Aminoamidines
7.* 2-(Arylaminomethyl)imidazolines and their acylated derivatives

E. E. Korshin, L. I. Sabirova, A. G. Akhmadullin, and Ya. A. Levin*

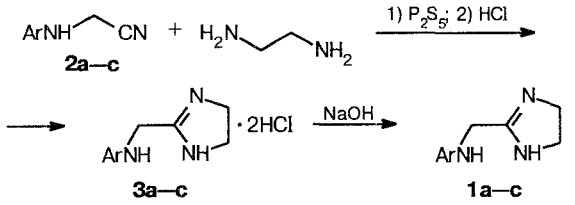
A. E. Arbuzov Institute of Organic and Physical Chemistry, Kazan' Research Center of the Russian Academy of Sciences, 8 ul. Akad. Arbuzova, 420083 Kazan', Russian Federation. Fax: +7 (095) 275 2253

2-(Arylaminomethyl)imidazolines were prepared by the reaction of arylaminoacetonitriles with ethylenediamine in the presence of catalytic amounts of P_2S_5. These imidazolines react with aroyl chlorides (1 : 2 ratio) to give diacylation products. In the case of a 1 : 1 mole ratio as well as on treatment with Ac_2O in Et_3N, monoacylation at the imidazoline ring predominantly occurs. Isomeric 2-(*N*-benzoyl-*N*-arylaminomethyl)imidazolines were obtained from *N*-benzoyl-*N*-arylaminoacetonitriles by the Pinner method. 2-(*N*-Aroyl-*N*-arylaminomethyl)benzimidazoles and -benzoxazoles were synthesized in a similar way.

Key words: 2-(arylaminomethyl)imidazoline; acylation; isomerism; hydrolysis; benzimidazole; benzoxazole.

2-(Arylaminomethyl)imidazolines (AIM), *i.e.*, cyclic amidines of *N*-aryl-substituted glycines, are of considerable interest owing to their biological activity.[2—10] For example, phentolamine, 2-[*N*-phenyl-*N*-(3′-hydroxyphenyl)aminomethyl]imidazoline,[2,3] and antazoline, 2-(*N*-benzyl-*N*-phenylaminomethyl)imidazoline,[2] are well known drugs with antihypertensive and anticardioarhytmic action, respectively. A wide range of AIMs have been recently proposed as pharmaceuticals[2,4,5] and pesticides.[6—8,10] In spite of this, the chemical behavior of AIMs possessing NH bonds in the imidazoline ring and in amino groups has been poorly studied,[6] and the structures of the products obtained require more accurate determination.

The AIMs are mostly obtained by treatment of 2-chloromethylimidazoline with aromatic amines,[3,7,10,11] interaction of arylaminoacetonitriles with ethylenediamine (EDA) *p*-toluenesulfonate,[4,5,7,10] or treatment of iminoesters or thioamides of α-arylaminocarboxylic acids with EDA.[7,10] To synthesize 2-(phenylaminomethyl)imidazoline (**1a**) and its *p*-tolyl analog (**1b**) we tested the former two methods. However, they proved to be less successful than those developed by us by analogy with the procedure proposed previously[12] which consisted of heating arylaminoacetonitriles (**2**) with EDA in the presence of catalytic amounts of P_2S_5 at 80—120 °C.



1—3: Ar = Ph (**a**), *p*-MeC_6H_4 (**b**), *p*-ClC_6H_4 (**c**)

Strong resinification of the reaction mixture occurs above 130 °C; furthermore, the reaction proceeds very slowly without the catalyst. When compound **1c** is obtained, there is no need to transform it into the hydrochloride (**3c**) with subsequent neutralization. However, these stages markedly ease the purification of the target products in the case of compounds **1a,b**. No doubt, other AIMs can also be obtained by the method proposed, but the introduction of substituents at the methylene group of nitrile **2** can dramatically decrease the efficiency of this process. For example, our repeated attempts to obtain an imidazoline from α-phenylaminophenylacetonitrile were unsuccessful.

It has been shown previously[13,14] that monoacylation of aryl-substituted α- and β-aminoamidines both in the presence and in the absence of bases occurs at the less basic amino group, while reactions of α-aminoamidines with aliphatic acyl chlorides give imidazolium salts.[15,16] Therefore, the result of the action of acylating reagents on compound **1** was not obvious, despite the substantial difference in the basicity of the nucleophilic centers in AIM **1** (pK_a of *N*-ethylaniline in water is 5.11 pK units,[17] while that of 2-methylimidazoline is 11.09 pK units[18]).

It turned out that the reactions of compound **1a** with AcCl and BzCl in the absence of bases afford complex mixtures; no individual products could be isolated from them. The reactions of AIM **1a** with BzCl or

For part 6, see Ref. 1.

Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 3, pp. 472—479, March, 1994.

