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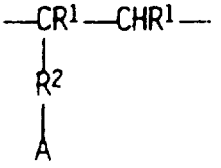
(54) **HOMOPOLYMERES OU COPOLYMERES ANALOGUES D'HEPARINE; LEUR PREPARATION ET LEUR UTILISATION**

(54) **HEPARIN-ANALOGOUS HOMO- OR COPOLYMERS, THEIR PREPARATION AND THEIR USE**



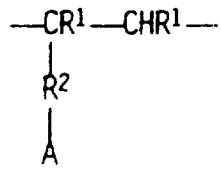
I

(57) L'invention porte sur des homopolymères ou des copolymères analogues d'héparine - renfermant des unités récurrentes de formule I (voir formule I), où R^1 est dans chaque cas indépendamment de l'hydrogène ou un radical méthyle, R^2 est un groupe de liaison, et A est un radical polyamine, (poly)amine(poly)ol ou polyol avec sulfatation, pouvant renfermer une ou plusieurs fonctions carbonyle acétalisées ou aminalisées - ainsi que sur une méthode pour les préparer. L'invention porte aussi sur des monomères avec ou sans groupe sulfate, comme précurseurs des homopolymères ou des copolymères. Enfin, elle porte sur l'emploi des homopolymères ou des copolymères analogues d'héparine pour le revêtement d'articles à usage médical, et sur les produits ainsi obtenus.

(57) The invention relates to heparin-analogous homo- or copolymers comprising repeating units of the formula I (see formula I) in which R^1 is in each case independently hydrogen or the methyl radical, R^2 is a linker and A is a sulfated polyol, polyamine or (poly)amine(poly)ol radical which may comprise one or more acetalized or aminalized carbonyl functionalities; and to a process for their preparation. The invention further relates to sulfate group-containing and sulfate group-free monomers as precursors of the homo- or copolymers. Finally, it relates to the use of the heparin-analogous homo- or copolymers for coating articles for medical use and to the products produced in this way.

Abstract:

The invention relates to heparin-analogous homo- or copolymers comprising repeating units of the formula I



I

in which R^1 is in each case independently hydrogen or the methyl radical, R^2 is a linker and A is a sulfated polyol, polyamine or (poly)amine(poly)ol radical which may comprise one or more acetalized or aminalized carbonyl functionalities; and to a process for their preparation. The invention further relates to sulfate group-containing and sulfate group-free monomers as precursors of the homo- or copolymers. Finally, it relates to the use of the heparin-analogous homo- or copolymers for coating articles for medical use and to the products produced in this way.

Heparin-analogous homo- or copolymers, their preparation and use

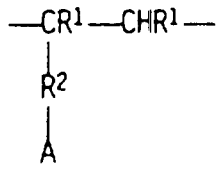
The invention relates to heparin-analogous, sulfated monomer-containing homo- or copolymers, to processes for preparing these homo- or copolymers and to the use thereof for medical purposes. The invention further relates to the sulfated monomers and to their precursors as intermediates for preparing the heparin-analogous polymers.

1. Prior art

It is well known that heparin is the name given to glycosaminoglycans (or mucopolysaccharides) composed of D-glucosamine and d-glucuronic acid which have a molecular weight of about 17,000 and are O- and N-sulfated. D-Glucosamine and D-glucuronic acid form disaccharide subunits which in each case have 1,4-glycosidic linkages and in turn undergo 1,4-glycosidic linkage a number of times appropriate for the molecular weight of heparin. Heparin acts as anticoagulant, that is to say prevents blood coagulating. In medicine, heparin is used for the therapy and prophylaxis of thromboembolic disorders, usually in the form of its readily water-soluble sodium salts. Heparin is often adsorbed onto polymers, and polymers "detoxified" in this way are suitable for articles which, when used medically, come into contact with blood, such as heart valves, catheters, endoscopes and drainage tubes. However, in most operations where blood comes into contact with polymeric materials, heparin is introduced prophylactically into the blood directly.

2. Heparin-analogous polymers of the invention

The invention provides heparin-analogous homo- or copolymers which comprise repeating units of the formula I



I

in which

R^1 is in each case independently hydrogen or the methyl radical,

R^2 is a linker and

A is a sulfated polyol, polyamine or (poly)amine-(poly)ol radical which may comprise one or more acetalized or aminalized carbonyl functional-ities.

R^1 in the repeating units of the formula I is preferably hydrogen.

The linker R^2 can be inorganic or organic in nature and is preferably O, S, SO, SO_2 or NR' where R' is a hydrocarbon radical having 1 to 12 carbon atoms, or a divalent organic radical, in particular an aliphatic, cycloaliphatic or aromatic hydrocarbon radical having up to 10 carbon atoms, a carboxylic ester bridge -O-CO-, a carboxamide bridge -NR'-CO- or a urethane bridge -O-CO-NR'- where R' has the stated meaning in each case, or a C-C single bond.

The radical A is derived from a compound having at least 2 hydroxyl and/or amino groups and preferably 2 to 8, in particular 5 or 6, carbon atoms, comprises at least one radical $-O-SO_3^-M^+$ (O-sulfate radical) or $-NH-SO_3^-M^+$ (N-sulfate or sulfamate radical), where M is an alkali metal ion, in particular a sodium ion, and comprises where appropriate in addition at least one, preferably one or two, carbonyl functionalities which, by intramolecular acetalization or aminalization, form a tetrahydrofuran or pyrrolidine ring (with 5 ring members in each case) or a pyran or pentamethyleneimine ring (with 6 ring members in each case).

The compounds from which the radical A can be derived include ethylene

glycol, ethylenediamine, ethanolamine, diethanolamine, neopentyl glycol, glycerol, glyceraldehyde, trimethylolpropane, pentaerythritol, erythrose, erythritol, threose, threitol, heptanoses, heptitols, octanoses, octitols and, in particular, monosaccharides having 5 or 6 carbon atoms (pentoses or hexoses) and aldehyde or keto groups (aldoses or ketoses), and the relevant sugar alcohols (pentitols or hexitols).

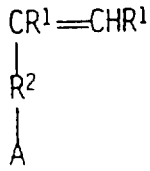
The heparin-analogous homo- or copolymers of the invention preferably have a molecular weight of from 5,000 to 1,500,000, in particular from 50,000 to 800,000, determined by membrane osmometry. They can be used like heparin and are particularly suitable for coating articles made of polymers which are intended for medical use. In some cases, they show a more potent anticoagulant effect than heparin itself. The thrombin time (TT) and the clotting time (PTT = partial thromboplastin time) are therefore increased. In addition, the anticoagulant effect of the heparin-analogous polymers according to the invention is of longer duration than that of heparin. The novel polymers are evidently, as nonphysiological substances, less easily degraded by heparinase, which is likely to derive from the non-glycosidic linkages of the radicals A to the polymer chain. In contrast thereto, the glycosidic linkages of heparin are more easily degradable.

The heparin-analogous homopolymers or copolymers can be assembled by polymerizing monomers or comonomers which already comprise the characteristic groups R^2 and A. Alternatively, suitable polymers can be subsequently altered appropriately. Thus, polymers with protected (for example by ketalization with acetone) repeating units can be deprotected and then sulfated. Polymerization of monomers having the groups R^2 and A is the more straightforward process and gives better yields and purer products, and is therefore preferred. The novel monomers are prepared from the compounds from which the radical A is derived by reactions which are known per se and are explained hereinafter. The preparation takes place in some cases over a whole series of stages but they all give good yields. A particular advantage is that the intermediates need no purification, and even the

monomers can be polymerized as crude products without any disadvantages to give the homo- or copolymers according to the invention.

3. Monomers for the novel heparin-analogous homo- or copolymers

The novel monomers of the formula II

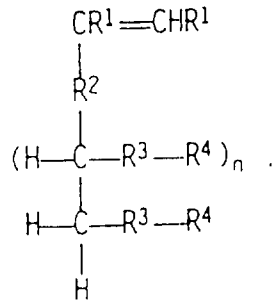


II

in which R^1, R^2 and A have the meanings stated for formula I, including the preferred meanings, correspond to the repeating units I in the novel heparin-analogous homo- or copolymers.

3.1 Monomers derived from pentitols or hexitols

A preferred class of monomers corresponds to the formula III (which is covered by formula II)



III

in which R^1 and R^2 have the meanings stated above, including the preferred meanings,

R^3 is O or NH,

R^4 is hydrogen or the radical $-SO_3^-Na^+$, and

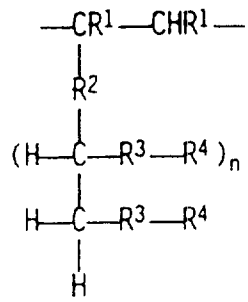
n is 4 or 5;

with the proviso that at least one of the substituents R^4 is a radical $-SO_3^-Na^+$.

R^2 in the monomers III is preferably an alkylene radical having 1 to 4 carbon

atoms, a phenylene radical or a C-C single bond.

The repeating units of the formula IIIa



IIIa

in which R^1, R^2, R^3, R^4 and $\underline{n}$ have the meanings stated for formula III, including the preferred meanings, correspond to the monomers III.

The formulae III and IIIa do not fix the stereochemistry of the substituents on the carbon chain; the depiction thus does not correspond to a Fischer projection.

The monomers III (and the repeating units IIIa) comprise as radical A (of formula II) groups which are derived from pentitols or hexitols and which in turn derive from pentoses such as arabinose, or hexoses. The groups comprise at least one of the radicals -O-$SO_3^-Na^+$ (O-sulfate) or -NH-$SO_3^-Na^+$ (N-sulfate), preferably adjacent to the radical R^2. They may comprise up to 5 (pentitols) or 6 (hexitols) sulfate radicals and preferably have 1 to 4 of these radicals. It is possible for both O-sulfate and N-sulfate radicals to be present in one and the same group, in which case the N-sulfate radical is preferably in the position adjacent to the radical R^2. Alternatively, however, the group may also comprise only one type of these radicals, for example only O-sulfate radicals.

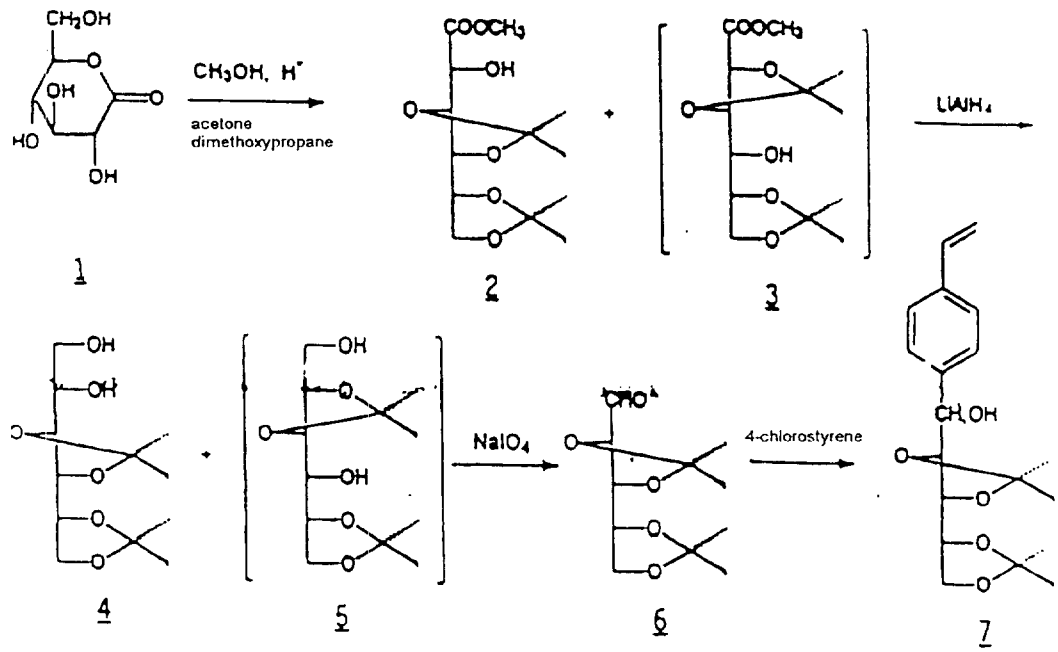
3.1.1 Monomers III derived from pentitols

The preparation of monomers III is described by means of a special case starting from D-glucono-1,5-lactone $\underline{1}$ and resulting in a monomer III which is

derived from a pentose, namely D-arabinose. However, the skilled worker will be able to apply the process without difficulty to other suitable precursors.

In a first stage, the hydroxyl groups of the lactone 1 are protected by acetalization, for example with acetone, and, at the same time, the (cyclic) lactone is transesterified with methanol to give the (open-chain) methyl ester. An isomer mixture consisting of methyl 3,4;5,6-di-O-isopropylidene-D-gluconate 2 and methyl 2,3;5,6-di-O-isopropylidene-D-gluconate 3 is obtained. This mixture is reduced in a second stage, for example with lithium aluminum hydride, whereby the carboxylic ester functionality becomes a carbinol functionality. Once again, a mixture of isomers is obtained, namely 3,4;5,6-di-O-isopropylidene-D-sorbitol 4 and 2,3;5,6-di-O-isopropylidene-D-sorbitol 5. In a third stage, this mixture of isomers is oxidized with an oxidizing agent such as sodium periodate with cleavage of the carbon chain to give a single product, the arabinose aldehyde 2,3;4,5-di-O-isopropylidenealdehydo-D-arabinose 6. In the subsequent fourth stage, a vinyl functionality is introduced, for example by a Grignard reaction with 4-vinylphenylmagnesium chloride. A partly protected 4-vinylphenylpentanepentaol, 2,3;4,5-di-O-isopropylidene-1-(4-vinylphenyl)-D-gluco(D-manno)-pentitol 7 is obtained and is referred to as arasty for brevity hereinafter.

