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# SYNTHESIS, CRYSTAL STRUCTURE, AND STABILITY OF N-LUPINYLPHTHALIMIDE CONFORMERS

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As a result of studying the interaction of chlorolupinine with potassium phthalimide, the optimal synthesis conditions for N-lupinylphthalimide by the Gabriel method are identified. The crystal structure of N-lupinylphthalimide is determined for the first time by single crystal XRD. The energy characteristics are calculated using the quantum chemical method. It is found that the conformer with the *chair* conformation of the cycles with the axial orientation of the phthalimide substituent is more stable than that with the equatorial orientation.

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## INTRODUCTION

The development of new drugs, the study of mechanisms of their receptor action are the topical issues of modern bioorganic chemistry. Promising areas include the creation of drugs by modifying naturally occurring compounds, including such a large class as alkaloids. In this aspect, the chemical structure of quinolizidine alkaloids corresponds to an interesting class of compounds with different combinations of carbo- and heterocycles, which causes the existence of various optical isomers and epimers. Specifically, the modification of quinolizidine alkaloids opens wide possibilities to search for highly effective, selective, stereospecific biologically active substances. One of those available for studying is the simplest quinolizidine alkaloid lupinine [1].

Previously, with the aim to expand the range of lupinine alkaloid derivatives, N-lupinylphthalimide (**1**) was synthesized, which can be a very promising synthon for the inclusion of a biologically active molecule of the lupinine alkaloid into various derivatives [2]. In continuation of this work, we have studied the optimal synthesis conditions for compound **1** and determined its spatial structure.

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## EXPERIMENTAL

$^1$H and $^{13}$C NMR spectra were recoreded on a JNN-ECA Jeol 400 spectrometer (399.78 MHz and 100.53 MHz respectively) using the DMSO-$d_6$ solvent. Chemical shifts were measured relative to the signals from residual protons or carbon atoms of deuterated DMSO.

The reaction course and the purity of the obtained compounds were controlled by thin-layer chromatography on Silufol UV-254 plates in the ethanol–chloroform system (1:4). The plates were exposed to iodine vapor. The reaction product was isolated by recrystallization from ethanol. The melting point was determined on a SMF-38 heating stage. All solvents used in the work were purified and absolutized according to standard procedures [3].

**Synthesis of N-lupinylphthalimide.** To 20 mL of a suspended solution of potassium phthalimide in DMF (4.607 g, 24.87 mmol) chlorolupinine (4.24 g, 22.61 mmol) was added. The reaction mixture was boiled for 8 h and then cooled. After settling for 15 h the reaction mixture was dissolved in 150 mL of ice water and extracted with chloroform (3×100 mL). The united extracts were rinsed with water (3×50 mL) and dried with $Mg_2SO_4$. The solvent was evaporated in vacuum; in the residue, N-lupinylphthalimide was obtained in the form of transparent crystals (3.98 g, 86%) with m.p. 161-164 °C.

$^1$H NMR spectrum, δ, ppm (*J*, Hz): 1.19-1.92, m (12H, $H2_{ax}$, $H3_{a,b}$, $H4_{a,b}$, H5, H6, $H7_{a,b}$, $H8_{a,b}$, $H9_{a,b}$, $H10_{ax}$), 2.69-2.85, m (2H, $H2_{eq}$, $H10_{eq}$), 3.57-3.90, m (2H, $H11_{a,b}$), 7.79-7.91, m (4H, H15–H18).

$^{13}$C NMR spectrum, δ, ppm: 20.68 (C3), 25.15 (C8), 25.79 (C9), 26.78 (C4), 29.75 (C7), 36.95 (C5), 40.07 (C11), 57.22 (C2, C10), 64.58 (C6), 123.51 (C15, C18), 132.08 (C14, C19), 134.93 (C16, C17), and 168.73 (C13, C20).

The calculations were performed within the MOPAC2009 software by the semi-empirical method of quantum chemistry using the PM6 parametrization [4].

**XRD experiment**. Single crystals for XRD were prepared by double crystallization of compound **1** from ethanol. The unit cell parameters and the intensities of 2863 reflections (2392 independent, $R_{int}$ = 0.0392) were measured on an Xcalibur Ruby diffractometer (λ Cu$K_\alpha$, graphite monochromator, ω-scanning, $4.33 \le \theta \le 76.08°$) at a temperature of 293 K.

