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ASYMMETRIC SYNTHESIS BY ACID CATALYZED SUBSTITUTION OF DITHIOACETALS AND MONOTHIOACETALS

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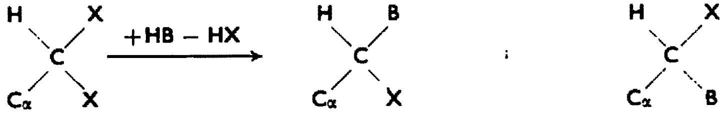
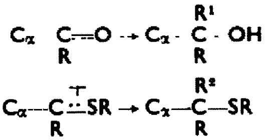
Abstract—A single ethylthio group of diethyl dithioacetals is substituted by acetoxy when dissolved in solutions of acetic acid and acetic anhydride which contain a mercuric salt or a catalytic amount of a strong acid. The substitution is stereoselective as dithioacetals with an asymmetric carbon adjacent to the site of substitution give unequal amounts of diastereomers. Substitution under conditions (with mercuric acetate) under which the diastereomers are stable yields products with a larger percentage of one diastereomer than under conditions (with strong acids) which catalyse epimerization of the monothioacetal products. The same isomer of each pair is the major product when prepared by different synthetic methods.

SUBSTITUTION of a single X in I leads to an asymmetric carbon. When C_α is asymmetric, I has structural requirements for asymmetric induction. An impressive number of papers[1-7] describe examples of the formation of a new asymmetric carbon adjacent to one already present which give predominantly one member of the diastereomeric pair. Most of the examples in the papers cited describe syntheses of asymmetric alcohols by the reaction of aldehydes and ketones with organometallic compounds and with metal hydrides. Other methods of stereoselective syntheses since the classical work of McKenzie[8] are given in a review by Turner and Harris.[9]

I



The reaction we now describe which leads to a new asymmetric center by substitution of I ($X = SC_2H_5$) has much in common with the formation of an asymmetric carbon by addition to carbonyl compounds. In each case the new center is adjacent to one already in the molecule. In each case the addition is to trigonal carbon with partial cationic character. This follows from evidence on the mechanism of acetal



$$C_\alpha\ \underset{R}{C}{=}O \rightarrow C_\alpha\text{-}\overset{R^1}{\underset{R}{C}}\text{-}OH$$

$$C_\alpha{-}\overset{+}{\underset{R}{C}}{\,\cdots\,}SR \rightarrow C_\alpha{-}\overset{R^2}{\underset{R}{C}}{-}SR$$

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[1] J. H. Stocker, P. Sidisunthorn, B. J. Benjamin and C. J. Collins, *J. Amer. Chem. Soc.* **82**, 3913 (1960).

[2] B. M. Benjamin, H. J. Schaeffer and C. J. Collins, *J. Amer. Chem. Soc.* **79**, 6160 (1957).

[3] D. J. Cram and F. A. Abd Elhafez, *J. Amer. Chem. Soc.* **74**, 5828 (1952).

[4] D. J. Cram and J. D. Knight, *J. Amer. Chem. Soc.* **74**, 5835 (1952).

[5] D. J. Cram and K. R. Kopecky, *J. Amer. Chem. Soc.* **81**, 2748 (1959).

[6] D. J. Cram and D. R. Wilson, *J. Amer. Chem. Soc.* **85**, 1245 (1963).

[7] J. W. Cornforth and R. H. Cornforth and K. K. Mathews, *J. Chem. Soc.* 112 (1959).

[8] A. McKenzie, *J. Chem. Soc.* 1249 (1904).

[9] E. E. Turner and M. M. Harris, *Quart. Rev.* **1**, 299 (1947).

hydrolysis[10–12] supporting the existence of a planar carbonium-oxonium ion[13] in the transition step. Although comparable experimental evidence on thioacetal hydrolysis is not available, it is reasonable to conclude that both sulphur and oxygen acetals substitute by the same mechanism. Bordwell *et al.*[14] have shown that the solvolysis of α-chloro-thioethers is best explained by ionization to a carbonium-sulfonium ion. This is analogous to formation of a carbonium-oxonium ion in the rate determining step in the solvolysis of α-halo-ethers[15] and in the acid catalyzed solvolysis of acetals.

When diethyl-dithioacetals are dissolved in a solution of mercuric acetate in acetic acid–acetic anhydride a single ethylthio group is substituted by acetoxy.[16] The reaction is stereoselective because optically active substrates give unequal amounts of the 1-ethylthio-1-acetoxy diastereomers.

Mercuric chloride in place of mercuric acetate also gives products with a single ethylthio group substituted but the rotation after substitution is different from that given by mercuric acetate. Acids which would not specifically bond to divalent sulphur such as perchloric, sulphuric and zinc chloride also catalyse the substitution of a single ethylthio group. These acids give the same rotation after the reaction with a given substrate. The rotation is much closer to that obtained with mercuric chloride than that obtained with mercuric acetate (Table 1).

