INDOLE ALKALOIDS IN PLANT HALLUCINOGENS[1]

By R. E. SCHULTES

„... I learnt that caapi was cultivated ... and I went ... to get specimens of the plant, and ... to purchase a sufficient quantity of the stems to be sent to England for analysis. ... I saw, not without surprise, that it belonged to the order Malpighiaccae and the genus Banisteria, of which I made it out to be an undescribed species. ... My surprise arose from the fact that there was no narcotic Malpighiad on record, nor indeed any species of that order with strong medicinal properties of any kind."

Richard Spruce (1852)

I

Many psychoactive plants owe their activity to structures containing an indole nucleus. This nucleus is evident in the synthetic LSD and in such well known compounds as yohimbine, reserpine, physostigmine and the strychnos alkaloids. And it is to the presence of indole alkaloids that many of the most striking hallucinogenic plants owe their biodynamic activity: iboga in Africa (with ibogaine and related alkaloids); the sacred mushrooms (with psilocybine) and morning glories (with ergoline alkaloids) of Mexico; and, in South America, the drinks called ayahuasca (with β-carbolines) and vinho de jurema (with N,N-dimethyltryptamine) and the snuffs known as yopo, huilca and epena (all with various tryptamines).

Indole alkaloids are not confined to plants: bufotenine (5-hydroxy-N,N-dimethyltryptamine) is found in the skin of certain toads and the biogenic amine serotonine (5-hydroxy-tryptamine) is present in minute amounts in the central nervous tissue of warm blooded animals.

There are about 600 alkaloids with an indole nucleus or a nucleus very close to an indole group in their molecule [25, 37, 49, 50, 57, 61, 67, 68]. It is an extremely difficult class of alkaloids to delimit and to classify because of chemical complexity. Of the more than twenty classes of indole alkaloids, those involved in hallucinogenic plants may be placed in four categories: 1) lysergic acid derivatives (the ergoline alkaloids); 2) tryptamines (N,N-dimethyltryptamine, psilocybine); 3) the carbolines (harmine); and 4) the iboga alkaloids (ibogaine).

It is believed that indole alkaloids arise from tryptophane and a monoterpenoid moiety [18]. Tryptamines are recognized as possible intermediates in the biogenetic pathways to the harman type (β-carboline) alkaloids on the one hand (*Malpighiaceae, Rutaceae*) and many of the more complicated indoles types

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(*Apocynaceae*) on the other [21]. The simple indole derivatives are rather widely distributed amongst the dicotyledons; whereas the more complex indole alkaloids are frequent in the metachlamydeous families *Apocynaceae, Asclepiadaceae, Loganiaceae* and *Rubiaceae,* although they occur also in the fungi [18, 68]. Indoles have been recognized since the early years of the present century [50].

II

The ancient Aztecs used mushrooms in religious, magical and curative ceremonies, calling them teonanacatl ("flesh of the gods"). These fungi are still employed as sacred hallucinogens in southern Mexico, especially in Oaxaca. Evidence points to this use in adjacent Guatemala as far back as 3500 years ago [71].

The many references to and descriptions of ritually administered intoxicating mushrooms in the early literature notwithstanding, there was, until 1939, doubt that teonanacatl did, in reality, refer to mushrooms; and the belief that it was another name for the peyote cactus was widely accepted [48]. It is now known that two dozen or more species of mushrooms in four genera (*Conocybe, Panaeolus, Psilocybe, Stropharia*) are variously employed [22, 24]. Medicine-men may use different mushrooms at different times of the year, for different purposes or from personal preference. All are, however, psychoactive, and psilocybine or 4-phosphoryloxy-N,N-dimethyltryptamine has been found in all four genera [23, 24, 30, 61].

Psilocybine is unique in several respects. It is the first indole with a phosphorylated hydroxyl radical to have been isolated from plants. It occurs apparently nowhere else in the Plant Kingdom. It is the only tryptamine with a 4-substitution. Since psilocybine is rather unstable, the phosphoric acid part disintegrating rapidly upon ingestion of the mushrooms, most of the activity may be due to psilocine or 4-hydroxy-N,N-dimethyltryptamine which results from the breakdown of psilocybine [29, 61].

