Synthesis of *N*-Glycosylthioureas, *N*-Glycosylrhodanines, and *N*-Glycosyl-2-aminothiazoles and Their Antimicrobial Activity

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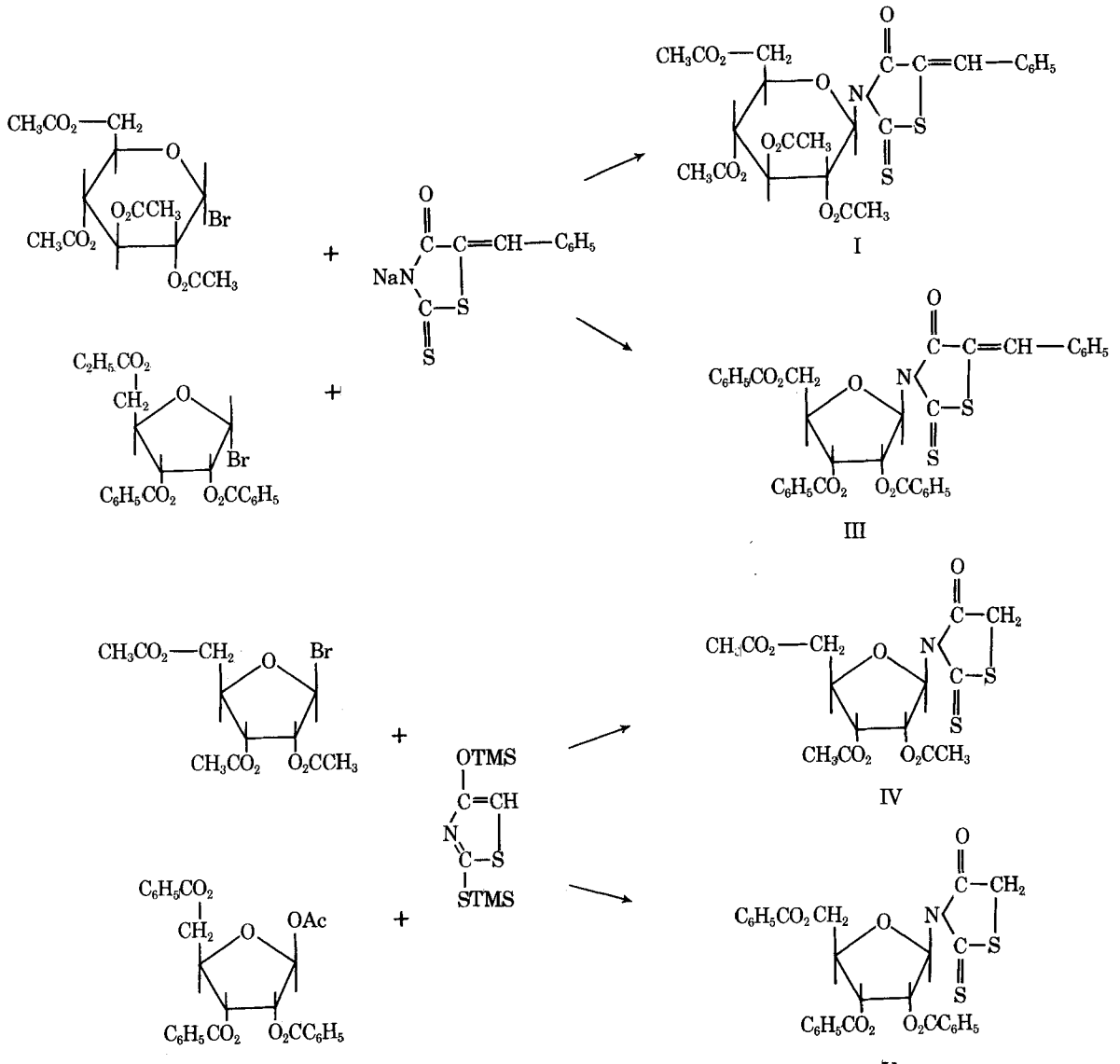
Abstract □ A method for obtaining *N*-β-D-glucopyranosylthioureas was found in the aminolysis of *N*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-5-aralkylidenerhodanines. Aminolysis of the triacetylated or tribenzoylated ribosylrhodanines generally did not give ribosylthioureas but resulted in glycosidic cleavage, although *N*-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)thioureas were obtained using morpholine and hydroxylamine. Ring closure of *N*-β-D-glucopyranosylthiourea with ethyl bromopyruvate gave ethyl 2-(*N*-β-D-glucopyranosyl)aminothiazole-4-carboxylate, and ammonolysis led to the corresponding 4-carboxamide. Antimicrobial screening against five microorganisms showed that *N*-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)rhodanine and the glucosylaminothiazole-4-carboxylate had the broadest spectrum of inhibitory activity, although the thioureas usually showed inhibition of some organisms.

Keyphrases □ *N*-Glycosylthioureas, rhodanines, and 2-aminothiazoles—synthesis, screened for antimicrobial activity □ Glucopyranosylthioureas—synthesis, screened for antimicrobial activity □ Antimicrobial activity—*N*-glycosylthioureas, *N*-glycosylrhodanines, and *N*-glycosyl-2-aminothiazoles

A method for obtaining *N*-β-D-glucopyranosylthiourea in good yield was previously reported (1). It involved the ammonolysis in methanol of *N*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-5-aralkylidenerhodanines (I), resulting in deacetylation, ring cleavage, and formation of the thiourea (II). Fischer (2) synthesized tetra-*O*-acetyl-



Scheme I—Glycosylation of rhodanine and 5-benzylidenerhodanine (TMS = trimethylsilyl).

