ALKALOIDS OF CALABASH-CURARE AND *STRYCHNOS* SPECIES

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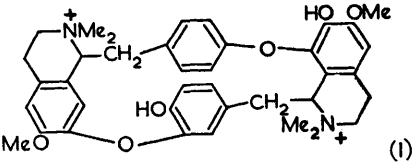
NEWS of the dramatic paralysing effect of the South American Indian arrow and dart poisons known as curare was carried back by the early explorers of that continent and has held the interest of men of science and medicine since the sixteenth century. This interest was increased by the mystery surrounding the preparation of the poison, and many fantastic stories became connected with it. These are included in an entertaining account of the history, preparation, and pharmacology of curare given in McIntyre's excellent monograph.[1] Recently a collection of authoritative accounts of all aspects of curare has been published[2] as the proceedings of a UNESCO Symposium held in 1957; the present Review is desirable because of the spectacular advances made in knowledge of the chemistry of curare since that time.

As pointed out by McIntyre, curare is a generic term which includes many types of arrow-head poison prepared in South America, and the constitution of individual preparations varies according to geographical origin. All curares are powerful poisons which paralyse voluntary muscle[2] and all are concentrated aqueous extracts of plant material. Boehm[3] classified curares according to the type of container used to pack the final product; he writes of tube-curare packed in bamboo tubes, pot-curare, for which earthen pots were used, and calabash-curare held in calabashes or gourds. Although the validity of this classification has been questioned,[4] in particular the existence of pot-curare as a distinct group, it is useful for this discussion to accept the broad division into tube-curare and calabash-curare.



(I)

It was early realised[3] that the active principles of curare are water-soluble quaternary alkaloids, and in 1935 King[5] isolated the now well-known curarising agent *d*-tubocurarine (1) from tube-curare; *d*-tubocurar-

[1] McIntyre, "Curare, Its Natural History and Clinical Use", University of Chicago Press, Chicago, 1947.
[2] Bovet, Bovet-Nitti, and Marini-Bettolo (editors), "Curare and Curare-like Agents", Elsevier, 1959; see also Craig, "The Alkaloids", Vol. V, ed. Manske, Academic Press, New York, 1955, p. 265.
[3] Boehm, *Abhandl. Kgl. sächs. Ges. Wissensch.*, 1895, **22**, 201; 1897, **24**, 1.
[4] Lewin, "Die Pfeilgifte", Barth, Leipzig, 1923; Gill, *Anesthesiol.*, 1946, **7**, 14.
[5] King, *J.*, 1935, 1381.

ine is an example of a quaternary bisbenzylisoquinoline alkaloid. Tube-curare is prepared mainly from the bark of Menispermaceous plants, particularly the genus *Chondrodendron*, and *d*-tubocurarine was later isolated by Wintersteiner and Dutcher from *C. tomentosum*.[6] Further work by King[7] and others led to the isolation and structural elucidation of many more bisbenzylisoquinoline alkaloids from these sources.

Calabash-curare originates in the northern parts of the South American continent, particularly in the Amazon and Orinoco basins. It is considerably more active physiologically than tube- or pot-curare, and has presented much more formidable chemical problems. Some of the major problems, however, have now been overcome and efforts have been increased owing, not only to the rich and fascinating chemistry involved, but also to the pharmacological interest of the curare alkaloids. *d*-Tubocurarine chloride and synthetic curare agents with essentially the same action are now extensively used in surgery in conjunction with light anæsthesia. With their aid it is possible to achieve the required degree of muscular relaxation necessary for successful surgery without recourse to potentially dangerous deep anæsthesia. The interest attaching to the much more active calabash-curare alkaloids is thus obvious.

Over a century ago, Robert Schomburgk[8] was able to see barks of *Strychnos toxifera* and other *Strychnos* species being used as important constituents of calabash-curare. This has been confirmed by later observations and is also apparent from the general similarity in alkaloid content between calabash-curare and extracts from the bark of various *Strychnos* species. It has been shown particularly well by the extensive chromatographic studies of Marini-Bettolo and his collaborators.[9] Thus chemical investigations of calabash-curare and of the barks of *Strychnos* species are mutually related topics and can be conveniently considered together in this Review. An exhaustive survey of work in this field, which has been largely carried out over the last decade, has been published by Bernauer.[10]

Isolation of Pure Alkaloids.—Serious chemical work on calabash-curare was started by Boehm[3] in 1897 and resulted in the isolation of a highly active amorphous principle; much later (1935), King[11] described the preparation of an equally active amorphous quaternary iodide from the bark of *S. toxifera*. However, the first isolation of crystalline calabash-curare alkaloids was achieved by H. Wieland and his school.[12–15] The

[6] Wintersteiner and Dutcher, *Science*, 1943, **97**, 467.
[7] King, *J.*, 1948, 265 and earlier papers.
[8] See ref. 1, page 33.
Penna, Iorio, Chiavarelli, and Marini-Bettolo, *Gazzetta*, 1957, **87**, 1163 and earlier papers.
[10] Bernauer, *Forschr. Chem. org. Naturstoffe*, 1959, **17**, 184.
[11] King, *Nature*, 1935, **135**, 469.
[12] Wieland, Konz, and Sonderhoff, *Annalen*, 1937, **527**, 160.
[13] Wieland and Pistor, *Annalen*, 1938, **536**, 68.
[14] Wieland, Pistor, and Bähr, *Annalen*, 1941, **547**, 140.
[15] Wieland, Bähr, and Witkop, *Annalen*, 1941, **547**, 156.

German workers precipitated the quaternary alkaloids as a mixture of reineckate salts which was then fractionated by adsorption chromatography on alumina; of the various reineckate fractions they obtained, some yielded crystalline chlorides and picrates. C-Curarine I chloride* was the first calabash-curare alkaloid to be so isolated; other well-characterised alkaloids isolated in this early work were C-calebassine and C-dihydrotoxiferine I from calabash-curare, and toxiferine I and toxiferine II from the bark of *S. toxifera*. Using the same chromatographic technique, King[16] also isolated toxiferine I and toxiferine II from *S. toxifera* together with a series of new alkaloids, all in small quantity, designated toxiferine III—XII. Recently it has been shown[17] that several of these salts III—XII are identical with well-characterised alkaloids described after King's original paper; toxiferine V and toxiferine XI are identical with toxiferine I.

Though chromatography of the alkaloidal reineckates was a major step forward in fractionation technique, the method has its drawbacks. For example, it has been found[17] that well-separated bands on the column can all contain the same quaternary alkaloid. It is now firmly established that the most satisfactory fractionation procedure in this field is partition chromatography on cellulose, developed by the Zürich and Munich schools.[18,19] Most of the present total of about seventy pure curare alkaloids have been isolated by this technique. Some idea of the complexity of the isolation problem can be gained from Schmid, Kebrle, and Karrer's demonstration[18] that at least forty-one alkaloids were present in a sample of calabash curare from the Amazon basin; even the single plant material, *Strychnos toxifera*, examined by Battersby, Binks, Hodson, and Yeowell,[17] contains at least thirty quaternary alkaloids. Extensive fractionation involving repeated chromatography on cellulose and alumina is usually required before crystalline alkaloids can be obtained.

The Table shows those alkaloids isolated from calabash-curare and *Strychnos* species which have been sufficiently studied to warrant their inclusion in this Review; little can be said at present about the other forty or so alkaloids and it will suffice to give their names and references to their isolation in the Appendix.

Even during the early investigations by Wieland and King, it became probable that the curare alkaloids are indole derivatives and with recent advances, particularly from Karrer and Schmid's group, it is possible to correlate the ultraviolet spectra of many of the alkaloids with one or other of six related chromophores. These are the indoline (2), methyleneindoline

* (*a*) The quaternary alkaloids are often isolated and handled as the chlorides and it is therefore convenient to use the name of the alkaloid as meaning alkaloid chloride. Thus, in the sequel, C-curarine I means C-curarine I chloride and other alkaloids will be treated in the same way. Anions other than chloride will be named. *e.g.*, toxiferine I picrate, (*b*) The letter C- denotes calabash.

[16] King, *J.*, 1949, 3263.
[17] Battersby, Binks, Hodson, and Yeowell, *J.*, in the press.
[18] Schmid, Kebrle, and Karrer, *Helv. Chim. Acta*, 1952, **35**, 1864.
[19] Wieland and Merz, *Chem. Ber.*, 1952, **85**, 731.

