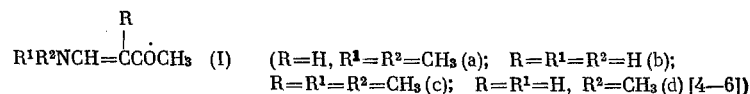# SOME TRANSFORMATIONS OF ENAMINO CARBONYL COMPOUNDS

Zh. A. Krasnaya, T. S. Stytsenko,
E. P. Prokof'ev, and V. F. Kucherov

UDC 542.91:547.447.5
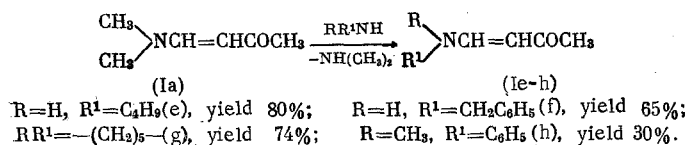
In previous papers [1-3] we described the peculiarities observed by us in the stereochemistry and properties of some dienic δ-amino carbonyl compounds of type $RR^1NCH = CHCH = C(X)COR^3$ (X = $COCH_3$, COOAlk, NO_2, $CONH_2$): a quite high reactivity of the carbonyl group, a rapid (on the NMR time scale) rotation around the α,β double bond under the equilibrium conditions for the geometric isomers, and a hindered rotation around the C−N bond. It was interesting to compare them with enamino carbonyl compounds. For this purpose we synthesized by known methods the ketones:

$$R^1R^2NCH=\overset{\overset{\displaystyle R}{|}}{C}COCH_3 \quad (I)$$

(R=H, R^1=R^2=CH_3 (a); R=R^1=R^2=H (b);
R=R^1=R^2=CH_3 (c); R=R^1=H, R^2=CH_3 (d) [4—6])

and the β-keto esters: $CH_3(CH_3)NCH = C(COCCH_3)COOR$ (II) [7, 8]. The monoalkylamino-β-keto esters were obtained by the transamination of (IIa)


R=C_4H_9 (IIb), $CH_2C_6H_5$ (IIc)
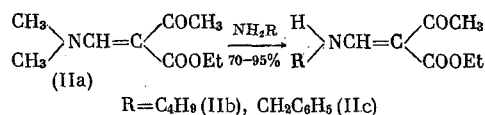
To synthesize ketones with various substituents on the nitrogen we subjected ketone (Ia) to transamination with primary and secondary amines

R=H, R^1=C_4H_9(e), yield 80%; R=H, R^1=$CH_2C_6H_5$(f), yield 65%;
RR^1=−$(CH_2)_5$−(g), yield 74%; R=CH_3, R^1=C_6H_5(h), yield 30%.

The indicated compounds were obtained for the first time by this procedure. It should be mentioned that this method is very convenient, since it eliminates the need of using such labile compounds as the sodium salt of hydroxymethyleneacetone, methyl ethyl ketone and chlorovinyl ketone.

When the enamino carbonyl compounds were studied by the NMR method it was found that, in harmony with the already existing literature data [5, 9, 10], equilibrium is established between the cis- and trans-isomers in ketones (Ib, d, e, f), in which connection the cis-isomers are found in the chelate form, stabilized by an intramolecular hydrogen bond
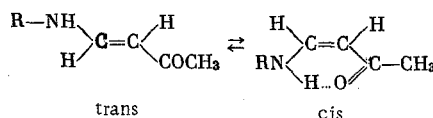
In amino ketone (Ie), which contains ~100% of the ^{15}N isotope, it was found that the cis-isomer has J_{15N-H} = 92 Hz, which is independent of the temperature. This additionally corroborates [11], based on the

already existing IR spectral data given in [12], that this form is not the imino enol, as was previously postulated [13]. The same conclusion can also be made for ketones (Ib, d, f), since their spectra are analogous to the spectra of (Ie).

