Synthesis of *N*-glucosyl derivatives of 5-amino-1,2,3-thiadiazole and 5-substituted 2-amino-1,3,4-thiadiazole

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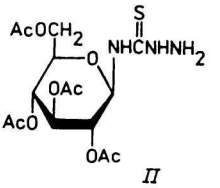
Oxidative cyclization of 4-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)thiosemicarbazone with $FeCl_3$ afforded the corresponding *N*-glucosides having 2-amino-5-aryl-1,3,4-thiadiazoles as aglycons. The cycloaddition of 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate with diazomethane gave 5-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylamino)-1,2,3-thiadiazole.

Реакцией окислительной циклизации 4-(2,3,4,6-тетра-*O*-ацетил-β-D-глюкопиранозил)тиосемикарбазонов с $FeCl_3$ были приготовлены *N*-глюкозиды, агликон которых образуют 2-амино-5-арил-1,3,4-тиадиазолы. Реакцией присоединения по циклу из 2,3,4,6-тетра-*O*-ацетил-β-D-глюкопиранозилизоцианата с диазометаном был получен 5-(2,3,4,6-тетра-*O*-ацетил-β-D-глюкопиранозиламино)-1,2,3-тиадиазол.

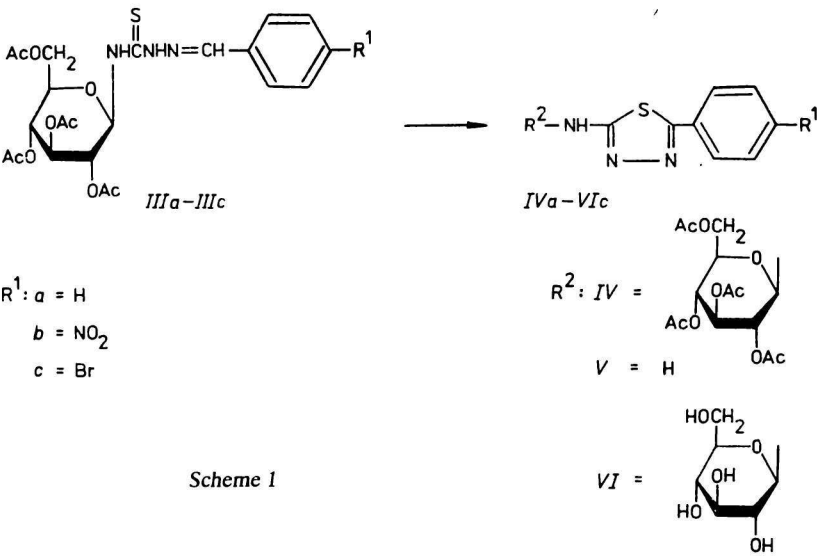
Derivatives of thiosemicarbazide are useful starting materials in syntheses of heterocyclic systems. Treatment with esters of imidate acids of 4-substituted thiosemicarbazides, depending upon pH, yields either 1,3,4-thiadiazoles or 3-mercapto-1,2,4-triazoles [1]. *Kurzer* [2, 3] prepared 2-amino-5-alkyl(aryl)-amino-1,3,4-thiadiazoles from aminoguanidine and isothiocyanates; 1-amidinothiosemicarbazide, formed as an intermediate, was isolated as the corresponding *p*-toluenesulfonate. An arrangement suitable for the synthesis of 1,3,4-thiadiazole constitute reaction products of thiosemicarbazides with aldehydes, *i.e.* thiosemicarbazones. Their cyclization effected with $FeCl_3$, yielded [4] 2-alkyl(aryl)-amino-1,3,4-thiadiazoles in very good yields.

In the present work the formation of 1,3,4-thiadiazole ring has been studied using as the starting material 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate (*I*). The latter compound can be readily obtained [5] by reacting 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide with silver thiocyanate. Treatment of *I* with hydrazine gave 4-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)thiosemicarbazide (*II*) in a better yield and less laboriously than described previously [6]. Condensation [6] of *II* with aromatic aldehydes afforded



II

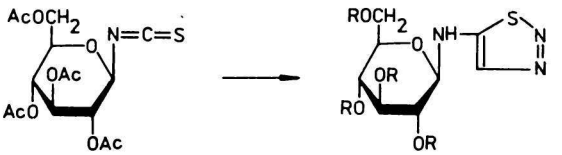
4-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)thiosemicarbazones (*IIIa—IIIc*). Subsequent oxidative cyclization of 4-substituted thiosemicarbazones using ferric chloride hexahydrate as the reagent was performed in boiling ethanol (Scheme 1). Owing to the presence of per-*O*-acetyl-D-glucose, the course of the reaction was



