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4-HYDROXY-2-QUINOLONES 143*. SYNTHESIS, STRUCTURE, AND SPECTROSCOPIC CHARACTERISTICS OF ETHYL 2-HYDROXY-4-OXO-4H-PYRAZINO[1,2-*a*]PYRIMIDINE-3-CARBOXYLATE

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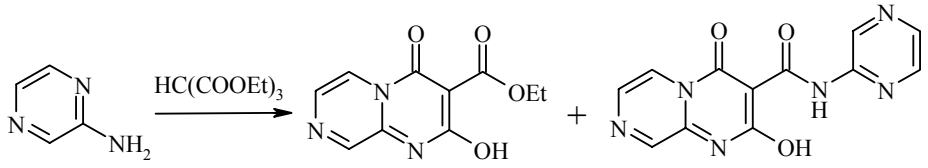
Condensation of aminopyrazine with triethyl methanetricarboxylate gave ethyl 2-hydroxy-4-oxo-4H-pyrazino[1,2-a]pyrimidine-3-carboxylate. According to X-ray analytical data the compound exists in the 2-hydroxy-4-oxo form in the crystal.

Keywords: aminopyrazine, 3-ethoxycarbonyl-2-hydroxy-4-oxo-4H-pyrazino[1,2-*a*]pyrimidine, tris-(ethoxycarbonyl)methane, X-ray analysis.

Following a detailed study of the various modifications of carrying out the condensation of 2-aminopyridines with triethyl methanetricarboxylate it was found that the most rational method for preparing ethyl 2-hydroxy-4-oxo-4H-pyrido[1,2-*a*]pyrimidine-3-carboxylates is to carry out the synthesis in refluxing xylene with a molar reagent ratio of 1:2 [2]. This same method was also used successfully in the preparation of an 8-aza analog of the heterocycles indicated above, namely ethyl 2-hydroxy-4-oxo-4H-pyrazino-[1,2-*a*]pyrimidine-3-carboxylate (**1**) which is of interest for the subsequent synthesis of biologically active materials structurally similar to the 4-hydroxyquinol-2-one derivatives extensively studied by us.



* For Communication 142 see [1].

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As in the case of the 2-aminopyridines the reaction of the aminopyrazine (**2**) with triethyl methanetricarboxylate unfortunately did not occur unambiguously and suppression of formation of the side 2-hydroxy-4-oxo-4H-pyrazino[1,2-*a*]pyrimidine-3-carboxylic acid pyrazin-2-ylamide (**3**) did not prove possible. Hence the question of an efficient product separation remains timely here. It was resolved by choosing a solvent suitable for this purpose and this proved to be acetone in which the ethyl ester **1** is readily soluble but the pyrazin-2-ylamide **3** is virtually insoluble.

An X-ray structural analysis of ethyl 2-hydroxy-4-oxo-4H-pyrido[1,2-*a*]pyrimidine-3-carboxylate showed that it exists in the crystal in the bipolar 2,4-dioxo form with the proton on the nitrogen atom in position 1 [2]. It would seem that such an insignificant change in structure as the exchange of the carbon atom in position 8 for nitrogen would not influence the pyrimidine part of the molecule. None the less, the ethyl 2-hydroxy-4-oxo-4H-pyrazino[1,2-*a*]pyrimidine-3-carboxylate (**1**) exists exclusively as the 2-hydroxy-4-oxo form under the same conditions (Fig. 1, Tables 1, 2).

