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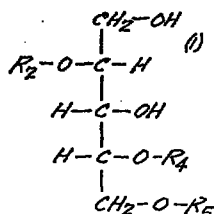


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(54) PENTOL DERIVATIVES, PROCESS FOR THEIR MANUFACTURE AND COMPOSITIONS CONTAINING THEM

(71) We CIBA-GEIGY AG. (formerly Ciba Limited), a body corporate organised according to the laws of Switzerland, of Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention concerns pentol derivatives, more particularly D-arabitol compounds of formula



wherein each of the residues R₂, R₄ and R₅ denotes an optionally substituted hydrocarbon residue, as well as O-acyl derivatives thereof.

The above compounds possess the configuration of D - arabinose.

Residues, radicals or compounds subsequently qualified by the expression "lower" contain preferably up to 7, primarily up to 4, carbon atoms unless otherwise specified.

Optionally substituted hydrocarbon residues are above all organic residues of alcohols, especially optionally substituted aliphatic, alicyclic, alicyclic-aliphatic or more especially araliphatic hydrocarbon residues, but may also represent optionally substituted aromatic hydrocarbon residues.

Aliphatic hydrocarbon residues are, for example, lower aliphatic hydrocarbon residues, above all lower alkyl, as well as lower alkenyl or lower alkynyl.

Optional substituents of these residues, especially of lower alkyl, may above all be

free or substituted amino groups, such as amino groups which are monosubstituted or disubstituted by lower alkyl, lower alkenyl, cycloalkyl or cycloalkenyl residues, as well as lower alkyleneamino, oxa-lower alkyleneamino or aza-lower alkyleneamino groups, free or functionally converted hydroxyl or mercapto groups, such as etherified or esterified hydroxyl or mercapto groups, for example, lower alkoxy groups or halogen atoms, as well as lower alkylmercapto groups, or free or functionally converted carboxyl groups, such as carbo-lower alkoxy, carbamyl or cyano groups, as well as heterocyclic residues, especially monocyclic heterocyclic residues or aromatic character, such as thienyl, furyl or pyridyl residues, these being optionally substituted like the aromatic residues referred to below. Optionally substituted aliphatic hydrocarbon residues, such as lower alkyl groups, may contain one, two or more of the same or different substituents, such as free or functionally converted hydroxyl groups, for example, lower alkoxy groups.

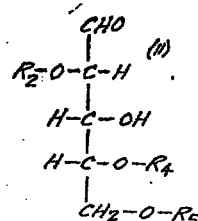
Alicyclic hydrocarbon residues, for example, contain up to 8 ring carbon atoms and above all represent corresponding cycloalkyl residues having, for example, 3—8, preferably 5—6, ring carbon atoms, as well as cycloalkenyl groups having, for example, 5—8, preferably 5—6, ring carbon atoms, these alicyclic groups being optionally mono-, di- or poly-substituted in the cycloaliphatic ring, for example, by lower alkyl residues.

Alicyclic-aliphatic hydrocarbon residues contain, for example, up to 8 ring carbon atoms and are above all corresponding cycloalkyl - lower alkyl groups, as well as cycloalkenyl-lower alkyl groups which may optionally be mono-, di- or poly-substituted in the cycloaliphatic ring, for example, by lower alkyl residues.

Araliphatic hydrocarbon residues are especially monocyclic, as well as bicyclic, arylalkyl or arylalkenyl residues, above all phenyl-lower

- alkyl, as well as phenyl-lower alkenyl residues, especially benzyl residues, as well phenylethyl, such as 1- or 2-phenylethyl residues, furthermore cinnamyl residues. They may optionally be monosubstituted, di-substituted or polysubstituted in the aromatic nucleus, for example, by lower alkyl groups, free, esterified or etherified hydroxyl or mercapto groups, for example, lower alkoxy or lower alkylenedioxy groups, as well as lower alkylmercapto groups, or halogen atoms and/or trifluoromethyl groups.
- Aromatic hydrocarbon residues are, for example, monocyclic or bicyclic residues of such type, above all phenyl groups. They may be substituted, for example, like the aromatic nucleus of an araliphatic hydrocarbon residue.
- Acyl residues of O-acyl derivatives especially represent residues of aliphatic carboxylic acids, such as fatty acids, above all lower alkanecarboxylic acids and lower alkanedicarboxylic acids, as well as carbonic acid or its half-esters, lower alkenecarboxylic acids, lower alkenedicarboxylic acids, higher alkanecarboxylic acids or higher alkenecarboxylic acids, as well as of alicyclic or alicyclicaliphatic carboxylic acids, of araliphatic or aromatic carboxylic acids, which may optionally be substituted in the aromatic nucleus, for example, as described above or of sulphonic acids, such as benzenesulphonic acids, such as benzenesulphonic acids, which may be optionally substituted in the aromatic nucleus, for example, as mentioned above.
- Lower alkyl residues are, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec.-butyl, tert.-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, isohexyl, n-heptyl, or isoheptyl residues, while lower alkenyl residues represent, for example, allyl, methallyl or 2-butenyl residues, and lower alkinyl residues, for example, propargyl residues.
- An amino group substituted by lower alkyl residues is, for example, a dimethylamino or diethylamino group, a lower alkyleneamino group, for example, a pyrrolidino or piperidino group, an oxa-lower alkyleneamino group, for example, a morpholino group, and an azalower alkyleneamino group, for example, a piperazino, such as a 4-methyl-1-piperazino group.
- Lower alkoxy groups are, for example, methoxy, ethoxy, n-propyloxy, isopropyloxy, n-butyloxy, isobutyloxy, n-pentyloxy or n-hexyloxy groups, lower alkylenedioxy groups for example, methylenedioxy groups.
- Lower alkylmercapto groups are, for example, methylmercapto or ethylmercapto groups.
- Halogen atoms are above all those having an atomic weight of 19 to 80, that is to say fluorine, chlorine or bromine atoms.
- Carbo-lower alkoxy groups are, for example, carbomethoxy or carbethoxy groups, while carbamyl groups may optionally be N-monosubstituted or N,N-disubstituted and may represent for example, N-methylcarbamyl, N-ethylcarbamyl or N,N-dimethylcarbamyl groups.
- Pyridyl residues are, for example, 2-, 3- or 4-pyridyl groups, while thienyl and furyl residues represent above all 2-thienyl or 2-furyl groups.
- In substituted aliphatic hydrocarbon residues, free or substituted amino groups or free or functionally converted hydroxyl or mercapto groups are, for example, separated by one, but preferably by more than one, carbon atom of the aliphatic hydrocarbon residue from the oxygen atom carrying such substituted aliphatic hydrocarbon residue.
- Hydroxyl-substituted and lower alkoxy-substituted aliphatic hydrocarbon residues are above all hydroxy-lower alkyl or lower alkoxy-lower alkyl residues, in which the hydroxyl or lower alkoxy group are preferably separated by at least 2 carbon atoms from the oxygen atom which carries such a substituted aliphatic hydrocarbon residue, e.g. 2 - hydroxyethyl, 2 - hydroxypropyl, 3 - hydroxypropyl, 2 - methoxyethyl, 2 - ethoxyethyl, 2 - methoxypropyl, 3 - methoxypropyl or 3 - ethoxypropyl residues, but may also be hydroxymethyl, furthermore 2,3 - dihydroxypropyl residues.
- Aliphatic hydrocarbon residues substituted by heterocyclic residues are, for example, thienyl-, furyl- or pyridyl-lower alkyl residues, such as thenyl, furfuryl or picolyl residues.
- Cycloalkyl residues are, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl residues optionally mono-, di- or polysubstituted by lower alkyl groups, above all by methyl groups, while cycloalkenyl residues are 2- or 3-cyclopentenyl, 2- or 3-cyclohexenyl, or 2-, 3-, 4-cycloheptenyl residues optionally substituted in the same way.
- Cycloalkyl-lower residues are, for example, cyclopentylmethyl, cyclopentylethyl or cyclohexylmethyl residues, while cycloalkenyl-lower alkyl residues, for example, represent 2- or 3-cyclohexenylmethyl residues, which may, for example, be mono-, di- or polysubstituted by lower alkyl groups, above all by methyl groups.
- Substituted phenyl residues preferably contain a substituent in the 4-position; in the case of multiple substitution, identical or different substituents may be present.
- In substituted araliphatic hydrocarbon residues, especially in benzyl residues, identical or different substituents may be present in the aromatic nucleus in the case of multiple substitution; a substituted phenyl-lower alkyl group, especially a benzyl group, preferably contains a substituent in the 4-position of the ring.
- A lower alkanecarboxylic acid is, for example, formic, acetic propionic or butyric acid. A lower alkanedicarboxylic acid contains, for example, 2-7, preferably 3-6, carbon atoms and is, for example, malonic, 2-methylsuccinic,

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- glutaric, 3-methylglutaric, 3-ethylglutaric, adipic or pimelic acid, above all succinic acid. A carbonic acid half-ester, is, for example, a carbonic acid lower alkyl half ester, such as carbonic acid ethyl half ester. A lower alkane-dicarboxylic acid contains, for example, 4-7 carbon atoms and is, for example, maleic or fumaric acid. An alicyclic carboxylic acid is, for example, cyclopentanecarboxylic acid, while an araliphatic carboxylic acid may, for example, be phenylacetic acid and an aromatic carboxylic acid, for example, benzoic acid, such acids being optionally substituted in the alicyclic or aromatic nucleus, for example, as mentioned above. A benzenesulphonic acid is, for example a toluenesulphonic acid.
- The compounds of the present invention possess valuable pharmacological properties. Thus, they show antiinflammatory effects which can be demonstrated in animal experiments, for example, those based on the turpentine pleuritis test of Spector, J. Path. Bact., vol. 72, p. 367 (1956), using experimental animals, such as rats, and administering the compounds intraperitoneally. The new compounds are, thereof, useful as substances possessing antiinflammatory properties, especially anti-exudative and anti-oedematous effects. In contrast to glucofuranoside compounds having a similar spectrum of pharmacological activity, the semi-acetal grouping is missing in the present compounds; they are, therefore, distinguished by outstanding stability. It was furthermore found that the compounds of the present invention are usually obtained in a crystalline form. In contrast to the abovementioned glucofuranoside compound, which are normally obtained in an oily form and have to be purified by means of high vacuum distillation, the new compounds are, therefore, more completely purified according to easier and cheaper procedures and with smaller losses in yield, and can furthermore be processed into pharmacological preparations, such as tablets, for which glucofuranoside compounds of the type mentioned above are not suitable.
- Particularly valuable compounds in respect of the pharmacological effects mentioned are D-arabitol of the above formula I, as well as their acyl derivatives, especially lower alkanoyl, such as acetyl derivatives, as well as carboxy-lower alkanoyl, such as succinyl derivatives, in which each of the groups R_2 , R_4 and R_5 represents a lower alkyl residue, e.g. methyl, ethyl, straight or branched propyl or butyl, a lower alkenyl residue, for example, allyl, or a cyclo-alkyl residue, for example, cyclopentyl or cyclohexyl, and above all a benzyl residue, which may optionally be substituted, for example, as mentioned above, and R_3 may also be a phenyl residue, which may optionally be substituted, for example, as mentioned above, and salts, especially non-toxic salts, of such compounds having salt-forming groups.
- Of this group of compounds there should especially be mentioned the 2 - O - R_3' - 4 - O - R_4' - 5 - O - R_5' - D - arabitols, wherein R_2' denotes a lower alkyl as well as lower alkenyl residue or a benzyl residue optionally substituted, preferably in the 4-position, by halogeno, especially chloro, or lower alkyl especially methyl, as well as lower alkoxy, especially methoxy, each of the residues R_4' and R_5' represents a benzyl residue optionally substituted, preferably in the 4-position, by halogeno, especially chloro, or lower alkyl, especially methyl, as well as lower alkoxy, especially methoxy, and R_3' also represents a phenyl residue optionally substituted, preferably in the 4-position, by halogeno, especially chloro, or by lower alkyl, especially methyl, as well as lower alkoxy, especially methoxy, as well as their O-lower alkanoyl and O-carboxy-lower alkanoyl, such as O-succinyl, derivatives, as well as salts, especially the non-toxic alkali metal or ammonium salts, of such compounds with salt-forming groups.
- Above all the 2,4,5 - tri - O - benzyl - D - arabitol, as well as the 2,4 - di - O - benzyl - 5 - O - phenyl - D - arabitol are to be noted, which in the above mentioned turpentine pleuritis test show excellent effects.
- The compounds of the present invention are obtained according to *per se* known methods, for example, by reducing in a D - arabinose compound of formula



or in a 3 - O - acyl derivative thereof the carbonyl group in the 1-position to the carbinol group, and, if desired, converting in a resulting compound an acyloxy group into a free hydroxyl group or a free hydroxyl group into an acyloxy group, and/or, if desired, converting a resulting compound having a salt-forming group into a salt or a resulting salt into the free compound.

