-dimethyl	4,5-dimethyl	G	S	24.0	6
4,6-dimethyl	4,6-dimethyl	G	S	11.4	6
4,7-dimethyl	4-methyl	MVK	Y	16.8	7
5,6-dimethyl	5,6-dimethyl	G	S	9.3	3
3,4,6-trimethyl	3,4,6-trimethyl	G	S	18.6	5
3,4,7-trimethyl	3,4-dimethyl	MVK	S	30.9	5
3,4,8-trimethyl	3,4-dimethyl	MAD	S	9.1	5
3,5,6-trimethyl	5,6-dimethyl	MAD	S	9.3	3
3,5,7-trimethyl	4,6-dimethyl	MAD	S	14.5	6
3,5,8-trimethyl	3,5-dimethyl	MAD	S	8.7	6
3,6,7-trimethyl	4,5-dimethyl	MAD	S	2.1	6
4,5,7-trimethyl	4,6-dimethyl	MVK	S	1.3	6
2,4,7,9-tetramethyl	2,4-dimethyl	HP	S	23.5	8
3,4,6,7-tetramethyl	3,4,6-trimethyl	MVK	S	4.9	5
3,4,6,8-tetramethyl	3,4,6-trimethyl	MAD	S	8.8	5
3,4,7,8-tetramethyl	3,4-dimethyl	MB	S	20.2	5
3,5,6,8-tetramethyl	3,5,6-trimethyl	MAD	S	22.2	3

Preparation of Substituted 8-Aminoquinolines Intermediate in the Formation of Methyl-1,10-Phenanthrolines

2-Methyl: by nitration of quinaldine followed by reduction.

3-Methyl: by a Skraup reaction involving o-nitroaniline and methylacrolein diacetate followed by reduction.

4-Methyl: by nitration of 4-methylquinoline followed by reduction.

6-Methyl: by nitration of p-acettoluide followed by hydrolysis and reduction.

2,3,-Dimethyl: by the action of o-nitroaniline and tiglic aldehyde in presence of concentrated HCl, arsenic acid and zinc chloride, followed by reduction.

2,4-Dimethyl: by nitration of 2,4-dimethylquinoline, followed by reduction.

3,4-Dimethyl: by a Skraup reaction involving o-nitroaniline and 4-hydroxy-3-methyl-2-butanone, followed by reduction.

3,5-Dimethyl: by a Skraup reaction involving 5-methyl-2-nitroaniline and α-methylacrolein diacetate, followed by reduction.

3,6-Dimethyl: by a Skraup reaction involving 4-methyl-2-nitroaniline and α-methylacrolein diacetate, followed by reduction.

4,5-Dimethyl: by a Skraup reaction involving 5-methyl-2-nitroaniline and methylvinylketone, followed by reduction.

4,6-Dimethyl: by a Skraup reaction involving 4-methyl-2-nitroaniline and methylvinylketone, followed by reduction.

5,6-Dimethyl: by nitration of 3,4-dimethyl acetanilide, followed by hydrolysis, a Skraup reaction with glycerol and reduction of the resulting product.

2,5,6-Trimethyl: by a Skraup reaction involving 4,5-dimethyl-2-nitroaniline and crotonaldehyde diacetate, followed by reduction.

3,4,6-Trimethyl: by a Skraup reaction involving 4-methyl-2-nitroaniline and 4-hydroxy-3-methyl-2-butanone, followed by reduction.

3,5,6-Trimethyl: by a Skraup reaction involving 4,5-dimethyl-2-nitroaniline and α-methylacrolein diacetate, followed by reduction.

Two tetramethyl phenanthrolines were not prepared by the Skraup method. 2,3,8,9-Tetramethyl-1,10-phenanthroline[8] was made by the action of 8-amino-2,3-dimethylquinoline, (see table of aminoquinolines), with tiglic aldehyde in presence of arsenic acid, zinc chloride and concentrated hydrochloric acid. The 2,5,6,9-tetramethyl isomer[8] resulted from a similar reaction involving 8-amino-2,5,6-trimethylquinoline and crotonaldehyde diacetate.

Ethyl-1,10-Phenanthrolines

Substituted 1,10-Phenanthroline	1st Component 8-Aminoquinoline	2nd Component	Method	Yield %	Literature Reference
3-ethyl	3-ethyl	G	S	47	11
4-ethyl	4-ethyl	G	S	18	11
5-ethyl	6-ethyl	G	S	14	11
3,8-diethyl	3-ethyl	EA	Y	16	11
4,6-diethyl	4,6-diethyl	G	S	19	11
4,7-diethyl	4-ethyl	CP	S	27	11
5,6-diethyl	5,6-diethyl	G	S	44	11

In the above table G stands for glycerol; EA for α-ethylacrolein, prepared from n-butyraldehyde, dimethylamine hydrochloride and formalin;[12] and CP for 1-chloropentanone-3, $ClCH_2CH_2COCH_2CH_3$, from propionyl chloride, ethene, and aluminum chloride.[13]

Preparation of Substituted 8-Aminoquinolines Intermediate in the Formation of Ethyl-1,10-Phenanthrolines

3-Ethyl: by a Skraup reaction involving o-nitroaniline and α-ethylacrolein, followed by reduction.

4-Ethyl: by a Skraup reaction involving o-nitroaniline and 1-chloropentanone-3, followed by reduction.

6-Ethyl: by a Skraup reaction involving 4-ethyl-2-nitroaniline and glycerol, followed by reduction.

4,6-Diethyl: by a Skraup reaction involving 4-ethyl-2-nitroaniline and 1-chloropentanone-3, followed by reduction.

5,6-Diethyl: o-diethylbenzene was prepared by the action of diethyl sulfate on o-ethylphenyl magnesium bromide. Nitration, followed by reduction, acetylation, and a second nitration, yielded 4,5-diethyl-2-nitroacetanilide. In a Skraup reaction with glycerol this afforded 5,6-diethyl-8-nitroquinoline, which was reduced to the amine.

Phenyl-1,10-Phenanthrolines Prepared by the Skraup Reaction

Substituted 1,10-Phenanthroline	1st Component 8-Aminoquinoline	2nd Component	Method	Yield %	Literature Reference
2-phenyl	2-phenyl	G	S	23.4	7
3-phenyl	3-phenyl [a]	A	Y		7
4-phenyl	unsubstituted	βClP	S	11.5	14
5-phenyl	6-phenyl	G	S	20.4	14
2,9-diphenyl	2-phenyl	CA	Y	5.5	7
4,6-diphenyl	4,6-diphenyl	G	S	9.6	14
4,7-diphenyl	4-phenyl	βClP	Y	58.8	7
2,9-dimethyl-4,7-dipenyl	2-methyl-4-phenyl	PPK	Y	17.8	8

[a] Isolated as hydrochloride.

In the above table G stands for glycerol; A for acrolein; βClP for β-chloropropiophenone, $ClCH_2CH_2COC_6H_5$,[15] prepared from β-chloropropionyl chloride, aluminum chloride and benzene; CA for cinnamic aldehyde; and PPK for phenyl-propenyl ketone, $C_6H_5COCH=CHCH_3$,[16] from benzene, crotonyl chloride and aluminum chloride.

