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Mendeleev Commun., 1993, **3**(4), 168–169
Mendeleev Communications

Ring–Ring Tautomerism of Aldohexose Thiocarbohydrazones

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Mannose, galactose and glucose thiosemicarbazones, and mannose thiocarbohydrazones exist in DMSO solutions as tautomeric mixtures of pyranose and linear hydrazone forms, but in solutions of galactose and glucose thiocarbohydrazones there are also hexahydro-1,2,4,5-tetrazine-3-thione tautomers.

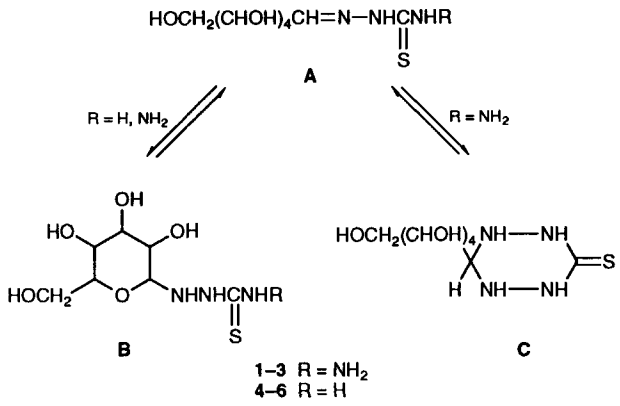
Carbohydrate thiocarbohydrazones have not been described previously. Meanwhile, thiocarbonohydrazones of monocarbonyl compounds have been of great interest for investigators as potential propellants.[1] On the other hand, thiosemicarbazones of some carbohydrates, the closest analogues of thiocarbonohydrazones, reveal antimicrobial activity.[2] At the same time, since two possible isomers of these compounds can be anticipated, *i.e.* a pyranose[3] and a hexahydro-1,2,4,5-tetrazine-3-thione,[4] we have synthesized thiocarbohydrazones of mannose, galactose and glucose (**1–3** respectively)† in order to investigate their structure in [$^2H_6$]DMSO solutions by means of ^{13}C and ^{15}N NMR spectroscopy.‡

Known thiosemicarbazones of the same aldohexoses **4–6**[5] were used as model pyranose structures. Previously the pyranose structure had been assigned to the glucose thiosemicarbazone **6** on the basis of its IR and ^1H NMR spectra.

We have found that compounds **4–6** in solution exhibit ring-

† Compounds **1–3** were obtained by refluxing 0.05 mol of thiocarbohydrazide with 0.05 mol of the appropriate carbohydrate in 50% aqueous Pr^{i}OH for 3 h. Following solvent removal *in vacuo*, the residue was washed with MeCN and recrystallized from MeCN–MeOH. Compounds **1–3** gave satisfactory elemental analyses. Yields of **1**: 85% (m.p.179–180 °C), **2**: 75% (166–167 °C), **3**: 60% (103–105 °C).

‡ ^{13}C NMR ([$^2H_6$] DMSO), δ(ppm) **1**: form **A** (all NMR data refer to the equilibrium state) (5%) 64.3, 68.2, 68.8, 69.0, 71.1, 149.0 (C=N), 178.3 (C=S); form **C** (95%) 63.9, 68.3, 68.5, 69.2, 71.2, 66.2 (^{6}C), 172.3 (C=S). **2**: form **A** (10%) 148.3 (C=N), 176.9 (C=S); form **B** (30%) 61.4, 68.9, 71.6, 74.1, 76.4, 91.6 (^{1}C), 181.2 (C=S); form **C** (60%) 63.6, 69.0, 69.8, 70.1, 70.5, 67.6 (^{6}C), 172.9 (C=S). **3**: form **A** (5%) 149.0 (C=N), 176.4 (C=S); form **B** (35%) 62.3, 70.6, 71.4, 77.3, 77.8, 90.8 (^{1}C), 181.2 (C=S); form **C** (60%) 63.9, 70.8, 71.1, 71.6, 72.1, 66.3 (^{6}C), 172.6 (C=S). Signals of the sugar moiety for tautomer **A** of compounds **2** and **3** can not be accurately assigned due to the low abundance of this form.



