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Preliminary communication

A facile *N*-acylation of chitosan with carboxylic anhydrides in acidic solutions

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Drastic procedures[1] are known for the *N*-acylation of chitosan [(1→4)-2-amino-2-deoxy-β-D-glucan] with carboxylic anhydrides at elevated temperature[2] and with acetic anhydride–dry HCl or conc HCl[3] A mild procedure[4,5] involving acetic anhydride in aqueous methanol (neutral or basic) was used[6] for the selective *N*-acetylation of oligosaccharides of chitosan However, polymeric chitosan is insoluble in water (neutral and basic), alcohols, and other solvents used for the acylation of amino sugars and mucopolysaccharides We now report on a novel, facile procedure for the *N*-acylation of chitosan *N*-Acylchitosans are of interest, as they effect the selective aggregation of some cancer cells[7].

Chitosan (100 mg), $[\alpha]_D^{15}$ −3 1° (*c* 1 3, formic acid), which had been prepared[8] from chitin by the action of 40% aqueous sodium hydroxide, was dissolved in 5 0 ml of one of the acidic solvents listed in Table I An excess of acid anhydride (see Table I) was added, and the mixture was left at room temperature overnight to afford a viscous, homogeneous solution in the acid solutions, or a solidified gel in the aqueous, acidic solutions For the reaction with higher fatty-acid anhydrides (C_{10} to C_{18}), an additional amount (~1 ml) of pyridine was added and the reaction was accelerated by heating in a boiling-water bath for a few seconds The product was poured into ~100 ml of acetone, and the suspension was stirred for a few hours at room temperature to afford the corresponding acylchitosan The presence of both *N*- and *O*-acyl groups in the acylchitosans was shown by absorptions at 1650 (C=O in *N*-acyl) and 1750 cm^{-1} (C=O in *O*-acyl) in the i r. spectra (KBr), and by the degree of substitution (d s = 2 6 for the acetylchitosan, 1 3 for the propionylchitosan, and 1 1 for the butyrylchitosan) per monosaccharide residue, the d s values are based on the ratio of (*N*-acyl protons)/(methine and methylene protons of sugar) in the n m r spectra (DCOOD) Acylchitosans from the higher fatty acids exhibited strong i.r absorption for NAc but very weak or almost no absorption for OAc.

O-Deacylation of the foregoing products was carried out by stirring with 0 5M KOH in 95% ethanol at room temperature overnight The resulting *N*-acylchitosans were collected by filtration, and showed i r absorption for NAc but not for OAc The structures were confirmed by elemental and component analyses

TABLE I

REACTION CONDITIONS FOR THE ACYLATION OF CHITOSAN

Acylchitosan	*Solvent*	*Carboxylic anhydride*	*Yield of N acylchitosan (mg)* [a]
Acetyl	10% Acetic acid (5 ml)	Acetic anhydride (2.5 ml)	93
Acetyl	50% Formic acid (5 ml)	Acetic anhydride (2.5 ml)	94
Acetyl	Formic acid (5 ml)	Acetic anhydride (0.4 ml)	93
Propionyl	10% Propionic acid (5 ml)	Propionic anhydride (3.4 ml)	84
Propionyl	10% Acetic acid (5 ml)	Propionic anhydride (2.5 ml)	100
Butyryl	Acetic acid [b] (5 ml)	Butyric anhydride (2.5 ml)	103
Butyryl	10% Butyric acid (5 ml)	Butyric anhydride (2.5 ml)	110
Lauroyl	Acetic acid [b] (5 ml) + pyridine (1 ml)	Lauric anhydride (1.3 g)	115
Palmitoyl	Acetic acid [b] (5 ml) + pyridine (1 ml)	Palmitic anhydride (2.0 g)	122
Benzoyl	Acetic acid [b] (5 ml) + pyridine (1 ml)	Benzoic anhydride (5.0 g)	102

[a] 100 mg of chitosan was acylated, and then *O* deacylation was carried out. The yields correspond to 50–78% of theory. [b] A solution of chitosan in ~ 10 ml of 10% acetic acid was evaporated *in vacuo*, acetic acid was added, and the solution was again evaporated to a small volume. This process was repeated until further addition of acetic acid resulted in incomplete dissolution of chitosan[9].

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