SYNTHESES OF DI- AND TETRAHYDROPYRROLES

X.* SYNTHESIS OF 3,3-DIMETHYL-2-METHYLENE-5-PYRROLIDONE AND ITS DERIVATIVES. INVESTIGATION OF THE ELECTROPHILIC ADDITION OF ALCOHOLS AND WATER TO THEM

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Dehydration of 2,3,3-trimethyl-2-hydroxy-5-pyrrolidone and its 1-methyl and 1-phenyl derivatives gave 3,3-dimethyl-2-methylene-5-pyrrolidone and its 1-methyl and 1-phenyl analogs. Their alcoholysis and hydration were studied.

2-Methylene-5-pyrrolidones and 2-hydroxy(alkoxy)-5-pyrrolidones are of interest as key compounds in the synthesis of model and natural corrins [2-4]. In this connection, the development of methods for the synthesis of these compounds and the investigation of their properties takes on great significance. 3,3-Dimethyl-2-methylene-5-pyrrolidone (Ia) and its 1-methyl (Ib) and 1-phenyl (Ic) analogs were obtained by dehydration of the corresponding 2-hydroxy-5-pyrrolidones (IIIa-c), which we previously described in [1, 4]. Methylenepyrrolidones Ia, c were isolated by vacuum sublimation of hydroxypyrrolidones IIIa, c at 130-160°C, while methylenepyrrolidone Ib was isolated by vacuum distillation of IIIb (or by keeping it in vacuo at 20°).

Methylenepyrrolidones Ia-c react exceptionally readily with moist air to give starting hydroxypyrolidones IIIa-c. Compounds Ia and Ic, which we were able to obtain without admixtures of starting IIIa and IIIc only in solutions (with rapid dissolving of freshly sublimed samples in anhydrous organic solvents), proved to be particularly unstable. The PMR spectra of these compounds show the presence of signals only of I (Table 2; see [4] for a description of their spectra). Compound Ib is somewhat more stable than Ia and Ic and was isolated in the individual state (according to the PMR spectroscopic data and elementary analysis). It should be emphasized that the signals of tautomeric 2,3,3-trimethyl-5-oxo-1-pyrroline in solutions of 3,3-dimethyl-2-methylene-5-pyrrolidone (Ia) were not detected in any of the solvents used (even when solutions of Ia in $CDCl_3$ and nitrobenzene were allowed to stand for 1-1.5 months). Thus, the imine–enamine tautomeric equilibrium in 3,3-dimethyl-2-methylene-5-pyrrolidone (Ia) is shifted markedly to favor the enamine form (evidently, as a consequence of the formation of the conjugated $\overset{|}{\underset{|}{C}}{=}\underset{|}{C}-\underset{|}{N}-\underset{|}{C}{=}O$ system), in contrast to 1-pyrrolines, in which it is shifted to favor the imine form [5].

It is known that the products of dehydration of 2-hydroxy-5-pyrrolidone derivatives that have a double bond in the ring readily add water [6-8] but do not add methanol (even in the presence of acid catalysts [9-10].

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*For Communication IX see [1].

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TABLE 1. Parameters of the PMR Spectra of 2,3,3-Trimethyl-2-alkoxy-5-pyrrolidone Derivatives (IIa-g)

Compound	R′	R	Solvent	Chemical shifts, δ, ppm				$J_{H_AH_B}$, Hz
				3-$(CH_3)_2C$, s		2-CH_3C, s	4-CH_AH_B, q	
IIIa[a]	H	CH_3	$CDCl_3$	1,02	1,07	1,27	1,72; 2,00; 2,33; 2,65	16,8
IIIa[a]	H	CH_3	$C_6H_5NO_2$	1,12	1,22	1,45	1,87; 2,14; 2,47; 2,75	16,5
IIIa	H	CD_3	CD_3OD	1,02	1,07	1,28	1,72; 2,02; 2,40; 2,66	16,8
IIIb	H	C_2D_5	$C_6H_5NO_2$	0,98	1,09	1,30	1,80; 2,07; 2,43; 2,70	16,2
IIIc	H	i-C_3D_7	$C_6H_5NO_2$	0,95	1,04	1,29	1,95; 2,23; 2,59; 2,86	15,6
IIId[b]	CH_3	CH_3	$C_6H_5NO_2$	1,00	1,19	1,40	1,96; 2,22; 2,45; 2,71	15,6
IIId[b]	CH_3	CD_3	CD_3OD	1,01	1,19	1,33	1,83; 2,10; 2,30; 2,67	16,5
IIIe[b]	CH_3	C_2D_5	C_2D_5OD	0,98	1,08	1,30	1,77; 2,05; 2,25; 2,54	16,8
IIIf[b]	CH_3	i-C_3D_7	i-C_3D_7OD	1,00	1,10	1,31	1,84; 2,12; 2,36; 2,64	16,8
IIIg[c]	C_6H_5	CH_3	$C_6H_5NO_2$	1,05	1,14	1,14	2,02; 2,30; 2,55; 2,82	16,5

