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DETERMINATION OF SUGAR HYDRAZIDE AND HYDRAZONE STRUCTURES IN SOLUTION

YASUKO TAKEDA*
Research Laboratories, Chugai Pharmaceutical Co. Ltd. Toshima-ku, Tokyo 171 (Japan)
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ABSTRACT

Condensation products of isonicotino- and benzo-hydrazide, and *p*-bromophenylhydrazine with D-glucose, D-mannose, D-arabinose, and D-ribose, respectively, and of isonicotinohydrazide with sodium D-glucuronate, D-glucofuranurono-6,3-lactone, and D-glyceraldehyde were prepared. The structure of the compounds in solution was examined by ^{1}H- and ^{13}C-n.m.r. spectroscopy and optical rotation, and in solid state by i.r. spectroscopy. The study of the anomerization and ring–chain interconversion on solutions in various solvents showed that both anomerization and interconversion depend upon the sugar configuration, basicity of the hydrazine group, and proton-acceptor ability of the solvent.

INTRODUCTION

Determination of the structure of sugar hydrazones both in crystalline form and in solution is important for the study of ring–chain isomery. X-Ray crystallography[1–4] and infrared spectroscopy[5] of several sugar phenylhydrazones and sugar *p*-bromophenylhydrazones has revealed that they may occur in cyclic or in acyclic forms in the solid state. Some inconsistency seems to exist between the structures obtained from the crystals and the previously proposed acyclic structures, which were based on acetylation[6,7] and on the formazan reaction[8,9]. However, an n.m.r. study of L-arabinose *p*-bromophenylhydrazone in solution has shown a rapid transition from the cyclic into the acyclic form[10]. These study indicate that the predominant isomer in the crystalline form is not always that in solution, owing to ring–chain interconversion dependent on solvent, sugar configuration (most probably on the proportion of aldehyde form in the aqueous solution[11]), and basicity of the hydrazine group[12].

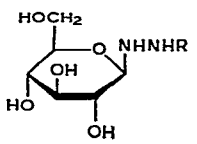
The present report describes the structures of several sugar hydrazones in crystalline form and the ring–chain interconversion of the compounds in solutions that were investigated by ^{1}H- and ^{13}C-n.m.r., and i.r. spectroscopy and optical

*Present address: Tokyo Biochemical Research Institute, Takada 3-41-8, Toshima-ku, Tokyo 171, Japan.

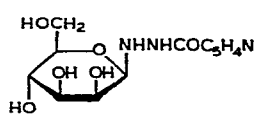
rotation. No information on the structure of sugar isonicotinoylhydrazones and sugar benzoylhydrazones has been found in the literature, with the exception of 2′-(sodium β-D-glucopyranosyluronate)isonicotinohydrazide (**9**), the structure of which was tentatively determined by i.r. spectroscopy[13]. In this study, n.m.r. spectroscopy was found to be useful for the determination at various times of the population of the isomers in solution.

RESULTS AND DISCUSSION

Glycosylhydrazides were obtained by condensation of isonicotinohydrazide with D-glucose[14] (**1**), D-mannose[14] (**4**), D-arabinose[14] (**5**), D-ribose[14] (**7**), sodium D-glucuronate[13] (**9**), and D-glucofuranurono-6,3-lactone[15] (**10**), and glycosylhydrazines by condensation of *p*-bromophenylhydrazine with D-glucose[3] (**3**), D-mannose[4] (**13**), D-arabinose[1] (**6**), and D-ribose[2] (**15**) according to the methods described in the literature. The condensation products of isonicotinohydrazide with D-glyceraldehyde (**11**), and benzohydrazide with D-glucose (**2**), D-mannose (**12**), D-arabinose (**14**), and D-ribose (**8**) were synthesized by heating equimolar amounts of the hydrazide and the



1 R = isonicotinoyl (COC_5H_4N)
2 R = Bz
3 R = $C_6H_4Br(p)$



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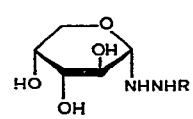
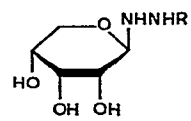
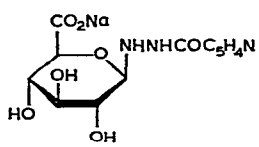


5 R = COC_5H_4N
6 R = $C_6H_4Br(p)$



7 R = COC_5H_4N
8 R = Bz



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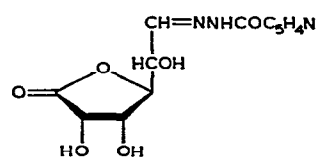

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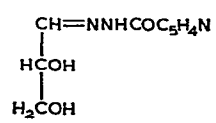

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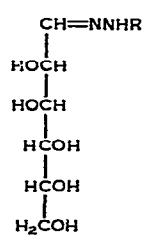
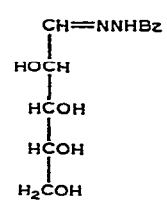


12 R = Bz
13 R = $C_6H_4Br(p)$



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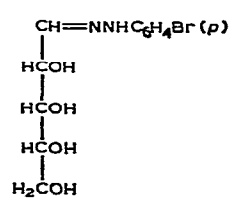

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TABLE I

^{1}H- AND ^{13}C-CHEMICAL SHIFTS AND TENTATIVE ASSIGNMENTS FOR **1**, **4**, AND **9**[a]

Chemical shifts	*Compound*		
	1	**4**	**9**
^{1}H-Shifts			
Hydrazine residue			
Arom. H-2′, H-6′	8.72	8.72	8.63
H-3′, H-5′	7.73	7.73	7.70
Sugar residue			
H-1	4.33, 4.80[b] (8.0)[c], (3.5)[c]	4.47, 4.79[b] (<2)[c], (<2)[c]	4.31, 4.84[b] (8.5)[c], (3.5)[c]
H-2		4.17, 4.05[b] (3.0)[c], (3.0)[c]	
^{13}C-Shifts			
Hydrazine residue			
Arom. C-2′, C-6′	150.5	150.7	150.9
C-3′, C-5′	122.9	123.0	123.1
C-4′	141.4	142.0	141.8
Carbonyl carbon	168.5	168.1	169.0
Sugar residue			
C-1	91.1	88.6, 90.2[b]	90.6, 88.9[b]
C-2	72.1	70.9, 71.8[b]	73.1, 74.1[b]
C-3	77.5	74.6	77.6
C-4	70.9	68.3	71.9
C-5	78.9	78.4	77.9
C-6	62.1	62.1	177.6

[a]Determined for solutions in deuterium oxide. [b]Chemical shift for minor peak due to α anomer. [c]Values in parentheses denote ^{1}H–^{1}H coupling constants (Hz).

sugar. Compounds **1–15** were obtained in crystalline form, except **7**, which was obtained as a lyophilized powder.

