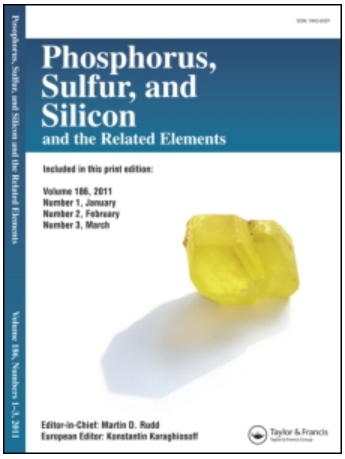


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

CARBOHYDRATES CONTAINING SULFUR

James R. Daniel[a]; Roy L. Whistler[a]; Ralph A. Zingaro[b]
[a] Department of Biochemistry, Purdue University, West Lafayette, IN [b] Department of Chemistry, Texas A & M University, TX

To cite this Article Daniel, James R. , Whistler, Roy L. and Zingaro, Ralph A.(1978) 'CARBOHYDRATES CONTAINING SULFUR', Phosphorus, Sulfur, and Silicon and the Related Elements, 7: 1, 31 — 40
To link to this Article: DOI: 10.1080/03086647808069919
URL: http://dx.doi.org/10.1080/03086647808069919

Phosphorus and Sulfur, 1979, Vol. 7, pp. 31–40
0308-664X/79/0701-0031$04.50/0

CARBOHYDRATES CONTAINING SULFUR

JAMES R. DANIEL, ROY L. WHISTLER† and RALPH A. ZINGARO‡

† Department of Biochemistry, Purdue University, West Lafayette, IN 47907 and ‡ Department of Chemistry, Texas A & M University, College Station, TX 77843

(*Received December 16, 1978*)

Thioglycosides with sulfur as the glycosidic bridge are naturally occurring. They have been examined chemically and also biochemically wherein they aid in establishment of enzyme activity. Sugars and sugar nucleoside derivatives with sulfur—and sometimes selenium and nitrogen—replacing the ring oxygen show interesting chemistry and are of great potential usefulness in medicine as indicated by initial biochemical investigations. Their value in biochemistry as analogs of natural structures is proving of useful interest. Carbohydrates with sulfur at positions other than at the anomeric carbon or with ring involvement have interesting chemical properties. This review presents a general survey of carbohydrates containing sulfur, of their special methods of synthesis, their special chemical properties and reactions and a very brief review of their biochemistry and potential clinical value.

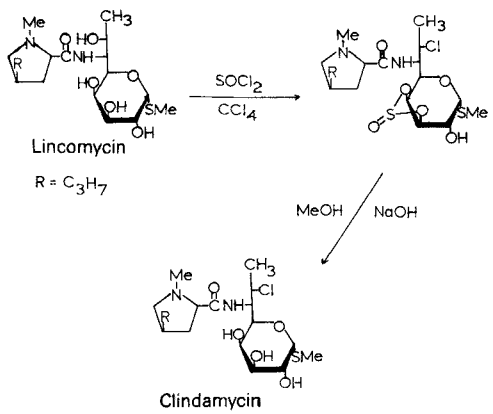
INTRODUCTION

Sulfur-containing carbohydrates have proven to be a fertile field for synthetic carbohydrate chemists. Possibly this research has been stimulated by the relative rarity of sulfur sugars in Nature, or possibly by the view of the organosulfur chemist that if an oxygen-containing compound has interesting physical, chemical, or biological properties the sulfur analog will be more interesting. This is by no means always the case but does have some validity. The usefulness of sulfur-containing carbohydrates lies in several areas: (1) comparison of oxygen and sulfur analogs to provide proof for or against a proposed theory, for example, a reaction mechanism, (2) preparation of sulfur sugars which have inherently interesting chemical or physical properties, (3) use of sulfur-containing intermediates in the preparation of other sugar derivatives such as deoxy sugars, and (4) preparation or isolation from natural sources, of sulfur sugars which may have unique or useful biological and medicinal properties.

The following is a brief review of some selected chemistry which is representative of that in the field of sulfur-containing carbohydrates. While there is much interesting chemistry involving sugar sulfates, sulfonates, thiocarbonates, etc., we have restricted our discussion to only those sugars containing one (or more) direct sulfur–sugar covalent bonds.

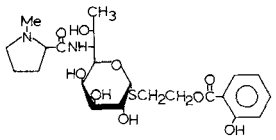
DISCUSSION

Among naturally occurring sulfur containing carbohydrates are lincomycin and related compounds. These thioglycoside antibacterials have been intensively examined at Upjohn. The synthesis of a related compound, clindamycin, has been reported by Birkenmeyer and Kagan[1] and is shown in Figure 1. Reaction of lincomycin with thionyl chloride produces the cyclic 3,4-sulfite ester. Subsequent reaction with excess thionyl chloride produces the 7-chloro derivative. Methanolysis then yields clindamycin. This Walden inversion and substitution of Cl



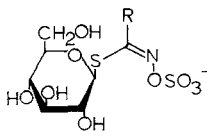
for OH at C-7 produces a product with 16 times the anti-bacterial activity of the parent compound. The analogous 7-Br and 7-I compounds were prepared by direct reaction of lincomycin with triphenylphosphine and CBr_4 or CI_4. Interestingly, the 7-I compound is 32 times as active as lincomycin. The compounds are highly active against Gram-negative bacteria and relatively non-toxic (LD_{50} 5000 mg/kg for clindamycin).

A related sulfur-containing carbohydrate is 7-*O*-demethylcelesticetin (Figure 2) which was isolated from a mutant of *Streptomyces caelestis*. This compound, intensively examined by Argoudelis and coworkers,[2] is as strongly anti-bacterially active as its 7-*O*-methyl derivative.



