CURARE - BOTANY, CHEMISTRY, AND PHARMACOLOGY. (*)

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SUMMARY

Some aspects of curare research carried out over the last 25 years are discussed. Accepting a pharmacological rather than purely ethnological definition means that curares are not limited to South America but that they are also known from Central Africa and South-East Asia. Among the criteria that have been suggested for classifying South American curares are: type of container, geographical origin, botanical sources of the active constituents, and chemical composition. A combination of botanical and geographical criteria leads to much the same regional groupings as a combination of criteria involving the type of container and the chemical composition. The active principles in curares may derive from members of the Loganiaceae (**Strychnos**) and/or Menispermaceae (mainly Chondrodendron and **Curarea**, but also **Abuta, Anomospermum, Cissampelos, Sciadotenia**, and **Telitoxicum**). Certain of the **Strychnos** dimeric indole alkaloids can undergo a variety of cleavages, oxidations, and isomerizations; hence, some of the compounds obtained by normal isolation procedures are almost certainly artefacts. The different genera of Menispermaceae produce a wide range of bisbenzyl and other types of isoquinoline alkaloids. Many of the plant additives also contain a variety of isoquinoline bases, and this has to be taken into account in assessing the contribution these ingredients may make to the overall activity of curare. Loganiaceae-based curares with toxiferine as major alkaloid tend to be the most toxic. In the case of Menispermaceae-based products, there is evidence that the process by which they are made may lead to a considerable increase in the toxicity of the finished poisons as compared with the original plant materials. The mechanism of action of the alkaloids is outlined, and the role of curare alkaloids in the development of present-day muscle-relaxant drugs used in surgery is indicated. Attention is drawn to reported medicinal uses of some of the alkaloid-bearing plants incorporated into curares, suggesting that further evaluation of these plants may be of interest.

INTRODUCTION

The dart and arrow poisons of the South American Indians have long been a source of fascination to scientists and laymen alike, and in studying **curare** - certainly the most famous of them - wide fields of botany, chemistry, and pharmacology have been opened up. The well-known symposium on **Curare and curare-like agents** (Bovet **et al.**, 1959), held in Rio de Janeiro just over 25 years ago, was a tremendous stimulus to curare research, and in the present paper the opportunity is taken to review briefly some of the developments which have taken place since that event.

The following references deal in greater detail with various aspects of more recent curare research: Bauer (1965, 1981); del Castillo & Anderson (1974); Curare - Symposium (1966); Grmek (1973); Marini-Bettolo (1981); Vellard (1973); Waser (1972); Waser & Hopff (1971).

DEFINITION

Depending on the point of view, the term **curare** can mean several different things.

1. To the anthropologist or ethnographer it stands for a group of dart (and arrow) poisons prepared by the Indians of tropical South America whose characteristic feature is to bring about paralysis.

2. To the pharmacologist curare is characterized by its action at the neuromuscular junction; this is to cause relaxation or paralysis of the musculature through blockade by a nondepolarizing, competitive mechanism, the effects of which are reversible by small doses of neostigmine.

3. To the anaesthetist curare often simply means the musclerelaxant alkaloid (+)-tubocurarine.

In view of the wide use of the verb "to curarize", as well as of the derived noun "curarization" and adjective "curarizing", it is reasonable to accept a definition based on the characteristic pharmacological effects as indicated above under 2. Such a definition is proposed by the ethnologist Bauer (1962/63), who has carried out a lengthy series of investigations on curare, and it is the one adopted here. Defined thus, and leaving aside the geographical qualification, it means that curares are no longer to be considered as exclusively South America, for there is good evidence that similar products are made in Central Africa and South-East Asia. This approach entails brief consideration of another highly reputed South American arrow poison, viz **guachamacá**, for reasons that will become clear when the pharmacology of muscle-relaxants comes to be discussed.

TYPES OF CURARE AND THEIR GEOGRAPHICAL DISTRIBUTION
Types of Curare

Curare is essentially a hunting poison characteristic of the tribes living in the tropical rain forest. But it has also been prepared by tribes further to the south.

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the savanna of the Mato Grosso plateau, and it has occasionally been used in warfare.

Early work led Boehm to group curares according to the type of container they were stored in – the three most important types being calabash, tube, and pot curare. This classification proved convenient in use over a period of more than 60 years, as it turned out that, in general, curare in calabashes was usually obtained from Loganiaceae; curares in bamboo tubes were derived from Menispermaceae; and pot curares were mixed Loganiaceae Menispermaceae products. However, it has become evident that nowadays some tribes may keep their curare in more than one type of container or even in tin cans or bottles which happen to be conveniently at hand (Vellard, 1965; Schultes, 1984). A further difficulty is that curare is a product in which there has been, and still is, a considerable trade; certain tribes have had a particular reputation for the quality of their product, and samples often travel hundreds of kilometres from their place of origin. Furthermore, a supposedly new type of curare has been encountered which is not stored but is painted directly on arrow tips; it is derived from Loganiaceae and/or Menispermaceae. The name "arrow-tip" curare is appropriate for this type.
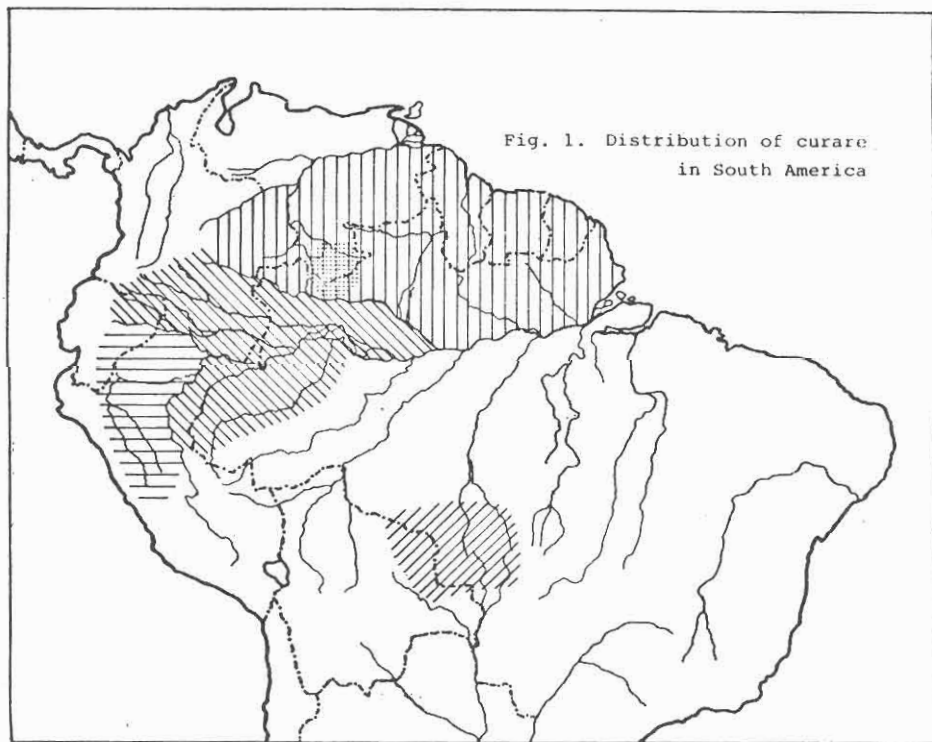

Fig. 1. Distribution of curare in South America

‖‖‖	Curares based on Loganiaceae
\\\\\\	Mixed Loganiaceae/Menispermaceae curares
≡	Curares based on Menispermaceae
/////	Curares based on Loganiaceae (savanna)
▓	Loganiaceae and/or Menispermaceae-based arrow-tip curares

Distribution of Curares

Vellard (1965) put forward a geographical classification based primarily on the botanical sources of the active ingredients; he noted that it was closely paralleled by the differences in the chemical composition of the various preparations. Nevertheless, here again there are problems, because of the long-distance trading mentioned above and also because the botanical origin of the product is often unknown.

As can be seen from the accompanying map (Fig. 1; modified from Vellard(1965,1973) curares based on Menispermaceae predominate in the montaña, in the region bounded by the Napo, Marañon, and Ucayali rivers. Mixed Loganiaceae/Menispermaceae curares are found chiefly in the area covered by the middle reaches of the Amazon; but there is some evidence that mixed curares were also made in Guyana (Moody, 1965; Snedden **et al.**, 1970). Loganiaceae curares come principally from the region between the Orinoco in the north and the Negro and lower reaches of the Amazon in the south (Vellard 1965,1973).The so-called arrow-tip curares are found in a small region on either side of the Venezuela/Brazil frontier (Biocca **et al.**, 1965; Galeffi & Marini-Bettolo, 1977; Galeffi **et al.**,1977; Lizot, 1972; Marini-Bettolo, 1973).

Bauer (1962/63; 1965a, b; 1969; 1971a, b; 1981), working with extensive museum material, has analysed numerous samples of curare both pharmacologically and by means of paper chromatography. He has classified his findings in terms of the main active alkaloidal constituents, which are an indication of the botanical origin as well as the geographical origin, and the container, which is usually a further indication of geographical origin.

On the basis of these chromatographic studies Bauer (1965a) has divided curares into three major groups, which come from regions coinciding largely with the ones put by Vellard:

1. Those in which C-curarine/C-calebassine are the main alkaloids;in some dihydrotoxiferine (C-alkaloid K) may also be present. These products are found mostly in calabashes and originate mainly from the eastern Amazonian region (Orinoco and Negro rivers).

2. Those in which toxiferine predominates; C-alkaloids A and E may also occur in large amounts; and in some diaboline is present.Occasionally,there are traces of C-curarine/C-calebassine and related alkaloids, and in certain samples there are **Chondrodendron** bases. Mostly, these curares are kept in unglazed clay pots of which there are several types, and they come from the western Amazonian region (Napo, Japurā, Javari rivers).

3. Those in which only **Chondrodendron** alkaloids occur. Curares of this group may be stored in pots or bamboo tubes (a container that first makes its appearance at the end of the 19th century) and are confined to the montaña.