Scheme 1

chain tautomerism **A**⇄**B** with the equilibrium position strongly dependent on the parent hexose.[8] Open-chain tautomers **A** show carbon signals due to C=N and C=S bonds at 147–150 and 177–178 ppm, respectively, while for cyclic tautomers **B** signals for the ^{1}C atom at 88–92 ppm and the C=S bond carbon at 181 ppm are characteristic. A greater chemical shift of the C=S carbon signals of thiosemicarbazides as compared to thiosemicarbazones seems to be the general phenomenon.[6] It is noteworthy that carbon signals of the sugar moiety in both tautomers **A–B** of the thiosemicarbazone **6** are practically at the same positions as those in the ^{13}C NMR spectra of similar tautomers of glucose arylhydrazones.[3a]

In the electron impact (EI) mass spectra (direct insert probe, 70 eV, ion source temperature 100 °C) of **5** and **6**, molecular ions are absent, but there are peaks for ions at 163 and 91. The latter, more abundant, corresponds to the thiosemicarbazide cation-radical which probably arises from the tautomer **B** due to bond cleavage with hydride shift. Fragments of the pyranose structure were also observed in the EI mass spectra, *e.g.* ions 119 (retro-Diels–Alder product) and 73 ($C_3H_5O_2$).[7] Accordingly, **5B** and **6B** are supposed to be the major isomers in the gas phase, but EI mass spectra show also (though less abundant) peaks due to ion 102 which may be produced only from the tautomer **A** by cleavage of the C–C bond adjacent to the azomethine group. In the fast atom bombardment (FAB) mass spectra (glycerol–EtOH matrix, Ar atoms accelerated at 5 keV) of **5** and **6** the base peaks are those of MH^+ ions. They lose primarily the ($CH_2OH + H$) fragment which is characteristic of the tautomer **B**. Unlike the EI spectra, in the FAB mass spectra the presence of tautomers **A** was not detected (ions 102 were absent).

In the ^{13}C NMR spectra of hexahydro-1,2,4,5-tetrazine-3-thiones,[6] C and ^{3}C signals appear at 66–68 and 172–173 ppm, respectively.[4] Therefore, the spectral differences of isomers **A–C** allowed us to make reliable structure assignments for thiocarbohydrazones **1–3**.

Comparison of the ^{13}C NMR spectra of fresh mannose and galactose thiocarbohydrazone solutions with spectra of the model compounds indicates that **C** is the only tautomer present in this case. This conclusion is also supported by the ^{15}N NMR spectrum of **1**, where two pairs signals from non-equivalent (due to asymmetry of the molecule) tetrazine nitrogens were observed at 89.2, 94.6 (^{1}N, ^{5}N) and 130.7, 131.2 ppm (^{2}N, ^{4}N; NH_3-scale). At the same time, a fresh solution of the glucose thiocarbohydrazone **3** shows two sets of signals from tautomers **B** and **C**.

Thus, in the ^{15}N NMR spectra signals at 89.5, 93.8, 129.7 and 130.9 correspond to the form **C**, while the tautomer **B** gives two amine and two thioamide signals at 66.0, 85.0 and 123.7, 127.1 ppm, respectively (*cf.*[4]).

It takes nearly a month for the tautomeric equilibrium **A**⇄**B**⇄**C** to be reached in thiocarbohydrazone solutions (as well as in solutions of thiosemicarbazones **4–6**). The proportion of **C** form in the equilibrium state decreases in the order **1**>**2**>**3**, and so does the share of the tautomer **A** in the thiosemicarbazones, order **4**>**5**>**6**. These data may possibly be used for a comparative estimation of the chain and cyclic forms of initial carbohydrates. We have no reliable data about this.

