

of the dimethyl ester, b.p. 174–177° (0.3–0.4 mm.),  $n_D^{25}$  1.5089.

*Anal.* Calcd. for  $C_{17}H_{24}O_7$ : C, 60.0; H, 7.1;  $OCH_3$ , 45.6; sapn. equiv., 170. Found: C, 59.8; H, 7.2;  $OCH_3$ , 45.3; sapn. equiv., 173.

**2,3,4-Trimethoxybenzocyclohepten-6-one (XI).**—Over a period of four hours in a nitrogen atmosphere a solution of 5.25 g. (0.0154 mole) of the dimethyl ester in 15 ml. of toluene was added to a stirred, refluxing mixture of 1.35 g. (0.059 mole) of sodium and 30 ml. of toluene to which a few drops of methanol had been added. Stirring and reflux were continued overnight, the excess sodium was decomposed by dropwise addition of methanol, and the solution was acidified in the cold with 50 ml. of 2 *N* hydrochloric acid. The aqueous phase was extracted with benzene and the combined benzene-toluene extracts were washed with water and sodium bicarbonate solution and evaporated. The residue, dissolved in 100 ml. of 0.5 *N* ethanolic potassium hydroxide, was allowed to stand at room temperature overnight after which 20 ml. of 3 *N* hydrochloric acid was added and the solution heated under reflux until carbon dioxide evolution ceased. This solution was then concentrated under reduced pressure to remove the alcohol and the residue was extracted with benzene. After washing with carbonate solution, the benzene solution was distilled to give 2.41

g., 64% yield, of the ketone as a solid distillate, b.p. 144° (0.4 mm.). After crystallization from ethanol-water, it melted at 46–46.5°.

*Anal.* Calcd. for  $C_{14}H_{18}O_4$ : C, 67.2; H, 7.3;  $OCH_3$ , 37.2. Found: C, 67.1; H, 7.3;  $OCH_3$ , 37.2.

The ketone forms a soluble bisulfite addition product and when dissolved in alcoholic potassium hydroxide in the presence of air forms a green solution which changes to orange on acidification.

The semicarbazone was prepared in the usual manner and was crystallized from methanol-water, m.p. 184–185°.

*Anal.* Calcd. for  $C_{15}H_{24}N_2O_4$ : C, 58.6; H, 6.9; N, 13.7;  $OCH_3$ , 30.3. Found: C, 58.7; H, 7.1; N, 13.6;  $OCH_3$ , 30.3.

The oxime, prepared as usual, melted at 130.5–131° after crystallization from methanol-water.

*Anal.* Calcd. for  $C_{14}H_{19}NO_4$ : C, 63.4; H, 7.2; N, 5.3. Found: C, 63.4; H, 7.5; N, 5.1.

The 2,4-dinitrophenylhydrazone was crystallized from methanol, m.p. 177–178°.

*Anal.* Calcd. for  $C_{20}H_{22}N_4O_7$ : C, 55.8; H, 5.2; N, 13.0. Found: C, 56.0; H, 5.4; N, 12.9.

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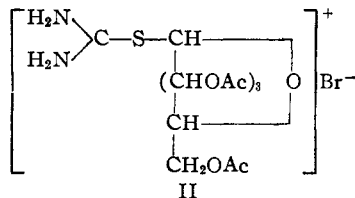
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, STANFORD UNIVERSITY]

## A Study of Some S-(Polyacetyl- $\beta$ -D-glycopyranosyl)-thiuronium Halides

BY WILLIAM A. BONNER AND JAMES E. KAHN

Several new S-(polyacetyl- $\beta$ -D-glycopyranosyl)-thiuronium halides have been prepared by the interaction of thiourea with the corresponding polyacetyl- $\alpha$ -D-glycopyranosyl halide in 2-propanol. The structure of S-(tetraacetyl- $\beta$ -D-glucopyranosyl)-thiuronium bromide has been substantiated by reductive desulfurization. With bromine in acetic acid this salt reverts to  $\alpha$ -D-glucose pentaacetate. The specific rotation of these salts is strongly dependent on the solvent. Their molecular rotation is partially determined by their anionic component. The kinetics of formation of these salts have been found second order, and a mechanism proposed in agreement with this fact. The salts are polarographically reducible in phosphate buffer of pH 6. The half-wave potentials lie in the neighborhood of –1.2 volts, and are rather independent of the structure of the cation. The infrared spectra of six of these salts have been measured and found dependent on both the anion and the carbohydrate cation. The ultraviolet spectra of these salts appear independent of the structure of the carbohydrate cation. The rotatory dispersion of four of these salts obeyed a simple Drude equation. In two cases, the position of an "active" absorption band predicted on the basis of dispersion measurements corresponded to the position of a band suggested by spectrophotometric measurement.

