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Thiosugars. XV.[1] Further Contribution on Anomalous High Reactivity of Secondary Methanesulfonic Esters in Thiosugars

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1,2-Di-S-acetyl-3,4,6-tri-O-acetyl-β-D-mannopyranose (X) and methyl 1,2-dithio-2-S-methyl-3,4,6-tri-O-acetyl-β-D-mannopyranoside (XI) were synthesized using an unequivocal route. A detailed comparison of the physical constants and NMR data of X with those of 1,2-di-S-acetyl-3,4,6-tri-O-acetyl-β-D-mannopyranose, which had been reported from our laboratory (H. Nakamura, S. Tejima, M. Akagi, *Chem. Pharm. Bull.* (Tokyo), **14**, 648 (1966).) clarified that the previous compound (VI) was the α-anomer of X. The corresponding methyl 1,2-dithio-2-S-methyl-3,4,6-tri-O-acetyl-α-D-mannopyranoside (VII) was prepared from VI.

Reaction of potassium thiolacetate with 2-O-mesyl-3,4,6-tri-O-acetyl-β-D-glucopyranosyl N,N-dimethyldithiocarbamate (XVI) afforded three products (XVII, XVIII, VIII) in proportions of 5:2:3. The structure of the main product (XVII), which had been assigned as 1,2-dithio-1-N,N-dimethyldithiocarbamoyl-2-S-acetyl-3,4,6-tri-O-acetyl-β-D-mannopyranose (S. Ishiguro, S. Tejima, *Chem. Pharm. Bull.* (Tokyo), **15**, 1478 (1967).), was corrected to 1,2-dithio-1-S-acetyl-2-N,N-dimethyldithiocarbamoyl-3,4,6-tri-O-acetyl-β-D-mannopyranose. The by-products, XVIII and VIII, were assigned as 2-N,N-dimethyldithiocarbamoyl-2-deoxy-3,4,6-tri-O-acetyl-D-*arabino*-hexopyranose-1-ene and 1,2-dideoxy-1,2-trithiocarbonyl-3,4,6-tri-O-acetyl-β-D-mannopyranose, respectively.

The reaction mechanisms on the facile substitution of secondary mesyl in thiosugars, which may be more reasonable than before, were discussed.

Since 1966 our laboratory have reported on an anomalous high reactivity of secondary methanesulfonic (mesyl) esters in thiosugars on nucleophilic substitution.[1,3] In contrast with the well-known substitution of secondary mesyl in carbohydrates under boiling N,N-dimethylformamide, which usually involves isomerization at the substitution center, our reaction occurs under very mild condition. Namely, it proceeds under reflux in acetone–ethanol for several minutes which is characteristic of our reaction. The fact prompts us to assume that a sort of anchimeric effect participates, presumably, during the course of the reaction. Up to the preceding paper the authors have presented some reaction mechanisms which involve the participation of sulfur or oxygen. However, additional accumulations of experimental data made us to settle different mechanisms, which may be more reasonable, and the rectify the erroneous structural assignments of the two compounds which had been reported in the previous papers.[3a,c] The present paper will describe full details of the work.

Reaction of one molar equivalent of potassium methyl or ethylxanthate upon 2-O-mesyl-3,4,6-tri-O-acetyl-α-D-glucopyranosyl bromide (I) at low temperature afforded the corresponding 2-O-mesyl-3,4,6-tri-O-acetyl-β-D-glucopyranosyl methyl or ethylxanthate (II or III). On the one hand, mesyl was no longer detectable in the resulting product (IV or V) when the reaction was carried out under the presence of two molars of the same reagent at elevated tem-

1) Part XIV: S. Ishiguro and S. Tejima, *Chem. Pharm. Bull.* (Tokyo), **16**, 2040 (1968).
2) Location: *Kita-12-jo, Nishi-6-chome, Sapporo.*
3) *a*) H. Nakamura, S. Tejima and M. Akagi, *Chem. Pharm. Bull.* (Tokyo), **14**, 648 (1966). b) K. Araki and S. Tejima, *Chem. Pharm. Bull.* (Tokyo), **14**, 1303 (1966). *c*) S. Ishiguro and S. Tejima, *Chem. Pharm. Bull.* (Tokyo), **15**, 1478 (1967).

perature, while it showed a strong ultraviolet (UV) absorption at 275 mμ. Both values of the absorbances were 18000, almost double of those of glycosyl monoxanthates (10000), which suggest that IV and V contain two alkyldithiocarbonyl radicals per molecule. In case of methylxanthate the resulting triacetate (IV) crystallized contaminating a small amount of by-product. The latter was less soluble and crystallized faster than IV, so it was easily isolated in pure state from IV. Though the exact structure is not yet completely elucidated the authors assume to be one isomer of diglycosyl sulfides. In ethyl, while the corresponding triacetate was a sirup, deacetylated product (V) crystallized which also gave crystalline monobenzylidene compound. The position of the condensation may be, presumably, between C_4 and C_6.

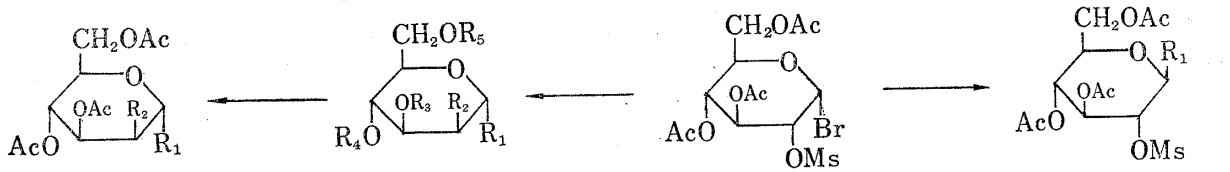
It is quite significant to point out that the secondary mesyl at C_2 in glucopyranose is susceptible to nucleophilic substitution by potassium alkylxanthates under very mild condition. The phenomenon is in accordance with that caused by potassium thiolacetate as reported in the previous paper.[3a)]

Structural assignment of IV was carried out by derivation of it to 1,2-dithiomethyl compound (VII) *via* 1,2-dithioacetate (VI). Namely, treatment of IV with acetic anhydride in pyridine at room temperature overnight gave dithioacetate (VI), mp 154—156°, $[\alpha]_D^{20}$ +32°, in 80% yield. Successive deacetylation of VI with sodium methoxide, treatment of the resulting sodium mercaptide with methyl iodide, and finally reacetylation of the resulting material gave crystals (VII), mp 95—96°, $[\alpha]_D^{20}$ +101°, in 82% yield. The nuclear mangetic resonance (NMR) spectroscopy showed the presence of three acetyls and two thiomethyls. The elemental analyses were in good agreement with that of tri-O-acetyl dithiomethyl hexose, $C_{14}H_{22}O_7S_2$. The coupling constant of H_2–H_3 was determined using double resonance method. The small value (3.5 cps) suggested that the proton at C_2 was equatorial against the original axial proton at C_3. Thus the configuration of VII wasassigned as D-*manno*.

