Anal. Calcd. for $C_{10}H_{15}NClI$: HCl, 11.71. Found: HCl, 11.59, 11.49.

Summary

1. A direct method for the synthesis of 6-halogenated carvacrylamines from *p*-cymene in good yields has been accomplished.

2. 6-Chlorocarvacrylamine as previously described has been shown to be impure.

3. The position of substituents in 2-chloro-6-nitro-*p*-cymene, 6-chloro, 6-bromo, and 6-iodocarvacrylamines has been located by synthesis.

4. 6-Chlorocarvacrylamine has been characterized by twelve salts, three acyl and four sulfonyl derivatives, a secondary picrylamine, a substituted urea, 2,2′-diazoamino-6,6′-dichloro-*p*-cymene, one azo and four diazo dyes.

5. The dyes gave varying shades of yellow, red and brown when applied to wool, silk, cotton, and rayon; they were fast to washing, light, alkali, and perspiration.

CHAPEL HILL, NORTH CAROLINA
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[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, COLLEGE OF AGRICULTURE, UNIVERSITY OF WISCONSIN]

Synthesis of Glycol Glucosides[1]

BY SULO KARJALA AND KARL PAUL LINK

During the last ten years the production and extensive use of the glycol solvents has created a need for comprehensive toxicological studies on these compounds. This Laboratory recently undertook the preparation of large quantities of diethylene glycol β-*d*-monoglucoside for pharmacological investigations.[2] The synthesis of glucosides of other members of the glycol solvent series was studied during the course of this work.

Prior to the time that the work reported in this communication was started, ethylene glycol β-*d*-monoglucoside prepared by Fischer and Fischer[3] was the only substance of this class that had been obtained in the crystalline state. Subsequently Vintilescu, Ionescu and Kizyk[4] reported the enzymatic synthesis of this glucoside by emulsin. Bourquelot, Bridel and Aubry[5] had previously reported the biochemical synthesis of sirupy propylene glycol glucoside by the same enzyme.

A short time after our work was started, Helferich and Hiltmann[6] reported the preparation of the monoglucosides of ethylene glycol monomethyl ether, trimethylene glycol, tetramethylene glycol and the *cis* and *trans* forms of cyclopentanediol, as well as the diglucosides of ethylene, trimethylene, pentamethylene and hexamethylene glycols. Some of the work reported by them already had been completed in this Laboratory, and reference is made in the experimental part to agreement in data obtained.

Experimental

β-*d*-Acetobromoglucose.—The following procedure gave a stable product in yields above those reported previously.[7,8]

To 60 g. of acetic anhydride in a 500-cc. round-bottomed flask, fitted with a rubber stopper bearing an inlet tube reaching to the bottom of the flask and with a calcium chloride tube outlet, was added 60 g. of glucose pentaacetate. The suspension was cooled in ice and dry hydrogen bromide was introduced through the inlet tube. After all the glucose acetate had gone into solution, the passage of hydrogen bromide was interrupted, and an additional 60-g. portion of the acetate was added. Passage of the gas was resumed until the second portion of acetate had gone into solution and the mixture was saturated. With the use of a conventional naphthalene generator,[9] about 350 g. of bromine is required. The reaction takes about five hours. After the solution had stood overnight at room temperature, it was evaporated to a sirup under reduced pressure. Crystallization occurred during the concentration or upon the addition of a small amount of anhydrous ether. The crystalline product was dried and recrystallized from anhydrous ether. The mother liquors were concentrated and worked up in the same way. The yield is 109 g. (86%); m. p. 88–89°. The product could be kept indefinitely in a desiccator over phosphorus pentoxide.

Ethylene Glycol β-*d*-Monoglucoside Tetraacetate.—To 40 g. of ethylene glycol were added 12 g. of acetobromoglucose and 14.4 g. of dry silver carbonate. The mixture

(1) Published with the permission of the Director of the Wisconsin Agricultural Experiment Station.

