Preparation of 4-*t*-Butylphthalic Acid (IV).—A mixture of II (13.5 g.), potassium permanganate (27 g.) and water (500 ml.) was refluxed for three hours, cooled and filtered. The manganese dioxide was extracted with 75 ml. of 7% sodium hydroxide and this solution was combined with the original filtrate. After adding about 100 ml. of 3% hydrogen peroxide the mixture was allowed to stand overnight. The alkaline solution was extracted with ether and the ether layer discarded. Acidification of the aqueous layer, extraction with ether and evaporation of the ether gave 4.0 g. of the acid IV. Recrystallization from xylene removed the yellow contaminating material and IV separated in white, odorless crystals which melted with decomposition at 155–157°. Heating the oily residue with 5 ml. of aniline for about five minutes gave N-phenyl-4-*t*-butylphthalimide (5.6 g.) which was crystallized from ethanol. The total yield of acid from oxidation of the quinone was 76%, 36% as free acid and 40% as the imide.

Anal. Calcd. for $C_{12}H_{14}O_4$: neut. equiv., 111.1. Found: neut. equiv., 110.

When IV was heated it was converted into 4-*t*-butylphthalic anhydride which sublimed readily and melted at 77.5–78.5°. Both the acid and the anhydride gave positive fluorescein tests. Since the decomposition point of our acid was lower than the melting point reported by Bromby, Peters and Rowe[9] and the melting point of our anhydride was higher, we repeated the preparation of the acid by the original method, the oxidation of 6-*t*-butyl-1,2,3,4-tetrahydronaphthalene. The resulting acid decomposed at 152°. Both samples of the acid, when heated with aniline, gave the same derivative, N-phenyl-4-*t*-butylphthalimide, melting points and mixed melting points 180–182°. Analysis for carbon and hydrogen agreed with the calculated values. Since our original preparation of N-phenyl-4-*t*-butylphthalimide in 1949, Larner and Peters[10] have prepared and described it.

Preparation of the Acid III.—A solution of 20 g. of potassium permanganate in 600 ml. of water was added with mechanical stirring to a boiling suspension of 10 g. of the quinone II in 300 ml. of water. The addition required six hours. After standing overnight the excess permanganate was destroyed by sodium bisulfite, the solution was made alkaline, filtered from manganese dioxide, and the acidified filtrate was extracted with ether. Removal of the ether left oily material which was crystallized from hexane containing a few drops of xylene. The white crystals melted at 105–107°; yield 30%.

Anal. Calcd. for $C_{17}H_{22}O_4$ (290): C, 70.3; H, 7.6. Found: C, 70.5; H, 7.8[11]; neut. equiv., 304.

Two grams of the diketo acid III was treated with 10 ml. of 10% sodium hydroxide solution and 50 ml. of 3% hydrogen peroxide. The mixture became deep yellow in color and was allowed to stand overnight. By morning the color had disappeared and the acidified solution was extracted with ether. Evaporation of the ether left about 2.0 g. of oily acid which was converted to N-phenyl-4-*t*-butylphthalimide by heating with 2 ml. of aniline. The yield was 1.42 g., 72%.

Heating 0.6 g. of III with aniline gave no solid product.

Preparation of the Diacetate of 2-*t*-Butyl-1,4-naphthalenediol.[12]—This compound was prepared by the reductive acetylation of 2-*t*-butyl-1,4-naphthoquinone in 17% yield. The quinone was boiled for about ten minutes with excess zinc, sodium acetate and acetic anhydride. Pouring the clear solution into water precipitated a white solid which melted at 115–116° after crystallization from ethanol.

Anal. Calcd. for $C_{18}H_{20}O_4$: C, 72.0; H, 6.7. Found: C, 72.1; H, 6.7.

Hydrolysis of the diacetate and reduction of the quinone gave the hydroquinone which was not isolated as it is easily oxidized by the oxygen of the air.

(9) N. G. Bromby, A. T. Peters and F. M. Rowe, *J. Chem. Soc.*, 144 (1943).

(10) B. W. Larner and A. T. Peters, *ibid.*, 680 (1952).

(11) Analysis for carbon and hydrogen by Clark Microanalytical Laboratory, Urbana, Ill.

(12) From the thesis presented by Rose Marie Covey in partial fulfillment of the requirements for the degree of Master of Science, June, 1952.

POUGHKEEPSIE, NEW YORK

[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

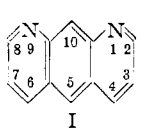
The Synthesis of Some 4,10-Disubstituted-1,7-phenanthroline Derivatives

BY ALEXANDER R. SURREY AND ROYAL A. CUTLER

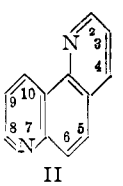
RECEIVED OCTOBER 22, 1953

The preparation of 4,10-dihydroxy-1,7-phenanthroline (VIII) from *m*-phenylenediamine by two methods is described. The hydroxy groups in VIII were replaced by chlorine to give either 4-chloro-10-hydroxy- or 4,10-dichloro-1,7-phenanthroline. The preparation of 4-, 10- and 4,10- basically substituted 1,7-phenanthroline derivatives is also reported.

