especially characteristic[5] of the uleine skeleton. The molecular weights and hence empirical formulae were obtained by mass spectral measurements, where necessary (e.g. V and VI) by the direct inlet procedure[9].

Des-N-methyluleine (II) (m.p. 143–144°, $[\alpha]_D$ −20° (EtOH), mol. weight 252 = $C_{17}H_{20}N_2$) upon refluxing with methyl iodide in acetone-benzene for 30 min. provided uleine (I) methiodide (m.p. 196–198°), identified with an authentic sample, while treatment of the evaporated filtrate with alkali and crystallization from methanol gave authentic (+)-uleine (I).

The ketone dasycarpidone (III) was obtained in an amorphous state ($[\alpha]_D$ +65° ($CHCl_3$), $\lambda_{max}^{CHCl_3}$ 6.10 μ, λ_{max}^{EtOH} 237 mμ (log ε 4.15) and 316 mμ (log ε 4.29)[10], mol. weight 268 = $C_{17}H_{20}N_2O$) and its structure confirmed by careful low-temperature ozonolysis of uleine (I), which afforded III in ca. 15% yield. The lower homolog, des-N-methyldasycarpidone (IV) (m.p. 208–210°, $\lambda_{max}^{CHCl_3}$ 6.08 μ, same ultraviolet spectrum as III, mol. weight 254 = $C_{16}H_{18}N_2O$) was converted into dasycarpidone (III) by treatment with methyl iodide in the same manner as described above for the synthesis of uleine (I) from its des-N-methyl analog II.

The structure of dasycarpidol (V) (m.p. 118–122°, $[\alpha]_D$ −54° (EtOH), λ_{max}^{EtOH} 220 mμ (log ε 4.54), 282 mμ (log ε 3.89) and 290 mμ (log ε 3.81), no infrared carbonyl band, mol. weight 270 = $C_{17}H_{22}N_2O$) was indicated by the NMR spectrum, which contained all of the relevant signals[3,5] of uleine (I), except for the absence of the methylene proton signals and the presence of a one-proton doublet at 5.1 p.p.m. (J = 6 cps.) due to CHOH. Full confirmation was provided by oxidation with chromium trioxide in pyridine which afforded dasycarpidone (III).

The constitution of the amorphous 1,13-dihydro-13-hydroxyuleine (VI) ($[\alpha]_D$ −96°, λ_{max}^{EtOH} 221 mμ (log ε 4.56), 282 mμ (log ε 3.91) and 289 mμ (log ε 3.87), mol. weight 284 = $C_{18}H_{24}N_2O$) followed from the NMR spectrum, which was completely consistent with expression VI, and especially from its partial synthesis in 79% yield by hydroboration of uleine (I). The high yield and stereospecific course of the hydroboration reaction constitutes good evidence for the equatorial orientation of the hydroxymethyl substituent in VI.

The characterization of additional alkaloids from *Aspidosperma dasycarpon* A. DC. as well as the details and biogenetic implications of the presently outlined results will be reported in a full paper[11].

Zusammenfassung. Aus der Rinde des brasilianischen Baumes *Aspidosperma dasycarpon* A. DC. wurden fünf neue Alkaloide (II–VI) isoliert, die das selten vorkommende Uleinskelett besitzen. Die Strukturen wurden durch chemische Korrelation mit Ulein (I) sichergestellt.

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[9] J. F. LYNCH, J. M. WILSON, H. BUDZIKIEWICZ, and C. DJERASSI, Exper. *19*, 211 (1963).

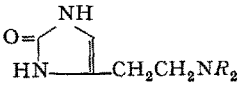
[10] For relevant infrared and ultraviolet data of 2-acylindoles, see J. A. BALLANTINE, C. B. BARRETT, R. J. S. BEER, B. G. BOGGIANO, S. EARDLEY, B. E. JENNINGS, and A. ROBERTSON, J. chem. Soc. *1957*, 2227.

[11] Financial support from the Rockefeller Foundation and the National Institutes of Health of the U.S. Public Health Service (grant No. GM 11309) is gratefully acknowledged, as are Fulbright travel grants to two of us (J.A.J. and M.O.).

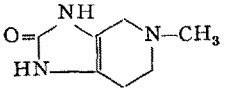
2-Imidazolone Analogues of Histamine

The problem of investigating the physiological activity of histamine is complicated by its spectacular peripheral effects which tend to mask any central function of the amine. In cooperation with a study designed mainly to elucidate the central effects of histamine and its derivatives[1] we sought to prepare analogues of histamine lacking in peripheral effects and which might be considered either as antimetabolites of histamine capable of crossing the blood-brain barrier or as hypothetical metabolites of this compound. It was considered that analogues of histamine which could be thought of as arising from a biological oxidative mechanism would be worthy of study.