3 - O - acyl derivatives of the starting materials contain the above mentioned acyl residues, particularly those of organic, such as aliphatic carboxylic acids, for example, of lower alkane carboxylic acids, i.e. acetic and especially formic acid.

The above reduction can be carried out with any suitable carbonyl-carbinol reducing agent. In choosing the reducing agent it is, however, necessary to bear in mind that certain organic groups R_2 , R_4 and/or R_5 may be hydrogenated simultaneously or hydrogenolytically split off; above all, this applies to aromatic residues, such as optionally substituted

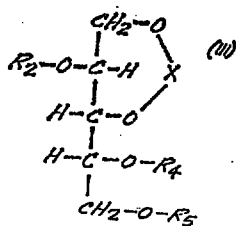
benzyl groups, as well as, for example, to halogeno-substituted organic residues.

Particularly suitable as reducing agents are hydride reducing agents, particularly optionally complex metal hydrides, such as alkali metal aluminium hydrides, for example, lithium aluminium hydride, as well as alkali metal tri-lower alkoxy-aluminium hydrides, for example, lithium tri-tert.-butoxy-aluminium hydride, but above all borohydrides, such as diborane, and especially alkali metal and alkaline earth metal borohydrides, for example, sodium borohydride. These reducing agents are usually employed in the presence of diluents or mixtures of solvents, with aluminium hydride compounds preferably being used in the presence of solvents with ether groupings, for example, ether or tetrahydrofuran, and borohydride compounds in the presence of such solvents with ether groupings, among others also diethylene glycol dimethyl ether, as well as solvents with hydroxyl groupings, such as lower alkanols, for example, methanol, ethanol, isopropanol, n-butanol or tert.-butanol. The process is, if necessary, carried out with cooling or preferably with heating and/or in an inert gas, for example, a nitrogen atmosphere.

The reduction of the formyl group to the carbinol group can also be effected with hydrogen in the presence of a suitable catalyst, such as platinum oxide, preferably under mild conditions, the process being carried out in the presence of a suitable diluent or solvent mixture, if necessary, with cooling or warming and/or under pressure.

Under the conditions of the reduction reaction, particularly in an alkaline medium, a 3 - O - acyl, particularly a 3 - O - formyl group may be split off simultaneously.

The compounds of the present invention are also obtained by splitting off the group X from a compound of the formula



in which X represents an optionally substituted methylene group, and, if desired, carrying out the optional steps.

An optionally substituted methylene group X is an unsubstituted, more especially a mono-substituted or disubstituted methylene group. Substituents are in the first place optionally substituted monovalent or divalent aliphatic hydrocarbon residues, preferably lower alkyl, for example, ethyl, n - propyl, isopropyl, or n - butyl, especially methyl residues, or lower alkylene radicals con-

taining 4 to 6 chain carbon atoms, such as 1,4 - butylene or 1,5 - pentylene residues. If desired, these hydrocarbon residues may be substituted, for example, by lower alkyl, hydroxyl or lower alkoxy groups or halogen atoms, as well as by aromatic groups, such as phenyl radicals which themselves may be substituted, for example, by lower alkyl, hydroxyl or lower alkoxy groups or halogen atoms. Further substituents of the methylene group X may also be, for example, aromatic hydrocarbon residues optionally substituted, for example, as indicated above, such as phenyl groups, as well as free or functionally modified, such as esterified carboxyl groups, for example, carbo-lower alkoxy, e.g. carbomethoxy or carboethoxy groups. A substituted methylene group X is above all the isopropylidene group and in the first place a benzylidene group optionally substituted in the aromatic ring as mentioned above.

The cleavage of the group X is preferably carried out by treatment with an acid, in the presence of water. Acids are generally Lewis acids, preferably mineral acids, for example, sulphuric acid, or especially hydrohalic acids, in the first place hydrochloric acid, as well as organic acids, such as organic carboxylic acids, in the first place lower alkane carboxylic or dicarboxylic acids, particularly acetic acid, also formic or oxalic acid, furthermore organic sulphonic acids, for example, p-toluenesulphonic acid, or, if desired, mixtures of acids, for example, acetic acid in admixture with hydrochloric acid or p - toluenesulphonic acid, as well as salts with the characteristics of Lewis acids.

The reaction may be performed in a heterogeneous or homogeneous phase and can, if desired, be accelerated by adding a catalyst, such as a catalytic amount of phosphoric acid. Preferentially, it is performed in the presence of a diluent (for which purpose an acid reagent, e.g. acetic acid, may in general also be used as diluent), if necessary, with cooling, in the first place, however, at room temperature or at an elevated temperature (for example, at 25°C to above 150°C), and/or under increased pressure and/or in an inert gas, such as nitrogen.

In compounds obtainable according to the invention having a 3 - O - acyl grouping, the acyl group can be replaced by hydrogen, for example, by treatment with an alkaline reagent, such as an alkaline earth metal or alkali metal hydroxide or carbonate, or silver oxide, in an aqueous or alcoholic medium; as mentioned above, this cleavage may take place under the reaction conditions.

In compounds having free hydroxyl groups, the latter may be acylated by treatment with acylating agents capable of introducing the acyl residue of an organic acid, in a manner which is in itself known. Acylating agents used for this purpose are suitable acid derivatives

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- (in the case of dicarboxylic acids, for example, their monoacid derivatives), especially anhydrides (also inner anhydrides, i.e. the corresponding ketenes), as well as halides, especially chlorides. The preferred procedure is to effect the reaction with anhydrides, such as, for example, acetic acid anhydride or succinic acid anhydride, in the presence of acidic or basic condensing reagents, for example, pyridine.
- The reaction with acid halides, for example, a chloride, such as acetic acid chloride or succinic acid mono-chloride, can be carried out in the presence of acid-binding condensation agents, such as tertiary bases or sodium acetate.
- A free hydroxyl group can also be esterified by means of carboxylic acids in the presence of suitable condensing reagents, such as carboimides or thiocarbodiimides, for example, dicyclohexylcarbodiimide, or with reactive esters of carboxylic acids, such as esters with N-hydroxyamino or N-hydroxyimino compounds, for example, N-hydroxysuccinimide.
- Compounds having an acyl residue with salt-forming groups, for example, free carboxyl groups may, depending on the reaction conditions, be obtained in the free form or in the form of salts; these forms may be converted into one another in a manner which is in itself known. Salts of compounds having a free carboxyl group are, for example, metal salts, especially alkali metal salts, for example, sodium or potassium salts, as well as alkaline earth metal salts, for example, magnesium or calcium salts, or ammonium salts, for example, salts with ammonia or with organic bases, such as trialkylamines, for example, trimethylamine or triethylamine, especially the non-toxic, pharmaceutically acceptable salts of the above nature.
- Such salts, especially the alkali metal salts of the new compounds, are distinguished by good solubility in water. Salts may also serve as intermediates for the purification of the corresponding free compounds. They are, for example, obtained by treating the free compounds with metal hydroxides or carbonates or with ammonia or amines, as well as with suitable ion exchangers.
- Compounds having basic groups can be converted in a manner which is in itself known into their salts with acids, especially with those acids which form non-toxic, pharmaceutically acceptable salts, with inorganic or organic acids, such as hydrohalic acids, for example, hydrochloric or hydrobromic acid, sulphuric acid, phosphoric acid, nitric acid or perchloric acid, as well as aliphatic, alicyclic, aromatic or heterocyclic carboxylic or sulphonic acids, such as formic, acetic, propionic, oxalic, succinic, glycollic, lactic, malic, tartaric citric, ascorbic, hydroxymaleic, dihydroxymaleic, pyruvic, phenylacetic, benzoic, p-aminobenzoic, anthranilic, p-hydroxybenzoic, salicylic, p-aminosalicylic, methanesulphonic, ethanesulphonic, hydroxyethanesulphonic, ethylenesulphonic, tolu-

enesulphonic, naphthalenesulphonic or sulph-anilic acid.

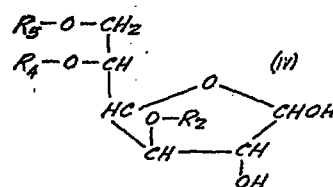
The resulting salts can be converted into the free compounds in the usual manner, salts with bases by treatment with acidic and salts with acids by treatment with alkaline reagents.

Because of the close relationships between the new compounds in the free form and in the form of their salts, reference in this context to a free compound or a salt is also intended to be a reference to the corresponding salt and free compound, respectively, provided such is possible or appropriate under the circumstances.

The procedures described above are carried out according to methods which are in themselves known, in the absence or preferably in the presence of diluents or solvents, if necessary with cooling or heating, in a closed vessel and/or in an inert gas, such as a nitrogen atmosphere.

Those starting materials are preferably used which according to the process lead to those compounds indicated above as being particularly valuable.

The starting substances of formula II are new; they represent a further subject of the present invention. Apart from being useful as intermediates, they also show antiinflammatory properties and are, therefore, useful as antiinflammatory agents. Such compounds are more especially those of the formula II, as well as 3 - O - acyl derivatives, in which each of the groups R_2 , R_4 and R_5 is lower alkyl, lower alkenyl, cycloalkyl and above all benzyl, which may optionally be substituted as indicated above, and R_3 may also be phenyl optionally substituted as mentioned above, and salts of such compounds having salt-forming groups. There should be especially mentioned the 2 - O - R_2' - 4 - O - R_4' - 5 - O - R_5' - D - arabinoses, in which R_2' , R_4' and R_5' have the previously given meaning, as well as their 3 - O - lower alkanoyl or 3 - O - carboxy - lower alkanoyl derivatives, or salts of such compounds having salt-forming groups, and primarily the 2,4,5 - tri - O - benzyl - D - arabinose, as well as the 2,4 - di - O - benzyl - 5 - O - phenyl - D - arabinose and their 3 - O - formyl derivatives. These starting materials are preferably obtained, when a D - glucufuranose of formula



is treated with a glycol-splitting oxidizing reagent, and, if desired, in a resulting compound

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ample, by treatment with a reactive derivative of an organic carboxylic acid, such as a halide, e.g. chloride, particularly a corresponding derivative of a lower alkane carboxylic acid, e.g. acetic acid or of an aromatic carboxylic acid, e.g. benzoic acid, and liberating in a resulting compound the hydroxy groups in 1- and 2-position selectively, for example, by treatment with acetic acid in an aqueous medium, if necessary, in the presence of a strong acid, such as phosphoric acid. The resulting D-glucofuranose with an etherified hydroxyl group in 3-position and esterified hydroxyl groups in 5- and 6-positions may also be obtained by splitting off the protecting grouping, for example, the group X, of the 1- and 2-hydroxy group by treatment with a hydrogen halide, e.g. hydrogen chloride, in the presence of an alcohol, such as a lower alkanol, e.g. ethanol, and converting the resulting D-glucoside, such as lower alkyl-D-glucoside, with the etherified hydroxy group in 3-position and the esterified hydroxy groups in 5- and 6-position into the corresponding D-glucofuranose by treatment with about 50% aqueous acetic acid at about 60°C.

