C-GLYCOSYL NUCLEOSIDES VII. SYNTHESES OF MODIFIED NUCLEOSIDES ANALOGS WITH ISOTHIOCYANATES+

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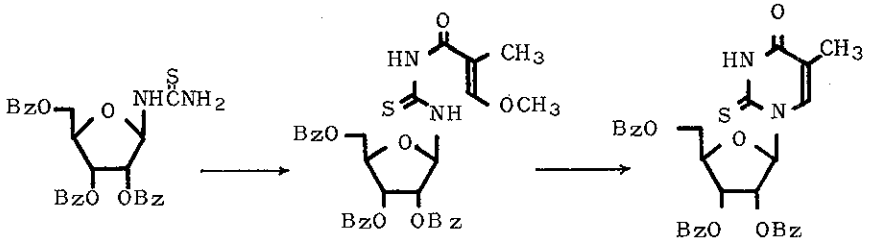
Syntheses of modified nucleoside analogs with glycosyl isothiocyanate and gluconyl isothiocyanate are reported. These reagents react with simple amines, hydrazines, amino acids, enamines, and diamines to yield modified nucleoside analogs. In case of enamines, isothiazolopyrimidines and pyrimidopyrimidines were obtained from the reaction with glycosyl and gluconyl isothiocyanate, respectively. Similarly, the reaction of diamines with glycosyl isothiocyanate and gluconyl isothiocyanate yield imidazole and triazepinethione derivatives, respectively.

+ This constitutes Part XIX of a series entitled "Studies on Heterocyclic Compounds."

Isocyanates and isothiocyanates are important reagents in heterocycles area. Recently, a review on isocyanates was published by Ozaki,[1] and a number of reports have been reported showing that isocyanates and isothiocyanates are useful reagents.[2] In this paper, we report the application of isothiocyanate reagents to the synthesis of modified nucleosides.

Synthetic research on various nucleoside antibiotics has been reported[3] and nucleoside analogs,[4] showdomycin,[5] pyrazomycin,[6] and coformycin[7] have been synthesized. Synthesis of glycosyl-2-thiothymine (3) from glycosyl thiourea was reported by Ukita[8] and Naito.[9] Treatment of 2,3,5-tri-O-benzoyl-β-D-ribofuranosyl thiourea (1), followed by condensation with 3-methoxy-2-methylacryloyl chloride and debenzoylation gives 1-β-D-ribofuranosyl-2-thiothymine (3).



1 2 3

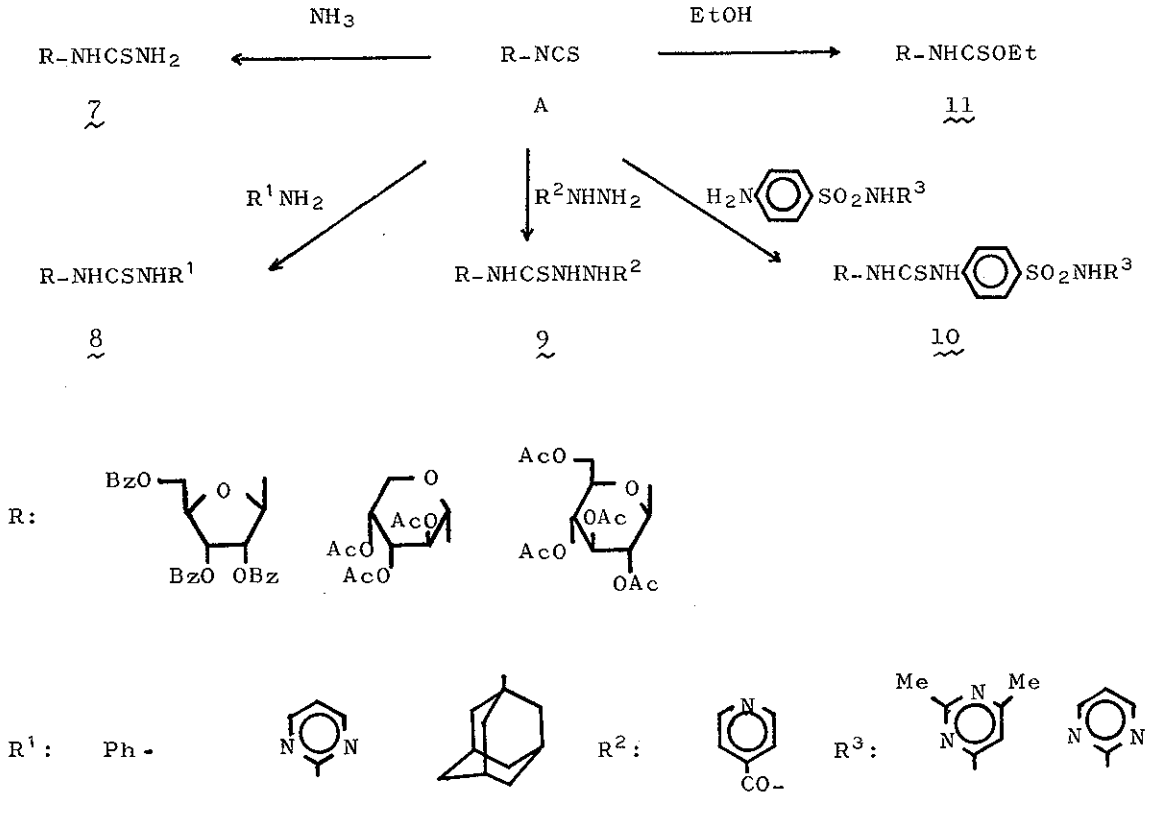
Treatment of isocyanate (4) with 2-methylisourea affords 1-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-4-methylisobiuret (5). Condensation of 5 with ethyl orthoformate results in formation of 1-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-4-methoxy-2-oxo-1,2-dihydro-1,3,5-triazine (6).[10] A review about glycosyl ureides was reported by Goodman.[11]

