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ATTEMPTS TO FIND NEW ANTIMALARIALS. VIII.[1] PHENYL β-D-GLUCOTHIOSIDES, DIPHENYL DISULFIDES, PHENYL THIOCYANATES, AND RELATED COMPOUNDS

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During the course of our investigations on the action of alkali on phenyl glycosides (1) an opportunity arose to have several of these compounds subjected to the screening tests for antimalarial activity. Although none of the O-glucosides was found to possess any appreciable activity, an S-glucoside, namely, phenyl β-D-glucothioside (SN 5,859),[2] was of relatively low toxicity in chicks (Dr. Nathan B. Eddy, 2) and had a slight effectiveness toward *Plasmodium gallinaceum* (Dr. G. Robert Coatney and Dr. W. Clark Cooper, 3). In order to explore this series, thirteen new glucothiosides were prepared for similar tests. Because the phenyl glucothiosides are hydrolyzable to thiophenols which in turn are readily oxidizable to diphenyl disulfides, and such transformations might occur in the chick, any antimalarial activity attributed to the phenyl glucothiosides might also be shown by the diphenyl disulfides. Some new data on these related disulfides, and descriptions of new phenyl thiocyanates which were prepared as intermediates in the syntheses of thiophenols containing substituted amino groups, are presented in the Experimental Part.

None of the fourteen phenyl β-D-glucothiosides, twelve diphenyl disulfides, six phenyl thiocyanates, or seven related sulfur compounds which we have submitted for testing seems to possess sufficient antimalarial activity, either as a therapeutic or prophylactic agent, to warrant further investigation of these classes of compounds.

EXPERIMENTAL PART

THIOCYANATES

p-Thiocyanodimethylaniline (SN 6,782), of m.p. 72–73°, was prepared from dimethylaniline, ammonium thiocyanate, and bromine in glacial acetic acid by the general method of Kaufmann and Oehring (4), as described by Brewster and Schroeder (5). Diethylaniline was thiocyanated similarly, and the product was isolated by pouring the reaction mixture into water, neutralizing with sodium bicarbonate, and extracting with 40–60° petroleum ether. The extract was washed with water, dried with Drierite, and concentrated to a pale yellow oil. The yield appeared to be practically quantitative. Fichter and Schönmann (6) have described the same product, prepared by an electrochemical method, as a yellow oil boiling at 138° at 1 mm.; its picrate melted at 134°. By the addition of ethyl alcoholic hydrochloric acid to a solution of the free base in anhydrous ether, *p-thiocyanodiethylaniline hydrochloride* (SN 9,148) was obtained; it was recrystallized from a mixture of absolute alcohol and anhydrous ether as plate-like prisms which melted *ca.* 172° to a yellow liquid. The hydrochloride is readily soluble in water, with hydrolysis to oily drops.

[1] For the seventh paper of this series see May and Mosettig, *J. Org. Chem.*, **11**, 296 (1946).

[2] The Survey Number, designated SN, identifies a drug in the records of the Survey of Antimalarial Drugs. The antimalarial activities of those compounds to which Survey numbers have been assigned will be tabulated in a forthcoming monograph.

Anal. Calc'd for $C_{11}H_{14}N_2S \cdot HCl$: C, 54.42; H, 6.23; N, 11.54.
Found: C, 54.55; H, 6.18; N, 11.46.

p-Thiocyanodi-n-propylaniline hydrochloride (SN 9,522) was prepared in the same manner. It separated from alcohol-ether as prismatic crystals, m.p. *ca.* 174° to a brownish yellow liquid.

Anal. Calc'd for $C_{13}H_{18}N_2S \cdot HCl$: C, 57.65; H, 7.07; N, 10.35.
Found: C, 57.70; H, 6.97; N, 10.27.

p-Thiocyanodi-n-propylaniline was obtained in crystalline form by stirring the hydrochloride into water, and cooling the liberated oily base. It was recrystallized from alcohol by the cautious addition of water. The small flakes melted at 32–33°.

Anal. Calc'd for $C_{13}H_{18}N_2S$: C, 66.62; H, 7.74; N, 11.96.
Found: C, 66.71; H, 7.66; N, 11.95.