(2) The pharmacological studies are being made by Dr. E. M. K. Geiling, Department of Pharmacology, University of Chicago.

(3) Fischer and Fischer, *Ber.*, **43**, 2529 (1910).

(4) Vintilescu, Ionescu and Kizyk, *Bull. soc. chim., Romania*, **16**, 151 (1934); *Chem. Abst.*, **29**, 4390 (1935).

(5) Bourquelot, Bridel and Aubry, *Compt. rend.*, **160**, 214 (1915).

(6) Helferich and Hiltmann, *Ann.*, **531**, 160 (1937).

(7) Freudenberg, Noë and Knopf, *Ber.*, **60**, 238 (1927).

(8) Levene and Raymond, *J. Biol. Chem.*, **90**, 247 (1931).

(9) Houben-Weyl, "Die Methoden der organischen Chemie," 3rd ed., Vol. III, Leipzig, 1930, p. 1156.

was shaken until no more carbon dioxide was evolved. Anhydrous benzene (75 cc.) was added and the mixture shaken overnight. The silver salts were removed, the two layers in the filtrate separated, and the glycol layer repeatedly extracted with anhydrous benzene. The benzene fractions were combined and concentrated[10] to a sirup which crystallized readily. Ten grams (87%) of the crude product, after recrystallization from water, gave 8 g. of the pure product; m. p. 105–106°, $[\alpha]^{23}D$ −26.3° (*c*, 3.5; H_2O).

Anal. Calcd. for $C_{16}H_{24}O_{11}$: C, 48.95; H, 6.17. Found: C, 49.15; H, 6.15.

Fischer and Fischer[3] reported a m. p. 101–103° cor., $[\alpha]D$ −26.23° in water (yield of 45%) and an uncrystallizable sirup which appeared to be an isomeric glucoside acetate. When we prepared the β-*d*-monoglucoside acetate following the original directions of Fischer and Fischer we again obtained a product melting at 105–106°. Helferich and Hiltmann[5] gave no constants on this compound.

Ethylene Glycol β-*d*-Monoglucoside.—Six grams of the above glucoside acetate was deacetylated by the method of Fischer and Fischer.[3] After standing for one month at 0°, the oily sirup was inoculated with a minute crystal of diethylene glycol β-*d*-monoglucoside (m. p. 116.5–118°). Crystallization occurred immediately. Upon recrystallization from absolute alcohol 2 g. of product was obtained; m. p. 117.5–118°, $[\alpha]^{22}D$ −28.5° (*c*, 3.4; H_2O). The melting point of a mixture with diethylene glycol *d*-monoglucoside was 102–106°.

Anal. Calcd. for $C_8H_{15}O_7$: C, 42.85; H, 7.19. Found: C, 42.73; H, 7.0.

Instead of 117.5–118°, Fischer and Fischer as well as Vintilescu, Ionescu and Kizyk[4] report a melting point of 137°. We were able to obtain this higher melting product by deacetylating a second portion of the glucoside acetate by the method of Zemplén and Pacsu.[11] The sirup crystallized readily, giving a product which after recrystallization from absolute alcohol melted at 136–137°. When a portion of the lower melting product was recrystallized using the higher melting form for inoculation, the crystals obtained melted at 136–137°. A mixture of the two products melted at 136–137°, with preliminary sintering at 123°.

The rotation of the higher melting form was $[\alpha]^{28}D$ −29.4° (*c*, 2.1; H_2O). Fischer and Fischer reported $[\alpha]^{16}D$ −30.20°, while Vintilescu, *et al.*, found $[\alpha]^{20}D$ −25.62°.

