SYNTHESIS OF DI- AND TETRAHYDROPYRROLES

VIII.* SYNTHESIS AND PROPERTIES OF 2,3,3-TRIMETHYL-2-HYDROXY-5-PYRROLIDONE

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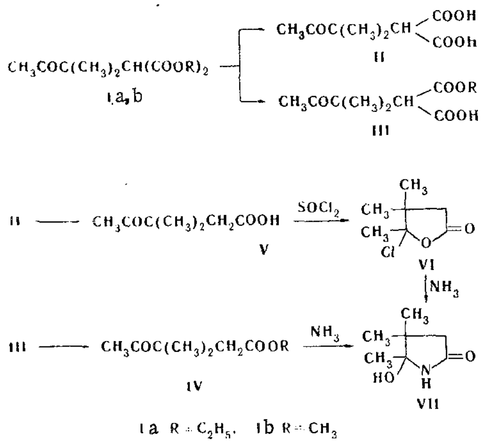
UDC 547.743.1'744'745.07

A method for the synthesis of 2,3,3-trimethyl-2-hydroxy-5-pyrrolidone has been developed. 3,3-Dimethyl-2-methylene-5-pyrrolidone is initially formed during its thermolysis and then readily dimerizes. 2,3,3-Trimethyl-2-cyano-5-pyrrolidone was synthesized by the reaction of 2,3,3-trimethyl-2-hydroxy-5-pyrrolidone with potassium cyanide.

Methods for the synthesis of dihydropyrrole derivatives – Δ^1-pyrrolines – were described in previous communications of this series [1] along with their chemical properties. This paper is devoted to the synthesis and investigation of some properties of tetrahydropyrrole derivatives, namely, 2,3,3-trimethyl-2-hydroxy-5-pyrrolidone (VII).

It should be noted that the product of the dehydration of hydroxypyrrolidone VII – 3,3-dimethyl-2-methylene-5-pyrrolidone (VIII) – is a key compound in the synthesis of corrins [2-5]. The synthesis of pyrrolidone VII was accomplished as follows:



In [6] we described a preparatively convenient method for the synthesis of ethyl 3,3-dimethyl-2-carbethoxylevulinate (Ia). Methyl 3,3-dimethyl-2-carbomethoxylevulinate (Ib) was synthesized from dimethyl isopropylidenemalonate and acetaldehyde in the presence of benzoyl peroxide in a manner similar to that used in the synthesis of γ-keto diester Ia [6]. Depending on the conditions used to carry out the process, the alkaline hydrolysis of Ia and Ib leads either to 3,3-dimethyl-2-carboxylevulinic acid (2) or to its acid ester (III). Acid ester IIIa in low yields (4-6%) is the chief product when Ia is hydrolyzed under

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*See [1] for communication VII.

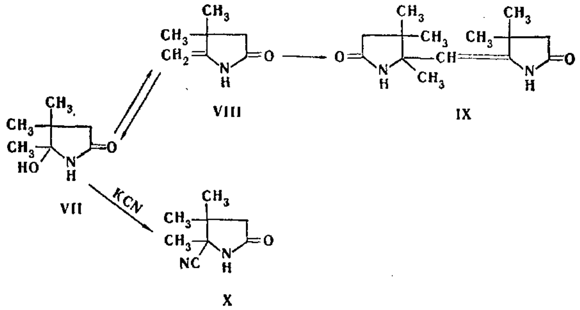
All-Union Scientific-Research Vitamin Institute, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1190-1193, September, 1971. Original article submitted November 4, 1970.

mild conditions (with 1 N NaOH at 90° for 30 min). Decarboxylation of IIIa at 170-180° leads to ethyl 3,3-dimethyllevulinate,* which proved to be identical to keto ester IVa obtained by esterification of 3,3-dimethyllevulinic acid (V) with ethyl orthoformate. Only the ketodicarboxylic acid (II) is formed in 75-82% yield when Ia and b are hydrolyzed under more severe conditions (3 N KOH at 100° for 80 h or 60% aqueous KOH at 25° for 24 h).

