352. N-*Substituted Glycosylamines derived from Sulphanilamide and* p-*Aminosalicylic Acid.*

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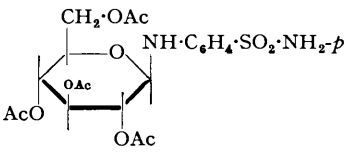
A number of *N*-arylglycosylamines derived from sulphanilamide and *p*-aminosalicylic acid, together with the methyl, ethyl, and *n*-propyl esters of the latter, have been synthesised and examined. Both the anomeric forms (I, II) of *N*-*p*-sulphamylphenyl-D-glucosylamine 2 : 3 : 4 : 6-tetra-acetate have been prepared, and it has been shown that on deacetylation they give *N*-*p*-sulphamylphenyl-D-glucosylamine (III). Acetylation of (I), (II), or (III) gives the *NN'* : 2 : 3 : 4 : 6-hexa-acetate (IV). The preparation of *N*-(4-carboxy-3-hydroxyphenyl)-D-glucosylamine 2 : 3 : 4 : 6-tetra-acetate is described, a new method is given for the synthesis of 2 : 3 : 4 : 6-tetra-acetyl 1-(4-amino-2-hydroxybenzoyl) D-glucose, and its conversion into the hexa-acetate is reported. By interaction of 2 : 3 : 4 : 6-tetra-acetyl D-glucosylamine with *N*-acetylsulphanilyl chloride, *N*-*p*-acetamidobenzenesulphonyl-D-glucosylamine 2 : 3 : 4 : 6-tetra-acetate (V) has been prepared. Ultraviolet absorption data for several *p*-aminosalicylic acid derivatives are included.

In 1938, because of the therapeutic effect of sulphanilamide, Kuhn and Birkofer (*Ber.*, 1938, **71**, 621) described *N*-*p*-sulphamylphenyl-D-glucosylamine, and later workers have prepared many analogous compounds (see E. H. Northey, " Sulfonamides and Allied Compounds," Reinhold Publ. Corp., New York, 1948). Although these glycosylated sulphonamides are not distinctly superior to the free sulphonamides in their effect (Lehr, Bloch, and Erlenmeyer, *Helv. Chim. Acta*, 1945, **28**, 1415) their greater solubility in water is of interest (*Chem. Abs.*, 1941, **35**, 6978). Despite their higher concentration in the blood certain *N*-*p*-sulphamylphenylglycosylamines are less toxic and better tolerated than the corresponding sulphanilamides (*Chem. Abs.*, 1940, **34**, 5857). Chemically, the chief interest lies in the possibilities of isomerism : in addition to displaying αβ-anomerism, which is theoretically possible in every glycosylamine, the sugar moiety may exist in the pyranose or furanose form ; further there are two nitrogen atoms in sulphanilamide at which glycosylation may take place, leading to, *e.g.*, (III) and (V). In *p*-aminosalicylic acid glycosylation is possible at the amino-, carboxyl, or hydroxyl group, giving respectively (VI), (VII), or (VIII).

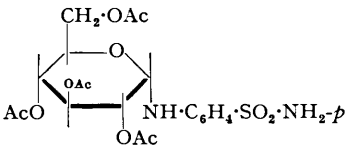
N-Arylglycosylamines were first prepared by Sorokin (*J. pr. Chem.*, 1888, **37**, 291) and since then many similar substances have been isolated. Initially it was doubtful whether these compounds were true glycosylamines or derivatives of the Schiff-base type, but later work favours the glycosylamine structure (concerning *N*-*p*-sulphamylphenylglycosylamine see Northey, *op. cit.*). Kuhn and Birkofer (*loc. cit.*) prepared the glucosylamine by direct condensation of glucose with sulphanilamide in 95% ethanol, using ammonium chloride as a catalyst. If the sugar is only slightly soluble in ethanol, as in our experiments with lactose and cellobiose, it was necessary to use Weygand's method (*Ber.*, 1940, **73**, 1259), which consists in fusing the reactants in the presence of a small quantity of dilute hydrochloric acid for a few minutes. *N*-Arylglycosylamines acetylated in the sugar residue have been prepared by Fischer and Helferich (*Ber.*, 1914, **47**, 2107), Sabalitschka (*Ber. deutsch. physikal. Ges.*, 1921, **31**, 439), J. W. Baker (*J.*, 1924, **125**, 268), and Butler, Smith, and Stacey (*J.*, 1949, 3371 and other papers) from acetobromo-sugars, by Frèrejacque (*Compt. rend.*, 1936, **202**, 1190; 1938, **207**, 638) from fully acetylated sugars, and by Weisz (Diss., Budapest, 1940), by Bognár (*Proc. Chem. Acad. Hungary*, 1951, I, **2**, 28), and by Butler *et al.* (*loc. cit.*) from partly acetylated sugars containing free glycosidic hydroxyl groups. All these syntheses involved condensation of the arylamino-nitrogen atom with the sugar residue but, while the present work was in progress, Helferich and Mitrowsky (*Ber.*, 1952, **85**, 1) reported the isolation of products formed by condensation of tetra-acetyl D-glycosylamine with arylsulphonyl chlorides, in which the sugar-nitrogen atom and

