in the spectrum of lactose do not disappear in the spectrum of the ureide but are considerably weaker and somewhat shifted in wave length position. This is, upon reflection, the effect to be expected. Lactose (glucose–β-galactoside) is a disaccharide containing 2 pyranose rings. Urea can react only with the glucose portion since only that part of the molecule has a free reducing group. There is little doubt from the spectrum that an amide group is present in the ureide. The changes at the longer wave lengths can be explained by the fact that the bands arising from the glucopyranose ring disappear as the reaction proceeds. The galactose portion, however, still remains in the ring form regardless of what happens to the glucose portion and, hence, the absorption bands associated with the ring vibrations can only be expected to become weaker. But, as these bands are now resolved from the glucopyranose ring bands, their exact wave length positions would be expected to exhibit slight shifts in position. These are exactly the changes observed. On the basis of these data, the spectrum can most readily be explained as arising from an aldehydo-glucose configuration in the lactose ureide molecule.

Conclusions

The tentative infrared band assignments for glucose ureide, glucose ureide urea and lactose ureide indicate the presence of an amide group in the respective molecules. In the glucose ureide and glucose ureide urea molecules there is evidence to suggest that the glucose is apparently in the aldehydo configuration. There is some evidence in the spectrum of lactose ureide to suggest that the glucose portion of the molecule is in the aldehydo form.

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[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY AND NUTRITION, GRADUATE SCHOOL OF PUBLIC HEALTH, UNIVERSITY OF PITTSBURGH]

The Conformations of Methyl Idopyranosides[1]

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Complex formation with cuprammonium solutions was studied with methyl α- and β-D-idopyranoside (compensating complexes), methyl 2-methyl-β-D-idopyranoside (levorotatory complex), methyl 3-methyl-β-D-idopyranoside (1*a*,3*a*-complex) and methyl 2,3-dimethyl-β-D-idopyranoside (no complex). The oxidation of methyl β-D-idoside by chlorine was more rapid than that of the α-anomer. Possible conformations for idose derivatives are based on these observations and results already in the literature. α-Idosides are assigned a 1C conformation. The closest representation of the β-idosides is believed to be a half-chair structure, HC3, with deviations from this ideal representation either toward the chair conformation C1 or the skew conformation 1B3. Methyl 2-methyl-β-D-idopyranoside and methyl 3-methyl-β-D-idopyranoside were prepared in the form of sirups and were characterized by means of optical rotations. The structures of these two compounds were confirmed by periodate oxidation experiments.

In his classic studies of the conformations of pyranose rings, Reeves[2] investigated the reactions of a number of idose derivatives with cuprammonium solutions. The following conformational assignments were made: 1C conformation, methyl α-D-idoside,[3] methyl 2-methyl-α-D-idoside, methyl 4,6-benzylidene-α-D-idoside. Of the two β-idosides examined, methyl 3-methyl-β-D-idoside was assigned the C1 conformation and methyl 4,6-benzylidene-β-D-idoside, a 1C conformation. In the latter case, complex formation with the cuprammonium reagent was very poor. It was concluded that the β-idosides could react in both chair conformations. Consideration of the "instability factors"[2] also suggested a C1 ⇄ 1C equilibrium for the β-idosides. With the realization that other stable conformations participate in the interconversion of the two chair forms,[4] the description of a compound as a C1 ⇄ 1C mixture is unsatisfactory unless it is established that the theoretical intermediates in this interconversion have no stable existence. In two other instances, lyxose and altrose, where C1 ⇄ 1C interconversions were originally postulated, Reeves has suggested[4] a stable shape in the flexible cycle of the six boat forms. The present paper describes experiments designed to provide more information about the possible conformations of idose derivatives.

Experimental

Methyl 4,6-benzylidene-α- and β-D-idosides were prepared from methyl α- and β-D-galactosides as described by Sorkin and Reichstein.[5] Removal of the benzylidene group was accomplished by catalytic hydrogenation[6] as follows: methyl 4,6-benzylidene-β-D-idoside (535 mg.) in glacial acetic acid (32 ml.) was shaken with 10% palladium–charcoal catalyst (450 mg.) in a hydrogen atmosphere. After about 2.5 hours no more hydrogen was taken up. The solution was filtered and evaporated to a sirup. The sirup was taken up in water (10 ml.) and extracted three times with chloroform (15 ml. in all). The aqueous solution was treated with a small amount of Amberlite MB 2, then Norite A. Filtration and evaporation gave methyl β-D-idoside as a sirup, $[\alpha]^{24}D$ −48.5° (*c* 1.39, H_2O). Sorkin and Reichstein[5] quote the specific rotation of this compound as $[\alpha]^{20}D$ −95.0° (*c* 3.799 in methanol) and $[\alpha]^{20}D$ −81.1° (*c* 3.265 in H_2O). However, in describing the conversion of this compound to D-idosan, they quote a specific rotation $[\alpha]^{18}D$ −47° for a 2.5% solution in 2.5% sulfuric acid after 3 minutes at room temperature. Wiggins[7] later reported $[\alpha]^{20}D$ −40.8° (*c* 10 in H_2O) for this compound.

(1) This work was supported in part by a Research Grant (A-725) from the National Institutes of Health, United States Public Health Service.

(2) R. E. Reeves, THIS JOURNAL, **72**, 1499 (1950).