Although Cherkasova, Sklyarenko, and Mel'nikov (7) were unable to prepare a thiocyanate derivative of dibutylaniline by their electrochemical method, the substance may be obtained readily by the method used above.

p-Thiocyanodi-n-butylaniline hydrochloride (SN 9,149) crystallized from alcohol-ether as acicular prisms which melted *ca.* 143° to a yellow liquid. The crystals are somewhat hygroscopic, become yellow-brown on continued exposure to the light, and hydrolyze in water to oily drops.

Anal. Calc'd for $C_{15}H_{22}N_2S \cdot HCl$: C, 60.28; H, 7.76; N, 9.38.
Found: C, 60.45; H, 7.65; N, 9.22.

p-Thiocyano-N-methyl-N-benzylaniline (SN 10,897) was prepared as above except that the product was extracted with ether instead of petroleum ether. It crystallized from alcohol in colorless plates which were often diamond-shaped, and melted at 68–69°. Kaufmann and Ritter (8) reported it as long, white needles from alcohol, melting at 63°. *p-Thiocyano-N-ethyl-N-benzylaniline* (SN 10,454) separated from alcohol as elongated, fibrous prisms, m.p. 52–53°; Kaufmann and Ritter (8) reported white needles, m.p. 54°. The yields were 75–80%.

1-Amino-2,4-dithiocyanonaphthalene (SN 7,477), m.p. *ca.* 200° (decomp.), was the only product isolated from the thiocyanation of α-naphthylamine, in agreement with the experiences of Kaufmann and Oehring (4). The assignment of the thiocyano groups to the 2 and 4 positions by those authors, and by Likhosherstov and Petrov (9), who prepared the same compound with the aid of dichlorourea and ammonium thiocyanate, appears to be based upon analogy only.

THIOPHENOLS

The *thiophenol*, *p-thiocresol*, and *2-amino-4-chlorothiophenol hydrochloride* were purchased from Eastman Kodak Co. The *4-bromo-*, *4-chloro-*, *2,5-dichloro-*, and *3-chloro-4-methyl-thiophenols* were prepared readily by reduction of the corresponding sulfonyl chloride with excess zinc dust and warm 1:1 aqueous hydrochloric acid, followed by extraction of the product with ether (10); the sulfonyl chlorides were obtained conveniently from the dry sodium sulfonates according to the directions of Baxter and Chattaway (11). The *4-methoxy-*, *4-ethoxy-*, and *4-acetyl-thiophenols* and the *1-thionaphthol* were prepared by the method of Leuckart (12), which consists in adding the appropriate diazotized amino compound to an excess of aqueous potassium ethyl xanthate at 80°, and decomposing the resulting oily xanthate with hot alkali.

The *4-dimethylamino-*, *4-diethylamino-*, *4-dipropylamino-*, and *4-methylbenzylamino-thiophenols* were prepared by reduction of the corresponding thiocyano compounds with metal and acid combinations (13). For the first two, tin and hydrochloric acid were used; the resulting mixture was made just neutral with sodium hydroxide, and the liberated thiophenol was separated by distillation with steam (14). The other two thiocyano compounds were reduced with zinc and hydrochloric acid as illustrated in the following example. To 20 g. of *p*-thiocyano-N-methyl-N-benzylaniline and 200 ml. of 1:1 aqueous hydrochloric acid was added 5 g. of zinc dust, and the mixture warmed to dissolve the zinc. Considerable

yellow material, presumably the disulfide, appeared. Two additional 5-g. portions of zinc dust were added and dissolved before the reduction was judged to be complete. The mixture was cooled, and the colorless solution was decanted from the grayish cake of the zinc and thiophenol compound on the bottom of the flask. This solid was then dissolved by shaking with a mixture of 300 ml. of 30% aqueous sodium hydroxide and 100 ml. of ether. The yellowish ether layer was separated, and the zinc was precipitated by bubbling hydrogen sulfide through the aqueous alkaline solution; the zinc sulfide was removed by centrifuging. The clear, colorless, supernatant liquid was decanted and made barely acid with hydrochloric acid. The liberated pale yellow oil was extracted with ether, the ethereal solution washed with water, dried with Drierite, and concentrated. The yield was 10.8 g.

