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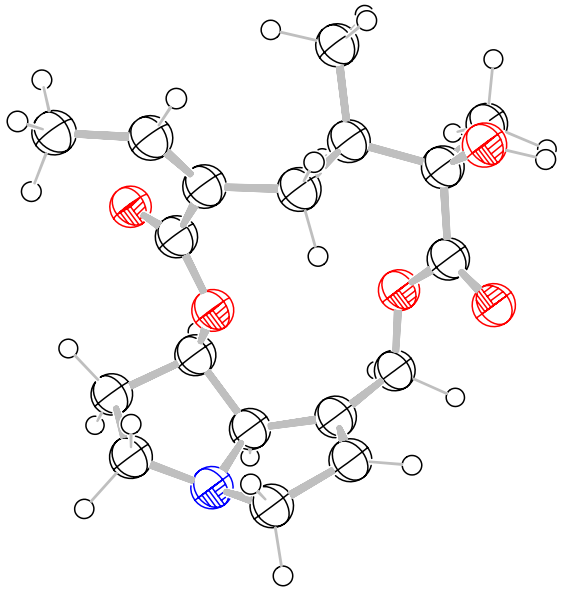
Thomas Bourauel / John Edgar

Pyrrolizidine Alkaloids

Structure and Toxicity



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Contents

1. Introduction

Many episodes of human and animal intoxication, resulting from consumption of certain plant genera belonging to the families Asteraceae, Leguminosae and Boraginaceae, were shown, in the middle of last century, to be caused by pyrrolizidine alkaloids [Schoental, 1959; Bull, Culvenor, et al., 1968].

Gilruth was the first to confirm earlier suspicions that *Senecio jacobaea* (Asteraceae) caused chronic liver disease in livestock [Gilruth, 1903/1904]. Demonstration that other *Senecio* spp., and *Crotalaria* spp. (Leguminosae) also produce a similar disease of livestock, soon followed [Bull, Dick, 1959]. Toxicity problems were not confined to livestock. It was shown, in 1920, that widespread, chronic liver disease of humans in South Africa was caused by the consumption of bread made from cereals contaminated by seeds of *Senecio* spp. [Willmott, Robertson, 1920; Steyn, 1933].

In the 1930s it was recognized that endemic liver disease in areas of the former USSR was also caused by consumption of pyrrolizidine alkaloid-contaminated bread [Bourkser, 1947; Milenkov, Kizhaikin, 1952]. In this case the source of pyrrolizidine alkaloids was seeds and dust from *Heliotropium lasiocarpum* (Boraginaceae), a common contaminant of grain in the affected regions. In more recent times there have been large-scale incidents of acute poisoning from pyrrolizidine alkaloid contamination of grain involving many thousands of people in central and south Asia. In one incident in Afghanistan approximately 8000 people were acutely poisoned by wheat contaminated by *Heliotropium popovii* subsp. *gillianum,* 5000 were seriously affected and many died [Tandon, Tandon, 1975; Mohabbat, Srivastava, et al., 1976]. Four thousand people were similarly poisoned by *H. lasiocarpum* contamination of wheat in Tadjikistan in 1992 [Chauvin, Dillon, et al., 1994; Mayer, Lüthy, 1993].

Seeds and dust from plants producing pyrrolizidine alkaloids growing as weeds in the crop can contaminate cereal grains in many countries [IPCS, 1988; ANZFA, 2001]. While grain cleaning methods, routinely used in industrialised countries, reduce pyrrolizidine alkaloid contamination to below the level causing acute poisoning by removing the foreign seeds, they do not remove the dust component and there are concerns that diseases such as cirrhosis, cancer and pulmonary arterial hypertension could, in some instances, result from chronic exposure to low levels of pyrrolizidine alkaloids in products such as cereal grains even in the industrialised world [Edgar, 2003].

Medicinal plants containing pyrrolizidine alkaloids have also been found to cause significant liver damage, especially in children [IPCS, 1988; Roeder, 1995/2000].

Recognition of this mode of human pyrrolizidine alkaloid intoxication followed investigations into herbal teas and their connection with liver disease in Jamaica and other parts of the West Indies in the 1950s. The use of herbal teas made from pyrrolizidine alkaloid-producing plants to treat minor illnesses is also recognised as a cause of liver disease in parts of Africa and other tropical and subtropical countries. While pyrrolizidine alkaloid poisoning is more common in developing countries, where traditional herbal medicines are widely used, industrialised countries such as the USA and UK have also reported pyrrolizidine alkaloid intoxications from consumption of herbal medicines. Germany, Switzerland and Austria, where it was claimed in the 1980s by some herbal medicine practitioners that traditional medicinal plants had therapeutic benefits without the undesirable side effects reported for other medicines, have also reported fatal cases of pyrrolizidine alkaloid intoxication from consumption of traditional herbal products that contain pyrrolizidine alkaloids.

As well as the known contamination of grain, there is potential for pyrrolizidine alkaloids to occur in several other foods. For example honey derived from the flowers of pyrrolizidine alkaloid plants, has been shown to greatly exceed the levels of pyrrolizidine alkaloids deemed tolerable by some health authorities [Deinzer, Thomson, et al., 1977; Culvenor, Edgar, et al., 1981; Roeder, 1995, 2000; Edgar, Roeder, et al. 2002; Beales, Betteridge, et al., 2004; Boppre, Colegate, et al., 2005; Betteridge, Cao, et al., 2005].

Milk has also been demonstrated as a source of pyrrolizidine alkaloids [Schoental, 1959; Dickinson, Cooke, et al., 1976; Dickinson, 1980; Johnson, Robertson, et al.,1978; Goeger, Cheeke, et al., 1982; Lüthy, Heim, et al. 1983; Candrian, Lüthy, et al., 1984; Molyneux, James, 1990]. Human milk, from women exposed to pyrrolizidine alkaloids, has caused veno-occlusive disease in neonates and infants [Roulet, Laurini, et al., 1988]. Eggs too are a possible source of pyrrolizidine alkaloid exposure [Edgar, Smith, 1999], and there are also reports of pyrrolizidine alkaloids in offal from animals fed plants containing pyrrolizidine alkaloids but no evidence has yet been reported for pyrrolizidine alkaloids in meat [IPCS, 1988; ANZFA, 2001].

There are a number of reports in the medical literature of liver damage typical of that caused by pyrrolizidine alkaloids, where the source of exposure could not be identified [e.g. Sergi, Beedgen, et al., 1999; Seibold-Weiger, Vochem, et al., 1997; Müller-Höcker, Weiss, et al., 1987; Tollmann, Neureiter, et al., 1999; Price, Walker, et al., 1996]. There is therefore an ongoing need for an appropriate control of all sources of dietary for the exposure to pyrrolizidine alkaloids.

As a result of increasing reports of pyrrolizidine alkaloid poisoning and growing awareness of the extent of potential pyrrolizidine alkaloid exposure through agricultural products and herbal medicines, the IPCS held a meeting of experts under the auspices of the United Nations Food and Agriculture Organisation, the World Health Organisation and the International Labor Organisation. The resulting authoritative report on the human health implications of pyrrolizidine alkaloids was published in 1988 [IPCS, 1988].

In 1992, after several years of investigation, the German Federal Department of Health [1992] promulgated regulations severely restricting manufacture and sale of all herbal medicines containing pyrrolizidine alkaloids with a 1,2-unsaturated necine moiety that confers carcinogenicity and hepatotoxicity. Exempt are pyrrolizidine alkaloid-containing pharmaceuticals with no more than 1 micrograms of 1,2-dehydropyrrolizidine alkaloids per daily oral dose or less than 100 micrograms in the case of a topically applied product. These regulations also apply to homeopathic pharmaceuticals having potency up to D6 for internal use and D4 for external application. The German regulations also require that these products are not prescribed for women who are pregnant or breast-feeding and they must have a warning label to that effect. Switzerland and Austria have banned all pyrrolizidine alkaloid-containing herbal medicines and the Netherlands has a regulation limiting pyrrolizidine alkaloids to 1 microgram per kg of food [Anon., 2001].

As with all other cases of intoxication by natural products, a basic requirement for understanding many aspects of poisoning has been the isolation, purification and structure elucidation of the toxic principals. While many physicochemical methods, such as nuclear magnetic resonance spectroscopy and mass spectrometry, give valuable structural information, X-ray crystallography is the most unequivocal and informative and provides basic knowledge that underpins the other methods. X-ray diffraction is indispensable when the structure is significantly different from known structures and especially where the number of asymetric centres is large. X-rays studies have been particularly valuable in the case of pyrrolizidine alkaloids. Among the detailed knowledge gained from X-ray studies are the structural formula, relative configuration, absolute configuration and most stable or preferred conformation in the crystal state. Bond lengths, bond angles and rotation about each bond can be calculated quantitatively from the experimentally determined coordinates and used in modelling studies.

Early methods of X-ray analysis required the presence of a heavy atom. Alkaloids, with a capacity to form Cl, Br and I salts, were particularly suited to these methods and many of the early pyrrolizidine alkaloid structures elucidated by X-ray crystallography were heavy atom salts. Modern methods for deriving structures from X-ray data have overcome this requirement.

This book reviews all of the X-ray diffraction studies of pyrrolizidine alkaloids reported in the scientific literature and gives their structures. These

studies have established the chemical structures and stereochemistry of many important pyrrolizidine alkaloid types. As well as the hazardous, pro-toxic 1,2-dehydropyrrolizidine alkaloids, X-ray diffraction studies have also confirmed the structures of their dihydropyrrolizine ("pyrrolic") metabolites that are responsible for their liver damaging and carcinogenic properties. The X-ray-derived structures of a number of simple, non-toxic pyrrolizidine alkaloids and of pyrrolizidine alkaloids with biological activity that differs from that of 1,2-dehydropyrrolizidine ester alkaloids, are also presented.

2. The Chemistry of pyrrolizidine alkaloids

Pyrrolizidine alkaloids form a large group of plant secondary chemicals that occur in an estimated 5 % of flowering plants [Smith, Culvenor, 1981]. They are made of two parts – a basic amino alcohol moiety, referred to as a necine, and one or more acids (necic acids) that esterify the alcohol groups of the necines [Bull, Dick, 1959; Bull, Culvenor, et al., 1968; Mattocks, 1986; Rizk, 1991].

2.1 Necines

Necines comprise a bicyclic ring system with a bridgehead nitrogen and a hydroxymethyl group on C-1 called. The necines referred to in this book are listed in figure 2.1. Necines can be saturated or possess a double bond in the 1,2-position. A second hydroxyl group commonly occurs at C-7. In some necines additional hydroxyls have been found at C-2, C-6 and – in a few cases – at C-1. Asymetric centres found at C-8 and (in case of no double-bond in position 1,2) at C-1 and produced by the presence of hydroxyls at C-2, C-6 and C-7 give rise to a number of possible stereoisomers. Dashed and thickened wedge shaped bonds shown in the structures depicted in Figure 2.1 denote alpha and beta orientations of bonds, respectively. Alpha means orientation away from the observer and beta towards the observer. With few exceptions, most pyrrolizidine alkaloids belong to the C-8 alpha series. The necines also occur in nature as highly water soluble and non-basic N-oxides.

The necine otonecine has a unique place. It is not strictly a bicyclic pyrrolizidine system but rather an N-methyl azacyclooctan-4-one that acts as a 1,2-dehydropyrrolizidine due to the transannular binding between the nitrogen and the carbonyl group (Fig. 2.1). The otonecine alkaloids and all pyrrolizidine alkaloids with necines incorporating a double bond in the 1,2-position are toxic.

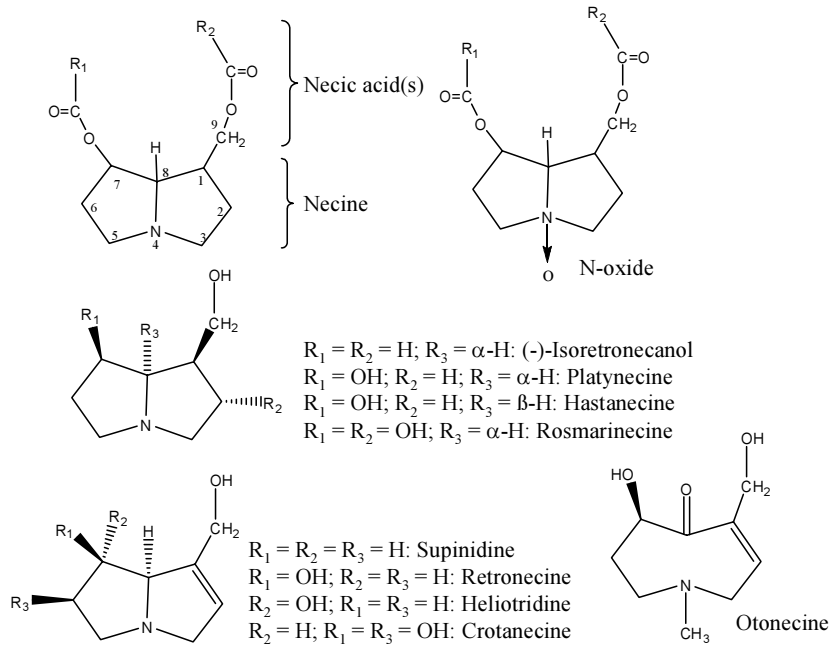


Figure 2.1

2.2 Necic acids

The acids esterifying the necine alcohol groups are called necic acids. The simplest is acetic acid, otherwise they are unique acids possessing from 5 to 10 carbon atoms. They can be mono or dicarboxylic acids with branched carbon chains bearing hydroxy, alkoxy (e.g. methoxy), epoxy and carboxyester groups. This allows for a unique range of structures and numerous stereo isomers [Bull, Culvenor, et al., 1968; Mattocks, 1986; Rizk,1991].

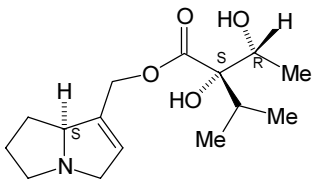
2.3 Representative pyrrolizidine alkaloids

The esterification possibilities are exemplified by several alkaloids. Necines containing only one hydroxyl group at C-9 are restricted to a single ester linkage with a monocarboxylic acid as shown for supinine (Fig. 2.2).

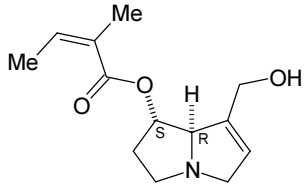
Necines bearing two hydroxyl groups, for example at C-9 and C-7 (7,9-necinediols) can be esterified by monocaboxylic acids on either hydroxyl.

Representative alkaloids of this type, O^7-angeloylheliotridine, echinatine, are examples of one-fold esterification shown in Figure 2.2.

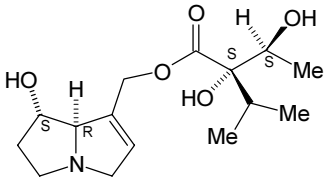
Lasiocarpine is an example of a two-fold esterification.



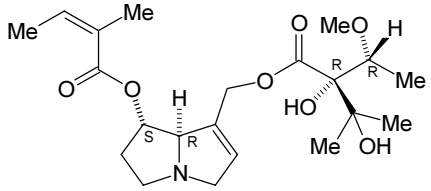
Supinine



O7-Angeloylheliotridine



Echinatine

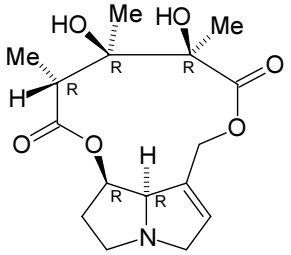


Lasiocarpine

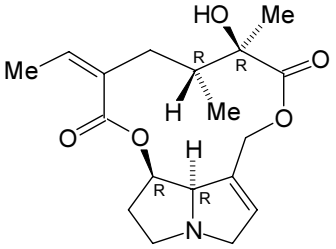
Figure 2.2

With dicarboxylic acids double esterification leads to formation of 11 to 14-membered macrocyclic ring systems. Examples shown in Figure 2.3 are the 11-membered ring alkaloid monocrotaline, the 12-membered ring alkaloids senecionine and senkirkine, the 13-membered ring doronenine and the 14-membered parsonsine. The latter is in fact a triester macrocyclic pyrrolizidine alkaloid in which a dicarboxylic acid esterifying the C-7 hydroxyl forms a macrocyclcic ring by esterifying a hydroxyl on the monocarboxylic acid esterifying the C-9 hydroxyl.

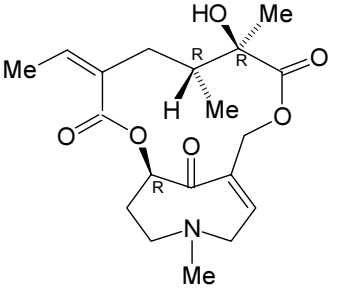
A very large range of pyrrolizidine alkaloids can theoretically be obtained by combining the known necines and necic acids. So far, more than 500 alkaloids have been found and their structures determined. With the exception of the approx. 35 otonecine alkaloids, e.g. senkirkine (Fig. 2.3), that cannot form N-oxides, if the N-oxides of these alkaloids are taken into consideration, more than 950 pyrrolizidine structures are known.



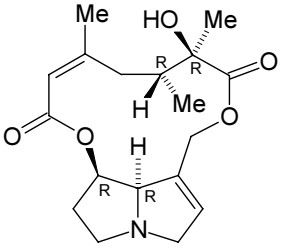
Monocrotaline



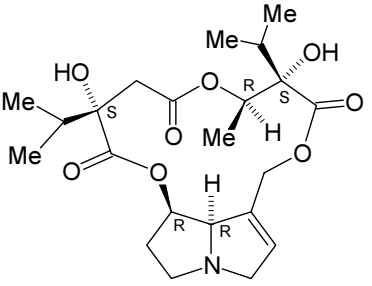
Senecionine



Senkirkine



Doronenine



Parsonsine

Figure 2.3

3. Occurrence of pyrrolizidine alkaloids

At least 13 families of flowering plants have been reported to produce pyrrolizidine alklaloids [Bull, Culvenor, et al., 1968; Mattocks, 1986; Furuya, Asada, et al., 1987; Rizk, 1991]. Of these, 6 families; viz. Apocynaceae, Boraginaceae, Asteraceae (Compositae), Leguminosae (Fabaceae), Ranunculaceae and Scrophulariaceae, produce 1,2-dihydropyrrolizidine ester alkaloids that are hepatotoxic, genotoxic, teratogenic, carcinogenic and pneumotoxic. In all, it has been estimated that pyrrolizidine alkaloid producing species represent 3% of all flowering plants [Smith, Culvenor, 1981]. They are widely distributed throughout the world and are found growing in many agricultural production environments [IPCS, 1988; Bull, Culvenor, et al., 1968; Mattocks, 1986; Furuya, Asada, et al., 1987; Rizk, 1991].

The genera that are primarily responsible for significant poisoning of humans and foraging lifestock are Senecio and Eupatorium (Asteraceae), Crotalaria (Leguminosae), Heliotropium and Trichodesma (Boraginaceae). Other toxic pyrrolizidine-producing genera hazardous to humans, where exposure can occur via food contamination (e.g. honey [Edgar, Roeder], et al., 2002]) and via consumption of traditional herbal medicines [Roeder, 1995, 2000], include Echium, Borago, Anchusa, Symphytum, Alkanna, Cynoglossum, (Boraginaceae) as well as Tussilago, Erechthites, Lithospermum, Brachyglottis, Cineraria and Petasites (Asteraceae) [Roeder, 1995, 2000; German Federal Department of Health, 1992].

3.1 Meat as a possible source of pyrrolizidine alkaloids

Many millions of meat-producing livestock are exposed to plants containing pyrrolizidine alkaloids. Pyrrolizidine alkaloid toxicosis is considered to be the most common poisoning disease of livestock worldwide [Prakash, Pereira, et al., 1999]. It is however not yet clear whether hazardous residues of pyrrolizidine alkaloids remain in meat entering the human food chain. Unattributed data has been reported that indicate pyrrolizidine alkaloid levels from >10 micrograms to 73 micrograms per kg have been found in the liver and kidney of domestic animals [ANZFA, 2001]. Experiments have also been reported in which puppies were fed cooked meat (or milk) from animals poisoned by a pyrrolizidine alkaloid-producing species of *Trichodesma*. This resulted in death or production of irreversible pathological changes within 3-4 months and it was concluded that the meat contained toxic alkaloid residues

that were not destroyed by heat treatment [Shevchenko, Fakhrutdinova, 1971].

Experiments in which radiolabelled pyrrolizidine alkaloids were given to animals, show that most of the radioactivity (80%) is excreted within 24 hours [Eastman, Dimenna, et al., 1982; Candrian, Lüthy, et al., 1985]. The residue that persists is probably mainly dihydropyrrolizine adducts of sulphydryl, hydroxyl and amino bearing molecules. Following administration of 1,2-dehydropyrrolizidine ester alkaloids dihydropyrrolizine adducts have been detected in liver tissue and in blood of experimental animals [Mattocks, 1968; Yan, Nichols, et al., 2002]. As previously mentioned, these adducts are also considered to form an *in vivo* reservoir of toxins that may go on to produce long-term chronic toxicity in initially apparently normal, unaffected individuals. Whether this potential is transferable to consumers of animal tissues containing dihydropyrrolizine adducts has not been established.

3.2 Milk containing pyrrolizidine alkaloids

Milk has been shown to be a source of pyrrolizidine alkaloid exposure experimentally in animals [Dickinson, Cooke, et al., 1976; Deinzer, Arbogast, et al., 1982; Goeger, Cheeke, et al., 1982; Miranda, Cheeke, et al., 1981; Schoental, 1959; Lüthy, Heim, et al., 1983; Candrian, Lüthy, et al., 1984; Eastman, Dimenna, et al., 1982; White, Krumperman, et al., 1984]. Both pyrrolizidine free bases and N-oxides were found in milk [Dickinson, Cooke, et al., 1976] but the more water-soluble N-oxides, the dominant form occurring in plants, are thought to be most readily transferred into milk [Molyneux, James, 1990].

No human cases of pyrrolizidine alkaloid poisoning via milk have been unequivocally established but Huxtable [1989] refers to several instances where veno-occlusive disease occurred in suckling babies in Jamaica where there was no history of direct herbal administration to the infants. Eight cases in Germany and Austria described by Wurm [1939] could also have been caused by pyrrolizidine alkaloids being transferred in their mothers' milk.

Molyneux and James [1990] have reviewed the potential for pyrrolizidine alkaloid contamination in milk from cows presenting a health risk and concluded that, because commercial cows milk comes from many sources and extensive mixing occurs during processing, pyrrolizidine alkaloids in commercial milk is unlikely to pose a significant health risk for most consumers although it could add to the cumulative dietary exposure to these natural toxicants.

3.3 Honey and pollen containing pyrrolizidine alkaloids

Honey made from the floral nectar of several pyrrolizidine alkaloid plants belonging to the genera *Senecio*, *Echium* and *Heliotropium* contains pyrrol-

izidine alkaloids [Deinzer, Thomsen, et al., 1977; Culvenor, Edgar, et al., 1981; Roeder, 1995; Beales, Betteridge, et al., 2004; Betteridge, Cao, et al., 2005]. The highest concentration of pyrrolizidine alkaloids reported in honey originating from *Senecio jacobaea* is 3900 micrograms/kg [Bull, Culvenor, et al., 1968, Deinzer, Arbogast, et al., 1977]. *Echium plantagineum* honey is said to contain up to 2300 micrograms/kg after correction for extraction efficiency [Culvenor, Edgar, et al., 1981; Beales, Betteridge, et al., 2004] and *E. vulgare* honey has been reported to contain 500 – 2800 micrograms/kg of pyrrolizidine alkaloids [Betteridge, Cao, et al., 2005]. *Heliotropium amplexicaule* honeys were found to contain up to 1650 micrograms of pyrrolizidine alkaloids per kg and up to 250 micrograms/kg was found in honey attributed to *Heliotropium europaeum* [Beales, Betteridge, et al., 2004]. *Senecio vernalis* honey has been reported to contain between 500 and 1000 micrograms of pyrrolizidine alkaloids per kg while seneciphylline, at a concentration of 30-70 micrograms per kg, was found in honey from the alpine foothills of Switzerland, apparently introduced from *Senecio* species flowering in the area [Roeder, 1995]. Other honeys, said to come from plants devoid of pyrrolizidine alkaloids, contained up to 810 micrograms/kg of pyrrolizidine alkaloids and three retail honeys with no floral attribution have been reported to contain between 120 and 280 micrograms/kg of pyrrolizidine alkaloids [Beales, Betteridge, et al., 2004].

These levels of pyrrolizidine alkaloids in honey compare very unfavourably with the maximum tolerable level of 1 microgram of pyrrolizidine alkaloids per kg of food allowed by law in the Netherlands [Anon., 2001; Edgar, Roeder, et al., 2002]. They also exceed the maximum of 1 micrograms of pyrrolizidine alkaloids allowed per daily dose of herbal medicines in Germany [German Federal Department of Health, 1992; Edgar, Roeder, et al., 2002]. The German regulations specifically prohibit sale of pyrrolizidine alkaloids-containing herbal medicines to pregnant or lactating women so that honeys containing these alkaloids raise grave concerns for foetuses and infants, especially since there is no monitoring of retail honeys for pyrrolizidine alkaloids. Significant volumes of commercial honey from *Echium* species are produced in several countries. Both *E. plantagineum* and *E. vulgare* yield popular, mild-tasting, widely traded honeys [Edgar, Roeder, et al., 2002].

While it was originally believed that nectar is the source of the alkaloids found in honey, it has also been suggested that the alkaloids may come primarily from pollen, a natural contaminant of honey introduced by bees and also by apiarists during harvesting of the honey. For example, pollen from *Echium vulgare* was shown to contain between 8000 and 14000 milligrams of pyrrolizidine alkaloids/kg, more than sufficient to explain the level of 500 to 1220 micrograms/kg present in *E. vulgare* honey. The pyrrolizidine alkaloids are present in pollen as highly water soluble N-oxides so that their

transfer from contaminating pollen grains into aqueous nectar is expected to be rapid [Boppré, Colegate, et al., 2005].

Bee-collected pollen granules are credited with having many health benefits and are being widely sold as a health food supplement that may, like honey, be contributing to unrecognised dietary exposure to pyrrolizidine alkaloids [Boppré, Colegate, et al., 2005].

3.4 Eggs containing pyrrolizidine alkaloids

There have been a number of reports of poultry being poisoned by pyrrolizidine alkaloids [Peterson, Culvenor, 1983; Gaul, Gallagher, et al., 1994]. In one incident involving commercial layer chickens, wheat containing seeds of *Heliotropium europaeum* was shown to be the principle cause and alkaloids characteristic of this plant were found in eggs laid by the chickens [Edgar, Smith, 1999]. Some of the eggs also contained alkaloids typical of *Echium plantagineum*, indicating this plant was also a contaminant in their diet. The levels of pyrrolizidine alkaloids in the eggs ranged up to 9.7 micrograms per egg, considerably in excess of the maximum tolerable level specified for human exposure in Dutch and German regulations [Anon., 2001; German Federal Department of Health, 1992].

