Synthesis of heterocyclic systems with a carbohydrate fragment
3.* Synthesis and structure of fused pyrimidine systems based on levoglucosenone

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The reactions of levoglucosenone with urea, thiourea and *N*-cyano- and *N*-nitroguanidines result in pyrimidine systems fused with a carbohydrate fragment. In all cases, the cyclization occurs stereospecifically. The structures of different products of conversion of levoglucosenone were established on the basis of NMR and X-ray diffraction data.

Key words: levoglucosenone, urea, thiourea, *N*-cyanoguanidine, *N*-nitroguanidine, stereoselective heterocyclization, X-ray diffraction analysis.

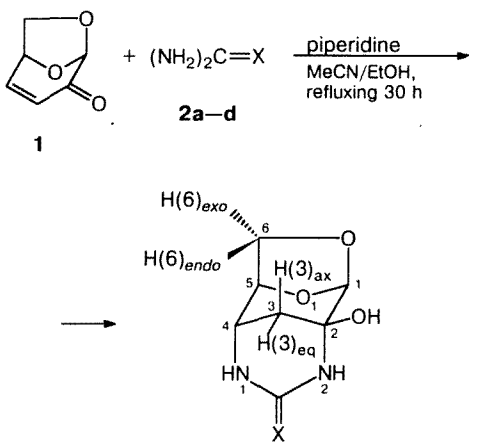
Cyclization of levoglucosenone with 1,3-binucleophiles that we have used for producing tetrahydropyridones fused with a carbohydrate fragment[1] can be applied to the synthesis of their pyrimidine analogs. The present work describes the synthesis of pyrimidine systems fused with a carbohydrate fragment by the interaction of levoglucosenone **1** with urea, thiourea, and guanidine derivatives. The formation of pyrimidines in reactions of ureas, thioureas, and guanidines with α,β-unsaturated ketones has been studied earlier,[2–5] but *N*-cyano- and *N*-nitroguanidine, used by us, have not been used previously in similar reactions.

The interaction of compound **1** with thiourea **2b**, *N*-cyanoguanidine **2c**, and *N*-nitroguanidine **2d** in the presence of a base results in the closure of the pyrimidine cycle with the formation of compounds **3b—d**. The reaction of urea **2a** with levoglucosenone under the same conditions affords an inclusion compound of **3a** · $0.5(NH_2)_2CO$ composition (Scheme 1).

It should be noted that in spite of the drastic reaction conditions used, cleavage of water from compounds **3** does not occur. As in the case of the cyclization of levoglucosenone with amides of α-methylene-active acids,[1] this probably results from the impossibility of formation of a double bond at the bridge head, according to the Bredt rule.

In addition to three broadened singlets at δ 6.2, 5.9, and 5.8 (with an integral intensity of one proton each) corresponding to the N(1)—H, N(2)—H, and OH protons, the ^1H NMR spectrum of the adduct of **1** with urea (Table 1) contains one more broadened singlet at δ 5.3 with an integral intensity of two protons. In the ^{13}C NMR spectrum (Table 2), two signals are present in the region of carbonyl groups at δ 159.15 and 160.28, the latter being significantly lower. The structure of the adduct was also confirmed by elementary analysis and ^{15}N NMR data (three signals are observed; two of them are doublets corresponding to the N(1)—H and N(2)—H nitrogen atoms, and the third one is a triplet of the NH_2 group nitrogen atom).

Scheme 1



3a—d

3a: X = O (58 %)
3b: X = S (53 %)
3c: X = NCN (31 %)
3d: X = NNO_2 (48 %)

The heterocycle is closed at the side opposite to the 1,6-anhydro bridge, which is proved by the coupling

* For Communication 2, see Ref. 1.

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Table 1. ^{1}H NMR spectra of compounds **3a—d**