It is very important to describe that dithioacetate (VI) is indistinguishable with an authentic sample which has been assigned in our laboratory as 1,2-di-S-acetyl-1,2,-dithio-3,4,6-tri-O-acetyl-β-D-mannopyranose[3a)] by mixed melting ponit and infrared (IR) spectroscopy. Namely, in 1966 our laboratory isolated unexpectedly glycosyl dithioacetate, mp 155—156°, $[\alpha]_D^{20}$ +33.3°, from a reaction mixture of potassium thiolacetate and I. The same product was also obtainable, instead of I, from 2-O-mesyl-3,4,6-tri-O-acetyl-β-D-glucopyranosyl ethylxanthate (III) or 1-S-acetyl-1-thio-2-O-mesyl-3,4,6-tri-O-acetyl-β-D-glucopyranose (XII).

The previous structure assignment was based on the data as follows. Firstly, reductive desulfurization gave 1,5-anhydro-2-deoxy-3,4,6-tri-O-acetyl-D-*arabino*-hexitol. Secondary, an aqueous solution of the deacetylated product showed a mutarotation, −109.3°→−34°, which suggested the β-configuration of thioacetyl at C_1. Thirdly, in NMR determination the anomeric proton appeared as a doublet at τ 4.04 with a coupling constant, $J_{1,2}$=2.5, which indicated equatorial–axial orientation of H_2 to H_1.

However, subsequent repetition of the rotatory measurement of the deacetylated product became clarify that it produced several complex products in course of time which was checked



VI : R_1=R_2=SAc
VII : R_1=R_2=SMe

IV : R_1=R_2=S·CS·OMe
R_3=R_4=R_5=Ac
V : R_1=R_2=S·CS·OEt
R_3=R_4=R_5=H

I

II : R_1=S·CS·OMe
III : R_1=S·CS·OEt

Chart 1

by thin-layer chromatography (TLC). Therefore, the value of the mutarotation not always suggests that it depends on the simple anomerization of β to α. Thus if the configuration of the thioacetyl at C_1 were not β we cannot exclude other configuration on the previous dithioacetate or VI.

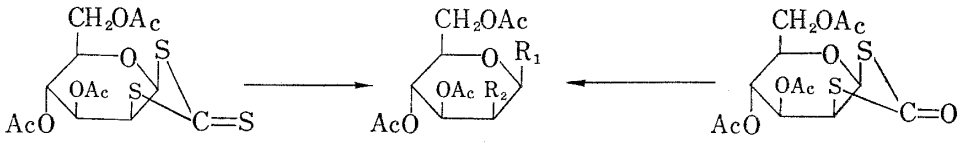
From the reason mentioned above we had a necessity to synthesize 1,2-di-S-acetyl-3,4,6-tri-O-acetyl-β-D-mannopyranose (X) using an unequivocal route. Treatment of 1,2-dideoxy-1,2-trithiocarbonyl-3,4,6-tri-O-acetyl-β-D-mannopyranose (VIII)[1] with sodium methoxide in methanol and successive acetylation gave crystals (X), mp 122—123°, $[\alpha]_D^{20}$ +25.7°, in 66% yield. The product was also obtainable in 96% yield starting from 1,2-dideoxy-1,2-dithiocarbonyl-3,4,6-tri-O-acetyl-β-D-mannopyranose (IX)[3b] with the similar procedure. However, the product was not identical with VI.

Nevertheless, X may be β-configuration similarly with that of the starting material (VIII or IX), because the preparative method rarely involves a chance of the Walden inversion. The small coupling constants of $J_{1,2}$=2.5 and $J_{2,3}$=3.3 suggest the presence of a pair of equatorial-axial orientations between H_2–H_1 and H_2–H_3 which supports the validity of the structure. Therefore, X was assigned as 1,2-dithio-1,2-di-S-acetyl-3,4,6-tri-O-acetyl-β-D-mannopyranose. The product did not anomerize when it was refluxed with potassium thiolacetate in acetone–ethanol.

Now, to our reglets, the authors have to recognize that the previous structural assignment of dithioacetate[3a] was erroneous.

Deacetylation of X and sequential methylation gave dithiomethyl derivative (XI), mp 154—156°, $[\alpha]_D^{20}$ −20°, in 76% yield. In NMR determination three O-acetyls and two S-methyls were indicated as independent singlets. The anomeric proton appeared at τ 5.18 with coupling constant, $J_{1,2}$=2.5. The small value, $J_{2,3}$=3.5, was reasonable as expected from the D-*manno* configuration. Thus XI was assigned as methyl 1,2-dithio-2-S-methyl-3,4,6-tri-O-acetyl-β-D-mannopyranoside.

As mentioned in the initial parts of this work, another dithiomethyl derivative (VII) also had D-*manno* configuration. The authors now conclude that VI and VII may be α-anomers of X and XI, respectively, because of the more positive specific rotations. Therefore, VI and VII were assigned as 1,2-dithio-1,2-di-S-acetyl-3,4,6-tri-O-acetyl-α-D-mannopyranose and methyl 1,2-dithio-2-S-methyl-3,4,6-tri-O-acetyl-α-D-mannopyranoside, respectively. Concurrently, the structure of IV, a precursor of VI, was assigned as 1,2-dithio-2-methoxydithiocarbonyl-3,4,6-tri-O-acetyl-α-D-mannopyranosyl methylxanthate. Further, owing to the structural similarity of V to IV, V must be 1,2-dithio-2-ethoxydithiocarbonyl-α-D-mannopyranosyl ethylxanthate.



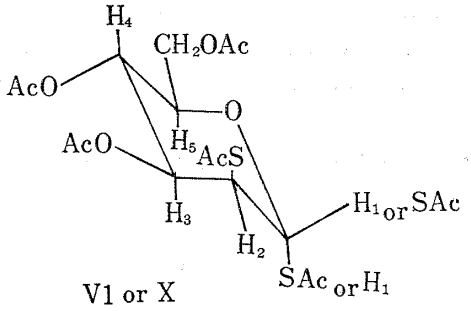
VIII X : R_1=R_2=SAc XI : R_1=R_2=SMe IX

Chart 2

To make facile understanding of the relation of the two anomeric pairs the authors will indicate the physical constants in Table I.

