Characterization of Deoxy Sugars by Mass Spectrometry[1]

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Abstract: The major classes of the biologically derived deoxy sugars as well as other deoxy sugars were investigated by mass spectrometry. Characteristic fragmentations were observed in the mass spectra which permit the location of the deoxy function(s) and allow definitive structure assignments to these compounds. The classes investigated include dialkyl dithioacetals of 2-deoxy-, 3-deoxy-, and 5-deoxyhexoses, terminal deoxyhexoses and -pentoses, a terminal branched-chain pentose, 2,3-dideoxy-, 2,6-dideoxy-, 3,6-dideoxy-, and 4,6-dideoxyhexoses, and some of their methylated analogs. The relative importance of each of these deoxy sugars from the biological and synthetic standpoints is discussed.

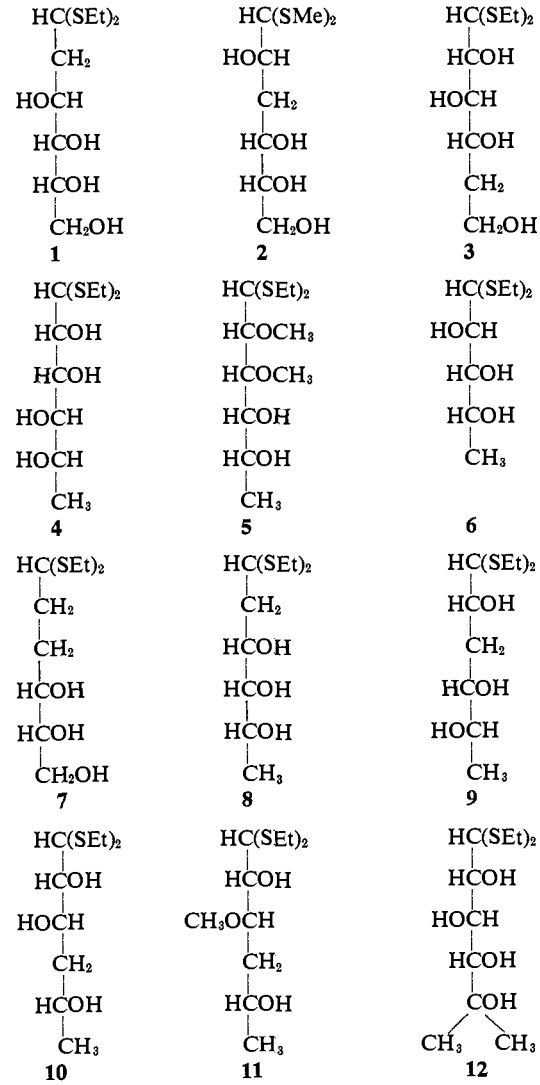
In preceding papers[2-6] the importance of mass spectrometry in the study of carbohydrate derivatives was discussed. The increasing emphasis on this technique was recently highlighted by its successful application in the characterization of amino sugars.[5,6] By subjecting various classes of N-acetylated amino sugar dialkyl dithioacetals to electron impact, characteristic fragmentation patterns were obtained which led to the assignment of the position of the amino functions in these derivatives. This information should prove valuable in the structure elucidation of amino sugars isolated by degradation of biological substances or those produced by synthesis.[7-9]

The deoxy sugars, an equally important class of carbohydrates, have been long known as components of biological materials.[10,11] Unlike other classes of carbohydrates, many deoxy sugars confer unique biological properties to the parent substances of which they are a part.[12,13] The present methods for structure elucidation of members of the deoxy sugars often involve tedious degradative reactions[10-13] and various colorimetric tests[14] that cannot be applied with equal success to all deoxy sugars and do not provide adequate means of characterization.

We wish to report in this paper on the application of mass spectrometry in assigning the position of deoxy functions in deoxy sugars. As in the case of the amino sugars,[5,6] the dialkyl dithioacetal derivatives have proven most satisfactory in providing informative and relatively easily interpretable mass spectra. This blocking function is advantageous since it can be introduced in the free sugars directly or obtained from glycosides, etc., by mercaptolysis in the presence of an acid catalyst.

The candidates for this study were carefully selected so as to include representative members of all the important classes of biologically derived deoxy sugars. In addition several other members as yet not encountered as components in biological materials were also studied. Chart I shows the structures that were investigated.