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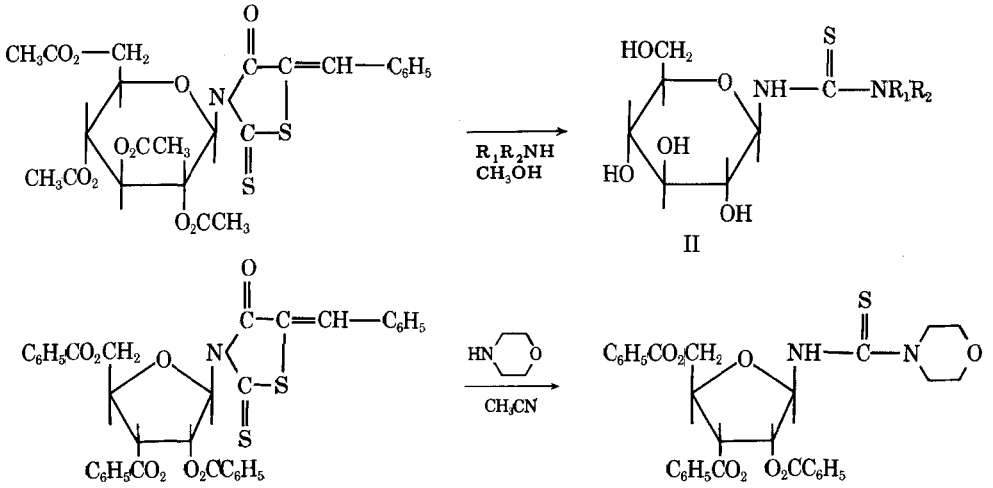


Scheme II—Aminolysis of glycosyl-5-benzylidenerhodanines.

glucopyranosylthiourea from tetra-*O*-acetylglucopyranosylisothiocyanate and ammonia and obtained the deacetylated product in good yield. Other investigators utilized the Fischer procedure to obtain deacetylated glucopyranosylthioureas but got only poor yield (3) or none at all (4). Fusion of glucose and thiourea resulted in a very low yield of glucopyranosylthiourea (5).

A logical extension of this reaction is the use of amines, in place of ammonia, to obtain *N*-substituted glucopyranosylthioureas. Such compounds have potential as antibacterial, antiviral, and anticancer agents. A number of thioureas have demonstrated activity as antiviral (6, 7) and as antibacterial–antifungal (8, 9) agents. Rhodanine and its derivatives have shown antibacterial (10) and antifungal (11) activities, as well as antiviral activity against Echovirus 12 (12) and activity as inhibitors of neuraminidases (13). To provide compounds with anticancer potential, attempts were made to prepare ribosyl derivatives of both rhodanine and the thioureas; ring closure of the glucosylthiourea to glucosylthiazoles also was performed.

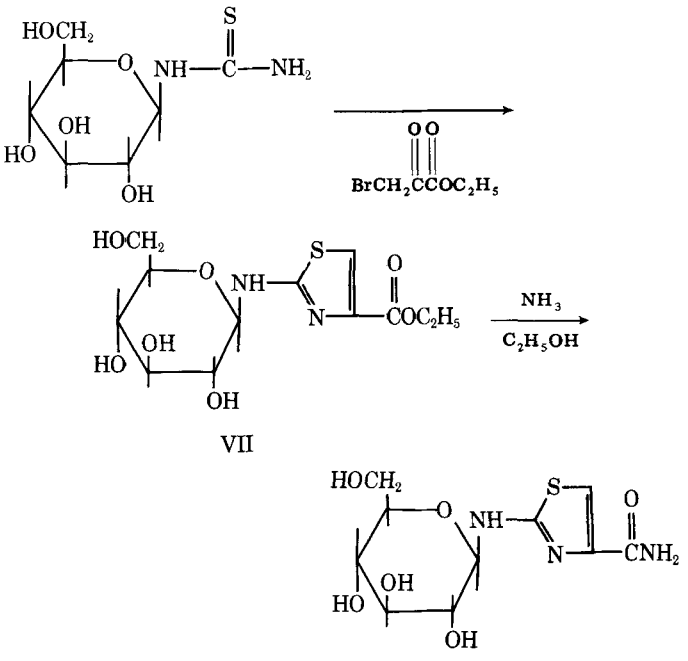
DISCUSSION

Chemistry—The glycosylrhodanines (I and III) were synthesized by glycosidation of 5-benzylidenerhodanine sodium salt with either 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide or 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide in acetone or acetonitrile. Yields of 65–82% were obtained. Another procedure, particularly useful for obtaining ribosylrhodanines, involved reaction of a silylated rhodanine with either 2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl bromide or 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose in the presence of stannic chloride. With unsubstituted rhodanine, 92 and 93% yields of the triacetyl (IV) and tribenzoyl (V) derivatives were realized, respectively; with the 5-benzylidene derivatives, 57 and 65% yields were obtained, respectively. Silylation was carried out using hexamethyldisilazane, chlorotrimethylsilane, and toluene. The glycosylation reactions are shown in Scheme I.

