malarial activities are against *P. lophurae* in the duck. Homogeneities were determined by the counter-current distribution method of Craig.[7] In the case of 6-methoxy-8-(2′-diethylaminoethylamino)-lepidine, this method showed that the dihydrochloride contained about 10% of a more basic impurity. To remove this, 22 g. of the salt was dissolved in 50 ml. of water, and phosphate buffer (*p*H 7.2) was added until no further turbidity was apparent. This mixture was then extracted with two 150-ml. portions of ether, and the extract was dried and distilled. The distillate solidified on cooling, and then melted at 71-72°.

Anal. Calcd. for $C_{17}H_{25}N_3O$: C, 71.1; H, 8.8. Found: C, 71.4; H, 8.7.

Summary

1. Improvements in the synthesis of 4-methyl-6-methoxy-8-aminoquinoline are recorded.

2. Several new derivatives of 4-methyl-6-methoxy-8-aminoquinoline have been synthesized for testing as antimalarials.

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[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF DEPAUW UNIVERSITY]

1-Methyl-4-carbostyrilcarboxaldehyde and Certain Condensation Products

BY D. J. COOK AND MARTHA STAMPER

Recently the preparation of 1,4-dimethylcarbostyril (I) (see Chart I) and its subsequent condensation with ethyl oxalate in the presence of potassium ethoxide was reported.[1]

Although attempts to condense chloral and aromatic aldehydes with the 4-methyl group of 1,4-dimethylcarbostyril were unsuccessful, it has been found that this group can be oxidized to the aldehyde (II) with selenium dioxide. This oxidation, when carried out in the usual solvents such as ethyl alcohol or xylene, was found to be very slow and the yield quite low, but when the selenium dioxide was added to the fused 1,4-dimethylcarbostyril, the oxidation proceeded rapidly and in yields of 60-70%.

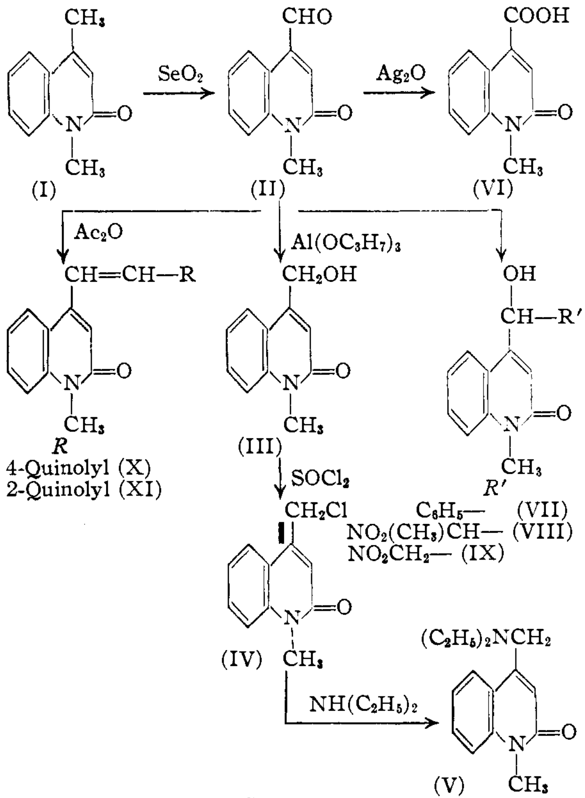

CHART I

The aldehyde was reduced to the alcohol (III) with aluminum *i*-propoxide and by treatment with thionyl chloride the alcohol was converted to 1-methyl-4-chloromethylcarbostyril (IV). This chloride was condensed with diethylamine to form the 1-methyl-4-diethylaminomethylcarbostyril (V). The aldehyde was oxidized with silver oxide to the 1-methyl-4-carbostyrilcarboxylic acid (VI).

By use of the proper Grignard reagent the aldehyde was converted to 1-methyl-4-carbostyrilphenylmethanol (VII). Various condensations were carried out with nitroethane, nitromethane, lepidine and quinaldine to give α-(1-methyl-4-carbostyril)-β-nitropropanol (VIII), α-(1-methyl-4-carbostyril)-β-nitroethanol (IX), 1-(1-methyl-4-carbostyril)-2-(4-quinolyl)-ethylene (X) and 1-(1-methyl-4-carbostyril)-2-(2-quinolyl)-ethylene (XI).

Of these compounds one was tested for antimalarial value. Compound V was found to have a Q value of 0.16 when tested against *p. lophurae* in ducklings. Thanks are due the Eli Lilly Research Laboratories for carrying out this test.

This study offers a method of preparing 1-methyl-carbostyrils with substituents in the 4-position.

