[Contribution from the Chemistry Department of Temple University]

SUBSTITUTED 1,10-PHENANTHROLINES. VIII. 2- AND 3-PHENYL DERIVATIVES[1]

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The work described in this paper was designed to complement that previously reported (1) on phenylphenanthrolines. Tests (2, 3) on these compounds by Dr. G. F. Smith have shown that the introduction of one or more phenyl groups in the 1,10-phenanthroline nucleus, in some cases [particularly the 4,7-diphenyl- and the 2,9-dimethyl-4,7-diphenyl derivatives (4)] greatly enhances the sensitivity of the color reaction toward Cu(I) and/or Fe(II). In addition to these studies further information on the steric effect of the phenyl group in inhibiting chelation is desired.

The synthesis of 2-phenyl-1,10-phenanthroline (II) was effected by the action of glycerol in a Skraup reaction on 8-amino-2-phenylquinoline (I) (5). The same amine when treated with cinnamic aldehyde under the conditions of the Yale (6) modification of the Skraup reaction afforded a small yield of 2,9-diphenyl-1,10-phenanthroline (III).

For the preparation of 3-phenyl-1,10-phenanthroline (V) the Skraup reaction between 1,3-diethoxy-2-phenylpropan-2-ol (7) and 8-aminoquinoline was first attempted without success. Another reagent, 1,3-diacetoxy-2-phenylpropan-2-ol [prepared by the action of anhydrous sodium acetate on 1,3-dichloro-2-phenylpropan-2-ol (8)] similarly treated with 8-aminoquinoline, also afforded no yield, but with *o*-nitroaniline, a small amount of 3-phenyl-8-nitroquinoline (IV) was produced. Subsequently it was found that (IV) is more conveniently made (though in poor yield) in a Doebner-Miller reaction employing *o*-nitroaniline, paraformaldehyde, and phenylacetaldehyde. Reduction of IV to the amine, and treatment with acrolein in the Yale modification of the Skraup reaction yielded 3-phenyl-1,10-phenanthroline (V) as a thick oil which would not solidify. From it the pure hydrochloride and picrate were made.

The action of ethyl α,α-formylphenylacetate (9) on aniline has previously been shown (10) to yield 4-hydroxy-3-phenylquinoline. By its action on 8-aminoquinoline followed by ring closure, we prepared 4-hydroxy-3-phenyl-1,10-phenanthroline (VI). From this by reduction of the corresponding bromo compound an oil was obtained, the analysis of which suggested a dihydro derivative although the deviation from the calculated carbon-hydrogen values for 3-phenyl-1,10-phenanthroline is not great. Though this oil yielded a picrate identical with that from 3-phenyl-1,10-phenanthroline previously prepared this cannot necessarily be taken to mean that the liquids were identical since Geissman (11) has shown that certain 2-phenyl-1,2-dihydropyridine derivatives yield the same picrates as the corresponding dehydrogenated compounds.

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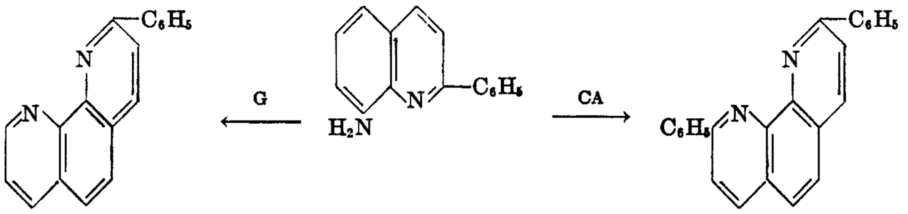
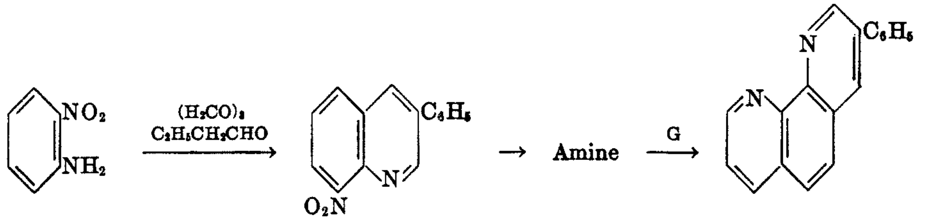
By the action of two moles of ethyl α,α-formylphenylacetate on *o*-phenylenediamine, followed by ring closure 4,7-dihydroxy-3,8-diphenyl-1,10-phenanthroline (VII) was prepared. Reduction of the corresponding dibromo compound with hydrogen in presence of Raney nickel yielded 3,8-diphenyl-1,10-phenanthroline (VIII).

