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Investigation in the Field of Alkaloids

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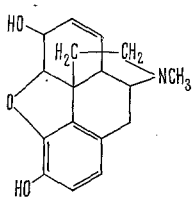
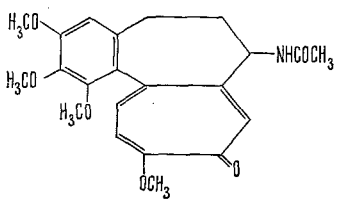
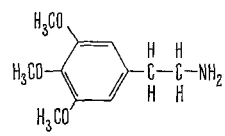
Alkaloids are natural products containing nitrogen which is usually basic and part of a heterocyclic ring system. In this condition the nitrogen can be secondary, tertiary, or quaternary. When primary, it is attached to an aliphatic chain, in rare cases the nitrogen has other functions. The overwhelming majority of alkaloids is of plant origin, a few like *samandarine* or *batrachotoxine* originate from animal sources. Many alkaloids possess a biologic activity, others are devoid of any observable action, at least in the dose ranges normally used in pharmacology. The following examples serve to demonstrate the diversity of structures in which nitrogen finds itself:



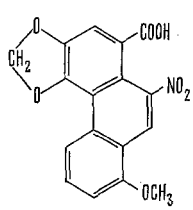
Morphine
N cyclic, reacts as a base, pharmacologically active.



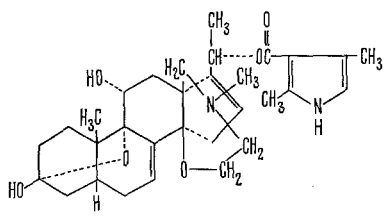
Colchicine
N not cyclic, reacts neutral, pharmacologically active.



Mescaline
N is primary, pharmacologically active.



Aristolochic acid
N has other function (activity?).



Batrachotoxine
from animal material, highly active.

It was the early exploration of the biological activity in plants which focussed attention on plant alkaloids and after the basic nature of morphine had been discovered by SERTÜRNER (1817), the isolation of other important alkaloids quickly followed: Narcotine and emetine in the same year 1817, then strychnine, veratrine (1818), brucine (1819), quinine, cinchonine, caffeine and solanine (1820) and at succeeding short intervals atropine, berberine, codeine, colchicine, coniine, corydaline, hyoscyamine, nicotine and sanguinarine. Later important findings were thebaine, papaverine, sparteine (1851), cocaine, physostigmine, lupinine (1884), ephedrine, chelerythrine (1890), yohimbine, lobeline, febrifugine, etc. Most of the alkaloids cited were physiologically or therapeutically important or were compounds which could be transformed into such substances (e.g. thebaine). The rate of new discoveries in the alkaloid field has continued unabated in the 20th century but has yielded few new therapeutically useful drugs of practical importance. In fact there has been nothing in the last 15 years, the most prolific period in the history of alkaloid work.

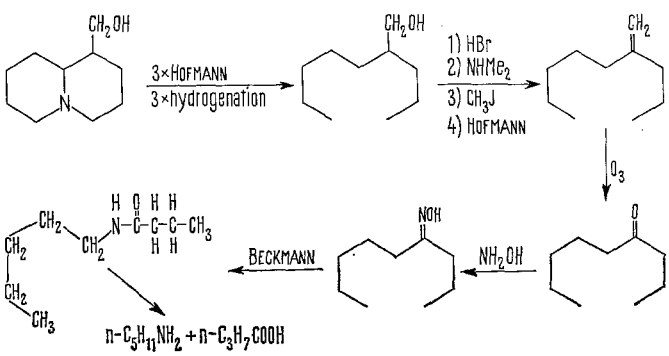
Viewed from a research point of view alkaloid chemistry, however, offers a wealth of interesting problems whose elucidation benefits nitrogen chemistry. Alkaloid problems seem to be more multifacetted than the chemistry of carotenoids, steroids or the vitamins. One has only to realize into how many different systems nitrogen can be incorporated or how different is the chemistry of the tropane alkaloids from the chemistry of the indole alkaloids.

In 1957, 2233 known alkaloids were counted and with today's isolation methods which are so much better than the ones used only 20 years ago, a considerable number of new alkaloids are added each year. The fourth and last edition of HENRY's *Plant Alkaloids* of 1949, a classical textbook of alkaloid chemistry, is obsolete and very few pages could stand unaltered a potential fifth edition. The contributions of the 'KARRER-Group' of the Zurich University Chemistry Department is responsible to quite a degree for this progress.

