Rotatory Dispersion of Sugar Derivatives. III.[1] Aldose Benzylphenylhydrazones

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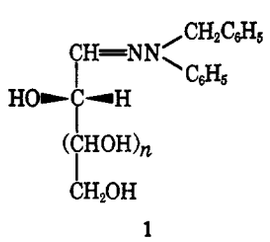
Received May 15, 1968

Optical rotatory dispersion and nmr spectroscopy have been used to examine the structure and conformation of two pentose and four hexose benzylphenylhydrazones. The compounds exist in solution as imines rather than *N*-glycosides. Compounds with *R* configuration at C-2 are dextrorotatory at long wavelength and have positive Cotton effects at about 300 nm. Acetylation removes intramolecular hydrogen bonding and shifts the conformational equilibria toward conformations of opposite rotatory sign. Acetates with *R* configuration at C-2 are levorotatory at long wavelength, and all but penta-*O*-acetyl-D-mannose benzylphenylhydrazone have strong negative Cotton effects at 300 nm. The same relationships apply to three other aldose arylhydrazones which have been shown previously to have the imine rather than the *N*-glycoside structure.

Despite availability of a large number of optically active phenylhydrazones from sugars, no systematic work has been done on the relationship of their optical rotatory dispersion to structure and conformation. The detailed structure of sugar phenylhydrazones involves *cis–trans* isomerism about the imine bond in acyclic cases and α and β stereochemistry at the anomeric center as well as pyranose *vs.* furanose ring size in cyclic cases. Observed mutarotation of sugar hydrazones indicates existence of more than one isomer in solution. Some aldose phenylhydrazone mutarotation curves indicate the presence of at least three isomers in the approach to equilibrium.[2] Chemical methods[3,4] have been used to distinguish cyclic from acyclic forms in favorable cases. Nmr spectroscopy has been used to examine solution structure of a few aldose phenylhydrazones[5] and X-ray crystallographic structures or partial structures are available for several aldose *p*-bromophenylhydrazones.[6] Crystalline arylhydrazones with acyclic structure are known for mannose,[7] galactose,[3,5] rhamnose,[4] and ribose.[8] Arabinose *p*-bromophenylhydrazone is cyclic.[9] Both cyclic and acyclic forms of glucose phenylhydrazone are known.[5,10] Information is available on the equilibrium concentrations of cyclic and acyclic forms in solution in only a few cases.[4,5] Little is known of the structure of the other common aldose arylhydrazones.



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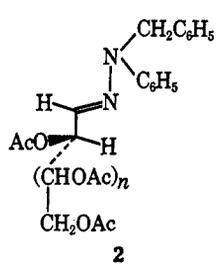

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Hudson proposed an empirical correlation between absolute stereochemistry and long wavelength optical rotation for sugar benzylphenylhydrazones, based on the observation that 11 sugar benzylphenylhydrazones are dextrorotatory at the sodium D line if C-2 has *R* chirality (**1**), or levorotatory if C-2 has *S* chirality.[11] The six sugar benzylphenylhydrazones prepared subsequently have been found to have long wavelength rotations of the expected sign.[12] The validity of Hudson's correlation suggests that aldose benzylphenylhydrazones do not exhibit the isomeric complexity of aldose phenylhydrazones. Consequently the series of benzylphenylhydrazones is a logical starting point for investigation of the relationship between stereochemistry, conformation, and rotatory properties of aldose hydrazones by ORD and nmr.

The optical rotatory dispersions of sugar benzylphenylhydrazones in methanol show plain curves in the region 350–600 nm, conforming throughout that region to the Hudson correlation (Table 1). The shape of the curve is controlled by an electronic transition in the vicinity of 300 nm (Figure 1). The Cotton effect of this transition has the same sign as the long wavelength rotation. The rotatory dispersions were generally not measured so far as the first extremum because of the unfavorable rotation to absorption ratio. Qualitative differences appear when the dispersions are measured in pyridine. The magnitude of rotation was found in general to be appreciably greater in pyridine than in methanol. Acetylation in pyridine inverted the sign relationship and further enhanced the magnitude of the rotation. The long wavelength rotation of mannose benzylphenylhydrazone changes sign on acetylation, but the shift is not so marked as for the other examples. The rotatory dispersions of acetylated fucose, galactose, and arabinose benzylphenylhydrazones in methanol are qualitatively similar to dispersions measured in pyridine. Several aldose arylhydrazones of known acyclic structure are initially dextrorotatory at long wavelength and have positive first Cotton effects if C-2 has *R* chirality (Table II). Their acetates are levorotatory at the sodium D line.

