bulk of the mass was crystallized from absolute ethanol; yield 4.7 g. (94%) of a *m*-terphenyl of m. p. 86–87°. The small amount of adsorbed material contained unchanged *o*-terphenyl.

C. Rearrangement, *ortho* to a Mixture of *meta* and *para*.—One gram of *o*-terphenyl in 80 cc. of dry benzene containing 50 mg. of catalyst was refluxed for seventy hours. The product contained a mixture of *m*- and *p*-terphenyl, in a yield of 0.16 and 0.58 g., respectively. No attempt was made at a tedious quantitative separation. Traces (6 mg.) of diphenyl were found.

D. Rearrangement, *ortho* to *para*.—To 1 g. of *o*-terphenyl in 85 cc. of solvent was added 50 mg. of the catalyst. After refluxing for two hundred and sixty-four hours, 0.82 g. of *p*-terphenyl was obtained after crystallization from absolute ethanol.

As there are known polymeric condensation products of *m*-terphenyl which melt in a similar range as *p*-terphenyl, it was thought desirable to check the approximate molecular weight of the product.

Anal. Calcd. for $C_{18}H_{14}$: mol. wt., 230. Found: mol. wt., 244, in boiling benzene.

Rearrangements with larger amounts of anhydrous aluminum chloride, especially in molar quantities, have been studied, but the reactions are complicated by tars and are of no particular interest in this connection.

E. Aluminum–Sodium Chloride Melts.—The effect of these on *o*-terphenyl was only studied in a qualitative way, for very complex mixtures resulted; but two instances will be described. (1) To about 20 g. of a 4:1 melt at 130° was added 2 g. of *o*-terphenyl. The mixture was cooled and decomposed by iced hydrochloric acid. The decolorized and dried benzene extract of the product left a residue on evaporation, which was treated with absolute ethanol; from this *p*-terphenyl crystallized. (2) A similar run, at 200°, gave a mixture from which were separated 0.4 g. (20%) of triphenylene and 0.15 g. of *p*-terphenyl.

Summary

o-Terphenyl has been prepared in quantity. Of the available methods, the Wurtz–Fittig was found to be most suitable.

A new synthesis that may be applicable for securing derivatives is described.

Ozonolysis of *o*-terphenyl gave the products expected.

o-Terphenyl is easily rearranged by aluminum chloride. With very small amounts, *m*-terphenyl is first formed; this then further rearranges to *p*-terphenyl. Large amounts, alone or with sodium chloride, give complex mixtures from which *p*-terphenyl and triphenylene were isolated.

ROCHESTER, NEW YORK RECEIVED FEBRUARY 26, 1942

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A New Type of Sulfanilamide Derivative of D-Glucose. Sulfanilyl-2-amino-α-D-glucose and Certain Derivatives