Aminolysis of *N*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-5-benzylidenerhodanine was carried out using an excess of various amines in methanol in a pressure bottle at room temperature for 1–4 days. Yields of 41–92% of the glucosylthioureas were obtained (Table I). The by-products, α-mercaptocinnamyl amides (13) and acetamides, were separated by column chromatography where fractional recrystallization was unsuccessful. The R_f values for the thioureas and the by-products are listed in Table II. Aminolysis of *N*-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-5-benzylidenerhodanine was attempted with several amines, using the same procedure. Ribosylthioureas were not obtained, apparently because of the instability of the glycosidic linkage. In the case of morpholine, however, *N*-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)morpholine-4-thiocarboxamide (VI) was isolated. When this compound was treated with methanolic ammonia, cleavage of the glycosidic linkage was again observed, and morpholine-4-thiocarboxamide was isolated. An *N*-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)thiourea was also isolated on reaction with hydroxylamine and triethylamine, but the ethoxythiourea was the product. Aminolysis of *N*-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-5-benzylidenerhodanine and *N*-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)rhodanine using several amines again resulted in glycosidic cleavage. Aminolyses are shown in Scheme II.

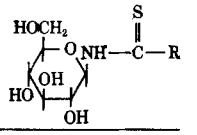
The *N*-β-D-glucopyranosylthiourea prepared from I (R = benzylidene) and methanolic ammonia was treated with ethyl bromopyruvate to give ethyl 2-(*N*-β-D-glucopyranosyl)aminothiazole-4-carboxylate (VII) in a 92% yield (Scheme III). Ammonolysis of this compound in methanol gave the corresponding 4-carboxamide (VIII).

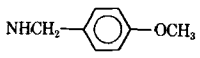
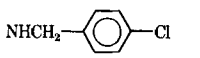
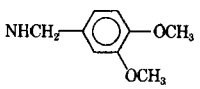
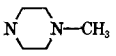
IR spectra of the glucosylthioureas revealed broad, hydrogen-bonded hydroxyl groups at 3300–3500 cm^{-1} and the appearance of NH at 1520–1570, C=S at 1060–1080, and a β-glycosidic linkage at 890–920 cm^{-1}. The characteristic acetylglucopyranosylrhodanine peaks at 1750 (acetyl C=O), 1675–1700 (rhodanine C=O), and 1240 (C=S) cm^{-1} were absent. The PMR spectra showed an absence of acetyl hydrogens in the 1.9–2.1-ppm region. A peak for the anomeric proton appeared at 5.07–5.40 ppm (J = 8–9 Hz), which also indicated a β-configuration (14). The NH



Scheme III—Synthesis of 2-(glucosyl)aminothiazoles.

Table I—Physical Properties of *N*-β-D-Glucopyranosylthioureas



R	Formula	Melting Point	Yield, %	$[\alpha]_D^{25}$ (Solvent)	Analysis, %	Calc.	Found
NH_2	$C_7H_{14}N_2O_5S$	207–209° dec.	87	−34.85° (water)	C	35.29	34.92
					H	5.92	6.20
					N	11.76	11.54
					S	13.46	13.38
$N(CH_3)_2$	$C_9H_{18}N_2O_5S \cdot \frac{1}{6} H_2O$	183–184° dec.	70	−4.40° (dimethylformamide)	C	40.14	40.34
					H	6.86	6.76
					N	10.40	9.94
					S	11.90	11.75
$N(C_2H_5)_2$	$C_{11}H_{22}N_2O_5S \cdot H_2O$	106–109° dec.	81	−11.0° (water)	C	42.29	42.57
					H	7.74	7.66
					N	8.96	8.87
					S	10.26	10.34
$NH(CH_2)_3CH_3$	$C_{11}H_{22}N_2O_5S \cdot \frac{2}{3} (CH_3)_2CO$	94–96° dec.	80	−15.4° (water)	C	46.87	46.40
					H	7.83	7.68
					N	8.41	8.42
					S	9.63	9.60
$NHCH_2CH{=}CH_2$	$C_{10}H_{18}N_2O_5S \cdot (CH_3)_2CO$	95–97° dec.	44	−25.8° (water)	C	46.41	45.95
					H	7.19	7.09
					N	8.33	8.18
					S	9.53	9.36
$NHCH_2C_6H_5$	$C_{14}H_{20}N_2O_5S \cdot (CH_3)_2CO$	97–100° dec.	64	−19.1° (water)	C	52.83	52.69
					H	6.78	6.56
					N	7.28	7.21
					S	8.30	8.10
$NHCH_2CH_2C_6H_5$	$C_{15}H_{22}N_2O_5S$	87–89° dec.	78	−19.0° (water)	C	52.62	52.35
					H	6.48	6.42
					N	8.18	7.90
					S	9.36	9.61
	$C_{15}H_{22}N_2O_6S$	82–85° dec.	73	−20.3° (water)	C	50.27	50.35
					H	6.19	6.14
					N	7.82	7.69
					S	8.96	9.13
	$C_{14}H_{19}ClN_2O_5S$	83–84° dec.	62	+6.2° (dimethylformamide)	C	46.35	46.31
					H	5.28	5.40
					Cl	9.77	9.63
					N	7.72	7.77
					S	8.84	8.88
	$C_{16}H_{24}N_2O_7S$	105° dec.	92	−1.3° (methanol)	C	49.47	50.00
					H	6.23	5.92
					N	7.21	7.06
					S	8.25	8.35
	$C_{10}H_{18}N_2O_5S \cdot (CH_3)_2CO$	95–97° dec.	44	−25.8° (water)	C	46.41	45.95
					H	7.19	7.09
					N	8.33	8.18
					S	9.53	9.36
	$C_{12}H_{23}N_3O_5S$	175–177° dec.	50	−12.2° (water)	C	44.84	44.94
					H	7.21	7.20
					N	13.07	12.97
					S	9.98	10.13
	$C_{11}H_{20}N_2O_6S \cdot H_2O$	179–181°	79	−8.2° (dimethylformamide)	C	40.48	40.54
					H	6.80	6.69
					N	8.56	8.58
					S	9.82	9.65
	$C_{11}H_{20}N_2O_5S_2$	148–151° dec.	40	+3.05° (dimethylformamide)	C	40.72	40.54
					H	6.21	6.38
					N	8.63	8.31
					S	19.77	19.44