The authors, in the next step, carried out two additional experiments to confirm further the high reactivity of the secondary mesyl on nucleophiles having sulfur and to elucidate the reaction mechanism.

A combined mixture of 1-S-acetyl-1-thio-2-O-mesyl-3,4,6-tri-O-acetyl-β-D-glucopyranose (XII)[3a] and sodium N,N-dimethyldithiocarbamate in acetone–ethanol was refluxed for ten



VI or X

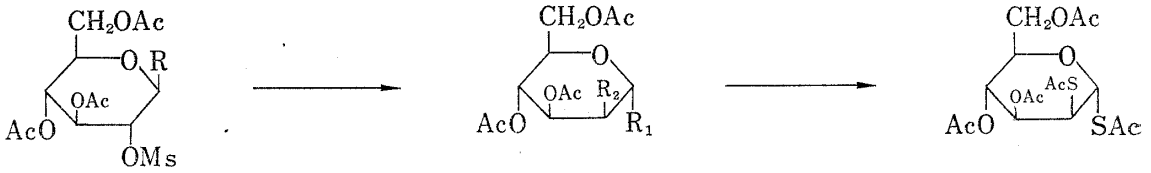
TABLE I.

	mp.	$[\alpha]_D$	Analysis (%) C Calcd	C Found	H Calcd	H Found	S Calcd	S Found	Chemical shifts τ H_1	H_2	Coupling constants cps $J_{H_1-H_2}$	$J_{H_2-H_3}$
VI	155—156	+ 33.3	45.48	45.67	5.25	5.45	15.18	14.98	4.04 (d)	5.75 (q)	2.5	3.5
X	122—123	+ 25.7	45.48	45.54	5.25	5.16	15.18	15.13	4.21 (d)	5.53 (q)	2.5	3.3
VII	95— 96	+100.5	45.88	46.11	6.05	6.06	17.50	17.43	4.65	6.59 (q)		3—4
XI	154—156	− 20.0	45.88	45.83	6.05	6.03	17.50	17.36	5.18 (d)	6.47 (q)	2.5	3.5

minutes, from which crystals (XIII), mp 124—125°, $[\alpha]_D^{20}$ −25.4°, were isolated in 55% yield. The IR of XIII suggested the presence of thioacetyl and dithiocarbamate, while showed neither absorption near 7.50 nor 8.43 μ corresponding to mesyl. The NMR revealed a singlet (3H) at τ 7.60 (thioacetyl) and three singlets at 7.90, 7.94, 8.02 which come from O-acetyls. The small coupling constant of $J_{2,3}$=2.5 suggested D-*manno* configuration. Reduction of XIII with sodium in liqiud ammonia and successive acetylation of the resulting product gave VI which was the isolated sole product. Thus the isolation of α-dithioacetate (VI) from XIII suggests the configuration of thioacetyl in C_1 is α.

It is quite significant to describe that the similar product (XIII) was also obtainable from a following series of experiments: stirring of 2-O-mesyl-3,4,6-tri-O-acetyl-β-D-glucopyranosyl methylxanthate (II) with sodium N,N-dimethyldithiocarbamate, sequential acetylation, and silica gel chromatography. Therefore, we assume that substitution of mesyl and introduction of methoxydithiocarbonyl occur to form unisolated intermediate (XIV) in the initial stage of the reaction, then follows decomposition of methoxydithiocarbonyl to thioacetyl.

Similarly, stirring of equimolar of 2-O-mesyl-3,4,6-tri-O-acetyl-β-D-glucopyranosyl ethylxanthate (III) and potassium thiolacetate in methanol at 40° gave a colorless sirup (XV), $[\alpha]_D^{20}$ −7°, in 29% yield after silica gel chromatography. The product showed UV absorption corresponding to monoglycosyl xanthate, suggested the presence of one thioacetyl and three O-acetyls by NMR, and afforded crystals, mp 155—156°, $[\alpha]_D^{20}$ +34°, which was indistinguishable with dithioacetate (VI), after alkaline degradation of XV and successive acetylation. The product (VI) was also obtainable when XV was refluxed with an additional amount of potassium thiolacetate in acetone.



VI

XII : R=SAc
II : R=S·CS·OMe
III : R=S·CS·OEt

XIII : R_1=S·CS·NMe_2, R_2=SAc
XIV : R_1=S·CS·NMe_2, R_2=S·CS·OMe
XV : R_1=SAc, R_2=S·CS·OEt

Chart 3

As mentioned in the initial parts of this work, our laboratory have reported[3a] an isolation of VI from a reaction mixture of III and potassium thiolacetate and presented a reaction mechanism at that time, while we could not isolate the intermediates which support of it. Now, we are able to claim that XV is undoubtedly an intermediate of the reaction. Therefore, the authors wish to represent another mechanism which may be more reasonable one than before.

In case of 2-O-mesyl glucopyranosyl alkylxanthates or thioacetates intramolecular back-side attack of either sulfur, thiocarbonyl, or carbonyl occurs the elimination of mesyl and formation of the corresponding episulfonium, dithiocarbonium, or monothiocarbonium in the initial stage of the substitution. Then nucleophiles such as potassium thiolacetate, alkyl-xanthates, or sodium N,N-dimethyldithiocarbamate attack from the bottom of C_1 to form products having α-configuration, during which scission of the intermediate and migration of the substituent in C_1 to C_2 take place simultaneously.

Therefore, it may be reasonable to assign XIII, XIV, and XV as 1,2-dithio-2-S-acetyl-3,4,6-tri-O-acetyl-α-D-mannopyranosyl N,N-dimethyldithiocarbamate, 1,2-dithio-2-S-methoxydithiocarbonyl-3,4,6-tri-O-acetyl-α-D-mannopyranosyl N,N-dimethyldithiocarbamate, and 1,2-dithio-1-S-acetyl-2-S-ethoxydithiocarbonyl-3,4,6-tri-O-acetyl-α-D-mannopyranose, respectively. The authors speculate on the formation of VI from XV that it depends on the Δ 2 effect, namely, the bulky ethoxydithiocarbonyl at C_2 in D-*manno* configuration makes XV to be highly susceptible to substitution involving an anchimeric effect from thioacetyl at C_1. To make facile understanding the authors will indicate the mechanism in Chart 4.

