Chemistry of Heterocyclic Compounds, Vol. 43, No. 10, 2007

4-HYDROXY-2-QUINOLONES 129*. SYNTHESIS AND STRUCTURE OF 2-BROMOMETHYL-4-CARBOXY-5-METHYL-1,2-DIHYDROOXAZOLO-[3,2-*a*]QUINOLINIUM BROMIDE

I. V. Ukrainets[1], N. L. Bereznyakova[1], V. A. Parshikov[1], and A. V. Turov[2]

By analogy with the 4-hydroxy derivatives, the bromination of N-allyl-4-methyl-2-oxo-1,2-dihydro-quinoline-3-carboxylic acid leads to the closure of a five membered oxazole ring but, in contrast, it forms the 2-bromomethyl-4-carboxy-5-methyl-1,2-dihydrooxazolo[3,2-a]quinolinium bromide salt.

Keywords: oxazolo[3,2-*a*]quinoline-4-carboxylic acid, bromination, heterocyclization, X-ray structural analysis.

The ability of N-allyl-substituted 4-hydroxy-2-oxo-1,2-dihydroquinolines and pyridines to undergo cyclization to 2-bromomethyl-5-oxo-1,2-dihydro-5H-oxazolo[3,2-*a*]aza heterocycles when brominated by molecular bromine is based on their potential to exist in the highly nucleophilic bipolar mesomeric 1,4-dihydro forms [1-3]. Indeed, thanks to this, at the final stage there occurs not the usual addition of remaining bromide ion to the positively charged $C_{(2)}$ atom of the former allyl fragment but rather closure of an oxazole ring involving the neighboring O-anionic center.

Continuing our examination of the synthetic potential of this reaction we have now studied the bromination of 1-allyl-4-methyl-2-oxo-dihydroquinoline-3-carboxylic acid (**1**). The interest in this study is mainly due to the fact that the 4-methyl-substituted acid **1** cannot undergo keto-enol tautomerism because of its structure. For this reason the formation of 1,4-dihydro forms making possible the heterocyclization seen in the case of the 4-hydroxy analogs cannot occur hence the reaction with bromine must occur somewhat differently.

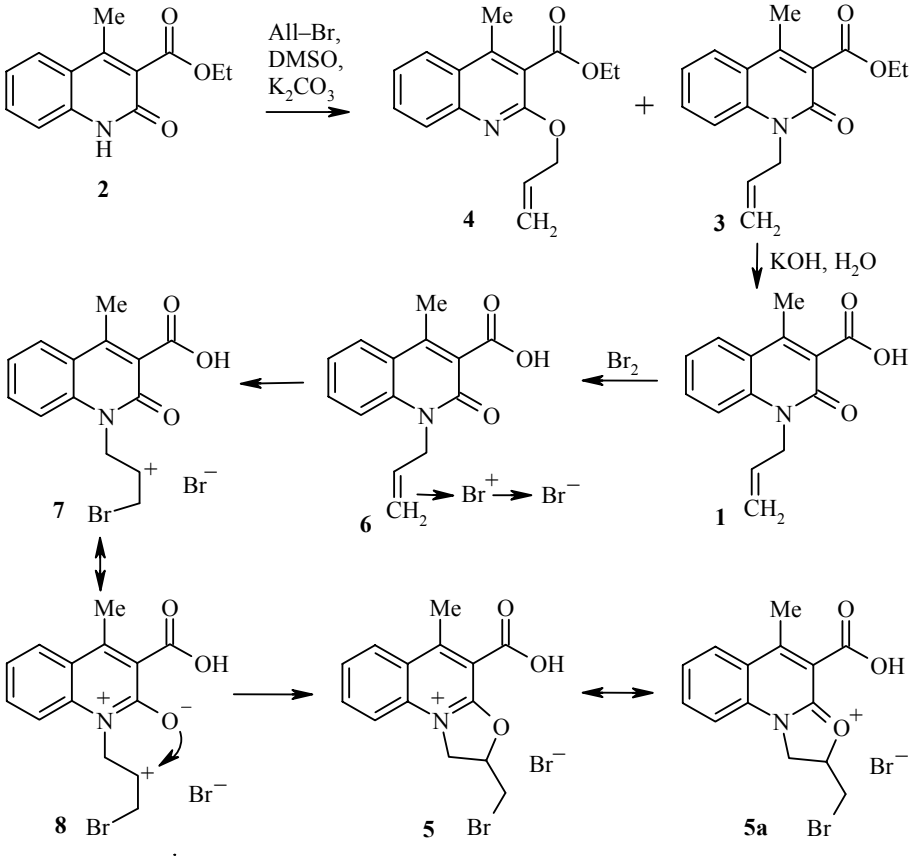
The starting acid **1** was prepared by the alkylation of the ethyl ester **2** by allyl bromide in the system $DMSO/K_2CO_3$ with subsequent basic hydrolysis to the N-allyl derivative **3**. The side O-allyl isomer **4** is formed in only 5% yield under these conditions. Bromination of acid **1** was carried out under standard conditions using molecular bromine in glacial acetic acid solution.

