SYNTHESES OF DI- AND TETRAHYDROPYRROLES

IX.* DEHYDRATION AND RING–CHAIN TAUTOMERISM OF 2,3,3-TRIMETHYL-2-HYDROXY-5-PYRROLIDONES

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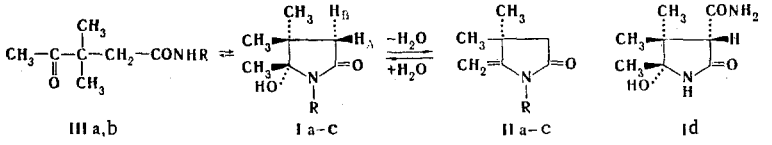
It is shown by means of IR and PMR spectra that the products of the aminolysis of esters of 3,3-dimethyl(2-carbethoxy)levulinic acid and γ-chloro-β,β,γ-trimethylbutyrolactone exist in the cyclic form of 2-hydroxy-5-pyrrolidones (Ia-d). It was established by PMR spectroscopy that, except for the 4-carbamido derivative (Id), these compounds undergo spontaneous dehydration in anhydrous solutions. In addition, ring–chain tautomeric equilibrium is established in solutions of the N-phenyl derivative (Ib). The rates of establishment of equilibrium and the equilibrium positions were investigated for both processes.

A small number of studies [2, 3] have been devoted to the prototropic ring–chain tautomerism of amides of γ-keto acids (the cyclic tautomers of which are 2-hydroxy-5-pyrrolidones), but this tautomeric equilibrium has not been quantitatively studied up to now. In most cases, either the cyclic or acyclic member of the pair of tautomers (rarely both) was isolated. Since tautomeric equilibrium can be established extremely slowly, one cannot draw clear conclusions relative to the stabilities of the tautomers from the fact of the isolation of one of the forms. To solve this problem, we studied the position of the 2-hydroxy-5-pyrrolidone (I) ⇌ γ-keto acid amide (III) ring–chain tautomeric equilibrium without recourse to the isolation of the individual tautomers. We also studied the phenomenon of spontaneous dehydration of 2-hydroxy-5-pyrrolidones (I) to enepyrrolidones (II) in solutions; up until now, the possibility of the occurrence of this sort of process has not been taken into account, and the dehydration products have not been detected.



III a,b — I a-c — II a-c — Id

a R=H; b R=C_6H_5; c R=CH_3

The 2-hydroxy-5-pyrrolidones (Ia-d) were synthesized by aminolysis of γ-chloro-β,β,γ-trimethylbutyrolactone at 0°C (Ia, c) and 95-100° (Ib), of methyl 3,3-dimethyllevulinate at 140-170° (Ia), and of ethyl 3,3-dimethyl-2-carbethoxylevulinate at 90-100° (Id). In the crystalline state, Ia-d apparently have cyclic hydroxylactam structure I,† as follows from the IR spectra of KBr pellets and mineral oil suspensions of crystals of these substances (Table 1) and a comparison of the spectra with those in [3, 4]. The possible

*See [1] for communication VIII.

† The structure of the ring–chain tautomers in the crystalline state depends on the method used for their synthesis. The amides of levulinic acids obtained by various methods usually have cyclic structure I in the crystalline state. However, it was recently demonstrated [3] that even for the same synthetic method, the structure of the amides obtained may be determined by the conditions used to carry out the process.

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TABLE 1. IR Spectra of Ia-d

Compound	Stretching vibrations, cm^{-1}			
	KBr[a]		$CHCl_3$ [a,b]	Mineral oil[a]
Ia	νOH, NH	3335 3220	3427 3230—3330[a, e]	3335 3220
	νCO	1660, 1700	1712[a] (shoulder 1670)	1670, 1705
Ib	νOH	3430[a]	3300—3550[c]	—
	νCO	1670— 1690 f	1655, 1710	—
Ic	νOH	—	3230—3500[a, d]	—
	νCO	—	1645 1680—1720[a, f]	—
Id	νNH, NH_2 νOH	3370, 3180	—	—
	νCO	1680, 1720	—	—

[a]Broad band. [b]For 2% solutions (the intensity and position of the bands did not change on passing from concentration of 0.05% to 3% in chloroform solution). [c]An absorption band at 3450 cm^{-1} was isolated on dilution of the solution. [d]An absorption band at 3470 cm^{-1} was isolated on dilution of the solution. [e]This band disappears in the spectrum of a chloroform solution of this compound on deuteration (by shaking twice in D_2O solution with subsequent removal of the solvent), and a ν^{OD} band appears at 2660 cm^{-1}. [f]The band is split.

