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Review Paper

BIOLOGICAL ACTIVITY OF THE ALKALOIDS OF *ERYTHROXYLUM COCA* AND *ERYTHROXYLUM NOVOGRANATENSE*

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Summary

The cultivated *Erythroxylum* varieties *E. coca* var. *coca*, *E. coca* var. *ipadu*, *E. novogranatense* var. *novogranatense* and *E. novogranatense* var. *truxillense* contain 18 alkaloids, identified so far, belonging to the tropanes, pyrrolidines and pyridines, with cocaine as the main alkaloid. The biological activity of the following alkaloids has been reported in the literature: cocaine, cinnamoylcocaine, benzoylecgonine, methylecgonine, pseudotropine, benzoyltropine, tropacocaine, α- and β-truxilline, hygrine, cuscohygrine and nicotine. The biological activity of cocaine and nicotine is not reviewed here, because it is discussed elsewhere in the literature. Hardly anything is known about the biological activity of the other alkaloids present in the four varieties mentioned. The biosynthesis of the coca alkaloids has been outlined.

Introduction

Historical background

Coca leaves have been chewed by the South American Indians to prevent hunger and to increase endurance for over 5000 years. Even today it is used as a stimulant and medicine in many parts of the Andes and in the Amazon basin (Martin, 1970; Plowman, 1979a). The coca shrub is one of the oldest cultivated plants of South America. As recently recognized (Plowman, 1982), the cultivated coca plants belong to two distinct species of the genus *Erythroxylum* (family Erythroxylaceae): *Erythroxylum coca* Lam. and *E. novogranatense* (Morris) Hieron. Within the genus *Erythroxylum*, these two

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cultivated species are more closely related to each other than to any of more than 200 wild species.

Each of the cultivated species of coca includes two varieties (Bohm et al., 1982; Plowman and Rivier, 1983). *E. coca* Lam. var. *coca*, "Bolivian" or "Huánuco coca", is the best known variety and is still widely cultivated in the Andean region for legal and illegal production of cocaine. *E. coca* var. *ipadu* Plowman, "Amazonian coca", is a little known variety of *E. coca* which is sparingly cultivated by a number of Indian tribes in the western part of the Amazon basin (Plowman, 1979b). *E. novogranatense* (Morris) Hieron. var. *novogranatense*, "Colombian coca", is now found as a plantation crop only in Colombia, where it is cultivated by a few isolated Indian tribes. It is, however, widely grown throughout tropical countries as an ornamental plant (Plowman and Rivier, 1983). *E. novogranatense* var. *truxillense* (Rusby) Plowman, "Trujillo coca", is mostly confined to the desert areas of northern Peru (Plowman, 1979b). It is cultivated for coca chewing as well as for the flavouring of beverages (Plowman, 1982; Merory, 1968). Based on morphological, chemical, ecological and reproductive studies, *E. coca* var. *coca* is considered the most primitive among the cultivated cocas and appears to be ancestral to the other three cultivated varieties; these three varieties are known only as cultivated plants and possibly arose through human selection in cultivation (Bohm et al., 1982).

The principal alkaloid found in the cultivated varieties of coca is cocaine. Today the use of cocaine in medicine as a topical anesthetic is limited, because of its ability to induce dependence.

In western society cocaine hydrochloride is used illicitly by sniffing it. Since the early 1970s, another form of cocaine abuse is smoking this alkaloid in the form of cocaine paste or cocaine base, mixed with tobacco or marihuana (Siegel, 1979; Paly et al., 1982). The grey-white cocaine paste is a crude extract of coca leaves, and is reported to contain 40–70% cocaine base along with cocaine salts, other coca alkaloids and traces of residual organic solvents (Paly et al., 1982). Recently an investigation of cocaine base smoking has appeared in the literature (Perez-Reyes et al., 1982).

As the abuse of coca leaf and cocaine creates problems for the health of individuals, they have been scheduled in the Single Convention on Narcotic Drugs, 1961, United Nations (see Appendix).

