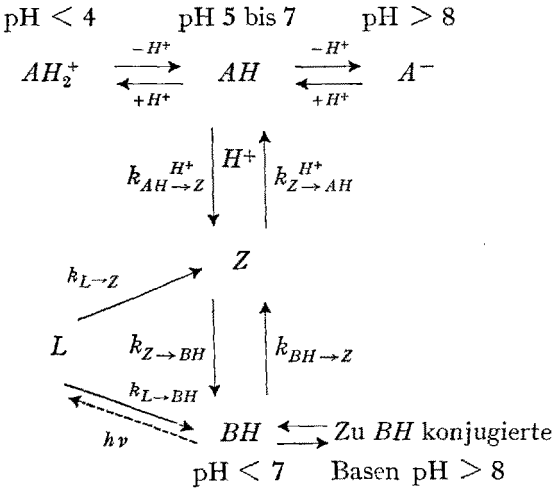
viel schwächer absorbiert; der Endwert der Extinktion ist daher bei 275 mμ grösser als der Anfangswert vor dem Blitz. Bei pH 7 geht L vollständig in BH über, der Endwert der Extinktion stimmt daher hier mit dem Anfangswert vor dem Blitz überein.

4. Überblick. Nach dem Vorangehenden kann das Verhalten von VI in methanolisch wässeriger Lösung durch das Schema



gedeutet werden. Da die Einstellung des Gleichgewichts zwischen AH_2^+, AH, A^- so schnell erfolgt, dass dieser Vorgang kinetisch nicht verfolgt werden konnte, ist auf Grund der vorliegenden Untersuchung nicht zu entscheiden, über welche dieser Formen das Zwischenprodukt Z gebildet wird. Es kann nicht entschieden werden zwischen der Möglichkeit, dass AH in Z übergeht mit einer Geschwindigkeit $k_{AH \to Z}^{H^+}[H^+][AH]$, die proportional $[H^+]$ ist, und der Möglichkeit, dass Z aus AH^+ gebildet wird mit der Geschwindigkeit

$$k_{AH^+ \to Z}^{H^+}[H^+] \cdot K_{H_2A^+} \frac{[H_2A^+]}{[H^+]} = k_{AH^+ \to Z}^{H^+} K_{H_2A^+}[H_2A^+],$$

welche von der Protonenkonzentration nicht abhängt.

Über die Ergebnisse von Versuchen zur Ermittlung der chemischen Struktur der Formen BH, Z und L wird an anderer Stelle berichtet.

Der Deutschen Forschungsgemeinschaft und dem Verband der Chemischen Industrie danken wir für die Unterstützung dieser Arbeit.

Summary

The anthocyanidin investigated here exists below pH 4 as a cation AH_2^+ (wave length of absorption maximum λ_{max} = 459 mμ), between pH 5 and 7 in the neutral form AH (λ_{max} = 492 mμ) and above pH 8 as an anion A^- (λ_{max} = 537 mμ). At pH 5 the freshly dissolved substance is partially converted into a colourless form BH (λ_{max} = 372 mμ) and a chemical equilibrium between AH and BH is reached within 1 h. A kinetic study of the process of formation of BH shows that an intermediate product Z is formed. This process can be reversed by light exposure. It can be concluded from a kinetic investigation by using flash light that BH is transformed by the absorbing light into a new substance L ($\lambda_{max} \simeq$ 275 mμ and 225 mμ), and L changes partially into BH, partially into Z, which itself is transformed partially into AH_2^+, AH, A^-, partially into BH. The reaction $Z \to AH$, AH_2^+, A^- is proportional to the concentration of protons $[H^+]$, the reaction $Z \to BH$ independent of $[H^+]$. Thus a photochemical production of AH_2^+, AH, A^- from BH is readily obtained in the presence of H^+ and not obtained in the absence of H^+.

