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3 Psychotomimetics of the Convolvulaceae

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INTRODUCTION

Man's desire to control and manipulate the workings of his mind is not a new phenomenon. Despite the current preoccupation of some elements of society with the apparent widespread use (or abuse) of what are loosely called 'drugs', by other groups, mostly younger people, there is evidence of attempts by man to find the means to elevate or depress his mood or his degree of consciousness, at will, throughout recorded history. Certain other findings bear witness to the fact that man has also sought to modify his perception of the world around him and to communicate with the forces that he believed controlled his destiny. It is of interest to note that this phenomenon does not appear to have been restricted to any particular race or creed or to any particular geographical location or historical epoch.

In addition to the purely spiritual and physical means employed by our early ancestors in the search for their 'ideal' state of mind and level of mental functioning, certain plants and fungi were recognised, in many parts of the world, to contain substances that often had powerful effects on the mental processes of a person eating them. In recent years, the synthetic organic chemist has added profusely to the array of products of this type, i.e., to what we now refer to as psychotropic agents, the majority of which (e.g. sedatives, tranquillisers, antidepressants, etc.) are used quite legitimately in everyday medical practice.

One of the most interesting facets of the story of the mind-modifying drugs is that of the so-called 'Magic Drugs of the Aztecs'. These drugs played a significant part in the lives of these people and in those of other tribes indigenous to this part of Central America in the pre-Hispanic era and to some extent they still do. The three best known examples of these drugs are Peyotle, Teonanacatle, and Ololiuqui, derived from a cactus, a mushroom, and a climbing vine, respectively. This review deals in some detail with Ololiuqui, the third of the above-mentioned sacred classical drugs of the Aztecs, together with another pre-Columbian Central American drug, Tlitliltzin, which was also derived from a climbing plant. The chemistry, pharmacology and psychopharmacology of some products extractable from certain of the Convolvulaceous plants, in particular those now known as 'morning glories', will be considered in this article. The fact that a state of intoxication can result from the ingestion of some readily available morning glory seeds was rediscovered in the last decade by certain groups in Western society, leading to the potential danger of a new form of drug abuse (or what might better be referred to as seed abuse, or the non-horticultural use of seeds). However this does not appear to have become a serious problem, certainly not serious enough to warrant interdiction of the general sale of

morning glory seeds. However, investigations in this area have led to some significant advances in the phytochemistry of the Convolvulaceae and pharmacology and psychopharmacology of the compounds isolated from their seeds.

OLOLIUQUI*, TLITLILTZIN AND RELATED PRE-COLUMBIAN CENTRAL AMERICAN CONVOLVULACEOUS DRUGS

NATURE OF THE DRUGS, HISTORICAL AND BOTANICAL CONSIDERATIONS

The lentil-like seeds of the tropical convolvulaceous plant *Rivea corymbosa* (L.) Hall., which have been in use for medicinal and divinatory purposes by the Aztecs in the uplands of the Southern Oaxaca region of Mexico, since pre-Hispanic times, were known in the Nahuatl language as 'ololiuqui' (meaning 'round thing') and as 'badoh' in Zapotec. This particular drug seems to have been more important to the Aztecs in divinity than Peyotl or Teonanacatle, two of their other classical sacred drugs. Ololiuqui is still in use today by certain tribes, namely, the Zapotecs, Chinantecs, Mazatecs and Mixtecs, in this remote isolated region of Southern Mexico [1–3]. The plant bearing the ololiuqui seed is meaningfully called coaxihuitl (snake-plant) in Nahuatl and as hiedra or bejuco by Spanish writers. In Spanish, the seed is also commonly known as Semilla de la Virgen (cf. Wasson [1]). Other colloquial names for ololiuqui used in different Mexican districts have been listed in articles by Hofmann [3,4].

The seed of another Convolvulaceous plant, *Ipomoea violacea* L., which also grows wild in parts of Mexico, particularly in the Oaxaca region, has also been used for centuries for similar purposes [5] and is known in Zapotec as 'badoh negro'. These seeds, which are generally considered by most authors to be more potent than those of *R. corymbosa,* are believed by Wasson to be the classical Aztec drug, Tlitliltzin [1]. The seeds of *R. corymbosa* are rounded and brown in colour, whilst those of *I. violacea* are black, long and angular.

There has been, and to some extent still is, a certain amount of disagreement among botanists as to the correct classification of these plants. Some authors insist that *R. corymbosa* (L.) Hall. should be cited as *Turbina corymbosa* (L.) Raf. Other authors have classified the plant as an *Ipomoea* species [i.e. *I. corymbosa* (L.) Roth and *I. sidaefolia* (HBK.) Chois.]. A detailed consideration

*Wasson, a leading authority on the magic drugs of the Aztecs, has stated that linguistic evidence indicates that this Nahuatl word is correctly spelled ololiuhqui [1]. However, since the shorter spelling ololiuqui has gained wide acceptance in the literature, it will be used throughout this chapter.

of the taxonomic aspects of the problem is outside the scope of this review, however, the subject is discussed at length in the following references: Wasson [1], Schultes [2,6–9], Roberty [10], Wilson [11], Shinners [12], Der Marderosian [13,14]. *Ipomoea violacea* L. has occasionally been cited by some authors as *I. tricolor* Cav. and *I. rubro-caerulea* Hook. However, all three names probably refer to the same species. Nevertheless, as in the case of *R. corymbosa,* there is some confusion among the taxonomists as to the correct classification of this plant [1,8,12–14].

The plants and their uses were first described by the chroniclers of the Spanish conquest of Mexico before the end of the sixteenth century. The monk Sahagun in his 'History of New Spain' written in the sixteenth century mentions a plant known as Coatlxoxouhqui (green snake) which gives seeds known as ololiuqui. These seeds were said to 'mislead the senses' of the person taking them and to 'deprive the user of his reason'. Francisco Hernandes, personal physician to the King of Spain, who carried out extensive field work on the flora and fauna of New Spain between 1570 and 1575, accurately illustrates the ololiuqui plant in his treatise which was published in Rome by Ximénez in the middle of the seventeenth century [15]. He further reported the Aztec priests 'communed with their gods and received messages from them, by eating the ololiuqui seeds to induce a delirium when a thousand visions and satanic hallucinations appeared to them' [15]. The ololiuqui seed also appears to have been a constituent of a magical ointment used by the Aztec priests which made them fearless and insensitive to pain [2].

The fact that the ritualistic use of these plants formed an integral part of the religion of the native population was a total anathema to the Spaniards. The Roman Catholic missionaries who followed on the heels of the conquistadores, supported by a strong secular arm, went to great lengths to suppress the use of what was referred to as this 'diabolic seed'. The fact that the Church completely misjudged the veneration in which these plants were held is illustrated by the ultimate failure of these vigorous attempts to suppress their use. This is further clearly demonstrated by the fact that these seeds, together with several of the other magic drugs of the Aztecs, are still in use for medicinal and religious purposes in parts of Mexico today. An example of the modern version of the ololiuqui ceremony has been graphically described by Wasson in his paper 'Notes on the present status of Ololiuhqui and other hallucinogens of Mexico', published in 1963 [1] and clearly illustrates the interweaving of the Christian religion with the ancient Aztec ceremony.