The decarboxylation of acid II yielded 3,3-dimethyllevulinic acid (V) (see [7]), which was converted to γ-chloro-γ,β,β-trimethylbutyrolactone (VI) by reaction with thionyl chloride. The nonequivalency of the geminal methyl groups and the protons of the methylene group (an AB system) displayed in the PMR spectrum of lactone VI attests to its cyclic structure.

The ammonolysis of keto ester IVa and lactone VI yielded the same product – the amide of 3,3-dimethyllevulinic acid which, according to the PMR and IR spectra, is the predominant form in solutions, while the cyclic form – 2,3,3-trimethyl-2-hydroxy-5-pyrrolidone (VII) – is apparently the exclusive form in the solid state.† Signals of two nonequivalent geminal methyl groups (1.01 and 1.10 ppm) and nonequivalent protons of the methylene group (1.80, 2.08, 2.41, and 2.69 ppm, AB system, J 16 Hz) are observed in the PMR spectrum of a chloroform solution of hydroxypyrrolidone VII, which unambiguously attests to the cyclic structure of this compound. The chemical shifts and intensities of the signals of the 2-CH$_3$ (1.32 ppm), OH (4.75 ppm), and NH (7.55 ppm) groups are also in agreement with structure VII.

Brief heating (10-15 min) of hydroxypyrrolidone VII in CDCl$_3$ and d$_5$-pyridine at 60-80° leads to its dehydration and conversion to 3,3-dimethyl-2-methylene-5-pyrrolidone (VIII):



The characteristic signals of two nonequivalent olefinic protons are displayed in the PMR spectra of VIII in the solvents indicated above: doublets at 4.00 and 4.20 ppm (J 1.8 Hz) in CDCl$_3$ and at 4.00 and 4.35 ppm (J 1.4 Hz) in d$_5$-pyridine.

More prolonged heating of VII (3-5 h) is accompanied by quantitative conversion to a dimer (IX) of the initially formed methylenepyrrolidone (VIII). The same dimer (IX) was isolated from the ammonolysis of 3,3-dimethyllevulinic acid under the conditions presented in [7]. The PMR spectrum of dimer IX in CDCl$_3$ contains a singlet from one olefin proton at 4.17 ppm, two geminal methyl groups at 1.00 ppm and two at 1.18 ppm, one methyl group at 1.23 ppm, the protons of two methylene groups at 2.08 and 2.15 ppm, and protons of NH groups at 8.55 ppm. The IR spectrum of this dimer contains absorption bands of the stretching vibrations of two carbonyl groups at 1680 and 1745 cm^{-1}, a double bond at 1655 cm^{-1} and lactam NH groups at 3435 cm^{-1}. On the basis of these data and a determination of the molecular weight, we assigned the 3,3-dimethyl-2-methylene-5-pyrrolidone structure (IX) to the dimer (see [4], for example).

Hydroxypyrrolidone VII readily reacts with potassium cyanide in aqueous potassium bicarbonate. The structure of the product of this reaction – 2,3,3-trimethyl-2-cyano-5-pyrrolidone (X) – was unambiguously established on the basis of the PMR and IR spectra, which proved to be identical to the spectra of X synthesized previously [2] by the addition of potassium cyanide to methylenepyrrolidone VIII under similar conditions. Our result is evidence that, in the latter case, the process may occur with preliminary conversion

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*The hydrolysis and decarboxylation of Ia are more conveniently carried out in one step, i.e., without isolation of IIIa in the pure state.

†A special communication will be devoted to the ring-chain tautomerism of amides and a number of other 3,3-dimethyllevulinic acid derivatives in solution.

of VIII in aqueous alkali to hydroxypyrrolidone VII, which also reacts with potassium cyanide, rather than by means of addition of the cyanide anion to the N-acylketimine form of methylenepyrrolidone VIII, as assumed in [2].

