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4-HYDROXY-2-QUINOLONES. 94*. IMPROVED SYNTHESIS AND STRUCTURE OF 1-HYDROXY-3-OXO-5,6- DIHYDRO-3H-PYRROLO[3,2,1-*i,j*]-QUINOLINE-2-CARBOXYLIC ACID ETHYL ESTER

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A modified method is proposed for preparation and purification, and the special features of the spatial structure have been studied for the ethyl ester of 1-hydroxy-3-oxo-5,6-dihydro-3H-pyrrolo[3,2,1-i,j]-quinoline-2-carboxylic acid.

Keywords: heterocyclic derivatives of tricarbonylmethane, ethyl esters of 4-hydroxy-2-oxoquinoline-3-carboxylic acids, X-ray structural analysis.

Esters of 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids display interesting pharmacological properties [2-4] and in addition are widely used for obtaining the corresponding alkyl, aryl and heterylamides, and hydrazides. The various hetaryl-substituted quinol-2-ones possess antithyroidal [5], anti-inflammatory [6], local anesthetic [7], antinephritic [8], antitubercular [9], herbicidal [10], antitumor [11], and other forms of biological activity.

Several methods of synthesizing such compounds are known today. However, only some of them are used, mostly for preparative purposes, and assume the interaction of alkylanthranilates [12], isatoic acid anhydrides [13, 14], or 2-carbalkoxyphenyl isocyanates [15] with derivatives of malonic acid. Subsequent heterocyclization catalyzed by bases leads to esters of 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids. On the whole these methods have been well studied, give excellent yields, and are limited only by the availability of the appropriate anthranilic acids.

Comparatively recently a new variant has been proposed for assembling 4-hydroxy-3-carbalkoxy-2-oxoquinoline systems, based on the interaction of trialkyl methanetricarboxylates with N-substituted anilines, including cyclic derivatives. As an example may be given the synthesis of the ethyl ester of 1-hydroxy-3-oxo-5,6-dihydro-3H-pyrrolo[3,2,1-*i,j*]quinoline-2-carboxylic acid (**1**). This includes the condensation of indoline **2** with the triethyl ester of methanetricarboxylic acid (**3**) [16]. The advantage of this method is that it is one stage, and also it is possible in certain cases to synthesize successfully desired compounds difficult to obtain by other methods. Regrettably, it is not devoid of drawbacks, the most important of which is the formation of side products, acyclic methanetri-N-R-carboxamides. For the suppression of this undesirable reaction a double [16], and sometimes a triple [14], excess of triethyl methanetricarboxylate is used, which reduces the overall

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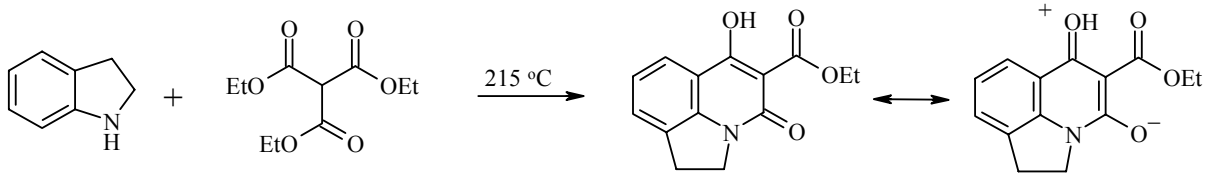
efficiency of the method. In addition, an insignificant modification of the procedure of carrying out the experiment permits high yields to be obtained with a high degree of purity of the final products, and at an equimolar ratio of reactants. This is achieved by gradually adding the amine component (such as indoline **2**) to triethyl methanetricarboxylate (**3**) heated to 215°C. This provides a constant excess of the latter in the reaction mixture and consequently prevents the undesirable formation of triamides. At the end of the reaction it is expedient to purify the resulting compound **1** as the sodium salt. For this, the reaction mixture is treated with aqueous Na_2CO_3 solution, purified with carbon, and after acidification ester **1** is isolated as a colorless crystalline substance. Otherwise the product has a yellow color even after numerous crystallizations.



