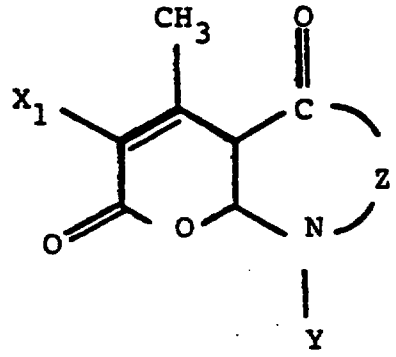
Pyrano Derivatives

DESCRIPTION:

The invention relates to pyrano derivatives, to methods for their preparation and to pharmaceutical compositions containing them.

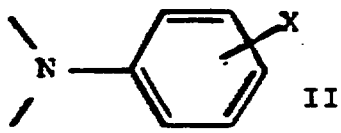
The invention provides pyrano derivatives of the general formula I



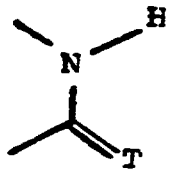
I

wherein X_1 represents a hydrogen, chlorine or bromine atom,

Z represents a residue of the general formula II or the general formula III



II



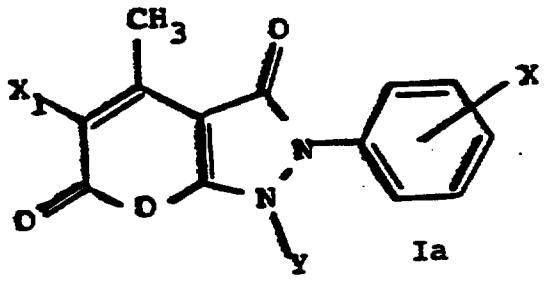
III

(X representing a hydrogen, chlorine or bromine atom and T representing an oxygen or sulphur atom), and

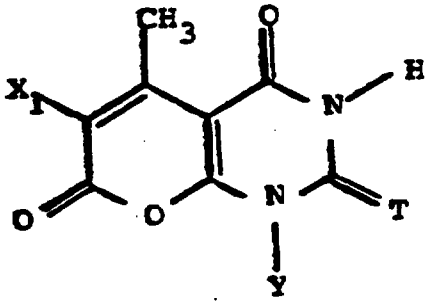
Y represents an arabinosyl, xylosyl or ribosyl residue, the residue Y having either a pyrane or furane configuration, being free or acetylated, and being bound to the nitrogen atom to give either the α or the β anomer.

The pyrano derivatives I may alternatively be represented

by the general formulae Ia and Ib



Ia

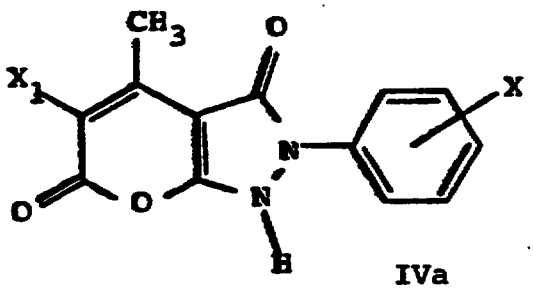


Ib

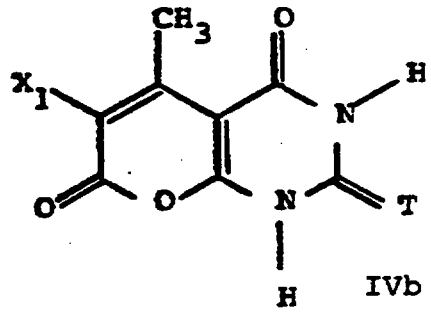
wherein X_1, X, Y and T are as above defined.

The compounds according to the invention are of interest for their therapeutic action in the field of virus- and bacteria-induced diseases and, for some of them, for their activity in the cardio-vascular field. Accordingly, the invention also provides a pharmaceutical composition comprising a pyrano derivative I in admixture with a pharmaceutically acceptable diluent or carrier.

The invention further provides a method for the preparation of the pyrano derivatives I, the method comprising reacting one of the compounds of the general formulae IVa and IVb



IVa



IVb

wherein X_1, X and T are as above defined with an acetylated arabinose, xylose or ribose in a solvent, such as acetonitrile. The reactants are preferably used in stoichiometric proportions, and the reaction proceeds under

stirring at room temperature over a period of from 12 to 24 hours. The reaction is preferably conducted under nitrogen circulation in the presence of 1,1,1,3,3,3--hexamethyldisilazane, trimethylchlorosilane and tin tetrachloride.

This leads to the acetylated form of the compounds of the invention. The corresponding non-acetylated compounds are obtained by the usual desacetylation techniques.

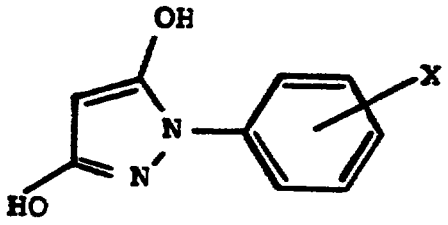
The starting materials may be obtained as follows:

A - The acetylated oses may be obtained from the corresponding oses by conventional acetylation using an excess of acetic anhydride in the presence of perchloric acid, under stirring at room temperature (0.5 to one hour). The reaction mixture is poured on icy water, which gives an oily product, extracted by chloroform and dried. The removal of the chloroform by evaporation under reduced pressure leads to an oil with a yield of about 55 to 85% according to the product. As these oses exist under pyranose and furanose form, each of these forms or their mixtures in various proportions may be used.

B - The condensed ring compounds IVa and IVb may be obtained as follows:

Compound IVa

$CH_3CO.CHX_1.COOC_2H_5$ +



For the compound in which both X_1 and X represent hydrogen atoms, 123 g of 1-phenyl-3,5-dihydroxypyrazole (0.7 mol) are treated with 270 ml of ethyl acetoacetate

(2.1 mol) at 130°C. After distilling off water and ethanol produced by the reaction, the temperature is raised to 180°C. After 3 hours, the mixture is cooled and poured into a boiling mixture of water and ethanol (50/50 by volume), leading to a suspension. The suspension is stirred, filtered, washed with 100 ml of a 50/50 by volume water and methanol mixture, dried under reduced pressure and recrystallized from ethylene glycol monomethyl ether, yield 105 g (73%).

The process is the same when either X_1 or X (or both) represents a chlorine or bromine atom.

Compound IVb

$CH_3CO.CHX_1.COOC_2H_5$ + thiobarbituric acid or barbituric acid → IVb

The process is the same as for compound IVa above but starting with 100 g (0.7 mol) of thiobarbituric acid. Yield 101 g (68%). Barbituric acid is used for T=O.

The invention is illustrated by the following Examples. As the process is strictly the same for all the compounds, only the first Example will be described in detail. For the other Examples, only starting materials and characteristics will be given.

Example A: Compounds Ia

1) 1-(β-D-2,3,5-tri-O-acetylribofuranosyl)-2-phenyl-4--methyl-pyrano-(2,3-c)-pyrazole-3,6-dione

Into a one litre reactor fitted with stirring means were poured, under nitrogen circulation, 19.4 g (0.08 mol) of 2-phenyl-4-methyl-pyrano-(2,3-c)-pyrazole-3,6-dione, 12.3 ml (0.0585 mol) of hexamethyldisilazane, 27.3 ml (0.0215 mol) of tetramethylchlorosilane, 18.7 ml (0.16 mol) of tin tetrachloride and 250 ml of acetonitrile. After stirring,

there was obtained a solution to which was added 25.5 g (0.08 mol) of β-D-tetraacetyl-ribofuranose. Stirring was maintained for 19 hours under nitrogen circulation. The reaction mixture was then poured into a cold 10% sodium bicarbonate solution and the pH was adjusted to 6.7. 320 ml of chloroform were added under stirring and the organic phase was separated, washed with water, dried on anhydrous sodium sulphate and evaporated to dryness. The dry product was then triturated with diethyl ether and recrystallized from hot ethanol. After separation, washing and drying, there was obtained 12.4 g (yield 31%) of a white crystalline powder, elemental analysis of which showed a good correspondence with the formula $C_{24}H_{25}N_2O_{10}$. Melting point 157°C (Tottoli). The compound is insoluble in water and soluble in dimethylsulphoxide.

