The Synthesis of Certain 4-Mono- and 4,7-Dihydroxy-1,10-phenanthrolines

Francis H. Case

Department of Chemistry, Temple University

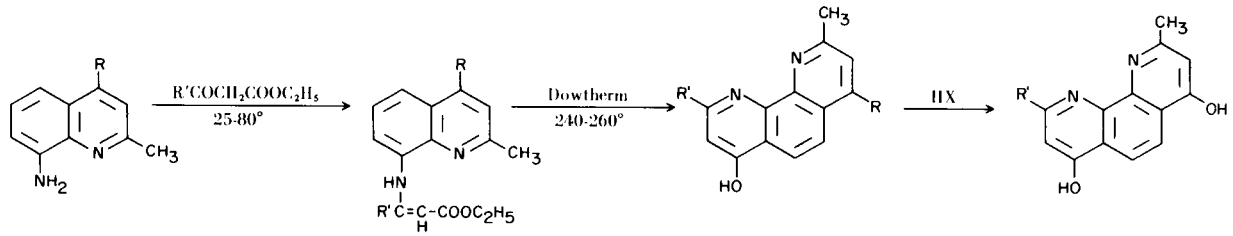
Aminocrotonates and cinnamates formed by the action of ethyl acetoacetate and ethyl benzoylacetate on substituted 8-aminoquinolines have been cyclized to 4-hydroxy and 4,7-dihydroxy-1,10-phenanthrolines.

Some years ago an attempt (1) was made in this laboratory to prepare 4,7-dihydroxy-2,9-dimethyl-1,10-phenanthroline (XIV) by treating 8-amino-4-methoxyquinaldine (II) with ethyl acetoacetate to yield ethyl β-(4-methoxy-2-methyl-8-quinolylamino)crotonate (VI), followed by cyclization to 4-hydroxy-7-methoxy-2,9-dimethyl-1,10-phenanthroline (X) and subsequent replacement of the methoxyl group by hydroxyl. This method failed because we were unable to prepare the crotonate. This has now been found possible by refluxing the reactants in boiling benzene with a trace of acetic acid and removing the water as formed [see preparation of ethyl β-phenylaminocrotonate (2)]. The unisolated liquid crotonate was then cyclized in Dowtherm. The succeeding steps proceeded normally.

The same procedure has been applied to 8-aminoquinaldine (I) and 8-amino-2,4-dimethylquinoline (III), yielding respectively (after cyclization) 4-hydroxy-2,9-dimethyl-1,10-phenanthroline (IX) and 4-hydroxy-2,7,9-trimethyl-1,10-phenanthroline (XI).

For the preparation of 8-amino-4-methoxyquinaldine the following method was found superior to that previously used in this laboratory: 4-chloroquinaldine, prepared by the method of Fischer, Diepolder and Wölfel (3), but not purified, was nitrated according to the directions of Halcrow and Kermack (4). However, the procedure described by these authors for the separation of isomers was unnecessary since two crystallizations of the nitration product from ethanol provided 8-nitro-4-chloroquinaldine of sufficient purity. The preparation of 8-nitro-4-methoxyquinaldine was according to Halcrow and Kermack's directions, and the amino compound was obtained by a stannous chloride reduction.

8-Nitroquinaldine (5) and 8-nitro-4-methylquinaldine



I: R = H
II: R = OCH_3
III: R = CH_3

IV: R = H; R' = CH_3
V: R = CH_3; R' = CH_3
VI: R = OCH_3; R' = CH_3
VII: R = H; R' = C_6H_5
VIII: R = OCH_3; R' = C_6H_5

IX: R = H; R' = CH_3
X: R = OCH_3; R' = CH_3
XI: R = CH_3; R' = CH_3
XII: R = H; R' = C_6H_5
XIII: R = OCH_3; R' = C_6H_5

XIV: R' = CH_3
XV: R' = C_6H_5

XVI: R = H; R' = CH_3
XVII: R = OCH_3; R' = CH_3
XVIII: R = OCH_3; R' = C_6H_5

(6) were best prepared by Skraup reactions involving crotonaldehyde and 3-penten-2-one, respectively, and *o*-nitroaniline, rather than by nitration of the methylquinolines.

