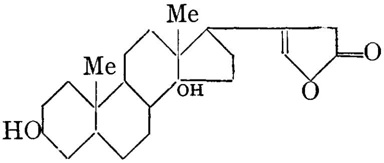
241. *Digitalis Glucosides. Part IV. The Existence of Two Anhydrodigitoxigenins.*

By Sydney Smith.

Digitoxigenin, when treated with dilute acids, readily loses the elements of water and forms a crystalline anhydrogenin which is of interest in the investigation of the constitution of the digitalis glucosides. The anhydrogenin has been prepared by several workers, and in a previous paper (Part II, J., 1930, 2480) the variations in m. p. and specific rotation were noted : Cloetta (*Arch. Exp. Path. Pharm.*, 1920, **88**, 113), m. p. 183—185°; Windaus and Freese (*Ber.*, 1925, **58**, 2507), m. p. 183—184°; Windaus and Stein (*Ber.*, 1928, **61**, 2438), m. p. 193°, $[\alpha]_{D}^{18^\circ}$ $-$ 4·68° (*c* in MeOH 1·71); Smith (*loc. cit.*), m. p. 183—184°, $[\alpha]_{\text{Hg gr.}}^{20^\circ}$ $-$ 0·7° (*c* in MeOH 1·89). Further investigation has shown that the product is, in fact, a mixture which can be separated by fractional crystallisation from suitable solvents into two isomeric *anhydrodigitoxigenins*, one of which (α) melts at 234° and the other (β) at 202°. No indication of a third isomeride was observed, and this is in accordance with the formula (I) for digitoxigenin recently proposed by Tschesche (*Angew. Chem.*, 1934, **47**, 731), which permits the elimination of the tertiary hydroxyl group as water in only two ways, giving rise to the $\Delta^{14:15}$ or the $\Delta^{14:8}$ unsaturated genin. Both isomerides give the Legal reaction and therefore retain the double bond in the lactone group, $\Delta^{20:21}$, without displacement; and both retain the secondary alcoholic group, since each forms an acetate and on oxidation gives rise to the expected ketone.

(I.)



Experimental.

Digitoxigenin (12·5 g.) was dissolved in hot alcohol (250 c.c.) and, after the addition of 10% sulphuric acid (250 c.c.), the solution was boiled under reflux for 2 hours. Water (250 c.c.) was added, and most of the alcohol removed by distillation under diminished pressure. During this process a crystalline solid separated, and this together with the aqueous liquid was extracted with chloroform. The extract was washed with dilute sodium carbonate solution and then with water. After being dried (magnesium sulphate), the chloroform solution was evaporated to dryness, and the residue crystallised from acetone. The first crop (9·1 g., well-formed prisms) had m. p. 180—183°. The second crop (1·19 g.) melted at 180—190°, and the third crop, which was sticky, after being spread on porous plate weighed 1·1 g. The fractionation was continued by repeated crystallisation either from ethyl acetate, which is convenient for the more soluble fractions, or from acetone. The process of fractionation was controlled by measurement of the specific rotations of the fractions, and was continued until there was no further change in m. p. or specific rotation.

α-*Anhydrodigitoxigenin* crystallises from acetone or ethyl acetate in stout prismatic needles, m. p. 234°, $[\alpha]_{\text{Hg gr.}}^{20^\circ}$ + 43·7°; $[\alpha]_{D}^{20^\circ}$ + 39·0° (in methyl alcohol, $c = 0{\cdot}43$). It is fairly readily soluble in chloroform, sparingly soluble in benzene. In general, it is less readily soluble in organic solvents than the β-compound. The Legal reaction gives a red colour (Found : C, 77·6; H, 9·0. $C_{23}H_{32}O_3$ requires C, 77·5; H, 9·1%). The *acetate*, from acetic anhydride in pyridine at room temperature, crystallised from dilute methyl alcohol in stout, rectangular plates, m. p. 144° (Found : C, 75·3; H, 8·6. $C_{25}H_{34}O_4$ requires C, 75·3; H, 8·6%).

α-*Anhydrodigitoxigenone.*—α-Anhydrodigitoxigenin (0·3 g.) was dissolved in warm 90% acetic acid (10 c.c.) and cooled to 25°. The solution was treated with Kiliani's chromic acid solution (1·5 c.c.), and after 10 mins. it was diluted with water. Crystallised from methyl alcohol, the *ketone* crystallised in needles, m. p. 203° (Found : C, 77·9; H, 8·6. $C_{23}H_{30}O_3$ requires C, 77·9; H, 8·5%). The oxidation liquor, after filtration, was extracted with chloroform and gave a substance which crystallised from methyl alcohol, in which it is sparingly soluble, in needles, m. p. 273°.

β-*Anhydrodigitoxigenin* crystallises from acetone, in which it is freely soluble, or more conveniently from ethyl acetate, in stout prismatic needles, m. p. 202°, $[\alpha]_{\text{Hg gr.}}^{20°}$ − 17·3°; $[\alpha]_{\text{D}}^{20°}$ − 13·3° (in methyl alcohol, *c* = 2·05). The Legal reaction gives a red colour (Found : C, 77·8; H, 9·0%). The *acetate*, prepared as for the α-compound, crystallises from dilute methyl alcohol in long, quadrilateral plates, m. p. 185° (Found : C, 75·3; H, 8·6%).

β-*Anhydrodigitoxigenone.*—β-Anhydrodigitoxigenin (1 g.) in 50 c.c. of warm 80% acetic acid was cooled to 25°, treated with chromic acid solution (5 c.c.), and worked up as above. The *ketone* is readily soluble in chloroform, rather sparingly soluble in acetone, benzene, alcohol, and ethyl acetate. It melts at 281° and has $[\alpha]_{\text{Hg gr.}}^{20°}$ − 13·9°, $[\alpha]_{\text{D}}^{20°}$ = − 10·0° (in chloroform, *c* = 1·22) (Found : C, 77·9; H, 8·8%).

My thanks are due to Mr. A. Bennett and Mr. H. C. Clarke for the microanalytical data.

WELLCOME CHEMICAL WORKS, DARTFORD.

[*Received, May* 23*rd*, 1935.]