SYNTHESIS AND PROPERTIES OF ANALOGS OF 5(4)-AMINOIMIDAZOLE-4(5)-CARBOXAMIDE AND PURINES.

14.* ACYLATION OF 5(4)-AMINOIMIDAZOLE DERIVATIVES

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The acylation of 5(4)-aminoimidazole derivatives was studied. It is shown that acylation by means of carboxylic acid anhydrides and chlorides takes place at the amino group, whereas acylation by means of chlorocarbonic acid esters takes place at the nitrogen atoms of the imidazole ring. Methods for the selective introduction of a carbomethoxy group in the 1, 3, and 5 positions of the 5(4)-aminoimidazole-4(5)-carboxamide molecule were developed.

The acylation of 5(4)-aminoimidazole-4(5)-carboxylic acid derivatives leads to the manifestation of biologival activity by these compounds [2-5]. The aim of the present research was to investigate the acylation of 5(4)-aminoimidazoles in order to obtain new acylimidazoles.

Like other aminoazoles [6], aminoimidazoles are polyfunctional compounds in these reactions. Thus 5-acetamido-1(or 3)-acetylimidazole is formed in the reaction of 5(4)-aminoimidazole with acetic anhydride [7]. The reactions of 5(4)-aminoimidazole-4(5)-carboxamide (Ia) with formic acid and acetic anhydride lead to the production of only 5(4)-acylamido derivatives [3-5]. In the acylation of this compound with chlorocarbonic acid esters under virtually identical conditions the 5(4)-carbalkoxyamidoimidazole-4(5)-carboxamide structure was assigned to the acylation product in one case [8], whereas the 1-carbalkoxy-5-aminoimidazole-4-carboxamide structure was assigned in the other [9]; clear evidence for the structure of the compound was not presented in either of the cited papers, and the reasons that influence the direction of the reaction were not investigated.

In the present research we attempted to investigate the primary reaction pathway in each specific case using the principle of hard and soft acids and bases (HSAB) as applied to ambident systems [10]. We used the MO LCAO method within the Pariser–Parr–Pople (PPP) approximation to calculate the charges, electron densities in the boundary orbitals, the energies of the π-electron systems, and the bond orders for both tautomeric forms of 5(4)-aminoimidazole-4(5)-carboxamide (Ia), 5(4)-aminoimidazole-4(5)-thioamide (Ib), and 5(4)-aminoimidazole-4(5)-carbonitrile (Ic). As expected, the higher electron density from all of the nitrogen atoms is concentrated on the nitrogen atoms of the imidazole ring, whereas the highest electron density of the highest occupied molecular orbital (HOMO) is localized on the nitrogen atom of the amino group. Thus the amino group is the soft center of the ambident system, and the $N_{(1)}$ and $N_{(3)}$ atoms of the imidazole ring are hard centers.

Acylating agents are arranged as follows in the order of increasing hardness [10]: $CH_3COCl < ClCH_2COCl < ClCOOC_2H_5$.

In accordance with the HSAB principle, in the acylation of imidazoles Ia-c with "softer" agents (carboxylic acid anhydrides and chlorides) one may expect the primary formation of 5-acylamidoimidazoles, whereas one may expect the primary formation of 1(or 3)-carbalkoxyimidazoles in acylation with "hard" agents (chlorocarbonic acid esters).

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TABLE 1. IR and PMR Spectra of Acylimidazoles I-VII

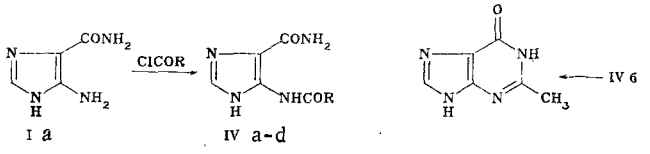
Compound	IR spectrum, ν_{CO}, cm^{-1}	PMR spectrum (in d_6-DMSO), δ, ppm	
		2-H	CH_3
Ia	1680	7,20	—
Ic	—	7,50	—
II	1680	7,65[a]	2,00
III	1680, 1720	8,51b, c	2,00; 2,51
IVb	1650, 1680	7,41	2,14
IVc	1660, 1705	7,35	—
IVd	1675		
Va	1680, 1765	7,65	4,00
Vb	1760	7,69	3,98
Vc	1760	7,69	3,97
VIa	1670, 1755		
VIc	1745	8,28	3,97
VII	1650, 1690	7,41	3,71

[a]7.37 ppm (1H, s, 4-H). [b]1H, d, J = 1.8 Hz. [c]8.05 ppm (1H, d, J = 1.8 Hz, 4-H).

