NEW METHOD FOR SYNTHESIS OF 3-PYRROLIN-2-ONE DERIVATIVES

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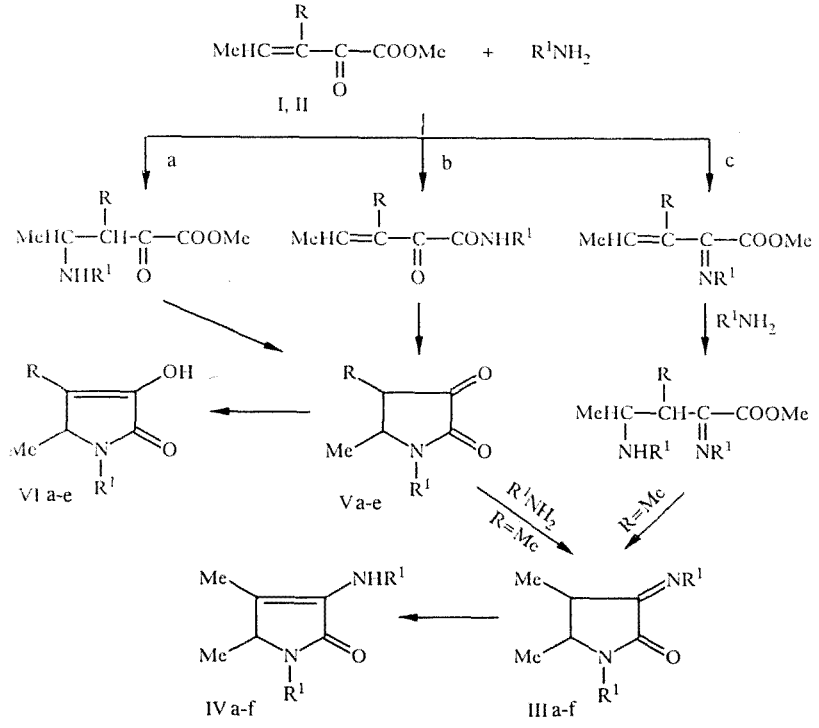
We propose a method for synthesis of derivatives of pyrrolinone by reaction of the methyl ester of 3-substituted 2-oxo-3-pentenoic acid with primary amines or acetylhydrazine.

Pyrrolinones and their derivatives are of interest as intermediates for organic synthesis and as physiologically active substances. Several methods are known for synthesis of pyrrolinone derivatives. Thus, for example, pyrrolinone derivatives can be obtained by reaction of β-ketoesters with primary amines [1]. We also know of synthesis methods based on cyclization of N-acetylaminoketones [2] or photolysis of pyridazinones, accompanied by contraction of the ring [3]. Earlier we reported that the methyl ester of 3-methyl-2-oxo-3-pentenoic acid (I) reacting with methyl- and ethylamines forms 3-pyrrolin-2-one derivatives [4].

With the goal of studying this reaction, in this paper we consider the reaction of ketoester I and its 3-phenyl analog II [5] with different primary amines.



I R = Me; II R = Ph; III, IV R = Me, a R^1 = Me, b R^1 = Et c R^1 = CH_2Ph, d R^1 = C_6H_{11}, e R^1 = $Me_2NCH_2CH_2$, f R^1 = Ph Va, VIa R = Me, R^1 = Ph Vb—e, VIb—e R = Ph, b R^1 = Me, c R^1 = Et, d R^1 = CH_2Ph, e R^1 = C_6H_{11}

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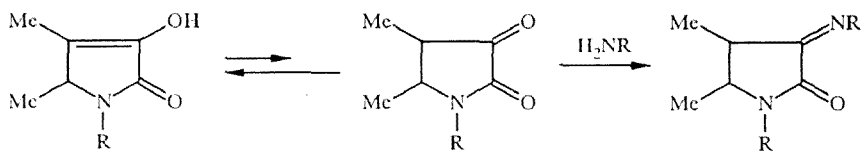
TABLE 1. Some Characteristics of Compounds IVa-g and VIa-g

