noch in Einzelheiten unerklärte Wirkung in der Biosynthese des Prothrombins haben; da auch hier die 2-Methylgruppe und die 2'-3'-Doppelbindung unerlässlich sind[75], kann man auch in dieser Wirkung des Vitamins K die intermediäre Bildung eines sehr reaktiven Methylenchinons annehmen. Dieses könnte natürlich ebenso gut statt mit Phosphat mit –SH-Gruppen von Proteinen oder anderen Substanzen reagieren. Die oben besprochenen Inhibitoren könnten z. B. ihre hemmende Wirkung durch Abfangen von –SH-Gruppen entfalten[110,111].

Summary. In the first part of this review the biogenesis of methyl-branched bacterial lipids through incorporation of the methyl group of methionin or of propionic acid is studied; it is shown that in the biogenesis of tuberculostearic acid, only two hydrogen atoms are transferred with the carbon of methionin. The same observation is made in the second part, concerning the origin of the 24-methyl group of ergosterol. Different mechanisms of C-methylation by methionin are discussed. It is also shown that the ethylidene group of fucosterol is formed by a double transfer of the methyl carbon of methionin.

In the third part the possible biological function of the 2-methyl group of vitamin K and the ubiquinones is studied; the acid catalysed isomerisation of these compounds to very reactive methylene-quinone-chromanes is discussed in detail.

[110] Siehe den Artikel von E. LARSSON [Kungl. Fysiografiska Sällskapets I Lund Förhandlingar *32*, 49 (1962)] betreffend die Reaktion von –SH-Gruppen mit Methylenverbindungen.

[111] Wir danken der Direktion der CIBA, Basel, und der Firma Firmenich & Cie., Genf, für ihr Interesse an unseren Arbeiten und Herrn Dr. O. ISLER (F. Hoffmann-La Roche, Basel) für die grosszügige Überlassung vieler Vitamin-K-Präparate.

Brèves communications – Kurze Mitteilungen – Brevi comunicazioni – Brief Reports

Synthesis of N-Protected Oxytoceines

In the last few years, new N-protecting groups (e.g. the *o*-nitrophenylsulphenyl group, etc., ZERVAS et al.[1]) as well as new S-protecting groups (e.g. acyl groups, etc., ZERVAS et al.[2]) have been introduced and applied in this laboratory for peptide synthesis. The removal of these protecting groups takes place under mild conditions to avoid undesired side reactions. We have applied this technique to synthesize some oxytocin-like peptides[2b–d] and the compounds I–V.

Bz Bz
Z-Cys-Tyr-Ile-Glu(NH_2)-Asp(NH_2)-Cys-Pro-Leu-Gly-NH_2
I

Z Bz
Z-Cys-Tyr-Ile-Glu(NH_2)-Asp(NH_2)-Cys-Pro-Leu-Gly-NH_2
II

Bz Bz
BOC-Cys-Tyr-Ile-Glu(NH_2)-Asp(NH_2)-Cys-Pro-Leu-Gly-NH_2
III

Bz Bz
NPS-Cys-Tyr-Ile-Glu(NH_2)-Asp(NH_2)-Cys-Pro-Leu-Gly-NH_2
IV

Z-Cys-Tyr-Ile-Glu(NH_2)-Asp(NH_2)-Cys-Pro-Leu-Gly-NH_2
V

$Z = C_6H_5CH_2OCO$ $BOC = (CH_3)_3COCO$
$Bz = C_6H_5CO$ $NPS = o\text{-}NO_2C_6H_4S$

By coupling *p*-nitrophenyl S-benzoyl-N-carbobenzoxy-L-cysteinate[3] with the tripeptide L-prolyl-L-leucylglycinamide[4], the protected tetrapeptide N-carbobenzoxy-S-benzoyl-L-cysteinyl-L-prolyl-L-leucylglycinamide was prepared (m.p. 160–161°, $[\alpha]_D$ –73°, c 2.5, DMF). When the carbobenzoxy group of this protected peptide was removed by means of HBr in acetic acid, the hydrobromide of the tetrapeptide was obtained. Coupling of the tetrapeptide with carbobenzoxy-L-asparagine by the mixed anhydride method (using pivaloyl chloride[5]) gave the protected pentapeptide, carbobenzoxy-L-asparaginyl-S-benzoyl-L-cysteinyl-L-prolyl-L-leucylglycinamide (m.p.

