322. N-*Substituted Glycosylamines. Part VI.** N-*Arylaldofuranosylamines*; N-p-*Nitrophenylaldosylamine Acetates.*

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2,3:5,6-Di-*O*-isopropylidene-*N*-aryl-D-mannosylamines have been prepared from acetone and *N*-aryl-D-mannosylamines; the mechanism of the reaction is discussed. A general method for preparing *N*-*p*-nitrophenylaldosylamine acetates has been devised.

Since *N*-substituted glycosylamines mutarotate [1] an equilibrium between pyranose, furanose, and acyclic forms can be expected in solution. Acetates, benzoates, and methyl ethers obtained from *N*-substituted glycosylamines have the pyranose structure.[1] *N*-Arylaldofuranosylamines have been prepared indirectly by condensing an arylamine with an isopropylidene derivative [2,3] or carbonate [4,5] of an aldofuranose that has a free reducing centre; for example, aniline and D-mannose 2,3:5,6-dicarbonate yield the corresponding *N*-phenyl-D-mannofuranosylamine.[5] An attempt to prepare *N*-phenyl-D-glucofuranosylamine by alkaline hydrolysis of the corresponding 5,6-carbonate yielded a product identical with that from the condensation of D-glucose with aniline; [4] this result is not surprising since it is now known that *N*-substituted glycosylamines mutarotate.[1]

Attempts have now been made to condense acetone with *N*-aryl-D-mannosylamines; these compounds were chosen because the free aldose forms a furanose isopropylidene derivative with a free lactol hydroxyl group. *N*-Phenyl-D-mannosylamine when condensed with acetone, zinc chloride–phosphoric acid being used as catalyst, gave 2,3:5,6-di-*O*-isopropylidene-*N*-phenyl-D-mannosylamine (5%) and 2,3:5,6-di-*O*-isopropylidene-D-mannose (30%); decomposition accompanied the reaction. Exposure of the

* Part V, *J.*, 1955, 3674.

[1] Ellis and Honeyman, *Adv. Carbohydrate Chem.*, 1955, **10**, 95, and references therein.
[2] Freudenberg and Wolf, *Ber.*, 1925, **58**, 300.
[3] Irvine and Skinner, *J.*, 1926, 1089.
[4] Haworth and Porter, *J.*, 1929, 2796.
[5] Haworth and Porter, *J.*, 1930, 151.

di-*O*-isopropylidene-*N*-phenyl-D-mannosylamine to the same reaction conditions gave di-*O*-isopropylidene-D-mannose (60%) and unchanged starting compound (2%), accounting for the low yield of the *N*-phenylmannosylamine derivative in the condensation. Reaction of acetone with *N*-*p*-nitrophenyl- and *N*-*p*-tolyl-D-mannosylamine, with the same catalyst, gave the corresponding *N*-aryl-2,3:5,6-di-*O*-isopropylidene-D-mannosylamines in yields of 17 and 8% respectively. These products were isolated by crystallisation and not by chromatography and it is probable therefore that di-*O*-isopropylidene-D-mannose was also formed. Interaction of *N*-*p*-nitrophenyl-D-mannosylamine and acetone, with sulphuric acid or phosphoric anhydride as catalyst, gave di-*O*-isopropylidene-*N*-*p*-nitrophenyl-D-mannosylamine in very low yield, accompanied by much decomposition. The structures of the *N*-phenyl and *N*-*p*-tolyl derivatives were shown by their identity with the products from the condensation of di-*O*-isopropylidene-D-mannose with aniline and *p*-toluidine respectively. *p*-Nitroaniline did not condense with di-*O*-isopropylidene-D-mannose, even in boiling ethanol for 24 hr. An authentic sample of the *p*-nitrophenyl derivative was, however, prepared by an interchange between di-*O*-isopropylidene-*N*-*p*-tolyl-D-mannosylamine and *p*-nitroaniline.

