7.99 w, 6.81 s, 6.03 vs (1), 5.36 s (2), 4.79 w, 4.57 m, 4.01 w, 3.59 m, 3.43 s (3), 3.11 vw, 3.02 vw, 2.92 w, 2.82 w.

Penta-*O*-acetyl-*aldehydo*-D-galactose *p*-Nitrophenylhydrazone.—This substance was prepared by the acetylation of D-galactose *p*-nitrophenylhydrazone[25] as described by Wolfrom and Christman,[5] $[\alpha]^{24}D$ +41° (*c* 2, acetonitrile, optical rotatory dispersion in Fig. 6, curve B); λ_{max}^{EtOH} 375 and 550 mμ (ϵ_{max} 2.34 × 10^4 and 266, respectively); X-ray powder diffraction pattern[24]: 12.63 w, 9.41 s (2), 7.20 w, 6.33 vs (1), 5.75 w, 5.40 w, 5.15 w, 4.65 w, 4.15 m, 3.92 s (3), 3.68 m, 3.53 vw, 3.40 w, 3.27 vw, 2.73 vw.

Penta-*O*-acetyl-*aldehydo*-D-mannose *p*-Nitrophenylhydrazone.—This substance was prepared by the acetylation of D-mannose *p*-nitrophenylhydrazone[25] according to the procedure of Wolfrom and Christman.[5] The sirupy product was dissolved in 50 ml. of benzene and chromatographed, in equal portions, on two columns (75 × 240 mm.) filled with Magnesol–Celite[26] (5:1 by weight) and developed with 1400 ml. of benzene–2-methyl-2-propanol (100:1 by volume). Extrusion and streaking with alkaline permanganate solution revealed the presence of two zones 90–175 and 220–230 mm. from the column top. The zones were excised, twice extracted with acetone, filtered; the solvent was removed under reduced pressure and the resulting sirups were crystallized from ethanol. Both zones gave the same bright yellow crystalline material as identified by melting point and mixture melting point, 3.47 g., m.p. 130–131°, $[\alpha]^{27}D$ −16.0° (*c* 4, pyridine), +4.5° (*c* 2, acetonitrile, optical rotatory dispersion shown in Fig. 6 curve C); λ_{max}^{EtOH} 370 (shoulder) and 540 mμ (ϵ_{max} 1100 and 166, respectively); n.m.r. spectrum shown in Fig. 3; X-ray powder diffraction pattern[24]: 12.40 w, 9.85 m, 8.12 m, 6.58 s (2), 6.13 vw, 5.36 vs (1), 5.01 w, 4.70 s (3), 4.33 w, 3.99 m, 3.73 m, 3.47 w, 3.25 w, 3.09 vw, 2.88 m, 1.98 vw.

Anal. Calcd. for $C_{12}H_{12}O_7N_3(CH_3CO)_5$: C, 50.29; H, 5.14; N, 8.00; CH_3CO, 10.74 ml. of 0.1 *N* NaOH for 100 mg. Found: C, 50.57; H, 5.50; N, 7.71; CH_3CO (as *O*-Ac),[20] 10.25 ml.

1-Acetyl-1-phenyl-2-(tetra-*O*-acetyl-β-D-glucopyranosyl)hydrazine.—D-Glucose "α"-phenylhydrazone was prepared according to the method of Stempel,[12b] m.p. 145–150°. This hydrazone was then acetylated in the manner described by Behrend and Reinsberg,[13] m.p. 151–153°, $[\alpha]^{32}D$ +20° (*c* 2.0, chloroform), +9.0° (*c* 2.0, pyridine), +2.0° (*c*, 2.0, acetonitrile, optical rotatory dispersion shown in Fig. 6, curve E); n.m.r. spectrum shown in Fig. 4; λ_{max}^{EtOH} no absorption between 285 and 600 mμ; λ_{max}^{KBr} 3.1, 3.4, 5.7 (carbonyl), 6.1, 6.3, 6.5, 6.7, 7.0, 7.3, 7.9, 8.1–8.3 (acetate), 9.1, 9.4, 9.6, 10.2, 11.0, 11.9, 12.5, 13.1, 13.9, 14.3, 15.5 μ; X-ray powder diffraction pattern[24]: 10.78 w, 9.61 m (3), 8.85 m, 6.71 vw, 5.40 s (1), 4.82 w, 4.51 m, 4.23 w, 3.87 s (2), 3.56 vw. Hofmann[27] reported m.p. 152–153° and $[\alpha]D$ +11.97° (pyridine) for this material while Behrend and Reinsberg[13] reported m.p. 151° and $[\alpha]D$ +17.5° (pyridine).

Acknowledgment.—Acknowledgment is made to Dr. Leroy F. Johnson of Varian Associates, Palo Alto, California, in obtaining and interpreting one of the n.m.r. spectra. Certain other spectra were obtained by Byron Bossenbroek and the optical rotatory dispersion measurements were carried out by Neal Franks. Stimulating discussions with Dr. R. D. Guthrie, University of Leicester, are acknowledged.

(25) W. Alberda van Ekenstein and J. J. Blanksma, *Rec. trav. chim.*, **22**, 434 (1903).

(26) W. H. McNeely, W. W. Binkley, and M. L. Wolfrom, *J. Am. Chem. Soc.*, **67**, 527 (1945).

(27) A. Hofmann, *Ann.*, **366**, 306 (1909).

The Synthesis of the *t*-Butyl 1-Thio-D-glucosides and of 2,4-Dinitrophenyl 1-Thio-β-D-glucopyranoside. The Reaction of Some 1-Thio-D-glucosides with Mercury Salts of Carboxylic Acids

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Both anomeric *t*-butyl 1-thio-D-glucopyranosides and *t*-butyl 1-thio-D-glucofuranosides, as well as 2,4-dinitrophenyl 1-thio-β-D-glucopyranoside, have been synthesized. The behavior of some of these thioglucosides with mercury salts of carboxylic acids has been investigated and a tentative mechanism of the formation of 1-*O*-acylaldoses by this pathway is proposed.

