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REACTION PRODUCT OF AMINO CARBOHYDRATES WITH THERAPEUTICALLY EFFECTIVE AMINO COMPOUNDS

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Claims priority, application Germany Mar. 14, 1957
12 Claims. (Cl. 260—211.5)

The present invention relates to therapeutically valuable compounds of increased compatibility and more particularly to condensation products of therapeutically valuable amino compounds with amino carbohydrates, and to a process of producing such condensation products.

The present application is a continuation-in-part of Serial No. 703,746, filed December 19, 1957, and entitled "Isonicotinic Acid Hydrazide Derivatives," which in turn is a continuation-in-part of application Serial No. 620,216, filed November 5, 1956, and entitled "Method of Preparing Therapeutically Effective D-Glucosamine Derivatives," now abandoned.

It is well known that compounds of vegetable or animal origin or synthetically produced compounds can be used for therapeutic purposes only if the desired therapeutic effect, and the like, is achieved by administration of a dose which is substantially lower than the toxic dose. Chemical compounds have a greater use as therapeutic agents, the greater the difference between their therapeutic doses and their toxic doses. This difference is designated as the therapeutic latitude or the therapeutic index of the respective chemical compound. It is the number of times the therapeutic dose can be given until the toxic level is attained.

Many chemical compounds have a therapeutic index which is so low that such compounds cannot be used as therapeutic agents although experimental tests might show that they have an excellent therapeutic activity. Other compounds have a sufficiently high therapeutic index; however, due to the necessity of repeated administration or prolonged use of such compounds undesired toxic effects are encountered.

Other properties of therapeutically valuable compounds, such as their solubility, stability, and the like are also of importance in their therapeutic applicabiliy. For instance their solubility may be too low or preparations containing such compounds, may be unstable on storage and/or exposure to air and/or humidity to permit administration.

It is one object of the present invention to provide new derivatives of therapeutically effective amino compounds which have substantially the same therapeutic activity as the starting amino compounds but which have a surprisingly low toxicity, which are well tolerated by humans and animals, and which are substantially more stable than the parent compounds.

Another object of the present invention is to provide new and valuable derivatives of isonicotinic acid hydrazide and 2-methyl-isonicotinic acid hydrazide which have substantially the same tuberculostatic effect as isonicotinic acid hydrazide and 2-methyl-isonicotinic acid hydrazide, but which have a very considerably lower toxicity.

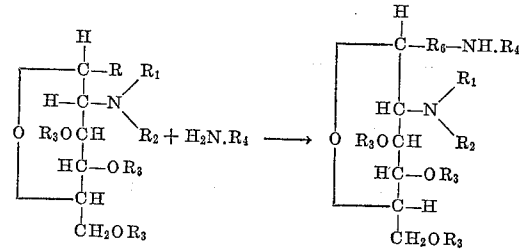
Still another object of the present invention is to provide new derivatives of therapeutically effective, bactericidal, bacteriostatic, and/or blood sugar lowering sulfonamides which are substantially less toxic and better soluble and tolerated than the starting sulfonamides.

A further object of the present invention is to provide new and valuable derivatives of analgesic and antipyretic 4-amino pyrazolone compounds which are substantially less toxic, better tolerated, and considerably more soluble than the starting compounds.

Another object of the present invention is to provide a simple and effective process of producing such new and valuable derivatives of therapeutically effective compounds, such as nicotinic acid hydrazides, sulfonamides, 4-amino-1-phenyl pyrazolone compounds, and the like.

Other objects of the present invention and advantageous features thereof will become apparent as the description proceeds.

In principle the new derivatives of therapeutically effective amino compounds, such as the isonicotinic acid hydrazides, sulfonamides, 4-amino-1-phenyl pyrazolones, and the like compounds are obtained by condensing said compounds with carbohydrates carrying amino groups, especially with glucosamine, galactosamine, and their derivatives. The reaction can take place on the glycosidic carbon atom (1) of the amino carbohydrate according to the following general equation:



In said formulas

R indicates the hydroxyl group, halogen, or the isothiocyanate group N=C=S;

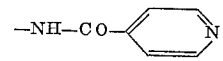
R_1 indicates hydrogen, an alkyl radical, or an acyl group;

R_2 indicates an alkyl, aryl, aralkyl, or cycloalkyl radical, or an acyl group;

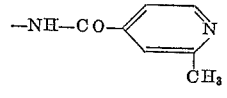
R_3 indicates hydrogen, the methyl radical, or an acyl group; and

R_4 indicates the residue of an isonicotinic acid hydrazide, a sulfonamide, a 4-amino-1-phenyl pyrazolone, or other therapeutically valuable compound, for instance, the following residues:

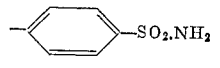
(1) Isonicotinic acid hydrazide



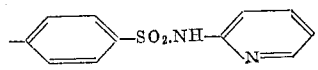
(2) 2-methyl isonicotinic acid hydrazide



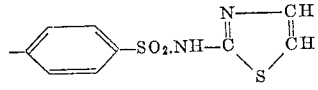
(3) Sulfanilamide



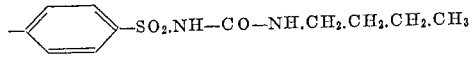
(4) Sulfapyridine



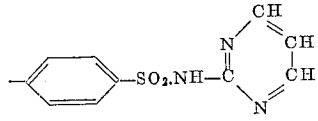
(5) Sulfathiazole



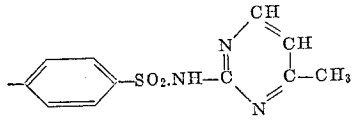
(6) N-sulfanilyl-n-butyl urea



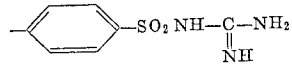
(7) Sulfapyrimidine



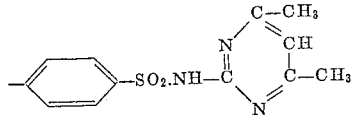
(8) Sulfa methyl pyrimidine



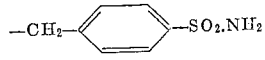
(9) Sulfaguanidine



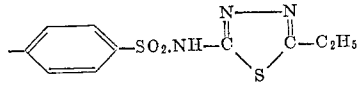
(10) Sulfa diamethyl pyrimidine



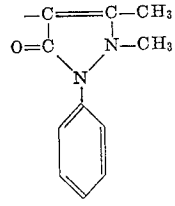
(11) p-Sulfonamido benzylamine



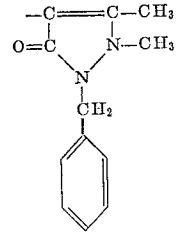
(12) 5-ethyl sulfa thiodiazole



(13) 4-amino-1-phenyl-2,3-dimethyl pyrazolone-(5)



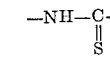
(14) 4-amino-1-benzyl-2,3-dimethyl pyrazolone-(5)



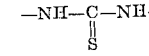
and others.

If R represents the hydroxyl group or halogen, R_0 is zero and the amino carbohydrate residue is directly attached to the amino group of the therapeutically valuable compound. Thereby water, or, respectively, hydrogen halide are split off.

If R represents the isothiocyanate group —N=C=S, R_0 indicates the



group and, by condensation with the amono group of the therapeutically valuable amino compound, a condensation product is formed in which the amino carbohydrate is connected to the therapeutically valuable amino compound by means of the thiosemicarbazide group



As stated above R_1 and R_2 may indicate the following substituents:

An alkyl radical, such as ethyl, isopropyl, n-butyl, n-hexyl, dodecyl, or an alkyl radical having functional groups, such as carbonyl groups, carboxyl groups, ester groups, and other groups of carboxyl derivatives.

A cycloalkyl radical, such as cyclopentyl, cyclohexyl, cyclooctyl.

An aryl radical, such as phenyl, pyridyl, naphthyl, or an aryl radical having at least one functional group, such as the 2,4,6-trinitrophenyl group.

An aralkyl radical, such as benzyl, tolyl, ethyl phenyl.

These alkyl, cycloalkyl, aryl, or aralkyl amino derivatives of amino carbohydrates may also be employed in the form of acid addition salts.

