SYNTHESIS OF DERIVATIVES OF N-SUBSTITUTED PYRIDONES FROM DIENIC MONOALKYLAMINOKETO ESTERS

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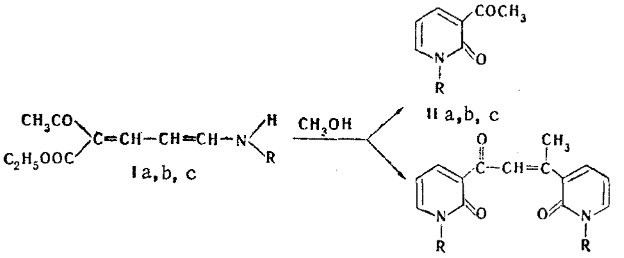
The conversion of dienic δ-monoalkylaminoketo esters into 1-alkyl-3-acetyl-2-pyridones and 1,3-bis[3-(1-alkyl-2-pyridonyl)]-2-buten-1-ones was studied. Heterocyclic analogs of chalcone were synthesized from 1-alkyl-3-acetyl-2-pyridones.

In our preceding paper we described the synthesis and stereochemistry of dienic δ-monoalkylaminoketo esters [1]. This paper is devoted to the study of some of their chemical transformations. We have observed that δ-monoalkylaminoketo esters (I), on dissolving in alcohol at room temperature, are converted in ~80% yield to a readily separable mixture of 1-alkyl-3-acetyl-2-pyridone (II) (Table 1) and 1,3-bis[3-(1-alkyl-2-pyridonyl)]-2-buten-1-one (III) (Table 2), the structures of which were confirmed by the PMR spectra (Tables 3 and 4).



I, II, III a $R=C_3H_7$; $R-C_4H_9$; c $R=CH_2C_6H_5$ III a, b, c

By changing the percentage of water in the alcohol, one can direct the reaction to favor the primary formation of either the 3-acetylpyridone (II) or the "butenone" (III) (some examples of this are presented in Table 5). The conversion of I to a mixture of II and III is accompanied by the generation of ethanol and water (see the experimental section), and the intensity of the absorption in the UV spectrum at 395 nm, which is characteristic for starting esters I, decreases simultaneously. The reaction commences after a certain induction period (from 15 min to several days), the duration of which depends on the concentration of the alcohol solution and the temperature; the reaction can be stopped by the addition of catalytic amounts of $RNHCOONH_3R$ (see Fig. 1), CH_3COONH_4, etc., which are inhibitors in this case. Pyridones II are formed as a result of intramolecular cyclization of keto esters I, which constitute an equilibrium mixture of cis and trans isomers with respect to the α,β-double bond [1]. We were unable to accomplish the cyclization of the ester of 5-butylamino-2,4-pentadienoic acid, which exists as the thermodynamically stable trans isomer.

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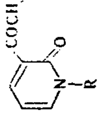
TABLE 1. Yields and Physical Constants of 1-Alkyl-3-acetylpyridones



Compound	R	mp, °C	bp, °C (mm)	n_D^{20}	Empirical formula	Found, %			Calculated, %			M		UV spectrum (in ethanol)		R_f*	Yield, %
						C	H	N	C	H	N	found (mass spectrum)	calculated	λ_{max}, nm	lg ε		
IIa	C_3H_7		115—117 (0,1)	1,5460	$C_{10}H_{13}NO_2$	66,7	7,4	7,6	67,0	7,3	7,8			243 350	3,6493 3,8976	0,54	50
IIb	C_4H_9		120—122 (0,1)	1,5490	$C_{11}H_{15}NO_2$	64,1	4,2	15,0	64,0	4,0	14,9	193	193	242 349	3,8842 4,1584	0,607	57
IIc	$CH_2C_6H_5$	63—64			$C_{14}H_{13}NO_2$	74,0	5,8	6,4	74,0	5,8	6,2	227	227	242 353	3,6542 3,8756	0,535	48

*The R_f values were obtained on SiO_2 [hexane–acetone (2:1)] with development in UV light (lilac-colored spot).