From ethyl α,α-formylphenylacetate and 8-amino-6-phenylquinoline (IX) (1) there was obtained 4-hydroxy-3,5-diphenyl-1,10-phenanthroline (X). Failure to prepare the bromo compound prevented conversion to the corresponding diphenylphenanthroline.

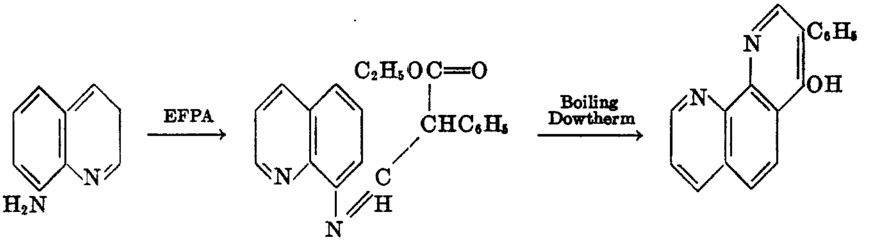
By the action of phenyllithium on 2,2′-bipyridine Geissman, *et al.* (11) obtained the corresponding 6,6′-diphenyl derivative. Similar treatment of 1,10-phenanthroline in our hands was without result, but from 4,7-dimethyl-1,10-phenanthroline (XI) (12) we obtained 4,7-dimethyl-2,9-diphenyl-1,10-phenanthroline (XII), and from 4,7-diphenyl-1,10-phenanthroline (XIII) (1), 2,4,7,9-tetraphenyl-1,10-phenanthroline (XIV) resulted. These two phenanthrolines had previously resisted attempts to prepare them by Skraup techniques.



II I III



IV V



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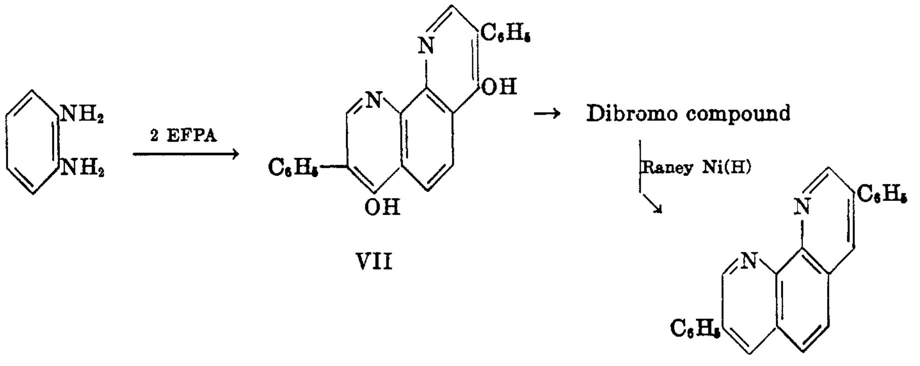
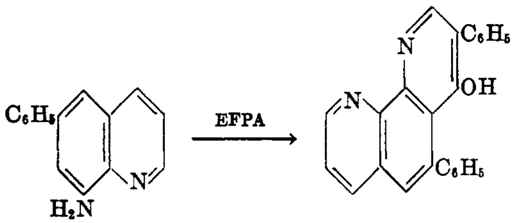


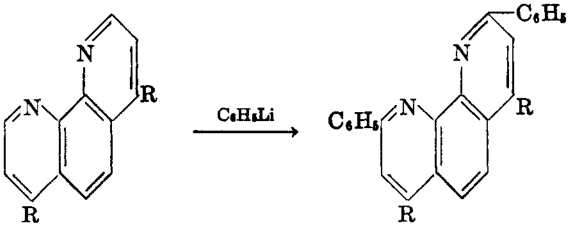
VII

VIII



IX

X



XI R = CH_3
XIII R = C_6H_5

XII R = CH_3
XIV R = C_6H_5

In this table G = glycerol; CA = cinnamic aldehyde; EFPA = ethyl α,α-formylphenylacetate, $C_2H_5OOCCH(C_6H_5)CHO$.