Earlier investigations in this laboratory[1-4] have shown that various 1-thioaldose derivatives (dithioacetals and alkyl 1-thioglycosides) undergo metathetical reactions with silver and mercury salts. Thus, ethyl 1-thio-β-D-glucopyranoside is converted into a mixture of the anomeric 1-*O*-mesitoyl-D-glucopyranoses when treated with silver mesitoate[1] (silver 2,4,6-trimethylbenzoate), and the condensation of 5-*O*-benzoyl-2-deoxy-D-*erythro*-pentose diisopropyl dithioacetal with chloromercuri-6-benzamidopurine leads (after the removal of masking groups) to a mixture of the anomeric 9-(2-deoxy-D-*erythro*-pentofuranosyl)adenines. In the studies of the behavior of ethyl 1-thioaldosides with silver salts of carboxylic acids,[1,4] prolonged boiling in acetonitrile was found necessary to effect complete reaction, although an ethyl 1-thioaldofuranoside[4] obviously reacted more readily than did an ethyl 1-thioaldopyranoside.[1] Under these conditions, acyl migrations (for example, conversion of 1-*O*-benzoyl-α-D-glucopyranose to 2-*O*-benzoyl-D-glucose) take place and the procedure is obviously less than ideal for inserting labile substituents at C-1 in an aldose. Pedersen and Fletcher[4] noted that mercuric acetate reacts with ethyl 5-*O*-benzoyl-1-thio-β-L-arabinofuranoside more readily than does silver benzoate. In seeking methods whereby this reaction can be carried out under comparatively mild conditions, we have, therefore, now turned our attention to some mercury salts of carboxylic acids, and, for glycosides, have used *t*-butyl 1-thio-β-D-glucopyranoside (II), *t*-butyl 1-thio-α-D-glucofuranoside (X), and 2,4-dinitrophenyl 1-thio-β-D-glucopyranoside (XIV) in the hope of revealing any influence of the electronegativity of the aglucon on the nature of the reaction.

Although 2-methyl-2-propanethiol (*t*-butyl mercaptan) is a readily available substance, no *t*-butyl thioglycosides appear to have been reported in the litera-

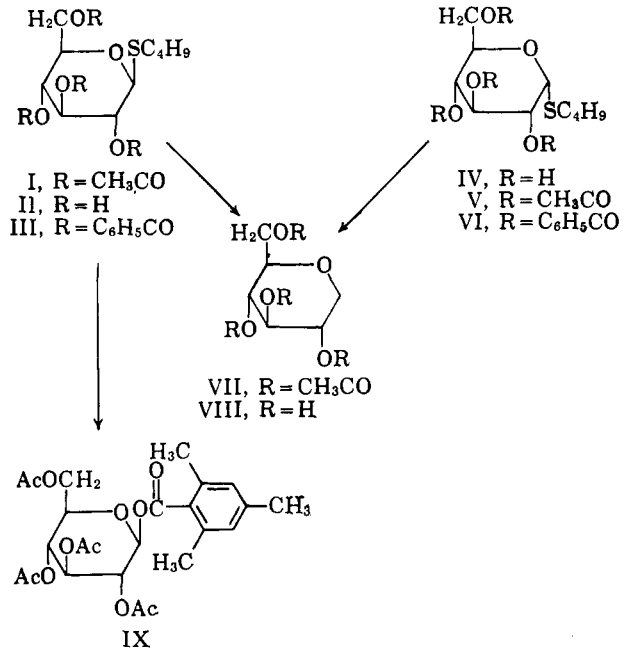
(1) C. Pedersen and H. G. Fletcher, Jr., *J. Am. Chem. Soc.*, **82**, 3215 (1960).

(2) C. Pedersen, H. W. Diehl, and H. G. Fletcher, Jr., *ibid.*, **82**, 3425 (1960).

(3) C. Pedersen and H. G. Fletcher, Jr., *ibid.*, **82**, 5210 (1960).

(4) C. Pedersen and H. G. Fletcher, Jr., *J. Org. Chem.*, **26**, 1255 (1961).

ture. However, the thiol was found to react readily with β-D-glucopyranose pentaacetate in ether solution in the presence of zinc chloride to give *t*-butyl 1-thio-β-D-glucopyranoside tetraacetate (I) in 69% yield; deacetylation afforded the parent glucoside (II). The reaction was repeated using benzene in place of ether, and *t*-butyl 1-thio-β-D-glucopyranoside tetraacetate (I) was obtained in 24% yield. Deacetylation of the material remaining in the mother liquor gave *t*-butyl 1-thio-α-D-glucopyranoside (IV) in 38% yield. Reductive desulfurization of I with Raney nickel gave 1,5-anhydro-D-glucitol tetraacetate (VII), whereas desulfurization of IV yielded the unsubstituted anhydride (VIII), demonstrating that both substances are 1-thio-D-glucopyranosides. Anomeric configurations were assigned to the 1-thio-D-glucopyranosides on the basis of their optical rotations.

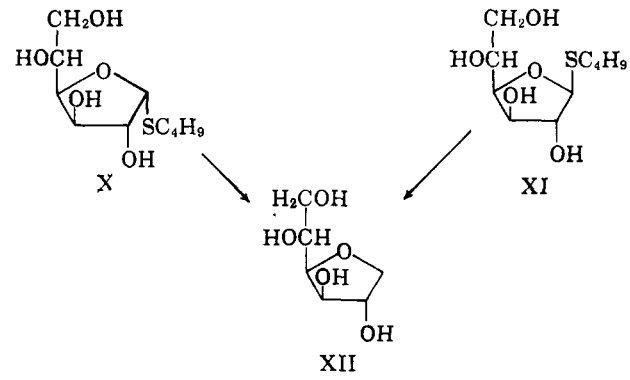


t-Butyl 1-thio-β-D-glucopyranoside (II) reacts readily with mercury mesitoate in acetonitrile solution at room temperature, giving, after acetylation, 2,3,4,6-tetra-*O*-acetyl-1-*O*-mesitoyl-β-D-glucopyranose (IX)[5] in 38% yield.

Condensation of β-D-glucofuranose pentabenzoate with 2-methyl-2-propanethiol in ethereal solution in the presence of zinc chloride gave, after debenzoylation, *t*-butyl 1-thio-α-D-glucofuranoside (X) in 48% yield. In a similar preparation, the crude *t*-butyl 1-thio-D-glucofuranoside tetrabenzoate was chromatographed, and a levorotatory fraction debenzoylated to give *t*-butyl 1-thio-β-D-glucofuranoside (XI). Both X and XI gave 1,4-anhydro-D-glucitol (XII) on reductive desulfurization with Raney nickel, confirming their furanoside structures; again, anomeric configurations were assigned on the basis of optical rotations.