Ring formations of base moieties obtained by reactions between isothiocyanates and amino acids, enamines, or diamines are not yet investigated. We now wish to report the synthesis of various nucleoside analogs by means of isothiocyanate derivatives.

Reactions of glycosyl isothiocyanate (A) and gluconyl isothiocyanate (B) with nucleophilic reagents are summarized in Chart 1 and 2. Treatment of A with ammonia or amines yielded glycosyl thioureide and N-glycosyl-N'-subsituted thioureide, respectively. Treatment of A with hydrazines at refluxing or room temperature gave the corresponding thiosemicarbazone derivatives.

Gluconyl isothiocyanate (B) was prepared by a similar method to the preparation of A. 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 the isothiocyanate reagents (A and B) with amino acids, enamines, and diamines are reported. Some compounds which have pharmacological interest are also reported in this paper.


NH3
EtOH
R-NHCSNH2
R-NCS
R-NHCSOEt
7
A
11
R1NH2
R2NHNH2
H2N
SO2NHR3
R-NHCSNHR1
R-NHCSNHNHR2
R-NHCSNH
SO2NHR3
8
9
10
R:
BzO
O
BzO
OBz
AcO
AcO
AcO
AcO
AcO
OAc
AcO
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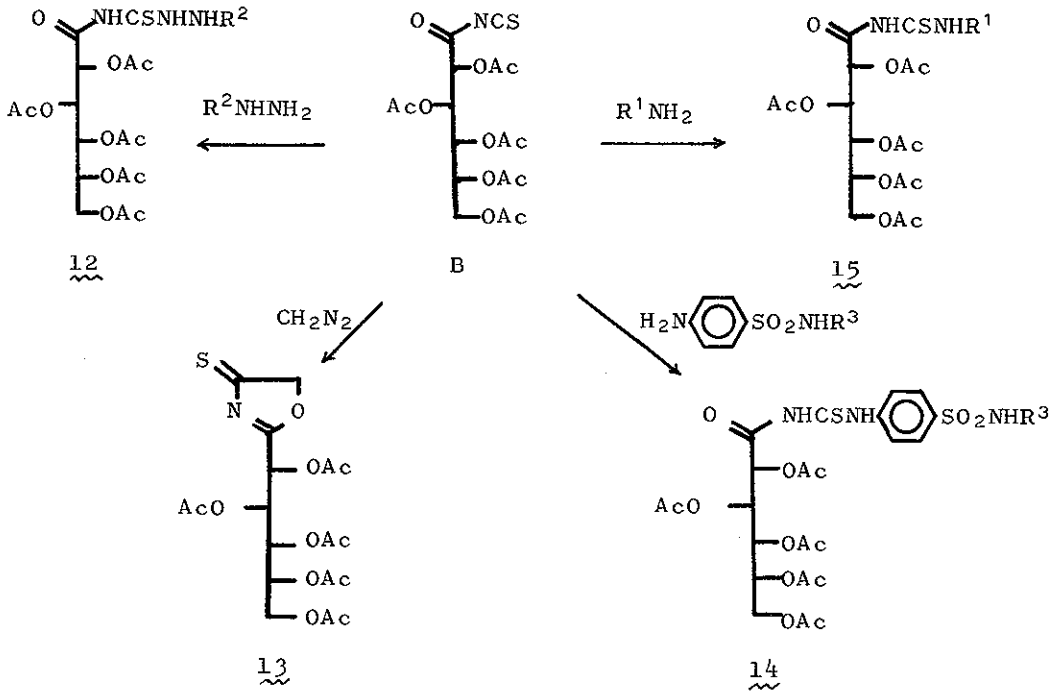
R1:
Ph-
N
N
R2:
N
CO-
R3:
Me
N
Me
N
N
N