[1] I am indebted to Dr. W. I. TAYLOR (I.F.F. of New Jersey) for helpful criticism and assistance in the translation of the manuscript.

It is an educational experience to study KARRER's earlier publications in this field. No doubt an interest in the pharmacologic activity of alkaloids was important, but also an intense curiosity to 'know' was responsible for the selection of the different topics. A strange colour change connected with the transformation of the free chelerythrine base into a salt stimulated the interest in the structure of this unusual isoquinoline alkaloid[2]. The degradation of nicotine to the optically active hygric acid[3] was probably triggered by more general investigations on amino acids which were carried out in KARRER's laboratory at that time. Other publications deal with new methods or new reagents like the $LiAlH_4$-reduction of *p*-toluene sulphonic esters[4] or the reduction of brucine[5] or apoyohimbine[6] with the same reducing agent. By a new method an intermediate of WILLSTÄTTERS tropinone synthesis was obtained and thus the yields were increased[7]. Investigations of the ipecac alkaloids were initiated, they stretch over a period of 30 years, but the elucidation of their structures has never become one of the main issues of the KARRER Laboratory[8].

Two investigations of this early period merit special attention: the structure elucidation of lupinine[9] and the contributions towards the structure elucidation of the alkaloid sparteine[10]. Although WILLSTÄTTER and FOURNEAU had already investigated the HOFMANN degradation of lupinine, KARRER's idea of hydrogenating the product of each successive HOFMANN reaction was instrumental to success (because the danger of polymerization of unsaturated intermediates was eliminated). After the nitrogen had been removed by a 'three-step HOFMANN', the product still contained a primary hydroxyl group. By an additional HOFMANN reaction this was transformed into an unsaturated methylene group whose ozonization gave a ketone. BECKMANN rearrangement of the corresponding oxime yielded n-amylamine and n-butyric acid. Thus, with the exception of the carbon of the primary hydroxyl group, all the carbon atoms in lupinine were accounted for and from the 2 end-products obtained an unambiguous conclusion as to the structure of lupinine could be drawn.

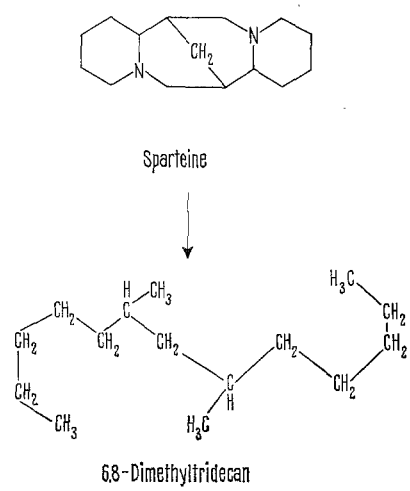


Even if the author writes: 'Der Weg ist lang und erfordert grosse Materialmengen, im ganzen gelangten über 600 g Lupinin zur Verarbeitung' this structure proof is convincing for its straight-forward execution.

The application of the same method to the structure elucidation of sparteine was less satisfactory. The end-product of the HOFFMANN degradation was not a ketone with 9 carbon atoms, but a hydrocarbon whose constitution could not be elucidated with certainty by methods available 40 years ago (b.p., density, molecular refraction, molecular dispersion). At that time the C-15 hydrocarbon was thought to have the following constitution[10]:

$$CH_3-(CH_2)_4-CH(-CH_2-CH_2-CH_3)-(CH_2)_5-CH_3$$

Only in 1942, when the constitution of sparteine was already known[11], SCHIRM and BESENDORF[12] demonstrated that KARRER's hydrocarbon was identical with 6,8-dimethyl tridecan:



