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Note

Isopropylidenation of aldosulose bis(phenylhydrazones)

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During our investigation on the acetal formation [1–10] of acyclic C-nucleoside analogues, we have developed an NMR shift rule [1,2] that describes a method for recognizing the configuration of a diol function in the acyclic alditolyl moieties via the chemical shifts of the methyl groups on the respective isopropylidene ring. More examples are required in order to understand the validity of this rule and the effect of remote substituents on the chemical shifts of the methyl groups of the isopropylidene ring. Towards this goal, aldosulose bis(phenylhydrazones) are subjected to the isopropylidenation, and the location of these rings, as well as their correlation with the configuration of the alditolyl moieties are the subject of the present study. To the best of our knowledge, the isopropylidenation of D-*arabino*-hexosulose bis(phenylhydrazone) is so far the only reported [11] example in this series.

The precursors of the target compounds are the aldosulose bis(phenylhydrazones) (**1–5**) having a triol or tetritol residue. When both of the D- and L-*erythro* isomers **1** and **2** were subjected to the action of acetone in the presence of *p*-toluenesulfonic acid, the products were found to have the terminal dioxolane ring as in **6** and **9**, respectively. On the other hand, under similar reaction conditions the respective D-*threo* isomer **3** afforded a mixture of products **11** and **13**. The latter, **13**, is the major product. The use of sulfuric acid or phosphorus pentoxide as a catalyst gave similar results; increasing reaction time did not have an effect on the pattern of the products of the latter case. On the other hand, when anhydrous copper(II) sulfate was used as a catalyst, the isopropylidene derivative **11** was the only product formed, albeit in poor yield. A more powerful

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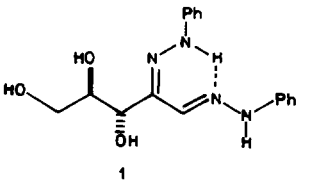

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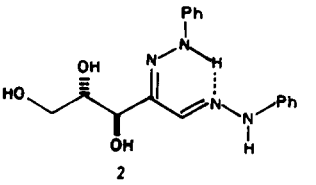

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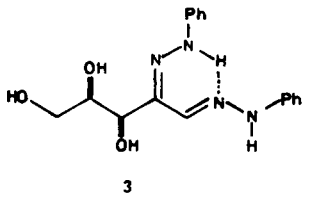

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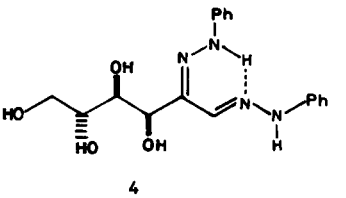

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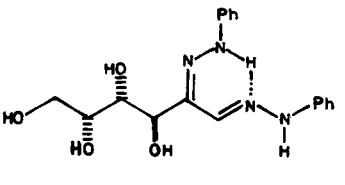
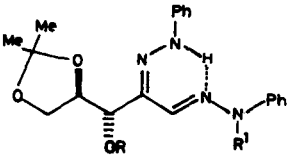


5

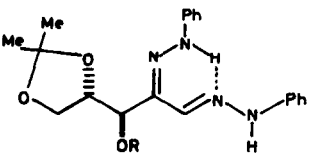
catalyst in this respect was found to be pyridinium *p*-toluenesulfonate, whereby **11** was formed as a major product in addition to **13**.

The isopropylidenation of the tetritolyl compound **4** was studied earlier [11]. The isopropylidenation gave two products, **15** and **17**. The former is a major one at the early stage of the reaction, but with time the latter became the major one. When the reaction was done on the D-*lyxo* analogue **5**, two products were formed, but **18** was the only one that could be isolated from the mixture.

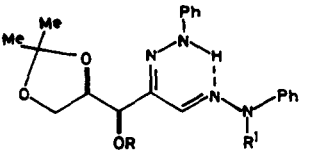
Inspection of the above data indicates that the terminal dioxolane was the first product to be detected. In the case of triols with D- or L-*erythro* configurations, the terminal dioxolanes were the only products from the reaction under the conditions which are suitable for their rearrangements. On the other hand, the respective D-*threo* analogue gave under such conditions a minor product having the terminal dioxolane ring in addition to the major product which has a *threo*-dioxolane ring. The latter presumably results from the rearrangements of the terminal dioxolane under the acid catalysis. Under conditions of kinetic control, the terminal ring was the one formed. In the case of tetritols, another dioxolane ring followed the formation of the terminal one, which probably proceeds faster than the rearrangement. The rearrangement of the *threo*-dioxolane is promoted by the presence of the 4- and 5-substituents in a *trans* orientation [5], whereas the terminal dioxolane has a bulky 4-substituent. On the other hand, the