(3) The abbreviated form, idoside, used in this paper, refers throughout to idopyranoside structures.

(4) R. E. Reeves, *Ann. Rev. Biochem.*, **27**, 15 (1958).

(5) E. Sorkin and T. Reichstein, *Helv. Chim. Acta*, **28**, 1 (1945).

(6) R. E. Reeves, THIS JOURNAL, **71**, 2116 (1949).

(7) L. F. Wiggins, *J. Chem. Soc.*, 1590 (1949).

TABLE I

COMPLEX FORMATION BY IDOSIDES IN CUPRAMMONIUM SOLUTION

Compound	$[\alpha]^{24}D$ in H_2O, c	$[\alpha]^{24}_{436}$ in H_2O, c	$[\alpha]^{24}_{436}$ in cupra B, c	Rotational shift, deg.	Sp. res., 0.01 M soln. in cupra A ohm, cm.	ΔSp. res. ohm, cm.
Methyl						
α-D-Idoside	+103.3°, 1.19	+188.8°, 1.19	+444.6°, 1.21	+ 496°	428	88
β-D-Idoside	− 48.5, 1.39	− 99.7, 1.39	−153.7, 0.29	− 105	418	78
2-Methyl-β-D-idoside	− 55.9, 1.64	−101.9, 1.64	−919.1, 1.12	−1670	..	..
3-Methyl-β-D-idoside	− 50.1, 1.49	− 92.7, 1.49	− 59.0, 0.33	+70.1	465	95

Methyl α-D-idoside prepared in the same way had $[\alpha]^{24}D$ +103.3° (*c* 1.19 in H_2O). It was obtained as a sirup which did not crystallize even after 2 years. Sorkin and Reichstein[5] report $[\alpha]^{20}D$ +103.3° (*c* 2.716 in H_2O) for the sirup and $[\alpha]^{21}D$ +99.8° (*c* 2.833 in H_2O) for crystals obtained after standing for many weeks.

Methyl 2,3-dimethyl-β-D-idoside was prepared from methyl 2,3-dimethyl-4,6-benzylidene-β-D-idoside[5] as follows. The benzylidene compound (171 mg.) in glacial acetic acid (8 ml.) was treated with 10% palladium–charcoal catalyst and hydrogenated at room temperature and pressure. When hydrogen uptake was complete (4 hr.) the filtered solution was evaporated to dryness. The sirup was kept overnight *in vacuo* with NaOH to complete removal of the acetic acid. The residue was dissolved in water (5 ml.) and the solution was extracted with four portions of chloroform (2.5 ml. each). Evaporation gave a slightly yellow oil; on addition of water, a little material remained insoluble and was filtered off. The clear solution obtained on treatment with Norite A was evaporated to yield a colorless sirup, $[\alpha]^{24}D$ −45.2° (*c* 1.86 in H_2O).

Anal. Calcd. for $C_9H_{18}O_6$: C, 48.6; H, 8.17. Found: C, 48.5; H, 8.27.

The removal of the benzylidene group was also confirmed by treatment of a dilute solution of the compound with 3 *N* HCl. There was no increase in the optical density at 275 mμ which is normally observed on cleavage of the benzylidene group with acid.

Methyl 3-methyl-β-D-idoside was prepared as described by Reeves.[6] Methyl 2-methyl-β-D-idoside prepared similarly by reduction of methyl 2-methyl-4,6-benzylidene-β-D-idoside[5] was obtained as a clear glass. Optical rotations for these two compounds are given in Table I.

Optical measurements in cupra B were carried out as described previously.[8] For resistance measurements, cupra A solution was prepared as described by Reeves and Jung.[9] It contained 0.75 g. of copper, 2.91 moles of ammonia and 10 ml. of ethanol per liter. Measurements were made at 22° with a Leeds and Northrup conductivity meter using a dip type cell having a cell constant of 1.075.

Periodate Oxidation Experiments.—Methyl 2-methyl-β-D-idoside (12.97 mg.) was treated with 0.01 *M* periodic acid solution (10 ml.) at 22°. Samples (2 ml.) were removed at intervals and the remaining periodic acid determined in the usual way. The consumption of periodic acid in terms of % theory for one mole per mole of glycoside, was: 1 hr., 46%; 17 hr., 104%. In a similar experiment, methyl 3-methyl-β-D-idoside (21.81 mg.) consumed only 5.7% of the theoretical amount after 41 hr.

Chlorine oxidation experiments were carried out essentially as described previously.[10] Experiments were performed with the α- and β-anomers at the same time and the rates of flow of chlorine were adjusted to be as close as possible.

The production of aldonic acid was determined by conversion of the aldonic acid to lactone and subsequent assay using a modification of the hydroxylamine method described by Hestrin.[11] The procedure was: aliquots of oxidation mixtures freed from chlorine by aeration, or of a standard solution of sodium L-idonate (kindly provided by Professor Reichstein) were treated with one drop of dilute phenolphthalein solution and titrated with 0.1 *N* NaOH to a permanent end-point; 1 ml. of 0.5 *N* HCl was added and the volume adjusted to 5 ml. The solutions were placed in a boiling water-bath for 15 minutes to complete lactonization and after cooling were treated with 2 ml. of a freshly prepared mixture of 4 *M* hydroxylamine hydrochloride and 7 *N* NaOH (1:1). After standing for 2 minutes at room temperature, 2 ml. of HCl (1:3 v./v.) and 1 ml. of 0.74 *M* ferric chloride were added. The optical density was determined in the Klett–Summerson photoelectric colorimeter using a 540 mμ filter. A straight-line response was obtained over the range 0 to 10 μmoles.