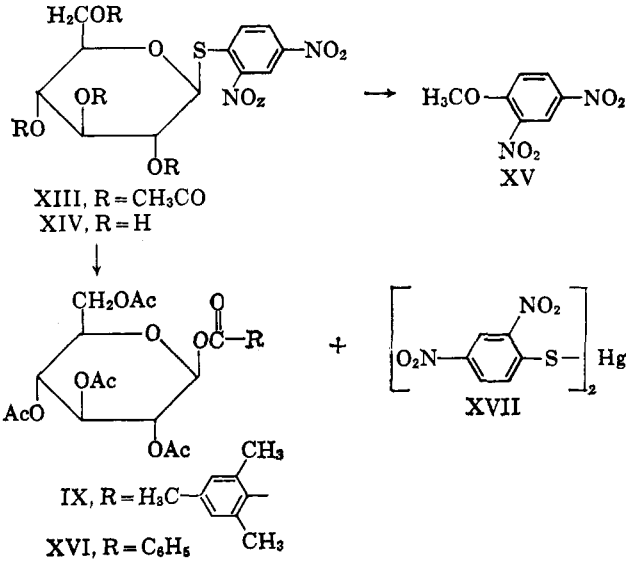
The behavior of *t*-butyl 1-thio-α-D-glucofuranoside (the only anomer available in sufficient quantity for testing) with mercury mesitoate in acetonitrile solution proved unique in our experience, inasmuch as the only crystalline product recoverable was mesitoic anhydride, a readily isolable and identifiable substance. The

(5) H. B. Wood, Jr., and H. G. Fletcher, Jr., *J. Am. Chem. Soc.*, **78**, 207 (1956).



mechanism of the formation of this unexpected substance must at this juncture remain a matter for speculation.

2,4-Dinitrophenyl 1-thio-β-D-glucopyranoside tetraacetate (XIII) was synthesized through condensation of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide with 2,4-dinitrobenzenethiol in the presence of ethanolic potassium hydroxide. Some difficulty was encountered in the deacetylation of XIII, since the two nitro groups labilize the S-aryl bond. Thus, barium methoxide gave only a poor yield of the deacetylated glucoside (XIV), but a considerable amount of 2,4-dinitroanisole (XV) was isolated and chromatographic evidence for the presence of di(β-D-glucopyranosyl) disulfide was obtained. On the other hand, deacetylation of XIII with methanolic ammonia gave XIV in good yield. Treatment of XIV in acetonitrile solution with either

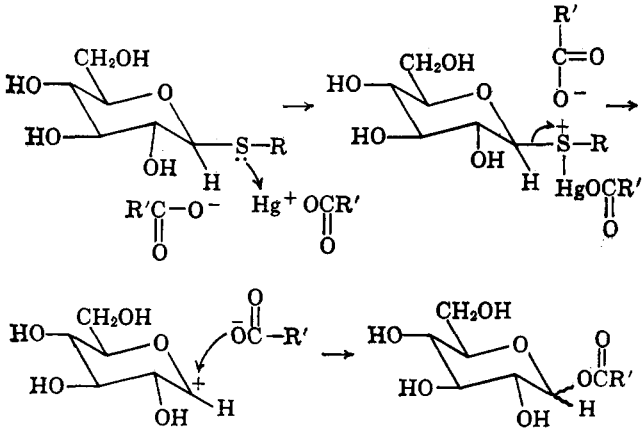


mercuric benzoate or mercuric mesitoate at room temperature gave 1-*O*-benzoyl-β-D-glucopyranose or 1-*O*-mesitoyl-β-D-glucopyranose (isolated as their tetraacetates XVI and IX in low yield). In both cases, di(2,4-dinitrophenylthio)mercury (XVII), the other expected product, was isolated in substantial yield.

Discussion

The condensation of 1-thioglycosides in acetonitrile solution with silver salts of carboxylic acids is a non-stereospecific reaction, giving a mixture of the anomeric 1-*O*-acylaldoses.[1] With both mercury and silver salts of carboxylic acids, 1-thioglycosides usually give, quite promptly, a precipitate which changes in appearance

as the reaction proceeds. This observation suggests that a complex is initially formed between the two components[6] and subsequently breaks down to the 1-*O*-acylaldose and a di(alkylthio)mercury. Such a transformation may be rationalized in the following fashion.



In this mechanism, the electronegativity of the aglucon would be expected to play a greater or lesser role by diminishing or increasing the electron density around the sulfur atom. The observation that *t*-butyl 1-thio-β-D-glucopyranoside gives a higher yield of 1-*O*-mesitoyl-β-D-glucopyranose than does 2,4-dinitrophenyl 1-thio-β-D-glucopyranoside may be regarded as supporting this concept.[7] However, in such apparently complex and often heterogeneous reactions, where a large proportion of the products are as yet unidentified, such a mechanism must at this point remain purely speculative. Irrespective of mechanistic considerations, the reaction appears to offer some potential utility as a synthetic method.

A simple technique for minimizing the dispersion of the vapors of volatile thiols during some typical manipulations is described in the Experimental section.

Experimental[8]

A Technique for Handling Volatile Thiols.—Dispersion of the objectionable vapors of volatile thiols may be minimized in several ways. In this work, evaporation of the thiols was always carried out as a codistillation (usually with carbon tetrachloride) *in vacuo*, the distillate being retained in the trap shown in Fig. 1. Dry Ice and acetone were used to cool the trap, and the distillate collected in the spherical flask was promptly treated with an excess of concentrated, aqueous calcium hypochlorite at the conclusion of the distillation. Alternatively, the calcium hypochlorite solution may be placed in the flask prior to the distillation.

In filtering solids contaminated with volatile thiols, the filter may be covered with a large conical funnel attached to the vacuum system through the trap shown in Fig. 1.

***t*-Butyl 1-Thio-β-D-glucopyranoside Tetraacetate (I).**—A mixture of 25 ml. of anhydrous ether and 5 g. of powdered, freshly fused zinc chloride in a glass-stoppered flask was stirred at room temperature until the solid had changed to an oil. 2-Methyl-2-propanethiol[9] (15 ml.) and β-D-glucopyranose pentaacetate (10 g.) were then added, and the reaction mixture was stirred at room temperature. After 2.5 hr., the pink reaction mixture was nearly homogeneous; shortly thereafter, the product began to crystallize as fine, silky needles. After a total of 12 hr., the mixture was a deep purple. Carbon tetrachloride (25 ml.) was added, the flask was attached to the trap described (Fig. 1), and the major part of the solvent and unchanged thiol was distilled into the trap under reduced pressure. Water (100 ml.) and carbon tetrachloride (100 ml.) were added to the residue, the mixture was filtered, and the solid was washed with carbon tetrachloride. The aqueous layer was separated, run directly into concentrated, aqueous calcium hypochlorite, and discarded; the carbon tetrachloride solution was dried (magnesium sulfate), filtered, and concentrated *in vacuo* to a thick sirup. Two 50-ml. batches of carbon tetrachloride were successively evaporated from this sirup to remove most of the thiol. The thick, colorless sirup was dissolved in 50 ml. of ethyl acetate and reconcentrated *in vacuo*, the residue was dissolved in 20 ml. of warm ethyl acetate, and the solution was filtered through a thin layer of decolorizing carbon, reheated, and diluted with 2–3 volumes of pentane. Crystallization was completed at 5° to give 5.8 g. of product, m.p. 144–145°. A second crop (1.62 g., slightly less pure) raised the total crude yield to 7.42 g. (69%). One recrystallization from ethanol–pentane gave pure I, m.p. 145–146°, $[\alpha]^{20}D$ −5.9° (*c* 0.65, chloroform).

