Chemistry of Heterocyclic Compounds, Vol. 43, No. 6, 2007

4-HYDROXY-2-QUINOLONES

120*. SYNTHESIS AND STRUCTURE OF ETHYL 2-HYDROXY-4-OXO-4H-PYRIDO-[1,2-*a*]PYRIMIDINE-3-CARBOXYLATE

I. V. Ukrainets[1], N. L. Bereznyakova[1], G. P. Petyunin[1], I. A. Tugaibei[1], V. B. Rybakov[2], V. V. Chernyshev[2], and A. V. Turov[3]

An improved method for the preparation and purification of ethyl 2-hydroxy-4-oxo-4H-pyrido[1,2-a]-pyrimidine-3-carboxylates is proposed. According to ^{1}H and ^{13}C NMR spectroscopic data the synthesized compounds exist in DMSO solution in the 2-hydroxy-4-oxo form while in the crystal (at least for the case of the unsubstituted derivative) X-ray analysis shows that it occurs in the bipolar 2,4-dioxo form.

Keywords: 2-aminopyridines, heterocyclic tricarbonylmethane derivatives, 2-hydroxy-4-oxo-4H-pyrido[1,2-*a*]pyrimidine-3-carboxylic acids, esters, X-ray analysis.

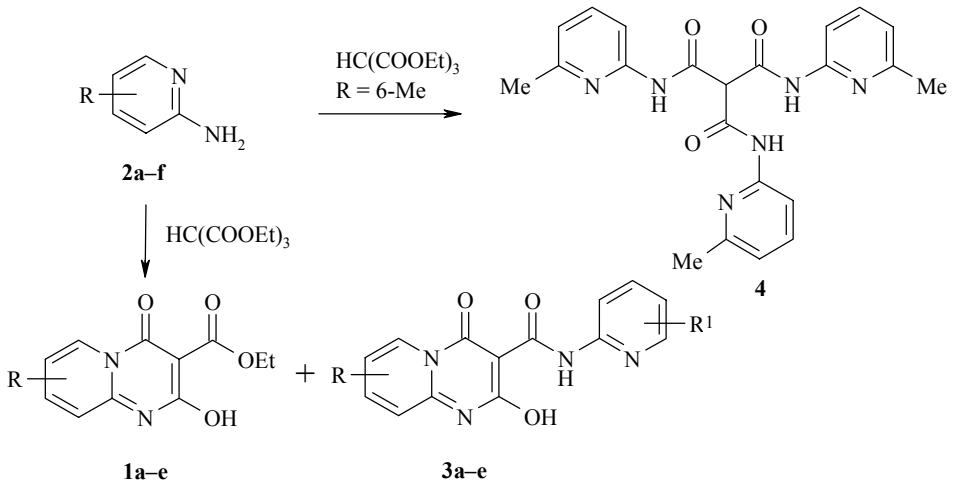
Interest in 4-oxo-4H-pyrido[1,2-*a*]pyrimidine derivatives is principally due to their broad spectrum of biological activity. Based on this molecular system there have been synthesized bicyclic diaza sugars which inhibit β-glucosidase with high specificity [2]. 2-(Benzothiazol-2-yl) derivatives are novel, oral inhibitors of human leukocyte elastase suitable for treating chronic obstructive illnesses of the lungs, asthma, emphysema, cystic fibrosis, and various inflammatory reactions [3]. Substituted ethylenediamines containing the pyrido-[1,2-*a*]pyrimidine fragment are effective in the fight against microbacterial infection, not just tubercular [4]. 4-Oxo-4H-pyrido[1,2-*a*]pyrimidine-3-carboxamides find use as agents for the prophylaxis of gastric problems arising from the use of nonsteroidal anti-inflammatory agents [5]. 2-Amino-4H-pyrido[1,2-*a*]pyrimidin-4-ones actively inhibit the aggregation of human thrombocytes [6] and their analogs with a tetrazole fragment in position 3 the synthesis of leukotrienes [7].

We have continued our work on preparative methods of synthesis and a study of the structure, chemical reactivity, and biological properties of 4-hydroxy-2-quinolinones and heterocycles related to them. This report concerns ethyl 2-hydroxy-4-oxo-4H-pyrido[1,2-*a*]pyrimidine-3-carboxylate.

* For Communication 119 see [1]

[1]National University of Pharmacy, Kharkiv 61002, Ukraine; e-mail: uiv@kharkov.ua. [2]M. V. Lomonosov Moscow State University, Moscow 119899, Russia; e-mail: rybakov@biocryst.phys.msu.su. [3]Taras Shevchenko National University, Kiev 01033, Ukraine; e-mail: nmrlab@univ.kiev.ua. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 864-876, June, 2007. Original article submitted February 20, 2006.

A method for preparing ethyl 2-hydroxy-4-oxo-4H-pyrido[1,2-*a*]pyrimidine-3-carboxylate (**1a**) consists of condensation of 2-aminopyridine **2a** with triethylmethanetricarboxylate in refluxing bromobenzene [8]. To avoid the formation of side product we proposed to use of a two fold excess of triethylmethanetricarboxylate and a relatively large solvent volume. Chromatographic monitoring (although not totally clear) allowed the content of the product to be checked and showed that the reaction is finished after 6 h. Removal of bromobenzene and crystallization gave the ester **1** in 68% yield. Repeated attempts at the reported method and a fuller analysis of the composition of the reaction mixture formed showed that unwanted chemical reactions could not all be suppressed because about 20% of the 2-aminopyridine is used up in forming the side product of 2-hydroxy-4-oxo-4H-pyrido[1,2-*a*]pyrimidine-3-carboxylic acid pyridyl-2-amide (**3a**).



1 a R = H, **b** R = 7-Cl, **c** R = 7-Me, **d** R = 8-Me, **e** R = 9-Me; **2 a** R = H, **b** R = 5-Cl, **c** R = 5-Me, **d** R = 4-Me, **e** R = 3-Me, **f** R = 6-Me; **3 a** R = R^1 = H, **b** R = 7-Cl, R^1 = 5-Cl, **c** R = 7-Me, R^1 = 5-Me, **d** R = 8-Me, R^1 = 4-Me, **e** R = R^1 = 6-Me

With the aim of choosing more rational conditions for the synthesis of the ester **1a** we have studied several modifications of the method used in its preparation. We have varied both the molar ratio of reagents entering into the reaction (from 10, 20, 50, and 100% excess of triethylmethanetricarboxylate) and the use of added solvents with a broad range of boiling points (toluene, xylene, nitrobenzene). Experiments with a three fold excess of pure triethylmethanetricarboxylate were also carried out.