Chart I



(1) Part of this investigation was presented at the EUCHEM Symposium on Mass Spectrometry, Sarlat, Dordogne, France, Sept 8–11, 1965.
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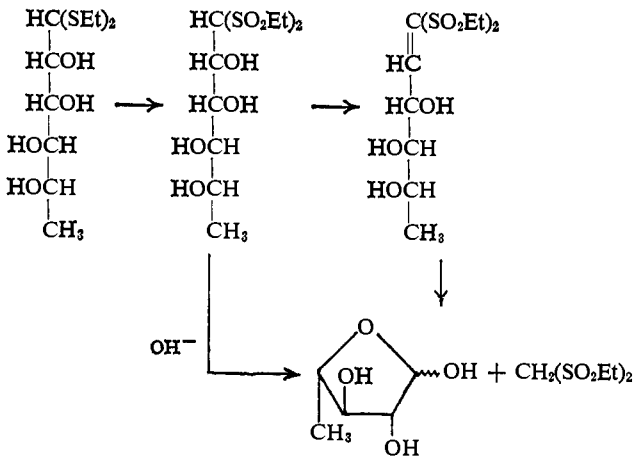
Their method of preparation involved conventional mercaptalation of small amounts of the free sugars, their glycosides or acetal derivatives, and purification of the crude products by crystallization directly or following chromatography. Many of the dithioacetals were obtained in crystalline form and thus provide, in addition to their useful mass spectra, a suitable new crystalline derivative of the parent sugar.

The mass spectra of isomeric methyl 2-, 3-, and 4-deoxytri-*O*-methyl-D-hexopyranosides were recently reported[15] and provide a convenient method of examining some of the deoxy sugars as cyclic derivatives (pyranosides).

An important aspect associated with the study of deoxy sugar dithioacetals by mass spectrometry is their adaptation to the MacDonald–Fischer[16] degradation reaction by way of the corresponding disulfones. This procedure can reveal the partial stereochemistry of the parent sugar and has been extremely useful in the elucidation of the stereochemistry of a number of amino sugar dithioacetals,[17–19] the structures of which were studied by mass spectrometry.[5,6] The MacDonald–Fischer degradation has scarcely been used in the deoxy sugar series;[20] a typical example[20] is illustrated.



Theoretically it should be applicable to all deoxy sugar dithioacetals except perhaps the 2-deoxy and 5,6-dideoxy derivatives according to the accepted mechanism.[17,21] In the first case the initial step in the degradation would require the unfavorable ejection of hydride ion from C-2, while in the second case the normal cyclization reaction involving the C-5 or C-6 oxygen function would be blocked.

Since the stereochemistry at C-2 is destroyed during the degradation, other independent methods which rely on optical rotation data have to be considered for this purpose. By utilizing the dithioacetals of deoxy sugars it should be possible to obtain useful information concerning their structures and the position of the deoxy functions from their mass spectra, and also to establish the partial stereochemistry of the sugar providing the lower aldose resulting from the degradation can be identified.

In the following sections, it is intended to discuss each of the deoxy sugars studied in terms of its relative importance, its occurrence in biological substances, and finally to demonstrate the utility of mass spectrometry in the elucidation of structures. The use of this technique in the study of deoxy sugars produced by synthetic pathways, on the other hand, could result in definitive distinctions between isomeric deoxy sugars formed in a given reaction. In general, fragmentation patterns are not affected by stereochemical differences and it is reasonable to assume that stereoisomeric deoxy sugars will fragment by the same general pathway, except for minor differences in the relative intensities of certain peaks.

As will be discussed later, 2-deoxy sugars can be readily recognized from the mass spectra of their dithioacetals. The example chosen, 2-deoxy-D-*arabino*-hexose diethyl dithioacetal[22] (**1**), has been investigated previously.[2] Although 2-deoxy-D-*erythro*-pentose is the biologically most frequently encountered member of this class of deoxy sugars,[10,11] the mass spectral data provided by **1** should be of general use.

The 3-deoxy sugars, frequently encountered in synthetic work, have only one representative member in the realm of biological substances. The antibiotic cordycepin[23] has been shown by nuclear magnetic resonance data[24] to be identical with 9-(3-deoxy-β-D-ribofuranosyl)adenine.[25] This identity has also been corroborated recently by mass spectral studies on the antibiotic.[26] For the more general aims of the present investigation, 3-deoxy-D-*arabino*-hexose dimethyl dithioacetal[27] (**2**) was chosen as representative of the 3-deoxy sugars.

Deoxy sugars having the methylene functions at C-4 and C-5 have not been found as components of biological substances as yet and interest in these is mainly chemical in nature. As a model of the latter class, the fragmentation characteristics of 5-deoxy-D-*xylo*-hexose diethyl dithioacetal (**3**) have been studied.

