N-Glucopyranosyl-5-aralkylidenerhodanines: Synthesis and Antibacterial and Antiviral Activities

WILLIAM O. FOYE [x] and PHICHAI TOVIVICH [*]

Abstract □ A series of N-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-5-aralkylidenerhodanines was synthesized, and the acetyl groups were removed to give N-β-D-glucopyranosyl-5-aralkylidenerhodanines without cleavage of the rhodanine ring by means of acid hydrolysis. Alkaline hydrolysis with ammonia in methanol resulted in cleavage to N-glucosylthiourea, providing evidence for N-glycoside formation. A number of the rhodanine derivatives, especially those with nitro or chloro groups in the aromatic ring, showed antibacterial activity. N-β-D-Glucopyranosyl-5-(4-nitrobenzylidene)rhodanine showed antiviral activity by inhibition of viral RNA synthesis. Some effect on blood sugar levels also was observed with several rhodanines.

Keyphrases □ Rhodanine derivatives, various—synthesized, evaluated for antibacterial and antiviral activities □ Antibacterial activity—evaluated in various rhodanine derivatives □ Antiviral activity—evaluated in various rhodanine derivatives □ Structure–activity relationships—various rhodanine derivatives evaluated for antibacterial and antiviral activities

Rhodanine (2-thioxo-4-thiazolidinone) has shown some antiviral properties, specifically in echovirus 12 as a result of the inhibition of the synthesis of the viral protein coat (1). In various other viruses, hydrolysis products of rhodanine derivatives (α-mercaptoacrylic acids and their disulfides) act as inhibitors of neuraminidases (2), enzymes involved with the entry and release of virus particles in host cells (3). Rhodanine and its derivatives also have the ability to complex iron and other metals (4). This ability enables the rhodanines to inhibit the ribonucleoside diphosphate reductase enzyme system, which requires iron as a cofactor, and thereby inhibit the synthesis of DNA (5).

In addition to these possibilities as a basis for antiviral action, rhodanines possibly may act as analogs of purine bases in nucleic acid synthesis. In this event, glycosylated derivatives should be more effective inhibitors. The presence of a sugar moiety attached to the rhodanine ring may also provide rhodanines with less toxicity. This reduction in toxicity by formation of sugar derivatives was observed with some antitubercular agents (6).

Rhodanine and its derivatives also have exhibited antibacterial (7), antitubercular (8), antimalarial (9), antifungal (10), insecticidal (11), pesticidal (11), and antiparasitic (12) activities. Nitrodan [3-methyl-5-[(p-nitrophenyl)azo]rhodanine] has been used as an anthelmintic agent (13). No glycosylated derivative of rhodanine or its derivatives has been screened for antiviral activity or for any of the biological activities listed. The only mention in the literature of previous glycosylated rhodanines was made by Bognar and Wieniawski (14), who prepared the N-tetraacetylglucosyl derivatives of the 5-isopropylidene, 5-benzylidene, and 5-anisylidene derivatives of rhodanine. They were unable to remove the acetyl groups without decomposition, but they showed that the sugar moiety was attached to the nitrogen of the rhodanine ring.

Accordingly, a series of N-tetraacetyl-D-glucosyl derivatives of 5-ylidenerhodanines, prepared from both al-

I
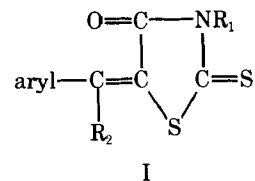
dehydes and ketones, was prepared for screening for antiviral and other biological activities. The N-tetraacetyl-D-glucosylrhodanines were obtained from reaction of the 5-ylidenerhodanines with acetobromo-D-glucose, and it was possible to remove the acetyl groups by acid hydrolysis without cleavage of the rhodanine ring. The compounds prepared can be represented by Structure I, where R_1 is tetraacetyl-D-glucosyl or D-glucosyl and R_2 is H or CH_3.

EXPERIMENTAL[1]

The following procedures are representative.

