3-Cyclohexene-1,1-dicarbonol.—White crystals; m. p. 92.5°; phenyl urethan, m. p. 118.5°.

Anal. Calcd. for $C_{22}H_{24}O_4N_2$: C, 69.45; H, 6.36. Found: C, 69.29; H, 6.57. Active hydrogens in the diol, 1.81.

Hydrogenation of 3,4,6-Trimethyl-3-cyclohexene-1,1-dicarbonol.—The compound was reduced at 2500 lb. pressure at 150°, using Raney nickel, to the known cyclohexane-1,1-dicarbonol, m. p. 95–96°.[7]

Oxidation of Cyclohexane-1,1-dicarbonol.—Oxidation with potassium permanganate in neutral and in alkaline solutions, using water and water–acetone solvents, gave only uncrystallizable oils. Nitric acid oxidation gave a small yield of a solid acid which was not identified.

1.7 g. of the diol was dissolved in 10 cc. of pyridine. A solution of 5.5 g. of potassium permanganate in 110 cc. of water was added with stirring, at a temperature of 0°. The mixture was stirred for eight hours at that temperature and allowed to warm slowly to room temperature. The excess permanganate was discharged with 1 cc. of ethyl alcohol. After filtering, the solution was concentrated on a water-bath to 10 cc. using vacuum. Hydrochloric acid was added and the solution placed in the ice chest. A yield of 0.8 g. of the known cyclohexane-1,1-dioic acid was obtained.

(7) Franke and Sigmund, *Monatsh.*, **46**, 61 (1925).

Summary

1. The action of alkaline solutions on certain cyclohexenecarbonals has been studied.

2. These aldehydes were found to undergo the Cannizzaro reaction, and to react with formaldehyde to yield cyclohexene-1,1-dicarbonols.

COLUMBIA, MISSOURI RECEIVED MARCH 30, 1942

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

Sulfanilamido Derivatives of Nitrogen Bases from California Petroleum[1]

BY LESLIE M. SCHENCK[2] AND HENRY R. HENZE

Bobranski[3] and Winterbottom[4] have reported syntheses in the sulfanilamidoquinoline series; however, no alkylation in the quinoline nucleus higher than methyl was included. Since detailed pharmacological tests of their compounds have not been published, it was considered of interest to prepare sulfanilamido derivatives of a series of alkylated quinoline homologs encountered in nitrogen bases extracted from California petroleum. Since quinolines substituted in positions 2, 3 and 8 occur in appreciable quantity among the complex petroleum base fractions, this series was selected for investigation. The compounds prepared in this work are sulfanilamido and acetylated sulfanilamido derivatives of 5-amino-2,3,8-trimethylquinoline, and of the hitherto unreported 5-amino-8-ethyl-2,3-dimethylquinoline and 5-amino-2,3-dimethyl-8-*n*-propylquinoline.

Through the courtesy and coöperation of Parke, Davis and Company, the 2,3,8-trimethyl and 2,3-dimethyl-8-*n*-propylquinoline sulfanilamido derivatives have received preliminary testing for possible pharmacological activity. No activity was found in mice infected with experimental Type I pneumococcus, *Staph. aureus* or *Strep. viridans*. The slight activity toward hemolytic streptococci indicates that the activity of sulfanilamide is lowered by substitution of the quinoline heterocycle at the N^1 position. Certainly the compounds here reported do not have the desirable properties obtained with other heterocycles such as pyridine, thiazole and pyrimidine.

Two of the new compounds reported herein have received preliminary testing for antimalarial activity (through the courtesy of Parke, Davis and Company). It is of interest to note the activity against avian malaria of 5-sulfanilamido-2,3,8-trimethylquinoline in the *blood*, whereas larger doses of this material are inactive in the tissue.

	Stage tested	Dose, mg.	Result
5-Sulfanilamido-2,3,8-trimethylquinoline	Blood	50	Active
	Tissue	100	Inactive
5-(N^4-Acetylsulfanilamido)-2,3-dimethyl-8-*n*-propylquinoline	Blood	50	Inactive

Experimental

2,3,8-Trimethyl-5-nitroquinoline.—Fourteen grams of 2,3,8-trimethylquinoline,[5] isolated from petroleum nitrogen bases, was converted to 2,3,8-trimethyl-5-nitroquinoline in accordance with Burger and Modlin.[6] There was obtained 13 g. of purified product, crystallizing from petroleum ether as pale yellow needles melting at 124° (cor.).

