THE POTENCY OF FIVE ADDITIONAL CARDIAC GLUCOSIDES, CALOTROPIN, α-ANTIARIN, EMICYMARIN, FOLINERIN AND SARMENTOCYMARIN.*

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In a previous report (1), the comparative potency of eleven crystalline cardiac principles of plant origin was recorded.[1] Through the kindness of Doctor Rudolf Tschesche, Allgemeines Chemisches Universitäts-Laboratorium, Göttingen, Germany, three additional cardiac crystalline glucosides, α-antiarin, folinerin and sarmentocymarin, were made available to our laboratory. Calotropin was courteously supplied by Doctor Gerhard Hesse, München, Germany. Mr. Howard B. Fonda, Experimental Research Laboratories, the Burroughs Wellcome and Company, Tuckahoe, New York, was good enough to supply us a fifth compound in the present series, that is, emicymarin.

Calotropin was first crystallized with chloroform by Wieland; the glucoside and its aglucone were studied by Hesse and Reicheneder (2). α-Antiarin was isolated by Killiani (3), (4), (5), (6) from the milk sap of *Antiaris toxicaria*, and its empirical formula together with β-antiarin has been recently revised to $C_{29}H_{42}O_{11}$ by Tschesche and Haupt (7). Sarmentocymarin was first crystallized by Jacobs and Heidelberger (8) from the seeds of *Strophanthus sarmentosus*, and the structural formula of its aglucone has been elucidated by Jacobs and Heidelberger (8) and more recently by Tschesche and Bohle (9). Folinerin is a proprietary product prepared from the leaves of *Nerium oleander* (10), presumably different from oleandrin. Emicymarin is a new glucoside isolated by Lamb and Smith (11) from *Strophanthus emini*.

The five substances were subjected to similar assays and studies as previously described (1). To prepare a 0.1 per cent stock solution, sarmentocymarin was dissolved in 19 per cent of alcohol (by volume), and calotropin, α-antiarin and emicymarin, in 28.5 per cent. Folinerin is much less soluble in water, requiring 57 per cent of alcohol to effect complete solution.

The results are given in Tables I, II and III, and summarized in Table IV. It should be noted that calotropin has exactly the same potency as ouabain, as shown by the cat unit, the frog minimal systolic dose, and the cat minimal emetic dose (1). It is slightly more potent than cymarin. Folinerin has an unusually high emetic action, its minimal emetic dose in cats being only 20 per cent of the cat unit, smaller than that for any of the substances under investigation. Its effect is, however, very slow, for a majority of the cats did not vomit until more than half an hour after the injection. Two cats required a little over an hour for vomiting, and a third one, 2 hours and 7 minutes. Like digitoxin, folinerin has a very persistent action. For example, a dose equivalent to 40 per cent of the cat unit had not been completely eliminated at the end of two weeks. The protocol of that experiment may be cited here for illustration:

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* From the Lilly Research Laboratories, Indianapolis, Indiana.

[1] A typographical error should be corrected in Tables II and IV, column 3, on pages 587, 588 and 589, that is, the abbreviation "Kg." ought to be changed to "Gm." In Table IV, column 4, the minimal emetic dose in cats for digoxin should be 0.070 mg. per Kg. instead of 0.075.

11–27–1936, 8:39 A.M.—Cat No. 1528, male, weighing 1.944 Kg. was injected intravenously 0.08 mg. of folinerin per Kg. of body weight. Original pulse rate was 216 per minute.

9:12 A.M.—Cat vomited.

11–30–1936—Pulse rate was 140 per minute, slightly irregular.

12– 1–1936—Pulse rate was 188 per minute.

12– 2–1936—Pulse rate was 170 per minute.

12– 3–1936—Pulse rate was 172 per minute.

12– 4–1936—Pulse rate was 132 per minute.

12– 7–1936—Pulse rate was 148 per minute.

12– 8–1936—Pulse rate was 112 per minute. There were extrasystoles about every 10 beats.

12– 9–1936—Pulse rate varied from 126 to 184 per minute.

12–10–1936—Pulse rate was 136 per minute.

12–11–1936—Cat had lost 660 Gm. in the course of 14 days. It was sacrificed for the determination of the fatal dose, which was found to be 0.133 mg. per Kg., smaller than any observed in the series of cats for the cat unit, as shown in Table I.

TABLE I.—CAT UNITS OF CALOTROPIN, α-ANTIARIN, EMICYMARIN, FOLINERIN AND SARMENTOCYMARIN.

