SYNTHESIS OF NUCLEOSIDE ANALOGS BY ADDITION-CYCLIZATION REACTION OF 2,3,4,6-TETRA-O-ACETYL-β-D-GLUCOPYRANOSYL ISOTHIOCYANATE

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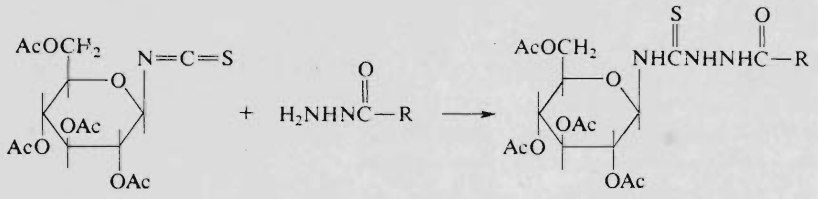
Reactions of 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl isothiocyanate (*I*) with various hydrazides gave 4-substituted 1-acylthiosemicarbazides. Their cyclization, by treatment with sodium methoxide, gave analogs of nucleosides. The reaction of *I* with thioglycolic acid to give substituted 1,3-thiadiazolidine has also been studied.

During the last decade several workers have described syntheses of nucleoside analogs using glycosyl isothiocyanates as starting substances. For example, reactions of glycosyl isothiocyanates with amines, hydrazines, amino acids, enamines and diamines to give analogs of nucleosides were described by Ogura[1]. Wieniawski and coworkers[2] obtained glycosides of 2-amino-5-(3-heteroaryl)-1,3,4-oxadiazole by desulphation of heteroaroyl-3-thiosemicarbazides with HgO. Thiosemicarbazides are convenient starting materials for syntheses of heterocyclic systems. The 4-substituted 1-acylthiosemicarbazides can be dehydrated to give, depending upon the reagent used, the corresponding 1,2,4-thiazoline-5-thiones or aminothiazoles[3].

In the present work nucleoside analog-leading cyclization reactions of thiosemicarbazides have been studied. The starting point was 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl isothiocyanate[4] (*I*) prepared from 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide and AgSCN. Treatment of *I* with hydrazides in dioxane afforded 4-(1-tetra-O-acetyl-β-D-glucopyranosyl)-1-acylthiosemicarbazides (*IIa*–*IIe*) in very good yields (Scheme 1). The expected addition products, namely 1-substituted 2-thiobiurets, were not formed when urea or ethyl allophanate had been used. Instead, N,N'-bis-(1-tetra-O-acetyl-β-D-glucopyranosyl)thiourea was isolated in both cases. The plausible mechanism for its formation is indicated by the following sequence of reactions. In a pyridine-catalyzed reaction the isothiocyanate *I* reacts preferentially with the traces of water, rather than with the used nitrogen-containing

component, to give *via* the unstable thiocarbamate acid 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)amine which, in turn, reacts with another molecule of the isothiocyanate to afford a symmetrically substituted thiourea derivative[5].