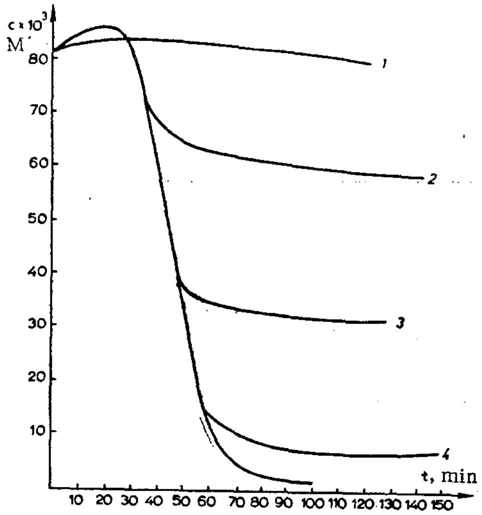
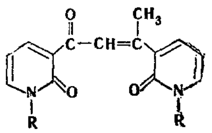


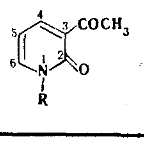
Fig. 1. Dependence of the concentration of Ib in CH_3OH on the time, determined from the UV spectrum [the decrease in intensity (ε) at 395 nm] without the addition of carbamate ($C_4H_9NHCOONH_3C_4H_9$). Carbamate (in quantities of 10% of the amount of Ib) was added to an aliquot of the reaction solutions: 1) immediately after Ib had dissolved; 2) after 40 min; 3) after 50 min; 4) after 60 min.

TABLE 2. Yields and Physical Constants of



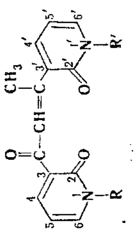
Compound	R	mp, °C	Empirical formula	Found, %				Calculated, %				UV spectrum		Yield, %
				C	H	N	C=O	C	H	N	C=O	λ_{max}, nm	lg ε	
IIIa	C_3H_7	203—205	$C_{20}H_{24}N_2O_3$	70,4	7,2	8,1	8,0	70,6	7,1	8,2	8,2	241 326	4,0 3,8751	60
IIIb	C_4H_9	211—212	$C_{22}H_{28}N_2O_3$	71,4	7,6	7,8	7,8	71,7	7,7	7,6	7,6	278 334	3,7634 3,9582	65
IIIc	$CH_2C_6H_5$	222—224	$C_{28}H_{24}N_2O_3$	76,9	5,4	6,4		77,0	5,5	6,4		335	3,7118	59

TABLE 3. Data from the PMR Spectra (in CD_3OD) of



Compound	R	Chemical shifts, δ, ppm							Coupling constants, Hz			
		CH_3–C	CH_3CO	N–CH_2	5-H	4-H	6-H	C_6H_5	$J_{NCH_2CH_2}$	J_{45}	J_{56}	J_{46}
IIb	C_4H_9	0,93	2,57	4,03	6,4	7,92	8,08	—	7	6,9	7,2	2,2
IIc	$CH_2C_6H_5$		2,55	5,18	6,37	7,93	8,07	7,28	—	7	7	2,07

TABLE 4. PMR Data (for CD_3OD solutions) of



Compound	R	R'	Chemical shifts, δ, ppm										Coupling constants, Hz							
			CH_3	CH_3—C=	CH	N—CH_2	5-H	6-H	4-H	N—CH_2	5'-H	4'-H	6'-H	J^* CH=C—CH_3	J CH_2—CH_2	$J_{5,6}$	$J_{5,4}$	J $C'H_2$—$C'H_2$	$J_{5',6'}$	$J_{4',5'}$	$J_{6',4'}$
IIIa	C_3H_7	C_3H_7	0,95	1,92	7,3	3,98	6,38	7,67	7,67	4,65	7,97	8,57	8,93	1	7	7	7	8	6,0	8	1,6
IIIb	C_4H_9	C_4H_9	0,92	1,9	7,23	4,0	6,33	7,63	7,63	4,63	7,92	8,53	8,9	1	7	7	7	8	6,2	8	1,4
IIIc**	$CH_2C_6H_5$	$CH_2C_6H_5$	—	1,6	7,22	5,22	6,32	7,68	7,58	5,83	7,95	8,55	9,02	1	—	7	7	—	6,0	8	1,4
V	C_4H_9	$CH_2C_6H_5$	0,98	1,72	7,3	4,07	6,38	7,65	7,65	5,92	8,0	8,62	9,07	1	7	7	7	—	7	8,4	1,6
IV	$CH_2C_6H_5$	C_4H_9	0,9	1,92	7,3	5,18	6,38	7,68	7,68	4,63	7,93	8,53	8,90	1,2	—	7	7	7	6,0	8,0	1,4