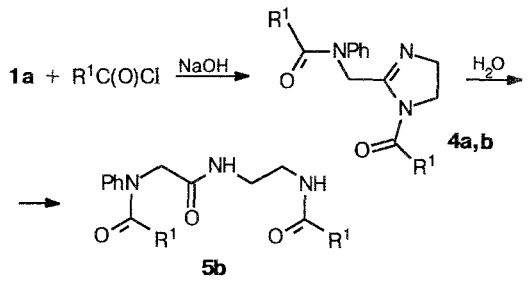
1066-5285/94/4303-0431 $12.50

Table 1. Parameters of the compounds synthesized

Compound	Yield (%)	M.p./°C	Found / Calculated (%)				Molecular formula
			C	H	Hal	N	
1a	78	85—86	68.22 68.57	7.39 7.43	—	23.39 24.00	$C_{10}H_{13}N_3$
1b	72	101—102	70.00 69.84	7.99 7.94	—	22.01 22.22	$C_{11}H_{15}N_3$
1c	83	147—148	57.41 57.28	5.92 5.73	16.71 16.94	19.96 20.05	$C_{10}H_{12}ClN_3$
3a	88	180—182	49.50 48.39	6.28 6.05	28.54 28.62	16.68 16.94	$C_{10}H_{15}Cl_2N_3$
3b	84	162—163	50.29 50.38	6.15 6.49	26.81 27.10	16.74 16.03	$C_{11}H_{17}Cl_2N_3$
4a	52	196—197	75.64 75.00	5.73 5.73	—	11.04 10.94	$C_{24}H_{21}N_3O_2$
4c	75	205—206	76.00 75.57	5.81 5.79	—	11.17 10.58	$C_{25}H_{23}N_3O_2$
4d	49	178—180	53.53 54.07	3.87 3.79	28.51 28.80	7.92 7.57	$C_{25}H_{21}Br_2N_3O_2$
5b	70	191—193	58.72 58.66	4.60 4.28	—	14.02 14.26	$C_{24}H_{21}N_5O_7$
6a	58	115—117	73.35 73.12	6.35 6.09	—	15.57 15.05	$C_{17}H_{17}N_3O$
6c	46.5	125—127	73.74 73.72	6.59 6.49	—	14.17 14.33	$C_{18}H_{19}N_3O$
6d	67	113—115	57.60 58.08	5.12 4.84	21.00 21.48	10.70 11.29	$C_{18}H_{18}BrN_3O$
6e	59	161—162	63.87 63.91	5.59 5.32	—	16.56 16.57	$C_{18}H_{18}N_4O_3$
6f	60	113—116	66.04 66.40	7.07 6.91	—	12.02 12.35	$C_{12}H_{15}N_3O$
6g	50	107—108	67.50 67.53	7.61 7.36	—	17.95 18.18	$C_{13}H_{17}N_3O$
7a	73	101—102	72.66 73.12	6.53 6.09	—	14.55 15.05	$C_{17}H_{17}N_3O$
7c	75	80—82	73.52 73.72	6.60 6.48	—	14.58 14.33	$C_{18}H_{19}N_3O$
9a	64	126—127	63.75 64.05	6.33 5.97	11.13 11.15	9.02 8.79	$C_{17}H_{18}ClN_2O_2$
9b	77	135—136	56.50 56.12	5.15 4.95	9.44 9.77	11.63 11.77	$C_{17}H_{18}ClN_3O_4$
9c	86	132—133	64.81 64.91	6.97 6.31	10.57 10.67	8.57 10.67	$C_{18}H_{20}ClN_2O_2$
10a	82	243—247 (dec.)	64.03 64.66	5.97 5.40	11.44 11.25	13.87 13.30	$C_{12}H_{18}ClN_3O$
10c	80	250—253 (dec.)	65.20 65.25	6.50 6.07	10.07 10.77	12.51 12.70	$C_{18}H_{20}ClN_3O$
11a	68	135—137	68.37 68.69	6.10 6.40	—	14.70 14.14	$C_{17}H_{19}N_3O_2$
12a	80	154—155	62.57 62.34	4.32 4.18	16.92 17.32	8.79 9.09	$C_{24}H_{20}BrN_3O_2$
13	88.5	101—102	64.53 64.57	4.97 4.93	—	12.59 12.56	$C_{24}H_{22}N_4O_5$
14a	97	241	77.33 77.06	5.35 5.20	—	12.72 12.84	$C_{21}H_{17}N_3O$
14b	96	263—264	68.16 67.74	4.38 4.30	—	15.27 15.05	$C_{21}H_{16}N_4O_3$
14c	75	252	76.92 77.42	5.81 5.57	—	12.64 12.32	$C_{22}H_{19}N_3O$
15a	77	145—146	77.00 76.83	5.24 4.88	—	8.81 8.54	$C_{21}H_{16}N_2O_2$
15c	26	113—114	76.40 76.30	5.56 5.20	—	8.17 8.09	$C_{22}H_{18}N_2O_2$

p-$NO_2C_6H_4C(O)Cl$ (reagent ratio 1 : 1) by the Schotten—Baumann method dominantly result in dibenzoylation products. However, an acylated AIM (**4a**) is obtained in the former case, while an ethylenediamide (**5b**), which is a product of hydrolytic opening of the imidazoline ring in di-(p-nitrobenzoyl)-AIM (**4b**), is formed in the latter case.

The yields, melting points, and elemental analysis data for the compounds obtained are presented in Table 1. The ^1H NMR, IR, and UV spectral data for the AIMs and their acylated derivatives are given in Table 2.



4, 5: R^1 = Ph (**a**), p-$NO_2C_6H_4$ (**b**)

