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AMINO- AND GUANIDINO-PENTADECYLPHENYL GLUCOSIDES

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In foregoing papers we have described aminophenyl and guanidinophenyl β-D-glucosides (1) and glucosaminides (2) which were synthesized for studies in experimental tuberculosis. The present investigation deals with glucosides of amino- and guanidino-pentadecylphenols which have been designed for similar studies.

Wasserman and Dawson (3) have found that the nitration of 3-pentadecylphenol (I) with fuming nitric acid (*d.* 1.49–1.50) yields 4- and 6-nitro-3-pentadecylphenols (III and IV) in a 1:1 ratio. On repeating the procedure[1] of these authors we obtained IV (12%) and an inseparable mixture (II, m.p. 61–64°, yield 26%). Glucosidation of II with acetobromoglucose, quinoline, and silver oxide gave a readily tractable solid consisting of equal amounts of a dinitro-3-pentadecylphenyl tetraacetyl-β-D-glucoside[2] (VI) and 4-nitro-3-pentadecylphenyl tetraacetyl-β-D-glucoside (V). Acid hydrolysis of V regenerated III while VI afforded a dinitro-3-pentadecylphenol (IX), m.p. 85–87°, identical with that described by Wasserman and Dawson (4) as probably the 2,4-dinitro derivative.

The use of nitric acid, *d.* 1.42, in the above nitration prevented the formation of IX, and III and IV were produced in yields of 20% and 10% respectively. Conversion of III and IV to the glucoside tetraacetates (V and VII) was effected with acetobromoglucose, silver oxide, and quinoline.

The tetraacetates V and VII were hydrogenated in ethyl acetate[3] with Raney nickel to the amino compounds (VIII and X) from which the guanidinophenyl glucosides (XII and XIII) were prepared essentially as described previously (1). Deacetylation of VIII and X with methanolic sodium methoxide yielded the phenyl glucosides (XI and XIV).

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EXPERIMENTAL[4]

Nitration of 3-pentadecylphenol.[1] The procedure used initially was that of Wasserman and Dawson (3)[1] which gave the mixture II, m.p. 61–64°, yield 20%, and pure IV (12%, m.p. 38–41°). Glucosidation of II and separation of the resultant mixture gave V and VI

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[1] Obtained from Mr. W. F. Hoffman, Jr. of the Irvington Varnish and Insulator Company.

[2] The β configuration is assigned to the glucosides described herein on the basis of their rotation and mode of preparation.

[3] Methanol proved less satisfactory as a solvent.

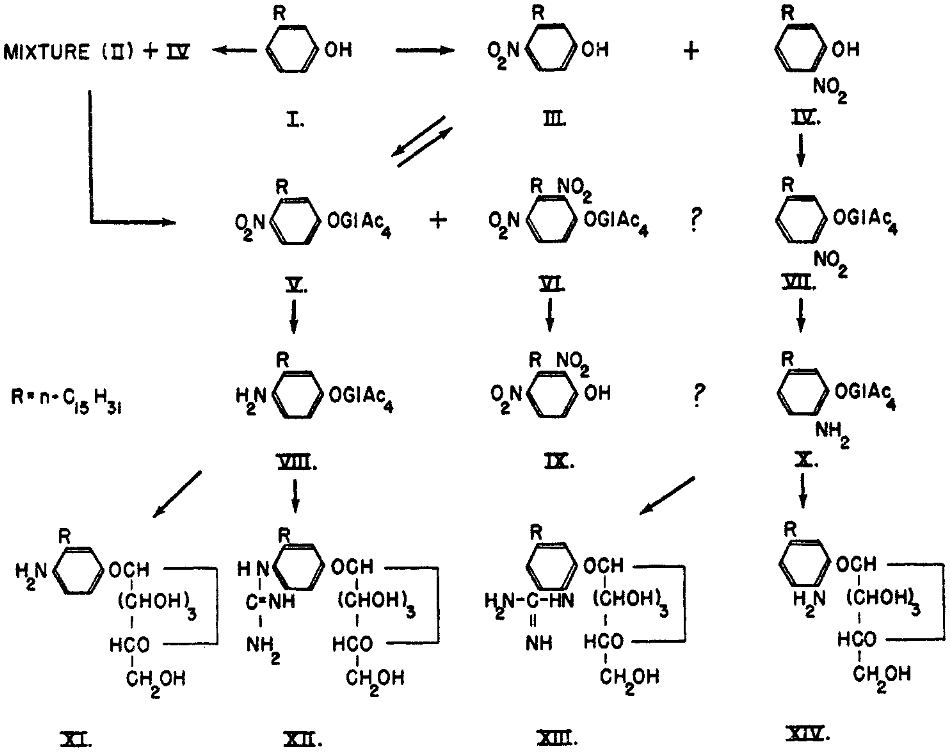
[4] Rotations were taken in a 4-dm. tube. The microanalyses are from the Institutes service analytical laboratory under the direction of Mr. William C. Alford. Melting points, observed in a capillary, are uncorrected.

