Chemistry of Heterocyclic Compounds, Vol. 42, No. 2, 2006

4-HYDROXYQUINOLONES-2. 91*. SYNTHESIS AND PROPERTIES OF ETHYL 1-R-4-HYDROXY-6-METHYL-2-OXO-DIHYDROPYRIDINE-5-CARBOXYLATES

I. V. Ukrainets[1], L. V. Sidorenko[1], O. V. Gorokhova[1], and O. V. Shishkin[2]

The reaction of ethyl aminocrotonates with derivatives of malonic acid is a suitable method for the preparation of ethyl 4-hydroxy-6-methyl-2-oxo-1,2-dihydropyridine-5-carboxylates. One of the synthesized materials has been studied by X-ray crystallography.

Keywords: 4-hydroxy-2-oxopyridinecarboxylic acids, 1,2-dihydropyridin-2-ones, ethyl 3-aminocrotonic acids, X-ray crystallography.

6-Alkyl-substituted 1,2-dihydropyridin-2-ones are used in medicine as selective inhibitors of phosphodiesterases [2,3] and AMPA-receptors*[2] [4]. Highly effective vasodilators [5], anticoagulants [6], fungicides [7], and anti-HIV agents [8] have been created based on them. To obtain these compounds a three component condensation of the corresponding ketone, a dimethyl acetal of DMF or ethyl formate, and a substituted amide of acetic acid is normally required. The ketone determines the nature of the substituents at positions 5 and 6 of the ring formed, the substituted formic acid is the source of $C_{(4)}$, and the substituted acetamide forms the $N_{(1)}$–CO–$C_{(3)}$–R unit of the dihydropyridine ring. In some cases an alternative route – the reaction of pyran-2-ones with amines – is used [9].