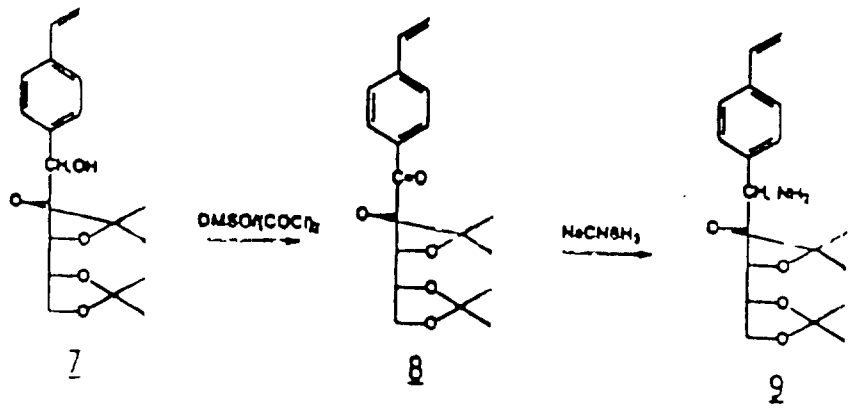
This sequence of stages 1 to 4 is illustrated by the following reaction scheme.



1 2 3 4 5 6 7

The sequence of reactions in stages 1 to 3 (that is to say up to compound 6) has been described by H. Regeling et al., Recl. Trav. Chim. Pays-Bas 1987, (106) 461 and D.Y. Jackson, Synth. Commun. 1988 (18) 337. Stage 4 (to compound 7) was published for the first time by G. Wulff et al., Macromol. Chem. Phys. 1996 (197) 1285.

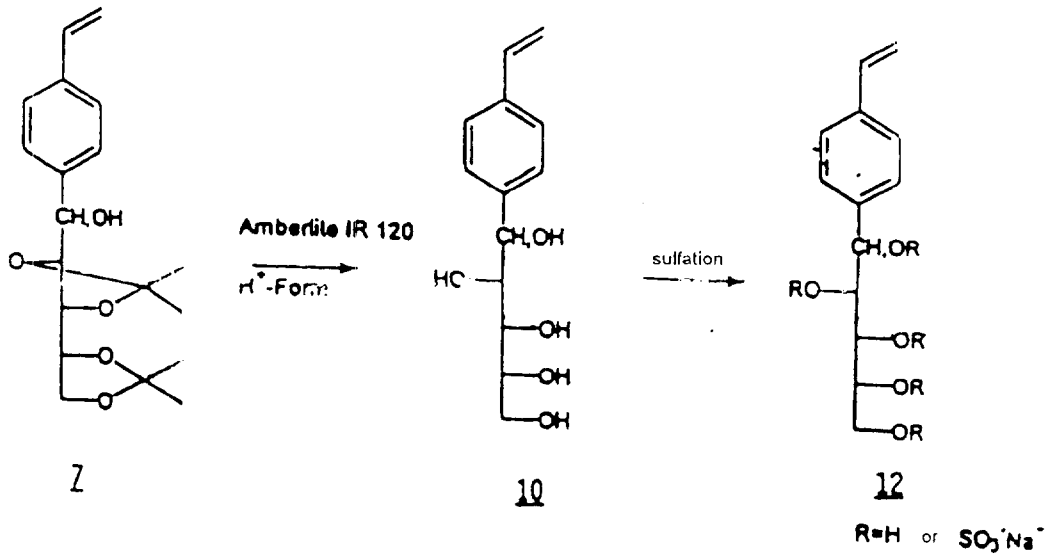
To prepare a compound corresponding to arasty 7 with an amino group in position 1 it is possible, in a first stage, to oxidize arasty to the corresponding ketone, 2,3;4,5-di-O-isopropylidene-D-arabino 4-vinylphenyl ketone 8. This is converted by reduction in a second stage to 1-amino-1-deoxy-2,3;4,5-di-O-isopropylidene-1-(4-vinylphenyl)-D-gluco(D-manno)-pentitol 9. This sequence of reactions is illustrated by the following formula diagram:

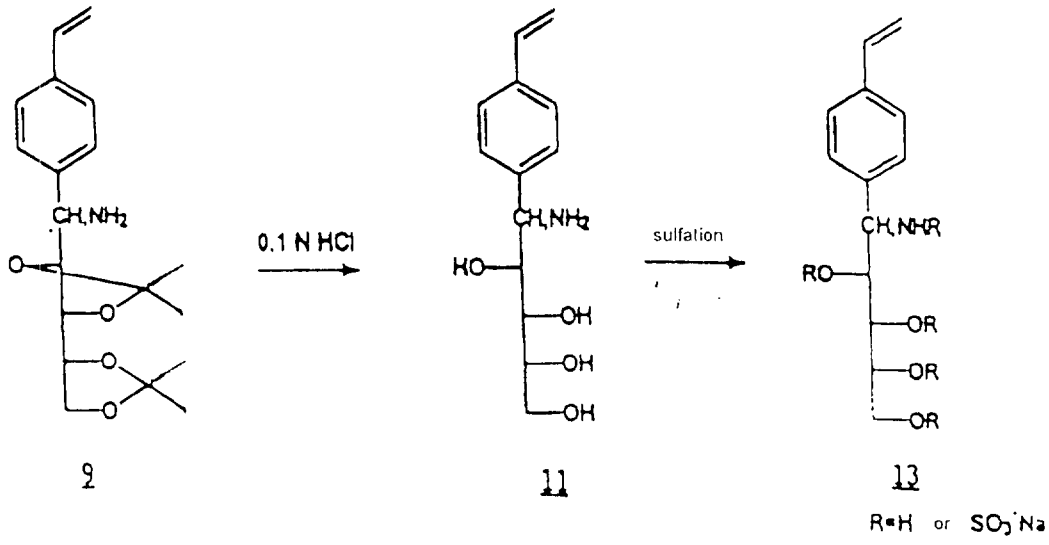


7 8 9

In the first stage, arasty 7 can be oxidized for example with oxalyl chloride and dimethyl sulfoxide at a temperature <-50°C in an inert solvent. The reductive amination in the second stage is advantageously achieved with sodium cyanoborohydride as reducing agent in the presence of ammonium acetate in a solvent with exclusion of water at room temperature.

Heparin contains unprotected hydroxyl groups and is O-sulfated and N-sulfated. Compounds 7 and 9 are therefore deprotected (deacetalized) in a first stage and O- and/or N-sulfated in a second stage so that the polymer prepared from them is as far as possible analogous to heparin. The deprotection takes place in acidic medium in which ketals are unstable. The protected compounds are heated, for example, with dilute mineral acid or an acidic ion exchanger to obtain from 7 1-(4-vinylphenyl)-D-gluco(D-manno)-pentitol 10 and from 9 1-amino-1-deoxy-1-(4-vinylphenyl)-D-gluco(D-manno)-pentitol 11. The deprotection and the subsequent sulfation are depicted in the following formula diagram:





The two compounds 10 and 11 are sulfated, expediently using a sulfur trioxide/pyridine complex. Because of the preceding deacetalization, the sulfation does not result in a single product with one or more sulfate groups in defined positions. However, the primary hydroxyl groups and the amino groups ought to be preferentially sulfated. The degree of sulfation can be controlled by choice of a suitable molar ratio of sulfur trioxide to hydroxyl and amino groups. It is advantageous for more than one sulfate group to be introduced on average per molecule, because heparin contains about 2.7 sulfate groups per disaccharide unit (equivalent to 1.35 sulfate groups per

molecule of monomer I). Sulfation of the deprotected amine compound 11 results in both O-sulfate and N-sulfate groups in the molecule, which is desired in the light of the intended analogy to heparin.

The sulfation is advantageously carried out at room temperature in order to avoid premature polymerization. It is nevertheless possible, by a relatively long reaction time, for example up to 100 hours, for the reaction to be continued until all the OH and NH_2 groups have reacted completely. It is possible to use as solvent for example excess pyridine or an ether such as tetrahydrofuran. Since the sulfate groups in the reaction products are unstable to acid, it is advisable to add a dehydrating agent, for example molecular sieves, to the precursor solution before adding the sulfur trioxide/pyridine complex. For the same reason it is advisable, after completion of the reaction, to hydrolyze the reaction mixture first by adding water and shortly thereafter a base (which keeps the pH in the alkaline range). An example of a suitable base is a saturated barium hydroxide solution, which also precipitates sulfate ions. Excess barium ions can be precipitated, for example, by passing in carbon dioxide, where appropriate after cautious concentration to remove solvent. The barium carbonate is filtered off and the filtrate is passed through an ion exchange column in the Na^+ form, or treated with the ion exchanger in another way, in order to replace the barium ions by socium ions. The products, O-sulfated 1-hydroxy-1-deoxy-1-(4-vinylphenyl)-D-gluco(D-manno)-pentitol 12 and N- and O-sulfated 1-amino-(4-vinylphenyl)-D-gluco(D-manno)-pentitol 13 can be isolated, in each case in the form of the sodium salt, as solid powders by freeze drying the solution which has been concentrated further.

3.1.2 Monomers III derived from hexitols

The preparation of these monomers is described by means of another special case which starts once again from D-glucono-1,5-lactone 1 and results in two monomers which are formally derived from a hexose, namely D-glucose. However, the skilled worker will be able without difficulty to apply

the process to other suitable precursors and prepare other monomers according to the invention.

D-Glucono-1,5-lactone 1 is first converted in a one-pot reaction with a secondary amine and acetone in acidic medium into a mixture of the regioisomers 3,4;5,6-di-O-isopropylidene-D-gluconic acid diethylamide 14 and 2,3;5,6-di-O-isopropylidene-D-gluconic acid diethylamide 15. A mixture of the isomers 3,4;5,6-di-O-isopropylidene-1-(4-vinylphenyl)-keto-D-glucose 16 and 2,3;5,6-di-O-isopropylidene-1-(4-vinylphenyl)-keto-D-glucose 17 is obtainable from this mixture by a Grignard reaction with phenylmagnesium chloride.

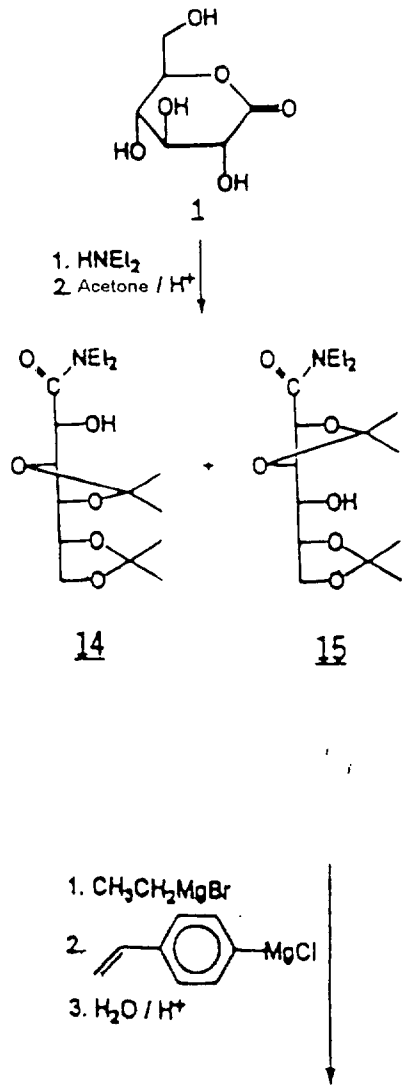
The mixture of isomers 16, 17 is hydrogenated (or reduced), for example with sodium borohydride or lithium aluminum hydride, resulting in two pairs of regioisomeric diastereomers 3,4;5,6-di-O-isopropylidene-1-(4-vinylphenyl)-D-glycero-D-gulo(D-ido)-hexitol and 2,3;5,6-di-O-isopropylidene-1-(4-vinylphenyl)-D-glycero-D-gulo(D-ido)-hexitol 20 (not depicted in the following formula diagram). These can be deprotected in acidic medium, resulting in 1-(4-vinylphenyl)-D-glycero-D-gulo(D-ido)-hexitol 21. Sulfation, for example with the sulfur trioxide/pyridine complex as described, thereof, results in the sulfation product 22, which is a monomer III.