(1) Constructed from a portion of a thesis presented to the Graduate Faculty of the University of Texas by Leslie M. Schenck in partial fulfillment of the requirements for the degree of Doctor of Philosophy, June, 1942.

(2) Parke, Davis Fellow, 1941–1942; present address, General Aniline and Film Corporation, Grasselli, N. J.

(3) Bobranski, *Arch. Pharm.*, **277**, 75 (1939).

(4) Winterbottom, THIS JOURNAL, **62**, 160 (1940).

(5) Poth, Schultze, King, Thompson, Slagle, Floyd and Bailey, *ibid.*, **52**, 1239 (1930).

(6) Burger and Modlin, *ibid.*, **62**, 1079 (1940).

2,3,8-Trimethyl-5-aminoquinoline.—Burger and Modlin[6] report the preparation of this compound by reduction of the corresponding nitro derivative with stannous chloride and 17% hydrochloric acid. When their method was tried upon larger quantities of 2,3,8-trimethyl-5-nitroquinoline, the isolation was found unsatisfactory, and it was necessary to steam distil the amine from the reduction mixture and to recover it from the large volume of distillate by ether extraction.

As an alternate method, promising less difficulties in isolation and purification of the desired intermediate, 12.5 g. of 2,3,8-trimethyl-5-nitroquinoline (0.058 mole) was hydrogenated over Raney nickel catalyst at 70° and 1000 lb./sq. in. pressure for thirty minutes, employing ethyl alcohol as the solvent. The catalyst was removed by filtration, the solvent diluted with water and the precipitated amine crystallized from dilute ethyl alcohol to give a quantitative yield of 2,3,8-trimethyl-5-aminoquinoline melting at 110–111° (cor.) identical with that prepared by the more laborious method of Burger and Modlin.

5-(N_4-Acetylsulfanilamido)-2,3,8-trimethylquinoline.—The amine (0.059 mole) was dissolved in 100 cc. of pyridine which had been dried by prolonged contact with potassium hydroxide pellets. To the solution was added 18 g. (0.077 mole) of acetylsulfanilyl chloride which had been purified by crystallization from acetone–benzene and thoroughly dried through vacuum desiccation over calcium chloride. Heat was immediately developed, and the solution was agitated until all the acid chloride was in solution. At this point, the reaction mixture was heated three hours on the steam-bath, a calcium chloride tube being employed to protect against atmospheric moisture.

The crude 5-(N^4-acetylsulfanilamido)-2,3,8-trimethylquinoline was precipitated by pouring its pyridine solution into 500 cc. of ice water. Separating first as a highly discolored oil, the product soon solidified and was removed by filtration. One-half the product was purified by repeated treatment with Norite in boiling ethyl alcohol. The purified compound, prepared in 47% yield, crystallized from this solvent as hair-like needles melting undecomposed at 260.5–261.5° (cor.).

Anal. Calcd. for $C_{20}H_{21}N_3O_3S$: N, 10.95. Found: N, 10.78.

5-Sulfanilamido-2,3,8-trimethylquinoline.—One-half of the crude 5-(N^4-acetylsulfanilamido)-2,3,8-trimethylquinoline described above was dissolved in 100 cc. of 4 *N* hydrochloric acid and hydrolyzed by refluxing thirty minutes. After cooling, the acid solution was neutralized with ammonium hydroxide and the product removed by filtration. Purification was effected by three crystallizations from ethyl alcohol, Norite being employed during the initial process. The final product, realized in 58% yield, was in the form of fine colorless needles melting without decomposition at 225.5–226° (cor.).

Anal. Calcd. for $C_{18}H_{19}N_3O_2S$: N, 12.31. Found: N, 12.26.

8-Ethyl-2,3-dimethyl-5-nitroquinoline.—Six grams of 8-ethyl-2,3-dimethylquinoline[7] (0.032 mole) was added slowly to 60 cc. of fuming nitric acid (sp. gr. 1.49) and heated on the steam-bath for five hours. Upon neutralization of the diluted acid with sodium carbonate, the nitrated base was recovered by filtration and crystallized in 83% yield from ethyl alcohol as fine needles melting undecomposed at 107–109° (cor.).