Progress in solving the ololiuqui problem was no doubt hampered by the confusion that existed for four centuries with regard to the botanical classification of the plant. It is also quite possible that the indigenous population of the

region deliberately misled their conquerors as to the true nature of their sacred drug. The attitude of the Church may also have helped to drive the native cults and their drugs into hiding. It is also of interest to note that no intoxicating or narcotic constituents were known to occur in the Convolvulaceae, despite the worldwide distribution of this plant family, before the relatively recent work that is described in this review.

The situation with regard to the true nature of ololiuqui was, however, essentially resolved when Schultes published his monograph in 1941 on 'A contribution to our knowledge of *R. corymbosa*, the narcotic ololiuqui of the Aztecs' [6]. Despite the fact that Mexican botanists had described ololiuqui as being the seeds of a morning glory and Urbina had identified the seeds as being from *R. corymbosa* (L.) Hall. (syn. *I. sidaefolia* HBK.) [16] at the end of the last century, one noted American economic botanist, Safford, accepted the earlier suggestion of Hartwich [17] that ololiuqui was a member of the Solanaceae [18] and should in fact be referred to as *Datura meteloides* Dunal ex DC. [19]. This claim was widely accepted at the time, and it was assumed that the psychotoxic effects ascribed to the plant were due to a form of *Datura* intoxication and even relatively recently some authors were insisting that the active hallucinogenic ingredient of ololiuqui was derived from one of the *Datura* species [20]. This is perhaps not too surprising in view of the similarity of the shape of the tubular flowers of the two plants and in the similarity of the symptoms of *Datura* and ololiuqui intoxications. It should be remembered that whereas at this time *Datura* poisoning was well known, psychological effects due to Convolvulaceous plants were not. Several publications review much of the earlier fascinating history of ololiuqui [2,3,6,18,21–26].

The other narcotic morning glory of the Aztecs, the badoh negro of the Zapotec region was finally identified in 1960 as a variety of *I. violacea* L. by MacDougall [5].

PHYTOCHEMICAL INVESTIGATIONS

Some of the first modern chemical and pharmacological investigations of the ololiuqui drug were carried out by Santesson in 1937 [27,28] who referred to the drug as 'piule'. In his monograph on the Mexican hallucinogens, Wasson suggests that piule is a generic name in Mexico for all hallucinogens and may have originally been derived from the word péyotl [1]. From the seeds Santesson isolated a compound which he was unable to fully identify and which he described as being a glucoalkaloid [27,28].

The problem was not solved, however, until the early 1960's when chemists

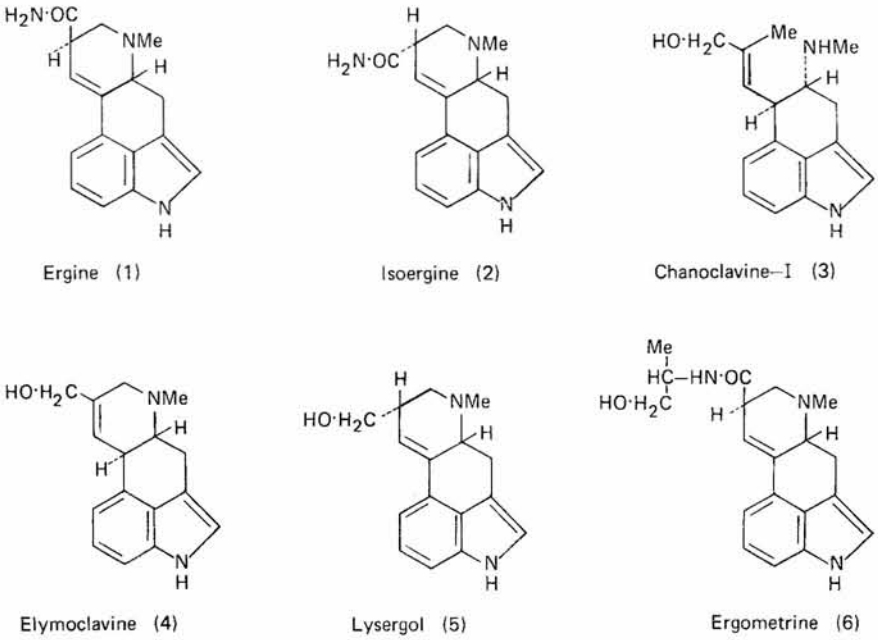


Figure 3.1.

in the Sandoz laboratories in Basle, using mild extraction procedures, finally isolated and identified several ergoline alkaloids from the seeds of both *R. corymbosa* and *I. violacea* [29–32]. These workers demonstrated that the seeds of *I. violacea* contained a higher percentage content of this group of indole alkaloids (ca. 0.06 per cent) than those of *R. corymbosa* (ca. 0.012 per cent), thus explaining the reported higher potency of the former [cf. 1]. The Swiss workers showed that the major alkaloids present in the seeds of both plants were *d*-lysergic acid amide (i.e. ergine, 1); *d*-isolysergic acid amide (i.e. isoergine, 2); chanoclavine (3) and elymoclavine (4). Lysergol (5) was also detected in extracts of *R. corymbosa* seeds but not in the relevant *Ipomoea* seeds, however, ergometrine* (6) was present in the latter extracts but not in the former [33,34] (see *Figure 3.1*).

*The alkaloid (6) had been discovered and named earlier by several different groups of workers working independently. Consequently the names ergonovine and ergobasine are also encountered sometimes in the literature for this compound. However, the name ergometrine will be used throughout this review.

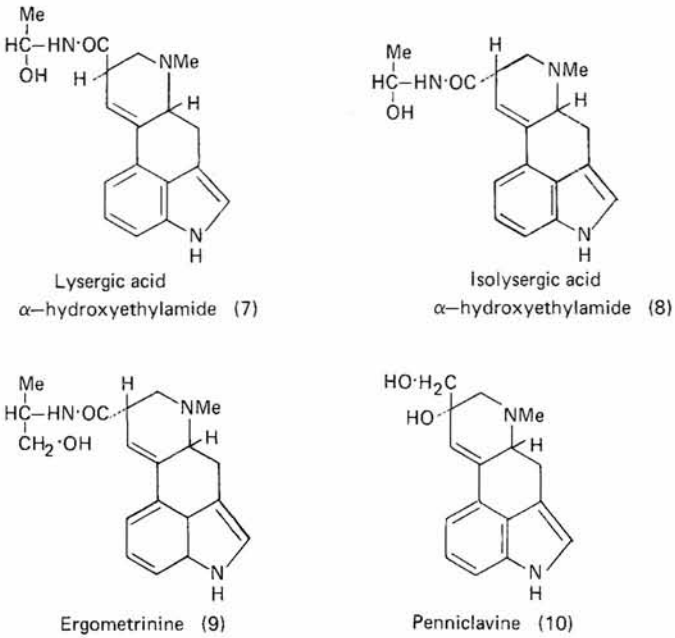


Figure 3.2.

