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SYNTHESES OF MODIFIED NUCLEOSIDES ANALOGS WITH ISOTHIOCYANATES

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Isocyanates and isothiocyanates are important reagents in heterocycles area. Recently, a review on isocyanate was published by Ozaki,[1] and a number of reports have been reported showing that isocyanates and isothiocyanates are useful reagents for cyclization of heterocycles.[2] Synthetic research on various nucleoside antibiotics, and nucleoside analogs, showdomycin, pyrazomycin, and coformycin have been synthesized.[3] Synthesis of glycosyl-2-thiothymine from glycosyl thiourea was reported by Ukita[4] and Naito.[5] Synthesis of thiothymine riboside and triazine riboside by using glycosyl isothiocyanate as starting materials was reported by Piskala and Sorm.[6] We now wish to report on the synthesis of various nucleoside analogs by means of isothiocyanate derivatives.

Reactions of glycosyl isothiocyanate (A) and gluconyl isothiocyanate (B) with nucleophilic reagents such as ammonia or amines gave glycosyl thioureide and N-glycosyl-N'-substituted thioureide, respectively. Treatment of B with amines, hydrazines afforded the corresponding thioureides and thiosemicarbazones.

Reaction of B with diazomethane gave 2-penta-O-acetyl-D-gluconyl)-4-thiooxazolone.

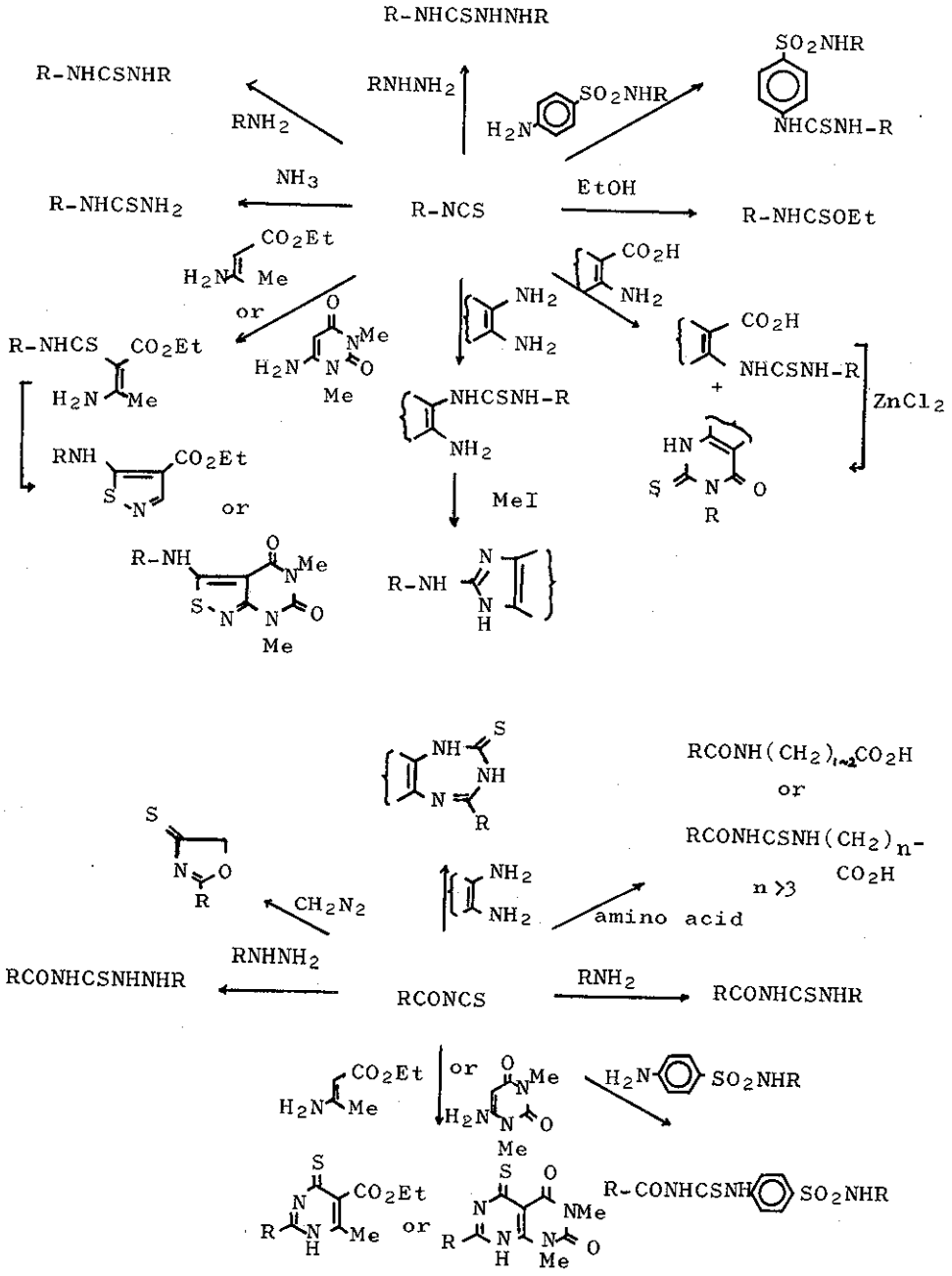
Further reactions of nucleoside synthetic reagents (A and B) with amino acids, enamines, and diamines are reported. Some compounds which have pharmacologically interest are also reported.

a. Reaction with Amino Acids

Synthesis of N-glycosyl-N'-carbomethoxyalkylthioureide from the reaction of acetylated D-glucopyranosyl isothiocyanate (A) with DL-alanine methyl ester was reported, but the yield was poor.[7] We carried out the reaction in benzene in the presence of pyridine, the corresponding thioureide derivatives were obtained in an excellent yield.

