

## 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.

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(\*) This paper is dedicated to the memory of B. A. Krukoff, who, over a period of almost fifty years, was the driving force behind much of the botanical and chemical investigation of the plants used in the preparation of curare.

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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 muscle-relaxant 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 in



### 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 dihydro toxiferine (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, Japurá, 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 Mazaroni in Guyana (Colson, 1973; Coppens, 1971; Thomas, 1972).

#### BOTANY

Once scientific field studies began, it was soon recognized that the active ingredients 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*, *Brevitubae*, and *Lanigeriae* (Bisset et al., 1973). One species *S. potatorum*, of section *Rouhamon*, occurs in both Africa and Asia. South America has ca. 75-80 species, which are representatives 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).<sup>a</sup>

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

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 supplements 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 *Rouhamon*) 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).<sup>a</sup>

Species	Region where used
<b>Triclisieae</b>	
<b>Chondrodendron</b> <sup>b</sup> Ruiz et Pavón	
<i>Ch. platiphyllum</i>	Brazil
<i>Ch. tomentosum</i>	Colombia (Putumayo), Ecuador (Napo-Pastaza), Peru (Loreto, San Martín, Huánuco)
<b>Curarea</b> Barneby et Krukoff	
<i>Ca. candicans</i>	Guyana, Brazil (western Amazonas)
<i>Ca. tecunaruam</i>	Colombia (Putumayo, Amazonas), Ecuador (Napo-Pastaza), Brazil (western Amazonas)
<i>Ca. toxicifera</i>	Colombia (Putumayo, Vaupés), Ecuador (Napo-Pastaza), Peru (Loreto), Brazil (western and central Amazonas)
<b>Sciadotenia</b> Miers	
<i>Sc. peruviana</i>	Peru
<i>Sc. toxifera</i>	Colombia (Putumayo), Ecuador (Napo-Pastaza), Peru (San Martín)
<b>Anomospermeae</b>	
<b>Abuta</b> Barrère ex Aublet	
<i>Ab. grisebachii</i>	Venezuela (Roraima)
<i>Ab. imene</i>	Brazil (western Amazonas)
<i>Ab. pahni</i>	Brazil (western Amazonas)
<i>Ab. rufescens</i>	Colombia (Putumayo, <sup>c</sup> Amazonas), Venezuela (Roraima), Ecuador (Napo), Brazil (western Amazonas)
<b>Anomospermum</b> Miers	
<i>An. grandifolium</i> <sup>d</sup>	Ecuador
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Tabela 2. continuação.

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

- <sup>a</sup> Later annotations can be traced via the 18th and final supplement on American Menispermaceae by Krukoff & Barneby (*Phytologia* 51: 458-462 (1982).
- <sup>b</sup> This is the correct spelling of the genus name (Sandwith, 1955) and was the one finally adopted by Krukoff in his later publications.
- <sup>c</sup> Here, there is the possibility that the plant collected may have been confused by the botanist's informant with **Curarea toxicifera** (Krukoff & Barneby, 1970, pp.16-17 under **Abuta splendida**).
- <sup>d</sup> 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. toxicifera** (Krukoff & Moldenke, 1938, pp. 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 seeds. 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. platiphylum**, and **Ch. microphyllum**, and a new one appropriately called **Curarea**, which has four species: **Cu. toxicifera** (incl. **Ch. iquitatum**, **Ch. polyanthum**, ? **Ch. bioccai**), **Cu. candicans** (incl. **Ch. limaciifolium**), and the new taxa **Cu. tecunarium** (= **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. tomentosum**, **Cu. tecunarium**, and, interestingly, **Ci. ovalifolia** and **Ci. pareira**.



**Tabela 3.** Genera which supply some of the plant additives in South American curares.

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

#### Additives

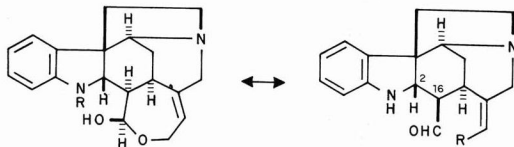
While members of the Loganiaceae and Menispermaceae are the primary sources of activity in curares, from the numerous accounts dealing with the poison it is clear that a variety of other ingredients - among them other plant and animal products, as well as insects - have been included in their composition. 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 *Guatteria* 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 Curare - botany ...

