[CONTRIBUTION FROM THE APPLIED CHEMISTRY DEPARTMENT, INDIAN INSTITUTE OF TECHNOLOGY]

Molecular Rotation and Absolute Configuration. II. Sugars[1]

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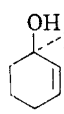
Received March 13, 1958

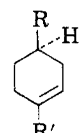
A generalization involving absolute configuration and molecular rotation of cyclic compounds has been enunciated which accommodates the following previously known empirical rules: Hudson's Isorotation rule and Lactone rule, Mills' rules, and the Klyne-Stokes rule. Besides serving as a mnemonic for these rules, this generalization can also be applied to several cases not covered by previous rules. The validity of this generalization, which is also empirical in nature, has been examined by applying it to the rotation of sugars of known absolute configuration. Hudson's classification of lactones into class A and class B has been shown to be unnecessary. New correlations between rotation and absolute configuration for several types of epimeric sugars have been presented, and this generalization has been found to be in accord with them.

Several empirical rules have been described for correlating the sign of rotation with the absolute configuration of cyclic compounds.[3] The most prominent among these are Hudson's Isorotation rule[4] and Lactone rule[5] for sugars. Recently Klyne[6] has extended the applicability of the latter to polycyclic compounds.

Mills[7] has found that of epimeric pairs of allylic terpene cyclohexenols, the alcohol with the absolute configuration I is more dextrorotatory than its epimer.



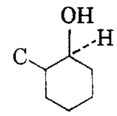
I



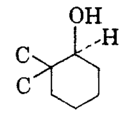
II

Mills[7] has further shown that the known monocyclic terpene derivatives of absolute configuration II (R and R′ are suitable combinations of the groups —CH_3, —$CH(CH)_{23}$, —$C(CH_2)=CH_2$, —CH_2OH, —$C(CH_3)_2OH$, —CH_2OCOCH_3, —$C(CH_3)_2OCOCH_3$) are all dextrorotatory.

According to the generalization of Klyne and Stokes,[8] the cyclohexanols III and IV (or corresponding acetates or benzoates) are more dextrorotatory than their hydroxy epimers. These authors stated that this rule might possibly be valid for substituents other than hydroxyl but felt that such an extension of the principle should await further evidence.



III



IV

Partly from a study of these rules, we have derived a generalization that appears to have a wider scope. Let the projection formulas V and VI represent the absolute configuration of a pair of epimeric cyclic (six- or five-membered; carbocyclic or heterocyclic) compounds: in these projections the ring is in the plane of the paper. The part of the ring on one side of the asymmetric carbon atom constitutes L and the part on the other side, S. For the purposes of this generalization only those parts of L and S that are in the immediate vicinity of the asymmetric carbon atom (one or two atoms of the ring next to the asymmetric carbon atom) need be taken into consideration. Table I should be used to decide which of the two endocyclic substituents is L and which is S. It will be noticed that L (large) is bulkier than S (small) in most cases but not all. Thus, $-\underset{\|}{\overset{}{C}}-$ (C=O) is listed under L in Table I and $-\overset{|}{\underset{|}{C}}-$

TABLE I

L		S
$-\overset{H}{\underset{C}{C}}-$ and $-\overset{C}{\underset{C}{C}}-$	>	$-\overset{H}{\underset{H}{C}}-$
$-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-$	>	$-C=C-$ (with single bonds below each C)
$-\overset{|}{\underset{|}{C}}-$	>	$-O-$
$-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-$	>	$-\overset{|}{\underset{|}{C}}-O-$
$-\underset{\underset{O}{\|}}{C}-$		$-\overset{|}{\underset{|}{C}}-$

(1) Based in part on a paper presented before the Indian Science Congress, 1956. For Part I, see *Ind. J. Pharmacy*, **18**, 185 (1956).

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(3) W. Klyne, *Progress in Stereochemistry I*, Butterworths Scientific Publications, London, 1954, p. 177.

(4) C. S. Hudson, *J. Am. Chem. Soc.*, **31**, 66 (1909).

(5) C. S. Hudson, *J. Am. Chem. Soc.*, **32**, 338 (1910).

(6) W. Klyne, *Chem. and Ind.* (*London*), 1198 (1954).

(7) J. A. Mills, *J. Chem. Soc.*, 4976 (1952).

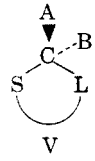
(8) W. Klyne and W. M. Stokes, *J. Chem. Soc.*, 1979 (1954).

under S, although a substituted carbon is definitely bulkier than a carbonyl group.

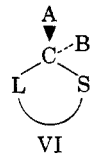
Of the two exocyclic substituents A and B, let the latter be the bulkier.

The generalization may now be enunciated as follows:

Looking at the asymmetric carbon atom from the center of the ring which is in the plane of the paper, place the bulkier of the two exocyclic substituents, B (big, below) below the plane of the ring; if now L (large) is to the *right* of S (small), the compound V is more *dextrorotatory* than its epimer (VI); if L is to the *left* of S, the compound VI is the more *levorotatory* of the two epimers.



