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4-HYDROXY-2-QUINOLONES. 107*. REACTION OF TRIETHYL METHANE-TRICARBOXYLATE WITH INDOLINE

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The first stage of the reaction of triethyl methanetricarboxylate with indoline is the formation of the diethyl ester of 2-(indoline-1-carbonyl)malonic acid, which then, depending on the conditions selected, may be converted into the ethyl ester of 2-(indoline-1-carbonyl)-3-(indolin-1-yl)-3-oxopropionic acid, methanetri-N-(indolin-1-yl)carboxamide, or the ethyl ester or (indolin-1-yl)amide of 1-hydroxy-3-oxo-5,6-dihydro-3H-pyrrolo[3,2,1-ij]quinoline-2-carboxylic acid.

Keywords: amides of 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids, heterocyclic derivatives of tricarbonylmethane, ethyl esters, X-ray structural analysis, thermolysis.

The condensation of N-substituted anilines with a double or triple excess of methanetricarboxylic acid triethyl ester is used as one of the variants of the synthesis of ethyl esters of 1-substituted 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids [2, 3]. We have shown in the example of indoline [4] and diphenylamine [5] that this reaction may also be fairly effectively carried out at an equimolar ratio of reactants, and the obtained 3-ethoxycarbonyl-4-hydroxy-2-oxoquinolines are best isolated and purified as the corresponding 4-O-sodium salts.

On repeating the described method with indoline **1** many times it was noted that occasionally after treatment of the reaction mixture with aqueous Na_2CO_3 solution, a portion of the obtained product remains insoluble. The original hypothesis that the isolated substance is a secondary acyclic methanetri-N-(indolin-1-yl)carboxamide is not justified since in its ^{1}H NMR spectrum there are two ethoxy groups (judging by the integral intensity of the signals). After recrystallization from ether monocrystals were successfully obtained, X-ray structural analysis of which gave the unequivocal answer that the sample investigated is the diethyl ester of 2-(indoline-1-carbonyl)malonic acid (**2**). The indoline fragment of this compound is planar with a precision of 0.01 Å (Fig. 1). The $C_{(9)}$–$O_{(1)}$ carbonyl group is coplanar with the plane of the bicycle [torsion angle $C_{(1)}$–$N_{(1)}$–$C_{(9)}$–$O_{(1)}$ is 2.9(4)°], in spite of the shortened intramolecular contact $O_{(1)}\cdots C_{(2)}$ at 2.88 Å (sum of van der Waals radii 3.00 Å [6]), $O_{(1)}\cdots H_{(2)}$ 2.34 Å). The ester substituents at the $C_{(10)}$ atom are in a conformation close to *sc* and *ap* relative to the $N_{(1)}$–$C_{(9)}$ bond [torsion angles $N_{(1)}$–$C_{(9)}$–$C_{(10)}$–$C_{(11)}$ -77.9(3)°, $N_{(1)}$–$C_{(9)}$–$C_{(10)}$–$O_{(14)}$ 161.7(2)°]. Such an orientation of substituents is probably caused by the presence of shortened intramolecular contacts $H_{(10)}\cdots C_{(8)}$ 2.63 Å, $H_{(10)}\cdots H_{(8b)}$ 2.21 Å, $H_{(8b)}\cdots C_{(10)}$ 2.79 Å. As a result of this, lengthening is observed of the $C_{(9)}$–$C_{(10)}$ bond 1.527 Å compared with the mean value of 1.511 Å [7]. The carbonyl groups of the ester

* For Part 106 see [1].

