tion was proportional to the logarithm of the ratio of verapamil to ionophore concentration, each 10fold increase in such a ratio causing a $^{1}/_{3}$ reduction in calcium translocation. This relationship is comparable to that characterizing the inhibitory action of organic calcium-antagonists upon physiological processes such as glucose-induced insulin release, which is likewise reduced by 30–40% for each 10fold increase in drug concentration[5–7]. Incidentally, it was already shown that verapamil also inhibits the secretory response evoked by the ionophore A23187 in both the neurohypophysis[8] and pancreatic B-cell[9].

The inhibitory effect of verapamil upon A23187-mediated calcium translocation was invariably present, whatever the calcium concentration of the initial aqueous phase. However, when the latter concentration was raised and the verapamil/ionophore ratio kept constant, the organic antagonist caused a lesser reduction in the apparent amount of active ionophore molecules, as judged by reference to the normal dose-action relationship for calcium translocation at variable calcium and A23187 concentrations. Thus, in the present model, as in living cells[10], calcium itself protected in a competitive manner against the inhibitory effect of the organic calcium-antagonist. Such a protective effect of calcium indicates that verapamil acts at the calcium-binding site of A23187, rather than causing an unspecific and direct alteration of the ionophore molecule itself. Verapamil exerted no obvious effect upon calcium movements in the absence of ionophore. It did not abolish the reversibility of A23187-mediated calcium translocation and failed to affect the apparent positive cooperativity between calcium and the residual active ionophore molecules (data not shown). Essentially the same results were obtained when verapamil was added to the initial aqueous as distinct from organic phase. Comparable results were also obtained with other organic calcium-antagonists, including R33711[7] and suloctidil[11].

In conclusion, organic calcium-antagonists interfere, in an artificial model, with the ionophoretic property of A23187. It is postulated that a similar interference of these drugs with the calcium-binding sites of native ionophoretic systems located in the plasma membrane may account for their inhibitory action upon calcium handling in living cells.

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Synthesis and properties of praziquantel, a novel broad spectrum anthelmintic with excellent activity against Schistosomes and Cestodes

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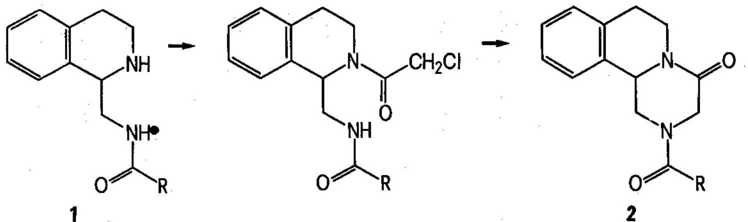
26 January 1977

Summary. Synthesis and properties of 2-cyclohexylcarbonyl-1,3,4,6,7,11b-hexahydro-2H-pyrazino [2,1-a] isoquinolin-4-one, a novel anthelmintic with excellent activity against all species of Schistosomes pathogenic to man and a wide range of cestodes, will be reported.

Although diseases caused by helmintic infections are of great importance in human and veterinary medicine, only few therapeutic agents are available for mass eradication programs[1]. Requirements for mass treatment include high efficacy against all stages and the different species of parasites, only a few doses per treatment, low toxicity and chemical stability. It has been estimated that some 200 million people are infected with schistosomes, but none of the presently available schistosomicides appears to meet all criteria desired for use in mass treatment programs[1,2]. About 100 million persons in the world are estimated to be infected with intestinal cestodes[3,4] and economic loss through cestode infections in animals is considerable. While satisfactory advances have been made in the treatment of many adult cestode infections, no drug is available which acts against all cestode species, that are of importance in human and veterinary medicine, and treatment of larval stages still presents an unsolved problem. In this note we want to report the discovery of Praziquantel[5–7], a highly promising broad spectrum anthelmintic for oral or parenteral use.

Praziquantel has been synthesized in E. Merck company and came out of an extensive investigation of the pharmaceutical potential of substituted isoquinolines derived from Reissert-compounds. Its anthelmintic activity was found by Bayer AG[7]. Praziquantel is 2-cyclohexylcarbonyl-1,3,4,6,7,11b-hexahydro-2H-pyrazino [2,1-a] isoquinolin-4-one (**2** for R = Cyclohexyl). From a large number of pyrazinoisoquinolinones (**2**), Praziquantel has been selected for further trials on grounds of its excellent therapeutic index[7,8] in experimental schistosomiasis and cestodiasis.



1 **2**

Pyrazinoisoquinolinones (**2**) can be synthesized by different methods, for instance starting from the easily available N- [1.2.3.4-tetrahydroisoquinolyl-1-methyl] carboxamides (**1**)[9,10]. Acylation of **1** with chloroacetylchloride is followed by ring closure in the presence of strong bases. Praziquantel ($C_{19}H_{24}N_2O_2$, Mol.wt 312,42) is a colourless, almost odourless crystalline compound having a bitter taste. It is stable under normal conditions and melts at 136–139 °C (decomposition). It is soluble in most organic solvents (9.7 g/100 ml ethanol; 56.7 g/100 ml chloroform at 25 °C) and only sparingly soluble in water (0.04 g/100 ml at 25 °C). Its structure is in full agreement with the IR, NMR, mass spectra and elemental analysis. Praziquantel has excellent activity against all species of Schistosomes pathogenic to man[12–14]. In addition it proves highly effective in a single oral dose against all intestinal cestode species in man and a great variety of cestode species in animals, including Echinococcus[15,16]. Preliminary experiments indicate that it is also effective against various larval stages of cestodes[15]. Praziquantel was well tolerated in acute and subacute toxicity tests in various animals. No teratogenic or mutagenic activity has been observed[17,18]. Clinical testing is now under way around the world fully to evaluate the field efficacy of Praziquantel[16,19–23].

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The biting edges of the chelae and pereiopods of Austropotamobius pallipes[1]

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Summary. The 'biting edges' of the chelae and pereiopods of A. pallipes are made up of individual setae of a specialized structure. Those making up the edges of the chelate appendages are modified for prehension, those of the non-chelate appendages, for preening.

At the first hatchling stage of A. pallipes the biting edges of the chelae, first 2 pairs of pereiopods, and the dactyls of the third and fourth pair of pereiopods bear single rows of setal buds. These setal buds are simple outgrowths of the integument (figure, A) which after the first moult become fully developed setae (figure, B). In these early stages these setae are spaced well apart (figure A, and C). During the subsequent growth of A. pallipes, these setae not only dramatically change their form, but increase spectacularly in number and distribution (figure, C, compared to figure D, and E) to form the so called 'biting' edges of the chelae and pereiopods.

Even at the first hatchling stage it can be seen that the setae forming the 'biting' edges are different from other setae in that one side of the setal wall is thickened (figure, A and C). The thickened side of the setae becomes the functional surface as the hatchlings become independent of the mother and abandon their lecithotrophic mode of feeding. The increase in number of setae, together with the exaggerated development of their walls, bring them very close together creating the 'biting' edges in the adult animals (figure, D and E). It is worth noting that the constituent setae on the 'biting' edges of the chelae and chelate pereiopods differ in form and arrangement to those of pereiopods 3 and 4 (figure D, and E).

During feeding in A. pallipes all small prey, e.g. Tubifex, algae, and pieces of detritus are passed to the mouth by the first pair, aided sometimes by the second pair of chelate pereiopods. In addition they are used to clean the dorsal and ventral surfaces of the cephalathorax. The

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[1] Acknowledgments. To the Central Research Committee of the University of London who provided the financial assistance for this research work.