[2] P. KARRER, Chem. Ber. *50*, 212 (1917); Helv. chim. Acta *4*, 703 (1921).
[3] P. KARRER and R. WIDMER, Helv. chim. Acta *8*, 364 (1925). – P. KARRER and T. TAKAHASHI, Helv. chim. Acta *9*, 458, 461 (1926).
[4] P. KARRER and G. WIDMARK, Helv. chim. Acta *34*, 34 (1951). – H. SCHMID and P. KARRER, Helv. chim. Acta *34*, 1948 (1951). – P. KARRER and R. SAEMANN, Helv. chim. Acta *36*, 605 (1953). – R. HEIZ and P. KARRER, Helv. chim. Acta *36*, 1788 (1953).
[5] P. KARRER and H. FLEISCH, Helv. chim. Acta *36*, 1529 (1953).
[6] J. BRÜESCH and P. KARRER, Helv. chim. Acta *38*, 905 (1955).
[7] P. KARRER and H. ALAGIL, Helv. chim. Acta *30*, 1776 (1947).
[8] P. KARRER, Chem. Ber. *49*, 2057 (1916); *50*, 582 (1917). – H. STAUB, Helv. chim. Acta *10*, 826 (1927). – P. KARRER, C. H. Eugster and O. RÜTTNER, Helv. chim. Acta *31*, 1219 (1948). – P. KARRER and O. RÜTTNER, Helv. chim. Acta *33*, 291 (1950).
[9] P. KARRER, F. CANAL, K. ZOHNER and R. WIDMER, Helv. chim. Acta *11*, 1062 (1928). – P. KARRER and A. VOGT, Helv. chim. Acta *13*, 1073 (1930). – Cf. also R. WILLSTÄTTER and E. FOURNEAU, Chem. Ber. *35*, 1910 (1902).
[10] P. KARRER, B. SHIBATA, A. WETTSTEIN and L. JACUBOWICZ, Helv. chim. Acta *13*, 1292 (1930).
[11] G. R. CLEMO and R. RAPER, J. chem. Soc. (London) *1933*, 644.
[12] M. SCHIRM and H. BESENDORF, Arch. Pharm., Berlin *280*, 64 (1942).

With the physical methods available today it would have been less difficult to correctly identify this C-15 degradation product.

KARRER's alkaloid work has reached its peak with his investigations of the calabash alkaloids[13]. Together with HANS SCHMID and an excellent staff of collaborators an enormous wealth of experimental data has been gathered and problems of unexpected difficulty were tackled and solved.

Natives of Venezuela and Northern Brazil use calabash gourds as containers for their arrow poisons. These concentrated extracts from different Strychnos species (Fam. Loganiaceae) are more poisonous than arrow poisons prepared from menispermaceous plants which are packed in hollow bamboo sections. Calabash curare was first investigated by BÖHM[14]; later investigations by KING[15] indicated that these highly poisonous compounds were nitrogenous and that the alkaloids were quaternary (and therefore ether-insoluble) yielding derivatives which could not be crystallized. WIELAND et al.[16] introduced the method of chromatographic separation of the reineckates over aluminium oxide and the Munich group succeeded in isolating and identifying several quaternary chlorides which were later re-isolated by the Zurich group. Inspite of the fact that chromatography of the reineckates yielded the first crystalline material, its exclusive use for fractionation was by no means perfect and separation of individual salts was not always possible[17].

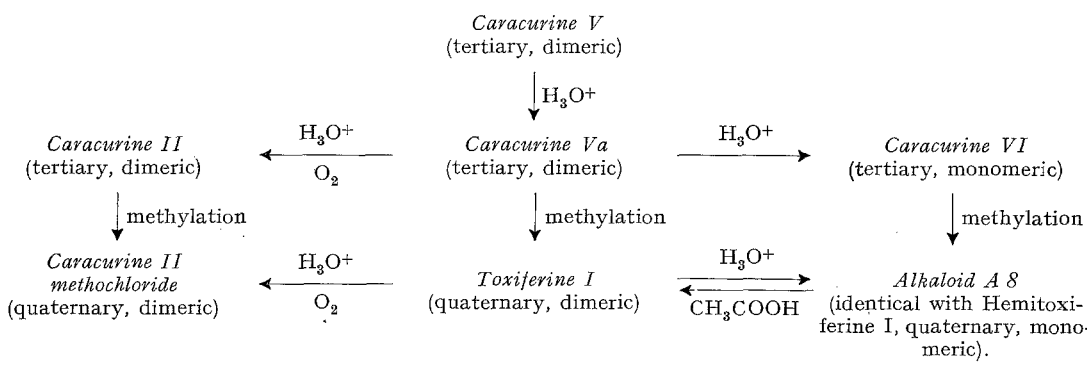
It is the lasting contribution of the Zurich group that it developed additional methods for the separation of these complicated alkaloidal mixtures. Two-dimensional paper chromatography and especially separation of the quaternary chlorides on cellulose columns proved to be enormously helpful. Thus it was possible to separate and identify 21 different calabash alkaloids in one chromatographic run[18]. It is obvious that the success of such refined methods of separation had a strong influence on alkaloid chemistry. In much of the earlier work attention had been paid exclusively to crystalline material and only in rare cases the total alkaloidal material has been investigated. Unlike the chemist who extracts biochemically active material, the alkaloid chemist has only rarely measured activity after each step of purification and has calculated the total activity still present. Such a procedure is only feasible if unambiguous biological tests are available. In most alkaloid isolations this was not the case; however, for the calabash alkaloids such methods could be used and proved to be valuable for the concentration of the active material. Parenthetically, in cases where such animal tests were not available progress of concentration has been monitored in humans, e.g. in the isolation of the hallucinogen of Psilocybe[19].