In 1939, SCHULTES and REKO collected *Panaeolus sphinctrinus* (FR.) QUÉLET in the Mazatec Indian country of Oaxaca, where it was one of the mushrooms in ritual use for hallucinogenic intoxication [51]. Later work, principally by WASSON [70] and HEIM [24], indicated that species of *Psilocybe* and *Stropharia* were more important and that many species of *Psilocybe* were involved. The list of species has grown as a result of additional work by SINGER [65] and GUZMÁN [20]. At the present time, well over twenty-four species are known to be employed in at least nine tribes of Mexican Indians.

The principal mushrooms involved are several species of *Psilocybe* (*P. aztecorum* HEIM, *P. caerulescens* MURRILL, *P. hoogshagenii* HEIM, *P. mexicana* HEIM, *P. za-*

potecorum HEIM) and *Stropharia cubensis* EARLE. *Panaeolus sphinctrinus*, it appears, represents one of the minor species used. Psilocybine has been found, however, to be the active principle in all of these genera, and this psychoactive indolealkylamine derivative has been isolated from other species of *Psilocybe* and *Panaeolus* in various parts of the world where, however, they are not used for their hallucinogenic properties [61]. Further chemical research will probably show that psilocybine is more widespread among the mushrooms. It is curious that apparently only in Mexico and adjacent Central America did aboriginal cultures value the effects of this compound in magico-religious rites.

Psilocybine and psilocine were first isolated from *Psilocybe mexicana* in 1958 by HOFMANN [29]. The chemical work was made possible by the successful laboratory cultivation of the mushroom by HEIM. Later, other species of *Psilocybe* were examined, and the active principles were found in many. HOFMANN elucidated the structure of both compounds and confirmed the results by synthesis. The biogenetic precursor of psilocybine appears to be tryptophane.

The morning glories or *Convolvulaceae* comprise another group of Mexican hallucinogens that owe their activity to indoles.

The early chroniclers referred frequently to ololiuqui and tlitliltzin [52, 70]. Although descriptions and several illustrations of the period indicated that ololiuqui was convolvulaceous, no use of morning glory seeds as intoxicants had been seen in modern Mexico, and no toxic constituent was known from this plant family. Consequently, the suggestion was offered and widely accepted that, to protect this sacred hallucinogen from persecution by the Spanish authorities, the Indians were pointing out morning glories as ololiuqui, whereas the true identity of the narcotic was a species of *Datura* [48].

Several Mexican botanists had long argued that ololiuqui did, in reality, represent a morning glory, but it was not until 1939 that SCHULTES and REKO collected a botanical specimen of a convolvulaceous plant employed in Oaxaca as a divinatory narcotic [52]. It was *Rivea corymbosa* (L.) HALLIER fil. and was identified as the ololiuqui of Aztec times. Later, MACDOUGALL [36] and WASSON [70] established the narcotic use of the seed of another morning glory, *Ipomoea violacea* L., also in Oaxaca, and identified the tlitliltzin of the Aztecs as this species.

It was not until 1960 that the active principles – ergoline alkaloids or lysergic acid derivatives – were isolated [27, 28, 31].

The main constituent of the seeds of *Rivea corymbosa* is ergine or d-lysergic acid amide. Minor alkaloids present are the related d-isolysergic acid amide (isoergine), chanoclavine, elymoclavine and lysergol. The seeds of *Ipomoea violacea* have a similar composition but, instead of lysergol, they have ergometrine (ergonovine). Later, very minor amounts of two alkaloids – ergometrinine and penniclavine – were found in *I. violacea* by chromatography [61].

The total alkaloid content of seeds of *Ipomoea violacea* is approximately five times as great as that of the seeds of *Rivea corymbosa:* 0.06% in the former; 0.012% in the latter. This difference in alkaloid content explains why Indians employ smaller doses of seeds of the *Ipomoea* than of the *Rivea* [28].

These ergoline alkaloids have subsequently been found in various other convolvulaceous species in the genera *Argyreia, Convolvulus, Ipomoea* and *Stictocardia* [9, 61]. They have also been reported to occur in the vegetative tissues of convolvulaceous plants [66].