In our search for new antimalarial agents, it seemed desirable to prepare some basically substituted pyridoquinoline compounds derived from *m*-phenylenediamine. The formation of two pyridine rings from appropriate derivatives of this diamine may proceed in two possible ways to give a benzodipyridine (I) or a 1,7-phenanthroline (II). In the present work, only derivatives of the angular structure II were obtained either by the Conrad–Limpach or Gould–Jacobs synthesis.



I



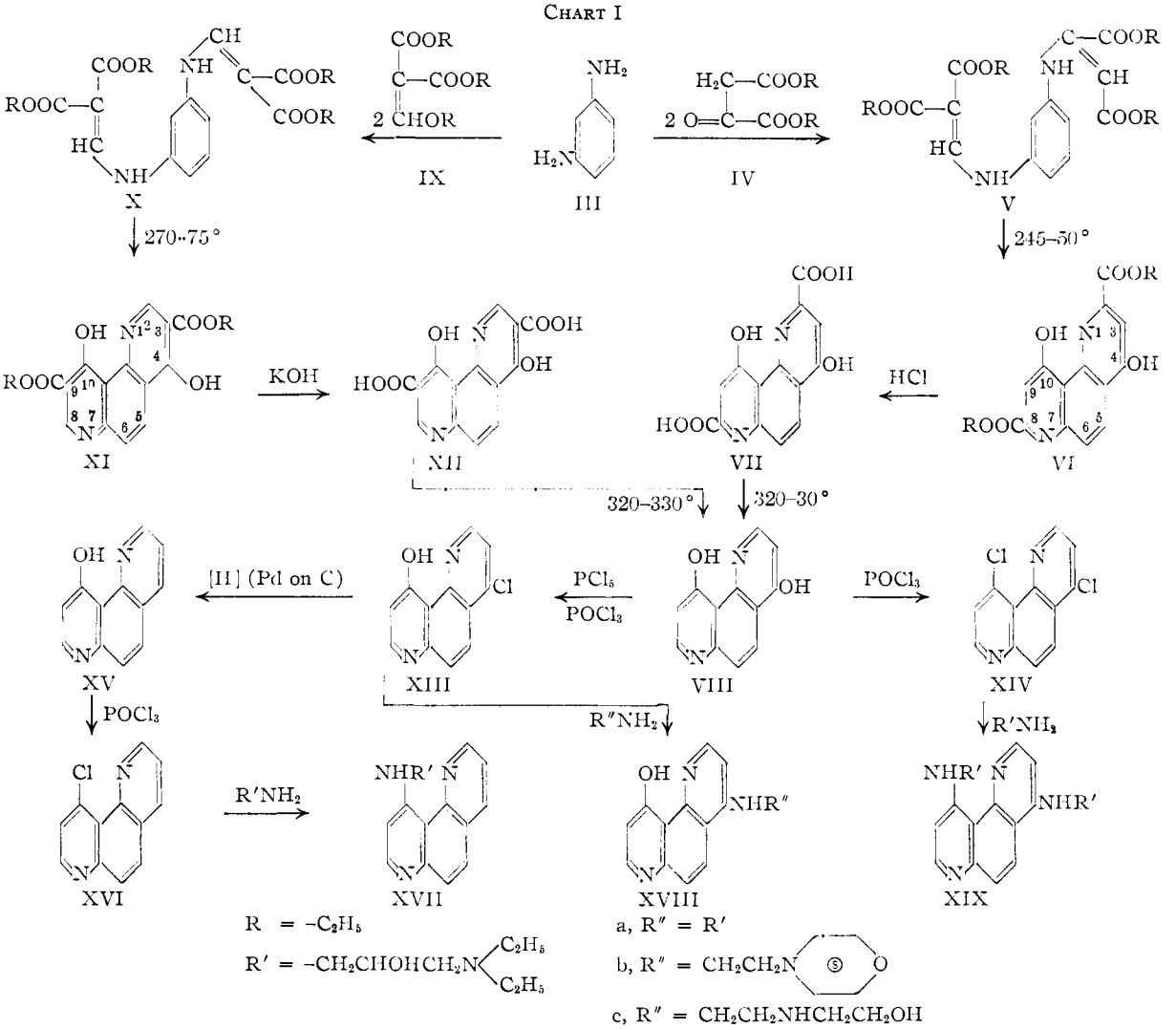
II

Condensation of *m*-phenylenediamine (III) (see Chart I) with two moles of ethyl oxalylacetate (IV) gave 1,3-bis-(α,β-dicarbethoxyvinylamino)-benzene (V), which on cyclization in boiling Dowtherm led to the isolation of only a single diester in 40–50% yield. This product VI was hydrolyzed and the resulting dibasic acid VII was decarboxylated to give a dihydroxy compound VIII melting at 390°. Treatment of the latter with phosphorus oxychloride gave the corresponding dichloro derivative XIV from which the chlorines were removed by reductive dehalogenation to yield 1,7-phenanthroline, m.p. 76–77°.[1]