Alkaloids of Calabash-curare and Strychnos *species*

No.	Alkaloid	Formula of cation or base	R_C[a] Value	Chromophore
1	Toxiferine I	$C_{40}H_{46}O_2N_4^{++}$	0·42	Methyleneindoline
2	C-Dihydrotoxiferine I	$C_{40}H_{46}N_4^{++}$	1.2	,,
3	C-Alkaloid H	$C_{40}H_{46}ON_4^{++}$[c]	0·71	,,
4	Nordihydrotoxiferine	$C_{38}H_{40}N_4$	1·2	,,
5	Caracurine VI	$C_{38}H_{40}ON_4$[c]	1·6	,,
6	Caracurine II	$C_{38}H_{40}O_2N_4$[c]	0·8	Indoline
7	Toxiferine IX ≡Caracurine II methochloride	$C_{40}H_{46}O_2N_4^{++}$[c]	0·42	,,
8	C-Alkaloid D	$(C_{20}H_{21}ON_2^{+})_n$[c]	0·34	,,
9	Caracurine V	$C_{38}H_{40}O_2N_4$	1·4	Modified indoline
10	Caracurine VII	$C_{19}H_{22}O_2N_2$	2·1	Indoline [N(*a*) as NH]
11	Hemitoxiferine I	$C_{20}H_{25}O_2N_2^{+}$	1·5	,, ,,
12	C-Calebassine	$C_{40}H_{48-50}O_2N_4^{++}$	0·8	Indoline carbinolamine
13	C-Alkaloid A	$C_{40}H_{48-50}O_4N_4^{++}$	0·23	,, ,,
14	C-Alkaloid F	$C_{40}H_{48-50}O_3N_4^{++}$[c]	0·49	,, ,,
15	C-Alkaloid Y	No analysis	1·6	,, ,,
16	C-Cararine I	$C_{40}H_{44-46}ON_4^{++}$	1·0	Unknown
17	C-Alkaloid E	$C_{40}H_{44-46}O_2N_4^{++}$	0·36	,,
18	C-Alkaloid G	$C_{40}H_{44-46}O_2N_4^{++}$[c]	0·65	,,
19	C-Curarine III ≡ C-Fluorocurarine	$C_{20}H_{23}ON_2^{+}$	2·2	See p. 97
20	Diaboline	$C_{21}H_{24}O_3N_2$		*N*-Acylindoline
21	C-Mavacurine	$C_{20}H_{25}ON_2^{+}$	2·7	Indole
22	Melinonine A	$C_{22}H_{27}O_3N_2^{+}$	4·0	,,
23	Melinonine B	$C_{20}H_{27}ON_2^{+}$	2·7	,,
24	C-Alkaloid T	$C_{20}H_{24}O_2N_2$	—	,,
25	Lochneram	$C_{21}H_{27}O_2N_2^{+}$	3·1	,,
26	C-Fluorocurine	$C_{20}H_{23}O_2N_2^{+}$	2·1	ψ-Indoxyl
27	Melinonine G	$C_{17}H_{15}N_2^{+}$	3·2	β-Carbolinium
28	Melinonine F	$C_{13}H_{13}N_2^{+}$	2·0	β-Carbolinium

[a] The mobilities of the alkaloids on paper are referred to that of C-curarine I as standard. Thus R_C for toxiferine I $= \frac{\text{distance moved by toxiferine I}}{\text{distance moved by C-curarine I}}$ in solvent "C".[18]

[c] These formulæ may still need revision, particularly in respect of the hydrogen content.

[20] Kebrle, Schmid, Waser, and Karrer, *Helv. Chim. Acta*, 1953, **36**, 102.
[21] Asmis, Waser, Schmid, and Karrer, *Helv. Chim. Acta*, 1955, **38**, 1661.
[22] Asmis, Schmid, and Karrer, *Helv. Chim. Acta*, 1954, **37**, 1983.
[23] Asmis, Bächli, Giesbrecht, Kebrle, Schmid, and Karrer, *Helv. Chim. Acta*, 1954, **37**, 1968.

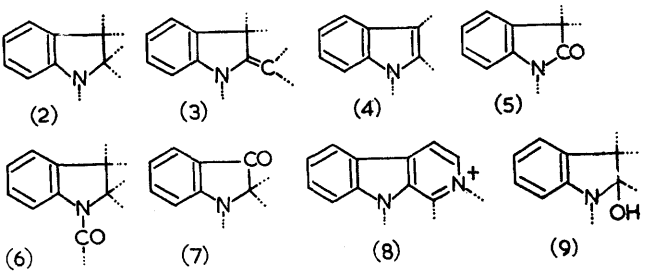
Alkaloids of Calabash-curare and Strychnos *species*—continued

No.	Colour with ceric sulphate immediate—After 20 min.	Physiological activity[b]	First isolation
1	Red-violet—Colourless	9γ [20]	*S. toxifera*[15] (Br. Guiana)
2	Blue-violet—Colourless	30γ [20]	Calabash[15]
3	Red-violet—Colourless	16γ [20]	Calabash[18]
4	Violet—Pale brown	—	*S. toxifera*[21] (Venezuela)
5	Purple—Brown	Inactive [22]	*S. toxifera*[22] (Venezuela)
6	Purple—Brown	Inactive [22]	*S. toxifera*[22] (Venezuela)
7	Violet	* Over 400γ [16]	*S. toxifera*[16,17] (Br. Guiana)
8	Red-violet—Yellowish	1100γ [20]	Calabash[18]
9	Purple-red—Brown	Inactive [22]	*S. toxifera*[22] (Venezuela)
10	Stable orange	Inactive [22]	*S. toxifera*[22] (Venezuela)
11	Stable orange	1140γ [21]	*S. toxifera*[17] (Br. Guiana)
12	Blue-violet—Carmine	240γ [20]	Calabash[15]
13	Blue-violet—Carmine	70γ [20]	Calabash[18] and *S. toxifera*[16,17]
14	Blue-violet—Carmine	75γ [20]	Calabash[18]
15	Red-violet—Olive green	—	Calabash[23]
16	Blue—Chrome green	30γ [20]	Calabash[18]
17	Blue—Chrome green	0·3—4·0γ [20]	Calabash[18]
18	Blue—Chrome green	0·6—5·0γ [20]	Calabash[18]
19	Blue-green—Yellow-green	1800γ [20]	Calabash[14]
20	Nil	*Inactive [24]	*S. diaboli*[24]
21	Carmine	†Inactive [19]	Calabash[19]
22	Nil	†Inactive [25]	*S. melinoniana*[25]
23	Nil	†Inactive [25]	*S. melinoniana*[25]
24	Very pale red	—	Calabash[26]
25	—	—	Calabash[27]
26	Red-violet—Brownish	4400γ [20]	Calabash[28]
27	Nil	—	*S. melinoniana*[29]
28	Nil	—	*S. melinoniana*[29]

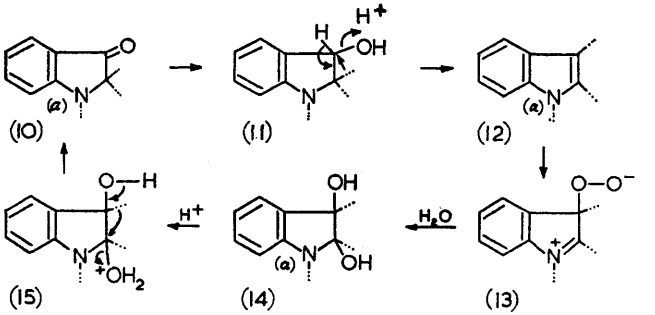
[b] The figures give the dose in γ (μg,) per kg. for the head-drop assay on the mouse;[30] the figures marked * are for head-drop assay on the rabbit,[16] and the results marked † are for toxicity test on the frog.[19,25]

[24] King, *J.*, 1949, 955.
[25] Schlittler and Hohl, *Helv. Chim. Acta*, 1952, **35**, 29.
[26] Arnold, von Philipsborn, Schmid, and Karrer, *Helv. Chim. Acta*, 1957, **40**, 705.
[27] Arnold, Berlage, Bernauer, Schmid, and Karrer, *Helv. Chim. Acta*, 1958, **41**, 1505.
[28] Schmid and Karrer, *Helv. Chim. Acta*, 1947, **30**, 2081.
[29] Bächli, Vamvacas, Schmid, and Karrer, *Helv. Chim. Acta*, 1957, **40**, 1167.
[30] Waser, *Helv. Physiol. Pharmacol. Acta*, 1950, **8**, 343.

(3), indole (4), oxindole (5) or *N*-acylindoline (6), ψ-indoxyl (7) and β-carbolinium (8) systems. In some alkaloids, simple modifications of these systems are involved, for example, the carbinolamine (9). The groups in the Table have been constructed on the basis of chromophore and it is worth drawing attention to the close connection between chromophore and colour reaction with ceric sulphate.



C-Mavacurine, C-Fluorocurine, and C-Alkaloid Y.—A first insight into the structures of alkaloids from calabash-curare came from a study of C-mavacurine and C-fluorocurine. The former was isolated by Wieland and Merz[19] and the latter by Schmid and Karrer;[28] both were subsequently found in *S. toxifera* from Venezuela.[22] Work on these alkaloids was greatly



facilitated by the discovery by Karrer, Schmid, and their co-workers[31] that they are structurally related. Thus the quaternary C-fluorocurine, $C_{20}H_{25}O_2N_2^+$, which clearly showed the 2,2-disubstituted ψ-indoxyl chromophore (10), was reduced to hydrofluorocurine (partial structure 11) by borohydride. Acid then catalysed the illustrated rearrangement which is typical[32] of 2,2-disubstituted 3-hydroxyindolines (11), to yield a 2,3-disubstituted indole (partial structure 12). The indolic product was identical with natural C-mavacurine. Fritz, Wieland, and Besch[33] were able to extend the relationships by making use of the extensive researches

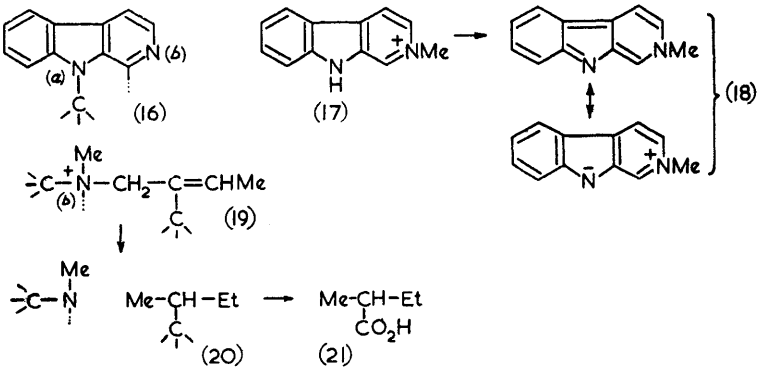
[31] Bickel, Giesbrecht, Kebrle, Schmid, and Karrer, *Helv. Chim. Acta*, 1954, **37**, 553; Bickel, Schmid, and Karrer, *ibid.*, 1955, **38**, 469.

[32] Witkop, *J. Amer. Chem. Soc.*, 1950, **72**, 614; Witkop and Patrick, *ibid.*, 1951, **73**, 713.