The corresponding desacetylated product (formula $C_{18}H_{19}N_2O_7$) is a white powder melting at 173-175°C (Tottoli), insoluble in water and soluble in dimethylsulphoxide.

2) 1-(β-D-2,3,5-tri-O-acetylribofuranosyl)-2-phenyl-4--methyl-5-chloro-pyrano-(2,3-c)-pyrazole-3,6-dione

IVa, X = H, X_1 = Cl β-D-tetraacetyl-ribofuranose

Reaction time 15 hours - yield 36.5% of a white crystalline product melting at 168°C (Tottoli). Insoluble in water, soluble in dimethylsulphoxide. Analysis shows a very good correspondence with the formula $C_{24}H_{24}N_2O_{10}Cl$.

The corresponding desacetylated product (formula $C_{18}H_{18}N_2O_7Cl$) is a beige powder melting at 189°C (Tottoli), insoluble in water and soluble in dimethylsulphoxide.

3) 1-(β-D-2,3,5-tri-O-acetylribofuranosyl)-2-(p-chlorophenyl)-4-methyl-5-chloro-pyrano-(2,3-c)-pyrazole-3,6-dione

IVa, $X = X_1 = Cl$ β-D-tetraacetyl-ribofuranose

Reaction time 12 hours - yield 38% of a white crystalline powder melting at 193°C (Tottoli). Insoluble in water, soluble in dimethylsulphoxide. Analysis shows a very good correspondence with the formula $C_{24}H_{23}N_2O_{10}Cl_2$.

The corresponding desacetylated product (formula $C_{18}H_{17}N_2O_7Cl_2$) is a beige powder melting at 233°C (Tottoli), insoluble in water and soluble in dimethylsulphoxide.

4) 1-(β-D-2,3,4-tri-O-acetylxylopyranosyl)-2--phenyl-4-methyl-pyrano-(2,3-c)-pyrazole-3,6-dione

IVa, $X = X_1 = H$ β-D-tetraacetyl-xylopyranose

Reaction time 17 hours - yield 39% of a white crystalline powder melting at 201°C (Tottoli). Insoluble in water, soluble in dimethylsulphoxide. Analysis shows a very good correspondence with the formula $C_{24}H_{25}N_2O_{10}$.

The corresponding desacetylated product (formula $C_{18}H_{19}N_2O_7$) is a beige powder melting at 246°C (Tottoli), insoluble in water and soluble in dimethylsulphoxide.

5) 1-(β-D-2,3,5-tri-O-acetylxylofuranosyl)-2--phenyl-4-methyl-pyrano-(2,3-c)-pyrazole-3,6-dione

IVa, $X = X_1 = H$ β-D-tetraacetyl-xylofuranose

Reaction time 22 hours - yield 29.5% of a white crystalline product melting at 168°C (Tottoli). Insoluble in water, soluble in dimethylsulphoxide. Analysis shows a very good correspondence with the formula $C_{24}H_{25}N_2O_{10}$.

The corresponding desacetylated product (formula $C_{18}H_{19}N_2O_7$) is a beige powder melting at 218°C (Tottoli), insoluble in water and soluble in dimethylsulphoxide.

6) 1-(β-D-2,3,5-tri-O-acetylxylofuranosyl)-2-(p-bromo--phenyl)-4-methyl-pyrano-(2,3-c)-pyrazole-3,6-dione

IVa, X = Br, X_1 = H β-D-tetraacetyl-xylofuranose

Reaction time 16 hours - yield 27% of a white crystalline powder melting at 159°C (Tottoli). Insoluble in water, soluble in dimethylsulphoxide. Analysis shows a very good correspondence with the formula $C_{24}H_{24}N_2O_{10}Br$.

The corresponding desacetylated product (formula $C_{18}H_{18}N_2O_7Br$) is a beige powder melting at 241°C (Tottoli), insoluble in water and soluble in dimethylsulphoxide.

7) 1-(β-D-2,3,4-tri-O-acetylxylopyranosyl)-2-phenyl--4-methyl-5-chloro-pyrano-(2,3-c)-pyrazole-3,6-dione

IVa, X = H, X_1 = Cl β-D-tetraacetyl-xylopyranose

Reaction time 23 hours - yield 42% of a white crystalline product melting at 188°C (Tottoli). Poorly soluble in water, soluble in dimethylsulphoxide. Analysis shows a very good correspondence with the formula $C_{24}H_{24}N_2O_{10}Cl$.

The corresponding desacetylated product (formula $C_{18}H_{18}N_2O_7Cl$) is a beige powder melting at 262°C (Tottoli), insoluble in water and soluble in dimethylsulphoxide.

8) 1-(D-2,3,5-tri-O-acetylarabinofuranosyl)-2-phenyl--4-methyl-pyrano-(2,3-c)-pyrazole-3,6-dione

IVa, X = X_1 = H D-tetraacetyl-arabinofuranose

Reaction time 17 hours - yield 28% of a white crystalline product melting at 144°C (Tottoli). Insoluble in water, soluble in dimethylsulphoxide. Analysis shows a very good correspondence with the formula $C_{24}H_{25}N_2O_{10}$.

The corresponding desacetylated product (formula $C_{18}H_{19}N_2O_7$) is a beige powder melting at 244°C (Tottoli), insoluble in water and soluble in dimethylsulphoxide.

9) 1-(D-2,3,5-tri-O-acetylarabinofuranosyl)-2-(p-chlorophenyl)-4-methyl-pyrano-(2,3-c)-pyrazole-3,6-dione

IVa, X = Cl, X_1 = H D-tetraacetyl-arabinofuranose

Reaction time 17 hours - yield 39% of a white crystalline product melting at 177°C (Tottoli). Insoluble in water, soluble in dimethylsulphoxide. Analysis shows a very good correspondence with the formula $C_{24}H_{24}N_2O_{10}Cl$.

The corresponding desacetylated product (formula $C_{18}H_{18}N_2O_7Cl$) is a beige powder melting at 201°C (Tottoli), insoluble in water and soluble in dimethylsulphoxide.

10) 1-(α-D-2,3,5-tri-O-acetylarabinofuranosyl)-2-(p-chlorophenyl)-4-methyl-pyrano-(2,3-c)-pyrazole-3,6-dione

IVa, X = Cl, X_1 = H α-D-tetraacetyl-arabinofuranose

Reaction time 18 hours - yield 32.5% of a white-grey crystalline powder melting at 189°C (Tottoli). Insoluble in water, soluble in dimethylsulphoxide. Analysis shows a very good correspondence with the formula $C_{24}H_{24}N_2O_{10}Cl$.

The corresponding desacetylated product (formula $C_{18}H_{18}N_2O_7Cl$) is a beige powder melting at 249°C (Tottoli), insoluble in water and soluble in dimethylsulphoxide.

Example B: Compounds Ib

1) 1-(β-D-2,3,5-tri-O-acetylarabinofuranosyl)-5-methyl--1,2,3,4-tetrahydro-7H-pyrano-(2,3-d)-pyrimidine-2,4,7--trione

IVb, X_1 = H, T = O β-D-tetraacetyl-arabinofuranose

Reaction time 22 hours - yield 33% of a white crystalline powder melting at 190°C (Tottoli). Insoluble in water, soluble in dimethylsulphoxide. Analysis shows a very good correspondence with the formula $C_{19}H_{20}N_2O_{11}$.

The corresponding desacetylated product (formula $C_{13}H_{14}N_2O_8$) is a beige powder melting at 210 to 212°C (Tottoli), insoluble in water and soluble in dimethylsulphoxide.

2) 1-(β-D-2,3,5-tri-O-acetylarabinofuranosyl)-5-methyl-6--chloro-1,2,3,4-tetrahydro-7H-pyrano-(2,3-d)-pyrimidine--2,4,7-trione

IVb, X_1 = Cl, T = O β-D-tetraacetyl-arabinofuranose

Reaction time 13 hours - yield 29.5% of a white crystalline product melting at 203°C (Tottoli). Insoluble in water, soluble in dimethylsulphoxide. Analysis shows a good correspondence with the formula $C_{19}H_{19}N_2O_{11}Cl$.

The corresponding desacetylated product (formula $C_{13}H_{13}N_2O_8Cl$) is a beige powder melting at 255°C (Tottoli), insoluble in water and in dimethylsulphoxide.

