nitroisoquinoline, 1-chloro-5-aminoisoquinoline, 1-chloro-4-bromoisoquinoline and 1-hydroxy-5-nitroisoquinoline were synthesized for the first time.

2. A number of isoquinoline derivatives bearing an active chlorine atom in the 1-position were condensed with several different aminobenzenearsonic acids.

3. The chlorine in 1-chloro-5-nitroisoquinoline was found to be non-reactive in acid solution but somewhat reactive in alkaline solution.

4. Several isoquinoline amines were coupled with various diazotized aminobenzenearsonic acids.

LINCOLN, NEBRASKA RECEIVED APRIL 8, 1946

[CONTRIBUTION FROM THE DIVISION OF PHYSIOLOGY, NATIONAL INSTITUTE OF HEALTH, U. S. PUBLIC HEALTH SERVICE]

4-Amino-4′-hydroxylaminodiphenyl Sulfone, its Acetyl and D-Glucosyl Derivatives

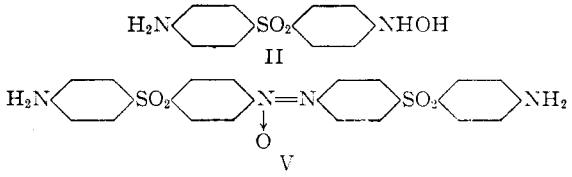
BY ERNEST L. JACKSON

The pronounced antibacterial activity[1] of 4,4′-diaminodiphenyl sulfone (I), especially its inhibitive action in experimental tuberculosis,[2] has stimulated the synthesis and biological study of a variety of derivatives[3] in an effort to reduce its toxicity and provide a drug suitable for clinical application. Certain N-glycosyl derivatives[4] have been tried and the therapeutic efficacy of sodium 4,4′-diaminodiphenylsulfone-N,N′-didextrosesulfonate (promin) in experimental tuberculosis and in leprosy[5] has been demonstrated. This investigation concerns the synthesis, constitution and chemical properties of 4-amino-4′-hydroxylaminidophenyl sulfone (II), two acetyl derivatives and a di-N-glucoside.

4-Amino-4′-hydroxylaminodiphenyl sulfone, m. p. 191–192°, is produced in high yield through reduction of 4-amino-4′-nitrodiphenyl sulfone in aqueous ethanol solution of ammonium chloride by zinc[6] at 48–50°. The reduction of 4-acetylamino-4′-nitrodiphenyl sulfone in a similar way yields 4-acetylamino-4′-hydroxylaminodiphenyl sulfone (III), m. p. 194–195°. Both of these compounds, in dry crystalline condition, apparently are stable at room temperature. Acetylation[7] of II under suitable conditions yields crystalline 4-acetylamino-4′-(N-acetyl-O-acetylhydroxylamino)-diphenyl sulfone (IV), m. p. 171–172°.

By virtue of the reducing action of the hydroxylamino group, compound II in aqueous dioxane solution consumes 0.9 molecular equivalent of sodium periodate. This reaction, it will be noted, differs in type from the characteristic periodate cleavage of α-glycols.[8] The hydroxylamine also is oxidized readily in aqueous organic solvents by atmospheric oxygen to yield 4,4′-bis-(*p*-aminobenzenesulfonyl)-azoxybenzene (V). The conversion to the azoxy derivative occurs in high yield in aqueous pyridine solution or in 95% methanol containing a trace of sodium bicarbonate. Similarly, 4,4′-bis-(*p*-acetylaminobenzenesulfonyl)-azoxybenzene (VI), identical with the product of acetylation of V, crystallizes from aqueous methanol solution of III. Heymann and Fieser[3b] have noted polymorphism among certain derivatives of I; also the dimorphism of 4,4′-bis-(dipiperidylphosphorosoamino)-diphenyl sulfone[9] has been reported. Two crystalline forms were observed in the case of V and its diacetyl derivative (VI); the melting points of the forms of V are 298–299° (dec.) and 306–307° (dec.), of its acetate 274–275° and 310–311° (dec.). The oxidation of 4-acetylamino-4′-aminodiphenyl sulfone by hydrogen peroxide[10] in acetic acid solution produced VI with a melting point of 274–275°.

