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Structure of Aldoses Condensation Products with 2-Hydroxy- and 2-Aminobenzohydrazides

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Abstract

The structure of the condensation products of 2-hydroxybenzohydrazide, 2-aminobenzohydrazide, and N-methyl-N-(2-aminobenzo) hydrazide with a series of aldoses (L-arabinose, D-ribose, L-rhamnose, D-galactose, D-glucose, and D-mannose) was studied by ^{1}H- and ^{13}C-NMR spectroscopy. The condensation products of aldoses with 2-hydroxybenzohydrazide and 2-aminobenzohydrazide in DMSOd_6 solutions exist as equilibrium mixtures of linear acylhydrazone and cyclic pyranose and furanose forms. The aldoses condensation products with N-methyl-N-(2-aminobenzo)hydrazide in the crystalline state and in DMSOd_6 solutions have cyclic benzo-1,2,4-triazepin structure.

Keywords

Aldoses 2-Hydroxy- and 2-Aminobenzohydrazides, Benzo-1,2,4-Triazepines, Ring-Chain-Ring Tautomerism

Subject Areas: **Organic Chemistry**

1. Introduction

Condensation products of aldoses with acylhydrazines and their derivatives have been reported to possess sig-

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nificant activity as antimicrobial, antifungal [1], and anti-HIV [2] agents. Among aldoses acylhydrazones containing in their structure a functional 2-hydroxybenzoyl and 2-aminobenzoyl group is known only 2-hydroxybenzoylhydrazones of arabinose, glucose and mannose [3], the structure of which is not proved. The presence of a functional nucleophilic NH_2-group in the aldosohydrazone fragment could give rise in appearance of new structural possibilities in further transformations. Intermolecular nucleophilic attacks of NH_2-fragments at the C=N polar bond contained in the linear structure can lead to repeated cyclization with the formation of new cyclic forms. Condensation products of N-methyl-N-(2-aminobenzo) hydrazide with monocarbonyl compounds tend to undergo intramolecular cyclization via nucleophilic addition of the NH_2-group at the C=N bond with formation of seven-membered benzo-1,2,4-triazepin ring [4] [5]. In some cases, this process is reversible, so that equilibrium mixture of linear hydrazone and cyclic benzotriazepin tautomer may exist in solution.

The aim of the present work was to study of the structure of the condensation products of aldoses with hydrazides of 2-hydroxybenzoic (2-$HOC_6H_4CONHNH_2$), 2-aminobenzoic (2-$H_2NC_6H_4CONHNH_2$), and N-methyl-N-2-aminobenzoic (2-$H_2NC_6H_4CONMeNH_2$) acids by ^{1}H- and ^{13}C-NMR spectroscopy methods.

2. Results and Discussion

Compounds **1a-1j** and **2a-2d** were synthesized in yields 55% - 90% by heating equimolar amounts of the corresponding aldose (L-arabinose, D-ribose, L-rhamnose, D-galactose, D-glucose, D-mannose) and corresponding acylhydrazine: 2-hydroxybenzohydrazide, 2-aminobenzohydrazide, and N-methyl-N-(2-aminobenzo) hydrazide in boiling methanol for a period of 1 - 3 h (**Figure 1**, **Figure 2** and **Table 1**).

In all experiments, the ^{1}H- and ^{13}C-NMR spectra were recorded at definite time intervals starting from the moment of dissolution until the end of transformations. In addition, the structure of the compounds under study in the crystalline state was confirmed by solid-phase high-resolution ^{13}C-NMR spectroscopy (CPMAS). For example, pyranose form **B** was expected to give a signal from the anomeric C-1 atom at δ 85 - 90 ppm; analogous signal from five-membered furanose tautomer **C** is located at δ 95 - 100 ppm [6] [7]. The C-1 signal of possible benzo-1,2,4-triazepin tautomer **D** should appear in a stronger field, at δ 70-75 ppm, which is typical of sp^3-hybridized carbon atom in seven-membered ring, located between two nitrogen atoms [4] [5]. Hydrazone structure **A** should give rise to a downfield signal at δ 145 - 155 ppm (C=N) in the ^{13}C-NMR spectrum. The formation of analogous seven-membered cyclic benzo-1,3,4-oxadiazepin tautomers for 2-hydroxybenzohydrazones **1a-1f** via attack by the OH group on the C=N bond should be ruled out. It is known that condensation products

