1,4:3,6-DIANHYDROHEXITES

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Abstract. It is known that derivatives of isosorbide and isomannide can impart a sweet taste, for example, dimethyl ether of isosorbide is used as an ingredient in the production of chewing gums, hard sweets [1], isosorbide dipropanoate is widely used in the production of bakery products [1]. Mixed isohexite esters and esters (especially isosorbide) are used as flavor enhancers. Currently, isosorbide is proposed to be used as a component of the mixture used for the water-base ink pigment. This component has excellent dispersion stability, which is necessary for printing [1]. All production methods leading to isohexites use the corresponding hexitol as the starting material. To obtain isohexites with a quantitative yield, and in order to avoid adverse reactions, a number of techniques have been developed. The rate of the dehydration sequence in reactions using as the starting compound: 1,4-anhydro derivatives of D-iditol, D-gulitol, D-glucitol, and D-mannitol (from which 1,4:3,6-dianhydro compounds of isoidide (5) and isomannide (4) are obtained) depends on the location of the hydroxyl group (with5 endo as in D-mannitol and D-glucitol, or exo as in D-iditol and D-glucitol). All three isohexites (3-5) were studied by mass spectrometry, especially D-isomannide and their O-deuterated isomers, and 5-nitroisosorbide [1]. The isomannide cation formed as a result of dehydration reactions was also detected in the mass spectra of some isomannide derivatives [1]. Mass spectrometric analysis is used to determine isosorbide and its 5-nitro derivative in human urine and blood plasma.

1 Introduction

1,4:3,6-dianhydro-D-mannitol (isomannide) as the first representative of dianhydrohexites [1, 2] was described by Faconner in 1884. The first report on the synthesis of crystalline dianhydro-D-sorbitol (3) was made by Harden in 1940 [3]. Then there was a flood of experimental work described in the chemical literature during the 1940s and 1950s, when intensive research was carried out on all possible isomers of 1,4:3,6-dianhydrohexites: 1,4:3,6-dianhydro-D-sorbitol (3), 1,4:3,6-dianhydro-D-mannitol (4) and 1,4:3,6-dianhydro-D-idite (5). The structural properties of these compounds were established and numerous derivatives were synthesized [3]. Later, interest in these compounds decreased, but an increase in the number of articles in subsequent years showed that considerable attention was again directed to this special class of compounds.

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This is followed by a period of intensive study of the chemical features of all possible isomers of 1,4:3,6-dianhydrohexites. These connections are a system formed by two rigidly condensed anhydrocycles having a common rib at positions 1,4 and 3,6, and located relative to each other at an angle of 110 °. A characteristic structural feature of these compounds is the presence of an internal chiral cavity and two hydroxyl groups that differ in mutual orientation.

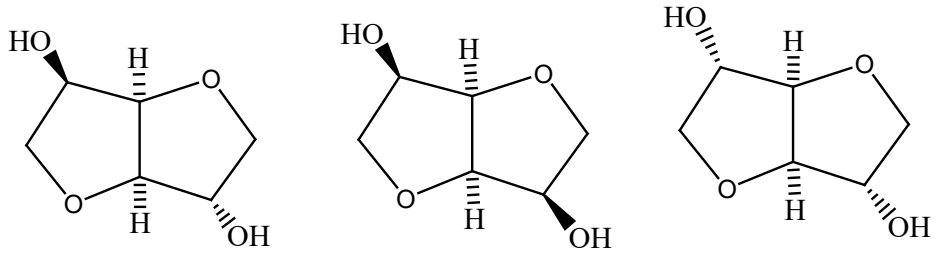

Fig.1. 1,4:3,6-dianhydro-D-hexites

The most widely used names in this class of compounds are based on the nomenclature of sugars, which reflects their properties as polyhydrogenated alcohols. The numbering of the ring system in this case remains the same as that of the related sugar.

It should be noted that in D-glucose (1) (as a starting material obtained from starch), carbon atoms from 2 to 6 retain their numbering during hydrogenation into D-glucitol (sorbitol, 2). Then, by dehydrotation of compound (2), 1,4:3,6-dianhydro-D-glucitol is obtained (3). The trivial name for the compound (2) is sorbitol. Compound (3) is usually (although incorrectly) called 1,4:3,6- dianhydrosorbitol. The same numbering applies to other diastereomeric 1,4:3,6-dianhydrohexitols obtained from D-mannose (D-mannitol) and from L-fructose (L-iditol); their names are 1,4:3,6-dianhydro-D-mannitol (4) and 1,4:3,6-dianhydro-L-iditol (5).