Another crystalline form of 4,4′-bis-(*p*-aminobenzenesulfonyl)-azoxybenzene was isolated[9] previously from the products of the reaction of aqueous sodium bicarbonate solution with 4,4′-bis-(dichlorophosphorosoamino)-diphenyl sulfone; it melts at 245–246° and is almost colorless in contrast to the yellow color of V. The crystals melting at 245–246° upon acetylation yielded a



II

V

(1) (a) Buttle, Stephenson, Smith, Dewing and Foster, *Lancet*, **232**, 1331 (1937); *Biochem. J.*, **32**, 1101 (1938); (b) Fourneau, Tréfouël, Nitti, Bovet and Tréfouël, *Compt. rend.*, **204**, 1763 (1937); **205**, 299 (1937).

(2) Rist, Bloch and Hamon, *Ann. inst. Pasteur*, **64**, 203 (1940); Smith, Emmart and Westfall, *J. Pharmacol.*, **74**, 163 (1942); Smith, *N. Y. State J. Med.*, **45**, 1665 (1945); Feldman, Hinshaw and Moses, *Am. Rev. Tuberc.*, **45**, 303 (1942); *Am. J. Med. Sci.*, **207**, 290 (1944).

(3) See, for example: (a) Roblin; Williams and Anderson, THIS JOURNAL, **63**, 1930 (1941); (b) Heymann and Fieser, *ibid.*, **67**, 1979 (1945); Heymann and Heidelberger, *ibid.*, **67**, 1986 (1945); (c) patent literature; *cf.* Bambas, THIS JOURNAL, **67**, 668, 671 (1945).

(4) Cavallini and Saccarello, *Chimica e industria (Italy)*, **24**, 425 (1942); *C. A.*, **38**, 4257 (1944); Burnet, Cuénod and Natef, *Bull. acad. med.*, **121**, 317 (1939); Tschesche and Bohle, German Patent 735,560 (1943); *C. A.*, **38**, 2668 (1944); Domagk, *Med. u. Chem.*, **4**, 82 (1942); *C. A.*, **38**, 6377 (1944).

(5) Faget and Pogge, *Pub. Health Repts.*, **60**, 1165 (1945).

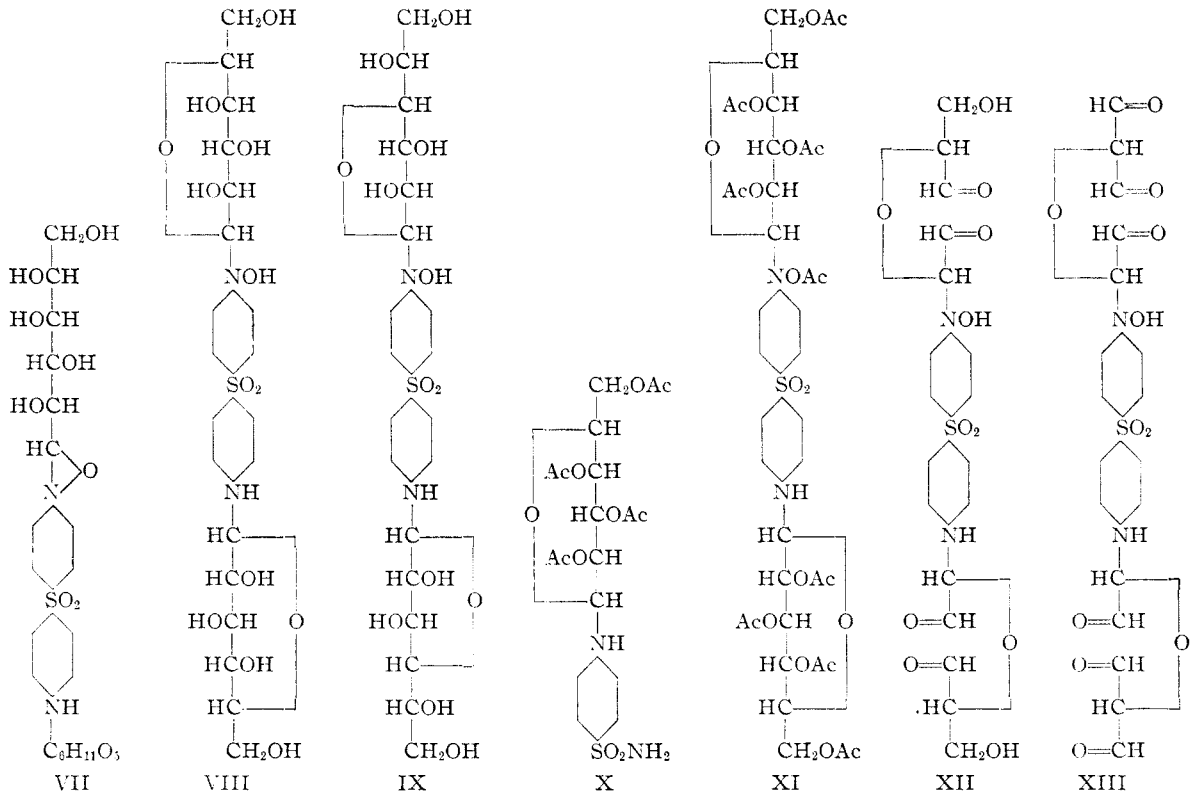
(6) Bamberger, *Ber.*, **27**, 1548 (1894).