From the overall series of experiments it was found that the best results could be achieved using refluxing xylene and a two fold excess of triethylmethanetricarboxylate. It was not possible to avoid formation of pyridyl-2-amide **3a** in any of the experiments. However, this is a direct result of the direct amidation of the initially formed heterocyclic ester **1a** by 2-aminopyridine since, in the first place amide **3a** is separated even when carrying out the reaction in the comparatively low boiling toluene and, in the second, a thermal intramolecular cyclization of the intermediate ethyl bis(pyridin-2-ylcarbamoyl)acetate needs much more forcing conditions [9]. None the less, exchange of bromobenzene for xylene leads to some increase in the yield of the target ester **1a** and simultaneous lowering of the amount of the unwanted pyridyl-2-amide **3a**.

Many substituted analogs **2b-e** behave similarly to the 2-aminopyridine under the conditions of the studied reaction. The corresponding ethyl 2-hydroxy-4-oxo-4H-pyrido[1,2-*a*]pyrimidine-3-carboxylates **1b-e** are separated in good yields although specific feature are found in some cases. Thus the reaction of triethylmethanetricarboxylate with 2-amino-3-methylpyridine (**2e**) gives the ester **1e** exclusively. It is likely that the amidation is suppressed by the neighboring methyl and amino groups in the aminopyridine **2e**. In the case of 2-amino-6-methylpyridine (**2f**) the "normal" reaction scheme is also hindered by the methyl group but also

blocks access to the other reaction center (the pyridine nitrogen atom or more accurately to the cyclic imino form NH group of the intermediate dicarbethoxyacetic acid pyridyl-2-amide). As a result, carrying out the reaction in bromobenzene gives a mixture of methanetri-N-(6-methylpyridin-2-yl)carboxamide (**4**) and the 6-methylpyridyl-2-amide **3e** in the ratio 1: 1 (from ^{1}H NMR data) whereas in refluxing xylene amide **3e** proves to be the only product of condensing triethylmethanetricarboxylate with compound **2f**. It was interesting to find that it was not possible to detect even traces of ethyl 2-hydroxy-6-methyl-4-oxo-4H-pyrido[1,2-*a*]pyrimidine-3-carboxlate in any of the experiments. This situation allows us to suggest that the route to formation of the amides **3** is not limited just to the variants discussed above.

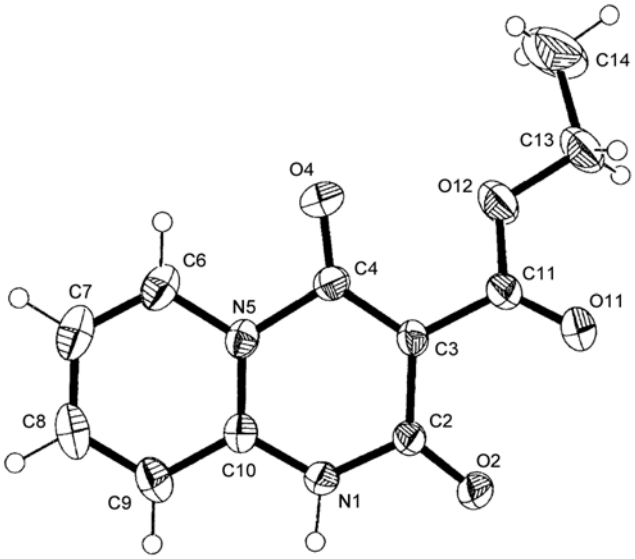


Fig. 1. Atomic numbering and spatial structure for the molecule of ester **1a.**

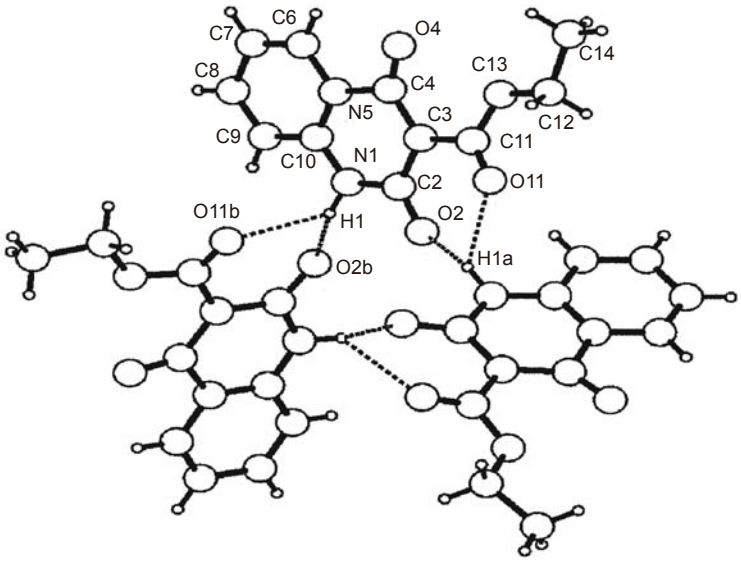


Fig. 2. System of intermolecular hydrogen bonds in the crystal of ester **1a.**

It should be noted that the need to separate the reaction products arises in the majority of examples independently of the reaction conditions. We have shown that the problem can be very efficiently resolved by treatment of the reaction mixture with hot water or other solvent indicated in the Experimental section for which amides **3** are virtually insoluble and the esters crystallize with an extremely high degree of purity.

All of the esters obtained **1a-e** are colorless, crystalline materials, soluble in DMF and DMSO and of low solubility in cold water but generally good in hot.

According to X-ray data carried out on ester **1a** (Figs. 1 and 2, Tables 1 and 2) it was found that the bicyclic fragment and atoms $O_{(2)}$ and $O_{(4)}$ lie in a single plane to within 0.02 Å. The alternating bonds in the

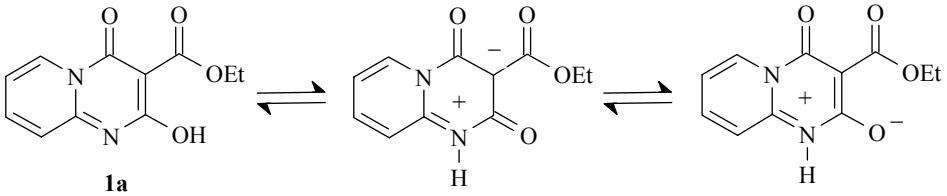
TABLE 1. Interatomic Distances (*l*) in the Structure of Ester **1a**