The objective of this review

Coca leaves were originally, and in South America still are, usually chewed. The use of cocaine, the main alkaloid from the cultivated coca plants – sniffed in more or less pure form — is strongly increasing and for some years a new development in this area has been the smoking of coca paste (mixed with tobacco or marihuana). The acute and chronic effects of coca paste smoking are more extreme than those of cocaine sniffing, e.g. severe person-

ality disintegration including paranoid and psychotic behavior as well as hallucinations, social isolation and anorexia may occur (Paly et al., 1980). For the latter more dramatic effects plant constituents other than the alkaloid cocaine might be responsible and the consequence of smoking the coca paste must be taken into consideration as well.

The objective of this paper is to review the available knowledge concerning the biological activity of the alkaloids present in *Erythroxylum coca* and *E. novogranatense*. The biological activity of cocaine will not be reviewed here since the pharmacology of cocaine has been adequately covered by others (Mulé, 1976; Ellinwood and Kilbey, 1977). Nicotine which is reported to occur in cultivated coca will not be discussed here since it is a very well known constituent of the tobacco plant and the pharmacology of nicotine has been summarized by others (Ryall, 1974).

The biological activity of the non-alkaloids identified so far from the cultivated coca plants will not be reviewed here, because little is yet known. However, these components may play an important role in coca paste smoking.

Literature sources

In preparing the present report the following literature sources have been searched (by computer):

Entries: *Erythroxylum; Erythroxylon;* coca; for
Chemical Abstracts 1967 — Volume 98, Issue 24, 1983
Entries: the individual alkaloids as listed in Table 1, for
Chemical Abstracts 1967 — Volume 98, Issue 24, 1983
Excerpta Medica 1975 — 1983, Issue 5
International Pharmaceutical Abstracts 1970 — June 1983

Chemistry

The chemistry of the cultivated coca plants has been reviewed by Boit (1961) up to 1960 and by Hegnauer (1966) up to 1965. Since then only dihydrocuscohygrine has been identified as a new coca alkaloid (Hanuš et al., 1981). Niemann in 1860 isolated cocaine as the first alkaloid from the leaves of cultivated coca (Wöhler and Niemann, 1860). Other alkaloids of the cultivated coca plants as listed in Table 1 belong to the tropane, pyrrolidine and pyridine alkaloids.

The genus *Erythroxylum* is the only natural source of the alkaloid cocaine, known so far. Cocaine has been identified to date in 18 wild *Erythroxylum* species, including several from the Old World (see Table 1). The wild species showed only trace quantities of cocaine, except two species from Venezuela, *E. recurrens* Huber and *E. steyermarkii* Plowman, which contained cocaine levels comparable to those found in the four cultivated varieties of coca (Plowman and Rivier, 1983).

TABLE 1

ALKALOIDS IDENTIFIED IN THE FOUR VARIETIES OF CULTIVATED COCA

	Other sources in *Erythroxylum* species
Tropane alkaloids	
Cocaine (Wöhler and Niemann, 1860)	*E. acuminatum* (Arn.) Walp. (Holmstedt et al., 1977)
	E. areolatum L. (Plowman and Rivier, 1983)
	E. campestre St. Hil. (Aynilian et al., 1974)
	E. deciduum St. Hil. (Aynilian et al., 1974)
	E. fimbriatum Peyr. (Plowman and Rivier, 1983)
	E. glaucum O.E. Schulz (Plowman and Rivier, 1983)
	E. gracilipes Peyr. (Plowman and Rivier, 1983)
	E. aff. *impressum* O.E. Schulz (Plowman and Rivier, 1983)
	E. incrassatum O.E. Schulz (Plowman and Rivier, 1983)
	E. lucidum H.B.K. (Plowman and Rivier, 1983)
	E. macrocnemium Mart. (Plowman and Rivier 1983)
	E. panamense Turcz. (Aynilian et al., 1974)
	E. pelleterianum St. Hil. (Aynilian et al., 1974)
	E. pulchrum St. Hil. (Aynilian et al., 1974)
	E. recurrens Huber (Plowman and Rivier, 1983)
	E. rotundifolium Lunan (Plowman and Rivier, 1983)
	E. shatona Macbride (Plowman and Rivier, 1983)
	E. steyermarkii Plowman (Plowman and Rivier, 1983)
Cinnamoylcocaine (Giesel, 1889)	*E. monogynum* Roxb. (Chopra and Ghosh, 1938)
cis-Cinnamoylcocaine (Moore, 1973)	*E. pulchrum* St. Hil. (Plowman and Rivier, 1983)
	E. recurrens Huber (Plowman and Rivier, 1983)
	E. rotundifolium Lunan (Plowman and Rivier, 1983)
	E. steyermarkii Plowman (Plowman and Rivier, 1983)
trans-Cinnamoylcocaine (Moore, (1973)	*E. recurrens* Huber (Plowman and Rivier, 1983)
	E. steyermarkii Plowman (Plowman and Rivier, 1983)
Benzoylecgonine (Merck, 1885)	
Methylecgonine (de Jong, 1939)	*E. dekindtii* (Engl.) O.E. Schulz (Campos Neves and Campos Neves, 1966)
Methylecgonidine (Matchett and Levine, 1941)	*E. dekindtii* (Engl.) O.E. Schulz (Al-Yahya et al., 1979)
Norformylecgonine (de Jong, 1948)	
Pseudotropine (Hegnauer and Fikenscher, 1960)	*E. dekindtii* (Engl.) O.E. Schulz (Campos Neves and Campos Neves, 1966)
	E. macrocarpum O.E. Schulz (Evans, 1981)
	E. monogynum Roxb. (Agar and Evans, 1976)