A D-glucofuranose with an etherified hydroxy group in 3-position and esterified hydroxy groups in 5- and 6-position is then degraded oxidatively as shown above, for example, by treatment with periodic acid or a salt thereof, such as sodium periodate, into a D-arabinose, in which the hydroxy group in 2-position is etherified and the hydroxy groups in 4- and 5-position are esterified, and which may contain in 3-position a hydroxy group acylated by a formyl group, which may be liberated under the reaction conditions. The resulting D-arabinose is then reduced to the corresponding D-arabitol according to the above procedure, e.g. by treatment with sodium borohydride, the optionally substituted methylene grouping of the formula -X- is then introduced into the 1,3-O-position, for example, by treatment with a ketone or an aldehyde, such as benzaldehyde, preferably in the presence of a suitable acidic condensing reagent, such as zinc-II-chloride, and in the resulting D-arabitol compound, in which the hydroxy groups in 1- and 3-position are bridged by the grouping of the formula -X-, with the etherified hydroxy group in 2-position and the esterified hydroxy groups in 4- and 5-positions, the latter are liberated by treatment with a basic reagent, such as an alkali metal hydroxide, e.g. sodium or potassium hydroxide. The free hydroxyl groups in 4- and 5-position are then etherified according to the previously described procedure, if necessary, step-wise.

The starting materials of the formula III, particularly those, in which the hydroxy group in 5-position is etherified by an aromatic, such as a phenyl residue, may also be obtained, for example, by esterifying in a D-glucofuranose with protected hydroxy groups in 1- and 2-

position and a hydroxyl group in 6-position etherified, for example, by an aromatic residue, the hydroxy groups in 3- and 5-positions, for example, by introducing benzoyl residues, liberating the hydroxyl groups in 1- and 2-position, for example, directly or step-wise as described above, and oxidatively degrading the resulting D-glucofuranose with the esterified hydroxyl groups in 3- and 5-positions, and the etherified hydroxyl group in 6-position to form the corresponding D-arabinose, which is reductively converted into the D-arabitol. In the latter, the two hydroxyl groups in 1- and 3-position are protected by introducing the group of the formula -X-, particularly of a benzylidene group, according to the above mentioned procedure, the esterified hydroxyl groups in 3- and 5-position are liberated by treatment with a basic reagent and as usually esterified by treatment with a reactive ester of an alcohol in the presence of a basic reagent; the resulting D-arabitol compound contains the hydroxy groups in 1- and 3-positions, protected by the group of the formula -X-, and the etherified hydroxyl groups in the 2-, 4- and 5-positions of the starting materials of the formula III.

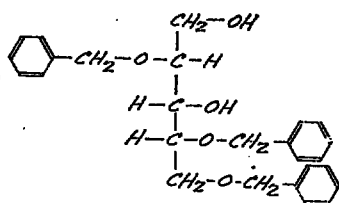
The new compounds or salts thereof may be employed as medicines, for example, in the form of pharmaceutical preparations, in which they are present mixed with a pharmaceutical organic or inorganic solid or liquid excipient suitable for administration, for example, for enteral or parental as well as topical administration. Suitable substances for forming the preparations are those which are inert towards the new compounds, such as water, gelatine, sugars, for example, lactose, glucose or fructose, starches, such as corn, wheat or rice starch, stearic acid or salts thereof, such as calcium or magnesium stearate, talc, vegetable oils, benzyl alcohols, gum, polyalkylene glycols, propylene glycol or other known medicinal excipients. The pharmaceutical preparations may, for example, be in the form of tablets, dragees or capsules, or in a liquid form as solutions, suspensions or emulsions. They are optionally sterilised and/or contain auxiliary substances such as preservatives, stabilisers, wetting agents or emulsifiers, salts for regulating the osmotic pressure or buffers. They may also contain further therapeutically valuable substances. The preparations are formulated according to usual methods.

The invention is illustrated in the following examples; temperatures are given in degrees centigrade.

EXAMPLE 1

A solution of 26.3 g of 2,4,5 - tri - O - benzyl - 3 - O - formyl - D - arabinose in 50 ml of methanol is added dropwise over the course of 30 minutes to a solution of 7.9 g of sodium borohydride in 125 ml of 20% aqueous methanol at 5°. The reaction mixture

is allowed to continue to react for another 10 minutes and is then mixed with 50 ml of water. The bulk of the methanol is distilled off under reduced pressure at 40° and the residue is extracted with methylene chloride. The methylene chloride solution is washed with water, 2N hydrochloric acid and again with water, dried over sodium sulphate and evaporated under reduced pressure. The residue is crystallised from a mixture of methylene chloride and petroleum ether; the 2,4,5-tri-O-benzyl-D-arabitol of formula



is obtained in the form of white crystals, m.p. 67—68°; $[\alpha]_D^{20} = -50^\circ \pm 1^\circ$ ($c = 1.184$ in chloroform).

The starting material used may be manufactured as follows:

A suspension of 500 g of crude ethyl-3,5,6-tri-O-benzyl-D-glucofuranoside in 500 ml of 50% aqueous acetic acid is warmed for 16 hours at an internal temperature of 70°, while stirring vigorously in a nitrogen atmosphere. The light yellow suspension is cooled to 30° and is then completely evaporated under reduced pressure at a bath temperature of 35°. The residue, obtained as a mobile syrup, is dissolved in 1200 ml of toluene, washed with a saturated aqueous sodium hydrogen carbonate solution and with water until neutral and dried over magnesium sulphate. On adding 4200 ml of hexane in portions, the 3,5,6-tri-O-benzyl-D-glucofuranose precipitates as a crystalline, almost colourless product; after recrystallisation at 0° from 2 parts by volume of a 1:1 mixture of ethanol and water, a completely colourless product is obtained, which melts at 68—71°; $[\alpha]_D^{20} = -30^\circ \pm 1^\circ$ ($c = 1$ in chloroform). According to a thin layer chromatogram on silica gel, the substance is uniform and shows Rf values of 0.18, 0.32 and 0.40 in the systems cyclohexane-acetone (70:30), chloroform-acetone (85:15) and chloroform-ethyl acetate (50:50), respectively.

The above intermediate can also be obtained as follows:

A suspension of 9.8 g of 1,2-O-isopropylidene-3,5,6-tri-O-benzyl-D-glucofuranose in a mixture of 65 ml of glacial acetic acid and 35 ml of 1N aqueous sulphuric acid is warmed for 30 minutes at an internal temperature of 80° while vigorously stirring in nitrogen atmosphere. The light yellow, clear reaction solution is cooled to 10°, adjusted to pH 2—3 with 40 ml of a 2N aqueous sodium hydroxide solution and subsequently evaporated

under reduced pressure at a bath temperature of 35°. The concentrate is dissolved in 100 ml of chloroform, washed with a 1N aqueous potassium hydrogen carbonate solution and with water until neutral, and dried over magnesium sulphate. The chloroform solution is evaporated under reduced pressure and the residue is completely freed of residual solvents by heating (bath temperature: 40°) in a high vacuum for 1 hour. The oily residue is dissolved in 40 ml of ethyl acetate and crystallised by adding 480 ml of hexane in portions; the colourless 3,5,6-tri-O-benzyl-D-glucofuranose thus obtained melts at 68—70°.

The intermediate can also be manufactured as follows:

A suspension of 10 g of 1,2-O-isopropylidene-3,5,6-tri-O-benzyl-D-glucofuranose in 1000 ml of 50% aqueous formic acid is stirred for 6 hours at 70° and is then extracted with toluene. The organic phase is washed with a saturated aqueous sodium hydrogen carbonate solution and with water until neutral, dried over sodium sulphate, filtered and adjusted to a volume of 100 ml by adding toluene. After dilution with 100 ml of petroleum ether (boiling point 60—90°) the solution is treated with 0.3 g of active charcoal and the mixture is boiled for a few minutes under reflux and filtered hot. After cooling to 30°, the filtrate is diluted by adding a total of 500 ml of petroleum ether in portions while stirring. The 3,5,6-tri-O-benzyl-D-glucofuranose precipitates in the form of colourless fine needles, the product being allowed to stand for some hours at 0° after completion of the addition, m.p. 64—66°.

A solution of 4000 ml of 50% aqueous acetic acid containing 53 g of 3,5,6-tri-O-benzyl-D-glucofuranose is mixed with a solution of 58.4 g of periodic acid in 135 ml of water at 20°. The reaction mixture is allowed to stand for 16 hours at 0—5° and the white crystalline precipitate is filtered off, washed with small amount of ice-water and dried in a water-pump vacuum at 60°; the resulting 2,4,5-tri-O-benzyl-3-O-formyl-D-arabinose melts at 78—79° and may be converted into the 2,4,5-tri-O-benzyl-D-arabinose by treatment with a base.

EXAMPLE 2

A solution of 13.2 g of sodium borohydride in 180 ml of 20% aqueous methanol is treated dropwise at 5°, over the course of 30 minutes, with a solution of 39.6 g of 2-O-n-propyl-4,5-di-O-(4-chlorobenzyl)-D-arabinose in 100 ml of methanol. After continuing to react for 2 hours at the same temperature, the reaction mixture is mixed with 40 ml of water. The methanol is distilled off under reduced pressure at 40° and

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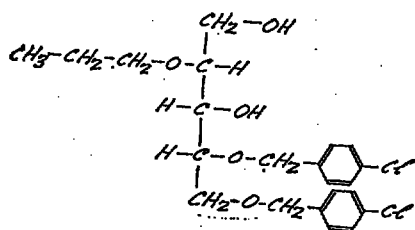
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the residue is extracted with chloroform. The chloroform solution is washed with water, 2N hydrochloric acid and again with water, dried over sodium sulphate and evaporated under reduced pressure. On treating the residue with a mixture of ether and petroleum ether, the 2 - O - n - propyl - 4,5 - di - O - (4 - chlorobenzyl) - D - arabitol of formula



10 is obtained in the form of white crystals, m.p. 84–84.5°; $[\alpha]_D^{20} = -27^\circ \pm 1^\circ$ ($c = 1.102$ in chloroform).

The starting material is manufactured as follows:

15 A solution of 82 g of 1,2 - O - isopropylidene - 3 - O - allyl - α - D - glucofuranose in 800 ml of ethanol is hydrogenated in the presence of 1 g of a 10% palladium-on-charcoal catalyst. The catalyst is filtered off, the
20 filtrate is evaporated and the residue, containing the 1,2 - O - isopropylidene - 3 - O - n - propyl - α - D - glucofuranose $[\alpha]_D^{20} = -49^\circ \pm 1^\circ$ ($c=1$ in chloroform) is degassed in a high vacuum.

