On the Reaction Products of Some Aldoses with Secondary Aliphatic Aromatic Amines

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N-Aryl-N-methyl-N-L-arabinopyranosylamines, 1H NMR Spectra.
N-Aryl-N-methyl-N-D-gluco-, -galacto- and -xylapyranosylamines, 2-O-Methylfructoside, Amadori Product

Reactions of L-arabinose, D-xylose, D-galactose and D-glucose with N-methylaniline and its p-methyl and p-methoxy derivatives were studied in methanol, in the presence and absence of an acidic catalyst, by employing the thin-layer chromatographic technique. Appropriate N-aryl-N-methyl-N-glycopyranosylamines found in the products underwent rapid transformations in the reaction medium.

Introduction

The mechanism of the reactions between amines and sugars has not been completely elucidated. This is, especially in the case of secondary aliphatic-aromatic amines where no reaction products have been isolated so far. On the other hand, successful condensations of aliphatic-aromatic amines with per-O-acyl-1-bromo-1-deoxyglycopyranoses have been reported. By successive cleavage of the ester groups from the condensation products, appropriate N-aryl-N-methyl-L-arabinopyranosylamines have been isolated. By employing the thin-layer chromatographic technique both the number and nature of products resulting from the reactions of L-arabinose, D-xylose, D-galactose and D-glucose with N-methylaniline and its p-methyl and p-methoxy derivatives were studied in methanol, in the presence and absence of an acidic catalyst, by employing the thin-layer chromatographic technique. Appropriate N-aryl-N-methyl-N-glycopyranosylamines found in the products underwent rapid transformations in the reaction medium.

Discussion

The comparison of the RF values of the products of the reactions with those of the standards (obtained by indirect methods, cf. 1 in the experimental section) at various time intervals, revealed that appropriate N-aryl-N-methylglycopyranosylamines (1–2, 5–13) were formed in all the system studied. Unfortunately, the latter compounds underwent rapid transformations in the reaction medium to afford certain other derivatives. Among N-glycosides, only N-methyl-p-anisidine and N-methyl-p-toluidine, were determined.

The aforementioned results reveals that secondary aliphatic-aromatic amines react with simple sugars in methanol similarly as do primary aliphatic [8] and...

A comparison of the rate of appearance of spots due to a variety of N-aryl-N-methyl-glycopyranosylamines, as well as their intensity in the chromatograms, supports conclusions relating to the reactivity of particular sugars drawn from the kinetics of the reactions of formation of the N-glycosides, derivatives of the primary aromatic amines [11, 12]. At the same time, it can be stated that the aliphatic aromatic amines react much slower with aldoses than do primary aromatic amines [13].

The fact of isolation of the N-glycosides derived from aliphatic aromatic amines should lead to the revision of the hitherto adopted views suggesting impossibility of their preparation by reacting simple sugars with amines. According to these suggestions the bromoacetate method [14] is the unique one leading to these compounds.

Tables I and II list characteristics of the new N-aryl-N-methyl-L-arabinopyranosylamines (1–2) and of their O-acetylated derivatives (3–4) used as standards. The compounds should have α-configuration. This follows from the preparation method employed. The ¹H NMR spectral evidence confirmed this suggestion and revealed the ⁴C₁ conformation of the pyranosidic ring. The spin coupling constants, J, of the anomeric protons of these compounds amounted to 10 Hz (cf. Table II). This value has been found to be characteristic of the trans bi-axial protons occurring at the adjacent C₁ and C₂ atoms.

It is remarkable that the signals of the H₂, H₃ and H₄ protons are shifted from the 4.46–3.88 ppm (α) region for the N-arabinopyranosylamine to the 5.36–4.99 ppm one for its O-acetylated, respectively. The shift is likely to be due to the interactions of the acetyl groups with adjacent protons which result in deshielding of the latter. A similar phenomenon was observed in the spectra of the O-acetylated N-aryl-N-methyl-D-galacto- [3] and O-xypopyranosylamines [1].

Investigation of the reactions of simple sugars with secondary aliphatic aromatic amines in methanol by the t.l.c. method showed that spots characteristic of the N-glycopyranosylamines were accompanied by other spots whose intensity increased during the course of the reactions.

Bearing in mind that in reactions between amines and sugars Amadori products may be formed together with N-glycosylamines an attempt was made to prepare the Amadori standards. By condensing 4,6-benzylidene-D-glucose successively with N-methylaniline and N-methyl-p-toluidine, followed by splitting off the benzylidene rest, Simon and Ardenne [15] obtained the corresponding 1-(N-aryl-N-methyl)amino-1-deoxy-2-ketose and assigned it an open-chain structure on the basis of the IR spectral evidence.

By repeating these reactions non-crystalline products (23, 24) were obtained in the form of dark green oils giving two spots. The oils underwent rapid decomposition. An attempt to separate the components by column chromatography was unsuccessful. In the IR spectrum of the oil the carbonyl band was missing.