Results and Discussion

Since in the β-series, only the methyl pyranosides of 3-methyl-idose and 4,6-benzylidene-idose had been examined,[2] it was desirable to extend these observations. Methyl 2-methyl-β-D-idoside and methyl β-D-idoside were therefore prepared and the reactions of these compounds and also those previously examined by Reeves with cuprammonium are shown in Table I. For methyl α-D-idoside and methyl 3-methyl-β-D-idoside, the values for rotational shift and Δ specific resistance agreed well with the results of Reeves.[2] Methyl β-D-idoside resembled methyl α-D-idoside forming a complex (as indicated by the specific resistance change) which had a low rotational shift; this complex could therefore have been either of the compensating or 1*a*,3*a*-type.[12] Methyl 2-methyl-β-D-idoside complexed well with cupra B, with a strongly levorotatory shift (−1,670°); this behavior was analogous to that reported by Reeves for the α-anomer (rotational shift −1,572°).

The possibility of complex formation between OH groups at positions 4 and 6 was also investigated. Methyl 2,3-dimethyl-β-D-idoside was prepared but conductivity measurements established that this compound did not form a complex with cupra A.

Since equatorial C_1–OCH_3 groups are more rapidly oxidized by chlorine than the same axial grouping,[10] a simple test of Reeves' earlier conclusions was possible. If methyl α-D-idoside had had the 1C conformation, the C_1–OCH_3 would be equatorial; similarly if methyl β-D-idoside were represented by the equilibrium mixture, $C1 \rightleftarrows 1C$, there would be an equilibrium between axial and equatorial positions for this same group. It was therefore to be expected that, contrary to the usual experience, the α-anomer would be oxidized at least as rapidly as and probably more rapidly than the β-form.

Short and long term experiments on the oxidation of methyl α- and β-D-idosides are shown in Table II. The highest yield of aldonic acid was obtained with the β-anomer after about 21 hr. and thereafter remained constant at a level of 5.25 μmoles per ml. For complete oxidation, the forma-

(8) R. Bentley, THIS JOURNAL, **81**, 1952 (1959).

(9) R. E. Reeves and J. R. Jung, *ibid.*, **71**, 209 (1949).

(10) R. Bentley, *ibid.*, **79**, 1720 (1957).

(11) S. Hestrin, *J. Biol. Chem.*, **180**, 249 (1949).

(12) The complexes formed by axial OH groups on carbon atoms separated by a central carbon atom will be referred to as 1*a*,3*a*-complexes rather than 1*e*,3*e*-complexes (see footnote 2). This change is required by current usage.

TABLE II

CHLORINE OXIDATION OF METHYL IDOSIDES

Time, hr.	Aldonic acid, μmoles per ml. Methyl α-D-idoside	Methyl β-D-idoside
	Experiment A[a]	
0.5	0.4	0.7
1	0.5	0.9
2	1.0	1.5
4	1.1	2.2
	Experiment B	
1	0.4	0.8
2	0.8	1.9
4	1.4	2.5
6	1.8	3.2
8	1.9	3.6
22	2.7	5.5
30	2.9	5.3
47	3.2	5.2

[a] In experiment A, methyl α-D-idoside (54.2 mg. in 27 ml. of H_2O) and methyl β-D-idoside (49.5 mg. in 25 ml. of H_2O) were treated with chlorine at 35°. Aliquots were removed at the indicated times and lactone assays were carried out as described in the text. Experiment B was carried out similarly with methyl α-D-idoside (54.9 mg. in 27 ml. of H_2O) and methyl β-D-idoside (52.4 mg. in 26 ml. of H_2O).

tion of 10 μmoles per ml. would have been predicted. The reason for this discrepancy is not clear. In control experiments with the more readily available methyl α- and β-D-galactosides, the theoretical yield of aldonic acid was obtained after about 24 hr. with the β-anomer, but in experiments carried out over a more prolonged period, the aldonic acid, estimated *via* the lactone method, actually declined (see Table III). In previous studies,[13,14] oxidation beyond the aldonic acid level has been established. A further complication in the present experiments would be the possibility of the conversion of the methyl idosides to idosan under the rather acidic experimental conditions.

TABLE III

CHLORINE OXIDATION OF METHYL GALACTOSIDES

Time, hr.	Aldonic acid, μmoles per ml. Methyl α-D-galactoside	Methyl β-D-galactoside
	Experiment A[a]	
0.5	0.6	1.0
1	0.7	1.6
2	1.1	3.0
4	1.7	5.1
6	2.3	6.1
8	2.6	8.2
24	3.1	8.6
	Experiment B	
24	3.4	10.0
48	4.0	10.2
72	4.0	9.2
96	3.7	8.8

[a] Experiment A was carried out at 34° using methyl α-D-galactoside (50.1 mg. in 25 ml. of H_2O) and methyl β-D-galactoside (50.3 mg. in 25 ml. of H_2O). Experiment B, carried out at 35°, used 50.0 mg. of α-anomer and 50.3 mg. of β-anomer in 25 ml. of H_2O. In all cases, 2-ml. samples were removed for analysis at the indicated times. The yield for 100% oxidation would be 10.3 μmoles per ml. Analyses were by the lactone method using calcium D-galactonate as the reference standard.