Although several of the above group of thiophenols have not been described previously, no effort was made to purify or characterize any of them further in view of their generally unpleasant odor and ease of oxidation.

DISULFIDES

Most of the disulfides were prepared readily by oxidizing an alkaline solution of the thiophenol with air, or more rapidly with a slight excess of iodine. The *bis-(4-N-methyl-N-benzylaminophenyl) disulfide* (SN 10,544), however, was obtained directly from the thiocyano compound in 45% yield by the action of alcoholic potassium hydroxide according to Kaufmann and Ritter (8); the product (m.p. 85–86°) crystallized from chloroform-ethyl alcohol as mustard-yellow, chunky prisms rather than in needles as described by those authors. *Bis-(p-dimethylaminophenyl) disulfide* (SN 5,986) was prepared in 30% yield by the interaction of dimethylaniline and sulfur chloride in petroleum ether according to Merz and Weith (15). *Bis-(p-bromophenyl) disulfide* (SN 7,533) was isolated as an intermediate product in the reduction of *p*-bromobenzenesulfonyl chloride by tin and hydrochloric acid. *Bis-(2,5-dichlorophenyl) disulfide* (SN 10,902) was found to melt at 81–82° in agreement with Stewart (16), and not at 129° as reported by de Crauw (17). The *bis-(3-chloro-4-methylphenyl) disulfide* (SN 10,903) appears to be a new substance. Prepared from the thiophenol by oxidation, and recrystallized thrice from methyl alcohol, it formed very pale yellow flakes, m.p. 77–78°.

Anal. Calc'd for $C_{14}H_{12}Cl_2S_2$: C, 53.33; H, 3.84; S, 20.34.
Found: C, 53.39; H, 4.02; S, 20.23.

GLUCOTHIOSIDES

Acetobromoglucose and the desired thiophenol were condensed by alcoholic potassium hydroxide in the presence of an excess of the thiophenol, according to the directions of Purves (18). The yields averaged about 50%, the values depending upon the purity of the thiophenol. Deacetylation of the tetraacetate thus formed was effected catalytically with sodium or barium methoxide. These glucothiosides and their tetraacetyl derivatives are believed to have β-configurations and pyranoid rings because of their method of synthesis from acetobromo-α-D-glucose, and because of their negative rotations; the alkaline degradation of the phenyl- and *p*-dimethylaminophenyl-β-D-glucothiosides to levoglucosan (1b) appears to be strictly analogous to that of the phenyl β-D-glucosides (1a). Because of the low solubility of some of the glucothiosides in water, all specific rotations were determined in pyridine solution. Brief descriptions and analytical data follow.

4-Methylphenyl tetraacetyl-β-D-glucothioside, needles from absolute alcohol; m.p. 118°; $[\alpha]_D^{20}$ −21.0° in chloroform (*c*, 2).

Anal. Calc'd for $C_{21}H_{26}O_9S$: C, 55.50; H, 5.77.
Found: C, 55.46; H, 5.76.

4-Methylphenyl β-D-glucothioside monohydrate (SN 9,159), plates from water; when heated rapidly the compound softens about 95°, and when heated slowly the m.p. 149° refers to the anhydrous form; $[\alpha]_D^{20}$, for the hydrate, −57.0° in pyridine (*c*, 1.5).

Anal. Calc'd for $C_{13}H_{18}O_5S \cdot H_2O$: C, 51.30; H, 6.62; H_2O, 5.92.
Found: C, 51.46; H, 6.55; H_2O, 6.02.
Calc'd for $C_{13}H_{18}O_5S$: C, 54.53; H, 6.34.
Found (on sample dried at 70° *in vacuo*): C, 54.48; H, 6.35.

4-Methoxyphenyl tetraacetyl-β-D-glucothioside, prismatic needles from ethyl alcohol; m.p. 101–102°; $[\alpha]_D^{20}$ −28.1° in chloroform (*c*, 1.6).

