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# SUCCINATES AND MALEATES OF SOME CARDENOLIDES, AND THEIR POTASSIUM SALTS

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*The succinates of corotoxigenin, digitoxigenin, and oleandrigenin, and the maleate of strophanthidin, and their potassium salts, have been synthesized. In contrast to the initial cardenolides (**1**, **4**, **7**, and **10**), the succinates (**2**, **5**, and **8**) and the maleate (**11**) and their potassium salts (**3**, **6**, **9**, and **12**) possess no cardiotonic activity.*

It is known that the cardiotonic activity of the cardenolides depends on the size of the lactone ring, the type of linkage of rings *A/B* of the steroid skeleton, the positions of attachment of substituents to it, their structure and spatial orientation, the degree of oxidation of the substituent at C-10, the nature of the sugar component, and, in glycosides, the configurations of the glycosidic bonds [1, 4].

Acetylation of the OH groups at C-3 of the aglycons leads to an increase in their cardiotonic activities. The biological activity of strophanthidin acetate amounts to 20,000 FAU or 5000 CAU [3] and is several times greater than the activity of strophanthidin. It appears of considerable scientific and practical interest to elucidate the influence on cardiotonic activity of the addition of dicarboxylic acids in the form of monoesters to the aglycons of cardenolides.

In this connection the succinates and maleates of cardenolides deserve attention. Succinic acid is an important product and a substrate of the tricarboxylic acid cycle and it is also a universal intermediate metabolite formed in the oxidation and interconversion of carbohydrates, proteins and fats in living cells. Succinic acid and some of its derivatives are used as drugs. Some of its derivatives have been shown to have an anticoagulant [4] and radioprotective action [5]. However, succinates and maleates of cardenolides have been little studied. In view of this we have now examined semiesters of these acids and cardenolides.

In order to obtained cardenolide succinates and maleates, as the alcoholic moieties we took aglycons of various structures: 3β,14β-dihydroxy-5α-card-20(22)-enolide (corotoxigenin, **1**), 3β,14β-dihydroxy-5β-card-20(22)-enolide (digitoxigenin, **4**) 16-acetoxy-3β,14β-dihydroxy-5β-card-20(22)-enolide (olandrigenin, **7**), and 3β,5β,14β-trihydroxy-5β-card-20(22)-enolide (strophanthidin, **10**), differing from one another by the type of *A/B* ring linkage (**1**, **4**, **7**, **10**), the number and positions of OH groups, and the degree of oxidation of the substituent at C-10 of the steroid nucleus. Acylation was achieved by mixing succinic or maleic anhydride with one of the aglycons (**1**, **4**, **7**, or **10**) in absolute pyridine with heating, and monitoring the synthesis by paper chromatography. To improve the solubilities of the substances synthesized, we obtained their potassium salts, these being isolated by mixing a methanolic solution of a dicarboxylic acid monoester of a cardenolide with an aqueous solution of potassium carbonate.

As a result, we synthesized monesters of succinic acid with corotoxigenin (**2**), digitoxigenin (**5**), and oleandrigenin (**8**), and of strophanthidin 3β-O-maleate (**11**) and also their potassium salts (**3**, **6**, **9**, and **12**). The potassium salts obtained were readily soluble in water, unlike the monoesters of succinic and maleic acids (**2**, **5**, **8**, **11**), which is very important in the search for and creation of drugs based on the substances obtained. In a determination of biological activities it was established that none of the dicarboxylic acid monesters synthesized or their potassium salts possessed a cardiotonic action.

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TABLE 1. Monoesters of Succinic and Maleic Acids with Some Cardenolide Aglycons, and Their Potassium Salts

| Substance and its structural characteristics | Empirical formula | mp, °C | Optical activity, deg | UV spectra of the initial substances and their potassium salts, $\lambda_{max}$ (log ε) | Cardiotonic activities of the substances, mg/kg (cat) |
|---|---|---|---|---|---|
| Trans-*A/B* | | | | | |
| 1. Corotoxigenin: 3β,14β-dihydroxy-5α-card-20(22)-enolide | $C_{23}H_{32}O_5$ | 220–222 | +43; MeOH | 218(4.2), 306(1.45) | 0.7 |
| 2. 3β-O-Succinylcorotoxigenin | $C_{27}H_{37}O_8$ | 235–242 | +41; MeOH | – | Inactive |
| 3. Potassium salt of 3β-O-succinylcorotoxigenin | $C_{27}H_{36}O_4K$ | 339 (decomp.) | +39; MeOH | 307(1.42) 218(4.14) | Inactive |
| *Cis-A/B* | | | | | |
| 4. Digitoxigenin: 3β,14β-dihydroxy-5β-card-20(22)-enolide | $C_{23}H_{34}O_4$ | 247–249 | +18; MeOH | 218.5(4.15) | 0.42–0.46 |
| 5. 3β-O-Succinyldigitoxigenin | $C_{27}H_{38}O_7$ | 234–237 (decomp.) | +17; MeOH | – | Inactive |
| 6. Potassium salt of 3β-O-succinyldigitoxigenin | $C_{27}H_{37}O_7K$ | 350 (decomp.) | +14; $H_2O$ | 219(4.12) | Inactive |
| 7. Oleandrigenin: 16β-OAc-3β,14β-dihydroxy-5β-card-20(22)-enolide | $C_{25}H_{36}O_6$ | 223–225 | +10; MeOH | 219(4.12) | 0.22–0.25 |
| 8. 3β-O-Succinyloleandrigenin | $C_{27}H_{40}O_9$ | 223–227 | +8.2; MeOH | – | Inactive |
| 9. Potassium salt of 3β-O-succinyloleandrigenin | $C_{29}H_{39}O_9K$ | 290–296 (decomp.) | +6.0; $H_2O$ | (218)4.09 | Inactive |
| 10. Strophanthidin: 3β,5β,14β-trihydroxy-5β-card-20(22)-enolide | $C_{23}H_{32}O_6$ | 223–225 | +44; MeOH | 220(4.12), 309(1.5) | 0.26–0.36 |
| 11. 3β-O-Maleoylstrophanthidin | $C_{27}H_{34}O_9$ | 235–243 | +42.5; MeOH | – | Inactive |
| 12. Potassium salt of 3β-O-maleoylstrophanthidin | $C_{27}H_{33}O_9K$ | 285 (decomp.) | +38; $H_2O$ | 220(4.15) | Inactive |