V



VI

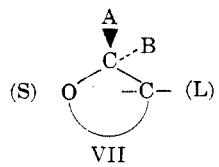
This generalization can easily be shown to embrace the rules of Klyne and Stokes[8] and of Mills.[7] It will be seen later that this generalization also covers Hudson's Isorotation rule and Lactone rule.

The generalization enunciated here can therefore serve as a mnemonic for the existing empirical correlations between molecular rotation and absolute configuration of cyclic compounds. As a matter of fact, this generalization goes beyond these correlations and permits the assignment of configuration in several cases where these earlier empirical rules do not apply. It should be noted that this generalization also is entirely empirical in nature.

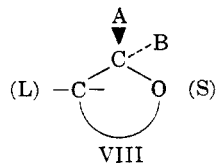
It is the purpose of this communication to test the validity of this empirical generalization by applying it to sugar derivatives of known absolute configuration. Other classes of compounds such as terpenes and alkaloids will be considered elsewhere.

The rotation data presented here have mainly been collected from the comprehensive tables in "Advances in Carbohydrate Chemistry" and the appropriate chapters of Rodd's[9] "Chemistry of Carbon Compounds." Original memoirs have also been examined but the search for rotation data from primary sources has not been exhaustive.

First to be considered will be the epimeric sugar derivatives represented by the projection formulas VII and VIII. From the generalization stated before one can predict that VII should be more dextrorotatory than VIII.



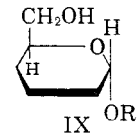
VII



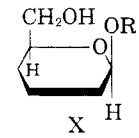
VIII

(9) E. H. Rodd, Chemistry of Carbon Compounds, Vol. IB, Elsevier Publishing Co., Amsterdam, 1952.

The anomeric (α and β as defined by Hudson[4]) sugars are prominent members of this group. For such sugars, Hudson's Isorotation rule[4,10] states that (*a*) the rotation of carbon 1 in the case of many substances of the sugar group is affected in only a minor degree by changes in the structure of the remainder of the molecule, (*b*) changes in the structure of carbon 1 in the case of many substances of the sugar group affect in only a minor degree the rotation of the remainder of the molecule. These relations do not hold quantitatively in all cases, but a qualitative inference is that an α-D-sugar (or derivative) (IX) is more dextrorotatory than the anomeric β-D-sugar (X). Since IX corresponds to the general structure VII and X to VIII, this qualitative aspect of the Isorotation rule is in accord with the generalization under discussion.



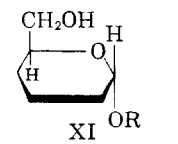
IX



X

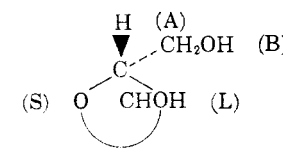
Klyne[11] has extended the basic idea of isorotation to steroid glycosides for predicting whether such compounds are α- or β-glycosides.

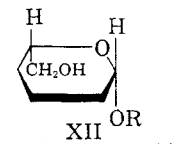
Another group corresponding to VII and VIII can be devised by pairing an α- or β-D-pyranoside XI (or the corresponding lactone) with a matching β- or α-L-pyranoside XII (or the corresponding lactone). In Table II are listed several pairs of such sugars epimeric at C_5. All except the last part agree with the prediction and even in that case the difference is so small as to be within the range of experimental error.



XI
α-D-Glycopyranoside

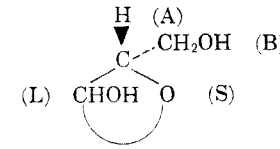
≡





XII
β-L-Glycopyranoside

≡



An analogous situation exists in the case of γ-lactones and furanosides (for example, XIII and XIV) that are epimeric at C_4. The available data (Table III) again bear out the prediction.

(10) W. W. Pigman and R. M. Goepp, *Chemistry of the Carbohydrates*, Academic Press, New York, N. Y., 1948, p. 80.

(11) W. Klyne, *Biochem. J.*, **47**, xli (1950).

