SYNTHESES OF DI- AND TETRAHYDROPYRROLES

XI.* ALCOHOLYSIS AND CYANATION OF 2,3,3-TRIMETHYL-2-HYDROXY-5-PYRROLIDONE AND ITS DERIVATIVES

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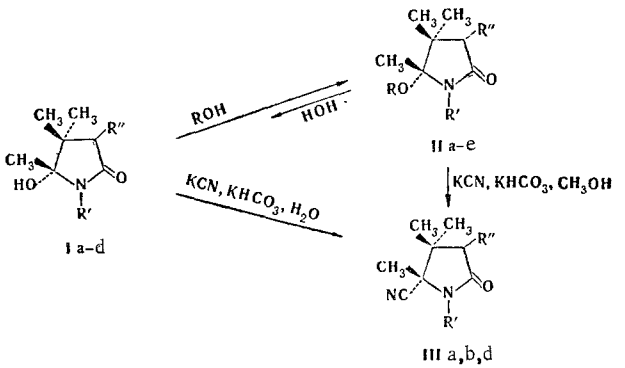
The alcoholysis and cyanation of 2-hydroxy-5-pyrrolidone derivatives are nucleophilic substitution reactions that take place at the hydroxyl and alkoxy groups.

2-Alkoxy- and 2-cyano-5-pyrrolidones are important intermediates in the synthesis of corrins [2, 3].

In the present research we have intestigated the alcoholysis and cyanation of 2,3,3-trimethyl-2-hydroxy-5-pyrrolidone (Ia) and its substituted derivatives (Ib-d). In contrast to the data in the literature regarding the inert character of the hydroxyl group of substituted 2-hydroxy-5-pyrrolidones in a number of chemical reactions (with diazomethane, dimethyl sulfate, isocyanate, acetic anhydride, acetyl chloride, and thionyl chloride) [4-11], we have shown that the hydroxyl group in the 2-position in 2,3,3-trimethyl-2-hydroxy-5-pyrrolidone (Ia) and its substituted derivatives (Ib-d) is readily replaced by alkoxy and cyano groups.

The alcoholysis of Ia-d proceeds with unusual ease in alcohol solutions in the absence of acid catalysts. Thus methanolysis of hydroxypyrrolidone Ia† at 20°C is complete in 3 h. According to all of the data obtained (IR, PMR, and mass spectra, elementary analysis, and vacuum thermolysis), IIa proved to be identical to the previously described [1] 2,3,3-trimethyl-2-methoxy-5-pyrrolidone. Like methoxy derivative IIa, the other alkoxy derivatives (IIb-f) have characteristic PMR spectra that are similar to those presented in [1].



I, III a R′=R″=H; b R′=CH_3, R″=H; c R′=C_6H_5, R″=H; d R′=H, R″=$CONH_2$; II a–e R″=H; 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=CD_3; e R′=C_6H_5, R=CH_3; II f R″=$CONH_2$, R′=H, R=CD_3

* For Communication X see [1].

†We have previously assumed [12, 13] the possibility of the development of the 2-iminotetrahydrofuran form, which is a tautomer of hydroxypyrrolidone Ia, for Ia in alcohol solution.

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The alcoholysis of hydroxypyrrolidones Ia and Id is readily followed quantitatively by comparison of the intensities of the signals of the protons of the methylene groups in the 4-position (AB system) or of the 2-CH_3 groups in the hydroxy(alkoxy) compounds. Monitoring of the alcoholysis of 1-methyl- and 1-phenyl-2,3,3-trimethyl-2-hydroxy-5-pyrrolidone (Ib and Ic, respectively) in alcohol solutions proved to be impossible because of the superimposition of the chemical shifts of the signals of the hydroxy and methoxy derivatives. In order to quantitatively follow the methanolysis of these compounds we used solutions of hydroxypyrrolidones Ib, c in nitrobenzene in the presence of a threefold excess of methanol. Under these conditions, it becomes possible to quantitatively follow the course of the process using a comparison of the intensities not only of the signals listed above but also of the signal of the methoxy group at 3.10 and 3.27 ppm of IId and IIe, respectively. The alcoholysis of hydroxypyrrolidone Ia in ethanol and 2-propanol proceeds with somewhat more difficulty than methanolysis. Thus, at 34° the percentage of ethoxy derivative IIb is 78% (after 6 days), while the percentage of IIc is 16% (after 7 days). It should be noted that in the face of such a prolonged time required to establish equilibrium, spontaneous dehydration of hydroxypyrrolidone Ia begins to appear (see [14]); the presence of 3,3-dimethyl-2-methylene-5-pyrrolidone (13% in ethanol and 18% in isopropyl alcohol, respectively) is detected in equilibrium mixtures of Ia-IIb, c.

