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4-HYDROXY-2-QUINOLONES. 124*. SYNTHESIS AND STRUCTURE OF ETHYL 2-BROMOMETHYL-5-OXO-1,2,6,7,8,9-HEXAHYDRO-5H-OXAZOLO-[3,2-*a*]QUINOLINE-4-CARBOXYLATE

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The hydrogenation of the benzene part of the molecule in N-allyl-substituted 4-hydroxy-2-quinolinones does not affect the nature of their bromination by molecular bromine and gives 2-bromomethyl-5-oxo-1,2,6,7,8,9-hexahydro-5H-oxazolo[3,2-a]quinolines.

Keywords: oxazolo[3,2-*a*]quinolines, bromination, heterocyclization, X-ray analysis.

There are two principal reaction schemes [2] for the synthesis of 5-oxo-1,2-dihydro-5H-thiazolo[3,2-*a*]-quinoline-4-carboxylic derivatives **1** which are used in the treatment of bacterial and fungal infections. In both cases the starting compounds are arylaminomercaptomethylenemalonates which are prepared by the reaction of arylisothiocyanates with malonic ester. The first method then involves protection of the mercapto group, closing of the quinolone ring, removal of the protecting group, and use of ethylenedibromides with the 2-mercapto-quinolinones formed to construct the thiazoline fragment. On the other hand, in the second variant the thiazoline ring is formed first and only then the 3-aryl-1,3-thiazolidin-2-ylidenemalonates are condensed to the thiazolo[3,2-*a*]quinolines in PFA.

Unfortunately, in none of these methods is it possible to prepare the carbo, aza, or oxa biosteres of the thiazolo[3,2-*a*]quinolones **1** in which the sulfur atom can be exchanged for carbon, nitrogen, or oxygen respectively. The study of such compounds is undoubtedly of theoretical interest in establishing a structure activity relationship which is the basis of a purposeful search for novel biologically active materials. Hence it is not surprising that this omission was rectified before long and initially pyrrolo [3] and then imidazolo and oxazolo[3,2-*a*]quinoline(or related 1,8-naphthyridine)-4-carboxylic acids [4] were synthesized from ethyl 3-(2-chloroaryl)-3-oxopropionates. The novel scheme for constructing the azolo[3,2-*a*]quinoline systems proved generally acceptable since it also allowed the synthesis of thio analogs. None the less, with regard to the oxazolo[3,2-*a*]quinolines it could not be considered efficient since the yield in the key stage of quinolone ring closure occurred in only 35% yield.

* For Communication 123 see [1].