which on acid hydrolysis yielded III and IX as described below. When nitric acid, *d.* 1.42, was used instead of the fuming nitric acid, no IX was encountered and III, m.p. 70–72° and IV, m.p. 38–41° were obtained in yields of 20% and 10% respectively. The melting points of III and IV were not depressed by authentic material (3).[1]

4-Nitro-3-pentadecylphenyl tetraacetyl-β-D-glucoside (V).[2] Acetobromoglucose (20 g.) (1), 10 g. of III, 20 g. of freshly prepared silver oxide, and 50 ml. of quinoline were shaken for several minutes, left overnight at 25°, and digested with boiling acetic acid. The filtered solution was diluted with water and ice-cooled. The brown solid resulting was recrystallized from ligroin (60–71°) to give 13.4 g. (70%) of V, m.p. 79–82°. The analytical sample melted at 85–86.5°, $[\alpha]_D^{20}$ $-20.6°$ (*c*, 0.67 in $CHCl_3$).

Anal. Calc'd for $C_{35}H_{53}NO_{12}$: C, 61.8; H, 7.9.

Found: C, 61.8; H, 7.6.



6-Nitro-3-pentadecylphenyl tetraacetyl-β-D-glucoside (VII). This isomer was obtained from IV in 57% yield as described for V; needles from ethanol, m.p. 96.5–97.5°, $[\alpha]_D^{20}$ $+38.0°$ (*c*, 1.00 in $CHCl_3$).

Anal. Calc'd for $C_{35}H_{53}NO_{12}$: C, 61.8; H, 7.9.

Found: C, 61.9; H, 7.8.

Glucosidation of II. The mixture II (2.0 g., m.p. 61–64°), subjected to reaction with acetobromoglucose, silver oxide, and quinoline as described above, gave 4.0 g. of crude glucoside mixture. This was dissolved in 100 ml. of boiling ethanol (Norit). The filtrate, left at 25° for three hours, gave 1.0–1.4 g. (26–40%) of needles (A). Four recrystallizations from ethanol gave a *dinitro-3-pentadecylphenyl tetraacetyl-β-D-glucoside* (VI), m.p. 131–133,°[5] $[\alpha]_D^{20}$ $-15.9°$ (*c*, 0.63 in $CHCl_3$).

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[5] If the temperature rise was slow the compound melted partially at *ca.* 118°, then completely at 131–133°. The resolidified melt gave only the 131–133° melting point.

Anal. Calc'd for $C_{35}H_{52}N_2O_{14}$: C, 58.0; H, 7.2.
Found: C, 58.3; H, 7.2.

Concentration of the filtrate from A to one-half volume and ice-cooling gave 1.3 g. (35%) of V, m.p. 78–80°, identical with that described above.

Hydrolysis of V and VI obtained from the glucosidation of II. A mixture of 0.5 g. of VI, 2.0 ml. of 6 *N* hydrochloric acid, and 6 ml. of acetic acid was heated on the steam-bath for four hours, diluted with 15 ml. of water, and ice-cooled overnight to give 0.25 g. of crude IX. After several recrystallizations from ligroin (60–71°) it melted at 85–87° alone or in mixture with the dinitro-3-pentadecylphenol (m.p. 86–87°)[1] described by Wasserman and Dawson as probably 2,4-dinitro-3-pentadecylphenol (4).

Similarly, hydrolysis of V gave III, m.p. 70–71.5°, identical with that prepared in the nitration of I with nitric acid, *d.* 1.42, and with that[1] prepared by Wasserman and Dawson (3).

*4-Amino-3-pentadecylphenyl tetraacetyl-β-*D*-glucoside* (VIII). Ten grams of V, 150 ml. of ethyl acetate,[3] and 3 g. of Raney nickel absorbed three moles of hydrogen during four hours. The filtered solution was evaporated to dryness *in vacuo*. The residue crystallized from ligroin (60–71°) in a yield of 8.3 g. (85%), m.p. 72–74°. The analytical sample melted at 74–75.5°, $[\alpha]^{20}_{D}$ −10.7° (*c*, 0.61 in $CHCl_3$).

Anal. Calc'd for $C_{35}H_{55}NO_{10}$: C, 64.7; H, 8.5.
Found: C, 64.7; H, 8.5.

*6-Amino-3-pentadecylphenyl tetraacetyl-β-*D*-glucoside* (X). Reduction of VII as described for V gave, from ethanol, a 90% yield of X, m.p. 94–95°, $[\alpha]^{20}_{D}$ −7.5° (*c*, 1.17 in $CHCl_3$).

Anal. Calc'd for $C_{35}H_{55}NO_{10}$: C, 64.7; H, 8.5.
Found: C, 64.7; H, 8.4.

