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4-HYDROXY-2-QUINOLONES. 111*. SIMPLE SYNTHESIS OF 1-SUBSTITUTED 4-METHYL-2-OXO-1,2-DIHYDROQUINOLINE-3-CARBOXYLIC ACIDS

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A preparative method of obtaining 1-substituted 4-methyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acids is proposed. Features of their spatial structure have been studied.

Keywords: 1-R-4-methyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid, 4-chloroquinolin-2-one, cyanoacetic ester, amidation, hydrolysis, decarboxylation, X-ray structural analysis.

1-Substituted 4-methyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acids **1** are of interest as the basis for the synthesis of various potentially biologically active substances. The obvious synthetic scheme for assembling such compounds presumes alkylation of the appropriate N-substituted *ortho*-aminoacetophenones with alkoxymalonyl chloride with subsequent closure of the quinoline ring by the action of basic catalysts. However, the practical execution of such a route is severely limited by the availability of the initial N-substituted *ortho*-aminoacetophenones.

Another possible variant for obtaining acids **1** is the N-alkylation of the previously isolated ethyl ester of 1H-4-methyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid. Regretably such a reaction does not occur unambiguously. The efficiency is reduced to a significant extent by the formation of byproduct 2-O-alkyl-substituted isomers [2].

We have proposed an unusual method of replacing the chlorine atom in the ethyl ester of 4-chloro-1H-2-oxo-1,2-dihydroquinoline-3-carboxylic acid by a methyl group [3]. Its structural analogs, i.e. 1-N-alkyl-substituted esters **2**, were also involved in the scope of the investigations. As it turned out these also readily react with cyanoacetic ester, like the 1H-derivative. However subsequently the reactions proceeddifferently and, after alkaline hydrolysis of the 4-(cyanoethoxycarbonylmethyl)-3-ethoxycarbonyl-2-oxo-1,2-dihydro-quinolines **3** synthesized in the first stage, the expected 4-methyl substituted acid **1** was not isolated, but only 1-R-4-carboxymethyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acids **4**. To convert the 4-carboxymethyl group into methyl in the hydrolysis process (as occurs in the case of the 1H derivative) was unsuccessful even after doubling the reaction time. Consequently 3-carboxy-1H-quinolin-2-ones exist in basic medium in the aromatic 2-hydroxy form, which surpasses somewhat the 1,2-dihydro form in electron-withdrawing influence on the substituent at position 4. One more of the few examples permitting graphical recording of the difference in reactivity of 2-hydroxyquinolines and 1,2-dihydroquinolin-2-ones is the reaction of the ethyl esters of 1-R-4-chloro-2-oxo-1,2-dihydroquinoline-3-carboxylic acids with pyridine [4].

* For Part 110 see [1].

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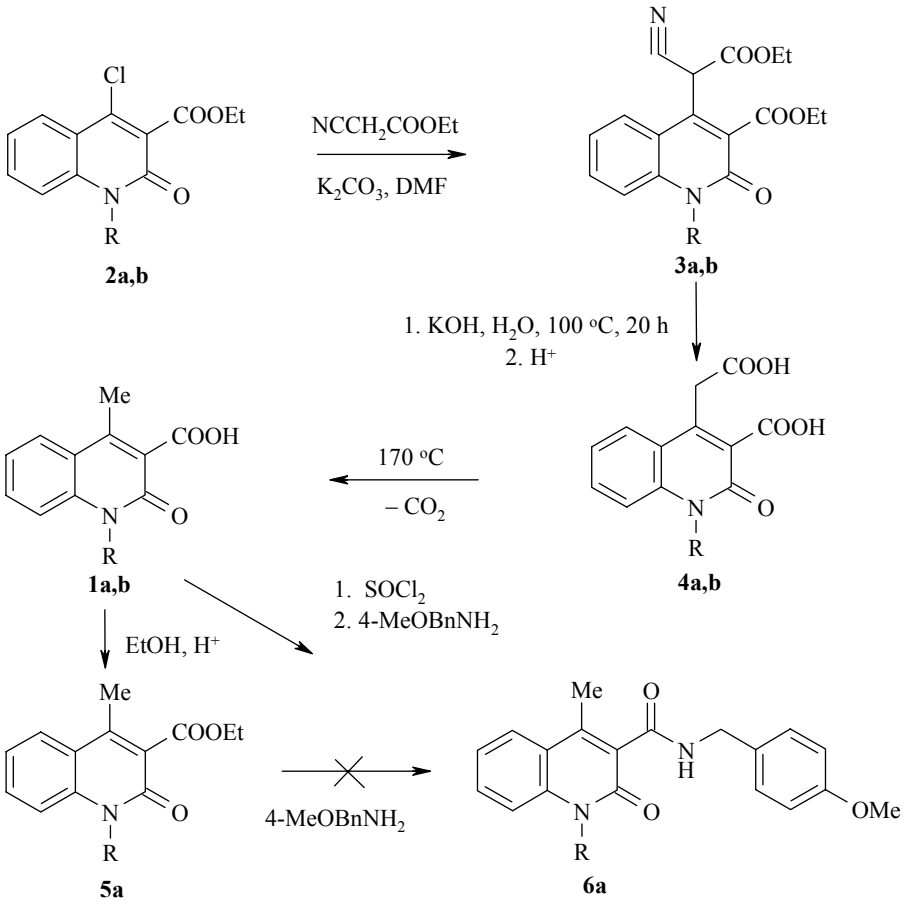