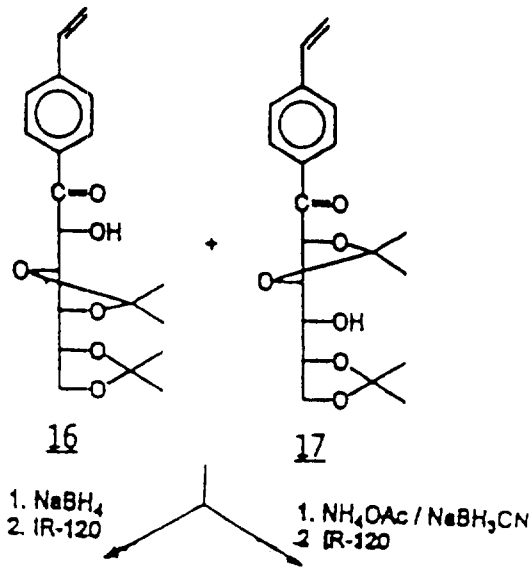
Alternatively, the mixture of isomers 16, 17 can be reductively aminated, for example with sodium cyanoborohydride and an ammonium salt. This results in two pairs of regioisomeric diastereomers 1-amino-1-deoxy-3,4;5,6-di-O-isopropylidene-1-(4-vinylphenyl)-D-glycero-D-gulo(D-ido)-hexitol and 1-amino-1-deoxy-2,3;5,6-di-O-isopropylidene-1-(4-vinylphenyl)-D-glycero-D-gulo(D-ido)-hexitol 23 (not depicted in the following formula diagram). These can in turn be deprotected in acidic medium, resulting in 1-amino-1-deoxy-1-(4-vinylphenyl)-D-glycero-D-gulo(D-ido)-hexitol 24. This is sulfated as described to give the sulfation product 25, which is likewise a monomer III.

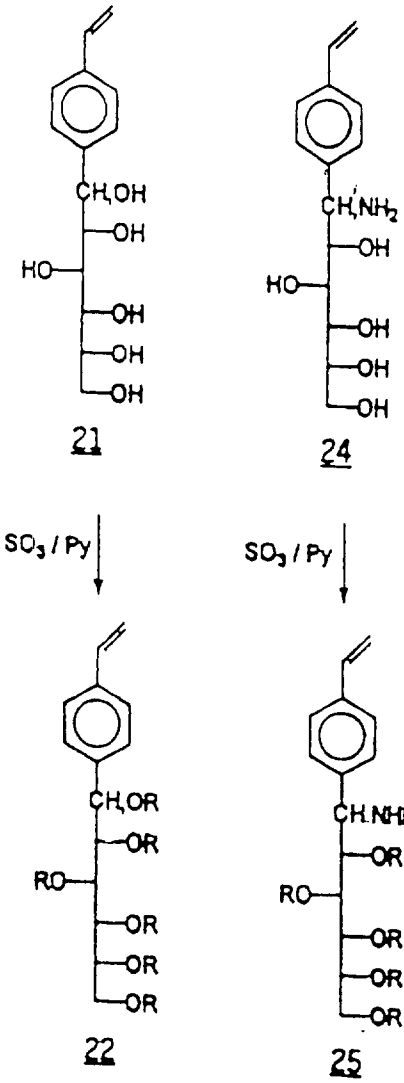
It is possible in both variants to reverse the sequence of hydrogenation or

reductive amination and deprotection.

The described reaction sequence is depicted by the following formula diagram, intermediates 20 and 23 not being depicted:

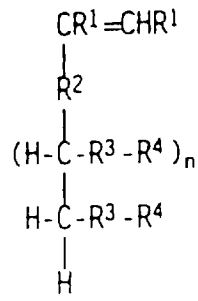



16
17
1. NaBH4
2. IR-120
1. NH4OAc / NaBH3CN
2. IR-120


21
24
SO3 / Py
SO3 / Py
22
25

3.1.3 Monomers with acetalized or aminalized carbonyl functionality

Preferred monomers of this type correspond to formula IV (which is covered by formula II)



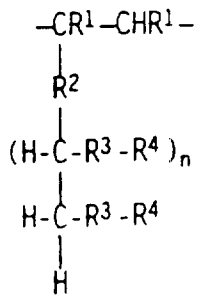
IV

in which R^1, R^2, R^3, R^4 and n have the meanings stated for formula III, including the preferred means; with the proviso that

(1) at least once, advantageously once or twice, per molecule, substituents H and $-R^3-R^4$ on the same carbon atom form with this carbon atom a carbonyl functionality C=O which has undergone intramolecular acetalization or amin-alization by a hydroxyl or amino functionality in position 3 relative to the carbonyl func-tionality to form a tetrahydrofuran or pyrrolidine ring or by a hydroxyl or amino functionality in position 4 relative to the carbonyl functionality to form a pyran or pentamethyle-neimine ring, and that

(2) at least one of the substituents R^4 is a radical $-SO_3^-Na^+$.

The monomers IV correspond in the (co)polymer to the repeating units of the formula IVa

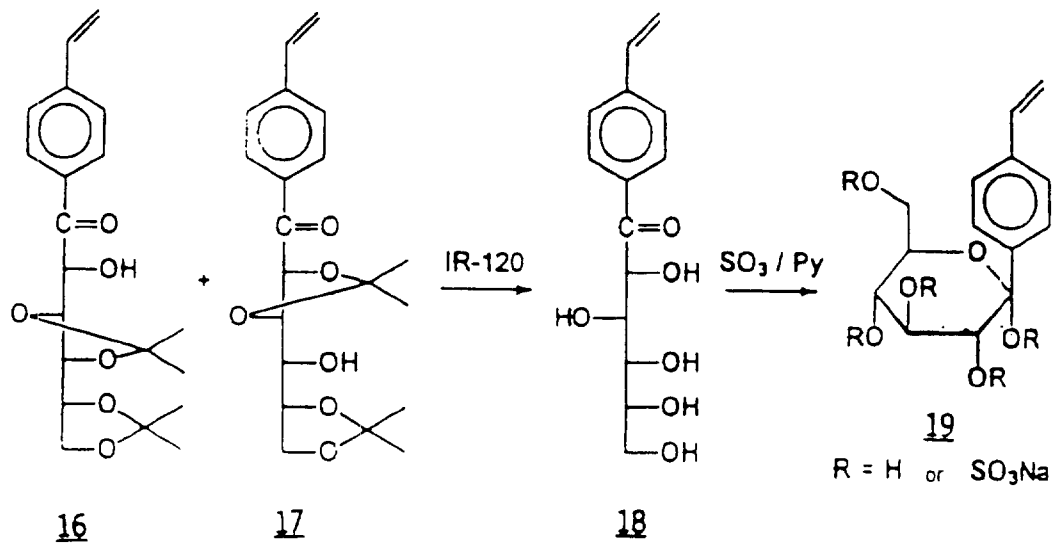


IVa

in which R^1, R^2, R^3, R^4 and n have the meanings stated for formula III, including the preferred meanings, and the proviso conditions for formula IV apply.

The monomers IV also prima facie correspond to formula III, but they differ from the monomers III by proviso condition (1). Monomers IV are derived from pentoses (n = 4) or from hexoses (n = 5). They may be sulfated aldoses or ketoses, both of which are in the form of their acetals or aminals. Formula IV once again does not represent the actual stereochemical relationships in the carbon chain; on the contrary it embraces all stereoisomer forms in which the pentoses or hexoses from which the monomers IV are derived may occur.

A monomer IV can be prepared, for example, by first proceeding as described under 3.1.2, but preparing from the mixture of isomers 16, 17, by deprotection in acidic medium, a single product, namely 1-(4-vinylphenyl)-keto-D-glucose 18. This is converted in its acetal form by sulfation, once again for example with sulfur trioxide/pyridine, into the sulfated compound 19, which is a monomer IV. The sequence of stages is depicted by the following formula diagram:

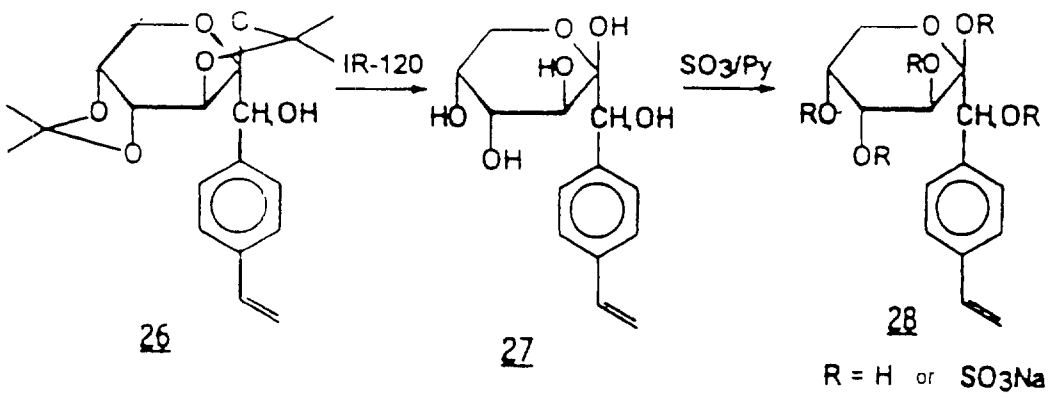


16 17 18 19

Other monomers IV of the invention can be prepared starting from monomers which are initially still protected by intermolecular acetalization (with acetone) and are free of sulfate groups. The preparation of an unprotected monomer which is free of sulfate groups and is derived from a ketohexose will be described taking the example of 1-(4-vinylphenyl)-D-manno(D-gluco)-hexulo-2,6-pyranose 27. This starts from the acetone-protected 2,3;4,5-di-O-isopropylidene-1-(4-vinylphenyl)-D-manno(D-gluco)-hexulo-2,6-pyranose 26, whose preparation has been described by G. Wulff, J. Schmidt, T.P. Venhoff in Macrom. Chem. Phys., 197, 1285 (1996). An example for the preparation of a monomer which is free of sulfate groups and is derived from an aldohexose is the synthesis of 6-(4-vinylphenyl)-D-glycero(L-glycero)-α-D-galactopyranose 30. The starting material in this case is 1,2;3,4-di-O-isopropylidene-6-(4-vinylphenyl)-D-glycero(L-glycero)-α-D-galactopyranose 29, whose preparation has likewise been described by G. Wulff, J. Schmidt, T.P. Venhoff loc. cit. Deprotection of the hydroxyl groups takes place in both cases using an acidic ionic exchanger in an inert solvent, for example an alcohol, at moderately elevated temperature, such as 50 to 100°C, expediently in an inert gas atmosphere and in the presence of an oxidation inhibitor.

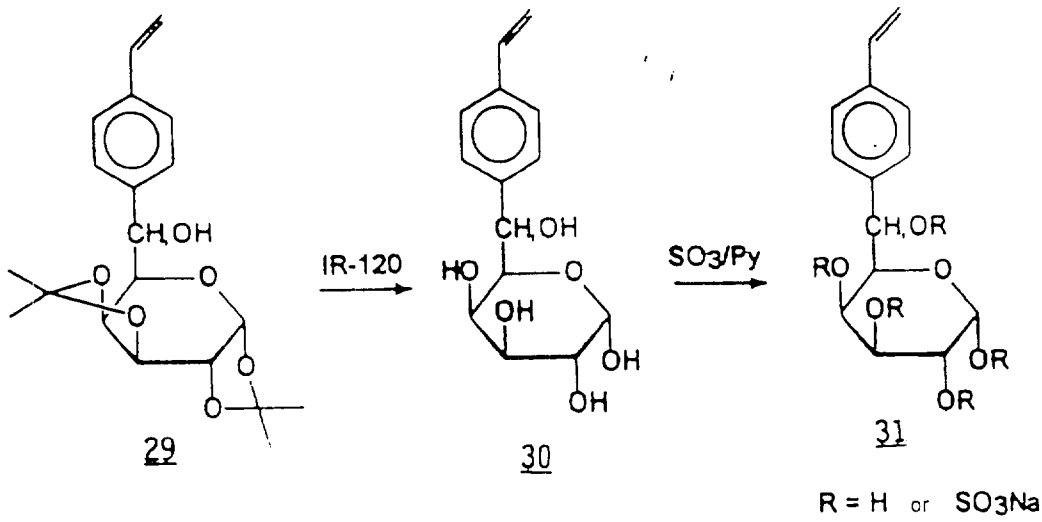
It is possible to prepare by sulfation of monomers 27 and 30 which are free of sulfate groups (R^4 = H in each case) their completely or partly sulfated (R

= $SO_3^-Na^+$) derivatives. Once again a sulfur trioxide/pyridine complex, for example, is used, expediently at room temperature in order to avoid premature polymerization. The reaction is nevertheless complete after a relatively long time. The degree of sulfation can be determined by choice of a suitable molar ratio of sulfur trioxide to hydroxyl groups.



