Acyclic *C*-Nucleoside Analogs of the Type of 5-*C*-Polyhydroxyalkyl-1,3,4-thiadiazoles[1)]

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The synthesis of some acyclic *C*-nucleoside analogs possessing thiadiazole rings was achieved by the heterocyclization of the 4-arylthiosemicarbazones of D-galactose, D-glucose, D-mannose, D-arabinose, and lactose, Acetylation of the thiadiazoles afforded the corresponding 2-(*N*-acetylarylamino)-5-polyacetoxyalkyl-1,3,4-thiadiazoles and periodate oxidation gave the corresponding 5-(arylamino)-1,3,4-thiadiazole-2-carbaldehyde.

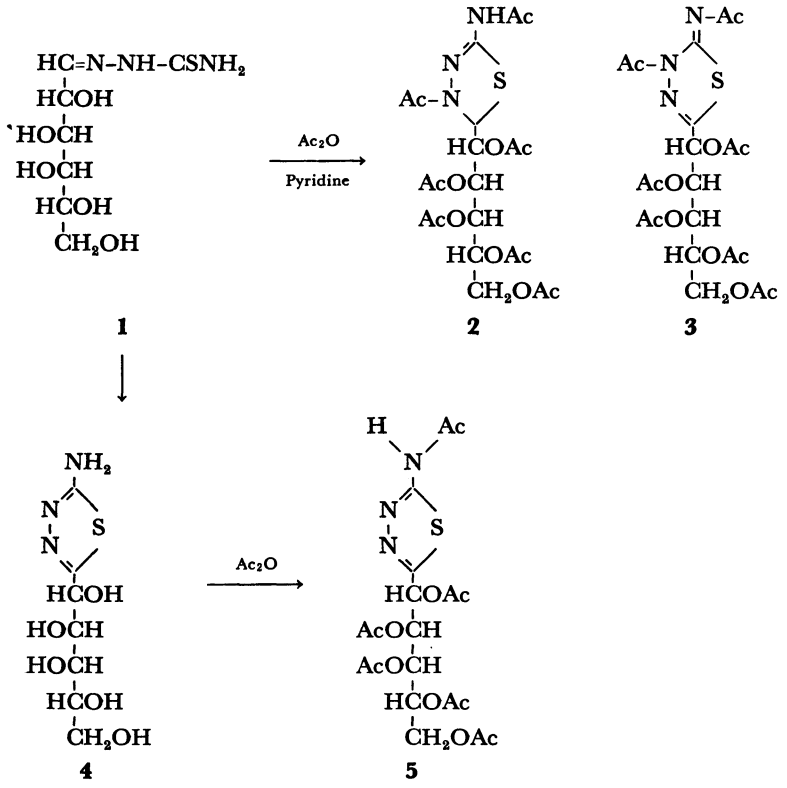
As a consequence of the biological significance of the naturally occurring *C*-nucleosides, various approaches have been explored for their synthesis. One of the main goals in this laboratory is the synthesis of the acylic *C*-nucleoside analogs,[2)] particularly via the heterocyclization of the nitrogen derivatives of sugars.

Thiadiazoles are interesting targets due to their chemotherapeutic value.[3-5)] Consequently, we report in this paper the synthesis of some corresponding acyclic *C*-nucleosides as a continuation of our interest[2,6)] in this work.

Results and Discussion

Acetylation of sugar hydrazones was found to be dependent upon the structure of the hydrazone residue as well as the acylating agent.[7-13)] Saccharide arylhydrazones gave *O*-acetylated derivatives upon reaction with acetic anhydride in pyridine, whereas boiling acetic anhydride caused further acetylation of the hydrazone residue to give *O,N*-acetylated derivatives.[7-9)] On the other hand, sugar aroylhydrazones showed a similar behavior to the arylhydrazones upon reaction with acetic anhydride in pyridine under mild conditions whereas boiling acetic anhydride caused cyclization of the aroylhydrazones residue to the corresponding 1,3,4-oxadiazoline derivatives.[10-12)] Reaction of D-galactose thiosemicarbazone (**1**) with hot acetic anhydride in pyridine gave 5-acetylamino-3-acetyl-2-(D-*galacto*-1,2,3,4,5-pentaacetoxypentyl)-2,3-dihydro-1,3,4-thiadiazole (**2**).[13)]

