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WHAT IS THE STRUCTURE OF BARETTIN ? NOVEL SYNTHESIS OF UNSATURATED DIKETOPIPERAZINES[1].

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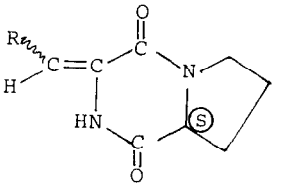
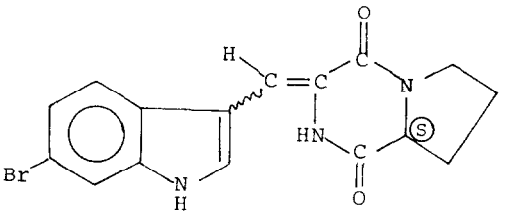
Abstract: Several unsaturated diketopiperazines 1a-1f as well as a compound with the proposed structure 2 of barettin were synthesized by a new method via esters of diketopiperazine phosphonic acid. The proposed structure of barettin was found to be incorrect.



1a-f



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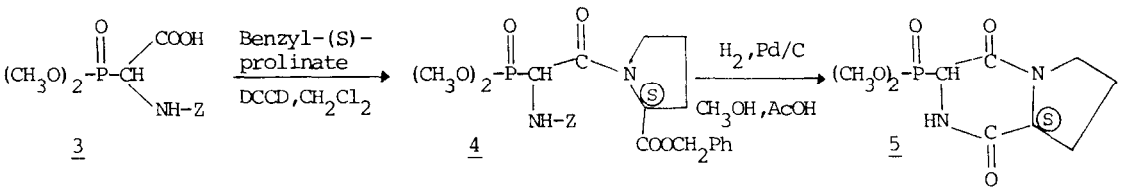
A new biologically active indol compound named barettin was isolated from the methanol extract of the cold water sponge Geodia baretti by Bohlin and Lidgren[2]. The authors determined its structure to be a mixed diketopiperazine of dehydro-6-bromotryptophane and proline. It was not clear whether the double bond in barettin had the E or Z configuration. We synthesized E-2 and Z-2 as well as the dehydrodiketopiperazines 1a-1f in a new straightforward way:

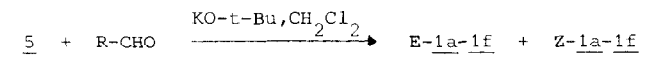
Z-phosphonoglycine[3] 3 a valuable synthon for the synthesis of unsaturated amino acid derivatives was condensed with benzyl-(S)-prolinate to give dipeptide 4, whose hydrogenation in the presence of acetic acid easily formed the methylester of diketopiperazine phosphonic acid 5.



3 4 5

Procedure: Z-phosphonoglycine 3 was treated with benzyl-(S)-prolinate (1 equiv.) and DCCD (1 equiv.) in CH_2Cl_2. The resulting Z-phosphonodipeptide 4 (yield 92 %) was hydrogenated (Pd/C) in CH_3OH in the presence of a catalytic amount of acetic acid to yield diketopiperazine 5 (95 %).

The condensation of 5 with various aldehydes gave dehydrodiketopiperazines 1a-1f as E/Z mixtures which could be separated by chromatography on silica gel (E < 30 %).



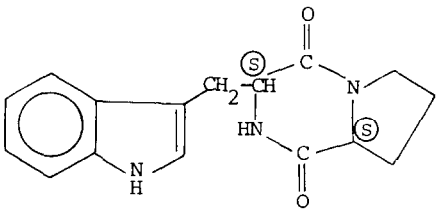
Procedure: At -70°C phosphonodiketopiperazine 5 (1 equiv.) was injected to a stirred suspension of potassium t-butylate (1 equiv) in CH_2Cl_2 under argon. After 10 min an aldehyde (1 equiv.) was added and the reaction mixture allowed to come to room temperature. The organic layer was washed with water, dried and evaporated. Silica gel chromatography with ethyl acetate/petroleum ether 7/3 gave the separated E- and Z-compounds 1a-1f in yields of > 80 %.

1	R	E/Z	mp (°C)	$[\alpha]_D^{20}$	C	a,b	R_f ethylacetate
a	CH_3-	E	90 dec.	-79.5	1.16	a	0.38
		Z	153-155	+31.9	0.37	a	0.29
b	CH_3 CH_3 CH-	E	169	-83.1	0.31	b	0.53
		Z	160-164	+54.3	0.53	b	0.49
c	CH_3O-	E*	-	-	-		0.42
		Z	185-186	+259	0.67	a	0.33
d		E	188	+281	0.46	b	0.51
		Z	199-201	+125	0.61	b	0.38
e	N Boc	E	263 dec.	+156	0.24	a	0.68
		Z	177-178	+79.8	0.46	a	0.56
f	Br N Boc	E	290 dec.	+134	0.21	a	0.72
		Z	amorphe	+39.1	0.16	a	0.60

* The yield of E was < 2 %. $[\alpha]_D^{20}$ values were measured in a: dichloromethane and b: methanol

Condensation of 5 with N-Boc-6-bromoindol-3-carbaldehyde gave the dehydrodiketopiperazines 1f in a E/Z ratio of 3/7. The separated compounds E-1f and Z-1f were treated with trifluoro acetic acid to give E-2 and Z-2. In contrast to barettin both isomers were insoluble in methanol. The analytical data[4] were completely different from the data reported for barettin.