Bond	*l*, Å	Bond	*l*, Å
$N_{(1)}–C_{(10)}$	1.339(4)	$C_{(7)}–H_{(7)}$	0.9300
$N_{(1)}–C_{(2)}$	1.386(4)	$C_{(8)}–C_{(9)}$	1.355(6)
$N_{(1)}–H_{(1)}$	0.91(5)	$C_{(8)}–H_{(8)}$	0.9300
$C_{(2)}–O_{(2)}$	1.232(4)	$C_{(9)}–C_{(10)}$	1.404(5)
$C_{(2)}–C_{(3)}$	1.441(4)	$C_{(9)}–H_{(9)}$	0.9300
$C_{(3)}–C_{(4)}$	1.414(5)	$C_{(11)}–O_{(11)}$	1.199(5)
$C_{(3)}–C_{(11)}$	1.472(5)	$C_{(11)}–O_{(12)}$	1.321(5)
$C_{(4)}–O_{(4)}$	1.197(4)	$O_{(12)}–C_{(13)}$	1.431(5)
$C_{(4)}–N_{(5)}$	1.500(5)	$C_{(13)}–C_{(14)}$	1.507(7)
$N_{(5)}–C_{(10)}$	1.352(4)	$C_{(13)}–H_{(13A)}$	0.9700
$N_{(5)}–C_{(6)}$	1.381(5)	$C_{(13)}–H_{(13B)}$	0.9700
$C_{(6)}–C_{(7)}$	1.353(7)	$C_{(14)}–H_{(14A)}$	0.9600
$C_{(6)}–H_{(6)}$	0.9300	$C_{(14)}–H_{(14B)}$	0.9600
$C_{(7)}–C_{(8)}$	1.402(7)	$C_{(14)}–H_{(14C)}$	0.9600

TABLE 2. Valence Angles (ω) in the Structure of Ester **1a**

Angle	ω, deg	Angle	ω, deg
$C_{(10)}–N_{(1)}–C_{(2)}$	125.9(3)	$C_{(7)}–C_{(8)}–H_{(8)}$	119.9
$C_{(10)}–N_{(1)}–H_{(1)}$	112(3)	$C_{(8)}–C_{(9)}–C_{(10)}$	120.1(4)
$C_{(2)}–N_{(1)}–H_{(1)}$	121(3)	$C_{(8)}–C_{(9)}–H_{(9)}$	120.0
$O_{(2)}–C_{(2)}–N_{(1)}$	117.1(3)	$C_{(10)}–C_{(9)}–H_{(9)}$	120.0
$O_{(2)}–C_{(2)}–C_{(3)}$	126.6(3)	$N_{(1)}–C_{(10)}–N_{(5)}$	118.9(3)
$N_{(1)}–C_{(2)}–C_{(3)}$	116.2(3)	$N_{(1)}–C_{(10)}–C_{(9)}$	122.2(3)
$C_{(4)}–C_{(3)}–C_{(2)}$	122.0(3)	$N_{(5)}–C_{(10)}–C_{(9)}$	118.9(3)
$C_{(4)}–C_{(3)}–C_{(11)}$	119.0(3)	$O_{(11)}–C_{(11)}–O_{(12)}$	121.5(4)
$C_{(2)}–C_{(3)}–C_{(11)}$	118.8(3)	$O_{(11)}–C_{(11)}–C_{(3)}$	125.2(4)
$O_{(4)}–C_{(4)}–C_{(3)}$	130.9(4)	$O_{(12)}–C_{(11)}–C_{(3)}$	113.2(3)
$O_{(4)}–C_{(4)}–N_{(5)}$	114.5(3)	$C_{(11)}–O_{(12)}–C_{(13)}$	117.7(4)
$C_{(3)}–C_{(4)}–N_{(5)}$	114.6(3)	$O_{(12)}–C_{(13)}–C_{(14)}$	106.9(4)
$C_{(10)}–N_{(5)}–C_{(6)}$	121.1(3)	$O_{(12)}–C_{(13)}–H_{(13A)}$	110.3
$C_{(10)}–N_{(5)}–C_{(4)}$	122.3(3)	$C_{(14)}–C_{(13)}–H_{(13A)}$	110.3
$C_{(6)}–N_{(5)}–C_{(4)}$	116.5(3)	$O_{(12)}–C_{(13)}–H_{(13B)}$	110.3
$C_{(7)}–C_{(6)}–N_{(5)}$	120.4(4)	$C_{(14)}–C_{(13)}–H_{(13B)}$	110.3
$C_{(7)}–C_{(6)}–H_{(6)}$	119.8	$H_{(13A)}–C_{(13)}–H_{(13B)}$	108.6
$N_{(5)}–C_{(6)}–H_{(6)}$	119.8	$C_{(13)}–C_{(14)}–H_{(14A)}$	109.5
$C_{(6)}–C_{(7)}–C_{(8)}$	119.3(4)	$C_{(13)}–C_{(14)}–H_{(14B)}$	109.5
$C_{(6)}–C_{(7)}–H_{(7)}$	120.3	$H_{(14A)}–C_{(14)}–H_{(14B)}$	109.5
$C_{(8)}–C_{(7)}–H_{(7)}$	120.3	$C_{(13)}–C_{(14)}–H_{(14C)}$	109.5
$C_{(9)}–C_{(8)}–C_{(7)}$	120.2(4)	$H_{(14A)}–C_{(14)}–H_{(14C)}$	109.5
$C_{(9)}–C_{(8)}–H_{(8)}$	119.9	$H_{(14B)}–C_{(14)}–H_{(14C)}$	109.5

fragment $N_{(5)}$–$C_{(6)}$–$C_{(7)}$–$C_{(8)}$–$C_{(9)}$–$C_{(10)}$–$N_{(1)}$ (bond length values $N_{(5)}$–$C_{(6)}$ 1.381(5), $C_{(7)}$–$C_{(8)}$ 1.402(7), $C_{(9)}$–$C_{(10)}$ 1.404(5) Å are closer to a single bond and $C_{(6)}$–$C_{(7)}$ 1.353(7), $C_{(8)}$–$C_{(9)}$ 1.355(6), $C_{(10)}$–$N_{(1)}$ 1.339(4) Å to a double bond), the absence of a hydrogen atom on $C_{(3)}$ (it being actually found on the $N_{(1)}$ atom), and also the bond lengths $C_{(2)}$–$C_{(3)}$ 1.441(4), $C_{(3)}$–$C_{(4)}$ 1.414(5), $C_{(3)}$–$C_{(11)}$ 1.472(5) Å leads us to infer that ester **1a** exists in the



