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SYNTHESIS OF 5-SUBSTITUTED 8,8-DIMETHYL-8,9-DIHYDRO-3*H*,7*H*-[1,2]OXAZINO[5,4,3-*de*]QUINOLIN-3-ONES

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The reaction of 2-substituted 7,7-dimethyl-5-oxo-5,6,7,8-tetrahydroquinoline-4-carboxylic acids with hydroxylamine results in the formation of 5-substituted 8,8-dimethyl-8,9-dihydro-3H,7H-[1,2]oxazino[5,4,3-de]quinolin-3-ones. The structure of the 5-phenyl derivative has been established by X-ray structural analysis. A possible mechanism of the reaction has been proposed on the basis of nonempirical quantum-chemical calculations.

Keywords: hydroxylamine, 8,8-dimethyl-8,9-dihydro-3*H*,7*H*-[1,2]oxazino[5,4,3-*de*]quionolin-3-ones, 7,7-dimethyl-5-oxo-5,6,7,8-tetrahydroquinoline-4-carboxylic acids, quantum-chemical calculation.

One method for the construction of 1,2-oxazine ring is the interaction of 1,4-dicarbonyl compounds with hydroxylamine. However, ring closure is not always observed in these reactions, hence the initially formed oximes must be additionally cyclized [1-3]. In cases where the 1,4-dicarbonyl unit is part of a cyclic system, reaction with hydroxylamine enables the synthesis of heterocycles containing a 1,2-oxazine [4].

2-Substituted 7,7-dimethyl-5-oxo-5,6,7,8-tetrahydroquinoline-4-carboxylic acids **1a**-**g**, obtained by the reaction of 3-amino-5,5-dimethylcyclohex-2-enone with acyl(aroyl)pyruvic acids [5], are 1,4-dicarbonyl compounds suitable as starting reagents in the synthesis of tricyclic heterocycles.

It has been found that the reaction of acids **1a**-**g** with hydroxylamine, generated *in situ* from its hydrochloride, leads to 5-substituted 8,8-dimethyl-8,9-dihydro-3*H*,7*H*-[1,2]oxazino[5,4,3-*de*]quionolin-3-ones **6a**-**g.**

The compounds **6a**-**g** are colorless crystalline substances, soluble in hot DMF and DMSO, and poorly soluble in common organic solvents and water. Yields, melting points, and the elemental analyses of the synthesized compounds **6a**-**g** are given in Table 1.

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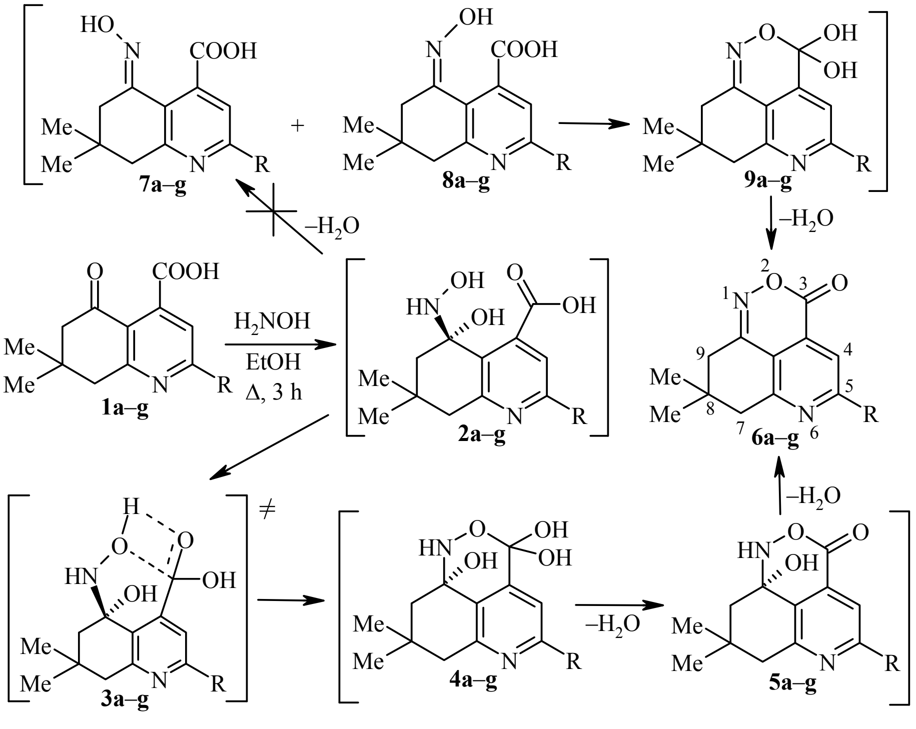
Formation of the reaction products **6a-g** can be explained by hydroxylamine nitrogen atom attack on ketone carbonyl of the acid **1a-g** and proton transfer from the nitrogen atom to the carbonyl oxygen atom (intermediates **2a-g**). Then in the intermediates **2a-g**, the oxygen atom of the hydroxyamino group attacks the carbon of the carboxyl group, which leads to the intermediates **4a-g**. The latter then successively eliminates two molecules of water to give the intermediates **5a-g** and then the reaction products **6a-g**.



