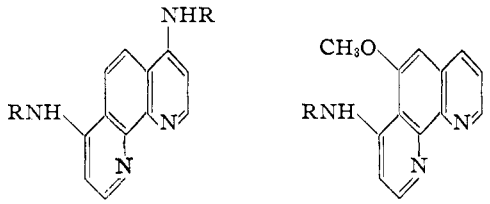
[CONTRIBUTION FROM NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Some Substituted 1,10-Phenanthrolines[1]

BY H. R. SNYDER AND HERBERT E. FREIER

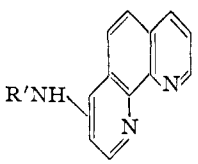
The conversion of an aniline to a 4-hydroxyquinoline by condensation with ethoxymethylenemalonic ester[1a] has been extended to the conversion of phenylenediamines and aminoquinolines to phenanthrolines. Substances of this type (compounds I, II, III) carrying the substituents present in SN-7618,[1a,2] plasmochin, and other effective antimalarial agents, but having the additional heterocyclic ring, were desired for testing as possible therapeutic agents.



R = —CH(CH₂)₃N(C₂H₅)₂
|
CH

I

II



R′ = —CH₂CH₂CH₂N(C₂H₅)₂

III

The compound I, 4,7-bis-(4-diethylamino-1-methylbutylamino)-1,10-phenanthroline (SN-11517[2]), was prepared from *o*-phenylenediamine and ethoxymethylenemalonic ester, the operations being carried out as previously described[1a] for the synthesis of analogous quinoline derivatives. The picrate of the substance II, 4-(4-diethylamino-1-methylbutylamino)-5-methoxy-1,10-phenanthroline (SN-12535[2]), was prepared similarly from 6-methoxy-8-aminoquinoline, and III, 4-(3-diethylaminopropylamino)-1,10-phenanthroline, was prepared from 8-aminoquinoline.

Experimental

1. Preparation of 4,7-*bis*-(4-Diethylamino-1-methylbutylamino)-1,10-phenanthroline (I)

(a) *o-bis*-(β-Dicarbethoxyvinylamino)-benzene.—A mixture of 32.4 g. of *o*-phenylenediamine and 129.6 g. of ethoxymethylenemalonic ester was heated on a steam-bath for four hours. The solid after recrystallization from 300 ml. of methyl alcohol weighed 106 g. (79%) and melted at 94–95°.

Anal. Calcd. for $C_{22}H_{28}N_2O_8$: C, 58.91; H, 6.29. Found: C, 59.07; H, 6.32.

(b). 3,8-Dicarbethoxy-4,7-dihydroxy-1,10-phenanthroline.—To 1500 ml. of refluxing diphenyl ether was added 60 g. of the above solid over a period of five minutes. The solution was refluxed for an additional twenty-five minutes and then allowed to cool to room temperature. To the semi-solid mass was added 500 ml. of petroleum ether (b. p. 85–110°), the mixture was stirred vigorously and then filtered. The precipitate was triturated with 500 ml. of petroleum ether; the mixture was filtered and the solid was washed with 250 ml. of ether. The crude, light brown product weighed 44.5 g. (93%). The analytical sample had a melting point of 264–265° after recrystallization from ethyl Cellosolve.

Anal. Calcd. for $C_{18}H_{16}N_2O_6$: C, 60.67; H, 4.53. Found: C, 60.53; H, 4.65.

(c) 3,8-Dicarboxy-4,7-dihydroxy-1,10-phenanthroline.—A mixture of 80 g. of the crude ester and 1800 ml. of a 5% potassium hydroxide solution was refluxed for three hours. The red solution was allowed to cool to room temperature and any diphenyl ether present was extracted with two 25-ml. portions of petroleum ether (b. p. 85–110°). The aqueous solution was made acidic with 10% hydrochloric acid and the precipitated product was collected by filtration and washed with cold water. The precipitate was transferred to an evaporating dish and was covered with concentrated hydrochloric acid. After the mixture had been evaporated to dryness, the light yellow acid was thoroughly washed with cold water and dried in an oven at 80°. The yield was 56 g. (83%); m. p. 300–310° (dec.).

Anal. Calcd. for $C_{14}H_8O_6N_2$: C, 56.00; H, 2.69. Found: C, 55.89; H, 2.95.

