2-Methyl-1,10-Phenanthroline: A Direct and a Serendipitous Synthesis

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The 1,10-phenanthroline system has long provided analytical chemists with popular ligands for studies of stability constants and chelation potentials with metal ions (1). Both the parent compound and 2,9-dimethyl-1,10-phenanthroline are now commercially available (2). Two literature techniques have been reported for the preparation of 2-methyl-1,10-phenanthroline by either the the condensation of 8-aminoquinaldine with glycerol (3) or of 8-aminoquinoline with crotonaldehyde (4). Although the latter Doebner-Miller route as outlined with *o*-nitrophenol as an oxidizing agent (4) provides the most satisfactory synthesis of the title compound (yields 64%), the former Skraup procedure (3), which claims only the preparation of a hydrated ligand, has not been reproducible in our hands.

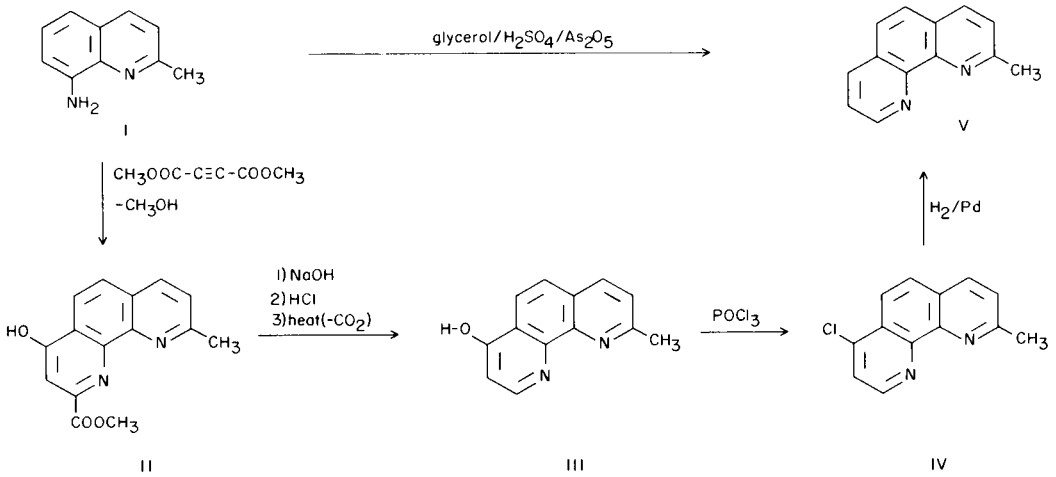
Since the simplicity of the experimental method and the availability of reagents might, on occasion, prejudice chemists toward utilization of the Skraup condensation we should like to report a modified technique which is both simple and workable. In addition, we wish to propose an alternative Conrad-Limpach (5) procedure employing 8-aminoquinaldine (6) and dimethyl acetylenedicarboxylate as a route to the anhydrous ligand (7). Although this latter method involves several additional steps for modification of the ring functions, the overall conversion is higher (25%) than in the Skraup (15%) and two other related phenanthrolines II and IV are made available for evaluation as ligands.

EXPERIMENTAL

Nmr spectra were obtained on a Varian A-60 Spectrometer and mass spectra on a Perkin-Elmer Hitachi RMU-6E. We acknowledge the generous support of the National Science Foundation which permitted the purchase of these instruments. Combustion analyses were obtained from Dr. George I. Robertson Microanalytical Laboratory, Florham Park, N. J.

Preparation of 2-Methyl-1,10-phenanthroline (V): Skraup Method.

Sixty g. (0.63 mole) of concentrated sulfuric acid was added dropwise over 15 minutes to a well-stirred solution of 44 g. (0.28 mole) of 8-amino-2-methylquinoline (I), 101 g. (1.12 moles) glycerol and 48 g. (0.21 mole) arsenic pentoxide (8). By this technique the exothermic reaction was moderated, and the solution temperature rose slowly to 80° during the addition process. The reaction was completed by raising the temperature to 130-135° for 1 hour and then to 150° (reflux) for 4 hours. After cooling to room temperature the reaction was hydrolyzed by the cautious addition of ice followed by 1.5 l. of cold water. When the solution was adjusted to basicity with aqueous ammonium hydroxide, a tarry material separated which was taken up in boiling benzene. This organic phase was combined with a benzene extract of the aqueous layer and concentrated *in vacuo* to an



