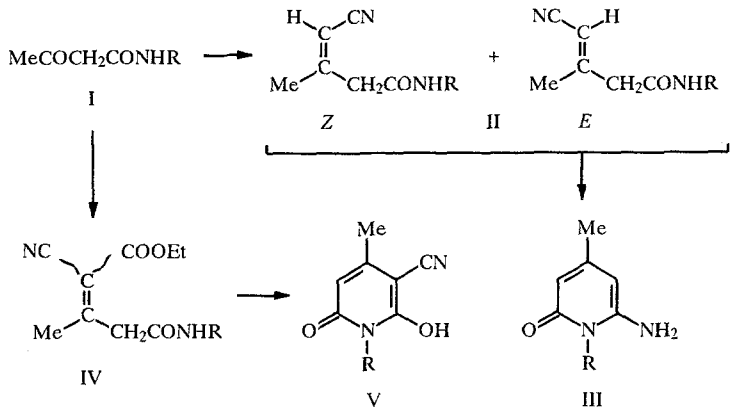
SYNTHESIS OF 3-METHYL-4-CYANO-3-BUTENOIC ACID AMIDES AND THEIR CYCLIZATION INTO 6-AMINO-2-PYRIDONES

Yu. S. Tsizin, O. B. Kuklenkova, B. V. Lopatin, and N. K. Bebris

Two groups of amides, derivatives of 3-methyl-4-cyano- and 3-methyl-4-cyano-4-carbethoxy-3 acids were obtained from acetoacetamides in the form of mixtures of Z, E-isomers and the pure E-isomers were isolated. It was shown that amides from the first group are cyclized by bases into the corresponding 6-amino-4-methyl-2-pyridones and amides from the second group are cyclized into 6-hydroxy-5-cyano-4-methyl-2-pyridones.

The formation of intermediates containing cyano and amide groups joined by a three-carbon chain and cyclized into 6-amino-2-pyridones was examined in [1], for example. We have shown that 3-methyl-4-cyano-3-butenoic acid (II), obtained in the Knoevenagel reaction from acetoacetamides I and cyanoacetic acid, are accessible substances with such a structure.



I—V a R = H; b R = Ph; c R = C_6H_4Cl-4; d R = CH_2Ph; e R = CH_2CH_2Ph

Cyanamides II were isolated as solid crystalline mixtures of *Z*, *E*-isomers melting in a wide range of temperatures. Their structure was confirmed by TLC data (separation of isomers), elemental analysis, and IR spectroscopy. As HPLC showed, compounds II contain 30-40% of one isomer and 60-70% of the other after one recrystallization (Table 1). This is in good agreement with the data in [2] that liquid 3-methyl-4-cyano-3-butenoic acid ethyl ester, also synthesized with the Knoevenagel reaction, contains 40% *Z*-isomer.

Pure isomers of compounds IIa and IIc with a distinct melting point were isolated after additional recrystallization of the corresponding mixtures. Their configuration as *E*-isomers was determined from the results in [3], where the PMR spectra of similar compounds contain the signal of *E*-isomer methylene group protons in a stronger field than the corresponding signal for the *Z*-isomer. The PMR spectrum of a mixture of isomers IIc contains signals of methylene group protons of the *Z*-isomer at 3.47 ppm and the *E*-isomer at 3.26 ppm, their sum is 2H, and the ratio of intensities is $E/Z = 1.86$. This value is close to the data obtained with HPLC. There is no signal at 3.47 ppm in the PMR spectrum of pure isomer IIc.

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TABLE 1. Characteristics of Compounds II-V