All of the non-hydrogen atoms of the ester molecule **1** lie in a single plane within 0.02 Å with the exception of $C_{(14)}$. The coplanarity of the ester substituent to the bicyclic fragment is stabilized by strong intramolecular hydrogen bonding $O_{(2)}$–$H_{(2)}$···$H_{(11)}$ (H···O 1.59 Å, O–H···O 158º) and this leads to a lengthening of

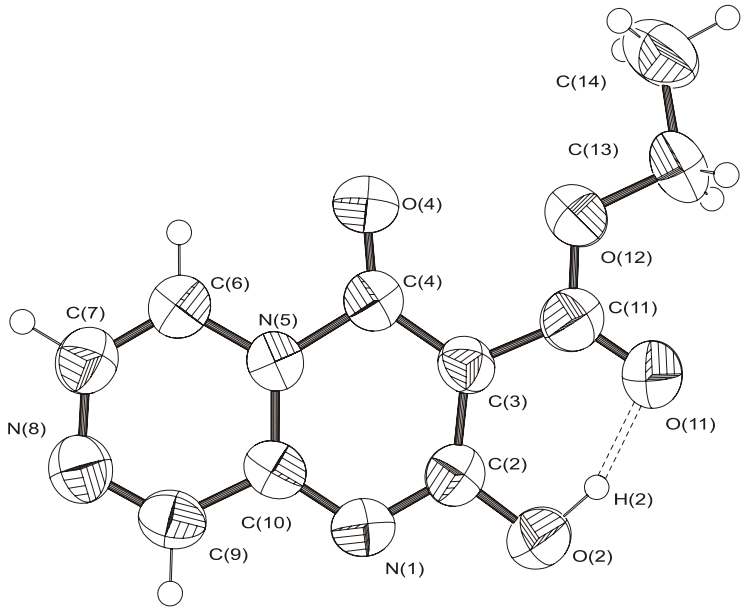


Figure 1. Atomic numbering and spatial structure of the ester **1** molecule. Dotted lines show the intramolecular hydrogen bond.

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

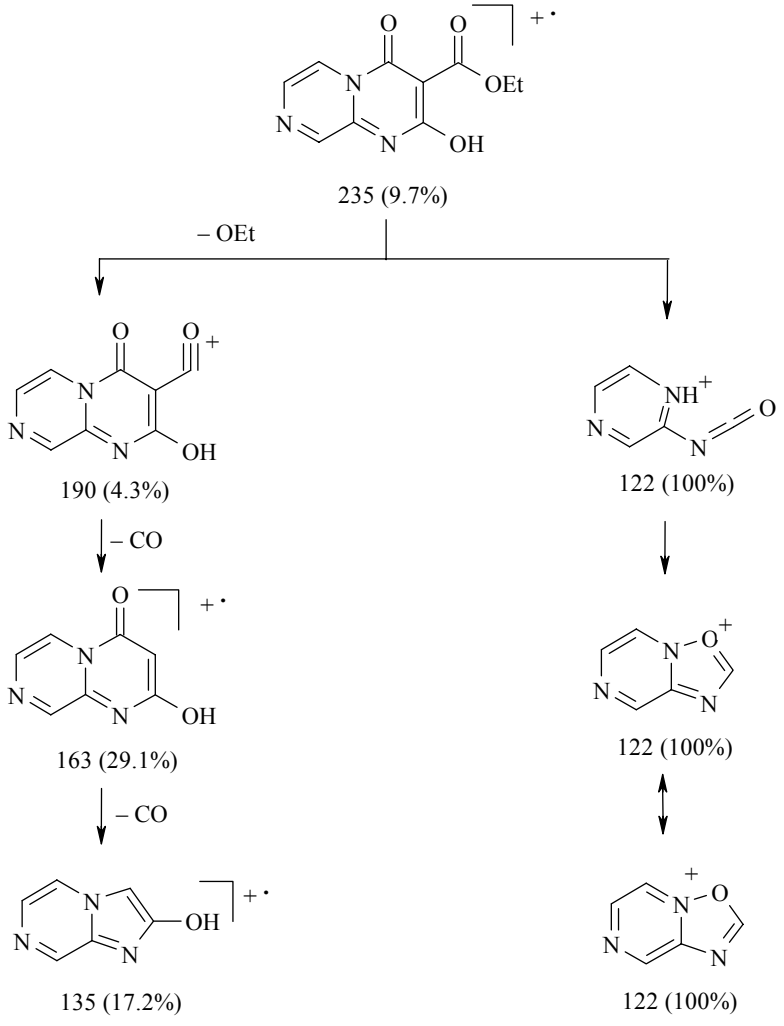
Bond	*l*, Å	Bond	*l*, Å
$N_{(1)}$–$C_{(10)}$	1.327(3)	$N_{(1)}$–$C_{(2)}$	1.332(4)
$C_{(2)}$–$O_{(2)}$	1.333(3)	$C_{(2)}$–$C_{(3)}$	1.402(4)
$C_{(3)}$–$C_{(4)}$	1.421(4)	$C_{(3)}$–$C_{(11)}$	1.452(4)
$C_{(4)}$–$O_{(4)}$	1.214(3)	$C_{(4)}$–$N_{(5)}$	1.449(3)
$N_{(5)}$–$C_{(10)}$	1.362(3)	$N_{(5)}$–$C_{(6)}$	1.374(3)
$C_{(6)}$–$C_{(7)}$	1.333(4)	$C_{(7)}$–$N_{(8)}$	1.358(4)
$N_{(8)}$–$C_{(9)}$	1.302(4)	$C_{(9)}$–$C_{(10)}$	1.423(4)
$C_{(11)}$–$O_{(11)}$	1.230(3)	$C_{(11)}$–$O_{(12)}$	1.319(3)
$O_{(12)}$–$C_{(13)}$	1.448(3)	$C_{(13)}$–$C_{(14)}$	1.483(4)