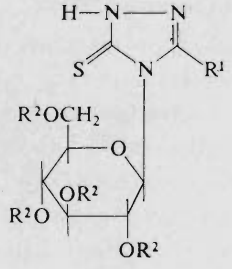


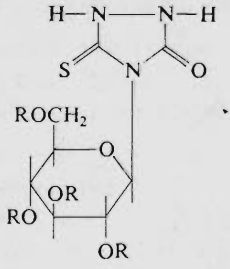
I

IIa; R = H
IIb; R = CH_3
IIc; R = CH_2CH_3
IId; R = $CH(CH_3)_2$
IIe; R = OCH_2CH_3

SCHEME 1

The cyclization dehydration of 1,4-substituted thiosemicarbazides was effected thermally (in boiling 3-methylbutanol) or by treatment with base (sodium methoxide). For R = H the 4-substituted 5-thioxo-1,2,4-triazoline (*IIIa*) was obtained in a yield of 52%. In addition to *IIIa*, as a product of the reversibly formed *I* with 3-methylbutanol, 1-tetra-O-acetyl-β-D-glucopyranosyl-O-(3-methylbutyl)thiocarbamate (*VI*) was isolated. For R = CH_3, C_2H_5, and $CH(CH_3)_2$ the formation of only *VI* was observed (TLC), compound *VI* being formed solely on account of a lower thermal stability of the corresponding 1-acylthiosemicarbazides. Much more successful was cyclization brought about with sodium methoxide. The expected deacylated nucleoside analogs were obtained in one step and in good yields. Substances *IVa*–*IVd* and *IVe* contain 3-alkyl-5-thioxo-triazolines and 5-thioxo-1,2,4-triazoline-3-one, respectively, as aglycons.



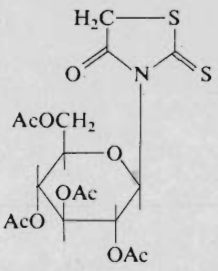


IIIa, R^1 = H; R^2 = CH_3CO
IIIb, R^1 = CH_3; R^2 = CH_3CO
IIIc, R^1 = C_2H_5; R^2 = CH_3CO
IIId, R^1 = $CH(CH_3)_2$; R^2 = CH_3CO

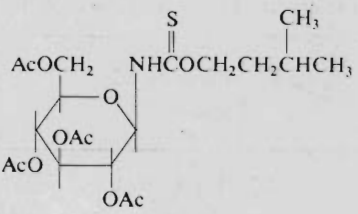
IVa, R^1 = R^2 = H
IVb, R^1 = CH_3, R^2 = H
IVc, R^1 = C_2H_5, R^2 = H
IVd, R^1 = $CH(CH_3)_2$, R^2 = H

IIIe, R = CH_3CO
IVe, R = H

In the just described series of reactions also the one with thioglycolic acid has been carried out. In boiling xylene and without isolation of the addition intermediate it afforded N-(1-tetra-O-acetyl-β-D-glucopyranosyl)-2-thioxo-1,3-thiazolidine-4-one (*V*).



V



VI

The structure of the synthesized substances is analogous to that of products of similar addition-cyclization reactions[3]. The presence of the carbohydrate component was reflected by the fragment ion peak at *m/z* 331 ($[C_{14}H_{19}O_9]^{\bullet+}$) formed from the fully acetylated D-glucopyranose part of the molecules, found in the mass spectra of *IIIa–IIId*, and *V*. The base peak in the spectra, containing also a weak peak of molecular ions, was that at *m/z* 43 ($[CH_3CO]^{\bullet+}$). The stereochemistry of the glycosidic linkage follows from the coupling constants $J_{1,2}$ ~8·0 Hz deduced from ^{1}H-NMR spectra of *IIIa–IIIe*, *IVa–IVe*, and *V*. The IR spectra of all synthesized substances show diagnostically significant absorption bands at ~1 060 cm^{-1} (symmetric C—O—C vibrations), ~1 270 cm^{-1} (asymmetric C—O—C vibrations), ~3 000 cm^{-1} (ν_{C-H}) and ~3 400 cm^{-1} (ν_{N-H}). The absorption band $\nu_{C=O}$ of the acetyl groups present in compounds *IIa–IIe*, *IIIa–IIIe*, and *V* was present in the spectra at ~1 740 cm^{-1}. The band at 1 668 (in the spectrum of *IIIe*) and 1694 cm^{-1} (in the spectrum of *IVe*) was assigned to $\nu_{C=O}$ of the heterocyclic part of the molecules.

EXPERIMENTAL

Melting points (uncorrected) were determined on a Kofler hot-stage. The course of the reactions and the purity of the products was monitored by thin-layer chromatography on silica gel foils (Silufol). The components were located with iodine vapours. The yields, melting points and analytical data for the synthesized derivatives are in Table I.