Table 2. IR, UV, and ^1H NMR spectra of AIMs and their acylated derivatives

Compound	IR, ν/cm^{-1} [a]				UV, λ_{max}/nm (log ε)[b]	^1H NMR, δ (*J*/Hz)[c]		
	C=N	C=O	NH	C=C arom.		CH_2(2 H)	CH_2CH_2 (4 H)	Ar, R^1, R^2, NH
1a	1620	—	3120; 3270	1505; 1605	240 (4.04); 290 (3.20)	3.87 (br.s)	3.57 s	4.56 (br.s, 2 H, 2 NH); 6.43—7.23 (m, 5 H, Ph)
1b	1608	—	3175; 3322	1508; 1608	239 (4.20); 295 (3.33)	3.80 (br.s)	3.52 s	2.20 (s, 3 H, Me); 4.37 (br.s, 2 H, 2 NH); 6.39 (d, 2 H, H arom., *J* = 8.5); 6.84 (2 H, H arom., *J* = 8.5)
1c	1620	—	3160; 3408	1508; 1603	246 (4.23); 299 (3.25)	3.72 d (*J* = 5)	3.40 s	5.33 (br.s, 1 H, NH im.); 5.88 (t, 1 H, NH am., *J* = 5); 6.53 (d, 2 H, H arom., *J* = 8.5); 7.02 (d, 2 H, H arom., *J* = 8.5)
3a	1620	—	2350; 2505; 2560; 2640; 2665; 3155; 3245	1495; 1585; 1612	242 (4.20); 292 (3.18)	4.28 (br.s)	3.92 s	6.57—7.33 (m, 5 H, Ph)
3b	1618	—	2405; 2515; 2560; 2660; 3090; 3245	1520; 1618	242 (4.27); 299 (3.26)	4.33 (br.s)	3.96 s	2.26 (s, 3 H, Me); 6.75 (d, 2 H, H arom., *J* = 9); 7.07 (d, 2 H, H arom., *J* = 9)
4a	1645	1662	—	1495; 1580; 1598	263 sh (4.04)	5.16 s	3.83 (br.s)	6.87—7.58 (m, 15 H, 3 Ph)
4c	1642	1662	—	1495; 1514; 1590; 1607	232 sh (4.39); 255 sh (4.25)	5.13 s	3.84 (br.s)	2.26 (s, 3 H, Me); 6.99 (d, 2 H, H arom., *J* = 8.0); 7.10 (d, 2 H, H arom., *J* = 8.0); 7.18—7.55 (m, 10 H, 2 Ph)
4d	1640	1668	—	1490; 1518; 1592; 1610	234 (4.41); 262 sh (4.19)	5.07 s	3.82 (br.s)	2.28 (s, 3 H, Me); 7.00 (br.s, 4 H, MeC_6H_4); 7.20 (s, 4 H, BrC_6H_4); 7.31 (d, 2 H, H arom., *J* = 9); 7.51 (d, 2 H, H arom., *J* = 9)
5b	—	1650; 1680	3308; 3373	1500; 1525; 1605	261 (4.28); 286 sh (4.19)	4.46 (br.s)	3.36 (br.s)	7.22 (br.s, 5 H, Ph); 7.53 (d, 2 H, H arom., *J* = 7.8); 8.05 (d, 2 H, H arom., *J* = 7.8); 8.27 (d, 2 H, H arom., *J* = 8.3); 8.82 (br.s, 2 H, 2 NH)
6a	1655 sh	1674	3410	1515; 1580; 1602	245 (4.30); 302 sh (3.47)	4.30 (br.s)	3.75 (br.s)	6.40—7.53 (m, 5 H, Ph); 7.33 (s, 5 H, Ph)
6c	1652	1672	3395	1580; 1620	245 (4.19); 296 sh (3.19)	4.26 (br.s)	3.77 (br.s)	2.20 (s, 3 H, Me); 6.43 (d, 2 H, H arom., *J* = 8.5); 6.84 (d, 2 H, H arom., *J* = 8.5); 7.33 (s, 5 H, Ph)

Table 2 (*Continued*)

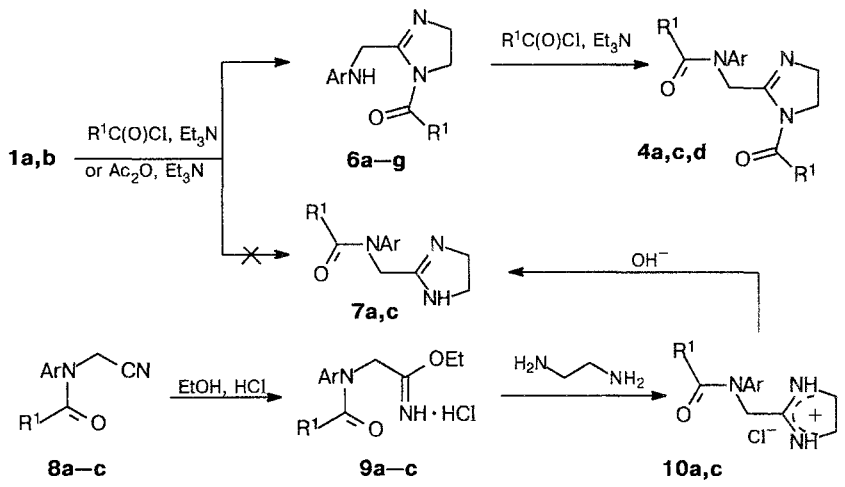
Compound	IR, ν/cm^{-1} [a]				UV, λ_{max}/nm ($\log\varepsilon$)[b]	^1H NMR, δ (J/Hz)[c]		
	C=N	C=O	NH	C=C arom.		CH_2(2 H)	CH_2CH_2 (4 H)	Ar, R^1, R^2, NH
6d	1650 sh	1669	3400	1485; 1590; 1619	244 (4.41)	4.30 (br.s)	3.73 (br.s)	2.20 (s, 3 H, Me); 6.45 (d, 2 H, H arom., J = 8.5); 6.85 (d, 2 H, J = 8.5); 7.21 (d, 2 H, J = 9.0); 7.44 (d, 2 H, J = 9.0)
6e	1657	1670	3415	1613	245 (4.37)	4.10 (br.s) (J = 4)	3.70 (br.s)	2.10 (s, 3 H, Me); 5.27 (br.s, 1 H, NH); 6.33 (d, 2 H, J = 8.5); 6.73 (d, 2 H, J = 8.5); 6.67 (d, 2 H, J = 9); 8.12 (d, 2 H, J = 9)
6f	1650	1680	3397	1510; 1580; 1604	239 (4.31); 291 (3.24)	4.33 (br.s)	3.81 (br.s)	2.13 (s, 3 H, MeCO); 4.63 (br.s, 1 H, NH); 6.43—7.20 (m, 5 H, Ph)
6g	1650	1680	3398	1580; 1615	240 (4.32); 293 (3.33)	4.35 (br.s)	3.88 (s.m)	2.11 (s, 3 H, MeCO); 2.23 (s, 3 H, Me); 5.16 (1 H, NH); 6.63 (d, 2 H, J = 8.3); 6.98 (d, 2 H, J = 8.3)
7a	1620	1645	3195	1495; 1597	—	4.54 s	3.47 s	4.82 (br.s, 1 H, NH); 6.93 (s, 5 H, Ph); 6.68—7.18 (m, 5 H, Ph)
7c	1630	1647	3210	1490; 1515; 1590; 1603	228 (4.20)	4.58 s	3.55 s	2.23 (s, 3 H, Me); 4.58 (s, 1 H, NH); 6.83 (s, 4 H, MeC_6H_4); 6.93—7.38 (m, 5 H, Ph)
10a	1615	1645	2400—2800	1505; 1590; 1598	228 sh (4.04)	4.85 s	3.80 s	6.83—7.48 (10 H, 2 Ph); 8.43 (br.s, 2 H, 2 NH)
10c	1615	1645	2400—2800	1498; 1520; 1585	228 sh (4.16)	4.90 s	3.87 s	2.23 (s, 3 H, Me); 6.83—7.67 (9 H, $Ph^+C_6H_4$); 8.80 (br.s, 2 H, 2 N^+H)
11a	—	1633; 1660; 1680	3357	1498; 1580; 1600	240 (4.23)	4.43 (br.s)	3.53 (br.s)	6.78—7.53 (m, 11 H, Ph^+NH); 7.80 (br.s, 2 H, 2 NH)
12a	1642	1665	—	1495; 1502; 1580; 1600	242 (4.30)	5.13 s	3.87 (br.s)	6.86—7.35 (m, 10 H, 2 Ph); 7.34 (d, 2 H, J = 8.5); 7.54 (d, 2 H, J = 8.5)
13b	—	1632; 1658; 1680	3285; 3375	1495; 1575; 1600	261 (4.28)	4.48 s	3.62 (br.s)	7.03—7.28 (m, 11 H, 2 Ph^+NH); 7.69 (br.s, 1 H, NH); 7.85 (d, 2 H, J = 8.8); 7.95 (d, 2 H, J = 8.8)

