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MONODEOXY-1,4:3,6-DIANHYDROHEXITOL NITRATES

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Abstract: Monodeoxy-1,4:3,6-dianhydrohexitol nitrates with (**5**) or without (**6**) an additional chloro substituent were synthesized , starting from 1,4:3,6-dianhydrohexitol-monoacetates, via **3** as key intermediates. Attempts to generate an unsaturated nitrate ester resulted in a DBN alkylation product (**9**).

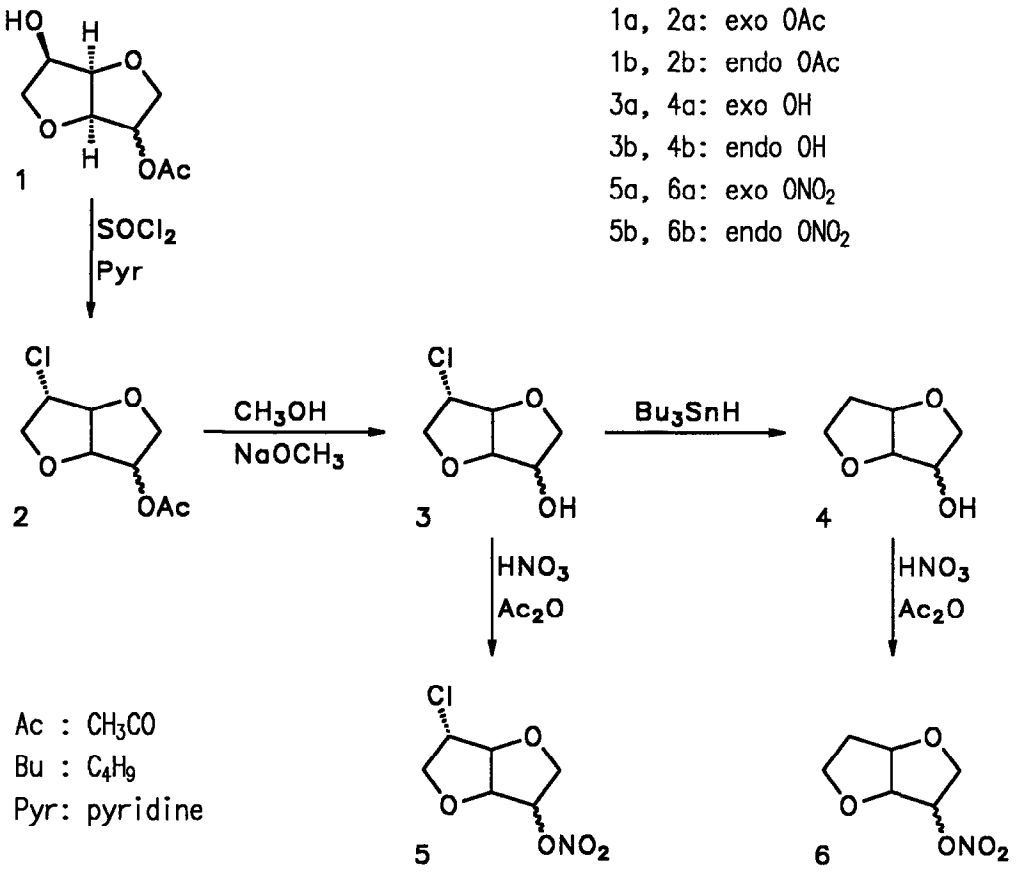
Several attempts have been undertaken to improve or modify the pharmaceutical properties of the well established cardiovascular drug isosorbide-2,5-dinitrate. The only successful example on the market so far is one of its metabolites, isosorbide-5-mononitrate. This compound was selected for therapeutic use because of favourable pharmacokinetic properties (e. g. Mono Mack [R]).

