

of the eventual ring C to yield the seco-compound (IV). It is not unreasonable to assume that oxidation of (III) would split the ring at the site of the quaternary carbon to give (IV) because of the resonance induced electron deficiency at this site as is indicated by the arrows. The subsequent steps leading to (V) and finally colchicine (VI) are self-explaining and do not require any special hypothesis. Although direct ring enlargement of (III) to give (V) cannot be excluded, little or no chemical evidence can be adduced in its favor. Therefore, it would appear on chemical and biochemical grounds that colchicine may be formed from hydroxylated phenylalanines and for this reason, its classification as an alkaloid belonging to the phenylethyl amine group of alkaloids would be a logical conclusion.

It is worthy of note that a structural relationship can be derived between morphine and colchicine. When the latter is written as in (VII) the relationship becomes striking. However, the biogenetical significance of this fact is not evident.

Experiments to test the validity of this mechanism of biogenesis are being attempted.

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Résumé

Exposé d'une nouvelle hypothèse sur l'origine biochimique de la colchicine dans la plante. Il est supposé que l'acide trihydroxyphénylpyruvique agit comme précurseur de cet alcaloïde en subissant les transformations décrites par les formules (I) à (VI).

On constate une analogie entre ce mécanisme biogénétique et l'origine chimique de la purpurogalline de

même qu'une ressemblance structurale entre la morphine et la colchicine. Le classement de la colchicine au nombre des alcaloïdes de la famille des phényléthylamines serait ainsi justifié.

Acylchlorides of Amino Acids and Peptides as Monomers for the Preparation of Polymeric Polypeptides. I. Syntheses of Poly- β -Alanine, Poly-DL-Alanine, Poly-L-Leucine and Poly-Glycyl-DL-Leucine

A method for the preparation of acylchlorides of amino acids and peptides was described by FISCHER¹. It consists in the action of phosphorus pentachloride on the suspension of the latter in freshly distilled acetylchloride under special conditions; they are obtained in the form of their hydrochlorides.

We have found that these acylchlorides undergo poly-condensation and can be used advantageously as monomers in the controlled preparation of polymeric polypeptides. The procedure is indicated in the following scheme.

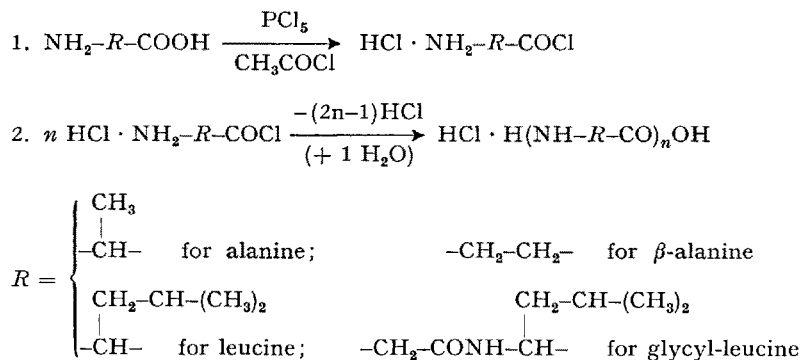
Polymerisation is carried out either by heating the acylchloride in high vacuo at elevated temperatures or by dissolving it in dimethylformamide containing trimethylamine, which latter eliminates hydrogen chloride from the monomer in the course of the reaction. The polymers thus produced are hydrochlorides of the respective polypeptides.

This procedure can also be applied in cases where the widely used polymerisation through N-carboxy anhy-

¹ E. FISCHER, Ber. deutsch. chem. Ges. 38, 605, 2914 (1905).

drides of α -amino acids (LEUCHS anhydrides) is not applicable (e.g., β -amino acids and peptides).

Until now we have prepared by this method the following polymers: poly- β -alanine, poly-D,L- α -alanine, poly-L-leucine and poly-(glycyl-D,L-leucine). Experiments on its extension to other amino acids and derivatives are going on in this laboratory.



In the following, as a typical example to illustrate the procedure involved, particulars on the preparation of poly- β -alanine are given.