* For Communication 128 see [1].

[1]National University of Pharmacy, Kharkiv 61002, Ukraine; e-mail: uiv@kharkov.ua. [2]Taras Shevchenko National University, Kiev 01033, Ukraine; e-mail: nmrlab@univ.kiev.ua. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1496-1502, October, 2007. Original article submitted June 25, 2006.

0009-3122/07/4310-1269

For an unambiguous answer, the structure of the compound obtained was studied by X-ray analysis which showed it to be 2-bromomethyl-4-carboxy-5-methyl-1,2-dihydrooxazolo[3,2-*a*]quinolinium bromide (**5**). In the independent part of the unit cell this compound has a positively charged 2-bromomethyl-4-carboxy-5-methyl-1,2-dihydrooxazol[3,2-*a*]quinolinium molecule and a Br^- anion (see Figure 1).



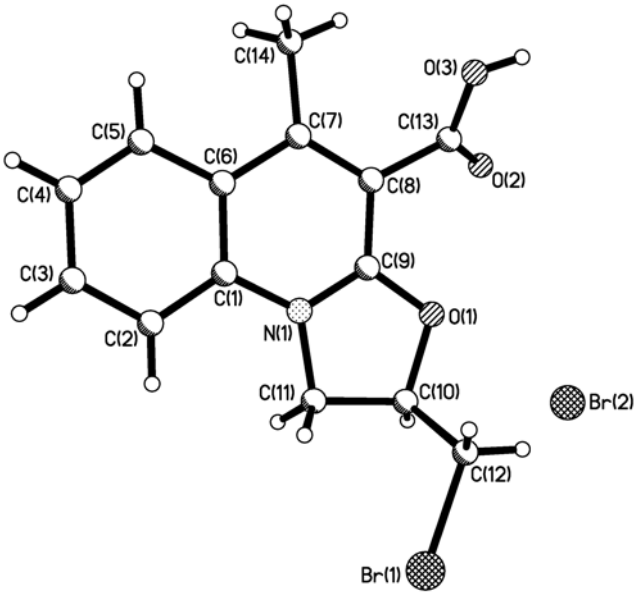


Fig. 1. Structure of the oxazoloquinolinium bromide **5** with atomic numbering.

The tricyclic fragment and the atoms $C_{(13)}$ and $C_{(14)}$ of the organic cation lie in a single plane to an accuracy of 0.02 Å, despite the presence of shortened intramolecular contacts $H_{(2)}\cdots C_{(11)}$ 2.64 (sum of van der Waal radii 2.87 [4]), $H_{(5)}\cdots C_{(14)}$ 2.55 (2.87), $H_{(5)}\cdots H_{(14c)}$ 2.20 (2.34), $H_{(14c)}\cdots C_{(5)}$ 2.69 (2.87), and $H_{(14a)}\cdots C_{(13)}$ 2.62 (2.87 Å). The $N_{(1)}$–$C_{(9)}$ 1.31(1) and $O_{(1)}$–$C_{(9)}$ 1.34(1) bond lengths are somewhat shortened when compared with their mean values of 1.355 and 1.370 Å [5] because the structure can be represented as a resonance hybrid of the two canonical structures **5** and **5a**.