the sulphonyl group are linked together. A similar compound (V) is described in this paper and glycosylamino-acids are in course of preparation in this laboratory.

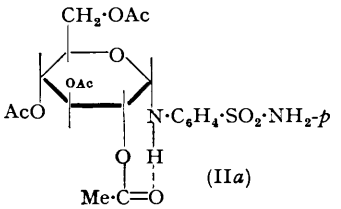
In the present researches, by means of Kuhn and Birkofer's technique crystalline *N*-*p*-sulphamylphenyl derivatives of L-arabinose, D-xylose, D-galactose, D-mannose, and maltose have been obtained. Similar crystalline derivatives of lactose and cellobiose have been isolated in good yield by the alternative method of Weygand (*loc. cit.*). *N*-*p*-Sulphamylphenyl-lactosylamine was found to be very soluble in water, and is being investigated pharmacologically.



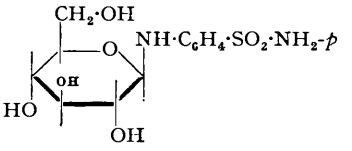
(I)



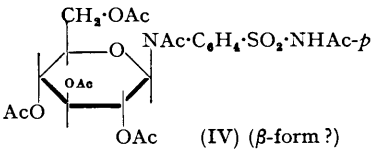
(II)



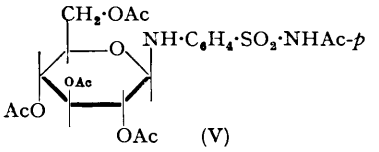
(II*a*)



(III)



(IV) (β-form ?)

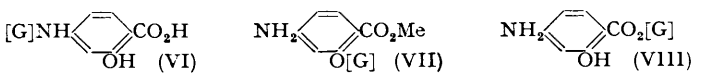


(V)

In addition to the unsubstituted *N*-*p*-sulphamylphenylglycosylamines, acetylated derivatives have been isolated by condensation of either acetobromoglucose (Braun *et al.*, *loc. cit.*) or 2 : 3 : 4 : 6-tetra-acetyl glucose with sulphanilamide. The latter method proved very suitable with hepta-acetyl cellobiose for the preparation of crystalline *N*-*p*-sulphamylphenylcellobiosylamine hepta-acetate. With acetobromoglucose a mixture of α- and β-anomers of *N*-*p*-sulphamylphenyl-D-glucosylamine 2 : 3 : 4 : 6-tetra-acetate was obtained from which was isolated a pure crystalline β-form (I), m. p. 204°, $[\alpha]_D$ −81° in pyridine, identical with the compound synthesised by Braun *et al.* and by Kuhn and Birkofer (*locc. cit.*). Addition of water to the mother-liquors gave a substance rich in the α-form (II); this material, after repeated recrystallisation from ethanol, had m. p. 204—205°, $[\alpha]_D$ +203° in pyridine, +197° in $CHCl_3$. A similar mixture, containing, however, a higher proportion of the β-isomer, was obtained from tetra-acetyl glucose. It is considered that (I) and (II) are anomers, and not structural isomers arising from substitution of the sulphamido-nitrogen atom, since they contain no primary arylamine-nitrogen and since condensation between benzenesulphamide and acetobromoglucose cannot be effected. The Schiff-base structure is unlikely because of the mode of the formation of the acetylated substances and because *N*-*p*-sulphamylphenylglucosylamine is not reduced even at 50 atm. Deacetylation of mixtures containing different proportions of α- and β-anomers always gave rise to the known *N*-*p*-sulphamylphenyl-D-glucosylamine (III), m. p. 204°, $[\alpha]_D$ −117° in pyridine, presumed to be the β-form. With acetic anhydride and zinc chloride, the α- and β-tetra-acetyl compounds (I) and (II), and the unacetylated compound (III), gave the same hexa-acetyl *N*-*p*-sulphamylphenyl-D-glucosylamine (IV), m. p. 115°, $[\alpha]_D$ +77° in pyridine. Similar properties have been reported for the α- and β-isomers of *N*-phenyl-D-glucosylamine 2 : 3 : 4 : 6-tetra-acetate (Honeyman and Tatchell, *J.*, 1950, 967) and of *N*-phenyl-D-galactosylamine 2 : 3 : 4 : 6-tetra-acetate (Butler *et al.*, *loc. cit.*), which are

