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Molecules of interest

Hemlock alkaloids from Socrates to poison aloes

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Abstract

Hemlock (*Conium maculatum* L. Umbelliferae) has long been known as a poisonous plant. Toxicity is due to a group of piperidine alkaloids of which the representative members are coniine and γ-coniceine. The latter is the more toxic and is the first formed biosynthetically. Its levels in relation to coniine vary widely according to environmental conditions and to provenance of the plants. Surprisingly, these piperidine alkaloids have turned up in quite unrelated species in the monocotyledons as well as the dicotyledons. Aloes, for instance, important medicinal plants, are not regarded as poisonous although some species are very bitter. Nevertheless a small number of mostly local species contain the alkaloids, especially γ-coniceine and there have been records of human poisoning. The compounds are recognized by their characteristic mousy smell. Both acute and chronic symptoms have been described. The compounds are neurotoxins and death results form respiratory failure, recalling the effects of curare. Chronic non-lethal ingestion by pregnant livestock leads to foetal malformation. Both acute and chronic toxicity are seen with stock in damp meadows and have been recorded as problems especially in North America. The alkaloids derive biosynthetically from acetate units via the polyketide pathway in contrast to other piperidine alkaloids which derive from lysine.

Keywords: Hemlock; Aloes; Piperidine alkaloids; Poisons; Biosynthesis

1. Introduction

"Few poisons are of greater interest, in a historical or scientific point of view, than Hemlock...the attention which it has received from scientific men...has been by no means commensurate". So wrote Professor Robert Christison of Edinburgh University in 1836. Things moved rapidly in the ensuing years up to the present day. It all started of course with the death of Socrates at the age of 70 from hemlock poisoning in 399 BC, a well known early example of the effect of a very biologically active plant constituent (de Boer, 1950), although Christison himself threw doubts as to the true identification of the toxic principle. The hemlock poison, a group of alkaloids, is contained in a water extract of the seeds or the young parts of the tall herb *Conium maculatum* L., the poison hemlock (Fig. 1), a member of the Umbelliferae, also known as spotted hemlock, poison parsley or spotted cowbane (Budavari, 1996). This should be distinguished from a quite different umbellifer, the very poisonous water hemlock, *Cicuta virosa* L., whose active principle is not an alkaloid but cicutoxin, a long chain alcohol containing double and triple bonds. Both plants are common and widespread in wet localities in North Temperate regions. A completely different plant often referred to as "hemlock" is a tree, the common hemlock or hemlock spruce of North America, *Tsuga canadensis* (L.)Carr (Pinaceae), not poisonous but not very pleasant to eat. The Western hemlock, *Tsuga heterophylla* Sarg. is a taller tree, used in construction work, while a smaller species, *T. mertensiana* (Bong.)-Carr, the black or mountain hemlock is used for lighter timber. The ground hemlock, *Taxus canadensis* Marsh.

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Fig. 1. Plant of *Conium maculatum* L., poison hemlock (photo: C. Leon).

(Taxaceae) is a low ornamental shrub and is poisonous like all yews but not from the same agent as the umbelliferous hemlock.

However these alkaloids are by no means confined to *Conium*, or even the Umbelliferae. The discovery of γ-coniceine in certain *Aloe* species is significant. Although sometimes intensely bitter, aloes were not generally known as poisonous and many are used locally for medicinal purposes. However, deleterious effects, even death, when some wild-gathered aloes were ingested, have been reported in several rather obscure, local publications. At the wider level this raises the need for caution when using only partially identified plants. The alkaloids have been found in other plants as well, so their chemotaxonomic position is by no means clear. Poisoning by hemlock itself continues to be a problem for livestock, especially in damp meadows in North America. Like with many plant poisons there is always the thought that this biological activity might be put to good use. There were suggestions at one time that coniine could be used as an alternative to curare but this was never followed up. Another fascinating conjecture is that coniine can take the place of nicotinamide in a respiratory dinucleotide such as NAD(P) to which signalling functions have also been attributed. Although the hemlock alkaloids are so simple structurally, perhaps Christison's injunction is still valid!