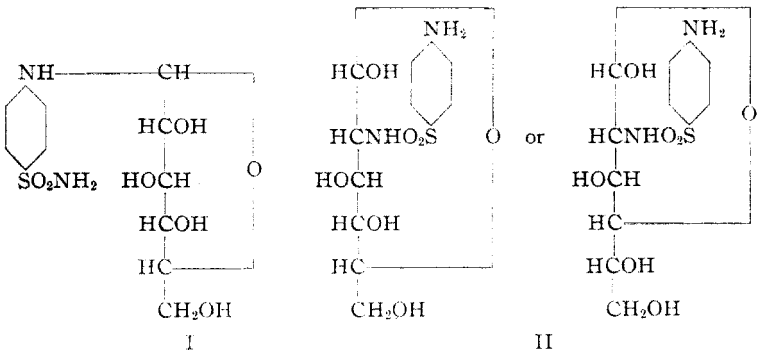
BY ERNEST L. JACKSON

Within recent years sulfanilamide derivatives[1,2] of a number of reducing sugars have been prepared by the reaction of sulfanilamide with the sugars under suitable conditions. The sulfanilamide component of these compounds is generally regarded as linked through the primary amino nitrogen atom (N^4) to carbon atom 1 of the sugar component either as a N-glycoside or an anil. Although the structure in no case has been fully established, the crystalline derivative of glucose having a specific rotation of $-123°$ in water has been shown by Kuhn and Birkofer[2] to be of the N-glycosidic type (I). This N-glucoside, which is known to be unstable in 0.1 *N* hydrochloric acid solution[2] even at room temperature, may be split *in vivo* to liberate sulfanilamide. The present article pertains to a new type (II) of sulfanilamide derivative of glucose in which the sulfanilamide component is linked through the amido nitrogen atom (N^1) to carbon atom 2 of the glucose component. A relatively stable union of the sulfanilamide and glucose components was expected in this type of compound, which offered the possibility of less toxicity and greater solubility in water than sulfanilamide.

D-Glucosamine reacts readily with N-acetylsulfanilyl chloride in aqueous-acetone solution to yield crystalline N-acetyl-sulfanilyl-2-amino-α-D-glucose. Deacetylation of this acetyl derivative in 0.5 *N* sulfuric acid solution at 100° yielded a highly colored sirup, which could be crystallized as a hydrochloride. The hydrochloride, though impure, proved to be a convenient intermediate for the preparation of crystalline sulfanilyl-2-

(1) Gray, Buttle and Stephenson, *Biochem. J.*, **31**, 724 (1937); Meyer and Schreiber, U. S. Patent 2,141,843 (1938); Établissements Mouneyrat et Cie., French Patent 839,711 (1939); Klingel and MacLennan, U. S. Patent 2,167,719 (1939); Vacirca, *Boll. sez. ital. Soc. intern. microbiol.*, **11**, 16 (1939); Schering, French Patent 842,726 (1939); Meyer, U. S. Patent 2,208,641 (1940); British Patent 519,661 (1940); Winthrop Chemical Co., British Patent 526,747 (1940); Weygand, *Ber.*, **73**, 1259 (1940).

(2) Kuhn and Birkofer, *ibid.*, **71**, 621 (1938).



I II

amino-α-D-glucose (II), which was obtained readily by the reaction of silver carbonate with the hydrochloride in methanol solution. In agreement with structure II sulfanilyl-2-amino-α-D-glucose reduces Fehling solution and is diazotized by nitrous acid. The alpha configuration is assigned to carbon atom 1 of the glucose component in both II and its acetyl derivative on account of their downward mutarotation in aqueous solution (Table I). The compounds probably are of the pyranose or furanose ring type.

TABLE I

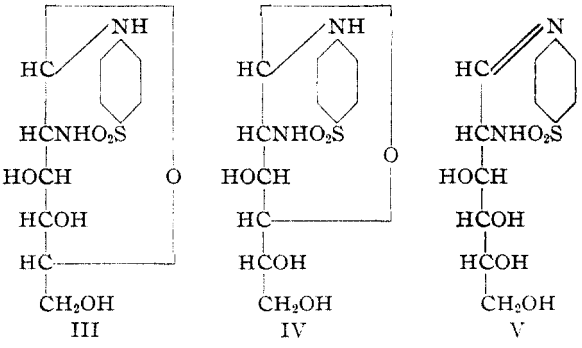
SPECIFIC ROTATION AND MELTING POINT OF SULFANILYL-2-AMINO-α-D-GLUCOSE AND DERIVATIVES

Substance	Yield, %	M. p. (uncor.), °C.	$[\alpha]^{20}D$ in water Initial	Constant
Sulfanilyl-2-amino-α-D-glucose	60	202[a]	+ 24.5	+14.4
N-Acetylsulfanilyl-2-amino-α-D-glucose	85	192–193[b]	+ 21.2	+10.1
Sulfanilyl-2-amino-N-D-glucoside dihydrate	55	...	+107.2[c]	...
Sulfanilyl-2-amino-N-D-glucoside, anhydrous	..	...	+119.7[c]	...

