Isomeric N-*Arylglycosylamine Tetra-acetates.*

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It is confirmed that a mixture of dextro- and lævo-rotatory isomers is formed in the preparation of *N*-arylglycosylamine tetra-acetates by a number of methods. Syntheses of seven such dextro- and lævo-rotatory compounds are recorded. The isomeric—probably anomeric—forms are interconvertible in solution and exhibit mutarotation in the presence of acid to reach an equilibrium. Structural problems and reactions of these compounds, which probably contain the strainless chair conformation of the pyranoside, are discussed.

In a previous paper it was recorded (Bognár and Nánási, *J.*, 1953, 1703) that reaction of acetobromoglucose or of D-glucose 2 : 3 : 4 : 6-tetra-acetate with sulphanilamide, or trans-glucosylation (*idem*, *Nature*, 1953, **171**, 475) of *N*-phenyl-D-glucosylamine 2 : 3 : 4 : 6-tetra-acetate with sulphanilamide in alcoholic hydrochloric acid, yields a mixture of two isomeric—probably anomeric—N^4-*p*-sulphamylphenyl-D-glucosylamine tetra-acetates. We now report formation and separation of other, similar *N*-arylglycosylamine tetra-acetates by (*a*) acetylation of *N*-arylglycosylamines in pyridine, and by reaction of an aromatic amine with (*b*) an acetobromo-sugar, (*c*) an acetylated aldopyranose, (*d*) a partly acetylated aldopyranose (*e.g.*, D-glucose 2 : 3 : 4 : 6-tetra-acetate), or (*e*) an acetylated *N*-arylglycosylamine (transglycosylation). All these methods give mixtures of anomers, but in proportions varying according to the method. One of the anomers is often formed in higher yield and is then isolated without difficulty, while separation of the other may be tedious.

Our results agree well with previous records on the preparation of isomeric glycosylamine tetra-acetates, *e.g.*, *N*-phenyl-D-glucosylamine tetra-acetate (Honeyman and Tatchell, *J.*, 1950, 967, and Pigman and Johnson, *J. Amer. Chem. Soc.*, 1953, **75**, 3464, methods *a* and *c*; Frèrejacque, *Compt. rend.*, 1936, **222**, 1190; 1937, **204**, 1480, and Weisz, Diss., Budapest, 1940, method *c*; Weisz, *loc. cit.*, method *d*), *N*-phenyl-D-galactosylamine tetra-acetate (Butler, Smith, and Stacey, *J.*, 1949, 3371, methods *a* and *d*), *N*-(4-chloro-2-nitrophenyl)-α- and -β-glucosylamine tetra-acetate, -α- and -β-D-xylosamine triacetate, and -α- and -β-D-arabinosylamine triacetate (Antaki and Petrow, *J.*, 1951, 2873, method *a*). Not only the α- and β-anomers of N^4-*p*-sulphamylphenyl-D-glucosylamine tetra-acetate have been isolated but other isomeric pairs as well, though Butler *et al.* (*loc. cit.*) and Ellis and Honeyman (*J.*, 1952, 2053) reported merely that a small quantity of the α-anomer appears to be formed by method (*b*) along with the main product, the β-anomer. Our results are tabulated on p. 188.

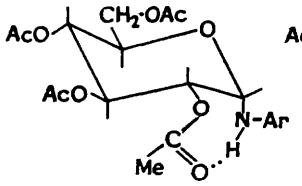
Mutarotation of the tetra-acetates does not occur in dry pyridine; in methanol it occurs slowly in some cases (*e.g.*, *N*-*p*-tolyl-D-glucosylamine or -mannosylamine tetra-acetate), but it is always very rapid (complete within a few minutes) in 0·1N-methanolic hydrogen chloride at room temperature. The α-anomers, otherwise difficulty accessible, are then relatively readily separated from the resulting mixture of the anomers.

The *N*-*p*-tolyl-D-glucosylamine tetra-acetate obtained by Ellis and Honeyman (*loc. cit.*) by method (*a*) is a mixture of anomers readily separable into its components by crystallisation. A similar mixture was obtained by method (*b*) in acetone containing sodium hydroxide.

