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Thiosugars. XVII.[1] Syntheses of Maltose Derivatives having Sulfur Atom in the Reducing Moiety

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Several maltose derivatives containing sulfur atom in C_1 and C_6 positions in maltose have been synthesized. Treatment of maltosan hexaacetate (II) with titanium tetrabromide in chloroform, followed by acetylation with mercuric acetate in acetic acid, afforded 1,2,3,2',3',4',6'-hepta-O-acetyl-β-maltose (III) in 41% yield. Heating of the corresponding 6-tosylate (V) with potassium thiolacetate in N,N-dimethylformamide afforded 1,2,3,2',3',4',6'-hepta-O-acetyl-6-S-acetyl-6-deoxy-6-thio-β-maltose (VII). Deacetylation of VII gave 6-deoxy-6-thio-maltose (IX) as a sirup which contained two products, disulfide and thiol.

Starting from 6-mesylate (IV) or 6-tosylate (V), crystalline 1,6-anhydro-2,3,2',3',4',6'-hexa-O-acetyl-6-deoxy-6-thio-β-maltose (6-thiomaltosan hexaacetate) (XV) was synthesized by an analogous reaction sequence describing in the preparation of 6-thiolactosan hexaacetate; S. Tejima, *Carbohyd. Res.*, **20**, 123 (1971). Deacetylation of XV afforded 1,6-anhydro-6-deoxy-6-thio-β-maltose (6-thiomaltosan) (XIX) as amorphous powders. Acetolysisof XV gave 1,2,3,2',3',4',6'-hepta-O-acetyl-6-deoxy-6-thio-6-S-acetyl-α-maltose (XVIII). Reductive desulfurization of XV, followed by deacetylation, yielded 1,5-anhydro-4-O-α-D-glucopyranosyl-6-deoxy-D-glucitol (XVII) as amorphous powders.

Syntheses of several 1-thio-β-maltose derivatives have also been described.

Several papers in which involved syntheses of maltose derivatives containing sulfur atom have been published during past ten years.[3] However, only two papers have referred to the biological activities in these compounds. According to the paper reported by Barker, *et al.*,[4] 1-thiomaltose at 0.05M concentration caused 80% inhibition of *Escherichia coli* amylomaltase activity. Mono and disulfuric acid esters of maltose were also synthesized by Takiura and Honda.[5] According to the literatures cited by the authors, the esters showed the anti-pepsin or anti-ulcer activity. In the preceding paper of this series, Tejima reported on the syntheses of cellobiose derivatives having sulfur atom in the reducing moiety. Therefore, as the further extension of chemical and biological studies of thiosugars we now describe on syntheses of the title compounds.

Recent publications[1,6] from this laboratory have pointed out the usefulness of lactosan hexaacetate and cellobiosan hexaacetate as the starting material for the chemical modification of reducing disaccharides, especially that of C_6 position. In this paper, the authors started from maltosan hexaacetate (II). Compound (II) was prepared in good yield by alkaline degradation of easily crystallizable *p*-chlorophenyl hepta-O-acetyl-β-maltoside (I),[7] followed by acetylation. In maltose series, as it has originally been pointed out by Asp and Lindberg,[8]

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[1] Part XVI: S. Tejima and Y. Okamori, *Chem. Pharm. Bull.* (Tokyo), **20**, 2036 (1972).

[2] Location: *Tanabe-dori, Mizuho-ku, Nagoya.*

[3] *a*) J. Kocourek, *Collection Czech. Chem. Commun.*, **29**, 316 (1964); *b*) J. Staněk, M. Sindlerovȧ, and M. Cerný, *ibid.*, **30**, 297 (1965); *c*) G.G.S. Dutton and K.N. Slessor, *Can. J. Chem.*, **44**, 1069 (1966); *d*) G. Wagner and R. Metzner, *Pharmazie*, **24**, 245 (1969).

[4] S.A. Barker, M.al Farisi, and J.W. Hopton, *Carbohyd. Res.*, **1**, 97 (1965).

[5] K. Takiura and S. Honda, *Yakugaku Zasshi*, **87**, 1052 (1967).

[6] *a*) S. Tejima, *Carbohyd. Res.*, **20**, 123 (1971); *b*) S. Tejima and T. Chiba, *Chem. Pharm. Bull.* (Tokyo), **21**, 546 (1973); *c*) T. Chiba, M. Haga, and S. Tejima, *ibid.*, **22**, 398 (1974).

[7] I.C.M. Dea, *Carbohyd. Res.*, **12**, 297 (1970).

[8] L. Asp and B. Lindberg, *Acta Chem. Scand.*, **6**, 941 (1952).

and later by Matsushima, *et al.*,[9] the β-1,6-linkage was more stable than that of lactose or cellobiose series. Treatment of II with titanium tetrachloride in chloroform scarcely cleaved the linkage, while recovered a large amount of II. In this cleavage, substitution of titanium tetrachloride for the corresponding bromide[10] proceeded the reaction smoothly. The resulting bromide was acetylated with mercuric acetate in acetic acid to afford 1,2,3,2′,3′,4′,6′-hepta-O-acetyl-β-maltose (III) in a yield of 41%. Methanesulfonylation[11] or *p*-toluenesulfonylation[8] of III afforded 1,2,3,2′,3′,4′,6′-hepta-O-acetyl-6-O-methanesulfonyl-β-maltose (IV) or 1,2,3,-2′,3′,4′,6′-hepta-O-acetyl-6-O-*p*-toluenesulfonyl-β-maltose (V), respectively. The physical constants were completely in agreement with the values reported in the literatures. Either treatment of IV (or V) with sodium iodide in acetonitrile or with sodium methoxide in methanol, followed by acetylation, gave 1,2,3,2′,3′,4′,6′-hepta-O-acetyl-6-deoxy-6-iodo-β-maltose (VI)[8] or II. This result further confirms structures assigned to IV and V, in which an acetoxyl group (β-configuration) is attached to C_1, and a sulfonyloxy group to C_6.[12]

A mixture of V and potassium thiolacetate in N,N-dimethylformamide (DMF) was heated for 1 hour on a steam bath. From the reaction mixture, white crystals, mp 130—131°, $[\alpha]_D^{23}$ $+72°$, was separated in a yield of 74%. The infrared (IR) spectrum showed an absorption at 1690 cm^{-1} corresponding to S-acetyl. The nuclear magnetic resonance (NMR) ($CDCl_3$) spectrum showed a three proton singlet (S-acetyl) at 7.62 τ, along with twenty-one proton singlets at 7.89, 7.95, and 7.99 τ (O-acetyl $\times$ 7). The elemental analyses were in good agreement with that of thioacetate, $C_{28}H_{38}O_{18}S$. Therefore, the crystals were assigned to 1,2,3,2′,3′,4′,6′-hepta-O-acetyl-6-S-acetyl-6-deoxy-6-thio-β-maltose (VII).

