RESEARCH PAPERS

SYNTHETIC COMPOUNDS RELATED TO THE CARDIAC GLYCOSIDES

PART I—*p*-HYDROXYPHENYL-$\Delta\alpha$:β-BUTENOLIDE GLUCOSIDE

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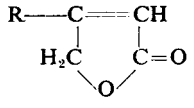
INVESTIGATIONS on the natural cardiac glycosides have revealed that the unsaturated lactone ring in the side chain of their aglucones is indispensable for the specific action on the heart. Thus Elderfield[1], Ruzicka[2], Reichsrein[3] and others have been engaged in the preparation of unsaturated lactones related to the natural aglucones, but the compounds they obtained did not show cardiotonic activity[4]. Comparing the potencies of some cardiac glycosides with those of their aglucones Chen[5] made it clear that glycosidal combination enhances the cardiotonic potency up to 12 times. So, whilst a synthetic aglucone of relatively small activity might show no activity whatsoever during pharmacological tests, it is much less likely that the potential cardiotonic activity of such a compound would be overlooked if it was examined in glycosidal form.

Some special monosaccharides have been found in nature only in combination with the cardiac aglucones, and might be supposed to have an optimum effect upon the activity of the aglucones with which they are combined. However, synthetic glucosides of strophanthidin, digitoxin and digoxin[6] possess a greater activity than the natural glycosides. Hence no specificity may be expected from the sugar fragment of the molecule. Certain comparatively simple molecules of the substituted butenolide structure have been prepared and examined for cardiotonic activity. These substances are shown in Table I.

TABLE I



R = CH_3[7]; -C_2H_5; -$CH_2.CH_2.CH_3$
= -C_6H_5; -C_6H_4(OH) [1 : 4]; -C_6H_4(OH) [1 : 3][8]; -C_6H_4(OCH_3) [1 : 3][9]
= *cyclo*hexyl; 2-chloro-*cyclo*hexyl; *cis* and *trans* 4-hydroxy
= *cyclo*hexyl[10]; 3 : 4-dihydroxy*cyclo*hexyl[11]
= Δ^3-*cyclo*hexenyl[11]
= *cyclo*pentanyl[12]
= α-naphthyl; β-naphthyl; 6-hydroxy-β-naphthyl, 6-methoxy-2-naphthyl; decahydro-β-naphthyl[1]
= 1-indanyl[3]

Although the methyl and the β-naphthyl derivatives showed a minute reaction in frogs (active at a dose of 2 mg./g.)[4]; all the other substances were inactive. This level of activity is hardly significant. However, none of the compounds has been converted into glycosides and tested in this form.

For these reasons it was decided to prepare some compounds which possess the characteristic unsaturated lactone ring in conjugation with simple hydroxylated carbon skeletons, and convert them into their respective glucosides before pharmacological testing. The first member of this series, *p*-hydroxyphenyl-Δ^{α}:β-butenolide glucoside, was obtained by the action of acetobromoglucose on *p*-hydroxyphenyl-Δ^{α}:β-butenolide[8] and subsequent deacetylation of the tetra-acetylglucoside thus obtained by means of barium methoxide. The glucoside was obtained as a white microcrystalline powder melting at 208° to 209°C.; it had a faint bitter taste and was very hygroscopic and freely soluble in alcohol and in water. It gave a positive Legal's test and was hydrolysed on boiling in water. The analytical figures were in accord with those required.

Pure acetobromoglucose necessary for the reaction was obtained in good yields by a modification of the process usually used for its preparation[13].

Neither the pure aglucone nor the glucoside showed any cardiotonic activity. The tetra-acetylglucoside was insoluble in ordinary solvents and thus could not be examined.

Experimental

Acetobromoglucose. The following method was found to be better than the normal method for the preparation of the compound.

Glucose penta-acetate (10 g.) was covered with commercial 50 per cent. solution of hydrogen bromide in glacial acetic acid (20 ml.) at 0°C. The mixture was left at room temperature overnight, then gradually poured with stirring into a large excess of ice-cold water. The acetobromoglucose, which separated as a white crystalline mass, was filtered, washed with ice-cold water and dissolved in warm methyl alcohol, and the solution kept in a refrigerator for 1 hour. The compound separated out in long colourless needles, which were filtered and recrystallised from *iso*propyl ether. Yield 95 to 98 per cent.; m.pt. 91°C.

p-O-Tetra-acetylglucosidoxyphenyl-Δ^{α}*:β-butenolide.* *p*-Hydroxyphenyl-Δ^{α}:β-butenolide[8] (1 g.) dissolved in 2 per cent. aqueous sodium hydroxide (10 ml.) was added to a solution of acetobromoglucose (2·5 g.) in acetone (10 ml.) and the mixture shaken for 5 hours. 2 per cent. sodium hydroxide solution (15 ml.) and acetobromoglucose (2 g.) were added and the mixture shaken for a further 12 hours. The precipitate that formed was filtered, washed with 10 per cent. sodium hydroxide solution and crystallised from alcohol. It formed colourless shining plates, m.pt. 195° to 195·5°C. Yield 36 per cent. Found: C, 56·72; H, 5·01; $C_{24}H_{26}O_{12}$ requires C, 56·89; H, 5·10 per cent.

p-Hydroxyphenyl-Δ^{α}:β-butenolide glucoside. 2N Barium methoxide[14] (0·1 ml.) was added to a suspension of the glucoside acetate (0·4 g.) in methyl alcohol (40 ml.) and the mixture kept at ordinary temperature in a stoppered flask for 5 days. The solution was exactly neutralised by the addition of 0·5N sulphuric acid (1 ml.) and, after allowing to stand for half an hour, the precipitate was filtered off. The filtrate was evaporated to dryness under reduced pressure and the residue dissolved in methyl alcohol; on adding dry ether to the solution a white precipitate was thrown down. The precipitate was rapidly filtered, washed with ether followed by light petroleum and then kept in a vacuum desiccator until dry. The glucoside formed a white microcrystalline powder, m.pt. 208° to 209°C. Yield 90 per cent. Found: C, 54·5; H, 5·64 per cent.; $C_{16}H_{18}O_8$ requires: C, 56·5; H, 5·4 per cent.

The aglucone, glucoside acetate and glucoside gave a positive Legal's test.

Attempts to form the glucoside acetate by shaking in presence of active silver oxide in different solvents alone[15] and in presence of pyridine[16] gave amorphous brown products which could not be purified.

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