25 A solution of 32 g of 1,2 - O - isopropylidene - 3 - O - n - propyl - α - D - glucofuranose in 100 ml of absolute dioxan is treated with 87.5 g of powdered potassium hydroxide. 30 A solution of 131 g of 4-chlorobenzyl chloride in 50 ml of absolute dioxan is then added dropwise over the course of 30 minutes while stirring; the mixture is then allowed to react for 5 hours at 80°. The excess 4 - chlorobenzyl chloride is distilled off with steam and after 35 cooling, the mixture is extracted with chloroform. The organic extract is washed with water, dried over sodium sulphate and evaporated under reduced pressure. On distilling the residue, the 1,2 - O - isopropylidene - 3 - 40 O - n - propyl - 5,6 - di - O - (4 - chlorobenzyl) - α - D - glucofuranose is obtained as a pale yellow oil at 230°/0.015 mm Hg; $[\alpha]_D^{20} = -22^\circ \pm 1^\circ$ ($c=1$ in chloroform).

A suspension of 5 g of 1,2 - O - isopropylidene - 3 - O - n - propyl - 5,6 - di - O - (4 - chlorobenzyl) - α - D - glucofuranose in a mixture of 35 ml of glacial acetic acid and 17.5 ml of 1N aqueous sulphuric acid is warmed for 30 minutes at an internal temperature of 80° in a nitrogen atmosphere while vigorously stirring. The reaction mixture is cooled to 10°, adjusted to pH 2—3 with a 2N aqueous sodium hydroxide solution, and sub-

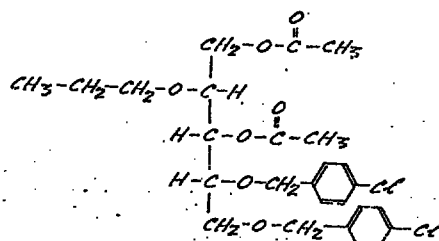
sequently evaporated at a bath temperature of 35°. The concentrate is extracted with ether and the organic phase is washed with a saturated aqueous sodium hydrogen carbonate solution and with water until neutral, dried over magnesium sulphate and evaporated. The residue corresponds to the 3 - O - n - propyl - 5,6 - di - O - (4 - chlorobenzyl) - D - glucofuranose, which in a thin layer chromatogram (silica gel) in the system chloroform: ethyl acetate (85:15) shows an *R_f*-value of 0.12; m.p. 60° after recrystallisation from a 1:3 mixture of toluene and hexane, and cooling to -17°

The 3 - O - n - propyl - 5,6 - di - O - (4 - chlorobenzyl) - D - glucufuranose can also be obtained by heating a mixture of 15 g of ethyl - 3 - O - n - propyl - 5,6 - di - O - (4 - chlorobenzyl) - D - glucufuranoside in 600 ml of glacial acetic acid and 600 ml of water for 16 hours at 70°, distilling off the excess acetic acid, extracting the aqueous residue with ether and working up the ether solution as described above.

A solution of 49.8 g of 3 - O - n - propyl - 5,6 - di - O - (4-chlorobenzyl) - D - glucofuranose in 2000 ml of acetic acid is mixed with a solution of 52.5 g of periodic acid in 400 ml of water. The mixture is allowed to continue to react for 1 hour at room temperature and the solution is filtered. After adding 1600 ml of water the filtrate is extracted with chloroform. The chloroform solution is washed with a saturated sodium hydrogen carbonate solution and with water and dried over sodium sulphate. On evaporating, the 2 - O - n - propyl - 4,5 - di - O - (4 - chlorobenzyl) - D - arabinose is obtained and is used without further purification.

EXAMPLE 3

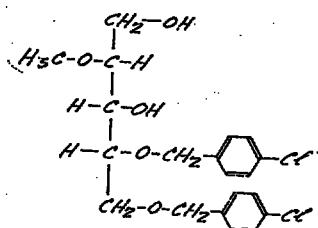
A mixture of 12 g of 2 - O - n - propyl - 4,5 - di - O - (4 - chlorobenzyl) - D - arabinitol in 12 ml of pyridine and 12 ml of acetic acid anhydride is allowed to stand for 16 hours and is then evaporated under reduced pressure. The residue is distilled and the 1,3 - di - O - acetyl - 2 - O - n - propyl - 4,5 - di - O - (4 - chlorobenzyl) - D - arabinitol of formula



is obtained at 220—225°/0.01 mm Hg; $[\alpha]_D^{20} = +21^\circ \pm 1^\circ$ ($c=1.214$ in chloroform).

EXAMPLE 4

- 5 A solution of 5.45 g of sodium borohydride in 30 ml of cold water is added dropwise in the course of 15 minutes to a suspension of 19 g of 2 - O - methyl - 3 - O - formyl - 4,5 - di - O - (4 - chlorobenzyl) - D - arabinose in 270 ml of methanol at 10°. The batch is allowed to stand for 30 minutes and is then treated with 50 ml of water. The bulk of the methanol is distilled off under reduced pressure at 40°, and the residue is extracted with methylene chloride. The methylene chloride extract is washed with water, 2N hydrochloric acid, and again with water dried over sodium sulfate, and evaporated under reduced pressure. The residue is crystallized from a mixture of methylene chloride and petroleum ether and 2 - O - methyl - 4,5 - di - O - (4 - chlorobenzyl) - D - arabinol of the formula



is obtained as white crystals, m.p. 82—85°; $[\alpha]_D^{20} = -20^\circ \pm 1^\circ$ ($c=1.046$ in chloroform).

- 25 The starting material used can be obtained as follows:

- 30 A solution of 42 g of 1,2 - O - isopropylidene - 3 - O - methyl - α - D - glucofuranose in 150 ml of absolute dioxan is mixed with 128 g of powdered potassium hydroxide. In the course of 30 minutes, 192 g of 4 - chlorobenzyl chloride are added dropwise while stirring and the reaction mixture is allowed to react for 5 hours at 80°. The excess 4 - chlorobenzyl chloride is distilled off with steam, the residue is allowed to cool and is then extracted with chloroform. The chloroform solution is dried over sodium sulfate and evaporated under reduced pressure. The residue is distilled and yields at 235°/0.02 mm Hg the 1,2 - O - isopropylidene - 3 - O - methyl - 5,6 - di - O - (4 - chlorobenzyl) - α - D - glucofuranose as a faintly yellowish oil; $[\alpha]_D^{20} = -22^\circ \pm 1^\circ$ ($c=1$ in chloroform).

- 45 A solution of 11 g of 1,2 - O - isopropylidene - 3 - O - methyl - 5,6 - di - O - (4 - chlorobenzyl) - α - D - glucofuranose in 300 ml of a 1N solution of hydrogen chloride in ethanol is kept for 20 hours at room temperature and then neutralized at 0 to 5° with a 10N aqueous sodium

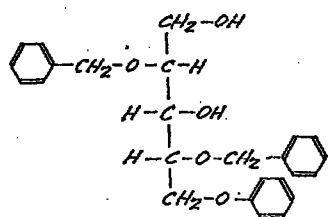
hydroxide solution. The bulk of ethanol is distilled off under reduced pressure and the residue is extracted with chloroform; the chloroform extract is washed with an aqueous sodium bisulfite solution and with water, dried over sodium sulfate and evaporated under vacuum; the residue is distilled to yield at 190°/0.01 mm Hg the ethyl - 3 - O - methyl - 5,6 - di - O - (4 - chlorobenzyl) - D - glucofuranoside as a faintly yellowish oil; $[\alpha]_D^{20} = -14^\circ \pm 1^\circ$ ($c=1$ in chloroform).

A solution of 68.6 g of ethyl - 3 - O - methyl - 5,6 - di - O - (4 - chlorobenzyl) - D - glucofuranoside in 600 ml of 60% aqueous acetic acid containing 2 g of calcium bromide is refluxed for 12 hours. The greater part of the acetic acid is then distilled off under reduced pressure, and the residue is extracted with ether. The ether solution is washed with a saturated sodium hydrogen carbonate solution and water, dried over sodium sulfate, and evaporated under reduced pressure. A solution of the residue in an 85:15 mixture of chloroform and ethyl acetate is filtered through a silica gel chromatography column. The 3 - O - methyl - 5,6 - di - O - (4 - chlorobenzyl) - D - glucofuranose is obtained as a yellowish oil, $[\alpha]_D^{20} = -12^\circ \pm 1^\circ$; thin-layer chromatogram Rf=0.1 (silica gel; system chloroform-ethyl acetate 85:15).

A solution of 26.8 g of 3 - O - methyl - 5,6 - di - O - (4 - chlorobenzyl) - D - glucofuranose in 800 ml of 75% aqueous acetic acid is treated with a solution of 30 g of periodic acid in 100 ml of water at 20°. After that, 400 ml of water are added and the white crystalline precipitate which forms is filtered off, the filter residue is washed with a small amount of ice-water, and the filtrate dried in a water-jet vacuum at 50°; the resulting 2 - O - methyl - 3 - O - formyl - 4,5 - di - O - (4 - chlorobenzyl) - D - arabinose melts at 108—109.5°; $[\alpha]_D^{20} = +7^\circ \pm 1^\circ$ ($c=1.167$ in chloroform).

EXAMPLE 5

A solution of 17.3 g of 2,4 - di - O - benzyl - 3 - O - formyl - 5 - O - phenyl - D - arabinose in 210 ml of methanol is added dropwise to a solution of 5 g of sodium borohydride in 90 ml of 65% aqueous methanol at 5°. The reaction mixture is allowed to stand for 30 minutes and is then treated with 50 ml of water. The greater part of the methanol is distilled off under reduced pressure at 40° and the residue neutralized with ice-cold 2N hydrochloric acid. The mixture is extracted with methylene chloride and the organic solution is washed with 2N hydrochloric acid and with water, dried over sodium sulfate and evaporated under reduced pressure. The residue is crystallized from a mixture of methylene chloride and petroleum ether; the 2,4 - di - O - benzyl - 5 - O - phenyl - D - arabinol of the formula



is obtained in the form of white crystals m.p. 88—89°C; $[\alpha]_D^{20} = -39^\circ \pm 1^\circ$ ($c=1.112$ in chloroform).

5 The starting material used can be prepared as follows:

To a melt of 50 g of 1,2 - O - isopropylidene - 5,6 - anhydro - α - D - glucopyranose (1,2 - O - isopropylidene - 5,6 - bis - desoxy - 5,6 - oxido - α - D - glucopyranose) and 23.5 g of phenol, 3 drops of pyridine are added at 110°. The exothermic reaction which sets in is cooled in such a manner that the temperature does not rise above 170°. The mixture is allowed to stand at 140° for 30 minutes, cooled to 80—90°, after which 100 ml of methanol are added dropwise while stirring. The methanolic solution is evaporated and the residue is dissolved in ether. The ether solution is washed with an ice-cold 1N aqueous sodium hydroxide solution and with water, dried over sodium sulfate, and evaporated under reduced pressure. The 1,2 - O - isopropylidene - 6 - O - phenyl - α - D - glucopyranose obtained as residue is purified as follows:

15 A solution of 65 g of crude 1,2 - O - isopropylidene - 6 - O - phenyl - α - D - glucopyranose in 60 ml of pyridine is treated with 60 ml of acetic acid anhydride and allowed to stand at room temperature for 12 hours before the bulk of the pyridine and the acetic acid anhydride is distilled off at 50—60° under reduced pressure. The residue is mixed with 100 ml of ice-water and extracted with ether. The ether solution is washed with ice-cold 1N hydrochloric acid and with water, dried over sodium sulfate and evaporated under reduced pressure. The residue is crystallized from a mixture of methanol and water to yield the 1,2 - O - isopropylidene - 3,5 - di - O - acetyl - 6 - O - phenyl - α - D - glucopyranose, m.p. 108°.