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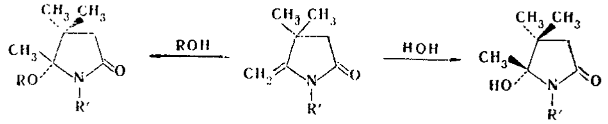
[a] δ OCH_3, s, 3.16 ppm ($CDCl_3$); 3.33 ppm (nitrobenzene); NH 7.8 ppm ($CDCl_3$). [b] $N-CH_3$, s, 2.30 ppm (nitrobenzene); 2.78 ppm (CD_3OD); 2.73 ppm (C_2D_5OD); 2.75 ppm (iso-C_3D_7OD); OCH_3, s, 3.10 ppm (nitrobenzene). [c] OCH_3, s, 3.27 ppm (nitrobenzene).

We have shown that 2-methylene-5-pyrrolidones Ia-c, which contain an exocyclic double bond, readily undergo not only hydration (to give hydroxypyrrolidones IIa-c) but also alcoholysis [to give the corresponding alkoxy derivatives (IIa-g)].

The alcoholysis of Ia-g proceeds at room temperature in an excess of the corresponding alcohol without the use of acid catalysts.



II a-g I a-c III a-c

I, III a R′=H; b R′=CH_3; c R′=C_6H_5; II a R′=H, R=CH_3; b R′=H, R=C_2D_5; c R′=H, R=i-C_3D_7; d R′=CH_3, R=CH_3; e R′=CH_3, R=C_2D_5; f R′=CH_3, R=i-C_3D_7; g R′=C_6H_5, R=CH_3

The structure of the 2-alkoxypyrrolidones (II) obtained was proved in detail in the case of 2,3,3-trimethyl-2-methoxy-5-pyrrolidone (IIa). The PMR spectra of this compound (Table 1) confirms its cyclic structure and (except for the signal of the CH_3-O group) coincides with the spectra of the previously investigated substituted 2-hydroxy-5-pyrrolidones. The characteristic (for the cyclic form) signals of nonequivalent geminal methyl groups and nonequivalent protons of the methylene group in the 4-position (AB system), as well as a singlet of the 2-CH_3 group in the strong-field region (1.20-1.45 ppm), are observed in the PMR spectra of this compound. As compared with the PMR spectra of hydroxypyrrolidone IIIa [1, 4], the PMR spectra of its methoxy derivative (IIa) contains a diamagnetic shift of the signal of the proton attached to the nitrogen (from 8.04 ppm to 8.53 ppm in saturated CD_3OD solution) and a small paramagnetic shift of the signals of all of the remaining protons (0.03-0.09 ppm in 0.4 M solutions of alcohols, chloroform, benzene, and nitrobenzene). A singlet of a methoxy group at 3.16 and 3.33 ppm, respectively, is present in the spectra of methoxypyrrolidone IIa in $CDCl_3$ and nitrobenzene solutuins. The most intense peaks in the mass spectrum of IIa are two peaks of ions with masses 125 and 110, which are formed as a consequence of successive splitting out of a methanol molecule and a methyl group upon electron impact. A low-intensity (3.5%) molecular ion peak with mass 157 is observed in the mass spectrum of IIa recorded at an ionizing voltage of 12 eV. The IR spectrum of a thin layer of methoxy derivative IIa contains the absorption of an associated NH group at 3330 cm^{-1} (in chloroform solution it is shifted to 3430 cm^{-1}) and the strong absorption of a lactam carbonyl group at 1700-1730 cm^{-1} with a shoulder at 1670-1680 cm^{-1}.

It should be noted that thermolysis of methoxy derivative IIa (in nitrobenzene or in vacuo at 120-140°) leads to starting methylenepyrrolidone Ia.

The structures of the other alkoxy derivatives (IIb-g) were established on the basis of the identical character of their PMR spectra and the spectrum of IIa.