This would indicate that the structures assigned in the sequence III → VIII are correct. That only the angular compound VI was obtained was not surprising since it is known that in the formation of cyclic compounds from phenylenediamine or quino-

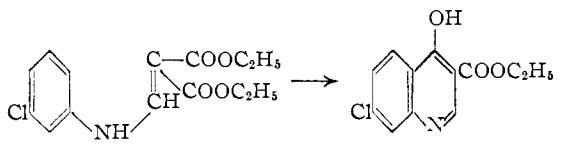
(1) (a) Zd. H. Skraup and G. Vortmann, *Monatsh.*, **3**, 570 (1882), reported 1,7-phenanthroline as melting at 78–78.5°; (b) benzodipyridine has been found to melt much higher, 164.5–165° [P. Ruggli, P. Hindermann and H. Frey, *Helv. Chim. Acta*, **21**, 1066 (1938)].

CHART I



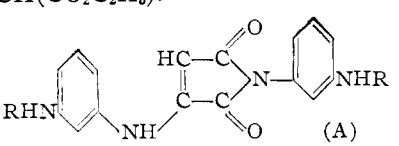
line derivatives the angular structure is obtained in preference to the linear one when both are possible.[1a,2]

Ethyl α-carbethoxy-β-*m*-chloroanilinoacrylate has been reported to cyclize to give mainly the 3-carbethoxy-7-chloro-4-hydroxyquinoline.[3] It



seemed reasonable, therefore, to assume that cyclization of 1,3-bis-(β,β-dicarbethoxyvinylamino)-benzene (X), prepared from *m*-phenylenediamine and ethyl ethoxymethylenemalonate, might lead to some of the linear product. When X was cyclized in boiling Dowtherm, a 90% yield of the diester XI was obtained. Hydrolysis of this material, followed by decarboxylation, gave a dihydroxy compound which was identical with 4,10-dihydroxy-1,7-phenanthroline (VIII) prepared by the previous method.

Of the two methods employed for the preparation of the dihydroxy compound VIII the one using ethyl ethoxymethylenemalonate gave an over-all yield of about 70% while the one using ethyl ethoxalylacetate gave over-all yields of only 10%. In the latter method considerable amounts of by-products were formed in the first two steps. One of these analyzed for a compound, which, on the basis of previous work,[4] and its physical properties, probably has one of the following two structures (A), where one R is H and the other R is —C($CO_2C_2H_5$)=CH($CO_2C_2H_5$).



(A)

Hydrolysis of the 2,8-dicarbethoxy compound VI with sodium hydroxide gave an insoluble monoso-

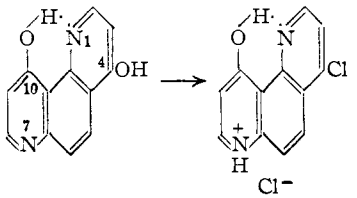
(2) (a) C. Willgerodt and E. Neander, *Ber.*, **33**, 2928 (1900); (b) M. G. Holdsworth and F. Lions, *J. Proc. Roy. Soc. N. S. Wales*, **66**, 273 (1932), *cf. C. A.*, **27**, 1351 (1933); (c) H. K. S. Rao and T. S. Wheeler, *J. Chem. Soc.*, 476 (1938); (d) G. Jacini, *Gazz. chim. ital.*, **69**, 405 (1939); (e) W. O. Kermack and W. Webster, *J. Chem. Soc.*, 213 (1942).

(3) C. C. Price and R. M. Roberts, THIS JOURNAL, **68**, 1204 (1946).

(4) A. R. Surrey and R. A. Cutler, *ibid.*, **68**, 514 (1946).

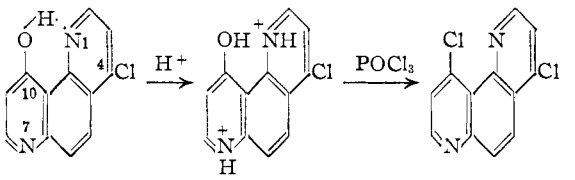
dium salt from which the free acid could not be obtained even after heating with 3 *N* hydrochloric acid. However, hydrolysis with dilute hydrochloric acid afforded the dicarboxylic acid VII in quantitative yield. Inasmuch as the isomeric diester XI also yielded an insoluble sodium salt, hydrolysis was carried out with potassium hydroxide. The decarboxylations of the diacids VII and XII were carried out in mineral oil at 320–330° to give good yields of the crude dihydroxy compound VIII.