The terminal deoxy hexoses and their partially methylated derivatives are abundant constituents of plant glycosides,[11,13] polysaccharides,[11] antibiotics,[7–9] and other biologically derived substances.[7,9,11] Of particular interest is the fact that partially methylated deoxy sugar dithioacetals are adaptable to study by mass spectrometry and are amenable to characterization and structure elucidation by this technique. A unique example is the case of 2,3-di-*O*-methyl-6-deoxy-D-allose (mycinose), which is one of two sugar residues in the antibiotic chalcomycin.[28] A 5-deoxypentose diethyl dithioacetal[29] (D-arabinose) (**6**) as well as 6-

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deoxy-L-mannose diethyl dithioacetal,[30] which has been investigated previously,[2] were also included in this study as further examples of terminal deoxyhexoses. It is interesting to note that some steroidal glycosides of 6-deoxyhexoses have been studied by mass spectrometry.[31]

The 2,6-dideoxyhexoses and some of their partially methylated derivatives are common constituents of many plant glycosides[13] and have more recently been isolated from the antibiotics rhodomycin,[32] olivomycin,[33] and chromomycin.[34] The example chosen as representative of this class of dideoxy sugars is 2,6-dideoxy-D-*ribo*-hexose diethyl dithioacetal (**8**). The parent sugar commonly known as digitoxose is one of the oldest known members of this class of compounds.[13]

The 3,6-dideoxyhexoses are known to occur in lipopolysaccharides elaborated by gram-negative bacteria.[12,35] They assume considerable biological significance since they have been shown to contribute to the serological specificity of many immunologically active polysaccharides. A member of this class was also isolated from a glycolipid obtained from the egg cell membrane of the Nematode worm *Parascaris equorum*.[36] The fragmentation pattern of a synthetically prepared member, 3,6-dideoxy-L-*lyxo*-hexose diethyl dithioacetal (**9**) will be discussed in detail.

The 4,6-dideoxyhexoses, a rare class of dideoxy sugars, were recently discovered as components in the antibiotics lankamycin,[37] chalcomycin,[28] and neutramycin.[38] A common sugar in these three antibiotics called lankavose and chalcose, respectively, was found, to be 4,6-dideoxy-3-*O*-methyl-D-*xylo*-hexose (**11**). This structural assignment was arrived at by a series of elegant degradative studies[28] involving periodate oxidation and isolation of the resulting fragments. This procedure, which has been used for the 3,6-dideoxyhexoses also, usually provides part of the carbon skeleton of the original structure and must be complimented by other chemical transformations. It is in such instances that the inherent advantages of mass spectrometry as a powerful tool in the study of structural aspects of these deoxy sugars can be fully recognized.

All the salient structural features of chalcose, including the position of attachment of the methoxyl function, can be recognized directly from the mass spectrum of its diethyl dithioacetal derivative. The parent 4,6-dideoxy-D-*xylo*-hexose diethyl dithioacetal (**10**) was also investigated as a model substrate. In several cases, nuclear magnetic resonance spectroscopy has also been extremely valuable in assigning almost complete structure and stereochemistry to the dideoxy sugars.[28,34]

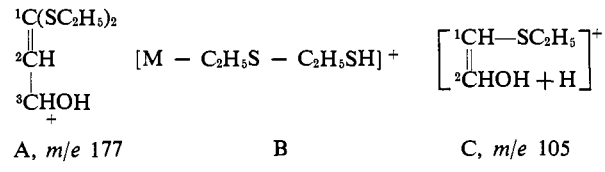
The fragmentation pattern of 2,3-dideoxy-D-*erythro*-hexose diethyl dithioacetal (**7**) was studied since the parent dideoxyhexose is structurally related to the last of the biologically significant straight-chain deoxy sugars, the 2,3,6-trideoxyhexoses.[7,11] Amicetose, 2,3,6-trideoxy-D-*erythro*-hexose,[39] is a component of the antibiotic amicetin.[39-42] The deoxy sugar components of the antibiotics rhodomycin[43] and streptolydigin[44] have been shown to be 2,3,6-trideoxy-L-*threo*-[43] and -D-*threo*-hexoses, respectively.[45]