In Table I are listed ^{1}H- and ^{13}C-chemical shifts of resonances for **1**, **4**, and **9** in deuterium oxide solutions. ^{13}C-N.m.r. resonances at ~90 p.p.m. became doublet in the partially proton-decoupled spectra and are assignable to the anomeric C-1 atoms of the pyranosyl group linked to the hydrazine group with an *N*-glycosyl bond, because the chemical shifts correspond to those reported for the pyranosyl group of nucleotides[16] and glycosylamines[17,18]. Absence of a ^{13}C-n.m.r. resonance due to the carbon atom of the C=N bond[19] ruled out the hydrazone structure. Appearance for **1**, **4**, **9**, at δ 4.33, 4.47, and 4.31, respectively, of ^{1}H-n.m.r. signals having spacings of 8.0, <2, and 8.5 Hz, respectively, indicate that the hydrogen atoms are linked to the pyranose ring in axial conformation[20,21]. The coupling constant for H-1 of **4** does not indicate straightforwardly the presence of the β anomer in **4**, because H-2 is in equatorial orientation. But appearance, in the n.m.r. spectra for the deuterium oxide solutions kept for 24 h at 20–23°, of small ^{1}H- and ^{13}C-n.m.r. signals (at δ 4.79 and 90.2 p.p.m., respectively) that may be assigned to H-1 and C-1

of the α anomer, suggests anomerization and the presence of the β anomer in the crystal form of **4**. The ^{1}H signal at δ 4.79 was made evident by increasing the temperature, as it had been masked completely by the large HOD signal. Hence, **1**, **4**, and **9** were unequivocally determined to be 2′-(β-D-glucopyranosyl)isonicotinohydrazide, 2′-(β-D-mannopyranosyl)isonicotinohydrazide, and 2′-(sodium β-D-glucopyranosyluronate)isonicotinohydrazide, respectively. The high negative values of optical rotation for freshly prepared aqueous solutions of **1**, **4**, and **9** at 20° (−22.6°, −55.8°, and −35.2°, *c* 2.0, respectively) also support these structures. Except for **3**, **6**, **13**, and **15**, the crystal structures of which were determined by the X-ray diffraction method[1-4], the structure of the other compounds was characterized by the method just described for **1**, **4**, and **9**. Compound **7**, a lyophilized powder, contained the α and β anomers of the pyranose form, and the acyclic form.

On being kept for 72 h at room temperature, the solutions of **1**, **4**, and **9** in deuterium oxide showed increasing amounts of the α anomer in the order of **4>9>1** ^{1}H- and ^{13}C-n.m.r. signals ascribable to the hydrazones were not observed, indicating that cyclic forms were dominant in deuterium oxide. Appearance, during 72 h, of small signals due to the α and β anomers of the parent sugars indicated a slight

TABLE II

100 MHz ^{1}H-N.M.R. SPECTRAL DATA FOR **1**, **4**, **5**, **7**, AND **9–11**[a]

Compound	*^{1}H-Chemical shifts (p.p.m. from Me_4Si)*								
	β Anomer			*α Anomer*			syn *Form*		
	H-1β	*NH-1β*	*NH-2β*	*H-1α*	*NH-1α*	*NH-2α*	*H-1$_{syn}$*	*H-2$_{syn}$*	*NH-2$_{syn}$*
1	3.89d	5.96bs	10.32d	4.47d	5.66d	10.21d			11.72s
4	4.18d	5.57dd	10.19d	4.52d	5.68d	10.05d	7.70	4.20	11.74s
5	4.57o	5.88t	101.5d	3.82dd	6.12t	10.22d	7.71d	4.42t	11.48s
7	4.30o	5.86dd	10.21d	4.6o	6.15bd	10.07d	7.7o	4.3o	11.52s
9	4.01bd	6.30bs	11.12bs	4.60d	b	b	7.85d	4.32t	b
10				4.78d	6.22d	10.16d	7.7o	4.36t	11.84s
11							7.78d	4.15t	11.85s

Compound	*^{1}H–^{1}H Coupling constants (Hz)*							
	β Anomer			*α Anomer*			syn *Form*	
	H-1β–2β	*H-1β–NH-1β*	*NH-1β–2β*	*H-1α–2α*	*H-1α–NH-1α*	*NH-1α–2α*	*NH-1$_{syn}$–2$_{syn}$*	
1	8.0	2	3.5	3.5		6.0		
4	<2	10.5	5.0	<2	5.0	5.0		
5	2.5	6.0	6.0	8.0	5.0	6.0	<2	
7	8.0	3.5	6.0	3.5				
9	8.5			5.0			6.0	
10				3.0		5.0	6.0	
11							6.0	

[a]Determined for solutions in dimethyl sulfoxide-d_6 kept for 24 h at 21°.