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.



1 Wieland-Gumlich aldehyde  
(closed form)

R = H

1a Diaboline

R = CO.CH<sub>3</sub>

2 Wieland-Gumlich aldehyde  
(open form)

(= Deacetyldiaboline)

R = CH<sub>2</sub>OH

2a 18-Deoxy-Wieland-Gumlich aldehyde

R = CH<sub>3</sub>

2b Wieland-Gumlich aldehyde metho salt

(= Caracurine VII)

R = CH<sub>2</sub>OH,  $\equiv N_b^+ - CH_3$

2c 18-Deoxy-Wieland-Gumlich aldehyde metho salt  
(= Hemi-dihydrotoxiferine = Dihydrofluorocurarine)

R = CH<sub>3</sub>,  $\equiv N_b^+ - CH_3$

2d Fluorocurarine

(= 2,16-Dehydro-18-Deoxy-Wieland-Gumlich aldehyde metho salt)

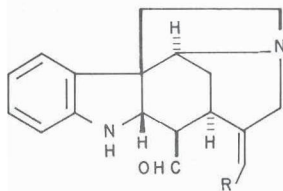
R = CH<sub>3</sub>,  $\equiv N_b^+ - CH_3$ ,  $\Delta^{2(16)}$

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 their N<sub>b</sub>-metho salts [2b] and [2c]. Wieland-Gumlich aldehyde (deacetyldiaboline) itself [2] 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<sub>b</sub>-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).

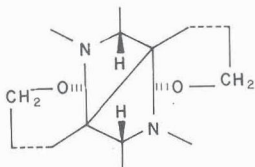
Species	Alkaloids
<b>Section Strychnos</b>	
<i>S. brachiata</i>	Wieland-Gumlich aldehyde (Galeffi et al., 1973)
<i>S. erichsonii</i>	Diaboline (Marini-Bettolo et al., 1978)
<i>S. jobertiana</i>	Diaboline
<i>S. mitscherlichii</i>	C-Alkaloid D; C-calebassine, C-curarine fluorocurarine
<i>S. sandwithiana</i>	Wieland-Gumlich aldehyde
<i>S. solerederi</i>	Diaboline, Wieland-Gumlich aldehyde
<i>S. solimoesana</i>	C-Alkaloid D, 0,5% C-calebassine, 0,1% C-curarine (Marini-Bettolo et al., 1978); C-alkaloids F and G; fluorocurarine, diaboline
<i>S. tomentosa</i>	C-Curarine; toxiferine, C-Alkaloid E
<i>S. toxifera</i>	Caracurines II and V, bisnor-dihydrotoxiferine; toxiferine
<b>Section Rouhamon</b>	
<i>S. guianensis</i>	C-Curarine
<i>S. subcordata</i>	Fluorocurarine, Wieland-Gumlich aldehyde
<b>Section Breviflorae</b>	
<i>S. castelnaeana</i>	C-Alkaloid D, diaboline (delle Monache et al., 1970)
<b>Section Rouhamon - Africa</b>	
<i>S. usambarensis</i>	Dihydrotoxiferine, C-calebassine, C-curarine; fluorocurarine; fluorocurarine (Angenot et al., 1975; Caprasso et al., 1981)
<b>Section Strychnos - Asia</b>	
<i>S. ignatii</i>	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  $\alpha$ -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].



