The Psuedo-Michael Reaction of 2-Aminoimidazolines 2. Part 1. Synthesis and Structure Assignment of Isomeric 5(1*H*)-Oxo and 7(1*H*)-Oxo-2,3-dihydroimidazo[1,2-*a*]pyrimidine-6-carboxylates

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Dedicated to Professor T. Tkaczyński with best wishes

The pseudo-Michael reaction of 1-aryl-2-aminoimidazolines-2 with diethyl ethoxymethylenemalonate (DEEM) was investigated. Extensive structural studies were performed to confirm the reaction course. For derivatives with N1 aromatic substituents, it was found that the reaction course was temperature dependent. When the reaction temperature was held at –10 °C only the formation of 1-aryl-7(1*H*)-oxo-2,3-dihydroimidazo[1,2-*a*]pyrimidine-6-carboxylates (**4**) was observed in contrast to earlier suggestions. Under the room temperature conditions, the same reaction yielded mixtures, with varying ratio, of isomeric 1-aryl-7(1*H*)-oxo- (**4a**-**4f**) and 1-aryl-5(1*H*)-oxo-2,3-dihydroimidazo[1,2-*a*]pyrimidine-6-carboxylates (**5a**-**5f**). The molecular structure of selected isomers, **4b** and **5c**, was confirmed by X-ray crystallography. Frontal chromatography with delivery from the edge was applied for the separation of the isomeric esters. The isomer ratio of the reaction products depended on the character of the substituents on the phenyl ring. The 1-aryl-7(1*H*)-oxo-carboxylates (**4a**-**4f**) were preferably when the phenyl ring contained H, 4-CH_3, 4-OCH_3 and 3,4-Cl_2 substituents. Chloro substitution at either position 3 or 4 in the phenyl ring favored the formation of isomers **5a**-**5f**. The isomer ratios were confirmed both by ^{1}H NMR and chromatography. The reaction of the respective hydrobromides of 1-aryl-2-aminoimidazoline-2 with DEEM, in the presence of triethylamine, gave selectively 5(1*H*)-oxo-esters (**5a**-**5f**).

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Diethyl ethoxymethylenemalonate (DEEM) is a well-known reagent for heterocyclic annelation. Its reaction with 2-aminoazaheterocycles has been widely used to obtain fused pyrimidines bearing the β-oxo-acid moiety. To date, the formation of 4-oxo-pyrimidine-3-carboxylates has been reported [1]. Only Agata [2] and Koekoesi *et al* [3,4] suggested that the NH-C=NH system (*e.g.* present in cyclic amidines) can yield mixtures of isomeric products (2- or 4-oxo esters) when reacted with Michael reagents such as DEEM. Their results indicated that the isomer ratio depended only on the ring size. The main product was always a 4-oxo isomer, which suggested that reaction starts at the *exo* N6 nitrogen atom.

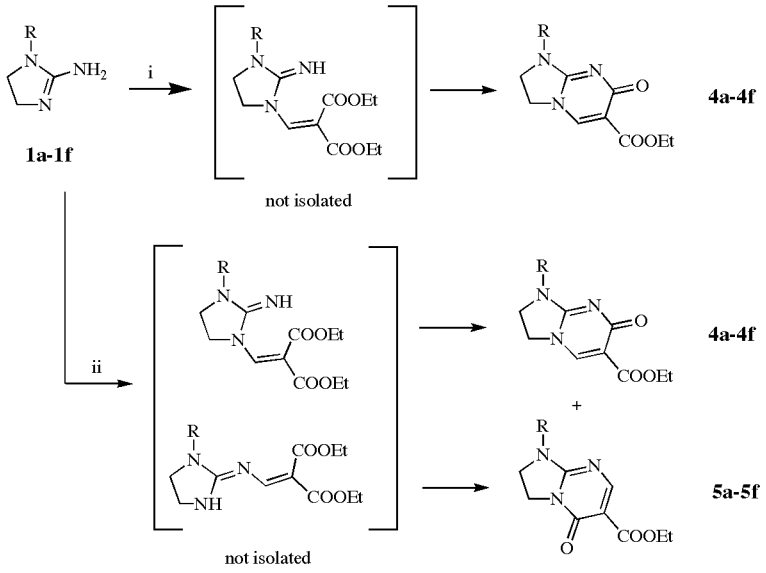
At present the molecular geometry of three 5(1*H*)-oxo-2,3-dihydroimidazo[1,2-*a*]pyrimidine derivatives are known; two with N8-phenyl [5,6] and one with N1-methyl [7] substitution. The 7(1*H*)-oxo-2,3-dihydroimidazo[1,2-*a*]pyrimidine system has not been reported earlier. Differences in the structures of 1-aryl-2,3-dihydroimidazo[1,2-*a*]pyrimidine result from the location of the carbonyl group; in the 5-oxo compound, one of the guanidine N-atoms is part of the lactam group whereas in the case of the 7-oxo compound the carbonyl and the C5-C6 double bond give the pyrimidine ring a pseudo-quinoid character.

Pharmacological activity of isomeric esters on the CNS of laboratory animals (mice, rats) was reported [8] and

evaluated in behavioral tests. The compounds exhibited antinociceptive activity that seemed to be connected with the opioid system, and also some serotonergic and CNS-depressive activity. Both the activity and acute toxicity of isomeric esters were structure-dependent. From this point of view, the separation and identification of isomers is important for further studies aimed at explaining their mechanism of action.

The reaction of 2-aminoimidazolines-2 with DEEM was studied to find a new method of annelation of the imidazoline ring. Previously, we found that 1-alkyl-5-aryl-2-aminoimidazolines-2 and DEEM yielded a single product, [8] whereas the 1-aryl-2-aminoimidazolines-2 yields mixtures of two isomeric oxo-dihydroimidazo[1,2-*a*]pyrimidine esters. The proposed course of the latter reaction is summarized in Scheme 1.