Poison hemlock is a tall (c.6 feet) glabrous umbelliferous plant with hollow purplish-spotted stems and much divided leaves. It has compound umbels of white flowers giving rise to ridged ovate fruit. In a recent histochemical study secretory ducts were found in all vegetative parts of the plant and these contained alkaloids, which appear however to be manufactured at the root and shoot tips (Corsi and Biasci, 1998). Vittae were present in the fruit mericarp and these also contained alkaloids which increased as the fruit ripened. Elsewhere these structures had been termed "pro-vittae" and considered to be perhaps compressed ducts (reviewed Fairbairn, 1971).

Conium maculatum plants have typically a mousy odour when bruised, due to the presence of piperidine alkaloids (Fig. 2). One of the chief components was identified long ago as coniine, 2-propyl-piperidine, although this is sometimes replaced by γ-coniceine, accompanied by six minor ones (reviewed Fairbairn, 1971; Huggins, 2002). There need be no fear of eating mice, however, as their smell is said to be due to acetamide (or perhaps impurities in this. Do mice smell of acetamide, or does acetamide smell of mice ?), not an alkaloid. Mousiness in wines has been attributed to various derivatives of pyrroline and tetrahydropyridine (Heresztyn, 1986), so perhaps there is some structural feature common to nitrogen heterocycles that is responsible for the odour, or do these wine compounds occur as traces alongside the coniine alkaloids in the plant?

2. Chemistry

These piperidine alkaloids have the simplest structures for alkaloids so far described. They are related structurally but not biogenetically to the widespread plant constituent, pipecolic acid (Rodwell, 1971) and also to a number of other plant alkaloids (Fig. 2). Early chemical studies were reported in a large number of papers by German workers, which have been vaguely and sometimes erroneously referred to in more recent literature. Isolation of the active principle of hemlock was achieved by Giseke(sic) (1826) and various reactions with salts described. Other properties and tests were described by Brandes (1826) and then further purification as the sulphate (Giseke, 1827) was reported indirectly in a French publication which referred to a prize-winning paper given for an open competition at the North German Society of Pharmacy at Halle. This was then published in full together with the preparation of several derivatives (Brandes and Giseke, 1829). An accurate description of the pure compound was given by Geiger (1831) and further, somewhat conflicting observations made by Christison (1836), who even thought that he had separated the poisonous properties from the characteristic smell. An incorrect elemental composition was reported by Ortigosa (1842) but the first detailed description of coniine and conhydrine seems to be that