acyclic keto-amide structure (III) is not confirmed in view of the absence in the spectra of Ib, c of absorption at 1510-1570 cm^{-1} (amide II band) and the absence of two absorption bands of equal intensity at 1720 and 1630-1680 cm^{-1} (ketone and amide C=O groups, respectively) (there are absorption bands of weak intensity in the spectra of Ib, c at 1660-1670 cm^{-1}). Compounds Ia-d also exist in cyclic form I in solutions. The IR spectra of chloroform solutions of Ia-c contain absorption bands at 3230-3500 cm^{-1} that are characteristic for the stretching vibrations of an OH group involved in an intermolecular hydrogen bond (these bands disappear on deuteration). The PMR spectra of these compounds, recorded immediately after dissolving, contain exclusively signals of the cyclic form of I, as, for example, in the spectrum of hydroxypyrrolidone Ia in D_2O solution (15 min after dissolving, Table 2). The signals of this form are readily distinguished from the signals of the other forms, since the nonequivalence of the protons of the methylene group (an AB system) and of the geminal methyl groups is manifested only in cyclic form I, and the signal of the methyl group in the 2 position is found at 1.3-1.5 ppm.

By means of PMR spectroscopy, we showed that hydroxypyrrolidones Ia-c in anhydrous solvents undergo spontaneous dehydration to 2-methylene-5-pyrrolidones (enepyrrolidones) IIa-c in 6-49% yields at room temperature (Table 3). The rate and extent of dehydration depend on the structure of the hydroxypyrrolidone and the character of the solvent. The assignment of the signals for enepyrrolidones II was made on the basis of a comparison with the spectrum of an analytically pure sample of IIa; the signals of the nonequivalent olefin protons at 4.0-4.3 ppm (Table 2) are characteristic. It should be noted that enepyrrolidone IIa is rapidly hydrated to hydroxypyrrolidone Ia in aqueous D_2O solution, while hydroxypyrrolidone Ia does not undergo spontaneous dehydration in aqueous D_2O solution. A hydroxypyrroldone $\rightleftharpoons$ enepyrrolidone (I $\rightleftharpoons$ II) equilibrium is apparently set up in anhydrous solvents. This is confirmed by data on the reversibility of this equilibrium as a function of temperature. Thus raising the temperature to 60-80° causes a considerable shift of the equilibrium to the right. The equilibrium is shifted to the left when the equilibrium mixture is cooled to room temperature. The equilibrium concentration of cyclic enepyrrolidones IIa, b is established in ~3 h in chloroform solutions and after 0.6 h (IIb) and 44 h (IIa) in pyridine solutions. The percentage of enepyrrolidone IIa 8 h after dissolving in CD_3NO_2 and CD_3COOD is 34 and 33%, respectively. It is interesting that hydroxypyrrolidone Id, which has an additional carbamido group in the 4 position, does not undergo dehydration.

2,3,3-Trimethyl-2-hydroxy-1-phenyl-5-pyrrolidone (Ib), which has a phenyl substituent attached to the nitrogen atom, undergoes a tautomeric conversion to an acyclic tautomer — the anilide of 3,3-dimethyl-