The major alkaloids present in both seeds were ergine (1) (0.0065 per cent in *R. corymbosa* and 0.035 per cent in *I. violacea*) and isoergine (2) (0.002 per cent and 0.005 per cent respectively) [33]. It was later shown, however, that these amides were present in the seeds to some extent at least as adducts with acetaldehyde, i.e. lysergic acid α-hydroxyethylamide (7) and isolysergic acid α-hydroxyethylamide (8) respectively [3]. The hydroxyamides (7) and (8) are somewhat unstable and are hydrolysed to the simple amides (1) and (2) (and acetaldehyde) during the extraction procedure.

More recent investigations, carried out by Taber, Vining and Heacock produced chromatographic evidence for the presence of ergometrine (6) and ergometrinine (9) and also penniclavine (10) in samples of ololiuqui obtained from Cuba [35] (see *Figure 3.2*). These results, with regard to the presence of (9) and (10) in *R. corymbosa*, were later confirmed by Der Marderosian and Youngken [36]. Taber, Heacock and Mahon showed that the ergot alkaloids ergine (1) and isoergine (2) were present in the leaf and stem, but not in the root of *R. corymbosa* which had been grown in a greenhouse at a northern latitude

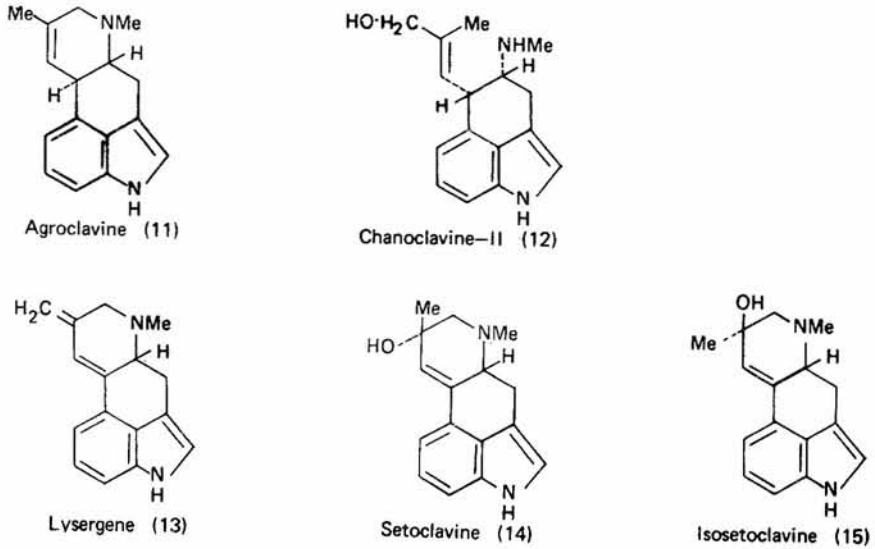
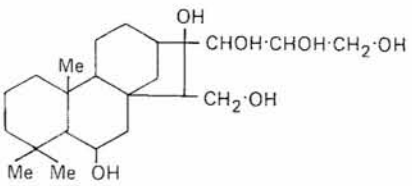


Figure 3.3.

(Saskatoon, Canada) [37]. Staba and Laursen did, however, report the presence of traces of indole alkaloids in *R. corymbosa* roots grown under greenhouse conditions [38]. A recent study by Chao, using two-dimensional thin layer chromatography, demonstrated that in addition to the ergoline alkaloids (1–10) mentioned above, several other alkaloids of this type, namely: agroclavine (11); chanoclavine-II (12)*; lysergene (13); setoclavine (14) and isosetoclavine (15) are present in *R. corymbosa* seeds together with several other unidentified indole alkaloids [39] (see *Figure 3.3*).

The discovery that lysergic acid and clavine type alkaloids were present in the seeds of some Convolvulaceous plants was of considerable phytochemical importance, since this was the first time in which bases of this type had been found in higher plants. Before these discoveries, they had only been isolated from certain lower fungi of the genera *Claviceps, Penicillium* or *Rhizopus*. It had been known for some time that ergot bases occurred naturally in the sclerotic mycelium of *Claviceps* species, when these had parasitised the ovaries of certain grasses; consequently the possibility that the ergot alkaloids found in the *Rivea* and *Ipomoea* seeds were due to fungal contamination had to be considered. How-

*Compound 3 will be referred to as Chanoclavine-I.



Turbicorytin (16)

Figure 3.4.

ever, Taber and Heacock have shown that, in the case of *R. corymbosa* seeds the ergot-type alkaloids were present in the embryo, but not the seed coat, seed membranes or resinous layer under the seed coat [40]. The alkaloids were also typically present in the seeds [40]. Fungi were present in the seed coat, but not in the embryo of surface-sterilised seeds. They also were typically present in the seed and were concentrated about the hilum [40]. The only fungi present in the seeds investigated were various *Chaetomium* species and *Fusarium moniliforme*. The absence of fungi in the region of the seed which contained the alkaloid suggests that the fungi were not the source of the alkaloid [40]. The fact that ergot alkaloids could also be found in some of the vegetative tissues of plants grown from these seeds [37] tended to substantiate the fact that the alkaloids were formed in the plant itself and were not due to fungal contamination. Hofmann reported the presence of alkaloids in the leaves, stalks and roots of *I. violacea* [33]. Ergot-type alkaloids were further reported to be present in the leaves and stems of mature *R. corymbosa* plants [37]. The amount per plant increased with time, reaching a maximum of 0.027 per cent and 0.012 per cent alkaloids respectively in the leaf and stem, calculated on the dry weight of the plant tissues [37]. The same workers further showed by paper and thin layer chromatography and fluorescence spectroscopy that (1) and (2), together with at least two other unidentified ergot alkaloids, were present in the plant tissue extracts [40]. Staba and Laursen later reported that traces of indole alkaloids could be detected in *Rivea* roots [38].

There appears to be little doubt that the alkaloids isolated from the seeds of *R. corymbosa* and *I. violacea* are the psychologically active principles of these magic plants. However, a white crystalline glucoside (m.p. 240–241°C) named turbicoryn* has been isolated from the seeds of *R. corymbosa* [41,42]. Enzy-

*Pérezamador and Herrán obtained this glucoside from the seeds of a plant they described as *Turbina corymbosa* [41]. This binomial is usually considered to be synonymous with *R. corymbosa*. (See p. 93.)

matic hydrolysis of turbicoryn yielded glucose and the corresponding aglycone turbicorytin (16) [41]. The molecular formulae of turbicoryn and turbicorytin were established as $C_{29}H_{50}O_{11}\cdot 1\frac{1}{2}H_2O$ and $C_{23}H_{40}O_6\cdot\frac{1}{2}H_2O$ respectively [42]. On the basis of an extensive physical and chemical investigation, the formula (16) was proposed for turbicorytin [42]. The stereochemistry of turbicorytin (16) has been discussed [43] (see *Figure 3.4*).

Cook and Keeland had previously reported the isolation of a glucoside [44], with a similar melting point, from *R. corymbosa* seeds but having a different molecular formula ($C_{28}H_{46}O_{12}$) and optical rotation from the product isolated by the Mexican workers. It is doubtful if the glucoside makes a significant contribution to the overall psychotomimetic activity of ololiuqui. However, Cook and Keeland reported that the central nervous stimulant activity of the glucoside, in rabbits, is about five times that of crude ethanolic extracts of *R. corymbosa* seeds [44].

