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31. Setsuzo Tejima and Susumu Ishiguro: Thiosugars. X.*1 Studies on Glycosyl N,N-Dialkyldithiocarbamates.

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Several crystalline β-D-glycopyranosyl N,N-dialkyldithiocarbamates (sugar=gluco, galacto, xylo or lacto; alkyl=methyl or ethyl) were synthesized by reaction of sodium N,N-dialkyldithiocarbamates with acetylated α-D-glycopyranosyl bromides and sequential deacetylation with methanolic ammonia or sodium methoxide in methanol.

Although the glycosyl dithiocarbamates were stable against chilled alkalis and which is a marked difference from glycosyl xanthates or isothiuronium, easily decomposed with mercury salts to form glycosides under the presence of alcohols or phenols.

D-Glucopyranosyl N,N-diethyldithiocarbamates having N,N-diethyldithiocarbamoyl radical $\left(\begin{matrix}C_2H_5\\C_2H_5\end{matrix}\!\!>\!N\!-\!\overset{\overset{S}{\|}}{C}\!-\!S-\right)$ at C6 in acetylated D-glucoses or methyl D-glucopyranosides, along with the didithiocarbamate having two carbamoyls at C1 and C6 in acetylated D-glucopyranose, were also synthesized.

Reflux of methyl β-D-glucopyranoside-6-deoxy-6-N,N-diethyldithiocarbamate with sodium methoxide in methanol afforded methyl 6-deoxy-6-thio-β-D-glucopyranoside, isolated as its tetraacetate. The method presented a novel synthetic way of thiosugars.

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Since several years ago the authors have synthesized sugar xanthates[1] ($R\text{-}S\overset{\overset{S}{\|}}{C}O\text{-}R'$, R=sugar moiety, R'=aralkyl), and confirmed that while acetylated sugar xanthates were a good intermediate for the preparation of thiosugars as pointed out by German chemists,[2] most free sugar xanthates were amorphous or hygroscopic solids and rather difficult to induce crystals.

It has been well known that potassium aralkyl xanthates, the starting material for the thiosugars synthesis, are unstable[3] and hygroscopic, and decompose in the moist air. In addition, as we have suggested in the earlier paper[4] of this series, potassium methyl- or benzylxanthate shows an anomalous reaction which do no yield sugar xanthates, but thioglycosides or β,β-diglycosyl sulfides. Although potassium thiolacetate is a good reagent for thiosugar synthesis, it is also hygroscopic, far more expensive and not suitable for a large scale preparation.

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*1 Part IX. K. Araki, S. Tejima: This Bulletin, **14**, 1303 (1966).

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1) M. Akagi, S. Tejima, M. Haga: This Bulletin, 8, 1114 (1960); *Idem*: *Ibid.*, **9**, 360 (1961), **10**, 562 (1962); S. Tejima, T. Maki, M. Akagi: *Ibid.*, **12**, 528 (1964); T. Maki, H. Nakamura, S. Tejima, M. Akagi: *Ibid.*, **13**, 764 (1965).

2) W. Schneider, R. Gille, K. Eisfeld: Ber., **61**, 1244 (1928); M. Gehrke, W. Kohler: *Ibid.*, **64**, 2696 (1931).

3) A. Pomianowski, J. Leja: Can. J. Chem., **41**, 2219 (1963).

4) M. Sakata, M. Haga, S. Tejima, M. Akagi: This Bulletin, **12**, 652 (1964).

From these standpoints we have been looking for other reagents suitable for introducing thiol group into sugar molecule. In 1956, Kulka[5] reported that aralkyl N,N-dimethyldithiocarbamate, which could be easily obtained from aralkyl chloride and sodium N,N-dimethyldithiocarbamate (I), gave the corresponding mercaptans in high yields when heated with alkali or hydrazine. The authors designed the expansion of his reaction in sugars.

On the one hand, salts of N,N-dialkyldithiocarbamic acid have been used widely as fungicides, insecticides or drugs for external use.[6] Tetraethylthiuram disulfide (Antabuse) which is obtainable by oxidation of N,N-diethyldithiocarbamates is known as an inhibitor to aldehydeoxidase. From these reasons we expected that the title compounds, the condensation products of sodium N,N-dialkyldithiocarbamates with sugars, presumably might have some physiological activities.

Concering to glycosyl N,N-dialkyldithiocarbamates, so far as we know, only two papers have been referred in literatures. The one which has been reported by Kaslander *et al.*[7] is that plant tissues are able to transform sodium N,N-dimethyldithiocarbamate into the corresponding thioglucoside. The other roport by the same author is the formation of S-glucuronide in human urine administrated with Antabuse.[8] However, as both of them are short communications, we cannot get detailed information on the properties or preparative method on the glycosyl dithiocarbamates.

The authors were able to synthesize several glycosyl N,N-dialkyldithiocarbamates, in which N,N-dialkyldithiocarbamoyl radical $\left(\begin{matrix}R\\R\end{matrix}\right)N-\overset{\overset{S}{\|}}{C}-S-$, R=methyl or ethyl) was introduced instead of the anomeric hydroxyl in sugars or the terminal in D-glucopyranose. The present paper describes full details of this work.

Reaction of sodium N,N-dialkyldithiocarbamate (alkyl=methyl or ethyl) (I or II) with acetylated glycosyl bromides in warm acetone afforded crystalline products which were easily recrystallizable from boiling alcohols to give pure material in good yields. In the case of D- or L-arabinose series neither methyl nor ethyl crystallized as yet, and only methyl derivative crystallized in D-xylose. Generally, glycosyl N,N-dimethyldithiocarbamates were more easily crystallizable, less soluble and had higher melting points than that of N,N-diethyl derivatives.

An ethanolic solution of glycosyl N,N-dialkyldithiocarbamate has strong absorptions near at 240 and 280 mμ. Reductive desulfurization of the acetylated carbamates resulted the corresponding acetylated 1,5-anhydroglycitols which confirmed the structure of the former. In the pyranose series which have been used in this paper, as acetylated bromides maintain the α-configuration, the resulting carbamates must be β owing to the Walden inversion involving in the course of the reaction.

Treatment of the acetylated carbamates with cold sodium methoxide, ammonia or hydrogen chloride in methanol afforded glycosyl dithiocarbamates which were easily recrystallizable, except one example, from warm water: β-D-glucopyranosyl N,N-diethyldithiocarbamate (IX) was rather difficult to crystallize from water and recrystallizable from isopropyl alcohol. Thus, glycosyl dithiocarbamates are stable against both chilled alkalis and acids. The property is the marked difference from glycosyl xanthates or isothiuronium which are very unstable against chilled alkalis and decompose to mercaptan.