The carboxyl group at the $C_{(8)}$ atom is twisted relative to the plane of the tricyclic fragment (torsional angle $C_{(9)}$–$C_{(8)}$–$C_{(13)}$–$O_{(2)}$ 43(1)º), very likely due to the repulsions between the methyl and carboxyl groups (shortened intramolecular contact $H_{(14a)}\cdots O_{(3)}$ 2.35 (2.46 Å)). This position for the carboxyl group is stabilized by an intermolecular hydrogen bond $O_{(3)}$–$H_{(O3)}\cdots Br_{(2')}$ (0.5+*x*, 0.5-*y*, -0.5+*z*) H···Br' 2.32 Å, O–H···Br' 168º. The bromomethyl substituent on atom $C_{(10)}$ occupies an equatorial position (torsional angle $C_{(12)}$–$C_{(10)}$–$C_{(11)}$–$N_{(1)}$ 119.2(7)º) and the bromine atom is found in an +*sc* configuration relative to the $C_{11)}$–$C_{10)}$ bond (torsional angle $C_{(11)}$–$C_{(10)}$–$C_{(12)}$–$Br_{(1)}$ 60.1(8)º). There is a shortened intramolecular contact $H_{(11b)}\cdots Br_{(1)}$ of 2.87 Å (3.23 Å).

In the crystal the oxazoloquinolinium bromide **5** forms stacks along the crystallographic (1 0 0) axis and are bonded with the bromine atoms by weak intermolecular hydrogen bonds $C_{(4)}$–$H_{(4)}\cdots Br_{(1')}$ (0.5-*x*, 0.5+*y*, 1.5-*z*) H···Br' 3.06 Å, C–H···Br' 3.06 Å, C–H···Br' 163º, $C_{(5)}$–$H_{(5)}\cdots Br_{(2')}$ (0.5-*x*, 0.5+*y*, 0.5-*z*) H···Br' 2.78 Å, C–H···Br' 166º, $C_{(11)}$–$H_{(11b)}\cdots Br_{(2')}$ (-0.5+*x*, 0.5-*y*, 0.5+*z*) H···Br' 2.92 Å, C–H…Br' 151º, $C_{(12)}$–$H_{(12a)}\cdots Br_{(2')}$ (0.5+*x*, 0.5-*y*, 0.5+*z*) H···Br' 2.89 Å, C–H···Br' 149º. The crystal also shows the shortened intermolecular contacts $H_{(14b)}\cdots C_{(3')}$ (1-*x*, 1-*y*, 1-*z*) 2.79 (2.87), $H_{(14b)}\cdots C_{(4')}$ (1-*x*, 1-*y*, 1-*z*) 2.76 (2.87), $H_{(14c)}\cdots C_{(3')}$ (-*x*, 1-*y*, 1-*z*) 2.79 (2.87), $H_{(11b)}\cdots Br_{(2)}$ (0.5+*x*, 0.5-*y*, 0.5+*z*) 3.15 (3.23), $Br_{(1)}\cdots Br_{(2')}$ (*x*, *y*, 1+*z*) 3.69 Å (3.94 Å).

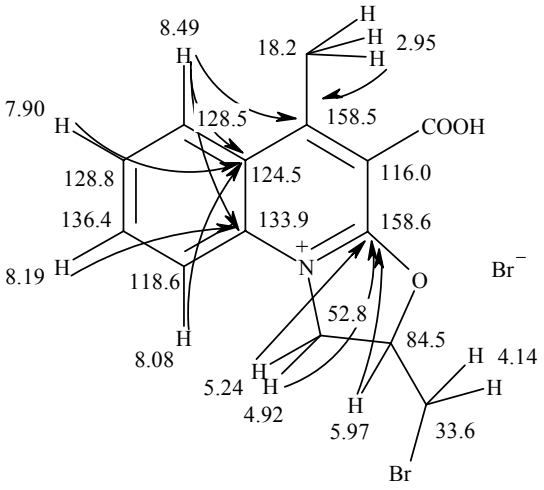
The structure of the oxazoloquinolinium bromide **5** was also investigated by correlation NMR spectroscopy. Recording of the COSY spectra permitted reliable assignments in the proton spectrum and the measurement of spectra with heteronuclear correlation *via* one bond (HMQC) and through 2-3 chemical bonds (HMBC) allowed us to assign the signals in the carbon spectrum of the compound. Table 1 lists all of the heteronuclear correlations found for this compound.

The assignments of signals in the proton and carbon spectra of compound **5** are given below. Important correlations in the HMBC spectra are indicated by arrows and serve as the basis for these signal assignments.