Der Marderosian determined the percentage of petroleum ether extractable material present in a number of morning glory seeds, including *R. corymbosa* and found the value varied between 9.2 and 17.0 per cent [45]. Sahasrabudhe and Genest reported a fat content of 8 per cent in the *Rivea* seeds [46,47].

PHYSIOLOGICAL ACTIVITY, PHARMACOLOGY AND PSYCHOPHARMACOLOGY

Taylor in his monograph on narcotics, first published in 1949, describes the psychological and physiological effects of ololiuqui 'as first producing hallucinations; sometimes preceded by, or punctuated by, giddiness, but always leading to a form of euphoric bliss ultimately leading to a form of hypnotic sleep' [48]. Although Santesson reported that the piule (see p. 95) extracts he worked with produced a form of 'half-narcosis' in frogs [27,28] and Schultes reported the results of some cases of self-experimentation with ololiuqui seeds [6], little systematic work on the psychological effects of ololiuqui has been reported until relatively recently. In 1955, Osmond reported the results of self-ingestion of 14*, 26, 60 and 100 powdered seeds [49]. Osmond mainly experienced a condition of apathy and anergia combined with some degree of heightened visual perception with an increase in hypnagogic phenomena eventually leading, after a period of about 4 hr, to feelings of alertness, calm and relaxed well-being [49]. The intoxication produced by ololiuqui appears, therefore, to be free from mental confusion and is characterised by extreme wakefulness, combined with a distorted perception of time. Some years later, however, Kinross-Wright reported

*According to Schultes in his monograph published in 1941 the original Indian dose was 13 seeds [6].

that he had failed to obtain any noticeable psychological effects from doses up to 125 powdered seeds or from ethereal or alcoholic extracts of up to 135 seeds [20]. It is possible that the negative results obtained by Kinross-Wright may have been due to inadequate preparation. In his definitive paper on the subject, Wasson describes the present Zapotec Indian ceremony in which the seeds are ground to a flour, the flour is soaked in cold water for a short time, strained and the solid-free filtrate drunk either in water alone or in a locally produced alcoholic beverage [1].

Hofmann has described his own self-experimentation with the crude indole fraction obtained from ololiuqui in which 2 mg of material produced clear-cut effects. He reported that a dream-like state resulted with drowsiness and alterations in the perception of objects and colours [33].

In 1966, Isbell and Gorodetzky reported doses of 5 mg (i.e. roughly the equivalent of 400 seeds) of either crude extracts of ololiuqui seeds, or a mixture of the relevant synthetic alkaloids caused drowsiness in a number of former morphine addicts but few other subjective effects [50]. These authors observed little difference in the effects produced by the crude extracts or synthetic alkaloid mixture [50]. In an earlier paper, Hofmann and Cerletti had also reported fatigue, sedation and sleep as being among the major effects of the drug [32]. Osmond had also reported apathy rather than hallucinations [49].

As a result of a study of the psychic effects of ololiuqui, Heim, Heimann and Lukács concluded that the drug does not produce many of the typical effects of psychotomimetic drugs in man [51]. In particular, there was little evidence that the drugs produced an alteration in consciousness or induced hallucinations. These workers suggested that the effects of the two major components of the crude drug, i.e. ergine (1) and isoergine (2) determined the effect of the total alkaloids of ololiuqui. With ergine (1) the clinical picture observed was essentially one of intoxication with strong autonomic side-effects, whereas in the case of (2), euphoria synesthesia and altered time experience were observed. In small doses, the response to the total alkaloids resembled that of the isolysergic acid derivative (2) whilst in higher doses, it resembled that of (1), i.e. heavy intoxication with reduced consciousness and autonomic side-effects. It was concluded that essentially the effects observed were more like those encountered in toxic psychoses resulting from the action of a drug such as scopolamine [51]. This finding was of interest in view of the earlier confusion of ololiuqui with a *Datura* drug.

Hofmann had previously described the action of synthetic ergine (1) as being primarily of a sedative nature [33]. A subcutaneous injection of 0.5–1.0 mg of (1) has been reported to produce a powerful hypnotic action, but a relatively weak psychedelic action [52]. As the result of a systematic psychopharmaco-

logical investigation of a number of lysergic acid derivatives, Solms describes the main actions of ergine (1) as causing indifference, a decrease in psychomotor activity, the feeling of sinking into nothingness and finally clouding of the consciousness and sleep [53,54]. The amide (1) brought about intense autonomic symptoms in rabbits: mydriasis, piloerection and hypothermia accompanied by a general motor restlessness [55]. Ergine (1) only had 4 per cent of the antiserotonin activity of the powerful psychotomimetic, lysergic acid diethylamide (LSD) [55].

Less pharmacological work has been carried out with the other alkaloids present in ololiuqui. Hofmann, as the result of ingesting 2 mg of isoergine (2), experienced a sensation of 'tiredness, apathy, a feeling of mental emptiness and unreality' [33]. In a recent paper the physiological disposition of isoergine (2) [obtained from the seeds of *Argyreia nervosa* (Burm. f.) Bojer] was determined in rat liver, brain and plasma [56]. Isoergine (2) was rapidly absorbed, distributed and metabolised in rats. Peak levels were reached in the liver after 5 min and in the brain and plasma after 15 min, after i.p. injection of 5 mg/kg. The minimum dose of (2) that produced a significant decrease in the conditioned avoidance response (CAR) was less than 5 mg/kg. The minimum brain level of (2) which interfered with the CAR was approximately 1 μg/kg. Brain levels of (2) correlated directly with changes in behaviour which suggested that (2) and not a metabolite was the psychoactive component [56]. However, isoergine (2) appears to be approximately 33 times less active psychologically than LSD [56].

Yui and Takeo claim that elymoclavine (4) and lysergol (5) in several animals cause an excitation syndrome which is due to central stimulation of the sympathetic nervous system [57]. Such an effect might suggest some psychotomimetic action was present [cf. 3]. Isbell and Gorodetzky, however, (referring to unpublished work by Isbell) claim that the primary effects of (4) are sedative [50].

d-Lysergic acid α-hydroxyethylamide (7) elicits contractions in the isolated guinea pig uterus *in situ*, exhibiting 30–50 per cent of the activity of the well known uterotonic agent ergometrine (6) [3]. Some symptoms of central sympathetic stimulation are also seen in mice which suggests that (7) might show some psychedelic activity, although this has not been demonstrated with human subjects [58, cf. 3].

No psychological effects have been reported for ergometrine (6), a drug widely used in obstetrics, nor for chanoclavine (3). Although there is evidence for a uterine stimulant principle in ololiuqui extracts, it was less potent than that present in some *I. violacea* seed extracts [59].

In conclusion, it would appear that there is still some doubt as to the nature of the experience produced by ololiuqui, and the compounds present in the

crude drug that are responsible for its activity. However, at this stage, it is not unreasonable to assume that the two simple amides, ergine (1) and isoergine (2) together with lysergic acid α-hydroxyethylamide (7), elymoclavine (4) and lysergol (5) are largely responsible for the psychological activity of the ololiuqui drug [cf. 3].

For further reading on some detailed aspects of the ololiuqui problem and that of the other Aztec drugs, derived from both Convolvulaceous plants and from other sources, the reader may wish to consult the following references [60–74] in addition to those already quoted in this article.