5) M. Kulka: Can. J. Chem., **34**, 1093 (1956).
6) E. E. Reid: "Organic Chemistry of Bivalent Sulfur," Vol. IV, 196 (1962), Chemical Publishing Co., Inc., New York.
7) J. Kaslander, A. K. Sijpesteijn, G. J. M. Van der Kerk: Biochem. et Biophys. Acta, **52**, 396 (1961).
8) J. Kaslander: *Ibid.*, **71**, 730 (1963).

On the contrary, glycosyl dithiocarbamates are very easily decomposed with mercury salts. Boiling with mercuric chloride in methanol for fifteen minutes yielded methyl α-D-glycopyranoside in good yields. The glycosidation also proceeded under more mild condition. Treatment with mercuric chloride and mercuric oxide mixture in methanol at room temperature afforded the same compound. The condition is that of the formation of glycofuranosides from dithioacetals of sugars[9] and the mother liquid, from which the α-D-glycoside had been separated, was still strong dextrorotatory. From the facts, the replacement with methoxy in glycosyl dithiocarbamates might have occurred by S_N2 without a cleavage of the lactol ring.

Fusion of the acetylated carbamate with *p*-nitrophenol in the presence of mercuric cyanide under vacuum afforded acetylated *p*-nitrophenyl β-D-glucopyranoside in good yields. Our finding might have been an interesting by contrast with that of Ferier and Westphal[10] who reported that mercuric cyanide was a good catalyst for obtaining an α-anomer from acetylated sugars by fusion method.

In treatment of β-D-glucopyranosyl N,N-dimethyldithiocarbamate (V) with silver benzoate in boiling acetonitrile and subsequent acetylation of the reaction product, only 1,3,4,6-tetra-O-acetyl-2-O-benzoyl-α-D-glucose was isolated as a crystalline product in low yield. Presumably, the product was formed by 1→2-O-benzoyl migration of an initially formed 1-O-benzoyl-α-D-glucose. The finding was almost an identical with that which has been reported by Pedersen and Fletcher[11] who obtained the same compound starting from D-glucose diethyldithioacetal or 1-thio-β-D-glucopyranoside with the similar treatment.

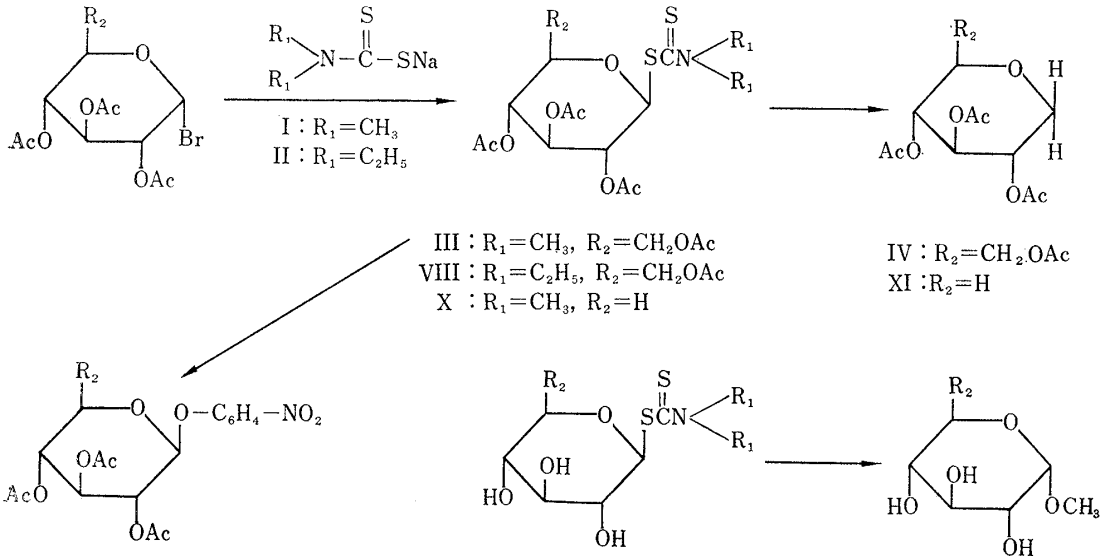

Chart 1.

In the next step, we projected the synthesis of glucosyl dithiocarbamate having dithiocarbamoyl radical on the terminal carbon in D-glucopyranose. A mixture of one of the anomeric 1,2,3,4-tetra-O-acetyl-6-deoxy-6-iodo-D-glucopyranoses and II in acetone was treated to give crystals, m.p. 131°, $[\alpha]_D^{20}$ +99° (XXIV) and m.p. 142°, $[\alpha]_D^{20}$ +12.8°

9) E. Pacsu : "Methods in Carbohydrate Chemistry," Vol. II, 354 (1963), Academic Press Inc., New York and London.
10) H. Ferier, O. Westphal : Chem. Ber., **89**, 589 (1956).
11) C. Pedersen, H.G. Fletcher, Jr. : J. Am. Chem. Soc., **82**, 3215 (1960).

(XXV), respectively. Reductive desulfurization of XXV afforded tetra-O-acetyl chinovose. Treatment of XXV with hydrogen bromide yielded bromide (XXVI). Crystals, m.p. 155°, $[\alpha]_D^{20}$ +24.4°, was obtained when a mixture of XXVI and II was treated in acetone, whose structure was confirmed to be 2,3,4-tri-O-acetyl-β-D-glucopyranosyl-1,6-dideoxy-1,6-di-N,N-diethyldithiocarbamate (XXVII) as follows. Reductive desulfurization gave 1,5-anhydro-2,3,4-tri-O-acetyl-6-deoxy-D-sorbitol which has been obtained by one of us[12] with the similar treatment of thiolevoglucosan. The product (XXVII) was also prepared by reaction of II with 2,3,4-tri-O-acetyl-6-deoxy-6-iodo-D-glucopyranosyl N,N-diethyldithiocarbamate which was prepared after replacement of the primary tosyl to iodine in 2,3,4-tri-O-acetyl-6-O-tosyl-β-D-glucopyranosyl N,N-diethyldithiocarbamate, prepared by one mole tosylation of IX.