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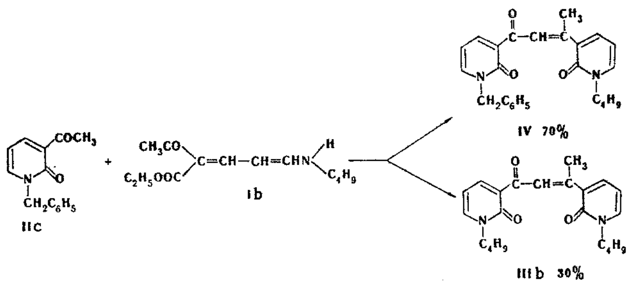
* The corresponding constant is zero when the methylidyne proton is replaced by deuterium.

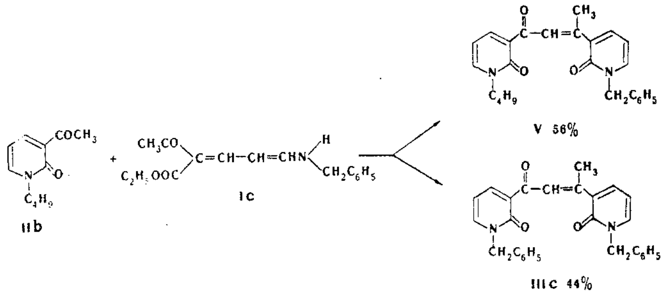
† The signals of the 4-H and 6-H protons in IIIc do not coincide, and J_{46} = 2 Hz.

TABLE 5. Effect of the Percentage of Water in Methanol on the Yields of II and III

R	Percentage of water in methanol, %	Yield, %	
		II	III
C_4H_9	0	12,5	65
	30	57	18
$CH_2C_6H_5$	0	10	59
	30	48	32,7



"Butenones" III are not the products of crotonic condensation of 3-acetylpyridones II, since "butenones" III could not be obtained from them by special experiments. However, it turned out that "butenone" IV is formed as the principal product when 1-benzyl-3-acetylpyridone IIc is added to an alcohol solution of Ib.