ORNAMENTAL MORNING GLORIES AND OTHER CONVOLVULACEOUS PLANTS

INTRODUCTORY REMARKS

The findings described above [29–34] that certain Convolvulaceous plants endogenous to Central America and the Caribbean area, namely *R. corymbosa* and a wild variety of *I. violacea*, contained ergot-type alkaloids undoubtedly prompted other workers to investigate the possibility that the seeds and vegetative tissues of additional members of the Convolvulaceae family also contained alkaloids of this type. The knowledge that the seeds of these wild tropical 'morning glories' produced psychological disturbances on ingestion has been available for centuries. It is, therefore, somewhat surprising that, as far as the author is aware, no reports of similar psychological effects being observed on the ingestion of seeds of horticultural or other uncultivated examples of this plant family, which grow freely in many other parts of the world, appeared in print until the early part of the last decade.

However, a number of assorted Convolvulaceous drug preparations, mainly using the dried latex and resin obtained from such plants, have been used in various branches of medicine for hundreds of years (e.g. the purgative Jalap) [75].

The crude drug Kaladana [76] well known in the Indian sub-continent is also used as a purgative [77]. According to Jain, the drug is made up of the dried seeds of *I. nil* (L.) Roth (syn. *I. hederacea* auct. non Jacq.) [77]. In his book on medicinal plants of India, Jain gives a number of local names for Kaladana and lists other *Ipomoeas* that have some drug uses in the area [77]. However, the nature of the species of *Ipomoea* in use in at least some samples of Kaladana has been disputed and interestingly some samples of Kaladana have been shown to contain significant amounts of ergoline alkaloids [78–80].

PHYTOCHEMICAL INVESTIGATIONS

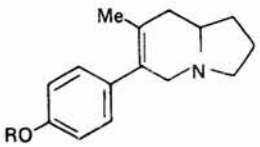
In 1963, several workers independently reported that ergoline alkaloids were present in the seeds of certain members of the Convolvulaceae family, other than the two tropical varieties mentioned above. Taber, Vining and Heacock showed, by using thin layer and paper chromatographic procedures, that several varieties of ornamental morning glory seeds readily available in the U.K. and in North America contained a number of clavine and lysergic acid alkaloids [35] including: ergine (1); isoergine (2); chanoclavine (3); elymoclavine (4); ergometrine (6); ergometrinine (9) and penniclavine (10) along with other unidentified indole alkaloids [35]. The total alkaloid content (van Urk assay) obtained using five different extraction procedures on one batch of seeds of the horticultural morning glory known as Pearly Gates varied between 0.067 and 0.12 per cent [35]. These workers further showed that, whilst there was little qualitative difference in the alkaloidal mixtures obtained from 'ololiuqui' (i.e. *R. corymbosa*) and Pearly Gates seeds, there were significant quantitative differences; the tropical varieties contained relatively more of the potentially psychotoxic compound ergine (1) [35]. In the same year Beyerman, Van de Linde and Henning reported that alkaloids of the ergot type including ergine (1), isoergine (2), chanoclavine (3) and elymoclavine (4), together with other indole alkaloids (up to 0.04 per cent total alkaloids) were present in seeds of what were described as the Pearly Gates variety of *Ipomoea* and *I. rubro-caerulea* var. *praecox* (Blue Skies) [81]. Beyerman also showed that ergot substances were absent from about 22 other *Ipomoea* and *Convolvulus* species [81].

It was reported also in 1963 that seeds of *I. coccinea* L. contained elymoclavine (4) [82], whilst the seeds of *I. rubro-caerulea* contained from zero to six different ergot-type alkaloids, depending on the source of the material [83]. These represented up to 0.05 per cent by weight from species obtained from Portugal and the Crimea and included ergine (1); isoergine (2); ergometrine (9) and two isomeric lysergic acid α-hydroxyethylamides (7 and 8) [83]. In the same year, Gröger further reported that detached leaves of *I. rubro-caerulea* were able to transform elymoclavine (4) into penniclavine (10) [84]. The reports [29–35,82] were the first indication that ergometrine (6) was present in higher plants; this base had previously only been encountered in nature as a mold metabolite derived from the *Claviceps* species. The identification of the α-hydroxyethylamides of lysergic acid and isolysergic acid (i.e. 7 and 8) was also the first time these compounds had been reported in higher plants [82–84], these substituted amides also being known as *Claviceps* metabolites. It is suspected that two of the indole compounds detected chromatographically were substituted amides of lysergic acid and isolysergic acid respectively [35].

The presence of indole alkaloids in the seeds of *R. corymbosa*, several *Ipomoea* species and certain other Convolvulaceous plants has subsequently been demonstrated by several other research groups. The attention of the reader is drawn to the fact that a certain degree of confusion appears to exist with regard to the taxonomy of the Convolvulaceae in general and the botanical description of some of the plant material referred to in certain phytochemical publications should be accepted with caution. The taxonomy of one of the most important examples of this type of plant *I. violacea*, L., has been considered at length by Der Marderosian [85] who points out that this binomial antedates the widely-used synonyms *I. tricolor* Cav. and *I. rubro-caerulea* Hook. (as well as several others) and suggests that the botanical, pharmacological and chemical evidence available to date points to the retention of *I. violacea* to avoid further confusion until the plant is finally typified [86].

It was reported in the mid-1960s [36,45,86] that the total indole alkaloid content of the seeds of a large number of *I. violacea* varieties and of several samples of *R. corymbosa* of different origin varied between 0.006 and 0.08 per cent. Among the popular morning glories freely available to horticulturists in North America and Great Britain, six which contain ergot alkaloids are varieties of *I. violacea*. Botanically these plants differ only in flower colour; the flowers are all blue or white or striped blue and white in colour. The horticultural names, which predate the modern use (or abuse) of the seeds for the psychotomimetic drug content are interesting and would fit well into the modern sub-cultural jargon that has grown up around the 'drug scene'. The names in question are: Heavenly Blue; Pearly Gates; Summer Skies; Blue Star; Flying Saucers and Wedding Bells [cf. 85]. Der Marderosian's results confirmed others [35] which also showed that ergot and lysergic acid alkaloids were found in white or blue flowering morning glories, but not in red varieties. Work carried out prior to 1967 on hallucinogenic indole compounds in the Convolvulaceae has been reviewed [14,36]. This survey lists the representatives of the Convolvulaceae known to contain indole alkaloids of the ergot type and refers to some of the author's own observations on the detection of indole alkaloids in species other than *I. violacea* including: *I. leptophylla* Torr., *I. tamnifolia, I. cardiophylla* and in *Stictocardia tiliafolia* Desr. [14]. In general, the horticultural morning glories with red flowers including varieties of *I. purpurea* (L.) Roth, *I. nil* and *I. sloteri* did not contain ergot alkaloids, neither did varieties of *I. alba* L. (Moon flowers or Moon vines) or varieties of *I. quamoclit* L. [36].

Whilst ergot-type alkaloids are present in Moon flower seeds, the indolizine alkaloid ipalbidine (1,2,3,5,8,9-hexahydro-6-β-hydroxyphenyl-7-methylindolizine) (17) and its β-D-glucoside ipalbine (18) were isolated from the seeds of



(R = H) Ipalbidine (17)
(R = β–D–glucosyl) Ipalbine (18)

Figure 3.5.

this plant [87]. These findings have subsequently been confirmed and the structure of (17) verified by synthesis [88,89] (see *Figure 3.5*).