Finally, the fragmentation of the diethyl dithioacetal (**12**) of a terminal branched-chain sugar, 6-deoxy-5-*C*-D-*xylo*-hexose,[46] was also studied. This sugar is structurally related to 6-deoxy-5-*C*-methyl-4-*O*-methyl-L-*lyxo*-hexose (noviose), the sugar component in the antibiotic substances novobiocin,[47] coumerimycin A_1,[48] and coumerimycin A_3.[49]

Results and Discussion

Characteristic of the mass spectra of diethyl dithioacetal derivatives of monosaccharides[2] such as D-arabinose and D-glucose are molecular ion peaks of relative intensity 20%; base peaks corresponding to a diethyl dithioacetal fragment, $^{+}CH(SC_2H_5)_2$, at *m/e* 135; the fragmentation $M\cdot^{+} \rightarrow M - C_2H_5S \rightarrow M - C_2H_5S - H_2O$; and three fragments referred to as A, B, and C (Chart II). Both thioalkyl groups are lost from

Chart II



A, *m/e* 177 B C, *m/e* 105

the molecule in the formation of fragment B, which probably exists as a cyclic structure.[2] Available data do not specify the origin of the hydrogen atom which is incorporated in fragment C.

An initial study with 2-deoxy-D-*arabino*-hexose diethyl dithioacetal[2] (**1**) showed differences between its mass spectrum and the mass spectrum of D-glucose diethyl dithioacetal which allow facile recognition of a 2-deoxy function. Fragment A and the diethyl dithioacetal fragment (*m/e* 135) do not form; fragments B and C and the molecular ion are found 16 mass units lower than in the mass spectrum of D-glucose diethyl dithioacetal.[2] Scheme I summarizes the fragmentation of compound **1**. Fragment A does not form because of the relatively high energy required for the elimination of a molecule of hydrogen from C-1–C-2.

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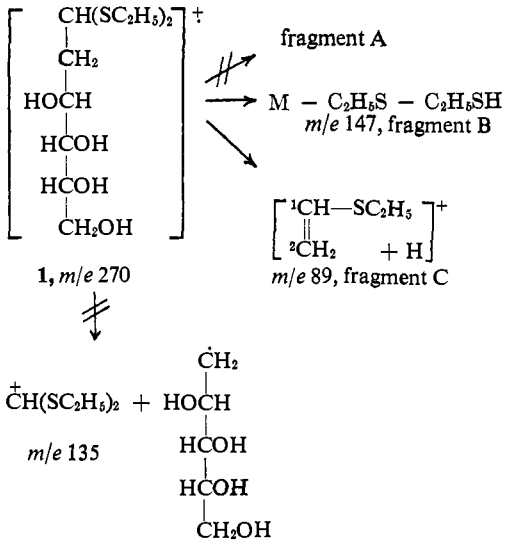
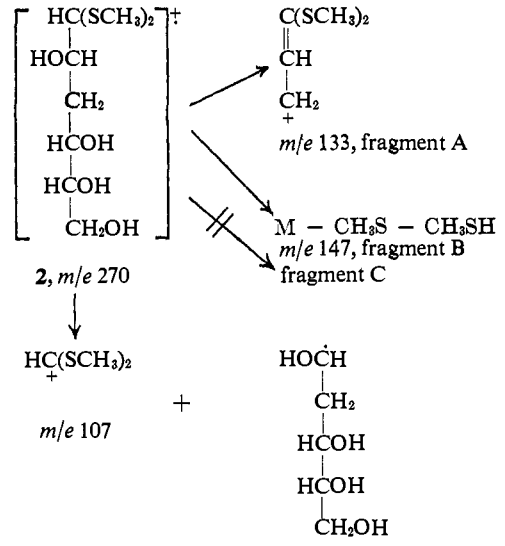
Scheme I



Fragments A and B and the dimethyl dithioacetal fragment (*m/e* 107) are present in the mass spectrum of 3-deoxy-D-*arabino*-hexose dimethyl dithioacetal (**2**); fragment C does not form (Scheme II).

Scheme II



Fragments A, B, and C and the *m/e* 135 fragment (base peak, 100% relative intensity) are present in the mass spectra of compounds **3**, **4**, and **5**. The molecular ion and fragment B from compounds **3** and **4** are found 16 mass units lower than the corresponding fragments[2] from D-glucose diethyl dithioacetal. Pertinent data on the monodeoxyaldose diethyl dithioacetals are summarized in Table I. The major differences in the mass spectra of the deoxy sugars listed in Table I can be explained in terms of the apparent reluctance of their molecular ions to fragment bonds which produce primary radicals. Thus, the formation of an *m/e* 135 fragment from compound **1** (Scheme I) would leave a primary radical on C-2; cleavage of C-2–C-3 in compound **2** to produce fragment C would leave a primary radical on C-3. The presence of a deoxy function on C-5 or C-6 does not affect the formation of these fragments, but only changes the *m/e* location of the molecular ion and fragment B; this is probably due to the remote position of the deoxy function with respect to the most susceptible bond cleavage sites.

