CONDENSATION REACTIONS INVOLVING THE α -METHYLENE GROUP IN SERIES OF 5-ALKYLPYRROLIDINE-2-THIONES AND 5-ALKYL-1-ACETYL-2-PYRROLIDONES

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It is shown that 1-substituted and N-unsubstituted 5-R-pyrrolidine-2-thiones, in contrast to their oxygen analogs, undergo methylenethioalkylation and the Mannich and Michael reactions at the 3 position of the ring; this is due to their higher CH acidity. The results of quantum-chemical calculations (by the MO LCAO method within the CNDO/2 approximation) confirm the similar reactivities of pyrrolidine-2-thiones and 1-acetyl-substituted 2-pyrrolidones.

We have previously reported [1, 2] that 5-R-1-acetyl-2-pyrrolidones Ia and 5-R-pyrrolidine-2-thiones (Ib, c) undergo the Mannich reaction and methylenethicalkylation under acidiccatalysis conditions.

In the present paper we present the results of a more extensive investigation of the indicated reactions, including the Michael reaction, which proceeds under alkaline-catalysis conditions:



I, II a $R^1 = C_3H_7$, $R^2 = COCH_3$, X = O; b $R^1 = C_3H_7$, $R^2 = H$, X = S; c $R^1 = C_4H_9$, $R^2 = CH_3$, X = S; III $R^1 = C_4H_9$; IV a $R^1 = C_3H_7$, $R^2 = H$, X = S; b $R^1 = C_4H_9$, $R^2 = H$, X = S; V $R^1 = C_3H_7$, $R^2 = H$, X = S; VI a $R^1 = C_3H_7$, $R^2 = CH_3$, $R^3 = p \cdot C_6H_4OCH_3$, X = S; b $R^1 = C_3H_7$, $R^2 = COCH_3$, $R^3 = p \cdot C_6H_4N(CH_3)_2$, X = S

Signals of the proton of an NH group at 8.05 ppm (s, 1H), a 3-H proton at 4.15 ppm (t, 1H), and $N(CH_3)_2$ group at 2.91 ppm (s, 6H), and a CH_2 -N group at 2.45 ppm (t, 2H) are recorded in the PMR spectra of bases IIa-c.

To confirm the proposed aminomethylation pathway, IIa was reduced with LiAlH₄; not only reduction of the carbonyl (IIa) and thiocarbonyl (IIb) groups but also, in the case of base IIa, splitting out of the acetyl group with the formation of 5-propyl-3-(N,N-dimethylaminomethyl)pyrrolidine (III) occurred in this case. Signals of a proton of an NH group (8.05 ppm), a 3-H proton (4.15 ppm), an N(CH₃)₂ group (3.11 ppm), and a CH₂-N group (2.55 ppm) are observed in the PMR spectrum of III. Oxidation of methylenethioalkylation products IVa,b with hydrogen peroxide in acetic acid leads to sulfones V. Intense absorption bands of an SO₂ group (1138 and 1310 cm⁻¹) appear in the IR spectra of sulfone V.

The synthesized Mannich bases II and sulfides IV may be mixtures of isomers. One isomer was isolated by preparative column chromatography. Judging from molecular models, the smallest amount of steric hindrance is present in the case of the trans isomer; however, the PMR spectral data do not make it possible to arrive at a rigorous assignment of the isomers to the cis or trans form.

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TABLE 1. Charge Distribution on the Ring Atoms in 2-Pyrrolidones and Pyrrolidine-2-thiones

Compound	N ₍₁₎	C ₍₂₎	C ₍₃₎	C ₍₄₎	C ₍₅₎	o or S
5-Butyl-2-pyrrolidone	$ \begin{array}{r} -0.237 \\ -0.234 \\ -0.129 \end{array} $	0,346	-0,072	-0,036	0,133	-0,331
5-Butyl-1-acetyl-2-pyrrolidone		0,344	-0,073	-0,039	0,132	-0,310
5-Butylpyrrolidine-2-thione		0,172	-0,033	-0,045	0,124	-0,389

Com- pound	T _{bp} , (mmHg) or T _{mp} , •C	Found, %			Empirical	Calc., % .				Yield,	
		с	н	N	s	formula	c	н	N	s	~/0
IIa IIb IIc IVI IVa IVb V VIa	$\begin{array}{c} 137-139 \ (4) \\ 152-154 \ (5) \\ 154-155 \ (5) \\ 140-141 \ (3) \\ 153-154 \ (3) \\ 132-134 \ (3) \\ 183-184 \\ 147-149 \end{array}$	64,9 60,4 64,7 72,3 57,3 60,3 52,4 72,9	8,3 10,4 10,8 13,4 10,0 10,0 8,6 7,9	12,9 14,6 13,3 15,6 6,1 6,1 6,1 4,0	16,1 15,0 28,2 26,2 13,5 8,4	$\begin{array}{c} C_{12}H_{18}N_2O_2\\ C_{10}H_{20}N_2OS\\ C_{11}H_{22}N_2S\\ C_{11}H_{24}N_2\\ C_{11}H_{24}N_2\\ C_{11}H_{21}N_2S_2\\ C_{13}H_{25}NS_2\\ C_{12}H_{23}NOS_2\\ C_{24}H_{29}NO_2S_2 \end{array}$	64,8 60,0 64,4 71,8 57,2 60,3 52,0 72,9	8,1 10,0 10,7 13,1 9,2 9,7 8,4 7,3	12.6 14,0 15,0 15,2 5,7 6,6 5,9 3,6	16,0 14,9 	65 64 67 63 67 47 65
VIA VIb	147 - 149 121 - 122	72,9 75,0	7,9 7,8	4,0 6 <u>,3</u>	8,4 8,2	$C_{24}H_{29}NO_2S_2$ $C_{26}H_{32}N_2OS$	72,9	7,3	3,0 6,6	0,1 7,5	69

