that are not oncogenically transformed (normal diploid rat smooth muscle and human lung fibroblasts), indicates that other processes are involved in transformation. Although all the cell lines contained 70- and 53-kD proteins detected with antisera against PDGF-1, the cells were heterogeneous with respect to size and intensity of other proteins detected with antisera to determinants predicted by the sequence of the PDGF-2 region. The nature of these differences is unknown. Generation of monoclonal antibodies against defined regions of PDGF, combined with pulse chase and partial digestion experiments, should help to resolve structural questions about the higher molecular weight forms of the molecule. Since these cells differ greatly in the rate of secretion of material that competes for binding to the PDGF receptor (*18, 21*), there may be cell-specific differences in the processing of intracellular PDGF-like molecules to activate secreted PDGF. Alternatively, the larger intracellular proteins reported here, although antigenically related to PDGF, may have functions other than as precursors to low molecular weight forms of PDGF (*22*).

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22. A preliminary report of these findings was presented at the Hybridoma Conference, San Diego, California (20 February 1984).
23. We thank B. Heilman for excellent technical assistance; R. Ross and E. Raines for providing purified PDGF; T. Hunter and L. Walker for providing cell lines; R. Seifert, R. Ross, T. Barrett, E. Benditt, and M. Murray for providing results prior to publication; and R. Lerner and D. Levy for helpful discussions. This work was supported in part by grants CA 25803 and HL18645 from the National Institute of Health and a grant from R. J. Reynolds, Inc. This is publication 3409MB from the Research Institute of Scripps Clinic.

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Pavoninins: Shark-Repelling Ichthyotoxins from the Defense Secretion of the Pacific Sole

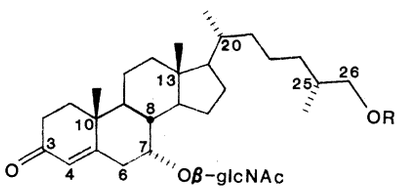
Abstract. *A series of ichthyotoxic and hemolytic steroid aminoglycosides, pavoninins-1 to -6, has been isolated from the defense secretion of the sole* Pardachirus pavoninus, *and their respective chemical structures have been established by spectroscopic studies and chemical conversions. The pavoninins exert repellent activity against sharks and are considered to be the factors responsible for the predator-repelling property of the sole.*

Certain fishes, called ichthyocrinotoxic fishes, secrete toxic substances that repel their predators (*1*). Among them, the Red Sea Moses sole *Pardachirus marmoratus* repels sharks presumably by emission of its toxic secretion at the moment when it is about to be bitten (*2*). Although isolation of an ichthyotoxic protein, pardaxin, from the sole has been reported (*3*), the actual source of the shark-repelling property is vague. We report here isolation and full characterization of six shark-repelling ichthyotoxins, pavoninins-1 to -6, from *P. pavoninus*, a kin of Moses sole, in the Western Pacific; this fish is also ichthyocrinotoxic (*4*).

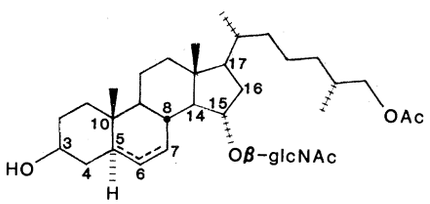
Seven individuals of *P. pavoninus* (20 to 30 cm long) were captured at the sandy bottom of a coral reef coast of Ishigaki Island, Ryukyu Archipelago, Japan; they were milked, on two successive days, by simply disturbing them. The secretion, collected along with some seawater, was lyophilized to yield 30 g of powder, which on resuspension in 0.1*M* aqueous ammonia and dilution with 10 volumes of acetone gave 10.7 g of a precipitate consisting mainly of proteinaceous substances. The solvent was removed from the filtrate, and the residue was partitioned between ethyl acetate and water; the toxicity resided in the ethyl acetate layer. Removal of the ethyl acetate yielded an oil (1.3 g), which was chromatographed on silica gel with a methanol-chloroform gradient (10:25) to yield 992 mg of mixed ichthyotoxins. This mixture was lethal to Japanese killifish *Oryzias latipes*; the lethal dose (killing 50 percent in 1 hour) was 8.5 μg/ml; and its hemolytic activity was comparable to that of saponin on rabbit erythrocytes. The total activity of the mixture accounted for 40 percent of the ichthyotoxicity and 80 percent of the hemolytic activity of the original lyophilized secretion, the remaining activity being present in the proteinaceous precipitate. Gel filtration of the precipitate has indicated that the activity is contained in the fraction having molecular weights of more than 10,000, possibly including pardaxin or related compounds.