The discovery of ergoline alkaloids in the *Convolvulaceae* is of extreme chemotaxonomic significance: they are known from only one other place in the Plant Kingdom – in the lower fungi: *Claviceps, Penicillium* and *Rhizopus* – wholly unrelated to the highly evolved metachlamydeous family *Convolvulaceae* [61]. The ascomycete, ergot or *Claviceps purpurea* (FR.) TULASNE, was the cause of occasional mass poisonings of European towns in the Middle Ages, when rye flour was contaminated with the sclerotium of the parasitic fungus which replaced the endosperm of the caryopsis. These mysterious attacks – causing delirium and hallucinations, loss of fingers, toes and ear lobes as a result of peripheral vasoconstriction and gangrene, often permanent insanity and sometimes death – were known as St. Anthony's Fire. Ergot was widely used by European midwives during the Middle Ages to aid in cases of difficult delivery, and several of the active principles are still employed for the same purposes in modern medicine [16].

III

South American indolic hallucinogens are of two kinds: those having β-carboline alkaloids as their active principles and those having various tryptamines.

The most famous South American hallucinogen is the drink variously known as ayahuasca, caapi, natema, pinde or yajé. Basically, it is prepared from the bark of either *Banisteriopsis caapi* (SPRUCE ex GRISEB.) MORTON or *B. inebrians* MORTON, extensive lianas of the *Malpighiaceae* [15, 17, 38, 54]. First identified botanically by the British explorer SPRUCE in 1852, it has fascinated investigators ever since. Ayahuasca is prepared in either a cold-water infusion or a decoction boiled for a long period. Now known to be employed in the western Amazon of Brazil, Colombia, Ecuador, Peru and Bolivia, in the headwaters of the Orinoco in Venezuela and in isolated localities on the Pacific coast of Colombia and Ecuador, this narcotic, despite years of investigation, still is poorly understood from many points of view.

The active principles in the bark of *Banisteriopsis caapi* and *B. inebrians* are β-carboline alkaloids: harmine, harmaline and tetrahydroharmine [11, 61]. These and several related simple indole derivatives, known as the "harmala bases," occur in a number of families, including (in addition to the *Malpighiaceae*) the

Apocynaceae, Cyperaceae, Leguminosae, Passifloraceae, Rubiaceae and *Zygophyllaceae* [18]. It is believed that the carboline alkaloids are derived from tryptophane.

Harmine was first isolated from the Asiatic *Peganum harmala* L. of the *Zygophyllaceae* – the so-called Syrian rue – more than a century ago [18]. This plant is known to possess hallucinogenic constituents, but, although extensively employed in folk medicine, there is no evidence that it was used purposefully as an hallucinogen in Asia.

The earliest chemical investigations of what is presumed to have been *Banisteriopsis caapi* did not yield pure compounds [11]. As early as 1905, a Colombian chemist, ZERDA BAYON, isolated an alkaloid and callet it telephathine [11]. In 1923, FISCHER CARDENAS found an alkaloid which he identified with telepathine [14]. At about the same time, BARRIGA VILLALBA crystallized an alkaloid from stems of a vine known as yajé and called it yajeine [5, 6]; the vine was erroneously identified as the apocynaceous *Prestonia amazonica* BENTHAM (*Haemadictyon amazonicum* [BENTH.] MACBRIDE).

The first chemical work on authentically identified botanical material was reported in 1927 by PERROT and RAYMOND-HAMET, who isolated a pure alkaloid with a melting point of 258°; they retained the name telepathine for it [41]. In 1928, LEWIN published a report of the isolation of an alkaloid which he named banisterine [35]. In the same year, ELGER [12] and WOLF and RUMPF [72] identified banisterine as harmine. ELGER's plant material, supplied by RAYMOND-HAMET, was determined as *Banisteriopsis caapi* at Kew. CHEN and CHEN, studying vouchered material of *B. caapi,* isolated harmine from the leaves, stems and roots [8].

In 1957, HOCHSTEIN and PARADIES analyzed material of *Banisteriopsis caapi* and found harmine, harmaline and tetrahydroharmine. The concentration of harmaline and tetrahydroharmine were rather high [26].

In 1969, SCHULTES, HOLMSTEDT and LINDGREN published a report of the phytochemical examination of SPRUCE's original material of *Banisteriopsis caapi* collected in the Brazilian Amazon in 1852. By the combination of gas chromatography-mass spectrometry, it was shown that the stems contained only harmine, no harmaline or tetrahydroharmine. Whether the plant originally contained only harmine or whether the harmaline and tetrahydroharmine were transformed in the 117 years since collection into the chemically more stable aromatic β-carboline harmine, there is no way of telling at the present time. The latter would seem to be the more probable explanation [63].