The pioneering WIELAND[20] publications indicated that the alkaloids isolated possessed different curare activity, but it was the Zurich group which succeeded in developing the interrelation between Rf-value in paper chromatography and the biologic activity.

A further basic contribution was the proof that the curare-active alkaloids had molecular weights twice as high as previously supposed, viz. 40 carbon atoms[21]. Also important was the observation that the bases, either quaternary or tertiary undergo structural rearrangements under the influence of cold mineral acids, monomeric bases being converted into dimeric ones and vice versa[22] (see Table I).

[13] For a recent short review see A. R. BATTERSBY and H. F. HODSON, *The Alkaloids* (Ed. R. H. F. MANSKE; Academic Press, New York and London 1965), vol. VIII, p. 515; (1968), vol. XI, p. 189.
[14] R. BOEHM, Arch. Pharm. Berlin *235*, 660 (1897).
[15] H. KING, Nature *135*, 496 (1935).
[16] H. WIELAND, W. KONZ and R. SONDERHOFF, Justus Liebigs Annln Chem. *527*, 160 (1937). – H. WIELAND and H. J. PISTOR, Justus Liebigs Annln Chem. *536*, 68 (1938). – H. WIELAND, H. J. PISTOR and K. BÄHR, Justus Liebigs Annln Chem. *547*, 140 (1941). – H. WIELAND, K. BÄHR and B. WITKOP, Justus Liebigs Annln Chem. *547*, 156 (1941). – H. WIELAND, B. WITKOP and K. BÄHR, Justus Liebigs Annln Chem. *558*, 144 (1947).
[17] A. R. BATTERSBY, R. BINKS, H. F. HODSON and D. A. YEOWELL, J. chem. Soc. *1960*, 1848.
[18] H. SCHMID, J. KEBERLE and P. KARRER, Helv. chim. Acta *35*, 1864 (1952).
[19] A. HOFMANN, R. HEIM, A. BRACK, H. KOBEL, A. FREY, H. OTT, TH. PETRZILKA and F. TROXLER, Helv. chim. Acta *42*, 1557 (1959).
[20] See e.g. H. WIELAND, B. WITKOP and K. BÄHR, Justus Liebigs Annln Chem. *558*, 179 (1941); see also Helv. chim. Acta *36*, 116 (1953).
[21] W. VON PHILIPSBORN, H. SCHMID and P. KARRER, Helv. chim. Acta *39*, 913 (1956).
[22] H. ASMIS, E. BÄCHLI, H. SCHMID and P. KARRER, Helv. chim. Acta *37*, 1993 (1954).
[23] A. R. BATTERSBY and H. F. HODSON, Proc. chem. Soc. *1958*, 287; J. chem. Soc. *1960*, 736.

Table I[23]



The truly basic result of all this hard work was the recognition that the 'WIELAND-GUMLICH-Aldehyde', a degradation product of strychnine, is the basic compound for most of the dimeric alkaloids[24] and also represented a convenient starting material for the synthesis of the active calabash alkaloids. The syntheses of toxiferine I[25] and dihydrotoxiferine[26] have been carried out in the following way (Tables II and III):

In place of methyliodide any other alkyliodide can be used for quaternization and curare preparations of different activities may thus be obtained. The synthetic N,N'-diallylnortoxiferine, Alloferine® has been introduced into therapy as a muscle relaxant.

[24] H. WIELAND and W. GUMLICH, Justus Liebigs Annln Chem. *494*, 191 (1932). – H. WIELAND and K. KAZIRO, Justus Liebigs Annln Chem. *506*, 60 (1933). – F. A. L. ANET and R. ROBINSON, J. chem. Soc. *1955*, 2253.

[25] A. R. BATTERSBY and H. F. HODSON, J. chem. Soc. *1960*, 736.

[26] K. BERNAUER, F. BERLAGE, W. VON PHILIPSBORN, H. SCHMID and P. KARRER, Helv. chim. Acta *42*, 201 (1959).