Domestic livestock, including poultry, are sometimes fed grain considered unsuitable for human consumption due to the level of contamination by foreign seeds. Removal of foreign seeds by screening the grain does not eliminate contamination. It has been found that, even when foreign seeds are no longer detectable, dust adhering to the grain can still be a source of hazardous levels of pyrrolizidine alkaloid contamination [Edgar, 2003]. Grain screenings with high levels of foreign seeds, generated by "cleaning" grain prior to flour milling operations, are also sometimes fed to livestock. Ensuring the quality of livestock feed is therefore an important factor in reducing human exposure to natural toxicants such as pyrrolizidine alkaloids.

4. Toxicity of pyrrolizidine alkaloids

1,2-Dehydropyrrolizidine ester alkaloids and their N-oxides, with 1,2-unsaturated necines i.e. esters of supinidine, retronecine, heliotridine, crotanecine and otonecine (conforme Fig. 2.1), are carcinogenic, mutagenic, genotoxic, fetototoxic and teratogenic to varying degrees.

Some of the 1,2-dehydropyrrolizidine alkaloids (e.g. fulvine and monocrotaline (Fig. 2.3) are also pneumotoxic. Pyrrolizidine alkaloids without the 1,2-double bond, those with platynecine, hastanecine, rosmarinecine and isoretronecanol (conforme Fig. 2.1) do not show these toxicities.

The reasons for the different degrees of toxicities of different 1,2-dehydropyrrolizidine alkaloids, and the absence of toxicity in the case of saturated pyrrolizidine alkaloids, are discussed below.

4.1 Metabolism

The relative toxicity of different pyrrolizidine alkaloids is determined by the nature of their liver metabolites and also by their lipophilic and hydrophilic properties that help determine their ease of metabolism and their pharmacokinetics.

4.1.1 Metabolic activation of 1,2-dehydro-pyrrolizidine alkaloids

The mechanism by which 1,2-dehydropyrrolizidine alkaloids (e.g. the typical diester Ia, (Fig. 4.1) cause toxicity in mammals is well established [Mattocks, 1968; Culvenor, Downing, et al., 1969; Jago, Edgar, et al., 1970; Mattocks, White, 1971b; Culvenor, Edgar, et al., 1971; Mattocks, 1972a; IPCS, 1988].

Following ingestion and absorption from the gut, cytochrome P-450 mono-oxygenase isozymes, located primarily in the liver, introduce a hydroxyl group on C-3 or C-8, adjacent to the nitrogen in the unsaturated ring (Fig. 4.1).

The resultant carbinolamines (IIa and IIb) are unstable and dehydrate to produce the didehydropyrrolizidine (dihydropyrrolizine) (III). The metabolites are no longer alkaloids because the electrons of the formerly basic nitrogen are delocalised in the aromatic system. Dehydration of IIa and IIb is driven by conjugation of the newly formed double bond with the 1,2-double bond and by subsequent spontaneously rearrangement of the diene to the aromatic dihydropyrrolizine ("pyrrolic") system shown in III.

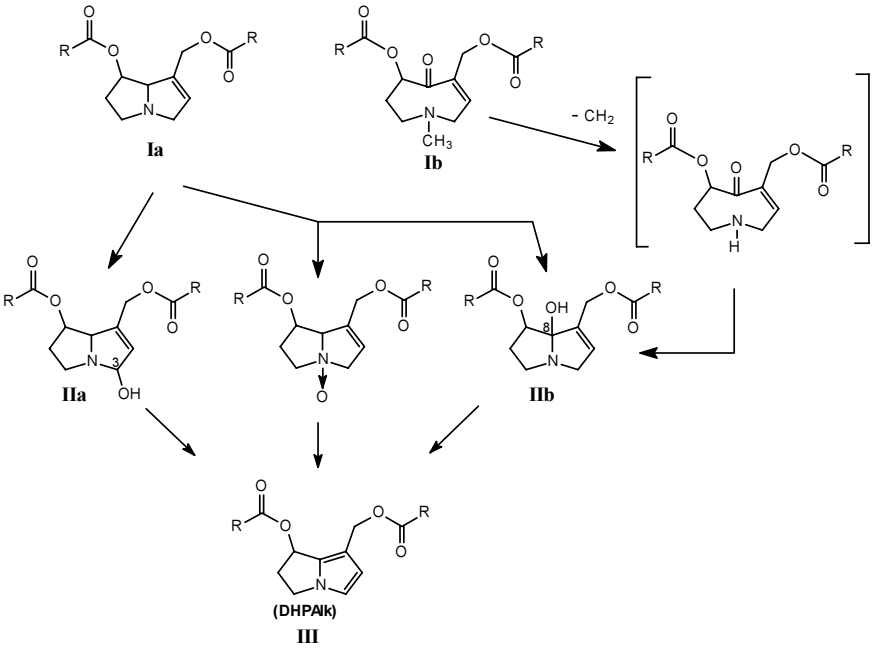


Figure 4.1

1,2-Dehydropyrrolizidine alkaloids occur in plants mainly as N-oxides that are resistant to conversion to dihydropyrrolizine metabolites by cytochromes P-450 [Jago, Edgar, et al., 1970; Mattocks, White, 1971a] but they display the same mammalian toxicity as the free base form because they are reduced to free bases by the gut microflora prior to absorption and also, to some extent, converted to the free base form by liver microsomes in the presence of NADH or NADPH, and thus behave as pyrrolizidine alkaloid free bases *in vivo* [Mattocks, White, 1971b; Powis, Ames, et al., 1979; Chou, Wang, et al., 2003; Wang, Yan, et al., 2005a; Wang, Yan, et al., 2005b; Wang, Yan, et al., 2005c].

The same biologically active didehydropyrrolizidine metabolites (e.g. III) are also generated from otonecine-type alkaloids (e.g. Ib, Fig. 4.1) [Culvenor, Edgar et al., 1971; Lin, Cui, et al., 1998; Lin, Cui, et al., 2000]. These seco-alkaloids have a methyl group on the nitrogen and a quasi ketonic function at C-8 (Fig. 4.1). It is envisaged that in these cases cytochome P-450 isozymes hydroxylate the N-methyl group [Culvenor, Edgar, et al., 1971]. The hydroxyl-methyl carbinolamine produced loses formaldehyde. Removal of the N-methyl group allows condensation of the keto function at C-8 with the

newly formed NH group to give the unstable intermediates, IIb, that spontaneously dehydrate to didehydropyrrolizidines such as III (Fig. 4.1).

The didehydropyrrolizidine metabolites (e.g. III) have chemically reactive centres at C9 and C7 that, as with similar benzylic-type alcohols and their esters, readily generate, by loss of the hydroxyl or acid anions, stabilized carbonium ions that immediately react with available nucleophiles (Nu^-) (Fig. 4.2).

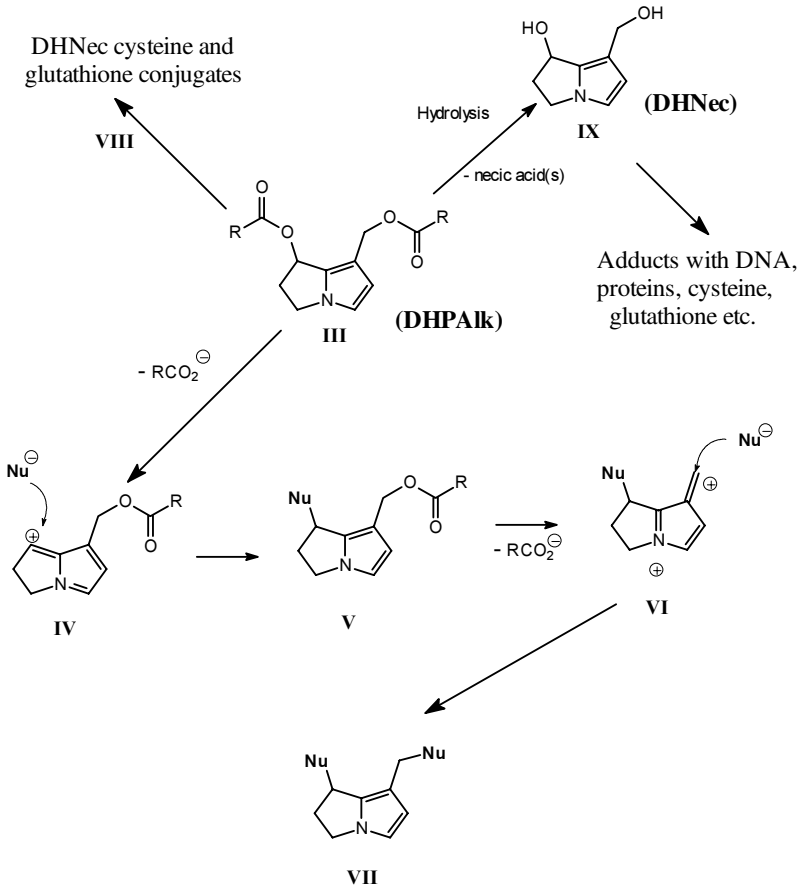


Figure 4.2

If the alcohols at C7 and C9 are esterified, as in the case of III, carbonium ion formation is greatly facilitated because the acid moiety provides a good leaving group. In the case of didehydropyrrolizidines with unesterified hydroxyls at C7 and/or C9 (e.g. the dehydronecines, Fig. 4.2, IX) formation of carbonium ions at C-7 and C-9 is not as spontaneous but can be facilitated, as for analogous benzylic hydroxyls, by protonation of the hydroxyls leading to loss of H2O. [Culvenor, Edgar, et al., 1970a].

The leaving groups (hydroxyl or acid anions) can also be displaced by nucleophiles by an S_N2 mechanism.

In vivo, following the generation of didehydropyrrolizidine metabolites (e.g. III) by cytochromes P-450 in hepatocytes, the C-7 and C-9 carbonium ions that are formed (e.g. IV and VI, Fig. 4.2) react rapidly and spontaneously with nucleophilic centres on, for example, vital proteins and nucleosides. In the case of proteins, mercapto, hydroxyl and amino groups are attacked and the amino groups of purine and pyrimidine bases are alkylated in the case of DNA and RNA. The resulting products, proteins and nucleosides with dehydropyrrolizine adducts, cannot perform their normal, often vital functions. In the case of DNA, mutations are a possible outcome. The extremely high chemical reactivity of the didehydropyrrolizidine metabolites (e.g. III) causes considerable tissue damage in the liver and disruptions to normal biochemical processes, resulting in the pathology and liver damage observed (see below). 7,9 -Diesters (e.g. III) and the equivalent metabolites of macrocyclic 7,9-diester alkaloids (e.g. senecionine and senkirkine (Fig. 2.3)) are particularly liver-damaging because cross-linking, e.g. of DNA strands, is possible [Curtain, Edgar, 1976; Hincks, Kim, et al., 1991; Kim, Stermitz, et al., 1995; Pereira, Webb, et al., 1998; Kim, Stermitz, et al.,1999; Coulombe, Drew, et al., 1999; Fu, Xia, et al., 2000 ; Chou, Wang, et al., 2003; Yan, Nichols, et al., 2002; Fu, Xia, et al., 2002 ; Xia , Chou, et al., 2006]. This is not the case, for example, with esters of supinidine (e.g. supinine (Fig. 2.2)) where a single alkylating centre at C-9 is involved. As a result of their inability to form cross-links, supinidine mono ester alkaloids are less damaging than retronecine and heliotridine (Fig. 2.1) ester alkaloids and especially C-7, C-9 diester alkaloids, such as Ia and Ib, that can produce cross-links. Mattocks has shown in the case of macrocyclic didehydropyrrolizidine diesters (e.g. dehydrosenecionine) that the C-7 carbon is more reactive than C-9. C-7 is therefore the first to react with nucleophiles as depicted in Figure 4.2. In the case of dehydroheliotridine esters (conforme Fig. 2.1) too the C-7 hydroxyl is the first to react with nucleophiles [Mattocks, 1986].

As well as reacting with nucleophilic amino, mercapto and hydroxyl groups on proteins and/or DNA and disrupting their cellular functions, the didehydropyrrolizidine metabolites (e.g. III) can also alkylate SH groups on less vital and more easily regenerated, soluble cellular components such as

glutathione and cysteine [Cheeke, Gorman, 1974; Nigra, Huxtable, 1992; Reed, Miranda, et al., 1992; Lin, Cui, et al., 1998]. The latter substances, when present in high concentrations, are protective against the effects of 1,2-dehydropyrrolizidine alkaloids *in vivo* because they reduce damage to more important proteins and nucleic acids [Cheeke, Gorman, 1974].

Didehydropyrrolizidine metabolites (e.g. III) also react with water *in vivo* to generate the dehydronecines (dehydroretronecine and dehydroheliotridine) IX (Fig. 4.2). Lacking ester groups, the dehydronecines (IX) are less reactive and more water soluble than the dehydropyrrolizidine ester alkaloids (e.g. III), although they still retain significant biological alkylating activity [Peterson, Jago, 1980; Robertson, 1982]. Their lower chemical reactivity enables then to escape from the liver cells in which they are formed and they can produce damage to other tissues as well as the liver [Peterson, Samuel, et al., 1972; IPCS, 1988; Prakash, Pereira, et al., 1999].

The dehydronecines are considered to be particularly important in the delayed effects of exposure to 1,2-dehydropyrrolizidine alkaloids, including carcinogenicity [Johnson, Robertson, 1978; Peterson, Culvenor, 1983]. The dihydropyrrolizine adducts left *in vivo* as residues attached to cellular constituents are thought to reversibly release the dehydronecines (IX) over time by hydrolytic processes, providing a continuing opportunity to damage vital cellular processes and induce mutations [Peterson, Samuel, et al., 1972; Prakash, Pereira, et al., 1999]. Thus a single exposure to 1,2-dehydropyrrolizi-dine ester alkaloids can produce residual macromolecular adducts that continually release hazardous dehydronecines (dehydroretronecine, dehydroheliotridine) (IX) that may have long-term, adverse health consequences [Peterson, Samuel, et al., 1972; Prakash, Pereira, et al., 1999]. Dehydroretronecine and dehydroheliotridine are, for example, carcinogenic, producing rhabdomyosarcoma, skin, liver and lung tumours [Allen, Hsu, et al., 1975; Shumaker, Robertson, et al., 1976; Johnson, Robertson, et al., 1978; Mattocks, Cabral, 1982; Peterson, Culvenor, 1983].

4.1.2 Detoxication

As well as metabolic activation, 1,2-dehydropyrrolizidine alkaloids (e.g. Ia) are also subject to competing metabolic detoxication *in vivo*. For example, hydrolysis of the ester linkages of potentially harmful 1,2-dehydropyrrolizidine alkaloids (e.g. Ia) gives non-toxic necic acids and highly water soluble necines that are readily excreted, via the kidneys, in urine. Many 1,2-dehydropyrrolizidine ester alkaloids however, and in particular the most toxic ones, have highly branched necic acids that are resistant to hydrolysis by esterases [Culvenor, Edgar, et al., 1976; Mattocks, 1986]. The higher the steric hinderance of the ester linkages, the greater the resistance to detoxication by non-specific esterases and the more hazardous is the alkaloid [Culvenor, Edgar, et al., 1976; Mattocks, 1986].

N-oxidation of 1,2-dehydropyrrolizidine alkaloids also occurs in the mammalian liver and is considered to be a detoxication [Mattocks, 1968; Jago, Edgar, et al., 1970; Mattocks, White 1971b; Williams, Reed, et al., 1989; Miranda, Chung, et al., 1991]. Pyrrolizidine N-oxides are very water soluble and thus more readily excreted in urine than are the parent alkaloids [Mattocks, 1968]. The N-oxides are not converted to didehydropyrrolizidine metabolites (e.g. III) by cytochromes P-450 associated with liver microsomes [Jago, Edgar, et al., 1970; Mattocks, White, 1971b]. Ironically however they are at the same oxidation level as the hazardous didehydropyrrolizidine metabolites (e.g. III) and can, *in vitro* at least, be easily converted to these by dehydration [Mattocks, 1986]. Acetylation of the N-oxide and elimination of acetic acid by warming is also a facile method to produce the didehydropyrrolizidine metabolites (e.g. III) *in vitro* [Culvenor, Edgar, et al., 1970a]. Whether this mechanism of formation of the toxic didehydropyrrolizidines (III) from N-oxides occurs to any extent *in vivo* is not known.

The susceptibility of different species and individuals to poisoning by 1,2-dehydropyrrolizidine alkaloids depends therefore on the relative activity of three main metabolic pathways: activation to give didehydropyrrolizidine metabolites (e.g III); ester hydrolysis to give non-toxic necic acids and necines; and formation of N-oxides. The latter two pathways are detoxications. The relative activity of these metabolic pathways are likely to vary between individuals so that some people may be more susceptible than others to poisoning by 1,2-dehydropyrrolizidine alkaloids.

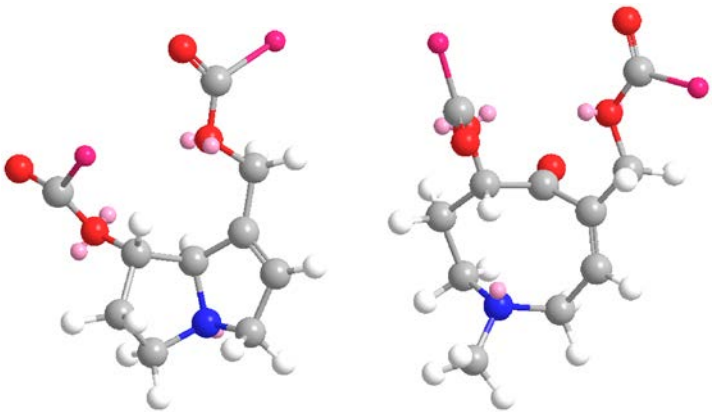
4.1.3 Structure and toxicity

As mentioned in 4.1.1, the key didehydropyrrolizidine metabolites (e.g. III) are also generated from pyrrolizidine alkaloids of the otonecine type (e.g. Ib, Fig. 4.1).

These otonecine derivatives do not show a C8-N bond but possess a keto function at C8 and a methyl group at the nitrogen atom. It is surprising therefore that these seco alkaloids are of identical toxicity to alkaloids of type Ia (1,2-dehydro-retronecine and heliotridine esters).

For energetic reasons, these seco compounds could be expected to occur in a different necine conformation than type Ia componds: the missing C8-N bond should lead to a stable 8-membered macrocycle which may be expected to prevent the metabolism via an intermediate to IIb (Fig. 4.1).

Molecular modelling experiments support this assumption and show the energy minimised structure as depicted in figure 4.3 (energy minimisation: Chem 3D ultra; V. 10.0; Cambridge Soft).



Ia **Ib**

Figure 4.3

Interpretation of the X-ray structure analysis data helps to explain the identical toxicity of pyrrolizidine alkaloids of type Ia and Ib: In all nine otonecine-type alkaloids measured to date a necine conformation was found which is identical to those found in those having the C8-N bond (type Ia).

Both the distances between C8 and N are similar and equal values can be found for the plane angles built between plane C1-C3-N-C8 and plane C7-C5-N-C8 (~125°). This indicates that the seco 1,2-dehydroesters do not exist in the optimal, energy minimised form (Ib, Fig. 4.3) but are of an equal conformation to those of type Ib, which finally enables the metabolisation as shown in figure 4.1.

Furthermore, X-ray data show that the dedihydro metabolites (e.g. III, Fig. 4.2) derived from 1,2-dehydrodiester have a high toxic potential compared with the low or missing toxicity of the monoesters of retronecine or heliotridine (Fig. 2.1). As mentioned in chapter 4.1.2, a possible detoxification mechanism is the hydrolysis of the ester bindings by esterases and the subsequent building of dehydronecine (IX, Fig. 4.2) which – due to their higher water solubility – can be easily excreted renally.

On the other hand, the disassociation to C7 as well as to C9 carbonium ions (especially the speed and therefore the rate of this cleavage) and the subsequent reaction with nucleophiles are seen as a key step concerning the level of toxicity. The concrete binding situation concerning the ester function can be found analysing the X-ray data. Interpretation of the bond lengths shown in figure 4.4 leads to the following results:

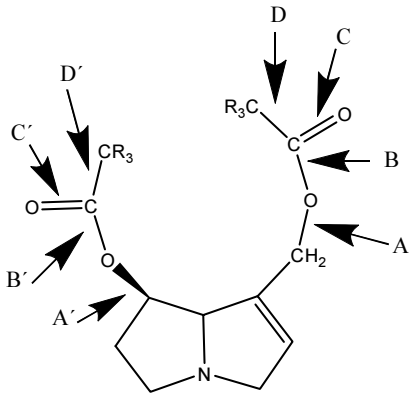


Figure 4.4

In pyrrolizidine alkaloids of type Ia and Ib (1,2-dehydropyrrolizidine diesters) the C-O bonds A and A´ occur in a normal range of 1.45 Å; the following C-O bonds B and B´ are considerably shortened, whereas the keto functions C and C´ show a moderate shortening. The C-C bonds D and D´ show – similar to A and A´ – normal values of about 1.54 Å.

In contrast to these findings, the data for monoesters with retronecine or heliotridine give evidence of a different situation: here, the A and A´ (C9 as well as C7) bonds are elongated and the corresponding keto bonds C or C´ are of nearly ideal length (1.21 Å).

These results show that in 1,2-dehydro diesters the ester functions are a conjugated system leading to the conclusion that the bonds C9-O and C7-O (= A and A´) are the target breaking points within the molecule, which makes possible a quick and easy carbonium ion formation and further reaction with nucleophiles as described in 4.1.1.

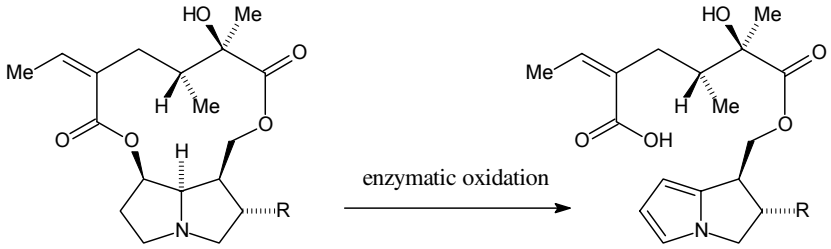
Contrary to that, in pyrrolizidine alkaloids of 1,2-dehydro monoesters more stable ester bonds are found (no conjugation) which leads to the fact that the building of the didehydrometabolites is more difficult and time-consuming. In this case, a hydrolysis by esterases can take place in higher amounts what leads to the detoxification via dehydronecines, which explains the missing or low toxicity of 1,2-dehydro monoester.

These findings show that X-ray structure analysis data give evidence of the toxic potential of a single pyrrolizidine alkaloid and that furthermore, by interpreting these data, the extent of this toxic potential can be estimated.

4.1.4 Metabolism of 1,2-saturated pyrrolizidine alkaloids

Metabolism of saturated pyrrolizidine alkaloids (necic acid esters of platynecine, hastanecine, rosmarinecine and isoretronecanol (Fig. 2.1)) by

mammals has not yet been extensively studied, in part because the saturated ester alkaloids and their necines do not display mammalian toxicity.



R = H : Platyphylline
R = OH : Rosmarinine

Figure 4.5

While 1,2-dehydropyrrolizidine alkaloids are metabolised by liver P-450 isozymes into hazardous dihydropyrrolizines (e.g. III) with a pyrrolic A ring (4.1.1), saturated pyrrolizidine alkaloids produce non-toxic, metabolites [Mattocks, White 1971a; Culvenor, Edgar, et al., 1976]. The saturated alkaloids platyphylline and rosmarinine (Fig. 4.5), for example, are converted by liver microsomes into pyrrolic metabolites with an aromatic B-ring [Mattocks, White, 1971a]. These are devoid of biological alkylating properties and are non-hepatotoxic and non-carcinogenic.

4.2 Pyrrolizidine alkaloid intoxication

There are three dose-related levels of poisoning of humans and animals by 1,2-dehydropyrrolizidine ester alkaloids: acute, sub-acute and chronic. These levels of toxicity can also be sequential, progressing from acute to sub-acute, and finally causing irreversible, chronic (long-lasting, irreversible) toxic effects [McLean, 1970; Peterson, Culvenor, 1983; IPCS, 1988; Huxtable, 1989; Prakash, Pereira, et al., 1999; Fu, Xia, et al., 2004; Stegelmeier, Edgar, et al., 1999].

4.2.1 Pathology, symptoms and progress of poisoning

In acute poisoning extensive hemorrhagic necrosis of the liver is seen in a pattern now recognizable as being determined by cytochrome P-450 enzyme distribution and blood flow. Damage occurs in areas of the liver where the 1,2-dehydropyrrolizidine alkaloids are converted into didehydropyrrolizidine metabolites (4.1.1) and where they alkylate cellular constituents. Clinically,

acute poisoning is characterized by hepatomegaly (enlarged liver) and ascites (excess fluid in peritoneal cavity). Death is due to acute liver failure as a result of extensive centrilobular necrosis and massive liver dysfunctions [Peterson, Culvenor, 1983; IPCS, 1988; Huxtable, 1989; Prakash, Pereira, et al., 1999].

In a clinical study of acute toxicity from drinking bush teas in the West Indies, Stuart and Bras [1957] reported that around 20% of patients died rapidly from acute toxicity and about 50% recovered completely. The remaining 30% of individuals progressed, either directly or after a period of apparent recovery, to sub-acute disease characterized by persistent hepatomegaly and recurrent ascites. In the sub-acute stage endothelial proliferation and medial hypertrophy cause occlusion of the smaller branches of the hepatic vein. The resultant veno-occlusive disease is considered pathognomonic of poisoning by 1,2-dehydropyrrolizidine ester alkaloids [Peterson, Culvenor, 1983; IPCS, 1988; Huxtable, 1989; Prakash, Pereira, et al., 1999; Fu, Xia, et al., 2004]. It causes centrilobular congestion, necrosis, fibrosis and eventually liver cirrhosis, all of which are characteristic of the chronic end-stage of pyrrolizidine alkaloid toxicity.

Metabolites of 1,2-dehydropyrrolizidine alkaloids also show strong antimitotic activity *in vivo* during late S or early G2 phase of the cell cycle [Schoental, Magee, 1957; Bull, Dick, 1959; Peterson, 1965; Jago, 1969; McLean, 1970; Samuel, Jago, 1975] and the combination of a stimulus to regenerate and the antimitotic action in the liver, following exposure a single sub-lethal dose or the cumulative effect of small doses of pyrrolizidine alkaloids, results in the appearance of greatly enlarged hepatocytes (megalocytes) that are highly characteristic of pyrrolizidine alkaloid poisoning in animals [Schoental, Magee, 1957; Bull, Dick, 1959; IPCS, 1988; Prakash, Pereira, et al., 1999]. This effect has not been seen in the poisoned human liver but has been reproduced in cultured human foetal liver cells exposed to lasiocarpine [Armstrong, Zuckerman, et al., 1972]. The dehydronecines (IX) are considered to be the agents primarily responsible for mitotic inhibition [Mattocks, 1986].