Compound	^{1}H NMR, δ (*J*/Hz)							
	H(1)	$H(3)_{eq}$	$H(3)_{ax}$	H(4)	H(5)	$H(6)_{exo}$	$H(6)_{endo}$	Other H atoms
3a	4.91 (d, *J* = 1.9)	1.73 (ddt, *J* = 12.0, 3.1, 1.9)	2.31 (dm, *J* = 12.0)	3.43 (dist.quint)	4.37 (m)	3.72 (dd, *J* = 7.8, 4.7)	4.04 (d, *J* = 7.8)	5.20—5.35 (br.s, NH_2) 5.76—5.83 (br.s) 5.90 (br.s) (N(2)—H, OH) 6.19—6.26 (br.s, N(1)—H)
3b	4.96 (d, *J* = 1.9)	1.68 (ddt, *J* = 12.2, 3.1, 1.9)	2.36 (dm, *J* = 12.2)	3.58 (dq, *J* = 4.7, 3.1)	4.45 (m)	3.73 (dd, *J* = 7.9, 4.7)	4.09 (d, *J* = 7.9)	7.48—7.55 (br.s) 6.45 (s) (N(2)—H, OH) 8.1—8.2 (br.s, N(1)—H)
3c	5.03 (d, *J* = 1.9)	1.77 (ddt, *J* = 12.4, 3.1, 1.9)	2.45 (br.dd, *J* = 12.4, 3.2)	3.73 (dist.quint)	4.50 (m)	3.78 (dd, *J* = 8.0, 4.7)	4.14 (d, *J* = 8.0)	6.1—6.3 (br.s) 6.8—6.9 (br.s) (N(2)—H, OH) 7.38—7.45 (br.s, N(1)—H)
3d	5.12 (d, *J* = 1.9)	1.86 (ddt, *J* = 12.5, 3.1, 1.9)	2.57 (dd, *J* = 12.5, 3.2)	3.96 (m)	4.62 (m)	3.84 (dd, *J* = 8.0, 4.7)	4.23 (d, *J* = 8.0)	6.43—6.51 (br.s) 8.56—8.66 (br.s) (N(2)—H, OH) 8.87—8.95 (br.s, N(1)—H)

Table 2. ^{13}C NMR spectra compounds **3a—d**

Compound	^{13}C NMR, δ						
	C(1)	C(2)	C(3)	C(4)	C(5)	C(6)	Other C atoms
3a	105.04 (d)	80.91 (s)	31.20 (dd)	48.15 (d)	78.20 (d)	67.84 (dd)	159.15 (s, NHCONH) 160.28 (s, $CO(NH_2)_2$)
3b	104.39 (d)	81.70 (s)	29.05 (dd)	50.22 (d)	78.05 (d)	67.88 (dd)	179.74 (s, CC)
3c	104.38 (d)	81.02 (s)	29.92 (dd)	48.73 (d)	77.97 (d)	67.99 (dd)	118.29 (s, CN) 161.23 (s, C=N)
3d	104.40 (d)	81.15 (s)	28.68 (dd)	48.70 (d)	78.32 (d)	68.33 (dd)	159.09 (s, $C=NNO_2$)

constants in the ^{1}H NMR spectrum, $J_{4,3ax}$~3 Hz and $J_{4,3eq}$ ~3 (see Table 1 and Ref. 1). X-ray diffraction analysis of compound **3b** (Fig. 1, Tables 3—5) presents one more evidence for the cyclization stereochemistry. It has been proved that the pyrimidine cycle, rather than the thiazine one, is closed in the reaction with thiourea.[4] We established that the pyranose cycle in the **3b** molecule has a practically undistorted chair conformation (the torsion angles along the perimeter of the pyranose cycle are close to 60°, the C(3) atom is 0.689 Å "above" the plane formed by the C(1)—C(2)—C(4)—C(5) atoms, and the O(1) atom is 0.836Å "below" this plane). The pyrimidine cycle has a sofa conformation (the C(3) atom is deflected from the plane by 0.806Å), and the dioxolane cycle has the envelope conformation (the O(1) atom is deflected from the plane by 0.650 Å).

A comparison of X-ray diffraction data for **3b** with those of the adduct of levoglucosenone with 3,4-dinitropyrazole **4** (see Ref. 6) allows one to understand the reasons for the specific differences between the ^{1}H NMR spectra of the products of the addition of levoglucosenone to the C=C bond,[6—9] on the one hand, and the cyclization products of type **3**, on the other hand

Table 3. Atomic coordinates in the **3b** molecule (×10^4, ×10^3 for H atoms)