[a] In vaseline oil. [b] In MeCN. The spectra of compounds **1a**, **3a**, and **10** were recorded in EtOH, and those of compounds **4a** and **6a** in dioxane. [c] In $CDCl_3$. The spectra of AIM **3** were recorded in CD_3OD, and those of compounds **5b** and **10** in DMSO-d_6.

The IR spectrum of benzoylated AIM **4a** does not contain νNH absorption bands, whereas that for nitrobenzoylation product **5b** displays intense absorption bands at 3303 and 3373 cm^{-1}. The ^1H NMR spectrum of the latter contains four doublets of protons in nitrobenzoyl groups, each with 2 H intensity. The signal of the methylene protons of the ethylenediamine moiety, like that of the methylene protons of the imidazoline ring in **4a**, is recorded as a broadened singlet, but a weak-field shift (by ~0.45 ppm relative to imidazoline **4a** and its analogs) of the $\delta(CH_2)_2$ signal occurs in the spectrum of the nitrobenzoylation product. All of these facts indicate that we are, in fact, dealing with acyclic compound **5b** rather than with the isomeric diacyl-AIM monohydrate **4b**.

The hydrolytic lability of imidazolines is well known,[19] but the much higher ease of hydrolytic opening of the imidazoline ring in N^1-*n*-nitrobenzoylated AIM **4b** in comparison with N^1-benzoylated AIM **4a** is remarkable. For example, AIM **4a** does not undergo

Scheme 1



4, 6—10: Ar = R^1 = Ph (**a**); Ar = Ph, R^1 = *p*-$NO_2C_6H_4$ (**b**); Ar = *p*-MeC_6H_4, R^1 = Ph (**c**); Ar = *p*-MeC_6H_4, R^1 = *p*-BrC_6H_4 (**d**); Ar = *p*-MeC_6H_4, R^1 = *p*-$NO_2C_6H_4$ (**e**); Ar = Ph, R^1 = Me (**f**); Ar = *p*-MeC_6H_4, R^1 = Me (**g**)

hydrolysis when boiled for 3 h in 10 % aqueous acetone, whereas the hydrolysis of **4b** occurs even at 10 °C. We also observed increased hydrolytic lability of the N^1-*n*-nitrobenzoylated imidazoline ring in other cases (see below).

Diaroyl-substituted AIMs **4** are also formed in good yields when AIMs **1** react with aroyl chlorides (reagent ratio 1 : 2) in the presence of excess Et_3N. When a reagent ratio of 1 : 1 is taken under the same conditions, monoaroylation products are formed. The acetylation of AIMs **1a,b** with acetic anhydride (1 : 1) in Et_3N also gives monoacetyl derivatives.

The monoacyl AIM derivatives can contain the acyl substituent at the nitrogen atom of the imidazoline ring (**6**) or at an α-amino group (**7**). To discriminate between these structures, we synthesized compounds definitely having the structures of 2-(*N*-benzoyl-*N*-arylaminomethyl)imidazolines **7a,c** by the Pinner method from the respective *N*-benzoyl-*N*-arylaminoacetonitriles (**8a,c**) *via* hydrochlorides of iminoesters (**9a,c**) and imidazolines (**10a,c**) (Scheme 1).

It should be mentioned that we could not synthesize AIM hydrochloride **10b** from iminoester **9b**. An attempt to obtain α-*N*-acetyl-substituted iminoester **9f** from nitrile **8f** by the Pinner method did not result in the target iminoester, probably due to its deacylation and transformation into the corresponding amide. This is quite typical of the behavior of α-aminonitriles under the Pinner reaction conditions.[20]

It turned out that compounds **7a,c** obtained by the Pinner reaction are not identical to the monobenzoylation products of AIMs **1a,b** but are their isomers. Thus, monobenzoylation of AIMs **1a,b** occurs at the imidazoline nitrogen atom to give compounds **6a,c**.

There are distinct differences in the spectral parameters of isomeric compounds **6a,c** and **7a,c** (see Table 2) which are valuable from the diagnostic viewpoint. For example, their electron spectra differ very strongly: isomers **6** have an intense absorption band with a maximum at 245 nm and a shoulder around 300 nm, which is typical of the nonacylated arylamino group.[13] On the other hand, the spectra of isomers **7** do not contain these bands but only incorporate a broad absorption band with λ_{max} < 220 nm (with a shoulder at 228 nm in the case of compound **7c**) probably consisting of an absorption band of the *N*-benzoylarylamino group[13] at 225—230 nm (the latter is easily seen in the spectra of compounds **8** and **9a,c**, Table 3) and of the imidazoline band[21,23] around 230 nm. The above difference arises from the fact that the absorption band of an aroylated arylamino group is shifted hypsochromically in comparison to that of a non-aroylated group, and the electronic spectra of imidazolines and their *N*-acylated derivatives do not contain absorption bands having maxima above 230 nm (*cf.* Refs. 21, 22).