[33] Fritz, Wieland, and Besch, *Annalen*, 1958, **611**, 268.

of Witkop and Patrick[34] on simple tetrahydrocarbazoles. Oxidation of C-mavacurine (partial structure 12) catalytically with oxygen over platinum gave a product to which the partial structure (14) was assigned; this is no doubt formed by way of the peroxide (13). The product had the properties of a glycol and—what was important—was rearranged by acid as illustrated, to give C-fluorocurine (partial structure 10). Since the intermediate (14) was found to be identical with C-Alkaloid Y previously isolated from a calabash,[23] a triad of related alkaloids was available; structural information derived from one alkaloid can thus be used for the other two.

C-Fluorocurine contains an ethylidene side chain $\left(\diagup\!\!\diagdown C{=}CHMe\right)$, an acetylatable hydroxyl group, and one *N*-methyl group, the last being attached to the quaternary N(*b*) atom.[31] These functions and the analytical evidence require that C-fluorocurine be pentacyclic and the foregoing correlations show that this also holds for C-mavacurine. A clue to the probable arrangement of three of these rings came from selenium dehydrogenation of normavacurine, the tertiary base derived by pyrolysis of the quaternary C-mavacurine. This degradation yielded a β-carboline derivative (16) which was not fully identified because of the minute amount

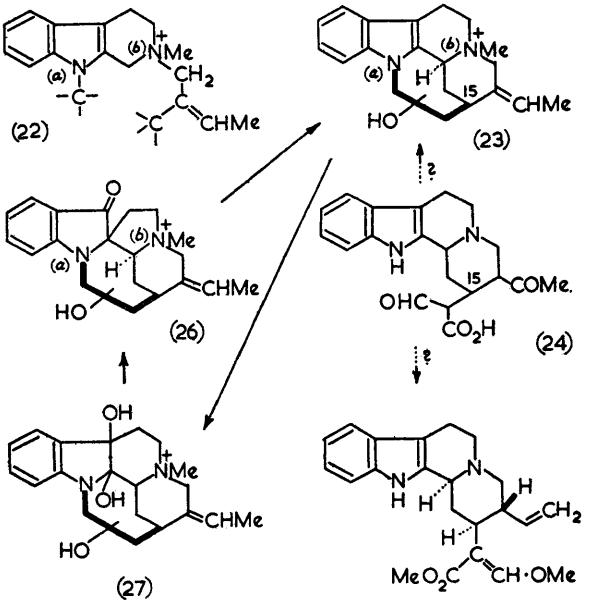


available, a common difficulty in the curare field. However, the spectral properties of the *N*(*b*)-methiodide of the degradation base, particularly the stability of the chromophore towards alkali, showed clearly that the indolic nitrogen N(*a*), is alkylated;[31] it should be mentioned for comparison that the spectrum of the salt (17) is profoundly changed by alkali owing to the formation of the anhydro-base (18). Further, catalytic hydrogenation of hydrofluorocurine (partial structure 11) resulted in Emde degradation to a tertiary base (20) which, unlike the starting material, gave α-methylbutyric acid (21) on Kuhn–Roth oxidation.[31] This result establishes the presence in hydrofluorocurine of a quaternary allylamine system as in (19) which would undergo Emde degradation and reduction as illustrated.

[34] Witkop and Patrick, *Experientia*, 1950, **6**, 183 and subsequent papers.

Because of the cyclic set of changes shown in the partial formulae (10) →(12)→(14)→(10), it is certain that the conversion of C-fluorocurine into C-mavacurine only involves the ψ-indoxyl to indole change, and so the same system (19) is also present in C-mavacurine.

The foregoing evidence can now be combined in partial structure (22) for C-mavacurine and there remain two carbon atoms for construction of two rings free from *C*-methyl groups. These requirements can be met by the constitution (23) which Bickel, Schmid, and Karrer propose[31] for the alkaloid; no firm proposal is made for the site of the hydroxyl group though position 15 is favoured.



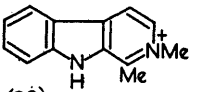
The plausible biogenetic arguments by which this structure is derived involve the indicated intramolecular cyclisation of the supposed intermediate (24) used in biogenetic theory for such alkaloids as corynantheine (25). Future developments here, both structural and stereochemical, will be of great interest, for though the proposed constitution for C-mavacurine is not yet fully established it is clear that this alkaloid represents a new twist in the biogenetic pattern for the indole alkaloids.

If formula (23) is correct for C-mavacurine, it is certain that structure (26) represents C-fluorocurine; C-Alkaloid Y then has structure (27).

Alkaloids of *Strychnos melinoniana*.—As a result of extensive fractionations by Schlittler and Hohl[25] and more recently by Bächli and his co-workers,[29] eleven new alkaloids have been isolated from this plant and named melinonine A and B and melinonine E to M inclusive. Structural studies have been described for four of these.

The structure of melinonine F, $C_{13}H_{13}N_2^+$, was fairly clear[29] on the basis of its ultraviolet absorption spectrum (β-carbolinium salt chromophore) and the alkaloid was shown by direct comparison to be the *N(b)*-metho-derivative (28) of harman. Melinonine F has the distinction of being the simplest quaternary alkaloid to be isolated from South American *Strychnos* species.

Melinonine G, $C_{17}H_{15}N_2^+$, is also notable for its low hydrogen content; in keeping with this, its ultraviolet and infrared spectra are very similar to those of sempervirine salts (29) and, moreover, the spectra established



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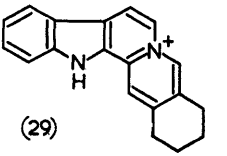

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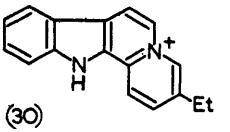

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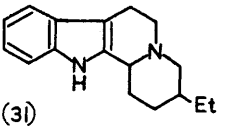


(31)

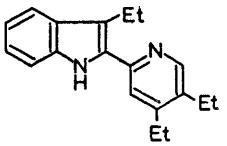
the absence of vinyl residues. On the basis of this and other evidence, particularly the catalytic reduction of the alkaloid to an indolic product which contained a *C*-ethyl group, Bächli and his co-workers[29] propose structure (30) for melinonine G. The constitution (31) then follows for the indolic reduction product. Structure (30) is in fact the one rigidly established by Bejar *et al.*[35] and by Hughes and Rapoport[36] for flavopereirine from *Geissospermum* species. There seems little doubt that melinonine G and flavopereirine are identical though no direct comparison has apparently been made.

Melinonine G is a particularly interesting molecule because in terms of current biogenetic thinking it must be regarded as a degraded indole alkaloid. Thus it could be formed from the common intermediate (24) proposed for many indole alkaloids by the loss of the three carbon atoms attached to $C_{(15)}$ in a reversed Michael reaction. Aromatisation could then give the required system.

The other two alkaloids, melinonine A and melinonine B have rather more complex structures. A key degradation product in the chemistry of the former was obtained by Schlittler and Hohl.[25] They found that melinonine A, $C_{22}H_{27}O_3N_2^+$, could be pyrolysed to give the corresponding tertiary base normelinonine A, $C_{21}H_{24}O_3N_2$, which yielded alstyrine (32) on selenium dehydrogenation. Further chemical and spectroscopic evidence derived from normelinonine A established the presence of an indole system together with the group $MeO_2C\text{-}\overset{|}{C}\text{=}\overset{|}{C}\text{-}O\text{-}$, a common feature in

[35] Bejar, Goutarel, Janot, and Le Hir, *Compt. rend.*, 1957, **244**, 2066.
[36] Hughes and Rapoport, *J. Amer. Chem. Soc.*, 1958, **80**, 1604.

the indole alkaloid field. These results led directly to the gross formula (33) as a likely one for normelinonine A, and direct comparison with tetra-



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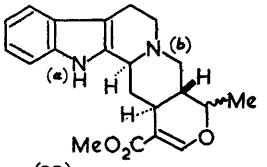
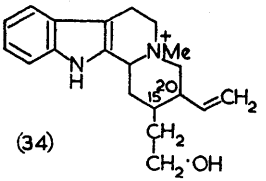


(33)

hydroalstonine[37] (33) established the identity of the two bases. Thus melinonine A is the *N(b)*-metho-derivative of the base (33).

The chemistry of the tetracyclic melinonine-B is not as yet so clear-cut though structure (34) is a likely one. The presence of an acetylatable hydroxyl group, a vinyl group, an indolic >NH, and a quaternary



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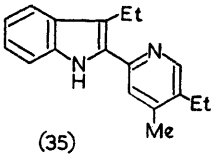

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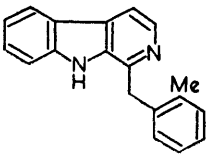

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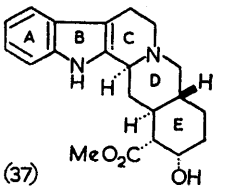


(37)

methylammonium group has been firmly established by Vamvacas *et al.*[38] There is no *C*-methyl group in the alkaloid, so that the hydroxyl group must be placed in the primary position as in formula (34) in order to accommodate the other evidence. Selenium dehydrogenation of dihydromelinonine B gave an α-pyridylindole having the highly characteristic ultraviolet absorption of this system; structural work on this degradation product was hampered by the very small amount available, but there is reasonable evidence in favour of structure (35). Surprisingly, dehydrogenation of melinonine B over palladium yielded yobyrine (36) which on the basis of structure (34) must have been formed by ring-closure of the side-chains. This result is rather disturbing in that it increases the difficulty of

[37] Elderfield and Gray, *J. Org. Chem.*, 1951, **16**, 506; Wenkert and Roychaudhuri, *J. Amer. Chem. Soc.*, 1957, **79**, 1519.

[38] Vamvacas, von Philipsborn, Schlittler, Schmid, and Karrer, *Helv. Chim. Acta*, 1957, **40**, 1793.

degradative work in the indole field; no longer can the isolation of yobyrine be taken as proof of the presence of a carbocyclic ring E in the parent alkaloid (*e.g.*, structure 37).