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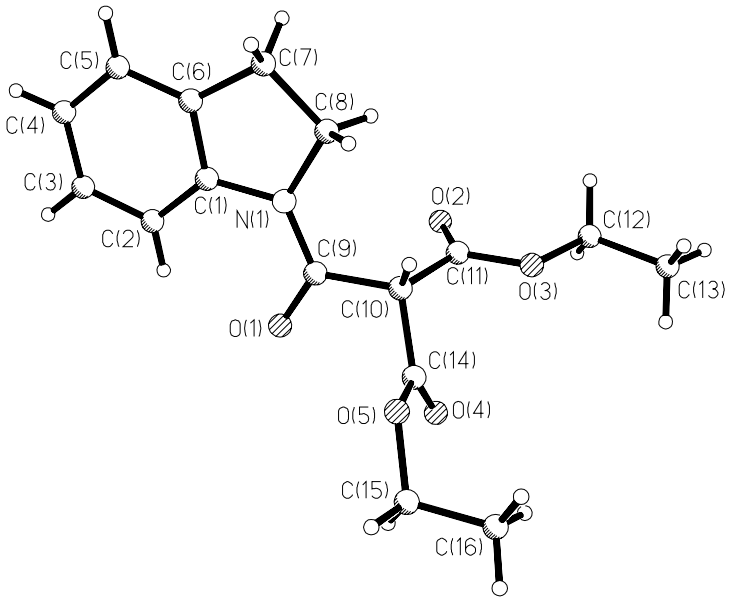


Fig. 1. Structure of the diester **2** molecule with numbering of the atoms.

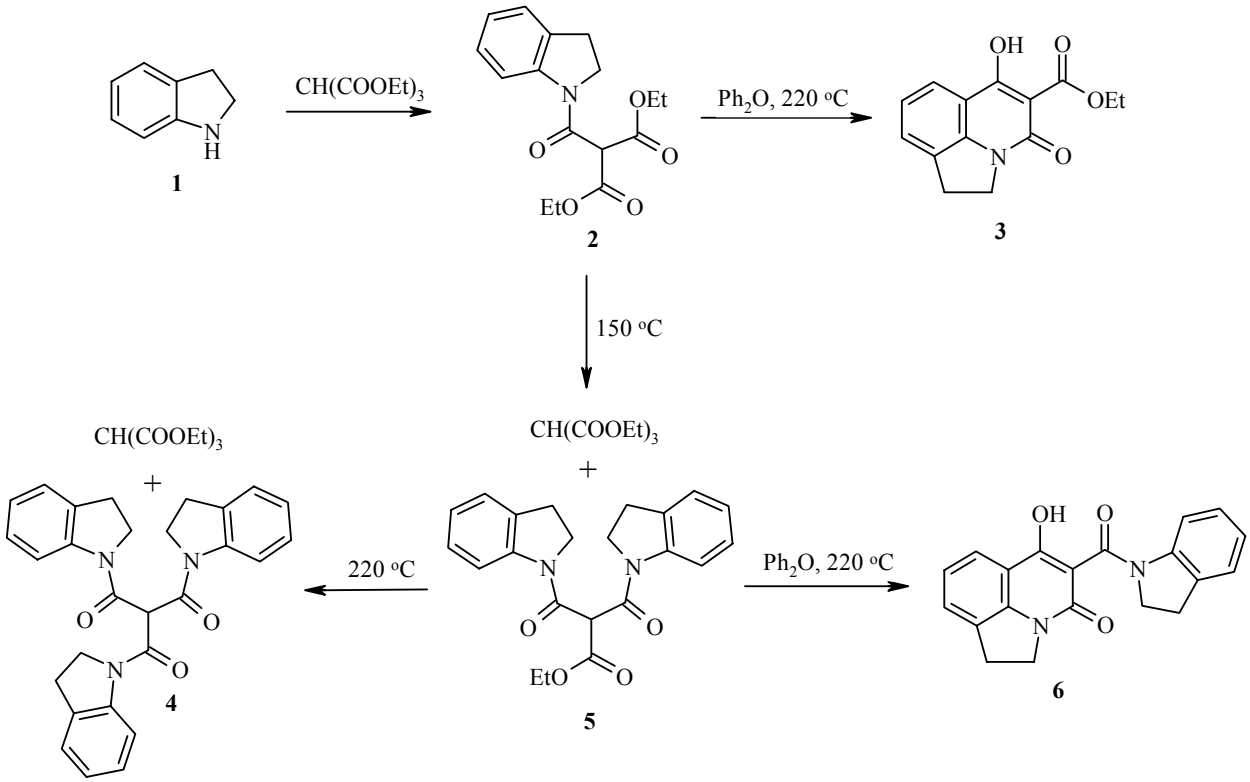
substituents also have a different conformation relative to the $C_{(9)}$–$C_{(10)}$ bond [torsion angles $C_{(9)}$–$C_{(10)}$–$C_{(11)}$–$O_{(2)}$ -2.3(3)°, $C_{(9)}$–$C_{(10)}$–$C_{(14)}$–$O_{(4)}$ 90.0(3)°]. The $C_{(13)}$ atom is in the *ap* conformation relative to the $C_{(11)}$–$O_{(3)}$ bond [torsion angle $C_{(11)}$–$O_{(3)}$–$C_{(12)}$–$C_{(13)}$ −171.2(2)°), and the $C_{(15)}$–$C_{(16)}$ bond is disposed practically perpendicular to the $C_{(14)}$–$O_{(5)}$ bond [torsion angle $C_{(14)}$–$O_{(5)}$–$C_{(15)}$–$C_{(16)}$ 81.9(3)°].