The IR absorption and ^1H NMR spectra of isomers **6a,c** and **7a,c** also differ significantly. For example, a narrow ν(N—H) band of the arylamino group in compounds **6a,c** is observed in the region of 3400 cm^{-1}, whereas the broad ν(N—H) absorption band of the imidazoline ring in **7a,c** has a maximum at 3200 cm^{-1} (see Table 2). A narrow medium-intensity ν(C=N) absorption band of the imidazoline ring in α-*N*-benzoylated compounds **7a,c** appears in the region of 1615—1630 cm^{-1} typical of *N*-unsubstituted imidazolines, whereas benzoylation at the imidazoline ring (isomers **6a,c**) results in a short-wave displacement of the ν(C=N) band to 1650—1655 cm^{-1}. The maxima of the ν(C=O) absorption bands for benzoylated AIMs **6a,c** are located notably higher (by up to 30 cm^{-1}) than for compounds **7a,c**.

The resonance signal of the methylene protons of the

imidazoline ring in compounds **7a,c** is recorded as a narrow singlet in the region of 3.5 ppm, and the signal of the methylene protons at C(2) has δ ~ 4.55, $\Delta[\delta(CH_2)-\delta(CH_2)_2]$ ~ 1.0. On the contrary, the signal of the methylene protons of the imidazoline ring in N^1-acylated AIMs **6a,c** appears as a broadened singlet or a poorly resolved multiplet in the region of 3.75 ppm, and the signal shape indicates the nonequivalence of the ring protons. The signal of the protons of the methylene group at C(2) in AIMs **6a,c** is also a broadened singlet with δ ~ 4.3, probably due to the presence of a coupling constant $^3J_{NHCH}$ ~ 1 Hz, while Δ is ~ 0.5 ppm.

An analysis of the spectral parameters of other monoacylation products derived from AIM **1** (see Table 2) indicates that they are analogous to the parameters of compounds **6a,c**, acylated at the imidazoline ring, rather than of **7a,c**. Hence, these products are also acylated at the ring (compounds **6d—f**).

In relation to the synthesis of diacyl-substituted AIMs **4**, it was interesting to reveal whether direct acylation at the α-amino group occurs or compounds **6** initially undergo isomerization into **7** with subsequent acylation at the imidazoline ring. We found that, according to ^{1}H NMR spectral data, mutual transformations **6** ⇄ **7** do not take place either on prolonged (30 days) storage of solutions of these compounds at ~20 °C or on heating the solutions in MeCN, Et_3N, or $CHCl_3$ for 3 h at 80—90 °C. Thus, direct acylation of monoacyl-derivatives **6** at the α-amino group is likely to occur.

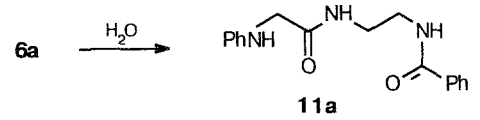
Type **6** AIMs are much less resistant to hydrolysis than dibenzoyl-substituted AIMs **4**. For example, keeping a solution of **6a** in 5 % aqueous acetone for ~20 min

Table 3. IR, UV, and ^{1}H NMR spectra of nitriles **8**, iminoesters **9**, benzimidazoles **14**, and benzoxazoles **15**

Compound	IR,[a] ν/cm^{-1}	UV,[b] λ/nm (log ε)	^{1}H NMR, δ (*J*/Hz)[c]
8a	1495, 1585, 1598 (C=C arom.); 1663 (C=O); 2262 (C≡N)	225 sh (4.11)	4.78 (s, 2 H, CH_2); 6.93—7.57 (m, 10 H, 2 Ph)
8b	1356, 1532 (NO_2); 1497, 1588, 1598, 1605 (C=C arom.); 1667 (C=O); 2267 (C≡N)	261 (4.08); 284 (4.04)	4.75 (s, 2 H, CH_2); 6.90—7.25 (m, 5 H, Ph); 7.37 (d, 2 H, *J* = 9); 7.91 (d, 2 H, *J* = 9)
8c	1495, 1515, 1580, 1603 (C=C arom.); 1646 (C=O); 2260 (C≡N)	230 sh (4.15)	2.21 (s, 3 H, Me); 4.63 (s, 2 H, CH_2); 6.93 (s, 4 H, MeC_6H_4); 6.97—7.32 (m, 5 H, Ph)
8f	1496, 1593 (C=C arom.); 1670 (C=O); 2260 (C≡N)	225 sh (3.78)	1.95 (s, 3 H, Me); 4.60 (s, 2 H, CH_2); 7.17—7.60 (m, 2 H, CH_2)
9a	1503, 1580, 1600 (C=C arom.); 1648 (C=N); 1657 (C=O); 2400—2800 (N—H)	231 sh (3.85); 252 sh (3.74)	1.35 (t, 3 H, Me, *J* = 7); 4.53 (s.m, 2 H, CH_2O, *J* = 7); 5.00 (s, 2 H, CH_2); 7.10—7.43 (m, 10 H, 2 Ph)
9b	1355, 1530 (NO_2); 1500, 1588, 1600 (C=C arom.); 1650 sh (C=N); 1662 (C=O); 2400—2800 (N—H)	261 (4.04); 283 (3.97)	1.37 (t, 3 H, Me, *J* = 7); 4.48 (q, 2 H, CH_2O, *J* = 7); 4.90 (s, 2 H, CH_2); 7.00—7.27 (m, 5 H, Ph); 7.37 (d, 2 H, *J* = 9); 7.88 (d, 2 H, *J* = 9)
9c	1518, 1580, 1603 (C=C arom.); 1648 (C=N); 1655 (C=O); 2400—2800 (N—H)	229 sh (4.11)	1.37 (t, 3 H, Me, *J* = 7); 2.23 (s, 3 H, Me); 4.59 (q, 2 H, CH_2O, *J* = 7); 4.96 (s, 2 H, CH_2); 6.80—7.55 (m, 9 H, Ph + C_6H_4)
14a	1498, 1585, 1597 (C=C arom.); 1642 (C=N); 1650 (C=O); 2400—3300 (N—H)	245 (4.15); 253 sh (4.11); 269 sh (4.03); 276 sh (4.07); 283 (3.99)	5.17 (s, 2 H, CH_2); 6.77—7.47 (14 H, 2 Ph + C_6H_4)
14b	1355, 1532 (NO_2); 1498, 1597, 1605 (C=C arom.); 1648 (C=N); 1655 (C=O); 2400—3300 (N—H)	244 (4.37); 256 sh (4.32); 277 (4.29); 284 (4.28)	5.27 (s, 2 H, CH_2); 6.88—7.60 (m, 9 H, Ph + C_6H_4); 7.47 (d, 2 H, *J* = 9); 7.93 (d, 2 H, *J* = 9)
14c	1497, 1520, 1585, 1605 (C=C arom.); 1647 (C=N and C=O); 2400—3300 (N—H)	270 (4.19); 276 (4.17); 282 sh (4.05)	2.20 (s, 3 H, Me); 5.23 (s, 2 H, CH_2); 6.88 (s, 4 H, MeC_6H_4); 7.05—7.37 (m, 7 H, Ph + 2 H benzim.); 7.43—7.60 (m, 2 H, 2 H benzim.)
15a	1496, 1587, 1600, 1615 (C=C arom.); 1652 (C=N and C=O)	232 (4.36); 272 (3.96)	5.28 (s, 2 H, CH_2); 6.93—7.37 (m, 12 H, 2 Ph + 2 H benzox.)
15c	1498, 1515, 1580, 1610, 1621 (C=C arom.); 1650 (C=N and C=O)	233 (4.42); 272 (4.07); 278 (4.03)	2.20 (s, 3 H, Me); 5.33 (s, 2 H, CH_2); 6.93 (s, 4 H, MeC_6H_4); 7.07—7.47 (m, 7 H, Ph + 2 H benzox.); 7.53—7.68 (m, 2 H, 2 H benzox.)