Scheme 1



i = DEEM (3), EtOH, -10 °C, 6h;
ii = DEEM (3), EtOH, room temp., 6h;

A careful analysis of the spectral and X-ray crystallographic data of selected crystals indicated that in the majority of reactions the main products were 1-aryl-7(1*H*)-oxo-esters (**4a-4f**). Condensation of 1-aryl-2-aminoimidazolines-2 (**1a-1f**) with DEEM (3) in ethanol at –10 °C (Method A) gave the products identified as the 1-aryl-7(1*H*)-oxo-2,3-dihydroimidazo[1,2-*a*]pyrimidine-6-carboxylates (**4a-4f**).

Carrying out the condensation of 1-aryl-2-aminoimidazolines-2 (**1a-1f**) at room temperature (Method B) led to the formation of a mixture of isomers **4a-4f** and **5a-5f**. ^{1}H NMR spectra of the crude product (Table 1) showed two characteristic singlets in the range of δ 8.0 - 8.5 ppm attributable to the presence of H5 and H7 hydrogens. These signals were usually separated by *ca.* 0.05 ppm but nevertheless they were easily recognizable even in the 100 MHz spectra. Their integrals gave the ratio of isomeric esters in the product mixture. Preparative thin-layer chromatography (PR-TLC) on silica gel with benzene/ethyl acetate (1:3) as an eluent confirmed the ^{1}H NMR results (Table 1).

Refluxing 1-aryl-2-aminoimidazoline-2 hydrobromides (**2a-2f**) with DEEM (**3**) in ethanol for 3 to 10 h (Method C) led to the formation of one single isomer (Scheme 2) – namely the 5(1*H*)-oxo esters (**5a-5f**) (Table 2). The exclusive formation of isomers **5** in this reaction was probably caused by a change in the nucleophilicity of the N3 *endo* nitrogen due to its protonation. Thus only the *exo* N6 nitrogen was able to initiate the reaction despite its obviously lower nucleophilicity.

The molecular structures of 7(1*H*)-oxo and 5(1*H*)-oxo esters were confirmed by X-ray structure analysis of single crystals of **4b** and **5c** (Figure 1). The geometry of the 7(1*H*)-oxo and 5(1*H*)-oxo isomers and selected bond lengths are presented in Table 3. The N1, N4 and N8 nitrogen atoms form a completely substituted guanidine moiety at the ring junction. The C8-N bond lengths are typical for this system, although a difference in the C8-N1 bond lengths was observed.

The solid-state conformation of the five-membered dihydroimidazole ring is an envelope for **4b** (maximal torsion angle less than 20°) and a twist for **5c** (torsion angles < 9°). The geometries of the nearly planar pyrimidine moieties

Table 1

Isomeric Compounds **4** and **5** Obtained by Method B

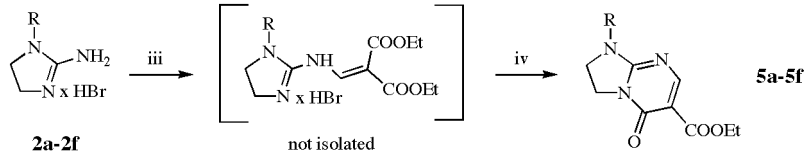
Symbol	R	m.p [°C]	The overall yield [%]	Ratio calculated from ^{1}H NMR spectra	Ratio calculated from TLC
4a	C_6H_5	262-4	83	75 %	69 %
5a	C_6H_5	190-2		25 %	31 %
4b	4-$CH_3C_6H_4$	235-7	85	66 %	64 %
5b	4-$CH_3C_6H_4$	200-2		33 %	36 %
4c	4-$CH_3OC_6H_4$	194-6	71	60 %	64 %
5c	4-$CH_3OC_6H_4$	173-5		40 %	36 %
4d	4-ClC_6H_4	229-31	89	40 %	47 %
5d	4-ClC_6H_4	255-6		60 %	53 %
4e	3-ClC_6H_4	213-5	67	33 %	39 %
5e	3-ClC_6H_4	181-3		66 %	61 %
4f	3,4-$Cl_2C_6H_3$	>330(dec.)	76	60 %	64 %
5f	3,4-$Cl_2C_6H_3$	289-91		40 %	36 %

Table 3

Selected Bond Lengths [Å] for **4b** and **5c**

4b		**5c**	
N(1)-C(8)	1.357(3)	N(1)-C(8)	1.340(2)
N(8)-C(8)	1.308(3)	N(8)-C(8)	1.315(2)
N(1)-C(2)	1.468(3)	N(1)-C(2)	1.467(2)
N(8)-C(7)	1.389(3)	N(8)-C(7)	1.350(3)
C(2)-C(3)	1.519(3)	C(2)-C(3)	1.514(3)
C(7)-O(7)	1.231(3)	C(5)-O(5)	1.222(2)
N(4)-C(3)	1.463(3)	N(4)-C(3)	1.462(2)
C(5)-C(6)	1.358(3)	C(6)-C(7)	1.373(3)
N(4)-C(5)	1.345(3)	N(4)-C(5)	1.386(3)
C(6)-C(7)	1.473(3)	C(5)-C(6)	1.445(3)
N(4)-C(8)	1.370(2)	N(4)-C(8)	1.364(2)
N(1)-C(9)	1.420(3)	N(1)-C(9)	1.417(2)
C(6)-C(16)	1.476(3)	C(6)-C(16)	1.471(3)

Scheme 2



iii = DEEM (3), EtOH, reflux, 3 -10h;
iv = NEt_3, reflux, 6h;