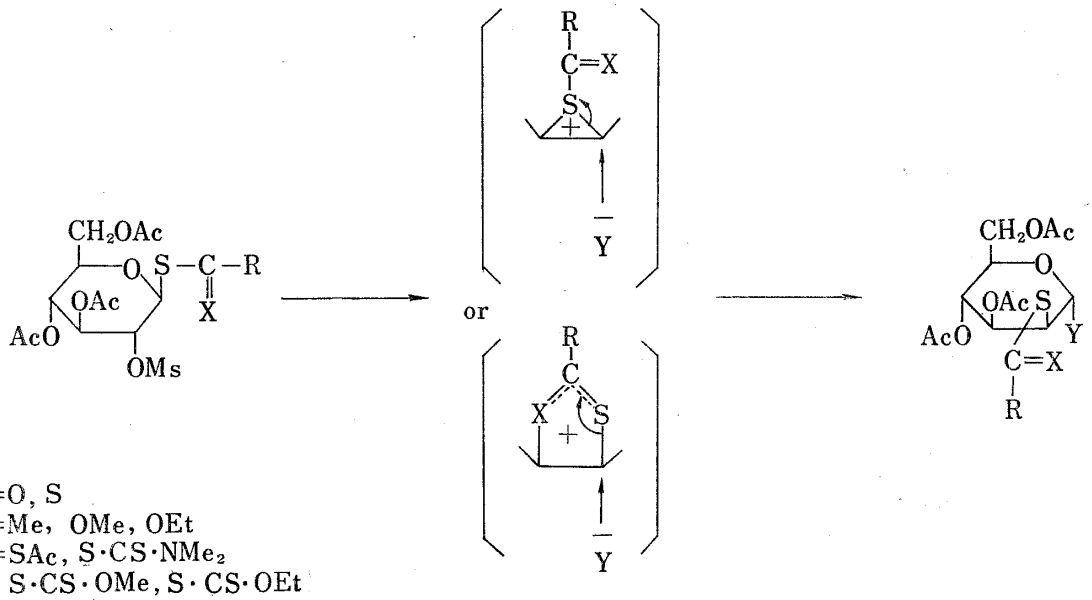


Chart 4

On the one hand, substitution of mesyl in 2-O-mesyl-3,4,6-tri-O-acetyl-β-D-glucopyranosyl N,N-dimethyldithiocarbamate (XVI) with potassium thiolacetate appears to proceed *via* a route with a slight modification. In the previous paper[3c] the authors have reported that reflux of XVI with potassium thiolacetate in acetone–ethanol for thirty minutes afforded crystals in 30 to 40% yield and assigned as 2-S-acetyl-2-thio-3,4,6-tri-O-acetyl-β-D-mannopyranosyl N,N-dimethyldithiocarbamate.

However, the repetition of the reaction clarified that two additional minor products were identified simultaneously by TLC. The authors were able to isolate the products in pure state using silica gel chromatography and assigned as 2-N,N-dimethyldithiocarbamoyl-2-deoxy-3,4,6-tri-O-acetyl-D-*arabino*-hexopyranose-1-ene (XVIII)[3c] and 1,2-dideoxy-1,2-trithiocar-

bonyl-3,4,6-tri-O-acetyl-β-D-mannopyranose (VIII)[1] by mixed melting point, IR, and TLC with authentic samples.

The main product (XVII), mp 182—183°, $[\alpha]_D^{20}$ +67°, was treated with sodium in liquid ammonia and then acetylated to afford crystals in 57% yield. The product was assigned as 1,2-dithio-1,2-di-S-acetyl-3,4,6-tri-O-acetyl-β-D-mannopyranose (X) by mixed melting point, IR, and TLC with an authentic sample. Therfore, the configuration of C_1 in XVII is β. In order to determine the exact positions of the two substituents we made following consideration.

Among the four plausible structures 1,2-dithio-1-S-acetyl-2-N,N-dimethyldithiocarbamoyl- and 1,2-dithio-1-N,N-dimethyldithiocarbamoyl-2-S-acetyl-3,4,6-tri-O-acetyl-α-D-mannopyranose were excluded owing to the α-configuration at C_1. Therefore, the remainder is 1,2-dithio-1-S-acetyl-2-N,N-dimethyldithiocarbamoyl- and 1,2-dithio-1-N,N-dimethyldithiocarbamoyl-2-S-acetyl-3,4,6-tri-O-acetyl-β-D-mannopyranose. If XVII were the latter as reported in the previous paper[3c] the structure is consistent with the β-anomer of XIII, and thus, the specific rotation of XVII should reflect more negative value than that of XIII. However, as described in the initial parts of this work XIII had a specific rotation, −25.4°, while XVII showed a positive one, +67°. Therefore, sturcture having carbamoyl at C_1 with β-configuration should be excluded. Consequently it is reasonable to assign XVII as 1,2-dithio-1-S-acetyl-2-N,N-dimethyldithiocarbamoyl-3,4,6-tri-O-acetyl-β-D-mannopyranose and the authors wish to rectify the previous assignment. The approximate proportions of formation between XVII, XVIII, and VIII were 5:2:3.

Methyl 1,2-dithio-2-N,N-dimethyldithiocarbamoyl-3,4,6-tri-O-acetyl-β-D-mannopyranoside (XIX), mp 108—110°, $[\alpha]_D^{20}$ +35.3°, was prepared starting from XVIII by usual method. Reduction of XVIII with sodium in liquid ammonia, successive acetylation and silica gel chromatography gave a yellow sirup (XX), $[\alpha]_D^{20}$ +53°, which was assigned as 2-S-acetyl-2-