The isolation of the *N*-aryl-D-mannofuranosylamine derivatives from the above reactions does not prove conclusively that the *N*-aryl-D-mannosylamines have reacted in the furanose form. There are two possible routes for the formation of the observed products. In the first the *N*-aryl-D-mannosylamine reacts in the furanose form and some of the resulting product is hydrolysed to di-*O*-isopropylidene-D-mannose. In the second the *N*-aryl-D-mannosylamine is hydrolysed to the free sugar which condenses with acetone to give di-*O*-isopropylidene-D-mannose, some of which reacts with the arylamine. The first route is more probable because of the lack of reaction between *p*-nitroaniline and di-*O*-isopropylidene-D-mannose, and also if *N*-arylaldofuranosylamines are hydrolysed more rapidly than the pyranose compounds, as are the corresponding *O*-glycosides.

Unsuccessful attempts were made to prepare *N*-phenyl- and *N*-*p*-nitrophenyl-D-mannosylamine 2,3:5,6-dicarbonate by the action of carbonyl chloride on the appropriate *N*-aryl-D-mannosylamine.

A general method for preparing *N*-*p*-tolylaldosylamines has been developed for characterising aldoses.[6] These derivatives have decomposition points which vary with the rate of heating. A method is now suggested for preparing *N*-*p*-nitrophenylaldosylamine acetates as better derivatives of aldoses. These are preferred because they have well-defined melting points and characteristic rotations in chloroform. The intermediate *N*-*p*-nitrophenylaldosylamines, whose mode of formation is characteristic, also have the advantage of being stable and not undergoing the Amadori rearrangement.[7] D-Glucose, D-mannose, D-galactose, D-xylose, L-arabinose, and maltose all yield crystalline products; D-ribose yields a syrup; D-fructose and L-sorbose did not react under the specified conditions. The optical rotation of *N*-*p*-nitrophenyl-D-xylosylamine 2,3,4-triacetate has been found to be incorrectly recorded.[8,9]

N-*p*-Bromophenyl-D-galactosylamine and -D-mannosylamine have also been prepared and characterised as their tetra-acetates.

Experimental

Rotations were determined for chloroform solutions unless otherwise stated. The identity of compounds was proved where necessary by mixed m. p., and infrared spectrometry. Alumina was Type H, 100/200 mesh, supplied by Messrs. Peter Spence, Ltd.

Reaction of Di-O-isopropylidene-D-mannose with Amines.—(a) p-*Toluidine.* A solution of

[6] Ellis and Honeyman, *J.*, 1952, 1490.
[7] Micheel and Schleppingoff, *Chem. Ber.*, 1956, **89**, 1702.
[8] Douglas and Honeyman, *J.*, 1955, 3674.
[9] Douglas, Ph.D. Thesis, London, 1955.

di-*O*-isopropylidene-D-mannose (1 g.) and *p*-toluidine (1 g.) in ethanol (10 ml.) was boiled under reflux for 6 hr. Evaporation left a crystalline mass which after two recrystallisations from cyclohexane–chloroform (4 : 1) gave 2,3:5,6-*di*-O-*isopropylidene*-N-p-*tolyl*-D-*mannosylamine* (80% after first recrystallisation), m. p. 142—143°, $[\alpha]_D^{16}$ −139° (*c* 0·4), $[\alpha]_D^{17}$ −104° (*c* 0·72 in pyridine), $[\alpha]_D^{17}$ −117° (8 min.) ⟶ +63·7° (80 hr.) (*c* 0·2 in ethanol) (Found: C, 65·6; H, 8·0. $C_{19}H_{27}O_5N$ requires C, 65·4; H, 7·8%).

(b) *Aniline.* A solution of di-*O*-isopropylidene-D-mannose (10 g.) in ethanol (100 ml.) containing aniline (11 ml.) was boiled under reflux for 16 hr., then concentrated to about 30 ml. After storage at 0°, a colourless solid (7 g.), m. p. 117—119°, was deposited, and a further crop (3·4 g., total yield 73%) on concentration of the mother-liquor. Recrystallisation from light petroleum–ethanol gave needles of 2,3:5,6-di-*O*-isopropylidene-*N*-phenyl-D-mannosylamine, m. p. 121—122°, $[\alpha]_D^{20}$ −149° (*c* 1·12) (Found: C, 64·4; H, 7·5. Calc. for $C_{18}H_{25}O_5N$: C, 64·4; H, 7·6%). Irvine and Skinner [3] reported m. p. 114°; a sample prepared by their method had m. p. 119—121°.