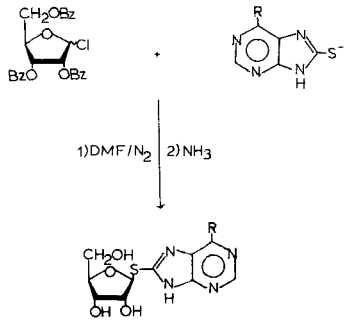
7-*O*-Demethylcelesticetin

Another important class of naturally occurring sulfur sugars is the D-glucosinolates (Figure 3) or, as they were previously known, the mustard oil glucosides. Approximately, 70–80 of these thio sugars are known, varying in the nature of the R substituent. The most important biological effect of the glucosinolates is associated with their role as flavor components in foodstuffs. The chemistry and biochemistry of these compounds has been recently reviewed.[3]



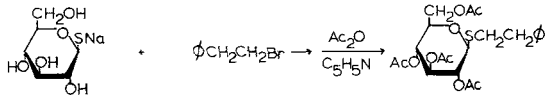
Glucosinolate anion

Synthetically, thioglycosides may be formed by reaction of a metal thiolate with a halosugar[4] in an S_N2 reaction. This is illustrated by the reaction of 8-mercaptoadenine with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride,[5] shown in Figure 4. Subsequent ammonia debenzoylation yields the adenosine thioglycoside. This thioglycoside, in contrast to the 6-mercaptouracil analog, is an effective antibacterial (in *E. coli*) and inhibits cell growth in several tumor systems (L1210 and Ehrlich ascites). Evidence has been accumulated that the compound acts as the



thioglycoside at the molecular level and is not cleaved, *in vivo*, chemically or enzymatically.

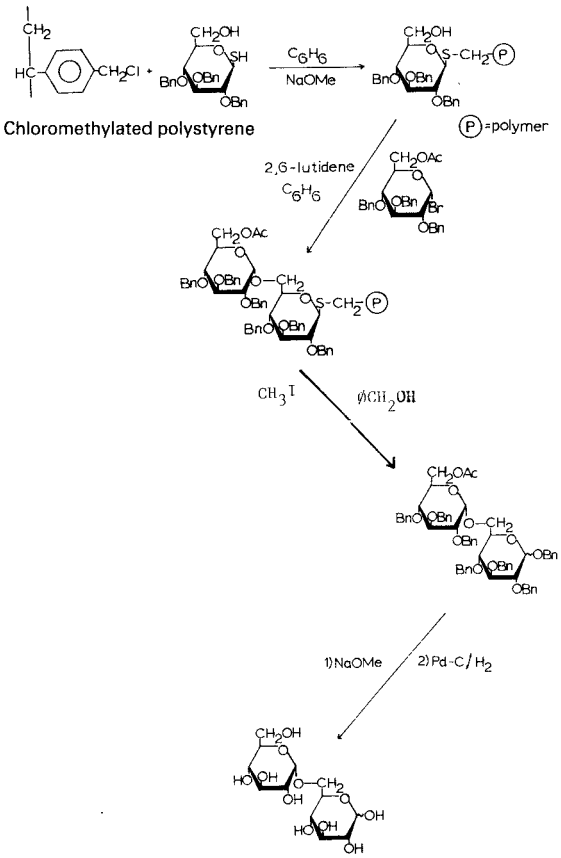
Alternatively, thioglycosides may be prepared by reacting a sugar thiolate with an alkyl halide[6] as exemplified by the work of Ishiguro[7] and coworkers. The sodium salt of 1-thio-D-glucose is reacted with phenethylbromide and subsequently acetylated under standard conditions to yield the thioglycoside (Figure 5). The thiosugar is moderately effective as a radioprotective agent.



When it is administered to mice an increase in survival rate is noted after exposure to 700 rad x-rays.

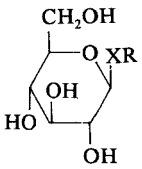
Chiu and Anderson[8] have utilized polymer-bound thioglycosides in a solid phase oligosaccharide synthesis which is reminiscent of the Merrifield peptide synthesis. This synthesis is shown in Figure 6. Reaction of 2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranose with chloromethylated polystyrene yields the polymer-bound thioglycoside, which is 92–95% pure α-anomer. Reaction of the functionalized polymer with a bromosugar produces the polymer-bound thiodisaccharide. The disaccharide may be cleaved from its polymer support by treatment with methyliodide and benzyl alcohol. Deacetylation and hydrogenolysis to remove the benzyl ether blocking groups produces the disaccharide, isomaltose. This synthesis may conceptually be repeated many times to produce oligosaccharides of various lengths.

Kinetic studies have also been made on various thioglycosides. Bamford and coworkers[9] were among the first to examine the acid catalyzed hydrolysis of thioglycosides and noted quite significant rate differences; the thioglycosides are hydrolyzed more slowly than their oxygen counterparts. The

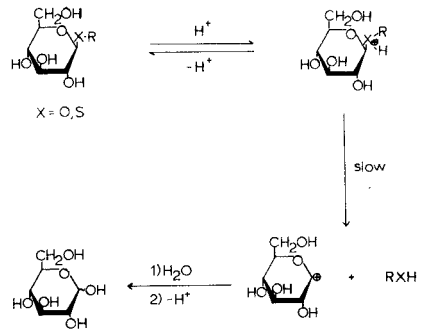


rate constants for the glycosides and thioglycosides which they measured are shown in Table I. These workers concluded that the mechanism for hydrolysis of thioglycosides is the same as that for normal glycosides. That is, an equilibrium protonation of the glycosidic atom is involved with subsequent slow loss of RXH (X = O, S). The carboxonium ion formed, quickly reacts further to produce the

