THE PHARMACOLOGY OF SQUILL*

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SINCE the introduction by Withering[1] in 1785 of digitalis as a diuretic, emphasis has been placed, both in the laboratory and in the clinic, on this preparation and its chemical constituents. Along with these developments have come reports of other substances that have digitalislike action: namely, a specific and powerful effect on the myocardium. Most of these substances are of vegetable origin; only a few have been found in the animal kingdom. For example, the venom of certain toads[2] contain digitalislike substances. Grasshoppers[3] store digitalislike substances after the ingestion of plants containing these materials. Since these compounds occur in nature combined with various sugars they have been given the general term of cardiac glycosides. Lyon and De Graff[4] estimate that more than 400 cardiac glycosides have been found in nature. Chemists have described the chemical structure of many of these compounds, and this has permitted speculation on the relation between their structure and their pharmacologic action. In addition, cardiac glycosides have been synthesized in the laboratory. It is of interest to speculate that in these many cardiac glycosides there may be one or more that are superior to digitalis. It is the purpose of the present review to focus attention on one of these cardiac glycosides—squill—and its chemical constituents.

Squill is an ancient remedy. Its use in antiquity is described by Stannard;[5] its use in the 17th and 18th centuries is given by Cowen.[6] Withering[7] compared the action of squill to that of digitalis and decided that digitalis gave "less disturbance to the system, than squill." Otherwise attention might have been focused on squill in place of digitalis.

There is very little clinical use of squill and its constituents in this country, although these preparations are used abroad. The last description of the drug in the *U.S. Pharmacopeia*[8] appeared in 1942; that in the *National Formulary*[9] in 1960. A short description of squill is given in

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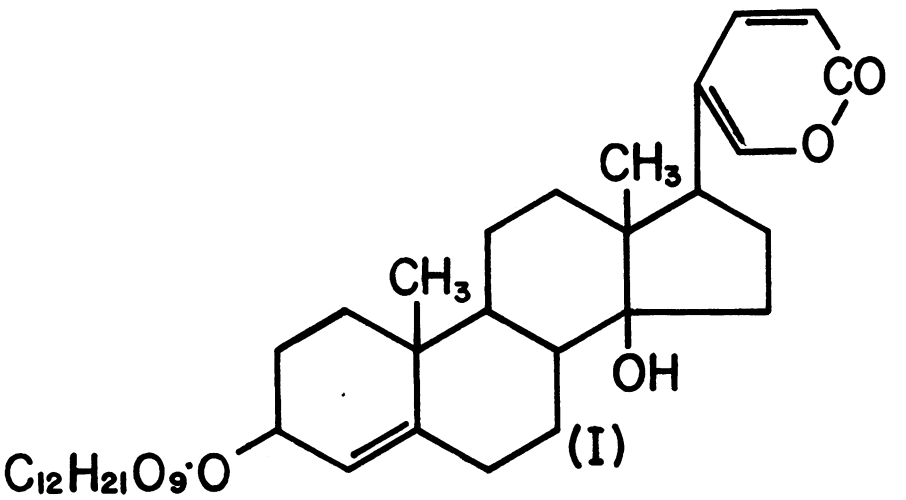

Scillaren A

Formula for scillaren A. The $C_{12}H_{21}O_9$-group is the rhamnose-glucose part of the molecule. Removal of the glucose produces the glycoside, proscillaridin A; additional removal of the rhamnose produces scillaridin A, the aglycone or genin.

the United States *Dispensatory*, 26th edition.[10] *New and Nonofficial Remedies*[11] for 1952 contains descriptions of scillaren, scillaren A and B, and Urginin. The British *Codex*[12] for 1968 also carries a description of squill, which is likewise described in the *Codex Français*[13] for 1965. Commercial supplies of squill and its derivatives[14] are no longer available in the United States.

Botany

Squill is obtained from *Urginea maritima*, a bulbous plant that grows on the shores of the Mediterranean. A related plant, *Urginea indica*, grows in India. These bulbs are generally termed the *white squill* in order to distinguish them from the *red squill*, which is used as a rat poison. Also the white squill should not be confused with scilla, a common garden plant. The bulbs are collected in August.[15] After removal of the outer scales and the central parts, the bulbs are cut into pieces and dried.

Chemistry

The chemistry of squill and its constituents have been reviewed by Stoll[16] and by Fieser and Fieser.[17] Earlier pharmacologists divided the components of squill into scillaren A and scillaren B. Scillaren A (see accompanying figure) is composed of an aglycone and rhamnose and glucose. The rhamnose (methyl pentose) and glucose are attached to the hydroxyl group at position 3. Scillaren A differs chemically from digilanid A. The digitalis compounds contain glucose and digitoxose attached to position 3 and have a five-member lactone ring in place of the six-membered ring in scillaren A. Scillaren has a double bond in the aglycone. Removal of the rhamnose and glucose from scillaren A produces the aglycone or genin, scillaridin A. Scillaren B is a mixture of cardiac glycosides. The activity of each of these glycosides has not been studied extensively.

Pharmacology

At present it is difficult to make an accurate comparison of the action of squill and its derivatives with that of digitalis, since most of the work was done 50 or more years ago. Very few recent references are found in *Chemical Abstracts* for the past 10 years. Eric Gaskell, an experienced librarian of the history of medicine, wrote that he could not find anything in the way of review articles on the use of squill in present-day medicine. It is necessary, therefore, to repeat the statements about the activity of squill without giving the experimental foundations on which these statements are based. It may be assumed that scillaren, a mixture of glycosides of squill in natural proportions, possesses a cardiac action similar to that of digitalis, though the action[15] may be less prolonged. Squill is more potent than digitalis in its vagal action and less potent in its muscular action.[10] It is more rapid and has shorter activity and therefore presents less danger of cumulative action. Scillaren A and scillaren B are absorbed[10] well from the gastrointestinal tract. The rapid action may be related to the rapid excretion of these drugs.

Grollman, Suki, and Ghavamian[18] studied the action of squill on the kidneys. Comparing a squill glycoside (scillaren substance) with digoxin, they found that the squill glycoside was more effective in its diuretic and natriuretic action than digoxin. They concluded that this effect is a direct one on the kidney and is not a result of its hemodynamic effects.

Toxicity

Chen and Henderson[2] in their study of 64 cardiac glycosides and aglycones report dose range for scillaren A in cats to be 0.1168 to 0.2097 mg./kg. with a mean of 0.1670. Values given for acetyl-digitoxin-alpha ranged from 0.4343 to 0.5758 mg./kg., with a mean of 0.5141 mg./kg. Only 11 in the series of 64 cardiac glycosides had potencies greater than those of scillaren A, proscillaridin A, and scillarenin.

Summary

An exact comparison of squill to digitalis cannot be made at the present time on account of the lack of recent information on the action of squill. The quick action of squill, the lack of cumulative action, and the diuretic action of squill merit additional study.

Acknowledgments

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