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CYCLOL FORMATION IN PEPTIDE SYSTEMS. IV. HYDROXY ACID INCORPORATION INTO PEPTIDES

V.K. Antonov, A.M. Shkrob, V.I. Shchelokov and M.M. Shemyakin
Institute for Chemistry of Natural Products,
USSR Academy of Sciences, Moscow, USSR

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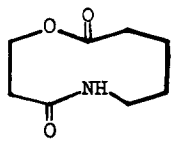
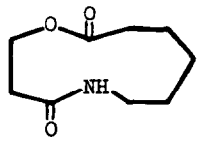
EARLIER we reported on the rearrangement of N-(β-hydroxypropionyl)-piperidone to the 10-membered cyclodepsipeptide (I) (1,2). Further study showed that this new reaction in which a hydroxy acid residue is directly incorporated into a peptide system is of general significance and occurs with both cyclic and acyclic peptides.

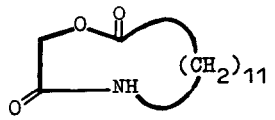
Under conditions similar to those described earlier (1,2,3), we obtained N-(β-benzyloxypropionyl)-pyrrolidone (II), N-(β-benzyloxypropionyl)-caprolactam (III) and N-benzyloxyacetyldodecalactam (IV) (see Tables 1 and 2). Hydrogenolysis of compound (III) and (IV) over Pd-black in abs. tetrahydrofurane led to the cyclodepsipeptides (V) and (VI). The structure of these compounds followed from a comparison



(I)



(V)



(VI)

TABLE 1

Constants and Analytical and U.V. Data of Acyllactams and Cyclodepsipeptides

Compound	M.P. °C	B.P. °C at $5 \cdot 10^{-2}$ mm	Found (%)			Required (%)			M.W.[a]		U.V. Absorption	
			C	H	N	C	H	N	Found	Req.	λ_{max}	ε_{max}
II	Oil	155-157	67,74	6,95	5,86	67,99	6,93	5,66			216	13400
III	Oil	162-165	69,61	7,60	5,14	69,79	7,69	5,09			221	11700
IV	55		72,71	8,95	4,15	73,00	9,05	4,05			220,5	9700
V	142		58,47	8,00	7,58	58,36	8,16	7,56	185	185		
VI	98		65,72	10,03	5,58	65,85	9,87	5,49	255	255,4		
IX	Oil	Dec.	53,29	7,00	8,54	53,49	7,05	8,91			219	8900
XI[b]	250		50,13	6,45	9,60	50,34	6,34	9,79				
XII	202		45,60	5,64	9,73	45,83	5,60	9,72				
XIII	231		50,40	6,44	9,83	50,34	6,34	9,79				

[a] Determined mass spectroscopically.

[b] $[\alpha]_D^{25}$ - 118° (c 0,4; 70% aq. CH_3OH).

TABLE 2

I.R. Spectra of Acyllactams and Cyclodepsipeptides

Compound	Conditions of Spectral Determinations	Band Position (cm^{-1})				
		CO-ester	-CONCO-	Amide I	Amide II	OH and NH
I	Nujol	1726		1658w,1635		3020(?),3300
	THF(c=1;l=0,2)	1744		1690	1546	3350
	CCl_4(c=0,1;l=4)	1729		1692,1672w	Solv.abs.	3080,3340,3400w,3450
II	THF(c=0,5;l=0,2)		1744,1698			
III	THF(c=0,5;l=0,2)		1705			
IV	THF(c=0,5;l=0,2)		1707			
V	Nujol	1729		1645	1568	3100,3300
	THF(c=0,3;l=0,5)	1747		1685	1556	3360
	CCl_4(c=0,1;l=4)	1748		1695	Solv.abs.	3370w,3450
VI	Nujol	1730		1680,1665	1540	3400
	THF(c=0,5;l=0,2)	1751		1690	1537	3350
	CCl_4(c=0,3;l=0,5)	1755		1695	1540	3450
IX	Film		1740,1695			3430br
	THF(c=0,5;l=0,2)		1746,1697			3400br
XI	Nujol	1738		1659	1550	3085,3285,3315
XII	Nujol	1738		1652	1560	3086,3285,3400
XIII	Nujol	1740		1650	1557	3090,3325

of their I.R. spectra with those of cyclodepsipeptide (I).[+,++]

The fact that the rearrangement takes place with N-glycolyldodecalactam in which the -CONCO- group possesses a configuration similar to that of acyclic acylamides (4) caused us to explore the possibility of incorporating hydroxy acids into linear peptides. Indeed, it was found that hydrogenolysis, sometimes followed by heating, of the N-benzyloxyacylamides (VII a-e) yields the linear depsipeptides (VIII a-e), whose structure has been proved by means of their I.R. spectra and by countersynthesis (see Table 3).

$$\underset{\text{(VII)}}{C_6H_5CH_2O(CH_2)_nCON(R^1)COR^2} \xrightarrow{H_2/Pd} \underset{\text{(VIII)}}{R^2COO(CH_2)_nCONHR^1}$$

a. n=1, $R^1=R^2=CH_3$; b. n=1, $R^1=CH_3$, $R^2=CH_2N(CO)_2C_6H_4$; c. n=1, $R^1=CH_2CO_2CH_3$, $R^2=CH_2N(CO)_2C_6H_4$; d. n=2, $R^1=CH_3$, $R^2=CH_2N(CO)_2C_6H_4$; e. n=2, $R^1=CH_2CO_2CH_3$, $R^2=CH_2N(CO)_2C_6H_4$.