TABLE 1. ROTATION OF SUBSTITUTED PRODUCTS OF DITHIOACETALS IN EQUAL VOLUMES OF ACETIC ACID–ACETIC ANHYDRIDE

Substrate	Specific rotation			
	Substrate	Substrate with strong acid*	Substrate with $HgCl_2$	Substrate with $Hg(OAc)_2$
2,3,4,5,6-Penta-O-acetyl-D-glucose diethyl-dithioacetal (IIa)	−6·4	8·0	7·9	7·8
2,3,4,5,6-Penta-O-acetyl-D-galactose diethyl-dithioacetal (IIb)	6·7	22·6	21·5	29·1
2,3,4,5,6-Penta-O-acetyl-D-mannose diethyl-dithioacetal (IIc)	24·2	16·2	18·4	12·1
2,3,4,5-Tetra-O-acetyl-L-arabinose diethyl-dithioacetal (IId)	−28·1	−11·4	15·0	−3·3

* The acids used are perchloric or sulphuric.

Specific rotation listed in Table 1 was calculated on the basis that the concentration of optically active compounds was that given when one acetoxy replaces one ethylthio of the dithioacetal substrates. With a mol. wt. change of only 496 to 494 by the substitution of a single ethylthio group of the hexose derivative, calculation of specific rotation is not significantly different when the concentration is based on original substrate, or on substrate in which one or two[17] of the ethylthio groups have been substituted.

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[10] D. McIntyre and F. H. Long, *J. Amer. Chem. Soc.* **76,** 3240 (1954).

[11] J. M. O'Gorman and H. J. Lucas, *J. Amer. Chem. Soc.* **72,** 5489 (1950).

[12] M. M. Kreevoy and R. W. Taft, Jr., *J. Amer. Chem. Soc.* **77,** 3146, 5590 (1955).

[13] M. M. Kreevoy, C. R. Morgan and R. W. Taft, Jr., *J. Amer. Chem. Soc.* **82,** 3064 (1960).

[14] F. G. Bordwell, G. D. Cooper and H. Morita, *J. Amer. Chem. Soc.* **79,** 376 (1957).

[15] F. H. Newth and G. O. Phillips, *J. Chem. Soc.* 2890, 2904 (1953).

[16] E. P. Painter, *Canad. J. Chem.* **42,** 2018 (1964).

[17] N. W. Pirie, *Biochem. J.* **30,** 374 (1936).

Data given in Tables 1 and 2 indicate that each reagent gives the same result by the substitution of IIa and that a single isomer is formed. Only one member of the diastereomeric pair, 1,2,3,4,5,6-hexa-O-acetyl-D-glucose-S-ethyl monothioacetal (α-IIIa),[18] was isolated from the reaction products of IIa with each reagent. The observation that the rotation of the products given by a strong acid differed from that given by mercuric acetate suggested the presence of both isomers from each of the other dithioacetals and served as a guide to product isolation. Isolation of products confirmed the formation of both diastereomers from each of the dithioacetals IIb, c, d. In addition to the three crystalline products isolated from the reaction with mercuric acetate,[16] we have isolated from the acid catalysed substitution 1,2,3,4,5,6-*hexa-O-acetyl-*D-*mannose-S-ethyl monothioacetal* (α-IIIc), 1,2,3,4,5,6,-*hexa-O-acetyl-*D-*galactose-S-ethyl monothioacetal* (β-IIIb) and 1,2,3,4,5-*penta-O-acetyl-*L-*arabinose-S-ethyl monothioacetal* (α-IIId). All 1-ethylthio-1-acetoxy products we have isolated are listed in Table 2.

Table 2. Rotation of acid catalysed equilibrium mixtures of 1-ethylthio-1-acetoxy derivatives in acetic acid–acetic anhydride

Substrate	Specific rotation		
	Substrate	Substrate with strong acid	Substrate with $HgCl_2$
1,2,3,4,5,6-Hexa-O-acetyl-D-glucose S-ethyl-monothioacetal (α-IIIa)	7·8	7·9	7·8
1,2,3,4,5,6-Hexa-O-acetyl-D-galactose S-ethyl-monothioacetal (α-IIIb)	33·8	22·5	21·4
1,2,3,4,5,6-Hexa-O-acetyl-D-galactose S-ethyl-monothioacetal (β-IIIb)	−17·2	22·7	
1,2,3,4,5,6-Hexa-O-acetyl-D-mannose S-ethyl-monothioacetal (α-IIIc)	24·6	16·0	18·3
1,2,3,4,5,6-Hexa-O-acetyl-D-mannose S-ethyl-monothioacetal (β-IIIc syrup)	11·5	16·4	15·8
1,2,3,4,5-Penta-O-acetyl-L-arabinose S-ethyl-monothioacetal (β-IIId)	3·5	−11·7	−15·6
1,2,3,4,5-Penta-O-acetyl-L-arabinose S-ethyl-monothioacetal (α-IIId)	−56·5	−10·9	−15·2