Chart 1



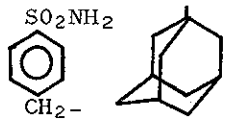
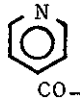
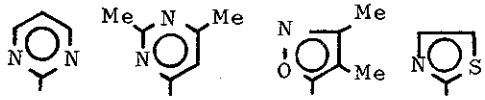
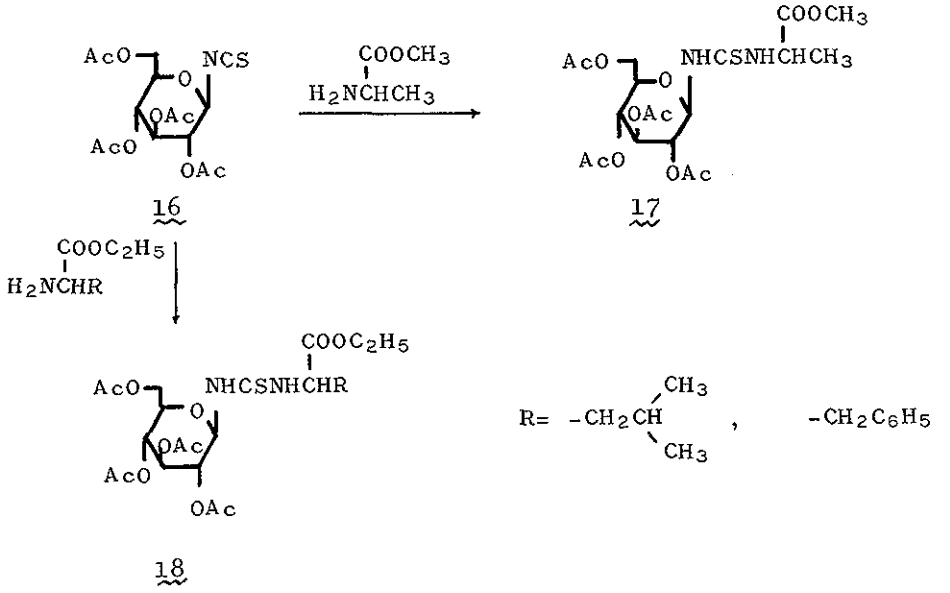
R¹: Ph-  R²:  R³: 

Chart 2

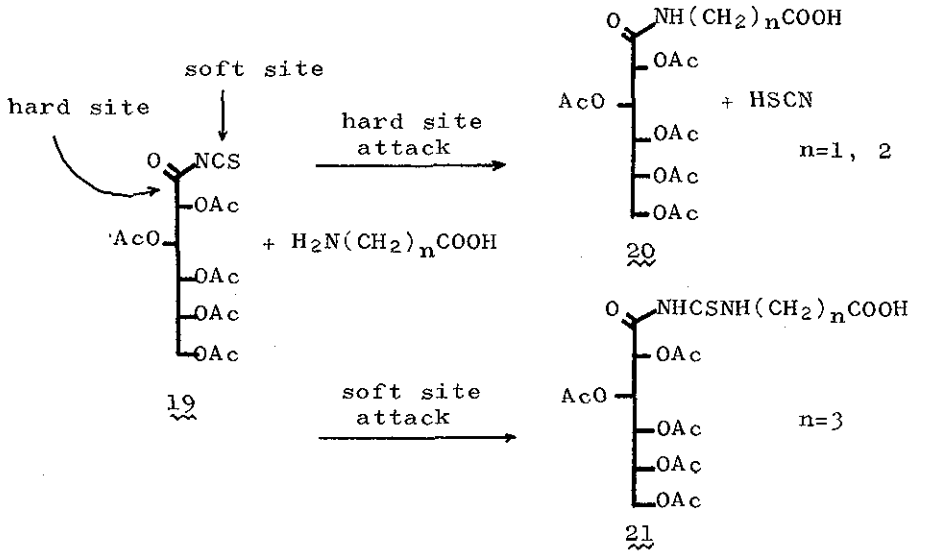
a. Reaction with Amino Acids

Micheel and co-workers[12,13] have reported that tetra-O-acetyl-β-D-glucopyranosyl isothiocyanate (16) was treated with DL-alanine methyl ester to yield N-glycosyl-N'-carbomethoxyalkylthioureide (17), but the yield was poor. We carried out the reaction in benzene solution in the presence of pyridine, and the corresponding thiourea derivatives (18) were obtained in excellent yields.