Compound	Empirical formula	T_{mp}, °C (from ethanol) [T_{bp}, °C (mm)]	Mass spectrum, *m/z* (I_{rel}, %)*	Yield, %
IVa	$C_8H_{14}N_2O$	[120 - 122(6)]	—	85
IVb	$C_{10}H_{18}N_2O$	[105 - 107(1)]	—	80
IVc	$C_{20}H_{22}N_2O$	—	—	91
IVd	$C_{18}H_{30}N_2O$	162 - 164	—	85
IVe	$C_{14}H_{28}N_4O$	—	—	83
IVf	$C_{18}H_{18}N_2O$	181 - 182	M^+ 279(17), 278(84), 264(20), 263(92), 235(31), 187(100), 158(28), 147(58), 146(11)	74
IVg	$C_{10}H_{16}N_4O$	179 - 181	M^+ 240(7), 198(10), 184(10), 182(89), 181(34), 156(18), 155(49), 142(80), 141(14), 140(26), 139(61), 137(50), 127(17), 126(17), 125(32), 112(42), 110(15), 101(15), 97(32), 69(15), 67(11), 60(26), 45(11), 44(30), 43(99), 31(24), 29(18), 28(21), 27(12)	40
VIa	$C_{12}H_{13}NO_2$	177 - 178	M 204(25), 203(100), 188(47), 120(18), 119(34), 118(27), 104(29), 93(16), 83(77), 77(47), 55(30), 29(16)	64
VIb	$C_{12}H_{13}NO_2$	189 - 191	—	90
VIc	$C_{13}H_{15}NO_2$	171 - 173	—	84
VId	$C_{18}H_{17}NO_2$	103 - 105	—	78
VIe	$C_{17}H_{21}NO_2$	176 - 178	—	85
VIf	$C_8H_{22}N_2O_3$	204 - 206	M^+ 184(22), 142(100), 127(10), 126(25), 125(25), 97(25), 83(77), 60(12), 55(23), 43(30)	63
VIg	$C_{13}H_{14}N_2O_3$	197 - 198	M^+ 246(46), 205(11), 204(84), 203(12), 188(22), 187(60), 159(35), 158(14), 145(72), 118(21), 117(100), 116(16), 115(21), 91(12), 49(18)	61

*Ion peaks having an intensity of at least 10% are presented.

Upon reaction of ketoester I with primary amines in a 1:2 ratio, the 3-aminopyrrolinones IV are obtained; and mainly 3-hydroxypyrrolinones VI are obtained for a 1:1 ratio.

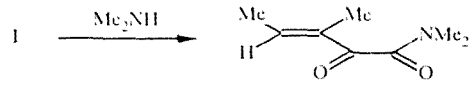
The ketoester II under the conditions indicated above forms exclusively the 3-hydroxypyrrolinones VIb-3. By means of a separate experiment we showed that compounds VIb, d both under the experimental conditions and upon heating at 50-55°C for 2 h do not react with methylamines and are recovered without change. Based on these data, we can conclude that the direction "c" is eliminated for ketoester II. This is probably connected with the fact that the initial product of cyclization of V, having a phenyl group in the 4 position, as it is formed rapidly undergoes prototropic isomerization with formation of the more stable polyconjugated system VI, which prevents further reaction with a second amine molecule.



VI V III

Based on the data presented above, we can say that in the case of ketoester I, imine formation is not the first even of the reaction and in all likelihood occurs even after cyclization, considering the existence to some extent of an equilibrium between the keto and enol forms.