[a] Decomposition. [b] Anhydrous crystals. Air-dried crystals containing 3.8% moisture melt at 180–182°. [c] Shows no mutarotation.

Primary aromatic amines are well-known to react with reducing sugars to yield N-glycosides,[1,2,3] the production of which is accelerated by acids. Since the molecule of sulfanilyl-2-amino-α-D-glucose possesses both a free primary aromatic amino group and a reducing group at carbon atom 1 of the glucose component, the formation of a N-glycoside by intramolecular reaction would be expected under appropriate conditions. This reaction has indeed been found to occur in 50% aqueous acetic acid solution at room temperature. The product, prepared either from pure crystalline II or more conveniently from the crude sirup resulting from the deacetylation of N-acetylsulfanilyl-2-amino-α-D-glucose, has a composition and properties corresponding to sulfanilyl-2-amino-N-D-glucoside. The compound shows no mutarotation in aqueous solution at 20°, and is not diazotized by nitrous acid. After being heated in 0.1 *N* hydrochloric acid solution diazotization occurs; the hydrolysis of the N-glucoside, presumably to sulfanilyl-2-amino-D-glucose, is substantially complete after one hour at 100°.

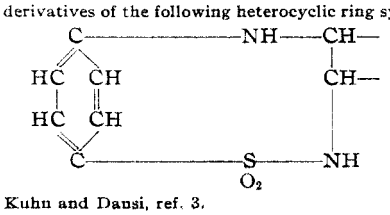
The data available at the present time do not show the ring structure of the N-glucoside. Because the pyranoside and furanoside structures occur most commonly among the glycosides, the N-glucoside is suggested to be either sulfanilyl-2-amino-N-D-glucopyranoside (III) or sulfanilyl-2-amino-N-D-glucofuranoside (IV).[4] The high dextrorotation of the N-glucoside, recorded in Table I, suggests the alpha configuration for carbon atom 1 of the glucose component. Although the anil,[1] or Schiff base, structure is sometimes ascribed to the products of the condensation of primary aromatic amines with reducing sugars, satisfactory evidence for this type of structure is lacking.[5]



III IV V

(3) Schiff, *Ann.*, **154**, 30 (1870); Sorokin, *Ber.*, **19**, 513 (1886); *J. prakt. Chem.*, **37**, 291 (1888); Marchlewski, *ibid.*, **50**, 95 (1894); Irvine and Gilmour, *J. Chem. Soc.*, **93**, 1429 (1908); **95**, 1545 (1909); Irvine and McNicoll, *ibid.*, **97**, 1449 (1910); Irvine and Hynd, *ibid.*, **99**, 161 (1911); Amadori, *Atti accad. Lincei*, [6] **2**, 337 (1925); **9**, 68, 226 (1929); **13**, 72, 195 (1931); Cameron, THIS JOURNAL, **48**, 2233, 2737 (1926); Cameron and Guest, *Can. J. Research*, **7**, 237 (1932); Kuhn and Dansi, *Ber.*, **69**, 1745 (1936); Kuhn and Weygand, *ibid.*, **70**, 769 (1937); Kuhn and Ströbele, *ibid.*, **70**, 773 (1937); Frèrejacque, *Compt. rend.*, **207**, 638 (1938); Weygand, *Ber.*, **72**, 1663 (1939).

(4) It should be noted that compounds III and IV may be considered as derivatives of the following heterocyclic ring system:



(5) *Cf.* Kuhn and Dansi, ref. 3.

The anil structure (V) for the product from sulfanilyl-2-amino-α-D-glucose is, therefore, improbable.