Reaction of 2,3,4,5,6-penta-O-acetyl-D-gluconyl isothiocyanate (19) with amino acids (glycine, L-phenylalanine, β-alanine, γ-aminobutyric acid, ε-aminocaproic acid) afforded amides (20) and/or thioureides (21). In case of glycine (n=1) and β-alanine, the nucleophilic reaction of 19 probably occurred at hard acidic site (hard-hard interaction), and

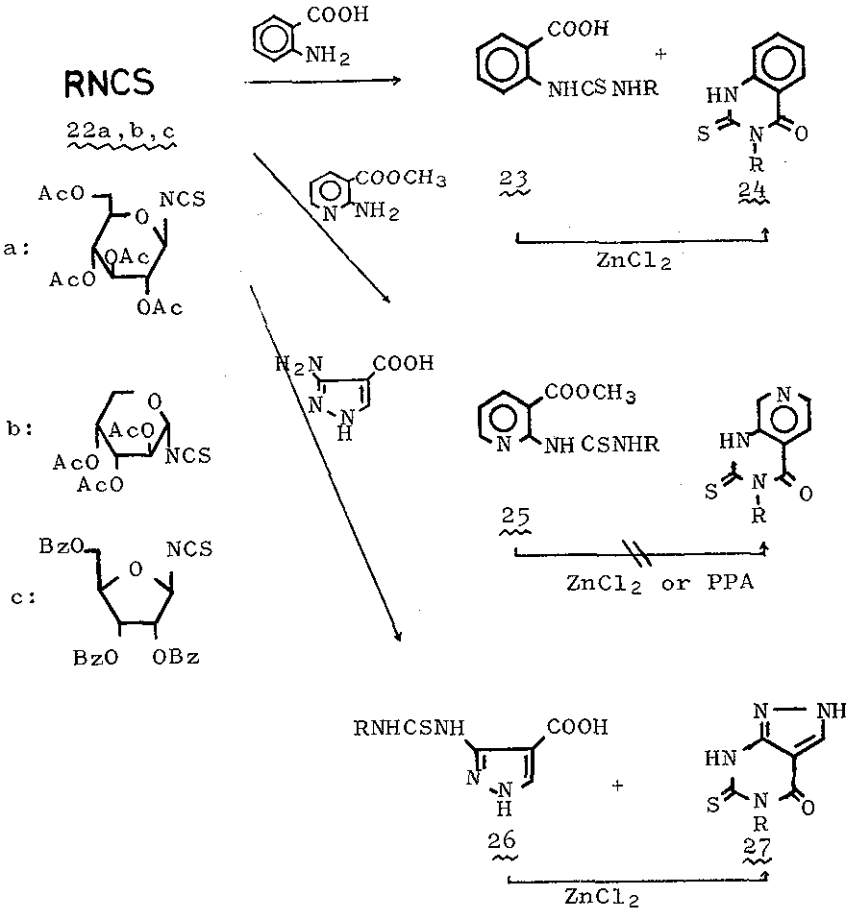
the amides (20) were obtained in a good yield under removal of HSCN.[14] On the other hand, in case of γ-aminobutyric acid (n=3) the reaction with 19 occurred at soft site (soft-soft interaction). A similar reaction using ε-aminocaproic acid (n=5) yielded a mixture of amide (20) and thoureide (21). In conclusion, the steric effects probably affected the HSAB principle.[15]



Reaction between ethoxycarbonyl isothiocyanate and 2-aminothiazole, 2-aminopyrimidine, 2- and 4-aminopyridine was discussed by Matsui et al.[16] by means of the HSAB principle.

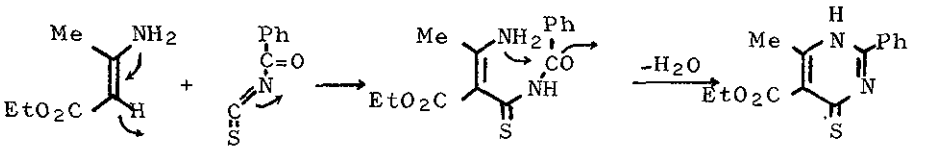
Reaction of isocyanate with aromatic amino acid has been reported to prepare heterocyclic compounds.[17] From our experiment, reaction of D-glycosyl isothiocyanate (22a,b,c) with anthranilic acid in benzene at refluxing temperature gave thioureides (23a,b,c) and thioquinazoline glycosides (24a,b,c) at the ratio of about 1:1. In the presence of zinc chloride,

the ratio changed to 3:8. Cyclization of 23a,b,c occurred with zinc chloride in refluxing toluene. Similarly, methyl 2-amino-nicotinate reacted with 22a,b,c to form thioureide (25), but attempted cyclization failed to occur. On the other hand, 3-aminopyrazole-4-carboxylic acid reacted with 22a,b,c to yield the thioureide (26) followed by cyclization to form 27.