a R = *t*-Bu, **b** R = Ph, **c** R = 4-MeC_6H_4, **d** R = 4-MeOC_6H_4, **e** R = 4-EtOC_6H_4,
f R = 4-BrC_6H_4, **g** R = 4-ClC_6H_4

With the objective of elucidating the fundamental possibility of the proposed scheme, we carried out calculations of the total energy, electronic and geometric characteristics of the intermediates **2b**, **5b**, and also the intermediates **7b-9b** using the CCP MO LCAO nonempirical method in the 6-31G(d) basis set.

According to the calculations, the distance $l_{O\cdots C}$ between the reaction centers in intermediate **2b** is 3.319 Å, and the values of the charges on the carboxyl group oxygen and carbon according to Löwdin are respectively -0.458 and 0.296 a.u., which does not inhibit them becoming close enough to form an O–C bond. This intermediate may be stabilized by an intramolecular hydrogen bond C(5)–O–H···O–CO–C(4), as indicated by the calculated interatomic distance $l_{H\cdots O}$ of 2.094 Å.

Modeling of the nucleophilic attack on the carbon atom of the carboxylic acid allowed us to identify an activated complex **3b**, which corresponds to the transition state of this reaction. An interatomic distance $l_{O\cdots C}$ equal to 1.708 Å corresponds to the maximum on the potential curve, while C=O bond length is increased to 1.289 Å. The calculated $l_{O\cdots H}$ bond length is equal to 1.004 Å, and the interatomic distance $l_{H\cdots O=C}$ is shortened to 1.241 Å. The charge on the oxygen atom is practically unchanged (q(O) = -0.461 a.u.), but the charge on the carbon atom increased to 0.371 a.u.

Thus, as the reaction centers approach, a proton is transferred from the hydroxyamino group oxygen atom to the carbonyl oxygen atom. Further shortening of the $l_{O\cdots C}$ distance leads to the formation of intermediate **4b**, in which the length of the N–<u>O–C</u> bond becomes equal to 1.400 Å. The lengths of the newly formed C–O and O–H bonds are equal to 1.374 and 0.952 Å, respectively.

TABLE 1. Physicochemical Characteristics of the Synthesized Compounds **6a-g**

Com-pound	Empirical formula	Found, % Calculated, %			Mp, °C	Yield, %
		C	H	N		
6a	$C_{16}H_{20}N_2O_2$	70.31 70.56	7.17 7.40	10.05 10.29	28-29	96
6b	$C_{18}H_{16}N_2O_2$	73.95 73.96	5.43 5.52	9.61 9.58	162-163	81
6c	$C_{19}H_{18}N_2O_2$	74.22 74.49	5.87 5.92	9.00 9.14	215-16	86
6d	$C_{19}H_{18}N_2O_3$	70.55 70.79	5.69 5.63	8.64 8.69	216-217	90
6e	$C_{20}H_{20}N_2O_3$	71.54 71.41	5.99 5.99	8.30 8.33	179-180	70
6f	$C_{18}H_{15}BrN_2O_2$	58.37 58.24	3.95 4.07	7.75 7.55	220-221	80
6g	$C_{18}H_{15}ClN_2O_2$	66.11 66.16	4.53 4.63	8.40 8.57	226-227	88

The most probable direction for the dehydration of intermediate **4b** is the formation of intermediate **5b**, which, according to calculations, is more stable by 13.9 kJ/mol than the alternative intermediate **9b**.

The oximes **7b** and **8b**, potentially formed through dehydration of the key intermediate **2b**, were not observed in the reaction mixture.