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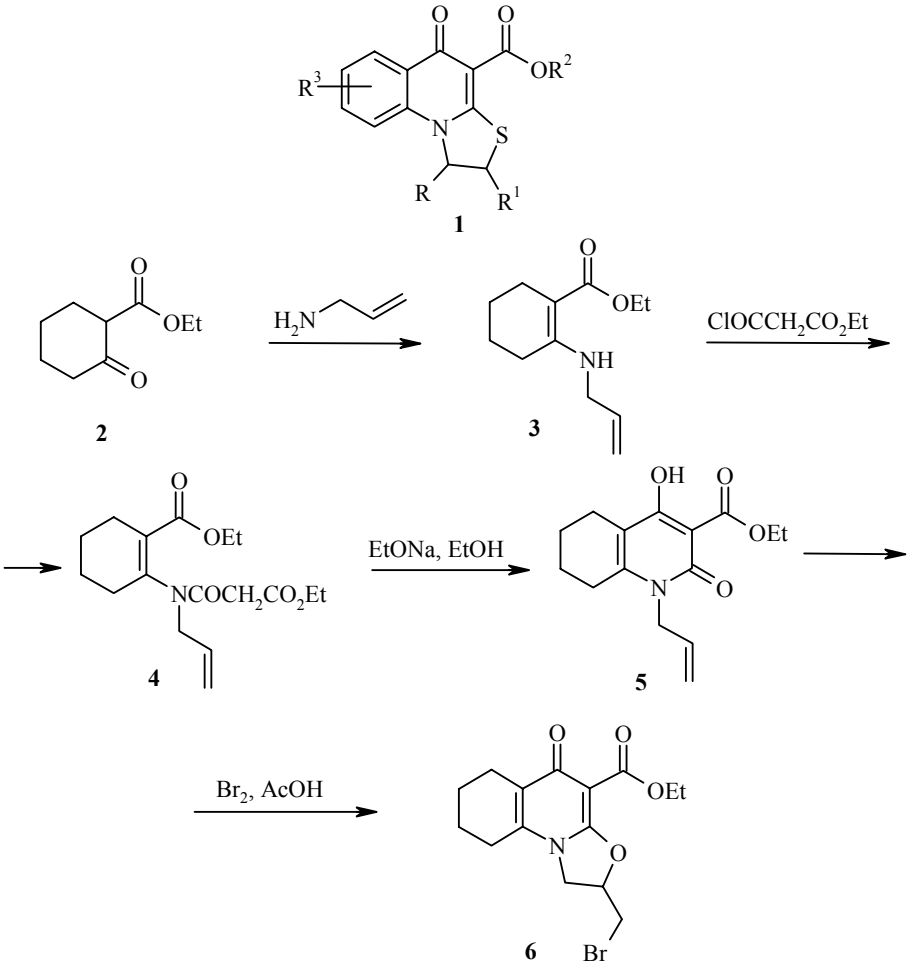
We have recently proposed a completely different route to the synthesis of oxazolo[3,2-*a*]quinoline-4-carboxylic acids which entails treatment of N-alkyl-substituted 4-hydroxy-2-oxo-1,2-dihydroquinolines with molecular bromine [5]. The main advantages of this method are the availability of the reagents used and the unusual simplicity of achieving high yields of the final products. With the aim of exploring the synthetic potential of this interesting reaction this report includes the area of 4-hydroxy-2-oxoquinolines which have been hydrogenated in the benzene part of the molecule. This synthetic scheme has repeatedly shown good results [6, 7]:



in which ethyl cyclohexanone-2-carboxylate **2** → enamine **3** → amide **4** → ethyl 1-allyl-4-hydroxy-2-oxo-1,2,5,6,7,8-hexahydroquinoline-3-carboxylate **5**. It was found that the reaction of ester **5** with molecular bromine does not basically differ from the bromination of the non-hydrogenated analog [5] and occurs just as readily and rapidly to give ethyl 2-bromomethyl-5-oxo-1,2,6,7,8,9-hexahydro-5H-oxazolo[3,2-*a*]quinoline-4-carboxylate (**6**).

According to X-ray analysis of this compound (Figure 1, Tables 1, 2) the pyridine ring and the $C_{(2)}$, $C_{(5)}$, $C_{(11)}$, $O_{(1)}$, and $O_{(2)}$ atoms lie in a single plane to an accuracy of 0.01 Å. As in the similar structures oxazolo-[3,2-*a*]pyridin-6-one [8], and 2-methylene or 2-bromomethyl-5-oxo-1,2-dihydro-5H-oxazolo[3,2-*a*]quinoline-4-carboxylates [5] the molecule of ester **6** shows a lengthening of the $O_{(2)}$–$C_{(7)}$ 1.260(5) and $C_{(8)}$–$C_{(9)}$ 1.377(6) Å bonds when compared with their mean values [9] of 1.210 and 1.326 Å respectively together with shortening of the $C_{(9)}$–$O_{(1)}$ 1.331(5) (mean value 1.354) and $N_{(1)}$–$C_{(9)}$ 1.340(6) (1.355 Å) bonds and this can be explained by configurational interactions between the π-donor fragment $N_{(1)}$–$C_{(9)}$–$O_{(1)}$ and π-acceptor carbonyl group $C_{(7)}$–$O_{(2)}$.