(7) *Cf.* Bamberger, *ibid.*, **51**, 636 (1918).

(8) (a) Malaprade, *Bull. soc. chim.*, (4) **43**, 683 (1928); (b) Jackson in R. Adams, "Organic Reactions," Vol. II, John Wiley & Sons, Inc., New York, N. Y., 1944, p. 341.

(9) Jackson, *J. Org. Chem.*, **9**, 457 (1944).

(10) *Cf.* Carrara and Monzini, *Chimica e industria (Italy)*, **23**, 391 (1941); *C. A.*, **36**, 6510 (1942); Seikel, THIS JOURNAL, **62**, 1214 (1940).



VII VIII IX X XI XII XIII

virtually colorless acetate as compared with the yellow acetyl derivative of V. This lower-melting azoxy derivative thus appears to be a stereoisomer[11] of V.

The reaction of D-glucose with II in hot ethanol solution of ammonium chloride yielded a glucosyl derivative of the hydroxylamine, which was isolated as an amorphous levorotatory solid. The compound was characterized as a diglucosyl derivative of II by its elementary composition, the results of periodate oxidation, and acetylation to yield the crystalline nonaacetate, which melts at 206–207° and shows $(\alpha)^{20}D$ — 6.5° in chloroform. The primary amino group of the hydroxylamine is substituted by a glucosyl radical, as demonstrated by the failure of the glucoside to show diazotization and coupling by the Bratton and Marshall[12] technique. The second glucosyl residue could be combined either with the nitrogen atom or the oxygen atom of the hydroxylamino group. The assignment of the N-glucosyl in preference to the O-glucosyl structure is based on two considerations: (a) the method of preparation[13] customarily yields an N-glucoside; (b) the glucoside in aqueous solution is characterized by the formation of a red color with aqueous ferric chloride solution. This color reaction has been observed[7,14] in the case of a number of N-disubstituted aromatic hydroxylamines and apparently is typical of the free hydroxyl group in these compounds. The cyclic oxide[14a] (VII), which is a possible product of the reaction of the *aldehydo*-form of glucose with the hydroxylamine, is an improbable structure since it possesses no N-hydroxyl group and accordingly should not show the color test. The results show the compound to be 4-D-glucosylamino-4′N-D-glucosylhydroxylaminodiphenyl sulfone (VIII) or (IX). Acetylation of the glucoside of sulfanilamide by acetic anhydride in pyridine solution was shown by Kuhn and Birkofer[13b] to yield the tetraacetyl derivative (X), the structure of which has been confirmed by Braun, Towle and Nichols[15] through synthesis from acetobromoglucose and sulfanilamide. Inasmuch as the secondary amino group in this N-glucoside is not attacked by the acetylating agent and since aryl hydroxylamines readily yield O-acetyl derivatives,[7,14c] the acetylation of the N-glucoside (VIII) or (IX) would be expected to yield 4-tetraacetyl-D-glucosylamino-4′-(O-acetyl-N-tetraacetyl-D-glucosylhydroxylamino)-diphenyl sulfone (XI or the corresponding acetyl derivative of IX).

Since the glucoside is a di-N-glucoside the pos-

(11) Müller, *Ann.*, **495**, 132 (1932).

(12) Bratton and Marshall, *J. Biol. Chem.*, **128**, 537 (1939); *cf.* Roblin and Winnek, THIS JOURNAL, **62**, 1999 (1940).

(13) (a) Kuhn and Ströbele, *Ber.*, **70**, 773 (1937); (b) Kuhn and Birkofer, *ibid.*, **71**, 621 (1938).

(14) (a) Bamberger, *ibid.*, **35**, 732 (1902); **39**, 4252 (1906); **51**, 613 (1918); Bamberger and Elger, *ibid.*, **36**, 3645 (1903); (b) Bratton, White and Marshall, *Proc. Soc. Exptl. Biol. Med.*, **42**, 847 (1939); (c) Bauer and Rosenthal, THIS JOURNAL, **66**, 611 (1944).