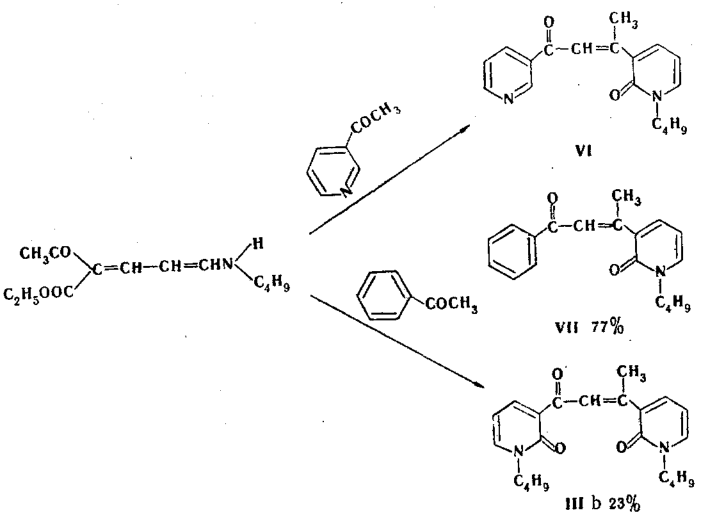


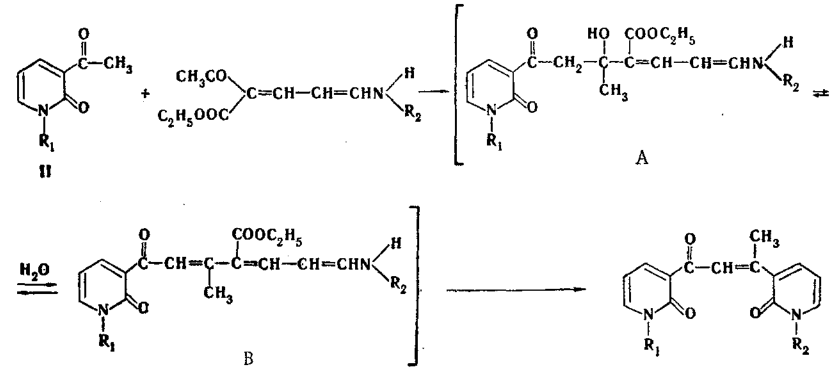
Similarly, "butenone" V predominates in the reaction mixture when 1-butyl-3-acetylpyridone (IIb) is added to an alcohol solution of Ic.

The structure of these mixed "butenones" (IV and V) was confirmed by PMR spectroscopy (see Table 4).

As a result of further investigations it was shown that other ketones, for example, acetophenone and 3-acetylpyridine, can also be used in this reaction. In the case of 3-acetylpyridine, only "butenone" VI was obtained (see scheme on following page).

It follows from the experimental facts presented above that "butenones" III are formed as a result of condensation of 3-acetylpyridones II with dienic δ-monoalkylaminoketo esters I with subsequent cyclization of the condensation products:

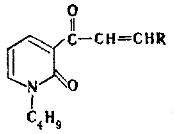




When the reaction is carried out in deuteromethanol (CD_3OD), the proton in the "butenone" chain in the resulting "butenone" is replaced by deuterium; this confirms the formation of intermediate ketol A.

The above-indicated transformations show that the keto group in the dienic δ-monoalkylaminoketo esters has an unexpected high reactivity, in contrast to the known facts of the decrease in activity of the carbonyl group in enamine carbonyl compounds [2, 3].

TABLE 6. Physical Constants and Yields of



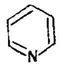
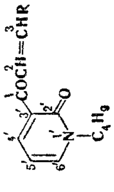
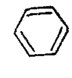
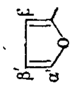
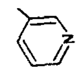
Compound	R	mp, °C	Empirical formula	Found, %			Calculated, %			UV spectrum		
				C	H	N	C	H	N	λ_{max}, nm	lg ε	
VIII	C_6H_5	55—57	$C_{18}H_{19}NO_2$	76,7	7,0	4,7	76,8	6,8	5,0	220 233 323 370	4,1697 4,0962 4,1405 4,0962	77
IX		67—68	$C_{16}H_{17}NO_3$	71,0	6,4	5,2	70,8	6,3	5,2	217 261 378	4,0382 3,5866 4,3032	80
X		50—52	$C_{17}H_{18}N_2O_2$	72,3	6,6	9,6	72,3	6,4	9,9	223 244 308 371	4,2148 4,0492 4,0828 4,0	72