There is no obvious pattern in the long wavelength optical rotation of most sugar hydrazones for which data are available. Only benzylphenylhydrazones

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TABLE I

ROTATORY DISPERSIONS OF ALDOSE BENZYLPHENYLHYDRAZONES

Benzylphenylhydrazone of	Solvent[a]	Molar rotation at wavelength 589 nm	550 nm	500 nm	450 nm	400 nm	350 nm
D-Ribose	M	−93.5	−115	−158	−233	−398	
	P	−176	−217	−300	−451	−793	
D-Arabinose	M	37.9	47.4	61.7	89.0	149	
	P	44.7	60.3	80.3	129	246	
D-Glucose	M	−61.8	−73.5	−103	−157	−276	−650
	P	−180	−215	−295	−430	−730	−1730
D-Mannose	M	70.5	87.4	123	186	314	
	P	152	188	264	404	692	
L-Fucose	M	43.7	53.4	72.0	104	182	
	P	37.5	48.0	64.0	103	202	
Lactose	M	−87.2	−106	−145	−208	−336	−723
	P	−184	−215	−271	−375	−577	
Tetra-*O*-acetyl-D-ribose	P	550	653	845	1060	1640	2880
Tetra-*O*-acetyl-D-arabinose	P	−362	−444	−581	−821	−1300	−2710
Penta-*O*-acetyl-D-glucose	P	522	618	800	1085	1580	2760
Penta-*O*-acetyl-D-mannose	P	−34.3	−38.4	−44.0	−48.1[b]	−27.4	196
Tetra-*O*-acetyl-L-fucose	P	−361	−438	−577	−801	−1260	
	M	−353	−423	−555	−783	−1230	−2730
Penta-*O*-acetyl-D-galactose	P	511	613	812	1140	1750	3580
	M	450	545	708	980	1510	3050

[a] Solvent: P = pyridine, M = methanol. [b] Trough, $[\phi]^{22}_{457}$ −48.5°.

TABLE II

ROTATORY DISPERSIONS OF SOME ALDOSE HYDRAZONES IN PYRIDINE

Compound	Molar rotation at wavelength 589 nm	550 nm	500 nm	450 nm	400 nm	350 nm
D-Galactose methylphenylhydrazone	−10.1	−10.2	−15.9	−26.0	−54.0	−173
Tetra-*O*-acetyl-D-galactose methylphenylhydrazone	148	181	222	260	288[a]	97
D-Mannose *p*-bromophenylhydrazone	102		204	310	546	1790
D-Ribose *p*-bromophenylhydrazone	−71.3	−94.7	−138	−216	−429	−1470

[a] Peak, $[\phi]^{22}_{390}$ 290°.

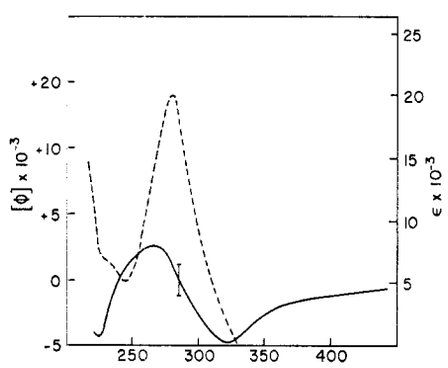

Figure 1.—Uv (– – –) and ORD (——) spectra of tetra-*O*-acetyl-L-fucose benzylphenylhydrazone in methanol.

and substituted benzylphenylhydrazones show a readily discernible relationship.[13] This indicates that for benzylphenylhydrazones, unlike most aldose hydrazones, the acyclic isomer predominates independent of stereochemistry. Cyclic and acyclic acetylated aldose phenylhydrazones are readily distinguished by nmr. In the acyclic compounds the C-1 aldimine proton resonance occurs in the region τ 0.5–3.8 while in the cyclic isomer the C-1 anomeric proton resonance occurs at τ 5.6.[5] The shielding resulting from the conversion of the imine into a glycosylamine is also detectable to a lesser extent in the shift of resonances of methine hydrogens at C-2 from τ 4.4 to *ca.* 5.0 and at C-3 from τ 4.5 to *ca.* 5.0. The chemical shift of the terminal methylene hydrogen is unaffected by cyclization. The lack of methine proton resonances above τ 5.0 and the presence of the H-1 doublet at τ 3.5 in the nmr spectra of acetylated aldose benzylphenylhydrazones (Table III) is consistent with acyclic structure **2**. The acyclic structure of penta-*O*-acetyl-D-galactose benzylphenylhydrazone has already been established by unambiguous synthesis from *aldehydo*-D-galactose pentaacetate.[3]