(15) Braun, Towle and Nichols, *J. Org. Chem.*, **7**, 19 (1942).

sibility of the existence of an alpha and a beta form for each of the glucose components is evident, and if more than one ring type should occur the number of possible isomers would be increased. The beta configuration for carbon atom 1 of one or both of the glucosyl radicals is suggested by the levorotation of the glucoside and of its nonaacetate. Because of the instability of the glucosyl–carbon to nitrogen linkage, periodate oxidation is not applicable to the determination of the ring structure, although the results corroborate the assigned composition as a diglucosyl derivative. Should this linkage be stable in the oxidation process, both the pyranoside (VIII) and the furanoside (IX) would be expected to consume four moles of periodate and yield respectively the aldehydes (XII) and (XIII); the furanoside should yield also two moles of formaldehyde. The consumption of the oxidant by the two glucose components was actually near ten moles and indicated the complete degradation of these groups; 1.5 moles of formaldehyde was isolated as its crystalline dimethone derivative in comparison with 2.0 moles expected from the oxidation of the equivalent amount of glucose.

It is unlikely that hydrolysis of the N-glucoside, in the course of the oxidation process, is responsible for this extensive breakdown of the molecule which occurred even in aqueous solution of sodium periodate buffered by sodium bicarbonate. The N-glucoside showed no hydrolysis[16] in aqueous solution at room temperature during at least twenty-four hours, although it is unstable in the presence of acids. A probable explanation is the presence of the secondary amino group and the N-substituted hydroxylamino group in the molecule. This provides in VIII or IX the 1,2-amino-alcohol[17] structure and in XII or XIII the 1,2-amino-aldehyde structure, either of which should react with periodate. The present case apparently is the first application of this oxidation reaction to the N-disubstituted 1,2-hydroxylamino-alcohol structure. Lythgoe and Todd[18] observed a similar breakdown of 4-glycosylaminopyrimidine and 6-glycosylaminopurine derivatives, although the oxidation reaction was applied successfully to the determination of the ring structure of several purine glycosides having the sugar residue attached to one of the imidazole nitrogen atoms. If the N-glucoside has the furanoside ring structure (IX), the oxidation product (XIII) would provide an additional point for attack by periodate, at the active hydrogen atom attached to the carbon atom situated between the two aldehyde groups.[19]

(16) *Cf.* Hanaoka, *J. Biochem. (Japan)*, **31**, 95 (1940); Mitts and Hixon, THIS JOURNAL, **66**, 483 (1944).

(17) Nicolet and Shinn, *ibid.*, **61**, 1615 (1939); see also ref. 8b.

(18) Lythgoe and Todd, *J. Chem. Soc.*, 592 (1944); see also Howard, Lythgoe and Todd, *ibid.*, 556 (1945); Berger and Lee, *J. Org. Chem.*, **11**, 75 (1946).

(19) Huebner, Lohmar, Dimler, Moore and Link, *J. Biol. Chem.*, **159**, 503 (1945); Niemann and Hays, THIS JOURNAL, **67**, 1302 (1945); Hockett, Nickerson and Reeder, *ibid.*, **66**, 472 (1944).

Experimental[20]

4-Amino-4′-hydroxylaminodiphenyl Sulfone (II).—A solution of 60 g. of ammonium chloride in 540 cc. of water at 48–50° was added, with stirring, to a solution of 30 g. of 4-amino-4′-nitrodiphenyl sulfone[1a] in 1270 cc. of 95% ethanol at the same temperature. After the addition of 42 g. of zinc dust in the course of three minutes, the stirring was continued at 48–50° for fifteen minutes. The mixture then was kept in ice water for thirty minutes, the solids filtered off and washed with cold 70% ethanol. The filtrate was concentrated immediately *in vacuo*, with the bath at 40–45°, to a volume of 375 cc. After the suspension had been cooled in ice water for thirty minutes, the crude crystals were collected, washed with cold water, and dried in an evacuated desiccator over calcium chloride; yield, 28 g.; m. p. 189–190°. To a filtered solution of the crystals in 250 cc. of cold acetone was added 475 cc. of water. After thirty minutes 1.7 g. of impure crystals of V melting near 300° was removed by suction filtration. Pure, pale-yellow crystals of II separated upon prompt dilution of the solution with 3000 cc. of water. After one hour the crystals were filtered, washed with cold water and dried in an evacuated desiccator over calcium chloride; weight, 23 g.; m. p. 191–192°. The crystals showed no loss in weight during one hour at 100° *in vacuo*.