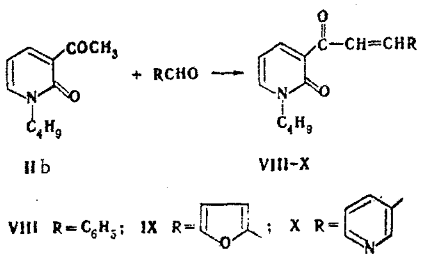
TABLE 7. Data from the PMR Spectra of



Compound	R	Chemical shifts, δ, ppm											Coupling constants, Hz						Solvent
		CH_3	N–CH_2	5'-H	4'-H	Ph	6'-H	2-H	3-H	β-H	β'-H (furyl)	α'-H	$J_{4',5'}$	$J_{5',6'}$	$J_{4',6'}$	$J_{2,3}$	$J_{\beta\beta'}$	$J_{\alpha'\beta'}$	
VIII		0,95	3,88	6,12	at 7,00—7,7		8,0	7,57	8,15	—	—	—	7	7	2,2	16	—	—	CCl_4
IX		0,92	3,90	6,12	7,50	—	8,00	7,35	7,93	6,37	6,60	7,45	7	7	2,2	16	3	1,8	CCl_4
X		0,95	4,05	6,42	—*	—	—*	—*	—*	—	—	—	7	7	—*	—*	—	—	CD_3OD

*Not determined because of the superimposition of the lines of the 2, 3, 4', and 6' protons and the protons of the pyridine ring.

Owing to the presence of an acetyl group, the 1-alkyl-3-acetylpyridones (IIa,b,c) may have interesting synthetic application. Thus we were able to synthesize various heterocyclic analogs of chalcone in high yields by condensation of 1-butyl-3-acetylpyridone with aromatic and heterocyclic aldehydes:



The yields, physical constants, and data from the PMR spectra of the compounds obtained are presented in Tables 6 and 7.

EXPERIMENTAL

The PMR spectra were recorded with a Varian DA-60-1L spectrometer with an operating frequency of 60 MHz. Hexamethyldisiloxane was used as the internal standard.

1,3-Bis[3-(1-butyl-2-pyridonyl)]-2-buten-1-one (IIIb) and 1-Butyl-3-acetyl-2-pyridone (IIb). A. In absolute methanol. A 3-g (12.5 mmole) sample of ethyl 5-butylamino-2-acetyl-2,4-pentadienoate (Ib) was dissolved in 14 ml of absolute methanol, and the solution, which turned red after 15 min, was allowed to stand for 24 h and then vacuum-evaporated. Dry acetone was added to the residue, which was a heavy red oil, and the resulting precipitate was separated and washed thoroughly with dry acetone to give 1.5 g (65%) of IIIb. "Butenone" IIIb can be isolated without the addition of acetone by chromatography on silica gel (elution with alcohol). The mother liquor after separation of IIIb was vacuum-distilled at 0.3 mm (bath temperature 150°) to give 0.3 g (12.5%) of IIb.

B. In 70% methanol. A 6.2-g (26 mmole) sample of Ib was dissolved in 67 ml of 70% methanol, and the following day the solution was heated at 30° for 15 min (the end of the reaction was determined from the disappearance of λ_{max} at 395 nm and the appearance of λ_{max} at 349 nm in the UV spectrum) and vacuum-evaporated. Ether was added to the residue, and the ether solution was separated, dried with calcined magnesium sulfate, and vacuum-evaporated. The residue (57%) was a transparent red oil (n_D^{20} 1.5460) of IIb with bp 120-122° (0.1 mm) and n_D^{20} 1.5490.

The aqueous layer was vacuum-evaporated, dry acetone was added to the residue, and 0.86 g (18%) of IIIb was separated.

C. In CD_3OD. A 1.3-g (5.5 mmole) sample of Ib was dissolved in 3 ml of CD_3OD, and the solution was treated as above to give 0.7 g (70%) of IIIb and 0.14 g (14%) of IIb. According to the PMR spectra, the proton attached to the double bond in the "butenone" chain of IIIb undergoes 70% replacement by deuterium; deuterium is absent in IIb.

Determination of Water Generated during Dissolving of Ib and Ic in Methanol. A. A 99.248-mg sample was dissolved in 5 ml of absolute methanol,and aliquots of the solution (1 ml each) were titrated with the Fischer reagent after 4 min, 1 h, and 3 h. The following amounts of water, respectively, were found: 0.34, 2.175, and 2.45%. In the quantitative formation of IIIb, 3.76% water should be generated.

B. A 103.324-mg sample of ethyl 6-benzylamino-2-acetyl-2,4-pentadienoate (Ic) was dissolved in 5 ml of absolute methanol, and aliquots of the solution were titrated as above after 11 min, 1 h, and 3 h. The amounts of water found were: 1.05, 2.75, and 2.91%. In the quantitative formation of IIIc from Ic, 3.3% water should be generated.