These results allowed some inferences to be made regarding the conditions for stabilisation and for directing the

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[+] The absence in compounds (V) and (VI) of a bathochromic shift of the ester band observed in (I) on passing from tetrahydrofuran to CCl_4 bears evidence of the absence of a transannular effect in the former compounds.

[++] The weak musk-like odor perceived on heating (VI) confirms the absence of association via hydrogen bonding (cf., Y. Iwakura and K. Uno, J. Org. Chem., 25, 1227 (1960)).

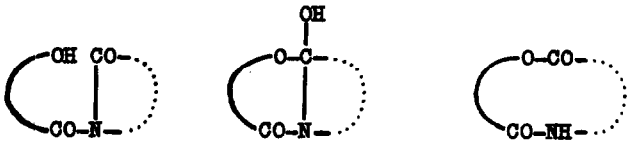
TABLE 3

Constants and Analytical and I.R. Data of Benzyloxyacylamides and Linear Depsipeptides[a]

Compound	M.P. °C	Found (%)			Required (%)			I.R. Band Positions, cm^{-1} (Nujol)					
		C	H	N	C	H	N	CO-Phth	-CONCO-	CO-ester	Amide I	Amide II	NH
VII a	71	65,66	6,69	6,24	65,14	6,83	6,33		1710				
VII b	146	65,86	5,20	7,35	65,56	4,95	7,65	1775,1708	1708				
VII c	120	62,27	4,66	6,64	62,26	4,75	6,60	1772,1725	1702	1758			
VII d	109	66,40	5,27	7,10	66,30	5,30	7,37	1780,1719	1719				
VII e	117	62,61	5,33	6,54	63,01	5,06	6,39	1780,1725	1725	1755			
VIIIa	39	45,98	6,96	10,54	45,79	6,92	10,68			1758	1680	1560	3100,3320
VIIIb	150	56,94	4,66	10,03	56,52	4,38	10,14	1778,1722		1751	1652	1569	3120,3320
VIIIc	131	53,95	4,42	8,50	53,89	4,22	8,38	1771,1725		1762, 1725	1702	1547	3390
VIIId	194	57,45	4,75	9,78	57,93	4,86	9,65	1778,1725		1751	1652	1569	3100,3300
VIIIe	172	55,38	4,76	8,21	55,17	4,63	8,04	1777,1727		1743, 1727	1647	1547	3100,3320

[a] These compounds were synthesized with the assistance of Yu.I. Krylova.

cleavage of cyclols. We believe that the cyclols (B) arising from interaction of hydroxyl with endocyclic carbonyl in N-hydroxyacylamides (A) are generally unstable, decomposing with the formation either of the initial N-hydroxyacylamides, or of cyclic or linear depsipeptides (C).



(A) (B) (C)

If, however, the cyclodepsipeptides possess strong steric hindrances or transannular interaction the cyclol may prove to be more stable than the macrocycle, as, for instance, in the case of the 9-membered cyclotridepsipeptides (cf. 5). The existence of stable cyclols is thus a possibility and a number have been formed from N-(α-hydroxyacyl)-diketopiperazines (1,3,6,7).+ In the series of N-glycolyllactams the cyclol structure, in conformity with Brown's rule (8,9), is observed with N-glycolylpiperidone (1,3).

The above said is confirmed by the fact that hydrogenolysis of (II) leads to the N-(β-hydroxypropionyl)-pyrrolidone (IX), rather than to the cyclol or cyclodepsipeptide. The structure of (IX) followed from comparison of its U.V. and

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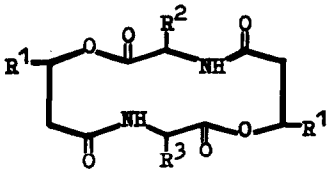
+ Recently, R.C. Sheppard (Experientia 19, 125 (1963)) on the basis of our earlier communicated spectral characteristics of cyclols (1), was able to demonstrate the possibility of cyclol formation by isomerization of the corresponding cyclotridepsipeptide.

I.R. spectra with those of N-acylpyrrolidones (1,3,4).

The unprecedented ease of formation of macrocyclic systems, we have observed in the above described transformations, led us to the belief that such reactions may possibly occur in the biogenesis of cyclodepsipeptides, in particular of serratamolide (10). This is supported by the readiness with which the model reaction of β-hydroxypropionic acid incorporation into diketopiperazine rings takes place. Thus in the hydrogenolysis of N,N-bis-(β-benzyloxypropionyl)-diketopiperazine ring closure spontaneously takes place to give the cyclotetradepsipeptide (X) (11). At present we have in a similar way synthesized a number of other serratamolide analogs, namely depsipeptides (XI), (XII) and (XIII) (see Tables 1 and 2).



(X). $R^1=R^2=R^3=H$; (XI). $R^1=H$, $R^2=R^3=CH_3$ (L,L);

(XII). $R^1=R^2=H$, $R^3=CH_2OH$ (DL); (XIII). $R^1=CH_3$, $R^2=R^3=H$ (DL)

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