A Canadian team obtained values in 1965, in the range 0.02–0.05 per cent for the ergot alkaloid content of several horticultural varieties of *I. violacea* and trace quantities (ca. 0.001 per cent) of alkaloids in some *I. nil* varieties [90–92]. Genest described a direct densitometric method for use with thin layer chromatograms to determine ergine (1), isoergine (2) and the clavine alkaloids present in morning glory seeds. This author also presented chromatographic evidence for the presence of chanoclavine (3), ergometrine (6), ergometrinine (9), ergine (1), isoergine (2) and lysergol (5) together with several unidentified alkaloids in extracts of seeds of the Heavenly Blue and Flying Saucers *I. violacea* varieties [90]. Genest was not able to confirm the suggestion of Taber, Vining and Heacock [35] that penniclavine (10) was present in the extracts of Heavenly Blue seeds [90], although Hylin and Watson did detect this alkaloid among the ergot alkaloids present in seeds of the Heavenly Blue *I. violacea* variety [93]. Genest and Sahasrabudhe have discussed possible applications of alkaloid and lipid contents to the chemotaxonomy of *Ipomoea, Rivea* and *Convolvulus* [47].

The advent of the non-horticultural use of morning glory seeds by people seeking a new form of psychedelic experience stimulated the search by public health and law enforcement agencies for improved and simpler methods to detect and characterise the alkaloids present in these seeds. Whilst at the same time analysis for other alkaloids in these plants was undertaken in academic circles. In addition to the work mentioned above [3,13,14,29–36,46,47,68, 86,90–92], there have been other studies dealing with the chromatographic and biological identification of morning glory seeds reported to have psychotomimetic properties e.g. [94,95]. Most of the above mentioned chromatographic studies on the identification of ergoline alkaloids present in morning glory seeds was of the thin layer type. However, the separation of alkaloids in the Heavenly Blue variety of a horticultural morning glory available in the U.S.A. by a combination of column and thin layer chromatography has been reported by

Niwaguchi and Inoue [96]. The separation of ergot and clavine alkaloids from the same variety of *I. violacea* by gel filtration on Sephadex has also recently been described by Nikolin and Nikolin [97].

Abou-Chaar and Digenis reported in the mid 1960s that the Pakistani drug Kaladana, which is prepared from the seeds of certain *Ipomoea* species contains significant quantities (0.49 per cent on a defatted basis) of ergot alkaloids [78–80] including lysergol (5) and chanoclavine (3), but apparently does not contain ergometrine (6). Whilst it has usually been considered that Kaladana was prepared from the seeds of *I. hederacea* Jacq. and *I. muricata* Jacq. (syn. *Calonyction muricatum* G. Den.), Abou-Chaar and Digenis suggest that this is not always the case, and point out that Groger [82] failed to find alkaloids in seeds of the former. Abou-Chaar and Digenis suggest that the exact identity of this commonly used purgative seed in Pakistan remains unknown [80]. It is also suggested that the relatively high alkaloid content of Kaladana might account for its toxicity if taken in large amounts [79].

There are a number of interesting references to the psychotomimetic effects of seeds of another Colvolvulaceous plant, *I. carnea*, which grows wild in the semi-arid zones of Coastal Ecuador [98,99,100]. The crude preparations are known under the names 'floróń', 'cadiente', 'borrachera' and 'matacabra' ('goat-killer') [98,100]. This plant is apparently attractive to livestock, particularly goats and is toxic to them [101].

Some early phytochemical and pharmacological studies on *I. carnea* carried out over 25 years ago did not reveal the presence of alkaloids, although two toxic principles, which were not identified chemically, were obtained. One caused hemolysis intravenously and another fraction which was toxic to the central nervous system [101]. However, more recent work has produced chromatographic evidence that the seeds of this particular *Ipomoea* do contain ergot alkaloids including ergine (1) and isoergine (2) [98,100]. It is possible that as in the case of some of the early work carried out with *R. corymbosa* and *I. violacea*, sufficiently mild extraction procedures to demonstrate the presence of ergoline alkaloids in *I. carnea* were not used. More recent studies have shown that extracts of this plant produce an intense psychotomotor excitation in mice followed by depression, failure of the ability to use the hind legs and walking was only possible by using the tail [99]. The excitation syndrome observed was similar to that produced by LSD [99].

Another example of the toxicity of an *Ipomoea* to domestic animals in a different part of the world has been reported. Gardiner, Royce and Oldroyd detected the amides of lysergic acid and isolysergic acid (i.e. 1 and 2) in *I. muelleri*. This plant is responsible for the 'intoxication' of sheep in parts of Western Australia [102]. In fact, serious sheep losses on some coastal stations in

the Gascoyne district of Western Australia have been attributed to its ingestion. The 'intoxicated' sheep show locomotory difficulties, behavioural disturbances, loss of weight, severe weakness and leucopenia, and they finally die from the combined effects of nutritional stress and ergot alkaloids (1 and 2) present in the seeds [102].

Gardiner and Bennetts in an earlier paper suggested that *I. muelleri* was being responsible for animal losses in Western Australia [103]. It is of interest to note that in this case the plant flowers are pink or red and not white or blue in colour.

Everist has suggested that sheep deaths in Queensland might be due to ingestion of the related species *I. calobra* Hillet F. Muell. [104]. Another vine *I. fistulosa* Mart. has been shown by Brazilian workers to cause wasting, depression and other ill-defined pathology in sheep, cattle and goats [105].

Nikolin and Nikolin have recently investigated the seeds of a dozen morning glories that are native to Yugoslavia, Hungary and Greece [106]. These authors demonstrated for the first time that seeds of a number of *Ipomoeas* of Hungarian origin, i.e. *I. undulata, I. criell, I. bayeriana* and *I. ailonii*, contained ergoline alkaloids [106], as did samples of *I. purpurea* of Yugoslavian origin (up to 0.008 per cent). The latter findings were in contrast to those of Der Marderosian and Youngken [36] who obtained negative results for ergot alkaloids from North American versions of this plant. It had previously been shown that seeds of *I. purpurea* obtained in England contained 0.001 per cent alkaloids [35]. Negative results were obtained for ergot alkaloids in seeds of *I. imperialis, I. sibirica, I. superba* and *I. learii* obtained from Greek or Hungarian sources [106].

The presence of agroclavine (11) in the seeds of *Cuscuta monogyna* was reported in 1968 [107]. The same group reported that a number of other *Ipomoea* and *Convolvulus* species growing in Israel, namely *I. stolonifera, Convolvulus betonicifolius, C. dorycnium, C. secundus* and *C. campestris,* did not contain indole alkaloids [107]. However, Mantle was unable to detect any indole alkaloids in the seeds of *Cuscuta monogyna,* parasitic on *Artemisia maritima* produced under glasshouse conditions in London [108].