An acyl group, such as formyl, acetyl, chloro acetyl, butyroyl, lauroyl, bromo caprinoyl, undecylenoyl, benzoyl, p-nitro benzoyl, acetyl salicoyl, nicotinoyl, isonicotinoyl, phenyl acryloyl, toluene sulfonyl, or acyl groups of mono-substituted dicarboxylic acids, such as of succinic acid, maleic acid, phthalic acid, o-sulfo benzoic acid.

R_3 may indicate one of the following substituents: Hydrogen, the methyl radical, or an acyl group such as the acetyl, chloro acetyl, propionyl, lauroyl, undecylenoyl, benzoyl, p-nitro benzoyl, acetyl salicoyl, nicotinoyl, isonicotinoyl, phenyl acryloyl, or the like acyl groups.

Suitable amino carbohydrates are, for instance, the following amino saccharides and their derivatives.

Amino monosaccharides:

Glucosamine	Talosamine
Isoglucosamine	4-amino-4-desoxy mannose
Galactosamine	6-amino-6-desoxy-d-galactose
Sorbosyl amine	6-amino-6-desoxy-d-glucose
Tagatosamine	3-amino-3-desoxy-d-ribose
Xylosamine	2-amino-2-desoxy-d-mannose
D-lyxosamine	2-amino-2-desoxy-glucose
Allosamine	2-amino-2-desoxy-d-altrose
Altrosamine	3-amino-3-desoxy-d-altrose
Mannosamine	3-amino-3-desoxy-d-idose
Idosamine	3-amino-3-desoxy-glucose
Gulosamine	and others.

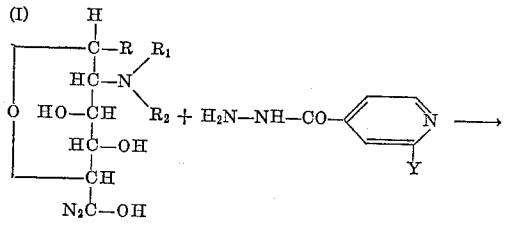
Amino disaccharides:

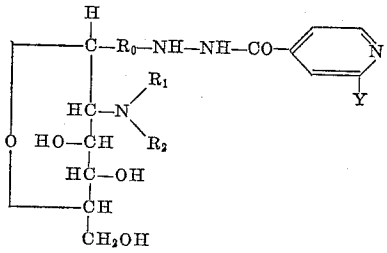
4-β-d-galactosido-d-glucosamine
6-β-d-galactosido-d-glucosamine
6-β-glucosaminido-d-glucose
O-β-d-galactopyranosyl-(1→4)-1-desoxy-1-acetamino-β-d-glucose
O - β - d - galactoso pyranosyl - (1→3) - 2 - desoxy-acetamino - O - βd - glucoso pyranosyl-(1→3) - d-galactose and others.

In place of such and other amino saccharides which are substituted at the amino group, or of their derivatives, there may also be used amino saccharides the hydroxyl groups of which are acylated or their derivatives. Acylation of the hydroxyl groups may also be effected after condensation with the therapeutically valuable amino compounds.

The following Equation I illustrates the reaction of an amino carbohydrate of aldose character with isonicotinic acid hydrazide or 2-methylisonicotinic acid hydrazide:

(I)





wherein

Y is either or the methyl radical; and wherein

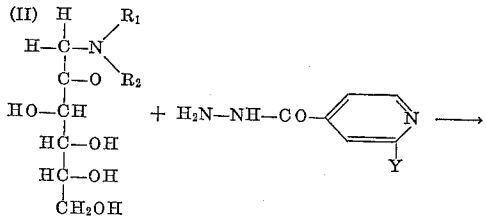
R_1 is either hydrogen, an alkyl, aryl, aralkyl, cycloalkyl radical or an acyl group; and

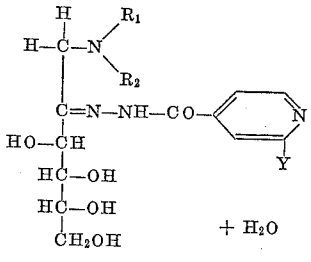
R_2 is either an alkyl, aryl, aralkyl, cycloalkyl radical or an acyl group.

These radicals will be more clearly described hereinafter.

The following Equation II illustrates the reaction of an amino carbohydrate of ketose character with isonicotinic acid hydrazide or 2-methyl isonicotinic acid hydrazide:

(II)

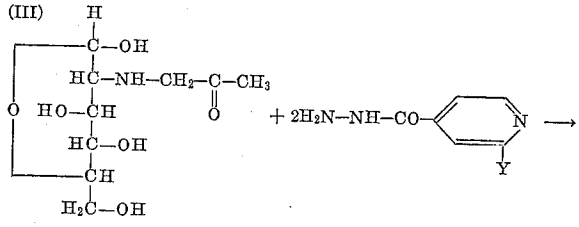


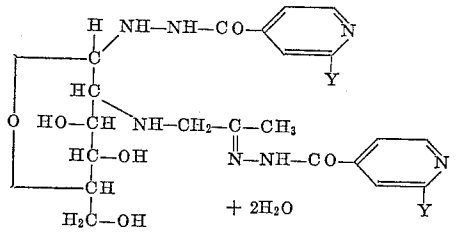


wherien Y, R_1, and R_2 have the same definitions as given above.

The following Equation III illustrates the reaction of 2 mols of isonicotinic acid hydrazide to react with two reactive groups of the amino carbohydrate, such as an amino hexose; in this equation one of the reactive groups is present in the substituted amino group:

(III)





wherein Y has the same definition as above.

As indicated above, R_1 may either be hydrogen, alkyl, aryl, aralkyl, cycloalkyl or acyl, and R_2 may either be alkyl, aryl, aralkyl, cycloalkyl, or acyl. R_1 and R_2 may be the same or different substitutents. The acyl radicals R_1 and/or R_2 may be aliphatic, isocyclic, heterocyclic carboxylic or sulfonic acid radicals and may be saturated, unsaturated, unsubstituted, or substituted.

Among the useful acyl radicals R_1 and R_2 there may be mentioned the following: N-chloro propionyl, N-chloro butyroyl, N-bromo isocapropyl, N-bromo bionoyl, N-hydroxy probionoyl, N-glycyl glucosamine, N-alanyl, N-phenyl alanyl, N-valinoyl, N-malonoyl, N-glutaryl, N-glutaminoyl, N-hydroxy glutaminoyl, N-2,4-dinitro-5-chloro phenyl, N-2,4-dinitro phenyl, N-2,4,6-trinitro phenyl, N-linoloyl, N-malinoyl, N-benzoyl, N-phthaloyl, N-phenyl acrylolyl, N-nicotinoyl, N-isonicotinoyl, or N-2,6-dichloro isonicotinoyl, N-sulfaminyl glucosamine, N-sulfo toluyl glucosamine, or sulfo-p-amino phenyl groups, or the residues of citric acid, other aliphatic hydroxy acids, keto acids, sulfur-containing acids, aromatic carboxylic acids and their substitution products such as aromatic amino acids, hydroxy carboxylic acids, nitro carboxylic acids, aromatic dicarboxylic acids, heterocyclic mono- and di-carboxylic acids, especially the pyrazine carboxylic acids, and aromatic or heterocyclic sulfonic acids.

Furthermore, in the equations given herein above the hydroxyl groups may be esterified or etherified either in one position or in all four positions or in two or three positions. Among suitable ester substitutions there may be mentioned the following acyl groups: acetyl, benzoyl, isonicotinoyl, the residues of sulfonic acids such as p-toluene sulfonic acid, and of phosphoric acids. Among the suitable ether groups there may be mentioned the following: methyl, ethyl, trityl, etc.

The following examples serve to illustrate the present invention without, however, limiting the same thereto.

EXAMPLE 1

44 g. of N-acetyl glucosamine are dissolved while heating in 100 cc. of water and added to a solution of 28 g. of pyridine-(4)-carboxylic acid hydrazide dissolved in 75 cc. of glacial acetic acid and 75 cc. of ethanol. The reaction mixture is allowed to stand at room temperature. The solution, which initially is highly fluid, turns into a thick sirup and, when acetone is admixed with stirring, a solid amorphous product is precipitated. This crude product is dissolved in a small quantity of cold water, triturated with acetone, and finally recrystallized from ethanol. Its melting point is 208° C. with decomposition and the yield is 70% of the theoretical yield. The compound is readily soluble in water, slightly soluble in hot ethanol, and insoluble in acetone.