Anal. Calcd. for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13. Found: C, 67.88; H, 6.37.

5-Amino-8-ethyl-2,3-dimethylquinoline.—Six grams of the nitro compound was hydrogenated under the identical conditions used in the reduction of the trimethyl analog to yield 5 g. (94%) of amine which crystallized from ligroin as irregular shaped needles melting at 101–102° (cor.).

Anal. Calcd. for $C_{13}H_{16}N_2$: N, 13.99. Found: N, 13.97.

5-(N^4-Acetylsulfanilamido)-8-ethyl-2,3-dimethylquinoline.—In the manner previously described, 5 g. of 5-amino-8-ethyl-2,3-dimethylquinoline was dissolved in 50 cc. of dry pyridine and heated with acetylsulfanilyl chloride for three hours on the steam-bath. The product was recovered from the pyridine by dilution with water, and crystallized only after prolonged standing. The crude material was divided into two equal portions, one of which was purified. Unlike its 2,3,8-lower homolog, 5-(N^4-acetylsulfanilamido)-8-ethyl-2,3-dimethylquinoline is extremely soluble in alcohol. Since no suitable solvent for recrystallization was found, purification was achieved by repeatedly dissolving the discolored compound in boiling ethyl alcohol, treating with Norite, and precipitating the colorless acetyl derivative by addition of water. Only 1 g. (20%) of pure material, melting at 244–245° (cor.), was obtained.

Anal. Calcd. for $C_{21}H_{23}N_3O_3S$: N, 10.57; S, 8.07. Found: N, 10.74; S, 8.20.

5-Sulfanilamido-8-ethyl-2,3-dimethylquinoline.—The second portion of the crude product referred to above was hydrolyzed as in the previous case by thirty minutes of refluxing with 60 cc. of 6 *N* hydrochloric acid. The product, precipitated by the addition of ammonium hydroxide, was purified to the constant melting point of 241–242° (cor.) by recrystallization from ethyl alcohol, from which solvent it crystallizes in fine needles.

Anal. Calcd. for $C_{19}H_{21}N_3O_2S$: N, 11.83. Found: N, 11.81.

2,3-Dimethyl-5-nitro-8-*n*-propylquinoline.—Fifteen grams (0.075 mole) of 2,3-dimethyl-8-*n*-propylquinoline[8] was nitrated by heating at steam-bath temperature with 150 cc. of nitric acid (sp. gr. 1.49) for three hours. The nitro derivative, precipitated by neutralizing the diluted solution with sodium carbonate, was recrystallized from petroleum ether in 93% yield. A small sample was further purified to a constant melting point of 97–99° (cor.).

Anal. Calcd. for $C_{14}H_{16}N_2O_2$: N, 11.47. Found: N, 11.51.

5-Amino-2,3-dimethyl-8-*n*-propylquinoline.—Reduction was realized in 95% yield by hydrogenating the nitro compound (17 g.) over Raney nickel at 70–100° and 1000 lb./sq. in. pressure. Following crystallization from petroleum ether, the amine melted at 90–92° (cor.).

Anal. Calcd. for $C_{14}H_{18}N_2$: N, 13.08. Found: N, 13.15.

(7) Key and Bailey, THIS JOURNAL, **60**, 3028 (1938).

(8) Axe and Bailey, *ibid.*, **60**, 3028 (1938).

5-(N^4-Acetylsulfanilamido)-2,3-dimethyl-8-*n*-propylquinoline.—Fourteen grams of 5-amino-2,3-dimethyl-8-*n*-propylquinoline (0.065 mole) reacted with 22 g. of acetylsulfanilyl chloride (0.094 mole) in 140 cc. of dry pyridine for three hours. The product, recovered by dilution with water, separated as an oil which did not crystallize upon standing. The aqueous layer was decanted, and the tarry product divided into two fractions of approximate equality. By repeatedly dissolving one portion of the oil in ethyl alcohol, refluxing with Norite, and precipitating the product with water, the acetyl derivative was obtained (in 15% yield) and melted at 208–209° (cor.).