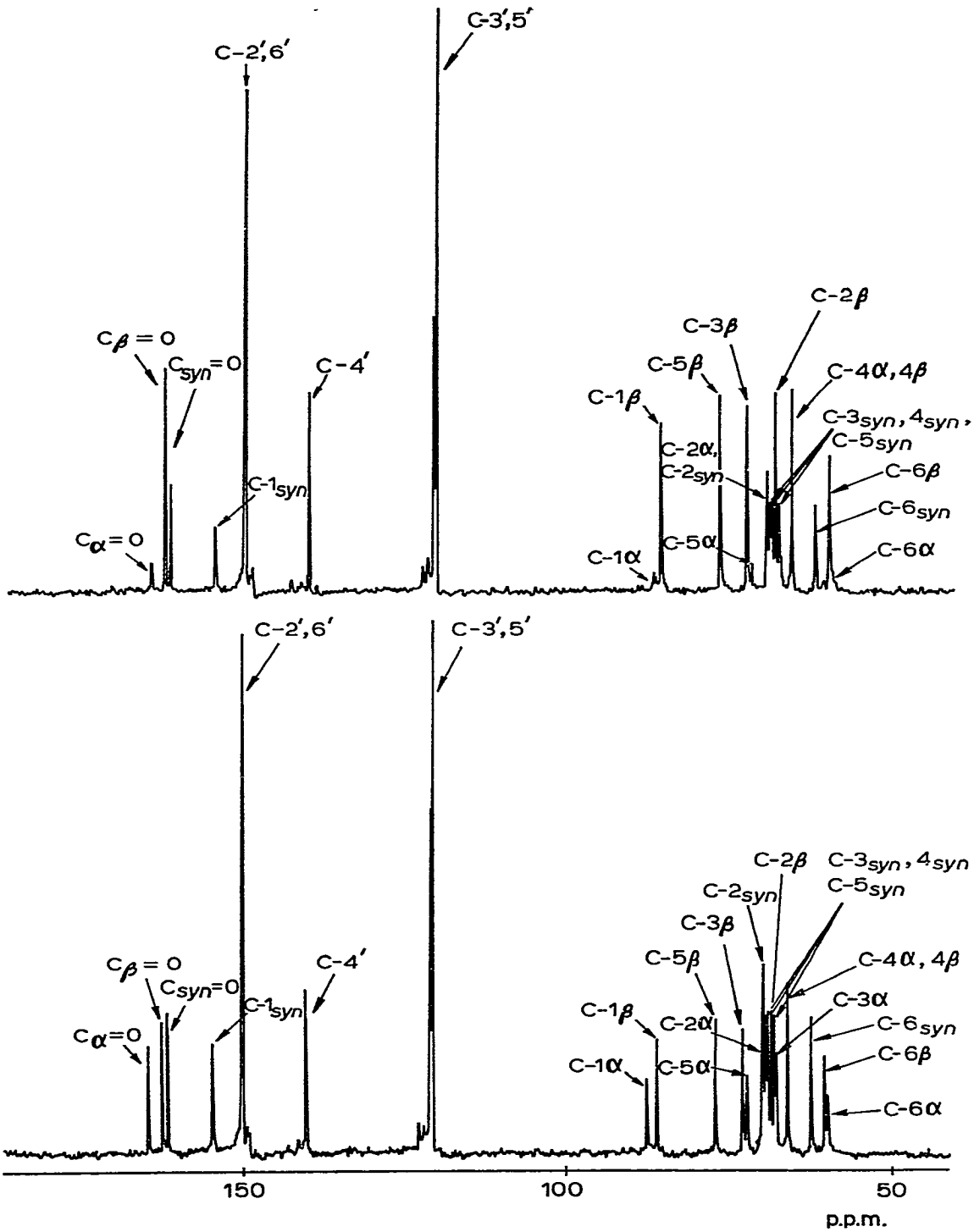

Fig. 1. 25.1-MHz ^{13}C-n.m.r. spectra of **4** in dimethyl sulfoxide-d_6 solution, after 3.5 h at room temperature (upper); and after 24 h (lower). Spectral assignments were based on comparison with chemically related compounds and with literature data[16–18].

hydrolysis. In dimethyl sulfoxide, the anomerization and interconversion took a somewhat different course. 100-MHz ^{1}H-n.m.r. data for solutions in dimethyl sulfoxide-d_6 of **1**, **4**, 2′-(α-D-arabinopyranosyl)isonicotinohydrazide (**5**), **7**, **9**, aldehydo-D-glucurono-6,3-lactone isonicotinohydrazone (**10**), and D-glyceraldehyde isonicotinohydrazone (**11**), being kept for 24 h at 21 °, are given in Table II. The signals were assigned by comparison with chemically related compounds. Compounds **1**, **4**, **5**, **7**, and **9** gave ^{1}H-n.m.r. resonances for the α and β anomers of the hydrazides and *syn* and *anti* forms of the hydrazones, **10** gave those for hydrazones and the cyclic form of the α anomer, and **11** only those for hydrazones. It has been reported that in solution the *syn* form of hydrazones is more abundant than the *anti* form[22–25]. Indeed, we observed for the *anti* form much smaller peaks at a slightly higher magnetic-field than for the corresponding *syn* form. Hence, the ^{1}H-n.m.r. data for the *anti* forms are not given in Table II. Fig. 1 shows the ^{13}C-n.m.r. spectra of **4** for a dimethyl sulfoxide-d_6 solution kept for 3.5 and 24 h at room temperature. All the ^{13}C signals expected for the three isomers appear separately, although the corresponding ^{1}H resonances corresponding to the sugar residue are mostly obscured by an envelope of overlapping signals. A comparison of the peak intensities of ^{13}C signals of the spectrum recorded after 3.5 h with those recorded after 24 h shows an increase of the α anomer and the *syn* form and a decrease of the β anomer with time, indicating

TABLE III

TIME DEPENDENCE OF AREA INTENSITY OF ^{1}H RESONANCES FOR **1**, **4**, **5**, **7**, AND **9–11** IN DIMETHYL SULFOXIDE-d_6[a]

Compound	*Conditions*[b]	*β Anomer*			*α Anomer*			syn *Form*	
		H-1β	*NH-1β*	*NH-2β*	*H-1α*	*NH-1α*	*NH-2α*	*H-1*$_{syn}$	*NH-2*$_{syn}$
1	A	1.0	0.9	0.95		0.05	0.05		<0.05
	B	0.67	0.60	0.58	0.40	0.37	0.37		0.05
	C	0.50	0.49	0.50	0.51	0.43	0.43	0.07	0.08
4	A	0.54	0.70[c]	0.59	0.17	[c]	0.09	0.17	0.21
	B	0.35	0.62[c]	0.30		[c]	0.24	0.32	0.35
	C	0.33	0.61[c]	0.33		[c]	0.29	0.35	0.38
5	A				0.92	0.90	0.87	0.10	0.07
	C	0.21	0.21	[c]		0.42	0.65[c]	0.38	0.40
7	A		0.57	0.56		0.21	0.20	0.24	0.22
	C		0.33	0.30		0.18	0.20	0.56	0.50
9	A	0.94	1.0[c]	0.92[c]	<0.05	[c]	[c]	<0.05	<0.05
	B	0.80	0.87[c]	0.82[c]	0.05	[d]	[d]	0.33	[d]
	C	0.65	[d]	[d]	0.05	[d]	[d]	0.33	[d]
10	A				0.05			0.95	0.93
	B				0.18	0.12	0.14	0.85	0.82
11	A							1.0	1.0
	B							1.0	1.0

[a]The area intensity was calculated relative to that of the ^{1}H signals at δ 8.7 due to aromatic ring H-2′ and H-6′. [b]A, immediately after dissolution; B, after 24 h at 21 °; and C, after 72 h (at the time of equilibrium). [c]The intensity is that of an unresolved peak corresponding to both anomers. [d]Extremely broad.