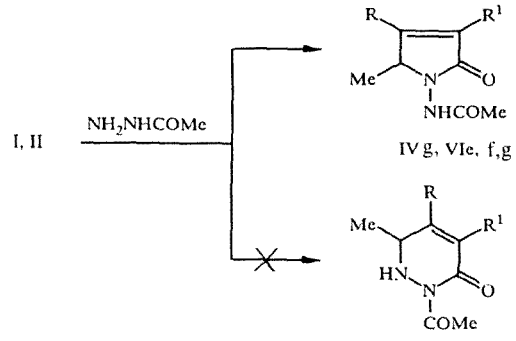
In order to choose between directions "a" and "b", we set up a special experiment. To prevent cyclization, we chose dimethylamine as the amine component. We monitored the course of the reaction by GLC and PMR. The reaction was investigated up to the moment when approximately 60% of the starting ketoester I had reacted (then the reaction considerably slowed down). We found that in this case, formation of only the N,N-dimethylamide of 3-methyl-2-oxo-3-pentenoic acid (VII) occurs; i.e., of the two indicated directions, the reaction occurs exclusively in the "b" direction.



VII

It was of definite interest to study the behavior of ketoesters I and II in the reaction with acetylhydrazine, since in this case formation of both pyrrolinone and pyridazinone derivatives is possible.

According to spectral data (IR, mass spectrum), the pyrrolinone derivatives IVg, VIf, g are formed upon reaction of ketoesters I and II with acetylhydrazine. Thus in the IR spectra of the products of this reaction, there is an absorption band in the 1710-1715 cm^{-1} region, the increased frequency of which makes it unlikely that it should be assigned to the carbonyl group on the six-membered pyridazinone ring. For the latter, a signal from the carbonyl group should be expected in the 1670 cm^{-1} region [6]. Upon formation of a five-membered ring of the pyrrolinone type, an increase in the absorption frequency of the carbonyl group in individual cases may be connected with a decrease in the bond angle in the ring and thus with an increase in the kinematic interaction between the vibrations of the carbonyl group and the adjacent C−C and C−N bonds. In the IR spectrum of compound VIf, we observe absorption bands at 1307, 1665, and 1712 cm^{-1}, characteristic for vibrations of amide groups on a five-membered ring and outside the ring, while an absorption band at 3280 cm^{-1} is typical for the NH group in compound VIf. Similar absorption bands also appear in the IR spectra of compounds IVg and VIg. Besides the presented facts, evidence in favor of formation of a five-membered ring also comes from mass spectral analysis data (Table 1).



IVg R=Me, R^1=NHNHCOMe; VIf R=Me, R^1=OH; VIg R=Ph, R^1=OH

According to the experimental data, acetylhydrazine acts like a primary amine in reaction with ketoesters I and II; i.e., under the indicated conditions we obtain only the 3-hydroxypyrrolinone VIg from ketoester II, and the results of reaction of ketoester I with acetylhydrazine depend on the ratio of the reacting components. Thus for a 1:1 ratio, mainly 3-hydroxypyrroline IVf is isolated, while for a 1:2 ratio only 3-acylhydrazinopyrrolinone IVg is obtained. We also showed that 3-acetylhydrazinopyrrolinone IVg is formed upon reaction of 3-hydroxypyrrolinone IVf with acetylhydrazine.

The spectral characteristics of the compounds obtained are presented in Tables 1 and 2.

EXPERIMENTAL

The IR spectra were taken on the UR-20 and Specord IR-75 in KBr pellets or a thin layer; the UV spectra were taken on the Specord UV-vis in ethanol. The PMR spectra were obtained on the Perkin−Elmer R-12B (60 MHz); as the solvents we used DMSO-d_6, D_2O, and CCl_4, internal standard TMS. The mass spectra were recorded on the MKh-1320 with direction injection of the sample into the ionization region for ionizing potential 50 eV.

Elemental analysis data for C, H, and N correspond to the calculated values. The α-ketoesters I and II were obtained according to the method in [5].