Anal. Calcd. for $C_{18}H_{28}O_9S$ (420.46): C, 51.41; H, 6.71; S, 7.62. Found: C, 51.57; H, 6.83; S, 7.51.

2,3,4,6-Tetra-*O*-acetyl-1,5-anhydro-D-glucitol (VII) from I.—A solution of I (0.5 g.) in 20 ml. of 70% aqueous ethanol was treated with 4 teaspoonfuls of freshly prepared Raney nickel (under ethanol). After being boiled under reflux for 3 hr., the suspension was cooled and filtered, and the filtrate was concentrated (*in vacuo*) at 40° to a colorless sirup which from 4 ml. of ether and 3 ml. of pentane gave a nearly quantitative yield of crystals, m.p. 70–74°, $[\alpha]^{20}D$ +38.8° (*c* 1.0, chloroform); lit.[10] m.p. 73–74°, $[\alpha]^{20}D$ +38.9° (chloroform).

***t*-Butyl 1-Thio-β-D-glucopyranoside (II).**—I (2 g.) was catalytically deacetylated with barium methoxide in methanol. The decationized product, crystallized from acetone–pentane and dried *in vacuo* at 40°, weighed 0.95 g. (76%), m.p. 113–115°. Recrystallized from acetone–pentane, the pure II had m.p. 115–116°, $[\alpha]^{20}D$ −52.8° (*c* 0.55, water).

Anal. Calcd. for $C_{10}H_{20}O_5S \cdot 0.5H_2O$ (261.33): C, 45.96; H, 8.10; S, 12.27. Found: C, 46.03; H, 7.95; S, 12.46.

Attempts to obtain anhydrous material failed. Acetylation (acetic anhydride–pyridine) gave I, 93% yield, m.p. 145–146°, $[\alpha]^{20}D$ −5.9° (*c* 1.0, chloroform). A mixture melting point with the original ester was not depressed.

***t*-Butyl 1-Thio-β-D-glucopyranoside Tetrabenzoate (III).**—II (0.15 g.) was benzoylated (benzoyl chloride–pyridine) and the product crystallized on adding water. Recrystallized from 5

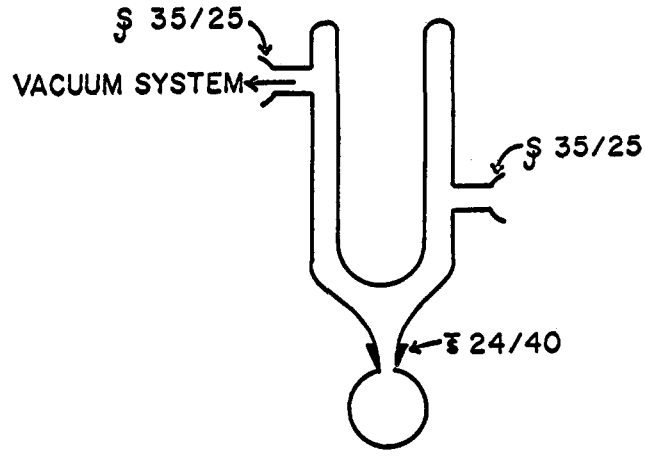


Figure 1.

(6) E. Hardegger, E. Schreier, and Z. El Heweihi [*Helv. Chim. Acta*, **33**, 1159 (1950)] described several addition compounds of aldose dithioacetals with mercuric chloride.

(7) It may be noted that no fully acylated 1-thioglycosides have yet been found to undergo displacements with mercury or silver salts, ref. 1, footnote 11. In the course of the present work, *t*-butyl 1-thio-β-D-glucopyranoside tetraacetate in acetonitrile solution was found to be unaffected by mercury mesitoate.

(8) Melting points are corrected. Selected absorption maxima, together with probable assignments, are given for infrared spectra, intensities being indicated as s (strong), m (medium), w (weak). Ar indicates a substituted benzene ring.

(9) A sample (*t*-butyl mercaptan) obtained from Phillips Petroleum Co., Special Products Division, Bartlesville, Okla., was found to be of high purity and was employed throughout this research.

(10) N. K. Richtmyer and C. S. Hudson, *J. Am. Chem. Soc.*, **65**, 64 (1943).

ml. of hot ethanol, III (0.33 g., 86%) had m.p. 183–184°, $[\alpha]^{20}D$ +32.2° (*c* 1.1, chloroform).

Anal. Calcd. for $C_{38}H_{36}O_9S$ (668.73): C, 68.24; H, 5.43; S, 4.79. Found: C, 68.26; H, 5.55; S, 4.76.

***t*-Butyl 1-Thio-α-D-glucopyranoside (IV).**—A mixture of 5 g. of freshly fused zinc chloride, 15 ml. of 2-methyl-2-propanethiol, 20 ml. of dry benzene, and 10 g. of β-D-glucopyranose pentaacetate was stirred at room temperature for 20 hr. and then processed as for I. The resulting sirup, dissolved in ethyl acetate–pentane, gave 2.6 g. (24%) of I, m.p. 144–145°. Solvent was removed from the mother liquor and the sirupy residue was deacetylated with barium methoxide in methanol. After the solution had been neutralized with carbon dioxide, the methanol was removed *in vacuo*, the residue was dissolved in 50 ml. of water, and the solution was filtered from a trace of flocculent material and deionized with ion-exchange resins. Concentration gave a sirup which was dissolved in a mixture of 5 ml. of ethyl acetate and 10 ml. of pentane to give 2.54 g. (38%) of product, m.p. 139–141°. Recrystallized from the same solvent mixture, IV had m.p. 142–143°, $[\alpha]^{20}D$ +233° (*c* 0.78, water).