EXPERIMENTAL PART[2]

2-Phenyl-1,10-phenanthroline. To a stirred mixture of 11 g. (0.05 mole) of 8-amino-2-phenylquinoline (5), 9 g. of arsenic acid, 24 ml. of concentrated sulfuric acid, and 8 ml. of water, heated to 100°, there was added 18.4 g. (0.2 mole) of glycerol. The temperature was raised to 140° and maintained there for two hours. The reaction mixture then was cooled and neutralized with sodium hydroxide solution. The precipitated product was dried and extracted with boiling benzene. After removal of the solvent by distillation, the residue was crystallized from petroleum ether (b.p. 90–100°). The yield of pure product, melting at 104°, was 3 g., or 23.4%.

Anal. Calc'd for $C_{18}H_{12}N_2$: C, 84.38; H, 4.69.
Found: C, 84.36; H, 4.76.

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[2] Analyses were done by Huffman Microanalytical Laboratories, Wheatridge, Colorado.

2,9-Diphenyl-1,10-phenanthroline. To a stirred mixture of 14.6 g. of 8-amino-2-phenylquinoline, 18 g. of arsenic acid, and 40 ml. of 85% phosphoric acid, heated to 100°, was added 16 g. of cinnamic aldehyde at such a rate that the temperature did not rise above 120°. After two hours' heating at 120–135°, the mixture was poured on ice and neutralized with potassium hydroxide solution. The resulting solution and precipitate were extracted with hot benzene. The tarry residue, after removal of benzene, was extracted with warm concentrated hydrochloric acid. Neutralization with sodium hydroxide, re-extraction with benzene, removal of solvent, and crystallization from benzene yielded 1.2 g. of a solid melting at 185–186°.

Anal. Calc'd for $C_{24}H_{16}N_2$: C, 86.71; H, 4.85.

Found: C, 86.74; H, 4.86.

8-Nitro-3-phenylquinoline. Method A. A mixture of 63 g. of 1,3-dichloro-2-phenylpropan-2-ol (8), 56 g. of anhydrous sodium acetate, and 85 ml. of absolute ethanol was heated under reflux for 24 hours. The reaction mixture then was poured on ice and extracted with ether. Removal of the ether and distillation *in vacuo* yielded 32.5 g. of a liquid boiling at 150–160° (10 mm.) which still gave a test for halogen but was used in the next experiment. To a stirred mixture of 13.5 g. of *o*-nitroaniline, 13.5 g. of arsenic acid, 42 ml. of concentrated H_2SO_4, and 12 ml. of water, heated to 100°, there was gradually added 32 g. of the above crude 1,3-diacetoxy-2-phenylpropan-2-ol, keeping the temperature below 120°. After two hours' heating at 120–130° the mixture was poured on ice, neutralized with sodium hydroxide, and extracted with hot benzene. Removal of the solvent yielded a tar which on extraction with petroleum ether (b.p. 90–100°), removal of solvent, and crystallization from methanol, afforded 1.2 g. of product melting at 110–120°. Pure 8-nitro-3-phenylquinoline melts at 116-117°.

Anal. Calc'd for $C_{15}H_{10}N_2O_2$: C, 71.97; H, 4.03.

Found: C, 72.14; H, 4.03.

Method B. To a mixture of 200 ml. of concentrated hydrochloric acid, 13.8 g. of *o*-nitroaniline, 11.5 g. of arsenic acid, and 10 g. of anhydrous zinc chloride, heated on the steam-bath, was added during one-half hour a suspension of 9 g. of paraformaldehyde in 55.2 g. of a 50% solution of phenylacetaldehyde (Eastman Kodak technical grade redistilled) in ethanol. Heating was continued at this temperature for 3 hours. The hot hydrochloric acid solution then was decanted from the resulting tar, which was re-extracted with the same acid. The combined acid extracts were made alkaline with sodium hydroxide, and the solution was extracted with benzene. Removal of the benzene left a residue which was repeatedly extracted with boiling petroleum ether (90–100°). The residue, after removal of the solvent and crystallization from methanol, yielded 3.5 g. of product melting at 105°, which could be further purified by recrystallization from the same solvent.