Anal. Calcd. for $C_{22}H_{25}N_3O_3S$: N, 10.21. Found: N, 10.26.

5-Sulfanilamido-2,3-dimethyl-8-*n*-propylquinoline.—The residual oil referred to above was refluxed for one hour with 150 cc. of 4 *N* hydrochloric acid. Following neutralization with ammonium hydroxide, the hydrolysis product was filtered and crystallized from ethyl alcohol with the aid of Norite as fine needles in 70% yield; melting point 237–238° (cor.).

Anal. Calcd. for $C_{20}H_{23}N_3O_2S$: N, 11.38; S, 8.66. Found: N, 11.46; S, 8.48.

Summary

The preparation of a series of sulfanilamido derivatives of nitrogen bases from California petroleum has been described. Preliminary pharmacological tests of these 2,3,8-trialkyl-5-sulfanilamidoquinolines show them to be practically inactive as sulfa drugs, indicating that such substitution of the quinoline nucleus for hydrogen of the amide group reduces the therapeutic effectiveness of sulfanilamide. One of the compounds exhibits some activity against avian malaria at the blood stage.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE STATE UNIVERSITY OF IOWA]

Azoyl Derivatives of Sugars and Separation by Chromatographic Adsorption[1]

BY GEORGE H. COLEMAN, ALFORD G. FARNHAM AND AARON MILLER

Reich[2] has reported the chromatographic separation of the *p*-phenylazobenzoyl esters of α-D-glucose and β-D-fructose on both alumina and silica as adsorbents.

The present work was undertaken to determine the applicability of the chromatographic adsorption method to similar derivatives of other sugars with the thought of applying the procedure to mixtures such as "hydrol."

p-Phenylazobenzoyl derivatives were prepared from the following sugars by the method described in the experimental part: α-D-glucose, β-D-glucose β-D-fructose, α-D-galactose, α-lactose, trehalose, sucrose, β-cellobiose, β-gentiobiose, β-maltose, D-xylose and melezitose. The compounds were analyzed for percentage azoyl and the specific rotations were measured in chloroform solution using both sodium and cadmium vapor lamps.

Several pairs of the sugar esters were separated by the chromatographic adsorption method. The following pairs of azoates were separated using Magnesol[3] as adsorbent with Dicalite as a filter aid: α-lactose and α-D-galactose, trehalose and β-D-glucose, α-lactose and sucrose, α-D-glucose and β-D-fructose, β-maltose and α-D-glucose, sucrose and α-D-glucose. On silicic acid[4] as adsorbent α-D-glucose and β-D-fructose, α-D-galactose and β-D-fructose, sucrose and β-D-fructose, α-D-glucose and melezitose were separated. Several other pairs of derivatives did not give satisfactory separation under the conditions employed.

Experimental

Preparation of Azoyl Derivatives.—The *p*-phenylazobenzoyl or "azoyl" derivatives were prepared by allowing the sugars to react in pyridine solution at 0° with *p*-phenylazobenzoyl chloride over a period of eight to twenty days. The mole ratio of azoyl chloride to sugar was about eight to one for monosaccharides and twelve to one for disaccharides. At the end of this time the excess acid chloride was decomposed by adding methanol. The products were precipitated by pouring the reaction mixture into water. The precipitate, after drying, was purified by dissolving in chloroform and reprecipitating by pouring into alcohol. The monosaccharide derivatives were recrystallized, the glucose derivatives from dioxane and the galactose and fructose derivatives from mixtures of chloroform and carbon tetrachloride. The disaccharide esters were purified by several reprecipitations.

Specific Rotations.—The specific rotations were measured at 25° in chloroform solution at a concentration of 0.5 g. per 100 ml. of solvent using a water-jacketed 2-decimeter tube. Two light sources were used, the sodium and cadmium vapor lamps, giving, respectively, the readings for the sodium D line and the cadmium 6438 Å. line.

(1) Presented at the meeting of the American Chemical Society, St. Louis, Missouri, April, 1941.

(2) Reich, *Compt. rend.*, **208**, 589, 748 (1939); *Biochem. J.*, **33**, 1000 (1939).

(3) "Magnesol" is a hydrous magnesium silicate manufactured by the Magnesol Co.

(4) Merck Reagent Silicic Acid.