Isolation of α-IIIc has permitted us to designate the syrup from the reaction of IIc with mercuric acetate as a product rich in β-IIIc. Acid catalysed substitution of IId has produced α-IIId in sufficient yield so that we have been able to obtain this diastereomer in crystalline form. We are unable to detect β-IIIa in the products of IIa but this diastereomer has been obtained by esterifying 2,3,4,5,6-O-acetyl-D-glucose-S-ethyl-monothiohemiacetal.[18] Thus seven of the eight expected products of the four dithioacetals have been isolated in crystalline form. The other product is a syrup. All but one of the crystalline diastereomers have been isolated by the reaction we now describe.

The diastereomer ratio is fixed when acetoxy bonds to carbon in the substitution step because each of the six crystalline and one non-crystalline 1-ethylthio-1-acetoxy

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[18] M. L. Wolfrom, D. I. Weisblat and A. R. Hanze, *J. Amer. Chem. Soc.* **62**, 3246 (1940).

products we have separated is stable in solutions of mercuric acetate in acetic acid. When, however, a strong acid or mercuric chloride is added to solutions of the above compounds (α-IIIa is a possible exception) in acetic acid each reacts to give an equilibrium mixture of diastereomeric pairs. The rotation of each compound and rotation of each pair at acid catalysed equilibrium is given in Table 2.

A result in Table 2 to note is that each member of the pairs of diastereomers (α and β-IIIb, c and d) gives the same (within the precision of the measurement) equilibrium rotation as the parent dithioacetal (IIb, c and d, Table 1) when dissolved in acetic acid–acetic anhydride with a strong acid. Rotation data and isolation experience support the conclusion that a single ethanethio group of dithioacetals is substituted by acetoxy and strong acids epimerize substitution products, also by a substitution process in which a C_1—O bond is cleaved and re-formed. The intermediate for the substitution process (IV) is, by analogy to similar reactions of acetals, a carbonium-sulfonium cation ($>C_1\underset{..}{+}SC_2H_5$). Since our substrates carry acetoxy groups in a position to participate in the reaction, other cationic species may be contributing forms.

$$\begin{tikzcd}
& \mathrm{II} \arrow[d, "k_s"', "\begin{array}{l}+H^+\\-C_2H_5SH\end{array}"] & \\
\alpha\text{-III} \arrow[r, shift right=2, "+H^+-AcOH", "k_{-\alpha}"'] & \mathrm{IV} \arrow[l, shift right=2, "+AcOH-H^+"', "k_{\alpha}"] \arrow[r, shift left=2, "+AcOH-H^+", "k_{\beta}"'] & \beta\text{-III} \arrow[l, shift left=2, "+H^+-AcOH"', "k_{-\beta}"]
\end{tikzcd}$$

When not catalysed by acids the diastereomer composition is kinetically controlled. Substitution by mercuric acetate then gives $\alpha/\beta = k_\alpha/k_\beta$. Diastereomer composition in the acid catalysed case is equilibrium controlled; $\alpha/\beta = k_\alpha k_{-\beta}/k_\beta k_{-\alpha}$. Kinetic measurements of the reaction[19] show that the substitution of ethylthio (of II) is first order in acid and that $k_{-\alpha}$ and $k_{-\beta}$ are larger than k_s.

Quantitative evidence for the acid catalysed equilibria is given by

$$\begin{tikzcd}
& \mathrm{II} \arrow[d] & \\
\alpha\text{-III} \arrow[r] & \begin{array}{c}\text{equilibrium mixture}\\ \text{of } \alpha\text{- and } \beta\text{-III}\end{array} & \beta\text{-III} \arrow[l]
\end{tikzcd}$$

rotation data. Yields of isolated products supply supporting evidence. Thus the same products and in essentially the same yields are obtained from the mixture at constant rotation when the source material is the parent thioacetal (II) or either of the diastereomeric substitution products (α- or β-III). The major product isolated is the same for each sugar derivative no matter which of the three (two for glucose) substrates is the starting material in each case tested. Treating one member of a pair of diastereomers with acid and, after equilibrium rotation is reached, isolating the other member from the solution is convincing evidence for the interconversion:

$$\alpha\text{-III} \rightleftarrows \beta\text{-III}$$

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[19] N. H. Kurihara and E. P. Painter. In preparation.

Experimentally we have isolated β-IIIb from α-IIIb, α-IIIc from β-IIIc (syrup), β-IIId from α-IIId and α-IIId from β-IIId.