Anal. Calcd. for $C_{12}H_{12}N_2O_3S$: C, 54.53; H, 4.58; N, 10.60; S, 12.13; diazotization, 46.9. Found: C, 54.59; H, 4.49; N, 10.76; S, 12.48; diazotization[12] as compared with I in aqueous acetone solution (3:2), 45%.

The hydroxylamine is readily soluble in acetone and pyridine; soluble in dioxane, ethanol and methanol; and slightly soluble in water. The crystalline compound apparently is stable at room temperature; it was kept without apparent change in a closed brown bottle for three months. It reduces ammoniacal silver nitrate solution. The addition of 3 cc. of 10% aqueous ferric chloride solution to a solution of 50 mg. of II in 2 cc. of dioxane produced a deep-green solution and a green precipitate of the oxidation product. An intense green color is formed with diphenylamine in concentrated sulfuric acid solution.

4-Acetylamino-4′-hydroxylaminodiphenyl Sulfone (III).—To a solution of 15 g. of 4-acetylamino-4′-nitrodiphenyl sulfone[21] in 2250 cc. of absolute ethanol at 50° was added a solution of 33.5 g. of ammonium chloride in 375 cc. of water. The solution was stirred at 48–50° during the addition of 23 g. of zinc dust in the course of three minutes. After the stirring had been continued for fifteen minutes, the product was isolated by a procedure similar to that described for II. The concentration of the solution *in vacuo* was interrupted, when the volume reached 1000 cc., to remove a little VI melting near 300°. The solution, concentrated to 75 cc. and kept at 0° for thirty minutes, deposited 13.5 g. of crystalline product melting at 192–193°. The hydroxylamine was purified by dissolving the crystals in five parts of hot absolute methanol, filtering and adding benzene to produce turbidity; at room temperature it crystallized as pale-yellow, short prisms which, after being dried for twenty-four hours in an evacuated desiccator over calcium chloride, lost 9.1% in weight at 100° *in vacuo* and then melted at 194–195° (dec.). It showed only a small diazotization,[12] less than 5% compared with I.

Anal. Calcd. for $C_{14}H_{14}N_2O_4S$: C, 54.89; H, 4.61; N, 9.15; S, 10.47. Found (dried at 100° *in vacuo*): C, 54.46; H, 4.43; N, 9.36; S, 10.62.

The compound is soluble in acetone, dioxane, ethanol and methanol; only slightly soluble in benzene, diethyl ether, petroleum ether and water. It reduces ammoniacal silver nitrate solution. Crystals of III, kept in a closed brown bottle at room temperature, showed no change in melting point and reducing action during one month.

4-Acetylamino-4′-(N-acetyl-O-acetylhydroxylamino)-diphenyl Sulfone (IV).—Fifteen grams of II was dissolved

(20) All melting points are uncorrected.

(21) Raiziss, Clemence, Severac and Moetsch, THIS JOURNAL, **61**, 2763 (1939).

in 150 cc. of acetic anhydride at room temperature. The solution was kept at 25° for seventeen hours and then decanted from 0.8 g. of crystals which had separated. These crystals were washed with cold benzene and recrystallized from a mixture of 2-ethoxyethanol and absolute ethanol, yielding yellow prismatic needles which, after being dried at 100° *in vacuo*, melted at 310–311° (dec.). The melting point, appearance and solubility of the crystals correspond to VI. The reaction solution, upon being mixed with 1125 cc. of benzene and kept at room temperature for three hours, deposited crystals of IV, which were filtered, washed with benzene and dried in the air at room temperature; yield, 23 g. melting at 118–120°. The compound was purified by recrystallization from absolute ethanol as well-formed, slightly orange colored prisms which, after being dried to constant weight at 100° *in vacuo*, melted at 171–172°. The crystals in the air-dried condition usually contained combined solvent and melted at 130–131°, but the compound occasionally was observed to crystallize solvent-free with a melting point of 171–172°. It is soluble in acetone, difficultly soluble in chloroform, ethanol and methanol, and slightly soluble in benzene.

Anal. Calcd. for $C_{18}H_{18}N_2O_6S$: C, 55.38; H, 4.65; N, 7.18; S, 8.21. Found (dried at 100° *in vacuo*): C, 54.90; H, 5.01; N, 7.06; S, 8.27.