3) 1-(β-D-2,3,5-tri-O-acetylarabinofuranosyl)-5-methyl-6--bromo-1,2,3,4-tetrahydro-7H-pyrano-(2,3-d)-pyrimidine--2,4,7-trione

IVb, X_1 = Br, T = O β-D-tetraacetyl-arabinofuranose

Reaction time 17 hours - yield 26% of a white crystalline product melting at 180°C (Tottoli). Insoluble in water, soluble in dimethylsulphoxide. Analysis shows a good correspondence with the formula $C_{19}H_{19}N_2O_{11}Br$.

The corresponding desacetylated product (formula $C_{13}H_{13}N_2O_8Br$) is a beige powder melting at 222°C (Tottoli), insoluble in water and in dimethylsulphoxide.

4) 1-(β-D-2,3,4-tri-O-acetylarabinopyranosyl)-5-methyl--1,2,3,4-tetrahydro-7H-pyrano-(2,3-d)-pyrimidine-2,4,7--trione

IVb, X_1 = H, T = O β-D-tetraacetyl-arabinopyranose

Reaction time 18 hours - yield 41% of a white crystalline powder melting at 175°C (Tottoli). Insoluble in water, soluble in dimethylsulphoxide. Analysis shows a good correspondence with the formula $C_{19}H_{20}N_2O_{11}$.

The corresponding desacetylated product (formula $C_{13}H_{14}N_2O_8$) is a beige powder melting at 218°C (Tottoli), insoluble in water and soluble in dimethylsulphoxide.

5) 1-(D-2,3,5-tri-O-acetylarabinofuranosyl)-5-methyl--4,7-dioxo-1,2,3,4-tetrahydro-7H-pyrano-(2,3-d)-pyrimidine--2-thione

IVb, X_1 = H, T = S D-tetraacetyl-arabinofuranose

Reaction time 20 hours - yield 36% of a powder melting at 202°C (Tottoli). Insoluble in water, soluble in dimethylsulphoxide. Analysis shows a very good correspondence with the formula $C_{19}H_{20}N_2O_{10}S$.

The corresponding desacetylated product (formula $C_{13}H_{14}N_2O_7S$) is a beige powder melting at 184°C (Tottoli), insoluble in water and soluble in dimethylsulphoxide.

6) 1-(α-D-2,3,5-tri-O-acetylarabinofuranosyl)-5-methyl--4,7-dioxo-1,2,3,4-tetrahydro-7H-pyrano-(2,3-d)-pyrimidine--2-thione

IVb, X_1 = H, T = S α-D-tetraacetyl-arabinofuranose

Reaction time 20 hours - yield 24.5% of a white crystalline powder melting at 165°C (Tottoli). Insoluble in water, soluble in dimethylsulphoxide. Analysis shows a good correspondence with the formula $C_{19}H_{20}N_2O_{10}S$.

The corresponding desacetylated product (formula $C_{13}H_{14}N_2O_7S$) is a beige powder melting at 242°C (Tottoli), insoluble in water and soluble in dimethylsulphoxide.

7) 1-(α-D-2,3,5-tri-O-acetylarabinofuranosyl)-5-methyl--6-chloro-4,7-dioxo-1,2,3,4-tetrahydro-7H-pyrano-(2,3-d)--pyrimidine-2-thione

IVb, X_1 = Cl, T = S α-D-tetraacetyl-arabinofuranose

Reaction time 15 hours - yield 36.5% of a white crystalline powder melting at 194°C (Tottoli). Insoluble in water, soluble in dimethylsulphoxide. Analysis shows a very good correspondence with the formula $C_{19}H_{19}N_2O_{10}SCl$.

The corresponding desacetylated product (formula $C_{13}H_{13}N_2O_7SCl$) is a beige powder melting at 229°C (Tottoli), insoluble in water and soluble in dimethylsulphoxide.

8) 1-(α-D-2,3,4-tri-O-acetylarabinopyranosyl)-5-methyl--4,7-dioxo-1,2,3,4-tetrahydro-7H-pyrano-(2,3-d)--pyrimidine-2-thione

IVb, X_1 = H, T = S α-D-tetraacetyl-arabinopyranose

Reaction time 19 hours - yield 36% of a white-grey crystalline powder melting at 230°C (Tottoli). Insoluble in water, soluble in dimethylsulphoxide. Analysis shows a good correspondence with the formula $C_{19}H_{20}N_2O_{10}S$.

The corresponding desacetylated product (formula $C_{13}H_{14}N_2O_7S$) is a beige powder melting at 207°C to 209°C (Tottoli), insoluble in water and soluble in dimethylsulphoxide.

9) 1-(β-D-2,3,4-tri-O-acetylarabinopyranosyl)-5-methyl--4,7-dioxo-1,2,3,4-tetrahydro-7H-pyrano-(2,3-d)--pyrimidine-2-thione

IVb, X_1 = H, T = S β-D-tetraacetyl-arabinopyranose

Reaction time 21 hours - yield 34% of a white crystalline powder melting at 226°C (Tottoli). Insoluble in water, soluble in dimethylsulphoxide. Analysis shows a good correspondence with the formula $C_{19}H_{20}N_2O_{10}S$.

The corresponding desacetylated product (formula $C_{13}H_{14}N_2O_7S$) is a beige powder melting at 248°C (Tottoli), insoluble in water and soluble in dimethylsulphoxide.

10) 1-(D-2,3,4-tri-O-acetylarabinopyranosyl)-5-methyl--4,7-dioxo-1,2,3,4-tetrahydro-7H-pyrano-(2,3-d)--pyrimidine-2-thione

IVb, X_1 = H, T = S D-tetraacetyl-arabinopyranose

Reaction time 23 hours - yield 44% of a crystalline powder melting at 163°C (Tottoli). Insoluble in water, soluble in dimethylsulphoxide. Analysis shows a very good correspondence with the formula $C_{19}H_{20}N_2O_{10}S$.

The corresponding desacetylated product (formula $C_{13}H_{14}N_2O_7S$) is a beige powder melting at 239°C (Tottoli), insoluble in water and soluble in dimethylsulphoxide.

11) 1-(D-2,3,4-tri-O-acetylarabinopyranosyl)-5-methyl--4,7-dioxo-6-chloro-1,2,3,4-tetrahydro-7H-pyrano-(2,3-d)--pyrimidine-2-thione

IVb, X_1 = Cl, T = S D-tetraacetyl-arabinopyranose

Reaction time 22 hours - yield 30.5% of a pale yellow crystalline powder melting at 193°C (Tottoli). Insoluble in water, soluble in dimethylsulphoxide. Analysis shows a very good correspondence with the formula $C_{19}H_{19}N_2O_{10}SCl$.

The corresponding desacetylated product (formula $C_{13}H_{13}N_2O_7SCl$) is a beige powder melting at 235°C (Tottoli), insoluble in water and soluble in dimethylsulphoxide.

12) 1-(α + β-D-2,3,4-tri-O-acetylarabinopyranosyl)-5--methyl-4,7-dioxo-1,2,3,4-tetrahydro-7H-pyrano-(2,3-d)--pyrimidine-2-thione

IVb, X_1 = H, T = S α + β-D-tetraacetyl-arabinopyranose (commercial product)

Reaction time 20 hours - yield 39.5% of a pale yellow crystalline powder melting at 214°C (Tottoli). Insoluble in water, soluble in dimethylsulphoxide. Analysis shows a good correspondence with the formula $C_{19}H_{20}N_2O_{10}S$.

The corresponding desacetylated product (formula $C_{13}H_{14}N_2O_7S$) is a beige powder melting at 241°C (Tottoli), insoluble in water and soluble in dimethylsulphoxide.

13) 1-(β-D-2,3,5-tri-O-acetylribofuranosyl)-5--methyl-1,2,3,4-tetrahydro-7H-pyrano-(2,3-d)--pyrimidine-2,4,7-trione

IVb, X_1 = H, T = O β-D-tetraacetyl-ribofuranose

Reaction time 18 hours - yield 26% of a white crystalline powder melting at 165°C (Tottoli). Insoluble in water, soluble in dimethylsulphoxide. Analysis shows a very good correspondence with the formula $C_{19}H_{20}N_2O_{11}$.

The corresponding desacetylated product (formula $C_{13}H_{14}N_2O_8$) is a beige powder melting at 249°C (Tottoli), insoluble in water and soluble in dimethylsulphoxide.