moderately stable and on deacetylation give single glycosylamines. Furthermore, a single penta-acetyl derivative was obtained by acetylation of either *N*-phenyl-α- or -β-D-glucosylamine tetra-acetate (Bognár, *loc. cit.*). It appears that in the unacetylated compound (III) and in the hexa-acetate (IV) only one isomer is stable whereas in the case of the tetra-acetate both anomers can be isolated and we consider it possible that the stabilisation of the α-form (II) is due to a type of hydrogen bonding (II*a*) similar to that tentatively suggested by Todd *et al.* (*J.*, 1946, 853) for acetylated *N*-glycosylamines. A comparable example of intramolecular hydrogen bonding in a seven-membered ring has been deduced from infra-red absorption measurements on acetylglycine *N*-methylamide by Mizushima *et al.* (*J. Amer. Chem. Soc.*, 1952, **74**, 270).

When this work began, no sugar derivatives of *p*-aminosalicylic acid had been reported, but since then Sannié and Lapin (*Bull. Soc. chim.*, 1950, 1234) have reported the isolation of compounds analogous to (VI), (VII), and (VIII). They prepared *N*-(4-carboxy-3-



[G] = D-Glucopyranosyl.

hydroxyphenyl)-D-glucosylamine (VI) by a variation of Sorokin's method (*loc. cit.*) and assigned its structure by analogy with the *N*-*p*-carboxyphenylglycosylamines (Sannié *et al.*, *Compt. rend.*, 1948, **226**, 182; *Bull. Soc. chim.*, 1948, 892). Reduction and deacetylation of the product obtained by interaction of acetobromoglucose with sodium *p*-nitrosalicylate gave amorphous 1-(4-amino-2-hydroxybenzoyl)-D-glucose (VIII); and 5′-amino-2′-carbomethoxyphenyl-D-glucoside (VII) was obtained in a similar way from the sodium salt of methyl *p*-nitrosalicylate. In the present work a modification of Kuhn and Birkofer's method (see p. 1707) has been used for the preparation of *N*-(4-carboxy-3-hydroxyphenyl)-D-glucosylamine (VI), and of its methyl, ethyl, and propyl esters, and for the preparation of *N*-(4-carboxy-3-hydroxyphenyl)-D-galactosylamine. Weygand's method (*loc. cit.*) was unsuitable because, under the conditions used, some decarboxylation of *p*-aminosalicylic acid occurred. Acetylated derivatives were prepared by a modification of Frèrejacque's method (Bognár, *loc. cit.*). *p*-Aminosalicylic acid and 2 : 3 : 4 : 6-tetra-acetyl D-glucose gave *N*-(4-carboxy-3-hydroxyphenyl)-D-glucosylamine 2 : 3 : 4 : 6-tetra-acetate. All these *N*-arylglycosylamines gave typical reactions for a carboxyphenol and negative tests for a primary arylamine group. Although Sannié and Lapin (*loc. cit.*) were unable to condense acetobromoglucose directly with *p*-aminosalicylic acid, yet with these reagents in the presence of acetone and sodium hydroxide we obtained 2 : 3 : 4 : 6-tetra-acetyl 1-(4-amino-2-hydroxybenzoyl) D-glucose, which gave positive tests for the phenolic and primary arylamine groups and negative tests for the carboxyl residue. Acetylation of this compound gave 1-(4-acetamido-2-acetoxybenzoyl) 2 : 3 : 4 : 6-tetra-acetyl D-glucose, the ultra-violet absorption spectrum of which closely resembled that of 4-acetamido-2-acetoxybenzoic acid. Hydrolysis with sodium methoxide gave crystalline methyl *p*-aminosalicylate.