Preparation of Substituted-8-Aminoquinolines Intermediate in the Formation of Phenyl-1,10-Phenanthrolines

2-Phenyl: from o-nitroaniline, cinnamic acid, arsenic acid, zinc chloride and concentrated hydrochloric acid, followed by reduction.

3-Phenyl: from o-nitroaniline, arsenic acid, zinc chloride, paraformaldehyde and phenylacetaldehyde in concentrated hydrochloric acid and ethanol followed by reduction.

4-Phenyl: from a Skraup reaction involving o-nitroaniline and β-chloropropiophenone, followed by reduction.

6-Phenyl: from a Skraup reaction involving o-nitroaniline and 3-nitro-4-acetamidobiphenyl, followed by reduction.

4,6-Diphenyl: from a Skraup reaction involving 3-nitro-4-aminobiphenyl and β-chloropropiophenone.

2-Methyl-4-Phenyl: from o-nitroaniline, arsenic acid, zinc chloride and phenyl propenyl ketone in presence of concentrated hydrochloric acid, followed by reduction.

In addition to the phenylphenanthrolines whose preparation is described above, certain others were prepared, as follows:

3,8-Diphenyl-1,10-phenanthroline[7] was prepared by reduction of 3,8-diphenyl-4,7-dibromophenanthroline by means of Raney nickel in hydrogen.

4,7-Dimethyl-2,9-diphenyl-1,10-phenanthroline[7] resulted from the action of phenyl lithium on 4,7-dimethylphenanthroline.

2,4,7,9-Tetraphenyl-1,10-phenanthroline[7] was synthesized by the action of phenyl lithium on 4,7-diphenylphenanthroline.

Bromo-1,10-Phenanthrolines Prepared by the Skraup Reaction

Substituted 1,10-Phenanthroline	1st Component 8-Aminoquinoline	2nd Component	Yield %	Literature Reference
3-bromo	3-bromo	G	20.4	17
5-bromo	6-bromo	G	46.0	4
3,5-dibromo	6-bromo	BAD	1.4	17
3,6-dibromo	3,6-dibromo	G	28.2	17
5,6-dibromo	5,6-dibromo	G	14.1	17
3,5,6-tribromo	3,5,6-tribromo	G	26.9	17
3,5,6,8-tetrabromo	3,5,6-tribromo	BAD	4.3	17

In the above table G indicates glycerol and BAD stands for α-bromoacrolein diacetate. The latter compound was prepared by adding bromine to acrolein. The resulting α,β-dibromopropionaldehyde was dehydrohalogenated with aqueous sodium acetate and the resulting aldehyde treated with acetic anhydride in presence of a drop of sulfuric acid.[18]

Preparation of Substituted 8-Aminoquinolines Intermediate in the Preparation of Bromo-1,10-Phenanthrolines

3-Bromo: by the bromination of 8-nitroquinoline, followed by reduction.

6-Bromo: by a Skraup reaction involving 4-bromo-2-nitroaniline and glycerol, followed by reduction.

3,6-Dibromo: by a Skraup reaction involving 4-bromo-2-nitroaniline and α-bromoacrolein diacetate, followed by reduction.

5,6-Dibromo: by a Skraup reaction involving 4,5-dibromo-2-nitroacetanilide and glycerol, followed by reduction.

3,5,6-Tribromo: by a Skraup reaction involving 4,5-dibromo-2-nitroacetanilide and α-bromoacrolein diacetate, followed by reduction.

The following bromo-1,10-phenanthrolines were prepared by the addition of a mixture of PBr_3 and $POBr_3$ to the corresponding hydroxyphenanthrolines: 4-bromo;[17] 4,7-dibromo;[17] 4-bromo-3-phenyl;[7] and 4,7-dibromo-3,8-diphenyl.[7]

Chloro-1,10-Phenanthrolines Prepared by Cyclization Reactions

Substituted 1,10-Phenanthroline	1st Component 8-Aminoquinoline	2nd Component	Yield %	Literature Reference
3-chloro	3-chloro	G	26.7	19
5-chloro	6-chloro	G	56.0	4
3,5-dichloro	6-chloro	CAD	2.0	19
3,8-dichloro	3-chloro	CAD	2.5	19
5,6-dichloro	5,6-dichloro	G	26.2	19
3,5,6-trichloro	5,6-dichloro	CAD	7.9	19
5-chloro-3-methyl	6-chloro	MAD	23.0	19
6-chloro-3-methyl	6-chloro-3-methyl	G	38.0	19
7-chloro-3-methyl	4-chloro	MAD	3.5	3

In the above table G refers to glycerol; MAD to α-methylacrolein diacetate; and CAD to α-chloroacrolein diacetate. The last mentioned reagent,[20] was prepared by addition of chlorine to acrolein, followed by dehydrochlorination with aqueous sodium acetate. The resulting chloroacrolein was converted to the diacetate by acetic anhydride and a drop of sulfuric acid.

The Skraup reaction (using sulfuric acid) was used in the preparation of all the above chlorophenanthrolines except 3,5- and 3,8-dichloro. These were made by the action of the chloroaminoquinoline indicated above with α-chloroacrolein diacetate in presence of concentrated hydrochloric acid, zinc chloride, and arsenic acid at 100°.

The following chloro-1,10-phenanthrolines were prepared by the action of a mixture of PCl_3 and $POCl_3$ on the corresponding hydroxyphenanthrolines: 4-chloro-[21]; 4,7-dichloro-[21]; 4-chloro-5-methoxy-[21]; 2-chloro-4-methyl-[23]; 4-chloro-3-phenyl-[7]; and 4,7-dichloro-3,8-diphenyl-[7].

2-Chloro-1,10-phenanthroline,[24] has been prepared by treatment of 1,10-phenanthroline methiodide (III) with alkaline ferricyanide solution, and of the resulting 1-methyl-2-oxo-phenanthroline (IV) with PCl_5.

Preparation of 8-Aminoquinolines Intermediate in the Formation of Chloro-1,10-Phenanthrolines

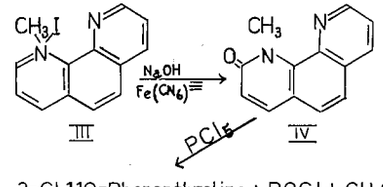
3-Chloro: 8-nitroquinoline was treated with chlorine in S_2Cl_2 and reduced.

4-Chloro: by nitration of 4-chloroquinoline, followed by reduction.

6-Chloro: by a Skraup reaction involving 4-chloro-2-nitroacetanilide and glycerol, followed by reduction.

5,6-Dichloro: nitration of 3,4-dichloroacetanilide yielded 4,5-dichloro-2-nitroacetanilide. This, in a Skraup reaction with glycerol, afforded 5,6-dichloro-8-nitroquinoline, which was reduced to the amino derivative.

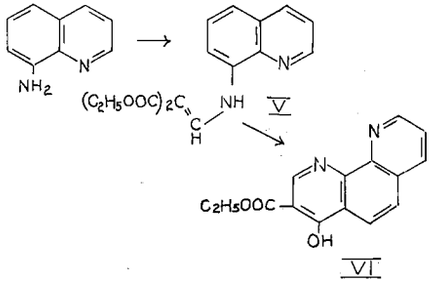
6-Chloro-3-Methyl: by a Skraup reaction involving 4-chloro-2-nitroaniline and methylacrolein diacetate, followed by reduction.