Table 2

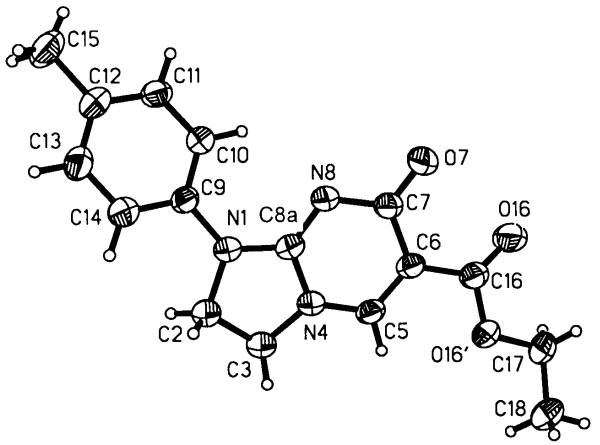
The Conditions for Formation of Isomeric Compounds **5**

Symbol	R	Reaction time	Yield [%]
5a	C_6H_5	3 h	32
5b	4-$CH_3C_6H_4$	4 h	27
5c	4-$CH_3OC_6H_4$	4 h	34
5d	4-ClC_6H_4	8 h	39
5e	3-ClC_6H_4	10 h	44
5f	3,4-$Cl_2C_6H_4$	10 h	48

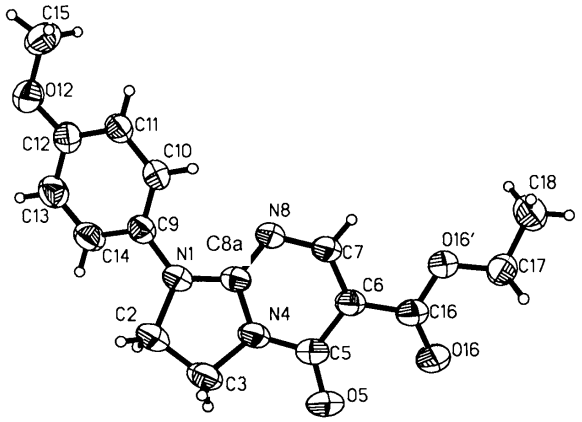
(torsion angles < 4°) of **4b** and **5c** are clearly different in the four-bond fragments of N4-C5-C6-C7-N8. A characteristic bond-distance pattern indicates a pseudoquinoid structure for **4b**. A comparison with other "quinoid" aminopyrimidinones [9] is complicated by the protonation of their nitrogen atoms and by the presence of N-H···N and N-H···O hydrogen bonds in the solid state, while in **4b** only C-H···O contacts exist. Although the ester group is nonplanar with the pyrimidine ring (angles between the planes are 20.7° and 17.1° for **5c** and **4b**, respectively), *syn*- orientation of the two C=O bonds is observed in both compounds.

The ^{1}H NMR spectra of isomeric esters differ only by the methylene –CH= hydrogen atom chemical shifts. Although in the mixtures of isomeric esters these signals are separated by 0.05-0.1 ppm only they can be used for calculating the ratio of the isomeric esters. The C(5)H signals are always shifted downfield compared to the respective C(7)H signals. The C2 and C3 hydrogen atoms are represented in the spectra by broad singlet or narrow multiplet signals at *ca.* 4.2 ppm. Usually they take a dd form and are separated by 0.2-0.4 ppm. The downfield shifting of the C2 is caused by deshielding by the C=N double bond but not by the carbonyl group located at C5 or C7.

The ^{13}C NMR spectra of compounds **4** and **5** mainly differ in the chemical shifts of the carbonyl (C=O) and carbimino (C=N) atoms. In both series the ester carbonyl carbons showed the highest chemical shift values (~165 and ~168 ppm, respectively). The amidic carbon atoms were observed at 160-164 ppm. The greatest difference was observed in the chemical shifts of the carbimino carbon atoms. The carbimino carbon atoms resonances in the 7-oxo esters were observed at ~158 ppm, whereas in the 5-oxo esters they were observed at ~150 ppm. The clearly higher value of this chemical shift in the 7-oxo isomers may be caused by a strong anisotropic effect on the C=N double bond exerted by other conjugated double bonds of the pseudo-quinoid moiety. Surprisingly, no differences were observed in the chemical shifts of the methylene carbon atoms (~108 ppm). The C2 and C3 signals in 7-oxo esters were separated by ~6 ppm whereas the same signals in 5-oxo esters were only separated by 1-1.5 ppm. The downfield shift of the C3 carbon atom signals of **5** by ~4.5 ppm in



4b



5c

Figure 1. Perspective view of the **4b** and **5c** molecules with the atom numbering.

comparison to **4** may be caused by the deshielding effect of the C5=O double bond specifically on the C3 carbon atom.

The UV spectrometry of **4** and **5** revealed two absorption maxima in the carbonyl region of the spectra (200-250 nm) for each isomer. For compounds **4**, peaks appearing at ~225 and ~250 nm had an absorption ratio 1.0 whereas for **5**, they appeared at ~205 and ~250 nm with an absorption ratio of 1.4. The location and equal intensities of the absorption maxima of compounds **4** confirmed the presence of the pseudo-quinoid moiety. It also suggests that in solution the C=O bonds and the quinoid system are predominantly in the *syn* conformation, which is consistent with the crystal geometry.

The 70-eV EI spectra of compounds **4** and **5** show clear differences between the 5-oxo and 7-oxo isomers due to regioselective fragmentations involving the ester function. The base peaks correspond to $[M\text{-}COOC_2H_4]^{+\bullet}$ and $[M\text{-}OC_2H_5]^+$ ions in the spectra of compounds **4** and **5**, respectively. Moreover, the contribution of $[M\text{-}OC_2H_5]^+$ ions to the total ion current in the spectra of compounds **5** is greater by an order of magnitude than in compounds **4**. The mass spectra are described in more details elsewhere [10].