As well as veno-occlusive disease of the liver, some 1,2-dehydropyrrolizidine alkaloids (e.g. monocrotaline, fulvine) induce pulmonary arterial hypertension and right ventricular hypertrophy leading to classical cor pulmonale. This sequence is considered to result from escape of pyrrolic metabolites from the liver cells into the pulmonary arterioles where they cause damage to the endothelial vessels similar to veno-occlusive changes in the liver, leading to increasing pressure in the pulmonary circulation [Huxtable, 1989]. Culvenor, Edgar, et al. [1976] have shown that chronic lung lesions are produced in rats by almost all of the 62 1,2-dehydropyrrolizidine alkaloids they tested, although higher doses were required with some alkaloids. Pulmonary hypertension is not considered to be a prominent character-

istic of pyrrolizidine poisoning of humans but there is concern that it may be an under-recognised consequence of long-term, low-level exposure [IPCS, 1988; Huxtable, 1989].
As previously indicated, pyrrolizidine alkaloid poisoning does not necessarily follow the progression observed by Stuart and Bras [1957]. In the cases they described, and in many other similar outbreaks of poisoning caused by herbal medicines and contaminated grain, the dose was sufficient to cause acute disease. However the effects of continuous or intermittent, low-level exposure to 1,2-dehydropyrrolizidine alkaloids from herbal teas, dietary sources such as honey and milk and from low-level grain contamination are likely to go undiagnosed and the first clinical conditions to be detected may be liver cirrhosis, cancer and/or pulmonary arterial hypertension with no obvious cause.

The seriousness of pyrrolizidine alkaloid intoxication is not only related to the level of exposure but also to age and gender. Males are more susceptible than females and foetuses and children are the most sensitive. Other liver damaging agents, nutritional factors, bacterial [Yee, Kinser, et al., 2000] and viral infections [Newberne, Rogers, 1973] and some medical drugs can also exacerbate the effects of 1,2-dehydropyrrolizidines [IPCS, 1988]. Kwashiorkor, frequently observed in children in central Africa, is, for example, exacerbated by liver damage caused by exposure to pyrrolizidine alkaloids and the consequent reduced ability of the liver to synthesise proteins. Barbiturates, that induce hepatic metabolism, greatly increase the production of didehydropyrrolizidine metabolites and the toxic effects observed [White, Mattocks, et al., 1973; Tuchweber, Kovacs, et al., 1974]. Aflatoxins have been shown to act synergistically with pyrrolizidine alkaloids in the production of cirrhosis and hepatomas in primates [Newberne, Rogers, 1973; Lin, Svoboda, et al., 1974]. High copper levels also increase the damage caused by pyrrolizidine alkaloids [Bull, Culvenor, et al., 1968; IPCS, 1988]. Excessive and damaging accumulation of copper occurs in the liver of sheep exposed to 1,2-dehydropyrrolizidine alkaloids and similar copper accumulation and toxicity is found in copper-associated cirrhosis in infants, a form of liver failure of unknown etiology but suspected in some cases to be a manifestation of pyrrolizidine poisoning [Tanner, 1998; Aston, Morris, et al., 1998; Müller-Hoecker, Weiss, et al., 1987; Müller, Müller, et al., 1998; Scheinberg, Sternlieb, 1994].

4.2.2 Dose levels and toxic effects

Considerable data on dose-response to pure 1,2-dehydropyrrolizidine alkaloids is available from animal experiments [Bull, Culvenor, et al., 1968, Mattocks, 1972; Culvenor, Edgar, et al., 1976; IPCS, 1988]. In the case of human poisoning, limited data has been obtained in a few cases where it was possible to estimate the level of alkaloids consumed [e.g. Mohabbat, Srivastava, et

al., 1976; Ridker, Ohkuma, et al., 1985; IPCS, 1988; Rasenack, Müller, et al., 2003]. It has been concluded that humans are especially susceptible to pyrrolizidine alkaloid poisoning but are possibly less subject to carcinogenicity than other species because of more efficient DNA repair mechanisms [Prakash, Pereira, et al., 1999], although this may also be attributed to insufficient monitoring of populations exposed to pyrrolizidine alkaloids and failure to link cancers with this cause.

The lowest daily estimated intake causing sub-acute poisoning (veno-occlusive disease) was 14.1µg of pyrrolizidine alkaloids (mainly echimidine) per kg body weight per day, consumed over a period of 120 days (total estimated minimum intake – 85 mg or 1.7 mg/kg) by a 49 year-old woman [Ridker, Ohkuma, et al., 1985; Huxtable, Lüthy, et al., 1986; IPCS, 1988]. Rasenack, Müller, et al. [2003] estimated that a total mean daily intake of 20 – 30 µg of pyrrolizidine alkaloids during pregnancy caused liver failure and death of a newborn child. The mother was apparently not affected by this level of exposure. In a poisoning incident in Afghanistan involving 8000 cases and many deaths it was estimated that over a 2-years period the individual uptake of PA (heliotrine from *Heliotropium* seeds) amounted to 1.46 g [Mohabbat, Sribastava, et al., 1976; IPCS, 1988].

Quantitative toxicity studies in animals have mainly involved rats. They appear to be more resistant to poisoning than humans [Culvenor, Edgar, et al., 1976; IPCS, 1988]. The minimum single, acute lethal doses administered by intra-peritoneal injection, causing the death of some 2-week-old rats within 2 to 8 days, depends on the particular 1,2-dehydropyrrolizidine alkaloid given but is normally between ten and several hundreds of mg of alkaloids per kg body weight [Culvenor, Edgar, et al. 1976;]. A high proportion of survivors progressed to the sub-acute and chronic condition.

4.3 Carcinogenicity of pyrrolizidine alkaloids

The metabolic conversion of 1,2-dehydropyrrolizidine ester alkaloids into strongly alkylating dihydropyrrolizine esters (4.1.1) and demonstration that these cause chemical modification to genetic material [Curtain, Edgar, 1976; Hincks, Coulombe, 1989; Hinks, Kim, et al., 1991; Kim, Stermitz, et al., 1995; Kim, Stermitz, et al., 1999; Pereira, Webb, et al., 1998; Coulombe, Drew, et al., 1999; Fu, Xia, et al., 2002; Yan, Nichols, et al., 2002; Chou, Wang, et al., 2003; Xia, Chou, et al., 2003; Xia, Chou, et al., 2004; Xia, Chou, et al., 2006; Wang, Yan, et al., 2005a; Wang, Yan, et al., 2005b; Wang, Yan, et al., 2005c] raises expectations that they will behave as genotoxic carcinogens *in vivo* and a number of 1,2-dehydropyrrolizidine alkaloids have been shown to be carcinogenic in experimental animals, primarily rats [Schoental, Head, et al., 1954; Schoental, Bensted, et al., 1963; Harris, Chen, 1970; Svoboda, Reddy, 1972; Newberne, Rogers, 1973; Hirono, Shimizu, et al., 1973; Hirono, Mori, et al., 1977; Hirono, Mori, et al.,

1978; Hirono, Haga, et al., 1979a; Hirono, Mori, et al., 1979b; Hirono, Ueno, et al., 1983; Shumaker, Robertson, et al., 1976; IARC, 1976; NCI, 1978; Rao, Reddy, 1978; Culvenor, Jago, 1979; Kuhara, Takanashi, et al., 1980; Petry, Bowden, et al., 1984; Furuya, Asada, et al., 1987; Reed, Ahern, et al., 1988; IPCS, 1988; Chan, Mahler, et al., 1994; Chan, Haseman, et al., 2003; CEPA, 1999]. Culvenor [1983], summarising doses reported to cause tumours, found that they ranged from 2 to 6 µg/kg per day for an initial short period and subsequently 0.2 to 3 µg/kg per day for periods up to one year. Intermittent rather than continuous dosing has been shown to give higher tumour yields [Hirono, Mori, et al., 1978; Kim, Stermitz, 1978] probably due to relief of the initial mitotic inhibition that is also associated with pyrrolizidine alkaloid toxicity [Jago, 1969; McLean, 1970; Mattocks, 1986]. This observation is particularly pertinant to humans where intermittent dietary exposure to low levels of pyrrolizidine alkaloids in cereal grains, honey and milk is expected.

Although liver tumours have been the cancers most commonly found, cancers of many other tissues, including the pancreas, urinary bladder, pituitary, bone, retro-peritoneal tissues and skin [IPCS, 1988], as well as leukemia [Culvenor, 1983; Chan, Haseman, et al., 2003] and rhabdomyosarcoma [Allen, Hsu, et al., 1975; Shumaker, Robertson, et al., 1976], have also been reported when purified 1,2-dehydropyrrolizidine alkaloids, extracts of plant containing these or dehydroretronecine and dehydroheliotridine metabolites, are administered to rats [IPCS, 1988].

While no cases of cancer in humans have been shown unequivocally to be caused by exposure to 1,2-dehydropyrrolizidine alkaloids, the high occurrence of primary liver tumours in Central and South Africa has been ascribed to the consumption of traditional medicinal plants belonging to the genera *Crotalaria*, *Cynoglossum*, *Heliotropium* and *Senecio* [Schoental, 1968]. There is also no reason to expect, from an understanding of the mechanism of carcinogenesis, that humans should be resistant to the carcinogenic effects of pyrrolizidine alkaloids [German Federal Department of Health, 1992].

4.4 Mutagenicity and genotoxicity of pyrrolizidine alkaloids

The mutagenicity and genotoxicity of pyrrolizidine alkaloids has been studied extensively in several systems. The data obtained up to 1988 is summarised in IPCS [1988] and more recently by Fu, Xia, et al., [2004]. Test systems that have been used are: *Escherischia coli* [Green, Muriel, 1975], *Salmonella typhimurium* (Ames test with liver S9/microsome mix required for activity to be seen) [Wehner, Thiel, et al., 1979; Koletsky, Oyasu, et al., 1978; Yamanaka, Nagao, et al.,1979; Pool, 1982; White, Krumperman, et al., 1983], *Aspergillus nidulans* [Rocha, Azevedo, 1986], *Vicia faba* [Furmanowa, Guzewska, et al., 1983] , *Allium cepa* [Avanzi, 1961] and *Drosophila melanogaster* [Clark, 1959; Clark, 1976; Candrian, Lüthy, et al., 1984; Yoon, Mason, et al., 1985; Mattocks, 1986; Frei, Lüthy, et al., 1992].

Also used were leucocytes from marsupials [Bick, Jackson, 1968; Bick, 1970; Bick, Culvenor, 1971], hepatic cells from rats [Green, Segall, et al., 1981; Mori, Sugie, et al., 1985], mice [Stoyel, Clark, 1980], Chinese hamsters [Takanashi, Umeda, et al., 1980; Bruggeman, Van der Hoefen, 1985], cattle and human lymphocytes [Ord, Herbert, et al., 1985; Kraus, Abel, et al., 1985; Martin, Thorburne, et al., 1972] demonstrated chromosomal damage in the blood cells of children suffering from veno-occlusive disease. These studies have established that many 1,2-dehydropyrrolizidine alkaloids act as strong dose-dependent mutagens.

Frei , Lüthy, et al. [1992] using the wing spot *Drosophila melanogaster* test was able to conduct a quantitative assessment of 16 pyrrolizidine alkaloids and established the following order of decreasing mutagenicity: senkirkine> monocrotaline> seneciphylline> senecionine> O^7-acetylintermedine> heliotrine> retrorsine> O^7-acetyllycopsamine> symphytine> jacoline> symlandine> intermedine> indicine> lycopsamine> indicine-N-oxide> supinine. The activity decreases 1000-fold from senkirkine to indicine-N-oxide. Supinine was inactive in this test. This sequence suggests that the macrocyclic alkaloids, senkirkine and monocrotaline, have the highest mutagenic activity. Increasing hydroxylation of the necic acids of the alkaloids results in decreasing mutagenicity. Retrorsine, for example, a 12-hydroxymethyl analogue of senecionine, exhibits a five-fold weaker mutagenicity than senecionine. Jacoline is also a hydroxylated analogue of senecionine and similarly exhibits much less mutagenicity. Where the hydroxyls are acetylated, as in O^7-acetylintermedine and O^7-acetyl-lycopsamine, they exhibited higher mutagenic behaviour than there un-acetylated derivatives. It appears therefore that lipophilicity is a factor favouring mutagenicity. The weakly mutagenic indicine-N-oxide is, for example, very water soluble. Earlier studies too had established that N-oxides of the alkaloids are less mutagenic than the corresponding free bases [Culvenor, Jago, 1979] also concluded that the mutagenicity of the alkaloids parallels the carcinogenicity of the alkaloids but not their hepatotoxicity.

The recent development of a method to study the reaction of the didehydropyrrolizidine metabolites (e.g. III) and their dehydronecine hydrolysis products (IX) with DNA and to monitor adduct formation *in vivo* has greatly enhanced the ability to study the genotoxicity of 1,2-dehydropyrrolizidine alkaloids [Yang, Yan, et al., 2001; Chou, Wang, et al., 2003]. This methodology, a ^{32}P-postlabeling-HPLC system for measuring formation of DNA adducts in animals exposed to pyrrolizidine alkaloids, has been applied to rats fed riddelliine. Dihydropyrrolizine-DNA adducts were detected in their blood within 48 hours of exposure, demonstrating the potential for using this methodology as a non-invasive biomarker for pyrrolizidine alkaloid exposure in human populations [Yan, Nichols, et al., 2002]. Treatment of human liver microsomes with riddelliine also resulted in the formation of dihydropyrroli-

zine-DNA adducts [Xia , Chou, et al., 2003]. The same adducts are produced with clivorine, lasiocarpine (Fig. 2.2) [Xia, Chou, et al., 2004; Xia, Chou, et al., 2006], retrorsine [Wang, Yan, et al., 2005a]; monocrotaline (Fig. 2.2) [Wang, Yan, et al., 2005b].

4.5 Teratogenicity and fetotoxicity of pyrrolizidine alkaloids

The teratogenic effect of pyrrolizidine alkaloids was demonstrated by a single intraperitoneal injection of heliotrine into female rats during the second week of pregnancy [Green, Christie, 1961]. Doses between 50 and 200 mg/kg caused musculoskeletal defects, the severity increasing with dose. Below 50 mg/kg no foetal abnormalities were found. Intra-uterine death and resorption of foetuses occurred above 200 mg/kg. Peterson, Jago [1980] obtained similar results when they administered 200 mg/kg of heliotrine by intra-peritoneal injection to rats on the 14th day of gestation. They also administered, for comparison, dehydroheliotridine (Fig. 4.2, IX), the common hydrolysis product of didehydropyrrolizidine metabolites of heliotridine-based 1,2-dehydropyrrolizidine alkaloids, and found it to be 2.5 times as effective on a molar basis as heliotrine in causing teratogenic effects.

While exposure of pregnant rats to 1,2-dehydropyrrolizidine alkaloids can cause teratogenic effects, premature delivery and many still-births, the alkaloids do not always cause liver damage in foetuses [Sundareson, 1942; Green, Christie, 1961; Bhattacharya, 1965; Persaud, Hoyte, 1974]. Rat foetuses appear to be more resistant than their mothers to hepatotoxicity [IPCS, 1988]. Lasiocarpine is an exception. It has been observed in rats that while both mother and foetus show liver necrosis when 100 mg/kg is administered on day 13 of pregnancy, when pregnant rats receive 35mg/kg of this alkaloid on days 13 and 17 of gestation only the foetuses exhibit liver necrosis [Newberne, Rogers, 1973]. Two pathways of foetal hepatotoxicity can be envisaged; activation of the alkaloids to dihydropyrrolizine ester (e.g. III) by cytochrome P-450 liver enzymes in the foetal liver and/or trans-placental transport of active metabolites from the maternal liver. Current evidence suggests that the foetal liver is unable to metabolise 1,2-dehydropyrrolizidine alkaloids and that, in the case of lasiocarpine at least, the liver-damaging metabolites formed in the maternal liver are transferred to the foetus [Mattocks, White, 1973; Mattocks, 1986]. Shortly before birth, and increasingly thereafter, the liver acquires the ability to metabolise 1,2-dehydropyrrolizidine alkaloids and newly born and suckling rats become highly susceptable to hepatotoxicity [Schoental, 1959; Mattocks, White, 1973; IPCS, 1988]. There have been reports of liver damage in foetuses and breast-feeding infants due to consumption of pyrrolizidine-containing products by mothers who show no evidence of poisoning [Roulet, Laurini, et al.,1988; Rasenack, Müller, et al., 2003].

The teratogenic properties of heliotrine (a monoester of heliotridine, Fig. 2.1) have also been demonstrated by experiments on larvae of fruit flies, *Drosophila melanogaster* [Brink, 1982; Clark, 1959; Clark, 1976; Frei, Lüthy, et al., 1992].

5. References

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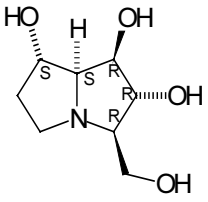
X-ray-structures

Necines
and simple alkaloids

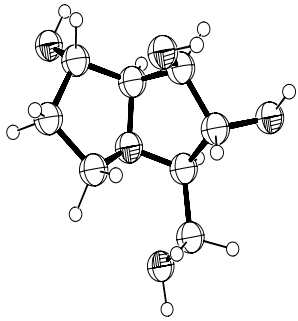
(+)-Alexine

$C_8H_{15}NO_4$ / 189.209

(1*R*,2*R*,3*R*,7*S*,7a*S*)-3-(hydroxymethyl)hexahydro-1*H*-pyrrolizine-1,2,7-triol



Structure-Drawing



Ortep-Drawing

Structure

Nash R.J., Fellows L.E., Dring J.V., Fleet G.W.J., Derome A.E., Hamor T.A., Scofield A.M., Watkin D.J.:
(1988) *Tetrahedron Lett.*, **29**, 2487-2490.

Glycosidase inhibitor

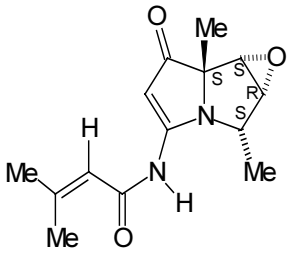
Nash R.J., Watson A.A., Asano N.:
Polyhydroxylated Alkaloids That Inhibit Glycosidases, in: Alkaloids:
Chemical And Biological Perspectives
(Edit: Pelletier S.W.) Vol. 11, chap. 5, 345-376,
New York, Pergamon 1996.

Occurrence in *Alexa leiopetala*.

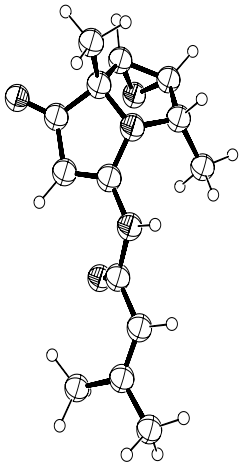
Bohemamine

$C_{14}H_{18}N_2O_3$ / 262.304

***N*-[(1a*R*,2*S*,6a*S*,6b*S*)-2,6a-dimethyl-6-oxo-1a,6,6a,6b-tetrahydro-2*H*-oxireno[*a*]pyrrolizin-4-yl]-3-methylbut-2-enamide**



Structure-Drawing



Ortep-Drawing

Structure

Doyle T.W., Nettleton D.E., Balitz D.M., Moseley J.E., Grulich R.E., McCabe T., Clardy J.:
(1980) *J. Org. Chem.*, **45**, 1324-1326.

Antitumor agent

Occurrence in *Streptomyces* spec.:

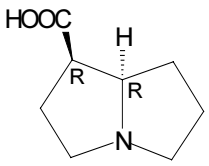
Zhang Q., Schrader K.K., ElSohly H.N., Takamatsu S.:
(2003) *J. Antibiot.*, **56**, 673-681.

1-*endo*-Carboxypyrrolizidine

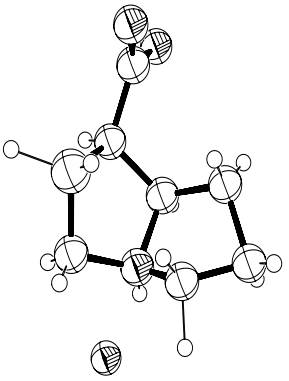
$C_8H_{13}NO_2 \cdot HBr$ / 155.194 · 80.912

(1*R*,7a*R*)-hexahydro-1*H*-pyrrolizine-1-carboxylic acid

Measured as Hydrobromide



Structure-Drawing



Ortep-Drawing

Structure

Söderberg E.:
(1971) *Acta Chem. Scand*., **25**, 615-624.

Non toxic
In analogy to:

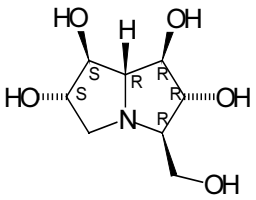
Mattocks A.R., White I.N.H.:
(1971) *Nature New Biol*., **231**, 114-115.

Occurrence in *Chysis bractescence*.

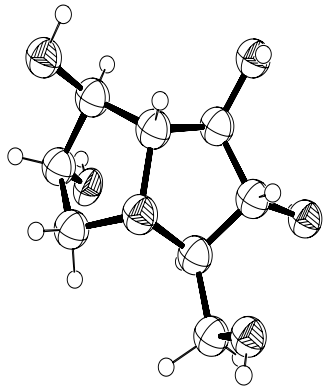
Casuarine

$C_8H_{15}NO_5$ / 205.208

(1*R*,2*R*,3*R*,6*S*,7*S*,7a*R*)-3-(hydroxymethyl)hexahydro-1*H*-pyrrolizine-1,2,6,7-tetrol



Structure-Drawing



Ortep-Drawing

Structure

Nash R.J., Thomas P.I., Waigh R.D., Fleet G.W.J., Wormald M.R., de Q.Lilley P.M., Watkin D.J.:
(1994) *Tetrahedron Lett.*, 7849-7852.

Glycosidase inhibitor

Occurrence in *Casuarina equisetifolia:*

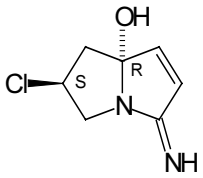
Nash R.J., Watson A.A., Asano N.:
Polyhydroxylated Alkaloids That Inhibit Glycosidases, in: Alkaloids:
Chemical And Biological Perspectives
(Edit: Pelletier S.W.) Vol. 11, chap. 5, 345-376,
New York, Pergamon, 1996.

Clazamycin A

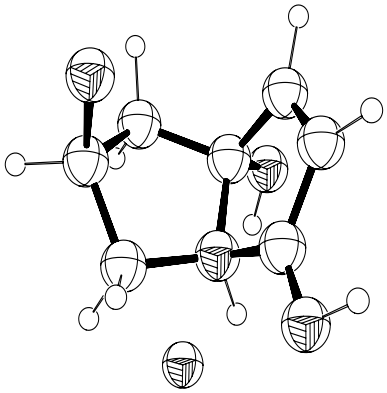
$C_7H_9ClN_2O \cdot HCl$ / 172.612 · 36.461

(2*S*,7a*R*)-2-chloro-5-imino-2,3-dihydro-1*H*-pyrrolizin-7a(5*H*)-ol

Mesured as Hydrochloride



Structure-Drawing



Ortep-Drawing

Structure

Nakamura H., Iitaka Y., Umezawa H.:
(1979) *J. Antibiot.*, **32**, 765-767.

Antitumor antibiotic

Occurrence in *Streptomyces puniceus:*

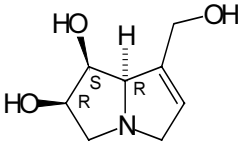
Buechter D.D., Thurston D.E.:
(1987) *J. Nat. Prod.*, **50**, 360-367.

Dolak L.A., DeBoer C.:
17th Interscience on Antimicrobial Agents and Chemotherpy, New York , Oct.1977.

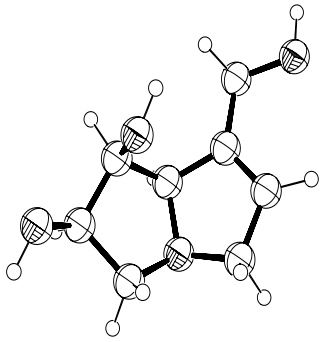
Crotanecine

$C_8H_{13}NO_3$ / 171.194

(1*S*,2*R*,7a*R*)-7-(hydroxymethyl)-2,3,5,7a-tetrahydro-1*H*-pyrrolizine-1,2-diol



Structure-Drawing



Ortep-Drawing

Structure

Richardson J.F., Culvenor C.C.J.:
(1985) *Acta Cryst. C***41**, 1475-1477.

Non toxic

Culvenor C.C.J., Edgar J.A., Jago M.V., Outteridge A., Peterson J.E., Smith L.W.:
(1976) *Chem. Biol. Interact.*, **12**, 299.

Mattocks A.R., White I.N.H.:
(1971) *Nature New Biol.*, **231**, 114-115.

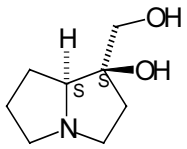
Occurrence in *Crotalaria madurensis*.

Curassanecine

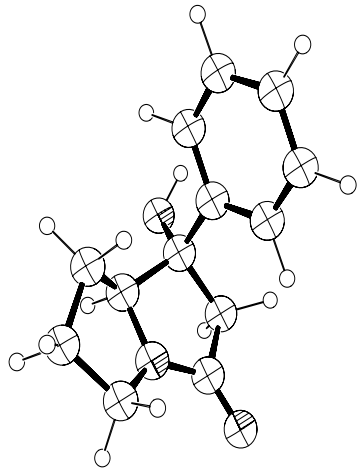
$C_8H_{15}NO_2$ / 157.210

(1*S*,7a*S*)-1-(hydroxymethyl)hexahydro-1*H*-pyrrolizin-1-ol

Structure deduced by measuring the (1*S*,7a*S*)-1-hydroxy-1-phenylhexahydro-3*H*-pyrrolizin-3-one derivative ($C_{13}H_{15}NO_2$ / 217.264)



Structure-Drawing



Ortep-Drawing

Structure

Gramain J.C., Remuson R., Vallee-Goyet D., Guilhem J., Lavaud C.:
(1991) *J. Nat. Prod.*, **54**, 1062-1067.

Non toxic
in analogy to:

Mattocks A.R., White I.N.H.:
(1971) *Nature New Biol.,* **231**, 114-115.

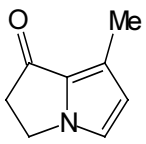
Occurrence in *Heliotropium curassavicum:*

Mohanraj S., Subramanian P.S., Herz W.:
(1982) *Phytochemistry*, **21**, 1775-1779

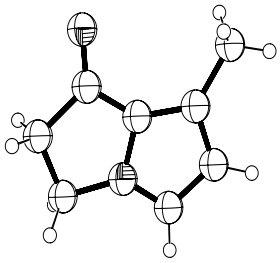
Danaidone

C_8H_9NO / 135.163

7-methyl-2,3-dihydro-1*H*-pyrrolizin-1-one



Structure-Drawing



Ortep-Drawing

Structure

Knoch F., Wiedenfeld H., Roeder E.;
(1991) *Z. Kristallogr.*, **194,** 135-136.

Pheromone
of *Lepidoptera* butterflies

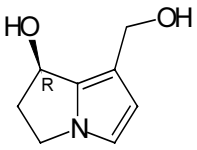
Edgar J.A.:
(1975) *Phil.Trans. R. Soc. London B*, **272**, 467-476.

Pliske T.E.:
(1975) *Environm. Entomol.*, **4**, 455-473.