When ketones (Id) and Ie) in either CD_3OD or CCl_4 were heated up to 100°C the equilibrium constant for the cis-trans isomers failed to change, and here we failed to observe rapid exchange between the isomers, which is observed in dienic δ-aminoketo esters, diesters, diketones, etc. [3]. An explanation of this difference may be obtained after determining the activation parameters of the cis—trans isomerization in the enamino ketones and comparing them with the activation parameters of rotation around the α,β-double bond in dienic compounds [3].
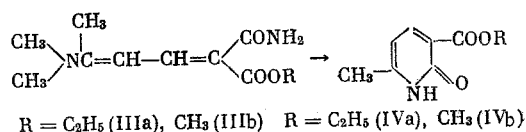
While studying the enamino ketones by the NMR method it was found that the α-proton in (Ia) is deuterated with exceeding ease (in CD_3OD to the extent of 70% and in D_2O to the extent of 100%) immediately after dissolving the sample.

$$\underset{CH_3}{\overset{CH_3}{>}}NCH{=}CHCOCH_3 \xrightarrow{D_2O,\ CD_3OD} \underset{CH_3}{\overset{CH_3}{>}}NCH{=}CDCOCH_3$$
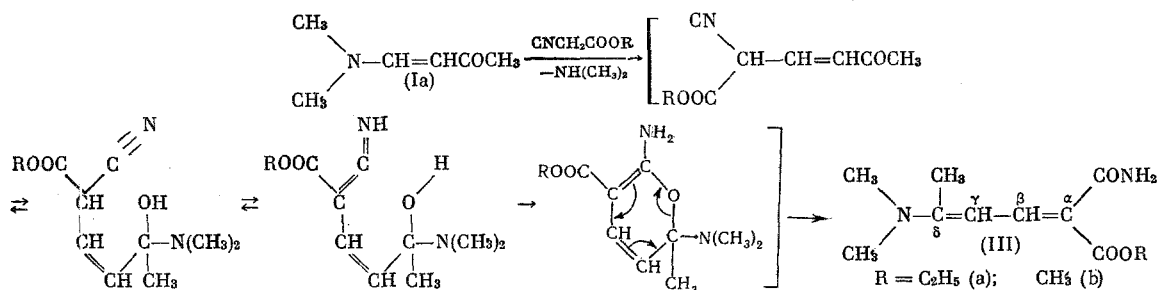(Ia)
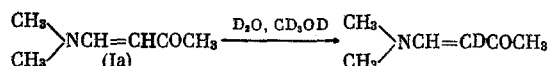
These facts show the inaccuracy of the data on the absence of deuteration in (Ia) [14]. It was shown by us that the deuteration of the α-proton in (Id, e, f) proceeds more slowly than in (Ia).

From the data of the NMR spectra it follows that the N-mono-substituted enamino-β-keto esters exist as one isomer, in which connection as the chelate, which is stabilized by an intramolecular hydrogen bond. Since the values of the chemical shift of the NH proton (11.08 ppm) in compounds (Ie) and IIb) are close, then it can be assumed that the intramolecular hydrogen bond is formed between the NH proton and the carbonyl of the acetyl group, and not of the carbethoxyl group. The chemical shift of the proton, which forms a hydrogen bond with the carbonyl of the carbethoxy group, is shifted by approximately 2.5 ppm upfield [15]. As was shown by us [3], the N-disubstituted β-keto esters, for example (IIa), represent an equilibrium mixture of the cis-trans isomers, between which rapid exchange takes place ($\Delta G_{C=C}^{\neq} = 11.18$ kcal/M in $CDCl_3$).

The activity of the carbonyl group in dienic monoalkylamino-β-keto esters was observed previously, which was manifested in the ability of these compounds to easily react with 3-acetylpyridones, acetophenone, etc. [1]. Enamino ketones and β-keto esters fail to enter similar condensations, and they also fail to react with acetoacetic ester, acetylacetone and malonic ester. However, it proved that they react under mild conditions (40°) with cyanoacetic ester. Thus, the reaction of (Ia)* with cyanoacetic ester unexpectedly gave the ester of 5-dimethylamino-2-carbamoyl-2-4-hexadienoic acid (III), the structure of which was proved by the UV, NMR, IR and mass spectra, and also by the elemental analysis and chemical transformations. The position of the methyl group in (IIIa, b) was established via the conversion of these compounds by heating them for a short time in an alcohol at 150° to the corresponding 3-carbalkoxy-6-methyl-2-pyridones (IVa, b), which were identical with the authentic specimens

$$\underset{CH_3}{\overset{CH_3}{>}}\overset{\overset{CH_3}{|}}{N}C{=}CH{-}CH{=}C\underset{COOR}{\overset{CONH_2}{<}} \rightarrow CH_3{-}\underset{NH}{\bigcirc}{-}COOR$$