Thus the possibility of the use of hydroxypyrrolidone VII instead of methylenepyrrolidone VIII for setting up a "nitrile" protection in the synthesis of corrins [3] is obvious. Since the proposed method for the synthesis of hydroxypyrrolidone VII has a number of advantages as compared with the literature method for the synthesis of methylenepyrrolidone VIII [2, 3, 7] (smaller number of steps, high yield, greater simplicity in isolating and purifying the final product), VII can apparently be successfully used in the synthesis of the right-hand half of model corrin systems (see [3]).

EXPERIMENTAL

The IR spectra of III (in mineral oil), V (thin layer), and VII and X (in $CHCl_3$) were recorded with a UR-10 spectrophotometer. The PMR spectra were recorded with a Varian DA-60 spectrometer (60 MHz). The internal standard was hexamethyldisiloxane. Thin-layer chromatography of the compounds was carried out on activity III aluminum oxide in a hexane–ethyl acetate system (13 : 3). The substances were detected with iodine vapors. Gas-liquid chromatography was accomplished with an LKhM-7A chromatograph with a 1-m long column, 12% polybutanediol succinate on Chromosorb W as the stationary phase, a column temperature of 145°, and a helium flow rate of 40 ml/min. The retention times were as follows: Ib 375 sec, IVa 90 sec, V 6868 sec, VI 90 sec, and VII 334 sec.

Dimethyl Isopropylidenemalonate. This compound [745 g (87%)] was obtained from 660 g (5 moles) of dimethyl malonate and 435 g (7.5 mole) of acetone by a method similar to that in [8] and had bp 72-73° (2 mm), R_f 0.66, d_4^{20} 1.076 and n_D^{20} 1.4559. Found %: C 56.2, 56.4; H 7.1, 7.1; MR_D 43.47. $C_8H_{12}O_4$. Calculated %: C 55.8; H 7.0; MR_D 41.98.

Methyl 3,3-Dimethyl-2-carbomethoxylevulinate (Ib). This compound [41.2 g (95%)] was obtained from 34.4 g (0.2 mole) of dimethyl isopropylidene malonate, 57 g (1.3 mole) of acetaldehyde, and 4.85 g of benzoyl peroxide by a method similar to that in [6] and had bp 92-93° (2 mm), R_f 0.52, d_4^{20} 1.1101, and n_D^{20} 1.4512. Found %: C 55.6, 55.6; H 7.5, 7.3; MR_D 52.35. $C_{10}H_{16}O_5$. Calculated %: C 55.5; H 7.5; MR_D 51.70.

Hydrolysis of γ-Keto Diester I. A. (Under severe conditions.) A mixture of 10.8 g (0.05 mole) of Ib, 6.5 g of KOH, and 20 ml of water was held at 18-20° for 24 h and extracted with ether. The aqueous layer was acidified and extracted with chloroform. The aqueous layer was then evaporated to dryness, and the residue was washed successively with chloroform and methanol. The combined methanol and chloroform extracts were dried, and the solvents were evaporated to give 7.75 g (82%) of 3,3-dimethyl-2-carboxylevulinic acid (II) with mp 120-121° [7] (from benzene–ethanol). IR spectrum, cm^{-1}: ν_{CO} 1710 and 1740, ν_{OH} 3340. PMR spectrum, δ, ppm (in $CDCl_3$): $(CH_3)_2C$ 1.02, CH_3CO 2.2, CH 2.63, COOH 5.2.

Acid II was obtained in 79% yield under the same conditions from Ia.

B. (Under mild conditions). A mixture of 12.2 g (0.05 mole) of Ia, 3.2 g of NaOH, and 52 ml of 30% aqueous ethanol was refluxed for 30 min. The mixture was worked up as described above and distilled to give 0.34 g (3.9%) of ethyl 3,3-dimethyllevulinate (IVa) with bp 55° (0.85 mm) [9] and R_f 0.58. PMR spectrum, δ, ppm (in CS_2): $(CH_3)_2$ 1.08, CH_3CO 2.0, CH_2 2.35, $COOC_2H_5$ quartet 3.92 and triplet 1.12. According to thin-layer chromatography and gas-liquid chromatography, this compound was identical to a sample of IVa [85% yield with bp 55-56° (0.85 mm)] obtained by heating a mixture of 77.7 g of 3,3-dimethyllevulinic acid (V) and 89 g of ethyl orthoformate for 7 h at 140°. In addition, 0.18 g (2%) of 3,3-dimethyllevulinic acid (V) with bp 90-91° (0.85 mm) [7] and R_f 0.22 was isolated. IR spectrum, cm^{-1}: ν_{CO} 1710, ν_{OH} 2970. PMR spectrum, δ, ppm (in CCl_4): $(CH_3)_2$ 1.15, CH_3CO 2.05, CH_2 2.49, COOH 10.6.