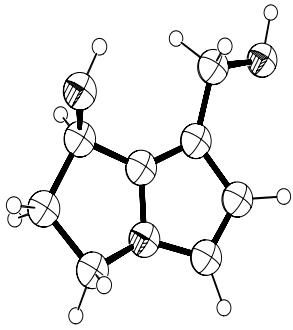
Dehydroretronecine

$C_8H_{11}NO_2$ / 153.178

(1*R*)-7-(hydroxymethyl)-2,3-dihydro-1*H*-pyrrolizin-1-ol



Structure-Drawing



Ortep-Drawing

Structure

Mackay M.F., Mitrprachachon P.P., Culvernor C.C.J.:
(1985) *Acta Cryst. C***41**, 1104-1106.

Toxicity

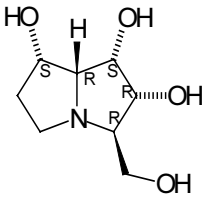
Reed R.L., Ahern K.G., Pearson G.D., Buhler D.R.:
(1988) *Carcinogen*., **9**,1355-1361.

1,7a-Diepialexine

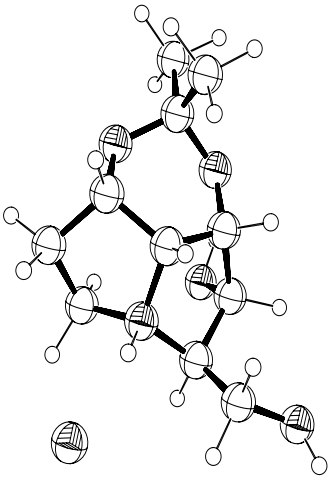
$C_8H_{15}NO_4 \cdot HCl$ / 189.209 · 36.461

(1*S*,2*R*,3*R*,7*S*,7a*R*)-3-(hydroxymethyl)hexahydro-1*H*-pyrrolizine-1,2,7-triol

Measured as Hydrochloride



Structure-Drawing



Ortep-Drawing

Structure

Nash R.J., Fellows L.E., Dring J.V., Fleet G.W.J., Girdhar A., Ramsden N.G., Peach J.M., Hegarty M.P., Scofield A.M.:
(1990) *Phytochemistry*, **29**, 111-114.

Glycosidase inhibitor

Nash R.J., Watson A.A., Asano N.:
Polyhydroxylated Alkaloids That Inhibit Glycosidases, in: Alkaloids:
Chemical And Biological Perspectives
(Edit: Pelletier S.W.) Vol. 11, chap. 5, 345-376, New York, Pergamon, 1996.

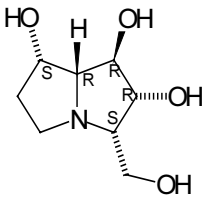
Occurrence in *Castanospermum australe*.

3,8-Diepialexine

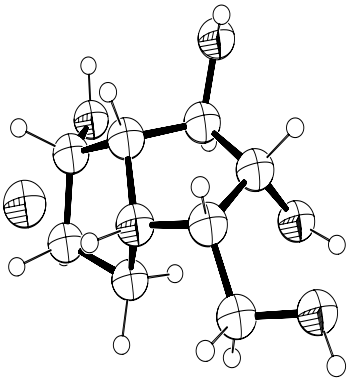
$C_8H_{15}NO_4$ · HCl / 189.209 · 36.461

(1*R*,2*R*,3*S*,7*S*,7a*R*)-3-(hydroxymethyl)hexahydro-1*H*-pyrrolizine-1,2,7-triol

Measured as Hydrochloride



Structure-Drawing



Ortep-Drawing

Structure

Nash R.J., Fellows L.E., Plant A.C., Fleet G.W.J., Derome A.E., Baird P.D., Hegarty, M.P., Scofield A.M.: (1988) *Tetrahedron*, **44**, 5959-5964.

Glycosidase inhibitor

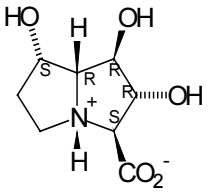
Nash R.J., Watson A.A., Asano N.: Polyhydroxylated Alkaloids That Inhibit Glycosidases, in: Alkaloids: Chemical And Biological Perspectives (Edit: Pelletier S.W.) Vol. 11, chap. 5, 345-376, New York, Pergamon, 1996.

Ocurrence in *Castanospermum australe*.

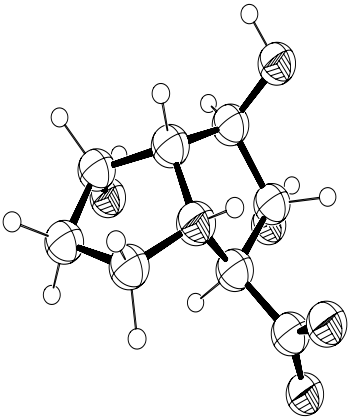
7a-Epialexaflorine

$C_8H_{13}NO_5$ / 203.193

(1*R*,2*R*,3*S*,7*S*,7a*R*)-1,2,7-trihydroxyhexahydro-1*H*-pyrrolizine-3-carboxylic acid



Structure-Drawing



Ortep-Drawing

Structure

De S.-Pereira A.C., Kaplan M.A.C., Maia J.G.S., Gottlieb O.R.,Nash R.J., Fleet G., Pearce L., Watkin D.J., Scofield A.M.:
(1991) *Tetrahedron*, **47**, 5637-5640.

Glycosidase inhibitor

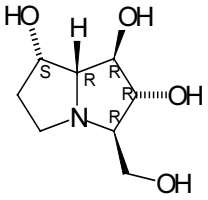
Nash R.J., Watson A.A., Asano N.:
Polyhydroxylated Alkaloids That Inhibit Glycosidases, in: Alkaloids:
Chemical And Biological Perspectives
(Edit: Pelletier S.W.) Vol. 11, chap. 5, 345-376, New York, Pergamon, 1996.

Occurrence in *Alexa grandiflora*.

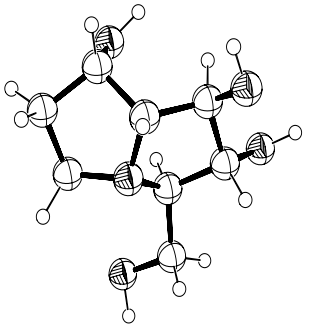
7a-Epialexine *syn.* Australine

$C_8H_{15}NO_4$ / 189.209

(1*R*,2*R*,3*R*,7*S*,7a*R*)-3-(hydroxymethyl)hexahydro-1*H*-pyrrolizine-1,2,7-triol



Structure-Drawing



Ortep-Drawing

Structure

Molyneux R.J., Benson M., Wong R.Y., Tropea J.E., Elbein A.D.: (1988) *J. Nat. Prod.*, **51**, 1198-1206.

Glycosidase inhibitor

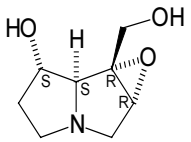
Nash R.J., Watson A.A., Asano N.: Polyhydroxylated Alkaloids That Inhibit Glycosidases, in: Alkaloids: Chemical And Biological Perspectives (Edit: Pelletier S.W.) Vol. 11, chap. 5, 345-376, New York, Pergamon, 1996.

Occurrence in *Castanospermum australe*.

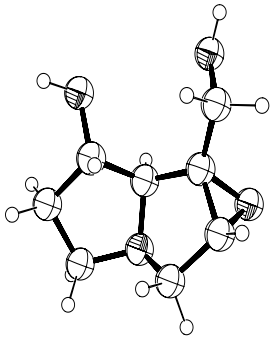
α-Epoxy-heliotridine

$C_8H_{13}NO_3$ / 171.194

(1a*R*,6*S*,6a*S*,6b*R*)-6b-(hydroxymethyl)hexahydro-2*H*-oxireno[*a*] pyrrolizin-6-ol



Structure-Drawing



Ortep-Drawing

Structure

Glinski J.A., Vanderveer D., Zalkow L.H.:
(1985) *Acta Cryst.C***41**, 1345-1348.

Toxicity

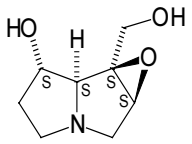
Schoental R.:
(1970) *Nature (London)*, **227**, 401-402:

Assumed intermediate in metabolic toxification.

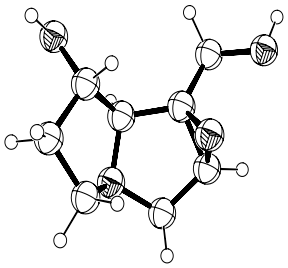
ß-Epoxy-heliotridine

$C_8H_{13}NO_3$ / 171.194

(1a*S*,6*S*,6a*S*,6b*S*)-6b-(hydroxymethyl)hexahydro-2*H*-oxireno[*a*] pyrrolizin-6-ol



Structure-Drawing



Ortep-Drawing

Structure

Glinski J.A., Vanderveer D., Zalkow L.H.:
(1985) *Acta Cryst. C***41**, 1345-1348.

Toxicity

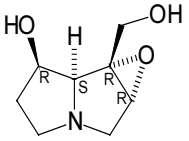
Schoental R.:
(1970) *Nature (London)*, **227**, 401-402:

Assumed intermediate in metabolic toxification.

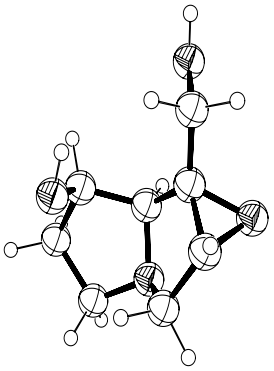
α-Epoxy-retronecine

$C_8H_{13}NO_3$ / 171.194

(1a*R*,6*R*,6a*S*,6b*R*)-6b-(hydroxymethyl)hexahydro-2*H*-oxireno[*a*] pyrrolizin-6-ol



Structure-Drawing



Ortep-Drawing

Structure

Glinski J.A., Vanderveer D., Zalkow L.H.:
(1985) *Acta Cryst.C***41**, 1345-1348.

Toxicity

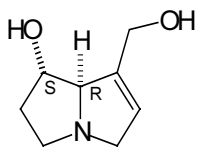
Schoental R.:
(1970) *Nature (London)*, **227**, 401-402:

Assumed intermediate in metabolic toxification.

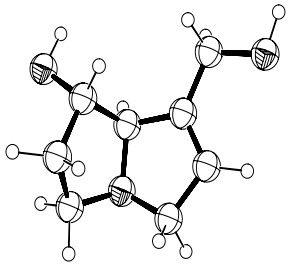
Heliotridine

$C_8H_{13}NO_2$ / 155.194

(1*S*,7a*R*)-7-(hydroxymethyl)-2,3,5,7a-tetrahydro-1*H*-pyrrolizin-1-ol



Structure-Drawing



Ortep-Drawing

Structure

Gelbaum L.T., Glinski J.A., Van Derveer D., Zalkow L.H.:
(1985) *Acta Cryst. C***41**, 1342-1345.

Toxicity

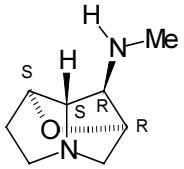
Culvenor C.C.J., Downing D.T., Edgar J.A., Jago M.V.:
(1969) *Ann. N.Y. Acad. Science*, **163**, 837-847.

Loline syn. **Festucine**

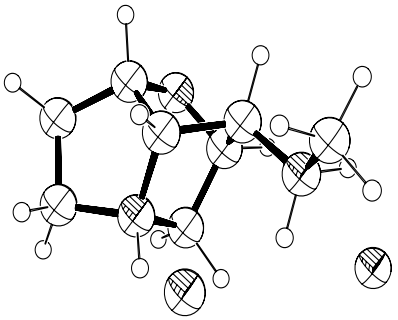
$C_8H_{14}N_2O \cdot 2\ HCl$ / 154.210 · 72.921

(1*S*,6*R*,7*R*,7a*S*)-*N*-methylhexahydro-1*H*-1,6-epoxypyrrolizin-7-amine

Measured as dihydrochloride



Structure-Drawing



Ortep-Drawing

Structure

Knoch F., Wiedenfeld H., Roeder E.:
(1993) *Z. Kristallogr.*, **205**, 346-347.

and:

Bates R.B., Morehead S.R.:
(1972) *Tetrahedron Lett.*, 1629-1630.

Yates S.G., Tookey H.L.:
(1965) *Aust. J. Chem.*, **18**, 53-60.

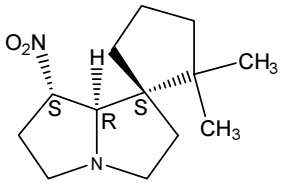
Alkaloid produced by endophyt
(*Acremonium coenophialum)* infected tall fescue

Powell R.G., Petroski J.:
In: Alkaloids: Chemical and Biological Perspectives,
The Loline Group of Pyrrolizidine Alkaloids
(Ed. Pelletier, S.W.) Vol. 8, Chap. **4**, 320-338,
New York, Pergamon, 1996.

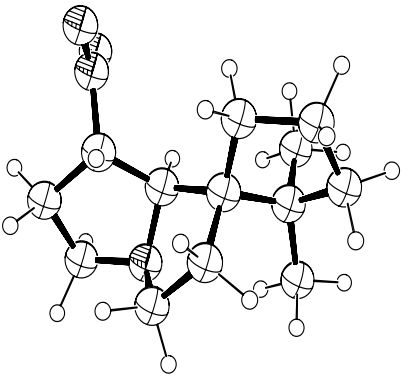
Nitropolyzonamine

$C_{13}H_{22}N_2O_2$ / 238.326

(1*S*,7'*S*,7a'*R*)-2,2-dimethyl-7'-nitrohexahydrospiro[cyclo-pentane-1,1'-pyrrolizine]



Structure-Drawing



Ortep-Drawing

Structure

Hutchinson K.D., Silverton J.V., Daly J.W.:
(1994) *Tetrahedron*, **50**, 6129-6136.

and as Perchlorate:

Miller R.W., McPhail A.T.:
(1978) *J. Chem. Res. (S),* 76.

Defensive secret

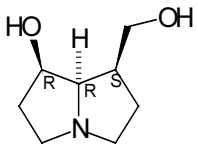
from milliped *Polyzonium rosalbum* and
Panamanian poison-frog *Dendrobates pumilio:*

Daly J.W.:
(1995) *Proc. Natl. Acad. Sci.*, USA, **92,** 9-13.

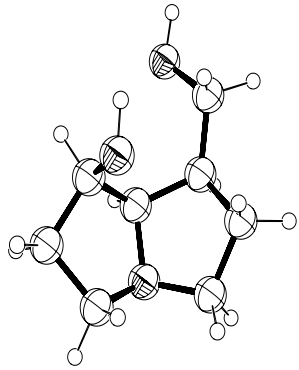
Platynecine

$C_8H_{15}NO_2$ / 157.210

(1*R*,7*S*,7a*R*)-7-(hydroxymethyl)hexahydro-1*H*-pyrrolizin-1-ol



Structure-Drawing



Ortep-Drawing

Structure

Freer A.A., Kelly H.A., Robins D.J.:
(1987) *Acta Cryst.* C**43**, 2020-2023.

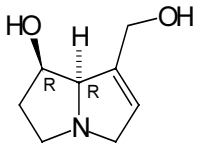
Non toxic

Mattocks A.R, White I.N.H.:
(1971) *Nature New Biol.*, **231**, 114-115.

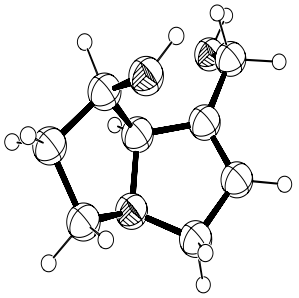
Retronecine

$C_8H_{13}NO_2$ / 155.194

(1*R*,7a*R*)-7-(hydroxymethyl)-2,3,5,7a-tetrahydro-1*H*-pyrrolizin-1-ol



Structure-Drawing



Ortep-Drawing

Structure

Gelbaum L.T., Glinski J.A.,Van Derveer D., Zalkow L.H.:
(1985) *Acta Cryst. C***41**, 1342-1345.

Toxicity

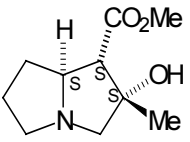
Culvenor C.C.J., Downing D.T., Edgar J.A., Jago M.V.:
(1969) *Ann. N.Y. Acad. Science*, **163**, 837-847.

Tussilagine

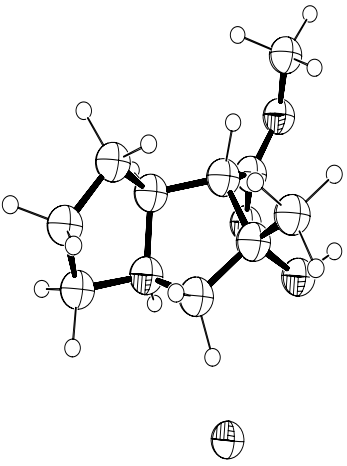
$C_{10}H_{17}NO_3 \cdot HCl$ / 199.247 · 36.461

Methyl (1*S*,2*S*,7a*S*)-2-hydroxy-2-methylhexahydro-1*H*-pyrrolizine-1-carboxylate Hydrochloride

Measured as Hydrochloride



Structure-Drawing



Ortep-Drawing

Structure

Wiedenfeld H., Roeder E., Kirfel A., Will G.:
(1983) *Arch. Pharm.*, **316**, 367-371.

Non toxic
in analogy to:

Mattocks A.R., White I.N.H.:
(1971) *Nature New Biol.,* **231**, 114-115.

Occurrence in *Tussilago farfara:*

Roeder E., Wiedenfeld H., Jost E.H.:
(1981) *Planta Med.*, **43**, 99-102.

Passreiter M., Willuhn G., Roeder E.:
(1992) *Planta Med.*, **58**, 556-557.

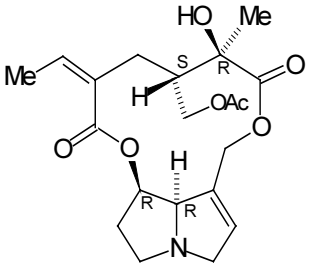
Alkaloids

Acetylgynuramine

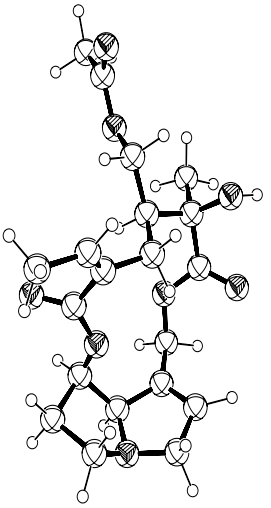
$C_{20}H_{27}NO_7$ / 393,431

[(3*Z*,5*S*,6*R*,14a*R*,14b*R*)-6-hydroxy-3-ethylidene-6-methyl-2,7-dioxo-2,3,4,5,6,7,9,11,13,14,14a,14b-dodecahydro[1,6]dioxacyclo-dodecino [2,3,4-*gh*]pyrrolizin-5-yl]methyl acetate

(15*Z*)-12-hydroxy-11,16-dioxosenecionan-19-yl acetate



Structure-Drawing



Ortep-Drawing

Structure

Wiedenfeld H., Kirfel A., Roeder E., Will G.:
(1983) *Phytochemistry,* **22,** 2065-2067.

Toxicity
not yet reported

Occurrence in *Gynura scandens:*

Wiedenfeld H.:
(1982) *Phytochemistry*, **21**, 2767-2768.

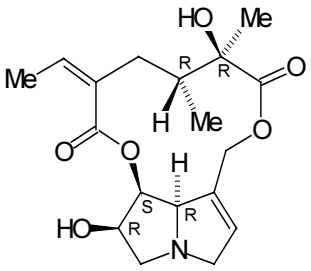
Anacrotine

$C_{18}H_{25}NO_6$ · ½ C_2H_5OH · ½ H_2O / 351.394 · 23.034 · 9.008

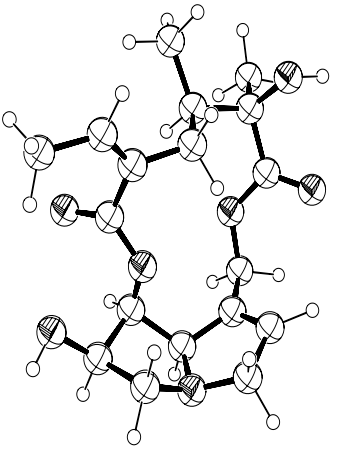
(3*Z*,5*R*,6*R*,14*R*,14a*S*,14b*R*)-6,14-dihydroxy-3-ethylidene-5,6-dimethyl-3,4,5,6,9,11,13,14,14a,14b-decahydro[1,6]dioxacyclo-dodecino[2,3,4-*gh*]pyrrolizine-2,7-dione

(6β,15*Z*)-6,12-dihydroxysenecionan-11,16-dione

Measured as Ethanol-water Solvate



Structure-Drawing



Ortep-Drawing

Structure

Mackay M.F., Sadek M., Culvenor C.C.J.: (1984) *Acta Cryst. C***40**, 1073-1077.

Toxicity

Culvenor C.C.J., Edgar J.A., Jago M.V., Outteridge A., Peterson J.E., Smith L.W.: (1976) *Chem. Biol. Interact.,* **12**, 299-324.

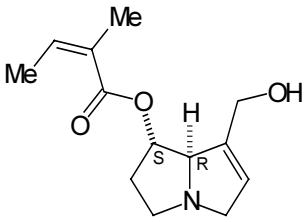
Occurrence in *Crotalaria anagyroides:*

Atal C.K., Kapur K.K., Culvenor C.C.J., Smith L.W.: (1966) *Tetrahedron Lett.*, 537-544.

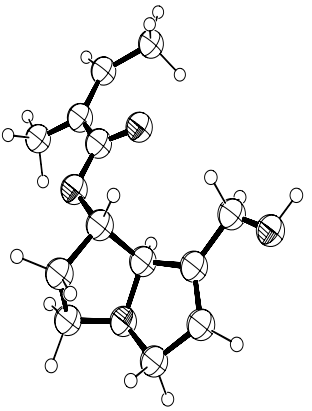
O^7-Angeloylheliotridine

$C_{13}H_{19}NO_3$ / 237.295

(1*S*,7a*R*)-7-(hydroxymethyl)-2,3,5,7a-tetrahydro-1*H*-pyrrolizin-1-yl (2*Z*)-2-methylbut-2-enoate



Structure-Drawing



Ortep-Drawing

Structure

Wiedenfeld H., Roeder E., Kirfel A., Will G.:
(1981) *Arch. Pharm.,* **314**, 737-740.

Toxicity

Culvenor C.C.J., Downing D.T., Edgar J.A., Jago M.V.:
(1969) *Ann. N.Y. Acad. Science,* **163**, 837-847.

Culvenor C.C.J., Edgar J.A., Jago M.V.,
Outteridge A., Peterson J.E., Smith L.W.:
(1976) *Chem. Biol. Interact.,* **12**, 299-324.

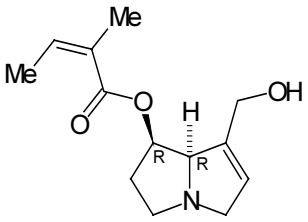
Occurrence in *Heliotropium supinum:*

Crowley H.C., Culvenor C.C.J.:
(1959) *Aust. J. Chem., **12**,* 694-704.

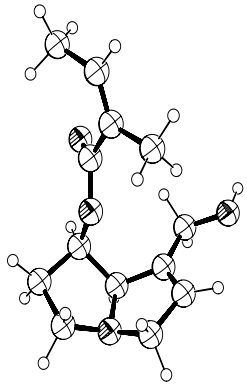
O^7-Angeloylretronecine

$C_{13}H_{19}NO_3$ / 237.295

(1*R*,7a*R*)-7-(hydroxymethyl)-2,3,5,7a-tetrahydro-1*H*-pyrrolizin-1-yl (2*Z*)-2-methylbut-2-enoate



Structure-Drawing



Ortep-Drawing

Structure

Wiedenfeld H., Kirfel A., Roeder E., Will G.: (1985) *Arch. Pharm.,* **318,** 294-299.

Toxicity

Culvenor C.C.J., Edgar J.A., Jago M.V., Outteridge A., Peterson J.E., Smith L.W.: (1976) *Chem. Biol. Interact.*, **12**, 299-324.

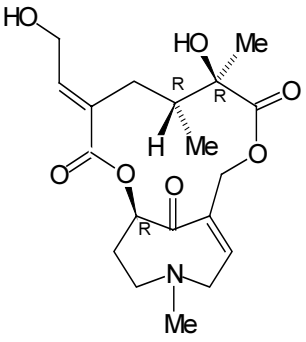
Occurrence in *Alkanna tinctoria*:

Roeder E., Wiedenfeld H., Schraut R.: (1984) *Phytochemistry*, **23**, 2125-2126.

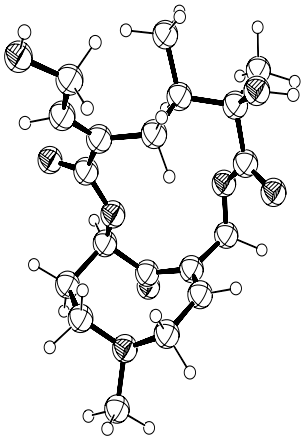
Anonamine

$C_{19}H_{27}NO_7$ / 381.420

(1*R*,4*E*,6*R*,7*R*)-7-hydroxy-4-(2-hydroxyethylidene)-6,7,14-trimethyl-2,9-dioxa-14-azabicyclo[9.5.1]heptadec-11-ene-3,8,17-trione



Structure-Drawing



Ortep-Drawing

Structure

Glinski J.A., Asibal C.F., Van Derveer D., Zalkow L.H.:
(1988) *Acta Cryst. C***44**, 1593-1598.

Toxicity
not yet reported

Occurrence in *Senecio anonymus*:

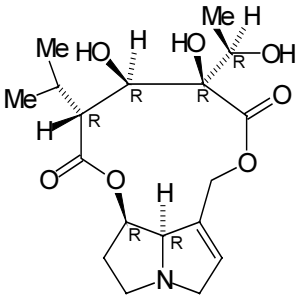
Zalkow L.H., Asibal C.F., Glinski J.A., Bonetti L.T., Van Derveer D., Powis, G.:
(1988) *J. Nat. Prod.,* **51**, 690-702

Axillarine

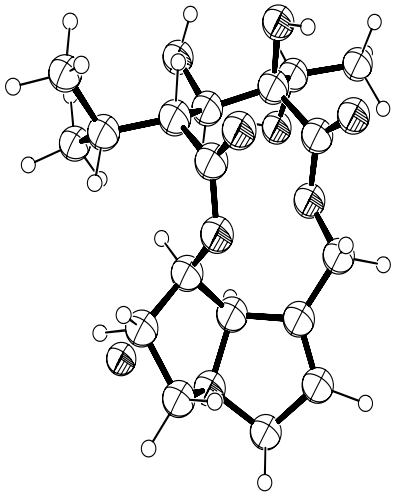
$C_{18}H_{27}NO_7 \cdot HBr \cdot C_2H_6O$ / 369.410 · 80.912 · 46.068

(3*R*,4*R*,5*R*,13a*R*,13b*R*)-4,5-dihydroxy-5-[(1*R*)-1-hydroxyethyl]-3-isopropyl-4,5,8,10,12,13,13a,13b-octahydro-2*H*-[1,6]dioxacyclo-undecino[2,3,4-*gh*]pyrrolizine-2,6(3*H*)-dione

Measured as Hydrobromide Ethanol Solvate



Structure-Drawing



Ortep-Drawing

Structure

Stoeckli-Evans H., Crout D.H.G.:
(1976) *Helv. Chim. Acta,* **59**, 2168-2178.