In the westernmost Amazon of Colombia and Ecuador, *Banisteriopsis inebrians,* closely related to *B. caapi,* may be employed in preparing the hallucinogenic drink [54]. Vouchered material of this species was analyzed by O'CONNELL and LYNN [39], who reported in 1953 that the stems contained harmine and the leaves

"an alkaloid which was partly identified as harmine." They did not find other β-carbolines in this species. In 1965, POISSON examined *B. inebrians* and found harmine in the stems and, in very small amounts, another alkaloid which he presumed was harmaline [44].

Although often prepared from a single ingredient, the drink occasionally has one or more additives. The list of these additives is already long, and there are still more to be identified [42, 43, 47, 54, 58, 59, 64]. Only a few of the additives have been subjected to chemical study, but those that have been analyzed are extremely significant. Among the plants added to the basic drink are such well known psychoactive species as *Datura suaveolens* HUMBOLDT et BONPLAND ex WILLDENOW (containing several tropane alkaloids) and *Nicotiana tabacum* L. (with nicotine). Over the extensive area of use of this narcotic preparation many poorly known plants are reported as admixtures: several ferns – *Lomariopsis japurensis* (MART.) J. SM. and *Lygodium venustum* SW.; several species of *Cactaceae* of the genera *Epiphyllum* and *Opuntia*; *Malouetia tamaquarina* A. DECANDOLLE (*Apocynaceae*); a species of *Cyperus* (*Cyperaceae*); *Capsicum* sp., *Datura suaveolens* HUMBOLDT et BONPLAND ex WILLDENOW, *Brunfelsia chiricaspi* PLOWMAN and possibly *Juanulloa ochracea* CUATRECASAS (*Solanaceae*); *Alternanthera lehmanii* HIERONYMUS and a species of *Iresine* (*Amaranthaceae*); *Calathea veitchiana* VEITCH ex HOOKER filius (*Maranthaceae*); possibly *Pontederia cordata* L. (*Pontederiaceae*); *Phrygilanthus eugenioides* (HBK.) EICHLER (*Loranthaceae*); *Teliostachya lanceolata* NEES var. *crispa* NEES ex MARTIUS and another unidentified acanthaceous plant; a species of *Clusia* (*Guttiferae*); *Ocimum micranthum* WILLDENOW (*Labiatae*); and an unidentified bignoniaceous species.

Perhaps, however, the most important additives are the leaves of the rubiaceous *Psychotria viridis* RUÍZ et PAVÓN [55] and the leaves of the malpighiaceous *Banisteriopsis rusbyana* (NDZ.) MORTON [61]. These plants apparently are never used together as additives. The natives assert that they employ these additives on occasion to lengthen and strengthen the hallucinatory effects of the drink, a purpose which they successfully accomplish. Analyses have revealed the presence in the leaves of both plants relatively high concentrations of N,N-dimethyltryptamine – the first time that this tryptamine has been known from either family [1, 10, 57, 61]. There is some evidence that several other species of *Psychotria* may be similarly used,[2] but corroboratory field studies are necessary before it can be positively stated.

Chemotaxonomically perhaps the most extraordinary discovery concerning additives of the ayahuasca-caapi drink is the finding of a tryptamine alkaloid in the leaves of *Banisteriopsis rusbyana,* a species so closely related to *B. caapi* and

[2] Through an erroneous identification, *Psychotria psychotriaefolia* was reported as one of the admixtures [55].

B. inebrians. In 1965, POISSON [44] reported that *Banisteriopsis rusbyana* contains N,N-dimethyltryptamine in relatively high concentration (0.64%). This was confirmed by DER MARDEROSIAN in 1968 [10]; and, again in 1968, AGURELL, HOLMSTEDT and LINDGREN, using gas chromatography-mass spectrometry methods, confirmed the presence of this tryptamine and noted minor constituents: N-methyltryptamine, 5-methoxy-N,N-dimethyltryptamine, N-methyltetrahydro-β-carboline and a non-indolic compound still to be identified [1].