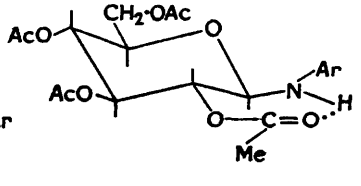
Acetic anhydride in the presence of anhydrous zinc chloride converts both anomers of *N*-*p*-tolyl-D-glucosylamine tetra-acetate into the same penta-acetate. Similarly *N*-*p*-sulphamylphenyl-D-mannosylamine tetra-acetate gives a hexa-acetate. The structures of these compounds and of the known *N*-phenyl-D-glucosylamine *N* : 2 : 3 : 4 : 6-penta-acetate and *N*-*p*-sulphamylphenyl-D-glucosylamine *N* : *N* : 2 : 3 : 4 : 6-hexa-acetate (Bognár and Nánási, *loc. cit.*) remain uncertain although these compounds are dextrorotatory: attempts at deacetylation and at their preparation from *N*-acetylarylamines by methods (*a*)—(*e*) failed.

Hudson's isorotation rule applies to some of our anomers and allows correlations of the pure α- and β-anomers.

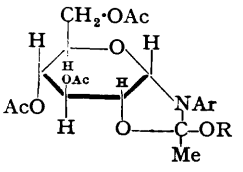
It was suggested in previous papers that the more soluble α-tetra-acetates might be stabilised by hydrogen bonding between the nitrogen atom and the carbonyl-oxygen atom of the 2-acetoxy-group. In fact similar hydrogen-bond formation cannot be excluded for the β-anomer if the sugar is in the strainless chair conformation. However, stabilisation



α-*Anomer*



β-*Anomer*



of the acetates in an oxazolidine system is also conceivable. The mutarotation in acid, deacetylation, and acetylation of the tetra-acetates (giving identical derivatives from the anomers) would involve reversible fission of both the oxazolidine and the pyranose ring.

Experimental

N-p-*Tolyl*-D-*glucosylamine* 2 : 3 : 4 : 6-*Tetra-acetates.*—*Method* (*a*). *N*-*p*-Tolyl-β-D-glucosylamine (Weygand, *Ber.*, 1939, **72**, 1666) (8·0 g.) was treated in pyridine (35 ml.) and acetic anhydride (20 ml.) with cooling. The mixture was kept for 2 days at room temperature, then poured into ice-water (400 ml.). The crude product (12 g., 92%) had $[\alpha]_D^{22}$ +25·5° (*c*, 0·9 in pyridine). Recrystallisation of 8 g. from 96% alcohol (30 ml.) gave product " A " (4·9 g.), m. p. 148°, $[\alpha]_D^{22}$ −63·5°. On addition of water to the alcoholic mother-liquors, product " B " (2·4 g.) crystallised, having m. p. 129°, $[\alpha]_D^{22}$ +114°. Product " A," recrystallised from a ten-fold quantity of methanol, yielded the pure β-isomer (2 g.) (see Table for this and other pure isomers). Product " B " was recrystallised twice from alcohol, and the substance remaining in the mother-liquor was precipitated with water and crystallised from methanol, giving the pure α-anomer (0·12 g.).

(*b*) *p*-Toluidine (6·0 g., 1 mol.) and acetobromoglucose (30·0 g., 1·2 mols.) in acetone were treated with 10% sodium hydroxide solution (30 ml.) with shaking during 90 min. The mixture was shaken for 2 days, then part of the acetone was removed *in vacuo*. This afforded product " A " (4·1 g.), m. p. 130—132°, $[\alpha]_D$ −54° in pyridine. Addition of water to the mother-liquor gave the crystalline product " B " (3·9 g.), m. p. 125—130°, $[\alpha]_D$ +32° in pyridine. Product " A " (4·0 g.) crystallised from 96% alcohol (30 ml.), to yield the pure β-anomer (1·8 g.). Product " B " (3·9 g.) crystallised from alcohol to give a substance (1·1 g.), of $[\alpha]_D$ −77°. This (1 g.) was recrystallised twice from alcohol giving a further 0·75 g. of β-anomer. When water was added to the alcoholic mother-liquor a substance (0·95 g.) separated having $[\alpha]_D$ +91° in pyridine. This purification was repeated several times and the substance which separated from the aqueous alcohol was finally crystallised from a ten-fold quantity of methanol to yield the pure α-anomer as needles (0·21 g.) (Found: C, 57·65; H, 6·3; N, 3·2, 3·2. $C_{21}H_{27}O_9N$ requires C, 57·7; H, 6·2; N, 3·2%).