1–6 a R = Et, **b** R = Pr

Nonetheless, transformation of dicarboxylic acids **4** into the desired 4-methyl derivatives **1** was effected successfully. It was established that on simply heating to the melting point these compounds were readily decarboxylated, losing a molcule of CO_2 from the 4-carboxymethyl fragment. Confirmation of precisely this reaction direction was provided by the ^{1}H NMR spectra of the obtained compounds, and also by the X-ray structural analysis of one of the samples, the N-ethyl-substituted acid **1a** (Fig. 1, Tables 1, 2).

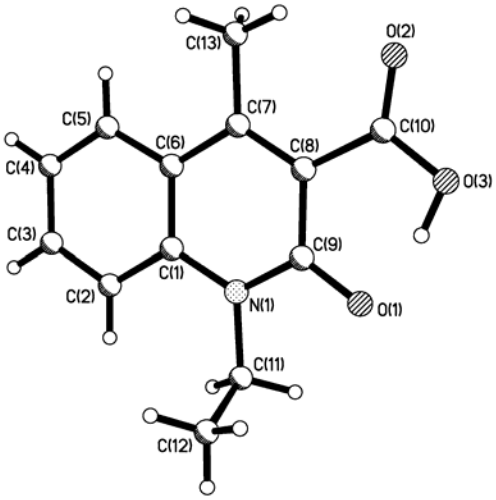

Fig. 1. Structure of the acid **1a** molcule with numbering of the atoms.

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

Bond	*l*, Å	Bond	*l*, Å
$N_{(1)}$–$C_{(9)}$	1.360(2)	$N_{(1)}$–$C_{(1)}$	1.386(2)
$N_{(1)}$–$C_{(11)}$	1.492(2)	$O_{(1)}$–$C_{(9)}$	1.246(2)
$O_{(2)}$–$C_{(10)}$	1.196(3)	$O_{(3)}$–$C_{(10)}$	1.308(3)
$C_{(1)}$–$C_{(2)}$	1.398(3)	$C_{(1)}$–$C_{(6)}$	1.419(3)
$C_{(2)}$–$C_{(3)}$	1.371(3)	$C_{(3)}$–$C_{(4)}$	1.385(3)
$C_{(4)}$–$C_{(5)}$	1.367(3)	$C_{(5)}$–$C_{(6)}$	1.413(3)
$C_{(6)}$–$C_{(7)}$	1.435(3)	$C_{(7)}$–$C_{(8)}$	1.370(3)
$C_{(7)}$–$C_{(13)}$	1.507(3)	$C_{(8)}$–$C_{(9)}$	1.459(3)
$C_{(8)}$–$C_{(10)}$	1.503(3)	$C_{(11)}$–$C_{(12)}$	1.502(3)