The reaction of alkyl halides with thiourea to form S-alkylthiuronium halides is well known. Only once, however, has this reaction been extended to the carbohydrate series. In 1928 Schneider and Eisfeld<sup>1</sup> obtained a 37% yield of a solid, m.p. 192°,  $[\alpha]_D^{20}$  –8.72° (water) on refluxing tetraacetyl- $\alpha$ -D-glucopyranosyl bromide (I) in dry toluene with thiourea. By analysis, analogy and the formation of the silver salt of 1-thio-D-glucose on its treatment with ammoniacal silver nitrate, this substance was designated as S-(tetraacetyl- $\beta$ -D-glucopyranosyl)-thiuronium bromide (II). Similar results were obtained with phenylthiourea. Since wider data on this



class of compounds are lacking, we have been interested in extending the earlier study, especially along the lines of physico-chemical information.

When I and thiourea in 2-propanol solution were

(1) W. Schneider and K. Eisfeld, *Ber.*, **61**, 1990 (1928).

either heated briefly or allowed to stand for longer periods at room temperature, II, m.p. 205°,  $[\alpha]_D^{25}$  –7.6° (water) resulted in 64% yield. Similar results were obtained with the acetylated halides of xylose, galactose and cellobiose. The resulting salts were readily soluble in water, sparingly so in alcohol and insoluble in non-polar media. II was non-reducing, giving a brownish-green solution on prolonged heating with Fehling solution. The structure of II, as suggested by Schneider and Eisfeld, has been confirmed by reductive desulfurization, where tetraacetyl-1,5-anhydro-D-glucitol results. In common with thioglycosides<sup>2</sup> and selenoglycosides,<sup>3</sup> II reverts to  $\alpha$ -D-glucose pentaacetate on treatment with bromine in acetic acid, presumably through an identical mechanism.

Since S-alkylthiuronium salts are useful in characterizing organic acids,<sup>4–8</sup> we have attempted to use II in this capacity. Such derivatives looked

(2) W. A. Bonner, *THIS JOURNAL*, **70**, 3491 (1948).

(3) W. A. Bonner and A. Robinson, *ibid.*, **72**, 356 (1950).

(4) J. J. Donleavy, *ibid.*, **58**, 1004 (1936).

(5) R. J. Anderson, *J. Biol. Chem.*, **74**, 548 (1927).

(6) S. Veibel, *et al.*, *Bull. soc. chim.*, [5] **5**, 1153 (1938); **6**, 1434 (1939).

(7) B. T. Dewey, *et al.*, *THIS JOURNAL*, **61**, 3251 (1939); **63**, 3526 (1941).

(8) W. A. Bonner, *ibid.*, **70**, 3508 (1948).

inviting, since they would offer specific rotation as an additional aid in acid identification. With sodium acetate, II readily formed S-(tetraacetyl- $\beta$ -D-glucopyranosyl)-thiuronium acetate, m.p. 143.5–144°,  $[\alpha]^{25}_D -10.7^\circ$  (water). With the sodium salts of many other organic acids, however, the reagent was unsuccessful. Yields were low, recrystallization was difficult and melting points were not sharp. On treatment of II with alcoholic silver nitrate followed by removal of the silver bromide by filtration, S-(tetraacetyl- $\beta$ -D-glucopyranosyl)-thiuronium nitrate, m.p. 159.5°,  $[\alpha]^{23}_D -22.2^\circ$  (ethanol) resulted in excellent yield.

The specific rotations of these salts were found to vary markedly with solvent. Thus II had  $[\alpha]_D -7.6^\circ$  in water and  $-18.8^\circ$  in ethanol. Similarly, S-(tetraacetyl- $\beta$ -D-glucopyranosyl)-thiuronium acetate had  $[\alpha]_D -10.7^\circ$  (water),  $-18.7^\circ$  (methanol),  $-31.1^\circ$  (ethanol) and  $-37.7^\circ$  (1-propanol), all rotations taken at room temperature without thermostatic control. These marked differences in rotation for such similar solvents are undoubtedly connected with the ionic nature of the solute. It is interesting to note that the nature of the anionic portion of the salt is important in determining its molecular rotation. Thus S-(tetraacetyl- $\beta$ -D-glucopyranosyl)-thiuronium bromide, acetate and nitrate have molecular rotations, respectively, of  $-9160$ ,  $-14480$  and  $-10400$  in ethanol. In the absence of an effect by the anion these values should be identical. The reason for this anionic effect is obscure at present, and under further investigation.