Ethylene Glycol bis-β-*d*-Glucoside Octaacetate.[12]—To 7 g. of ethylene glycol monoglucoside tetraacetate (m. p. 105–106°) in 100 cc. of anhydrous benzene was added acetobromoglucose (4 g.) and dry silver carbonate (5 g.). The mixture was shaken for twenty-four hours, filtered and the filtrate concentrated to a thick sirup. This sirup was heated to 60–70° with 350 cc. of water and filtered. The crystalline residue and the crystals obtained from the filtrate on cooling were recrystallized from absolute alcohol: yield, 3.8 g. (54%); m. p. 169–170° (cor.); $[\alpha]^{23}D$ −31.76° (*c*, 4.6; $CHCl_3$). Helferich and Hiltmann[6] report m. p. 170–171° (cor.), $[\alpha]D$ −31.80° ($CHCl_3$).

Diethylene Glycol β-*d*-Monoglucoside Tetraacetate.—This compound was prepared by the procedure used for ethylene glycol β-*d*-monoglucoside tetraacetate. The crude product (10 g., m. p. 81–84°) on recrystallization from a benzene–petroleum ether mixture gave 8 g. (63%) of the pure compound, m. p. 92–93° (cor.); $[\alpha]^{24}D$ −27.62° (*c*, 3.4; H_2O).

Anal. Calcd. for $C_{18}H_{28}O_{12}$: C, 49.52; H, 6.47. Found: C, 49.54; H, 6.58.

In order to prepare this compound in large quantities the following procedure was adopted. A solution of 100 g. of acetobromoglucose and 400 g. of diethylene glycol in 400 cc. of anhydrous dioxane was shaken for twenty-four hours at room temperature with 70 g. of dry silver carbonate. The silver salts were removed and the filtrate concentrated to remove the dioxane. The concentrate, after filtration through asbestos, was diluted with 400 cc. of water. This solution was extracted 6–8 times with thiophene-free benzene (1 liter). The combined benzene fractions were dried over sodium sulfate and concentrated until the crystallization of the glucoside acetate made distillation difficult. Enough petroleum ether (about 600 cc.) was added to throw out the glucoside acetate, and the mixture was allowed to stand overnight at 0° to ensure complete crystallization. The total yield from five such runs was 386 g., or an average of 77 g. to a run, representing a yield of 73%. The melting point of the crude product was 85–88°. This product was satisfactory for deacetylation.

Diethylene Glycol β-*d*-Monoglucoside.—Three grams of the above pure tetraacetate was dissolved in 50 cc. of absolute methanol and 2 cc. of 0.1 *N* sodium methoxide was added. The solution was refluxed for three minutes, cooled and concentrated to a sirup. A small amount of absolute alcohol was added, and the sirup warmed. Crystallization began immediately. After standing for twelve hours at 0°, 1.55 g. (84%) of the deacetylated product was obtained. Upon recrystallization from absolute alcohol, the product melted at 116.5–118°; $[\alpha]^{23}D$ −22.4° (water; *c*, 3.1).

Anal. Calcd. for $C_{10}H_{20}O_8$: C, 44.74; H, 7.52. Found: C, 44.81; H, 7.52.

For the deacetylation of large quantities of the glucoside tetraacetate the same procedure was used with 50 g. of the crude tetraacetate (m. p. 85–88°) in 200 cc. of absolute methanol and 5 cc. of 0.2 *N* sodium methoxide. By this procedure 386 g. of the tetraacetate gave 210 g. (89%) of the crude, slightly colored glucoside (m. p. 113–115°), which was recrystallized twice (carbon clarification) from two liters of absolute alcohol, yielding 202 g. of glucoside (m. p. 115–116.5°).

Diethylene Glycol bis-β-*d*-Glucoside Octaacetate.—Nineteen grams of diethylene glycol β-*d*-monoglucoside tetraacetate, 10 g. of silver carbonate and 12 g. of acetobromoglucose were shaken in 100 cc. of anhydrous dioxane for twenty-four hours, filtered, the precipitate washed with hot dioxane, and the filtrate concentrated to a thick sirup, which was heated in 400 cc. of water. The hot aqueous solution was decanted from the insoluble oil, which was washed with small portions of hot water and allowed to crystallize. On recrystallization from ab-

(10) All solvents were removed under a reduced pressure of 12 mm. unless otherwise stated.