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

Angle	ω, deg.	Angle	ω, deg.
$C_{(10)}$–$N_{(1)}$–$C_{(2)}$	17.0(2)	$N_{(1)}$–$C_{(2)}$–$O_{(2)}$	113.6(3)
$N_{(1)}$–$C_{(2)}$–$C_{(3)}$	125.1(3)	$O_{(2)}$–$C_{(2)}$–$C_{(3)}$	121.2(3)
$C_{(2)}$–$C_{(3)}$–$C_{(4)}$	118.9(3)	$C_{(2)}$–$C_{(3)}$–$C_{(11)}$	118.8(3)
$C_{(4)}$–$C_{(3)}$–$C_{(11)}$	122.2(3)	$O_{(4)}$–$C_{(4)}$–$C_{(3)}$	129.1(3)
$O_{(4)}$–$C_{(4)}$–$N_{(5)}$	117.2(3)	$C_{(3)}$–$C_{(4)}$–$N_{(5)}$	113.7(3)
$C_{(10)}$–$N_{(5)}$–$C_{(6)}$	119.8(3)	$C_{(10)}$–$N_{(5)}$–$C_{(4)}$	121.8(3)
$C_{(6)}$–$N_{(5)}$–$C_{(4)}$	118.5(2)	$C_{(7)}$–$C_{(6)}$–$N_{(5)}$	119.7(3)
$C_{(6)}$–$C_{(7)}$–$N_{(8)}$	123.7(3)	$C_{(9)}$–$N_{(8)}$–$C_{(7)}$	115.9(3)
$N_{(8)}$–$C_{(9)}$–$C_{(10)}$	125.0(3)	$N_{(1)}$–$C_{(10)}$–$N_{(5)}$	123.5(3)
$N_{(1)}$–$C_{(10)}$–$C_{(9)}$	120.6(3)	$N_{(5)}$–$C_{(10)}$–$C_{(9)}$	115.9(3)
$O_{(11)}$–$C_{(11)}$–$O_{(12)}$	121.8(3)	$O_{(11)}$–$C_{(11)}$–$C_{(3)}$	122.7(3)
$O_{(12)}$–$C_{(13)}$–$C_{(14)}$	107.5(3)		

the $C_{(11)}$–$O_{(11)}$ bond to 1.230(3) Å when compared with its mean value of 1.210 Å [3]. Such a substituent position at the $C_{(3)}$ atom leads to strong repulsion between the negatively charged atoms $O_{(4)}$ and $O_{(12)}$ which likely causes the a marked increase in the $C_{(3)}$–$C_{(4)}$–$O_{(4)}$ valence angle to 129.1(3)º. The ethyl group in the ester