Recorded rotations of products formed with mercuric chloride (Tables 1 and 2) are much closer to those with a strong acid than those with mercuric acetate. Removal of an ethanethio group by mercuric chloride is well known; epimerization of 1-ethanethio-1-acetoxy compounds (α-III $\rightleftarrows$ β-III) is an unexpected result. This must mean that mercuric chloride is an acid in acetic acid-acetic anhydride. That this is the case was confirmed by inversion of glucose pentaacetates. At room temperature mercuric chloride did not produce a measured change in the rotation of β-glucose pentaacetate in acetic acid–acetic anhydride, but at boiling temperatures the reaction

$$\alpha\text{-glucosepentaacetate} \rightleftarrows \beta\text{-glucosepentaacetate}$$

occurs at a slow but measurable rate. The reaction of mercuric chloride with III is then a substitution by cleavage of the C_1—O bond of acetoxy. Unlike the proton acid catalysed substitution, $k_{-\alpha}$ and $k_{-\beta}$ are much smaller than k_s when substitutions occur in solutions of mercuric chloride. Due to the slow epimerization rate and experimental difficulty with polarimetric measurements of solutions after prolonged heating with mercuric chloride, equilibrium between the α and β forms (of III) may not have been reached in all measurements recorded in the Tables.

Pirie[17] dissolved the substrates listed in Table 1 in acetic anhydride, added sulphuric acid (to approximately 1·8 M) and after the solutions were held at 37° for 24 hr, isolated products (C_1-*gem*-diacetates) with both ethylthio groups substituted. We isolate products with a single ethylthio substituted. We have repeated Pirie's procedure and our results confirm his. We have also carried a sample of IIIa through Pirie's procedure and isolated (in about 25% yield) glucose heptaacetate. This result certainly is the one expected since the reaction must be stepwise i.e.

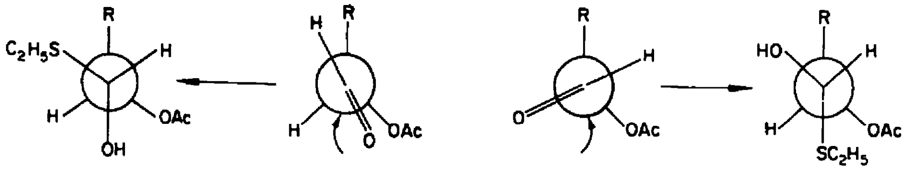
$$\text{II} \rightarrow \text{III} \rightarrow C_1\text{-}gem\text{-diacetates.}$$

The question then arises as to whether C_1-*gem*-diacetate is a product under our experimental conditions so that we should include a step indicating its formation in our equilibrium mixture. We have been unable to isolate C_1-*gem*-diacetates from the reaction products of II in acetic acid–acetic anhydride solutions with catalytic amounts of sulphuric or perchloric acid, or in solutions saturated with mercuric salts, after standing more than two months at room temperature. The substitution rate[19] (II → III) initially increases as the ratio acetic anhydride–acetic acid increases but, at near 100% acetic anhydride, the rate decreases. On long standing with proton acids solutions darken so that evidence for the formation of products in addition to the diastereomers we describe cannot be obtained by following the rotation.

Substitution of IIa is close to 100% stereospecific with each reagent. Substitution of the other substrates is stereoselective: the ratio, major isomer–minor isomer, is larger when the reaction is kinetically controlled than when equilibrium between diastereomers is attained. A comparison of rotations given in Tables 1 and 2 shows that substitution of thioacetals (IIb, c and d) by the action of mercuric acetate gives a higher yield of one diastereomer than is obtained after epimerization by acid catalysts. We do not know the rotation of pure β-IIIc but, assuming the syrup is pure, the yield of this diastereomer drops from 100% with mercuric acetate to 65% at acid catalysed equilibrium. Relative amounts of the major diastereomer of the other pairs by substitution with mercuric acetate and at acid equilibrium are: for α-IIIb, 91% and 78%; for β-IIId, 88% and 75%.

Two of the isomers listed in Table 2 were prepared[18] by treating *aldehydo* pentaacetates (V) of glucose and galactose with ethanethiol and esterifying the products (2,3,4,5,6-penta-O-acetyl-1-S-ethyl-monothiohemiacetals, VI). The yield of α-1,2,3,4,5,6-hexa-O-acetyl-D-glucose S-ethyl-monothioacetal (α-IIa) was larger than the yield of the β-isomer. Only one of the galactose isomers (α-IIIb) was isolated. Acetolysis of 1-bromo-2,3,4,5,6-penta-O-acetyl-D-galactose-S-ethyl-monothioacetal (VIII) (obtained by bromination of IIb)[20] was stereoselective as α-IIIb was the only diastereomer isolated.[21] Rotation after substitution of bromine and yield indicated VIII gave α-IIIb in nearly 100% yield. Excess sodium acetate was present in the solution during acetolysis to prevent epimerization of products.

