REVIEW ARTICLE

THE ALKALOIDS OF CURARE

Alkaloids from Calabashes and Strychnos Barks*

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CURARE is one of the many arrow poisons which have been known for centuries. Such poisons have been found in certain regions of Africa, Asia, and also Europe and South America. The African and Asiatic poisons are almost exclusively of a glucoside nature. In certain Asiatic countries the most common and most important arrow poison is made from the latex of *Antiaris toxifera*, a Moraceæ, from which a recent investigation has isolated two toxic glucosides having the formula $C_{29}H_{42}O_{11}$ and which have been given the names α- and β-antiarin. In Europe, from prehistoric times until about the fifteenth century it is likely that extracts of *Aconite*, *Veratrum* and *Helleborus* species and also snake venoms were used as arrow poisons.

Of a quite different chemical nature are the arrow poisons of South and Central America. In these, alkaloids form the toxic principles.

From their first contact with that continent, Europeans knew of the existence of the South American arrow poisons. On Magellan's first voyage around the world (1519–22) one of his sailors, whilst ashore in Patagonia, was killed by a poisoned arrow. During the invasion of the South American continent by Cortez and Pizarro the invaders were often attacked by natives using curare tipped arrows. This was for the Europeans a new and mysterious weapon and gave rise to many fantastic stories, some of which were brought back by Sir Walter Raleigh in 1596. Not until 150 years later were more reliable reports brought to Europe by more scientific workers. In 1745 La Condamine reported that curare was made mainly from a liana "Bajuco" together with other plants. The first exact and reliable description of curare production from Bajuco de Mavacure was given by Alexander von Humboldt, who also made some very good observations on the physiological and toxicological effects of the arrow poison.

In the Tupi language curare is called Urary, meaning "a liquid that can kill birds." This gives an indication of its original application.

The distribution of South American curare extends from the north of this continent to the upper La Plata river-basin; that is, it stretches from about ten degrees north to fifteen degrees south of the equator and from west to east over about twenty degrees of longitude. However, the type and the method of extraction of these arrow poisons is not the same throughout this vast area.

In Columbia the natives make an arrow poison out of a toad (*Phyllobatus melanorrhinus* Dum). According to Lewin[1], in the Orinoco region

* Lectures delivered by invitation of the University of London on March 10 and 11, 1955.

(Venezuela) two *Strychnos* species, *Strychnos toxifera* and *Strychnos gubleri* are said to be the sources of calabash curare. According to the same worker, in the region between the Orinoco and the Rio Negro live the most famous poison makers. Furthermore curare is produced in British Guiana, in Ecuador (probably from *Strychnos castelnaei*), in the Rio Negro region (*Strychnos castelnaei*), in the river-basin Yapura-Solimoes (tributaries of the Amazon) as well as in Peru.

The regions of curare production are obviously determined by the location of the plants necessary for poison production and therefore the natives living in such regions possess a monopoly of the curare production. The tribes of the Macusi (or Macu), Umaua, Juri, Ticua, Mesaya, Peba, Orejones and others produce high grade curare. Where those *Strychnos* species most suitable for curare production do not occur or have been exhausted, a poison of inferior quality is made out of Menispermaceæ, *Cocculus* species and other plants.

For past centuries and even up to the present day good quality curare fetches a high price and is used by the natives for bartering. In the year 1923 Lewin gave the following report. "A pot of curare which sells at four German marks on the banks of the Yagua, costs about 16 marks at the upper Içа. Twenty years ago 30 g. of the best quality curare could be bought from the Tucuna people from Marañon, near Loreto, for four marks and this same amount could be bought for 60–62 marks in Germany up to ten years ago. Many years ago in British Guiana it was possible to trade an axe, worth about eight marks, for a calabash of curare. Nowadays this curare has totally disappeared and is found only in museums. Even pot curare has already become rare. Only the so called tubocurare (or paracurare), sold in bamboo tubes, is now available."

From this it can be seen how difficult it is nowadays to get the quantities of curare necessary for chemical research, especially calabash curare, on which our work has been done and which, according to the report just cited, totally disappeared from the market fifty years ago. However after much trouble we have succeeded in finding a source, which provides a certain amount of calabash curare.

The three kinds of curare, tubocurare, pot curare and calabash curare are identified by their containers. Tubocurare is packed in bamboo tubes, pot curare in unglazed clay pots, and calabash curare in calabashes or gourds. The differences between the three types of curare are quite pronounced, they come from different plants, contain different alkaloids and show great variations in toxicity.

The calabash curare is by far the most toxic and therefore the most desirable but also difficult to obtain. In most recent times the containers are not always a guide to the type of poison in them. As an example of this, part of the calabash curare which we received, was not in gourds but in clay pots.

There are many data and numerous reports and opinions to be found in the literature concerning the plants used in curare production. However most of this information is very unreliable. Nevertheless Humboldt and various other investigators after him have pointed out the fact, that

Strychnos species are most frequently used for curare production. There were mentioned for instance: *Str. toxifera, Str. gubleri, Str. castelnaei, Str. rubiginosa, Str. hirsuta, Str. yapurensis, Str. triplinervia, Str. curare baillon*, etc. Most of the workers agree that besides strychnos extracts those of other plants are used, for instance *Cocculus* species (*Cocculus toxiferus, C. wedell, C. amazonum* Mart., *Menispermum cocculus* L; the latter containing the toxic bitter principle picrotoxin, which produces central nervous convulsions). Furthermore, Menispermaceæ are said to be used (for instance *Abuta rufescens* Aubl., *Abuta imene* Eichl.) as well as Aracæ (*Dieffenbachia Seguine*) and possibly Euphorbiaceæ. According to the opinion of certain investigators the addition of all these plants to the strychnos extract has little value and rather serves to make the process of poison production, which is already accompanied by much ceremonial ritual, still more mysterious.

There is already a report given by Humboldt about the technique of curare production. Another more recent one is given by the pharmacologist Freise[2,3], who reports as follows:—

"For curare production barks of various *Strychnos* species are used. In the Araraquare mountains live the Maupes indians, known to be excellent poison makers. In this region many *Strychnos* species can be found, mainly *Str. letalis, Str. icaja*, and *Str. lanceolaris*, some of which occur as lianas up to 200 feet long with widely spread branches. Strips of the bark, each about three to four inches wide and 20–30 inches long (about 40–60 kg. are obtained from one stem during the harvest period, that is during the dry season) are soaked in wooden troughs filled with water, the cork tissue being stripped off cautiously from the inner layers. Only the cork layer is retained. This is dried and powdered in hard mortars with wooden pestles, the process taking several days and the daily production being scarcely more than 200 g. per mortar. Each patch of bark powder produced in one mortar during one day is worked up separately. The powder is slowly extracted with warm water in wooden vessels in which the extraction temperature of 70–80 degrees Celsius has been previously produced by heated stones. Boiling is never mentioned. The amount of water for 200 g. of powder is about 2 litres. The extraction of the bark with warm water takes about four days. Then the contents of the vessel have become a red to dark brown liquid which has a penetratingly bitter taste. Straining through a bast filter separates it from the bark residues. During several days' concentration, under very cautious warming, the liquid thickens to a syrupy consistency and is poured into gourds."

Recently a different opinion is expressed by Lazzarini-Peckolt[4] on the formation of the toxic curare alkaloids. He states that these alkaloids do not occur in the plant, or if so only in small amounts, but are formed during the boiling of the various plant juices, the quaternary curare active compounds being formed by some methylation processes from the tertiary inactive bases. In his opinion three different kinds of plants are necessary to produce active curare:

1. Plants containing alkaloids capable of being alkylated.

2. Plants capable of making the mixture of the extracts alkaline during concentration.

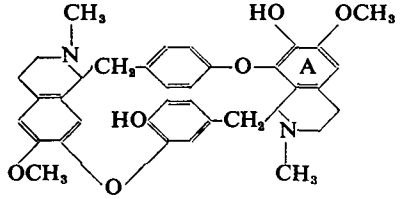
3. Plants containing methyl and other esters, which supply the necessary alkyl groups to form the active quaternary ammonium bases from the alkaloids of the first mentioned group of plants.