2-Cl-1,10-Phenanthroline + $POCl_3$ + CH_3Cl

Hydroxy-1,10-Phenanthrolines

4-Hydroxy-1,10-phenanthroline:[21] Ethylethoxymethylenemalonate, $C_2H_5OOCC(=CHOC_2H_5)COOC_2H_5$, and 8-aminoquinoline were heated at 100°. The resulting compound (V) was cyclized in Dowtherm (diphenyl-ether + biphenyl).



The 3-carbethoxy-4-hydroxyphenanthroline formed (VI) was then hydrolyzed to the hydroxycarboxylic acid, and decarboxylated.

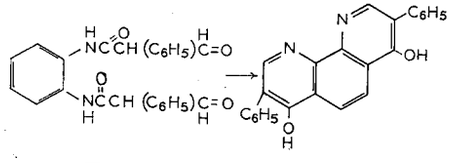
4,7-Dihydroxy-1,10-phenanthroline:[21] This was prepared by the action of two moles of ethyl ethoxymethylenemalonate on o-phenylenediamine. The resulting 3,8-dicarbethoxy-4,7-dihydroxyphenanthroline was then hydrolyzed to the dihydroxydicarboxylic acid and decarboxylated. 5,6-Dihydroxy-1,10-phenanthroline is formed on hydrolysis of the 5,6-dimethoxy derivative.[22]

4-Hydroxy-5-methoxy-1,10-phenanthroline:-[21] 6-Methoxy-8-aminoquinoline was treated with ethyl ethoxymethylenemalonate, and the resulting compound cyclized in Dowtherm, yielding 3-carbethoxy-4-hydroxy-5-methoxy-1,10-phenanthroline. Hydrolysis yielded the free acid, which on decarboxylation afforded 4-hydroxy-5-methoxy-1,10-phenanthroline.

2-Hydroxy-4-methyl-1,10-phenanthroline:-[23] 2-Hydroxy-4-methylquinoline was converted to the chloro derivative, nitrated, hydrolyzed to 2-hydroxy-4-methyl-8-nitroquinoline,[25] and reduced. A Skraup reaction with glycerol yielded 2-hydroxy-4-methyl-1,10-phenanthroline.

4-Hydroxy-3-phenyl-1,10-phenanthroline:-[7] 8-Aminoquinoline and α,α-formylphenylacetate, $HC(O)CH(C_6H_5)COOC_2H_5$, were allowed to stand in presence of a trace of glacial acetate acid. The resulting oil was heated in Dowtherm to close the ring.

4,7-Dihydroxy-3,8-diphenyl-1,10-phenanthroline[7] (VIII): o-phenylenediamine and two moles of α,α-formylphenylacetate were allowed to stand in presence of a trace of glacial acetic acid. The resulting substance (VII) was heated in Dowtherm, resulting in double ring closure.



VII VIII

4-Hydroxy-3,5-diphenyl-1,10-phenanthroline:-[7] 8-Amino-6-phenylquinoline and α,α-formylphenylacetate were allowed to react in presence of glacial acetic acid. The resulting compound was cyclized by heating in Dowtherm.

Alkoxy-1,10-Phenanthrolines

2-Methoxy-1,10-phenanthroline[26] results from the action of sodium methoxide on 2-chlorophenanthroline.

5-Methoxy-1,10-phenanthroline[27] has been prepared from 5-chlorophenanthroline in presence of potassium hydroxide, copper and methanol.

4,7-Dimethoxy- and 4,7-diphenoxy-1,10-phenanthrolines[22] have been prepared by the action of sodium methoxide and potassium phenoxide respectively on 4,7-dichloro-1,10-phenanthroline.

The preparation of 5,6-dimethoxy-1,10-phenanthroline[22] involves the following steps: nitroveratrole (1,2-dimethoxy-4-nitrobenzene) is reduced to the amine, which is acetylated and nitrated to yield 4-acetamido-1,2-dimethoxy-5-nitrobenzene. A modified Skraup reaction (Yale method) yields 5,6-dimethoxy-8-nitroquinoline. Reduction followed by a second Skraup reaction affords 5,6-dimethoxy-1,10-phenanthroline.

Nitro-1,10-Phenanthrolines

5-nitro-1,10-phenanthroline[24, 28] and 5-methyl-6-nitrophenanthroline[4] have been prepared by direct nitration of the parent compounds.

Amino-1,10-Phenanthrolines

While the preparation of 5-amino-1,10-phenanthroline from the 5-bromo derivative by the action of ammonia was unsuccessful,[24] it has now been prepared by the reduction of 5-nitro-1,10-phenanthroline.[29]

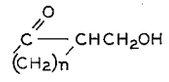
Although the number of known simple amino derivatives of 1-10-phenanthroline is limited to the 5-isomer many substituted amino derivatives have been made in connection with therapeutic studies. Thus from 2-chloro-1,10-phenanthroline the following have been prepared by treatment with the appropriate amine:-[24] 2-piperidino-; 2-anilino-; 2-diethylaminoethylamino-; and 2-diethylaminopropylamino-. From 2-chloro-4-methyl-1,10-phenanthroline, 2-[4-(2-aminoethyl)] morpholino-4-methyl-1,10-phenanthroline,[23] was prepared by treatment with the amine

$$NH_2CH_2CH_2\text{-}N\begin{matrix}\diagup CH_2CH_2\diagdown\\ \diagdown CH_2CH_2\diagup\end{matrix}O.$$

From 4-chloro-1,10-phenanthroline,[21] and 3-diethylaminopropylamine, $(C_2H_5)_2NHCH_2CH_2CH_2NH_2$, was prepared 4-(3-diethylaminopropylamino)-1,10-phenanthroline. With 4-diethylamino-1-methylbutylamine, $(C_2H_5)_2NCH_2CH_2CH_2CH(CH_3)NH_2$, 4,7-dichloro-1,10-phenanthroline yielded 4,7-bis-(4-diethylamino-1-methylbutylamino)-1,10-phenanthroline, and 4-chloro-5-methoxy-1,10-phenanthroline afforded 4-(4-diethylamino-1-methylbutylamino)-5-methoxy-1,10-phenanthroline.[21]

Cycloalkeno-1,10-Phenanthrolines[30]

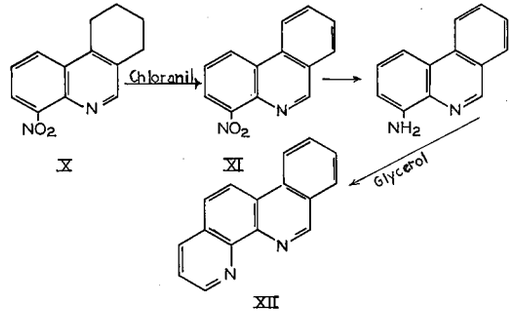
The action of formalin on various cycloalkanones (n=5,6,7,8) in presence of calcium hydroxide yields the corresponding α-hydroxymethyl-cycloalkanone (IX) which may serve in the Skraup reaction as a reagent



IX

for the preparation of 3,4-cycloalkeno-8-nitroquinolines, and of 3,4-mono-, and 3,4,7,8-dicycloalkeno-1,10-phenanthrolines. In this way, using the Yale modification of the Skraup reaction with o-nitroaniline, cyclopenteno-, cyclohexeno-, cycloheptено-, and cyclooctено-8-nitroquinolines were prepared and reduced to the aminoquinolines. From these, using glycerol in an ordinary Skraup reaction the four corresponding mono-cycloalkeno-1,10-phenanthrolines were prepared. Using a second mole of hydroxymethyl-cycloalkanone on the cycloalkenoaminoquinoline in the Yale procedure, 3,4-dicyclopenteno-, hexeno-, and hepteno-, 1,10-phenanthrolines were synthesized.