TABLE II

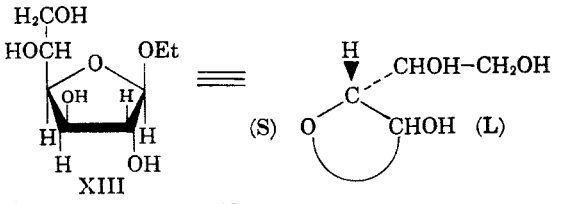
Pyranose Sugar XI	$[\alpha]_D$, Degree	Ref.	C_5 Epimer XII	$[\alpha]_D$, Degree	Ref.
Pentaacetyl-α-D-glucopyranose	+102(C)	18	Pentaacetyl-β-L-idopyranose	−13[a]	30
Methyl α-D-glucopyranoside	+158	18	Methyl β-L-idopyranoside	+95[a]	19
2,3,4,6-Tetraacetyl-	+131	27	2,3,4,6-Tetraacetyl-	+64(C)[a]	26
Pentaacetyl-β-D-glucopyranose	+4(C)	18	Pentaacetyl-α-L-idopyranose	−54[a]	30
Methyl β-D-glucopyranoside	−32	18	Methyl α-L-idopyranoside	−100[a]	19
2-Deoxy-	−48	20	2-Deoxy-	−130(M)[a]	20
2-*O*-methyl-	−38	25	2-*O*-methyl-	−86[a]	23
D-Gluconolactone (δ)			L-Idonolactone (δ)		
2,4,6-Tri-*O*-methyl-	+87	28, 29	2,4,6-Tri-*O*-methyl-	+15[a]	15
2,3,4,6-Tetra-*O*-methyl-	+99	25	2,3,4,6-Tetra-*O*-methyl-	+32[a]	15
α-D-Galactopyranose	+144	19	β-L-Altropyranose	+69[a]	22
Methyl α-D-galactopyranoside	+196	18	Methyl β-L-altropyranoside	+52[a]	22
2,4,6-Tri-*O*-methyl-	+164	24	2,4,6-Tri-*O*-methyl-	+33[a]	23
2,3,4,6-Tetra-*O*-methyl-	+190	24	2,3,4,6-Tetra-*O*-methyl-	+38(C)[a]	22
β-D-Galactopyranose pentaacetate	+25(C)	18	α-L-Altropyranose pentaacetate	−63(C)[a]	22
Methyl β-D-galactopyranoside	+0.61	18	Methyl α-L-altropyranoside	−126[a]	22
2-Deoxy-	±0	20	2-Deoxy-	−143(C)[a]	47
2,4,6-Tri-*O*-methyl-	−41	24	2,4,6-Tri-*O*-methyl-	−145(C)[a]	22
2,3,4,6-Tetra-*O*-methyl-	+20	24	2,3,4,6-Tetra-*O*-methyl-	−129(C)[a]	22
D-Galactonolactone (δ)			L-Altronolactone (δ)		
3,4,6-Tri-*O*-methyl-	+47	24	3,4,6-Tri-*O*-methyl-	+10[a]	22
	+105	24			
β-D-Allopyranose	+0.6	19	α-L-Talopyranose	<−68[a]	52
β-D-Mannopyranose	−16	19	α-L-Gulopyranose	<−11[b]	19
Methyl β-D-mannopyranoside	−53	18	Methyl α-L-gulopyranoside	−112[a]	23
Methyl α-D-mannopyranoside	+82	18	Methyl β-L-gulopyranoside	+83[a]	19

[a] Rotation derived from that of the D-sugar. [b] Computed from mutarotation data assuming that the β-isomer (equatorial OH at C_1) will not be less than 50% in the equilibrium mixture.

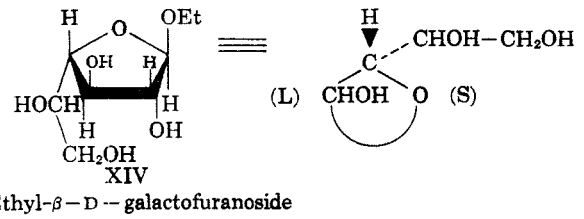
TABLE III

Furanose Sugar XIII	$[\alpha]_D$, Degree	Ref.	C_4 Epimer XIV	$[\alpha]_D$, Degree	Ref.
D-Xylonolactone (γ)			L-Arabinolactone (γ)		
3,5-Di-*O*-methyl-	+75	31	3,5-Di-*O*-methyl-	−84	31
2,3,5-Tri-*O*-methyl-	+74	31	2,3,5-Tri-*O*-methyl-	−45	31
D-Ribonolactone (γ)			L-Lyxonolactone (γ)		
2,3,5-Tri-*O*-methyl-	−20	31	2,3,5-Tri-*O*-methyl-	−83[a]	31
D-Gluconolactone (γ)	+68	32	D-Galactonolactone (γ)	−78	33
2,3,5-Tri-*O*-methyl-	+62	25	2,3,5-Tri-*O*-methyl-	−37	24
2,3,5,6-Tetra-*O*-methyl-	+63	25	2,3,5,6-Tetra-*O*-methyl-	−30	24
Ethyl β-D-glucofuranoside	+86	19	Ethyl β-D-galactofuranoside	−97	19
D-Mannonolactone (γ)	+52[a]	32	D-Talonolactone (γ)	−35	32

[a] Rotation derived from that of the corresponding sugar of the opposite series.

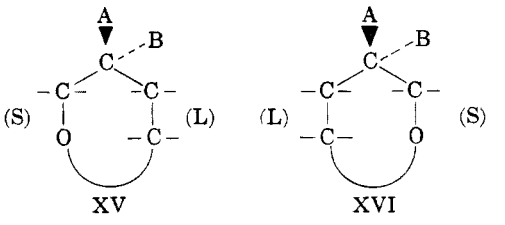


Ethyl-β-D-glucofuranoside



Ethyl-β-D-galactofuranoside

Next to be considered are the epimeric sugar derivatives represented by XV and XVI. Again it can be predicted that XV should be more dextrorotatory than XVI.