Anal. Calc'd for $C_{21}H_{26}O_{10}S$: C, 53.61; H, 5.57.
Found: C, 53.64; H, 5.50.

4-Methoxyphenyl β-D-glucothioside monohydrate (SN 10,223), clusters of plates from ethyl alcohol; m.p. 77° when heated rapidly; $[\alpha]_D^{20}$ −51.3° in pyridine (*c*, 1.5).

Anal. Calc'd for $C_{13}H_{18}O_6S \cdot H_2O$: C, 48.74; H, 6.29; H_2O, 5.63.
Found: C, 48.70; H, 6.20; H_2O, 5.59.

4-Ethoxyphenyl tetraacetyl-β-D-glucothioside, acicular prisms from absolute alcohol; m.p. 109–111°; $[\alpha]_D^{20}$ −33.1° in chloroform (*c*, 2).

Anal. Calc'd for $C_{22}H_{28}O_{10}S$: C, 54.53; H, 5.82.
Found: C, 54.35; H, 5.94.

4-Ethoxyphenyl β-D-glucothioside monohydrate (SN 10,073), needles from acetone-petroleum ether. The m.p. was 110° when heated rapidly, and 137° when heated slowly; $[\alpha]_D^{20}$ −50.2° in pyridine (*c*, 1.5).

Anal. Calc'd for $C_{14}H_{20}O_6S \cdot H_2O$: C, 50.28; H, 6.63; H_2O, 5.39.
Found: C, 50.38; H, 6.64; H_2O, 5.36.

4-Acetylphenyl tetraacetyl-β-D-glucothioside, prismatic needles from absolute alcohol; m.p. 132–133°; $[\alpha]_D^{20}$ −25.6° in chloroform (*c*, 2).

Anal. Calc'd for $C_{22}H_{26}O_{10}S$: C, 54.76; H, 5.43.
Found: C, 54.70; H, 5.44.

4-Acetylphenyl β-D-glucothioside (SN 10,074), fine, short needles from alcohol; m.p. 199°, sintering a few degrees lower; $[\alpha]_D^{20}$ −88.3° in pyridine (*c*, 1.5).

Anal. Calc'd for $C_{14}H_{18}O_6S$: C, 53.49; H, 5.77.
Found: C, 53.39; H, 5.83.

1-Naphthyl tetraacetyl-β-D-glucothioside, needles from absolute alcohol; m.p. 147–148°; $[\alpha]_D^{20}$ −39.7° in chloroform (*c*, 2).

Anal. Calc'd for $C_{24}H_{26}O_9S$: C, 58.76; H, 5.34.
Found: C, 58.90; H, 5.40.

1-Naphthyl β-D-glucothioside (SN 10,222), needles from absolute alcohol; m.p. 197°, sintering from 192°; $[\alpha]_D^{20}$ −76.2° in pyridine (*c*, 2).

Anal. Calc'd for $C_{16}H_{18}O_5S$: C, 59.61; H, 5.63.
Found: C, 59.50; H, 5.76.

4-Bromophenyl tetraacetyl-β-D-glucothioside, elongated prisms from absolute alcohol; m.p. 128°; $[\alpha]_D^{20}$ −24.6° in chloroform (*c*, 2).

Anal. Calc'd for $C_{20}H_{23}BrO_9S$: C, 46.25; H, 4.46.
Found: C, 46.17; H, 4.48.

4-Bromophenyl β-D-glucothioside (SN 9,158), acicular prisms from absolute alcohol; m.p. 174–176°; $[\alpha]_D^{20}$ −59.7° in pyridine (*c*, 2).

Anal. Calc'd for $C_{12}H_{15}BrO_5S$: C, 41.03; H, 4.30.
Found: C, 41.14; H, 4.34.

4-Chlorophenyl tetraacetyl-β-D-glucothioside, slender prisms from ethyl alcohol; m.p. 113°; $[\alpha]_D^{20}$ −25.0° in chloroform (*c*, 2).

Anal. Calc'd for $C_{20}H_{23}ClO_9S$: C, 50.58; H, 4.88.
Found: C, 50.56; H, 5.03.