4,4'-Bis-(*p*-aminobenzenesulfonyl)-azoxybenzene (V).—Due to the ready oxidation of II in mixtures of water and organic solvents, the azoxy derivative crystallizes from an aqueous pyridine solution of the hydroxylamine; also from a 0.3% solution of the hydroxylamine in methanol containing about 5% of water and 0.3% of sodium bicarbonate; and from the aqueous acetone mother liquor of recrystallization of II. The crystals which separated from a solution of the hydroxylamine in aqueous pyridine, after further recrystallization as yellow plates from a mixture of pyridine and water, melted at 298–299° (dec.). The yellow crystals from methanol usually melted at 306–307° (dec.), which was unchanged by recrystallization from aqueous pyridine; in one experiment, however, the crystals melted at 298–299° (dec.).

Anal. Calcd. for $C_{24}H_{20}N_4O_5S_2$: C, 56.68; H, 3.96; N, 11.02; S, 12.61. Found: (m. p. 298–299°) C, 57.13; H, 3.97; N, 11.08; S, 12.31; (m. p. 306–307°) S, 12.38.

The compound is soluble in pyridine, somewhat soluble in acetone and 2-ethoxyethanol, slightly soluble in dioxane and virtually insoluble in water.

4,4'-Bis-(*p*-acetylaminobenzenesulfonyl)-azoxybenzene (VI).—A filtered solution of 1.5 g. of III in 350 cc. of absolute methanol at room temperature, after the addition of a solution of 0.1 g. of sodium bicarbonate in 25 cc. of water, deposited overnight 1.4 g. of the azoxy derivative melting at 270–275°. Following purification from a mixture of dioxane and absolute ethanol (2:3) the pale-yellow prismatic needles, dried at 100° *in vacuo*, melted at 310–311° (dec.); the air-dried solvated crystal sometimes melted at 274–275°. The compound was prepared also by acetylation of V. A solution of 0.2 g. of V (melting either at 298–299° or 306–307°) in 12 cc. of anhydrous pyridine and 10 cc. of acetic anhydride, after twenty-four hours at 25°, was poured into ice water, the mixture neutralized substantially by the addition of solid sodium bicarbonate, the acetate collected, purified from dioxane–ethanol mixture and dried at 100° *in vacuo;* m. p. 310–311° (dec.). The acetate is soluble in pyridine and hot phenol, difficultly soluble in the majority of organic solvents and virtually insoluble in water.

Anal. Calcd. for $C_{28}H_{24}N_4O_7S_2$: C, 56.74; H, 4.08; S, 10.82. Found (dried at 100° *in vacuo*): C, 56.28; H, 4.05; S, 11.01.

Oxidation of 4-acetylamino-4'-aminodiphenyl sulfone[3b,21,22] by hydrogen peroxide yielded crystals of the azoxy compound melting at 274–275°. A mixture of 1 g. of the amine, 9 cc. of glacial acetic acid and 1.9 cc. of 30% hydrogen peroxide was kept at 63–65° for one and one-half hours. After about twenty minutes the brown solution began to deposit crystals; at the end of the reaction the mixture was cooled in ice water, the crystals collected, washed first with glacial acetic acid and finally with water. A second crop increased the yield to 0.7 g. Purified by recrystallization from dioxane–ethanol mixture and dried at 100° *in vacuo*, the yellow prismatic needles melted at 274–275°. Found (dried at 100° *in vacuo*): C, 56.59; H, 4.41; S, 10.94.