To this category belong pyranosides and furanosides epimeric at C_2 (Table IV), pyranosides epimeric at C_4 (Table V) and furanosides epimeric at C_3 (Table VI).

From Table IV it is apparent that 1,6-anhydropyranosides follow the same pattern as pyranosides. The large variety of epimeric pyranoses and

TABLE IV

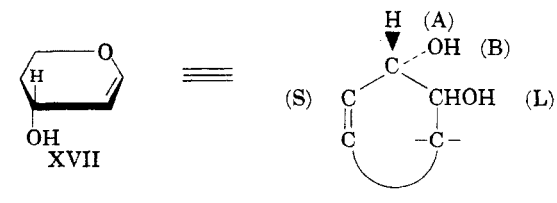
Pyranose or Furanose Sugar XV	$[\alpha]_D$, Degree	Ref.	C_2 Epimer XVI	$[\alpha]_D$, Degree	Ref.
α-D-Glucopyranose	+113	19	α-D-Mannopyranose	+30	19
Pentaacetate	+102(C)	18	Pentaacetate	+57(C)	18
Pentabenzoate	+139(C)	18	Pentabenzoate	−19(C)	18
β-D-Glucopyranose	+19	19	β-D-Mannopyranose	−16	19
Pentaacetate	+4(C)	18	Pentaacetate	−25(C)	18
Pentabenzoate	+24(C)	18	Pentabenzoate	−82(C)	18
Methyl α-D-glucopyranoside	+181	18	Methyl α-D-mannopyranoside	+82	18
2,3-Di-*O*-methyl-	+150	25	2,3-Di-*O*-methyl-	+44(C)	34
2,3,4,6-Tetra-*O*-methyl-	+144(A)	25	2,3,4,6-Tetra-*O*-methyl-	+43, +76(E)	34
6-Deoxy-	+153	37	6-Deoxy-	+63	37
α-D-Ribopyranose tetraacetate	+51(M)	18	α-D-Arabinopyranose tetraacetate	−44(C)	18
Methyl α-D-ribopyranoside	+103	18	Methyl α-D-arabinopyranoside	−17	18
β-D-Ribopyranose			β-D-Arabinopyranose		
Tetraacetate	−58(C)	18	Tetraacetate	−147(C)	18
Tetrabenzoate	−102(C)	18	Tetrabenzoate	−323(C)	18
Methyl β-D-ribopyranoside	−105	18	Methyl β-D-arabinopyranoside	−244	18
Phenyl β-D-ribopyranoside	−108(Dioxane)	18	Phenyl β-D-arabinopyranoside	−244	18
Methyl α-D-xylopyranoside	+154	18	Methyl α-D-lyxopyranoside	+59	38
1,5-Anhydro-D-sorbitol	+43	39	1,5-Anhydro-D-mannitol	−57	39
1,5-Anhydro-D-galactitol	+77	39	1,5-Anhydro-D-talitol	−11	39
2,3,4,6-Tetraacetate	+49(C)	39	2,3,4,6-Tetraacetate	−16(C)	39
1,5-Anhydro-D-xylitol	0	40	1,5-Anhydro-D-lyxitol	−99	40
Methyl β-D-glucopyranoside	−32	18	Methyl β-D-mannopyranoside	−53	18
2,3,4,6-Tetra-*O*-methyl-	−17(E)	25	2,3,4,6-Tetra-*O*-methyl	−80	34
Phenyl α-D-glucopyranoside	+181	18	Phenyl α-D-mannopyranoside	+114	18
Tetraacetate	+168(C)	18	Tetraacetate	+74(C)	18
Phenyl β-D-glucopyranoside	−72	18	Phenyl β-D-mannopyranoside	−72	18
Tetraacetate	−23(C)	18	Tetraacetate	−63(C)	18
β-D-Allopyranose	+1	19	β-D-Altropyranose	−69	19
Methyl α-D-gulopyranoside	+106	35	Methyl α-D-idopyranoside	+100	19
3-Deoxy-	+143(M)	36	3-Deoxy-	+98(M)	36
Methyl β-D-gulopyranoside	−83	19	Methyl β-D-idopyranoside	−95	19
1,6-Anhydro-β-D-allopyranoside	−76	41	1,6-Anhydro-β-D-altropyranoside	−213	43
1,6-Anhydro-β-D-glucopyranoside	−66	43	1,6-Anhydro-β-D-mannopyranoside	−128	43
2,3,4-Triacetate	−46(E)	43	2,3,4-Triacetate	−104	43
β-D-Glucopyranuronic Acid	+12	42	β-D-Mannopyranuronic Acid	−48	42
Methyl α-D-glucofuranoside			Methyl α-D-mannofuranoside		
2,3,5,6-Tetra-*O*-methyl-	+107(M)	39	2,3,5,6-Tetra-*O*-methyl-	+99	34
2,3,4-Tri-*O*-methyl-D-glucopyranuronic acid, methyl α-glycoside, methyl ester	+156(M)	44	2,3,4-Tri-*O*-methyl-D-mannopyranuronic acid, methyl α-glycoside, methyl ester	+74(M)	44

furanoses cited in Table IV all obey the predictions made.