Scheme 1



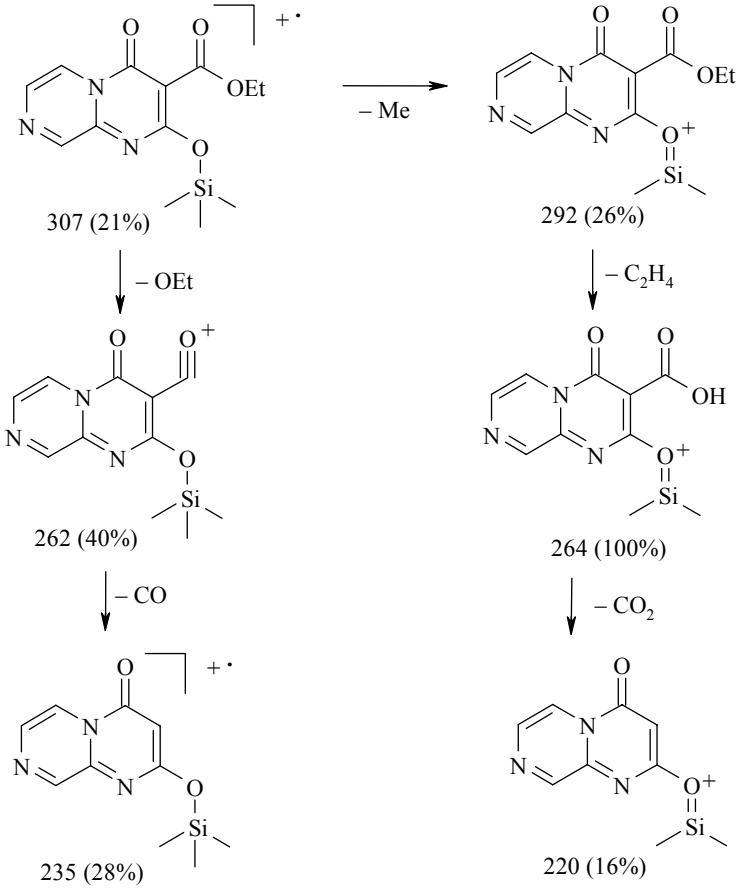
substituent occurs in an *ap*-conformation relative to the $C_{(11)}$–$O_{(12)}$ bond (torsional angle $C_{(11)}$–$O_{(12}$–$C_{(13)}$–$C_{(14)}$ 172.97º). A tendency to localization of electron density is noted in the pyrazine ring. The bond lengths $C_{(6)}$–$C_{(7)}$ 1.333(4) and $N_{(8)}$–$C_{(9)}$ 1.302(4) Å are close in value to a mean double bond 1.260 and the $N_{(5)}$–$C_{(6)}$ 1.374(3), $C_{(7)}$–$N_{(8)}$ 1.358(4), and $C_{(9)}$–$C_{(10)}$ 1.423(4) Å bond lengths close to the mean value for an ordinary Csp^2–Csp^2 bond. In the pyrimidone ring the $N_{(1)}$–$C_{(2)}$ 1.332(4) and $C_{(3)}$–$C_{(4)}$ 1.421(4) bond lengths are shortened and the $C_{(2)}$–$C_{(3)}$ bond 1.402(4) lengthened when compared with their mean values of 1.376, 1.455, and 1.322 Å [3] respectively.