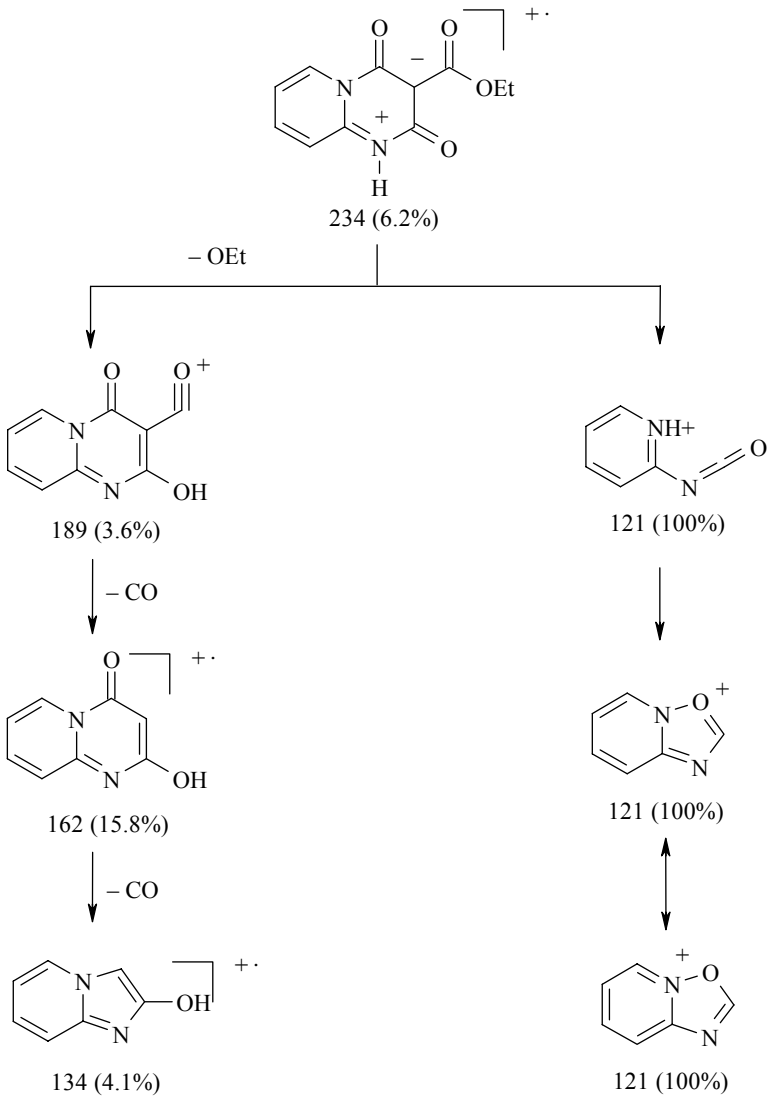
crystal as an internal salt in which the positive charge is concentrated on the $N_{(1)}$ atom and the negative on the $C_{(3)}$ atom. The lengthening of the $C_{(2)}$–$O_{(2)}$ bond 1.232(4) Å when compared with its mean value of 1.210 Å [10] which also encourages the intermolecular hydrogen bond $N_{(1)}$–$H_{(1)}$···$O_{(2b)}$ (0.33-y, -0.66+*x*-*y*, *z*-0.3) H···O 2.01 Å, N–H···O 149º and shortening of the $C_{(2)}$–$C_{(3)}$ bond 1.441(4) Å compared with the mean value of 1.455 Å allow us to propose that the molecular structure of ethyl 2-hydroxy-4-oxo-4H-pyrido[1,2-*a*]pyrimidine-3-carboxylate (**1a**) is a resonance hybrid of the two bipolar structures **5** and **6** with a predominance of the 2,4-dioxo form **5**.

The carbonyl group of the ester substituent at atom $C_{(3)}$ is slightly non-planar with that of the bicycle (torsional angle $O_{(11)}$–$C_{(11)}$–$C_{(3)}$–$C_{(2)}$ -16.39º). Such a position of the ester substituent leads to a marked repulsion between the negative charged oxygen which produces a marked increase in the valence angles $O_{(4)}$–$C_{(4)}$–$C_{(3)}$ to 130.9(4) and $O_{(2)}$–$C_{(2)}$–$C_{(3)}$ to 126.6(3)º. Shortening of the intramolecular contact $H_{(6)}$···$O_{(4)}$ also occurs 2.29 Å (sum of van der Waal radii 2.46 Å [11]). The ethyl substituent in the ester function occurs in an *ap*-position relative to the $C_{(3)}$–$C_{(11)}$ bond and atom $C_{(14)}$ in an *ap*-conformation relative to the bond $C_{(11)}$–$O_{(12)}$ (torsional angles $C_{(13)}$–$O_{(12)}$–$C_{(11)}$–$C_{(3)}$ 176.1 and $C_{(14)}$–$C_{(13)}$–$O_{(12)}$–$C_{(11)}$ -176.1º). An interesting system of intermolecular $N_{(1)}$–$H_{(1)}$···$O_{(2b)}$ and $N_{(1)}$–$H_{(1)}$···$O_{(11b)}$ hydrogen bonds is formed thanks to which three molecules are located and held around a third order axis (Fig. 2).

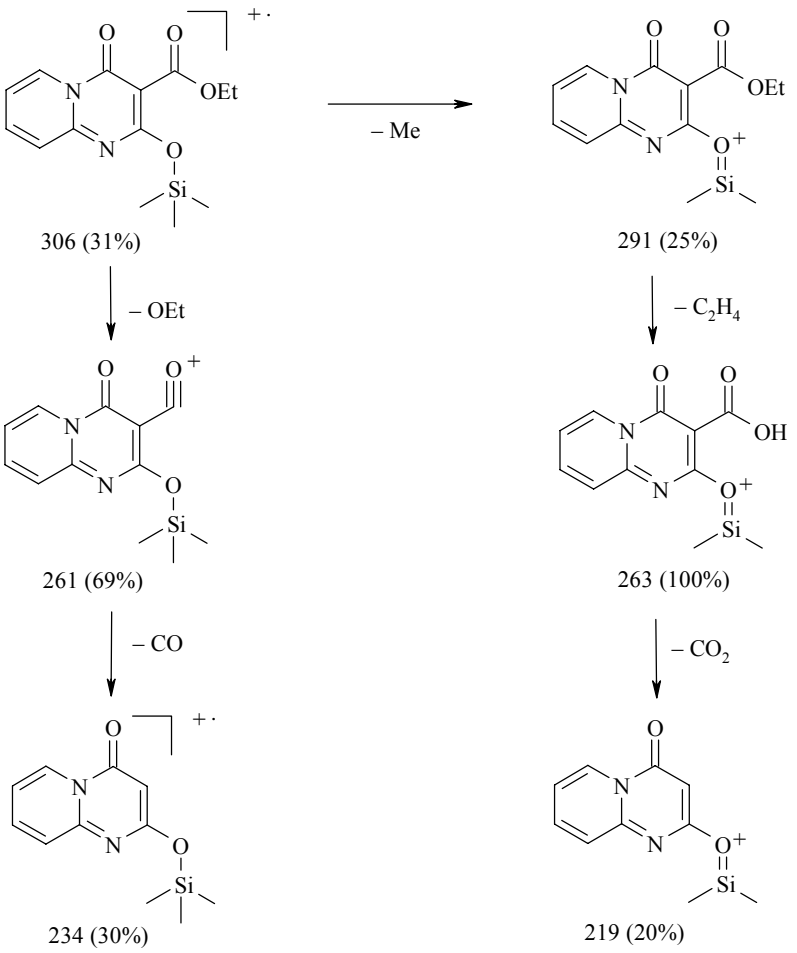
Hence the X-ray analytical results show that in at least one of the synthesized 3-ethoxycarbonyl-2-hydroxy-4-oxo-4H-pyrido[1,2-*a*]pyrimidines (in fact ester **1a**) it exists in the bipolar 2,4-dioxo form in the crystal state.

