

ppm³ present in the starting material (indicative of the presence of a vinyl proton) and exhibited a singlet at 3.02 ppm (NMe) which integrated for 3 protons. Cyclizations of this nature are known to occur in the imidazole series, notably with histidine⁴; however, the recorded instances wherein cyclization has taken place are under experimental conditions (refluxing HCl) which are much more severe than those employed in the present study. This type of reaction may play a significant role in biological systems, however, as shown by the isolation of spinacine (4, 5, 6, 7-tetrahydroimidazo[4, 5-c]pyridine-5-carboxylic acid) from the shark (*Acanthias vulgaris*)⁵ and the crab (*Crango vulgaris*)⁶ as well as the very recent announcement of the isolation of Spinaceamine (4, 5, 6, 7-tetrahydroimidazo[4, 5, c]pyridine and 6-methylspinaceamine⁷ from *Leptodactylus pentadactylus labyrinthicus*. These compounds have been postulated as arising from the enzymatic cyclization, methylation and decarboxylation of histidine *in vivo*.

All of the compounds reported have proved to be pharmacologically inactive in the course of preliminary tests.

They also appear to be ineffective as CNS agents as judged by their inability to influence locomotor activity, and their lack of potentiation or antagonism of the effects of reserpine in drug pretreated or reserpinized mice⁸.

Zusammenfassung. Die 2-Imidazolon-Analoge der Histamine und 6-Methylspinaceamin wurden synthetisiert. Die neuen Imidazolonstoffe scheinen pharmakologisch unwirksam.

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³ NMR spectra were recorded on a Varian A-60 spectrometer. Chemical shifts are recorded as parts per million relative to tetramethyl silane used as an external standard. D₂O was used as solvent for the amine salts.

⁴ For a comprehensive review see E. S. SCHIPPER and A. R. DAY, *Imidazoles and Condensed Imidazoles, Heterocyclic Compounds*, vol. V (Ed. R. C. Elderfield, John Wiley and Sons, New York 1957).

⁵ D. ACKERMANN and M. MOHR, *Z. Biol.* **98**, 37 (1937).

⁶ D. ACKERMANN, *Z. physiol. Chem.* **328**, 275 (1962).

⁷ V. ERSFAMER, T. VITALI, M. ROSEGHINI, and J. M. CEI, *Exper.* **19**, 346 (1963).

⁸ The biological results were obtained in the Biological Sciences Section of these laboratories. We are grateful to Dr. B. BALTES and his staff for making these data available.

Total Synthesis of the Antibiotic Polymyxin B₁

In the course of our work¹ on polymyxin B₁ we were able to synthesize the four compounds corresponding to the structures proposed by HAUSMANN and CRAIG² for this antibiotic, which according to BIZERTE and DAUTREVAUX³ should have a D-Dab residue in position 1' (Figure 1) of the side chain. Although two of them (7 α and 7 γ) proved to be highly active polymyxin-like antibacterial agents *in vitro* and *in vivo*⁴, none was identical with the natural antibiotic^{1d}. Recently SUZUKI et al.⁵, in contrast to the French workers, demonstrated that the natural product does not contain D-Dab. Furthermore, they were able to locate the side chain in the N α -position

- ¹ (a) K. VOGLER, R. O. STUDER, W. LERGIER, and P. LANZ, *Helv. chim. Acta* **43**, 1751 (1960). – (b) R. O. STUDER, K. VOGLER, and W. LERGIER, *Helv. chim. Acta* **44**, 131 (1961). – (c) R. O. STUDER, W. LERGIER, and K. VOGLER, *Helv. chim. Acta* **46**, 612 (1963). – (d) K. VOGLER, R. O. STUDER, P. LANZ, W. LERGIER, E. BÖHNI, and B. FUST, *Helv. chim. Acta* **46**, 2823 (1963).
- ² W. HAUSMANN and L. C. CRAIG, *J. Am. chem. Soc.* **76**, 4892 (1954). – W. HAUSMANN, *J. Am. chem. Soc.* **78**, 3663 (1956).
- ³ G. BIZERTE and M. DAUTREVAUX, *Bull. Soc. Chim. biol.* **39**, 795 (1957).
- ⁴ K. VOGLER, R. O. STUDER, P. LANZ, W. LERGIER, and E. BÖHNI, *Exper.* **17**, 223 (1961).
- ⁵ T. SUZUKI, K. HAYASHI, K. FUJIKAWA, and K. TSUKAMOTO, *J. Biochem. (Japan)* **54**, 555 (1963).
- ⁶ G. T. YOUNG, *Peptides*, Proceedings of the Fifth European Symposium, Oxford (September 1962), p. 261 (Pergamon Press, 1962).