TABLE I

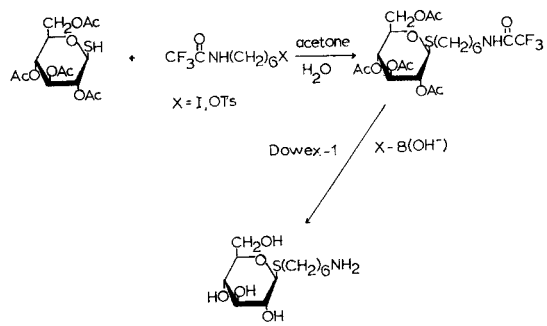
Rate Constants for Hydrolysis of 

RX	$10^5 k$ (sec^{-1})
EtO	7.07
EtS	2.13
ϕ0	31.6
ϕS	0.088

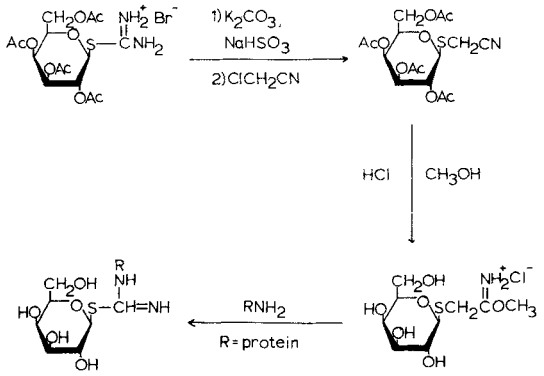


observed carbohydrate products, as shown in Figure 7. The mechanistic interpretation of the kinetic data is that RSH (in the protonated glycoside) is a poorer leaving group than ROH. However, since the sulfonium ion is thermodynamically less stable than the corresponding oxonium ion its concentration in solution must be lower. This decrease in concentration of the conjugate acid in the rate determining step would account qualitatively for the rate decrease in the hydrolysis of the thioglycosides.

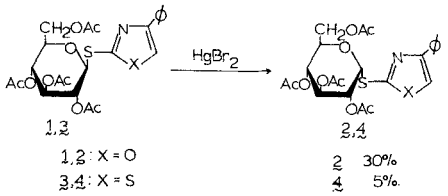
One of the more interesting uses of thioglycosides is in affinity chromatography.[10] Chipowsky and Lee have prepared thioglycosides bearing an amino group at the aglycon terminal.[11] Such compounds are useful in affinity chromatography since thioglycosides are not hydrolyzed by glycosidases. These derivatives may be coupled to Sepharose or Sephadex and the usefulness of such preparations has been demonstrated in the study of cellular adhesion.[12] A typical preparation is illustrated in Figure 8. Similar D-galactose and D-glucosamine derivatives were prepared by Chipowsky and Lee. Preparation of thioglycoside derivatives for the affinity chromatography of α-L-fucosidase,[13] β-D-mannosidase,[14] and *N*-acetyl-β-D-hexoaminidase[15] have also been described.



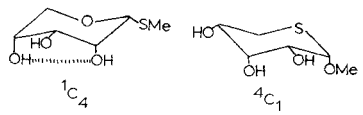
Lee and coworkers[16] have described the preparation of 2-imino-2-methoxyethyl-1-thioglycosides as new reagents for linking carbohydrates to proteins. A representative synthesis of the galactose derivative is indicated in Figure 9. These thioglycoside imidates are useful in attaching carbohydrate haptens to proteins for immunological work. Lee has attached thiogalactoside moieties to α-amylase and lysozyme and has noted that at low levels of modification there is no effect on enzyme activity. Further, these are very stable enzyme preparations, an important consideration in enzyme work.



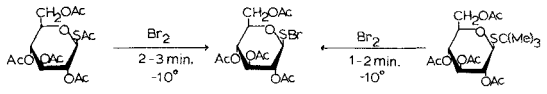
Most synthetic thioglycosides are β-D-anomers since they are prepared either from the 1-thio-β-D-sugar or by S_N2 reaction of a thiolate and α-halosugar. Nuhn and Wagner[17] have described a $\beta \rightarrow \alpha$ anomerization for heterocyclic thioglycosides in the presence of mercuric bromide which is shown in Figure 10. The anomerization is accomplished by refluxing equimolar amounts of the thio-β-D-glycoside and $HgBr_2$ in xylene for 5 h. Although the yields are quite low this is one of the few methods for preparing the thio-α-D-glycosides. The mechanism of the reaction is not known.

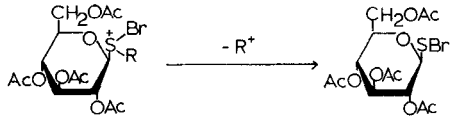


Crystallographic data on thioglycosides and some of their isomers have been obtained by Girling and Jeffrey.[18] A striking example of the effect of the placement of an atom upon the geometry of a molecule is provided by a comparison of the solid state conformations of methyl 1-thio-α-D-ribopyranoside and methyl 5-thio-α-D-ribopyranoside. Figure 11 shows that the former isomer exists in the "alternate" $^1C_4$ conformation due to a stabilizing hydrogen bond between the C-2 and C-4 hydroxyls while the latter exists in the "normal" $^4C_1$ conformation, due presumably to the anomeric effect of the methoxyl group, that is the tendency of an electronegative group at C-1 to assume an axial orientation. The anomeric effect of the SR group has been calculated to be smaller than that of an OR group, due to its smaller electronegativity.



