4. 4-Vinylquinoline, lepidine and pyridine were found to react with maleic anhydride with evolution of carbon dioxide.

5. Several new quinoline compounds were prepared from 2-hydroxy-4-(bromomethyl)-quinoline.

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[CONTRIBUTION FROM THE AVERY LABORATORY OF CHEMISTRY OF THE UNIVERSITY OF NEBRASKA]

Syntheses in the Quinoline Series. III. The Nitration of 2-Chloro-4-methylquinoline and the Preparation of Some 2-Hydroxy-4-methyl-8-(dialkylaminoalkyl)-aminoquinolines

BY OSCAR H. JOHNSON[1] AND CLIFF S. HAMILTON

The introduction of a hydroxy group in the 2-position of certain pyridine and quinoline arsonic acids has been shown to have a beneficial effect upon the activity of these compounds as therapeutic agents.[2] Hence it seemed of interest to study the effect of such a group upon the antimalarial activity of 8-(dialkylaminoalkyl)-aminoquinolines.

Nitration of 2-chloro-4-methylquinoline gave the 8-nitro derivative as the major product together with some of the 6-nitro isomer. The structures were proved by conversion to known quinoline derivatives and comparison with authentic samples. 2-Chloro-4-methyl-8-nitroquinoline was reduced to the corresponding amine with the aid of Raney nickel catalyst. Treatment with sodium methylate then gave 2-methoxy-4-methyl-8-aminoquinoline which was found satisfactory for side chain condensations. While seeking other means for obtaining 2-methoxy-4-methyl-8-aminoquinoline, several new quinoline compounds were prepared.

The hydrobromides of β-N-diethylaminoethyl bromide and γ-N-diethylaminopropyl bromide were prepared by application of the method of Cortese.[3] Condensation of these halides with 2-methoxy-4-methyl-8-aminoquinoline followed by cleavage of the methoxy group gave the desired 2-hydroxy-4-methyl-8-(dialkylaminoalkyl)-aminoquinolines. Condensation of the same quinoline amine with quinoline-4-aldehyde gave the expected anil.

Experimental

Nitration of 2-Chloro-4-methylquinoline and Separation of the Products

A mixture of 140 cc. of concentrated sulfuric acid and 80 cc. of fuming nitric acid (d. 1.5) was cooled to $-5°$. To this was added, with mechanical stirring and over a two-hour period, 50 g. of 2-chloro-4-methylquinoline. The mixture was allowed to stand at room temperature for two hours, then poured on ice and the solid product separated by filtration and washed well with ammonium hydroxide and with water.

In order to separate the isomeric products, the crude material was extracted with five 250-cc. portions of hot ethanol. The combined extract was diluted with water and filtered. This solid was then recrystallized from benzene to give 38 g. (63% yield) of white hexagonal needles, m. p. 135°. This was found to be **2-chloro-4-methyl-8-nitroquinoline.**

Anal. Calcd. for $C_{10}H_7O_2N_2Cl$: Cl, 15.92. Found: Cl, 16.02, 16.01.

The residue from the alcohol extraction was recrystallized from benzene to give 6.5 g. of white hexagonal needles (12% yield) melting at 212–213°. This was identified as **2-chloro-4-methyl-6-nitroquinoline.**

Anal. Calcd. for $C_{10}H_7O_2N_2Cl$: Cl, 15.92. Found: Cl, 15.71, 15.58.

Structure Proof of the Nitration Products

2-Chloro-4-methyl-6-nitroquinoline.—A mixture of 29 g. of 2-hydroxy-4-methyl-6-nitroquinoline[4] and 50 cc. of phosphorus oxychloride was heated under reflux on an oil-bath for one hour. The mixture was poured on ice and the solution neutralized with ammonium hydroxide. The solid which separated was recrystallized from benzene to give 28.5 g. (90% yield) of white hexagonal needles, m. p. 212–213°. Balaban[4] reported a melting point of 207° for this compound. A mixed melting point with the minor product of the nitration of 2-chloro-4-methylquinoline showed no depression.