In spite of the significant difference found by the X-ray analytical method for the ethyl pyrido[1,2-*a*]-pyrimidine- and pyrazino[1,2-*a*]pyrimidine-3-carboxylates their behavior under electron impact proved remarkably similar. Hence, similarly to the previously reported pyridopyrimidine [2], electron impact ionization caused an initial cleavage of the $C_{(4)}$–$N_{(5)}$ and $C_{(2)}$–$C_{(3)}$ bonds which also markedly predominates over an alternative break up of the ethoxycarbonyl group in the pyrazinopyrimidine **1** (Sheme 1).

A uniform fragmentation of the molecular ions, fully excluding initial destruction of both the pyridopyrimidine [2] and pyrazinopyrimidine ring was also noted in the chromato-mass spectrometric investigation of the volatile 2-trimethylsilyloxy derivatives. In addition to the possibility of confirming the purity of the studied samples (the starting 2-oxo or 2-hydroxy derivatives readily decompose on conversion to the gaseous phase) the change indicated also serves to point to the higher thermal stability of the fixed 2-hydroxy forms. In the starting material the potential for tautomeric conversion prevails and hence a rapid cleavage of the heterocyclic ring is observed.

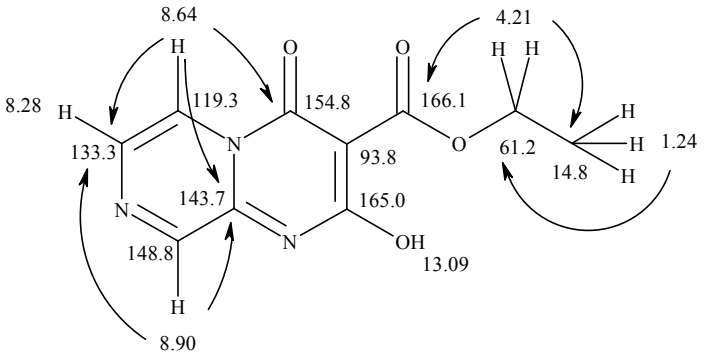
As a whole, the virtually identical behavior of the ethyl pyridopyrimidine- and pyrazinopyrimidine-3-carboxylates suggests that at the moment of recording the mass spectra both occur as approximately the same resonance hybrid even though, under normal conditions, the tautomeric equilibrium is strongly shifted to one of the sides mentioned above (Sheme 2).

Scheme 2

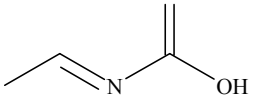


The ^{1}H NMR spectrum of ester **1** is in full agreement with the X-ray analytical data. The aromatic proton region shows two doublets and a singlet for the pyrazine fragment and the signals for the ethoxy group appear as a characteristic quartet and triplet at 4.21 and 1.24 ppm respectively. In addition, the spectrum shows a broadened signal for the hydroxyl proton at 13.09 ppm.

The ^{13}C NMR spectrum, although not in disagreement with the structure proposed, shows strongly broadened signals at 165.0, 148.8, and 93.8 ppm. This points to the occurrence of exchange process in solution in DMSO which are most likely tautomeric. The nature of the tautomerism can be explained if an absolute assignment of signals in the carbon spectra is made. With this in view we have measured the 2D HMQC and HMBC spectra to reveal $^{1}H–^{13}C$ heteronuclear correlations through 1 or 2-3 chemical bonds respectively.



Although the number of heteronuclear correlations found was small (Table 3) it did permit a reliable assignment of all of the signals in the carbon spectrum. Hence the presence of a three bond interaction between the methylene group proton signal and the carbon signal at 166.1 ppm allowed the latter to be assigned to the carbonyl carbon atom in the ethoxycarbonyl group. Similarly, the signal for the carbonyl carbon atom in the pyrimidin-4-one fragment can be assigned through its correlation with one of the pyrazine proton doublets. It was not possible to correlate the signals at 93.8 and 165.0 ppm but their assignment is readily made on the basis of their chemical environment. All of the signal assignments found in the proton and carbon spectra of ester **1** and their HMBC correlations used in this way are shown in the scheme. As is apparent from this scheme the signals broadened in the carbon spectrum prove to be those corresponding to carbon atom occurring in the fragment of composition:



This suggests that the tautomeric conversion in fact occurs in this part of the molecule. However, heteronuclear correlations could not be found for it due to broadening of the OH (or NH) signal and we were unable to localize the active proton in DMSO solution.