Anal. Calcd. for $C_{10}H_{20}O_5S \cdot 0.5H_2O$ (261.33): C, 45.96; H, 8.10; S, 12.27. Found: C, 45.81; H, 8.22; S, 12.01.

1,5-Anhydro-D-glucitol (VIII) from IV.—IV (0.5 g.) was desulfurized by boiling with a suspension of 2 teaspoonfuls of freshly prepared Raney nickel in 10 ml. of 70% aqueous ethanol. After filtration, the solution was concentrated *in vacuo* and the product crystallized from methanol, 0.13 g. (41%), m.p. 142–143°, $[\alpha]^{20}D$ +42.7° (*c* 1.0, water). A mixture melting point with an authentic sample of VIII[10] was not depressed.

***t*-Butyl 1-Thio-α-D-glucopyranoside Tetraacetate (V).**—IV (0.15 g.) was acetylated (acetic anhydride–pyridine) to give a clear, colorless sirup which, from ethyl acetate–pentane, gave 0.19 g. (79%) of crystals, m.p. 63–65°. Recrystallization from warm hexane afforded pure V, m.p. 62–64°, $[\alpha]^{20}D$ +185° (*c* 0.6, chloroform).

Anal. Calcd. for $C_{18}H_{28}O_9S$ (420.46): C, 51.41; H, 6.71; S, 7.62. Found: C, 51.53; H, 6.92; S, 7.41.

***t*-Butyl 1-Thio-α-D-glucopyranoside Tetrabenzoate (VI).**—IV (0.22 g.) was benzoylated (benzoyl chloride–pyridine) to give a sirup which, from 5 ml. of ethanol, gave 0.55 g. (96%) of product, m.p. 167–168°. Recrystallization from ethanol afforded needles which were dried *in vacuo* at 110°, m.p. 168–169°, $[\alpha]^{20}D$ +96.8° (*c* 0.85, chloroform).

Anal. Calcd. for $C_{38}H_{36}O_9S \cdot 0.5H_2O$ (677.74): C, 67.33; H, 5.55; S, 4.73. Found: C, 67.53; H, 5.92; S, 4.58.

Attempts to dehydrate this compound completely were unsuccessful.

Mercuric 2,4,6-Trimethylbenzoate (Mesitoate.)—The following procedure for the preparation of mercuric mesitoate proved convenient. A suspension of mesitoic acid[11] (30 g.) in 150 ml. of water was nearly neutralized by the cautious addition of 6 *N* ammonium hydroxide. Care was taken to avoid an excess of base, and a trace of the acid was filtered off (decolorizing carbon). A solution of 60 g. of mercuric nitrate monohydrate in 18 ml. of water was added, the solution was heated (until the salt had dissolved) and cooled to room temperature; after 10 min. the crystals were filtered off, washed thoroughly with water, and dried *in vacuo* at 60° to yield 40.2 g. of fine needles (84%). This salt is adequate for most purposes; it may be recrystallized from acetonitrile or 2-ethoxyethanol with considerable loss. The above product was recrystallized from hot 2-ethoxyethanol (5 ml./g.) to give 15.4 g. of pure salt; a second crop (10 g.) was obtained from the mother liquor. A sample of the first crop, dried *in vacuo* at 100°, was used for analysis.

Anal. Calcd. for $C_{20}H_{22}HgO_4$ (526.99): C, 45.58; H, 4.21. Found: C, 45.63; H, 4.40.

2,3,4,6-Tetra-*O*-acetyl-1-*O*-mesitoyl-β-D-glucopyranose (IX) from II.—II (1 g.) was dissolved in 100 ml. of dry acetonitrile, and 5.0 g. of mercuric mesitoate was added. The mixture was stirred at room temperature overnight and filtered through a layer of decolorizing carbon. Solvent was removed from the filtrate *in vacuo* at 40°, and the residue was dissolved in water–methanol (10:1) and treated with hydrogen sulfide to remove mercuric ions. After being filtered through a thin layer of decolorizing carbon, the solution was concentrated *in vacuo*, and the resulting sirup was dried by evaporation therefrom *in vacuo* of several portions of benzene. Acetylation with 10 ml. of dry pyridine and 8 ml. of acetic anhydride afforded a clear, colorless sirup. From absolute ethanol, 0.45 g. (38%) of material was obtained, m.p. 139–140°, $[\alpha]^{20}D$ +9.5° (*c* 0.9, chloroform). Recrystallization from benzene–hexane gave pure IX, m.p. 141–142°, $[\alpha]^{20}D$ +4.2° (chloroform). A mixture melting point with authentic material[5] was undepressed.

***t*-Butyl 1-Thio-α-D-glucofuranoside (X).**—Freshly fused zinc chloride (5 g.) was added to 50 ml. of anhydrous ether, and the mixture was stirred until the solid had been converted to an oil. 2-Methyl-2-propanethiol (15 ml.) and 10 g. of β-D-glucofuranose pentabenzoate[12] (m.p. 141–143°, $[\alpha]^{20}D$ −56.8° in chloroform) were added, and the mixture was stirred at room temperature (20 hr.). The solvent, zinc chloride, and unchanged mercaptan were removed as for I to give a sirup which was debenzoylated with barium methoxide in methanol. The methanolic solution was neutralized with carbon dioxide and concentrated *in vacuo*, and the semisolid residue was diluted with 10 ml. of water. Methyl benzoate was removed by extraction with two 3-ml. portions of cyclohexane and the aqueous phase, after being filtered through a thin bed of decolorizing carbon, was concentrated to a sirup. From methanol–isopropyl ether, the product (0.9 g., 48%) was obtained in crystalline form, m.p. 135–136°. Recrystallization from the same solvent mixture gave pure X, m.p. 139–140°, $[\alpha]^{20}D$ +84.9° (*c* 0.5, water).

Anal. Calcd. for $C_{10}H_{20}O_5S \cdot 0.5H_2O$ (261.33): C, 45.96; H, 8.10; S, 12.27. Found: C, 45.85; H, 8.16; S, 12.25.

1,4-Anhydro-D-glucitol (XII) from X.—(0.5 g.) was desulfurized by boiling for 3 hr. in 10 ml. of 70% aqueous ethanol containing 2 teaspoonfuls of freshly prepared Raney nickel. The suspension was cooled and filtered, the filtrate was concentrated *in vacuo*, and the resulting sirup was dissolved in 0.5 ml. of isopropyl alcohol to give 0.1 g. (32%) of crystals, m.p. 105–110°. A second recrystallization afforded pure XII, $[\alpha]^{20}D$ −21.7° (*c* 1.0, water); its m.p. 114–115° was not depressed on admixture with an authentic sample; lit.[13] m.p. 115–116°, $[\alpha]^{20}D$ −21.9° (water).