2-Chloro-4-methyl-8-aminoquinoline.—Eight grams of 2-chloro-4-methyl-8-nitroquinoline, the predominant isomer from the nitration of 2-chloro-4-methylquinoline, was dissolved in a mixture of equal portions of dioxane and methanol at 50° and reduced with the aid of Raney nickel catalyst and mechanical shaking. It was necessary to add fresh catalyst and reheat to 50° twice in order to complete the reduction. The catalyst was filtered from the warm solution and the filtrate concentrated and diluted with water to give the product which was recrystallized from ethanol giving 5.7 g. (83% yield) of monoclinic rods, m. p. 102°.

(1) Parke, Davis and Company Fellow.

(2) Binz and Rath, *Biochem. Z.*, **203**, 218 (1928).

(3) Cortese, THIS JOURNAL, **58**, 191 (1936).

(4) Balaban, *J. Chem. Soc.*, 2346 (1930).

Anal. Calcd. for $C_{10}H_9N_2Cl$: N, 14.54. Found: N, 14.52, 14.55.

2-Hydroxy-4-methyl-8-chloroquinoline.—Ten grams of *o*-chloroacetoacetanilide was dissolved in 30 cc. of concentrated sulfuric acid and heated at 65–70° on a water-bath for four hours, then at 95° for one hour. A solid product was obtained by pouring the solution into cold water and filtering. Recrystallization from ethanol gave 1 g. (12% yield) of white monoclinic rods, m. p. 212°.

Kermack and Muir[5] reported a much higher yield in the ring closure reaction and a melting point of 230° for the product.

Anal. Calcd. for $C_{10}H_8ONCl$: N, 7.23. Found: N, 7.27, 7.27.

2,8-Dichloro-4-methylquinoline. (1) From 2-Chloro-4-methyl-8-aminoquinoline.—Four grams of 2-chloro-4-methyl-8-aminoquinoline with 25 cc. of concentrated hydrochloric acid was treated slowly at −5° with a solution of 1.5 g. of sodium nitrite in 5 cc. of water. After diazotization was complete, a suspension of 5 g. of copper powder in 10 cc. of 20% hydrochloric acid was added. There was rapid evolution of nitrogen and a green solid formed. The mixture was diluted with 75 cc. of water, heated to boiling for five minutes and filtered while hot. The residue was dissolved in hot concd. hydrochloric acid, the copper filtered off and the product precipitated from the filtrate by diluting and cooling. Recrystallization from ethanol gave 1 g. (20% yield) of white tetragonal rods, m. p. 105°. Kermack and Muir[5] reported a melting point of 87–88° for the same compound.

Anal. Calcd. for $C_{10}H_7NCl_2$: N, 6.60. Found: N, 6.57, 6.62.

(2) From 2-Hydroxy-4-methyl-8-chloroquinoline.—A mixture of 0.7 g. of 2-hydroxy-4-methyl-8-chloroquinoline and 5 cc. of phosphorus oxychloride was refluxed at 135° for two hours. It was then poured on ice and made alkaline by addition of ammonium hydroxide. Filtration gave 0.4 g. (60% yield) of product; m. p. from ethanol was 105°. A mixed melting point with the product from (1) was 105°. Thus the major product of the nitration is the 8-nitro isomer.

Other Quinoline Compounds

2-Chloro-4-methyl-6-aminoquinoline.—Three grams of 2-chloro-4-methyl-6-nitroquinoline was reduced by the same method used for the isomeric 8-nitro derivative. Recrystallization from ethanol gave 2.2 g. (84% yield) of the amine, m. p. 154°.

Anal. Calcd. for $C_{10}H_9N_2Cl$: N, 14.54. Found: N, 14.30, 14.30.

2-Hydroxy-4-methyl-8-nitroquinoline.—Twenty-six grams of 2-chloro-4-methyl-8-nitroquinoline was refluxed for five hours with 75 cc. of 80% by volume acetic acid. The mixture was then poured into cold water and the dried product recrystallized from benzene to give 23 g. (92% yield) of monoclinic plates, m. p. 196°.

Anal. Calcd. for $C_{10}H_8O_3N_2$: C, 58.82; H, 3.95. Found: C, 59.09, 58.55; H, 3.97, 4.00.

