Synthesis of Glucosides of Digitoxigenin, Digoxigenin and Periplogenin[1]

BY ROBERT C. ELDERFIELD, FREDERICK C. UHLE AND JOSEF FRIED

In a previous communication the synthesis of several glycosides of strophanthidin has been reported.[2] Pharmacological tests on these substances[3] revealed the interesting fact that the nature of the carbohydrate component played a dominant role in determining the cardiac activity of the glycosides.

We now wish to report the synthesis of three additional glycosides, digitoxigenin-(3)-β-*d*-glucoside, digoxigenin-(3)-β-*d*-glucoside and periplogenin-(3)-β-*d*-glucoside. These were all prepared *via* the tetraacetyl glucosides by the classical Koenigs and Knorr synthesis from the aglycones and acetobromoglucose which establishes the configuration of the glucosides. The point of attachment of the glucose to the aglycone is most likely the 3-position because of the low reactivity of the other hydroxyl groups in the aglycones. Deacetylation of the acetyl glucosides was accomplished with barium methoxide.

Details of the pharmacological examination of these substances have already been reported.[4] All of the glucosides thus prepared were more powerful than the parent natural glycosides, digitoxin, digoxin and periplocymarin.

Experimental[5,6]

The procedures used for the synthesis of the new glucosides was similar to those used in the cases of the strophanthidin glycosides[2] with some deviations in each case. A typical example is given with variations as indicated being used in the other cases.

Digitoxigenin-(3)-tetraacetyl-β-*d*-glucoside.—A mixture of 373 mg. of digitoxigenin, 500 mg. of dry silver oxide, 1 g. of anhydrous magnesium sulfate and 10 ml. of absolute dioxane was stirred at room temperature for one hour in a 3-necked flask equipped with a dropping funnel and a calcium chloride tube. A solution of 820 mg. of acetobromoglucose in 4 ml. of absolute dioxane was then added dropwise over a period of an hour. After the mixture had been allowed to react at room temperature for twenty-four hours, the silver salts and the magnesium sulfate were filtered off and the filtrate was concentrated under reduced pressure. The remaining viscous, colorless oil was stirred with 5 ml. of anhydrous ether until it had completely solidified. The crystalline material was freed from liquid by decantation and was stirred three or four more times with fresh 5-ml. portions of dry ether. When pentane was added carefully to the combined ether washings until a slight turbidity appeared, an additional amount of crystalline material was obtained. This precipitation of the mother liquors with pentane was continued until no more solid material separated. The crystals obtained in this way consisted of almost pure digitoxigenin tetraacetyl-β-*d*-glucoside. It was obtained in analytically pure state by recrystallizing it several times from dilute alcohol, from which it separated in fine, long needles, which melted with decomposition at 163–168°. For analysis the compound was dried over phosphorus pentoxide at 100° and 15 mm.: $[\alpha]^{25}D$ −8.6°; (*c* 0.348 in 95% alcohol).

Anal. Calcd. for $C_{37}H_{52}O_{13}$: C, 63.1; H, 7.4. Found: C, 63.1; H, 7.7.

The crystalline material obtained by digesting the original oily reaction product with ether consisted of a mixture of unreacted digitoxigenin and its tetraacetyl glucoside. Separation was effected by fractional crystallization from dilute alcohol, in which digitoxigenin is less soluble then its acetyl glucoside. Pure digitoxigenin tetraacetyl-β-*d*-glucoside was obtained from the mother liquors having the properties described above, the total yield being 15%. The recovered digitoxigenin was used again in the reaction after recrystallization from ethyl acetate.

Digitoxigenin-(3)-β-*d*-glucoside.—To a solution of 96 mg. of digitoxigenin β-*d*-tetraacetylglucoside in 15 ml. of absolute methanol was added 0.2 ml. of approximately 0.5 *N* barium methylate solution in absolute methanol. After the solution had been allowed to stand overnight in the refrigerator, the barium was quantitatively precipitated by adding two drops of 10% sulfuric acid. The solution was rendered slightly alkaline by the addition of 1–2 drops of ammonia, and the barium sulfate was removed by filtration. The filtrate was concentrated under reduced pressure and the residue taken up in 5 ml. of absolute alcohol. After centrifuging off some undissolved ammonium sulfate, the solution was concentrated to about half its volume and ether was carefully added. The solution was kept at room temperature overnight, when rosets of needles as well as amorphous particles settled out. More ether was added in small portions to complete the precipitation of the glucoside. When this process of slow crystallization was repeated twice or three times, using 95% alcohol instead of absolute, the digitoxigenin-(3)-β-*d*-glucoside was obtained in very well formed flat platelets, which contained 1 mole of water and melted with decomposition at 242–246°. For analysis the substance was dried at 80° and 15 mm. over phosphorus pentoxide: $[\alpha]^{25}D$ −4.9; (*c* 0.516 in 95% alcohol).

