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SOME NEW MYCOTOXINS

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Abstract - The advances on the structural chemistry of some recently discovered mycotoxins, *e.g.* the tremorgens, cytochalasins, austocystins, tetramic acids, azaphilones and cyclic peptides are briefly reviewed.

INTRODUCTION

Mycotoxins are secondary fungal metabolites which cause a variety of acute or chronic toxicological manifestations in susceptible animals. These toxins occur sporadically in fungal cultures and are complex and diverse in structure and have no obvious utility for the cells which produce them. These hazardous compounds are produced by a consecutive series of enzyme-catalyzed reactions which are related to and make use of the intermediates of primary metabolism. The majority of mycotoxins are formed from either the polyketide route (aflatoxins), the terpenoid route (trichothecanes), the biosynthesis of the amino acids (fumitremorgens) or from the intermediates of the tricarboxylic acid cycle (rubratoxins) (1). The structural complexity of these molecules makes it impossible to speculate on their biological activity. Fortunately, some short term tests are now available with a high predictive value for mammalian carcinogens (2).

The importance of mycotoxins to the public health and agricultural economy, especially in countries with higher humidities and temperatures, becomes evident from the well documented history of the epidemics of ergotism, alimentary toxic aleukia, stachybotryotoxicosis, yellowed rice toxicosis, facial eczema and particularly aflatoxicosis. The hepatocarcinogen, aflatoxin introduced the quantitative phase in mycotoxin research and clearly stimulated subsequent investigations with the resulting rapid increase in the number of papers describing mycological, chemical, toxicological and epidemiological aspects of mycotoxins.

The wide distribution of toxinogenic fungi and the possible existence of new mycotoxins are evidenced by the pertinent reports on the microflora of foods and feeds and those from material incriminated in mouldy feed poisoning of farm animals. A scientific assessment of the public health significance of these new mycotoxins would require data of both the level of exposure and the association of that exposure with a specific disease entity. A chemical approach is, therefore, a prerequisite for these studies - this paper highlights progress made on the structural chemistry of the recently studied mycotoxins.

COMPOUNDS WHICH ACT UPON THE CENTRAL NERVOUS SYSTEM (CNS)

Citreoviridin, a carbocyclic polyene metabolite of several *P. spp.** affects the CNS and causes ascending paralysis to experimental animals, sometimes followed by convulsions and respiratory arrest. Citreoviridin, however, does not cause trembling in animals. The same symptoms were observed in the case of acute cardiac beri-beri, a disease which was reported to have occurred in Japan. Citreoviridin was recently reviewed by Ueno (3).

There is one common feature among all of the subsequent nitrogen-containing metabolites which affect the CNS, namely the presence of tryptophan as a pivotal biosynthetic unit, *e.g.* the ergot alkaloids. These metabolic products of several *Claviceps* spp. have a broad action spectrum including central, neurohumoral and peripheral effects. The ergot toxins have been adequately reviewed (4,5) and are excluded from this paper.

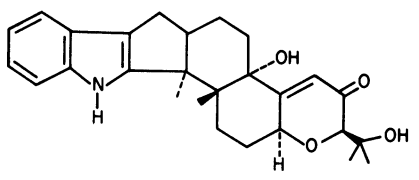
Compounds which contain one N atom

Penitrem A was initially isolated from *P. crustosum* (6); Ciegler and Pitt (7) established

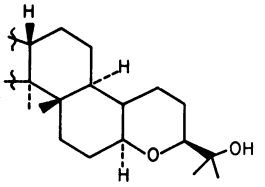
* In this paper *Penicillium*, *Aspergillus* and *Fusarium* are abbreviated as *P.*, *A.* and *F.*, respectively.

that its intense production was confined to strains of *P. crustosum*, *P. granulatum*, *P. cyclopium* and *P. palitans*. The large scale production, purification and spectral properties (^{1}H and $^{13}CNMR$) of penitrem A were recently reported (8). Its structural elucidation, however, remains a challenging problem. Its UV data indicated the presence of a substituted monomeric indole nucleus. The dechloro-analogue, penitrem B and penitrem C were recently isolated (9).