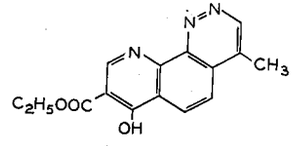
Dehydrogenation of 3,4-cyclohexeno-8-nitroquinoline (X) by chloranil, yielded 4-nitrophenanthridine (XI). This was reduced to 4-aminophenanthridine, which in a Skraup reaction with glycerol yielded 3,4-benzo-1,10-phenanthroline, (XII).



X XI XII

Aza-1,10-Phenanthrolines

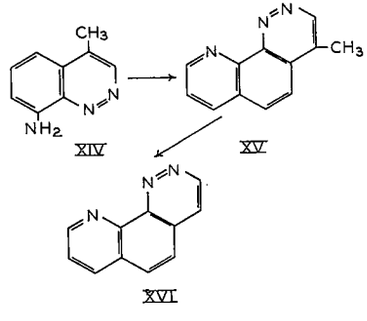
2-Aza-4-methyl-7-hydroxy-8-carbethoxy-1,10-phenanthroline (XIII) has been synthesized,[31] by the action of ethyl ethoxymethylenemalonate,



XIII

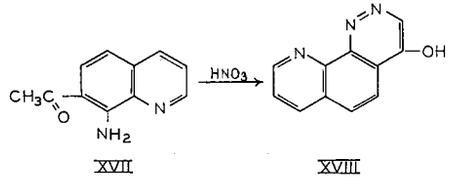
$C_2H_5OOCC(=CHOC_2H_5)COOC_2H_5$, on 4-methyl-8-aminocinnoline, followed by ring closure in Dowtherm (see analogous preparation of 4,7-dihydroxy-3,8-dicarbethoxy-phenanthroline[21]). Hydrolysis of the above azaphenanthroline yielded the free acid which was decarboxylated to 2-aza-4-methyl-7-hydroxy-1,10-phenanthroline.

2-Aza-1,10-phenanthroline[32] (XVI) has recently been synthesized in the following manner: 8-amino-4-methyl-cinnoline (XIV) was converted in a Skraup reaction to 4-methyl-2-aza-1,10-phenanthroline (XV), from which the methyl group was removed by oxidation and subsequent decarboxylation.



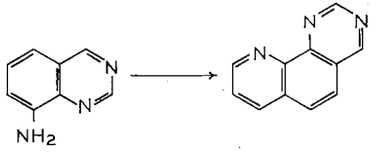
XIV XV XVI

Reduction of 7-acetyl-8-nitroquinoline with iron and acetic acid yielded the corresponding amine (XVII) which on diazotization in sulfuric acid yielded 4-hydroxy-2-aza-1,10-phenanthroline[32] (XVIII).



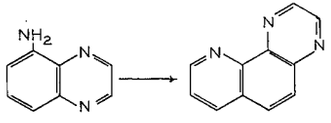
XVII XVIII

From 8-aminoquinazoline (XIX) in a Skraup reaction was obtained 3-aza-1,10-phenanthroline[31] (XX).



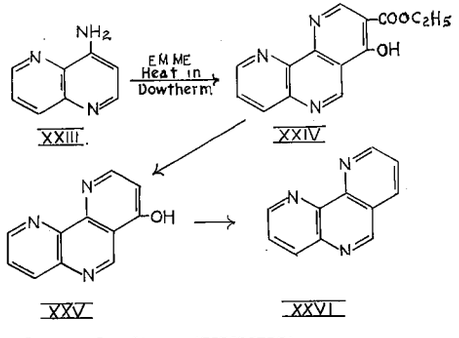
XIX XX

A Skraup reaction on 5-aminoquinoxaline (XXI) yielded 4-aza-1,10-phenanthroline[32] (XXII).



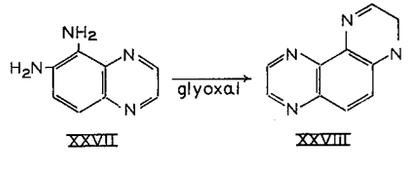
XXI XXII

For the preparation of 5-aza-1·10-phenanthroline (XXVI) 4-amino-1,5-naphthyridine (XXIII) was treated with ethyl ethoxymethylenemalonate followed by cyclization in Dowtherm to yield (XXIV) which on hydrolysis and decarboxylation yielded 4-hydroxy-6-aza-1,10-phenanthroline (XXV). Treatment with phosphorus oxychloride followed by reduction in presence of palladium yielded XXVI.



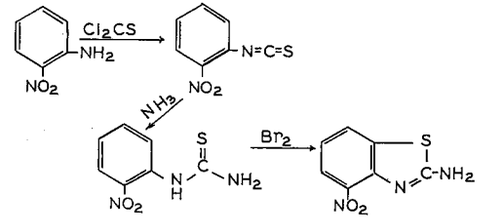
XXIII XXIV XXV XXVI

4-7-Diaza-1,10-phenanthroline (XXVIII) was prepared[32] by reducing 5,6-dinitroquinoxaline to the diamine (XXVII) and treating with glyoxal.



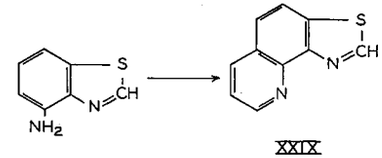
XXVII XXVIII

A thio analogue of 1,10-phenanthroline, pyrido-2′,3′,4,5-benzothiazole[33] (XXIX) has been made by the following series of reactions: In the result-



XXX

ing 2-amino-l-nitro-benzothiazole (XXX) the amino group was replaced by chlorine in a Sandmeyer reaction, the nitro group reduced, and the chlorine replaced by hydrogen using hydrogen iodide and phosphorus in successive reactions. The final step was a Skraup reaction involving glycerol.



XXIX

2,2′-Bipyridines

The parent compound, 2,2′-bipyridine (XXXI) has been prepared by the following different methods:

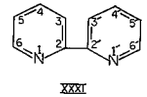
a. Pyrolysis of copper picolinate[34]

b. Action of anhydrous ferric chloride on pyridine at 300°[35]

c. Action of sodium on pyridine, followed by oxidation[36]

d. Dehydrogenation of pyridine by nickel at 300°[37]

e. Action of copper on 2-bromopyridine[38]



XXXI

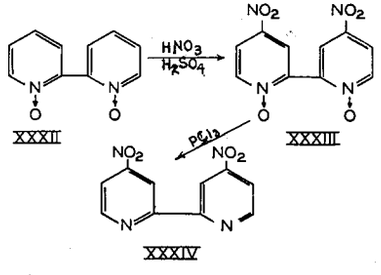
The preparation of substituted 2,2′-bipyridines may involve (a) substitution reactions applied to bipyridine itself or (b) reactions which join together in the 2-position two substituted pyridine nuclei. Class (a) will be considered first.