Condensation of Rhodanine with Aldehydes and Methyl Ketones—*Method A*—2,6-Dichlorobenzaldehyde (8.75 g, 0.05 mole) was added to a solution of rhodanine (6.66 g, 0.05 mole) in 75 ml of acetic acid, followed by the addition of 12.5 g of anhydrous sodium acetate. The reaction mixture was refluxed on a water bath for 1 hr, cooled to room temperature, and poured into 500 ml of water. After refrigeration, it was filtered; the precipitate was washed with water and dried *in vacuo* to give 11.8 g (81% yield) of crude product. Recrystallization from methanol gave yellow needles, mp 184–186°; IR (KBr): ν 3190 (NH), 1705 (C=O), and 1230 (C=S) cm^{-1}.

Anal.—Calc. for $C_{10}H_5Cl_2NOS_2$: C, 41.39; H, 1.74; N, 4.83; S, 22.10. Found: C, 41.50; H, 2.06; N, 4.93; S, 21.64.

Method B—2-Acetylthiophene (12.13 g, 0.096 mole) was added to rhodanine (12.8 g, 0.096 mole) in 100 ml of ethanol containing 7.5 ml of concentrated ammonium hydroxide and ammonium chloride (7.5 g in 15 ml of water). The mixture was refluxed for 1.5 hr and refrigerated overnight. Yellow crystals were isolated, washed with water, and dried in a vacuum oven. A second crop was obtained by adding the filtrate to 500 ml of water and chilling; the crude yellow product was recrystallized from acetone. The total yield was 6.5 g (28%), mp 230–233° [lit. (15) mp 218–221.5° dec.].

Condensation of 5-Arylalkylidenerhodanines with 2,3,4,6-Tetra-O-acetyl-β-D-glucose: N-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-5-p-Dimethylaminobenzylidene)rhodanine—5 - p - Dimethylaminobenzylidenerhodanine (5.28 g, 0.02 mole) was dissolved in 1250 ml of acetone and 250 ml of tetrahydrofuran with heating. The solution was cooled to room temperature, and 8.22 g (0.02 mole) of acetobromo-α-D-glucose was added followed by 8 ml of 10% sodium hydroxide solution. The mixture was stirred at room temperature for 68 hr and filtered. The filtrate was evaporated in a rotary evaporator at 30° under reduced pressure. A red syrup was obtained, which crystallized from methanol to give 7.8 g (66% yield) of orange solid, mp 197–201°; IR (KBr): ν 1750

O=C—NCH(CHOCOCH₃)₃ CHCH₂OCOCH₃ ... (structural diagram)

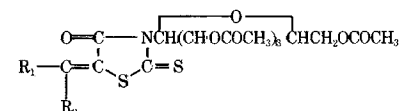$$O=C-NCH(CHOCOCH_3)_3 \; CHCH_2OCOCH_3$$
$$R_1-C=C-S-C=S$$
$$R_2$$

Table I—N-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-5-arylalkylidenerhodanines

