Chemistry and Ecology of Toxic Birds

Stefan Bartram and Wilhelm Boland*[a]

KEYWORDS:

alkaloids · batrachotoxins · chemical defense · chemical ecology · neurotoxins

Although many birds are regarded to be unpalatable and/or malodorous,[1] the toxicity of birds was long ignored and up to now only a few examples are known. Nevertheless, one unique case of a "toxic bird" is known since antiquity. In the *Book of Numbers*, Moses reports the death of numerous Israelites after the consumption of quail during their exodus from Egypt.[2]

31 *Now there went forth a wind from the LORD and it brought quail from the sea, and let them fall beside the camp, about a day's journey on this side and a day's journey on the other side, all around the camp and about two cubits deep on the surface of the ground.*

32 *The people spent all day and all night and all the next day, and gathered the quail (he who gathered least gathered ten homers) and they spread them out for themselves all around the camp.*

33 *While the meat was still between their teeth, before it was chewed, the anger of the LORD was kindled against the people, and the LORD struck the people with a very severe plague.*

34 *So the name of that place was called Kibroth-hattaavah, because there they buried the people who had been greedy.*

According to Pliny the Elder (23 – 79 A.C., *Naturalis historia*) poisoning by quails was also rather common in the Roman Empire and, therefore, their consumption was banned during the 1st century. The origin of this disease called coturnism (human poisoning after eating European migratory quail (*Coturnix coturnix* L.))[3] remained unknown for a long time. As a matter of fact, quails are only toxic during migration and, curiously enough, only in certain flight directions. In the western flyway, across West Africa to Europe, quail are poisonous on their way from Africa to Europe. On their eastern route from the Great Lake region of East Africa to Europe, the birds are not toxic in spring, but clearly when they return to Africa in autumn.[3] Owing to this strict link of quail toxicity to the migratory behaviour, the toxic principle is obviously ingested during migration. With respect to the symptoms of coturnism (like, for example, muscle pain, lower limb paralysis, vomiting, and discoloured urine due to myoglobinuria),[3] already medieval writers proposed feeding on henbane (*Hyoscyamus niger*), aconite (*Aconitum napellus*), hellebore (*Veratrum* ssp.) or hemlock (*Conium maculatum*) to be responsible for the birds' toxicity. Although there is, as yet, no rigorous proof for the molecular basis of coturnism, recent analyses of typical quail crops identified a wide variety of seeds potentially toxic to humans, among them *Ballota nigra*, *Galeopsis* sp., *Hyoscyamus niger*, *Lathyrus* sp., *Lolium* sp. and *Stachys annua*.[3] Considering the seasonal – geographical pattern of the coturnism outbreaks, today's research focuses on *Stachys annua* which exhibits a geobotanical differentiation in annual growth cycles coinciding with the coturnism seasons.[3]

The seasonal toxicity of the European migratory quail is not unique. Currently about thirteen bird species are known or believed to be toxic.[1, 4] Some of the better documented examples are compiled in Table 1. The spur-winged geese endemic to the African Niger river area display an interesting defense. The birds feed on beetles from the family of *Meloidae* that produce cantharidin (Figure 1).[4] Cantharidin, known since antiquity as an aphrodisiac, is highly toxic, causes blistering upon skin contact and may lead to

Table 1. *Bird species reported to be toxic.*[1, 4]

Bird species		Toxin	Origin	Geographic distribution
European migratory quail	*Coturnix coturnix*	unknown	unknown	Africa/Europe
hooded pitohui rusty pitohui variable pitohui black pitohui	*Pitohui dichrous* *Pitohui ferrugineus* *Pitohui kirhocephalus* *Pitohui nigrescens*	batrachotoxins	unknown	New Guinea
blue-capped ifrita	*Ifrita kowaldi*	batrachotoxins	unknown	New Guinea
spur-winged goose	*Plectropterus gambensis*	cantharidin	beetles (*Meloidae*)	North Benin
red warbler	*Ergaticus ruber*	unidentified alkaloids	unknown	Mexico
ruffed grouse	*Bonasa umbellus*	andromedotoxin	mountain laurel (*Kalmia latifolia*)	North America
brush bronzewing common bronzewing	*Phaps elegans* *Phaps chalcoptera*	monofluoroacetate (?)	*Gastrolobium* spp. *Oxylobium* spp.	Australia

[a] *Prof. Dr. W. Boland, Dr. S. Bartram*
Max-Planck-Institut für Chemische Ökologie
Carl-Zeiss-Promenade 10, 07745 Jena (Germany)
Fax: (+49) 3641-643670
E-mail: boland@ice.mpg.de