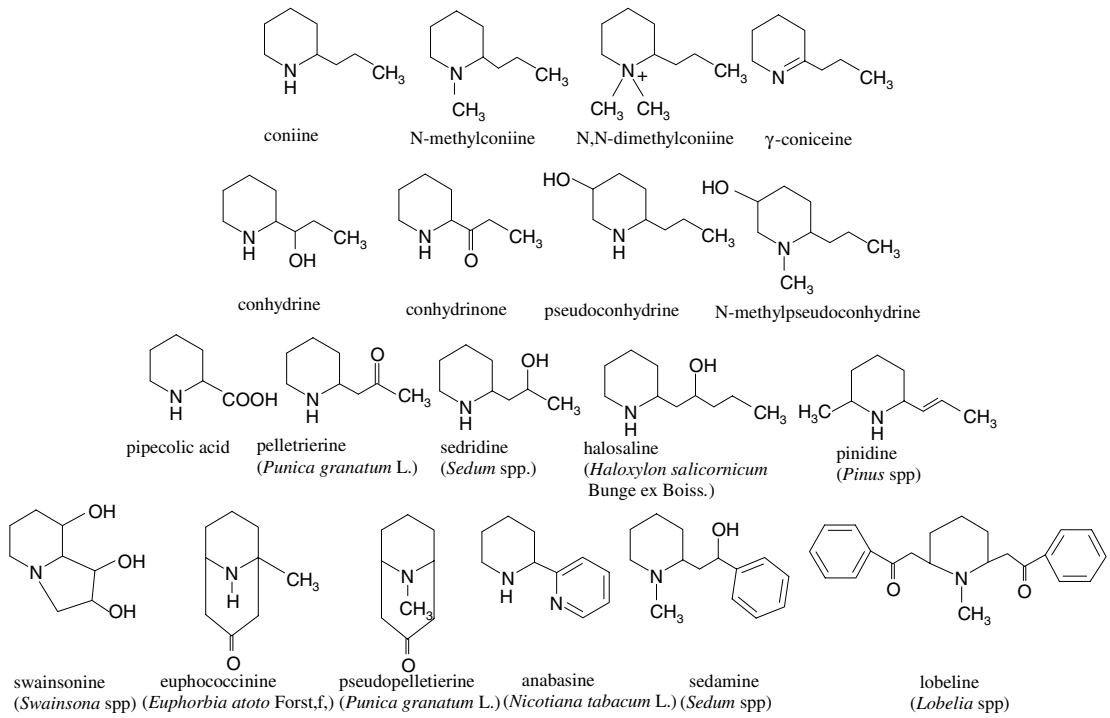

Fig. 2. Some piperidine alkaloids found in plants. They are structurally similar but are formed by different biosynthetic pathways.

of Wertheim (1856). The correct formula of coniine was established by Hofmann (1881) and the synthesis by Ladenburg (1886), said to be the first synthesis of an alkaloid. We can picture those German pharmacological worthies excited over the discovery of the toxic principle of one of the legendary poisonous plants, carrying out a number of researches, each resulting in a paper. In modern times chemists are still tinkering with ever more sophisticated reactions for synthesis of the various stereoisomers, resulting in a multitude of papers reporting all the structural and synthetic details of these alkaloids up to the present day. It is interesting that such a simple structure should generate so many publications in the early days, whereas now a far more complex alkaloid can be described in three or four papers. Coniine and its relatives are simple structurally (Fig. 2), so it is not surprising that their compositions were determined at a very early date and this early work referred to above was summarized by Blyth (1849) and Henry (1913).

Coniine (2-propylpiperidine) can occur in two optically active forms according to configuration at C2, the (*S*) and (*R*) forms of which the former is the naturally occurring one. It is liquid at room temperature (melting point, −2 °C) and boils at 166 °C. Because of its volatility it is best isolated as the hydrochloride (melting point, 220 °C), which crystallizes easily. Many synthetic routes have been described in the literature, the earliest ones being a condensation between α-picoline and acetaldehyde or reduction of 2-allylpyridine by sodium in ethanol (Ladenburg, 1886) and the latest using modern, sophisticated reactions (see Moody et al., 1997 and references therein).

γ-Coniceine (2,3,4,5-tetrahydro-6-propylpyridine) often accompanies coniine, sometimes occurring in greater quantities and is more toxic. As the free base is liquid (boiling point, 171 °C) at room temperature it was better isolated as the hydrochloride (melting point 143 °C) by Wolffenstein (1895), who also determined the correct molecular but not structural formula. The structure was later revised to the present version (Beterman et al., 1961). It is worth mentioning that the name "δ-coniceine" was given to the only distantly related octahydroindolizine, not of natural origin. The alkaloid was first synthesized by alkylation of phthalidimide, followed by hydrolysis by Gabriel (1909).

Conhydrine (2-(1-hydroxypropyl)piperidine) was recognized from early days as a minor, poisonous component of hemlock, where it occurs in the (+) form (Wertheim, 1856) and could be separated by fractional distillation or crystallization (von Braun, 1905). It is more soluble in water than coniine and crystallizes readily from ether (melting point, 121 °C). It was separated on a large scale from coniine by Chemnitius (1928).

