lauben die im Formelschema für (7) und (11) gegebenen Zuordnungen.

Der sterische Verlauf der COREY-Methylenierung von Δ^1-3-Keto-Steroiden der A/B-cis- und A/B-trans-Reihe ist also unabhängig von der angulären C_{10}-Methylgruppe.

Im Tierversuch wird an Kaninchen bei peroraler Applikation im Clauberg-Test die Aktivität des 19-Nor-17α-acetoxy-progesterons durch die Einführung der 1,2α-Methylengruppe stark erhöht und durch die 1,2β-Methylengruppe abgeschwächt.

Summary. The syntheses and structure-determinations of 1,22α- and 1,2β-methylene-19-nor-17α-acetoxy-progesterones described prove that there is no influence of the angular C_{10}-methylgroup on the steric course of the COUREY-methylenations of Δ^1-3-keto-steroids.

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Diketopiperazines from Fermentations: Metabolites, Artifacts, or Both

The frequent isolation in our laboratory of L-leucyl-L-proline anhydride (I) and, occasionally, other diketopiperazines from extracts of fermentations designed either for modification of steroids or preparation of antibiotics led us to consider the source of this material. In our hands, at this stage, the isolation of I was fortuitous in every instance and was usually due to similarity in solubility properties with the desired product.

Numerous authors have reported the isolation of I and other diketopiperazines from microbiological sources[1-12]. Studies in some laboratories[1,7,10,11] claim that I cannot be isolated from unfermented culture media, and these reports, combined with the reported isolation of I from silkworm pupae[13] and adrenal cortex extracts[14,15] made it appear that I is a common metabolite. Our frequent encounters with I initially lent some support to this view. However, when we examined several typical unfermented media, we were always able to isolate I by extraction with ethyl acetate and chromatography over alumina. The isolated crystalline product is identical in melting point, optical rotation, analytical data, IR- and nmr-spectra with authentic I and, further, gave leucine and proline upon hydrolysis. Minor amounts of other diketopiperazines were encountered occasionally.

Looking further into the matter, we have isolated 181 mg of I/kg of peptone, 227 mg/kg of corn steep liquor and a smaller amount from lactalbumin hydrolyzate. TAMURA et al.[16] have also found diketopiperazines in unfermented peptone and their data show about 1% of I and smaller amounts of other diketopiperazines. In fermentations wherein we encountered I, the above complex nitrogen sources were invariably present, and always in sufficient quantity to explain the presence of I in the extracts.

In view of these data, it is not surprising that relatively large quantities of diketopiperazines, especially I, are frequently isolated from fermentation mixtures. The occurrence of these substances may often reflect the previous history of the media constituents, particularly in regard to hydrolysis of protein and subsequent exposure of the products to heat[17].

As microbes are quite capable of protein hydrolysis it is also likely, indeed probable, that a certain proportion of the diketopiperazines present may arise during the fermentation to replace or supplement the quantity supplied in the medium. This may rationalize the conflicting claims on the subject. Nevertheless, we feel that the apparent production of simple diketopiperazines in fermentation processes should be viewed with some measure of restraint and invariably be accompanied by careful control experiments to eliminate the strong possibility of mistaking an artifact for a valid metabolite. This precaution is especially important as a number of complex or more highly elaborated diketopiperazine derivatives (e.g. sporidesmins-gliotoxins etc.) have been isolated from fermentations and their biological properties have made their biosynthetic origin a subject of considerable importance[12,18-21].

Zusammenfassung. Es wird gezeigt, dass Diketopiperazine, insbesondere L-Leucyl-L-prolin-anhydrid, eher aus dem Medium stammende Artefakte als echte mikrobielle Stoffwechselprodukte sind.

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