Table I. Mass Spectra of Diethyl Dithioacetals of Monodeoxy Sugars

Compound	$M\cdot^+$	$CH(SC_2H_5)_2$	A	B	C
	m/e				
D-Glucose[c]	286	135	177	163	105
2-Deoxyhexose (**1**)[c]	270	...[a]	...[a]	147	89
3-Deoxyhexose (**2**)[b]	242[b]	105[b]	133[b]	147	...[a]
5-Deoxyhexose (**3**)	270	135	177	147	105
6-Deoxyhexose (**4**)[c]	270	135	177	147	105
5-Deoxypentose (**6**)	240	135	177	117	105

[a] The dash indicates that the fragment is either absent or of minor relative intensity. [b] Dimethyl dithioacetal. [c] See ref 2.

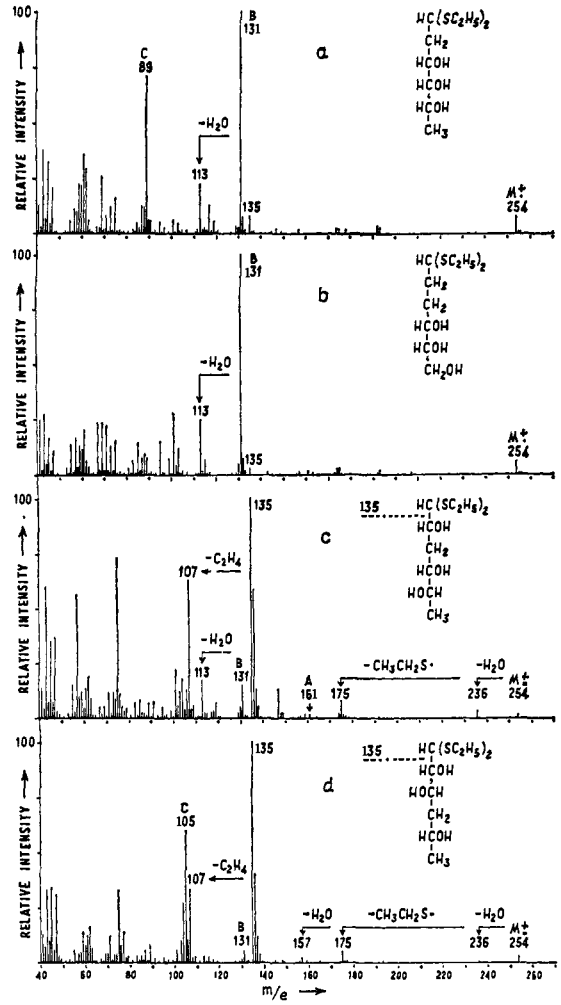


Figure 1. Mass spectra of (a) 2,6-dideoxy-D-*ribo*-hexose diethyl dithioacetal (**8**), (b) 2,3-dideoxy-D-*erythro*-hexose diethyl dithioacetal (**7**), (c) 3,6-dideoxy-L-*lyxo*-hexose diethyl dithioacetal (**9**), and (d) 4,6-dideoxy-D-*xylo*-hexose diethyl dithioacetal (**10**). The losses of H_2O, C_2H_4, and C_2H_5S shown by the arrows are indicated by the presence of appropriate metastable ion peaks.

The mass spectra of dideoxyhexose diethyl dithioacetals **7**–**10** are shown in Figure 1 and are summarized in Table II. These mass spectra show characteristics similar to those discussed for the compounds in Table I.