EXPERIMENTAL

Melting points were determined on a Boetius apparatus and are uncorrected. NMR spectra (^1H and ^{13}C) were recorded on a Varian Gemini 200 MHz spectrometer in [D_6]DMSO with TMS as an external standard at 295 K. EI-MS spectra were recorded at 70 eV (direct insertion probe, ion source temp. 160 °C) on a VG ZabSpec spectrometer (Manchester, UK). UV spectra were recorded on a Specord M40 (Carl-Zeiss Jena) spectrophotometer in a 200-450 nm range. TLC was performed on commercial Merck 60 F_{254} SiO_2 plates with eluent system: $CHCl_3$-CH_3OH (9:1), visualization: UV light, $I_2/CHCl_3$ solution. DEEM was purchased from Merck and was used without further purification.

Ethyl 1-Aryl-7(1*H*)-oxo-2,3-dihydroimidazo[1,2-*a*]pyrimidine-6-carboxylates (**4a**-**4f**) and Ethyl 1-Aryl-5(1*H*)-oxo-2,3-dihydroimidazo[1,2-*a*]pyrimidine-6-carboxylates (**5a**-**5f**).

Method A.

DEEM (**3**) 21.6 g (0.1 mol) was added slowly to the solution of 0.1 mol of the respective 1-aryl-2-aminoimidazoline-2 (**1a**-**1f**) in 150 mL of ethyl alcohol cooled to the –10 °C. The mixture was stirred for 6 h at this temperature. The precipitated solid was separated by suction filtration, washed with cold 2-propanol and crystallized from a DMF/2-propanol (1:2) mixture, to give carboxylates **4a**-**4f**.

Method B.

DEEM (**3**) 21.6 g (0.1 mol) was added to the solution of 0.1 mol of the respective 1-aryl-2-aminoimidazoline-2 (**1a**-**1f**) in 150 mL of ethyl alcohol. The solution became orange-red and after 15-30 minutes a solid started to precipitate. A slight exothermic effect (+6 to +10 °C) was observed. The mixture was stirred at ambient temperature for 6 h. The crude product was collected by filtration and separated by preparative TLC (see the Chromatography section) to give carboxylates **4a**-**4f** and **5a**-**5f**.

Method C.

1-Aryl-2-aminoimidazoline-2 hydrobromide (**2a**-**2f**) (0.1 mol) and 21.6 g (0.1 mol) of DEEM (**3**) were dissolved in 200 mL of ethyl alcohol. The solution was stirred under reflux for 3 to 10 h and then 10.2 g (0.1 mol) of triethylamine was added dropwise over a period of 15 min, and the mixture was refluxed for additional 6 h. The precipitate was collected and recrystallized from methanol, to give carboxylates **5a**-**5f**.

The physical and spectral properties of the obtained compounds are listed below.

Ethyl 1-Phenyl-7(1*H*)-oxo-2,3-dihydroimidazo[1,2-*a*]pyrimidine-6-carboxylate (**4a**).

This compound has mp 202-4 °C; R_f = 0.68; EIMS (15eV), m/z: 285 (M^+, 42%), 213 (100%). UV (CH_3OH), λ_{max} (A): 223

(0.4922), 252 (0.5019), 294 (0.2195), 347 (0.3291), 415 (0.344). ^{1}H NMR, δ: 8.24 (s, 1H, C(5)H), 7.15-7.3 (m, 5H, C_6H_5), 4.23 (s, 4H, C(2,3)H), 4.2 (q, *J* = 9 Hz, 2H, O-CH_2-CH_3), 1.15 (t, *J* = 9 Hz, 3H, O-CH_2-CH_3). ^{13}C NMR, δ: 164.4 (*C*O-O), 163.1 (*C7*=O), 158.1 (*C*8'), 134.2 (C_{ar}-N), 129.8 (C_{ar}(2,6)), 126.3 (C_{ar}(4)), 123.7 (C_{ar}(3,5)), 107.6 (=*C*H), 60.5 (O-*C*H_2-CH_3), 45.3 (*C2*), 44.1 (*C3*), 14.2 (O-CH_2-*C*H_3).

Anal. Calcd for $C_{15}H_{15}N_3O_3$: C 63.15; H 5.30; N 14.73. Found: C 63.03; H 5.22; N 14.80.

Ethyl 1-(4-Methylphenyl)-7(1*H*)-oxo-2,3-dihydroimidazo-[1,2-*a*]pyrimidine-6-carboxylate (**4b**).

This compound has mp 228-230 °C; R_f = 0.71; EIMS (15eV), m/z: 299 (M^+, 40%), 227 (100%). UV (CH_3OH), λ_{max} (A): 226 (0.4973), 252 (0.5009), 298 (0.2207), 341 (0.3278), 412 (0.3434). ^{1}H NMR, δ: 8.38 (s, 1H, C(5)H), 7.24,7.65 (2 x d, 4H, $C_6H_4CH_3$), 4.27 (s, 4H, C(2,3)H), 4.23 (q, *J* = 9 Hz, 2H, O-CH_2-CH_3), 2.3 (s, 3H, C_6H_4CH_3), 1.2 (t, *J* = 9 Hz, 3H, O-CH_2-CH_3). ^{13}C NMR, δ: 164.8 (*C*O-O), 162.9 (*C7*=O), 158.1 (*C*8'), 135.6 (C_{ar}-N), 135.2 (C_{ar}-CH_3), 129.9 (C_{ar}(2,6)), 120.6 (C_{ar}(3,5)), 108.0 (=*C*H), 60.5 (O-*C*H_2-CH_3), 46.4 (*C2*), 40.2 (*C3*), 21.0 (C_{ar}-*C*H_3), 14.4 (O-CH_2-*C*H_3).

Anal. Calcd for $C_{16}H_{17}N_3O_3$: C 64.20; H 5.72; N 14.04. Found: C 64.20; H 5.64; N 14.07.