Table II. Synthesis of Toxiferine I

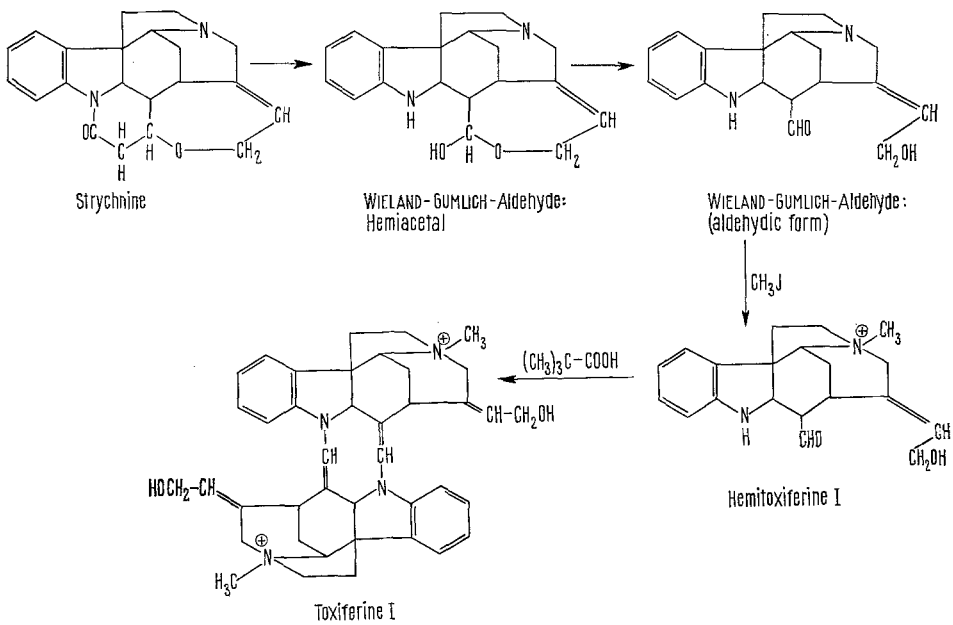
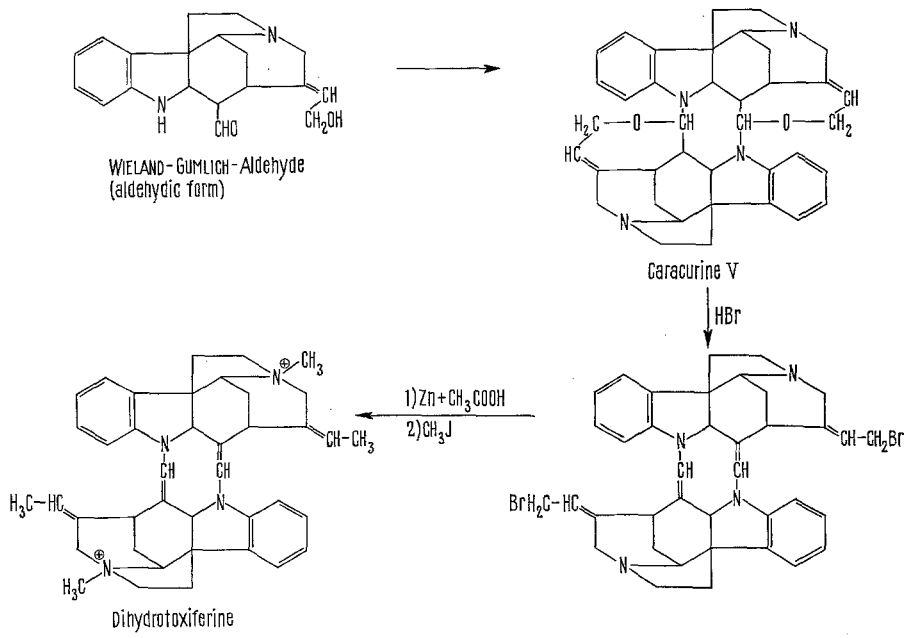


Table III. Synthesis of Dihydrotoxiferine



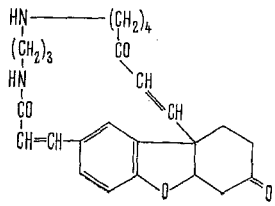
All this work on curare alkaloids is published in about 60 papers; its importance does not lie in the preparation of a therapeutically useful drug (Alloferine®), but in the hard-won chemical knowledge.

Origin and composition of the curare poisons vary to a great extent and alkaloids have been isolated from curare which could not be found in *Str. toxifera*. The question thus arose what other Strychnos species and possibly what other plant extracts had been used in concocting these arrow poisons. With this question in mind the Zurich group has investigated a number of other *Str.* species. The problem becomes even more complicated if other genera are taken into account as well. This has already been considered more than 30 years ago when FREISE[27] investigated extracts of Moraceae, Menispermaceae and Euphorbiaceae. Although these experiments were carried out by simple methods, they should not be disposed of lightly.