Drug.	Solution.	Cat Number.	Sex.	Weight, Kg.	Fatal Dose, Mg. per Kg.
Calotropin	1:100,000	1635	F	1.656	0.119
		1636	M	1.658	0.116
		1637	M	2.071	0.108
		1638	M	1.796	0.123
		1639	F	2.467	0.125
		1640	F	1.955	0.113
		1641	M	2.605	0.106
		1642	F	2.469	0.115
		1643	F	2.503	0.132
		1644	F	2.322	0.137
α-Antiarin	1:100,000	1483	M	2.280	0.135
		1484	M	2.151	0.141
		1485	F	1.949	0.109
		1486	F	1.995	0.116
		1487	F	1.907	0.137
		1488	F	2.495	0.157
		1489	M	1.970	0.123
		1490	M	1.895	0.119
		1491	M	2.016	0.147
		1492	M	1.898	0.166
		1554	M	1.821	0.159
		1555	F	2.058	0.138
		1546	F	2.532	0.097
		1547	F	2.493	0.105
		1548	F	2.109	0.130
		1549	F	2.380	0.118
		1550	M	2.480	0.143
		1551	F	2.303	0.126
		1552	F	1.933	0.104
		1553	F	1.788	0.119
Emicymarin	1:100,000	1610	F	2.628	0.132
		1611	F	2.481	0.140
		1612	M	2.339	0.194
		1613	M	1.898	0.143
		1614	M	2.344	0.166
		1615	M	2.311	0.129
		1616	F	3.140	0.141
		1617	F	1.946	0.241
		1627	F	2.074	0.251
		1628	F	2.765	0.133
Folinerin	1:100,000	1534	M	2.030	0.144
		1535	M	1.772	0.274
		1536	M	2.299	0.217
		1537	F	2.056	0.185
		1538	F	1.941	0.229
		1539	F	2.335	0.191
		1567	M	1.972	0.205
		1568	F	2.195	0.173
		1569	F	2.086	0.163
		1570	M	2.082	0.218
Sarmentocymarin	1:100,000	1502	F	2.320	0.215
		1503	M	2.600	0.225
		1504	M	2.579	0.183
		1514	M	2.695	0.234
		1515	F	2.938	0.229
		1516	F	1.882	0.182
		1517	M	2.374	0.157
		1518	F	2.170	0.309
		1519	M	2.495	0.161
		1520	F	2.548	0.212
		1544	M	1.765	0.193
		1545	M	1.956	0.166

The action of sarmentocymarin is moderately persistent since a dose equivalent to 62 per cent of the cat unit partly remained in the circulation for more than 5 days. Calotropin, α-antiarin and emicymarin are the least persistent of the five glucosides.

TABLE II.—MINIMAL SYSTOLIC DOSE OF CALOTROPIN, α-ANTIARIN, EMICYMARIN, FOLINERIN AND SARMENTOCYMARIN IN FROGS.

Drug.	Solution.	Dose, Mg. per Gm.	No. in Systolic Standstill/ No. of Frogs Used.
Calotropin	1:20,000	0.00042	0/4
		0.00046	1/4
		0.00050	6/8
		0.00054	3/4
		0.00058	4/4
α-Antiarin	1:20,000	0.00036	0/4
		0.00046	1/4
		0.00050	3/4
		0.00055	3/4
		0.00064	4/4
Folinerin	1:5,000	0.00091	0/4
		0.00109	2/8
		0.00127	3/4
		0.00145	4/4
Emicymarin	1:5,000	0.00182	1/8
		0.00205	3/4
		0.00227	3/4
		0.00273	4/4
Sarmentocymarin	1:2,000	0.00409	0/4
		0.00455	1/4
		0.00500	1/4
		0.00545	3/4
		0.00591	3/4
		0.00636	4/4

TABLE III.—MINIMAL EMETIC DOSE OF CALOTROPIN, α-ANTIARIN, EMICYMARIN, FOLINERIN AND SARMENTOCYMARIN IN CATS.