Reaction of methanolic hydrogen chloride upon XXV yielded the corresponding methyl glucosides with concomitant deacetylation. The β-anomer, m.p. 176°, $[\alpha]_D^{20}$ +32.8°, was first crystallized and, the sirupy α-anomer separated as its triacetate, m.p. 128~131°, $[\alpha]_D^{20}$ +112°, after acetylation of the mother liquid. The structures were confirmed by the facts that the β-anomer was also prepared starting from the bromide (XXVI) after

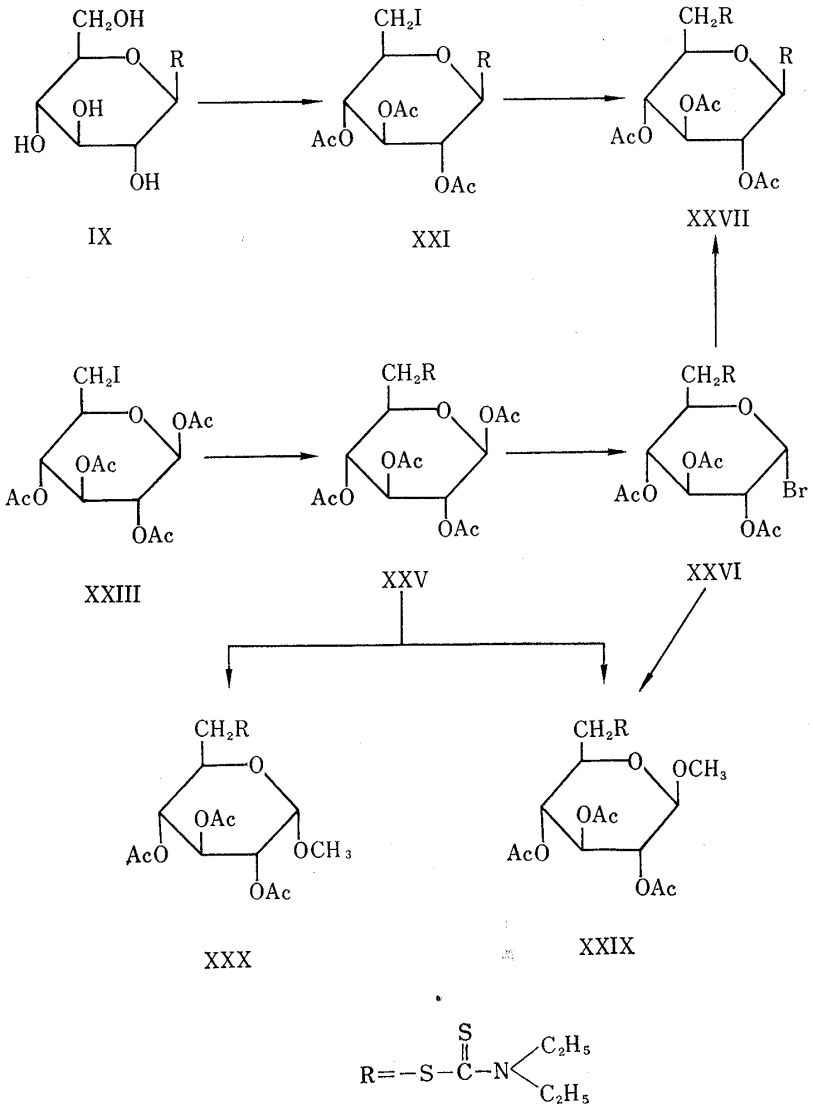

Chart 2.

12) M. Akagi, S. Tejima, M. Haga : This Bulletin, **11**, 58 (1963).

treatment with the Koenigs-Knorr's methylglucosidation and α-anomer obtained by condensation of Ⅱ with methyl 2,3,4-tri-O-acetyl-6-deoxy-6-iodo-α-D-glucopyranoside.

Reflux of the β-anomer with excess sodium methoxide in methanol for 13 hours gave methyl 6-deoxy-6-thio-β-D-glucopyranoside, isolated as its tetraacetate. The method presents a novel synthetic way of thiosugars. However, thiosugars having sulfhydryl at C1 are not able to synthesize by this method because of the instability of reducing sugars against alkalis.

Synthesis of glycosyl dithiocarbamates having N,N-dialkyldithiocarbamoyl radical in the place of a secondary hydroxyl in sugars and studies on physiological activities of the preparations described in this paper, will be mentioned in the near future.

Experimental

Unless stated otherwise, solvents were evaporated *in vacuo* at a bath temperature of 40° in a rotary evaporator. Sodium N,N-diethyldithiocarbamate (Ⅱ), which was recrystallized from 5 parts of boiling Me_2CO, was prepared from NaOH, CS_2 and Et_2NH by a slight modification of Kulka[5] for the preparation of Na N,N-dimethyldithiocarbamate (I).

2,3,4,6-Tetra-O-acetyl-β-D-glycopyranosyl N,N-Dimethyldithiocarbamate (III)——A mixture of I (20 g.) and 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide (57 g.) in Me_2CO (100 ml.) was warmed for a few min. to a boiling. Then remove the heating and allowed to stand for 1 hr. at room temperature. The mixture was poured into ice-H_2O (2 L.) containing AcOH (20 ml.), the resulting white powder separated by filtration, dried in the air and recrystallized from 4 parts of boiling MeOH to give pure material (57 g., 90%), m.p. 114°, $[\alpha]_D^{20}$ +25.8°(c=2.44, $CHCl_3$), UV λ_{max}^{EtOH} mμ : 238, 278. *Anal.* Calcd. for $C_{17}H_{25}O_9NS_2$: C, 45.23; H, 5.58; N, 3.10; S, 14.20. Found : C, 45.24; H, 5.63; N, 3.09; S, 14.13.

1,5-Anhydro-2,3,4,6-tetra-O-acetyl-D-glucitol (Tetraacetylpolygalitol) (IV)——A mixture of Ⅲ (5 g.) and approximately 60 g. of freshly prepared Raney Ni in 70% aq. EtOH (200 ml.) was boiled gently under reflux for 4 hr. The supernatant solution was then removed, the Ni washed with 70% aq. EtOH, and the combined filtrate and washings were concentrated to dryness. The residue was recrystallized twice from benzene-petr. ether to give pure material (2.5 g., 70%), m.p. 64~65°, $[\alpha]_D^{20}$ +40.2°(c=2.14, $CHCl_3$). *Anal.* Calcd. for $C_{14}H_{20}O_9$: C, 50.66; H, 6.07. Found : C, 50.72; H, 5.97. Richtmyer and Hudson[13] reported m.p. 65~67° or 73~74°(dimorphism), $[\alpha]_D^{20}$ +38.9°(c=2, $CHCl_3$) for tetraacetylpolygalitol.

β-D-Glucopyranosyl N,N-Dimethyldithiocarbamate (V)——Dry NH_3-gas was passed to saturation at 0° through a chilled suspension of Ⅲ (20 g.) in dry MeOH (200 ml.). After 48 hr. at room temperature, the solvent was removed to give a gelatinous residue (15 g.). Twice recrystallizations from 2 parts of warm H_2O gave pure material, m.p. 101~102°, $[\alpha]_D^{20}$ −44.9°(c=1.76, H_2O), UV λ_{max}^{EtOH} mμ : 243, 278. *Anal.* Calcd. for $C_9H_{17}O_5NS_2$: C, 38.14; H, 6.05; N, 4.94; S, 22.63. Found : C, 38.08; H, 6.05; N, 4.79; S, 22.82.