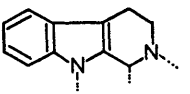
It can be seen that the foregoing evidence is not sufficient to establish firmly structure (34) for melinonine B; it could be objected, for example, to constitution (34) that the side-chains on positions 15 and 20 might be interchanged as Vamvacas *et al.* have been careful to point out.[38] The resulting structure would be less attractive biogenetically, but clearly further investigation of melinonine B is desirable. However, with the present knowledge of its structure, we can add melinonine B to the growing number of α-indole alkaloids* which do not contain a carboxyl group. Until recently, the presence of a carboxyl group seemed to be general in the α-indole series. Yohimbine (37) is just one example of the many bases which display this feature.

C-Alkaloid T (*O*-Methylsarpagine) and Lochneram.—The non-phenolic C-Alkaloid T, $C_{20}H_{24}O_2N_2$, isolated in Zürich from a Brazilian calabash,[26] is now known to be identical with *O*-methylsarpagine[39] which in turn is identical with lochnerine;[40] thus, structural studies on this interesting base are available from several laboratories.

There is rigid evidence for an isolated double bond, which is present in part as $\rangle CH{-}CH{=}CH_2$ and in part as $\rangle C{=}CHMe$ since ozonolysis gives a mixture of formaldehyde and acetaldehyde. This means that "C-Alkaloid T" is really a difficultly separable mixture of vinyl and ethylidene isomers. It is also established that a 5-methoxyindole residue unsubstituted at N(*a*), three more rings, and a *C*-methyl group are present. The primary nature of the hydroxyl group was shown very neatly[26] by reducing the *O*-tosyl derivative to the corresponding deoxy-derivative. This contained a new *C*-methyl group, probably located as Me·CH$\langle^{C}_{C}$ or less probably as Me·C$\langle^{C}_{C}$—C since its Kuhn–Roth oxidation products did not contain propionic acid, only acetic acid.

All this evidence can be accommodated by the constitution (38) for

* α-Indole alkaloids are those involving the β-carboline system (*a*) or some simple derivative of it, *e.g.*, (*b*).



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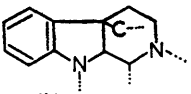
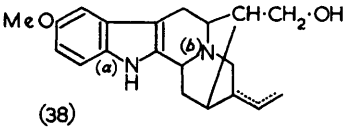


(b)

[39] Stoll and Hofmann, *Helv. Chim. Acta*, 1953, **36**, 1143; Stauffacher, Hofmann, and Seebeck, *ibid.*, 1957, **40**, 508; Poisson, Le Men, and Janot, *Bull. Soc. chim. France*, 1957, 610.

[40] Mors, Zaltzman, Beereboom, Pakrashi, and Djerassi, *Chem. and Ind.*, 1956, 173.

C-Alkaloid T which is based[26] on an assumed relation between this alkaloid and ajmaline; ajmaline has been rigidly proved[41] to have structure (39). However, there are considerable gaps to be filled before structure (38) is proved to be valid.



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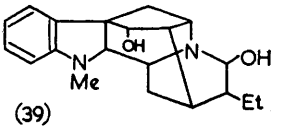

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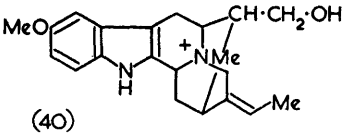


(40)

Lochneram was isolated by Arnold *et al.*[27] from the calabash which yielded C-Alkaloid T, and is the *N*(*b*)-metho-derivative of the latter. It seems, though, that lochneram is the pure ethylidene isomer on the basis of cleavage with ozone. Thus, if the constitution (38) is correct for C-Alkaloid T, structure (40) follows for lochneram.

The C_{40} Alkaloids.—(a) *General.* As work on the alkaloids of calabash-curare and *Strychnos* species progressed, it became apparent that they fall naturally into two more or less clearly defined groups. One group contains those alkaloids which have relatively high mobilities in the solvent systems used for partition chromatography and have little or no physiological activity; all the alkaloids discussed in detail so far in this Review belong to this group. The second group contains the alkaloids with high curare activity, which account for all the physiological effects of the curares or bark extracts. These alkaloids all move slowly on paper chromatograms and on cellulose partition columns.

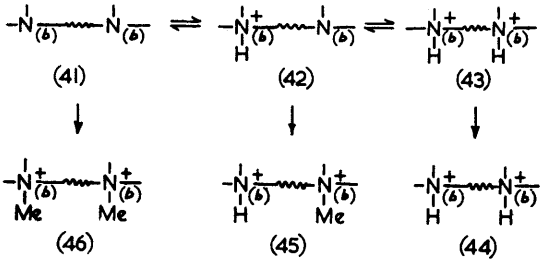
As is the case with the "fast-running" alkaloids, the "slow-running" alkaloids have two nitrogen atoms in a C_{19}–C_{21} unit. One nitrogen, N(*a*), is non-basic or only weakly basic and is involved in the indole or, more usually, modified indole chromophore; the second, N(*b*), is the basic or quaternary basic centre.

One of the most significant advances in the chemistry of the "slow-running" highly active alkaloids came with von Philipsborn, Schmid, and Karrer's demonstration that they have molecular formulæ based upon C_{38}—C_{40} skeletons; that is, two basic or quaternary nitrogen atoms are present in the molecule. Previously all alkaloids from calabash-curare and *Strychnos* species had been assigned formulæ based upon C_{19}–C_{21} molecules. The method employed by the Swiss chemists is that of partial quaternisation[42] which in this series depends upon the fact (and incidentally

[41] Woodward, *Angew. Chem.*, 1956, **68**, 13; Robinson, *ibid.*, 1957, **69**, 40.
[42] von Philipsborn, Schmid, and Karrer, *Helv. Chim. Acta*, 1956, **39**, 913; cf. Battersby and Craig, *J. Amer. Chem. Soc.*, 1951, **73**, 1887.

provides evidence for this fact) that the two basic nitrogen atoms in the tertiary base prepared from the quaternary alkaloid are sufficiently far apart for protonation or quaternisation at one basic nitrogen atom not significantly to affect either of these processes at the second basic centre.

The tertiary base nor-C-curarine I, obtained by pyrolysis of the quaternary C-curarine I chloride, was treated with half an equivalent of mineral acid to give an equilibrium mixture of the species (41), (42), and (43).



Methylation then gave a mixture of nor-C-curarine I (44=43), monometho-nor-C-curarine I (45), and C-curarine I (46). The monometho-derivative (45) was readily separated by partition chromatography and by further methylation was converted into C-curarine I. This preparation of a C-curarine I derivative with one *N*(*b*)-methyl group in each C_{40} unit is decisive evidence that this alkaloid has a C_{40} skeleton; the molecular formula was accordingly modified to $C_{40}H_{44-46}ON_4^{++}$.

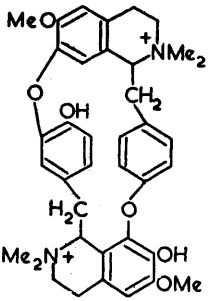
By the same method, C-calebassine was shown[42] to be $C_{40}H_{48-50}O_2N_4^{++}$, and C-dihydrotoxiferine I to be $C_{40}H_{46}N_4^{++}$, and it was suggested that all the highly active calabash-curare alkaloids have C_{40} molecules; this is almost certainly true. However, the converse that all C_{40} quaternary curare alkaloids are powerful curarising agents is certainly not true, as is shown by the surprisingly low activity of caracurine V dimethochloride, $C_{40}H_{46}O_2N_4^{++}$ (p. 95)

Now it is known that the active calabash-curare alkaloids contain two quaternary centres, they fall satisfyingly into place with the other quaternary curarising agents. Thus the bisbenzylisoquinoline alkaloids such as *d*-tubocurarine (47) have two quaternary nitrogen atoms set some distance apart, as do the synthetic preparations such as succinylcholine (48). Indeed, it is interesting from the point of view of structure–activity relations that with the structure of toxiferine I known (p. 94) it turns out that the two quaternary centres are very nearly the same distance apart as those in *d*-tubocurarine (approximately 14 Å).

(b) *Toxiferine I, C-dihydrotoxiferine I, and diaboline.* During their pioneer work (1947) in the curare field, Wieland, Bähr, and Witkop[15] isolated the highly physiologically active alkaloid toxiferine I from *S. toxifera* grown in British Guiana. Schmid and Karrer[43] later obtained the

[43] Schmid and Karrer, *Helv. Chim. Acta*, 1947, **30**, 1162.

same quaternary alkaloid from a Venezuelan calabash. Wieland's group[15] also isolated from a Venezuelan calabash preparation what they took to be a relative of toxiferine I because of the close similarity between the known and the new alkaloid's properties. The new material was named C-dihydrotoxiferine I although no formal relation to toxiferine I was demonstrated, and it is now known that the alkaloid has been misnamed; as will be seen later, C-dihydrotoxiferine I is in fact C-deoxytoxiferine I. In



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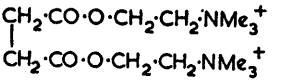
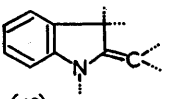


(48)

addition, nordihydrotoxiferine I, the tertiary base corresponding to the quaternary C-dihydrotoxiferine I, was found by Karrer and Schmid's group[21] in the tertiary bases from Venezuelan *S. toxifera* bark.