The ultra-violet absorption spectra of a number of these substances were examined. In the case of sulphanilamide, *N*-glycosylation of either nitrogen atom does not alter significantly the positions of the maxima. With *p*-aminosalicylic acid, however, appreciable differences are observed, although *N*-glycosylation has a less marked effect than *N*-acetylation.

Experimental

N-p-*Sulphamylphenylglycosylamines*.—Several of these glycosylamines were prepared by direct combination of sulphanilamide with the free sugar (Kuhn and Birkofer, *loc. cit.*). The sugar (1 mol.) was refluxed in 96% ethanol (10 vol.) with sulphanilamide (1 mol.) for 2—3 hr. The crude glycosylamines from D-glucose and D-mannose crystallised from the boiling solution; those from L-arabinose, D-xylose, and D-galactose crystallised on cooling. Removal of some of the ethanol was necessary to induce crystallisation of the maltose derivative. The glycosylamines from D-galactose, lactose, and cellobiose were synthesised by Weygand's method (*loc. cit.*) : The finely powdered sugar (1 mol.), and sulphanilamide (1 mol.) were fused with a small quantity of 0·25N-hydrochloric acid on the steam-bath for a few min. The crude product was

recrystallised from aqueous ethanol. The properties of these compounds are summarised in Table 1.

N-p-*Sulphamylphenyl*-D-*glucosylamine* 2 : 3 : 4 : 6-*Tetra-acetate*.—(*a*) Sulphanilamide (6·8 g., 1 mol.) and acetobromoglucose (16·3 g., 1·2 mol.) were dissoved in acetone (46 ml.), and 10% aqueous sodium hydroxide (16·3 ml.) was added with continuous shaking during 30—60 min. Acetone (4 ml.) was added, and the mixture shaken for 1—2 days and then set aside overnight. After evaporation to small volume the pale yellow lower phase was separated, washed with water, and crystallised from 50% aqueous ethanol (yield, 9 g.). The two anomeric forms were separated

TABLE 1. N-p-*Sulphamylphenylglycosylamines*.

Glycosylamine component	Recryst. from	M. p. (decomp.): present work	M. p. (decomp.): lit.	Rotation: present work *	Rotation: lit.	Found: N (%)	Calc.: N (%)
L-Arabinosylamine	H_2O	191°	194° [a] 195 [b]	+42·7° (0·9, 50% aq. C_5H_5N)	—	9·1	9·2
D-Xylosylamine	50% Aq. EtOH	168—169	150 [b]	−62·3° (0·5)	—	8·9	8·7
D-Galactosylamine (monohydrate)	H_2O–MeOH–EtOH (1 : 20 : 10)	174—175	—	−97° (1·9); −90° (1·8, H_2O)	—	7·8	8·0
D-Galactosylamine	75—80% Aq. EtOH	171—174	142—144 [b]	−110° (1·0)	—	8·3	8·4
D-Mannosylamine (monohydrate)	70% Aq. EtOH	194	202 [a] 196 [b]	−186° (1·0)	−163° (in EtOH); [a] −180° [b]	8·1	8·0
Maltosylamine	80% Aq. EtOH	212—214	236 [b]	−59° (0·9)	+80°, −14° [c]	6·0	5·7
Lactosylamine (trihydrate)	83% Aq. EtOH	210—212	190 [b, d]	−69° (1·7); −76° (1·8, H_2O)	—	5·1	5·1
Cellobiosylamine (tetrahydrate)	83% Aq. EtOH	215—216	—	−81° (0·9); −88° (0·9, H_2O)	—	5·0	4·9 †

[a] Kuhn and Birkofer, *loc. cit.* [b] Schering, Fr.P. 842,726/1939; *Chem. Abs.*, 1940, **34**, 5857. [c] Winthrop Chem. Co. (Klingel and MacLennan), U.S.P. 2,167,719/1939; B.P. 526,747/1940; *Chem. Abs.*, 1941, **35**, 6978. [d] Cavallini and Saccarello, *Chim. et Ind.*, 1942, **24**, 425; *Chem. Abs.*, 1944, **38**, 4257.

