58. *Preparation of Isomeric* N-*Arylglycosylamines.*

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A method has been developed for separation of lævo- and dextro-rotatory isomers of *N*-arylglycosylamines after catalytic deacetylation of the anomers or anomeric mixtures of *N*-arylglycosylamine tetra-acetates. Structural problems, of these isomeric probably anomeric forms, are discussed.

CRYSTALLINE isomeric *N*-arylglycosylamines with different melting points and optical rotations have been isolated,[1-3] but their structures have not been precisely determined.

In our opinion, the two isomeric *N*-*p*-tolyl-D-glucosylamines are anomeric, as indicated by their optical activities and mutarotations, and Ellis and Honeyman [4] describe them as *N*-*p*-tolyl-α- and -β-D-glucosylamines, m. p. 135—136°, 117—118°, $[\alpha]_D$ +208·9° ⟶ −44·6°, −100° ⟶ −46° (in MeOH), respectively.

We have prepared isomeric *N*-arylglycosylamines, in all probability anomers, by a novel method, namely hydrolysis of the acetates. In a previous paper [5] we described the separation of isomeric *N*-arylglycosylamine tetra-acetates by various methods, it being assumed that they were α- and β-anomers, and this was supported by our investigations

[1] Berger and Lee, *J. Org. Chem.*, 1946, **11**, 75, 84; Howard, Kenner, Lythgoe, and Todd, *J.*, 1946, 855; Butler, Laland, Overend, and Stacey, *J.*, 1950, 1433; Weygand, Perkow, and Kuhner, *Chem. Ber.*, 1951, **84**, 594; Kuhn and Ströbele, *Ber.*, 1937, **70**, 773; Irvine and Gilmour, *J.*, 1907, 1429; 1909, 1545.
[2] Ellis and Honeyman, *J.*, 1952, 1490.
[3] Rosen, Woods, and Pigman, *J. Org. Chem.*, 1957, **22**, 1727.
[4] Ellis and Honeyman, *Adv. Carbohydrate Chem.*, 1955, **10**, 95.
[5] Bognár and Nánási, *J.*, 1955, 185.

of their mutarotation.[6] The acetates were hydrolysed at room temperature in concentrated anhydrous methanol solutions, in the presence of 0·1—0·2 mol. of sodium methoxide.[7] The deacetylated products either crystallised directly or were precipitated by ether–light petroleum. The free glycosylamines do not mutarotate in dry methanol alone or in the presence of sodium methoxide, or do so only relatively slowly; so it may be assumed that neither anomerisation nor change in the number of atoms forming the ring occurs to any great extent under the above conditions, so that the pure anomeric acetates afford the pure *N*-arylglucosylamines. Experimentally the products from pure anomeric acetates appeared to be homogeneous. When mixtures of anomeric acetates were hydrolysed, the first fractions precipitated were almost pure α- or β-anomer, depending on the relative solubilities; the other anomer was later isolated from the mother-liquors. From mixed anomeric *N*-*p*-nitrophenyl-D-glucosylamine tetra-acetates and from *N*-*p*-bromophenyl-D-glucosylamine tetra-acetates almost pure, highly lævorotatory β-anomers were first obtained, but a mixture *N*-*p*-tolyl-D-glucosylamine tetra-acetates (80% of the α-anomer) gave first the dextrorotatory α-anomer.[2,3] This α-anomer had a higher dextrorotation than was recorded in the literature; however, when the α-anomer prepared by Pigman's method [3] was extracted with cold anhydrous methanol, the insoluble crystalline residue was identical with the α-anomer obtained by direct saponification.

The *N*-arylglycosylamine isomers obtained by deacetylation are stable in methanolic solution, but in the presence of acids mutarotate in a few minutes to equilibrium values of negative rotation. Exceptions are the *N*-*p*-tolyl-D-glucosylamine isomers which (similarly to the *N*-phenyl-D-glucosylamine isomers [1–3]) mutarotate also in absolute methanol, although very slowly (equilibration requires a few days). This agrees with our earlier observations [6] of a connection between the basicity of the arylamine and the tendency of the *N*-arylglycosylamine to mutarotate.

Treatment of the active glucosylamines at room temperature with acetic anhydride in pyridine gave active tetra-acetates. Dextrorotatory *N*-*p*-bromophenyl-, *N*-*p*-nitrophenyl-, or *N*-*p*-tolyl-D-glucosylamine gave dextrorotatory tetra-acetates; the other isomers gave lævorotatory tetra-acetates. Crystallising the acetylated dextrorotatory *N*-*p*-nitrophenyl-D-glucosylamine gave an α-tetra-acetate stereochemically more homogeneous than that obtained by repeated recrystallisation of the isomeric acetate mixture (cf. ref. 5). During the reacetylation anomerisation occurs only to a small extent, which seems to depend on the basicity of the arylamine. Thus, the α- or β-isomer of *N*-*p*-tolyl-D-glucosylamine gave mixed tetra-acetates, though the α-isomer predominated (about 83% for the α- and 65% for the β-form [5]).