Some ten years after its isolation, little was known about C-dihydrotoxiferine I. In common with toxiferine I, it had been shown[20] to contain the methyleneindoline chromophore (49). Its molecular formula had been



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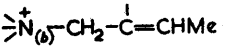


(50)

established as $C_{40}H_{46}N_4^{++}$, with two *N*-methyl groups[21] attached to the quaternary N(*b*)-nitrogen atoms, and ozonolysis[21] had furnished acetaldehyde. The usual attack by various dehydrogenating agents unfortunately gave only glimpses of the molecule. Thus dehydrogenation with sulphur and with zinc dust had yielded isoquinoline;[44] distillation with zinc dust gave a mixture of 3-methyl- and 3-ethyl-indole, and palladium dehydrogenation of the corresponding nor-base gave traces of a β-carboline derivative.[21] As will be discussed in the sequel, C-dihydrotoxiferine I can be transformed into C-calebassine and C-curarine I, both known to contain the grouping (50). In view of the production of acetaldehyde by ozonolysis of C-dihydrotoxiferine I, it was taken as probable that the same quaternary allylamine system (50) also occurs in this alkaloid.

In 1957 still less was known about toxiferine I, but against this lack of

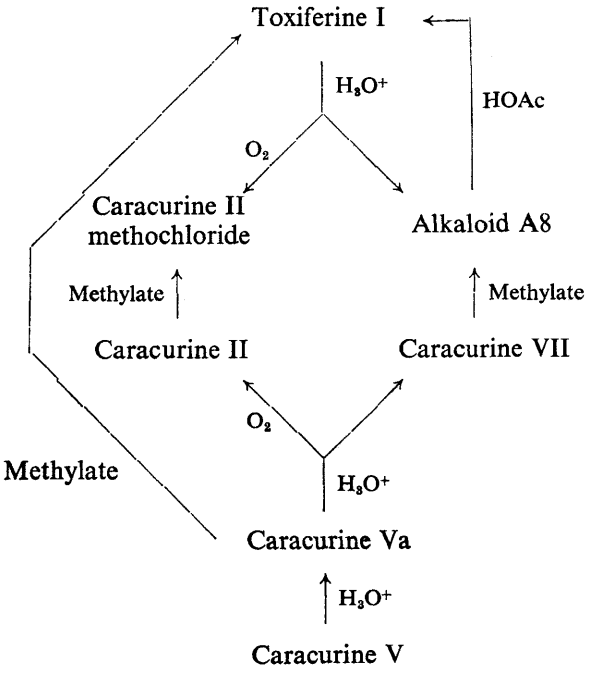
[44] Wieland, Witkop, and Bähr, *Annalen*, 1947, **558**, 144.

progress must be set the great difficulty of obtaining even a hundred milligrams of the alkaloid. von Philipsborn, Schmid, and Karrer[42] gave evidence for a C_{40} molecule, and the earlier formulæ were revised to $C_{40}H_{46-48}O_2N_2^{++}$. Moreover, toxiferine I had been found to undergo a change of unknown nature when treated with dilute acid; C-dihydrotoxiferine I behaved similarly.[45]

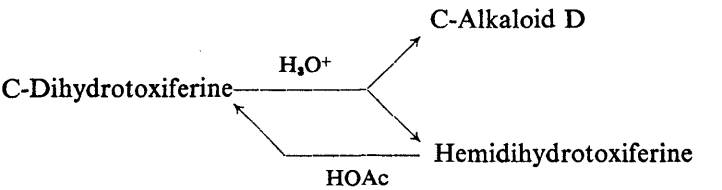
The structure of C-dihydrotoxiferine I has recently been elucidated in an outstanding series of studies[46,47] by Karrer, Schmid, and their collaborators; in addition, work at Zürich and at Bristol led[47-49] to the structure of toxiferine I. Papers on the chemistry of these and other C_{40} curare alkaloids have been appearing steadily from four different laboratories and it is impossible in the space available to pay the mass of information full justice. The following account is confined to the essentials necessary for a logical presentation.

Asmis, Schmid, and Karrer[22] in 1954 isolated nine tertiary alkaloids, caracurine I—IX from Venezuelan *S. toxifera*, and in a later paper[45] it was shown that caracurine V is readily transformed by dilute mineral acid into an unstable methyleneindoline base named caracurine Va. After this initial stage, further acid-catalysed changes occur to give a mixture of caracurine II and caracurine VII, both of which are stable to dilute acid. Battersby and Hodson[48,49] examined the very similar changes which occur when toxiferine I, also a methyleneindoline, is treated with dilute acid and isolated two crystalline products. One was identical with a new quaternary alkaloid, provisionally called A8, which they had isolated[17,48] from *S. toxifera* grown in British Guiana. This alkaloid showed indoline ultraviolet absorption, and the indoline nitrogen atom was proved to be secondary. Since in earlier work they had shown that Alkaloid A8 is identical with caracurine VII methochloride, it follows[47-49] that the above acid-catalysed transformations are taking place on related tertiary and quaternary molecules. Thus caracurine Va must be nortoxiferine I, and the second product from toxiferine I must be caracurine II methochloride which was confirmed[49] by preparing this material from authentic caracurine II. Toxiferine I was also prepared[47] by methylating caracurine Va. The set of interconversions was completed by showing[47-49] that alkaloid A8 in acetic acid is converted into toxiferine I in moderate yield. These transformations are summarised in the annexed scheme which includes the demonstration[50] that the formation of caracurine II methochloride from toxiferine I involves atmospheric oxygen. There can be no doubt that this also holds in the tertiary caracurine Va series.

[45] Asmis, Bächli, Schmid, and Karrer, *Helv. Chim. Acta*, 1954, **37**, 1993.
[46] Bernauer, Schmid, and Karrer, *Helv. Chim. Acta*, 1958, **41**, 1408.
[47] Bernauer, Berlage, von Philipsborn, Schmid, and Karrer, *Helv. Chim. Acta*, 1958, **41**, 2293.
[48] Battersby and Hodson, *Proc. Chem. Soc.*, 1958, 287.
[49] Battersby and Hodson, *J.*, 1960, 736.
[50] Battersby and Rao, unpublished work.

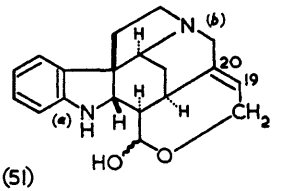


In addition, Karrer, Schmid, and their collaborators[46,47] had shown that C-dihydrotoxiferine I, $C_{40}H_{46}N_4^{++}$, is converted by dilute mineral acid into the C_{20} alkaloid, hemidihydrotoxiferine, which, like Alkaloid A8, had indoline ultraviolet absorption and contained > NH, but in addition the infrared spectrum showed the presence of an aldehyde group. As with toxiferine I, a second product is also formed, identical with C-Alkaloid D, isolated earlier[18] in Zürich from a calabash. Moreover, hemidihydrotoxiferine in aqueous acetic acid was converted[46] back into C-dihydrotoxiferine I. When these facts are combined with the knowledge that hemidihydrotoxiferine has colour reactions and an ultraviolet spectrum identical with those of Alkaloid A8 and caracurine VII, they leave little doubt that the interconversions summarised in the scheme below are analogous to those outlined above for toxiferine I and its nor-derivative (caracurine Va).



A complex of inter-related alkaloids had thus been established by the foregoing experiments when the Zürich group made the important identifi-

cation[51] of caracurine VII with the Wieland–Gumlich aldehyde (51). The latter had been known for over 25 years as a degradation product obtained during H. Wieland's studies on the structure of strychnine (52). This identification was of great interest, being the first reported natural occurrence of the intermediate proposed by Woodward in his seminal biogenetic scheme for strychnine.[52]



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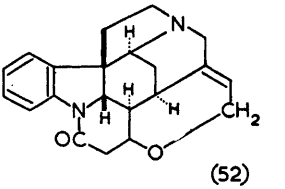

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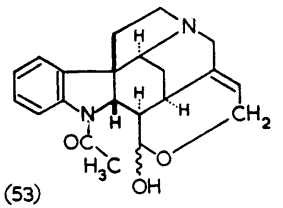

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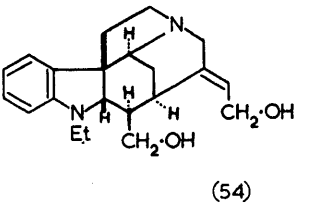


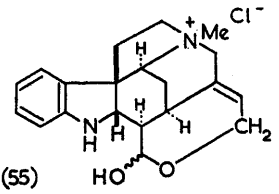
(54)

A very similar biogenetic interest attaches to the tertiary base diaboline and it is convenient to leave the main theme for a moment to consider this alkaloid. It was isolated by King[24] from the bark of *S. diaboli*, and Bader, Schlittler, and Schwarz[53] showed that it is an *N*(*a*)-acetylindoline derivative. With the structure of caracurine VII known, indications derived from colour reactions and from reduction of diaboline by lithium aluminium hydride to a glycol led Battersby and Hodson[54] to compare deacetyldiaboline with the Wieland–Gumlich aldehyde (51), and the two were identical. Thus diaboline is *N*(*a*)-acetyl-Wieland–Gumlich aldehyde (53), and its reduction product is the glycol (54). Diaboline is intermediate in complexity between Wieland–Gumlich aldehyde (51) and strychnine (52), and its occurrence in *S. diaboli* gives further support to Woodward's biogenetic proposals.

We can now return to the way in which the identification of caracurine VII as the Wieland–Gumlich aldehyde leads, when combined with the above results, to the structures of toxiferine I and C-dihydrotoxiferine I. Since alkaloid A8 is caracurine VII methochloride (p. 92). the former is the Wieland–Gumlich aldehyde *N*(*b*)-methochloride (55) and this was rigorously confirmed;[49] A8 is now better named hemitoxiferine I.

Bernauer, Schmid, and Karrer[46] proposed structure (56) for hemidihydro-

[51] Bernauer, Pavanaram, von Philipsborn, Schmid, and Karrer, *Helv. Chim. Acta*, 1958, **41**, 1405.
[52] Woodward, *Nature*, 1948, **162**, 155.
[53] Bader, Schlittler, and Schwarz, *Helv. Chim. Acta*, 1953, **36**, 1256.
[54] Battersby and Hodson, *Proc. Chem. Soc.*, 1959, 126.