A View of Progress in the Chemistry of Indole Alkaloids*

By E. SCHLITTLER and W. I. TAYLOR**

The last decade has been witness to an accelerated development in the successful structural investigation of indole alkaloids. The beginning of this period coincided roughly with the availability of accurate and trouble free infrared and ultraviolet spectrophotometers, whose intelligent use has made an essential contribution to the remarkable advances realised. Credit is also due to analytical methods: Column chromatography (although not a new tool) is now universally used along with paper chromatography and countercurrent distribution for the isolation, separation, and purification of natural products and their derivatives. Recently a new tool, nuclear magnetic resonance spectroscopy, has been applied to some of these problems and in due course when more experience will be gained, structural studies will benefit accordingly. Finally there is the well known method for the determination of structure by X-ray crystallographic analysis which requires a single suitable crystal. This technique can now compete on favorable terms with degradative work, thanks to electronic computers which solve the necessary Fourier syntheses at an almost incredible speed. These dramatic advances in instrumentation and analytical techniques merely serve to shorten the labors of the researcher, who would in actual fact not profit very much unless he would apply to his problems all the consequences of modern organic theory.

* This essay reflects the authors' approach to this subject. Only the major theme is developed but certain ideas buried in text may act as catalysts for further thought.

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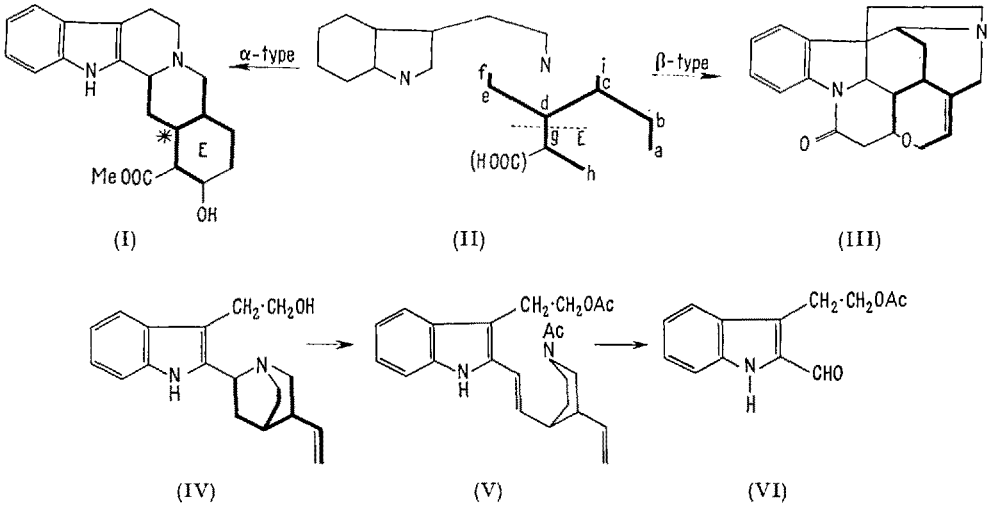
In addition to a general stimulus given by such perfected equipment to natural product chemistry, indole alkaloid chemistry derived specific profit from the isolation of reserpine[1] from *Rauwolfia serpentina* in the early fifties. In spite of the fact that reserpine did not offer any major structural problems (apart from its stereochemistry), the recognition of its valuable therapeutic properties must have acted as a catalyst for the investigation of indole bases. Evidence for this lies in a notable synthesis of the alkaloid[2] and in the interest which many pharmaceutical houses now take in plant chemistry.



Ten years ago the greater number of indoles and indolines could be divided into two formal classes, α-condensed systems e.g. yohimbine (I) and β-condensed systems[3] such as strychnine (III). Much of the work of the fifties has been devoted to the elucidation of the complete structures and relative stereochemistry of the α-type compounds, that is, known and new yohimbine isomers, ring E open and ring E oxygen heterocyclic bases. The determination of absolute stereochemistry of many of the indoles followed as a study in its own right as well as a corollary to work then being done, in the terpenoids and steroids. It should be pointed out, however, that with the exception of strychnine[4], the absolute stereochemistry of none of the dihydroindoles has yet been determined.

Examination of all this data has led two widely separated groups[5a] to suggest that thereis a common stereochemical denominator among these bases which betrays a common biosynthetic origin[5b]. That centre (C_{15} of yohimbine (I)) is marked with an asterik. Experimental work to test this hypothesis among the indoles has been successful and no exceptions have been found so far[6].