A particular feature of the ^{13}C NMR spectrum of compound **5** was the fact that the chemical shifts of the $C_{(3a)}$ and $C_{(5)}$ carbon atoms are extremely similar. Both of them absorb at 158.6 ppm with hardly any difference in chemical shifts. However, the assignment of these signals follows from the presence of a correlation for atom $C_{(3a)}$ with the proton signals of the oxazoline ring and for $C_{(5)}$ with the signal for the methyl group protons and H-6 (which are respectively 2 and 3 chemical bonds distant from the $C_{(5)}$ atom).

TABLE 1. Heteronuclear ^{1}H–^{13}C Correlations found for the Oxazoloquinolinium Bromide **(5)**

δ, ppm	HMQC	HMBC
8.49	128.5	136.4; 133.9; 124.5; 158.5
8.19	136.4	133.9; 128.5; 124.5
8.08	118.6	136.4; 128.8; 124.5
7.90	128.8	136.4; 133.9; 128.8; 124.5; 118.6
5.97	84.5	158.6
5.24	52.8	158.6; 84.5; 33.6
4.92	52.8	158.6; 84.5; 33.6
4.14	33.6	84.5; 52.8
2.95	18.2	158.5; 124.5; 116.0



Hence the work carried out allows us to state that the impossibility of some N-allyl-1,2-dihydro-2-quinolinones to exist as a 1,4-dihydro form does not hinder their heterocyclization.

In these examples the initial stages of the bromination have the general features shown by alkenes: allyl derivative **1** → π- complex **6** → secondary carbocation **7**. However, in contrast to 4-hydroxy-2-quinolinones, the resultant cyclization becomes possible due to the presence noted by us previously [6] of a significant contribution to the resonance hybrid of similar compounds with quite differently structured aromatic bipolar forms. Hence in the intermediates of type **8** the quaternary nitrogen does not take part in further reactions and the final product can only be an overall neutral oxazoloquinolinium bromide.

TABLE 2. Bond Lengths (*l*) in the Oxazoloquinolinium Bromide Structure **(5)**

Bond	*l*, Å	Bond	*l*, Å	Bond	*l*, Å
$Br_{(1)}$–$C_{(12)}$	1.956(9)	$C_{(6)}$–$C_{(7)}$	1.45(1)	$O_{(3)}$–$C_{(13)}$	1.32(1)
$N_{(1)}$–$C_{(1)}$	1.38(1)	$C_{(7)}$–$C_{(14)}$	1.49(1)	$C_{(1)}$–$C_{(6)}$	1.41(1)
$O_{(1)}$–$C_{(9)}$	1.34(1)	$C_{(8)}$–$C_{(13)}$	1.51(1)	$C_{(3)}$–$C_{(4)}$	1.39(1)
$O_{(2)}$–$C_{(13)}$	1.212(9)	$C_{(10)}$–$C_{(11)}$	1.55(1)	$C_{(5)}$–$C_{(6)}$	1.43(1)
$C_{(1)}$–$C_{(2)}$	1.40(1)	$N_{(1)}$–$C_{(9)}$	1.31(1)	$C_{(7)}$–$C_{(8)}$	1.39(1)
$C_{(2)}$–$C_{(3)}$	1.40(1)	$N_{(1)}$–$C_{(11)}$	1.47(1)	$C_{(8)}$–$C_{(9)}$	1.41(1)
$C_{(4)}$–$C_{(5)}$	1.34(1)	$O_{(1)}$–$C_{(10)}$	1.485(9)	$C_{(10)}$–$C_{(12)}$	1.49(1)