(11) Zemplén and Pacsu, *Ber.*, **62**, 1613 (1929).

(12) Helferich and Hiltmann system of nomenclature[6] where "bis" connotes a *diglucoside*.

solute alcohol 7 g. (31%) of the product was obtained, m. p. 125.5–126.5°; $[\alpha]^{22}D$ −23.5° (*c*, 3.0; $CHCl_3$).

Anal. Calcd. for $C_{32}H_{46}O_{21}$: C, 50.12; H, 6.06. Found: C, 50.20; H, 6.07.

Deacetylation of Diethylene Glycol bis-β-*d*-Glucoside Octaacetate.—Three grams of the octaacetate, on deacetylation with sodium methoxide as described above, yielded an oil which could not be induced to crystallize. The oil was quite insoluble in cold absolute alcohol. An attempt was made to distil the product in a molecular still at 190° and 0.004 mm. pressure. The pressure changed from 0.004 mm. to 0.1 mm. during the distillation. Apparently cleavage of the glucoside occurred.

Propylene Glycol β-*d*-Monoglucoside Tetraacetate.—To 50 g. of freshly distilled racemic propylene glycol were added 12 g. of acetobromoglucose, 14.4 g. of silver carbonate and 50 cc. of anhydrous benzene. The mixture was shaken for twenty-four hours. After filtration and repeated extraction of the propylene glycol with benzene, the combined benzene extracts were concentrated to a sirup. A portion of the sirup, on scratching on a watch glass, crystallized, and the crystals were used to inoculate the main portion, which then slowly crystallized to give a mass of colorless crystals and a small amount of a red oil. The mass was treated with 100–150 cc. of water in which the red oil, which probably consisted of some diglucoside, was insoluble. The aqueous solution on evaporation to dryness gave a mass of colorless crystals which were taken up in cellosolve and treated with petroleum ether. When the solution was kept at 0°, an oil separated, but when it was allowed to stand for some time at 10–15°, a small amount of crystalline material, m. p. 67–72°, was obtained. Repeated recrystallization from cellosolve–petroleum ether or alcohol–petroleum ether mixture slowly raised the melting point until it finally remained constant at 99–101°. The yield was about 1 g. of pure material; $[\alpha]^{26}D$ −6.8° (*c*, 2.9; $CHCl_3$).

Anal. Calcd. for $C_{17}H_{26}O_{11}$: C, 50.24; H, 6.45. Found: C, 50.20; H, 6.49.

The intermediate fractions could be obtained crystalline upon evaporation to dryness. However, when the crystals were taken up in solvents, in an effort to separate the isomers by fractional crystallization, oily products were obtained.

Propylene Glycol β-*d*-Monoglycoside.—The deacetylation was carried out as above with sodium methoxide, 0.8 g. of the tetraacetate yielding 0.2 g. (43%) of product melting at 136–138°. The product was crystallized from absolute alcohol–ether; $[\alpha]^{22}D$ −25.5° (*c*, 2.0; H_2O).

Anal. Calcd. for $C_9H_{18}O_7$: C, 45.37; H, 7.62. Found: C, 45.47; H, 7.62.

A small portion of the glucoside gave a faint, but definitely positive, iodoform test which indicates that the glucosidic linkage is on the primary alcohol group of propylene glycol. Ethylene glycol β-*d*-monoglucoside, as would be expected, gave a negative test under the same conditions.

Triethylene Glycol β-*d*-Monoglucoside Tetraacetate.—To a solution of 100 g. of freshly distilled triethylene glycol and 12 g. of acetobromoglucose in 100 cc. of anhydrous benzene was added 14.4 g. of dry silver carbonate. After shaking for twenty-four hours the mixture was filtered, and the homogeneous filtrate was treated with 100 cc. of water. The aqueous solution was extracted repeatedly with benzene, the benzene solution dried over anhydrous sodium sulfate and concentrated. The resulting oil could not be induced to crystallize and was not investigated further.