Bauer places Siusi and Witoto products from the Brazil/Colombia frontier region in a separate category. Together with traces of C-curarine/C-calebassine and associated alkaloids, they contain a series of unidentified components. One possible ingredient in

the Witoto curare is a **Telitoxicum** species (Barneby & Krukoff, 1971, p. 30; Krukoff & Barneby, 1970, p. 47).

Thus, as far as museum specimens of curare are concerned, the container can be used as an indicator of their origin but **not** of their composition (Bauer,1965a;1971a). Chemical analysis is essential in order to determine the composition and hence to obtain some idea of the botanical materials used.

While it is understandable that the composition of a curare will be governed largely by the plants available to the maker(s),in a given area it will tend to be fairly constant; and this is evident from the very similar alkaloid composition of curares obtained in both Ecuador and southern Venezuela recently and more than a century ago (Bauer, 1981). Nevertheless, the same range of ingredients may not necessarily be used each time, and the fact that the composition is similar throughout wide regions is due as much to the lively intertribal trade, especially in curares which enjoy a particular reputation. In the past, Macushi curare from Guyana reached tribes situated along the upper Orinoco;and in later times, Piaroa curare from the Orinoco has reached the Akawaio living on the upper Mazaruni in Guyana (Colson, 1973; Coppens, 1971; Thomas, 1972).

BOTANY

Once scientific field studies began, it was soon recognized that the active ingredi ents in South American curares were derived chiefly from plants belonging to the two families Loganiaceae and Menispermaceae.

Loganiaceae

The plants concerned are all **Strychnos** species. The genus reaches its greatest diversity in Africa, and the ca. 75 species found there belong to 11 of the 12 sections distinguished by Leeuwenberg (1969) on the basis of various combinations of flower and seed characters, as well as the arrangement of the tendrils. In Asia there are probably about 44 species, grouped in five of the sections: Strychnos, Rouhamon,Penicillatae,Bre vitubae, and Lanigerae (Bisset **et al.**, 1973). One species **S. potatorum**,of section Rouha mon, occurs in both Africa and Asia. South America has ca. 75-80 species,which are repre sentatives of only three of the sections: Strychnos, Rouhamon, and Breviflorae (Krukoff 1972).

Evidence in the form of annotations to herbarium specimens (Krukoff,1972) indicates that the South American Indians have utilized at least 21 species in preparing curares, although not all of them have been a main component. Table 1 lists the species and where they have been used, which is throughout the greater part of the curare-producing region of South America. The majority of the species reported to be ingredients in curare belong to the section Strychnos; species of section Rouhamon form a poor second; and only one species comes from section Breviflorae.

Table 1. The **Strychnos** species known to have been used in South American curares (Krukoff, 1972). [a]

Species	Region where used
Section **Strychnos**	
S. brachiata	Colombia (Putumayo)
S. bredemeyeri	Brazil (Roraima), Guyana
[S. darienensis	Guyana]
S. cf. diaboli	Guyana
S. erichsonii	Colombia (Putumayo), Guyana, Surinam
S. javariensis	Colombia (Putumayo, Amazonas), Brazil (western Amazonas)
S. jobertiana	Colombia (Vichada, Putumayo), Ecuador (Napo-Pastaza),Brasil (western Amazonas)
[S. macrophylla	Brazil (Manaus)]
S. mitscherlichii	
var. mitscherlichii	Colombia (Putumayo), Ecuador (Napo-Pastaza), Guyana
var. pubescentior	Colombia (Amazonas)
S. peckii	Colombia (Putumayo), Venezuela (Amazonas), Ecuador (Napo-Pastaza, Morona, Santiago), Brazil (western Amazonas)
S. rondeletioides	Colombia (Vaupés), Venezuela (Bolívar, Amazonas), Brazil (central Amazonas)
S. sandwithiana	Brazil (western Amazonas)
S. solerederi	Brazil (western Amazonas)
S. solimoesana	Brazil (western and central Amazonas)
S. tomentosa	Brazil (Roraima, Amapá)
S. toxifera	Panama (?), Venezuela (Amazonas), Ecuador (Napo-Pastaza), Guyana, Brazil
Section **Rouhamon**	
S. cogens	Venezuela (Bolívar), Guyana, Brazil (western Amazonas)
S. glabra	Brazil (central and northern Amazonas)
S. guianensis	Colombia (Putumayo), Venezuela (Bolívar, Amazonas), Guyana, Surinam, Ecuador (Napo-Pastaza), Brazil (Roraima,Rio Branco, north-western Amazonas, Mato Grosso)
S. melinoniana	Guyana, French Guyana (?)
S. panurensis	Venezuela (upper Orinoco)
S. subcordata	Colombia (Putumayo), Brazil (western and central Amazonas) (western and northern Amazonas)
Section **Breviflorae**	
S. castelnaeana	Peru (Loreto), Brazil (widely in western and central Amazonas, Pará)
Doubtful species	
[S. gubleri	Venezuela (upper Orinoco)]
[S. yapurensis	Brazil (western Amazonas)]

a - Later annotations can be traced via Krukoff's 21st and final supplement on the American species of **Strychnos** (**Phytologia** 51: 433-439 (1982)).

About eight of the **Strychnos** species included in Table 1 have been noted as principal ingredient in curares: **S. jobertiana, S. peckii, S. rondeletioides,** and S. **toxifera** of section Strychnos; **S. cogens, S. glabra,** and **S. guianensis** of section Rouhamon.

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and S. **castelnaeana** of section Breviflorae.

Bauer (1965a) has tried to reconstruct the plant sources of the various types of curare from the results of his chromatographic analyses. But his attempt must be considered unsatisfactory, especially in regard to the **Strychnos** species involved. It does not take into account current knowledge of their distributions, as given in the 21 supple ments to the original monograph by Krukoff & Monachino (1942). Nor is allowance made for the present incomplete data on their alkaloid composition - little is known about the active principles of many of the species reportedly incorporated into curares (cf. Table 4) - and the variation to which this is known to be subject (Galeffi **et al.**,1973) Marini-Bettolo **et al.**, 1980).

It is also species of **Strychnos** that have proved to be the essential components of the muscle-relaxant poisons made in Africa and South-East Asia. Banyambo hunters of the Rwanda-Tanzania frontier region make use a poison based on S. **usambarensis** (section Bouhamon) on their arrowheads (Angenot, 1971) and Semai Senoi aborigines of Western Malaysia have almost certainly included S. **ignatii** (section Strychnos) in their dart poison lampong (Bisset **et al.**, 1977.

Table 2. Species of Menispermaceae utilized in the preparation of South American curares (Barneby & Krukoff, 1971).[a]

Species	Region where used
Triclisieae	
Chondrodendron[b] Ruiz **et** Pavón	
Ch. platiphyllum	Brazil
Ch. tomentosum	Colombia (Putumayo), Ecuador (Napo-Pastaza), Peru (Loreto, San Martín, Huánuco)
Curarea Barneby et Krukoff	
Cu. candicans	Guyana, Brazil (western Amazonas)
Cu. tecunarum	Colombia (Putumayo, Amazonas), Ecuador (Napo-Pastaza), Brazil (western Amazonas)
Cu. toxicofera	Colombia (Putumayo, Vaupés), Ecuador (Napo-Pastaza), Peru (Loreto), Brazil (western and central Amazonas)
Sciadotenia Miers	
Sc. peruviana	Peru
Sc. toxifera	Colombia (Putumayo), Ecuador (Napo-Pastaza), Peru (San Martín)
Anomospermeae	
Abuta Barrère ex Aublet	
Ab. grisebachii	Venezuela (Roraima)
Ab. imene	Brazil (western Amazonas)
Ab. pahni	Brazil (western Amazonas)
Ab. rufescens	Colombia (Putumayo,[c] Amazonas), Venezuela (Roraima), Ecuador (Napo), Brazil (western Amazonas)
Anomospermum Miers	
An. grandifolium[d]	Ecuador

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Tabela 2. continuação.

Species	Region where used
Telitoxicum Mold.	
T. minutiflorum	Brazil (western Amazonas)
T. peruvianum	Peru (Loreto)
Cocculeae	
Cissampelos L.	
Ci. ovalifolia	Guyana
Ci. pareira	Ecuador (Napo-Pastaza)

[a] Later annotations can be traced via the 18th and final supplement on American Menis-permaceae by Krukoff & Barneby (**Phytologia** 51: 458-462 (1982).

[b] This is the correct spelling of the genus name (Sandwith, 1955) and was the one final adopted by Krukoff in his later publications.

[c] Here, there is the possibility that the plant collected may have been confused by the botanist's informant with **Curarea toxicofera** (Krukoff & Barneby, 1970, pp.16-17 under **Abuta splendida**).

[d] This species, under the above name or **Elisarrhena grandifolia**,used often to be mentioned as an ingredient of the curare produced by the Indians in Brazilian Amazonas. This appears to be based on a mis-identification and the plant concerned was almost certainly **Chondrodendron limaciifolium**, now **Curarea candicans**. **Anomospermum grandifolium** has also been mis-identified as **Ch. polyanthum**, now **Cu. toxicofera** (Krukoff & Moldenke,1938, 71 et seq.).

Menispermaceae

With the exception of Cissampelos, all the Menispermaceae genera (Barneby & Krukoff 1971) used in curare are placed in the two tribes Triclisieae and Anomospermeae (see Table 2) - characterized, respectively, by the absence and presence of albumen in the seed Over the years, views on several of the species have become modified and in some cases this has necessitated nomenclatural changes. Thus, on the basis of differing flower and fruit characters Barneby and Krukoff (1971) have split the genus **Chondrodendron** into **Chondrodendron** sensu **stricto**, with the three species **Ch. tomentosum,Ch.platiphyllum**, and **Ch. microphyllum**, and a new one appropriately called **Curarea**, which has four species: **Cu. toxicofera** (incl. **Ch. iquitanum, Ch. polyanthum**, ? **Ch. bioccai**), **Cu. candicans** (incl. **Ch. limaciifolium**), and the new taxa **Cu. tecunarum** (= **Ch. limaciifolium** as interpreted by Krukoff and his co-workers between 1938 and 1971 (Krukoff & Moldenke, 1938; Barneby & Krukoff, 1971)) and **Cu. cuatrecasasii**.