When ethyl benzoylacetate was substituted for ethyl acetoacetate and the reaction run in benzene as before it was found that 8-aminoquinaldine did not react satisfactorily, while 8-amino-4-methoxyquinaldine yielded the amine, (XVIII) rather than the cinnamate.

The cinnamates were, however, obtained with ethyl benzoylacetate by allowing the reactants to stand for two weeks in an ethanol solution containing a few drops of hydrochloric acid. The cinnamates were then isolated and cyclized in Dowtherm to yield 4-hydroxy-9-methyl-2-phenyl (XII) and 4-hydroxy-7-methoxy-9-methyl-2-phenyl-1,10-phenanthroline (XIII). The methoxy group of the latter compound was hydrolyzed yielding 4,7-dihydroxy-9-methyl-2-phenyl-1,10-phenanthroline (XV).

In order definitely to establish the identity of the liquids obtained using ethyl acetoacetate as crotonates and not anilides the corresponding anilides were prepared in the case of 8-aminoquinaldine and 8-amino-4-methoxyquinaldine by heating the amines briefly with the keto ester, and shown to be reasonably high melting solids. The anilide derived from 8-aminoquinaldine was heated in Dowtherm but underwent practically no cyclization. This is in keeping with the statement of Hauser and Reynolds (7) that acetoacetanilide is not cyclized under similar conditions.

A study of the chelating properties of these hydroxy-1,10-phenanthrolines for Cu (I) will be made by Dr. A. Schilt.

EXPERIMENTAL

4-Chloro-8-nitroquinaldine.

To 67 ml. of ice-cold phosphoryl chloride there was gradually added 20 g. of 4-hydroxyquinaldine (2), followed by 35 g. of phosphorus pentachloride. The mixture was then heated one hour at 110-115°, cooled and poured into ice water. The resulting solution was made alkaline with sodium hydroxide and extracted with ether. After drying with anhydrous magnesium sulfate and removal of ether, 24 g. of crude 4-chloroquinaldine was obtained.

To a solution of 24 g. of the above crude 4-chloroquinaldine dissolved in 153 g. of 100% sulfuric acid, 18 g. of potassium nitrate was gradually added with stirring at 10-15°. After standing overnight the mixture was then poured on ice and made alkaline with sodium hydroxide. The resulting precipitate was removed by filtration, dried, and crystallized twice from ethanol, yielding 9 g. of product melting at 110-111° [lit. (4) 111-112°].

8-Amino-4-methoxyquinaldine.

A solution of 17 g. of 4-methoxy-8-nitroquinaldine (4) in 60 ml. of concentrated hydrochloric acid was added to one of 56 g. of stannous chloride dihydrate in 180 ml. of the same acid, keeping the temperature below 10°. After standing at room temperature for 3 hours, the solution was made alkaline with sodium hydroxide, and extracted with ether. Removal of the ether and crystallization from ethanol yielded 10.5 g. (71.4%) of amine, melting at 114-115° [lit. (4) 115-116°].

4-Hydroxy-7-methoxy-2,9-dimethyl-1,10-phenanthroline (X).

A solution of 7.5 g. of 8-amino-4-methoxyquinaldine, 5.6 ml. of ethyl acetoacetate and 1 ml. of glacial acetic acid in 60 ml. of benzene was heated at reflux, using a Dean-Stark water separator. After 5½ hours (after 1 ml. of water had been removed) the benzene was evaporated and the resulting oil (VI) added slowly to 46 ml. of Dowtherm at 200°. The temperature was maintained at 250° for one half hour. The mixture was cooled, diluted with petroleum ether (b.p. 60-70°) and filtered. The precipitate, after crystallization from ethanol, melted at 271-272°. The yield of hydrate was 6.5 g. (59.6%).

Anal. Calcd. for $C_{15}H_{14}O_2N_2 \cdot H_2O$: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.40; H, 5.84; N, 10.40.

8-Acetoacetamido-4-methoxyquinaldine (XVII).

A mixture of 0.8 g. of ethyl acetoacetate and 1 g. of 8-amino-4-methoxyquinaldine was heated at 150° for 4 hours. The solid which formed on cooling was crystallized from ethanol, yielding a product melting at 129-130°.