When the thiadiazole **4** was acetylated, a product **5** was obtained whose ^{1}H NMR spectrum showed a singlet at δ 13.2 indicating the presence of only one NH. This as well as the presence of six singlets corresponding to six acetyl groups confirmed the acetylation of the amino group in addition to the hydroxyl groups. The spectrum did not show a



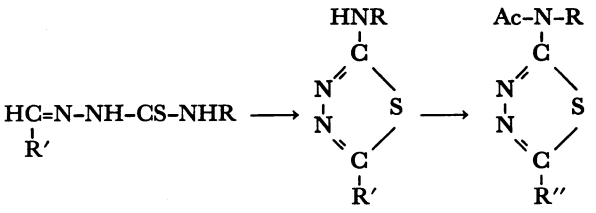
1 2 3 4 5

Scheme 1.

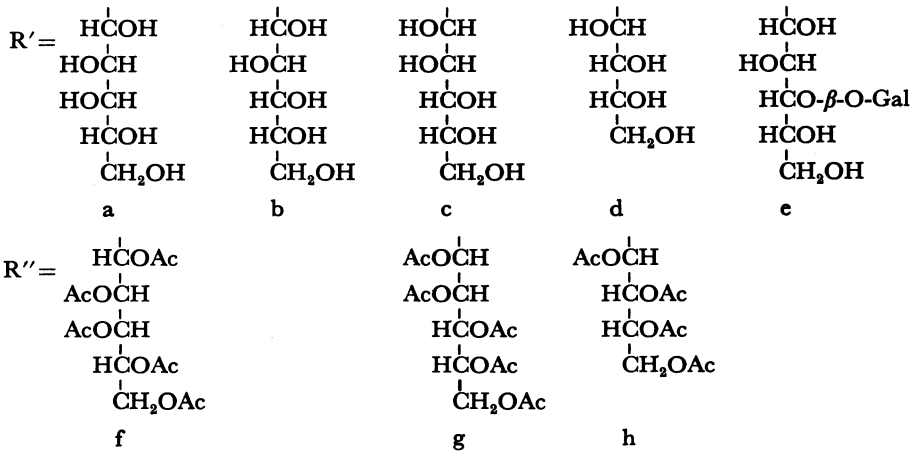
doublet at δ 5.83 which appeared in the ^{1}H NMR spectrum of the dihydrothiadiazole derivative (**2**) and attributed to the H-2 of the heterocyclic ring. Moreover, the spectrum showed a doubled at δ 6.37 due to H-1 of the polyacetoxyalkyl side chain. The pronounced downfield shift of H-1 of **5** compared with that of **2** can be attributed to the difference in hybridization of the heterocyclic carbon attached to C-1 of the acetoxyalkyl side chain. These data agreed with structure **5** rather than **2** or **3**.

To explore the scope of heterocyclization of thiosemicarbazones, the 4-substituted thiosemicarbazones were prepared by the condensation of equimolar equivalents of the sugars with 4-substituted thiosemicarbazides. Two variants have been changed; the substituents on the 4-position of the thiosemicarbazide as well as the saccharides, whereby monosaccharides such as D-galactose, D-glucose, D-mannose, and D-arabinose as well as the oligosaccharide lactose were used. Thus the saccharide 4-arylthiosemicarbazones (**6**—**21**) were prepared, and most of them are crystalline compounds (see Table 1). The infrared (IR) spectra of the sugar 4-arylthiosemicarbazones (**6**—**21**) showed NH absorption at 3120—3210 cm^{-1} in addition to the OH band at 3300—3450 cm^{-1}.