R = C_2H_5 (IIIa), CH_3 (IIIb)   R = C_2H_5 (IVa), CH_3 (IVb)

The formation of (III) can be depicted by the scheme:

*The aldehyde $\underset{CH_3}{\overset{CH_3}{>}}\overset{\overset{CH_3}{|}}{N}C{=}CHCHO$, which is isomeric with ketone (Ia), does not react with cyanoacetic ester.

TABLE 1. NMR Spectra of (IIIa) and (IIIb)

Compound	Chemical shifts, δ, ppm							$J_{H_\beta - H_\gamma}$, Hz	Solvent
	CH₃C=	NCH₃	OCH₃	OC₂H₅		CH_γ	CH_β		
				CH₃	CH₂				
(IIIa)*	2,20 2,25	3,13 3,13		1,30 1,37	4,13 4,20	7,03 6,38	8,12 8,30	13 13	CD₃ OD + CCl₄
(IIIb)†	2,15	3,05	3,65			6,85 6,30	8,05 8,30	13 13	CD₃OD

* The signals of the protons of the amide group, with shifts of 7.93 and 6.52 ppm, are present in the NMR spectrum in DMSO.

† The NMR spectrum was taken at 58° due to the poor solubility of the sample.

The reaction proceeds in a similar manner when N-monosubstituted amino ketones (Ie, f) are reacted with CNCH₂COOR, but the corresponding dienes of the (III) type, in view of their lability (due to the presence of a proton on the nitrogen atom [16]), were not isolated in the pure state, and were identified only by the UV spectrum and by TLC.

The 5-substituted derivatives, namely the 3-carbalkoxy-6-methyl-2-pyridones (Va, b), are formed in 70-73% yield from the enamino-β-keto esters (IIa), and also from the α-substituted ketones (Ic), by reaction with cyanoacetic ester at 40°. Since dienes of the (III) type were completely absent when the course of this transformation was checked by the UV spectra, it may be assumed that the (Va, b) are not formed under such mild conditions as the result of the cyclization of the corresponding dienes, but rather by the following scheme, which includes intramolecular rearrangement, similar to that described in [17]

R = CH₃ (Ic), R = COOC₂H₅ (IIa)

R = R¹ = CH₃ (a); R = COOC₂H₅, R¹ = C₂H₅ (b)

It should be mentioned that the N-monoalkylamino-β-keto esters (IIb), (IIc) and (IId, R = CH₃) are completely inert toward cyanoacetic ester; this is apparently explained by the fact that they are found exclusively as the chelate, which is stabilized by a fairly strong intramolecular hydrogen bond.

EXPERIMENTAL METHOD

The NMR spectra (δ, ppm) were taken on a DA-60-1L instrument. We used HMDS as the internal standard.

Ethyl Ester of 3-Butylamino-2-acetoacrylic Acid (IIb). To 2.8 g (0.015 M) of (IIa) was added 1.1 g (0.015 M) of butylamine. Here the temperature of the reaction mass rose to 45° and dimethylamine was

TABLE 2. NMR Spectra of

Compound	R	R¹	Chemical shifts, δ, ppm							Coupling constants, Hz		Solvent
			CH₃ at C₆	OCH₃	OC₂H₅		H₅	H₄	CH₃ at C₅	$J_{4,5}$	$J_{CH_2CH_3}$	
					CH₃	CH₂						
(IVa)	C₂H₅	H	2,25	3,7	1,25	4,18	6,14	8,04		7,5	7,0	CD₃OD
(IVb)	CH₃	H	2,23	3,7			6,08	8,03		7,5		CD₃OD
(Va)	CH₃	CH₃	2,26	3,77				7,97	2,03			CDCl₃ + +CD₃OD
(Vb)	C₂H₅	COOC₂H₅	2,77	—	1,31	4,25 4,28		8,72			7,0	CDCl₃