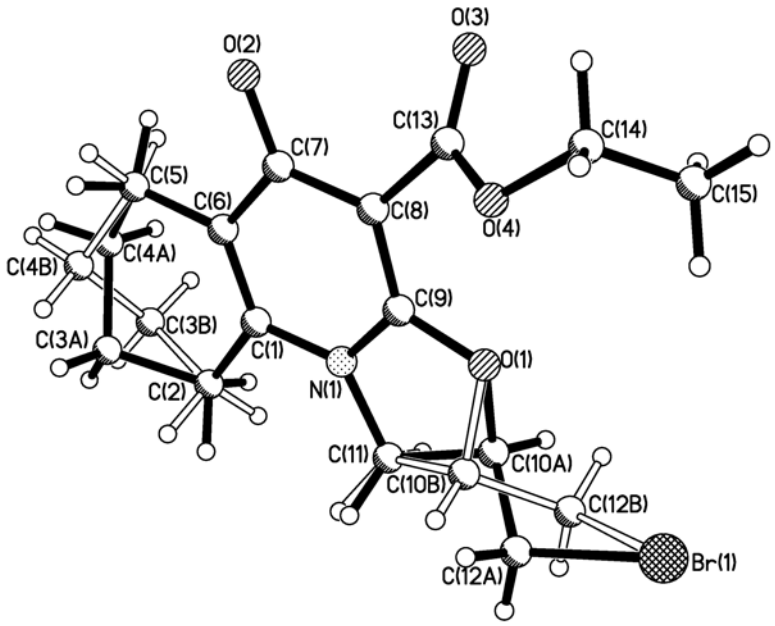


Fig. 1. Structure of the ester **6** molecule with atomic numbering.

The molecule of ester **6** is disordered into two conformations **A** and **B** in the ratio 66: 34% respectively which differ in the spatial structure of the hydroquinoline and oxazole fragments in the molecule. The tetrahydro ring in both conformations occurs as a *half chair* (folding parameters [10]: $S = 0.79$, $\theta = 34.4^\circ$, $\Psi = 29.9^\circ$ for **A** and $S = 0.88$, $\theta = 35.2^\circ$, $\Psi = 24.9^\circ$ in **B**). The deviation of atoms $C_{(3)}$ and $C_{(4)}$ from the mean plane of the remaining atoms is 0.39 and -0.37 Å in **A** and -0.52 and 0.35 Å in **B**). The oxazole ring is disordered into two *envelope* conformations. Atom $C_{(10)}$ deviates from the mean plane of the remaining ring atoms by -0.26 Å in **A** and 0.44 Å

TABLE 1. Bond Lengths (*l*) in the Ester **6** Structure

Bond	*l*, Å	Bond	*l*, Å
$Br_{(1)}–C_{(12A)}$	1.92(1)	$Br_{(1)}–C_{(12B)}$	1.93(1)
$N_{(1)}–C_{(9)}$	1.340(6)	$N_{(1)}–C_{(1)}$	1.379(6)
$N_{(1)}–C_{(11)}$	1.464(5)	$O_{(1)}–C_{(9)}$	1.331(5)
$O_{(1)}–C_{(10B)}$	1.474(9)	$O_{(1)}–C_{(10A)}$	1.481(7)
$O_{(2)}–C_{(7)}$	1.260(5)	$O_{(3)}–C_{(13)}$	1.207(6)
$O_{(4)}–C_{(13)}$	1.324(6)	$O_{(4)}–C_{(14)}$	1.464(7)
$C_{(1)}–C_{(6)}$	1.351(6)	$C_{(1)}–C_{(2)}$	1.500(6)
$C_{(2)}–C_{(3B)}$	1.532(9)	$C_{(2)}–C_{(3A)}$	1.542(8)
$C_{(3A)}–C_{(4A)}$	1.526(8)	$C_{(4A)}–C_{(5)}$	1.532(8)
$C_{(10A)}–C_{(12A)}$	1.521(9)	$C_{(10A)}–C_{(11)}$	1.529(8)
$C_{(3B)}–C_{(4B)}$	1.53(1)	$C_{(4B)}–C_{(5)}$	1.53(1)
$C_{(10B)}–C_{(11)}$	1.538(9)	$C_{(10B)}–C_{(12B)}$	1.540(9)
$C_{(5)}–C_{(6)}$	1.492(7)	$C_{(6)}–C_{(7)}$	1.470(6)
$C_{(7)}–C_{(8)}$	1.426(7)	$C_{(8)}–C_{(9)}$	1.377(6)
$C_{(8)}–C_{(13)}$	1.484(6)	$C_{(14)}–C_{(15)}$	1.38(1)

