NOTES

ASYMMETRIC SYNTHESIS BY THE REACTION OF MERCURIC ACETATE WITH OPTICALLY ACTIVE THIOACETALS

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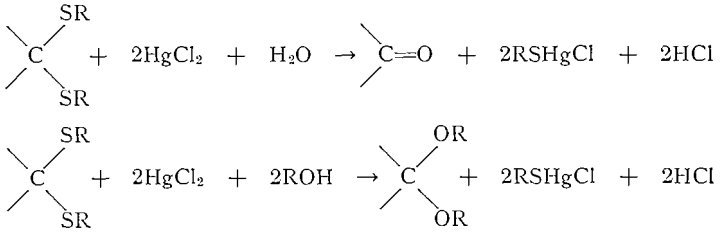
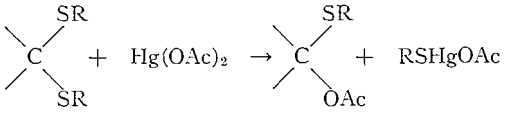
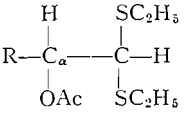
Fischer (1) found that mercuric chloride removes —SR groups of thioacetals. The product in aqueous or alcohol solution with excess mercuric chloride is an aldehyde (or *gem*-diol) or an acetal formed by the overall reactions:



Unlike the above reactions where both thio groups are substituted, we find that acetoxy substitutes a single —SR group when thioacetals are dissolved in acetic acid – acetic anhydride mixtures with mercuric acetate (reaction 1).

[1] 

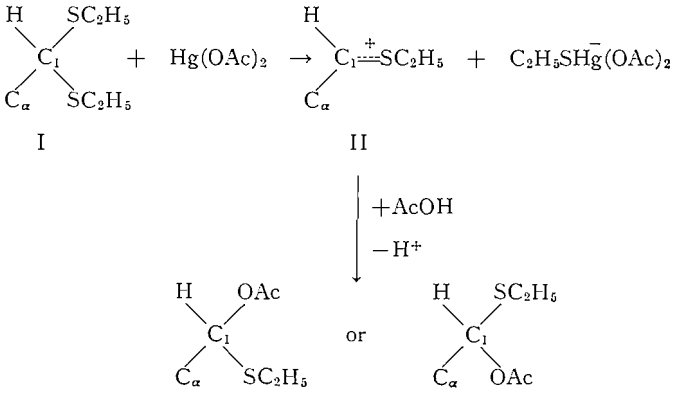
Thioacetals which contain an asymmetric carbon (C_α in I) bonded to the acetal carbon have structural requirements for asymmetric induction so that unequal amounts of the thiohemiacetal acetates produced in reaction 1 would be expected. This is indeed the experimental result as each of four optically active substrates (which differ by R in I) give unequal amounts of diastereomers.



I

When one makes the reasonable assumption that substitution of thioacetals by the action of Lewis acids is in essence a process analogous to acid-catalyzed substitution of acetals (2, 3, 4), the reactive intermediate in the present case can be considered a carbonium (or sulphonium) ion.

By analogy to the cationic intermediate in the substitution of acetals (4), II may be considered planar. Bonding to C_1 (of II) is then similar to the many examples of asymmetric synthesis achieved by addition of nucleophiles to carbonyl compounds (5–9). In each case the new asymmetric center is the result of bonding to planar carbon adjacent



to an asymmetric carbon already in the molecule. Rules suggested by Cram and Abd Elhafez (7) to predict the major product by asymmetric induction in the carbonyl systems should then be applicable to our substrates.

