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SYNTHESIS AND PROPERTIES OF AMIDES OF 2-SUBSTITUTED 3-ARYL- AND 3-PYRIDYLAMINOACRYLIC ACIDS

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The reaction of aryl- or pyridylamines with ethyl orthoformate and malonanilic acid gave amides of 2-(N-arylcarbamoyl)-, 2-cyano-, 2-ethoxycarbonyl-3-arylaminoacrylic acids and their corresponding 3-pyridyl analogs. IR and PMR spectroscopy indicates that these compounds exist in the enamine form with strong intramolecular hydrogen bonds. Amides of 3-(2-pyridylamino)-2-ethoxycarbonylacrylic acid cyclize to give amides of pyrido[1,2-a]pyrimidine-3-carboxylic acid, which react with hydrazine hydrate to give amides of 3-aminopyrazole-4-carboxylic acid.

Enaminocarbonyl compounds, including enaminoamides, have found use in the synthesis of heterocyclic compounds [1] and serve as models for studying tautomeric transformations [2]. Podanyi et al. [3] have obtained 3-(2-pyridylamino)-2-cyanoacrylonitriles and found that these compounds display ring–chain tautomerism.

We have synthesized previously unreported amides of 2-substituted 3-aryl- and 3-pyridylaminoacrylic acids I-III and studied their conversion into amide derivatives of pyrazoles and pyridopyrimidines.

Amides I-III were obtained by heating equimolar amounts of aryl- or pyridylamines, ethyl orthoformate, and ethyl esters or arylamides of malonanilic acids or cyanoacetamides. Good yields of 2-cyano (Ia-Ik, Table 1), 2-ethoxycarbonyl- (IIa-IIc), and 2-(N-*p*-tolylcarbamoyl)-3-aryl(or pyridyl)aminoacrylic acids were obtained.

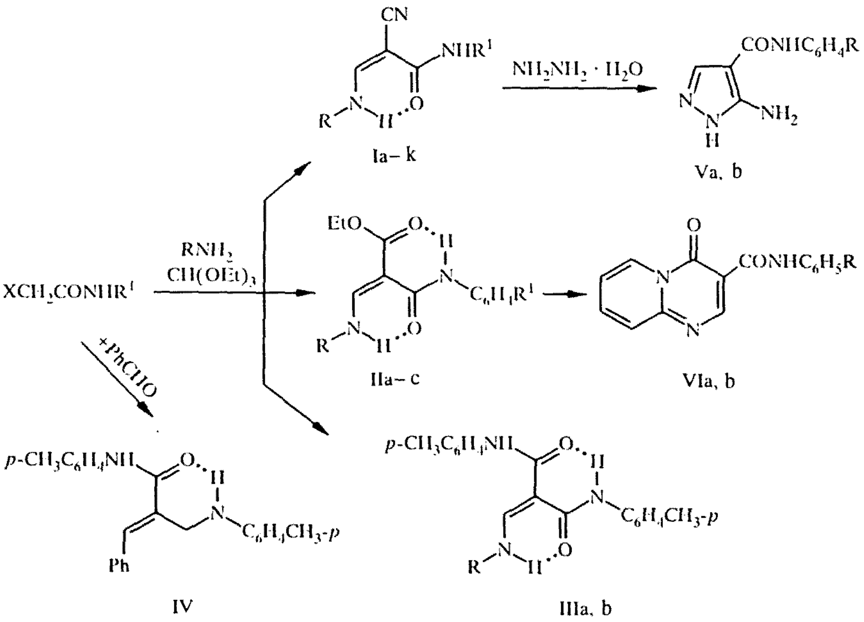

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TABLE 1. Characteristics of Products Synthesized