1,4,5-Trimethyl-3-methylaminopyrrolin-3-one (IVa). Gaseous methylamine (0.01 moles) was passed through a cooled (0.5°C) solution of 5.7 g (0.04 moles) ketoester I in 10 ml methanol or ether. The reaction mixture was held at room temperature for 24 h. 5.2 g compound IVa was isolated by distillation; bp 120-122°C/6 mm.

TABLE 2. Spectral Characteristics of Compounds IVa, c, e, f and VIa, b, f, g

Compound	UV spectrum, λ_{max}, nm (log ε)	IR spectrum cm^{-1}				PMR spectrum, δ, ppm (solvent)
		C=C	C=O	H(OH)	C_6H_5	
IVa	—	1635	1680	3340 - 3530	—	1,15 (3H, d, CH_3CH), 1,91 (3H, s, CH_3C=), 2,83 (3H, s, CH_3NH), 2,87 (3H, s, CH_3NCO), 3,48 (1H, q, CH_3CH, J = 6,6) (DMSO-D_6)
IVc	—	1630	1675	3350	710, 750, 785, 1580, 1600, 3035, 3065, 3085	1,02 (3H, d, CH_3CH, J = =6,7), 1,64 (3H, s, CH_3C=), 3,42 (1H, q, CH_3CH, J = =6,7), 3,8 - 5,0 (5H, m, $CH_2C_6H_5$, NH), 7,13 and 7,19 (10H, s, C_6H_5) (DMSO-d_6)
IVe	—	1635	1680	3360	—	1,16 (3H, d, CH_3CH), 1,89 (3H, s, CH_3C=), 2,16 (12H, s, NCH_3), 2,34 and 2,40 (4H, t, CH_3NCH_2, J = 6,7), 2,9 - 3,5 (4H, m, CH_2NCO and $NHCH_2$), 3,71 (1H, q, CH_3CH, J = 6,6), 2,9 - 4,2 (1H, br, NH) (DMSO-d_6)
IVf	207(4,6435), 258(4,3201)	1630	1675	3330	715, 765, 1580, 1597, 3035, 3065, 3085	1,04 (3H, d, CH_3CH, J = =6,8), 1,74 (3H, s, CH_3C=), 4,64 (1H, q, CH_3CH, J = =6,8), 6,6 - 7,5 (10H, m, C_6H_5) (DMSO-d_6)
VIa	207(4,5315), 232(4,3032), 272(3,9518)	—	1680	(3420 - 3435)	720, 770, 1500, 1580, 1610, 3035, 3078	1,05 (3H, d, CH_3CH, J = =6,8), 1,82 (3H, s, CH_3C=), 4,55 (1H, q, CH_3CH, J = =6,8), 7,0...7,7 (5H, m, C_6H_5) (DMSO-d_6)
VIb	—	—	1680	(3420 - 3435)	720, 770, 1580, 1610, 3035, 3080	1,29 (3H, d, CH_3CH, J = =6,6), 3,02 (3H, s, NCH_3), 4,30 (1H, q, $CHCH_3$, J = =6,6), 7,2 - 7,7 (5H, m, C_6H_5), 8,3 (1H, m, OH) (DMSO-d_6)
VIf	217(4,4502), 250(4,1761)	1625	1665, 1712	1307, 3280	—	0,89 (3H, d, CH_3CH, J = =6,7), 1,53 (3H, s, CH_3C=), 1,80 (3H, s, CH_3CO), 4,50 (1H, q, CH_3CH) (D_2O)
VIg	222(3,3010), 287(4,0645)	—	1670, 1712	1310, 3280	698, 761, 1518, 1600	1,08 (3H, d, CH_3CH, J = =6,8), 1,88 (3H, s, CH_3CO), 4,52 (1H, q, CH_3CH), 7,1 - 7,7 (5H, m, C_6H_5) (DMSO-d6)

4,5-Dimethyl-1-ethyl-3-ethylamino-3-pyrrolin-2-one (IVb). A solution of 3.6 g (0.08 moles) ethylamine in 5 ml ether was added dropwise to a solution of 5.7 g (0.04 moles) ketoester I in 5 ml ether. The mixture was held at room temperature for 24 h. 5.8 g compound IVb was isolated by distillation; bp was 105-107°C/1 mm, n_D^{20} 1.5050.