According to Lazzarini-Peckolt there are a great number of plants which can be used for curare production: Loganiaceæ (of the *Strychnos* species), Menispermaceæ (of the *Chondrodendron, Elissarrhena, Anomospermum, Sciadotenia, Telitoxicum, Abuta, Cocculus* and other species), Lauraceæ (of the *Nectandra* species and others), probably Solanaceæ and species of other families too. Also a great number of plants can be used to make the mixture alkaline. Those used most frequently are: *Dieffenbachia, Arum, Melothria, Cyclanthera, Clavija, Piper* and *Ipomoena* species. The plants used for giving the alkyl groups necessary for quaternary salt formation are mostly of the species *Aristolochia, Duguetia, Xylopia, Zinziber, Petiveria, Gallesia, Octotea, Fagara* and others. Therefore, according to Lazzarini-Peckolt, the composition of the curare can be changed as the producer wishes.

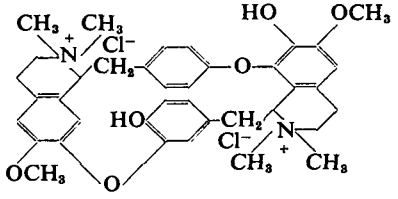
A point to note is that Wieland, who examined the calabash curare alkaloids during the years 1937–41, was not able to find the main calabash quarternary bases in the bark of *Str. toxifera.* Only very recently has more light been thrown on the origin of these toxic principles.

Chemistry

The alkaloids of tubocurare are the best known. From tubocurare Boehm and King extracted along with the tertiary base (−)-curine (I) the quaternary (+)-tubocurarine (II) as the active principle. The constitutions of both were elucidated by the work of King[5–10] and of Wintersteiner and Dutcher[11] and Dutcher[12]. Both compounds are relatively complicated di-*iso*quinoline derivatives with the following constitution:



I
(−)-Curine



II
(+)-Tubocurarine

The elucidation of the constitution of these compounds was accomplished mainly by studies of their degradation products, which are formed by zinc dust distillation, alkaline fusion and Hofmann degradation of the bases.

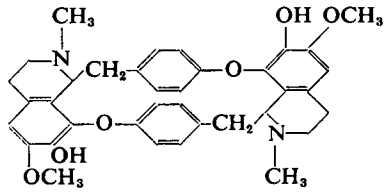
According to Wintersteiner and Dutcher, (+)-chondrocurine from *Chondrodendron tomentosum,* a tertiary base, differs from (−)-curine in

that the positions of the hydroxyl and methoxyl groups in ring A are interchanged.

Most probably tubocurare is made from Brazilian Menispermaceæ such as *Chondrodendron* species, for King and Wintersteiner succeeded in isolating the quaternary alkaloids (+)-tubocurarine and the related (+)-chondrocurarine as well as the tertiary bases (−)-curine, (+)-chondrocurine, (+)-*iso*chondrodendrine and (+)-*iso*chondrodendrine dimethyl ether from chondrodendron bark. (Once also the other tubocurarine antipode was encountered.) (+)-Tubocurarine to-day is still the only natural curare alkaloid used in medicine. Its activity and toxicity appear to be low compared with those of certain calabash alkaloids.

Pot curare, coming mainly from the Orinoco region, has relatively little toxicity and is used largely by the indians for killing small animals and birds. *Chondrodendron* species seem to be the initial material, as some substances isolated from this arrow poison, like (+)-protocuridine *i*-neoprotocuridine and (+)-*iso*chondrodendrine have also been found in *Chondrodendron* species (*Ch. tomentosum*, *Ch. platyphyllum*, *Ch. candicans*, etc.). They are tertiary bases of low activity. (+)-Protocuridine and *i*-neoprotocuridine have the formula $C_{36}H_{38}O_6N_2$. For (+)-*iso*chondrodendrine, structure III has recently been proposed:

Those quaternary alkaloids occurring in pot curare, which probably represent the main sources of activity, have not yet been isolated. Perhaps they come from a variety of *Strychnos* species.



III

(+)-*iso*Chondrodendrine $C_{36}H_{38}O_6N_2$

The most important and most active South American arrow poison is the calabash curare, the toxicity for the frog being from 0·5 to 1 mg. per kg. The first chemical work on this arrow poison dates back to the pharmacologist Boehm. However it was not until 1937–41 that Wieland and his colleagues[13–15] were able to isolate for the first time some pure alkaloids in a crystalline form. Since 1945 our Chemical Institute in Zürich has been occupied with the investigation of the components of the calabash curare[16–31]. Furthermore, King[32] in England and more recently Wieland[33,34] have worked on calabash alkaloids. Qualitative experiments on the occurrence of alkaloids in several *Strychnos* species have also been made by Bovet, Marini-Bettolo and others[35].

The calabash curare, originating from the Rio Negro region, contains a large number of different compounds. With the aid of paper chromatograms, we have been able to demonstrate the occurrence of more than thirty different alkaloids. For distinguishing the different spots on the paper chromatograms we have used the colour reactions with ceric sulphate, which with the different bases give red, blue, yellow, green, purple or yellowish green colours. Furthermore colour tests with cinnamic aldehyde, nitric acid and sulphuric acid have been made, as has also an

examination of the fluorescence shown by some of these alkaloids under ultra-violet light.

Figure 1 shows a chromatogram of the total alkaloids from calabash curare.

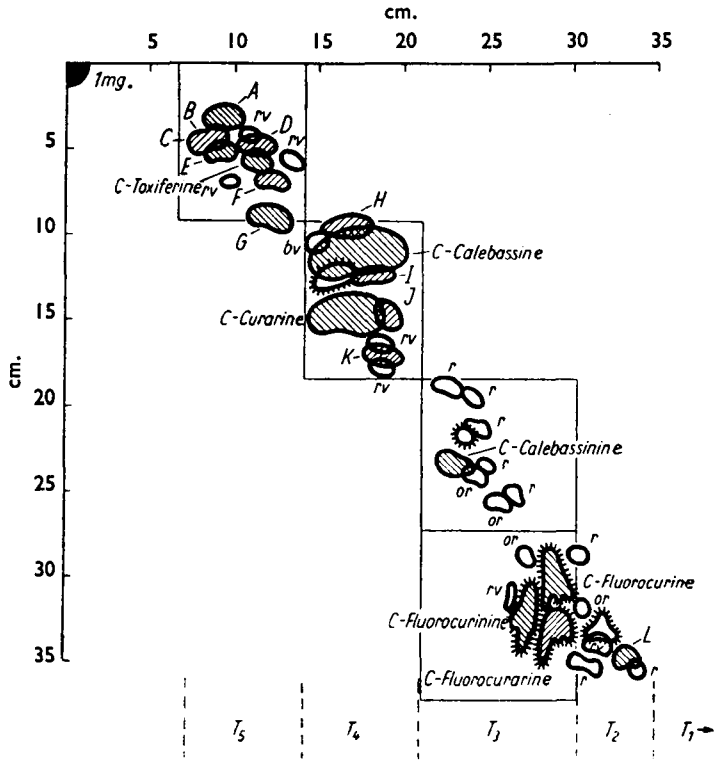


FIG. 1. Paper chromatogram of 1 mg. of purified chlorides from calabash curare No. III. The different spots were made visible by ceric sulphate or iodine solution. The hatched spots correspond to the isolated alkaloids, r = red, bv = blue-violet, rv = red-violet, or = orange spots after treatment with ceric sulphate.

The separation of the calabash alkaloids was achieved by Wieland *et al.*[13] by chromatography of the Reinecke's salts. In the beginning we also used this procedure, but lately we have obtained better results with chromatographic separations of the chlorides using a column of paper powder.

From the calabash curare at our disposal we have now been able to isolate the compounds in Table I in a chromatographically homogeneous form.