TABLE 3. Valence Angles (ω) in the Oxazoloquinolinium Bromide Structure **(5)**

Angle	ω,deg	Angle	ω, deg	Angle	ω, deg
$C_{(9)}$–$N_{(1)}$–$C_{(1)}$	122.1(7)	$O_{(1)}$–$C_{(9)}$–$C_{(8)}$	122.8(7)	$C_{(5)}$–$C_{(6)}$–$C_{(7)}$	122.3(7)
$C_{(1)}$–$N_{(1)}$–$C_{(11)}$	125.8(7)	$O_{(1)}$–$C_{(10)}$–$C_{(11)}$	104.4(6)	$C_{(8)}$–$C_{(7)}$–$C_{(14)}$	124.5(7)
$N_{(1)}$–$C_{(1)}$–$C_{(2)}$	120.4(7)	$N_{(1)}$–$C_{(11)}$–$C_{(10)}$	101.5(6)	$C_{(7)}$–$C_{(8)}$–$C_{(9)}$	117.6(7)
$C_{(2)}$–$C_{(1)}$–$C_{(6)}$	122.0(7)	$O_{(2)}$–$C_{(13)}$–$O_{(3)}$	126.2(7)	$C_{(9)}$–$C_{(8)}$–$C_{(13)}$	118.7(7)
$C_{(4)}$–$C_{(3)}$–$C_{(2)}$	121.4(7)	$O_{(3)}$–$C_{(13)}$–$C_{(8)}$	113.0(6)	$N_{(1)}$–$C_{(9)}$–$C_{(8)}$	123.7(8)
$C_{(4)}$–$C_{(5)}$–$C_{(6)}$	120.4(8)	$C_{(9)}$–$N_{(1)}$–$C_{(11)}$	112.0(7)	$O_{(1)}$–$C_{(10)}$–$C_{(12)}$	107.4(7)
$C_{(1)}$–$C_{(6)}$–$C_{(7)}$	120.3(7)	$C_{(9)}$–$O_{(1)}$–$C_{(10)}$	108.5(6)	$C_{(12)}$–$C_{(10)}$–$C_{(11)}$	114.2(7)
$C_{(8)}$–$C_{(7)}$–$C_{(6)}$	118.6(7)	$N_{(1)}$–$C_{(1)}$–$C_{(6)}$	117.6(7)	$C_{(10)}$–$C_{(12)}$–$Br_{(1)}$	108.2(6)
$C_{(6)}$–$C_{(7)}$–$C_{(14)}$	116.9(7)	$C_{(3)}$–$C_{(2)}$–$C_{(1)}$	117.3(8)	$O_{(2)}$–$C_{(13)}$–$C_{(8)}$	120.8(7)
$C_{(7)}$–$C_{(8)}$–$C_{(13)}$	123.5(7)	$C_{(5)}$–$C_{(4)}$–$C_{(3)}$	121.4(8)		
$N_{(1)}$–$C_{(9)}$–$O_{(1)}$	113.6(7)	$C_{(1)}$–$C_{(6)}$–$C_{(5)}$	117.4(7)		

EXPERIMENTAL

^{1}H NMR and ^{13}C NMR spectra of the oxazoloquinolinium bromide **5**, two dimensional ^{1}H NMR COSY experiments, and HMQC and HMBC correlations were measured on a Varian Mercury-400 spectrometer (400 and 100 MHz respectively for ^{1}H and ^{13}C). All of the two dimensional experiments were carried out with gradient selection of useful signals. The mixing times in the pulse sequences were respectively $^1J_{CH}$ = 140 and $^{2\text{-}3}J_{CH}$ = 8 Hz. The number of increments in the COSY and HMQC spectra was 128 and in the HMBC spectrum 400. The ^{1}H NMR spectra of the allyl compounds were taken on a Varian Mercury-VX-200 (200 MHz) instrument. In all case the solvent was DMSO-d_6 and the internal reference TMS. The ethyl 4-methyl-2-oxo-1,2-dihydroquinoline-3-carboxylate (**2**) was prepared as in method [6].