orange oil. Distillation of the oil (0.20 mm Hg) yielded the following fractions: 107-150°, 11.5 g., mainly 8-amino-2-methylquinoline; 150-165°, 2.0 g. of mixed starting amine and V; and 165-175°, 12.1 g. of V. The oily product fraction was dissolved in 20 ml. of benzene, diluted with 100 ml. of petroleum ether (b.p. 60-70°), and aerated by the passage of moist atmospheric air. The hydrated 2-methyl-1,10-phenanthroline (V) began to precipitate; and after the mixture was cooled to 0° for 12 hours, 10.9 g. of yellow crystals were filtered off. The product was taken up in a minimum of boiling petroleum ether (b.p. 60-70°) and decanted from a small quantity of orange gum. The crystals which resulted on cooling the solution were dried over calcium chloride at 0.1 mm Hg and 65° for 20 hours and the anhydrous V was obtained as pale yellow crystals (8.09 g., 15%), m.p. 84-86°. The nmr spectrum (in deuteriochloroform vs. tetramethylsilane standard) revealed the methyl resonance at δ = 2.88 p.p.m. and an aromatic complex from δ = 7.25 to 8.1 p.p.m. The deshielded H_9 proton appeared at δ = 9.12 p.p.m. as a double-doublet ($J_{8,9}$ = 4 and $J_{7,9}$ = 2 c.p.s.) outside the aromatic complex and the H_5 and H_6 protons were evident as a fortuitously isochronous singlet integrating for two proton units at δ = 7.49 p.p.m.

Anal. Calcd. for $C_{13}H_{10}N_2$: C, 80.39; H, 5.19; N, 14.42. Found: C, 80.14; H, 5.07; N, 14.33.

Preparation of 2-Methyl-1,10-phenanthroline (V): Modified Conrad-Limpach Method.

A solution of 4.1 g. (26 mmoles) of I and 3.8 g. (27 mmoles) of dimethyl acetylenedicarboxylate was refluxed in 35 ml. of anhydrous methanol for 10 hours. Evaporation of the solvent produced a semisolid oil which was added to 35 g. of boiling diphenyl ether and refluxed for 30 minutes. The ring-closed product (II) was precipitated by the addition of light petroleum ether, 6.04 g. (86%). An analytical sample was prepared by recrystallization from methanol and sublimation *in vacuo* at 210°/0.1 mm Hg, m.p. 237-239°. The mass spectrum of the product displayed an intense parent peak at m/e 268 and the expected high mass fragments at 237 (P-OCH_3) and 209 (P-$COOCH_3$).

Anal. Calcd. for $C_{15}H_{12}N_2O_3$: C, 67.15; H, 4.51; N, 10.44. Found: C, 66.89; H, 4.72; N, 10.72.

The ester was saponified by refluxing 6.0 g. for 4 hours in 100 ml. of methanol-100 ml. of 25% (w/w) aqueous sodium hydroxide. Neutralization with cold 10% hydrochloric acid solution precipitated the acid, which was dried *in vacuo* and added in small portions to 50 g. of refluxing diphenyl ether. After the foaming (carbon dioxide) subsided, the mixture was refluxed for 30 minutes and the crude 2-methyl-7-hydroxy-1,10-phenanthroline was precipitated by the addition of 100 ml. petroleum ether. This crude material, 3.1 g., was directly chlorinated by refluxing for 10 hours in 50 g. of phosphorus oxychloride. Hydrolysis with ice and neutralization with aqueous ammonium hydroxide precipitated the 2-methyl-7-chloro-1,10-phenanthroline (IV) which was recrystallized twice from cyclohexane, 2.6 g., 51% (based on (II)), m.p. 145-146°. The mass spectrum revealed an intense parent peak at m/e 228 and a P + 2 in the expected 3:1 ratio for a monochloro compound.

Anal. Calcd. for $C_{13}H_9ClN_2$: C, 68.28; H, 3.97; N, 12.25. Found: C, 67.98; H, 4.10; N, 12.39.

A solution of 1.5 g. of IV was prepared in 50 ml. of methanol and hydrogenated at 24 hours at 48 p.s.i. over 0.2 g. of 5% palladium on carbon. The catalyst was filtered off and the methanol concentrated to dryness. The crude hydrochloride of V was dissolved in a minimum amount of water and neutralized with 0.1 *N* sodium hydroxide. The free base precipitated as a fluffy white solid, but on attempted filtration it began to transform to a yellow gum. Crystalline material was obtained by extracting the product into a benzene phase, then by diluting with pentane and cooling. The precipitated hydrate was dried in a vacuum as described previously, and 0.69 g. (57%) (based on IV) of 2-methyl-1,10-phenanthroline (V) were obtained. Spectral and melting point comparisons revealed that the material was identical with that prepared by the Skraup method.

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(7) Because of the potential non-stoichiometric character of hydrated materials, the anhydrous free-base is preferred as a primary standard ligand. Chelate luminescence studies carried out in non-aqueous media require the availability of the anhydrous ligand: see K. R. Wunschel, Jr. and W. E. Ohnesorge, *J. Am. Chem. Soc.*, 89, 2777 (1967) and references cited therein.

(8) Although it has been claimed that the portionwise addition of sulfuric acid has no beneficial effect in a Skraup synthesis, it does appear to us to improve the yield in phenanthroline syntheses: see R. H. F. Manske and M. Kulka, in "Organic Reactions," Vol. 7, R. Adams, Ed., John Wiley and Sons, Inc., New York, N. Y., 1953, p. 68. The modified Skraup employed herein is derived from the procedure suggested by F. Richter and G. F. Smith, *J. Am. Chem. Soc.*, 66, 396 (1944).

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