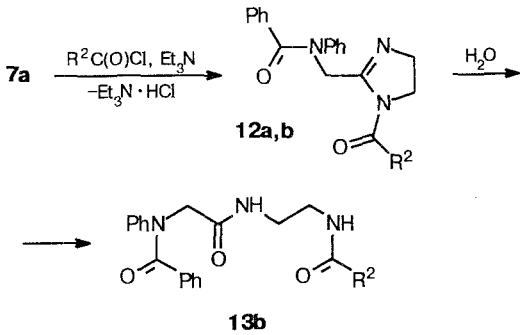
[a] In vaseline oil. [b] In dioxane. The spectra of iminoester salts **9** were recorded in EtOH, those of compounds **8a,f** and **14a,b** in MeCN. [c] In $CDCl_3$, spectra of compounds **9** in DMSO-d_6.

results in opening of the imidazoline ring to give ethylenediamide **11a**. The IR spectrum of this compound, unlike that of **6a**, contains a broad intense ν(N—H) absorption band with a maximum at 3357 cm^{-1}. The signal of the CH_2CH_2 moiety in the ^1H NMR spectrum is displaced ~0.2 ppm upfield relative to its position for **6a**.



11a

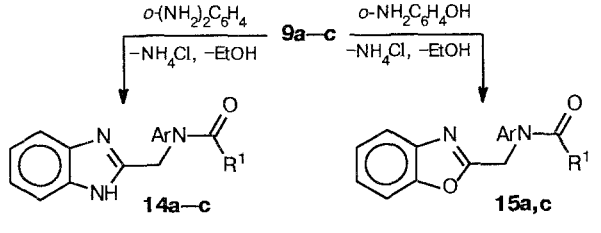
Like unsubstituted AIMs **1**, α-*N*-benzoyl-substituted AIM **7a** readily reacts with aroyl chlorides. For example, the reaction of **7a** with benzoyl chloride in the presence of Et_3N gives **4a** in 82 % yield. The reaction with *p*-bromobenzoyl chloride also occurs readily. The N^1-*p*-nitrobenzoylation product (**12b**), like its analog **4b**, is hydrolytically labile and cannot be isolated in an analytically pure form. Hydrolysis gives an acyclic ethylenediamide (**13b**). This compound was also obtained in a reaction of **7a** with *p*-$NO_2C_6H_4C(O)Cl$ by the Schotten—Baumann method.



13b

12, 13: R^2 = *p*-BrC_6H_4 (**a**), *p*-$NO_2C_6H_4$ (**b**)

The reactions of α-*N*-benzoylated iminoesters **9** with binucleophilic reagents can also be used in syntheses of the respective benzimidazoles (**14**) and benzoxazoles (**15**) (see Tables 1 and 3).



14, 15: Ar = R^1 = Ph (**a**); Ar = Ph, R^1 = *p*-$NO_2C_6H_4$ (**b**); Ar = *p*-MeC_6H_4, R^1 = Ph (**c**)

Experimental

IR spectra were recorded on a UR-20 spectrophotometer, and UV spectra were obtained on Specord UV-VIS and Specord M-40 spectrophotometers. ^1H NMR spectra were obtained on Varian T-60 (60 MHz) and Bruker WM-250 (250 MHz) spectrometers using Me_4Si as the internal standard.

The syntheses of α-aminonitriles **2** (*cf.* Refs. 23, 24) and their acylated derivatives (*cf.* Ref. 25) have been reported previously.

2-(Arylaminomethyl)imidazolines 1a,b and hydrochlorides 3a,b. A mixture of α-aminonitrile **2a,b** (0.2 mol), abs. EDA (0.7 mol), and P_2S_5 (0.01 mol) was heated for 2.5 h at 100—110 °C in a stream of Ar. The mixture cooled to ~20 °C was poured into ice-water, extracted with CH_2Cl_2 (3×100 mL), and dried with Na_2SO_4. The drying agent was then filtered off, and excess gaseous HCl was passed through the filtrate. The precipitate of compound **2** was filtered off, dried with CH_2Cl_2 and ether, and kept in a vacuum desiccator with KOH. The suspension of **2** in CH_2Cl_2 was kept for two days with a fivefold amount of granulated KOH and filtered, and the filtrate was concentrated *in vacuo*. The precipitate was recrystallized from Pr^i_2O to give AIMs **1a,b**.