Scheme 1

a complicated process. The ratio of the products formed depended on the reaction time. After a reaction period of 1 1/2 h the following products were isolated: unreacted thiosemicarbazone (*IIIa—IIIc*), 2-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylamino)-5-aryl-1,3,4-thiadiazole (*IVa—IVc*), and 2-amino-5--aryl-1,3,4-thiadiazole (*Va—Vc*) [1, 7]. The yields of 1,3,4-thiadiazole *N*-glucosides were in the range 22—38%. When the reaction time was prolonged to 6 h 2-amino-5-aryl-1,3,4-thiadiazole derivatives (*Va—Vc*) were isolated in yields of 87%. In the first stage of the reaction oxidation of thiosemicarbazones *IIIa—IIIc* yields *N*-glucosides of 1,3,4-thiadiazole (*IVa—IVc*). The latter derivatives are unstable under acidic conditions and hydrolyze splitting off the aglycon, 2-amino-5-aryl-1,3,4-thiadiazoles (*Va—Vc*). Thus, after the reaction time of 6 h the only substance isolated was the product of acid hydrolysis of the *N*-glycoside formed as the primary product.

The reaction of isothiocyanates with 1,3-dipolar compounds has been extensively studied [8]. Cycloaddition reaction of diazo compounds with isothiocyanates give iminothiadiazolines which rearrange immediately to form 5-substituted 1,2,3-thiadiazoles [9]. In this series of reactions the reactivity of *I* with diazoalkanes has been studied. Reaction of *I* with diazomethane (Scheme 2) in tetrahy-



I *VII*: R = Ac
VIII: R = H

Scheme 2

drofuran produced 5-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylamino)-1,2,3--thiadiazole (*VII*). Diazoethane or ethyl diazoacetate did not react with *I* to produce 5-substituted 1,2,3-thiadiazole even at higher temperature and with prolonged reaction time, showing that *I* is less reactive in cycloaddition reactions than other isothiocyanates.

The analysis of mass spectral fragmentation of *IIIb* and *IVb* shows clearly that the cycloaddition dehydrogenation took place in the expected manner. The intense peak at *m/z* 222, corresponding to the protonized aglycon, *i.e.* 2,5-disubstituted 1,3,4-thiadiazole, is present only in the spectrum of *IVb* but not in that of 4-substituted thiosemicarbazone *IIIb*. Its further fragmentation occurs in the manner characteristic of 1,3,4-thiadiazoles. Characteristic fragments are formed also from the original substance *IVb*. The presence of the carbohydrate residue is evident from the characteristic fragmentation of the substance, producing the ion at *m/z* 331. The most intense peaks in the spectra of *IIIb*, *IVa—IVc*, and *VII* are those corresponding to the fragments formed from the acetylated glucose part of the molecule. The molecular ion peaks in the spectra are relatively weak. The β configuration of the glycosidic linkage follows from the value of the coupling constant $J_{1,2} \sim 8.0$ Hz, found in the ^{1}H-n.m.r. spectra of *IVa—IVc*, *VIa—VIc*, *VII*, and *VIII*. The i.r. spectra of *IVa—IVc* and *VIa—VIc* show strong bands at 1300—1650 cm^{-1}. Owing to a great number of absorption bands in this region (aromatic C—N and C—C stretchings and skeletal stretchings of the thiadiazole ring), the individual bands are not easy to be assigned. The spectra of *IVa—IVc* and *VII* show a characteristic band at 1750 cm^{-1}, the one of the carbonyl group associated with the acetyl functions. The broad bands at 3200—3400 cm^{-1} in the spectra of *VIa—VIc* and *VIII* manifest the stretching vibrations of free and associated hydroxyl groups.

Experimental

Melting points were determined on a Kofler hot-stage. All reactions and the purity of substances were monitored by thin-layer chromatography (t.l.c.) on Silufol (commercial silica gel-coated aluminium foil). Detection was effected with iodine vapours. The yields, melting points and analytical data for the synthesized compounds are in Table 1. The i.r. spectra (700—3800 cm^{-1}) were measured for chloroform solutions or compounds in KBr pellets (compounds *IVa—IVc*, *VII* and *VIa—VIc* and *VIII*, respectively) with a UR-20 (Zeiss, Jena) spectrometer. The instrument was calibrated against a polystyrene foil. ^{1}H-N.m.r. spectra for solutions in $CDCl_3$ (compounds *IVa—IVc*, *VII*) and DMSO-d_6 (compounds *VIa—VIc*, *VIII*) were measured with a Tesla BS 487 C (80 MHz) spectrometer at 25°C, using tetramethylsilane as the internal standard. Mass spectra were measured at an ionization current of 100 μA, using an MS 902 S spectrometer. The temperature of the ionization chamber was 110°C, and the direct sample-introduction technique was applied. Electronic spectra (200—480 nm) were measured with a Specord UV VIS (Zeiss, Jena) spectrometer. Diazomethane and diazoethane were prepared from *N*-nitroso-*N*-(methyl or ethyl)urea [10].

4-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)thiosemicarbazide (II)

Hydrazine hydrate (0.2 g) in ethanol (15 ml) was added dropwise at room temperature and with stirring to a solution of *I* (1 g; 0.003 mol) in ethanol (60 ml), and the mixture was stirred for 15 min. The precipitate was filtered off, washed with ethanol, to give *II* (1.02 g, 95%) melting at 167—168°C [6].