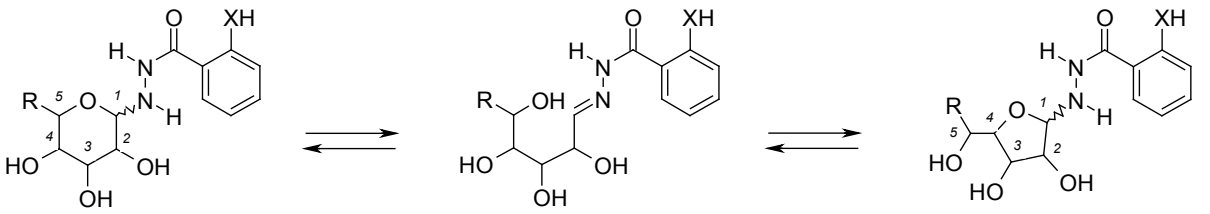

Figure 1. Aldoses 2-hydroxy- and 2-aminobenzoyl hydrazones **1a-1j**.

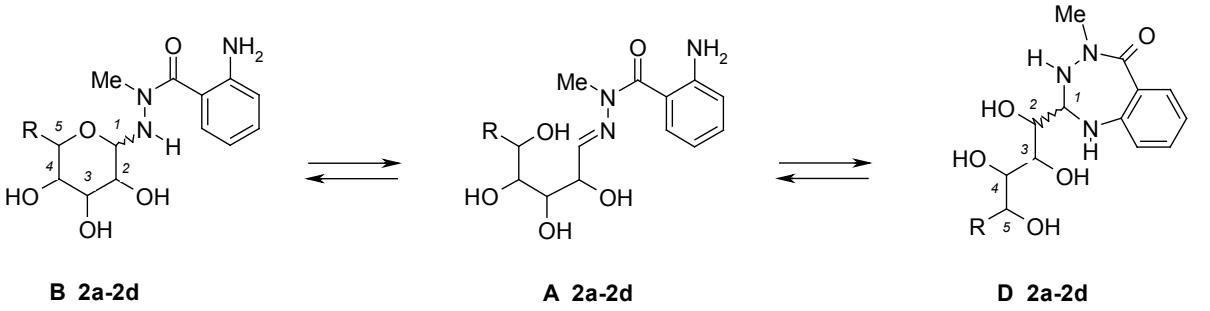

Figure 2. Aldoses N-methyl-N-(2-aminobenzoyl) hydrazones **2a-2d**. **2a** R = H (L-arabinose), **2b** R = H (D-ribose), **2c** R = CH_2OH (D-glucose), **2d** R = CH_2OH (D-mannose).

Table 1. Tautomeric composition of the aldoses 2-hydroxy- and 2-aminobenzoyl hydrazones **1a-1j** (72 h after dissolution).

Compound	X	R	Initial aldose	Form in crystals	Tautomeric composition (%) in DMSOd_6		
					Form **B**	Form **A**	Form **C**
1a	O	H	L-Arabinose	**B**	45	30	25
1b	O	H	D-Ribose	**B**	50	40	10
1c	O	CH_3	L-Rhamnose	**B**	80	20	-
1d	O	CH_2OH	D-Galactose	**B**	70	30	-
1e	O	CH_2OH	D-Glucose	**B**	95	5	-
1f	O	CH_2OH	D-Mannose	**B**	35	65	-
1g	NH	H	L-Arabinose	**B**	65	25	10
1h	NH	H	D-Ribose	**A**	25	60	15
1i	NH	CH_2OH	D-Glucose	**B**	100	-	-
1j	NH	CH_2OH	D-Mannose	**B**	100	-	-

of 2-hydroxybenzohydrazide with aldehydes and ketones have exclusively linear structure and they do not tend to undergo the above cyclization [8].

