

5-(N⁴-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 acetyl-sulfanilyl 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 C₂₂H₂₅N₃O₂S: 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 C₂₀H₂₃N₃O₂S: 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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Azoyl Derivatives of Sugars and Separation by Chromatographic Adsorption¹

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Reich² 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 Magnesol³ 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 acid⁴ 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.

The cadmium lamp gave more satisfactory readings, especially at higher concentrations. Physical constants are listed in Table I.

TABLE I

SPECIFIC DATA ON AZOYL DERIVATIVES				
Sugar azoate	M. p., °C. ^a	$[\alpha]^{25}_D$	$[\alpha]^{25}_{435}$	% Azoyl
α -D-Glucose	234-236	+282°	+226°	85.14
β -D-Glucose	204-206	+111	+ 86	86.00
β -D-Fructose	128-130	-511	-394	82.64
α -D-Galactose	224-226	+504	+399	85.77
α -Lactose	218-220	+355	+274	83.32
Trehalose	123-125	+276	+217	82.89
Sucrose	125-126	+ 43	+ 35	82.92
β -Cellobiose	206-208		+101	82.00
β -Gentiobiose	159-161		+ 28	82.03
D-Xylose	146-148	+285	+225	84.83
β -Maltose	242-244	- 30	- 22	78.50
	253-255			80.20
Melezitose	135-137	+110	+ 81	

Calculated per cent of azoyl:

Hexose pentaazoate = 85.66

Hexose tetraazoate = 82.61

Pentose tetraazoate = 85.13

Pentose triazoate = 81.01

Disaccharide octaazoate = 83.35

Disaccharide heptaazoate = 81.37

^a The melting points were determined between cover glasses using a Fisher Johns apparatus.

Some of these constants may be revised when perfectly pure derivatives unmixed with isomers are prepared. In certain cases complete azoylation and purification of the product was difficult by the methods used. Since the primary interest in the present work was to determine the value of these derivatives in the separation of sugars, extended study was not given to methods of preparation and purification. The work is being continued and special attention given to modification of the method of preparation and the characterization of the pure compounds.

Analysis for Percentage of Azoyl.—The derivatives were analyzed by hydrolyzing the esters and weighing the free *p*-phenylazobenzoic acid formed. The azoyl derivative was dissolved in 20 ml. of dioxane, and 15 ml. of methanol containing about 12 mg. of sodium methylate was added. The mixture was refluxed for thirty minutes and then 3 ml. of sodium hydroxide (6 *N*) and 30 ml. of water were added. Refluxing was continued for another half hour and the solution was diluted to about 200 ml. with water and 125-150 ml. removed by distillation. The residual solution was filtered, cooled, and made slightly acid with dilute hydrochloric acid. After cooling for some time to allow complete precipitation, the solid acid was collected in a crucible with sintered glass bottom, dried and weighed.

Chromatographic Adsorption.—For chromatographic adsorption a column (23 mm. by 30 cm.) was packed by suspending the solid adsorbent in petroleum ether containing about 10% of benzene and filtering under a pressure of 10 cm. of mercury. A solvent mixture of equal volumes of chloroform, benzene and petroleum ether was passed down the column followed by a solution of the azoyl derivatives. The solution contained 120 mg. of each of a pair of sugar azoates dissolved in 35-50 ml. of chloroform to which

were then added corresponding volumes of benzene and petroleum ether. The solutions were all filtered through the column under a nitrogen pressure of 10 cm. of mercury and the column was not allowed to run dry, as this caused channeling.

After adding all of the solution of sugar derivatives the chromatogram was developed using a solvent mixture of the same composition as the solution. When development was complete the column was allowed to run partially dry, the adsorbent was removed, and the bands were separated. Elution of the adsorbed materials was accomplished by extracting the adsorbent layers with hot chloroform containing a small amount of methanol. The solvent was evaporated from the eluted materials, which were then transferred in chloroform to volumetric flasks. The optical rotations were measured and the weights determined by evaporating aliquot portions of the solutions.

Typical Chromatographic Adsorption Separations

α -D-Glucose and Sucrose Azoates.—From 100 mg. of each derivative was obtained an upper band of 106.7 mg. $[\alpha]^{25}_{6435} +47^\circ$ as compared to $+35^\circ$ for the pure sucrose derivative; calcd. sucrose azoate, 93.8%. The lower band of 88.1 mg. had a specific rotation of $[\alpha]^{25}_{6435} +212^\circ$ as compared to $+225^\circ$ for the pure α -D-glucose derivative; calcd. α -D-glucose azoate, 93.2%.

β -D-Fructose and α -D-Galactose Azoates.—From 120 mg. of each derivative was obtained an upper band of 128 mg. $[\alpha]^{25}_{6435} -340^\circ$ as compared to -394° for the pure fructose derivative; calcd. fructose azoate, 93.2%. The lower band contained 104 mg.; $[\alpha]^{25}_{6435} +413^\circ$ as compared to $+399^\circ$ for the pure galactose derivative; calcd. galactose azoate, 101.6%.

α -Lactose and Sucrose Azoates.—From 120 mg. of each azoate was obtained an upper band of 144.5 mg., $[\alpha]^{25}_{6435} +206^\circ$ as compared to $+274^\circ$ for the pure lactose derivative; calcd. lactose azoate, 71.6%. The lower band contained 89.2 mg., $[\alpha]^{25}_{6435} +36^\circ$ as compared to $+35^\circ$ for the pure sucrose derivative; calcd. sucrose azoate, 99.4%.

α -D-Glucose and Melezitose Azoates.—From 55 mg. of each derivative was obtained an upper band of 52.5 mg., $[\alpha]^{25}_D +115^\circ$ as compared to $+110^\circ$ for the pure melezitose azoate; calcd. melezitose azoate, 82.8%. The lower band of 50.5 mg. had a specific rotation of $[\alpha]^{25}_D +261^\circ$ as compared to $+282^\circ$ for the pure α -D-glucose azoate; calcd. α -D-glucose azoate, 89.3%.

Summary

1. The *p*-phenylazobenzoyl esters of several sugars have been prepared. These derivatives were analyzed for percentage azoyl and the specific rotations measured in chloroform solution.

2. Several pairs of these sugar esters have been separated by the chromatographic adsorption method using silicic acid and mixtures of Magnesol and Dicalite as adsorbents. This included the separation of two monosaccharides, a monosaccharide and disaccharide, two disaccharides, and the separation of a monosaccharide and trisaccharide.