26 27 28

Preparation of monomers IV 28 and 31 is described by the following formula diagram:

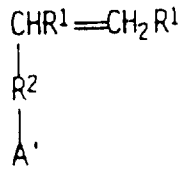


29 30 31

4. Novel precursors of monomers II, III and IV

The precursors free of sulfate groups for the monomers II, III and IV containing sulfate groups are also novel substances from which the monomers II, III and IV containing sulfate groups are produced by sulfation as described. Exceptions are 1-(4-vinylphenyl)-D-gluco(D-manno)-pentitol (J. Schmid,

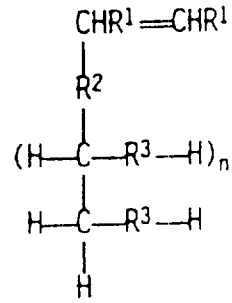
Thesis, Düsseldorf University, 1993; T. Venhoff, Thesis, Düsseldorf University, 1993), 6-(4-vinylphenyl)-D,L-glycero-α,β-D-galactopyranose (T. Venhoff, Thesis, Düsseldorf University, 1993), 1-(4-vinylphenyl)-D-manno(D-gluco)-hexulo-2,6-pyranose (H. Diederichs, Thesis, Düsseldorf University, 1996) and 1-vinyl-β-D-fructopyranose (T. Venhoff, Thesis, Düsseldorf University, 1993). The novel precursors are represented by the following formulae:



V

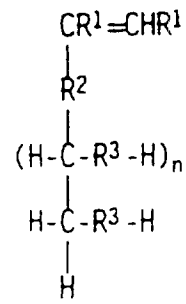
in which R^1 and R^2 have the meanings or preferred meanings stated for formula II, and

A' is a non-sulfated polyol, polyamine or (poly)amine(poly)ol radical which may comprise one or more acetalized or aminalized carbonyl functionalities:



VI

in which R^1, R^2, R^3 and $\underline{n}$ have the meanings stated for formula III, including the preferred meanings;



VII

in which

R^1, R^2, R^3 and $\underline{n}$ have the meaning or preferred meaning stated for formula IV; with the proviso that at least once, advantageously once or twice, per molecule, substituents H and $-R^3-H$ on the same carbon atom form with this carbon atom a carbonyl functionality C=O which has undergone intramolecular acetalization or aminalization by a hydroxyl or amino functionality in position 3 relative to the carbonyl functionality to form a tetrahydrofuran or pyrrolidine ring or by a hydroxyl or

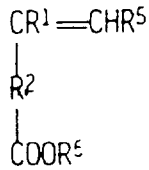
amino functionality in position 4 relative to the carbonyl functionality to form a pyran or pentamethyleneimine ring.

5. Preparation of the heparin-analogous homo- or copolymers

The novel heparin-analogous polymers are expediently prepared by polymerization or copolymerization of monomers II, III and/or IV. The polymers may, for example, comprise exclusively the repeating units I, IIIa or IVa as only one species, for example as repeating unit of the formula IIIa which has on average 2.5 O-sulfate radicals. The products in this case and in corresponding cases are homopolymers. The repeating unit IIIa can, however, also consist of a mixture of two or more species, for example of the abovementioned species and of another which has an N-sulfate radical adjacent to R^2 and, in addition, on average 1 to 3 O-sulfate radicals. The polymer in this case is a copolymer. The molar ratio of the various species may vary within wide limits. If, for example, the repeating unit IIIa consists of one species exclusively with O-sulfate radicals and of one species with an N-sulfate radical and possibly further O-sulfate radicals, it may be from 100:0 to 0:100. A narrower range which has proven suitable is 20:1 to 1:20.

Copolymers are also produced when one or more monomers II, III or IV are copolymerized with other sulfate-free comonomers V, VI, VII, VIII or IX.

Suitable comonomers VIII correspond to the general formula VIII



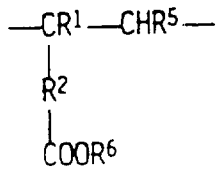
VIII

in which R^1 and R^2 have the meanings stated for formula III, including the preferred meanings,

R^5 is hydrogen, the methyl radical or the radical $-R^2-COOR^6$ and

R^6 is hydrogen or an alkali metal ion, in particular a sodium ion.

Comonomers VIII result in repeating units of the formula VIIIa



VIIIa

in which R^1, R^2, R^5 and R^6 have the meanings stated for formula VIII.

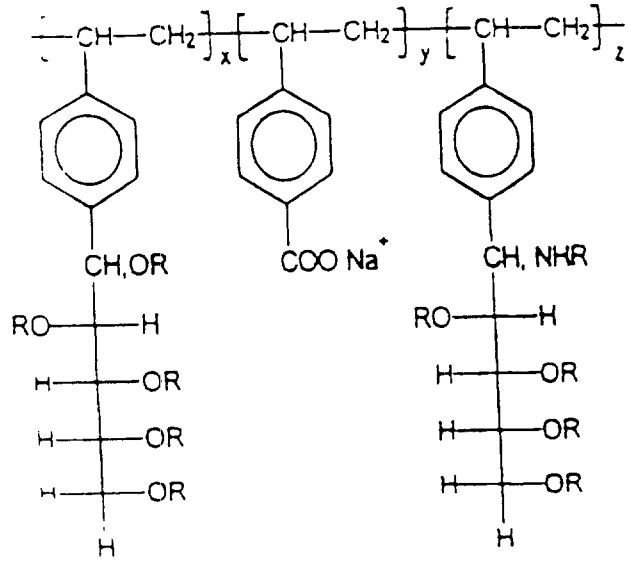
The comonomers VIII are ethylenically unsaturated mono- or dicarboxylic acids or their carboxylates, that is to say their alkali metal salts, in particular the sodium salts. Examples of suitable monomers VIII are (meth)acrylic acid, crotonic acid, 4-vinylbenzoic acid, maleic acid, fumaric acid, vinylsalicylic acid, itaconic acid, vinylacetic acid, cinnamic acid, 2- and 4-vinylbenzoic acid, methylmaleic acid, dimethylfumaric acid, methylfumaric acid, dihydroxymaleic acid and allylacetic acid or their sodium salts. In place of comonomers VIII it is also possible to copolymerize derivatives whose functional groups can be converted after the polymerization into carboxyl or carboxylate groups. Groups of this type which may be mentioned are aldehyde, carboxylic ester, carboxylic anhydride and carbonitrile groups. Comonomers VIII and their said derivatives are preferred comonomers having regard to the heparin-analogous properties of the copolymers. It is possible once again to copolymerize various species of comonomers VIII, for example a mono- and a dicarboxylic acid. The molar ratio of carboxyl and/or carboxylate groups to the total of O-sulfate and/or N-sulfate groups in the copolymer may vary within wide limits, for example 100:1 to 1:100 and advantage-ously once again 20:1 to 1:20.

The compounds referred to as comonomers IX are those vinyl monomers which comprise neither sulfate nor carboxyl or carboxylate groups and which modify the properties of the heparin-analogous copolymers in the desired

manner. Thus, repeating units IXa derived from comonomers IX conferring hydrophilicity or from other comonomers IX may be present and improve the compatibility of the heparin-analogous copolymer with, and its adhesion to, a substrate polymer which is to be coated. Examples of suitable comonomers IX which may be mentioned are ethylene, propylene, 1-butene, 1,3-butadiene, C_5- and C_6-alkylenes, styrene, vinyltoluene, (meth)acrylonitrile, -(meth)acrylamide, acetylene, acrolein, (meth)acrylic esters, allyl chloride, cinnamates, crotonates, N-vinylimidazole, maleimide, N-vinylpyrrolidine, N-vinylpyrrolidone, N-vinylsuccinimide, vinyl acetate, vinyl chloride, vinyl methyl, ethyl and butyl ether, and vinyl methyl and ethyl ketone. If other repeating units are present, their content is, as a rule, up to 90 mole percent, in particular up to 70 mole percent, based on the total of repeating units I and II. The above statements about the molecular weight of the heparin-analogous polymers and about the molar ratio of the various species of repeating units I, IIa, IIIa and/or IVa and about the ratio of carboxyl and/or carboxylate groups to O-sulfate and/or N-sulfate groups also apply to copolymers with other repeating units.

The monomers II, III and/or IV, possibly also two or more species of II, III and/or IV, and possibly comonomers VIII and/or IX can be polymerized in a manner known per se. Thus, a heparin-analogous homopolymer can be prepared from monomers 22, 25 or 31. To prepare a copolymer, it is possible to employ, for example, compound 12 as monomer I and sodium acrylate, sodium maleate and/or sodium 4-vinylbenzoate as monomer VIII. An alternative possibility is also to start from compound 13 and use the same monomers VIII. Very good heparin-analogous effects are obtained when compounds 12 and 13 with, in each case, on average 1 to 4 sulfate groups per molecule and a monomer VIII, for example sodium 4-vinylbenzoate, are copolymer-ized. As mentioned previously, the molar ratios of the carboxyl and/or carboxylate groups to the O-sulfate and/or N-sulfate groups in said monomers or in the corresponding repeating units may vary within wide limits and may be, for example, 1:100 to 100:1, advantageously 20:1 to 1:20. The molar ratio of O-sulfate to N-sulfate groups may also, as previously mentio-

ned, vary within wide limits and can be, for example, 0:100 to 100:1. Once again, a narrower range which has proven suitable is 20:1 to 1:20. Copolymers of this type can be described by the following formula:



In the formula, R is hydrogen or the radical $-SO_3^-Na^+$, with the proviso that at least one radical R is an $-SO_3^-Na^+$ radical. In each case, x and z are 0 or integers, and y is an integer. The copolymers preferably have molecular weights of from 50,000 to 800,000, determined by membrane osmometry. Accordingly, the total x+y+z is, depending on the ratio of repeating units, about 80 to 1100.

The polymerization takes place in aqueous solution at elevated temperature, for example at 60 to 90°C. The reaction time varies considerably depending on the monomers, initiator, amount of initiator and temperature, and is, as a rule, from 5 to 80 hours. An initiator which has proven particularly suitable is 2,2'-azobis(2-amidinopropane) dihydrochloride. It is advantageously used in amounts of from 0.5 to 4 mole percent based on the total of monomers I and II in order to achieve complete conversion. The copolymer can be precipitated from the reaction mixture by addition of alcohol, and water and alcohol residues can be removed under mild conditions in a conventional way.

6. Use of the heparin-analogous copolymers

The heparin-analogous copolymers are outstandingly suitable for coating articles, in particular articles which consist of polymers and are intended for medical use, that is to say come into contact with blood. Examples of such articles are heart valves, prostheses, implants, catheters, endoscopes, oxygenators, dialysis membranes and tubing.

The coating can take place in a conventional way, for example with aqueous solutions, by dipping, brush-coating, spraying or spincoating. The adhesion of the copolymer to the polymer substrate can be influenced beneficially by appropriate choice of the polymer substrate and copolymer.

The following examples are given to improve understanding of the invention, but are not intended to limit the range of application of the invention.

5. Examples

5.1 Preparation of methyl 3,4;5,6-di-O-isopropylidene-D-gluconate 2 and methyl 2,3;5,6-di-O-isopropylidene-D-gluconate 3

A mixture of 142.4 g (0.8 mol) of D-glucono-1,5-lactone 1, 240 ml of 2,2-dimethoxypropane, 80 ml of acetone, 24 ml of methanol and 1.2 g of p-toluenesulfonic acid is stirred at room temperature for 48 h. The resulting mixture is neutralized with sodium bicarbonate solution. After filtration and concentration of the filtrate, the resulting viscous syrup is taken up in about 500 ml of dichloromethane and washed with water. The solution is concentrated and the residue is distilled under oil pump vacuum. Yield: 198 g (85%), boiling point 112°C/0.04 mbar, n_D^{20}: 1.455.

5.2 Preparation of 3,4;5,6-di-O-isopropylidene-D-sorbitol 4 and 2,3;5,6-di-O-isopropylidene-D-sorbitol 5

40 g of $LiAlH_4$ are introduced into 1.3 l of dry THF in a 4 l three-neck flask which is fitted with a stirrer with glass shaft and bearing, efficient condenser and dropping funnel with bubble counter and is flushed with nitrogen, and 232 g (0.8 mol) of the esters 2 and 3, dissolved in 300 ml of dry THF, are slowly added dropwise while cooling in an ice/salt bath. The solution is heated under reflux for 16 h and, after cooling, a mixture of 400 ml of 1,2-dimethoxyethane and about 120 ml of ice (dropping funnel) is added. Then a mixture of 150 ml of ice and 150 ml of water is added. The resulting precipitate is centrifuged, thoroughly washed with THF and again centrifuged. The combined organic phases are concentrated in a rotary evaporator, taken up in dichloromethane, and washed with 10 % strength ammonium sulfate solution and then with sodium chloride solution. The organic phase is dried over sodium sulfate and concentrated in a rotary evaporator. The product is fractionally distilled in vacuo. The distillate solidifies after some time to give white crystals. Yield: 180 g (86%), boiling point: 115-120°C/0.1 mbar, melting point: 40-41°C.

5.3 Preparation of 2,3;4,5-di-O-isopropylidene-aldehydo-D-arabinose 6

131 g (0.5 mol) of the two diols 4 and 5 are dissolved in 1.3 l of dichloromethane in a 2 l three-neck flask with a stirrer with glass shaft and bearing, reflux condenser and dropping funnel and, while stirring vigorously, 160.4 g (0.75 mol) of sodium metaperiodate are added. The suspension is stirred vigorously at 33-35°C for 2 h after 50 ml of saturated sodium bicarbonate solution have been added. Then 250 g of magnesium sulfate are added and stirring is continued for 15 min. Filtration is followed by washing the filter cake thoroughly with dichloromethane several times. The filtrates are combined, the solvent is removed in a rotary evaporator, and the product is fractionally distilled.