In the late forties WOODWARD[7] put forward a chemically plausible biogenesis for strychnine, the essential element of which involved the 3:4-ring fission of dopa or its equivalent. This fragment plus one carbon (carbon i) is shown in heavy type in (II), and in the other formulae in this essay. This idea of fission was to represent a real step forward in our understanding of the interrelationships between many indole classes. WOODWARD's idea was used directly a short time later in a rationalisation of the structure of the isoquinoline alkaloid emetine[8] and in solving the structure of the unusual base cinchonamine[9]. Because only a very small amount of cinchonamine was available all experiments were first carried out on a micro scale, the reaction products being examined spectrophotometrically. The key reaction turned out to be acetylation, the product was an O,N-diacetyl derivative (IR and Pk_a) which possessed a 2-vinyl indole chromophore (UV). This result, along with use of the WOODWARD concept, led to consideration of structure (IV) for cinchonamine and (V) for the diacetyl derivative which was confirmed by oxidation to the readily synthesisable (VI). The significance of cinchonamine as a link between indole and Cinchona bases was now obvious and bore out a conclusion recognised intuitively by ROBINSON[10] some years earlier.

[1] J. M. MÜLLER, E. SCHLITTLER, and H. J. BEIN, Exper. *8*, 338 (1952).

[2] R. B. WOODWARD, F. E. BADER, H. BICKEL, A. J. FREY, and R. W. KIERSTED, Tetrahedron *2*, 1 (1958).

[3] For the use of these terms see R. ROBINSON, *The Structural Relations of Natural Products* (Oxford at the Clarendon Press, 1955), p. 100.

[4] By an X-ray method, A. F. PEERDEMAN, Acta cryst. *9*, 824 (1956). No chemical proof is yet available.

[5] *a*) A. K. BOSE, B. G. CHATTERJEE, and R. S. IYER, Ind. J. Pharm. *18*, 185 (1956); *b*) E. WENKERT, E. W. ROBB, and N. V. BRINGI, J. Amer. chem. Soc. *79*, 6570 (1957).

[6] E. WENKERT and N. V. BRINGI, J. Amer. chem. Soc. *81*, 1474 (1959), and earlier papers.

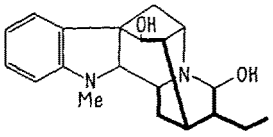
[7] R. B. WOODWARD, Nature *162*, 155 (1948).

[8] R. ROBINSON, Nature *162*, 524 (1948).

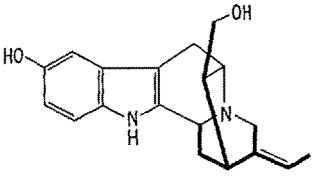
[9] R. GOUTAREL, M.-M. JANOT, V. PRELOG and, W. I. TAYLOR, Helv. chim. Acta *33*, 150 (1950). – W. I. TAYLOR, Helv. chim. Acta *33*, 164 (1950).

[10] H. T. OPENSHAW and R. ROBINSON, Nature *157*, 438 (1946).

A similar consideration of this fragment pictured in (II) led to a proposal and proof the structure of ajmaline[11] (VII), to which the Oxford school had contributed most of the experimental work[12]. The later derivation of a plausible structure for sarpagine[13] (VIII) was almost a matter of course.

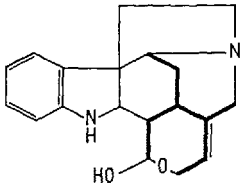


(VII)

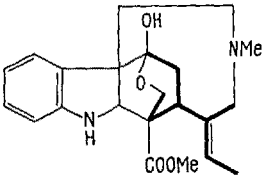


(VIII)