Amongst the few known derivatives of monodeoxy-1,4:3,6-dianhydrohexitol nitrates previously prepared as potential drugs, one of the hydroxyl groups has always been replaced by other functional groups, such as purines [2], purine-alkylamines [3], amines [4], and piperazines [5]. Several different aromatic and heterocyclic benzyl ether derivatives of monodeoxy-1,4:3,6-dianhydrohexitols have been claimed as herbicides [6]. The synthesis of three interesting dideoxy-1,4:3,6-dianhydro-D-mannitol compounds, namely 4,8-dinitro-, 4,4,8-trinitro-, and 4,4,8,8-tetranitro-2,6-dioxabicyclo[3.3.0]octane, represents the first derivatives of this ring system with a C-nitro group [7]. However there was no indication of the pharmacological behavior of these explosives.

In continuation of our investigations with different derivatives of organic nitrates [8, 9] , we have started the synthesis of monodeoxy-1,4:3,6-dianhydrohexitol nitrates. Whilst retaining the main structural features of the parent isohexide-mononitrates, these compounds are characterized by the lack of an additional OH-group. It was thought that their reduced polarity and enhanced lipophilicity could contribute further to the elucidation of structure-activity relationship.

Starting from suitable 1,4:3,6-dianhydrohexitol-derivatives, reductive dehalogenation was considered to be the method of choice for the preparation of the target molecules. Due to low yields in direct chlorination of 1,4:3,6-dianhydro-D-glucitol to form 2-chloro-2-deoxy-1,4:3,6-dianhydro-L-iditol [10], we suggested that chlorination of a mono-protected derivative would be a superior method. In fact, chlorination of isosorbide-2-acetate **1a** [11] and isomannide-2-acetate **1b** [12] by thionyl chloride and catalytic ammounts of pyridine afforded the acetylated exo-chloro compounds **2a** and **2b** [13].

These were deprotected by conventional transesterification, using sodium methoxide in methanol, to yield products **3a** and **3b** respectively. The halogen remains unaffected during this procedure. This two step reaction afforded the exo-chloro deoxy compunds via complete inversion of the starting endo-hydroxyl group, in excellent yields.



Scheme 1

3a and **3b** have been known for a long time, although the originally assigned structures [10, 14] were later revised [15], and confirmed by an independent synthesis [12]. **3a** appears as a well crystallized material, which facilitates purification. The liquid **3b** can be distilled unchanged in vacuo or purified via flash chromatography [16].

Attempts to split off the chlorine by hydrogenation over palladium / charcoal in ethanol with or without base, with zinc in acetic acid, or with lithium aluminum hydride proceeded only with low yields in our hands. Satisfactory results were then obtained by application of tributyltin hydride [17]. Surprisingly, the resultant monodeoxy-1,4:3,6-dianhydrohexitols **4** have not yet been described in the literature [18]. They can be converted to the target molecules **6** by a routine operation, using nitric acid / acetic anhydride for nitrate ester formation [19] (see Scheme 1).

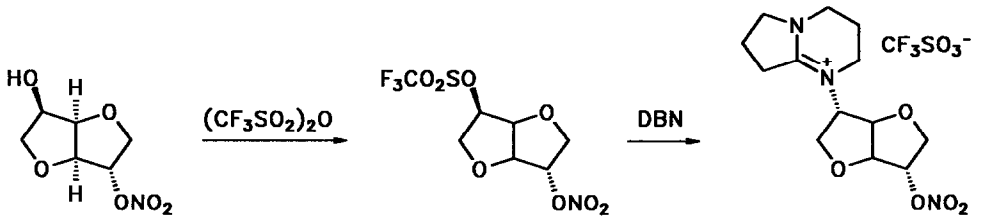
Both anomers of **6** were isolated as slightly yellowish liquids, which were purified via flash chromatography. Following this treatment the endo-nitrate **6b** solidified to yellowish crystals, the exo derivative **6a** remained oily [20]. By an analoguous procedure, both chloro intermediates **3a** and **3b** were transformed into the appropriate nitrate esters **5a** and **5b** [21].

In extension of these results, the preparation of unsaturated nitrate esters, containing the chiral cis-2,6-dioxabicyclo[3.3.0]octane framework, offered another interesting challenge. Due to altered physicochemical parameters and probable different metabolic behaviour, modified pharmacological effects could be expected from such target molecules. To date, only a very limited number of deoxy-1,4:3,6-dianhydrohexitols with a ring-double bond are known. They include chloro- [22], dimethylamino- [15], benzyl- [23], azido- [24] substituted compounds as well as the unsubstituted bis-olefine [25].