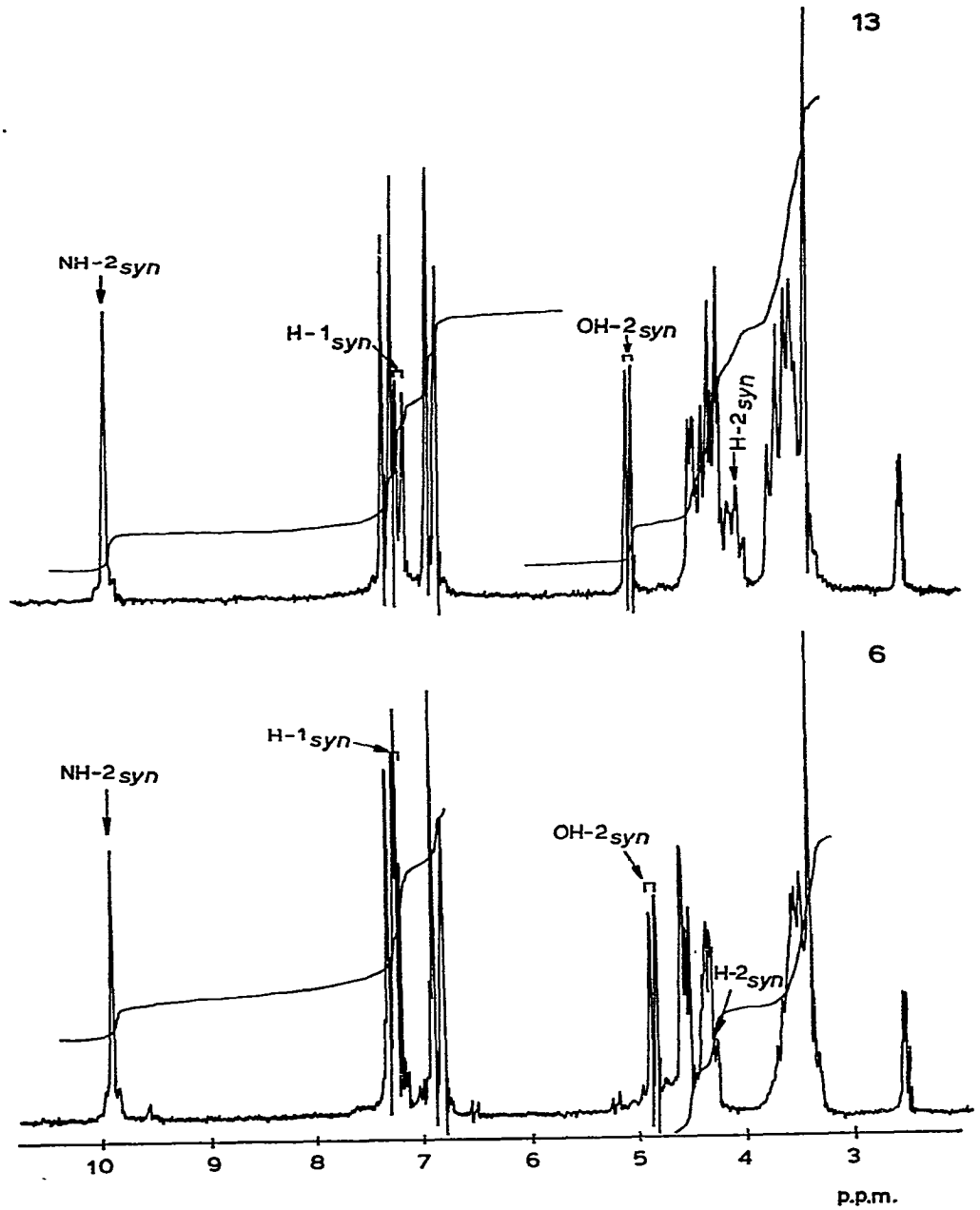

Fig. 2. 100-MHz ^{1}H-n.m.r. spectra of **13** (upper) and **6** (lower) in dimethyl sulfoxide-d_6 solution.

anomerization and ring-to-chain conversion. The time dependence of the amount of each isomer was examined by integration of the peak areas of ^{1}H signals for **1**, **4**, **5**, **7**, and **9**–**11** in dimethyl sulfoxide (see Table III). The values observed at 72 h were taken as those of the reaction equilibrium, as the optical rotations of **1**, **4**, **5**, **7**, and

9–11 were constant at this time. The relative intensity values were based on the intensity of the signal at δ 8.7 (which is assigned to the aromatic ring H-2′ and H-6′) taken as to 2.0. The values reflect the relative abundance of the isomers in solution, as the rates of anomerization and interconversion are slow as compared to the n.m.r. time-scale. The time dependence of the proportion of isomers varied with the sugar configurations, and the ratio of acyclic to cyclic forms at equilibrium increased in the order **7** > **5** > **4** > **1**, suggesting a relation between ring-to-chain interconversion and concentration of the aldehyde form in aqueous solution[11]. Compound **10** was found to be gradually converted into the α anomer[26,27] in the presence of a trace of water, whereas **11** maintained the hydrazone structure under the same conditions. The results of the mutarotation determination for solutions in water and dimethyl sulfoxide of **1**, **4**, **5**, **7**, and **9–11** were consistent with the result of the n.m.r. spectroscopy. The 100-MHz n.m.r. spectra of *aldehydo*-D-mannose *p*-bromophenylhydrazone (**13**) and *N*-(α-D-arabinopyranosyl)-*N*′-*p*-bromophenylhydrazine (**6**) in dimethyl sulfoxide-d_6 are shown in Fig. 2. Appearance of doublets around 7.2 p.p.m., which may be assigned to H-1 with the C=N bond[28], of singlets at δ 9.88 due to NH-2 protons of the hydrazones[1,9], and lack of ^{1}H resonances due to NH-1 protons of the α and β anomers of the hydrazines indicate that both compounds are acyclic hydrazones in solution. The hydrazone structure is inconsistent with the crystal structure[1] of **6**. However, **6** showed a rapid mutarotation in dimethyl sulfoxide, reaching an equilibrium within 30 min at 20°, whereas **13** exhibited no mutarotation, hence confirming a rapid ring–chain conversion for **6**.