4-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-(4-bromobenzylidene)thiosemicarbazone (IIIc)

The substance, m.p. 214—216°C, was prepared according to the method of van de Kamp and Micheel in 88% yield. IR data ($CHCl_3$, cm^{-1}): 1756 (C=O), 3050 (C—H), 3335 (N—H). ^{1}H-NMR data (δ): 2.05 (4 × 3H, s, acetyl); 3.88—4.38 (3H, m, H-6, H-6′, H-5); 5.05—5.22 (3H, m, H-2, H-3, H-4); 5.71 (1H, dd, H-1, $J_{1,2}$ = 8.4 Hz); 7.55 (4H, m, phenyl); 7.82 (1H, s, —CH=); 8.31 (1H, d, N—H, $J_{1,2}$ = 8.4 Hz); 10.23 (1H, s, N—H).

For $C_{22}H_{26}BrN_3O_9S$ (588.4) calculated: 5.43% S, 13.53% Br; found: 5.58% S, 13.71% Br.

2-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosylamino)-5-aryl--1,3,4-thiadiazoles (IVa—IVc)

A mixture of 4-substituted thiosemicarbazone (*IIIa—IIIc*, 0.0017 mol) and $FeCl_3 \cdot 6H_2O$

Table 1

Characteristic data for the synthesized substances

Compound	Formula	*M*	Calculated/found			Yield %	M.p., °C[a]	UV λ_{max}/nm (log ε)[b]
			% C	% H	% N			
IVa	$C_{22}H_{25}N_3O_9S$	507.7	52.04	4.96	8.31	23	208—210	316 (4.45)
			52.47	4.55	7.95			
IVb	$C_{22}H_{24}N_4O_{11}S$	552.5	47.82	4.38	10.14	38	227—229	347 (4.29)
			47.48	4.98	9.92			
IVc	$C_{22}H_{24}BrN_3O_9S$	586.4	44.90	4.45	7.14	25	238—240	312 (4.50)
			44.97	4.76	7.41			
VIa	$C_{14}H_{17}N_3O_5S$	339.4	49.54	5.05	12.38	23		323 (4.54)
			49.12	4.87	11.80			
VIb	$C_{14}H_{16}N_4O_7S$	384.4	43.74	4.20	14.58	38	216—218	355 (4.28)
			43.32	4.51	14.10			
VIc	$C_{14}H_{16}BrN_3O_5S$	418.4	40.19	3.86	10.04	25		322 (4.57)
			39.80	3.51	10.68			
VII	$C_{16}H_{21}N_3O_9S$	431.4	37.07[c]	4.02	7.63	35	86—88	290 (4.11)
			37.25	4.13	7.68			
VIII	$C_8H_{13}N_3O_5S$	263.3	36.50	4.94	15.97	35		306 (4.01)
			36.14	4.59	15.82			

a) Solvent for crystallization: *IVa*, *IVb* — ethyl acetate—petroleum ether; *IVc* — benzene—acetone; *VIb* — ethanol; *VII* — chloroform—petroleum ether.

b) Measured in methanol.

c) Calculated for $C_{16}H_{21}N_3O_9S \cdot CHCl_3$ (compound *VII* crystallized with 1 mole of chloroform).

(0.005 mol) in ethanol (25 ml) was heated under reflux for 1 1/2 h, cooled, and concentrated at reduced pressure. Water was added, and the precipitate was filtered off, washed with water and dried. The material was chromatographed on a column of silica gel (benzene—acetone—methanol 8:1:1) to give *IVa* (0.2 g, 23%) and 2-amino-5-phenyl-1,3,4--thiadiazole [1] (*Va*, 0.13 g, m.p. 219—220°C), or *IVb* (0.31 g, 38%) and 2-amino-5-(*p*--nitrophenyl)-1,3,4-thiadiazole [1] (*Vb*, 0.11 g, m.p. 257—259°C), or *IVc* (0.25 g, 25%) and 2-amino-5-(*p*-bromophenyl)-1,3,4-thiadiazole [7] (*Vc*, 0.15 g, m.p. 215—218°C.

5-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosylamino)-1,2,3-thiadiazole (VII)

A cold solution of diazomethane (0.006 mol) in ether was added portionwise to a cold solution of isothiocyanate *I* (1.5 g; 0.004 mol) in tetrahydrofuran, and the solution was left at room temperature for 12 h. After concentration at reduced pressure, the residue was chromatographed on a column of silica gel (ethyl acetate—cyclohexane 8:2).

5-Aryl-2-(β-D-glucopyranosylamino)-1,3,4-thiadiazoles (VIa—VIc) and 5-(β-D-glucopyranosylamino)-1,2,3-thiadiazole (VIII)

Compounds *IVa—IVc* and *VII* (0.001 mol) were treated under reflux with a mixture of methanol (10 ml) and 1 M methanolic sodium methoxide (0.3 ml) for 30 min. After cooling, the solution was deionized with Dowex 50 W (H^+) resin, concentrated at reduced pressure, and the residue was recrystallized (Table 1).

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