The formation of derivatives IIa-g was followed quantitatively by means of PMR spectroscopy. It was found that the rate of electrophilic addition of alcohols depends markedly on the substituents attached to the

TABLE 2. Parameters of the PMR Spectra of 3,3-Dimethyl-2-methylene-5-pyrrolidone and Its Derivatives (Ia-c)

Compound	R	Solvent	Chemical shifts, δ, ppm				
			3-$(CH_3)_2$, s	4-CH_2, s	H_A[a], e	H_B[a], e	$J_{H_AH_B}$, Hz
Ia	H	CCl_4	1,25	2,50	3,97	4,25	1,87
Ia	H	C_6H_6	0,96	2,11	3,97	4,40	1,50
Ia	H	$CDCl_3$	1,27	2,35	4,01	4,25	1,87
Ia	H	$C_6H_5NO_2$	1,20	2,30	4,05	4,32	1,80
Ia	H	C_5D_5N	1,09	2,27	4,00	4,32	1,80
Ia	H	CD_3COOD	1,27	2,42	4,21	4,33	1,80
Ia	H	D_2O	1,24	2,20	4,24	4,38	1,80
Ib	CH_3[b]	$CDCl_3$	1,27	2,32	4,18 s		
Ic	C_6H_5	$C_6H_5NO_2$	1,30	2,50	3,95	4,08	1,95
Ic	C_6H_5	$CDCl_3$	1,35	2,48	4,02	4,12	1,80
Ic	C_6H_5	C_6H_5N	1,15	2,41	4,00	4,07	1,15
Ic	C_6H_5	DMSO	1,30	2,43	3,90	4,21	1,80
Ic	C_6H_5	D_2O+CD_3OD	1,40	2,60	4,00	4,31	1,95

[a] Center of a doublet. [b] $\delta_{N\text{-}CH_3}$ 2.95 ppm.

nitrogen atom of the methylenepyrrolidone molecule (Ia-c) and decreases in the order $CH_3 > H > C_6H_5$ (Ib > Ia > Ic) in conformity with the decrease in this order of the nucleophilicity of the nitrogen atom and the associated magnitude of the negative charge on the carbon of the methylene group. Thus, at 20° and in the presence of excess alcohol (at a Ia-c concentration of 0.4 mole/liter) the addition of methanol to 1,3,3-trimethyl-2-methylene-5-pyrrolidone (Ib) proceeds very rapidly (in 7 min). Methanol adds much more slowly to 3,3-dimethyl-2-methylene-5-pyrrolidone (Ia) – the process is complete in 22 days – whereas methanol does not add to 3,3-dimethyl-1-phenyl-2-methylene-5-pyrrolidone (Ic) under these conditions (in the course of 30 days). Methanol (in an approximately threefold excess) adds much more rapidly to methylenepyrrolidone Ia in nitrobenzene solution (see [11] for the acceleration of such reactions by aromatic solvents), and the reaction is 85% complete after 1.5 h and goes to completion after ~ 24 h. In nitrobenzene solution, methanol adds to 3,3-dimethyl-1-phenyl-2-methylene-5-pyrrolidone (Ic). In the equilibrium mixture (equilibrium is established after 7 min), the percentage of 2,3,3-trimethyl-1-phenyl-2-methoxy-5-pyrrolidone (IIg) is 53-55%. Ethanol and isopropyl alcohols add more slowly than methanol to 3,3-dimethyl-2-methylene-5-pyrrolidone (Ia) in nitrobenzene solution – the equilibrium mixtures contain 80 and 60% of alkoxy derivatives IIb and IIc, respectively. The more highly reactive 1,3,3-trimethyl-2-methylene-5-pyrrolidone (Ib) adds ethanol and isopropyl alcohols quantitatively in 5-10 min to give IIe and IIf, respectively.

Water adds to methylenepyrrolidones Ia-c more readily than alcohols. The 2-hydroxy-5-pyrrolidone derivatives (IIIa-c) that we previously described in [1, 4] are formed as a result of hydration. The same effect of the substituting groups attached to the nitrogen of methylenepyrrolidones Ia-c on the rate of addition of water as in the case of the addition of alcohosl is observed. Thus, in 0.4 M solutions of methylene pyrrolidines Ia, b in D_2O, hydration of 1,3,3-trimethyl-2-methylene-5-pyrrolidine (Ib) is 100% complete after 20 min, while in the case of 3,3-dimethyl-2-methylene-5-pyrrolidone (Ia) the reaction is 80% complete after 20 min (it is 100% complete after 30 min). In view of the fact that 3,3-dimethyl-1-phenyl-2-methylene-5-pyrrolidone (Ic) is insoluble in water, its hydration was carried out in CD_3OD-D_2O (1:1). Equilibrium was established in 6 h after dissolving in this mixture: 92% hydroxypyrrolidone IIIc and 8% methylenepyrrolidone Ic.

Our data on the addition of alcohols and water to Ia-c are in agreement with the principles of electrophilic addition of alcohols and waters to olefins, which occurs under acid catalysis conditions, obeys the Markownikoff rule, and is accelerated by electron-donor substituents attached to the double bond [12-14].