30 A suspension of 62.5 g of 1,2 - O - isopropylidene - 3,5 - di - O - acetyl - 6 - O - phenyl - α - D - glucopyranose in 200 ml of methanol is mixed with a solution of 20.2 g of potassium hydroxide in 466 ml of methanol. The mixture is allowed to stand for 10 minutes and is then evaporated under reduced pressure. The residue is extracted with ether and the ether solution is washed neutral with water, dried over sodium sulfate and evaporated under reduced pressure. The residue is crystallized from a mixture of methanol and water to yield the 1,2 - O - isopropylidene - 6 - O - phenyl - α - D - glucopyranose, m.p. 60—61°.

45 A suspension of 62.5 g of 1,2 - O - isopropylidene - 3,5 - di - O - acetyl - 6 - O - phenyl - α - D - glucopyranose in 200 ml of methanol is mixed with a solution of 20.2 g of potassium hydroxide in 466 ml of methanol. The mixture is allowed to stand for 10 minutes and is then evaporated under reduced pressure. The residue is extracted with ether and the ether solution is washed neutral with water, dried over sodium sulfate and evaporated under reduced pressure. The residue is crystallized from a mixture of methanol and water to yield the 1,2 - O - isopropylidene - 6 - O - phenyl - α - D - glucopyranose, m.p. 60—61°.

In an atmosphere of nitrogen, a solution of 90 g of 1,2 - O - isopropylidene - 6 - O - phenyl - α - D - glucopyranose in 60 ml of dimethylsulfoxide is added dropwise while stirring vigorously to a suspension of 58.3 g of powdered potassium hydroxide in 120 ml of dimethylsulfoxide. In the course of 70 minutes, the mixture is treated dropwise at 40° with 115 g of benzyl chloride. Stirring is continued at room temperature for 12 hours.

The reaction mixture is then poured into 200 ml of ice-water and the mixture is extracted with chloroform. The chloroform solution is washed neutral with water, dried over sodium sulfate and evaporated under a water-jet vacuum. The residue is mixed with 60 g of potassium hydroxide and the mixture is subjected to steam distillation until chlorine can no longer be detected in the distillate. The residue is cooled and extracted with chloroform. The chloroform solution is washed with water and dried over sodium sulfate, then evaporated under reduced pressure. The resulting 1,2 - O - isopropylidene - 3,5 - di - O - benzyl - 6 - O - phenyl - α - D - glucopyranose crystallizes from a mixture of methanol and water, m.p. 62.5—63.5°; $[\alpha]_D^{20} = -26^\circ \pm 1^\circ$ ($c=1.03$ in chloroform).

A solution of 96 g of 1,2 - O - isopropylidene - 3,5 - di - O - benzyl - 6 - O - phenyl - α - D - glucopyranose in 1500 ml of 1N ethanolic hydrogen chloride is allowed to stand at room temperature, then cooled to 0—5° and finally neutralized with an ice-cold 10N aqueous sodium hydroxide solution. The resulting sodium chloride is filtered off and the bulk of the ethanol in the filtrate is expelled under reduced pressure at 40—45°. The residue is extracted with ether and the ether solution is washed with a saturated aqueous sodium hydrogen sulfite solution and with water, dried over sodium sulfate, and evaporated at 40° in a water-jet vacuum. On de-gassing of the residue in a high vacuum, ethyl - 3,5 - di - O - benzyl - 6 - O - phenyl - D - glucopyranoside is obtained; $[\alpha]_D^{20} = -18^\circ \pm 1^\circ$ ($c=0.91$ in chloroform).

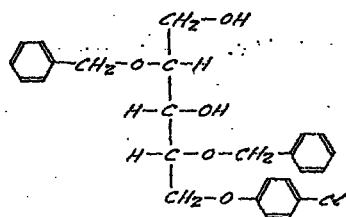
A solution of 24 g of ethyl 3,5 - di - O - benzyl - 6 - O - phenyl - D - glucopyranoside in 1800 ml of 50% aqueous acetic acid is stirred at 70° during 6 hours. The main portion of the acetic acid is removed under reduced pressure and the residue is extracted with ether. The ether solution is washed with a saturated aqueous sodium hydrogen carbonate solution and with water, dried over sodium sulfate and evaporated under reduced pressure. The 3,5 - di - O - benzyl - 6 - O - phenyl - D - glucopyranose crystallizes from a mixture of ether and hexane in the form of white crystals, m.p. 90—91°; $[\alpha]_D^{20} = -8^\circ \pm 1^\circ$ ($c=1.013$ in chloroform).

A solution of 35.6 g of 3,5 - di - O - benzyl - 6 - O - phenyl - D - glucopyranose in 850 ml of 65% aqueous acetic acid is mixed

- at 20° with a solution of 40.5 g of periodic acid in 70 ml of water. The mixture is allowed to stand for 5 minutes and then mixed with 700 ml of water and extracted with ether. The ether solution is washed with a saturated aqueous sodium hydrogen carbonate solution and with water, dried over sodium sulfate, and evaporated in a water-jet vacuum at 40°. The residue is crystallized from a mixture of ether and hexane to yield the 2,4 - di - O - benzyl - 3 - O - formyl - 5 - O - phenyl - D - arabinose in the form of white crystals, m.p. 52—54°; $[\alpha]_D^{20} = +8^\circ \pm 1^\circ$ ($c=1.096$ in chloroform). The 2,4 - di - O - benzyl - 5 - O - phenyl - D - arabinose is obtained from it by treatment with a base.

EXAMPLE 6

- A solution of 5.2 g of sodium borohydride in 190 ml of 85% aqueous methanol is mixed with a suspension of 19 g of 2,4 - di - O - benzyl - 3 - O - formyl - 5 - O - (4 - chlorophenyl) - D - arabinose in 210 ml methanol at 0—5°. The mixture is allowed to stand at this temperature for 30 minutes and the methanol is then distilled off at 40° in a water-jet vacuum. The residue is neutralized with ice-cold 2N hydrochloric acid and extracted with methylene chloride. The methylene chloride solution is washed with 2N hydrochloric acid and with water, dried over sodium sulfate and evaporated under reduced pressure. The residue is crystallized from a mixture of methanol and water; the 2,4 - di - O - benzyl - 5 - O - (4 - chlorophenyl) - D - arabitol of the formula



is obtained in the form of slightly brownish crystals, m.p. 88—89°; $[\alpha]_D^{20} = -30^\circ \pm 1^\circ$ ($c=1.073$ in chloroform).

- The starting material can be prepared as follows:

- A melt of 50 g of 1,2 - O - isopropylidene - 5,6 - anhydro - α - D - glucofuranose and 38.5 g of 4 - chlorophenol is treated at 110° with 6 drops of pyridine. The mixture is allowed to react for another 30 minutes at 140° and is then cooled to 80—90°, and mixed with 100 ml of methanol. The bulk of the methanol is then distilled off under reduced pressure, and the residue is extracted with ether. The ether solution is washed with an aqueous sodium hydroxide solution and with water, dried over sodium sul-

fate, and evaporated under a water-jet vacuum. The 1,2 - O - isopropylidene - 6 - O - (4 - chlorophenyl) - α - D - glucofuranose obtained as a residue is purified as follows:

A solution of 80.2 g of the crude 1,2 - O - isopropylidene - 6 - O - (4 - chlorophenyl) - α - D - glucofuranose in 160 ml of a 1:1 mixture of pyridine and acetic acid anhydride is kept at 90° for an hour and a half. The mixture is evaporated under reduced pressure, the residue is mixed with 100 ml of ice-cold water, and the whole is extracted with ether. The ether solution is washed with 1N hydrochloric acid and with the water, dried over sodium sulfate and evaporated under reduced pressure. The 1,2 - O - isopropylidene - 3,5 - di - O - acetyl - 6 - O - (4 - chlorophenyl) - α - D - glucofuranose crystallizes from a mixture of methanol and water, m.p. 76—77.5°; $[\alpha]_D^{20} = 13^\circ \pm 1^\circ$ ($c=1.264$ in chloroform).

A suspension of 76 g of the resulting 1,2 - O - isopropylidene - 3,5 - di - O - acetyl - 6 - O - (4 - chlorophenyl) - α - D - glucofuranose in 200 ml of methanol is mixed with a solution of 21.7 g of potassium hydroxide in 450 ml of methanol. The mixture is stirred at room temperature for 30 minutes and the bulk of the methanol is then distilled off under reduced pressure. The residue is extracted with ether and the ether solution is washed with water, dried over sodium sulfate, evaporated in a water-jet vacuum, and the residue is crystallized from a mixture of methanol and water. The resulting 1,2 - O - isopropylidene - 6 - O - (4 - chlorophenyl) - α - D - glucofuranose melts at 103.5—104.5°; $[\alpha]_D^{20} = -6^\circ \pm 1^\circ$ ($c=1.297$ in chloroform).

In an atmosphere of nitrogen, a solution of 47 g of 1,2 - O - isopropylidene - 6 - O - (4 - chlorophenyl) - α - D - glucofuranose in 40 ml of dimethylsulfoxide is added dropwise, while stirring vigorously, to a suspension of 28.8 g of powdered potassium hydroxide in 50 ml of dimethylsulfoxide. In the course of 70 minutes, 54 g of benzyl chloride are added dropwise to this mixture. The mixture is stirred for 30 minutes, and the reaction product poured into 150 ml of ice-water, and the whole is extracted with chloroform. The chloroform solution is washed with water, dried over sodium sulfate and evaporated under reduced pressure. The residue is mixed with 30 g of powdered potassium hydroxide and the mixture is subjected to steam distillation until chlorine can no longer be detected in the distillate. The residue is extracted with chloroform and the chloroform solution is washed with water, dried over sodium sulfate, and evaporated in a water-jet vacuum. The residue is distilled; the 1,2 - O - isopropylidene - 3,5 - di - O - benzyl - 6 - O - (4 - chlorophenyl) - α - D - glucofuranose is obtained as a yellowish oil at 250—255°/0.01 mm Hg; $[\alpha]_D^{20} = -24^\circ \pm 1^\circ$ ($c=1.19$ in chloroform).

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A solution of 66.5 g of 1,2 - O - isopropylidene - 3,5 - di - O - benzyl - 6 - O - (4 - chlorophenyl) - α - D - glucofuranose in 1000 ml of 1N ethanolic hydrogen chloride is allowed to stand at room temperature for 18 hours, then cooled to 0—5° and neutralized with a ice-cold 10N aqueous sodium hydroxide solution. The resulting sodium chloride is filtered off and the filtrate is freed from the bulk of the ethanol at 40° under a water-jet vacuum. The residue is extracted with ether; the ether solution is washed with a saturated aqueous sodium hydrogen sulfite solution and with water, dried over sodium sulfate and evaporated at 40° under reduced pressure. The residue is crystallized from a mixture of ether and hexane to yield the ethyl - 3,4 - di - O - benzyl - 6 - (4 - chlorophenyl) - D - glucofuranoside in the form of white crystals, m.p. 83.5—84.5°; [α]_D²⁰ = -37° ± 1° (c=1.089 in chloroform).