Some of the alkaloids isolated by Wieland and his colleagues from calabashes are identical with some of the members of the above mentioned groups, whilst others are different. Besides this both he and King have isolated some alkaloids from the bark of *Str. toxifera* (for example toxiferine I and II). As this was before the time of paper chromatography

TABLE I

R_c WITH SOLVENT C*

C-alkaloid A	$C_{20}H_{23}O_2N_2^+$	0·23	C-curarine	$C_{20}H_{21}N_2^+$	1·00
C-alkaloid B	$C_{20}H_{23}ON_2^+$	0·34	C-alkaloid J	$C_{19}H_{21}N_2^+$	1·04
C-alkaloid C	?	0·34	C-dihydrotoxiferine (= C-alkaloid K)	$C_{20}H_{22}N_2$	1·22
C-alkaloid D	$C_{20}H_{21}ON_2^+$	0·25	C-alkaloid UB	$C_{19}H_{23}O_2N_2$	—
C-alkaloid E	$C_{19}H_{19}ON_2^+$	0·36	C-alkaloid M		1·45
C-toxiferine I	$C_{20}H_{21}N_2^+$	0·42	C-alkaloid Y		1·59
C-alkaloid F	$C_{20}H_{23}O_2N_2^+$	0·49	C-calebassinine	$C_{19}H_{23}O_2N_2$	1·68
C-alkaloid G	$C_{20}H_{23}ON_2^+$	0·65	C-fluorocurine	$C_{20}H_{23}O_2N_2$	2·10
C-alkaloid H	?	0·71	C-fluorocurinine	$C_{21}H_{25}O_2N_2$	2·23
C-calebassine	$C_{20}H_{23}ON_2^+$	0·80	C-fluorocurarine (= C-curarine III)	$C_{20}H_{23}ON_2^+$	2·25
C-alkaloid I	$C_{19}H_{23}N_2^+$ ($C_{20}H_{25}N_2^+$)	0·89	C-alkaloid L	?	2·50
			C-mavacurine	$C_{20}H_{24}ON_2$	2·70

* $R_C = \frac{\text{distance travelled by the alkaloid}}{\text{distance travelled by the curarine}}$

Solvent C = methyl-ethyl ketone saturated with water + 1 to 3 per cent. methanol.

no suitable method was available for assessing the purity of these compounds.

We observed more than once that the composition of the poison of calabashes can show great differences. We had the opportunity to investigate two made by the indian tribe Isana, who live in the territory of the river Içа near the frontier of Columbia. These calabashes contained only one alkaloid which has been found before in other calabashes, calebassine, and even this in small quantity. But we were able to isolate from these calabashes four new alkaloids which we call C-alkaloid O and P, xanthocurine and guaianine. Xanthocurine is characterised by its intense yellow colour. Guaianine has also been found in the bark of *Strychnos guaianensis*.

Lately we have been fortunate in being able to examine the alkaloids of the bark of a *Strychnos* species, which has been identified by Prof. Frey-Wyssling as belonging to the *Str. mitscherlichii* group. In the extract of this bark we were able to identify the following alkaloids by paper chromatography and by their colour reactions[25]:

C-fluorocurinine, C-fluorocurarine, C-curarine, C-calebassine, C-alkaloid I and C-alkaloids of the B-, C-, D-group.

These alkaloids occurred in the bark in about the same proportion as in the calabashes and the main alkaloids in the bark likewise were C-curarine and C-calebassine. The two-dimensional paper-chromatogram of the alkaloids of *Str. mitscherlichii* shows very great resemblance with that of a calabash.

The identified alkaloids from the bark of *Str. mitscherlichii* are representatives of five of the eight groups or types, into which we have divided the calabash alkaloids. The representatives of the toxiferine group, occurring in *Str. toxifera*, are missing, a fact which is also found in many calabashes. Therefore it can now be stated that the natives of the middle and upper Rio Negro region use the bark of *Str. mitscherlichii* for production of calabash curare and if this contains alkaloids of the toxiferine group, it indicates that *Str. toxifera* has also been used. What further plants are used, has to be ascertained by examination of other barks.

The fact that quaternary alkaloid salts occur in the bark of *Str. mitscherlichii* shows that the assumption of Lazzarini-Peckolt, that the quaternary bases are formed by a methylation process during the concentration stage, cannot find any support in the light of our observations. But we cannot of course exclude a small measure of methylation of tertiary alkaloids during the concentration process.

The bark of a *Strychnos toxifera* species, which we received from Venezuela (the plant was grown in the district Fed. Amazonas on the mountain, Imutinava) contained partly other alkaloids. Besides mavacurine and fluorocurine and the above mentioned C-alkaloid Y we have so far isolated from this bark 10 new pure crystalline substances[30]: fedamazine (a quaternary alkaloid) caracurine I to IX (tertiary bases).

A further tertiary base which we found in this bark is of special interest. It is the nordihydrotoxiferine; the quaternary methylderivative of this is the

TABLE II

ALKALOIDS FOUND IN CALABASHES OR IN BARKS OF *Strychnos* SPECIES

	Isolated from	
	Calabashes	Barks of
C-curarine I[18,14,23,24,25]	+	*Str. mitscherlichii*
C-curarine II[18] (C-strychnotoxine Ia)[27]	+	
C-curarine III = C-fluorocurarine[15,23,24,25]	+	*Str. mitscherlichii*
C-toxiferine I = toxiferine I[18,23,24,26,40]	+	*Str. toxifera*
C-toxiferine II = C-calebassine[14,23–25,26,40] (= C-strychnotoxine I)	+	*Str. mitscherlichii*
Toxiferine II[26] (= strychnotoxine II)[27]	+	*Str. toxifera*
C-dihydrotoxiferine I = C-alkaloid K[23,24,26]	+	
C-isodihydrotoxiferine[26]	+	
C-alkaloid A[16,23–25]	+	*Str. mitscherlichii*
C-alkaloid B[15,23–25]	+	*Str. mitscherlichii*
C-alkaloid C[23–25]	+	*Str. mitscherlichii*
C-alkaloid D[23,24]	+	
C-alkaloid E[23,24]	+	
C-alkaloid F[23,24]	+	
C-alkaloid G[23,24]	+	
C-alkaloid H[23,24]	+	
C-alkaloid J[23,24]	+	
C-alkaloid I[23–25]	+	*Str. mitscherlichii*
C-alkaloid L[23,24]	+	
C-alkaloid M[23]	+	
C-alkaloid O[23]	+	
C-alkaloid P[23]	+	
C-alkaloid UB[19,23,24]	+	
C-alkaloid Y[16,23]	+	*Str. toxifera*
C-alkaloid X[19,23,24]	+	
C-calebassinine[23,24]	+	
C-fluorocurine[23,24,30]	+	*Str. toxifera*
C-fluorocurinine[23–25]	+	*Str. mitscherlichii*
C-mavacurine[27,30]	+	*Str. toxifera*
C-xanthocurine[29]	+	
C-guaianine[29]	+	
C-alkaloid 1[27]	+	
C-alkaloid 2[27]	+	
Fedamazine[14]	−	*Str. toxifera*
Caracurine I[30]	−	*Str. toxifera*
Caracurine II[30]	−	*Str. toxifera*
Caracurine III[30]	−	*Str. toxifera*
Caracurine IV[30]	−	*Str. toxifera*
Caracurine V[30]	−	*Str. toxifera*
Caracurine VI[30]	−	*Str. toxifera*
Caracurine VII[30]	−	*Str. toxifera*
Caracurine VIII[30]		*Str. toxifera*
Caracurine IX[30]		*Str. toxifera*
Nor-dihydrotoxiferine[25]		*Str. toxifera*
Melinonine A[39] (= tetrahydroalstoninechlormethylate)		*Str. melinoniana*
Melinonine B[39]		*Str. melinoniana*
"Toxiferines III to XII" of King[40]*		*Str. toxifera*
Diaboline[42,43]		*Str. diaboli*

* The homogeniousness of these compounds is doubtful and we do not know their relation to other alkaloids of calabashes and strychnos barks.

important calabash alkaloid dihydrotoxiferine. It is the first time that the tertiary base of a quaternary calabash alkaloid salt has been observed in a plant.

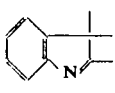
Other alkaloids occurring in this bark are still being studied in our laboratory.

