Synthesis of nucleoside analogues using 2,3,4,6-tetra-*O*-acetyl--β-D-glucopyranosyl isothiocyanate

[a]M. VALENTINY and [b]A. MARTVOŇ

[a]*Department of Organic Chemistry, Slovak Technical University, 812 37 Bratislava*

[b]*Institute of Drug Research, 811 04 Bratislava*

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Synthesis of nucleoside analogues by cyclodehydration reaction of substituted thiourea derivatives is described. The starting thiourea derivatives were obtained by the reaction of 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate with α-oxoammonium chlorides.

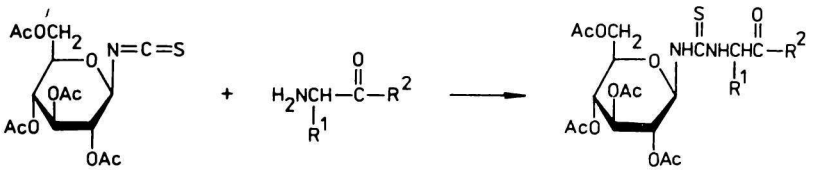
В работе приводится синтез аналогов нуклеозидов реакцией циклодегидратирования замещенных тиомочевин. Последние были приготовлены реакцией 2,3,4,6-тетра-*O*-ацетил-β-D-глюкопиранозилизотиоцианата с хлоридами α-оксоаммония.

We have previously described [1] syntheses of some nucleoside analogues by cyclization reaction of 4-substituted 1-acylthiosemicarbazides, using 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate as the starting material. In continuation of this work nucleoside analogues where 4,5-disubstituted imidazoline-2-thione forms the aglycon have now been prepared.

Gabriel and *Pinkus* [2] prepared 4-methylimidazoline-2-thione by heating an aqueous solution of aminoacetone hydrochloride and potassium thiocyanate. *Kjellin* and *Sandström* [3] refluxed a toluene solution of α-aminoacetophenone and methyl isothiocyanate in the presence of triethylamine and, in addition to the corresponding imidazoline-2-thione, isolated also the intermediate thiourea derivative. A series of *N*,5-disubstituted imidazoline-2-thiones have been synthesized by *Doney* and *Altland* [4] who applied Kjellin's method, without the isolation of the thiourea derivative.

We have prepared our starting material, namely 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate (*I*), following the described procedure [5]. Reaction of *I* with oxoammonium chlorides in the presence of triethylamine gave *N, N'*-disubstituted thioureas (*IIa—IIe*, Scheme 1). When the reaction was conducted in boiling

xylene *N*,5-disubstituted imidazoline-2-thione (*IIIa*, $R^3 = H$) was not obtained. In this case the decomposition of the adduct *IIa* into its components was observed (t.l.c.). This property is characteristic of urea and thiourea derivatives having bulky substituents [6]. Nucleoside analogues *IVa—IVe* having disubstituted im-

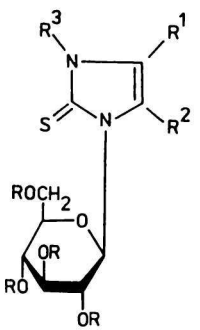


I

IIa: $R^1 = H$, $R^2 = CH_3$
IIb: $R^1 = R^2 = CH_3$
IIc: $R^1 = CH_3$, $R^2 = C_2H_5$
IId: $R^1—R^2 = (CH_2)_3$
IIe: $R^1—R^2 = (CH_2)_4$

Scheme 1

idazoline-2-thiones as aglycons were obtained in yields of 34—92%, with simultaneous deacetylation, by treatment of *IIa—IIe* with sodium methoxide. The lower yields of methylene-bridged imidazoline-2-thiones were caused obviously by steric factors. Deacetylated products *IVa—IVe* were acetylated with acetic anhydride—pyridine, to give *IIIa—IIIe*. The expected structures *IIIb—IIIe* followed



	R	R^1	R^2	R^3
IIIa	Ac	H	CH_3	CH_3CO
IIIb	Ac	CH_3	CH_3	H
IIIc	Ac	CH_3	C_2H_5	H
IIId	Ac	$(CH_2)_3$		H
IIIe	Ac	$(CH_2)_4$		H
IVa	H	H	CH_3	H
IVb	H	CH_3	CH_3	H
IVc	H	CH_3	C_2H_5	H
IVd	H	$(CH_2)_3$		H
IVe	H	$(CH_2)_4$		H

from mass and ^{1}H-n.m.r. spectra; compound *IIIa* was a product of both *O* and *N* acetylation. The nitrogen atom of the heterocyclic part of the nucleoside analogue was localized by ^{13}C-n.m.r. spectroscopy. The product of *N* acetylation was obtained also in cases where theoretical amount of acetic anhydride, required for *O* acetylation only, was used. *N* acetylation was not observed with the other derivatives of this series.