Ethyl 1-(4-Methoxyphenyl)-7(1*H*)-oxo-2,3-dihydroimidazo-[1,2-*a*]pyrimidine-6-carboxylate (**4c**).

This compound has mp 194 – 196 °C; R_f = 0.72; EIMS (15eV), m/z: 315 (M^+, 31%), 243 (100%). UV (CH_3OH), λ_{max} (A): 229 (0.5013), 250 (0.4977), 294 (0.2123), 349 (0.3228), 427 (0.3098). ^{1}H NMR, δ: 8.4 (s, 1H, C(5)H), 7.25, 7.55 (2 × d, 4H, $C_6H_4OCH_3$), 4.3 (s, 4H, C(2,3)H), 4.25 (q, *J* = 9 Hz, 2H, O-CH_2-CH_3), 2.78 (s, 3H, $C_6H_4OCH_3$), 1.2 (t, *J* = 9 Hz, 3H, O-CH_2-CH_3). ^{13}C NMR, δ: 163.9 (*C*O-O), 161.7 (*C7*=O), 158.9 (*C*8'), 137.6 (C_{ar}-OCH_3), 134.7 (C_{ar}-N), 130.1 (C_{ar}(2,6)), 124.5 (C_{ar}(3,5)), 108.3 (=*C*H), 60.5 (O-*C*H_2-CH_3), 58.3 (C_{ar}-O*C*H_3), 47.5 (*C2*), 42.7 (*C3*), 14.6 (O-CH_2-*C*H_3).

Anal. Calcd for $C_{16}H_{17}N_3O_4$: C 60.94; H 5.43; N 13.33. Found: C 61.18; H 5.34; N 13.21.

Ethyl 1-(4-Chlorophenyl)-7(1*H*)-oxo-2,3-dihydroimidazo[1,2-*a*]-pyrimidine-6-carboxylate (**4d**).

This compound has mp 257-258 °C; R_f = 0.74; EIMS (15eV), m/z: 319 (M^+, 48%), 247 (100%). UV (CH_3OH), λ_{max} (A): 220 (0.5111), 259 (0.5093), 279 (0.215), 339 (0.3231), 407 (0.3148). ^{1}H NMR, δ: 8.38 (s, 1H, C(5)H), 6.9, 7.45 (2 × d, 4H, C_6H_4Cl), 4.28 (s, 4H, C(2,3)H), 4.18 (q, *J* = 9 Hz, 2H, O-CH_2-CH_3), 1.27 (t, *J* = 9 Hz, 3H, O-CH_2-*C*H_3). ^{13}C NMR, δ: 163.7 (*C*O-O), 162.1 (*C7*=O), 158.4 (*C*8'), 138.2 (C_{ar}-Cl), 134.1 (C_{ar}-N), 131.8 (C_{ar}(2,6)), 126.2 (C_{ar}(3,5)), 108.4 (=*C*H), 60.6 (O-*C*H_2-CH_3), 47.1 (*C2*), 41.1 (*C3*), 14.4 (O-CH_2-*C*H_3).

Anal. Calcd for $C_{15}H_{14}ClN_3O_3$: C 56.34; H 4.41; N 13.14; Cl 11.09. Found: C 56.55; H 4. 47; N 13.07; Cl 11.14.

Ethyl 1-(3-chlorophenyl)-7(1*H*)-oxo-2,3-dihydroimidazo[1,2-*a*]-pyrimidine-6-carboxylate (**4e**).

This compound has mp 210-212 °C; R_f = 0.7; EIMS (15eV), m/z: 319 (M^+, 48%), 247 (100%). UV (CH_3OH), λ_{max} (A): 229 (0.5031), 247 (0.5023), 273 (0.2281), 337 (0.3312), 418 (0.3334). ^{1}H NMR, δ: 8.44 (s, 1H, C(5)H), 7.22-8.05 (m, 4H, C_6H_4Cl), 4.18 (s, 4H, C(2,3)H), 4.15 (q, *J* = 9 Hz, 2H, O-CH_2-CH_3), 1.25 (t, *J* = 9 Hz, 3H, O-CH_2-CH_3). ^{13}C NMR, δ: 163.5 (*C*O-O), 160.3 (*C7*=O), 159.4 (*C*8'), 135.3 (C_{ar}-Cl), 134.3 (C_{ar}-N), 129.1 (C_{ar}(2)), 128.4 (C_{ar}(4)), 124.7 (C_{ar}(6)), 118.4 (C_{ar}(5)), 107.9 (=*C*H), 61.0 (O-*C*H_2-CH_3), 45.7 (*C2*), 40.1 (*C3*), 14.5 (O-CH_2-*C*H_3).

Anal. Calcd for $C_{15}H_{14}ClN_3O_3$: C 56.34; H 4.41; N 13.14; Cl 11.09. Found: C 56.76; H 4.50; N 13.08; Cl 11.21.

Ethyl 1-(3,4-Dichlorophenyl)-7(1*H*)-oxo-2,3-dihydroimidazo[1,2-*a*]pyrimidine-6-carboxylate (**4f**).

This compound has mp >330 °C (dec.); R_f = 0.67; EIMS (15eV), m/z: 354 (M^+, 48%), 282 (100%). UV (CH_3OH), λ_{max} (A): 219 (0.4995), 247 (0.5037), 283 (0.2234), 340 (0.3201), 413 (0.3353). ^{1}H NMR, δ: 8.54 (s, 1H, C(5)H), 7.15-7.95 (m, 3H, $C_6H_3Cl_2$), 4.24 (s, 4H, C(2,3)H), 4.2 (q, *J* = 9 Hz, 2H, O-CH_2-CH_3), 1.24 (t, *J* = 9 Hz, 3H, O-CH_2-CH_3). ^{13}C NMR, δ: 165.1 (*C*O-O), 161.5 (*C7*=O), 159.7 (*C*8'), 133.3 (C_{ar}-N), 136.7 (C_{ar}(4)-Cl), 135.2 (C_{ar}(3)-Cl), 129.1 (C_{ar}(2)), 128.8 (C_{ar}(5)) 128.3 (C_{ar}(6)), 107.4 (=*C*H), 60.3 (O-*C*H_2-CH_3), 47.9 (*C2*), 43.1 (*C3*), 14.1 (O-CH_2-*C*H_3).