*4-Amino-3-pentadecylphenyl β-*D*-glucoside* (XI) (NIH 4212).[6] Two grams of VIII, 1 ml. of methanolic sodium methoxide[7] and 15 ml. of methanol were shaken to solution and left for two hours at 25°, then overnight at 5° to give 1.4 g. (94%) of pink XI, m.p. 137–140°. The pink color could be removed only after several recrystallizations from methanol under hydrogen; m.p. 138.5–140°, $[\alpha]^{20}_{D}$ −27.9° (*c*, 0.73 in acetone).

Anal. Calc'd for $C_{27}H_{47}NO_6$: C, 67.3; H, 9.8.
Found: C, 67.1; H, 9.6.

*6-Amino-3-pentadecylphenyl β-*D*-glucoside* (XIV) (NIH 4213). Deacetylation of X as described above gave a 93% yield of XIV. It melted at 147.5–149.5° after a recrystallization from ethanol; $[\alpha]^{20}_{D}$ −33.9° (*c*, 0.45 in dioxane).

Anal. Calc'd for $C_{27}H_{47}NO_6$: C, 67.3; H, 9.8.
Found: C, 67.2; H, 9.8.

*6-Guanidino-3-pentadecylphenyl β-*D*-glucoside* (XIII). One gram of X, 0.2 g. of cyanamide (1), 0.13 ml. of conc'd HCl, and 5 ml. of ethyl acetate were refluxed for two hours, diluted with 20 ml. of ligroin (30–60°) and cooled overnight at 5°. The supernatant liquid was decanted from a sirup which was washed twice with ligroin, dried in the vacuum-desiccator, and dissolved in 10 ml. of methanol. Addition of 1.5 ml. of sodium methoxide solution[7] gave, after two hours at 25° and ice-cooling, 0.6 g. (75%) of XIII. Recrystallized from a large volume of ethanol, it melted at 190–195° (dec.) and had $[\alpha]^{20}_{D}$ −84.9° (*c*, 0.24 in pyridine).

Anal. Calc'd for $C_{28}H_{49}N_3O_6$: C, 64.2; H, 9.4; N, 8.0.
Found: C, 64.2; H, 9.6; N, 7.7.

*4-Guanidino-3-pentadecylphenyl β-*D*-glucoside* (XII) *perchlorate.* One gram of VIII was brought to reaction with cyanamide as described for X. The dried, sirupy guanidino tetraacetate hydrochloride in 1 ml. of methanol and 2 ml. of sodium methoxide solution[7] was

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[6] Compounds designated with NIH numbers were submitted for *in vitro* testing (Dubos-Davis medium, $H_{37}Rv$), to Dr. Bernard D. Davis, Tuberculosis Research Laboratory, U. S. Public Health Service, Cornell University Medical College, New York, N. Y.

[7] Three grams of sodium in 100 ml. of methanol.

left for two hours at 25°. The mixture was diluted with 1.5 ml. of ether, filtered, and the filter washed with ethanol. After 60 hours at 5°, the combined filtrate and washings gave 0.3 g. (40%) of waxy base, which was converted to the perchlorate in methanol. The perchlorate [0.25 g., precipitated with ether-ligroin (30–60°)], crystallized from methanol-ether in fine, hydrated needles of no definite melting point. It softened from 100° and was a clear wax at 210°; $[\alpha]_D^{20}$ −25.7° (*c*, 0.50 in water). Three hours of drying at 78° *in vacuo* gave the anhydrous compound which was hygroscopic and had to be weighed in a "pig" for analysis.

Anal. Calc'd for $C_{28}H_{50}ClN_3O_{10}$: C, 53.9; H, 8.1.
Found: C, 53.9; H, 8.3.

The *hydrochloride* (NIH 4210) was prepared by acidification (alcoholic hydrogen chloride) of a methanol solution of the base followed by dilution with ether. It was recrystallized by gradual addition of ether to its warm methanol solution; fine hydrated needles, which decompose at 207–209° after shrinking gradually from 140°, $[\alpha]_D^{20}$ −28.0° (*c*, 0.66 in water). A sample, dried to constant weight at 78°, was very hygroscopic and gave the following analysis.

Anal. Calc'd for $C_{28}H_{50}ClN_3O_6$: C, 60.0; H, 9.0; Cl, 6.3.
Found: C, 59.1; H, 9.0; Cl, 6.2.

SUMMARY

The nitration of 3-pentadecylphenol in chloroform with fuming nitric acid (*d.* 1.49–1.50) at 10–20° has given a mixture of 2,4-dinitro-3-pentadecylphenol (?) (IX), 4-nitro-3-pentadecylphenol (III), and 6-nitro-3-pentadecylphenol (IV). With nitric acid, *d.* 1.42, only the mononitrophenols III and IV were obtained.

These two mononitrophenols have been converted to the corresponding glucoside tetraacetates which, by a three-step route (Raney nickel hydrogenation, reaction with cyanamide, and deacetylation) gave 4- and 6-guanidino-3-pentadecylphenyl β-D-glucosides.

Catalytic deacetylation of 4- and 6-amino-3-pentadecylphenyl tetraacetyl-β-D-glucosides has afforded 4- and 6-amino-3-pentadecylphenyl β-D-glucosides in 90% yield.

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