glycoside peak appeared at 7.25–8.40 ppm (J = 8 Hz) and was replaceable with deuterium oxide.

The ribosylrhodanines and ribosylthioureas gave the expected IR absorptions, with benzoyl C=O stretching frequencies appearing at 1725–1730 cm^{-1} for the benzoylribose compounds and acetyl C=O stretching appearing at 1750 cm^{-1} for the acetyl derivatives. The C=S stretching vibration appeared at 1230–1270 cm^{-1} in the rhodanine ring and at 1110–1115 cm^{-1} in the thioureas. The C=O stretching vibration in the ribosylrhodanines was at 1720–1740 cm^{-1}, a higher frequency than that for the C=O of the 5-substituted rhodanines (1675–1700 cm^{-1}).

The most characteristic PMR peaks of the ribosylrhodanines were of the benzylidene CH or 5-CH_2 of the rhodanine ring, appearing as singlets at 7.67–7.78 or 3.90–4.19 ppm, respectively. The anomeric proton was seen as a doublet (J = 2–4 Hz) at 6.15–6.77 ppm. The anomeric proton of the ribosylthioureas was found as a broad singlet at 5.80–5.86 ppm, and the NH glycosidic proton appeared at 8.40–9.10 ppm. In general, the β-glycosidic linkages of heterocyclic ribosides have been observed (15) rather than the α-forms. The three protons on C-4 and C-5 of the ribose ring overlapped as a multiplet at 3.57–4.70 ppm.

The anomeric proton of the glucosylaminothiazoles was unclear in the PMR spectrum. The NH proton appeared at 8.20 ppm (J = 8 Hz), and the C-5 proton of the thiazole ring was seen as a singlet at 7.30–7.62 ppm. The methylene protons of the glucosyl moiety appeared as a multiplet at 3.50 ppm.

Antimicrobial Activity—Antimicrobial activities were observed by the agar plate screening method using *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Candida albicans*, and *Aspergillus niger*. These organisms represent a Gram-positive and two Gram-negative bacteria, a yeast, and a mold, respectively. Compounds showing some inhibitory activity were then measured by the serial tube dilution method previously described (1) to obtain minimal inhibitory concentrations (Table III).

Most prepared compounds showed inhibitory activity against *S. aureus*. All glucosylthioureas showing inhibitory activity were derived from primary amines, except those prepared from piperidine and dimethylamine, indicating that antimicrobial activity tends to decrease as the degree of substitution on the thiourea nitrogen increases.

A good percentage of the compounds were inhibitory to *C. albicans* and *A. niger*, *N*-β-D-glucopyranosyl-*N'*-butylthiourea being the most active against these organisms. Ethyl 2-(*N*-β-D-glucopyranosyl)aminothiazole-4-carboxylate showed inhibitory activity against four organisms, comparable to that from rhodanine, but not against *A. niger*. The glucosylthioureas derived from diethylamine, *N*-methylpiperazine, morpholine, and thiomorpholine did not show any antimicrobial activity. This result could be due to poor solubility, except in the case of diethylamine.

Among the ribosylrhodanines and ribosylthioureas, none of the benzoyl-protected compounds revealed any activity. *N*-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)rhodanine was active against all five organisms, however, possibly because of *in vivo* hydrolysis of the acetyl groups. The corresponding 5-benzylidene derivative was active against only *S. aureus* and *C. albicans*.

The best activity of the compounds reported here was shown by *N*-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)rhodanine, which had comparable activity to that of rhodanine itself. Nearly as broad antimicrobial activity was found with ethyl 2-(*N*-β-D-glucopyranosyl)aminothiazole-4-carboxylate, which showed comparable activity against four organisms and slightly better activity against *S. aureus* than rhodanine itself. The thioureas generally were inhibitory against two or three of the five organisms observed.