5(4)-Acetamidoimidazole (II) and a diacylation product (III), which were obtained by the method in [7], were used as model compounds. However, evidence for the structure of III is not presented in [7]. Splitting of the signals of the 2-H and 4-H protons of the imidazole ring to give a doublet with a large spin–spin coupling constant is observed in the PMR spectrum of III (Table 1); this constitutes umambiguous evidence that the substituent is incorporated at the $N_{(1)}$ atom rather than at the $N_{(3)}$ atom. On the basis of this it may be assumed that the diacylation product has the 1-acetyl-5-acetamidoimidazole (III) structure. A comparison of the IR and PMR spectra of II and III makes it possible to conclude that the introduction of an acyl group into the imidazole ring leads to a weak-field shift of the signal of the 2-H proton and a shift of the frequency of the carbonyl absorption above 1700 cm^{-1} as compared with ν_{CO} 1680 cm^{-1} for the acetamido group.

We also used 5(4)-acetamidoimidazole-4(5)-carboxamide (IVb), the preparation of which was realized by the method in [4] and the structure of which was confirmed by conversion to 2-methylxanthine, which was identical to a genuine sample [12], as a model compound. As compared with the spectrum of imidazole Ia, a weak-field shift of the signal of the 2-H proton, but lower than the shift observed when an $N_{(1)}$-acyl group is introduced, is observed in the PMR spectrum of IVb. As in the case of II, the frequency of the carbonyl absorption of the acetamido group is found at 1650-1680 cm^{-1} in the IR spectrum (Table 1).

To investigate the effect of a solvent on the direction of the reaction we carried out the acylation of aminoimidazole Ia with acetyl chloride in polar and nonpolar solvents. In all cases we isolated only 5(4)-acetamidoimidazole-4(5)-carboxamide (IVb), the structure of which was confirmed by IR and PMR spectroscopy. Consequently, the choice of solvent does not determine the direction of this reaction.



I a IV a-d

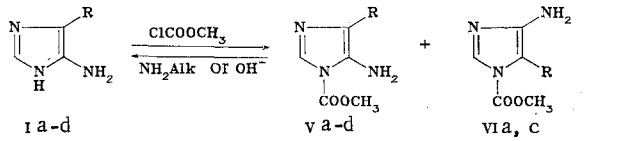
IV a R=H, b R=CH_3, c R=C_6H_5, d R=p-NO_2—C_6H_4

Individual compounds, in the IR spectra of which in the region of carbonyl absorption at 1650-1705 cm^{-1}, along with the ν_{CO} band of the carboxamide group, additional bands, which were assigned to the stretching vibrations of the acyl carbonyl group (Table 1), appear, were isolated in the acylation of imidazole Ia with benzoyl chloride and p-nitrobenzoyl chloride both in organic solvents and by the Schotten–Baumann method. A comparison of the IR and PMR spectra of these compounds with the spectra of model compounds II, III, and IVb made it possible to establish that they have 5(4)-acylamidoimidazole structures IVc, d.

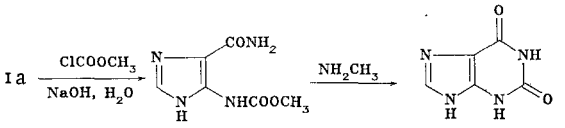
The reaction of aminoimidazole Ia with methyl chlorocarbonate in polar and nonpolar solvents at 20-100°C leads to the formation of only a single product, in the IR spectrum of which two strong bands of carbonyl absorption at 1680 and 1765 cm^{-1} are observed; this makes

it possible to assume that the acyl group is attached to one of the nitrogen atoms of the imidazole ring. A strong-field shift of the $C_{(2)}$ and $C_{(5)}$ signals and a weak-field shift of the $C_{(4)}$ signal are observed in the ^{13}C NMR spectrum of the product obtained [$C_{(COOCH_3)}$ 149.53, $C_{(CONH_2)}$ 166.13, $C_{(5)}$ 142.79, $C_{(2)}$ 127.15, and $C_{(4)}$ 111.12 ppm] as compared with the spectrum of 5(4)-aminoimidazole-4(5)-carboxamide (Ia) [$C_{(CONH_2)}$ 163.84, $C_{(5)}$ 146.94, $C_{(2)}$ 130.05, and $C_{(4)}$ 109.19 ppm]; this constitutes evidence that the substituent is incorporated in the 1 position of the imidazole ring. Thus the product is 1-carbomethoxy-5-aminoimidazole-4-carboxamide (Va), which is in agreement with the data in [9] rather than with the data in [8].