TABLE 2. Valence Angles (ω) in the Ester **6** Structure

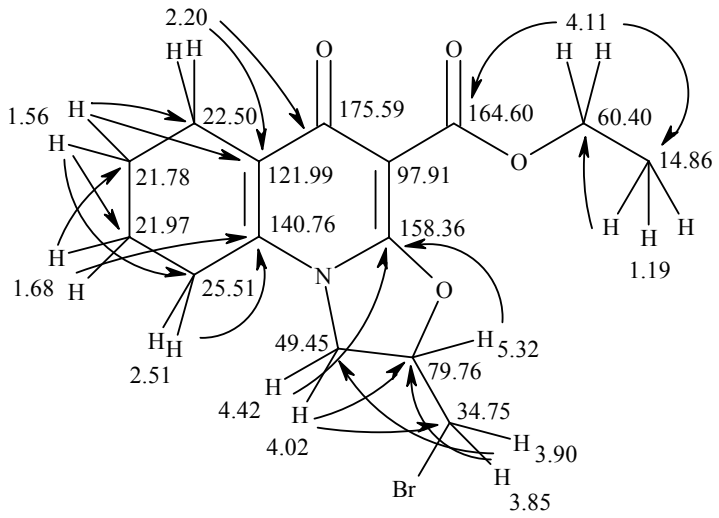
Angle	ω, deg	Angle	ω, deg
$C_{(9)}$–$N_{(1)}$–$C_{(1)}$	122.3(3)	$C_{(9)}$–$N_{(1)}$–$C_{(11)}$	110.8(4)
$C_{(1)}$–$N_{(1)}$–$C_{(11)}$	126.8(4)	$C_{(9)}$–$O_{(1)}$–$C_{(10B)}$	106.8(4)
$C_{(9)}$–$O_{(1)}$–$C_{(10A)}$	109.1(4)	$C_{(13)}$–$O_{(4)}$–$C_{(14)}$	118.9(5)
$C_{(6)}$–$C_{(1)}$–$N_{(1)}$	119.7(4)	$C_{(6)}$–$C_{(1)}$–$C_{(2)}$	124.3(4)
$N_{(1)}$–$C_{(1)}$–$C_{(2)}$	116.0(4)	$C_{(1)}$–$C_{(2)}$–$C_{(3B)}$	109.7(9)
$C_{(1)}$–$C_{(2)}$–$C_{(3A)}$	112.2(5)	$C_{(4A)}$–$C_{(3A)}$–$C_{(2)}$	109.0(7)
$C_{(3A)}$–$C_{(4A)}$–$C_{(5)}$	110.6(7)	$O_{(1)}$–$C_{(10A)}$–$C_{(12A)}$	105.6(6)
$O_{(1)}$–$C_{(10A)}$–$C_{(11)}$	103.1(5)	$C_{(12A)}$–$C_{(10A)}$–$C_{(11)}$	110.0(7)
$C_{(10A)}$–$C_{(12A)}$–$Br_{(1)}$	112.5(7)	$C_{(4B)}$–$C_{(3B)}$–$C_{(2)}$	106(2)
$C_{(3B)}$–$C_{(4B)}$–$C_{(5)}$	109(1)	$O_{(1)}$–$C_{(10B)}$–$C_{(11)}$	103.0(6)
$O_{(1)}$–$C_{(10B)}$–$C_{(12B)}$	104.1(9)	$C_{(11)}$–$C_{(10B)}$–$C_{(12B)}$	112.6(9)
$C_{(10B)}$–$C_{(12B)}$–$Br_{(1)}$	109.0(8)	$C_{(6)}$–$C_{(5)}$–$C_{(4B)}$	111(1)
$C_{(6)}$–$C_{(5)}$–$C_{(4A)}$	113.3(5)	$C_{(1)}$–$C_{(6)}$–$C_{(7)}$	119.9(4)
$C_{(1)}$–$C_{(6)}$–$C_{(5)}$	121.2(4)	$C_{(7)}$–$C_{(6)}$–$C_{(5)}$	118.9(4)
$O_{(2)}$–$C_{(7)}$–$C_{(8)}$	122.9(4)	$O_{(2)}$–$C_{(7)}$–$C_{(6)}$	119.4(4)
$C_{(8)}$–$C_{(7)}$–$C_{(6)}$	117.7(4)	$C_{(9)}$–$C_{(8)}$–$C_{(7)}$	118.3(4)
$C_{(9)}$–$C_{(8)}$–$C_{(13)}$	120.4(4)	$C_{(7)}$–$C_{(8)}$–$C_{(13)}$	121.3(4)
$O_{(1)}$–$C_{(9)}$–$N_{(1)}$	111.8(3)	$O_{(1)}$–$C_{(9)}$–$C_{(8)}$	126.2(4)
$N_{(1)}$–$C_{(9)}$–$C_{(8)}$	122.0(4)	$N_{(1)}$–$C_{(11)}$–$C_{(10A)}$	102.4(4)
$N_{(1)}$–$C_{(11)}$–$C_{(10B)}$	99.6(5)	$O_{(3)}$–$C_{(13)}$–$O_{(4)}$	124.0(5)
$O_{(3)}$–$C_{(13)}$–$C_{(8)}$	123.4(5)	$O_{(4)}$–$C_{(13)}$–$C_{(8)}$	112.6(4)
$C_{(15)}$–$C_{(14)}$–$O_{(4)}$	112.3(6)		