14) 1-(β-D-2,3,5-tri-O-acetylribofuranosyl)-5-methyl-6--chloro-1,2,3,4-tetrahydro-7H-pyrano-(2,3-d)-pyrimidine--2,4,7-trione

IVb, X_1 = Cl, T = O β-D-tetraacetyl-ribofuranose

Reaction time 15 hours - yield 32% of a white crystalline product melting at 208°C (Tottoli). Insoluble in water, soluble in dimethylsulphoxide. Analysis shows a very good correspondence with the formula $C_{19}H_{19}N_2O_{11}Cl$.

The corresponding desacetylated product (formula $C_{13}H_{13}N_2O_8Cl$) is a beige powder melting at 199°C (Tottoli), insoluble in water and soluble in dimethylsulphoxide.

15) 1-(β-D-2,3,5-tri-O-acetylribofuranosyl)-5--methyl-6-bromo-1,2,3,4-tetrahydro-7H-pyrano-(2,3-d)--pyrimidine-2,4,7-trione

IVb, X_1 = Br, T = O β-D-tetraacetyl-ribofuranose

Reaction time 16 hours - yield 31% of a white crystalline

product melting at 271°C (Tottoli). Insoluble in water, soluble in dimethylsulphoxide. Analysis shows a good correspondence with the formula $C_{19}H_{19}N_2O_{11}Br$.

The corresponding desacetylated product (formula $C_{13}H_{13}N_2O_8Br$) is a beige powder melting at 260°C (Tottoli), insoluble in water and soluble in dimethylsulphoxide.

16) 1-(β-D-2,3,4-tri-O-acetylribopyranosyl)-5-methyl--1,2,3,4-tetrahydro-7H-pyrano-(2,3-d)-pyrimidine-2,4,7--trione

IVb, X_1 = H, T = O β-D-tetraacetyl-ribopyranose

Reaction time 14 hours - yield 38% of a white powder melting at 123°C (Tottoli). Insoluble in water, soluble in dimethylsulphoxide. Analysis shows a very good correspondence with the formula $C_{19}H_{20}N_2O_{11}$.

The corresponding desacetylated product (formula $C_{13}H_{14}N_2O_8$) is a beige powder melting at 190°C (Tottoli), insoluble in water and soluble in dimethylsulphoxide.

17) 1-(β-D-2,3,4-tri-O-acetylribopyranosyl)-5-methyl-6--bromo-1,2,3,4-tetrahydro-7H-pyrano-(2,3-d)-pyrimidine--2,4,7-trione

IVb, X_1 = Br, T = O β-D-tetraacetyl-ribopyranose

Reaction time 21 hours - yield 24% of a white crystalline powder melting at over 300°C (Tottoli). Insoluble in water, soluble in dimethylsulphoxide. Analysis shows a good correspondence with the formula $C_{19}H_{19}N_2O_{11}Br$.

The corresponding desacetylated product (formula $C_{13}H_{13}N_2O_8Br$) is a beige powder melting at 255°C (Tottoli), insoluble in water and soluble in dimethylsulphoxide.

18) 1-(α-D-2,3,4-tri-O-acetylribopyranosyl)-5-methyl--1,2,3,4-tetrahydro-7H-pyrano-(2,3-d)-pyrimidine-2,4,7--trione

IVb, X_1 = H, T = O α-D-tetraacetyl-ribopyranose

Reaction time 22 hours - yield 33% of a white crystalline powder melting at 172°C (Tottoli). Insoluble in water, soluble in dimethylsulphoxide. Analysis shows a good correspondence with the formula $C_{19}H_{20}N_2O_{11}$.

The corresponding desacetylated product (formula $C_{13}H_{14}N_2O_8$) is a beige powder melting at 233°C (Tottoli), insoluble in water and soluble in dimethylsulphoxide.

19) 1-(D-2,3,5-tri-O-acetylribofuranosyl)-5-methyl--4,7-dioxo-1,2,3,4-tetrahydro-7H-pyrano-(2,3-d)--pyrimidine-2-thione

IVb, X_1 = H, T = S D-tetraacetyl-ribofuranose

Reaction time 20 hours - yield 43% of a white crystalline powder melting at 188°C (Tottoli). Insoluble in water, soluble in dimethylsulphoxide. Analysis shows a very good correspondence with the formula $C_{19}H_{20}N_2O_{10}S$.

The corresponding desacetylated product (formula $C_{13}H_{14}N_2O_7S$) is a beige powder melting at 212°C

(Tottoli), insoluble in water and soluble in dimethylsulphoxide.

20) 1-(β-D-2,3,5-tri-O-acetylribofuranosyl)-5-methyl-4,7--dioxo-1,2,3,4-tetrahydro-7H-pyrano-(2,3-d)-pyrimidine-2--thione

IVb, X_1 = H, T = S β-D-tetraacetyl-ribofuranose

Reaction time 15 hours - yield 40% of a white crystalline powder melting at 295°C (Tottoli). Insoluble in water, soluble in dimethylsulphoxide. Analysis shows a very good correspondence with the formula $C_{19}H_{20}N_2O_{10}S$.

The corresponding desacetylated product (formula $C_{13}H_{14}N_2O_7S$) is a beige powder melting at 260°C (Tottoli), insoluble in water and soluble in dimethylsulphoxide.

21) 1-(α-D-2,3,5-tri-O-acetylribofuranosyl)-5-methyl-4,7--dioxo-1,2,3,4-tetrahydro-7H-pyrano-(2,3-d)-pyrimidine-2--thione

IVb, X_1 = H, T = S α-D-tetraacetyl-ribofuranose

Reaction time 19 hours - yield 37% of a white crystalline powder melting at 276°C (Tottoli). Insoluble in water, soluble in dimethylsulphoxide. Analysis shows a good correspondence with the formula $C_{19}H_{20}N_2O_{10}S$.

The corresponding desacetylated product (formula $C_{13}H_{14}N_2O_7S$) is a beige powder melting at 236°C (Tottoli), insoluble in water and soluble in dimethylsulphoxide.

22) 1-(D-2,3,4-tri-O-acetylribopyranosyl)-5-methyl-4,7--dioxo-1,2,3,4-tetrahydro-7H-pyrano-(2,3-d)-pyrimidine-2--thione

IVb, X_1 = H, T = S D-tetraacetyl-ribopyranose

Reaction time 17 hours - yield 27% of a white crystalline powder melting at 215°C (Tottoli). Insoluble in water, soluble in dimethylsulphoxide. Analysis shows a very good correspondence with the formula $C_{19}H_{20}N_2O_{10}S$.

The corresponding desacetylated product (formula $C_{13}H_{14}N_2O_7S$) is a white powder melting at 260°C (Tottoli), insoluble in water and soluble in aqueous sodium bicarbonate.

23) 1-(α-D-2,3,4-tri-O-acetylribopyranosyl)-5-methyl-4,7--dioxo-1,2,3,4-tetrahydro-7H-pyrano-(2,3-d)-pyrimidine-2--thione

IVb, X_1 = H, T = S α-D-tetraacetyl-ribopyranose

Reaction time 22 hours - yield 34% of a white crystalline powder melting at 233°C (Tottoli). Insoluble in water, soluble in dimethylsulphoxide. Analysis shows a very good correspondence with the formula $C_{19}H_{20}N_2O_{10}S$.

The corresponding desacetylated product (formula $C_{13}H_{14}N_2O_7S$) is a white powder melting at 174°C (Tottoli), insoluble in water and soluble in aqueous sodium bicarbonate.

24) 1-(β-D-2,3,4-tri-O-acetylribopyranosyl)-5-methyl-4,7--dioxo-1,2,3,4-tetrahydro-7H-pyrano-(2,3-d)-pyrimidine-2--thione

IVb, X_1 = H, T = S β-D-tetraacetyl-ribopyranose

Reaction time 21 hours - yield 37% of a white crystalline powder melting at 199°C (Tottoli). Insoluble in water, soluble in dimethylsulphoxide. Analysis shows a good correspondence with the formula $C_{19}H_{20}N_2O_{10}S$.

The corresponding desacetylated product (formula $C_{13}H_{14}N_2O_7SH_2O$) is a white crystalline powder melting at 280°C (Tottoli), insoluble in water and soluble in aqueous sodium bicarbonate.