Compound	Empirical formula	Mp, °C	Solvent for crystallization	E/Z ratio according to HPLC	IR spectrum, ν, cm^{-1}	Yield, %
IIa	$C_6H_8N_2O$	65...74	–	2,2	3410, 3220 (NH_2), 2231 (C ≡ N), 1678 (C=O)	60
IIb	$C_{12}H_{12}N_2O$	82...92	Benzene	1,6	3258 (NH), 2230 (C ≡ N), 1660 (C=O)	66
IIc	$C_{12}H_{11}ClN_2O$	94...102	Benzene	1,9	3352 (NH), 2235 (C ≡ N), 1687 (C=O)	67
IId	$C_{13}H_{14}N_2O$	68...74	Heptane	1,4	3300, 3272 (NH), 2228 (C ≡ N), 1646 (C=O)	92
IIe	$C_{14}H_{16}N_2O$	62...72	Ester	1,8	3328 (NH), 2228 (C ≡ N); 1648 (C=O)	89
IIIa	$C_6H_8N_2O$	250...252**	H_2O	–	3425, 3300...2500 (NH_2, NH), 1630 (C=O)	61
IIIb	$C_{12}H_{12}N_2O$	222...223	EtOAc–hexane 1 : 1	–	3478, 3287, 3138 (NH_2), 1659 (C=O)	82 (75)
IIIc	$C_{12}H_{11}ClN_2O$	203...205	EtOAc–hexane 3 : 2	–	3320, 3165 (NH_2), 1660, 1640 (C=O)	68
IIId	$C_{13}H_{14}N_2O$	186...188	Acetone	–	3382, 3347 (NH_2), 1660, 1640 (C=O)	91 (82)
IIIe	$C_{14}H_{16}N_2O$	201...202	*i*-PrOH–H_2O, 1 : 3	–	3320, 3129 (NH_2), 1660 (C=O)	70 (62)
IVa	$C_9H_{12}N_2O_3$	94...100	EtOAc–hexane 1 : 1	2,0	3402, 3358, 3206 (NH_2), 2235 (C ≡ N), 1712 (C=O), 1662 (C=O), 1273 (C– O)	30
IVc	$C_{15}H_{15}ClN_2O_3$	92...99	EtOH–H_2O, 1 : 1	****	3368 (NH), 2237 (C ≡ N), 1740, 1676 (C=O), 1290 (C=O)	39
Va	$C_7H_6N_2O_2$	300...303***	EtOH	–	3300...2500 (NH, OH), 2230 (C ≡ N), 1630, 1600 (C=O)	79
Vc	$C_{13}H_9ClN_2O_2$	295...297	DMF–H_2O, 1 : 3	–	3100 (OH), 2228 (C ≡ N), 1660 (C=O)	99

*The yield obtained in conditions of phase-transfer catalysis (PTC) is indicated in parentheses.

**According to the data in [6], mp = 247-248°C.

***According to the data in [7], mp = 300-302°C.

****The ratio of isomers was not determined.

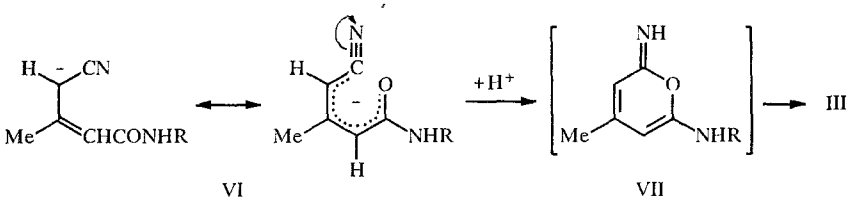
TABLE 2. UV Spectra of Compounds II and IV

Compound	λ_{max}, nm ($\varepsilon_{max} \cdot 10^3$ $cm^{-1} \cdot mole^{-1} \cdot liter$)	
	in ethanol	in 0.1 N alcohol NaOH
IIa (*E*-)	210,0 (11,6)	238,0* (3,9); 303,0 (4,0)
IIc (mixture of isomers)	250,0 (16,5)	247,0 (8,2); 331,1 (10,4)
IIc (*E*-)	250,0 (17,2)	248,0 (9,1); 331,1 (10,9)
IVa (mixture of isomers)	235,2 (11,9); 339,0 (0,05)	211,2 (11,4); 338,9 (20,4)
IVc (mixture of isomers)	250,0 (21,4)	250,0* (12,1); 259,7 (12,8); 367,6 (30,5)

*Shoulder.

Compounds IVa,c, prepared with the Knoevenagel reaction from acetoacetamides and cyanoacetic ester, are also a mixture of isomers.

Cyanamides II form anions VI in basic medium, stabilized by delocalization. Compounds IVa, c, which contain an additional electron-acceptor substituent — a carbethoxy group which increases the C—H acidity, are deprotonated even more easily. This follows from an examination of the UV spectra of compounds IIa,c and IVa,c, which have only one intense band in the short-wave region in ethanol. Another, more intense absorption band near 350 nm appears in the UV spectra of the same compounds in 0.1 N alcohol NaOH, but the intensity of the short-wave band decreases significantly (Table 2). These changes were previously observed in the UV spectrum for a series of compounds of similar structure in going from neutral to basic solutions [4, 5]. The analysis of the UV spectra suggested, as in [5], that all of these compounds are deprotonated in basic solutions to a significant degree. At the same time, only compound IVa has a small maximum in the long-wave region assigned to the corresponding anion in neutral solutions.



Under the effect of bases and discontinuous heating in aqueous medium or in PTC conditions (solid phase — liquid), cyanamides II are rapidly and irreversibly isomerized into aminopyridones III with high yields. The configuration of the substituents at the double bond is not important, since conducting the reaction with a mixture of isomers or with pure *E*-isomer produces the same results. The process probably takes place via iminopyran VII, formed as a result of nucleophilic attack of the nitrile group carbon of the anion [5].

In contrast to cyanamides II, compounds IV in basic conditions are cyclized into 6-hydroxy-2-pyridones V. Cyclization yielding 6-hydroxy-2-pyridones and not 6-amino-2-pyridones, thus takes place when both a cyano and an ester group ar present in the γ-position to the amide group.