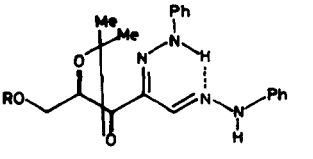
6 R = R¹ = H
7 R = Ac, R¹ = H
8 R = R¹ = Bz



9 R = H
10 R = Ac



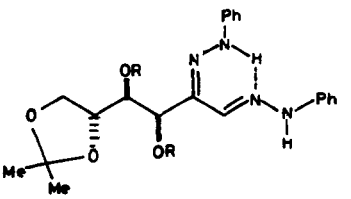
11 R = R¹ = H
12 R = R¹ = Bz



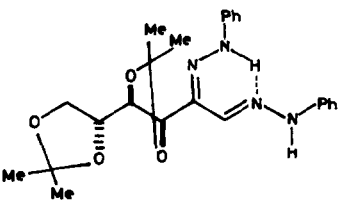
13 R = H
14 R = Ac

erythro-dioxolane ring would have the 4- and 5-substituents in a *cis* orientation which retarded its formation.

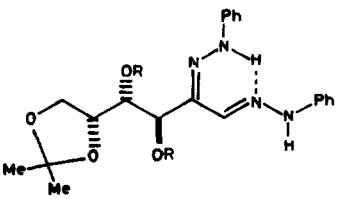
Acetylation of **6**, **9**, and **13** with acetic anhydride in pyridine afforded the mono-*O*-



15 R = H
16 R = Ac



17



18 R = H
19 R = Ac

acetyl derivatives **7**, **10**, and **14**, respectively, whereas **15** and **18** gave the di-*O*-acetyl derivatives **16** and **19**. Benzoylation of **6** and **11** gave the benzoyl derivatives **8** and **12**.

The infrared (IR) spectra of the acylated derivatives showed a band in the carbonyl frequency region at 1750–1725 cm^{-1} for the acetyl derivatives. The benzoyl derivatives showed two bands in the same region at 1748–1740 and 1680–1670 cm^{-1}, indicating the presence of NBz groups in addition to the OBz groups.

The ^1H NMR spectra of **7** and **10** showed downfield shifts (from δ 4.41 to 5.65 and from 4.41 to 5.71) for the doublet for H-3 upon acetylation of the 3-OH group. Similarly *O*-benzoylation of **6** and **11** to **8** and **12**, respectively, caused a downfield shift of H-3. In addition, the ^1H NMR spectrum of **14** showed a downfield shift of H-5 and H-5′.

The location of the isopropylidene ring in **15** was deduced from the downfield shift of H-3 and H-4 upon acetylation to give **16**. Similarly that of **18** was deduced. However, the structure of **17** could not be deduced from its ^1H NMR spectrum.

The chemical shift difference ($\Delta\delta$) of the two methyl groups of the isopropylidene rings in this series ranged between 0.06–0.12 ppm for the terminal ring and 0.01 ppm for the *threo* ring, agreeing with the shift rule [1,2]. On the other hand, the structure of **17** could not be deduced by using this value. The respective acetyl or benzoyl derivatives have smaller values for $\Delta\delta$ than anticipated, and this could be attributed to the anisotropic effect of the carbonyl ester group.

The assignment of the ^{13}C NMR spectra of the acetal derivatives was made by comparison with those of the parent compounds [12], as well as those of the isopropylidene acetals [13,14]. Although in the present work no conclusive results could be obtained from the ^{13}C NMR chemical shifts of the methyl groups, the values of the acetal carbons (δ 109–110) could be correlated well with those of 1,3-dioxolane ring as in **16** and **17**; larger rings would require more higher field signals.

C-1 and C-2, as well as the phenyl carbons, are readily assigned by their consistency with the spectra of the parent compounds [12,15,16].

The most deshielded carbon of the alditolyl moieties of the parent bishydrazone has been reported [12] for C-3. A strong deshielding of α-carbons (5–10 ppm) usually accompanies the formation of cyclic acetals [13]. The C-3 in **6** is probably little affected by the isopropylidene whereby it experiences a small shielding effect from the presence of an isopropylidene group on C-4 and C-5, both of which show downfield shifts. On the other hand, the C-3 and C-4 resonances in **13** are shifted downfield, whereas C-5 is little affected. The acetyl derivative **14** showed almost the same chemical shifts for the carbons except for C-4, which is shifted to a high field due to the β-effect of the acetyl group. The carbons of **17** appeared at lower field positions than those of the parent compound.