TABLE 1 (*continued*)

	Other sources in *Erythroxylum* species
Tropane alkaloids (continued)	
Benzoyltropine (Wolfes and Hromatka, 1933)	*E. ellipticum* R. Br. (Johns et al., 1970)
	E. macrocarpum O.E. Schulz (Evans, 1981)
Tropacocaine (Liebermann, 1891)	*E. dekindtii* (Engl.) O.E. Schulz (Campos Neves and Campos Neves, 1966)
	E. macrocarpum O.E. Schulz (Evans, 1981)
Dihydroxytropane (Wolfes and Hromatka, 1933)	
α-Truxilline (Liebermann, 1888)	
β-Truxilline (Liebermann, 1888)	
Pyrrolidine alkaloids	
Hygrine (Liebermann, 1889)	*E. australe* F. Muell. (Klein and Soos, 1929)
Hygroline (Späth and Kittel, 1943)	
Cuscohygrine (Liebermann and Cybulski, 1895)	
Dihydrocuscohygrine (Hanuš et al., 1981)	
Pyridine alkaloids	
Nicotine (Fikenscher, 1958)	

Both cocaine and cinnamoylcocaine were identified in all four varieties of cultivated coca (Plowman and Rivier, 1983). Cinnamoylcocaine was found in higher concentration in the two varieties of *E. novogranatense* than in either variety of *E. coca*. *E. coca* var. *ipadu* contained less cocaine than *E. coca* var. *coca*. The dried leaves of the most cultivated variety, *E. coca* var. *coca*, contain approx. 0.6% cocaine (Plowman and Rivier, 1983). The content of cocaine decreases significantly during storage due to hydrolysis (Aynilian et al., 1974; de Jong, 1948).

The possibility of formation of artifacts during the extraction of alkaloids from the coca leaves has been mentioned (Rivier, 1981). Using a mild extraction method and analysis by gas chromatography—mass spectrometry, it was established that cocaine and *cis*- and *trans*-cinnamoylcocaine were the endogenous alkaloids in the coca leaves; none of the other volatile alkaloids previously reported in the literature could be detected in the material used (Rivier, 1981). The occurrence of nicotine in the coca leaves, identified only by thin-layer chromatography and colour reactions with specific reagents (Fikenscher, 1958), could not be confirmed (Rivier, 1981).