Anal. Calcd for $C_{15}H_{13}Cl_2N_3O_3$: C 50.86; H 3.70; N 11.86; Cl 20.02. Found: C 51.02; H 3.73; N 11.83; Cl 19.94.

Ethyl 1-Phenyl-5(1*H*)-oxo-2,3-dihydroimidazo[1,2-*a*]pyrimidine-6-carboxylate (**5a**).

This compound has mp 182-4 °C; R_f = 0.24; EIMS (15eV), m/z: 285 (M^+, 100%). UV (CH_3OH), λ_{max} (A): 208 (0.5087), 253 (0.3564), 328 (0.3715), 388 (0.1793), 421 (0.5501). ^{1}H NMR, δ: 8.28 (s, 1H, C(7)H), 7.15-7.3 (m, 5H, C_6H_5), 4.2 (s, 4H, C(2,3)H), 4.18 (q, *J* = 9 Hz, 2H, O-CH_2-CH_3), 1.19 (t, *J* = 9 Hz, 3H, O-CH_2-CH_3). ^{13}C NMR, δ: 167.9 (*C*O-O), 164.3 (*C5*=O), 150.1 (*C*8'), 136.8 (C_{ar}-N), 129.8 (C_{ar}(3,5)), 125.4 (C_{ar}(4)), 120.8 (C_{ar}(2,6)), 107.7 (=*C*H), 60.1 (O-*C*H_2-CH_3), 45.7 (*C2*), 44.6 (*C3*), 14.4 (O-CH_2-*C*H_3).

Anal. Calcd for $C_{15}H_{15}N_3O_3$: C 63.15; H 5.30; N 14.73. Found: C 63.21; H 5.27; N 14.7.

Ethyl 1-(4-Methylphenyl)-5(1*H*)-oxo-2,3-dihydroimidazo[1,2-*a*]-pyrimidine-6-carboxylate (**5b**).

This compound has mp 196-198 °C; R_f = 0.25; EIMS (15eV), m/z: 299 (M^+, 100%), 254 (94%). UV (CH_3OH), λ_{max} (A): 206 (0.5197), 251 (0.3654), 320 (0.3634), 383 (0.1715), 426 (0.5433). ^{1}H NMR, δ: 8.42 (s, 1H, C(7)H), 7.18, 7.6 (2 × d, 4H, $C_6H_4CH_3$), 4.26 (s, 4H, C(2,3)H), 4.18 (q, *J* = 9 Hz, 2H, O-CH_2-CH_3), 2.3 (s, 3H, C_6H_4CH_3), 1.23 (t, *J* = 9 Hz, 3H, O-CH_2-CH_3). ^{13}C NMR, δ: 167.5 (*C*O-O), 163.9 (*C5*=O), 150.6 (*C*8'), 135.6 (C_{ar}-N), 134.4 (C_{ar}-CH_3), 129.5 (C_{ar}(3,5)), 119.3 (C_{ar}(2,6)), 108.0 (=*C*H), 60.8 (O-*C*H_2-CH_3), 45.8 (*C2*), 44.3 (*C3*), 20.8 (C_{ar}-*C*H_3), 14.3 (O-CH_2-*C*H_3).

Anal. Calcd for $C_{16}H_{17}N_3O_3$: C 64.20; H 5.72; N 14.04. Found: C 63.84; H 5.63; N 14.10.

Ethyl 1-(4-Methoxyphenyl)-5(1*H*)-oxo-2,3-dihydroimidazo[1,2-*a*]-pyrimidine-6-carboxylate (**5c**).

This compound has mp 173-175 °C; R_f = 0.26; EIMS (15eV), m/z: 315 (M^+, 100%). UV (CH_3OH), λ_{max} (A): 201 (0.5037), 248 (0.3313), 327 (0.3512), 397 (0.2001), 419 (0.5353). ^{1}H NMR, δ: 8.45 (s, 1H, C(7)H), 7.2, 7.5 (2 × d, 4H, $C_6H_4OCH_3$), 4.27 (s, 4H, C(2,3)H), 4.19 (q, *J* = 9 Hz, 2H, O-CH_2-CH_3), 2.8 (s, 3H, $C_6H_4OCH_3$), 1.22 (t, *J* = 9 Hz, 3H, O-CH_2-CH_3). ^{13}C NMR,

δ: 166.9 (*C*O-O), 164.7 (*C5*=O), 151.3 (*C*8'), 138.9 (C_{ar}-OCH_3), 136.8 (C_{ar}-N), 127.7 (C_{ar}(3,5)), 121.3 (C_{ar}(2,6)), 108.4 (=*C*H), 60.1 (O-*C*H_2-CH_3), 59.3 (C_{ar}-O*C*H_3), 46.9 (*C2*), 44.8 (*C3*), 14.4 (O-CH_2-*C*H_3).

Anal. Calcd for $C_{16}H_{17}N_3O_4$: C 60.94; H 5.43; N 13.33. Found: C 60.98; H 5.49; N 13.41.

Ethyl 1-(4-Chlorophenyl)-5(1*H*)-oxo-2,3-dihydroimidazo-[1,2-*a*]pyrimidine-6-carboxylate (**5d**).