The ^{1}H- and ^{13}C-NMR spectra of the condensation product of 2-hydroxybenzoic acid hydrazide with L-arabinose **1a**, recorded in DMSOd_6 immediately after dissolution, contained one set of signals corresponding to cyclic pyranose structure **B**. It is characterized by two downfield singlets at δ 10.22 and 12.20 ppm in the ^{1}H-NMR spectrum from protons in the NHCO group and phenolic OH group, respectively, and the sp^3-hybridized C-1 atom gives a signal at δ 90.80 ppm in the ^{13}C-NMR spectrum. Taking into account that the ^{1}H- and ^{13}C-NMR spectra were recorded immediately after dissolution, *i.e.*, possible tautomeric and configurational transformations had no time to occur, we presumed that the observed spectral parameters reflect the structure of compound **1a** in the crystalline state. The ^{1}H- and ^{13}C-NMR spectra of **1a** changed with time, and signals assignable to the second stereoisomer of six-membered structure **A**, as well as to linear tautomer **A** and furanose structure **C**, appeared. Structure **A** is characterized by a doublet at δ 7.74 ppm in the ^{1}H-NMR spectrum from the N=CH azomethine proton and a signal at δ 155.05 ppm (C=N) in the ^{13}C-NMR spectrum. The presence of five-membered furanose tautomer **C** in a solution of **1a** in DMSOd_6 follows from the presence of signals at δ 84.63 (C-4) and 95.55 ppm (C-1) in the ^{13}C-NMR spectrum. After some time, the NMR spectra of compound **1a** no longer changed, indicating establishment of ring-chain-ring equilibrium. The equilibrium tautomer mixture consists of 45% of pyranose tautomer **B**, 30% of linear structure **A**, and 25% of furanose form **C** (**Table 1**).

Analogous pattern was observed for a solution of compound **1b** (condensation product of 2-hydroxybenzohydrazide and D-ribose) in DMSOd_6; the fractions of structures **A**, **B**, and **C** in the equilibrium tautomer mixture of **1b** differ insignificantly from those found for compound **1a**. Unlike arabinose and ribose derivatives **1a** and **1b**, the condensation products **1c-1f** derived from 2-hydroxybenzohydrazide and hexoses do not give rise to cyclic furanose form **C**. Compounds **1c-1f** in the crystalline state have cyclic structure **B**. The cyclic pyranose structure of crystalline compound **1e** (condensation product of 2-hydroxybenzohydrazide with glucose) was confirmed by its solid-phase ^{13}C-NMR spectrum. In going to solutions in DMSOd_6, compounds **1c-1f** undergo partial transformation into linear hydrazone tautomer **A**. Insofar as the fraction of the linear tautomer for all the examined condensation products of 2-hydroxybenzohydrazide with aldoses did not exceed 30% - 40%, the term "2-hydroxybenzoyl hydrazone" should be regarded as arbitrary as applied to such systems.

A single set of signals corresponding to cyclic pyranose form **B** is observed for the condensation product of 2-aminobenzohydrazide with L-arabinose **1g** immediately after dissolution. As in the case of compound **1a**, we may assume that the spectral data reflect the structure of compound **1g** in the crystalline state. Sets of signals corresponding both to the five-membered furanose form **C** and linear aldosohydrazone form **A** gradually arise in the ^{13}C-NMR spectrum in DMSOd_6. The ^{13}C-NMR signal at δ 151.35 ppm for the C=N carbon is characteristic for linear form **A** (**Table 1**). One set of signals belonging to linear form **A** is observed in the ^{13}C NMR spectrum of the 2-aminobenzohydrazide condensation product with ribose **1h** taken immediately after dissolution. This finding suggests that compound **1h** has the same structure in the crystalline state. After 2 days, sets of signals

arise corresponding to the cyclic pyranose form **B** and furanose form **C** in the ^{13}C-NMR spectrum of the solution. The ^{13}C-NMR signal for atom C-1 at δ 88.13 ppm is characteristic for form **C**. The presence of the five-membered furanose form **C** in ^{13}C-NMR spectra of compounds **1g**, **1h** is indicated by the signals for C-4 and C-1 at δ 83 and 95 ppm, respectively. The spectrum of compound **1h** stops changing after some time, indicating the establishment of a ring-chain equilibrium in which linear form **A** (60%) exists along with the cyclic pyranose **B** (25%) and furanose **C** forms (15%).

Thus, in contrast to the results of a study of El-Barbary *et al*. [1] on the structure of a series of 3,5-disubstituted 2-aminobenzohydrazones of aldoses, in which the linear aldosohydrazone structure was adopted, we have shown that in the case of aldose 2-aminobenzoylhydrazones **1g**, **1h**, these compounds may convert to alternative cyclic pyranose and furanose forms, as well as both ring-chain and ring-linear-ring tautomeric equilibria are possible.

Going from arabinose derivative **1g** and ribose derivative **1h** to products of condensation with hexoses **1i**, **1j** is accompanied by disappearance of the cyclic furanose form **C** and linear aldosohydrazone form **A** from the equilibrium. In the crystalline state compounds **1i**, **1j** have pyranose structure **B**, while the ^{13}C-NMR spectra indicate that these compounds in DMSOd_6 solution are represented by geometric α, β-isomers of this form.