2/2a

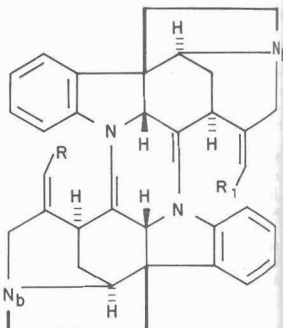
2b/2c



Bis-tertiary base:

Caracurine V

3



Bis-tertiary bases:

4 Bisnor-dihydrotoxiferine

R = R<sub>1</sub> = CH<sub>3</sub>

4a Bisnor-C-alkaloid H

R = CH<sub>3</sub>, R<sub>1</sub> = CH<sub>2</sub>OH

4b Bisnor-toxiferine

R = R<sub>1</sub> = CH<sub>2</sub>OH

Bis-quaternary bases [2 x N<sup>+</sup>-CH<sub>3</sub>]:

4c Dihydrotoxiferine

R = R<sub>1</sub> = CH<sub>3</sub>

4d C-Alkaloid H

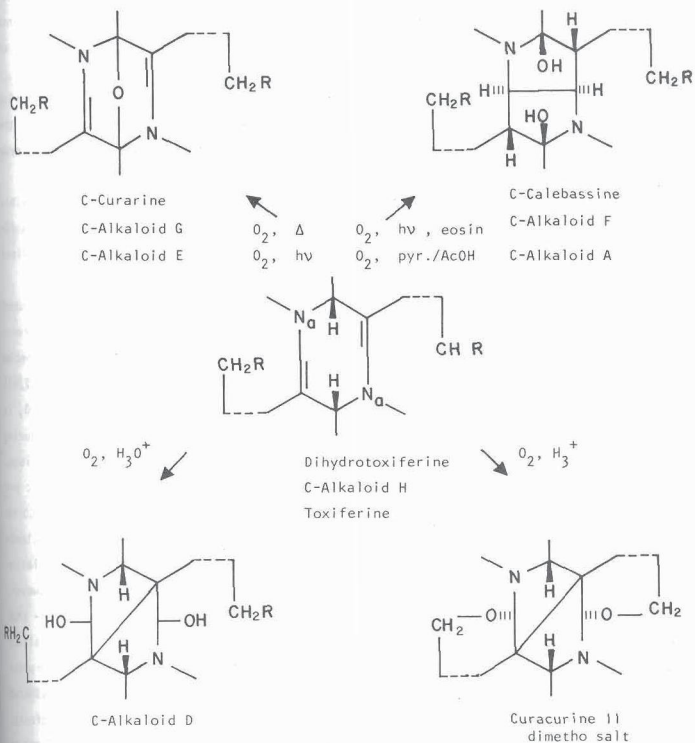
R = CH<sub>3</sub>, R<sub>1</sub> = CH<sub>2</sub>OH

4e Toxiferine

R = R<sub>1</sub> = CH<sub>2</sub>OH



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



R = H and/or OH

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 curacurine II dimetho salt, C-alkaloid E and C-alkaloid A; while dihydrotoxiferine furnishes C-alkaloid D, C-curarine, and C-talebassine, as well as a number of further oxidation products of as yet unknown structure.

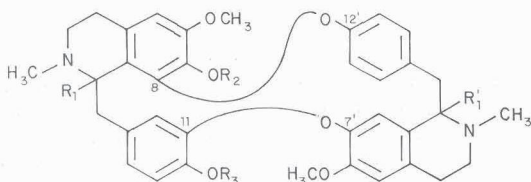
The hybrid C-alkaloid H [4d] yields C-alkaloids G and F. Although, as indicated above, dihydrotoxiferine (and also toxiferine and C-alkaloid H) can be cleaved with acid into the corresponding monomers, the more highly oxidized derivatives undergo a series of isomerizations instead.

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. subcordata*, *S. tomentosa*, etc Cf. Table 4.

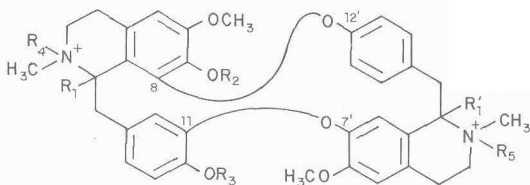
With ordinary methods of extraction, i.e. using acid, it is usually not possible to isolate bisnor-dihydrotoxiferine [4], because, in addition to being cleaved to 18-deoxy-Wieland-Gumlich aldehyde (nor-hemidihydrotoxiferine = nor-dihydrofluorocurarine) [2a], it is highly labile and readily isomerized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