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

Angle	ω, deg.	Angle	ω, deg.
$C_{(9)}$–$N_{(1)}$–$C_{(1)}$	122.7(1)	$C_{(9)}$–$N_{(1)}$–$C_{(11)}$	116.2(2)
$C_{(1)}$–$N_{(1)}$–$C_{(11)}$	121.1(1)	$N_{(1)}$–$C_{(1)}$–$C_{(2)}$	120.8(2)
$N_{(1)}$–$C_{(1)}$–$C_{(6)}$	118.7(2)	$C_{(2)}$–$C_{(1)}$–$C_{(6)}$	120.5(2)
$C_{(3)}$–$C_{(2)}$–$C_{(1)}$	120.2(2)	$C_{(2)}$–$C_{(3)}$–$C_{(4)}$	120.7(2)
$C_{(5)}$–$C_{(4)}$–$C_{(3)}$	119.7(2)	$C_{(4)}$–$C_{(5)}$–$C_{(6)}$	122.4(2)
$C_{(5)}$–$C_{(6)}$–$C_{(1)}$	116.5(2)	$C_{(5)}$–$C_{(6)}$–$C_{(7)}$	123.4(2)
$C_{(1)}$–$C_{(6)}$–$C_{(7)}$	120.1(2)	$C_{(8)}$–$C_{(7)}$–$C_{(6)}$	119.4(2)
$C_{(8)}$–$C_{(7)}$–$C_{(13)}$	121.7(2)	$C_{(6)}$–$C_{(7)}$–$C_{(13)}$	118.9(2)
$C_{(7)}$–$C_{(8)}$–$C_{(9)}$	120.1(2)	$C_{(7)}$–$C_{(8)}$–$C_{(10)}$	123.2(2)
$C_{(9)}$–$C_{(8)}$–$C_{(10)}$	116.7(2)	$O_{(1)}$–$C_{(9)}$–$N_{(1)}$	118.6(2)
$O_{(1)}$–$C_{(9)}$–$C_{(8)}$	122.5(2)	$N_{(1)}$–$C_{(9)}$–$C_{(8)}$	118.9(2)
$O_{(2)}$–$C_{(10)}$–$O_{(3)}$	119.2(2)	$O_{(2)}$–$C_{(10)}$–$C_{(8)}$	123.2(2)
$O_{(3)}$–$C_{(10)}$–$C_{(8)}$	117.6(2)	$N_{(1)}$–$C_{(11)}$–$C_{(12)}$	112.8(2)

All the non-hydrogen atoms in the molcule with the exception of the $C_{(12)}$ atom of the ethyl substituent, which is disposed perpendicular to the plane of the bicyclic fragment [torsion angle $C_{(9)}$–$N_{(1)}$–$C_{(11)}$–$C_{(12)}$ is 89.6(2)°], lie in one plane with a precision of 0.02 Å. The coplanar disposition of the carboxyl group at $C_{(8)}$ relative to the plane of the quinolone fragment is stabilized by the strong intramolcular hydrogen bond $O_{(3)}$–$H_{(30)}$…$O_{(1)}$ [H…O 1.55(5) Å, C–H…O 160(4)°], which is also the reason for the $C_{(9)}$–$O_{(1)}$ bond length of 1.246(2) Å in comparison with a mean value of 1.210 Å [5]. Between the methyl group on $C_{(7)}$ and the $O_{(2)}$ atom of the carboxyl group a weaker intramolcular hydrogen bond was detected $C_{(13)}$–$H_{(13a)}$…$O_{(2)}$ (H…O 1.98 Å, C–H…O 133°). Marked steric stress exists between the substituents at the $C_{(7)}$ and $N_{(1)}$ atoms and the bicyclic fragment in the investigated molcule of acid **1a,** which shows in the shortened intramolcular contacts $H_{(5)}$…$C_{(13)}$ 2.60 (sum of van der Waals radii 2.87 [6]), $H_{(5)}$…$H_{(13c)}$ 2.25 (2.34), $H_{(13c)}$…$C_{(5)}$ 2.74 (2.87), $H_{(2)}$…$C_{(11)}$ 2.53 (2.87), $H_{(2)}$…$H_{(11b)}$ 2.00 (2.34), $H_{(11b)}$…$C_{(2)}$ 2.54 (2.87) and $H_{(11a)}$…$O_{(1)}$ 2.30 Å (2.46 Å).

A weak intermolcular hydrogen bond was detected between the molcules in the crystal of acid **1a** at $C_{(2)}$–$H_{(2)}$…$O_{(2)}$, (x-1, y, z) H…O 2.41 Å, C-H…O 160° and an intermolcular shortened contact at $H_{(13b)}$…$H_{(11b)}$ (1-x, -y, 1-z) 2.28 Å (sum of van der Waals radii 2.34 Å).

The esterification of acids **1** with alcohols proceeds without any complications. The esters obtained in this way, such as the ethyl **5**, did not react with alkylamines under the usual conditions. For this it is expedient to convert acids **1** into the corresponding acid chlorides by the action of thionyl chloride, amidation of which does not cause problems and leads to the corresponding amide **6** in high yield.

On summarizing the investigations carried out it should be mentioned that the method proposed by us for obtaining 1-substituted 4-methyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acids is characterized by simplicity and good yields. And although only two examples of one type are considered, it is clear that it is possible to subject not only N-alkyl derivatives to an analogous conversion, but also other available 4-chloro-3-ethoxycarbonyl-2-oxo-1,2-dihydroquinolines, such as N-aryl, tricyclic $C_{(8)}/N_{(1)}$ annelated, and others substituted in the benzene portion of the quinolone nucleus, etc. [4, 7].