4-β-aminoethyl-2-imidazolone hydrochloride, (I) m.p. 255° (prev. dec.) was obtained crystalline from ethanol by heating 1,4-diaminobutanone-2-dihydrochloride[2] with potassium cyanate in water as a thick syrup. The reaction product obtained in this way was contaminated with inorganic salts which were difficult to remove due to the amphoteric nature of the compound. Separation of I from inorganic material could be effected by forming the benzoyl derivative, m.p. 270–272° (MeOH) followed by acid hydrolysis (conc. HCl) to afford the imidazolone hydrochloride or preferably by conversion to the carbobenzyloxy derivative, m.p. 242–244° (EtOH) followed by hydrogenolysis.



I R = H; II R = Me



III

In an attempt to form 4-β-N,N-dimethylaminoethyl-2-imidazolone (II) by reductive alkylation of (I) with methanolic formaldehyde and hydrogen in the presence of a palladium-carbon catalyst, 5-methyl-4,5,6,7-tetrahydroimidazo (4,5,c)pyridin-2-one-hydrochloride (III) vac. m.p. 175° (EtOH), was obtained. The cyclic structure was demonstrated by the nuclear magnetic resonance spectrum which lacked the characteristic signal at 6.33

[1] L. GOLDSTEIN, C. C. PFEIFFER, and C. MUNOZ, Fed. Proc. *22*, 424 (1963).

[2] M. M. FRASER and R. A. RAPHAEL, J. chem. Soc. *1952*, 226.

ppm[3] 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 histidine[4]; 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-methylspinaceamine[7] 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 mice[8].

Zusammenfassung. Die 2-Imidazolon-Analoge der Histamine und 6-Methylspinaceamin wurden synthesiert. 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. D_2O 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. *93*, 37 (1937).

[6] D. Ackermann, Z. physiol. Chem. *328*, 275 (1962).

[7] V. Erspamer, 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 B_1

In the course of our work[1] on polymyxin B_1 we were able to synthesize the four compounds corresponding to the structures proposed by Hausmann and Craig[2] for this antibiotic, which according to Bizerte and Dautrevaux[3] should have a D-Dab residue in position 1′ (Figure 1) of the side chain. Although two of them (7α and 7γ) 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. Fujikava, 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).

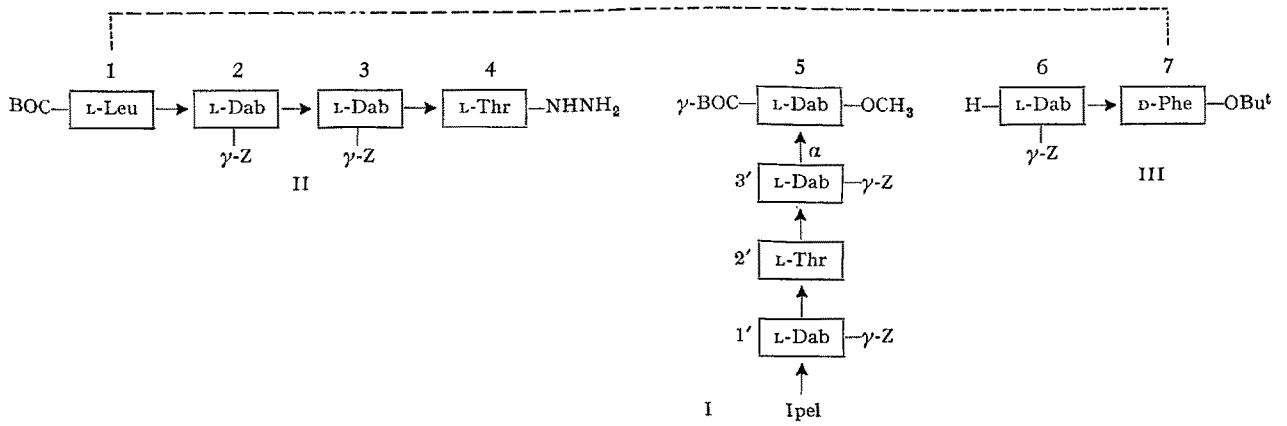

Fig. 1. Reaction scheme. Abbreviations according to G. T. Young[6]: Dab = α,γ-diaminobutyric acid, BOC = tert. butyloxycarbonyl, Z = benzyloxycarbonyl, OBu^t = tert. butyl-ester, Ipel = isopelargonic acid ((+)-6-methyloctanoic acid) → = C- to N-bond in –CONH–.