Anal. Calcd. for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.01; H, 5.95; N, 10.33.

4-Hydroxy-2,9-dimethyl-1,10-phenanthroline (IX).

A mixture of 6.3 g. of 8-aminoquinaldine, 5.6 ml. of ethyl acetoacetate, 1 ml. of glacial acetic acid and 60 ml. of benzene was treated as in the preparation of X. The resulting oil (IV) was cyclized in Dowtherm as before, and the precipitate after addition of petroleum ether crystallized from water, yielding 5.8 g. (60.4%) of a hydrate melting at 237-238°.

Anal. Calcd. for $C_{14}H_{12}N_2O \cdot H_2O$: C, 69.41; H, 5.82; N, 11.56. Found: C, 69.17; H, 5.65; N, 11.42.

4-Hydroxy-2,7,9-trimethyl-1,10-phenanthroline (XI).

The oil (V) obtained by treating a mixture of 5.5 g. of 8-amino-4-methylquinaldine (8), 4.5 ml. of ethyl acetoacetate, 1 ml. of glacial acetic acid and 60 ml. of benzene as above was cyclized in Dowtherm. The precipitate obtained after addition of petroleum ether yielded, on crystallization from water, 5.9 g. (75.6%) of a hydrate melting at 211-212°.

Anal. Calcd. for $C_{15}H_{14}N_2O \cdot H_2O$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.32; H, 6.32; N, 10.88.

8-Acetoacetamidoquinaldine (XVI).

A mixture of 2 g. each of ethyl acetoacetate and 8-aminoquinaldine was heated at 190° for 10 minutes. After cooling and crystallization from ethanol, the product melted at 102-103°.

Anal. Calcd. for $C_{14}H_{14}N_2O_2$: C, 69.41; H, 5.82; N, 11.56. Found: C, 69.15; H, 5.92; N, 11.30.

4,7-Dihydroxy-2,9-dimethyl-1,10-phenanthroline (XIV).

A mixture of 6.5 g. of 4-hydroxy-7-methoxy-2,9-dimethyl-1,10-phenanthroline, 100 ml. of 47% hydriodic acid, and 0.5 g. of red phosphorus was heated under reflux for 3.5 hours. After cooling it was made alkaline with sodium hydroxide and the phosphorus was removed by filtration. After addition of acetic acid to *p*H 6, the precipitate was removed by filtration, and crystallized from dimethylformamide. The yield of hydrate, melting over 400°, was 4.5 g. (72.9%).

Anal. Calcd. for $C_{14}H_{12}N_2O_2 \cdot H_2O$: C, 65.11; H, 5.46; N, 10.85. Found: C, 64.84; H, 4.97; N, 10.96.

The anhydrous product was obtained on drying the hydrate at 120°.

Anal. Calcd. for $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.03; N, 11.66. Found: C, 70.11; H, 5.04; N, 11.71.

The symmetrical nature of this compound was confirmed by an NMR determination by Dr. A. Schilt.

4-Methoxy-8-benzoylacetamidoquinaldine (XVIII).

A solution of 7.5 g. of 8-amino-4-methoxyquinaldine, 8.2 g. of ethyl benzoylacetate and 1 ml. of glacial acetic acid in 60 ml. of benzene was heated at reflux, using a Dean-Stark tube. After 23 hours, during which only 0.3 ml. of water had separated, the benzene was removed by evaporation, and the residue crystallized from dimethylformamide. The yield of product melting at 180° was 5.0 g. (37.6%). An analytical sample melted at 189-190°.

Anal. Calcd. for $C_{20}H_{18}N_2O_3$: C, 71.84; H, 5.43; N, 8.38. Found: C, 71.38; H, 5.59; N, 8.56.

The same compound was prepared by heating equimolecular quantities of 8-amino-4-methoxyquinaldine and ethyl benzoylacetate for 4 hours at 150°. A mixed melting point of the two samples showed no depression.

Ethyl β-(2-Methyl-8-quinolylamino)cinnamate (VII).

A mixture of 10.6 g. of 8-aminoquinaldine, 13.4 g. of ethyl benzoylacetate, 120 ml. of absolute ethanol and 3 drops of concentrated hydrochloric acid was allowed to stand for five days at room temperature. The resulting precipitate was separated by filtration and crystallized from ethanol yielding 8.5 g. (38.1%) of product melting at 145-146°. An analytical sample melted at 147-148°.