8-Amino-3-phenylquinoline. To a stirred suspension of 10.5 g. of crude 8-nitro-3-phenylquinoline in 100 ml. of 50% acetic acid, maintained at 60°, was added 6.5 g. of powdered iron. Heating then was continued on the steam-bath for one hour. After neutralization with sodium hydroxide, the mixture was extracted with ether. The residue from removal of the ether was extracted with petroleum ether (60–70°), and after removal of solvent yielded 7.5 g. of crude amine which was used for the preparation of the phenanthroline. Crystallization from light petroleum ether yielded the pure amine, m.p. 74–75°.

Anal. Calc'd for $C_{15}H_{12}N_2$: C, 81.78; H, 5.49.

Found: C, 81.38; H, 5.65.

The amine when heated with acetic anhydride on the steam-bath yielded the acetyl derivative, crystallizing from methanol and melting at 147–148°.

Anal. Calc'd for $C_{17}H_{14}N_2O$: C, 77.83; H, 5.38.

Found: C, 78.02; H, 5.38.

3-Phenyl-1,10-phenanthroline. To a stirred mixture of 5.8 g. of 8-amino-3-phenylquinoline, 8 g. of arsenic acid, and 40 ml. of 85% phosphoric acid, maintained at 100°, there was added 3.8 ml. of acrolein. Heating was continued for one hour. The mixture then was made alkaline with potassium hydroxide and extracted with hot benzene. Removal of the benzene and extraction with petroleum ether (b.p. 90–100°) yielded 1.7 g. of a viscous oil which would not solidify, but was converted to a monopicrate, which was crystallized from Cellosolve[3]; it melted at 221–222°.

Anal. Calc'd for $C_{24}H_{15}N_5O_7$: C, 59.38; H, 3.11.

Found: C, 59.35; H, 3.15.

3-Phenyl-1,10-phenanthroline monohydrochloride. A mixture of 5.5 g. of pure 3-phenyl-1,10-phenanthroline monopicrate, 12.5 ml. of water, 10 ml. of concentrated hydrochloric acid, and 40 ml. of benzene was heated on the steam-bath until the precipitate dissolved. The aqueous layer, after five extractions with benzene, was made alkaline and extracted with benzene. After removal of solvent, the residue was extracted with petroleum ether (90–100°), which on evaporation, left 2.4 g. of an oil which would not solidify. Addition of 2 ml. of concentrated hydrochloric acid, evaporation to dryness, and crystallization from absolute ethanol yielded 2.2 g. of 3-phenyl-1,10-phenanthroline monohydrochloride, m.p. 210–211°.

Anal. Calc'd for $C_{18}H_{13}ClN_2$: Cl, 12.11. Found: Cl, 12.34.

4-Hydroxy-3-phenyl-1,10-phenanthroline. A mixture of 43.2 g. (0.3 mole) of 8-aminoquinoline, 57.6 g. (0.3 mole) of ethyl α,α-formylphenylacetate (9), and two drops of glacial acetic acid was allowed to stand in a vacuum desiccator for three days. The resulting light yellow oil was added dropwise to 300 ml. of refluxing Dowtherm A and was boiled under reflux for two hours. The solid which separated from the cooled solution was separated by filtration, washed thoroughly with petroleum ether, and crystallized from ethanol. The yield of pure product, melting at 235–236°, was 34.3 g. or 42%.

Anal. Calc'd for $C_{18}H_{12}N_2O$: C, 79.41; H, 4.41.

Found: C, 79.21; H, 4.18.

4-Chloro-3-phenyl-1,10-phenanthroline. To a mixture of 20 g. of PCl_5 and 30 g. of $POCl_3$ in a 200-ml. three-neck round-bottom flask, equipped with a mercury seal, stirrer, thermometer, and reflux condenser, was added 10.88 g. (0.04 mole) of 3-hydroxy-4-phenyl-1,10-phenanthroline and the mixture was boiled under reflux for three hours. The mixture was cooled and carefully poured upon 200 g. of ice with stirring, made basic with sodium hydroxide solution, and the solid was separated by filtration. The product then was dried and extracted with boiling benzene. After removal of the solvent and crystallization of the residue from benzene-petroleum ether, 3 g. (25.9%) of product melting at 149–150° was obtained.