25) 1-(β-D-2,3,5-tri-O-acetylxylofuranosyl)-5-methyl--1,2,3,4-tetrahydro-7H-pyrano-(2,3-d)-pyrimidine-2,4,7--trione

IVb, X_1 = H, T = O β-D-tetraacetyl-xylofuranose

Reaction time 17 hours - yield 28% of a pale yellow crystalline powder melting at 218°C (Tottoli). Insoluble in water, soluble in dimethylsulphoxide. Analysis shows a very good correspondence with the formula $C_{19}H_{20}N_2O_{11}$.

The corresponding desacetylated product (formula $C_{13}H_{14}N_2O_8$) is a beige powder melting at 249°C (Tottoli), insoluble in water and soluble in dimethylsulphoxide.

26) 1-(β-D-2,3,5-tri-O-acetylxylofuranosyl)-5-methyl-6--chloro-1,2,3,4-tetrahydro-7H-pyrano-(2,3-d)-pyrimidine--2,4,7-trione

IVb, X_1 = Cl, T = O β-D-tetraacetyl-xylofuranose

Reaction time 19 hours - yield 26% of a pale yellow product melting at 247°C (Tottoli). Insoluble in water, soluble in dimethylsulphoxide. Analysis shows a good correspondence with the formula $C_{19}H_{19}N_2O_{11}Cl$.

The corresponding desacetylated product (formula $C_{13}H_{13}N_2O_8Cl$) is a beige powder melting at 208°C (Tottoli), insoluble in water and in dimethylsulphoxide.

27) 1-(β-D-2,3,4-tri-O-acetylxylopyranosyl)-5-methyl--1,2,3,4-tetrahydro-7H-pyrano-(2,3-d)-pyrimidine-2,4,7--trione

IVb, X_1 = H, T = O β-D-tetraacetyl-xylopyranose

Reaction time 22 hours - yield 34% of a yellow powder melting at 270°C (Tottoli). Insoluble in water, soluble in dimethylsulphoxide. Analysis shows a good correspondence with the formula $C_{19}H_{20}N_2O_{11}$.

The corresponding desacetylated product (formula $C_{13}H_{14}N_2O_8$) is a beige powder melting at 243°C (Tottoli), insoluble in water and soluble in dimethylsulphoxide.

28) 1-(α-D-2,3,5-tri-O-acetylxylofuranosyl)-5-methyl-4,7--dioxo-1,2,3,4-tetrahydro-7H-pyrano-(2,3-d)-pyrimidine-2--thione

IVb, X_1 = H, T = S α-D-tetraacetyl-xylofuranose

Reaction time 20 hours - yield 29% of a white crystalline powder melting at 202°C (Tottoli). Insoluble in water, soluble in dimethylsulphoxide. Analysis shows a good

correspondence with the formula $C_{19}H_{20}N_2O_{10}S$.

The corresponding desacetylated product (formula $C_{13}H_{14}N_2O_7S$) is a beige powder melting at 234°C (Tottoli), insoluble in water and soluble in dimethylsulphoxide.

29) 1-(D-2,3,5-tri-O-acetylxylofuranosyl)-5-methyl-4,7--dioxo-1,2,3,4-tetrahydro-7H-pyrano-(2,3-d)-pyrimidine-2--thione

IVb, X_1 = H, T = S D-tetraacetyl-xylofuranose

Reaction time 19 hours - yield 30% of a powder melting at 222°C (Tottoli). Insoluble in water, soluble in dimethylsulphoxide. Analysis shows a very good correspondence with the formula $C_{19}H_{20}N_2O_{10}S$.

The corresponding desacetylated product (formula $C_{13}H_{14}N_2O_7S$) is a beige powder melting at 255°C (Tottoli), insoluble in water and soluble in dimethylsulphoxide.

30) 1-(β-D-2,3,4-tri-O-acetylxylopyranosyl)-5-methyl-4,7--dioxo-1,2,3,4-tetrahydro-7H-pyrano-(2,3-d)-pyrimidine-2--thione

IVb, X_1 = H, T = S β-D-tetraacetyl-xylopyranose

Reaction time 22 hours - yield 31% of a white crystalline powder melting at 221°C (Tottoli). Insoluble in water, soluble in dimethylsulphoxide. Analysis shows a good correspondence with the formula $C_{19}H_{20}N_2O_{10}S$.

The corresponding desacetylated product (formula

TOXICITY

Preliminary toxicity studies per os on rats and mice have not revealed any toxicity at 650 mg/kg for any of the compounds. As maximum efficient therapeutic doses are of about 50 mg/kg, slightly varying with the compounds, higher doses have not been tested.

PHARMACOLOGY

I Effect of topical treatment with the compounds of the invention on genital infections of guinea pigs.

Groups of each 4 white guinea pigs aged 3-4 months and weighing approximately 200 gms were inoculated vaginally with cotton wool swabs impregnated with either WAL strain of HSV-1 ($10^{7.5}$ pfu/ml) or 333 strain of HSV-2 ($10^{7.3}$ pfu/ml) ; swabs soaked in virus were rubbed on to the external surfaces and implanted internally into the vagina. Twentyfour hours following virus inoculation, the animals were divided into 18 groups and 17 were treated with either 15 of the compounds of the invention (1.5 % in cream base), Acyclovir as obtained commercially, or cream base placebo : the 18th group (control) were not treated. Treatments were given four times a day throughout the observation period of 11 days. Animals were examined daily for clinical evidence of HSV infection ; these included erythema, exudate, a combination of erythema and exudate and urine retention which is a common feature in the latter part of HSV infection. Previous studies had shown that genital infection with HSV-1 (WAL strain) or HSV-2 (333 strain) produced erythema and exudate without necessarily producing vesicles.

The results are reported in Table 1, central portion, showing a clinical score on days ; in this table, the

compounds are identified by the number of their example as such for the acetylated form or followed by (OH) for the desacetylated form. Observations of clinical reactions were made on days 1 - 11 after virus inoculations. For HSV-1 infected control animals, no reactions were seen until day 6 post-inoculation ; at this time extensive erythema and exudate was observed and this continued to day 11 when urine retention was found : this course of infection usually precedes fatal encephalitis, but the experiments were not allowed to proceed to this end. Animals treated with placebo cream showed similar reactions to those found in untreated animals (control). In contrast, animals treated with the compounds of the invention and Acyclovir showed delayed onset of erythema and minimal exudate in the period 7 - 11 days following virus inoculation. The results indicate clinical amelioration of the symptoms of genital HSV-1 infection in guinea pigs by the compounds of the invention and Acyclovir.

The clinical events for animals inoculated with HSV-2 and treated with antiviral compounds were more clear cut. Thus, uninoculated controls and placebo treated animals developed erythema and/or exudate from days 6-7 following virus inoculation, and urine retention was observed on days 10 - 11. In contrast, no erythema or exudate was observed in animals treated with either Acyclovir and little with the compounds of the invention.

The results are shown in same Table 1, right hand portion. From these figures it clearly appears that, compared to Acyclovir, the compounds of the invention have a quite similar activity on HSV-2 viruses but a superior activity on HSV-1 viruses.

T A B L E 1

COMPOUNDS	HSV-1 (WAL) Clinical score on days					HSV-2 (333)				
	7	8	9	10	11	7	8	9	10	11
Placebo	2	2	2	2	2	3	3	3	2R	2R
Acyclovir	2	1	2	1	1	-	-	-	-	-
A_4	1	-	-	1	-	-	1	-	-	-
A_7	-	1	-	1	-	-	1	-	-	-
A_8	-	-	1	-	-	1	-	-	-	-
B_5	-	-	1	-	-	-	-	-	-	-
B_8	1	-	-	-	-	-	-	-	-	-
B_{10}	-	-	1	-	-	-	-	-	-	-
B_{13}	-	-	-	-	-	-	1	-	-	-
B_{16}	-	1	-	-	-	-	-	1	1	-
B_{17}	-	1	-	1	-	-	-	-	-	-
B_{19}	-	1	1	-	-	-	-	-	-	-
B_{20} (OH)	-	-	1	-	-	-	1	-	-	-
B_{24}	-	-	-	-	-	-	1	-	1	-
B_{27}	-	1	-	-	-		-	-	-	-
B_{30}	-	-	1	-	-		-	1	-	-
B_{30} (OH)	-	1	-	-	-		-	-	-	-

The following symbols denote :

- same aspect as non infected subjects, 1 slight erythema,

2 erythema, 3 erythema + profuse exudate, R urine retention.