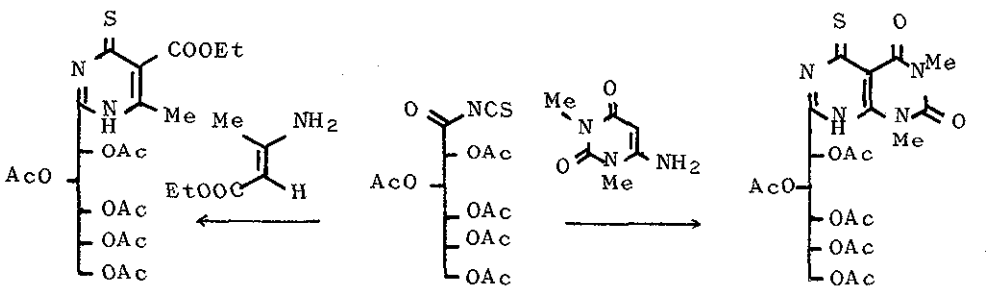
b. Reaction with Enamines

1,2-Disubstituted 4-thiopyrimidines (28) were obtained with reaction of aroyl isothiocyanates and ethyl 2-amino-crotonate.[18]

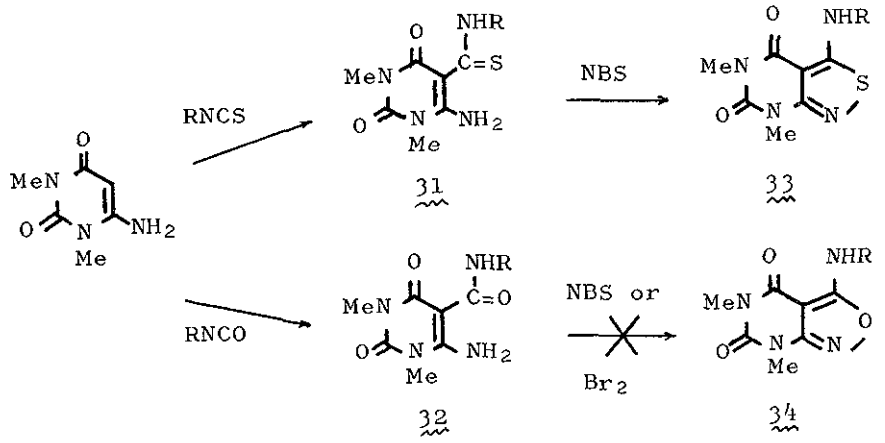


28

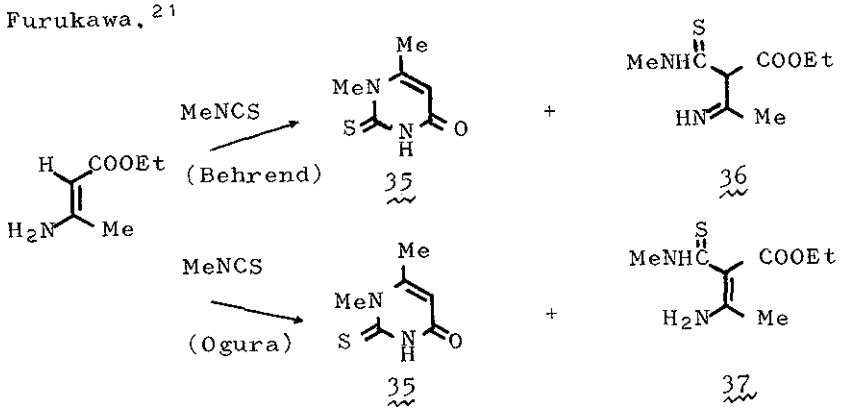
Application of this reaction to D-gluconyl isothiocyanate (19) afforded D-gluco-penta-O-acetoxypentylthiopyrimidine (29) in a good yield.[19] Reaction of 19 and 6-amino-1,3-dimethyluracil gave pyrimidopyrimidine (30) in a good yield.[19]