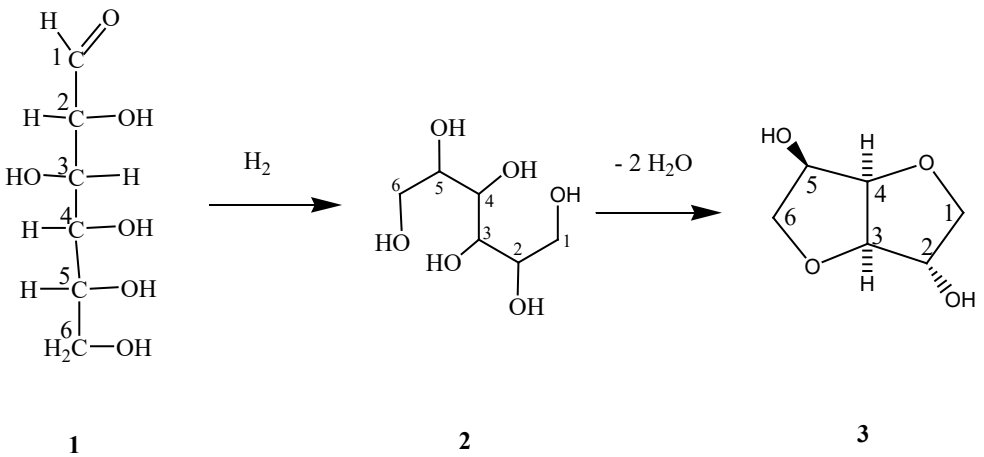

Fig. 2. Synthesis scheme of 1,4:3,6-dianhydro-D-sorbitol

In addition, compounds 3, 4, and 5 are usually assigned trivial names: "isosorbide" (3), "isomannide" (4), and "isoide" (5), respectively.

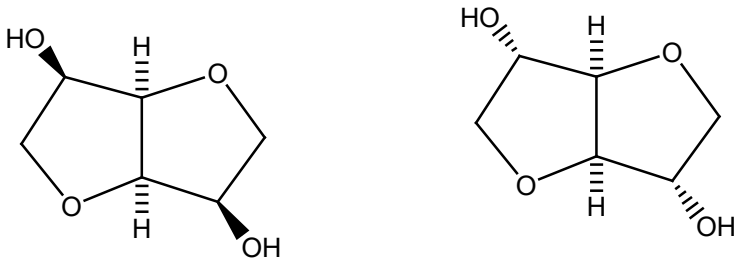

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Fig. 3. 1,4:3,6-dianhydro-D-mannitol and 1,4:3,6-dianhydro-D-idite

1.1 Dianhydrohexites as bridge systems

Since 1,4:3,6-dianhydrohexites are bicyclic systems, it is possible to use not only the nomenclature of sugars, but also a systematic nomenclature for them. The numbering of atoms differs from that used in names formed from sugar derivatives. Moreover, the stereochemistry for each anomeric center is specially designated. The compounds under discussion have a 2,6-dioxabicyclo backbone [3.3.0] octane and include hydroxyl groups at positions C-4 and C-8, (formula 6).

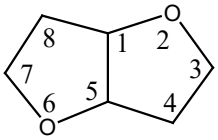

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Fig. 4. 2,6-dioxabicyclo [3.3.0] octane

According to this system, diols 3, 4, and 5, respectively, are called
(1R, 4R, 5R, 8S)-2,6-dioxabicyclo [3.3.0] octane-4,8-diol (3),
(1R, 4R, 5R, 8R)-2,6-dioxabicyclo [3.3.0] octane-4,8-diol (4),
(1R, 4R, 5R, 8S)-2,6-dioxabicyclo [3.3.0] octane-4,8-diol (5).