Toxicity
not yet reported

Occurrence in *Crotalaria axillaris:*

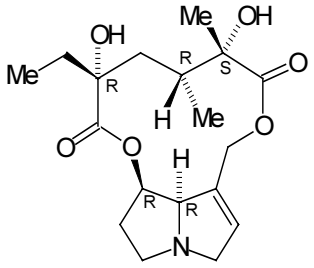
Crout D.H.G.:
(1969) *J. Chem. Soc. (C),* 1379-1385.

Bisline

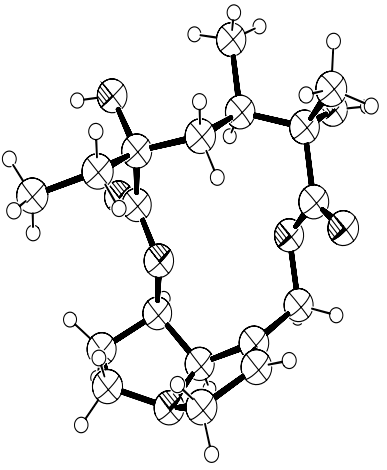
$C_{18}H_{27}NO_6$ / 353.410

(3*R*,5*R*,6*S*,14a*R*,14b*R*)-3,6-dihydroxy-3-ethyl-5,6-dimethyl-3,4,5,6,9,11,13,14,14a,14b-decahydro[1,6]dioxacyclododecino[2,3,4-*gh*]pyrrolizine-2,7-dione

(12*S*,15*R*)-12,15-dihydroxy-15,20-dihydrosenecionan-11,16-dione



Structure-Drawing



Ortep-Drawing

Structure

Susag L., Parvez M., Mathenge S., Benn M. H.:
(2000) *Phytochemistry,* **54,** 933-935.

Toxicity
not yet reported

Occurrence in *Senecio othonniformis:*

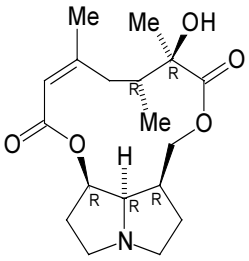
Coucourakis E.D., Gordon-Gray C.G.:
(1970) *J. Chem. Soc.* (*C)*, 2312-2315.
.

Bulgarsenine

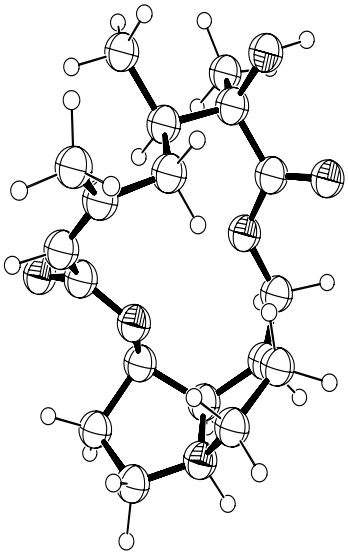
$C_{18}H_{27}NO_5 \cdot C_4H_6O_6$ / 337.411 · 150.087

(6*R*,7*R*,10a*S*,15a*R*,15b*R*)-7-hydroxy-4,6,7-trimethyl-6,7,10,10a,11,12,14,15,15a,15b-decahydro-2*H*-[1,6]dioxacyclotridecino[2,3,4-*gh*]pyrrolizine-2,8(5*H*)-dione

Measured as Bitartrate



Structure-Drawing



Ortep-Drawing

Structure

Stoeckli-Evans H.:
(1980) *Acta Cryst. B***36**, 3150-3153.

Non toxic
in analogy to:

Mattocks A.R., White I.N.H.:
(1971) *Nature New Biol.,* **231**, 114-115.

Occurrence in *Senecio nemorensis var. bulgaricus:*

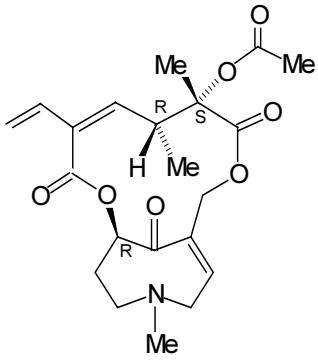
Nghia T.H., Sedmera P., Klasek A., Boeva A., Drjanovska A., Doleje L., Santavy F.:
(1976) *Collect. Czech. Chem. Commun.,* **41**, 2952-2963.

Clivorine

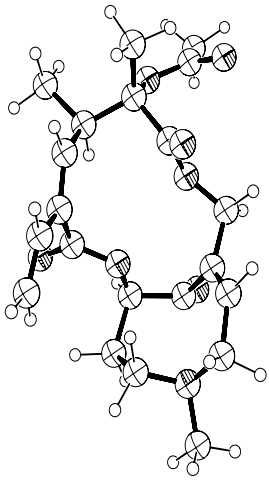
$C_{21}H_{27}NO_7 \cdot H_2O$ / 405.442 · 18.015

(1*R*,6*R*,7*S*)-6,7,14-trimethyl-3,8,17-trioxo-4-vinyl-2,9-dioxa-14-azabicyclo[9.5.1]heptadeca-4,11-dien-7-yl acetate

Measured as Hydrate



Structure-Drawing



Ortep-Drawing

Structure

Birnbaum K.B., Klasek A., Sedmera P., Snatzke G., Johnson L.F., Santavy F.: (1971) *Tetrahedron Lett.*, 3421-3424.

Birnbaum K.B.: (1972) *Acta Cryst. B***28**, 2825-2833.

Toxicity

Ji L.L., Tang A.M., Tang J., Zhang M., Wang Z.T.: (2004) *Zhongguo Tianran Yaowu*, **2**, 239-241.

Occurrence in *Ligularia clivorum:*

Klasek A., Sedmera P., Santavy F.: (1970) *Collect. Czech. Chem. Commun.*, ***35***, 956-969.

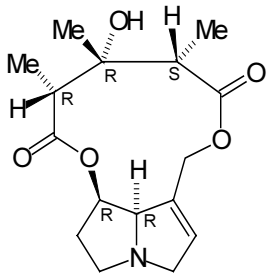
Crispatine

$C_{16}H_{23}NO_5 \cdot H_2O$ / 309.358 · 18.015

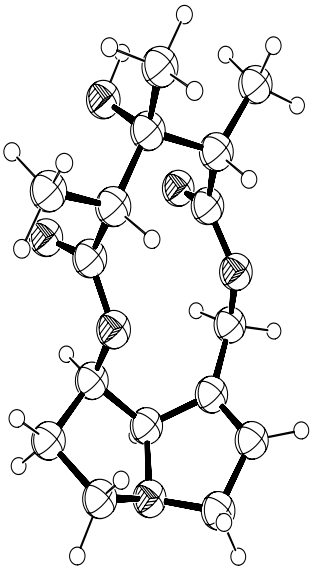
(3*R*,4*R*,5*S*,13a*R*,13b*R*)-4-hydroxy-3,4,5-trimethyl-4,5,8,10,12,13,13a,13b-octahydro-2*H*-[1,6]dioxacycloundecino

[2,3,4-*gh*]pyrrolizine-2,6(3*H*)-dione

Measured as Monohydrat



Structure-Drawing



Ortep-Drawing

Structure

Mackay M.F., Sadek M., Culvenor C.C.J.:
(1984) *Acta Cryst. C***40**, 470-472.

Toxicity

Culvenor C.C.J., Downing D.T., Edgar J.A., Jago M.V.:
(1969) *Ann. N.Y. Acad. Science,* **163**, 837-847.

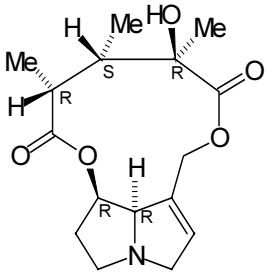
Occurrence in *Crotalaria crispata*:

Culvenor C.C.J., Smith L.W.:
(1963) *Aust. J. Chem.,* **16**, 239-25.

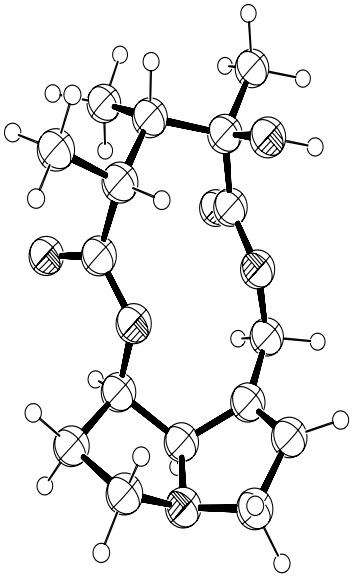
Crotaleschenine

$C_{16}H_{23}NO_5$/ 309.358

(3*R*,4*S*,5*R*,13a*R*,13b*R*)-5-hydroxy-3,4,5-trimethyl-4,5,8,10,12, 13,13a,13b-octahydro-2*H*-[1,6]dioxacycloundecino[2,3,4-*gh*] pyrrolizine-2,6(3*H*)-dione



Structure-Drawing



Ortep-Drawing

Structure

Smith, L.W., Edgar, J.A., Willing, R.I., Gable, R.W., Mackay, M.F., Suri, O.P., Atal, C.K., Culvenor, C.C.J.: (1988) *Aust. J. Chem.,* **41**, 429-436.

Toxicity

Culvenor C.C.J., Downing D.T., Edgar J.A., Jago M.V.: (1969) *Ann. N.Y. Acad. Science*, **163**, 837-847.

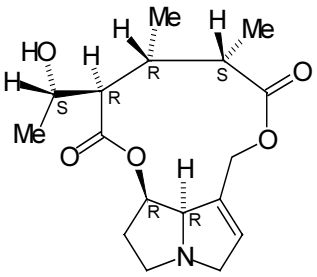
Occurrence in *Crotalaria leschenaultii*.

Crotananine

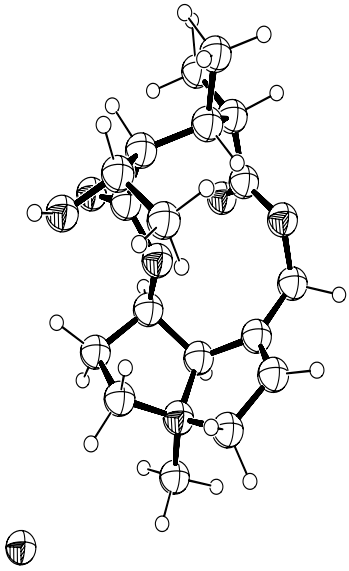
$C_{17}H_{25}NO_5 \cdot CH_3I$ / 323.384 · 141.939

(3*R*,4*R*,5*S*,13a*R*,13b*R*)-3-[(1*S*)-1-hydroxyethyl]-4,5-dimethyl-4,5,8,10,12,13,13a,13b-octahydro-2*H*-[1,6]dioxacycloundecino[2,3,4-*gh*]pyrrolizine-2,6(3*H*)-dione

Measured as N-methyl Iodide



Structure-Drawing



Ortep-Drawing

Structure

Sharma, S.D., Padmanabhan, V.M., Goswami, K.N., Gupta, V.K.: (1993) *Cryst. Res. Technol.*, **28**, 945.

Toxicity

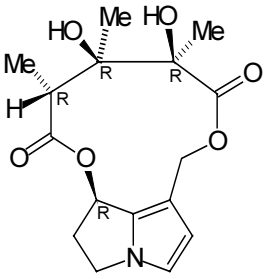
Tandon B.N., Puri B.K., Tandon A.K., Joshi Y.K.: (1978) *Ind. J. Med. Res.*, **68**, 790-797.

Ocurrence in *Crotalaria nana*.

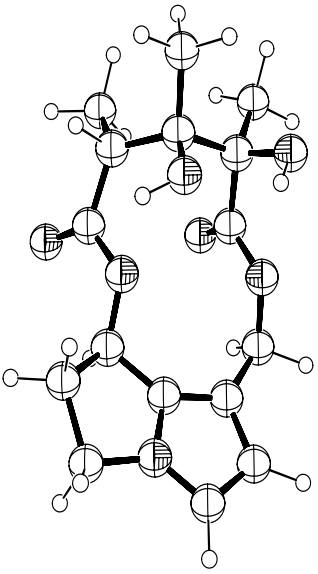
Dehydromonocrotaline

$C_{16}H_{21}NO_6$ / 323.341

(3*R*,4*R*,5*R*,13a*R*)-4,5-dihydroxy-3,4,5-trimethyl-4,5,8,12,13,13a-hexahydro-2*H*-[1,6]dioxacycloundecino[2,3,4-*gh*]pyrrolizine-2,6(3*H*)-dione



Structure-Drawing



Ortep-Drawing

Structure

Mackay M.F., Sadek M.,
Culvenor C.C.J., Smith L.W.:
(1984) *Acta Cryst.* C**40,** 473-476.

Toxicity

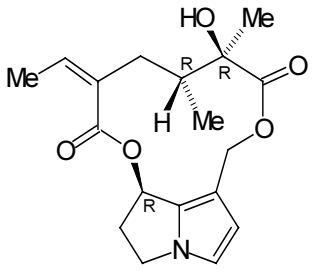
Kim H.Y., Stermitz F.R., Li J.K.K., Coulombe Jr. R.A.:
(1999) *Food Chem. Tox.*, **37,** 619-625.

Dehydrosenecionine

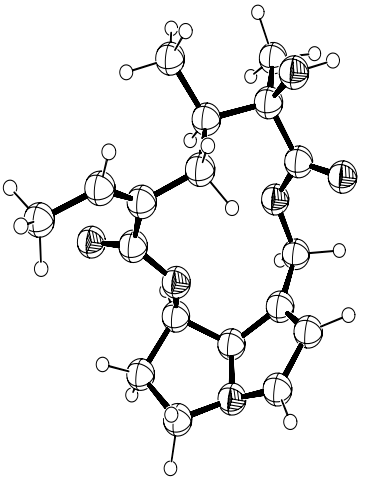
$C_{18}H_{25}NO_5$ / 333.379

(3*Z*,5*R*,6*R*,14a*R*)-6-hydroxy-3-ethylidene-5,6-dimethyl-3,4,5,6,9,13,14,14a-octahydro[1,6]dioxacyclododecino[2,3,4-*gh*]pyrrolizine-2,7-dione

(15*Z*)-12-hydroxy-3,8-didehydrosenecionan-11,16-dione



Structure-Drawing



Ortep-Drawing

Structure

Mackay M. F., Sadek M., Culvenor C.C.J., Smith L.W.:
(1983) *Acta Cryst. C***39**, 1230-1233.

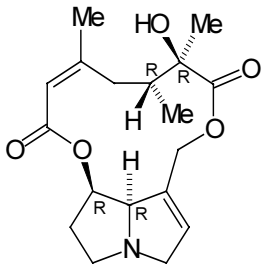
Toxicity

Kim H.Y., Stermitz F.R., Li J.K.K., Coulombe Jr. R.A.:
(1999) *Food Chem. Tox*., **37,** 619-625.

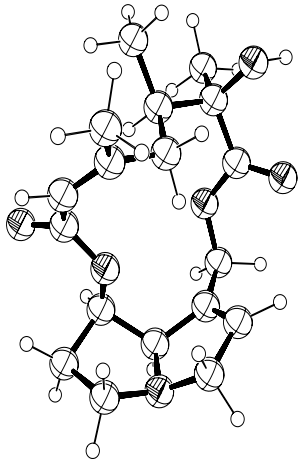
Doronenine

$C_{18}H_{25}NO_5$ / 335.395

(6*R*,7*R*,15a*R*,15b*R*)-7-hydroxy-4,6,7-trimethyl-6,7,10,12,14, 15,15a,15b-octahydro-2*H*-[1,6]dioxacyclotridecino[2,3,4-*gh*] pyrrolizine-2,8(5*H*)-dione



Structure-Drawing



Ortep-Drawing

Structure

Kirfel A., Will G., Wiedenfeld H., Roeder E.:
(1980) *Cryst. Struct. Comm.,* **9**, 353-361.

Toxicity
not yet reported

Occurrence in *Senecio doronicum:*

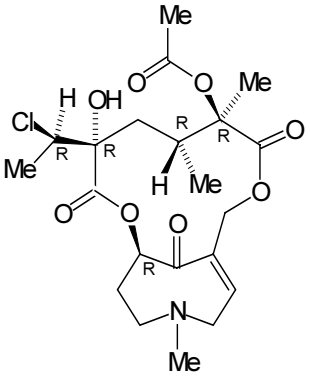
Roeder E., Wiedenfeld H., Frisse M.:
(1980) *Phytochemistry*, **19**, 1275-1277.

Doronine

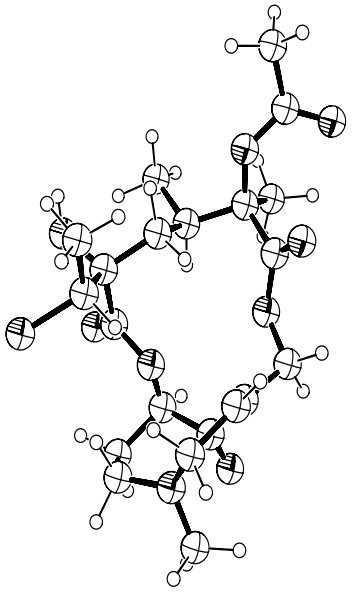
$C_{21}H_{30}ClNO_8 \cdot C_6H_6$ / 459.918 · 78.112

(1*R*,4*R*,6*R*,7*R*)-4-[(1*R*)-1-chloroethyl]-4-hydroxy-6,7,14-trimethyl-3,8,17-trioxo-2,9-dioxa-14-azabicyclo[9.5.1]heptadec-11-en-7-yl acetate

Measured as a Benzene (1:1) adduct



Structure-Drawing



Ortep-Drawing

Structure

Wong R.Y., Roitman J.N.:
(1984) *Acta Cryst. C***40**, 163-166.

Toxicity
not yet reported

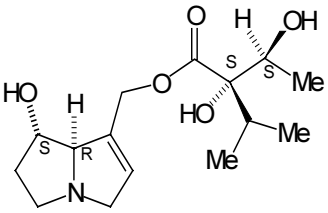
Occurrence in *Senecio clevelandii* and *S. othonnae:*

Smith L.W., Culvenor C.C.J.:
(1981) *J. Nat. Prod.*, **44**, 121-152.

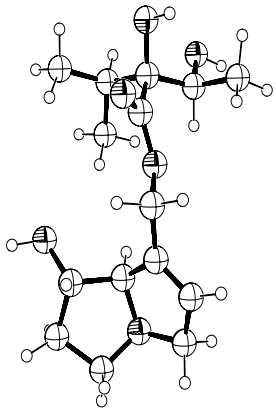
Echinatine

$C_{15}H_{25}NO_5$ / 299.363

[(1*S*,7a*R*)-1-hydroxy-2,3,5,7a-tetrahydro-1*H*-pyrrolizin-7-yl]methyl (2*S*,3*S*)-2,3-dihydroxy-2-isopropylbutanoate



Structure-Drawing



Ortep-Drawing

Structure

Gable R.W., Mackay M.F., Culvenor C.C.J.: (1988) *Acta Cryst. C***44,** 1478-1481.

Toxicity

Culvenor C.C.J., Downing D.T., Edgar J.A., Jago M.V.: (1969) *Ann. N.Y. Acad. Science,* **163**, 837-847.

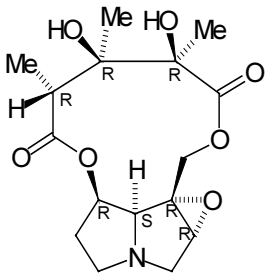
Occurrence in *Heliotropium supinum*:

Crowley H.C., Culvenor C.C.J.: (1959) *Aust. J. Chem.*, **12**, 694-705.

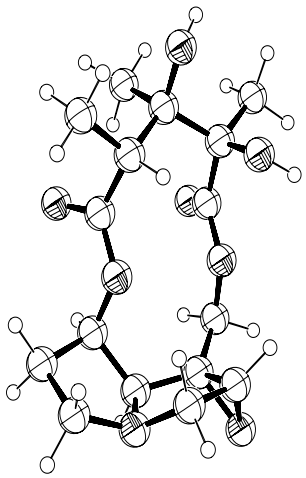
(1,2)-α-Epoxy-monocrotaline

$C_{16}H_{23}NO_7$ / 341.356

(1a*R*,5a*R*,8*R*,9*R*,10*R*,13a*R*,13b*S*)-9,10-dihydroxy-8,9,10-trimethyl-octahydro-7*H*-[1,6]dioxacycloundecino[2,3,4-*gh*]oxireno[*a*]pyrrolizine-7,11(8*H*)-dione



Structure-Drawing



Ortep-Drawing

Structure

Mackay M.F., Sadek M., Culvenor C.C.J.:
(1984) *Acta Cryst. C***40**, 2064-2068.

Toxicity

Schoental R.:
(1970) *Nature (London)*, **227**, 401-402:

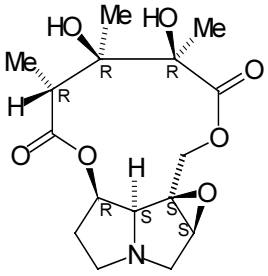
Assumed intermediate in metabolic toxification.

(1,2)-β-Epoxy-monocrotaline

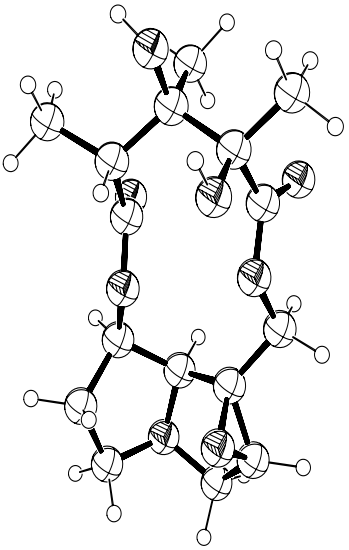
$C_{16}H_{23}NO_7 \cdot H_2O$ / 341.356 · 18.015

(1a*S*,5a*R*,8*R*,9*R*,10*R*,13a*S*,13b*S*)-9,10-dihydroxy-8,9,10-trimethyl-octahydro-7*H*-[1,6]dioxacycloundecino[2,3,4-*gh*]oxire-no[*a*] pyrrolizine-7,11(8*H*)-dione

Measured as Monohydrat



Structure-Drawing



Ortep-Drawing

Structure

Mackay M.F., Sadek M., Culvenor C.C.J.:
(1984) *Acta Cryst.* C**40**, 2064-2068.

Toxicity

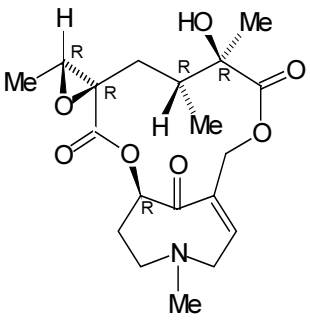
Schoental R.:
(1970) *Nature (London)*, **227**, 401-402:

Assumed intermediate in metabolic toxification.

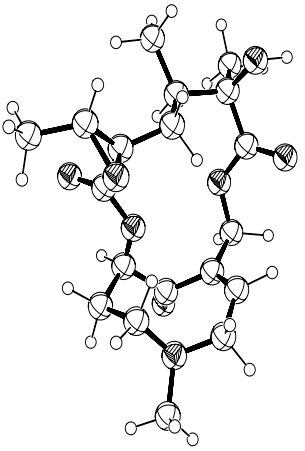
Fukinotoxine, *syn*. Petasitenine

$C_{19}H_{27}NO_7$ / 381.420

(1*R*,3'*R*,4*R*,6*R*,7*R*)-7-hydroxy-3',6,7,14-tetramethyl-8*H*,17*H*-spiro [2,9-dioxa-14-azabicyclo[9.5.1]heptadec-11-ene-4,2'-oxirane]-3,8,17-trione



Structure-Drawing



Ortep-Drawing

Structure

Furuya T., Hikichi M., Iitaka Y.:
(1976) *Chem. Pharm. Bull.,* **24**, 1120-1122.

Toxicity

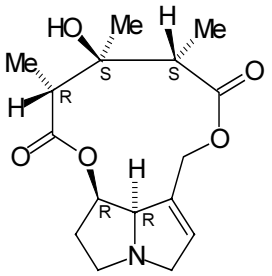
Yamanaka H., Nagao M., Sugimura T., Furuya T., Shirai A., Matsushima T.:
(1979) *Mut. Res.*, **68**, 211-216.

Occurrence in *Petasites japonicus.*

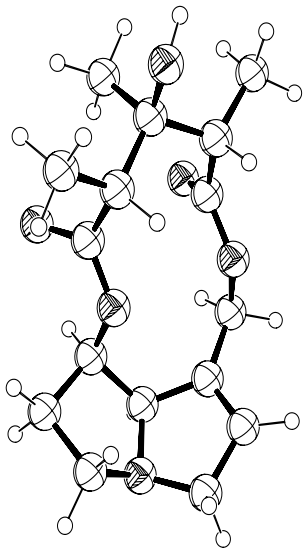
Fulvine

$C_{16}H_{23}NO_5$ / 309.358

(3*R*,4*S*,5*S*,13a*R*,13b*R*)-4-hydroxy-3,4,5-trimethyl-4,5,8,10,12,13,13a,13b-octahydro-2*H*-[1,6]dioxacycloundecino[2,3,4-*gh*]pyrrolizine-2,6(3*H*)-dione



Structure-Drawing



Ortep-Drawing

Structure

Sussmann J.L., Wodak S.J.:
(1973) *Acta Cryst. B***29**, 2918-2926.

Toxicity

Culvenor C.C.J., Downing D.T.,
Edgar J.A., Jago M.V.:
(1969) *Ann. N.Y. Acad. Science*, **163**, 837-847.

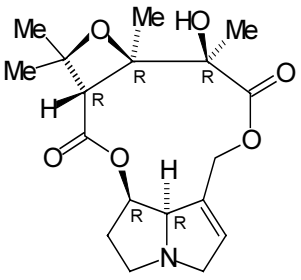
Occurrence in *Crotalaria fulva:*

Schoental R.:
(1963) *Aust. J. Chem.*, **16**, 233-238.

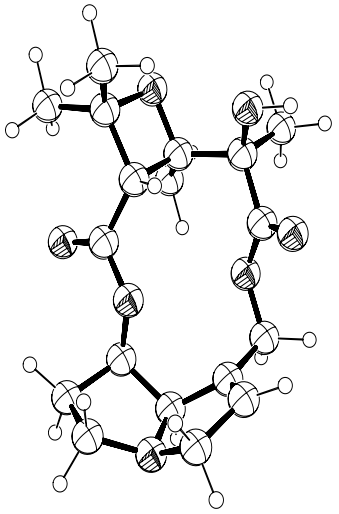
Grantaline

$C_{18}H_{25}NO_6$ / 351.394

(9*R*,9a*R*,11a*R*,13a*R*,13b*R*)-9-hydroxy-9,9a,11,11-tetramethyl-1,2,4,6,9,9a,11,11a,13a,13b-decahydro-8*H*,12*H*-oxeto[2',3':9,10][1,6]dioxacycloundecino[2,3,4-*gh*]pyrrolizine-8,12-dione



Structure-Drawing



Ortep-Drawing

Structure

Mackay M.F., Culvenor C.C.J.:
(1983) *Acta Cryst. C***39**, 1227-1230.