| R_1	R_2	Formula	Melting Point	Yield, %	$[\alpha]_D^{20}$ (Solvent)	IR (KBr), cm^{-1}	Analysis, % Calc.	Found
C₆H₅	H	$C_{24}H_{25}NO_{10}S_2$	192–194° [a]	79	−169.0° (pyridine)	1750, 1225, 910	—	—
4-NO₂C₆H₄	H	$C_{24}H_{24}N_2O_{12}S_2$	222–224°	30	−195.0° (pyridine)	1750, 1240, 910	C 48.32	48.39
							H 4.06	4.10
							N 4.70	4.78
							S 10.75	10.49
2-NO₂C₆H₄	H	$C_{24}H_{24}N_2O_{12}S_2$	185–187°	65	—	1750, 1235, 900	C 48.32	48.26
							H 4.06	4.30
							N 4.70	4.57
							S 10.75	10.43
4-(CH₃)₂NC₆H₄	H	$C_{26}H_{30}N_2O_{10}S_2$	197–201°	66	−104.0° (tetrahydrofuran)	1750, 1225, 900	C 52.52	52.74
							H 5.08	5.08
							N 4.71	4.75
							S 10.78	10.91
3,4-[CH₂(O)₂]C₆H₃	H	$C_{25}H_{25}NO_{12}S_2$	195–196°	78	−159.3° (pyridine)	1750, 1225, 900	C 50.42	50.76
							H 4.23	4.35
							N 2.35	2.53
							S 10.77	10.96
3,4-(CH₃O)₂C₆H₃	H	$C_{26}H_{29}NO_{12}S_2$	186–189°	57	−273.0° (tetrahydrofuran)	1750, 1225, 900	C 51.06	50.95
							H 4.75	4.99
							N 2.29	2.31
							S 10.47	10.16
2,5-(CH₃O)₂C₆H₃	H	$C_{26}H_{29}NO_{12}S_2$	207–211°	64	−137.7° (tetrahydrofuran)	1750, 1225, 900	C 51.06	50.79
							H 4.75	4.78
							N 2.29	2.31
							S 10.47	10.22
2-CH₃OC₆H₄	H	$C_{25}H_{27}NO_{11}S_2$	189–190°	30	−150.0° (pyridine)	1750, 1230, 900	C 51.62	51.67
							H 4.68	4.90
							N 2.41	2.35
							S 11.03	11.16
2,6-Cl₂C₆H₃	H	$C_{24}H_{23}Cl_2NO_{10}S_2$	78–81°	65	−52.0° (pyridine)	1750, 1230, 900	C 46.56	46.43
							H 3.74	4.00
							N 2.26	1.99
							S 10.34	10.03
4-ClC₆H₄	H	$C_{24}H_{24}ClNO_{10}S_2$	226–228°	85	−170.0° (pyridine)	1740, 1225, 900	C 49.19	49.56
							H 4.13	4.23
							N 2.39	2.27
							S 10.94	11.20
2-ClC₆H₄	H	$C_{24}H_{24}ClNO_{10}S_2$	200–202°	61	−146.3° (pyridine)	1750, 1225, 908	C 49.19	49.24
							H 4.13	4.47
							N 2.39	2.42
							S 10.94	10.89
(furyl)	H	$C_{22}H_{23}NO_{11}S_2$	189–193°	—	−200.0° (pyridine)	1750, 1225, 900	C 48.79	48.39
							H 4.28	4.62
							N 2.59	2.72
							S 11.84	12.03
(furyl)	CH₃	$C_{23}H_{25}NO_{11}S_3$	118–122°	56	−173.5° (tetrahydrofuran)	1750, 1225, 910	C 49.72	49.30
							H 4.54	4.74
							N 2.52	2.54
							S 11.54	11.25
(thienyl)	H	$C_{22}H_{23}NO_{10}S_3$	217–220°	60	−175.5° (pyridine)	1750, 1240, 908	C 47.39	46.95
							H 4.16	4.46
							N 2.51	2.58
							S 17.25	16.93
(thienyl)	CH₃	$C_{23}H_{25}NO_{10}S_3$	187–190°	54	−78.0° (pyridine)	1750, 1225, 900	C 48.33	48.38
							H 4.41	4.70
							N 2.45	2.42
							S 16.83	16.31
(methylthienyl)	H	$C_{23}H_{25}NO_{10}S_3$	192–193°	91	−210.0° (pyridine)	1750, 1225, 900	C 48.34	48.50
							H 4.38	4.61
							N 2.45	2.39
							S 16.81	16.36
(bromothienyl)	H	$C_{22}H_{22}BrNO_{10}S_3$	182–187°	94	−130.0° (pyridine)	1730, 1215, 900	C 41.51	41.62
							H 3.46	3.30
							N 2.21	2.24
							S 15.09	14.90
(pyridyl)	H	$C_{23}H_{24}N_2O_{10}S_2$	177–181°	78	−180.0° (pyridine)	1748, 1230, 903	C 50.00	50.06
							H 4.35	4.46
							N 5.01	5.14
							S 11.59	11.47
(pyridyl)	CH₃	$C_{24}H_{26}N_2O_{10}S_2$	184–187°	72	−143.0° (tetrahydrofuran)	1750, 1225, 902	C 50.87	50.50
							H 4.62	4.72
							N 4.95	5.23
							S 11.32	11.52
(pyridyl)	H	$C_{23}H_{24}N_2O_{10}S_2$	191–193°	54	−195.0° (tetrahydrofuran)	1748, 1223, 902	C 50.00	49.61
							H 4.35	4.42
							N 5.01	5.24
							S 11.59	11.35