The obtained result undoubtedly indicates that the first stage of the reaction of triethyl methanetricarboxylate with indoline **1** is the formation of monoamide **2**, the intramolecular cyclization of which must lead to the desired ethyl ester of 1-hydroxy-2-oxo-5,6-dihydro-3H-pyrrolo[3,2,1-*ij*]quinoline-2-carboxylic acid (**3**), while interaction with unreacted indoline leads to the byproduct methanetri-N-(indolin-1-yl)carboxamide (**4**). Nevertheless, as it turned out under the conditions of the reaction being investigated, another route forming triamide **4** is possible. Simple heating of chromatographically pure diester **2** causes its conversion into the ethyl ester of 2-(indoline-1-carbonyl)-3-(indolin-1-yl)-3-oxopropionic acid (**5**), which, in its turn, may be transformed in an analogous manner into triamide **4** (Scheme 1). In both cases the chemical conversions are accompanied by the separation of free triethyl methanetricarboxylate, which is readily detected by TLC.

With the aim of determining the thermodynamic characteristics of esters **2** and **5** we carried out studies of the reactivity and thermal stability of the indicated compounds in a derivatographic investigation under conditions of dry heat. The results of the experiments carried out show that esters **2** and **5** are extremely complex in thermal behavior (Fig. 2).

The endothermal peaks with minima at 65 and 195°C on the DTA curves are probably caused by melting processes of esters **2** and **5** respectively, although these properties are somewhat below the melting points of the indicated substances determined in a capillary (see Experimental). In the derivatogram of ester **2** (Fig. 2, *1*) both the mentioned peaks are observed, which confirms its conversion into monoester **5** under thermolysis conditions. Loss of mass begins smoothly from 125°C, then increases sharply from 165°C, and stops at 290°C, after which steady volatilization of the substance occurs (analogous parameters for ester **5** are 147, 180, and 285°C). The overall loss of mass was 64% of the initial (68% for ester **5**), which is somewhat higher than expected, and is probably explained by the ability of certain compounds formed on thermolysis to