2-Hydroxy-4-methyl-8-aminoquinoline.—Seventeen grams of 2-hydroxy-4-methyl-8-nitroquinoline was suspended in hot acetone and reduced with the aid of Raney nickel and hydrogen at 45 pounds pressure. When the reduction was complete, the solid material was filtered off and the filtrate evaporated to dryness. The total solid was dissolved in 250 cc. of 5% sodium hydroxide solution (warm), the catalyst removed by filtration and the filtrate made acidic by addition of concentrated hydrochloric acid. After treating with charcoal and filtering, the filtrate was made alkaline by addition of ammonium hydroxide and cooled to give 14 g. (theoretical yield) of an amorphous powder, m. p. above 300°. The substance is not appreciably soluble in the common organic solvents.

Anal. Calcd. for $C_{12}H_{10}ON_2$: N, 16.08. Found: N, 16.18, 16.40.

2-Hydroxy-4-methyl-8-acetaminoquinoline.—Five grams of 2-hydroxy-4-methyl-8-aminoquinoline was refluxed for three hours with 30 cc. of glacial acetic acid and 15 cc. of acetic anhydride, then poured into cold water and recrystallized from an ethanol–water mixture to give 5.2 g. (84% yield) of white monoclinic rods, m. p. 252°.

Anal. Calcd. for $C_{12}H_{12}O_2N_2$: N, 12.95. Found: N, 12.82, 12.85.

2-Methoxy-4-methyl-8-nitroquinoline.—A mixture of 35 g. of 2-chloro-4-methyl-8-nitroquinoline, 12 g. of sodium hydroxide, 6 g. of manganese dioxide and 0.3 g. of cobaltic oxide in 225 cc. of methanol was refluxed for seventeen hours. The alcohol was removed by distillation and the residue extracted with benzene. After treating this solution with charcoal and concentrating the filtrate, the product was separated and recrystallized from ethanol to give 30 g. (87% yield) of tetragonal pyramids, m. p. 119°.

Anal. Calcd. for $C_{11}H_{10}O_3N_2$: C, 60.55; H, 4.62. Found: C, 60.20, 60.25; H, 4.63, 4.59.

2-Methoxy-4-methyl-8-aminoquinoline.—To a solution of 6 g. of sodium in 75 cc. of methanol was added 7.5 g. of 2-chloro-4-methyl-8-aminoquinoline. After refluxing for five hours, the solvent was removed and water added to the residue. The solid material was filtered off and recrystallized from an ethanol–water mixture to give 6 g. (82% yield) of tetragonal needles, m. p. 96°.

Anal. Calcd. for $C_{11}H_{12}ON_2$: N, 14.89. Found: N, 14.80, 14.65.

This compound was also prepared by catalytic reduction of 2-methoxy-4-methyl-8-nitroquinoline.

Condensation Products of 2-Methoxy-4-methyl-8-aminoquinoline

2-Hydroxy-4-methyl-8-(β-*N*-diethylaminoethyl)-aminoquinoline.—Eight grams of 2-methoxy-4-methyl-8-aminoquinoline, 21 g. of β-*N*-diethylaminoethyl bromide hydrobromide and 8 g. of sodium acetate in 100 cc. of absolute ethanol was refluxed for fifteen hours. The alcohol was then removed by distillation and the residue was refluxed for one hour with 50 cc. of 20% hydrochloric acid to cleave the methoxy group. The solution was made alkaline by addition of ammonium hydroxide and the solid which separated was recrystallized from benzene to give 5.5 g. (48% yield) of triclinic rods, m. p. 140°.

Anal. Calcd. for $C_{16}H_{23}ON_3$: N, 15.37. Found: N, 15.30, 15.40.

(5) Kermack and Muir, *J. Chem. Soc.*, 300 (1933).

2-Hydroxy-4-methyl-8-(γ-N-diethylaminopropyl)-aminoquinoline.—Four grams of 2-methoxy-4-methyl-8-aminoquinoline, 11 g. of the hydrobromide of γ-N-diethylaminopropyl bromide and 4 g. of sodium acetate in 50 cc. of absolute ethanol was refluxed for twelve hours. The product was cleaved and isolated as was the ethyl derivative to give 2.5 g. (41% yield) of white tetragonal needles, m. p. 115°.