Dramatic differences between the NMR spectra of synthesized E-2 and Z-2 and that of barettin were observed (see NMR-table). Signals for the NH-protons and for all proline protons come at lower field in E-2 and Z-2 than in barettin. In contrast to barettin only one proline β- or γ-proton is shifted to lower field. We suggest that this is due to its interaction with the C=O anisotropic field in the condensed bicyclic compound. This property was observed in the spectra of all synthesized products 1a-1f. In MS we found the molpeak m/z 359.027 with the relative intensity of 100. For barettin the authors found m/z with the relative intensity of 4. The fragmentation pattern differs from the reported one[4]. For a further proof we hydrogenated Z-2 in the presence of Pd/C - by simultaneously hydrogenolytic elimination of Br - and obtained the known[5] saturated (S,S)-diketopiperazine 6. An analogous diastereoselective H_2-addition was observed by us in the hydrogenation of the corresponding benzylidene compound[6].



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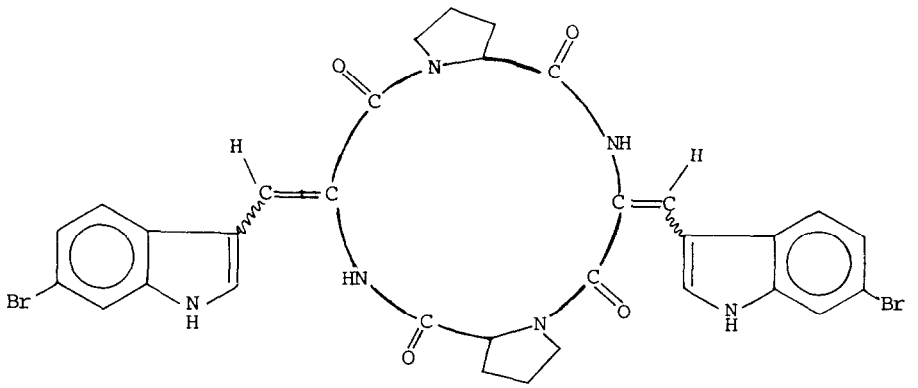
From our experience in the synthesis of cyclic peptides containing proline and of dehydroamino acids we suggest that the structure of barettin could be the cyclic tetramer 7.



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^{1}H-NMR Data [δ]ppm

	E/Z	H-N	HC=	proline protons			
				(1H)	(2H)	(1H)	(3H)
1a	E	9.52	5.70	4.17	3.67	2.38	1.95
	Z	8.88	6.18	4.22	3.70	2.43	2.00
b	E	8.95	5.40	4.20	3.70	2.43	2.00
	Z	9.15	5.95	4.20	3.68	2.42	2.00
c	E	9.40	6.37	4.22	3.65	2.40	2.02
	Z	7.90	6.96	4.32	3.75	2.45	2.05
d	E	10.70	6.45	4.25	3.70	2.45	2.02
	Z	8.95	6.73	4.32	3.72	2.45	2.05
e	E	8.33	6.48	4.26	3.72	2.45	2.10
	Z	7.90	7.08	4.32	3.72	2.45	2.03
f	E	8.95	6.50	4.30	3.75	2.45	2.05
	Z	8.40	7.05	4.32	3.70	2.45	2.05
5	-	8.15	-	4.45	3.75	2.40	2.05
2	E	11.56	6.69	4.28	3.58 3.44	2.21	1.90
	Z	11.73	6.94	4.35	3.50	2.22	1.88
Barettin		8.43	6.97	4.05	3.16	1.75 (2H)	1.55 (2H)

References and notes

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4 E-2: ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 11.56 (s br,1H), 10.2 (s br,1H), 8.55 (s,1H), 7.6 (d,J=1.7Hz,1H), 7.49 (d,J=8.5Hz,1H), 7.23 (dd,J_1=1.7Hz,J_2=8.6Hz,1H), 6.69 (s,1H), 4.28 (m,1H), 3.58 (m,1H), 3.44 (m,1H), 2.21 (m,1H), 1.90 (m,3H). MS (70 eV) m/z (rel. int.): 361, 359 (100), 333, 331 (11), 292, 290 (13); 264, 262 (15) 236. 234 (26), 155 (38), 128 (23), 70 (98); $C_{16}H_{14}N_3O_2Br$ (360.21): calc. C 53.35 H 3.92 N 11.67 Br 22.18, found C 53.48 H 3.90 N 11.63 Br 22.26; Fp 258°C dec.
Z-2: ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 11.73 (s br,1H), 9.64 (s br,1H), 7.94 (s,1H), 7.62 (d,J=1.7Hz,1H), 7.62 (d,J=8.5Hz,1H), 7.22 (dd,J_1=1.7Hz,J_2=8.5Hz,1H), 6.94 (s,1H), 4.35 (m,1H), 3.50 (m,2H), 2.22 (m,1H), 1.88 (m,3H). MS (70 eV) m/z (rel.int.): 361.359 (100), 333, 331 (10); 292, 290 (11), 264, 262 (12), 236, 234 (20), 155 (25), 128 (13), 70 (48) $C_{16}H_{14}N_3O_2Br$ (360.21): calc. C 53.35 H 3.92 N 11.67 Br 22.18; found C 53.23 H 3.93 N 11.64 Br 22.43; Fp 162°C.

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