Scheme 1



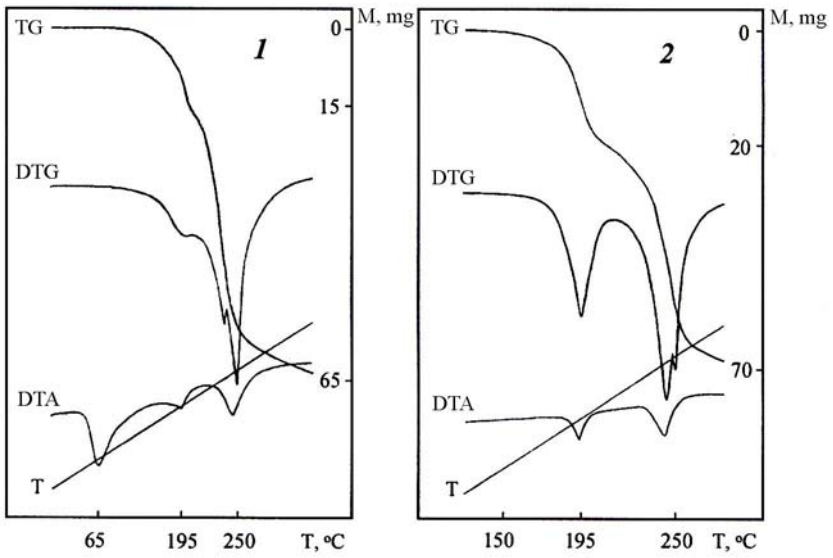


Fig. 2. Derivatograms of esters **2** (*1*) and **5** (*2*): T is the thermal analysis curve; DTA – the differential thermal analysis curve; TG – the thermogravimetric curve; DTG – the differential thermogravimetric curve. Sample weight 100 mg.

sublime. As an interesting feature of the derivatograms of esters **2** and **5** it is possible to mention the intense double peaks on the DTG curves at 240 and 250°C, accompanied by a significant loss of mass and corresponding to the decomposition of the triethyl methanetricarboxylate formed.

In all, it is necessary to emphasize that esters **2** and **5** under thermolysis conditions behave like the ethyl ester of malonanilic acid, i.e. their thermally activated chemical conversions evidently proceed by the mechanism described by us previously in [8], with the only difference that the final products proved to be not symmetrical dianilides of malonic acids and diethyl malonate, but respectively di- **5** or tri(indolin-1-yl)amides **4** of methanetricarboxylic acid and triethyl methanetricarboxylate.

However the slow addition of esters **2** or **5** to diphenyl oxide heated to 215-225°C, a procedure used recently in the synthesis of 3-ethoxycarbonylquinolin-4-ones [9], enables preparation of the ethyl ester **3** or the (indolin-1-yl)amide (**6**) of 1-hydroxy-3-oxo-5,6-dihydro-3H-pyrrolo[3,2,1-*ij*]quinoline-2-carboxylic acid in high yield.

TABLE 1. Bond Lengths (*l*) in the Structure of Diester **2**

Bond	*l*, Å	Bond	*l*, Å
$N_{(1)}–C_{(9)}$	1.342(3)	$N_{(1)}–C_{(1)}$	1.415(3)
$N_{(1)}–C_{(8)}$	1.490(3)	$O_{(1)}–C_{(9)}$	1.224(3)
$O_{(2)}–C_{(11)}$	1.200(3)	$O_{(3)}–C_{(11)}$	1.333(3)
$O_{(3)}–C_{(12)}$	1.448(3)	$O_{(4)}–C_{(14)}$	1.197(3)
$O_{(5)}–C_{(14)}$	1.317(3)	$O_{(5)}–C_{(15)}$	1.448(3)
$C_{(1)}–C_{(2)}$	1.381(3)	$C_{(1)}–C_{(6)}$	1.387(3)
$C_{(2)}–C_{(3)}$	1.369(3)	$C_{(3)}–C_{(4)}$	1.377(3)
$C_{(4)}–C_{(5)}$	1.375(3)	$C_{(5)}–C_{(6)}$	1.375(3)
$C_{(6)}–C_{(7)}$	1.503(3)	$C_{(7)}–C_{(8)}$	1.512(3)
$C_{(9)}–C_{(10)}$	1.527(3)	$C_{(10)}–C_{(14)}$	1.511(3)
$C_{(10)}–C_{(11)}$	1.514(3)	$C_{(12)}–C_{(13)}$	1.484(4)
$C_{(15)}–C_{(16)}$	1.467(5)		