Pseudoconhydrine (ψ-conhydrine, 6-propyl-3-piperidinol) is an isomer of conhydrine with the hydroxyl group on C5 (melting point, 105 °C), present in *Conium* usually as a minor component but reported unexpectedly as a major component in a certain American strain, growing in a greenhouse in early autumn (Leete and Adityachaudhury, 1967), where it is formed from

γ-coniceine. The alkaloid was first isolated by the Merck (1891) and its properties studied by Ladenburg and Adam (1891) and by Engler and Kronstein (1894), its constitution by Löffler (1909) and its structure finally established by Yanai and Lipscomb (1959).

Leaves and stems of a South African *Conium* species (perhaps *C. chaerophylloides* Eckl. & Zeyh.) growing at high altitudes were found to contain *N*-methylpseudoconhydrine as a major component along with conhydrine (Roberts, 1980; Roberts and Brown, 1981). It occurred as only a minor alkaloid in plants growing at low altitudes. The free base is a liquid and is best prepared as its hydrochloride (melting point 157 °C).

Oxidation of the secondary alcoholic group of conhydrine yields conhydrinone, isolated from the plant as the crystalline hydrochloride (melting point, 249 °C) by Leete and Olson (1972) who showed it to be derived biosynthetically from γ-coniceine.

N-methylconiine was first synthesized from coniine and the correct formula determined by von Planta and Kekulé (1854). The d-stereoisomer was separated from coniine, from which it was distinguished by its rotary power, in a plant extract provided by the Merck factory, by Wolffenstein (1894) and the l-stereoisomer separated as the hydrobromide, again from coniine, in a plant extract also from the Merck factory, by Ahrens (1902).

Five unidentified polar compounds from *Conium* fruits and leaves were recognized chromatographically and distinguished by their differing solubilities in aqueous ethanol. On hydrolysis they yielded coniine or related alkaloids (Fairbairn and Ali, 1968a). It is postulated that the alkaloid moiety may be part of a molecule resembling NAD, replacing the nicotinamide portion (Fairbairn and Ali, 1968b). Furthermore, other activities for NAD and NADP have been described, especially those involving signalling (Berger et al., 2004) and, who knows, maybe coniine is involved in these.

3. Distribution

These alkaloids have been found in a surprising range of plants. The most remarkable discovery of coniine alkaloids was made in aloes (Fig. 3). These plants from Africa and Arabia do not generally contain poisons, although a rat-like odour was recorded for *Aloe ballyi* Reynolds (Reynolds, 1966). Many *Aloe* species are intensely bitter due to the presence of anthrone-C-glycosides, notably barbaloin, which give them their purgative properties and many other phenolic compounds have been noted throughout the genus (Reynolds, 1985, 2004) but none of these substances are toxic. While investigating the aloe exudate compounds by TLC, a zone staining yellow with Fast Blue B (0.5% aqueous solution) was noted in a few species. This reagent reacts with both phenols and amines, so eventually the latter was pursued leading to the isolation of γ-coniceine as its hydrochloride from *A. sabaea* Schweinf. (= *A. gillilandii* Reynolds) (Dring et al., 1984). Coniine, conhydrinone and conhydrin were also found in some of the species (Dring et al., 1984; Nash et al., 1992) (Table 1). Later, γ-coniceine and coniine were again isolated from *A. sabaea*, together with a new compound *N*,*N*-dimethylconiine as a minor component (Blitzke et al., 2000). Although not generally known as poisonous plants, some obscure references point towards the toxic properties of a few species and there is a tale of their use in meat as a hyaena bait (R.G. Wieland, private communication). Infusions of three *Aloe* species, *A. chabaudii* Schönl., *A. globuligemma* Pole Evans and *A. ortholopha* Christian & Milne-Redh., which had been drunk as a herbal medicine caused deaths in rural Africa (Drummond et al., 1975). Later a hospital survey of poisoning by herbal remedies added another species, *A. christianii* Reynolds to the hazardous list (Nyazema, 1984). This was followed by more observations on the toxic nature of these species (Parry and Matambo, 1992; Parry and Wenyika, 1994). In these cases harmful effects were due to misidentification of the plants, so that an uncommon poisonous species was mistaken for a more usual one, used previously with beneficial results. In no instance was the nature of the poisonous principle suspected. Although only a small number of species out of the c 400 known from Africa and Arabia are poisonous, this emphasizes the need for accurate taxonomy when using wild-derived plants medicinally.