Four substrates, the penta-O-acetyl diethyl dithioacetal of D-glucose (III), D-galactose (IV), D-mannose (V), and the tetra-O-acetyl diethyl dithioacetal of L-arabinose (VI), which have an asymmetric carbon bonded to the acetal carbon, are stable in solutions of acetic acid – acetic anhydride. Mercuric acetate reacts with each substrate. In each case a single ethylthio group is substituted by acetoxy to give 1-ethylthio-1-acetoxy products: III → VII; IV → VIII; V → IX; VI → X. Each of the crystalline products isolated (VII, VIII, and X) is one member of the pair of diastereomers expected. The product IX is a syrup which, presumably, is a mixture.

Measured rotations of the substrates, of the products in solution after the reaction with mercuric acetate, and of the isolated products are shown in Table I. Since the change

TABLE I

Measured rotation of 5% solutions of substrate and isolated products in equal volumes of acetic acid – acetic anhydride

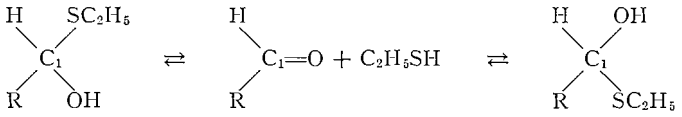
Substrates		Rotation after reaction with $Hg(OAc)_2$	Products	
No.	Rotation		No.	Rotation
III	−0.33°	+0.39°	α-VII	+0.40°
IV	+0.34°	+1.45°	α-VIII	+1.72°
V	+1.21°	+0.61°	IX	+0.55°
VI	−1.40°	−0.17°	β-X	+0.18°

in mass in the substitution reaction is small (for the hexose derivative the molecular weight changes from 496 to 494), the rotations serve as a useful guide to product composition.

From the measured rotation and the yields of VII, it is seen that III is converted nearly quantitatively to α-VII. This example is then comparable to an addition to a carbonyl compound leading almost exclusively to a single isomer, as described by Benjamin, Schaeffer, and Collins (6). The high yields of α-VIII and β-X show that these are the major products in each case. The diastereomer from IV is designated α-VIII because we have isolated from the reaction mixture of IV crystalline products which are more levorotatory than the compound listed in Table I. The mother liquor from the crystallization of the diastereomer from VI gives a syrup more levorotatory than the reaction

products; therefore, the product described (a member of the L-series) is designated β-X.

Since the isolated products, α-VII, α-VIII, and β-X, are stable in acetic acid – acetic anhydride solutions containing mercuric acetate, the α/β ratio of each pair of diastereomers is given by irreversible bonding of acetoxy to II; i.e., II does not form from 1-ethylthio-1-acetoxy products. Both α-VII and α-VIII have been prepared by esterifying the parent 2,3,4,5,6-penta-0-acetyl-1-S-ethyl monothiohemiacetals of D-glucose and D-galactose with acetic anhydride (10). In one case the substrate was isolated as a solid; in the other case the mixture of thiohemiacetals formed in the equilibrium

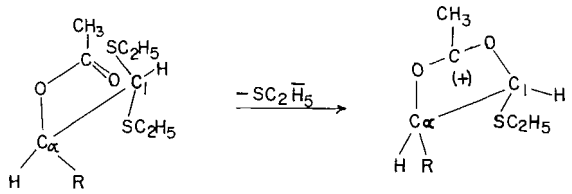
[2] 

XII XI XIII

was esterified. The diastereomer isolated in the larger amount from the glucose derivative was α-VII; a single diastereomer (α-VIII) was isolated from the galactose derivative. It is tempting to conclude that the same steric forces influence the product distribution (XII and XIII) in equation 2 that control the steric course of direct substitution described by equation 1. We cannot, however, be sure the esterified product composition is a measure of the above equilibrium because XII and XIII may not esterify at equal rates.

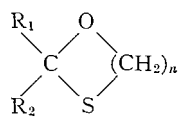
Heptaacetate (10, 11) was also identified as one of the products formed by esterification of the mixture in equation 2. This is a product of XI as we find that *aldehydo* pentaacetates of hexoses are converted to C_1-*gem*-diacetates in nearly quantitative yields by acetic anhydride with a catalyst. We are unable to find evidence for the formation of *gem*-diacetates in the reaction of dithioacetals with mercuric salts.