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

Valence angle	ω, deg.	Valence angle	ω, deg.
$C_{(9)}–N_{(1)}–C_{(1)}$	125.5(2)	$C_{(9)}–N_{(1)}–C_{(8)}$	124.8(2)
$C_{(1)}–N_{(1)}–C_{(8)}$	109.7(2)	$C_{(11)}–O_{(3)}–C_{(12)}$	116.5(2)
$C_{(14)}–O_{(5)}–C_{(15)}$	116.3(2)	$C_{(2)}–C_{(1)}–C_{(6)}$	120.6(2)
$C_{(2)}–C_{(1)}–N_{(1)}$	129.4(2)	$C_{(6)}–C_{(1)}–N_{(1)}$	110.0(2)
$C_{(3)}–C_{(2)}–C_{(1)}$	118.0(2)	$C_{(2)}–C_{(3)}–C_{(4)}$	122.2(2)
$C_{(5)}–C_{(4)}–C_{(3)}$	119.5(2)	$C_{(4)}–C_{(5)}–C_{(6)}$	119.5(2)
$C_{(5)}–C_{(6)}–C_{(1)}$	120.3(2)	$C_{(5)}–C_{(6)}–C_{(7)}$	129.9(2)
$C_{(1)}–C_{(6)}–C_{(7)}$	109.9(2)	$C_{(6)}–C_{(7)}–C_{(8)}$	105.2(2)
$N_{(1)}–C_{(8)}–C_{(7)}$	105.1(2)	$O_{(1)}–C_{(9)}–N_{(1)}$	123.2(2)
$O_{(1)}–C_{(9)}–C_{(10)}$	119.4(2)	$N_{(1)}–C_{(9)}–C_{(10)}$	7.5(2)
$C_{(14)}–C_{(10)}–C_{(11)}$	109.1(2)	$C_{(14)}–C_{(10)}–C_{(9)}$	108.5(2)
$C_{(11)}–C_{(10)}–C_{(9)}$	111.8(2)	$O_{(2)}–C_{(11)}–O_{(3)}$	124.4(2)
$O_{(2)}–C_{(11)}–C_{(10)}$	125.8(2)	$O_{(3)}–C_{(11)}–C_{(10)}$	109.7(2)
$O_{(3)}–C_{(12)}–C_{(13)}$	107.5(2)	$O_{(4)}–C_{(14)}–O_{(5)}$	124.3(2)
$O_{(4)}–C_{(14)}–C_{(10)}$	124.0(2)	$O_{(5)}–C_{(14)}–C_{(10)}$	111.6(2)
$O_{(5)}–C_{(15)}–C_{(16)}$	111.5(3)		

It therefore follows from the results of the investigations that in the course of the reaction of triethyl methanetricarboxylate with indoline, apart from the order of mixing reactants mentioned previously [4], observance of the temperature regimen also shows a significant effect. When obtaining the ethyl ester of 1-hydroxy-3-oxo-5,6-dihydro-3H-pyrrolo[3,2,1-*ij*]quinoline-2-carboxylic acid it is necessary to control strictly the temperature of the reaction mixture, maintaining it within the limits 215-225°C, to prevent the formation of contaminating methanetri-N-(indolin-1-yl)carboxamide.

EXPERIMENTAL

The ^{1}H NMR spectra of the synthesized compounds were recorded on a Varian Mercury VX 200 instrument (200 MHz) in DMSO-d_6, internal standard was TMS. Commercial indoline and triethyl methanecarboxylate from Fluka were used in the work.