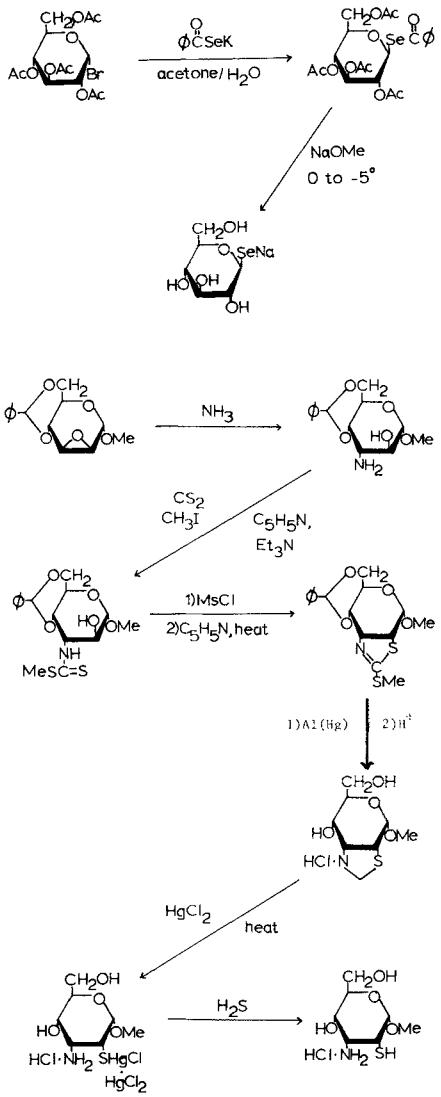
Bell and Horton[19] have described work on the formation and decomposition of D-glucopyranosylsulfenyl bromide derivatives. These derivatives, containing an electrophilic sulfur atom, are formed by the action of bromine on carbohydrates containing sulfur at C-1 (Figure 12). Reaction with bromine at higher temperatures or for longer reaction times produces *bis*(tetra-*O*-acetyl-β-D-glucopyranosyl) disulfide or acetobromoglucose. The mechanism (Figure 13) of the formation of the sulfenyl bromide is thought to involve the heterolysis of an intermediate bromosulfonium ion.





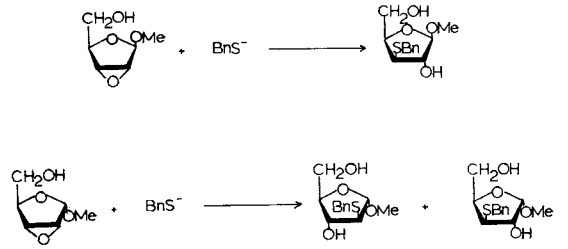
Just as there exists an interest in comparing the chemical, physical, and biological properties of oxygen and sulfur analogs, so also there exists an interest in comparing sulfur and selenium analogs. Kocourek and coworkers[20] reported in 1963 the preparation of the sodium salt of 1-seleno-D-glucose as illustrated in Figure 14. This selenolate sugar may be used in the preparation of selenoglycosides and other derivatives. It is to be noted that selenium analogs are generally less chemically stable than their sulfur counterparts. In general, sulfur and selenium analogs are distinguished more by their differences than similarities.

Carbohydrate derivatives with sulfur at a position other than C-1 are also known. Figure 15 shows



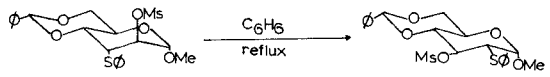
Goodman and Christensen's[21] preparation of methyl 2,3-dideoxy-2-mercapto-3-amino-α-D-allopyranoside by a multi-step route. The β-mercaptoethylamine moiety of cysteamine, $H_2NCH_2CH_2SH$, was incorporated into a carbohydrate structure. Cysteamine is a powerful antiradiation drug but is quite toxic. It was believed that incorporation of the vicinal mercaptoamino function into a carbohydrate molecule might lower the toxicity of the drug without affecting its radioprotectant action.

Van Es[22] has described the preparation of pentofuranosides bearing a sulfur atom at positions 2 or 3 by the interaction of thiobenzylate anion with methyl 2,3-anhydro-D-ribofuranoside. Not surprisingly the



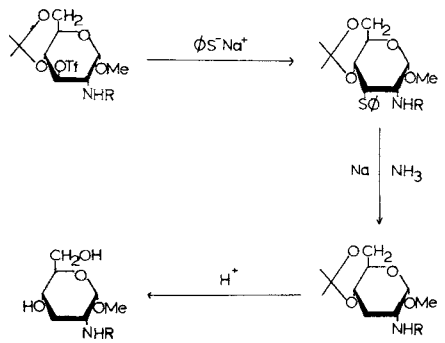
β-D-anomer yields mainly the 3-S-benzyl product while the α-anomer yields a 7:3 mixture of 2- and 3-S-benzyl products as shown in Figure 16. These general tendencies would be predicted on steric grounds.

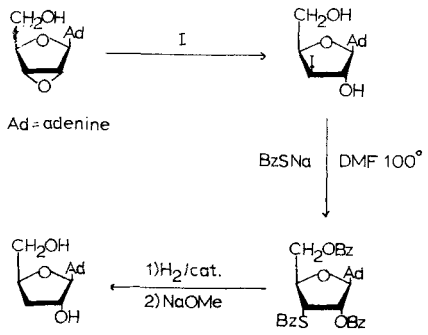
Hanessian[23] has described a unique diaxial–diequatorial rearrangement as shown in Figure 17.



The diaxial *altro* sugar rearranges quantitatively to the diequatorial D-*gluco* isomer. The direction of the rearrangement could be predicted on thermodynamic grounds but the mechanism of the reaction is unknown. It is presumed to involve an intermediate cyclic sulfonium ion. Also, Acton and coworkers[24] have reported on the synthesis of some 2-thio-D-ribose and 2′-thioadenosine derivatives. These derivatives bear 2-SMe, 2-SBn, and 2-SBz substituents on the sugar ring.

Several interesting reports of sugars bearing sulfur substituents at C-3 have recently appeared. Figure 18 details Haskell and coworkers'[25] synthesis of methyl 3-deoxy-α-D-glucosaminide via a sulfur-containing intermediate. Especially noteworthy is the use of the trifluoromethanesulfonate ester as an excellent leaving group. Rarely are nucleophilic displacements at secondary positions done at 5°. This is an extremely facile reaction. The 3-deoxy position

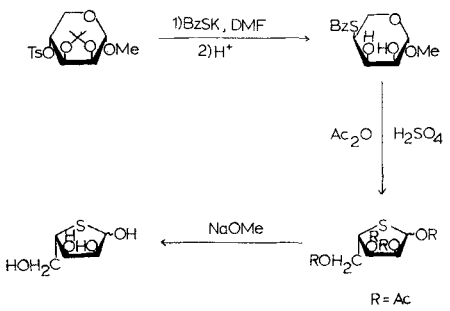




in this pyranoside system is of interest because such sugars occur in some of the aminoglycoside antibiotics. Reduction of the 3-S-ϕ group may also be effected by Raney nickel or tributylstannane but only in low yield.