Further silica-gel chromatography of the lipophilic ichthyotoxins yielded two

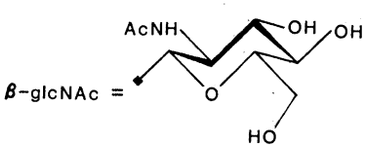
fractions, 145 and 617 mg. Reversed-phase column chromatography (*5*) of the smaller and less polar fraction gave a single major component, pavoninin-1 (**1**, 111 mg) with a specific rotation at 20°C ($[\alpha]_D^{20°}$) of +19° (1.1 g per 100 ml; *c*, 1.1, chloroform). The same method with the larger fraction gave pavoninin-2 (**2**, 34 mg), $[\alpha]_D^{29°}$ +31° (*c*, 1.6, ethanol), pavoninin-3 (**3**, 143 mg), $[\alpha]_D^{29°}$ +15° (*c*, 0.7, ethanol), and pavoninin-4 (**4**, 49 mg), $[\alpha]_D^{30°}$ +36° (*c*, 0.8, ethanol), in order of elution. In addition, a mixture of two compounds eluted between **2** and **3** was separated by 10 percent silver nitrate–impregnated silica-gel chromatography eluted with a mixture of 15 to 20 percent



1, R = Ac
2, R = H



3, 5-en-3α-ol
4, 3α-ol
5, 5-en-3β-ol
6, 6-en-3β-ol



methanol and ethyl acetate; the products were pavoninin-5 (**5**, 210 mg), $[\alpha]_D^{29°}$ +21° (*c*, 0.7, ethanol), and pavoninin-6 (**6**, 44 mg), $[\alpha]_D^{29°}$ −25° (*c*, 2.5, ethanol). The ichthyotoxicity of individual pavoninins, all isolated as amorphous solids, were practically equivalent to that of the unseparated mixture.

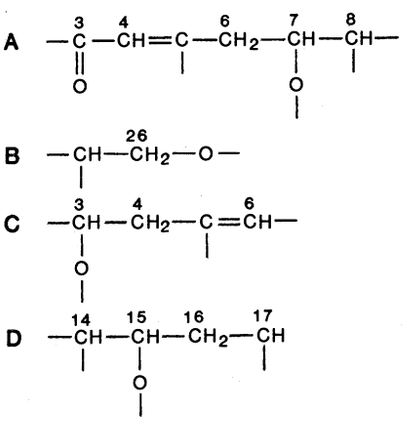
The structures of **1** to **6** were elucidated by chemical degradation and conversion. ^{1}H-Nuclear magnetic resonance (^{1}H-NMR) together with spectroscopic data of **1** indicated the presence of acetate and secondary acetamide groups (*6*, *7*), two tertiary and two secondary methyls, structural blocks **A**, with infrared; 1660 cm^{-1}; and ultraviolet in methanol, 244 nm (log ε, 4.1), and **B** (*6*). These functional groups together with ^{13}C-NMR (*7*) and secondary-ion mass spectrum data (*8*): *m/z* 662, $(M + H)^+$, led to a molecular formula $C_{37}H_{59}NO_9$ for **1**. Acid methanolysis of **1** (with 5 percent hydrogen chloride in methanol, 65°C, 5 hours) gave a ninhydrin-positive substance in the hydrophilic portion, which was identified as methyl α-D-glucosaminide by derivatization to its tri-*p*-bromobenzoate (*9*), circular dichroism (in methanol): $\Delta\epsilon_{232/252}$ +9/−20 (*10*). The lipophilic portion of the methanolysis product gave (25*R*)-26-hydroxycholesta-4,6-dien-3-one (**7**); electron-impact mass spectrum: *m/z* 398, base peak, M^+; ultraviolet (in methanol): 285 nm (conjugated dienone); infrared: 3400 and 1660 cm^{-1}. The structure **7**, including the entire stereochemistry, was established by catalytic hydrogenation (Pd/C) of the dienone system to (25*R*)-26-hydroxy-5β-cholestan-3-one; which was tosylated at the 26-hydroxyl; the tosylate was reduced with lithium aluminum hydride and subjected to Jones reoxidation at C-3 to provide 5β-cholestan-3-one, which was identical with an authentic sample.