Table I—(Continued)

R₁	R₂	Formula	Melting Point	Yield, %	$[\alpha]_D^{20}$ (Solvent)	IR (KBr), cm⁻¹	Analysis, % Calc.	Found
[pyridyl-methyl]	CH₃	$C_{24}H_{26}N_2O_{10}S_2$	183–187°	37	−84.0° (dimethyl-formamide)	1750, 1235, 900	C 50.87	51.05
							H 4.62	4.89
							N 4.95	5.09
							S 11.32	10.97
[pyridyl]	H	$C_{23}H_{24}N_2O_{10}S_2$	228–231°	19	−161.8° (pyridine)	1750, 1225, 900	C 50.00	49.67
							H 4.35	4.11
							N 5.01	5.00
							S 11.59	11.22
[methylpyridyl]	CH₃	$C_{24}H_{26}N_2O_{10}S_2$	227–229°	41	−170.0° (pyridine)	1750, 1225, 910	C 50.87	50.55
							H 4.62	4.67
							N 4.95	4.97
							S 11.32	11.08
[naphthyl]	H	$C_{28}H_{27}NO_{10}S_2$	215–216°	30	−182.0° (tetrahy-drofuran)	1750, 1210, 890	C 55.91	55.92
							H 4.49	4.64
							N 2.33	2.45
							S 10.65	10.38
[naphthyl]	H	$C_{28}H_{27}NO_{10}S_2$	229–230°	66	−60.8° (pyridine)	1750, 1230, 895	C 55.91	55.83
							H 4.49	4.51
							N 2.33	2.42
							S 10.65	10.44
[indolyl]	H	$C_{26}H_{26}N_2O_{10}S_2$	251–253°	96	−80.0° (pyridine)	1750, 1230, 902	C 52.88	52.65
							H 4.41	4.50
							N 4.74	4.56
							S 10.85	10.80

[a] Lit. (16) mp 193–194°.

(C=O), 1225 (C=S), and 900 (β-form) cm⁻¹; $[\alpha]_D^{20}$ −104.0° (c = 3.1, tetrahydrofuran).

Hydrolysis of N-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-5 - arylalkylidenerhodanines—N-β-D-*Glucopyranosyl-5-benzylidenerhodanine*—N-(2,3,4,6 - Tetra-O-acetyl-β-D-glucopyranosyl)-5-benzylidenerhodanine (2.56 g, 0.0046 mole) was suspended in 700 ml of methanol, and 10.5 ml of 1.9 M HCl was added. The reaction mixture was stirred in a stoppered flask at room temperature for 4 days, and the resulting solution was filtered. The filtrate was evaporated under reduced pressure in a rotary evaporator at a temperature below 30°, and a yellow-brown semisolid was obtained and then dissolved in ethanol. The ethanolic solution was added to water until cloudiness first appeared, and the solution was refrigerated overnight. Yellow crystals were filtered and dried in a vacuum oven, yielding 1.7 g (96%), mp 104–110°; IR (KBr): ν 3500–3300 (OH), 1715 (C=O), 1230 (C=S), and 890 (β-form) cm⁻¹; $[\alpha]_D^{20}$ −78.0° (c = 0.8, pyridine).

**N-β-D - ***Glucopyranosylthiourea*—N-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-5-benzylidenerhodanine (2.0 g, 0.0036 mole) was added to a solution of methanol saturated with ammonia at 0° in a pressure bottle. The bottle was stoppered, and the mixture was shaken at room temperature for 20 hr. Then the mixture was filtered, and the filtrate was evaporated under reduced pressure in a rotary evaporator at a temperature below 30°. The resulting white powder was washed with anhydrous acetone and recrystallized from methanol, yielding 0.6 g (70%) of hygroscopic white crystals, mp 211–212° [lit. (16) mp 210°]; IR (KBr): ν 3500 (OH), 3400 (NH₂), 3220 (NH), 1650 (NH₂), 1030 (C=S), and 910 (β-form) cm⁻¹; $[\alpha]_D^{20}$ +33.5° (c = 3.0, H₂O).