Of the large number of C_4 epimeric pairs cited in Table V all but one are in accord with the generalization.

Table Va compares the rotations of several corresponding galactopyranoside and mannopyranoside derivatives. The rotation of the corresponding glucopyranosides are not available but since galactopyranosides are more dextrorotatory than glucopyranosides (Table V) and the latter are more dextrorotatory than mannopyranosides (Table IV), it can be predicted that galactopyranosides should be more dextrorotatory than the corresponding mannopyranosides. Three exceptions to this prediction are found in Table Va. It is interesting to note that none of the galactonolactones involved here have so far been isolated in the crystalline form. It is conceivable that some of these discrepancies may have resulted from possible lack of purity of these galactonolactones. Only one exception is noted in Table VI.

For C_3 epimers of type XVII and XVIII, the



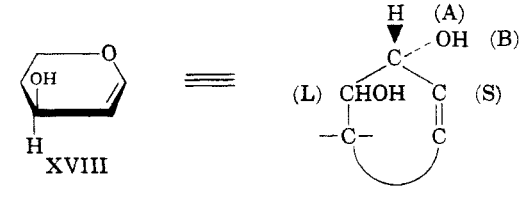


TABLE V

Pyranose Sugar XV	$[\alpha]_D$, Degree	Ref.	C_4 Epimer XVI	$[\alpha]_D$, Degree	Ref.
α-L-Xylopyranose tetraacetate	−89(C)[a]	18	β-D-Arabinopyranose tetraacetate	−147(C)	18
β-L-Xylopyranose tetraacetate	+25(C)[a]	18	α-D-Arabinopyranose tetraacetate	−44(C)	18
Methyl α-L-xylopyranoside	−154[a]	18	Methyl β-D-arabinopyranoside	−244	18
Methyl β-L-xylopyranoside	+66[a]	18	Methyl α-D-arabinopyranoside	−17	18
α-D-galactopyranose	+144	19	α-D-Glucopyranose	+113	19
Pentaacetate	+107(C)	18	Pentaacetate	+102(C)	18
Pentabenzoate	+187(C)	18	Pentabenzoate	+139(C)	18
Methyl α-D-galactopyranoside	+196	18	Methyl α-D-glucopyranoside	+158	18
2-Deoxy-	+170	20	2-Deoxy-	+138	20
6-Deoxy-	+197[a]	46	6-Deoxy-	+153	46
Methyl β-D-galactopyranoside	−0.4	20	Methyl β-D-glucopyranoside	−32	20
2-Deoxy-	±0	20	2-Deoxy-	−48	20
6-Deoxy-	−14[a]	46	6-Deoxy-	−55	46
Phenyl α-D-galactopyranoside	+217	18	Phenyl α-D-glucopyranoside	+181	18
Tetraacetate	+176(C)	18	Tetraacetate	+168(C)	18
Phenyl β-D-galactopyranoside	−43	18	Phenyl β-D-glucopyranoside	−72	18
Methyl 2-deoxy-α-D-gulopyranoside (sirup)	+125(C)	21	Methyl 2-deoxy-α-D-allopyranoside (amorphous)	+143(C)	47
2-Amino-2-deoxy-α-D-galactopyranose pentaacetate	+102(C)	48	2-Amino-2-deoxy-α-D-glucopyranose pentaacetate	+94(C)	48
2-Amino-2-deoxy-β-D-galactopyranose pentaacetate	+11(C)	48	2-Amino-2-deoxy-β-D-glucopyranose pentaacetate	+1(C)	48
1,6-Anhydro-β-D-gulopyranose	+50	49	1,6-Anhydro-β-D-allopyranose	−76	41
1,6-Anhydro-β-D-galactopyranose	−22	43	1,6-Anhydro-β-D-glucopyranose	−66	43
2,3,4-Triacetate	−6(C)	43	2,3,4-Triacetate	−46(E)	43
1,5-Anhydro-D-talitol	−11	40	1,5-Anhydro-D-mannitol	−51	40
1,5-Anhydro-D-galactitol	+77	40	1,5-Anhydro-D-glucitol	+42	40
1,5-Anhydro-4(β-D-galactopyranosyl)-D-glucitol	+50	40	1,5-Anhydro-4(β-D-glucopyranosyl)-D-glucitol	+29	40
4-(β-D-galactopyranosyl)hydro-D-glucal (hydrolactal)	+29	40	4-(β-D-glucopyranosyl)hydro-D-glucal (hydrocellobial)	+5	40
Hydro-D-galactal	+48	40	Hydro-D-glucal	+17	40
α-D-Galactopyranuronic acid, methyl ester, tetraacetate	+143(C)	18	α-D-Glucopyranuronic acid, methyl ester, tetraacetate	+98(C)	18
β-D-Galactopyranuronic acid, methyl ester, tetraacetate	+58(C)	18	β-D-Glucopyranuronic acid, methyl ester, tetraacetate	+9(C)	18
D-Galactonolactone (δ)			D-Gluconolactone (δ)		
3,4,6-Tri-*O*-methyl-	+152 +105 +67	24	3,4,6-Tri-*O*-methyl-	+87	25
2,4,6-Tri-*O*-methyl-	+152	24	2,4,6-Tri-*O*-methyl-	+87	14, 29
2,3,4,6-Tetra-*O*-methyl-	+167	24	2,3,4,6-Tetra-*O*-methyl-	+99	25

[a] Rotation derived from that of the corresponding sugar of the opposite series.