Reductive desulfurization of VII afforded 1,2,3,2′,3′,4′,6′-hepta-O-acetyl-6-deoxy-β-maltose (VIII), mp 165—166°, $[\alpha]_D^{22}$ $+64.3°$, which was indistinguishable with the compound obtained from VI by catalytic hydrogenation. Matsushima, *et al.*[9] reported that compound VIII had mp 163—164.5° and $[\alpha]_D^{19}$ $+17°$. However, according to the recent publication reported by Guerrera and Weill,[13] VIII showed mp 160—161° which was almost the same with that previously reported value, while more dextrorotatory (+70.5°). Our result was in agreement with the values reported by the latter authors.

Deacetylation of VII with sodium methoxide in methanol gave 6-deoxy-6-thio-maltose (IX) as a sirup. Paper chromatography indicated two products, disulfide and thiol. No homogeneous product could be separated.

In 1966, Dutton and Slessor,[3c] in the paper entitled synthesis of 6′-substituted maltoses, referred to the synthesis of 6′-deoxy-6′-mercapto-maltose. However, synthesis of 6-deoxy-6-mercapto-maltose or the related derivatives not yet has been reported. Moreover, in the studies on iodo substitution of methyl β-maltoside tosylates, Sleeter and Sinclair[14] have reported on the difference of reactivity between the tosyloxy groups in C_6 and C_6'; 6′-tosylate was more reactive than 6-tosylate. While, so far as the substitution with potassium thiolacetate have concerned, no remarkable difference between the reactivities in the two tosylates was observed.

Tejima and coworkers[15] have prepared the thio derivative of 1,6-anhydro-D-glucose that has a sulfur atom in the 1,6-anhydro ring; this is the so-called "thiolevoglucosan". Since this publication, as further examples of this series, the preparation of 2-deoxy-thiolevoglucosan,[16] and 6-thiolactosan,[6a] and 6-thiocellobiosan[1] have been reported from this laboratory.

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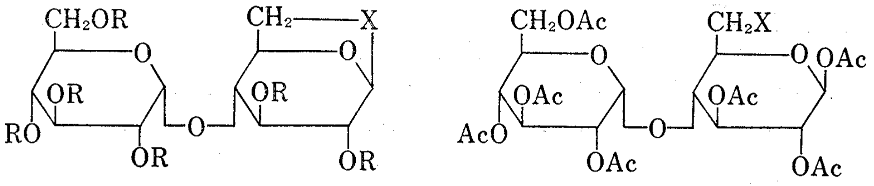
9) H. Arita, M. Isemura, T. Ikenaka, and Y. Matsushima, *Bull. Chem. Soc. Japan*, **43**, 818 (1970).
10) S. Haq and W.J. Whelan, *J. Chem. Soc.*, **1956**, 4543.
11) H. Arita and Y. Matsushima, *J. Biochem.* (Tokyo), **69**, 409 (1971).
12) M. Akagi, S. Tejima, and M. Haga, *Chem. Pharm. Bull.* (Tokyo), **10**, 905, 1039 (1962).
13) J. Guerrera and C.E. Weill, *Carbohyd. Res.*, **27**, 471 (1973).
14) R.T. Sleeter and H.B. Sinclair, *J. Org. Chem.*, **35**, 3804 (1970).
15) M. Akagi, S. Tejima, and M. Haga, *Chem. Pharm. Bull.* (Tokyo), **11**, 58 (1963).
16) T. Maki and S. Tejima, *Chem. Pharm. Bull.* (Tokyo), **15**, 1367 (1967).

Therefore, as the other derivative having sulfur atom at C_6 position in maltose, we designed the synthesis of 6-thiomaltosan.

Starting from IV and V, crystalline 1,6-anhydro-2,3,2′,3′,4′,6′-hexa-O-acetyl-6-deoxy-6-thio-β-maltose (6-thiomaltosan hexaacetate) (XV) was obtained by a reaction sequence comprising formation of 2,3,2′,3′,4′,6′-hexa-O-acetyl-6-O-sulfonyl-β-maltosyl ethylxanthate (X or XI), treatment of X or XI with sodium methoxide in methanol, acetylation, and deacetylation. The overall yield was 35% from IV, or 21% from V. Deacetylation of XV afforded 1,6-anhydro-6-thio-β-maltose(6-thiomaltosan) (XIX) as amorphous powders.

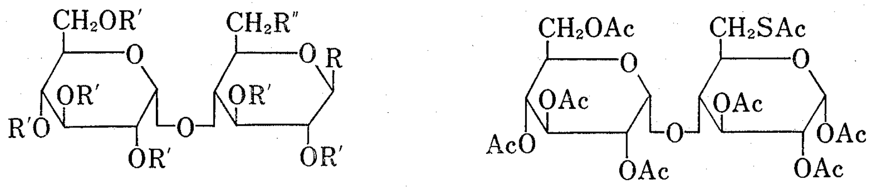
During the synthesis of XV, an attempt was made to simplify the route to compound (IV or V). Treatment of sirupy 2,3,2′,3′,4′,6′-hexa-O-acetyl-α-maltosyl bromide with potassium ethylxanthate in ethanol, followed by silica gel column chromatography, afforded 2,3,2′,3′,4′,6′-hexa-O-acetyl-β-maltosyl ethylxanthate (XIV). Methanesulfonylation or *p*-toluenesulfonylation of XIV afforded X or XII, respectively. However, because of the low overall yield, 16 to 21%, we gave up the attempt.