- 5 (-)-Curine [(-)-Bebeerine]  
 $R_2 = R_3 = H; R_1 = R_1' = \text{---} H \text{ (R,R)}$
- 5a (+)-Curine [(+)-Bebeerine, Chondrodendrine]  
 $R_2 = R_3 = H; R_1 = R_1' = H \text{ (S,S)}$
- 5b Chondrocurine (+)-Tubocurine  
 $R_2 = R_3 = H; R_1 = \text{---}H, R_1' = \text{---}H \text{ (R,S)}$
- 5c (-)-Tubocurine  
 $R_2 = R_3 = H; R_1 = \text{---}H, R_1' = \text{---}H \text{ (S,R)}$
- 5d Chondrofoline  
 $R_2 = CH_3, R_3 = H; R_1 = R_1' = \text{---}H \text{ (S,S)}$
- 5e 12-O-Methylcurine  
 $R_2 = H, R_3 = CH_3; R_1 = R_1' = \text{---}H \text{ (R,R)}$
- 5f 12-O-Methylcurine  
 $R_2 = H, R_3 = CH_3; R_1 = R_1' = \text{---}H \text{ (S,S)}$
- 5g 0,0'-Dimethylcurine  
 $R_2 = R_3 = CH_3; R_1 = R_1' = \text{---}H \text{ (R,R)}$



- 6 (+)-Tubocurarine  
 $R_2 = R_3 = R_5 = H, R_4 = CH_3; R_1 = \text{---}H, R_1' = \text{---}H \text{ (R,S)}$
- 6a (-)-Tubocurarine  
 $R_2 = R_3 = R_5 = H, R_4 = CH_3; R_1 = H, R_1' = \text{---}H \text{ (S,R)}$
- 6b (+)-Chondrocurarine  
 $R_2 = R_3 = H, R_4 = R_5 = CH_3; R_1 = \text{---}H, R_1' = \text{---}H \text{ (R,S)}$
- 6c N,0,0'-Trimethyl-(+)-tubocurarine [Metocurine]  
 $R_2 = R_3 = R_4 = R_5 = CH_3; R_1 = \text{---}H, R_1' = \text{---}H \text{ (R,S)}$
- 6d (+)-Isotubocurarine  
 $R_2 = R_3 = R_4 = H, R_5 = CH_3; R_1 = \text{---}H, R_1' = \text{---}H \text{ (R,S)}$

## ALKALOIDS OF THE MENISPERMACEAE

 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.

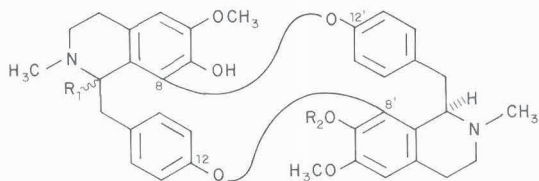
Species	Plant part <sup>a</sup>	Alkaloids present	References
<b>Chondrodendron</b>			
<b>Ch. platyphyllum</b>	r	(+)-Isochondrodendrine, (+)-curine	King (1940)
	st	(-)-Curine	King (1940)
	l	(+)-Isochondrodendrine, (-)-curine, (-)-chondrofoline	King (1940) Baldas et al. (1971)
<b>Ch. microphyllum</b>	r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

<sup>a</sup>] = 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

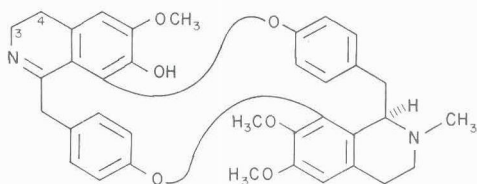


lographic (Coddington & James, 1972; Reynolds et al., 1975) studies, that this compound is a mono- rather than a bis-quaternary alkaloid [6]; this structural revision has necessitated some adjustment to the theoretical understanding of the mechanism of its muscle-relaxant action.