Although the same isomer predominates when a pair of diastereomers is prepared by different stereoselective reactions (α-IIIb for example) we do not know whether the main product is *erythro* or *threo*. Absolute configuration at C_1 is not known for any of the isomers listed in Table 2. Models which serve to rationalize examples of the known steric course of asymmetric induction[6] do not, when applied to our reactions, lead to the same answer. The least steric barrier to reaction (direction indicated by arrow) producing a new asymmetric center presents no problem because the effective bulk of the groups bonded to C_α can be unambiguously assigned ($R > OAc > H$). Selection of the rotational conformer is the problem. Based on structures of the "open chain" model drawn by Cram and Elhafez[3] the conformer of *aldehydo* pentaacetates of lowest energy is Va;[22] based on evidence cited by Wilson[23] that acetaldehyde, propene and acetyl chloride have the double bond eclipsed with hydrogen, the conformer to choose is Vb. The steric step in the synthesis, V → VI → III, is addition of ethanethio to V because the C_1—O bond of the alcohol



VIa Va Vb VIb

is not cleaved by ester formation, and the final product (III) does not epimerize under the conditions of the synthesis. As seen in Table 3 rotational conformers Va and Vb give opposite results. An added complication arises because the ratio of the monothiohemiacetals (VIa/VIb) converted to III may not be kinetically controlled.

Cornforth *et al.*[7] present arguments that due to the influence of dipole-dipole interaction, the rotational conformer of V with the greatest charge separation is Vc. Since electrophilic reactivity of the carbonyl carbon depends upon charge separation, the "dipolar" model may be the reactive species influencing the steric course of the reaction even though this conformer may be a minor species in solution. The major

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[20] F. Wegand and H. J. Bestman, *Chem. Ber.* 91, 2534 (1958).

[21] W. H. Pippin, Ph.D. Thesis, University of California, Davis (1964).

[22] Illustrations give the correct configuration at C_α for IIa, b, and d and products given by these substrates.

[23] E. B. Wilson, Jr. *Advances in Chemical Physics* Vol. II; p. 383. Interscience, N.Y. (1959).

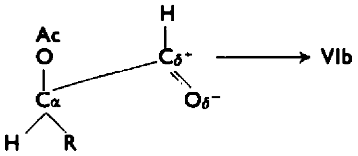
TABLE 3. MAJOR ISOMER EXPECTED FROM MODELS

Model	Rotational conformer	Method of preparation	Major isomer of III predicted
Open	Va	1	*threo*
Chain[8]	Vb	1	*erythro*
	IVa	2 and 3*	*erythro*
	IVb	2 and 3*	*threo*
Dipolar[7]	Vc	1	*erythro*
C_α Acetoxy participation	IVc	2, 3*, 4	*erythro*

Methods of Preparation: (1) V → VI → III, Ref. 18: (2) II → III, mercuric acetate: (3) II → III, perchloric acid: (4) II → VII → III, reference 21.

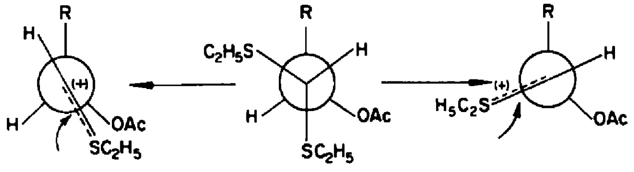
* For the steric step only.

diastereomer obtained from the addition of cyanide to arabinose was mannonitrile.[24] This is the product (*erythro*) predicted by addition to Vb or Vc, but again we cannot be sure the isomer composition is set by the addition step.



Vc

The choice of the rotational conformer of IV when this species is drawn as the sulphonium-carbonium ion taken from the acetal model[10–18] requires a decision much like that presented by V. Both are alike in the spatial arrangement of groups of relative size; both are planar at C_1; both have approximately the same bond angles at C_1. Based on bulk of groups at C_1 and C_α, IVa is the choice; based on a sulphonium ion with the double bond eclipsed with hydrogen, IVb is the choice. Due to the sequence of addition, a different isomer is expected when the steric step is addition of ethanethio to Va than when the steric step is addition of acetoxy to IVa (Table 3).



IVa II IVb

We believe participation by acetoxy to give a cyclic cationic intermediate similar to that proposed by Winstein and Buckles[25] to explain the steric result when they treated 2-acetoxy-3-bromopropanes with silver acetate in acetic acid provides the best model to describe substitution of our thioacetals. Conformers of II which have different acetoxy groups in a position to give anchimeric assistance can be drawn, but we will confine our model (IVc) to participation of C_α acetoxy to cleave a C_1-S

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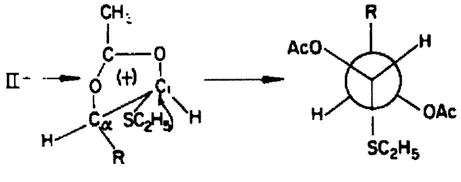
[24] E. L. Eliel, *Stereochemistry of Carbon Compounds* p. 68. McGraw-Hill, New York (1962).