Reaction of D-galactose 4-phenylthiosemicarbazone (**6**) with iron(III) chloride, in a similar manner to that reported[14] for thiosemicarbazones and thiobenzoylhydrazones, gave the colorless crystalline product **22**, whose elemental analysis agreed with the structure, 2-anilino-5-(D-*galacto*-1,2,3,4,5-pentahydroxypentyl)-1,3,4-thiadiazole (**22**), indicating the loss of two hydrogen atoms. This oxidative cyclization could be extended to the whole series of the prepared thiosemicarbazones to give the corresponding thiadiazoles **22**—**34**. As the nitrogen heterocycles derived



6	R = C_6H_5,	R′ = a	⟶ **22**	⟶ **37**	R″ = f
7	R = C_6H_4Me-*p*,	R′ = a	⟶ **23**	⟶ **38**	R″ = f
8	R = C_6H_4Me-*m*,	R′ = a	⟶ **24**	⟶ **39**	R″ = f
9	R = C_6H_4OMe-*p*,	R′ = a	⟶ **25**	⟶ **40**	R″ = f
10	R = C_6H_4Cl-*m*,	R′ = a	⟶ **26**	⟶ **41**	R″ = f
11	R = C_6H_4Br-*p*,	R′ = a	⟶ **27**	⟶ **42**	R″ = f
12	R = 1-Naphthyl,	R′ = a	⟶ **28**		
13	R = 2-Naphthyl,	R′ = a	⟶ **29**		
14	R = C_6H_4Cl-*p*	R′ = b			
15	R = C_6H_4Me-*p*,	R′ = c	⟶ **30**	⟶ **43**	R″ = g
16	R = C_6H_4OMe-*p*,	R′ = c	⟶ **31**	⟶ **44**	R″ = g
17	R = C_6H_4Cl-*p*,	R′ = c	⟶ **32**	⟶ **45**	R″ = g
18	R = C_6H_4Me-*p*,	R′ = d	⟶ **33**	⟶ **46**	R″ = h
19	R = C_6H_4Cl-*p*,	R′ = d	⟶ **34**	⟶ **47**	R″ = h
20	R = C_6H_4Me-*p*,	R′ = e	⟶ **35**		
21	R = C_6H_4Cl-*p*,	R′ = e	⟶ **36**		

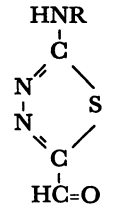


Scheme 2.

from oligosaccharides may have the tendency to be more soluble than the corresponding monosaccharides, a behavior of great advantage in preparing a chemotherapeutic agent, the thiadiazoles **35** and **36** were prepared from the corresponding thiosemicarbazones of lactose.

Acetylation of the thiadiazoles **22—27** and **30—36** gave **37—47**, whose elemental analysis agreed with the molecular formulas having six acetyl groups, indicating that acetylation of the amino groups has occurred in addition to the per-*O*-acetylation of the hydroxyl groups. The IR spectra of the acetates showed the absorptions due to the *O*-Ac groups at 1755—1780 cm^{-1} and the *N*-Ac groups at 1670—1695 cm^{-1}.

Periodate oxidation of the 2-(substituted anilino)-5-(D-*galacto*-1,2,3,4,5-pentahydroxypentyl)-1,3,4-thiadiazoles, afforded the anticipated aldehydes 5-(substituted anilino)-1,3,4-thiadiazole-2-carbaldehyde **48—50**, whose IR spectra showed bands due to the formyl group (1685 cm^{-1}) and the NH group (3200 cm^{-1})



48 R = C_6H_4Me-*p*
49 R = C_6H_4OMe-*p*
50 R = C_6H_4Cl-*m*

Experimental

General. Melting points were determined with a Kofler block apparatus and are uncorrected. Infrared spectra were recorded in Nujol film, with a Pye Unicam SP-1025 spectrophotometer. ^1H NMR spectra were carried out, in deuteriochloroform solutions containing tetramethylsilane as the internal standard, with a Jeol-100 spectrometer. Chemical shifts are given on the δ scale. Microanalyses were performed in the Chemistry Department, Faculty of Science, Cairo University, Cairo, Egypt.

5-Acetylamino-3-acetyl-2-(D-*galacto*-1,2,3,4,5,-pentaacetoxypentyl)-1,2-dihydro-1,3,4-thiadiazole (2). Acetic anhydride (7 ml) was added to a suspension of D-galactose thiosemicarbazone (**1**) (1 g) in dry pyridine (10 ml). This mixture was heated under reflux at 110 °C for 1.5 h, cooled, and then poured onto crushed ice, and the separated solid was collected by filtration, washed with water, and dried, mp 215 °C (lit,[13] mp 217 °C).