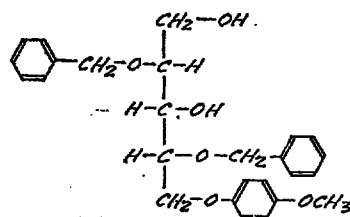
A solution of 38.4 g of ethyl - 3,5 - di - O - benzyl - 6 - (4 - chlorophenyl) - D - glucofuranoside in 500 ml of 50% aqueous acetic acid is refluxed for 12 hours and then freed from the bulk of the acetic acid under reduced pressure. The residue is extracted with ether and the ether solution is washed with a saturated aqueous sodium hydrogen carbonate solution and with water, dried over sodium sulfate and evaporated in a water-jet, vacuum. The 3,5 - di - O - benzyl - 6 - O - (4 - chlorophenyl) - D - glucofuranose recrystallized from a mixture of methylene chloride and hexane and obtained in the form of faintly yellowish crystals, m.p. 80—82°; [α]_D²⁰ = 0° ± 1° c=1.075 in chloroform).

A solution of 27 g of 3,5 - di - O - benzyl - 6 - O - (4 - chlorophenyl) - D - glucofuranose in 800 ml of 65% aqueous acetic acid is mixed at 20° with a solution of 28.4 g of periodic acid in 70 ml of water. After the addition of 530 ml of water, the mixture is extracted with ether. The ether solution is washed with a saturated aqueous sodium hydrogen carbonate solution and with water, dried over sodium sulfate, and evaporated under reduced pressure. From a mixture of ether and hexane, the 2,4 - di - O - benzyl - 3 - O - formyl - 5 - O - (4 - chlorophenyl) - D - arabinose crystallizes in the form of white crystals, m.p. 59—61°; [α]_D²⁰ = +6° ± 1° (c=1.148 in chloroform).

EXAMPLE 7

A solution of 21.8 g of 2,4 - di - O - benzyl - 3 - O - formyl - 5 - O - (4 - methoxyphenyl) - D - arabinose in 220 ml of methanol is added dropwise in the course of 15 minutes at 10°, while stirring, to a solution of 6 g of sodium borohydride in 180 ml of 80% aqueous methanol. Stirring is continued for another 30 minutes, the bulk of the methanol is distilled off under reduced pressure, and the residue is neutralized with ice-cold 2N

hydrochloric acid. The mixture is extracted with ether and the ether solution is washed with 2N hydrochloric acid and with water, dried over sodium sulfate and evaporated in a water-jet vacuum. The residue is crystallized from a mixture of ether and petroleum ether, and the 2,4 - di - O - benzyl - 5 - O - (4 - methoxy phenyl) - D - arabitol of the



is obtained in the form of white crystals, m.p. 81—82°; [α]_D²⁰ = -35° ± 1° (c=1.150 in chloroform).

The starting material can be prepared as follows:

At 110° 6 drops of pyridine are added to a melt of 50 g of 1,2 - O - isopropylidene - 5,6 - anhydro - α - D - glucofuranose and 30.7 g of 4 - methoxyphenol. By cooling, the exothermic reaction is kept at a temperature not exceeding 170°. The mixture is stirred at 140° for 30 minutes, then cooled to 80—90° with continued stirring, and 100 ml of methanol are then added. The bulk of the methanol is distilled off and the mixture is extracted with ether. The ether solution is washed with an 1N aqueous sodium hydroxide solution and with water, dried over sodium sulfate, and evaporated under reduced pressure. The resulting 1,2 - O - isopropylidene - 6 - O - (4 - methoxyphenyl) - α - D - glucofuranose is purified as follows:

A mixture of 72 g of the crude product in a mixture of 144 ml of pyridine and 144 ml of acetic acid anhydride is allowed to stand at room temperature for 12 hours. Then the mixture of pyridine and acetic acid anhydride is distilled off under reduced pressure at 60—70°. The residue is distilled in a high vacuum.

The 1,2 - O - isopropylidene - 3,5 - di - O - acetyl - 6 - O - (4 - methoxyphenyl) - α - D - glucofuranose is obtained at 210°/0.02 mm Hg and is crystallized from a mixture of methanol and water, m.p. 90.5—92°; [α]_D²⁰ = -12° ± 1° (c=1.161 in chloroform).

A suspension of 69.3 g of 1,2 - O - isopropylidene - 3,5 - di - O - acetyl - 6 - O - (4 - methoxyphenyl) - α - D - glucofuranose in 360 ml of methanol is mixed with a solution of 20.6 of potassium hydroxide in 150 ml of methanol. The mixture is stirred at room temperature for 30 minutes, then evaporated at 40° in a water-jet vacuum, and extracted with ether. The ether solution is washed with water, dried over sodium sulfate and evaporated un-

der reduced pressure. The pure 1,2 - O - isopropylidene - 6 - O - (4 - methoxyphenyl) - α - D - glucofuranose obtained as the residue is degassed in a high vacuum; $[\alpha]_D^{20} = +3^\circ \pm 1^\circ$ ($c=1.004$ in chloroform).

5 A solution of 56 g of 1,2 - isopropylidene - 6 - O - (4 - methoxyphenyl) - α - D - glucofuranose in 90 ml of dimethylsulfoxide is stirred dropwise, in an atmosphere of nitrogen, 10 to a suspension of 31.8 g of powdered potassium hydroxide in 60 ml of dimethylsulfoxide. After that, 65.4 g benzyl chloride are added dropwise in the course of 75 minutes at 40° . The reaction mixture is stirred for 2 hours, 15 then poured into 100 ml of ice-water and the whole is extracted with chloroform. The chloroform solution is washed with water, dried over sodium sulfate and evaporated in a water-jet vacuum. The residue is distilled in the high 20 vacuum under a pressure of 0.05 mm Hg until the vapor temperature reaches 200° . The crude 1,2 - O - isopropylidene - 3,5 - di - O - benzyl - 6 - O - (4 - methoxyphenyl) - α - D - glucofuranose obtained as the residue is 25 processed without further purification.

A solution of 79 g of 1,2 - O - isopropylidene - 3,5 - di - O - benzyl - 6 - O - (4 - methoxyphenyl) - α - D - glucofuranose in 1200 ml of 1N ethanolic hydrogen chloride is allowed to stand at room temperature for 17 30 hours. The mixture is then cooled to $0-5^\circ$ and neutralized with an ice-cold 10N aqueous sodium hydroxide solution. At 40° and under reduced pressure, the bulk of the ethanol is distilled off and the 35 concentrate is extracted with ether. The ether solution is washed with a saturated aqueous sodium hydrogen sulfite solution and with water, dried over sodium sulfate, and 40 evaporated at 40° in a water-jet vacuum. On degassing in a high vacuum, ethyl - 3,5 - di - O - benzyl - 6 - O - (4 - methoxyphenyl) - D - glucofuranoside is obtained as a yellowish 45 oil; $[\alpha]_D^{20} = -72^\circ \pm 1^\circ$ ($c=1.069$ in chloroform).

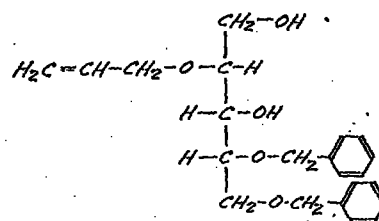
A solution of 60 g of ethyl - 3,5 - di - O - benzyl - 6 - O - (4 - methoxyphenyl) - D - glucofuranoside in 3000 ml of 50% aqueous acetic acid is stirred at 70° for 5 hours. After 50 that, the bulk of the acetic acid is distilled off under reduced pressure at $60-70^\circ$ and the residue is extracted with ether. The ether solution is washed with a saturated aqueous sodium hydrogen carbonate 55 solution and with water, dried over sodium sulfate and evaporated in a water-jet vacuum. The 3,5 - di - O - benzyl - 6 - O - (4 - methoxyphenyl) - D - glucofuranose crystallizes in the form of white crystals from a 60 mixture of ether and petroleum ether, m.p. $99-100^\circ$; $[\alpha]_D^{20} = -7^\circ \pm 1^\circ$ ($c=1.228$ in chloroform).

65 A solution of 30.3 g of 3,5 - di - O - benzyl - 6 - O - (4 - methoxyphenyl) - D - glucofuranose in 400 ml of 65% aqueous acetic

acid is mixed at 20° with a solution of 32.1 g of periodic acid in 70 ml of water. The resulting white, crystalline precipitate is filtered off and washed with a small amount of ice-water, then dried at 30° in a water-jet vacuum. The resulting 2,4 - di - O - benzyl - 3 - O - formyl - 5 - O - (4 - methoxyphenyl) - D - arabinose melts at $74-75^\circ$; $[\alpha]_D^{20} = +8^\circ \pm 1^\circ$ ($c=1.251$ in chloroform).

EXAMPLE 8

A solution of 18.5 g of 2 - O - allyl - 3 - O - formyl - 4,5 - di - O - benzyl - D - arabinose in 200 ml of methanol is added dropwise in the course of 30 minutes at 10° to a solution of 6 g of sodium borohydride in 200 ml of 85% aqueous methanol. The mixture is stirred for 30 minutes at 10° and the bulk of the methanol then distilled off at 40° under reduced pressure. After the addition of 100 ml of water, the residue is extracted with ether. 85 The ether solution is washed with ice-cold 2N hydrochloric acid and with water, dried over sodium sulfate, and evaporated in a water-jet vacuum. On degassing in a high vacuum 2 - O - allyl - 4,5 - di - O - benzyl - D - arabinol of the formula 90



is obtained as a colourless oil, b.p. $220^\circ/0.008$ mm Hg (microdistillation); $[\alpha]_D^{20} = -37^\circ \pm 1^\circ$ ($c=0.895$ in chloroform).

The starting material can be prepared as follows:

A suspension, prepared in an atmosphere of nitrogen, of 121 g of powdered potassium hydroxide in 300 ml of dimethylsulfoxide is mixed with a solution of 214 g of 1,2 - isopropylidene - 3 - O - allyl - α - D - glucofuranose in 500 ml of dimethylsulfoxide and the mixture is treated dropwise in the course of 3 hours under nitrogen with 227.2 g of benzyl chloride in such manner that the temperature does not rise above $40-45^\circ$. The mixture is stirred for another hour at 40° and then poured into 1500 ml of ice-water and extracted with ether. The ether extract is washed with water, dried over sodium sulfate, and evaporated. The residue is distilled and the 2 - O - isopropylidene - 3 - O - allyl - 5,6 - di - O - benzyl - α - D - glucofuranose is obtained at $192-198^\circ/0.01$ mm Hg; $[\alpha]_D^{20} = -30^\circ \pm 0.5^\circ$ ($c=1.993$ in chloroform).

A solution of 12.75 g of 1,2 - O - isopropylidene - 3 - O - allyl - 5,6 - di - O - benzyl - α - D - glucofuranose in 298 ml of a 1N ethanolic solution of hydrogen chloride is kept for 120

tion of 22.1 g
r. The salt
is filtered off
of ice-water,
vacuum. The
-O-formyl-
-O-arabinose
1° ($c=1.251$)

- allyl - 3 -
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added drop-
at 10° to a
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the mixture is
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kept for

17 hours at room temperature and then neu-
tralized at 0° to 5° with a 10N aqueous sodium
hydroxide solution. The bulk of ethanol is dis-
tilled off under reduced pressure and the resi-
due is extracted with chloroform. The chloro-
form extract is washed with a saturated sodium
bisulfite solution and with water, dried over
sodium sulfate and evaporated under reduced
pressure. The residue is distilled and yields
at 200°/0.03 mm Hg the ethyl - 3 - O -
allyl - 5,6 - di - O - benzyl - D - glucofurano-
side as a faintly yellowish oil; [α]_D²⁰ = -18°
±1° ($c=1$ in chloroform).