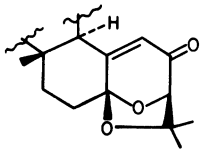
The structures of paxilline (10) and of paspalinine (11) were recently reported. These tremorgens are derived from the metabolism of *P. paxilli* and are closely related to the alkaloids, paspalicine and paspaline, isolated from *Claviceps paspali* (12). These metabolites are formed from one tryptophan unit and several mevalonate units.



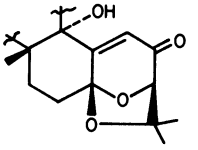
Paxilline



Paspaline



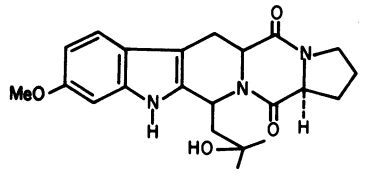
Paspalicine



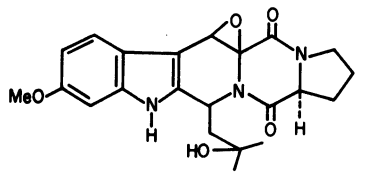
Paspalinine

Cyclic peptides

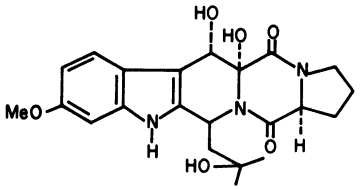
Crude extracts of *A. fumigatus* caused strong tremorgenic action in mice (13). Fractionation led to the isolation of fumitremorgen A (14), fumitremorgen B (15), fumitremorgen C (16) and epoxy-fumitremorgen C (17); their structures are based on X-ray crystallography. The related verruculogen TR_1 was isolated from *P. verruculosum* (18) and from *A. caespitocus* which also produces fumitremorgen B (19); we have also observed the production of TR_2 (20) from the latter fungus. These findings corroborate the biosynthetic relationships of these compounds. Brevianamide A (21) was the first known member of this growing number of fungal dioxopiperazines biogenetically derived from tryptophan, proline and one or more unit of mevalonic acid. Steyn (22) isolated the related austamide and its congeners from *A. ustus*, including the apparent common precursor of brevianamide A and austamide, *viz.* *cyclo*-L-2-(1,1-dimethylallyl)tryptophanyl-L-proline. The inital cyclic precursor of brevianamide A, *viz.* *cyclo*-L-tryptophanyl-L-proline was found to be incorporated intact into brevianamide A (23).



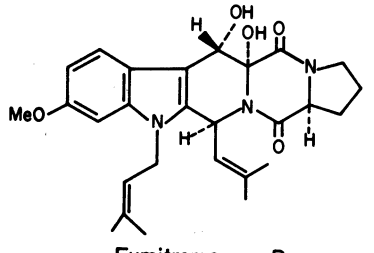
Fumitremorgen C



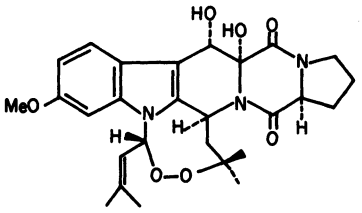
Epoxy-fumitremorgen C



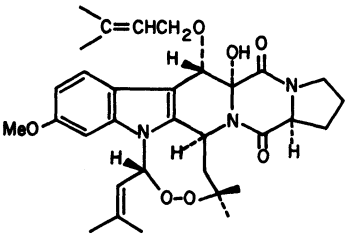
TR_2



Fumitremorgen B

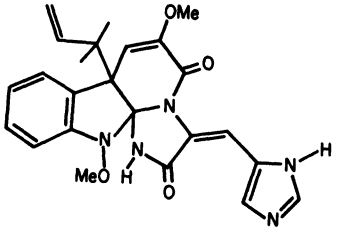


Verruculogen TR_1

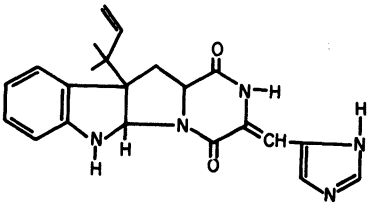


Fumitremorgen A

Scott *et al.*(24) isolated roquefortine from cultures of *P. roqueforti*. Roquefortine exhibits neurotoxic properties and was found in samples of blue cheese (25). *P. roqueforti* is used in the production of Roquefort cheese. Roquefortine is obviously biogenetically related to oxaline, a novel alkaloid from several strains of *P. oxalicum* (26). Oxaline contains tryptophan and histidine as the main structural units, linked in a most unusual fashion.