The solvent effect on ring–chain interconversion was followed by n.m.r. and mutarotation determination. The ratios of cyclic to acyclic form in various solvents at equilibrium, estimated on the basis of ^{1}H-n.m.r. for solutions of **3** kept for 72 h at 21°, were 3 : 17, 7 : 13, and 3 : 2 for dimethyl sulfoxide-d_6, pyridine-d_5, and methanol-d_4 solutions, respectively. The data for the deuterium oxide solution of **3** are lacking because of insufficient solubility for n.m.r. measurement, but a comparison of the solution of **12** in methanol-d_4 and 1 : 1 (v/v) methanol-d_4–deuterium oxide shows an increasing proportion of the acyclic form in the order methanol-d_4 > methanol-d_4–

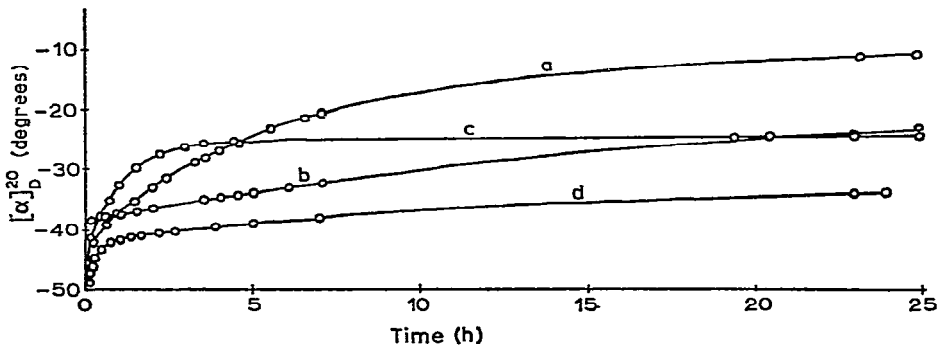

Fig. 3. Solvent effect on ring–chain interconversion. Mutarotations at 20° for solutions of **13** (*c* 2.0) in: (a) dimethyl sulfoxide, (b) pyridine, (c) methanol, and (d) 1 : 1 (v/v) methanol–water.

deuterium oxide, suggesting a correlation between proton-acceptor ability of the solvent and ring–chain interconversion. The mutarotations of **3** in the various solvents used for ^{1}H-n.m.r. (see Fig. 3) were in good agreement with the results from ^{1}H-n.m.r., indicating that equilibrium was reached more rapidly in methanol and water than in dimethyl sulfoxide and pyridine. The effect of basicity of the hydrazine groups on the interconversion was examined for solutions of **5**, **6**, and *aldehydo*-D-arabinose benzoylhydrazone (**14**) (which have the same sugar moiety) in dimethyl sulfoxide. The pH values for isonicotino- and benzo-hydrazides and *p*-bromophenylhydrazine at equal concentration (20mM in 1:1, v/v, ethanol–water) were 4.51, 4.64, and 5.30, respectively. The ratios of cyclic to acyclic form at equilibrium were 3:2, 1:1, and 0:1 for **5**, **6**, and **14**, respectively, suggesting a correlation between basicity of the hydrazine and hydrazides and the interconversion. Furthermore, a relationship between the rate of equilibration and the basicity of the hydrazine group was also observed (see Fig. 4). The possibility that both the increase in the basicity and proton-acceptor ability of the solvent might stimulate the ring-to-chain conversion may be interpreted in terms of electronic theory (see Scheme 1). As the strongly basic nitrogen atom of the hydrazine group is in high electron-density, the electron should move from N to C-1 carbon of the sugar residue (**16**) to form a C=N bonding, concomitantly with ring-opening of the sugar residue (**17**), with subsequent transfer of the proton from N to O-5 (**18**). The reverse reaction is also expected to take place when the hydrazine nitrogen atom is in electron deficiency, or when a proton attacks the imino nitrogen atom. In the case of a solvent having a proton-acceptor ability (*A*, see Scheme 2), the basicity of the hydrazire group would increase as the result of hydrogen bonding with the NH proton and, hence, ring-to-chain conversion would proceed. In addition, in such a solvent as methanol (*B*), which possesses proton-acceptor as well as proton-donor ability, proton transfer may be quite easy, resulting

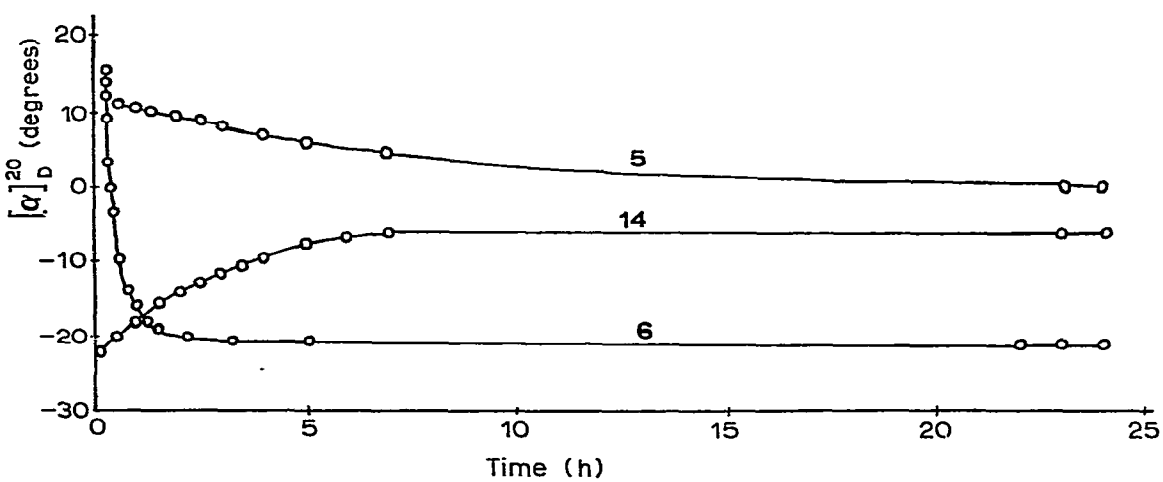

Fig. 4. Effect of basicity of the hydrazines on ring–chain interconversion. Mutarotations at 20° for dimethyl sulfoxide solutions of **5**, **6**, and **14** (*c* 2.0).