* *c* is given in parentheses. The solvent is pyridine unless otherwise stated.

† Formula: $C_{18}H_{28}O_{12}N_2S,4H_2O$.

by repeated fractional crystallisation from 96% ethanol. The crystals first separating were richer in the β-isomer; material richer in the α-isomer was obtained by addition of water to the mother-liquor. Finally, two pure substances were obtained by recrystallisation from ethanol: (i) *N-p*-sulphamylphenyl-β-D-glucosylamine 2 : 3 : 4 : 6-tetra-acetate, m. p. 204° (not depressed on admixture with the product of acetylation of *N-p*-sulphamylphenyl-D-glucosylamine), $[\alpha]_D^{22}$ −81° (*c*, 1·0 in C_5H_5N), $[\alpha]_D^{22}$ −56·5° (*c*, 1·7 in $CHCl_3$) (Found: N, 5·5. Calc. for $C_{20}H_{26}O_{13}N_2S$: N, 5·6%); (ii) N-p-*sulphamylphenyl*-α-D-*glucosylamine* 2 : 3 : 4 : 6-*tetra-acetate*, m. p. 204—205° (decomp.), $[\alpha]_D^{22}$ +203° (*c*, 1·2 in C_5H_5N), $[\alpha]_D^{22}$ +197° (*c*, 0·5 in $CHCl_3$) (Found: C, 48·1; H, 5·2; N, 5·6. $C_{20}H_{26}O_{13}N_2S$ requires C, 47·8; H, 5·2; N, 5·6%). A mixture of the two forms melted at 190—192°.

(*b*) Although varying conditions were employed, condensation of sulphanilamide with D-glucose penta-acetate (Frèrejacque, *loc. cit.*) was unsuccessful.

(*c*) A solution of sulphanilamide (6 g., 3·5 mol.) and D-glucose 2 : 3 : 4 : 6-tetra-acetate (3·4 g., 1 mol.) in 96% ethanol (100 ml.) containing acetic acid (3·4 ml.) was allowed to react at 30° for 1 day. The product was a mixture.

(*d*) A solution of sulphanilamide (1·0 g., 1·2 mol.) and D-glucose 2 : 3 : 4 : 6-tetra-acetate (1·7 g., 1 mol.) in 99% ethanol (50 ml.) containing acetic acid (3·4 ml.) and concentrated hydrochloric acid (3 drops) was refluxed for 1 hour and then kept at room temperature for 3 days. The product (0·5 g.), after recrystallisation from ethanol, had m. p. 204° (decomp.) [not depressed on admixture with the lævorotatory product from (*a*) above], $[\alpha]_D^{21}$ −74° (*c*, 0·9 in C_5H_5N). Later crops resembled the product from (*c*).

N-p-*Sulphamylphenyl*-D-*glucosylamine*.—(*a*) The above product ($[\alpha]_D$ +39·5° in C_5H_5N) (1·5 g.) was suspended in absolute methanol (7 ml.), and 1·0N-sodium methoxide in methanol (0·45 ml.) added. The solution was kept at 30° for 1 hr. and at 0° for 2 days. The product (0·7 g.) was filtered off, and recrystallised from 90% aqueous ethanol as fine needles, m. p. 204°

(decomp.), $[\alpha]_D^{22}$ −117° (*c*, 0·9 in C_5H_5N), $[\alpha]_D^{22}$ −128° (*c*, 0·9 in H_2O). From the rotation it would appear to be the β-form, and no mutarotation was observed.

(*b*) An identical product was obtained in 63% yield by similar treatment of a sample having $[\alpha]_D$ +91° in pyridine. Mixed m. p.s showed the identity of these two products with each other and with the product obtained directly from D-glucose and sulphanilamide.

N-p-*Sulphamylphenyl*-D-*glucosylamine* N : N′ : 2 : 3 : 4 : 6-*Hexa-acetate*.—Acetylation, on the steam-bath with acetic anhydride and anhydrous zinc chloride for 15 min., of *N*-*p*-sulphamylphenyl-D-glucosylamine tetra-acetate (dextro- or lævo-rotatory), or of the unacetylated compound, gave, by addition to water, an identical crystalline solid, N-p-*sulphamylphenyl*-D-*glucosylamine* N : N′ : 2 : 3 : 4 : 6-*hexa-acetate*. Recrystallisation from 25% aqueous ethanol gave needles, m. p. 115°, $[\alpha]_D^{25}$ +77° (*c*, 0·9 in C_5H_5N) (Found : N, 4·85; Ac, 44·2. $C_{24}H_{30}O_{13}N_2S$ requires N, 4·8; Ac, 44·0%).