TABLE 3. Heteronuclear $^{1}H–^{13}C$ Correlations Found for Ester **1**

δ, ppm	HMQC	HMBC
13.09	—	—
8.90	148.8	154.8; 143.7; 133.3; 119.3
8.64	119.3	154.8; 143.7; 133.3
8.28	133.3	143.7; 119.3
4.21	61.2	166.1; 14.8
1.24	14.8	61.2

UV spectroscopy also confirmed the existence of the ethyl ester **1** and its pyridopyrimidine analog as an equilibrium mixture of tautomers in neutral solvents (Figures 2 and 3). The spectra recorded in ethanol showed minimal differences implying a similar system of conjugated bonds in their molecules. As might have been expected common changes in the spectra occurred on crossing to basic medium and the 2-hydroxy forms evidently predominate over other possible tautomers in both cases. On the other hand, protonation of the additional nitrogen atom when acidifying the pyrazinopyrimidine **1** causes a marked change in the spectrum whereas the pyridopyrimidine derivative in acid medium shows virtually no effect on the tautomeric equilibrium.

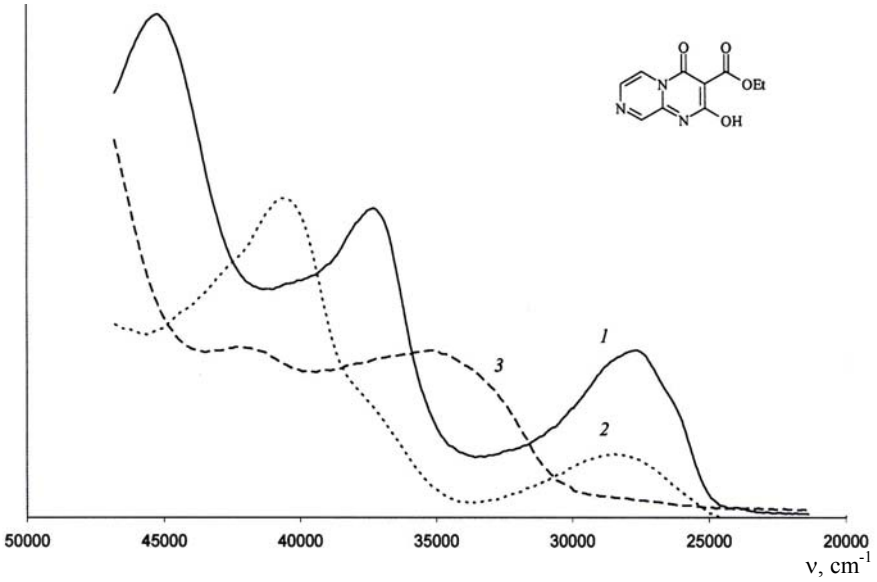


Figure 2. Correlated UV spectra of the ethyl ester **1**:*1* in ethanol;
2 with addition of NaOH; *3* with addition of HCl