TABLE III

CHEMICAL SHIFTS AND COUPLING CONSTANTS OF ACETYLATED ALDOSE BENZYLPHENYLHYDRAZONES IN CHLOROFORM

Derivative	H-1, τ	H-2, τ	H-3, τ	$J_{1,2}$, Hz	$J_{2,3}$, Hz
Ribose	3.51	4.37	4.57	5.5	5
Arabinose	3.59	4.34	*Ca.* 4.6	4.8	5
Galactose	3.58	4.36	*Ca.* 4.6	4.8	1
Fucose	3.57	4.34	4.64	4.5	2
Mannose	3.47[a]	*Ca.* 4.5	*Ca.* 4.5	*a*	
Glucose	3.49	*Ca.* 4.4	*Ca.* 4.6	4.5	

[a] Unresolved, broak peak.

Structures of *cis* and *trans* isomers about the imine bond of hydrazones can be assigned on the basis of the deshielding of the aldimine hydrogen by about 30–40 Hz when the β nitrogen is *cis* to H-1.[14] However, the chemical shift of the aldimine hydrogen is strongly dependent on the nature of substituents on the β nitrogen and the solvent. A range of 3.3 ppm has been observed for monosubstituted arylhydrazones. To

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(14) G. J. Karabatsos, F. M. Vane, R. A. Taller, and N. Hsi, *J. Amer. Chem. Soc.*, **86**, 3351 (1964).

make assignment of *cis* and *trans* structures on the basis of chemical-shift difference it is necessary to have both isomers. *cis* or *trans* structures cannot be assigned to the aldose benzylphenylhydrazones on this basis because only one isomer is obtained from each aldose. Since no mutarotation was detected by ORD or by nmr, the set of isomers obtained are probably the sterically more stable isomers with H-1 and β-N *cis* (2). The conformation about the bond between C-1 and C-2 is unknown; however, the coupling constant, $J_{1,2}$ = 5 Hz, is comparable with the coupling constant between H-1 and H-2 of acetaldehyde phenylhydrazone[15] consistent with a time average of appreciable contribution from several conformations.

As found for other acyclic imine derivatives of sugars,[1,5,16] deshielding of the proton resonance decreases systematically with the number of bonds intervening between the proton and imine group, reaching a limiting value of *ca.* τ 5.0 for methine hydrogen. Consequently nonfirst-order effects are more marked in hexoses than in pentoses. The terminal methylene signal for the ribose, arabinose, mannose, and glucose derivatives occurs at *ca.* τ 5.9 and is a typical ABX pattern with J_{AB} = 12 Hz and J_{AB}/δ_{AB} = 1; for the galactose derivative J_{AB}/δ_{AB} = 2. Chemical shifts between H-2 and H-3 for the mannose and glucose derivatives are insufficient at 60 MHz to permit determination of $J_{2,3}$. Virtual coupling of the aldimine hydrogen of the mannose derivative to three other hydrogens is responsible for filling in of the expected doublet. Each acetate methyl resonance of proper area could be distinguished at *ca.* τ 8.0 for many of the compounds. This is further evidence of the presence of only one geometrical isomer in the equilibrated chloroform solution. The wide variation in $J_{2,3}$ and $J_{3,4}$ indicates considerable conformational homogeneity for at least some stereochemistries of the polyacetoxyalkyl chain.

The unacetylated aldose benzylphenylhydrazones are also acyclic since acetylation of equilibrated pyridine solutions at room temperature gives acyclic products. The fact that configuration at C-2 has the dominant effect on the optical rotation of both acetylated and unacetylated aldose benzylphenylhydrazones means that it is the closest asymmetric center to the chromophore. This excludes a cyclic structure in which the new center of asymmetry at C-1, being closer to the chromophore, would have the dominant effect on the optical rotation. The ORD fits a Drude equation between 350 and 600 nm with λ_0 = 300 ± 20 nm for both acetylated and unacetylated aldose benzylphenylhydrazones with the exception of penta-*O*-acetyl-D-mannose benzylphenylhydrazone. An optically active electronic transition at about 300 mμ is consistent with an acyclic hydrazone structure. The absorption band for a pyranosylhydrazone would be expected at shorter wavelength. Neither the rotation data nor the acetylation evidence precludes the presence of some cyclic isomer in equilibrium with acyclic hydrazone.