Atom	*x*	*y*	*z*	U_{iso}
S	−6330(3)	−5815(0)	−4706(5)	7.9(07)
O(1)	−3367(8)	−6878(13)	1824(12)	7.6(1)
O(2)	−1155(8)	−5507(12)	3867(12)	7.7(2)
O(3)	−2180(10)	−2616(13)	0737(15)	8.7(2)
N(1)	−3535(11)	−7027(16)	−2634(16)	7.9(2)
N(2)	−4146(12)	−4371(17)	−1382(16)	8.4(2)
C(1)	−2696(16)	−5249(20)	−2443(23)	8.9(3)
C(2)	−2638(13)	−4334(19)	0324(19)	7.4(2)
C(3)	−1417(14)	−5157(20)	−0748(21)	7.8(3)
C(4)	−1858(12)	−7035(18)	−1040(17)	7.0(2)
C(5)	−2050(17)	−7718(24)	1249(23)	8.9(3)
C(6)	−0678(13)	−7171(18)	3206(18)	7.7(2)
C(7)	−4514(15)	−5714(23)	−2794(21)	8.3(2)
H(N(1))	−407(12)	−832(16)	−349(16)	9.9
H(N(2))	−490(11)	−318(15)	−167(14)	10.9
H(1)	−334(11)	−452(15)	340(14)	6.1
$H(3)_{eq}$	−010(12)	−507(17)	058(17)	8.6
$H(3)_{ax}$	−134(13)	−462(15)	−242(17)	6.7
H(4)	−203(11)	−878(16)	134(14)	6.7
H(5)	−105(12)	−798(16)	−179(16)	9.5
$H(6)_{exo}$	−047(11)	−820(16)	456(17)	8.6
$H(6)_{endo}$	067(12)	−711(15)	289(17)	3.2

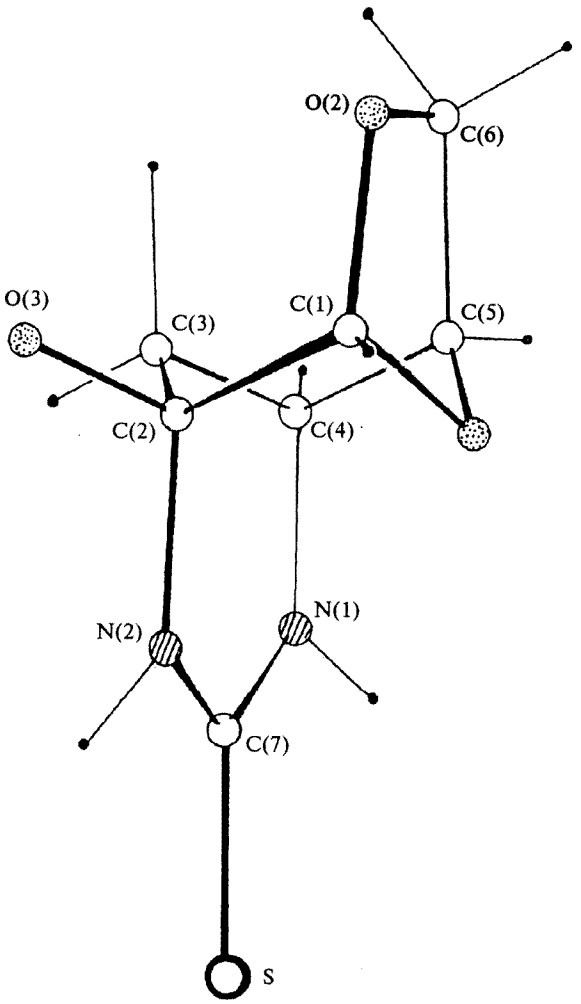
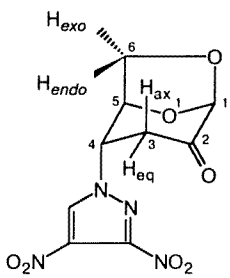


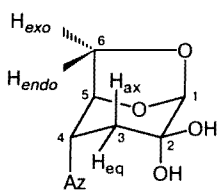
Table 4. Bond lengths (d) and bond angles (ω) in the **3b** molecule