TABLE 2. Chemical Shifts (δ, ppm) of the Protons of I, II, and III

Compound	Solvent	3-$(CH_3)_2$	2-CH_3	4-CH_2
Ia[a]	$CDCl_3$	1,02 1,10	1,33	1,80; 2,07; 2,41; 2,68 (J_{AB} 16,2 Hz)
Ia	d_5-Pyridine	0,99 1,20	1,47	1,94; 2,21; 2,62; 2,88 (J_{AB} 15,9 Hz)
Ia	D_2O	1,05 1,09	1,39	1,93; 2,20; 2,44; 2,73 (J_{AB} 16,8 Hz)
Ia	CD_3NO_2	1,00 1,03	1,32	1,71; 1,97; 2,24; 2,52 (J_{AB} 16,2 Hz)
Ia	CD_3COOD	0,99 1,06	b	1,90; 2,20; 2,44; 2,74 (J_{AB} 15,8 Hz)
Ib	$CDCl_3$	1,05 1,08	1,31	1,90; 2,17; 2,48; 2,77 (J_{AB} 16,8 Hz)
Ib	d_5-Pyridine	1,04 1,24	1,27	2,07; 2,34; 2,67; 2,95 (J_{AB} 16,5 Hz)
Ic[c]	$CDCl_3$	1,02 1,12	1,34	1,87; 2,13; 2,32; 2,60 (J_{AB} 16,2 Hz)
Id[d]	d_5-Pyridine	1,05 1,32	1,45	3,48
IIa	$CDCl_3$	1,25	2-CH_2	
			4,08[e] 4,30[e]	2,31
IIa	d_5-Pyridine	1,09	4,00[e] 4,35[e]	2,26
IIb	$CDCl_3$	1,09	4,02[e] 4,15[e]	2,45
		1,31		
IIb[f]	d_5-Pyridine	1,15	4,0[e] 4,1[e]	2,41
IIc[f]	$CDCl_3$	1,24	4,12	2,31
			CH_3—CO	CH_2CO
IIIa	D_2O	1,18	2,25	2,63
IIIb	$CDCl_3$	1,16	2,15	2,45
IIIb	d_5-Pyridine	1,15	2,22	2,79

[a] δ_{OH} 4.60-4.85; δ_{NH} 7.55 ppm. [b] Signal not detected. [c] δ_{N-CH_3} 2.76 ppm. [d] δ_{OH} 4.87 ppm. [e] Center of a doublet. [f] δ_{N-CH_3} 2.92 ppm.

TABLE 3. Percent of I–III Present As a Function of Time in Solution of Hydroxypyrrolidones Ia-c

Compound	Solvent	τ, h	Amount in the mixture, %		
			I	II	III
Ia	$CDCl_3$	0,27	95	5	—
		0,52	86,5	13,5	—
		1,75	76,5	23,5	—
		3,5	75	25	—
		72	75	25	—
Ia	C_5D_5N	1,3	98	2	—
		22,3	90	10	—
		44	74	26	—
		146	74	26	—
Ia	D_2O	0,3	100	—	—
		2,0	100	—	Traces
		8	97	—	3
		31	96	—	4
		48	96	—	4
Ic	$CDCl_3$	108	65	35	—
		240	51	49	—
		360	51	49	—
Ib	$CDCl_3$	0,3	71	29	—
		1,6	68	32	—
		3,5	67	33	—
		30,5	51	39	10
		264	46	39	15
		360	46	39	15
Ib	C_5D_5N	0,6	94	6	0
		33	91	6	3
		144	88	6	6
		264	84	6	10
		658	84	6	10

levulinic acid (IIIb) – in anhydrous solvents.* The establishment of the prototropic ring–chain tautomeric equilibrium proceeds more slowly than the dehydration reaction. Signals, the chemical shifts and intensity ratio of which correspond to linear form IIIb (Table 2), appear after 30 or more hours in the PMR spectra of hydroxypyrrolidone Ib recorded in $CDCl_3$ and d_5-pyridine. The percentage of IIIb in the equilibrium mixture reaches 10% in d_5-pyridine (the tautomeric equilibrium constant $K_T = [IIIb]/[Ib] = 0.119$) and 15% in $CDCl_3$ ($K_T = 0.326$). The percentage of acyclic form IIIa in a solution of hydroxypyrrolidone Ia in D_2O is 4%, but the establishment of tautomeric equilibrium proceeds much more rapidly (Table 3). Linear tautomer IIIb is stable, and the percentage of it does not change after removal of the solvent ($CDCl_3$) and redissolving; i.e., it is not converted to the cyclic tautomer (see [6], for example). Thus the ring–chain tautomeric equilibrium in solutions of 2-hydroxy-5-pyrrolidones, which are cyclic tautomers of the amides

*The presence of geminal methyl groups adjacent to the carbonyl group in the investigated compounds should, on the one hand, hinder cyclization of acyclic tautomer III, but, on the other hand, owing to the "gem-dimethyl effect" [5], it should increase the tendency for the formation of cyclic form I.

of γ-keto acids, is established slowly, in contrast to the γ-keto acids themselves, in solutions of which the corresponding equilibrium is established extremely rapidly [7].