^{13}NMR Chemical Shift Data *(continued)*

Compound	Solvent[a]	δ(CO)[b]		References and remarks
		$\delta CO)_{trans}$	$\delta(CO)_{cis}$	
$(CO)_5WC(OMe)Me$	C_6H_6	203.6	197.6	27, 25 *cis*($J(^{183}W—^{13}C)$ 127 Hz)
	$CHCl_3$	203.4	197.2	23
$(CO)_5WC(OH)Ph$	CH_2Cl_2	203.5	197.4	29
$(CO)_5WC(NH_2)Ph$	$CHCl_3$	203.8	198.2	23
$(CO)_5WC(OMe)$-*p*-BrC_6H_4	CH_2Cl_2	203.7	197.3	23
$(CO)_5WC(OMe)$-*p*-ClC_6H_4	CH_2Cl_2	203.7	197.3	23
$(CO)_5WC(OMe)$-*p*-FC_6H_4	CH_2Cl_2	203.5	197.4	23
$(CO)_5WC(OMe)Ph$	$CHCl_3$	203.6	197.2	23
	$CDCl_3/C_6F_6$	204.6	198.6	20, 22
	CH_2Cl_2	204.2	197.8	23
$(CO)_5WC(OMe)$-*p*-$CF_3C_6H_4$	CH_2Cl_2	203.9	197.1	23
$(CO)_5WC(OEt)Ph$	$CHCl_3$	203.5	197.2	23
$(CO)_5WC(OMe)$-*p*-MeC_6H_4	CH_2Cl_2	203.8	197.8	23
$(CO)_5WC(OMe)$-*p*-$MeOC_6H_4$	CH_2Cl_2	203.4	197.9	23
$(CO)_5WC[N(CH_3)_2]CH_3$	$(CH_3)_2CO$	204.3	199.7	74
$(CO)_5WC[N(CH_3)(C_2H_5)]CH_3$ (two isomers)	$(CH_3)_2CO$	204.22 204.22	199.7 199.9	74
$(CO)_5WC(SeCH_3)CH_3$	$(CH_3)_2CO$	205.0	197.8	75
(π-cycloheptatriene)$W(CO)_3$	CH_2Cl_2	211.6		39, 71
(π-cyciooctatetraene)$W(CO)_3$	C_6F_5Br	193.8		52
(π-mesitylene)$W(CO)_3$	CH_2Cl_2	212.6		39, 71
(π-hexamethylbenzene)$W(CO)_3$	CH_2Cl_2	215.7		71
(π-durene)$W(CO)_3$	CH_2Cl_2	213.7		39($J(^{183}W—^{13}C)$ 189 Hz)
	CH_2Cl_2	213.7		71
(π-norbornadiene)$W(CO)_4$	$CHCl_3$	209.4	203.6	15
$Br(CO)_4W{\equiv}C—CH_3$	CH_2Cl_2	192.7		32
$Cl(CO)_4W{\equiv}C—CH_3$	CH_2Cl_2	194.0		32
$I(CO)_4W{\equiv}C—CH_3$	CH_2Cl_2	191.7		32
(π-C_5H_5)$W(CO)_3Me$	$CHCl_3$	217.8	239.2	30
$MeO—\overset{Me}{\underset{PMe_3}{C}}—W(CO)_5$	$(CH_3)_2CO$	203.6	203.0	27 *cis*($J(^{183}W—^{13}C)$ 128 Hz)
$[HW_2(CO)_{10}][Ph_3P{=}N{=}PPh_3]$	CH_2Cl_2	201.4	198.9	55
(π-C_5H_5)$W(CO)_2PMe_3SnMe_3$	C_6H_6	223.0		70, 77
(π-C_5H_5)$W(CO)_2PMe_2PhSnMe_3$	C_6H_6	223.2		70, 77
(π-C_5H_5)$W(CO)_2PMe_2Ph_2SnMe_3$	C_6H_6	223.3		70, 77
(π-C_5H_5)$W(CO)_2P(OMe)_3SnMe_3$	C_6H_6	220.6		70, 77
(π-C_5H_5)$W(CO)_2P(OPh)_3SnMe_3$	C_6H_6	220.5		70, 77
$[(CO)_5WBr][Me_2N{=}CHMe]$	$(CH_3)_2CO$	201.9	198.9	74[e]
$[(CO)_5WBr][\overset{Me}{\underset{Et}{>}}N{=}CHMe]$	$(CH_3)_2CO$	202.0	199.0	74[e]
$(n\text{-}C_4H_9)_4N[W(CO)_5I]$	CH_2Cl_2	201.9	196.6	55 *cis*($J(^{183}W—^{13}C)$ 129 Hz)
Manganese compounds				
$Mn_2(CO)_{10}$	$CHCl_3$	223.1	212.9	55 (broad resonances)
$MeMn(CO)_5$	CH_2Cl_2	213.4		36
(π-C_5H_5)$Mn(CO)_3$	CH_2Cl_2	225.7		55
		220.4		19
	$CHCl_3$	224.9		76
		225.1		15
(π-$C_5H_4CH_3$)$Mn(CO)_3$	CH_2Cl_2	225.4		36
	$CHCl_3$	224.4		76
(π-$C_5H_4CO_2CH_3$)$Mn(CO)_3$	$CHCl_3$	222.7		76
(π-$C_5H_4COCH_3$)$Mn(CO)_3$	$CHCl_3$	223.2		76
(π-$C_5H_4CH_2CH_3$)$Mn(CO)_3$	$CHCl_3$	224.7		76

(continued)

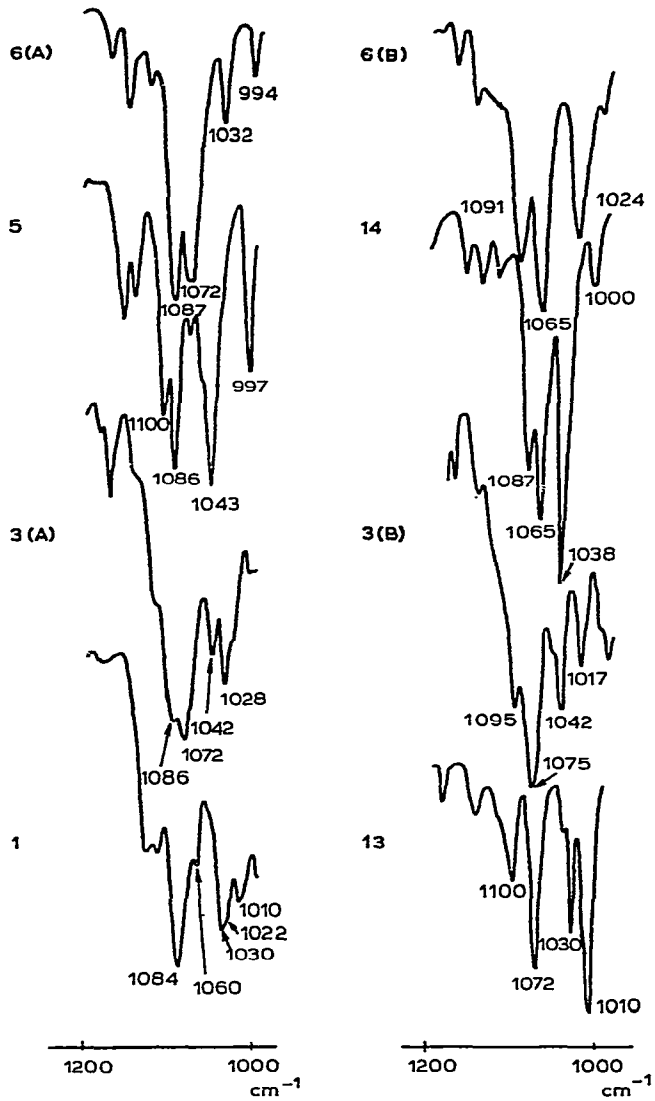

Fig. 5. I.r. spectra for potassium bromide discs of **1**, **3** (A and B), **5**, **6** (A and B), **13**, and **14**. (A), Freshly prepared crystal; (B), crystal or lyophilized powder obtained from dimethyl sulfoxide solution kept for 72 h at room temperature.