We have assumed that the *N*-arylglycosylamine pairs are anomers because of the mild conditions that have been used in the preparations and conversions. The values of initial specific rotations and of those obtained after mutarotation are in agreement with this.

Experimental

N-p-*Tolyl*-α-D-*glucosylamine*.—(*a*) Mixed *N*-*p*-tolyl-D-glucosylamine tetra-acetates (2 g.; containing about 80% of α-anomer; $[\alpha]_D$ +165° in pyridine) were left in anhydrous methanol (5 ml.) containing N-methanolic sodium methoxide (0·5 ml.) at room temperature for 10 min. The crystals (0·34 g., 27·5%) which separated after the solution had been kept at 0° for an hour were filtered off. They had m. p. 124°, $[\alpha]_D^{22}$ +160° (*c* 0·5 in pyridine).

The mother-liquor was left for a day in a refrigerator. The crystalline precipitate (0·44 g., 36%) had m. p. 140° (decomp.), $[\alpha]_D^{22}$ +194° (*c* 0·5 in pyridine), + 226° (*c* 0·5 in MeOH) (Found: C, 57·65; H, 6·8; N, 5·1. Calc. for $C_{13}H_{19}NO_5$: C, 58·0; H, 7·1; N, 5·2%). A mixed m. p. determination with a product prepared by Pigman's method showed no depression. *N*-*p*-Tolyl-α-D-glucosylamine had been prepared [2,3] with m. p. 135—136°, 133—134°, $[\alpha]_D$ +209° ⟶

[6] Bognár and Nánási, *Magyar Kém. Folyóirat*, 1958, **64**, 66
[7] Cf. Zemplén, *Ber.*, 1926, **59**, 1254.

$-45°$ (in MeOH), $[\alpha]_D$ $+206·4° \longrightarrow -44·9°$. When ether (40 ml.) was added to the mother-liquor after removal of the second crop there separated an additional amorphous material (0·4 g.), $[\alpha]_D$ $-25·2°$ (*c* 0·5 in pyridine).

(*b*) The product, m. p. 134°, $[\alpha]_D$ $+192°$ (*c* 1·0 in pyridine), obtained by Pigman's method was mixed at room temperature with a twenty-fold quantity of anhydrous methanol. The insoluble residue had m. p. 139°, $[\alpha]_D^{22}$ $+225°$ (*c* 0·5 in MeOH), $+194°$ (*c* 0·5 in pyridine).

N-p-*Tolyl*-β-D-*glucosylamine*.—The pure β-tetra-acetate (0·5 g.; $[\alpha]_D$ $-76°$ in pyridine) was deacetylated with anhydrous methanol (1·25 ml.) and N-sodium methoxide (0·1 ml.), as in (*a*) above. No precipitate separated after the solution had been left at 0° for a day. Addition of ether (10 ml.) resulted in instantaneous crystallisation. The product [0·21 g.; m. p. 112° (decomp.)], when recrystallised from anhydrous methanol, had m. p. 117—120°, $[\alpha]_D^{22}$ $-86·8°$ (*c* 0·5 in pyridine), $-101°$ (*c* 0·5 in anhydrous MeOH) (Found: N, 5·0%).

α- and β-Anomers of *N-p*-tolyl-D-glucosylamines mutarotate also in anhydrous methanol. In 110 hr. the α- and the β-anomer attain $[\alpha]_D$ $-40°$ and about $-60°$, respectively.

In the presence of a small amount of hydrochloric acid a transient negative rotation is observed, then both anomers very quickly attain $[\alpha]_D$ $+35°$. It was shown in our previous experiments [6] that this is the result of hydrolysis.

The literature [8,2] records for *N-p*-tolyl-β-D-glucosylamine m. p. 112—113°, 113°, 117—118°, $[\alpha]_D^{24}$ $-101·2° \longrightarrow -45·8°$ (in MeOH), $[\alpha]_D^{18}$ $-101° \longrightarrow -46°$.

N-p-*Tolyl*-α-D-*glucosylamine Tetra-acetate*.—*N-p*-Tolyl-α-D-glucosylamine, $[\alpha]_D$ $+194°$ (in pyridine), was acetylated with acetic anhydride in the presence of pyridine. The crude product (90%), m. p. 115—120°, $[\alpha]_D^{22}$ $+168°$ (*c* 0·5 in pyridine), $+187°$ (*c* 0·5 in MeOH), was recrystallised from methanol to give about 40% of the pure α-acetate, m. p. 143°, $[\alpha]_D^{22}$ $+223°$ (in MeOH) (Found: N, 3·3. Calc. for $C_{21}H_{27}NO_9$: N, 3·2%); in the presence of hydrochloric acid, mutarotation gave $[\alpha]_D$ $+30·2°$ in about 5 min. {lit.,[5,6] $[\alpha]_D$ $+228·3° \longrightarrow +27·8°$ (in MeOH)}.