We know to-day as many as 50 different alkaloids which have been found in calabashes or in barks of *Strychnos* species. Some of them are mentioned in the literature under different names (Table II).

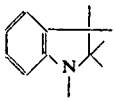
All calabash alkaloids isolated by us, contain 19 to 21, but generally about 20 C-atoms and 2 nitrogen atoms, one of which belongs to a

TABLE III

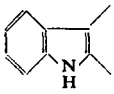
GROUPING OF CALABASH ALKALOIDS



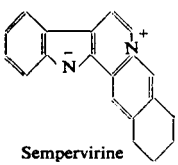
C-curarine $C_{20}H_{21}N_2^+$
C-alkaloid G $C_{20}H_{23}ON_2^+$
C-alkaloid E $C_{19}H_{23}ON_2^+$(?)
C-guaianine $C_{21}H_{25}ON_2^+$ or $C_{20}H_{25}N_2^+$



C-calebassine $C_{20}H_{23}ON_2^+$
C-alkaloid A $C_{20}H_{23}O_2N_2^+$
C-alkaloid F $C_{20}H_{25}O_2N_2^+$
C-alkaloid I $C_{20}H_{25}N_2^+$(?)
C-curarine II $C_{20}H_{23}ON_2^+$
C-alkaloid X

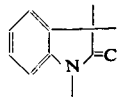


C-alkaloid J $C_{19}H_{21}N_2^+$
C-alkaloid L
C-mavacurine $C_{20}H_{23}ON_2$
Toxiferine III from *Str. toxifera*
Melinonine B from *Str. melinoniana*

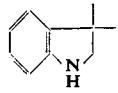


Sempervirine

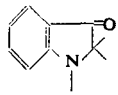
The spectrum of xanthocurine is very similar to those of sempervirine, *N*-methylyobyrine and flavocorynantheine, i.e., it possesses the character of the spectrum of the so-called anhydronium bases. The substance has the high specific optical rotation of more than +800°.



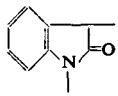
C-toxiferine I $C_{20}H_{23}ON_2^+$
C-dihydrotoxiferine $C_{20}H_{23}N_2^+$
C-alkaloid H
C-alkaloid 2



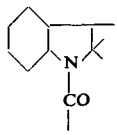
C-alkaloid B $C_{20}H_{23}ON_2^+$
C-alkaloid D $C_{20}H_{21}ON_2^+$
C-alkaloid C



C-fluorocurine $C_{20}H_{25}O_2N_2^+$
C-fluorocurinine $C_{21}H_{25}O_2N_2^+$



or



C-calebassinine $C_{19}H_{23}O_2N_2^+$
C-alkaloid UB $C_{19}H_{23}O_2N_2^+$

quaternary ammonium salt grouping, whilst the other in most or all cases probably belongs to an indole grouping. According to the absorption spectra, colour reactions, specific rotations and degradation products most of the calabash alkaloids can be put into groups, which contain the indole ring probably variously substituted in the form of the chromophores in Table III.

Transformation of the Alkaloids under the Influence of Acids

Several alkaloids of calabashes and of strychnos barks are very sensitive to acids and can be transformed into other compounds under the influence

of H^+. In this way Wieland and colleages[36] obtained from toxiferine-II-picrate under the influence of diluted hydrochloric acid, toxiferine IIa and the adsorption of the latter substance on aluminium-oxide lead to a new isomer, IIb. In a similar way C-toxiferine II is converted into C-toxiferine IIa by small amounts of acetic acid or hydrochloric acid[33].

Caracurine V is also very sensitive to acids. The end-products of this rearrangement are the caracurines II and VII which have been found in the same bark as caracurine V[31]. As a very unstable intermediate product of this transformation we were able to isolate a compound which possesses the characteristic ultra-violet spectrum of the C-toxiferine-alkaloids with the typical absorption maximum at 292 mμ. From this intermediate product caracurine Va the above mentioned alkaloids caracurine II and VII are formed under the influence of H^+. By heating caracurine Va caracurine V can be recovered.

The following formulæ show these various transformations:

caracurine V $C_{20}H_{21}ON_2Cl$

$H^+ \downarrow\uparrow$

caracurine Va $C_{20}H_{23}O_2N_2Cl$

caracurine II $C_{20}H_{23}O_2N_2Cl$ caracurine VII $C_{20}H_{23}O_2N_2Cl$

The transformation of caracurine V in Va seems to be connected with the addition of one molecule of H_2O.

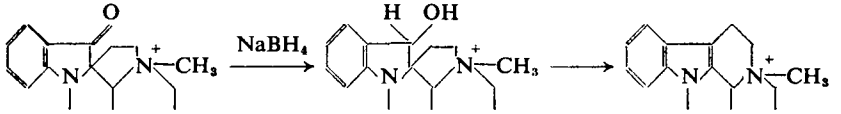
Caracurine VII shows a characteristic yellow reaction with ceric sulphate and a relatively large R_c value. Its spectrum is that of an indoline-derivative. Caracurine II however is a representative of the B,C,D-group, which migrates slowly and shows a violet ceric sulphate-reaction.

A third example of a transformation of an alkaloid of the C-toxiferine-group in a substance belonging to the B,C,D-group is the rearrangement of the C-alkaloid C-dihydrotoxiferine I into the C-alkaloid D[23] under the influence of diluted hydrochloric acid; this reaction was completed in 8 days. We observed as an intermediate compound a substance with an orange ceric sulphate reaction and a large R_c value.

So far fluorocurine is the best example we have found to illustrate the rearrangement caused by H^+. This contains the atom grouping A. By reduction it was converted into another, colourless alkaloid, which shows a characteristic indole spectrum (like the C-alkaloids J, L, I, etc.). This alkaloid has been shown to be identical with mavacurine on the basis of analyses, mixed melting point, colour reaction, ultra-violet spectrum and paper chromatograms. Mavacurine was first isolated by Wieland[37] from the South American drug "mavacurine" and from calabashes which also contained fluorocurine. We have isolated the same compound from calabashes, from the bark of *Strychnos toxifera* and *Strychnos melinoniana* and from barks of other *Strychnos* species[30], it always occurs together with fluorocurine.

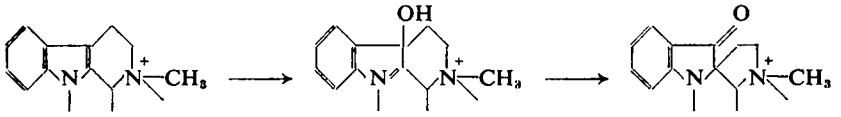
By transforming fluorocurine into mavacurine[27] we have achieved the transformation of a calabash alkaloid into another alkaloid that has been

found in calabashes. These reactions may be represented by the following formulæ:



The formation of mavacurine from hydrofluorocurine is a kind of retropinacoline rearrangement.

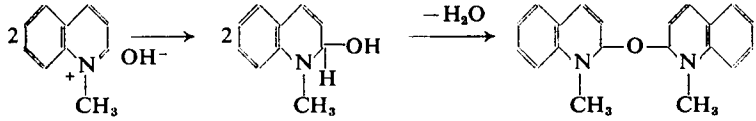
Presumably the reaction occurring in the plant is a reversal of the one observed *in vitro*, that is fluorocurine probably arises from mavacurine. From Witkop's similar observation with indole derivatives we assume that the indole compound mavacurine is first oxidised in β-position to the indole nitrogen and that the reaction product formed is immediately afterwards rearranged to give the indoxyl derivative fluorocurine:



Investigations on the Chemical Structure of the Curare Alkaloids

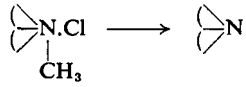
The elucidation of the constitution of all the calabash-alkaloids still lies in a rather distant future. Chemical examinations in this field are hindered by the difficulty of obtaining calabashes and of separating the various alkaloids; for example we chromatographed for more than a year before twenty-one alkaloids were separated. A further difficulty was due to the small quantities in which most of these compounds were obtained. Some of them we have only obtained in milligrams, whilst from others, grams have been isolated.