***t*-Butyl 1-Thio-β-D-glucofuranoside (XI).**—Freshly fused zinc chloride (5 g.) was stirred at room temperature with 50 ml. of anhydrous ether for 15 min. 2-Methyl-2-propanethiol (15 ml.), chloroform (15 ml., U.S.P.), and β-D-glucofuranose pentabenzoate (10 g.) were added, and the mixture was stirred at room temperature. After 10 min., dissolution was not complete, and 55 ml. of methylene chloride was added to give a solution. After being kept for 16 hr. at room temperature, the mixture was filtered to remove 0.45 g. of material, m.p. >300°. The filtrate was concentrated to about one-third of its volume, and was diluted with methylene chloride (50 ml.) and water (50 ml.). After being shaken, the aqueous layer was discarded, and the organic layer was washed with water (50 ml.) and with saturated aqueous bicarbonate, dried (anhydrous magnesium sulfate), and concentrated *in vacuo* to a sirup. This sirup (8 g.) was chromatographed on a column of 300 g. of alumina (acid-washed Alcoa, equilibrated with atmospheric moisture). Elution with 200-ml. portions of benzene led to the collection of a substantial peak of levorotatory material, $[\alpha]^{20}D$ *ca.* −65° (chloroform). Efforts to obtain this material crystalline being unsuccessful, it was debenzoylated (barium methoxide in methanol) in the usual way to yield, from ether, fine needles (0.57 g.), m.p. 89–90°. Recrystallized from ethyl acetate and dried at 56° *in vacuo*, the product had m.p. 89–90°, $[\alpha]^{20}D$ −140° (*c* 0.38, water).

Anal. Calcd. for $C_{10}H_{20}O_5S$ (252.32): C, 47.60; H, 7.99. Found: C, 47.68; H, 8.01.

Desulfurization of 0.40 g. of XI with Raney nickel was performed as for the α-D anomer to give 0.0656 g. (25%) of crystals, m.p. 106–110°; on recrystallization from isopropyl alcohol, m.p. 112–114°, undepressed by admixture with authentic XII. XII had $[\alpha]^{20}D$ −21.1° (*c* 0.83, water).

Reaction of X with Mercuric Mesitoate.—X (1 g., 3.83 mmoles) was dissolved in 200 ml. of acetonitrile, half of the acetonitrile was removed by boiling, and the solution was cooled to room temperature, treated with 5 g. of mercuric mesitoate (9.49 mmoles), and stirred overnight. A trace of a fine precipitate was removed by filtration (decolorizing carbon), and the clear, colorless solution was concentrated *in vacuo* to a thin sirup which crystallized spontaneously. The crystals were removed and washed with 1 ml. of methanol, 0.44 g., m.p. 92–100°; a second crop (0.10 g., m.p. 96–100°) formed on standing; total yield, 0.54 g., 1.74 mmoles. After recrystallization from acetone, the

(11) K & K Laboratories, Inc., 177-10 93rd Avenue, Jamaica 33, N. Y.

(12) P. A. Levene and G. M. Meyer, *J. Biol. Chem.*, **76**, 513 (1928).

(13) S. Soltzberg, R. M. Goepp, Jr., and W. Freudenberg, *J. Am. Chem. Soc.*, **68**, 919 (1946).

product was obtained as prisms, m.p. 102–103°, mixed with authentic mesitoic anhydride,[14] m.p. 102–103° and had infrared spectrum identical with that of an authentic sample.

A blank run, in which mercury mesitoate in acetonitrile was boiled for an extended period, failed to yield detectable amounts of mesitoic anhydride.

2,4-Dinitrophenyl 1-Thio-β-D-glucopyranoside Tetraacetate (XIII).—A solution of 12 g. of potassium hydroxide in 325 ml. of 95% ethanol was mixed with 48 g. of 2,4-dinitrobenzenethiol, and the resulting, dark red suspension was treated with a solution of 81.55 g. of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide in 400 ml. of chloroform. After being boiled under reflux for 2 hr., the reaction mixture was cooled, diluted with 100 ml. of chloroform, and washed with 1/5-saturated, aqueous sodium bicarbonate. A small quantity of insoluble, yellow powder was filtered from the organic layer, which was then washed four times with dilute, aqueous sodium bicarbonate and twice with water. The dark red chloroform solution was filtered through a thick layer of decolorizing carbon on Filter-Cel, and was concentrated to a small volume. From its solution in chloroform–acetone–pentane, the product was obtained as pale yellow needles which were dried at 60° for 1 hr., 67.1 g. (64% based on the bromide), m.p. 199–200°. Successive recrystallizations from acetone–ethanol and from hot 2-methoxyethanol afforded pure XIII, m.p. 199–200°, $[\alpha]^{20}D$ −98.0° (*c* 0.80, chloroform); ν_{max}^{Nujol} 1762 s and 1747 s (OAc), 1604 m (Ar), 1530 m ($ArNO_2$) $cm.^{-1}$.

Anal. Calcd. for $C_{20}H_{22}N_2O_{13}S$ (530.46): C, 45.28; H, 4.18; N, 5.28; S, 6.04. Found: C, 45.08; H, 4.19; N, 5.48; S, 6.47.

Deacetylation of XIII. A. With Methanolic Ammonia.—XIII (10 g.) was suspended in 300 ml. of methanol, the suspension cooled in ice, and dry ammonia gas passed in for 2 hr. The mixture was then stirred at 0° for 1.5 hr. and at room temperature for 1.5 hr., and concentrated to a brown sirup. Most of the acetamide was removed at 100° *in vacuo*, the residue was dissolved in hot acetone, and the red solution passed through a pad of Darco X. On being cooled, the solution deposited pale yellow needles of the acetone solvate of XIV which were dried at 60°, 5.6 g. (71%, based on the solvate), m.p. 184–185° (sintering at 113°). Recrystallization from acetone–ethanol–benzene and then from acetone containing a little methanol gave pure XIV containing acetone of crystallization, m.p. 117–119° (foaming), $[\alpha]^{20}D$ −207° (*c* 0.57, methanol); ν_{max}^{Nujol} 3300 s (OH), 1680 s (acetone), 1593 s (Ar), 1530 s, shoulder ($ArNO_2$), 1516 s (Ar) $cm.^{-1}$. Drying *in vacuo* at 120° for 1 hr. gave the solvent-free compound (weight loss, 13.3%; theoretical, 13.82%).