3-Anilino-4,5-dimethyl-1-phenyl-3-pyrrolin-2-one (IVf). A solution of 3.7 g (0.04 moles) aniline in 5 ml methanol was added dropwise to a solution of 2.8 g (0.02 moles) ketoester I in 5 ml methanol at 0-5°C with stirring. The mixture was held for 30 min at 0-5°C, then at room temperature for 24 h. The solvent was driven off, the residue was washed with ether and dried in a dessicator, then recrystallized from ethanol. Obtained: 5.6 g compound IVf.

Compounds IVc-e and VIc-e were obtained similarly to compound IVf.

1-Acylamino-4,5-dimethyl-3-hydroxy-3-pyrrolin-2-one (VIf). A solution of 1.4 g (0.019 moles) acetylhydrazine in 5 ml methanol was added dropwise to a solution of 2.7 g (0.019 moles) ketoester in 5 ml methanol at 0-5°C with stirring. The reaction mixture was held under the specified conditions for 30 min, then at room temperature for 24 h. The methanol was driven off, the residue was washed with absolute ether, filtered off and recrystallized from ethanol. Obtained: 2.2 g compound VIf.

Compounds IVg and VIg were obtained similarly to compound VIf.

1-Acylamino-4,5-dimethyl-3-acylhydrazino-3-pyrrolin-2-one (IVg). Acetylhydrazine (0.52 g, 0.7 mmoles) in 5 ml methanol was added dropwise to a solution of 1.1 g (0.6 moles) 1-acylamino-4,5-dimethyl-3-hydroxy-3-pyrrolin-2-one (VIf) in 5 ml methanol at 0-5°C with stirring. The reaction mixture was held at room temperature for 24 h. The methanol was driven off, the residue was washed with absolute ether, filtered off, and recrystallized from ethanol. Obtained: 0.5 g compound IVg, no depression of mp in a mixture with a known sample.

1,5-Dimethyl-3-hydroxy-4-phenyl-3-pyrrolin-2-one (VIb). Gaseous methylamine (0.025 moles) was passed through a solution of 2 g (0.01 moles) ketoester II in 10 ml ether, cooled down to 0-5°C. The reaction mixture was held for 24 h at 0-5°C. The precipitate was filtered off, washed with ether, and recrystallized from ethanol. Obtained: 1.8 g compound VIb.

N,N,-Dimethylamide of 3-Methyl-2-oxo-3-pentenoic Acid (VII). Dimethylamine (0.6 g, 0.014 moles) was added to a solution of 2.0 g (0.014 moles) ketoester I in 3 ml CCl_4 cooled down to −10°C. The reaction mixture was held for 13 days at −10 to 5°C, and then in ice water for 22 days (the reaction was monitored using GLC and PMR spectroscopy). In this time, 64% of the starting ketoester I reacted, and in the last seven days the amount of ketoester I remained practically constant. 0.3 g(15%) ketoester I was isolated by distillation by 60-65°C/5 mm, n_D^{20} 1.4620 [5] and 0.76 g (35%) N,N-dimethylamide of 3-methyl-2-oxo-3-pentenoic acid (VII). bp 99-102°C/2 mm, n_D^{20} 1.4950. IR spectrum: 820, 1645 (C=CH); 1660 (CON); 1670 cm^{-1} (C=O). PMR spectrum, CCl_4: 1.9 (3H, d, $\underline{CH_3}CH=$), 2.07 (3H, s, $CH_3C=$), 2.9 and 3.1 [6H, s, $CON(CH_3)_2$], 6.25-6.7 ppm (1H, m, ($CH_3\underline{CH}$=CCOO) [7-9].

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