(d) 4,7-Dihydroxy-1,10-phenanthroline.—In each of five 500-ml. Erlenmeyer flasks was placed 13.4 g. of the dicarboxylic acid (total being 67 g.). The flasks were immersed in a Wood's metal-bath maintained at temperatures between 310 and 330°. The time required for decarboxylation was fifty minutes. The crude product weighed 46 g. (95%) and it decomposed at about 475° (block). The dihydroxy compound was not analyzed as no suitable solvent could be found for recrystallization.

(e) 4,7-Dichloro-1,10-phenanthroline.—In a 200-ml. three-necked flask, equipped with a stirrer and reflux condenser, a mixture of 32 g. of phosphorus pentachloride and 50 g. of phosphorus oxychloride was heated to 90°. To this mixture was added, as quickly as possible, 16 g. of the crude dihydroxy compound. The temperature of the mixture was then raised to 130° and maintained there for one hour. The excess phosphorus oxychloride was removed by distillation and the brown residue was poured onto ice. After a few hours the solid had dissolved and the resulting brown solution was treated with Darco and filtered. The filtrate was made alkaline with a 15% sodium hydroxide solution and the precipitated product was collected by filtration and dried in an oven at 80°

The dried product was dissolved in 1200-ml. of boiling methyl alcohol and the alcohol solution, after it was treated with Darco and filtered, was concentrated to half its volume. To this was added 50 ml. of water and the mixture was then cooled in ice and filtered. The yield of dichloro compound melting at 249–250° was 12.5 g. (67%).

Anal. Calcd. for $C_{12}H_6N_2Cl_2$: C, 57.86; H, 2.43. Found: C, 57.88; H, 2.49.

(f) 4,7-*bis*-(4-Diethylamino-1-methylbutylamino)-1,10-phenanthroline (I).—A mixture of 20 g. of the dichloro compound and 75 g. of 4-diethylamino-1-methylbutylamine was heated at 170° for four hours. The mixture

(1) The work reported in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Illinois.

(1a) Price and Roberts, THIS JOURNAL, **68**, 1204 (1946).

(2) The Survey Number, designated SN- refers to the number assigned a drug by the Survey of Antimalarial Drugs.

solidified as it cooled to room temperature; it was then stirred with 75-ml. of 15% sodium hydroxide solution. The excess 4-diethylamino-1-methylbutylamine was removed by extraction with five 100-ml. portions of water and the residual brown oil was dissolved in 300 ml. of ether. The ether solution was washed thoroughly with water and dried over potassium carbonate. After the dried solution had been treated with Darco and filtered, the solvent was removed by distillation and the resulting red oil solidified upon the addition of petroleum ether (b. p. 30–55°). The crude amine melting at 146–152° weighed 32 g. (81%).

The crude amine (40 g.) was dissolved in a boiling mixture of 2500 ml. of petroleum ether (b. p. 85–110°) and 300 ml. of benzene. This solution was filtered while hot through a fluted filter and the filtrate was decanted from the red oil which first settled on the bottom of the flask. After the decanted solution had been cooled in ice, the precipitated product was collected by filtration. This purification process was repeated three times and the product obtained from the third recrystallization was washed well with 500 ml. of petroleum ether (b. p. 30–55°). The pure, light brown material weighed 18 g. and had a melting point of 152–155°. (An additional 9 g. of the crude product was recovered from the red oil which settled on the bottom of the flask.)

Anal. Calcd. for $C_{30}H_{48}N_6$: C, 73.13; H, 9.82. Found: C, 73.35; H, 10.02.

In the following preparations only departures from the procedures employed in the corresponding sections of part 1 are noted.

2. Preparation of 4-(4-Diethylamino-1-methylbutylamino)-5-methoxy-1,10-phenanthroline (II)

(a) **8-(β-Dicarbethoxyvinylamino)-6-methoxyquinoline,** recrystallized from 95% ethyl alcohol, melted at 149–150°; yield, 95%.

Anal. Calcd. for $C_{18}H_{20}O_5N_2$: C, 62.77; H, 5.85. Found: C, 62.85; H, 6.10.