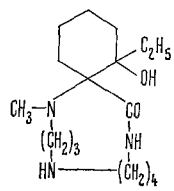
During the last few years work in curare alkaloids has diminished and attention has turned towards new varieties of indole alkaloid problems. The Zurich group has worked out the constitution of alkaloids obtained from Apocynaceous plants like Pleiocarpa[28], Kopsia[29], Alstonia[30], Aspidosperma[31], Hunteria[32], Callichilia[33], Conopharyngia[34], Vinca[35]. Physicochemical methods which had already been used in the latter part of the curare research were also applied in the structure elucidation of these partly new alkaloids. It was still necessary for the chemist to isolate and prepare pure alkaloids which was greatly helped by the refined methods discussed above. Thus in many cases only very small amounts of an alkaloid were available for a structure elucidation and methods were used for this purpose whose efficiencies were unheard of 30 years ago. This actually represents an enormous progress over the methods and amounts used for the lupinine work mentioned earlier.

In the years 1910 to 1930 the isoquinolines were the alkaloid group which was most often investigated. However, already in 1934, at the International Congress for Pure and Applied Chemistry in Madrid, GEORGE BARGER pointed to the fact that indole alkaloids would outdo the isoquinolines in importance and complexity and this has certainly become true by now. Already in 1966 more than 500 different indole alkaloids were known[36] and in their work of the last 20 years KARRER's group has demonstrated how diverse and complex the many indole alkaloids can be. Whether indole alkaloids will once be surpassed in importance by any other alkaloid group is mute question.

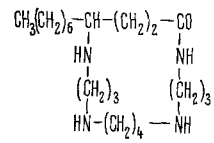
More and more 'large ring alkaloids' are being recognized at present and the Zurich group has made its



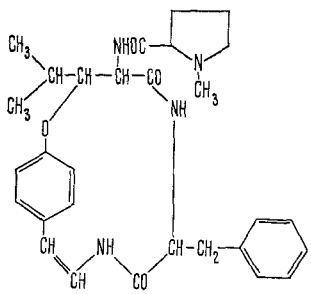
Lunarine



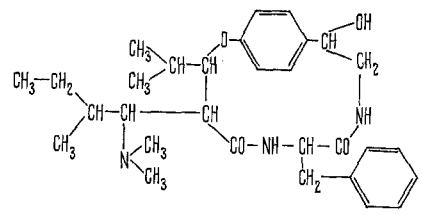
Palustrine



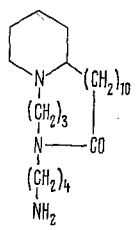
Pithecolobine



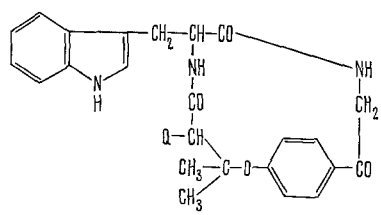
Ceanothine B

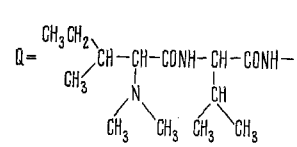


Pandamine



Ocinotine

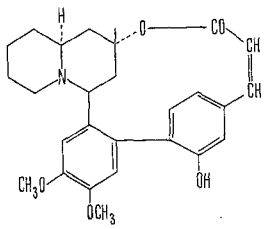




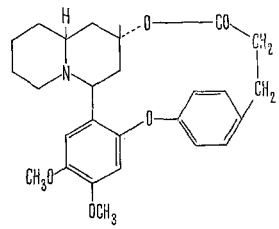
Hymenocardine

contribution to this field as well. Such alkaloids have been isolated from *Cruciferae* (Lunarine, from *Lunaria biennis*[34]), *Equisetae* (Palustrine, from *Equisetum palustris*[38]), *Rhamnaceae* (Ceanothine B, from *Ceanothus americanus*[39]), *Leguminosae* (Pithecolobine, from *Pithecolobium*[40]), *Pandaceae* (Pandamine, from *Panda oleosa*[41]), *Apocynaceae* (Ocinotine, from *Ocinotis nitida*[42]), *Sterculiaceae* (Adouetine, from *Waltheria indica*[42]), *Hymenocardiaceae* (Hymenocardine, from *Hymenocardia acida*[44]). The structures of these large ring alkaloids point to their relationship with amino acids and hydrolysis yields derivatives of such acids. Comparatively little is known about their pharmacologic activity, but it seems that these alkaloids have no well-recognized action.