TABLE Va

Galactopyranose Derivative	$[\alpha]_D$, Degree	Ref.	Mannopyranose Derivative	$[\alpha]_D$, Degree	Ref.
Methyl 2,3,4-tri-*O*-methyl-α-D-fucopyranoside	+209[a]	31	Methyl 2,3,4-tri-*O*-methyl-α-D-rhamnopyranoside	+15[a]	31
β-Anomer	+21[a]	31	β-Anomer	−106[a]	31
2,3,4-Tri-*O*-methyl-D-fuconolactone (δ)	+138[a]	31	2,3,4-Tri-*O*-methyl-D-rhamnolactone (δ)	+130[a]	31
Methyl α-D-galactopyranoside			Methyl α-D-mannopyranoside		
2,3-Di-*O*-methyl-	+174(C)	24	2,3-Di-*O*-methyl-	+44(C)	34
2,3,4-Tri-*O*-methyl-	+154	24	2,3,4-Tri-*O*-methyl-	+47	34
2,3,4,6-Tetra-*O*-methyl-	+190	24	2,3,4,6-Tetra-*O*-methyl-	+43	34
Methyl β-D-galactopyranoside			Methyl β-D-mannopyranoside		
2,3,4,6-Tetra-*O*-methyl-	+20	24	2,3,4,6-Tetra-*O*-methyl-	−80	34
D-Galactonolactone (δ)			D-Mannonolactone (δ)		
3,4-Di-*O*-methyl- (sirup)	+89	24	3,4-Di-*O*-methyl-	+178	34
4,6-Di-*O*-methyl- (sirup ?)	+91	24	4,6-Di-*O*-methyl-	+165	34
2,4,6-Tri-*O*-methyl-	+152	24	2,4,6-Tri-*O*-methyl-	+141	34
3,4,6-Tri-*O*-methyl- (sirup)	+47	24	3,4,6-Tri-*O*-methyl-	+168	34
2,3,4,6-Tetra-*O*-methyl-	+166	24	2,3,4,6-Tetra-*O*-methyl-	+150	34

[a] Rotation derived from that of the L-sugar.

TABLE VI

Furanolactone XV	$[\alpha]_D$, Degree	Ref.	C_3 Epimer XVI	$[\alpha]_D$, Degree	Ref.
D-Xylonolactone (γ)	+90	31	D-Ribonolactone (γ)	+18[a]	28
2,3,5-Tri-*O*-methyl-	+74	31	2,3,5-Tri-*O*-methyl-	−20	31
D-Lyxonolactone (γ)	+84	28	D-Arabonolactone (γ)	+74	28
2,3,5-Tri-*O*-methyl-	+83	31	2,3,5-Tri-*O*-methyl-	+47[a]	31
D-Gluconolactone (γ)	+68	32	D-Allonolactone	−6	32
D-Galactonolactone (γ)	−73	32	D-Gulonolactone (γ)	−57	32
2,3,5,6-Tetraacetyl-	−22(A)	45	2,3,5,6-Tetraacetyl-	−37(A)	45

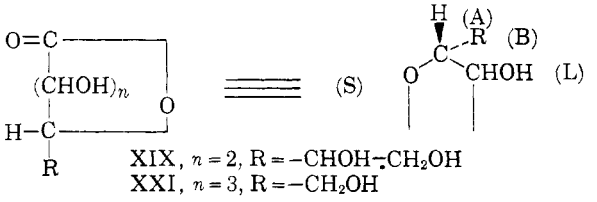
[a] Rotation derived from that of the L-sugar.

TABLE VII

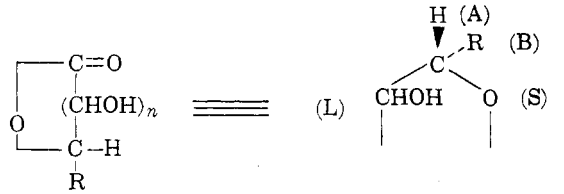
Glycol XVII	$[\alpha]_D$, Degree	Ref.	C_3 Epimer XVIII	$[\alpha]_D$, Degree	Ref.
D-Arabinal (D-ribal)	+101	28	D-Lyxal (D-xylal)	−255	28
Diacetate	+266(C)	28	Diacetate	−315(C)	28

prediction is that XVII should be more dextrorotatory than XVIII. From Table VII it will be seen that D-arabinal and D-xylal conform to this prediction.