[1] L. ZERVAS, D. BOROVAS, and E. GAZIS, J. Am. chem. Soc. *85*, 3660 (1963).

[2] (a) L. ZERVAS and I. PHOTAKI, J. Am. chem. Soc. *84*, 3887 (1962). – (b) L. ZERVAS, I. PHOTAKI, and N. GHELIS, J. Am. chem. Soc. *85*, 1337 (1963). – (c) L. ZERVAS, I. PHOTAKI, A. COSMATOS, and N. GHELIS, *Peptides*, Proceedings of the Fifth European Peptide Symposium, Oxford (September 1962), (Ed. G. T. YOUNG, Pergamon Press, Oxford 1963), p. 27. – (d) A. COSMATOS, I. PHOTAKI, and L. ZERVAS, *Peptides*, Proceedings of the Sixth European Peptide Symposium, Athens (September 1963), (Ed. L. ZERVAS, Pergamon Press, Oxford, in press). – A. BERGER, J. NIGUCHI, and E. KATCHALSKI, J. Am. chem. Soc. *78*, 4483 (1956). – M. SOKOLOVSKY, M. WILCHEK, and A. PATCHORNIK, J. Am. chem. Soc. *86*, 1202 (1964).

[3] m.p. 130°, $[\alpha]_D$ –55°, c 2, DMF (unpublished work of this laboratory).

[4] R. A. BOISSONNAS, ST. GUTTMANN, P.-A. JAQUENOUD, and J.-P. WALLER, Helv. chim. Acta *38*, 1491 (1955). – M. ZAORAL and J. RUDINGER, Coll. Czech. Chem. Commun. *20*, 1183 (1955).

[5] M. ZAORAL, Coll. Czech. Chem. Commun. *27*, 1273 (1962).

214–215°, $[\alpha]_D$ −71.5°, c 2.5, DMF). The N-decarbobenzoxylation of the latter by means of HBr in acetic acid followed by step-by-step peptide synthesis, using each time the appropriate carbobenzoxy amino acid *p*-nitrophenyl ester[6], afforded the fully protected nonapeptide I (m.p. 227–229°, $[\alpha]_D$ −64.5°, c 1, DMF). By a similar procedure, other fully protected nonapeptides[7], having the same sequence of amino acids[8], have been prepared, e.g. II (m.p. 224–226°, $[\alpha]_D$ −60.6°, c 1, DMF), III (m.p. 217–220°, $[\alpha]_D$ −55.2°, c 1, DMF), and IV (m.p. 226–229°, $[\alpha]_D$ −56.6°, c 1, DMF). Removal of the S-protecting acyl groups from the protected nonapeptides I and II by methanolysis in the presence of sodium methoxide gave the N-carbobenzoxy-nonapeptide V with free –SH groups (m.p. 234–235°, $[\alpha]_D$ −46.2°, c 1, DMF). The compound V may be called N-carbobenzoxy-oxytoceine according to the nomenclature proposed by du Vigneaud. Using as starting materials III and IV, the N-t-butyloxycarbonyl- and the N-*o*-nitrophenylsulphenyl-oxytoceines have been prepared in the same manner.

The details of the synthesis of all the above compounds and their transformation to oxytocin will be described in a forthcoming publication[9].

Zusammenfassung. Es wird die Synthese von N-substituierten Oxytoceinen beschrieben. In einem Fall wurde die Synthese durch Benutzung des S-Benzoyl- und S-Carbobenzoxy-L-cysteins ermöglicht.

IPHIGENIA PHOTAKI

Laboratory of Organic Chemistry, University of Athens (Greece), May 11, 1964.

[6] M. BODANSZKY and V. DU VIGNEAUD, J. Am. chem. Soc. *81*, 5688 (1959).

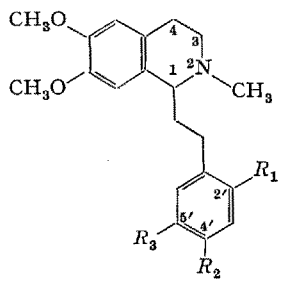
[7] Dicyclohexylammonium salt of N-t-butyloxycarbonyl-S-benzoyl-L-cysteine (m.p. 151–153°, $[\alpha]_D$ +18°, c 1, DMF), and *p*-nitrophenyl-S-benzoyl-N-*o*-nitrophenylsulfenyl-L-cysteinate (m.p. 101–102°. $[\alpha]_D$ −51.5°, c 2, DMF) were used (unpublished work of this laboratory) for the last step of the synthesis of nonapeptides III and IV, respectively.