In view of a possibly different conformation for idose in the 4,6-benzylidene compounds, a study of the rate of oxidation of methyl 4,6-benzylidene α- and β-D-idosides was attempted. When chlorine was bubbled through aqueous solutions of these compounds (and of the corresponding galactosides) a white precipitate soon separated. The precipitates were characterized as mixtures, principally of the dichlorobenzoic acids. It is apparent that on treatment with the acidic solution of aqueous chlorine, the benzylidene group was cleaved, initially yielding benzaldehyde which in turn underwent oxidation and chlorination. In view of the lability of the benzylidene group under the experimental conditions it was impossible to make any valid conclusions concerning the rate of oxidation of these compounds.

Although accurate values for the rate ratio k_β/k_α cannot be determined from the results of these experiments, it was always the case that oxidation was more rapid with the β-anomer. Over the period 1–24 hr. the average yield was 1.8 times as much aldonic acid formed from the β-anomer as from the α-form. This value may be compared with that of 2.8 obtained in similar experiments with the galactosides. Although the difference is less pronounced with the idosides, the result is unequivocal. It is therefore concluded from these experiments that Reeves' earlier hypothesis cannot be correct in its entirety. These experiments do not rule out the 1C conformation for the α-idosides since it is possible that the β-idosides also have a conformation with an equatorial group. Since this conformation is not one of the chair forms it must be of higher energy than either of the chair forms, and the observed more rapid oxidation of the β-form would be accounted for.

Reeves[4] has pointed out that identifiable conformations exist in the transformation of chair to boat forms, which are more stable than the boat forms, but less stable than the chair forms. In order of increasing energy these are the skew and half-chair forms. All of the skew forms are intermediate between two boat structures of the types xB and By; the nomenclature xBy is therefore suggested as a logical extension of that of Reeves.[15] Thus, 2B3 is the skew form between the two boat structures 2B and B3; the "mirror image," 3B2 is the skew intermediate between 3B and B2. Half-chair forms will be designated as HC1, HC2, ... HC6 and the mirror images as 1CH, 2CH, ... 6CH as identified in Fig. 1. Despite suggestions for systems alternate to that of Reeves,[16,17] the original nomenclature has gained general acceptance and its easy modification to include the other possible conformations is a very definite advantage. In the skew forms, three adjacent atoms and a fourth atom of the pyranose ring are in a plane, and there are two such planes for each skew form. The possible skew forms are indicated conventionally in Fig. 2. In the half-chair forms, four adjacent atoms of the ring are in

(13) A. Dyfverman, B. Lindberg and D. Wood, *Acta Chem. Scand.*, **5**, 253 (1951).

(14) B. Lindberg and D. Wood, *ibid.*, **6**, 791 (1952).

(15) R. E. Reeves, THIS JOURNAL, **71**, 215 (1949).

(16) H. S. Isbell, *J. Research Natl. Bur. Standards*, **57**, 171 (1956).

(17) R. D. Guthrie, *Chemistry & Industry*, 1593 (1958).

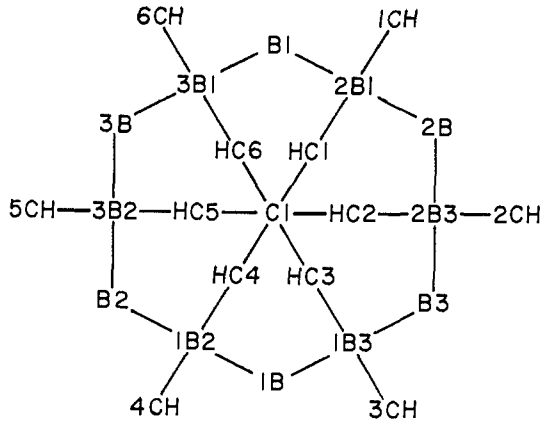

Fig. 1.—The flexible cycle of boat and skew forms and its relationship to the chair and half-chair forms. The cycle is modified from that first presented by Reeves (footnote 4). Each of the half-chair forms 1CH to 6CH leads directly to the same chair conformation, 1C. This chair conformation has been omitted in each case in the interest of clarity.