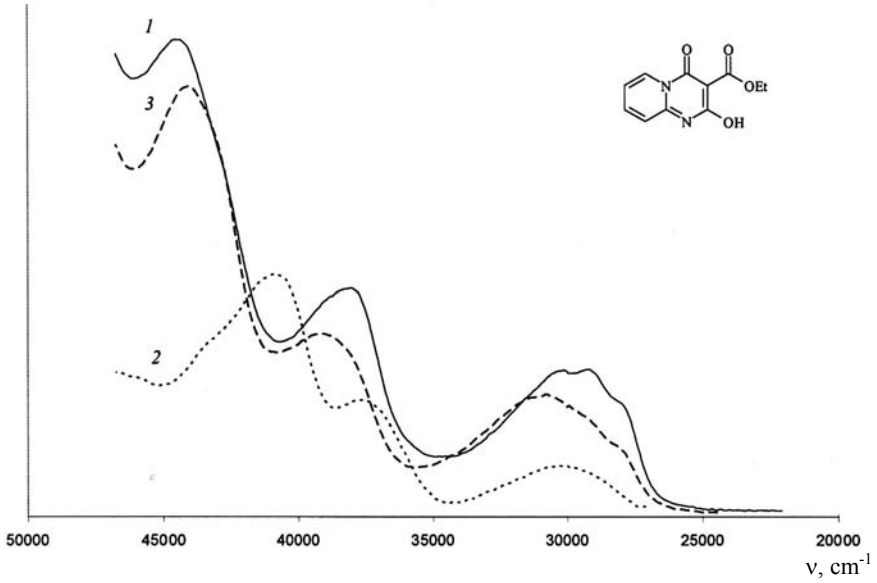


Figure 3. Correlated UV spectra of ethyl 2-hydroxy-4-oxo-4H-pyrido[1,2-*a*]pyrimidine-3-carboxylate: *1* in ethanol; *2* with addition of NaOH; *3* with addition of HCl

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra for ethyl ester **1** and the HMQC and HMBC heteronuclear correlation spectra were recorded on a Varian Mercury-400 spectrometer (400 and 100 MHz respectively). The number of increments in the HMQC and HMBC spectra was 128 and 400, respectively. The ^{1}H NMR spectrum of the pyrazin-2-ylamide **3** was taken on a Varian Mercury VX-200 (200 MHz) instrument. In all cases the solvent was DMSO-d_6 and internal standard TMS. The mass spectrum of ester **1** was obtained on a Varian 1200L spectrometer with full scanning in the range 45-550 *m/z*, EI ionization of 70 eV, and with direct sample introduction. Chromato mass spectra were recorded on a Hewlett Packard 5890/5972 instrument in full scan mode in the range 35-700 *m/z* and 70 eV EI. To increase the volatility of ester **1** it was converted to the 2-trimethylsilyloxy derivative using N,O-bis(trimethylsilyl)trifluoroacetamide reagent and Hewlett Packard 5MS chromatography column: length 25 m, internal diameter 0.2 mm, polysiloxane film (5%, diphenylpolysiloxane, 95% dimethylpolysiloxane) stationary phase, thickness 0.33 microns, and with helium gas carrier. UV spectra were recorded on a Specord M-40 spectrometer. Commercial aminopyrazine and triethyl methanetricarboxylate from Fluka were used in the work.