The action of phosphorus oxychloride on 4,10-dihydroxy-1,7-phenanthroline (VIII) afforded the 4,10-dichloro derivative XIV in 80% yield. If, however, a mole of phosphorus pentachloride was included in the above reaction medium, a 77% yield of a monochloro compound was obtained. Reductive dehalogenation of this product to 10-hydroxy-1,7-phenanthroline[5] (XV), m.p. 105.5–107°, established its structure as 4-chloro-10-hydroxy-1,7-phenanthroline (XIII). The role of phosphorus pentachloride in the above reaction is not clear. The observed facts are that solution occurs soon after the reaction is initiated, followed almost immediately by the separation of a yellow solid. If the reaction mixture is worked up at this point, the monochloro product XIII is obtained. The preferential replacement of the 4-hydroxyl group by chlorine may be explained by the masking of the 10-hydroxyl group through hydrogen bonding with the 1-nitrogen atom. The hydrogen chloride liberated



in the reaction is taken up by the more basic 7-nitrogen atom and the solid product which precipitates may result from a salting-out action of the phosphorus pentachloride or from the formation of a solid complex with it.

4-Chloro-10-hydroxy-1,7-phenanthroline (XIII) may be prepared more conveniently by warming a solution of the 4,10-dichloro derivative XIV in dilute hydrochloric acid for a few minutes at 80°. The reverse reaction, XIII to XIV, may be accomplished by heating with phosphorus oxychloride. The addition of a small amount of water or hydrochloric acid to the reaction medium greatly increases the speed of the reaction as well as the yield of product.[6] Apparently the effect of water is to increase the hydrogen ion concentration, from its reaction with phosphorus oxychloride, which eliminates the hydrogen bonding in XIII by protonization of the ring nitrogens (XIIIa), and makes the 10-hydroxyl group readily available for replacement by chlorine.



XIII XIIIa XIV

The basically substituted compounds (XVII, XVIII, XIX) were prepared from the corresponding chloro compounds by condensation with the appropriate diamine. With 4-chloro-10-hydroxy-1,7-phenanthroline (XIII) the reactions were carried out in refluxing isopropyl alcohol in the presence of phenol and about one equivalent of alcoholic hydrogen chloride. This proved to be a very simple and effective method of preparation inasmuch as the dihydrochlorides of the bases XVIIIa,-b,c separated directly from the hot reaction mixture as colorless crystalline solids in 87–97% yields.[7,8]

Preliminary screening of the basically substituted compounds was carried out in ducks (*Pl. lophurae*). None showed any noteworthy antimalarial activity.[9]

Acknowledgment.—We are indebted to Mr. M. E. Auerbach and Mr. K. D. Fleischer and staffs for the analyses recorded.

Experimental[10]

1,3-Bis-(α,β-dicarbethoxyvinylamino)-benzene (V).—A benzene solution of ethyl ethoxalylacetate was prepared by treating 262 g. (1.25 moles) of the sodium salt, suspended in a well-stirred mixture of 800 ml. of water and 500 ml. of benzene, with 105 ml. (1.25 moles) of concd. hydrochloric acid. The benzene layer was washed with dilute bicarbonate solution and water and combined with a solution of 54 g. (0.5 mole) of *m*-phenylenediamine in 400 ml. of hot benzene. The mixture was heated at 40–50° for ten hours[11] under slight vacuum and the benzene and water were allowed to distil slowly. Additional benzene was supplied as needed. After cooling and filtering from any solid material present,[12]

(5) The product is a monohydrate. It appears to be identical with the product prepared by W. O. Kermack and W. Tebrich, *J. Chem. Soc.*, 375 (1945), from 4-hydroxy-5-aminoquinoline. The low melting point of the 10-hydroxy derivative was attributed to chelation of the hydroxyl group with the 1-nitrogen atom.

(6) In one experiment in which carefully dried chlorohydroxy compound XIII and freshly distilled phosphorus oxychloride were used the time required to effect complete solution was four hours. During this time the mixture became very dark and only a 10% yield of 4,10-dichloro derivative XIV was obtained. In the presence of a trace of water the reaction was complete in about 15 minutes and the yield was 75–80%.

(7) The use of phenol and hydrogen chloride to speed up these reactions is based on the results of experiments carried out on the condensation of 4,7-dichloroquinoline with novoldiamine, A. R. Surrey and R. A. Cutler, THIS JOURNAL, **73**, 2623 (1951).