2-(4-Chlorophenylaminomethyl)imidazoline 1c. A mixture of 4-chlorophenylaminoacetonitrile **2c** (0.2 mol), abs. EDA (0.7 mol), and P_2S_5 (0.01 mol) was heated for 1.5 h at 100—110 °C in a stream of Ar. The P_2S_5 was filtered off from the hot reaction mixture, which was then cooled to 20 °C and poured into ice-water. The precipitate was filtered off, washed with ether, and kept in a vacuum desiccator with KOH. Recrystallization from benzene gave product **1c**.

1-Benzoyl-2-(*N*-benzoylphenylaminomethyl)imidazoline 4a.

a. A solution of BzCl (0.56 g, 4.0 mmol) in CH_2Cl_2 (8 mL) was added at 0 °C to a two-phase mixture of AIM **1a** (0.60 g, 3.4 mmol) in CH_2Cl_2 (12 mL) and NaOH (0.18 g, 4.3 mmol) in water (8 mL), and the reaction mixture was stirred for 30 min at 20 °C. The organic layer was separated, washed with water, dried with Na_2SO_4, and concentrated *in vacuo*. The residue was recrystallized from MeOH, filtered off, and washed with MeOH and Et_2O to give compound **4a** (69 % with respect to BzCl).

b. BzCl (1.805 g, 12.9 mmol) in THF (5 mL) was added at −10 °C to a solution of **1a** (1.085 g, 6.2 mmol) and Et_3N (5 mL) in abs. THF (20 mL). The mixture was stirred for 3 h at 20 °C, the residue was filtered off, and the filtrate was concentrated *in vacuo*. The residue was crystallized in MeOH, filtered off, and washed with MeOH and Et_2O to give compound **4a** in 52 % yield. AIMs **4c,d** were obtained similarly according to procedure ***b***.

***N*-(*p*-Nitrobenzoyl)-*N*-phenylglycine 2-(*p*-nitrobenzamido)-ethylamide 5b.** A solution of *p*-nitrobenzoyl chloride (1.66 g, 8.6 mmol) in CH_2Cl_2 (10 mL) was added at 0 °C to a mixture of compound **1a** (0.71 g, 4.1 mmol) in CH_2Cl_2 (10 mL) and NaOH (0.41 g, 10.2 mmol) in water (10 mL). The reaction mixture was stirred for 30 min at 0 °C. The organic layer was separated, washed with ice-water, and dried with Na_2SO_4. The filtrate was concentrated *in vacuo*. The residue was recrystallized from a THF—ether mixture (1 : 2) to give product **5b** in 70 % yield.

1-Aroyl-2-(arylaminomethyl)imidazolines 6a,c—e. An aroyl chloride (5.1 mmol) in THF (5 mL) was added at 20 °C to a solution of AIM **1a,b** (5.0 mmol) and Et_3N (10 mmol) in abs. THF (25 mL). The mixture was stirred for 2 h, the precipitate

was filtered off and thoroughly washed with THF, the filtrate was concentrated *in vacuo*, and the residue was crystallized in abs. MeOH. The precipitate was filtered off, washed with abs. Et_2O, and dried *in vacuo*.

1-Acetyl-2-(arylaminomethyl)imidazolines 6f,g. Ac_2O (10.2 mmol) was added to a suspension of AIM **1a,b** (10.0 mmol) in Et_3N (15 mL), and the mixture was stirred for 3 h and kept for 20 h at 20 °C. The precipitate was filtered off, washed with Et_2O, recrystallized from Et_3N, and dried *in vacuo*.

Hydrochlorides of *O*-ethyl-α-*N*-aroyl-α-*N*-arylglycineimidates 9a—c. A fivefold excess of dry gaseous HCl was passed at 0—5 °C through a solution of *N*-aroyl-*N*-arylaminoacetonitrile **8a—c** (0.1 mol) and abs. EtOH (20 mL) in abs. CH_2Cl_2 (200 mL). The mixture was kept for 20 h at 0 °C, filtered off, and concentrated *in vacuo* at 20 °C. The residue was crystallized in a mixture CH_2Cl_2—ether (1 : 2) at −5 °C, filtered off, washed with ether, and dried *in vacuo*.

Hydrochlorides of 2-(*N*-benzoyl-*N*-arylaminomethyl)imidazolines 10a,c and free 2-(*N*-benzoyl-*N*-arylaminomethyl)imidazolines 7a,c. An iminoester hydrochloride **9a,c** (3.3 mmol) was added portionwise to a solution of EDA (3.0 mL, 4.5 mmol) in abs. EtOH (150 mL) cooled to −10 °C, and the mixture was stirred at this temperature for 1.5 h. Then a solution of HCl (2.0 g, 55.0 mmol) in abs. EtOH (100 mL) was added, and the mixture was kept for 20 h at 0—5 °C. The precipitate was filtered off, and the filtrate was concentrated *in vacuo* to 40—50 mL. The precipitate of hydrochloride **10a,c** was filtered off and washed with ether. Free bases **7** were obtained by treatment of suspensions of salts **10** in CH_2Cl_2 with a fivefold excess of 20 % NaOH; the organic extracts were washed with water, dried with Na_2SO_4, concentrated *in vacuo*, and recrystallized from a mixture CH_2Cl_2—ether (1 : 2).

***N*-Phenylglycine 2-benzamidoethylamide 11a.** A solution of AIM **6a** (0.42 g, 1.5 mmol) in 5 % acetone (10 mL) was stirred for 20 min at 20 °C and precipitated with petroleum ether (25 mL) at 40—70 °C. The precipitate was filtered off and recrystallized from an acetone—petroleum ether mixture (1 : 2) at 40—70 °C.