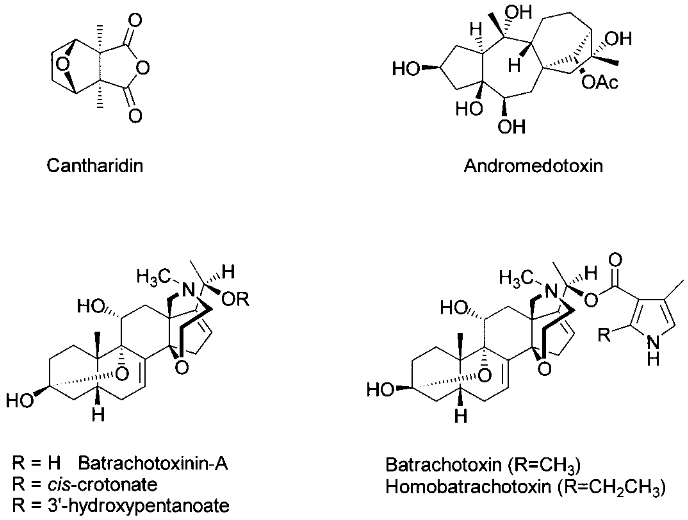


Figure 1. *Toxic compounds isolated from "toxic birds".*

death when ingested in rather low concentrations. Cantharidin is a potent inhibitor of the protein phosphatase A2 (PPA2), which is involved in the dynamic process of protein phosphorylation and dephosphorylation controlling intracellular signalling and regulation.[5]

However, the most spectacular report on a "toxic bird" providing the first unequivocal identification of a toxic principle was published in 1992 by Dumbacher et al.[6] During collection and handling of the hooded pitohui (*Pitohui dichrous*) (Figure 2), endemic in New Guinea, the authors recognised that contact with skin and feathers caused numbness, burning and sneezing. Native New Guineans referred to this species as "rubbish birds" and avoided the bird due to its bitter taste and allergenic potential; people may become nauseated from simply smelling the bird.[7] Chemical analysis of feathers, skin and other tissues of several species of the genus *Pitohui* (family Pachycephalidae) revealed the presence of the highly potent neurotoxin homobatrachotoxin (Figure 1).

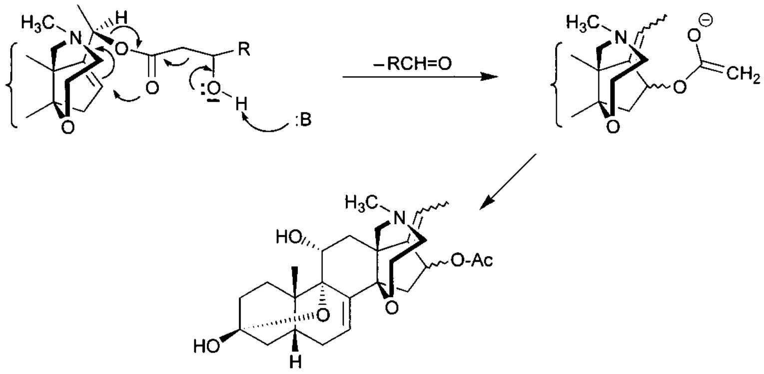
Figure 2. *Picture of a* Pitohui *bird (*Pitohui dichrous*) from New Guinea. (Photograph: J. Dumbacher. Reproduced with permission from ref. [14]. Copyright 2000 Wissenschaftliche Verlagsgesellschaft mbH.)*

Homobatrachotoxin is a member of a family of steroidal alkaloid toxins, collectively called batrachotoxins, which belong to the most potent of all naturally occurring nonprotein poisons known for vertebrates.[8] Batrachotoxins bind to the receptor site II of voltage-dependent sodium channels in a wide variety of tissues and depolarise electrogenic nerve, cardiac and skeletal muscle membranes in nearly every vertebrate and invertebrate tested so far.[8] Binding results in a persistent activation of the channel, thus leading to depolarisation of the cell. Observed symptoms in mice include strong muscle contractions, violent convulsions, salivation, and dyspnoea and death even at doses of less than 0.1 μg per individual. Interestingly, the terpenoid andromedotoxin (Figure 1, Table 1), supposed to be responsible for the occasional toxicity of the American ruffed grouse (*Bonasa umbellus*) in the winter, has the same target and has also caused human death.[4]

Prior to the isolation from feathers of the pitohui, batrachotoxins were considered to be unique to neotropical poison-dart frogs of the genus *Phyllobates*.[8] The skin of these brightly coloured frogs (family Dendrobatidae) was widely used by the indians from the Choco region in Colombia for poisoning of blowgun darts. Frogs removed from their natural environment lost their toxicity, indicating that the animals are not capable of synthesising the toxins de novo. The second generation of frogs raised in captivity were completely nontoxic, but rapidly accumulated dietary alkaloids unchanged in their skin glands,[9] supporting the idea that the wild frogs acquire their toxins from an, as yet, unknown dietary arthropod.[8]

The levels of homobatrachotoxin in pitohuis are up to three orders of magnitude lower than in the frog skin and differ between the individual species listed in Table 1. The highest amount (>80%) of the toxin was found in the skin of the hooded pitohui, ca. 13% were associated with the feathers and less than 4% with the muscles and other tissues. More recent analyses of extracts from feather and skin of the *Pitohui* birds by HPLC-CIMS (CIMS = chemical-ionization mass spectrometry) revealed the presence of additional batrachotoxin congeners (Figure 1) not previously described.[10] Besides batrachotoxinin-A, the corresponding crotonate and the 3′-hydroxypentanoate were identified as new compounds in freshly extracted skin. The crotonate, under base catalyis, can add water to give a hydroxybutanoate in a biomimetic (?) fashion and cleave directly by a retro-aldol process to give the acetate of the starting compound or undergo a concerted [3,3] sigmatropic rearrangement to afford the acetate of likely pseudoaxial conformation (Scheme 1).