Large ring alkaloids with lactone rings have also been found, mostly in the family of the *Lythraceae*. Mention should be made to *lythrine* from *Heimia salicifolia*[45] and to *vertaline* from *Decodon verticillata*[46] for which the following structures have been proposed:



Lythrine



Vertaline

With the more efficient extraction methods of which we avail ourselves today, we begin to detect alkaloids even in plant families which in earlier times were believed to be alkaloid-free. From *Spirea japonica* (Fam. Rosaceae) 3 alkaloids have been isolated which belong to the diterpenoid alkaloids[48].

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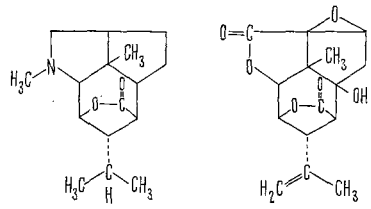
For a long time the *Dendrobium* species seemed to be the only alkaloid-containing members of the Orchid family. During the last few years B. LUNING in Stockholm has isolated alkaloids from a number of other orchids[48]. *Cryptostylis*[49] gives a tetrahydroisoquinoline base, *Malaxis* and *Chysis*[50] give pyrrolizidine alkaloids. *Dendrobine* from *D. nobilis*, has a carbon skeleton which is constructed differently resembling picrotoxinin, a non-nitrogenous poison from *Anamirta cocculus*[51]:



Dendrobine Picrotoxinin

Interesting families which have not been investigated thoroughly are e.g. the *Labiatae* and the *Scrophulariaceae*. From *Labiatae stachydrine* has been isolated repeatedly[52], but it is believed that *Ocimum, Marrubium, Teucrium, Rosmarinus* etc. might give additional alkaloids[53]. Among Scrophulariaceae *Scoparia*[54], *Pedicularis*[55], *Verbascum*[56], *Bartsia*[57] etc. might be interesting. From Scrophulariaceous plants nicotine[58] and quinazoline and quinolizidine alkaloids have already been isolated[59], but this plant family still offers interesting possibilities. Close to our interest is the big family of the Solanaceae which has already yielded so many interesting alkaloids. At an American university a large investigational program on tropical Solanaceae has been started and this certainly promises to be interesting. Inspite of this remarkable scientific activity in the alkaloid field, it is questionable whether an alkaloid of the same therapeutic importance as morphine or quinine could be found today, although the literature contains numerous folklore indications as to the use of alkaloid bearing plants by natives of Africa, South America and Asia, most of which cannot be confirmed. Although this scepticism seemed to be justified, reserpine, an alkaloid of seemingly great therapeutic and economic importance was found in the 1950s[60]. The isolation of this sedative and antihypertensive alkaloid triggered an intense search for other important plant products. Academic and industrial laboratories competed in this search, numerous botanical expeditions were sent to tropical countries and thousands of plants were extracted and their extracts tested. Some pharmaceutical companies even erected research laboratories in tropical countries in order to be closer to their plant raw material and good taxonomists became the cherished collaborators of pharmaceutical companies. Chemistry certainly profited from this trend although the economical yield was minimal since no alkaloid of therapeutic importance was found.

Therapeutic success is a function of the time. Today it would be difficult to introduce acetyl salicylic acid into therapy. Pyrazolone analgetics are almost as old as acetyl salicylic acid, they are still used in enormous quantities although in some countries they are highly suspect and no more used. Today, newly introduced products are 'metabolized' much faster and do not command the field as authoritatively as some old ones still do. For this reason a comparison of the importance of reserpine with morphine and quinine is difficult. The doctor of today already avails himself of more suitable antihypertensives and more potent tranquilizers than reserpine, but this does not impair the importance of this product. One can only guess that reserpine today would not be as unique as it was 15 years ago. Reserpine was certainly instrumental in opening a new field of therapy and in this respect it may equal morphine and quinine in importance. Alkaloids which will lead into virgin territories may always be found again, but it is doubtful whether alkaloids will ever be found which will retain their position in therapy as long as this has been held by morphine or quinine.

Zusammenfassung. Die Arbeit, die als Vortrag zum 80. Geburtstag von Herrn Prof. Dr. P. KARRER am 18. April 1969 am Chemischen Institut der Universität Zürich gehalten wurde, bespricht in ihrem ersten

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Teil die Arbeiten des Karrerschen Instituts auf dem Gebiet der Alkaloidchemie. Dabei werden vor allem die Bedeutung der Strukturaufklärung des Lupinins und die Arbeiten zur Strukturaufklärung von Spartein betont. Anschliessend folgt eine Besprechung der Arbeiten auf dem Gebiet der Kalebassen-Kurarealkaloide, soweit dies in einem solchen Rahmen überhaupt möglich ist. In etwa 60 Publikationen wurde hier ein riesiges Tatsachenmaterial zusammengetragen, und es sind chemische Probleme von ungeheurer Komplexität gelöst worden.