A similar pattern is observed in the methanolysis of the methyl (Ib) and phenyl (Ic) analogs of hydroxypyrrolidone Ia. Thus, in nitrobenzene solution in the presence of a threefold excess of methanol, the percentages in the equilibrium mixture of the corresponding methoxy derivative (II) and methylenepyrrolidone are ~42 and 35% (after 31 days) for the methyl analog (Ib) and ~24 and 32% (after 42 days) for the phenyl derivative (Ic).

2,3,3-Trimethyl-2-hydroxy-4-carbamido-5-pyrrolidone (Id) [14], which is resistant to dehydration in solutions, does not undergo this reaction in methanol solution; methoxy derivative IIf (44%) and starting hydroxypyrrolidone Id (56%) are detected in it 8 months after dissolving.

Practically no deuterium exchange of the hydrogen attached to nitrogen or in the methyl group in the 2-position occurs in the alcoholysis of hydroxypyrrolidones Ia-d in deuterated alcohol solutions. This provides a basis for assuming that the reaction proceeds as direct nucleophilic substitution with the participation of the hydroxyl group of I rather than by addition of alcohol to the initially formed (as a consequence of dehydration) 2-methylene-5-pyrrolidone (5-oxo-1-pyrroline) derivatives or to the open tautomeric forms of Ia-c (with subsequent recyclization), inasmuch as deuterium exchange in the NH or 2-CH_3 groups should have been observed in these cases. In addition, as we have shown in [1], genuine substituted 2-methylene-5-pyrrolidones add alcohol (under similar conditions) and form alkoxy derivatives very slowly.

As it turned out, the alcoholysis of 2-hydroxypyrrolidones Ia-d is a reversible process. Methoxypyrrolidone IIa is very readily converted to hydroxypyrrolidone Ia by the action of water. An increase in the temperature accelerates the alcoholysis and shifts the equilibrium to the right. When the hydroxypyrrolidone concentration is increased, alcoholysis is inhibited, and the equilibrium is shifted to the left. The addition of acidic (phenols and acetic acid) and alkaline (NaOD, CD_3ONa) agents does not have a significant effect on the rate of the process and the state of the equilibrium.

We have previously [15] shown that the hydroxyl group in hydroxypyrrolidone Ia is capable of being replaced by a cyano group. In the present research we have established that 1,2,3,3-tetramethyl-2-hydroxy-5-pyrrolidone (Ib) and 2,3,3-trimethyl-2-hydroxy-4-carbamido-5-pyrrolidone (Ib) undergo cyanation in the presence of potassium bicarbonate and potassium cyanide in D_2O solution, while 2,3,3-trimethyl-2-methoxy-5-pyrrolidone (IIa) undergoes cyanation in methanol solution. In this case, methoxypyrrolidone IIa forms 2,3,3-trimethyl-2-cyano-5-pyrrolidone (IIIa), which has a characteristic PMR spectrum that is identical to the spectrum of the sample previously obtained in [15].

In contrast to nitrogen-unsubstituted hydroxypyrrolidone Ia, cyanation does not proceed at all in the case of Ib and Id. Carbamidohydroxypyrrolidone Id forms unstable cyano derivative IIId (which decomposes on subsequent cyanation). In this case the process is interrupted (it is carried out for a few minutes), and the yield of cyano derivative IIId in this case is 51%.