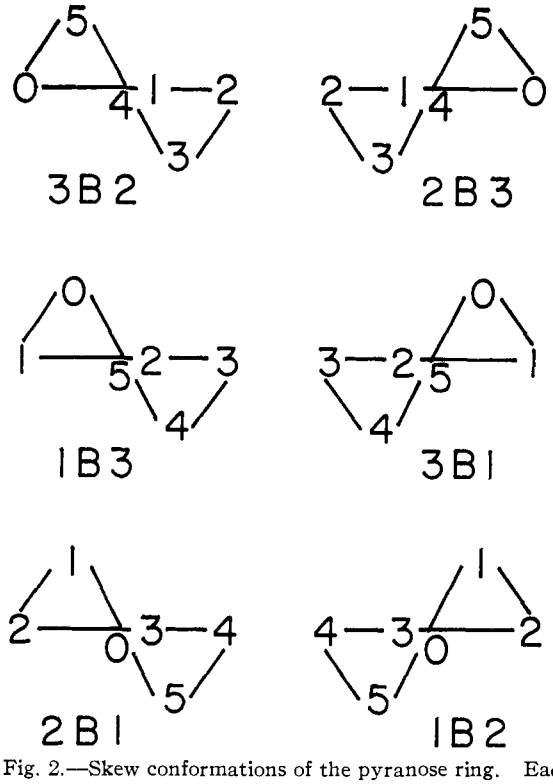

Fig. 2.—Skew conformations of the pyranose ring. Each skew form shows two planes which contain three adjacent atoms and a fourth atom. The planes are defined by the atoms in the horizontal or long diagonal lines and the fourth atoms are those in the center of the drawings. In each case the atoms in the long diagonal line are toward the observer and in front of the atoms in the horizontal line.

a plane; six of these forms are indicated conventionally in Fig. 3. The orientation of substituent groups in the chair and boat forms of idose is given in Table IV, and in the six skew forms and six of the half-chair forms in Table V.

In 1C conformation, α-idosides have one instability factor, the axial CH_2OH group at C_5. Although the skew conformation 2B3 puts this group into an equatorial alignment, two $a - e$ orientations are introduced at C_1 and C_4, and the OH groups at C_3 and C_4 are less favorably arranged to account for the strongly levo complex formed by methyl 2-methyl-α-D-idoside. Other skew conformations putting the C_5 substituent into an equatorial position are 3B1 and 2B1, but then the complex with the 2-methyl derivative would be impossible. Skew conformation 1B3 provides an a–e orientation for the CH_2OH group, but also has a–e orientation for the C_2-OH, and axial orientation for the C_1-OH. Similar considerations would also apply to any of the half-chair conformations, and there seems therefore to be no strong reason for assuming that the α-idosides have other than the 1C conformation.

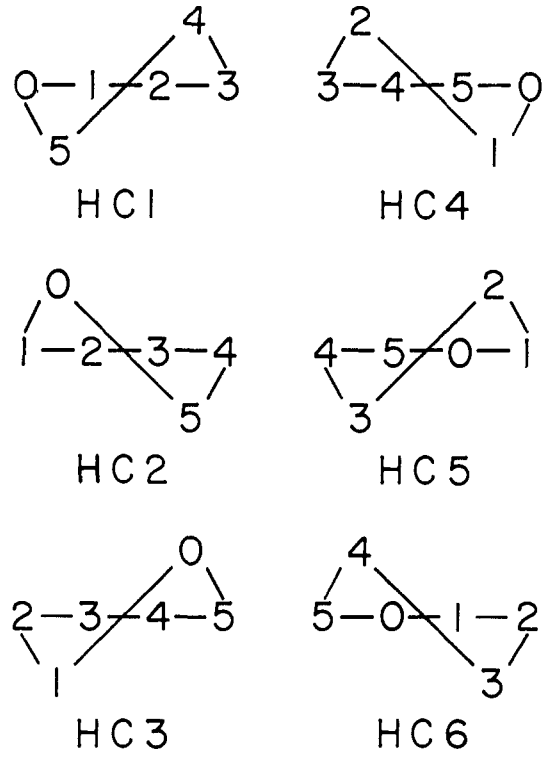

Fig. 3.—Half-chair conformations of the pyranose ring. The four adjacent atoms in the horizontal line lie in a plane. The atoms at the ends of the diagonal lines project forward toward the observer. The ring skeletons of the six other half-chair conformations, 1CH to 6CH, may easily be derived by drawing mirror images of the conformations presented here.

With the β-idosides, a more complex situation is encountered. In the original synthetic studies of Sorkin and Reichstein,[5] the compounds believed to be methyl 2-methyl-4,6-benzylidene-β-D-idoside and the corresponding 3-methyl compound were prepared. Reeves[6] removed the benzylidene group from the supposed 3-methyl derivative to yield a presumed methyl 3-methyl-β-D-idoside and the same reaction with the supposed 2-methyl compound is reported here. Wiggins' proof[18] of structure for methyl 3-methyl-4,6-benzylidene-β-D-idoside was based on impure products,[7] and it was

(18) L. F. Wiggins, *J. Chem. Soc.*, 522 (1944).

TABLE IV

GROUP ORIENTATIONS AND PROJECTED ANGLES FOR CHAIR AND BOAT FORMS OF D-IDOSE

Conformation	C1	1C	B1	2B	B3	1B	B2	3B
				Group orientation[a]				
C_1–α	*a*	*e*	*e*	*e*	*a*	*a*	*a*	*e*
C_1–β	*e*	*a*	*a*	*a*	*e*	*e*	*e*	*a*
C_2	*a*	*e*	*e*	*e*	*e*	*a*	*a*	*a*
C_3	*a*	*e*	*a*	*e*	*e*	*e*	*a*	*a*
C_4	*a*	*e*	*a*	*a*	*e*	*e*	*e*	*a*
C_5	*e*	*a*	*e*	*e*	*e*	*a*	*a*	*a*
				Projected angle				
C_2,C_3–OH	180	+60	+120	+ 60	+60	+120	180	180
C_3,C_4–OH	180	−60	180	−120	−60	− 60	−120	180

[a] The group orientations given in the table are for the OCH_3 at C_1, the OH groups at C_2, C_3 and C_4, and the CH_2OH group at C_5. The projected angles are derived as described by Reeves (see ref. 19). The boat conformations are arranged in the clockwise order given in Fig. 1.