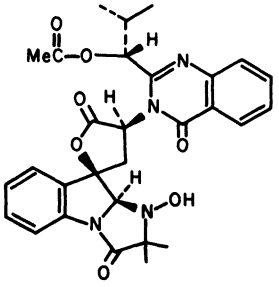


Oxaline

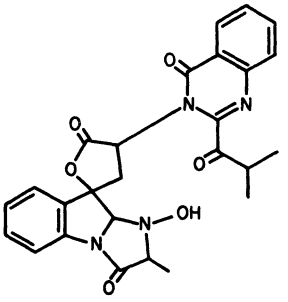


Roquefortine

A toxinogenic strain of *A. clavatus* was found to produce three toxins *viz.* cytochalasin E, tryptoquivaline and tryptoquivalone (27). The structures of the latter two tremorgen-producing metabolites were elucidated by X-ray crystallography of the *p*-bromophenacyl urethane derivative of tryptoquivaline and subsequent comparison of their spectroscopic properties. These novel tetrapeptides appear to be biogenetically derived from tryptophan, anthranilic acid, valine and methylalanine (or alanine).



Tryptoquivaline

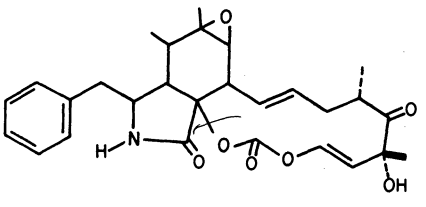


Tryptoquivalone

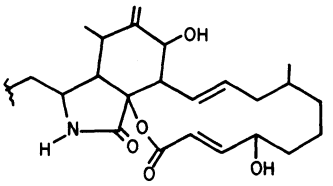
TOXIC CYTOCHALASINS

The cytochalasins and chaetoglobosins comprise a unique group of metabolites. Their biological (28) and chemical characteristics (29) were recently reviewed. These compounds are related by certain shared structural features and an analogous biosynthetic origin [phenylalanine (cytochalasins) or tryptophan (chaetoglobosins) linked to a polyketide chain]. All the cytochalasins inhibit cytoplasmic cleavage in cultured mammalian cells as well as cell movement, and the most curious of all is the phenomenon of nuclear extrusion. Only those compounds with established *in vivo* toxicity will be discussed.

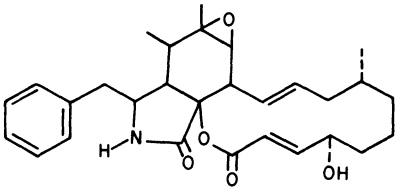
Cytochalasin B was one of the first characterized members of this group. We have found that it is contributing to the toxigenicity of *Phoma exigua*. Büchi *et al.* (30) solved the structure of cytochalasin E by X-ray crystallography of its silver complex. Cytochalasin E is unusual in containing a vinyl carbonate moiety. In experimental animals, it appears to act directly on the walls of the blood capillaries permitting extravascular effusion of plasma fluid, albumin and globulin; cause of death is apparently due to shock.



