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SYNTHESIS OF NEW DIESTERS OF 1,4:3,6-DIANHYDRO-D-GLUCITOL BY ESTERIFICATION WITH FATTY ACID CHLORIDES

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Abstract

A new series of esters was prepared by esterification of 1,4:3,6-dianhydro-D-glucitol with long chain fatty acid chlorides. The experimental conditions prevented thermal degradation of the sugar and led to diesters with a high degree of purity. The final products were readily isolated and characterized by IR and NMR. Molecular modelling confirmed that the exo and endo configurations of the o-alkyl groups of the diesters of isosorbide were retained. This work reports a novel synthesis of diesters of natural origin which shows promise in environmentally sensitive applications, such as phytosanitory adjuvants, requiring biodegradable materials as replacements for fossil-derived products.
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Key words: isosorbide, long-chain fatty acids, esterification, anhydro sugar, carbohydrate esters, molecular modelling.

INTRODUCTION

We describe here the synthesis of new carbohydrate esters with oleic and stearic long chain fatty acids. The sugar is a natural product derived from biomass: 1,4:3,6-dianhydro-D-glucitol, referred to as 'isosorbide'. Isosorbide is an important by-product of the starch industry and obtained by dehydration of D-sorbitol. It is a chiral heterocyclic molecule bearing two secondary alcohol groups (one in the *endo* position and the other in the *exo* position) with different reactivities (Jacquet, 1983; Fleche and Huchette, 1986). Isosorbide is non-toxic and has applications in the pharmaceutical industry. For example, the 2- and 5-mononitrates are excellent vasodilators (Fleche and Huchette, 1986; Jett et al., 1978; Krantz et al., 1939; Stoss, 1981a,b) employed in the treatment of angina pecto (Danahy et al., 1979; Kato et al., 1979).

The precursors of these nitrate derivatives are generally the corresponding 5- and 2-monoacyl esters, prepared by acylation or esterification with reagents containing short-chain alkyl residues (Stoss et al., 1987; Cekovic and Tokic, 1987; Seemayer et al., 1992; Le Lem et al., 1988; Abenhaim et al., 1994). The regioselectivity depends on the synthetic method employed. Although the 2-hydroxyl group in the *exo* position is readily esterified by a carboxylic acid under normal conditions, the 5-hydroxyl group in the endo position can only be acylated using an acid chloride (Le Lem et al., 1988).

The present experiments were designed to prepare diesters of isosorbide from long-chain fatty acids such as oleic and stearic acid.

METHODS

Materials

Isosorbide was purified by recrystallisation from ethyl acetate and was then dried at 40°C for 12 h. DMF and pyridine were dried over zeolites. Fatty acid chlorides were used as received (purity 96–98%). Solvents and chemical reagents were supplied by Aldrich company (France).

Synthesis

1,4:3,6-dianhydro-D-glucitol (Table 1) (0.01 mol) and the acyl chlorides (**2a–b**) (0.02 mol) were dissolved in pyridine (10 ml) and DMF (15 ml). The solution was heated for 4 h at 45°C with stirring. Ethanol (30 ml) was added to the mixture, transforming any

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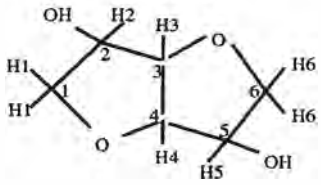
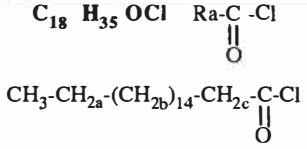
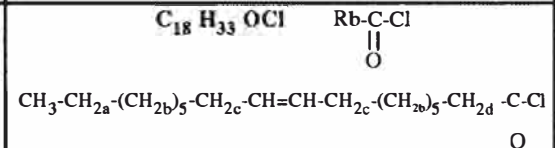
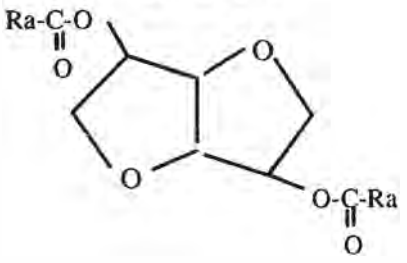
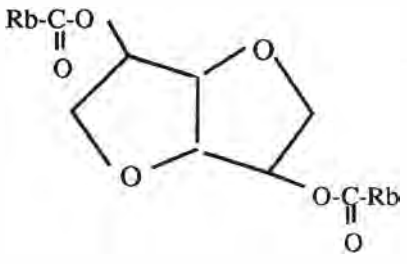
excess acyl chloride into the ethyl ester which was soluble in this solvent.