A solution of 277 g of ethyl - 3 - O - allyl -
5,6 - di - O - benzyl - D - glucofuranoside in
4500 ml of 55% aqueous acetic acid is stirred
for 6 hours at 70°. After that, the bulk of the
acetic acid is distilled off under reduced pres-
sure at 60—70°. The residue is neutralized at
0—5° with ice-cold 10N aqueous sodium hy-
droxide and extracted with ether. The ether
solution is washed with water, dried over
sodium sulfate and evaporated at 40° in a
water-jet vacuum. From a mixture of ether
and petroleum ether, the 3 - O - allyl - 5,6 -
di - O - benzyl - D - glucofuranose crystallizes
in the form of white crystals, m.p. 58—59°;
[α]_D²⁰ = -19°±1° ($c=1.013$ in chloroform).

A solution of 30 g of 3 - O - allyl - 5,6 -
di - O - benzyl - D - glucofuranose in 530 ml
of 57% aqueous acetic acid is mixed at 20°
with a solution of 37.4 g of periodic acid in 70
ml of water. The reaction mixture is then
diluted with 550 ml of water and extracted
with ether, the ether solution is washed with a
saturated sodium hydrogen carbonate solution
and with water, dried over sodium sulfate, and
evaporated at 30° under reduced pressure.
The 2 - O - allyl - 3 - O - formyl - 5,6 -
di - O - benzyl - D - arabinose is obtained in
the form of white, deliquescent crystals, m.p.
47—49°.

EXAMPLE 9

A solution of 1g of 1,3 - O - benzylidene -
2,4,5 - tri - O - benzyl - D - arabinol in 10
ml of dioxan is treated with 5 ml of concen-
trated hydrochloric acid and allowed to stand
at 20° for 4 hours. The bulk of dioxan and
hydrochloric acid is then distilled off under
reduced pressure and at a temperature of
40°. The residue is neutralized at 0—5° with
a 10N aqueous sodium hydroxide solution and
extracted with ether; the ether solution is
dried over sodium sulfate and evaporated un-
der reduced pressure. Using preparative thin
layer chromatography (silica gel PF 254 of
Merck AG, Darmstadt; system: chloroform-
ethyl acetate 85:15), the pure 2,4,5 - tri -
O - benzyl - D - arabinol is obtained in the
form of white needles, Rf=0.2; F. 66.5—
67.5°.

The starting material may be obtained by
reacting 1,2 - O - isopropylidene - 3 - O -
benzyl - α - D - glucofuranose with 2 moles
of benzoyl chloride in pyridine and treating

the resulting 1,2 - O - isopropylidene - 3 -
O - benzyl - 5,6 - di - O - benzoyl - α - D -
glucofuranose with a 10% solution of
dry hydrogen chloride in absolute
ethanol for 16 hours. The resulting ethyl - 3 -
O - benzyl - 5,6 - di - O - benzoyl - D -
glucofuranoside in 50% aqueous acetic acid is
heated at 60° and the resulting 3 - O - benzyl -
5,6 - di - O - benzoyl - D - glucofuranose in
acetic acid is degraded with periodic acid
according to the procedure described in Ex-
ample 1 to form the 2 - O -
benzyl - 3 - O - formyl - 4,5 -
di - O - benzoyl - D - arabinose. A solution of
the product in methanol is treated at 10—20°
with sodium borohydride and the resulting 2 -
O - benzyl - 4,5 - di - O - benzoyl - D -
arabitol is treated with benzaldehyde in the
presence of zinc chloride to yield the 1,3 -
O - benzylidene - 2 - O - benzyl - 4,5 -
di - O - benzoyl - D - arabitol, which is
hydrolyzed by treatment with an aqueous eth-
anolic sodium hydroxide solution. The 1,3 -
O - benzylidene - 2 - O - benzyl -
D - arabitol thus obtained is dis-
solved in dioxan and treated with
benzyl chloride in the presence of powdered
potassium hydroxide; the resulting 1,3 - O -
benzylidene - 2,4,5 - tri - O - benzyl - D -
arabitol melts at 143—144° after recrystal-
lization from ethanol; thin layer chromato-
gram; Rf=0.75 (silica gel SL 254 of Merck
AG, Darmstadt; system: chloroform-ethyl
acetate 85:15).

EXAMPLE 10

A solution of 1 g of 1,3 - O - benzylidene -
2 - O - n - propyl - 4,5 - di - O - (4 -
chlorobenzyl) - D - arabitol in 40 ml of 75%
aqueous acetic acid is allowed to stand for
12 hours at 70°. The bulk of the acetic acid
is removed under water-jet vacuum and the
residue is neutralized at 0—5° with a 10N
aqueous sodium hydroxide solution, then ex-
tracted with ether. The ether solution is
washed with water, dried over sodium sulfate
and evaporated under reduced pressure. The
residue is subjected to preparative thin layer
chromatography (silica gel Pf 254 of Merck
AG, Darmstadt; system: chloroform - ethyl
acetate 85:15). The pure 2 - O - n - propyl -
4,5 - di - O - (4-chlorobenzyl) - D - ara-
bitol is obtained in the form of white crystals,
m.p. 84°; thin layer chromatogram: Rf=
0.13 (silica gel SL 254 of Merck AG, Darm-
stadt; system: chloroform-ethyl acetate 85:
15).

The starting material is obtained according
to the procedure described in Example 9 by
selecting the appropriate starting materials;
the 1,3 - O - benzylidene - 2 - O - n -
propyl - 4,5 - di - O - (4 - chlorobenzyl) -
D - arabitol melts at 132—133° after re-
crystallization from a mixture of acetone
and petroleum ether; Rf=0.7 (silica gel SL

254 of Merck AG, Darmstadt; system: chloroform-ethyl acetate 85:15).

EXAMPLE 11

5 Capsules containing 0.4 g of the active substance can be manufactured as follows:

Composition (for 10000 capsules):

2,4,5-Tri-O-benzyl-D-arabitol 4000 g
Absolute ethanol 400 g

10 The 2,4,5 - tri - O - benzyl - D - arabitol is mixed with the ethanol and the mixture is filled into soft gelatine capsules with the aid of a suitable capsule machine. Instead of the 2,4,5 - tri - O - benzyl - D - arabitol, the 2 - O - n - propyl - 4,5 - di - O - (4 - chlorobenzyl) - D - arabitol or the 2,4 - di - O - benzyl - 5 - O - phenyl - D - arabitol may be used in the above example.

EXAMPLE 12

20 Tablets containing 0.2 g of the active substance can be manufactured as follows:

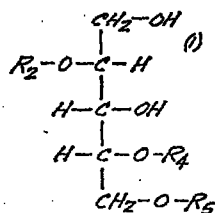
Composition (for 10000 tablets):

2,4,5-Tri-O-benzyl-D-arabitol 2000 g
Magnesium trisilicate 1000 g
Wheat starch 1350 g
25 Polyvinylpyrrolidone 200 g
Colloidal silica 250 g
Talc 150 g
Magnesium stearate 50 g

30 The 2,4,5 - tri - O - benzyl - D - arabitol is mixed with the magnesium trisilicate, a part of the wheat starch and the colloidal silica and the sieved mixture is moistened with a solution of polyvinylpyrrolidone in methylene chloride until a slightly plastic mass has been produced. This is forced through a sieve and dried; the granules are again sieved. The remainder of the wheat starch, the talc and the magnesium stearate are mixed in and the mixture is processed into tablets weighing 0.5 g. Instead of the 2,4,5 - tri - O - benzyl - D - arabitol, the 2 - O - n - propyl - 4,5 - di - O - (4 - chlorobenzyl) - D - arabitol or the 2,4 - di - O - benzyl - 5 - O - phenyl - D - arabitol may be used to manufacture 45 the abovementioned tablets.

WHAT WE CLAIM IS:—

1. D - arabitol compounds of formula



wherein each of the residues R_2 , R_4 and R_5

denotes an optionally substituted hydrocarbon residue.

2. D - arabitols of the formula I according to claim 1, in which each of R_2 , R_4 and R_5 is a lower alkyl, a lower alkenyl, a cycloalkyl or an optionally substituted benzyl residue and R_5 in addition may be an optionally substituted phenyl residue.

3. O - acyl derivatives of the compounds of claim 1 or 2.

4. 2 - O - R_2' - 4 - O - R_4' - 5 - O - R_5' - D - arabitols, in which R_2' is a lower alkyl or a benzyl residue optionally substituted by halogen or lower alkyl and each of R_4' and R_5' is a benzyl residue optionally substituted by halogeno or lower alkyl.

5. 2 - O - R_2' - 4 - O - R_4' - 5 - O - R_5' - D - arabitols, in which R_2' is a lower alkyl or lower alkenyl group, or a benzyl group optionally substituted by halogeno, lower alkyl or lower alkoxy, each of R_4' and R_5' is a benzyl group optionally substituted by halogeno, lower alkyl or lower alkoxy, and R_5' also stands for a phenyl group optionally substituted by halogeno, lower alkyl or lower alkoxy.

6. 2 - O - R_2' - 4 - O - R_4' - 5 - O - R_5' - D - arabitols, in which R_2' is a lower alkyl group or a benzyl group optionally substituted by chloro or methyl, and each of R_4' and R_5' represents a benzyl group optionally substituted by chloro or methyl.

7. 2 - O - R_2' - 4 - O - R_4' - 5 - O - R_5' - D - arabitols, in which R_2' is a lower alkyl group or a benzyl group optionally substituted by chloro, methyl or methoxy, each of R_4' and R_5' represents a benzyl residue optionally substituted by chloro, methyl or methoxy, and R_5' is also a phenyl group optionally substituted by chloro, methyl or methoxy.

8. 2 - O - R_2' - 4 - O - R_4' - 5 - O - R_5' - D - arabitols, in which R_2' is a lower alkyl group or a benzyl group optionally substituted in 4-position by chloro or methyl, and each of R_4' and R_5' is a benzyl group optionally substituted in 4-position by chloro or methyl.

9. 2 - O - R_2' - 4 - O - R_4' - 5 - O - R_5' - D - arabitols, in which R_2' is a lower alkyl group or a benzyl group optionally substituted in 4-position by chloro, methyl or methoxy each of R_4' and R_5' is a benzyl group optionally substituted in 4-position by chloro, methyl or methoxy, and R_5' is also a phenyl group optionally substituted in 4-position by chloro methyl or methoxy.

10. O - Lower alkanoyl or O - carboxy - lower alkanoyl derivatives of compounds of any one of claims 4, 6 and 8.

11. O - Lower alkanoyl or O - carboxy - lower alkanoyl derivatives of compounds of any one of claims 5, 7 and 9.

12. 2,4,5 - Tri - O - benzyl - D - arabitol.



254 of Merck AG, Darmstadt; system: chloroform-ethyl acetate 85:15).

EXAMPLE 11

5 Capsules containing 0.4 g of the active substance can be manufactured as follows:

Composition (for 10000 capsules):
2,4,5-Tri-O-benzyl-D-arabitol 4000 g
Absolute ethanol 400 g

10 The 2,4,5 - tri - O - benzyl - D - arabitol is mixed with the ethanol and the mixture is filled into soft gelatine capsules with the aid of a suitable capsule machine. Instead of the 2,4,5 - tri - O - benzyl - D - arabitol, the 2 - O - n - propyl - 4,5 - di - O - (4 - chlorobenzyl) - D - arabitol or the 2,4 - di - O - benzyl - 5 - O - phenyl - D - arabitol may be used in the above example.