Anal. Calcd. for $C_{17}H_{25}ON_3$: N, 14.63. Found: N, 14.57, 14.57.

2-Methoxy-4-methyl-8-(4-quinolylmethyleneamino)-quinoline.—One gram of the hydrate of quinoline-4-aldehyde and 1.05 g. of 2-methoxy-4-methyl-8-aminoquinoline in 25 cc. of absolute ethanol were refluxed for twelve hours. The product was precipitated by dilution with water and recrystallized from ethanol to give 1.4 g. (70% yield) of the anil, m. p. 144°.

Anal. Calcd. for $C_{21}H_{17}ON_3$: N, 12.83. Found: N, 12.50, 12.40.

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Summary

1. Nitration of 2-chloro-4-methylquinoline gave largely 2-chloro-4-methyl-8-nitroquinoline and a small amount of the isomeric 6-nitro derivative.

2. 2-Methoxy-4-methyl-8-aminoquinoline was most conveniently prepared by catalytic reduction of 2-chloro-4-methyl-8-nitroquinoline followed by treatment with sodium methylate. While investigating other means for obtaining this compound, several new quinoline compounds were prepared.

3. 2-Methoxy-4-methyl-8-aminoquinoline was condensed with quinoline-4-aldehyde to give an anil. The same amine was condensed with β-N-diethylaminoethyl and γ-N-diethylaminopropyl bromide hydrobromides followed by cleavage of the methoxy group to give 2-hydroxy-4-methyl-8-(dialkylaminoalkyl)-aminoquinolines.

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[CONTRIBUTION FROM THE RESEARCH AND BIOLOGICAL LABORATORIES OF PARKE, DAVIS AND COMPANY]

The Preparation and Properties of Sodium *d*-Pantothenate

BY HERVEY C. PARKE AND ELMER J. LAWSON

Since the announcement by Williams and Major[1] of the structure and synthesis of pantothenic acid, the synthetic vitamin has been available chiefly in the form of the calcium salt. We have found that the sodium salt possesses certain advantages, including ease of preparation and manipulation, which indicate it to be the most suitable form of *d*-pantothenic acid for use as a primary vitamin standard. A similar conclusion has been reached by Gätzi-Fichter, Reich and Reichstein,[2] although the data which they have furnished do not seem completely adequate to characterize the material for such a standard.

Sodium *d*-pantothenate is crystallized readily from absolute ethanol or isopropanol, and may thus be obtained in a high state of purity as fluffy needles which are considerably less hygroscopic than either the microcrystalline calcium salt or the amorphous sodium salt. Samples of the salt were subjected to a crystallographic study under the polarizing microscope through the kindness of Dr. Chester B. Slawson of the University of Michigan. He states: "The hair-like crystals show parallel extinction and are probably orthorhombic. The plane of the optic axes is parallel to the elongation with the obtuse bisectrix perpendicular to the elongation. The index of refraction parallel to the elongation is 1.486 ± 0.001 and perpendicular to the elongation 1.464 ± 0.003."

Sodium pantothenate has been prepared by a variety of methods, of which perhaps the simplest is the fusion of α-hydroxy-β,β-dimethyl-γ-butyrolactone with the sodium salt of β-alanine.[3]

We have found that sodium pantothenate can also be prepared by (1) the fusion of α,γ-dihydroxy-β,β-dimethylbutyramide with the sodium salt of β-alanine, (2) by the fusion of sodium α,γ-dihydroxy-β,β-dimethylbutyrate with β-alanine, and (3) by refluxing a solution of α-hydroxy-β,β-dimethyl-γ-butyrolactone and the sodium salt of β-alanine in ethanol or isopropanol. The second method is particularly interesting and, as far as we are aware, has no parallel in the literature.

(1) Williams and Major, *Science*, **91**, 246 (1940).

(2) Gätzi-Fichter, Reich and Reichstein, *Helv. Chim. Acta*, **24**, 185 (1941).

(3) Williams, Mitchell, Weinstock and Snell, THIS JOURNAL, **62**, 1784 (1940).