Replacement of the hydroxyl group in Id by a cyano group in the 2-position leads to a shift to strong field of the signal of the 4-H proton (by 0.21 ppm) and a small shift to weak field of the signal of the 2-CH_3 group (by 0.06 ppm; see [14]) in the PMR spectrum of cyano derivative IIId in pyridine solution.

Cyanation of Ib gives an equilibrium mixture containing, according to PMR spectroscopic data, 67% 1,2,3,3-tetramethyl-2-cyano-5-pyrrolidone (IIIb) and 33% of starting hydroxypyrrolidone Ib, which could not be separated. The conclusion regarding the formation of cyano derivative IIIb in this case was made on the

basis of the coincidence of its PMR spectra with the PMR spectra of 1-unsubstituted analog IIIa in D_2O, CCl_4, and $CDCl_3$ solutions. In the PMR spectrum of IIIb in $CDCl_3$, for example, one observes the characteristic (also for IIIa) signals of geminal methyl groups at 1.09 and 1.36 ppm and of the 2-CH_3 group at 1.51 ppm, which are shifted to the weaker field as compared with the corresponding signals of starting hydroxypyrrolidone Ib (see [14]). The protons in the 4-position of IIIb appear as a singlet at 2.32 ppm, while the signal of the methyl group attached to the nitrogen appears at 2.88 ppm. In contrast to IIIa, cyano derivative IIIb is readily hydrolyzed by water to hydroxypyrrolidone Ib; this is apparently related to the +I effect of the methyl group in the 1-position. 2,3,3-Trimethyl-1-phenyl-2-hydroxy-5-pyrrolidone (Ic) does not undergo cyanation. The effect of substituents attached to the nitrogen atom of hydroxypyrrolidones Ia-c on cyanation makes it possible to suppose that this reaction does not proceed through ring opening with subsequent recyclization, inasmuch as N-phenylhydroxypyrrolidone Ic, which forms an open tautomeric form most readily of all of the compounds [14], should be most reactive in this case.

In the cyanation of substituted 2-hydroxy-5-pyrrolidone Ia, b in D_2O solution, cyano derivatives IIIa, b are formed more rapidly (on the basis of an analysis of the PMR spectra) than the protons of the 2-CH_3 group undergo deuterium exchange. It follows from this that the cyanation of Ia, b does not proceed via addition of a cyanide ion to the initially formed (during dehydration) 2-methylene-5-pyrrolidone or its N-acylketimine form (see [3, 16]). Thus, the cyanation (like the alcoholysis) of substituted 2-hydroxy-5-pyrrolidones Ia-d probably should be considered to be a reaction involving nucleophilic substitution of the hydroxyl group in the 2-position.

In this case, the increased electron density on the 2-C atom, which arises as a consequence of the inductive effective (or the +C effect) of the nitrogen atom, will probably facilitate the formation of the transition state during nucleophilic reactions.

EXPERIMENTAL

The IR spectra of the compounds were recorded with a UR-10 spectrometer. The PMR spectra were recorded with a Hitachi-Perkin-Elmer R-20A spectrometer. The solution concentrations were 0.4 mole/liter. Hexamethyldisiloxane and sodium 2,2-dimethyl-4-silapentane-1-sulfonate (for D_2O solutions) were used as the internal standard. The mass spectra were recorded with JMS-01SG2 spectrometer with "direct" introduction of the sample into the ion source at an ionizing voltage of 75 eV and a sample temperature of 50°.*

2,2,3-Trimethyl-2-methoxy-5-pyrrolidone (IIa). A 0.70-g (5 mmole) sample of 2,3,3-trimethyl-2-hydroxy-5-pyrrolidone was dissolved in 100 ml of absolute methanol, and the mixture was maintained at 20° for 24 h, after which the methanol was removed by vacuum distillation at 20-30°, and the residue was dried thoroughly in vacuo (2 mm) at 20° to give a quantitative yield of oily methoxypyrrolidone IIa.