(*c*) Penta-*O*-acetyl-D-glucose (10·0 g., 1 mol.) in 99% alcohol (200 ml.) and glacial acetic acid (10 ml.) was treated with *p*-toluidine (10·0 g., 4 mols.). After 24 hr. crystallisation began on scratching. The product " A " (8·6 g.) had m. p. 145° and $[\alpha]_D$ −67° in pyridine. This (4·5 g.) crystallised from 96% alcohol (30 ml.), to yield pure β-anomer (3·2 g.). The crude substance (3·5 g.) precipitated from the mother-liquor by water was recrystallised from alcohol. This alcoholic mother-liquor yielded with water the α-anomer (1·5 g.), m. p. 126—127°, $[\alpha]_D^{22}$ +82° in pyridine, which could be purified further.

(*d*) Tetra-*O*-acetyl-D-glucopyranose (5·0 g., 1 mol.) and *p*-toluidine (4·0 g., 3 mols.) in 99% alcohol (30 ml.) were boiled for 1 hr. On cooling to 0° a product (0·7 g.) " A " separated, m. p. *ca.* 141°, $[\alpha]_D$ −46·9° in pyridine. Water was added to the mother-liquor until it became turbid; product " B " separated (0·65 g.) which showed no rotation. A further product (1·7 g.), $[\alpha]_D$ +80°, was obtained from the mother-liquor and yielded on recrystallisation from alcohol 0·43 g. of a substance of $[\alpha]_D$ +130°. Repeated crystallisation from methanol led to the pure α-anomer.

N-p-*Tolyl*-D-*glucosylamine* N : 2 : 3 : 4 : 6-*Penta-acetate*.—The α- and the β-tetra-acetate were severally treated with acetic anhydride (10 pts.) and zinc chloride (0·5 pt.) for 15 min. on the water-bath, then poured into cold water. The crude products were recrystallised from aqueous alcohol. A mixture of the two penta-acetates thus obtained showed no depression of the m. p. (143°); $[\alpha]_D^{22}$ +50·4° (*c*, 0·9 in pyridine), +63·3° (*c*, 1·1 in $CHCl_3$) (Found: C, 57·7; H, 6·2; N, 2·9, 2·9. Calc. for $C_{23}H_{29}O_{10}N$: C, 57·6; H, 6·11 N, 2·9%). Weisz (*loc. cit.*) gives m. p. 142°, $[\alpha]_D$ +64·2° in $CHCl_3$.

N-p-*Bromophenyl*-D-*glucosylamine* 2 : 3 : 4 : 6-*Tetra-acetates*.—*Method* (*b*). *p*-Bromoaniline (2·3 g., 1 mol.) and acetobromoglucose (6·5 g., 1·2 mols.), treated in acetone with 10% sodium hydroxide solution (6·5 ml.) during 30 min., gave two layers. The mixture was shaken for 2 days, the solvent removed *in vacuo*, and the oily residue crystallised from alcohol (20 ml.), to yield product "A" (2·5 g.), $[\alpha]_D$ −48·3° in pyridine. Product "B" (1·9 g.), $[\alpha]_D$ +50° in pyridine, was separated from the mother-liquor on addition of water. Product "A" was twice recrystallised from 90% alcohol, to yield the pure β-anomer (1·5 g.). Product "B" was crystallised from alcohol, and water added to the mother-liquor. The precipitated *α-anomer*, purified by repeated fractionation with alcohol and water, and then by crystallisation from ether–light petroleum, had m. p. 150—152° (0·12 g.) (Found: C, 46·8; H, 4·6; N, 2·8. $C_{20}H_{24}O_9NBr$ requires C, 47·8; H, 4·8; N, 2·8%).