Anal. Calcd. for $C_{21}H_{20}N_2O_2$: C, 75.88; H, 6.06; N, 8.43. Found: C, 75.48; H, 6.11; N, 8.43.

Ethyl β-(2-Methyl-4-methoxy-8-quinolylamino)cinnamate (VIII).

From a mixture of 11.5 g. of 8-amino-4-methoxyquinaldine, 12.2 g. of ethyl benzoylacetate, 109 ml. of absolute ethanol and 5 drops of concentrated hydrochloric acid, there was obtained, after two weeks' standing, a precipitate which yielded, after crystallization from ethanol, 9.2 g. (41.6%) of a product melting at 157°. An analytical sample melted at 159-160°.

Anal. Calcd. for $C_{22}H_{22}N_2O_3$: C, 72.91; H, 6.12; N, 7.73. Found: C, 72.98; H, 6.18; N, 7.70.

4-Hydroxy-9-methyl-2-phenyl-1,10-phenanthroline (XII).

A mixture of 3 g. of ethyl β-(2-methyl-8-quinolylamino)-cinnamate (VII) and 25 ml. of Dowtherm was heated for 0.5 hour at 250°. After cooling and addition of petroleum ether, the resulting precipitate was separated by filtration and crystallized from benzene. The yield of pure product, melting at 177-178°, was 1.9 g. (73.6%).

Anal. Calcd. for $C_{19}H_{14}N_2O$: C, 79.70; H, 4.93; N, 9.78. Found: C, 79.95; H, 5.08; N, 9.68.

4-Hydroxy-7-methoxy-9-methyl-2-phenyl-1,10-phenanthroline (XIII).

A solution of 7 g. of ethyl β-(2-methyl-4-methoxy-8-quinolylamino)cinnamate (VIII) in 50 ml. of Dowtherm was heated for 0.5 hour at 250°. The precipitate, resulting from the addition of petroleum ether to the cooled solution, was separated and crystallized from ethanol. Five g. (82.0%) of product was thus obtained, melting at 233-234°.

Anal. Calcd. for $C_{20}H_{16}N_2O_2$: C, 75.93; H, 5.10; N, 8.85. Found: C, 75.82; H, 5.04; N, 8.97.

4,7-Dihydroxy-9-methyl-2-phenyl-1,10-phenanthroline (XV).

A mixture of 2.5 g. of 7-hydroxy-4-methoxy-2-methyl-9-phenyl-1,10-phenanthroline and 60 ml. of 48% hydrobromic acid was heated at reflux for 6 hours. After cooling the mixture was made alkaline with sodium hydroxide, and brought to *p*H 6 with acetic acid. The resulting precipitate was dried and crystallized from ethylene glycol monomethyl ether. The yield of product melting at 321-322° was 1.4 g. (58.6%). An analytical sample melted at 323-324°.

Anal. Calcd. for $C_{19}H_{14}N_2O_2$: C, 75.48; H, 4.67; N, 9.27. Found: C, 75.05; H, 4.56; N, 9.31.

REFERENCES

(1) D. E. Zacharias and F. H. Case, *J. Org. Chem.*, 27, 3878 (1962).

(2) G. Reynolds and C. Hauser, *Org. Synthesis, Coll.* Vol. III, 374 (1955).

(3) O. Fischer, E. Diepolder and E. Wölfel, *J. Prakt. Chem.*, 109, 59 (1925).

(4) B. Halcrow and W. Kermack, *J. Chem. Soc.*, 415 (1945).

(5) K. Madeja, *J. Prakt. Chem.*, 17, 97 (1962).

(6) G. Badger, H. Crocker, B. Ennis, J. Gayler, W. Matthews, W. Raper, E. Samuel, and T. Spotswood, *Aust. J. Chem.*, 16, 814 (1963).

(7) C. Hauser and G. Reynolds, *J. Am. Chem. Soc.*, 70, 2402 (1948).

(8) W. Vaughn, *ibid.*, 70, 2294 (1948).

Received February 24, 1970 Philadelphia, Pa. 19122