The more important Menispermaceae incorporated into curares appear to be **Ch. tomen-tosum, Cu. tecunarum**, and, interestingly, **Ci. ovalifolia** and **Ci. pareira**.

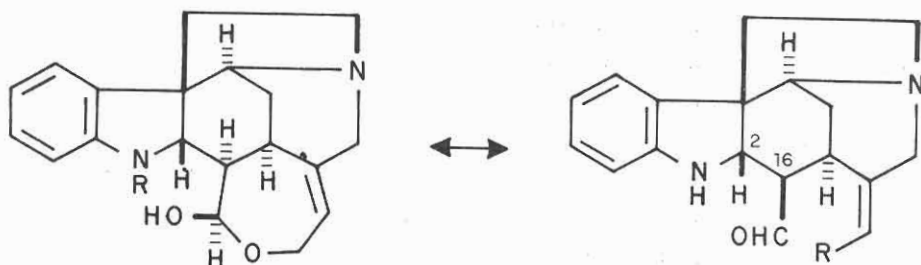| Family	Genera
Annonaceae	Annona, Duguetia, Guatteria, Unonopsis, Xylopia
Apocynaceae	Tabernaemontana
Araceae	Dieffenbachia
Aristolochiaceae	Aristolochia
Capparidaceae	Capparis
Clusiaceae (Guttiferae)	Caraipa
Cucurbitaceae	Cucurbita
Euphorbiaceae	Euphorbia, Hippomane, Hura
Fabaceae	Lonchocarpus
Gentianaceae	Lisianthus
Lauraceae	Ocotea
Phytolaccaceae	Petiveria
Piperaceae	Piper
Rutaceae	Fagara, Erythrochiton
Sapotaceae	Pouteria
Solanaceae	Capsicum, Nicotiana
Theophrastaceae	Jacquinia

Additives

While members of the Loganiaceae and Menispermaceae are the primary sources of activity in curares, from the numerous accounts dealing with the poison it is clear that a variety of other ingredients - among them other plant and animal products, as well as insects - have been included in their composition. It is not possible to discuss this aspect in detail here, but it is worth while drawing attention to certain of the plant additives (Table 3). Some, e.g the latex of **Euphorbia** and the juice of **Annona** and **Guat**teria species, are said to be used as adhesives. But members of the latter two genera, like certain of the other additives, also contain alkaloids; they may therefore have their own particular activities which can contribute to the overall effect; and the possibility of synergism must not be overlooked. Others, e.g Piper and Capsicum species, are often obligatory additives and it is supposed that through the presence of vasodilating constituents they help to promote absorption of the curarizing principles from the wound made by the dart or arrow.

CHEMISTRY

Alkaloid Composition of Strychnos Species

It is now well understood that the muscle-relaxant activity in **Strychnos** species is due mainly to the presence of bis-quaternary dimeric indole alkaloids, but in recent

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years these compounds have received comparatively little attention. Most investigations have focused on the accompanying range of mono-quaternary bases, which exhibit at best a rather weak curarizing action, and dimeric and monomeric tertiary alkaloids, which exhibit little or no such activity but may have other pharmacological effects.

| ! | Wieland-Gumlich aldehyde (closed form) | 2 | Wieland-Gumlich aldehyde (open form) (= Deacetyldiaboline) $R = CH_2OH$ |

!   Wieland-Gumlich aldehyde
     (closed form)

     R = H

1a   Diaboline

     $R = CO.CH_3$

2   Wieland-Gumlich aldehyde
    (open form)
    (= Deacetyldiaboline)
    $R = CH_2OH$

2a   18-Deoxy-Wieland-Gumlich aldehyde
     $R = CH_3$

2b   Wieland-Gumlich aldehyde metho salt
     (= Caracurine VII)
     $R = CH_2OH$, $\equiv N_b^+ - CH_3$

2c   18-Deoxy-Wieland-Gumlich aldehyde metho salt
     (= Hemi-dihydrotoxiferine = Dihydrofluoro-curarine)
     $R = CH_3$, $\equiv N_b^+ - CH_3$

2d   Fluorocurarine
   (= 2,16-Dehydro-18-deoxy-Wieland-Gumlich aldehyde metho salt)
     $R = CH_3$, $\equiv N_b^+ - CH_3$, $\Delta^{2(16)}$

The dimeric bases are derived from the three possible combinations of the monomeric units Wieland-Gumlich aldehyde [1/2] and 18-deoxy-Wieland-Gumlich aldehyde [2a] or the N_b-metho salts [2b] and [2c]. Wieland-Gumlich aldehyde (deacetyldiaboline) itself [1] has been obtained from a number of species, e.g. S. brachiata (Galeffi et al., 1973) S. diaboli, S. solerederi, and S. subcordata, and its N_b-metho salt, caracurine VII [2b] has been isolated from S. toxifera (Marini-Bettolo & Bisset, 1972). Cf. Table 4, which lists mainly those alkaloids used by Bauer in classifying curares.

Table 4. Selected alkaloids present in some **Strychnos** species used in curares (mostly from: Marini-Bettolo & Bisset, 1972).

Species	Alkaloids
Section **Strychnos**	
S. brachiata	Wieland-Gumlich aldehyde (Galeffi **et al.**, 1973)
S. erichsonii	Diaboline (Marini-Bettolo **et al.**, 1978)
S. jobertiana	Diaboline
S. mitscherlichii	C-Alkaloid D; C-calebassine, C-curarine fluorocurarine
S. sandwithiana	Wieland-Gumlich aldehyde
S. solerederi	Diaboline, Wieland-Gumlich aldehyde
S. solimoesana	C-Alkaloid D, 0,5% C-calebassine, 0,1% C-curarine (Marini-Bettolo **et al.**, 1978); C-alkaloids F and G; fluorocurarine, diaboline
S. tomentosa	C-Curarine; toxiferine, C-Alkaloid E
S. toxifera	Caracurines II and V, bisnor-dihydrotoxiferine; toxiferine
Section **Rouhamon**	
S. guianensis	C-Curarine
S. subcordata	Fluorocurarine, Wieland-Gumlich aldehyde
Section **Breviflorae**	
S. castelnaeana	C-Alkaloid D, diaboline (delle Monache **et al.**, 1970)
Section **Rouhamon** - Africa	
S. usambarensis	Dihydrotoxiferine, C-calebassine, C-curarine;afrocurarine; fluorocurarine (Angenot **et al.**, 1975; Caprasse **et al.**, 1981)
Section **Strychnos** - Asia	
S. ignatii	Toxiferine-type and/or caracurine-type bases; bisnor-toxiferine (Bisset **et al.**, 1977)

The monomers readily undergo dimerization. Thus, heating Wieland-Gumlich aldehyde [1/2] in acetic acid-sodium acetate or pivalic acid leads to the formation mainly of caracurine V [3] together with a little bisnor-toxiferine [4]. On heating caracurine V in acetic acid in the absence of oxygen or its hydrochloride salt in distilled water at pH 6.7 it isomerizes to bisnor-toxiferine; brief warming with methanolic hydrochloric acid reverses the process. Similarly, with the corresponding N_b-metho compound [2b], under very mild acid conditions an equilibrium is set up which lies predominantly on the side of the toxiferine [4e].
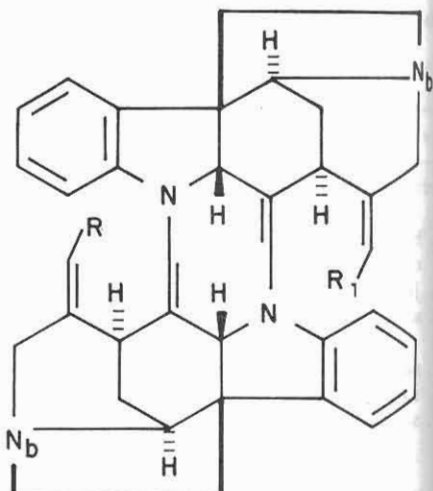
H

N
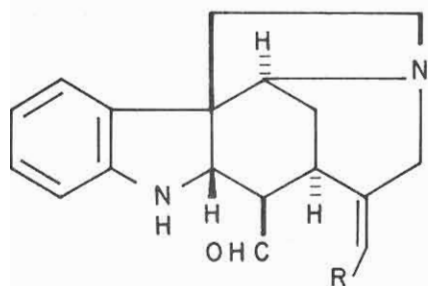
2/2a

2b/2c

Bis-tertiary base:
3   Caracurine V

H

N_b

R

H

H

R_1

H

H

N

N_b

H
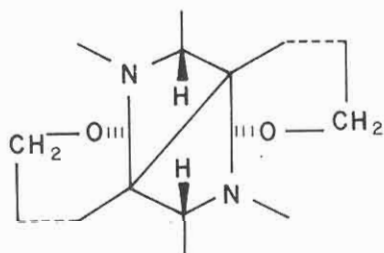
Bis-tertiary bases:
4   Bisnor-dihydrotoxiferine
       $R = R_1 = CH_3$