Im zweiten Teil der Arbeit werden einige heute besonders aktuelle Gebiete der Alkaloidforschung besprochen, so zum Beispiel die Chemie der grossringigen Peptidalkaloide, die in zunehmender Zahl in verschiedenen Pflanzenfamilien aufgefunden werden. Es wird ferner darauf hingewiesen, dass mit den heute verfeinerten Isolierungsmethoden Alkaloide in Pflanzenfamilien aufgefunden werden, wo solche früher nie vermutet wurden. Schliesslich werden einige Pflanzenfamilien aufgeführt, deren Bearbeitung wissenschaftlich besonders aussichtsreich erscheint.

SPECIALIA

Les auteurs sont seuls responsables des opinions exprimées dans ces brèves communications. – Für die Kurzmitteilungen ist ausschliesslich der Autor verantwortlich. – Per le brevi comunicazioni è responsabile solo l'autore. – The editors do not hold themselves responsible for the opinions expressed in the authors' brief reports. – Ответственность за короткие сообщения несёт исключительно автор. – El responsable de los informes reducidos, está el autor.

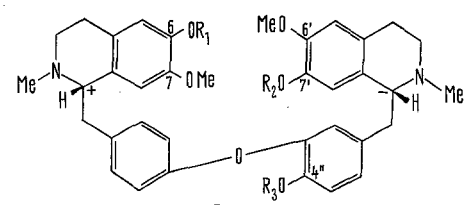
Alkaloids of *Berberis laurina* Billb. II. Two New Phenolic Biscoclaurine Alkaloids

In addition to the alkaloids previously reported[1,2] from the alkali-insoluble fractions of *Berberis laurina* Billb., we have now isolated 2 phenolic alkaloids which we have named espinine (Ia), $C_{36}H_{40}N_2O_6$, and espinidine (Id), $C_{37}H_{42}N_2O_6$.

Espinine, mp 123–125° (Kofler), Rf 0.08, $[\alpha]_D + 25°$ ($CHCl_3$), crystallized from a methanol solution of the alkali-soluble bases, and the mother liquors, submitted to counter-current distribution between benzene and pH 11.9 buffer (120 transfers), afforded 5 distinct bases which gave single spots on TLC. Tubes 1–7 contained espinine, and tubes 64–68 yielded the related amorphous base espinidine, Rf 0.15, $[\alpha]_D + 31°$ ($CHCl_3$).

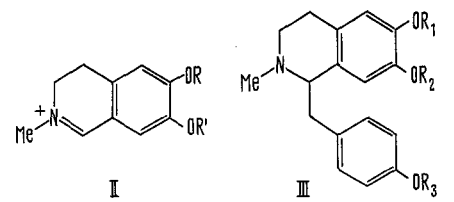
Both bases had practically identical UV-spectra, characteristic of *bis*benzyltetrahydroisoquinoline alkaloids. The NMR-spectrum of espinine showed 2 methylimino groups at τ 7.59 and 7.51, and 2 methoxyls at τ 6.43 and 6.23. The aromatic region showed the presence of 11 protons, including 2 high-field ones at τ 3.98 and 3.75. On treatment with diazomethane, espinine yielded an *O*-trimethyl derivative (Ib), $[\alpha]_D + 14°$ ($CHCl_3$), which shows 5 methoxy groups at 6.39, 6.35, 6.19 and 6.17 (6 protons), as well as 2 methylimino groups at τ 7.50 and 7.46, and the 2 high-field aromatic singlets at τ 3.86 and 3.81.

These data are consistent with a *bis*coclaurine alkaloid of type (I) with a single diaryloxy bridge, and this is confirmed by the m.s. of espinine: the spectrum has comparatively few peaks, the molecular ion (m/e 596) is of very low relative intensity (< 1%) and there are no double-charged ions, as with other bases of this type[3]. The base peak of m/e 192 corresponds to the ion or ions (II, R=H, R'=Me or vice versa), which loses a methyl group to form the ion m/e 177 (26%), as shown by the metastable ion at m/e 163.0. Thus espinine must have one methoxyl and



I

	R_1	R_2	R_3
Ia:	H	H	H (Espinine)
Ib:	Me	Me	Me
Ic:	Et	Et	Et
Id:	H	H	Me (Espinidine)
Ie:	Et	Et	Me



II III

	R_1	R_2	R_3
IIIa:	Et	Me	H
IIIb:	Me	Et	Et
IIIc:	Me	Et	Me

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