N-p-*Acetamidobenzenesulphonyl*-D-*glucosylamine* 2 : 3 : 4 : 6-*Tetra-acetate*.—A solution of D-glucosylamine 2 : 3 : 4 : 6-tetra-acetate (0·70 g.) and *N*-acetylsulphanilyl chloride (0·41 g.) in pyridine (5 ml.) was set aside at room temperature for 3 days. After addition of water (60 ml.) the solution was kept for a further 2 days; a crystalline solid was then filtered off (0·8 g.). After recrystallisation from ethanol, N-p-*acetamidobenzenesulphonyl*-D-*glucosylamine* 2 : 3 : 4 : 6-*tetra-acetate* had m. p. 197—198° (decomp.), $[\alpha]_D^{22}$ +12·8° (*c*, 1·0 in C_5H_5N) (Found : C, 48·5; H, 5·0; N, 5·23; Ac, 39·9. $C_{22}H_{28}O_{12}N_2S$ requires C, 48·6; H, 5·2; N, 5·2; Ac, 39·6%).

N-p-*Sulphamylphenylcellobiosylamine Hepta-acetate*.—A modification of the Frèrejacque synthesis (Bognár, *loc. cit.*) was employed. A solution of cellobiose hepta-acetate (1·85 g., 1 mol.) and sulphanilamide (0·6 g., 1·2 mol.) in 99% ethanol (30 ml.) containing glacial acetic acid (1 ml.) and concentrated hydrochloric acid (1 drop) was refluxed for 1 hr. The crude product obtained on cooling (1·1 g., 42%) was recrystallised from 90% ethanol, giving N-p-*sulphamylphenylcellobiosylamine hepta-acetate*, m. p. 274—275° (decomp.), $[\alpha]_D^{23}$ −31·4° (*c*, 1·8 in C_5H_5N) (Found : C, 48·6; H, 5·5; N, 3·5. $C_{32}H_{42}O_{19}N_2S$ requires C, 48·6; H, 5·4; N, 3·5%).

N-(4-*Carboxy*-3-*hydroxyphenyl*)-D-*galactosylamine*.—A solution of *p*-aminosalicylic acid (3·1 g., 1 mol.), D-galactose (3·7 g., 1 mol.), and ammonium chloride (0·2 g.) in ethanol (80 ml.) was boiled for 45 min. After recrystallisation from ethanol or methanol the *product* (2·6 g., 38%) decomposed at 180° after darkening at 170°, and had $[\alpha]_D$ +134° (*c*, 0·6 in C_5H_5N) (Found : N, 4·2; H_2O, 4·1. $C_{13}H_{17}O_8N,H_2O$ requires N, 4·2; H_2O, 5·4%).

N-(4-*Carboxy*-3-*hydroxyphenyl*)-D-*glucosylamine*.—(*a*) Preparation by the Weygand method, as described for sulphanilamide derivatives, gave a crystalline product which, after recrystallisation from aqueous ethanol (18% yield), had m. p. 142° (decomp.), $[\alpha]_D^{22}$ −124° (*c*, 1·0 in C_5H_5N).

(*b*) Under the conditions used for the galactosylamine gave an impure product in 40% yield when boiling was for 30 min. On boiling for 15 min. a relatively pure product was isolated in 71% yield. Recrystallisation from aqueous methanol gave crystals, m. p. 142° (decomp.), $[\alpha]_D^{22}$ −132° (*c*, 0·9 in C_5H_5N) (Found : C, 47·2; H, 5·7; N, 4·2. Calc. for $C_{13}H_{17}O_8N,H_2O$: C, 46·8; H, 5·75; N, 4·2%).