EXAMPLE 2

44 g. of acetyl glucosamine and 28 g. of pyridine-(4)-carboxylic acid hydrazide are mixed with a mixture of 200 cc. of ethanol, 100 cc. of water, and 20 cc. of glacial acetic acid. The reaction mixture is then heated in a water bath for a short time until a clear solution is obtained. Immediately thereafter about 220 cc. of the solution are distilled off in a vacuum and the remaining oil is poured into a crystallizing dish. The oil is allowed to remain in the dish overnight with only a few crystals being deposited. These are then crushed with a spatula and pulverized whereupon the entire mass solidifies into a solid white mass. The mass is triturated with acetone and then filtered. The yield is about 70 g. of the crude product, which is worked up as described in Example 1.

EXAMPLE 3

Production of Formyl Glucosaminyl Isonicotinic Acid Hydrazide (or 1-Isonicotinoyl-2-(N-Formyl Glucosaminylidene) Hydrazine)

21 g. of N-formyl glucosamine and 14 g. of pyridine-(4)-carboxylic acid hydrazide are heated in a water bath in 200 cc. of ethanol for 4 hours. The solution is then concentrated in a vacuum and the oily residue is triturated with acetone to a solid mass. A yield of crude product amounting to 60% of the theoretical yield is obtained and, on recrystallization from aqueous acetone, the compound is purified to a melting point of 118° C. with decomposition. The compound crystallizes with 1 mole of water.

EXAMPLE 4

3.5 g. of butyric acid glucosamide and 1.4 g. of isonicotinic acid hydrazide are heated in 3 cc. of water and 0.3 cc. of glacial acetic acid on a water bath for 5 minutes. The reaction product is then precipitated with acetone and is purified by dissolving it in water and again precipitating it with acetone. The compound, 1-isonicotinoyl-2-(N-butyroyl glucosaminylidene) hydrazine, has a melting point of 194° C. with decomposition. It may also be designated as butyric acid glucosaminyl isonicotinic acid hydrazide.

EXAMPLE 5

9.4 g. of stearic acid glucosamide and 3 g. of isonicotinic acid hydrazide in 300 cc. of methanol and 4 cc. of glacial acetic acid are heated in a water bath for 27 hours. The reaction solution is then filtered from undissolved residue and concentrated in a vacuum. An oil separates which crystallizes upon cooling. The crude product is purified by recrystallization from ethanol. The resulting compound is 1-isonicotinoyl-2-(N-stearoyl glucosaminylidene) hydrazine which has a melting point of 180° C. with decomposition. It may also be designated as stearic acid glucosaminyl isonicotinic acid hydrazide.

EXAMPLE 6

4.5 g. of α-bromo capric acid glucosamide and 1.5 g. of isonicotinic acid hydrazide in 150 cc. of methanol and 2 cc. of glacial acetic acid are heated in a water bath for 32 hours. The reaction solution is then concentrated in a vacuum. The residual brown oil is triturated with acetone and the crude product is recrystallized from ethanol. The resulting compound is 1-isonicotinoyl-2-(N-α-bromo caprinoyl glucosaminylidene) hydrazine having a melting point of 175° C. with decomposition and crystallizing with one-half mole of water. The compound may also be designated as α-bromo capric acid glucosaminyl isonicotinic acid hydrazide.

EXAMPLE 7

2.6 g. of chloro acetyl glucosamine and 1.4 g. of isonicotinic acid hydrazide are covered with 20 cc. of ethanol, 5 cc. of water, and 1 cc. of glacial acetic acid. On heating on a water bath a clear solution is obtained which is concentrated in a vacuum. The remaining dark yellow oil is triturated with acetone thereby yielding a solid mass. The reaction product is 1-isonicotinoyl-2-(N-chloro acetyl glucosaminylidene) hydrazine. The compound may also be designated as chloro acetyl isonicotinic acid hydrazone.

Analysis.—Calculated: C=40.9%; H=5.6%; N=13.6%. Found: C=41.3%; H=5.8%; N=13.4%.

The compound crystallizes with 2 moles of water.

EXAMPLE 8

10.0 g. of N-carbethoxy glucosamine and 5.6 g. of pyridine-(4)-carboxylic acid hydrazide are heated in a water bath with 40 cc. of methanol for 2 hours. The solution is then concentrated in a vacuum. Upon standing overnight, crystals separate from the oily residue and, on trituration with acetone a substantially pure reaction product is obtained in an 80% yield. On recrystallization from ethanol the compound has a melting point of 182° C. with decomposition. The compound is 1-isonicotinoyl-2-(N-carbethoxy glucosaminylidene) hydrazine. The compound crystallizes with 1½ moles of water. It may also be designated as carbethoxy glucosaminyl isonicotinic acid hydrazide.

EXAMPLE 9

7.8 g. of succinic glucosamido acid (produced by reacting glucosamine with succinic acid anhydride in aqueous dioxane) and 4.2 g. of isonicotinic acid hydrazide are heated in a water bath with 50 cc. of ethanol, 10 cc. of water, and 4 cc. of glacial acetic acid for 20 minutes. The solution is then concentrated by evaporation and the remaining oily reaction product is triturated with acetone to yield a solid amorphous mass. A crystalline reaction product is obtained from warm ethanol in 45% yield. It crystallizes with 1 mole of water. The melting point is 170–172° C. with decomposition. The product is 1-isonicotinoyl-2-(N-succinoyl glucosaminylidene) hydrazine. The product may also be designated as succinic acid glucosaminyl isonicotinoyl hydrazide. On recrystallization of the amorphous reaction product from aqueous acetone, there are obtained in somewhat better yield crystals having a melting point of 130° C. with decomposition, these crystals containing 1½ moles of water.

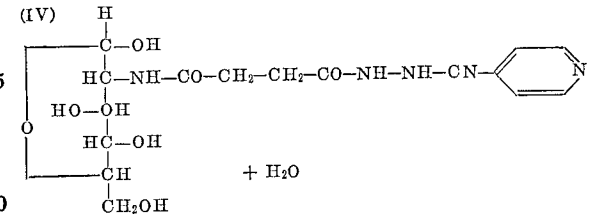
EXAMPLE 10

2.3 g. of phenyl acetic acid glucosamide and 1.1 g. of isonicotinic acid hydrazide are heated under reflux in 40 cc. of ethanol, 8 cc. of water, and 2 cc. of glacial acetic acid for 1 hour. The reaction solution is concentrated in a vacuum and the resulting oil is solidified by standing in a crystallization dish. By recrystallization from ethanol the product is purified and is found to have a melting point of 215° C. with decomposition. The compound is 1-isonicotinoyl-2-(N-phenylacetyl glucosaminylidene hydrazine. The product may also be designated as phenyl acetic acid glucosaminyl isonicotinic acid hydrazone.

EXAMPLE 11

Preparation of a condensation product with the isonicotinic acid hydrazide of an amino carbohydrate of the following structural formula:

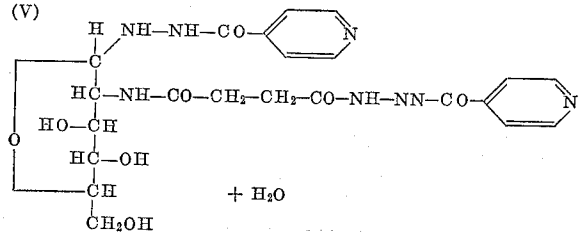
(IV)



1.5 g. of the above set forth amino carbohydrate is heated in a water bath with 1 g. of isonicotinic acid hydrazide (twice the required theoretical amount) in 100 cc. of ethanol, 2 cc. of glacial acetic acid, and 40 cc. of water for

5 hours. The solution is then concentrated in a vacuum and an amorphous compound is precipitated by the addition of acetone. The compound is purified by dissolution in cold water and precipitation with acetone. Analysis shows that the resulting condensation product corresponds to the following formula:

(V)



EXAMPLE 12

4.4 g. of oleic acid glucosamide and 1.4 g. of isonicotinic acid hydrazide are heated in a water bath with 150 cc. of methanol and 2 cc. of glacial acetic acid for 27 hours. The reaction solution is then concentrated in a vacuum and the oily residue is triturated with acetone to a white crude product which is recrystallized from ethanol. Its melting point is 188° C. with decomposition. The resulting 1-isonicotinoyl-2-(N-oleyl glucosaminylidene) hydrazine crystallizes with ½ mole of water. The product may also be designated as oleic acid glucosaminyl isonicotinic acid hydrazone.