Mass spectrometric analysis of the structure of esters **1a-e** leads to a similar conclusion. It was found that these compounds form molecular ions under electron impact which fragment by a single scheme as discussed for ester **1a**. The low intensity for the peaks of both the molecular ion and subsequent fragment ions through to the peak fragment with *m/z* 121 suggest that, for the 2,4-dioxo form, the probability of initial decomposition of the ester group is much lower than fission of the $C_{(4)}$–N and $C_{(2)}$–$C_{(3)}$ bond which leads to the formation of a protonated isocyanate with *m/z* 121 (evidently further isomerizing to the more stable aromatic oxadiazolopyridine ion.

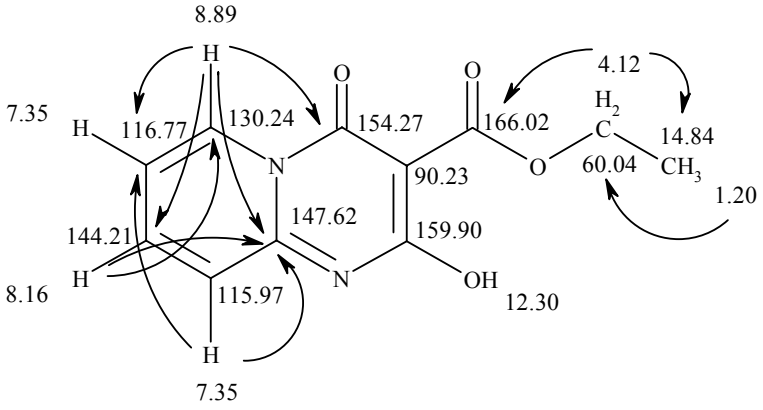
Attempts to check the purity of esters **1a-e** on an instrument package consisting of a gas chromatograph and mass spectrometer detector proved unsuccessful because of the ready decomposition of the compounds studied in transition to the gaseous phase. In order to increase the volatility they were converted to the 2-trimethylsilyoxy derivatives which allowed us to confirm the chromatographic purity of the compounds synthesized and also to record completely the mass spectrometric behavior of modified samples when compared with the starting esters **1a-e**. Blocking of the 2-hydroxy groups (i.e. effectively removing the potential of esters **1a-e** for tautomeric conversion) leads to total suppression of the primary fragmentation of the pyrido[1,2-*a*]-pyrimidine ring.



However, the ester **1a** has been reported in the literature as the 2-hydroxy-4-oxopyrido[1,2-*a*]pyrimidine derivative [8]. Analysis of the ^{1}H NMR spectra of esters **1a-e** shows that all of them are of a single type and, in principle, consistent with either of the possible tautomeric forms. In other words it did not prove possible to interpret the structure of the compounds obtained in solution on the basis of just this data. For example it is proposed that in the ^{1}H NMR spectrum of ester **1a** the hydroxyl signal occurs at lowest field at 12.30 ppm. This signal is strongly broadened. At the same time the signal for the residual water at 3.3 ppm is broadened. This points to a quite rapid proton exchange between the hydroxyl proton and water. The presence of such an exchange is a major obstacle in correlating the experiments since the hydroxyl proton has time to relax fully during the pulse sequence mixing time. Hence a correlation for the hydroxyl group is not found in the HMBC spectrum and it was not possible to localize it in the spectrum. The aromatic proton signals gave a pattern in the spectrum typical of a pyridine. The pyridine H-6 signal was found at lowest field at 8.89 ppm. Its chemical shift is governed on the one hand by the presence of a neighboring heterocyclic nitrogen atom and on the other by the oxygen electron pair at $C_{(4)}$. The H-8 signal is found at quite low field at 8.16 ppm and this is formally a γ-pyridine. The remaining two aromatic protons fall together at 7.35 ppm. The assignment of signals in the ^{13}C



NMR spectrum was made on the basis of an HMBC correlation spectrum. In this case there are few signals and the protonated carbon atoms can be assigned on the basis of the presence of residual correlations *via* one bond and the quaternary carbon atoms on the basis of the correlation through 2-3 chemical bonds (Table 3).



The assignment of the $C_{(4)}$ signal follows from its correlation with proton H-6. The bridging carbon atom between the two heterocyclic nitrogen atoms can be assigned by the correlation with atoms H-6,8 and H-9. The ester group carbonyl carbon can be assigned from its correlation with the methylene group proton signal. A correlation could not be observed for two carbon atoms. Since these occur in the unassigned spectrum at 90.23 and 159.90 ppm the first must be the $C_{(3)}$ carbon atom and the second $C_{(2)}$.

TABLE 3. Correlations Identified for Ester **1a**

δ, ppm	HMBC, one bond	HMBC, 2–3 chemical bonds
12.30	—	—
8.89	130.24	154.27, 147.62, 144.21, 116.77
8.16	144.21	147.62, 130.24
7.35	116.77, 115.97	147.62, 130.24, 116.77, 115.97
4.12	60.04	166.02, 14.84
1.20	14.84	60.04

The ^{13}C NMR spectra of esters **1a-e** also proved to be similar and a detailed study showed that the $C_{(2)}$ and $C_{(9)}$ signals had a width 3-4 time greater than the width of the remainder. These signals correspond to the carbon atoms placed close to the $N_{(1)}$ atom.

Signal broadening is frequently associated with the presence of exchange processes, from which it follows that in esters **1a-e** the hydrogen is most likely not fixed at the hydroxyl group 2-OH but the equilibrium shown in the scheme of the two tautomeric forms occurs, even though this fact is not an unambiguous confirmation of the presence of such an equilibrium.

Additional useful information also comes from comparison of experimental and calculated ^{13}C NMR spectra. The calculations carried out for the two tautomers using several programs showed that the calculated spectra of the 2-hydroxy form are the closest to reality. The carbon atom in position 3 of the pyrido[1,2-*a*]pyrimidines are specially indicative in this scheme. Their mean value for the 2-hydroxy form is 89.4 ppm while for all of the remaining tautomers it is about 65 ppm. In the experimental spectra the indicated signals are found in the 90 ppm region and so it is logical to suggest that the synthesized compounds are principally in the 2-hydroxy forms in DMSO solution.