7 Isochondrodendrine  $R_2 = \text{H}$ ;  $R_1 = \text{--- H}$  (R, R)

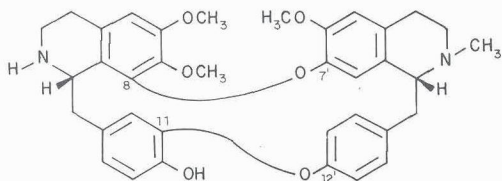
7a Sciadanine  $R_2 = \text{CH}_3$ ;  $R_1 = \text{--- H}$  (S, R)



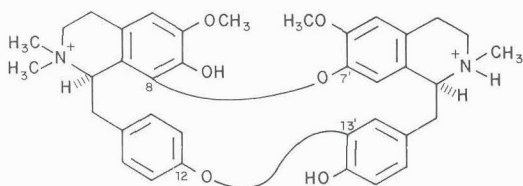
8 Sciadoline

8a Sciadoferine  $\Delta^3$

*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 sciadanine [7a] (Galeffi et al., 1978; Takahashi & Cava, 1976; Takahashi et al., 1976).



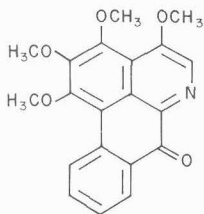
9 Peinamine (S, R)



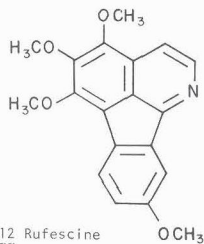
10 Macoline (R, S)

#### Alkaloids of the Anomospermeae - *Abuta*, *Anomospermum*, and *Telitoxicum*

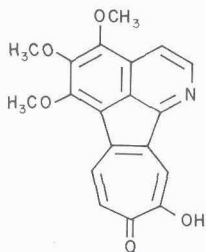
Perhaps the most significant find in regard to the genus *Abuta* is the isolation by Galeffi and Marini-Bettolo (1977) from the stem wood of *Ab. grisebachii*, in addition to the main bis-tertiary base peinamine [9], of the monoquaternary macoline [10] and its 7-O-demethyl and N-methyl-O-demethyl derivatives. 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.



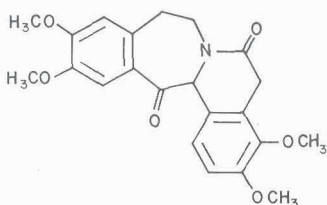
11 Iminenine



12 Rufescine



13 Grandirubrine



14 Saülaline

The other *Abuta* species listed in Table 2 have also been investigated, and they have been shown to contain a variety of other dimeric bases (Ahmad & Cava, 1977; Cava et al., 1969; Saã 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 saülaline [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-O-methylcurine [5f] (Haynes et al., 1966; see also: Guha et al., 1979).

#### ALKALOID-CONTAINING CURARE ADDITIVES

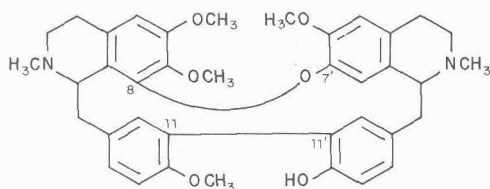
Alkaloids, mostly isoquinoline derivatives, are found in several other plants entering into the composition of curares, and this has to be borne in mind when assessing the possible contribution these ingredients may make to the overall effects of the curares into which they are incorporated. The topic 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 Curare - botany ...

tetrahydroberberines, along with benzylisoquinolines and several groups of aporphinoids; *Duguetia* species are also known to have aporphinoids present (The Alkaloids, 1971/83). Several species of *Gutteria* 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], (-)-2'-0-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*, representatives of which have recently been shown to contain (-)-curine [5], as well as a benzylisoquinoline and tetrahydroberberine and several aporphinoids and phenanthrenes (Eltohai *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 dioxoporphines (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*, provide an ingredient for one of the arrow poisons prepared by the Kofán Indians of eastern Ecuador and Colombia. The seeds and bark of this species contain at least eight alkaloids. 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 & de Marderosian, 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
<b>Calabash</b>		
C-Curarine/C-calebassine	2-10	>2-15
Toxiferine	2 <sup>a</sup>	-
Tubocurarine	1-10	-
<b>Pot</b>		
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
<b>Tube</b>		
C-Curarine/C-Calebassine	5 <sup>a</sup>	10
Tubocurarine	2.5 <sup>a</sup>	5
<b>Arrow-tip</b>		
C-Curarine/C-Calebassine	1.0-1.2	2.75-5