(c) p-*Bromoaniline.* Reaction of *p*-bromoaniline (1·66 g.) with di-*O*-isopropylidene-D-mannose (1 g.) in ethanol (10 ml.) as in (a) gave, after recrystallisation from light petroleum, N-p-*bromophenyl*-2,3:5,6-*di*-O-*isopropylidene*-D-*mannosylamine* (44%), m. p. 135—136°, $[\alpha]_D^{25}$ −129° (*c* 0·5) (Found: C, 52·1; H, 5·8. $C_{18}H_{24}O_5NBr$ requires C, 52·2; H, 5·8%).

(d) p-*Nitroaniline.* A solution of di-*O*-isopropylidene-D-mannose (0·25 g.) and *p*-nitroaniline (0·25 g.) in ethanol (20 ml.) was boiled under reflux for 24 hr. The optical rotation of the solution did not change during this time.

Reaction of Acetone with N-*Aryl*-D-*mannosylamines.*—(a) N-p-*Nitrophenyl*-D-*mannosylamine.* The D-mannosylamine (5 g.) was suspended in acetone (20 ml.), and anhydrous zinc chloride (2·4 g.) and phosphoric acid (0·15 g.) were quickly added. After the mixture had been stirred at room temperature for 24 hr., undissolved starting compound (1·68 g.) was collected and washed with acetone. After the filtrate and washings had been neutralised with aqueous sodium hydroxide, the mixture was again filtered, then was concentrated and extracted three times with chloroform; after 5 days at 0° the concentrated extracts deposited pale yellow needles (17%), m. p. 178—180°. Two recrystallisations from cyclohexane gave 2,3:5,6-*di*-O-*isopropylidene*-N-p-*nitrophenyl*-D-*mannosylamine*, m. p. 182—183°, $[\alpha]_D^{15}$ −212° (*c* 0·6), $[\alpha]_D^{20}$ −188° (*c* 0·44 in pyridine) (Found: C, 56·8; H, 6·1. $C_{18}H_{24}O_7N_2$ requires C, 56·8; H, 6·4%).

When *N*-*p*-nitrophenyl-D-mannosylamine (1 g.) was shaken for 5 min. with acetone (20 ml.) containing sulphuric acid (0·8 ml.), the solution darkened considerably. Undissolved starting compound (0·04 g.) was removed and the solution neutralised with aqueous ammonia. After filtration, the solution was concentrated to a brown gum, which when crystallised twice from ethanol gave 2,3:5,6-di-*O*-isopropylidene-*N*-*p*-nitrophenyl-D-mannosylamine (60 mg.), m. p. 180—182°.

N-*p*-Nitrophenyl-D-mannosylamine (1 g.) and phosphoric anhydride (5 g.) in acetone (100 ml.) were shaken together for 10 min. at room temperature; this was followed by addition of saturated aqueous sodium carbonate, filtration, concentration, and extraction with chloroform; evaporation of the extracts and crystallisation of the residue from cyclohexane gave 2,3:5,6-di-*O*-isopropylidene-*N*-*p*-nitrophenyl-D-mannosylamine (40 mg.).

(b) N-p-*Tolyl*-D-*mannosylamine.* Anhydrous zinc chloride (2·68 g.) and phosphoric acid (0·17 g.) were quickly added to a suspension of the D-mannosylamine (5 g.) in acetone (50 ml.). After the mixture had been stirred at room temperature for 3·5 hr. undissolved starting compound (3·9 g.) was removed, and the filtrate neutralised with sodium hydroxide solution. The chloroform extracts of the concentrated filtrate were evaporated to a red gum which was dissolved in chloroform–cyclohexane. Tan crystals and a dark viscous syrup were obtained by slow evaporation of the solvents at room temperature. The crystals were collected, washed, and recrystallised from light petroleum as white needles (8%), m. p. 139—141°. A further recrystallisation gave 2,3:5,6-di-*O*-isopropylidene-*N*-*p*-tolyl-D-mannosylamine, m. p. 141—142°, $[\alpha]_D^{23}$ −135° (*c* 0·2).