cm^{-1}, which may be assigned to coupled modes of C–C and C–O stretching vibrations of the sugar residue[29,30], may be used for determination of the structure, as both position and intensity have been related to sugar configurations and conformations[30]; in addition, almost no strong bands due to the aglycon groups appear in that region. A comparison of the spectra of **5** and **6** (freshly prepared) with those of **14** and **6** (solution kept for 72 h) shows the presence of bands at 1087–1086 cm^{-1} in the first two compounds, and the disappearance of these bands and the appearance of new

TABLE IV

RING–CHAIN INTERCONVERSION OF **1–15** IN DIMETHYL SULFOXIDE SOLUTIONS AT 21°

Compound	*Dominant isomer in crystal*	*Interconversion (A⇄B)*[a]	*Ratio A:B at equilibrium*[b]	*Mutarotation* (°)[c]
1	β Anomer	A→B	9:1	59.5
2	β Anomer	A→B	17:3	5.0
3	β Anomer	A→B	3:17	42.0
4	β Anomer	A→B	13:7	48.1
5	α Anomer	A→B	3:2	−12.5
6	α Anomer	A→B	0:1	−43.8
7	β Anomer	A→B	1:1	6.6
8	β Anomer	A→B	2:3	2.2
9	β Anomer	A→B	7:3	44.6
10	*syn* Form	B→A	3:17	−7.0
11	*syn* Form	B	0:1	0
12	*syn* Form	B→A	11:9	5.6
13	*syn* Form	B	0:1	0
14	*syn* Form	B→A	1:1	15.5
15	*syn* Form	B	0:1	0

[a]A, cyclic forms (α and β anomers); B, acyclic hydrazones (*syn* and *anti* forms). [b]The ratio was calculated from n.m.r. data for solutions in dimethyl sulfoxide-d_6 kept for 72 h at 21°. [c]Difference of $[\alpha]_D^{20}$ for freshly prepared solution and after 24 h at 20°.

bands at 1065 cm^{-1} in the two last compounds. A similar observation was made for the pairs of compounds **1** and **3** (fresh), and **13** and **3** (aged), suggesting that the absorption bands in the 1087–1080 cm^{-1} region are characteristic for the pyranose form of hydrazines, and those in the 1075–1065 cm^{-1} region for the acyclic form of hydrazones.

The ring–chain interconversions for **1–15** in solution in dimethyl sulfoxide are summarized in Table IV. In conclusion, α to β anomerization and ring–chain interconversion of sugar hydrazones in solution depend from the sugar configuration, most probably from the proportion of aldehyde form in aqueous solution, from the basicity of the hydrazine groups, and from the proton-acceptor ability of the solvent.

EXPERIMENTAL

General methods. — Optical rotations were measured at the D line in 1-dm cells with a Perkin–Elmer 241 polarimeter, equipped with a thermo-bath. I.r. spectra for potassium bromide discs were recorded with a Hitachi 285 instrument. ^{1}H-N.m.r. spectra were recorded for solutions in deuterium oxide, dimethyl sulfoxide-d_6, pyridine-d_5, and methanol-d_4 with a Jeol PS-100 spectrometer, tetramethylsilane and sodium 4,4-dimethyl-4-sila(2,3-^{2}H)valerate being the internal standards. ^{1}H-N.m.r.

spectra were recorded at 48° to unmask small signal that were completely overlapped by the large HDO signal. Key: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; m, multiplet; o, overlapping signal. ^{13}C-N.m.r. spectra were recorded for solutions in deuterium oxide and dimethyl sulfoxide-d_6 with a Jeol FX-100 pulse-Fourier-transform, n.m.r. instrument locked on the deuterium signal; chemical shifts were measured relative to the proton-decoupled ^{13}C signal of tetramethylsilane by data reduction.

2'-(β-D-Glucopyranosyl)isonicotinohydrazide[14] (**1**). — This compound was prepared according to the method described earlier[14], by heating an aqueous solution containing equiv. amounts of isonicotinohydrazide and D-glucose for 20 min at 95–100°. It was crystallized by addition of 1,4-dioxane, m.p. 164° (dec.), $[\alpha]_D^{20}$ −22.6→−8.0° (24 h, *c* 2.0, water); lit.[14] m.p. 164° (dec.), $[\alpha]_D^{17}$ −19.8→−11.2° (24 h, *c* 3.45, water).

2'-(β-D-Glucopyranosyl)benzohydrazide (**2**). — A mixed solution of benzohydrazide (3mM) in ethanol (3 mL) and D-glucose (3mM) in water (1.5 mL) was heated for 30 min at 80°, and evaporated to one third of its volume under reduced pressure. Addition of 1,4-dioxane gave crystalline **2**, which was recrystallized from 60% (v/v) ethanol–water (2.0 mL) in 80% yield; m.p. 169° (dec.), $[\alpha]_D^{20}$ −25.0→−20.1° (24 h, *c* 2.0, dimethyl sulfoxide); n.m.r. (dimethyl sulfoxide-d_6): δ 9.86 (d, 1 H, $J_{NH\text{-}2,NH\text{-}1}$ 5.0 Hz, NH-2β), 5.91 (dd, 1 H, $J_{NH\text{-}1,H\text{-}1}$ 3.5 Hz, NH-1β), 5.16 (d, 1 H, $H_{H\text{-}2,OH\text{-}2}$ 4.0 Hz, OH-2), and 3.9 (dd, 1 H, $J_{H\text{-}1,H\text{-}2}$ 8.0 Hz, H-1β).

Anal. Calc. for $C_{13}H_{18}N_2O_6 \cdot 0.5\ H_2O$: C, 50.80; H, 6.23; N, 9.11. Found: C, 50.69; H, 6.20; N, 8.58.

N-(*β-D-Glucopyranosyl*)-N'-p-*bromophenylhydrazine*[3] (**3**). — This compound was prepared according to the method described in the literature[3], m.p. 160° (dec.), $[\alpha]_D^{20}$ −57.8→−11.3° (24 h, *c* 2.0, dimethyl sulfoxide); lit.[3] m.p. 166°, $[\alpha]_D$ −43.7→+18.9° (pyridine).