Acetylation of Ⅴ (1 g.) with pyridine (5 ml.) and Ac_2O (5 ml.) for 18 hr. gave acetate (1.4 g., 83%) which was identical with Ⅲ in mixed m.p. and infrared (IR). While, D-glucose phenylosazone did not appear after heating a mixture of Ⅴ (1 g.), $PhNHNH_2HCl$ (2 g.) and $AcONa \cdot 3H_2O$ (3 g.) in H_2O (20 ml.) in a steam bath for 3 hr.

Methyl α-D-Glucopyranoside (VI)——a) A mixture of Ⅴ (4 g.) and $HgCl_2$ (10 g., 3 mole) in dry MeOH (60 ml.) was boiled under reflux for 15 min. After cooling, the mixture was filtered from the precipitate. The Hg was removed with H_2S and, after filtration, the colorless filtrate eveporated to give a sirup which crystallized on trituration with cold EtOH. Crystals (1.8 g., 65%) were collected by filtration and recrystallized from 15 parts of boiling EtOH to give pure material, m.p. 166°, $[\alpha]_D^{20}$ +157°(c=1.86, H_2O). Fischer[14] gave m.p. 166°, $[\alpha]_D^{20}$ +157° for methyl α-D-glucopyranoside.

Acetylation of Ⅵ (1 g.) with Ac_2O (5 ml.) and pyridine (5 ml.) for 18 hr. gave tetraacetate (1.5 g., 80%), m.p. 102~103°, $[\alpha]_D^{20}$ +175°(c=1.57, benzene). Koenigs and Knorr[15] reported m.p. 100~101°, $[\alpha]_D^{20}$ +175.35° (c=5.7, benzene) for methyl 2,3,4,6-tetra-O-acetyl-α-D-glucopyranoside.

b) A mixture of Ⅴ (6.5 g.), $HgCl_2$ (13 g.) and yellow HgO (10.5 g.) in MeOH (130 ml.) was shaken for 2.5 hr. at room temperature. The mixture was filtered and pyridine (3 ml.) added to the filtrate. After standing overnight in a refrigerator, the solution was filtered and concentrated to a sirup. This was dissolved in a minimum amount of cold H_2O, and the solution filtered from a small amount of the pyridine complex. After addition of a few drops of dil. alkali (phenolphthalein), the solution was concentrated to dryness. Crystallization was induced after addition of EtOH (10 ml.), then filtered. Recrystallization from 15 parts of EtOH gave pure material (3 g., 65%), m.p. 166°, $[\alpha]_D^{20}$ +157°(c=2.08, H_2O).

13) N. K. Richtmyer, C. S. Hudson : J. Am. Chem. Soc., **65**, 64 (1943).
14) E. Fischer : Ber., **26**, 2400 (1893).
15) W. Koenigs, E. Knorr : *Ibid.*, **34**, 957 (1901).

***p*-Nitrophenyl 2,3,4,6-Tetra-O-acetyl-β-D-glucopyranoside (VII)**——A mixture of *p*-nitrophenol (6 g.), III (6 g.) and $Hg(CN)_2$ (3 g.) was heated in an oil bath at 130° under a suction pump (15 mm. Hg). After 30 min. the bath temperature was risen at 160°, the heating continued for further 30 min. and then stopped the heating. At room temperature, $CHCl_3$ (70 ml.) was added to separate organic material from Hg-salts, the $CHCl_3$-layer washed with an equal vol. of H_2O and then with 0.5*N* NaOH until the aq. layer was almost colorless. The solution was finally washed twice with H_2O, dried over $CaCl_2$ and evaporated to dryness. Recrystallization from warm EtOH (50 ml.) gave pure material (4.5 g., 75%), m.p. 173~174°, $[\alpha]_D^{20}$ −39.8° (c=1.65, $CHCl_3$). *Anal.* Calcd. for $C_{20}H_{23}O_{12}N$: C, 51.19; H, 4.94. Found: C, 51.06; H, 5.02. Goebel and Avery[16] reported m.p. 172~173°, $[\alpha]_D^{20}$ −40.8°(c=1.06, $CHCl_3$) for *p*-nitrophenyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside.

A suspension of VII (3 g.) in MeOH (30 ml.), previously saturated with dry NH_3-gas at 0°, was allowed to stand at room temperature for 48 hr. The mixture was evaporated to dryness and the residue recrystallized from boiling MeOH (30 ml.) to give glucoside, m.p. 165~166°, $[\alpha]_D^{20}$ −76.4°(c=0.8, MeOH). Goebel and Avery[16] reported m.p. 165°, $[\alpha]_D^{20}$ −79.6°(c=0.94, MeOH) for *p*-nitrophenyl β-D-glucopyranoside.

Reaction of β-D-Glucopyranosyl N,N-Dimethyldithiocarbamate (V) with Silver Benzoate——Two grams of V dissolved in AcCN (50 ml.) was treated with Ag benzoate (6 g.) and the solution boiled under reflux for 3 hr. The cooled mixture was filtered, the solvent removed from the filtrate and the amorphous residue dissolved in MeOH (50 ml.). The Ag was removed with H_2S and, after filtration, the solution was concentrated to a sirup. It was then dissolved in H_2O and extracted with ether to remove benzoic acid. Upon reconcentration there was obtained a sirup which acetylated with pyridine (5 ml.) and Ac_2O (5 ml.) at room temperature for 15 hr. to give an amorphous product. Twice recrystallizations from MeOH gave crystalline material (170 mg., 6%), m.p. 185~186°, $[\alpha]_D^{20}$ +48.4°(c=0.8, $CHCl_3$). *Anal.* Calcd. for $C_{21}H_{24}O_{11}$: C, 55.75; H, 5.35. Found: C, 55.93; H, 5.40. Pedersen and Fletcher[11] reported m.p. 185~186°, $[\alpha]_D^{20}$ +49.9°(c=0.55, $CHCl_3$) for 1,3,4,6-tetra-O-acetyl-2-O-benzoyl-α-D-glucose.

2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl N,N-Diethyldithiocarbamate (VIII)——A mixture of II (24 g.) and 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide (58 g.) in Me_2CO (120 ml.) was treated by a slight modification*3 in III to give crude VIII. Twice recrystallizations from 3 parts of boiling EtOH gave pure material (55 g., 79%), m.p. 83~85°, $[\alpha]_D^{20}$ +32.9°(c=2.89, $CHCl_3$), UV λ_{max}^{EtOH} mμ: 243, 258. *Anal.* Calcd. for $C_{19}H_{29}O_9NS_2$: C, 47.54; H, 6.09; N, 2.92; S, 13.37. Found: C, 47.58; H, 5.95; N, 3.01; S, 13.59.