Thus, the introduction of succinic or maleic acid into the molecule of a cardenolide enables cardiotonically inactive compounds to be obtained, which makes it possible to perform a determination of other types of biological action in this unique class of natural compounds.

## EXPERIMENTAL

Melting points were determined on a Kofler block. Optical activities were measured on a SPU-E instrument with a cell 1 dm long, and UV spectra were taken on a Specord UV/VIS spectrophotometer. The crystalline substances for synthesis were dried over phosphorus pentoxide in vacuum at 110-115°C for 5 h. The initial substances and their acyl derivatives were chromatographed on paper in the chloroform/formamide and benzene–chloroform (2:1)/formamide system.

**3β-O-Succinylcorotoxigenin (2).** A mixture of 150 mg of corotoxigenin (**1**) and 300 mg of succinic anhydride was treated with 2 ml of absolute pyridine. Acylation was carried out in an oil bath at 105-110°C for 3 h, the course of the reaction being monitored by paper chromatography in the benzene–chloroform (7:3)/formamide (25%) system. Then the pyridine was evaporated off under vacuum, the residue was dissolved in 5 ml of chloroform, and this solution was carefully washed with 1% hydrochloric acid to eliminate pyridine and then with distilled water to neutrality. The monoester (**2**) was extracted from the chloroform with a dilute solution of sodium carbonate, the extract was acidified with dilute hydrochloric acid to pH 3-3.5, and the resulting precipitate (153 mg) was separated off and recrystallized from a mixture of acetone and ether (see Table 1).

**Potassium Salt of 3β-O-Succinylcorotoxigenin (3).** A solution of 120 ml of succinylcorotoxigenin (**32**) in 3 ml of methanol was treated with 0.18 ml of a 10% aqueous solution of potassium carbonate, the mixture was carefully concentrated in vacuum to 1-1.5 ml, and acetone was added dropwise until crystals deposited, which were filtered off (119 mg) (see Table 1).

**3β-O-Succinyldigitoxigenin (5).** The product of the reaction of 150 mg of digitoxigenin (**4**) and 300 mg of succinic anhydride in absolute pyridine was isolated as in the case of (**2**). After recrystallization from acetone with the addition of ether, 168 mg of the desired product (**5**) was obtained (see Table 1).

**Potassium Salt of 3β-O-Succinyldigitoxigenin (6).** A solution of 150 mg of succinyldigitoxin in 1 ml of methanol was treated with 0.8 ml of a 10% solution of potassium carbonate, and then with 2 ml of a 1:1 mixture of acetone and ether. This gave 146 mg of the desired product (**6**), which was additionally recrystallized from ethanol–acetone–ether (see Table 1).

**Oleandrigenin (7) from Oleandrin.** With heating, 500 mg of oleandrin, obtained from oleander leaves by the method described in [6], was dissolved in 10 ml of ethanol, and then 10 ml of 0.1 N hydrochloric acid was added, and the mixture was kept at the boil for 2 h. After cooling, the reaction mixture was neutralized with 10 ml of 0.1 N potassium carbonate solution to a weakly acid reaction and was left for crystallization. The flocculent precipitate that deposited (340 mg) was filtered off, dried in the air, and recrystallized from 50% ethanol (see Table 1)

**3β-O-Succinyloleandrigenin (8).** A mixture of 310 mg of oleandrigenin and 1.0 g of succinic acid was dissolved in 2 ml of absolute pyridine, and the reaction as conducted at 110°C for 2 h, as described for (**2**).

This gave 372 mg of yellowish crystals of (**8**), which, after drying, were recrystallized from a mixture of acetone and ether, having first been purified with activated carbon. This gave 321 mg of colorless crystals (see Table 1).

**Potassium Salt of 3β-O-Succinyloleandrigenin (9).** A solution of 253 mg of (**8**) in 1 ml of methanol and 0.35 ml of 10% aqueous potassium carbonate was processed as described for (**3**). On recrystallization from a mixture of methanol and acetone, 258 mg of substance (**9**) was obtained (see Table 1).

**3β-O-Maleoylstrophanthidin (11).** To 450 mg of strophanthidin were added 1.2 g of maleic anhydride and 2.5 ml of absolute pyridine, and the reaction was carried out at 110°C for 2 h. The further procedure was as described above. This gave 532 mg of yellow-brown crystals of (**11**), which were recrystallized from methanol (see Table 1).

**Potassium Salt of 3β-O-Maleoylstrophanthidin (12).** A solution of 400 mg of substance (**11**) in 6 ml of methanol was treated with 0.4 ml of 10% aqueous potassium carbonate. Then compound (**12**) was isolated as described above for compound (**3**). After recrystallization, 397 mg of substance (**12**) was obtained.

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