A very valuable correlation in sugar chemistry is Hudson's Lactone rule[5,12] which states that if the 1,4-lactonic ring comes on the right of the (standard projection of the) structure as in XIX, the lactone is dextrorotatory and if on the left as in XX, it is levorotatory.



XIX, $n = 2$, R = −CHOH−CH_2OH
XXI, $n = 3$, R = −CH_2OH



XX, $n = 2$, R = −CHOH−CH_2OH
XXII, $n = 3$, R = −CH_2OH

Hudson[5] has pointed out that in a sugar lactone, the rotational contribution of the asymmetric carbon atom C_4, linked to the ester oxygen of lactone group is generally much higher than the total rotational contribution of the other centers of asymmetry in the molecule. Hudson's Lactone rule, therefore, amounts to predicting that the rotational contribution of the carbon linked to the lactonic oxygen is dextrorotatory in XIX and levorotatory in XX, a prediction that follows from the generalization also. If, however, the total rotational contribution of the other centers of asymmetry exceeds that of this carbon atom, the resultant rotation of the lactone will be levo even when the C_4 contribution is dextrorotatory. This actually happens in the case of D-allonofuranolactone, $[\alpha]_D$ −6°, which should have been dextrorotatory according to Hudson's Lactone rule.

To get around such an anomaly, Freudenberg[13] suggested that the Lactone rule should be stated in the following form: A γ-lactone having the ring on the right (for example, D-allonolactone or D-ribonolactone) should be more dextrorotatory than its C_4 epimer (D-gulonolactone or L-lyxonolactone). This statement is identical with the deduction from the generalization under study. As predicted, D-allonofuranolactone, $[\alpha]_D$ −6° is indeed more dextrorotatory than its C_4 epimer, D-gulonofuranolactone, $[\alpha]_D$ −57°.

On the basis of the generalization, it can be predicted that the δ-lactone XXI should be more dextrorotatory then its C_5 epimer, XXII. All δ-lactones of the D-hexoses should, therefore, be dextrorotatory if the total rotation contribution of the other centers of asymmetry be smaller than that of C_5. Although this indeed is the case with most of the δ-lactones of hexoses reported so far,[12] at least three levorotatory D-pyranolactones are known: 3,4,6-tri-*O*-methyl-D-altronolactone,[14] $[\alpha]_D$ −9.6°; 2,4,6-tri-*O*-methyl-D-idonolactone,[15] $[\alpha]_D$ −15.4° and 2,3,4,6-tetra-*O*-methyl-D-idonolactone,[15] $[\alpha]_D$ −32°. The δ-lactones of pentoses differ from those of hexoses in that the ester oxygen of the lactone ring is not attached to an asymmetric carbon. It thus appears that no predictions can be made about δ-lactones from pentoses.

Klyne's[6] modification of the Lactone rule rests on the observation that the rotation contribution of a

(12) W. W. Pigman and R. M. Goepp, *Chemistry of the Carbohydrates*, Academic Press, New York, N. Y., 1948, p. 296.

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(14) W. H. G. Lake and S. Peat, *J. Chem. Soc.*, 1417 (1938).

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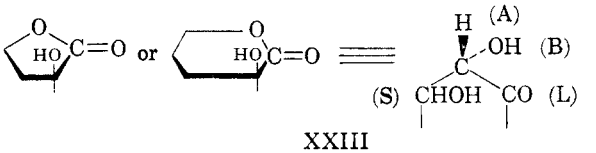
TABLE VIII

Lactone XXIII	$[\alpha]_D$, Degree	Ref.	C_2 Epimer XXIV	$[\alpha]_D$, Degree	Ref.
D-Arabonolactone (γ)	+74	28	D-Ribonolactone (γ)	+18	28
2,3,5-Tri-*O*-methyl-D-Arabonolactone (δ)	+47[a]	31	2,3,5-Tri-*O*-methyl-D-Ribonolactone (δ)	−20	31
2,3,4-Tri-*O*-methyl- (sirup)	−145[a]	31	2,3,4-Tri-*O*-methyl- (sirup)	−4	31
D-Lyxonolactone (γ)	+84	16	D-Xylonolactone	+90	16
2,3,5-Tri-*O*-methyl-D-Lyxonolactone (δ)	+83	31	2,3,5-Tri-*O*-methyl-D-Xylonolactone (δ)	+74	31
2,3,4-Tri-*O*-methyl-	+36	31	2,3,4-Tri-*O*-methyl-	−4	31
D-Mannonolactone (γ)	+52[a]	32	D-Gluconolactone (γ)	+68	32
2,3,6-Tri-*O*-methyl-	+73	34	2,3,6-Tri-*O*-methyl-	+55	25
2,3,5-Tri-*O*-methyl-	+67	34	2,3,5-Tri-*O*-methyl-	+62	25
2,3,5,6-Tetra-*O*-methyl-D-Mannonolactone (δ)	+65	34	2,3,5,6-Tetra-*O*-methyl-D-Gluconolactone (δ)	+63	25
3,4,6-Tri-*O*-methyl-	+168	34	3,4,6-Tri-*O*-methyl-	+87	25
2,4,6-Tri-*O*-methyl-	+141	34	2,4,6-Tri-*O*-methyl-	+87 +96	14, 29
2,3,4,6-Tetra-*O*-methyl-	+150	34	2,3,4,6-Tetra-*O*-methyl-	+99	25