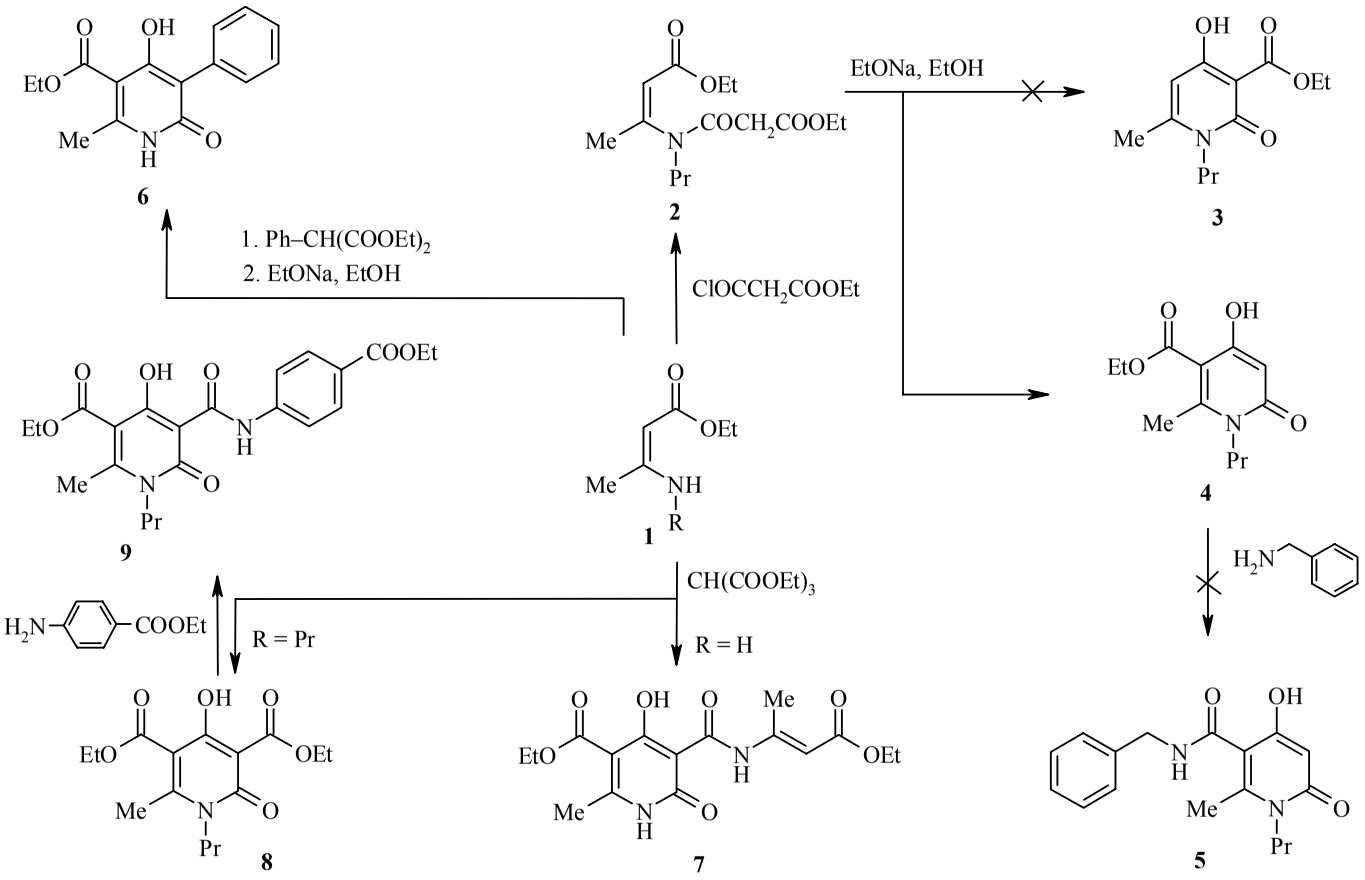
In a continuation of our study of the physicochemical and biological properties of 4-hydroxyquinolones-2, we have connected reports of molecular systems similar to ours – 1-R-4-hydroxy-2-oxo-1,2-dihydropyridine. We have used the same principle as in obtaining 4-hydroxyquinolones-2, i.e., the acylation of amino esters with ethoxymalonyl chloride with subsequent closing of the ring under Dieckman reaction conditions. It is known [10] that N-acylanthranilates unambiguously form 3-ethoxycarbonyl-4-hydroxy-quinolones -2 under these conditions. However after acylation of ethyl aminocrotonates **1** the cyclization of the diesters **2** is theoretically possible by two routes since both carbonyl and active methylene groups are present in both the malonyl and crotonyl fragments. Consequently the end products of the reaction studied may be ethyl 4-hydroxy-6-methyl-2-oxo-1-propyl-1,2-dihydropyridine-3-carboxylate (**3**) or the isomeric ethyl 4-hydroxy-6-methyl-2-oxo-1-propyl-1,2-dihydropyridine-5-carboxylate (**4**). Unfortunately neither ^{1}H NMR spectroscopy nor chromatomass spectrometry permitted an unambiguous conclusion on the structure of this substance. Nevertheless a failure to prepare the benzamide **5** under normal conditions suggested that the ester produced is a

---

* For part 90, see [1].

*[2] AMPA – α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid.

[1] National Pharmaceutical University, Kharkov 61002, Ukraine; e-mail: uiv@kharkov.ua. [2] Institute of Scintillation Materials, Ukraine National Academy of Sciences, Kharkov 6101, Ukraine; e-mail: shishkin@xray.isc.kharkov.com. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, 217-223, February, 2006. Original article submitted September 16, 2004.


EtO
OH
Me
N
H
O
6
OEt
COCH2COOEt
Pr
2
EtONa, EtOH
OH
OEt
3
1. Ph–CH(COOEt)2
2. EtONa, EtOH
ClOCCH2COOEt
COOEt
9
NH
R
1
4
H2N
CH(COOEt)3
R = Pr
R = H
8
7
5

derivative pyridine-5-carboxylic acid, since it would be expected that the 3-ethoxycarbonyl isomer **3** would be the more reactive because of its similarity to the esters of 1-R-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylates.