Compound	R	R^1	Chemical formula	mp, °C	PMR spectral parameters, δ, ppm					Yield, %
					ArH, m	-CH=C=, d	1H, s, NH (amide)	1H, d, NH (chelate)	other protons	
1	2	3	4	5	6	7	8	9	10	11
Ia	2-Pyridyl	H	$C_9H_8N_4O$	234...235	7,50	8,63	9,47	11,77	5,2 (s, NH_2)	87
Ib	4-Pyridyl	CH_3	$C_{10}H_{10}N_4O$	208...210	7,61	8,60	9,55	11,63	2,73 (s, CH_3)	84
Ic	4-Pyridyl	$CH_2{=}CH{-}CH_2$	$C_{12}H_{12}N_4O$	131...133	7,40	8,40	9,60	11,55	—	80
Id	2-Pyridyl	C_6H_5	$C_{15}H_{12}N_4O$	191...192	7,44	8,46	9,28	11,02	—	81
Ie	2-Pyridyl	o-ClC_6H_4	$C_{15}H_{11}ClN_4O$	163...164	7,40	8,50	9,30	11,40	—	88
If	4-Pyridyl	p-$CH_3C_6H_4$	$C_{16}H_{14}N_4O$	195...197	7,44	8,60	9,89	11,43	2.55 (s, CH_3)	85
Ig	C_6H_5	C_6H_5	$C_{16}H_{13}N_3O$	143...145	7,35	8,40	9,30	11,45	—	72
Ih	C_6H_5	$C_6H_5CH_2$	$C_{17}H_{15}N_3O$	140...142	7,30	8,33	9,27	11,35	—	74
Ii	C_6H_5	p-$CH_3C_6H_5$	$C_{17}H_{15}N_3O$	152...153	7,36	8,46	9,48	11,60	2,4 (s, CH_3)	75
Ij	m-$CH_3C_6H_5$	C_6H_5	$C_{17}H_{15}N_3O$	121...123	7,26	8,48	9,20	11,43	2.3 (s, CH_3)	77
Ik	m-$CH_3C_6H_5$	m-$C_2H_5OC_6H_4$	$C_{19}H_{19}N_3O_2$	153...155	7,35	8,50	9,35	11,20	3,35 (q, CH_2), 1,2 (t, CH_3)	70
IIa	2-Pyridyl	H	$C_{17}H_{17}N_3O_3$	103...104	7,76	9,17	—	10,87 s, 12,10	1,27 (t, $CH_3\underline{CH_2}OCO$), 4,27 (q, $\underline{CH_3}CH_2OCO$)	75
IIb	2-Pyridyl	p-Br	$C_{17}H_{16}BrN_3O_3$	134...135	7,75	9,17	—	10,80 s, 12,00	1,27 (t, $CH_3\underline{CH_2}OCO$), 4,23 (q, $\underline{CH_3}CH_2OCO$)	78
IIc	p-$CH_3C_6H_4$	p-CH_3	$C_{20}H_{22}N_2O_3$	168...170	7,75	8,53	—	10,85 s, 12,20	1,27 (t, $CH_3\underline{CH_2}OCO$), 4,20 (q, $\underline{CH_3}CH_2OCO$)	62
IIIa	C_6H_5	—	$C_{24}H_{23}N_3O_2$	203...205	7,43	8,33	9,87	11,4, 11,8	2,2 (s CH_3)	85
IIIb	2-Pyridyl	—	$C_{23}H_{22}N_4O_2$	193...195	7,53	8,77	9,85	11,17, 11,83	2,2 (s, CH_3)	87
IVa	H	—	$C_{24}H_{22}N_2O_2$	170...172	7,47	8,10	9,87	11,20	2,2 (s, CH_3)	82

TABLE 2. Characteristics of Va, Vb, VIa, and VIb

Compound	R	Chemical formula	mp, °C	IR spectrum, ν, cm^{-1}				PMR spectrum, δ, ppm				Yield, %
				CO	NH (pyrazole)	NH (amide)	NH_2	ArH, M	NH, S. (pyrazole)	NH, S. (amide)	other protons	
Va	2-Pyridyl	$C_{10}H_{10}N_4O$	195..197	1670	3110	3200	3270, 3300	7,40	8,55	9,15	3,9 (NH_2)	56
Vb	4-Pyridyl	$C_{19}H_{19}N_3O_2$	153..155	1680	3120	3220	3260, 3310	7,53	8,60	9,20	4,1 (s, NH_2) 3,4 (q CH_2) 1,2 (t CH_3)	70
VIa	2-Pyridyl	$C_{15}H_{11}N_3O_2$	248...250	1670	—	3200	—	7,55	—	9,1	—	88*
VIb	4-Pyridyl	$C_{15}H_{10}BrN_3O$	278...280	1680	—	3180	—	7,5	—	9,15	—	83*

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*Yields upon cyclization in acetic acid.

In order to compare the properties of amides I-III, we obtained the di-*p*-toluidide of benzylidenemalonic acid (IV) by the condensation of the di-*p*-toluidide of malonic acid with benzaldehyde.

The PMR signals for amides Ia-Ik at 8.33-8.63 (—CH═C═) and 11.02-11.77 ppm (NH) indicate that these compounds, similar to their analogs [2], exist in enamine form as the *Z* form with strong intramolecular hydrogen bonding. The PMR spectra of Ia-Ik show signals for the amide group protons at 9.20-9.89 ppm. On the other hand, the chemical shifts of the protons of both nitrogen atoms in IIa-IIc are greater than 10 ppm. This finding suggests that the hydrogen atoms of the amino and amide groups are involved in a chelation-type intramolecular hydrogen bond, while IIa-IIc have *E* configuration. This hypothesis was also supported by IR spectroscopy, which shows that the ester CO stretching bands are unusually shifted toward lower frequencies to 1670-1680 cm^{-1}.

The amine and amide group hydrogen atoms in IIIa and IIIb are also involved in intramolecular hydrogen bonding and their PMR signals are found downfield at 10.87-12.1 ppm. Furthermore, the PMR spectra of IIIa and IIIb have a singlet for the protons of the free amide group at 9.85-9.87 ppm. The capacity of diamides to form an intramolecular hydrogen bond is supported by the PMR spectrum of IV, which displays signals of the chelate proton at 11.2 ppm and of the proton of the free amide group at 9.87 ppm.

We might have expected ring–chain tautomerism for Ia-Ik by analogy with 3-(2-pyridylamino)-2-cyanoacrylonitriles [3]. However, the UV maximum at 390 nm characteristic for the ring is absent in the spectrum of amide Id in ethanol, indicating that this compound exists as the open-chain tautomer.