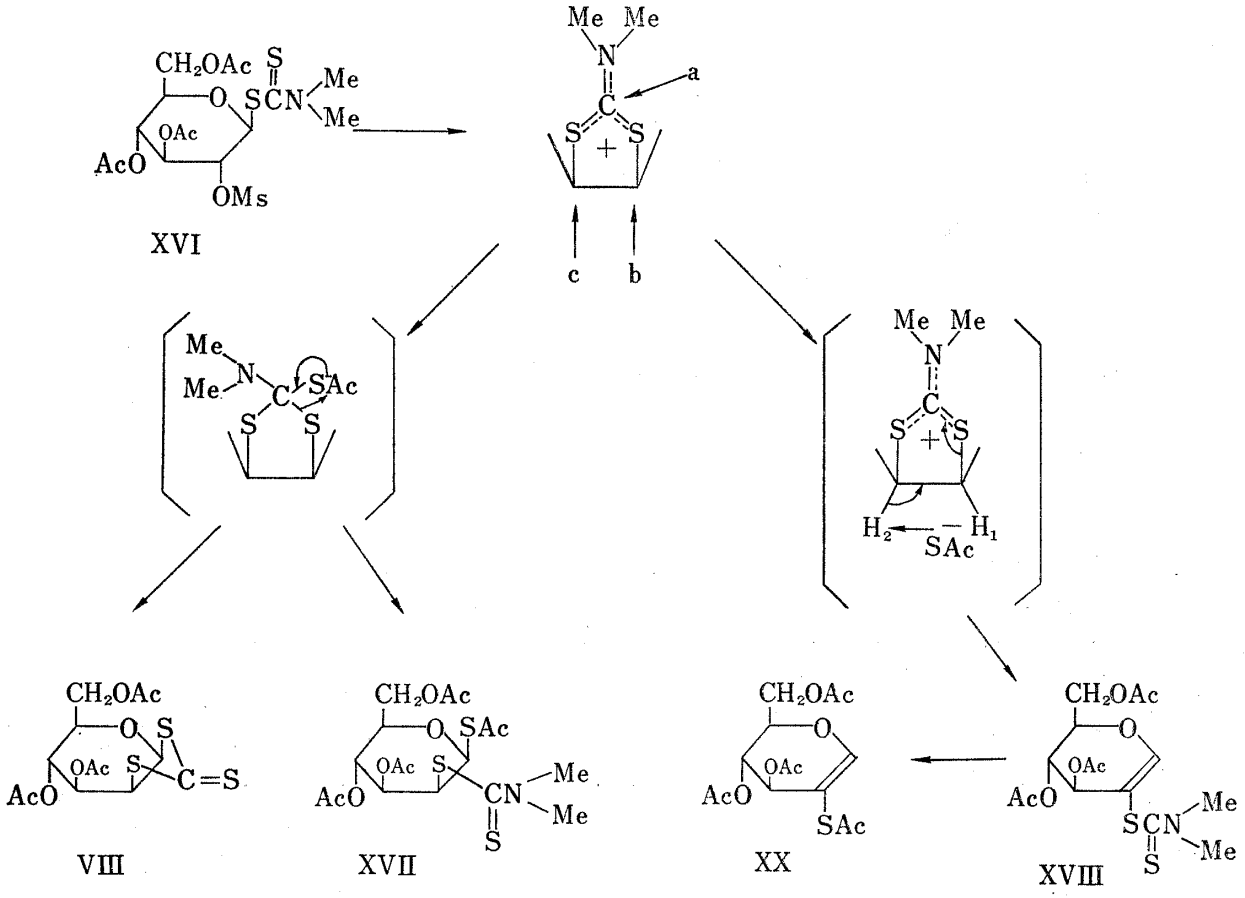


Chart 5

deoxy-3,4,6-tri-O-acetyl-D-*arabino*-hexopyranose-1-ene. The NMR and IR data supported the assigned structures.

It may be concluded that in the formation of XVII from XVI the initial stage may proceed with the analogous mechanism which was described in Chart 4. Namely, formation of five-membered intermediate may be preponderant under the influence of an anchimeric effect from the substituent at C_1. In case of 2-O-mesyl-D-glucosyl N,N-dimethyldithiocarbamate (XVI) the resulting intermediate is stable and we are able to isolate it in crystalline state as mentioned in the previous papers.[1,4] In the intermediate, three routes (a, b, c) are conceivable on the successive nucleophilic attack as will be indicated in Chart 5. Among which exo-carbon (a) is the most plausible. Because the formations of XVII and VIII, which carry the similar β-configurations with that of the intermediate, and isolation of XVIII suggest the validity of this consideration.

On the other hand, 2-O-mesyl-D-glucosyl xanthate or thioacetate (III or XII) affords product having α-configuration which results from downside attack of nucleophiles on the intermediate carbanions. The authors, for the present, assume merely that the difference may be attributed to the stabilities of the corresponding intermediates on the reason why the differences appear between these analogous substitutions.

Experimental

Unless stated otherwise, solvents were evaporated *in vacuo* at a bath temperature of 40° in a rotary evaporator. TLC was performed by ascending method on silica gel GF_{254} (E. Merck, Darmstadt, Germany). The ratios of mixed solvents were exhibited by v/v. Spots were located on plates by irradiating with UV lamp or by spraying with 10% H_2SO_4 and then heated in an oven. NMR spectra were measured by H-6013 (Hitachi Ltd., Tokyo) in $CDCl_3$ at 60 Mc with Me_4Si as an internal standard. Chemical shifts were given in τ values and coupling constants (J) cps.

2-O-Mesyl-3,4,6-tri-O-acetyl-β-D-glucopyranosyl Methylxanthate (II)——A mixture of I (5 g) and potassium methylxanthate (1.7 g) in MeOH (50 ml) was stirred at 5—10° until to complete a solution. It was left to stand for 1 hr at 0° and then poured into ice–H_2O (200 ml). Gummy precipitates were extracted with $CHCl_3$ and the organic layer was dried over Na_2SO_4. Removal of the solvent afforded a sirup which was dissolved in MeOH (30 ml) and left in a refrigerator to crystallize. Crystals were collected by filtration and recrystallized from EtOH to give pure material (1.6 g, 30%), mp 156—157°, $[\alpha]_D^{20}$ +6° (c=1.34, $CHCl_3$). *Anal.* Calcd. for $C_{15}H_{22}O_{11}S_3$: C, 37.97; H, 4.67; S, 20.27. Found: C, 38.01; H, 4.60; S, 20.22.

2-O-Mesyl-3,4,6-tri-O-acetyl-β-D-glucopyranosyl Ethylxanthate (III)——The product was prepared with a slight modification of the previous method[3a] to improve the yield markedly. A mixture of I (5 g) and potassium ethylxanthate (1.6 g) was treated similarly as the preparation of II. The product (5 g, 92%), mp 98°, was indistinguishable with an authentic sample.

1,2-Dithio-2-methoxydithiocarbonyl-3,4,6-tri-O-acetyl-α-D-mannopyranosyl Methylxanthate (IV)——A mixture of I (3 g) and potassium methylxanthate (2.1 g) in MeOH (30 ml) was stirred at room temperature until to complete a solution. It was left to stand for 1 hr, poured into ice–H_2O (150 ml) and then extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4, and the solvent was removed to give a sirup which crystallized from EtOH to afford unidentified product (0.7 g), mp 145—148°, $[\alpha]_D^{20}$ −24° (c=1, $CHCl_3$), UV λ_{max}^{EtOH} mμ (ε): 275 (11000). *Anal.* Calcd. for $C_{28}H_{38}O_{16}S_5$: C, 42.52; H, 4.84; S, 20.27. Found: C, 42.81; H, 4.84; S, 20.40.