2 **3** **1** **1a**

According to data of X-ray structural analysis, there are two molecules (**A** and **B**) in the symmetrically independent portion of the unit cell, differing in certain features of the structure. All the non-hydrogen atoms of the **A** molecule, with the exception of atoms $C_{(11A)}$ and $C_{(14A)}$, lie in one plane with a precision of 0.02 Å (see Fig. 1). The $C_{(11A)}$ and $C_{(14A)}$ atoms deviate from the mean square plane of the remaining nonhydrogen atoms by -0.08 and 0.25 Å respectively. In molecule **B** only atom $C_{(11B)}$ deviates from the mean square plane of all the remaining nonhydrogen atoms (precision 0.02 Å) by -0.11 Å.

In molecule **A** the $C_{(7)}$–$C_{(8)}$ bond at 1.414(7) Å is lengthened in comparison with its mean value of 1.326 Å [17]. This might be explained by the significant contribution to the geometry of the molecule of a

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

Bond	*l*, Å	Bond	*l*, Å
$N_{(1A)}$–$C_{(9A)}$	1.390(6)	$N_{(1A)}$–$C_{(1A)}$	1.393(6)
$N_{(1A)}$–$C_{(10A)}$	1.446(7)	$O_{(1A)}$–$C_{(9A)}$	1.222(6)
$O_{(2A)}$–$C_{(7A)}$	1.330(7)	$O_{(3A)}$–$C_{(12A)}$	1.206(6)
$O_{(4A)}$–$C_{(12A)}$	1.353(5)	$O_{(4A)}$–$C_{(13A)}$	1.480(6)
$C_{(1A)}$–$C_{(6A)}$	1.353(8)	$C_{(1A)}$–$C_{(2A)}$	1.359(7)
$C_{(2A)}$–$C_{(3A)}$	1.400(8)	$C_{(2A)}$–$C_{(11A)}$	1.498(9)
$C_{(3A)}$–$C_{(4A)}$	1.38 (1)	$C_{(4A)}$–$C_{(5A)}$	1.401(9)
$C_{(5A)}$–$C_{(6A)}$	1.425(7)	$C_{(6A)}$–$C_{(7A)}$	1.414(7)
$C_{(7A)}$–$C_{(8A)}$	1.414(7)	$C_{(8A)}$–$C_{(12A)}$	1.479(7)
$C_{(8A)}$–$C_{(9A)}$	1.485(7)	$C_{(10A)}$–$C_{(11A)}$	1.563(6)
$C_{(13A)}$–$C_{(14A)}$	1.484(9)	$N_{(1B)}$–$C_{(9B)}$	1.373(7)
$N_{(1B)}$–$C_{(1B)}$	1.374(7)	$N_{(1B)}$–$C_{(10B)}$	1.470(7)
$O_{(1B)}$–$C_{(9B)}$	1.249(7)	$O_{(2B)}$–$C_{(7B)}$	1.304(6)
$O_{(3B)}$–$C_{(12B)}$	1.214(7)	$O_{(4B)}$–$C_{(12B)}$	1.331(6)
$O_{(4B)}$–$C_{(13B)}$	1.438(6)	$C_{(1B)}$–$C_{(6B)}$	1.404(8)
$C_{(1B)}$–$C_{(2B)}$	1.405(8)	$C_{(2B)}$–$C_{(3B)}$	1.415(8)
$C_{(2B)}$–$C_{(11B)}$	1.494(9)	$C_{(3B)}$–$C_{(4B)}$	1.35 (1)
$C_{(4B)}$–$C_{(5B)}$	1.41 (1)	$C_{(5B)}$–$C_{(6B)}$	1.443(8)
$C_{(6B)}$–$C_{(7B)}$	1.424(8)	$C_{(7B)}$–$C_{(8B)}$	1.404(8)
$C_{(8B)}$–$C_{(9B)}$	1.432(8)	$C_{(8B)}$–$C_{(12B)}$	1.507(8)
$C_{(10B)}$–$C_{(11B)}$	1.534(7)	$C_{(13B)}$–$C_{(14B)}$	1.519(9)