[8] For the abbreviations used to denote amino acid residues see: Report of the Committee on Nomenclature, *Peptides*, Proceedings of the Fifth European Peptide Symposium, Oxford (September 1962) (Ed. G. T. YOUNG, Pergamon Press, Oxford 1963), p. 261.

[9] This investigation was supported by the Royal Hellenic Research Foundation, to which I am greatly indebted. I also thank Dr. H. MANTZOS for the microanalyses and Mr. V. BARDAKOS for helpful technical assistance.

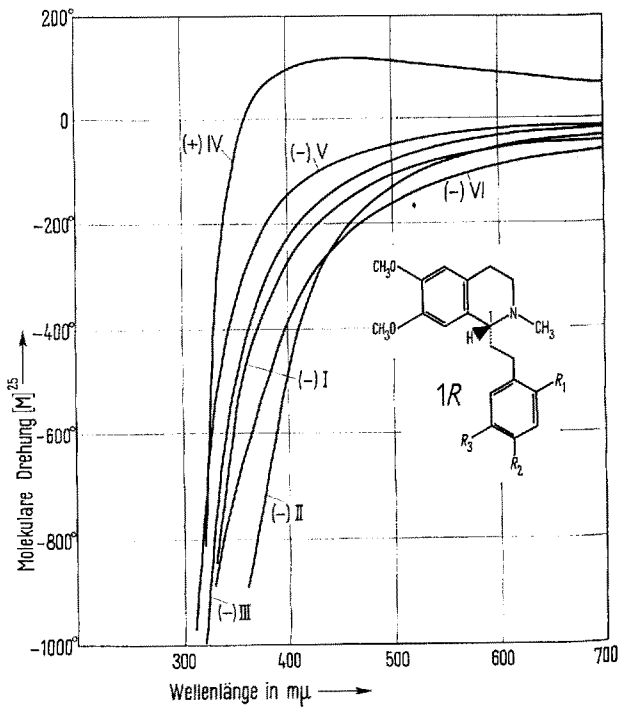
Konfiguration und pharmakologische Aktivität bei 1-phenäthylsubstituierten 1,2,3,4-Tetrahydroisochinolinen

Verschiedene im Phenylrest der Phenäthylseitenkette substituierte 1-Phenäthyl-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisochinolinderivate zeichnen sich durch pharmakologische Aktivität aus. Als Analgetika beanspruchen die 4′-Chlor-(I)[1–3] und die 4′-Nitroverbindung (II)[4], als Antitussiva die 3′,4′-Dichlor-(III)[1] und die 2′,4′,5′-Trichlorverbindung (IV) besonderes Interesse. Zur Abklärung der Zusammenhänge zwischen Konfiguration und Wirkung wurden diese vier Racemate in ihre optischen Antipoden gespalten. Die pharmakologische Auswertung ergab, dass praktisch die gesamte analgetische Aktivität[5] jeweils nur einem Antipoden zukommt[6]. Der gleiche Antipode zeigt auch hustenlindernde Eigenschaften[7], während die analgetisch inaktiven Enantiomeren höchstens schwach antitussiv wirken[8]. Die analgetische Aktivität nimmt in der Reihe IV < III < I < II zu, die antitussive dagegen in der Reihe I < III < IV < II.



I $R_1 = R_3 = H$, $R_2 = Cl$
II $R_1 = R_3 = H$, $R_2 = NO_2$
III $R_1 = H$, $R_2 = R_3 = Cl$
IV $R_1 = R_2 = R_3 = Cl$
V $R_1 = R_2 = R_3 = H$
VI $R_1 = R_3 = H$, $R_2 = NH_2$

Bei den Verbindungen I, II und III war jeweils der im Na-Licht negativ drehende[9] Antipode der analgetisch und antitussiv wirksame Bestandteil; im Falle von IV erwies sich hingegen der positiv drehende Antipode als die aktive Komponente. Es war deshalb von Interesse, alle diese optisch aktiven Substanzen durch chemische Reaktionen



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