II : R=Ac, X=O
XV : R=Ac, X=S
XIX : R=H, X=S

III : X=OH
IV : X=OMs
V : X=OTs
VI : X=I
VII : X=SAc
VIII : X=H

Chart 1



X : R=SSCOEt, R′=Ac, R″=OMs
XI : R=$SSCNMe_2$, R′=Ac, R″=OMs
XII : R=SSCOEt, R′=Ac, R″=OTs
XIII : R=$SSCNMe_2$, R′=Ac, R″=OTs
XIV : R=SSCOEt, R′=Ac, R″=OH
XVI : R=R″=H, R′=Ac,
XVII : R=R′=R″=H

XVIII

Chart 2

In order to confirm the structure of XV, the authors further performed the additional two experiments. Namely, reductive desulfurization of XV gave crystalline 2,3-di-O-acetyl-1,5-anhydro-4-O-(2′,3′,4′,6′-tetra-O-acetyl-α-D-glucopyranosyl)-6-deoxy-D-glucitol (XVI). The NMR spectrum showed a three proton doublet ($J_{5,6}$=5.5 Hz), corresponding to the C_5–CH_3- Deacetylation of XVI afforded 1,5-anhydro-4-O-α-D-glucopyranosyl-6-deoxy-D-glucitol (XVII) as amorphous powders.

In the preceding paper of this series[1], the authors reported that the 1,6-anhydro-6-thio linkage in 6-thiocellobiosan was cleaved by acetolysis mixture to α-acetate without breakdown of the disaccharide linkage. When XV was treated with acetolysis mixture, the optical rotation rapidly changed to strong positive value, then became constant after three hours. On the other hand, in acetolysis of maltosan hexaacetate (II) under the same condition, the mutarotation stopped after only one hour. The fact suggests that the 1,6-anhydro-6-thio linkage is more stable against acetolysis than the corresponding oxygen analogue. Recently, Clayton and Hughes reported that, in methyl 1,5-dithio-α- and β-D-ribopyranoside, the lactol ring was surprisingly stable under acidic conditions.[17] The result is analogous with the fairly stability of 1,6-anhydro-6-thio linkage in comparison with the corresponding oxygen analogue.

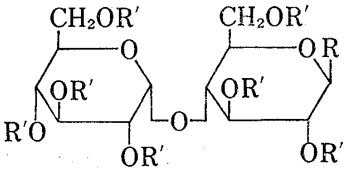
From the brown acetolysis mixture mentioned above 1,2,3,2′,3′,4′,6′-hepta-O-acetyl-6-S-acetyl-6-deoxy-6-thio-α-maltose (XVIII), the anomer of VII, was separated in a yield of 23%. The elemental analyses, IR spectrum, and NMR data were in good agreement with those of the assigned structure.

The authors also synthesized 2,3,2′,3′,4′,6′-hexa-O-acetyl-6-sulfonyl-β-maltosyl N,N-dimethyldithiocarbamates (XI and XIII). Syntheses and chemical properties of glycosyl N,N-dimethyldithiocarbamates have been reported in the previous papers.[18] Alkaline treatment of XI and XIII gave a complex mixture other than thiomaltosan as judged by thin-layer chromatography (TLC).

In order to introduce sulfur atom at C_1 in maltose, we investigated the method which started from hepta-O-acetyl-α-maltosyl bromide, *via* acetylated β-maltosyl ethylxanthate and N,N-dimethyldithiocarbamate. However, 1-thiomaltose and 2,3,6,2′,3′,4′,6′-hepta-O-acetyl-1-thio-β-maltose have already been synthesized using another ways by Barker, *et al.*[4] and Staněk, *et al.*[3b] Therefore, in this paper, we describe briefly about syntheses of 1-thiomaltose derivatives.

Either warming of hepta-O-acetyl-α-maltosyl bromide with potassium ethylxanthate in ethanol or with sodium N,N-dimethyldithiocarbamate in acetone afforded 2,3,6,2′,3′,4′,6′-hepta-O-acetyl-β-maltosyl ethylxanthate (XX) or the corresponding N,N-dimethyldithiocarbamate (XXI), respectively. The ultraviolet (UV) spectrum and NMR data were described in experimental part. Reductive desulfurization introduced XX or XXI to the reference 2,3,6-tri-O-acetyl-1,5-anhydro-4-O-(2′,3′,4′,6′-tetra-O-acetyl-α-D-glucopyranosyl)-D-glucitol (XXII),[19] which suggested that the sulfur atom attached to C_1 in maltose. Treatment of XX with sodium methoxide in methanol gave 1-thiomaltose sodium salt (XXIII) as hygroscopic amorphous powders. On the other hand, alkaline degradation of XXI proceeded deacetylation only, and afforded β-maltosyl N,N-dimethyldithiocarbamate (XXV) as hygroscopic amorphous powders.

Acetylation of XXIII afforded 1-S-acetyl-1-thio-2,3,6,2′,3′,4′,6′-hepta-O-acetyl-β-maltose (XXIV). This compound was also obtainable by treatment of hepta-O-acetyl-α-maltosyl bromide with potassium thiolacetate in acetone.



XX : R=SSCOEt, R′=Ac
XXI : R=SSCNMe$_2$, R′=Ac
XXII : R=H, R′=Ac
XXIII : R=SNa, R′=H
XXIV : R=SAc, R′=Ac
XXV : R=SSCNMe$_2$, R′=H

Chart 3

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[17] C.J. Clayton and N.A. Hughes, *Carbohyd. Res.*, **27**, 89 (1973).

[18] S. Tejima and S. Ishiguro, *Chem. Pharm. Bull.* (Tokyo), **15**, 255 (1967); S. Ishiguro and S. Tejima, *ibid.*, **15**, 1478 (1967); *idem*, *ibid.*, **16**, 1567, 2040 (1968); S. Ishiguro, M. Sakata, M. Haga, and S. Tejima, *ibid.*, **17**, 2571 (1969).

[19] H.G. Fletcher, Jr, L.H. Koehler, and C.S. Hudson, *J. Am. Chem. Soc.*, **71**, 3679 (1949).