N-p-*Bromophenyl*-α-D-*glucosylamine*.—*N-p*-Bromophenyl-D-glucosylamine tetra-acetate (2·0 g.; containing about 58% of the α-anomer), $[\alpha]_D$ $+70°$ (in pyridine), was deacetylated in methanol as above. After a day at 0°, the crystals were collected {0·24 g.; m. p. 127—133° (decomp.), $[\alpha]_D^{21}$ $-107°$ (*c* 0·5 in pyridine)}. Ether (40 ml.) and light petroleum (60 ml.) were added to the mother-liquor, and the precipitate was extracted with cold methanol. The insoluble crystals (0·18 g., 13·7%) softened at 150° and melted at 154° (decomp.) and had $[\alpha]_D^{22}$ $+167°$ (*c* 0·5 in pyridine), $+198°$ (*c* 0·5 in MeOH). These were dissolved in methanol (3 ml.)–ether (9 ml.), and light petroleum (9 ml.) was added. The crystals (0·1 g.) obtained after storage at 0° had m. p. 163—164° (decomp.), $[\alpha]_D^{22}$ $+237°$ (*c* 0·5 in MeOH), $+207°$ (*c* 0·5 in pyridine) (Found: N, 4·1. Calc. for $C_{12}H_{16}BrNO_5$: N, 4·2%).

The α- and β-anomer of *N-p*-bromophenyl-D-glucosylamine show barely detectable mutarotation in methanol even in 48 hr. In the presence of hydrochloric acid, both anomers show $[\alpha]_D$ $-22°$ within a few minutes. In 48 hr., $[\alpha]_D$ changed in the positive direction because of hydrolysis.

N-p-*Bromophenyl*-β-D-*glucosylamine*.—Pure β-*N-p*-bromophenyl-D-glucosylamine tetra-acetate (0·35 g.), $[\alpha]_D$ $-65°$ (in pyridine), was deacetylated as described above. The directly precipitated crystals (0·2 g., 86%) had m. p. 150°, $[\alpha]_D^{22}$ $-105°$ (*c* 0·5 in MeOH), $-92·3°$ (*c* 0·5 in pyridine). Recrystallisation of the crude product from four parts of methanol yielded the pure product in a good yield, with m. p. 153°, $[\alpha]_D^{22}$ $-110°$ (*c* 0·5 in MeOH) (Found: N, 4·1%).

N-p-*Bromophenyl*-α-D-*glucosylamine Tetra-acetate*.—Almost pure *N-p*-bromophenyl-α-D-glucosylamine, $[\alpha]_D$ $+192°$ (in MeOH), with acetic anhydride in pyridine gave a product containing mostly the α-tetra-acetate (83%), m. p. 150°, $[\alpha]_D^{22}$ $+159°$ (*c* 0·5 in pyridine), $+154°$ (*c* 0·5 in MeOH), changing in hydrochloric acid to $+35°$ in 5 min. The material was dissolved in ether, and recrystallised by addition of light petroleum. Three recrystallisations gave material of m. p. 149°, $[\alpha]_D^{23}$ $+203°$ (*c* 0·5 in MeOH), which is higher than the recorded value,[5] $+147·0°$ (in MeOH) (Found: N, 2·7%).

N-p-*Bromophenyl*-β-D-*glucosylamine Tetra-acetate*.—*N-p*-Bromophenyl-β-D-glucosylamine, $[\alpha]_D$ $-97°$ (in pyridine), with acetic anhydride in pyridine gave a product (91%), m. p. 156°, $[\alpha]_D$ $-37·5° \longrightarrow +31·8°$ (*c* 1·0 in MeOH–HCl), which, crystallised twice from 90% alcohol, gave pure β-tetra-acetate,[5] m. p. 162°, $[\alpha]_D^{23}$ $-64·3°$ (*c* 0·5 in pyridine), $-52·4°$ (*c* 0·5 in MeOH) (Found: N, 2·7%).

[8] Weygand, *Ber.*, 1939, **72**, 1666; Honeyman and Tatchell, *J.*, 1950, 967.