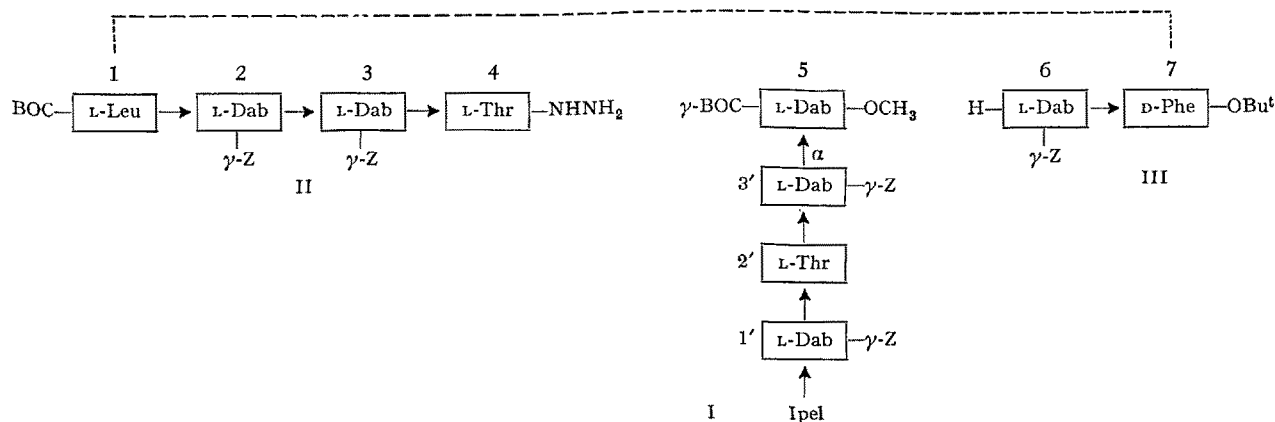


Fig. 1. Reaction scheme. Abbreviations according to G. T. YOUNG⁶: Dab = α,γ -diaminobutyric acid, BOC = tert. butyloxycarbonyl, Z = benzyloxycarbonyl, OBu^t = tert. butyl-ester, IpeI = isopelargonic acid ((+)-6-methyloctanoic acid) \Rightarrow C- to N-bond in -CONH-.

of the branching Dab residue, a possibility already envisaged by HAUSMANN and CRAIG² and also favoured by us on biogenetic considerations⁷. We have now synthesized the substance possessing this revised structure (7 α , all L-Dab, Figure 2 [IV]) according to the following scheme.

Removal of the tert. butyloxycarbonyl group in I by trifluoroacetic acid and coupling with the azide of II led to the protected octapeptide. This was transformed into

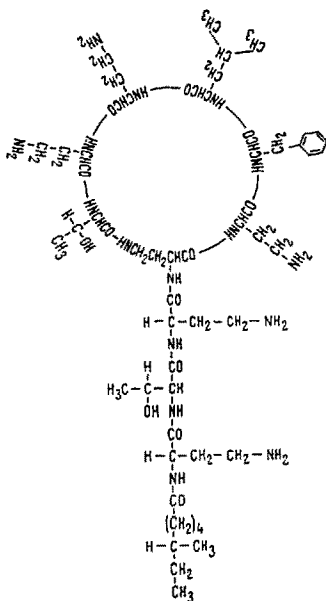


Fig. 2. Polymyxin B₁ (IV).

the corresponding hydrazide and condensed with III by means of the azide procedure. After removal of the C- and N-protecting groups the decapeptide was submitted to cyclization and was then reduced and purified in the way previously described¹. The end product (Figure 2 [IV]) was isolated as pentahydrochloride and carefully compared with the pentahydrochloride of natural polymyxin B₁.