Experimental

Melting points were determined on a Yanagimoto micro melting points apparatus and uncorrected. Solutions were evaporated in a rotary evaporator below 40° under diminished pressure. Optical rotations were measured with a Yanagimoto Model OR-10 polarimeter in a 0.5 dm tube. IR spectra were recorded with a Jasco Model IRA-2 spectrometer, UV spectra, with a Hitachi Model EPS-3T recording spectrophotometer, and NMR spectra at 60 MHz, with a Jeol Model JNM-MH-60 spectrometer. Tetramethylsilane was used as the internal standard in $CDCl_3$. Chemical shifts are given on the τ scale. TLC on Silica gel GF_{254} (E. Merck, Darmstadt, Germany) activated at 110° was performed with solvent systems (A) 6: 1 (v/v) CH_2Cl_2–acetone, (B) 2: 1 ether–benzene, and (C) 2: 1 70% iso-PrOH–AcOEt. Detection was effected with H_2SO_4 and UV light (short wave length). Paper chromatography was performed on Toyo Filter Paper No. 50 by the ascending method20) with 6: 4: 3 (v/v) *n*-BuOH–pyridine–H_2O. Spots were detected by (A) Tollens' reagent21) and (B) Grote's reagent with 5% KCN.22) Column chromatography was performed on a column of Wakogel C-200 (Wako Pure Chemical Industries, Ltd., Osaka) as the adsorbent, with 1 g of the mixture to be separated per 20 g of adsorbent.

Maltosan Hexaacetate (II)——*p*-Chlorophenyl hepta-O-acetyl-β-maltoside (I), mp 181—182°, $[\alpha]_D^{26}$ +44.3° (c=1, $CHCl_3$) (lit.7) mp 174—176°, $[\alpha]_D$ +44.7°) was synthesized according to the method described by Dea.7)

A mixture of I (60 g) with 3N KOH (460 ml) was refluxed for 10 hr; it was completely freed of I by TLC. The solution was made neutral at 0° with 6N H_2SO_4, concentrated to a sirup, and a trace of H_2O was removed completely by repeated azeotropic distillation with EtOH and benzene. To the completely dried residue, contaminated with inorganic materials, were added Ac_2O (240 ml) and anhyd. AcONa (24 g). The mixture was heated to reflux for 2 hr on a mantle heater and was then poured into ice-H_2O. The precipitated brown crystals were collected by filtration and air-dried. The crude material was dissolved in CH_2Cl_2 (240 ml), decolorized with charcoal, and concentrated to half-volume. Addition of petr. ether (bp 30—60°) caused formation of a precipitate (37 g, 80%), mp 182—184°, which was used for further experiment. One recrystallization from AcOEt gave pure II, mp 186—187°, $[\alpha]_D^{14}$ +49° (c=0.86, $CHCl_3$) (lit.8) mp 182—183° and $[\alpha]_D$ +48°, or mp 184°23)).

1,2,3,2′,3′,4′,6′-Hepta-O-acetyl-β-maltose (III)——To a chilled solution of II (6 g) in dry $CHCl_3$ (30 ml) was added a solution of titanium tetrabromide (12 g) in dry $CHCl_3$ (30 ml). The mixture, protected from moisture, was warmed gently for about 30 min, then heated under reflux for 5 hr on an oil bath. The cooled reaction mixture was poured into ice-H_2O (300 ml), traces being transfered with the aid of $CHCl_3$ (30 ml). The $CHCl_3$-layer was separated, washed with ice-H_2O (4×100 ml), dried ($CaCl_2$), and evaporated to dryness to afford amorphous 2,3,2′,3′,4′,6′-hexa-O-acetyl-α-maltosyl bromide (6.5 g), $[\alpha]_D^{25}$ +173.9° (c=3.6, $CHCl_3$). Without further purification, a part of the bromide (4.5 g) was dissolved in a solution of mercuric acetate (4 g) in glacial AcOH (40 ml), and the solution was kept at room temperature overnight, poured into ice-H_2O (300 ml), and the mixture extracted with CH_2Cl_2 (4×50 ml). The extracts were combined, washed successively with saturated aq. $NaHCO_3$ and H_2O, dried ($CaCl_2$), and evaporated to dryness to afford an amorphous powder. The residue was dissolved in hot EtOH (10 ml). On cooling almost pure II (0.7 g) precipitated which was collected by filtration. The mother liquid was concentrated to dryness and the residue dissolved in hot 1: 4 (v/v) aq. MeOH (90 ml), and then H_2O (40 ml) was added to persist turbidity. After standing the mixture at room temperature, precipitated white crystals (1.8 g, 41%), mp 137—140°, were collected by filtration. Recrystallization from EtOH–H_2O (1: 9, v/v) gave pure III, mp 141—143°, $[\alpha]_D^{11}$ +66° (c=1, $CHCl_3$) (lit.8) mp 140—141°, $[\alpha]_D^{20}$ +65°).

1,2,3,2′,3′,4′,6′-Hepta-O-acetyl-6-O-methanesulfonyl-β-maltose (IV)——Compound (IV) was prepared by methanesulfonylation of III (2 g) according to the method of Arita and Matsushima.11) Recrystallization from EtOH gave pure IV (1.8 g, 80%), mp 175—176°, $[\alpha]_D^{18}$ +58.4° (c=0.6, $CHCl_3$) (lit.11) mp 173—174°, $[\alpha]_D^{30}$ +63.6° (c=1.07, $CHCl_3$)). TLC: *Rf* 0.38 (solvent A), 0.23 (B).

1,2,3,2′,3′,4′,6′-Hepta-O-acetyl-6-O-*p*-toluenesulfonyl-β-maltose (V)——Compound (V) was prepared by *p*-toluenesulfonylation of III (1.1 g) according to the method of Asp and Lindberg.8) Recrystallization from EtOH gave pure V (0.95 g, 70%), mp 145—147.5°, $[\alpha]_D^{13}$ +58.9° (c=1, $CHCl_3$) (lit.8) mp 140—141°, $[\alpha]_D^{20}$ +50°)). TLC: *Rf* 0.50 (solvent A), 0.34 (B).

1,2,3,2′,3′,4′,6′-Hepta-O-acetyl-6-deoxy-6-iodo-β-maltose (VI)——A mixture of (V) (145 mg) and NaI (100 mg) in acetonitrile (5 ml) was heated in a sealed tube at 95° for 2.5 hr, filtered, and the filtrate evaporated to dryness. The residue was triturated with ice–H_2O, to afford a solid which was collected by filtration. The air-dried powder was recrystallized from EtOH–H_2O to give pure product (110 mg, 80%), mp 84—86°, $[\alpha]_D^{14}$ +51° (c=1, $CHCl_3$) (lit.8) mp 88—90°, $[\alpha]_D^{20}$ +50°). The product was also obtainable from IV.