In 1965, erogisine (19), ergosinine (20) and agroclavine (11) were isolated from seeds of *I. argyrophylla* Vatke of Kenyan origin [109]. This was the first case in which ergot alkaloids of the peptide type (i.e. 19 and 20) had been found in higher plants [109]. More recently, the Sandoz group has reported the isolation of a new alkaloid, cycloclavine (21) from the seeds of *I. hildebrandtii* Vatke, also from Kenya [110]. This ergoline alkaloid is an isomer of agroclavine (11) with C-8, C-9 and C-10 forming a three-membered ring in place of the 8,9-double bond in (21) [110] (see *Figure 3.6*).

In a study of morning glory tissue cultures, Staba and Laursen reported that

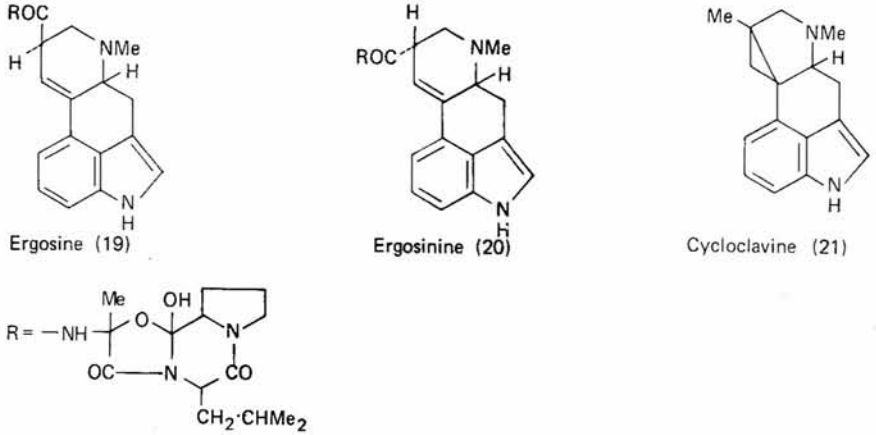


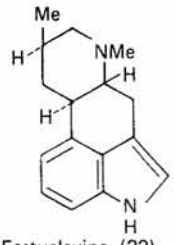
Figure 3.6.

the seeds and aerial portions of three horticultural varieties of *I. violacea* contained significant amounts of indole alkaloids [38]. The roots, callus tissue and callus medium of these varieties also contained trace quantities of these bases [38]. More recently, Dobberstein and Staba have shown that suspension cultures of *I. violacea* (var. Pearly Gates), *R. corymbosa* and *A. nervosa* produce indole alkaloids [111]. Modification of the medium did not have any predictable or regular effects on the alkaloid production [111]. The *I. violacea* in a medium supplemented with mevalonic acid and to which L-tryptophan had been added gave the best yield [111].

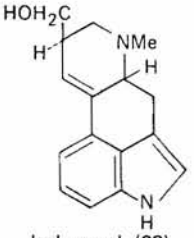
Genest has studied the effects of gibberellic acid treatment on *I. violacea* (var. Heavenly Blue) and *I. nil* (var. Scarlet O'Hara) grown under greenhouse conditions. Excessive longitudinal growth was observed in the early stages of the procedure with both species; eventually flower and seed production was affected lowering the ergoline alkaloid content of the mature seed [112,113].

In 1965, Hylin and Watson examined the alkaloids present in two other Convolvulaceous plants, namely the tropical wood roses *A. nervosa* and *I. tuberosa* L. Although no alkaloids were found in the latter, the seeds of *A. nervosa* are probably one of the best plant sources of ergot-type alkaloids so far discovered [93]. The seeds are reported to contain up to ca. 3 mg of alkaloidal material per gram of seed, approximately one eighth of this being ergine (1) [93].

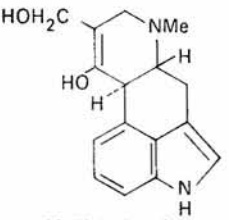
The discovery that *Argyreia* seeds contain larger quantities of psychotomimetic ergot alkaloids than those of other Convolvulaceous plants undoubtedly



Festuclavine (22)



Isolysergol (23)



Molliclavine (24)

Figure 3.7.

stimulated much research, in both scientific and lay circles, into the phytochemistry and psychopharmacology of this morning glory. *A. nervosa*, known as the Hawaiian Baby Wood Rose, probably originated on the Indian sub-continent but is readily available in Southern California and Florida as well as Hawaii. It has recently been the subject of extensive studies by several authors including Der Marderosian and Chao [14,39,114,115] and is characterised by heart-shaped leaves with dense white silky hairs below. It has a long history of use in Hindu folk medicine. In a very recent paper, it is reported that seeds of *A. nervosa* do in fact contain the highest percentage of indole alkaloids in any of the genera of the Convolvulaceae so far studied (i.e. 0.5–0.9 per cent) [115]. A total of nineteen indole alkaloids were obtainable together with trace quantities of eleven other indole alkaloids, which were not identified. The ergoline alkaloids from *A. nervosa* isolated by column chromatography and characterised by thin layer chromatography and infrared analysis include: lysergene (13), festuclavine (22), setoclavine (14), isosetoclavine (15), agroclavine (11), elymoclavine (4), ergine (1) and isoergine (2). Penniclavine (10), chanoclavine-I (3), chanoclavine-II (12), ergometrine (6), ergometrinine (9), lysergic acid α-hydroxyethylamide (7), isolysergol (23), racemic chanoclavine-II (cf. 12), molliclavine (24), lysergol (5) and isolysergic acid α-hydroxyethylamide (8) were identified by TLC only [115]. A number of these ergoline bases were identified for the first time in the Convolvulaceae. The amides (1) and (2) were found in high concentrations (0.136 per cent and 0.188 per cent respectively) [115]. In addition, eleven unidentified indole compounds were detected in the seed extracts (see *Figure 3.7*).

In some of the earlier studies (Hylin and Watson, 1965) on *Argyreia* seeds, the only two ergoline alkaloids that had been identified by thin layer chromatography were ergine (1) and isoergine (2) [93]. McJunkins, Thornton and Dillon confirmed this fact and accurately described the plant botanically [116], whilst

Miller isolated (1) and (2) from the Baby Wood Rose and identified them by TLC, UV and IR spectroscopy [117]. Crawford identified (1) and (2) extracted from seeds of this plant by mass spectrometry [118] and then compared the spectra of the natural products with synthetic specimens [118]. The mass spectrum of (1), along with some other lysergic acid derivatives, has also recently been reported [119].

Other phytochemical investigations of Convolvulaceous plants which might be mentioned involve the isolation of an unidentified alkaloid Sankhpuspine from *C. pluricaulis* [120]. It is of interest to note that this drug is used in the Ayurvedic system of medicine as a 'brain tonic' and for treatment of some forms of insanity [120]. Crystalline glycosidic constituents have been isolated from the seeds of *I. parasitica* (HBK.) Dor. [121] and *I. muricata* [122].

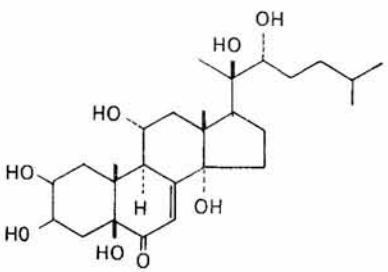
Muristerone A, a new phytoecdysone isolated from *I. calonyction* (Chois.) Hall. f. has been identified as 2β,3β,5β,11α,14α,20R,22R-heptahydroxycholest-7-en-6-one (24) [122] (see *Figure 3.8*).