Both conformed in thin-layer chromatography, amino acid content, $[\alpha]_D^{25}$ and optical rotatory dispersion of the nickel-complex⁸ especially sensitive to isomeric structures¹⁴. The microbiological activity against *Klebsiella pneumoniae* ATCC 100 131 agreed with that of the natural antibiotic¹⁴.

The synthetic product could be crystallized as the pentaphosphate⁹.

Full details will be given in Helvetica chimica Acta.

Zusammenfassung. Es wird über die Synthese des cyclo-Decapeptides 7 α , in welchem alle Dab-Reste die L-Konfiguration aufweisen, berichtet. Dieses erwies sich als identisch mit natürlichem Polymyxin B₁ (Figur 2).

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⁷ R. O. STUDER and K. VÖGLER, *Helv. chim. Acta* **45**, 819 (1962).

⁸ H. BRINTZINGER, *Helv. chim. Acta* **44**, 744 (1961).

⁹ We are very much indebted to Dr. S. WILKINSON, Wellcome Research Laboratories, Langley Court, Beckenham, Kent (England), for informing us of the method of crystallizing the natural antibiotic.

Psychotomimetic Amphetamines: Methoxy 3,4-Dialkoxyamphetamines¹

Both 3,4,5-trimethoxyamphetamine (I, TMA)² and 3-methoxy-4,5-methylenedioxyamphetamine (II, MMDA)³ have exhibited psychotropic potencies greater than that of mescaline. Both the lengthening of the aliphatic chain of I⁴ and the enlargement of the heterocyclic ring in II⁵ have resulted in a decreased human effectiveness. On the contrary, it has been found that the repositioning of the *meta*-methoxy group, in either of these compounds, to an available *ortho*-location, can result in an appreciable increase in potency. The syntheses and preliminary pharmacological evaluation of these positional isomers are described.

Two methods of synthesis were employed. With the two bases possessing the 2,4,5-alkoxy orientation, the appropriately substituted propenylbenzene was oxidized with tetranitromethane to the corresponding β -nitropropene. LiAlH₄ reduction of these nitrostyrenes to the amphetamines was performed as previously described⁶. The propene required for III, asarone, was obtained by the fractional distillation of oil of Parsley. The necessary precursor of IV, 2-methoxy-4,5-methylenedioxy propenyl-

benzene was obtained by conventional steps from sesamol. The Claisen rearrangement of allyl sesamyl ether occurred predominantly to the unhindered side; O-methylation and base-catalyzed isomerization yielded the requisite propenylbenzene.

The vicinal analogs V and VI were both prepared from the corresponding benzaldehydes by condensation with nitroethane followed by reduction of the resulting nitrostyrene as described above. The properties of these products, together with those of the 3,4,5-analogs for comparison, are listed in the Table.

Behavioral and toxicological studies were performed on male Swiss white mice, and these results are also recorded in the Table. All four isomers were found to be somewhat

¹ Psychotomimetic Amphetamines, part II; for part I see ².

² D. I. PERETZ, J. R. SMYTHIES, and W. C. GIBSON, *J. mental Sci.* **101**, 317 (1955). – A. T. SHULGIN, S. BUNNELL, and T. SARGENT III, *Nature* **189**, 1011 (1961).

³ A. T. SHULGIN, *Nature*, **201**, 1120 (1964). (To be considered paper I of this series.)

⁴ A. T. SHULGIN, *Exper.* **19**, 127 (1963).

⁵ F. A. RAMIREZ and A. BURGER, *J. Am. chem. Soc.* **72**, 2781 (1950).