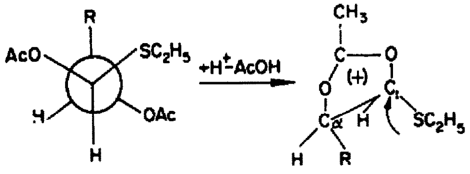
[25] S. Winstein and R. E. Buckles, *J. Amer. Chem. Soc.* **64**, 2780 (1942).

bond. Substitution of the 2-acetoxy-3-bromopropanes gave 2,3-diacetoxy butanes with more than 90% retention. Our substitution with mercuric acetate is equally stereoselective and should likewise go primarily by retention so that the major product is *erythro* III. It follows that the bromide (VII) is *erythro* and the major acetolysis product of VII is *erythro* (α-IIIb).



IVc III (*erythro*)

The steric step, IVc → III, is independent of the reagent necessary to substitute thioacetals. For the kinetically controlled formation (with mercuric acetate) of the isomeric 1,2,3,4,5-penta-O-acetyl-arabinose S-ethyl monothioacetals the ratio k_β/k_α = 7·3. Perchloric acid epimerizes to give an equilibrium mixture of diastereomers, β-IIId/αIIId = 3. From these values we find $k_{-\beta}/k_{-\alpha}$ = 2·4. Anchimeric assistance does not provide a pathway leading to epimerization. The rotational conformer of *threo* (III) with C_α acetoxy trans to the group substituted at C_1 is not the conformer of lowest energy and the anchimerically assisted cyclic intermediate (IVd) with the large groups at C_1 and C_α eclipsed is not the same as the cyclic intermediate given by *erythro* III. The cyclic intermediates predict the rate, *erythro* → *erythro*, faster than the rate, *threo* → *threo*, under epimerizing conditions. A comparison, now underway, of the rates of acid catalysed epimerization with the rates of acid catalysed exchange of C^{14} acetoxy at C_1 on substrates which represent *erythro* and *threo* (III) and a substrate without acetoxy bonded at C_α may yield results bearing on the course of the reactions we describe.



III(*threo*) IVd

EXPERIMENTAL

The O-acetyl diethyl dithioacetals are those described previously.[16] The acid catalysed substitution, II → III, occurs in all mixtures of acetic acid and acetic anhydride tested. Rotation (sodium-D line) of the three arabinose derivatives is more sensitive to solvent composition (Table 4) than that of the

TABLE 4. ROTATION OF ARABINOSE DERIVATIVES IN DIFFERENT MIXTURES OF ACETIC ACID AND ACETIC ANHYDRIDE

Solvent		Specific rotation	
Acetic acid %	Acetic anhydride %	IId	Acid catalysed equilibrium of α- and β-IIId
95	5	−21·3	−8·3
50	50	−28·0	−11·5
3	97	−33·5	−15·5

other acyclic derivatives. A mixture of equal volumes of acetic acid and acetic anhydride will be called the solvent in the experimental work we describe.

Substitution catalysed by proton acids was carried out as follows: One drop of 18 M H_2SO_4 or 60% $HClO_4$ was added to 100 ml of a solution which contained 5 g of substrate in the solvent. When the rotation reached an equilibrium value (within a few min with most substrates) the acid was neutralized by the addition of anhydrous sodium acetate. As the last of the solvent was removed *in vacuo* using a rotating evaporator connected to a dry-ice cooled trap, crystals formed in the product from each substrate. The solvent-free product was washed with small portions of ice water to remove salt and dried at room temp.

Substitution by the action of $HgCl_2$ was essentially complete within a few min in the solvent at 100° with excess $HgCl_2$ as the rotation changed rapidly to that of substituted products. With some substrates, however, the rotation continued to change at a very slow rate at elevated temp and the solutions became so dark the rotation could not be measured. For this reason equilibrium rotations given for some substrates with $HgCl_2$ may be measurements recorded before equilibrium was reached.

1,2,3,4,5,6-*Hexa-O-acetyl-*D*-glucose S-ethyl-monothioacetal* (α-IIIa)

(a) The solid residue (4·6 g) from the acid catalysed substitution of 5 g of IIa obtained by the procedure described above was purified by recrystallization from 96% EtOH as previously described.[16] The yield of α-IIIa with properties previously reported[16,18] was 3·6 g (72%).

(b) A mixture of 5 g of IIa plus 6 g $HgCl_2$ was transferred with the aid of solvent to a volumetric flask, the volume adjusted to 100 ml and the content of the flask heated in a water bath until the temp reached 80°. After the flask cooled to near room temp in the water bath, the volume was reduced *in vacuo* to about 20 ml. Ice was added in small portions and the contents of the flask shaken at intervals until the acetic anhydride hydrolysed. A crystalline mass slowly formed. After several hr in ice water, the liquid (not more than 100 ml) was poured off and the solid mass washed with several small portions of ice cold water and dried with the aid of an air current at room temp. The product was then dissolved in methylene dichloride, filtered to remove a small solid residue and upon evaporation of the methylene dichloride, 4·2 g IIIa was obtained. Recrystallizations gave 3·1 g purified product.