EXPERIMENTAL[1]

Glucopyranosylthioureas: *N*-β-D-Glucopyranosyl-*N'*-butylthiourea — *N*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-5-(3,4-dimethoxybenzylidene)rhodanine (1) (1 g, 0.0016 mole) was added to a solution of *n*-butylamine (1.08 g, 0.016 mole) in 50 ml of methanol in a pressure bottle. The reaction mixture was stirred at room temperature for 20 hr with the pressure bottle well closed. The mixture was filtered, and the filtrate was evaporated to dryness *in vacuo* below 30°.

The residue was dissolved in the minimum amount of acetone and stored at 5° for 18 hr. The white precipitate was filtered, washed with acetone, and dried *in vacuo* at room temperature, yielding 0.426 g (80%), mp 94–96° dec.; $[\alpha]_D^{25}$ −15.4° (*c*, 0.54); IR (KBr): 3500–3300 (OH, NH), 3100 (NH), 1550 (NH), 1080 (C=S), and 900 (β-form) cm^{-1}; NMR (dimethyl sulfoxide-d_6 + D_2O): δ 5.07 (d, H1, *J* = 8 Hz), 3.52 (m, 2H6), 3.17 (m, NCH_2), 1.40 (m, 4H, CH_2CH_2), and 0.96 (m, 3H, CH_3) ppm.

Anal.—Calc. for $C_{11}H_{22}N_2O_5S \cdot \frac{2}{3}(CH_3)_2CO$: C, 46.87; H, 7.83; N, 8.41; S, 9.63. Found: C, 46.40; H, 7.68; N, 8.42; S, 9.60.

Ethyl 2-(*N*-β-D-Glucopyranosyl)aminothiazole-4-carboxylate Hydrobromide—Ethyl bromopyruvate (8.99 g, 0.047 mole) was added to a suspension of *N*-β-D-glucopyranosylthiourea (10 g, 0.042 mole) in 120 ml of hot ethanol, and the mixture was heated for 30 min. The resulting solution was evaporated to dryness *in vacuo*, and the residue was crystallized from ethanol–acetone, filtered, and dried *in vacuo* at room temperature, yielding 16.03 g (91.9%) of white powder, mp 162–163° dec.; $[\alpha]_D^{25}$ −48.4° (*c*, 1.1); IR (KBr): 3500–3300 (OH, NH), 3160 (NH), 1725 (C=O), 1090 (β-ring), and 895 (β-form) cm^{-1}; NMR (dimethyl sulfoxide-d_6): δ 7.62 (s, H5), 6.09 (bs, OH, NH), 4.24 (q, CH_2), 3.51 (m, 2H6′), and 1.30 (t, CH_3) ppm.

Anal.—Calc. for $C_{12}H_{18}N_2O_7S \cdot HBr$: C, 34.71; H, 4.61; N, 6.75; S, 7.72. Found: C, 34.88; H, 4.71; N, 6.72; S, 7.92.

2- (*N*-β-D-Glucopyranosyl)aminothiazole-4-carboxamide—Ethyl 2-(*N*-β-D-glucopyranosyl)aminothiazole-4-carboxylate hydrobromide (4.15 g, 0.01 mole) was added to a solution of methanol (50 ml) saturated with ammonia at 0° in a pressure bottle. The mixture was stirred at room temperature for 48 hr in the stoppered bottle and then evaporated to dryness *in vacuo*. The residue was mixed with a small amount of ethyl acetate and chromatographed on a silica gel column (2.54 × 20 cm) using acetone as the first solvent (300 ml) and methanol as the second (300 ml).

The methanol effluent was concentrated to 75 ml, and ethyl acetate (500 ml) was added. The creamy-yellow precipitate was filtered and dried *in vacuo* at room temperature, yielding 2.77 g (76%), mp 96° dec.; $[\alpha]_D^{25}$ −22.2° (*c*, 1.4); IR (KBr): 3500–3300 (OH, NH), 1660 (NH), 1080 (β-ring), and 895 (β-form) cm^{-1}; NMR (dimethyl sulfoxide-d_6): δ 8.20 (d, NH, *J* = 8 Hz), 7.30 (s, H5), and 3.50 (m, 2H6′) ppm.

Anal.—Calc. for $C_{10}H_{15}N_3O_6S \cdot 2H_2O \cdot \frac{1}{2}C_2H_5OH$: C, 36.26; H, 6.09; N, 11.53; S, 8.80. Found: C, 36.41; H, 5.72; N, 11.92; S, 8.84.

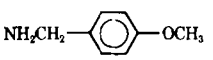
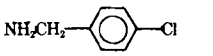
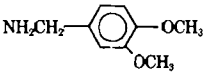
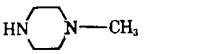
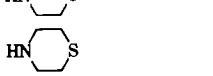
***N*-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)rhodanine**—To a suspension of rhodanine (1.34 g, 0.01 mole) in toluene (25 ml), hexamethyldisilazane (4 ml, 0.02 mole) and chlorotrimethylsilane (10 ml, 0.08 mole) were added. The mixture was refluxed 2 hr with exclusion of moisture. It was filtered, and the filtrate was evaporated to a syrup *in vacuo*. A solution of 2,3,5-tri-*O*-acetyl-D-ribofuranosyl bromide (16) (3.2 g, 0.01 mole) in acetonitrile was added at 0°, along with molecular sieves (8–12 mesh, 1 g) and stannic chloride (0.29 ml, 0.0025 mole) in acetonitrile (10 ml). The mixture was stirred at 0° for 3 hr and filtered, and the filtrate was evaporated to a syrup.