In another development the chemistry of the Curare alkaloids, for the most part bis-quaternary compounds and a major puzzle for many years, has suddenly become understandable. Two findings were crucial in bringing about this sudden transition from difficult experimentation to rational synthesis[14]. One was the recognition of Caracurine VII as the Wieland-Gumlich aldehyde (IX)[15] and the other was the identification of the chromophoric moiety of C-fluorocurarine with that of a β-anilino-α,β-unsaturated aldehyde[16]. Many of the Curare alkaloids have turned out to be essentially derivatives of the Wieland-Gumlich aldehyde, the biologically interesting ones being in the bis-quaternary class. Other alkaloids have turned out to be related to this aldehyde, e.g. strychnospermine, spermostrychnine, diaboline (Strychnos), akuammicine (Picralima), and very recently echitamine (X)[17] (Alstonia). Since strychnine is readily available, the importance of the Wieland-Gumlich aldehyde[18] (IX) for the synthetic investigation of alkaloids is clear.



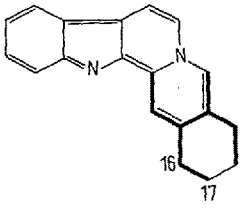
(IX)



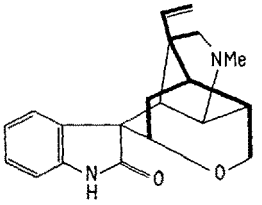
(X)

Examples of 'dimeric' alkaloids are becoming recognised more frequently and among others there are geissospermine (indole and dihydroindole)[19], serpentinine (indole and serpentine)[20], and quite a number of Voacanga and Vinca alkaloids. The nature of the linkages in the latter cases has not yet been elucidated.

By the mid-fifties one had learnt how to handle the oxindole alkaloids, principally those from the genus Mitragyna and Uncaria (more recently also from Pseudocinchona) and successful structural work was based on a combination of spectrophotometric analysis plus the recognition of the formulae of potash fusion and dehydrogenation products[21]. None of these alkaloids has been synthesised, although partial or total routes appear on the surface to be simple[22]. One of these alkaloids, mitragynine[23], has a 4-methoxy group and was the only natural product so substituted until the discovery of psilocybine, the phosphoric ester of 4-hydroxydimethyltryptamine[24], the hallucinogen of Mexican mushrooms. The most defiant of the oxindole alkaloids was the pentacyclic base, gelsemine, and its structure was bound to be interesting because it had been felt that there should be some relationship to co-occurring sempervirine (XI). A brilliant piece of inductive and degradative work led to its constitution simultaneously with the same solution by X-ray work[25]. The presence in (XII) of the same fragment as in (II) and (XI) is clearly indicated.



(XI)



(XII)

[11] R. B. WOODWARD and K. SCHENKER, Angew. Chem. *68*, 13 (1956). We have shown (in preparation) that the stereochemistry of ajmaline as well as sarpagine (VIII) is as indicated in the above formulae, i. e. in agreement with the postulate of Ref. [6].

[12] F. A. L. ANET, D. CHAKRAVARTI, R. ROBINSON, and E. SCHLITTLER, J. chem. Soc. *1954*, 1242.

[13] W. ARNOLD, W. v. PHILIPSBORN, H. SCHMID, and P. KARRER, Helv. chim. Acta *40*, 705 (1957). – D. STAUFFACHER, A. HOFMANN, and E. SEEBECK, Helv. chim. Acta *40*, 1866 (1957).

[14] P. KARRER, H. SCHMID, K. BERNAUER, F. BERLAGE, and W. v. PHILIPSBORN, Angew. Chem. *70*, 644 (1958). For a review see K. BERNAUER, Fortschr. Chem. org. Naturst. *17*, 184 (1959).

[15] K. BERNAUER, S. K. PAVARANAM, W. v. PHILIPSBORN, H. SCHMID, and P. KARRER, Helv. chim. Acta *41*, 1405 (1958).

[16] H. FRITZ, E. BESCH, and T. WIELAND, Liebigs Ann. *617*, 166 (1958). – W. v. PHILIPSBORN, H. MEYER, H. SCHMID, and P. KARRER, Helv. chim. Acta *41*, 1257 (1958).

[17] H. CONROY, Tetrahedron Letters No. 6, *1* (1960).