In addition to Va, a second product, which differs from Va with respect to its chromatographic mobility and IR spectrum (Table 1), is also formed at room temperature in the acylation of aminoimidazole Ia with methyl chlorocarbonate in chloroform, in contrast to other solvents. On the basis of a comparison of the IR spectra of the newly obtained compound and imidazoles III, IVb, and Va we concluded that acylation takes place at the nitrogen atoms of the imidazole ring, and the difference between the IR spectrum of this substance and the spectrum of Va makes it possible to consider it to be 1-carbomethoxy-4-aminoimidazole-5-carboxamide (VIa) [13]:



I a-d V a-d VI a, c



VII VIII

VI a $\xrightarrow[60^\circ]{HCCl_3}$ V a $\xrightarrow{180^\circ}$ VII $\xrightarrow{180^\circ}$ VIII

I, V, VI a R=$CONH_2$, b R=$CSNH_2$; c R=CN; d R=$COOC_2H_5$

Just as in other organic solvents, only product Va was detected in the reaction mixture and isolated by means of TLC when the reaction time was increased at 24 h or when the temperature was raised to 60°C. Thus the choice of solvent does not determine the direction of the reaction both in the case of acylation with methyl chlorocarbonate and in the case of acylation with acetyl chloride (Table 2).

We found that fused Va undergoes trans aminoacylation to give 5(4)-carbomethoxyamidoimidazole-4(5)-carboxamide (VII), the IR and PMR spectra of which differ from those of $N_{(1)}$- and $N_{(3)}$-acyl derivatives Va and VIa. As in the IR spectra of 5(4)-acetamidoimidazoles II and IVb-d, the bands of carbonyl absorption in its IR spectrum are found at 1650-1690 cm^{-1}, and the signal of the 2-H proton is shifted to strong field as compared with N-substituted derivatives III and Va (Table 1). Upon further heating urethane VII undergoes cyclization to xanthine (VIII), which was identical to a genuine sample with respect to all of its physicochemical parameters [14]. Similar cyclization also occurs when urethane VII is treated with methylamine.

Compounds Va-d and VIa, c react readily with aliphatic amines in alcohol and in aqueous solution at pH 9-14 to give starting aminoimidazoles Ia-d. The facile hydrolysis of 1-carbomethoxyimidazoles enabled us to obtain individual VII without Va and VIa impurities via the Schotten–Baumann reaction.

As in the case of aminoimidazolcarboxamide Ia, in the acylation of 5(4)-aminoimidazole-4(5)-carbonitrile (Ic) with methyl chlorocarbonate we isolated two isomers, a comparison of the IR spectra of which with the spectra of Va, VIa, VII, and 5(4)-carbomethoxyamidoimidazole-4(5)-carbonitrile, which was obtained by the method in [15], made it possible to establish that 1-carbomethoxy-5-aminoimidazole-4-carbonitrile (Vc) and 1-carbomethoxy-4-aminoimidazole-5-carbonitrile (VIc) are formed. In the reaction of 5(4)-aminoimidazole-4(5)-thioamide (Ib) and ethyl 5(4)-aminoimidazole-4(5)-carboxylate (Id) with methyl chlorocarbonate we were able to isolate only 1-carbomethoxy-5-aminoimidazoles (Vb, d), the structures of which were confirmed by means of IR and PMR spectroscopy.

TABLE 2. Acylation of 5(4)-Aminoimidazole-4(5)-carboxamide (Ia) with Methyl Chlorocarbonate

Compound formed	Solvent	Reaction temp., °C	Base	Yield,[a] %
Va	Ethanol	20	$N(C_2H_5)_3$	85
Va	Ethanol	78	$N(C_2H_5)_3$	70
Va	Ethanol	78	$NaHCO_3$	67
Va	Acetone	56	$NaHCO_3$	63
Va	Benzene	80	Pyridine	48
Va	CCl_4	20	$N(C_2H_5)_3$	76
Va	CCl_4	76	$N(C_2H_5)_3$	65
Va	$CHCl_3$	20[a]	$N(C_2H_5)_3$	72
Va+VIa	$CHCl_3$	20	$N(C_2H_5)_3$	44+27
Va	$CHCl_3$	60	$N(C_2H_5)_3$	58

[a]The reaction time was 24 h.