<sup>a</sup>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<sub>100</sub> 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<sub>100</sub> of 4 mg/kg. Bauer (1971a) examined a sample of the famous Tikuna curare, collected by de Castelnau in 1846, and determined LD<sub>100</sub> 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 Nambikuara 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 ( <i>Chondrodendron</i> -based)	0.3	0.3
Wood of <i>Chondrodendron</i> sp.	25.0 <sup>a</sup>	1.25
Yanomano curare ( <i>Strychnos</i> -based)	1.2	2.5
Bark of <i>Strychnos</i> sp.	0.3	1.25

<sup>a</sup> 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. 30.0mg/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<sub>100</sub> 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 O,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] emphasizes 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 (Coddington & 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 conformation of the dichloride is similar to the crystal conformation determined for the dibromide and the N<sub>10</sub>,O<sub>1'</sub>-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 opposite sides of the molecule. The alternative suggestion has been made that the protonated nitrogen could exert an electrostatic repulsion on acetylcholine (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 reversed. 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 inhibition of acetylcholine. It is concluded that situating the quaternized function next to the 5-centre endows the molecule with greater potency; also these authors question the role of protonation of the tertiary amine moiety.

#### SYNTHETIC MUSCLE-RELAXANTS

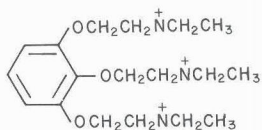
##### Non-depolarizing drugs

Modification of the highly potent toxiferine molecule by replacing the two N<sub>2</sub>-methyl groups with N<sub>2</sub>-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.

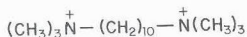
The original formulation of (+)-tubocurarine as a bis-quaternary alkaloid, a structure



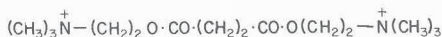
now known to be that of chondrocurarine [6b], focused attention on this type of compound and through the early work of Bovet and others (see: Bovet, 1959) led to the successful introduction into clinical practice of the synthetic gallamine triethiodide or flaxedil [16], a muscle-relaxant of moderate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



16 Gallamine (Flaxedil)



17 Decamethonium



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 lepto-curares). 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 homologues 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).

### 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.

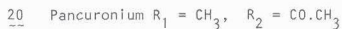
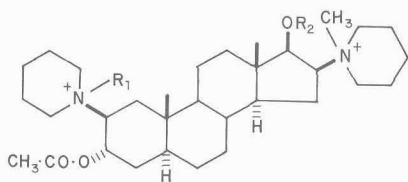
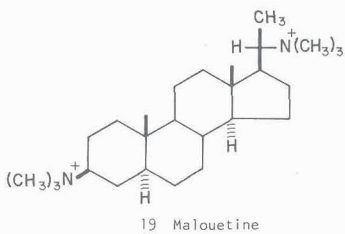
Increased knowledge of the structural requirements for non-depolarizing neuromuscular-blocking drugs has laid the basis for a less empirical and more positive approach to the design of such drugs. Thus, in striving to produce second- and third-generation muscle-relaxants which will fulfil the above criteria 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 Venezuela.

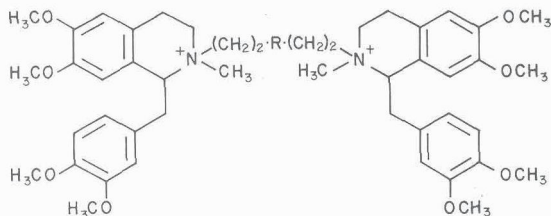
zuela, and it was tentatively identified about a century ago as a species of *Malouetia* (Apocynaceae); more recent gatherings of the plant have been assigned to *Malouetia* as well as to *Tabernaemontana* (also Apocynaceae) (Bisset, 1958; Khuong-Huu-Lainé et al. 1965). There is in addition one report,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

Early work on *guachamacá* led to the isolation of an alkaloidal substance with curare-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 (Khuong-Huu-Lainé & Pinto-Scognamiglio, 1964). Although South American *Malouetia* species are indeed known to exhibit muscle-relaxant activity, none of the compounds responsible has yet been isolated.