1-(*p*-Bromobenzoyl)-2-(*N*-benzoyl-*N*-phenylaminomethyl)imidazoline 12a. A solution of *p*-bromobenzoyl chloride (0.57 g, 2.6 mmol) in THF (3 mL) was added to a solution of AIM **7a** (0.56 g, 2.0 mmol) and Et_3N (0.26 g, 2.6 mmol) in abs. THF (10 mL). The mixture was stirred for 3 h at 20 °C and filtered off. The filtrate was concentrated *in vacuo*, and the residue was crystallized in abs. MeOH.

***N*-Benzoyl-*N*-phenylglycine 2-(*p*-nitrobenzamido)ethylamide 13b** was obtained similarly to amide **5b** from AIM **7a** (1.20 g, 4.3 mmol), *p*-nitrobenzoyl chloride (0.84 g, 4.5 mmol), and NaOH (0.27 g, 6.6 mmol). The product was recrystallized from an acetone—petroleum ether mixture (1 : 2).

2-(*N*-Aroyl-*N*-arylaminomethyl)benzimidazoles 14a—c. A mixture of iminoester hydrochloride **9a—c** (3.4 mmol) and *o*-phenylenediamine (4.3 g, 4.0 mmol) was dissolved in abs. EtOH (70 mL). The solution was stirred for 1 h at 20 °C and 20 min at 40—50 °C and then kept for 1 day to form a precipitate at 20 °C. The precipitate was filtered off and washed with water (3×20 mL) and EtOH (30 mL). Recrystallization from EtOH gave products **14**.

2-(*N*-Benzoyl-*N*-arylaminomethyl)benzoxazoles 15a,c were synthesized similarly to compounds **14**.

References

1. E. E. Korshin, R. M. Eliseenkova, T. A. Zyablikova, L. G. Zakharova, A. G. Akhmadullin, V. D. Nusinovich, and Ya. A. Levin, *Izv. Akad. Nauk, Ser. Khim.*, 1993, 1116 [*Russ. Chem. Bull.*, 1993, **42**, 1071 (Engl. Transl.)].
2. R. J. Grout, in *The Chemistry of Amidines and Imidates*, Ed. S. Patai, Interscience, London, 1975, 255.
3. M. V. Rubtsov and A. G. Baichikov, in *Sinteticheskie khimiko-farmatsevticheskie preparaty* [*Synthetic Chemico-pharmaceutical Preparations*], Meditsina, Moscow, 1971, 169 (in Russian).
4. US Pat. 4343810, *Chem. Abstrs.*, 1982, **97**, 175075.
5. US Pat. 4344958, *Chem. Abstrs.*, 1982, **97**, 188298.
6. US Pat. 4226876, *Chem. Abstrs.*, 1981, **95**, 43102.
7. US Pat. 4254133, *Chem. Abstrs.*, 1981, **94**, 186843.
8. Pat. FRG 2750902, *Chem. Abstrs.*, 1978, **89**, 141911.
9. Pat. FRG 3407072, *Chem. Abstrs.*, 1986, **104**, 16543.
10. Canadian Pat. 1109787, *Chem. Abstrs.*, 1982, **96**, 81362.
11. E. Urech, A. Marxer, and K. Miescher, *Helv. Chim. Acta*, 1950, **33**, 1386.
12. Japan Pat. 8354, *R. Zh. Khim.*, 1968, No. 24, 538.
13. E. E. Korshin, G. I. Soboleva, Ya. A. Levin, L. G. Zakharova, I. A. Litvinov, V. A. Naumov, E. A. Podval'nyi, and Yu. Ya. Efremov, *Zh. Org. Khim.*, 1992, **28**, 1242 [*J. Org. Chem. USSR*, 1992, **28** (Engl. Transl.)].
14. E. E. Korshin, L. G. Zakharova, Ya. A. Levin, L. Kh. Ashrafullina, E. A. Podval'nyi, and Yu. Ya. Efremov, *Izv. Akad. Nauk, Ser. Khim.*, 1992, 2633 [*Bull. Acad. Sci., Div. Chem. Sci.*, 1992, **41**, 2082 (Engl. Transl.)].
15. E. E. Korshin, G. I. Soboleva, Ya. A. Levin, E. A. Podval'nyi, and Yu. Ya. Efremov, *Zh. Org. Khim.*, 1993, **29**, 577 [*J. Org. Chem. USSR*, 1993, **29** (Engl. Transl.)].
16. E. E. Korshin, G. I. Mingazova, and Ya. A. Levin, *Khim. Geterotsikl. Soedin.*, 1989, 1694 [*Chem. Heterocycl. Compd.*, 1989 (Engl. Transl.)].
17. A. Albert and E. Sergeant, *Konstanty ionizatsii kislot i osnovanii* [*Ionization Constants of Acids and Bases*], Khimiya, Moskva—Leningrad, 1964, 139 (Russ. Transl.).
18. J. Elguero, E. Gonsales, J.-L. Imbach, and R. Jacquer, *Bull. Soc. Chim. Fr.*, 1969, 4075.
19. I. Perillo, B. Fernandez, and S. Lamdam, *J. Chem. Soc., Perkin Trans. 2*, 1977, 2068.
20. D. G. Nielson, in *The Chemistry of Amidines and Imidates*, Ed. S. Patai, Interscience, London, 1975, 385.
21. T. N. Kuz'micheva, M. N. Kudryavtseva, E. M. Kazinik, B. S. Kolomiets, and E. B. Tarkhanova, *Zh. Prikl. Khim.*, 1973, **46**, 2284 [*J. Appl. Chem. USSR.*, 1973, **46** (Engl. Transl.)].
22. P. L. Barker, P. L. Gendler, and H. Rapoport, *J. Org. Chem.*, 1981, **46**, 2455.
23. H. Bucherer and A. Schwalbe, *Chem. Ber.*, 1906, **39**, 2796.
24. A. Marxer, *Helv. Chim. Acta*, 1954, **37**, 166.
25. I. W. Elliott, *J. Am. Chem. Soc.*, 1955, **77**, 4408.

Received August 25, 1992