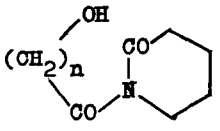
Tetrahedron Letters No. 7, pp. 439-443, 1963. Pergamon Press Ltd.
Printed in Great Britain.

CYCLOL FORMATION IN PEPTIDE SYSTEMS. III. REARRANGEMENT OF N-(β-HYDROXYPROPIONYL)-PIPERIDONE INTO A 10-MEMBERED CYCLODEPSIPEPTIDE

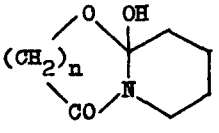
V.K. Antonov, A.M. Shkrob and M.M. Shemyakin
Institute for Chemistry of Natural Products,
USSR Academy of Sciences, Moscow

(Received 21 December 1962)

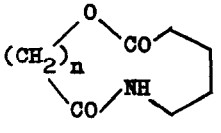
PREVIOUS communications[1,2] have described the tautomeric conversion of N-glycolyldiketopiperazines and N-glycolylpiperidone into the corresponding cyclols (e.g. Ia ⇌ IIa). None of the compounds investigated revealed any tendency to undergo reactions of the type IIa ⇌ IIIa, the possibility of which we had postulated earlier.[3]



Ia, n=1
Ib, n=2



IIa, n=1
IIb, n=2



IIIa, n=1
IIIb, n=2

---

[1] M.M. Shemyakin, V.K. Antonov, A.M. Shkrob, L.B. Senyavina, Yu.N. Sheinker, Tetrahedron Letters, № 16, 701 (1962).

[2] V.K. Antonov, A.M. Shkrob, M.M. Shemyakin, Report to the V European Peptide Symposium, 1962, Oxford.

[3] G.A. Ravdel, N.A. Krit, L.A. Shchukina, M.M. Shemyakin, Dokl.Akad.Nauk SSSR, 137, 1377 (1961).

Compound	Conditions of obtaining the spectra	Band position (cm^{-1})			
		CO ester	Amide I	AmideII	N-H frequencies
IIIb	Nujol	1726	1658w,1635		3020(?),3300
	THF (c=1;l=0.2)	1744	1690	1546	3350
	$C_2H_4Cl_2$ (c=0.1;l=4)	1740	1686	Solv.abs.	3440
	CCl_4 (c=0.1;l=4)	1729	1692,1672w	Solv.abs.	3080,3340inf.,3400w,3450
	CCl_4 (c=1;l=0.2)	1730	1690,1670	1525	3080,3340,3400w,3450w
	EtOH (c=5;l=0.06)	1746	1666	1566	Solvent abs. region
	EtOD (c=5;l=0.06) after 30 min.	1745	1662		" " "
Dodecalactam	Nujol		1645	1555	3080,3310
	THF (c=1;l=0.2)		1678	1541	3360
	CCl_4 (c=0.1;l=4)		1682	Solv.abs.	3090w,3360w,3450,3470
	CCl_4 (c=1;l=0.2)		1681,1652w	1515	3080,3320,3450w,3470w
	EtOH (c=5;l=0.06)		1652	1560	Solvent abs. region
	EtOD (c=5;l=0.06) after 30 min.		1650	1562	" " "
	after 24 h.		1650		" " "
Pentadecanolide	THF (c=1;l=0.2)	1736			
	CCl_4 (c=1;l=0.2)	1739			
	EtOH (c=5;l=0.06)	1736,1717			

Table 1. Infra-red spectra of cyclodepsipeptide IIIb and model compounds

The failure to undergo such conversions could have been due to steric hindrances that would have arisen in the resultant 9-membered ring. In order to investigate the possibility of formation of the less hindered 10-membered ring (cf.[4]), we undertook the synthesis of N-(β-hydroxypropionyl)-piperidone (Ib).