Purification

The isosorbide distearate (**3a**) precipitated as a white solid. The mixture was filtered and the solid was washed with ethanol and dried for 48 h at 60°C.

The isosorbide dioleate (**3b**) was formed as a yellow oil which was soluble in diethyl ether. Water was added to solubilize excess isosorbide, and the oleic ester was extracted by liquid–liquid extraction. The organic phase was dried over anhydrous $MgSO_4$ and evaporated under reduced pressure to give the crude ester.

Table 1. Spectral Data of isosorbide 1 and isosorbide diesters (3a) and (3b)

Product	Molecular Formula	IR (KBr) γ (cm^{-1})	^{1}H - NMR (200 MHz, $CDCl_3$/TMS) δ (ppm)
Isosorbide **1**	$C_6H_{10}O_4$ 	3400, 2951, 2877, 1747, 1651, 1417, 1361, 1277, 1202, 1124, 1079	**3,0 (s, 2 OH)** ; 3,5 (m, 1H, H_6) ; 3,8 - 4,0 (m, 3 H, H_1, H_2, H_6) ; **4,2 - 4,4 (m, 3H, H_3, H_2, H_5)** ; 4,6 (t, 1H, H_4)
Stearoyl chloride **2 a**	$C_{18}H_{35}OCl$ 	2921, 2845, 1801, 1466, 1404, 952, 720, 680	0,9 (m, 3H, CH_3) ; 1,3 (s, 28H, 14 (CH_{2b})) ; 1,7 (q, 2H, CH_{2a}) ; **2,9 (t, 2H, CH_{2c})**
oleoyl chloride **2 b**	$C_{18}H_{33}OCl$ 	2925, 2854, 1800, 1464, 1404, 966, 723, 680, 567	0,9 (t, 3H, CH_3) ; 1,3 (s, 20H, 10 $(CH_2)_b$) ; 1,7 (q, 2H, CH_{2a}) ; 2,0 (t, 4H, CH_{2c}) ; **2,9 (t, 2H, CH_{2d})** ; 5,4 (m, 2H, CH=CH)
Isorbide distearate **3 a**	$C_{42}H_{78}O_6$ (1)  Yield (3) : 48%	2919, 2849, **1731**, 1468, 1168, 1093, 887, 664, 721	0,9 (t, 3H, CH_3) ; 1,3 (s, 28H, 14 (CH_{2b})) ; 1,6 (q, 2H, CH_{2a}) ; **2,2-2,4(2t,2H, CH_{2c})** ; 3,8 - 4,0 (m,4H, H_1,H_1,H_6,H_6) ; 4,5 (d,1H , H_3) ; 4,8 (t,1H, H_4) ; **5,1 (m, 2H, H_2, H_5)**
Isosorbide dioleate **3 b**	$C_{42}H_{74}O_6$ (2)  Yield (3): 74%	2924, 2853, **1743**, 1464,1378,1239, 1167, 1096, 977, 723	0,9 (t, 3H, CH_3) ; 1,3 (s, 20H, 10 $(CH_2)_b$) ; 1,6 (q, 2H, CH_{2a}) ; 2,0 (t, 4H, $2CH_{2c}$) ; **2,2 - 2,4(2t,2H, CH_{2d})** ; 3,8 - 4,0 (m,4H, H_1,H_1,H_6,H_6) ; 4,5 (d,1H , H_3) ; 4,8 (t,1H, H_4) ; **5,1 (m, 2H, H_2, H_5)** ; 5,4 (m , 2H, CH = CH)

(1) Satisfactory microanalyses: C:-0.4; H:+0.2 melting point: 68°C: measured with a Mettler Toledo FP 62 apparatus

(2) Satisfactory microanalyses: C:-0.3; H:+0.2

(3) Mass yield determined after purification

Characterization

Infra-red analysis

The infra-red spectra were recorded on a PERKIN ELMER 1600 FTIR analyser using Kbr pellets and discs.

NMR analysis

The NMR spectra were recorded at 200 MHz on a BRUKER AC 200 spectrometer in deuterated chloroform. The surface areas corresponding to one proton could be obtained by integration of the signals of isosorbide and fatty acid chains. The ratio of these areas gave the degree of substitution of isosorbide.