The ^1H NMR spectra of the isopropylidene and their *O*-acetyl derivatives showed the presence of two NH groups as two singlets in the downfield region; one in the range of δ 12.11–12.34, whereas the other one appeared at a higher field in the range δ 7.67–7.98. The former signal is highly deshielded as a consequence of its involvement in hydrogen-bonding as reported for their precursor [17], whereas the other one is not hydrogen bonded as shown in the formulas. The benzoyl derivatives showed only the former resonance, indicating that the other proton was displaced by the benzoyl group.

1. Experimental

General methods.—Melting points were determined on a Meltemp apparatus and are uncorrected. IR spectra were recorded with a Unicam SP 200 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were measured with a Jeol JNM-GX 400 spectrometer for solutions in Me_2SO-d_6 or $CDCl_3$, using Me_4Si as an external or internal reference, respectively. Chemical shifts are given on the δ scale. TLC was performed on Bakerflex Silica Gel IB-F (2.5–7.5 cm) plates. The solvent mixtures used for TLC were solvent *A* (2:5 EtOAc–hexane), solvent *B* (1:4 EtOAc–hexane), solvent *C* (3:5 EtOAc–hexane), and solvent *D* (2:3 EtOAc–hexane). Microanalyses were performed in the Chemistry Department, Faculty of Science, Cairo University, Cairo, Egypt.

Isopropylidenation of aldosulose bis(phenylhydrazones).—*(a)* A suspension of the aldosulose bis(phenylhydrazone) (10 mmol) in dry acetone (60 mL) and *p*-toluenesulfonic acid (0.05 g, 0.26 mmol) was stirred vigorously for 1 h. The mixture was kept overnight at room temperature, neutralized by the addition of anhyd sodium carbonate, and filtered. The inorganic salts were washed with acetone, and the combined filtrate and washings were evaporated in vacuo at 40°C. Petroleum ether was added to the resulting viscous syrup, and the product that separated out was filtered, washed with ethanol, and dried. The product was crystallized from ethanol as yellow-orange needles.

(b) A mixture of the aldosulose bis(phenylhydrazone) (10 mmol) in dry acetone (90 mL) and two drops of 90% sulfuric acid was stirred vigorously for 2 h. The mixture was then processed as above.

(c) A mixture of the aldosulose bis(phenylhydrazone) (10 mmol) was stirred vigorously with dry acetone (90 mL) and phosphorus pentoxide (1.5 g, 0.01 mmol) for 2 h. The mixture was processed as above.

(d) A mixture of the aldosulose bis(phenylhydrazone) (10 mmol) in dry acetone (90 mL) and (7.0 g, 0.04 mmol) of copper(II) sulfate was stirred vigorously for 3 days at room temperature. The mixture was processed as usual. The residue was chromatographed on silica gel, eluting with solvent *C*. The fractions enriched with the products were collected, evaporated under reduced pressure, and crystallized from ethanol.

(e) A mixture of the aldosulose bis(phenylhydrazone) (10 mmol) in dry acetone (90 mL) and pyridinium *p*-toluenesulfonate (0.1 g) and *N*,*N*-dimethylformamide (3 mL) was stirred vigorously for 2 h. The mixture was kept overnight at room temperature and then processed as usual. The product was chromatographed on silica gel, eluting with solvent *C*. The fraction enriched with the products were collected, the solvent was evaporated under reduced pressure, and the products were crystallized from ethanol.

(f) A mixture of D-*arabino*-hexulose bis(phenylhydrazone) (3.42 g, 10 mmol) in *N*,*N*-dimethylformamide (10 mL) and 2,2-dimethoxypropane (10 mL) in the presence of *p*-toluenesulfonic acid (0.1 g, 0.52 mmol) was heated under reflux for 20 min. The mixture was cooled, neutralized with anhyd sodium carbonate, and filtered. The solvent was evaporated, and the product was recrystallized from ethanol as yellow-orange needles.