Method (*d*). *p*-Bromoaniline (2·5 g., 2·5 mols.) and tetra-*O*-acetyl-D-glucose (2 g., 1 mol.) were boiled for 1 hr. in 99% alcohol, to yield a mixture of dextro- and lævo-rotatory *N-p*-bromophenyl-D-glucosylamine 2 : 3 : 4 : 6-tetra-acetates. A product with m. p. 160—162° and $[\alpha]_D^{22}$ −64·2° (*c*, 1·2 in pyridine) and another with $[\alpha]_D$ +100°, containing much of the dextrorotatory isomer, were isolated in the usual way.

N-(3-*Hydroxy*-4-*propoxycarbonylphenyl*)-D-*glucosylamine* 2 : 3 : 4 : 6-*Tetra-acetates*.—*Method* (*b*). Propyl 4-aminosalicylate (2·0 g., 1 mol.) and acetobromoglucose (4·5 g., 1·1 mols.) reacted in the usual way in acetone (20 ml.) in the presence of 10% sodium hydroxide solution. The mixture was shaken for a day, the solvent removed, and the residue washed with water and crystallised from 96% ethanol (5 ml.). After precipitation of a part of the unchanged ester (0·35 g.) water was added. The oil thus obtained crystallised from aqueous alcohol (product "A"; 0·6 g.). Addition of water to the mother-liquor from "A" yielded a fraction "B" (0·9 g.). Product "A", twice crystallised from alcohol (5 ml.), afforded 0·35 g. of pure β-*anomer* (Found: N, 2·6. $C_{24}H_{31}O_{12}N$ requires N, 2·7%). A lævorotatory product was also obtained from product "B," but the mother-liquors therefrom yielded a dextrorotatory substance after further crystallisation.

Method (*d*). Propyl 4-aminosalicylate [(i) 1·2, (ii) 1·5 mols.] was treated in absolute alcohol with D-glucose 2 : 3 : 4 : 6-tetra-acetate (1 mol.) in the presence of small quantities of (i) concentrated hydrochloric acid and (ii) acetic acid. Working up in the usual way gave the β- and the *α-anomer* (Found: N, 2·8%).

N-p-*Sulphamylphenyl*-D-*mannosylamine* 2 : 3 : 4 : 6-*Tetra-acetates*.—*Method* (*a*). *N-p*-Sulphamylphenyl-D-mannosylamine (Bognár and Nánási, *loc. cit.*) (5·0 g.) was kept in pyridine (50 ml.) with acetic anhydride (20 ml.) for 3 days. Evaporation to dryness *in vacuo* and crystallisation from alcohol gave the β-*anomer* (5·3 g., 70%), m. p. 184°, obtained pure by further crystallisation (Found: N, 5·6. $C_{20}H_{26}O_{11}N_2S$ requires N, 5·6%).

Method (*b*). Acetobromomannose (5·0 g., 1·2 mols.) and sulphanilamide (1·7 g., 1 mol.) were treated in acetone (15 ml.) with 10% sodium hydroxide solution (5 ml.). The product was worked up in the usual way. The alcoholic solution yielded a product "A" (0·8 g.), $[\alpha]_D$ −107°. From the mother-liquor a crystalline product "B" (0·45 g.) was obtained, having $[\alpha]_D$ −82°, which was a mixture. Product "A" was purified by repeated crystallisation from methanol, giving the pure β-*anomer* (Found: N, 5·6; Ac, 35·0. $C_{20}H_{26}O_{11}N_2S$ requires N, 5·6; Ac, 34·25%). The methanolic liquor afforded the α-anomer, which was purified from ether–light petroleum.

N-p-*Sulphamylphenyl*-D-*mannosylamine* N : N : 2 : 3 : 4 : 6-*Hexa-acetate*.—The D-mannosylamine 2 : 3 : 4 : 6-tetra-acetate (1·0 g.) with acetic anhydride (10 ml.) and zinc chloride (1 g.) at 100° during 10 min. gave the *hexa-acetate*, m. p. 133—134° (from alcohol), $[\alpha]_D^{22}$ +62·5° (*c*, 1·1 in pyridine), +73·3° (*c*, 0·6 in $CHCl_3$) (Found: N, 4·7; Ac, 44·3. $C_{24}H_{30}O_{13}N_2S$ requires N, 4·8; Ac, 44·0%).