Mass spectrum: 27 (22.8), 28 (14.9), 29 (20.6), 39 (48.7), 40 (16.5), 41 (85.1), 42 (48.1), 43 (11.1), 53 (13.0), 55 (21.3), 56 (49.6), 57 (16.4), 67 (25.7), 82 (46.4), 83 (14.9), 110 (100), 125 (30.9), 126 (10). PMR spectrum, δ, ppm (in nitrobenzene): 3-$(CH_3)_2$ 1.10 (s, 3H) and 1.17 (s, 3H); 2-CH_3 1.40 (s, 3H); 4-CH_AH_B 1.87/2.14/2.47/2.75/ (q, AB system, 2H, J_{AB} = 16.5 Hz); 2-OCH_3 3.16 (s, 3H). The PMR spectrum of a nitrobenzene solution of the sample showed that it contained 0.37 mole of methanol. Found: C 59.5; H 9.4; N 8.2%; M (Mass spectrometrically) 157. $C_8H_{15}NO_2 + 0.37\ CH_3OH$. Calculated: C 59.4; H 9.8; N 8.2%; M 157.2.

Reaction of 2,3,3-Trimethyl-2-methoxy-5-pyrrolidone (IIa) with Potassium Cyanide. A 0.33-g (3.3 mmole) sample of potassium bicarbonate and 0.22 g (3.3 mmole) of potassium cyanide were added to a solution of 0.47 g (3 mmole) of methoxypyrrolidone IIa in 3 ml of absolute methanol, and the mixture was refluxed and stirred for 40 h, after which the alcohol was removed by distillation, and the residue was extracted with chloroform. The extract was evaporated, and the product was vacuum dried at 20° (2 mm) to give 0.23 g (51%) of crystalline 2,3,3-trimethyl-2-cyano-5-pyrrolidone (IIIa) with mp 192-192.5° (mp 192° [15]). PMR spectrum, δ, ppm (in $CHCl_3$): 3-$(CH_3)_2$ 1.18 (s, 3H) and 1.43 (s, 3H); 2-CH_3 1.59 (s, 3H); 4-CH_AH_B 2.05/2.33/2.43/2.71 (q, 2H, J_{AB} = 16.8 Hz).

Reaction of 1,2,3,3-Tetramethyl-2-hydroxy-5-pyrrolidone (Ib) with Potassium Cyanide. As in the preparation of IIa, a solution of 1.1 g (7 mmole) of hydroxypyrrolidone Ib, 0.5 g (7.7 mmole) of KCN, and 0.77 g (7.7 mmole) of $KHCO_3$ in 20 ml of water was heated at 85-95° for 1.5 h to give 1.04 g of a colorless

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oily product containing, according to the PMR spectrum, 75% 2-cyanopyrrolidone IIIb (67% yield) and 25% of 2-hydroxypyrrolidone Ib (23.6% yield). PMR spectrum of IIIb, δ, ppm (in $CHCl_3$): 3-$(CH_3)_2$ 1.09 (s, 3H) and 1.36 (s, 3H); 2-CH_3 1.51 (s, 3H); 4-CH_2 2.32 (s, 2H); CH_3–N 2.88 (s, 3H).

2-Cyano-2,3,3-trimethyl-4-carbamido-5-pyrrolidone (IIId). A 1.1-g (11 mmole) sample of potassium bicarbonate and 0.72 g (11 mmole) of potassium cyanide were added to a refluxing solution of 1.36 g (10 mmole) of 2,3,3-trimethyl-2-hydroxy-4-carbamido-5-pyrrolidone in 7 ml of water. After 7 min, the reaction mixture was poured over ice, and the precipitated crystals were removed by filtration, washed with water, and vacuum dried to give 1 g (51.3%) of 2-cyano-2,3,3-trimethyl-4-carbamido-5-pyrrolidone with mp 213-213.5°. PMR spectrum, δ, ppm (in C_5H_5N): 3-$(CH_3)_2$ 1.02 (s, 3H) and 1.09 (s, 3H); 2-CH_3 1.51 (s, 3H); 4-CH 3.27 (s, 1H). Found: C 55.2; H 6.7; N 21.7%. $C_9H_{13}N_3O_2$. Calculated: C 55.3; H 6.7; N 21.5%.

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