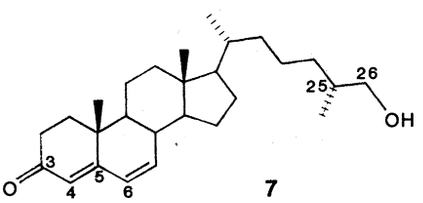
Upfield shifts in NMR signals of protons at C-26 from 3.85 to 3.94 ppm in **1** to 3.43 to 3.50 ppm in **7** show that the acetate is attached to C-26. The sugar is thus attached to the axial oxygen on C-7 (*11*). The C-25 configuration was determined by pertinent difference between the lanthanide-induced shifts of respective methoxyl peaks in the ^{1}H-NMR spectrum of the diastereomeric (2*R*)- and (2*S*)-2-methoxy-2-phenyl-2-trifluoromethylacetates (MPTA esters) prepared from **7** (*12*).

The structure of pavoninin-2 (**2**), field-desorption mass spectrum (FD-MS): *m/z* 620, $(M + H)^+$, was indicated by the ~0.5 ppm upfield chemical shifts of 26-protons, as compared to **1**, and obtaining the identical peracetate from **1** and **2**.

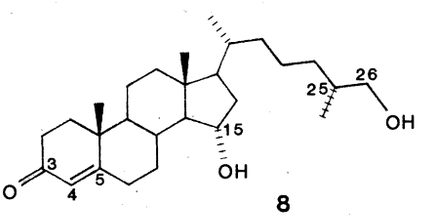
^{1}H-NMR studies of pavoninin-3 (**3**), FD-MS: *m/z* 664, $(M + H)^+$, clarified the presence of blocks **C**, in which 3-H appears at 3.95 (half-height width, 9 Hz), and **D**; in addition, as in **1**, β-glcNAc, an acetate, and block **B** were also present. The shift of the 3-equatorial proton at 3.95 to 4.98 ppm on peracetylation shows that the 3α-hydroxyl is free in **3**; that is, the sugar is on C-15. Acid methanolysis of **3** yielded (25*R*)-cholest-5-ene-3α,15α,26-triol, the ^{1}H-NMR decoupling studies of which made it possible to connect C-3 through C-17, including blocks **C** and **D**. Jones oxidation of **3** (*13*) followed by methanolysis to (25*R*)-15α,26-dihydroxycholest-4-en-3-one (**8**) and selective silylation (with *t*-butyldimethylsilyl chloride, immidazole, and neopentyl alcohol in *N,N*-dimethylformamide) gave 26-*O*-*t*-butyldimethylsilyl-**8**. Hydrogenation of the 26-*O*-silyl-**8** (Pd/C), followed by dehydroxylation at C-15 (with *O*-phenyl chlorothioformate in pyridine, then with tri-*n*-butyltin hydride and α,α′-azobisisobutyronitrile in toluene, 110°C, 12 hours) (*14*) and deprotection of the 26-hydroxyl (with 5 percent hydrogen chloride in methanol) yielded aforementioned (25*R*)-26-hydroxy-5β-cholestan-3-one, that is, tetrahydro-**7**.

The C-15 configuration for **3** was determined by application of the exciton chirality method (*15*) on the 26-*O*-silyl-**8** *p*-bromobenzoate. Namely, it gave a split circular dichroism (in acetonitrile):





7



8

p-bromobenzoate. Namely, it gave a split circular dichroism (in acetonitrile): $\Delta\epsilon_{228/247}$ +8/−12, which was due to the negative chirality between the enone and the *p*-bromobenzoate chromophores.