Yield: 86 g (75%), boiling point: 85-90°C/0.1 mbar, n_D^{20}: 1.444

5.4 Preparation of 2,3;4,5-di-O-isopropylidene-1-(4-vinylphenyl)-D-gluco(D-manno)-pentitol 7

9.9 g (0.41 mol) of magnesium are introduced under inert conditions (nitrogen atmosphere and exclusion of moisture) into a 1 l three-neck flask with a stirrer with glass shaft and bearing, reflux condenser and dropping funnel. 57 g (0.41 mol) of 4-chlorostyrene are dissolved in 200 ml of dry THF and, after the reaction has been started with a little 1,2-dibromomethane, added dropwise so that the reaction mixture boils gently. After the addition is complete, the mixture is stirred at room temperature for 2 h. The reaction mixture is cooled with an ice/salt bath to below 15°C. Then 80 g (0.34 mol) of the aldehyde 6 in 200 ml of dry THF are added dropwise so that the temperature does not exceed 15°C. The mixture is then stirred at room temperature for a further 2 h. It is hydrolyzed by pouring into ice-water. The precipitated magnesium salts are dissolved by cautiously metering in 10% strength hydrochloric acid. The pH should not fall below 4.5 during this. The aqueous phase is extracted with ether. The combined organic phases are neutralized with sodium bicarbonate solution and dried over sodium sulfate. The solvent is removed in a rotary evaporator. The resulting syrup can be purified by column chromatography (eluent A, R_f = 0.40). This removes in particular styrene, which elutes first, and polymer which has been produced. After this prepurification, the product crystallizes in a refrigerator and can be recrystallized from petroleum ether/diethyl ether. Yield 60-70%. Melting point: 77°C (diastereomer A) or 59°C (mixture of diastereomers A + B).

5.5 Preparation of 2,3;4,5-di-O-isopropylidene-D-arabino 4-vinylphenyl ketone 8

15.7 ml (0.18 mol) of oxalyl chloride are introduced under inert conditions into 160 ml of dry dichloromethane, and the mixture is cooled to -60°C using an acetone/dry ice bath. A temperature of -50°C must not be exceeded in the subsequent reactions. While stirring vigorously, 15.3 ml (0.22 mol) of dimethyl sulfoxide dissolved in 50 ml of dichloromethane are added dropwise. After the addition is complete, the mixture is stirred for 15 min. Then 50 g (0.15 mol) of arasty 7 in 150 ml of dichlormethane are added, and the mixture is stirred for a further 25 min. Finally, 55.0 ml (0.39 mol) of triethylamine are

added and the mixture is stirred for 10 min. After the solution has warmed to room temperature, the same volume of water is added to the reaction mixture. The aqueous phase is extracted twice with dichloromethane, and the combined organic phases are washed successively with 10% HCl, saturated $NaHCO_3$ solution and water. Drying over sodium sulfate is followed by concentration in a rotary evaporator. The crude product is purified by column chromatography using eluent A (R_f = 0.53). The resultant crystalline product forms white needles.

Yield: 86%

Elemental analysis: $C_{19}H_{24}O_5$ 332.40	C(%)	H(%)
	calculated	68.66 7.28
	found 68.75	7.14

5.6 Preparation of 1-amino-1-deoxy-2,3;4,5-di-O-isopropylidene-1-(4-vinylphenyl)-D-gluco(D-manno)-pentitol 9

20 g of the ketone 8 (60.2 mmol) and 60 g of anhydrous ammonium acetate (0.78 mol) which are dissolved in 600 ml of dry methanol are introduced into a secured 1 l three-neck flask with bubble counter and N_2 inlet. To remove traces of water, some 3 Å molecular sieves are added. After stirring at room temperature for 30 minutes, 3 g of sodium cyanoborohydride (47.7 mmol) are added in a countercurrent of nitrogen, and the mixture is stirred at room temperature for 48 h. The reaction solution is filtered, concentrated to about 200 ml (33°C) and mixed with 200 ml of distilled water. The pH of the aqueous solution is adjusted to 10 with solid potassium hydroxide, and it is extracted with ether. The organic phase is dried with magnesium sulfate, concentrated in a rotary evaporator and purified by column chromatography (eluent D, R_f = 0.19 (diastereomer A), R_f = 0.27 (diastereomer B) or eluent E, R_f = 0.16 (diastereomer A), R_f = 0.21 (diastereomer B)). The product is a yellowish oil.

Yield: 11.58 g (57.7%)

Elemental analysis: $C_{19}H_{27}O_4N$ 333.42	C(%)	H(%)	N(%)

calculated	68.44	8.16	4.20
found	68.31	8.17	4.06

5.7 1-(4-vinylphenyl)-D-gluco(D-manno)-pentitol 10

Before the reaction, the strongly acidic ion exchanger Amberlite IR 120 is freshly activated each time. For this purpose, 15 g of ion exchanger are washed on a sintered glass filter successively with 200 ml of methanol, 1 l of distilled water, 200 ml of 2N HCl and again with distilled water until the filtrate is no longer acidic. 25 g of the protected 7, dissolved in 100 ml of distilled ethanol, are introduced into a 1 l three-neck flask with a stirrer with glass shaft and bearing (Teflon blades), dropping funnel with N_2 flushing and open neck. 250 mg of p-methoxyphenol are added, and 50 ml of distilled water are slowly added while stirring through the dropping funnel, and then 15 g of the activated ion exchanger are added. The mixture is heated slowly to 80°C and, above 50°C, 650 ml of water are slowly added dropwise. During the reaction, N_2 is continuously passed through the apparatus in order to remove the acetone produced, and ethanol, from the reaction mixture. The mixture is left to stir at 80°C for 18 h. The reaction can be followed by thin-layer chromatography (eluent A). In contrast to the precursor, the product remains on the baseline. The mixture is allowed to cool to room temperature, the ion exchanger is filtered off, and the aqueous phase is extracted with diethyl ether. The aqueous phase is concentrated in a

rotary evaporator at 33°C and is freeze-dried. The product can be recrystallized from ethanol or ethyl acetate.

Yield: 17.1 g(90%)

Melting point: 140-141°C

Sulphation of 1-(4-vinylphenyl)-D-gluco(D-manno)-pentitol 10

11.27 g (44.3 mmol) of the unprotected vinyl-sugar 10 are dissolved in 450 ml of dry pyridine in a flask which is flushed with nitrogen and, after the addition of some 4Å molecular sieves, stirred with 27.71 g (170.6 mmol = 3.85 mole equivalents) of the sulphur trioxide/pyridine complex (98%) at room temperature. The reaction is stopped after 48 hours by hydrolysis with half the volume of distilled water. The mixture is adjusted to pH 7 with saturated barium hydroxide solution and filtered. The pyridine is removed from the filtrate azeotropically with water at a bath temperature below 40°C, it being necessary to check maintenance of the pH frequently and, if necessary, correct it by further addition of barium hydroxide solution. Excess barium ions are precipitated by passing in a stream of CO_2 gas and are filtered off. The solution is finally stirred with Amberlite IR-120 (Na^+ form) ion exchanger, again filtered, concentrated and freeze-dried. The product 12 results from this as an amorphous whitish/yellowish solid for which investigation by elemental analysis found a degree of substitution with sulphate groups of DS = 3.82.

Yield: 22.5 g (79%)

5.8 Preparation of 1-amino-1-deoxy-1-(4-vinylphenyl)-D-gluco(D-manno)-pentitol 11

1 g of the amine 9 (3 mmol) is dissolved in 10 ml of distilled ethanol, and a spatula tip of inhibitor (p-methoxyphenol) is added. The mixture is then heated slowly to 80°C while a total of 60 ml (6 mmol) of 0.1 N HCl are added dropwise. After 8 h at 80°C, the aqueous solution is allowed to cool and is extracted with diethyl ether. The solution is stirred with a large excess of IRA 400 anion exchanger (OH^- form), and the ion exchanger is subsequently filtered off. The solution is then strongly alkaline. It is concentrated to a small volume in a rotary evaporator (33°C) and freeze-dried. Yield: 0.5 g (65.8%)

Elemental analysis: $C_{13}H_{19}O_4N$ 253.30	C(%)	H(%)	N(%)
calculated	61.64	7.56	5.53
found	61.53	7.53	5.45

5.9 Preparation of N- and O-sulfated (sodium salt) 1-amino-1-deoxy-1-(4-vinylphenyl)-D-gluco(D-manno)-pentitol 13.

1 g (3.95 mmol) of deprotected amine 11 is dissolved in 60 ml of pyridine in a secured 500 ml three-neck flask with bubble counter and N_2 inlet, and some molecular sieves (4 Å) are added. After stirring at room temperature for 15 min, 3.77 g (23.7 mmol) of sulfur trioxide/pyridine complex are added, and the mixture is stirred at room temperature for 68 hours. Hydrolysis takes place first with 100 ml of distilled water and then with saturated barium hydroxide solution until

a pH of about 9.5 is reached. The pyridine is removed azeotropically with water (35°C). The solution is continuously alkaline during this. The excess of barium ions is precipitated as barium carbonate by passing in carbon dioxide. After centrifugation, the solution is stirred with a large excess of amberlite IR 120 (Na^+ form). Concentration in

a rotary evaporator and freeze drying result in a white powder.

Yield: 84%

Elemental analysis: $C_{13}H_{15.3}O_{15.1}NS_{3.7}Na$ 630.84

	C(%)	H(%)	N(%)	S(%)
calculated	24.75	2.44	2.22	18.80
found	24.45	2.46	2.00	19.20

5.10 Preparation of 4-vinylbenzoic acid

A solution of 28 g (0.20 mol) of 4-chlorostyrene in 150 ml of dry THF is added dropwise under inert conditions to 4.9 g (0.20 mol) of magnesium turnings in such a way that the reaction mixture boils gently. After the addition is complete, the mixture is allowed to cool to room temperature with stirring. A stream of dry carbon dioxide is passed onto this solution. During this, it is cooled with an ice/salt bath so that the internal temperature does not exceed 15°C. When no further rise in temperature is detected, carbon dioxide is passed in for a further 30 min. The Grignard solution is hydrolyzed by pouring into ice-water. The solution is cautiously acidified with 10% strength hydrochloric acid until the pH finally reaches 1. The aqueous phase is extracted with 200 ml of diethyl ether, saturated with NaCl and again extracted three times with 100 ml of diethyl ether each time. The combined organic phases are shaken three times with 100 ml of 10% strength sodium carbonate solution each time, and the combined sodium carbonate extracts are washed with diethyl ether. The aqueous phase is cautiously acidifed with concentrated hydrochloric acid, again saturated with NaCl and exhaustively extracted with diethyl ether. The combined organic phases are evaporated to dryness by a rotary evaporator. The resulting residue is recrystallized from ethanol/water.

Yield: 16 g (52%), melting point 143°C

Elemental analysis: $C_{21}H_{28}O_6$ 376.45

	C(%)	H(%)
calculated	67.00	7.50
found	67.00	7.67

5.11 Preparation of sodium 4-vinylbenzoate

39.9 ml of a 1N NaOH solution (39.9 mmol) are added to 5.93 g of 4-vinylbenzoic acid (40 mmol). The aqueous phase is extracted with ether to remove excess 4-vinylbenzoic acid. The aqueous solution is freeze-dried. 6.79 g of sodium 4-vinylbenzoate are obtained as a white solid.

5.12 Preparation of a terpolymer from monomers 12, 13 and sodium 4-vinylbenzoate

1 g (2 mmol) of the deacetalized, O-sulfated (sodium salt) compound 12, 1 g (2 mmol) of the deacetalized, N- and O-sulfated (sodium salt) compound 13, 0.35 g (2 mmol) of sodium 4-vinylbenzoate and 0.012 g of ABAH (0.75 mol% based on all the monomers employed) are introduced into a secured 25 ml one-neck flask which is provided with a three-way tap for connection to a vacuum line and septum. Double-distilled water is degassed three times by freezing and thawing the solution in vacuo. A Hamilton syringe is used to remove 8 ml of the degassed water in a countercurrent of N_2 and add it to the monomers, likewise in countercurrent. The solution is heated with magnetic stirring in an oil bath at 80°C for 72 h. After the reaction is complete, the mixture is cooled and the polymer is precipitated in 150 ml of cold ethanol. The polymer is dried with phosphorus pentoxide at the oil pump. Yield: 75%.

5.13 Determination of the heparin-analogous activity of the terpolymer 5.12 by comparison of the coagulation times on addition of the terpolymer and of heparin to two donated plasmas

The coagulation time measured by the partial thrombo-plastin time (PTT) is influenced by anticoagulant substances such as heparin. The PTT is determined by mixing blood plasma with a contact activator and with phospholipids and calcium ions, and thus initiating activation of the contact activators and catalyzing the activation of the intrinsic coagulation system. When the test is carried out in practice, blood plasma is mixed with the contact activator (for example kaolin) and phospholipids (for example cephalin) and incubated at 37°C for 3 minutes. Then calcium chloride is added and the coagulation time (PTT) is measured. To test for heparin-analogous activity, the PTT of the terpolymer was compared with the PTT of heparin as a function of the dose. The doses are indicated in I.U./ml. The I.U. (international heparin unit) is the amount of heparin defined in US Pharmacopeia XXIII which, under defined conditions, catalyzes the conversion of

1 µmol of substrate per min.