Crystals are monoclinic, space group $P2_1$, $a$ = 5.3783(7) Å, $b$ = 14.124(1) Å, $c$ = 10.280(2) Å, β = 96.72(1)°, $V$ = 775.5(2) Å$^3$, $Z$ = 2 ($C_{18}H_{22}N_2O_2$, $M$ = 298.37 g/mol, $d_{calc}$ = 1.278 g/cm$^3$, μ = 0.667 mm$^{-1}$). The initial dataset of measured intensities was processed and the absorption correction was applied using the CrysAlisPro program (multiscan, $T_{min}$ = 0.763538, $T_{max}$ = 1.0) [5].

The structure was determined by a direct method. The positions of non-hydrogen atoms were refined in the anisotropic approximation by full-matrix LSM. The hydrogen atoms were placed in geometrically calculated positions, which were refined in the isotropic approximation with fixed positional and thermal parameters (riding model). 1429 independent reflections with $I \ge 2\sigma(I)$ were used in the calculations; the number of refined parameters was 200. The final divergence factors are $R_1$ = 0.0531, $wR_2$ = 0.1166 (for the reflections with $I \ge 2\sigma(I)$), $R_1$ = 0.0897, $wR_2$ = 0.1366 (for all reflections), GOOF = 0.986. The residual density peaks are Δρ = 0.152 e/Å$^3$ and –0.164 e/Å$^3$.

The structure was determined and refined using the SHELXS-97 [6] and SHELXL-2018/3 [7] software. The XRD data in the form of a CIF file have been deposited with the Cambridge Crystallographic Data Center (CCDC 1999403).

## RESULTS AND DISCUSSION

In order to identify the optimal synthesis conditions for compound **1** the interaction of chlorolupinine with potassium phthalimide within the Gabriel method to form N-alkylphthalimide was studied. The chlorolupinine precursor was synthesized by the interaction of lupinine with thionyl chloride in the absolutized benzene medium [8] (Fig. 1).

The results showed that the 86% yield of N-lupinylphthalimide (**1**) is maximum when chlorolupinine and potassium phthalimide are used in a 0.11:0.1 molar ratio in the DMF medium at 130-140 °C and the reaction time of 8 h. The structure of N-lupinylphthalimide (**1**) was proved by the $^1$H and $^{13}$C NMR spectral data, and the physicochemical constants coincided with those previously described in [2].

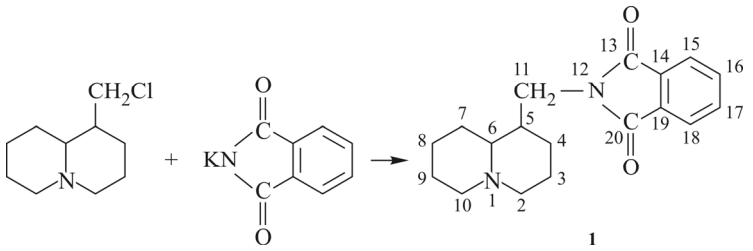

**Fig. 1.** Synthesis scheme of N-lupinylphthalimide (**1**).

The $^{1}$H NMR spectrum of compound **1** is characterized by the presence of a large number of protons with similar chemical shifts, resulting in overlapping of the signals, which complicates the identification. Thus, in the range 1.19-1.92 ppm there is a broad multiplet with the integral intensity of 12H, which includes most protons of the lupinine cycle both with axial and equatorial orientations. Some of them were identified by two-dimensional ($^{1}$H–$^{13}$C) HMQC NMR spectroscopy. The next multiplet signal in the range 2.69-2.85 ppm with the intensity of 2H belongs to the equatorially oriented $H2_{eq}$, $H10_{eq}$ protons of the lupinine framework. The bridging protons of the C11–$H_2$ methylene group appeared as a multiplet in the range 3.57-3.90 ppm. The aromatic protons in the multiplet form resonate in the range 7.79-7.91 ppm.

In the $^{13}$C NMR spectrum of compound **1**, the signals from the lupinine cycles are observed at 20.68 ppm (C3), 25.15 ppm (C8), 25.79 ppm (C9), 26.78 ppm (C4), 29.75 ppm (C7), 36.95 ppm (C5), 57.22 ppm (C2 and C10), and 64.58 ppm (C6). Carbon atoms of the benzene core resonated at 123.51 ppm (C15 and C18), 132.08 ppm (C14 and C19), and 134.93 ppm (C16 and C17). The signal with the chemical shift at 40.07 ppm corresponds to the carbon atom of the bridging methylene group. In a weak field region at 168.73 ppm, signals from carbonyl C13 and C20 atoms appeared.