After removal of the crystals, the mother liquid was concentrated to 20 ml and left to stand at room temperature to afford another crystals (2 g, 60%) which recrystallized from EtOH to give pure material, mp 88—89°, $[\alpha]_D^{20}$ −76° (c=1, $CHCl_3$), UV λ_{max}^{EtOH} mμ (ε): 275 (18000). *Anal.* Calcd. for $C_{16}H_{22}O_9S_4$: C, 39.49; H, 4.55; S, 26.36. Found: C, 39.58; H, 4.58; S, 25.90.

1,2-Dithio-2-ethoxydithiocarbonyl-α-D-mannopyranosyl Ethylxanthate (V)——A mixture of I (5 g) and potassium ethylxanthate (3.7 g) in MeOH (50 ml) was warmed at 40° for 1 hr. After cooling, it was poured into H_2O (200 ml) and extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4, and the solvent was removed to give a sirup (5.2 g), $[\alpha]_D^{20}$ −74° (c=0.58, EtOH), UV λ_{max}^{EtOH} mμ (ε): 274 (18300).

To a solution of the sirup in MeOH (25 ml) was added MeOH (25 ml) saturated with dry HCl gas at 0°, and left overnight in a refrigerator. Complete removal of the solvent afforded solids which recrystallized from EtOH–petr. ether to give pure material (3.3 g, 70%), mp 135—136°, $[\alpha]_D^{20}$ −164° (c=1, MeOH). *Anal.* Calcd. for $C_{12}H_{20}O_6S_4$: C, 37.09; H, 5.19; S, 33.01. Found: C, 37.30; H, 5.02; S, 32.75.

4) S. Ishiguro and S. Tejima, *Chem. Pharm. Bull.* (Tokyo), **16**, 1567 (1968).

To a mixture of V (2 g) and PhCHO (3 ml) was added $ZnCl_2$ (2 g). The mixture was stirred overnight. After addition of H_2O and petr. ether the mixture was stirred to deposite crystals which were collected by filtration. Recrystallization from EtOH gave pure material (2 g, 80%), mp 158—159°, $[\alpha]_D^{20}$ −112° (c=1.25, $CHCl_3$), UV λ_{max}^{EtOH} mμ (ε): 275 (18000). The product is, presumably, 1,2-dithio-2-ethoxydithiocarbonyl-4,6-O-benzylidene-α-D-mannopyranosyl ethylxanthate. *Anal.* Calcd. for $C_{19}H_{24}O_6S_4$: C, 47.87; H, 5.07; S, 26.91. Found: C, 47.89; H, 4.97; S, 26.97.

1,2-Dithio-1,2-S-acetyl-3,4,6-tri-O-acetyl-α-D-mannopyranose (VI)——To a solution of IV (2 g) in Ac_2O (2 ml), which was completed under warming, was added pyridine (1 ml) at room temperature. The mixture was left to stand overnight, then poured into ice–H_2O (100 ml). Precipitates were collected by filtration and recrystallized from EtOH to afford pure material (1.4 g, 80%), mp 154—156°, $[\alpha]_D^{20}$ +32° (c=1, $CHCl_3$). The product was indistinguishable with an authentic sample which had been reported from our laboratory as 1,2-di-S-acetyl-1,2-dithio-3,4,6-tri-O-acetyl-β-D-mannopyranose[3a] by mixed mp and IR.

Methyl 1,2-Dithio-2-S-methyl-3,4,6-tri-O-acetyl-α-D-mannopyranoside (VII)——To a mixture of VI (2 g) in dry MeOH (25 ml) containing Na (0.45 g, 4 mole), which had been stirred previously for a few min at room temperature to deacetylation, was added CH_3I (2 ml). Stirring was continued for further a few min. Removal of the solvent afforded a sirup which was acetylated with pyridine–Ac_2O (40 ml). After standing at room temperature overnight, it was poured into ice–H_2O (300 ml) and extracted with $CHCl_3$. The $CHCl_3$–layer was washed successively with 3N H_2SO_4, aq. $NaHCO_3$, H_2O, and dried over Na_2SO_4. Removal of the solvent afforded a sirup which crystallized after addition of a small amount of EtOH. Crystals were collected by filtration. Recrystallization from EtOH gave pure material (1.5 g, 82%), mp 95—96°, $[\alpha]_D^{20}$ +101° (c=1.1, $CHCl_3$). NMR τ: 4.65 (3H, m, H_1, H_2, H_3), 6.59 (1H, q, $J_{2,3}$=3.5, H_2), 7.76, 7.83 (each 3H, s, SCH_3), 7.86—7.90 (9H, d, $3CH_3CO$). *Anal.* Calcd. for $C_{14}H_{22}O_7S_2$: C, 45.88; H, 6.05; S, 17.50. Found: C, 46.11; H, 6.06; S, 17.43.

1,2-Dithio-1,2-di-S-acetyl-3,4,6-tri-O-acetyl-β-D-mannopyranose (X)——a) From 1,2-Dideoxy-1,2-trithiocarbonyl-3,4,6-tri-O-acetyl-β-D-mannopyranose (VIII).[1] A mixture of VIII (1 g) and MeONa in dry MeOH (25 ml) containing Na (0.37 g, 4 mole) was warmed in a steam–bath for a few min until the yellow color discharged. Removal of the solvent afforded a sirup which was acetylated with pyridine-Ac_2O (40 ml). The mixture wastreated as described in the preparation of VII to afford crystals. Recrystallization from EtOH gave pur material (1.1 g, 66%), mp 122—123°, $[\alpha]_D^{20}$ +25.7° (c=1.48, $CHCl_3$), IR λ_{max}^{Nujol} μ: 5.70 (OAc), 5.87 (SAc). NMR τ: 4.21 (1H, d, $J_{1,2}$=2.5, anomeric proton), 5.53 (1H, q, $J_{2,3}$=3.3, H_2), 7.50, 7.56 (each 3H, s, SCH_3CO), 7.82, 7.87, 7.97 (each 3H, s, OCH_3CO). *Anal.* Calcd. for $C_{16}H_{22}O_9S_2$: C, 45.48; H, 5.25; S, 15.18. Found: C, 45.54; H, 5.16; S, 15.13.

b) From 1,2-Dideoxy-1,2-dithiocarbonyl-3,4,6-tri-O-acetyl-β-D-mannopyranose (IX).[3b] A mixture of IX (0.5 g) and MeONa in dry MeOH (20 ml) containing Na (0.1 g, 3 mole) was stirred at room temperature for a few min. Removal of the solvent afforded a sirup which was acetylated with pyridine–Ac_2O (10 ml). The mixture was treated similarly in a) to yield solids which were recrystallized from EtOH to afford pure material (0.5 g, 96%), mp 122—123°, $[\alpha]_D^{20}$ +25.8° (c=1.2, $CHCl_3$). The product was identical with the product prepared by a) in mixed mp and IR.