GC analysis

GC analyses were performed on a HEWLETT PACKARD 5890 chromatograph with flame ionization and a Capillary Column of Carbowax 50 m. Samples were prepared with 10 μl of isosorbide dioleate diluted with 990 μl of hexane.

Elemental analysis

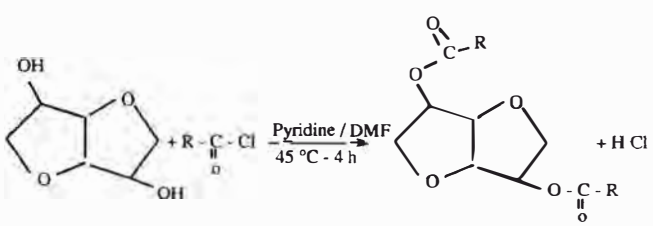
The microanalyses were carried out using a CARLO ERBA Elemental Analyser 1106.

Molecular modelling

Molecular modelling was performed on a SILICON GRAPHIC Computer with the modules Insight and Discover from BIOSYM/molecular Simulations: version 2.97. The program researches the minimization of the total energy of the molecule.

RESULTS AND DISCUSSION

Preliminary experiments on the direct esterification of isosorbide (**1**) with fatty acids under conventional conditions did not produce satisfactory results due to degradation of the sugar even with relatively mild heating. We were thus prompted to use fatty acid chlorides (**2a–b**), which are much more reactive than the fatty acids themselves, enabling the reaction to be carried out at a lower temperature. The reaction conditions are indicated in the following reaction scheme:



1 **2a** R = $C_{17}H_{35}$ **3a** R = $C_{17}H_{35}$

2b R = $C_{17}H_{33}$ **3b** R = $C_{17}H_{33}$

1,4:3,6-dianhydro-D-glucitol (**1**) was readily esterified with the acid chlorides (**2a–b**) at 45°C in the presence of a mixture of pyridine and dimethylformamide (DMF), giving rise to the corresponding diesters (**3a–b**).

The reactions between 1,4:3,6-dianhydro, D-glucitol (**1**) and the acid chlorides (**2a–b**) were carried out with excess acid chloride to displace the equilibrium towards formation of the ester. Acylation was carried out in a mixture of DMF and pyridine: the polar DMF activates the hydroxyl groups of isosorbide and the acyl groups of the acid chlorides, while pyridine traps the hydrochloric acid formed during the esterification. In the DMF/pyridine solvent mixture, isosorbide was readily acylated by acid chlorides without requirement of catalyst.

Experimentally, pyridine also acts as solvent, while DMF prevents formation of crystals and solidification of the medium on contact with the acid chloride and pyridine (Thiebaud, 1995). In this reaction medium, isosorbide distearate (**3a**) precipitated spontaneously as a white solid, which greatly facilitated purification. Isosorbide dioleate (**3b**) was produced in the form of an oil due to the presence of a double bond in the hydrocarbon chain.

The course of the reaction was readily monitored by IR spectroscopic analysis of the products (**3a**) and (**3b**), which exhibited the characteristic bands of ester carbonyl stretching between 1730 and 1740 cm^{-1} (Table 1).

The results of the NMR analysis reported in Table 1 confirmed the production of diesters: The NMR spectra of the two compounds (**3a**) and (**3b**) showed the disappearance of the hydroxyl signals of isosorbide at 3.0 ppm, and 1 ppm downfield shift of the protons H_2 and H_5 on carbons C_2 and C_5 of the sugar which has undergone esterification. In addition, there was a marked change in the (CH_2) signal along with that of the ester groups of the long

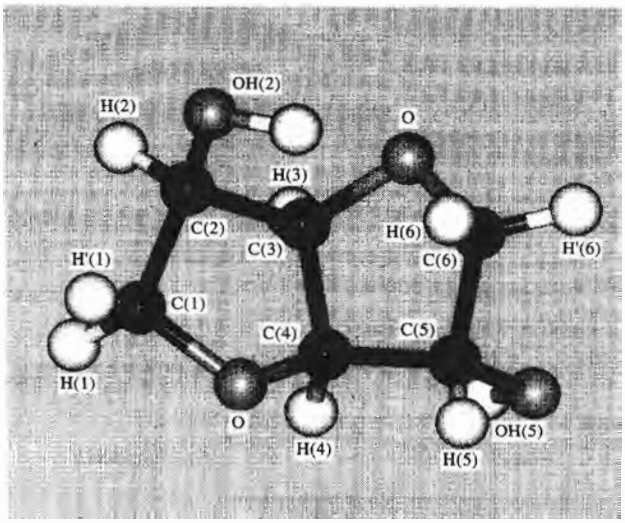


Figure 1. Representation of the molecule of isosorbide (**1**). Note exo configuration of the hydroxyl group at position 2 and endo configuration of the hydroxyl group at position 5.