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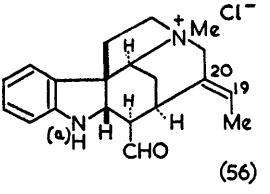

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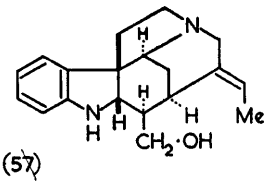

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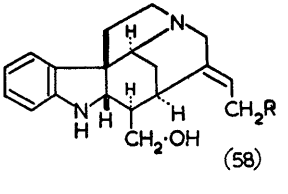


(58)

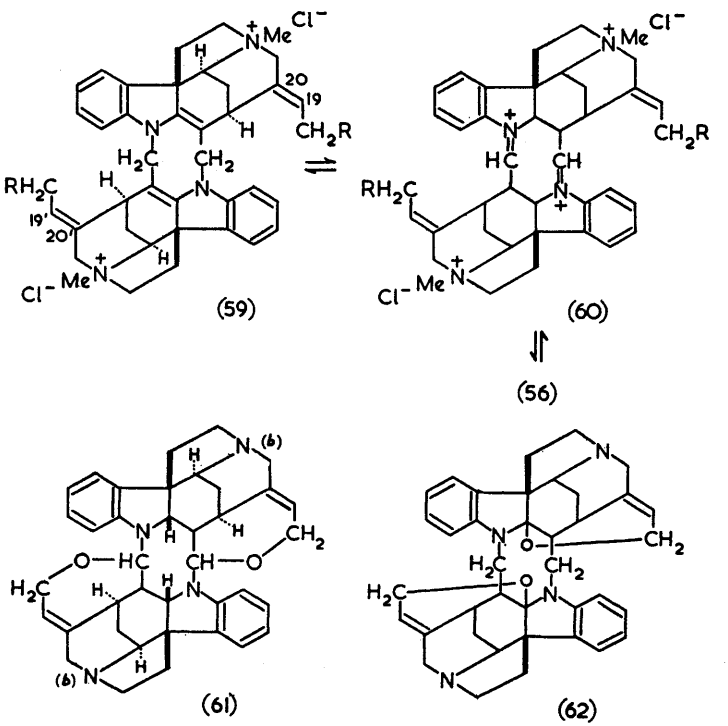
toxiferine, *i.e.*, that of the deoxy-Wieland–Gumlich aldehyde methochloride, and soon afterwards this was confirmed[47] as follows. The degradation of C-dihydrotoxiferine I can be duplicated on the corresponding tertiary base nordihydrotoxiferine I to give heminordihydrotoxiferine (tertiary base corresponding to 56) which was reduced at the aldehyde function by borohydride to the primary alcohol (57). This was identical with that prepared from the Wieland–Gumlich glycol (58; R = OH) by selective bromination of the reactive allylic hydroxyl group to give the base (58; R = Br) followed by reductive removal of the halogen.

We must now consider the processes by which the oxygen-free C-dihydrotoxiferine I with a methyleneindoline chromophore is formed from two molecules of the aldehyde (56) with loss of water and loss of the *N*(*a*)-hydrogen atoms. Moreover, the fact that this reaction is reversed in the presence of mineral acid must be explained. The only constitution for C-dihydrotoxiferine I which satisfactorily accommodates this evidence is (59; R = H), first proposed by Bernauer, Schmid, and Karrer.[46] Structure (60) can be written[46] as a *formal* representation of the intermediate in both dimerisation and fission with the postulate of a double prototropic shift to move the double bond into or out of the methyleneindoline position. In the same way, by combination of all the evidence outlined above, the structure (59; R = OH) must be given to toxiferine I.[47–49] C-Dihydrotoxiferine I and toxiferine I are thus examples of a new type of natural product.

It remains to fit caracurine V into the picture. This base has an indoline chromophore and is readily converted into caracurine Va by dilute mineral acids or dilute acetic acid. Karrer, Schmid, and their co-workers[47] have assigned to it the amino-hemiacetal structure (61) although the published chemical evidence does not exclude the alternative arrangement (62). Either of these hemiacetals would be expected readily to yield caracurine Va (nor-base corresponding to 59, R=OH) under acidic conditions. Models of the molecules (61) and (62) show that, whereas the former is

relatively unstrained, there is considerable steric compression in the latter and on this basis the former seems much more likely.

We have already mentioned that dimerisation of Wieland–Gumlich aldehyde methochloride (hemitoxiferine I) (55) with hot acetic acid gives[49] a reaction mixture from which only about 20% of toxiferine I (59; R=OH)



can be isolated directly and a similar result is obtained in buffered solution.[55] Caracurine V dimethochloride [61 with both *N(b)*-nitrogen atoms methylated] is one of the side products, but the major one is *OO*-diacetyltoxiferine I dichloride (59; R=OAc). Battersby and Hodson[49] have shown that dimerisation of hemitoxiferine I (55) by means of pivalic acid (trimethylacetic acid), in which there is strong steric hindrance of acylation, gives a product from which toxiferine I (59; R=OH) can be isolated by direct crystallisation in at least 70% yield. In contrast, dimerisation of the tertiary base Wieland–Gumlich aldehyde (51) both in buffered aqueous acetic acid[46] and in pivalic acid[49] gives mainly caracurine V (61) and only a little nortoxiferine I (tertiary base corresponding to 59, R=OH). The factors controlling the various possible cyclisations are thus delicately balanced.

[55] Berlage, Bernauer, von Philipsborn, Waser, Schmid, and Karrer, *Helv. Chim. Acta*, 1959, **42**, 394.

An interesting but no doubt very annoying difficulty arose when the synthesis of C-dihydrotoxiferine I was attempted by Bernauer, Berlage, von Philipsborn, Schmid, and Karrer.[47] Deoxygenation of the Wieland–Gumlich aldehyde (51) was achieved when the allylic hydroxyl group formed by ring-opening was replaced by bromine and the product was reduced with zinc and acetic acid. The resulting aldehyde then dimerised as expected in buffered aqueous acetic acid, but though the product had colour reactions, ultraviolet spectrum, R_c values, infrared spectrum, and rotation identical with those of C-dihydrotoxiferine I, it gave a picrate melting more than 60° higher than that of the natural alkaloid; the two picrates were not interconvertible. By elimination, the Swiss workers were forced to conclude that this product, which they designate C-dihydrotoxiferine I*, is stereoisomeric with C-dihydrotoxiferine I (59; R=H) about the 19,20- and 19′,20′-double bonds. However, C-dihydrotoxiferine I, identical with the natural material, was prepared[56] from caracurine V (61) obtained in turn from the Wieland–Gumlich aldehyde (51) (see above) by reaction with hydrogen bromide to give the allylic bromide (tertiary base corresponding to 59; R=Br) followed by reduction with zinc and acetic acid. Conversion of the final base into the corresponding methochloride gave the desired material (59; R=H).

(c) *C-Fluorocurarine* (*C-curarine III*). The yellow quaternary alkaloid C-fluorocurarine was first isolated by H. Wieland, Pistor, and Bähr[14] from a calabash-curare preparation and more recently it has been identified[57] chromatographically in extracts from the bark of *S. mitscherlischii*. Although it has been established[58] by the partial quaternisation method (p. 88) that C-fluorocurarine is a C_{20} alkaloid, it is discussed in this section because of its important relations to the C_{40} alkaloids of the C-dihydrotoxiferine I "family" (p. 98). Thus both Boekelheide's[59] and T. Wieland's[60] group have shown that C-fluorocurarine is produced by the action of concentrated hydrochloric acid on C-curarine I, and Volz and T. Wieland[61] obtained it by treatment of C-calebassine with the mixed anhydride of formic and acetic acid.

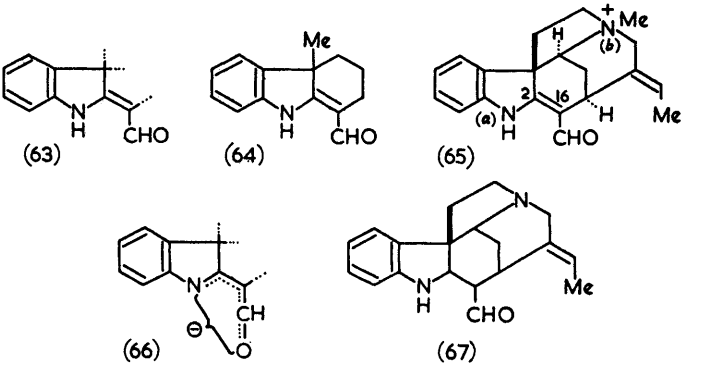
C-Fluorocurarine has one *N*-methyl group on the quaternary *N*(*b*)-nitrogen atom and one *C*-methyl group in an ethylidene side chain. *N*(*a*)-Acetylfluorocurarine can be prepared, so that the *N*(*a*)-nitrogen atom is secondary. The most striking feature of the alkaloid is, however, its chromophore, of a kind not hitherto encountered; its ultraviolet spectrum has a long-wavelength peak at 358 mμ which undergoes a reversible bathochromic shift in the presence of alkali. With dimethyl sulphate, C-fluorocurarine gives the corresponding *N*(*a*)-methyl derivative having

[56] Bernauer, Berlage, Schmid, and Karrer, *Helv. Chim. Acta*, 1959, **42**, 201.
[57] Kebrle, Schmid, Waser, and Karrer, *Helv. Chim. Acta*, 1953, **36**, 345.
[58] von Philipsborn, Meyer, Schmid, and Karrer, *Helv. Chim. Acta*, 1958, **41**, 1257.
[59] Zürcher, Ceder and Boekelheide, *J. Amer. Chem. Soc.*, 1958, **80**, 1500.
[60] Fritz and Wieland, *Annalen*, 1958, **611**, 277.
[61] Volz and Wieland, *Annalen*, 1957, **604**, 1.

ultraviolet absorption identical with that of C-fluorocurarine itself but which does not show the bathochromic shift in alkali.[58] Thus this shift must involve the removal of a proton from the *N*(*a*)-nitrogen of C-fluorocurarine.