Spectroscopic similarities to **3** showed pavoninin-4 (**4**), FD-MS: *m/z* 666, $(M + H)^+$, to be a dihydro analog of **3**. ^{1}H- and ^{13}C-NMR spectra show its 10-methyl signals at 0.81 and 11.9 ppm, respectively, typical for 5α-steroids (*7*). The configuration of the 3-axial hydroxyl, ^{1}H-NMR: 3.94 ppm (half-height width 8 Hz; 3-H), is thus α.

The ^{1}H-NMR spectrum of pavoninin-5 (**5**) showed the 3-axial proton at 3.39 ppm (tt, 10, 4), but otherwise resembled that

of **3**. Jones oxidation (*13*) and subsequent methanolysis gave **8** as in the case of **3**, thus **5** is the epimer of **3** at C-3.

The proton system for the moiety C-6 to C-15 in pavoninin-6 (**6**) was clarified by ^{1}H-NMR studies. As in **4**, the 5α-proton and 3β-hydroxyl configurations are based on NMR data of 10-methyl, 0.79 and 11.7 ppm, and 3-proton, 3.55 ppm (tt, 10, 4). Hydrogenation of **6** (over platinum in acetic acid) gave dihydro-**6**, which was identical with one of the two hydrogenation products of **5**. Furthermore, Jones oxidation and subsequent methanolysis of both dihydro-**6** and **4** gave the identical (25*R*)-15α,26-dihydroxy-5α-cholestan-3-one. The conversions described above chemically correlate all six pavoninins and thus establish their full structures (*16*).

Exposure of the dog shark *Mustelus griseus* to pavoninins suggested that they are repellents that act on the shark's olfactory sense, whereas the proteinaceous toxin is possibly an antifeedant that acts on its gustatory sense. Tests based on termination of tonic immobility (TI tests) of the lemon shark *Negaprion brevirostris*, have been developed for screening potential shark repellents (*17*). According to preliminary TI tests, the pavoninins have been shown to be relatively strong repellents by acting on buccal receptors and possibly on the olfactory rosette at 5 mg/ml, a concentration well below that of pavoninins in the secretion discharged by the sole. In contrast to pavoninins, the common steroidal saponins are only weakly active in these tests (*18*). Since the amount of pavoninins available from the sole fish is insufficient to carry out proper biological tests, pavoninin-4 and a simpler model are now being synthesized in gram quantities from diosgenin (*19*). Detailed biological tests remain to be determined (*20*).

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4. E. Clark and A. George, *Envir. Biol. Fish.* **4**, 103 (1979); Y. Hashimoto, *Marine Toxins and Other Bioactive Marine Metabolites* (Japan Scientific Societies Press, Tokyo, 1979), p. 330.
5. Octylsilanized silica (Merck LiChroprep RP-8) eluted with 80 percent aqueous methanol.
6. The ^{1}H-NMR spectra were recorded on Nicolet NT-360 at 360 MHz in CD_3 OD (**1**–**6**) or $CDCl_3$ (derivatives). The data represent chemical shifts from tetramethylsilane in parts per million (multiplicity, coupling constants in hertz; assignments). For details see K. Tachibana, M. Sakaitanai, K. Nakanishi, *Tetrahedron*, in press.
7. ^{13}C-NMR spectra were recorded on Jeol FX100 at 25 MHz in D_3OD. Carbons were assigned by multiplicity of signals and comparison with published data of steroids [J. W. Blunt and J. B. Stothers, *Org. Magn. Reson.* **9**, 439 (1977)].
8. A. Benninghoven and W. K. Sichtermann, *Anal. Chem.* **50**, 1180 (1978).
9. With acetic anhydride and pyridine in methanol, then with *p*-bromobenzoyl chloride and *N,N*-dimethyl-4-aminopyridine in pyridine, 60°C, overnight.
10. Compare H. Liu and K. Nakanishi, *J. Am. Chem. Soc.* **103**, 5591 (1981).
11. Configurations at oxygenated methines, whether the oxygen is axially or equatorially attached, were derived from the ^{1}H-NMR coupling constants between the methine proton and its neighboring protons.
12. With (+)- or (−)-MPTA chloride in pyridine, 60°C. Induced shifts by 1.0*M* equivalent $Eu(fod)_3$ added to a solution of the diastereomeric mixture in $CDCl_3$: 0.68 ppm for the (+)-MPTA ester and 0.66 ppm for the (−)-MPTA ester; compare F. Yasuhara and S. Yamaguchi, *Tetrahedron Lett.* (1977), p. 4085.
13. Oxygen-free media and an immediate acid treatment were necessary to avoid overoxidation of the 5-en-3-one [C. Djerassi, R. R. Engle, A. Bowers, *J. Org. Chem.* **21**, 1547 (1956)].
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16. The glcNAc moieties of **3** to **5** were all characterized by ^{1}H-NMR studies as in **1**. In addition, ^{13}C-NMR and FD-MS data showed **3**, **5**, and **6** to be isomers to one another.
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18. TI tests were carried out by Dr. S. H. Gruber, Rosenstiel School of Marine and Atmospheric Science, University of Miami.
19. D. Repeta and T. Blizzard, Columbia University, unpublished results.
20. We thank T. Yoshino, Ryukyu University, for assistance in collecting the sole; the instrumental analysis team, this institute, for spectroscopic measurements: S. Uchida, director, Okinawa Expo Aquarium, for assistance in the shark assay, and S. H. Gruber for the TI tests.