Drug.	Dose, Mg. per Kg.	No. of Cats Vomited/ No. of Cats Used.
Folinerin	0.03	0/2
	0.04	2/2
	0.05	1/1
	0.06	1/1
	0.07	1/1
Calotropin	0.05	0/2
	0.06	2/3
	0.07	3/3
	0.08	1/1
α-Antiarin	0.05	0/2
	0.06	2/2
	0.07	1/1
	0.08	2/2

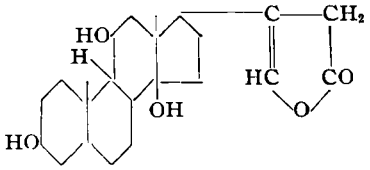
TABLE III.—*Concluded.*

Drug.	Dose, Mg. per Kg.	No. of Cats Vomited/ No. of Cats Used.
Sarmentocymarin	0.08	0/2
	0.09	2/2
	0.10	2/3
	0.11	1/1
Emicymarin	0.08	0/2
	0.09	2/2
	0.10	1/1
	0.12	1/1

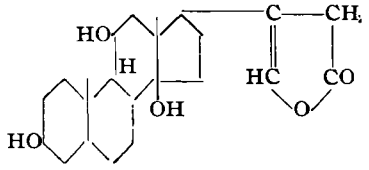
TABLE IV.—SUMMARY OF ALL RESULTS.

Drug.	Cat Unit (Mean ± Probable Error), Mg. per Kg.	Frog Minimal Systolic Dose, Mg. per Gm.	Cat Minimal Emetic Dose, Mg. per Kg.
Calotropin	0.12 ± 0.002	0.00050	0.06
α-Antiarin	0.13 ± 0.003	0.00050	0.06
Emicymarin	0.17 ± 0.010	0.00205	0.09
Folinerin	0.20 ± 0.008	0.00127	0.04
Sarmentocymarin	0.21 ± 0.008	0.00545	0.09

It may be interesting to point out that α-antiarin having the same empirical formula as β-antiarin (6), (7) and differing from the latter only by the sugar molecule (6), has a definitely lower activity than β-antiarin, the value of which was given previously (1). In the structural studies made by Tschesche and Bohle (9), sarmentogenin was shown to be an isomer of digoxigenin as follows:

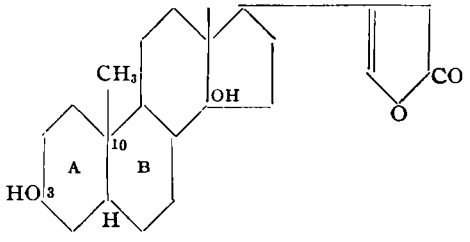


Sarmentogenin



Digoxigenin

It is therefore of more than casual interest that sarmentocymarin and digoxin have a similar potency in cats, the cat unit for the former being 0.21 mg. per Kg. and that for the latter 0.22 mg. per Kg. (1). Digoxin, $C_{41}H_{64}O_{14}$, has a larger molecule than sarmentocymarin, $C_{33}H_{46}O_8$, and thus requires a slightly larger dose. This is in contrast with digitoxin, uzarin and thevetin which have the same structural formula for their aglucone, as shown below:



Uzarigenin, Thevetigenin or Digitoxigenin

(12), (13), but which differ greatly in their cardiac activity (1). The difference is very likely due to that of the spatial arrangement of their molecules. According to Tschesche and Bohle (13), the OH group on C_3 and CH_3 group on C_{10} in uzarigenin are in *cis*-form, and its rings A and B are in *trans*-form. In thevetigenin, the OH and CH_3 groups, and rings A and B, are both in *cis*-form, while in digitoxigenin the OH and CH_3 groups are in *trans*-form and rings A and B in *cis*-form. Hesse and Reicheneder (2) showed that calotropagenin has a structural resemblance to strophanthidin. It is thus interesting to note that calotropin is only slightly more potent than cymarin, which is a conjugation product of strophanthidin and cymarose.

Regarding sarmentocymarin and digoxin in frogs, there is a considerable difference in their minimal systolic doses, the former being apparently less than half as potent as the latter. Similarly, emicymarin is more potent than folinerin according to the cat method, but is just the reverse according to the frog method. With further accumulation of data, it is hoped that an explanation for discrepancy of results between the cat method and the frog method may be forwarded at a later date.

SUMMARY.

The potency of five additional cardiac glucosides, calotropin, α-antiarin, sarmentocymarin, emicymarin and folinerin, has been carefully determined in cats and frogs.

α-Antiarin is definitely less potent than β-antiarin, Gm. for Gm.

Calotropin has exactly the same potency as ouabain.

Folinerin has a very high emetic action. Like digitoxin, it has a very slow but persistent action in the animal body.

Sarmentocymarin, which has the same structural formula for its aglucone as digoxin, possesses a similar potency as digoxin in cats.

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