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20) M. Ueda, *Yakugaku Zasshi*, **90**, 1322 (1970).
21) W.E. Travelyan, D.P. Procter, and J.S. Harrison, *Nature*, **166**, 444 (1950).
22) I.W. Grote, *J. Biol. Chem.*, **93**, 25 (1931).
23) P. Karrer and L. Kamienski, *Helv. Chim. Acta*, **15**, 739 (1932).

Maltosan Hexaacetate (II) from Sulfonate IV or V——To a stirred suspension of IV (150 mg) in MeOH (1 ml) was added dropwise 2 ml of 1N sodium methoxide in MeOH at room temperature. After stirring for few min, the mixture was kept overnight at 5°, then made neutral with AcOH evaporated to dryness, and the residue acetylated with Ac_2O (2 ml) and pyridine (2 ml) to afford a pale-brown powder. After recrystallization from EtOAc, the product (83 mg, 69%) had mp 185—187°, $[\alpha]_D^{19}$ +48.5° (c=1, $CHCl_3$); it was indistinguishable with authentic II (IR spectrum and TLC). The product was also obtainable from V in 58% yield.

1,2,3,2′,3′,4′,6′-Hepta-O-acetyl-6-S-acetyl-6-deoxy-6-thio-*β*-maltose (VII)——To a solution of V (600 mg) in dry DMF (10 ml) was added potassium thiolacetate (140 mg). The mixture was heated on a steam bath for 1 hr. To the cooled solution was added H_2O (60 ml), and the mixture was extracted with CH_2Cl_2 (4 × 40 ml). The combined extracts were thoroughly washed with H_2O (9 × 90 ml), dried ($CaCl_2$), and evaporated to a sirup. The residue was dissolved in hot iso-PrOH–EtOH (2: 3, v/v), and allowed to cool to yield crystals which were collected by filtration. Recrystallization from EtOH gave white crystals (380 mg, 74%), mp 130—131°, $[\alpha]_D^{23}$ +72° (c=1, $CHCl_3$). IR ν_{max}^{Nujol}: 1690 cm^{-1} (SAc). NMR ($CDCl_3$): 7.62 (3H, s, AcS), 7.89, 7.95, 7.99 (21H, s, 7 × OAc); TLC: *Rf* 0.48 (solvent A), 0.44 (B). *Anal.* Calcd. for $C_{28}H_{38}O_{18}S$: C, 48.41; H, 5.51. Found: C, 48.47; H, 5.59.

1,2,3,2′,3′,4′,6′-Hepta-O-acetyl-6-deoxy-*β*-maltose (VIII)——1) Catalytic Reduction of VI: A solution of VI (145 mg) in AcOEt (10 ml) containing triethylamine (10 drops) was shaken with hydrogen in the presence of freshly prepared Raney Ni catalyst (1 g) at room temperature under atmospheric pressure. The theoretical amount of hydrogen was absorbed in 5 hr. After removal of the catalyst, the combined filtrate and washings were concentrated to dryness. The residue was dissolved in CH_2Cl_2 (20 ml) and the solution was successively washed with 10% aq. $Na_2S_2O_3$ and H_2O. After being dried over $CaCl_2$, the filtrate was evaporated to dryness to give a sirup. This was dissolved in CH_2Cl_2 and chromatographed on a column of silica gel, by elution with 3: 2 (v/v) AcOEt–petr. ether. The fractions were judged by TLC (solvent A and B). Removal of the solvent from fractions containing a single spot gave a sirup which crystallized from EtOH. The crystals were collected by filtration and recrystallized from EtOH to give pure VIII (95 mg, 79%), mp 164—166°, $[\alpha]_D^{13}$ +64.1° (c=1.2, $CHCl_3$) (lit.[9] mp 163—164.5°, $[\alpha]_D^{19}$ +17° (c=1, $CHCl_3$)). NMR ($CDCl_3$): 7.91, 7.96, 8.00 (21H, s, 7 × OAc), 8.58 (3H, d, $J_{5,6}$=5 Hz, C_5–CH_3); TLC: *Rf* 0.48 (solvent A), 0.43 (B). *Anal.* Calcd. for $C_{26}H_{36}O_{17}$: C, 50.40; H, 5.70. Found: C, 50.16; H, 5.84.

2) Reductive Desulfurization of VII: A mixture of VII (90 mg) and freshly prepared Raney Ni (1 g) in AcOEt (8 ml) was boiled under reflux for 2 hr, filtered, and the residue washed with AcOEt. The combined filtrate and washings were evaporated to dryness which recrystallized from EtOH to give pure product (55 mg, 67%), mp 165—166°, $[\alpha]_D^{22}$ +64.3° (c=0.8, $CHCl_3$); it was indistinguishable with an authentic sample (IR spectrum and TLC) prepared by method 1).

6-Deoxy-6-thio-maltose (IX)——To a solution of VII (150 mg) in dry MeOH (5 ml) was added 0.2 ml of 0.5N sodium methoxide in MeOH. After keeping the solution overnight at room temperature, it was neutralized with Amberlite IR-120 (H^+), filtered, and evaporated to a sirup. Paper chromatography indicated two products (*Rf* 0.21 and 0.37), which were the disulfide and free thiol, respectively. When excess 2-mercaptoethanol and 1 drop of concentrated NH_4OH were added, only the mobile compound was present.

2,3,2′,3′,4′,6′-Hexa-O-acetyl-6-O-methanesulfonyl-*β*-maltosyl Ethylxanthate (X)——To an ice-cold solution of IV (1.8 g) in glacial AcOH (8 ml) was added satd. HBr–AcOH (4 ml). After stirring for 2.5 hr at room temperature, CH_2Cl_2 (30 ml) was added, and the mixture was poured into ice-H_2O (80 ml). The organic layer was separated, successively washed with H_2O, aq. $NaHCO_3$ and H_2O, dried ($CaCl_2$), and evaporated to give 2,3,2′,3′,4′,6′-hexa-O-acetyl-6-O-methanesulfonyl-α-maltosyl bromide, amorphous powder, $[\alpha]_D^{25}$ +159° (c=1.5, $CHCl_3$), which was used without further purification.