The compound (IIIa) is apparently unchanged in the solvent by catalytic amounts of a strong acid or $HgCl_2$ as it can be recovered from the solution after treatment with these reagents in yields expected if no reaction occurred.

1,2,3,4,5,6-*Hexa-O-acetyl-*D*-galactose S-ethyl-monothioacetal* (α-IIIb)

(a) The crude product (4·5 g) from the acid catalysed substitution of 5 g IIb was recrystallized twice from MeOH as formerly described[18] to give 3.1 g (62% based on substrate of α-IIIb, the same product described by Wolfrom *et al.*[18] and obtained by us by substitution with mercuric acetate.

The same compound has been isolated from the reaction of IIb with $HgCl_2$ and from β-IIIb in solvent after treatment with a catalytic concentration of $HClO_4$.

1,2,3,4,5,6-*Hexa-O-acetyl-*D*-galactose S-ethyl-monothioacetal* (β-IIIb)

This compound remained in MeOH solution after α-IIIb was first crystallized at −23°. Crude product was accumulated by treating α-IIIb with $HClO_4$ in the same way α-IIIb was prepared from IIb and saving the MeOH filtrates (45 ml for 10 g substrate) from the first crystallization of the α-diastereomer. This step was repeated on the α-form first crystallized from MeOH. In this way the α-form crystallized from the equilibrium mixture served as the source of the β-form. The MeOH filtrates were combined and the solvent removed at red. press. The solid product which separated as the solvent evaporated was dissolved by warming in anhydrous ethyl ether. After the ether solution had been kept overnight at −23°, solid, m.p. 74–77°, in a yield near 1 g per 10 g substrate was obtained. After a second crystallization from ethyl ether at −23°, the product was dissolved in a small volume of absolute MeOH and crystals separated at −23°. After a second crystallization from MeOH the yield of product m.p. 76–78°, obtained in several trials averaged near 0·3 g per 10 g substrate. Specific rotation −24·5 ($c = 1$, 24°, $CHCl_3$), −17·0 ($c = 1$, 24°, solvent). (Found: C, 48·60; H, 6·17; S, 6·42; acetoxy, 6·02 equiv/494 g. $C_{20}H_{30}O_{12}S$ requires: C, 48·57; H, 6·11; S, 6·48%; acetoxy, 6 equiv/494 g.)

1,2,3,4,5,6-*Hexa-O-acetyl*-D-*mannose* S-*ethyl-monothioacetal* (α-IIIc)

The product from the $HClO_4$ catalyzed substitution of IIc (a mixture of crystals and viscous syrup) was dissolved in absolute MeOH. A crystalline product separated at −23°. After washing the crystals with cold MeOH, the solid was recrystallized as just described to give 1·6 g (32% based on substrate) pure α-IIIc, m.p. 104–105; specific rotation, +30·8 ($c = 4$, 26°, $CHCl_3$), 24·5 ($c = 4$, 23°, solvent). (Found: C, 48·75; H, 6·23; S, 6·45; acetoxy, 6·06 equiv/494 g. $C_{20}H_{30}O_{12}S$ requires: C, 48·57; H, 6·11; S, 6·48%; acetoxy, 6 equiv/494 g).

This compound has also been isolated from the products of substitution of IIc in solutions of acetic acid and $HgCl_2$ and from the β-diastereomer[16] (β-IIIc syrup), by treating the latter with $HClO_4$.

1,2,3,4,5,6-*Hexa-O-acetyl*-D-*mannose* S-*ethyl-monothioacetal* (β-IIIc)

Evaporation of the MeOH mother liquor from the first crystallization of α-IIIc (above) yielded a syrup. A small yield of crystalline product (α-IIIc) was obtained by dissolving the syrup in warm isopropyl ether and cooling to room temp but the major portion was a syrup we have been unable to crystallize. Rotation, solubility and analysis for acetoxy all indicate this product is the same as the product reported from IIc by the action of mercuric acetate[16] in acetic acid solutions. Both products give a mixture which contains α-IIIc with a catalytic amount of $HClO_4$ in acetic acid.

1,2,3,4,5-*Hexa-O-acetyl*-L-*arabinose* S-*ethyl-monothioacetal* (β-IIId)

The crude product from the $HClO_4$ catalysed substitution of IId, a mixture of crystalline β-IIId and α-IIId, was dissolved in 50 ml absolute MeOH and the crystals which formed after standing overnight at −23° were filtered and washed with cold MeOH. A second crystallization gave 2·6 g pure β-IIId (52% based on substrate) with m.p. unchanged when mixed with the sample isolated by substitution with mercuric acetate.[16]

The same compound was obtained from a solution of $HgCl_2$ (4 g) with IId (3 g), in 20 ml solvent after heating to 100°. When cooled, ice was added and the precipitate, which slowly formed, washed with ice cold water, and dried. The hemithioacetal acetate was dissolved in methylene dichloride, filtered and the solvent removed at red. press. The crystalline product was dissolved in 20 ml MeOH and crystallized as described above to give 0·6 g β-IIId.