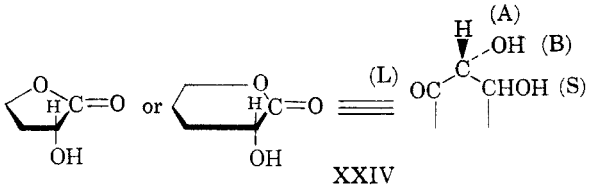
[a] Rotation derived from that of the L-sugar.

carbon atom carrying a hydroxy group is usually enhanced when the hydroxy oxygen becomes part of a lactone ring. There is also an implicit assumption that the rotation contribution of the other asymmetric centers taken together is smaller than that of this lactone oxygen-bearing carbon atom. Klyne's lactone rule will therefore fail if either of these assumptions prove untenable in an individual case.

The generalization under discussion can also lead to Klyne's modification of Lactone rule if the same assumptions are made. Without making these assumptions, the generalization can be used to predict which one of an epimeric pair of lactones will be more dextrorotatory. The epimeric pairs of polycyclic lactones listed by Klyne[6] obey such predictions.



XXIII



XXIV

Sugar lactones (γ or δ) epimeric at C_2 form a category represented by XXIII and XXIV. From the generalization under study, we can predict that XXIII should be more dextrorotatory than XXIV. Hudson[16] has recorded that lactones of D-arabonic type (Hudson's Class A lactones) are indeed more dextrorotatory than the epimers of the D-ribonic type. An exception seems to be the epimeric pair 2,3,4-tri-*O*-methyl-D-arabonolactone (δ) and the corresponding D-ribonolactone. He has, however, pointed out that the epimeric pairs, D-xylonic and D-lyxonic lactones, and D-gluconic and D-mannonic lactones (Hudson's Class B lactones), do not conform to this pattern. Evidently vicinal effects between the *cis* hydroxy groups on C_3 and C_5 (or C_4) play a part. Table VIII shows that this vicinal effect may be suppressed by methylating the hydroxy groups; methylated lactones from xylose, lyxose, glucose, and mannose follow the prediction from the generalization. Hudson's[16] classification of lactones is therefore unnecessary.

Tables II to VIII represent correlations of molecular rotation with absolute configuration for several types of epimeric sugars. Some of these correlations do not seem to have been studied before. Of the 140 cases cited in these tables, all but 9 agree with the generalization under study. It is noteworthy that even of these 9 possible exceptions to the generalization, 5 cases involve noncrystalline sugars the purity of which is not beyond question.

The data presented, therefore, testify to the validity of the generalization enunciated here. In applying this generalization to the determination of absolute configuration, caution must be exercised because of its empirical nature. In comparing the rotation of sugar derivatives, it is essential to bear in mind the effect of the solvent on rotation. It has been pointed out[17] that in some sugar derivatives a change of solvent may even reverse the sign of rotation. Thus, for the same sample of 2,3,4-tri-*O*-methyl-D-lyxonolactone the following rotations were observed:[17] $[\alpha]_D^{20}$ + 35.5° (water), −60.4° (chloroform), −87° (ether), −102° (benzene). Used with proper care however, the generaliza-

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tion presented here could be a useful supplement to the standard methods for determining absolute configuration.

In all tables, unless otherwise specified, the rotations were measured in water. A solvent other than water is indicated by the following symbols appearing after the specific rotation value: A—acetone, C—chloroform, E—ethanol, M—methanol, P—pyridine. The epimeric pairs that do not conform to our predictions are underlined.

Acknowledgments. Thanks are due to Dr. S. R. Sen-Gupta and Dr. S. K. Bhattacharyya for their interest and to Dr. F. Kagan for valuable suggestions.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TENNESSEE]

Physiologically Active Compounds. II. Hydrochlorides of Aminoesters of Substituted Benzilic and Glycolic Acids[1]

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Received March 14, 1958

Thirty-nine aminoester hydrochlorides of substituted benzilic and glycolic acids were synthesized. Two of these compounds appear to be more active in experimental animals than atropine in preventing mortality from an anticholinesterase compound and four of them exhibit the highest anticholinergic activity. One compound previously reported offers some advantage over three of these as an anticholinergic.

In a previous paper[3] it was shown that many aminoesters of benzilic acids show some physiological activity. This article reports further studies of the preparation and physiological activity of such compounds.

The benzilic acids, with the exception of certain phenyl-substituted ones, utilized in the preparation of the hydrochlorides listed in Table I, were prepared by or were available from the methods of Smith and Shacklett.[4] The syntheses of the exceptions are listed below. Ethyl-3-phenylbenzilate (II) was prepared from 3-bromodiphenyl (I) which

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