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Varian Mercury VX-200 (200 MHz) instrument in DMSO-d_6, internal standard was TMS.

4-Carboxymethyl-1-ethyl-2-oxo-1,2-dihydroquinoline-3-carboxylic Acid (4a). A mixture of the ethyl ester of 4-chloro-1-ethyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid (**2a**) (2.79 g: 0.01 mol), cyanoacetic ester (1.17 ml: 0.011 mol), and K_2CO_3 (2 g) in DMF (15 ml) was stirred at 90°C for 10 h. The reaction mixture was cooled, diluted with water, and acidified with HCl to pH 5. The isolated solid ester **3a** was extracted with CH_2Cl_2 (3×20 ml). The organic extracts were combined, and the solvent removed (finally at reduced pressure). A 20% aqueous KOH solution (30 ml) was added to the residue, and the mixture boiled until the end of ammonia evolution (~20 h). The mixture was cooled, and acidified with HCl to pH 3. The isolated solid acid **4a** was filtered off, washed with water, anddried. Yield was 2.31 g (84%). Mp 156-158°C (from ethanol, decomp.). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 13.80 (1H, br. s, COOH); 12.84 (1H, br. s, COOH); 7.90 (1H, d, *J* = 8.0, H-5); 7.64-7.75 (2H, m, H-7, 8); 7.31 (1H, t, *J* = 6.7, H-6); 4.26 (2H, q, *J* = 7.1, NCH_2); 3.87 (2H, s, $C\underline{H}_2COOH$); 1.19 (3H, t, *J* = 7.1, CH_3). Found, %: C 61.21; H 4.87; N 5.17. $C_{14}H_{13}NO_5$. Calculated, %: C 61.09; H 4.76; N 5.09.

4-Carboxymethyl-2-oxo-1-propyl-1,2-dihydroquinoline-3-carboxylic Acid (4b) was obtained analogously. Yield 82%. Mp 161-163°C (from ethanol, decomp.). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 13.72 (1H, br. s, COOH); 12.93 (1H, br. s, COOH); 7.90 (1H, d, *J* = 8.0, H-5); 7.62-7.76 (2H, m, H-7, 8); 7.34 (1H, t, *J* = 6.8, H-6); 4.23 (2H, t, *J* = 7.3, NCH_2); 4.00 (2H, s, $C\underline{H}_2COOH$); 1,63 (2H, m, $NCH_2C\underline{H}_2$); 0.96 (3H, t, *J* = 7.4, CH_3). Found, % : C 62.20; H 5.35; N 4.72. $C_{15}H_{15}NO_5$. Calculated, %: C 62.28; H 5.23; N 4.84.

1-Ethyl-4-methyl-2-oxo-1,2-dihydroquinoline-3-carboxylic Acid (1a). The 4-carboxymethyl acid **4a** (2.75 g: 0.01 mol) was maintained at 170°C for 10 min. Initially, brisk evolution of CO_2 was observed. The residue was cooled, cold alcohol (10-15 ml) was added, the mixture stirred thoroughly, and filtered. Compound **1a** (2.15 g: 93%) was obtained. Mp 180-182°C (from ethanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 13.39 (1H, br. s, COOH); 7.90 (1H, dd, *J* = 8.0 and *J* = 1.2, H-5); 7.68 (1H, td, *J* = 7.8 and *J* = 1.4, H-7); 7.61 (1H, d, *J* = 8.5, H-8); 7.33 (1H, td, *J* = 7.3 and *J* = 1.6, H-6); 4.29 (2H, q, *J* = 7.1, NCH_2); 2.44 (3H, s, 4-CH_3); 1.20 (3H, t, *J* = 7.0, $NCH_2C\underline{H}_3$). Found, %: C 67.67; H 5.56; N 6.13. $C_{13}H_{13}NO_3$. Calculated, %: C 67.52; H 5.67; N 6.06.

4-Methyl-2-oxo-1-propyl-1,2-dihydroquinoline-3-carboxylic Acid (1b) was obtained by an analogous procedure. Yield 90%. Mp 187-189°C (from ethanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 13.37 (1H, br. s, COOH); 7.90 (1H, dd, *J* = 7.9 and *J* = 1.2, H-5); 7.67 (1H, td, *J* = 7.6 and *J* = 1.4, H-7); 7.60 (1H, d, *J* = 8.5, H-8); 7.32 (1H, td, *J* = 7.3 and *J* = 1.4, H-6); 4.19 (2H, t, *J* = 7.7, NCH_2); 2.44 (3H, s, 4-CH_3); 1.62 (2H, m, $NCH_2C\underline{H}_2$); 0.94 (3H, t, *J* = 7.1, $NCH_2CH_2C\underline{H}_3$). Found, %: C 68.65; H 6.27; N 5.84. $C_{14}H_{15}NO_3$. Calculated, %: C 68.56; H 6.16; N 5.71.