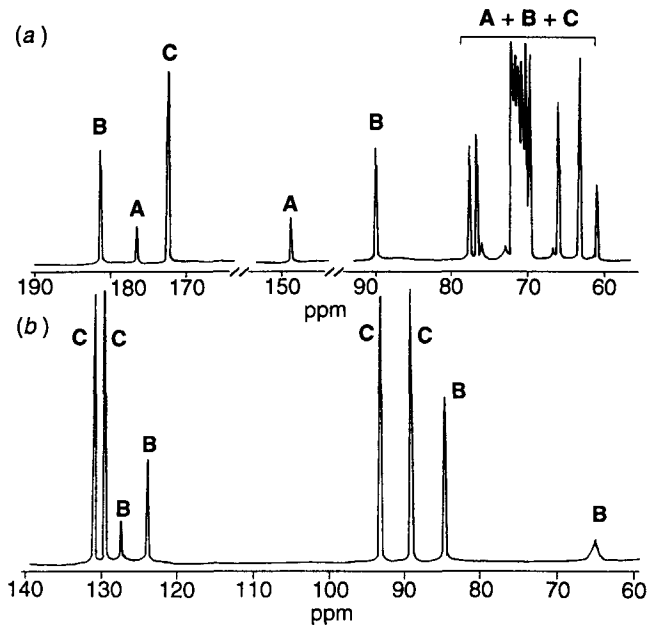


Fig. 1 NMR spectra of glucose thiocarbonohydrazone in [$^{2}H_6$]DMSO solution. (*a*) ^{13}C spectrum; (*b*) ^{15}N spectrum.

Molecular ions could not be detected in the EI mass spectra of **1–3**, but there were abundant peaks of ions 116, which have undoubtedly a dihydrotetrazinethione structure, and may be produced from the **C** form of the molecular ion by cleavage of the carbohydrate moiety. The same ions, but in the protonated form ($m/z-117$), together with MH^+ ions are the most intensive in the FAB mass spectra of **1–3**. Also in the FAB spectra are prominent peaks of ion 180 ($MH^+ - CH_3N_3S$) and peaks due to its fragments: 149, 121 and 119, supporting the **C** structure for MH^+ ions.

In conclusion, galactose and glucose thiocarbohydrazones show the first example of ring–ring tautomerism involving both oxygen- and nitrogen-containing six-membered heterocycles.

References

1 G. Rajendran and S. R. Jain, *Org. Magn. Reson.*, 1984, **22**, 6.
2 (*a*) T. S. Gardner, F. A. Smith, E. Wenis and J. Lee, *J. Am. Chem. Soc.*, 1952, **74**, 2106; (*b*) F. H. H. Carlsson, A. I. Charlson and E. C. Watton, *Carbohydr. Res.*, 1974, **36**, 359.
3 (*a*) A. A. Potekhin and S. L. Zhdanov, *Zh. Org. Khim.*, 1979, **15**, 1384 [*J. Org. Chem. USSR (Engl. Transl.)*, 1979, **15**, 1237]; (*b*) L. Szilagyi, Z. Gyordydeak and H. Duddeck, *Carbohydr. Res.*, 1986, **158**, 67.
4 K. N. Zelenin, V. V. Alekseyev, T. Ye. Gabis, S. I. Yakimovitch and T. J. Pehk, *Tetrahedron Lett*, 1990, **31**, 3927.
5 J. R. Holker, *Chem. Ind.*, 1964, **13**, 546.
6 K. N. Zelenin, O. V. Solod, V. V. Alekseyev and T. J. Pehk, *Khim. Geterotsikl. Soedin*, 1990, 1260 [*Chem. Heterocycl. Compds. (Engl. Transl.)*, 1990, 1051].
7 P. B. Terent'ev, *Mass-spektrometriya v organicheskoi khimii (Mass spectrometry in organic chemistry)*, Vysshaya Shkola, Moscow, 1979, p. 137–147 (in Russian).

Received: Moscow, 1st February 1993
Cambridge, 2nd March 1993; Com. 3/00806A