(*c*) Best results were obtained by dissolution of D-glucose (2·0 g., 1·0 mol.) and ammonium chloride (0·1 g.) in warm water (4 ml.), followed by addition of methanol (20 ml.) and *p*-aminosalicylic acid (1·7 g., 1·0 mol.) and shaking at room temperature until all the solid had dissolved. After 24 hours at room temperature crystallisation was induced by scratching. The product (3·15 g., 85%) had m. p. 142° (decomp.), $[\alpha]_D^{22}$ −133° (*c*, 0·8 in C_5H_5N). The rotation of ethanolic or pyridine solutions did not change on storage. An aqueous solution (*c*, 0·9) showed $[\alpha]_D$ −80·5° (5 min.), −72° (20 min.), +5·4° (16 hr.), +23·5° (40 hr., const.). Calculated on the theoretical amount of D-glucose in the solution the $[\alpha]_D$ after 40 hr. is +44°, which is approximately the equilibrium rotation of D-glucose. The yield is double that obtained by Kuhn and Birkofer's original method.

N-(4-*Carbomethoxy*-3-*hydroxyphenyl*)-D-*glucosylamine*.—(*a*) The above product (1·0 g.), dissolved in methanol (25 ml.), was treated at 0° with excess of ethereal diazomethane. Evaporation to dryness gave a solid which was recrystallised from ethanol (yield, 0·51 g., 50%). After a further recrystallisation from ethanol the *product* had m. p. 187—188° (decomp.), $[\alpha]_D^{22}$ −144° (*c*, 0·5 in C_5H_5N) (Found : N, 4·3. $C_{14}H_{19}O_8N$ requires N, 4·25%).

(*b*) Methyl *p*-aminosalicylate (1·4 g.), D-glucose (1·5 g.), and ammonium chloride (0·15 g.) were treated according to Kuhn's method for 1 hr. The product (1·45 g., 53%), after repeated recrystallisation from ethanol, had m. p. 187—189° (decomp.) [unchanged on admixture with the product from (*a*)], $[\alpha]_D^{22}$ −145° (*c*, 1·0 in C_5H_5N) (Found : N, 4·2; OMe, 8·7. $C_{14}H_{19}O_8N$ requires N, 4·25; OMe, 9·4%).

N-(4-*Carbethoxy*-3-*hydroxyphenyl*)-D-*glucosylamine*.—Ethyl *p*-aminosalicylate (1·3 g.), D-

glucose (1·3 g.), and ammonium chloride (0·1 g.) were refluxed in 99% ethanol for 2·5 hr. After recrystallisation from 75% aqueous ethanol the *product* (0·7 g.) had m. p. 187° (decomp.), $[\alpha]_D^{22}$ −136° (*c*, 1·0 in C_5H_5N) (Found : N, 4·1; OEt, 12·9. $C_{15}H_{21}O_8N$ requires N, 4·1; OEt, 13·2%).

N-(4-*Carbopropoxy*-3-*hydroxyphenyl*)-D-*glucosylamine*.—Propyl *p*-aminosalicylate (4·0 g.; m. p. 105°), D-glucose (3·6 g.), and ammonium chlroide (0·3 g.) were refluxed in 99% ethanol for 3 hr. The crude crystalline solid (2·5 g.) was repeatedly recrystallised from aqueous ethanol, giving a *product*, m. p. 135—137° (decomp.), $[\alpha]_D^{22}$ −126° (*c*, 0·9 in C_5H_5N) (Found : N, 4·2. $C_{16}H_{23}O_8N$ requires N, 3·9%).

N-(4-*Carboxy*-3-*hydroxyphenyl*)-D-*glucosylamine* 2 : 3 : 4 : 6-*Tetra-acetate*.—(*a*) Penta-acetyl glucose was treated with *p*-aminosalicylic acid according to Frèrejacque's method (*loc. cit.*). After 2 weeks at room temperature a solid (20% yield) was obtained. After repeated recrystallisation from ethanol the product had m. p. 183—184° (decomp.), $[\alpha]_D^{22}$ −96° (*c*, 0·5 in C_5H_5N), $[\alpha]_D^{22}$ −69° (*c*, 0·5 in $CHCl_3$) (Found : N, 2·9. $C_{21}H_{25}O_{12}N$ requires N, 2·9%).