By following the reaction of I with thiourea polarimetrically, we have found that the formation of II follows a second order rate expression very closely. Figure 1 gives rotation-time plots for the concentration ranges studied. At each experimental point in Fig. 1 the value of the second order rate constant was calculated using the integrated rate expressions (1) for equal concentrations of I and thiourea and (2) for unequal concentrations. In

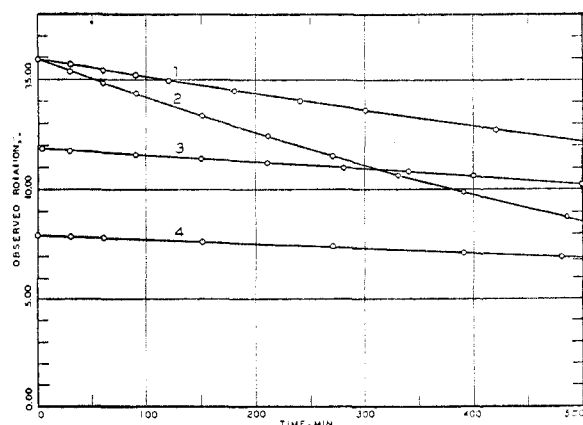


Fig. 1.—Mutarotation on reaction of tetraacetyl- $\alpha$ -D-glucosyl bromide with thiourea as a function of concentration of reagents:

Curve	[I], mole/liter	[Thiourea], mole/liter
1	0.10	0.10
2	.10	.20
3	.075	.05
4	.05	05

$$k = \frac{1}{t} \times \frac{x}{a(a-x)} \quad (1)$$

$$k = \frac{1}{t} \times \frac{2.303}{(a-b)} \log \frac{b(a-x)}{a(b-x)} \quad (2)$$

(1)  $a$  represents the original identical concentrations of the components and  $x$  the quantity of each reacted in time  $t$ . In (2)  $a$  is the original concentration of I and  $b$  that of thiourea. The validity of (1) and (2) over the time range studied is indicated in Table I. The agreement among values is about typical of all the runs. The validity of (1) and (2) over the concentration ranges studied is seen in Table II, where the rate constant values are averages obtained from data such as appear in Table I. At 35° the reaction obeyed (1) and  $k$  had the average value  $(1.38 \pm 0.11) \times 10^{-2}$  liter/mole min.

TABLE I

RATE CONSTANT VALUES AS A FUNCTION OF TIME. 0.1 M TETRAACETYL- $\alpha$ -D-GLUCOSYL BROMIDE AND 0.2 M THIOUREA IN 2-PROPANOL AT 25°

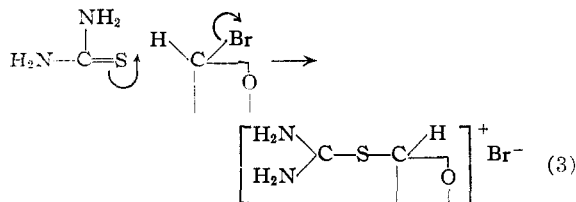
Time, min.	Rotation, °	$k \times 10^3$ , liters/mole min.
30	15.41	5.36
60	14.91	5.38
90	14.39	5.13
150	13.40	5.14
210	12.44	5.39
270	11.55	5.45
330	10.69	5.64
390	9.91	5.60
485	8.75	5.75

TABLE II

AVERAGE RATE CONSTANT VALUES IN 2-PROPANOL AT 25°

Original concentration, mole/liter Tetraacetyl- $\alpha$ - D-glucosyl bromide	Thiourea	$k \times 10^3$ , liters/mole min.
0.05	0.05	$5.60 \pm 0.52$
.10	.10	$4.87 \pm .12$
.10	.20	$5.43 \pm .16$
.075	.05	$5.66 \pm .12$

The irreversibility of the process and absence of serious side reactions in the kinetic study were shown by the lack of mutarotation of II and the negligible mutarotation of I in 2-propanol. The second order kinetics are in accord with (3), a nucleophilic, Walden inversion attack of the sulfur atom of thiourea on the rear face of the number one carbon of I, as the mechanism of the reaction.