With longer reaction times a gum was isolated that did not crystallise.

(c) N-*Phenyl*-D-*mannosylamine.* A suspension of the D-mannosylamine (2·5 g.) in acetone (25 ml.) containing anhydrous zinc chloride (1·33 g.) and phosphoric acid (0·085 g.) was stirred at room temperature for 2·5 hr. After removal of unused starting compound (2·11 g.), the mixture was neutralised with saturated aqueous sodium carbonate solution, then treated as in

the previous experiment to yield a red gum which was chromatographed on alumina in benzene–chloroform. Elution with benzene–chloroform (10 : 1) gave *N*-phenyl-2,3:5,6-di-*O*-isopropylidene-D-mannosylamine (5%), m. p. 120—122°. Elution with chloroform yielded 2,3:5,6-di-*O*-isopropylidene-D-mannose (30%), m. p. 122—123°.

Exposure of N-*Phenyldi-O-isopropylidene-D-mannosylamine to the Above Reaction Conditions.*—The D-mannosylamine derivative (2 g.) and phosphoric acid (0·017 g.) were added to a filtered solution of anhydrous zinc chloride (2·66 g.) in acetone (50 ml.). After being shaken for 2·75 hr. the solution was neutralised with saturated aqueous sodium carbonate solution, and the mixture treated as above. Chromatography yielded unchanged starting compound (2%) and di-*O*-isopropylidene-D-mannose (60%).

*Interchange between Di-O-isopropylidene-*N-p-*tolyl-D-mannosylamine and* p-*Nitroaniline.*—A solution of the D-mannosylamine (2 g.) in methanol (20 ml.) and water (4 ml.) was mixed with a solution of *p*-nitroaniline (1 g.) in methanol (1 ml.) containing 0·5% of concentrated aqueous hydrochloric acid. After the mixture had been boiled under reflux for 7 min. and left at room temperature for 2 days the resulting crystals (45%), m. p. 139—141°, were collected and recrystallised from light petroleum as unchanged di-*O*-isopropylidene-*N*-*p*-tolyl-D-mannosylamine, m. p. 141—143°. On further storage at 0°, the mother-liquor yielded a crop of pale yellow crystals, m. p. 130—137°. After three recrystallisations from light petroleum these gave *N*-*p*-nitrophenyl-2,3:5,6-di-*O*-isopropylidene-D-mannosylamine (10%), m. p. 178—179°.

N-p-*Nitrophenylaldosylamines and Their Acetates.*—The following general method was developed for the preparation of *N*-*p*-nitrophenylaldosylamines acetates of mono- and di-saccharides: the sugar (1 g. of monosaccharides, 2 g. of disaccharides) and *p*-nitroaniline (1 g.) in methanol–water (2·25 ml.; 8 : 1) were boiled under reflux with glacial acetic acid (1 ml.). If complete dissolution occurred the solution was boiled for a further 3 min.; if dissolution did not occur a *total* heating time of 8 min. was used. After the reaction mixture had been stored at 0°, the yellow product was collected, washed with ethanol and ether, dried, and acetylated without further purification. If no product separated on cooling, it was precipitated by the addition of ether.

The aldosylamine (1 g.) from above was dissolved or suspended in pyridine–acetic anhydride (10 ml.; 1 : 1), and the mixture was kept at 0° overnight. Pouring into ice-water gave the acetate as a pale yellow solid, which was recrystallised from ethanol. For disaccharides the quantity of acetylating mixture was doubled.

The results are summarised in the Table: further necessary details are as follows.