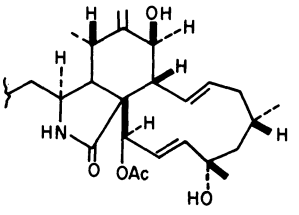
Cytochalasin E



Cytochalasin B



Cytochalasin F



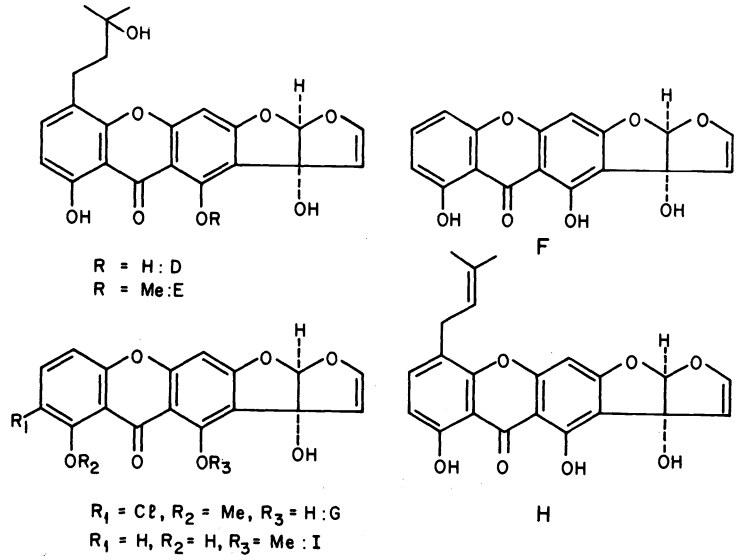
Cytochalasin H

Cytochalasin H is a potent [11]-cytochalasin which is produced by an unidentified *Phoma* spp. (31). Two toxic metabolites, kodo-cytochalasin-1 and kodo-cytochalasin-2 were isolated from *Phomopsis paspali*, a toxinogenic fungus from Indian Kodo millet (32). However, it should be noted that kodo-cytochalasin-1 is identical to cytochalasin H.

The chaetoglobosins were initially investigated due to the effect of polynucleation and multipolar division of HeLa cells. Recently chaetoglobosin A was found to be acutely toxic to mice with LD_{50} values similar to those reported for cytochalasin E (33).

BISDIHYDROBENZOFURAN METABOLITES

Sterigmatocystin, a pale yellow hepatocarcinogen, is produced by several *A.* spp. and contains a xanthone nucleus linked in an angular fashion to the dihydrofuro[2,3-b]benzofuran ring system. The latter system is present in a number of derivatives of sterigmatocystin; the aflatoxins; the versicolorins and austocystins. The biosynthesis of averufin, sterigmatocystin and aflatoxin B_1 was studied in detail in our laboratory (34). The results indicated a C_{20} polyketide precursor which is then converted into averufin→sterigmatocystin→aflatoxins.



The Structures of Austocystins D-I

Fractionation of toxic extracts of *A. ustus* gave averufin and versicolorin C and in addition nine new xanthones, which are collectively called the austocystins (A-I) (35,36). Novel features of the austocystins are the linear fusion of the xanthone and bisdihydrofuran moieties and the frequent presence of either an isopentyl side-chain or a chlorine atom. The *cis*-ring fusion of the bisdihydrofuran unit is well established; comparison of the c.d. spectrum of (3*a*-R, 12*c*-S)-sterigmatocystin with those of the austocystins confirms the proposed absolute configuration as shown in the formulae.

The cytotoxicity of these compounds was evaluated by exposing confluent layers of primary kidney epithelial cells of *Cercopithecus aethiops pygerythrus* to austocystins A-F and sterigmatocystin (37). These criteria led to a tentative classification in terms of decreasing toxicity: austocystin A>C>B>sterigmatocystin>austocystin F>E>dihydroaustocystin A. The most toxic compounds caused severe lesions in the cells (nucleolar segregation) an indication of disturbed nucleic acid metabolism. In analogy with the findings on aflatoxin and sterigmatocystin, it was observed that austocystins containing the vinyl ether moiety were the most toxic.

