15915

Some New Esters of Strophanthidin.

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During the last few years, 22 esters of strophanthidin were studied pharmacologically in this laboratory.[1-4] It was observed that more potent derivatives than strophanthidin could be prepared, and that 3-acetyl strophanthidin (identical with strophanthidin-3-acetate) was the most potent of the entire series. Additional investigations with several of these esters were carried out elsewhere.[5,6] To explore the changes of cardiac activity resulting from substitution in a single ester, 8 new derivatives of 3-acetyl strophanthidin were synthesized and tested intravenously in cats. They were 3-bromo-, 3-iodo-, 3-phenyl-, 3-phenoxy-, 3-methoxy-, 3-diethyl-, 3-trichloro-, and 3-trimethyl-, acetyl strophanthidin.

The strophanthidin used in the present investigation was obtained from the seeds of *Strophanthus kombé* according to the method of Jacobs and Heidelberger.[7] The esters were prepared by suspending the dry, powdered strophanthidin in a mixture of the desired acid chloride and equal parts of dry benzene and dioxane. The suspension was heated on the steam bath until complete solution had taken place and then poured into petroleum ether to terminate the reaction. In the preparation of the bromo- and iodoacetyl derivatives the benzene-dioxane solution was not heated above 55°C. Recrystallization of the products was carried out in ethanol solution. The results of the combustion analyses confirmed the purity of the compounds. Their melting points are recorded in Table I.

These new esters are sparingly soluble in water, and require ethanol for solution. In order to avoid the effects of alcohol, minimal amounts were employed for each of the compounds. It required 47.5% ethanol by volume to make a 1:1000 solution of 3-phenylacetyl strophanthidin; 76% for that of 3-iodoacetyl or 3-methoxyacetyl strophanthidin; and 95% for that of 3-bromoacetyl strophanthidin. Solutions of 1:500 were prepared with 3-diethylacetyl strophanthidin in 57% ethanol by volume; and with 3-trichloroacetyl and 3-trimethylacetyl strophanthidin in 95%. 3-Phenoxyacetyl strophanthidin was so insoluble that it was necessary to use absolute ethanol in order to make a 1:2000 solution.

Six of the above stock solutions were diluted with physiologic saline prior to administration to cats. The dilutions, governed by the toxicity and solubility of the strophanthidin esters, were as follows: 1:50,000 with the 3-diethylacetyl and 3-methoxyacetyl; 1:25,000 with the 3-trimethylacetyl, 3-iodoacetyl, and 3-phenylacetyl; and 1:20,000 with the 3-trichloroacetyl.

Etherized cats were injected with the diluted solutions by a continuous intravenous infusion until death occurred.[8] The rate of injection was 1 cc per minute with the 3-iodoacetyl, 3-phenylacetyl, 3-methoxyacetyl, and 3-trichloroacetyl strophanthidins; and 2 cc per minute with the 3-diethylacetyl and 3-tri-

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TABLE I.
Results in Cats.

Ester of Strophanthidin	Melting point, °C	No. of cats			Dose range to kill μg per kg	Mean (geometric) lethal dose ± standard error μg per kg
		Male	Female	Total		
3-Bromoacetyl	220-222	0	2	2	7651.0-7976.0	7803
3-Iodoacetyl	186-188	7	3	10	572.5- 762.7	677.8 ± 19.5
3-Trichloroacetyl	181-183	3	6	9	354.7- 663.4	453.9 ± 27.9
3-Trimethylacetyl	223-224	3	3	6	1422.0-2699.0	1799.0 ± 188.0
3-Methoxyacetyl	221-222	6	3	9	203.9- 521.6	334.5 ± 29.5
3-Diethylacetyl	207-209	6	4	10	607.2-1934.0	1047.0 ± 125.3
3-Phenylacetyl	204-205	6	4	10	558.1-1394.1	1061.0 ± 89.1
3-Phenoxyacetyl	231-232	5	1	6	235.0- 655.3	334.8 ± 48.7

methylacetyl strophanthidins. The 3-bromoacetyl and 3-phenoxyacetyl esters were administered in stock solutions owing to their insolubility in saline, the rate being 0.1 cc per minute for the former, and 0.05 cc per minute for the latter, both followed by 1 cc of saline through a 3-way stopcock after each injection. Of 62 cats the body weight ranged from 1.763 to 2.778 kg, averaging 2.184 kg. The number of animals used for 7 esters varied from 6 to 10 each. Only 2 cats were injected with 3-bromoacetyl strophanthidin since its activity was decidedly lower than the others.

All the 8 compounds retain their digitalis-like action as judged by bradycardia, arrhythmia, secondary tachycardia, and terminal ventricular tachycardia in cats during the slow intravenous injection of each. In Table I, the mean (geometric) lethal doses are shown in the last column. None of them is as potent as 3-acetyl strophanthidin which has a mean lethal dose of 186.6±24.6 μg per kg in cats.[1] By comparison of the toxicity values previously published[2] with those of the present series, it will be noted that the 3-chloroacetyl strophanthidins have the following order of activity: dichloroacetyl> trichloroacetyl > chloroacetyl. Considering strophanthidin-3-propionate and 3-*iso*butyrate as methyl- and dimethyl-, acetyl strophanthidins, respectively, it can then be seen that the 3 methylacetyl derivatives have the following order of activity: methylacetyl> dimethylacetyl>trimethylacetyl. In other words, chlorination of acetyl strophanthidin does not alter the cardiac activity in the same direction as methylation of the same. Of the 3 monohalogen substituents, the iodoacetyl derivative is the most active, and the bromoacetyl the least active. The high activity of 2 ether-like compounds, 3-methoxyacetyl and 3-phenoxyacetyl strophanthidins, is noteworthy although neither exceeds the activity of the parent aglycone, strophanthidin. Equally interesting is the low potency of 3-phenylacetyl as compared with 3-phenoxyacetyl strophanthidin, in the ratio of 1 to 3. A reverse order of activity, although not to the same extent, exists between 3-methylacetyl (identical with strophanthidin-3-propionate) and 3-methoxyacetyl strophanthidins.

Summary. Eight derivatives of 3-acetyl strophanthidin have been synthesized and studied pharmacologically in cats. None of the new compounds is as active as 3-acetyl strophanthidin, although 2 of them approach the parent aglycone, strophanthidin, in potency. The significance of certain structural changes against cardiac activity has been pointed out.

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