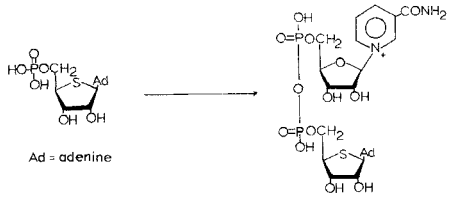
Mengel and Griesser[26] have reported on the preparation of 3′-deoxyadenosine derivatives as shown briefly in Figure 19. Adenosine is converted by standard methods into its 2′,3′-epoxide and the epoxide is opened to yield the 3-iodo compound. Nucleophilic displacement with sodium thiobenzoate in DMF at 100° yields the 3-SBz *ribo* compound which on catalytic reduction and saponification produces 3′-deoxyadenosine. The 2′-deoxyadenosine derivatives were similarly prepared. Some of the 3′-deoxy nucleosides show cell growth inhibitory action. This and the previous synthesis are good examples of the utility of sulfur carbohydrates and their conversion to the biologically important deoxy sugars.

Sugars containing a sulfur atom at C-4, especially those pentose derivatives where the sulfur atom is a part of the sugar furanose ring structure, have been investigated. The basic strategy for introducing heteroatoms into sugar rings was first devised by Whistler and used in the preparation of 4-thio-D-ribose and even earlier in the preparation of 5-thio-D-xylose.[37] Reist and coworkers[27] have used this method of introducing a sulfur atom into the sugar ring to prepare 4-thio-L-ribose (Figure 20). Generally, a suitable sulfur-containing derivative is formed which, on deblocking, will isomerize to the thermodynamically more stable thiohemiacetal. This method of preparing sulfur ring sugars is the same regardless of whether the conversion is pyranose to furanose (as in the case of the ribose derivatives) or furanose to pyranose (as in 5-thio-D-glucose[40,41]). The presence of sulfur in the furanose ring in 4-thio-L-ribose was illustrated by the absence of carbonyl or SH absorptions in the UV spectrum. A carbonyl



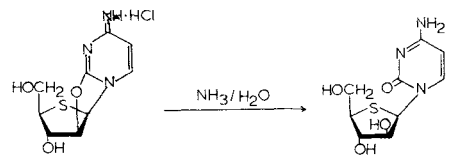
absorption would support an open chain structure while an SH band would indicate a pyranose structure. Owen and Ragg[28] have also used this general method of attack to prepare 4,6-dideoxy-4-mercapto-L-talofuranose, another thiofuranose sugar.

Hoffman and Whistler[29] have prepared some nucleotide analogs containing 4-thio-D-ribose. 4′-Thioadenosine 5′-phosphate was converted into the NAD analog shown in Figure 21, under literature conditions.



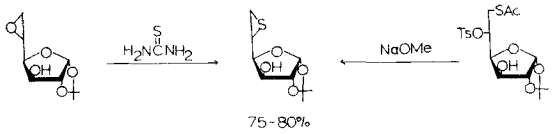
4′-Thioadenosine 5′-phosphate, just as its 4′-oxygen analog, is a substrate for adenosine 5′-phosphate deaminase and is an allosteric effector of pig heart malate dehydrogenase. Similarly, the NAD analog is active as a coenzyme with several oxidoreductases, just as is the natural compound. However, the rates of enzymic reaction are altered generally being lower with the sulfur analog, but in one case (liver alcohol dehydrogenase) the rate is greater than with the natural coenzyme.

Ototani and Whistler[30] have also prepared analogs of the antitumor agent 1-β-D-arabinofuranosylcytosine, which contains the 4-thioarabinofuranose ring. The conversion of 2,2′-anhydro-4′-thio-1-β-D-arabinofuranosylcytosine hydrochloride into 4′-thio-1-β-D-arabinofuranosylcytosine is illustrated in Figure 22. Both of the compounds were as

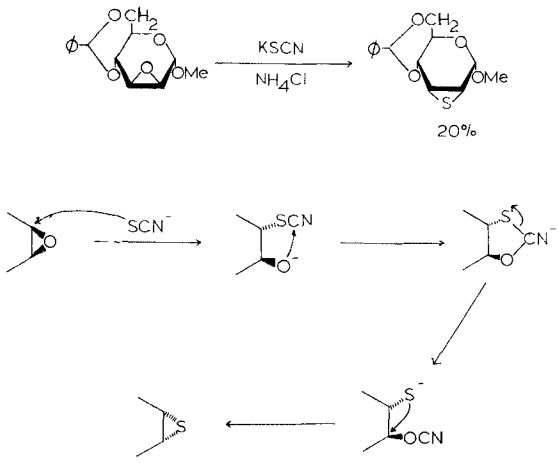


effective in inhibiting the growth of KB cells *in vitro* as their 4′-oxygen analogs.

Sugar episulfides have been widely examined, both as intermediates in the synthesis of deoxy sugars and for introducing a sulfur atom into a sugar ring. Early work by Hall and coworkers[31] established two alternate methods for preparing sugar episulfides, one from the complimentary epoxide and the second from a vicinal thioacetate–sulfonate ester as illustrated in Figure 23. Since the episulfide resulting

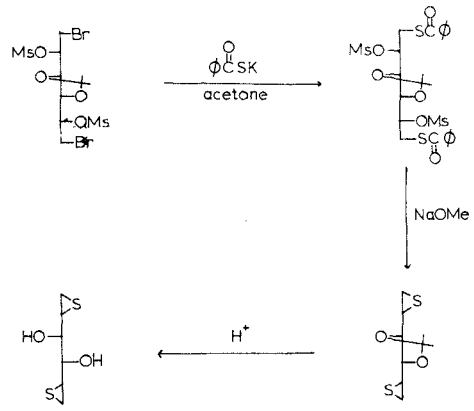


from the sodium methoxide reaction of the vicinal thioacetate–sulfonate diester is known to take place with inversion of configuration at C-5 and since the identical product is formed on reaction of thiourea with the C-5 epimeric epoxide, it is clear that the thiourea reaction takes place with Walden inversion at C-5. Guthrie[32] has examined the thiocyanate conversion of epoxides to episulfides as illustrated for the *manno* epoxide to *altro* episulfide conversion (Figure 24). The mechanism presumably involves a 1,3-oxathiolane-type intermediate as shown in Figure 25. The yield of the 2,3-epithio-*altro* product