Anal. Calcd. for $C_{29}H_{44}O_9 \cdot H_2O$: C, 62.8; H, 8.4. Found: C, 62.8; H, 8.6.

Digoxigenin-(3)-tetraacetyl-β-*d*-glucoside.—This was prepared similarly using 390 mg. of digoxigenin. Recrystallization of the combined material from the ether pentane treatment of the crude product from dilute alcohol yielded a first crop of digoxigenin monohydrate, m. p. 170–172°; from the mother liquors, after several recrystallizations, 150 mg. of light feathery needles melting at 183–204°. This was pure enough for the subsequent deacetylation. In order to secure an analytically pure sample, five further recrystallizations from dilute alcohol were necessary. The pure acetyl glucoside formed felty needles which melted at 194–199°: $[\alpha]^{25}D$ −3.3°, (*c* 0.766 in 95% alcohol).

Anal. Calcd. for $C_{37}H_{52}O_{14}$: C, 61.5; H, 7.3. Found: C, 61.5; H, 7.4.

Digoxigenin-(3)-β-*d*-glucoside.—The acetyl glucoside (235 mg.), m. p. 183–204°, obtained above was deacetylated as before. Contaminating digoxigenin was removed by concentration of the absolute alcoholic solution to a small volume on which the aglycone crystallized. The filtrate from the digoxigenin was evaporated to dryness under reduced pressure and the residue was taken up in 15 ml. of absolute alcohol. To this solution 8 ml. of ether was carefully added. On refrigeration, the glucoside crystallized as clusters of prisms. After several more recrystallizations from the same solvents it melted at 268° (dec.). Yield was 90 mg.: $[\alpha]^{27}D$ −1.4°; (*c* 0.356 in 95% alcohol).

Anal. Calcd. for $C_{29}H_{44}O_{10}$: C, 63.3; H, 8.0. Found: C, 62.9; H, 8.2.

Periplogenin-(3)-tetraacetyl-β-*d*-glucoside.—This was prepared as in the above cases. The crude oily product was practically completely soluble in anhydrous ether.

(1) Part of this work was done under a grant from Eli Lilly & Co., to whom we wish to express our sincere appreciation.

(2) Uhle and Elderfield, *J. Org. Chem.*, **8**, 162 (1943).

(3) Chen and Elderfield, *J. Pharmacol. Exp. Therap.*, **76**, 81 (1942).

(4) Chen, Elderfield, Uhle and Fried, *ibid.*, **77**, 401 (1943).

(5) All melting points are corrected for stem exposure.

(6) Microanalyses by Mr. Saul Gottlieb.

When petroleum ether (Skellysolve B) was added to this clear ether solution, an oily product separated. After the mixture had been allowed to stand overnight, the oil had not crystallized but crystalline material was present throughout the solution. This crystalline material, when carefully separated from the oil, gave a negative Legal (nitroprusside) test. The oil was crystallized from a mixture of alcohol and water. After two recrystallizations, 350 mg. (19%) of product was obtained. The compound crystallizes as needles, which contain 1.5 moles of water of crystallization. The melting point depends upon the rate of heating, but ordinarily the compound melts at 145–150° after preliminary sintering. For analysis it was dried over calcium chloride at 75° and 10 mm.

Anal. Calcd. for $C_{37}H_{52}O_{14}\cdot 1.5H_2O$: C, 59.4; H, 7.4. Found: C, 59.4; H, 7.4.

Periplogenin-(3)-β-*d*-glucoside.—The viscous oil obtained on deacetylation was crystallized initially from ethyl acetate saturated with water, and recrystallized from 95% alcohol–ether. It crystallized as fine needles containing two waters of crystallization and melted at 195–200° (dec.). For analysis it was dried over calcium chloride at 75° and 10 mm.

Anal. Calcd. for $C_{29}H_{44}O_{10}\cdot 2H_2O$: C, 59.2; H, 8.2. Found: C, 59.5; H, 8.0.

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Pyrolysis of Diketene

BY J. T. FITZPATRICK

There is considerable evidence in favor of the Boese–Wilson[1] vinylaceto-β-lactone structure for diketene.[1–5] However, on pyrolysis this structure would be expected to give allene and carbon dioxide as well as the previously observed product, ketene.[1,3] It has now been found that significant amounts of these by-products are present in ketene made in a "ketene lamp"[1] with a Nichrome filament. The amount of impurities depends on both the temperature and the condition of the filament. A filament which had been used for some time gave a product containing 13% allene and carbon dioxide in approximately equal amounts; after thorough cleaning with nitric acid the filament gave only 8% by-products. When a used filament was operated at a voltage lower than usual, the by-products accounted for more than 18% of the reacted diketene.