(8) A discussion of the differences in reactivity of the 4- and 10-chlorine atoms of various 1,7-phenanthroline compounds will be presented in a forthcoming publication.

(9) We are indebted to Dr. E. W. Dennis and the chemotherapy division for the antimalarial screening.

(10) All melting points are uncorrected unless otherwise specified.

(11) The time of heating was varied from 3 to 12 hours with yields ranging from 30–40%. A mixture of alcohol and benzene was also used as a solvent with similar results. At the reflux temperature of benzene, practically the theoretical amount of water was collected in five hours and a 62% yield of crude product was obtained. The solid which formed on standing was recrystallized from ethanol, to give large yellow crystals, m.p. 72.5–73.5° (48%). *Anal.* Calcd. for $C_{22}H_{28}N_2O_8$: N, 6.25. Found: N, 6.30. Cyclization of this product in Dowtherm followed by recrystallization from pyridine, gave a 58% yield of VI.

(12) This solid was present in the greatest quantities in those reactions which were allowed to stand a few days before working up. The amount was especially large in one run to which a small amount of glacial acetic acid had been added. Recrystallization of the by-product from ethanol gave small yellow needles which melted at 245–246°. Analytical data and the fact that the material is soluble in dilute mineral acids suggested the possibility of this substance of having one of two structures as indicated (A). *Anal.* Calcd. for $C_{24}H_{24}N_4O_6$: C, 62.06; H, 5.21; N, 12.06. Found: C, 62.65, 62.59; H, 5.48, 5.25; N, 11.79.

the solution was brought up to a volume of 1 liter with fresh benzene and washed with four portions, 130 ml. each, of 3 *N* hydrochloric acid.[13] This was followed by three washings, 110 ml. each, with 3 *N* sodium hydroxide, two with 1 *N* sodium hydroxide and one with water. After drying over anhydrous sodium sulfate, removal of the solvent gave 90 g. (0.2 mole, 40%) of a deep ruby-red, viscous oil. This was used directly for cyclization to VI.

An analytically pure sample was obtained by heating the crude product with about eleven times its weight of Skellysolve A, pouring off the supernatant liquid from any undissolved material and filtering the hot solution with charcoal. Cooling in an ice-bath and scratching gave beautiful pale yellow needles which on further recrystallization from Skellysolve A melted at 53–54.5°, $n^{18}D$ 1.5815 (supercooled liquid).

Anal. Calcd. for $C_{22}H_{28}N_2O_8$: N, 6.25. Found: N, 6.26.

2,8-Dicarbethoxy-4,10-dihydroxy-1,7-phenanthroline (VI).—Cyclization was accomplished in yields ranging from 40–50% by dropping crude V into well-stirred quantities of either Dowtherm (three volumes) or white mineral oil (6 volumes) at temperatures of 245–250° and holding it at that point for 8 to 10 minutes. The alcohol which separated was collected by distillation. An atmosphere of nitrogen was helpful in decreasing the amount of decomposition during cyclization. After allowing to cool to 100°, the mixture was filtered and washed with acetone and ether. The product, usually gray or brown in color, was purified by slurrying with portions of acetone and then recrystallized from pyridine to give small white leaflets melting at 269.5–270° dec.

Anal. Calcd. for $C_{12}H_{16}N_2O_6$: C, 60.67; H, 4.53; N, 7.86. Found: C, 60.77; H, 4.77; N, 7.59.

2,8-Dicarboxy-4,10-dihydroxy-1,7-phenanthroline (VII).—Hydrolysis was easily accomplished by boiling the diester VI for about half an hour with dilute sodium hydroxide solution. However, on acidification with concd. hydrochloric acid to congo red the insoluble monosodium salt precipitated. This salt was so insoluble in dilute hydrochloric acid that it resisted the effects of boiling for a long period with 3 *N* hydrochloric acid. A sample of this salt on further purification analyzed as follows.

Anal. Calcd. for $C_{14}H_7N_2O_6Na$: N, 8.70. Found: N, 8.74, 8.70.

The free acid was prepared in quantitative yield by refluxing VI for 8 to 10 hours with twelve volumes of 3 *N* hydrochloric acid, filtering hot and washing the residue with water. The acid was purified by dissolving in aqueous pyridine, treating with charcoal, filtering and precipitating the free acid from a hot solution with excess dilute hydrochloric acid. The dried white acid melted at 340° dec.

Anal. Calcd. for $C_{14}H_8N_2O_6$: N, 9.33. Found: N, 9.81.

1,3-Bis-(β,β-dicarbethoxyvinylamino)-benzene (X).—A mixture of 139 g. (1.29 moles) of *m*-phenylenediamine and 585 g. (2.7 moles) of ethyl ethoxymethylenemalonate were mixed together and warmed on a steam-bath until homogeneous. After allowing to stand overnight at about 40° the resulting white solid cake was warmed on a steam-bath with 200 ml. of Skellysolve C until most of the solid had dissolved. The resulting solution was cooled rapidly in an ice-bath with stirring to give a slurry of solid which was filtered, washed twice with Skellysolve A and sucked dry. Yields ranged from 92–97%. An analytical sample was prepared by recrystallization from ethanol; m.p. 109–110°.