(b) **3-Carbethoxy-4-hydroxy-5-methoxy-1,10-phenanthroline.**—A 95% yield (65 g.) of the crude ester (m. p. 185–191°) was obtained from the cyclization. The analytical sample was recrystallized from one part of ethyl alcohol and two parts of water. It melted at 217–220°.

Anal. Calcd. for $C_{16}H_{14}O_4N_2$: C, 64.42; H, 4.73. Found: C, 64.43; H, 4.70.

(c) **3-Carboxy-4-hydroxy-5-methoxy-1,10-phenanthroline.**—The hydrolysis was carried out on 25 g. of the ester and 300 ml. of 5% potassium hydroxide; total time of refluxing was two hours. It was not necessary to treat the precipitate with concentrated hydrochloric acid.

The yield of the crude acid was 20.5 g. (90%); it decomposed at 270–280°. After recrystallization from nitromethane, the pure product decomposed at 278–284°.

Anal. Calcd. for $C_{14}H_{10}O_4N_2$: C, 62.22; H, 3.73. Found: C, 62.05; H, 3.93.

(d) **4-Hydroxy-5-methoxy-1,10-phenanthroline.**—To 50 ml. of refluxing diphenyl ether was added, over a period of one hour, 8 g. of the acid. After the mixture had cooled to room temperature the solid was collected by filtration, washed with petroleum ether (b. p. 30–55°), and then it was dried between filter papers. This material was then dissolved in 90-ml. of boiling chloroform, the mixture was filtered and then most of the solvent was removed by distillation. To the cooled residue was added 60 ml. of carbon tetrachloride, the mixture was filtered and the brown solid was dried in an oven at 80°. The product melting at 165–185° weighed 3.5 g.

Attempts to purify the compound failed; however, the monopicrate was prepared and analyzed. It had a melting point of 215–221° after recrystallization from nitromethane.

Anal. Calcd. for $C_{19}H_{13}O_9N_5$: C, 50.12; H, 2.88. Found: C, 50.10; H, 3.01.

(e) **4-Chloro-5-methoxy-1,10-phenanthroline.**—The amounts of starting materials used were 3.5 g. of phosphorus pentachloride, 10 g. of phosphorus oxychloride and 3.5 g. of the hydroxy compound (m. p. 165–185°). The temperature of the mixture was kept at 130° for thirty minutes instead of one hour. The yield of chloro compound melting at 150–158° was 1 g.

Difficulties were encountered in the purification of this chloro compound. The analytical sample was purified in the following way. The crude compound (4 g.) was dissolved in 20 ml. of 95% alcohol and to this was added 30 ml. of a saturated solution of picric acid in 95% alcohol. The monopicrate was filtered, washed with alcohol and dried. It weighed 5 g. and melted at 205–215°. This picrate was decomposed by shaking with concentrated hydrochloric acid. The picric acid was extracted with benzene and the hydrochloric acid solution was made basic with a 20% sodium hydroxide solution. The chloro compound was extracted with 25-ml. of chloroform and the chloroform solution was washed with water and dried over sodium sulfate. The dried solution was treated with Norit, filtered and the solvent was removed by distillation. The residual solid which weighed 1 g. and melted at 158–162° was sublimed *in vacuo*. The light yellow chloro compound obtained by sublimation had a melting point of 164–167°.

Anal. Calcd. for $C_{13}H_9OClN_2$: C, 63.81; H, 3.71. Found: C, 63.67; H, 3.77.

The above monopicrate after recrystallization from nitromethane melted at 218–220°.

Anal. Calcd. for $C_{19}H_{12}O_8ClN_5$: C, 48.16; H, 2.55. Found: C, 48.35; H, 2.70.

(f) **4-(4-Diethylamino-1-methylbutylamino)-5-methoxy-1,10-phenanthroline (II).**—A mixture of 1 g. of the chloro compound and 4 g. of 4-diethylamino-1-methylbutylamine was heated at 170° for three hours. The resulting dark viscous mixture was made basic with 15% sodium hydroxide and the excess 4-diethylamino-1-methylbutylamine was removed by extraction with water. The residual black oil was dissolved in 95% alcohol and the solution was added to a saturated solution of picric acid in alcohol. A brown oil formed which solidified after standing for two days. The dipicrate after recrystallization from nitromethane melted at 196–200°

Anal. Calcd. for $C_{34}H_{36}O_{16}N_{10}$: C, 49.51; H, 4.40. Found: C, 48.91; H, 4.31.