EXPERIMENTAL

^{13}C NMR spectra of the esters **1a-e**, ^{1}H NMR and also the heteronuclear HMBC spectrum of ester **1a** were obtained on a Varian Mercury-400 spectrometer (100 and 400 MHz respectively). The ^{1}H NMR spectra of the remaining compounds were taken on a Varian Mercury VX-200 (200 MHz) instrument using DMSO-d_6 solvent. In all cases the internal standard was TMS. The mass spectra of esters **1a-e** were obtained on a Varian 1200L spectrometer in full scanning mode in the range 45-550 m/z and EI ionization 70 eV. Chromato mass spectra were recorded on a Hewlett Packard 5890/5972 instrument in full scanning mode in the range 35-700 m/z and EI ionization 70 eV. To increase their volatility the esters **1a-e** were converted to the 2-trimethylsilyloxy derivatives using N,O-bis(trimethylsilyl)trifluoroacetamide and chromatographed on a Hewlett Packard 5MS column of length 25 m, internal diameter 0.2 mm, stationary phase polysiloxane (5% diphenylpolysiloxane, 95% dimethylpolysiloxane) of thickness 0.33 μm, and helium gas carrier. Commercial 2-aminopyridines and triethylmethanetricarboxylate from Fluka were used in this work.

Ethyl 2-Hydroxy-4-oxo-4H-pyrido[1,2-*a*]pyrimidine-3-carboxylate (1a). A solution of 2-amino-pyridine **2a** (0.94 g, 0.01 mol) and triethylmethanetricarboxylate (4.21 g, 0.02 mol) in xylene (10 ml, commercial mixture of isomers) was refluxed for 1-1.5 h allowing the liberated ethanol to evaporate through the reflux condenser. It was then cooled and hexane (50 ml) was added. After 2-3 h the crystals separated were filtered off, washed with hexane, and dried (major amounts of unreacted triethylmethanetricarboxylate were readily regenerated from the filtrate). The compound obtained was treated with boiling water and filtered. The ester **1a** crystallized from the filtrate. Yield 1.78 g (76%); mp 220-222ºC (water). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 12.30 (1H, br. s, OH); 8.89 (1H, dd, *J* = 7.4 and 1.0, H-6); 8.16 (1H, td, *J* = 7.8 and 1.4, H-8); 7.41-7.32

(2H, m, H-7,9); 4.12 (2H, q, J = 7.0, OCH_2); 1.20 (3H, t, J = 7.0, CH_3). ^{13}C NMR spectrum, δ, ppm: 166.02 (CO_2), 159.90 ($C_{(2)}$), 154.27 ($C_{(4)}$), 147.62 ($C_{(9a)}$), 144.21 ($C_{(8)}$), 130.24 ($C_{(6)}$), 116.77 ($C_{(7)}$), 115.97 ($C_{(9)}$), 90.23 ($C_{(3)}$), 60.04 (OCH_2), 14.84 (CH_3). Mass spectrum, *m/z* (I_{rel}, %): 234 $[M]^+$ (6.2), 189 $[M\text{-}OEt]^+$ (3.6), 162 $[M\text{-}COOC_2H_4]^+$ (15.8), 134 $[M\text{-}COOC_2H_4\text{-}CO]^+$ (4.1), 121 (100). Mass spectrum of 2-trimethylsilyl derivative, *m/z* (I_{rel}, %): 306 $[M]^+$ (31), 291 $[M\text{-}Me]^+$ (25), 263 $[M\text{-}Me\text{-}C_2H_4]^+$ (100), 261 $[M\text{-}OEt]^+$ (69), 234 $[M\text{-}OEt\text{-}CO]^+$ (30), 233 $[M\text{-}OEt\text{-}CO]^+$ (58), 219 $[M\text{-}Me\text{-}C_2H_4\text{-}CO_2]^+$ (20), 206 (38).

Compounds 1b-e were prepared by the preceding method.

Ethyl 7-Chloro-2-hydroxy-4-oxo-4H-pyrido[1,2-*a*]pyrimidine-3-carboxylate (1b). Yield 70%; mp 203-205ºC (ethanol). ^1H NMR Spectrum, δ, ppm (*J*, Hz): 12.66 (1H, br. s, OH), 8.88 (1H, d, J = 2.4, H-6); 8.23 (1H, dd, J = 8.3 and 2.4, H-8); 7.38 (1H, d, J = 9.3, H-9); 4.14 (2H, q, J = 7.1, OCH_2); 1.21 (3H, t, J = 7.1, CH_3). ^{13}C NMR spectrum, δ, ppm: 165.90 (CO_2), 160.50 ($C_{(2)}$), 153.72 ($C_{(4)}$), 147.12 ($C_{(9a)}$), 143.76 ($C_{(8)}$), 127.84 ($C_{(9)}$), 123.15 ($C_{(6)}$), 118.86 ($C_{(7)}$), 90.03 ($C_{(3)}$), 60.26 (OCH_2); 14.80 (CH_3). Mass spectrum, *m/z* (I_{rel}, %): 268 $[M]^+$ (34.6), 223 $[M\text{-}OEt]^+$ (4.7), 196 $[M\text{-}COOC_2H_4]^+$ (27.7), 168 $[M\text{-}COOC_2H_4\text{-}CO]^+$ (59.6), 155 (100). Mass spectrum of 2-trimethylsilyloxy derivative, *m/z* (I_{rel}, %): 340 $[M]^+$ (38), 325 $[M\text{-}Me]^+$ (30), 297 $[M\text{-}Me\text{-}C_2H_4]^+$ (100), 295 $[M\text{-}OEt]^+$ (62), 268 $[M\text{-}OEt\text{-}CO]^+$ (37), 267 $[M\text{-}OEt\text{-}CO]^+$ (51), 253 $[M\text{-}Me\text{-}C_2H_4\text{-}CO_2]^+$ (26), 240 (30). In both cases the *m/z* value refers only to the ^{35}Cl isotope. Found, %: C 49.30; H 3.47; N 10.35. $C_{11}H_9ClN_2O_4$. Calculated, %: C 49.18; H 3.38; N 10.43.