Reductive desulfurization of VIII with Raney Ni as described in IV also yielded IV in 75% yield.

β-D-Glucopyranosyl N,N-Diethyldithiocarbamate (IX)——A suspension of VIII (20 g.) in dry MeOH (60 ml.) was cooled to −15° and treated, under stirring and cooling, with an equally cold MeOH solution (60 ml.) of MeONa containing Na (2 g.). The stirring was continued for 1 hr., and then allowed to stand for 4 hr. in a refrigerator. AcOH was added dropwise until a drop of the solution was neutral to phenolphthalein. The solvent was evaporated to dryness and the residue dissolved in H_2O (100 ml.) and passed through a column of Amberlite IR-120 (H^+). The effluent was concentrated to a sirup which solidified after seeding*4 and scratching the side of the flask. The meterial (12 g., 95%) was recrystallized from warm iso. PrOH (25 ml.) to give pure material, m.p. 121~122°, $[\alpha]_D^{20}$ −40°(c=1.5, H_2O), UV λ_{max}^{EtOH} mμ: 246, 282. *Anal.* Calcd. for $C_{11}H_{21}O_5NS_2$: C, 42.39; H, 6.80; N, 4.50; S, 20.59. Found: C, 42.37; H, 6.80; N, 4.53; S, 20.61.

2,3,4-Tri-O-acetyl-β-D-xylopyranosyl N,N-Dimethyldithiocarbamate (X)——A mixture of 2,3,4-tri-O-acetyl-α-D-xylopyranosyl bromide (48 g.) and I (21 g.) in dry Me_2CO (120 ml.) was treated as described in III to afford crude X. Recrystallization from MeOH gave pure material (40 g., 76%), m.p. 137~139°, $[\alpha]_D^{20}$ +54.4°(c=3.09, $CHCl_3$), UV λ_{max}^{EtOH} mμ: 238, 278. *Anal.* Calcd. for $C_{14}H_{21}O_7NS_2$: C, 44.31; H, 5.58; N, 3.70; S, 16.90. Found: C, 44.34; H, 5.65; N, 3.97; S, 17.05.

2,3,4-Tri-O-acetyl-1,5-anhydroxylitol (XI)——Desulfurization of X (5 g.) with the similar method in IV gave the title compound. Recrystallization from EtOH gave pure material (2.5 g., 70%), m.p. 122°, optical inactive. *Anal.* Calcd. for $C_{11}H_{16}O_7$: C, 50.73; H, 6.19. Found: C, 50.62; H, 6.19. Fletcher and Hudson[17] reported m.p. 122~123°, for 2,3,4-tri-O-acetyl-1,5-anhydroxylitol.

β-D-Xylopyranosyl N,N-Dimethyldithiocarbamate (XII)——Deacetylation of X (10 g.) was performed with the similar method in IX. Evaporation of the effluent from the cation resin gave a solid which recrystallized from 2 parts of warm H_2O to give pure material (6 g., 89%), m.p. 173~174°, $[\alpha]_D^{20}$ +9°(c=2.47, $CHCl_3$), UV λ_{max}^{EtOH} mμ: 243, 280. *Anal.* Calcd. for $C_8H_{15}O_4NS_2$: C, 37.94; H, 5.97; N, 5.53; S, 25.32. Found: C, 37.68; H, 6.03; N, 5.54; S, 25.17.

2,3,6,2′,3′,4′,6-Hepta-O-acetyl-β-D-lactopyranosyl N,N-Dimethyldithiocarbamate (XIV)——A mixture of 2,3,6,2′,3′,4′,6′-hepta-O-acetyl-α-D-lactopyranosyl bromide (XIII) (33 g.) and I (7 g.) in Me_2CO (70 ml.) was treated similarly in III. Recrystallization from 4 parts of boiling MeOH gave pure material (27 g., 77%),

*3 When the reaction mixture was poured into ice-H_2O, crude VIII appeared as a gummy precipitates. Solidification was induced after standing for a few days in a refrigerator.

*4 Seeds of IX were first obtained from cyclohexane-benzene mixture.

16) W. F. Goebel, O. T. Avery: J. Expt. Med., **50**, 521 (1929).

17) H. G. Fletcher, Jr., C. S. Hudson: J. Am. Chem. Soc., **69**, 921 (1947).

m.p. 132～136°, $[\alpha]_D^{20}$ +3.9°(c=4.11, $CHCl_3$), UV λ_{max}^{EtOH} mμ : 239, 278. *Anal.* Calcd. for $C_{29}H_{41}O_{17}NS_2$: C, 47.07; H, 5.58; N, 1.89; S, 8.67. Found : C, 46.93; H, 5.56; N, 1.95; S, 8.47.

β-D-Lactopyranosyl N,N-Dimethyldithiocarbamate (XV)——A suspension of XIV (7 g.) in dry MeOH (70 ml.) was treated with dry NH_3 similarly in V. The residue, obtained after evaporation of the solvent, was recrystallized twice from 2 parts of H_2O to give pure material (3.5 g., 83%), m.p. 293～294°, $[\alpha]_D^{20}$ −34.2°(c=1.78, H_2O), UV λ_{max}^{EtOH} mμ : 243, 281. *Anal.* Calcd. for $C_{15}H_{27}O_{10}NS_2$: C, 40.36; H, 6.10; N, 3.14; S, 14.38. Found : C, 40.25; H, 5.96; N, 3.08; S, 14.60.

1,5-Anhydro-4-(β-D-galactopyranosyl)-D-glucitol——Desulfurization of XV (4 g.) with the similar method in IV gave the title compound. Recrystallization from aq. EtOH gave pure material (1.7 g., 63%), m.p. 240°, $[\alpha]_D^{20}$ +54°(c=2.48, H_2O). *Anal.* Calcd. for $C_{12}H_{22}O_{10}$: C, 44.17; H, 6.80. Found : C, 43.85; H, 6.71. Fletcher *et al.*[18] reported m.p. 233～237°, $[\alpha]_D^{20}$ +49.4°(c=2.51, H_2O) for 1,5-anhydro-4-(β-D-galactopyranosyl)-D-glucitol.

2,3,6,2′,3′,4′,6′-Hepta-O-acetyl-β-D-lactopyranosyl N,N-Diethyldithiocarbamate (XVI)——A mixture of XIII (53 g.) and II (12.5 g.) in Me_2CO (125 ml.) was treated similarly in III. Recrystallization from 4 parts of boiling EtOH gave pure material (45 g., 78%), m.p. 143°, $[\alpha]_D^{20}$ +7°(c=2.71, $CHCl_3$), UV λ_{max}^{EtOH} mμ : 241, 282. *Anal.* Calcd. for $C_{31}H_{45}O_{17}NS_2$: C, 48.44; H, 5.91; N, 1.82; S, 8.35. Found : C, 47.89; H, 5.76; N, 1.90; S, 5.84.