This syrup was dissolved in chloroform (50 ml) and filtered. The chloroform solution was washed with 10% potassium iodide solution (50 ml) and water (50 ml). The resulting solution was dried (sodium sulfate), evaporated to a thin syrup, and dried below 25° *in vacuo*, yielding 3.61 g (92%) of amorphous material; $[\alpha]_D^{25}$ +34.9° (*c*, 1.86, chloroform); IR (KBr): 1750 (C=O), 1380 (ring CH_2), 1240–1220 (C=S), and 890 (β-form) cm^{-1}; NMR (chloroform-d_1): δ 6.37 (d, H1′, *J* = 3.5 Hz), 5.80 (m, H2′), 5.45 (m, H3′), 4.30 (m, 3H4′,5′), 3.95 (s, 2H5), and 2.15 (9H, s, $3CH_3$) ppm.

Anal.—Calc. for $C_{14}H_{17}NO_8S_2$: C, 42.96; H, 4.38; N, 3.58; S, 16.38. Found: C, 42.76; H, 4.43; N, 3.71; S, 16.08.

***N*-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)-5-benzylidenerhodanine**—A solution of 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose (3.18 g, 0.01 mole) in dry methylene chloride (20 ml) was added at −60° to dry methylene chloride (40 ml) saturated with dry hydrogen bromide. The mixture was protected from moisture and allowed to warm to room temperature. The solvent was removed *in vacuo* below 30°, and the residue was evaporated with dry toluene (20 ml).

Table II—R_f Values for Reactants and Products in the Synthesis of Glucosylthioureas[a]

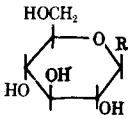
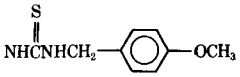
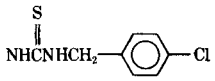
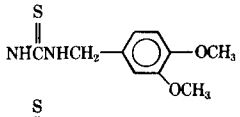
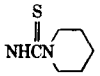
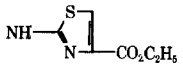
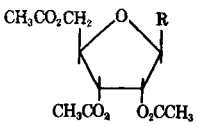
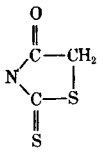
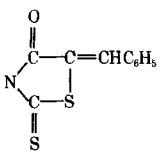
Amine	R_f Values: Rhodanine Derivative[b]	Thiourea Derivative	Cinnamamide	Acetamide
NH_3	0.72	0.41	0.67	0.56
	0.94[c]	0.10[c]	0.27[c]	0.83[c]
$NH(CH_3)_2$	0.91	0.50	0.71	—
$NH(C_2H_5)_2$	0.86	0.65		
$NH_2(CH_2)_3CH_3$	0.87	0.72	0.62	
$NH_2CH_2CH{=}CH_2$	0.88	0.71	0.56	
$NH_2CH_2C_6H_5$	0.87	0.76	0.53	0.33
$NH_2CH_2CH_2C_6H_5$	0.90	0.75	0.56	0.27
	0.81	0.65	0.49	0.31[d]
	0.91	0.67	0.83	
	0.82	0.54	0.74	
	0.85	0.66		
	0.84	0.15	0.41	0.31
	0.89	0.57		
	0.87	0.72	0.69	0.18[d]

[a] Solvent system: acetone–butanol–water (5:4:1); silica gel plate. [b] *N*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-5-benzylidenerhodanine. [c] Aluminum oxide plate. [d] R_f value of amine.

[1] Melting points were determined in capillaries with a Mel-Temp block and are uncorrected. IR absorption spectra were recorded with a Perkin-Elmer 457A grating spectrophotometer. NMR spectra were determined with a Varian T60 spectrometer with tetramethylsilane as the internal standard. Optical rotations were measured with a Perkin-Elmer 241MC polarimeter and a Carl Zeiss polarimeter. Elemental analyses were performed by Dr. F. B. Strauss, Oxford, England. TLC was carried out on Eastman silica gel plates with fluorescent indicator or alumina plates. For the glycosides, an efficient solvent system was *n*-butanol–acetone–water (4:5:1).

Rhodanine, the amines, 1,2,3,5-tetra-O-acetyl-β-D-ribofuranose, 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose, 1,1,1,3,3,3-hexamethyldisilazane, chlorotrimethylsilane, and stannic chloride were supplied by Aldrich Chemical Co. Silica gel and alumina for column chromatography were supplied by Fisher Scientific Co. Anhydrous ammonia, hydrogen bromide, and dimethylamine were obtained from Matheson Gas Products. The amines were purified by distilling with zinc powder prior to use. Solvents were dried with 3- or 4-Å molecular sieves.