To the bromide were added potassium ethylxanthate (0.25 g) and EtOH (18 ml). The mixture was warmed for few min at 70° under shaking to effect dissolution. After keeping for 4.5 hr at room temperature, the mixture was poured into ice-H_2O (60 ml), and extracted with CH_2Cl_2 (3 × 20 ml). The combined extracts were washed with H_2O, dried ($CaCl_2$), and evaporated to dryness which crystallized from EtOH (1 g, 54%). Recrystallization from EtOH gave pure material, mp 143—144°, $[\alpha]_D^{17}$ +73.1° (c=1.18, $CHCl_3$); UV λ_{max}^{EtOH} mμ (log ε): 273 (3.94); NMR ($CDCl_3$): 6.85 (3H, s, SO_2CH_3), 7.87, 7.92, 7.93 (18H, s, 6 × OAc), 8.52 (3H, t, J= 7.5 Hz, CH_2–$C\underline{H}_3$); TLC: *Rf* 0.55 (solvent A), 0.44 (B). *Anal.* Calcd. for $C_{28}H_{40}O_{19}S_3$: C, 43.29; H, 5.19. Found: C, 42.97; H, 5.25.

2,3,2′,3′,4′,6′-Hexa-O-acetyl-6-O-methanesulfonyl-*β*-maltosyl N,N-Dimethyldithiocarbamate (XI)——To amorphous 2,3,2′,3′,4′,6′-hexa-O-acetyl-6-O-methanesulfonyl-α-maltosyl bromide (1.4 g), prepared from IV (1.4 g) with the procedure described in the preparation of X, were added sodium N,N-dimethyldithiocarbamate (0.3 g) and acetone (10 ml), and the mixture was boiled under reflux for 5 min. After keeping for 1 hr at room temperature, the mixture was poured into ice-H_2O (150 ml) containing AcOH (1.5 ml). The resulting precipitate was collected by filtration and air-dried. Recrystallization from MeOH gave pure product (0.9 g, 61%), mp 189.5—190.5°, $[\alpha]_D^{15}$ +77.8° (c=1, $CHCl_3$); UV λ_{max}^{EtOH} mμ (log ε) 278 (4.29); NMR ($CDCl_3$): 6.37, 6.54 (6H, s, $N(CH_3)_2$), 6.84 (3H, s, SO_2CH_3), 7.82, 7.85, 7.89 (18H, s, 6 × OAc); TLC: *Rf* 0.48 (solvent A), 0.25 (B). *Anal.* Calcd. for $C_{28}H_{41}O_{18}NS_3$: C, 43.35; H, 5.33; N, 1.81. Found: C, 43.06; H, 5.35; N, 1.78.

2,3,2′,3′,4′,6′-Hexa-O-acetyl-6-O-*p*-toluenesulfonyl-*β*-maltosyl Ethylxanthate (XII)——Amorphous 2,3,2′,3′,4′,6′-hexa-O-acetyl-6-O-*p*-toluenesulfonyl-*α*-maltosyl bromide (1 g) was prepared from V (1 g) with the similar procedure described in the preparation of X. The bromide was treated with potassium ethylxanthate (0.2 g) in EtOH (15 ml) to afford crude XII (0.95 g), amorphous powder, contaminated with a small amount of side products judged by TLC. This was dissolved in CH_2Cl_2 and chromatographed on a column of silica gel, by elution with CH_2Cl_2–acetone (25: 1, v/v). The fractions were judged by TLC (solvent A and B). Removal of the solvent from fractions containing a single spot gave a sirup which crystallized from EtOH. Recrystallization from EtOH afforded white prisms (360 mg, 36%), mp 178—179°, $[\alpha]_D^{14}$ +70.3° (c=1.4, $CHCl_3$); UV λ_{max}^{EtOH} mμ (log ε): 273 (4.00); NMR ($CDCl_3$): 7.52 (3H, s, SO_2–C_6H_4–$C\underline{H}_3$), 7.88, 7.94, 7.98 (18H, s, 6×OAc), 8.56 (3H, t, J=7 Hz, CH_2–$C\underline{H}_3$); TLC: *Rf* 0.58 (solvent A), 0.50 (B). *Anal.* Calcd. for $C_{34}H_{44}O_{19}S_3$: C, 47.88; H, 5.20. Found: C, 47.42; H, 5.36.

2,3,2′,3′,4′,6′-Hexa-O-acetyl-6-O-*p*-toluenesulfonyl-*β*-maltosyl N,N-Dimethyldithiocarbamate (XIII)——Amorphous 2,3,2′,3′,4′,6′-hexa-O-acetyl-6-O-*p*-toluenesulfonyl-*α*-maltosyl bromide (0.9 g) and sodium N,N-dimethyldithiocarbamate (0.17 g) in acetone (5 ml) was treated similarly with the procedure described for the preparation of XI to afford crude XIII. Recrystallization from MeOH gave pure product (0.6 g, 64%), mp 154—155°, $[\alpha]_D^{17}$ +73.4° (c=0.9, $CHCl_3$); UV $\lambda_{max}^{EtOH\text{-}dioxane}$ mμ (log ε): 277 (4.25); NMR ($CDCl_3$): 6.35, 6.53 (6H, s, $N(CH_3)_2$), 7.43 (3H, s, SO_2–C_6H_4–$C\underline{H}_3$), 7.80, 7.84, 7.87, 7.90 (18H, s, 6×OAc); TLC: *Rf* 0.56 (solvent A), 0.34 (B). *Anal.* Calcd. for $C_{34}H_{45}O_{18}NS_3$: C, 47.94; H, 5.32; N, 1.64. Found: C, 47.64; H, 5.55; N, 1.80.

2,3,2′,3′,4′,6′-Hexa-O-acetyl-*β*-maltosyl Ethylxanthate (XIV)——Crude 2,3,2′,3′,4′,6′-hexa-O-acetyl-*α*-maltosyl bromide was prepared from II and titanium bromide as described for the preparation of III. To the bromide (1 g) were added potassium ethylxanthate (0.3 g) and EtOH (5 ml), and the mixture was warmed for few min at 70° under stirring to effect dissolution. After keeping for 5 hr at room temperature, the mixture was poured into ice-H_2O (80 ml). The precipitate was collected by filtration and air-dried (0.63 g). This was dissolved in CH_2Cl_2 (3 ml) and chromatographed on a column of silica gel, by elution with CH_2Cl_2–acetone (50: 1, 30: 1, v/v). The fractions were judged by TLC (solvent A and B). Removal of the solvent from fractions containing a single spot gave a sirup which crystallized from EtOH. Recrystallization from EtOH gave white needles (0.35 g, 33%), mp 155—156°, $[\alpha]_D^{14}$ +86.8° (c=1, $CHCl_3$); UV λ_{max}^{EtOH} mμ (log ε): 273 (3.99); IR ν_{max}^{Nujol} 3670 cm^{-1} (OH); NMR ($CDCl_3$): 7.52 (1H, broade singlet, OH). 7.92, 7.96, 7.98, 8.00 (18H, s, 6×OAc), 8.53 (3H, t, J=7 Hz, CH_2–$C\underline{H}_3$); TLC: *Rf* 0.43 (solvent A), 0.47 (B). *Anal.* Calcd. for $C_{27}H_{38}O_{17}S_2$: C, 46.41; H, 5.48. Found: C, 46.47; H, 5.71.