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evolved vigorously. After 30 min the reaction mass was distilled. We obtained 2.4 g (75%) of (IIb) with bp 131-132° (2 mm); n_D^{20} 1.5090. λ_{max} (in C_2H_5OH): 238 nm (ε 15000), 297 nm (ε 14800). Found: C 61.91; H 8.93%. $C_{11}H_{19}NO_3$. Calculated: C 61.94; H 8.98%. NMR spectrum of (IIb) in CCl_4 (δ, ppm): 1.25 (CH_3 ·CH_2O); 4.08 (CH_3CH_2O); 0.95 (CH_3 in C_4H_9); 1.42 (CH_2)$_2$; 3.35 (NCH_2); 2.35 (CH_3CO); 7.93 (CH); 11.08 (NH); $J_{CH_3CH_2} = 7$ Hz, $J_{CH_3CH_2}$ (in C_4H_9) $= 6$ Hz, $J_{CH_2CH_2N} = 7$ Hz, $J_{CH, NH} = 14$ Hz.

Ethyl Ester of 3-Benzylamino-2-acetoacrylic Acid (IIc). The ester was obtained in 83% yield by the above described method, mp 66-67° (from hexane). λ_{max} (in C_2H_5OH): 236 nm (ε 15700), 299 nm (ε 17500). Found: C 67.94; H 6.90; N 5.68%. $C_{14}H_{17}NO_3$. Calculated: C 67.99; H 6.93; N 5.66%.

Methyl Ester of 3-Methylamino-2-acetoacrylic Acid (IId). Ester (IId) was obtained as described in [8], mp 58-61°. λ_{max} (in C_2H_5OH) 294 nm. NMR spectrum of (IId) in CCl_4 (δ, ppm): 2.4 (CH_3CO); 3.18 (N$-CH_3$); 3.67 ($COOCH_3$); 7.85 (CH); 11.12 (NH); $J_{NH, CH} = 13.4$ Hz, $J_{CH_3, H} = 5.3$ Hz.

Transamination of Ketone (Ia). An equimolar mixture of ketone (Ia) and the amine was heated at 70° for 10 h ($C_4H_9NH_2$), at 140-160° for 10 h ($C_6H_5CH_2NH_2$), at 110° for 2 h ($C_5H_{10}NH$), and at 200° for 2 h (CH_3·NHC_6H_5). The end of reaction was determined by TLC (SiO_2, acetone:hexane, 1:2), after which the reaction mass was distilled. The purity of the ketones and the ratio of the cis-trans isomers were checked by the NMR spectra.

Ethyl Ester of 5-Dimethylamino-2-carbamoyl-2,4-hexadienoic Acid (IIIa). A mixture of 3 g of (Ia) and 3.2 g of ethyl cyanoacetate in 10 ml of absolute ethanol was heated at 40° for 10 h. After cooling we separated 1.2 g of a yellow precipitate, which gave one spot when subjected to TLC ($R_f = 0.37$, SiO_2, acetone−chloroform−ethanol, 12:6:1), which represents the ethyl ester of 5-dimethylamino-2-carbamoyl-2,4-hexadienoic acid (IIIa) as a mixture of the cis−trans isomers at the α,β-double bond (based on the NMR data), with mp 158-159° (from an ethanol−acetone mixture).* The yield of (IIIa) was 30% when based on the reacted ketone (Ia). Found: C 58.35; H 8.02; N 12.39%; mol. wt. 226 (mass spectrometry). $C_{11}H_{18}N_2O_3$. Calculated: C 58.39; H 8.02; N 12.38%; mol. wt. 226. λ_{max} (in C_2H_5OH): 298 nm (ε 10,000); 394 nm (ε 58,500). In the IR spectrum (2% solution in $CHCl_3$) the bonds at 3340 and 3490 cm^{-1} belong to the NH_2 group.