In our hands, several attempts to generate a double bond by splitting off halogens, tosylates or mesylates from appropriately substituted 1,4:3,6-dianhydrohexitols failed. Either the compounds remain unaffected, or ring fission occurred. Even sterically hindered amidine bases, such as 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), which have proven to be useful reagents for elimination [26], gave disappointing results.

However, 5-trifluoromethanesulfonyl-isosorbide-2-nitrate (**8**) [27] (which is easily available from **7** [28] and trifluoromethanesulfonic acid anhydride) when treated with DBN resulted in a nucleophilic displacement instead of the anticipated elimination. The resulting N-substituted cyclic amidinium salt **9** comprises an exo-configurated amine bond (see Scheme 2). This is in accordance with manifold observations on this ring system, whereby endo-leaving groups are more easily replaced by exo-substituents via Walden-inversion than in the opposite case [24, 29, 30]. As a consequence, the appropriate isosorbide-5-nitrate derivative with a 2-exo-trifluoromethanesulfonyl group was not prone to an analogous reaction.

9 appeared as a well crystallized material, which was fully characterized by analytical and spectroscopical data [31]. To our knowledge **9** represents the first example of a carbohydrate-derived DBN alkylation product. Experiments to perform an analogue reaction with DBU have proved unsuccessful so far. The reason for this favoured substitution over double bond formation, which is in contrast to other observations from carbohydrates [32], has to be investigated further.



7 8 9

Scheme 2

Preliminary pharmacological investigations demonstrate compounds **5** and **6** to be less active than isosorbide-5- and 2-mononitrate or ISDN (see Table). This result gives further evidence for the observation that the aforementioned nitrates seem to represent the optimum therapeutic compounds. All kinds of derivatives tested by us so far showed decreased or total loss of vasodilating activity.

Table: Pharmacological results

Compound	guinea pig heart Langendorff [a] ED_{50} mol/liter	T-wave increase of rat EKG [b] dose mg/kg	reduction after 30 min	arterial medium pressure of rabbits [c] ED_{30} mg/kg
ISDN	not measured	4	-75 +/- 1%*** [d]	0.08
IS-2-N	1.7×10^{-3}	8	-59 +/- 3%***	0.31
IS-5-N	3.6×10^{-3}	60	-43 +/- 2%***	3.43
5a	2.7×10^{-4}	200	-38 +/- 6%**	0.1
5b	1.15×10^{-3}	100	no effect	0.14
6a	2.6×10^{-4}	200	-38 +/- 3%***	0.60
6b	1.8×10^{-4}	200	-33 +/- 7%*	1.00

significance: *$p<0.05$; **$p<0.01$; ***$p<0.001$

a) E. Langendorff, Pflügers Arch. ges. Physiol. **1895**, 61, 291.

b) M. Leitold, S. Hader, Arzneim.-Forsch./Drug Res. **1986**, 36, 1454.

c) J. Litchfield, C. Wilcoxon, J. Pharmacol. Exp. Ther. **1946**, 96, 99. (ED_{30} for reduction of arterial medium pressure by 30 mm Hg).

d) after 10 min.

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13. **2a**: 2-chloro-2-deoxy-1,4:3,6-dianhydro-L-iditol-5-acetate; yield: 96.5 %; colourless oil; b. p. 135°/1.3 kPa; $[\alpha]_D^{20}$ + 79.5° (c = 1, MeOH), [Lit. [12]: + 99.0° (c = 1, $CHCl_3$)].
2b: 2-chloro-2-deoxy-1,4:3,6-dianhydro-D-glucitol-5-acetate; yield: 75.4 %; colourless oil (silicagel flash-chromatography/$CHCl_3$-EtOAc); $[\alpha]_D^{20}$ + 131.5° (c = 1, MeOH), [Lit. [12]: + 117° (c = 1.2, $CHCl_3$)].
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16. **3a**: 2-chloro-2-deoxy-1,4:3,6-dianhydro-L-iditol; yield: 95.2 %; m. p. 68-69° (Et_2O), [Lit.[12]: 64.6-65.5°]; b. p. 88°/13 Pa; $[\alpha]_D^{20}$ + 60.0° (c = 1, MeOH), [Lit.[12]: + 52° (c = 0.5, $CHCl_3$)].
3b: 2-chloro-2-deoxy-1,4:3,6-dianhydro-D-glucitol; yield: 93.9 %; colourless oil (silicagel flash-chromatography/EtOAc); $[\alpha]_D^{20}$ + 82.0° (c = 1, MeOH), [Lit.[12]: + 52° (c = 1, $CHCl_3$)].
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18. For all new compounds ^{1}H-NMR, MS and IR-spectra are consistent with the assigned structures, and satisfactory combustion analysis were obtained.