2-Acetylamino-5-(D-*galacto*-1,2,3,4,5-pentaacetoxypentyl)-1,3,4-thiadiazole (5). A solution of **4**[14] (2 g) in pyridine (10 ml) was treated with acetic anhydride (15 ml) and the mixture was kept overnight at room temperature. The reaction mixture was poured onto crushed ice, and the product that separated out was filtered off, washed repeatedly with water and sodium hydrogencarbonate solution, and dried. It was crystallized from ethanol in colorless needles, (yield: 60%), mp 165 °C; ν_{max}^{Nujol} 1750 (OAc) and 1670 cm^{-1} (NCO); ^1H NMR ($CDCl_3$) δ=2.00, 2.03, 2.04, 2.13, 2.17, 2.43 (6s, 18H, 6Ac), 3.09 (q, 1H, $J_{5,5'}$=12.0, $J_{4,5'}$=6.0 Hz, H-5'), 4.30 (q, 1H, $J_{5,5'}$=12.0, $J_{4,5}$=5.0 Hz, H-5), 5.30 and 5.38 (2 m, 3H, H-2, -3, -4), 6.37 (d, 1H, $J_{1,2}$=2.0 Hz, H-1), and 13.2 (s, 1H, NH).

Found: C, 45.6; H, 5.3: N, 7.9%. Calcd for $C_{19}H_{25}N_3O_{11}S$: C, 45.3; H, 5.0; N, 8.3%.

Saccharide 4-Arylthiosemicarbazones (6—21). A solution of the sugar (0.01 mol) in water (5 ml) was treated with a solution of 4-substituted thiosemicarbazide (0.01 mole) in ethanol (50 ml) and the mixture was heated under reflux for 1 h. The resulting solution was concentrated, and the product that separated out upon cooling, was filtered off, washed with ethanol, and dried. It was crystallized from ethanol, giving colorless needles. The noncrystalline thiosemicarbazones were directly transformed into the corresponding thiadiazoles, (yield ≈75%). (see Table 1).

2-Arylamino-5-polyhydroxyalkyl-1,3,4-thiadiazoles (22—36). A 2 M iron(III) chloride solution in ethanol (5 ml) was

Table 1. Elemental Analyses and IR Spectral Data of Saccharide 4-Arylthiosemicarbazones (**7**, **12**, **14—19**)

Compound	Mp θ_m/°C	Molecular formula	Analysis/%					ν_{max}^{Nujol}/cm^{-1}	
			C	H	N	S	X	OH	NH
7	190	$C_{14}H_{21}N_3O_5S$	Calcd 49.0 Found 49.1	6.1 5.8	12.2 12.3	9.3 9.4	—	3450	3210
12	165	$C_{17}H_{21}N_3O_5S$	Calcd 53.8 Found 53.7	5.6 5.4	11.1 10.8	8.5 8.6	—	3450	3210
14	188	$C_{13}H_{18}ClN_3O_5S$	Calcd 42.9 Found 43.1	5.0 4.8	11.6 11.8	8.6 8.8	9.7 10.1	3390	3200
15	187	$C_{14}H_{21}N_3O_5S$	Calcd 49.0 Found 49.3	6.1 5.8	12.2 11.9	9.3 9.1	—	3450	3200
16	177°	$C_{14}H_{21}N_3O_6S$	Calcd 46.8 Found 46.8	5.9 5.7	11.7 11.5	8.9 8.6	—	3410	3170
17	180	$C_{13}H_{18}ClN_3O_5S$	Calcd 42.9 Found 43.1	5.0 4.6	11.6 11.2	8.8 8.9	9.7 9.6	3400	3150
18	220	$C_{13}H_{19}N_3O_4S$	Calcd 49.8 Found 50.1	6.1 5.8	13.4 13.2	10.2 10.1	—	3395	3210
19	205	$C_{12}H_{16}ClN_3O_4S$	Calcd 43.2 Found 43.4	4.8 4.9	12.6 12.4	9.6 9.6	10.6 10.7	3400	3150