The IR spectra (700–3 800 cm^{-1}) for chloroform solutions in a 0·6 mm NaCl cell (compounds *IIa–IIe*, *IIIa–IIId*, *V*, and *VI*), or taken by the KBr technique (compounds *IIIe* and *IVa–IVe*) were measured with a UR-20 (Zeiss, Jena) spectrometer. The instrument was calibrated against a polystyrene foil. The ^{1}H-NMR spectra for solutions in chloroform-*d* (compounds *IIa–IIe*, *IIIa–IIId*, *V*, and *VI*) or dimethylsulphoxide-d_6 (compounds *IIIe* and *IVa–IVe*) were taken at 80 MHz with a Tesla BS-487 C spectrometer using tetramethylsilane as the internal standard. The mass spectra were measured with an MS 902 S instrument applying the direct

sample-introduction technique. The ionizing current was 100 μA, and the temperature in the ionizing chamber was 110°C. The electron absorption spectra (200—480 nm) were measured with a Specord UV VIS (Zeiss) spectrometer. The starting hydrazides were prepared from the corresponding ethyl esters and hydrazine hydrate[6].

TABLE I

Data characteristic of the synthesized substances

Compound	Formula (mol. mass)	Calculated/Found			M.p.[a] (yield, %)[b]	UV[c] λ_{max}, nm (log ε)
		% C	% H	% N		
IIa	$C_{16}H_{23}N_3O_{10}S$	42·76	5·16	9·35		252 (4·11)
	(449·4)	42·92	5·18	9·30	(94)	
IIb	$C_{17}H_{25}N_3O_{10}S$	44·05	5·43	9·06		252 (4·15)
	(463·5)	43·50	5·23	8·79	(75)	
IIc	$C_{18}H_{27}N_3O_{10}S$	45·27	5·70	8·80		254 (4·10)
	(477·5)	45·28	5·60	8·37	(84)	
IId	$C_{19}H_{29}N_3O_{10}S$	46·42	5·95	8·55		254 (4·12)
	(491·5)	46·43	5·83	8·12	(82)	
IIe	$C_{18}H_{27}N_3O_{10}S$	43·81	5·52	8·52		250 (4·11)
	(493·5)	43·93	5·50	7·91	(88)	
IIIa	$C_{16}H_{21}N_3O_9S$	44·54	4·91	9·74	185—186	259 (4·19)
	(431·4)	44·53	4·80	9·45	(67)	
IIIb	$C_{17}H_{23}N_3O_9S$	45·84	5·20	9·43	194—195	251 (4·38)
	(445·4)	45·71	5·43	9·88	(53)	
IIIc	$C_{18}H_{25}N_3O_9S$	47·05	5·48	9·14	203—204	266 (4·19)
	(459·5)	47·50	5·70	8·82	(51)	
IIId	$C_{19}H_{27}N_3O_9S$	48·19	5·75	8·87	208—209	275 (3·96)
	(473·5)	48·02	5·51	8·77	(23)	
IVa	$C_8H_{13}N_3O_5S$	36·49	4·97	15·96	186—188	259 (4·20)
	(263·3)	36·47	4·94	15·99	(67)	
IVb	$C_9H_{15}N_3O_5S$	38·98	5·45	15·15	271—272	260 (4·21)
	(277·5)	38·40	5·59	15·25	(53)	
IVc	$C_{10}H_{17}N_3O_5S$	41·22	5·88	14·42	271—272	260 (4·18)
	(291·3)	40·69	6·09	13·90	(51)	
IVd	$C_{11}H_{19}N_3O_5S$	43·27	6·27	13·76	201—202	252 (4·17)
	(305·3)	43·44	6·50	13·90	(23)	

[a] Compounds *IIa—IIe* could not be crystallized, compounds *IIIa—IIId* were crystallized from ethanol, and *IVa—IVd* from methanol; [b] the yields given for *IV—d* are those of the cyclization reaction effected with sodium methoxide (acetylation reaction gave virtually theoretical yield of the products; [c] UV spectra taken for solutions in methanol.