β-D-Lactopyranosyl N,N-Diethyldithiocarbamate (XVII)——A suspension of XVI (40 g.) in MeOH (120 ml.) was treated with MeONa in MeOH (120 ml.) containing Na (3.5 g.) similarly in IX to deacetylate. Recrystallization from 10 parts of boiling MaOH gave pure material (20 g., 80%), m.p. 229～231°, $[\alpha]_D^{20}$ −26.8° (c=3.70, H_2O), UV λ_{max}^{EtOH} mμ : 245, 281. *Anal.* Calcd. for $C_{17}H_{31}O_{10}NS_2$: C, 43.12; H, 6.60; N, 2.96; S, 13.53. Found : C, 42.64; H, 6.73; N, 2.80; S, 13.35.

2,3,4,6-Tetra-O-acetyl-β-D-galactopyranosyl N,N-Diethyldithiocarbamate (XVIII)——A mixture of 2,3,4,6-tetra-O-acetyl-α-D-galactopyranosyl bromide (56 g.) and II (24 g.) in EtOH (150 ml.) was treated as described in III. Recrystallization from boiling EtOH gave pure material (56 g., 90%), m.p. 172～174°, $[\alpha]_D^{20}$ +60.3°(c=2.72, $CHCl_3$), UV λ_{max}^{EtOH} mμ : 243, 282. *Anal.* Calcd. for $C_{19}H_{29}O_9NS_2$: C, 47.54; H, 6.09; N, 2.92; S, 13.37. Found : C, 47.62; H, 6.11; N, 3.14; S, 13.37.

β-D-Galactopyranosyl N,N-Diethyldithiocarbamate (XIX)——A suspension of XVIII (20 g.) in MeOH was deacetylated with MeONa as described in IX. Recrystallization from H_2O gave pure material (12 g., 95%), m.p. 136～140°, $[\alpha]_D^{20}$ −7°(c=4.45, H_2O), UV λ_{max}^{EtOH} mμ : 245, 281. *Anal.* Calcd. for $C_{11}H_{21}O_5NS_2$: C, 42.39; H, 6.80; N, 4.50; S, 20.59. Found : C, 42.38; H, 6.88; N, 4.49; S, 20.82.

2,3,4-Tri-O-acetyl-6-O-tosyl-β-D-glucopyranosyl N,N-Diethyldithiocarbamate (XX)——A mixture of IX (2 g.) and tosyl chloride (1.3 g.) in pyridine (14 ml.) was allowed to stand overnight. To the chilled mixture Ac_2O (14 ml.) was added and left for further 48 hr. at room temperature. The mixture was poured into ice-H_2O (200 ml.) and the resulting powder separated by filtration (3 g., 94%). Recrystallization from boiling EtOH (15 ml.) gave pure material, m.p. 138～140°, $[\alpha]_D^{20}$ +39.2°(c=1.76, $CHCl_3$), UV λ_{max}^{EtOH} mμ : 243, 281. *Anal.* Calcd. for $C_{24}H_{33}O_{10}NS_3$: C, 48.70; H, 5.63; N, 2.37; S, 16.25. Found : C, 48.80; H, 5.90; N, 2.56; S, 16.32.

2,3,4-Tri-O-acetyl-6-deoxy-6-iodo-β-D-glucopyranosyl N,N-Diethyldithiocarbamate (XXI)——A mixture of XX (2 g.) and NaI (2 g.) in N,N-dimethylformamide (10 ml.) was heated at 95～105° for 3 hr. in an oil bath. After cooling, the mixture was poured into ice-H_2O (200 ml.) and the resulting solid filtered and recrystallized from 4 parts of warm Me_2CO to give pure material (1.2 g., 66%), m.p. 184～185°, $[\alpha]_D^{20}$ +1.8° (c=3.32, $CHCl_3$), UV λ_{max}^{EtOH} mμ : 243, 281. *Anal.* Calcd. for $C_{17}H_{26}NS_2I$: C, 37.33; H, 4.79; N, 2.74; S, 11.71. Found : C, 37.26; H, 4.71; N, 2.42; S, 11.76.

1,2,3,4-Tetra-O-acetyl-α-D-glucopyranosyl-6-deoxy-6-N,N-diethyldithiocarbamate (XXIV)——1,2,3,4-Tetra-O-acetyl-6-deoxy-6-iodo-α-D-glucopyranose (XXII) and its β-anomer (XXIII) were prepared in a similar method to that used by Hardegger, *et al.*[19] A mixture of XXII (2 g.) and II (1.5 g., 2 mole) in dry Me_2CO (30 ml.) was refluxed for 10 min. After cooling, the mixture was poured into ice-H_2O (200 ml.) and left to stand overnight. The resulting solid was collected by filtration, dissolved in warm EtOH and filtered, followed by treatment with charcoal. Colorless crystals, precipitated after keeping in a refrigerator, were filtered and recrystallized from EtOH to give pure material (1.8 g., 85%), m.p. 131°, $[\alpha]_D^{20}$ +99°(c=1.56, $CHCl_3$), UV λ_{max}^{EtOH} mμ : 248, 278. *Anal.* Calcd. for $C_{19}H_{29}O_9NS_2$: C, 47.58; H, 6.10; N, 2.92. Found : C, 47.66; H, 6.14; N, 2.94.

1,2,3,4-Tetra-O-acetyl-β-D-glucopyranosyl-6-deoxy-6-N,N-diethyldithiocarbamate (XXV)——A mixture of XXIII (12 g.) and II (9 g., 2 mole) in Me_2CO (180 ml.) was treated similarly in XXIV. Recrystallization from EtOH gave crystals (11 g., 88%), m.p. 142°, $[\alpha]_D^{20}$ +12.8°(c=2.34, $CHCl_3$), UV λ_{max}^{EtOH} mμ : 248, 278. *Anal.* Calcd. for $C_{19}H_{29}O_9NS_2$: C, 47.58; H, 6.10; N, 2.92. Found : C, 47.47; H, 6.00; N, 3.01.