29 19 30

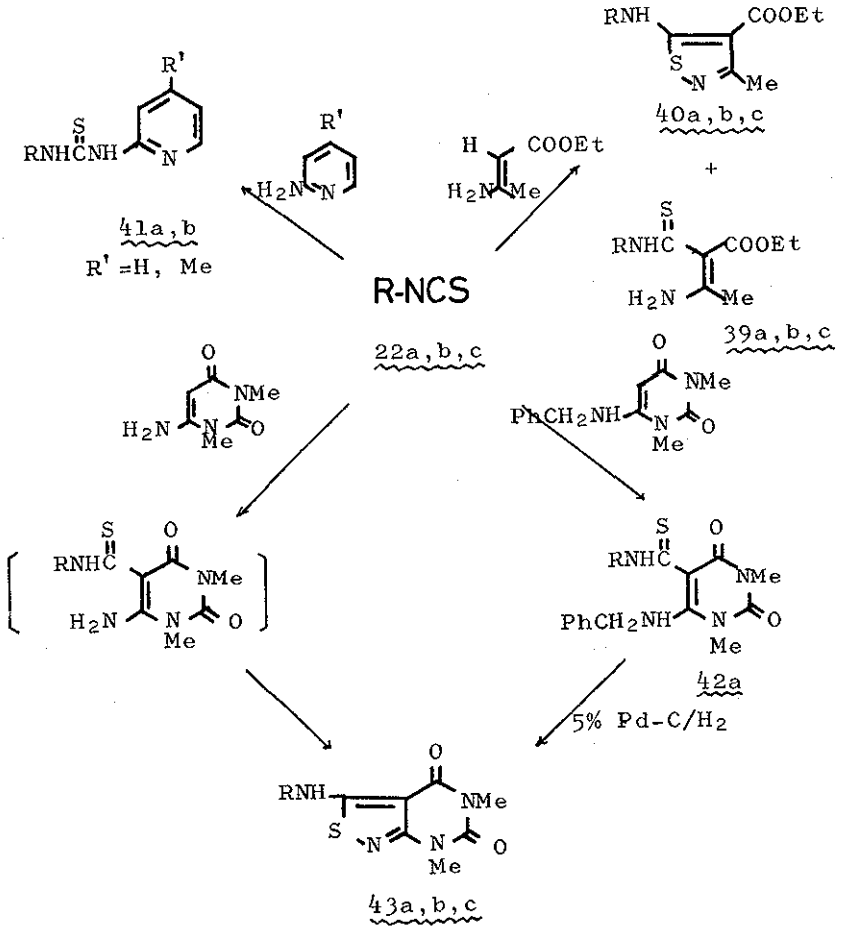


The reaction between alkyl or aryl iso(thio)cyanate and 6-amino-1,3-dimethyluracil gave the corresponding carbamoyluracil (31, 32). Oxidation of 31 with NBS at 0-5° for 45 min afforded N-substituted aminoisothiazolo[3,4-d]pyrimidines (33: R=Me, mp 180-183°; R=Ph, mp 220-223°) in a good yield, while, attempted cyclization of carbamoyluracil (32) with NBS or bromine failed to occur. Similar reaction was reported by Niess[20] and Furukawa.[21]



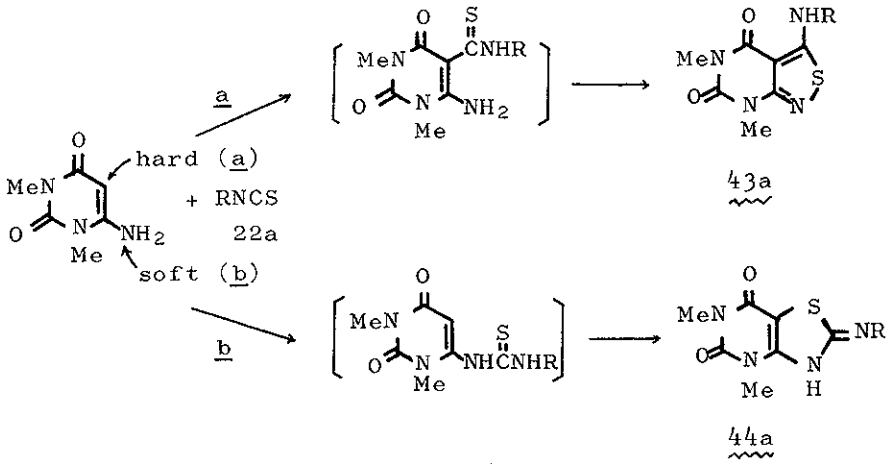
Behrend and his co-workers[22] reported that reaction of ethyl 3-aminocrotonate and methyl isothiocyanate without

solvent afforded dimethyluracil (35) and imino-type compound (36). In our experiments, the imino-type compound (36) was not obtained and a 32% yield of ethyl 3-amino-2-methylthiocarbamoylcrotonate (37; mp 83-85°) could be isolated by chromatography. Attempted preparation of thiopyrimidine nucleosides (38) by the above method was unsuccessful, and aminoisothiazole nucleosides (39) were obtained in a poor yield.

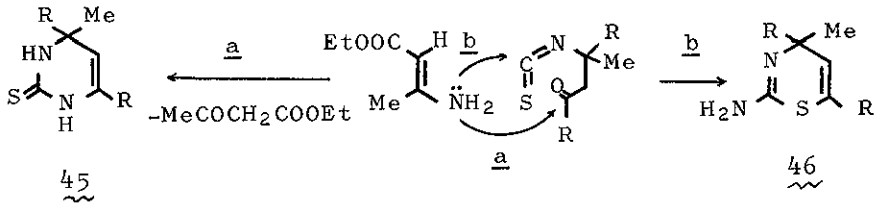


When the reaction between 22a,b,c and ethyl aminocrotonate was carried out in acetonitrile or THF at room temperature, a mixture of 39a,b,c and 40a,b,c was obtained in 2:1 ratio, and the former (39a,b,c) was easily cyclized to 40a,b,c by heating in an appropriate solvent.

Reaction of 22a,b with 2-aminopyridines in THF gave N-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-N'-(substituted pyridyl)thioureide (41a,b) in a high yield and cyclized product was not obtained. This result shows that 2-aminopyridines react as simple amine, and not as the enamine. On the other hand, reaction of D-glycosyl isothiocyanate (22a,b,c) with 6-amino-1,3-dimethyluracil or 6-benzylamino-1,3-dimethyluracil followed by cyclization afforded isothiazolo[3,4-d]pyrimidine derivatives (43a,b,c). This experiment shows that the isothiocyanate group attack to 5-position and not 6-amino group in DMF or acetonitrile solution.