The thrombin time (TT) is another measure of the anticoagulant effect of a substance. In the final phase of coagulation, fibrinogen becomes insoluble fibrin, a soft clot, which is converted by covalent crosslinking into a hard clot. This reaction is catalyzed by thrombin and slowed down by anticoagulant substances such as heparin. To determine the heparin-analogous activity of the terpolymer, the TT of the terpolymer was compared with the TT of heparin as a function of the dose. The doses are once again indicated in I.U./ml.

For comparing the coagulation times (PTT and TT) of the terpolymer with those of heparin, a standard heparin sample (molecular weight 13,000), whose content was stated by the manufacturer to be 1000 I.U. per milliliter, was used with 30 mg of heparin per milliliter. The measured molecular weight of the terpolymer of 149,000 (GPC/light scattering) was rounded down to 100,000 because an error in the molecular weight in a downward direction may lead to a smaller weight of the polymer sample and thus can influence the result of the coagulation test only to the disadvantage of the terpolymer. On the other hand, a molecular weight assumed to be too large would simulate a stronger effect. Thus, a sample weight of 0.23 g of terpolymer/ml provides a content likewise of 5000 I.U./ml. The effects of the terpolymer on the coagulation times (PTT and TT) by comparison with heparin were investigated in the range between 0.1 and 5 I.U. To carry out the comparative test, 9 parts by volume of whole blood were mixed with 1 part by volume of appropriately diluted standard solution of heparin or of the terpolymer. The coagulation times PTT and PT were determined after centrifugation of the blood and removal of the plasma as described previously. Coagulation times above 10 minutes were not measured by the coagulator (supplied by Amelung, D-32657 Lemgo) and have therefore been reported as > 600 s.

Table 1

Effects of the terpolymer from 5.12 (TP) compared with heparin (HP) on the

PTT of two donated plasmas

Dosage (I.U.)	PTT (sec)			
	Donor 1		Donor 2	
	HP	TP	HP	TP
-	34.5	33.9	31.9	33.3
0.01	35.5	30.9	34.3	30.7
0.05	46.0	32.6	46.0	37.3
0.1	68.5	36.7	68.0	43.3
0.2	109.7	53.5	97.1	54.6
0.3	155.5	84.6	104.5	67.9
0.4	179.7	157.3	123.9	109.0
0.5	248.8	209.3	184.5	128.9
1.0	574.6	>600	387.4	>600
5.0	>600		>600	

Table 2

Effects of the terpolymer from 5.12 (TP) compared with heparin (HP) on the TT of two donated plasmas

Dosage (I.U.)	TT (sec)			
	Donor 1		Donor 2	
	HP	TP	HP	TP
-	17.2	17.0	14.9	14.5
0.01	19.5	16.9	15.5	15.4
0.05	34.6	16.9	41.7	18.6
0.1	375	18.2	280.9	20.9
0.2	>600	21.9	425.8	26.1
0.3		26.3	>600	37.1
0.4		32.4		39.2
0.5		32.3		39.2
1.0		47.4		56.4
5.0		>600		>600

It is evident from the tables that the terpolymer achieves a higher PTT by comparison with heparin, even with a lower dosage. It emerged from measurement of the TT that the level reached with 0.2 I.U. heparin is achieved only with 5.0 I.U. terpolymer and above.

5.14 3,4;5,6-di-O-isopropylidene-D-gluconic acid diethylamide 14 and 2,3;5,6-di-O-isopropylidene-D-gluconic acid diethylamide 15

250 g of D-gluconolactone 1 are suspended in 500 ml of diethylamine and stirred at room temperature overnight. The solution is concentrated in vacuo, and before the viscous syrup solidifies it is placed in a dish in order to allow remaining diethylamine to evaporate from the crystallizing D-gluconic acid diethylamide. 80 g of the yellow crude product are added to a mixture of 1500 ml of acetone and 35 ml of concentrated sulfuric acid and stirred at room temperature for 15 hours. The mixture is neutralized by pouring into

1800 ml of 1N sodium hydroxide solution while cooling in ice, the acetone is removed in a rotary evaporator, and the aqueous solution is exhaustively extracted with methylene chloride. The combined organic phases are washed with water, dried over anhydrous sodium sulfate and concentrated. The crude product is fractionally distilled under oil pump vacuum. The yield of the mixture of the two protected regioisomeric amides 14, 15 in the form of a yellow syrup is 88%.

5.15 2,3;5,6-Di-O-isopropylidene-1-(4-vinylphenyl)-keto-D-glucose 16 and 3,4;5,6-Di-O-isopropylidene-1-(4-vinylphenyl)-keto-D-glucose 17

79.20 g (0.24 mol) of the protected regioisomeric amides 14, 15 are introduced into 120 ml of dry tetrahydrofuran in an apparatus which is flushed with nitrogen. At an internal temperature of <0°C, 210 ml of a 1M ethylmagnesium bromide solution (0.21 mol) are slowly added dropwise before, after increasing the temperature to 15°C, 460 ml of a 1M solution of 4-vinylphenylmagnesium chloride in tetrahydrofuran (0.46 mol) are added. After stirring at room temperature for 3 hours, the mixture is hydrolyzed by cautious dropwise addition of 500 ml of water while cooling in ice, the pH is adjusted to 2 with concentrated hydrochloric acid, and the organic phase is separated off. The aqueous phase is extracted three times with diethyl ether, and the combined organic phases are washed with saturated sodium bicarbonate solution to neutrality, dried over anhydrous sodium sulfate and concentrated at a bath temperature of <35°C. The resulting crude product is a yellow syrup obtained in a yield of 100%. An analytically pure mixture of isomers 16, 17 can be obtained by final purification by column chromatography with the eluent petroleum ether 40/60 and diethyl ether (3:2). However, the crude product is always employed for the subsequent reactions without any disadvantages for the purity of the final products being detectable.

5.16 1-(4-Vinylphenyl)-keto-D-glucose 18

For deprotection, 25 g of the crude products 16, 17 are added dropwise to 300 ml of distilled ethanol, and the precipitated polymer portions are filtered off. The filtrate is slowly added dropwise over the course of 5 hours to a mixture of 1300 ml of water, 200 ml of distilled ethanol, 20 g of Amberlite(R) IR-120 ion exchanger (H^+ form) and 300 mg of 4-methoxyphenol at 80°C. After a further hour, the ion exchanger is filtered off, and the filtrate is concentrated to 150 ml and extracted twice with diethyl ether. Freeze drying of the aqueous phase results in an amorphous white powder in a yield of 70 to 75% based on 16, 17.

5.17 1-(4-Vinylphenyl)-D-glycero-D-gulo(D-ido)-hexitol 21

The starting material once again is the crude product 16, 17. For reduction, 10 g (max. 28 mmol) are added dropwise to 100 ml of distilled ethanol, and precipitated polymer portions are filtered off. A solution of 0.76 g (20 mmol) of sodium borohydride in 40 ml of distilled ethanol is added over the course of one hour to the ice-cooled filtrate. After stirring at room temperature for a further 2 hours, the reduction is complete (checked by TLC with the mobile phase n-hexane/ethyl acetate 2:1). The reaction solution is concentrated to half the volume, 100 ml of water are added, and the mixture is extracted with diethyl ether. The combined organic phases are washed with water, dried over anhydrous sodium sulfate and concentrated.

The yellow syrupy residue is taken up in 150 ml of distilled ethanol and added dropwise over the course of 3 hours to a mixture of 500 ml of water, 80 ml of distilled ethanol, 8 g of Amberlite(R) IR-120 ion exchanger (H^+ form) and 120 mg of 4-hydroxyphenol at 80°C. The mixture is stirred for a further hour, then the ion exchanger is filtered off, and the filtrate is concentrated to about 150 ml, extracted twice with diethyl ether and freeze-dried. The product 21 results in this case as an amorphous white powder and can be recrystallized from ethyl acetate or ethanol, although this affects merely the diastereomer ratio but not the purity of the product. The yield is 75 to 80% based on 16, 17.

5.18 1-Amino-1-deoxy-1-(4-vinylphenyl)-D-glycero-D-gulo(D-ido)-hexitol 24

For the reductive amination, 10 g of the crude product 16, 17 are added dropwise to 100 ml of dry methanol, and precipitated polymer portions are filtered off. The filtrate is blanketed with nitrogen and some 3Å molecular sieves are added. In a countercurrent of nitrogen, 21.58 g (0.28 mol) of ammonium acetate are added and, after stirring at room temperature for one hour, 1.31 g (18.8 mmol) of sodium cyanoborohydride (90%) are added. After 48 hours, the mixture is filtered, concentrated to half the volume, mixed with 100 ml of water and extracted with diethyl ether. The aqueous phase is then adjusted to pH 10 with solid potassium hydroxide and is again extracted with diethyl ether. The combined organic phases are washed with water, dried over anhydrous sodium sulfate and concentrated. Unconsumed precursor and by-products are removed by means of a filtration column (Rf>0.35, eluent acetic acid/n-hexane/triethylamine 80:20:1).

All the later fractions are concentrated, taken up in 150 ml of distilled ethanol and added dropwise over the course of 4 hours to a mixture of 500 ml of water, 80 ml of distilled ethanol, 8 g of Amberlite$^{(R)}$ IR-120 ion exchanger (H^+ form) and 120 mg of 4-methoxyphenol. One hour after the addition is complete, the ion exchanger is filtered off, and the filtrate is concentrated to about 150 ml, extracted twice with diethyl ether and freeze-dried. The product 24 results in this case as an amorphous white powder. The yield is up to 17% based on 16, 17.

5.19 Sulfation of 18; 21; 24/ standard method

The deprotected vinyl monomers are introduced into a flask flushed with nitrogen and dissolved by adding 40 ml of dry pyridine per gram of vinyl monomer in a countercurrent of nitrogen. After addition of some 4Å molecular sieves, the mixture is stirred at room temperature for half an hour before the amount of SO_3/pyridine complex (98%) in mole equivalents corresponding to the required degree of sulfation is added. After 24 hours, the reaction is

stopped by adding half the volume of distilled water. The mixture is adjusted to pH 7 with saturated barium hydroxide solution and filtered. The pyridine is removed from the filtrate as azeotrope with water at <40°C, the pH being checked frequently and corrected if necessary by adding further barium hydroxide solution. Excess barium ions are precipitated by passing in a stream of CO_2 gas, and the precipitate is filtered. The solution is then stirred with Amberlite(R) IR-120 ion exchanger (Na^+form), filtered again, concentrated and freeze-dried. The sulfated products 22 and 25 result in this case as white powders, and the sulfated products 19 result as yellow powder. The yield is 70 to 95% based on the respective precursors.

5.20 Copolymers from monomers II, III and/or IV and comonomer VIII
Standard method

The water-soluble sulfated monomers II, III and/or IV are introduced together with sodium 4-vinylbenzoate as comonomer VIII into a flask fitted with three-way tap and septum together with the free-radical initiator V50 (2,2'-azobis(2-amidinopropane) dihydrochloride). Double-distilled water is degassed three times by freezing and thawing the solution in vacuo. This water is added through the septum using a gas-tight syringe. The resulting solution is heated to 60°C in a temperature-controlled oil bath. To stop the polymerization, the cooled mixture is added to 15 times the volume of cold ethanol, and the precipitated polymer is isolated by centri-fugation. After drying over phosphorus pentoxide at the oil pump, the copolymers comprising monomers 22 and 25 are in the form of a white powder, and those comprising monomer 19 have a yellowish/brownish color. The yields are 50 to 98%.

5.21 Determination of the heparin-like activity of the copolymers from 22, 25 and/or 19 plus sodium 4-vinylbenzoate

The heparin-like activity of the copolymers was checked by comparing the partial thromboplastin times (PTT) and the prothrombin times (PT) on addition of copolymer or of standardized heparin as described under 5.13.

The copolymers according to the invention show better effects than standard heparin in both tests.

5.22 1-(4-Vinylphenyl)-D-manno(D-gluco)-hexulo-2,6-pyranose

Amberlite(R) IR 120 ion exchanger is activated by treating 10 g with 100 ml of 2N HCl for 10 min and washing successively with 100 ml of distilled water, 100 ml of methanol and again with 100 ml of distilled water. Then 10 g of 2,3;4,5-di-O-isopropylidene-1-(4-vinylphenyl)-D-manno(D-gluco)-hexulo-2,6-pyranose are introduced into 100 ml of ethanol in a flask under nitrogen, and 250 mg of 4-methoxyphenol are added. 50 ml of water are slowly added while stirring, and then the activated ion exchanger is added. To retain the particulate structure of the ion exchanger, a stirrer with Teflon(R) blades is used. The mixture in the flask is heated slowly while stirring. When the temperature reaches 50°C, dropwise addition of water is started. The mixture in the flask is kept at 70 to 80°C for 18 to 24 h. The extent of deprotection is checked by thin-layer chromatography. The mobile phase used is a mixture of petroleum ether (40-60°C) and diethyl ether in the ratio 3:2 by volume. After cooling the mixture, the ion exchanger is filtered off, and the aqueous solution is extracted three times with diethyl ether. The aqueous solution is concentrated in a rotary evaporator in vacuo at 35 to 38°C. Freeze drying results in the crude final product as a white powder. The pure product is obtained in the form of white crystals of melting point 161-163°C by dissolving in ethanol and filtering the solution into excess diethyl ether. $[\alpha]_D$ = -40.8°·dm^{-1}·g^{-1}cm^3 (c = 1.0 g/dl H_2O). IR (KBr): 3,520, 3,400 (OH), 3,180 (C=CH), 2,960, 2,920, 2,880 ((C-H), 1,630 (C=C), 1,510 cm^{-1} (C=C arom.)