Methanesulfonylation or *p*-toluenesulfonylation of XIV afforded X or XII in 52 or 65% yield, respectively.

1,6-Anhydro-2,3,2′,3′,4′,6′-hexa-O-acetyl-6-deoxy-6-thio-*β*-maltose (6-Thiomaltosan Hexaacetate) (XV)——A mixture of X (1.2 g) in sodium methoxide in MeOH (0.5 g of Na in 25 ml of MeOH) was stirred for 20 min at room temperature, and then the mixture was left to stand overnight. It was neutralized with glacial AcOH (*ca.* 0.6 ml) and evaporated to dryness. The residue was acetylated with pyridine (10 ml) and Ac_2O (12 ml) for 40 hr at 0°. The mixture was poured into ice-H_2O (200 ml). The resulting precipitate was collected by filtration and air-dried. Further crops of crystals were extracted from the filtrate with CH_2Cl_2 (2×30 ml). The combined crude product was recrystallized from MeOH to give pure XV (0.6 g, 65%), mp 135—137°, $[\alpha]_D^{21}$ +82° (c=1, $CHCl_3$); NMR ($CDCl_3$): 7.88, 7.93, 7.97, 7.98 (18H, s, 6×OAc); TLC: *Rf* 0.46 (solvent A), 0.40 (B). *Anal.* Calcd. for $C_{24}H_{32}O_{15}S$: C, 48.64; H, 5.44. Found: C, 48.51; H, 5.40.

Compound (XV) (70 mg, 59%) was also obtainable from XII (170 mg) with the similar procedure.

2,3-Di-O-acetyl-1,5-anhydro-4-O-(2′,3′,4′,6′-tetra-O-acetyl-*α*-D-glucopyranosyl)-6-deoxy-D-glucitol (XVI)——A mixture of XV (0.22 g) and freshly activated Raney Ni (3 g) in AcOEt (25 ml) was boiled gently under reflux for 5 hr, filtered, and the residue was washed with AcOEt. The combined filtrate and washings were evaporated to dryness to give a sirup which crystallized from EtOH. The crystals were collected by filtration and recrystallized from EtOH to give pure XVI (0.14 g, 67%), mp 130—131°, $[\alpha]_D^{15}$ +79.6° (c=0.6, $CHCl_3$); NMR ($CDCl_3$): 7.91, 7.98, 8.00 (18H, s, 6×OAc), 8.62 (3H, d, $J_{5,6}$=5.5 Hz, C_5–CH_3); TLC: *Rf* 0.46 (solvent A), 0.43 (B). *Anal.* Calcd. for $C_{24}H_{34}O_{15}$: C, 51.24; H, 6.09. Found: C, 51.14; H, 6.39.

1,5-Anhydro-4-O-(*α*-D-glucopyranosyl)-6-deoxy-D-glucitol (XVII)——Deacetylation of XVI (150 mg) was performed with the similar method described for the preparation of IX to afford amorphous powders (68 mg, 82%), $[\alpha]_D^{23}$ +111° (c=1, H_2O), homogeneous by TLC; *Rf* 0.56 (solvent C).

1,2,3,2′,3′,4′,6′-Hepta-O-acetyl-6-S-acetyl-6-deoxy-6-thio-*α*-maltose (XVIII)——Compound (XV) (100 mg) was dissolved in acetolysis mixture (5 ml, 1: 70: 30 (v/v) H_2SO_4–Ac_2O–AcOH). After stirring for 3.5 hr at room temperature, the solution was poured into ice-H_2O (70 ml), and the mixture was extracted with CH_2Cl_2 (3×20 ml). The combined extracts were washed successively with satd. $NaHCO_3$ solution and H_2O, dried ($CaCl_2$), and evaporated to dryness to afford a sirup which crystallized from MeOH. Crystals were collected by filtration and recrystallized from MeOH to afford pure XVIII (27 mg, 23%), mp 177—178°, $[\alpha]_D^{25}$ +138.4° (c=0.5, $CHCl_3$); IR ν_{max}^{Nujol}: 1690 cm^{-1} (SAc); NMR ($CDCl_3$): 7.63 (3H, s, SAc), 7.78, 7.91, 7.94, 8.00, 8.02 (21H, s, 7×OAc); TLC: *Rf* 0.49 (solvent A), 0.40 (B). *Anal.* Calcd. for $C_{28}H_{38}O_{18}S$: C, 48.41; H, 5.51. Found: C, 48.25; H, 5.58.

1,6-Anhydro-6-deoxy-6-thio-*β*-maltose (6-Thiomaltosan) (XIX)——To a suspension of XV (110 mg) in dry MeOH (3 ml) was added 0.1 ml of 1 N sodium methoxide in MeOH. After stirring for 6 hr at room temperature, complete deacetylation was judged by TLC (solvent C). Dry Amberlite IR-120 (H^+) resin was added, and the suspension was stirred for 30 min. Removal of the solvent from the filtrate afforded hygroscopic amorphous powders (56 mg, 89%), $[\alpha]_D^{16}$ +66.1° (c=0.8, MeOH), homogeneous by TLC; *Rf* 0.55 (solvent C).