1-(3-Pyridyl)-3-[3-(1-butyl-2-pyridonyl)]-2-buten-1-one (VI). A 0.3-g (1.25 mmole) sample of Ib was dissolved in a mixture of 3 ml of absolute methanol and 0.46 g (3.8 mmole) of 3-acetylpyridine, and the solution was allowed to stand at room temperature for 24 h. The solvents were vacuum-evaporated, and dry acetone was added to the residue. The precipitate was separated and washed thoroughly with dry acetone to give 0.23 g (62%) of VI as the crystal hydrate with mp 94-96°. Found: C 65.4; H 7.2; N 8.6; H_2O 10.9%. $C_{18}H_{20}N_2O_2 \cdot 2H_2O$. Calculated: C 65.1; H 7.2; N 8.4; H_2O 10.8%. UV spectrum (in ethanol: λ_{max} 278, 313 nm (log ε 3.850, 3.766). PMR spectrum in CD_3OD, δ, ppm: 0.92 $CH_3(CH_2)_3$, 2.05 ($CH_3C = C$), 4.62 (NCH_2), 7.00 (CH), 7.33-9.07 (pyridine and pyridone).

1-Phenyl-3-[3-(1-butyl-2-pyridonyl)]-2-buten-1-one (VII). A 0.2-g (0.84 mmole) sample of Ib was dissolved in a mixture of 2 ml of absolute methanol and 0.3 g (1.5 mmole) of acetophenone, and the solution was allowed to stand at room temperature for 24 h. Workup as described above gave 0.18 g of a crystalline substance, which was a mixture of 77% VII and 23% IIIb (the ratio was determined by means of the PMR spectra from the integral of the methylidyne protons). PMR spectrum in CD_3OD, δ, ppm: 0.97 $CH_3(CH_2)_3$, 2.02 ($CH_3C=C$), 4.6 ($N = CH_2$), 6.90 (CH), 7.9 (5-H), 8.53 (4-H), 8.9 (6-H), 7.3-7.7 (phenyl): $J_{CH_2CH_2N} = 7$ Hz, $J_{CH=CCH_3} = 1$ Hz, $J_{45} = 8$ Hz, $J_{56} = 6$ Hz, and $J_{46} = 1.6$ Hz.

1-[3-(1-Butyl-2-pyridonyl)]-3-[3-(1-benzyl-2-pyridonyl)]-2-buten-1-one (V). A mixture of 0.35 g (1.28 mmole) of Ic and 0.24 g (1.24 mmole) of IIb was dissolved in 7 ml of absolute methanol, and the solution was allowed to stand. It was then worked up by the usual method to give 0.18 g of a mixture of 56% V and 44% IIIc (according to the PMR spectrum); the mother liquor contained 3-acetylpyridones IIb and IIc, according to thin-layer chromatography.

1-[3-(1-Benzyl-2-pyridonyl)]-3-[3-(1-butyl-2-pyridonyl)]-2-buten-1-one (IV). Similarly, 0.16 g (0.67) mmole) of Ib and 0.14 g (0.62 mole) of IIc in 2 ml of absolute methanol gave 0.7 g of a substance, which contained 70% IV and 30% IIIb, according to the PMR spectrum.

1-[3-(1-Butyl-2-pyridonyl)]-3-furylpropen-1-one (IX). Compounds VIII and X were also obtained via the following method. A 0.4-g (4.2 mmole) sample of furfural and 0.4 g (2.1 mmole) of 1-butyl-3-acetyl-2-pyridone were added successively with stirring to a cooled (to −10°) solution of 0.8 ml of 10% NaOH and 0.4 ml of methanol, after which the mixture was stirred at 0° for 2.5 h. Ether was added, and the organic layer was separated, washed with water, dried, and evaporated to give 0.46 g (80%) of IX with mp 67-68° (from 80% ethanol).

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