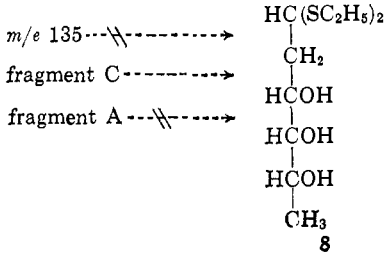
The reluctance to form primary radicals upon electron impact can be seen in the mass spectra of 2,6-dideoxy-D-*ribo*-hexose diethyl dithioacetal (**8**, Figure 1a) and 2,3-dideoxy-D-*erythro*-hexose diethyl dithioacetal (**7**, Figure 1b). As expected for this class of deoxy sugars, the relative intensity of the dithioacetal frag-

Table II. Mass Spectra of Dideoxyhexose Diethyl Dithioacetals

Compound	$M\cdot^+$	$+CH(SC_2H_5)_2$	A	B	C
		m/e			
2,6-Dideoxy (**8**)	254	...[a]	...[a]	131	89
2,3-Dideoxy (**7**)	254	...[a]	...[a]	131	...[a]
3,6-Dideoxy (**9**)	254	135	161	131	...[a]
4,6-Dideoxy (**10**)	254	135	...[a]	131	105

[a] The dash indicates that the fragment is either absent or of minor relative intensity.

ment, *m/e* 135, is only 8 and 3% for **8** and **7**, respectively. Fragment C (71% relative intensity) is found at *m/e* 89 in Figure 1a, as it was in the mass spectrum of compound **1**, due to the presence of the 2-deoxy



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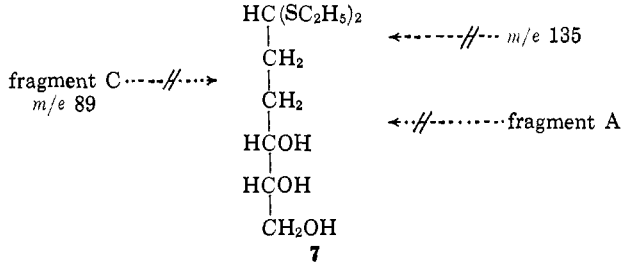
function. It is relatively insignificant in the mass spectrum of compound **7** (Figure 1b), as it was in the mass spectrum of compound **2**, due to the presence of the 3-deoxy function. The presence or absence of fragment C differentiates the isomers **8** and **7** and reflects the relative instability of the primary radical left on C-3 in compound **7**. The base peak for com-



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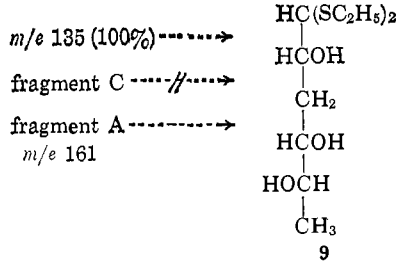
pound **7** and **8** is at *m/e* 131 (fragment B).

The utility of the absence of fragment C to recognize 3-deoxy sugars is also evident in the mass spectrum of 3,6-dideoxy-L-*lyxo*-hexose diethyl dithioacetal (**9**, Figure 1c, Table II). The base peak in the mass spectrum is



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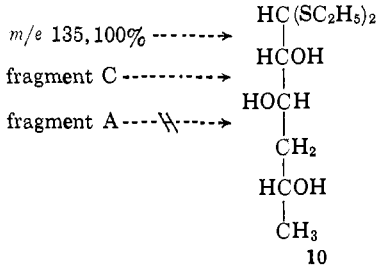
due to the dithioacetal fragment, *m/e* 135. Fragment A, *m/e* 161, is of low relative intensity, but the assignment is supported by the shift of the corresponding fragment in the spectrum of 3,6-dideoxy-L-*lyxo*-hexose di-*n*-propyl dithioacetal (spectrum not shown). Fragment A is of low intensity also in the mass spectrum of compound **2**.

A characteristic feature of the mass spectra of 4-deoxy sugars is that fragment C becomes intense once again but fragment A is not formed. This is illustrated in the mass spectrum of 4,6-dideoxy-D-*xylo*-hexose diethyl dithioacetal (**10**, Figure 1d). Cleavage of the C-3–C-4 bond, necessary for the formation of



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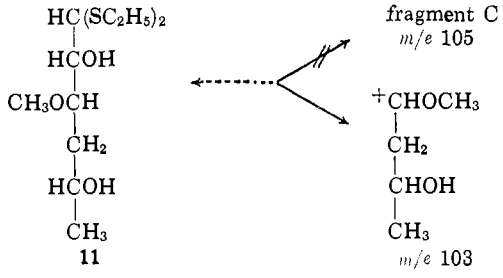
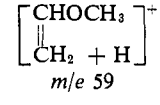
fragment A, would result in the unfavorable situation of a primary radical at C-4.