The structures of reaction products **6a-g** were established by the data of IR, ^{1}H and ^{13}C NMR spectroscopy (Tables 2 and 3). The assignments of ^{1}H and ^{13}C NMR signals were based on heteronuclear 2D ^{1}H–^{13}C gHSQC and gHMBC experiments. For example, of the two ^{13}C NMR signals at 174.3 and 163.1 ppm exhibited by compound **6a,** the weaker signal is assigned to atom C–5 by analogy with the α-carbon

TABLE 2. IR and ^{1}H NMR Spectra of Compounds **6a–g**

Com-pound	IR spectrum, ν, cm^{-1}		^{1}H NMR spectrum δ, ppm (*J*, Hz)				
	C=S, C=N	C=O	8-(CH$_3$)$_2$ (6H, s)	7-CH$_2$ 2H, s)	9-CH$_2$ (2H, s)	H-4 (1H, s)	R
6a	1596	1742	1.08	2.98	2.75	7.87	1.39 (9H, s, C(CH$_3$)$_3$))
6b	1591	1747	1.10	3.05	2.78	8.37	7.54–7.56 (3H, m, H Ph); 8.22–8.26 (2H, m, H Ph)
6c	1588	1745	1.10	3.03	2.77	8.31	2.39 (3H, s, CH$_3$); 7.36 (2H, d, *J* = 8.4, H Ar); 8.14 (2H, d, *J* = 8.4, H Ar)
6d	1584	1741	1.10	3.02	2.76	8.27	3.86 (3H, s, OCH$_3$); 7.09 (2H, d, *J* = 8.9, H Ar); 8.21 (2H, d, *J* = 8.9, H Ar)
6e	1588	1742	1.10	3.02	2.76	8.26	1.37 (3H, t, *J* = 6.9, $OCH_2C\underline{H_3}$); 4.14 (2H, q *J* = 6.9, $OC\underline{H_2}CH_3$); 7.07 (2H, d, *J* = 9.0, H Ar); 8.19 (2H, d, *J* = 9.0, H Ar)
6f	1585	1746	1.11	3.05	2.78	8.38	7.73 (2H, d, *J* = 8.9, H Ar); 8.19 (2H, d, *J* = 8.9, H Ar)
6g	1588	1746	1.11	3.05	2.78	8.37	7.58 (2H, d, *J* = 8.8, H Ar); 8.25 (2H, d, *J* = 8.8, H Ar)

TABLE 3. ^{13}C NMR Spectra of Compounds **6a**-**g**

Com-pound	Chemical shifts, δ, ppm															
	C-5	C-6a	C-3	C-9a	C-3a	C-9b	C-4	C-7	C-9	C-8	8-$(CH_3)_2$	R				
												C-*i*	C-*o*	C-*m*	C-*p*	Others
6a	174.3	163.1	158.7	153.9	128.1	114.7	112.3	44.8	39.3	32.3	27.4	—	—	—	—	38.4 ($\underline{C}(CH_3)_3$); 29.7 ($C(\underline{C}H_3)_3$)
6b	162.9	160.1	159.7	153.9	129.0	115.7	113.4	44.9	39.3	36.4	27.4	136.9	127.4	129.2	130.8	—
6c	162.6	160.2	159.4	153.6	129.0	115.1	112.6	44.8	39.2	32.0	27.2	134.1	129.5	127.0	140.4	20.7 ($Ar\underline{C}H_3$)
6d	162.7	159.9	159.4	153.6	128.5	114.6	112.0	44.8	39.2	32.0	27.2	129.3	128.8	114.4	161.4	55.3 (OCH_3)
6e	162.7	160.0	159.4	153.6	128.5	114.6	112.0	44.8	39.2	32.0	27.2	129.2	128.8	114.8	160.7	63.3 ($\underline{C}H_2CH_3$); 14.6 ($CH_2\underline{C}H_3$)
6f	162.5	159.6	158.9	153.6	128.8	115.8	113.3	44.7	39.2	32.0	27.2	136.0	129.1	131.8	124.3	—
6g	162.3	159.4	158.8	153.4	128.5	115.6	113.1	44.7	39.1	31.8	27.0	135.3	128.8	128.7	135.5	—

in the pyridine molecule. At the same time, this signal appears as a cross peak in the 2D gHMBC spectrum with the protons of the *tert*-butyl substituent. The corresponding signals of the carbon atoms of the methylene groups were assigned from the 2D gHSQC spectra on account of the direct constants of the spin-spin interactions similar to other carbon atoms bound with hydrogen atoms.

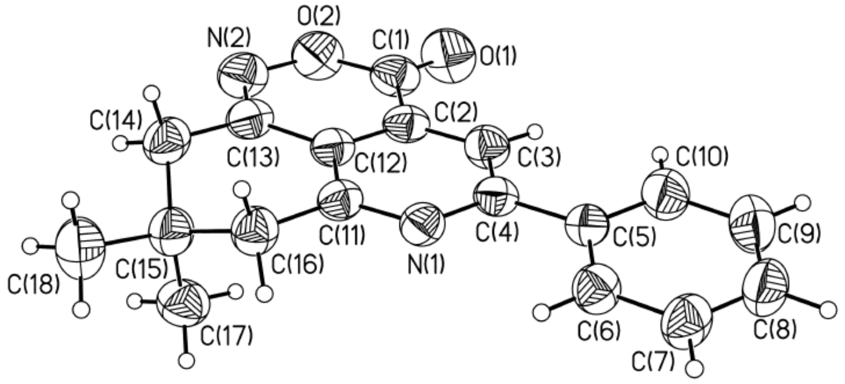


Fig. 1. Molecular structure of compound **6b** with atoms represented by thermal vibration elipsoids of 50% probability (the EtOAc molecule found in the composition of the crystal is not shown).