EXPERIMENTAL

The PMR spectra were recorded with a Hitachi-Perkin-Elmer R-20A spectrometer. The solution concentration was 0.4 mole/liter, and the internal standards were hexamethyldisiloxane (HMDS) and sodium 2,2-dimethyl-2-silapentane-5-sulfonate (for aqueous solutions). The mass spectra were recorded with a JMS-01G2 spectrometer with "direct" introduction of the sample into the ion source at an ionizing voltage of 75 eV and a sample temperature of 50°. Peaks with intensities greater than 10% of the maximum are presented. The numbers in front of the parentheses indicate the mass number, while the numbers in parentheses indicate the relative intensity of the ion peak with respect to the maximum peak.

3,3-Dimethyl-2-methylene-5-pyrrolidone (Ia). A) A 2-g (0.014 mole) sample of 2,3,3-trimethyl-2-hydroxy-5-pyrrolidone (IIIa) was vacuum sublimed at 160-165° and 1-2 mm for 6 min to give 1.75 g (87.5%) of white crystals, which dissolved rapidly in an anhydrous organic solvent (benzene, chloroform, etc.) in a dry nitrogen atmosphere. According to the PMR spectra the compound is pure methylenepyrrolidone Ia, which does not contain admixtures of other compounds (Table 2).

The compound is very readily hydrated by moist air, and a mixture of methylenepyrrolidone Ia and hydroxypyrrolidone IIIa (1 : 1 according to the PMR spectrum of a solution in chloroform) is formed during elementary analysis. Found: C 62.6; H 9.3; N 10.3%. $C_7H_{11}NO \cdot C_7H_{13}NO_2$. Calculated: C 62.7; H 9.1; N 10.4%.

B) Similar treatment of 0.47 g (3 mmole) of 2,3,3-trimethyl-2-methoxy-5-pyrrolidone (IIa) gave 0.36 g (96%) of white crystals of IIIa, which was identical to the compound described above, according to the PMR spectra.

3,3-Dimethyl-1-phenyl-2-methylene-5-pyrrolidone (Ic). The procedure used to obtain Ia was used to prepare 0.19 g (95%) of this compound by sublimation of 0.22 g (10 mmole) of 2,3,3-trimethyl-1-phenyl-2-hydroxy-5-pyrrolidone (IIIc). Found: C 75.3; H 7.4; N 6.7%. $C_{13}H_{15}NO \cdot 0.5C_{13}H_{17}NO_2$. Calculated: C 75.5; H 7.6; N 6.8%.

1,3,3-Trimethyl-2-methylene-5-pyrrolidone (Ib). A 20-ml sample of liquid methylamine was added to a solution of 1.62 g (0.01 mole) of 4-chloro-3,3,4-trimethyl-4-butanolide in 10 ml of chloroform, and the mixture was maintained in a bomb at 20° for 4 days. The solvent was allowed to evaporate freely, and the methylamide hydrochloride was separated to give 1.54 g (98%) of oily 1,2,3,3-tetramethyl-2-hydroxy-5-pyrrolidone (IIIb), which, according to the PMR spectra, was identical to the sample obtained by another method [1]. The isolated hydroxypyrrolidone (IIIb) was then maintained in a vacuum (8-10 mm) at 20° for 3 h to give a quantitative yield of methylenepyrrolidone Ib. Found: 9.8%. $C_8H_{13}NO$. Calculated: N 10.0%.

The yield of methylenepyrrolidone Ib with bp 75-79° (0.03 mm) was 83% when 1,2,3,3-tetramethyl-2-hydroxy-5-pyrrolidone (IIIb) was vacuum distilled.

2,3,3-Trimethyl-2-methoxy-5-pyrrolidone (IIa). A 0.50-g (4 mmole) sample of 3,3-dimethyl-2-methylene-5-pyrrolidone (Ia) was dissolved in 50 ml of absolute methanol, and the mixture was maintained at 20° for 30 days. The methanol was then removed by vacuum distillation at 30-40° and a residual pressure of 15 mm, and the residue was dried thoroughly in vacuo (2 mm) at 20° to give 0.63 g (100%) of an oily product. Found: C 61.4; H 9.0; N 8.9%; M (Mass spectrometrically): 157. $C_8H_{15}NO_2$. Calculated: C 61.1; H 9.6; N 8.9%; M 157.2. Mass spectrum: 27 (25.3), 28 (11.9), 29 (15.5), 39 (54.7), 40 (18.8), 41 (97.3), 42 (44.0), 53 (12.1), 55 (20.4), 56 (32.4), 57 (11.5), 67 (20.4), 82 (49.3), 83 (12.1), 110 (100), 125 (29.1).

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