4a   Bisnor-C-alkaloid H
       $R = CH_3$, $R_1 = CH_2OH$

4b   Bisnor-toxiferine
       $R = R_1 = CH_2OH$

Bis-quaternary bases [$2 \times N_b^+-CH_3$]:
4c   Dihydrotoxiferine
       $R = R_1 = CH_3$
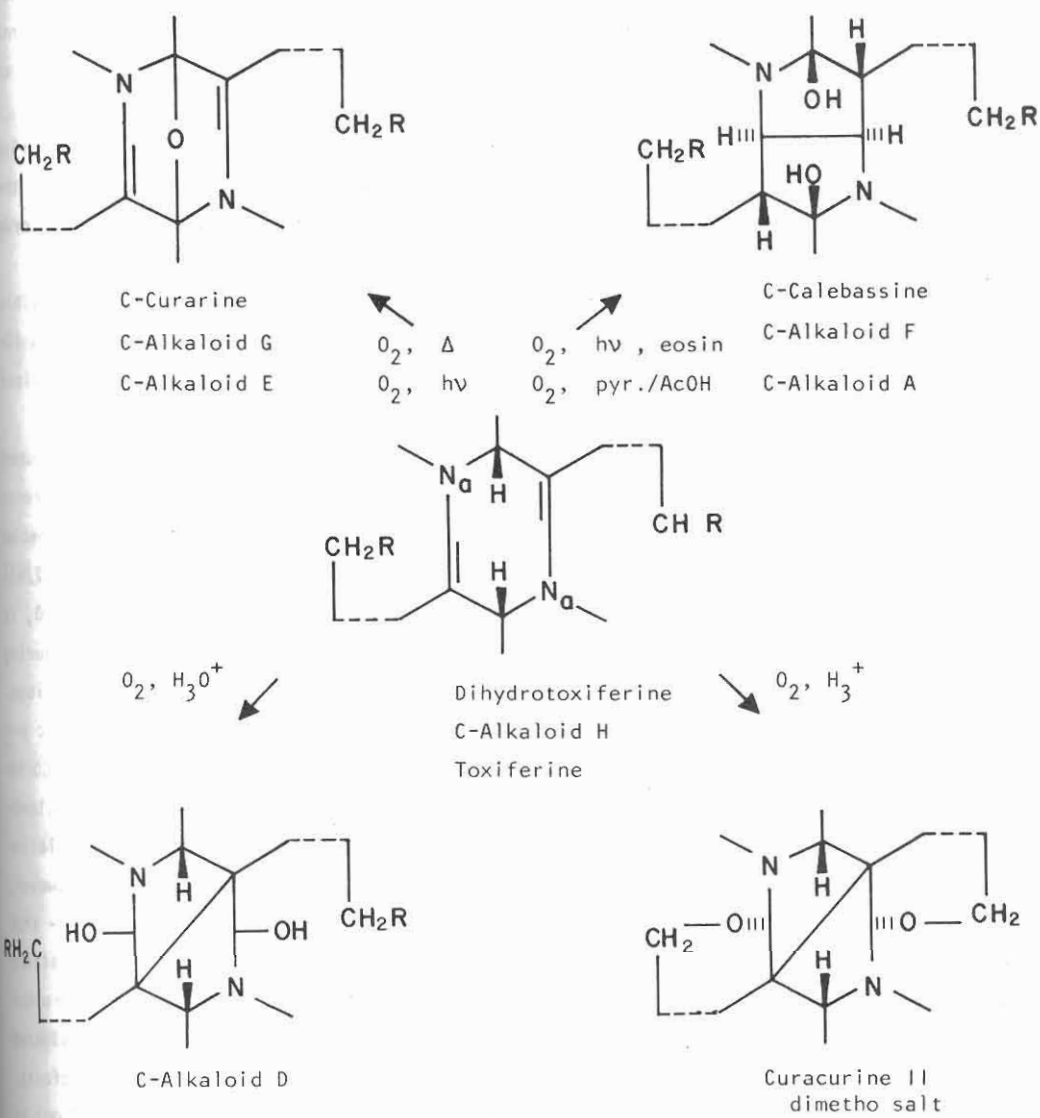
4d   C-Alkaloid H
       $R = CH_3$, $R_1 = CH_2OH$

4e   Toxiferine
       $R = R_1 = CH_2OH$

Acid hydrolysis of dihydrotoxiferine [4c] under oxygen-free conditions yields the metho salt of 18-deoxy-Wieland-Gumlich aldehyde (= hemi-dihydrotoxiferine = dihydrofluoo curarine [2c] and treatment with dilute acetic acid converts it back to the dimer.

FIG. 2. Effect of heat, light, and acid, in the presence of oxygen, on the dimeric Strychnos alkaloids.

These dimeric compounds readily undergo further chemical change, depending on the conditions of pH and heat and on the presence or absence of oxygen. In the presence of oxygen, the central ring of the dimeric bases undergoes changes in oxygenation level (see Fig. 2). Thus, toxiferine gives rise to caracurine II dimetho salt, C-alkaloid E and C-alkaloid A; while dihydrotoxiferine furnishes C-alkaloid D, C-curarine, and C-calebassine, as well as a number of further oxidation products of as yet unknown structure.

The hybrid C-alkaloid H [4d] yields C-alkaloids G and F. Although, as indicated above, dihydrotoxiferine (and also toxiferine and C-alkaloid H) can be cleaved with acid into the corresponding monomers, the more highly oxidized derivatives undergo a series of isomerizations instead.

On heating at 60° with concentrated hydrochloric acid for 5 hours, C-curarine breaks down to, among other things, fluorocurarine [2d], a frequent component of the alkaloid mixtures from **Strychnos** species, e.g. **S. trinervis, S. solimoesana, S. subcorda ta, S. tomentosa**, etc Cf. Table 4.

With ordinary methods of extraction, i.e. using acid, it is usually not possible to isolate bisnor-dihydrotoxiferine [4], because, in addition to being cleaved to 18-deoxy-Wieland-Gumlich aldehyde (nor-hemidihydrotoxiferine = nor-dihydrofluorocurarine) [2a], it is highly labile and readily isomerized and oxidized.

A more detailed treatment of the cleavages, oxidations, and isomerizations discussed briefly in the foregoing paragraphs is given by Gorman **et al.** (1971). Their occurrence makes it abundantly clear why the alkaloid composition of extracts from **Strychnos** species and from curares prepared with them are so complex. Since, according to Bauer (1962/63) aqueous solutions of curares tend to be acid, with pH values ranging from 4.5 to 6.0, it is not surprising that considerable changes in the alkaloid composition take place during the long boiling that most methods of preparation require for concentrating the poison.

As regards artefact formation, dimers that are readily formed from monomeric precursors under mild conditions are obvious candidates. Among the examples cited by Gorman **et al.** (1971) are dihydrotoxiferine [4c] and toxiferine [4e]; since 18-deoxy-Wieland-Gumlich aldehyde metho salt [2c] dimerizes so rapidly to dihydrotoxiferine, the isolation of the latter compound from an extract is no proof of its occurrence in nature. However, these authors also suggest - although the grounds on which they do so are clear - that the presence of C-calebassine as a main alkaloid does indicate the natural existence of dihydrotoxiferine. C-alkaloid E and C-curarine are readily formed by oxidation under mild conditions from toxiferine and dihydrotoxiferine, respectively, but are considered to have been isolated under conditions which do not suggest that they are artefacts. However, control experiments to test these suggestions have not yet been carried out. In this connection it is of interest to note that Biocca **et al.** (1965) have identified C-curarine as one of the principal bases in a sample of arrow-tip curare, which is usually produced under relatively mild conditions.
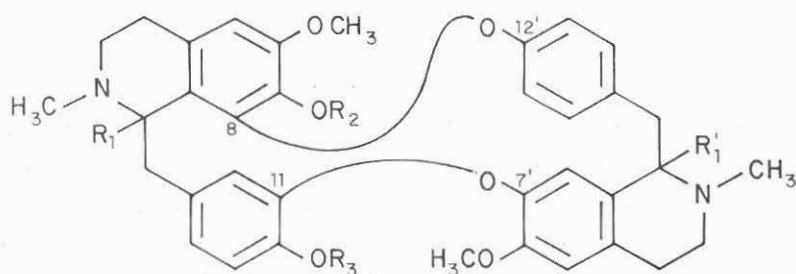
<u>5</u> (-)-Curine [(-)-Bebeerine]

$R_2 = R_3 = H; R_1 = R_1' = --- H \underline{(R,R)}$

5a (+)-Curine [(+)-Bebeerine, Chondrodendrine]

$R_2 = R_3 = H; R_1 = R_1' = H \underline{(S,S)}$

5b Chondrocurine (+)-Tubocurine

$R_2 = R_3 = H; R_1 = ---H, R_1' = \rightarrow H \underline{(R,S)}$

5c (-)-Tubocurine

$R_2 = R_3 = H; R_1 = \rightarrow H, R_1' = \cdots H \underline{(S,R)}$

5d Chondrofoline

$R_2 = CH_3, R_3 = H; R_1 = R_1' = \rightarrow H \underline{(S,S)}$

5e 12-O-Methylcurine

$R_2 = H, R_3 = CH_3; R_1 = R_1' = ---H \underline{(R,R)}$

5f 12-O-Methylcurine

$R_2 = H, R_3 = CH_3; R_1 = R_1' = \rightarrow H \underline{(S,S)}$

5g O,O'- Dimethylcurine

$R_2 = R_3 = CH_3; R_1 = R_1' = ---H \underline{(R,R)}$
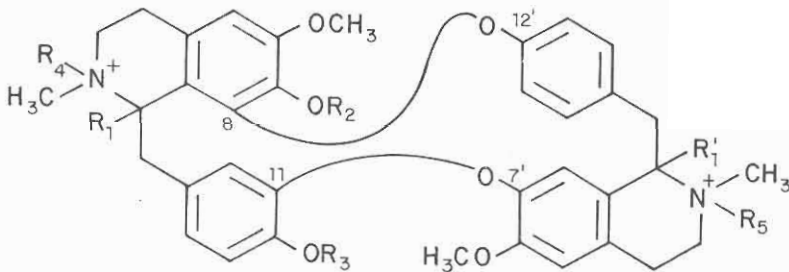
<u>6</u> (+)-Tubocurarine

$R_2 = R_3 = R_5 = H, R_4 = CH_3; R_1 = ---H, R_1' = \rightarrow H \underline{(R,S)}$

6a (-)-Tubocurarine

$R_2 = R_3 = R_5 = H, R_4 = CH_3; R_1 = H, R_1' = ---H \underline{(S,R)}$

6b (+)-Chondrocurarine

$R_2 = R_3 = H, R_4 = R_5 = CH_3; R_1 = ---H, R_1' = \rightarrow H \underline{(R,S)}$

6c N,O,O'-Trimethyl-(+)-tubocurarine [Metocurine]

$R_2 = R_3 = R_4 = R_5 = CH_3; R_1 = ---H, R_1' = \rightarrow H \underline{(R,S)}$

6d (+)-Isotubocurarine

$R_2 = R_3 = R_4 = H, R_5 = CH_3; R_1 = ---H, R_1' = \rightarrow H \underline{(R,S)}$

Alkaloids of the Triclisieae - Chondrodendron, Curarea, and Sciadotenia

It has long been recognized that the alkaloids occurring in **Chondrodendron** and **Curarea** species are bisbenzylisoquinolines. A variety of bis- and mono-quaternary and bis-tertiary derivatives have been found, in which the two halves are joined head-to-tail through two ether linkages: in the curine skeleton between 8-12' and 11-7' [cf. 5] and in the isochondrodendrine skeleton between 8-12' and 12-8' [cf. 7].   Again, it is the quaternary derivatives that are the main active principles. Cf. Table 5.