Anal. Calcd. for $C_{22}H_{28}N_2O_8$: N, 6.25. Found: N, 6.34.

3,9-Dicarbethoxy-4,10-dihydroxy-1,7-phenanthroline (XI).—Cyclization was accomplished in better than 90% yields by either of the following methods.

One part of X was added, with efficient stirring, to six volumes of Dowtherm preheated to 240°. The solution was then heated to reflux and maintained at that point for 20–30 minutes. During this time the mixture became very thick due to the separated product. The slurry was allowed to cool, diluted with about two volumes of acetone (to aid filtration), filtered, washed with acetone and dried.

The second method used ten volumes of white mineral oil, the heating being carried out at 270–275° for 15 minutes after the addition of X. Unless an oil-bath or a Glas-Col heater was used, there was danger of scorching the product as the mass became very thick and efficient stirring was difficult to maintain throughout the course of the reaction.

An analytical sample was prepared by refluxing a portion of the product with a large volume of acetone, filtering hot and repeating the procedure on the residue to yield a white powder melting at 314–315° dec.

Anal. Calcd. for $C_{18}H_{16}N_2O_6$: N, 7.86. Found: N, 7.93.

3,9-Dicarboxy-4,10-dihydroxy-1,7-phenanthroline (XII).—As this acid also forms a sodium salt which is insoluble in dilute acids, hydrolysis was effected by refluxing one mole of the diester for one hour with three liters of water containing four moles of potassium hydroxide. The hot solution was filtered with charcoal, the filtrate reheated to boiling and the acid thrown out by adding a large excess of concd. hydrochloric acid. The yield of acid, after removal by filtration, washing with water and drying, was practically quantitative. An analytical sample prepared from pure diester XI was a white powder melting at 373–374° dec.

Anal. Calcd. for $C_{14}H_8N_2O_6$: C, 56.00; H, 2.69; N, 9.33. Found: C, 56.02; H, 2.56; N, 9.53.

4,10-Dihydroxy-1,7-phenanthroline (VIII).—This compound was prepared from either VII or XII by decarboxylation in white mineral oil (7 volumes) at 320–330° for one hour. The yield of crude decarboxylated material was practically quantitative. The reaction was best carried out by using a Glas-Col heater in order to prevent decomposition due to local overheating. When pure acid was decarboxylated, little decomposition occurred and the product was light colored. The usual procedure, however, was to use the crude products directly from each of the steps in the series of reactions so that the resulting decarboxylated material was usually tan to dark brown or black in color. The latter was typical when the acid VII from the ethyl oxalylacetate method was used while VIII from the ethoxymethylenemalonic ester method was usually tan colored. The dihydroxyphenanthroline was purified by dissolving in hot dilute sodium hydroxide solution, filtering with charcoal and acidifying the filtrate with acetic acid. The product which separated could be further purified by recrystallization from 30% acetic acid solution (filtered hot with charcoal) to give long silky white needles containing one molecule of water of crystallization. This was removed by drying over phosphorus pentoxide at 140° in a vacuum or by vacuum sublimation at 310° to give a white solid melting at 390°.

Anal. Calcd. for $C_{12}H_8N_2O_2$: C, 67.92; H, 3.80; N, 13.20. Found: C, 68.24; H, 3.64; N, 13.37, 13.24.

VIII is also soluble in hot sodium carbonate solution from which the sodium salt crystallizes in the form of needles on cooling.

4-Chloro-10-hydroxy-1,7-phenanthroline (XIII).—A mixture of 5 g. (0.024 mole) of anhydrous VIII, 12.5 g. of phosphorus pentachloride and 25 ml. of phosphorus oxychloride was refluxed on an oil-bath for 20 minutes. Considerable solid separated soon after the initial reaction. The mixture was poured into ice and water (the temperature being held below 10°)[14] and stirred until all the solid had dissolved. After filtering with charcoal, the solution was treated with concentrated ammonium hydroxide (ice added to keep temperature below 25°). The product was filtered off, dissolved in chloroform and the solution dried with Drierite. After distilling off the chloroform, a pale yellow solid was obtained, 4.2 g. (77%). After two recrystallizations from ethanol the product melted at 196–196.5°. The material is insoluble in sodium hydroxide solution.

Anal. Calcd. for $C_{12}H_7ClN_2O$: Cl, 15.37; N, 12.15. Found: Cl, 15.21; N, 12.06.