TABLE 3. Properties of the Synthesized Compounds

Compound	mp, °C	UV spectrum (in ethanol) λ_{max}, nm	UV spectrum (in ethanol) lg ε	R_f 1	R_f 2	R_f 3	Found, % C	Found, % H	Found, % N	Empirical formula	Calculated, % C	Calculated, % H	Calculated, % N	Yield, %
IVa	260—265	230; 267	3,76; 4,11	0,50	0,30	—	38,7	3,7	36,6	$C_5H_6N_4O_2$	38,9	3,9	36,3	86
IVb	211—212	230; 267	3,80; 4,16	0,53	—	0,36	44,2	5,9	29,4	$C_6H_8N_4O_2 \cdot 0{,}5C_2H_5OH$	44,0	5,8	29,3	75 (A) 67 (B)
IVc	205—206	237; 260	4,22; 4,11	0,60	0,76	0,65	57,3	4,6	24,0	$C_{11}H_{10}N_5O_2$	57,4	4,4	24,4	64
IVd	288—290	270	4,42	0,67	0,60	0,34	48,0	3,3	25,3	$C_{11}H_9N_5O_2$	48,0	3,3	25,5	44
Va	192—195	265	4,10	0,60	0,40	0,53	39,1	4,0	30,1	$C_6H_8N_4O_3$	39,2	4,4	30,4	44 (A) 85 (B)
Vb	210	205; 268; 330	3,99; 3,88 3,95	0,57	0,40	—	36,4	4,0	28,1	$C_6H_8N_6O_2S$[b]	36,0	4,0	28,0	85
Vc	170	252; 270	3,99; 3,74	—	0,65	0,42	43,1	3,9	33,6	$C_6H_6N_4O_2$	43,4	3,6	33,7	42
Vd	135	275	3,60	0,51	0,44	0,70	45,4	4,9	19,9	$C_8H_{11}N_3O_4$	45,0	5,2	19,7	34
VIa	200—202	265	3,93	0,80	0,52	0,89	39,4	4,5	30,3	$C_6H_8N_4O_3$	39,2	4,4	30,4	27[c]
VIc	163—165	210; 230; 280	4,11; 3,80 3,86	—	0,65	0,42	43,8	4,0	33,5	$C_6H_6N_4O_2$	43,4	3,6	33,7	95
VII	250	230; 265	3,75; 4,02	—	0,35	—	39,2	4,4	30,4	$C_6H_8N_4O_3$	39,2	4,4	30,4	35 (A)[c] 57 (B)

[a]Crystallized from ethanol. [b]Found: S 16.4%. Calculated: S 16.0%. [c]Crystallized from water.

Thus, in contrast to aminotriazoles [6], the site of incorporation of an acyl group in the case of aminoimidazoles Ia-c is determined primarily by the character of the acylating agent.

EXPERIMENTAL

The IR spectra of KBr pellets of the synthesized compounds were recorded with a UR-20 spectrometer. The UV spectra of solutions in ethanol were measured with a Beckman-26 spectrophotometer. The PMR spectra of solutions in d_6-DMSO were recorded with a Perkin-Elmer 12B spectrometer (60 MHz) on the δ scale with tetramethylsilane as the internal standard. The ^{13}C NMR spectra of solutions in d_6-DMSO were measured with a Brucker HX-90/22 (62 MHz) spectrometer with d_6-DMSO as the internal standard. The purity of the compounds obtained was monitored by TLC on Silufol UV-254 plates in the following solvent systems: 1) propanol—0.2 N NH_4OH (3:1), 2) butanol—acetic acid—water—ethyl acetate (4:1:1:1), and 3) chloroform—ethanol (9:1).

The properties of the synthesized compounds are presented in Table 3.

The melting points were not corrected.

5(4)-Formamidoimidazole-4(5)-carboxamide (IVa). A 0.2-g (1.6 mmole) sample of Ia was refluxed in 15 ml of 98.5% formic acid for 8 h, after which the solvent was evaporated in vacuo.

5(4)-Acetamidoimidazole-4(5)-carboxamide (IVb). A) A 0.26-g (2.0 mmole) sample of Ia was refluxed in a mixture of 10 ml of acetic acid and 5 ml of acetic anhydride for 4 h, after which the solvent was evaporated in vacuo.

B) A 0.16-g (1.3 mmole) sample of Ia was suspended in 30 ml of chloroform, 0.32 g (3.0 mmole) of Na_2CO_3 was added, 0.2 ml (3.0 mmole) of acetyl chloride was added gradually dropwise, and the mixture was stirred at 20°C from 5 h. The solvent was then evaporated in vacuo.