Ecgonine can be easily converted to cocaine by chemical processes. All other alkaloids from the plant material besides cocaine which yield ecgonine after hydrolysis, e.g. cinnamoylcocaine, benzoylecgonine, methylecgonine,

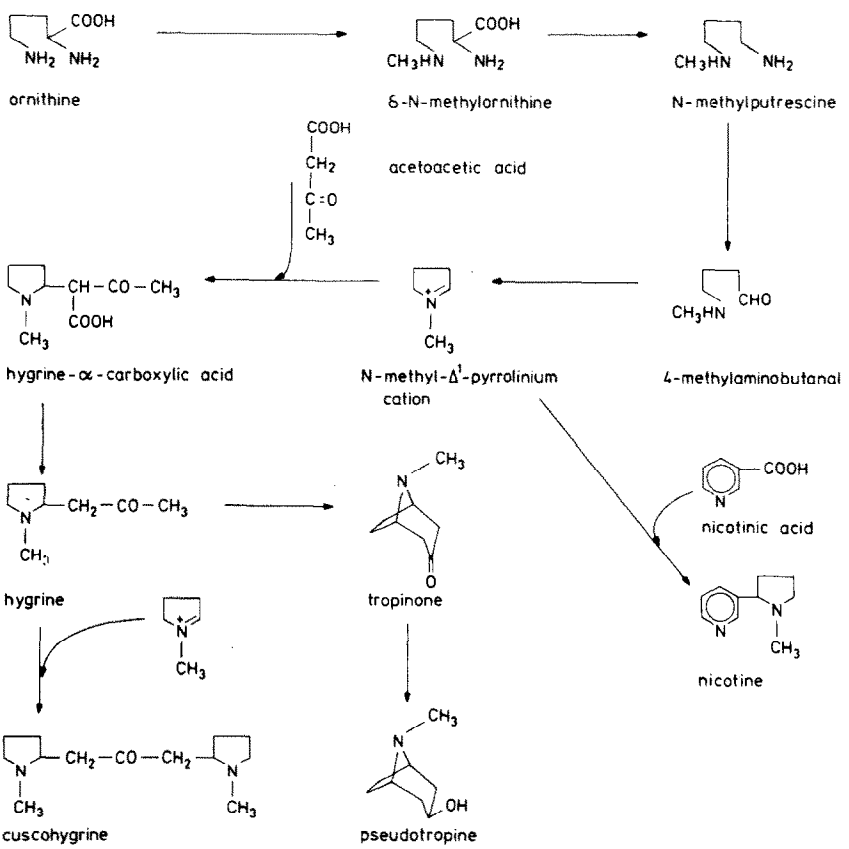
α- and β-truxilline, cannot be neglected as they are still useful for the synthesis of cocaine via ecgonine.

The alkaloids of *Erythroxylum* species have been compiled by Evans (1981). The chemotaxonomy of the Erythroxylaceae has been reviewed by Hegnauer (1981).

The biosynthesis of tropane alkaloids has been extensively investigated in solanaceous plants (Romeike, 1978; Leete, 1979) and in *E. coca* (Leete, 1982, 1983). It has been shown that the pyrrolidine ring of tropane originates from ornithine and that the C-atoms 2, 3 and 4 derive from two molecules of acetate (Romeike, 1978). The same situation has been shown to hold for the pyrrolidine alkaloids hygrine (McGaw and Woolley, 1979) and cuscohygrine (Romeike, 1978). Nicotine is derived from ornithine and nicotinic acid (Geissman and Crout, 1969). An outline of the biosynthesis of the alkaloids identified in the cultivated coca plants is presented in Fig. 1.

Biological activity

The biological activity of cocaine and nicotine is not discussed here, for reasons mentioned earlier. No recent literature was found concerning the