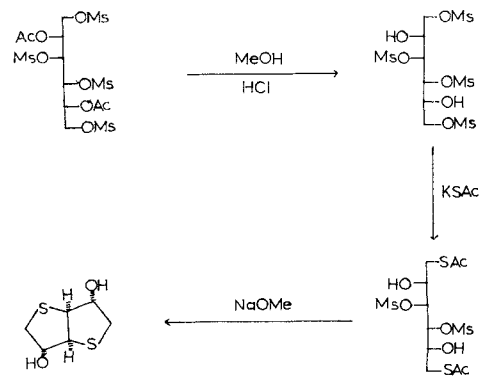


was increased by substituting thiourea for thiocyanate as described by Guthrie and Murphy.[33] Further, the 2,3-epithio *manno* sugar, previously unknown, was prepared in 65% yield by the reaction of methyl, 4,6-*O*-benzylidene-2,3-anhydro-α-D-altropyranoside with thiourea. Subsequent work has generally indicated that the thiourea conversion is superior to the thiocyanate reaction.

Research by Kuszmann and coworkers[34,35] has involved the preparation and characterization of sugar alcohol episulfides and other cyclic thioanhydro derivatives. In view of the antitumor activity of diepoxides such as 1,2:5,6-dianhydro-D-mannitol,[36] Kuszmann and Vargha prepared a diepisulfide iditol derivative for testing for antitumor activity (Figure 26). Unfortunately, the diepisulfide

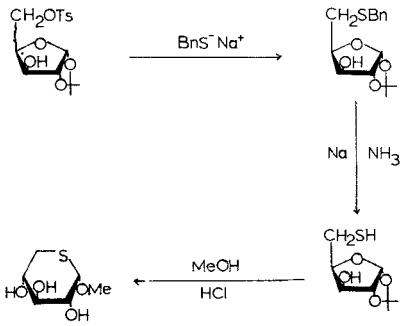


showed no cytostatic activity against Yoshida sarcoma, Walker 256 carcinosarcoma, or Ehrlich ascites sarcoma. It was postulated that this lack of biological activity may be due to polymerization of the diepisulfide, which is known to be sensitive to both acid and base. In a related series of researches Kuszmann and Sohar describe the preparation of 1,4:3,6-*bis*(thioanhydro)-D-iditol as shown in Figure 27. This compound showed no cytostatic effect in Ehrlich ascites carcinoma or S-180 sarcoma but was somewhat effective against Yoshida sarcoma. While these compounds neither exhibit striking bioactivity, their preparation is illustrative of the synthetic routes

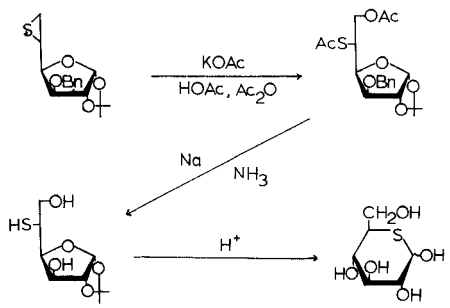


used in preparing episulfides and thioanhydro sugars.

Whistler and coworkers[37] and Adley and Owen[38] reported the preparation of 5-thio-D-xylopyranose derivatives in the early sixties. Whistler's synthesis which locks the sulfur into the ring by glycoside formation is illustrated in Figure 28. Hexose

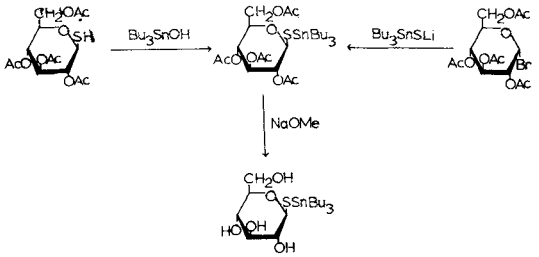


derivatives containing sulfur in pyranose ring are also known. Adley and Owen[39] have reported the preparation of a 5-thio-L-idopyranose derivative. Feather and Whistler[40] described the synthesis of 5-thio-D-glucose and improvements of the preparation of this compound were reported by Nayak and Whistler[41] and Figure 29 shows the incorporation of

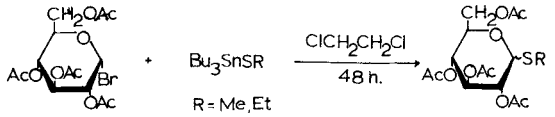


the sulfur atom into the D-glucopyranose ring. 5-Thio-D-glucose has a number of extremely interesting biochemical properties, primary among them its induction of temporary sterility in male mice and rats at low, non-toxic doses.[42] These results make 5-thio-D-glucose a prime candidate for use as a male contraceptive although such experiments have not been performed on human subjects. Other reports on the preparation of 5-thio-L-rhamnose[43] and 6-thio-β-D-fructose[44] have appeared and the whole field of introducing sulfur (and other) atoms into sugar rings has recently been reviewed.[45]

Reports of organometallic and organometalloid derivatives have appeared in the past few years. Husain and Pollar[46] have reported the preparation of trialkylstannane thiosugars as shown in Figure 30.