The pharmacologic properties of sulfanilyl-2-amino-α-D-glucose were examined by Doctor M. I. Smith and associates. Given orally in rabbits in 0.5 g. per kilogram it failed to show appreciable absorption. Only about 15% of the dose administered was recovered from the urine in forty-eight hours. Given subcutaneously 0.3 g. per kilogram the blood level reached a concentration of 33 mg. % within an hour; at six hours it dropped to 10 mg. %; and at twenty-four hours the drug could not be demonstrated in the blood stream. Ninety-five per cent. of the dose administered was recovered from the urine in twenty-four hours, practically none of it having been acetylated. Similar results were obtained on intravenous injection, except that the initial level was higher and the rate of disappearance of the drug from the blood stream was more rapid. In mice 3.0 g. per kilogram on subcutaneous injection were tolerated. The bacteriostatic action of the drug was low. It failed to inhibit the growth of tubercle bacilli (human strain A 27) on a glycerol broth medium in concentrations up to 100 mg. %. Sulfanilamide under similar conditions inhibits at a level of 50 mg. %. In concentrations of 100 mg. % it had a slight bacteriostatic action on a strain of hemolytic streptococcus and none on a strain of type I pneumococcus. In mice 1.0 g. per kilogram given subcutaneously had no effect on experimental streptococcus or pneumococcus infection.

Experimental

N-Acetylsulfanilyl-2-amino-α-D-glucose.—To a solution of 33 g. of pure D-glucosamine hydrochloride in 200 cc. of cold water were added 200 cc. of acetone and 35.8 g. of N-acetylsulfanilyl chloride, which had been purified by recrystallization from a mixture of acetone and water and dried at 25° over calcium chloride. After the substance had dissolved, 26 g. of sodium bicarbonate was added, the mixture shaken for forty-five minutes, and then kept overnight at room temperature. The light yellow solution, after filtration, was concentrated *in vacuo* with the bath temperature at 40–50° until a cake of colorless needles had separated. The crystals were filtered and washed with cold water; additional crops were isolated by concentrating the filtrate *in vacuo*. The yield of crystals, dried in the air at room temperature, was 52 g., or 86%. Recrystallized twice as colorless needles from seven parts of water, the pure air-dried crystals showed the specific rotation[6] in water (*c*, 0.81): +20.4° (11 min.); +20.4° (18 min.); +19.3° (28 min.); +15.2° (77 min.); +9.7°, constant (24 hours). These crystals lost 3.8% in weight at 60° *in vacuo*. The rotation of the anhydrous compound, calculated from the data on the air-dried crystals, is thus +21.2° (11 min.) and +10.1°, constant. The air-dried substance melted at 180–182° (uncor.), the value being somewhat variable with the rate of heating; the anhydrous compound melted at 192–193° (uncor.). The solubility of the compound in water was not determined accurately, although a 1.6% solution was prepared readily at room temperature. It is soluble in methanol, difficultly soluble in acetone and cold ethanol, and virtually insoluble in benzene.

Anal. Calcd. for $C_{14}H_{20}O_8N_2S$: C, 44.67; H, 5.36; N, 7.44; S, 8.52. Found (dried at 60° *in vacuo*): C, 44.49, 44.45; H, 5.34, 5.26; N, 7.12, 7.12; S, 8.58, 8.65.