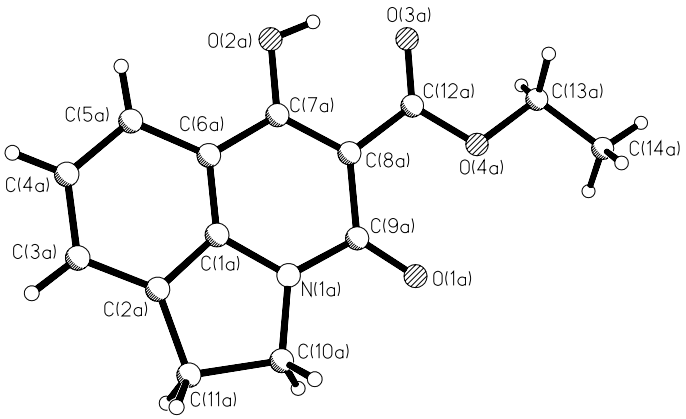


Fig. 1. Structure of the ester **1** molecule with numbering of atoms.

resonance structure with a double-bonded character of the $C_{(7)}$–$O_{(2)}$ bond as a result of the formation of a fairly strong intramolecular hydrogen bond $O_{(2)}$–$H_{(20)}$···$O_{(3)}$ (H···O 1.76 Å, O–H···O 149°). However the other bonds in the $O_{(3)}$–$C_{(12)}$–$C_{(8)}$–$C_{(7)}$–$O_{(2)}$ fragment remain within the limits of their usual values (Table 1).