The vacuum-distillation of the mother liquor from the separation of (IIIa), besides 1 g of the starting ketone (Ia), gave 0.3 g of 3-carbethoxy-6-methyl-2-pyridone (IVa) with bp 125-127° (0.7 mm), which crystallized on cooling. After sublimation, (IVa) had mp 145-146° and failed to depress the mixed melting point with the ethyl ester obtained by the esterification of 3-carboxy-6-methyl-2-pyridone [18]. Found: C 59.27; H 6.17; N 7.56%. $C_9H_{11}NO_3$. Calculated: C 59.6; H 6.08; N 7.79%. λ_{max} (in C_2H_5OH): 241 nm (ε 8200), 338 nm (ε 10300).

In a similar manner, from (Ia) and methyl cyanoacetate we obtained the methyl ester of 5-dimethylamino-2-carbomoyl-2,4-hexadienoic acid (IIIb) with mp 177-178° (from a methanol−acetone mixture). Found: C 56.82; H 7.54; N 13.43%. $C_{10}H_{16}N_2O_3$. Calculated: C 56.59; H 7.60; N 13.20%. λ_{max} (in C_2H_5OH): 255 nm (ε 6360), 396 nm (ε 72000).

The NMR spectra of (IIIa) and (IIIb) are given in Table 1.

3-Carbethoxy-6-methyl-2-pyridone (IVa). A solution of 0.3 g of (IIIa) in 2.4 ml of ethanol was heated in a sealed ampul at 150° for 20 min. After evaporation, we isolated from the residue 0.2 g of (IVa) with mp 147-148° (from benzene), which was identical with an authentic specimen.

3-Carbomethoxy-6-methyl-2-pyridone (IVb). In a similar manner, from (IIIb) by heating in methanol we obtained (IVb) with mp 165-166° (from methanol), which was identical with an authentic specimen. λ_{max} (in C_2H_5OH): 240 nm (ε 6500), 336 nm (ε 9540). Compound (IVb) is also formed when (IIIa) is heated in methanol.

3-Carbomethoxy-5,6-dimethyl-2-pyridone (Va). A mixture of 0.5 g of (Ic) and 0.5 ml of methyl cyanoacetate in 3 ml of absolute MeOH was heated at 40° for 1 h, after which the solvent was evaporated. We obtained 0.5 g (70%) of (Va) with mp 215-216° (from benzene). Found: C 59.63; H 6.16; N 7.74%. $C_9H_{11}NO_3$. Calculated: C 59.66; H 6.12; N 7.73%. λ_{max} (in C_2H_5OH): 243 nm (ε 7760), 350 nm (ε 9100).

3,4-Dicarbethoxy-6-methyl-2-pyridone (Vb). A mixture of 0.7 g of (IIa) and 0.43 ml of ethyl cyanoacetate was heated at 40° for 1 h. After cooling, the obtained precipitate was separated and washed with

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*A mixture of 75% of methyl ester (IIIb) and 25% of ethyl ester (IIIa) (based on the NMR spectral data) was obtained when the reaction was run in methanol.

ether. We obtained 0.7 g (73%) of (Vb) with mp 185-187°. Found: C 56.75; H 5.91; N 5.72%. $C_{12}H_{15}NO_5$. Calculated: C 56.91; H 5.97; N 5.53%. λ_{max} (in C_2H_5OH): 263 nm (ε 16700), 330 nm (ε 28450).

The NMR spectra of (IVa), (IVb), (Va) and (Vb) are given in Table 2.

CONCLUSIONS

1. Based on the data of the NMR spectra, the en-N-monoalkylamino-β-keto esters represent exclusively the cis-isomers as the chelates, which are stabilized by an intramolecular hydrogen bond NH . . . O = $C(CH_3)$; exchange between the cis- and trans-isomers is absent in the enamino ketones under equilibrium conditions when the temperature is varied; in enamino ketones, including those containing a tertiary amino group, the $H\alpha$ proton is easily replaced by deuterium.

2. Enamino ketones react with cyanoacetic ester under mild conditions to give the esters of 5-amino--2-carbamoyl-2,4-hexadienoic acid, while enamino-β-keto esters and α-alkyl ketones react to give 2-pyridone derivatives.

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