Fig. 3. Plant of *Aloe ruspoliana* Baker, growing in Illaut, N. Kenya (photo: P. Brandham).

The insectivorous pitcher plant, *Sarracenia* was found to contain coniine in its roots (Lambert, 1879) but apart from the characteristic smell none could be detected chemically from the pitchers. Later work found it in the leaves of *S. flava* L. (Mody et al., 1976) but again not in the pitchers, although a decided insecticidal activity of the alkaloid was demonstrated in vitro. The mousy smell has been reported from bruised *Euphorbia stricta* L. although no chemical investigation has been made (A. Radcliffe Smith, private communication). Also *Fritillaria imperialis* L. has a similar smell (M. Fay, private communication). It is stated that another poisonous umbellifer, *Aethusa cynapium* L. contains coniine (Power and Tutin, 1905) but a rigorous chemical

Table 1
Coniine alkaloids present in *Aloe* species revealed by TLC and levels of γ-coniceine, when present, determined by reaction with sodium nitroprusside. (summarized from Dring et al., 1984; Nash et al., 1992)

Species	Compounds present	γ-coniceine level % Dry weight of leaf
A. sabaea Schweinf.	γ-coniceine	5.2
A. ballyii Reynolds	γ-coniceine + conhydrinone	Present
A. ruspoliana Baker (Fig. 3)	γ-coniceine	6.0
A. ibitiensis Perrier	γ-coniceine	3.0
A. deltoideodonta Baker	γ-coniceine + pseudoconhydrine	1.0
A., viguieri Perrier	Coniine + trace of γ-coniceine	Trace
A. gracilicaulis Reynolds & P.R.O.Bally	γ-coniceine	Present
A. globuligemma Pole Evans	Coniine + conhydrine	0
A. ortholopha Christian & Milne-Redh.	Coniine + conhydrine	0
A. krapholiana Marloth.	Coniine + conhydrine	0
A. gariepensis Pillans	γ-coniceine + conhydrine	Present
A. descoingsii Reynolds	Coniine + conhydrine	0

identification was not achieved and more recent attempts also failed (Fairbairn, 1971). Similarly an early study suggested the presence of alkaloids in the aroids *Amorphophallus*, *Arisarum*, *Arum* and *Caladium* (Hébert and Heim, 1898) but no convincing isolations were made. Other obscure records list coniine in *Sarcolobus* (Asclepiadaceae), *Punica* (Punicaceae) and *Parietaria* (Urticaceae) (reviewed Raffauf, 1970). This distribution of odd organic compounds between Monocotyledon and Dicotyledon species is not unique. We can think of sulphur compounds in garlic and in many Crucifers. It would be nice for someone to work out the biosynthesis of these substances and their genetic basis as a comparison, in the two disparate groups

4. Biological activity

Despite its poisonous nature *Conium* is included in several herbals as Succus conii, described as a narcotic, sedative, analgesic, spasmolytic, anti-aphrodisiac and anti-cancer agent. It was even listed at one time (up to 1934) in the British Pharmacopoeia and the British Pharmaceutical Codex as a sedative and antispasmodic, the latter property leading it to be recommended as an antidote to strychnine (Grieve, 1995–2004). More recently it was speculated that by modifying the structure to remove some of the toxic properties, notably the teratogenic effects (López et al., 1999), a substitute for curare could be obtained for surgical purposes (de Boer, 1950). The coniine alkaloids are neurotoxins and death results from respiratory failure. Problems arise with livestock eating the plants which may grow in fields adjoining watercourses, or dried material inadvertently becoming included in hay.