The fatty acid composition of morning glory seed oil has been examined by gas chromatography. The oils present were predominantly C_{18} unsaturated acids [46].

A recent phytochemical investigation of the aerial parts of *C. arvensis* L. resulted in the isolation and identification of several n-alkanes and n-alkanols, α-amyrin, campesterol, stigmasterol and β-sitosterol [124].

THE NON-HORTICULTURAL USE OF CONVOLVULACEOUS SEEDS

Almost coincidentally with the earliest of the reports in the scientific literature (i.e. 1963) concerning the presence of known psychotomimetic compounds in readily available seeds, articles began to appear in the popular press to the effect that surprised seed merchants were reporting that their stocks of morning glory



Muristerone A (25)

Figure 3.8.

seeds were being depleted by certain elements of society who did not appear to be amateur gardeners. In fact, it appeared that a considerable amount of self-experimentation, with the view to obtaining a form of LSD-type experience from morning glory seeds [with exotic names such as Heavenly Blue, Flying Saucers and Pearly Gates (see p. 105)] was taking place. The proliferation of obviously non-horticultural use of morning glory seeds raised fears among law-enforcement agencies and public health officials that a new type of potentially dangerous psychoactive drug abuse might be arising. A number of forensic scientists have recently described chromatographic procedures that could be used for the identification of morning glory seeds, seed fragments or extracts likely to be encountered in seized materials [94,95].

The situation with regard to the possible widespread abuse of morning glory seeds has been discussed [125–128] and it has also been considered editorially in the medical and pharmaceutical literature [129–132]. Cohen has also reported one case of an intense psychotic reaction following the ingestion of 300 Heavenly Blue seeds, which was probably responsible for the subsequent suicide of the person in question 3 weeks later [125]. Long term effects resulting in a recurrence of the psychotic symptoms is known to occasionally result from the use of certain hallucinogenic drugs including LSD [133] and this author points out that similar dangers could exist in cases of morning glory intoxication [125]. Ingram has described a psychotic episode experienced by a 20-year old university student, following the ingestion of 250 *Ipomoea* seeds, which was sufficiently severe to require hospitalisation [134]. This author also underlines the danger that latent psychoses may be activated by excessive ingestion of such seeds [134]. In 1966, a study of three cases of morning glory seed intoxication showed that the effects observed were similar to those following LSD ingestion [135].

The possibility of additional toxic reactions resulting from the ingestion of such seeds, which have been treated with potentially toxic fungicides and pesticides to prevent spoilage on storage, should also not be overlooked.

Very little systematic psychopharmacological work has been carried out, so far, on the psychotoxic constituents of the ornamental morning glories. (cf. [13].) Savage and Stolaroff (cited by Der Marderosian [45]) [136] report that low doses (20–50 seeds) of Heavenly Blue seeds are capable of inducing 'beginning imagery' and that higher doses (100–150 seeds) produced definite psychological effects (i.e. spatial distortions, visual and auditory hallucinations and other effects characteristic of the LSD experience). It has been estimated that a total of ca. 125 seeds of a morning glory variety rich in ergine (1) would be needed to produce definite psychotomimetic effects [91]. Aqueous extracts of *I. violacea* (Heavenly Blue) produced a definite lowering of the activity level

in rats in several test situations. However, no effects were observed on the acquisition of a perceptually based discriminative response [137].

The acute toxicity of extracts of morning glory seeds has been studied [91,92]. The LD_{50} values for extracts of the seeds of the *Ipomoea* varieties Pearly Gates and Wedding Bells were reported to be 164.3 and 214.1 mg/kg respectively. Extracts of the *I. nil* variety Scarlet O'Hara, which does not contain significant quantities of ergot bodies, were relatively nontoxic. It has also been reported that extracts of seeds of the psychotomimetic *I. violacea* morning glory varieties will produce a definite uterine stimulant effect due to the presence in the extracts of ergometrine (6), a compound with known oxytocic properties [138]. It is estimated that 500 Heavenly Blue or Pearly Gates seeds could contain up to 1 mg of ergometrine (6) and it is usually considered that between 0.2 and 0.5 mg of (6) is oxytocic in humans. Several workers have warned against the dangers of ergot poisoning due to excessive morning glory seed ingestion [138].

SOME COMMENTS ON THE CHEMISTRY AND BIOCHEMISTRY OF THE ERGOLINE ALKALOIDS ENCOUNTERED IN THE CONVOLVULACEAE

It is of interest to note that virtually all the ergoline alkaloids that have been encountered in phytochemical investigations of the Convolvulaceae had been obtained previously either as mould metabolites or by synthetic procedures in the laboratory. In fact, the work at Sandoz published in the early 1960s gave the ergot 'alkaloids' a certain air of respectability in organic chemistry texts which had always classified these compounds as alkaloids, presumably because they were complex basic heterocyclic compounds, although they were in fact mould metabolites. They had not at that time gained the right to be called 'alkaloids' which are essentially plant products. There are numerous reviews on the chemistry of the ergot alkaloids, one of the most recent being that by Stoll and Hofmann [139].

d-Lysergic acid amide [i.e. ergine (1)] and the isomeric *d*-isolysergic acid amide [i.e. isoergine (2)] were obtained some 30 years ago as cleavage products on alkaline hydrolysis of the ergot alkaloids [140,141]. These amides together with the relevant hydroxyethylamides have also been found in the ergot of *Paspalum* grass [142]. Chanoclavine (3) [143] and elymoclavine (4) [144] had previously been discovered in the ergot of *Pennisetum typhoideum* Rich. and *Elymus mollis* Trin. respectively. Lysergol (5), ergometrine (6) and the amides (7) and (8) had been synthesised in the laboratories of the Sandoz group several years earlier [145,146].

Mention should be made of the fact that the amides of *d*-lysergic and *d*-isolysergic acid (i.e. 1 and 2) readily epimerise under the influence of alkali. The reaction is also brought about to a lesser extent by acids and will occur spontaneously in some hydroxylic solvents [cf. 147 and references cited therein]. This fact may mean the ratio of amides of the lysergic acid series to the isolysergic acid series obtained may depend on the isolation and work-up procedures used [139].

In contrast to the number of studies that have been carried out with respect to the biosynthesis, interrelationships and metabolism of ergoline alkaloids in moulds [148–155], relatively little work has been carried out on the biosynthesis of these alkaloids in the higher plants. Some early work was carried out on the biosynthesis and metabolism of the ergoline alkaloids in some *Ipomoeas* [82–84]. The subject has also been considered by Genest, who studied the alkaloid content of the seeds during ontogeny of *I. violacea* [156]. The alkaloid content was apparently higher during the early stages of seed development. Chanoclavin (3) was the most abundant alkaloid in the immature seed.

The subject has also been considered by Der Marderosian [14], Mothes [157] and Chao [39]. Chao found that incorporation of DL-tryptophan-3-^{14}C occurred in *I. violacea*. The radioactivity was mostly found in the stem, with lesser quantities in the leaves, flowers and immature fruits [39]. No radioactivity or alkaloids were found in the roots [39]. Chao reported that the biosynthetic pathways found in this study on higher plants were essentially the same as those found in micro-organisms [39].

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