EXPERIMENTAL

The IR spectra were made on a UR-20 in KBr pellets; the PMR spectra were made on a Bruker WH-60 (60 MHz); the UV spectra were recorded on a Specord UV-VIS spectrophotometer. The HPLC of compounds IIa-e and IVa were made on a model 850 chromatograph (Du Pont, USA), with a Zorbax-Sil column, hexane—isopropanol eluent 3:1, and detection at 254 nm. The purity of the compounds, presence of isomers, and course of the reactions were monitored by TLC on Silufol UV-254 plates in the systems: benzene—acetone, 2:1 (for compounds II and IV) and ethyl acetate—ethanol, 5:1 (for the other compounds), development with UV light and iodine vapors.

The properties of compounds II-V are reported in Tables 1 and 2.

The data from elemental analysis of the synthesized compounds for C, H, N, and Cl correspond to the calculated data.

Acetoacetamides I were synthesized from diketene and the corresponding amines according to [8].

General Method of Preparation of Isomeric 3-Methyl-4-cyano-3-butenoic Acid Amides (IIa-e, IVa,c). A mixture of 40 mmole of the corresponding acetoacetamide I, 4.0 g (47 mmole) of cyanoacetic acid (for preparation of substances IIa-e), or 5.2 g (46 mmole) of cyanoacetic ester (for substances IVa,c), 0.68 g (8.6 mmole) of ammonium hydrocarbonate, and 1.8 ml (32 mmole) of glacial acetic acid in 12 ml of benzene was heated with a water trap at 125-130°C (in a bath) until separation of water stopped (3.5-4 h). After cooling, the reaction mass was diluted with 100 ml of ethyl acetate. The solution obtained was washed with a 15% solution of NaCl (4 × 10 ml) and dried with $MgSO_4$; the solvents were eliminated in a vacuum, and the residue (except for compound IIa) was recrystallized. Compound IIa was separated chromatographically on silica gel; impurities were first eluted from the column with chloroform, and then a mixture of *Z, E*-isomers of substance IIa was eluted with chloroform—acetone mixture, 85:15.

3-Methyl-4-cyano-3-butenoic Acid Amide *E*-isomer (IIa). It was prepared by two recrystallizations of a mixture of isotherms IIa from water. Mp = 107-109°C. R_f = 0.20. IR spectrum: 3410, 3220 (NH_2), 2231 (C≡N), 1678 cm^{-1} (C=O). PMR spectrum (D_2O): 5.57 (1H, br. s, =CH—); 3.36 (2H, br. s, CH_2); 2.25 ppm (3H, s, CH_3).

3-Methyl-4-cyano-3-butenoic Acid 4-chlorophenylamide *E*-isomer (IIc). It was prepared by recrystallization of a mixture of isomers IIc first twice from ethanol—water mixture, 1:1, and then twice from ethanol. Mp = 131-134°C. R_f = 0.65. IR spectrum: 3352 (NH), 2233 (C≡N), 1688 cm^{-1} (C=O). PMR spectrum ($CDCl_3$): 7.2-7.5 (m, H_{arom}); 5.38 (1H, br. s, =CH—); 3.26 (2H, br. s, CH_2); 2.20 ppm (3H, s, CH_3).

A mixture of *Z*- and *E*-isomers IIc produces two spots in TLC with R_f = 0.65 (*E*-isomer) and R_f = 0.74 (*Z*-isomer). PMR spectrum of the mixture ($CDCl_3$): 7.2-7.5 (m, H_{arom}); 5.38 (1H, br. s, =CH—); 3.47 (0.7H, br. s, CH_2, *Z*-isomer); 3.26 (1.3H, br. s, CH_2, *E*-isomer); 2.20 (s, CH_3, *E*-isomer); 2.10 ppm (3H, d, J = 1.5 Hz, CH_3).

General Method of Preparation of Pyridones III and V. A. A solution of 0.1 g of NaOH in 10 ml of water was added to a solution of 2.5 mmole of the corresponding amide (IIa-e, Va,c) in 5 ml of ethanol and the mixture was heated while boiling with a reflux condenser for 30 min. The ethanol was eliminated in a vacuum, and the residue was acidified with 18% HCl to pH 5-6. The sediment was filtered off, washed with water, dried, and recrystallized.

B. Here 55 mg (0.25 mmole) of TEBAC and 0.20 g (5 mmole) of NaOH powder were added to a solution of 5 mmole of the corresponding amide (IIb,d,e) in 5 ml of dioxane (or methylene chloride) and stirred at 20°C until the compound disappeared in TLC (30-90 min). After the reaction ended, 20 ml of water was added to the mixture and it was acidified to pH 5-6 with 18% HCl. The organic solvent was eliminated in a vacuum, the sediment was filtered off, washed with water, dried, and recrystallized.

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