Toxicity

Rubiolo P., Pieters L., Calomme M., Bicchi C., Vlietinck A., Van dem Berghe D.:
(1992) *Mutat. Res.*, **281**, 143-147.

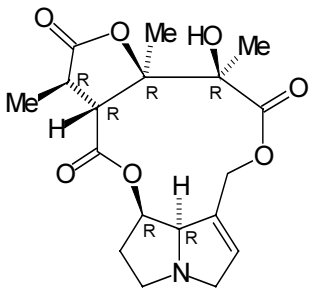
Occurrence in *Crotalaria virgulata* subspec. *grantiana:*

Adams R., Gianturco M.:
(1956) *J. Am. Chem. Soc., **78**,* 4458-4464.

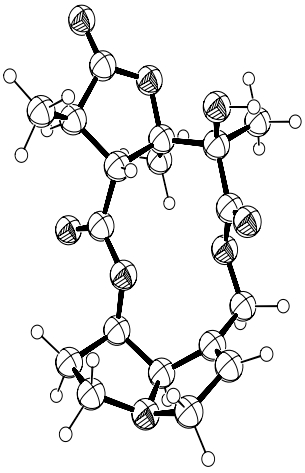
Grantianine

$C_{18}H_{23}NO_7$ / 365.378

(9*R*,9a*R*,12*R*,12a*R*,14a*R*,14b*R*)-9-hydroxy-9,9a,12-trimethyl-1,2,4,6,9,9a,12,12a,14a,14b-decahydro-8*H*-furo[2',3':9,10][1,6]dioxacycloundecino[2,3,4-*gh*]pyrrolizine-8,11,13-trione



Structure-Drawing



Ortep-Drawing

Structure

Stoeckli-Evans H., Robins D.J.:
(1984) *Acta Cryst. C***40**, 1445-1449.

Toxicity
not yet reported

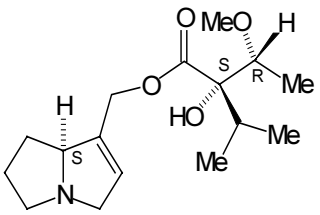
Occurrence in *Crotalaria grantiana* and *C. globifera:*

Brown K., Devlin J.A., Robins D.J.:
(1984) *Phytochemistry*, **23**, 457-459.

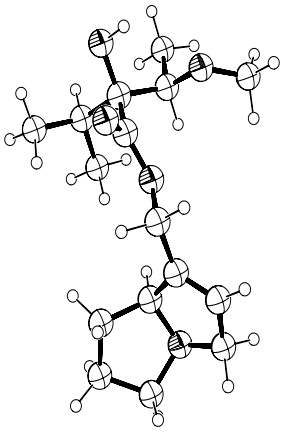
Heleurine

$C_{16}H_{27}NO_4$ / 297.390

(7a*S*)-2,3,5,7a-tetrahydro-1*H*-pyrrolizin-7-ylmethyl (2*S*,3*R*)-2-hydroxy-2-isopropyl-3-methoxybutanoate



Structure-Drawing



Ortep-Drawing

Structure

Mackay M.F., Mitrprachachon P., Oliver P.J., Culvenor C.C.J.: (1985) *Acta Cryst. C***41**, 722-725.

Toxicity

Culvenor C.C.J., Downing D.T., Edgar J.A., Jago M.V.: (1969) *Ann. N.Y. Acad. Science,* **163**, 837-847.

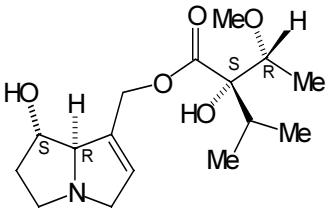
Occurrence in *Heliotropium supinum:*

Crowley H.C., Culvenor C.C.J.: (1959) *Aust. J. Chem.,* **12**, 694-705.

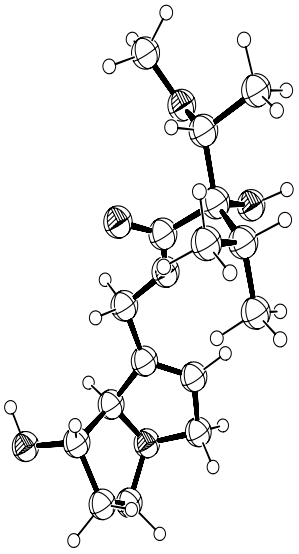
Heliotrine

$C_{16}H_{27}NO_5$ / 313.389

[(1*S*,7a*R*)-1-hydroxy-2,3,5,7a-tetrahydro-1*H*-pyrrolizin-7-yl]methyl (2*S*,3*R*)-2-hydroxy-2-isopropyl-3-methoxybutanoate



Structure-Drawing



Ortep-Drawing

Structure

Wodak S.J.:
(1975) *Acta Cryst. B***31**, 569-573.

and:

Zalkow L.H., Bonetti S., Gelbaum L., Gordon M.M., Patil B.B., Shani A., Van Derveer D.:
(1979) *J. Nat. Prod.*, **42**, 603-614.

Toxicity

Culvenor C.C.J., Downing D.T., Edgar J.A., Jago M.V.:
(1969) *Ann. N.Y. Acad. Science,* **163**, 837-847.

Yamanaka H., Nagao M., Sugimura T., Furuya T., Shirai A., Matsushima T.:
(1979) *Mutat. Res.*, **68**, 211-216.

Frei H., Lüthy J., Brauchli J., Zweifel U., Würgler F.E., Schlatter C.:
(1992) *Chem. Biol. Interact.*, **83,** 1-22.

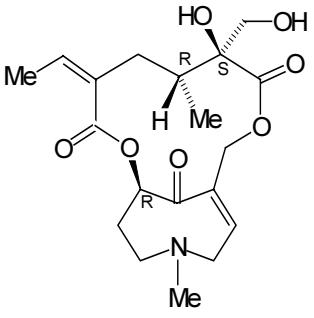
Occurrence in *Heliotropium europaeum:*

Culvenor C.C.J.:
(1954) *Aust. J. Chem.*, **7**, 287-297.

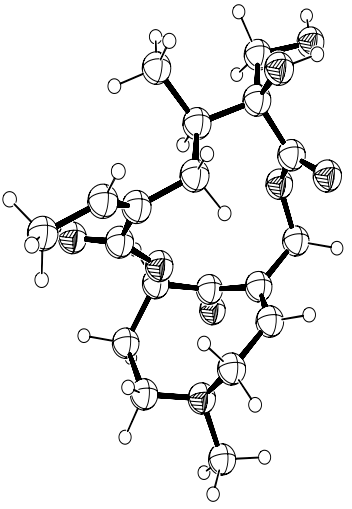
Hydroxysenkirkine

$C_{19}H_{27}NO_7$ / 381 420

(1*R*,4*Z*,6*R*,7*S*)-4-ethylidene-7-hydroxy-7-(hydroxymethyl)-6,14-dimethyl-2,9-dioxa-14-azabicyclo[9 5 1]heptadec-11-ene-3,8,17-trione



Structure-Drawing



Ortep-Drawing

Structure

Glinski J.A., Asibal C.F., Van Derveer D., Zalkow L.H.:
(1988) *Acta Cryst. C***44,** 1593-1598.

Toxicity

Anonymous :
(1976) *IAR Monogr.,* **10**, 265-268.

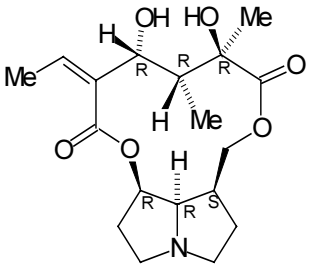
Occurrence in *Senecio anonymus*.

Hygrophylline

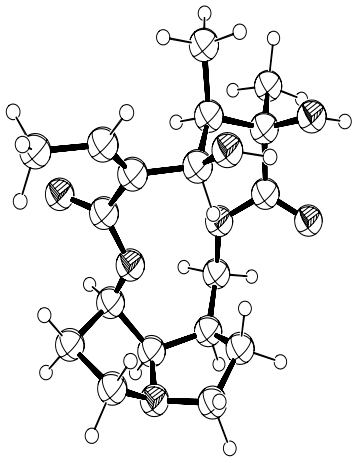
$C_{18}H_{27}NO_6$ / 353.410

(3*Z*,4*R*,5*R*,6*R*,9a*S*,14a*R*,14b*R*)-3-ethylidene-4,6-dihydroxy-5,6-dimethyldodecahydro[1,6]dioxacyclododecino[2,3,4-*gh*] pyrrolizine-2,7-dione

(1a,14*R*,15*Z*)-12,14-dihydroxy-1,2-dihydrosenecionan-11,16-dione



Structure-Drawing



Ortep-Drawing

Structure

Mackay M.F., Mitrprachachon P., Culvenor C.C.J.:
(1985) *Acta Cryst. C***41**, 395-397.

Non toxic
in analogy to:

Mattocks A.R., White I.N.H.:
(1971) *Nature New Biol.*, **231**, 114-115.

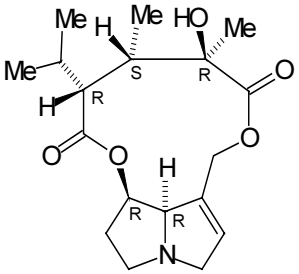
Occurrence in *Senecio hygrophyllus*:

Richardson M.F., Warren F.L.:
(1943) *J. Chem. Soc.*, 452-454.

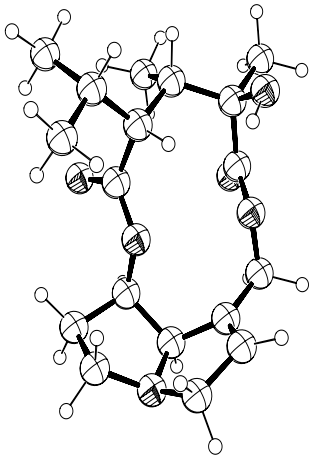
Incanine

$C_{18}H_{27}NO_5$ / 337.411

(3*R*,4*S*,5*R*,13a*R*,13b*R*)-5-hydroxy-3-isopropyl-4,5-dimethyl-4,5,8,10,12,13,13a,13b-octahydro-2*H*-[1,6]dioxacyclo-undecino[2,3,4-*gh*]pyrrolizine-2,6(3*H*)-dione



Structure-Drawing



Ortep-Drawing

Structure

Tashkhodzhaev B., Telezhenetskaya M.V., Yunusov S.Y.:
(1979) *Khim. Prir. Soedin.* 363-373:
Chem. Abstr., **92**, 111199 (1980).

Toxicity

Turakulov Y.K.:
(1970) *Vop. Med. Khim., Biochim. Gorm.*, 52-54.

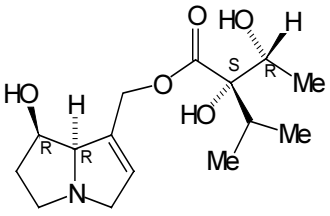
Occurrence in *Trichodesma incanum*:

Menshikov G.P., Rubinstein W.:
(1935) *Ber. Dtsch. Chem. Ges.* B**68**, 2039-2044.

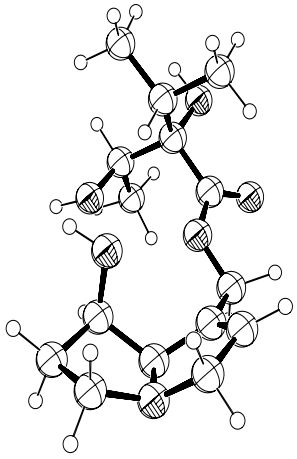
Intermedine

$C_{15}H_{25}NO_5$ / 299.363

[(1*R*,7a*R*)-1-hydroxy-2,3,5,7a-tetrahydro-1*H*-pyrrolizin-7-yl] methyl (2*S*,3*R*)-2,3-dihydroxy-2-isopropylbutanoate



Structure-Drawing



Ortep-Drawing

Structure

Tashkhodzhaev B., Telezhenetskaya M.V., Yunusov S.Y.:
(1979) *Khim. Prir. Soedin*. 363-373.
Chem. Abstr., **92**, 111199 (1980).

Mackay, F.M., Sadek, M., Culvenor, C.C.J.:
(1983) *Acta Cryst. C***39**, 785.

Toxicity

Culvenor C.C.J., Edgar J.A., Jago M.V., Outteridge A., Peterson J.E., Smith L.W.:
(1976) *Chem. Biol. Interact.,* **12**, 299-324..

Frei H., Lüthy J., Brauchli J., Zweifel U., Würgler F.E., Schlatter C.:
(1992) *Chem. Biol. Interact.*, **83,** 1-22.

Occurrence in *Amsinckia* spec.:

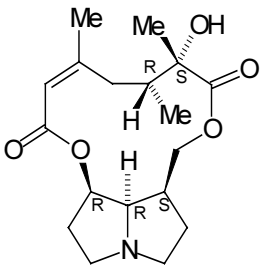
Culvenor C.C.J., Smith L.W.:
(1966) *Aust. J. Chem.*, **19**, 1955-1964.

Iodanthine

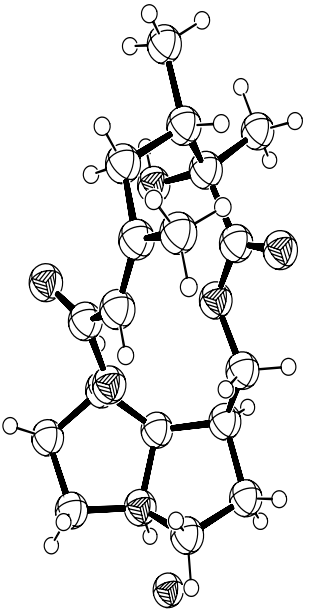
$C_{18}H_{27}NO_5 \cdot HCl$ / 337.411 · 36.461

(6*R*,7*S*,10a*S*,15a*R*,15b*R*)-7-hydroxy-4,6,7-trimethyl-6,7,10,10a,11,12,14,15,15a,15b-decahydro-2*H*-[1,6]dioxacyclotridecino[2,3,4-*gh*]pyrrolizine-2,8(5*H*)-dione

Measured as Hydrochloride



Structure-Drawing



Ortep-Drawing

Structure

Perez-Castorena A.-L., Arciniegas A.,
Pérez R., Gutierrez H., Toscano R.A.,
Villasenor J.L., Romo de Vivar A.:
(1999) *J. Nat. Prod.,* **62**, 1039-1043.

Non toxic
in analogy to:

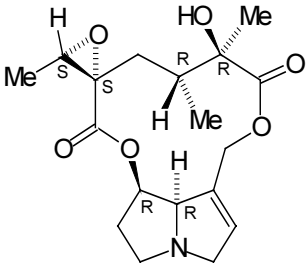
Mattocks A.R., White I.N.H.:
(1971) *Nature New Biol.*, **231**, 114-115.

Occurrence in *Senecio iodanthus.*

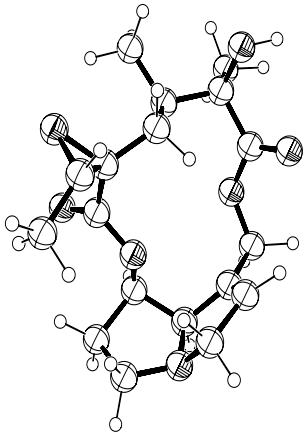
Jacobine

$C_{18}H_{25}NO_6$ / 351.394

(3*S*,3'*S*,5*R*,6*R*,14a*R*,14b*R*)-6-hydroxy-3',5,6-trimethyl-5,6,9,11,13,14,14a,14b-octahydrospiro[1,6-dioxacyclododecino[2,3,4-*gh*]pyrrolizine-3,2'-oxirane]-2,7(4*H*)-dione



Structure-Drawing



Ortep-Drawing

Structure

Perez-Salazar A.:
(1978) *An. Quim.,* **74**, 196-198.

Perez-Salazar A., Cano F.H., Garcia-Blanco S.:
(1978) *Cryst. Struct. Comm.*, **7**, 105-109.

and as Bromohydrin Ethanol Solvate:

Fridrichsons J.A., McL.Mathieson A., Sutor D.J.:
(1960) *Tetrahedron Lett.,* 35-37.

Fridrichsons J.A., McL.Mathieson A., Sutor D.J.:
(1963) *Acta Cryst.*, **16**, 1075-1085.

and as Methanol Solvate:

Rohrer D.C., Karchesy J., Deinzer M.:
(1984) *Acta Cryst. C***40**, 1449-1452.

Toxicity

Anonymous:
(1976) *IARC, Monogr.,* **10**, 275-280.

Occurrence in *Senecio jacobaea:*

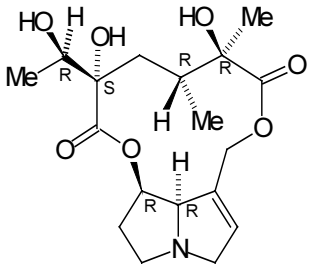
Bradbury R.B., Culvenor C.C.J.:
(1954) *Aust. J. Chem.,* **7**, 378-383.

Jacoline

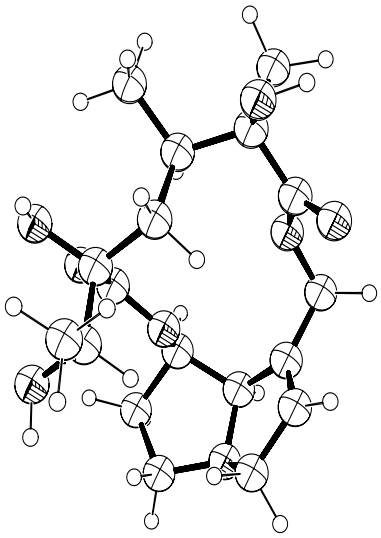
$C_{18}H_{27}NO_7$ / 369.410

(3*S*,5*R*,6*R*,14a*R*,14b*R*)-3-[(1*R*)-1-hydroxyethyl]- 3,6-dihydroxy-5,6-dimethyl-3,4,5,6,9,11,13,14,14a,14b-ecahydro[1,6]dioxacyclo-dodecino[2,3,4-*gh*]pyrrolizine-2,7-dione

(15*S*,20*R*)-12,15,20-trihydroxy-15,20-dihydrosenecionan-11,16-dione



Structure-Drawing



Ortep-Drawing

Structure

Gable R.W., Mackay M.F., Culvenor C.C.J.:
(1988) *Acta Cryst. C***44**, 1942-1947.

Toxicity

Buhler D.R., Kedzierski B.:
(1986) *Adv. Exp. Med. Biol.,* **97**, 611-620.

Frei H., Lüthy J., Brauchli J., Zweifel U.,
Würgler F.E., Schlatter C.:
(1992) *Chem. Biol. Interact.*, **83**, 1-22.

Occurrence in *Senecio jacobaea:*

Bradbury R.B., Culvenor C.C.J.:
(1954) *Aust. J. Chem.,* **7**, 378-383.

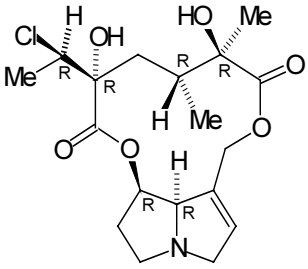
Jaconine

$C_{18}H_{26}ClNO_6 \cdot HCl \cdot C_2H_6O$ / 387.855 · 36.461 · 46.068

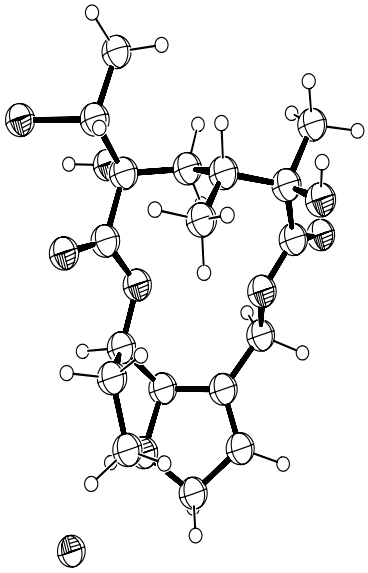
(3*R*,5*R*,6*R*,14a*R*,14b*R*)-3-[(1*R*)-1-chloroethyl]-3,6-dihydroxy-5,6-dimethyl-3,4,5,6,9,11,13,14,14a,14b-decahydro[1,6]dioxacyclo dodecino[2,3,4-*gh*]pyrrolizine-2,7-dione

(15*R*,20*R*)-20-chloro-12,15-dihydroxy-15,20-dihydrosenecionan-11,16-dione

Measured as Hydrochloride Ethanol Solvate



Structure-Drawing



Ortep-Drawing

Structure

Gable R.W., Mackay M.F., Culvenor C.C.J.:
(1988) *Acta Cryst. C***44**, 1942-1947.

Toxicity

Lüthy J., Zweifel U., Schlatter C.:
(1981) *Mitt. Gebiete Lebensm. Hyg.*, **72**, 55-61.

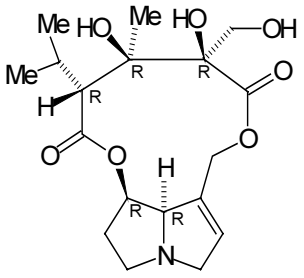
Occurrence in *Senecio jacobaea:*

Bradbury R.B., Culvenor C.C.J.:
(1954) *Aust. J. Chem.,* **7**, 378-383.

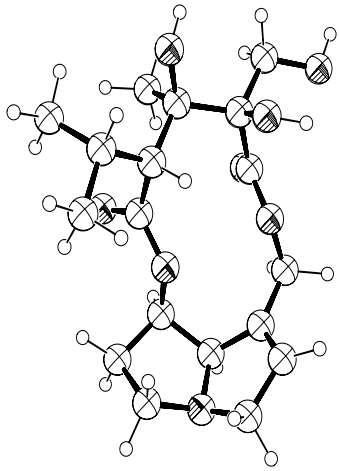
Junceine

$C_{18}H_{27}NO_7$ / 369.410

(3*R*,4*R*,5*R*,13a*R*,13b*R*)-4,5-dihydroxy-5-(hydroxymethyl)-3-isopropyl-4-methyl-4,5,8,10,12,13,13a,13b-octahydro-2*H*-[1,6]dioxacycloundecino[2,3,4-*gh*]pyrrolizine-2,6(3*H*)-dione



Structure-Drawing



Ortep-Drawing

Structure

Stoeckli-Evans H.:
(1982) *Acta Cryst. B***38**, 1614-1617.

Toxicity
not yet reported

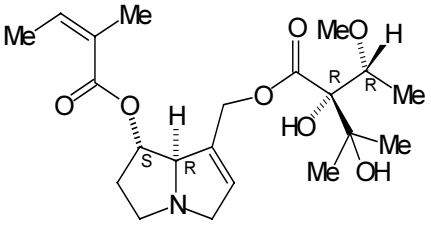
Occurrence in *Crotalaria juncea:*

Adams R., Gianturco M.:
(1956) *J. Am. Chem. Soc.*, **78**, 1919-1921.

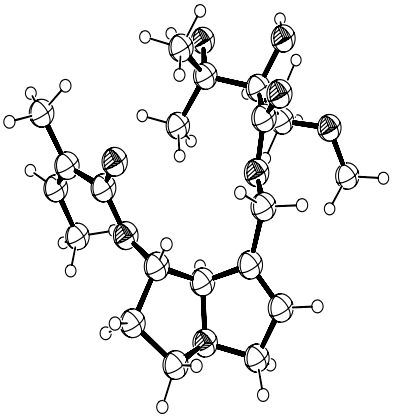
Lasiocarpine

$C_{21}H_{33}NO_7$ / 411.489

1,5-dideoxy-2-*C*-methyl-4-*O*-methyl-3-*C*-{[((1*S*,7a*R*)-1-{[(2*Z*)-2-methylbut-2-enoyl]oxy}-2,3,5,7a-tetrahydro-1*H*-pyrrolizin-7-yl)methoxy]carbonyl}-D-arabinitol



Structure-Drawing



Ortep-Drawing

Structure

Hay D.G., Mackay M.F., Culvenor C.C.J.: (1982) *Acta Cryst. B***38**, 155-159.

Toxicity

Culvenor C.C.J., Downing D.T., Edgar J.A., Jago M.V.: (1969) *Ann. N.Y. Acad. Science,* **163**, 837-847.

Culvenor C.C.J., Edgar J.A., Jago M.V., Outteridge A., Peterson J.E., Smith L.W.: (1976) *Chem. Biol. Interact.*, **12**, 299-324.

Yamanaka H., Nagao M., Sugimura T., Furuya T., Shirai A., Matsushima T.: (1979) *Mutat. Res.*, **68**, 211-216.

Occurrence in *Heliotropium lasiocarpum* and *H. europaeum:*

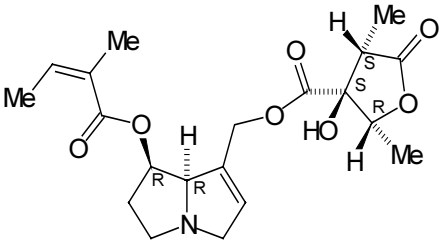
Smith L.W., Culvenor C.C.J.: (1981) *J. Nat. Prod.,* **44**, 121-152.

Latifoline

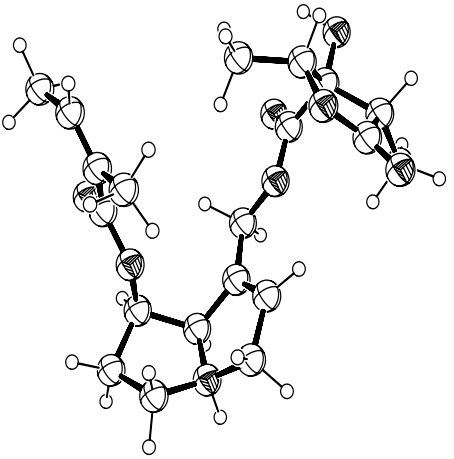
$C_{20}H_{27}NO_7 \cdot HBr \cdot H_2O$ / 393.431 · 80.912 · 18.015

(1*R*,7a*S*)-1-{[(2*Z*)-2-methylbut-2-enoyl]oxy}-2,3,5,7a-tetrahydro-1*H*-pyrrolizin-7-yl (2*R*,3*S*,4*S*)-2,4-dimethyl-3-hydroxy-5-oxotetrahydrofuran-3-carboxylate

Measured as Hydrobromide Monohydrate



Structure-Drawing



Ortep-Drawing

Structure

Culvenor C.C.J., Mackay M.F.:
(1992) *Aust. J. Chem.,* **45**, 451-456.

Toxicity

Kim H.Y., Stermitz F.R., Li J.K.K., Coulombe Jr. R.A.:
(1999) *Food Chem. Tox*., **37,** 619-625.