In fact, an X-ray crystallographic study confirmed this prediction and established that the pyridine ring of the ester **4** (Fig. 1) has a strongly compressed *bath* conformation. The deviations of atoms $C_{(1)}$ and $C_{(4)}$ from the mean-square plane of the remaining atoms of the ring are -0.05 and -0.04 A respectively. Contacts between the methyl, propyl, and ethoxycarbonyl groups [shortest contacts $H_{(6B)}\cdots C_{(7)}$ 2.75 (sum of the van der Waals radii [11] 2.87), $H_{(6C)}\cdots H_{(7B)}$ 2.22 (2.32) and $H_{(7A)}\cdots O_{(1)}$ 2.37A (2.45A)] lead to lengthening of the bonds $N_{(1)}\cdots C_{(5)}$ 1.400(3), $N_{(1)}\cdots C_{(1)}$ 1.416 and $N_{(1)}\cdots C_{(7)}$ 1.496 Å in comparison with average values [12] of 1.352, 1.385, and 1.469 Å respectively. The substituent at $N_{(1)}$ is in the *ap*-conformation and is rotated practically perpendicular relative to the mean-square plane of the ring (torsion angles $C_{(1)}$–$N_{(1)}$–$C_{(7)}$–$C_{(8)}$ 84.9(2)° and $N_{(1)}$–$C_{(7)}$–$C_{(8)}$–$C_{(9)}$ 180.0(2)°). Conjugation between the π-systems of the pyridine ring and the ester group is considerably decreased as a result of rotation of the latter about the $C_{(4)}$–$C_{(10)}$ bond (torsion angle $C_{(5)}$–$C_{(4)}$–$C_{(10)}$–$O_{(3)}$ -64.3(3)°), which explains the stability of ester **4** to amidation. The ethyl substituent of the ester group is in the *ap*-conformation (torsion angle $C_{(10)}$–$O_{(4)}$–$C_{(11)}$–$C_{(12)}$ 166.1(2)°). In the crystal molecules of ester **4** form dimers via the intermolecular hydrogen bonds $O_{(2)}$–$H_{(2C)}\cdots O_{(1)}$ (x + 0.5, -y - 0.5, -z + 2) (H···O 1.80(3) A, O···H···O' 167(3)°).Probably as a result of this the $C_{(1)}$=$O_{(1)}$ is lengthened to 1.272 A in comparison with the average value of 1.210 Å [12].

Interesting data which confirmed the formation of derivatives of pyridine-5-carboxylic acid during the course of the reaction under discussion were obtained by using ethyl phenylmalonate in place of ethoxymalonyl chloride. As in the first case two possible compounds are formed, but they are not isomers so that the interpretation of their structures is eased considerably. Thus the formation of ethyl 4-hydroxy-6-methyl-2-oxo-3-phenyl-1,2-dihydropyridine-5-carboxylate (**6**) indicates that in the ester condensation of the corresponding diester of type **2** catalyzed by sodium ethoxide the electrophilic center is in the malonic unit while the nucleophilic is in the crotonic unit. In the opposite case the cyclization should occur with elimination of the ethoxycarbonyl groups of the malonic unit [13] to give as the final product 4-hydroxy-6-methyl-2-oxo-3-phenyl-1,2-dihydropyridine which does not correspond to the experimental data.

A complex result was obtained from the reaction aminocrotonic esters **1** with triethyl methanetricarboxylate, the high reactivity of which allows closure of the pyridine ring without basic catalysis. In the case of the unsubstituted aminocrotonic ester (**1**, R = H) it was not possible to stop the reaction at the stage of diethyl pyridon-3,5-dicarboxylate even with a two-fold excess of triethyl methanetricarboxylate – the ester group in position 3 is very easily amided by the aminocrotonates starting material to give ethyl 3-(2-ethoxycarbonyl-1-methylvinylcarbamoyl)-4-hydroxy-6-methyl-2-oxo-1,2-dihydropyridin-5-carboxylate (**7**).

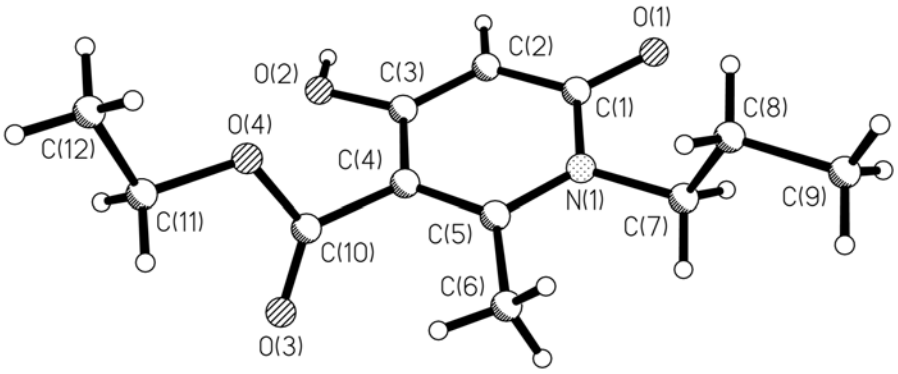


Fig. 1 Structure of the molecule of ester **4** showing numbering of the atoms.