EXAMPLE 13

3.5 g. of undecylenic acid glucosamide are dissolved in 100 cc. of water. 1.4 g. of isonicotinic acid hydrazide are added and, after the addition of 2 cc. of glacial acetic acid, the reaction mixture is heated on a water bath for 9 hours. The solution is then concentrated in a vacuum and the oily residue is treated with acetone to yield a crystalline solid product. The crude product is purified by recrystallization from ethanol. The compound has an unsharp melting point at 180–185° C. with decomposition. The resulting 1-isonicotinoyl-2-(N-undecylenic acid glucosaminylidene) hydrazine contains ½ mole of water. The compound may also be designated as undecylenic acid glucosaminyl isonicotinic acid hydrazide.

EXAMPLE 14

14.1 g. of N-benzoyl glucosamine and 6.3 g. of pyridine-(4)-carboxylic acid hydrazide is covered with a mixture of 100 cc. of water and 5 cc. of glacial acetic acid. The resulting reaction mixture is heated in a water bath for 5 hours. The solution is then concentrated by evaporation in a vacuum. The remaining oil is triturated with acetone yielding a solid crude reaction product in 90% yield. On recrystallization from ethanol isonicotinoyl-2-(N-benzoyl glucosaminylidene) hydrazine, crystallizing with 1 mole of water, of the melting point 209–210° C. with decomposition is obtained. The compound may also be designated as benzoic acid glucosaminyl isonicotinic acid hydrazide.

EXAMPLE 15

1 g. of phthalic glucosamido acid and 0.5 g. of isonicotinic acid hydrazide in 10 cc. of ethanol, 2.5 cc. of water and 1 cc. of glacial acetic acid are heated in a water bath for half an hour. The reaction solution is then concentrated in a vacuum. By triturating the oily residue with acetone a crude product is obtained which, upon dissolution in water and concentration over phosphorus pentoxide, is isolated in crystalline form. The resulting crystals are recrystallized from a small amount of ethanol. The pure compound has a melting point of 141° C. with decomposition. 1-isonicotinoyl-2-(N-phthaloyl glucosaminylidene) hydrazine crystallizes with 1 mole of water. The compound may also be designated as phthalic glucosamido acid isonicotinic acid hydrazide.

EXAMPLE 16

3.6 g. of β-phenyl acrylic acid glucosamide and 1.7 g. of isonicotinic acid hydrazide in 50 cc. of alcohol, 12 cc. of water, and 2.5 cc. of glacial acetic acid are heated in a water bath for 6 hours. The reaction solution is then concentrated in a vacuum. By triturating the remaining oil with acetone, a crude product is obtained which, on recrystallization from ethanol, is found to have a melting point of 200° C. with decomposition. The compound is 1-isonicotinoyl-2-(N-β-phenyl acrylic glucosaminylidene) hydrazine. The compound may also be designated as β-phenyl acrylic acid glucosamino isonicotinic acid hydrazone.

EXAMPLE 17

1.9 g. of tetra-acetyl glucosamine-1-isothiocyanate and 0.7 g. of isonicotinic acid hydrazide in 50 cc. of acetonitrile are heated in a water bath for 2½ hours. The reaction solution is concentrated in a vacuum. The resulting yellow glass-like reaction product can be purified by dissolution in acetic acid and precipitation with ligroin. 1-isonicotinoyl-4-tetraacetyl-glucosamino thiosemicarbazide is obtained thereby.

EXAMPLE 18

2.8 g. of isonicotinic acid hydrazide (2 moles) are dissolved in 150 cc. of warm acetonitrile. 4.1 g. of tetra-acetyl bromo glucosamine (1 mole) in solid form is added thereto. The reaction solution is then heated on a water bath for 2 hours. After cooling, the residue, which consists of isonicotinic acid hydrazide hydrobromide, is filtered off and the filtrate is treated with decolorizing carbon and is concentrated in a vacuum. The resulting oil is triturated with ether and yields N-acetyl-3,4,6-triacetyl glucosaminyl isonicotinic acid hydrazide.

EXAMPLE 19

This example illustrates the production of a condensation product of isonicotinic acid hydrazide and a reaction product of glucosamine hydrochloride and ammonium thiocyanate.

The reaction product of glucosamine hydrochloride and ammonium thiocyanate is prepared as follows:

10 g. of glucosamine hydrochloride and 4.5 g. of ammonium thiocyanate are separately dissolved in water. The hot solutions are then poured together and the reaction mixture is heated in a water bath for 2 hours. The reaction solution is then concentrated in a vacuum and the remaining viscous oil is boiled with methanol. On concentrating the methanol solution, the desired reaction product is obtained.

2.2 g. thereof and 1.4 g. of isonicotinic acid hydrazide in 100 cc. of ethanol, 10 cc. of water, and 4 cc. of glacial acetic acid are heated in a water bath for 6 hours. The reaction solution is then filtered from undissolved residue. Crystals separate from the filtrate and on recrystallization from ethanol relatively pure crystals of the melting point 190° C. with decomposition are obtained. The general formula of said compound is $C_{12}H_{18}O_5N_4S_1$.

Analysis.—Found: C=43.41%; H=5.48%; N=18.05%; S=9.54%.

EXAMPLE 20

2.9 g. of heptanoic acid glucosamide and 1.4 g. of isonicotinic acid hydrazide are heated in a water bath in 5 cc. of water, 10 cc. of ethanol, and 1 cc. of glacial acetic acid. After 10 minutes the solution is concentrated in a vacuum and the reaction product is precipitated with acetone. The crude product can be purified by precipitation from its ethanol solution. It has a melting point of 204° C. with decomposition. The resulting condensation product is the 1-isonicotinoyl-2-(N-heptoyl glucosaminylidene) hydrazine. The compound may also be designated as heptanoic acid glucosaminyl isonicotinic acid hydrazone.

EXAMPLE 21

8.8 g. of N-acetyl isoglucosamine and 5.6 g. of isonicotinic acid hydrazide are dissolved in 16 cc. of water and 40 cc. of ethanol with the addition of 4 cc. of glacial acetic acid as catalyst. The reaction solution is heated in a water bath at a temperature of 80° C. for 45 minutes. Thereafter, the reaction solution is concentrated in a vacuum and the remaining sirup is treated with absolute ethanol. 1-isonicotinoyl-2-(N-acetyl isoglucosaminylidene) hydrazine crystallizes. The calculated amount of isonicotinic acid hydrazide in said compound is 40.4% and the amount found upon analysis is 39.9%. Determination was made by titration according to Haugers and Mitchell, "J. Pharm. Pharmacol.," vol. 4 (1952), page 687.

EXAMPLE 22

18 g. of N-p-tolyl isoglucosamine and 9.2 g. of isonicotinic acid hydrazide are dissolved in 30 cc. of water and 80 cc. of ethanol with the addition of 7 cc. of glacial acetic acid. The reaction solution is heated on a water bath at 80° C. for 1 hour. After concentration in a vacuum the residue is treated with cold acetone. This results in the crystallization of 1-isonicotinoyl-2-(N-p-tolyl isoglucosaminylidene) hydrazine. The calculated amount of isonicotinic acid hydrazide in said compound is 35.3%, the amount found on analysis is 35.0%.

EXAMPLE 23

11 g. of N-acetyl sorbosylamine and 7 g. of isonicotinic acid hydrazide are dissolved in 20 cc. of water and 50 cc. of ethanol with the addition of 5 cc. of glacial acetic acid. The reaction solution is heated on a water bath at 80° C. for 1 hour. After concentration in a vacuum, the residue is triturated with absolute ethanol. Thereby 1-isonicotinoyl-2-(N-acetyl sorbosylaminylidene) hydrazine is obtained in crystalline form. The calculated amount of isonicotinic acid hydrazide in said compound is 40.4%, the amount found on analysis is 40.8%.