Experimental[2]

Selenium Dioxide.—The selenium dioxide was prepared according to the directions outlined by Waitkins and Clark.[3] The selenium dioxide was purified immediately by sublimation and stored in a glass-stoppered bottle. The use of this material over a period of several months showed no change in its oxidizing capacity.

1,4-Dimethylcarbostyril (I).—The starting material was prepared as described by Kaslow and Cook.[1]

1-Methyl-4-carbostyrilcarboxaldehyde (II).—In a 500-ml., three-necked, round-bottomed flask equipped with an air condenser and mechanical stirrer was placed 19 g. (0.11 mole) of I. The flask was heated in an oil-bath to 150°. To the fused material 14 g. (0.126 mole) of sele-

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[1] Kaslow and Cook, THIS JOURNAL, **67**, 1969 (1945).

[2] All melting points were taken on a Fisher-Johns melting block.

[3] Waitkins and Clark, *Chem. Rev.*, **36**, 235 (1945).

nium dioxide was added gradually over a period of thirty minutes. During this time the temperature was allowed to rise to 175°. The reaction mixture was maintained at 175° for an additional forty-five minutes or until the mass solidified. When cool the mixture was ground to a fine powder and extracted twice with 200-ml. portions of boiling benzene and three times with 100-ml. portions of boiling benzene. The combined extracts were evaporated to 300 ml., 1 g. of Norite was added and the hot solution filtered. Twenty-five milliliters of petroleum ether (b. p. 50–60°) was added to the solution. Yellow needles of 1-methyl-4-carbostyrilcarboxaldehyde (II), m. p. 177–179°, were obtained. The yield was 14.3 g. (70%). Repeat preparations gave yields of 60–70%. Recrystallization from benzene-petroleum ether gave a m. p. 179–180°.

Anal. Calcd. for $C_{11}H_9NO_2$: N, 7.48. Found: N, 7.18.

The **2,4-dinitrophenylhydrazone** of II was prepared according to the directions given by Shriner and Fuson.[4] A sample was recrystallized from chloroform, m. p. 315° (dec.).

1-Methyl-4-carbostyrilcarboxaldehyde Oxime.—The oxime was prepared from 1.5 g. (0.008 mole) of II according to the method of Shriner and Fuson.[5] The yield was 0.9 g. (55%) and when recrystallized from 300 ml. of boiling butyl alcohol gave a m. p. 246–247° (dec.).

Anal. Calcd. for $C_{11}H_{10}N_2O_2$: N, 13.86. Found: N, 13.69.

1-Methyl-4-carbostyrilmethanol (III).—Eight grams of II (0.043 mole) and 3 g. of aluminum *i*-propoxide were suspended in 150 ml. of *i*-propyl alcohol (99%) and heated on a steam-bath for four hours until the distillate gave a negative test with the 2,4-dinitrophenylhydrazine reagent. The *i*-propyl alcohol was removed and the residue poured into 150 ml. of water and 50 ml. of concentrated hydrochloric acid. The solution was heated to boiling, 0.5 g. of Norite added and filtered while hot. The yield of the alcohol was 8.0 g. (98%), m. p. 187–188°.

Anal. Calcd. for $C_{11}H_{13}NO_2$: N, 7.40. Found: N, 7.41.

1-Methyl-4-chloromethylcarbostyril (IV).—Eight grams of III (0.042 mole) and 15 g. of thionyl chloride in 100 ml. of anhydrous benzene were refluxed for seven hours. The excess thionyl chloride and benzene was evaporated and the solid residue dissolved in 150 ml. of water and 200 ml. of 95% ethanol. Pale yellow needles of the chloride were obtained; yield 6.3 g. (72%), m. p. 170–174°. Recrystallization from alcohol–water gave a m. p. 174–175°.

Anal. Calcd. for $C_{11}H_{10}NOCl$: N, 6.76. Found: N, 6.48.

1-Methyl-4-diethylaminomethylcarbostyril (V).—A mixture of 5.8 g. (0.028 mole) of IV and 17.4 g. of diethylamine (b. p. 55–56°) was refluxed for eight hours. The mixture was poured with stirring into 340 ml. of a 10% sodium hydroxide solution. The solid, which formed on cooling, was dissolved in 90 ml. of alcohol, 0.5 g. of Norite added and the solution filtered. With the addition of 140 ml. of water and after cooling for four hours the flakey white product was obtained. Further yields from the mother liquor gave a total of 4.1 g. (60%), m. p. 92–93°. Recrystallization gave a m. p. of 95–95.5°.

Anal. Calcd. for $C_{15}H_{20}N_2O$: N, 11.47. Found: N, 11.57.