Anal. Calc'd for $C_{18}H_{11}ClN_2$: Cl, 12.22. Found: Cl, 12.20.

4-Bromo-3-phenyl-1,10-phenanthroline. To 20 g. of PBr_3 in the above apparatus, there was added 10.88 g. (0.04 mole) of 4-hydroxy-3-phenyl-1,10-phenanthroline. The temperature of the mixture was maintained at 130° for four hours. After cooling to room temperature, the mixture was carefully poured upon 200 g. of ice and neutralized with sodium hydroxide solution. The resulting solid was separated by filtration, dried, and extracted with boiling benzene. After removal of the solvent, the residue was crystallized from benzene-petroleum ether. The yield of white needles, melting at 158–159°, was 4 g. or 22.3%.

Anal. Calc'd for $C_{18}H_{11}BrN_2$: C, 64.47; H, 3.28.

Found: C, 64.49; H, 3.30.

Reduction of 4-bromo-3-phenyl-1,10-phenanthroline. A mixture of 3 g. of 4-bromo-3-phenyl-1,10-phenanthroline, 1 g. of Raney nickel catalyst, 10 ml. of 10% sodium hydroxide solution, and 50 ml. of absolute ethanol was treated with hydrogen in a Parr shaker for two hours. The catalyst was separated and the ethanol was removed from the filtrate by distillation. The light yellow oil which remained was distilled at reduced pressure, the fraction boiling at 235–238° (1 mm.) being collected. The analysis suggests a dihydro compound.

Anal. Calc'd for $C_{18}H_{14}N_2$: C, 83.72; H, 5.43.

for $C_{18}H_{12}N_2$: C, 84.34; H, 4.73.

Found: C, 83.79; H, 5.40.

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[3] Cellosolve is the trade name for 2-ethoxyethanol of Carbide and Carbon Chemicals Co.

The *picrate* of this oil melted unchanged when mixed with that of 3-phenyl-1,10-phenanthroline, m.p. 221–222°.

4,7-Dihydroxy-3,8-diphenyl-1,10-phenanthroline. A mixture of 10.8 g. (0.1 mole) of *o*-phenylenediamine, 38.4 g. (0.2 mole) of ethyl α,α-formylphenylacetate and two drops of glacial acetic acid was allowed to stand in a vacuum desiccator for three days. The resulting viscous oil was added dropwise to 300 ml. of refluxing Dowtherm A, and then boiled under reflux for 12 hours. The solid which separated from the cooled solution was separated by filtration, washed thoroughly with petroleum ether, and crystallized from N,N-dimethylformamide. The yield of product, melting at 336–337°, was 12.2 g. or 33.5%. An analytical sample, crystallized from a large amount of ethanol, melted at 337–338°.

Anal. Calc'd for $C_{24}H_{16}N_2O_2$: C, 79.12; H, 4.38.
Found: C, 79.03; H, 4.44.

4,7-Dichloro-3,8-diphenyl-1,10-phenanthroline. This was prepared by the action of 40 g. of PCl_5 and 60 g. of $POCl_3$ on 10.9 g. of the dihydroxy derivative in the same way as 4-chloro-3-phenyl-1,10-phenanthroline. The yield of pure product, crystallized from benzene, and melting at 235–236° was 3.2 g., or 26.7%.

Anal. Calc'd for $C_{24}H_{14}Cl_2N_2$: Cl, 17.71. Found: Cl, 17.44.

4,7-Dibromo-3,8-diphenyl-1,10-phenanthroline. This was prepared from 50 g. of PBr_3 and 10.9 g. of the dihydroxy compound in the same way as 4-bromo-3-phenyl-1,10-phenanthroline. The yield of product, crystallized from benzene-petroleum ether, and melting at 240–241°, was 2.7 g. or 18.4%.

Anal. Calc'd for $C_{24}H_{14}Br_2N_2$: C, 58.81; H, 2.86.
Found: C, 59.62; H, 3.02.

3,8-Diphenyl-1,10-phenanthroline. A mixture of 2.5 g. (0.0051 mole) of 3,8-diphenyl-4,7-dibromo-1,10-phenanthroline, 1 g. of Raney nickel catalyst, 10 ml. of 10% potassium hydroxide solution, and 50 ml. of absolute ethanol was shaken with hydrogen in a Parr shaker for one hour. The catalyst was separated by filtration and the solvent was removed from the filtrate by distillation. Crystallization of the residue from benzene-petroleum ether yielded 1 g. (59%) of product melting at 190–191°.