4-Chlorophenyl β-D-glucothioside (SN 9,157), small prisms from alcohol; m.p. 172–175°; $[\alpha]_D^{20}$ −64.7° in pyridine (*c*, 1.5).

Anal. Calc'd for $C_{12}H_{15}ClO_5S$: C, 46.98; H, 4.93.
Found: C, 46.84; H, 5.01.

2,5-Dichlorophenyl tetraacetyl-β-D-glucothioside, acicular prisms from absolute alcohol; m.p. 124°; $[\alpha]_D^{20}$ −30.2° in chloroform (*c*, 1.5).

Anal. Calc'd for $C_{20}H_{22}Cl_2O_9S$: C, 47.16; H, 4.35.
Found: C, 47.17; H, 4.36.

2,5-Dichlorophenyl β-D-glucothioside hemihydrate (SN 10,542), needles from ethyl alcohol. The m.p. was 172° when heated not too rapidly; put in the bath at 120°, the compound melted only partially; $[\alpha]_D^{20}$ −96.5° in pyridine (*c*, 2).

Anal. Calc'd for $C_{12}H_{14}Cl_2O_5S \cdot \frac{1}{2} H_2O$: C, 41.15; H, 4.32; H_2O, 2.57.
Found: C, 41.29; H, 4.29; H_2O, 2.59.

3-Chloro-4-methylphenyl tetraacetyl-β-D-glucothioside, elongated prisms from absolute alcohol; m.p. 116°; $[\alpha]_D^{20}$ − 29.6° in chloroform (*c*, 1.7).

Anal. Calc'd for $C_{21}H_{25}ClO_9S$: C, 51.58; H, 5.15.
Found: C, 51.71; H, 5.17.

3-Chloro-4-methylphenyl β-D-glucothioside hemihydrate (SN 10,899), needles from ethyl acetate; m.p. 115°; $[\alpha]_D^{20}$ −59.8° in pyridine (*c*, 1.5).

Anal. Calc'd for $C_{13}H_{17}ClO_5S \cdot \frac{1}{2} H_2O$: C, 47.34; H, 5.50; H_2O, 2.73.
Found: C, 47.51; H, 5.57; H_2O, 2.78.
Calc'd for $C_{13}H_{17}ClO_5S$: C, 48.67; H, 5.34.
Found (on sample dried at 80° *in vacuo*): C, 48.67; H, 5.31.

2-Amino-4-chlorophenyl tetraacetyl-β-D-glucothioside, prismatic needles from absolute alcohol; m.p. 169–170°; $[\alpha]_D^{20}$ −24.3° in chloroform (*c*, 3).

Anal. Calc'd for $C_{20}H_{24}ClNO_9S$: C, 49.03; H, 4.94; N, 2.86.
Found: C, 49.09; H, 4.92; N, 2.90.

2-Amino-4-chlorophenyl β-D-glucothioside (SN 10,904), small needles from alcohol; m.p. 170–172; $[\alpha]_D^{20}$ −72.2° in pyridine (*c*, 1.2).

Anal. Calc'd for $C_{12}H_{16}ClNO_5S$: C, 44.79; H, 5.01; N, 4.35.
Found: C, 44.68; H, 5.03; N, 4.42.

2-Acetamino-4-chlorophenyl tetraacetyl-β-D-glucothioside, by acetylation of either of the 2-amino compounds just described, with acetic anhydride and pyridine. Needles from absolute alcohol; m.p. 162–163°; $[\alpha]_D^{20}$ −18.7° in chloroform (*c*, 4).

Anal. Calc'd for $C_{22}H_{26}ClNO_{10}S$: C, 49.67; H, 4.93; N, 2.63.
Found: C, 49.62; H, 4.87; N, 2.81.

4-Dimethylaminophenyl tetraacetyl-β-D-glucothioside, long, slender prisms from alcohol; m.p. 150–151°; $[\alpha]_D^{20}$ −47.0° in chloroform (*c*, 1.2).

Anal. Calc'd for $C_{22}H_{29}NO_9S$: C, 54.64; H, 6.05; N, 2.90.
Found: C, 54.48; H, 5.88; N, 2.89.