TABLE 1. Bond Lengths (*l*) in the Structure of Ester **4**

Bond	*l*, Å	Bond	*l*, Å	Bond	*l*, Å
$N_{(1)}$–$C_{(5)}$	1.400(3)	$O_{(4)}$–$C_{(10)}$	1.356(3)	$C_{(4)}$–$C_{(10)}$	1.525(3)
$N_{(1)}$–$C_{(1)}$	1.416(3)	$O_{(4)}$–$C_{(11)}$	1.474(3)	$C_{(5)}$–$C_{(6)}$	1.524(3)
$N_{(1)}$–$C_{(7)}$	1.496(3)	$C_{(1)}$–$C_{(2)}$	1.423(3)	$C_{(7)}$–$C_{(8)}$	1.532(3)
$O_{(1)}$–$C_{(1)}$	1.272(3)	$C_{(2)}$–$C_{(3)}$	1.388(3)	$C_{(8)}$–$C_{(9)}$	1.531(3)
$O_{(2)}$–$C_{(3)}$	1.347(3)	$C_{(3)}$–$C_{(4)}$	1.442(3)	$C_{(11)}$–$C_{(12)}$	1.510(4)
$O_{(3)}$–$C_{(10)}$	1.203(3)	$C_{(4)}$–$C_{(5)}$	1.385(3)		

TABLE 2. Bond Angles (ω) in the Structure of Ester **4**

Angle	ω, deg.	Angle	ω, deg.	Angle	ω,deg.
$C_{(5)}$–$N_{(1)}$–$C_{(1)}$	122.36(2)	$O_{(2)}$–$C_{(3)}$–$C_{(2)}$	124.36(2)	$N_{(1)}$–$C_{(5)}$–$C_{(6)}$	117.92(2)
$C_{(5)}$–$N_{(1)}$–$C_{(7)}$	121.37(2)	$O_{(2)}$–$C_{(3)}$–$C_{(4)}$	116.49(2)	$N_{(1)}$–$C_{(7)}$–$C_{(8)}$	113.78(2)
$C_{(1)}$–$N_{(1)}$–$C_{(7)}$	116.22(2)	$C_{(2)}$–$C_{(3)}$–$C_{(4)}$	119.13(2)	$C_{(9)}$–$C_{(8)}$–$C_{(7)}$	111.70(2)
$C_{(10)}$–$O_{(4)}$–$C_{(11)}$	115.46(2)	$C_{(5)}$–$C_{(4)}$–$C_{(3)}$	120.23(2)	$O_{(3)}$–$C_{(10)}$–$O_{(4)}$	123.40(2)
$O_{(1)}$–$C_{(1)}$–$N_{(1)}$	117.38(2)	$C_{(5)}$–$C_{(4)}$–$C_{(10)}$	120.85(2)	$O_{(3)}$–$C_{(10)}$–$C_{(4)}$	126.10(2)
$O_{(1)}$–$C_{(1)}$–$C_{(2)}$	125.53(2)	$C_{(3)}$–$C_{(4)}$–$C_{(10)}$	118.92(2)	$O_{(4)}$–$C_{(10)}$–$C_{(4)}$	110.49(2)
$N_{(1)}$–$C_{(1)}$–$C_{(2)}$	117.09(2)	$C_{(4)}$–$C_{(5)}$–$N_{(1)}$	119.31(2)	$O_{(4)}$–$C_{(11)}$–$C_{(12)}$	107.90(2)
$C_{(3)}$–$C_{(2)}$–$C_{(1)}$	121.62(2)	$C_{(4)}$–$C_{(5)}$–$C_{(6)}$	122.77(2)		

Similarly, N-propyl-substituted ethyl aminocrotonate (**1**, R = Pr) under the same conditions gave diethyl 4-hydroxy-6-methyl-2-oxo–1-propyl-1,2-dihydropyridin-3,5-dicarboxylate (**8**) which can then be converted into the amido ester **9** without complications.