Ethyl 2-Hydroxy-7-methyl-4-oxo-4H-pyrido[1,2-*a*]pyrimidine-3-carboxylate (1c). Yield 77%; mp 207-209ºC (water). ^1H NMR spectrum, δ, ppm (*J,* Hz): 12.31 (1H, br. s, OH); 8.73 (1H, s, H-6); 8.05 (1H, dd, J = 8.6 and 1.6, H-8); 7.30 (1H, d, J = 8.9, H-9); 4.13 (2H, q, J = 7.2, OCH_2); 2.36 (3H, s, CH_3); 1.21 (3H, t, J = 7.1, $CH_2C\underline{H}_3$). ^{13}C NMR spectrum, δ, ppm: 166.11(CO_2), 159.82 ($C_{(2)}$), 154.20 ($C_{(4)}$), 146.19 ($C_{(9a)}$); 146.08 ($C_{(8)}$), 127.72 ($C_{(6)}$), 126.55 ($C_{(7)}$), 115.60 ($C_{(9)}$), 90.22 ($C_{(3)}$), 60.04 (OCH_2), 17.88 ($CH_{(3)}$), 14.83 ($OCH_2C\underline{H}_3$). Mass spectrum, *m/z*, (I_{rel}, %): 248 $[M]^+$ (35.9), 203 $[M\text{-}OEt]^+$ (18.9), 176 $[M\text{-}COOC_2H_4]^+$ (42.7), 148 $[M\text{-}COOC_2H_4\text{-}CO]^+$ (61.5), 135 (100). Mass spectrum of 2-trimethylsilyloxy derivative, *m/z* (I_{rel}, %): 320 $[M]^+$ (37), 305 $[M\text{-}Me]^+$ (33), 277 $[M\text{-}Me\text{-}C_2H_4]^+$ (100), 275 $[M\text{-}OEt)^+$ (60), 248 $[M\text{-}OEt\text{-}CO]^+$ (34), 247 $[M\text{-}OEt\text{-}CO]^+$ (52), 233 $[M\text{-}Me\text{-}C_2H_4\text{-}CO_2]^+$ (26), 220 (34). Found, %: C 58.19; H 4.94; N 11.36. $C_{12}H_{12}N_2O_4$. Calculated, %: C 58.06; H 4.87; N 11.28.

Ethyl 2-Hydroxy-8-methyl-4-oxo-4H-pyrido[1,2-*a*]pyrimidine-3-carboxylate (1d). Yield 72%; mp 231-233ºC (water). ^1H NMR spectrum, δ, ppm (*J,* Hz): 12.26 (1H, br. s, OH); 8.78 (1H, d, J = 7.1, H-6); 7.22 (1H, dd, J = 7.0 and 1.5. H-7); 7.11 (1H, s, H-9); 4.12 (2H, q, J = 7.1, OCH_2); 2.44 (3H, s, CH_3); 1.20 (3H, t, J = 7.1, $CH_2C\underline{H}_3$). ^{13}C NMR spectrum, δ, ppm: 166.03 (CO_2), 159.89 ($C_{(2)}$),156.98 ($C_{(4)}$),154.20 ($C_{(9a)}$), 146.97 ($C_{(8)}$), 126.59 ($C_{(7)}$), 118.78 ($C_{(6)}$), 114.03 ($C_{(9)}$), 89.73 ($C_{(3)}$), 59.95 (OCH_2), 21.88 (CH_3), 14.85 ($OCH_2C\underline{H}_3$). Mass spectrum, *m/z* (I_{rel}, %): 248 $[M]^+$ (35.4), 203 $[M\text{-}OEt]^+$ (23.4), 176 $[M\text{-}COOC_2H_4]^+$ (59.1), 148 $[M\text{-}COOC_2H_4\text{-}CO]^+$ (41), 135 (100). Mass spectrum of the 2-trimethylsilyloxy derivative, *m/z* (I_{rel}, %): 320 $[M]^+$ (40), 305 $[M\text{-}Me]^+$ (36). 277 $[M\text{-}Me\text{-}C_2H_4]^+$ (100), 275 $[M\text{-}OEt]^+$ (55), 248 $[M\text{-}OEt\text{-}CO]^+$ (39), 247 (M-OEt-CO)$^+$ (48), 233 (M-Me-C_2H_4-CO_2)$^+$ (21), 220 (27). Found, %: C 58.12; H 4.75; N 11.17. $C_{12}H_{12}N_2O_4$. Calculated, %: C 58.06; H 4.87; N 11.28.

Ethyl 2-Hydroxy-9-methyl-4-oxo-4H-pyrido[1,2-a]pyrimidine-3-carboxylate (1e). Yield 84%; mp 189-191ºC (acetone). ^1H NMR spectrum, δ, ppm (*J,* Hz): 1.247 (1H, br. s, OH); 8.82 (1H, d, J = 7.1, H-6); 7.97 (1H, dd, J = 7.1 and 1.0, H-8); 7.26 (1H, d, J = 7.0, H-7); 4.23 (2H, q, J = 7.1, OCH_2); 2.41 (3H, s, CH_3); 1.25 (3H, t, J = 7.1, $CH_2C\underline{H}_3$). ^{13}C NMR spectrum, δ, ppm: 169.14 (CO_2), 159.17 ($C_{(2)}$), 155.49 ($C_{(4)}$), 150.08 ($C_{(9a)}$), 141.04 ($C_{(8)}$), 127.40 ($C_{(6)}$), 120.21 ($C_{(9)}$), 116.00 ($C_{(7)}$), 89.43 ($C_{(3)}$), 61.00 (OCH_2), 17.73 (CH_3), 14.73 ($OCH_2C\underline{H}_3$). Mass spectrum, *m/z* (I_{rel}, %): 248 $[M]^+$ (32.2), 203 $[M\text{-}OEt]^+$ (23.4), 176 $[M\text{-}COOC_2H_4]^+$ (56.3), 148 $[M\text{-}COOC_2H_4\text{-}CO]^+$ (65.6), 135 (100). Mass spectrum of the 2-trimethylsilyloxy derivative, *m/z* (I_{rel}, %): 320 $[M]^+$ (33), 305 $[M\text{-}Me]^+$ (30), 277 $[M\text{-}Me\text{-}C_2H_4]^+$ (100), 275 $[M\text{-}OEt]^+$ (54), 248 $[M\text{-}OEt\text{-}CO]^+$ (28), 247 $[M\text{-}OEt\text{-}CO]^+$ (49), 233 $[M\text{-}Me\text{-}C_2H_4\text{-}CO_2]^+$ (32), 220 (36). Found, %: C 58.20; H 4.96; N 11.22. $C_{12}H_{12}N_2O_4$. Calculated, %: C 58.06; H 4.87; N 11.28

X-Ray Investigation of Ethyl 2-Hydroxy-4-oxo-4H-pyrido[1,2-*a*]pyrimidine-3-carboxylate (1a). Crystals of ester **1a** are trigonal (water). At 20ºC: $a = b = 25.475(8)$, $c = 8.662(7)$ Å, $\alpha = \beta = 90º$, $\gamma = 120º$, $V = 4868(4)$ Å^3, M_r 234.2 1, $Z = 18$, space group $R3c$, $d_{calc} = 1.438$ g/cm^3, $\mu(MoK\alpha) = 0.946$ mm^{-1}, $F(000) = 2196$. The parameters for the unit cell and intensities of 3200 reflections (1180 independent, $R_{int} = 0.113$) were measured and refined for 25 reflexes in the angle range θ 28-30º on a CAD4 diffractometer (CuKα radiation, graphite monochromator, ω-scanning). The diffraction experiment was carried out on a crystal of linear dimensions 4.0×0.2×0.2 mm ($3.47 \le \theta \le 74.91º$), index range h, k, l: $0 \le h \le 31$, $-31 \le k \le 27$, $-10 \le l \le 0$).