The position of the ring–chain equilibrium in anhydrous solutions differs as a function of the structures of the substituted 2-hydroxy-5-pyrrolidones. Linear forms IIIa, c are not formed in solutions of nitrogen-unsubstituted and N-methyl derivatives of the hydroxypyrrolidones (Ia,c) in chloroform and pyridine, while solutions of the N-phenyl derivative of hydroxypyrrolidone (Ib) in the same solvents contain 10-15% of linear form IIIb in addition to cyclic forms Ib and IIb. The appearance of this linear form in solutions of N-phenyl derivative (Ib) is associated with the decrease in the resistance of cyclic form Ib to ring opening (as compared with forms Ia,c) because of a decrease in the nucleophilicity of the nitrogen atom (on passing from R = H to R = C_6H_5).

EXPERIMENTAL

The IR spectra were recorded with a UR-10 spectrophotometer. The PMR spectra were recorded with a Hitachi-Perkin Elmer R-20A spectrometer; the accuracy of the shifts was ±0.005 ppm (c 0.4 mole/liter). The internal standards were hexamethyldisiloxane and 2,2-dimethyl-4-silapentane-1-sulfonate sodium salt (for solutions in D_2O). The percentages of I-III in the solutions were determined from the ratio of the integral intensities of the signals of the 2 – CH_3, 4 – CH_2, and 3 – $C(CH_3)_2$ groups of form I to the corresponding signals of forms II and III (the mean square error was ±3.5%).

2,3,3-Trimethyl-2-hydroxy-5-pyrrolidone (Ia). This compound was obtained by the method in [1].

2,3,3-Trimethyl-1-phenyl-2-hydroxy-5-pyrrolidone (Ib). A mixture of 3.55 g (22.6 mmole) of γ-chloro-β,β,γ-trimethylbutyrolactone [1] and 4.2 g (45 mmole) of aniline in 14 ml of toluene was heated at 95-100° for 20 h, after which it was cooled, and the precipitate was removed by filtration and washed with toluene. The filtrate was washed successively with 1 N HCl, 5% sodium carbonate solution, and water. The solvent was removed, and the residue was recrystallized from hexane to give 4.67 g (97%) of a product with mp 84-84.5°. Found: C 71.4; 71.3; H 7.6; 7.3; N 6.8; 6.8%. $C_{13}H_{17}NO_2$. Calculated: C 71.2; H 7.8; N 6.4%.

1,2,3,3-Tetramethyl-2-hydroxy-5-pyrrolidone (Ic). A mixture of 1.58 g (0.01 mole) of methyl 3,3-dimethyllevulinate, 10 ml of 25% methylamine solution, and 4 ml of methanol was heated in a glass ampul at 140-170° for 3 h. The mixture was evaporated, and the residue was vacuum dried to give 0.46 g (30%) of oily Ic. Found: C 61.7; 61.5; H 8.8; 8.8; N 8.9; 9.1%. $C_8H_{15}NO_2$. Calculated: C 61.1; H 9.6; N 8.9%.

2,3,3-Trimethyl-4-carbamido-2-hydroxy-5-pyrrolidone (Id). A solution of 49 g (0.2 mole) of ethyl 3,3-dimethyl-2-carbethoxylevulinate [8] in 200 ml of anhydrous ethanol saturated with ammonia was heated at 90-100° in a bomb for 36 h. The solvent was removed by distillation, and the residue was washed with ether to give 20.8 g (56%) of a product with mp 152-152.5° (from benzene–ethanol). Found: C 51.2; 51.5; H 7.5; 7.8; N 15.3; 15.0%. $C_8H_{14}N_2O_3$. Calculated: C 51.6; H 7.6; N 15.0%.

LITERATURE CITED

1. B. M. Sheiman, L. Ya. Denisova, S. F. Dymova, I. M. Kustanovich, and V. M. Berezovskii, Khim. Geterotsikl. Soedin., 1190 (1971).
2. P. R. Jones, Chem. Rev., 63, 471 (1963).
3. W. Flitsh, Chem. Ber., 103, 3205 (1970).
4. R. Lukes and Z. Linhartova, Coll. Czech. Chem. Commun., 25, 502 (1960).
5. D. Hammond, in: Steric Effects in Organic Chemistry, M. S. Newman (editor), Wiley (1956).
6. B. V. Unkovskii, L. A. Ignatova, and M. G. Zaitseva, Khim. Geterotsikl. Soedin., 889 (1969).
7. I. Finkelstein, T. Willams, V. Toome, and S. Traiman, J. Org. Chem., 32, 3229 (1967).
8. B. M. Sheiman, L. Ya. Denisova, S. F. Dymova, I. M. Kustanovich, and V. M. Berezovskii, Zh. Organ. Khim., 5, 238 (1969).