Anal.—Calc. for C₇H₁₄N₂O₅S: C, 35.29; H, 5.88; N, 11.78; S, 13.44. Found: C, 35.60; H, 6.01; N, 11.58; S, 13.26.

An identical product was obtained when N-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-5-(3,4-dimethoxybenzylidene)rhodanine was subjected to the same conditions.

Antibacterial Activity—Tests for antibacterial activity were first done by the agar plate method, using 20–30 mg of each compound and measuring the zones of inhibition. The organisms used included *Staphylococcus aureus* (ATCC 6538), *Escherichia coli* (ATCC 15221), *Aspergillus niger* (ATCC 16404), and *Candida albicans* (ATCC 10231). Plates inoculated with *S. aureus* and *E. coli* were incubated at 37° for 24–48 hr, and those inoculated with *A. niger* and *C. albicans* were incubated at 25° for 48–72 hr.

Compounds showing activity by the agar plate method were screened by the *in vitro* serial tube dilution procedure. Trypticase soy broth was used for growing *S. aureus* and *E. coli*, and the preparation was sterilized for 15 min at 172 × 10⁴ dynes/cm² at 120°. Stock solutions (0.1 M) of compounds to be tested were made in acetone and sterilized by membrane filtration.

Five colonies of each organism were inoculated into 5.0 ml of the broth preparation and incubated at 37° for 18–24 hr. Serial dilutions of the test compounds were made from the 0.1 M stock solutions, and to each dilution was added 0.1 ml of the broth culture. Tubes were incubated for 24–48 hr at 37° and were then examined for growth.

Antiviral Activity—The rate of viral and host cell RNA synthesis was measured in the presence of various drug concentrations and compared to normal viral and host cell RNA synthesis. Measurements were made using vesicular stomatitis virus growth in Chinese hamster ovary cell suspension culture. ¹⁴C-Uridine was used as a marker to measure RNA synthesis. Viral RNA synthesis was measured by adding 5 μg/ml of dactinomycin to inhibit host cell RNA synthesis.

RESULTS AND DISCUSSION

Chemistry—The 5-aralkylidenerhodanines were readily obtained from reaction of rhodanine with aromatic aldehydes and ketones, using either acetic acid–sodium acetate or ammonium hydroxide–ammonium chloride as the reaction medium. Essentially all of these compounds are known, and they are not tabulated here. The N-tetra-O-acetyl-D-glucosyl derivatives (Table I) were prepared essentially by the procedure of Michael (17), which utilized acetobromo-α-D-glucose in acetone with sodium hydroxide. Yields of product varied from 30 to 96%.

Proof that the N-glycoside was obtained was given by hydrolysis to N-glucosylthiourea (II) (Scheme I), previously synthesized by Fischer (16), from the 5-benzylidene- and 5-(3,4-dimethoxybenzylidene)rhodanine tetraacetyl-D-glucosyl derivatives using ammonia in methanol. The IR spectra of the products also indicated N-glycosylation. The doublet characteristic of NH stretching between 3100 and 3400 cm⁻¹ was changed to a weak singlet after glycosylation, and no change was observed in the thionyl and carbonyl absorptions at 1200–1250 and 1700–1760 cm⁻¹, respectively. Furthermore, the NMR spectra for rhodanine and 5-substituted derivatives showed a broad peak at 11.7 ppm for one proton, which was exchangeable with deuterium, characteristic of an imino proton. This peak disappeared after glycosylation, providing further evidence of N-glycosylation.