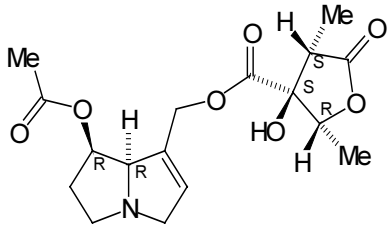
Occurrence in *Cynoglossum latifolium:*

Crowley H.C., Culvenor C.C.J.:
(1962) *Aust. J. Chem.,* **15,** 139-144.

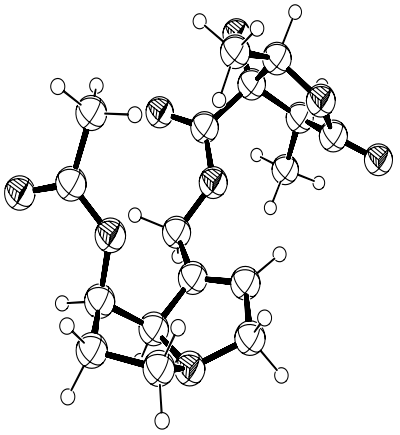
Longitubine

$C_{17}H_{23}NO_7$ / 353.367

[(1*R*,7a*R*)-1-(acetyloxy)-2,3,5,7a-tetrahydro-1*H*-pyrrolizin-7-yl] methyl(2*R*,3*S*,4*S*)-2-hydroxy-3,4-dimethyl-5-oxotetrahydrofuran-3-carboxylate



Structure-Drawing



Ortep-Drawing

Structure

Stermitz F.R., Hope H.:
(1989) *Tetrahedron Lett.,* 7153-7156.

Toxicity

Roitman J.N., Molyneux R.J., Johnson A.:
(1979) Symposium on Pyrrolizidine Alkaloids: Toxicity, Metabolism, and Poisonous Plant Control Measures. Ed. P.R. Cheeke.
The Nutrition Research Institute Oregon State University, Corvallis, Oregon, USA.

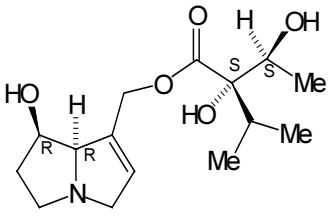
Occurrence in *Hackelia longituba:*

Roitman J.N.:
(1988) *Aust. J. Chem.,* **41**, 1827-1833.

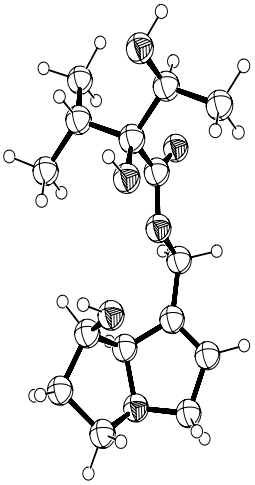
Lycopsamine

$C_{15}H_{25}NO_5$ / 299.363

[(1*R*,7a*R*)-1-hydroxy-2,3,5,7a-tetrahydro-1*H*-pyrrolizin-7-yl] methyl (2*S*,3*S*)-2,3-dihydroxy-2-isopropylbutanoate



Structure-Drawing



Ortep-Drawing

Structure

Mackay F.M., Sadek M., Culvenor C.C.J.:
(1983) *Acta Cryst.* C**39**, 785.

and:

Stermitz F.R., Hope H.:
(1989) *Tetrahedron Lett.,* 7153-7156.

Toxicity

Culvenor C.C.J., Edgar J.A., Jago M.V., Outteridge A., Peterson J.E., Smith L.W.:
(1976) *Chem. Biol. Interact.*, **12**, 299-324.

Frei H., Lüthy J., Brauchli J., Zweifel U., Würgler F.E., Schlatter C.:
(1992) *Chem. Biol. Interact.*, **83**, 1-22.

Occurrence in *Amsinckia* spec.:

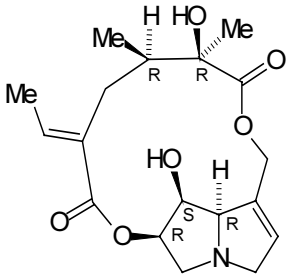
Culvenor C.C.J., Smith L.W.:
(1966) *Aust. J. Chem.*, **19**, 1955-1964.

Madurensine

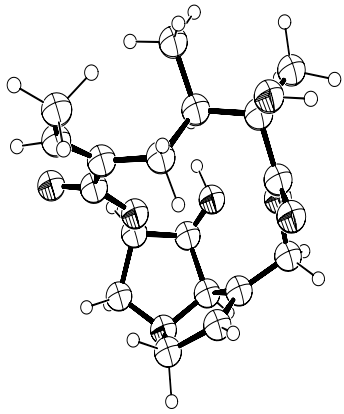
$C_{18}H_{25}NO_6$ · ½ C_2H_5OH · ½ H_2O / 351.394 · 23.034 · 9.008

(7*R*,8*R*,10*E*,13*R*,14*S*,14a*R*)-10-ethylidene-7,14-dihydroxy-7,8-dimethyl-2,7,8,9,10,13,14,14a-octahydro-4*H*-1,13-methano[1,7]dioxacyclotridecino[4,3-*b*]pyrrole-6,11-dione

Measured as Ethanol-water Solvate



Structure-Drawing



Ortep-Drawing

Structure

Mackay M.F., Sadek M., Culvenor C.C.J.: (1984) *Acta Cryst. C***40**, 1073-1077.

Toxicity

Culvenor C.C.J., Edgar J.A., Jago M.V., Outteridge A., Peterson J.E., Smith L.W.: (1976) *Chem. Biol. Interact.*, **12**, 299-324.

Occurrence in *Crotalaria madurensis* and *C. agatiflora*:

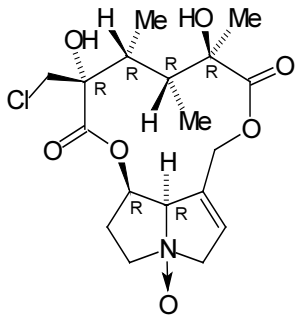
Atal C.K., Kapur K.K., Culvenor C.C.J., Smith L.W.: (1966) *Tetrahedron Lett.*, 537- 544.

Merenskine-*N*-oxide

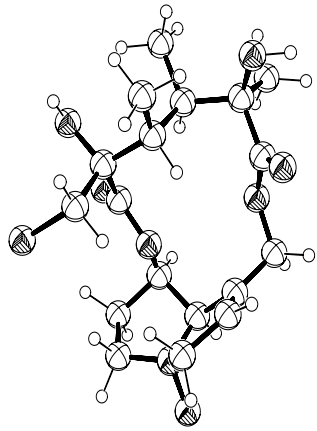
$C_{18}H_{26}ClNO_7 \cdot C_2H_5OH$ / 403.854 · 46.068

(3*R*,4*R*,5*R*,6*R*,14a*R*,14b*R*)-3-(chloromethyl)-3,6-dihydroxy-4,5,6-trimethyl-3,4,5,6,9,11,13,14,14a,14b-decahydro[1,6]dioxacyclododecino[2,3,4-*gh*]pyrrolizine-2,7-dione-*N*-oxide

Measured as: Ethanol Solvate



Structure-Drawing



Ortep-Drawing

Structure

Bredenkamp M.W., Wiechers A., Van Rooyen P.H.: (1985) *Tetrahedron Lett.,* 929-932.

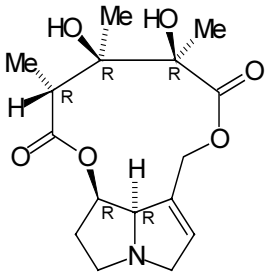
Toxicity
not yet reported

Occurrence in *Senecio latifolius, syn. S. sceleratus.*

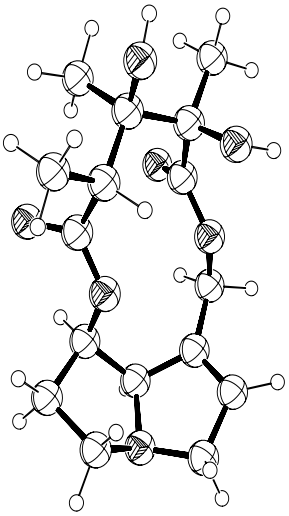
Monocrotaline

$C_{16}H_{23}NO_6$ / 325.357

(3*R*,4*R*,5*R*,13a*R*,13b*R*)-4,5-dihydroxy-3,4,5-trimethyl-4,5,8,10,12,13,13a,13b-octahydro-2*H*-[1,6]dioxacycloundecino[2,3,4-*gh*]pyrrolizine-2,6(3*H*)-dione



Structure-Drawing



Ortep-Drawing

Structure

Stoeckli-Evans H.:
(1979) *Acta Cryst. B***35**, 231-234.

and as Sulfite Hydrochloride:

Wang S.D.:
(1979) *Kexue Tongbao,* **24**, 1115-1118.
Chem. Abstr., **92**, 164133 (1980).

Wang S.D.:
(1981) *Sci. Sin.,* **24**, 497-507.
Chem. Abstr., **95**, 16382 (1981).

Toxicity

Anonymous:
(1976) *IARC, Monogr.*, **10**, 291-302.

Culvenor C.C.J., Downing D.T., Edgar J.A., Jago M.V.:
(1969) *Ann. N.Y. Acad. Science,* **163**, 837-847.

Culvenor C.C.J., Edgar J.A., Jago M.V.,
Outteridge A., Peterson J.E., Smith L.W.:
(1976) *Chem. Biol. Interact.,* **12**, 299-324.

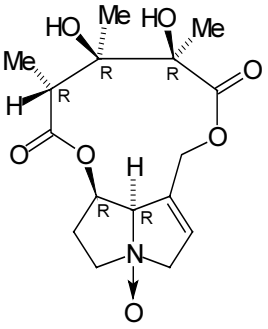
Frei H., Lüthy J., Brauchli J., Zweifel U.,
Würgler F.E., Schlatter C.:
(1992) *Chem. Biol. Interact.*, **83,** 1-22.

Occurrence in many *Crotalaria* spec..

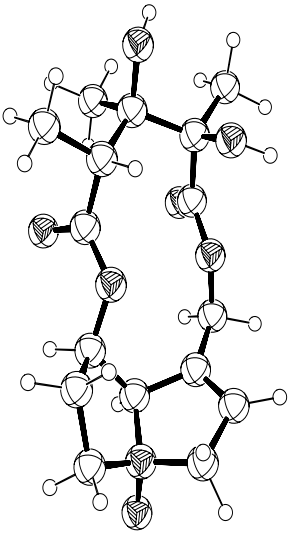
Monocrotaline-*N*-oxide

$C_{16}H_{23}NO_7$ / 341.356

(3*R*,4*R*,5*R*,13a*R*,13b*R*)-4,5-dihydroxy-3,4,5-trimethyl-4,5,8,10,12,13,13a,13b-octahydro-2*H*-[1,6]dioxacycloundecino[2,3,4-*gh*]pyrrolizine-2,6(3*H*)-dione-*N*-oxide



Structure-Drawing



Ortep-Drawing

Structure

Wang S.D., Hu N.H.:
(1978) *Kexue Tongbao,* **25**, 1071-1074.
Chem. Abstr., **94**, 157121 (1981).

Wang S.D., Hu N.H.:
(1981) *Scient. Sin.,* **24**, 1536-1544.
Chem. Abstr., **96**, 44186 (1982).

Toxicity

Anonymous:
(1976) *IARC, Monogr.*, **10**, 291-302.

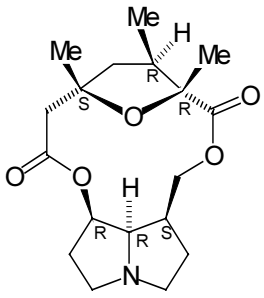
Culvenor C.C.J., Edgar J.A., Jago M.V.,
Outteridge A., Peterson J.E., Smith L.W.:
(1976) *Chem. Biol. Interact.*, **12**, 299-324.

Occurrence in *Crotalaria retusa* and other *Crotalaria* spec..

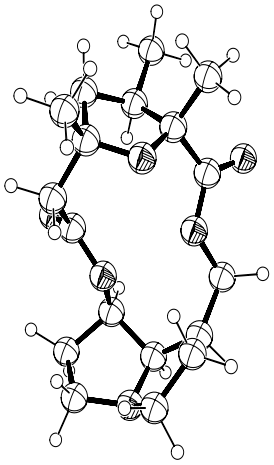
Nemorensine

$C_{18}H_{27}NO_5$ / 337.411

(4*S*,6*R*,7*R*,10a*S*,15a*R*,15b*R*)-4,6,7-trimethyldodecahydro-2*H*-4,7-epoxy[1,6]dioxacyclotridecino[2,3,4-*gh*]pyrrolizine-2,8(3*H*)-dione



Structure-Drawing



Ortep-Drawing

Structure

Dillon M.P., Lee N.C., Stappenbeck F., White J.D.:
(1995) *J. Chem. Soc., Chem. Commun.*, 1645-1646.

Non toxic
in analogy to:

Mattocks A.R., White I.N.H.:
(1971) *Nature New Biol.,* **231**, 114-115.

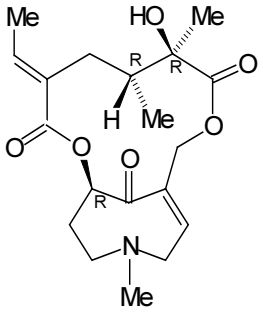
Occurrence in *Senecio nemorensis:*

Klasek A., Sedmera P., Boeva A., Santavy F.:
(1973) *Coll. Czech. Chem. Commun.,* **38**, 2504-2512.

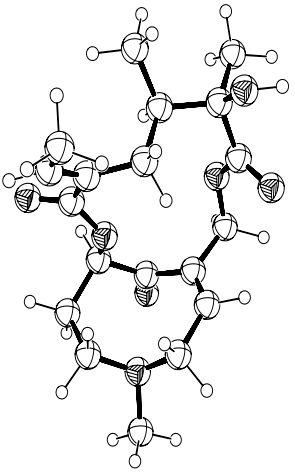
Neosenkirkine

$C_{19}H_{27}NO_6$ / 365.421

(1*R*,4*E*,6*R*,7*R*)-4-ethylidene-7-hydroxy-6,7,14-trimethyl-2,9-dioxa-14-azabicyclo[9.5.1]heptadec-11-ene-3,8,17-trione



Structure-Drawing



Ortep-Drawing

Structure

Glinski J.A., Asibal C.F., Van Derveer D., Zalkow L.H.:
(1988) *Acta Cryst. C***44**, 1593-1598.

Toxicity
not yet reported

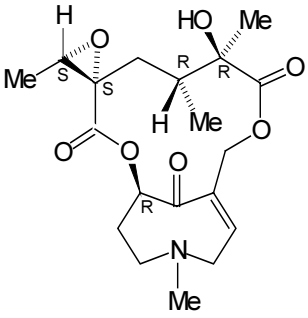
Occurrence in *Senecio anonymus:*

Zalkow L.H., Asibal C.F., Glinski J.A., Bonetti L.T., Van Derveer D., Powis, G.:
(1988) *J. Nat. Prod.,* **51**, 690-702.

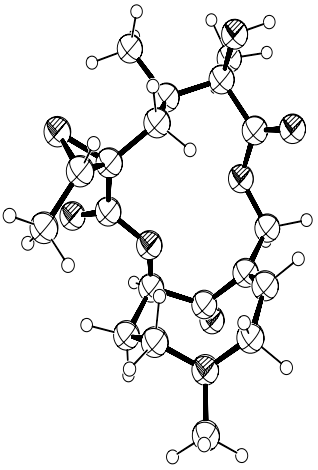
Otosenine

$C_{19}H_{27}NO_7$ / 381.420

(1*R*,3'*S*,4*S*,6*R*,7*R*)-7-hydroxy-3',6,7,14-tetramethyl-8*H*,17*H*-spiro [2,9-dioxa-14-azabicyclo[9.5.1]heptadec-11-ene-4,2'-oxirane]-3,8,17-trione



Structure-Drawing



Ortep-Drawing

Structure

Wiedenfeld H., Roeder E., Knoch F.:
(1990) *Acta Cryst. C***46**, 1345-1347.

and:

Perez-Salazar A., Cano F.H., Fayos G., Martinez-Carrera S., Garcia-Blanco S.:
(1977) *Acta Cryst. B***33**, 3525-3527.

Toxicity

Culvenor C.C.J., Edgar J.A., Smith L.W., Jago M.V., Peterson J.E.:
(1971) *Nature New Biol.*, **29**, 255-256.

Culvenor C.C.J., Downing D.T., Edgar J.A., Jago M.V.:
(1969) *Ann. N.Y. Acad. Science*, **163**, 837-847.

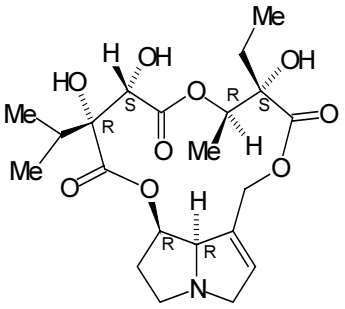
Occurrence in *Senecio aquaticus:*

Kompis I., Shroter H.B., Potesilova H., Santavy F.:
(1960) *Coll. Czech. Chem. Commun.*, **25**, 2449-2453.

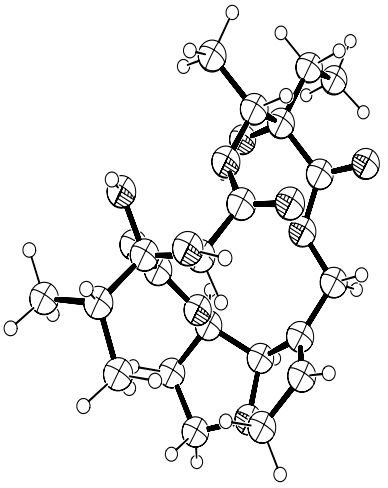
Parsonsianine

$C_{21}H_{31}NO_9$ / 441.472

(3*R*,4*S*,7*R*,8*S*,16a*R*,16b*R*)-8-ethyl-3,4,8-trihydroxy-3-isopropyl-7-methyl-3,4,11,13,15,16,16a,16b-octahydro-7*H*-[1,5,10]trioxacyclotetradecino[7,8,9-*gh*]pyrrolizine-2,5,9(8*H*)-trione



Structure-Drawing



Ortep-Drawing

Structure

Abe F., Nagao T., Okabe H., Yamauchi T., Marubayashi N., Ueda I.:
(1990) *Chem. Pharm. Bull.,* **38**, 2127-2129.

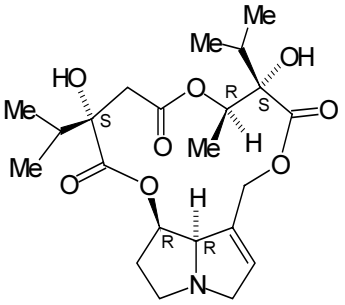
Toxicity
not yet reported

Occurrence in *Parsonsia laevigata.*

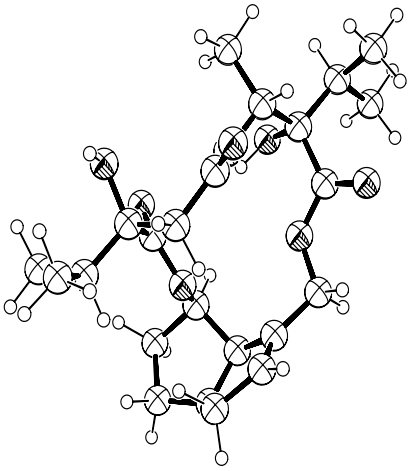
Parsonsine

$C_{22}H_{33}NO_8$ / 439.499

(3*S*,7*R*,8*S*,16a*R*,16b*R*)-3,8-dihydroxy-3,8-diisopropyl-7-methyl-3,4,11,13,15,16,16a,16b-octahydro-7*H*-[1,5,10]trioxacyclotetradecino[7,8,9-*gh*]pyrrolizine-2,5,9(8*H*)-trione



Structure-Drawing



Ortep-Drawing

Structure

Eggers N.J., Gainsford G.J.:
(1979) *Cryst. Struct. Comm.*, **8**, 597-603.

Gainsford G.J.:
(1980) *Cryst. Struct. Comm.* **9**, 173-180.

Toxicity
not yet reported

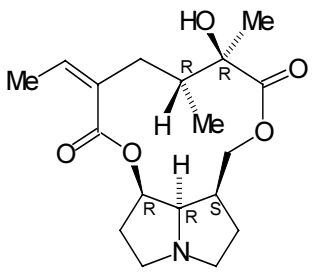
Occurrence in *Parsonsia heterophylla* and *P. spiralis.*

Platyphylline

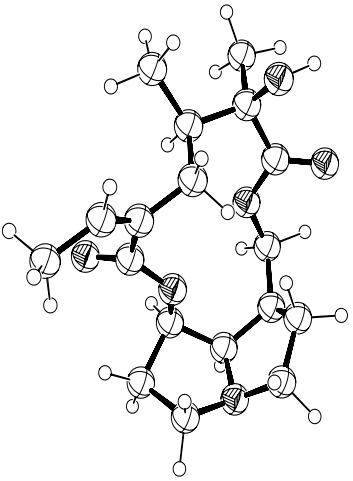
$C_{18}H_{27}NO_5$ / 337.411

(3*Z*,5*R*,6*R*,9a*S*,14a*R*,14b*R*)-6-hydroxy-3-ethylidene-5,6-dimethyldodecahydro[1,6]dioxacyclododecino[2,3,4-*gh*]pyrrolizine-2,7-dione

(1a,15*Z*)-12-hydroxy-1,2-dihydrosenecionan-11,16-dione



Structure-Drawing



Ortep-Drawing

Structure

Wiedenfeld H., Roeder E., Kirfel A., Will G.:
(1982) *Arch. Pharm.*, **315**, 165-169.

and:

Öztürk S., Ide S., Sener B., Fun H.K.:
(2000) *Spectr. Lett.,* **33**, 495-507.

Non toxic

Mattocks A.R., White I.N.H.:
(1971) *Nature New Biol.,* **231**, 114-115.

Culvenor C.C.J., Edgar J.A., Jago M.V.,
Outteridge A., Peterson J.E., Smith L.W.:
(1976) *Chem. Biol. Interact.*, **12**, 299-324.

Occurrence in *Senecio congestus:*

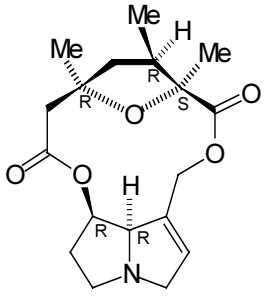
Roeder E., Wiedenfeld H., Jost E.J.:
(1982) *Planta Med.,* **44**, 182-183.

Retroisosenine

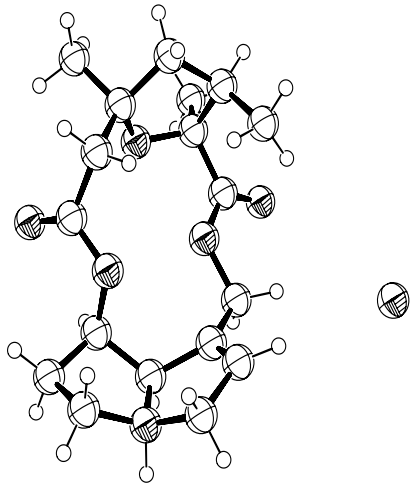
$C_{18}H_{25}NO_5$ · HCl / 335.395 · 36.461

(4*R*,6*R*,7*S*,15a*R*,15b*R*)-4,6,7-trimethyl-4,5,6,7,10,12,14, 15,15a,15b-decahydro-2*H*-4,7-epoxy[1,6]dioxacyclotridecino[2,3,4-*gh*] pyrrolizine-2,8(3*H*)-dione

Measured as Hydrochloride



Structure-Drawing



Ortep-Drawing

Structure

Pérez-Castorena A.L., Arciniegas A., Castro A., Villasenor J.L., Toscano A.R., Romo de Vivar A.: (1997) *J. Nat. Prod.,* **60**, 1322-1325.

Toxicity
not yet reported

Occurrence in *Senecio roseus* and *S. helodes:*

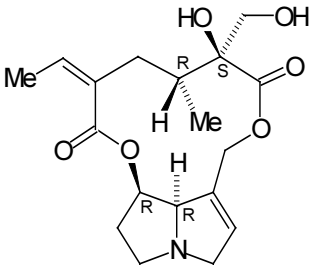
Romo de Vivar A., Perez A.L., Arciniegas A., Vidales P., Gavino R., Villasenor J.L.:
(1995) *Tetrahedron,* **51**, 12521-12528.

Retrorsine

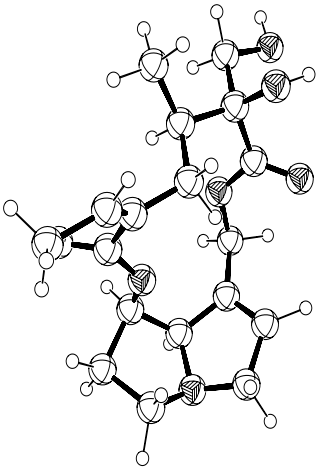
$C_{18}H_{25}NO_6$ / 351.394

(3*Z*,5*R*,6*S*,14a*R*,14b*R*)-6-hydroxy-6-(hydroxymethyl)-3-ethylidene-5-methyl-3,4,5,6,9,11,13,14,14a,14b-decahydro[1,6]dioxa-cyclo-dodecino[2,3,4-*gh*]pyrrolizine-2,7-dione

(15*Z*)-12,18-dihydroxysenecionan-11,16-dione



Structure-Drawing



Ortep-Drawing

Structure

Coleman P.C., Coucourakis, E.D., Pretorius J.A.:
(1980) *S. Afr. J. Chem.*, **33**, 116-119.

measured as Hydrobromide Ethanol Solvate:

Stoeckli-Evans H.:
(1979) *Acta Cryst. B***35**, 2798.

Toxicity

Culvenor C.C.J., Edgar J.A., Jago M.V., Outteridge A., Peterson J.E., Smith L.W.:
(1976) *Chem. Biol. Interact.*, **12**, 299-324.

Buhler D.R., Kedzierski B.:
(1986) *Adv. Exp. Med. Biol.*, **197**, 611-620.

Frei H., Lüthy J., Brauchli J., Zweifel U., Würgler F.E., Schlatter C.:
(1992) *Chem. Biol. Interact.*, **83,** 1-22.

Occurrence in *Senecio retrorsus* and other *S.* spec.:

Barger G., Seshadri T.R., Watt H.E., Yatuba T.:
(1935) *J. Chem. Soc.*, 11-15.