The structure was solved by a direct method using the SHELXTL program package [12]. The positions of the hydrogen atoms were calculated geometrically and refined isotropically. The structure was refined in F^2 full matrix least squares analysis in the anisotropic approximation for non-hydrogen atoms to $wR_2 = 0.115$ for 1180 reflections ($R_1 = 0.049$, $S = 1.089$). The full crystallographic information has been placed in the Cambridge structural data bank (reference CCDC no. 297490). The spatial positions of the atoms in the molecule of the investigated compound and their numbering are given in Fig. 1 obtained using the ORTEP3 program [13]. Individual interatomic distances are given in Table 1 and valence angles in Table 2.

2-Hydroxy-4-oxo-4H-pyrido[1,2-*a*]pyrimidine-3-carboxylic acid pyrid-2-ylamide (3a). The residue of water insoluble material on the filter (see the example of the synthesis of ester **1a**) was dried. Yield 0.2 g (14%); mp 250-252ºC (DMF). ^{1}H NMR spectrum, δ, ppm: 14.15 (1H, s, OH); 12.00 (1H, s, NH); 8.97-7.10 (8H, m, $H_{arom.}$).

Compounds 3b-e were prepared similarly.

7-Chloro-2-hydroxy-4-oxo-4H-pyrido[1,2-*a*]pyrimidine-3-carboxylic acid 5-chloropyrid-2-ylamide (3b). Yield 19%; mp 316-318ºC (DMF). ^{1}H NMR spectrum, δ, ppm: 14.01 (1H, s, OH); 12.03 (1H, s, NH); 9.00-7.52 (6H, m, $H_{arom.}$). Found, %: C 47.77; H 2.41; N 20.32. $C_{14}H_8Cl_2N_4O_3$. Calculated, %: C 47.89; H 2.30; N 20.19.

2-Hydroxy-7-methyl-4-oxo-4H-pyrido[1,2-*a*]pyrimidine-3-carboxylic acid 5-methylpyrid-2-ylamide (3c). Yield 11%; mp 324-326ºC (DMF). ^{1}H NMR spectrum, δ, ppm: 14.43 (1H, s, OH); 11.86 (1H, s, NH); 8.82-7.44 (6H, m, $H_{arom.}$); 2.42 (3H, s, CH_3); 2.26 (3H, s, CH_3). Found, %: C 61.85; H 4.47; N 18.20. $C_{16}H_{14}N_4O_3$. Calculated, %: C 61.93; H 4.55; N 18.05.

2-Hydroxy-8-methyl-4-oxo-4H-pyrido[1,2-*a*]pyrimidine-3-carboxylic acid 4-methypyrid-2-ylamide (3d). Yield 8%; mp >340ºC (DMF). ^{1}H NMR, δ, ppm: 14.30 (1H, s, OH); 11.94 (1H, s, NH); 8.90-7.00 (6H, m, $H_{arom.}$); 2.43 (3H, s, CH_3); 2.31 (3H, s, CH_3). Found, %: C 61.80; H 4.43; N 18.13. $C_{16}H_{14}N_4O_3$. Calculated, %: C 61.93; H 4.55; N 18.05

2-Hydroxy-6-methyl-4-oxo-4H-pyrido[1,2-*a*]pyrimidine-3-carboxylic acid 6-methylpyrid-2-ylamide (3e). Yield 26%; mp 226-228ºC (DMF). ^{1}H NMR spectrum, δ, ppm: 14.15 (1H, s, OH); 11.96 (1H, s, NH); 8.03-6.92 (6H, m, $H_{arom.}$); 2.91 (3H, s, CH_3); 2.40 (3H, s, CH_3). Found, %: C 61.81; H 4.67; N 18.00. $C_{16}H_{14}N_4O_3$. Calculated, %: C 61.93; H 4.55; N 18.05.

REFERENCES

1. I. V. Ukrainets, N. L. Bereznyakova, V. A. Parshikova, and S. V. Shishkina, *Khim. Geterotsikl. Soedin.*, 856 (2007). [*Chem. Heterocycl. Comp.,* **43,** 722 (2007)]
2. D. D. Dhavale, M. M. Matin, T. Sharma, and S. G. Sabharwal, *Bioorg. Med. Chem.*, **12**, 4039 (2004).
3. M. Varga, Z. Kapui, S. Batori, L. T. Nagy, L. Vasvari-Debreczy, E. Mikus, K. Urban-Svabo, and P. Aranyi, *Eur. J. Med. Chem.*, **38**, 421 (2003).
4. M. N. Protopopova, R. E. Lee, R. A. Slayden, C. E. Barry, and L. Einck, WO Patent 03096989 (2003). http://ep.espacenet.com
5. I. Hermecz, J. Sipos, L. Vasvari-Debreczy, K. Gyires, and Z. Kapui, *Acta Physiol. Hung.*, **80**, 225 (1992).

6. G. Roma, M. Di. Braccio, G. Leoncini, and B. Aprile, *Farmaco*, **48** 1225 (1993).
7. Y. Hamasaki, M. Zaitu, K. Tsuji, M. Miyazaki, R. Hayasaki, E. Muro, S. Yamamoto, I. Kobayashi, M. Matsuo, T. Ichimaru, and S. Miyazaki, *Int. J. Immunopharmacol.*, **22**, 483 (2000).
8. A. Kutyrev and T. Kappe, *J. Heterocycl. Chem.*, **34**, 969 (1997).
9. I. V. Ukrainets, O. V. Gorokhova, L. V. Sidorenko, and N. L. Bereznyakova, *Khim. Geterotsikl. Soedin.*, 1191 (2006). [*Chem. Heterocycl. Comp.*, **42**, 1032 (2006)].
10. H.–B. Burgi and J. D. Dunitz, *Struct. Correl.*, Vol. 2, VCH, Weinheim (1994), p. 741.
11. Yu. V. Zefirov, *Krystallografiya,* **42**, 936 (1997).
12. G. M. Sheldrick, *SHELXTL PLUS PC Version. A System of Computer Programs for the Determination of Crystal Structure from X ray Diffraction Data, Revision 5.1* (1998).
13. L. J. Farrugia, *J. Appl. Crystallogr.*, **30**, 565 (1997).