Table III—Antimicrobial Activities

R	Minimum Inhibitory Concentration, *M*				
	S. aureus	*E. coli*	*P. aeruginosa*	*C. albicans*	*A. niger*
					
	10^{-4}	—	—	10^{-3}	10^{-2}
	10^{-2}	—	—	—	—
	10^{-3}	—	—	10^{-4}	10^{-3}
	10^{-4}	—	—	—	—
	—	10^{-2}	10^{-2}	—	—
	10^{-3}	—	—	—	—
	10^{-2}	—	—	10^{-3}	10^{-2}
	10^{-3}	10^{-2}	—	10^{-2}	—
	10^{-2}	—	—	10^{-2}	—
	10^{-2}	—	10^{-3}	—	—
	10^{-4}	10^{-3}	10^{-3}	10^{-3}	—
					
	10^{-3}	10^{-3}	10^{-2}	10^{-3}	10^{-3}
	10^{-3}	—	—	10^{-2}	—
Rhodanine	10^{-3}	10^{-3}	10^{-3}	10^{-3}	10^{-2}

The sodium salt of 5-benzylidenerhodanine was prepared by adding 5-benzylidenerhodanine (2.21 g, 0.01 mole) to a suspension of sodium hydride (0.24 g, 0.01 mole) in anhydrous ether (40 ml) (prepared from 57% sodium hydride oil suspension by removing mineral oil with hexane under nitrogen). The mixture was stirred at room temperature until no hydrogen was evolved. The solvent was removed by evaporation, and the residue was dried *in vacuo*.

To a suspension of the sodium salt of 5-benzylidenerhodanine (2.43 g, 0.01 mole) in acetonitrile (70 ml) was added a solution of 2,3,5-tri-*O*-acetyl-D-ribofuranosyl bromide (16) (3.39 g, 0.01 mole) in acetonitrile (30 ml), followed by 7 g of molecular sieves (8–12 mesh). The mixture was stirred at room temperature for 4 days. The insoluble material was filtered and washed with acetonitrile, and the combined filtrates were evaporated *in vacuo* below 30°. The residue was dissolved in chloroform (50 ml), and the solution was washed with 10% potassium iodide solution (20 ml) and water (40 ml), dried (sodium sulfate), and evaporated to a thin syrup.

The residue was dissolved in the minimum amount of methanol and chromatographed on an alumina column (neutral, 2.54 × 20 cm) with methanol as the eluant. The fast moving component was collected (150 ml) and evaporated to dryness. The residue was dissolved in the minimum amount of 95% ethyl alcohol and stored at −20°, and the crystals were collected and dried *in vacuo* at room temperature, yielding 2.76 g (57%),

mp 89–92°; $[\alpha]_D^{25}$ −78.5° (*c*, 2.42, chloroform); IR (KBr): 1750 (C=O), 1250–1220 (C=S), 900 (β-form), and 780 (=CH) cm^{-1}; NMR (chloroform-d_1): δ 7.67 (s, =CH), 7.45 (s, 5H, aromatic), 6.52 (d, H1′, J = 3 Hz), 5.95 (m, H2′), 5.65 (m, H3′), 4.35 (m, 3H4′,5′), and 2.15 (9H, s, $3CH_3$) ppm.

Anal.—Calc. for $C_{21}H_{21}NO_8S_2$: C, 52.60; H, 4.41; N, 2.92; S, 13.37. Found: C, 52.41; H, 4.63; N, 2.83; S, 13.23.

***N*-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)rhodanine**—To a suspension of rhodanine (0.64 g, 0.005 mole) in toluene (20 ml), hexamethyldisilazane (2 ml, 0.01 mole) and chlorotrimethylsilane (5 ml, 0.04 mole) were added. The mixture was stirred at 65° for 2 hr with exclusion of moisture. It was then filtered and evaporated to a thin syrup. A solution of 1-*O*-acetyl-2,3,4-tri-*O*-benzoyl-β-D-ribofuranose (2.52 g, 0.005 mole) in ethylene dichloride (10 ml) was added, and stannic chloride (0.44 ml, 0.0037 mole) in ethylene dichloride (10 ml) was added dropwise with stirring at 0°. The mixture was diluted with 15 ml of ethylene dichloride, and the resulting mixture was neutralized with saturated sodium bicarbonate solution (70 ml).

The emulsion was filtered over a layer of sand–diatomaceous earth, and the organic phase was separated, extracted with 10% potassium iodide solution (60 ml), washed with water (60 ml), and dried (sodium sulfate). The separated organic layer was evaporated to a semisolid below 30° and dried *in vacuo* at room temperature, yielding 2.69 g (93%); $[\alpha]_D^{25}$ −17.5° (*c*, 0.86, chloroform); IR (KBr): 1750–1720 (C=O), 1450 (ring CH_2), 1280–1240 (C=S), and 890 (β-form) cm^{-1}; NMR (chloroform-d_1): δ 8.00–7.10 (m, 15H, aromatic), 6.65 (d, H1′, J = 3 Hz), 6.28 (m, H2′), 6.00 (m, H3′), 4.68 (m, 3H4′,5′), and 3.90 (s, 2H5) ppm.

Anal.—Calc. for $C_{29}H_{23}N_2O_8S$: C, 60.32; H, 4.01; N, 2.42; S, 11.10. Found: C, 60.12; H, 4.24; N, 2.26; S, 10.89.