Table 5. Occurrence of bisbenzylisoquinoline alkaloids in **Chondrodendron** and **Curarea** species.

Species	Plant part[a]	Alkaloids present	References
Chondrodendron			
Ch. platiphyllum	r	(+)-Isochondrodendrine,(+)-curine	King (1940)
	st	(-)-Curine	King (1940)
	l	(+)-Isochondrodendrine,(-)-curine, (-)-chondrofoline	King (1940) Baldas et al.(1971)
Ch. microphyllum	r	(+)-Isochondrodendrine,(+)-curine	King (1940)
Ch. tomentosum	st	(+)- and/or (-)-Tubocurarine, (+)-chondrocurarine,(+)-and/or (-)-curine, (+)-chondrocurine, tomentocurine, cycleanine, N-benzylphthalimide	Bick & Clezy (1960) Dutcher (1946,1952) King (1947,1948), Wintersteiner I Dutcher (1943)
Curarea			
Cu. candicans	st	(+)-Curine, (+)-isochondrodendrine	King (1940)
Cu. toxicoferum		(-)-Curine, (-)-chondrocurine, (+)-isochondrodendrine	Cava et al.(1969)
Cu. tecunarum	w	(+)-Isochondrodendrine, 2 other bases	Barltrop & Jeffreys (1954)

[a] l = leaves, r = root, st = stem, w = wood.

In recent years there has been little advance in our knowledge   of the alkaloid composition of these plants, and the only reported natural source of (+)-tubocurarine [6] is still the single species **Ch. tomentosum**. A second noteworthy point is the proof well established by n.m.r. (Everett **et al.**, 1970; Koike **et al.**, 1981) and X-ray crystal

lographic (Codding & James, 1972; Reynolds **et al.**, 1975) studies, that this compound is a mono- rather than a bis-quaternary alkaloid [6]; this structural revision has necessi tated some adjustment to the theoretical understanding of the mechanism, of its muscle- relaxant action.
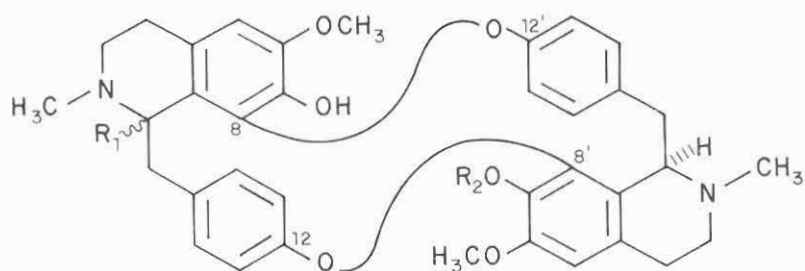
| 7 | Isochondrodendrine | R_2 = H; R_1 = --- H | (R, R) |
| 7a | Sciadenine | R_2 = CH_3; R_1 = ⟶H | (S, R) |
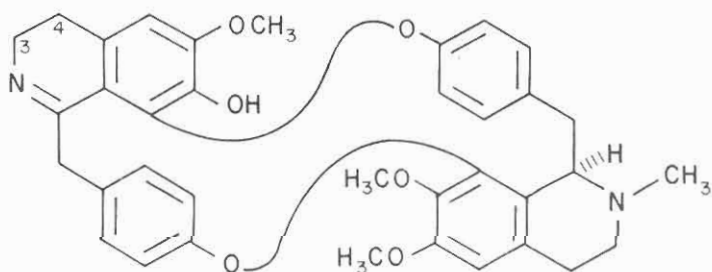
8 Sciadoline

8a Sciadoferine Δ^3

Sciadotenia toxifera has furnished several bisbenzylisoquinoline derivatives with the isochondrodendrine skeleton [7]. These include such compounds as sciadoline [8] and sciadoferine [8a], with an imino grouping, as well as bases of the (R,R) series, like isochondrodendrine [7] itself, and of the (S,R) series, like sciadenine [7a] (Galeffi et al., 1978; Takahashi & Cava, 1976; Takahashi et al., 1976).
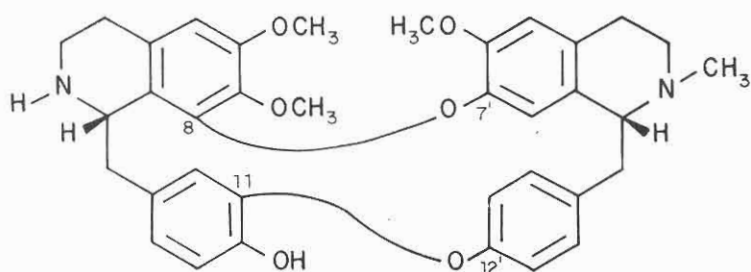
9 Peinamine (S, R)
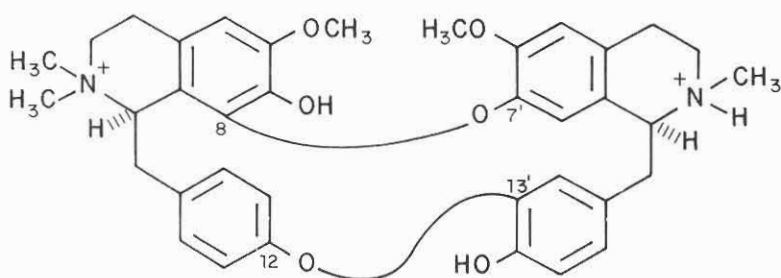
10 Macoline (R, S)

Alkaloids of the Anomospermeae - Abuta, Anomospermum, and Telitoxicum

Perhaps the most significant find in regard to the genus **Abuta** is the isolation by Galeffi and Marini-Bettolo (1977) from the stem wood of Ab. **grisebachii**, in addition to the main bis-tertiary base peinamine [9], of the monoquaternary macoline [10] and its 7-0-demethyl and N-methyl-0-demethyl derivatives. Since peinamine has also been obtained from an arrow-tip curare, it is very likely that the curare was made with material of this plant (Galeffi et al., 1977a, b). In contrast with the alkaloids discussed in the previous section, these compounds have the two benzylisoquinoline moieties joined head-to-head and tail-to-tail through an 8-7' and an 11-12' or 12-13' ether bridge, respectively.
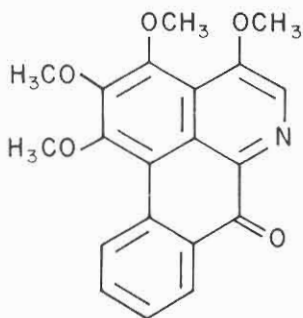
11 Imenine
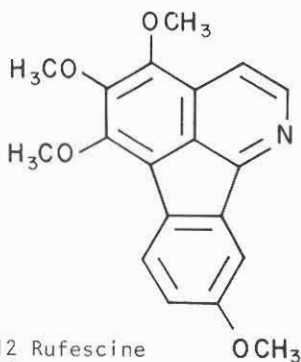
12 Rufescine
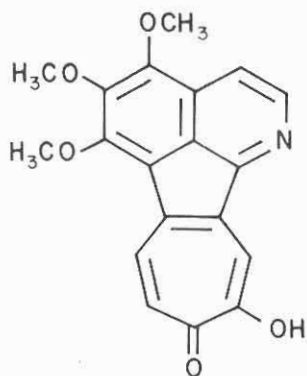
13 Grandirubrine

14 Saülatine

The other **Abuta** species listed in Table 2 have also been investigated,   and they have been shown to contain a variety of oth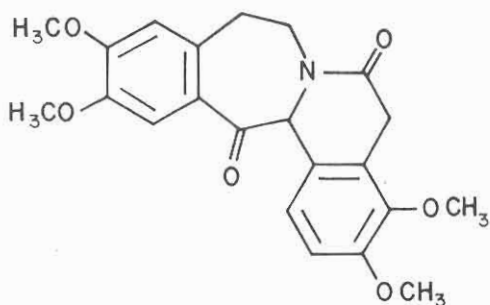er dimeric bases (Ahmad & Cava, 1977;Cava et al., 1969; Saá et al., 1976), all of which are bis-tertiary   compounds, as   well as oxoaporphines (Cava et al., 1972, 1975b; Glick et al., 1969; Skiles et al., 1979), such as imenine [11], and azafluoranthenes (Cava et al., 1972, 1975b), among   them rufescine [12]. More recently, the tropoloisoquinoline grandirubrine [13] has been obtained from the species **Ab. grandifolia** (Menachery & Cava, 1980) and an isohomoprotoberberine saüla tine [14] has been isolated from the roots of **Ab. bullata** (Hocquemiller et al., 1984).

Although **Anomospermum grandifolium** contains quaternary alkaloids with curarizing activity (King, 1948), contrary to the assertion of Guha et al. (1979) none of them has been identified.