EXPERIMENTAL

^{1}H NMR spectra of the compounds synthesized were recorded with a Varian Mercury VX-200 (200 MHz) in DMSO-d_6 with TMS as internal standard. Mass spectra were recorded on a Finnigan MAT Incos 50 quadrupole spectrometer by direct insertion, with total scanning over the range 33-700 *m/z*, with an ionizing voltage of 70 eV, and a rate of heating of 5°/s. The ethyl esters of the aminocrotonic acids were prepared by a known method [14].

Ethyl 4-Hydroxy-6-methyl-2-oxo-1-propyl-1,2-dihydropyridine-5-carboxylate (4). Triethylamine (1.54 ml, 0.011 mol) was added to a solution of ethyl N-propylaminocrotonate (1.71 g, 0.01 mol) (**1**, R = Pr) in CH_2Cl_2 (30 ml), then ethoxymalonyl chloride (1.66 g, 0.011 mol) was added dropwise with cooling and intensive stirring and the mixture was kept at room temperature for 4-5 h. The reaction mixture was diluted with water and stirred thoroughly. The organic layer was separated and dried over anhydrous $CaCl_2$. The solvent was evaporated (finally under reduced pressure. Sodium ethoxide (from metallic sodium (0.23 g, 0.01 mol) and absolute ethanol (20 ml)) was added to the residue (the diester **2**) and boiled for 1 h, after which the reaction mixture was cooled, diluted with water, and acidified with 1:1 HCl to pH 4.5-5. The precipitated ester **4** was filtered off, washed with water, and dried. Yield 1.98 g (83%); mp 107-109°C (ethanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 10.86 (1H, s, OH); 5.60 (1H, s, H-3); 4.23 (2H, q, *J* = 7.0, OCH_2); 3.85 (2H, t, *J* = 7.6, NCH_2); 2.33 (3H, s, CH_3); 1.53 (2H, m, $NCH_2\underline{CH_2}$); 1.26 (3H, t, $OCH_2\underline{CH_3}$); 0.89 (3H, t, *J* = 7.6, $NCH_2CH_2\underline{CH_3}$). Mass spectrum, *m/z* (I_{rel}, %): 239 [M^+] (15), 224 [M - CH_3]$^+$ (18), 197 [M - C_3H_6]$^+$ (17), 178 [M - CH_3 - EtOH]$^+$ (15),

151 [M - C_3H_6 - EtOH]$^+$ (100), 137 (10), 123 (31), 69 (19), 42 (21). Found, %: C 60.41; H 7.10; N 5.73. $C_{12}H_{17}NO_4$. Calculated, %: C 60.24; H 7.16; N 5.85.

X-ray Crystallography. Crystals of the ester **4** are rhombic. At 20°C: a = 8.215(2), b = 10.956(4), c = 14.154(5) Å; V = 1273.9(7) Å^3; d_{calc} = 1.248 g/cm^3; space group $P2_12_12_1$; Z = 4. Elementary cell parameters and the intensities of 2104 independent reflexions (R_{int} = 0.03) were measured on a Siemens P3/PC four-circle automatic diffractometer (λMoKα, graphite monochromator, θ/2θ scanning, $2\theta_{max}$ = 60°). The structure was refined by direct methods using the SHELXTL PLUS suite of programs [15]. The positions of the hydrogen atoms were found from difference syntheses of the electron density and refined by the "riding" method with fixed $U_{iso} = nU_{eq}$ for the non-hydrogen atoms bonded to the hydrogen atoms (n = 1.5 for methyl groups and 1.2 for the remaining hydrogen atoms). Refinement according to F^2 was carried out with full matrix least squares analysis in the anisotropic approximation for non-hydrogen atoms using 2104 reflexions to wR_2 = 0.115 (R_1 = 0.049 for 1308 reflexions with $F > 4\sigma(F)$, S = 0.98). Complete crystallographic information has been deposited in the Cambridge Crystals Data Bank (deposit no. CCDC 250565). Interatomic distances and bond angles are given in Tables 1 and 2.

