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STRUCTURE AND SYNTHESIS OF LEUCETTIDINE

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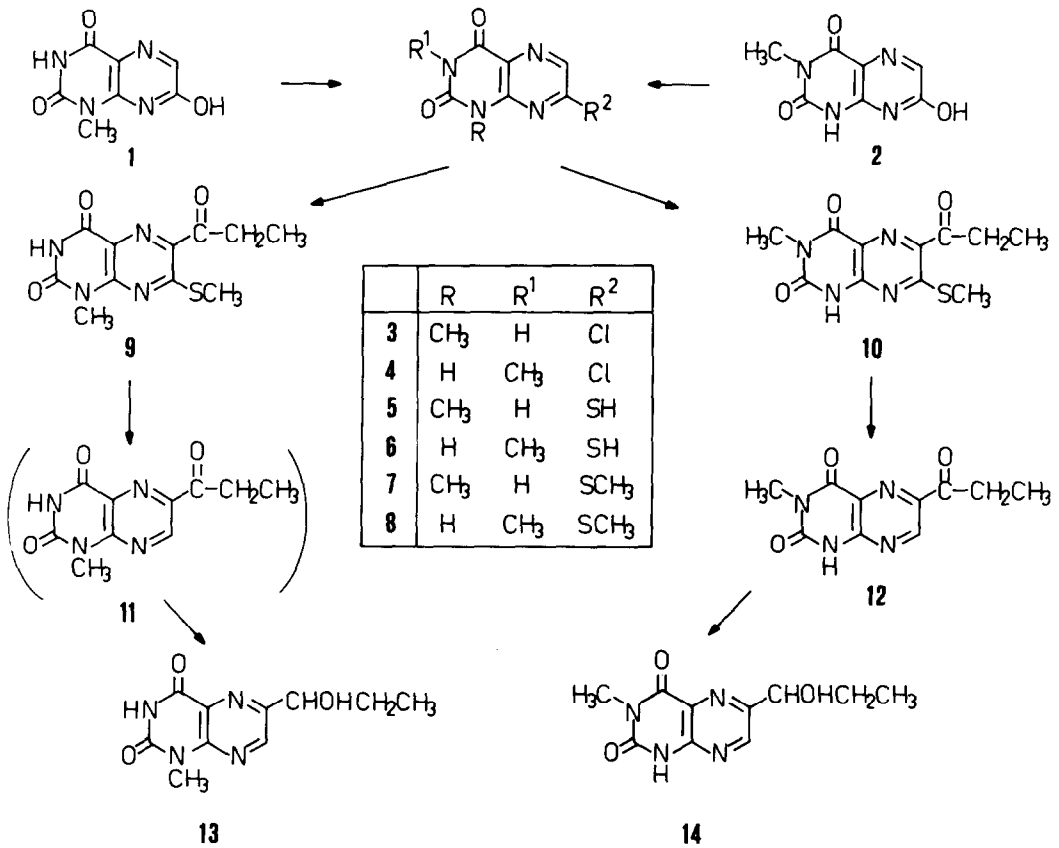
Summary: The structure of leucettidine (13) has been revised according to its UV-data to 6-(1-hydroxypropyl)-1-methyllumazine and has been proven by an unambiguous synthesis of this natural product.

In 1981 Cardellina and Meinwald [1] isolated from the calcareous sponge Leucetta microraphis a novel pteridine derivative and called it leucettidine. Its structure was deduced by analysis of spectral data including high resolution mass spectrometry to determine the empirical formula $C_{10}H_{12}N_4O_3$, NMR-spectra to elucidate the nature of the substituents and IR- and UV-spectra to find the pteridinedione nucleus. Further examination of, and correlation of the data of leucettidine with, the pteridine literature has led to propose the 6-(1-hydroxypropyl-3-methylpteridine-2,4-(1H)-dione structure. Unfortunately placement of the methyl group on the nitrogen at position 3 has been derived only from comparisons of chemical shift data of various model substances, whereas the more precise structural distinctions on the basis of the UV-spectral properties has been completely overlooked. The reported UV-data of the natural product indicate very clearly that the methyl group cannot be located at N-3 but at N-1. Anion formation of an N-1 substituted lumazine is always associated with a small bathochromic shift of the long wavelength absorption band, whereas substitution at N-3 effects a much stronger red shift due to a more pronounced resonance stabilization on the monoanion [2].