Sulfanilyl-2-amino-α-D-glucose.—A suspension of 29 g. of pure N-acetylsulfanilyl-2-amino-α-D-glucose in 290 cc. of 0.5 *N* sulfuric acid solution was heated at 99–100° under a reflux condenser. After a few minutes the crystals had dissolved and at the end of one hour the dark red solution, cooled to room temperature, was freed from sulfate ions by the addition of the exact amount of barium hydroxide solution. Some activated carbon was added, the mixture was heated on the steam-bath for a few minutes, and the solids removed by filtration. The red filtrate was concentrated *in vacuo* (bath, 40–50°) virtually to dryness. The dark red, thick sirup was dissolved in 25 cc. of 38% hydrochloric acid at room temperature. Crystals frequently separate at this stage. After the addition of 50 cc. of absolute ethanol with thorough stirring at 0°, the mixture was left overnight in the refrigerator. The crystals were then filtered and washed with 25 cc. of cold absolute ethanol. The first crop of light brown, air-dried crystals usually weighed about 19 g. The substance reduced Fehling solution readily and was diazotized by nitrous acid. A second crop (3 g.) crystallized at 5° after concentration of the combined mother liquor and washings *in vacuo* (bath, 35°) to a volume of 15 cc. and addition of 5 cc. of absolute ethanol. The hydrochloride is soluble in water and absolute methanol; it is only slightly soluble in absolute ethanol. The compound could be recrystallized as small, compact clusters of short needles by dissolving it in about eight parts of 28% hydrochloric acid at 35°, filtering, and adding sufficient ethanol, usually an equal volume, to produce crystallization at 5°. Recrystallization in this way, however, was not advantageous, since the crystals were always colored and impure, and especially since pure sulfanilyl-2-amino-α-D-glucose could be prepared readily from the crude hydrochloride.

A mixture of 19.4 g. of the crude hydrochloride and 950 cc. of absolute methanol was shaken at room temperature for a short time; all but 0.4 g. of the substance dissolved. Most of the color was removed from the red solution by shaking it awhile at room temperature with activated carbon followed by filtration. The solution was then shaken with sufficient dry silver carbonate, about 17 g., to remove the chlorine completely. Some activated carbon was added, the mixture shaken awhile, and the solids filtered off. The colorless, neutral filtrate was concentrated *in vacuo* with the bath at 35–40° to a volume of about 150 cc., colorless needles of sulfanilyl-2-amino-α-D-glucose having crystallized during the distillation. After being kept at 5°

(6) All rotations in this article are specific rotations at 20° for sodium light; *c* = g. per 100 cc. of solution.

for several hours, the crystals were filtered and washed with cold absolute methanol. The first crop, dried in the air at room temperature, weighed 12 g. The crystals, which melted at 201° (uncor.) with decomposition and showed an initial specific rotation of +19.4° in water and equilibrium rotation of +14.9°, were suitable for chemotherapeutic tests. Calcd. for $C_{12}H_{18}O_7N_2S$: S, 9.59. Found: S, 9.86. The yield was increased to 13.8 g. by concentrating *in vacuo* the combined mother liquor and washings from the first crop. The over-all yield was thus about 60% on the N-acetylsulfanilyl-2-amino-α-D-glucose. To obtain the pure α-form, the compound was recrystallized from water as colorless needles which, after being dried in the air at room temperature, melted at 202° (uncor., dec.). The specific rotation of these crystals in water (*c*, 0.89) was +24.3° (8 min.); +24.3° (12 min.); +23.3° (25 min.); +22.4° (36 min.); +21.1° (76 min.); +20.4° (88 min.); +19.0° (133 min.); +18.7° (158 min.); +14.4°, constant (24 hrs.). The air-dried crystals lost 1.0% in weight at 60° *in vacuo* and then rotated +24.5° (10 min.) in water (*c*, 0.50).

Anal. Calcd. for $C_{12}H_{18}O_7N_2S$: C, 43.11; H, 5.43; N, 8.38; S, 9.59. Found (dried at 60° *in vacuo*): C, 43.34, 42.99; H, 5.73, 5.47; N, 8.10, 8.10; S, 9.85, 9.95.

Sulfanilyl-2-amino-α-D-glucose is considerably more soluble in water than sulfanilamide. It is somewhat soluble in methanol, slightly soluble in ethanol, and virtually insoluble in benzene. Its aqueous solution is neutral to litmus, and reduces Fehling solution readily. The compound is diazotized by nitrous acid.