While the S-alkylthiuronium salts have recently been studied<sup>9</sup> electrolytically, their polarographic reduction has not. As part of a general polarographic study of these salts, we have found the present carbohydrate analogs reducible at the dropping mercury cathode. Figure 2 gives the polarographic wave for II in phosphate buffer at pH

(9) W. A. Bonner, THIS JOURNAL, 78, 464 (1951).

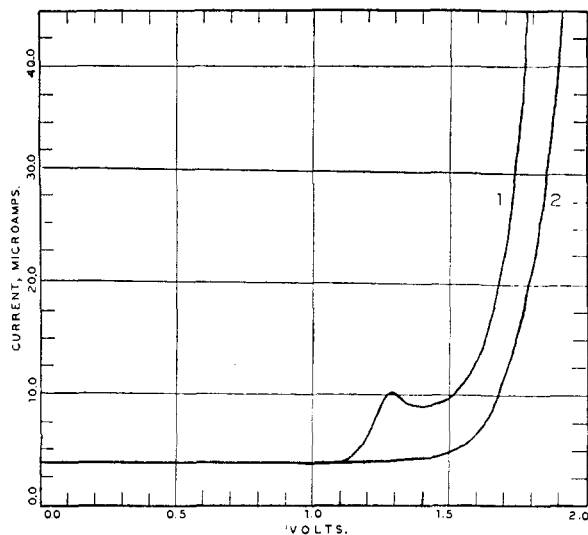


Fig. 2.—Polarographic reduction of S-(tetraacetyl- $\beta$ -D-glucopyranosyl)-thiuronium bromide at pH 6.0 in phosphate buffer: 1, salt; 2, phosphate buffer.

6.0. All the salts showed marked maxima in their waves, which could be more or less suppressed by addition of gum arabic solution. The following half-wave potentials, *vs.* the saturated calomel electrode, were found under these conditions for the indicated salts: S-(tetraacetyl- $\beta$ -D-glucopyranosyl)-thiuronium bromide ( $-1.17$  v.); S-(tetraacetyl- $\beta$ -D-galactopyranosyl)-thiuronium bromide ( $-1.22$  v.); S-(heptaacetyl- $\beta$ -D-cellobiosyl)-thiuronium bromide ( $-1.24$  v.); S-(triacetyl- $\beta$ -D-xylopyranosyl)-thiuronium chloride (*ca.*  $-1.3$  v.). The similarity in half-wave potentials regardless of the carbohydrate moiety is striking, and reminiscent of the results of Cantor and Peniston,<sup>10</sup> who found the half-wave potentials of a large number of aldoses to lie within the narrow range  $-1.50$  to  $-1.80$  volts.

The infrared spectra of carbohydrates has lately been studied by Kuhn.<sup>11</sup> Despite earlier reports<sup>12</sup> to the contrary, each carbohydrate, including anomers, had its characteristic infrared pattern. We have measured the infrared spectra (Fig. 3) of our thiuronium salts, obtaining results according with the observations of Kuhn. The variation in spectral shape when the anion of III is changed from bromide to nitrate and acetate is noteworthy.

The similarities in the ultraviolet absorption spectra of glycosides containing chromophoric aglycones have recently been pointed out.<sup>13</sup> Measurement of the ultraviolet pattern of two of our thiuronium salts (Fig. 4) confirms our earlier results. The monotonous trend in Fig. 4 is reminiscent of the spectrum of S-benzylthiuronium chloride,<sup>9</sup> except that the continuous absorption occurs at a somewhat shorter wave length.

We have measured the rotatory dispersions of our thiuronium salts in order to extend our previous test<sup>14</sup> of the agreement between spectrophotomet-