3. Preparation of 4-(3-Diethylaminopropylamino)-1,10-phenanthroline (III)

(a) **8-(β-Dicarbethoxyvinylamino)-quinoline.**—A mixture of 44 g. of 8-aminoquinoline and 61 g. of ethoxymethylenemalonic ester was heated on a steam-bath for one and one-half hours. The solid after recrystallization from 150-ml. of alcohol weighed 84 g. (87%). It had a melting point of 110–112°.

Anal. Calcd. for $C_{17}H_{18}O_4N_2$: C, 64.95; H, 5.77. Found: C, 64.78; H, 5.89.

(b) **3-Carbethoxy-4-hydroxy-1,10-phenanthroline.**—A 95% yield (96 g.) of the crude product was obtained from the cyclization of 118 g. of the ester (in 1500 ml. of diphenyl ether). The analytical sample was recrystallized from ethyl Cellosolve. It had a melting point of 237–241°.

Anal. Calcd. for $C_{15}H_{12}O_3N_2$: C, 67.15; H, 4.51. Found: C, 67.41; H, 4.62.

(c) **3-Carboxy-4-hydroxy-1,10-phenanthroline.**—The hydrolysis was carried out on 96 g. of the ester and 722-ml. of 10% potassium hydroxide; total time of refluxing was two hours. It was not necessary to treat the precipitate with concentrated hydrochloric acid. The yield of the crude acid was 85 g. (98%). After recrystallization from ethyl Cellosolve, the pure product decomposed at 300–305°.

Anal. Calcd. for $C_{13}H_8O_3N_2$: N, 11.66. Found: N, 11.69.

(d) **4-Hydroxy-1,10-phenanthroline.**—A 97% yield (32 g.) of the crude hydroxy compound was obtained from the decarboxylation of 40 g. of the acid during ten minutes. The solid, after recrystallization from 500-ml. of nitromethane, melted at 211–214° and weighed 20 g.

The analytical sample was recrystallized from xylene. It had a melting point of 214–215°.

Anal. Calcd. for $C_{12}H_5ON_2$: C, 73.46; H, 4.11. Found: C, 73.73; H, 4.20.

(e) **4-Chloro-1,10-phenanthroline.**—To a mixture (at 90°) of 11 g. of phosphorus pentachloride and 20 ml. of phosphorus oxychloride was added 10 g. of the hydroxy compound. The temperature of the mixture was then raised to 130° and maintained there for two hours.

The crude chloro compound, after it was dried in an oven at 80° for five hours, melted at 180–230° and weighed 10 g. (95%). The chloro compound apparently exists as a hydrate as the solid melts at 80° and then solidifies. This vesicant product was not purified. However the monopicrate was prepared and analyzed; after recrystallization from nitromethane the picrate melted at 203–206°.

Anal. Calcd. for $C_{18}H_{10}N_5O_7Cl$: C, 48.72; H, 2.27. Found: C, 48.89; H, 2.27.

(f) **4-(3-Diethylaminopropylamino)-1,10-phenanthroline** (III).—A mixture of 23 g. of crude chloro compound and 65 g. of 3-diethylaminopropylamine was heated at 165° for two and one-half hours. To the red colored solution was added 100-ml. of concentrated potassium hydroxide and the mixture was then cooled in ice. The amine layer separated and was extracted with 250-ml. of chloroform. The chloroform solution was thoroughly washed with cold water, dried over potassium carbonate, filtered, and the solvent was removed by distillation. After the excess 3-diethylaminopropylamine was removed *in vacuo*, the solid residue was washed with petroleum ether (b. p. 50–60°). The crude product which melted at 130–150° weighed 30 g. To this was added 2500-ml. of methylcyclohexane and the mixture was boiled for a few minutes and then filtered. The red oil which did not dissolve was discarded. The methylcyclohexane solution was cooled in an ice-bath and the product which was collected by filtration was recrystallized from 2500 ml. of methylcyclohexane.

The yield of white crystalline product melting at 166–168° was 10 g. (32%).