Sulfanilyl-2-amino-N-D-glucoside.—Thirty-five grams of pure N-acetylsulfanilyl-2-amino-α-D-glucose was deacetylated in 350 cc. of 0.5 *N* sulfuric acid solution at 99–100° and the solution freed from sulfate ions, all as described for the preparation of sulfanilyl-2-amino-α-D-glucose. After the solution had been concentrated *in vacuo* with the bath at 50° to a volume of 65 cc., an equal volume of glacial acetic acid was added, and the solution left at room temperature for twenty-four hours. The crystals, clusters of fine needles, were filtered, washed first with cold 50% acetic acid, and finally with a little absolute ethanol. The yield of air-dried N-glucoside was 18.5 g., or 56%. Concentration of the filtrate *in vacuo* to dryness and crystallization of the residual red sirup from a mixture of 8 cc. of 38% hydrochloric acid and 12 cc. of absolute ethanol gave 6 g. of sulfanilyl-2-amino-α-D-glucose hydrochloride. Sulfanilyl-2-amino-N-D-glucoside crystallized readily from thirty parts of water as colorless plates of the dihydrate rotating, when pure, +107.2° in water (*c*, 0.40); the rotation at the end of twenty-four hours at 20° was unchanged. The anhydrous crystals, dried at 60° *in vacuo*, rotated +119.7° in water (*c*, 0.40). This value is in agreement with the rotation of +119.4° calculated from the figure for the dihydrate. Crystals of the dihydrate show no definite melting point; they begin to darken at 235–240° and thereafter gradually become black without melting, when the temperature is raised to 275°. The compound is not diazotized by nitrous acid. It does not reduce Fehling solution immediately, but shows some reduction if the solution is kept at 100° for a short time. It is difficultly soluble in water and slightly soluble in the usual organic solvents.

Anal. Calcd. for $C_{12}H_{16}O_6N_2S \cdot 2H_2O$: H_2O, 10.23. Found (dried at 75° *in vacuo*): H_2O, 10.31, 10.37. Calcd. for $C_{12}H_{16}O_6N_2S$: C, 45.56; H, 5.10; N, 8.86; S, 10.13. Found: C, 45.31, 45.30; H, 4.99, 5.16; N, 8.59, 8.59; S, 10.46, 10.40.

The N-glucoside was prepared also from pure, crystalline sulfanilyl-2-amino-α-D-glucose. A solution of 2.7 g. of the latter compound in 40 cc. of hot water was cooled to room temperature and filtered. After the addition of 40 cc. of glacial acetic acid, the solution was kept at room temperature for eleven days. During the first two days crystallization of the N-glucoside was negligible, but thereafter the rate of crystallization increased markedly. The colorless, fine needles were filtered, washed first with 50% acetic acid, and then with a little absolute ethanol. The yield of air-dried crystals of the dihydrate rotating +102.8° in water was 2 g., or 71%.

Summary

D-Glucosamine through reaction with N-acetylsulfanilyl chloride has yielded crystalline N-acetylsulfanilyl-2-amino-α-D-glucose from which was prepared crystalline sulfanilyl-2-amino-α-D-glucose. The two glucose derivatives are designated alpha forms on account of their downward mutarotation in aqueous solution, the specific rotation of sulfanilyl-2-amino-α-D-glucose decreasing at 20° from +24.5° to +14.4° and that of the N-acetyl derivative from +21.2° to +10.1°. Sulfanilyl-2-amino-α-D-glucose, having its sulfanilamide component linked through the amido nitrogen atom (N^1) to carbon atom 2 of its glucose component, is a new type of sulfanilamide derivative of glucose.

Sulfanilyl-2-amino-α-D-glucose in 50% aqueous acetic acid solution at room temperature yields through intramolecular reaction a crystalline N-glucoside, which is probably either sulfanilyl-2-amino-N-D-glucopyranoside or sulfanilyl-2-amino-N-D-glucofuranoside.

BETHESDA, MD. RECEIVED MARCH 2, 1942