***N*-(2,3,5-Tri-*O*-benzoyl -β- D-ribofuranosyl)-5-benzylidenerhodanine**—To a solution of 5-benzylidenerhodanine (1.77 g, 0.08 mole) in acetonitrile (50 ml) was added 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide (17) (4.1 g, 0.008 mole), followed by 3.2 ml of 10% NaOH. The mixture was stirred at room temperature for 6 days and then was filtered and evaporated to a semisolid *in vacuo* below 30°. The residue was triturated with methanol (15 ml) to give a yellow precipitate, which was filtered and chromatographed on alumina (neutral) with methanol as the eluant. The first effluent (100 ml) was collected and evaporated. The resulting precipitate was filtered and dried *in vacuo* at room temperature, yielding 3.46 g (65%), mp 146–148°; $[\alpha]_D^{25}$ −128.6° (*c*, 1.0, tetrahydrofuran); IR (KBr): 1730 (C=O), 1270–1250 (C=S), and 770 (=CH) cm^{-1}; NMR (dimethyl sulfoxide-d_6): δ 8.10–7.50 (m, 20H, aromatic), 7.78 (s, =CH), 6.77 (d, H1′, J = 2 Hz), 6.28 (m, 2H2′,3′), and 4.70 (m, 3H4′,5′) ppm.

Anal.—Calc. for $C_{36}H_{27}NO_8S_2$: C, 64.95; H, 4.09; N, 2.10; S, 9.63. Found: C, 65.20; H, 4.48; N, 1.83; S, 9.82.

***N*-(2,3,5-Tri-*O*-benzoyl -β- D-ribofuranosyl)morpholine-4-thiocarboxamide**—To a suspension of *N*-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-5-benzylidenerhodanine (3.32 g, 0.005 mole) in acetonitrile (40 ml) were added 0.5 ml of water and then morpholine (4.38 g, 0.05 mole) in small portions with stirring over 10 min. The solution was stirred at room temperature for 2 days, and a small amount of precipitate was filtered. The filtrate was evaporated to a syrup and dried *in vacuo*. The residue was dissolved in the minimum amount of acetone and chromatographed on silica gel with acetone as the eluant. The fast moving band was collected (50 ml) and evaporated to dryness *in vacuo* at room temperature, yielding 2.86 g (96%), mp 75–77°; $[\alpha]_D^{25}$ −19.5° (*c*, 2.3, chloroform); IR (KBr): 1725 (C=O), 1115 (C=S), and 880 (β-form) cm^{-1}; NMR (dimethyl sulfoxide-d_6): δ 9.10 (bs, NH), 7.70 (m, 15H, aromatic), 5.86 (bs, H1′), 3.80 (m, 2H5′), 3.68 (m, 4H, CH_2OCH_2), and 3.54 (m, 4H, CH_2NCH_2) ppm.

Anal.—Calc. for $C_{31}H_{30}N_2O_8S$: C, 63.04; H, 5.12; N, 4.74; S, 5.43. Found: C, 63.12; H, 5.67; N, 4.89; S, 5.64.

***N*-(2,3,5-Tri-*O*-benzoyl -β- D-ribofuranosyl)-*N*′-ethoxythiourea**—A solution of *N*-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-5-benzylidenerhodanine (1.66 g, 0.0025 mole) in acetonitrile (40 ml) was treated with pulverized hydroxylamine hydrochloride (0.7 g, 0.01 mole), and triethylamine (1.4 ml, 0.01 mole) was added dropwise with stirring over 5 min. The mixture was stirred for 1 hr, the precipitate was filtered, and the filtrate was treated with ethyl acetate (100 ml) to give a precipitate. This precipitate was filtered, and the filtrate was extracted with 0.1 *N* HCl (40 ml), water (100 ml), and saturated sodium chloride solution (50 ml). It was dried (sodium sulfate) and evaporated, and the residue was chromatographed on alumina (neutral), using 2-propanol as the first solvent (200 ml) and methanol as the second (200 ml).

The methanol effluent was evaporated to 40 ml to give a yellow precipitate, which was filtered and dried at room temperature *in vacuo*, yielding 1.32 g (93%), mp 106° dec.; $[\alpha]_D^{25}$ −13.2° (*c*, 1.1, chloroform); IR (KBr): 1725 (C=O), 1270 (C—O), and 1120 (C=S) cm^{-1}; NMR (chloroform-d_1): δ 8.40 (bs, NH), 7.88–7.30 (m, 15H, aromatic), 5.80 (bs, H1′), 4.05 (q, CH_2), 3.95 (m, 2H5′), and 1.14 (t, CH_3) ppm.

Anal.—Calc. for $C_{29}H_{28}N_2O_8S$: C, 61.69; H, 5.00; N, 4.96; S, 5.68. Found: C, 61.88; H, 4.76; N, 4.88; S, 5.62.

Antimicrobial Activity—Tests were first carried out by the agar plate method, using 20–30 mg of each compound and measuring the zones of inhibition. The organisms used were *S. aureus* (ATCC 6538), *E. coli* (ATCC 11229), *P. aeruginosa* (ATCC 15442), *C. albicans* (ATCC 10259), and *A. niger* (ATCC 1015). Portions of four or five discrete colonies of the organisms were inoculated into 10.0 ml of a suitable broth medium and streaked on agar plates. Trypticase soy agar (BBL) was used for bacteria, and Sabouraud maltose agar (BBL) was used for the yeast and mold. Incubations were at 37° for 24–48 hr for the bacteria and at 25° for 48–72 hr for the yeast and mold.

Minimum inhibitory concentrations by the serial tube dilution procedure were carried out for the compounds found active by the agar plate procedure as previously described (1). Inhibitory concentrations were expressed in moles.

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