Methyl 1,2-Dithio-2-S-methyl-3,4,6-tri-O-acetyl-β-D-mannopyranoside (XI)——Treatment of X (2 g) with the similar method described in the preparation of VII afforded crystals (1.4 g, 76%), mp 154—156°, $[\alpha]_D^{20}$ −20° (c=0.75, $CHCl_3$). NMR τ: 5.18 (1H, d, $J_{1,2}$=2.5, anomeric proton), 6.47 (1H, q, $J_{2,3}$=3.5, H_2), 7.66, 7.68 (each 3H, s, SCH_3), 7.83, 7.85, 7.87 (each 3H, s, CH_3CO). *Anal.* Calcd. for $C_{14}H_{22}O_7S_2$: C, 45.88; H, 6.05; S, 17.05. Found: C, 45.83; H, 6.03; S, 17.36.

1,2-Dithio-2-S-acetyl-3,4,6-tri-O-acetyl-α-D-mannopyranosyl N,N-Dimethyldithiocarbamate (XIII)—— a) From 1-S-Acetyl-1-thio-2-O-mesyl-3,4,6-tri-O-acetyl-β-D-glucopyranose (XII).[3a] A mixture of XII (0.4 g) and sodium N,N-dimethyldithiocarbamate (0.3 g) in dry acetone–abs. EtOH (15 ml, 1:2) was refluxed for 10 min. It became turbid and Na methanesulfonate precipitated in the course of the reaction. After cooling, it was poured into ice–H_2O (80 ml) and extracted with $CHCl_3$. The $CHCl_3$–layer was washed with H_2O and dried over Na_2SO_4. Removal of the solvent gave a sirup which crystallized from a small amount of EtOH. Recrystallization from EtOH gave pure material (0.23 g, 55%), mp 124—125°, $[\alpha]_D^{20}$ −25.4° (c=1, $CHCl_3$), UV λ_{max}^{EtOH} mμ (ε): 278 (10200), IR λ_{max}^{Nujol} μ: 5.83 (SAc), 6.63 (dithiocarbamate). NMR τ: 3.52 (1H, d, $J_{1,2}$=2.2, anomeric proton), 5.54 (1H, q, $J_{2,3}$=2.5, H_2), 6.52 (6H, d, NMe_2), 7.60 (3H, s, $SCOCH_3$), 7.90, 7.94, 8.02 (each 3H, s, $3CH_3CO$). *Anal.* Calcd. for $C_{17}H_{25}O_8NS_3$: C, 43.66; H, 5.39; N, 3.00; S, 20.57. Found: C, 43.37; H, 5.31; N, 2.75; S, 20.42.

Finely powdered XIII (0.7 g) was added gradually to liq. NH_3 (50 ml) which had been preserved in a round flask chilled with dry ice and acetone. After complete to a solution, small pieces of Na were added under constant stirring until the blue color persisted for 10 min. At the end of the time NH_4Cl was added until the blue color discharged, from which NH_3 was allowed to evaporate under N_2. The residue was then acetylated with pyridine–Ac_2O (20 ml) at 0°. It was treated similarly as described in the preparation of VII to afford solids. Recrystallization from EtOH gave pure material (0.07 g, 11%), mp 155—156°, $[\alpha]_D^{20}$ +35° (c=0.5, $CHCl_3$), which was indistinguishable with VI in mixed mp and IR.

b) From 2-O-Mesyl-3,4,6-tri-O-acetyl-β-D-glucopyranosyl Methylxanthate (II): A mixture of II (2 g) and sodium N,N-dimethyldithiocarbamate (0.6 g) in dry MeOH (50 ml) was stirred at room temperature for

1 hr, then poured into ice–H_2O (100 ml) and extracted with $CHCl_3$. The combined extracts were washed with H_2O and dried over Na_2SO_4. Removal of the solvent gave a sirup (2 g) which was acetylated with pyridine–Ac_2O (30 ml) for 3 days at room temperature. The mixture was treated with the similar procedure described in the preparation of VII to afford a sirup (2 g) which was dissolved in benzene and chromatographied on silica gel (70 g). Elution was carried out using benzene and 5% ether–benzene. The latter effluent was evaporated to give a colorless sirup which crystallized from a small amount of EtOH. Recrystallization from EtOH gave pure material (1.1 g, 56%), mp 124—125°, $[\alpha]_D^{20}$ −25.2° (c=0.58, $CHCl_3$) which was indistinguishable with the product prepared by a) in mixed mp and IR.

1,2-Dithio-1-S-acetyl-2-ethoxydithiocarbonyl-3,4,6-tri-O-acetyl-α-D-mannopyranose (XV)——A mixture of III (2 g) and AcSK (0.5 g) in dry MeOH (20 ml) was stirred at 40° for 2 hr. After cooling it was poured into ice–H_2O (100 ml) and extracted with $CHCl_3$. The combined extracts were washed with H_2O and then dried over Na_2SO_4. Removal of the solvent gave a sirup which was dissolved in benzene and chromatographied on silica gel (40 g). Elution was carried out successively with benzene and 5% ether–benzene. The latter effluent was evaporated to give a colorless sirup (0.61 g, 29%), $[\alpha]_D^{20}$ −7° (c=1.2, $CHCl_3$). λ_{max}^{EtOH} mμ (ε): 275 (9000), NMR τ: 3.80 (1H, $J_{1,2}$=3, anomeric proton), 7.52 (3H, s, $SCOCH_3$), 7.85—7.96 (9H, t, $3CH_3CO$), 8.50 (3H, t, $OCH_2C\underline{H}_3$).

A combined mixture of XV (0.4 g) in dry acetone (5 ml) and AcSK (0.2 g) in abs. EtOH (10 ml) was refluxed for 10 min. After cooling, it was poured into ice–H_2O (100 ml) and extracted with $CHCl_3$. The $CHCl_3$–layer was washed with H_2O and dried over Na_2SO_4. Removal of the solvent gave a sirup which crystallized after trituration with EtOH. Recrystallization from EtOH gave pure material (0.16 g, 44%), mp 155—156°, $[\alpha]_D^{20}$ +34° (c=1, $CHCl_3$), which was indistinguishable with VI by mixed mp and IR.