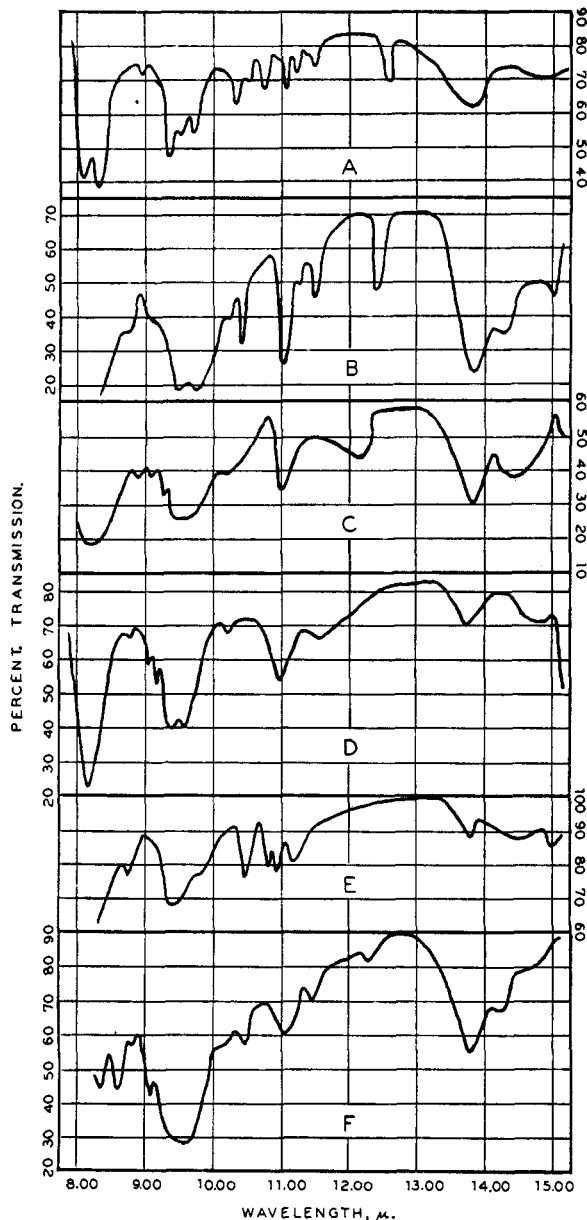


Fig. 3.—Infrared spectra of S-(polyacetyl- $\beta$ -D-glucosyl)-thiuronium salts: 1, sugar in S-(polyacetyl- $\beta$ -D-glucosyl)-thiuronium cation; 2, anion. A, 1, xylose, 2, chloride; B, 1, glucose, 2, bromide; C, 1, glucose, 2, nitrate; D, 1, glucose, 2, acetate; E, 1, galactose, 2, bromide; F, 1, cellobiose, 2, bromide.

rically measured absorption bands and bands predicted from dispersion equations. The acetylated thiuronium halides of glucose, galactose, xylose and cellobiose obeyed (Fig. 5) a simple Drude equation quite well within the region 4990 to 6670 Å. The slopes of the lines in Fig. 5 give rotation constant ( $k$ ) values of  $-3050$ ,  $+2860$ ,  $-7910$  and  $-6510$ , respectively, for the salts of glucose, galactose, xylose and cellobiose. Knowing  $k$ , the dispersion constant ( $\lambda_0^2$ ) for a simple Drude equation was calculated at each experimental point, and the average taken for each salt. As a further test of simple dispersion, these values of  $k$  and  $\lambda_0^2$  were used to recalculate the molecular rotatory dispersion of each salt. The

(10) S. M. Cantor and Q. P. Peniston, *THIS JOURNAL*, **62**, 2113 (1940).

(11) L. P. Kuhn, *Anal. Chem.*, **22**, 276 (1950).

(12) L. H. Rogers and D. Williams, *THIS JOURNAL*, **60**, 2619 (1938).

E. S. Barr and C. H. Chrisman, Jr., *J. Chem. Phys.*, **8**, 51 (1940).

(13) R. P. Zelinski and W. A. Bonner, *ibid.*, **71**, 1791 (1949).

(14) W. A. Bonner, *ibid.*, **71**, 3384 (1949).

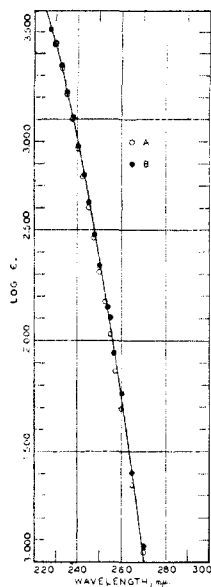


Fig. 4.—Ultraviolet absorption spectra of S-(polyacetyl- $\beta$ -D-glycosyl)-thiuronium halides: A, S-(triacetyl- $\beta$ -D-xylopyranosyl)-thiuronium chloride; B, S-(tetraacetyl- $\beta$ -D-galactopyranosyl)-thiuronium bromide.