Bromination of 2,2′-bipyridine at 500° has been found,[39] to yield 6-bromo- and 6,6′-dibromo-2,2′-bipyridine. These on treatment with cuprous cyanide yielded the corresponding mono- and dinitriles, and the dinitriles in turn were hydrolyzed to the mono- and dicarboxylic acids.

Amination of 2,2′-bipyridine with sodamide,[40] yielded 6,6′-diamino-2,2′-bipyridine.

By the action of phenyl lithium on 2,2′-bipyridine, 6-phenyl and 6,6′-diphenyl-2,2′-bipyridine have been prepared.[41,42] The latter has also been made by the action of copper on 2-bromo-6-phenylpyridine.[43]

A new method of synthesis of 4,4′-disubstituted 2,2′-bipyridines starts from 2, 2′-bipyridine di-N-oxide (XXXII), prepared[44] by the action of hydrogen peroxide in glacial acetic acid on 2,2′-bipyridine. Nitration of the dioxide yields 4,4′-dinitro-2,2′-bipyridine-dioxide (XXXIII) which on treatment with phosphorus trichloride in chloroform yields 4,4′-dinitro-2,2′-bipyridine[44] (XXXIV).



On treatment with iron and acetic acid the dinitrodioxide is converted directly to 4,4′-diamino-2,2′-bipyridine.[45] The structure of this compound was confirmed by oxidizing 4,4′-dimethyl-2,2′-bipyridine to the dicarboxylic acid, forming the diethyl ester and converting it to the diamide which, on treatment with sodium hypobromite, yielded a product identical with the diamino bipyridine previously prepared.[45]

On treatment with acetyl chloride, 4,4′-dinitro-2,2′-bipyridine dioxide was converted to the 4,4′-dichloro dioxide and this with $POCl_3$ in chloroform yielded 4,4′-dichlorobipyridine.[44] Substituting acetyl bromide and phosphorus tribromide in the above reactions produced 4,4′-dibromo-2,2′-bipyridine.[45] The dichloro dioxide on heating with aqueous diethyl amine in a sealed tube yielded the bis-diethylamino dioxide from which 4,4′-bis-diethylamino-2,2′-bipyridine was obtained on treatment with phosphorus trichloride in chloroform.[45]

Treatment of 4,4′-dinitro-2,2′-bipyridine dioxide with sodium ethoxide,

sodium methoxide, and sodium phenoxide yielded the respective diethoxy-, dimethoxy-, and diphenoxy-bipyridine dioxides from which by the action of PCl_3 in chloroform were obtained 4,4′-diethoxy-, dimethoxy-, and diphenoxy-2,2′-bipyridines. An attempt to hydrolyze diethoxy bipyridine to the dihydroxy derivative with hydrobromic acid yielded 4-hydroxy-4′-ethoxy-2,2′bipyridine.[45]

The second class, (b), of reactions used in the preparation of substituted 2,2′-bipyridines is similar to those used for the preparation of 2,2′-bipyridine from pyridine, *i.e.*, either an Ullmann reaction involving treating a 2-halopyridine with copper, catalytic dehydrogenation, or mild oxidation with anhydrous ferric chloride.[35]

Thus, α-picoline, heated with ferric chloride, has been found to yield 4,4′-dimethyl-2,2′-bipyridine[46] and this has also been made by the action of copper on 2-bromo-4-methylpyridine. β-Picoline with ferric chloride yields 5,5′-dimethyl-2,2′bipyridine, (also obtainable from 2-bromo-5-methylpyridine and copper) as well as a small amount of 3,3′-dimethyl-2,2′-bipyridine, which was synthesized from 2-bromo-3-methyl pyridine and copper. From the 4,4′- and 5,5′-dimethyl derivatives the dimethyl esters of the carboxylic acids were prepared by permanganate oxidation followed by treatment with methanol and sulfuric acid.[46]

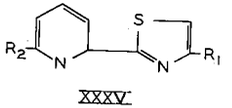
6,6′-Dimethyl-2,2′-bipyridine has been made both by dehydrogenation of α-picoline with nickel,[40] and by an Ullmann reaction from 2-bromo-6-methylpyridine.

2,2′-Bipyridine-3,3′-dicarboxylic acid has been prepared by the oxidation of 1,10-phenanthroline.[40]

5,5′-Dichloro-2,2′-bipyridine is formed in an Ullmann reaction on 2-bromo-5-chloropyridine, and 5,5′-dibromobipyridine similarly from 2,5-dibromopyridine.[46] 2-Bromo-4-phenylpyridine yields with copper 4,4′-diphenyl-2,2′bipyridine.[47] From 2-iodo-5-nitropyridine and copper was obtained 5,5′-dinitro-2,2′-bipyridine.[46]

Pyridines Substituted by Heterocyclic Radicals Forming a Ferroïn System

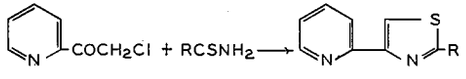
Substituted 2-(2′-pyridyl)-thiazoles[41] (XXXV): Pyridine- and 6-methylpyridine-2-thiocarboxamides (prepared by the action of hydrogen sulfide on the nitriles) were condensed with the reagents indicated in the table to form the products indicated.



XXXV

Starting Products	Compounds Formed (see Formula XXXV) R_1	R_2
$NC_5H_4CSNH_2 + ClCH_2CHClOC_2H_5$	H	H
$NC_5H_4CSNH_2 + ClCH_2COCH_3$	CH_3	H
$NC_5H_4CSNH_2 + ClCH_2COC_6H_5$	C_6H_5	H
$NCH_3C_5H_3CSNH_2 + ClCH_2COCH_3$	CH_3	CH_3
$N(CH_3)C_5H_3CSNH_2 + ClCH_2COC_6H_5$	C_6H_5	CH_3

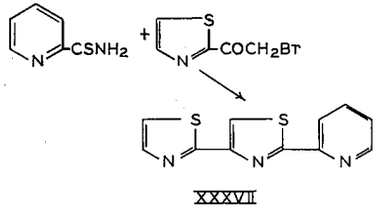
4-(2′-pyridyl) thiazoles[41,48] (XXXVI):- 2-Acetylpyridine was converted to ω-bromo-, or ω-chloro-acetylpyridine, from which were formed the following substituted thiazoles by the use of thiourea, thiophenylacetamide, and thioformamide, respectively.



XXXVI

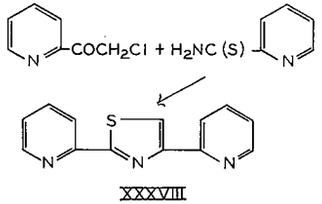
R=NH_2-, $C_6H_5CH_2$-, and H.

The action of pyridine-2-thiocarboxamide and 2-bromoacetyl thiazole produced 2-(2″-pyridyl)-4,2′-dithiazolyl[48] (XXXVII).



XXXVII

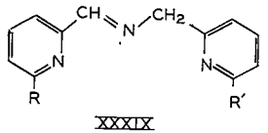
From 2-chloroacetylpyridine and pyridine-2-thiocarboxamide was obtained 2,4-bis-(2′pyridyl) thiazole[49] (XXXVIII).