The diketene used was commercial material which had been redistilled in the laboratory; it boiled at 62° at 75 mm., and froze at −6.5 to −7.0°; its purity was estimated to be well over 99%. It was cracked in a ketene lamp with a filament made of approximately 14 ft. of no. 22 B. and S. gage Nichrome wire. The rate of cracking was 320–350 g./hour with 75 volts, or 50–55 g./hour with 55 volts on the filament. After passing through a partial condenser to remove unreacted diketene, the products were condensed and weighed in tared traps cooled with liquid air. The material was vaporized from these traps and passed through 0.25% aqueous sulfuric acid at 50–55° to remove the ketene. The small amount of residue which did not vaporize at room temperature was considered to be unreacted diketene. The blow-off gas from the absorber was again collected in tared traps and weighed. Samples of this condensate were analyzed in the mass spectrograph by the South Charleston Works Laboratory of this Company. A typical analysis was: carbon dioxide, 53.9%; allene, 45.1%; acetone, 0.4%; and trifling amounts of other compounds, including 0.1% ketene. Lack of a reaction with silver nitrate solution showed the absence of methylacetylene, which is nearly indistinguishable from allene in the mass spectrograph.

(1) Boese, *Ind. Eng. Chem.*, **32**, 16 (1940).
(2) Hurdis and Smyth, THIS JOURNAL, **65**, 89 (1943).
(3) Rice and Roberts, *ibid.*, **65**, 1677 (1943).
(4) Taufen and Murray, *ibid.*, **67**, 754 (1945).
(5) Bauer, Bregman and Wrightson, paper presented before the Division of Physical Chemistry of the American Chemical Society at the Atlantic City meeting, April, 1946.

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Selenenyl Sulfur Compounds

BY OLAV FOSS

Twiss, Jones and Hadley[1] reported the reactions of *o*-nitrobenzeneselenenyl bromide[2] with mercaptobenzthiazole and thiocarbonyl salts. We have found that *o*-nitrobenzeneselenenyl bromide reacts rapidly with sodium or potassium thiocyanate, di-O-alkylmonothiophosphates,[3] thiosulfonates, and sulfinates, to give *o*-nitrobenzeneselenenyl thiocyanate, di-O-alkylmonothiophosphates, thiosulfonates and sulfinates, respectively. The general procedure consists in dissolving 1 g. of the bromide in 3–4 ml. of ethyl acetate and 5 ml. of methanol, and adding a slight excess of the thio salt or sulfinate, dissolved in 10 ml. of methanol. The product thereon crystallizes out rapidly (in the case of di-O-alkylmonothiophosphates after addition of some water). Potassium *o*-nitrobenzeneselenenyl thiosulfate was obtained by reaction of the bromide, dissolved in benzene, with a slight excess of potassium thiosulfate in the double amount of water. The crystals are stable, and have a yellowish green color. The di-O-ethylmonothiophosphate was obtained as a yellowish green oil. Among the compounds prepared are these in Table I.

TABLE I

Compound (R = *o*-nitrophenyl)	M. p., °C. (uncor.)	Selenium, % Calcd.	Found
RSeSCN	107[a]	30.5	30.4
$RSeSPO(OCH_3)_2$	79[b]	23.1	23.1
$RSeSPO(OC_2H_5)_2$	Oil	21.3	21.5
$RSeS_2O_2CH_3$	96[b]	25.3	25.3
$RSeS_2O_2C_2H_5$	90[b]	24.2	24.0
$RSeS_2O_2C_6H_5$	147[c]	21.1	21.3
$RSeS_2O_2C_6H_4CH_3$-*p*	148[c]	20.3	20.2
$RSeS_2O_2C_6H_4Br$-*p*	169[c]	17.4	17.1
$RSeSO_2C_6H_5$	109[d]	23.1	23.1
$RSeSO_2C_6H_4CH_3$-*p*	118[d]	22.2	22.0
$RSeSO_2C_6H_4CH_3$-*o*	95[e]	22.2	22.2
$RSeSO_2C_6H_4Br$-*p*	126[c]	18.8	18.7
$RSeS_2O_3K$	*ca.* 190[d] dec.	22.4	22.4

[a] Crystallized from carbon tetrachloride. [b] Crystallized from carbon disulfide. [c] Crystallized from benzene. [d] Crystallized from ethanol. [e] Crystallized from methanol.

(1) Twiss, Jones and Hadley, British Patent 441,653 (1936).
(2) Behaghel and Seibert, *Ber.*, **66**, 708 (1933).
(3) Foss, *Acta Chemica Scandinavica*, **1**, 8 (1947).