Ethyl 4-Hydroxy-6-methyl-2-oxo-3-phenyl-1,2-dihydropyridine-5-carboxylate (6). A mixture of ethyl aminocrotonate (**1**, R = H) (1.29 g, 0.01 mol) and diethyl phenylmalonate (2.60 g, 0.01 mol) was maintained at 160°C for 5 h. The mixture was cooled, added to a solution of sodium ethoxide (from metallic sodium (0.46 g, 0.02 mol) in absolute ethanol (40 ml)), boiled for 2 h, and then acidified with aqueous HCl. The precipitate of ester **6** was filtered off, washed with water, and dried. Yield 1.55 g (57%); mp 300-302°C (ethanol). ^{1}H NMR spectrum, δ, ppm (J, Hz): 11.97 (1H, s, OH); 11.78 (1H, s, NH_2); 7.40 -7.12 (5H, m, C_6H_5); 4.32 (2H, q, J = 7.0, OCH_2); 2.58 (3H, s, CH_3); 1.30 (3H, t, J = 7.0, $OCH_2\underline{CH_3}$). Mass spectrum, *m/z* (I_{rel}, %): 273 [M]$^+$ (36), 227 [M - EtOH]$^+$ (100), 199 [M - EtOH - CO]$^+$ (37), 143 (14), 128 (11). Found, %: C 65.80; H 5.42; N 5.20. $C_{15}H_{15}NO_4$. Calculated, %: C 65.93; H 5.53; N 5.13.

Ethyl 3-(2-Ethoxycarbonyl-1-methylvinylcarbamoyl)-4-hydroxy-6-methyl-2-oxo-1,2-dihydropyridine-5-carboxylate (7). A mixture of ethyl 3-aminocrotonate (**1**, R = H) (1.29 g, 0.01 mol) and triethyl methanetricarboxylate (4.64 g, 0.02 mol) was kept at 200-210°C for 15 min. It was cooled, hexane (30 ml) was added, and the mixture was vigorously stirred. The amino ether **7** was filtered off, washed on the filter several times with hexane, and dried. Yield 1.30 g (73% based on the aminocrotonate); mp 181-183°C (ethanol). ^{1}H NMR spectrum, δ, ppm (J, Hz): 15.50 (1H, s, OH); 13.02 (1H, s, NH); 12.09 (1H, s, NH); 5.19 (1H, s, =CH); 4.28 (2H, q, J = 7.0, OCH_2); 4.09 (2H, q, J = 7.0, OCH_2); 2.35 (3H, s, CH_3); 2.27 (3H, s, CH_3); 1.30-1.10 (6H, m, 2 $OCH_2\underline{CH_3}$). Mass spectrum, *m/z* (I_{rel}, %): 352 [M]$^+$ (3), 307 [M - OEt]$^+$ (4), 279 [M - OEt - CO]$^+$(27), 233 (11), 224 (16), 178 (100), 129 (18), 84 (21), 42 (25). Found, %: C 54.68; H 5.81; N 7.88. $C_{16}H_{20}N_2O_7$. Calculated, %: C 54.54; H 5.72; N 7.95.

Diethyl 4-Hydroxy-6-methyl–2-oxo-1-propyl-1,2-dihydropyridine-3,5-dicarboxylate (8) was prepared from ethyl N-propylaminocrotonate (**1**, R = Pr) and triethyl methanetricarboxylate in 1:1 molar ratio as in the previous experiment. Yield 78%; mp 65-67°C (ethanol). ^{1}H NMR spectrum, δ, ppm (J, Hz): 12.82 (1H, s, OH); 4.27 (4H, q, J = 7.0, 2 OCH_2); 3.92 (2H, t, J =7.4, NCH_2); 2.40 (3H, s, CH_3); 1.56 (2H, m, $NCH_2\underline{CH_2}$); 1.29 (6H, t, J = 7/0, 2 $OCH_2\underline{CH_3}$); 0.90 (3H, t, J = 7.4, $NCH_2CH_2\underline{CH_3}$). Found, %: C 57.78; H 6.87; N 4.63. $C_{15}H_{21}NO_6$. Calculated, %: C 57.87; H 6.80; N 4.50.

