Phytochemistry, 1970, Vol. 9, pp. 1163 to 1165. Pergamon Press. Printed in England.

REPORT

FOURTH INTERNATIONAL SYMPOSIUM ON THE BIOCHEMISTRY AND PHYSIOLOGY OF THE ALKALOIDS

Academy-Verlag GmbH, 108 Berlin, Leipziger Straße, East Germany

THIS Symposium was held in Halle in June 1969 and a bound copy of the main lectures has been issued, a month or two after the conference, and these are the subjects of this review.

The first paper by D. H. R. Barton and D. A. Widdowson deals with the application of phenol-coupling concepts to the biosynthesis of the aromatic *Erythrina* alkaloids. Tyrosine was shown to be incorporated but the suggested bisphenethylamine resulting from phenol coupling was not incorporated. An alternative possible intermediate is *N*-norprotosinomenine and the authors used an interesting approach to show that this was enzymatically incorporated. The (+) and (−) enantiomers were prepared and fed; with the (+) enantiomer the incorporation was at least 100 times that of the (−). Several attempts to establish the next stages were made and led to the suggestion that the route is from tyrosine to *N*-norprotosinomenine, to a biphenyl, to the alkaloid erysodienone, then to erythraline and other alkaloids. Although the broad lines of biosynthesis of the ergot alkaloids from mavalonate and tryptophan are well known, H. G. Floss in the second article shows that detailed knowledge is very fragmentary. The ergoline structure is started by incorporation of γ-γ-dimethylallyl pyrophosphate at position 4 of tryptophan. Chanoclavine I is then an important intermediate in the pathway to agroclavine; hydroxylation of the latter leads to elymoclavine and the lysergic acid alkaloids. The ability of ergot strains to produce alkaloids depends on active take-up of L-tryptophan into the cell; this in turn seems to be associated with the presence of several nuclei (heterokaryon), since monokaryotic strains produce no alkaloids. During the early stages of mycelial growth little alkaloid is formed; however, as protein synthesis slows down, the amount of mycelial-free tryptophan rises rapidly. This in turn stimulates alkaloid production, possibly by inducing the synthesis of the necessary enzymes. Since excess of tryptophan normally represses its own synthesizing enzymes by feedback regulation, the author suggests that, in ergot, excess tryptophan stimulates the synthesis of an independent set of enzymes necessary to maintain the supply of tryptophan for continued alkaloid production. The name of L. Fowden, the next author, has long been associated with work on non-protein amino acids of plants. During the last 20 years the number known has risen from less than ten to more than 200. They differ from the twenty protein amino acids by possession of ethylenic, acetylenic and cyclopropanol groups and a great variety of heterocyclic amino and imino acids are also known. Their principal site of accumulation is storage organs and seeds, suggesting they represent a storage form of nitrogen. This is supported by the facts that they are rich in nitrogen, often in an *N*-acetyl form, and that traces of the corresponding stored forms occur in rapidly growing green tissues. Some are formed only in actively growing tissues and these may be concerned with transport of nitrogen. Some may have a regulatory function in normal amino acid metabolism as they exhibit "analogue" behaviour; examples of this behaviour are given at the end of the article. Because of the low turnover of most of these substances, biosynthetic studies by tracer techniques is difficult. About half of the article is concerned with chemotaxonomy and an interesting

account is given of their use in subdividing the genus *Aesculus* and relating it to the family Sapindaceae.

Although many workers would assume that unequivocal evidence for the incorporation of an amino acid into a particular alkaloid carries with it proof that the N has come from the same source, E. Leete ("The biosynthetic origin of the nitrogen in the heterocyclic rings of alkaloids"), while agreeing with this view for the isoquinoline alkaloids, points out that useful work could be done using ^{15}N to study the biosynthesis of such alkaloids as withasomnine from ornithine, camptothecin from tryptophan etc. He gives references to about twenty plants whose alkaloidal biosynthesis has been studied using ^{15}N precursors and suggests it is always advisable to use double labelling, with ^{14}C in the α-amino acid, to check whether transamination has removed the nitrogen from the precursor.

F. Lingens ("Uber Regulationsmechanismen bei der Biosynthese von alkaloidvorstufen") deals with the interesting fact that rate-limiting processes involving amino acids will also limit the production of alkaloids. Using a special strain of *Claviceps paspali*, he fractionated the DAHP-synthetase (the enzyme system which catalyses the combination of phosphoenol pyruvate and erythro-4-phosphate to form the precursor of shikimic acid and ultimately either tyrosine or tryptophan) into three isoenzymes. In one the activity was suppressed by L-tryptophan, in another by L-tyrosine and in a third by L-phenylalanine. Of special interest is another enzyme, chorismate-mutase, which canalizes the conversion of chorismate to phenylalanine, and tyrosine and therefore limits its conversion to anthranilic acid and tryptophan and the alkaloids. This enzyme is repressed by phenylalanine and tyrosine but activated by small amounts of tryptophan.

The complicated structures of the *Bisindole alkaloids* is dealt with by H. Schmid. They can be divided into two groups; in the first the dimers have identical or almost identical halves with a structural centre of symmetry. In the other group the two halves are dissimilar and vary in the position of link-up. The importance of the Wieland-Gumlich-aldehyde reaction in structure elucidation of both groups is discussed. Examples discussed from the first group are the curare alkaloids toxiferin and alloferin; from the second, villastonine, pycnanthine and pycnanthinine (all sharing a common monomer pleiocarpanine) and macralstonine (from alstophylline and macroline).

In the chapter "Biochemie der Steroidalkaloide", K. Schreiber deals first with recent work on what are virtually steroids with an amine group attached to Ring A or to a sugar group. Although it is doubtful whether they can be considered alkaloids, recent work on them sheds important light on the occurrence of steroidal saponins in plants. Over 20 years ago, Marker and Lopez suspected that the spirostan structure of these saponins was an artefact. Schreiber reports on the structure of a steroidal "alkaloid" in *Solanum paniculatum* L. which is a 3β-amino-furostan glucoside. On hydrolysis the open chain "Ring E" spontaneously cyclizes to form the spirostan structure, and this may well represent the normal method of producing these "artefact" structures. Details of recent work on the more truly steroidal alkaloids of *Veratrum*, *Lycopersicon* and *Solanum* are also given.

The last paper, "Alkaloids with anti-tumour activity", by M. E. Wall, gives recent news on the exciting possibilities of the use of alkaloids in cancer therapy. Brief mention is made of the relatively successful *Vinca* alkaloids and details of the chemistry and present pharmacological status of tylocebrine, ellipticine, thalicarpine, acronycine and related alkaloids are given. However, the most promising new development, on which Wall has worked during the last 15 years, is camptothecin, from *Camptotheca acuminata*. This is "one of the most active, natural anti-tumour agents" possessing a high activity in animals against leukemias and

solid tumour systems and recently clinical trials have been initiated. Details of the isolation and structure determination are given. As camptothecin may well become newsworthy, I suggest that we now decide, in view of its unusual properties, whether it is an alkaloid or not; and if it is, let us add the terminal *e*!

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