4-(Tetra-O-acetyl-β-D-glucopyranosyl)-1-formyl-3-thiosemicarbazide (*IIa*)

A solution of formylhydrazide (0·24 g, 0·004 mol) in dioxane (15 ml) was added slowly (15 min) with stirring at room temperature into a solution of *I* (1·56 g, 0·004 mol) in dioxane (20 ml). The mixture was stirred for 15 min and concentrated to give a crude product (1·8 g) suitable for the next step. A portion was purified by chromatography on silica gel (chloroform–acetone 9 : 1) to give the analytical sample.

4-(Tetra-O-acetyl-β-D-glucopyranosyl)-1-acyl-3-thiosemicarbazides *IIb*—*IId*

A mixture of *I* (1·94 g, 0·005 mol) and the respective hydrazide (0·005 mol) in dioxane was heated under reflux for 2 h. The solution was concentrated and the residue was chromatographed on a column of silica gel. Elution with chloroform–acetone 9·5 : 0·5 gave unreacted *I* and subsequent elution with ethyl acetate afforded the desired pure product.

4-(Tetra-O-acetyl-β-D-glucopyranosyl)-1-ethoxycarbonyl-3-thiosemicarbazide (*IIe*)

A solution of ethoxycarbonyl hydrazide (0·42 g, 0·004 mol) in benzene (15 ml) was added at room temperature dropwise and with stirring into a solution of *I* (1·56 g, 0·004 mol) in benzene (30 ml). The mixture was stirred for 4 h and then concentrated at reduced pressure to give a crude product (0·86 g) which was used for the next step. A portions was purified by chromatography on silica gel (benzene–methanol–acetone 8 : 1 : 1) to afford the analytical sample.

4-(1-Tetra-O-acetyl-β-D-glucopyranosyl)-5-thioxo-1,2,4-triazoline (*IIIa*)

A solution of *IIa* (0·33 g) in 3-methylbutanol (15 ml) was heated under reflux for 2 h. The solution was cooled, concentrated at reduced pressure and the syrupy residue was eluted from a column of silica gel with chloroform–acetone 9 : 1 to give first amorphous N-(1-tetra-O-acetyl--β-D-glucopyranosyl)-O-(3-methylbutyl)thiocarbamate (*VI*, 0·1 g, 29%). IR Data (chloroform, cm^{-1}): 1 756 (C=O), 2 962 (C—H), 3 382 (N—H). UV Data (methanol): λ_{max}, nm (log ε) 250 (4·10). For $C_{20}H_{31}O_{10}NS$ (477·5) calculated: 50·30% C, 6·54% H, 2·93% N; found: 48·83% C, 6·30% H, 2·68% N. No molecular ion peak was present in the mass spectrum of the substance. ^{1}H-NMR Data ($CDCl_3$, δ): 0·98 (6 H, d, dimethyl group); 2·05 (4 × 3 H, s, acetyl); 3·88—4·62 (8 H, m, H-5, H-6, H-6′, CH—CH_2—CH_2 of the 3-methylbutyl group); 4·98—5·65 (3 H, m, H-2, H-3; H-4); 6·00 (1 H, t, H-1); 6·94 (1 H, d, N—H).

Subsequently eluted was *IIIa* (0·15 g, 52%).