MYCOTOXINS WHICH CONTAIN THE β-TRICARBONYL MOIETY

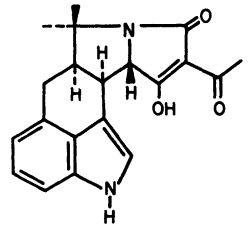
Cyclopiazonic acid

P. cyclopium and *P. viridicatum* appear to be the most important toxinogenic fungi among the *P.* spp. in terms of occurrence in feeds and foods (38). Holzapfel (39) characterized cyclopiazonic acid (αCA) as the main toxin from several South African strains of *P. cyclopium*. Radiolabelling experiments established that αCA is formed from tryptophan *via* α-acetyl-γ-(β-indolyl)methyltetramic acid and bissecodehydrocyclopiazonic acid (βCA). The enzyme which utilizes DMAPP and the above tetramic acid to furnish βCA has been isolated (40). Furthermore, the five iso-enzymes of the enzyme responsible for converting βCA into αCA were isolated from the mycelium of *P. cyclopium* (41). Steyn *et al.* (42) investigated the stereochemistry of the final cyclization step and observed a stereospecific loss of the pro-3S-proton. The formation of the new C-C bond, therefore, occurs from the opposite side of the molecule to proton removal.

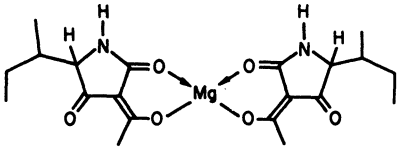
Viridicatumtoxin

Hutchison *et al.* (43) isolated viridicatumtoxin, a pale yellow pigment, as the only significant toxin from South African strains of *P. viridicatum*. In rats, hyaline droplet degeneration of the myocardium, renal tubular necrosis and changes in the hepatocytes were observed. Derivatisation and degradation of viridicatumtoxin gave mostly intractable mixtures except for the facile preparation of its diacetate. A single crystal X-ray analysis of viridicatumtoxin was undertaken by direct methods applying the quartet invariants approach (44). It contains the β-tricarbonyl moiety and is structurally related to the tetracyclines. A novel structural feature is the spiro arrangement of the two isoprenoid units giving rise to the additional two rings. The X-ray structure indicates that the spiro cyclohexene ring has a half-chair conformation.

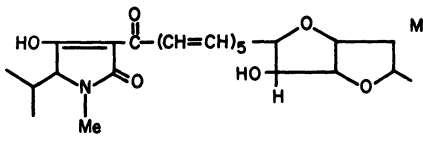
Pohland and Stack (45) reported that the toxicity of some strains of *P. viridicatum*, isolated in the United States of America, was due to viomellein and xanthomegnin.



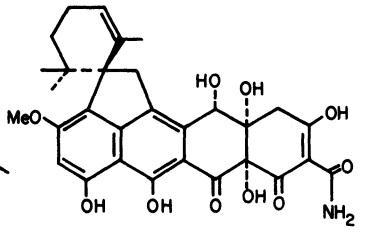
Cyclopiazonic acid



Magnesium Tenuazonate Complex



Erythroskyrine



Viridicatumtoxin

Tenuazonic acid

Phoma sorghina, an ubiquitous fungus in the tropical and subtropical regions has been implicated in the aetiology of onyalai, a haematologic disorder among Black African populations living south of the Sahara (46). Steyn and Rabie (47) recently investigated a toxinogenic culture of *Phoma sorghina*. Extraction, solvent partition and column chromatography gave the covalent magnesium-and calciumtenuazonates as the toxic components. Tenuazonic acid is biologically highly active and was previously investigated for its antineoplastic and antiviral properties, and extensively for blocking of the peptide bond formation during protein synthesis. Its role in haematologic disorders requires further study. Tenuazonic acid is a common metabolite and is frequently produced by *Alternaria alternata* and *Pyricularia oryzae*, the latter being the causal fungus in the rice blast disease.

Tetramic acids (*e.g.* tenuazonic acid and cyclopiazonic acid) may play an important role in the control mechanism of fungi by complexation with bivalent cations; their toxic effects in animals may also be related to these properties. Magnesidin is a magnesium-containing antibiotic which is produced by *Pseudomonas magnesiorubra* (48). In magnesidin, the magnesium is linked to complex tetramic acids, therefore, related to the above complexes.

Erythroskyrine

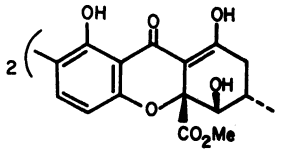
This metabolite is produced by *P. islandicum*, the fungus implicated in yellowed rice toxicosis. It contains a similar β-triketonic lactam involving N-methylvaline, a polyene system and a bicyclic oxygen-containing system. Its toxicity was recently studied by Ueno *et al.* (49).