calculated and measured molecular rotations agreed within 1% or better in each case throughout the wavelength region. Dispersion constants (average) of 0.0393, 0.0194, 0.0294 and 0.0391  $\mu^2$ , respectively, were obtained for the salts of glucose, galactose, xylose and cellobiose. The square roots of these values,  $\lambda_0$ , were 198, 139, 170 and 198  $m\mu$ , respectively. These, corresponding to positions of "optically active" absorption bands, may be compared to the spectra in Fig. 4. Unfortunately the spectral measurements do not extend low enough, but it is probable that the intense band appearing in Fig. 4 determines the rotatory dispersion of the salts of glucose and cellobiose, while more distant bands determine that of the salts of galactose and xylose. It is interesting that glucose and cellobiose, both of the same configuration adjacent to the chromophoric group, have identical dispersion constants, though different rotation constants.

### Experimental

**S-(Tetraacetyl- $\beta$ -D-glucopyranosyl)-thiuronium Bromide (II).**—Tetraacetyl- $\alpha$ -D-glucosyl bromide (12.3 g.) in hot 2-propanol (35 ml.) and finely ground thiourea (3.4 g.) in hot 2-propanol (45 ml.) were mixed and permitted to stand overnight. The product (7.7 g.) had m.p. 200.5° (dec.). A second crop (1.6 g., total yield 64%) was obtained on adding hexane to the mother liquors and chilling, m.p. 160–170° (dec.). The highest m.p. obtained on recrystallization from 2-propanol was 205° (dec.). The material had  $[\alpha]^{25D}$   $-7.6^\circ$  (water;  $c$ , 1.443) and  $-18.8^\circ$  (ethanol;  $c$ , 0.957).

*Anal.* Calcd. for  $C_{16}H_{28}O_9N_2SBr$ : C, 37.00; H, 4.76; N, 5.75; S, 6.57; Br, 16.40. Found: C, 37.12; H, 4.62; N, 5.85; S, 6.52; Br, 16.74.

**S-(Tetraacetyl- $\beta$ -D-galactopyranosyl)-thiuronium Bromide.**—Tetraacetyl- $\alpha$ -D-galactosyl bromide (5.1 g.) and thiourea (1.4 g., 1.5 equiv.) were refluxed in 2-propanol (20 ml.) for 45 minutes. The mixture was diluted slightly with hexane, scratched and cooled, giving 4.5 g. (75%) of crude product. After four recrystallizations from 2-propanol this had m.p. 169.5° and  $[\alpha]^{25D}$  16.0° (ethanol;  $c$ , 1.560).

*Anal.* Calcd. for  $C_{16}H_{28}O_9N_2SBr$ : N, 5.75. Found: N, 5.75.

**S-(Triacetyl- $\beta$ -D-xylopyranosyl)-thiuronium Chloride.**—Triacetyl- $\alpha$ -D-xylosyl chloride (2.9 g.) and thiourea (1.14 g., 1.5 equiv.) were refluxed in 2-propanol (15 ml.) for 45 minutes. The solution was treated with Norit, filtered and the hot filtrate treated with hexane to incipient turbidity. Cooling and scratching produced two crops totalling 2.9 g. (78%). After three recrystallizations from 2-propanol the long needles had m.p. 181° and  $[\alpha]^{25D}$   $-71.5^\circ$  (ethanol;  $c$ , 0.587).

*Anal.* Calcd. for  $C_{12}H_{19}O_7N_2S$ : N, 7.56; Cl, 9.58. Found: N, 7.39; Cl, 9.61, 9.71.

**S-(Heptaacetyl- $\beta$ -D-cellobiosyl)-thiuronium Bromide.**—Heptaacetyl- $\alpha$ -D-cellobiosyl bromide (7.0 g.) and thiourea (1.14 g.) were refluxed in 2-propanol (40 ml.) for one hour and the product, 5.0 g. (64%), isolated as before. Two