X-Ray Crystallographic Investigation. Crystals of acid **1a** obtained from ethanol were monoclinic. At 20°C, *a* = 9.086(2), *b* = 14.270(4), *c* = 9.164(2) Å., β = 112.44(2)°, *V* = 1098.3(5) Å^3, d_{calc} = 1.398 g/cm^3, space group $P2_1/c$, M_r = 231.24, *Z* = 4, μ(MoKα) = 0.100 mm^{-1}, *F*(000) = 488. The parameters of the unit cell and the intensities of 2029 reflections (1917 were independent, R_{int} = 0.03) 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 with the SHELXTL set of programs [8]. The positions of the hydrogen atoms were revealed by an electron density difference synthesis and were refined with a rider model with $U_{iso} = nU_{eq}$ for a non-hydrogen atom bound to the given hydrogen (n = 1.5 for a methyl group and n = 1.2 for the remaining hydrogen atoms), with the exception of the $H_{(30)}$ atom which was refined isotropically. The structures were refined on F^2 by the full matrix least squares method in an anisotropic approximation for the non-hydrogen atoms to wR_2 = 0.141 on 1825 reflections (R_1 = 0.050 on 1299 reflections with $F > 4\sigma(F)$, S = 1.038). The full crystallographic information has been deposited in the Cambridge Structural Data Bank (deposit No. CCDC 283295). Interatomic distances and valence angles are given in Tables 1 and 2.

Ethyl Ester of 1-Ethyl-4-methyl-2-oxo-1,2-dihydroquinoline-3-carboxylic Acid (5a). Conc. H_2SO_4 (0.5 ml) was added to a solution of acid **1a** (2.31 g: mol) in alcohol (20 ml) and the mixture was boiled for 5 h. The reflux condenser was exchanged for a downward condenser and the ethanol was distilled off. The residue was cooled anddiluted with cold water. The separated solid ester **5a** was filtered off, washed with water, anddried. Yield was 2.45 g (95%). Mp 72-74°C (from aqueous ethanol).

A mixed melting point test with a sample of ester **5a**, obtained by the ethylation of the ethyl ester of 4-methyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid [2], gave no depression of melting point. The ^{1}H NMR spectra of these compounds were identical.

4-Methoxybenzylamide of 1-Ethyl-4-methyl-2-oxo-1,2-dihydroquinoline-3-carboxylic Acid (6a). Thionyl chloride (1.44 ml: 0.02 mol) was added to a solution of compound **1a** (2.31 g: 0.01 mol) in dry CCl_4 (20 ml) and the mixture was boiled with protection from air moisture until the end of HCl and SO_2 evolution (~2 h). The reflux condenser was exchanged for a downward condenser and the solvent and excess of $SOCl_2$ were distilled off (finally at reduced pressure). The residue (acid **1a** chloride) was dissolved in dry acetone (20 ml) and the solution obtained was addeddropwise with stirring and cooling to a mixture of 4-methoxybenzylamine (1.43 ml: 0.011 mol) and triethylamine (1.54 ml: 0.011 mol) in dry acetone (30 ml). After 3-4 h the reaction mixture was diluted with water and acidified with dilute (1 : 1) HCl to pH 4. The solid amide **6a** was filtered off, washed with cold water, anddried. Yield 3.26 g (93 %). Mp 165-167°C (from ethanol). ^{1}H NMR spectrum, δ, ppm (J, Hz): 8.72 (1H, t, J = 5.9, NH); 7.86 (1H, d, J = 8.0, H-5); 7.65 (1H, t, J = 8.1, H-7); 7.58 (1H, d, J = 8.6, H-8); 7.25-7.37 ((3H, m, H-6, 3', 5'); 6.89 (2H, d, J = 8.8, H-2', 6'); 4.37 (2H, d, J = 5.9, $NC\underline{H}_2$); 4.28 (2H, q, J = 7.1, $NC\underline{H}_2CH_3$); 3.73 (3H, s, OCH_3); 2.33 (3H, s, 4-CH_3); 1.21 (3H, t, J = 7.0, $NCH_2C\underline{H}_3$). Found, %: C 71.82; H 6.20; N 8.08. $C_{21}H_{22}N_2O_3$. Calculated, %: C 71.98; H 6.33; N 7.99.

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