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

Angle	ω, deg.	Angle	ω, deg.
$C_{(9A)}$–$N_{(1A)}$–$C_{(1A)}$	123.5(4)	$C_{(9A)}$–$N_{(1A)}$–$C_{(10A)}$	124.3(4)
$C_{(1A)}$–$N_{(1A)}$–$C_{(10A)}$	112.1(4)	$C_{(12A)}$–$O_{(4A)}$–$C_{(13A)}$	114.7(4)
$C_{(6A)}$–$C_{(1A)}$–$C_{(2A)}$	127.0(5)	$C_{(6A)}$–$C_{(1A)}$–$N_{(1A)}$	124.0(5)
$C_{(2A)}$–$C_{(1A)}$–$N_{(1A)}$	109.0(5)	$C_{(1A)}$–$C_{(2A)}$–$C_{(3A)}$	116.8(6)
$C_{(1A)}$–$C_{(2A)}$–$C_{(11A)}$	112.1(5)	$C_{(3A)}$–$C_{(2A)}$–$C_{(11A)}$	131.1(6)
$C_{(4A)}$–$C_{(3A)}$–$C_{(2A)}$	118.5(6)	$C_{(3A)}$–$C_{(4A)}$–$C_{(5A)}$	123.9(5)
$C_{(4A)}$–$C_{(5A)}$–$C_{(6A)}$	116.6(6)	$C_{(1A)}$–$C_{(6A)}$–$C_{(7A)}$	116.2(5)
$C_{(1A)}$–$C_{(6A)}$–$C_{(5A)}$	117.2(5)	$C_{(7A)}$–$C_{(6A)}$–$C_{(5A)}$	126.6(5)
$O_{(2A)}$–$C_{(7A)}$–$C_{(6A)}$	117.1(5)	$O_{(2A)}$–$C_{(7A)}$–$C_{(8A)}$	120.7(5)
$C_{(6A)}$–$C_{(7A)}$–$C_{(8A)}$	122.2(6)	$C_{(7A)}$–$C_{(8A)}$–$C_{(12A)}$	116.8(5)
$C_{(7A)}$–$C_{(8A)}$–$C_{(9A)}$	120.3(5)	$C_{(12A)}$–$C_{(8A)}$–$C_{(9A)}$	122.8(5)
$O_{(1A)}$–$C_{(9A)}$–$N_{(1A)}$	120.4(4)	$O_{(1A)}$–$C_{(9A)}$–$C_{(8A)}$	125.9(4)
$N_{(1A)}$–$C_{(9A)}$–$C_{(8A)}$	113.7(4)	$N_{(1A)}$–$C_{(10A)}$–$C_{(11A)}$	104.3(4)
$C_{(2A)}$–$C_{(11A)}$–$C_{(10A)}$	102.0(4)	$O_{(3A)}$–$C_{(12A)}$–$O_{(4A)}$	122.2(4)
$O_{(3A)}$–$C_{(12A)}$–$C_{(8A)}$	123.9(4)	$O_{(4A)}$–$C_{(12A)}$–$C_{(8A)}$	113.8(5)
$O_{(4A)}$–$C_{(13A)}$–$C_{(14A)}$	105.7(7)	$C_{(9B)}$–$N_{(1B)}$–$C_{(1B)}$	121.8(4)
$C_{(9B)}$–$N_{(1B)}$–$C_{(10B)}$	128.1(5)	$C_{(1B)}$–$N_{(1B)}$–$C_{(10B)}$	110.0(4)
$C_{(12B)}$–$O_{(4B)}$–$C_{(13B)}$	114.5(4)	$N_{(1B)}$–$C_{(1B)}$–$C_{(6B)}$	123.7(5)
$N_{(1B)}$–$C_{(1B)}$–$C_{(2B)}$	110.4(4)	$C_{(6B)}$–$C_{(1B)}$–$C_{(2B)}$	125.9(5)
$C_{(1B)}$–$C_{(2B)}$–$C_{(3B)}$	114.5(6)	$C_{(1B)}$–$C_{(2B)}$–$C_{(11B)}$	110.0(5)
$C_{(3B)}$–$C_{(2B)}$–$C_{(11B)}$	135.4(6)	$C_{(4B)}$–$C_{(3B)}$–$C_{(2B)}$	121.3(6)
$C_{(3B)}$–$C_{(4B)}$–$C_{(5B)}$	125.0(6)	$C_{(4B)}$–$C_{(5B)}$–$C_{(6B)}$	116.1(7)
$C_{(1B)}$–$C_{(6B)}$–$C_{(7B)}$	116.7(5)	$C_{(1B)}$–$C_{(6B)}$–$C_{(5B)}$	117.2(6)
$C_{(7B)}$–$C_{(6B)}$–$C_{(5B)}$	126.1(6)	$O_{(2B)}$–$C_{(7B)}$–$C_{(8B)}$	125.7(5)
$O_{(2B)}$–$C_{(7B)}$–$C_{(6B)}$	116.0(5)	$C_{(8B)}$–$C_{(7B)}$–$C_{(6B)}$	118.3(5)
$C_{(7B)}$–$C_{(8B)}$–$C_{(9B)}$	123.7(5)	$C_{(7B)}$–$C_{(8B)}$–$C_{(12B)}$	113.1(5)
$C_{(9B)}$–$C_{(8B)}$–$C_{(12B)}$	123.1(5)	$O_{(1B)}$–$C_{(9B)}$–$N_{(1B)}$	116.8(5)
$O_{(1B)}$–$C_{(9B)}$–$C_{(8B)}$	127.4(5)	$N_{(1B)}$–$C_{(9B)}$–$C_{(8B)}$	115.8(5)
$N_{(1B)}$–$C_{(10B)}$–$C_{(11B)}$	105.9(5)	$C_{(2B)}$–$C_{(11B)}$–$C_{(10B)}$	103.0(5)
$O_{(3B)}$–$C_{(12B)}$–$O_{(4B)}$	121.0(5)	$O_{(3B)}$–$C_{(12B)}$–$C_{(8B)}$	124.5(5)
$O_{(4B)}$–$C_{(12B)}$–$C_{(8B)}$	114.2(5)	$O_{(4B)}$–$C_{(13B)}$–$C_{(14B)}$	107.1(5)

Analysis of the bond lengths in molecule **B** (bonds $O_{(1)}$–$C_{(9)}$ at 1.249(7) and $C_{(7)}$–$C_{(8)}$ at 1.404(8) Å were lengthened (mean values 1.210 and 1.326 Å) but bonds $O_{(2)}$–$C_{(7)}$ at 1.304(6) and $C_{(8)}$–$C_{(9)}$ 1.432(8) Å were shortened (mean values 1.333 and 1.464 Å)] permitted the suggestion that the geometry of the ester **1** molecule is described as a resonance hybrid of two canonical structures **1** ↔ **1a** (Scheme 1). This was also confirmed by the fairly weak character of the intramolecular hydrogen bond in the **B** molecule $O_{(2)}$–$H_{(20)}$···$O_{(3)}$ (H···O 1.94 Å, O–H···O 126°), which excludes the possibility of transferring a proton from the 4-hydroxy group to the carbonyl $O_{(3)}$ atom.