Table 2. Elemental Analyses and IR Spectral Data of 2-Arylamino-5-polyhydroxyalkyl-1,3,4-thiadiazoles (**4, 22—36**)

Compound	Mp θ_m/°C	Molecular formula		Analysis/% C	H	N	S	X	IR ν_{max}^{Nujol}/cm^{-1} OH	NH	C=N
4	203	$C_7H_{13}N_3O_5S$	Calcd	33.5	5.2	16.7	12.8	—	3400	3150	1620
			Found	33.8	4.9	16.4	12.4				
22	240	$C_{13}H_{17}N_3O_5S$	Calcd	47.7	5.2	12.8	9.8	—	3390	3210	1610
			Found	48.1	5.3	12.4	9.9				
23	234	$C_{14}H_{19}N_3O_5S$	Calcd	49.3	5.6	12.3	9.4	—	3350	3100	1610
			Found	49.1	5.8	12.2	9.4				
24	230	$C_{14}H_{19}N_3O_5S$	Calcd	49.3	5.6	12.3	9.4	—	3500	3250	1610
			Found	48.8	5.5	11.9	9.4				
25	248	$C_{14}H_{19}N_3O_6S$	Calcd	47.1	5.4	11.8	9.0	—	3400	3220	1605
			Found	46.7	5.1	11.6	9.3				
26	240	$C_{13}H_{16}ClO_5N_3S$	Calcd	43.2	4.5	11.6	8.9	9.8	3400	3150	1605
			Found	42.9	4.4	11.4	8.7	9.8			
27	230	$C_{13}H_{16}BrN_3O_5S$	Calcd	38.4	4.0	10.3	7.9	19.7	3380	3215	1620
			Found	38.7	3.8	10.6	8.2	20.0			
28	262	$C_{17}H_{19}N_3O_5S$	Calcd	54.1	5.1	11.1	8.5	—	3250	3100	1605
			Found	54.1	5.4	11.5	8.7				
29	250	$C_{17}H_{19}N_3O_5S$	Calcd	54.1	5.1	11.1	8.5	—	3350	3150	1610
			Found	54.1	4.9	11.3	8.5				
30	214	$C_{14}H_{19}N_3O_5S$	Calcd	49.3	5.6	12.3	9.4	—	3330	3100	1605
			Found	49.5	5.7	12.1	9.5				
31	220	$C_{14}H_{19}N_3O_6S$	Calcd	47.1	5.4	11.8	9.0	—	3400	3200	1610
			Found	46.7	5.1	11.6	8.9				
32	222	$C_{13}H_{16}ClN_3O_5S$	Calcd	43.2	4.5	11.6	8.8	9.8	3400	3200	1605
			Found	43.5	4.4	11.7	8.9	9.9			
33	226	$C_{13}H_{17}N_3O_4S$	Calcd	50.1	5.5	13.5	10.3	—	3350	3100	1610
			Found	50.1	5.4	13.2	10.5				
34	220	$C_{12}H_{14}ClN_3O_4S$	Calcd	43.4	4.3	12.7	9.7	10.7	3450	3300	1605
			Found	43.6	4.4	12.5	9.7	11.0			
35	195	$C_{20}H_{29}N_3O_{10}S$	Calcd	47.7	5.8	8.3	6.4	—	3400	3200	1620
			Found	47.3	5.5	8.1	6.4				
36	205	$C_{19}H_{26}ClN_3O_{10}S$	Calcd	34.6	5.0	8.0	6.1	6.8	3420	3100	1610
			Found	43.1	4.7	7.7	6.2	6.9			

Table 3. Elemental Analyses and IR Spectral Data of 2-(*N*-Acetylarylamine)-5-polyacetoxyalkyl-1,3,4-thiadiazoles (**37—47**)