EXAMPLE 24

1.5 g. of N-acetyl lactosamine and 0.55 g. of isonicotinic acid hydrazide are dissolved in 5 cc. of water and 15 cc. of ethanol with the addition of 1 cc. of glacial acetic acid. The reaction solution is heated on a water bath at a temperature of 80° C. for 90 minutes. After careful concentration in a vacuum, the remaining sirup is triturated with acetone. The resulting precipitated reaction product consists of crystals of 1-isonicotinoyl-2-(N-acetyl lactosaminylidene) hydrazine. The calculated amount of isonicotinic acid hydrazide in said compound is 35.77%, the amount found on analysis is 34.8%.

EXAMPLE 25

1.2 g. of acetyl salicylic acid glucosamide and 0.5 g. of isonicotinic acid hydrazide are heated on a water bath with 20 cc. of ethanol, 4 cc. of water, and 1 cc. of glacial acetic acid for ½ hour. The reaction solution is then concentrated in a vacuum. The resulting oil is triturated with acetone to yield a solid mass. On dissolution of the crude product in water and precipitation with acetone, a crystalline product of the melting point 207° C. with decomposition is obtained. The reaction product is the condensation product of acetyl salicylic acid glucosamide with isonicotinic acid hydrazide.

EXAMPLE 26

5.6 g. of maleic glucosamido acid and 2.8 g. of isonicotinic acid hydrazide with 40 cc. of ethanol, 10 cc. of water, and 2 cc. of glacial acetic acid are heated on a water bath for half an hour. The reaction solution is concentrated in a vacuum and the resulting oil is triturated with acetone to yield a solid mass. This crude product is recrystallized. The crystalline 1-isonicotinoyl-2-(N-maleinoyl glucosaminylidene) hydrazine has noteworthy tuberculostatic activity.

EXAMPLE 27

Solutions of 23.5 g. (0.1 mole) of N-(2-desoxyglucose) amino acetone in 120 cc. of water and 27.5 g. (0.2 mole) of isonicotinic acid hydrazide in 200 cc. of ethanol are combined. 12.0 cc. of glacial acetic acid as catalyst are added and the reaction mixture is heated at 80° C. for 60 minutes. After standing overnight, the solution is evaporated to dryness in a vacuum and the residue is covered with water. Unreacted starting material goes into solution while the condensation product remains substantially undissolved as it is difficultly soluble in water. The reaction product is precipitated from aqueous ethanol and the resulting 1-isonicotinoyl-2-[(α-glucosaminyl isonicotinic acid hydrazide) acetonyl]-hydrazone has a melting point of 207–208° C.

EXAMPLE 28

Precipitation of N-Acetyl-d-Glucosaminyl-2-Methyl Isonicotinic Acid Hydrazide

50 g. of N-acetyl glucosamine and 34.3 g. of 2-methyl isonicotinic acid hydrazide are dissolved in a mixture of 100 cc. of water and 20 cc. of glacial acetic acid. The solution is heated on the water bath for one hour. After concentration in a vacuum, the resulting sirup is triturated with acetone. The resulting crystals consist of N-acetyl-d-glucosaminyl-2-methyl isonicotinic acid hydrazide.

Cleavage and subsequent titration of the hydrazine with potassium iodate proves that said compound is obtained. Calculated amount of 2-methyl isonicotinic acid hydrazide: 42.28%. Found: 41.80%.

In a similar manner there are obtained condensation products of amino substituted sulfonamides with amino carbohydrate compounds as will be described in the following examples which also only serve to illustrate the invention without, however, limiting the same thereto.

EXAMPLE 29

The solution of 10 g. of N-acetyl galactosamine in 40 cc. of water and 14 g. of N_1-sulfanilyl-N_2-n-butyl urea in 150 cc. of ethanol are combined. 0.5 cc. of concentrated hydrochloric acid are added as catalyst and the clear solution is kept at 40° C. overnight. The precipitated crystals are filtered off by suction, washed with a mixture of ethanol and ether (2:3), and dried at 70° C. The resulting N-acetyl gelactosaminyl-N_1-sulfanilyl-N_2-n-butyl urea is recrystallized from a mixture of alcohol and water.

EXAMPLE 30

12 g. of 6-(sulfanilamido)-2,4-dimethyl pyrimidine and 12 g. of N-acetyl galactosamine are heated in 40 cc. of water and 2 cc. of concentrated hydrochloric acid until completely dissolved. 160 cc. of ethanol are added and the mixture is allowed to stand for 12 hours. The reaction mixture is then neutralized with the calculated amount of sodium hydroxide solution. The neutralized solution is evaporated to dryness in a vacuum and extracted with absolute ethanol to remove sodium chloride. The ethanol solution is distilled in a vacuum. The resulting residue is recrystallized from a mixture of ethanol and ether. Its solubility in water is considerably improved and its toxicity is reduced when compared with the starting sulfonamide, while its therapeutic activity is about the same.

EXAMPLE 31

12 g. of 2-(sulfanilamido)-4,6-dimethyl pyrimidine and 12 g. of N-acetyl xylosamine are dissolved in a mixture of 150 cc. of ethanol and 50 cc. of water with the addition of 1 cc. of concentrated hydrochloric acid as catalyst. The reaction mixture is allowed to stand at room temperature for 8 hours and is then concentrated by evaporation in a vacuum. Dilute sodium hydroxide solution in an amount sufficient to render the mixture neutral is added and the neutralized mixture is evaporated to dryness in a vacuum. The residue is extracted with absolute ethanol. The

ethanol extract is evaporated and yields N-acetyl xylosaminyl-2-(sulfanilamido)-4,6-dimethyl pyrimidine. The compound is readily soluble in water in contrast to the starting sulfanilamide.

EXAMPLE 32

2.2 g. of N-acetyl glucosamine and 1.7 g. of sulfanilamide are heated on the water bath in 130 cc. of methanol. As soon as a clear solution has formed, 0.12 cc. of concentrated hydrochloric acid are added. The resulting solution is heated under reflux for 5 hours and concentrated by evaporation in a vacuum. The residue is triturated with ethanol to a solid mass of N-acetyl glucosaminyl sulfanilamide. The crude compound is soluble in hot ethanol and crystallizes on cooling. In contrast to sulfanilamide the condensation product is readily soluble in water.

EXAMPLE 33

10 g. of 2-sulfanilamido pyridine and 8.8 g. of N-acetyl glucosamine are dissolved in a mixture of 50 cc. of water, 200 cc. of ethanol, 50 cc. of dioxane, and 3 cc. of glacial acetic acid as catalyst by heating on the water bath. The reaction mixture is allowed to stand at room temperature for 12 hours, is neutralized by the addition of the calculated amount of sodium bicarbonate, and is evaporated to dryness in a vacuum. The residue is extracted with absolute ethanol and the ethanol is evaporated from the extract. The resulting condensation product of 2-sulfanilamido pyridine and N-acetyl glucosamine is extremely readily soluble in methanol in contrast to 2-sulfanilamido pyridine.

EXAMPLE 34

7 g. of N-acetyl glucosamine and 6 g. of sulfaguanidine are heated at 80° C. in a mixture of 20 cc. of water, 200 cc. of ethanol, and 2 cc. of concentrated hydrochloric acid as catalyst for one hour. After allowing the reaction mixture to stand at room temperature for 12 hours, it is neutralized by the addition of the calculated amount of sodium hydroxide solution and evaporated to dryness in a vacuum. Sodium chloride is removed by extracting the residue with absolute ethanol. The condensation product is obtained on distilling off in a vacuum the ethanol from the ethanol extract. In contrast to the starting sulfanilamide it is very readily soluble in methanol.

EXAMPLE 35

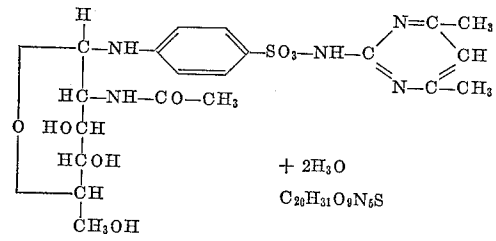
8 g. of 2-sulfanilamido thiazole and 6.9 g. of N-acetyl glucosamine are heated under reflux in a water bath in a mixture of 50 cc. of water, 200 cc. of dioxane, and 20 cc. of glacial acetic acid for 3 hours. The reaction mixture is then evaporated to dryness in a vacuum. The residue is extracted with absolute ethanol and the extract is evaporated to dryness yielding the condensation product as residue which is readily soluble in methanol in contrast to the starting materials.