In 1957, HOCHSTEIN and PARADIES reported an analysis of an aqueous extract of the leaves of what they called "yajé" [26]. Their "identification" of the source of this extract – the apocynaceous *Prestonia amazonica* – was made without voucher specimens through an erroneous identification of the common name yajé. The source of their aqueous solution, which came from the Iquitos region of Peru, was probably either *Psychotria viridis* or *Banisteriopsis rusbyana*, since the active constituent of the solution was N,N-dimethyltryptamine [64].

It is generally believed that dimethyltryptamine is inactive when taken orally, unless in the presence of a monoamine oxidase inhibitor. In the case of this narcotic preparation, the monoamine oxidase inhibitor may be the β-carboline content of the basic species, *Banisteriopsis caapi* and *B. inebrians* [69].

In the dry parts of Pernambuco, Brazil, an infusion of the roots of the leguminous *Mimosa hostilis* (MART.) BENTHAM is called vinho de jurema and is the hallucinogen basic to the ancient Jurema Cult. The drink induces glorious visions of the spirit world and was formerly taken before battles and other difficult feats. In 1946, GONÇALVES DE LIMA reported a new alkaloid from this plant and called it nigerine [19]. It was later shown to be identical with N,N-dimethyltryptamine [61]. How this tryptamine can be effective without a monoamine oxidase inhibitor is still an enigma. Is there possibly an inhibitor still undetected in the roots, or do the natives perhaps add some other ingredient which contains the needed inhibitor?

Of the sundry snuffs employed in South America, three owe their psychoactivity to tryptamines.

Historically, the most important hallucinogenic snuff is yopo, used in the Orinoco basin in Colombia and Venezuela and possibly in isolated areas in the southern part of the Brazilian Amazon [4]. The flat, black beans of a tree known now as *Anadenanthera peregrina* (L.) SPEGAZZINI, formerly as *Piptadenia peregrina* (L.) BENTHAM, are toasted, pulverized and mixed with an alkaline admixture – usually ashes of vegetal materials or calcined shells. The tree grows in open plains areas, not in tropical forests. It was early taken by invading Indians to the West Indies, where even today its distribution indicates its adventitious nature. Shortly after their arrival, the European conquerors discovered the use of the snuff under the name cohoba in Hispaniola, but its use completely disappeared with the extinction of indigenous populations in the West Indies.

Until recently, there was much uncertainty concerning the intoxicating principles of *Anadenanthera peregrina* and the snuff prepared from its seeds. Early explorers – GUMILLA and VON HUMBOLDT – believed that the activity of the snuff was attributable to the alkaline admixture. During the 1950's, HORNING and his co-workers [13, 33, 34], interested in the properties of the crude snuff, discovered, by means of paper chromatography, colour reactions, fluorescence and infrared spectra, that indole alkaloids were the active constituents, and they reported the presence of N,N-dimethyltryptamine-N-oxide and bufotenine (5-hydroxy-N,N-dimethyltryptamine). Their work led eventually to the use by psychiatrists of synthetic dimethyltryptamine to induce temporary states of hallucinations. Later, the mass spectrometer and gas chromatography have enabled HOLMSTEDT and his co-workers [32] to show the presence in seeds of *Anadenanthera peregrina* the following indole derivatives: N,N-dimethyltryptamine, N-monomethyltryptamine, 5-methoxy-N-monomethyltryptamine, 5-methoxy-N,N-dimethyltryptamine, N,N-dimethyltryptamine-N-oxide, and 5-hydroxy-N,N-dimethyltryptamine-N-oxide.

Another South American snuff, only recently identified botanically [53], is variously called epena, nyakwana and yakee. Prepared from any of several species of the myristicaceous genus *Virola* – *V. calophylla* WARBURG, *V. calophylloidea* MARKGRAF, *V. elongata* (SPRUCE ex BENTH.) WARBURG and especially *V. theiodora* (SPRUCE ex BENTH.) WARBURG – this snuff is used by tribes in the Rio Negro basin of Brazil, in the Colombian Vaupés and in the headwater regions of the Orinoco in Venezuela [46, 61]. Methods of preparation vary from locality to locality, but the basis of the narcotic powder is always the blood-red resin of the inner bark. Among certain groups of Waiká Indians in Brazil, for example, the resin is scraped into a pot, boiled down to a thick syrup which is allowed to sundry, powdered with a stone and sifted. An alkaline ash of the bark of *Theobroma subincanum* MARTIUS or *Elizabetha princeps* SCHOMBURGK ex BENTHAM is added [62].