In order to prove our new structural assignment [3] of leucettidine we syn-

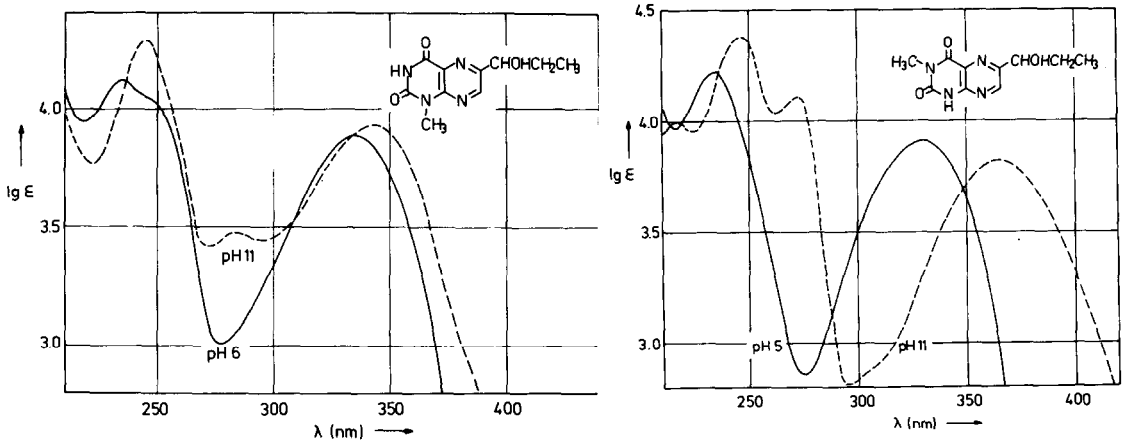


	R	R^1	R^2
3	CH_3	H	Cl
4	H	CH_3	Cl
5	CH_3	H	SH
6	H	CH_3	SH
7	CH_3	H	SCH_3
8	H	CH_3	SCH_3

thesized the two isomeric 6-(1-hydroxypropyl)-1-(13) und 6-(1-hydroxypropyl)-3-methyllumazines (14) by unambiguous syntheses. Starting from 1-(1) and 3-methyl-7-hydroxylumazine (2) [4] respectively a selective chlorination to the corresponding 7-chloro-1-(3) and 7-chloro-3-methyllumazine (4) was achieved by $POCl_3$/KCl at 80-90°C in 75 and 85 % yield respectively. Subsequent treatment with sodium hydrogensulfide led to the 7-mercapto derivatives 5 and 6, the methylations of which with methyl iodide in dilute sodium hydrogencarbonate afforded 1-(7) and 3-methyl-7-methylmercaptolumazine (8) in good yields. The introduction of the three carbon side chain in position 6 was then performed by a Minisci reaction [5,6] taking into account that the π-deficient pyrazine moiety of the lumazine nucleus can be acylated by a radical nucleophilic substitution mechanism [3]. Reaction of 7 and 8 with propionaldehyde/-Fe^{++}/tert-butylhydroperoxide in aqueous acetic acid yielded 1-methyl-(9) and 3-methyl-7-methylmercapto-6-propionyllumazine (10) respectively in 78 %

yield each. During desulfurization experiments to remove the methylmercapto group by Raney-nickel treatment the known difficulties with thiopteridines [7] became evident due to the fact that product formation is strongly dependent on the type of Raney-nickel, its activity as well as the polarity of the solvent. An improvement could be achieved by use of aluminum-copper alloy in alkaline medium, which converted 9 obviously via 11 directly into 6-(1-hydroxypropyl)-1-methyllumazine (13), whereas 10 reacted under the same conditions with clean desulfurization to 3-methyl-6-propionyllumazine (12). Sodium borohydride reduction of 12 yielded then 6-(1-hydroxypropyl)-3-methyllumazine (14).

Comparisons of the UV- and NMR-data of leucettidine with those of 13 and 14 prove undoubtedly that 13 is the correct structure of the natural product (Tab.). The relatively low extinction coefficients of the isolated material indicate that so far no analytically pure natural sample has been prepared consistent with the also missing elementary analysis [1], which reveals 0,5 mol of crystal water.



UV-Absorption spectra of the neutral and monoanion form of leucettidine (13) and 6-(1-hydroxypropyl)-3-methyl-lumazine (14).

Physical Data of 6-(1-Hydroxypropyl)-lumazines

Compound	UV-Absorption Spectra λ_{max} (nm)	UV-Absorption Spectra lg ε	pH	NMR-Spectra in $CDCl_3$ 7-H (1H)	CHOH (1)	$N-CH_3$ (3H)	CH_2 (2H)	CH_3 (3H)
Natural leucettidine [1]	238 334 246 292 344	3.93 3.62 4.15 3.48 3.66	MeOH MeOH+ NaOH	8.76 s	4.84 dd	3.63 s	1.85 m	0.97 t
6-(1-Hydroxy-propyl)-1-methyl-lumazine (13)	237 [248] 334 234 [248] 335 245 285 343	4.12 [4.08] 3.85 4.14 [4.08] 3.88 4.29 3.44 3.92	MeOH 5.0 13.0	8.78 s	4.91 dd	3.66 s	1.86 m	0.99 t
6-(1-Hydroxy-propyl)-3-methyl-lumazine (14)	235 331 234 330 247 273 366	4.21 3.86 4.22 3.92 4.28 4.12 3.82	MeOH 5.0 13.0	8.70 s	4.88 dd	3.49 s	1.86 m	0.98 t

[ ] = Shoulder; s = singlet; dd = double dublet; t = triplet; m = multiplet.

R E F E R E N C E S

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