An acetoxy group in the favored conformation of I is in a position to give anchimeric assistance (12) when a C–S bond is broken by the action of mercuric salt.



The intermediate II*a* can react with acetic acid at C_1 to give substituted product VII, or at the acetoxy carbon to give (when the substrate is III) 3,4,5,6-tetra-0-acetyl-1,2-0-(1-acetoxy-ethylidine)*aldehydo*-D-glucose S-ethyl monothioacetal. The two products are analytically identical. There is no reason to question the structures of VII and VIII but the possibility of orthoacid structures among our products is not eliminated. Acetoxy is in a better position to give anchimeric assistance in our acyclic systems than it is in the favored conformation in some cyclic forms which give orthoester products.

Preferential C–O cleavage of hemithioacetals and ketals of the type has been demonstrated by Eliel and co-workers (13, 14) with aluminum chloride as the catalyst. Leggetter



and Brown (15) recently applied the reaction to other substrates and found that aluminum chloride cleaved dioxolanes faster than oxathiolanes and dithiolanes not at all. Preferential bonding of Al^{3+} to oxygen to give C–O cleavage is expected; Hg^{2+} would be expected to preferentially bond to divalent sulphur but the C–S bond in our 1-ethylthio-1-acetoxy compounds was not cleaved. A question arises about why $C_2H_5S-\underset{|}{\overset{|}{C}}-SC_2H_5$ substitutes rapidly whereas $C_2H_5S-\underset{|}{\overset{|}{C}}(-O-\overset{O}{\overset{\|}{C}}-CH_3)$ does not in acetic acid solutions of mercuric acetate. The answer must lie in the cationic intermediate given by cleavage of a C–S bond. Whereas divalent sulphur is an electron donor to carbon giving the relatively stable intermediate,

$$\text{>}\overset{+}{C}-SC_2H_5 \longleftrightarrow \text{>}C=\overset{+}{S}C_2H_5$$

oxygen of the acetoxy group is such a poor electron donor that we are unable to detect substitution products of the unstable intermediate

$$\text{>}\overset{+}{C}-O-\overset{O}{\overset{\|}{C}}-CH_3 \longleftrightarrow \text{>}C=\overset{+}{O}-\overset{O}{\overset{\|}{C}}-CH_3.$$

EXPERIMENTAL

The O-acetyl derivatives of the diethyl dithioacetals were prepared by slow addition of the thioacetals (1 part) to acetic anhydride (8 parts) saturated with sodium acetate at 100–110°. After 2 h at this temperature the solution was allowed to cool to room temperature and the product was isolated and recrystallized by procedures described by Wolfrom (16).

Each of the four substrates was heated with from 1 to 3 moles of mercuric acetate in mixtures of acetic acid – acetic anhydride and the rotation (sodium D line) measured (in portions of the solutions cooled to room temperature) until there was no further change. In all cases the substitution reaction was essentially complete in a 1:1 mixture of acetic acid and acetic anhydride with excess mercuric acetate before the temperature reached 100°. Dissolved mercuric acetate does not significantly modify the rotation of isolated substitution products.

The following procedure was followed for the preparation of products. Five grams of substrate (III, IV, V or VI) plus 5 g of mercuric acetate were dissolved in 100 ml of acetic acid – acetic anhydride (equal volumes) and the flask heated in a water bath until the temperature in the reaction mixture reached 80°. When the reaction mixture had cooled to room temperature the volume of solvent was reduced under vacuum to about 20 ml. Twenty-five grams of sodium acetate and a quantity of crushed ice to give a final volume near 200 ml were added. The contents of the flask was frequently stirred until the acetic anhydride hydrolyzed (no separate phase evident) and kept at 0° or colder for an additional hour. The product from V was an oil; the other substrates gave a white crystalline mass. Each product was washed with several small portions of ice water and dried at room temperature.