Anal. Calcd. for $C_{19}H_{24}N_4$: C, 73.99; H, 7.84. Found: C, 73.86; H, 8.06.

The dipicrate after recrystallization from acetone melted at 172–174°.

Anal. Calcd. for $C_{31}H_{30}N_{10}O_{14}$: C, 48.57; H, 3.94. Found: C, 48.68; H, 4.11.

Summary

A series of reactions is described for the preparation of dialkylaminoalkylamino-1,10-phenanthrolines. The steps include condensation of the appropriate phenylenediamine or aminoquinoline with ethoxymethylenemalonic ester, ring closure in diphenyl ether, hydrolysis, decarboxylation, treatment with a mixture of phosphorus oxychloride and phosphorus pentachloride, and the condensation of the chloro compounds with dialkylaminoalkylamines.

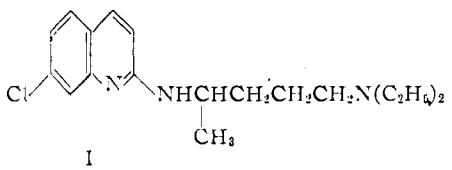
URBANA, ILL. RECEIVED APRIL 5, 1946

[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY OF THE UNIVERSITY OF VIRGINIA]

Antimalarials. *dl*-7-Chloro-2-(4-diethylamino-1-methylbutylamino)-quinoline[1]

BY ROBERT E. LUTZ, GILBERT ASHBURN AND RUSSELL J. ROWLETT, JR.[2]

Because of the antimalarial activity shown by 7-chloro-4-(-diethylamino-1-methylbutylamino)-quinoline (SN[1] 7618), it seemed important to synthesize for comparison the isomer in which the diamine chain is located in the 2- instead of the 4-position (I) (SN[1] 11,427).



I

In this synthesis 2,7-dichloroquinoline (IV) was needed as the intermediate for condensation with noval diamine. Because of the availability in this Laboratory of a quantity of 2,4,7-trichloroquinoline which could be hydrolyzed easily to 4,7-dichlorocarbostyril (II),[3] the quickest and most straightforward path to 2,7-dichloroquinoline which presented itself was the partial and selective catalytic hydrogenolysis of the latter (II) to 7-chlorocarbostyril (III) and subsequent replacement of the hydroxyl by chlorine. The obvious alternative syntheses were (a) the Skraup reaction on *m*-chloroaniline,[4] separation of the 7-chloroquinoline from the mixture of isomers, introduction of the 2-chlorine by the method of Decker[5] through the N-methyl compound, oxidation and replacement by chlorine chlorination, and (b) a similar synthesis from the now available 4,7-dichloroquinoline, involving partial catalytic reduction to eliminate the 4-chlorine,[6] a path which was excluded at the time because all of the available starting material was needed for the preparation of SN-7618 for the Armed Forces.

The dichloroquinoline reported long ago by Fischer[4c] as the 2,7-compound (m. p. 98–99°) was made from the supposed 7-chloroquinoline.[4a,b] Fourneau[4d] showed later, however, that the structures of the 5 and 7-chloroquinolines made by the Skraup reaction on *m*-chloroaniline were re-

(1) The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Virginia.

The Survey Number, designated SN, identifies a drug in the records of the Survey of Antimalarial Drugs. The antimalarial activities of those compounds to which Survey Numbers have been assigned will be tabulated in a forthcoming monograph.

(2) Present location: Jackson Laboratory, E. I. du Pont de Nemours and Co., Wilmington, Del.

(3) (a) Lutz and co-workers, THIS JOURNAL, **68**, 1285 (1946); (b) Rowlett and Lutz, *ibid.*, **68**, 1288 (1946).

(4) (a) La Coste, *Ber.*, **18**, 2940 (1885); (b) Claus and Junghanns, *J. prakt. Chem.*, [2] **48**, 253 (1893); (c) Fischer, *Ber.*, **35**, 3683 (1902); (d) Fourneau, Tréfouel, Tréfouel and Wancolle, *Bull. soc. chim.*, [4] **47**, 749 (1930).

(5) Decker, *J. prakt. Chem.*, [2] **45**, 171 (1892).

(6) Surrey and Hammer, THIS JOURNAL, **68**, 116 (1946), reported after the completion of this work.