EXAMPLE 36

5 g. of 5-sulfanilamido-2-ethyl-1,3,4-thiodiazole and 3.9 g. of N-acetyl glucosamine are heated under reflux in a water bath in a mixture of 10 cc. of water and 400 cc. of ethanol for 3 hours. The reaction mixture is evaporated to dryness in a vacuum. The residue is extracted with absolute ethanol. The condensation product is recovered from the ethanol extract by evaporating the ethanol. In contrast to the starting materials it is readily soluble in methanol.

EXAMPLE 37

14 g. (0.05 mole) of sulfanilamido-4,6-dimethyl pyrimidine are heated under reflux with 12.5 g. (0.055 mole) of acetyl glucosamine in a mixture of 150 cc. of methanol and 25 cc. of glacial acetic acid for 6 hours. Solution is achieved after 3 hours. The solvents are then evaporated in a vacuum. The sirupy residue is dissolved in 200 cc. of warm ethanol, filtered over decolorizing carbon, and again evaporated to dryness in a vacuum. On heating the sirupy residue on the boiling water bath for a short period of time, it is converted into powder form. Its solution in warm ethanol is precipitated by the addition of petroleum ether after cooling. The resulting condensation product decomposes on heating to 160° C. 21 g. to 24 g. are obtained corresponding to a yield of 81% to 93%. The analytical values correspond to those of a compound of the following formula



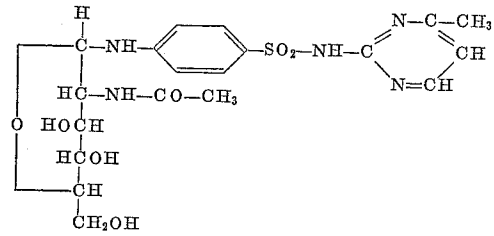
Molecular weight: 517.57.

EXAMPLE 38

The procedure is the same as described in Example 37, but the equimolecular amount of sulfanilamido-6-methyl pyrimidine is used as the one reaction component in place of sulfanilamido 4,6-dimethyl pyrimidine. The resulting condensation product has a melting point of 160° C. with decomposition. Yield: 79.5% to 87.5%.

Analysis.—$C_{19}H_{29}O_9N_5S$: Molecular weight, 503.55. Calculated: C=45.32%; H=5.80%; N=13.91%; S=6.39%. Found: C=45.48%; C=45.58%; H=5.99%; H=6.13%; N=13.76%; S=6.57%.

The compound corresponds to the following formula:



EXAMPLE 39

14.2 g. of 3-(p-amino phenyl sulfonamido)-2-phenyl pyrazole and 10 g. of N-acetyl glucosamine are dissolved in a mixture of 250 cc. of methanol, 50 cc. of water, and 30 cc. of glacial acetic acid and treated under reflux in the water bath for 8 hours. The reaction mixture is evaporated to dryness in a vacuum. The resulting residue is extracted with cold acetone. The acetone solution is precipitated by the addition of ether and yields N-acetyl-D-glucosaminyl-3-(p-amino phenyl sulfonamido)-2-phenly pyrazole. Its sugar content is 43.0% (calculated: 42.9%).

EXAMPLE 40

2.8 g. of 5-sulfanilamido-2-ethyl-1,3,4-thiodiazole and 2.5 g. of butyric acid glucosamide are heated on the water bath in 100 cc. of methanol and 10 cc. of glacial acetic acid for 6 hours. The resulting solution is concentrated in a vacuum and the crude condensation product is recrystallized from ethanol. Melting point: 132° C. with decomposition.

EXAMPLE 41

1.4 g. of benzoyl glucosamine and 0.85 g. of sulfanilamide are heated on the water bath in 100 cc. of methanol with the addition of 4 drops of concentrated hydrochloric acid for 3 hours. The reaction solution is concentrated by evaporation in a vacuum and the oily residue is triturated with ethanol to yield a solid mass. The resulting crude product is dissolved in dimethylformamide. On diluting with water, the condensation product is obtained

in crystalline form. Melting point: 231° C. with decomposition.

EXAMPLE 42

2.1 g. of formyl glucosamine and 1.7 g. of sulfanilamide are heated on the water bath in 1.5 cc. of water and 0.3 cc. of glacial acetic acid. As soon as a clear solution has formed, heating is continued for 10 more minutes. The reaction solution is then cooled. Acetone is added until the solution becomes turbid. On scratching with a glass rod, the condensation product precipitates. It can be recrystallized from water. Melting point: 239° C. with decomposition.

The same compound is obtained on heating on the water bath 2.1 g. of formyl glucosamine and 1.7 g. of sulfanilamide in 100 cc. of methanol and 10 cc. of glacial acetic acid for 6 hours and working up the reaction mixture as described above.

EXAMPLE 43

3.25 g. of phthaloyl glucosamine and 1.7 g. of sulfanilamide are heated on the water bath in 4 cc. of water and 0.5 cc. of glacial acetic acid for one hour. The resulting crystalline paste is triturated with water, filtered, and recrystallized from aqueous dimethyl formamide. Crystals which melt above 300° C. are obtained thereby. Sulfur determination showed a sulfur content of 6.72% (calculated: 6.66%).

EXAMPLE 44

2.5 g. of carbethoxy glucosamine and 1.7 g. of sulfanilamide are heated on the water bath in 100 cc. of methanol and 10 cc. of glacial acetic acid for 7 hours. The resulting reaction solution is concentrated by evaporation and the oily residue is triturated with ethanol to yield a solid mass which can be recrystallized from water. Melting point: 203° C. with decomposition.

EXAMPLE 45

2.1 g. of formyl glucosamine and 2.1 g. of sulfa-urea are heated on the water bath in 100 cc. of methanol and 5 cc. of formic acid for 5 hours. The resulting reaction solution is concentrated by evaporation in a vacuum. Crystals precipitate from the oily evaporation residue on standing overnight. A solid condensation product is isolated on trituration with ethanol. It can be recrystallized from dilute ethanol. Melting point: 179° C. with decomposition.

EXAMPLE 46

10 g. of 2-(sulfanilamido)-4,6-dimethyl pyrimidine and 10.05 g. of succinoyl glucosamine are dissolved in a mixture of 400 cc. of ethanol, 70 cc. of water, and 70 cc. of glacial acetic acid and the mixture is treated under reflux in a water bath. The reaction solution is then carefully evaporated to dryness in a vacuum. The evaporation residue is extracted with cold absolute ethanol, filtered, and N-succinoyl glucosaminyl-2-(sulfanilamido)-4,6-dimethyl pyrimidine is precipitated from the ethanol filtrate by the addition of ether. The condensation product can be purified by again dissolving it in ethanol and precipitating the solution with ether. The compound is readily soluble in water in contrast to the starting sulfanilamide.

EXAMPLE 47

10 g. of 2-(sulfanilamido)-4,6-dimethyl pyrimidine and 8.95 g. of butyroyl glucosamine are dissolved in 400 cc. of ethanol, 40 cc. of water, and 40 cc. of glacial acetic acid while heating. The solution is boiled under reflux in a water bath for 8 hours and is then evaporated to dryness in a vacuum. The residue is dissolved in a small quantity of cold methanol, filtered, and N-butyroyl glucosaminyl-2-(sulfanilamido)-4,6-dimethyl pyrimidine is precipitated by the addition of ether. The compound is purified by again dissolving it in methanol and precipitating it with ether. It is very readily soluble in water in contrast to the starting sulfanilamide.

EXAMPLE 48

10 g. of sulfamethoxypyridazine and 7.9 g. of N-acetyl glucosamine are dissolved in a mixture of 170 cc. of ethanol, 20 cc. of water, and 30 cc. of glacial acetic acid, while heating. The solution is heated under reflux in a water bath for 8 hours and then evaporated to dryness in a vacuum. The crude N-acetyl glucosaminyl sulfamethoxypyridazine is recrystallized from a mixture of ethanol and ether. The compound is very readily soluble in water in contrast to the starting sulfanilamide.

EXAMPLE 49

10 g. of sulfamethoxypyridazine and 10 g. of succinoyl glucosamine are dissolved in 170 cc. of ethanol, 20 cc. of water, and 30 cc. of glacial acetic acid. The solution is heated under reflux in a water bath for 8 hours and is evaporated to dryness in a vacuum. The residue is dissolved in a small quantity of ethanol and filtered. Succinoyl glucosaminyl sulfamethoxypyrazine is precipitated from the filtrate by the addition of ether. It is soluble in water in contrast to the starting sulfanilamide.