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

The crude product (above) from 5 g of III weighed 4.3 g and melted by 101°. Two crystallizations, by dissolving the product in hot 96% ethanol and cooling in the refrigerator, gave 3.3 g (66%) of pure α-VII, m.p. 104; α_D = +7.9 (acetic acid – acetic anhydride, C = 4, 29°), +12.6 (chloroform, C = 4, 26°), Calc. for $C_{20}H_{30}O_{12}S$: C, 48.57; H, 6.11; S, 6.48; acetoxy, 6 equiv./494 g. Found: C, 48.37; H, 6.10; S, 6.26; acetoxy, 6.02 equiv.

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

The crude product from 5 g of IV weighed 4.6 g and melted by 90°. This was dissolved in 20 ml of absolute methanol and the crystals, which formed overnight at −19°, were filtered and washed with methanol at −19°. A second recrystallization by the procedure just described gave 3.9 g (78%) of pure materials, m.p. 95–96°, α_D = +38.5 (chloroform, C = 4, 25°), +34.3 (acetic acid – acetic anhydride, C = 4, 25°). Calc. for $C_{20}H_{30}O_{12}S$: C, 48.57; H, 6.11; S, 6.48; acetoxy, 6 equiv./494 g. Found: C, 48.69; H, 6.03; S, 6.34; acetoxy, 6.08 equiv.

*1,2,3,4,5,6-Hexa-O-acetyl-*D*-mannose S-ethyl Monothioacetal (IX)*

This product has not been crystallized. Different preparations gave α_D = 10.7 to 11.5 (acetic acid – acetic anhydride C = 4, 25°). The product contains S and gives a reducing sugar after treatment with sodium methoxide in methanol. Saponification gave 6.08 equiv. acetoxy/494 g.

*1,2,3,4,5-Penta-O-acetyl-*L*-arabinose S-ethyl Monothioacetal (β-X)*

The crude product was dissolved in $CHCl_3$ and filtered, and the solvent was removed at reduced pressure. The solid residue was dissolved in ethyl acetate and the volume reduced until crystallization began at room temperature. Two volumes of hexane were then added and after allowing the solution to stand overnight in the refrigerator the crystals were filtered and washed with hexane. The product was dissolved in hot absolute methanol and the volume reduced until crystals formed at room temperature. After the product was left overnight in the refrigerator it was washed with ice cold methanol. Yield 2.8 g (56%), m.p. 120°, α_D = +3.5 (acetic acid – acetic anhydride, C = 4, 25°), +6.3 (chloroform, C = 4, 24°). Calc. for $C_{17}H_{26}O_{10}S$; C, 48.34; H, 6.16; S, 7.58; acetoxy, 5 equiv./422 g. Found: C, 48.37; H, 6.02; S, 7.60; acetoxy, 4.99 equiv.

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Department of Chemistry,
University of California,
Davis, California.

THE ELECTRON PARAMAGNETIC RESONANCE SPECTRA OF THE 2-CYANO-2-PROPYL RADICAL AND RELATED SPECIES*

J. T. Pearson, P. Smith,† and T. C. Smith

The 2-cyano-2-propyl radical, $(CH_3)_2\dot{C}(CN)$, is a commonly used radical chain initiator and a model radical similar to some involved in vinyl polymerization (1, 2). Nevertheless it does not appear that the e.p.r. spectrum of this radical has been reported despite the considerable extra interest (3–9) originating from the observation (10) that it can react as though the unpaired electron is appreciably delocalized

$$(CH_3)_2\dot{C}—C\equiv N \leftrightarrow (CH_3)_2C=C=N\bullet.$$

The aim of the present investigation was to obtain a well-resolved e.p.r. spectrum for the 2-cyano-2-propyl radical in solution by use of the new and simple flow technique of Dixon and Norman (11).

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†To whom correspondence should be addressed.