Anal. Calcd. for $C_{12}H_{14}N_2O_9S \cdot C_3H_6O$ (420.39): C, 42.85; H, 4.79; N, 6.67; S, 7.63. Found: C, 42.55; H, 4.75; N, 6.51; S, 7.66.

Anal. Calcd. for $C_{12}H_{14}N_2O_9S$ (362.31): C, 39.78; H, 3.89. Found: C, 39.86; H, 4.07.

Crystallization of XIV from hot water or from water containing a little ethanol yielded pale yellow tufts of needles which were dried overnight at 60°, m.p. 184–186° dec. (sintering from 108°), $[\alpha]^{20}D$ −249° (*c* 0.74, methanol); ν_{max}^{Nujol} 3550 s, 3400 s, and 3300 s (OH), 1650 w (H_2O), 1600 s (Ar), 1526 s ($ArNO_2$) $cm.^{-1}$.

Anal. Calcd. for $C_{12}H_{14}N_2O_9S \cdot 0.5H_2O$ (371.32): C, 38.81; H, 4.07; N, 7.55; S, 8.63. Found: C, 38.91; H, 4.19; N, 7.52; S, 8.57.

B. With Barium Methoxide.—Deacetylation of XIII (9.18 g.) in a mixture of 200 ml. of methanol and 200 ml. of dichloromethane, using 10 ml. of 1.5 *N* barium methoxide, was allowed to proceed for 22 hr. at room temperature. The pale orange suspension was diluted with methanol (1 l.) and the solution was deionized by passage through Amberlite IR-120 (H^+), 5 × 12 cm. and Amberlite IR-45(OH^-), 5 × 15 cm. Concentration of the solution gave a bright yellow residue which crystallized from aqueous ethanol as pale yellow needles, 0.77 g. (22%), m.p. 85–87°. Recrystallization from ethanol–isopropyl ether gave nearly colorless needles of 2,4-dinitroanisole, m.p. 88–89°, $[\alpha]^{20}D$ 0° (*c* 1.05, chloroform). The infrared spectrum of the material (potassium bromide disk) was identical with that of an authentic specimen; a mixture melting point was undepressed.

The material remaining in the mother liquor was crystallized from acetone containing a little ethanol, to give the acetone solvate of XIV, 2.45 g. (34%).

Examination of the mother liquor by paper chromatography, using ethyl acetate–acetic acid–water (9:2:2, v./v.) and a periodate–silver nitrate spray, revealed that, in addition to XIV ($R_{glucose}$ 3.33), a second compound ($R_{glucose}$ 0.73) was present. The latter substance cochromatographed with di(β-D-glucopyranosyl) disulfide, prepared by catalytic deacetylation of its octaacetate.[15]

The Reaction of XIV with Mercuric Benzoate.—A mixture of 0.61 g. of the acetone solvent of XIV, 0.71 g. (1.1 molar equiv.) of dried mercuric benzoate, and 100 ml. of dry acetonitrile was stirred at room temperature for 21 hr. The pale yellow opalescent solution was evaporated to dryness, and the residue was treated with 20 ml. of methanol. A pale yellow solid was filtered off, washed thoroughly with methanol, and dried at 60°, 0.232 g. (53%), m.p. 256.5–257° dec. Recrystallized from boiling acetonitrile, this product was obtained as pale yellow needles, m.p. 258.5°; mixed with an authentic sample of bis(2,4-dinitrophenylthio)mercury (prepared as described later), the material melted at 257° dec.

Anal. Calcd. for $C_{12}H_6HgN_4O_8S_2$ (598.93): C, 24.06; H, 1.01; Hg, 33.49; N, 9.35; S, 10.71. Found: C, 24.35; H, 1.29; Hg, 32.8; N, 9.99; S, 10.88.

The pale yellow mother liquor was saturated with hydrogen sulfide and was evaporated to dryness to coagulate the precipitated mercuric sulfide. Methanol (15 ml.) and dichloromethane (15 ml.) were added, and the suspension was centrifuged; the decantate was concentrated to a yellow sirup which crystallized from water, yielding 40 mg. of impure XIV. The mother liquor was extracted twice with ether to remove benzoic acid, concentrated to dryness, the acetylated (acetic anhydride–pyridine). Crystallization of the resulting sirup from ethanol afforded 120 mg. of pale yellow needles, m.p. 193–198°, undepressed on admixture with XIII, $[\alpha]^{20}D$ −93° (*c* 1.37, chloroform). On standing, the aqueous ethanolic mother liquor afforded clusters of colorless needles, 0.063 g. (10%), m.p. 139–141°. Recrystallization from aqueous ethanol gave XVI, $[\alpha]^{20}D$ −31.4° (*c* 0.74, chloroform), m.p. 142–145°, m.m.p. 142–146° with authentic material.

Bis(2,4-dinitrophenylthio)mercury (XVII).—2,4-Dinitrobenzenethiol (0.17 g.) was shaken with 10 ml. of dry acetonitrile, contaminating disulfide was removed by centrifugation, the residue being washed with 10 ml. of acetonitrile. The combined solution and washing was treated with a solution of 0.348 g. of mercuric benzoate in 30 ml. of acetonitrile, and the pale yellow mixture was kept at room temperature for 20 hr. Concentration gave a dark yellow solid which was triturated with methanol; the yellow crystals were removed by filtration, 0.145 g., m.p. 255–256° dec. Recrystallization from hot acetonitrile gave pale yellow needles, 0.083 g., m.p. 257.5° dec.

Anal. Calcd. for $C_{12}H_6HgN_4O_8S_2$ (598.93): C, 24.06; H, 1.01; Hg, 33.49; N, 9.35; S, 10.71. Found: C, 24.42; H, 1.26; Hg, 32.6; N, 9.78; S, 10.51.

The Reaction of XIV with Mercuric Mesitoate.—A mixture of 525 mg. of the monoacetone solvate of XIV, 1.314 g. of mercuric mesitoate (2 molar equiv.), and 40 ml. of dry acetonitrile was stirred at room temperature for 24 hr. during which time the suspended solid dissolved, yielding a pale yellow, opalescent solution. Concentration of the solution to dryness gave a bright yellow sirup to which 20 ml. of methanol was added. After *ca.* 1 min., yellow crystals started separating from the mixture, which was kept at 0° for 1 hr.; washed with methanol and dried, XVII (165 mg., 44%) had m.p. 257.5–258.5° dec.