Acetylation of the isopropylidene derivatives.—A cold solution of the isopropylidene derivative (1.0 mmol) in dry pyridine (2 mL) was treated with acetic anhydride (1 mL),

Table 1
^{1}H NMR spectral data for compounds 6–19 [a]

Compound No.	CH_3	$CH_3C{=}O$	OH	H-6′ $J_{5,6'}$ $J_{6,6'}$	H-6 $J_{5,6}$	H-5′ $J_{4,5'}$ $J_{5,5'}$	H-5 $J_{4,5}$	H-4	H-3 $J_{3,4}$	H-C =	2 NH
6	1.38, 1.50 (2 s, 6 H)		3.33 (s, 1 H)			←	4.17 (m, 3 H)	→	4,41 (s, 1 H)	7.55 (s, 1 H)	7.74, 12.17 (2 s, 2 H)
7	1.33, 1.36 (2 s, 6 H)	2.07 (s, 3 H)				4.10 (q, 1 H) 6.0 Hz 9.0 Hz	4.32 (q, 1 H) 7.5 Hz	4.57 (m, 1 H)	5.65 (d, 1 H) 4.0 Hz	7.47 (s, 1 H)	7.88, 12.28 (2 s, 2 H)
8	1.24, 1.30 (2 s, 6 H)					←	4.13(m, 2 H)	→	4.53 (m, 1 H)	5.66 (d, 1 H) 4.5 Hz	a [b] 11.92 (s, 1 H)
9	1.38, 1.50 (2 s, 6 H)		3.28 (d, 1 H) 4.9 Hz			←	4.17 (m, 3 H)	→		4.41 (t, 1 H) 5.1 Hz	7.56 (s, 1 H) 7.71, 12.16 (2 s, 2 H)
10	1.38, 1.40 (2 s, 6 H)	2.13 (s, 3 H)				4.15 (t, 1H) 6.5 Hz 8.5 Hz	4.30 (t, 1 H) 6.9 Hz	4.60 (m, 1 H)	5.71 (d, 1 H) 3.9 Hz	7.58 (s, 1 H)	7.77, 12.34 (2 s, 2 H)
11	1.36, 1.43 (2 s, 6 H)		3.03 (d, 1 H) 1.5 Hz			←	3.85 (m, 2 H)	→	4.08 (m, 1 H)	4.36 (t, 1 H) 6.3 Hz	7.53 (s, 1 H) 7.67, 12.11 (2 s, 2 H)
12	1.23, 1.27 (2 s, 6 H)					←	4.08 (m, 2 H)	→	4.47 (m, 1 H)	5.62 (d, 1 H) 4.5 Hz	a [b] 11.98 (s, 1 H)
13	1.50, 1.51 (2 s, 6 H)		2.20 (bs, 1 H)			3.80 (dd, 1 H) 4.4 Hz 11.9 Hz	3.95 (dd, 1 H) 3.5 Hz	4.25 (m, 1 H)	4.67 (d, 1 H) 3.4 Hz	7.61 (s, 1 H)	7.78, 12.28 (2 s, 2 H)
14	1.50, 1.52 (2 s, 6 H)	2.08 (s, 3 H)				4.18 (q, 1 H) 6.0 Hz 11.6 Hz	4.36 (ddd, 1 H) 3.0 Hz	4.49 (dd, 1 H) 3.0 Hz	4.59 (d, 1 H) 8.4 Hz	7.59 (s, 1 H)	7.76, 12.29 (2 s, 2 H)
15	1.25, 1.32 (2 s, 6 H)		3.40 (s, 2 H)	←	3.97 (m, 3 H)	→		4.36 (m, 1 H)	4.97 (d, 1 H) 7.6 Hz	7.80 (s, 1 H)	10.75, 12.19 (2 s, 2 H)
16	1.29, 1.36 (2 s, 6 H)	2.09 (s, 6 H)		←	4.02 (m, 2 H) →		4.24 (m, 1 H)	← 5.60 (m, 2 H) →		7.52 (s, 1 H)	7.80, 12.26 (2 s, 2 H)
17	1.34, 1.37 1.47, 1.48 (4 s, 12 H)			4.02 (q, 1 H) 5.6 Hz 8.5 Hz	4.11 (q, 1 H) 6.3 Hz		4.29 (q, 1 H) 5.9 Hz	4.40 (dd, 1 H)	4.68 (d, 1 H) 7.4 Hz	7.56 (s, 1 H)	7.68, 12.28 (2 s, 2 H)
18	1.26, 1.32 (2 s, 6 H)		3.50 (bs, 2 OH)	←	3.99 (m, 3 H)	→		4.70 (d, 1 H) 6.0 Hz	5.40 (d, 1 H) 7.5 Hz	7.73 (s, 1 H)	10.60, 12.16 (2 s, 2 H)
19	1.32, 1.38 (2 s, 6 H)	2.01, 2.07 (2 s, 6 H)		←	4.10 (m, 3 H)	→		← 5.56 (m, 2 H) →		7.53 (s, 1 H)	7.97, 12.33 (2 s, 2 H)

[a] Chemical shifts are given on the δ-scale. Coupling constants are given in Hz.
[b] The signal is obscurred in the aromatic region. Aromatic protons appeared as a multiplet in the range of δ 6.43–7.84.