Ethyl 3-(4-Ethoxycarbonylphenylcarbamoyl)-4-hydroxy-6-methyl-2-oxo-propyl-1,2-dihydropyridine-5-carboxylate (9). A mixture of ester **8** (3.11 g, 0.01 mol), benzocaine (1.65 g, 0.01 mol), and DMF (1 ml) was stirred an kept on a metal bath at 160-180°C for 3 min. The mixture was cooled, ethanol (30 ml) was added, the mixture was thoroughly mixed and filtered. The amino ester **9** obtained was washed on the filter with ethanol and dried. Yield 4.0 g (93%); mp 157-159°C (DMF). ^{1}H NMR spectrum, δ, ppm (J, Hz): 15.56 (1H, s, OH); 12.64 (1H, s, NH); 7.96 (2H, d, J = 7.9, H-3',5'); 7.75 (2H, d, J = 7.9, H-2',6'), 4,32 (4H, m, 2 OCH_2); 4.00 (2H, t, J = 7.6, NCH_2); 2.46 (3H, s, CH_3); 1.62 (2H, m, $NCH_2\underline{CH_2}$); 1.30 (6H, m, 2 $OCH_2\underline{CH_3}$); 0.91 (3H, t, J = 7.6, $NCH_2CH_2\underline{CH_3}$). Found, %: C 61.47, H 6.18, N 6.44. $C_{22}H_{26}N_2O_7$. Calculated, %: C 61.39; H 6.09; N 6.51.

REFERENCES

1. I. V. Ukrainets, L. V. Sidorenko, L. A. Petrushova, and O. V. Gorokhova. *Khim. Geterotsikl. Soedin.,* 70 (2006).
2. P. Kaheinen, P. Pollsello, J. Levijoki, and H. Haikala. *J. Cardiovasc. Pharmacol.*, **43**, 555 (2004).
3. L. Nagata, M. Iwase, T. Sobue, and M. Yokota, *J. Am. Coll. Cardiol.,* **25**, 295 (1995).
4. L. Rivers, A. J. Groom, S. Hatakeyama, K. Kawano, H. Naka, K. Ueno, M. Ueno, H. Amino, T. Hanada, K. Ito, M. Nagato, M. Ogo, Y. Urawa, and Y. Norimine. US Pat. 2004023973 (2004); http://ep.espacenet.com
5. S.Suda, M. Yamanaka, T. Ogawa, K. Miyake, and H. Ohara. *Chem. Pharm. Bull.,* **39**, 1556 (1991).
6. R. C. Isaacs, K. J. Kutrona, C. L. Newton, P. E. Sanderson, M. G. Solinsky, E. P. Baskin, I. W. Chen, C. M. Cooper, J. J. Cook, S. J. Gardell, S. D. Lewis, R. J. Lucas, E. A. Lyle, J. J. Lynch, A. M. Naylor-Olsen, M. J. Stranieri, K. Vastag, and J. P. Vacca. *Bioorg. Med. Chem. Lett.,* **8**, 1719 (1998).
7. M. A. Ghannoum, V. Chaturvedi, A. Espinel-Ingroff, M. A. Pfaller, M. G. Rinaldi, W. Lee-Yang, and D. W. Warnock. *J. Clin. Microbiol.,* **42**, 2977 (2004).
8. W. S. Saari, J. S. Wai, T. E. Fischer, C. M. Thomas, J. M. Hoffman, C. S. Rooney, A. M. Smith, J. H. Jones, D. L. Bamberger, and M. E. Goldman. *J. Med. Chem.,* **35**, 3792 (1992).
9. A. Kleeman and J. Engel. *Pharmaceutical Substances. Synthesis, Patents, Applications, Multimedia Viewer, Version 2.00.* Georg Thieme Verlag, Stuttgart, 2001.
10. I. V. Ukrainets, O. V. Gorokhova, S. G. Taran, P. A. Bezuglii, A. V. Turov, N. A. Marusenko, and O. A. Evtifeeva. *Khim. Geterotsikl. Soedin.,* 958 (1994).
11. Yu. V. Zefirov and I. M. Zorkii. *Uspekhi Khimii,* **64**, 446 (1995).
12. H.-B. Burgi and J. D. Dunitz, *Struc. Correl.,* VCH, Weinheim, 1994, **2**, 741.
13. I. V. Ukrainets, K. A. Taran, L. V. Sidorenko, I. Yu. Petukhova, and N. I. Filimonova. *Visnik Farmatsii*, No. 2 (26), 3 (2001).
14. Weygand-Gilgetag. *Experimental Methods in Organic Chemistry* [Russian translation], Khimiya, Moscow, 1969, 473.
15. G. M. Sheldrick. *SHELXTL PLUS. PC Version. A System of Computer Programs for the Determination of Crystal Structures from X-ray Diffraction Data.* Rev. 5.02 (1994).