Shortened intermolecular contacts were detected between the **A** and **B** molecules at $H_{(11C)}$···$C_{(9A)}$ (x, y, z) 2.78 (sum of Van der Waals radii 2.87 [18]) and $H_{(10B)}$···$C_{(3B)}$ (x, y, z) 2.84 Å.

EXPERIMENTAL

Commercial indoline and triethyl methanetricarboxylate from Fluka were used in the synthesis of ester **1**. The ^{1}H NMR spectra were recorded on a Bruker WM 360 (360 MHz) instrument in DMSO-D_6, internal standard was TMS.

Ethyl Ester of 1-Hydroxy-3-oxo-5,6-dihydro-3H-pyrrolo[3,2,1-*i,j*]quinoline-2-carboxylic Acid (1). Indoline **2** (11.2 ml, 0.1 mol) was added dropwise with stirring to triethyl methanetricarboxylate (21.1 ml, 0.1 mol) heated to 215°C, at such a rate that the temperature of the reaction mixture was maintained within ±5°C of the initial temperature. The ethanol eliminated during the reaction was distilled through a suitable still-head. After adding all the indoline the reaction mixture was maintained at the same temperature for 10-15 min, after which it was cooled. Aqueous 10% Na_2CO_3 solution (300 ml) was added, and the mixture was heated to 70-80°C. The obtained solution of the sodium salt of ester **1** was purified with carbon, and filtered. After cooling, the filtrate was acidified with dilute, 1:1 HCl to pH 4.5-5. The solid ester **1** was filtered off, washed with water, and dried. Yield 22.5 g (87%); mp 140-142°C (heptane). ^{1}H NMR spectrum, δ, ppm (J, Hz): 13.96 (1H, s, OH); 7.65 (1H, d, J = 7.9, H-9); 7.41 (1H, d, J = 7.6, H-7); 7.08 (1H, t, J = 7.4, H-8); 4.42 (2H, q, J = 7.1, OCH_2); 4.26 (2H, t, J = 8.1, NCH_2); 3.37 (2H, t, J = 8.1, $NCH_2C\underline{H}_2$); 1.43 (3H, t, J = 7.1, $OCH_2C\underline{H}_3$).

X-ray Structural Investigation. Crystals of ester **1** were monoclinic. At 20°C a = 7.887(3), b = 13.690(5), c = 11.124(4) Å; V = 1188.1(8) Å^3; d_{calc} = 1.449 g/cm^3; space group $P2_1$; M_r = 259.25; Z = 4; μ(MoKα) = 0.107 mm^{-1}, F(000) = 544. The parameters of the unit cell and the intensities of 2069 reflections (1921 independent, R_{int} = 0.029) were measured on a Siemens P3/PC automatic four-circle diffractometer (λMoKα, graphite monochromator, θ/2θ scanning, $2\theta_{max}$ = 50°). A profile analysis using the program PROFIT [19] was carried out to improve the quality of the mass of reflections.

The structure was solved by the direct method with the SHELX97 set of programs [20]. The positions of the hydrogen atoms were calculated geometrically and were refined with a rider model with $U_{iso} = nU_{eq}$ (n = 1.5 for methyl and hydroxyl groups and 1.2 for the remaining hydrogen atoms). The structure was refined on F^2 by a full matrix least squares method in an anisotropic approach for the nonhydrogen atoms to wR_2 = 0.173 for 1921 reflections [R_1 = 0.064 for 1376 reflections with $F > 4\sigma(F)$, S = 1.002]. The full crystallographic information has been deposited in the Cambridge structural data bank (deposit No. CCDC 257523). Interatomic distances and valence angles are given in Tables 1 and 2.