Chalcose diethyl dithioacetal (**11**), which is similar to compound **10** except for the presence of a methoxyl function at C-3, fragments essentially in the same manner. Cleavage of the C-2–C-3 bond could lead to fragment C or to a fragment at *m/e* 103 depending on the preference to retain the charge. Since fragment C is not seen in the mass spectrum of compound **11** (Figure



11

2a) it appears that the presence of the C-3 methoxyl function favors the formation of the *m/e* 103 charged fragment. The mass spectrum[2] of 3-*O*-methyl-D-glucose diethyl dithioacetal also shows a decreased relative intensity of fragment C and the presence of fragments resulting from C-2–C-3 bond cleavage with charge retention on C-3. The fragment at *m/e* 59 in the mass spectrum of compound **11** (Figure 2a) retains



m/e 59

C-3 and C-4 and incorporates a rearranged proton. Analogous fragments are found at 16 mass units higher, *m/e* 75, in the mass spectra[2] of 3-*O*-methyl-D-glucose diethyl dithioacetal and of partially methylated monosaccharides.[50]

Mycinose diethyl dithioacetal (**5**, Figure 2b) contains methoxyl functions at C-2 and C-3. The presence of substituent on C-3 can be deduced from the presence of fragment A at *m/e* 191 and a fragment at *m/e* 75. The

fragment A, *m/e* 191 *m/e* 75

(50) N. K. Kochetkov, N. S. Wulfson, O. S. Chizlov, and B. M. Zolotarev, *Tetrahedron*, **19**, 2209 (1963).

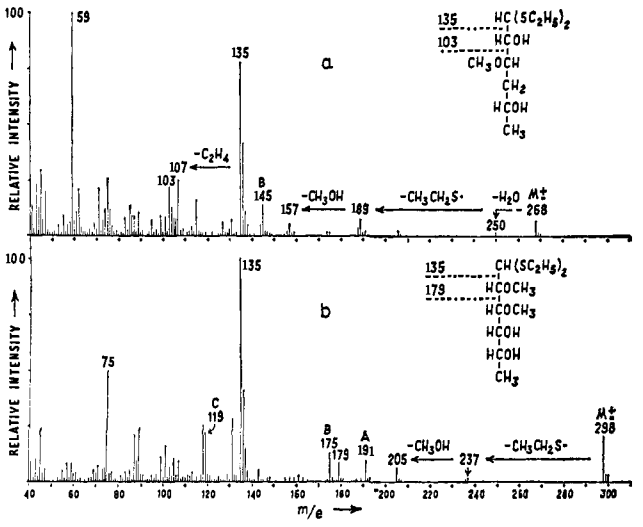
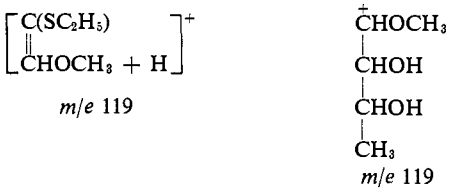


Figure 2. Mass spectra of (a) 4,6-dideoxy-3-*O*-methyl-D-*xylo*-hexose diethyl dithioacetal (**11**), and (b) 6-deoxy-2,3-di-*O*-methyl-D-allose diethyl dithioacetal. The losses of H_2O, CH_3OH, C_2H_4, and C_2H_5S shown by the arrows are supported by appropriate metastable ion peaks.

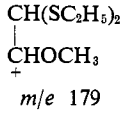
fragment at *m/e* 119 which results from C-2–C-3 bond cleavage could contain only one or both of the



m/e 119

m/e 119

two possible charged species shown. The peak at *m/e* 179 and the fragmentation $M\cdot^+ \rightarrow M - S_2H_5S$



m/e 179

$\rightarrow M - C_2H_5S - CH_3OH$ are also characteristic of the mass spectrum[2] of 2-*O*-methyl-D-glucose diethyl dithioacetal. The fragment at *m/e* 131 (Figure 2b) as well as the fragment at *m/e* 101 in the mass spectrum of **11** (Figure 2a) are formed by loss of C-1, followed by elimination of methanol according to the equation

$$M^+ \longrightarrow M - CH(SC_2H_5)_2 - CH_3OH$$

m/e 131 (Figure 2b)
m/e 101 (Figure 2a)

The mass spectrum of 6-deoxy-5-*C*-methyl-D-*xylo*-hexose diethyl dithioacetal (**12**) is shown in Figure 3. The 5-methyl substituent and the 6-deoxy function do not influence the formation of fragments A, B, C, or *m/e* 135.

Experimental Section

Mass Spectra. The mass spectra were determined with an Atlas CH4 mass spectrometer at an ionizing potential of 70 ev and an ionizing current of 18 μa. The samples were vaporized into an enameled reservoir and leaked into an electron-impact source through a leak in a gold leaf; the temperature of the ion source and reservoir was 140°. The mass spectrometer was purchased by Wayne State University under Grant CP-1474 from the National Science Foundation.