[18] H. WIELAND and W. GUMLICH, Liebigs Ann. *494*, 191 (1932). – H. WIELAND and K. KAZIRO, Liebigs Ann. *506*, 60 (1933).

[19] K. WIESNER, W. RIDEOUT, and J. A. MANSON, Exper. *9*, 369 (1953).

[20] Unpublished observations of Dr. S. UYEO.

[21] Mitragyna Alkaloids by J. D. LOUDON, *Recent Work on Naturally Occurring Nitrogen Heterocyclics*, Chemical Society Special Publication No. 3, p. 14 (1955).

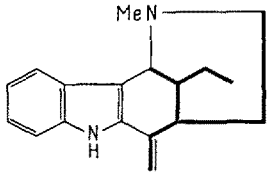
[22] This adjective is used advisedly since paper routes often do not work, examples are illustrated in early approaches to the total synthesis of yohimbine and especially colchicine.

[23] J. W. COOK, J. D. LOUDON, and P. MCCLOSKEY, J. chem. Soc. *1952*, 3904.

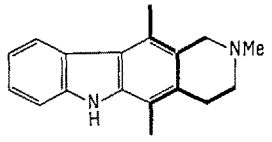
[24] A. HOFMANN, R. HEIM, A. BRACK, and H. KOBEL, Exper. *14*, 107 (1958). – A. HOFMANN, A. FREY, H. OTT, T. H. PETRZILKA, and F. TROXLER, Exper. *14*, 397 (1958).

[25] F. M. LOVELL, R. PEPINSKY, and A. J. C. WILSON, Tetrahedron Letters No. *4*, 1 (1959), H. CONROY and, J. K. CHAKRABARTI, Tetrahedron Letters No. *4*, 6 (1959).

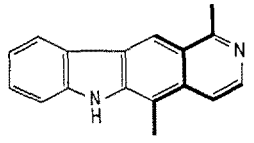
Until a year ago it was almost axiomatic that a tryptamine residue should be discernable whenever biogenetic arguments were used in formulating working hypothesis for structures of indole or indoline alkaloids. It came as somewhat of a shock to find that the Aspidosperma plants gave rise to a group of bases e.g. uleine (XIII)[26], ellipticine (XIV)[27], and olivacine (XV)[28] in which the number of carbons between the indole β-position and the basic nitrogen was not two. In these compounds however, there was discerned[27] the structural element which has been common to all the previous alkaloids discussed.



(XIII)



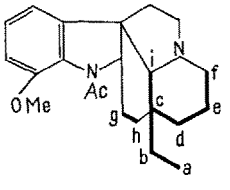
(XIV)



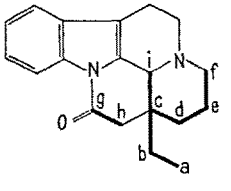
(XV)

Are these substances being derived from the fragment (II), ammonia and indole, or from tryptamine followed by a loss of two carbons?

Recently the structures of some alkaloids have been deduced in which the fragment (II) can only be recognised if rearrangement reactions are permitted. One of these bases is aspidospermine isolated from plants of the same genus as yield the above carbazole derivatives. It is of some interest since outside of the chromophoric moiety, it has resisted chemical examination. Now it has fallen to the X-ray technique[29] and its constitution (XVI) is consonant with the hard won chemical evidence[30]. A possible derivation from (II) would involve at some stage bond fission between carbon atoms d and g and the position of the atoms after recombination is shown in (XVI)[31]. The position of the carbomethoxy group in some newly isolated aspidosperma bases[32] accordingly will be, on this basis, on carbon g[33].



(XVI)



(XVII)

From *Hunteria eburnea* we have recently isolated and proved the structures of a group of interconvertible bases[34] and the key compound, eburnamonine (XVII), the indole equivalent of aspidospermine, has been synthesised in a simple fashion from 4-ethyl-4-dichloromethyl cyclohexadienone, readily prepared from *p*-ethylphenol[35]. This suggests an alternative biogenesis[35,36] for these compounds which might be considered to proceed from say tyrosine (or equivalent), formate, and tryptamine[37], but then this is a special hypothesis apparently not fitting into the above scheme. One way out of this difficulty would be to assume that the formation of (II), proceeds from an aromatic amino acid via an acid catalysed rearrangement of a first formed cyclohexadienone! Such a cyclohexadienone derived from 3:4-dihydroxyphenylalanine could function just as well as prephenic acids (see below) for the biosynthesis of indole alkaloids.