Some preliminary degradation experiments on calabash alkaloids were conducted by Wieland and his colleagues. By dehydration reactions on dehydrotoxiferine I they succeeded in obtaining β-ethylindole and *iso*quinoline whilst from C-toxiferine II some β-ethylpyridine was obtained. These observations together with the fact that C-curarine I like aromatic compounds, can be nitrated and brominated and like quaternary quinolinium bases is said to be transformed into a bimolecular ether base

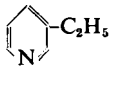


caused the above mentioned authors to suspect the presence of an *iso*-quinoline or quinoline ring in C-curarine I. Or alternatively an indole ring was considered to be part of the molecule.

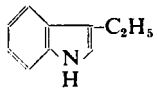
Our own investigations started with the thermal decomposition of C-curarine I chloride in high vacuum. Thereby the quaternary salt is decomposed to methyl chloride and norcurarine I. The latter compound being a tertiary base, it is not acetylatable and this indicates that the demethylated nitrogen atom must be common to two rings.



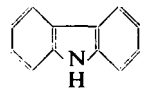
From this nor-C-curarine base the compounds IV-VII could be isolated after zinc dust distillation.



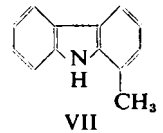
IV
β-Ethylpyridine



V
β-Ethylindole + scatole



VI
Carbazole

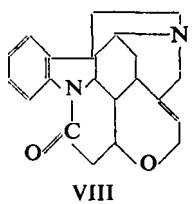


VII
1-Methylcarbazole

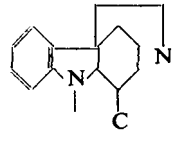
As carbazole is not changed by zinc dust distillation, it can be concluded that the ethyl group in β-ethylindole does not come from those nor-base carbon atoms, which are found in the decomposition products, carbazole and 1-methylcarbazole. Eighteen of the nineteen carbon atoms of the nor-base ($C_{19}H_{18}N_2$) are found in the above degradation-products.

The nonbasic indolo-nitrogen atom in C-curarine I is most probably substituted in a ring for these reasons: The NH-band is missing from the infra-red spectrum, the Zerewitinoff test of the base shows no active hydrogen and in the nor-base only a trace of *N*-methyl can be found.

The production of β-ethylindole after zinc dust distillation of norcurarine makes it possible that C-curarine, like many other plant bases, is derived from tryptamine. The isolation of carbazole and 1-methylcarbazole however excludes a constitution based upon the harman type (yohimbine bases). The dehydrogenation products obtained indicate a probable relationship of C-curarine with the strychnos alkaloids. Thus strychnine (VIII) for instance on vigorous degradation gave β-ethylindole β-collidine and carbazole.

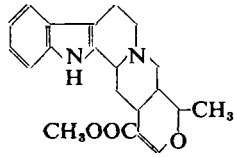


VIII



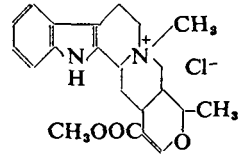
From a South American strychnos plant, *Strychnos melinoniana*, of which it is not known, whether or not the natives use it for poison production, Schlittler and Hohl[39] have isolated two alkaloids of quaternary ammonium salt character, melinonine A (X) and melinonine B. The

elucidation of the structure of melinonine A was easily achieved, whereas there is nothing yet known about the constitution of melinonine B. Melinonine A is nothing more than the methachloride of tetrahydroalstonine (IX).



IX

Tetrahydroalstonine



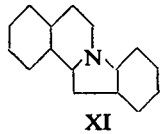
X

Melinonine A

Melinonine A has only a minimal curarising activity and has not yet been found in calabash curare.

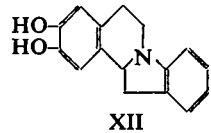
In connection with this it may be pointed out that recently a group of alkaloids has been found, which are tertiary, not quaternary bases but which nevertheless show strong curare activity. These alkaloids are found in the seeds of a member of the Leguminosæ family, *Erythrina* occurring in South America. Ramirez and Ribera[43], later Lehmann[44], Cicardo[45], Unna and Greslin[46–48] have noticed the curare activity of the extracts of these seeds and have ascertained the unusual fact that they show their activity after application by mouth, whereas tubocurare, pot curare and calabash curare only show high activity when they are directly introduced into the blood. Later Folkers[49–54] and colleagues isolated a series of pure substances from erythrina seeds, especially the so-called erythroidines $C_{16}H_{19}NO_3$. From about fifty kinds of *Erythrinæ* investigated, *E. americana*, *E. glauca*, *E. cristagalli* and *E. Eggersii* were especially rich in alkaloids.

The constitution of the erythrina bases has not yet been elucidated. Probably they are derived from the tetracyclic ring system A (XI)[56,57]; apo-erysopine (XII), a degradation product of many erythrina alkaloids, seems to correspond to formula B:



XI

(A)



XII

Apo-erysopine (B)

Some erythrina alkaloids (erysothiopine, erysothiovine) contain sulphur.

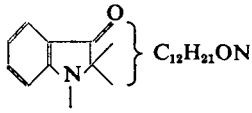
The erythrina alkaloids lower the blood pressure, have a toxic effect on the heart and, unlike the proper curare poisons, they cause central nervous system depression.

Wieland and his colleagues[34] recently studied the problem of the constitution of C-toxiferine II which is also called calebassine. This alkaloid is, according to the ultra-violet spectrum, probably an indole-derivative substituted in the α- and the β-position. This opinion is in harmony with the fact that after the dehydrogenation with sulphur β-ethylpyridine

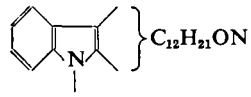
could be obtained. One of the two non-aromatic carbon double-bonds of C-toxiferine II lies, according to Wieland, in the vinyl-position to the indoline-nitrogen, because after oxidation and following saponification of the oxidised compound, formic acid was isolated. Finally the second carbon double bond of calebassine is believed to belong to an ethylidene side chain, because after oxidation with ozone, acetaldehyde was formed.

Recently we have been making experiments[57] to elucidate the constitutions of two calabash curare alkaloids, which possess a certain resemblance to the yohimbine alkaloids. The two alkaloids concerned, fluorocurine and mavacurine, always occur together and for this reason alone are presumably related in their manner of formation.

Fluorocurine exhibits the typical spectrum of an indoxyl derivative substituted at the N(1)-atom. It can therefore be assigned the partial formula XIII. Mavacurine can be recognised from its spectrum as an indole derivative and, since it can be prepared from fluorocurine, we may assign it the partial formula XIV:

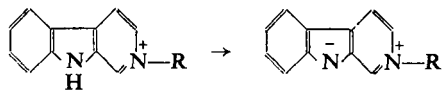


XIII
Fluorocurine



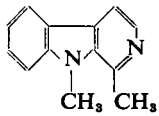
XIV
Mavacurine

Selenium dehydrogenation of nor-mavacurine yields a base which has the same spectrum as N(1)-methylharmane; since the spectrum of its chlormethylate is not altered by treatment with alkali, the indole nitrogen atom must carry a C-atom as substituent. Quaternary β-carbolinium salts, which are not alkylated at the indole-nitrogen, are transformed by alkali into deep coloured anhydronium-bases XV, XVI.

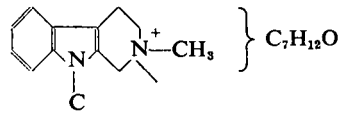


XV XVI

Hence the partial formula of mavacurine may now be expanded as follows (XVII):



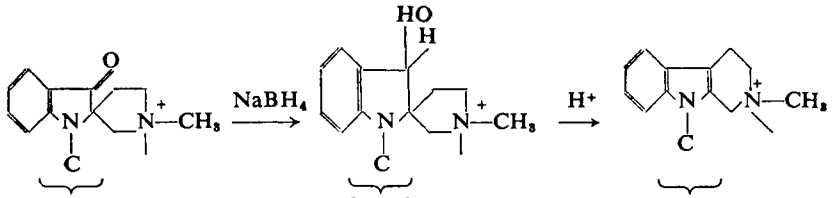
Methylharmane



XVII

Fluorocurine can be reduced with $NaBH_4$ to dihydrofluorocurine, which in turn, is readily converted to mavacurine under the influence of hydrogen ions. This conversion may now be represented by the partial formulæ XVIII, XIX, XX, which show it to be a retropinacoline rearrangement.