1,2,3,4-Tetra-O-acetyl-β-D-quinovose——A solution of XXV (2 g.) in EtOH (100 ml.) was treated with freshly prepared Raney Ni (40 g.) and refluxed for 4 hr. The Ni was removed by filtration and the filtrate

18) H.G. Fletcher, Jr., L.H. Koehler, C.S. Hudson : *Ibid.*, **71**, 3679 (1949).
19) E. Hardegger, R.M. Montavon : Helv. Chim. Acta, **29**, 1199 (1946).

was concentrated to give a sirup which crystallized on trituration with ether. After filtration, it was recrystallized from EtOH to give pure material (0.5 g., 37%), m.p. 151°, $[\alpha]_D^{20}$ +22.1°(c=1, $CHCl_3$). *Anal.* Calcd. for $C_{14}H_{20}O_9$: C, 50.60; H, 6.06. Found : C, 50.52; H, 5.98. Hardegger and Montavon[19] reported m.p. 151°, $[\alpha]_D^{20}$ +22°(c=0.9, $CHCl_3$) for 1,2,3,4-tetra-O-acetyl-β-D-quinovose.

1-Deoxy-1-bromo-2,3,4-tri-O-acetyl-α-D-glucopyranosyl-6-deoxy-6-N,N-diethyldithiocarbamate (XXVI)——A solution of XXV (4 g.) in glacial AcOH (12 ml.) containing 35% HBr, was stirred for 3 hr. at room temperature, then, the mixture was poured into ice-H_2O (200 ml.), followed by addition of $CHCl_3$ (50 ml.). The $CHCl_3$-layer was separated from the aq. layer and the latter extracted with $CHCl_3$. The combined $CHCl_3$-layer was washed with aq. $NaHCO_3$ and H_2O, dried over Na_2SO_4, and filtered. The filtrate was evaporated to give a sirup which dissolved in warm AcOEt and left in a refrigerator. Precipitated crystalline mass was separated by filtration and recrystallized from AcOEt to give pure material (2.1 g., 50%), m.p. 122°, $[\alpha]_D^{20}$ +164°(c=1.55, $CHCl_3$), UV λ_{max}^{EtOH} mμ : 248, 278. *Anal.* Calcd. for $C_{17}H_{26}O_7NS_2Br$: C, 40.80; H, 5.24; N, 2.80. Found : C, 40.60; H, 5.25, N; 2.56.

2,3,4-Tri-O-acetyl-β-D-glucopyranosyl-1,6-dideoxy-1,6-di-N,N-diethyldithiocarbamate (XXVII)——a) A mixture of XXI (1 g.) and II (1 g.) in Me_2CO (10 ml.) was refluxed for 15 min. After cooling, the mixture was poured into ice-H_2O, filtered and recrystallized from boiling EtOH to give pure material (0.7 g., 70%), m.p. 155°, $[\alpha]_D^{20}$ +21.6° (c=3.21, $CHCl_3$), UV λ_{max}^{EtOH} mμ : 245, 281. *Anal.* Calcd. for $C_{22}H_{36}O_7N_2S_4$: C, 46.45; H, 6.37; N, 4.93; S, 22.55. Found : C, 46.60; H, 6.42; N, 4.71; S, 22.63.

b) A mixture of XXVI (1.6 g.) and II (1.3 g., 4.2 mole) in dry Me_2CO (15 ml.) was refluxed for 5 min. After cooling, the mixture was poured into ice-H_2O (200 ml.) and left to stand overnight. The resulting solid was filtered and twice recrystallizations from EtOH gave pure material (1.7 g., 93%), m.p. 155°, $[\alpha]_D^{20}$ +23.4°(c=1.33, $CHCl_3$), UV λ_{max}^{EtOH} mμ : 245, 281. *Anal.* Calcd. for $C_{22}H_{36}O_7N_2S_4$: C, 46.45; H, 6.37; N, 4.93; S, 22.55. Found : C, 46.58; H, 6.46; N, 4.83; S, 22.72. The product was identical with that prepared by a) in mixed m.p. and IR.

1,5-Anhydro-2,3,4-tri-O-acetyl-6-deoxy-D-sorbitol——A solution of XXVII (4 g.) in EtOH (150 ml.) was treated with Raney Ni (60 g.) and refluxed for 6.5 hr. After the similar treatment of it as the preparation of 1,2,3,4-tetra-O-acetyl-β-D-quinovose, the title compound crystallized. Recrystallization from EtOH–ether gave needles (0.6 g., 32%), m.p. 118~120°, $[\alpha]_D^{20}$ +11.6°(c=0.69, $CHCl_3$). *Anal.* Calcd. for $C_{12}H_{18}O_7$: C, 52.55; H, 6.62. Found : C, 52.60; H, 6.61. One of us[12] reported m.p. 119~121°, $[\alpha]_D^{16}$ +7.7°(c=1.8, $CHCl_3$) for 1,5-anhydro-2,3,4-tri-O-acetyl-6-deoxy-D-sorbitol.

Methyl β-D-Glucopyranoside-6-deoxy-6-N,N-diethyldithiocarbamate (XXVIII)——A mixture of XXV (15 g.) in MeOH (250 ml.) containing 1% dry HCl, was refluxed for 1 hr. After cooling, the solvent was evaporated to a sirup which dissolved in warm EtOH (100 ml.) and left in a refrigerator to give crystalline product. Recrystallization from EtOH gave needles (4 g., 40%), m.p. 176°, $[\alpha]_D^{20}$ +32.8°(c=0.85, pyridine), UV λ_{max}^{EtOH} mμ : 252, 280. *Anal.* Calcd. for $C_{12}H_{23}O_5NS_2$: C, 44.30; H, 7.13; N, 4.35. Found : C, 44.56; H, 7.18; N, 4.35.

Methyl 2,3,4-Tri-O-acetyl-β-D-glucopyranoside-6-deoxy-6-N,N-diethyldithiocarbamate (XXIX)——a) To a chilled mixture of Ac_2O (10 ml.) and pyridine (10 ml.) was added XXVIII (1 g.) and left overnight at room temperature. The mixture was poured into ice-H_2O (200 ml.) and extracted with $CHCl_3$. The $CHCl_3$-layer was washed with 3*N* H_2SO_4, aq. $NaHCO_3$ and H_2O, respectively. After drying over Na_2SO_4, the filtrate was evaporated to a sirup which dissolved in warm EtOH and left in a refrigerator to give crystals. Recrystallization from EtOH gave pure material (1 g., 72%), m.p. 125~126°, $[\alpha]_D^{20}$ +14°(c=1.3, $CHCl_3$), UV λ_{max}^{EtOH} mμ : 249, 278. *Anal.* Calcd. for $C_{18}H_{29}O_8NS_2$: C, 47.88; H, 6.47; N, 3.12. Found : C, 47.96; H, 6.57; N, 3.43.

b) To a solution of XXVI (2.2 g.) which had beed dissolved in a mixture of MeOH (60 ml.) and a small amount of $CHCl_3$ was added freshly prepared Ag_2CO_3 (4 g.). The mixture was stirred for 7 hr. and kept 48 hr. at room temperature, then filtered. The filtrate was concentrated to a sirup which dissolved in warm EtOH, filtered, followed by treatment with charcoal and kept in a refrigerator. Precipitated crystals were collected by filtration and recrystallized twice from EtOH to give pure material (0.7 g., 35%), m.p. 125~126°, $[\alpha]_D^{20}$ +10°(c=1.21, $CHCl_3$), UV λ_{max}^{EtOH} mμ : 249, 278. *Anal.* Calcd. for $C_{18}H_{29}O_8NS_2$: C, 47.88; H, 6.47; N, 3.12; S, 14.20. Found : C, 48.00; H, 6.66; N, 3.36; S, 14.54. The product did not show mixed m.p. depression with the product prepared by a).

