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SYNTHESIS OF INULIN AND STARCH DERIVATIVES WITH A 2,6-DIISOBORNYL-4-METHYLPHENOL (DIBORNOL^{TM}) FRAGMENT

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Water-soluble polysaccharide derivatives containing covalently bound 2,6-diisobornyl-4-methylphenol (dibornol^{TM}) were synthesized by a Williams reaction of inulin and starch with 2,6-diisobornyl-4-bromomethylphenol. The conversion of 2,6-diisobornyl-4-bromomethylphenol was 85–95%.

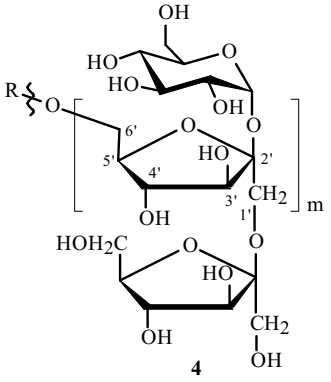
Keywords: terpenophenols, inulin, starch, transport polymers.

Conjugation of various low-molecular-weight physiologically active antioxidants to polymers is successful in creating drugs because of advantages such as timed release, targeted delivery, reduced toxicity, and the ability to produce water-soluble forms for transporting hydrophobic low-molecular-weight compounds [1–3]. The most promising direction is the use of highly biocompatible plant polysaccharides.

The choice of inulin (**2**) and starch (**3**) to transport a terpenophenol is justified by their availability, degradability as the result of biochemical transformations into harmless assimilated sugars, and lack of extraneous protein contamination.

We used 2,6-diisobornyl-4-bromomethylphenol (**1**) as the synthon for synthesizing conjugates of inulin and starch with a 2,6-diisobornyl-4-methylphenol fragment.

Ethers were formed via a Williamson reaction in the presence of NaOH or Na_2CO_3 in DMSO solution. The synthesized inulin (**4**) and starch (**5**) derivatives were slightly colored hydrophilic compounds.



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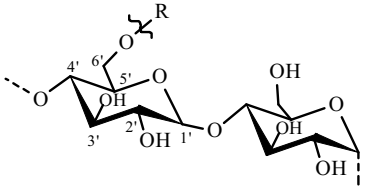

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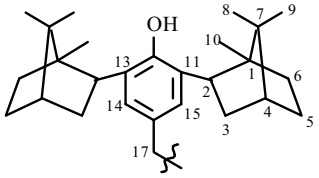

The content of aromatic fragment in the synthesized high-molecular-weight conjugates was determined by UV spectroscopy by comparing absorptions at 280 nm.

IR spectra of the *O*-alkylated polysaccharides with terpenophenol content >15 mass% exhibited absorption bands at 1615 cm^{-1} that were characteristic of benzene C–H bending vibrations. Furthermore, absorption bands for stretching and bending vibrations of terpene CH_3- and CH_2-groups appeared at 2900 and 1400, respectively.

The structure of the terpene substituent did not change during the reaction based on ^{13}C NMR spectral data. Resonances of C atoms in the dibornol terpene part were observed at 51–13 ppm in the ^{13}C NMR spectrum. In contrast with the starting polysaccharides, ^{13}C NMR spectra of derivatives **4** and **5** showed resonances belonging to C atoms of an aromatic ring (156–125 ppm). Resonances at 61–63 ppm in the ^{13}C NMR spectrum of inulin derivative **4** corresponded to resonances of C1′ and C6′ of the anhydrofructose ring; at 85–70 and 105, C3′–C5′ and C2′. Resonances for C atoms of the anhydroglucose ring in starch conjugate **5** appeared at 62 ppm (C6′), 72–74 and 80 (C2′, C4′, and C5′ and C3′, respectively), and 101 (C1′).

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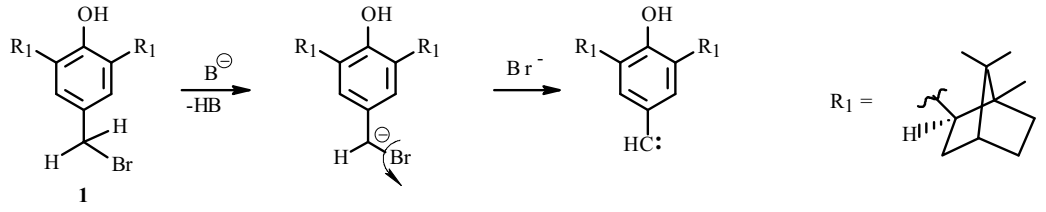
TABLE 1. Conditions for Modifying Polysaccharides with 2,6-Diisobornyl-4-bromomethylphenol in the Presence of Na_2CO_3

2,6-Diisobornyl-4-bromomethylphenol, mol/mol polysaccharide	Terpenophenol content in polysaccharide, mass%
Starch	
0.50	15.30*
0.15	18.96
0.07	10.17
0.05	8.34
Inulin	
0.40	41.05
0.20	22.80
0.10	9.56

*Base = NaOH.