Ethyl 1-Allyl-4-methyl-2-oxo-1,2-dihydroquinoline-3-carboxylate (3). Allyl bromide (1.3 ml, 0.015 mol) was added to a mixture of compound **2** (2.31 g, 0.01 mol) and K_2CO_3 (2.76 g, 0.02 mol) in DMSO (20 ml) and stirred for 2 h at 90ºC. The product was cooled and diluted with water. The precipitate was extracted with CH_2Cl_2 (3×20 ml). The organic extracts were combined, solvent distilled off, and the residue was treated with hexane (3×15 ml). The material not soluble in hexane was dissolved in ether (30 ml), purified using carbon, and solvent was distilled off to give the N-ethyl-substituted ester **3** (2.28 g, 84%) with R_f 0.42 (Silufol UV-254, Et_2O-hexane, 2:1) and mp 66-68ºC (aqueous ethanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.88 (1H, dd, *J* = 8.2, 1.2, H-5); 7.64 (1H, td, *J* = 7.9, 1.2, H-7); 7.47 (1H, d, *J* = 8.3, H-8); 7.32 (1H, td, *J* = 7.4, 1.0, H-6); 5.91 (1H, m, C<u>H</u>=CH_2); 5.13 (1H, dd, *J* = 10.5, 1.3, NCH_2CH=C<u>H</u>$_{cis}$); 4.95 (1H, dd, *J* = 17.4, 1.3, NCH_2CH=C<u>H</u>$_{trans}$); 4.84 (2H, d, *J* =4.7, NCH_2); 4.30 (2H, q, *J* = 7.1, OCH_2); 2.41 (3H, s, 4-CH_3); 1.27 (3H, t, *J* = 7.1, OCH_2C<u>H</u>$_3$). Found, %: C 70.75; H 6.23; N 5.08. $C_{16}H_{17}NO_3$. Calculated, %: C 70.83; H 6.32; N 5.16.

Ethyl 2-Allyloxy-4-methylquinoline-3-carboxylate (4). The hexane extract remaining after separation of the N-ethyl-substituted ester **3** (see preceding compound) was purified using carbon and solvent was removed to give the 2-allyloxy derivative (0.13 g, 5%) as a colorless, oily liquid with R_f 0.89 (Silufol UV-254, Et_2O–hexane, 2:1). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.04 (1H, d, *J* = 8.3, H-5); 7.75 (2H, m, H-7,8); 7.49 (1H, td, *J* = 7.3, 1.9, H-6); 6.07 (1H, m, C<u>H</u>=CH_2); 5.37 (1H, dd, *J* = 17.0, 1.9, OCH_2CH=C<u>H</u>$_{trans}$); 5.22 (1H, dd, *J* = 10.6, 1.9, OCH_2CH=C<u>H</u>$_{cis}$); 4.96 (2H, d, *J* = 4.8, O<u>C</u>H_2CH=); 4.37 (2H, q, *J* = 7.2, O<u>C</u>H_2CH_3); 2.58 (3H, s, 4-CH_3); 1.30 (3H, t, OCH_2C<u>H</u>$_3$). Found, %: C 70.73; H 6.40; N 5.21. $C_{16}H_{17}NO_3$. Calculated, %: C 70.83; H 6.32; N 5.16.

1-Allyl-4-methyl-2-oxo-1,2-dihydroquinoline-3-carboxylic Acid (1). A mixture of compound **3** (2.71 g, 0.01 mol) and 20% aqueous KOH solution (30 ml) was refluxed for 3 h, cooled, and acidified with HCl to pH 3. The precipitated acid **1** was filtered off, washed with water, and dried to give the product (2.20 g, 90%) with mp 131-133ºC (ethanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 13.46 (1H, br. s, COOH); 7.90 (1H, d, *J* = 8.0, H-5); 7.64 (1H, t, *J* = 7.9, H-7); 7.47 (1H, d, *J* = 8.3, H-8); 7.32 (1H, t, *J* = 7.6, H-6); 5.92 (1H, m, C<u>H</u>=CH_2); 5.14 (1H, dd, *J* = 10.5, 1.3, NCH_2CH=C<u>H</u>$_{cis}$); 4.97 (1H, dd, *J* = 17.5, 1.3, NCH_2CH=C<u>H</u>$_{trans}$); 4.89 (2H, d, *J* = 4.7, NCH_2); 2.45 (3H, s, CH_3). Found, %: C 69.22; H 4.46; N 5.69. $C_{14}H_{13}NO_3$. Calculated, %: C 69.12; H 5.39; N 5.76.