Bond	d/Å	Angle	ω/deg
S—C(7)	1.713(12)	S—C(7)—N(1)	118.5(10)
C(7)—N(1)	1.331(21)	S—C(7)—N(2)	119.9(14)
C(7)—N(2)	1.354(20)	N(1)—C(7)—N(2)	121.5(13)
N(2)—C(2)	1.455(13)	C(4)—N(1)—C(7)	122.5(12)
N(1)—C(4)	1.536(13)	C(2)—N(2)—C(7)	119.7(14)
C(1)—C(2)	1.491(20)	C(5)—O(1)—C(1)	100.6(13)
C(2)—C(3)	1.525(19)	C(6)—O(2)—C(1)	104.5(10)
C(3)—C(4)	1.535(21)	O(2)—C(1)—O(1)	107.0(13)
C(4)—C(5)	1.542(19)	O(2)—C(1)—C(2)	111.6(15)
C(5)—O(1)	1.441(18)	O(1)—C(1)—C(2)	108.1(8)
O(1)—C(1)	1.427(20)	N(2)—C(2)—C(1)	112.8(14)
C(1)—O(2)	1.416(14)	C(3)—C(2)—N(2)	106.6(9)
O(2)—C(6)	1.468(17)	C(3)—C(2)—C(1)	109.9(13)
C(5)—C(6)	1.522(16)	N(2)—C(2)—O(3)	108.0(11)
		C(3)—C(2)—O(3)	106.9(13)
		C(1)—C(2)—O(3)	112.4(9)
		C(2)—C(3)—C(4)	106.4(13)
		C(3)—C(4)—C(5)	108.4(10)
		C(3)—C(4)—N(1)	105.8(13)
		C(4)—C(5)—O(1)	109.3(12)
		C(4)—C(5)—C(6)	111.5(14)
		C(5)—C(6)—O(2)	104.5(12)

(see also Ref. 1). These differences involve mainly changes in the coupling constants and, consequently, changes in the form of certain signals. In turn, the change in coupling constants results from the change in the geometry of the pyranose cycle on passing from the addition products to the cyclization products. The pyranose cycle in molecule **4** has actually the form of a noticeably distorted (unlike **3b**) chair (some torsion angles along the perimeter of the pyranose cycle deviate significantly from 60°, the C(3) atom is 0.45 Å "higher" than the plane formed with the C(1)—C(2)—C(4)—C(5) atoms, and the O(1) atom is 0.83 Å "lower" than this plane). Thus, the closure of heterocycle compensates somehow the distortion of the pyranose cycle caused with 1,6-anhydro bridge. The elimination of the distortion should be explained precisely by the closure of the heterocycle rather than by the change in hybridization of the C(2) atom, since the coupling constants in *gem*-diols of type **5** (see Ref. 6) are approximately the same (except for the geminal $J_{3_{ax},3_{eq}}$) as in compounds of type **4**, in spite of sp^3-hybridization. Comparative values of some torsion angles in molecules **3b** and **4** and the corresponding coupling constants are given in Table 5.



4



5

(Az is the azole residue)

Experimental

^{1}H NMR spectra were obtained on a Bruker WM-250 spectrometer with a 250.13 MHz operating frequency, and ^{13}C and ^{15}N NMR spectra on a Bruker AM-300 spectrometer at 75.47 and 30.42 MHz, respectively. $CH_3{}^{15}NO_2$ (60% ^{15}N) was used as the external standard for recording the ^{15}N NMR spectra. Upfield chemical shifts are given with a minus sign. ^{1}H NMR spectra were recorded in DMSO-d_6. IR spectra of compounds **3a—d** were recorded in KBr pellets on a Specord M-80 instrument. Elemental analyses of the products gave satisfactory results.

Table 5. Some torsion angles (φ) and coupling constants in molecules **3b** and **4**

Angle	Molecule **3b**		Molecule **4**	
	φ/deg	*J*/Hz	φ/deg	*J*/Hz
O(1)—C(1)—C(2)—C(3)	68.8		55.0	
C(1)—C(2)—C(3)—C(4)	54.1		34.4	
C(2)—C(3)—C(4)—C(5)	51.2		35.9	
C(3)—C(4)—C(5)—O(1)	64.3		58.5	
C(4)—C(5)—O(1)—C(1)	73.1		77.9	
C(5)—O(1)—C(1)—C(2)	74.8		75.0	
H(4)—C(4)—C(3)—H(3)$_{eq}$	61.2	$J_{4,3eq}$ = 3.1	83.5	$J_{4,3eq}$ < 1
H(4)—C(4)—C(3)—H(5)	39.5	$J_{4,5}$ = 3.1	60.5	$J_{4,5}$ < 1
H(4)—C(4)—C(3)—H(3)$_{ax}$	56.4	$J_{4,3ax}$ = 3.1	34.4	$J_{4,3ax}$ = 7.8
H(4)—C(4)—N(1)—H(N(1))	38.1	$J_{4,H(N(1))}$ = 4.7		
H(5)—C(5)—C(6)—H(6)$_{exo}$	23.6	$J_{5,6exo}$ = 4.7	23.7	$J_{5,6exo}$ = 5.7
H(5)—C(5)—C(6)—H(6)$_{endo}$	88.2	$J_{5,6endo}$ < 1	98.0	$J_{5,6endo}$ = 1.2