The prepared, substituted thioureas contain a carbonyl group in the noncarbohydrate component. This group took part in the cyclization reaction and, therefore, we wanted to take advantage of its presence in preparing further derivatives. Reactions of carbonyl compounds with hydrazine are known to produce substituted hydrazones in high yields. The analysis of the reaction mixture formed by allowing to react *II* with hydrazine hydrate in ethanol under reflux for 3 h showed that no condensation had taken place and that the cyclization product *IVa*, with simultaneous deacetylation, had been formed. When similar derivatives, 4-substituted 1-acylthiosemicarbazides, were cyclized [7], the formation of triazoline-2-thiones was explained by the reaction in this process of the preponderating enol form of the starting material.

The structure of the synthesized substances was confirmed by analyzing the spectral data. The mass spectra of *IIIa—IIIe* contained weak molecular ion peaks. The base peak of the spectra was that at *m/z* 331 ($[C_{14}H_{19}O_9]^+$) of the tetraacetylglucosyl part of the molecule. Intense were also ions originating from the disintegration of the latter residue after electron impact, as described by *Biemann* and *DeJongh* [8]: *m/z* 331, 271, 229, 211, 169, 127, and 109. Fragments of these *m/z* values are formed by gradual eliminations of ketene (*m/z* 42) and acetic acid (*m/z* 60) from the molecular ions. Characteristic of the fragmentation of the aglycon portion of the molecule is the elimination of HCN (*m/z* 27) and the cleavage of SH groups (*m/z* 33) from the protonized, substituted imidazoline-2-thiones [9]. The β configuration of the glycosidic linkage follows from the coupling constant $J_{1,2} \sim 8.5$ Hz found in the ^{1}H-n.m.r. spectra of *IIIa—IIIe* and *IVa—IVe*. The chemical shift found in the spectra for aromatic and aliphatic protons of the substituted imidazoline-2-thiones is in agreement with the literature [10]. The i.r. spectra of all synthesized derivatives show bands at ~ 1060 and 1270 cm^{-1} reflecting symmetrical and asymmetrical C—O—C stretchings, respectively. The bands characteristic of the presence of C—H and N—H arrangements were at 3000 and 3400 cm^{-1}, respectively. The spectra of *IIa—IIe* and *IIIa—IIIe* show at 1750 cm^{-1} a band characteristic of the CO groups associated with the acetyl functions. The wide bands present in the spectra of *IVa—IVe* at 3200—3400 cm^{-1} are those of stretching vibrations of free and associated OH groups. The absorption bands of imidazole (*IIIa—IIIe*, *IVa—IVe*) are in three main regions: 760—880 cm^{-1} (imidazole ring), 1500—1620 cm^{-1} (aromatic C—N and C—C bonds), and 3300—3500 cm^{-1} (N—H bonds) [11].

Table 1

Characteristic data for the synthesized substances

Compound	Formula	*M*	Calculated/found			Yield[b] %	M.p., °C[a]	UV λ_{max}/nm (log ε)[c]
			% C	% H	% N			
IIa	$C_{18}H_{26}N_2O_{10}S$	462.5	46.74	5.66	6.06	88	211—214	276 (4.23)
			46.73	5.57	6.56			
IIb	$C_{19}H_{28}N_2O_{10}S$	476.5	47.88	5.92	5.88	74	215—217	250 (4.27)
			48.01	5.91	5.90			
IIc	$C_{20}H_{30}N_2O_{10}S$	490.5	48.96	6.16	5.71	82		251 (4.03)
			49.11	6.21	5.90			279 (3.98)
IId	$C_{20}H_{28}N_2O_{10}S$	488.5	49.16	5.77	5.73	61	201—203	249 (4.36)
			49.43	6.28	5.68			
IIe	$C_{21}H_{30}N_2O_{10}S$	502.5	50.18	6.02	5.58	73	209—210	252 (4.23)
			49.90	5.99	5.72			
IIIa	$C_{20}H_{26}N_2O_{10}S$	486.5	49.37	5.38	5.76	83	159—162	281 (4.18)
			49.06	5.30	5.76			
IIIb	$C_{19}H_{26}N_2O_9S$	458.5	49.77	5.72	6.11	83	153—154	280 (4.29)
			49.45	5.71	6.40			
IIIc	$C_{20}H_{28}N_2O_9S$	472.5	50.84	5.98	5.93	77	185—186	280 (4.27)
			50.54	6.20	6.29			
IIId	$C_{20}H_{26}N_2O_9S$	470.5	51.05	5.57	5.95	35	182—185	282 (4.16)
			50.64	5.18	5.84			
IIIe	$C_{21}H_{28}N_2O_9S$	484.5	52.05	5.82	5.78	45	184—186	282 (4.25)
			51.90	5.75	5.78			
IVa	$C_{10}H_{16}N_2O_5S$	276.3	43.46	5.84	10.14	83	262—264	273 (4.29)
			43.37	5.76	10.19			
IVb	$C_{11}H_{18}N_2O_5S$	290.3	45.50	6.24	9.65	83		276 (4.13)
			45.58	6.40	9.61			