When the source of the snuff was first identified, it was suggested that perhaps the active principle was myristicine, common in the *Myristicaceae*. Examination by HOLMSTEDT and his coworkers of different parts of several species of *Virola* trees and of snuff prepared from *Virola theiodora*, however, established the presence of several tryptamines – the first evidence of indole alkaloids in the Nutmeg Family [3, 32]. Tryptamines are present in some species of *Virola* but absent in others. Snuff prepared by the Waiká Indians of Tototobí in Amazonian Brazil, for example, may contain up to 11% of several tryptamines, including 8% of 5-methoxy-N,N-dimethyltryptamine and lesser amounts of N,N-dimethyltryptamine [62]. Furthermore, the new β-carboline alkaloids 2-methyl-6-methoxy-**1**, 2,3,4-tetrahydro-β-carboline and 1,2-dimethyl-6-methoxy-1,2,3,4-tetrahydro-β-carboline are known to occur in *Virola theiodora* and *V. rufula* [2]. These β-carboline alkaloids are monoamine oxidase inhibitors which are probably the reason

for the psychoactivity of pellets of the resin of *Virola theiodora* when they are taken orally among the Witoto and Bora Indians of Colombia and when the resin is ingested directly from the bark by the very primitive Makú of the Colombian Vaupés [56].

There are still unsolved problems in the preparation and use of *Virola* snuff. Many Indians who prepare ebena or nyakwana add to the powder the pulverized leaves of the highly aromatic acanthaceous *Justicia pectoralis* JACQ. var. *stenophylla* LEONARD [62]. Their reason for using this admixture is reputedly to scent the snuff. While it is true that *Virola*-snuff is active without this added powder, there is ample evidence that some tribes elaborate a psychoactive snuff solely from the leaves of the *Justicia,* suggesting that *Justicia* itself may have hallucinogenic constituents [7]. Indeed, it has been reported that tryptamines have been found in species of *Justicia* used in the preparation of snuff [7], but corroborative evidence is needed.

IV

It is extraordinary that the *Apocynaceae,* the family believed to be richest in alkaloids, has given apparently only one hallucinogenic species to primitive cultures: iboga. Iboga, an African narcotic of great and increasing social importance in Gabon and the Congo, is the root of a bush, *Tabernanthe iboga* BAILLON [45]. It was discovered by Europeans in the middle of the last century, and, by the turn of the century, the principal alkaloid – 5-methoxy-indole ibogaine – had been isolated. Later work has established the presence in *Tabernanthe iboga* of twelve closely related alkaloids, and the total alkaloid content of the yellowish root may reach 5% or 6% in dried material [57, 61].

Although possessing an indole nucleus, the iboga-alkaloids are often not classed with the indolic groups. It is believed that they arise from tryptophane and two mevalonate residues. They are closely related to the voacanga alkaloids, which include the Vinca alkaloids. Both groups are confined to the *Apocynaceae.*

Ibogaine, to which probably the greater part of the psychoactivity may be attributed, acts as a cholinesterase inhibitor, as a strong central stimulant and as an hallucinogen. Its structure, together with its stereochemistry, has only recently been clarified [61].

Other plants – as many as ten – may be taken together with iboga, but few have been botanically identified, and fewer have been chemically studied. One of the most interesting is the euphorbiaceous *Alchornea floribunda* MUELLER-ARGOVIENSIS, which, it has been stated, can be used in the same way as *Tabernanthe iboga.* The intoxicating principle of *Alchornea floribunda* has been reported to be yohimbine, another indole alkaloid, but this report has not yet been confirmed [40].

V

There is every probability that future research will show that other narcotic preparations from both the New and the Old World are effective because of indole alkaloids. At the present time, however, we do know that many of the most important of the hallucinogenic plants of tropical America owe their activity to these compounds. We know, also, that primitive cultures in the New World have exhibited an uncanny perspicacity in discovering in such an overwhelmingly rich flora a large number of psychoactive species. And, finally, we know that undoubtedly new hallucinogenically active chemical constituents still await discovery in the rich psychoactive flora of both the Old and the New Worlds.

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