Table 2
^{13}C NMR spectral data for compounds **1**, **3**, **4**, **6**, **13**, **14**, **16**, and **17** [a]

	6 (**1**) [12]	**13** (**3**) [12]	**14**	**16**	**17** (**4**) [12]
$(H_3C)_2C$	25.16, 26.71	27.01, 27.16	26.87, 27.18	25.32, 26.31	25.38, 26.59, 27.06, 27.21
$(H_3CO)_2C$	109.46	109.48	109.94	109.41	109.63, 109.86
CH_3CO			20.81	20.82, 20.94	
CH_3CO			170.74	169.74, 170.02	
C-1	132.41(134.1)	130.20(134.1)	129.41	128.39	130.19(134.5)
C-2	133.38(136.8)	132.65(137.1)	132.38	132.43	133.28(137.7)
C-3	72.96(74.1)	80.16(74.6)	79.70	74.39	80.68(74.5)
C-4	78.94(74.1)	79.00(73.3)	77.76	72.22	79.29(72.2)
C-5	66.64(63.5)	61.96(62.7)	63.97	74.12	76.31(71.4)
C-6				64.88	66.33(63.4)
C-a, *C*-a′	143.06, 144.04	143.09, 144.06	143.07, 144.02	142.95, 143.77	143.15, 144.22
C-b, *C*-b′	112.78, 113.40	112.77, 113.58	112.76, 113.61	112.76, 113.78	112.75, 113.65
C-c, *C*-c′	129.38, 129.62	129.37, 129.64	129.36, 129.65	129.34, 129.62	129.30, 129.61
C-d, *C*-d′	121.27, 121.38	121.39	121.41, 121.45,	121.45, 121.70	121.27, 121.29

[a] Chemical shifts are given on the δ-scale.

and the mixture was kept overnight at room temperature. The mixture was poured onto crushed ice, and the product that separated out was filtered, washed repeatedly with water, and dried. The products were crystallized from ethanol as yellow crystals.

Benzoylation of the isopropylidene derivatives.—A cold solution of the isopropylidene derivatives (1.0 mmol) in dry pyridine (4 mL) was treated with benzoyl chloride

Table 3
Physicochemical data of isopropylidene derivatives **6**, **9**, **11**, **13**, **15**, **17**, and **18**

Compound No.	Method	Yield (%)	R_f (solvent)	mp °C)	Molecular formula	Anal. Calcd/Found			ν_{max} (cm^{-1})	
						C	H	N	OH	C=N
6	*a*	82	0.46 (A)	153–155	$C_{20}H_{24}N_4O_3$	65.2 65.2	6.6 6.3	15.2 15.0	3490	1610
9	*a*	54	0.43 (C)	153–155	$C_{20}H_{24}N_4O_3$	65.2 65.2	6.6 6.3	15.2 15.2	3510	1615
11 [a]	*e*	50	0.31 (C)	171–173	$C_{20}H_{24}N_4O_3$	65.2 65.6	6.6 6.7	15.2 15.3	3500	1610
13 [b]	*c*	60	0.28 (C)	180–182	$C_{20}H_{24}N_4O_3$	65.2 65.5	6.6 6.6	15.2 15.1	3500	1615
15	*c*	51	0.20 (D)	170–172 (146–150) [11]	$C_{21}H_{26}N_4O_4$	63.3 63.6	6.6 6.2	14.1 14.0	3400	1610
17 [c]	*f*	77	0.50 (D)	180–181	$C_{24}H_{30}N_4O_4$	65.7 65.8	6.9 6.6	12.8 13.0		1620
18	*a*	65	0.50 (D)	197–199	$C_{21}H_{26}H_4O_4$	63.3 63.5	6.6 6.5	14.1 14.0	3500	1615

[a] Method *a*, 39%; *b*, 30%; *c*, 25%; *d*, 45%.
[b] Method *a*, 54%; *b*, 52%; *e*, 30%.
[c] Method *c*, 25%.

