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Action of Strophanthidin-3-propionate, -butyrate, and -benzoate.

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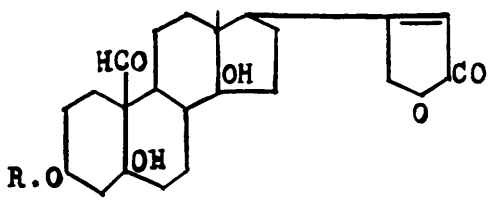
The secondary hydroxy group on carbon atom 3 of cardiac aglycones is chemically very reactive. By the interaction of a molecule of sugar with the aglycone at this position, synthetic glycosides of strophanthidin, digitoxigenin, digoxigenin, and periplogenin were successfully prepared at the Department of Chemistry, Columbia University under the direction of Professor Robert C. Elderfield.[1,2] It has been shown[3,4] that these synthetic glycosides are more potent than their parent glycosides, namely, cymarin, digitoxin, digoxin, and periplocymarin, respectively. Esters of strophanthidin can be also conveniently synthesized.[5] The present study consisted of the preparation of 3 such compounds, and the determination of their potency in cats. They are, chemically, strophanthidin-3-*n*-propionate, -*n*-butyrate, and -benzoate, and conform to the following structure:



wherein R denotes $CH_3 \cdot CH_2 \cdot CO$, $CH_3 \cdot (CH_2)_2 \cdot CO$, or $C_6H_5 \cdot CO$.

The aglycone strophanthin was isolated from the seeds of *Strophanthus kombé* according to the method of Jacobs and Heidelberger.[6] We are much indebted to Professor Robert C. Elderfield for his generosity in giving us his modification for the improvement of the yield of this aglycone. The propionate and the butyrate were obtained by Neumann's procedure,[5] and the benzoate by that of Windaus and Hermanns.[7] In principle, strophanthidin was allowed to react with the acid chloride in the presence of pyridine. The esters were all purified by repeated recrystallization from methanol. The propionate melted at 234.5-235°C, the butyrate at 212-213°C, and the benzoate at 225-226°C (corrected), the rate of heating being moderate. The results of combustion analyses satisfied the required compositions.

For cat experiments, stock solutions of 1:1000 were made with strophanthidin-3-*n*-propionate and -*n*-butyrate, containing 47.5% ethanol by volume. Dilutions of 1:50,000 were employed for intravenous injection until death occurred in the same manner as previously reported.[8] The rate of injection was 1 cc per minute. The benzoate was much less soluble in water, requiring 71.25% ethanol by volume for a solution of 1:500. The material would crystallize out in further dilutions. It was thus necessary to inject the stock solution intravenously at the rate of 0.08 cc per minute followed by 1 cc of saline by means of a 3-way stopcock—a procedure previously adopted in this laboratory.[9]

The results are shown in Table I. Judging from the geometric mean, that is, the antilogarithm of the mean of logarithms of in-

1 Uhle, F. C., and Elderfield, R. C., *J. Org. Chem.*, 1943, **8**, 162.

2 Fried, J., and Elderfield, R. C., *J. Org. Chem.*, in press.

3 Chen, K. K., and Elderfield, R. C., *J. Pharm. and Exp. Therap.*, 1942, **76**, 81.

4 Chen, K. K., Elderfield, R. C., Uhle, F. C., and Fried, J., *J. Pharm. and Exp. Therap.*, 1943, **77**, 401.

5 Neumann, W., *Arch. exp. Path. u. Pharm.*, 1937, **185**, 329.

6 Jacobs, W. A., and Heidelberger, M., *J. Biol. Chem.*, 1922, **54**, 253.

7 Windaus, A., and Hermanns, L., *Ber. deut. chem. Gesellsch.*, 1915, **48**, 991.

8 Chen, K. K., Chen, A. L., and Anderson, R. C., *J. Am. Pharm. Assn.*, 1936, **25**, 579.

9 Chen, K. K., Robbins, E. B., and Worth, H., *J. Am. Pharm. Assn.*, 1938, **27**, 189.

TABLE I.
Results in Cats.

Compound	Sex	Body wt, kg	Dose to kill, mg per kg	Mean (geometric) lethal dose ± standard error, mg per kg
Strophanthidin				0.3250 ± 0.0232*
Strophanthidin-3-acetate				0.1866 ± 0.0246†
	F	1.900	0.1726	
	M	1.878	0.3695	
	M	1.972	0.2779	
	M	1.858	0.6362	
Strophanthidin-3-*n*-propionate	M	1.904	0.2626	0.2573 ± 0.0377
	F	2.144	0.4300	
	F	2.081	0.2379	
	F	2.707	0.1101	
	F	2.117	0.2834	
	F	1.964	0.1874	
	F	1.857	0.4157	
	F	1.977	0.4982	
	F	1.861	0.4449	
	M	1.783	0.2961	
Strophanthidin-3-*n*-butyrate	M	1.694	0.4534	0.4263 ± 0.0220
	F	2.103	0.5544	
	F	2.049	0.3348	
	F	2.574	0.6267	
	F	2.169	0.4168	
	F	2.014	0.3307	
	M	2.238	2.8776	
	F	1.825	2.3233	
	M	1.806	2.5692	
	F	1.840	4.5217	
Strophanthidin-3-benzoate	F	1.937	1.4042	2.717 ± 0.2610
	F	2.348	2.7257	
	M	1.918	2.7320	
	M	2.502	2.6219	
	M	1.803	2.7510	
	M	2.068	3.7524	

* Mean of combined data published previously.[3,8]
† Previously reported.[3]

dividual doses, the propionate is more potent than strophanthin in cats; but the butyrate and the benzoate are both less active. Our data on the butyrate are thus in agreement with those of Neumann.[5] In a previous communication,[3] evidence was presented that strophanthidin-3-acetate was more powerful than strophanthidin. It is apparent that among the acyl radicals which form esters with strophanthidin, the members of the lower molecular weight, namely, acetyl and propionyl, enhance the activity of strophanthidin in cats. On the other hand, butyryl and benzoyl groups decrease its activity.

Summary. Weight for weight, strophanthidin-3-*n*-propionate is more potent than strophanthidin in cats, while strophanthidin-3-*n*-butyrate and -benzoate prove to be less active.