XXXVIII

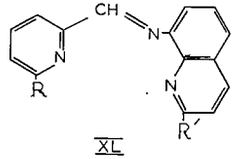
Schiff Bases Containing the Ferroïn Group

A series of these compounds has been prepared by causing the pairs of compounds indicated in the following tables to react. The crude product was then converted to the metal chelate.



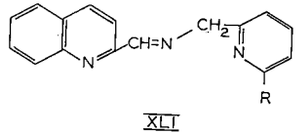
XXXIX

Formula XXXIX	Name	Derived From
R = R′ = H	2-(α-pyridylmethyleneaminomethyl)-pyridine[50]	A + E
R = CH_3; R′ = H	2-(6′-methyl-α-pyridylmethyleneaminomethyl)-pyridine[51]	D + E
R = H; R′ = CH_3	6-methyl-2-(α-pyridylmethyleneaminomethyl)-pyridine[51]	A + F
R = R′ = CH_3	6-methyl-2-(6′-methyl-α-pyridylmethyleneaminomethyl)-pyridine[51]	D + F



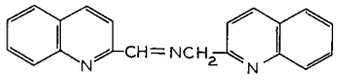
XL

Formula XL	Name	Derived From
R = R′ = H	8-(α-pyridylmethyleneamino)-quinoline[52]	A + G
R = H; R′ = CH_3	8-(α-pyridylmethyleneamino)-quinaldine[50]	A + H
R = CH_3; R′ = H	8-(6′-methyl-α-pyridylmethyleneamino)-quinoline[51]	D + G
R = R′ = CH_3	2-methyl-8-(6′-methyl-α-pyridylmethyleneamino)-quinoline[51]	D + H



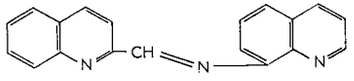
XLI

Formula XLI	Name	Derived From
R = H	2-(2′-quinolylmethyleneaminomethyl)-pyridine[51]	B + E
R = CH_3	6-methyl-2-(2′-quinolylmethyleneaminomethyl)-pyridine[51]	B + F



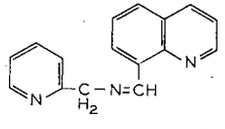
XLII

Formula XLII	Name	Derived From
	2-(2′-quinolylmethyleneaminomethyl)-quinoline[51]	B + I



XLIII

Formula XLIII	Name	Derived From
	8-(2′-quinolylmethyleneamino)-quinoline[51]	B + G



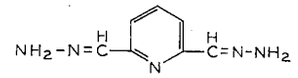
XLIV

Formula XLIV	Name	Derived From
	2-(8′-quinolylmethyleneaminomethyl)-pyridine[50]	C + E

In formulas XXXIX to XLIV of the above tables: A represents pyridine-2-carboxaldehyde; B=quinoline-2-carboxaldehyde; C=quinoline-8-carboxaldehyde; D = 6-methylpyridine-2-carboxaldehyde; E = 2-aminomethylpyridine, prepared by reduction of the oxime of A; F=6-methyl-2-aminomethylpyridine, similarly prepared from the oxime of D; G=8-aminoquinoline; H=8-aminoquinaldine; I=2-aminomethylquinoline, from the reduction of the oxime of B.

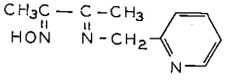
Compounds of similar structure which have recently been prepared are:

2,6-Pyridinedialdihydrazone[53] (XLV) prepared from pyridine-2,6-dicarboxaldehyde and hydrazine.



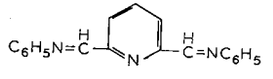
XLV

2-Oximino-3-methyl-4-aza-α-pyridyl-△[3]-pentene[50] (XLVI), prepared from biacetyl monoxime and 2-pyridylmethylamine.



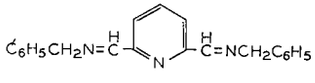
XLVI

2,6-Pyridylene-bis-methylene-aniline[50] (XLVII) from pyridine-2,6-dicarboxaldehyde and aniline.



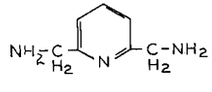
XLVII

2,6-Pyridylene-bis-methylenebenzylamine[50] (XLVIII) from pyridine-2,6-dicarboxaldehyde and benzylamine.



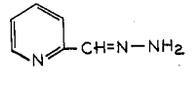
XLVIII

2,6-Bis-(aminomethyl) pyridine[50] (XLIX) from the reduction by zinc and acetic acid of pyridine-2,6-dialdoxime.



XLIX

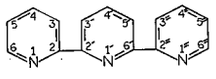
The preparation of 2-pyridinal hydrazone (L) has also been reported.[53]



L

Preparation of 2,2′,2″-Terpyridines

2,6-Bis-(2′-pyridyl)-pyridine or 2,2′,2″-terpyridine (LI) is a byproduct in the manufacture of 2,2′-bipyridine by the action of anhydrous ferric chloride on pyridine. It remains in the residue after the bipyridine has been removed by steam distillation. It has been synthesized by the action of 2-bromopyridine, 6-bromo-2,2′-bipyridine and copper.[39]



LI

On bromination at 500° terpyridine yields 2-(2′-pyridyl)-6-(6′-bromo-2′-pyridyl)-pyridine and 2,6-bis-(6′-bromo-2′-pyridyl)-pyridine.[39]

The preparation of substituted 4-phenylterpyridines involves Chichibabin's reaction as modified by Frank and Seven,[54] in which a substituted 2-acetyl pyridine is condensed with benzaldehyde, ammonia and ammonium acetate at 250°. The following table indicates the starting ketone and resulting substituted terpyridine.

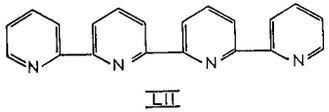
Ketone	2,6-Bis-(R)-4-Phenylpyridine R	Yield %	Literature Reference
2-acetylpyridine	(2′-pyridyl)	17.2	55
2-acetyl-4-methylpyridine	(4′-methyl-2′-pyridyl)	18.0	47
2-acetyl-4-ethylpyridine	(4′-ethyl-2′-pyridyl)	16.0	47
2-acetyl-4-phenylpyridine	(4′-phenyl-2′-pyridyl)	21.0	47
2-acetyl-6-phenylpyridine	(6′-phenyl-2′-pyridyl)	17.0	47
2-acetylquinoline	(2′-quinolyl)	18.0	47

Preparation of Polypyridines[39]

Tetrapyridine (LII) has been prepared in two ways:

(a) 6-Bromo-2,2′-bipyridine + copper

(b) Two moles of 2-bromopyridine + 6,6′-dibromo-2,2′bipyridine + copper

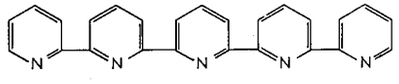


LII

Pentapyridine (LIII) has been made from:

(a) Two moles of 6-bromo-2,2′-bipyridine + 2,6-dibromopyridine + copper

(b) Two moles of 2-bromopyridine + 2,6-bis-(6′-bromo-2′-pyridyl) pyridine + copper

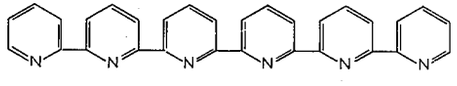


LIII

Hexapyridine (LIV) has been prepared from:

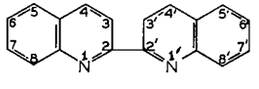
(a) Two moles of 6-bromo-2,2′-bipyridine + 6,6′-dibromo-2,2′-bipyridine + copper

(b) Two moles of 6′-bromo-2,6-bis-(2′-pyridyl) pyridine + copper



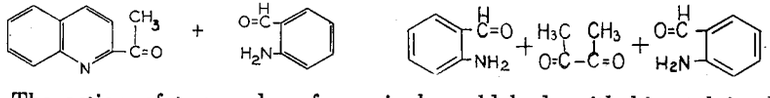
LIV

Preparation of 2,2′-Biquinolines



LV

The preparation of 2,2′-biquinoline (LV) has been effected (a) by catalytic dehydrogenation of quinoline in presence of nickel [56] and (b) by a synthetic process such as treatment of 2-acetylquinoline with o-amino-benzaldehyde in presence of sodium hydroxide.[57]



The action of two moles of o-aminobenzaldehyde with biacetyl is also claimed as a method[57] but the yield has been found to be negligible. Whereas substituted biquinolines prepared by catalytic dehydrogenation of a substituted quinoline are likely to be of uncertain structure, this is not true of those made by method (b).