Table 1 (Continued)

Compound	Formula	*M*	Calculated/found			Yield[b] %	M.p., °C[a]	UV λ_{max}/nm (log ε)[c]
			% C	% H	% N			
IVc	$C_{12}H_{20}N_2O_5S$	304.4	47.35	6.62	9.21	77	202—205	274 (4.20)
			47.05	6.35	8.82			
IVd	$C_{12}H_{18}N_2O_5S$	302.4	47.67	6.00	9.26	35		277 (4.18)
			47.21	5.81	9.05			
IVe	$C_{13}H_{20}N_2O_5S$	316.4	49.34	6.37	8.86	45		276 (4.25)
			49.11	6.28	8.50			

a) Compounds *IIc*, *IVb*, *IVd*, and *IVe* are amorphous; compound *IVa* was crystallized from methanol and *IVe* from water; all other compounds were crystallized from ethanol.

b) Yields of *IVa*—*IVe* were calculated for cyclization reaction effected with sodium methoxide; acetylation is assumed to produce acetates in theoretical yield.

c) Measured in methanol.

Experimental

Melting points were measured on a Kofler hot-stage. The course of reactions and the purity of products were monitored by thin-layer chromatography (t.l.c.) on commercial silica gel-coated aluminium foils (Silufol). Detection was effected by iodine vapours. Characteristics of the synthesized derivatives are given in Table 1.

The i.r. spectra (700—3800 cm^{-1}) for solutions in chloroform (compounds *IIa—IIe*, *IIIa—IIIe*) or substances in KBr pellets (*IVa—IVe*) were measured with a UR-20 spectrometer, which was calibrated against a polystyrene foil. ^{1}H-N.m.r. spectra (80 MHz) were measured at 25°C, for solutions in $CDCl_3$ (compounds *IIa—IIe*, *IIIa—IIIe*) or DMSO-d_6 (*IVa—IVe*) using a Tesla BS 487 C spectrometer. ^{13}C-N.m.r. spectra of *IIIa* were measured in $CDCl_3$ at 25°C with a Jeol FX-60 spectrometer. Tetramethylsilane was used as the internal standard in all n.m.r. measurements. The mass spectra were measured at an emission of 100 μA and the temperature of the ionization chamber of 110°C, with an MS 902 S instrument, applying direct sample-introduction technique. The electronic spectra were measured in the range from 200 to 480 nm, using a Specord UV VIS (Zeiss, Jena) spectrometer. The α-oxoammonium chlorides were prepared by the Gabriel reaction, starting with the corresponding carbonyl compounds [12]; α-aminocyclopentanone and α-aminocyclohexanone were prepared by rearrangements of *N,N*-dichloroalkyl amines [13].

N′-Substituted N-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)thioureas (IIa—IIe)

A solution of α-oxoammonium chloride (0.002 mol) in ethanol was added dropwise at room temperature during 30 min to a solution of *I* (0.78 g; 0.002 mol) and triethylamine (0.002 mol) in benzene, and the mixture was stirred for 2 h. After concentration, crystallization from ethanol gave *IIa* (0.79 g, 86%) or *IIb* (0.74 g, 74%). Compounds *IIc—IIe* were isolated by chromatography on a column of silica gel (chloroform—acetone 9.5:0.5) in yields given in Table 1. For the preparation of analytical samples, the substances were recrystallized from ethanol.

1-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-4,5-dialkylimidazoline-2-thiones (IIIa—IIIe)

Compounds *IIa—IIe* (0.002 mol) were treated with 0.1 M methanolic sodium methoxide (20 ml) as described for the preparation of *IVa—IVe*. The mixture was deionized with Dowex 50 W (H^+) resin, concentrated at reduced pressure, and acetic anhydride (50%

excess over the theoretical amount) was added to the solution of the residue in pyridine (1.5 ml, 0°C). After 2 h at room temperature, methanol was added with cooling, and the mixture was concentrated at reduced pressure with coevaporation with toluene. Compounds *IIIa* and *IIIc* were crystallized from ethanol, and compounds *IIIb*, *IIId*, and *IIIe* were isolated by chromatography as described for the preparation of *IIe*.

4,5-Dialkyl-1-β-D-glucopyranosylimidazoline-2-thiones (IVa—IVe)

Compounds *IIa—IIe* (0.002 mol) were treated with 0.1 M methanolic sodium methoxide (20 ml): *IIa* — 30 min, room temperature; *IIb*, *IIc* — 2 h, reflux; *IId*, *IIe* — 90 min, room temperature. The mixture was deionized with Dowex 50 W (H^+) resin, concentrated at reduced pressure and compounds *IVa* and *IVd* were obtained by crystallization from methanol and water, respectively. Compounds *IVb*, *IVc*, and *IVe* were obtained by chromatography of the crude material on a column of silica gel (chloroform—methanol 7:2).

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