4-D-Glucosylamino-4'-N-D-glucosylhydroxylaminodiphenyl Sulfone (VIII or IX).—A mixture of 5.0 g. of II (1.0 molecular equivalent), 10.2 g. of anhydrous D-glucose (3.0 molecular equivalents), 1.0 g. of ammonium chloride and 450 cc. of absolute ethanol was refluxed for two and one-half hours, a homogeneous solution resulting after about one and one-half hours. After the solvent had been removed by distillation *in vacuo* with the bath at 50°, the residual sirup was extracted with 150 cc. of cold water to separate a small amount of water-insoluble solid. The filtered aqueous solution was concentrated immediately *in vacuo* (bath, 50°) to a thick sirup, which was taken up in 50 cc. of cold water, some Norit carbon added and filtered off. After the solution had been concentrated *in vacuo* to a thick sirup, 25 cc. of absolute ethanol was added and evaporated *in vacuo*. The sirup then was soluble in methanol, difficultly soluble in absolute ethanol, and slightly soluble in acetone. The glucoside was precipitated twice from its concentrated solution in absolute methanol by the addition of a relatively large volume of acetone and then extracted twice with 5-cc. portions of cold absolute ethanol. It was taken up in 20 cc. of cold pyridine, the solution filtered to remove some insoluble solid and the glucoside precipitated by the addition of 400 cc. of acetone. After a final precipitation from its concentrated aqueous solution by acetone, the glucoside was obtained in solid condition by stirring it thoroughly with acetone, then filtered, washed with acetone and dried in an evacuated desiccator over calcium chloride. The slightly yellow, hygroscopic powder weighed 6.5 g. It lost 10.7% in weight at 100° *in vacuo* and then showed a specific rotation[23] in water (*c*, 0.54) of −29.1° (3.5 min.); −33.2° (20 min.); −45.2° (17 hr.); −45.2° (42 hr.). The analytical sample was obtained by additional precipitations of the material just described. After being dried at 100° *in vacuo*, its specific rotation in water (*c*, 0.45) was −35.4° (4 min.); −40.6° (6 hr.); −44.9° (24 hr.); −42.5° (72 hr.). The decrease in levorotation to −42.5°, observed at the end of seventy-two hours, apparently is due to some hydrolysis of the glucoside which is indicated by the separation from the solution of a small amount of solid toward the end of the period. Since the analytical data indicate that the amorphous substance is substantially free of D-glucose, the change in rotation from −35.4 to −44.9° is attributed to mutarotation[24] of the N-glucoside

Anal. Calcd. for $C_{24}H_{32}N_2O_{13}S$: C, 48.97; H, 5.48; N, 4.76; S, 5.45. Found (dried at 100° *in vacuo*): C, 49.29; H, 5.76; N, 4.81; S, 4.86.

The glucoside is readily soluble in water, soluble in methanol and in pyridine, somewhat soluble in ethanol, and only slightly soluble in acetone; a concentration of 20% in water at room temperature is attained readily. The addition of dilute aqueous ferric chloride solution to a 1.3% solution of the glucoside in water produced a deep-red color; the color test was demonstrated in a concentration of 129 micrograms of glucoside per cc. The compound showed no diazotization.[12] The stability of the glucoside in aqueous solution at room temperature during at least twenty-four hours is indicated by the negative diazotization test; after several days, however, the solution begins to deposit solid material and then shows diazotization. The glucoside is decomposed by dilute hydrochloric acid at room temperature. After a solution in *N* hydrochloric

(22) Shonle and VanArendonk, THIS JOURNAL, **65**, 2375 (1943); Pöhls and Behnisch, U. S. Patent 2,291,285 (1942).

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

(24) *Cf.* Irvine and Gilmour, *J. Chem. Soc.*, **93**, 1429 (1908); Wolfrom and Thompson, THIS JOURNAL, **53**, 622 (1931).

acid (97 micrograms per cc.) had been kept at 28° for one hour, the diazotization value was 20% as compared with I; a similar solution after one hour at 100° showed 15%; calculated for complete hydrolysis to II, 21%. The lower value obtained after hydrolysis at 100° probably is due to secondary reactions of the hydrolysis product.[9]

Oxidation of the glucoside by sodium metaperiodate in aqueous solution was shown to yield formaldehyde and a water-insoluble solid. A solution of 0.0431 g., dried at 100° *in vacuo*, in 25 cc. of 0.0473 *M* aqueous sodium periodate solution at about 30° began to deposit the solid within a few minutes. The results of analyses of 5-cc. samples of the filtered solution, after intervals of two hours and twenty-one hours, were in substantial agreement and showed the consumption of 10.2 molecular equivalents of periodate. The crude solid product, isolated after twenty-four hours, evidently was mixture; it melted at 240–250° with previous coloration at about 215°. For the identification of formaldehyde, a solution of 0.0254 g. of the dried glucoside in 1 cc. of water was treated with 1.5 cc. of *N* aqueous sodium bicarbonate solution and 1.5 cc. of 0.4733 *M* aqueous sodium periodate solution. After being kept at room temperature for two and one-half hours, the solid was removed by filtration and washed with 1 cc. of water. The formaldehyde was isolated from the filtrate as its crystalline dimethone derivative by a procedure similar to that described by Reeves[25]; yield 0.0189 g. or 75% of the amount calculated for two molecular equivalents of formaldehyde; m. p. 189–190°, not depressed by crystals of the authentic compound.