The reaction of enaminonitriles with hydrazine hydrate and enaminonitriles Ia-Ik, which contain a carbamoyl residue in addition to the nitrile group, had not been studied. We showed that heating Ij and Ik with hydrazine hydrate in dioxane at reflux gives substituted amides of 3-aminopyrazole-4-carboxylic acid Va and Vb (Table 2). The amide group does not undergo hydrazinolysis. The reaction of hydrazine hydrate with the enamine fragment of Ij and Ik is probably the initial step, giving an amide of 3-hydrazino-2-cyanoacrylic acid as an intermediate, which then cyclizes.

Amides of 2-carboethoxy-3-(2-pyridylamino)acrylic acid (IIa and IIb) cyclize upon heating in ethyleneglycol and also upon the action of polyphosphoric acid or concentrated acetic acid to give amides of 4-oxopyrido[1,2-*a*]pyrimidine-3-carboxylic acid (VIa and VIb, Table 2).

EXPERIMENTAL

The IR spectra were taken on a UR-20 spectrometer in vaseline mull. The PMR spectra were taken on an RYa-2310 spectrometer at 60 MHz with HMDS as the internal standard and DMSO-d_6 as the solvent. The UV spectra were taken on an SF-16 spectrometer. The characteristics of the compounds obtained are given in the tables.

The elemental analysis data for C, H, and N corresponded to the calculated values.

Amides of 2-Cyano- (Ia-Ik) and 2-Ethoxycarbonyl-3-aryl(or pyridyl)aminoacrylic Acids (IIa-IIc). A solution of 0.01 mole aryl- or pyridylamine and 0.01 mole corresponding amide of cyanoacrylic or ethyl ester of malonanilic acid in 20 ml ethyl orthoformate was heated at reflux for 6 h and cooled. The residue was filtered off and crystallized from ethanol. IR spectra of Ia-Ik: 1635-1680 (CO), 2205-2220 (CN), 3120-3220, 3340-3380 (NH) cm^{-1}. IR spectra of IIa-IIc: 1635-1640 (CO), 1670-1680 (ester CO), 3190-3220, 3300-3380 (NH) cm^{-1}. UV spectrum of Id, λ_{max} (log ε): 278 (4.1), 334 nm (4.57).

***p*-Toluidides of 2-(*p*-Tolylcarbamoyl)-3-phenyl(or 2-pyridyl)aminoacrylic Acids (IIIa and IIIb).** A solution of 0.01 mole aniline or 2-aminopyridine and 0.01 mole malonic acid di-*p*-toluidide in 20 ml ethyl orthoformate was heated at reflux for 8 h and cooled. The precipitate formed was crystallized from dioxane.

Di-*p*-toluidide of 3-Benzylidenemalonic Acid (IV). A mixture of 2.82 g (0.01 mole) malonic acid di-*p*-toluidide and 1.6 g (0.015 mole) benzaldehyde in 20 ml *o*-xylene was heated at 180°C for 6 h and cooled. The precipitate was filtered and crystallized from dioxane.

Arylamides of 2-Aminopyrazole-4-carboxylic Acid (Va and Vb). A solution of 0.01 mole of corresponding amide Ij or Ik and 0.015 mole 85% hydrazine hydrate in 10 ml dioxane was heated at reflux for 4 h and cooled. The precipitate formed was crystallized from ethanol.

Arylamides of 4-Oxopyrido[1,2-*a*]pyrimidine-3-carboxylic Acid (VIa and (VIb). A. A solution of 0.01 corresponding amide of 2-ethoxy-(3-(2-pyridylamino)acrylic acid (IIa or IIb) in 10 ml concentrated acetic acid was heated at reflux for 12 h, cooled, diluted by adding water, and neutralized by adding 10% aqueous NaOH. The precipitate formed was filtered and crystallized from dioxane.

B. A mixture of 3.11 g (0.01 mole) IIa and 1 g polyphosphoric acid was heated at 150°C for 6 h, cooled, diluted by adding water, and neutralized by adding 10% aqueous NaOH. The precipitate formed was filtered and crystallized to give 2.0 g (75%) VIa.

C. A sample of 3.11 g (0.01 mole) IIa in 15 ml ethyleneglycol was heated at 180°C for 5 h, cooled, and diluted by adding water to give 2.12 g (80%) VIa. The melting points of the samples obtained in procedures A, B, and C were identical. IR spectra of Va and Vb [this should be VIa and VIb]: 1645-1660, 1670-1680 (CO), 3200-3300 (NH) cm^{-1}.

Ethyl Ester of *p*-Bromomalonanilic Acid. A mixture of 17.2 g (0.1 mole) *p*-bromomalonaniline, 24 g (0.15 mole) ethyl malonate was heated at 130°C for 3 h. The reaction mixture was diluted with 50 ml hot ethanol and the precipitate was filtered off. The filtrate was diluted with water and the precipitate formed was separated and crystallized from benzene. The product yield was 14.3 g (50%), mp 95°C.

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