Preparation of N-p-*nitrophenylaldosylamine acetates.*

	Aldosylamine		Aldosylamine acetate		
Sugar	Mode of formation	Yield (%)	$[\alpha]_D$	M. p.	Yield (%)
D-Glucose	Separates on cooling	90	−101°	182—183°	50
D-Mannose	Incomplete solution	96	−153	210—211	40
D-Galactose	Incomplete solution	60	−72·3	98	82
D-Xylose	Separates at 0°	65—90	−39·6	212—213	82
L-Arabinose	Separates in later stages of refluxing	80	+5·1	177—178	60
Maltose	Very sol.; pptd. with ether	65	+14·5	226	70
D-Ribose	Separates at 0°	49			

N-p-*Nitrophenyl-D-galactosylamine* 2,3,4,6-*tetra-acetate.* This compound had m. p. 95—105°, after recrystallisation from ethanol. The crude tetra-acetate, after being dissolved in boiling carbon tetrachloride, deposited a white pasty solid, the β-anomer–carbon tetrachloride complex. This was collected, and after being washed with light petroleum and dried was a pale yellow solid. Two recrystallisations of this from methanol gave the product, m. p. 98°, $[\alpha]_D^{15}$ −72·3° (*c* 1·0). Frèrejacque [10] reported $[\alpha]_D$ −73°, but no m. p.

N-p-*Nitrophenyl-D-xylosylamine* 2,3,4-*triacetate.* *N*-*p*-Nitrophenyl-D-xylosylamine was more soluble in ethanol than the other aldose derivatives and loss occurred during washing. Examination of Douglas and Honeyman's sample of the triacetate showed it to have $[\alpha]_D$ −39°, in agreement with the present work and not −11·5° as reported.[8,9]

N-p-*Nitrophenyl-D-ribosylamine* 2,3,4-*triacetate.* This was isolated only as a syrup.

N-p-*Nitrophenylmaltosylamine hepta-acetate.* Two recrystallisations from ethanol followed by two from methanol gave white needles of N-p-*nitrophenylmaltosylamine hepta-acetate*, m. p.

[10] Frèrejacque, *Compt. rend.*, 1938, **207**, 638.

226°, $[\alpha]_D^{18}$ +14·5° (*c* 0·79) (Found: C, 50·9; H, 5·1; N, 3·7. $C_{32}H_{40}O_{19}N_2$ requires C, 50·8; H, 5·3; N, 3·7%).

N-p-*Bromophenyl*-D-*mannosylamine*.—A solution of D-mannose (1 g.) in methanolic hydrochloric acid (2 ml.; as above) was boiled under reflux with *p*-bromoaniline (1·25 g.). On cooling and storage at 0°, the deep red solution deposited a white solid, which on recrystallisation from ethanol gave N-p-*bromophenyl*-D-*mannosylamine*, m. p. 178—179° (decomp.), $[\alpha]_D^{22}$ −169° (*c* 1·15 in pyridine), constant for 8 hr. (Found: C, 43·3; H, 4·6. $C_{12}H_{16}O_5NBr$ requires C, 43·1; H, 4·8%).

Four recrystallisations, from light petroleum–ethanol (2 : 1), of the crude product from acetylation of the D-mannosylamine gave N-p-*bromophenyl*-D-*mannosylamine* 2,3,4,6-*tetra-acetate* (50%), m. p. 154·5—155·5°, $[\alpha]_D^{20}$ −91·9° (*c* 0·5) (Found: C, 47·8; H, 5·0. $C_{20}H_{24}O_9NBr$ requires C, 47·8; H, 4·8%).

N-p-*Bromophenyl*-D-*galactosylamine*.—This was prepared by the general method outlined for *N*-*p*-nitrophenylaldosylamines, to give *N*-*p*-bromophenyl-D-galactosylamine (72%), m. p. 176·5—177·5° (decomp.).

Recrystallisation, from ethanol, of the product from acetylation of the D-galactosylamine gave N-p-*bromophenyl*-D-*galactosylamine* 2,3,4,6-*tetra-acetate* (48%), m. p. 160—161·5°, $[\alpha]_D^{18}$ −28·4° (*c* 0·98) (Found: C, 47·6; H, 4·9. $C_{20}H_{24}O_9NBr$ requires C, 47·8; H, 4·8%).

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