4,4′- and 6,6′-Dimethylbiquinoline,[58] have been prepared by the catalytic dehydrogenation (nickel) of 4- and 6-methylquinolines. In the former

case the structure was confirmed by synthesis from 2-chloro-4-methylquinoline and copper. Attempts to dehydrogenate 7- and 8-methylquinolines were unsuccessful.

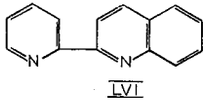
4,4′-Diphenyl-2,2′-biquinoline results from the action of 2-bromo-4-phenylquinoline and copper,[59] and 8,8′-diethyl-2,2′biquinoline is prepared similarly from 2-bromo-8-ethylquinoline.[60] 8,8′-Diphenyl- and 8,8′-dimethyl-2,2′biquinoline[60] result (in very low yield) from the action of 2-bromo-8-phenyl- and 8-methyl-quinoline, respectively, with hydrazine hydrate and palladium on calcium carbonate in presence of alcoholic potassium hydroxide (method of Ueda[61]). The preparation of the 8,8′-dimethylquinoline was previously claimed to have been effected by the action of sodium on 8-methylquinoline, but the results of the preparation described above appear to refute the claims.

The following substituted 2,2′-biquinolines have been prepared by the action of a quinolyl ketone and an aminoaldehyde or ketone:

2,2′-Biquinoline	Aminoaldehyde or Ketone	2-Quinolyl Alkyl Ketone	Yield %	Literature Reference
3-methyl	o-aminobenzaldehyde	ethyl	80	62
3-ethyl	"	n-propyl	60	59
3-n-propyl	"	n-butyl	33.5	59
3-phenyl	"	benzyl	60	59
3-carbethoxy	"	$C_2H_5OOCCH_2$-	69	59
4-methyl	o-aminoacetophenone	methyl	5	59
4-phenyl	o-aminobenzophenone	methyl	17	59

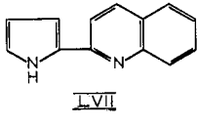
Quinolines Substituted by Heterocyclic Radicals

2-(2′-pyridyl)-quinoline[57] (LVI) has been prepared by the action of 2-acetylpyridine and o-aminobenzaldehyde in the presence of dilute alkali.



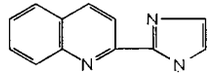
LVI

If 2-acetyl pyrrole is used in this reaction, 2-(2′-pyrryl) quinoline (LVII) is the result.[57]



LVII

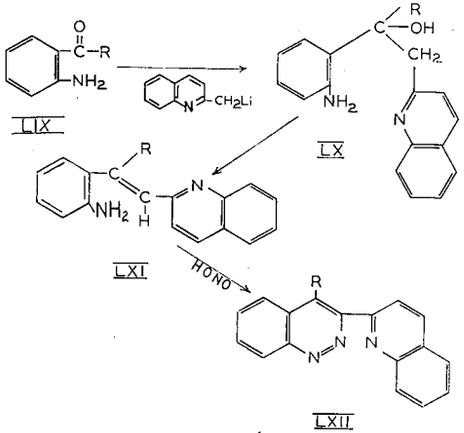
When 2-propionyl pyridine is used, 2-(2′-pyridyl)-3-methylquinoline is formed.[62] 2-(2′-imidazolyl)-Quinoline (LVIII) was prepared from 2-chloroquinoline and the silver salt of imidazole.[57]



LVIII

An Azabiquinoline and-pyridylquinoline[63]

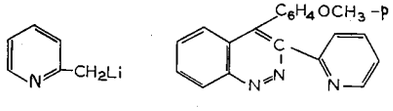
2-Amino-4′-methoxybenzophenone (LIX) was treated with quinaldyl lithium, and the resulting carbinol (LX) dehydrated to an alkene, (LXI). Diazotization of the amino group then yielded 3-(2′-quinolyl)-4-(p-methoxyphenyl)-cinnoline (LXII) by closing the cinnoline ring.



LIX LX LXI LXII

(R = p-$C_6H_4OCH_3$)

By the use of α-picolyl lithium (LXIII) instead of quinaldyl lithium, the pyridyl analogue (LXIV) resulted.

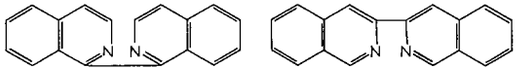


LXIII LXIV

Two other derivatives were prepared by the same method in which p-methoxyphenyl was replaced by phenyl in the above compounds.

Biisoquinolines

By the action of 1-bromoisoquinoline and copper, 1,1′biisoquinoline[64]



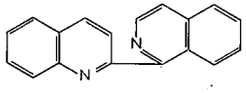
LXV

LXVI

(LXV) was obtained. The preparation of 3,3′-biisoquinoline (LXVI) was effected similarly from 3-bromoisoquinoline, prepared from 3-methylisoquinoline[64] through successive formation of the aldehyde, acid, ester, amide, amine, and bromo derivative.

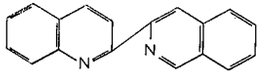
Isoquinolines Substituted by Heterocyclic Radicals

1-(2′-quinolyl) Isoquinoline[62] (LXVII) was prepared from 1-acetylisoquinoline and o-aminobenzaldehyde in alkaline solution.



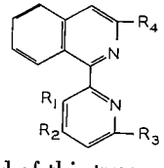
LXVII

3-(2′-quinolyl) Isoquinoline (LXVIII) was similarly prepared using 3-acetylisoquinoline.[65]



LXVIII

A series of substituted 1-(2′-pyridyl) isoquinolines[41] (LXIX) has been prepared by treating isoquinolines with the lithium derivative of the substituted pyridine.