On account of the probable occurrence of II among the products of the periodate oxidation of the glucoside, the estimation of the consumption of the oxidant by the two glucose components requires the consideration of the possible reduction of some of the reagent by the hydroxylamine. To test the reaction a solution of 0.0500 g. of II in 15 cc. of dioxane was mixed with 5 cc. of 0.0473 *M* aqueous sodium periodate solution and kept at 28–30° for twenty hours; analysis of 10 cc. of the solution, after filtration to remove some inorganic crystals, showed the consumption of 0.9 molecular equivalent of sodium periodate. In obtaining this figure a correction was applied for the result of a control experiment, which was carried out under identical conditions with a solution of 15 cc. of dioxane and 5 cc. of 0.0473 *M* aqueous sodium periodate solution. An application of the procedure to 0.0506 g. of I showed no consumption of periodate. Since the oxidation of the glucoside was carried out in aqueous solution any liberated II, due to its slight solubility in water, might not reduce an amount of periodate corresponding exactly to the figure found in aqueous dioxane solution. The data, therefore, demonstrate the consumption by the two glucose components of a minimum of 9.3 molecular equivalents of periodate. Although the oxidation results do not disclose the ring structure of the glucose components, they confirm the composition of the compound as a diglucosyl derivative of II.

4-Tetraacetyl-D-glucosylamino-4′-(O-acetyl-N-tetraacetyl-D-glucosylhydroxylamino)-diphenyl Sulfone (XI).—To a solution of 1 g. of the N-glucoside (VIII) or (IX) in 10 cc. of anhydrous pyridine was added 10 cc. of acetic anhydride, some cooling being necessary to keep the solution at room temperature. After being kept at 25° for eighteen hours, the solution was poured into 250 cc. of ice water. The mixture was neutralized substantially by the addition of solid sodium bicarbonate, the solid acetylation product filtered off, washed with cold water and dried in the air at room temperature; yield, 1.2 g. A filtered solution of the substance in 20 cc. of hot absolute ethanol, upon being cooled to room temperature, deposited some sirup, which was dissolved by the addition of a little acetone. The acetate then crystallized slowly as fine, closely packed, colorless needles. Purified by recrystalization from acetone–ethanol mixture and dried at 100° *in vacuo*, it melted at 206–207° and showed a specific rotation in chloroform (*c*, 0.36; *l*, 4) of −6.5°. The crystals are readily soluble in acetone and in chloroform, difficultly soluble in ethanol, and virtually insoluble in water.

Anal.[26] Calcd. for $C_{42}H_{50}N_2O_{22}S$: C, 52.17; H, 5.21; N, 2.90; S, 3.32; CH_3CO, 40.1. Found (dried at 100° *in vacuo*): C, 51.85; H, 5.44; N, 2.55; S, 3.38; CH_3CO, 40.4.

Summary

4-Amino-4′-hydroxylaminodiphenyl sulfone, 4-acetylamino-4′-hydroxylaminodiphenyl sulfone and 4-acetylamino-4′-(N-acetyl-O-acetylhydroxylamino)-diphenyl sulfone have been prepared.

Two crystalline forms of 4,4′-bis-(*p*-aminobenzenesulfonyl)-azoxybenzene melting at 298–299° (dec.) and 306–307° (dec.) and two forms of 4,4′-bis-(*p*-acetylaminobenzenesulfonyl)-azoxybenzene melting at 274–275° and 310–311° (dec.) have been isolated.

D-Glucose and 4-amino-4′-hydroxylaminodiphenyl sulfone yield the amorphous di-N-glucoside, 4-D-glucosylamino-4′-N-D-glucosylhydroxylaminodiphenyl sulfone, which was characterized conclusively by the preparation of its crystalline nonaacetate. Periodate oxidation effects complete degradation of the glucose components of the N-glucoside molecule. A probable explanation of this result on structural grounds is suggested.

BETHESDA, MARYLAND RECEIVED MARCH 23, 1946

(25) Reeves, THIS JOURNAL, **63**, 1476 (1941).

(26) For the acetyl determination a solution of 10 mg. of the compound in 15 cc. of pure acetone at 0–5° was treated with 2.5 cc. of 0.1 *N* aqueous sodium hydroxide solution and kept at 0–5° for three hours. After the acetone had been removed by evaporation *in vacuo* at room temperature, the steam distillation and titration was carried out as described by E. P. Clark, "Semimicro Quantitative Organic Analysis," Academic Press, Inc., New York, N. Y., 1943, p. 73. In obtaining the correction for the blank 3.8 mg. of glucose was added to the reagents.