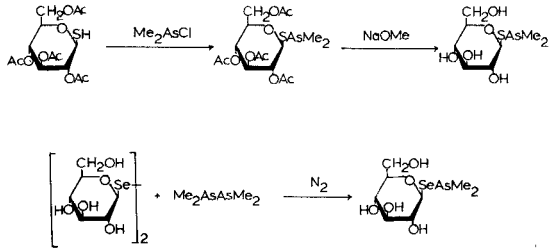


Ogawa and coworkers[47] have described a similar reaction in a new approach to thioglycoside synthesis (Figure 31). The anomerically pure thioglyco-



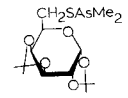
sides could be equilibrated by treatment with stannic chloride in 1,2-dichloroethane, the ratio of α to β anomers being 2.5 : 1, due presumably to the anomeric effect.

The preparation of D-glucose derivatives bearing an $-S-MR_2$ (M = P, As, Sb; R = alkyl, aryl) moiety at C-1 and/or C-6 have been reported by Zingaro and coworkers.[48–52] Similar selenium–metalloid bonded derivatives have also been prepared. In Figure 32 representative preparations are



illustrated, both for sulfur and selenium. It is to be noted that the instability of the sugar selenols generally precludes their formation, isolation, and condensation with dimethylchloroarsine as in the case of the sugar thiols. In the case of the selenium compounds the preparation of the Se–As bonded sugars is accomplished by the 4-center reaction of an appropriate diselenide and diarsine. The Se–As

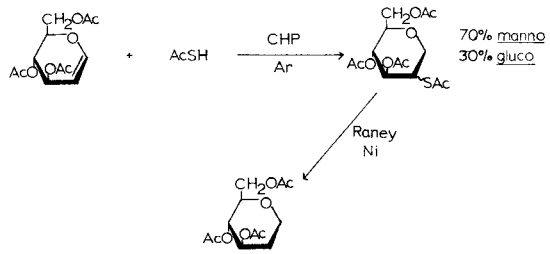
bonded species are generally less stable oxidatively and hydrolytically than their sulfur analogs. Similar 1- and 6-$XAsMe_2$ (X = S, Se) D-galactose derivatives have recently been reported.[53,54] It is especially worth noting about the $SAsMe_2$ sugars that some of them possess significant antitumor activity in both *in vitro* (KB5 or KB9) and *in vivo* (PS388 leukemia or Walker carcinosarcoma) test systems. The most active of the sugars so far examined is the D-galactose derivative shown in Figure 33, which has a test/control (T/C) ratio of



T/C 141%
P388 mouse leukemia
200 mg/kg

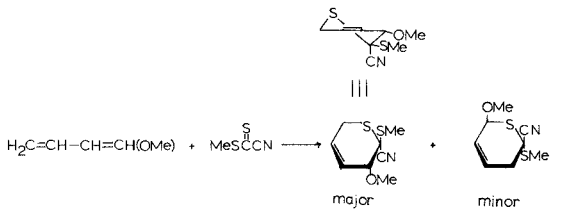
141% at 200 mg/kg in the PS 388 mouse leukemia system. In this series of thio- and selenosugar derivatives it is significant that these arsenic compounds are quite nontoxic and that while the sulfur analogs frequently show biological activity, the selenium compounds show lesser activity, presumably due to their shorter biochemical half lives.

The interaction of reactive carbohydrate intermediates, such as glycals, with sulfur-containing compounds has been explored by Igarashi and coworkers.[55,56] Figure 34 illustrates the free radical



addition of thioacetic acid to triacetyl-D-glucal. The reaction is conducted under an inert argon atmosphere with initiation by cumene hydroperoxide (CHP). The epimeric mixture of 2-SAc products may be reductively desulfurized to yield 2-deoxy-1,5-anhydro-D-glucitol triacetate. If oxygen is used as the free-radical initiator a complex mixture of sulfur-containing carbohydrates is obtained.

Vyas and coworkers[57–59] have reported a novel synthesis of carbohydrate derivatives containing sulfur in the ring. The synthesis (Figure 35) involves a Diels–Alder type interaction of methyl cyanodithioformate with an appropriate diene. The major



product, methyl 4,5-dideoxy-3-*O*-methyl-2,6-dithio-*β*-DL-glycerohex-4-en-2-ulopyranosidononitrile, has the preferred conformation shown in Figure 35 in solution as determined by nuclear magnetic resonance. Oxidation reactions of these compounds at both the double bond and the sulfur atom have been investigated by these workers.

CONCLUSION

Sulfur containing carbohydrates have a recent and varied history. The utility of sulfur sugars both as modified biological substrates and synthetic intermediates has been well documented and the search for new and interesting sulfur sugars continues apace today. New reagents for introducing sulfur into carbohydrate structures are the subject of many investigations and these also continue unabated. Potential uses for sulfur-containing carbohydrates include their use as non- or difficulty-metabolized medicinals and as synthetic non-caloric sweeteners. An almost unlimited amount of research, chemical, biochemical, and medical, remains to be done and there is every reason to believe that the field of thiosugars will remain a rich area of investigation for many years to come.

ACKNOWLEDGEMENT

The work of R.A.Z. was done in part under the grants provided by The Robert A. Welch Foundation, Houston, TX and NIH Grant No. CA 16912. The work of R.L.W. was done in part under a grant from NIH No. AM 18482. This is Journal Paper No. 7541 of the Purdue University Experiment Station.

REFERENCES

1. R. D. Birkenmeyer and F. Kagan, *J. Med. Chem.* **13**, 616 (1970).
2. A. D. Argoudelis, J. H. Coats, P. G. Lemans and O. K. Sebek, *J. Antibiot.* **25**, 445 (1972).
3. M. Benn, *Pure Appl. Chem.* **49**, 197 (1977).
4. B. Helferich, H. Grünewald and F. Langenhoff, *Ber.* **86**, 873 (1953).
5. D. A. Shuman, A. Bloch, R. K. Robins and M. J. Robins, *J. Med. Chem.* **12**, 653 (1969).