Monocrystal X-ray diffraction study of compound **6b** also confirmed the proposed product structure for the reaction discussed (Fig. 1). The compound crystallized in the centrosymmetric space group of the triclinic class. The fused heterocyclic fragment is planar within limits of 0.04 Å, but the phenyl substituent is at an angle of 7.2° relative to that plane. The distribution of bond lengths in the oxazine ring allows its characterization as a system of conjugated multiple bonds, but not as an aromatic system. At the same time, the bond lengths in the pyridine ring are noticeably equalized. The molecular packing is formed by molecule layers with planes of the fused heterocyclic systems at an angle of 55.86° relative to the [1 0 0] plane. There are no conspicuous close contacts in the packing.

Thus the reaction studied is a convenient and effective method for the preparation of annelated three-membered heterocyclic compounds containing an oxazine unit. The quantum-chemical calculations did not contradict the proposed reaction scheme.

EXPERIMENTAL

IR spectra of nujol suspensions were recorded with a Bruker IFS 66ps spectrometer. ^{1}H and ^{13}C NMR spectra in DMSO-d$_6$ with HMDS as internal standard were recorded with a Varian Mercury 300 Plus spectrometer (300 and 75 MHz, respectively). Elemental analysis was carried out with a LECO CHNS-932 apparatus. Melting points were determined with a PTP apparatus. Purity of the compounds synthesized was confirmed by HPLC (Agilent 1260 chromatograph, MeCN eluent, detection at 254 and 300 nm). Quantum-chemical calculations were carried out with the Firefly suite of software [6] on a Toshiba Portege M400 PC.

The starting acids **1a-g** were prepared by a known method [5].

5–Substituted 8,8-Dimethyl-8,9-dihydro-3*H*,7*H*-[1,2]oxazino[5,4,3-*de*]quinolin-3-ones 6a-g (General Method). $H_2NOH\cdot HCl$ (1.0 g, 14.4 mmol) was ground in a mortar with anhydrous NaOAc (1.18 g, 14.4 mmol), the mixture was transferred to a glass beaker and boiled in EtOH (10 ml) for 1 min. The hot solution was filtered, and the corresponding acid **1a-g** (2.0 mmol) was added to the filtrate and refluxed for 3 h. The reaction mixture was cooled, the precipitate was filtered off and washed on the filter with hot EtOH.

X-ray Structural Study of Compound 6b. A crystal was grown from EtOAc as a 1:1 solvate, empirical formula $C_{18}H_{16}N_2O_2{\cdot}C_4H_8O_2$ (M 380.45). Crystals of compound **6a** were triclinic, space group $P1$; a 6.0405(6), b 11.845(11), c 12.0501(12) Å, α 117.838(10)°, β 93.803(10)°, γ 95.908(8)°, V 751.92(13) $Å^3$, d_{calc} 1.291 g/cm^3, Z 2. The unit cell parameters and the set of experimental reflections were measured by a standard method [7] with an automatic four-cycle Xcalibur 3 diffractometer with a CCD detector by ω/2θ-scanning method with monochromatic MoKα irradiation over the interval of angles 3.35<θ<28.28. Reflections (5129) were measured, of which 3401 were independent (R_{int} 0.0204), 1605 with $I > 2\sigma(I)$. The completeness of the experiment for θ 25.50° was 95.5%. Correction for absorption was not used (μ 0.085 mm^{-1}). The structure was determined by a direct statistical method and was refined by complete matrix least squares method with respect to F^2 in the anisotropic approximation for all non-hydrogen atoms. Hydrogen atoms were placed in geometrically calculated positions and refined in isotropic approximation. All calculations were carried out with the SHELXTL suite of software (8). The final results of the refinement were R_1 0.0428, wR_2 0.0929 for reflections with $I > 2\sigma(I)$, R_1 0.1049, wR_2 0.1036 for all reflections, S 1.005. The maximum and minimum peaks of the residual electronic density were 0.189 and -0.174 e·$Å^{-3}$. The results of the X-ray structural study have been deposited at the Cambridge Crystallographic Data Center (CCDC 903807).

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