Scheme I

$$O=C-NCH(CHOH)_4CHCH_2OH$$
$$R_1-C=C_S\diagup\overset{O}{C}=S$$
$$R_2$$

Table II—N-β-D-Glucopyranosyl-5-arylalkylidenerhodanines

R_1	R_2	Formula	Melting Point	Yield, %	$[\alpha]_D^{20}$ (Solvent)	IR (KBr), cm^{-1}	Analysis, % Calc.	Found
C_6H_5	H	$C_{16}H_{17}NO_6S_2$	104–110°	96	−78.0° (pyridine)	3400 (br), 1715, 1230, 890	C 50.11	49.80
							H 4.47	4.62
							N 3.66	3.49
							S 16.72	16.97
$4\text{-}NO_2C_6H_4$	H	$C_{16}H_{16}N_2O_8S_2$	130–135°	93	−131.8° (tetrahydrofuran)	3400 (br), 1720, 1230, 900	C 44.85	44.80
							H 3.76	4.03
							N 6.54	6.35
(furyl)	H	$C_{14}H_{15}NO_7S_2\cdot1/2H_2O$	150–155°	72	−74.4° (tetrahydrofuran)	3400 (br), 1710, 1225, 885	C 43.99	44.12
							H 4.19	4.06
							N 3.66	3.67
(furyl)	CH_3	$C_{15}H_{17}NO_7S_2\cdot H_2O$	135–140°	95	−104.0° (methanol)	3400 (br), 1700, 1225, 882	C 44.44	44.48
							H 4.69	4.58
							N 3.45	3.60
(thienyl)	H	$C_{14}H_{15}NO_6S_3\cdot H_2O$	130–135°	74	−108.8° (methanol)	3400 (br), 1710, 1225, 910	C 41.28	41.10
							H 4.17	4.15
							N 3.44	3.35
(pyridyl)	H	$C_{15}H_{16}N_2O_6S_2$	130–135°	78	−104.0° (pyridine)	3400 (br), 1720, 1225, 900	C 46.90	47.12
							H 4.17	3.74
							N 7.29	6.93

Whether the N-glycosylated derivatives were the α- or β-forms was determined by the IR spectra. Glycoside formation, using acetobromo-α-D-glucose, invariably proceeds with Walden inversion at C-1 (18), yielding the β-glycoside from the α-halide. In addition, α-D-glucopyranose structures show absorption between 833 and 855 cm⁻¹, whereas the β-structures absorb in the 876–905-cm⁻¹ region (19). All of the N-tetraacetylglucosylrhodanines were found to be β-glucosides by their absorption between 882 and 910 cm⁻¹.

Deacetylation of the tetraacetylglucosyl derivatives was complicated by the sensitivity of the rhodanine ring to alkaline hydrolysis. A mild hydrolytic method, ammonia in methanol, resulted in cleavage to give N-glucosylthiourea. Direct condensation between the 5-substituted rhodanines and glucose also failed. A successful method for deacetylation was the use of 2 N HCl in methanol. Yields of deacetylated glucosides were generally better than 90% by this method. The compounds prepared are listed in Table II.

Biology—A cell culture test for antiviral activity was carried out on N-glucosyl-5-p-nitrobenzylidenerhodanine². When using vesicular stomatitis virus growth in Chinese hamster ovary cell suspension culture, rhodanine itself (150 µg/ml) had no effect on either Chinese hamster ovary cells or vesicular stomatitis viral RNA synthesis. This result supports the previous observation of Eggers et al. (1). N-Glucosyl-5-p-nitrobenzylidenerhodanine, however, at the same concentration, inhibited RNA synthesis of both host cells and virus to a similar extent. At concentrations of 50 and 100 µg/ml, the rhodanine derivative inhibited 10% of cellular RNA synthesis but 40% of viral RNA synthesis. This difference in inhibition of RNA synthesis is sufficient to state that the rhodanine derivative has definite antiviral activity.

Antibacterial activities were observed by the agar plate screening method using S. aureus, E. coli, A. niger, and C. albicans. These organisms represent a Gram-positive and a Gram-negative bacterium, a mold, and a yeast, respectively. None of the rhodanines showed inhibitory activity against A. niger and C. albicans. Compounds showing inhibitory activity against the bacteria were then measured by the serial tube dilution method.

Only rhodanine and o-nitrobenzylidenerhodanine showed activity against E. coli. Many of the 5-substituted rhodanine derivatives were active against S. aureus, but in general the tetraacetylglucosyl derivatives were not. Exceptions were found with the tetraacetyl derivatives of 5-(5-bromothienylmethylene)rhodanine and 5-(1-naphthylidene)rhodanine. With the benzylidene derivatives, electron-withdrawing substituents increased activity, whereas electron-releasing substituents decreased activity. Methyl substitution at the methylene side chain either decreased or removed inhibitory activity.