REFERENCES

1. I. V. Ukrainets, L. V. Sidorenko, O. V. Gorokhov, and N. A. Jaradat, *Khim. Geterotsikl. Soedin.*, 542 (2006).
2. P. Molnar and S. L. Erdo, *Eur. J. Pharmacol.*, **311**, 311 (1996).
3. C. A. Hicks, M. A. Ward, N. Ragumoorthy, S. J. Ambler, C. P. Dell, D. Dobson, and M. J. O'Neill, *Brain. Res.*, **819**, 65 (1999).

4. M. Rowley, J. J. Kulagowski, A. P. Watt, D. Rathbone, G. I. Stevenson, R. W. Carling, R. Baker, G. R. Marshall, J. A. Kemp, A. C. Foster, S. Grimwood, R. Hargreaves, C. Hurley, K. L. Saywell, M. D. Tricklebank, and P. D. Leeson, *J. Med. Chem.*, **40**, 4053 (1997).
5. I. V. Ukrainets, P. A. Bezuglyi, O. V. Gorokhova, V. I. Treskach, and A. V. Turov, *Khim. Geterotsikl. Soedin.*, 105 (1993).
6. X. Collin, J. M. Robert, M. Duflos, G. Wielgosz, G. Le Baut, C. Robin-Dubigeon, N. Grimaud, F. Lang, and J. Y. Petit, *J. Pharm. Pharmacol.*, **53**, 417 (2001).
7. I. V. Ukrayinecz and P. A. Bezuhliy, US Patent 6340692 (2002); http://ep.espacenet.com.
8. K. Tsuji, G. W. Spears, K. Nakamura, T. Tojo, N. Seki, A. Sugiyama, and M. Matsuo, *Bioorg. Med. Chem. Lett.* , **12**, 85 (2002)
9. I. V. Ukrainets, S. A. El Kayal, O. V. Gorokhova, L. V. Sidorenko, and T. V. Alekseeva, *Vestn. Farm.*, No. 1 (37), 12 (2004).
10. T. Kappe, C. Nuebling, K.-O. Westphalen, U. Kardorff, W. Deyn, M. Gerber, and H. Walter, DE Patent 4138820 (1993); http://ep.espacenet.com.
11. S. R. Khan, A. Mhaka, R. Pili, and J. T. Isaacs, *Bioorg. Med. Chem. Lett.*, **11**, 451 (2001).
12. I. V. Ukrainets, O. V. Gorokhova, S. G. Taran, P. A. Bezuglyi, A. V. Turov, N. A. Marusenko, and O. A. Evtifeeva, *Khim. Geterotsikl. Soedin.*, 958 (1994).
13. H. Hayashi, Y. Miwa, S. Ichikawa, N. Yoda, I. Miki, A. Ishii, M. Kono, T. Yasuzawa, and F. Suzuki, *J. Med. Chem.*, **36**, 617 (1993).
14. S. Jönsson, G. Andersson, T. Fex, T. Fristedt, G. Hedlund, K. Jansson, L. Abramo, I. Fritzson, O. Pekarski, A. Runström, H. Sandin, I. Thuvesson, and A. Björk, *J. Med. Chem.*, **47**, 2075 (2004).
15. M. Rowley, P. D. Leeson, G. I. Stevenson, A. M. Moseley, I. Stansfield, I. Sanderson, L. Robinson, R. Baker, J. A. Kemp, G. R. Marshall, A. C. Foster, S. Grimwood, M. D. Tricklebank, and K. L. Saywell, *J. Med. Chem.*, **36**, 3386 (1993).
16. A. Kutyrev and T. Kappe, *J. Heterocycl. Chem.*, **34**, 969 (1997).
17. H.-B. Burgi and J. D. Dunitz, *Struct. Correl., Vol. 2*, VCH Weinheim (1994), p. 741.
18. Yu. V. Zefirov and P. M. Zorkii, *Usp. Khim.*, **58**, 713 (1989).
19. V. A. Strel'tsov and V. E. Zavodnik, *Kristallografiya*, **34**, 1369 (1989).
20. G. M. Sheldrick, *SHELX97. PC Version. A System of Computer Programs for Crystal Structure Solution and Refinement*. Rev. 2 (1998).