2 Materials and methods

2.1 Obtaining 1,4:3,6-dianhydro-D-sorbitol

Of the known isohexites, isosorbide is of the greatest importance, since its dinitro derivative has found wide pharmaceutical use, and the dimethyl ether of isosorbide has good solvent properties. All production methods leading to isohexites use the corresponding hexitol as the starting material. For example, D-glucitol, D-galactol, D-gulitol, D-mannitol, D-talitol, D-allitol, or D-iditol, or their characteristic enantiomers are used to produce dianhydrohexites [1, 3]. Protonation is preferably performed by the primary hydroxyl group. The first stage of dehydration can also take place between the 3- and 6-positions. This is followed by the second stage of water cleavage from both 1,4- and 3,6-, anhydro-D-glucitol, which leads to the formation of D-isosorbide.To obtain isohexites with a quantitative yield, and in order to avoid adverse reactions, a number of techniques have been developed (see works [1-5]). The rate of the dehydration sequence in reactions using as the starting compound: 1,4-anhydro derivatives of D-iditol, D-gulitol, D-glucitol, and D-mannitol (from which 1,4:3,6-dianhydro

compounds of isoidide (5) and isomannide (4) are obtained) depends on the location of the hydroxyl group (with5 endo as in D-mannitol and D-glucitol, or exo as in D-iditol and D-glucitol).

Thus, the formation of 1,4:3,6-dianhydrohexitols obtained from 1,4-anhydro derivatives of D-iditol and D-gulitol occurs approximately 40 times faster than from D-glucitol and D-mannitol [1]. A more detailed consideration of the stereochemical pathway of the dehydration reaction is presented in [1].

3 Results and discussion

3.1 Tosylated derivatives of 1,4:3,6-dianhydro-D-sorbitol

The comparative reactivity of hydroxyl groups in carbohydrate derivatives was discussed in the review [1]. Among isohexites, isosorbide (3) has two hydroxyl groups with different directions, that is, the OH-2 group occupies exo-, and the OH-5 group occupies endo-positions relative to the bicyclic ring system. Many attempts have been made to control the regioselectivity of reactions involving these groups. In isosorbide (3), the intramolecular bond between the endohydroxyl group at C-5 and the oxygen atom located inside the ring between C-1 and C-4 was confirmed by spectroscopy. The hydrogen bond increases the nucleophilic properties and also the reactivity of the OH-5 group with respect to the exo-hydroxyl group at C-2. In [6] it was shown that the interaction of 1,4:3,6-dianhydro-D-sorbitol (3) with an equimolecular amount of tosyl chloride in pyridine gives a mixture of the following products: 2,5-ditosyl derivative – 17% (9), 2-mono – 12% (7) and 5-mono - 45% (8).

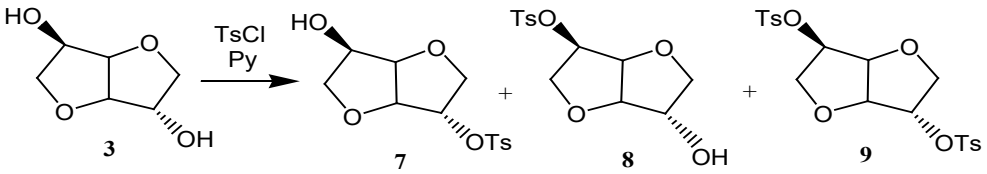

Fig. 5. Scheme of synthesis of tosylated derivatives 1,4:3,6-dianhydro-D-sorbitol

It is also necessary to mention the works of the authors of [5-8], where a similar reaction of 1,4:3,6- dianhydro-D-sorbitol (3) was carried out with an equimolecular amount of p-phenylazobenzoyl chloride in pyridine, which led to a mixture of products containing: 2,5-di derivative – 9%, 2- mono – 12%, 5- mono – 36%.

4 Conclusion

Thus, anhydrohexite derivatives have found wide application in medicine and pharmacology. Thus, a large number of publications [1] are devoted to various aspects of drugs based on dinitroisosorbide and 5-mononitroisosorbide, which have high cardio-vascular activity. In recent decades, attempts have been made to chemically modify them, in order to change the polarity and lipophilicity, by introducing additional substituents into 5-mononitroisosorbide, which would change the biological activity and make it possible to obtain substances with a wider spectrum of action. New potential pacemakers were obtained from mono- and dinitroisohexides, when replacing hydroxo- or nitro groups with purine bases [1]. One compound in this series has passed clinical trials and is known as (INN) as a medicinal product "Theopranitol". "Sornidipine" (INN) is one of the derivatives of another series of

medicinal substances, which has also passed clinical trials [1]. In addition to the fields of medicine mentioned above, isohexide derivatives are also used in the treatment of angina, and for other inflammatory processes.

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