EXAMPLE 50

25 g. of 3-(p-amino phenyl sulfonamido)-2-phenyl pyrazole and 22.3 g. of succinoyl glucosamine are dissolved in 400 cc. of ethanol, 50 cc. of water, and 75 cc. of glacial acetic acid. The solution is heated under reflux in a water bath for 8 hours and is then carefully evaporated to dryness in a vacuum. The residue is treated with a small quantity of cold dioxane and filtered. Succinoyl glucosaminyl-3-(p-amino phenyl sulfonamido)-2-phenyl pyrazole is precipitated from the filtrate by the addition of ether. The compound can be purified by dissolving it in ethanol and precipitating it with ether. Its content of succinoyl glucosamine is 45.0% (calculated: 45.6%).

EXAMPLE 51

10 g. of sulfaquinoxaline and 7.7 g. of N-acetyl glucosamine are dissolved in 400 cc. of ethanol and 360 cc. of glacial acetic acid. The solution is heated under reflux in a water bath for 8 hours and is then carefully evaporated to dryness in a vacuum. The residue is treated with a small quantity of absolute ethanol. The insoluble residue is filtered off and N-acetyl glucosaminyl sulfaquinoxaline is precipitated from the filtrate by the addition of ether. The compound is purified by again dissolving it in ethanol and precipitating it with ether. It is readily soluble in ethanol in contrast to the starting sulfanilamide.

EXAMPLE 52

10 g. of sulfaquinoxaline and 9 g. of succinoyl glucosamine are dissolved in 470 cc. of a mixture of ethanol and dioxane (1:1), 20 cc. of water, and 40 cc. of glacial acetic acid. The solution is heated under reflux in a water bath for 8 hours and is carefully evaporated to dryness in a vacuum. The residue is treated with a small quantity of cold dioxane and is filtered. Succinoyl glucosaminyl sulfaquinoxaline is precipitated from the filtrate by the addition of ether. The compound is purified by dissolving it in ethanol and precipitating it with ether. It is readily soluble in ethanol in contrast to the starting sulfanilamide.

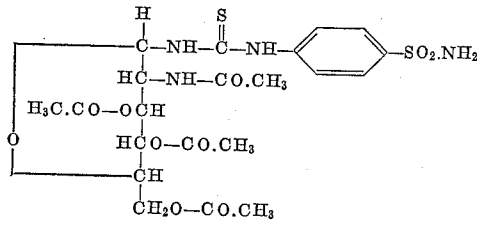
EXAMPLE 53

1.95 g. of 2,3,4,6-tetraacetyl glucosaminyl-1-isothiocyanate and 0.85 g. of sulfanilamide are heated on the water bath in 25 cc. of acetone for 3 hours. The reaction solution is then evaporated to dryness in a vacuum at room temperature whereby an oily residue remains which

solidifies rapidly. It is dissolved in acetone and the filtered solution is evaporated to dryness in a vacuum at room temperature. Thereby N-(2,3,4,6-tetraacetyl glucosaminyl)-N¹-(p-sulfonamido phenyl) thiourea is isolated in the form of a solid glassy mass. The condensation product which is insoluble in water and ether, but is readily soluble in most organic solvents, cannot be isolated in crystalline form.

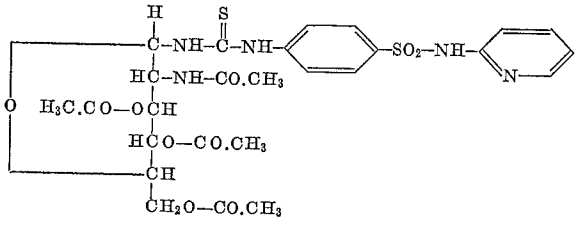
Analysis.—Calculated: C=44.99%; H=5.03%; N=10.00%; S=11.44%. Found: C=44.24%; H=5.21%; N=9.97%; S=10.64%.

The compound corresponds to the following formula:



EXAMPLE 54

1.95 g. of 2,3,4,6-tetraacetyl glucosaminyl-1-isothiocyanate and 25 g. of sulfapyridine are heated on the water bath in 25 cc. of acetonitrile for 2 hours. The resulting reaction solution is concentrated by evaporation and the remaining oil is triturated with ether to yield a solid mass. The crude product is dissolved in acetone. The filtered solution yields a solid glassy mass on slow evaporation at room temperature which cannot be converted into a crystalline product. The compound corresponds to the following formula:



EXAMPLE 55

8 g. of amino antipyrine (4-amino-1,5-dimethyl-2-phenyl-3-pyrazolone) and 8.8 g. of N-acetyl glucosamine are heated to 70° C. in 50 cc. of water and 10 cc. of glacial acetic acid for a short period of time. The mixture is allowed to stand at room temperature overnight. The reaction mixture is then neutralized with sodium bicarbonate and evaporated to dryness in a vacuum. The residue is treated with cold absolute ethanol and filtered. The alcoholic filtrate is evaporated to dryness. Unreacted amino antipyrine is removed by treating the residue with benzene whereby the amino antipyrine is dissolved. The residue is the N-acetyl glucosaminyl amino antipyrene, a very hygroscopic compound. Its N-acetyl glucosamine content is 52.86% (calculated: 52.8%).

This condensation product has a substantially reduced toxicity and an excellent therapeutical activity.

When administering intraperitoneally to rats 80 mg. of amino antipyrine per 100 g. of body weight, the animals started to struggle, then lay down, took up a lateral position, and convulsions were observed 3 to 5 minutes after injection. Death occurred after 30 minutes as a result of severe toxic effects of said compound.

On administration of an equivalent amount of N-acetyl glucosaminyl amino antipyrine, the animals did not exhibit any changes and toxic effects. Even administration of 120 mg. per 100 g. of body weight causes only a certain fatigue while the manner of walking is still normal.

The antipyretic effect of the amino antipyrin and the new condensation product was compared in rabbits:

Three groups each comprising 4 rabbits were first treated, each animal, with 0.2 cc. of the fever producing bacterial protein sold under the trademark "Pyrifer No. 4 (IV)" by ASTA-Werke A.G. of Brackwede, Germany. One hour thereafter, the first group of animals received 125 mg. of amino antipyrine per kg. of body weight, the second group 125 mg. of amino antipyrin in the form of the N-acetyl glucosaminyl amino antipyrine compound whereas the third group did not receive an antipyretic agent. "Pyrifer" was administered intravenously and the antipyretic agents subcutaneously in a 2.5% or, respectively, 5% solution(calculated for amino antipyrine). The temperature of the animals was taken hourly. The antipyretic effect of the two compounds was substantially the same within the experimental errors.

The above described condensation products of amino carbohydrates and sulfonamides are remarkably less toxic than it was to be expected from their content of sulfonamide without, however, showing any decrease in thereapeutical activity in vivo.

For instance, sulfamethylpyrimidine has an LD_{50} of about 1 g./kg. mouse on intravenous administration while the corresponding condensation product with N-acetyl glucosamine has an LD_{50} of 5 g./kg. mouse on intravenous administration. It is evident that considerable detoxification has been achieved by producing the condensation product according to the present invention inasmuch as the N-acetyl glucosaminyl-2-sulfanilamido-6-methyl pyrimidine contains about 56% of the sulfanilamide and, thus, should have an expected LD_{50} of about 2 g./kg. The other condensation products of amino carbohydrates with sulfonamides, as they are described hereinabove, are also considerably less toxic than the sulfonamides themselves.

Another important advantage of the new condensation products over the starting sulfonamides is their substantially greater solubility in water. It is, therefore, possible to prepare injectable aqueous solutions of a physiological pH-value. In contrast thereto, the starting sulfonamides can be dissolved only in the form of their sodium compounds. However, injectable solutions of such sodium compounds have a strongly alkaline pH-value and, therefore, are not well tolerated on injection. While, for instance, 6-sulfanilamido-2,4-dimethyl pyrimidine, 2-sulfanilamido-4,6-dimethyl pyrimidine, sulfanilamide, 2-sulfanilamido pyridine, sulfaguanidine, and sulfanilamido thiazole are water insoluble or difficultly water soluble, the condensation products of such sulfonamides with amino carbohydrates have a considerably improved water solubility.