Ethylene Glycol Monoethyl Ether β-*d*-Monoglucoside Tetraacetate.—A mixture of 25 g. of freshly distilled cellosolve, 6 g. of acetobromoglucose and 7.2 g. of silver carbonate was shaken until no more carbon dioxide was evolved. The reaction was very rapid, and a slight evolution of heat was observed. The mixture was filtered, the precipitate washed with hot cellosolve, and the filtrate concentrated at 45–50° to a colorless sirup, which soon crystallized. Upon recrystallization from cellosolve–water the product was isolated as long rods, yield 5 g. (82%); m. p. 65–67°; $[\alpha]^{28}D$ −19.5° ($CHCl_3$; *c*, 3.4).

Anal. Calcd. for $C_{18}H_{28}O_{11}$: C, 51.43; H, 6.72. Found: C, 51.25; H, 6.72.

Ethylene Glycol Monoethyl Ether β-*d*-Monoglucoside.—Five grams of the glucoside acetate was deacetylated with sodium methoxide. The free glucoside crystallized on evaporation of the methanol under reduced pressure and was recrystallized from absolute alcohol. The yield of the substance was 2.5 g. (83%); m. p. 139–140°; $[\alpha]^{23}D$ −26.0° (*c*, 3.1; H_2O).

Anal. Calcd. for $C_{10}H_{20}O_7$: C, 47.61; H, 7.99. Found: C, 47.5; H, 7.9.

Trimethylene Glycol β-*d*-Monoglucoside Tetraacetate.—This substance was prepared in 78% yield by the same method used for the preparation of ethylene glycol β-*d*-monoglucoside tetraacetate. Recrystallized from water, it melted at 97–98°; $[\alpha]^{26}D$ −17.3° (*c*, 4.1; $CHCl_3$). Helferich and Hiltmann[6] report a melting point of 97.5–98.5° (cor.) and $[\alpha]D$ −17.0° for this compound.

A small amount of water-insoluble material was isolated. Upon recrystallization from absolute alcohol, 0.5 g. of substance melting at 171–172° (uncor.) was obtained; $[\alpha]^{26}D$ −15.8° (*c*, 2.8; $CHCl_3$).

This substance is without doubt trimethylene glycol *bis*-β-*d*-glucoside octaacetate, for which Helferich and Hiltmann[6] report a melting point of 175–176.5° (cor.) and an $[\alpha]D$ of −16.9°.

Diethylene Glycol Monoethyl Ether β-*d*-Monoglucoside Tetraacetate.—The procedure was the same as that given for the triethylene glycol β-*d*-monoglucoside tetraacetate. A colorless sirup was obtained which could not be crystallized. The sirup was taken up in benzene which was then extracted two times with water. From the benzene solution an oil was obtained again. The aqueous extract, on evaporation to dryness, yielded crystals. On recrystallization from absolute alcohol–petroleum ether the product had m. p. 104–105.5°. This substance was identical with the monoglucoside acetate of ethylene glycol, m. p. 105–106°, a mixture of the two having m. p. 105–106°. Thus the original carbitol solution contained significant quantities of ethylene glycol as an impurity.

Distillation of the carbitol glucoside acetate in a molecular still at 160–180° and 0.004 mm. pressure gave a glassy film on the condenser. The film reverted to an uncrystallizable oil when brought to room temperature.

Deacetylation of the above Carbitol Glucoside Acetate.—A portion of the oil obtained above was deacetylated with a trace of sodium methoxide, yielding an uncrystallizable oil. Upon distillation in a molecular still at 180° and 0.004 mm. pressure a slight decrease in vacuum (to 0.01 mm.) was observed. The substance distilled, however, to give a glassy film similar to the one obtained above which reverted to an oil on warming to room temperature.