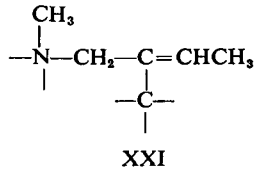
Mavacurine and fluorocurine each contains a C-CH_3 group and yields acetaldehyde on degradation with ozone. Consequently, their only carbon-carbon double bond must belong to an ethylidene grouping, C=$CHCH_3$.



The fact that the two alkaloids give one molecule of acetic acid when they are oxidised with chromic acid, according to the method of Kuhn-Roth agrees with this observation. A further proof for the ethylidene grouping could be ascertained by its selective hydrogenation and subsequent oxidation, which was effected with a new, modified carbon-methyl-determination. If during the oxidation with chromic acid the fatty acids of low molecular weight formed are continously distilled off, we are able to demonstrate in the distillate not only acetic acid but also propionic acid and further aliphatic acids with more carbon atoms, if a corresponding alkyl-group had been present in the substance which we oxidised.

Nor-hydrofluorocurine, the nor-base corresponding to the hydrofluorocurine could easily be reduced to a dihydro-derivative, which still possessed the absorption spectrum of the starting material and therefore still its chromophoric grouping. For that reason only the ethylidene group was reduced in the catalytical hydrogenation. This dihydro-nor-hydrofluorocurine gave, when oxidised with chromic acid, not only acetic acid, but also propionic acid, by which the grouping C-CH_2CH_3 was definitely proved.

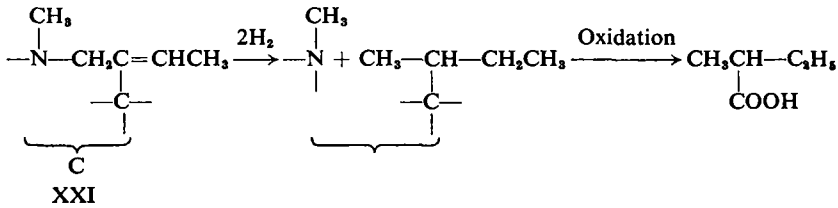
The following experiments showed that the ethylidene-grouping derives from a part of the molecule which may be represented by formula XXI.



XXI

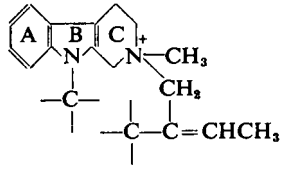
Hydrofluorocurine readily undergoes the so-called Emde degradation, i.e., when subjected to reduction with Pt and hydrogen in ethanolic solution, a C-atom attached to the quaternary nitrogen atom is split off; at the same time hydrogenation takes place at the C=C double bond.

On the degradation with chromic acid the Emde base gave as volatile acids not only acetic acid but also methylethylacetic acid, an especially important compound. Therefore the reaction which occurred in the Emde-degradation can be shown in the following way:



XXI

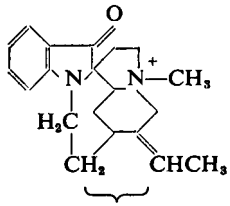
By this observation the grouping C is proved to occur in the molecule of fluorocurine. It can easily be understood that in our example the Emde degradation takes place without any difficulty, because allyl- and vinyl-amines are especially appropriate to it. We may therefore establish the partial formula XXII for mavacurine.



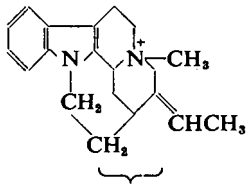
XXII

18 of the 20 carbon atoms present in the alkaloid are contained in this partial formula, in addition to the two nitrogen atoms. The two remaining C-atoms must be included in the formula in such a way that two carbon-rings more are formed, which are free of methyl-groupings.

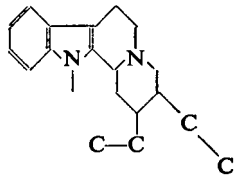
Biogenetic considerations are strongly in favour of the assumption that the missing carbon atom in the formula XXII should be so placed as to produce the carbon skeleton XXV of corynantheine, alstonine and yohimbine. If this is done, we arrive at the structural formulæ XXIII and XXIV, in which the position of the OH-group is still undetermined.



XXIII
Fluorocurine

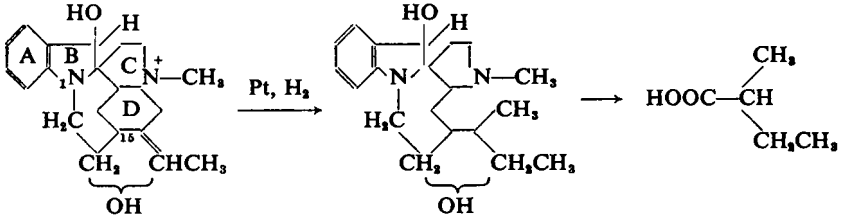


XXIV
Mavacurine



XXV

These formulæ are able to account for all the experimental findings made so far. The Emde degradation of hydrofluorocurine Emde base, and the oxidation of the latter to methylethylacetic acid, may then be represented in the following way:



XXVI
Hydrofluorocurine

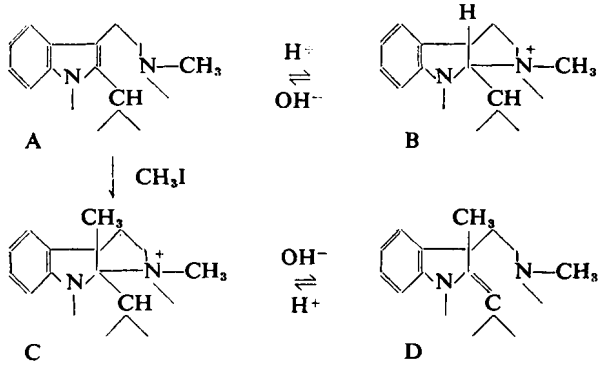
XXVIa
Hydrofluorocurine Emde base

According to this formulation, positions 1 and 15 in fluorocurine and mavacurine are connected by a carbon-carbon bridge, leading to the formation of heterocyclic 7-membered rings. Calotte models show that such structures are sterically possible.

In the same way that hydrofluorocurine XXVI is transformed by hydrogen ions into the indole derivative mavacurine, hydrofluorocurine

Emde base XXVIa undergoes rearrangement to a corresponding indole derivative under the influence of acids.

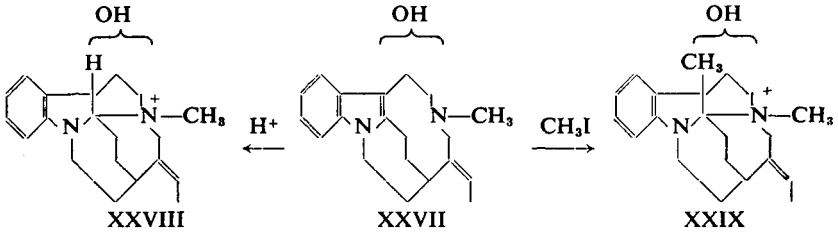
In favour of the existence of the 6-membered ring D in the two alkaloids the following further arguments can be mentioned. In the hydrogenation with platinum and hydrogen in 0·1N ethanolic potassium hydroxide mavacurine also undergoes an Emde degradation, whereby one mol. H_2 is taken up. But the reduction product contains—in contrast to the Emde base obtained from norhydrofluorocurine—only one methyl-group attached to a carbon-atom, because only one molecule of acetic acid is formed in the oxidation. The new Emde base has a typical indole spectrum, while its salts with acids possess an indoline spectrum. The same indoline spectrum was also observed in an addition product of CH_3I to the Emde base. These shifts in the spectra must be caused by a correlation of the indole chromophor and the $N_{(b)}$ of the alkaloid and they can be regarded as reversible, transannular interactions in the sense of the following formulæ:



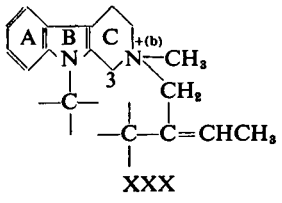
The addition product of CH_3I to the Emde-base A can be written corresponding to formula C, which like formula B, contains the indoline chromophor, while substance A, as we mentioned, possesses an indole spectrum. We could unambiguously prove that in compound C the newly entered CH_3-group is really attached to a carbon- and not to a nitrogen atom. We combined substance A with radioactive CH_3I which contained ^{14}C, and afterwards oxidised the formed addition-product with chromic acid; then the whole radioactivity was found in the acetic acid which was produced by the oxidation. Therefore the radio-active CH_3-group must have been fixed to a carbon atom.