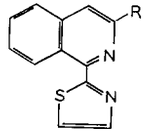


LXIX

The compounds prepared of this type are indicated in the following table:

Compound	R_1	R_2	R_3	R_4
A	H	H	H	H
B	H	CH_3	H	H
C	CH_3	H	H	H
D	H	H	H	CH_3
E	CH_3	H	H	CH_3
F	H	H	CH_3	CH_3
G	H	CH_3	H	CH_3

By using the lithium derivative of thiazole with isoquinoline two compounds of the general formula (LXX) were prepared, where R=H and CH_3.[41]



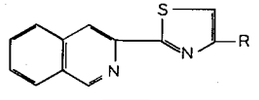
LXX

Three 3-(2′-thiazolyl) isoquinolines,[65] of formula LXXI were prepared by condensing isoquinoline 3-thiocarboxamide (from the nitrile + hydrogen sulfide) with:

(a) ethyl, α,β-dichloroethylether (R = H);

(b) chloroacetone (R = CH_3);

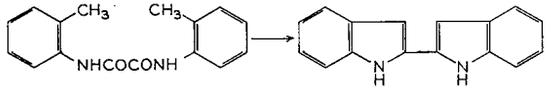
(c) ω-chloroacetophenone (R = C_6H_5).



LXXI

Biindyl

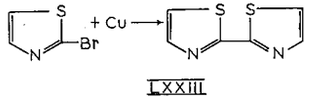
2,2′-Blindyl (LXXII) has been prepared by the action of sodium amylate and the ditoluide of oxalic acid at 360°.[66]



LXXII

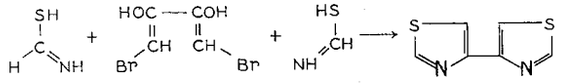
Di- and Polythiazolyls

2-aminothiazole subjected to the diazonium reaction yielded the 2-bromo derivative, which yielded 2,2′-dithiazolyl[67] (LXXIII) in an Ullmann reaction.



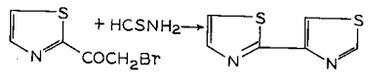
LXXIII

The action of thioformamide, $HCSNH_2$ (2 moles) and 1,4-dibromodiacetyl yielded 4,4′-dithiazolyl[68] (LXXIV).



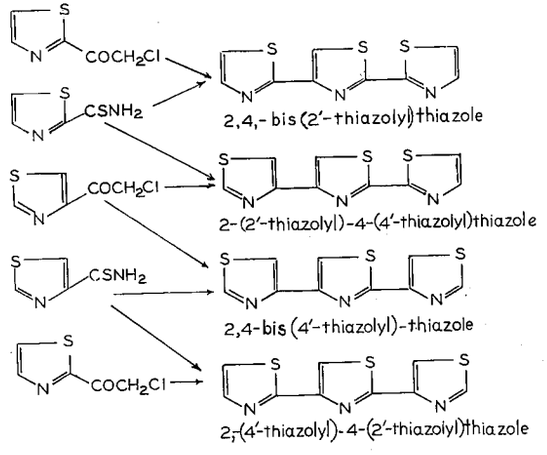
LXXIV

2-Ethylthiazole was converted to the acetyl derivative by reaction with benzaldehyde followed by ozonolysis. Its ω-bromoacetyl derivative on treatment with thioformamide yielded 2,4′-dithiazolyl[69] (LXXV).



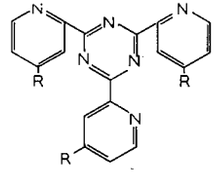
LXXV

A number of trithiazolyls,[48] were prepared using the pairs of reactants indicated in the following scheme.



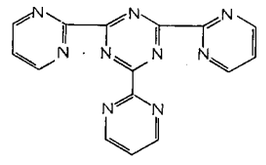
Substituted 1,3,5-Triazines Containing the Ferroïn Group[70]

By the trimerization of certain 2-cyanopyridines by means of sodium hydride a series of substituted triazines of the general formula LXXVI was prepared. Thus 2-cyanopyridine yielded 2-4,6-tris-(2′-pyridyl)-1,3,5-



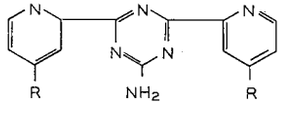
LXXVI

triazine (R = H); 4-methyl-2-cyanopyridine yielded 2,4,6-tris-(4′-methyl-2′-pyridyl)-1,3,5-triazine ($R = CH_3$); 4-ethyl-2-cyanopyridine yielded 2,4,6-tris-(4′-ethyl-2′-pyridyl)-1,3,5-triazine, ($R = C_2H_5$); 4-phenyl-2-cyanopyridine yielded 2,4,6-tris-(4′-phenyl-2′-pyridyl)-1,3,5-triazine, ($R = C_6H_5$). From 2-cyanoquinoline was obtained 2,4,6-tris-(2′-quinolyl-1,3,5-triazine. 2-Cyanopyrimidine on long standing yielded 2,4,6-tris (2′-pyrimidyl)-1,3,5-triazine (LXXVII).



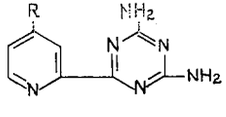
LXXVII

By the action of guanidine with 2-cyanopyridine was obtained 2-amino-4,6-(bis-2′-pyridyl)-1,3,5-triazine (LXXVIII) (R = H); from 4-ethyl-2-cyanopyridine and 4-phenyl-2-cyanopyridine were obtained the corresponding triazines, ($R = C_2H_5$- and C_6H_5-) respectively. 2-Cyanoquinoline yielded 2-amino-4,6-bis(2′quinolyl)-1,3,5-triazine.



LXXVIII

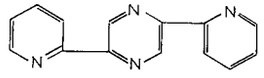
With dicyandiamide, 2-cyanopyridine yielded 2,4-diamino-6-(2′-pyridyl)-1,3,5-triazine, (LXXIX), (R = H). 4-Ethyl-, and 4-phenyl-2-cyanopyridine yielded the corresponding substituted triazines ($R = C_2H_5$- and C_6H_5- respectively).



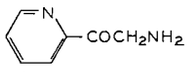
LXXIX

Pyridylpyrazines and Quinoxalines

2,5-bis-(2′-pyridyl)-pyrazine (LXXX) has been synthesized by the self-condensation of 2-pyridylaminomethylketone (LXXXI) followed by dehydrogenation.

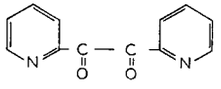


LXXX

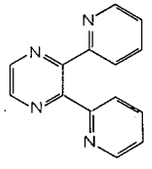


LXXXI

Interaction of 2,2′-pyridil (LXXXII) with ethylenediamine, followed by dehydrogenation of the resulting dihydro compound, yields 2,3-bis (2′-pyridyl)-pyrazine[51] (LXXXIII).

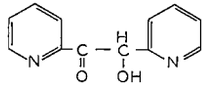


LXXXII

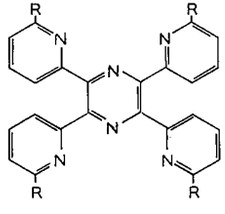


LXXXIII

By the reaction of 2,2′-pyridoin (LXXXIV) and 6,6′-dimethyl-2,2′-pyridoin with ammonium acetate were prepared 2,3,5,6-tetrakis-(2′-pyridyl)-pyrazine (LXXXV) and 2,3,5,6-tetrakis-(6′methyl-2′pyridyl)-pyrazine (LXXXVI) respectively.[51]

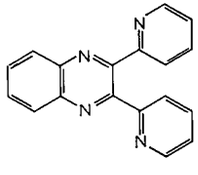


LXXXIV



LXXXV; R=H
LXXXVI; R=CH_3

Treatment of 2,2′-pyridil with o-phenylene diamine resulted in the formation of 2,3-bis-(2′-pyridyl)-quinoxaline[51] (LXXXVII).



LXXXVII

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