5.23 6-(4-Vinylphenyl)-D-glycero(L-glycero)-α-D-galactopyranose

The procedure is as in Example 5.22 but the starting material employed is 15 g of 1,2;3,4-di-O-isopropylidene-6-(4-vinylphenol)-D-glycero(L-glycero)-α-D-galactopyranose. The product is obtained as a white powder which cannot be recrystallized. The yield is 80%.

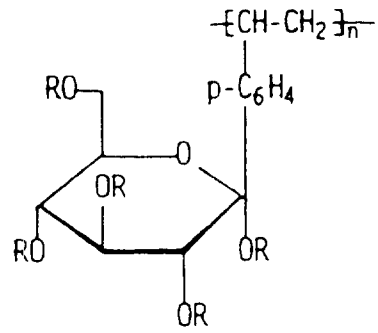
$[\alpha]_D$ = +45.1°·dm^{-1}·g^{-1}·cm^3 (c 1.0 g/dl H_2O). IR (KBr): 3,330 (OH), 2,900 (C-H), 1625 (C=C) and 1,510 cm^{-1} (C=C arom.).

5.24 Sulfation of 1-(4-vinylphenyl)-D-manno(D-gluco)-hexulo-2,6-pyranose

1 g (3.5 mmol) of starting material is dissolved in 60 ml of pyridine in a secured 500 ml three-neck flask with bubble counter and three-way tap, and some 3Å molecular sieves are added. After stirring for 15 min, 1.69 g of sulfur trioxide/pyridine complex are added, and the mixture is stirred at room temperature for ... hours. Hydrolysis takes place by adding first 100 ml of distilled water and then saturated barium hydroxide solution until a pH of 9.5 is reached. The pyridine is removed as azeotrope with water (35°C), the solution being continuously alkaline. The excess of barium ions is precipitated as barium carbonate by passing in carbon dioxide. After removal thereof by centrifugation, the solution is stirred with a large excess of Amberlite(R) IR 120 in the Na^+ form. Concentration in a rotary evaporator results in the product as white powder.

5.13 Determination of the heparin-analogous activity of a sulfated homopolymer

The homopolymer had the formula

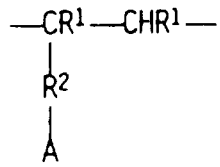


(R = H or -SO_3Na, degree of sulfation 2.68; n corresponds to a molecular weight of about 100,000 determined by light scattering). Measurement of the PTT as in Example 5.13 yielded a figure of 63 sec on addition of the

homopolymer (dosage 0.5 I.U./ml) compared with a PTT of 30 sec without this addition. The homopolymer thus had an anticoagulant effect. The dosage of 0.5 I.U./ml is equivalent to a dosage of unfractionated heparin of 0.17 I.U./ml. The anticoagulant activity is thus distinctly less pronounced than that of heparin.

Claims

1. A heparin-analogous homo- or copolymer comprising repeating units of the formula I



I

in which

R^1 is in each case independently hydrogen or the methyl radical,

R^2 is a linker and

A is a sulfated polyol, polyamine or (poly)amine-(poly)ol radical which may comprise one or more acetalized or aminalized carbonyl functional-ities.

2. A polymer as claimed in claim 1, wherein

R^1 is in each case hydrogen;

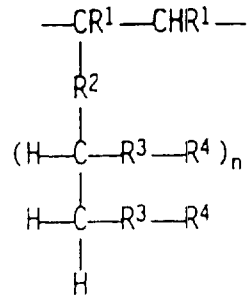
R^2 is inorganic or organic in nature and is O, S, SO, SO_2 or NR' where R' is a hydrocarbon radical having 1 to 12 carbon atoms, a divalent organic radical, in particular an aliphatic, cycloaliphatic or aromatic hydrocarbon radical, having up to 10 carbon atoms, a carboxylic ester bridge -O-CO-, a carboxamide bridge -NR'-CO- or a urethane bridge -O-CO-NR'-, where R' has the stated meaning, or a C-C single bond; and/or

A is a monovalent radical which is derived from a compound which has at least 2 hydroxyl and/or amino groups and comprises at least one radical $-O-SO_3^-M^+$ (O-sulfate radical) or $-NH-SO_3^-M^+$ (N-sulfate or sulfamate radical), where M is an alkali metal ion, and may additionally comprise at least one carbonyl functionality which, by intramolecular acetalization or aminalization, forms a tetrahydrofuran or pyrrolidine ring (with 5 ring members in each case) or a pyran or pentamethyleneimine ring (with 6 ring members in each case).

3. A polymer as claimed in claim 2, wherein R^2 is an aliphatic, cycloaliphatic or aromatic hydrocarbon radical having up to 10 carbon atoms, and/or A is derived from a compound which comprises 2 to 8 carbon atoms, in which M^+ is a sodium ion, and which comprises 1 or 2 carbonyl functionalities which have undergone intramolecular acetalization or aminalization.

4. A polymer as claimed in claim 2 or 3, wherein A is derived from a compound which comprises 5 or 6 carbon atoms.

5. A polymer as claimed in any of claims 2 to 4, which comprises repeating units of the formula IIIa



IIIa

in which

R^1 and R^2 have the meanings stated in claims 1 to 4,

R^3 is O or NH,

R^4 is hydrogen or the radical $-SO_3^-Na^+$, and

n is 4 or 5;

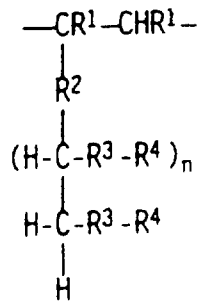
with the proviso that at least one of the substituents R^4 is a radical $-SO_3^-Na^+$.

6. A polymer as claimed in claim 5, wherein the repeating units are derived from a pentitol.

7. A polymer as claimed in claim 5, wherein the repeating units are derived from a hexitol.

8. A polymer as claimed in any of claims 2 to 4, which comprises

repeating units of the formula



IVa

in which

R^1, R^2, R^3, R^4 and n have the meanings stated in claims 1 to 4; with the proviso that

(1) at least once per molecule, substituents H and $-R^3-R^4$ on the same carbon atom form with this carbon atom a carbonyl functionality C=O which has undergone intramolecular acetalization or aminalization by a hydroxyl or amino functionality in position 3 relative to the carbonyl functionality to form a tetrahydrofuran or pyrrolidine ring or by a hydroxyl or amino functionality in position 4 relative to the carbonyl functionality to form a pyran or pentamethyleneimine ring, and that

(2) at least one of the substituents R^4 is a radical $-SO_3^-Na^+$.

9. A polymer as claimed in claim 8, wherein the repeating units comprise 1 or 2 carbonyl functionalities which have undergone intramolecular acetalization or aminalization.

10. A polymer as claimed in any of claims 5 to 9, wherein R^2 is an alkylene radical having 1 to 4 carbon atoms, a phenylene radical or a C-C single bond.

11. A polymer as claimed in any of claims 8 to 10, wherein the repeating units are derived from a pentose.

12. A polymer as claimed in any of claims 8 to 10, wherein the repeating units are derived from a hexose.

13. A polymer as claimed in any of claims 5 to 12, wherein 1 to 4 substituents R^4 are $-O-SO_3^-Na^+$ (O-sulfate) and/or $-NH-SO_3^-Na^+$ (N-sulfate).

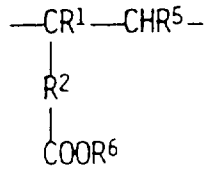
14. A polymer as claimed in any of claims 1 to 13, which is a homopolymer having only one repeating unit covered by formulae I, IIIa or IVa.

15. A polymer as claimed in any of claims 1 to 13, which is a copolymer composed of at least two repeating units covered by formulae I, IIIa or IVa.

16. A copolymer as claimed in claim 15, which has a repeating unit IIIa or IVa which comprises only O-sulfate radicals, and another repeating unit IIIa or IVa which comprises an N-sulfate radical adjacent to R.

17. A copolymer as claimed in claim 15, wherein the molar ratio of the two species is from 1:100 to 100:1.

18. A copolymer as claimed in any of claims 15 to 17, which is a copolymer composed of at least one repeating unit covered by the formulae I, IIIa or IVa and at least one other repeating unit of the formula VIIIa



VIIIa

in which

R^1 and R^2 have the meanings stated in claims 1 to 4,

R^5 is hydrogen, the methyl radical or the radical $-R^2-COOR^6$ and

R^6 is hydrogen or a sodium ion.

19 A copolymer as claimed in claim 18, wherein the molar ratio of

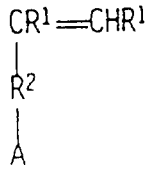
carboxyl and/or carboxylate groups in the repeating unit(s) VIIIa to the total of the O-sulfate and/or N-sulfate groups in the repeating unit(s) I, IIIa or IVa is 100:1 to 1:100.

20. A copolymer as claimed in any of claims 15 to 19, which additionally has at least one repeating unit which comprises neither sulfate nor carboxyl or carboxylate groups.

21. A homo- or copolymer as claimed in any of claims 1 to 20, which has a molecular weight of from 5000 to 1,500,000.

22. A homo- or copolymer as claimed in claim 21, which has a molecular weight of from 50,000 to 800,000.

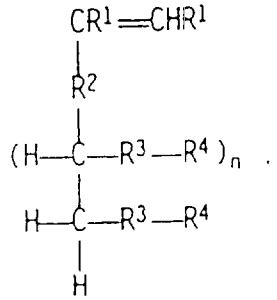
23. A sulfate group-containing monomer of the formula II



II

in which R^1, R^2 and A have the meanings stated in claims 1 to 4.

24. A sulfate group-containing monomer as claimed in claim 23, which corresponds to the formula III, which is covered by formula II,



III

in which R^1 and R^2 have the meanings stated in claims 1 to 4,

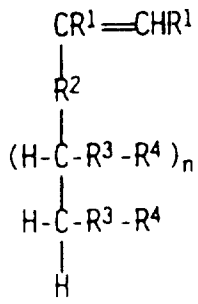
R^3 is O or NH,

R^4 is hydrogen or the radical $-SO_3^-Na^+$, and

n is 4 or 5;

with the proviso that at least one of the substituents R^4 is a radical $-SO_3^-Na^+$.

25. A sulfate group-containing monomer as claimed in claim 23, which corresponds to formula IVa, which is covered by formula II



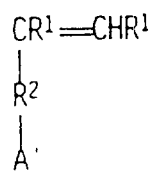
IVa

in which R^1, R^2, R^3, R^4 and n have the meanings stated in claim 24; with the proviso that

(1) at least once per molecule, substituents H and $-R^3-R^4$ on the same carbon atom form with this carbon atom a carbonyl functionality C=O which has undergone intramolecular acetalization or amin-alization by a hydroxyl or amino functionality in position 3 relative to the carbonyl func-tionality to form a tetrahydrofuran or pyrrolidine ring or by a hydroxyl or amino functionality in position 4 relative to the carbonyl functionality to form a pyran or pentamethyleneimine ring, and that

(2) at least one of the substituents R^4 is a radical $-SO_3^-Na^+$.

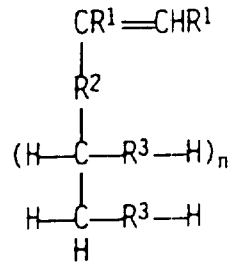
26. A sulfate group-free monomer of the formula V, VI or VII:



V

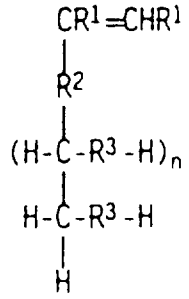
in which R^1 and R^2 have the meanings stated in claims 1 to 4, and

A' is a nonsulfated polyol, polyamine or (poly)amine(poly)ol radical which may comprise one or more acetalized or aminalized carbonyl functionalities:



VI

in which R^1, R^2, R^3 and n have the meanings stated in claim 24;



VII

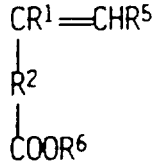
in which R^1, R^2, R^3 and n have the meanings stated in claim 25; with the proviso that

at least once per molecule, substituents H and $-R^3-R^4$ on the same carbon atom form with this carbon atom a carbonyl functionality C=O which has undergone intramolecular acetalization or aminalization by a hydroxyl or amino functionality in position 3 relative to the carbonyl functionality to form a tetrahydrofuran or pyrrolidine ring or by a hydroxyl or amino functionality in position 4 relative to the carbonyl functionality to form a pyran or pentamethyleneimine ring;

excepting 1-(4-vinylphenyl)-D-gluco(D-manno)-pentitol, 6-(4-vinylphenyl)-D,L-glycero-α,β-D-galactopyranose 1-(4-vinylphenyl)-D-manno(D-gluco)-hexulo-2,6-pyranose and 1-vinyl-β-D-fructopyranose.