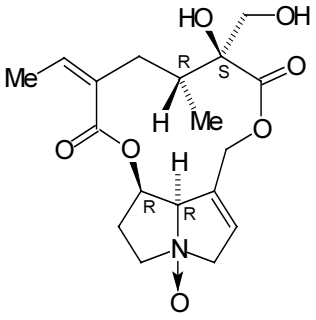
Retrorsine-*N*-oxide

$C_{18}H_{25}NO_7 \cdot 2\ H_2O$ / 367.394 · 36.03

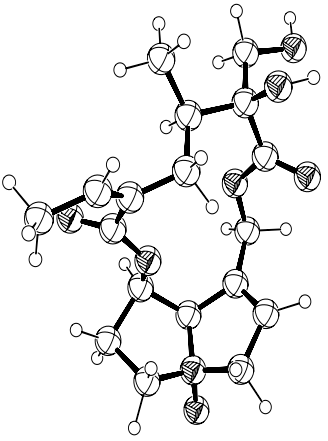
(3*Z*,5*R*,6*S*,14a*R*,14b*R*)-6-hydroxy-6-(hydroxymethyl)-3-ethylidene-5-methyl-3,4,5,6,9,11,13,14,14a,14b-decahydro[1,6]dioxa-cyclododecino[2,3,4-*gh*]pyrrolizine-2,7-dione-*N*-oxide

(15*Z*)-12,18-dihydroxysenecionan-11,16-dione-*N*-oxide

Measured as Dihydrate



Structure-Drawing



Ortep-Drawing

Structure

De Ugaz O.L., Franco J., Seminario G., Delle Monache F., Millan B., Sanchez R.P.U., Schlemper E.O., Tempesta M.S.:
(1990) *Phytochemistry,* **29**, 2373-2375.

Toxicity

Culvenor C.C.J., Edgar J.A., Jago M.V., Outteridge A., Peterson J.E., Smith L.W.:
(1976) *Chem. Biol. Interact.*, **12**, 299-324.

Frei H., Lüthy J., Brauchli J., Zweifel U., Würgler F.E., Schlatter C.:
(1992) *Chem. Biol. Interact.*, **83,** 1-22.

Wang Y.P., Yan J., Fu P., Chou M.:
(2005) *Tox. Lett.,* **155**, 411-420.

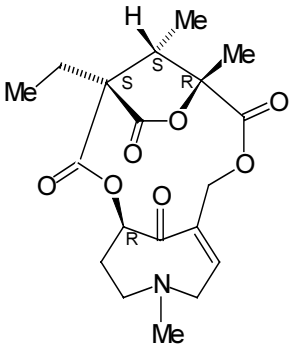
Occurrence in *Werneria decora* and *Senecio* spec..

Retusamine

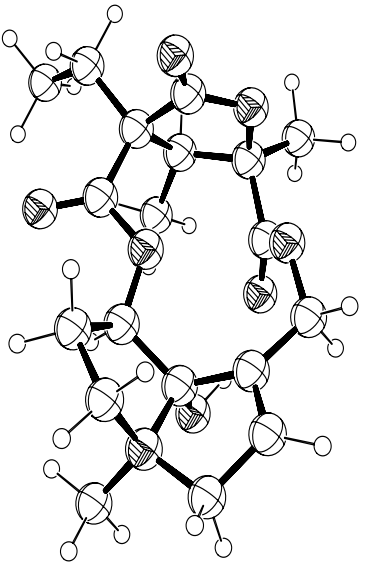
$C_{19}H_{25}NO_7 \cdot C_{10}H_{15}O_4SBr \cdot H_2O$ / 379.404 · 311.194 · 18.015

(3*S*,6*R*,12*R*,14a*R*,14b*S*,15*S*)-3-ethyl-14b-hydroxy-6,12,15-trimethyl-2,4,7-trioxo-3,4,6,7,9,11,13,14,14a,14b-decahydro-2*H*-3,6-methano [1,4,8]trioxacyclododecino[11,10,9-*gh*]pyrrolizin-12-ium

Measured as α´-Bromo-D-camphor-π-sulphonate Monohydrate



Structure-Drawing



Ortep-Drawing

Structure

Wunderlich J.A.:
(1967) *Acta Cryst.,* **23**, 846-855.

Toxicity

Culvenor C.C.J., Edgar J.A., Jago M.V., Outteridge A., Peterson J.E., Smith L.W.:
(1976) *Chem. Biol. Interact.*, **12**, 299-324.

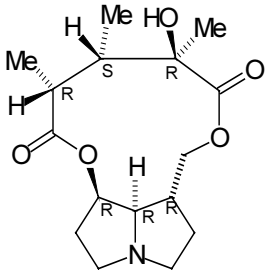
Occurrence in *Crotalaria retusa*:

Culvenor C.C.J., Smith L.W.:
(1957) *Aust. J. Chem.*, **10**, 464-475.

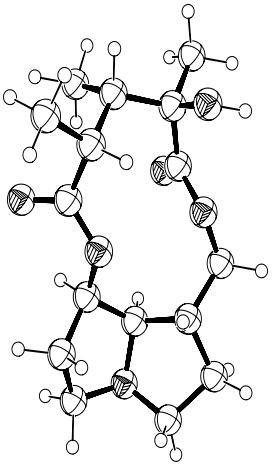
Retusine

$C_{16}H_{23}NO_5$ / 309.358

(3*R*,4*S*,5*R*,8a*R*,13a*R*,13b*R*)-5-hydroxy-3,4,5-trimethyldecahydro-2*H*-[1,6]dioxacycloundecino[2,3,4-*gh*]pyrrolizine-2,6(3*H*)-dione



Structure-Drawing



Ortep-Drawing

Structure

Wang S.D.:
(1979) *Kexue Tongbao*, **24**, 1023-1026.
Chem. Abstr., **92**, 181444 (1980).

Non toxic
in analogy to:

Mattocks A.R., White I.N.H.:
(1971) *Nature New Biol.*, **231**, 114-115.

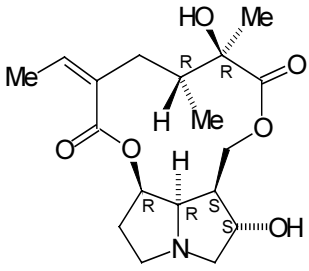
Occurrence in *Crotalaria retusa*.

Rosmarinine

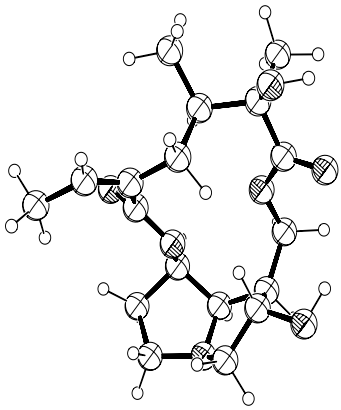
$C_{18}H_{27}NO_6$ / 353.410

(3*Z*,5R,6R,9aS,10S,14aR,14bR)-3-ethylidene-6,10-dihydroxy-5,6-dimethyldodecahydro[1,6]dioxacyclododecino[2,3,4-*gh*]pyrrolizine-2,7-dione

(1a,2a,15*Z*)-2,12-dihydroxy-1,2-dihydrosenecionan-11,16-dione



Structure-Drawing



Ortep-Drawing

Structure

Freer A.A., Kelly H.A., Robins D.J.:
(1986) *Acta Cryst. C***42,** 1348-1350.

Non toxic

Mattocks A.R., White I.N.H.:
(1971) *Nature New Biol.*, **231,** 114-115.

Occurrence in *Senecio pleistocephalus* and other *S.* spec.**:**

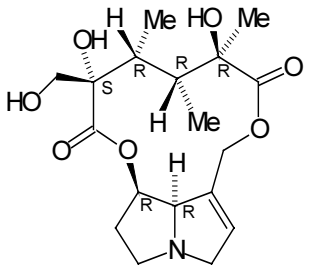
Kunec E.K., Robins D.J.:
(1986) *J. Chem. Soc., Chem. Commun*., 250-252.

Sceleratine

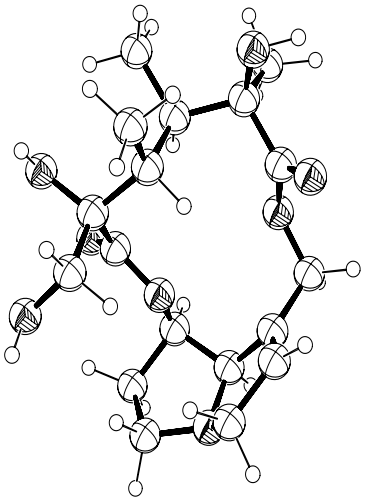
$C_{18}H_{27}NO_7 \cdot 2\ C_2H_5OH$ / 369.410 · 92.136

(3*S*,4*R*,5*R*,6*R*,14a*R*,14b*R*)-3,6-dihydroxy-3-(hydroxymethyl)-4,5,6-trimethyl-3,4,5,6,9,11,13,14,14a,14b-decahydro[1,6]dioxacyclododecino[2,3,4-*gh*]pyrrolizine-2,7-dione

Measured as Diethanol Solvate



Structure-Drawing



Ortep-Drawing

Structure

Bredenkamp M.W., Wiechers A.,
Van Rooyen P.H.:
(1985) *Tetrahedron Lett.,* **26**, 5721-5724.

Toxicity
not yet reported

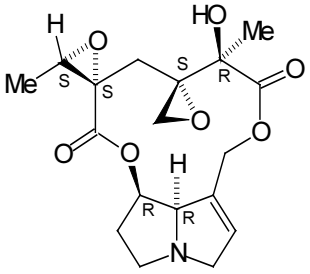
Occurrence in *Senecio latifolius:*

Barger G., Seshadri T.R., Watt H.E., Yabuta T.:
(1935) *J. Chem. Soc.,* 11-15.

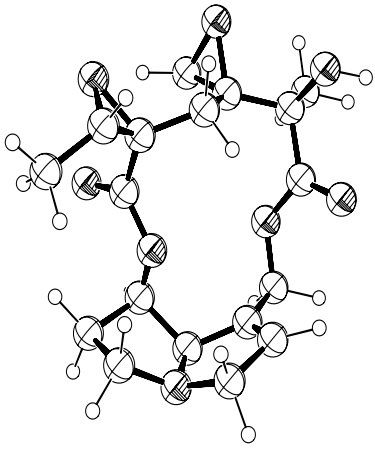
Senecicannabine

$C_{18}H_{23}NO_7$ / 365.378

(2*S*,3*S*,5''*S*,6'*R*,14a'*R*,14b'*R*)-6'-hydroxy-3,6'-dimethyl-9',11',13',14',14a',14b'-hexahydrodispiro[oxirane-2,3'-[1,6]dioxacyclododecino[2,3,4-*gh*]pyrrolizine-5',2''-oxirane]-2',7'(6'*H*)-dione



Structure-Drawing



Ortep-Drawing

Structure

Asada Y., Furuya T., Shiro M., Nakai H.:
(1982) *Tetrahedron Lett.*, 189-192.

Toxicity

Mori H., Sugie S., Yoshimi N., Asada Y., Furuya T., Williams G.M.:
(1985) *Cancer Res.*, **45**, 3125-3129.

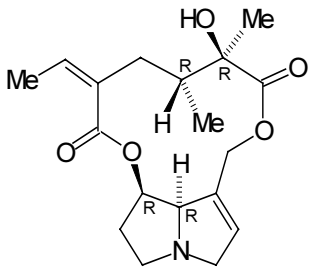
Occurrence in *Senecio cannabifolius*.

Senecionine

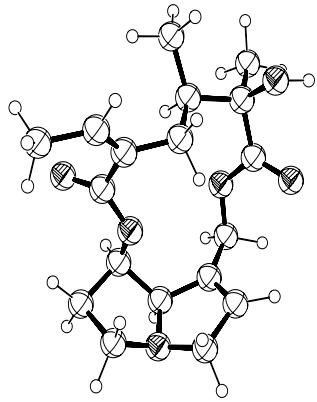
$C_{18}H_{25}NO_5$ / 335.395

(3*Z*,5*R*,6*R*,14a*R*,14b*R*)-6-hydroxy-3-ethylidene-5,6-dimethyl-3,4,5,6,9,11,13,14,14a,14b-decahydro[1,6]dioxacyclo-dodecino[2,3,4-*gh*]pyrrolizine-2,7-dione

(15*Z*)-12-hydroxysenecionan-11,16-dione



Structure-Drawing



Ortep-Drawing

Structure

Mackay M.F., Culvenor C.C.J.:
(1982) *Acta Cryst. B***38**, 2754-2758.

Wiedenfeld H., Roeder E., Kirfel A., Will G.:
(1982) *Unpublished results*.

Hua Z., Xu X., Wei X., Tang S., Wu Y.:
(1983) *Beijing Daxue Xuebao, Ziran Kexueban*, 89-96.
Chem. Abstr., **100**, 139425 (1984).

Toxicity

Culvenor C.C.J., Downing D.T., Edgar J.A., Jago M.V.:
(1969) *Ann. N.Y. Acad. Science*, **163**, 837-847.

Culvenor C.C.J., Edgar J.A., Jago M.V., Outteridge A., Peterson J.E., Smith L.W:
(1976) *Chem. Biol. Interact.*, **12**, 299-324.

Frei H., Lüthy J., Brauchli J., Zweifel U., Würgler F.E., Schlatter C.:
(1992) *Chem. Biol. Interact.*, **83,** 1-22.

Occurrence in many *Senecio spec.:*

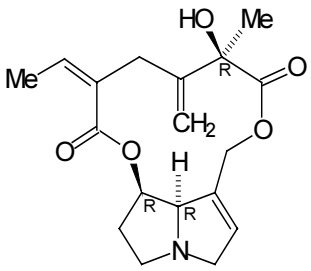
Culvenor C.C.J.:
(1966) *Tetrahedron Lett.*, 1091-1099.

Seneciphylline

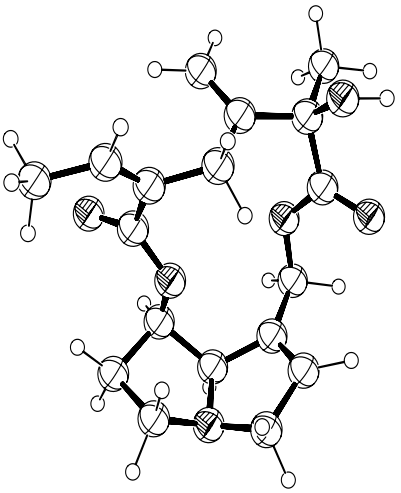
$C_{18}H_{23}NO_5$ / 333,379

(3*Z*,6*R*,14a*R*,14b*R*)-6-hydroxy-3-ethylidene-6-methyl-5-methylene-3,4,5,6,9,11,13,14,14a,14b-decahydro[1,6]dioxacyclo-dodecino[2,3,4-*gh*]pyrrolizine-2,7-dione

(15*Z*)-12-hydroxy-13,19-didehydrosenecionan-11,16-dione



Structure-Drawing



Ortep-Drawing

Structure

Wiedenfeld H., Knoch F., Roeder E., Appel R.:
(1984) *Arch. Pharm.*, **317**, 97-102.

Toxicity

Anonymous:
(1976) *IARC, Monogr.*, **10**, 319-325.

Culvenor C.C.J., Downing D.T., Edgar J.A., Jago M.V.:
(1969) *Ann. N.Y. Acad. Science*, **163**, 837-847.

Occurrence in *Adenostyles glabra* and *Senecio* spec.:

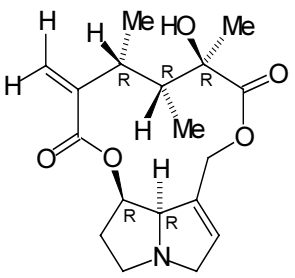
Roeder E., Plassmeier C.:
(1991) *Sci. Pharm.*, **59**, 301-306.

Senecivernine

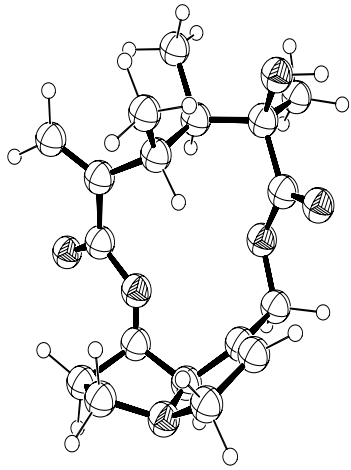
$C_{18}H_{25}NO_5 \cdot 2\ H_2O$ / 335.395 · 36.03

(4*R*,5*R*,6*R*,14a*R*,14b*R*)-6-hydroxy-4,5,6-trimethyl-3-methylene-3,4,5,6,9,11,13,14,14a,14b-decahydro[1,6]dioxa-cyclo-dodecino[2,3,4-*gh*]pyrrolizine-2,7-dione

Measured as Dihydrate



Structure-Drawing



Ortep-Drawing

Structure

Parvez M., Benn M.H.:
(1995) *Acta Cryst. C***51**, 1202-1204.

Toxicity

Rubiolo P., Pieters L., Calomme M., Bicchi C., Vlietinck A., Van dem Berghe D.:
(1992) *Mutat. Res.*, **281**, 143-147.

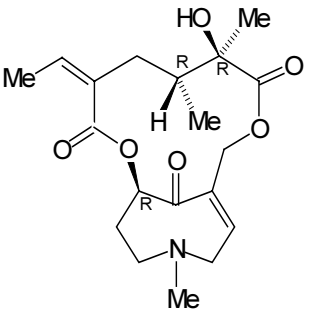
Occurrence in *Senecio vernalis:*

Roeder E., Wiedenfeld H., Pastewka U.:
(1979) *Planta Med.,* **37,** 131-136.

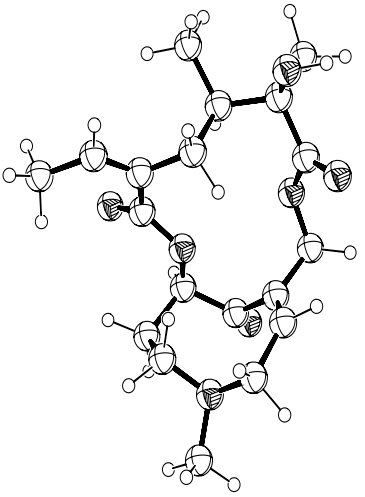
Senkirkine

$C_{19}H_{27}NO_6$ / 365.421

(1*R*,4*Z*,6*R*,7*R*)-4-ethylidene-7-hydroxy-6,7,14-trimethyl-2,9-dioxa-14-azabicyclo[9.5.1]heptadec-11-ene-3,8,17-trione



Structure-Drawing



Ortep-Drawing

Structure

Bimbaum G.I.:
(1974) *J. Am. Chem. Soc.*, **96**, 6165-6168.

and:

Dodson G.G., Hall D.:
(1966) *Acta Cryst.*, **20**, 42-48.

and measured as Chloroplatinate:

Culvenor C.C.J., Mackay M.F.:
(1991) *Aust. J. Chem.*, **44**, 635-637.

Toxicity

Anonymous:
(1976) *IARC*, *Monogr.,* **10**, 327-343.

Anonymous:
(1983) *IARC*, *Monogr.*, **31**, 231-238.

Frei H., Lüthy J., Brauchli J., Zweifel U.,
Würgler F.E., Schlatter C.:
(1992) *Chem. Biol. Interact.*, **83,** 1-22.

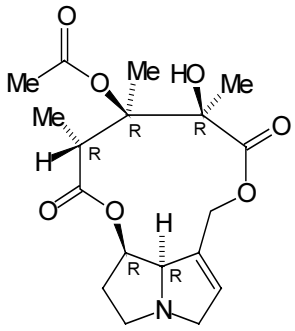
Occurrence in *Senecio kirkii* and other *S.* spec.:

Briggs L.H., Cambie R.C., Candy B.J., O´Donovan G.M.,
Russell W.E., Selye R.N.:
(1948) *J. Chem. Soc.*, 2492-249.

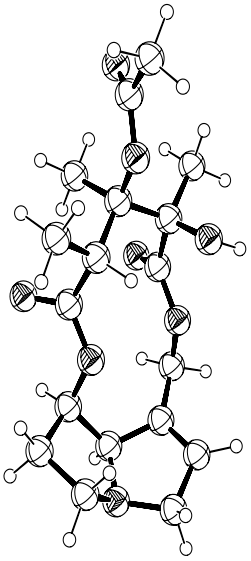
Spectabiline

$C_{18}H_{25}NO_7$ / 367.394

(3*R*,4*R*,5*R*,13a*R*,13b*R*)-5-hydroxy-3,4,5-trimethyl-2,6-dioxo-3,4,5,6,8,10,12,13,13a,13b-decahydro-2*H*-[1,6]dioxacyclo-undecino [2,3,4-*gh*]pyrrolizin-4-yl acetate



Structure-Drawing



Ortep-Drawing

Structure

Wang S.T., Chen B.:
(1982) *Kexue Tongbao,* **27**,1023-1027.
Chem. Abstr., **97**, 198430 (1982).

Toxicity

Culvenor C.C.J., Downing D.T., Edgar J.A., Jago M.V.:
(1969) *Ann. N.Y. Acad. Science,* **163**, 837-847.

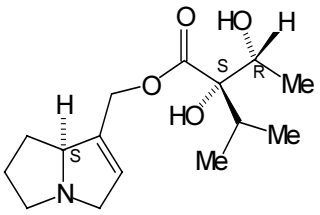
Occurrence in *Crotalaria retusa:*

Klasek A., Reichstein T., Santavy F.:
(1968) *Helv. Chim. Acta,* **51**, 1088-1095.

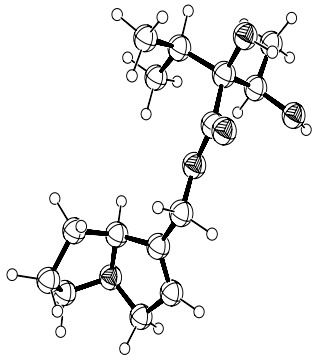
Supinine

$C_{15}H_{25}NO_4$ / 283.363

(7a*S*)-2,3,5,7a-tetrahydro-1*H*-pyrrolizin-7-ylmethyl (2*S*,3*R*)-2,3-dihydroxy-2-isopropylbutanoate



Structure-Drawing



Ortep-Drawing

Structure

Mackay M.F., Mitrprachachon P., Oliver P.J., Culvenor C.C.J.: (1985) *Acta Cryst. C***41**, 722-725.

Toxicity

Culvenor C.C.J., Downing D.T., Edgar J.A., Jago M.V.: (1969) *Ann. N.Y. Acad. Science*, **163**, 837-847.

Frei H., Lüthy J., Brauchli J., Zweifel U., Würgler F.E., Schlatter C.: (1992) *Chem. Biol. Interact.*, **83,** 1-22.

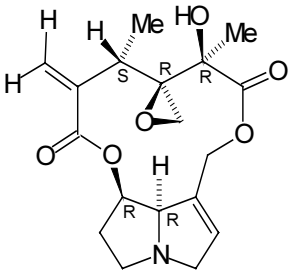
Occurrence in *Heliotropium europaeum:*

Culvenor C.C.J.: (1954) *Aust. J. Chem.*, **7**, 287-297.

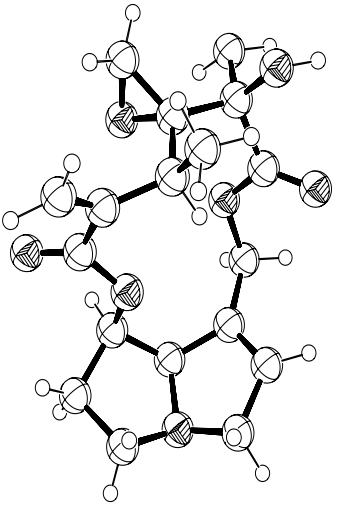
Swazine

$C_{18}H_{23}NO_6$ / 349.378

(4*S*,5*R*,6*R*,14a*R*,14b*R*)-6-hydroxy-4,6-dimethyl-3-methylene-3,4,9,11,13,14,14a,14b-octahydro-2*H*-spiro[1,6-dioxacyclododecino[2,3,4-*gh*]pyrrolizine-5,2'-oxirane]-2,7(6*H*)-dione



Structure-Drawing



Ortep-Drawing

Structure

White J.D., Amedio Jr. J.C., Hmciar P., Lee N.C., Ohira S., Yokochi A.F.T.: (1998) *Chem. Commun.,* 603-604.

and measured as Methiodide:

Laing M., Sommerville P.: (1972) *Tetrahedron Lett.,* 5183-5186.

Toxicity
not yet reported

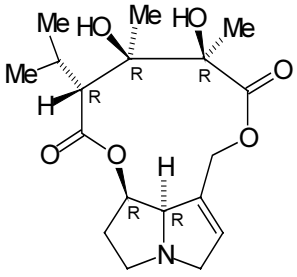
Occurrence in *Senecio swaziensis:*

Laing M., Sommerville P.: (1972) *Tetrahedron Lett.,* 5183-5186.

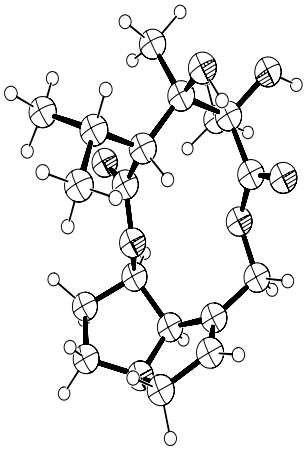
Trichodesmine

$C_{18}H_{27}NO_6$ / 353.410

(3*R*,4*R*,5*R*,13a*R*,13b*R*)-4,5-dihydroxy-3-isopropyl-4,5-dimethyl-4,5,8,10,12,13,13a,13b-octahydro-2*H*-[1,6]dioxacycloundecino[2,3,4-*gh*]pyrrolizine-2,6(3*H*)-dione



Structure-Drawing



Ortep-Drawing

Structure

Tashkhodzhaev B., Yagudaev M.R., Yunusov S.Y.:
(1979) *Khim. Prir. Soedin.,* 368-373.
Chem. Abstr., **92**, 111194 (1980).

Toxicity

Turakulov Y.K.:
(1970) *Vop. Med. Khim., Biochim. Gorm.*, 52-54.

Occurrence in *Trichodesma incanum:*

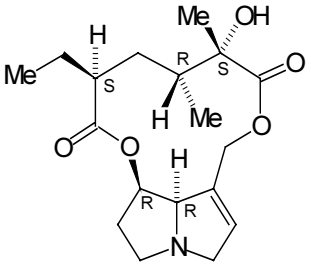
Menshikov G.P., Rubinstein W.:
(1935) *Ber. Dtsch. Chem. Ges.* B**68**, 2039-2044.

Yamataimine

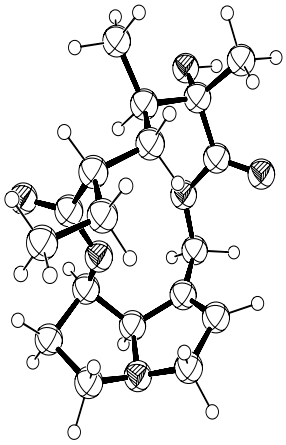
$C_{18}H_{27}NO_5$ / 337.411

(3*S*,5*R*,6*S*,14a*R*,14b*R*)-6-hydroxy-3-ethyl-5,6-dimethyl-3,4,5,6,9,11,13,14,14a,14b-decahydro[1,6]dioxacyclododecino [2,3,4-*gh*]pyrrolizine-2,7-dione

(12*S*,15*S*)-12-hydroxy-15,20-dihydrosenecionan-11,16-dione



Structure-Drawing



Ortep-Drawing

Structure

Hikichi M., Furuya T., Iitaka Y.: (1978) *Tetrahedron Lett.*, 767-770.

Toxicity
not yet reported

Occurrence in *Cacalia yatabei*.