2'-(β-D-Mannopyranosyl)isonicotinohydrazide[14] (**4**). — M.p. 144° (dec.), $[\alpha]_D^{20}$ −55.8→−34.1° (24 h, *c* 2.0, water); lit.[14] m.p. 86° (trihydrate), $[\alpha]_D^{25}$ −54.7→+27.1° (24 h, *c* 1.64, water); m.p. 152–154° (dec., monohydrate), $[\alpha]_D^{25}$ −44.4→−27.7° (24 h, *c* 1.38, water).

2'-(α-D-Arabinopyranosyl)isonicotinohydrazide[14] (**5**). — M.p. 144° (dec.), $[\alpha]_D^{20}$ +10.9→−1.5° (24 h, *c* 2.0, dimethyl sulfoxide); lit.[14] m.p. 167° (dec.), $[\alpha]_D^{25}$ +16.1→+28.9° (24 h, *c* 2.04, water).

N-(*α-D-Arabinopyranosyl*)-N'-p-*bromophenylhydrazine*[1] (**6**). — M.p. 157° (dec.), $[\alpha]_D^{20}$ +14.2→−20.5° (24 h, *c* 2.0, dimethyl sulfoxide); lit.[1] m.p. 155–160°.

2'-(β-D-Ribopyranosyl)isonicotinohydrazide[14] (**7**). — Compound **7** was obtained as a lyophilized powder, in an equilibrium mixture consisting of the α and β anomers of the hydrazide, and the *syn* and *anti* forms of acyclic hydrazone; $[\alpha]_D^{20}$ −2.3° (initial and after 24 h, *c* 2.0, water); lit.[14]: freeze-dried material having strong hygroscopic character.

2'-(β-D-Ribopyranosyl)benzohydrazide (**8**). — The reaction conditions were the same as those described for **2**, and **8** was obtained as hygroscopic crystals, in 77%

yield, by addition of 1,4-dioxane and acetone. Crystalline **8** may contain appreciable amount of the acyclic hydrazone; $[\alpha]_D^{20}$ −14.7→−12.5° (24 h, *c* 2.0, dimethyl sulfoxide); n.m.r. (dimethyl sulfoxide-d_6): δ 9.85 (d, 1 H, $J_{NH\text{-}1,NH\text{-}2}$ 6.0 Hz, NH-2β), 5.85 (dd, 1 H, $J_{NH\text{-}1,H\text{-}1}$ 3 Hz, NH-1β), and 3.92 (bd, 1 H, $J_{H\text{-}1,H\text{-}2}$ 8.0 Hz, H-1β).

Anal. Calc. for $C_{12}H_{16}N_2O_5$: C, 53.73; H, 6.01; N, 10.44. Found: C, 53.89; H, 6.32; N, 8.54.

*2′-(Sodium β-*D*-glucopyranosyluronate)isonicotinohydrazide*[13] (**9**). — M.p. 175° (dec.), $[\alpha]_D^{20}$ −35.2→−17.5° (24 h, *c* 2.0, water); lit.[13] m.p. 169–176° (dec.), $[\alpha]_D^{20}$ −52→−13° (24 h, *c* 1.0, water).

aldehydo-D-*Glucurono-6,3-lactone isonicotinohydrazone*[15] (**10**). — Water was eliminated as much possible throughout the reaction in order to avoid the formation of the cyclic α anomer and of 2′-(1-isonicotinohydrazono)-*aldehydo*-D-glucurono-6-isonicotinohydrazide[31], abs. methanol being the reaction solvent, m.p. 144° (dec.), $[\alpha]_D^{20}$ −6.6→−12.3° (24 h, *c* 1.0, dimethyl sulfoxide). Upon addition of alkali to the aqueous solution, **10** was converted into **9** within 3 h at room temperature, the formation of which being monitored by n.m.r.

D-*Glyceraldehyde isonicotinohydrazone* (**11**). — A suspension of isonicotinohydrazide (1.48mM) and D-glyceraldehyde (1.48mM) in water (1 mL) was heated for 10 min at 80°, and then kept in the cold. Addition of methanol and acetone gave crystalline **11** in 65% yield, m.p. 151° (dec.), $[\alpha]_D^{20}$ +10.7° (initial and after 24 h, *c* 2.0, dimethyl sulfoxide); n.m.r. (dimethyl sulfoxide-d_6): see Table II.

Anal. Calc. for $C_9H_{11}N_3O_3$: C, 51.67; H, 5.30; N, 20.08. Found: C, 51.56; H, 5.35; N, 20.09.

aldehydo-D-*Mannose benzohydrazone* (**12**). — The reaction conditions were the same as those for the preparation of **2**. Crystallization by addition of a little acetone to the reaction mixture gave white rods in 70% yield, m.p. 172° (dec.), $[\alpha]_D^{20}$ −9.5→−2.7° (24 h, *c* 2.0, dimethyl sulfoxide); n.m.r. (dimethyl sulfoxide-d_6): δ 10.38 (s, 1 H, NH-2_{syn}), 7.7 (m, 3 H, H-1_{syn} and arom. ring 2 H), 5.26 (d, 1 H, $J_{H\text{-}2syn,OH\text{-}2}$ 5.0 Hz, OH-2), and 4.1 (m, 2 H, H-2_{syn} and sugar 1 H).

Anal. Calc. for $C_{13}H_{18}N_2O_6$: C, 52.34; H, 6.08; N, 9.39. Found: C, 52.14; H, 6.14; N, 9.14.

aldehydo-D-*Mannose* p-*bromophenylhydrazone*[4] (**13**). — M.p. 183° (dec.), $[\alpha]_D^{20}$ −7.3° (initial and after 24 h, *c* 2.0, dimethyl sulfoxide).

aldehydo-D-*Arabinose benzohydrazone* (**14**). — This compound precipitated from the reaction solution during heating at 80°, and was washed with methanol and dried (quantitative yield), m.p. 183° (dec.), $[\alpha]_D^{20}$ −22→−6.8° (24 h, *c* 1.0, dimethyl sulfoxide); n.m.r. (dimethyl sulfoxide-d_6): δ 11.30 (s, 1 H, NH-2_{syn}), 7.8 (m, 3 H, H-1_{syn} and arom. ring 2 H), 5.07 (d, 1 H, $J_{HH\text{-}2syn,OH\text{-}2}$ 6.0 Hz, OH-2), and 4.4 (m, 2 H, H-2_{syn} and sugar 1 H).

Anal. Calc. for $C_{12}H_{16}N_2O_5$: C, 53.73; H, 6.01; N, 10.44. Found: C, 53.97; H, 5.93; N, 10.46.

aldehydo-D-*Ribose* p-*bromophenylhydrazone*[2] (**15**). — M.p. 150° (dec.), $[\alpha]_D^{20}$ +11.6° (initial and after 24 h, *c* 2.0, dimethyl sulfoxide).

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