The toxic effects on a rabbit of an extractive called coniin from *Conium* were recorded by Brandes and Giseke (1829) but the first systematic description of the physiological action was given by Christison (1829, 1836). Acute symptoms have been described by Panter (1988) and López et al. (1999). In addition, foetal malformations follow chronic non-lethal ingestion (“crooked calf disease”, Keeler, 1974, 1983). Some creatures, e.g., quail are said to eat *Conium* seeds with impunity although their flesh becomes poisonous. In Mexico it is said that the crushed root thrown into slowly moving water is used by the Tarahumar people to stupefy fish (Pennington, 1958). Classical toxic symptoms include paralysis, muscular tremors and weakness and respiratory failure preceding death and these have been confirmed and extended by modern authors (e.g., Brooks, 2001). Extensive physiological tests demonstrated a resemblance to the effects of nicotine, the main activity being to block spinal reflexes and there also being peripheral activity on autonomic ganglia (Bowman and Sanghvi, 1963). These authors recorded ED_{50} values for mice by oral route for coniine as 100 mg/kg, for methylconiine as 204.5 mg/kg and for γ-coniceine as 12 mg/kg. These differences explain why hemlock is more poisonous in the spring when γ-coniceine levels are highest (Panter, 1988).

5. Biosynthesis

Biosynthesis of these compounds proceeds through a completely different route from that of the other piperidine alkaloids (Fig. 4). Early work pointed to γ-coniceine as the first alkaloid to be formed, followed by transformation to coniine, conhydrine and *N*-methylconiine (Cromwell, 1956). Levels of these compounds varied greatly within the plant and under different environmental conditions (Fairbairn and Challen, 1959) and between varieties (reviewed Fairbairn, 1971). Variations were even found between two or four-hour periods of a day and between days (Fairbairn and Suwal, 1961). This can be surprising, when for instance Leete and co-workers usually found coniine and conhydrine in equal amounts in their plants (Leete, 1964) but on a subsequent occasion when the plants were grown