Table 4
Physicochemical data of acyl derivatives. **7**, **10**, **12**, **14**, **16**, and **19**

Compound No.	Yield (%)	R_f (solvent)	mp (°C)	Molecular formula	Anal. Calcd/Found			ν_{max} (cm^{-1})	
					C	H	N	OCO	NCO
Acetyl derivatives									
7	67	0.52	128–130	$C_{22}H_{26}N_4O_4$	64.4	6.4	13.7	1725	
		(*B*)			64.8	6.8	14.0		
10	80	0.43	120–122	$C_{22}H_{26}N_4O_4$	64.4	6.4	13.7	1750	
		(*B*)			64.0	6.3	13.5		
14	75	0.40	125–127	$C_{22}H_{26}N_4O_4$	64.4	6.4	13.7	1730	
		(*A*)			64.9	6.6	14.0		
16	72	0.38	165–166	$C_{25}H_{30}N_4O_6$	62.2	6.3	11.6	1770,	
		(*C*)	(166–167) [11]		62.0	6.0	11.0	1750	
19	74	0.60	146–148	$C_{25}H_{30}N_4O_6$	62.2	6.3	11.6	1760	
		(*D*)			62.0	6.0	11.6		
Benzoyl derivatives									
8	70	0.60	166–168	$C_{34}H_{32}N_4O_5$	70.8	5.6	9.7	1748	1670
		(*B*)			71.0	5.3	10.0		
12	75	0.50	129–131	$C_{34}H_{32}N_4O_5$	70.8	5.6	9.7	1740	1680
		(*B*)			70.5	5.3	10.1		

(0.5 mL), and the mixture was kept overnight at room temperature. The mixture was poured onto crushed ice, and the product that separated out was filtered, dried, and crystallized from ethanol.

Acknowledgement

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References

[1] E.S.H. El Ashry, *J. Chem. Soc., Chem. Commun.*, (1986) 1024–1026.
[2] E.S.H. El Ashry, *European Carbohydr. Symp.*, Darmstadt, FRG, 1987, C-35.
[3] E.S.H. El Ashry, Y. El Kilany, and A. Mousaad, *J. Carbohydr. Chem.*, 8 (1989) 507–513.
[4] E.S.H. El Ashry, Y. El Kilany, S. Kandil, and N. El Shimy, *J. Carbohydr. Chem.*, 8 (1989) 497–506.
[5] E.S.H. El Ashry, Y. El Kilany, and F. Singab, *J. Chem. Soc., Perkin Trans. 1*, (1988) 133–137.
[6] E.S.H. El Ashry, Y. El Kilany, and F. Singab, *Carbohydr. Res.*, 154 (1986) 256–269.
[7] E.S.H. El Ashry, Y. El Kilany and A. Mousaad, *J. Carbohydr. Chem.*, 163 (1987) 262–264.
[8] Y. El Kilany, L. Awad, F. Singab, and E.S.H. El Ashry, *Alex. J. Pharm. Sci.*, 11 (1988) 142–143.
[9] N. Rashed, H. Abdel Hamid, and E.S.H. El Ashry, *Carbohydr. Res.*, 243 (1993) 399–405.
[10] E.S.H. El Ashry, A. Mousaad, and R. Rashed, *Adv. Heterocycl. Chem.*, 53 (1992) 233–312.
[11] S. Akiya and S. Tejima, *J. Pharm. Soc. Jpn.*, 72 (1952) 894–898.
[12] G.W. Schnarr, D.M. Vyas, and W.A. Szarek, *J. Chem. Soc., Perkin Trans. 1*, (1979) 496–503.
[13] J.G. Buchanan, A.R. Edgar, D.I. Rawson, P. Shahidi, and R.H. Wightman, *Carbohydr. Res.*, 100 (1982) 75–86.

[14] G. Aslani-Shotorbani, J.G. Buchanan, A.R. Edgar, D. Henderson, and M.P. Shahidi, *Tetrahedron Lett.*, 21 (1980) 1791–1792.
[15] N. Naulet, M.L. Filleux, G.J. Martin, and J. Pornet, *Org. Magn. Reson.*, 7 (1975) 326–330.
[16] G.L. Nelson, G.C. Levy, and T.D. Cargioli, *J. Am. Chem. Soc.*, 94 (1972) 3089–3094.
[17] H. El Khadem, *Adv. Carbohydr. Chem.*, 20 (1965) 139–181.