in **B**. In both conformers the bromomethyl group has a pseudoequatorial orientation (torsional angle $C_{(9)}$–$O_{(1)}$–$C_{(10)}$–$C_{(12)}$ -132.2(7) in **A** and 144.7(8)º in **B**). The bromine atom is not disordered and occurs in +*sc*- and -*sc*-conformations relative to the $O_{(1)}$–$C_{(10)}$ bond (torsional angle $O_{(1)}$–$C_{(10)}$–$C_{(12)}$–$Br_{(1)}$ -73.6(8) in **A** and 80(1)º in **B**). The ester molecule **6** shows shortened intramolecular contacts between the atoms of the five membered heterocycle and the cyclohexene ring: $H_{(2a)}\cdots C_{(11)}$ 2.65 Å (sum of van der Waal radii 2.87 Å [11]) and $H_{(2d)}\cdots C_{(11)}$ 2.59 (2.87 Å).

The ester substituent is not coplanar with the plane of the pyridone ring (torsional angle $C_{(9)}$–$C_{(8)}$–$C_{(13)}$–$O_{(3)}$ 136.1(5)º. The ethyl group occurs in an ap conformation relative to the $C_{(8)}$–$C_{(13)}$ bond and the $C_{(14)}$–$C_{(15)}$ bond is virtually perpendicular to the $C_{(13)}$–$O_{(4)}$ bond (torsional angles $C_{(8)}$–$C_{(13)}$–$O_{(4)}$–$C_{(14)}$ 172.6(5), $C_{(13)}$–$O_{(4)}$–$C_{(14)}$–$C_{(15)}$ -97.7(8)º). A shortening of the $H_{(14a)}\cdots O_{(3)}$ contact is seen 2.37 (2.46 Å).

Shortened intermolecular contacts are seen in the crystal of ester **6**: $H_{(12a)}\cdots O_{(2')}$ (-*x*, -0.5+*y*, 1.5-*z*) 2.50 (2.46), $H_{(12d)}\cdots O_{(2')}$ (-*x*, -0.5+y, 1.5-*z*) 2.25 (2.46), and $Br_{(1)}\cdots H_{(3bb')}$ (1+*x*, *y*, *z*) 3.03 (3.23 Å).

Ester **6** also undoubtedly presents interest for NMR spectroscopy. It is clear that an unambiguous resolution of this structure was not possible without the use of special NMR methods hence we undertook the structural investigation of the compound using ^{13}C-^{1}H heteronuclear spectroscopy. On the one hand this allowed us to make reliable signal assignments in the carbon spectrum and on the other to confirm the stability of the structure of the compound studied when in solution. We have used HMQC spectra for assignment of the protonated carbon atoms which reveals the ^{13}C-^{1}H spin spin interactions through one bond. The HMBC method was used to interpret the signals of the quaternary carbon atoms and this revealed the ^{13}C-^{1}H spin spin interactions through 2-3 chemical bonds. The most important HMBC correlations and signal assignments thus made in the carbon spectrum of ester **6** are presented in the Scheme.



We turned first to the many correlations for the cyclohexene ring protons with the neighboring carbon atoms. This enables a safe assignment of all of the aliphatic carbon atoms despite their closeness in the spectrum. In addition, correlation between the signal for the 6-CH_2 group protons and the carbon atom at 175.59 ppm permits assignment of the latter signal to the $C_{(5)}$ carbonyl group. Similarly, correlation of the 9-CH_2 proton signal with chemical shift of 2.51 ppm with the carbon signal at 140.76 ppm leads to its assignment as the junction atom $C_{(9a)}$. A further junction atom $C_{(5a)}$ is also assigned on the basis of its correlation with the proton signal for the 6-CH_2 group.

