82. *Digitalis Glucosides. Part VI. The Existence of Two Anhydrodigoxigenins.*

By Sydney Smith.

In Part IV (J., 1935, 1050) it was shown that digitoxigenin, when treated with dilute acids, loses its single tertiary hydroxyl group and forms a mixture of the $\Delta^{14:15}$- and $\Delta^{14:8}$-unsaturated anhydrogenins, which can be separated by fractional crystallisation into the two isomerides. Since the constitution of digoxigenin (Part V; J., 1935, 1305) is similar to that of digitoxigenin, the former also should give rise to two anhydrogenins. This is in fact the case. The action of dilute acids on digoxigenin (Part II; J., 1930, 2479) gives a non-homogeneous product, from which the crystalline anhydrogenin, m. p. 182°, can be isolated as originally described. The mother-liquors from the crystallisation of this anhydrogenin do not lend themselves to crystallisation and a second isomeride was not isolated from this source. Eventually it was found that, when digoxigenin is dissolved in concentrated hydrochloric acid, an unstable *chloro*-compound is formed, which is rapidly decomposed by water to give the expected second ***monoanhydrodigoxigenin***, m. p. 192°. As in the case of anhydrodigitoxigenin, the isomeride of higher m. p. is termed the α-compound and the previously described anhydrodigoxigenin, m. p. 182°, must now be distinguished as the β-compound. Both isomerides give the Legal reaction and therefore retain the double bond in the lactone group at $\Delta^{20:21}$ without displacement and retain the two secondary hydroxyl groups, since each forms a diacetate and on oxidation gives rise to the expected diketone.

Additional evidence for the similarity in constitution of digitoxigenin and digoxigenin is afforded by a comparison of the specific rotations of the four anhydrogenins as follows : $[\alpha]_{5461}^{20°} = + 43{\cdot}7°$ and $+ 46{\cdot}0°$ for α-anhydrodigitoxigenin and α-anhydrodigoxigenin respectively and $- 17{\cdot}3°$ and $- 16{\cdot}3°$ for the corresponding β-compounds (in methyl alcohol in each case).

Note.—Owing to a typographical error the sign of the rotation of β-anhydrodigoxigenin is shown as + in Part II (J., 1930, 2479).

EXPERIMENTAL.

α-Anhydrodigoxigenin.—Digoxigenin (5 g.) was dissolved in concentrated hydrochloric acid (37 c.c.) at 10°. On keeping over-night in a refrigerator and stirring, 3·3 g. of an unstable *chloro-*

compound crystallised. It frothed at 120° and then melted at 185°. It was rapidly decomposed by water. A portion of the crystals after exposure to the air for a short time was stirred with water, the resulting anhydrogenin removed by filtration, and the liberated hydrochloric acid was determined by titration (Found: Cl, 9·5. $C_{23}H_{33}O_4Cl$ requires Cl, 8·7%).

The chloro-compound was conveniently converted into *α-anhydrodigoxigenin* by crystallisation from hot aqueous methyl alcohol. This formed needles, m. p. 192°, $[\alpha]_{5461}^{20^\circ} + 46^\circ$ (in methyl alcohol, $c = 1$), readily soluble in acetone and methyl alcohol and moderately easily soluble in benzene, chloroform, ether, and ethyl acetate. It gave a red colour in the Legal test for $\Delta^{\beta\gamma}$-unsaturated lactones [Found (air dry): C, 67·6; H, 8·9; loss on drying, 9·3. $C_{23}H_{32}O_4,2H_2O$ requires C, 67·6; H, 8·9; H_2O, 8·8%. Found (dried at 100°): C, 74·1; H, 8·7. $C_{23}H_{32}O_4$ requires C, 74·2; H, 8·7%. Lactone titration: 13·78 mg. required 0·36 c.c. 0·1*N*-potassium hydroxide. One equiv. requires 0·37 c.c.].

The *diacetate*, prepared by the action of acetic anhydride in pyridine solution at laboratory temperature, crystallised from aqueous methyl alcohol in needles, m. p. 155°, $[\alpha]_{5461}^{20^\circ} + 68·0^\circ$ (in methyl alcohol, $c = 0·7$) (Found: C, 71·2; H, 8·1; Ac, 21·7. $C_{27}H_{36}O_6$ requires C, 71·0; H, 8·0; Ac, 18·8%).

α-Anhydrodigoxigenone.—α-Anhydrodigoxigenin (1 g.) was dissolved in a mixture of glacial acetic acid (20 c.c.) and water (5 c.c.) with the aid of heat. The solution was cooled to 20° and treated immediately with Kiliani's chromic acid solution (5 c.c.), being cooled at the same time so that the temperature did not rise. After dilution with water and keeping in the refrigerator for 20 hours, a crystalline solid (0·55 g.) separated, m. p. 165°. After crystallisation from dilute methyl alcohol the *ketone* melted at 178° and had the specific rotation $[\alpha]_{5461}^{20^\circ} + 136^\circ$ (in methyl alcohol, $c = 0·8$). It was sparingly soluble in ethyl acetate, benzene, and methyl alcohol, more soluble in acetone, but crystallised readily from hot aqueous acetone, or aqueous methyl alcohol. It gave a red colour in the Legal test (Found: C, 74·7; H, 7·6. $C_{23}H_{28}O_4$ requires C, 75·0; H, 7·7%).

The oxidation mother-liquor after removal of this substance was extracted with chloroform. The extract, after being washed with sodium carbonate solution and dried with magnesium sulphate, gave on evaporation a residue (0·4 g.), which crystallised from aqueous methyl alcohol in needles, m. p. 187°. The m. p. was raised by repeated crystallisation from aqueous methyl alcohol and from ethyl acetate to 215°. The substance was still apparently not quite pure and requires further investigation. It gives the Legal reaction for $\Delta^{\beta\gamma}$-lactones.

The *semicarbazone* was prepared from the ketone (0·1 g.) in methyl-alcoholic solution, semicarbazide hydrochloride (0·1 g.) in a little water, and potassium acetate (0·15 g.) in methyl alcohol at laboratory temperature. After recrystallisation from alcohol, in which it was sparingly soluble, it formed micro-needles, m. p. 235° (decomp.) (Found: N, 9·8. $C_{24}H_{31}O_4N_3$ requires N, 9·9%).

The *dioxime*, prepared by boiling the ketone in methyl-alcoholic solution with a reagent prepared from hydroxylamine hydrochloride and potassium acetate, could not be crystallised (Found: N, 6·9. $C_{23}H_{30}O_4N_2$ requires N, 7·0%).

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