The only species of **Telitoxicum** that has been investigated,T.peruvianum, contains oxoaporphines and azafluoranthenes which are the same as or similar to those   occurring in **Abuta** species (Menachery & Cava, 1981).

Alkaloids of the Cocculeae - Cissampelos

So far, only bis.tertiary bisbenzylisoquinolines with the two halves arranged head-to-tail and joined through 8-12' and 12-7' ether bridges have been found in **Cissampelos ovalifolia** (Snedden et al., 1970). On the other hand, most of the bisbenzylisoquinolines present in **Ci. pareira** are curine derivatives and among those isolated are 0.3% (-)-curine [5] and a small amount of (+)-12-0-methylcurine [5f] (Haynes et al., 1966;see also:Guha et al., 1979).

ALKALOID-CONTAINING CURARE ADDITIVES

Alkaloids, mostly isoquinoline derivatives, are found in several   other   plants entering into the composition of curares, and this has to be borne in mind   when   assessing the possible contribution these ingredients may make to the overall   effects of the curares into which they are incorporated. The topic requires more space than can be devoted to it here.

In the case of the five genera of Annonaceae listed in Table 3 they are   known to contain a broad range of such compounds. Thus, **Annona** and **Xylopia** have berberines and

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tetrahydroberberines,along with benzylisoquinolines and several groups of aporphinoids; Du-guetia species are also known to have aporphinoids presente (The Allaloids,1971/83). Several species of **Guatteria** have been examined and, in addition to the presence of various tetrahydroberberines and aporphinoids (Hocquemiller **et al.**, 1983), the stem bark of one of them, **G. megalophylla**, has been found to contain (+)-isochondrodendrine [7], (-)-12' -O-methylcurine [5e], and 0,0-dimethylcurine [5g] (Galeffi et al., 1975).**G.veneficiorum** originally described by von Martius as an adjunct to the curare of the Jurí,a now extinct western Amazonian tribe, has since been transferred to the genus Unonopsis, representa tives of which have recently been shown to contain (-)-curine [5], as well as a benzyl isoquinoline and tetrahydroberberine and several aporphinoids and phenanthrenes(Eltohani et al., 1984)

Numerous species of **Tabernaemontana**, a genus which belongs to the Apocynaceae,have been examined and an enormous variety of indole alkaloids, some of which are highly active pharmacologically, have been isolated. A detailed review has recently appeared (Van Beek **et al.**, 1984).

The Aristolochiaceae contain a mixture of alkaloids comprising aristolochic acids aristolactams, and related compounds, as well as phenanthrenes, aporphinoids,and dioxoa porphines (The Alkaloids, 1971/83).
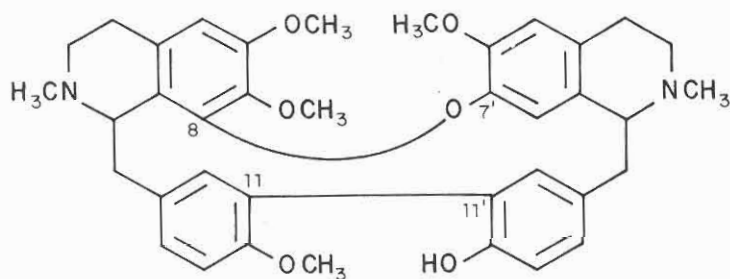
15 Rodiasine

Ocotea, of the family Lauraceae, is one of many genera which are rich sources of various groups of isoquinoline alkaloids; and the fruits of one species,O. **venenosa**,pro vide an ingredient for one of the arrow poisons preparaed by the Kofán Indians of eastern Ecuador and Colombia. The seeds and bark of this species contain at least eight alka-loids. These include rodiasine [15] and a demethyl derivative, which, unlike the other dimeric isoquinoline bases mentioned so far, have an 8-7'-ether bridge and an 11-11'-biphenyl bridge joining the two halves (Kostermans **et al.**, 1969; Murthy & der Mardero-sian, 1973). Other **Ocotea** species contain benzylisoquinolines, morphinans, and various aporphinoids (The Alkaloids, 1971/83).

PHARMACOLOGY

It is not possible within the limits of the present paper to do more than briefly discuss a few selected aspects of the pharmacology of the active principles present in curare. The role of the poison and its alkaloids in the development of modern muscle-relaxants is also considered.

Toxicity of Curares

Over a period of almost 20 years, Bauer (1962/63; 1965a, b; 1969; 1971a, b; 1981) and Bauer & Fondi (1962) have determined the head-drop and lethal doses in white mice of more than 100 museum samples of curare covering most of the region where the poison is made. Their findings are summarized in Table 6.

Table 6. Head-drop and lethal doses of curares in the white mouse (Bauer, 1962/63; 1965a, b; 1969; 1971a, b; 1981; Bauer & Fondi, 1962; Biocca et al., 1965).

Type of curare (Main alkaloids)	Head-drop dose mg/kg	Lethal dose mg/kg
Calabash		
C-Curarine/C-calebassine	2-10	>2-15
Toxiferine	2[a]	-
Tubocurarine	1-10	-
Pot		
C-Curarine/C-Calebassine	0.2-15	4-20
Toxiferine	0.5-4	0.8-6
Toxiferine/tubocurarine	0.5-4	1-6
Tubocurarine	1-15	2-25
Tube		
C-Curarine/C-Calebassine	5[a]	10
Tubocurarine	2.5[a]	5
Arrow-tip		
C-Curarine/C-Calebassine	1.0-1.2	2.75-5

[a]Results from only one sample.

Curares containing toxiferine tend to be the most active and, usually, those whose main alkaloids are C-curarine/C-calebassine or (+)-tubocurarine are somewhat less active. It is also noteworthy that the (two) samples of arrow-tip curare tested are among the strongest poisons. Some of the oldest curare samples examined still rank with the most

powerful. Thus, two samples of toxiferine-based poison from the western Brazilian Amazon region, one a Jurí Indian product collected by von Martius in 1820, and the other a Mayoruna Indian preparation obtained by Natterer in 1830, were assayed by Bauer and Fondi (1962) and found to have an LD_{100} in white mice of, respectively, 1 and 0.8 mg/kg. A calabash curare from southern Venezuela, of Mainatari origin, also collected by Natterer in 1830 proved to have C-curarine/C-calebassine as principal alkaloids and an LD_{100} of 4 mg/kg. Bauer (1971a) examined a sample of the famous Tikuna curare, collected by de Castelnau in 1846, and determined LD_{100} 1 mg/kg; the product contained mainly **Chondrodendron** alkaloids, including (+)-tubocurarine, along with some toxiferine and other **Strychnos** alkaloids (Bauer, 1971b; delle Monache **et al.**, 1970).

It is often asserted by the Indians themselves that curare must be stored under dry conditions if it is to keep its activity; and it is believed that curare filled into pots, allowed to dry, and then well sealed does not lose its activity as readily as do the softer and more paste-like or syrupy products that are poured into calabashes or bamboo tubes (Vellard, 1965). The findings of Bauer and Fondi (1962) cited above confirm that curares kept under dry conditions are very stable and do not lose their activity. Although a number of experiments carried out by them to determine the effect of humidity on curare did not demonstrate any drop in activity, it seems likely that the experimental period - 30 days at 100% humidity - was not long enough, particularly with curares that were already hard and dry.

A number of authors (Biocca, Lazzarini Peckolt) have attributed particular functions to certain of the components added during the preparation of curare. It has been suggested for example, that some of them aid liberation of the alkaloids and that others augment the activity by bringing about N-methylation and hence the formation of additional quaternary ammonium groups. That this is not always necessary is amply demonstrated by certain Yanomano and Nambikuára curares, as well as the **Chondrodendron** curare produced on a large scale in Peru in the basin of the river Huallaga, all of which derive from material of a single plant (Galeffi **et al.**, 1977a; Vellard, 1965).

Table 7. Effect of methyl-iodide treatment on the toxicity of quaternary-alkaloid extracts in white mice (Marini-Bettolo **et al.**, 1967).

Material	LD i.v. before MeI treatment mg/kg	LD i.v. after MeI treatment mg/kg
Makú curare (**Chondrodendron**-based)	0.3	0.3
Wood of **Chondrodendron sp.**	25.0[a]	1.25
Yanomano curare (**Strychnos**-based)	1.2	2.5
Bark of **Strychnos sp.**	0.3	1.25

[a] The alkaloids had been extracted 20 years previously.
Alkaloids freshly isolated from wood of the same batch after storage at ambient temperature for 20 years had LD i.v. 30.0 mg/kg before and after methyl-iodide treatment, indicating that period of time the wood had lost a considerable proportion of its active principles.

As shown in Table 7, Marini-Bettolo et al. (1967) found that the quaternary bases from a sample of Makú curare from the upper R. Negro were about 100 x as toxic as those extracted directly from the plant material. Evidently, the procedure used in making the curare is responsible for this huge increase in activity. Attempted N-methylation of the two quaternary-base extracts did not change the toxicity of that from the curare but brought about a 20 x increase in that from the plant material. Seemingly, there is a considerable proportion of mono-quaternary (or bis-tertiary) bisbenzylisoquinoline alkaloids still present which can undergo quaternization. On the other hand, there were relatively minor changes in the toxicities of the quaternary-alkaloid fractions from a Yanomano curare from the R. Cauaburi and from the **Strychnos** bark used in its preparation. It appears that there are little or no mono-quaternary (or bis-tertiary) dimeric indole bases present that are able to undergo further methylation.

MUSCLE-RELAXANT ACTIVITY OF CURARE ALKALOIDS

The bis-quaternary dimeric alkaloids found in **Strychnos** species (see Fig. 2) are highly active muscle-relaxants: the three parent bases - dihydrotoxiferine, C-alkaloid H, and toxiferine - cause head-drop in mice at i.v. dose levels of, respectively, 30, 16, and 9 mcg/kg; while the three compounds with the 2,2'-oxide function - C-curarine, C-alkaloid G, and C-alkaloid E - are even more active and require 30, 5, and 4 mcg/kg. In contrast, the C-calebassine group of derivatives have considerably less activity. Within each set of compounds the most polar member is also the most powerful. LD_{100} for these compounds is generally about twice the head-drop dose (Waser, 1972).