TABLE V

GROUP ORIENTATIONS AND PROJECTED ANGLES FOR SKEW AND HALF-CHAIR FORMS OF D-IDOSE

Conformation	2B1	2B3	1B3	1B2	3B2	3B1	HC1	HC2	HC3	HC4	HC5	HC6
					Group orientation							
C_1–α	*e*	*a*–*e*	*a*	*a*	*a*–*e*	*e*	*a*–*e*	*a*	*a*	*a*	*a*	*a*–*e*
C_1–β	*a*	*a*–*e*	*e*	*e*	*a*–*e*	*a*	*a*–*e*	*e*	*e*	*e*	*e*	*a*–*e*
C_2	*e*	*e*	*a*–*e*	*a*	*a*	*a*–*e*	*a*–*e*	*a*–*e*	*a*	*a*	*a*	*a*
C_3	*a*–*e*	*e*	*e*	*a*–*e*	*a*	*a*	*a*	*a*–*e*	*a*–*e*	*a*	*a*	*a*
C_4	*a*	*a*–*e*	*e*	*e*	*a*–*e*	*a*	*a*	*a*	*a*–*e*	*a*–*e*	*a*	*a*
C_5	*e*	*e*	*a*–*e*	*a*	*a*	*a*–*e*	*e*	*e*	*e*	*a*–*e*	*a*–*e*	*e*
					Projected angle							
C_2,C_3–OH	+ 90	+60	+90	+150	180	+150	+135	+120	+135	+165	180	+165
C_3,C_4–OH	−150	−90	−60	− 90	−150	180	−165	−135	−120	−135	−165	180

[a] The orientations are for the same groups as those listed in Table IV, and were derived by inspection of models. The terms axial (*a*) and equatorial (*e*) refer to the plane most nearly containing all of the atoms of the pyranose ring. The description *a*–*e* refers to groups having an orientation intermediate between that of the axial or equatorial positions. The projected angles are approximations derived on the assumption that for the skew forms the angles lie half way between those of the two related boat forms; for the half-chair forms the angles were assumed to be half way between those of the related skew and C1 form. The orientations in the other six half-chair forms not listed may be obtained by taking the appropriate mirror image orientation. These conformations 1CH–6CH are not listed since they would not give rise to 1*a*, 3*a* complexes. The conformations are arranged in the clockwise order given in Fig. 1.

therefore desirable to carry out periodate oxidations on these materials. The presumed methyl 2-methyl-β-D-idoside consumed very slightly more than 1 mole of periodic acid per mole of glycoside, and the presumed 3-methyl compound consumed only 5% of the expected amount after standing for 42 hr. These observations establish the validity of the assigned structures.

The following observations on complex formation with cuprammonium by the β-idosides have to be explained. Methyl β-D-idoside most probably forms a compensating type of complex, methyl 2-methyl-β-D-idoside a strongly levorotatory complex, methyl 3-methyl-β-D-idoside a complex of the 1*a*,3*a*-type, and methyl 4,6-benzylidene-β-D-idoside reacts rather poorly forming a dextrorotatory complex. With the exception of the 3-methyl idoside, these observations could be accommodated by the 1C conformation; Reeves previously postulated a C1 structure to account for the 1*a*, 3*a*-complex with methyl 3-methyl-β-D-idoside, and assumed that the β-idosides could react in either conformation. The present measurements with methyl β-D-idoside and methyl 2-methyl-β-D-idoside, and also the oxidation studies make this unlikely. On general grounds, the C1 conformation leaves much to be desired since it requires axial OH groups at C_2, C_3 and C_4 and further has the Δ2 instability condition. In view of the importance of Reeves' observation of the 1*a*,3*a*-complex for methyl 3-methyl-β-D-idoside, the resistance of cupra A solutions of this compound were determined at various glycoside concentrations. The results, shown in Fig. 4, are in fact typical of those obtained by Reeves[19] with other complex-forming compounds; in view of the almost negligible rotational shift in cupra B the postulated 1*a*,3*a*-complex is undoubtedly correct. Since it seems unlikely that substitution of CH_3 for H should lead to such a change as to give rise to a separate conformation for the 3-methyl idoside, it will be assumed initially that all of the methyl idosides of the β-series have the same single conformation.

In considering such a single conformation, the chair forms are first ruled out by the previous discussion. The Hassel–Ottar effect[2] must have a considerable influence on the stability of the 1C form, where the C_1-OH and C_5-CH_2OH are both axial on the same side of the ring. Although the boat structure B3 has all equatorial substituents (see Table IV) the observed complexes could not be formed and in any case ring structures of still lower energy are available in the skew and half-

(19) R. E. Reeves, THIS JOURNAL, 71, 212 (1949).