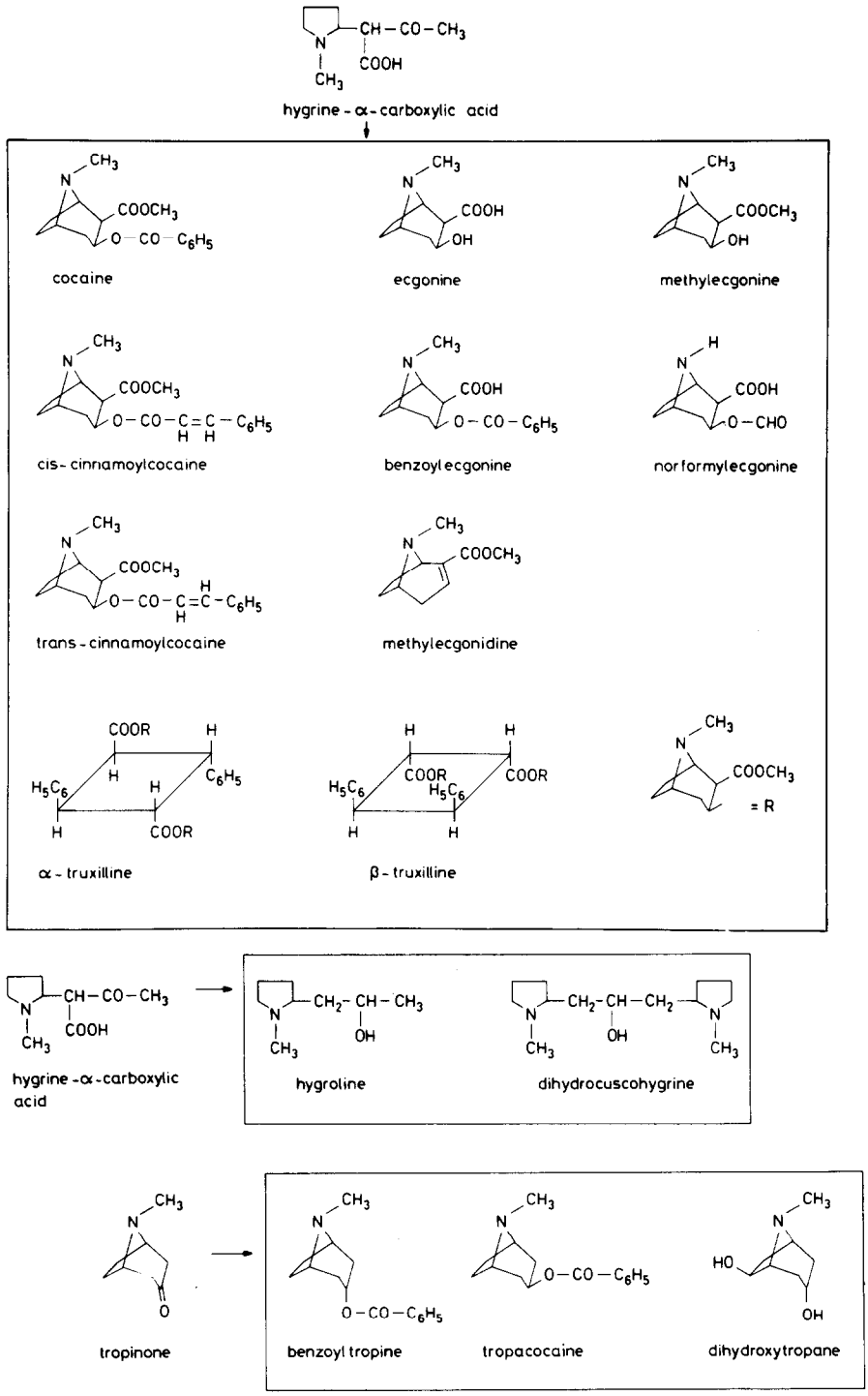


Fig. 1. Alkaloids identified in the cultivated coca plants — an outline of their biosynthesis.

biological activity of the tropane alkaloids methylecgonidine, norformylecgonine, pseudotropine, dihydroxytropane, α-truxilline and β-truxilline, and the pyrrolidine alkaloids hygrine, hygroline and dihydrocuscohygrine.

Cinnamoylcocaine

A 3% solution of cinnamoylcocaine in diluted hydrochloric acid showed no mydriatic and anesthetic properties in cats (Chopra and Ghosh, 1938). Cinnamoylcocaine has no pharmacological activity (Woker, 1953a). At daily doses of 60 mg/kg cinnamoylcocaine orally, mice exhibited normal immune responses (Watson et al., 1983). Mice dosed with 60 mg/kg cinnamoylcocaine had suppressed plaque forming cell/10^6 spleen cell responses (Watson et al., 1983). The plaque forming cell/spleen responses were significantly suppressed in mice treated with cinnamoylcocaine (Watson et al., 1983).