5(4)-Benzamidoimidazole-4(5)-carboxamide (IVc). A 0.3-g (2.4 mmole) sample of Ia was suspended in 30 ml of methylene chloride, 0.53 g (5.0 mmole) of Na_2CO_3 was added, 0.7 g (5.0 mmole) of benzoyl chloride was added dropwise, and the mixture was stirred at 20°C for 3.5 h. The solvent was then evaporated in vacuo.

5(4)-(p-Nitrobenzamido)imidazole-4(5)-carboxamide (IVd). A 1.0-g (6.2 mmole) sample of Ia hydrochloride was dissolved in 10 ml of water, 0.36 g (6.5 mmole) of KOH was added, 1.4 g (7.6 mmole) of p-nitrobnezoyl chloride and 0.51 g (9.1 mmole) of KOH were added gradually at no higher than 20°C, and the mixture was stirred at 20°C for 4 h. The mixture was then cooled, and the precipitate was removed by filtration and washed with 100 ml of acetone.

1-Carbomethoxy-5-aminoimidazole-4-carboxamide (Va). A) A 1.25-g (12.4 mmole) sample of triethylamine was added to a suspension of 1.0 g (6.2 mmole) of Ia hydrochloride in 150 ml of chloroform, the mixture was cooled to 0°C, and 0.7 g (7.4 mmole) of methyl chlorocarbonate was added dropwise. The mixture was then stirred at 20°C for 30 min, after which it was cooled to 0°C, and the precipitate was removed by filtration.

The filtrate was evaporated to dryness. The product was identified as 1-carbomethoxy-4-aminoimidazole-5-carboxamide (VIa).

B) A 3.5-g (37.0 mmole) sample of methyl chlorocarbonate was added dropwise at 0°C to a suspension of 5.0 g (30.7 mmole) of the hydrochloride of Ia in 250 ml of ethanol and 7.3 g (72.3 mmole) of triethylamine, and the mixture was stirred at 20°C for 1 h. The precipitate was removed by filtration.

The reaction proceeded similarly in other solvents. The amount of acid-binding agent was 70 mmole. After addition of methyl chlorocarbonate, the mixture was stirred at 20-80°C for 1 h (Table 2).

1-Carbomethoxy-5-aminoimidazole-4-thioamide (Vb). A 0.5-g (2.7 mmole) sample of Ib was suspended in 50 ml of chloroform, 0.9 g (9.0 mmole) of triethylamine was added, and the mixture was cooled to 0°C. A 0.57-g (6.0 mmole) sample of methyl chlorocarbonate was added dropwise at no higher than 0°C, and the mixture was stirred at 20°C for 2 h. It was then cooled to 0°C, and the precipitate was removed by filtration.

Ethyl 1-Carbomethoxy-5-aminoimidazole-4-carbonate (Vd). This compound was obtained by a procedure similar to that used to prepare Vb.

1-Carbomethoxy-5-aminoimidazole-4-carbonitrile (Vc) and 1-Carbomethoxy-4-aminoimidazole-5-carbonitrile (VIc). These compounds were obtained by a procedure similar to that used to prepare imidazole Va by method A.

5(4)-Carbomethoxyamidoimidazole-4(5)-carboxamide (VII). A) A 0.1-g (0.5 mmole) sample of Va was heated to 180°C and maintained at that temperature for 15 min, after which the residue was crystallized from water.

B) A 2.5-g (15.3 mmole) sample of the hydrochloride of Ia was dissolved in 10 ml of water, 0.62 g (16 mmole) of NaOH in 10 ml of water was added, and the mixture was cooled to 0°C. A 2.25-g (24 mmole) sample of methyl chlorocarbonate and a solution of 1 g (25 mmole) of NaOH in 10 ml of water were then added simultaneously while maintaining the temperature at no higher than 10°C, the mixture was stirred for 3 h, and the precipitate was removed by filtration.

Xanthine (VIII). A) A 0.1-g (0.5 mmole) sample of Va was heated to 180°C and maintained at that temperature for 1 h. The residue was extracted with hot ethanol to give 0.01 g of VII. The residue was suspended in 5 ml of 2 N NaOH and filtered, and the filtrate was acidified to pH 1-2 with concentrated HCl. The precipitate was removed by filtration

to give 40 mg of a product that was identical to xanthine with respect to all of its physicochemical parameters [14].

B) A 0.1-g (0.05 mmole) sample of VII was stirred in a mixture of 2 ml of a 33% aqueous solution of methylamine for 20 min, after which the solvent was evaporated to dryness in vacuo, and the residue was dried in vacuo to give 50 mg of product.

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