EXAMPLE 12

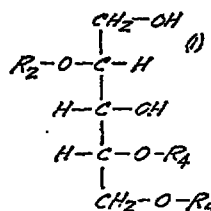
20 Tablets containing 0.2 g of the active substance can be manufactured as follows:

Composition (for 10000 tablets):
2,4,5-Tri-O-benzyl-D-arabitol 2000 g
Magnesium trisilicate 1000 g
Wheat starch 1350 g
25 Polyvinylpyrrolidone 200 g
Colloidal silica 250 g
Talc 150 g
Magnesium stearate 50 g

30 The 2,4,5 - tri - O - benzyl - D - arabitol is mixed with the magnesium trisilicate, a part of the wheat starch and the colloidal silica and the sieved mixture is moistened with a solution of polyvinylpyrrolidone in methylene chloride until a slightly plastic mass has been produced. This is forced through a sieve and dried; the granules are again sieved. The remainder of the wheat starch, the talc and the magnesium stearate are mixed in and the mixture is processed into tablets weighing 0.5 g. Instead of the 2,4,5 - tri - O - benzyl - D - arabitol, the 2 - O - n - propyl - 4,5 - di - O - (4 - chlorobenzyl) - D - arabitol or the 2,4 - di - O - benzyl - 5 - O - phenyl - D - arabitol may be used to manufacture 45 the abovementioned tablets.

WHAT WE CLAIM IS:—

1. D - arabitol compounds of formula



wherein each of the residues R_2 , R_4 and R_5

denotes an optionally substituted hydrocarbon residue.

2. D - arabitols of the formula I according to claim 1, in which each of R_2 , R_4 and R_5 is a lower alkyl, a lower alkenyl, a cycloalkyl or an optionally substituted benzyl residue and R_5 in addition may be an optionally substituted phenyl residue.

3. O - acyl derivatives of the compounds of claim 1 or 2.

4. 2 - O - R_2' - 4 - O - R_4' - 5 - O - R_5' - D - arabitols, in which R_2' is a lower alkyl or a benzyl residue optionally substituted by halogen or lower alkyl and each of R_4' and R_5' is a benzyl residue optionally substituted by halogen or lower alkyl.

5. 2 - O - R_2' - 4 - O - R_4' - 5 - O - R_5' - D - arabitols, in which R_2' is a lower alkyl or lower alkenyl group, or a benzyl group optionally substituted by halogen, lower alkyl or lower alkoxy, each of R_4' and R_5' is a benzyl group optionally substituted by halogen, lower alkyl or lower alkoxy, and R_5' also stands for a phenyl group optionally substituted by halogen, lower alkyl or lower alkoxy.

6. 2 - O - R_2' - 4 - O - R_4' - 5 - O - R_5' - D - arabitols, in which R_2' is a lower alkyl group or a benzyl group optionally substituted by chloro or methyl, and each of R_4' and R_5' represents a benzyl group optionally substituted by chloro or methyl.

7. 2 - O - R_2' - 4 - O - R_4' - 5 - O - R_5' - D - arabitols, in which R_2' is a lower alkyl group or a benzyl group optionally substituted by chloro, methyl or methoxy, each of R_4' and R_5' represents a benzyl residue optionally substituted by chloro, methyl or methoxy, and R_5' is also a phenyl group optionally substituted by chloro, methyl or methoxy.

8. 2 - O - R_2' - 4 - O - R_4' - 5 - O - R_5' - D - arabitols, in which R_2' is a lower alkyl group or a benzyl group optionally substituted in 4-position by chloro or methyl, and each of R_4' and R_5' is a benzyl group optionally substituted in 4-position by chloro or methyl.

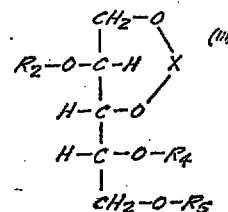
9. 2 - O - R_2' - 4 - O - R_4' - 5 - O - R_5' - D - arabitols, in which R_2' is a lower alkyl group or a benzyl group optionally substituted in 4-position by chloro, methyl or methoxy each of R_4' and R_5' is a benzyl group optionally substituted in 4-position by chloro, methyl or methoxy, and R_5' is also a phenyl group optionally substituted in 4-position by chloro methyl or methoxy.

10. O - Lower alkanoyl or O - carboxy - lower alkanoyl derivatives of compounds of any one of claims 4, 6 and 8.

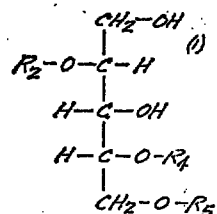
11. O - Lower alkanoyl or O - carboxy - lower alkanoyl derivatives of compounds of any one of claims 5, 7 and 9.

12. 2,4,5 - Tri - O - benzyl - D - arabitol.

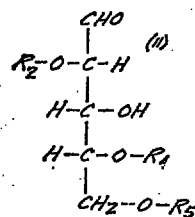
propyl - 4,5 - di - O - (4 - chlorobenzyl -
 15. 2 - O - Methyl - 4,5 - di - O - (4 -
 chlorobenzyl) - D - arabinol.
 16. 2,4 - Di - O - benzyl - 5 - O - phenyl -
 D - arabinol.
 17. 2,4 - Di - O - benzyl - 5 - O - (4 -
 chlorophenyl) - D - arabinol.
 18. 2,4 - Di - O - benzyl - 5 - O - (4 -
 methoxyphenyl) - D - arabinol.
 19. 2 - O - Allyl - 4,5 - di - O - benzyl -



D - arabinol.
 20. The salts of compounds of claims 1—3
 and 10 with salt-forming groups.
 21. Non-toxic salts of compounds of claims
 1—3 and 10 with salt-forming groups.
 22. Non-toxic alkali metal or ammonium
 salts of compounds of claims 1—3 and 10
 with a carboxyl group.
 23. Salts of compounds of claim 11 with a
 carboxyl group.
 24. Non-toxic salts of compounds of claim
 11 with a carboxyl group.
 25. Non-toxic alkali metal or ammonium
 salts of compounds of claim 11 with a carb-
 oxyl group.
 26. Pharmaceutical preparations containing
 a compound of claims 1—4, 6, 8, 10, 12—
 14, 21 and 22 together with a pharmaceutical
 carrier material.
 27. Pharmaceutical preparations containing
 a compound of claims 5, 7, 9, 11, 15—19,
 24 and 25 together with a pharmaceutical car-
 rier material.
 28. Process for the manufacture of D - ara-
 binol compounds of formula



wherein each of the residues R_2 , R_4 and R_5
 denotes an optionally substituted hydrocarbon
 residue, as well as O-acyl derivatives there-
 of and salts of compounds with salt-forming
 groups, which comprises reducing in a D -
 arabinose compound of formula



in which X represents an optionally substi-
 tuted methylene group.

29. Process according to claim 28, which
 comprises reducing in a D-arabinose of the
 formula II according to claim 28 or in a 3 -
 O - acyl derivative thereof the carbonyl group
 in 1-position into the carbinol group, and, if
 desired, converting in a resulting compound an
 acyloxy group into a free hydroxyl group or
 a free hydroxyl group into an acyloxy group,
 and/or, if desired, converting a resulting com-
 pound having a salt-forming group into a salt
 or a resulting salt into the free compound.

30. Process according to claim 29, wherein
 3 - O - acyl derivatives of starting materials
 of the formula II according to claim 29 con-
 tain acyl residues of organic carboxylic acids.

31. Process according to claim 29, where-
 in 3-O-acyl derivatives of starting materials
 of the formula II according to claim 2 con-
 tain the acyl residue of formic acid.

32. Process according to claim 29 or 30,
 wherein a suitable carbonyl-carbinol reduct-
 ing agent is used.

33. Process according to any one of claims
 29, 31 and 32, wherein a hydride reducing
 agent is used.

34. Process according to any one of claims
 29 and 31—33, wherein an alkali metal
 aluminium hydride is used.

35. Process according to any one of claims
 29 and 31—33, wherein an alkali metal tri-
 lower alkoxy-aluminium hydride is used.

36. Process according to any one of claims
 29 and 31—33, wherein a borohydride is
 used.

37. Process according to any one of claims
 29, 31—33 and 36, wherein an alkali metal
 borohydride is used.

38. Process according to any one of claims
 29, 31—33, 36 and 37, wherein sodium boro-
 hydride is used.

39. Process according to any one of claims
 29, 31 and 32, wherein hydrogen in the
 presence of a suitable catalyst is used.

40. Process according to claim 39, wherein
 the catalyst is platinum oxide.

41. Process according to claim 28, wherein
 the residue of the formula -X- in the start-
 ing material of the formula III represents a
 mono- or disubstituted methylene group.

residue, or 3 - O - acyl derivatives thereof, as
 well as salts of compounds with salt-forming
 groups.

57. D-arabinose compounds of the formula
 II according to claim 56, in which each of
 R_2 , R_4 and R_5 is a lower alkyl, a lower
 alkenyl, a cycloalkyl or an optionally substi-
 tuted phenyl residue and R_5 in addition may
 be an optionally substituted phenyl residue,

or methoxy, and R_5 is also a phenyl group
 optionally substituted in 4-position by chloro,
 methyl or methoxy, or 3-O-lower alkanoyl or
 3-O-carboxyl-lower alkanoyl derivatives there-
 of, as well as salts of compounds having a
 carboxyl group.

64. 2,4,5 - Tri - O - benzyl - 3 - O -
 formyl - D - arabinose.

65. 2,4,5 - Tri - O - benzyl - D - arabinose.





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66. 2 - O - n - Propyl - 4,5 - di - O - (4 - chlorobenzyl) - D - arabinose.

67. 2 - O - Methyl - 3 - O - formyl - 4,5 - di - O - (4 - chlorobenzyl) - D - arabinose.

68. 2,4 - Di - O - benzyl - 3 - O - formyl - 5 - O - phenyl - D - arabinose.

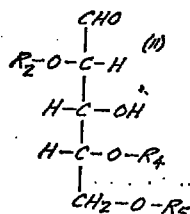
69. 2,4 - Di - O - benzyl - 5 - O - phenyl - D - arabinose.

70. 2,4 - Di - O - benzyl - 3 - O - formyl - 5 - O - (4 - chlorophenyl) - D - arabinose.

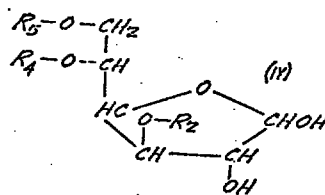
71. 2,4 - Di - O - benzyl - 3 - O - formyl - 5 - O - (4 - methoxyphenyl) - D - arabinose.

72. 2 - O - Allyl - 3 - O - formyl - 4,5 - di - O - benzyl - D - arabinose.

73. A process for the manufacture of D - arabinose compounds of the formula



wherein each of the residues R_2 , R_4 and R_5 denotes an optionally substituted hydrocarbon residue, or 3-O-acyl-derivatives thereof, as well as salts of compounds with salt-forming groups, which comprises treating a D - glucururanose of formula



with a glycol-splitting oxidizing reagent, and, if desired, converting in a resulting compound a formyloxy group into a free hydroxyl group or a free hydroxyl group into an acyloxy group, and/or if desired, converting a resulting compound having a salt-forming group into a salt or a resulting salt into the free compound.

74. Process according to claim 73, wherein periodic acid or a salt thereof is used as the oxidizing agent.

75. Process according to claim 73, wherein oxidative heavy metal carboxylates are used as oxidizing agents.

76. Process according to any one of claims 73-75, wherein the reaction is carried out in the presence of an organic carboxylic acid.

77. Process according to claim 76, wherein the reaction is carried out in the presence of acetic acid.

ABEL & IMRAY,
Chartered Patent Agents,
Quality House, Quality Court,
Chancery Lane, London, W.C.2.

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