Benzoylecgonine

Benzoylecgonine does not show an appreciable anesthetic action (Carney, 1955). When tested for pharmacological activity in rats, benzoylecgonine was inactive after systemic administration, but had potent stimulant activity when administered centrally (Williams et al., 1977). The dopamine uptake into the synaptosomal fraction of rat striatum is affected by benzoylecgonine; the dose is biphasic/response curve with inhibition of dopamine uptake at concentrations of 10^{-7} M or lower (Williams et al., 1977). No observable pharmacological effects are noted in the rat after doses of 250 mg/kg benzoylecgonine intravenously (Misra et al., 1975). At the concentration of 1 mg/kg benzoylecgonine (intracisternally), piloerection, running and jumping activity, jerking, rapid breathing and squeaking appeared within 5 min and these effects lasted for approximately 4 h; with higher doses (2 mg/kg) these effects became more violent without ensuing mortality (Misra et al., 1975). Benzoylecgonine mildly depresses the excitability and contractility of striated muscle of the frog and the rat (Kubota and Macht, 1919). Also in doses from 1 to 3 mg, benzoylecgonine produced no effect upon the behavior of white rats in the circular maze (Macht and Bloom, 1921). Benzoylecgonine showed no motility increase in mice after doses of 1—50 mg/kg subcutaneously and 10—50 mg/kg orally, and no impairment of retention capability after administration of 0.3—50 mg/kg orally (Nieschulz, 1971). The activity of mice impaired by chloropromazine was increased after administration of 0.1—10 mg/kg benzoylecgonine orally (Nieschulz, 1971). Benzoylecgonine failed to show cocaine-induced liver damage in mice (Thompson et al., 1979). It is approximately 20 times less toxic than cocaine (Woker, 1953a). In rats, benzoylecgonine failed to inhibit the accumulation of [^{3}H]norepinephrine and [^{3}H]dopamine by synaptosomes from the cortex and striatum, respectively (Komiskey et al., 1977). At a concentration of 10^{-3} M, benzoylecgonine produced approximately 40% inhibition of veratridine-stimulated $^{22}Na^+$ uptake in an assay with rat brain membrane homo-

genate (Matthews and Collins, 1983). At daily doses of 60 mg/kg benzoylecgonine orally, mice exhibited normal immune responses (Watson et al., 1983). Mice dosed with 60 mg/kg benzoylecgonine had suppressed plaque forming cell/10^6 spleen cell responses (Watson et al., 1983). Benzoylecgonine did not affect the formation and release of [^{14}C]dopamine in synaptosomal-mitochondrial preparations from the caudate nucleus of rat brain (Bagchi and Reilly, 1983). In the presence of reserpine, which inhibited the synthesis and enhanced the release of [^{14}C]dopamine, benzoylecgonine had no effect on the formation of [^{14}C]dopamine at a concentration of 9.1×10^{-6} M, but at the 36.4×10^{-6} M level it showed small but significant additional inhibitory effect; the release of [^{14}C]dopamine in the presence of reserpine was not further enhanced by the addition of benzoylecgonine (Bagchi and Reilly, 1983).

Methylecgonine

Methylecgonine shows no anesthetic properties (Takman and Camougis, 1970). At concentrations of 5×10^{-3} M and higher, it has significant inhibiting effect on dopamine uptake into the synaptosomal fraction of rat striatum (Williams et al., 1977). At a concentration of 10^{-4} M, methylecgonine produced approximately 30% inhibition of veratridine-stimulated $^{22}Na^+$ uptake in an assay with rat brain membrane homogenate (Matthews and Collins, 1983). In the rat, no observable pharmacological effects are noted with methylecgonine after high doses (200 mg/kg intravenously or 10 mg/kg intracisternally) (Misra et al., 1975). Methylecgonine failed to show cocaine-induced liver damage in mice (Thompson et al., 1979). At daily doses of 60 mg/kg methylecgonine orally, mice exhibited normal immune responses (Watson et al., 1983). Mice dosed with 60 mg/kg methylecgonine did not have suppressed plaque forming cell/10^6 spleen cell responses (Watson et al., 1983).

Pseudotropine

Pseudotropine is almost devoid of atropine-like activity; it has only slight activity on ganglia (Gyermek and Nádor, 1957).