1-Methyl-4-carbostyrilcarboxylic Acid (VI).—One gram of II (0.0053 mole) was oxidized with 1.5 g. of silver oxide in 75 ml. of alcohol after refluxing for twelve hours. Three-tenths of a gram (30%) of the acid formed on acidification with dilute sulfuric acid. Recrystallization from boiling water gave a m. p. 237–241° (dec.). The m. p. has been reported as 242–243°.[6]

1-Methyl-4-carbostyrilphenylmethanol (VII).—To the Grignard reagent prepared from 0.26 g. of magnesium turnings and 4 g. of bromobenzene in 100 ml. of anhydrous ether was added 2 g. of II (0.01 mole) dissolved in 50 ml. of anhydrous benzene. After refluxing for one hour, the mixture was poured into 200 ml. of ice and water acidified with 1 ml. of concentrated sulfuric acid. The product formed as an insoluble white precipitate, yield 0.9 g. (32%). Recrystallization from alcohol gave a m. p. 190–191°.

Anal. Calcd. for $C_{17}H_{15}NO_2$: N, 5.17. Found: N, 5.07.

α-(1-Methyl-4-carbostyril)-β-nitropropanol (VIII).—Five grams of II (0.027 mole) was dissolved in 200 ml. of absolute ethyl alcohol and cooled. To this solution was added 15 ml. of nitroethane (b. p. 113–114°) and 35 drops of diethylamine (b. p. 55°). The solution was set aside for three days. The total yield was 4.9 g. (70%); m. p. 168–171°. Recrystallization from alcohol gave white plates, m. p. 174–176° (dec.).

Anal. Calcd. for $C_{13}H_{14}N_2O_4$: N, 10.68. Found: N, 10.51.

α-(1-Methyl-4-carbostyril)-β-nitroethanol (IX).—In the same manner as for the preparation of VIII, 1 g. of II was treated with 2 ml. of nitromethane and 8 drops of diethylamine in 40 ml. of absolute alcohol. The yield was 0.7 g. (54%), m. p. 168–170° (dec.).

Anal. Calcd. for $C_{12}H_{12}N_2O_4$: N, 11.29. Found: N, 10.76.

1-(1-Methyl-4-carbostyril)-2-(4-quinolyl)-ethylene (X).—One gram of II (0.0053 mole), 1 g. of lepidine and 7 ml. of acetic anhydride was refluxed at 140–150° for seven and one-half hours. When the mixture was poured into 150 ml. of water and made basic with sodium hydroxide, a cream colored product formed. The material was recrystallized from 100 ml. of alcohol; yield 0.9 g. (54%), m. p. 224–225°.

Anal. Calcd. for $C_{21}H_{16}N_2O$: N, 8.97. Found: N, 8.51.

1,2-Dibromo-1-(1-methyl-4-carbostyril)-2-(4-quinolyl)-ethane.—To 0.2 g. of X dissolved in 30 ml. of carbon tetrachloride was added 10 ml. of a 5% solution of bromine in carbon tetrachloride. The bright yellow product could not be dissolved in the ordinary solvents and was purified by washing with hot acetone–alcohol mixture (2:1). The m. p. is 265–270° (dec.).

Anal. Calcd. for $C_{21}H_{16}N_2OBr_2$: N, 5.93. Found: N, 5.66.

1-(1-Methyl-4-carbostyril)-2-(2-quinolyl)-ethylene (XI).—Two grams of II, 2 g. of quinaldine and 14 ml. of acetic anhydride were treated as in the preparation of X. The product when recrystallized from alcohol gave yellow needles, m. p. 185–186°, yield 1.6 g. (48%).

Anal. Calcd. for $C_{21}H_{16}N_2O$: N, 8.97. Found: N, 9.06.

1,2-Dibromo-1-(1-methyl-4-carbostyril)-2-(2-quinolyl)-ethane.—This derivative was prepared in the same manner as for the preparation of the dibromide of X. The product gave a m. p. 240–245° (dec.).

Anal. Calcd. for $C_{21}H_{16}N_2OBr_2$: N, 5.93. Found: N, 5.86.

Summary

1. A satisfactory method for the oxidation of 1,4-dimethylcarbostyril to 1-methyl-4-carbostyrilcarboxaldehyde by means of selenium dioxide is given.

2. Several reactions are described which give methods for introducing substituents at the 4 position of 1-methylcarbostyril.

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(4) Shriner and Fuson, "Identification of Organic Compounds," 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1943, p. 143.

(5) Shriner and Fuson, ref. 4, p. 167.

(6) Kaufman and Albertine, *Ber.*, **42**, 3776 (1909).