II Antiviral activity of the compounds of the invention on influenza A/Bangkok/79 virus infection of mice.

A group of Swiss A mice from a closed colony at the university of Sheffield aged 4-5 weeks and weighing approximately 15-20 gms, were divided into groups of 25. Groups were inoculated daily for 6 days, intraperitoneally with compounds under test in an 0.2 ml volume : all the compounds were dissolved in Phosphate Buffered Saline (PBS) containing 0.2 % carboxymethylcellulose and 0.2 % Tween 80. 'Tween' is a Trade Mark. Twenty four hours after this first drug administration all mice were inoculated intranasally with $10^{5.0}$ EID_{20} of influenza A virus in an 0.05 ml volume of PBS. Three mice from each group were killed at daily intervals for five days after viral inoculation : the lungs were removed, separately ground in PBS containing 2.0 % bovine serum albumin to give a 40 % suspension, centrifuged at 2000 r.p.m. for 10 mins, and the supernatent fluid titrated by the allantoin-on-shell (AOS) method for infectivity. On completion of the study at day 15, the remaining 10 animals in each group were killed and the lungs scored for consolidation. Preliminary assays have shown that preferred i.p. dose was, for the tested compounds, around 1 mg/kg so this figure was retained in the experiment.

Using the above experimental protocol, 15 groups of 25 mice were given each, one of the compounds of the invention by the intraperitoneal (i.p.) route at the concentration of 1.0 mg/kg in an 0.2 ml volume of phosphate buffered saline (PBS) containing 0.2 % carboxymethylcellulose and 0.2 % tween 80. A control group of mice were given buffer alone. The compounds were administered once a day for 6 days from 24 hours prior to infection with influenza A/Bangkok/79 virus.

Table 2, left hand part, shows the titres of virus present in the lungs from days 1 - 5 following virus infection. For untreated mice virus titres increased to a

maximum of $10^{2.5}$ - $10^{2.9}$ $EBID_{50}$/ml on days 2 and 3, post-inoculation ; after this time, the titres declined, but at day 5 the mean titre of virus present in the lung was $10^{1.8}$ $EBID_{50}$/ml.

The degree of lung consolidation following infection of mice with influenza virus A/Bangkok/79 was measured : the lungs from each animal were graded 1 (25 % consolidation), 2 (25 - 50 % consolidation), 3 (50 - 75 % consolidation) and 4 (total consolidation) ; and the mean score of each group of animals is shown in Table 2, right hand part. For control mice the lung consolidation ranged from 2 - 3 with a mean value of 2.6.

Conclusion

The results show that the compounds of the invention at a concentration of 1.0 mg/kg given i.p. to mice significantly decreased the titres of virus in the lungs and the degree of lung consolidation compared to the results obtained for control animals.

A comparable experiment was conducted but with an oral administration of the compounds of the invention : similar results were obtained at doses, varying with the compound and comprised between 15 and 60 mg/kg.

PRESENTATION - POSOLOGY

The compounds of the invention may be presented under the form of creams or gels, lotions and sprays containing 1 to 5 % in weight of active ingredient, dissolved in diethyleneglycol monoethyl ether for topical applications. Usual posology in human therapy comprises 1 - 4 daily applications.

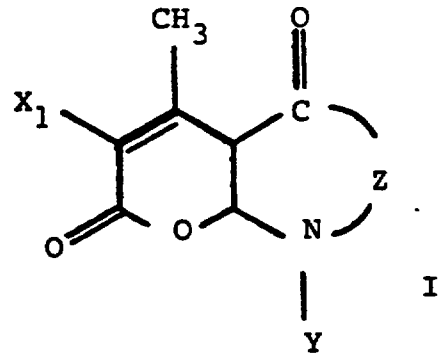
Presentations for oral administration comprise tablets or gelatine capsules in dose units containing 100 mg of active ingredient, associated with an appropriate carrier. Posology, per os, in human therapy is from 1 to 8 dose unit per diem.

TABLE 2

Days after infection					Compounds	Lung Consolidation	
Virus titre in lungs ($EBID_{50}$/ml) on day						Range	Mean
1	2	3	4	5	Control	2-3	2.6
< 0.5	< 0.5	< 0.5	< 0.5	< 0.5	A_4	1-3	1.4
< 0.5	< 0.5	< 0.5	< 0.5	< 0.5	A_7	1-3	1.4
< 0.5	0.6	< 0.5	< 0.5	< 0.5	A_8	1-2	1.4
< 0.5	0.5	< 0.5	< 0.5	< 0.5	B_5	1-3	1.6
< 0.5	0.5	< 0.5	< 0.5	< 0.5	B_8	1-2	1.5
< 0.5	< 0.5	0.5	< 0.5	< 0.5	B_{10}	1-2	1.2
< 0.5	0.5	0.5	< 0.5	< 0.5	B_{13}	1-3	1.3
< 0.5	0.6	< 0.5	< 0.5	< 0.5	B_{16}	1-2	1.6
< 0.5	0.5	0.5	< 0.5	< 0.5	B_{17}	1-2	1.6
< 0.5	< 0.5	0.5	< 0.5	< 0.5	B_{19}	1-2	1.2
< 0.5	< 0.5	< 0.5	< 0.5	< 0.5	B_{20}(OH)	1-2	1.2
< 0.5	0.5	0.6	< 0.5	< 0.5	B_{24}	1-3	1.1
< 0.5	0.6	< 0.5	< 0.5	< 0.5	B_{27}	1-3	1.3
< 0.5	0.6	< 0.5	< 0.5	< 0.5	B_{30}	1-2	1.6
< 0.5	< 0.5	< 0.5	< 0.5	< 0.5	B_{30}(OH)	1-3	1.1

CLAIMS:

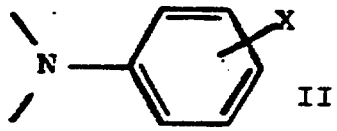
1. A pyrano derivative of the general formula I



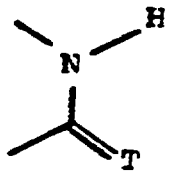
I

wherein X_1 represents a hydrogen, chlorine or bromine atom,

Z represents a residue of the general formula II or the general formula III



II



III

(X representing a hydrogen, chlorine or bromine atom and T representing an oxygen or sulphur atom), and

Y represents an arabinosyl, xylosyl or ribosyl residue, the residue Y having either a pyrane or furane configuration, being free or acetylated, and being bound to the nitrogen atom to give either the α or the β anomer.

2. 1-(β-D-2,3,5-tri-O-acetylribofuranosyl)-2-phenyl-4-methyl-pyrano-(2,3-c)-pyrazole-3,6-dione.

3. 1-(β-D-ribofuranosyl)-2-phenyl-4-methyl-pyrano-(2,3-c)-pyrazole-3,6-dione.

4. 1-(β-D-2,3,5-tri-O-acetylribofuranosyl)-2-phenyl-4-methyl-5-chloro-pyrano-(2,3-c)-pyrazole-3,6-dione.

* C L M S *

5. 1-(β-D-ribofuranosyl)-2-phenyl-4-methyl-5-chloro--pyrano-(2,3-c)-pyrazole-3,6-dione.

6. 1-(β-D-2,3,5-tri-O-acetylribofuranosyl)-2-(p-chlorophenyl)-4-methyl-5-chloro-pyrano-(2,3-c)-pyrazole-3,6--dione.

7. 1-(β-D-ribofuranosyl)-2-(p-chlorophenyl)-4-methyl-5--chloro-pyrano-(2,3-c)-pyrazole-3,6-dione.

8. 1-(β-D-2,3,4-tri-O-acetylxylopyranosyl)-2-phenyl-4--methyl-pyrano-(2,3-c)-pyrazole-3,6-dione.

9. 1-(β-D-xylopyranosyl)-2-phenyl-4-methyl-pyrano--(2,3-c)-pyrazole-3,6-dione.

10. 1-(β-D-2,3,5-tri-O-acetylxylofuranosyl)-2-phenyl-4--methyl-pyrano-(2,3-c)-pyrazole-3,6-dione.