This compound has mp 201-203 °C; R_f = 0.25; EIMS (15eV), m/z: 319 (M^+, 100%). UV (CH_3OH), λ_{max} (A): 218 (0.5235), 264 (0.3793), 329 (0.3513), 374 (0.2015), 404 (0.5339). ^{1}H NMR, δ: 8.42 (s, 1H, C(7)H), 6.85, 7.4 (2 × d, 4H, C_6H_4Cl), 4.25 (s, 4H, C(2,3)H), 4.16 (q, *J* = 9 Hz, 2H, O-C*H*$_2$-CH_3), 1.3 (t, *J* = 9 Hz, 3H, O-CH_2-C*H*$_3$). ^{13}C NMR, δ: 166.4 (*C*O-O), 163.2 (*C5*=O), 151.2 (*C*8'), 138.8 (C_{ar}-Cl), 136.9 (C_{ar}-N), 130.5 (C_{ar}(3,5)), 124.6 (C_{ar}(2,6)), 108.1 (=*C*H), 61.7 (O-*C*H_2-CH_3), 44.9 (*C2*), 44.1 (*C3*), 14.1 (O-CH_2-*C*H_3

Anal. Calcd for $C_{15}H_{14}ClN_3O_3$: C 56.34; H 4.41; N 13.14; Cl 11.09. Found: C 56.49; H 4.53; N 13.27; Cl 11.17.

Ethyl 1-(3-Chlorophenyl)-5(1*H*)-oxo-2,3-dihydroimidazo-[1,2-*a*]pyrimidine-6-carboxylate (**5e**).

This compound has mp 203-205 °C; R_f = 0.23; EIMS (15eV), m/z: 319 (M^+, 100%). UV (CH_3OH), λ_{max} (A): 221 (0.5201), 268 (0.3683), 333 (0.3603), 372 (0.2107), 413 (0.5393). ^{1}H NMR, δ: 8.49 (s, 1H, C(7)H), 7.2-7.9 (m, 4H, C_6H_4Cl), 4.22 (s, 4H, C(2,3)H), 4.17 (q, *J* = 9 Hz, 2H, O-C*H*$_2$-CH_3), 1.28 (t, *J* = 9 Hz, 3H, O-CH_2-C*H*$_3$). ^{13}C NMR, δ: 168.8 (*C*O-O), 164.9 (*C5*=O), 151.7 (*C*8'), 139.8 (C_{ar}-Cl), 136.6 (C_{ar}-N), 130.1 (C_{ar}(2,4)), 123.1(C_{ar}(6)), 121.1 (C_{ar}(5)), 107.3 (=*C*H), 59.7 (O-*C*H_2-CH_3), 45.2 (*C2*), 44.2 (*C3*), 14.3 (O-CH_2-*C*H_3).

Anal. Calcd for $C_{15}H_{14}ClN_3O_3$: C 56.34; H 4.41; N 13.14; Cl 11.09. Found: C 56.56; H 4.45; N 13.19; Cl 11.23.

Ethyl 1-(3,4-Dichlorophenyl)-5(1*H*)-oxo-2,3-dihydroimidazo-[1,2-*a*]pyrimidine-6-carboxylate (**5f**).

This compound has mp 289-291 °C; R_f = 0.21; EIMS (15eV), m/z: 354 (M^+, 100%). UV (CH_3OH), λ_{max} (A): 213 (0.5195), 270 (0.3723), 337 (0.3692), 379 (0.1995), 417 (0.5374). ^{1}H NMR, δ: 8.61 (s, 1H, C(5)H), 7.2-7.95 (m, 3H, $C_6H_3Cl_2$), 4.25 (s, 4H, C(2,3)H), 4.21 (q, *J* = 9 Hz, 2H, O-C*H*$_2$-CH_3), 1.25 (t, *J* = 9 Hz, 3H, O-CH_2-C*H*$_3$). ^{13}C NMR, δ: 168.9 (*C*O-O), 164.1 (*C5*=O), 150.9 (*C*8'), 137.7 (C_{ar}(3)-Cl), 137.2 (C_{ar}(4)-Cl), 133.7 (C_{ar}-N), 130.1 (C_{ar}(2)), 129.7 (C_{ar}(5)), 127.3 (C_{ar}(6)), 107.9 (=*C*H), 60.1 (O-*C*H_2-CH_3), 45.1 (*C2*), 44.7 (*C3*), 14.2 (O-CH_2-*C*H_3).

Anal. Calcd for $C_{15}H_{13}Cl_2N_3O_3$: C 50.86; H 3.70; N 11.86; Cl 20.02. Found: C 50.94; H 3.67; N 11.74; Cl 20.13.

Chromatography.

Thin layer chromatography (TLC) is frequently used for the isolation of compounds required for physicochemical (*e.g.* structure assignment), biological or other investigations. The use of "frontal + elution TLC" for separation of the mixture of isomeric compounds has been described in the literature [11-15]. The delivery of the sample to be separated from the edge of the layer, in the frontal chromatography mode, markedly improved the preparative separation owing to partial separation of the mixture during the sample application.

Microscale preparative and analytical TLC was performed on 200 x 200 mm precoated silica gel plates ($Si60F_{254}$, Merck, Germany) with 0.5-mm layer thickness in sandwich-type chambers (ChromDes, Lublin, Poland) [16,17]. The mixture of isomers (60 mg) was dissolved in DMF (4 ml) and subsequently introduced from the edge of the layer. The chromatograms were developed with binary mixture of ethyl acetate:toluene (7:3 v/v) and dried. Chromatograms were detected under UV light at λ = 254 nm. The stripes of absorbent containing separated isomers were scraped off the plate, and the fractions were isolated by extraction with hot methanol. The solvent was evaporated and the residue was crystallized from an appropriate solvent (methanol or DMF/2-propanol mixture). Compound purity was confirmed by analytical TLC.

Crystal data for **4b**.