So we come to the conclusion that during the transformation of the Emde-base XXVII into its salt XXVIII or into the methyliodide-addition product XXIX, a transannular interaction takes place which may be represented by formulæ XXVII-XXIX.

Now it is well known that such transannular interactions only occur in 8, 9 and 10 membered rings and that they consist in the formation of a new ring with 5 or 6 ring atoms. In the partial formula XXX of mava-curine, the new ring D which is to be attached to ring C can only be 5- or 6-membered. A further conclusion is, that the new ring D must be



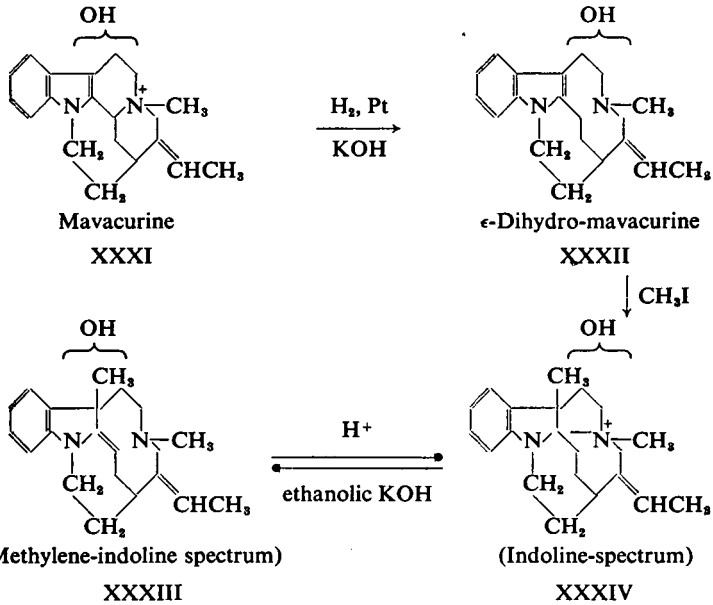
XXVIII XXVII XXIX



XXX

fixed to the carbon atom 3 of ring C. Finally we may conclude that in the Emde degradation of mavacurine the bond between carbon atom 3 and nitrogen atom b (C_3–$N_{(b)}$) is split off.

The Emde-degradation of the mavacurine can therefore be succinctly summarised by the formulæ XXXI-XXXIV:



Mavacurine — XXXI

ϵ-Dihydro-mavacurine — XXXII

(Methylene-indoline spectrum) — XXXIII

(Indoline-spectrum) — XXXIV

A whole series of other transformations have been carried out with the new mavacurine and fluorocurine derivatives, but it is not possible to give details of these here. It is obvious that these substances are representatives of a new type of indole alkaloid, which is characterised by its ability to undergo a large number of rearrangements.

PHARMACOLOGY OF CURARE[47–58]

I would now like to turn briefly to the pharmacology of curare. Curare acts at the connection between the motor nerves and the muscle fibres, the so-called motor end-plates. It thereby represses or prevents

the impulse transmission from the nerve to the muscle, but does not change the conductivity of the nerve fibre itself nor the action potential of a directly stimulated nerve. The transfer of the excitation on to the muscle fibre results under normal conditions from the effect of the acetylcholine formed by the excitation of the nerve. If the muscle has been previously curarised and the nerve then excited, acetylcholine is still produced but this cannot reach the receptor cells and the muscle which therefore remains relaxed. The threshold of excitation of the muscle for the acetylcholine set free has been very much raised by the effect of curare. By using substances which repress cholinesterase and which therefore increase the duration of acetylcholine activity (for instance eserine or neostigmine) the curarisation of the muscle can be interrupted.

During the last ten years compounds with curare activity have aroused great medical interest.

TABLE IV

ACTIVITIES OF CURARE ALKALOIDS IN THE MOUSE TEST

C-Alkaloid-chlorides	Head-drop dose (HD) μg./kg.	Righting reflex abolished μg./kg.	Min. LD μg./kg.	$\frac{\text{Min. LD}}{\text{HD}}$	Time of paralysis min.
E	0·3–4·0	0·5 –5·0	0·95–8·0	3·2	18
G	0·6–5·0	0·65–7·0	0·7–12·0	1·2	7
Toxiferine	9	12	23	2·5	12
H	16	21	24	1·5	3·7
Curarine	30	35	50	1·7	4
Dihydro-toxiferine (K)	30	40	60	2·0	5·5
A	70	100	150	2·1	2
F	75	85	120	1·6	1·3
I	174	180	195	1·1	2·75
Calebassine	240	260	320	1·3	3
C	240	280	380	1·6	2·75
B	280	310	350	1·25	1·3
J	290	460	560	1·9	1·5
D	1100	1600	2000	1·8	1·3
Fluorocurarine	1800	2100	4000	2·2	2
L	1900	2200	2400	1·3	2
Fluorocurinine	2750	2900	3250	1·2	1·2
Fluorocurine	4400	5500	8000	1·8	1·5
Calebassinine	22,000	25,000	44,000	2	0·3
(+)-Tubocurarine chloride	75	100	130	1·7	1

Griffith and Johnson[59] in 1942 showed that curare compounds during anæsthesia caused complete relaxation of the skeletol muscle, thereby enabling the quantity of the anaesthetic to be reduced.

To-day it is very often applied in operations of the stomach and abdomen and in thoracic surgery, often being combined with simultaneous artificial respiration of the patient. It is useful but less important for prevention of spasms during leptazol and electro-shock. The introduction by Wintersteiner of a pure standardised curare preparation, the (+)-tubocurarine, was the beginning of its general clinical application. Good curare preparations show practically no side effects, the circulation especially remains unaffected.

For instance C-toxiferine can be given to an animal, undergoing artificial respiration, in a hundred times greater doses than the paralysing dose without it suffering any change of blood pressure or heart frequency.

The curarisation symptoms of a mouse or a rabbit begin with unsteady, trembling steps. Then the so-called head-drop symptom is seen, that is

the head cannot be held in the normal manner and slowly drops. As paralysis proceeds the animal falls in a lateral position in which it can be moved without resistance. Death then occurs as a result of paralysis of the respiratory muscles, or with small doses a recovery is made in which the various stages of paralysis are undergone in reversed order.

The calabash curare alkaloids isolated by us show very different toxicities. They lie between 0·3 μg. to 20 mg./kg. mouse corresponding to a ratio of $1 : 10^5$ (Table IV).

It is of interest to observe that the highly active alkaloids have small R_c values on the paper chromatogram, that is they travel only a short distance. The far moving alkaloids like C-fluorocurine, C-fluorocurarine, C-fluorocurinine, calebassine, C-alkaloid L and mavacurine show none at all or only very small curarising effects. Within the different groups of the highly active alkaloids the biological activity decreases with increasing R_c values or increasing partition coefficient between the organic phase and water respectively. It appears therefore that the intensity of the curare activity is influenced by this partition coefficient, that is by a high water solubility (Table V).