11. 1-(β-D-xylofuranosyl)-2-phenyl-4-methyl-pyrano--(2,3-c)-pyrazole-3,6-dione.

12. 1-(β-D-2,3,5-tri-O-acetylxylofuranosyl)-2-(p-bromophenyl)-4-methyl-pyrano-(2,3-c)-pyrazole-3,6-dione

13. 1-(β-D-xylofuranosyl)-2-(p-bromophenyl)-4-methyl--pyrano-(2,3-c)-pyrazole-3,6-dione

14. 1-(β-D-2,3,4-tri-O-acetylxylopyranosyl)-2-phenyl--4-methyl-5-chloro-pyrano-(2,3-c)-pyrazole-3,6-dione.

15. 1-(β-D-xylopyranosyl)-2-phenyl-4-methyl-5-chloro--pyrano-(2,3-c)-pyrazole-3,6-dione.

16. 1-(D-2,3,5-tri-O-acetylarabinofuranosyl)-2-phenyl--4-methyl-pyrano-(2,3-c)-pyrazole-3,6-dione.

17. 1-(D-arabinofuranosyl)-2-phenyl-4-methyl-pyrano-(2,3-c)-pyrazole-3,6-dione.

18. 1-(D-2,3,5-tri-O-acetylarabinofuranosyl)-2-(p-chlorophenyl)-4-methyl-pyrano-(2,3-c)-pyrazole-3,6-dione.

19. 1-(D-arabinofuranosyl)-2-(p-chlorophenyl)-4-methyl-pyrano-(2,3-c)-pyrazole-3,6-dione.

20. 1-(α-D-2,3,5-tri-O-acetylarabinofuranosyl)-2-(p-chlorophenyl)-4-methyl-pyrano-(2,3-c)-pyrazole-3,6-dione.

21. 1-(α-D-arabinofuranosyl)-2-(p-chlorophenyl)-4-methyl-pyrano-(2,3-c)-pyrazole-3,6-dione.

22. 1-(β-D-2,3,5-tri-O-acetylarabinofuranosyl)-5-methyl-1,2,3,4-tetrahydro-7H-pyrano-(2,3-d)-pyrimidine-2,4,7-trione.

23. 1-(β-D-arabinofuranosyl)-5-methyl-1,2,3,4-tetrahydro-7H-pyrano-(2,3-d)-pyrimidine-2,4,7-trione.

24. 1-(β-D-2,3,5-tri-O-acetylarabinofuranosyl)-5-methyl-6-chloro-1,2,3,4-tetrahydro-7H-pyrano-(2,3-d)-pyrimidine-2,4,7-trione.

25. 1-(β-D-arabinofuranosyl)-5-methyl-6-chloro-1,2,3,4-tetrahydro-7H-pyrano-(2,3-d)-pyrimidine-2,4,7-trione.

26. 1-(β-D-2,3,5-tri-O-acetylarabinofuranosyl)-5-methyl-6-bromo-1,2,3,4-tetrahydro-7H-pyrano-(2,3-d)-pyrimidine-2,4,7-trione.

27. 1-(β-D-arabinofuranosyl)-5-methyl-6-bromo-1,2,3,4-tetrahydro-7H-pyrano-(2,3-d)-pyrimidine-2,4,7-trione.

28. 1-(β-D-2,3,4-tri-O-acetylarabinopyranosyl)-5-methyl--1,2,3,4-tetrahydro-7H-pyrano-(2,3-d)-pyrimidine-2,4,7--trione.

29. 1-(β-D-arabinopyranosyl)-5-methyl-1,2,3,4-tetrahydro--7H-pyrano-(2,3-d)-pyrimidine-2,4,7-trione.

30. 1-(D-2,3,5-tri-O-acetylarabinofuranosyl)-5-methyl--4,7-dioxo-1,2,3,4-tetrahydro-7H-pyrano-(2,3-d)-pyrimidine--2-thione.

31. 1-(D-arabinofuranosyl)-5-methyl-4,7-dioxo-1,2,3,4--tetrahydro-7H-pyrano-(2,3-d)-pyrimidine-2-thione.

32. 1-(α-D-2,3,5-tri-O-acetylarabinofuranosyl)-5-methyl--4,7-dioxo-1,2,3,4-tetrahydro-7H-pyrano-(2,3-d)-pyrimidine--2-thione.

33. 1-(α-D-arabinofuranosyl)-5-methyl-4,7-dioxo-1,2,3,4--tetrahydro-7H-pyrano-(2,3-d)-pyrimidine-2-thione.

34. 1-(α-D-2,3,5-tri-O-acetylarabinofuranosyl)-5-methyl--6-chloro-4,7-dioxo-1,2,3,4-tetrahydro-7H-pyrano-(2,3-d)--pyrimidine-2-thione.

35. 1-(α-D-arabinofuranosyl)-5-methyl-6-chloro-4,7-dioxo--1,2,3,4-tetrahydro-7H-pyrano-(2,3-d)-pyrimidine-2-thione.

36. 1-(α-D-2,3,4-tri-O-acetylarabinopyranosyl)-5-methyl--4,7-dioxo-1,2,3,4-tetrahydro-7H-pyrano-(2,3-d)-pyrimidine--2-thione.

37. 1-(α-D-arabinopyranosyl)-5-methyl-4,7-dioxo-1,2,3,4--tetrahydro-7H-pyrano-(2,3-d)-pyrimidine-2-thione.

38. 1-(β-D-2,3,4-tri-O-acetylarabinopyranosyl)-5-methyl--4,7-dioxo-1,2,3,4-tetrahydro-7H-pyrano-(2,3-d)-pyrimidine--2-thione.

39. 1-(β-D-arabinopyranosyl)-5-methyl-4,7-dioxo-1,2,3,4--tetrahydro-7H-pyrano-(2,3-d)-pyrimidine-2-thione.

40. 1-(D-2,3,4-tri-O-acetylarabinopyranosyl)-5-methyl--4,7-dioxo-1,2,3,4-tetrahydro-7H-pyrano-(2,3-d)-pyrimidine--2-thione.

41. 1-(D-arabinopyranosyl)-5-methyl-4,7-dioxo-1,2,3,4--tetrahydro-7H-pyrano-(2,3-d)-pyrimidine-2-thione.

42. 1-(D-2,3,4-tri-O-acetylarabinopyranosyl)-5-methyl--4,7-dioxo-6-chloro-1,2,3,4-tetrahydro-7H-pyrano-(2,3-d)--pyrimidine-2-thione.

43. 1-(D-arabinopyranosyl)-5-methyl-4,7-dioxo-6-chloro--1,2,3,4-tetrahydro-7H-pyrano-(2,3-d)-pyrimidine-2-thione.

44. 1-(α + β-D-2,3,4-tri-O-acetylarabinopyranosyl)-5--methyl-4,7-dioxo-1,2,3,4-tetrahydro-7H-pyrano-(2,3-d)--pyrimidine-2-thione.

45. 1-(α + β-D-arabinopyranosyl)-5-methyl-4,7-dioxo--1,2,3,4-tetrahydro-7H-pyrano-(2,3-d)-pyrimidine-2-thione.

46. 1-(β-D-2,3,5-tri-O-acetylribofuranosyl)-5-methyl--1,2,3,4-tetrahydro-7H-pyrano-(2,3-d)-pyrimidine-2,4,7--trione.

47. 1-(β-D-ribofuranosyl)-5-methyl-1,2,3,4-tetrahydro--7H-pyrano-(2,3-d)-pyrimidine-2,4,7-trione.

48. 1-(β-D-2,3,5-tri-O-acetylribofuranosyl)-5-methyl-6--chloro-1,2,3,4-tetrahydro-7H-pyrano-(2,3-d)-pyrimidine--2,4,7-trione.

49. 1-(β-D-ribofuranosyl)-5-methyl-6-chloro-1,2,3,4--tetrahydro-7H-pyrano-(2,3-d)-pyrimidine-2,4,7-trione.

50. 1-(β-D-2,3,5-tri-O-acetylribofuranosyl)-5-methyl-6--bromo-1,2,3,4-tetrahydro-7H-pyrano-(2,3-d)-pyrimidine--2,4,7-trione.

51. 1-(β-D-ribofuranosyl)-5-methyl-6-bromo-1,2,3,4--tetrahydro-7H-pyrano-(2,3-d)-pyrimidine-2,4,7-trione.