The HPLC-MS approach also led to the discovery of a second poisonous bird from New Guinea, the passerine bird *Ifrita kowaldi*.[10] This bird displays a similar spectrum of batrachotoxins, but is not



Scheme 1. Base-catalyzed rearrangement of batrachotoxinin-A crotonate.

related to the pitohui. The amounts and relative proportions of batrachotoxins may differ widely among the different species and, especially, among their habitats. In some areas of New Guinea, pitohuis seem to be not poisonous at all.[4, 10] These findings clearly reflect the situation of the poison-dart frogs, quails and goose and are, again, indicative of sequestration of the toxin from the diet. However, as is true for poison-dart frogs, the source of the toxin is still a mystery.[7, 9] No batrachotoxin-related alkaloids were detected in the stomach of *Pitohui* or *Ifrita* specimens, and no alkaloids were detected in ants, termites, millipedes, earthworms and grasshoppers belonging to the diet of the *Pitohui*.[10]

The accumulation of toxins in feathers and skin is assumed to protect the birds against predators such as rodents, snakes, raptors or arboreal marsupials. Pitohuis emit a sour odour (see above) and are brightly coloured (as are the poison-dart frogs). The wings, tail and head of the variable pitohui (*P. kirhocephalus*) are black, the remaining portions of the body display a contrasting orange-brown. The strong odour along with the conspicuous plumage may, therefore, serve as aposematic signals to predators.[10] Studies with other birds displaying a similar conspicuous plumage clearly showed a negative correlation between visibility and edibility.[11]

Owing to the high level of the toxins in the breast and belly feathers, the compounds may be also transferred to the eggs or nest material for protection against egg-eating predators. The toxins are clearly active against ectoparasites since *Pitohui* birds display the second lowest infection rate by ticks of all thirty passerine genera that have been examined.[12] Homobatrachotoxin has also a strong effect on chewing lice.[13]

It is surprising that such phylogenetically and geographically different species such as toxic birds from New Guinea and poison-dart frogs from Colombia and Central America have independently evolved the ability to sequester and to tolerate the extremely neurotoxic batrachotoxins. The frogs appear to be insensitive towards their own toxins due to a genetically controlled modification of their sodium channel protein in the nerves and muscles.[9] The molecular basis for the resistance of *Pitohui* and *Ifrita kowaldi* is still unknown, but the evolution of a similar mechanism appears to be highly likely.

[1] P. J. Weldon, J. H. Rappole, *J. Chem. Ecol.* **1997**, *23*, 2609 – 2633.
[2] The Bible, Num. 11: 31 – 34.
[3] D. C. Lewis, E. S. Metallinos-Katsaras, L. E. Grivetti, *J. Cult. Geogr.* **1987**, *7*, 51 – 65.
[4] J. P. Dumbacher, S. Pruett-Jones in *Current Ornithology* (Eds.: V. Nolan, Jr., E. D. Ketterson), Plenum, New York, **1996**, pp. 137 – 174.
[5] Y. M. Li, J. E. Casida, *Proc. Natl. Acad. Sci. USA* **1992**, *89*, 11 867 – 11 870.
[6] J. P. Dumbacher, B. M. Beehler, T. F. Spande, H. M. Garraffo, *Science* **1992**, *258*, 799 – 801.
[7] J. M. Diamond, *Nature* **1992**, *360*, 19 – 20.
[8] J. W. Daly, *J. Nat. Prod.* **1998**, *61*, 162 – 172.
[9] J. W. Daly, C. W. Myers, J. E. Warnick, E. X. Albuquerque, *Science* **1980**, *208*, 1383 – 1385.
[10] J. P. Dumbacher, T. F. Spande, J. W. Daly, *Proc. Natl. Acad. Sci. USA* **2000**, *97*, 12 970 – 12 975.
[11] F. Götmark, *Behav. Ecol. Sociobiol.* **1997**, *40*, 41 – 49.
[12] K. N. Mouritsen, J. Madsen, *Oikos* **1994**, *69*, 357 – 358.
[13] J. P. Dumbacher, *Auk* **1999**, *116*, 957 – 963.
[14] D. Mebs, *Gifttiere. Ein Handbuch für Biologen, Toxikologen, Ärzte und Apotheker,* 2nd ed., Wissenschaftliche Verlagsgesellschaft, Stuttgart, **2000**, p. 333.