2-Bromomethyl-4-carboxy-5-methyl-1,2-dihydrooxazolo[3,2-*a*]quinolinium Bromide (5). Bromine (0.52 ml, 0.01 mol) was added to a solution of the N-allyl-substituted acid **1** (2.43 g, 0.01 mol) in acetic acid (20 ml) and was immediately decolorized. The product was diluted with water and the precipitate was filtered off, washed with cold water, and dried to give the product (3.26 g, 81%) with mp 213-215ºC (ethanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.49 (1H, d, *J* = 7.9, H-6); 8.19 (1H, t, *J* = 7.9, H-8); 8.08 (1H, d, *J* = 7.9, H-9); 7.90 (1H, t, *J* = 7.9, H-7); 5.97 (1H, m, CHO); 5.24 (1H, t, *J* = 11.3, NCH); 4.92 (1H, dd, *J* = 11.3, 7.0, NCH); 4.14 (2H, m, CH_2Br); 2.95 (3H, s, 5-CH_3). ^{13}C NMR spectrum, δ, ppm: 163.9 (COO), 158.6 ($C_{(3a)}$), 158.5 ($C_{(5)}$), 136.4 ($C_{(8)}$), 133.9 ($C_{(9a)}$), 128.8 ($C_{(7)}$), 128.5 ($C_{(6)}$), 124.5 ($C_{(5a)}$), 118.6 ($C_{(9)}$), 116.0 ($C_{(4)}$), 84.5 ($C_{(2)}$), 52.8 ($C_{(1)}$), 33.6 (CH_2Br), 18.2 (5-CH_3). Found, %: C 41.81; H 3.30; N 3.36. $C_{14}H_{13}BrNO_3$.Br. Calculated, %: C 41.72; H 3.25; N 3.47.

X-ray Structural Investigation. Crystals of compound **5** are monoclinic (ethanol), at -173ºC: a = 7.140(2), b = 23.844(5), c = 8.128(2) Å, β = 90.06(2)º, V = 1383.8(5) Å^3, M_r = 403.07, Z = 4, space group $P2_1/n$, d_{calc} = 1.935 g/cm^3, μ(MoKα) = 5.864 mm^{-1}, F(000) = 792. The unit cell parameters and intensities of 7700 reflections (2443 independent with R_{int} = 0.133) were measured on an Xcalibur-3- diffractometer (MoKα radiation, CCD detector, graphite monochromator, ω-scanning to $2\theta_{max}$ = 50º). The absorption was included semiempirically from the results of Ψ-scanning (T_{min} = 0.319, T_{max} = 0.752). The structure was solved by a direct method using the SHELXTL program package [7]. The positions of the hydrogen atoms were calculated geometrically and refined using the *riding* method with $U_{iso} = nU_{eq}$ for a non hydrogen atom bonded to the given hydrogen (n = 1.5 for a methyl group and n = 1.2 for all other hydrogen atoms). The structure was refined by F^2 full matrix least squares analysis in the anisotropic approximation for non-hydrogen atoms to wR_2 = 0.117 for 2355 reflections (R_1 = 0.073 for 1901 reflections with $F > 4\sigma(F)$, S = 1.060). A full set of crystallographic information has been placed in the Cambridge structural data bank (deposit No CCDC 619575). The interatomic distances and valence angles are given in Tables 2 and 3.

REFERENCES

1. I. V. Ukrainets, N. L. Bereznyakova, A. V. Turov, and S. V. Slobodzyan, *Khim. Geterotsikl. Soedin.*, 1365 (2007). [*Chem. Heterocycl. Comp.*, **43**, 1159 (2007)].
2. I. V. Ukrainets, L. V. Sidorenko, O. V. Gorokhova, S. V. Shishkina, and A. V. Turov, *Khim. Geterotsikl. Soedin.*, 736 (2007). [*Chem. Heterocycl. Comp.*, **43**, 617 (2007)].
3. I. V. Ukrainets, N. L. Bereznyakova, O. V. Gorokhova, A. V. Turov, and S. V. Shishkina, *Khim. Geterotsikl. Soedin.*, 1180 (2007). [*Chem. Heterocycl. Comp.*, **43**, 1001 (2007)].
4. Yu. V. Zefirov, *Kristallografiya,*, **42**, 936 (1997).
5. H.–B. Burgi and J. D. Dunitz, *Structure Correlation*, Vol. 2, VCH, Weinhem (1994), p. 741.
6. I. V. Ukrainets, L. V. Sidorenko, O. V. Gorokhova, and S. V. Shishkina, *Khim. Geterotsikl. Soedin.*, 887 (2006). [*Chem. Heterocycl. Comp.*, **42**, 776 (2006)].
7. G. M. Sheldrick, *SHELXTL PLUS PC Version. A System of Computer Programs for the Determination of Crystal structure from X-ray Diffraction Data*, Rev. 5.1 (1998).