(*b*) A solution of D-glucose 2 : 3 : 4 : 6-tetra-acetate (1·7 g., 1 mol.) and *p*-aminosalicylic acid (2·7 g., 3·5 mol.) in 99% ethanol (50 ml.) containing glacial acetic acid (1·7 ml.) was refluxed for 30 min. and set aside for 2 days. The solution was evaporated to one-third volume and a solid (1·2 g.) obtained by addition of water. Further material (1·2 g.) was obtained by concentration of the mother-liquor. After recrystallisation from 50% aqueous ethanol, N-(4-*carboxy*-3-*hydroxyphenyl*)-D-*glucosylamine* 2 : 3 : 4 : 6-*tetra-acetate* had m. p. 185—186° (decomp.) [unchanged on admixture with the product from (*a*)], $[\alpha]_D^{22}$ −99° (*c*, 1·0 in C_5H_5N), $[\alpha]_D^{22}$ −70° (*c*, 1·0 in $CHCl_3$) (Found : C, 52·4; H, 5·2; N, 2·9. $C_{21}H_{25}O_{12}N$ requires C, 52·2; H, 5·2; N, 2·9%).

2 : 3 : 4 : 6-*Tetra-acetyl* 1-(4-*Amino*-2-*hydroxybenzoyl*) D-*Glucose*.—*p*-Aminosalicylic acid (6·0 g., 1 mol.) and acetobromoglucose (20·0 g., 1 mol.) were dissolved in acetone (52 ml.) and treated with 10% sodium hydroxide (20 ml.) as described in the preparation of *N*-*p*-sulphamylphenyl-D-glucosylamine tetra-acetate. The yield was 5·7 g. (30%). After two recrystallisations from ethanol the product was obtained as colourless needles (4·8 g.), m. p. 202° (decomp.), $[\alpha]_D^{21}$ −56° (*c*, 1·7 in $CHCl_3$), $[\alpha]_D^{22}$ −28·5° (*c*, 1·0 in C_5H_5N) [cf. Sannié and Lapin (*loc. cit.*), who record m. p. 191—193° (decomp.), $[\alpha]_D$ −56·9° (in $CHCl_3$)] (Found : C, 51·6; H, 5·3; N, 3·0; Ac, 36·7. Calc. for $C_{21}H_{25}O_{12}N$: C, 52·2; H, 5·2; N, 2·9; Ac, 35·6%). On hydrolysis with sodium methoxide, methyl *p*-aminosalicylate (m. p. 120°) was isolated in 63% yield. Diazotisation and ferric chloride colour tests were positive.

1-(4-*Acetamido*-2-*acetoxybenzoyl*) 2 : 3 : 4 : 6-*Tetra-acetyl* D-*Glucose*.—The above product (1·0 g.) was acetylated by acetic anhydride in pyridine at room temperature for about 7 days. Pyridine was removed under reduced pressure and the residue recrystallised from ethanol (yield, 1·05 g., 89·5%). After a further recrystallisation from ethanol the *product* had m. p. 192—193° (decomp.), $[\alpha]_D^{22}$ −48° (*c*, 1·0 in $CHCl_3$), $[\alpha]_D^{22}$ −40° (*c*, 1·0 in C_5H_5N) (Found : N, 2·5; Ac, 45·1. $C_{25}H_{29}O_{14}N$ requires N, 2·5; Ac, 45·5%). The diazotisation test was negative.

Ultra-violet Absorption Measurements.—All measurements were made on M/20,000-solutions in ethanol. In each of the results below, $\lambda_{max.}$ in Å is followed by the corresponding molecular extinction coefficient (ε) : *p*-Aminosalicylic acid : 2370 (7720); 2770 (12,100); 3030 (13,280). Methyl *p*-aminosalicylate : 2420 (7780); 2870 (16,140); 3070 (19,500). Methyl *p*-acetamidosalicylate : 2750 (20,820); 3070 (9000). 4-Acetamido-2-acetoxybenzoic acid : 2670 (20,040). 2 : 3 : 4 : 6-Tetra-acetyl 1-(4-amino-2-hydroxybenzoyl) D-glucose : 2440 (8260); 3100 (28,320). 1-(4-Acetamido-2-acetoxybenzoyl) 2 : 3 : 4 : 6-tetra-acetyl D-glucose: 2750 (25,180). *N*-(4-Carboxy-3-hydroxyphenyl)-D-glucosylamine: 2280 (10,520); 2680 (15,740); 3000 (12,440). *N*-(4-Carboxy-3-hydroxyphenyl)-D-glucosylamine tetra-acetate : 2300 (9800); 2740 (19,760); 3020 (15,040). *N*-(4-Carbomethoxy-3-hydroxyphenyl)-D-glucosylamine : 2380 (10,440); 2830 (19,580); 3050 (20,640).

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