N-p-*Tolyl*-D-*mannosylamine* 2 : 3 : 4 : 6-*Tetra-acetates*.—*Method* (*a*). *N-p*-Tolyl-D-mannosylamine (Weygand, *loc. cit.*) in pyridine (50 ml.) with acetic anhydride (20 ml.) at room temperature gave a product (5·7 g.) which, worked up in the usual way and crystallised from alcohol, was a mixture of $[\alpha]_D$ −31·5° in pyridine. After 5 crystallisations from methanol the pure α-isomer

(0·55 g.) was obtained. The material precipitated by water from the mother-liquor was purified as described below, the β-isomer being obtained.

Method (*b*). Acetobromomannose (8·0 g., 1·2 mols.) reacted in the usual way with *p*-toluidine (1·6 g., 1 mol.) in acetone in the presence of sodium hydroxide. Crystallisation from alcohol yielded directly pure deacetylated *N*-*p*-tolyl-D-mannosylamine (0·3 g.), m. p. 180°, $[\alpha]_D$ −176° in pyridine. Addition of water to the mother-liquor gave a product (3·85 g., 50%), $[\alpha]_D$ −40° in pyridine; when this crystallised from ethanol or methanol the crops became gradually

	Method of prep.	α-Anomer M. p.*	α-Anomer $[\alpha]_D$ (Solvent) *	β-Anomer M. p.*	β-Anomer $[\alpha]_D$ (Solvent) *
D-*Glucosylamine tetra-acetate derivatives.*					
N-*p*-Tolyl	*a*—*d*	145°	+ 216° (Pyr); + 194·2° ($CHCl_3$) + 228·3 ⟶ +27·8° (HCl–MeOH)	148° (147[a,b]; 144—145[c]; 141—142[d])	− 78·0° (Pyr); − 53·7° ⟶ + 25·8° (HCl–MeOH) − 47·2 (− 47·1,[a] − 35·0,[d] − 33·4[c]) ($CHCl_3$)
N-*p*-Bromophenyl	*b*, *d*	150—152	+ 168·0 (Pyr) + 147·0 ⟶ + 33·4 (HCl–MeOH)	162 (157,[a] 160[b])	− 65·0 (Pyr); − 53·0 ⟶ + 31·3 (HCl–MeOH) − 44·7 (− 42·9[a]) ($CHCl_3$)
N-(4-Carboxy-3-hydroxyphenyl)	*b*, *d*	87	+ 107 (Pyr) (? impure)	133—134	− 87·8 (Pyr); − 51·0 ($CHCl_3$)
N-*p*-Sulphamylphenyl	*a*, *b*, *d*	(204—205[a])	+ 210·0 ⟶ + 26 (HCl–MeOH) (+ 203[a]) (Pyr); (+ 197[a]) ($CHCl_3$)	(204[a])	− 44·5 ⟶ + 28° (HCl–MeOH) (− 81[a]) (Pyr); (− 56·5[a]) ($CHCl_3$)
N-*p*-Nitrophenyl	*a*	168	+ 206·2 (Pyr) + 229·2 ⟶ + 44·0 (HCl–MeOH)	(180[f])	− 99·2 ⟶ + 38·2 (HCl–MeOH) (− 120[f]) (Pyr)
D-*Mannosylamine tetra-acetate derivatives.*					
N-*p*-Tolyl	*a*, *b*	168	+ 80·2 (Pyr); + 59·4 ($CHCl_3$) + 111·0° ⟶ − 22·5 (HCl–MeOH)	138	− 153·0 (Pyr); − 87·5 ($CHCl_3$) − 125·0 ⟶ − 18·0 (HCl–MeOH)
N-*p*-Sulphamylphenyl	*a*, *b*	196	+ 48·0° (Pyr) + 77·2 ⟶ 29·0 (HCl–MeOH)	193	− 149·8 (Pyr) − 113·0 ⟶ − 33·1 (HCl–MeOH)
D-*Galactosylamine tetra-acetate derivative.*					
N-*p*-Tolyl	*a*, *b*, *c*	128	+ 189·1 (Pyr) + 212·0 ⟶ + 43·7 (HCl–MeOH)	127	− 53·0 (Pyr) − 24·9 ⟶ + 43·5 (HCl–MeOH)