The structure of compound **1** was also confirmed by two-dimensional ($^{1}$H–$^{13}$C) HMQC NMR spectroscopy, which allows one to determine heteronuclear spin-spin couplings. Heteronuclear proton couplings with the carbon atoms through one bond were established for the following pairs in the compound: $H2_{ax}$, $H10_{ax}$–C2, C10 (1.81; 57.56), $H2_{eq}$, $H10_{eq}$–C2, C10 (2.71; 57.73), H5–C5 (1.95; 37.52), H15, H18–C15, C18 (7.80; 123.97), and H16, H17–C16, C17 (7.80; 135.25).

The general view of the molecule of **1** is depicted in Fig. 2. The configuration of chiral C1 and C9 centers is correlated with the absolute one in the crystal structure of lupinine chloride [9].

From the obtained data it follows that the bond lengths and bond angles in compound **1** are nearly normal [10].

The conformations of six-membered N1, C2…C6 (A) and N1, C6…C10 (B) cycles in the quinolizidine framework are similar to the respective conformations in the crystal structure of lupinine [11]. The cycles are in the conformation close to a slightly distorted *chair* ($\Delta C_S^3 = 2.7$ and $\Delta C_2^{3,4} = 0.5°$ for cycle A and $\Delta C_S^7 = 0.8$ and $\Delta C_2^{6,7} = 1.8°$ for cycle B). Atoms of the phthalimide substituent are practically in one plane (±0.02 Å). This substituent connected to the lupinine bicycle through the axially oriented methylene $CH_2$ group takes the orientation allowing the maximum parallel arrangement to the plane

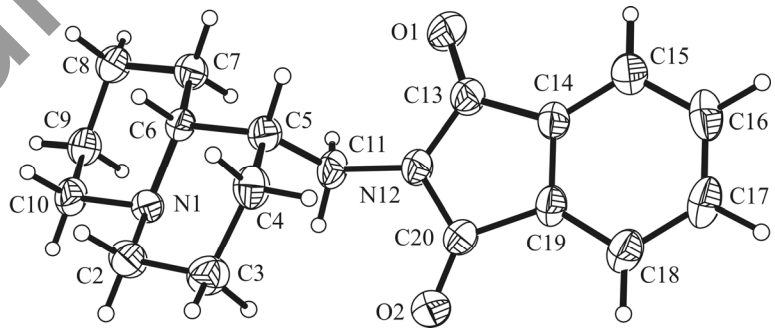


**Fig. 2.** Structure of N-lupinylphthalimide (**1**) (thermal ellipsoids are shown at the 30% probability level).

passing through N1, C3, C4, and C6 atoms (±0.02 Å) of cycle A. The dihedral angle between this plane and the phthalimide substituent is 30.6°; between the C5, C11, N12 atoms and this substituent is 81.8°.

It should be noted that in the crystal structures of lupinine and lupinine hydrochloride the methanol group is also axially oriented. Meanwhile, it is known that the conformers, the derivatives of cyclic compounds with the equatorial substituent orientation, are more stable than those with the axial orientation. For example, the ethylcyclohexane molecule taking the *chair* conformation with the equatorial orientation of the ethyl group is far more stable than the same conformer with the axial orientation ($\Delta G^0$ = 7.3 kJ/mol) [12]. In the crystal structure of lupinine C5 epimer ((+)-lupinine) in the *chair* conformation of cycles A and B the equatorial orientation of the methanol group is also observed [13].

Therefore, to determine the relative stability, the formation heat ($\Delta H_f$) and total energies ($E_{tot}$) of two conformers with the *chair* conformation of cycles A and B with axial (**1a**) and equatorial (**1b**) orientations of the ethyl group were compared for the molecule of **1**. From quantum chemical calculations with the full geometry optimization of the conformers it follows that their total energies are the same within an error. The formation heat of conformer **1a** with the axial orientation of the phthalimide substituent is even somewhat lower than that of **1b** ($\Delta H_f$ = 0.3 kJ/mol), which agrees with the theory about the occurrence of the most stable conformer in the crystal [14].

Thus, the study of the interaction of chlorolupinine with potassium phthalimide identified the optimal synthesis conditions for N-lupinylphthalimide in the Gabriel method. The spatial structure of N-lupinylphthalimide was determined and it was shown that the conformer with the *chair* conformation of the cycles with the axial orientation of the phthalimide substituent was more stable than that with the equatorial orientation.

## CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

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