Quantum-chemical calculations of the molecules by the MO LCAO method within the CNDO/2 approximation [3] were carried out to explain the lability of the hydrogen atoms of the α -methylene group. A comparison of the charges on the atoms in the 5-R-2-pyrrolidone and 5-R-1-acetyl-2-pyrrolidone molecules showed that the introduction of an acetyl group relative to the ring nitrogen atom in the 2-pyrrolidone molecule does not affect the charge distribution in the ring: the charges on the C(2) and C(3) atoms virtually coincide.

Replacement of the oxygen atom by a sulfur atom leads to a decrease in the negative charges on the nitrogen and $C_{(3)}$ atoms (Table 1).

A study of maps of the distribution of the molecular electrostatic potential in the examined molecules showed that the distribution in the 5-butyl-2-pyrrolidone molecule differs significantly from the distribution in the 5-butyl-1-acetyl-2-pyrrolidone and 5-butylpyrrolidine-2-thione molecules, in which the field distribution has identical character. The boundary between the positive and negative regions in the 2-pyrrolidone molecule passes along a line that intersects the N-C($_5$) bond, whereas in the case of 1-acetyl-2-pyrrolidone and pyrrolidine-2-thione it is shifted toward the ring heteroatom. The C($_3$) atom in 2-pyrrolidone is located on the zero-potential line, while in the 1-acetyl derivative and pyrrolidine-1-thione molecules the C($_3$) ring atoms lie in the region of a rather strong positive field; this may explain their greater CH acidity.

Thus the similar behavior of pyrrolidine-2-thiones and 1-acetyl-2-pyrrolidones in the indicated reactions is due to the collective properties of the system of charges of the molecules, i.e., to the distribution of the electrostatic potential rather than to the charges on the ring atoms.

EXPERIMENTAL

The PMR spectra were recorded with a Tesla BS-467 spectrometer (60 MHz) with hexamethyldisiloxane (MHDS) as the internal standard. The IR spectra of suspensions of the compounds in mineral oil were recorded with a UR-20 spectrometer. The purity of the compounds obtained was monitored by TLC on Silufol UV-254 plates with chloroform as the eluent.

<u>5-Propyl-3-(dimethylaminomethyl)pyrrolidine-2-thione (IIb) (Table 2)</u>. A 0.9-g (0.01 mole) sample of dimethylamine hydrochloride and 3 ml of 40% formaldehyde were added to 1.5 g (0.01 mole) of 5-propylpyrrolidine-2-thione (Ib) [4] in solution in alcohol, and the reaction mixture was acidified with hydrochloric acid and heated for 40 min. The isolated salt of the Mannich base was treated with alkali. Amine IIb was isolated after extraction with ether and preparative separation by column chromatography (silica gel, hexane-acetone).

<u>5-Propyl-3-(propylthiomethyl)pyrrolidine-2-thione (IVa) (Table 2)</u>. An alcohol solution of equimolar amounts of 5-propylpyrrolidine-2-thione and propyl mercaptan was heated for 40 min, after which the solvent was removed, and the residue was fractioned in vacuo.

<u>5-Propyl-3-(propylsulfonylmethyl)pyrrolidine-2-thione (V)</u>. A 6-ml sample of 28% H₂O₂ was added dropwise with stirring to an ice-cooled solution of 4.62 g (0.02 mole) of sulfide VIb in 10 ml of glacial CH₃COOH. The crystals that precipitated when the mixture was allowed to stand were washed with water. The yield of sulfone V was 2.1 g (47\%).

<u>5-Propyl-1-methyl-3-[1-(4-methoxyphenyl)-3-phenyl-3-oxopropyl]pyrrolidine-2-thione (VIa)</u>. An alcohol solution of 2.86 g (0.02 mole) of 5-propyl-1-methylpyrrolidine-2-thione and 5.3 g (0.3 mole) of p-methoxybenzylideneacetophenone was added dropwise with stirring to a solution of sodium ethoxide (20 ml of absolute ethanol, 0.5 g of Na metal), after which the mixture was heated at 35-40°C for 3 h and then maintained at 20°C for 24 h. The resulting solution was diluted with water and neutralized with 3% hydrochloric acid. The precipitated crystals were separated and dried. The yield of VIa was 4.2 g (65%). Compound VIb was similarly obtained.

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