Diethyl Ester of 2-(Indoline-1-carbonyl)malonic Acid (2). Indoline **1** (33.6 ml, 0.3 mol) was added dropwise with stirring to triethyl methanetricarboxylate (63.3 ml, 0.3 mol) heated to 220°C, not allowing the temperature of the reaction mixture to fall below 215°C. After adding all the indoline the reaction mixture was maintained at the same temperature for 10 min, after which it was cooled (at the more extended time of 20-25 min the intermediate diester **2** was practically completely cyclized into ester **3**). A 10% aqueous solution (1 liter) of Na_2CO_3 was added, and the mixture heated to 70-80°C. The obtained solution of the sodium salt of ester **3** was filtered, The residue on the filter was washed with water, and dried. After recrystallization from ether, diester **2** (6.41 g, 7%) was obtained; mp 86-88°C (in a capillary), R_f 0.24 (Silufol UV 254, hexane–ether, 1:1). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.02 (1H, d, *J* = 8.0, H-7); 7.26 (1H, d, *J* = 7.4, H-4); 7.17 (1H, t, *J* = 8.0, H-6); 7.04 (1H, t, *J* = 7.4, H-5); 5.24 (1H, s, CH); 4.20 (4H, q, *J* = 6.9, 2OCH_2); 4.01 (2H, t, *J* = 8.3, NCH_2); 3.13 (2H, t, *J* = 8.3, $NCH_2C\underline{H}_2$); 1.20 (6H, t, *J* = 6.9, 2$OCH_2C\underline{H}_3$). Found, %: C 62.80; H 6.12; N 4.64. $C_{16}H_{19}NO_5$. Calculated, %: C 62.94; H 6.27; N 4.59.

X-Ray Structural Investigation. Crystals of diester **2** are monoclinic. At 20°C *a* = 9.8384(2), *b* = 16.371(6), *c* = 10.590(2) Å; β = 99.80(2)°; *V* = 1603.2(7) Å^3; d_{calc} = 1.265 g/cm^3; space group $P2_1/c$; M_r = 305.32; *Z* = 4; μ(MoKα) = 0.094 mm^{-1}; *F*(000) = 648. Parameters of the unit cell and the intensities of 2831 reflections (2674 independent, R_{int} = 0.036) were measured on a Siemens P3/PC automatic four-circle diffractometer (λMoKα, graphite monochromator, θ/2θ scanning, $2\theta_{max}$ = 50°).

The structure was solved by the direct method using the SHELX97 set of programs [10]. The positions of the hydrogen atoms were found from an electron density difference synthesis and refined by the rider model with $U_{iso} = nU_{eq}$ (*n* = 1.5 for a methyl group and 1.2 for the remaining hydrogen atoms). The structure was refined on F^2 with a full matrix least squares method in an anisotropic approximation for the nonhydrogen atoms to wR_2 = 0.116 for 2674 reflections (R_1 = 0.047 for 1617 reflections with $F > 4\sigma(F)$, *S* = 0.991). The complete crystallographic information has been deposited in the Cambridge structural data bank (deposit No. CCDC 283291). Interatomic distances and valence angles are given in Tables 1 and 2.

Ethyl Ester of 1-Hydroxy-3-oxo-5,6-dihydro-3H-pyrrolo[3,2,1-*ij*]quinoline-2-carboxylic Acid (3). Diester **2** (3.05 g, 0.01 mol) was added in small portions with stirring to diphenyl oxide (20 ml) heated to 220°C. After adding all the diester **2** the reaction mixture was maintained at the same temperature for 15 min, and then cooled. A 5% aqueous solution (50 ml) of Na_2CO_3 was added, the mixture heated to 70-80°C, and shaken thoroughly. The aqueous layer was separated, and the obtained solution of the sodium salt of ester **3** was purified with carbon, and filtered. After cooling, the filtrate was acidified with dilute (1:1) HCl to pH 4.5-5.0. The solid ester **3** was filtered off, washed with water, and dried. Yield 2.43 g (94%); mp 140-142°C (heptane). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 13.99 (1H, s, OH); 7.66 (1H, d, *J* = 7.9, H-9); 7.43 (1H, d, *J* = 7.6, H-7); 7.09 (1H, t, *J* = 7.4, H-8); 4.41 (2H, q, *J* = 7.1, OCH_2); 4.24 (2H, t, *J* = 8.1, NCH_2); 3.37 (2H, t, *J* = 8.1, $NCH_2C\underline{H}_2$); 1.44 (3H, t, *J* = 7.1, $OCH_2C\underline{H}_3$).