HIGHLY OXYGENATED COMPOUNDS

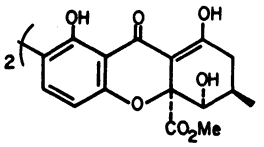
Highly oxygenated compounds are certainly the most frequently encountered and best known mycotoxins (aflatoxins). However, only a few will be discussed; several toxins *e.g.* terreic acid, fumagitin, spinulosin, moniliformin, desmethoxyviridiol, viriditoxin, altenuisiol and alternariol are omitted.

Ergochromes

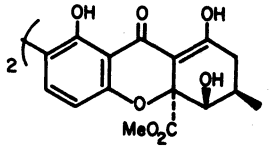
These compounds comprise a group of closely related bis(hexahydroxanthonyl) pigments elaborated mainly by the parasitic fungus *Claviceps purpurea*. The first production of an ergochrome, secalonic acid D as the mycotoxin from a saprophytic mould, *P. oxalicum*, was reported by Steyn (50). Yamazaki *et al.* (51) subsequently isolated secalonic acid A, the antipode of secalonic acid D from *A. ochraceus*. *Phoma terrestris* similarly produced secalonic acids A and E (52). Wells *et al.* isolated emodin as the diarrheagenic toxin from cultures of *A. wentii* (53). Emodin is the established precursor of the ergochromes.



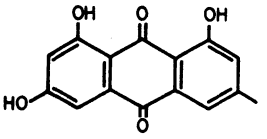
Secalonic acid D



Secalonic acid A



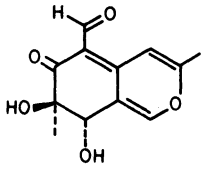
Secalonic acid E



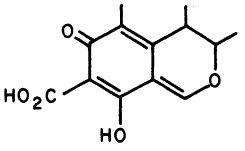
Emodin

Azaphilones

Austdiol was characterized by Vleggaar *et al.* (54) as the main toxic component from *A. ustus*. It is a gastro-intestinal toxin and the first reported toxic azaphilone. The structure was deduced from physico-chemical data and the absolute configuration established by the method of Horeau and X-ray crystallography. These data were employed to deduce the absolute configuration of all known azaphilones (55). Austdiol is related biogenetically to the mycotoxin, citrinin. Citrinin is a known nephrotoxin which furthermore impairs the normal liver metabolism. Dietary citrinin also results in increased water consumption and severe diarrhea in chickens.



Austdiol



Citrinin

CYCLIC PEPTIDES

A number of cyclic peptides have been investigated due to their biological activity. A well known compound in this category is tentoxin, isolated from *Alternaria tenuis* (56). This cyclic peptide induces chlorosis in germinating seedlings of many cotyledonous plant species.

The malformins (A_1, A_2, B_1, B_2 and C) are metabolites from *A. niger*. They induce malformations in plants, inhibit adventitious root formation, have antibacterial and cytostatic properties and under some conditions stimulate plant growth. Malformin C, a highly toxic metabolite, was isolated from a strain of *A. niger* collected from mould damaged rice. It was established to be the disulfide of *cyclo*-D-cysteinyl-D-cysteinyl-L-valyl-D-leucyl-L-leucyl. (57). The amino acid sequencing was done using gas chromatographic mass spectrometry.

The best known compound in this category is certainly cyclochloritine, the water-soluble toxin from *P. islandicum*, the fungus implicated in toxic yellowed rice. Enemoto and Ueno (58) described cyclochloritine as a 'periportal toxic agent'.

CONCLUSION

It is impossible to present a comprehensive report on such a wide subject within the scope of this paper. From the foregoing it is evident that nature has endowed us with a rich variety of complex and interesting metabolites. The significance of these newly discovered mycotoxins in naturally occurring intoxications are not yet known. However, these compounds afford new challenges to the structural organic chemist and are useful tools in biochemical research.

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