N-p-*Nitrophenyl-α- and -β-D-glucosylamine.*—An about 1 : 1 anomeric mixture of α- and β-*N-p*-nitrophenyl-D-glucosylamine tetra-acetate (8·0 g.) was deacetylated in methanol (15 ml.) and N-sodium methoxide (1·5 ml.). Crystallisation occurred immediately after dissolution. The mixture was left overnight at room temperature. The precipitated crystals (3·65 g., 71%), $[\alpha]_D^{22}$ −74·6° (*c* 0·5 in pyridine), were extracted twice with hot ethanol. The insoluble pure β-anomer (2·4 g., 47%) had m. p. 184°, $[\alpha]_D^{22}$ −189° ⟶ −204° (*c* 0·5 in pyridine), −165° (*c* 0·2 in MeOH) {lit.,[9] m. p. 183°, $[\alpha]_D$ −192°, −193° ⟶ −202°, −200° (in pyridine)}.

The mother-liquor was treated with ether (150 ml.) and light petroleum (300 ml.); there separated a deacetylated product rich in the α-anomer (1·13 g., 22%), $[\alpha]_D^{22}$ +233° (*c* 0·5 in MeOH), m. p. 167° (decomp.).

Recrystallised from a little anhydrous methanol, this gave a product (30%) of m. p. 174°, $[\alpha]_D^{22}$ +337° (*c* 0·5 in MeOH), ⟶ −67° (in MeOH–HCl in 5 min.), +288° (*c* 0·5 in pyridine) (Found: C, 47·5; H, 5·2; N, 9·3. Calc. for $C_{12}H_{16}N_2O_7$: C, 48·0; H, 5·4; N, 9·3%).

In another experiment, with the same anomeric acetate as starting material, filtering the first precipitate after 15 min. gave a better yield of the α-anomer (35%), m. p. 160°, $[\alpha]_D^{22}$ +235° (*c* 0·5 in pyridine); a second precipitate (0·12 g., 9·4%) was almost pure α-anomer, m. p. 164°, $[\alpha]_D^{22}$ +252° (*c* 0·5 in pyridine), +291° (*c* 0·5 in MeOH).

The α- and β-anomers did not mutaroate in anhydrous methanol, even in 168 hr. On the addition of hydrochloric acid, they reached $[\alpha]_D$ −66° and −68°, respectively, which shifted within a few days towards 0° and to positive values as a consequence of hydrolysis.

N-p-*Nitrophenyl-α-D-glucosylamine Tetra-acetate.*—Almost pure *N-p*-nitrophenyl-α-D-glucosylamine, $[\alpha]_D$ +235° (in pyridine), with acetic anhydride in pyridine gave a product (85%), m. p. 142°, $[\alpha]_D^{21}$ +273° (*c* 0·5 in MeOH), +248° (*c* 0·5 in pyridine). This was recrystallised from a ten-fold quantity of ethanol–ether by addition of light petroleum. The needles produced had m. p. 153°, $[\alpha]_D^{22}$ +310° (*c* 0·5 in MeOH); mutarotation occurred in 5 min. in the presence of hydrochloric acid, giving $[\alpha]_D^{22}$ +271° (*c* 0·5 in pyridine) (Found: N, 5·9%) {lit.,[5,6] m. p. 168°, $[\alpha]_D$ +229·2° (in MeOH), +206·2° (in pyridine)}.

N-p-*Sulphamoylphenyl-α-D-glucosylamine.*—*N-p*-Sulphamoylphenyl-D-glucosylamine tetra-acetate (1·0 g.; containing about 83% of α-anomer), $[\alpha]_D$ +155° (in pyridine), was deacetylated in methanol (3 ml.) by means of N-sodium methoxide (0·3 ml.). The material dissolved at room temperature, and the small amount {0·08 g.; $[\alpha]_D$ −82° (in pyridine)} precipitated by the next day was filtered off. Ether (20 ml.) was added to the mother-liquor. The amorphous precipitate was dissolved in cold methanol and filtered from the insoluble residue {0·06 g.; $[\alpha]_D$ −99·5° (in pyridine); m. p. 195° (decomp.)}. The methanolic solution was mixed with ether (15 ml.). The amorphous, sticky material then precipitated was again filtered off, and finally light petroleum (20 ml.) was added. A solid (0·35 g., 52%) was precipitated on storage at 0° overnight, that was partly crystalline. This was extracted with ten parts of cold methanol. The residue (0·15 g. from 0·25 g.) had m. p. 189° (decomp.), $[\alpha]_D^{21}$ +182° (*c* 1 in pyridine), and, recrystallised from methanol, m. p. 189° (decomp.), $[\alpha]_D^{23}$ +184° (*c* 0·5 in MeOH), +182° (*c* 0·5 in pyridine) (Found: N, 8·1%).

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[9] Bognár and Nánási, *J.*, 1955, 189; Bognár and Nánási, *Magyar Kém. Folyóirat*, 1956, **62**, 90; also Weygand *et al.*, ref. 1.