Different behavior is found for compounds **2a-2d**, which are the products of the condensation of aldoses with N-methyl-N-(2-aminobenzo)hydrazide (**Figure 2**). The change in the ^{13}C-NMR spectra of all these products indicates that they have the cyclic benzo-1,2,4-triazepin structure **D** in the crystalline state. The ^{13}C-NMR signal for atom C-1 at δ 75 - 80 ppm characteristic for sp^3-hybridized carbon atom in a seven-membered ring attached to two nitrogen atoms [4] [5] is diagnostic for benzo-1,2,4-triazepin form **D**. Signals corresponding to a second configurational isomer of the benzo-1,2,4-triazepin form **D**' are found in the ^{1}H- and ^{13}C-NMR spectra of compounds **2a-2d** in DMSOd_6. It was impossible to determine the 2*R*- or 2*S*-configuration of these derivatives. The ^{1}H- and ^{13}C-NMR spectra of solutions of the aldoses condensation products with N-methyl-N-(2-aminobenzo)-hydrazide stop changing after 4 - 7 days, indicating that transition to the possible linear form **A** and cyclic pyranose form **B** does not occur. A tendency to cyclize with formation of a seven-membered benzo-1,2,4-triazepin ring through attack of the nitrogen atom at the C=N bond is a common feature of compounds **2a-2d**.

3. Conclusion

The ability to undergo ring-chain or ring-chain-ring tautomeric transformation involving two different cyclic structures was found for the aldoses condensation products with 2-hydroxy- and 2-aminobenzohydrazides. The aldoses condensation products with N-methyl-N-(2-aminobenzo) hydrazide were found to strongly tend to form seven-membered benzo-1,2,4-triazepin form via intramolecular nucleophilic addition of the NH_2 group at the hydrazone C=N bond.

4. Experimental Part

^{1}H- and ^{13}C-NMR spectra in DMSOd_6 were registered on a spectrometer Bruker AV-400 at operating frequencies 400 and 100 MHz respectively (internal reference hexamethyldisiloxane). The solid-phase ^{13}C-NMR spectra were obtained on a Bruker AM-500 spectrometer (125 MHz) using a standard procedure utilizing cross polarization and magic angle spinning (CPMAS) technique (frequency 4.5 kHz; internal reference hexamethylbenzene). The tautomeric composition of obtained compounds was estimated by the integration of the appropriate signals in the ^{1}H NMR spectra. Elemental analysis of newly obtained compounds was carried out on a CHN Analyzer Hewlett Packard 185B. The purity of prepared compounds was checked by TLC on Silufol UV-254 plates, eluent butanol-water-acetone, 8:1:1.

Synthesis of aldoses 2-hydroxy- and 2-aminobenzoylhydrazones (1a-1j) and (2a-2d). To a solution of 0.01 mol of 2-hydroxybenzohydrazide or 2-aminobenzohydrazide in 25 ml of methanol, 0.01 mol of an appropriate aldose was added, and the mixture was boiled for a period of 1 - 3 h. The solvent was removed at a reduced pressure, the residue was washed with ether (3 × 50 ml), and the colorless crystalline substance was filtered off on a glass filter funnel (40 - 100 μm), dried and stored in a desiccator over P_2O_5.

4.1. L-Arabinose 2-Hydroxybenzoylhydrazone (1a)

Yield 65%, m.p. 191˚C - 192˚C (lit. [3] m.p. 191˚C). ^{1}H-NMR spectrum (DMSOd_6): δ = form **A** (30%): 7.74 (d,

J = 4.4 Hz, HC=N), 11.60 (br.s, NHCO), 12.11 (br.s, OH); form α-**B** (20%): 10.22 (br.s, NHCO), 12.50 (br.s, OH); form β-**B** (25%): 10.22 (br.s, NHCO), 12.20 (br.s, OH); form α-**C** (25%): 10.35 (br.s, NHCO), 11.96 (br.s, OH) ppm. ^{13}C-NMR spectrum (DMSOd_6): δ = form **A**: 63.88 (C-5), 65.52 (C-2), 70.29 (C-3), 71.13 (C-4), 155.05 (C-1), 159.50 (ArC-O), 165.33 (C=O); form α-**B**: 63.55 (C-5), 67.92 (C-4), 69.52 (C-3), 70.32 (C-2), 85.85 (C-1), 159.05 (ArC-O), 166.05 (C=O); form β-**B**: 65.30 (C-5), 69.01 (C-4), 72.35 (C-3), 73.65 (C-2), 90.80 (C-1), 159.31 (ArC-O), 166.65 (C=O); form α-**C**: 61.83 (C-5), 84.63 (C-4), 95.55 (C-1), 117.44 - 134.04 (Ar in **A**-**C**) ppm. Found, %: C 50.63; H 5.84; N 9.78. $C_{12}H_{16}N_2O_6$. Calculated, %: C 50.70; H 5.67; N 9.85.