Ethyl 2-Hydroxy-4-oxo-4H-pyrazino[1,2-*a*]pyrimidine-3-carboxylate (1). A solution of the aminopyrazine **2** (0.95 g, 0.01 mol) and triethyl methanetricarboxylate (4.21 ml, 0.02 mol) in xylene (commercial isomer mixture, 10 ml) was refluxed for 1.5 h allowing any ethanol evolved to distil off through a reflux condenser. The product was cooled and hexane (50 ml) was added. After 2-3 h the crystalline precipitate produced was filtered off, washed with hexane, and dried. The technical material obtained was treated with refluxing acetone (20 ml) and filtered hot. The residue obtained after evaporation of solvent from the filtrate was the target ester **1**. Yield 1.95 g (83%); mp 191-193ºC (acetone). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 13.09 (1H, br. s, OH); 8.90 (1H, d, *J* = 1.0, H-9); 8.64 (1H, dd, *J* = 4.6 and *J* = 1.1, H-6); 8.28 (1H, d, *J* = 4.6, H-7); 4.21 (2H, q, *J* = 7.1, OCH_2); 1.24 (3H, t, *J* = 7.1, CH_3). ^{13}C NMR spectrum, δ, ppm: 166.1 (CO_2), 165.0 ($C_{(2)}$), 154.8 ($C_{(4)}$), 148.8 ($C_{(9)}$), 143.7 ($C_{(9a)}$) 133.3 ($C_{(7)}$), 119.3 ($C_{(6)}$), 93.8 ($C_{(3)}$), 61.2 (OCH_2), 14.8 (CH_3). Mass spectrum, *m/z* (I_{rel}, %): 235 $[M]^+$ (9.7). 190 $[M–OEt]^+$ (4.3), 163 $[M–CO_2C_2H_4]^+$ (29.1), 135 $[M–COOC_2H_4–CO]^+$ (17.2), 122 (100). Mass spectrum of 2-trimethylsilyloxy derivative, *m/z* (I_{rel}, %): 307 $[M]^+$ (21), 292 $[M–Me]^+$ (26), 264 $[M–Me–C_2H_4]^+$ (100), 262 $[M–OEt]^+$ (40), 235 $[M–OEt\text{-}CO]^+$ (28), 234 $[M–OEt–CO–H]^+$ (39), 220 $[M–Me–C_2H_4–CO_2]^+$ (16), 207 (16). Found, %: C 51.16; H 3.97; N 17.78. $C_{10}H_9N_3O_4$. Calculated, %: C 51.07; H 3.86; N 17.87.

2-Hydroxy-4-oxo-4H-pyrazino[1,2-*a*]pyrimidine-3-carboxylic Acid Pyrazin-2-ylamide (3). The residue insoluble in hot acetone on the filter (see synthesis of ester **1**) was dried. Yield 0.28 g (10%); mp 314ºC (decomp., DMF). ^{1}H NMR spectrum, δ, ppm: 14.65 (1H, s, OH); 13.03 (1H, s, NH); 9.43 (1H, d, H-3'); 9.08 (1H, s, H-9); 8.77 (1H, d, *J* = 4.5, H-6); 8.47 (2H, s, H-5',6'); 8.39 (1H, d, *J* = 4.8, H-7). Found, %: C 50.63; H 2.75; N 29.68. $C_{12}H_8N_6O_3$. Calculated, %: C 50.71; H 2.84; N 29.57.

X-ray Structural Investigation. Crystals of ester **1** (Tables 1, 2) are monoclinic (ethanol). At 20ºC: *a* = 4.867(3), *b* = 23.872(7), *c* = 8.920(3) Å, β = 91.13(4)º, *V* = 1036.2(8) Å^3, M_r = 235.20, *Z* = 4, space group $P2_1/c$, d_{calc} = 1.508 g/cm^3, μ(MoKα) = 1.019 mm^{-1}, *F*(000) = 488. Unit cell parameters and intensities of 1852 reflections (1738 independent, R_{int} = 0.038) were measured on a CAD4 diffractometer (CuKα radiation, graphite monochromator, ω-scanning). The diffractometric experiment was carried out on a crystal with the linear dimensions 0.3×0.3×0.01 mm ($3.70 \le \theta \le 65.02$º, index *h*, *k*, *l* range: $-5 \le h \le 5$, $0 \le k \le 28$, $0 \le l \le 10$).

The structure was solved by a direct method using the SHELX97 program package [4]. The positions of the hydrogen atoms were calculated geometrically and refined isotropically. The structure was refined by F^2 full matrix least squares analysis in the anisotropic approximation for non-hydrogen atoms to R_1 = 0.046, wR_2 = 0.090 for 1738 reflections (*S* = 0.948). The full crystallographic information for compound **1** has been

placed in the Cambridge structural database (reference CCDC 650130). The spatial positions of the atoms in the molecule of the compound studied and their numbering are shown in Fig. 1 and were obtained using the ORTEP3 program [5].

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