4,10-Dichloro-1,7-phenanthroline (XIV).—A mixture of one part by weight of VIII and two parts by volume of phosphorus oxychloride was heated gently on an oil-bath. After the initial exothermic reaction, the mixture was refluxed for 30 minutes. The reaction mixture was poured into ice and water (temperature kept below 30°) and worked up as for XIII above. Yields up to 80% were obtained depending upon the purity of the dihydroxy compound VIII.

The product XIV was also obtained in about 80% yield by refluxing the chlorohydroxy compound (XIII) with five

(13) More of the yellow solid[12] was isolated from the first acid washing by neutralizing the chilled solution with alkali.

(14) The reason for maintaining the low temperature in this experiment was to show that the monochloro compound was formed in the reaction and not by hydrolysis of the dichloro compound.

volumes of phosphorus oxychloride, to which a small amount of water was added for 20 minutes or until solution was effected.

An analytical sample of XIV was prepared by recrystallization from Skellysolve C followed by recrystallization from ethanol to give long white needles melting at 155–155.5°.

Anal. Calcd. for $C_{12}H_6N_2Cl_2$: Cl, 28.47; N, 11.25. Found: Cl, 28.45; N, 10.97.

10-Hydroxy-1,7-phenanthroline (XV).—A solution of 2.3 g. of 4-chloro-10-hydroxy-1,7-phenanthroline (XIII) and 4 g. of sodium acetate in 100 ml. of ethanol was reduced catalytically with palladium-on-charcoal. After filtering off the catalyst and distilling the solvent the residue was dissolved in dilute hydrochloric acid and the product precipitated with bicarbonate solution; yield 1.5 g. After several recrystallizations from water the product melted at 105.5–107[5] (lit.[5] m.p. 107–108°).

Anal. Calcd. for $C_{12}H_8N_2O \cdot H_2O$: C, 67.29; H, 4.67; N, 13.08. Found: C, 67.62; H, 4.49; N, 12.91.

10-Chloro-1,7-phenanthroline (XVI).—This was prepared in the usual manner from the 10-hydroxy-1,7-phenanthroline monohydrate (XV) by refluxing for 15 minutes with three volumes of phosphorus oxychloride to which a few drops of water had been added. The product was obtained in good yield by pouring into ice, adding ammonium hydroxide solution and extracting with chloroform. Removal of the dried solvent followed by recrystallization from Skellysolve B gave small white needles. An analytical sample was further recrystallized from alcohol and then Skellysolve B; m.p. 93–94°.

Anal. Calcd. for $C_{12}H_7ClN_2$: N, 13.05. Found: N, 13.07.

The picrate, after recrystallization from acetone, melted at 190–191°.

Anal. Calcd. for $C_{18}H_{10}ClN_6O_7$: N, 15.78. Found: N, 15.68.

1,7-Phenanthroline.—Catalytic reduction of 1.25 g. of 4,10-dichloro-1,7-phenanthroline (XIV) with palladium–charcoal catalyst yielded a solid which was recrystallized from water and vacuum dried; m.p. 76–77° (lit.[1] m.p. 78–78.5°).

10-(3-Diethylamino-2-hydroxypropylamino)-1,7-phenanthroline (XVII).—A mixture of 4.45 g. of XVI and 8 g. of 3-diethylamino-2-hydroxypropylamine was heated at 130° for 20 minutes after the initial reaction had subsided. The cooled mixture was dissolved in dilute acetic acid solution, treated with ammonium hydroxide solution until just alkaline to phenolphthalein and filtered with charcoal. Addition of an excess of ammonium hydroxide to the filtrate caused the base to separate. The latter was extracted with ether, washed with water and dried. Removal of the ether gave 5 g. (75%) of a pale yellow oil. This was converted to the diphosphate by dissolving in 60 ml. of warm methanol followed by the addition of 9.6 ml. of methanolic phosphoric acid solution containing 1 g. of phosphoric acid in 3 ml. of solution. A white gum separated which gradually solidified on warming on a steam-bath. Filtration of the cooled solution gave a quantitative yield of the diphosphate. This was further purified by dissolving in 32 ml. of water, diluting to 60 ml. with methanol and adding ethanol to turbidity. On standing overnight the diphosphate separated in the form of white rosettes which sintered slightly at 135–140° and melted at 218–219° dec.

Anal. Calcd. for $C_{19}H_{30}N_4O_9P_2$: N, 10.76; H_3PO_4, 37.66. Found: N, 10.79; H_3PO_4, 37.24.