4.2. D-Glucose 2-Hydroxybenzoylhydrazone (1e)

Yield 70%, m.p. 196˚C - 198˚C (lit. [3] m.p. 198˚C). ^{1}H-NMR spectrum (DMSOd_6): δ = form **A** (5%): 7.76 (d, J = 4.6 Hz, HC=N), 11.60 (br.s, NHCO), 11.95 (br.s, OH); form α-**B** (30%): 10.09 (br.s, NHCO), 12.00 (br.s, OH); form β-**B** (65%):10.22 (br.s, NHCO), 11.87 (br.s, OH) ppm. ^{13}C-NMR spectrum (solid phase): δ = form β-**B** (100%): 59.70 (C-6), 68.23 (C-4), 69.04 (C-2), 74.96 (C-5), 79.24 (C-3), 90.93 (C-1), 112.50, 118.91, 120.57, 128.66, 136.71 (Ar), 160.44 (ArC-O), 172.12 (C=O) ppm. ^{13}C-NMR spectrum (DMSOd_6): δ = form **A**: 63.50 (C-6), 159.47 (ArC-O); form α-**B**: 60.95 (C-6), 70.22 (C-4), 71.15 (C-5), 71.25 (C-2), 73.72 (C-3), 87.98 (C-1), 159.00 (ArC-O), 166.95 (C=O); form β-**B**: 61.42 (C-6), 70.50 (C-4), 71.55 (C-2), 76.85 (C-5), 78.18 (C-3), 91.05 (C-1), 158.55 (ArC-O), 166.95 (C=O), 114.37-135.26 (Ar in **A** and **B**) ppm. Found, %: C 49.62; H 5.80; N 8.96. $C_{13}H_{18}N_2O_7$. Calculated, %: C 49.68; H 5.77; N 8.91.

4.3. L-Arabinose 2-Aminobenzoylhydrazone (1g)

Yield 75%, m.p. 189˚C - 191˚C. ^{13}C-NMR spectrum (DMSOd_6): δ = form **A** (25%): 63.78 (C-5), 68.98 (C-2), 70.80 (C-3), 71.17 (C-4), 151.35 (C-1), 147.22 (ArC-N), 165.69 (C=O); form β-**B** (65%): 65.08 (C-5), 69.05 (C-4), 72.75 (C-3), 73.65 (C-2), 89.13 (C-1), 145.33 (ArC-N), 168.74 (C=O); form α-C (10%): 61.82 (C-5), 76.89 (C-3), 78.81 (C-2), 85.53 (C-4), 95.94 (C-1), 145.80 (ArC-N), 168.01 (C=O), 114.67 - 147.22 (Ar in **A**-**C**) ppm. Found, %: C 57.71; H 5.76; N 13.39. $C_{12}H_{17}N_3O_5$. Calculated, %: C 57.67; H 5.81; N 13.45.

4.4. L-Arabinose N-Methyl-N-(2-Aminobenzoyl)Hydrazone (2a)

Yield 50%, m.p. 168˚C - 171˚C. ^{13}C-NMR spectrum (DMSOd_6): δ = form **D** (65%): 38.35 (CH_3), 63.96 (C-5), 65.35 (C-2), 70.21 (C-3), 71.52 (C-4), 75.37 (C-1), 145.42 (ArC-N), 172.33 (C=O); form **D**' (35%): 38.60 (CH_3), 63.75 (C-5), 65.35 (C-2), 70.30 (C-3), 71.52 (C-4), 76.88 (C-1), 145.50 (ArC-N), 172.15 (C=O), 117.65 - 145.50 (Ar in **D** and **D**') ppm. Found, %: C 52.59; H 6.50; N 14.06. $C_{13}H_{19}N_3O_5$. Calculated, %: C 52.52; H 6.44; N 14.13.

Spectral characteristics of compounds 1b, 1c, 1d, 1f, and 2b-2d were described in works [6] [7].

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