Three years ago we had examined in detail the alkaloids of *Tabernanthe iboga* and from the then known chemistry it was clear that their constitution had to be unusual. Although they were indoles they did not readily give characteristic dehydrogenation products. However, under certain experimental conditions small yields of two selenium dehydrogenation products were obtained, from which it was possible to arrive at structures for the parent bases[38]. These were so unfamiliar looking that it was considered desirable to obtain an unequivocal proof, especially of the presence of the seven membered ring C first proposed by JANOT *et al.* Using ibogaine (XVIII) for illustration, a method was devised which took advantage of the ease of formation of pseudo-indoxyls in this series to cut the molecule in

[26] G. BÜCHI and E. W. WARNHOFF, J. Amer. chem. Soc. *81*, 4433 (1959).

[27] R. B. WOODWARD, G. A. IACOBUCCI, and F. A. HOCHSTEIN, J. Amer. chem. Soc. *81*, 4434 (1959).

[28] G. B. MARINI-BETTÓLO and J. SCHMUTZ, Helv. chim. Acta *42*, 2146 (1959).

[29] J. F. D. MILLS and S. C. NYBURG, Tetrahedron Letters No. 11, 1 (1959).

[30] H. CONROY, P. R. BROOK, and Y. AMIEL, Tetrahedron Letters No. *11*, (1959) and earlier references.

[31] In Wenkert's biogenetic scheme [Exper. *15*, 165 (1959)] a similar fission has to occur if it is to account for the quaternary C-Et group of aspidospermine.

[32] B. GILBERT, L. D. ANTONACCIO, A. A. P. G. ARCHER, and C. DJERASSI, Exper. *16*, 61 (1960).

[33] Analogy would suggest this anyway, since the carbomethoxy group occupies an equivalent position in such compounds as voacangine, akuammicine, and echitamine.

[34] M. F. BARTLETT, W. I. TAYLOR, and RAYMOND-HAMET, C. R. Acad. Sci., Paris *249*, 1259 (1959).

[35] M. F. BARTLETT and W. I. TAYLOR, Tetrahedron Letters No. *20*, 20 (1959).

[36] R. ROBINSON, Tetrahedron Letters No. *18*, 14 (1959).

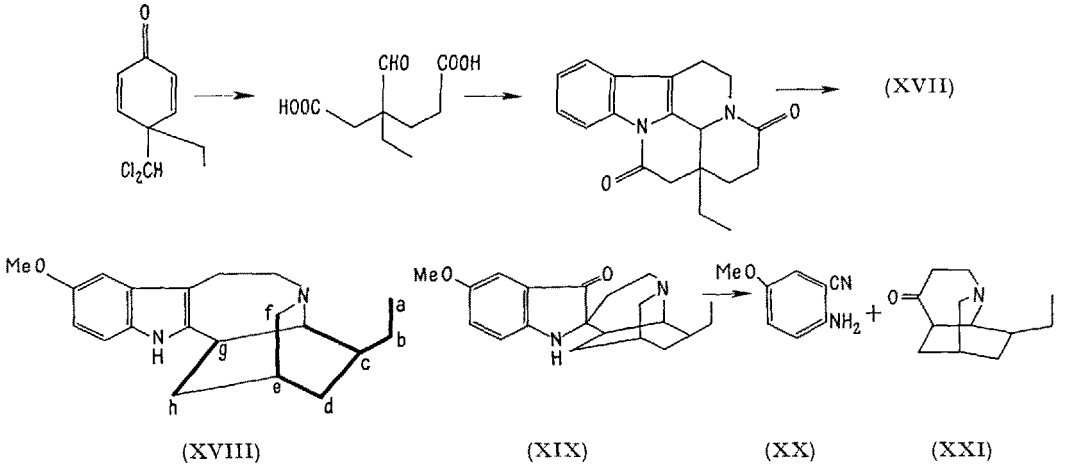
[37] On this basis the carbomethoxy group in the alkaloids ref. [32], could be on g or the ethyl side chain.