TABLE V

CONNECTION BETWEEN ACTIVITY AND R_c VALUES OF SOME CURARE ALKALOIDS[22]

Group	C-alkaloid-chlorides	Head-drop dose µg./kg.	R_C
Curarine-group	E	0·3–4·0	0·36
	G	0·6–5·0	0·65
	curarine	30	1·0
Toxiferine-group	toxiferine	9	0·42
	H	16	0·71
	dihydro-toxiferine (K)	30	1·22
Calebassine-group	A	70	0·23
	F	75	0·49
	I	174	0·89
	calebassine	240	0·80
B,C,D-group	C	240	0·34
	B	280	0·34
	D	1100	0·35

In Figure 2 the activities of the different alkaloids are plotted taking the head-drop and lethal doses on the abscissæ and the duration of paralysis and a dose lying in between as the ordinate, both scales being logarithmic.

Each rectangle corresponds to an alkaloid, the abscissæ representing the therapeutic range and the ordinate the intensity of paralysis. Alkaloids with large rectangles, in particular C-curarine, C-toxiferine, and the C-alkaloids E, G and K, are especially fitted for curarising mice, for they show a strong paralysing activity and a large therapeutic range. Seven of the alkaloids investigated are more active than tubocurarine, for instance C-alkaloid E 250 times, C-alkaloid G 120 times. One gram of E would paralyse at least 100 tons of mice.

The importance that curare has recently gained in medicine has led numerous investigators and many pharmaceutical companies to produce synthetic curare-like substances. With the exception of the erythrina alkaloids, which have the character of tertiary bases, the naturally occurring curare alkaloids are quaternary or bi-quaternary ammonium salts.

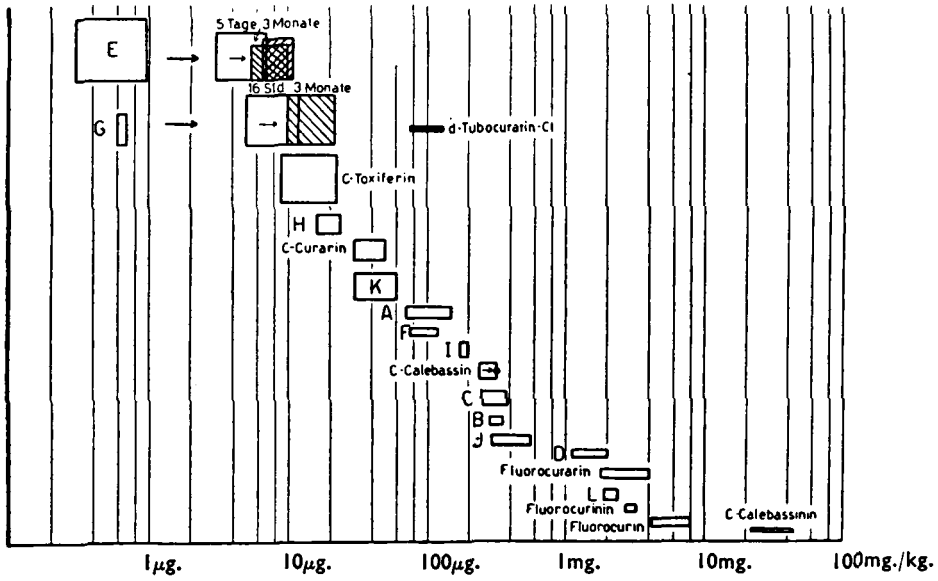
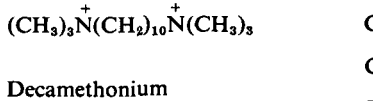


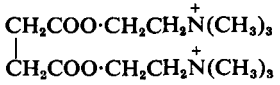
FIG. 2. Activities of the alkaloids and duration of paralysis.

This has led to attempts to synthesise various kinds of quaternary ammonium salts.

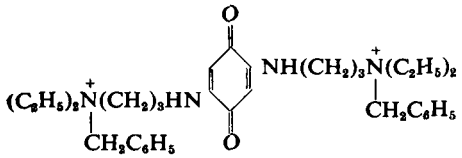
To many of these synthetic works the formula of (+)-tubocurarine served as a model, the main property of which is the two quaternary ammonium salt groups. Thus many compounds have been synthesised containing two ammonium salt groupings. Among these the following ones, because of their relatively high activity have found limited clinical application:



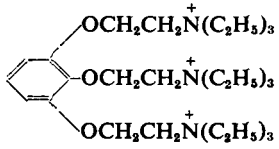
Decamethonium
Barlow and Ing[60]
Paton and Zaimis[61]



Succinylcholine
Ginzel, Klupp, Werner[62]



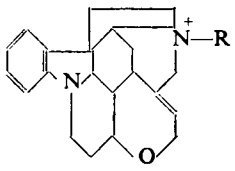
Mytolon
Cavallito, Soria, Hoppe[63]



Gallamine
Bovet[64]

In our laboratories a fairly large number of halogen alkylates of strychnidine, dihydrostrychnidine, neostrychnidine and brucidine were synthesised for pharmacological testing. These, like the calabash curare alkaloids, contain only one quaternary ammonium salt grouping. Mention has already been made that C-curarine is probably related to strychnine. Some of the synthesised and pharmacologically tested chloro- and

iodo-alkylates of strychnidine and neostrychnidine have proved to be highly curare active although they do not reach the paralysing activity and toxicity of C-curarine or even C-toxiferine I.



Strychnidine chloro-alkylates

The potency and toxicity of these compounds have been determined (Table VI).

So far little is known of the fate of these alkaloids in the organism and the form in which they are excreted. It has been known for a long time that curare when injected into the blood stream is very rapidly absorbed, whereas when administered by mouth the assimilation takes place only very slowly. The excretion in the urine takes place rapidly. In order to be able to study the excretion and distribution better, a radioactive C-curarine was made in our laboratory by reacting $^{14}CH_3I$ with norcurarine.

TABLE VI

Compound	Active doses for frogs in mg./kg.	Lethal doses for rabbits in mg./kg.
Strychnidine methylchloride	8	1·4
Strychnidine ethylchloride	10	0·6
Strychnidine propylchloride	23	?
Strychnidine butylchloride..	14	1·9
Strychnidine benzylchloride	21	1·3
Dihydrostrychnidine methylchloride	35	1·7
Dihydrostrychnidine benzylchloride	28	2·3
C-curarine	0·1	0·03
C-toxiferine	0·005–0·009	0·008–0·012

High doses of this radioactive C-curarine were given to cats. In an experiment during which the normal excretion was maintained, about 25 per cent. of the injected curarine could be detected in the urine two hours after the injection and only 0·5 per cent. in the air breathed out.

TABLE VII

CAT ♂ 3·0 KG. 4·352 MG. RADIOACTIVE C-CURARINE CHLORIDE INJECTED INTRAVENOUSLY (12·2 RE. $10 \cdot 146.10^6$ CPM.). TIME OF THE EXPERIMENT 2 HOURS

Organs	Observed activity as a percentage of the applied activity	Curarine in μg. per g. or ml. of the organ
Liver	17·54	9·51
Muscle	12·25	0·41
Gut	4·74	1·21
Kidney	2·87	8·06
Lungs	0·93	2·23
Spleen	0·33	2·09
Heart	0·10	0·34
Thymus	0·06	0·84
Thyroid	0·01	1·10
Ganglion	—	1·84
Suprarenal glands ..	0·01	0·82
Bile	11·01	159·8
Urine	1·4	10·4
Serum	5·54	1·75
Brain	traces	traces
CO_2 expired	traces	traces
	56·8	

In a second experiment the normal excretion of the curarine through the kidneys had been rendered impossible by a shunt of the kidney ducts. Now the injected alkaloid was found to be distributed over muscles, liver, intestine, kidneys and bile. Referred to the weight the muscles had taken up only a little curarine and in the air breathed out there were only traces. This is shown in Table VII.

Acknowledgement

Several pupils of mine participated in the investigations on calabash curare. I mention Prof. H. Schmid, who took part in these investigations from their beginning, Dr. P. Waser, Dr. A. Ebnöther, Dr. J. Kebrle, Dr. H. Asmis, Dr. H. Bickel, Miss E. Bächli and H. Meyer, to all of whom I offer my thanks for their assistance and help.

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