Hepta-O-acetyl-*β*-maltosyl Ethylxanthate (XX)——Amorphous hepta-O-acetyl-α-maltosyl bromide, $[\alpha]_D^{14}$ +170.6° (c=1.4, $CHCl_3$) was prepared according to the method described by Scheurer and Smith.[24] To a solution of potassium ethylxanthate (4 g) in EtOH (60 ml) was added the bromide (16 g). The mixture was warmed for 5 min on a steam bath (80—85°) to effect dissolution, left to stand for 30 min at room temperature, and then poured into ice-H_2O (400 ml). The resulting powders were collected by filtration and air-dried. Recrystallization from ether–petr. ether (bp 30—60°) gave pure XIX (14 g, 85%), mp 83—85°, $[\alpha]_D^{24}$ +75.4° (c=3.56, $CHCl_3$); UV λ_{max}^{EtOH} mμ (log ε): 273 (4.08); NMR ($CDCl_3$): 7.84, 7.90, 7.93, 7.97 (21H, s, 7×OAc), 8.58 (3H, t, J=7.5 Hz, CH_2–$C\underline{H}_3$); TLC: *Rf* 0.54 (solvent A), 0.47 (B). *Anal.* Calcd. for $C_{29}H_{40}O_{18}S_2$: C, 47.02; H, 5.44. Found: C, 47.05; H, 5.39.

Hepta-O-acetyl-*β*-maltosyl N,N-Dimethyldithiocarbamate (XXI)——A mixture of hepta-O-acetyl-α-maltosyl bromide[24] (4 g) and sodium N,N-dimethyldithiocarbamate (1 g) in acetone (15 ml) was warmed for few min to a boiling, left to stand for 1 hr at room temperature, and then poured into ice-H_2O (120 ml). The resulting precipitate was collected by filtration and air-dried. Recrystallization from MeOH gave pure XXI (2 g, 45%), mp 132—133°, $[\alpha]_D^{25}$ +79.3° (c=1, $CHCl_3$); UV λ_{max}^{EtOH} mμ (log ε): 242 (3.49), 278 (3.84); NMR ($CDCl_3$): 6.44, 6.62 (6H, s, $N(CH_3)_2$), 7.87, 7.91, 7.93, 7.97 (21H, s, 7×OAc); TLC: *Rf* 0.50 (solvent A), 0.32 (B). *Anal.* Calcd. for $C_{29}H_{41}O_{17}NS_2$: C, 47.07; H, 5.58; N, 1.89. Found: C, 46.71; H, 5.54; N, 1.93.

2,3,6-Tri-O-acetyl-1,5-anhydro-4-O-(2′,3′,4′,6′-tetra-O-acetyl-*α*-D-glucopyranosyl)-D-glucitol (XXII)——

1) From Compound (XX): A mixture of XX (2 g) and freshly activated Raney Ni (20 g) in EtOH (30 ml) was boiled gently under reflux for 3 hr. The Ni was removed by filtration and washed with EtOH. The combined filtrate and washings were evaporated to dryness to afford a sirup which crystallized from EtOH. The crystals were collected by filtration and recrystallized from EtOH to give pure XXII (1 g, 60%), mp 125—127°, $[\alpha]_D^{14}$ +83.3° (c=1, $CHCl_3$) (lit.[19] mp 133—134°, $[\alpha]_D^{20}$ +82° ($CHCl_3$)). *Anal.* Calcd. for $C_{26}H_{36}O_{17}$: C, 50.32; H, 5.80. Found: C, 50.27; H, 6.15.

2) From Compound (XXI): A mixture of XXI (100 mg) and freshly activated Raney Ni (1.5 g) in AcOEt (13 ml) was boiled under reflux for 5 hr. Similar treatment of the mixture as described in method 1) afforded crystal (60 mg, 71%), which was indistinguishable with a product prepared by method 1).

1-Thio-*β*-maltose Sodium Salt (XXIII)——A solution of XX (1.2 g) in $CHCl_3$ (5 ml) was cooled to −15° and treated, under stirring and cooling, with an equally cold methanolic solution (10 ml) of sodium methoxide containing 0.15 g of Na; the mixture became turbid as the reaction took place. Stirring and cooling were continued for 15 min. The resulting precipitate was collected by filtration, washed with $CHCl_3$, and dried in a vacuum desiccator to afford hygroscopic amorphous powders (0.58 g, 94%), $[\alpha]_D^{24}$ +90.7° (c=1.86, H_2O).

1-S-Acetyl-1-thio-2,3,6,2′,3′,6′-hepta-O-acetyl-*β*-maltose (XXIV)——1) A solution of XXIII (150 mg) in dry pyridine (1.5 ml) was treated at 0° with Ac_2O (1.5 ml). The solution was kept at room temperature overnight, and was then poured into ice-H_2O (30 ml). The precipitate was separated, washed with H_2O, and air-dried. Recrystallization from EtOH gave white crystals (130 mg, 48%), mp 152—153°, $[\alpha]_D^{24}$ +69° (c=1, $CHCl_3$); IR ν_{max}^{Nujol}: 1700 cm^{-1} (SAc); NMR ($CDCl_3$): 7.63 (3H, s, SAc), 7.84, 7.88, 7.91, 7.95, 7.98, 8.00 (21H, s, 7×OAc); TLC: *Rf* 0.44 (solvent A), 0.41 (B). *Anal.* Calcd. for $C_{28}H_{38}O_{18}S$: C, 48.41; H, 5.51. Found: C, 48.00; H, 5.44.

2) A mixture of hepta-O-acetyl-α-maltosyl bromide[24] (3 g) and potassium thiolacetate (0.58 g) in acetone (30 ml) was boiled gently under reflux for 7 min. After keeping for 1.5 hr at room temperature, the mixture was poured into ice-H_2O (200 ml). The resulting precipitate was collected by filtration and air-dried. Recrystallization from EtOH gave white crystal (1.4 g, 47%), mp 153—155°, which was indistinguishable with a product prepared by method 1).

β-Maltosyl N,N-Dimethylditiocarbamate (XXV)——To a suspension of XXI (0.5 g) in dry MeOH (12 ml) was added 0.5 ml of 0.5N sodium methoxide in MeOH. The mixture was stirred for 1 hr at room temperature and was kept overnight. Dry Amberlite IR-120 (H^+) resin was added, stirred for 30 min, and the mixture was filtered. Evaporation of the solvent from the filtrate afforded hygroscopic amorphous powders (210 mg, 67%), $[\alpha]_D^{24}$ +46.7° (c=1.2, H_2O); TLC: *Rf* 0.58 (solvent C). *Anal.* Calcd. for $C_{15}H_{27}O_{10}NS_2 \cdot H_2O$: C, 38.87; H, 6.31; N, 3.02. Found: C, 38.93; H, 6.14; N, 2.45.

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[24] P.G. Scheurer and F. Smith, *J. Am. Chem. Soc.*, **76**, 3224 (1954).