[38] W. I. TAYLOR, J. Amer. chem. Soc. *79*, 3298 (1957).

two, with a pair of chemical scissors as it were[39] (XIX →XX and XXI). At the time when this work was being carried out biogenetic considerations were of little help, but once the structure was established with certainty one could certainly try to fit it into current ideas. Proceeding in the same way as for aspidospermine, it could have been formed from the same fragments [40] as was involved for that alkaloid, although once again an alternative seems to be possible[41].

tions, the genesis of all these alkaloids might well be from an open chain $C_6 + C_1$ unit (carbons $a \rightarrow f$, i in II), and a C_3 unit (carbons g and h in II plus the bracketed carboxyl)[43].

The contribution of the organic chemist to the problem of biogenesis has been in the determination of the detailed structures of classes of natural products and the recognition in them of repetitive units. The indole alkaloids discussed above are no exception to this approach. However the detailed course and meaningfulness of alkaloid elaboration will only be elucidated through intensive work in those laboratories where biosynthesis is being studied *in vivo*. The outcome is bound to reveal subtleties similar to those now so well known in the case of the isoprene rule.



(XVIII) (XIX) (XX) (XXI)

In this article we have not been concerned with specific compounds from which the hydroaromatic fragment in (II) might arise. In early speculations concerning alkaloid biogenesis (WINTERSTEIN, BARGER, ROBINSON, SCHÖPF) amino acids were regarded as precursors so that for yohimbine, tryptophan plus tyrosine or dopa were logical choices. In his facile synthesis of an aromatic analogue of yohimbine, HAHN[42] appeared to strengthen this idea. Fission of ring E (Woodward) then enabled the other alkaloids to be incorporated into the general scheme. Nevertheless the origin of the carboxy group in ring E of the α-type indoles was either avoided or not satisfactorily explained. Recently WENKERT[6,31] put forward an ingenious theory, to which we have already alluded. According to him, precursors of the aromatic amino acids, shikimic and prephenic acids are the raw material for the biosynthesis of these bases. In this theory ring E of the yohimbines preexists in the intermediate and the genesis of its carboxyl group is plausible but different from the source of the carboxyl in indoles such as voacangine (XVIII; COOMe on carbon g). One might however consider two ideas, firstly that the origin of the carboxyls in the indole alkaloids is the same and secondly that ring E of the yohimbines is not derived from a carbocyclic precursor but rather is a product of a ring closure reaction. One of the intermediates in the Wenkert theory could accommodate these suggestions. However, rather than prephenic acid-type transforma-

Zusammenfassung

Neuere Erkenntnisse der theoretischen Chemie, Entwicklungen der chemischen Experimentierkunst und neue und verbesserte physikalische Instrumentation haben die Entwicklung der Indolalkaloidchemie im letzten Dezennium entscheidend gefördert. Die erfolgreiche Konstitutionsermittlung einer Reihe längst bekannter Indolalkaloide wurde dadurch ermöglicht. Ihre Konstitution sowie die Strukturen unlängst isolierter Indolbasen lassen auf eine grosse Mannigfaltigkeit im strukturellen Bau der Indolalkaloide schliessen. Die Biosynthese der Indolalkaloide wird kurz diskutiert, zusammen mit Kommentaren über den Ursprung des Rings E und der Carboxylgruppe in den Yohimbinen.

[39] M. F. BARTLETT, D. F. DICKEL, and W. I. TAYLOR, J. Amer. chem. Soc. *80*, 126 (1958).

[40] For a scheme with only one fission of prephenic acid see E. WENKERT ref. [31].

[41] W. I. TAYLOR, Exper. *13*, 454 (1957).

[42] G. HAHN and H. WERNER, Liebigs Ann. *520*, 123 (1935).

[43] Such a $C_6 + C_1$ unit plus tryptamine would account for flavopereirine (XI; minus carbons 16 and 17).