4-(1-Tetra-O-acetyl-β-D-glucopyranosyl)-5-thioxo-1,2,4-triazolines *IIIb*—*IIIe*

Acetic anhydride (10 ml) was added at 0°C to a solution of *IVb*—*IVe* (0·15 g) in pyridine (10 ml), the mixture was allowed to react for 12 h and then processed conventionally. Compounds *IIIb* to *IIId* were obtained by chromatography on silica gel (chloroform–acetone 9 : 1). In the case of *IIIe* the solution of the crude product in ethanol was treated with charcoal, filtered and crystallized from the same solvent to give material melting at 244—246°C. Properties of *IIIe*: IR Data (KBr, cm^{-1}): 1 668 (C=O, heterocyclic), 1 755 (C=O, acetyl groups), 2 985 (C—H), 3 410 (N—H). UV Data (methanol): λ_{max}, nm (log ε) 247 (3·92) 282 (3·68). For $C_{16}H_{21}N_3O_{10}S$ (447·4) calculated: 42·95% C, 4·73% H, 9·39% N; found: 43·07% C, 4·30% H, 9·19% N. ^{1}H-NMR Data: DMSO-d_6, δ): 1·95 (4 × 3 H, s, acetyl); 4·07 (3 H, m, H-5, H-6, H-6′); 4·93*b*—5·37 (3 H, m, H-2, H-3, H-4); 5·94 (1 H, d, H-1, $J_{1,2}$ 7·9 Hz).

3-Alkyl-4-(1-β-D-glucopyranosyl)-5-thioxo-1,2,4-triazolines *IVa—IVd*

A mixture of *IIa—IId* (0·004 mol) and 0·1M sodium methoxide (20 ml) was heated under reflux for 4 h, and, after cooling, deionized with Dowex 50 W (H^+) resin. The crude product, which crystallized after filtration, was purified by chromatography on silica gel with chloroform–methanol 7 : 2.

4-(1-β-D-Glucopyranosyl-5-thioxo-1,2,4-triazoline-3-one (*IVe*)

The title substance (1·14 g, 79·7%, m.p. 279—282°C) was obtained from *IIe* (2·5 g, 0·005 mol) following the procedure described in the preparation of *IVa—IVd*, except that no purification by chromatography was necessary. IR Data (KBr, cm^{-1}): 1 694 (C=O, heterocyclic), 2 920 (C—H), 3 300 (O—H). UV Data (methanol): λ_{max}, nm (log ε) 248 (415). For $C_8H_{13}N_3O_6S$ (279·3) calculated: 34·40% C, 4·69% H, 15·05% N; found: 34·36% C, 4·92% H, 14·62% N. ^{1}H-NMR Data (DMSO-d_6, δ): 3·65 (4 H, m, OH); 5·33 (6 H, m, H-2, H-3, H-4, H-5, H-6, H-6′); 5·64 (1 H, d, H-1, $J_{1,2}$ 9·8 Hz).

N-(1-Tetra-O-acetyl-β-D-glucopyranosyl)-2-thioxo-1,3-thaiazolidine-4-one (*V*)

A mixture of *I* (0·78 g, 0·002 mol) and thioglycolic acid (0·18 g, 0·002 mol) in xylene was refluxed for 12 h. The mixture was cooled, concentrated at reduced pressure and the residue was crystallized from ethanol to give *V* (0·58 g, 65%), melting at 168—170°C. IR Data ($CHCl_3$, cm^{-1}): 1 758 (C=O), 3 010 (C—H). UV Data (methanol) λ_{max}, nm (log ε) 251 (4·15), 297 (5·12). For $C_{17}H_{21}NO_{10}S_2$ (463·5) calculated: 44·05% C, 4·56% H, 3·04% N; found: 43·54% C, 4·46% H, 2·97% N. Mass spectral data (*m/z*): 463 ([$M^{+\bullet}$]. ^{1}H-NMR Data ($CDCl_3$, δ) [2·01 (4 × 3 H, s, acetyl); 3·86 (2 H, s, CH_2, heterocyclic); 4·22 (3 H, m, H-5, H-6, H-6′); 5·10—6·02 (3 H, m, H-2, H-3, H-4); 6·18 (1 H, d, H-1, $J_{1,2}$ 8·0 Hz).

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