* Values in parentheses are from the literature. Mutarotations were complete in 5 min.
[a] Weisz, Diss., Budapest, 1940. [b] Baker, *J.*, 1928, 1583. [c] Honeyman and Tatchell, *J.*, 1950, 967. [d] Ellis and Honeyman, *J.*, 1952, 2053. [e] Bognár and Nánási, *J.*, 1953, 1703. [f] Weygand, *Chem. Ber.*, 1951, **84**, 594.

enriched in the α-*anomer* (Found: N, 3·15; Ac, 40·7. $C_{21}H_{27}O_9N$ requires N, 3·2; Ac, 39·4%); the β-*anomer* (Found: N, 3·3%) was separated from the mother-liquors by addition of water and recrystallised from carbon tetrachloride (0·29 g.).

Method (*c*). *p*-Toluidine (2·0 g., 4 mols.) and penta-*O*-acetyl-D-mannose (2·0 g., 1 mol.) were dissolved in ethanol (20 ml.), and acetic acid (1 ml.) was added. After 2 days the mixture was poured into water, and the solidified crude product (2·0 g.) crystallised from ethanol (20 ml.) (yield, 0·7 g.; $[\alpha]_D^{22}$ −27° in pyridine). The material (1·1 g.) precipitated from the ethanolic mother-liquor by water crystallised from methanol (11 ml.) (yield, 0·7 g.). The products were purified and identified as usual.

N-p-*Tolyl*-D-*galactosylamine* 2 : 3 : 4 : 6-*Tetra-acetates.*—*Method* (*a*). *N*-*p*-Tolyl-D-galactosylamine (5 g.; Ellis and Honeyman, *J.*, 1952, 1496) was treated in pyridine with acetic anhydride. The crude product could not be crystallised from ethanol. From the ether solution a crystalline substance (0·45 g.), m. p. 123°, $[\alpha]_D$ −51° in pyridine, was precipitated on addition of light petroleum; crystallisation from alcohol then afforded the pure β-*anomer* (Found: N, 3·3%).

Method (*b*). *p*-Toluidine (0·8 g.) and acetobromogalactose (4·0 g.) in acetone containing alkali gave only 0·07 g. of pure β-anomer.

Method (*c*). Keeping penta-*O*-acetyl-D-galactose (2·0 g.) and *p*-toluidine (2·2 g.) in absolute ethanol (30 ml.) containing acetic acid (1 ml) for 2 days at room temperature, then pouring the mixture in water, gave a product (1·15 g.), $[\alpha]_D^{23}$ +22° in pyridine. Recrystallisation from 96% alcohol yielded pure β-anomer (0·35 g.).

Preparation of (+)-N-p-*Tolyl*-D-*galactosylamine* 2 : 3 : 4 : 6-*Tetra-acetate from the* (−)-*Isomer.* —(−)-*N*-*p*-Tolyl-D-galactosylamine tetra-acetate (1·57 g.) was dissolved in methanol (6 ml.), and N-methanolic hydrogen chloride (0·5 ml.) was added. After 10 min. at room temperature the solution was poured into water (50 ml.), and the crude product crystallised from ethanol, giving material (0·64 g.) of $[\alpha]_D$ −37° in pyridine. By treating the mother-liquor with water and by further crystallisation the *α-isomer* (Found : N, 3·1%) was obtained.

(+)-*N*-*p*-Nitrophenyl-D-glucosylamine 2 : 3 : 4 : 6-tetra-acetate was similarly obtained from the (−)-isomer (prepared by method *a*; cf. Weygand, *Chem. Ber.*, 1951, **84**, 594).

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