Compound **4b** has $C_{16}H_{17}N_3O_3$, *FW* = 299.33, triclinic, *P*, *a* = 6.880(1) Å, *b* = 7.417(1) Å, *c* = 15.056(3) Å, α = 101.08(3)°, β = 95.77(3)°, γ = 104.60(3)°, *V* = 720.6(2) Å ^{3}, *Z* = 2, d_{calcd} = 1.380 g cm^{-3}, μ(CuKα) = 0.799 mm^{-1}. Crystals were obtained from a DMF solution. A colorless crystal (0.55 x 0.07 x 0.07 mm) was used for measurements at 293 K on a KM-4 diffractometer using graphite-monochromated CuK_α radiation (λ = 1.54178 Å) and ω-2θ scan method. Up to θ_{max} = 65.1°, 2360 reflections were collected. The structure was solved by direct methods using the program SHELXS-86 [18]. Full-matrix least-squares refinement on F^2 was carried out using the SHELXL-97 program system [19]. Non-H atoms were refined with anisotropic displacement parameters. H-atoms were located from the geometry and were given isotropic factors of 1.2 U_{eq} of the bonded C-atom; the 'riding' model was used in the refinement. 200 parameters were refined, the final discrepancy factors were *R*1 = 0.0556, *wR*2 = 0.1616, and *S* = 1.038, for 2040 reflections with $I > 2\sigma(I)$.

Crystal Data for **5c**.

Compound **5c** has $C_{16}H_{17}N_3O_4$, *FW* = 315.33, monoclinic, $P2_1/c$, a = 6.962(1) Å, b = 29.693(6) Å, c = 7.514(2) Å, β = 107.89(3)°, *V* = 1478.2(5) Å ^{3}, Z = 4, μ(Cu Kα) = 0.862 mm^{-1}. Crystals were obtained from a methanol solution. A colorless crystal (0.6 x 0.19 x 0.22 mm) was used for measurements at 293 K on a KM-4 diffractometer using graphite monochromated Cu K_α radiation (λ=1.54178 Å) and ω-2θ scan. Up to θ_{max} = 80.0°, 3229 reflections were collected. The structure was solved by direct methods using the program SHELXS-97 [18]. Full-matrix least-squares refinement on F^2 was carried out using the SHELXL-97 program system [19]. Non-H atoms were refined with anisotropic parameters. H-atoms were located from the geometry and were given isotropic factors of 1.2U_{eq} of the bonded C-atoms, 'riding' model was used in the refinement. 209 parameters were refined, final discrepancy factors were *R*1 = 0.0558, *wR*2 = 0.1360, *S* = 1.096, and an extinction coefficient κ = 0.089(5), for 3091 reflections $I > 2\sigma(I)$.

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications numbers CCDC-171746 and 171747. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: int. code + 44(1223)336-033; E-mail: deposit@ccdc.cam.ac.uk].

REFERENCES AND NOTES

[1] The literature concerning pseudo-Michael reactions of 2-aminoazaheterocycles with DEEM contains about 150 items. The full list of references is available upon request.

[2] J. Agata, S. Naguchi and K. Tanaka, JP 73 34 897 (1973), *Chem. Abstr*., **79**, 42537d (1974).

[3] J. Koekoesi, G. Szasz, J. Hermecz, Z. Meszaros, C. M. Pongar and G. Toth, *Magy. Kem. Foly.*, **88**, 222 (1982), *Chem. Abstr.* **97**, 109954t (1983).

[4] J. Koekoesi, J. Hermecz, G. Szasz, Z. Meszaros, G. Toth, and C. M. Pongar, *J. Heterocyclic Chem*., **19**, 909 (1982).

[5] Cambridge Structural Database: F. H. Allen and O. Kennard, *Chemical Design Automation News*, **8**, 31 (1993).

[6] H. P. Weber and T. J. Petcher, *Helv. Chim. Acta*, **59**, 1389 (1976).

[7] J. V. Greenhill, I. Chaaban, and P. J. Steel, *J. Heterocyclic Chem*., **29**, 1375 (1992).

[8] D. Matosiuk, T. Tkaczyński, E. Jagiełło-Wójtowicz, M. Wielosz, G. Szurska, A. Chodkowska, W. Janusz and Z. Kleinrok, *Pol. J. Pharmacol. Pharm*., **44**, 307 (1992).

[9] The CSD refcodes are: FETSEC, ICYTIN, VIPXEX, ZERLUD, ZERMAK, ZUKXOS, ZUKXUY.

[10] V. V. Ovcharenko, K. Pihlaja and D. Matosiuk, *Rapid Commun. Mass Spectrom.*, **15**, 2502 (2001).

[11] E. Soczewiński and W. Maciejewicz, *J. Chromatogr.*, **176**, 247 (1979).

[12] E. Soczewiński, J. Kuczmierczyk and B. Psionka, *J. Liq. Chromatogr.*, **3**, 1829 (1980).

[13] T. Wawrzynowicz, E. Soczewiński and K. Czapińska, *Chromatographia*, **20**, 223 (1985).

[14] H. Szumiło and T. Dzido, *J. Liq. Chromatogr.*, **115**, 337 (1992).

[15] M. Waksmundzka-Hajnos, M. Gadzikowska and W. Gołkiewicz, *J. Planar Chromatogr,*, **13**, 205 (2000).

[16] T. Dzido, *J. Planar Chromatogr*., **3**, 199 (1990).

[17] T. Dzido and E. Soczewiński, *J. Chromatogr.*, **516**, 461 (1990).

[18] G. M. Sheldrick, SHELXS-86: *Acta Crystallogr. A*, **46**, 467 (1990).

[19] G. M. Sheldrick, SHELXL-97: Program for the refinement of a crystal structure from diffraction data, Univ. Göttingen, Germany, 1997.