Reactions of B with amino acids (glycine, L-phenylalanine, β-alanine, γ-aminobutyric acid and ε-aminocaproic acid) afforded amides and/or thioureides. The formation mechanism of these products was discussed based on HSAB principle.

Reaction of isocyanate with aromatic amino acid has been reported to prepare heterocyclic compounds.[8] From our experiment, reaction of A with anthranilic acid in benzene under reflux gave thioureides and thioquinazoline glycosides at the ratio of about 1:1. In the presence of zinc chloride, the ratio changed to 3:8. Similarly, methyl 2-aminonicotinate reacted with A to form thioureides, but attempted cyclization failed to occur. On the other hand, 3-aminopyrazole-4-carboxylic acid reacted with A to yield the thioureide, and cyclization followed to form pyrazolopyrimidine glycosides.


R-NHCSNHNHR
R-NHCSNHR
RNHNH2
RNH2
SO2NHR
H2N
NHCSNH-R
NH3
R-NHCSNH2
R-NCS
EtOH
R-NHCSOEt
CO2Et
H2N
Me
or
R-NHCS
CO2Et
H2N
Me
RNH
CO2Et
S
N
or
R-NH
Me
Me
NH2
NH2
NHCSNH-R
MeI
CO2H
NH2
CO2H
NHCSNH-R
+
HN
S
N
O
R
ZnCl2
RCONH(CH2)1~2CO2H
or
RCONHCSNH(CH2)n-
CO2H
n>3
amino acid
RCONHCSNHNHR
RCONCS
RNH2
RCONHCSNHR
CH2N2
RNHNH2
or
R-CONHCSNH
SO2NHR

Reactions of A and B with 6-aminopenicillanic acid and ampicillin in the presence of triethylamine afforded the corresponding thioureides in a good yield. In comparison with antibacterial activities of ampicillin, D-gluconyl ampicillin was found to possess significant activity against Proteus vulgaris OX-19.

b. Reaction with Enamines

4-Thiopyrimidine derivatives were synthesized from reactions of ethyl 3-aminocrotonate with aroyl isothiocyanates[9] or methyl isothiocyanate[10] and reaction of enamines with ethoxycarbonyl isothiocyanate.[11] Application of this reaction to B afforded D-gluco-penta-O-acetoxypentylthiopyrimidine in a good yield. Similarly, the reaction of B with 6-amino-1,3-dimethyluracil gave D-gluconyl pyrimidopyrimidine in an excellent yield.[12]

The reaction between A and ethyl 3-aminocrotonate was carried out in acetonitrile or THF at room temperature, a mixture of thioureides and cyclized products was obtained in 2:1 ratio, and the former was easily cyclized by heating in an appropriate solvent. Reaction with 2-aminopyridine and A in THF afforded N-glycosyl-N'-pyridyl thioureide in a high yield and cyclized product was not obtained. On the other hand, reaction of A with 6-amino-1,3-dimethyluracil or 6-benzylamino-1,3-dimethyluracil followed by cyclization afforded isothiazolo[3,4-d]pyrimidine derivatives.

c. Reaction with Diamines

We have investigated the possibility that 1,3,5-triazepine-2-thione derivatives might be prepared from reaction of phenylacetyl isothiocyanate with diamines, o-phenylenediamine, diaminomaleonitrile, 5,6-diamino-1,3-dimethyluracil, and 4,5-diamino-2,6-dimercaptopyrimidine. The reaction of phenylacetyl isothiocyanate with diamines gave the corresponding 1-substituted 3-phenylacetyl thioureides in a good yield. Attempted cyclization of the thioureides under thermal condition was unsuccessful. Treatment of the thioureide with ammonium hydroxide gave 1-(6-amino-1,3-dimethyluracil)thioureide. On the other hand, the reaction of B with o-phenylenediamine and diaminopyrimidine in an appropriate solvent yielded D-gluconyl benzotriazepine-2-thione derivatives in an excellent yield.

Reactions of A with o-phenylenediamine, 5,6-diamino-1,3-dimethyluracil, and 2,3-diaminopyridine gave the corresponding thioureides in an excellent yield. Treatment of the thioureides with methyl iodide afforded N-glycosyl-2-aminobenzimidazole, amino-3-deazapurine, and aminotheophylline, through the cyclodesulfurization.

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