That the new condensation products of amino carbohydrates and sulfonamides have an excellent therapeutic activity, will become clearly evident from the following pharmacological tests with rats infected by Streptococcus Aronson. As representative of the condensation products according to the present invention there was employed in these tests the N-acetyl glucosaminyl-2-sulfanilamido-4,6-dimethyl pyrimidine.

Three groups, each group of 12 rats of about 120 g. body weight, were intraperitoneally infected, each animal with 3 cc. of a 24 hours culture of Streptococcus Aronson in standard nutrient bouillon. 45 minutes thereafter, group II of the animals received a subcutaneous injection of the condensation product and group III a subcutaneous injection of the sodium compound of the sulfonamide while group I was not treated. Each dose in groups II and III corresponded to 150 mg. of the sulfonamide per kg. of body weight. After 24 hours all the animals in group I had died while in groups II and III all the animals survived the infection.

The same detoxifying and solubility increasing effects are observed with other condensation products of bacteriostatic sulfonamides and amino carbohydrates, like-

wise, with the condensation products of blood sugar lowering sulfonamides and amino carbohydrates such as N-acetyl glucosaminyl-N_1-sulfanilyl-N_2-n-butyl urea.

The toxicity of said sulfonyl urea compound was determined and compared with that of N_1-sulfanilyl-N_2-n-butyl urea whereby, of course, equivalent doses calculated for the blood sugar lowering sulfonamide were administered.

Two groups, each of four rats of a body weight between 180 g. and 200 g., received an intraperitoneal injection of 300 mg. of the sulfonamides per 100 g. of body weight. On injection of N_1-sulfanilyl-N_2-n-butyl urea convulsions were observed about 1½ hours after the injection. After 5½ to 6 hours, increased nodding movements and lateral and abdominal position was observed and all the animals died. In contrast thereto, all animals survived the administration of N-acetyl glucosaminyl-N_1-sulfanilyl-N_2-n-butyl urea and convulsions were not encountered although the animals were apathetic and the coat of some of them was ruffled up.

Tests with rabbits showed that both compounds have a blood sugar lowering effect. Thereby, it was found that, on administration of a dose of 300 mg. calculated for N_1-sulfanilyl-N_2-n-butyl urea per kg. of body weight, the N-acetyl glucosaminyl-N_1-sulfanilyl-N_2-n-butyl urea compound was 5% to 10% less effective than the starting sulfanilamide which was adminstered as sodium compound. This slightly lower activity, however, is more than compensated for by the considerably lower toxicity.

The condensation products of isonicotinic acid hydrazides and amino carbohydrates are also much better tolerated than the isonicotinic acid hydrazides themselves while their tuberculostatic activity remains about the same as has been proved in clinical tests.

Tolerance tests were performed with white mice and other experimental animals. Intraperitoneal administration, for instance, of 120 mg. of N-acetyl-D-glucosaminyl isonicotinic acid hydrazide per 20 g. of body weight for three days was well tolerated while of isonicotinic acid hydrazide only 2.5 mg. per 20 g. of body weight can be given.

It is evident that other therapeutically valuable amino group-containing sulfonamides, amino pyrazolones, isonicotinic acid hydrazides than those mentioned hereinabove and in the examples can be condensed with amino carbohydrates and their derivatives whereby similar detoxifying and/or solubilizing effects are achieved. In fact, the present invention is applicable generally to all amino group-containing therapeutic agents and is by no means limited to those mentioned herein.

We claim:

1. The reaction product of a 2-amino carbohydrate selected from the group consisting of a 2-amino hexose and a 2-amino pentose, its amino group being substituted by a member selected from the group consisting of the alkanoyl, alkenoyl, halogeno alkanoyl, phenyl lower alkanoyl, phthaloyl, and carbo(lower)alkoxy groups with a therapeutically effective amino compound selected from the group consisting of isonicotinic acid hydrazides, amino substituted phenyl sulfonamides, and amino substituted pyrazolones, the amino group of said sulfonamides and pyrazolones being a primary amino group, the hydrazine and amino groups of said compound being attached to the carbon atom of said amino carbohydrate in 1-position to the 2-carbon atom carrying the substituted amino group thereof.

2. The reaction product of a 2-amino carbohydrate selected from the group consisting of a 2-amino hexose and a 2-amino pentose, its amino group being substituted by a member selected from the group consisting of the alkanoyl, alkenoyl, halogeno alkanoyl, phenyl lower alkanoyl, phthaloyl, and carbo(lower)alkoxy groups, with isonicotinic acid hydrazide, the hydrazine group of said isonicotinic acid hydrazide being attached to the carbon atom of said amino carbohydrate in 1-position to the 2-carbon atom carrying the substituted amino group thereof.

3. The reaction product of claim 2, wherein the amino carbohydrate is a 2-amino hexose.

4. The reaction product of a 2-amino carbohydrate selected from the group consisting of a 2-amino hexose and a 2-amino pentose, its amino group being substituted by a member selected from the group consisting of the alkanoyl, alkenoyl, halogeno alkanoyl, phenyl lower alkanoyl, phthaloyl, and carbo(lower)alkoxy groups, with a p-amino phenyl sulfonamide compound, the amino group of said compound being attached to the carbon atom of said amino carbohydrate in 1-position to the 2-carbon atom carrying the substituted amino group thereof.

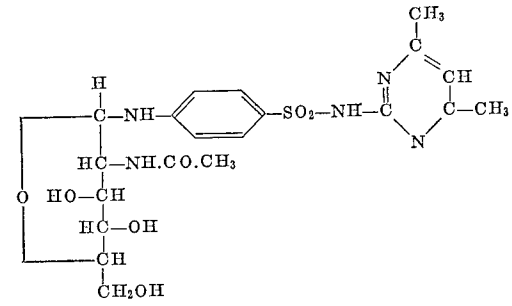
5. The reaction product of a 2-amino carbohydrate selected from the group consisting of a 2-amino hexose and a 2-amino pentose, its amino group being substituted by a member selected from the group consisting of the alkanoyl, alkenoyl, halogeno alkanoyl, phenyl lower alkanoyl, phthaloyl, and carbo(lower) alkoxy groups, with 4-amino-1-phenyl-2,3-dimethyl pyrazolone-(5), the amino group of said pyrazolone compound being attached to the carbon atom of said amino carbohydrate in 1-position to the 2-carbon atom carrying the substituted amino group thereof.

6. The reaction product of claim 4, wherein the amino carbohydrate is a 2-amino hexose.

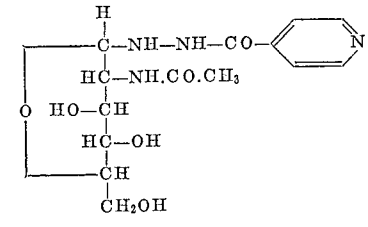
7. The reaction product of claim 5, wherein the amino carbohydrate is a 2-amino hexose.

8. The reaction product of claim 1, wherein the amino carbohydrate is a 2-amino hexose.

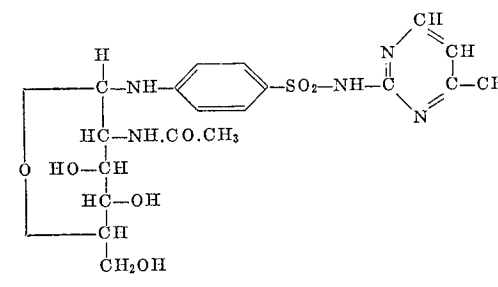
9. N-acetyl glucosamine-2-sulfanilamido-4,6-dimethyl pyrimidine of the formula



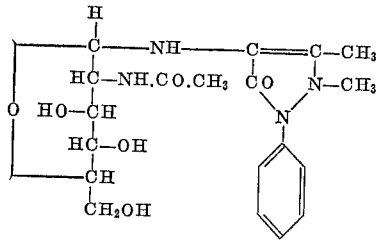
10. N-acetyl glucosamine isonicotinic acid hydrazide of the formula



11. N-acetyl glucosamine-2-sulfanilamido-6-methyl pyrimidine of the formula



12. N - acetyl glucosamine-4-amino-1-phenyl-2,3-dimethyl pyrazolone-(5) of the formula



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