4-Dimethylaminophenyl β-D-glucothioside monohydrate (SN 6,773), small plates from alcohol; m.p. 116° when heated rapidly, and as high as 140° when heated slowly; $[\alpha]_D^{20}$ −52.0° in pyridine (*c*, 1.2).

Anal. Calc'd for $C_{14}H_{21}NO_5S \cdot H_2O$: C, 50.43; H, 6.95; N, 4.20; H_2O, 5.40.
Found: C, 50.47; H, 7.10; N, 4.16, 4.27; H_2O, 5.44.

4-Diethylaminophenyl tetraacetyl-β-D-glucothioside, many-sided prisms from absolute alcohol; m.p. 141–142°; $[\alpha]_D^{20}$ −43.7° in chloroform (*c*, 2).

Anal. Calc'd for $C_{24}H_{33}NO_9S$: C, 56.34; H, 6.50; N, 2.74.
Found: C, 56.23; H, 6.51; N, 2.70.

4-Diethylaminophenyl β-D-glucothioside monohydrate (SN 7,479), small prisms from alcohol; m.p. 162–163° when heated slowly; $[\alpha]_D^{20}$ −51.5° in pyridine (*c*, 1.5).

Anal. Calc'd for $C_{16}H_{25}NO_5S \cdot H_2O$: C, 53.16; H, 7.53; N, 3.88; H_2O, 4.99.
Found: C, 53.31; H, 7.43; N, 3.91; H_2O, 4.93.
Calc'd for $C_{16}H_{25}NO_5S$: C, 55.95; H, 7.34; N, 4.08.
Found (on sample dried at 80° *in vacuo*): C, 55.87; H, 7.22; N, 4.14.

4-Di-n-propylaminophenyl tetraacetyl-β-D-glucothioside, small needles from alcohol; m.p. 121–122°; $[\alpha]_D^{20}$ −43.7° in chloroform (*c*, 2).

Anal. Calc'd for $C_{26}H_{37}NO_9S$: C, 57.87; H, 6.91; N, 2.60.
Found: C, 58.04; H, 6.84; N, 2.66.

4-Di-n-propylaminophenyl β-D-glucothioside monohydrate (SN 11,578), plates from water; m.p. 58° when heated rapidly, higher when heated more slowly; $[\alpha]_D^{20}$ −47.9° in pyridine (*c*, 1.5).

Anal. Calc'd for $C_{18}H_{29}NO_5S \cdot H_2O$: C, 55.50; H, 8.02; N, 3.60; H_2O, 4.63.
Found: C, 55.56; H, 7.95; N, 3.65; H_2O, 4.60.
Calc'd for $C_{18}H_{29}NO_5S$: C, 58.19; H, 7.87.
Found (on sample dried at 65° *in vacuo*): C, 58.43; H, 7.80.

4-(N-Methyl-N-benzylamino)phenyl tetraacetyl-β-D-glucothioside, needles from alcohol; m.p. 120–121°; $[\alpha]_D^{20}$ −43.3° in chloroform (*c*, 2).

Anal. Calc'd for $C_{28}H_{33}NO_9S$: C, 60.09; H, 5.94; N, 2.50.
Found: C, 60.08; H, 6.10; N, 2.49.

4-(N-Methyl-N-benzylamino)phenyl β-D-glucothioside (SN 10,905), aggregates of prisms from alcohol; m.p. 133–134°; $[\alpha]_D^{20}$ −66.3° in pyridine (*c*, 1.2).

Anal. Calc'd for $C_{20}H_{25}NO_5S$: C, 61.35; H, 6.44; N, 3.58.
Found: C, 61.40; H, 6.37; N, 3.41.

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SUMMARY

Fourteen new aromatic β-D-glucothiosides and their tetraacetates, three new phenyl thiocyanates, and one new diphenyl disulfide have been described. Thirty-nine members of these and closely related types of sulfur compounds have been submitted to screening tests for antimalarial activity. While many of these substances have an appreciable effect upon *Plasmodium gallinaceum*, none is of sufficiently high activity to warrant further study, either as a therapeutic or prophylactic agent.

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