Penta-*O*-acetyl-D-mannose benzylphenylhydrazone has a rotatory dispersion which appears to be a composite of two close-lying Cotton effects of opposite sign. A very shallow trough occurs displaced to 450 nm and a maximum, not observable in pyridine, occurs below 335 nm. The dominance of negative rotation at wavelengths above 450 nm suggests that a positive Cotton effect is superimposed on a stronger negative one centered at somewhat shorter wavelength. Presumably both Cotton effects contribute to the long wavelength rotation of the other benzylphenylhydrazones examined as well, but the shorter wavelength effect is the dominant of the two. Failure to take the weaker effect into account in a one term Drude equation may explain the range in values found for λ_0 (300 ± 20 nm).

(15) G. J. Karabatsos, R. A. Taller, and F. M. Vane, *J. Amer. Chem. Soc.*, **85**, 2327 (1963).

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Experimental Section

Rotations were determined on a Cary Model 60 spectropolarimeter at temperatures between 21 and 24° using a 10-cm path length above 400 nm and 10- and 1-cm path lengths below 400 nm. Concentrations between 0.1 and 0.2% were used for all measurements above 350 nm. Solutions of benzylphenylhydrazones were allowed to stand 24 hr before rotations were measured. No mutarotation was observed after this period. Nmr spectra of acetylated benzylphenylhydrazones were measured on a Varian Model A-60 spectrometer at 10% concentration in chloroform with tetramethylsilane as internal standard.

Acetylation of Aldose Benzylphenylhydrazones.—Aldose benzylphenylhydrazones were acetylated at room temperature by adding 1 ml of acetic anhydride to 50 ml of 0.1% aldose benzylphenylhydrazone in pyridine. Progress of acetylation was followed polarimetrically. The rotation became constant after 12 hr. Rotatory dispersions were measured 24 hr after addition of acetic anhydride. The ORD remained constant over a period of at least 48 hr. Acetylated aldose benzylphenylhydrazones were recovered by removal of pyridine under vacuum and freed of traces of pyridine by repeated solution in chloroform and removal of chloroform under vacuum. Penta-*O*-acetyl-D-glucose benzylphenylhydrazone, $[\alpha]^{24}D$ 92° (*c* 0.2, pyridine), and penta-*O*-acetyl-D-galactose benzylphenylhydrazone, mp 128–130°, $[\alpha]^{24}D$ 79° (methanol), $[\alpha]^{23}D$ 90° (pyridine), had properties similar to those previously reported.[17]

Tetra-*O*-actyl-L-fucose benzylphenylhydrazone was crystallized from ethanol: mp 135–136°; $[\alpha]^{23}D$ −69.0° (*c* 0.2 methanol), $[\alpha]^{22}D$ −71° (*c* 0.2, pyridine).

Anal. Calcd for $C_{27}H_{32}N_2O_8$: C, 63.72; H, 6.29; N, 5.47. Found: C, 63.19; H, 6.31; N, 5.35.

Penta-*O*-acetyl-D-mannose benzylphenylhydrazone was obtained as an oil, $[\alpha]^{22}D$ −6° (*c* 0.2, pyridine).

Anal. Calcd for $C_{29}H_{34}N_2O_{10}$: mol wt, 570.2214. Found: mol wt, 570.2237 (mass spectral).

Tetra-*O*-acetyl-D-arabinose benzylphenylhydrazone was obtained as an oil which crystallized after a few days: mp 85–88°; $[\alpha]^{22}D$ −73° (*c* 0.1, pyridine).

Anal. Calcd for $C_{26}H_{30}N_2O_8$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.34; H, 5.94; N, 6.02.

Tetra-*O*-acetyl-D-ribose benzylphenylhydrazone was obtained as an oil, $[\alpha]^{22}D$ 110° (*c* 0.1, pyridine).

Anal. Calcd for $C_{26}H_{30}N_2O_8$: mol wt, 498.2002. Found: mol wt, 498.2006 (mass spectral).

Registry No.—Penta-*O*-acetyl-D-glucose benzylphenylhydrazone, 17693-40-2; penta-*O*-acetyl-D-galactose, benzylphenylhydrazone, 17693-41-3; tetra-*O*-acetyl-L-fucose benzylphenylhydrazone, 17693-41-4; penta-*O*-acetyl-D-mannose benzylphenylhydrazone, 17693-43-5; tetra-*O*-acetyl-D-arabinose benzylphenylhydrazone, 17693-44-6; tetra-*O*-acetyl-D-ribose benzylphenylhydrazone, 17693-45-7.

Acknowledgment.—The Cary Model 60 spectropolarimeter was purchased with funds from Public Health Service Grant GM-11966 of the National Institute of Medical Sciences and from National Science Foundation Grant GP-2125.

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