A mixture of XV (0.39 g) and MeONa in dry MeOH (5 ml) containing Na (0.09 g, 4 mole) was stirred at room temperature for a few min. Removal of the solvent gave a sirup which was acetylated with pyridine–Ac_2O (10 ml), and the mixture treated similarly as described in the preparation of VII. Recrystallization from EtOH gave pure material (0.1 g, 28%), mp 155—156°, $[\alpha]_D^{20}$ +34° (c=1.2, $CHCl_3$) which was indistinguishable with VI by mixed mp and IR.

1,2-Dithio-1-S-acetyl-2-N,N-dimethyldithiocarbamoyl-3,4,6-tri-O-acetyl-β-D-mannopyranose (XVII)——A combined mixture of 2-O-mesyl-3,4,6-tri-O-acetyl-β-D-glucopyranosyl N,N-dimethyldithiocarbamate (XVI)[3c] (2 g) in dry acetone (10 ml) and AcSK (1 g) in abs. EtOH (15 ml) was refluxed for 30 min. It became turbid and potassium methanesulfonate precipitated in the course of the reaction. After cooling, it was poured into ice–H_2O (150 ml) and extracted with $CHCl_3$. The $CHCl_3$–layer was washed with H_2O and dried over Na_2SO_4. Removal of the solvent afforded a sirup which showed three spots in TLC using ether–petr. ether (1:1) as the solvent. The sirup was dissolved in warm EtOH and left to stand overnight at room temperature. The resultant precipitates were separated by filtration and recrystallized from EtOH to give pure material (XVII) (0.45 g), mp 182—183°, $[\alpha]_D^{20}$ +67.2° (c=1.35, $CHCl_3$). From the mother liquid further crops of the product were isolated after silica gel chromatography. Namely, removal of the solvent from the mother liquid gave a sirup which was dissolved in benzene and chromatographied on silica gel (30 g). Elution was carried out successively with benzene, 3%, and 5% ether–benzene. From the forthcoming effluent of 5% ether–benzene the product (0.22 g) crystallized after removal of the solvent and trituration of the resulting sirup with EtOH. The total yield was 0.67 g or 35%. The product was indistinguishable with an authentic sample which had been reported previously as 2-S-acetyl-2-thio-3,4,6-tri-O-acetyl-β-D-mannopyranosyl N,N-dimethyldithiocarbamate[3c] by TLC and mixed mp.

The product (2 g) in liq. NH_3 (60 ml) was treated with Na and then acetylated similarly as described in the preparation of VI from XIII. The resultant crystals (1.03 g, 57%), mp 122—123°, $[\alpha]_D^{20}$ +25.7° (c=1, $CHCl_3$) was indistinguishable with X by mixed mp and TLC.

In the above mentioned chromatographic separation of XVII, another crystals (0.22 g, 14%) were separated from the second effluent of the same solvent: it was obtainable after removal of the solvent and trituration of the resulting sirup with a small amount of EtOH. Recrystallization from EtOH gave pure material, mp 104°, $[\alpha]_D^{20}$ +186.5° (c=0.75, $CHCl_3$) which was assigned as 2-N,N-dimethyldithiocarbamoyl-2-deoxy-3,4,6-tri-O-acetyl-D-*arabino*-hexopyranose-1-ene (XVIII)[3c] by mixed mp, IR, and TLC.

From the latest effluent of the same solvent the third crystals (0.34 g, 22%), mp 120—121,° $[\alpha]_D^{20}$ +46° (c=0.8, $CHCl_3$) were isolated as yellow needles and assigned as 1,2-dideoxy-1,2-trithiocarbonyl-3,4,6-tri-O-acetyl-β-D-mannopyranose (VIII)[1] by mixed mp, IR, and TLC.

Methyl 1,2-Dithio-2-N,N-dimethyldithiocarbamoyl-3,4,6-tri-O-acetyl-β-D-mannopyranoside (XIX)——To a mixture of XVII (1 g) in dry MeOH (30 ml) containing Na (0.08 g, 1.5 mole), which had been stirred previously for a few min at room temperature to deacetylation, was added CH_3I (0.5 ml). The mixture was treated similarly as described in the preparation of VII to afford crystals which were recrystallized from EtOH. Crystals (0.2 g, 21%), mp 108—110°, $[\alpha]_D^{20}$ +35.3° (c=1.22, $CHCl_3$), IR λ_{max}^{Nujol} μ: 5.75 (OAc), 6.65 (dithiocarbamate). UV λ_{max}^{EtOH} mμ (ε): 240 (8300), 276.5 (8600) (dithiocarbamate). NMR τ: 3.80 (1H, d, anomeric proton), 6.42 (6H, m, NMe_2), 7.68 (3H, s, SCH_3), 7.82—7.86 (9H, d, $3CH_3CO$). *Anal.* Calcd. for $C_{16}H_{25}O_7NS_3$: C, 43.72; H, 5.73; N, 3.19; S, 21.88. Found: C, 43.86; H, 5.90; N, 2.94; S, 21.61.

2-S-Acetyl-2-deoxy-3,4,6-tri-O-acetyl-D-arabino-hexopyranose-1-ene (XX)——Finely powdered XVIII

(1.5 g) was gradually added to liq. NH_3 (50 ml) which had been preserved in a round flask chilled with dry ice–acetone. Small pieces of Na were then added to the solution under constant stirring until the blue color persisted for 10 min. After complete a solution NH_4Cl was added until the blue color discharged, from which NH_3 was allowed to evaporate under N_2. The resulting residue was acetylated with pyridine-Ac_2O (40 ml) at 0° under stirring for 1 hr and the mixture left to stand for further 5 hr at room temperature. It was poured into ice–H_2O (300 ml) and the resulting solution extracte with $CHCl_3$. The extract was washed with dil. H_2SO_4, aq. $NaHCO_3$, H_2O and then dried over Na_2SO_4. Removal of the solvent gave a sirup (1 g) which was dissolved in benzene and chromatographied on silica gel (30 g). Elution was carried out using benzene and 5% ether–benzene. From the latter effluent a yellow sirup (0.2 g, 15%), $[\alpha]_D^{20}$ +53° (c=1.1, $CHCl_3$), IR λ_{max}^{Nujol} μ: 5.70 (OAc), 5.83 (SAc), 6.15 (C=C). NMR τ: 3.27 (1H, s, anomeric proton), 4.52 (1H, d, H_3), 4.80 (1H, m, H_4), 5.50—5.70 (2H, m, CH_2 at C_6), 7.70 (3H, s, $SCOCH_3$), 7.90 (6H, s, $2CH_3$-CO), 7.96 (3H, s, CH_3CO).

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