Results of this study confirm previous findings that either 3- or 5-substituted rhodanines are active antimicrobials and that the 3,5-disubstituted rhodanines are not (10), with the exception of N-phenyl-5-(5-nitrofurylidene)rhodanine (20). The presence of a nitro group seems to be essential for high activity against bacteria, protozoa, and schistosomes but has little effect toward other helminths than schistosomes and fungi (21). Antimicrobial testing results by serial tube dilution are listed in Table III.

Table III—Antibacterial Activities

$$O=C-NR_3$$
$$R_1-C=C_S\diagup C=S$$
$$R_2$$

R_1	R_2	R_3	Minimum Inhibitory Concentration, 1/M S. aureus	E. coli
C_6H_5	H	H	<1,000	—
$4\text{-}NO_2C_6H_4$	H	H	<10,000	—
$2\text{-}NO_2C_6H_4$	H	H	<100,000	<1000
$2,6\text{-}Cl_2C_6H_3$	H	H	<10,000	—
$2\text{-}ClC_6H_4$	H	H	<1,000	—
(furyl)	H	H	<1,000	—
(furyl)	CH_3	H	<100	—
(thienyl)	H	H	<10,000	—
Br-(thienyl)	H	$C_6H_7(OCOCH_3)_4$	<1,000	—
(naphthyl)	H	H	<1,000	—
(naphthyl)	H	$C_6H_7(OCOCH_3)_4$	<1,000	—
C_6H_5	H	$C_6H_{11}O_5$	<1,000	—
Rhodanine	—	—	<1,000	<1000

Effects on blood sugar levels in Charles River rats were observed for several of the rhodanine derivatives[3]. 5-(2-Pyrrolylmethylene)rhodanine (22) (150 mg/kg) increased blood glucose significantly at 1, 2, and 4 hr after oral dosing, and 5-(2-thienylmethylene)rhodanine (150 mg/kg) increased blood glucose at 4 hr after oral dosing. No effect on blood glucose was observed for 5-(4-pyridylmethylene)rhodanine (150 mg/kg) or for 5-(2-pyridylethylidene)rhodanine (150 mg/kg). Increases in blood glucose at 4 hr after oral administration were also found for 2,2'-dithiobis[3-(2-furyl)acrylic acid] (22) (100 mg/kg) and 2,2'-dithiobis-(3-phenylacrylic acid) (23) (75 mg/kg). Significant effects on blood glucose levels may be caused either by suitable 5-substituted rhodanines or their hydrolysis products, the dithioacrylic acids.

REFERENCES

(1) H. J. Eggers, M. A. Koch, A. Furst, G. D. Daves, Jr., J. J. Wilczynski, and K. Folkers, *Science,* 167, 294 (1970).

(2) T. H. Haskell, F. E. Peterson, D. Watson, N. R. Plessas, and T. Culbertson, *J. Med. Chem.,* 13, 697 (1970).

(3) A. P. Grollman and S. B. Horwitz, in "Drug Design," vol. II, E. J. Ariens, Ed., Academic, New York, N.Y., 1971, p. 261.

(4) F. G. Moers, J. W. M. Goossens, and J. P. M. Langhout, *J. Inorg. Nucl. Chem.,* 35, 855 (1973).

(5) R. W. Brockman, R. W. Sidwell, G. Arnett, and S. Shaddix, *Proc. Soc. Exp. Biol. Med.,* 133, 609 (1970).

(6) W. O. Foye and E. G. Feldmann, *J. Am. Pharm. Assoc., Sci. Ed.,* 45, 30 (1956). W. O. Foye, W. E. Lange, and E. G. Feldmann, *ibid.,* 47, 831 (1958).

(7) T. Zsolnai, *Arzneim.-Forsch.,* 19, 558 (1969).

(8) H. Taniyama, S. Takemura, B. Yasui, and H. Uchida, *J. Pharm. Soc. Jpn.,* 74, 113 (1954).

(9) L. M. Werbel, N. Headen, and E. F. Elslager, *J. Med. Chem.,* 11, 364 (1968).