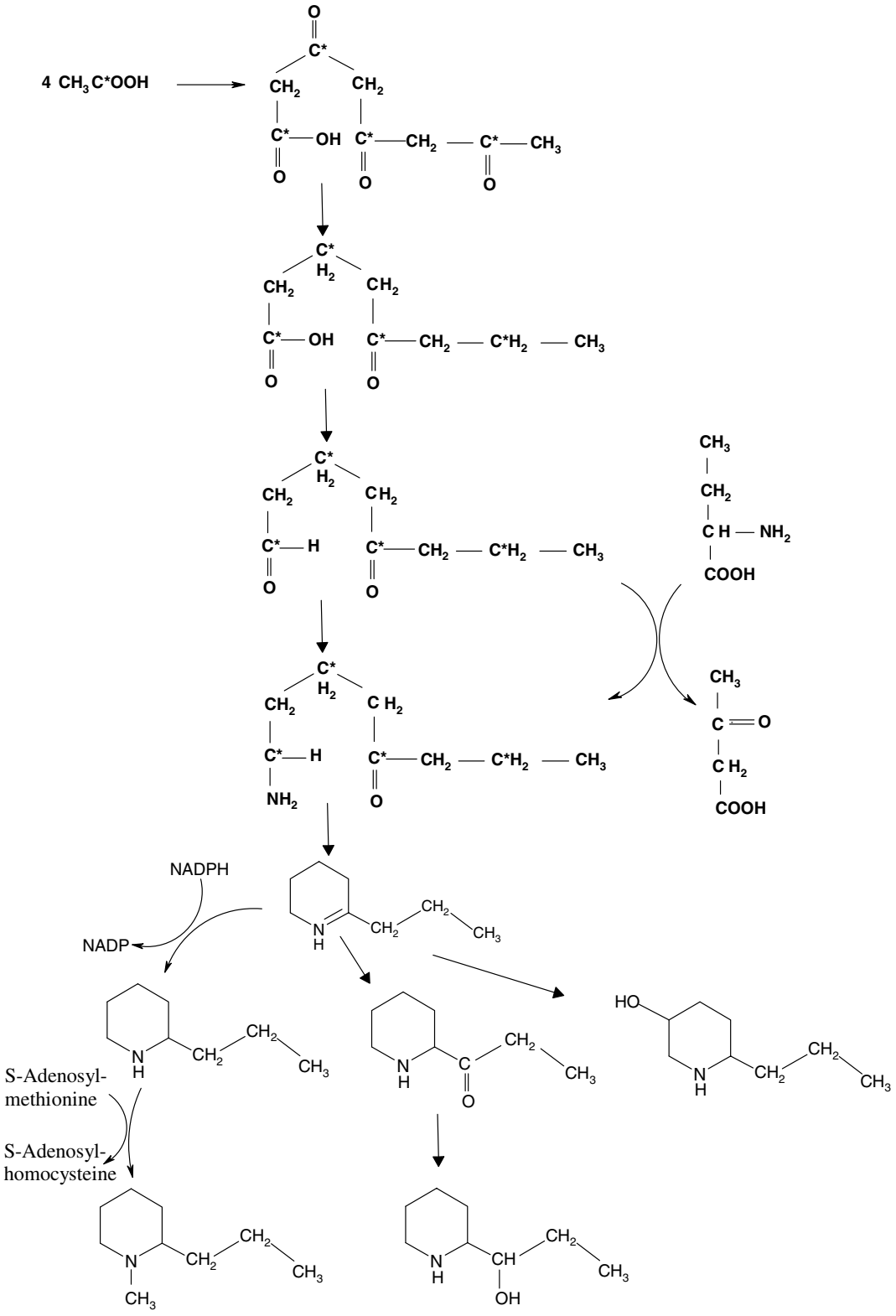

Fig. 4. Biosynthetic pathway to the hemlock alkaloids (summarized from Leete and Adityachaudhury, 1967; Leete and Olson, 1972; Roberts, 1971, 1974a,b, 1975, 1977).

in a greenhouse in the early autumn, coniine and pseudoconhydrine were the major components (Leete and Adityachaudhury, 1969).

The classical route for this type of structure is from L-lysine, although pipecolic acid derives from D-lysine (Gupta, 1968). Attempts to confirm this pathway for

γ-coniceine failed because of the absence of an amine oxidase in hemlock tissues, needed to metabolize key intermediates (Cromwell and Roberts, 1964). Around the same time, Leete having found that coniine was formed from acetic acid (Leete, 1963, 1964) then showed that 5-oxooctanoic acid and 5-oxooctanal were good precursors of γ-coniceine (Leete, 1970; Leete and Olson, 1970, 1972) (Fig. 3). Concurrent research showed that an enzyme isolated from *Conium* catalysed the transamination between 5-oxooctanal and alanine giving γ-coniceine (Roberts, 1971) (Fig. 3), probably via 5-aminooctanol (Roberts, 1977). Conversion to coniine and pseudoconhydrine took place readily and was demonstrated in vivo (Leete and Adityachaudhury, 1967) although conhydrinone was also mentioned as a product in some plants (Leete and Olson, 1972). Methylation to *N*-methylconiine took place (Roberts, 1974a) using *S*-adenosyl-L-methionine as a methyl donor and the coniine-*N*-methyl transferase was extracted from fruits and leaves (Roberts, 1974b). The transferase was then found to exist as two isoenzymes, A and B (Roberts, 1978). γ-Coniceine reductase was demonstrated in crude plant preparations but lost activity on purification (Roberts, 1975). NADPH was identified as the hydrogen donor. All this work was carried out with *Conium* and there is no evidence at present to show that the same pathways are used in *Aloe* or the other species to produce the alkaloids.

In hemlock, levels of the various alkaloids are fluid with formation and interconversions being strongly influenced by plant variety, plant part, age, season and growing conditions (e.g., Fairbairn and Challen, 1959; Leete and Adityachaudhury, 1967; Roberts, 1975). It has been suggested that the compounds are involved in an oxidation–reduction system of metabolic significance in the plant (Fairbairn and Suwal, 1961; Leete and Olson, 1972; Fairbairn and Ali, 1968b). If this is true then it would be an example of a so-called "secondary" metabolite with a primary function. Whether this activity is present in other species containing the alkaloids is a matter for future research.

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