Methyl 2,3,4-Tri-O-acetyl-α-D-glucopyranoside-6-deoxy-6-N,N-diethyldithiocarbamate (XXX)——a) The EtOH solution which had been obtained in the preparation of XXVIII, and from which XXVIII separated, was concentrated to a sirup (3.8 g., 38%). Acetylation with pyridine (50 ml.) and Ac_2O (50 ml.), treatment with the similar method in the section XXIX a), and finally recrystallization from EtOH gave pure material (3.8 g., 72%), m.p. 128~131°, $[\alpha]_D^{20}$ +112° (c=1.22, $CHCl_3$), UV λ_{max}^{EtOH} mμ : 249, 278. *Anal.* Calcd. for $C_{18}H_{29}O_8NS_2$: C, 47.88; H, 6.47; N, 3.12; S, 14.20. Found : C, 47.64; H, 6.48; N, 3.15.

b) Methyl 2,3,4-tri-O-acetyl-6-deoxy-6-iodo-α-D-glucopyranoside (2 g.), prepared in a fashion similar to that used by Compton,[20] and II (1.5 g., 2 mole) were treated with the similar method in XXIV. Recystallization from EtOH gave pure material (1.5 g., 72%), m.p. 128~131°, $[\alpha]_D^{20}$ +116°(c=1.05, $CHCl_3$), UV λ_{max}^{EtOH}

20) J. Compton : J. Am. Chem. Soc., **60**, 395 (1938).

mμ : 249, 278. *Anal.* Calcd. for $C_{18}H_{29}O_8NS_2$: C, 47.88; H, 6.47; N, 3.12. Found : C, 47.92; H, 6.44; N, 3.22. The product did not show mixed m.p. depression with the product prepared by a).

Methyl 2,3,4-Tri-O-acetyl-6-S-acetyl-6-deoxy-6-thio-β-D-glucopyranoside (XXXI)——a) A mixture of XXVIII (2 g.) and MeONa in dry MeOH (50 ml.) containing Na (1 g., 7 mole) was refluxed for 13 hr. After cooling, the solvent was removed to afford a sirup which acetylated with pyridine (20 ml.) and Ac_2O (20 ml.) at 0°. After standing at room temperature for 15 hr., the mixture was treated as described in XXIX a) to give a sirup. It was dissolved in benzene and chromatographied on silica gel (50 g.). Elution was performed using benzene, 5% ether-benzene (v/v) and ether, successively. The ether-effluent was evaporated to give a sirup which dissloved in small amount of warm ether. Petr. ether was added to give a slight turbidity and left in a refrigerator to induce crystallization. The resulting crystalline mass was collected by filtration and recrystallized from ether-petr. ether to give pure material (1 g., 40%), m.p. 94.5°, $[\alpha]_D^{20}$ −24° (c=1.05, $CHCl_3$), IR λ_{max}^{Nujol} μ : 5.9 (-SAc). *Anal.* Calcd. for $C_{15}H_{22}O_9S$: C, 47.62; H, 5.86; S, 8.47. Found : C, 47.62; H, 5.99; S. 8.57.

b) A mixture of methyl 2,3,4-tri-O-acetyl-6-O-tosyl-β-D-glucopyranoside (2 g.), prepared in a fashion similar to that used by Compton[20] and AcSK (0.7 g., 1.3 mole) in dry Me_2CO (30 ml.) was refluxed for 6 hr. After cooling, the mixture was poured into ice-H_2O, extracted with $CHCl_3$, and the $CHCl_3$-layer washed with H_2O. Moisture was removed with Na_2SO_4, filtered and the filtrate evaporated to a sirup which chromatographed as described in a). From ether-effluent crystals (1 g., 63%), m.p. 94°, $[\alpha]_D^{20}$ −28°(c=1.05,$CHCl_3$) were obtained. *Anal.* Calcd. for $C_{15}H_{22}O_9S$: C, 47.62; H, 5.86. Found : C, 47.35; H, 6.00. The product was identical with that, prepared by a), in mixed m.p. and IR.

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32. Manki Komatsu, Tsuyoshi Tomimori, and Michiko Ito : Studies on the Constituents of *Swertia japonica*. I.*[1] On the Structures of Swertisin and Isoswertisin.

(*Research Laboratory, Taisho Pharmaceutical Co., Ltd.*[*2])

Swertisin, $C_{22}H_{22}O_{10}$, m.p. 243°(decomp.), was isolated in a pure state from the whole herb of *Swertia japonica* Makino (Gentianaceae), and identified as 6-C-β-D-glucopyranosylgenkwanin.

Isoswertisin, $C_{22}H_{22}O_{10}$, m.p. 295°(decomp.), was obtained by the acid-treatment of swertisin, and formulated as 8-C-β-D-glucopyranosylgenkwanin.

At the same time, it was found that they were interconvertible into each other, reminiscent of the interrelationship between vitexin and isovitexin.

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Swertia japoncia Makino (Japanese name "Senburi") is a biennial herb of the family Gentianaceae, which is widely distributed in Japan, Korea, and China.

In 1927, swertisin was first isolated from the whole herb of this plant by Nakaoki,[1] who proposed the empirical formula $C_{13}H_{10}O_6 \cdot H_2O$ which was presumed a sort of flavonoid or xanthone compound. Subsequently, Asahina, *et al.*[2] revised the formula for swertisin to $C_{23}H_{24}O_{11}$. No further investigations, however, have been made.

It has now been found that crude swertisin, obtained from this plant by Nakaoki's procedure, consisted of swertisin and a small amount of two other flavonoid compounds,

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*1 Preliminary communications were published in Tetrahedron Letters, No. 15, 1611 (1966). A part of this work was reported at the Regular Meeting of Kanto Branch, Pharmaceutical Society of Japan, in Tokyo (December, 1965).

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1) T. Nakaoki : Yakugaku Zasshi, **47**, 144 (1927).

2) Y. Asahina, J. Asano, Y. Ueno : *Ibid.*, **62**, 22 (1942).