52. 1-(β-D-2,3,4-tri-O-acetylribopyranosyl)-5-methyl--1,2,3,4-tetrahydro-7H-pyrano-(2,3-d)-pyrimidine-2,4,7--trione.

53. 1-(β-D-ribopyranosyl)-5-methyl-1,2,3,4-tetrahydro-7H--pyrano-(2,3-d)-pyrimidine-2,4,7-trione.

54. 1-(β-D-2,3,4-tri-O-acetylribopyranosyl)-5-methyl-6--bromo-1,2,3,4-tetrahydro-7H-pyrano-(2,3-d)-pyrimidine--2,4,7-trione.

55. 1-(β-D-ribopyranosyl)-5-methyl-6-bromo-1,2,3,4--tetrahydro-7H-pyrano-(2,3-d)-pyrimidine-2,4,7-trione.

56. 1-(α-D-2,3,4-tri-O-acetylribopyranosyl)-5-methyl--1,2,3,4-tetrahydro-7H-pyrano-(2,3-d)-pyrimidine-2,4,7--trione.

57. 1-(α-D-ribopyranosyl)-5-methyl-1,2,3,4-tetrahydro-7H--pyrano-(2,3-d)-pyrimidine-2,4,7-trione.

58. 1-(D-2,3,5-tri-O-acetylribofuranosyl)-5-methyl-4,7--dioxo-1,2,3,4-tetrahydro-7H-pyrano-(2,3-d)-pyrimidine-2--thione.

59. 1-(D-ribofuranosyl)-5-methyl-4,7-dioxo-1,2,3,4--tetrahydro-7H-pyrano-(2,3-d)-pyrimidine-2-thione.

60. 1-(β-D-2,3,5-tri-O-acetylribofuranosyl)-5-methyl-4,7--dioxo-1,2,3,4-tetrahydro-7H-pyrano-(2,3-d)-pyrimidine-2--thione.

61. 1-(β-D-ribofuranosyl)-5-methyl-4,7-dioxo-1,2,3,4--tetrahydro-7H-pyrano-(2,3-d)-pyrimidine-2-thione.

62. 1-(α-D-2,3,5-tri-O-acetylribofuranosyl)-5-methyl-4,7--dioxo-1,2,3,4-tetrahydro-7H-pyrano-(2,3-d)-pyrimidine-2--thione.

63. 1-(α-D-ribofuranosyl)-5-methyl-4,7-dioxo-1,2,3,4--tetrahydro-7H-pyrano-(2,3-d)-pyrimidine-2-thione.

64. 1-(D-2,3,4-tri-O-acetylribopyranosyl)-5-methyl-4,7--dioxo-1,2,3,4-tetrahydro-7H-pyrano-(2,3-d)-pyrimidine-2--thione.

65. 1-(D-ribopyranosyl)-5-methyl-4,7-dioxo-1,2,3,4--tetrahydro-7H-pyrano-(2,3-d)-pyrimidine-2-thione.

66. 1-(α-D-2,3,4-tri-O-acetylribopyranosyl)-5-methyl-4,7--dioxo-1,2,3,4-tetrahydro-7H-pyrano-(2,3-d)-pyrimidine-2--thione.

67. 1-(α-D-ribopyranosyl)-5-methyl-4,7-dioxo-1,2,3,4--tetrahydro-7H-pyrano-(2,3-d)-pyrimidine-2-thione.

68. 1-(β-D-2,3,4-tri-O-acetylribopyranosyl)-5-methyl-4,7--dioxo-1,2,3,4-tetrahydro-7H-pyrano-(2,3-d)-pyrimidine-2--thione.

69. 1-(β-D-ribopyranosyl)-5-methyl-4,7-dioxo-1,2,3,4--tetrahydro-7H-pyrano-(2,3-d)-pyrimidine-2-thione.

70. 1-(β-D-2,3,5-tri-O-acetylxylofuranosyl)-5-methyl--1,2,3,4-tetrahydro-7H-pyrano-(2,3-d)-pyrimidine-2,4,7--trione.

71. 1-(β-D-xylofuranosyl)-5-methyl-1,2,3,4-tetrahydro-7H--pyrano-(2,3-d)-pyrimidine-2,4,7-trione.

72. 1-(β-D-2,3,5-tri-O-acetylxylofuranosyl)-5-methyl-6--chloro-1,2,3,4-tetrahydro-7H-pyrano-(2,3-d)-pyrimidine--2,4,7-trione.

73. 1-(β-D-xylofuranosyl)-5-methyl-6-chloro-1,2,3,4--tetrahydro-7H-pyrano-(2,3-d)-pyrimidine-2,4,7-trione.

74. 1-(β-D-2,3,4-tri-O-acetylxylopyranosyl)-5-methyl--1,2,3,4-tetrahydro-7H-pyrano-(2,3-d)-pyrimidine-2,4,7--trione.

75. 1-(β-D-xylopyranosyl)-5-methyl-1,2,3,4-tetrahydro-7H--pyrano-(2,3-d)-pyrimidine-2,4,7-trione.

76. 1-(α-D-2,3,5-tri-O-acetylxylofuranosyl)-5-methyl-4,7--dioxo-1,2,3,4-tetrahydro-7H-pyrano-(2,3-d)-pyrimidine-2--thione.

77. 1-(α-D-xylofuranosyl)-5-methyl-4,7-dioxo-1,2,3,4--tetrahydro-7H-pyrano-(2,3-d)-pyrimidine-2-thione.

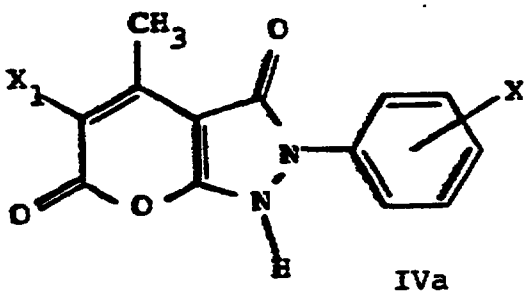
78. 1-(D-2,3,5-tri-O-acetylxylofuranosyl)-5-methyl-4,7--dioxo-1,2,3,4-tetrahydro-7H-pyrano-(2,3-d)-pyrimidine-2--thione.

79. 1-(D-xylofuranosyl)-5-methyl-4,7-dioxo-1,2,3,4--tetrahydro-7H-pyrano-(2,3-d)-pyrimidine-2-thione.

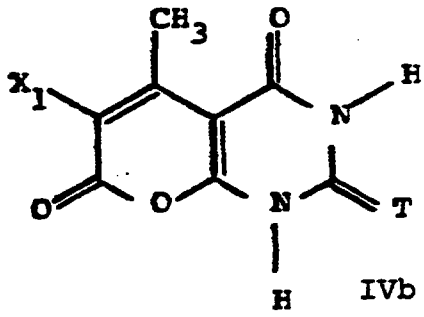
80. 1-(β-D-2,3,4-tri-O-acetylxylopyranosyl)-5-methyl-4,7--dioxo-1,2,3,4-tetrahydro-7H-pyrano-(2,3-d)-pyrimidine-2--thione.

81. 1-(β-D-xylopyranosyl)-5-methyl-4,7-dioxo-1,2,3,4--tetrahydro-7H-pyrano-(2,3-d)-pyrimidine-2-thione.

82. A method for the preparation of a pyrano derivative according to claim 1, the method comprising reacting one of the compounds IVa and IVb



IVa



IVb

wherein X_1, X and T are as defined in claim 1 with an acetylated arabinose, xylose or ribose in a solvent and optionally desacetylating the product.

83. A method according to claim 82 in which the reaction is conducted under nitrogen circulation in the presence of 1,1,1,3,3,3-hexamethyldisilazane, trimethylchlorosilazane and tin tetrachloride.

* C L M S *

84. A method according to claim 82 or claim 83 in which the solvent is acetonitrile.

85. A method according to any of claims 82 to 84 in which the reactants are used in stoichiometric proportions.

86. A method according to any of claims 82 to 85 in which the reaction is carried out at ambient temperature for from 12 to 24 hours.

87. A method for the preparation of a pyrano derivative according to claim 1, the method being substantially as described herein with reference to any of the Examples.

88. A pharmaceutical composition comprising a pyrano derivative according to claim 1 in admixture with a pharmaceutically acceptable diluent or carrier.