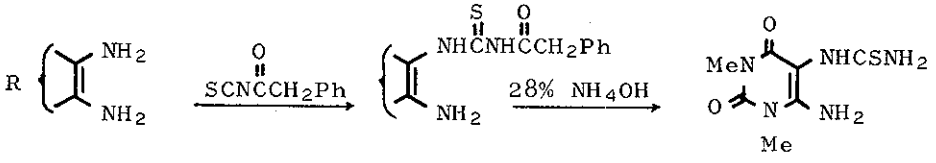
On the other hand, reaction of 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl isothiocyanate (22a) with 6-amino-1,3-dimethyluracil in THF at room temperature gave two products. The major product was aminoisothiazolopyrimidine glucoside (43a), and the minor product was iminothiazolopyrimidine glycoside (44a). According to HSAB principle, the reaction mechanism can possibly be explained in such a way that the isothiocyanate group of 22a attacked the hard site (C-5 position) to give the thiocarbamoyl uracil as an intermediate, followed by oxidative ring closure to afford 43a. While, the isothiocyanate group of 22a attacked the soft site (6-NH_2) to yield 44a in THF solution via thioureide intermediate. Both structures were confirmed by various physical data.



Singh and singh[23] reported the formation of 1,4-dihydro-1,4-pyrimidine-2-thiol (45) and 2-amino-1,3-thiazine (46) during the condensation of ethyl 3-aminocrotonate with β-keto isothiocyanate in non-polar aprotic solvent (hexane, benzene, toluene) and in polar solvent (ether, acetonitrile, butanol, ethyl acetate, chloroform), respectively.

c. Reaction with Diamines

We have investigated the possibility that 1,3,5-triazepine-2-thione derivatives might be prepared from the reaction of phenylacetyl isothiocyanate with diamines, o-phenylenediamine, diaminomaleonitrile (DAMN), 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 thioureide (47) in a good yield. Attempted cyclization of 47 under thermal condition in the presence of zinc chloride was unsuccessful. Treatment of 47 with ammonium hydroxide gave 1-(6-amino-1,3-dimethyluracil)thiourea (48).[24]



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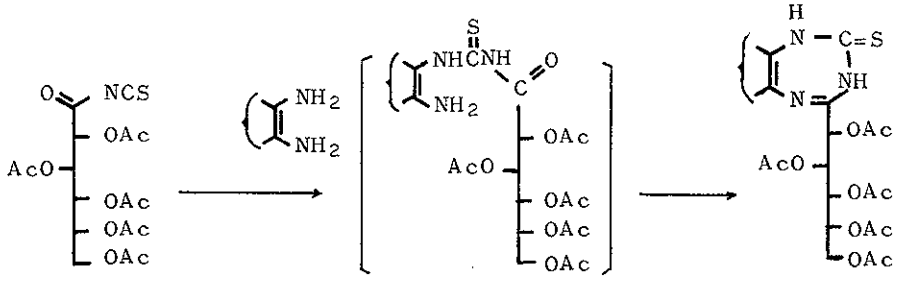
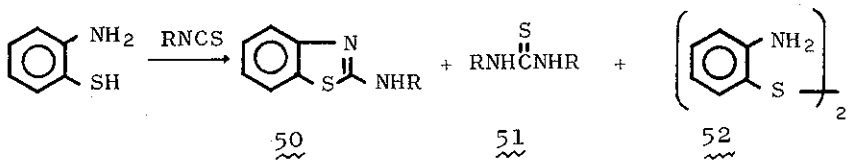
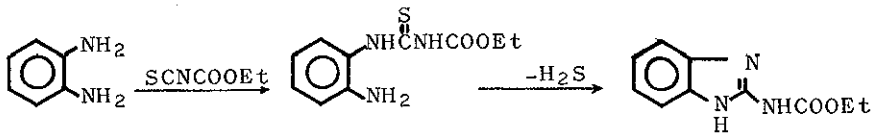


19 49

On the other hand, the reaction of 2,3,4,5,6-penta-O-acetyl-D-gluconyl isothiocyanate (19) with diamines was carried out in dry benzene, tetrahydrofuran, or dimethylformamide. When the mixture of 19 and o-phenylenediamine was refluxed for 30 min, benzotriazepine-2-thione derivatives (49) were obtained in an excellent yield. Similarly, treatment of 19 with diaminopyrimidine in THF or DMF at refluxing temperature gave pyrimidotriazepine-2-thione derivative (49). Although, we could not determine the presence of the ring opened intermediate.



