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Novel Acyclic Analogues of Pyrimidine Nucleosides: 1-Methoxy-2, 3-Dihydroxypropyl and 1-Methoxy-3-hydroxypropyl Derivatives

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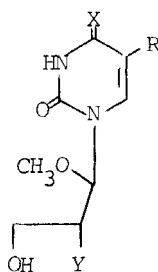
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NOVEL ACYCLIC ANALOGUES OF PYRIMIDINE NUCLEOSIDES: 1-METHOXY-2,3-DIHYDROXYPROPYL AND 1-METHOXY-3-HYDROXYPROPYL DERIVATIVES.

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Summary The preparation of a series of novel pyrimidine nucleoside analogues in which the N-1 ribosyl moiety is replaced by 1-methoxy-2,3-dihydroxypropyl and 1-methoxy-3-hydroxypropyl substituents is described.



	<u>R</u>	<u>X</u>	<u>Y</u>		<u>R</u>	<u>X</u>	<u>Y</u>		<u>R</u>	<u>X</u>	<u>Y</u>
<u>1</u>	H	O	OH	<u>7</u>	CF ₃	O	OH	<u>13</u>	H	O	H
<u>2</u>	CH ₃	O	OH	<u>8</u>	CN	O	OH	<u>14</u>	CH ₃	O	H
<u>3</u>	F	O	OH	<u>9</u>	NO ₂	O	OH	<u>15</u>	F	O	H
<u>4</u>	Cl	O	OH	<u>10</u>	CH=CH ₂	O	OH	<u>16</u>	Br	O	H
<u>5</u>	Br	O	OH	<u>11</u>	C≡CH	O	OH	<u>17</u>	I	O	H
<u>6</u>	I	O	OH	<u>12</u>	H	NH	OH	<u>18</u>	NO ₂	O	H
								<u>19</u>	H	NH	H

Synthesis of the uracil derivatives (1-11, 13-18) was achieved by reaction of the appropriate bis-trimethylsilylated pyrimidine base with either 2,3-diacetoxy-1,1-dimethoxypropane or 1,3-diacetoxy-1-methoxypropane in the presence of stannic chloride and subsequent removal of the O-acetyl groups with methanolic ammonia or sodium methoxide in methanol. Cytosine derivatives (12, 19) were prepared under similar conditions from the trimethylsilylated 4-N-acetyl base. Attempted deprotection of 1-(1-methoxy-2,3-diacetoxypropyl)-5-trifluoromethyluracil with methanolic ammonia gave the 5-cyanouracil 8 in high yield. With 1,3-diacetoxy-1-methoxypropane, 1,3-bis-substituted pyrimidines were sometimes obtained but, under the conditions used for deprotection of hydroxyl groups, these also yielded the required 1-monosubstituted pyrimidines. The ¹³C and ¹H nmr spectra of the 1-methoxy-2,3-dihydroxypropyl derivatives (1-12) indicated that in each case a mixture of diastereoisomers was obtained.

None of the acyclonucleosides was significantly active when tested against herpes simplex virus type 1 or influenza A virus in cell culture.