27. A process for preparing the heparin-analogous homo- or copolymers

as claimed in any of claims 1 to 22, which comprises subjecting at least one sulfate group-containing monomer as claimed in any of claims 23 to 25 with or without at least one other monomer of the formula VIII



VIII

in which R^1, R^2, R^5 and R^6 have the meanings stated in claim 18, and/or at least one sulfate and carboxyl or carboxylate group-free vinyl monomer IX to copolymer-ization initiated by free radicals.

28. The use of the heparin-analogous homo- or copolymers as claimed in any of claims 1 to 22 for coating articles for medical use.

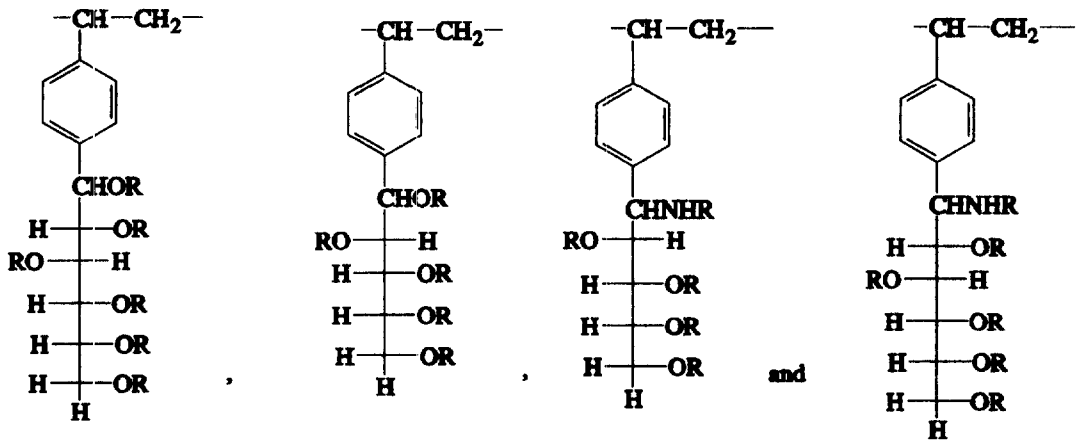
29. A product for medical use which is coated with a heparin-analogous homo- or copolymer as claimed in any of claims 1 to 22.

30. A product as claimed in claim 29, which is a heart valve, prosthesis, implant, catheter, endoscope, oxygenator, dialysis membrane or tubing.

31. The polymer as claimed in claim 5, wherein R^2 in the formula (IIIa) is a single bond or an unsubstituted aliphatic, cycloaliphatic or aromatic hydrocarbon radical having up to 10 carbon atoms.

32. The polymer as claimed in claim 5, wherein in the formula (IIIa), R^1 is hydrogen; R^2 is an alkylene radical having 1 to 4 carbon atoms, a phenylene radical or a single bond; R^3 is -O- or -NH-; R^4 is hydrogen or $-SO_3^-Na^+$; and n is 4.

33. The polymer as claimed in claim 5, wherein the repeating unit of the formula (IIIa) is represented by at least one of the formulae:



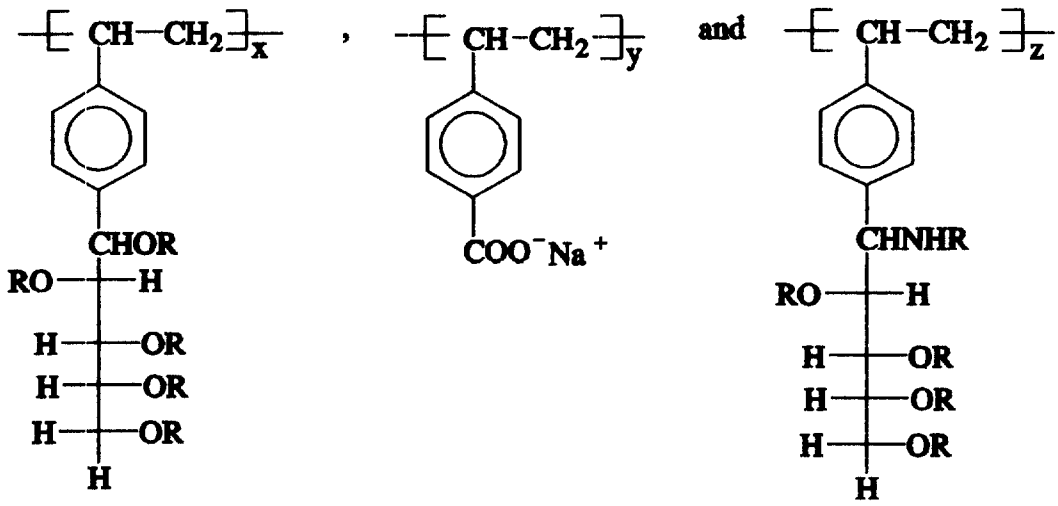
(wherein R is hydrogon or $SO_3^-Na^+$, provided that 1 to 4 of the substituents R in each unit are $SO_3^-Na^+$).

34. The copolymer as claimed in claim 18, wherein the other repeating unit is of an unsaturated carboxylic acid selected from the group consisting of acrylic acid, methacrylic acid, crotonic acid, 4-vinylbenzoic acid, maleic acid, fumaric acid, vinylsalicylic acid, itaconic acid, vinylacetic acid, cinnamic acid, 2-vinylbenzoic acid, methylmaleic acid, dimethylfumaric acid, methylfumaric acid, dihydroxymaleic acid and allylacetic acid.

35. The copolymer as claimed in claim 34, wherein the unsaturated carboxylic acid is selected from the group consisting of acrylic acid, methacrylic acid, 4-vinylbenzoic acid, 2-vinylbenzoic acid, vinylacetic acid and allylacetic acid.

36. The copolymer as claimed in claim 18 wherein in the formula (VIIIa), R^1 is hydrogen; R^2 is an alkylene radical having 1 to 4 carbon atoms, a phenylene radical or a single bond; R^5 is hydrogen or $-R^2-COO^-Na^+$; and R^6 is hydrogen or Na.

37. A heparin-analogous copolymer having a molecular weight of from 50,000 to 800,000 and being composed essentially of repeating units of formulae:



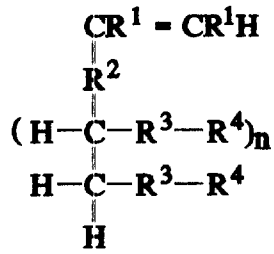
(wherein R is hydrogen or $-SO_3^-Na^+$, provided that at least one of the groups R in each unit is $-SO_3^-Na^+$; x and z are each 0 or an integer of at least 1 and y is an integer, provided that x and z are not 0 simultaneously).

38. The copolymer as claimed in claim 37, wherein both x and z are an integer of at least 1.

39. The copolymer as claimed in claim 37 or 38, which has a molar ratio of the COO^-Na^+ group to the total of the $-SO_3^-Na^+$ groups of 20:1 to 1:20.

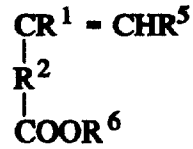
40. A process for the preparation of the copolymer as claimed in claim 19 having a repeating unit of the formula (IIIa), which comprises polymerizing a monomer mixture

comprising monomers of the formulae:



(IV)

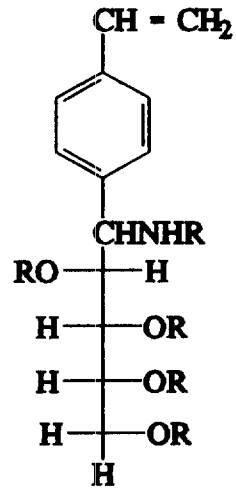
and



(VII)

(wherein R^1, R^2, R^3, R^4, R^5, R^6 and n are as defined in claim 5 and claim 19) under free radical initiation.

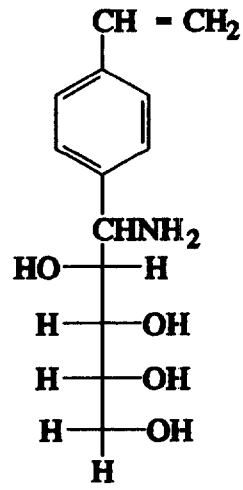
41. A process for producing sodium salt of N- and O-sulfated 1-amino-1-deoxy-1-(4-vinylphenyl)-D-gluco(or D-manno)pentitol of the formula:



13

(wherein R is hydrogen or $-SO_3^-Na^+$, provided that at least one of the groups R is $-SO_3^-Na^+$), which comprises:

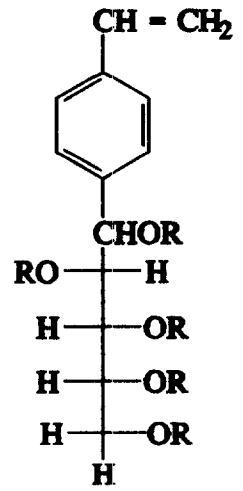
sulfating 1-amino-1-deoxy-1-(4-vinylphenyl)-D-gluco (or D-manno)pentitol of the formula:



11 , and

converting the sulfated product to its sodium salt.

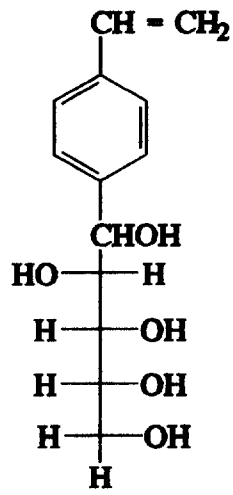
42. A process for producing sodium salt of O-sulfated 1-(4-vinyplenyl)-D-gluco (or D-manno)pentitol of the formula:



12

(wherein R is hydrogen or $-SO_3^-Na^+$, provided that at least one of the groups R is $-SO_3^-Na^+$), which comprises:

sulfating 1-(4-vinylphenyl)-D-gluco(or D-manno)pentitol of the formula:



10 , and

converting the sulfated product to its sodium salt.

43. The process of claim 41 or 42, wherein the sulfation is conducted using a sulfur trioxide-pyridine complex at room temperature in excess pyridine or other solvent in the presence of a water-binding agent.

44. The process of any one of claims 41 to 43, wherein the conversion of the sulfated product to the sodium salt comprises:

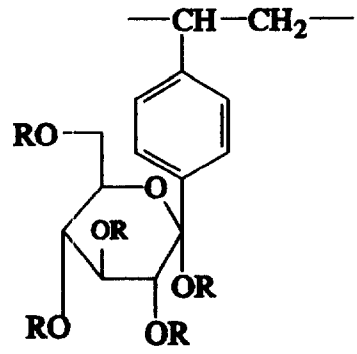
treating the sulfation reaction mixture with water and thereafter with a saturated barium hydroxide solution to keep

a pH value of the reaction mixture in the alkaline range and to precipitate out sulfate ions;

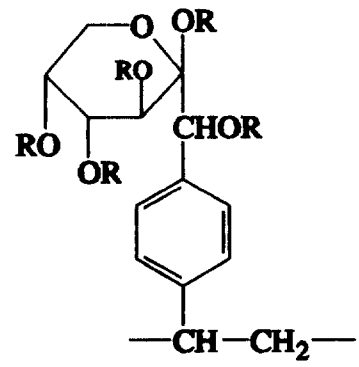
precipitating excess barium ions by passing carbon dioxide in the reaction mixture and filtering off resulting barium carbonate to obtain a filtrate; and

passing the filtrate over an ion exchanger in the Na^+ form to exchange the barium ions for sodium ions.

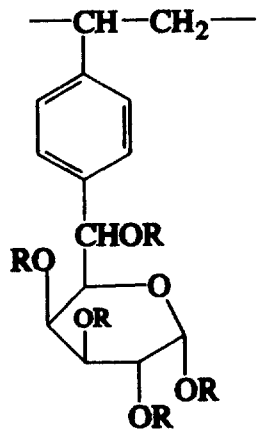
45. The polymer as claimed in claim 8, wherein the repeating unit of the formula (IVa) is represented by at least on of the formulae:



,



and



(wherein R is hydrogen or $SO_3^-Na^+$, provided that 1 to 4 of the substituents R in each unit are $SO_3^-Na^+$).

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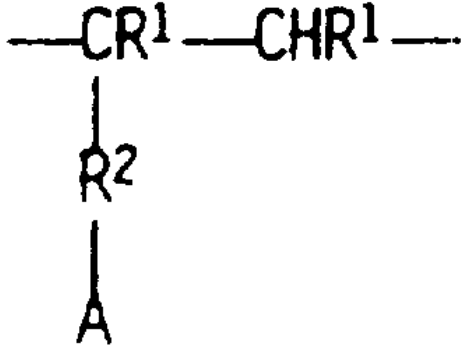

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