4-(3-Diethylamino-2-hydroxypropylamino)-10-hydroxy-1,7-phenanthroline (XVIIIa).—A mixture of one mole of 4-chloro-10-hydroxy-1,7-phenanthroline (XIII), 1.5 moles of 3-diethylamino-2-hydroxypropylamine, phenol (equal in weight to chloro compound), 1.1 moles of alcoholic hydrogen chloride and six volumes of isopropyl alcohol (based on chloro compound) was refluxed with stirring for three hours. The solid dihydrochloride separated from solution. After cooling, the product was filtered, washed with isopropyl alcohol and ether and dried; yield 87%. An analytical sample of the dihydrochloride, prepared from purified base (below) melted at 285–287° dec.

Anal. Calcd. for $C_{19}H_{26}Cl_2N_4O_2 \cdot 2HCl$: Cl, 17.16. Found: Cl, 17.00.

The free base prepared from the dihydrochloride was recrystallized from absolute alcohol. It appears to exist in two crystalline modifications. When the melting point was taken very slowly, the sample started to melt at 162°, but before fusion was complete it resolidified and remelted at 185–187°. If the melting point was taken rapidly, it melted completely at 162–163°. In one instance during recrystallization of a sample, a small amount of alcohol insoluble material was removed by filtration from the hot solution and was found to melt at 185–187°. Recrystallization of this high melting material from a large volume of absolute alcohol gave only the lower melting material, m.p. 162–163°.

Anal. Calcd. for $C_{19}H_{24}N_4O_3$: C, 67.03; H, 7.11; N, 16.46. Found: C, 66.98; H, 7.42; N, 16.60.

10-Hydroxy-4-(2-morpholinoethylamino)-1,7-phenanthroline (XVIIIb).—Condensation of 2-(1-morpholino)-ethylamine with XIII according to the procedure described for XVIIIa gave a 97% yield of the dihydrochloride. It was purified by dissolving in water, filtering with charcoal and adding ethanol to turbidity. The product melted over 320°.

Anal. Calcd. for $C_{18}H_{20}N_4O_2 \cdot 2HCl$: N, 14.10; Cl^-, 17.85. Found: N, 14.08; Cl^-, 17.75.

The free base, after recrystallization from ethanol then benzene formed small pale yellow platelets melting at 188.6–189.2° cor.

Anal. Calcd. for $C_{18}H_{20}N_4O_2$: N, 17.27. Found: N, 17.38.

4-(2-Hydroxyethylaminoethylamino)-10-hydroxy-1,7-phenanthroline (XVIIIc).—Condensation of 2-hydroxyethylaminoethylamine with XIII, according to the procedure described for XVIIIa gave a 97% yield of the crude dihydrochloride which was purified as in XVIIIb to give small white crystals melting over 320°.

Anal. Calcd. for $C_{16}H_{18}N_4O_2 \cdot 2HCl$: N, 15.09; Cl^-, 19.10. Found: N, 14.83; Cl^-, 18.76.

The free base, after liberation from an aqueous solution of the dihydrochloride with excess KOH, was recrystallized from ethanol to yield a pale yellow solid; m.p. 183.2–184.0° cor.

Anal. Calcd. for $C_{16}H_{18}N_4O_2$: N, 18.78. Found: N, 18.91.

The use of sodium hydroxide for the liberation of the base caused the precipitation of a hygroscopic sodium salt.

4,10-Bis-(3-diethylamino-2-hydroxypropylamino)-1,7-phenanthroline (XIX).—A mixture of 25 g. (0.1 mole) of XIV and 61 g. (0.42 mole) of 3-diethylamino-2-hydroxypropylamine was heated with stirring to 90° at which point the temperature of the reaction mixture rose rapidly to 145°. When the initial reaction had subsided heating was resumed, the temperature being maintained at 150–160° for five hours. After cooling, the mixture was dissolved in 200 ml. of 50% acetic acid, filtered with charcoal and the base liberated with sodium hydroxide solution. The gummy solid which separated was stirred with a large volume of ether and the latter solution decanted from the insoluble material and dried. Evaporation of the ether yielded 18 g. of clear, amber, glassy solid.

The trihydrochloride of this base was prepared by treating a solution of the residue in a mixture of ethanol and isopropyl alcohol with alcoholic hydrogen chloride. The product was recrystallized from ethanol and isopropyl alcohol to give hygroscopic, fine white needles; m.p. 238–240°.

Anal. Calcd. for $C_{26}H_{43}Cl_3N_6O_2$: Cl, 18.40; N, 14.54. Found: Cl, 17.99; N, 14.41.

The free base was obtained from the above salt in the usual manner in the form of a yellow viscous oil. The latter was dissolved in a large volume of ether, the ether dried and removed by distillation. The residue crystallized from a minimum amount of ether on standing. Recrystallization from ethyl acetate yielded white hygroscopic crystals, m.p. 116.5–117.5°.

Anal. Calcd. for $C_{26}H_{40}N_6O_2$: C, 66.63; H, 8.60; N, 17.94. Found: C, 66.41, 66.71; N, 8.38, 8.41; N, 17.58.

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