The synthesized conjugates (**4**) with various contents of hydrophobic terpenophenol were very soluble in H_2O and several organic solvents (DMSO, DMF, DMA). Starch derivatives (**5**) with a high (>20 mass%) content of terpenophenol fragments were insoluble in H_2O. The *O*-alkylated conjugates of inulin and starch apparently have different solubilities because of the structure of the starch macromolecule. It has a higher molecular weight and more H-bonds that form intra- and intermolecular links [4].

It was noticed during the study that the yield of desired polymer and conversion of 2,6-diisobornyl-4-bromomethylphenol were influenced considerably by the type of base. Use of Na_2CO_3 to neutralize the HBr released during the reaction of 2,6-diisobornyl-4-bromomethylphenol with the polysaccharides gave better results than NaOH. Products with high amounts of 2,6-diisobornyl-4-methylphenol were obtained if Na_2CO_3 was used (Table 1). This is probably explained by possible $\pm\alpha$-dehydrobromination to form an active carbene that is involved in various side reactions [5] through the action of the stronger base NaOH.



EXPERIMENTAL

^{13}C NMR spectra were recorded in DMSO-d_6 on a Bruker Avance II 300 instrument (75 MHz operating frequency). IR spectra were taken from KBr pellets in the range 700–4000 cm^{-1} on a Prestige-21 spectrometer. The number of 2,6-diisobornyl-4-methylphenol fragments covalently bound to the polysaccharide was determined by spectrophotometry in EtOH:H_2O (2:3) on a Shimadzu UV-1700 instrument by comparing absorptions of the aromatic chromophore (λ 280 nm). The reference standard was 2,6-diisobornyl-4-methylphenol. The reproducibility of the results was confirmed by repeated syntheses under identical conditions.

We used inulin (MP Biomedicals, LLS, MW_{av} 5×10^3) and starch (analytically pure, MW_{av} 30×10^3). DMSO was dried over 5-Å molecular sieves before use. EtOH and acetone were distilled. Other reagents were used without further purification. The C atoms in the scheme are numbered for convenience in reading the spectral data.

Synthesis of Dibornol Conjugate of Inulin (4). Inulin (0.40 g, 2.5 mmol) was dissolved in DMSO (10 mL) under N_2, treated with ground Na_2CO_3 (0.106 g), stirred for 1 h, treated with 2,6-diisobornyl-4-bromomethylphenol (0.45 g, 1.0 mmol), stored for 24 h at 22 ± 2°C, filtered through a glass filter to remove inorganic salts, and diluted with acetone (50 mL). The precipitated polymer was separated by centrifugation, washed with acetone, extracted with petroleum ether in a Soxhlet apparatus, and dried in vacuo. Yield 0.60 g, dibornol content 41.05 mass%.

IR spectrum (KBr, ν_{max}, cm^{-1}): 3323 (νOH), 2930 (νCH_3, CH_2), 1573 (ν_{ar} C–C), 1410 (δCH_3, CH_2), 1031 (νC–O–C).

^{13}C NMR spectrum (75 MHz, DMSO-d_6, δ, ppm): 155.6 (C-12), 131.5 (C-11, C-13), 129.1 (C-15), 125.8 (C-14, C-16), 104.0 (C-2′), 83.16–82.12 (C-5′), 78.9–77.6 (C-3′), 75.7–70.88 (C-4′), 63.2–60.9 (C-1′, C-6′), 50.7 (C-1), 48.8 (C-7), 46.0 (C-4), 45.6 (C-2), 34.4 (C-3), 28.2 (C-5), 22.3 (C-8), 21.0 (C-9), 13.4 (C-10).

Synthesis of Dibornol Conjugated with Starch (5). Starch (0.50 g, 3.1 mmol) was dissolved in DMSO (15 mL) under N_2, heated to 80°C, cooled to room temperature, treated with ground Na_2CO_3 (0.05 g), stirred for 1 h, treated with 2,6-diisobornyl-4-bromomethylphenol (0.198 g, 0.45 mmol), reacted for 24 h at 22 ± 2°C, filtered through a glass filter to remove inorganic salts, and treated with EtOH (100 mL). The precipitated polymer was separated by centrifugation, washed with aqueous EtOH (80%) and acetone, purified by extraction in a Soxhlet apparatus with petroleum ether, and dried *in vacuo*. Yield 0.54 g (18.96 mass%).

IR spectrum (KBr, ν_{max}, cm^{-1}): 3402 (νOH), 2931 (νCH_3, CH_2), 1640 (C=O, adsorb. H_2O), 1454–1367 (δCH_3, CH_2), 1047 (νC–O–C), 933 (νC–O), 760 (δCH benzene ring).

^{13}C NMR spectrum (75 MHz, DMSO-d_6, δ, ppm): 131.5 (C-11, C-13), 125.8 (C-14, C-16), 101.0 (C-1′), 80.2 (C-3′), 74.2 (C-4′), 74.2–72.6 (C-2′, C-5′), 61.4 (C-6′), 50.7 (C-1), 48.6 (C-7), 46.1 (C-4), 45.6 (C-2), 34.4 (C-3), 28.2 (C-5), 22.4 (C-8), 21.1 (C-9), 13.3 (C-10).

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