50 51 52



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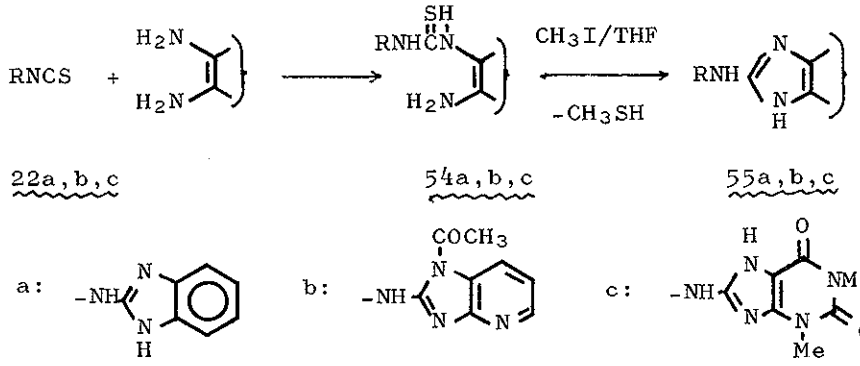
Reactions of 2-mercaptoaniline and isothiocyanate gave N-substituted 2-aminobenzothiazole (50), thioureide (51), and disulfide (52).[25] By a similar method the reaction of o-phenylenediamine with ethoxycarbonyl isothiocyanate in the presence of heavy metal ions afforded aminobenzimidazole derivatives (53).[26]



The nucleophilic reaction of D-glycosyl isothiocyanates (22a,b,c) with diamines, o-phenylenediamine, 5,6-diamino-1,3-dimethyluracil, and 2,3-diaminopyridine gave the corresponding thioureides (54a,b,c) in an excellent yield. Treatment of 54a with lead acetate followed by acetylation gave N-acetylaminobenzimidazole, and the desired product (55a) was obtained only in a poor yield. Treatment of 54a,b,c with methyl iodide afforded N-substituted 2-aminobenzimidazole (55a), amino-3-deazapurine (55b), and aminotheophylline (55c) nucleoside analogs, through the cyclodesulfurization.

Table I. Antibacterial Activity of Penicillin Derivatives (1)

[MIC (mcg/ml)]

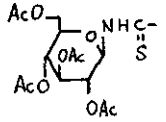
Compound	D-Gl-Pc.NEt$_3$	D-Ara-Pc.NEt$_3$	D-Gl-Am.NEt$_3$	D-Ara-Am.NEt$_3$	D-Ara-Am
Organism					
Staphylococcus aureus Rosenbach FDA-209-P	100	>100	100	3.12	3.12
Staphylococcus aureus no.26	>100	>100	>100	100	>100
Salmonella typhi O-901-W	>100	>100	>100	6.25	>100
Klebsiella pneumoniae	>100	>100	>100	50	>100
Escherichia coli K-12 IAM-1264	>100	>100	>100	50	>100
Pseudomonas aeruginosa IAM-1007	>800	>800	>800	>200	>100
Proteus vulgaris OX-19	>100	>100	>100	>100	25

Table I. Antibacterial Activity of Penicillin Derivatives (2)

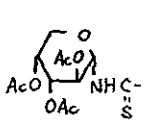
[MIC (mcg/ml)]

Compound	D-Gc-Pc	D-Gc-Am	D-Gc-Cm	Ampicillin
Organism				
Staphylococcus aureus Rosenbach FDA-209-P	>100	0.78	12.5	0.1
Staphylococcus aureus no.26	>100	>100	>100	100
Salmonella typhi O-901-W	>100	50	>100	0.39
Klebsiella pneumoniae	>100	>100	>100	1.56
Escherichia coli K-12 IAM-1264	>100	>100	>100	6.25
Pseudomonas aeruginosa IAM-1007	>100	>100	>100	>100
Proteus vulgaris OX-19	>100	1.56	>100	>100

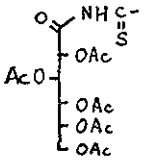
Abbreviation:



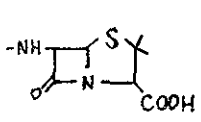
D-Gl



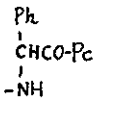
D-Ara



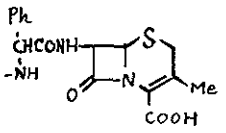
D-Gc



Pc



Am



Cm

d. Pharmacology

Condensation of numerous isothiocyanate with 6-aminopenicillanic acid (6-APA) has been carried out to afford triethylammonium 6-(substituted thioureido)penicillanate. Similarly, reactions of glycosyl isothiocyanate (22a,b,c) with 6-APA in the presence of triethylamine afforded the corresponding thioureides. Treatment of 6-APA or ampicillin with D-gluconyl isothiocyanate (19) in THF at room temperature provided thioureides in a good yield.

Antibacterial activities of these penicillin derivatives in comparison with ampicillin are shown in Table I. As seen from the results, penta-O-acetyl-D-gluconyl ampicillin was found to possess significant activity against Proteus vulgaris OX-19.

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