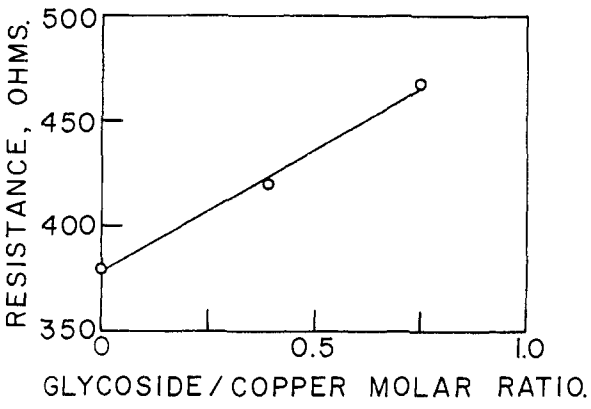

Fig. 4.—The resistance of methyl 3-methyl-β-D-idoside in cupra A solutions.

chair forms. Two of the skew conformations would probably allow the correct 1*a*,3*a*-complex for the 3-methyl idoside (3B2 and 3B1: see Table V) but not the observed complexes with the other idosides. The half-chair possibilities HC1–6 are well suited to the formation of the 1*a*,3*a* complex but only two, HC2 and HC3 (see Table V), warrant further consideration. In these cases the 1*a*,3*a*-complex would need to be formed with OH groups having one axial and one axial-equatorial arrangement. This seems reasonable when models are consulted and the main question is whether 2,3- and 3,4-complexes would be formed with OH groups having projected angles as large as 135°. There is little evidence on which to base a definitive answer. In studies of possible complex formation at the 120° projected angle, Reeves[19] examined *trans* spaced hydroxyls in the furanoid compounds D-glucosan<1,4> β <1,6> and 2,5 anhydrosorbitol; for the 180° angle, methyl 4,6-benzylidene-α-D-altroside was used as a model. In none of these cases was there marked evidence of any ability to form cuprammonium complexes and it was concluded that complex formation was restricted to OH groups having projected angles from 0 to 60°. In all of the above model compounds, the OH groups are held rigidly because of the presence of a second ring system. Evidence has been presented that effective complex formation may take place at the −90° angle in the skew conformation believed to be present in the non-reducing glucose moiety of maltose.[8] In more flexible structures, complex formation may take place with compounds where the maximum projected angle for a given theoretical structure is >90°, but there is a large degree of uncertainty regarding complex formation at the 135° angle. Nevertheless, the closest approach to a single conformation for the β-idosides is found with the half-chair forms, HC2 and HC3.

Reeves[4] has pointed out that the conformations currently specified are conveniently recognized shapes which are observed in the continuous series of structures found in the interconversions of chair and boat forms. It is therefore possible that a precise description of the β-idosides in terms of a single conformation may be impossible. Using the half-chair structures as a starting point, with the unsubstituted and 2-methyl idosides the actual conformation might be closer to the skew form in either of the following directions: HC2 ⇄ 2B3; HC3 ⇄ 1B3. This would decrease somewhat the 2,3 and 3,4 projected angles and facilitate formation of the cuprammonium complexes with these compounds. For the methyl β-idoside and 2-methyl derivative, these skew conformations have substantial advantages over the 1C form when the instability factors are considered. In 1C conformation there is the Hassel–Ottar effect at C_1 and C_5. This effect is minimized in 2B3 with two *a–e* groups at C_1 and C_4, and in 1B3 with two *a–e* groups at C_2 and C_5. The elimination of the full Hassel–Ottar effect in both of these conformations may more than compensate for the extra ring energy in the skew as opposed to the 1C form. There are even more instability factors in the half-chair forms 2CH and 3CH which must be reached before the 1C conformation. With the 3-methyl idoside, where only the 1*a*,3*a*-complex is formed, the equilibrium may be slightly in the direction of the chair forms as follows: HC2 ⇄ C1; HC3 ⇄ C1. The three axial groups of the C1 structure may prevent the full development of this conformation.

It is therefore suggested that the structure of the β-idosides is best interpreted in terms of an incomplete C1 to 1C interconversion by one of the following pathways: C1 ⇄ HC2 ⇄ 2B3; C1 ⇄ HC3 ⇄ 1B3. The interconversion probably does not go much beyond the skew forms in the direction of 1C for the reasons previously outlined. Further information is provided by a consideration of the 4,6-benzylidene compounds where an important factor must be the necessity to maintain a low energy conformation for the second ring. Reeves[2] originally assigned 1C conformations both to methyl 4,6 - benzylidene - α - D - idoside (rotational shift, +1,856°; Δ specific resistance, 61 ohm cm.) and to the β-anomer (rotational shift, +875°; Δ specific resistance, 24 ohm cm.), but commented on the poor reaction of the β-idoside. If, in fact, both compounds are 1C, there is no reason for the observed different reactivities. No cuprammonium reaction is possible in C1 conformation. In the skew conformations 1B3 and 2B3, it is not possible for the second ring to maintain a chair conformation but both rings could have the skew conformation; for 2B3 the projected 2,3-angle is +60°, so a high rotational shift would be expected, as in the 1C situation. With 1B3 the projected angle is +90°; a calculation of the rotational shift for the −90° angle in the 3B1 skew conformation of the non-reducing glucose unit of maltose is possible as follows. The contributions to the total rotational shift of maltose are from the −90° oriented 2,3-OH groups (= *x*) and the +60° oriented 3,4-OH groups (+2,150°) in the non-reducing glucose unit, and from the C1 reducing glucose unit (−1,990°). Since the observed[8] rotational shift for methyl β-maltoside is −854°, x = 1,990 −854 −2,150 = −1,014°. For a +90° projected angle, a rotational shift of about +1,000° would therefore be expected. The observed value of +875° in methyl 4,6-benzylidene-β-D-idoside is in good agreement with this prediction. It may also