β -Alanine which had been reprecipitated from its aqueous solution by ethanol, dried at 110°C and driven through a fine hair sieve, was suspended in about ten times its weight of freshly distilled acetylchloride and shaken on a shaking machine with finely ground phosphorus pentachloride. In this special case the reaction had to be continued for about nineteen hours, with several additions of fresh phosphorus pentachloride, until the resulting material gave the required chlorine values. (In other instances only a few hours were sufficient for the completion of the reaction). β -Alanylchloride hydrochloride thus obtained was filtered under careful exclusion of moisture, washed with acetylchloride and petrol ether and dried in a vacuum desiccator over phosphorus pentaoxide.

(a) *Polymerisation in high vacuo.* β -Alanylchloride hydrochloride was introduced into the reaction vessel of a high vacuum still and heated in high vacuo at 135° until gas evolution ceased (about 2 h). The resulting yellowish polymer was hygroscopic and gave positive biuret and ninhydrin reactions. It was purified by dissolving in water and reprecipitating with absolute ethanol. End-group determinations of amino nitrogen on the one hand and chlorine on the other proved it to have an average degree of polymerisation of 10 units.

(b) *Polymerisation by means of trimethylamine.* The monomer was dissolved in dry dimethylformamide containing trimethylamine and kept in a glass-stoppered bottle, at room temperature, for five days. A precipitate consisting of trimethylamine hydrochloride and the polymer accumulated gradually. It was separated by filtration, dissolved in a small quantity of water, and the polymer reprecipitated by addition of absolute ethanol. The polymer preparation thus obtained had an average chain length of 14 units and behaved like the one prepared by thermal polymerisation.—

Poly-D,L- α -alanine hydrochloride, produced by thermal polycondensation of D,L-alanylchloride hydrochloride, was composed of 18 units on the average and by careful fractionation polymers up to 32 units, according

to endgroup determinations, were obtained. It was very soluble in water and gave a strongly red biuret reaction.

Poly-L-leucine hydrochloride, prepared by heating L-leucylchloride hydrochloride in high vacuo, was insoluble in water as well as in dilute acids and slightly soluble in alkali. A positive biuret reaction was, therefore, only obtained on prolonged standing. On boiling

with an aqueous solution of ninhydrin, merely the particles of the substance acquired a blue colour. This polymer had an average chain length of 20 units. By polymerisation with trimethylamine polymers with an average chain length of ten were produced.

Poly-(glycyl-D,L-leucine), obtained by heating glycyl-D,L-leucylchloride hydrochloride in high vacuo, was only slightly soluble in water, but readily soluble in dilute alkali and glacial acetic acid. It gave positive biuret and ninhydrin reactions and end-group determinations showed it to consist of four units of the dipeptide.

There seems to be no doubt that the average chain length of polymeric preparations described here is in no way due to inherent limitations of the method and that it will be possible to obtain products of higher chain length by varying the experimental conditions.

Details of the procedure and results will be given elsewhere¹.

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Zusammenfassung

Es wird gezeigt, dass die Chlorhydrate der Azychloride von Aminosäuren und Peptiden der Polykondensation unterworfen werden können und hierbei polymere Polypeptide liefern. Die beschriebene Methode ist auch in den Fällen anwendbar, in denen die Polymerisation, basiert auf den N-Carboxyanhydriden von Aminosäuren nach LEUCHS, nicht möglich ist, wie bei β -Aminosäuren oder bei Peptiden. Als Beispiele für die ausgeführte Polykondensation werden Poly- β -Alanin (mit einem durchschnittlichen Polymerisationsgrad $n = 14$), Poly-D,L-Alanin ($n = 32$), Poly-L-Leucin ($n = 20$) und Poly-(Glycyl-D,L-Leucin) ($n = 4$) angeführt.

¹ Cf. also thesis submitted to the Senate of the Hebrew University in partial fulfilment of the requirements for the Ph. D. degree by Y. LIWSCHITZ (November, 1952).