A mixing test with an authentic sample of ester **3** [4] gave no depression of melting point, the ^{1}H NMR spectra of these compounds were identical.

Ethyl Ester of 2-(Indoline-1-carbonyl)-3-(indolin-1-yl)-3-oxopropionic Acid (5). Diester **2** (3.05 g, 0.01 mol) was maintained at 150°C for 15-20 min. The initial diester melts but after a certain time the reaction product begins to crystallize. The reaction mixture was cooled, and treated with ether.The residue of ester **5** was filtered off, washed with ether, and dried. Triethyl methanetricarboxylate of R_f 0.57 (Silufol UV 254, hexane–ether, 1:1) was determined in the filtrate by comparison with an authentic specimen. The residue on the filter was crystallized from ethanol and ester **5** (1.51 g, 80%) was obtained; mp 214-216°C (capillary was placed in the instrument previously heated to 200-205°C for determining mp). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.05 (2H, d, *J* = 7.8, 2H-7); 7.26 (2H, d, *J* = 7.2, 2H-4); 7.18 (2H, t, *J* = 7.5, 2H-6); 7.04 (2H, t, *J* = 7.2, 2H-5); 5.48 (1H, s, CH); 4.23 (2H, q, *J* = 7.0, OCH_2); 4.05 (4H, t, *J* = 8.4, $2NCH_2$); 3.14 (4H, t, *J* = 8.4, $2NCH_2C\underline{H_2}$); 1.22 (3H, t, *J* = 7.0, $OCH_2C\underline{H_3}$). Found, %: C 69.95; H 5.77; N 7.32. $C_{22}H_{22}N_2O_4$. Calculated, %: C 69.83; H 5.86; N 7.40.

Methanetri-N-(indolin-1-yl)carboxamide (4) was obtained by the thermolysis of ester **5** at 220°C by the method of the previous experiment in 85% yield. The triethyl methanetricarboxylate formed was determined chromatographically as described above; mp 325-327°C (DMF) (lit. mp 320°C [2]). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.08 (3H, d, *J* = 7.5, 3H-7); 7.26 (3H, d, *J* = 7.7, 3H-4); 7.18 (3H, t, *J* = 7.8, 3H-6); 7.04 (3H, t, *J* = 7.5, 3H-5); 5.59 (1H, s, CH); 4.12 (6H, t, *J* = 8.4, $3NCH_2$); 3.15 (6H, t, *J* = 8.3, $3NCH_2C\underline{H_2}$).

(Indolin-1-yl)amide of 1-Hydroxy-3-oxo-5,6-dihydro-3H-pyrrolo[3,2,1-*ij*]quinoline-2-carboxylic Acid (6). Ester **5** (3.78 g, 0.01 mol) was added in small portions with stirring to diphenyl oxide (25 ml) heated to 220°C. The reaction mixture was cooled 15 min after adding all the ester **5**, hexane (50 ml) was added, and thoroughly mixed. The separated solid amide **6** was filtered off, washed with hexane, and dried. Yield 2.43 g (91%); mp 244-246°C (ethanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 10.68 (1H, s, OH), 6.94-7.70 (7H, m, H arom.); 4.10-4.46 (4H, m, $2NCH_2$); 3.23-3.40 (4H, m, $2NCH_2C\underline{H_2}$). Found, %: C 72.39; H 4.97; N 8.34. $C_{20}H_{16}N_2O_3$. Calculated, %: C 72.28; H 4.85; N 8.43.

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