6. R. T. Lee and Y. C. Lee, *Carbohydr. Res.* **34**, 151 (1974).
7. S. Ishiguro, M. Sekiya, Y. Arai and H. Tanooka, *Chem. Pharm. Bull.* **20**, 1332 (1972).
8. S.-H. L. Chiu and L. Anderson, *Carbohydr. Res.* **50**, 227 (1976).
9. C. Bamford, B. Capon and W. G. Overend, *J. Chem. Soc.* 5138 (1962).
10. P. Cuatrecasas, *Ann. Rev. Biochem.* **40**, 259 (1971).
11. S. Chipowsky and Y. C. Lee, *Carbohydr. Res.* **31**, 339 (1973).
12. S. Chipowsky, Y. C. Lee and S. Roseman, *Proc. Nat. Acad. Sci. U.S.* **70**, 2309 (1973).
13. K. L. Matta, R. N. Girotra and J. J. Barlow, *Carbohydr. Res.* **43**, 101 (1975).
14. K. L. Matta and J. J. Barlow, *Carbohydr. Res.* **48**, 294 (1976).
15. A. A. Artyukov and N. V. Molodtsov, *Bioorg. Khim.* **1**, 1577 (1975).
16. Y. C. Lee, C. P. Stowell and M. J. Krantz, *Biochemistry* **15**, 3956 (1976).
17. P. Nuhn and G. Wagner, *Z. Chem.* **7**, 154 (1967).
18. R. L. Girling and G. A. Jeffrey, *Carbohydr. Res.* **27**, 257 (1973).
19. R. H. Bell and D. Horton, *Carbohydr. Res.* **9**, 187 (1969).
20. J. Kocourek, J. Klenha and V. Jiracek, *Chem. Ind.* 1397 (1963).
21. L. Goodman and J. E. Christensen, *J. Am. Chem. Soc.* **83**, 3823 (1961).
22. T. Van Es, *Carbohydr. Res.* **21**, 156 (1972).
23. S. Hanessian and A. P. A. Staub, *Carbohydr. Res.* **14**, 424 (1970).
24. E. M. Acton, K. J. Ryan and L. Goodman, *J. Org. Chem.* **36**, 2646 (1971).
25. T. H. Haskell, P. W. K. Woo and D. R. Watson, *J. Org. Chem.* **42**, 1302 (1977).
26. R. Mengel and H. Griesser, *Tet. Lett.* 1177 (1977).
27. E. J. Reist, D. E. Gueffroy and L. Goodman, *J. Am. Chem. Soc.* **85**, 3715 (1963).
28. L. N. Owen and P. L. Ragg, *J. Chem. Soc. C., Org.* 1291 (1966).
29. D. J. Hoffman and R. L. Whistler, *Biochemistry* **9**, 2367 (1970).
30. N. Ototani and R. L. Whistler, *J. Med. Chem.* **17**, 535 (1974).
31. L. D. Hall, L. Hough and R. A. Pritchard, *J. Chem. Soc.* 1537 (1961).
32. R. D. Guthrie, *Chem. Ind.* 2121 (1962).
33. R. D. Guthrie and D. Murphy, *J. Chem. Soc.* 6666 (1965).
34. J. Kuszmann and L. Vargha, *Carbohydr. Res.* **11**, 165 (1969).
35. J. Kuszmann and P. Sohar, *Carbohydr. Res.* **21**, 19 (1972).
36. M. Jarman and W. C. J. Ross, *Chem. Ind.* 1789 (1967).
37. R. L. Whistler, M. S. Feather and D. L. Ingles, *J. Am. Chem. Soc.* **84**, 122 (1962).
38. T. J. Adley and L. N. Owen, *Proc. Chem. Soc.* 418 (1961).
39. T. J. Adley and L. N. Owen, *J. Chem. Soc., C. Org.* 1287 (1966).
40. M. S. Feather and R. L. Whistler, *Tet. Lett.* 667 (1962).
41. U. G. Nayak and R. L. Whistler, *J. Org. Chem.* **34**, 97 (1969).
42. J. R. Zysk, A. A. Bushway, R. L. Whistler and W. W. Carlton, *J. Reprod. Fert.* **45**, 69 (1975).
43. A. K. M. Anisuzzaman and R. L. Whistler, *Carbohydr. Res.* **55**, 205 (1977).
44. M. Chmielewski, M.-S. Chen and R. L. Whistler, *Carbohydr. Res.* **49**, 479 (1976).
45. R. L. Whistler and A. K. M. Anisuzzaman, *Synthetic Methods for Carbohydrates* (American Chemical Society, Wash., D.C., 1976) Chap. 8, pp. 133–154.
46. A. F. Husain and R. C. Poller, *J. Organomet. Chem.* **118**, C11 (1976).
47. T. Ogawa and M. Matsui, *Carbohydr. Res.* **54**, C17 (1977).
48. G. C. Chen, R. A. Zingaro and C. R. Thompson, *Carbohydr. Res.* **39**, 61, (1975).
49. C. D. Mickey, P. H. Javora and R. A. Zingaro, *J. Carbohyd. Nucleosides, Nucleotides* **1**, 291 (1974).
50. C. L. Baimbridge, C. D. Mickey and R. A. Zingaro, *J. Chem. Soc., Perkin Trans. I*, 1395 (1975).
51. R. A. Zingaro, *Chem. Scripta* **8A**, 51 (1975).
52. G. C. Chen, J. R. Daniel and R. A. Zingaro, *Carbohydr. Res.* **50**, 53 (1976).
53. J. R. Daniel and R. A. Zingaro, *Carbohydr. Res.* **64**, 69 (1978).
54. J. R. Daniel and R. A. Zingaro, *Phosphorus and Sulfur* **4**, 179 (1978).
55. K. Igarashi and T. Honma, *J. Org. Chem.* **35**, 606 (1970).
56. K. Igarashi and T. Honma, *J. Org. Chem.* **32**, 2521 (1967).
57. D. M. Vyas and G. W. Hay, *J. Chem. Soc. Perkin Trans. I*, 180 (1975).
58. D. M. Vyas and G. W. Hay, *Can. J. Chem.* **53**, 1362 (1975).
59. D. M. Vyas and G. W. Hay, *Carbohydr. Res.* **55**, 215 (1977).