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Growth Inhibitor from BSC-1 Cells Closely Related to Platelet Type β Transforming Growth Factor

Abstract. *Purified growth inhibitor from BSC-1 cells and type β transforming growth factor from human platelets are shown to have nearly identical biological activity and to compete for binding to the same cell membrane receptor. These findings suggest that the growth inhibitor and the type β transforming growth factor are similar molecules. The data also show that the same purified polypeptide can either stimulate or inhibit cell proliferation depending on the experimental conditions.*

The regulation of the growth of cells in culture is a highly complex process in which the cells interact with growth-inhibitory and growth-stimulatory polypeptides as well as with nutrients and ions. African green monkey kidney cells (BSC-1) produce a polypeptide growth inhibitor (GI) when arrested at saturation density (*1*). This GI has been purified from medium conditioned by these cells and shown to cause arrest of the same cells at low density in the G_1 phase of the cell cycle (*2*). Similar effects of the GI have also been observed with certain lung and mammary cell lines but not with Swiss mouse 3T3 cells or human skin fibroblasts (*2, 3*).

Transforming growth factors (TGF's) are operationally defined as polypeptides that stimulate anchorage-dependent cells to grow in soft agar and have been detected in neoplastic and non-neoplastic cells in culture and in tissues in vivo (*4*). Two types of TGF have been purified: TGFα, which binds to the epidermal growth factor (EGF) membrane receptor (*5*), shows significant sequence homology with both mouse and human EGF (*6*), and has biological activities similar to those of EGF when purified free of TGFβ (*7*); and TGFβ, a different molecule that is a potent growth stimulator of mouse embryo-derived AKR-2B cells in soft agar with or without added EGF (*8*) and of rat kidney-derived (NRK) cells when added in the presence of EGF (*4*). However, TGFβ has been reported to have little or no mitogenic activity for NRK (*9, 10*) or AKR-2B (*11*) cells in monolayer culture. Recently, TGFβ has been shown to have specific membrane receptors on responsive cells (*12*).

Both the GI (*2*) and TGFβ (*9*) were shown by sodium dodecyl sulfate–polyacrylamide gel electrophoresis to have apparent molecular weights in the 24,000 to 26,000 range and, when reduced with β-mercaptoethanol, exhibit a single band at approximately 12,500. The apparently similar molecular weights and subunit composition of the GI and TGFβ, the observation that TGFβ occurs widely (*4*), and initial data indicating that TGFβ is actually inhibitory for EGF- and insulin-stimulated mitogenesis in serum-free monolayer cultures of AKR-2B cells, suggest that the GI and TGFβ may be the same molecule. We now show that GI purified from medium conditioned by BSC-1 cells and TGFβ purified from human platelets have almost identical biological activities in stimulation of the