Compound	Mp θ_m/°C	Molecular formula		Analysis/% C	N	H	S	X	ν_{max}^{Nujol}/cm^{-1} OAc	NAc
37	210	$C_{25}H_{29}N_3O_{11}S$	Calcd	51.8	5.0	7.3	5.5	—	1770	1695
			Found	51.8	5.0	7.2	5.9			
38	201	$C_{26}H_{31}N_3O_{11}S$	Calcd	52.6	5.3	7.1	5.4	—	1755	1690
			Found	52.3	5.3	7.2	5.8			
39	201	$C_{26}H_{31}N_3O_{11}S$	Calcd	52.6	5.3	7.1	5.4	—	1775	1690
			Found	52.3	5.3	7.2	5.6			
40	162	$C_{26}H_{31}N_3O_{12}S$	Calcd	51.2	5.1	6.9	5.3	—	1775	1690
			Found	51.5	5.2	7.1	5.8			
41	226	$C_{25}H_{28}ClN_3O_{11}S$	Calcd	48.9	4.6	6.8	5.2	5.8	1770	1690
			Found	49.2	4.7	7.0	5.6	5.9		
42	204	$C_{25}H_{28}BrN_3O_{11}S$	Calcd	45.6	4.3	6.4	4.9	12.1	1780	1690
			Found	46.0	4.1	6.3	5.3	12.2		
43	134	$C_{26}H_{31}N_3O_{11}S$	Calcd	52.6	5.3	7.1	5.4	—	1780	1690
			Found	53.0	5.3	7.0	5.6			
44	162	$C_{26}H_{31}N_3O_{12}S$	Calcd	51.2	5.1	6.9	5.3	—	1780	1690
			Found	51.5	5.2	6.6	5.7			
45	148	$C_{25}H_{28}ClN_3O_{11}S$	Calcd	48.9	4.6	6.8	5.2	5.8	1780	1680
			Found	49.1	4.8	6.9	5.2	6.0		
46	115	$C_{23}H_{27}N_3O_9S$	Calcd	53.0	5.2	8.1	6.2	—	1760	1670
			Found	53.2	5.5	7.8	5.9			
47	143	$C_{22}H_{24}ClN_3O_9S$	Calcd	48.8	4.5	7.8	5.9	6.5	1780	1690
			Found	49.1	4.6	7.5	5.8	6.6		

Table 4. Elemental Analyses and IR Spectral Data of 5-(Substituted Anilino)-1,3,4-thiadiazole-2-carbaldehydes (**48**—**50**)

Compound	Mp θ_m/°C	Molecular formula	Analysis/%					IR ν_{max}^{Nujol}/cm^{-1}		
			C	H	N	S	X	NH	HC=O	C=N
48	211	$C_{10}H_9N_3OS$	Calcd 54.8 Found 54.7	4.1 4.2	19.2 19.5	14.6 14.5	—	3100	1682	1620
49	186	$C_{10}H_9N_3O_2S$	Calcd 51.1 Found 51.3	3.9 4.0	17.9 17.5	13.6 13.8	—	3200	1685	1615
50	207	$C_9H_6ClN_3OS$	Calcd 45.1 Found 45.4	2.5 2.8	17.5 17.2	13.4 13.6	—	3150	1675	1610

added dropwise to a boiling solution of the saccharide 4-substituted thiosemicarbazone (1 g) in ethanol (100 ml). Boiling was continued for further 10 min, and the mixture was then concentrated. The product which separated out on cooling, was filtered off, washed with ethanol, dried and crystallized from ethenol in colorless needles, (yield ≈80%), (see Table 2).

2-(*N*-Acetylarylamino)-5-polyacetoxyalkyl-1,3,4-thiadiazoles (37—47). A solution of saccharide 4-arylthiosemicarbazone (1 g) in a mixture of *N*,*N*-dimethylformamide (10 ml) and dry pyridine (7 ml) was treated with acetic anhydride (10 ml) and the mixture was kept overnight at room temperature. The reaction mixture was poured onto crushed ice, and the product that separated out was filtered off, washed repeatedly with water, and sodium hydrogencarbonate solution and dried. The product was recrystallized from ethanol in colorless needles, (yield ≈ 60%), (see Table 3).

5-(Substituted Anilino)-1,3,4-thiadiazole-2-carbaldehyde (48—50). A suspension of compounds **7,9,10** (0.01 mol) in water (100 ml) was treated with a solution of sodium periodate (0.05 mol) in water (50 ml). The mixture was stirred at room temperature for 2 h, and kept overnight in the dark. The product was filtered off, washed with water, dried and crystallized from ethanol in yellow needles, (yield ≈70%), (see Table 4).

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