Reactions of levoglucosenone with urea 2a, thiourea 2b, and guanidine derivatives 2c,d. General procedure. The starting compound **2** (0.01 mol) was dissolved in a mixture of EtOH (10 mL) and MeCN (10 mL) (in the case of **2b**, 15 mL of MeCN was taken). Piperidine (6 drops, 10 mol. %) and then levoglucosenone (1.26 g, 0.01 mol) were added to the solution obtained. The reaction mixture was refluxed for 30 h; the residue precipitated was filtered off every five hours (the precipitation began ~10 h after boiling was started). All of the products **3a—d** are colorless crystals; DMSO was used for recrystallization.

(1*S*,2*R*,5*S*,6*S*)-Hydroxy-3,11-dioxa-7,9-diazatricyclo-[4.3.1.1^{2,5}]undecan-8-one (3a)* · 0.5(NH$_2$)$_2$CO was obtained from compound **1** and urea **2a**, yield 0.84 g (58 % with respect to the amount of urea taken). M.p. 175—176 °C. IR, ν/cm^{-1}: 3520, 3280, 3130, 1675. ^{15}N NMR (DMSO-d$_6$), δ: −304.70 (t, *J* = 87.2 Hz); −291.05 (d, *J* = 91.2 Hz); −271.37 (d, *J* = 90.6 Hz). Found (%): C, 41.3; H, 5.7; N, 19.1. $C_7H_{10}N_2O_4 \cdot 0.5(NH_2)_2CO$. Calculated (%): C, 41.67; H, 5.59; N, 19.44.

(1*S*,2*R*,5*S*,6*S*)-Hydroxy-3,11-dioxa-7,9-diazatricyclo-[4.3.1.1^{2,5}]undecan-8-thione (3b) was obtained from compound **1** and thiourea **2b**, yield 1.07 g (53 %). M.p. >230 °C (decomp.). IR, ν/cm^{-1}: 3305, 3240, 1545, 1490—1500.

(1*S*,2*R*,5*S*,6*S*)-Cyanoimino-3,11-dioxa-7,9-diazatricyclo-[4.3.1.1^{2,5}]undecan-8-ol (3c) was obtained from **1** and cyanoguanidine **2c**, yield 0.65 g (31 %). M.p. 197—199 °C (decomp.). IR, ν/cm^{-1}: 3330, 3280, 2185, 2160, 1605, 1570, 1540.

(1*S*,2*R*,5*S*,6*S*)-Nitroimino-3,11-dioxa-7,9-diazatricyclo-[4.3.1.1^{2,5}]undecan-8-ol (3d) was obtained from **1** and nitroguanidine **2d**, yield 1.10 g (48 %). M.p. 209 °C (decomp.). IR, ν/cm^{-1}: 3300, 1575.

X-Ray diffraction analysis. (1*S*,2*R*,5*S*,6*S*)-Hydroxy-3,11-dioxa-7,9-diazatricyclo[4.3.1.1^{2,5}]undecan-8-thione (3b). Single crystals were grown from DMSO, monoclinic; $C_7H_{10}N_2O_3S$, *a* = 8.695(1) Å, *b* = 7.918(1) Å, *c* = 6.088(1) Å, β = 104.50(1)°, *V* = 405.65 Å^3, *Z* = 2; $P2_1$ space group. The unit cell parameters and intensities of 537 independent reflections with $I > 2\sigma(I)$ were obtained on an RED-4 four-circle automatic diffractometer (λ(Cu-Kα), ω-θ/2θ-scanning, graphite monochromator, θ < 60°). The structure was solved by the direct method. The coordinates of non-hydrogen atoms were refined by the least-squares method in the anisotropic approximation. The coordinates of H atoms obtained from the difference series were refined in the isotropic approximation. The final discrepancy value was *R* = 0.084.

* The systematic nomenclature and the corresponding atomic numbering used in the names of the compounds are not used anywhere else in this work.

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