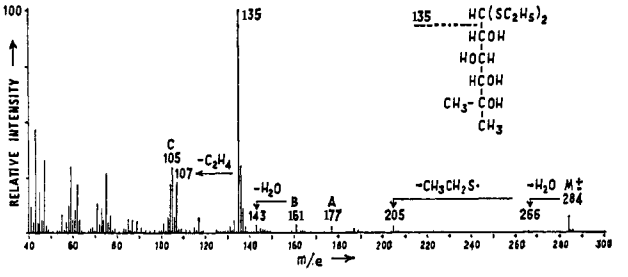


Figure 3. Mass spectrum of 6-deoxy-5-*C*-methyl-D-*xylo*-hexose (**12**) diethyl dithioacetal. The losses of H_2O, C_2H_4, and C_2H_5S shown by the arrows are supported by the appropriate metastable ion peaks.

General. Melting points were determined with a Fisher-Johns type of apparatus and are uncorrected. Infrared spectra were recorded with a Beckman IR-9 spectrometer. Paper chromatography was carried out on Whatman No. 1 paper in *n*-butyl alcohol–ethanol (3:1:1) (solvent A).

Spots were detected with the alkaline silver nitrate reagent[51] and with the bromine–methyl orange spray[52] for dithioacetals. Thin layer chromatography[11] was carried out using silica gel H (E. Merck, Darmstadt, Germany) with the solvent systems chloroform–methanol (100:15) for monodeoxyaldose dialkyl dithioacetals and chloroform–2,2,4-trimethylpentane–methanol (50:15:5) for dideoxy- and branched-chain aldose dialkyl dithioacetals. Spots were detected by the acid permanganate spray[53] and with the bromine–methyl orange spray.[52]

All the dithioacetals reported in this investigation had infrared spectra which were compatible with their structures and were chromatographically homogeneous substances.

Preparation of the Dithioacetals. Small amounts (20–100 mg) of the aldose were dissolved in 0.2 ml of concentrated hydrochloric acid and stirred with 0.2 ml of ethanethiol at 0° for 15 min. The mixtures were then neutralized with lead carbonate and diluted with ethanol containing a little water. In the case of glycosides or isopropylidene derivatives the samples were stirred with the acid at room temperature for 5 min prior to the addition of ethanethiol. The mixtures were then cooled, stirred for 15 min, and processed. Evaporation of the ethanolic solutions usually afforded the crude dithioacetal which was examined on thin layer chromatograms. Small amounts of by-products were usually formed and the crude substances were therefore separated by preparative thin layer chromatography and afforded crystalline products in the majority of cases. Yields were satisfactory.

The following new dithioacetals were prepared as described above: (a, from free deoxy sugars) 6-deoxy-2,3-di-*O*-methyl-D-allose diethyl dithioacetal (**5**, liquid), 2,6-dideoxy-D-*ribo*-hexose diethyl dithioacetal (**8**, mp 40–41°, R_f 0.84, A), 3,6-dideoxy-L-*lyxo*-hexose diethyl dithioacetal (**9**, liquid), 3,6-dideoxy-L-*lyxo*-hexose di-*n*-propyl dithioacetal (liquid); (b, from 1,2-*O*-isopropylidene derivatives) 5-deoxy-D-*xylo*-hexose diethyl dithioacetal (**3**, mp 56–57°, R_f 0.87, A), 6-deoxy-5-*O*-methyl-D-*xylo*-hexose diethyl dithioacetal (**13**, low-melting crystals, R_f 0.81, A); (c, from glycosides) 2,3-dideoxy-D-*erythro*-hexose diethyl dithioacetal (**7**, liquid, R_f 0.8, A), 4.6-dideoxy-D-*xylo*-hexose diethyl dithioacetal (**10**, mp 101–102°, R_f 0.95, A), 4,6-dideoxy-3-*O*-methyl-D-*xylo*-hexose diethyl dithioacetal (**11**, mp 51–52°).

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(51) W. E. Trevelyan, D. P. Proctor, and J. S. Harrison, *Nature*, **166**, 444 (1950).
(52) F. Weygand, H. J. Bestmann, and H. Ziemann, *Chem. Ber.*, **91**, 1040 (1958).
(53) J. E. G. Barnett and P. W. Kent, *Nature*, **192**, 556 (1961).