As the result of a masterly study of the three products obtained by borohydride reduction of *N*(*a*)-methyl-C-fluorocurarine, the Zürich group suggested[58] that the assembly (63) must be the chromophore of the alkaloid. The presence of an aldehyde function was confirmed by the formation of an unstable oxime and by the infrared spectrum of C-fluorocurarine which shows bands characteristic of $\alpha\beta$-unsaturated β-amino-aldehydes.[58]

By studying C-fluorocurarine and also model compounds, Fritz, Besch, and T. Wieland[62] derived the same chromophore for the alkaloid although the aldehydic nature of the carbonyl group was not recognised. However, all doubt about the chromophoric system was removed by Fritz's synthesis[63] of the aldehyde (64), the simplest compound which contains the proposed C-fluorocurarine chromophore. The absorption spectrum of



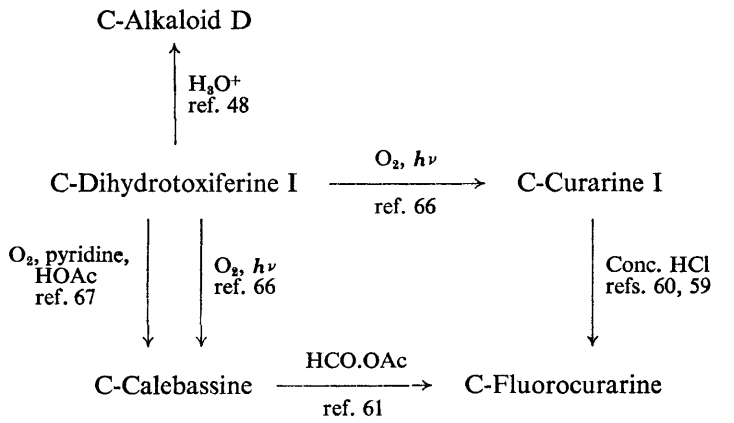
this material is closely similar to that of C-fluorocurarine in neutral and in alkaline solution. It is safe then to explain the bathochromic shift in alkali as being due to generation of the mesomeric anion (66).

From a consideration of its relation to C-curarine I and C-calebassine and on biogenetic grounds, the Swiss workers[58] proposed (65) as a hypothetical structure for C-fluorocurarine and this was soon confirmed by Fritz, Besch, and Wieland.[64] Hydrogenolysis of the allylic hydroxyl group in the Wieland–Gumlich glycol (58; R=OH) yielded the corresponding deoxy-derivative (58; R=H) which underwent Oppenauer oxidation to give norhemidihydrotoxiferine (67). No details are available for the next step which involves autoxidation of the aldehyde (67) to nor-C-fluorocurarine (tertiary base corresponding to 65); *N*(*b*) methylation then gave C-fluorocurarine (65) identical with the natural material. The Zürich

[62] Fritz, Besch and Wieland, *Annalen*, 1958, **617**, 166.
[63] Fritz, *Chem. Ber.*, 1959, **92**, 1809.
[64] Fritz, Besch, and Wieland, *Angew. Chem.*, 1959, **71**, 126.

group provided independent proof[65] from another angle; they reduced C-fluorocurarine to norhemidihydrotoxiferine (67) which was then dimerised as described earlier to yield C-dihydrotoxiferine I (59; R=H). Since the structure of C-dihydrotoxiferine I has been related chemically to that of the Wieland–Gumlich aldehyde, C-fluorocurarine must have the constitution (65).

(d) *The "families" of alkaloids.* Several important reactions have been described by various workers which show that many of the calabash-curare and *Strychnos* alkaloids can be grouped together in so-called "families" containing mutually related alkaloids. Thus, when solid C-dihydrotoxiferine I is irradiated in the presence of oxygen, it is converted into C-curarine I, whereas C-calebassine is formed when the irradiation is carried out in solution containing eosin as a sensitiser. The formation of C-alkaloid D from C-dihydrotoxiferine I under acidic conditions was mentioned earlier (p. 92), as was the production of C-fluorocurarine by degradation of C-curarine and C-calebassine (p. 96). These reactions are summarised in the annexed chart.

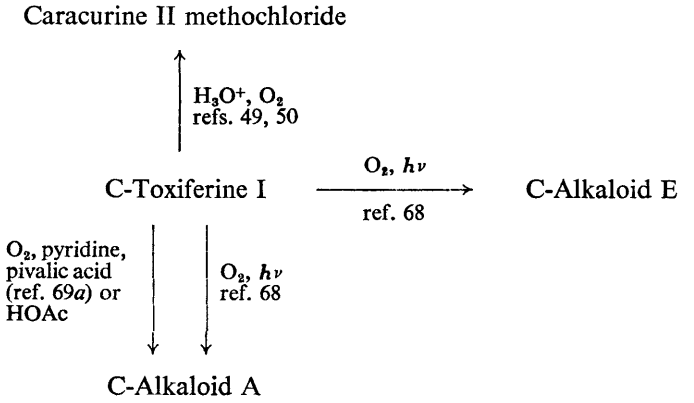


Inter-relations in the C-dihydrotoxiferine I "family".

A similar scheme was established for alkaloids related to toxiferine I and there can be no doubt that the corresponding fundamental changes involved in the two families are strictly analogous. Thus C-Alkaloid E in the toxiferine I "family" corresponds to C-curarine I in the C-dihydrotoxiferine I "family"; C-Alkaloid A corresponds to C-calebassine and caracurine II methochloride to C-Alkaloid D. In passing, it is worth noting the recent work[17] on King's alkaloids[16] which has shown that caracurine II methochloride and C-Alkaloid A can be isolated from the bark of *S. toxifera.* The separation of C-Alkaloid A is the first example of

[65] von Philipsborn, Bernauer, Schmid, and Karrer, *Helv. Chim. Acta*, 1959, **42**, 461.
[66] Bernauer, Schmid, and Karrer, *Helv. Chim. Acta*, 1957, **40**, 1999.
[67] Asmis, Schmid, and Karrer, *Helv. Chim. Acta*, 1956, **39**, 440.

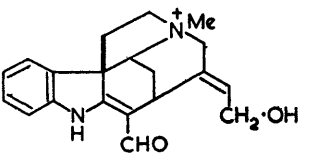
an alkaloid of the C-calebassine type to be isolated in substance from a plant; all previous isolations of this type of alkaloid and those of the C-curarine I type have been from calabash-curare preparations which have undergone largely unknown treatments by their native manufacturers.[10]



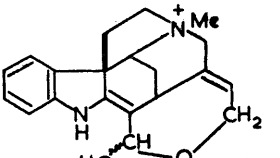
Inter-relations in the toxiferine I "family".

The analogue of C-fluorocurarine in the toxiferine I family has not so far been isolated from natural sources. It would have the structure (68), or, perhaps less probably, the hemiacetal form (69); attempts to make it by oxidation of the Wieland–Gumlich aldehyde (51) both at Bristol[69] and at Zürich[70] have so far been unsuccessful.

Berlage, Bernauer, Schmid, and Karrer have recently[69a] proved that C-Alkaloid H is the toxiferine-like mixed condensation product of Wieland–Gumlich aldehyde methochloride (hemitoxiferine I) and its 18-deoxy-derivative (hemidihydrotoxiferine), which gives constitution (70) for C-Alkaloid H. The tertiary caracurine VI is said to be the nor-base from this "hybrid" and it has been shown[69a] that C-Alkaloids F and G are respectively the C-calebassine and the C-curarine analogue in this "family".

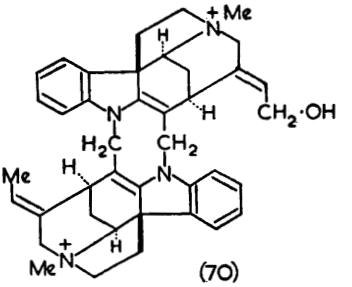


(68)



(69)

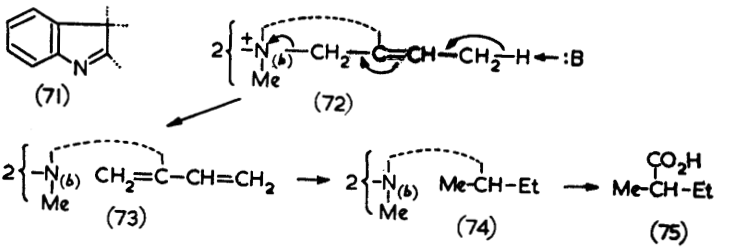
[68] Bernauer, Berlage, Schmid, and Karrer, *Helv. Chim. Acta*, 1958, **41**, 1202.
[69] Battersby and Hodson, unpublished work.
[69a] Berlage, Bernauer, Schmid, and Karrer, *Helv. Chim. Acta*, 1959, **42**, 2650.
[70] Professor H. Schmid, personal communication.



(70)

The key position of the Wieland–Gumlich aldehyde (51) in this group of alkaloids is now obvious. From this compound, its 18-deoxy-derivative, and their *N(b)*-metho-derivatives can be derived no fewer than nineteen* of the tertiary and quaternary alkaloids isolated from calabash-curares and the barks of South American *Strychnos* species.

(e) *C-Curarine I and C-calebassine.* No structures have yet been proposed for C-curarine I and C-calebassine which were the first properly characterised alkaloids to be isolated from calabash-curare.[12,13] The photo-oxidation of C-dihydrotoxiferine I, $C_{40}H_{46}N_4^{++}$ (59; R=H), to give C-curarine I, $C_{40}H_{44-46}ON_4^{++}$, has already been mentioned (p. 98), and the oxygen atom introduced is presumably in an ether linkage. Little help comes from the ultraviolet absorption of C-curarine I which was earlier attributed[20,71,72] to an indolenine chromophore (71), but is now thought to be of a unique type;[10] however, it is worth noting that the spectrum is very similar to that of the amino-hemiacetal caracurine V (61).