The presence of the oxazolidine ring is confirmed by correlations of the signals of the 1-CH_2 and H-2 protons with the $C_{(3a)}$ atom at 158.36 ppm. The only carbon atom for which a correlation with protons signals was not observed is the peak at 97.91 ppm and this can be assigned to the $C_{(4)}$ atom by the exclusion method. It should be noted that the latter carbon atom is characterised by a carbon chemical shift which is at higher field than other olefinic carbon atoms. This is associated with the localization of negative charge on it via the conjugative effect of the two adjacent carbonyl groups. The full list of correlations found is given in Table 3.

TABLE 3. Full List of Heterocyclic Correlations found for Ester **6**

δ, ppm	HMQC	HMBC
5.32	79.76	158.36
4.42	49.45	34.75; 158.36; 79.76
4.11	60.40	164.60; 14.86
4.02	49.45	34.75; 79.76; 158.36
3.90	34.75	79.76; 49.45
3.85	34.75	79.76; 49.45
2.51	25.51	140.76; 121.99; 21.78
2.20	22.50	140.76; 121.99; 21.97; 175.59
1.68	21.97	140.76; 21.97
1.56	21.78	121.99; 21.97; 25.51
5.32	14.86	60.40

EXPERIMENTAL

The ^{1}H NMR spectrum of ester **5** was recorded on a Varian Mercury VX-200 (200 MHz) instrument. The ^{1}H and ^{13}C NMR spectra of the oxazoloquinoline **6** and the heteronuclear HMQC and HMBC experiments were recorded on a Varian Mercury-400 (400 and 100 MHz respectively) spectrometer. All of the two dimensional experiments were carried out with gradient selection of useful signals. The mixing time in the pulse sequences were $^1J_{CH}$ = 140 and $^{2,3}J_{CH}$ = 8 Hz respectively. 128 increments were used in the HMQC and 400 in the HMBC experiments. In all cases the solvent was DMSO-d_6 and the internal standard was TMS. Commercial ethyl cyclohexanone-2-carboxylate and allylamine from the Fluka company were used.

Ethyl 1-Allyl-4-hydroxy-2-oxo-1,2,5,6,7,8-hexahydroquinoline-3-carboxylate (5). Ethyl cyclohexanone-2-carboxylate (13.8 ml, 0.1 mol) and allylamine (11.3 ml, 0.15 mol) were mixed. The reaction mixture heated markedly and became turbid due to the water evolved. Stirring was continued for 5 h at 45ºC, hexane (30 ml) was added, and the product was transferred to a separating funnel and left at room temperature for 8-10 h. The aqueous layer was separated and the excess hexane and allylamine were removed *in vacuo*. The residue (technical enamine **3**) was dissolved in methylene chloride (100 ml) and triethylamine (15.4 ml, 0.11 mol) was added. Ethoxymalonyl chloride (16.6 g, 0.11 mol) was added with cooling and stirring and the product was allowed to stand for 4-5 h at room temperature. The product was diluted with water and the organic layer was separated and dried with anhydrous $CaCl_2$. Solvent was removed (at the end *in vacuo*). The residue (diester **4**) was treated with a solution of sodium ethylate (prepared from metallic sodium (3.45 g, 0.15 mol) and absolute ethanol (100 ml)), refluxed for 30 min on a water bath, after which heating was stopped and the product was left for 7-8 h at room temperature. The reaction mixture was diluted with water and acidified with dilute HCl (1:1) to pH 4.5-5. The precipitated ester **5** was filtered off, washed with cold water, and dried. Yield 21.6 g (78%); mp 107-109ºC (ether). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 13.43 (1H, s, OH); 5.85 (1H, m, C<u>H</u>=CH$_2$); 5.08 (1H, dd, *J* = 10.0, 1.5, NCH$_2$CH=C<u>H</u>$_{cis}$); 4.90 (1H, dd, *J* = 17.0, 1.5, NCH$_2$CH=C<u>H</u>$_{trans}$); 4.56 (2H, d, *J* = 4.5, NCH$_2$); 4.28 (2H, q, *J* = 7.2, OCH$_2$); 2.65 (2H, m, 8-CH$_2$); 2.37 (2H, m, 5-CH$_2$); 1.64 (4H, d, 6,7-CH$_2$); 1.27 (3H, t, *J* = 7.1, CH$_3$). Found, %: C 64.85; H 6.77; N 5.01. $C_{15}H_{19}NO_4$. Calculated, %: C 64.97; H 6.91; N 5.05.