be noted that the compensating complex with methyl β-idoside itself has an over-all levorotational shift (−105°); this would be expected on the basis of the 1B3 conformation (2,3-angle, +90; 3,4-angle, −60°) but not the 2B3 conformation (2,3-angle, +60; 3,4-angle, −90°). It therefore seems likely that the β-idosides are best represented by the continuous series of structures, C1 ⇄ HC3 ⇄ 1B3. The reason for the adoption of this pathway over the alternate possibility, C1 ⇄ HC2 ⇄ 2B3 may lie in the fine structure of the skew and half-chair intermediates. When models of the two skew forms are compared, the OH groups at C_1 and C_2 are found to be nearly eclipsed in 2B3 and there is a closer approach of the OH at C_4 to the ring oxygen than in 1B3. In 1B3 there is, however, a possible slight Δ2 condition. The situation is similar in the half-chair conformations, and in addition in HC2 the oxygens at C_1, C_2 and C_4 are more crowded than in HC3. Despite the slight Δ2 conditions in both HC3 and 1B3 these conformations are apparently the more stable.

Of the possibilities considered here, the closest approach to a single geometrical description of the β-D-idosides is probably the half-chair structure, HC3, with the actual conformation somewhere in the series C1 ⇄ HC3 ⇄ 1B3. The extreme skew structure may be reached under the influence of the 4,6-benzylidene group; in 3-methyl idoside, where only the 1*a*,3*a*-complex is possible, the conformation may move in the direction of the chair structure, C1. With the α-idosides, on the other hand, the single chair conformation 1C accounts for all of the observations. Methyl α-D-idoside in 1C conformation has an equatorial arrangement for the C_1–OCH_3 group; the same is true of methyl β-D-idoside in the conformational series C1 ⇄ HC3 ⇄ 1B3. The somewhat more rapid chlorine oxidation of the β-anomer is therefore a result of the lower stability of the half-chair and skew conformations as opposed to the chair conformation.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE OHIO STATE UNIVERSITY]

Acetals and Dithioacetals of 2-*S*-Ethyl-2-thio-D-xylose(lyxose)

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The free hydroxyl of carbon two of 3,4,5-tri-*O*-benzoyl-D-xylose diethyl dithioacetal was substituted by an ethylthio group by the action of ethanethiol and dry hydrogen chloride, to initiate a series of acetal and dithioacetal derivatives. The position of the ethylthio substituent was determined to be C2 by desulfurization of the debenzoylated derivative followed by periodate oxidation to produce propionaldehyde, isolated as its dimedone derivative.

In the previous paper of this series,[2] the synthesis of 3,4,5-tri-*O*-benzoyl-D-xylose diethyl dithioacetal (I) was described. The corresponding 3,4,5,6-tetra-*O*-benzoyl-D-glucose diethyl dithioacetal had been reported by Brigl and Mühlschlegel[3] and its unsubstituted hydroxyl on carbon two had been replaced by an ethylthio group.[4] We report herein a series of reactions starting with the substitution of an ethylthio group for the free hydroxyl in 3,4,5-tri-*O*-benzoyl-D-xylose diethyl dithioacetal (I).[2] Substance I was treated with ethanethiol[4,5] and dry hydrogen chloride to replace the hydroxyl on carbon two with an ethylthio group, producing 3,4,5-tri-*O*-benzoyl-2-*S*-ethyl-2-thio-D-xylose(lyxose) diethyl dithioacetal (II). Position C2 was established as the point of ethylthio substitution by reductive desulfurization of the debenzoylated substance VI with Raney nickel followed by periodate oxidation to produce propionaldehyde and formaldehyde, isolated as their dimedone derivatives. As it is not established whether the replacement of hydroxy by ethylthio occurs with or without Walden inversion, the configuration of C2 is unknown in these 2-*S*-ethyl-2-thio derivatives. Treatment of II with mercuric chloride and methanol in the presence of cadmium carbonate[6] produced sirupy 3,4,5-tri-*O*-benzoyl-2-*S*-ethyl-2-thio-D-xylose(lyxose) dimethyl acetal (III) which was debenzoylated to yield sirupy 2-*S*-ethyl-2-thio-D-xylose(lyxose) dimethyl acetal (V) and this upon acetylation produced crystalline 3,4,5-tri-*O*-acetyl-2-*S*-ethyl-2-thio-D-xylose(lyxose)dimethyl acetal (IV). Sirupy II was debenzoylated to yield sirupy 2-*S*-ethyl-2-thio-D-xylose(lyxose) diethyl dithioacetal (VI) which produced a crystalline triacetate VII. Removal of the dithioacetal group from VII with mercuric chloride and cadmium carbonate in methanol or in benzyl alcohol yielded the crystalline acetylated dimethyl acetal IV or the crystalline acetylated dibenzyl acetal VIII, respectively. Sirupy 2-*S*-ethyl-2-thio-D-xylose(lyxose) dimethyl acetal (V) was obtained in an analytically pure condition by deacetylation of its crystalline triacetate.

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