The early chemical investigations showed that C-curarine I gives acetaldehyde on ozonolysis and that it contains the system (72). von Philipsborn, Schmid, and Karrer[73] recognised that this undergoes an

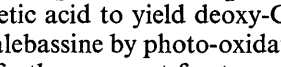
* Caracurine VII, hemitoxiferine I, C-fluorocurarine, diaboline, toxiferine I, C-dihydrotoxiferine I, nordihydrotoxiferine, caracurine V, C-Alkaloid A, C-Alkaloid E, caracurine II methochloride, caracurine II, C-calebassine, C-curarine I, C-Alkaloid D, C-Alkaloid H, C-Alkaloid F, C-Alkaloid G. caracurine VI,

[71] Schmid and Karrer, *Angew. Chem.*, 1955, **67**, 361.

[72] Karrer, *Bull. Soc. chim. France*, 1958, 99.

[73] von Philipsborn, Schmid, and Karrer, *Helv. Chim. Acta*, 1955, **38**, 1067.

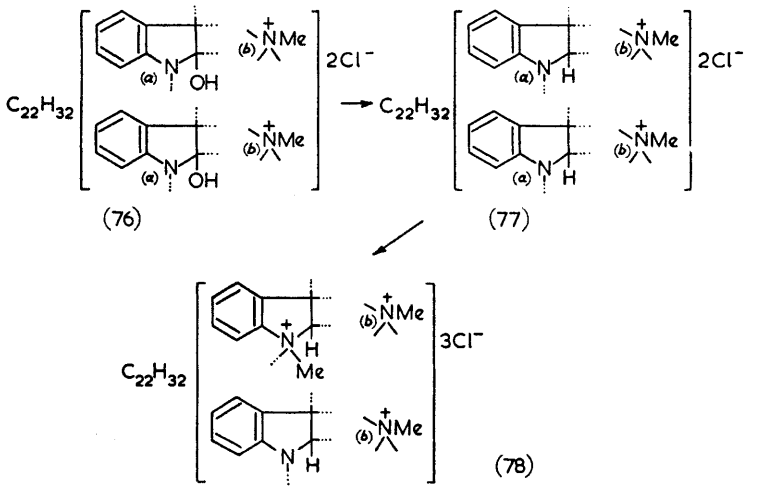
interesting vinylogous Hofmann elimination, as indicated, when it is attacked by alkali to give a bis-tertiary base containing two diene residues (partial structure 73). Hydrogenation of the latter gave the corresponding octahydro-derivative (partial structure 74) which yielded α-methylbutyric acid (75) when oxidised by the modified (micro-)Kuhn–Roth method;[74] this was the first application in the alkaloid field of a technique which has since been widely used. A major clue concerning the structure of this alkaloid comes from its degradation to C-fluorocurarine (65) by the action of concentrated hydrochloric acid,[59,60] but much more experimental information will be required before even reasonable working hypotheses can be formulated. That there may be considerable difficulties ahead is indicated by the experiments of Boekelheide *et al.*[75] on the Hofmann degradation of C-curarine I which are considered by the authors to point to an unsymmetrical structure for the alkaloid. It looks at present as though C-curarine I, the first calabash-curare alkaloid to be crystallised, may well represent the most difficult structural problem in the field.

C-Calebassine, $C_{40}H_{48}O_2N_2^{++}$, also contains two of the systems (72), but unlike C-curarine I it does not undergo vinylogous Hofmann elimination; however, the $^+NMe(b)$–CH_2 bonds can be reductively cleaved over platinum.[76] The alkaloid contains two oxygen atoms more than C-dihydrotoxiferine I and they are present as hydroxyl groups. Evidence for their carbinolamine nature  comes from their reductive removal by zinc and acetic acid to yield deoxy-C-calebassine[77] which can be reconverted into C-calebassine by photo-oxidation.[68] Bernauer, Schmid, and Karrer[78] provided further support for two carbinolamine systems by showing that a dimethyl ether can be formed from C-calebassine by treatment with dry methanolic acid. This ether formation is readily reversed in dilute aqueous acid at room temperature. Tetrahydro-C-calebassine, in which both ethylidene side chains of the two groupings (72) have been reduced, forms an analogous dimethyl ether.[78]

It is certain that the hydroxyl groups are intimately connected with the chromophore of the alkaloid since the ultraviolet spectra of C-calebassine and of tetrahydro-C-calebassine undergo a shift of some 10 mμ in alkaline solution that is not shown by the corresponding dimethyl ethers. Indeed, the alkali-induced shift is held[33] to be diagnostic for the 2-hydroxyindoline chromophore (as in 76). Further, removal of the hydroxyl groups to form the deoxy-derivative increases the basicity of the *N(a)*-nitrogen atoms, and perhaps in addition increases their steric accessibility, such that a *N(a)*, *N(b)*,*N(b)*-trimethyl derivative can be formed by the action of methyl

[74] Garbers, Schmid, and Karrer, *Helv. Chim. Acta*, 1954, **37**, 1336.
[75] Boekelheide, Ceder, Natsume, and Zürcher, *J. Amer. Chem. Soc.*, 1959, **81**, 2256.
[76] Bernauer, Schmid, and Karrer, *Helv. Chim. Acta*, 1957, **40**, 731.
[77] Volz and Wieland, *Naturwiss.*, 1957, **44**, 376.
[78] Bernauer, Schmid, and Karrer, *Helv. Chim. Acta*, 1958, **41**, 673.

iodide on deoxy-C-calebassine at elevated temperatures.[79] Incidentally, this gives further proof of the C_{40} nature of this alkaloid. The non-formation of a tetra-*N*-methyl derivative from deoxy-C-calebassine can readily be rationalised in terms of the field effect, and probably steric effect also, of what is presumably the closely placed quaternary *N*(*a*)-atom; this is in contrast to the relatively large distance between the *N*(*b*)-atoms noted earlier.

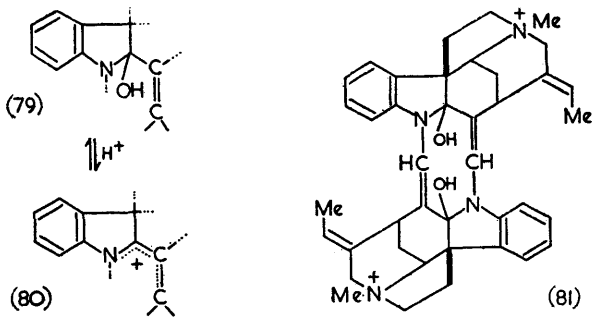


Thus it is possible to write[79] the partial structure (76) for C-calebassine and illustrate the formation of the trimethyl derivative (78) from deoxy-C-calebassine (77).

In 10N-acid, the ultraviolet spectra of C-calebassine and its tetrahydro-derivative show peaks at *ca.* 320 mμ indicating extended conjugation. This is interpreted by the Zürich school[78] in terms of the partial structure (79) for the alkaloid which in strong acid reversibly gives the mesomeric cation (80).

We have mentioned earlier (p. 98) the relation of C-calebassine to C-fluorocurarine and also the formation of C-calebassine by photo-oxidation of C-dihydrotoxiferine I. The latter oxidation can also be achieved[66] under acid–base catalysis (pyridine–acetic acid) in presence of oxygen. With this knowledge of its close relation to C-dihydrotoxiferine I, it is tempting to fit the partial structure (79) into the C-dihydrotoxiferine I skeleton to give constitution (81) for C-calebassine. However, this is unlikely on a number of grounds, particularly the stability of deoxy-C-calebassine towards acids;[10] the analogue in the toxiferine I "family", namely, deoxy-C-Alkaloid A is also stable under strongly acidic conditions.[69]

[79] Bernauer, Schmid, and Karrer, *Helv. Chim. Acta*, 1958, **41**, 26.



The structures of C-curarine and C-calebassine and those of their hydroxy-analogues C-Alkaloid E and C-Alkaloid A represent the major challenge at present to chemists working in this field; no less interesting are the structures of C-Alkaloid D and caracurine II methochloride formed under such mild conditions from the methyleneindoline alkaloids. However, even when these problems are solved, there remains much to do in this difficult field, as the Appendix makes amply clear.

Appendix

The following alkaloids of unknown structure (not listed in the Table on p. 81) have been isolated from calabash-curare or *Strychnos* species:

C-Guianine;[80] C-Alkaloids Q, R, and S;[81] C-Alkaloid X;[28] C-curarine II;[13,78] C-isodihydrotoxiferine;[15] C-Alkaloids B, C, I, J, UB, and L;[18] C-Alkaloids M, O, and P;[23,80] caracurine I, III, and IV;[22] caracurine VIII and IX methochlorides;[21] melinonine E, H, I, K, L, and M;[29] C-fluorocurinine;[18] pseudofluorocurine;[81] xanthocurine;[80] fedamazine;[22] C-calebassinine;[18] alkaloids 1 and 2;[19] toxiferine II;[44] croceocurine;[82] macrophylline-A;[83] kryptocurine;[82] toxiferine III, VIII, and XII;[16,17] macusine A and B.[17]

[80] Giesbrecht, Meyer, Bächli, Schmid, and Karrer, *Helv. Chim. Acta*, 1954, **37**, 1974.
[81] Meyer, Schmid, and Karrer, *Helv. Chim. Acta*, 1956, **39**, 1208.
[82] Meyer, Schmid, Waser, and Karrer, *Helv. Chim. Acta*, 1956, **39**, 1214.
[83] Iorio, Corvillon, Alves, and Marini-Bettolo, *Gazetta*, 1956, **86**, 923.