By treating α-IIId with $HClO_4$ as described when IId was the substrate, β-IIId was isolated in a yield comparable to that obtained from the dithioacetal.

1,2,3,4,5-*Penta-O-acetyl*-L-*arabinose* S-*ethyl-monothioacetal* (α-IIId)

The filtrates from the first crystallization of β-IIId are strongly levorototary. Since the specific rotation of β-IIId is near −3·0 in MeOH, this observation indicated that a more levorototary compound than β-IIId, presumably the other diastereomer, remained in solution. Attempts to separate the second diastereomer were without success until a few large transparent crystals were noted in the crystalline product after the solid residue, obtained by evaporation of the MeOH mother liquor from the crystallization of β-IIId, was dissolved in heptane and slowly cooled to - 23°. Crystals which proved to be the same compound were also obtained by dissolving the residue (above) in anhydrous ethyl ether, adding two volumes pet ether (30–60) and allowing the solvent to evaporate slowly at room temp. After crystals first formed, solvent composed of ethyl ether (1 part) and pet. ether (2 parts) was added in small portions to assure slow crystallization. Two distinct crystals formed. The large transparent crystals were separated with tweezers (a small amount of β-IIId adhered to the large crystals) and found to melt below 60°. The specific rotation was −43 (acetic acid). Several recrystallizations were necessary to remove all of the β-IIId.

Once crystalline α-IIId was obtained, the following procedure was followed in order to obtain several grams. The sample of crystalline β-IIId first filtered from 20 g IId was dissolved in solvent, a drop of $HClO_4$ added, and β-IIId crystallized as described. This step (β-IIId converted to the equilibrium mixture so that one diastereomer served as a source of the other) was repeated several times and the MeOH filtrates rich in α-IIId combined. The MeOH solution was slowly evaporated and the rotation change measured. Since the negative rotation is contributed mostly by α-IIId, the product, volume times measured rotation, is nearly constant until α-IIId starts to crystallize. The first product to crystallize is β-IIId as indicated by the rotation and m.p. (above 100° for the crude crystals). When α-IIId began to crystallize the solution was decanted from the small amount of crystalline product (mostly the β-isomer) and the solvent removed at red. pressure. The crystalline mass after evaporation of the MeOH was dissolved in anhydrous ethyl ether (12 ml/g), pet. ether (15 ml/g) was then added and the solution cooled slowly. Seed crystals were added and the contents of the flask frequently shaken to prevent liquid phase separation at the beginning of crystallization. When the compound started to crystallize the flask was placed in the refrigerator overnight and then kept at −23° for at least 24 hr. The cold supernatant was poured off, the crystals immediately rinsed with a little pet. ether and the residue solvent evaporated. The product was a mixture of the diastereomers. The β-form separated as fine crystals forming a thin mat on the flask surface; the α-form gave large transparent crystals which formed clusters growing from the bottom of the flask upward. These were separated mechanically. Spreading on black, gloss paper provides a good background to facilitate separation. Two more recrystallizations, with mechanical separation after each, removed nearly all of the contamination by the β-isomer. After two more recrystallizations, this time from a solvent of 15 ml ether and 20 ml pet. ether for each gram of solid, by slow evaporation of the solvent at room temp, gave α-IIId m.p. 59·5–61° which did not change on further recrystallization. Specific rotation −70·3(c = 1·3; 26°, $CHCl_3$), −56·5 (c = 3, 25°, solvent). (Found: C, 48·63; H, 6·23; S, 7·48; acetoxy, 5·1 equivs. $C_{17}H_{26}O_{10}S$ requires: C, 48·34; H, 6·16; S, 7·58; acetoxy, 5 equivs/422 g.)

This compound exhibits polymorphism. After melting at 61° the compound crystallizes upon cooling. The latter melts (not sharp) at 72°. The entire product which crystallized from ethyl ether–pet. ether (no seed of m.p. 61 added) has been the higher melting form after seed of this form was in the laboratory.

1,2,3,4,5,6-*Hepta-O-acetyl-aldehydo-*D*-glucose*

To 2 g of α-IIIa in 20 ml acetic anhydride (99·3% by supplier's label) 1 ml H_2SO_4 was added and the solution left at room temp for 36 hr. Solid sodium acetate was then added to neutralize the H_2SO_4 and the acetic anhydride decomposed with ice water. The solid was filtered, washed with ice water and dried. Two recrystallizations of the solid from 96% EtOH gave 0·45 g material, m.p. 120°, not depressed by a sample of heptaacetate prepared from *aldehydo* glucose pentaacetate.[26]

[26] M. L. Wolfrom, *J. Am. Chem. Soc.* **57**, 2498 (1935).