4a: 5-deoxy-1,4:3,6-dianhydro-D-glucitol; yield: 78.5 %; colourless oil (silicagel flash-chromatography/$CHCl_3$-EtOAc); $[\alpha]_D^{20}$ + 19.5° (c = 1, MeOH).
4b: 2-deoxy-1,4:3,6-dianhydro-D-glucitol; yield: 91.7 %; colourless oil (silicagel flash-chromatography/$CHCl_3$-EtOAc); $[\alpha]_D^{20}$ + 53.5° (c = 1, MeOH).

19. Although compounds **4** and **6** are still derivatives of polyhydric alcohols, the loss of one of the chiral centers of their precursors makes sugar derived names unequivocal. Thus a distinction between L-iditol, D-glucitol and D-mannitol configuration is no longer suggestive. Only for reason of uniformity this nomenclature has been retained here. These compounds would preferrably be refered to as 4-hydroxy-2,6-dioxabicyclo[3.3.0]octanes, together with the appropriate stereochemical prefixes for the anomeric centers (**4a**: 1R, 4R, 5R; **4b**: 1R, 4S, 5R).
20. **6a**: 5-deoxy-1,4:3,6-dianhydro-D-glucitol-2-nitrate; yield: 90.4 %; colourless oil (silicagel flash-chromatography/$CHCl_3$-EtOAc); $[\alpha]_D^{20}$ + 56.0° (c = 1, MeOH).
6b: 2-deoxy-1,4:3,6-dianhydro-D-glucitol-5-nitrate; yield: 88.2 %; m. p. 30°; (silicagel flash-chromatography/$CHCl_3$-EtOAc); $[\alpha]_D^{20}$ + 200.0° (c = 1, MeOH).
21. **5a**: 2-chloro-2-deoxy-1,4:3,6-dianhydro-L-iditol-5-nitrate; yield: 93.1 %; m. p. 34-35° (Et_2O-pentane); $[\alpha]_D^{20}$ + 56.0° (c = 1, MeOH).
5b: 2-chloro-2-deoxy-1,4:3,6-dianhydro-D-glucitol-5-nitrate; yield: 93.5 %; m. p. 38° (Et_2O-pentane); $[\alpha]_D^{20}$ + 166.5° (c = 1, MeOH).
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27. **8**: yellowish solid, m. p. 62-63° (purified via flash chromatography, silicagel, $CHCl_3$/EtOAc), yield: 97 %, $[\alpha]_D^{20}$ + 84.7° (c = 1, $CHCl_3$).
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31. **9**: 1-(8-nitrooxy-cis-2,6-dioxabicyclo[3.3.0]oct-4-yl)-1,5-diazabicyclo[4.3.0]non-5-ene trifluoromethanesulfonate; $C_{14}H_{20}F_3N_3O_8S$ (447.38); calc.: C 37.58, H 4.51, F 12.74, N 9.39, S 7.16; found: C 37.36, H 4.53, F 13.0, N 9.57, S 7.39; yield: 82.7 %; colourless solid, m. p. 160.5° (purified via MPLC, silicagel, MeOH/$CHCl_3$); $[\alpha]_D^{20}$ + 40.5° (c = 1, MeOH).
32. As an example see: Flechtner, T. W., *Carbohydr. Res.* **1979**, 77, 262-266.