Refluxing of piperidone in benzene with slight excess of $C_6H_5CH_2OCH_2CH_2COCl$ led to N-(β-benzyloxypropionyl)-piperidone in high yield - b.p. 164 - 165°/0.06 mm; n_D^{20} 1.5387; u.v. spectrum: λ_{max} 214 mμ, ε 11100 (dioxane); i.r. spectrum: 1698 cm^{-1} (film), 1700 cm^{-1} (0.5, THF) (-CONCO-).(Found: C, 69.22; H, 7.41; N, 5.11%. Required for $C_{15}H_{19}O_3N$: C, 68.94; H, 7.33; N, 5.36%). On hydrogenolysis of this compound in abs. THF solution over Pd-black a crystalline substance was obtained in almost quantitative yield (m.p. 109 -110° from CCl_4). (Found: C, 55.79; H, 7.67; N, 8.19%. Required for $C_8H_{13}O_3N$: C, 56.12; H, 7.65; N, 8.18%). A study of its u.v. and i.r. spectra showed it to have the structure of the cyclodepsipeptide IIIb.

This compound lacks the 214 - 220 mμ absorption characteristic of N-acyllactams.[1,2,5] Its i.r. spectra in THF (Table 1) exhibit absorption bands at 1744 cm^{-1} (CO ester), 1690 cm^{-1} (amide I) and 1546 cm^{-1} (amide II). The assignment of the last band has been confirmed by its disappearance on deuteration by dissolving the compound in C_2H_5OD and by its

---

[4] W. Treibs, I. Thormer, Chem. Ber. 94, 1915 (1961).

[5] H.K. Hall, R. Zbinden, J.Amer.Chem.Soc. 80, 6428 (1958).

appearance on dissolving the deuterated compound in C_2H_5OH.*

Determination of the molecular weight of IIIb in benzene (Table 2) revealed the existence of association, the nature of which was elucidated from a study of the i.r. spectra of IIIb in CCl_4. Increase in the concentration of IIIb in the solution was accompanied by considerable augmentation in the intensity of the bound NH band, weakening of the free NH band and splitting of the first amide band. These are exactly the spectral changes which occur in the association of secondary amides with trans-configuration at the amide group[6] (for comparison the spectra of dodecalactam are given in Table 2).

Table 2. Thermoelectric molecular weight determination of the cyclodepsipeptide IIIb in benzene.

Concentration in molar parts $\times 10^3$	Appearent molecular weight (Mean of 3 measurements)
2.35	171.2
3.75	176.4
5.30	186.5
6.10	193.5
Calculated	171.2

* It should be mentioned that the i.r. spectrum of crystalline IIIb does not exhibit the second amide band. This may be due to the cis-configuration of the amide group under such conditions. At the same time it is known that the 10-membered lactam has a trans-amide group both in the crystalline state and in solution (R. Huisgen, H. Brade, H. Walz, I. Glogger, Chem. Ber. 90, 1437 (1957)).

6 G.C. Pimentel, A.L. McClellan, The Hydrogen Bond, W.H. Freeman & Co, San Francisco, Calif., 1960, p. 79.

The diminished capacity of the IIIb ester carbonyl to participate in hydrogen bonding is confirmed by the absence of splitting of the ester band in the spectrum of IIIb in absolute alcohol solution, characteristic of the common esters carbonyl band (cf.[7]).

The more rapid deuteroexchange in IIIb than in dodecalactam, as well as the shift in the ester band on passing from CCl_4 to such polar solvents as dichloroethane, tetrahydrofuran or alcohol, evidently bears evidence of transannular interactions of the ester carbonyl with peptide nitrogen (cf.[8]).

The rearrangement of Ib into IIIb which has been described, points out to the nessesity of taking into account the possibility of conversions of the type $I \rightleftharpoons II \rightleftharpoons III$ in various peptide systems during their chemical and biochemical conversions.

Acknowledgement - We are greatly indebted to Mrs. L.B. Senyavina for the i.r. spectra.

---

[7] J.H. Fellman, T.S. Fujita, Biochim.et Biophys.Acta 56, 227 (1962).

[8] L.A. Cohen, B. Witkop, J.Amer.Chem.Soc. 77, 6595 (1955).