(10) F. C. Brown, C. K. Bradsher, S. M. Bond, and R. J. Granthan, *Ind. Eng. Chem.,* 46, 1508 (1954). G. Matolcsy, B. Bordas, and M. Hamran, *Acta Phytopathol.,* 4, 345 (1969).

(11) T. Takematsu, M. Furushima, Y. Hasegawa, M. Morioka, and

T. Tsuchiyama, Japanese pat. 7,243,812 (1972). M. Mousseron, S. African pat. 6,803,535 (1969).

(12) A. Mackie and G. M. Stewart, *Arch. Int. Pharmacodyn. Ther.,* 102, 476 (1955).

(13) W. C. McGuire, C. O. O'Neill, and G. Brody, *J. Parasitol.,* 52, 528 (1966).

(14) R. Bognar and W. Wieniawski, *Acta Chim. Acad. Sci. Hung.,* 33, 415 (1962).

(15) F. C. Brown, C. K. Bradsher, S. G. McCallum, and M. Potter, *J. Org. Chem.,* 15, 174 (1950).

(16) E. Fischer, *Chem. Ber.,* 47, 1377 (1914).

(17) A. Michael, *Am. Chem. J.,* 6, 336 (1885).

(18) J. Conchie, G. A. Levvy, and C. A. Martin, *Adv. Carbohydr. Chem.,* 12, 157 (1957). J. Stanek, M. Cerny, J. Kocourek, and J. Pacak, "The Monosaccharides," Academic, New York, N.Y., 1963.

(19) H. Spedding, in "Methods in Carbohydrate Chemistry," vol. I, R. L. Whistler and M. L. Wolfrom, Eds., Academic, New York, N.Y., 1962, p. 548.

(20) S. K. Mallick and A. R. Martin, *J. Med. Chem.,* 14, 528 (1971).

(21) E. Grunberg and E. H. Titsworth, *Ann. Rev. Microbiol.,* 27, 317 (1973).

(22) P. Tovivich, M.S. thesis, Massachusetts College of Pharmacy, Boston, Mass., 1972.

(23) E. Campaigne and R. E. Cline, *J. Org. Chem.,* 21, 32 (1956).

[3] Results were made available through the courtesy of Dr. J. W. Wilson, Smith Kline & French Laboratories.

Effects of Polyelectrolytes on Drug Transport II: Permeation

K. F. FARNG * and K. G. NELSON ˣ

Abstract ☐ The permeation rate of salicylate across a dialysis membrane was studied in the presence of various types of carboxymethylcellulose. The presence of the polymer in the salicylate solution increased the permeation rate of salicylate. The data were analyzed with a diffusional model in which the viscosity and charge effects were evaluated separately.

Keyphrases ☐ Salicylate—permeation rate across a dialysis membrane in presence of various types of carboxymethylcellulose ☐ Permeation rate—salicylate across a dialysis membrane in presence of various types of carboxymethylcellulose ☐ Drug transport—permeation rate of salicylate across a dialysis membrane in presence of various types of carboxymethylcellulose ☐ Carboxymethylcellulose, various types—effect on permeation rate of salicylate across a dialysis membrane ☐ Polyelectrolytes—various types of carboxymethylcellulose, effect on permeation rate of salicylate across a dialysis membrane

Previously (1), it was observed that the presence of the polyelectrolyte carboxymethylcellulose decreased the aqueous diffusivity of a small solute (salicylate) only moderately and that salicylate, which was present as a co-ion of the polymer, was transported out of the polymer solution and into an aqueous environment more rapidly than if the polymer were not present. This report describes further studies on this enhanced transport phenomenon involving an *in vitro* permeation apparatus.

EXPERIMENTAL

Permeation Cell—A permeation cell was constructed from plastic[1] and consisted of two symmetrical parts clamped together with a dialysis membrane at the plane of symmetry. The diffusion cell was described previously (2). Each compartment holds about 125 ml of liquid, and the area of the membrane available for permeation is 16.8 cm². The cell was immersed in a water bath for temperature control, and each compartment was stirred with a stirring rod tipped with flattened rubber tubing and rotated at 2000 rpm.

[1] Lucite, Rohm & Haas, Philadelphia, Pa.