The bisbenzylisoquinoline alkaloid (+)-tubocurarine, now recognized as a mono-quaternary compound [6], is less active than the parent bis-quaternary indole bases and it has a head-drop dose in the mouse of about 100 mcg/kg (Waser, 1972). For man, the head-drop dose is about 150 mcg/kg. In the 0,0'-dimethyl derivative the potency is raised by a factor of 1.5-3 and in the N,0,0'-trimethyl compound, metocurine [6c], by a factor of 2-3. The weak activity exhibited by (-)-tubocurarine [6a] emphasisez the importance of steric factors in the interaction with the receptors. Bis-quaternized (+)-isochondrodendrine [cf. 7] also shows little activity (Waser, 1972). Although a bis-tertiary alkaloid, rodiasine [15] is reported to exhibit neuromuscular effects similar to those of (+)-tubocurarine (Murthy & der Marderosian, 1973).

Mechanism of action

The mechanism of action of toxiferine and (+)-tubocurarine and related compounds is of the competitive or non-depolarizing type, i.e. they compete with acetylcholine for recognition sites on the acetylcholine receptor channels. Each channel has two binding sites; and while the channel will open when only one site is occupied by an agonist, it is more likely to do so when they are both occupied. However, these recognition sites are relatively non-specific, since not only agonists but also antagonists can bind to them. Such substances, e.g. (+)-tubocurarine and related compounds, unlike acetylcholine do not bring about opening of the ionic channel. In addition to binding to and blocking

the recognition sites, they can also block open ionic channels. See further:Cavallito (1980), Lambert **et al.** (1983), Wray (1980).

The bis-quaternary indole alkaloids have a rigid cage-like structure and in the case of curarine (cf. Fig. 2), one of the pharmacologically more active bases, the distance between the two quaternary nitrogens is 8.50 Å (Jones & Nowacki, 1972).

(+)-Tubocurarine [6] in acid solution, and in the body, is protonated; it is therefore able to function as a doubly charged cation and is the reason why its neuromuscular blocking potency is pH-dependent. X-Ray crystallographic studies have shown that the conformations adopted by (+)-tubocurarine in the dichloride (Codding & James, 1972) and dibromide (Reynolds **et al.**, 1975) salts are somewhat different, with the inter-onium distance fixed at 10.7 Å and 8.97 Å, respectively. The aromatic rings of the two benzyl moieties are oriented perpendicular to the tetrahydro-isoquinoline rings. N.m.r. work on various curine derivatives, including (+)-tubocurarine dichloride, indicates that in solution the disubstituted benzene ring has some degree of rotational freedom unlike the trisubstituted one which is fixed because of its **meta**-attachment.The solution conformat ion of the dichloride is similar to the crystal conformation determined for the dibromide and the N,0,0,'-trimethylated derivative metocurine [6c]. This has an almost entirely hydrophobic concave surface and a hydrophilic convex surface with the six ether oxygens lying along a fold which divides the molecule into two halves (Sobell **et al.**, 1972).

The molecular disposition of these bisbenzylisoquinolines **in vivo** is not known; and while it is probable that it is the hydrophilic side that will become fixed to the protein of the receptor site, simultaneous attachment of the two charged nitrogen atoms appears unlikely, since they are on opposites sides of the molecule. The alternative suggestion has been made that the protonated nitrogen could exert an electrostatic repulsion on acetyl choline (cf. Reynolds **et al.**, 1975).

Soine and Naghaway (1974) have prepared (+)-isotubocurarine [6d] in which, as compared with (+)-tubocurarine, the positions of the quaternized and tertiary nitrogens are re- versed. The neuromuscular blocking activity, determined in the cat tongue-hypoglossal nerve preparation, is ca. 0.03 mg/kg for the iso-compound and ca. 0.07 mg/kg for (+)- tubocurarine itself. The difference is receptor-related and not due to preferential inhi bition of acetylcholine. It is concluded that situating the quaternized function next to the S-centre endows the molecule with greater potency; also these authors question the role of protonation of the tertiary amine moiety.

SYNTHETIC MUSCLE-RELAXANTS

Non-depolarizing drugs

Modification of the highly potent toxiferine molecule by replacing the two N_b- methyl groups with N_b-allyl functions produced the semisynthetic compound alcuronium or alloferine (Gorman et al., 1971; Schlittler, 1971) which is in use as a short-lasting muscle-relaxant in minor surgery; it is somewhat more potent than (+)-tubocurarine.

The original formulation of (+)-tubocurarine as a bis-quaternary alkaloid, a structure

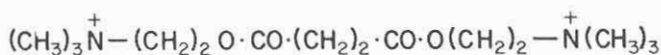now known to be that of chondrocurarine [**6b**], focused attention on this typy of compound and through the early work of Bovet and others (see: Bovet, 1959) led to the successful introduction into clinical practice of the synthetic gallamine triethiodide or flaxedil [**16**], a muscle-relaxant of moderate duration - a so-called pachycurare; it is still in use.

$$OCH_2CH_2\overset{+}{N}CH_2CH_3$$
$$OCH_2CH_2\overset{+}{N}CH_2CH_3$$
$$OCH_2CH_2\overset{+}{N}CH_2CH_3$$

16 Gallamine (Flaxedil)

$$(CH_3)_3\overset{+}{N}-(CH_2)_{10}-\overset{+}{N}(CH_3)_3$$

17 Decamethonium

$$(CH_3)_3\overset{+}{N}-(CH_2)_2\,O\cdot CO\cdot(CH_2)_2\cdot CO\cdot O(CH_2)_2-\overset{+}{N}(CH_3)_3$$
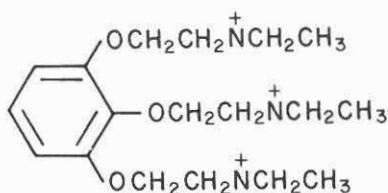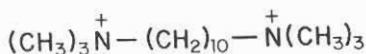
18 Suxamethonium

Depolarizing drugs

Simpler molecules with two positively charged centres like decamethonium [**17**] and esters of the suxamethonium (or succinylcholine) type [**18**] and their analogues were also shown to be muscle-relaxants (Bovet, 1959), but with a rather short period of action (so-called leptocurares). Both decamethonium and suxamethonium have been used in surgery; and while decamethonium has been largely superseded, suxamethonium because of its brief duration of action - a few minutes only - is still used in minor surgical procedures.

Compounds like decamethonium and suxamethonium operate by a depolarizing mechanism i.e. by mimicking the effects of acetylcholine itself, which when present for long enough in high concentration causes blockade by preventing action potentials being propagated away from the zone surrounding the motor end-plate. In the case of acetylcholine, hydrolysis by cholinesterases soon puts an end to its effects, but decamethonium and suxamethonium are more tightly bound to the receptor and they are more resistant to hydrolysis. In homo logues of these two compounds, particularly when N-methyl groups are successively replaced by N-ethyl groups, the depolarizing mode of action may gradually give way to a non-depolarizing mechanism (Bowman & Rand, 1980).

Curare - botany ...

Some more recent developments

Among the generally recognized requirements for a muscle-relaxant for use in surgery (Bowman & Rand, 1980) are the following:

1. It should be non-depolarizing, i.e. competitive, in action; in other words, it should be capable of being displaced by large doses of the natural neurotransmitter acetylcholine. This allows the anaesthetist full control in reversing the blockade, and hence the muscle paralysis, in an emergency or at the end of an operation.

2. It should have a high specificity for the neuromuscular junction and it should not exert cardiovascular effects.

3. A rapid of action is desirable for use in emergencies.

4. Consistency of response is important, with a combination of short duration of action, non-cumulative response on repeat doses, and rapid recovery, which should not be affected by the clinical status of the patient.

These criteria demonstrate a clear preference for muscle-relaxants of the non-depolarizing type. Those with a depolarizing-type of action type suffer from a number of disadvantages: like acetylcholine, their initial response before paralysis sets in is to stimulate muscle contraction and this can cause severe post-operative muscle-pain and cramp. It also means that there is a prolonged period during which the muscle is unable to respond to stimulation and the effects of the muscle-relaxant are not readily reversed by anticholinesterases such as neostigmine.

Increased knowledge of the structural requirements for non-depolarizing neuromuscular-blocking drugs has laid the basis for a less empirical and more positive approach to the design of such drugs. Thus, in striving to produce second- and third-generation muscle-relaxants which will fulfil the above criteria the following design features are among those which have been taken into account (Bowman & Rand, 1980):

1. Ammonium, i.e. quaternary nitrogen, rather than other onium functions, as they afford greater blocking power.

2. Bis- rather than mono-quaternary structure tends to be more potent.

3. The two nitrogen atoms should be separated by a distance of about 11 Å to give maximum neuromuscular- rather than ganglion-blocking potency.

4. Bulky molecule and bulky substituents on the nitrogens in order to favour a non-depolarizing mode of action.

5. Inclusion of acetylcholine-like moieties to allow hydrolysis and also to increase affinity for the appropriate receptors.

Another South American plant that has played a small but significant part in the development of present-day muscle-relaxants is **guachamacá**. Most reports on this plant, which has the reputation of being very deadly, have come from different parts of Vene-

zuela, and it was tentatively identified about a century ago as a species of **Malouetia** (Apocynaceae); more recent gatherings of the plant have been assigned to **Malouetia** as well as to **Tabernaemontana** (also Apocynaceae) (Bisset, 1958; Khuong-Huu-Lainé **et al.** 1965). There is in addition one report, by Crevaux (1883) and based on hearsay infor mation he obtained in 1881, that Salivá Indians living on a tributary of the Rio Vichada in Colombia used the violent poison **guachamacá** on their arrows.