We are indebted to Dr. H. A. Campbell, Research Assistant in Biochemistry, for the micro carbon and hydrogen determinations. Our thanks are also due to Dr. P. N. Leech, Director of the Chemical Laboratory of the American Medical Association, Chicago, Illinois, and Dr. E. W. Schoeffel, chemist for the A. M. A. Chemical Laboratory, for the chemicals used in this study. Dr. Schoeffel also has checked some of the C–H determinations.

Summary

1. The properties of the monoglucosides, the monoglucoside tetraacetates, the diglucosides and the diglucoside octaacetates of ethylene and trimethylene glycol were checked with those appearing in the literature. Improvements in the methods of preparation of these glucosides are described.

2. The β-*d*-monoglucosides and the β-*d*-monoglucoside tetraacetates of diethylene glycol, propylene glycol and ethylene glycol monoethyl ether, and the β-diglucoside octaacetate of diethylene glycol have been prepared and the constants reported.

3. Triethylene glycol β-*d*-monoglucoside tetraacetate, the β-monoglucoside tetraacetate of diethylene glycol monoethyl ether and the free glucoside from the latter have been obtained as sirups.

4. A procedure is described for the large-scale preparation of diethylene glycol β-*d*-monoglucoside tetraacetate and diethylene glycol β-*d*-monoglucoside.

MADISON, WIS. RECEIVED JANUARY 22, 1940

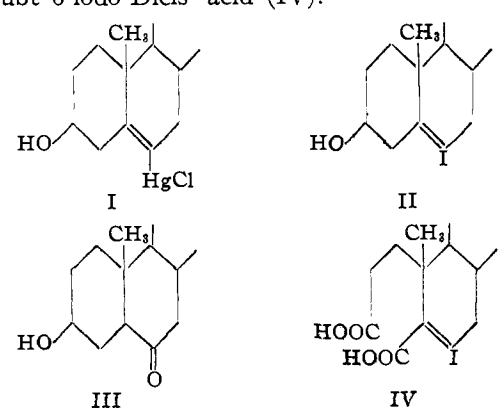
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

The Mercuration of Cholesterol

BY R. H. LEVIN AND M. A. SPIELMAN

Merz[1] mercurated cholesterol with mercuric acetate in hot glacial acetic acid, and after treating the product with sodium chloride he was able to isolate in poor yield a chloromercuricholesterol of unknown constitution. The chloromercuri derivative reacted smoothly with iodine to give an iodocholesterol which, because of the inertness of the halogen atom, resisted all efforts at structure proof. This paper presents a reinvestigation of the problem.

We have prepared chloromercuricholesterol and iodocholesterol with minor modifications of the Merz method. In agreement with him we have found iodocholesterol to be an exceedingly inert compound. Hydrolysis was, however, achieved with the aid of copper catalysis in a steel bomb at 225°. The product was a saturated hydroxy ketone identified as 6-ketocholestanol (III) by comparison with a synthetic specimen made by the usual methods.[2] It follows, therefore, that the compounds in question are 6-chloromercuricholesterol (I) and 6-iodocholesterol (II). The dibasic acid $C_{27}H_{43}O_4I$ from the sodium hypobromite oxidation of 6-iodocholesterol is without doubt 6-iodo-Diels' acid (IV).



No other products of mercuration could be isolated from the sirupy mercury-containing residues after isolation of the 6-chloromercuricholesterol. The large amounts of mercurous acetate formed indicate dehydrogenation, but no

(1) Merz, *Z. physiol. Chem.*, **154**, 225 (1926). Compare also Montignie, *Bull. soc. chim.*, [4] **43**, 1403 (1928); [5] **2**, 1367 (1935).

(2) Mauthner and Suida, *Monatsh.*, **24**, 652 (1903); Heilbron Jackson, Jones and Spring, *J. Chem. Soc.*, 102 (1938).