Anal. Calc'd for $C_{24}H_{16}N_2$: C, 86.73; H, 4.92.
Found: C, 86.58; H, 4.74.

4-Hydroxy-3,5-diphenyl-1,10-phenanthroline. A mixture of 22.2 g. (0.1 mole) of 8-amino-6-phenylquinoline, 19.2 g. (0.1 mole) of ethyl α,α-formylphenylacetate, and two drops of glacial acetic acid was allowed to stand in a vacuum desiccator for three days. The resulting light yellow oil was added dropwise to 300 ml. of refluxing Dowtherm A and the mixture was boiled under reflux for five hours. The solid which separated from the cooled solution was filtered and washed thoroughly with petroleum ether. The product, after crystallization from ethanol, melted at 248–249°. Yield: 10.2 g. (29.3%).

Anal. Calc'd for $C_{24}H_{16}N_2O$: C, 82.76; H, 4.60.
Found: C, 82.91; H, 4.77.

4,7-Dimethyl-1,10-phenanthroline. This was prepared from one mole of 8-amino-4-methylquinoline and 2 moles of methyl vinyl ketone in a Yale type Skraup reaction. The yield of product (16.8%) melting at 191–192°, was better than that previously reported (12).

4,7-Diphenyl-1,10-phenanthroline. The following procedure proved much more satisfactory than that previously described (1): To a stirred mixture of 13.5 g. of 8-amino-4-phenylquinoline (1), 17 g. of arsenic acid, and 57 g. of 85% phosphoric acid, heated to 100°, was added gradually 15 g. of β-chloropropiophenone, keeping the temperature below 120°. After two hours at this temperature the mixture was poured on ice, made alkaline with potassium hydroxide, and extracted (both precipitate and solution) with hot benzene. Removal of solvent and recrystallization from benzene yielded 12 g. or 58.8% of pure product melting at 216–217°.

4,7-Dimethyl-2,9-diphenyl-1,10-phenanthroline. An ether solution of phenyllithium was prepared from 1.1 g. of lithium, 14 g. of bromobenzene, and 50 ml. of absolute ether. Six-tenths of the total volume of this solution was now added slowly to a stirred solution of 3.5 g. of 4,7-dimethyl-1,10-phenanthroline in 75 ml. of benzene in a nitrogen atmosphere. The ether then was distilled from the mixture, and after three hours refluxing with stirring it was poured on ice and made alkaline. After complete solution, and separation of the benzene layer, 15 ml. of nitrobenzene was added to it and the benzene was removed. The residual liquid, after four hours heating at 100° was steam-distilled, and the solid residue was crystallized from benzene. The yield of product melting at 258° was 2.0 g., or 33.0%. The pure product melts at 259–260°.

Anal. Calc'd for $C_{26}H_{20}N_2$: C, 86.67; H, 5.56.

Found: C, 86.59; H, 5.58.

2,4,7,9-Tetraphenyl-1,10-phenanthroline. This was prepared in exactly the same way as the previous compound, using 4,7-diphenyl-1,10-phenanthroline instead of the 4,7-dimethyl derivative. The yield of pure product, crystallized from benzene and melting at 318–319°, was 29.3%.

Anal. Calc'd for $C_{36}H_{24}N_2$: C, 89.23; H, 4.99.

Found: C, 89.31; H, 4.77.

SUMMARY

1. Procedures are described for the syntheses of 2- and 3-phenyl- and 2,9-diphenyl-1,10-phenanthroline and of 8-nitro-3-phenylquinoline, based on modified Skraup techniques.

2. Using ethyl α,α-formylphenyl acetate on appropriate amines, the following phenanthrolines have been prepared: 4-hydroxy-3-phenyl; 4-hydroxy-3,5-diphenyl; and 4,7-dihydroxy-3,8-diphenyl, from which 3,8-diphenyl-1,10-phenanthroline was made.

3. By the action of phenyllithium on the appropriate 4,7-disubstituted 1,10-phenanthroline, 4,7-dimethyl-2,9-diphenyl-, and 2,4,7,9-tetraphenyl-1,10-phenanthrolines have been prepared.

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