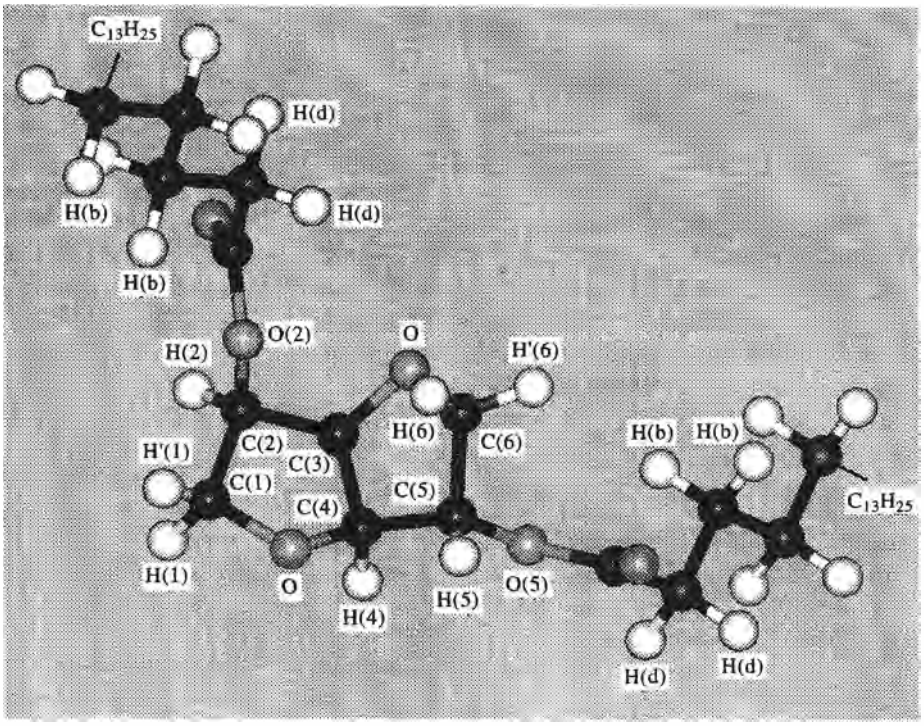


Figure 2. Conservation of exo and endo configurations of *o*-alkyl groups of diesters of isosorbide after acylation.

hydrocarbon chain, which coupled with the neighboring CH_2 exhibited a split triplet due to the *exo* and *endo* conformation of the esterification sites. Integration of these NMR spectra indicated a degree of substitution of two, corresponding to two long acyl chains for each molecule of isosorbide.

Disubstitution of compounds (**3a**) and (**3b**) was supported by elemental analysis (Table 1) and also by GC analysis of isosorbide dioleate (**3b**) which gave rise to a single peak corresponding to the diester.

These results were subjected to molecular modelling: Figures 1 and 2 represent isosorbide (**1**) and the lowest energy configurations (59.19 kcal) of (**3b**) retaining an angle of 120° between the two rings of isosorbide, and the *exo* configurations at C_2 and *endo* at C_5 of the *o*-alkyl moieties of the esters formed which present a long hydrocarbon chain at the back and the other hydrocarbon chain in front. The molecular model of (**3a**) is not shown as it was identical to that of (**3b**).

In conclusion we effected a total disubstitution of 1,4:3,6-dianhydro-D-glucitol with long chain fatty acid chlorides (C_{18} mono-unsaturated and saturated). Under these reaction conditions, the diesters were readily isolated and purified: isosorbide distearate as a solid and isosorbide dioleate as a liquid. IR, NMR spectroscopy, GC and elemental microanalysis as well as molecular modelling demonstrated conservation of the initial stereochemistry of isosorbide on esterificaiton of the hydroxyl groups in the *exo* and *endo* positions.

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