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

2 $\beta$ -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 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 dacrurium [20a] and the mono-quaternary vecuronium [20b] (Bowman, 1980; Symposium, 1980; Tannières-Ruffié & Vourc'h, 1983).



21 Laudexium R = (CH<sub>2</sub>)<sub>6</sub>

21a Atracurium R = CO.O.(CH<sub>2</sub>)<sub>5</sub>.O.CO

Following on from laudexium [21], which is modelled more directly on the (+)-tubocurarine 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 hydrolysis, 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
<b>Strychnos</b>			
St. erichsonii	BW s.n. 4/11/14	Surinam	Aphrodisiac, stomach troubles
	BW 358	Surinam	Aphrodisiac, stomach troubles.

Table 8. (continuação)

Plant species	Collection	Locality	Reported use
	BW 5568	Surinam	venereal diseases Aphrodisiac, menstrual problems
<i>St. melinoniana</i>	Stahei s.n.-3/44	Surinam	Aphrodisiac
<i>Curarea</i>			
<i>Ca. tecunarium</i>	Prance et al.16463	Brazil, Amazonas	Extract of crushed stem drunk as contraceptive Denf, Rio Cunhuã)
<i>Sciadotenia</i>			
<i>Sc. cf. pachnococca</i>	Prance et al.15558	Brazil, Amazonas	Scraped root bark against toothache (Makú, Rio Uneixi)
<i>Sc. toxifera</i>	J.Schunke V. 4637	Peru, San Martín	Macerated in aguardiente for diabetes and tertian fevers (Lamista)
<i>Sc. paraensis</i>	M. H. Lima 15	Brazil, Pará	Plant said to act as an abortifacient
<i>Abuta</i>			
<i>Ab. brevifolia</i>	M.Barbosa da Silva 109	Brazil, Pará	Much sought after by local drugstores for use in remedies
<i>Ab. convexa</i>	Glaziou 3860	Brazil, Rio de Janeiro	Bark and root as bitter,digestive deobstruent, antifebrile
<i>Ab. grandifolia</i>	Frões 20365 G. Klug 1962 Martin et al.1650 Plowman 2521 Grubb et al. 1635	Brazil, Amazonas Colombia,Putumayo Peru,vicinity of Iquitos Ecuador,nr.Tena	For Fevers Against malaria Roots macerated in aguardiente or water against rheumatism
<i>Ab. ? grandifolia</i>	Aluisio s.n.	Brazil, Amazonas	Bark as a cure for colic A tea of the well-crushed leaves as an abortifacient
<i>Ab. obovata</i>	Bassett Maguire et al. 41700	Colombia, Amazonas	Sap for treating "pink eye" (contagious conjunctivitis)
<i>Ab. rufescens</i>	L.A.Maia et al.244	Brazil, Amazonas	A tea of the grated stem against the poison of the pico-de-jaca
<i>Ab.sandwithiana</i>	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 (Karitia-na)
<i>Cissampelos</i>			
<i>Ci. ovalifolia</i>	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 primarily on the neurological and muscle-relaxant properties of curare and its active principle - botany ...

ples, especially the bisbenzylisoquinolines - (+)-tubocurarine and congeners. Some of these compounds, however, are known to exhibit significant anti-tumour activity, the following ED<sub>50</sub> data (mcg/ml) have been determined for the KB nasopharynx cell system: (-)-curarine 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 *Telitoxicum* 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 principles are believed to have effective medicinal properties as well. Table 8 draws attention 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 and as indicated in Table 8 some of its component plants are indeed believed to have antifebrile properties. Prance (1972) reports the observation that Dani 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 tecunarium* 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 Ecuador apply their dart poison, which is prepared from *Cu. tecunarium*, directly to skin infections 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 (including those of the eyes); a tea prepared from the roots or bark of *Cissampelos ovalifolia* 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 evaluation of curare ingredients could yield results of interest.

#### ACKNOWLEDGEMENT

The help of Arie Bisset in locating relevant annotations in the collections of several Brazilian herbaria is greatly appreciated.

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