Benzoyltropine

Benzoyltropine shows a strong cholinolytic action, but has hardly any anesthetic effect (Nádor and Scheiber, 1972). It has mild mydriatic properties (Woker, 1953b). Benzoyltropine shows both potency and selectivity as an antagonist of 5-hydroxytryptamine on the rabbit heart (Fozard et al., 1979). In rats, benzoyltropine inhibits the [^{3}H]norepinephrine and [^{3}H]-dopamine uptake in the cortex and striatum, respectively (Komiskey et al., 1977).

Tropacocaine

Tropacocaine, although more irritant than cocaine, is reported to have approximately the same anesthetic action as cocaine with one half of its toxicity (Doerge, 1971; Nádor and Scheiber, 1972). It is used principally in spinal anesthesia (Doerge, 1971). Tropacocaine failed to show cocaine-induced liver damage in mice (Thompson et al., 1979). When administered intraperitoneally to phenobarbital-induced mice, tropacocaine did not produce hepatotoxicity (Freeman and Harbison, 1981). It shows much less cholinolytic action than benzoyltropine, especially on the postganglionic receptors of the eye (Nádor and Scheiber, 1972). In rats, tropacocaine inhibits the [^{3}H]norepinephrine and [^{3}H]dopamine uptake in the cortex and striatum, respectively (Komiskey et al., 1977). It shows both potency and selectivity as an antagonist of 5-hydroxytryptamine on the rabbit heart (Fozard et al., 1979). Tropacocaine has no mydriatic properties (Woker, 1953b).

α- and β-Truxilline

α- and β-Truxilline have no anesthetic action (Woker, 1953a). They are strong heart toxins (Liebermann, 1888).

Hygrine

Hygrine has no anesthetic action (Woker, 1953a).

Cuscohygrine

Cuscohygrine was found to inhibit the delayed type hypersensitivity response to 2,4-dinitrofluorobenzene in mice; it produced 24% inhibition at daily doses of 60 mg/kg (Watson et al., 1983). Mice dosed with 60 mg/kg cuscohygrine had suppressed plaque forming cell/10^6 spleen cell responses (Watson et al., 1983).

Conclusions

The cultivated coca plants include four varieties: *Erythroxylum coca* var. *coca*, *E. coca* var. *ipadu*, *E. novogranatense* var. *novogranatense* and *E. novogranatense* var. *truxillense*. In most of the investigated wild *Erythroxylum* species only trace amounts of cocaine were detected. However, two species from Venezuela, *E. recurrens* and *E. steyermarkii*, contained cocaine levels comparable to those found in the four cultivated varieties of coca.

In contrast to the large amount of literature concerning the pharmacology of cocaine, there is relatively little known about the biological activity of

the minor alkaloids from the cultivated coca plants. With regard to the euphoric effect, not one of the minor alkaloids can be compared with cocaine.

Plant constituents other than cocaine — alkaloids and non-alkaloids — may contribute to the overall effect achieved by chewing the coca leaf or smoking cocaine paste. Therefore further investigations of the chemical composition of coca leaves and of cocaine paste are needed. This research should preferably be guided by pharmacological screening. The several fractions obtained from the plant material will be tested pharmacologically and those with high activity should be chemically analyzed first.

Appendix

Single Convention on Narcotic Drugs, 1961, United Nations

Article 26 — The coca bush and coca leaves

(1) If a Party permits the cultivation of the coca bush, it shall apply thereto and to coca leaves the system of controls as provided in article 23 respecting the control of the opium poppy, but as regards paragraph 2(d) of that article, the requirements imposed on the Agency therein referred to shall be only to take physical possession of the crops as soon as possible after the end of the harvest.

(2) The Parties shall so far as possible enforce the uprooting of all coca bushes which grow wild. They shall destroy the coca bushes if illegally cultivated.

Article 27 — Additional provisions relating to coca leaves

(1) The Parties may permit the use of coca leaves for the preparation of a flavouring agent, which shall not contain any alkaloids, and, to the extent necessary for such use, may permit the production, import, export, trade in and possession of such leaves.

(2) The Parties shall furnish separately estimates (article 19) and statistical information (article 20) in respect of coca leaves for preparation of the flavouring agent, except to the extent that the same coca leaves are used for the extraction of alkaloids and the flavouring agent, and so explained in the estimates and statistical information.

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