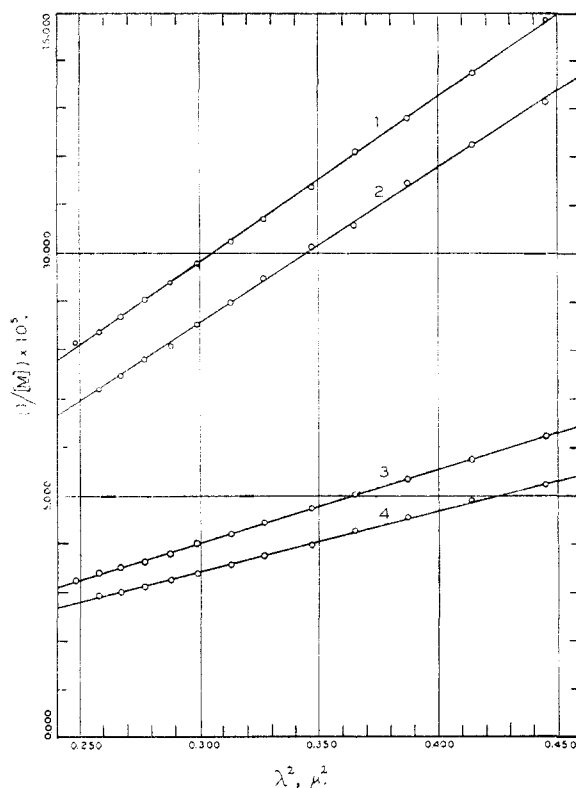


Fig. 5.—Simple rotatory dispersion plots for S-(polyacetyl- $\beta$ -D-glycosyl)-thiuronium halides: 1, S-(tetraacetyl- $\beta$ -D-galactopyranosyl)-thiuronium bromide; 2, S-(tetraacetyl- $\beta$ -D-glucopyranosyl)-thiuronium bromide; 3, S-(heptaacetyl- $\beta$ -D-cellobiosyl)-thiuronium bromide; 4, S-(triacetyl- $\beta$ -D-xylopyranosyl)-thiuronium chloride.

crystallizations from 2-propanol gave the pure substance, m.p. 178–179° (dec.),  $[\alpha]^{25D}$   $-26.7^\circ$  (ethanol;  $c$ , 1.050).

*Anal.* Calcd. for  $C_{27}H_{43}O_{17}N_2SBr$ : N, 3.62. Found: N, 3.50

**S-(Tetraacetyl- $\beta$ -D-glucopyranosyl)-thiuronium Acetate.**—II (0.49 g.) was placed in hot 2-propanol (5 ml.) and fully dissolved by addition of a few drops of methanol. Acetic acid (0.06 g.) was dissolved in hot 2-propanol (5 ml.), and neutralized to phenolphthalein by addition of sufficient sodium methylate solution. The two solutions were mixed while hot, filtered through Celite and cooled. The product, 0.30 g. (64%) had m.p. 143.5–144°, unchanged after three recrystallizations from 2-propanol.  $[\alpha]^{20-25D}$  was  $-10.7^\circ$  (water;  $c$ , 1.027),  $-18.7^\circ$  (methanol;  $c$ , 0.587),  $-31.1^\circ$  (ethanol;  $c$ , 1.093) and  $-37.7^\circ$  (1-propanol;  $c$ , 0.743).

*Anal.* Calcd. for  $C_{17}H_{28}O_{11}N_2S$ : N, 6.00. Found: N, 6.19.

**S-(Tetraacetyl- $\beta$ -D-glucopyranosyl)-thiuronium Nitrate.**—Finely powdered silver nitrate (0.68 g.) was dissolved in hot methanol (25 ml.), adding water (1 ml.) to aid solution. II (1.95 g., 1 equiv.) was dissolved in hot methanol (5 ml.). The two solutions were mixed, boiled briefly and the silver bromide filtered (Celite) and rinsed with methanol. The filtrate was evaporated in an air stream to a few ml., and the residue dissolved in 2-propanol (20 ml.) and chilled. The crude product, 1.62 g. (87%), had m.p. 159.5° (dec.). Recrystallization from 2-propanol gave a product, m.p. 155° (dec.) on more gradual heating.  $[\alpha]^{25D}$  was  $-22.2^\circ$  (ethanol;  $c$ , 1.940).

*Anal.* Calcd. for  $C_{15}H_{23}O_{12}N_3S$ : C, 38.40; H, 4.95; N, 8.96. Found: C, 38.74; H, 5.11; N, 8.98.

**Reductive Desulfurization of II.**—II (1.5 g.) was refluxed with Raney nickel (ca. 15 g.) in absolute ethanol (30 ml.) for eight hours. The mixture was filtered and vacuum distilled to dryness at 100°, leaving a white solid. The residue was leached several times with ether, leaving 0.32 g. of a