The products of the reactions between D-glucose and N-methylaniline or N-methyl-p-toluidine in methanol, obtained in the presence of a catalytic
amount of NH₄Cl, gave among others spots with identical Rₓ's as those of the oil components. Column separation of the products of the reaction between D-glucose and N-methyl-p-toluidine gave additional a crystalline compound with sharp melting point. Its molecular weight and fragmentation pattern in the mass spectrum allowed to identify it as N-methyl-N-p-methoxyphenyl(1-deoxy, 2-O-methyl-D-fructopyranosyl)-amine (25).

It can be concluded that the reaction of D-glucose with secondary aliphatic aromatic amines, carried out in methanol in the presence or absence of an acid catalyst, affords N-glycoside, similarly as is the case with primary or secondary aliphatic amines.

However, N-glycosides being derivatives of secondary aliphatic aromatic amines undergo rapid Amadori rearrangement and cyclic Amadori product formed reacts under favourable conditions (catalyst) with methanol to give the appropriate O-methylfructopyranoside.

The isolation of the O-methylfructoside of the Amadori product suggests that it occurs in the cyclic form. This form is likely to be in equilibrium with the open-chain form.

**Experimental**

1. **Preparation of standard compounds**


| Compound                                                                 | Empirical formula | Molecular weight Calcd | Found | M.p. [°C] | Yield [%] | Analysis Calculated C[%, H[%, N[%, Found C[%, H[%, N[%, Mₒ°D [c] in abs. ethanol | |
|-------------------------------------------------------------------------|-------------------|-------------------------|-------|-----------|-----------|---------------------------------------------| |
| 1. N-Methyl-N-p-methoxyphenyl-α-L-arabinopyranosylamine                  | C₁₃H₁₉O₅N         | 269                     | 264   | 148–150   | 86        | 58.0 7.1 5.2 57.6 7.2 5.1 +182 c = 0.29 | |
| 2. N-Methyl-N-p-methylphenyl-α-L-arabinopyranosylamine                   | C₁₉H₂₅O₄N         | 253                     | 249   | –         | 60        | 61.6 7.5 5.5 60.1 7.4 5.5 +64 c = 0.32 | |
| 3. 2,3,4-Tri-O-acetyl-N-methyl-N-p-methoxyphenyl-α-L-arabinopyranosylamine | C₁₉H₂₅O₄N         | 395                     | –     | 98–99    | 45        | 57.7 6.4 3.5 57.0 6.5 3.7 +410 c = 0.22 | |
| 4. 2,3,4-Tri-O-acetyl-N-methyl-N-p-methylphenyl-α-L-arabinopyranosylamine | C₁₉H₂₅O₄N         | 379                     | –     | 111–112  | 38        | 60.2 6.6 3.6 60.0 6.7 3.6 +485 c = 0.33 | |

* In pyridine.
Table II. Chemical shifts, \( \delta \) [ppm], and coupling constants, \( J \) [Hz], of hydrogen atoms in \( \text{N-aryl-N-methyl-L-arabinosides} \) and their O-acetyl derivatives.

<table>
<thead>
<tr>
<th>Compound</th>
<th>( H_1 )</th>
<th>( J_{1,2} )</th>
<th>( H_2 )</th>
<th>( H_3 )</th>
<th>( H_4 )</th>
<th>( H_5e )</th>
<th>( H_5a )</th>
<th>( N-CH_3 )</th>
<th>( O-CH_3 )</th>
<th>( C-CH_3 )</th>
<th>( CH_3CO ) axial</th>
<th>( CH_3CO ) equat</th>
<th>H-aromatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-Methyl-N-( p )-methoxy-( \alpha )-L-arabinopyranosyd</td>
<td>4.71</td>
<td>10</td>
<td>4.46</td>
<td>4.25–3.88</td>
<td>3.62–3.37</td>
<td>2.85</td>
<td>3.45</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>6.87</td>
</tr>
<tr>
<td>N-Methyl-N-( p )-methyl-( \alpha )-L-arabinopyranosyd</td>
<td>4.82</td>
<td>10</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>6.82</td>
</tr>
<tr>
<td>2,3,4-Tri-O-acetyl-N-( p )-methoxyphenyl-( \alpha )-L-arabinopyranosyd</td>
<td>4.55</td>
<td>10</td>
<td>5.36</td>
<td>4.99</td>
<td>5.25</td>
<td>3.90</td>
<td>3.52</td>
<td>2.78</td>
<td>3.65</td>
<td>2.12</td>
<td>1.93</td>
<td>6.71</td>
<td></td>
</tr>
<tr>
<td>2,3,4-Tri-O-acetyl-N-( p )-methylphenyl-( \alpha )-L-arabinopyranosyd</td>
<td>4.65</td>
<td>10</td>
<td>5.46</td>
<td>5.08</td>
<td>5.29</td>
<td>3.96</td>
<td>3.62</td>
<td>2.83</td>
<td>2.88</td>
<td>2.18</td>
<td>1.98</td>
<td>6.79</td>
<td></td>
</tr>
</tbody>
</table>