Ethyl 2-Bromomethyl-5-oxo-1,2,6,7,8,9-hexahydro-5H-oxazolo[3,2-a]quinoline-4-carboxylate (6). Bromine (0.52 ml, 0.01 mol) was added with vigorous stirring to a solution of compound **5** (2.77 g, 0.01 mol) in acetic acid (15 ml). The reaction mixture was diluted with water. The precipitate was filtered off, washed with cold water, and dried. Yield 3.20 g (90%); mp 241-243ºC (ethanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 5.32 (1H, m, C<u>H</u>CH$_2$Br); 4.42 (1H, t, *J* = 9.4, NCH); 4.11 (2H, q, *J* = 7.1, COOCH$_2$); 4.02 (1H, dd, *J* = 10.3, 6.7, NCH); 4.11 (2H, q, *J* = 7.1, COOCH$_2$); 4.02 (1H, dd, *J* = 10.3, 6.7, NCH); 3.92 (1H, dd, *J* = 11.2, 4.4, CHBr); 3.84 (1H, dd, *J* = 11.2, 4.9, CHBr); 2.51 (2H, m, 6-CH$_2$); 2.20 (2H, m, 9-CH$_2$); 1.68 (2H, m, 7-CH$_2$); 1.56 (2H, m, 8-CH$_2$); 1.19 (3H, t, *J* = 7.5, COOCH$_2$C<u>H</u>$_3$). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 175.59 (C$_{(5)}$); 164.60 (COO); 158.36 (C$_{(3a)}$); 140.76 (C$_{(9a)}$); 121.99 (C$_{(5a)}$); 97.91 (C$_{(4)}$); 79.76 (C$_{(2)}$); 60.40 (OCH$_2$); 49.45 (C$_{(1)}$); 34.75 (CH$_2$Br); 25.51 (C$_{(6)}$); 22.50 (C$_{(9)}$); 21.97 (C$_{(7)}$); 21.78 (C$_{(8)}$); 14.86 (CH$_3$). Found, %: C 50.67; H 5.20; N 3.85. $C_{15}H_{18}BrNO_4$. Calculated, %: C 50.58; H 5.09; N 3.93.

X ray Structural Analysis. Crystals of ester **6** are monoclinic (from ethanol), at 20ºC: *a* = 11.553(1), *b* = 16.443(1), *c* = 8.185(1) Å, β = 101.30(1)º, *V* = 1524.7(3) Å^3, M_r = 356.21; *Z* = 4, space group $P2_1/c$, d_{calc} = 1.552 g/cm^3, μ(MoKα) = 2.711 mm^{-1}, *F*(000) = 728. The unit cell parameters and intensities of 12058 reflections (2685 independent with R_{int} = 0.070) were measured on an Xcalibur-3 diffractometer (MoKα radiation, CCD detector, graphite monochromator, ω-scanning to $2\theta_{max}$ = 50º). The absorption was included analytically (T_{min} = 0.452, T_{max} = 0.806).

The structure was solved by a direct method using the SHELXTL program package [12]. For refinement of the structure limits were placed on the bond lengths of O–C$_{sp3}$ 1.44 and C$_{sp3}$–C$_{sp3}$ 1.54 Å. The positions of the hydrogen atoms were revealed from electron density difference synthesis and refined using the "riding" model

with $U_{iso} = nU_{eq}$ for a non-hydrogen atom bonded to the given hydrogen (n = 1.5 for a methyl and 1.2 for the remaining hydrogen atoms). The structure was refined in F^2 full matrix least squares analysis in the anisotropic approximation for non-hydrogen atoms with wR_2 = 0.168 for 2633 reflections (R_1 = 0.069 for 1855 reflections with $F>4\sigma(F)$, S = 1.118). The complete crystallographic information has been placed in the Cambridge structural data bank, reference CCDC 604005.

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