The combined filtrate and washings were diluted with 60 ml. of dichloromethane, saturated with hydrogen sulfide, and evaporated to dryness to coagulate the mercuric sulfide. The black residue was extracted with 100 ml. of 1:1 (v./v.) methanol–dichloromethane, and the extracts were filtered through a layer of charcoal on Filter-Cel. Concentration of the filtrate gave an orange mass which was treated with 50 ml. of water and then was extracted with two 30-ml. portions of dichloromethane to remove mesitoic acid. Evaporation of the aqueous layer afforded a sirup which, on trituration with ether–ethanol, deposited some yellow amorphous powder. After filtration, removal of the solvent gave a pale yellow sirup which was acetylated (acetic anhydride–pyridine). Crystallization from ethanol–pentane yielded 40 mg. (6%) of square prisms of 2,3,4,6-tetra-*O*-acetyl-1-*O*-mesitoyl-β-D-glucopyranose, m.p. 137–138°. Recrystallization from ben-

(14) R. C. Fuson, J. Corse, and N. Rabjohn, *J. Am. Chem. Soc.*, **63**, 2852 (1941).

(15) N. K. Richtmyer and C. S. Hudson, *ibid.*, **65**, 1477 (1943).

zene–hexane gave material with m.p. 139–140°, undepressed on admixture with an authentic specimen.[5] Dissolution of the material remaining in the original mother liquor led to the isolation of 30 mg. of crystalline material, m.p. 110–140°; this was not further investigated.

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Greenheart Alkaloids. II. Isolation and Characterization of Seven Alkaloids[1,2]

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Seven alkaloid hydrochlorides were isolated from the ether-soluble alkaloids of the bark of greenheart (*Ocotea rodiaei*). These alkaloids fall into two groups with properties pointing to bisbenzylisoquinoline structures with one diphenyl ether linkage and two diphenyl ether linkages, respectively. The first group includes rodiasine, which previously had been isolated as the methiodide, and also norrodiasine and dirosine. The second group includes ocoteamine, otocamine, demerarine, and ocodemerine. None of these alkaloids has the properties of chondrodendrine, commonly called "bebeerine," which has been believed to be the predominant alkaloid in greenheart bark.

The ether-soluble alkaloids from greenheart bark (*Ocotea rodiaei*) generally have been believed to consist predominantly of the well characterized alkaloid chondrodendrine, commonly called "bebeerine."[3] However, this belief was based on an old comparison of the amorphous alkaloids from greenheart with alkaloids from other sources, and it was not found possible to isolate chondrodendrine from greenheart by previously reported methods.[1] Rodiasine dimethiodide, which was obtained by the treatment of the ether-soluble alkaloids with methyl iodide, appears to be the first pure alkaloid isolated from greenheart. This compound had the characteristics of a bisbenzylisoquinoline alkaloid (or biscoclaurine alkaloid) with one diphenyl ether linkage.[1]

Preliminary investigations showed that the ether-soluble alkaloids consisted of many components rather than of one predominant alkaloid. Attempted fractional crystallization from organic solvents gave only amorphous products and showed evidence of some decomposition of the alkaloids in organic solvents. Crystalline alkaloid hydrochlorides were obtained from dilute hydrochloric acid solutions of the ether-soluble alkaloid mixtures, but such crystallizations were very slow. Additional crystalline hydrochlorides were obtained by countercurrent distribution of the alkaloids with acetate buffer and chloroform; further additional alkaloid hydrochlorides were obtained by conventional chromatography on alumina, employing the stepwise addition of more polar solvents. However, better separation was obtained by gradient elution chromatography.

Chromatography of the ether-soluble alkaloids on neutral alumina with a gradient eluent consisting of methylene chloride and methanol gave the curve shown in Fig. 1. The composition of the eluent was changed in an exponential manner, as shown in Fig. 1, by adding to a constant volume mixer[4] methylene chloride containing geometrically increasing proportions of methanol. To minimize decomposition, the chromatograms were run as rapidly and with as little solvent as appeared practical.

From the majority of the chromatography fractions, crystalline alkaloid hydrochlorides were obtained. Fractional crystallization gave eight alkaloid hydrochlorides which were purified to constant specific rotation.[2a] Distribution coefficients were determined for the various batches of hydrochlorides obtained in the crystallization scheme, because in some cases the specific rotations were quite similar and the decomposition points were not only similar but also depended on the rate of heating and were not depressed in mixtures.

The eight products obtained were tentatively designated alkaloids C, D, E, F, G, H, I, and J hydrochlorides. The specific rotations and distribution coefficients of these hydrochlorides are listed in Table I.

TABLE I

ALKALOIDS FROM GREENHEART

Name of alkaloid	Original designation	$[\alpha]D$,[a] deg.	K[b]	R_f[c,d]	Phenolic peak,[d] cm.$^{-1}$	Functional groups[d,e] OH	NH
			Group A				
Rodiasine	D	+74	0.7	0.46	3385	1	0
Norrodiasine	C	+74	2.3	0.42	3365	1	1
Dirosine	E	+97	2.8	0.40	3360	1	1
			Group B				
Ocoteamine	G	+250	10.5	0.33	3555	1	1
Otocamine	H	+268	0.4	0.34	None	(0)	(1)
Demerarine	F	−181	11.5	0.33	3545	1	1
Ocodemerine	J[f]	−170	0.5	(0.33)	(None)	(0)	(1)
			Mixtures				
	I	+148	0.5	0.35 0.48	3380	½	½
	J	−38	1.4	0.33 0.43	3350		

[a] Specific rotation of the hydrochloride (*c* 1.0, water). [b] Distribution coefficient of the hydrochloride in 0.5 *M* acetate buffer, pH 4.17, chloroform. [c] For amyl alcohol, pyridine, water (110:110:90) on buffered paper. [d] Values in parentheses were not obtained directly but are indicated by various considerations, as indicated in the text. [e] As deduced from the absorption peaks of the acetylated alkaloids, 0 = none. [f] Originally a component of this mixture of hydrochlorides.

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(2) Presented in part by P. J. Hearst and H. Hochman, before the Organic Chemistry Division of the American Chemical Society (a) at Dallas, Tex., April, 1956, and (b) at Miami, Fla., April, 1957.

(3) T. A. Henry, "The Plant Alkaloids," 4th Ed., The Blakiston Co., Inc., New York, N. Y., 1949, p. 363; M. Kulka, "The Alkaloids," Vol. IV, R. H. F. Manske and H. L. Holmes, Ed., Academic Press, Inc., New York, N. Y., 1954, p. 227 (also Vol. VII, 1960, p. 439).

(4) R. M. Bock and N. S. Ling, *Anal. Chem.*, **26**, 1451 (1954).