Early work on **guachamacá** led to the isolation of an alkaloidal substance with cu- rare-like properties (Bisset, 1958). Most species of **Malouetia** are found in tropical South America, but there are 2-3 species which occur in Central Africa; and from one of these, **M. bequaertiana** from Zaire, a bis-quaternary steroidal base malouetine [19] has been obtained which in the rabbit elicits head-drop at ED_{50} 0.15 mg/kg - a dose level similar to that of (+)-tubocurarine (Khuoung-Huu-Lainé & Pinto-Scognamiglio, 1964). Al though South American **Malouetia** species are indeed known to exhibit muscle-relaxant ac tivity, none of the compounds responsible has yet been isolated.

19   Malouetine
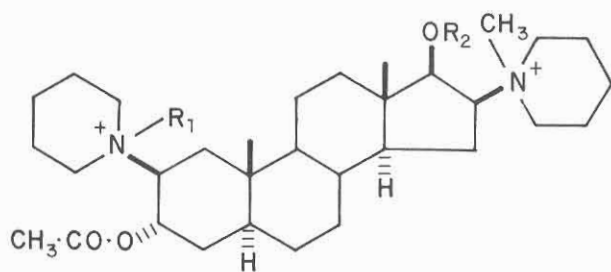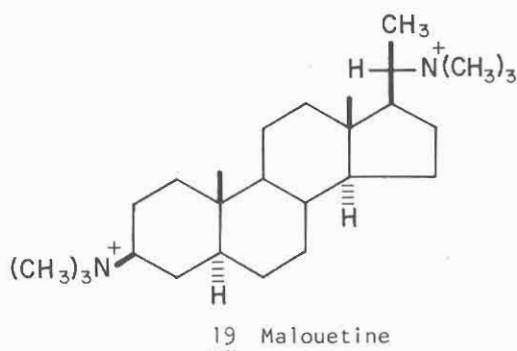
20   Pancuronium $R_1 = CH_3$, $R_2 = CO.CH_3$

20a Dacuronium $R_1 = CH_3$, $R_2 = H$

20b Vecuronium (ORG NC 45) $R_1 = H$, $R_2 = CO.CH_3$

In attempting to satisfy these desiderata, comparison of a steroid derivative known to have a moderate degree of neuromuscular blocking activity, and having 3α-acetoxy and

2β-N-methylpiperidinium substituents simulating an acetylcholine moiety, with the semi-rigid structures of (+)-tubocurarine [6] and malouetine [19] suggested that addition of a second simulated acetylcholine moiety in ring D would improve improve activity (Buckett et al., 1973).Such considerations culminated in the synthesis and development of pancuronium [20], the required dose of which is about one-fifth of that of (+)-tubocurarine. In it the bulk is supplied by the steroid skeleton, which also situates the nitrogen functions at about the correct distance from each other, and bulky substituents and acetylcholine-like moieties are provided by the N-methylpiperidinium groups. Among the newer drugs of this type are the bis-quaternary dacuronium [20a] and the mono-quaternary vecuronium [20b] (Bowman, 1980; Symposium, 1980; Tannières-Ruffié & Vourc'h, 1983).
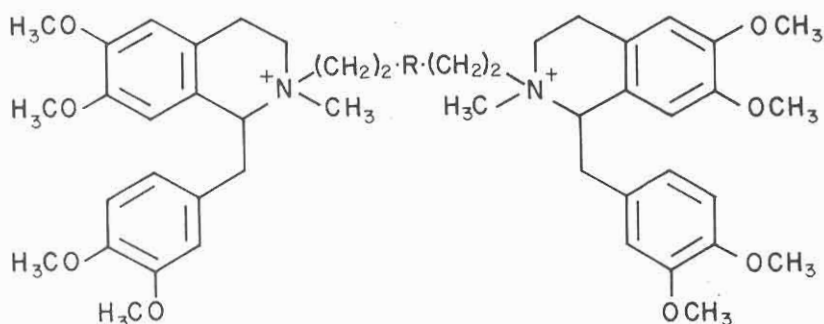
21 Laudexium R = $(CH_2)_6$

21a Atracurium R = $CO.O.(CH_2)_5.O.CO$

Following on from laudexium [21], which is modelled more directly on the (+)-tubo-curarine molecule, is the more recent atracurium [21a]. Stenlake (1982) has given an account of the reasoning which led to the development of this molecular structure. The compound is used in the form of its benzenesulphonate (besylate) salt, and it achieves full neuromuscular block in man with 0.25-0.30 mg/kg. The compound is a significant advance in that cardiovascular side-effects are minimal and it can be used in patients with serious hepatic and renal dysfunction. The drug combines features of a suxamethonium homologue with the bulk of two quaternary benzylisoquinoline substituents.Its period of action is self-limiting, since in the body tissues, in addition to enzymatic ester hy-drolysis, most of it undergoes spontaneous Hofmann elimination which in human blood is complete after about 35 mins. (Hughes & Chapple, 1980; Hunt et al.,1980;Stenlake,1982).

Table 8. Some reported uses for certain curare ingredients and related species.

Plant species	Collection	Locality	Reported use
Strychnos			
St. erichsonii	BW s.n. 4/11/14	Surinam	Aphrodisiac, stomach troubles
	BW 358	Surinam	Aphrodisiac, stomach troubles.

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Table 8. (continuação)

Plant species	Collection	Locality	Reported use
	BW 5568	Surinam	venereal diseases Aphrodisiac, menstrual problems
St. melinoniana	Stahel s.n.-3/44	Surinam	Aphrodisiac
Curarea			
Cu. tecunarum	Prance et al.16453	Brazil, Amazonas	Extract of crushed stem drunk as contraceptive Dení, Rio Cunhuá)
Sciadotenia			
Sc. cf. pachno- cocca	Prance et al.15558	Brazil, Amazonas	Scraped root bark against toothache (Makú, Rio Uneiuxi)
Sc. toxifera	J.Schunke V. 4637	Peru, San Martín	Macerated in aguardiente for diabetes and tertian fevers (Lamista)
Sc. paraensis	M. H. Lima 15	Brazil, Pará	Plant said to act as an abortifacient
Abuta			
Ab. brevifolia	M.Barbosa da Silva 109	Brazil, Pará	Much sought after by local drugstores for use in remedies
Ab. convexa	Glaziou 3860	Brazil, Rio de Janeiro	Bark and root as bitter,digestive deobstruent, antifebrile
Ab. grandifolia	Fróes 20365	Brazil, Amazonas	For Fevers
	G. Klug 1962	Colombia,Putumayo	Against malaria
	Martin et al.1650	Peru,vicinity of Iquitos	Roots macerated in aguardiente or water against rheumatism
	Plowman 2521		
	Grubb et al. 1635	Ecuador,nr.Tena	Bark as a cure for colic
Ab. ? grandifolia	Aluísio s.n.	Brazil,Amazonas	A tea of the well-crushed leaves as an abortifacient
Ab. obovata	Bassett Maguire et al. 41700	Colombia,Amazonas	Sap for treating "pink eye" (contagious conjunctivitis)
Ab. rufescens	L.A.Maia et al.244	Brazil,Amazonas	A tea of the grated stem against the poison of the pico-de-jaca
Ab.sandwithiana	J.M.Ayres 02	Brazil,Mato Grosso	Probably good for malaria
	B.W.Nelson P21305	Brazil,Rondônia	A tea from scraped root as a female contraceptive (Karitiana)
Cissampelos			
Ci. ovalifolia	M.T.Silva 661	Brazil, Pará	Tuber against bite of cobra jararaca (**Bothrops**)

OTHER BIOLOGICAL ACTIVITIES

Pharmacological and related studies continue quite naturally to be focused prima_
rily on the neurological and muscle-relaxant properties of curare and its active princi_

ples, especially the bisbenzylisoquinolines - (+)-tubocurarine and congeners.   Some of
these compounds, however, are known to exhibit significant anti-tumour activity, the follow-
ing ED_{50} data (mcg/ml) have been determined for the KB nasopharynx cell system:(-)-curine
0.14, (+)-isochondrodendrine 0.17, cissampareine 1.1(Kupchan et al., 1965). An alkaloid
fraction from Abuta panurensis is also reported to display activity in this test;the main
alkaloids present in it are the bisbenzylisoquinolines panurensine   and norpanurensine
(Cava et al., 1975a).   There is little or no published information on the pharmacological
properties of most of the newer alkaloids isolated from Abuta, Sciadotenia, and Telito-
xicum species, and the same is also true for many of the compounds obtained   from   the
other alkaloid-bearing ingredients of curares.

    It is desirable that such studies be carried out, for it is evident from herbarium
annotations and other sources that some of these plants which yield the active   princi-
ples are believed to have effective medicinal properties as well.   Table 8   draws at-
tention to some of these indications in order to encourage evaluation both of the plants
and of their active constituents for other potentially useful properties.

    Humboldt & Bonpland, for example, mentioned that curare was used in small doses as
a cure for intermittent fevers ans as indicated in Table 8 some of its component plants
are indeed believed to have antifebrile properties.   Prance (1972) reports the observation
that Deni men and women living on the upper Rio Cunhuã (western Amazonian Brazil) drink
large quantities of an aqueous extract made from the crushed stems of Curarea tecunarum
as a contraceptive; and as Table 8 again shows, species of Abuta and Sciadotenia   are
used similarly.   Davis & Yost (1983) indicate that the Waorani Indians of Amazonian Equa-
dor apply their dart poison, which is prepared from Cu. tecunarum, directly to skin in-
fections of bacterial or fungal origin with "proven results".   According to Van den Berg
(1982), in Brazilian Amazonia the stem or root bark of Abuta concolor is used as an
antifebrile and in the treatment of renal calculi, contusions,   and   inflammations (in-
cluding those of the eyes); a tea prepared from the roots or bark of Cissampelos ovali-
folia is employed as a diuretic, tonic, resolutive, and in the treatment   of contusions
and inflammations.

    Further uses are listed in Table 8.   It would seem that a broader biological evalu-
ation of curare ingredients could yield results of interest.

ACKNOWLEDGEMENT

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