γ-Chloro-γ,β,β-trimethylbutyrolactone (VI). A mixture of 14.4 g (0.1 mole) of 3,3-dimethyllevulinic acid (V) and 16.6 g (0.14 mole) of thionyl chloride was refluxed until hydrogen chloride evolution ceased (3 h) and then distilled to give 5.6 g (43%) of lactone VI* with bp 78° (7 mm), d_4^{20} 1.081 and n_D^{20} 1.4565. Found %: C 52.1, 52.2; H 6.8, 6.6; MR_D 40.89. $C_7H_{11}ClO_2$. Calculated %: C 51.7; H 6.8; MR_D 39.42. PMR spectrum, δ, ppm (in CCl_4): $(CH_3)_2C$ 1.1 and 1.29, 5-CH_3 1.83, CH_2 1.98, 2.25, 2.59, 2.85 (AB system, J 16 Hz).

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*Only a melting point of 86° is given in the literature for lactone VI [2].

2,3,3-Trimethyl-2-hydroxy-5-pyrrolidone (VII). A. Dry ammonia was passed through a solution of 1.62 g (0.01 mole) of lactone VI in 15 ml of toluene with cooling to 0° for 2 h. Evaporation of the reaction mixture and separation of the ammonium chloride yielded 1.42 g (99%) of hydroxypyrrolidone VII* with mp 83-83.5° (from toluene). Found %: C 58.7, 58.9; H 9.1, 9.0; N 9.8, 9.8. $C_7H_{13}NO_2$. Calculated %: C 58.7; H 9.2; N 9.8. IR spectrum, cm^{-1}: ν_{CO} 1708-1715, ν_{NH} 3425, ν_{OH} 3610.

B. A solution of 51.6 g (0.3 mole) of IVa in 200 ml of anhydrous ethanol saturated with ammonia was heated in a bomb at 90-100° for 80 h. The solvent was then removed by distillation, and the residue was recrystallized from benzene–ethanol to give 37.8 g (91%) of a product with mp 83-83.5°. This product did not depress the melting point of a sample obtained by method A.

Dimer of 3,3-Dimethyl-2-methylene-5-pyrrolidone (IX). A total of 2.1 g of an oily substance was obtained from 4.34 g (0.03 mole) of 3,3-dimethyllevulinic acid and 25 ml of ammonium hydroxide by the method in [7]. This substance was vacuum distilled, and the residue from the distillation was washed successively with methanol and ether to give 0.24 g (6.5%) of dimer IX with mp 189.5-190.5°. Found %: C 67.2, 67.4; H 9.2, 9.1; N 10.5, 10.8; mol. wt. (from mass spectrometry) 250. $C_{14}H_{22}N_2O_3$. Calculated %: C 67.2; H 8.9; N 11.2; mol. wt. 250.

2,3,3-Trimethyl-2-cyano-5-pyrrolidone (X). Potassium bicarbonate [3.3 g (0.033 mole)] and 2.15 g (0.033 mole) of potassium cyanide were added to a solution of 4.3 g (0.03 mole) of VII in 16 ml of water, and the mixture was heated at 85-95° for 3 h. The upper oily layer was separated, and the aqueous layer was extracted with ether. The aqueous layer was then evaporated to dryness, and the residue was extracted with chloroform. The combined extracts were dried with sodium sulfate, the solvent was evaporated, and the residue was recrystallized from hexane–chloroform to give 3.82 g (85%) of a product with mp 192-192.5° [3].

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* The yield of VII was 90% based on acid V in the ammonolysis of undistilled lactone VI.