Amadori products, \( D \)-glucose derivatives of \( N \)-methylalanine and \( N \)-methyl-\( p \)-toluidine

\( 4,6 \)-Benzyldene-\( D \)-glucose was successively condensed with \( N \)-methylalanine and \( N \)-methyl-\( p \)-toluidine in dioxan in the presence of the acetic acid catalyst [15]. The products, \( 1-(\text{N-aryl-N-methyl-} \text{-a}-\text{deoxy-4,6-benzyldene-} \text{-D-fructoses}} \), had identical m.p.'s and IR spectra of those reported in the literature [15]. Removal of the benzylidene groups, lyophilisation after [15] and repeated attempts of purification gave dark green oils each giving two spots in the chromatograms developed in the system methanol-chloroform-ethyl ether (1:2:9).

\( 1-(N \text{-phenyl-} N \text{-methyl-} \text{amine-1-deoxy-4,6-benzyldene-} \text{-D-fructose}} \) \( \text{R}_F \) = 0.36 and 0.60; \( 1-(N \text{-p-methylphenyl-N-methyl-} \text{amine-1-deoxy-} \text{-D-fructose}} \) \( \text{R}_F \) = 0.38 and 0.63

The oils reduced the Fehling’s solution in the cold and after approximately 1 h underwent further transformations as evidenced by increasing number of spots. In the IR spectra of the oils the carbonyl band was missing.

II. Monitoring of the reaction between an aldose and \( N \)-aryl-\( N \)-methylalanine by t.l.c. technique

In a round-bottomed flask fitted with a reflux condenser protected from the access of air moisture 0.001 mole of an aldose (\( \text{L-arabinose, D-xylose, D-galactose, D-glucose} \)) in 0.005 dm\(^3\) of abs. methanol was dissolved, followed by addition of 0.001 mole of an amine(\( N \)-methylalanine, \( p \)-methylalanine, \( p \)-methoxyaniline) and 20 mg of \( N \)-HCl (or without the catalyst). The flask was kept in a thermostat at 338 K. At predetermined time intervals aliquots of the solution were withdrawn and applied on plates coated with silica gel (MN Kieselgel H) along with \( N \)-aryl-\( N \)-methylglycopyranosylamines and Amadori products (oils) as standards. Chromatograms were developed in the system methanol-chloroform-ethyl ether (1:2:9). Spots were rendered visible in iodine vapours followed by thermal decomposition.

III. Isolation of the reaction products

1. \( N \)-aryl-\( N \)-methylglycopyranosylamines

The reagent mixture described under II was kept in a thermostat at 338 K for 3–6 h and applied onto a chromatographic column packed with silica gel (MN Kieselgel 60; particle size 0.08 mm). Compounds were eluted with the methanol-chloroform-ethyl ether (1:2:3) mixture. Fractions were collected by means of an automatic collector and analyzed by t.l.c. Those containing \( N \)-aryl-\( N \)-methylglycopyranosylamine (\( \text{R}_F \) = 0.19–0.25) were combined and evaporated in \text{vacuo}. The crude products (yield \( 6–12\% \), only \( N \)-methyl-\( N \)-p-methoxyphenyl-\( \alpha \)-arabinopyranosylamine was obtained in 60% yield) were crystallized from a methanol-ether mixture and identified by determining their molecular weights, specific rotation as well as IR and \( ^1 \text{H} \) NMR spectra (1–2, 5–13).

Acetyl derivatives of the \( N \)-glycosides were obtained by acetylation with acetic anhydride in dry pyridine [1–4] (3–4, 14–22).
All the compounds (1–22) were identical with those obtained by the indirect bromoacetate method [1–4].

2. Attempts to isolate Amadori products, D-glucose derivatives of N-methylaniline and N-methyl-p-toluidine

By employing the procedure described under III, successive fractions were collected containing compounds with \( R_F = 0.35 \) and 0.6. After evaporation of the solvent under reduced pressure, dark green, chemically inhomogeneous oils were obtained. Their properties were identical with those obtained under I.

3. Isolation of N-methyl-N-p-methylphenyl-(1-deoxy-2-O-methyl-D-fructopyranosyl)-amine

By using the procedure described under III, a fraction with \( R_F = 0.50 \) was collected. Removing the solvent under reduced pressure left crystals with m.p. 112–114 °C after crystallisation from a methanol-ether mixture (25).

The mass spectra were obtained with a Varian Mat 711 spectrometer at 70 eV.

Ms: \( m/e = 297 \) (M\(^+\), 4%), \( m/e = 265 \) (1.3%), \( m/e = 163 \) (8.6%), \( m/e = 134 \) (100%).

Calcd C 60.60 H 7.74 N 4.71,

Found C 58.30 H 7.80 N 4.50.